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MEYLER'S Side Effects of Drugs

The International Encyclopedia of Adverse Drug Reactions and Interactions

Fifteenth Edition

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Foreword

My doctor is
A good doctor
He made me no
Iller than I was

Willem Hussem (The Netherlands) 1900–1974
Translation: Peter Raven

"*Primum non nocere*"—in the first place, do no harm—is often cited as one of the foundation stones of sound medical care, yet its origin is uncertain. Hippocrates? There are some who will tell you so;[1] but the phrase is not a part of the Hippocratic Oath, and the Father of Medicine wrote in any case in his native Greek.[2] It could be that the Latin phrase is from the Roman physician Galenius, while others attribute it to Scribonius Largus, physician to one of the later Caesars,[3] and there is a lot of reason to believe that it actually originated in 19th century England.[4] Hippocrates himself, in the first volume of his *Epidemics*, put it at all events better in context: "When dealing with diseases have two precepts in mind: to procure benefit and not to harm."[5] One must not become overly obsessed by the safety issue, but it is a necessary element in good medical care.

The ability to do good with the help of medicines has developed immensely within the last century, but with it has come the need to keep a watchful eye on the possibility of inflicting harm on the way. The challenge is to recognize at the earliest possible stage the adverse effects that a valuable drug may induce, and to find ways of containing them, so that risk never becomes disproportionate to benefit. The process of drug development will sometimes result in methods of treatment that are more specific to their purpose than were their predecessors and hence less likely to produce unwanted complications; yet the more novel a therapeutic advance the greater the possibility of its eliciting adverse effects of a type so unfamiliar that they are not specifically looked for and long remained unrecognized when they do occur. The entire process of keeping medicines safe today involves all those concerned with them, whether as researchers, manufacturers, regulators, prescribers, dispensers, or users, and it demands an effective and honest flow of information and thought between them.

For several decennia, concerned by its own errors in the past, the science of therapeutics put unbounded faith in the ability of well-planned clinical trials to arrive at the truth about the properties of medicines. Insofar as efficacy was concerned that was and remains a sound move, closing the door to charlatanism as well as to well-meant amateurism. Therapeutic trials with a new medicine were also able to delineate those adverse effects that occurred in a fair proportion of users. If serious, they would bar the drug from entry to the market altogether, while if transient and reasonably tolerable they would form the basis for warnings and precautions as well as the occasional contraindication. The problem lay with those adverse drug reactions that occurred rather less commonly or not at all in populations recruited for therapeutic trials, yet which could soon arise in the much broader spectrum of patients exposed to the drug once it was marketed across the world. The influence of race or climate might explain some of them; others might reflect interactions with foods, alcohol, or other drugs; yet others could only be explained, if at all, in terms of the particular susceptibility of certain individuals. Scattered across the globe, these effects might readily be overlooked, regarded as coincidental, or at worst dismissed contemptuously as "merely anecdotal".

The seriousness of the adverse effects issue became very apparent even as the reputation of controlled trials deservedly grew, and it touched on both newer and older drugs. The thalidomide calamity, involving several thousand cases of drug-induced phocomelia, was fortunately recognized by Widukind Lenz and others in the light of individual case reports within two years of the introduction of the product. On the other hand, generations elapsed between the patenting of aspirin in 1899 and the realization in 1965 that it might induce Reye's syndrome when used to treat fever in children. Such events, and many less spectacular, showed that, however vital well-controlled studies had become, there was good reason to remain alert for signals emerging from individual cases. Unanticipated events occurring during drug treatment might indeed reflect mere coincidence, but again they might not; and for many of the patients who suffered in consequence there was nothing in the least anecdotal about them.

Fortunately, the 1950s and 1960s of the 20th century saw the first positive reactions to the adverse reaction issue. Effective drug regulation emerged in one country after another. In 1952, Prof. Leo Meyler of The Netherlands produced his first "Side Effect of Drugs" to pull together data from the world literature. A number of national adverse reaction monitoring bureaux were established to gather data from the field and examine carefully reports of suspected side effects of medicines, creating the basis for the World Health Organization to establish its global reporting system. The pharmaceutical industry has increasingly realized its duty to collect and pass on the information that comes into its possession through its wide contacts with the health professions. Later years have seen the emergence, notably in Sweden and in Britain, of systems through which patients themselves can report possible adverse effects to the medicines they have taken. All these processes fit together in what the French language so appropriately terms "pharmacovigilance", with vigilance as the watchword for all concerned.

In this continuing development, the medical literature provides a resource with vast potential. The world is believed to have some 20 000 medical journals, of which a nuclear group of a thousand or so can be relied upon to publish reports and analyses of adverse effects—not only in the framework of formal investigations but also in letters, editorials, and reports of meetings large and small. Much of that information comprises not so much firm facts as emergent knowledge, based directly on experience in the field and calling urgently for attention. The book that Leo Meyler created has, in the course of fifteen editions and with the support of an ever-larger team of professionals, provided the means by which that attention can be mobilized. It has become the world's principal tool in bringing together, encyclopedically but critically, the evidence on the basis of which adverse drug effects and interactions can be recognized, discussed, and accommodated into medical practice. Together with its massive database and its complementary *Side Effects of Drugs Annuals*, it has evolved into a vital instrument in ensuring that drugs are used wisely and well and with due caution, in the light of all that is known about them. There is nothing else like it, nor need there be; across the world, *Meyler* has become a pillar of responsible medical care.

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Notes

1. Lichtenhaeler C. Histoire de la Médicine, Fayard, Paris, 1978:117.
2. Smith CM. Origin and uses of *Primum non nocere*. J Clin Pharmacol 2005;45:371–7.
3. Albrecht H. Primum nil nocere. Die Zeit, 6 April, 2005.
4. Notably in a book by Inman T. *Foundation for a New Theory and Practice of Medicine*. London, 1860.
5. I am indebted to Jeffrey Aronson for his own translation of the Greek original from Hippocrates *Epidemics*, Book I, Section XI, which seems to convey the meaning of the original [ἀσκεῖν περὶ τὰ νοσημάτα δῦο, ὠφελειν ἢ μὴ βλάπτειν] rather better than the published translations of his work.

Preface

This is a completely new edition of what has become the standard reference text in the field of adverse drug reactions and interactions since Leopold Meyler published his first review of the subject 55 years ago. Although we have retained the old title, *Meyler's Side Effects of Drugs*, the subtitle of this edition, *The Encyclopedia of Adverse Drug Reactions and Interactions*, reflects both modern terminology and the scope of the review. The structure of the book may have changed, but the *Encyclopedia* remains the most comprehensive reference source on adverse drug reactions and interactions and a major source of informed discussion about them.

Scope

The scope of the *Encyclopedia* remains wide. It covers not only the vast majority of prescription drugs, old and new, but also non-prescribed substances (such as anesthetics, antiseptics, lifestyle compounds, and drugs of abuse), herbal medicines, devices (such as blood glucose meters), and methods in alternative and complementary medicine. For this edition, entries on some substances that were regarded as obsolete, such as thalidomide and smallpox vaccine, have been rewritten and restored. Other compounds, such as diethylstilbestrol, although no longer in use, continue to cast their shadow and are included. Yet others, currently regarded as obsolete, have been retained, both for historical reasons and because one can never be sure when an old compound may once more become relevant or provide useful information in relation to another compound. Some drugs have been withdrawn from the market in some countries since the last edition of *Meyler* was published; rofecoxib, cisapride, phenylpropanolamine, and kava (see Piperaceae) are examples. Nevertheless, detailed monographs have been included on these substances because of the lessons that they can teach us and in some cases because of their relevance to other compounds in their classes that are still available; it is also not possible to predict whether these compounds will eventually reappear in some other form or for some new indication.

In the last 15 years there has been increasing emphasis on the use of high-quality evidence in therapeutic practice, principally as obtained from large, randomized clinical trials and from systematic reviews of the results of many such trials. However, while it has been possible to obtain useful information about the beneficial effects of interventions in this way, evidence about harms, including adverse drug reactions, has been more difficult to obtain. Even trials that yield good estimates of benefits are poor at providing evidence about harms for several reasons:

- benefits are usually single, whereas harms are usually multiple;
- the chance of any single form of harm is usually smaller than the chance of benefit and therefore more difficult to detect; however, multiple harms can accumulate and affect the benefit-to-harm balance;
- benefits are identifiable in advance, whereas harms are not or not always;
- the likely time-course of benefits can generally be predicted, while the time-course of harms often cannot and may be much delayed by comparison with the duration of a trial.

For all these reasons, larger and sometimes longer studies are needed to detect harms. In recent years attempts have been made to conduct systematic reviews of adverse reactions, but these have also been limited by several problems:

- harms are in general poorly collected in randomized trials and trials may not last long enough to detect them all;
- even when they are well collected, as is increasingly happening, they are often poorly reported;
- even when they are well reported in the body of a report, they may not be mentioned in titles and abstracts;
- even when they are well reported in the body of a report, they may be poorly indexed in large databases.

All this means that it is difficult to collect information on adverse drug reactions from randomized, controlled trials for systematic review. This can be seen from the evidence provided in Table 1, which shows the proportion of different types of information that have been used in the preparation of two volumes of the *Side Effects of Drugs Annual*, proportions that are likely be the same in this *Encyclopedia*.

Wherever possible, emphasis in this *Encyclopedia* has been placed on information that has come from systematic reviews and clinical trials of all kinds; this is reflected in new headings under which trial results are reported (observational studies, randomized studies, placebo-controlled studies). However, because many reports of adverse drug reactions (about 30%) are anecdotal, with evidence from one or just a few cases, many individual case studies (see below) have also been included. We need better methods to make use of the information that this large body of anecdotes provides.

Structure

The first major change that readers will notice is that the chapter structure of previous editions has given way to a monographic structure. That is because some of the information about individual drugs has previously been scattered over different chapters in the book; for example ciclosporin was previously covered in Chapter 37 and in scattered sections throughout Chapter 45; it is now dealt with in a single monograph. The monographs are arranged in alphabetical order, with cross-referencing as required. For example, if you turn to the monograph on cetirizine, you will be referred to the complementary general monograph on antihistamines, where much information that is relevant to cetirizine is given; the monograph on cetirizine itself contains information that is relevant only to cetirizine and not to other antihistamines. Within each monograph the material is arranged in the same way as in the *Side Effects of Drugs Annuals* (see "How to use this book").

Case Reports

A new feature, recognizable from the Annuals, but not incorporated into previous editions, is the inclusion of case reports of adverse effects. This feature reflects the fact that about 30% of all the literature that is reported and discussed in the Annuals derives from such reports (see Table 1). In some cases the only information about an adverse effect is contained in an anecdotal report; in other cases the report illustrates a variant form of the reaction. A case report also gives more immediacy to an adverse reaction, allowing the reader to appreciate more precisely the exact nature of the reported event.

Classification of Adverse Drug Reactions

Another new feature of this edition is the introduction of the DoTS method of classifying adverse drug reactions, based on the **Dose** at which they occur relative to the beneficial dose, the **Time-course** of the reaction, and individual **Susceptibility factors** (see "How to use this book"). This has been done for selected adverse effects, and I hope that as volumes of SEDA continue to be published and the *Encyclopedia's* electronic database is expanded, it will be possible to classify increasing numbers of adverse reactions in this way.

References

Because all the primary and secondary literature is thoroughly surveyed in the Annuals, the *Encyclopedia* has become increasingly compact relative to the amount of information available (even though it has increased in absolute size), with many unreferenced statements and cross-references to the Annuals, on the assumption that all the information would be readily available to the reader, although that may not always be the case. To restore all the reference material on which the *Encyclopedia* has been based as it has evolved over so many years would be a gargantuan task, but in this edition a major start has been made. Many references to original material have been restored, and there is now hardly a statement that is not backed up by at least one reference to primary literature. In addition, almost all of the material that was published in Annuals 23 to 27 (SEDA-23 to SEDA-27) has been included, complete with citations. This has resulted in the inclusion of more than 40 000 references in this edition. Readers will still have to refer to earlier editions of the Annual (SEDA-1 to SEDA-22) and occasionally to earlier editions of *Meyler's Side Effects of Drugs* for more detailed descriptions, but now that the *Encyclopedia* is available electronically this will be repaired in future editions.

Methods and Contributors

I initially prepared the text of the *Encyclopedia* by combining text from the 14th edition of *Meyler's Side Effects of Drugs* and the five most recent annuals (SEDA-23 to SEDA-27). [Later literature is covered in SEDA-28 and the forthcoming SEDA-29.] I next restored missing references to the material and extended it where important information had not been included. The resulting monographs were then sent to experts for review, and their comments were incorporated into the finished monographs. I am grateful to all those, both authors of chapters in previous editions and Annuals and those who have reviewed the monographs for this edition, for their hard work and for making their expertise available.

Acknowledgements

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Table 1 Types of articles on adverse drug reactions published in 6576 papers in the world literature during 1999 and 2003 (as reviewed in SEDA-24 and SEDA-28)

Type of article	Number of descriptions* (%)
An anecdote or set of anecdotes (that is reported case histories)	2084 (29.9)
A major, randomized, controlled trial or observational study	1956 (28.1)
A minor, randomized, controlled trial or observational study or a non-randomized study (including case series)	1099 (15.8)
A major review, including non-systematic statistical analyses of published studies	951 (13.7)
A brief commentary (for example an editorial or a letter)	362 (5.19)
An experimental study (animal or in vitro)	263 (3.77)
A meta-analysis or other form of systematic review	172 (2.47)
Official statements (for example by Governmental organizations, the WHO, or manufacturers)	75 (1.07)
Total no. of descriptions*	6962
Total no. of articles	6576

* Some articles are described in more than one way

electronically into templates under the guidance of Joke Zwetsloot from Elsevier. Christine Ayorinde provided excellent assistance while I expanded and edited the material. The International Non-proprietary Names were checked by Renée Aronson. At Elsevier the references were then checked and collated by Liz Perill, who also copyedited the material, with Ed Stolting, and shepherded it through conversion to different electronic formats. Bill Todd created the indexes. Stephanie Diment oversaw the project and coordinated everyone's efforts.

The History of Meyler

The history of *Meyler's Side Effects of Drugs* goes back 55 years; a full account can be found at http://www.elsevier.-com/locate/Meyler and the various volumes are listed before the title page of this set. When Leopold Meyler, a physician, experienced unwanted effects of drugs that were used to treat his tuberculosis, he discovered that there was no single text to which medical practitioners could turn for information about the adverse effects of drug therapy; Louis Lewin's text *Die Nebenwirkungen der Arzneimittel* ("The Untoward Effects of Drugs") of 1881 had long been out of print (SEDA-27, xxv–xxix). Meyler therefore surveyed the current literature, initially in Dutch as *Schadelijke Nevenwerkingen van Geneesmiddelen* (Van Gorcum, 1951), and then in English as *Side Effects of Drugs* (Elsevier, 1952). He followed up with what he called surveys of unwanted effects of drugs. Each survey covered a period of two to four years and culminated in Volume VIII (1976), edited by Graham Dukes (SEDA-23, xxiii-xxvi), Meyler having died in 1973. By then the published literature was too extensive to be comfortably encompassed in a four-yearly cycle, and an annual cycle was started instead; the first *Side Effects of Drugs Annual* (SEDA-1) was published in 1977. The four-yearly review was replaced by a complementary critical encyclopaedic survey of the entire field; the first encyclopaedic edition of *Meyler's Side Effects of Drugs*, which appeared in 1980, was labeled the ninth edition.

Since then, *Meyler's Side Effects of Drugs* has been published every four years, providing an encyclopaedic survey of the entire field. Had the cycle been adhered to, the 15th edition would have been published in 2004, but over successive editions the quantity and nature of the information available in the text has changed. In the new millennium it was clear that for this edition a revolutionary approach was needed, and that has taken a little longer to achieve, with a great deal of effort from many different individuals.

We have come a long way since Meyler published his first account in a book of 192 pages. I think that he would have approved of this new *Encyclopedia*.

Jeffrey K. Aronson
Oxford, October 2005

Using the Encyclopedia

In a departure from its previous structure, this edition of *Meyler's Side Effects of Drugs* is presented as individual drug monographs in alphabetical order. In many cases a general monograph (for example Antihistamines) is complemented by monographs about specific drugs (for example acrivastine, antazoline, etc.); in that case a cross-reference is given from the latter to the former.

Monograph Structure

Within each monograph the information is presented in sections as follows:

GENERAL INFORMATION
Includes, when necessary, notes on nomenclature, information about the results of observational studies, comparative studies, and placebo-controlled studies in relation to reports of adverse drug reactions, and a general summary of the major adverse effects.

ORGANS AND SYSTEMS
- Cardiovascular (includes heart and blood vessels)
- Respiratory
- Ear, nose, throat
- Nervous system (includes central and peripheral nervous systems)
- Neuromuscular function
- Sensory systems (includes eyes, ears, taste)
- Psychological, psychiatric
- Endocrine (includes hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, sex hormones)
- Metabolism
- Nutrition (includes effects on amino acids, essential fatty acids, vitamins, micronutrients)
- Electrolyte balance (includes sodium, potassium)
- Mineral balance (includes calcium, phosphate)
- Metal metabolism (includes copper, iron, magnesium, zinc)
- Acid–base balance
- Fluid balance
- Hematologic (includes blood, spleen, and lymphatics)
- Mouth and teeth
- Salivary glands
- Gastrointestinal (includes esophagus, stomach, small bowel, large bowel)
- Liver
- Biliary tract
- Pancreas
- Urinary tract (includes kidneys, ureters, bladder, urethra)
- Skin
- Hair
- Nails
- Sweat glands
- Serosae (includes pleura, pericardium, peritoneum)
- Musculoskeletal (includes muscles, bones, joints)
- Sexual function
- Reproductive system (includes uterus, ovaries, breasts)
- Immunologic (includes effects on the immune system and hypersensitivity reactions)
- Autacoids
- Infection risk
- Body temperature
- Multiorgan failure
- Trauma
- Death

LONG-TERM EFFECTS
- Drug abuse
- Drug misuse
- Drug tolerance
- Drug resistance
- Drug dependence
- Drug withdrawal
- Genotoxicity
- Mutagenicity
- Tumorigenicity

SECOND-GENERATION EFFECTS
- Fertility
- Pregnancy
- Teratogenicity
- Fetotoxicity
- Lactation

SUSCEPTIBILITY FACTORS (relates to features of the patient)
- Genetic factors
- Age
- Sex
- Physiological factors
- Cardiac disease
- Renal disease
- Hepatic disease
- Thyroid disease
- Other features of the patient

DRUG ADMINISTRATION
- Drug formulations
- Drug additives
- Drug contamination (includes infective agents)
- Drug adulteration
- Drug dosage regimens (includes frequency and duration of administration)
- Drug administration route
- Drug overdose

DRUG–DRUG INTERACTIONS
FOOD–DRUG INTERACTIONS
SMOKING
OTHER ENVIRONMENTAL INTERACTIONS
INTERFERENCE WITH DIAGNOSTIC TESTS
DIAGNOSIS OF ADVERSE DRUG REACTIONS
MANAGEMENT OF ADVERSE DRUG REACTIONS
MONITORING THERAPY

Classification of Adverse Drug Reactions

Selected major reactions are classified according to the DoTS system (BMJ 2003;327:1222–5). In this system adverse reactions are classified according to the **Dose** at which they usually occur relative to the beneficial dose, the **Time-course** over which they occur, and the **Susceptibility factors** that make them more likely, as follows:

1 Relation to dose
- *Toxic reactions* (reactions that occur at supratherapeutic doses)
- *Collateral reactions* (reactions that occur at standard therapeutic doses)
- *Hypersusceptibility reactions* (reactions that occur at subtherapeutic doses in susceptible patients)

2 Time-course
- *Time-independent reactions* (reactions that occur at any time during a course of therapy)
- *Time-dependent reactions*
  - Immediate reactions (reactions that occur only when a drug is administered too rapidly)
  - First-dose reactions (reactions that occur after the first dose of a course of treatment and not necessarily thereafter)
  - Early reactions (reactions that occur early in treatment then abate with continuing treatment)
  - Intermediate reactions (reactions that occur after some delay but with less risk during longer- term therapy, owing to the "healthy survivor" effect)
  - Late reactions (reactions the risk of which increases with continued or repeated exposure), including withdrawal reactions (reactions that occur when, after prolonged treatment, a drug is withdrawn or its effective dose is reduced)
  - Delayed reactions (reactions that occur some time after exposure, even if the drug is withdrawn before the reaction appears)

3 Susceptibility factors
- *Genetic*
- *Age*
- *Sex*
- *Physiological variation*
- *Exogenous factors* (for example drug–drug or food–drug interactions, smoking)
- *Diseases*

Drug Names And Spelling

Drugs are usually designated by their recommended or proposed International Non-proprietary Names (rINN or pINN); when these are not available, chemical names have been used. If a fixed combination has a generic combination name (for example co-trimoxazole for trimethoprim + sulfamethoxazole) that name has been used; in some cases brand names have been used.

Spelling

Where necessary, for indexing purposes, American spelling has been used, for example anemia rather than anaemia, estrogen rather than oestrogen.

Cross-references

The various editions of *Meyler's Side Effects of Drugs* are cited in the text as SED-l3, SED-14, etc.; the *Side Effects of Drugs Annuals* 1-22 are cited as SEDA-1, SEDA-2, etc. This edition includes most of the contents of SEDA-23 to SEDA-27. SEDA-28 and SEDA-29 are separate publications, which were prepared in parallel with the preparation of this edition.

Searching the online edition

The print edition of this Reference Work contains two indexes, the "Index of Drug Names" and the "Index of Adverse Reactions". Both indexes are print oriented and point at pages in the main text in which a reaction is discussed or a drug name used.

In the online environment these are redundant as free-standing indexes since on ScienceDirect simple searches can achieve the same results more efficiently and quickly. In addition, whilst the print "Index of Adverse Reactions" was necessarily selective no such constraint affects the online edition.

On ScienceDirect (and assuming you are subscribed to this Reference Work) you may use either the Basic Search Form or Advanced Search. For the purposes of simplicity in these notes only the Basic Search is described. (Quick Search is also supported but offers less granular options than the other search types.)

Familiarity with the structure of the monographs in the print encyclopedia can be used to advantage in targeting precise locations in the text. As with all other searches on ScienceDirect, the results are returned as article titles (including citation information) and (for Reference Works) in book order by default.

For example, to locate the article on "Venlafaxine" you can either navigate to it via clicking on the "Article Titles" browse tab and then on the letter "V" and scroll down to this entry.

Alternatively, on the Basic Search form you can enter the term "Venlafaxine" in the search box and run the search against the "Article Titles" index. By default a search is run across "All Fields" and each field that is separately searchable is listed in the "within" drop-down list.

To extend the search to find this term wherever it occurs in the encyclopedia then you should run this search against "Full Text". Such a search will generate a list of all monographs in which the term appears. To rank the results by relevance rather than alphabetically by monograph title, select the option "by relevance" in the drop down on the Search Results List.

As noted above consistency of structure in the encyclopedia is a huge benefit in the online environment. For example, to recover all articles in which "Fluid balance" is affected in some way by any drug then you should run a search on the term "Fluid balance" in the field "Subheadings". This will recover all drugs for which some impact on fluid balance has been recorded.

Abacavir

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Abacavir is a guanidine analogue that inhibits HIV reverse transcriptase. In vitro, its potency is similar to that of zidovudine, protease inhibitors, and dual nucleoside combinations. There is evidence that abacavir is effective in reducing viral load and increasing the CD4 count in HIV-infected patients. Viral resistance is not rapidly selected for, but cross-resistance has been shown to other analogues of cytosine and guanidine (didanosine, lamivudine, and zalcitabine).

Abacavir has good oral systemic availability and penetrates the nervous system. It does not interfere with drugs that are metabolized by liver microsomal cytochrome P450 (1). It has no other significant drug interactions and can be administered without food restrictions.

Observational studies

The effects of abacavir have been evaluated in a study in over 13 000 adults who no longer responded to commercially available treatment regimens (2). By month 2 of treatment with abacavir, plasma HIV-1 RNA concentrations fell by at least half a log unit in 31% of patients, and in 5.6% of the patients HIV-1 RNA concentrations fell to under 400 copies/ml. Serious drug-related adverse events were reported by 7.7% of patients. The most common were nausea, skin rash, diarrhea, malaise or fatigue, and fever. About 4.6% of patients had a hypersensitivity reaction that was possibly drug-related.

General adverse effects

The adverse effects of abacavir that have been most often observed in clinical trials are fatigue, nausea and vomiting, abdominal pain, diarrhea, headache, rash, and dyspepsia (3,4). Allergic reactions lead to withdrawal of therapy in about 3% of patients (5). These can be severe, and anaphylaxis has been reported after rechallenge in a patient with an apparent allergic reaction to abacavir (6). It is wise to avoid rechallenge when allergy is suspected (7). In one study nausea and vomiting occurred in 38–57% of patients, headache in 27–41%, malaise and fatigue in 28%, diarrhea in 18–23%, and weakness in 29% (8). There was also one case of agranulocytosis accompanied by a skin rash.

Organs and Systems

Nervous system

Vertigo has been attributed to abacavir (9).

- A 44-year-old African-American developed vertigo, tinnitus in both ears, headache behind the eyes, and left ear pain and hearing loss soon after starting to take abacavir, lamivudine, and stavudine. There was left-sided nystagmus and vestibular tests showed evidence of vestibular impairment. An MRI scan was normal. All the antiretroviral drugs were withdrawn and he improved. When lamivudine and stavudine were restarted, with nevirapine, the vertigo did not recur.

Metabolism

While abacavir has been associated with hyperglycemia in individual cases (10), there were no significant effects on blood glucose concentration in clinical trials.

- A 47-year-old man, with normoglycemia and no family history of diabetes mellitus, who was taking highly active antiretroviral therapy, was given abacavir for treatment intensification. He became lethargic and hyperglycemic. Despite metformin and glibenclamide, the hyperglycemia continued. Abacavir was withdrawn, and within 2 weeks his blood glucose concentration returned to baseline and the hypoglycemic drugs were withdrawn.

This patient was also taking hydrochlorothiazide, but the time-course of onset and resolution were consistent with abacavir-induced hyperglycemia.

Immunologic

The risk of allergic reactions to abacavir may be as high as 10% (11). However, the incidence is more usually reported to be 3–5% (12,13). Allergic reactions usually occur within the first 28 days of therapy and rarely thereafter. They are characterized by non-specific complaints suggestive of an upper respiratory tract infection, fever, rash, nausea, and vomiting. Resolution of the symptoms occurs within days of withdrawal. Severe and even fatal reactions to readministration have been observed, and it has been suggested that rechallenge is contraindicated in any patients who have had an allergic reaction (7). However, it is safe to rechallenge patients who have stopped treatment because of other types of adverse reaction. Of 1201 patients treated in clinical trials, 219 interrupted abacavir therapy for reasons other than allergy; on reintroduction there were no cases of allergy or anaphylaxis (14).

The susceptibility factors associated with allergic reactions have been sought in an analysis of all protocols conducted by GlaxoSmithKline that involved abacavir exposure for at least 24 weeks with a quality-assured or validated clinical database by 30 June 2000 ($n = 5332$) (15). There were 197 allergic reactions (3.7%). The risks of allergic reactions were lower in black people (OR = 0.59; 95% CI = 0.38, 0.91) than in other ethnic groups, and in patients who had received previous therapy for HIV-1 infection with other antiretroviral agents (OR = 0.58; 95% CI = 0.44, 0.78) compared with those receiving therapy for the first time.

Genetic factors affecting the immune response to abacavir have been sought in patients who had taken abacavir for more than 6 weeks, 18 with hypersensitivity reactions and 167 without (16). HLA-B*5701 was present in 14 of the 18 patients with abacavir hypersensitivity, and in four of the 167 others (OR = 117; 95% CI = 29, 481). The combination of HLA-DR7 and

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HLA-DQ3 was found in 13 of the 18 and five of the 167 (OR = 73; CI = 20, 268). HLA-B*5701, HLA-DR7, and HLA-DQ3 were present in combination in 13 of the 18 and none of the 167 (OR = 822; CI = 43, 15 675). Other MHC markers also present on the 57.1 ancestral haplotype to which these three markers belong confirmed the presence of haplotype-specific linkage disequilibrium, and mapped potential susceptibility loci to a region bounded by C4A6 and HLA-C. HLA-B*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97%. The authors concluded that susceptibility to abacavir hypersensitivity is carried on the 57.1 ancestral haplotype and that withholding abacavir from those with HLA-B*5701, HLA-DR7, and HLA-DQ3 should reduce the prevalence of hypersensitivity from 9% to 2.5% without inappropriately denying abacavir to any patient.

In a retrospective case-control study of patients with allergic reactions, HLA-B57 was present in 39 of 84 patients compared with 4 of 113 controls (17). However, there were few women and other ethnic groups in the study, and so these findings relate largely to white men.

In a multicenter trial, 128 children were randomly assigned to zidovudine + lamivudine ($n = 36$), to zidovudine + abacavir ($n = 45$), or to lamivudine + abacavir ($n = 47$) (18). One child had an allergic reaction to abacavir and stopped taking it, as did three with possible reactions.

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Abciximab

See also Monoclonal antibodies

General Information

Abciximab is a Fab fragment of the chimeric human-murine monoclonal antibody 7E3, which binds to the platelet glycoprotein IIb/IIIa receptor and inhibits platelet aggregation (1).

Abciximab is used for prevention of cardiac ischemic events in patients undergoing percutaneous coronary intervention and to prevent myocardial infarction in patients with unstable angina who do not respond to conventional treatment. It has also been used for thrombolysis in patients with peripheral arterial occlusive disease and arterial thrombosis (2).

Besides bleeding, other adverse reactions that have been associated with abciximab include back pain,

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HLA-DQ3 was found in 13 of the 18 and five of the 167 (OR = 73; CI = 20, 268). HLA-B*5701, HLA-DR7, and HLA-DQ3 were present in combination in 13 of the 18 and none of the 167 (OR = 822; CI = 43, 15 675). Other MHC markers also present on the 57.1 ancestral haplotype to which these three markers belong confirmed the presence of haplotype-specific linkage disequilibrium, and mapped potential susceptibility loci to a region bounded by C4A6 and HLA-C. HLA-B*5701, HLA-DR7, and HLA-DQ3 had a positive predictive value for hypersensitivity of 100%, and a negative predictive value of 97%. The authors concluded that susceptibility to abacavir hypersensitivity is carried on the 57.1 ancestral haplotype and that withholding abacavir from those with HLA-B*5701, HLA-DR7, and HLA-DQ3 should reduce the prevalence of hypersensitivity from 9% to 2.5% without inappropriately denying abacavir to any patient.

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Besides bleeding, other adverse reactions that have been associated with abciximab include back pain,

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hypotension, nausea, and chest pain (but with an incidence not significantly different from that observed with placebo).

Organs and Systems

Respiratory

Lung hemorrhage is a rare but potentially lethal complication of antithrombotic and antiplatelet therapy. The incidence of spontaneous pulmonary hemorrhage after the use of platelet glycoprotein IIb/IIIa inhibitors has been analysed from the medical records of 1020 consecutive patients who underwent coronary interventions (3). Diffuse pulmonary hemorrhage developed in seven patients, two of whom died and five of whom had activated clotting times greater than 250 seconds during the procedure. Activated partial thromboplastin time measured at the time of lung hemorrhage was raised in all cases (mean 85, range 69–95 seconds). All had a history of congestive heart failure, and had raised pulmonary capillary wedge pressures and/or left ventricular end-diastolic pressures at the time of the procedure. Six patients also had evidence of baseline radiographic abnormalities.

Nervous system

Seven patients undergoing neurointerventional procedures who received abciximab developed fatal intracerebral hemorrhages (4). The procedures included angioplasty and stent placement in the cervical internal carotid artery ($n = 4$), angioplasty of the intracranial carotid artery ($n = 1$), and angioplasty of the middle cerebral artery ($n = 2$). Aggressive antithrombotic treatment is used as adjuvant to angioplasty and/or stent placement to reduce the rate of ischemic and thrombotic complications associated with these procedures. Intravenous abciximab has a short life (10 minutes), but its inhibitory effect on platelets lasts for 48 hours. The exact cause of abciximab-associated intracerebral hemorrhage is unclear.

Hematologic

Bleeding

The primary risk associated with abciximab is bleeding. In the EPIC trial in high-risk angioplasty, 14% of patients who received a bolus of abciximab followed by an infusion had a major bleeding complication rate, versus 7% in the placebo group (5). The most marked excess of major bleeding episodes occurred at the site of vascular puncture, but there were also a substantial number of gastrointestinal haemorrhages. However, the therapeutic regimen used was not adjusted for body weight, and the risk of major bleeding was also related to the heparin dose per kg and not only to the use of abciximab (6).

In 7800 patients with chest pain and either ST segment depression or a positive troponin test, the addition of abciximab to unfractionated heparin or low molecular weight heparin in the treatment of acute coronary syndrome was not associated with any significant reduction in cardiac events, but a doubled risk of bleeding (7).

An analysis of data from the EPIC trial identified a series of factors that predicted vascular access site bleeding or the need for vascular access site surgery in abciximab-treated patients (8). They comprised larger vascular access sheath size, the presence of acute myocardial infarction at enrolment, female sex, higher baseline hematocrits, lower body weight, and a longer time spent in the catheterization laboratory.

It must be emphasized that patients in the EPIC trial received high-dose heparin and that vascular access site sheaths were left in place for 12–16 hours. In subsequent studies, the risk of vascular site bleeding was probably reduced by using lower doses of heparin and removing sheaths sooner. This was the case in the EPILOG trial in which heparin was withdrawn immediately after the coronary procedure and vascular sheaths were removed as soon as possible (9). The incidence of major bleeding in this study was not significantly higher with abciximab than with placebo. Nevertheless, the incidence of minor bleeding complications was significantly higher in the abciximab plus standard dose heparin group (but not in the abciximab plus low dose heparin group) compared with placebo. In the EPISTENT trial, all patients received low dose, body weight-adjusted heparin: Here the incidence of both major and minor bleeding complications was low and not significantly different between treatment groups (10).

It would therefore seem possible to reduce the incidence of bleeding complications when using abciximab during prophylactic coronary revascularization procedures. This is unfortunately not the case so far in the setting of primary angioplasty for myocardial infarction after intense anticoagulation (17% of major hemorrhagic complications versus 9.5 in placebo recipients) (11). The risk of serious bleeding complications is also increased in rescue situations when high doses of heparin have been used (12), but here it can be reduced by giving protamine to reverse heparin anticoagulation before abciximab therapy (13). There is also a high incidence of major bleeding in patients who receive abciximab during percutaneous coronary revascularization after unsuccessful thrombolytic therapy. It has been suggested that abciximab should not be administered within 18 hours after thrombolytic therapy (14).

It must be emphasized that very few episodes of abciximab-related bleeding are life-threatening and that in none of the trials with abciximab as well as with other glycoprotein IIb/IIIa antagonists has there been an excess of intracranial hemorrhage (15).

However, the bleeding risk in patients enrolled in trials may not be representative of the population actually being given abciximab. To clarify this, a review of adverse events in patients receiving glycoprotein IIb/IIIa inhibitors reported to the FDA has been undertaken (16,17). The FDA received 450 reports of deaths related to treatment with glycoprotein IIb/IIIa inhibitors between November 1, 1997 and December 31, 2000; these were reviewed and a standard rating system for assessing causation was applied to each event. Of the 450 deaths, 44% were considered to be definitely or probably attributable to glycoprotein IIb/IIIa inhibitors.

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The mean age of patients who died was 69 years and 47% of the deaths were in women. All of the deaths that were deemed to be definitely or probably associated with glycoprotein IIb/IIIa inhibitors were associated with excessive bleeding, most often in the nervous system.

Thrombocytopenia

The other significant risk associated with abciximab is thrombocytopenia. Data pooled from three major trials showed that thrombocytopenia (under 100×10^9/l) was significantly more frequent in those who received a bolus dose of abciximab followed by an infusion than in placebo recipients (3.7 versus 2%). Severe thrombocytopenia (under 50×10^9/l) was also more frequent with abciximab (1.1 versus 0.5%) (18). Very acute and profound thrombocytopenia (under 20×10^9/l) within 24 hours after administration has been observed in 0.3–0.7% of patients treated with abciximab for the first time (15,18–20).

During postmarketing surveillance of the first 4000 patients treated with abciximab in France, 25 cases of thrombocytopenia (0.6%) were reported, with five severe cases (0.15%) and three acute profound forms (0.08%). In all cases reported, the role of heparin must be taken into account. The thrombocytopenia associated with abciximab differs with that associated with heparin by its rapid onset (within 24 hours), its reversal after platelet transfusion, and its possible association with hemorrhage but not with thrombosis.

Positive human anti-chimeric antibodies have been detected in 6% of patients (generally in low titers) but were not associated with hypersensitivity or allergic reactions. Preliminary data indicate that abciximab can be safety readministered, although a greater incidence of thrombocytopenia after administration has been reported with a lesser efficacy of platelet transfusion (12).

Thrombocytopenia due to abciximab usually occurs within 12–96 hours, but there has been a report of acute profound thrombocytopenia after 7 days (21).

- A 65-year-old woman with type 2 diabetes mellitus and coronary artery disease received a 0.25 mg/kg bolus of abciximab at the time of intervention followed by an infusion of 10 micrograms/minute for 12 hours. Her baseline platelet counts were 286×10^9/l before use, 385×10^9/l at 2 hours, and 296×10^9/l at 18 hours. On day 7 she developed petechiae over her legs and her platelet count was 1×10^9/l. Coagulation tests were normal and there was no evidence of heparin-induced thrombocytopenia. She received 10 units of single-donor platelets and recovered slowly over the next 4 days. The platelet count was 114×10^9/l on day 12.

In another case of profound thrombocytopenia after abciximab there was a delayed onset (6 days after therapy) (22). The authors speculated that preceding treatment with methylprednisolone may have delayed the onset of thrombocytopenia.The mechanism of severe thrombocytopenia associated with abciximab is unclear. Further administration should be avoided, but other glycoprotein IIb/IIIa inhibitors (eptifibatide and tirofiban) have been successfully used in patients with history of abciximab-induced thrombocytopenia.

Thrombocytopenia after a second exposure to abciximab in nine patients showed that each had a strong immunoglobulin IgG antibody that recognized platelets sensitized with abciximab (23). Five patients also had IgM antibodies. Thrombocytopenia occurred four times as often as after the first exposure. The mechanism is not understood, but these findings suggest that it may be antibody-mediated. These antibodies were also found in 77 of 104 healthy patients, but in the patients the antibodies were specific for murine sequences in abciximab, causing the life-threatening thrombocytopenia.

Nine patients who developed profound thrombocytopenia after a second exposure to abciximab had an IgG antibody that recognized platelets sensitized with abciximab. In contrast, in 104 healthy subjects, in whom IgG antibodies reactive with abciximab-coated platelets were found in 77, the antibodies were specific for murine sequences in abciximab and were capable of causing life-threatening thrombocytopenia (23).

Ethylenediaminetetra-acetate can cause pseudothrombocytopenia by activating platelet agglutination, resulting in a spuriously low platelet count (SEDA-21, 250). Of 66 patients who received abciximab after coronary revascularization, 17 developed thrombocytopenia and 9 developed severe thrombocytopenia (24). However, of these 26 patients, 18 had pseudothrombocytopenia. True thrombocytopenia occurred at 4 hours after infusion whereas pseudothrombocytopenia occurred within the first 24 hours. The mechanism of pseudothrombocytopenia may be the effect of EDTA on the calcium-dependant glycoprotein IIb/IIIa complex, which frees the antigenic binding site on glycoprotein IIb available to IgM antibody. This increased antibody binding may cause platelet clumping and lead to false thrombocytopenia. True thrombocytopenia did not lead to hemorrhagic complications, but the patients required platelet transfusion.

Immunologic

Human antichimeric antibodies, specific to the murine epitope of Fab antibody fragments, have been observed in patients treated with abciximab. These antibodies are IgG antibodies and have so far not correlated with any adverse effects (12).

Because of its antigenic potential, there are theoretical concerns about the readministration of abciximab, and this has been studied in 1342 patients, who underwent percutaneous coronary interventions and received abciximab at least twice (25). There were no cases of anaphylaxis, and there were only five minor allergic reactions, none of which required termination of the infusion. There was clinically significant bleeding in 31 patients, including one with intracranial hemorrhage. There was thrombocytopenia (platelet count below 100×10^9/l) in 5% and profound thrombocytopenia (platelet count below 20×10^9/l) in 2%. In patients who received abciximab within 1 month of a previous treatment ($n = 115$), the risks of thrombocytopenia and profound thrombocytopenia were 17 and 12% respectively. Human chimeric antibody titers before

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readministration did not correlate with adverse outcomes or bleeding, but were associated with thrombocytopenia and profound thrombocytopenia.

An anaphylactic reaction to abciximab has been reported (26).

- An obese 46-year-old woman with prolonged angina pectoris underwent coronary angiography. She had no known drug allergies, but on administration of an iodinated contrast media she developed anaphylactic shock. After successful resuscitation angiography was completed and she was given aspirin, ticlopidine for a month, and metoprolol. Five months later she developed chest pain again, and angiography was repeated after pretreatment with prednisone and diphenhydramine and she was given abciximab. Within 5 minutes she had an anaphylactic reaction, requiring resuscitation.

This case shows that anaphylactic reactions to abciximab can occur even after pretreatment with prednisone and diphenhydramine for a known allergy to iodine.

Susceptibility Factors

Renal disease

The available data do not suggest an increased risk of bleeding with abciximab among patients with mild to moderate renal insufficiency (19), even though there is reduced platelet aggregation in renal insufficiency.

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Abecarnil

General Information

Abecarnil is a partial agonist at the benzodiazepine-GABA receptor complex, and is used in generalized anxiety disorder. Its pharmacology suggests that it may be less likely to produce sedation and tolerance, but data thus far have not shown clear differences in its adverse effects from those of classical benzodiazepines, such as alprazolam, diazepam, and lorazepam. As expected, both acute adverse effects and tolerance are dose-related.

In a multicenter, double-blind trial, abecarnil (mean daily dose 12 mg), diazepam (mean daily dose 22 mg), or placebo were given in divided doses for 6 weeks to 310 patients with generalized anxiety disorder (1). Those who had improved at 6 weeks could volunteer to continue double-blind treatment for a total of 24 weeks. Slightly more patients who took diazepam (77%) and placebo (75%) completed the 6-week study than those who took abecarnil (66%). The major adverse events during abecarnil therapy were similar to those of diazepam, namely drowsiness, dizziness, fatigue, and difficulty in coordination. Abecarnil and diazepam both produced statistically significantly more symptom relief than placebo at 1 week, but at 6 weeks only diazepam was superior to placebo. In contrast to diazepam, abecarnil did not cause withdrawal symptoms. The absence of a placebo control makes it difficult to interpret the results of another study of the use of abecarnil and diazepam in alcohol withdrawal, which appeared to show comparable efficacy and adverse effects of the two drugs (2).

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Abetimus

General Information

Abetimus is a selective immunomodulator for the treatment of systemic lupus erythematosus. It induces tolerance in B lymphocytes directed against double-stranded DNA by cross-linking surface antibodies. It also reduces serum double-stranded DNA antibodies and splenic double-stranded DNA antibody-producing cells in BXSB mice, giving improved renal function and histopathology, as well as prolonged survival (1).

In a phase-2, partly randomized, double-blind, placebo-controlled study of three different doses of abetimus in 58 patients, seven did not receive all doses because of adverse events (2). Five withdrew because of adverse events related to their lupus erythematosus: non-renal exacerbations ($n = 2$), hematuria and hypertension ($n = 1$), worsening rash ($n = 1$), and nephritis ($n = 1$). One patient withdrew because of cellulitis and another because of a localized *Herpes zoster* infection. None of the reported adverse events was considered to be definitely related to the drug.

Subsequently, La Jolla Pharmaceuticals terminated two previously established licensing agreements for abetimus (3). One of the agreements was with Leo Pharmaceutical Products of Denmark, which was licensed to market abetimus in Europe and the Middle East, and the other was with Abbott Laboratories. Abbott returned all rights to abetimus to La Jolla Pharmaceuticals in September 1999, based on the results of an analysis of a phase-2/phase-3 trial of abetimus in patients with systemic lupus erythematosus and a history of renal disease, which had been stopped in May 1999 because the primary end-point (the time to worsening of renal function) was much shorter than expected. A further analysis then showed that the number of exacerbations in responders treated with abetimus was less than half the number in the patients treated with placebo. Responders also had a significant reduction in the use of high-dose glucocorticoids and cyclophosphamide.

Another phase-3 placebo-controlled trial called PEARL (Program Enabling Antibody Reduction in Lupus) was conducted in the USA in 317 patients with lupus nephritis, who were treated with abetimus 100 mg/week. The trial was completed in December 2002 and preliminary results were reported in February 2003. However, in April 2003, La Jolla Pharmaceuticals ended the trial, in order to conserve resources for the continued development of the drug.

In September 2000, the US FDA granted orphan drug status to abetimus for the treatment of lupus nephritis; the EU did likewise in November 2001.

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Acamprosate

General Information

Acamprosate (calcium acetylhomotaurinate) has been postulated to act by restoring the alcohol-induced neurotransmission imbalance of inhibition-excitation inputs believed to underlie alcohol dependence (1,2). The molecular structure of acamprosate explains its specificity toward the basic molecular mechanisms involved in the pathophysiology of alcohol dependence. A competitive interaction has been described between spermidine and acamprosate, suggesting a specific binding site for acamprosate on *N*-methyl-D-aspartate receptors (3).

To test the role of acamprosate as an aid in preventing relapse after detoxification, 296 alcohol-dependent patients entered a prospective, multicenter, randomized, double-blind, placebo-controlled study of acamprosate 666 mg tablets tds for 180 days (4). Unlike previous studies, acamprosate was prescribed from the start of alcohol withdrawal, rather than after the detoxification process. During the treatment period, 110 patients dropped out. The two treatment groups were balanced with regard to baseline values and reasons for discontinuation. There was no difference between the groups in the severity of withdrawal symptoms, as measured by the CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol scale). Acamprosate given during withdrawal did not cause unwanted effects. The overall incidence of adverse events was similar in the two groups. The number of patients who presented at least one new adverse event (not present at baseline) during the course of the study was 99 with acamprosate and 94 with placebo. Nevertheless, there was a trend for gastrointestinal adverse events to be reported more often in the acamprosate-treated patients ($n = 61$) compared with placebo ($n = 46$). The individual adverse events that were reported more often with acamprosate were diarrhea, dyspepsia, constipation, and flatulence. Pruritus was reported by seven of those who took acamprosate and five of those who took placebo.

Organs and Systems

Gastrointestinal

Acamprosate can cause diarrhea and mild abdominal pain (5).

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Acebutolol

See also Beta-adrenoceptor antagonists

General Information

Acebutolol is a beta-adrenoceptor antagonist with membrane-stabilizing activity that is sometimes cited as being cardioselective but has considerable effects on bronchioles and peripheral blood vessels.

Organs and Systems

Respiratory

Bronchiolitis obliterans has been attributed to acebutolol (1).

Liver

Six cases of reversible hepatitis have been attributed to acebutolol (2).

Immunologic

Patients taking acebutolol relatively commonly develop antinuclear antibodies (3,4).

Drug Administration

Drug overdose

The membrane-stabilizing activity of beta-blockers can play a major role in toxicity. Of 208 deaths in subjects who had taken beta-blockers, 206 occurred with drugs that have membrane-stabilizing activity. This quinidine-like effect can be reversed by sodium bicarbonate, which is also used to counteract the cardiotoxic effects of cyclic antidepressants, which also have membrane-stabilizing activity.

- An overdose of acebutolol (6.4 mg) in a 48-year-old man caused cardiac arrest with ventricular tachycardia (5). An intravenous bolus of sodium bicarbonate 50 mmol produced sinus rhythm.

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Acecainide

See also Antidysrhythmic drugs

General Information

Acecainide (*N*-acetylprocainamide) is the main metabolite of procainamide, and it has antidysrhythmic activity (1). However, in contrast to procainamide, which has Class Ib activity, the main action of acecainide is that of Class III.

Apart from the lupus-like syndrome, the adverse effects of acecainide are as common as those of procainamide. The commonest affect the gastrointestinal tract and the central nervous system. Anorexia, nausea, vomiting, diarrhea, and abdominal pain are common, as are insomnia, dizziness, light-headedness, tingling sensations, and blurred vision. Other reported unwanted effects include skin rashes, constipation, and reduced sexual function (2–5).

Organs and Systems

Cardiovascular

Acecainide prolongs the QT interval and can therefore cause ventricular dysrhythmias (6). The risk is increased in renal insufficiency, since acecainide is mainly eliminated unchanged via the kidneys.

Immunologic

The main advantage of acecainide over procainamide is the lower incidence of the lupus-like syndrome. Many fewer patients develop antinuclear antibodies during long-term treatment with acecainide than during long-term treatment with procainamide (7).

There are also reports of remission of lupus-like syndrome without recurrence in patients in whom acecainide has been used as a replacement for procainamide (8–10). Furthermore, patients in whom procainamide has previously caused a lupus-like syndrome have been reported not to suffer from the syndrome on subsequent long-term treatment with acecainide (8). However, one patient suffered mild arthralgia while taking acecainide, having had a more severe arthropathy while taking procainamide (8).

Susceptibility Factors

Renal disease

Because acecainide is eliminated mostly unchanged by renal excretion, with a half-life of about 7 hours, its clearance is reduced in patients with renal impairment, who are at increased risk of adverse effects. This means that elderly people, who generally have a degree of renal impairment, are also at increased risk.

Monitoring Drug Therapy

The target plasma concentration range of acecainide is 15–25 μg/ml. The adverse effects of acecainide increase in frequency at concentrations above 30 μg/ml (11).

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Aceclofenac

See also Non-steroidal anti-inflammatory drugs

General Information

Despite claims that aceclofenac is a COX-2 selective inhibitor, experience shows that its adverse effects profile is similar to that of the non-selective NSAIDs.

Organs and Systems

Gastrointestinal

Symptoms of gastrointestinal intolerance in patients taking aceclofenac commonly require withdrawal, at a rate of 3–15% (SEDA-20, 91).

Liver

Acute hepatitis has been reported with aceclofenac (SEDA-21, 103).

Skin

Aceclofenac cream can cause erythema, itching, and a burning sensation in under 3% of patients (SEDA-20, 91).

Aceclofenac can cause photosensitivity.

- After starting twice-daily topical application of a cream containing aceclofenac, a woman developed acute eczema affecting the sun-exposed areas of her legs (1).

Immunologic

A hypersensitivity reaction characterized by multiple purpuric lesions and reduced renal function has been described in an elderly patient (SEDA-18, 103), and there have been reports of hypersensitivity vasculitis (SEDA-20, 91) (SEDA-21, 103).

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Acemetacin

See also Non-steroidal anti-inflammatory drugs

General Information

Acemetacin is an indometacin derivative with the same adverse effects profile (SEDA-6, 94). In an open multicenter study, 187 of 280 patients had adverse effects (57% gastrointestinal); treatment had to be stopped in 7% (1). The use of acemetacin is limited and there is no justification for claims that it has advantages over existing NSAIDs.

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Acetylcholinesterase inhibitors

General Information

Cholinesterase inhibitors increase parasympathetic nervous system (cholinergic) activity indirectly by inhibiting acetylcholinesterase, thereby preventing the breakdown of acetylcholine. They are only effective in the presence of acetylcholine. They are listed in Table 1.

The cholinesterase inhibitors are used in the treatment of Alzheimer's disease (tacrine, 7-methoxytacrine, donepezil, metrifonate, and rivastigmine), the treatment and diagnosis of myasthenia gravis (distigmine, edrophonium, neostigmine, physostigmine, prostigmine, and pyridostigmine), and the treatment of atony of the intestine or bladder. In the eye, they increase the flow rate of aqueous humor across the trabeculum, reduce resistance to its flow, and consequently lower the intraocular pressure.

Use of acetylcholinesterase inhibitors in Alzheimer's disease

Of the acetylcholinesterase inhibitors, tacrine, methoxytacrine, metrifonate, donepezil hydrochloride, and rivastigmine are used in the treatment of Alzheimer's disease. In 12–30% of patients with Alzheimer's disease, tacrine causes an increase in hepatic transaminase activity. Abdominal adverse effects are very frequent, for example nausea, anorexia, diarrhea. The peripheral cholinomimetic effects of tacrine occur in a very high proportion of patients, probably the majority. The hepatic effects seem to be such that the use of these new (and in some cases still experimental) drugs would not be justified in

Table 1 Acetylcholinesterase inhibitors

Ambenonium
Diisopropyl fluorophosphate (Diflos)
Distigmine
Donepezil
Ecothiopate
Edrophonium
Eserine
Methoxytacrine
Metrifonate
Neostigmine
Physostigmine
Prostigmine
Pyridostigmine
Rivastigmine
Tacrine and 7-methoxytacrine

other-than-serious disease states, but they are reversible if the drug is withdrawn.

General adverse effects

The acetylcholinesterase inhibitors have the effects that one would expect to result from their promoting nicotinic and muscarinic cholinergic activity, including unwanted effects such as bradycardia, miosis, colic, and hypersalivation. Adverse reactions have been stated to be relatively more common with neostigmine than with some other drugs such as pyridostigmine or ambenonium, but it is doubtful whether the benefit to harm balance indeed differs, since neostigmine also tends to be more effective in certain patients. Ambenonium is relatively likely to cause headache. When neostigmine and pyridostigmine are used as bromide salts, bromide rashes can occur.

Local adverse effects

Acetylcholinesterase inhibitors as eye drops have more intense effects in myopic and young patients, causing aggravation of myopia, blurred vision, and periorbital pain, due to congestion of the iris and ciliary body. Anterior and posterior synechiae can develop. Allergic reactions have been reported as has epithelial toxicity. The acetylcholinesterase inhibitors can cause pseudopemphigoid reactions in the eyelids and occlusion of the lacrimal puncta (SED-12, 1198) (1). The danger that a miotic agent will produce retinal detachment is directly proportional to the capacity of the drug to produce spasm of the ciliary body. Retinal detachment has been reported after the use of cholinergic agents, but they can also be coincidental.

Systemic effects

The commonest effects of the acetylcholinesterase inhibitors are headache and periorbital pain. Signs of vagal stimulation can occur, with nausea, vomiting, sweating, hypersalivation, lacrimation, hypotension, bradycardia, bronchial constriction, respiratory failure, and nightmares. These reactions essentially occur during intensive treatment for acute closed-angle glaucoma, requiring frequent instillations of pilocarpine. Elderly people and young children are at particular risk.

Organs and Systems

Cardiovascular

With any acetylcholinesterase inhibitor, bradycardia can, with excessive dosage, proceed to dysrhythmias (SEDA-13, 114) and even asystole.

- A 67-year-old man underwent left upper lobectomy for a presumed malignancy 11 years after cardiac transplantation (2). He had had no cardiac symptoms since his transplant. Suxamethonium was used as a muscle relaxant and was reversed with glycopyrrolate 0.8 mg and neostigmine 4 mg. Within a few minutes, he developed asystole, which lasted for about 45 seconds. He subsequently made a full recovery.

The authors speculated that some degree of cardiac reinnervation may have occurred; they recommended that this type of response should be anticipated in future anesthesia in such patients and that therapeutic measures, such as a beta-adrenoceptor agonist, should be available.

Another case of asystole has been reported with the very short-acting cholinesterase inhibitor edrophonium (3).

- A 49-year-old woman was given intravenous edrophonium chloride 2 mg as part of the investigation of an acute myopathy following gastrointestinal surgery. She had also received 60 mg of intravenous labetalol in the 14 hours before the edrophonium was given: presumably this was for a raised blood pressure, but that was not specified. Labetalol caused transient but severe bradycardia (heart rate about 20/minute). Immediately after the injection of edrophonium, she developed asystole, which was treated immediately with atropine and recovered in 10 seconds.

Such reactions are extremely rare, but in this case the risk was undoubtedly enhanced by previous beta-blockade.

With physostigmine, hypertension has been both demonstrated in animal experiments and observed in a series of patients after intravenous use in relatively high doses; it has also occurred during use of low doses of oral physostigmine in an elderly patient with Alzheimer's disease (SEDA-12, 125).

Nervous system

During a trial of oral physostigmine, myoclonus occurred in two patients with probable Alzheimer's disease (SEDA-12, 125).

Gastrointestinal

To reduce the incidence of residual paralysis after the administration of non-depolarizing neuromuscular blocking agents, some advocate the routine use of anticholinesterase drugs at the end of surgery. However, it has been suggested that this practice might increase the risk of postoperative nausea and vomiting. Clinical trials have produced contradictory results. A meta-analysis of the available data suggested that omitting routine neostigmine may reduce the incidence of emesis only when a large dose (2.5 mg) is used (4). With a smaller dose (1.5 mg), there was no difference. The incidence of clinically relevant residual paralysis was 1 in 30 in the control groups. There were no cases of residual curarization in the treatment groups when either edrophonium 500 μg/kg or neostigmine 1.5 mg was given in combination with atropine. Therefore, the question of whether or not routine anticholinesterase administration is beneficial for the patient is still open to debate. Other adverse effects of anticholinesterase drugs, such as bronchial hypersecretion or intestinal hypermotility, could increase morbidity, and we do not know whether all of these adverse effects are completely blocked by the concomitant use of a parasympatholytic agent (5). It should be taken into account that the incidence of residual curarization may be reduced as effectively by the use of neuromuscular transmission monitoring (6,7). Some believe that anticholinesterase drugs should be used to reverse residual neuromuscular block that produces clinical symptoms or is detected by neuromuscular transmission monitoring.

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Musculoskeletal

Any acetylcholinesterase inhibitor can produce muscular fasciculation followed by voluntary muscle paralysis, and these muscular effects can serve as a valuable sign of approaching overdosage. Two patients, one with dystrophia myotonica and the other with progressive muscular dystrophy, presented with respiratory difficulties, necessitating prolonged mechanical ventilation. As these difficulties are as good as impossible to predict, short-acting neuromuscular blockers should preferably be used, thus avoiding the need for pharmacological reversal (8).

Immunologic

Severe urticaria and anaphylaxis associated with pyridostigmine (an unspecified dose) occurred in a 54-year-old woman with myasthenia gravis (9). Urticaria started almost immediately after introduction of the drug but was partially controlled by the antihistamine cetirizine. However, pyridostigmine was stopped after 2 months and the urticaria resolved completely. Rechallenge with oral pyridostigmine led to an anaphylactic reaction that was treated with subcutaneous adrenaline. There were no sequelae.

Second-Generation Effects

Teratogenicity

Microcephaly occurred in the child of a woman taking a high dose of pyridostigmine (10).

- A 24-year-old woman had suffered from myasthenia gravis from the unusually early age of 10 years. During her first pregnancy, pyridostigmine was her sole medication. Because of deterioration in her symptoms during the pregnancy, the dosage was increased until she was taking 1500–3000 mg/day, or 4–8 times the maximum recommended dose. This still did not produce much clinical improvement but was nevertheless continued throughout the pregnancy. She needed an emergency cesarean section at 36 weeks because of fetal bradycardia. The baby was microcephalic.

The authors failed to find any other cause for this abnormality and concluded that the excessive dose of pyridostigmine had been responsible for the fetal damage.

Fetotoxicity

Acetylcholinesterase inhibitors can probably be safely used in pregnancy when needed, provided the dosage is carefully regulated. Reversible muscle weakness in a newborn infant was attributed to relative overdosage of the mother with pyridostigmine bromide (11).

Susceptibility Factors

Age

Elderly people need to be treated with caution because of their greater susceptibility to the cardiovascular effects of the acetylcholinesterase inhibitors; this is particularly relevant to their use in Alzheimer's disease.

Other features of the patient

Special caution is recommended when acetylcholinesterase inhibitors are given to patients with inflammatory, infiltrative, or degenerative disease of the cardiac conducting system, patients taking digitalis, calcium channel blockers, or beta-blockers, and patients with myocardial ischemia. Appropriate resuscitative equipment should be readily available.

Neostigmine or other anticholinesterase inhibitors are regularly used in anesthesia to reverse neuromuscular block; however, in patients with neuromuscular disorders, this reversal can present unforeseen difficulties. All anticholinesterase inhibitors must be cautiously dosed if severe adverse reactions are to be avoided. When these drugs are given orally, administration should be suspended during periods of severe constipation, in light of one reported case in which neostigmine accumulated in the gastrointestinal tract of a child during a constipative phase and was thereafter rapidly absorbed, with fatal results (SED-12, 326). Anticholinesterase drugs are contraindicated in bronchial asthma.

Drug–Drug Interactions

Anticholinergic drugs

The effect of acetylcholinesterase inhibitors can be reduced by drugs with anticholinergic effects, such as antihistamines or neuroleptic drugs (12).

Suxamethonium

Acetylcholinesterase inhibitor eye drops or exposure to organophosphate insecticides can reduce the activity of plasma cholinesterase and pseudocholinesterase, creating a potentially fatal hazard for surgical patients receiving suxamethonium. During induction of general anesthesia, the presence of anticholinesterase activity in the serum can potentiate the effect of curare-like drugs, such as suxamethonium, used as muscle relaxants, with prolonged apnea after intubation and death. Such eye drops should be stopped 6 weeks before the operation. The importance of inquiring about the use of drugs cannot be overemphasized. Patients often do not regard eye drops as medications and omit this information from their medical history. Complaints of excessive sweating, intermittent diarrhea, muscle weakness, and fatigue over a long period may be due to the usage of ecothiopate eye drops (phospholine iodide 0.25%) for glaucoma and can disappear when the eye drops are withdrawn (13).

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Acetylcysteine

General Information

Acetylcysteine (*N*-acetylcysteine) is used as a mucolytic and to treat paracetamol overdose.

Acetylcysteine splits disulfide bonds in mucoproteins and thus lowers mucus viscosity, resulting in a larger volume of sputum. It is normally administered by inhalation as a nebulized solution or aerosol, although it can also be taken orally. Acetylcysteine is also an antioxidant and may protect the lung from free radicals generated by inflammatory cells activated by influenza virus infection. Treatment for 6 months with acetylcysteine 600 mg bd significantly reduced the frequency and severity of influenza-like episodes. Adverse effects were reported by 9% of patients who complained of dysuria, epigastric pain, nausea and vomiting, constipation or diarrhea, and flushing (SEDA-22, 195).

The place of mucolytic drugs in respiratory disease has recently been reviewed (1). The authors suggested that they have been inappropriately used in the past. As mucolytic agents do not improve lung function tests in COPD, the European Respiratory Society and the American Thoracic Society guidelines discourage their use in the treatment of COPD. Future trials should evaluate clinical symptoms and quality of life as well as lung function tests. Mucolytic agents should be evaluated earlier in the natural history of COPD, when mucus hypersecretion is the major feature and before lung function has deteriorated.

Acetylcysteine is used intravenously as an antidote for severe paracetamol poisoning, in which it acts as a thiol donor.

Oral acetylcysteine has been investigated for the treatment of cancer. Acetylcysteine 600 mg/day was compared with retinol 300 000 U/day, the combination, and a placebo in a total of 2191 patients treated for 2 years. Adverse effects were reported by 14% of those who took acetylcysteine, compared with 23% of those who took retinol and 25% of those who took the combination. The most common adverse effect attributed to acetylcysteine was dyspepsia. In healthy volunteers, higher doses of acetylcysteine, 600 mg taken two or three times daily for 4 weeks, caused more adverse effects: 25 and 61% of the volunteers, respectively, reported gastrointestinal adverse effects (SEDA-20, 184).

There has been a systematic review of published randomized studies of the use of *N*-acetylcysteine in chronic bronchitis (2). A total of 39 trials were considered, of which only nine were included in the meta-analysis. In all cases, oral *N*-acetylcysteine had been used in a dosage of 200–300 mg bd for 4–32 weeks. There were gastrointestinal adverse effects (dyspepsia, diarrhea, and heartburn) in 10% of 2011 patients, and 6.5% withdrew because of their symptoms. However, the rate of gastrointestinal adverse effects was higher in the placebo group (11% with a withdrawal rate of 7.1%). There was no exacerbation of chronic bronchitis in 49% of patients treated with acetylcysteine compared with 31% of placebo-treated patients, a relative benefit of 1.56 (95% CI = 1.37, 1.77). There was also symptom improvement with treatment: 61% reported improvement in symptoms with acetylcysteine compared with 35% with placebo.

Organs and Systems

Respiratory

Aerosol therapy with acetylcysteine can cause bronchoconstriction. In 31 ambulant asthmatics using 10% acetylcysteine solution, there was a mean reduction of 55% in the FEV_1 in 19 subjects. The addition of 0.05% isoprenaline reduced the number of patients who developed bronchoconstriction from 19 to 5 (SEDA-5, 170). In two placebo-controlled studies, involving over 700 patients, there was no difference in adverse effects between oral acetylcysteine and a placebo. There was, however, no improvement in FEV_1 in these studies (3).

Immunologic

Hypersensitivity reactions have been reported when acetylcysteine is given intravenously in paracetamol overdose. A generalized erythematous rash can develop, and itching, nausea, vomiting, dizziness, and severe breathlessness with bronchospasm and tachycardia have been reported (SEDA-5, 170). Angioedema with hypotension and bronchospasm have also been described (4). Wheal responses to high concentrations of acetylcysteine (20 mg/ml) were significantly greater in those who reacted to the drug. In two patients with a positive reaction the response could be inhibited by prior therapy with an antihistamine. As hypersensitivity reactions have been reported in up to

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3% of patients receiving intravenous acetylcysteine for paracetamol overdose, physicians need to be prepared for these reactions (5). A pseudo-allergic reaction on the basis of histamine liberation, rather than an immunological etiology, is suggested as the mechanism (6,7).

Management guidelines for the treatment of anaphylactoid reactions to intravenous acetylcysteine have been developed. Patients who develop only flushing of the skin require no treatment. Urticaria should be treated with diphenhydramine and acetylcysteine infusion can be continued. If angioedema or respiratory distress occur, diphenhydramine should be given and the acetylcysteine infusion stopped; it can be restarted 1 hour after the administration of diphenhydramine if no symptoms are present (SEDA-22, 195).

Drug–Drug Interactions

Antibiotics

The 5% solution, for inhalation, almost completely inactivates penicillin and cephalosporins in vitro and reduces the activity of tetracycline.

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Acetylsalicylic acid

General Information

A century after its introduction, acetylsalicylic acid (aspirin) is by far the most commonly used analgesic, sharing its leading position with the relative newcomer paracetamol (acetaminophen), and notwithstanding the fact that other widely used compounds of their class, like ibuprofen and naproxen, have in recent years been introduced in over-the-counter versions. Both are also still being prescribed by physicians and are generally used for mild to moderate pain, fever associated with common everyday illnesses, and disorders ranging from head colds and influenza to toothache and headache. Their greatest use is by consumers who obtain them directly at the pharmacy, and in many countries outside pharmacies as well. Perhaps this wide availability and advertising via mass media lead to a lack of appreciation by the lay public that these are medicines with associated adverse effects. Both have at any rate been subject to misuse and excessive use, leading to such problems as chronic salicylate intoxication with aspirin, and severe hepatic damage after overdose with paracetamol. Both aspirin and paracetamol have featured in accidental overdosage (particularly in children) as well as intentional overdosage.

In an investigation of Canadian donors who had not admitted to drug intake, 6–7% of the blood samples taken were found to have detectable concentrations of acetylsalicylic acid and paracetamol (1). Such drugs would be potentially capable of causing untoward reactions in the recipients.

To offer some protection against misuse of analgesics, many countries have insisted on the use of packs containing total quantities less than the minimum toxic dose (albeit usually the one obtained for healthy young volunteers and thus disregarding the majority of the population), and supplied in child-resistant packaging. Most important, however, is the need to provide education for the lay public to respect such medicines in general for the good they can do, but more especially for the harm that can arise but which can be avoided. There is a definite role for the prescribing physician, as informing the patient seems to prevent adverse events (2).

The sale of paracetamol or aspirin in dosage forms in which they are combined with other active ingredients offers considerable risk to the consumer, since the product as sold may not be clearly identified as containing either of these two analgesics. Brand names sometimes obscure the actual composition of older formulations that contain one or both of these analgesics in combination with, for example, a pyrazolone derivative and/or a potentially addictive substance. For instance, in Germany, with the EC harmonization of the Drug Law of 1990, the manufacturers of drugs already marketed before 1978 had the opportunity of exchanging even the active principles without being obliged to undergo a new approval procedure or to abandon their brand name. Combination formulations are still being promoted and sold, and not exclusively in developing countries. Consequently, the patient who is so anxious to allay all his symptoms that he takes several medications concurrently may without knowing it take several doses of aspirin or paracetamol at the same time, perhaps sufficient to cause toxicity. It is essential that product labels clearly state their active ingredients by approved name together with the quantity per dosage form (3).

The antipyretic analgesics, with the non-steroidal anti-inflammatory drugs (NSAIDs), share a common mechanism of action, namely the inhibition of prostaglandin synthesis from arachidonic acid and their release. More precisely their mode of action is thought to result from inhibition of both the constitutive and the

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inducible isoenzymes (COX-1 and COX-2) of the cyclooxygenase pathway (4). However, aspirin and paracetamol are distinguishable from most of the NSAIDs by their ability to inhibit prostaglandin synthesis in the nervous system, and thus the hypothalamic center for body temperature regulation, rather than acting mainly in the periphery.

Endogenous pyrogens (and exogenous pyrogens that have their effects through the endogenous group) induce the hypothalamic vascular endothelium to produce prostaglandins, which activate the thermoregulatory neurons by increasing AMP concentrations. The capacity of the antipyretic analgesics to inhibit hypothalamic prostaglandin synthesis appears to be the basis of their antipyretic action. Neither aspirin nor paracetamol affects the synthesis or release of endogenous pyrogens and neither will lower body temperature if it is normal.

While aspirin significantly inhibits peripheral prostaglandin and thromboxane synthesis, paracetamol is less potent as a synthetase inhibitor than the NSAIDs, except in the brain, and paracetamol has only a weak anti-inflammatory action. It is simple to ascribe the analgesic activity of aspirin to its capacity to inhibit prostaglandin synthesis, with a consequent reduction in inflammatory edema and vasodilatation, since aspirin is most effective in the pain associated with inflammation or injury. However, such a peripheral effect cannot account for the analgesic activity of paracetamol, which is less well understood.

As a prostaglandin synthesis inhibitor, aspirin, like other NSAIDs, is associated with irritation of and damage to the gastrointestinal mucosa. In low doses it can also increase bleeding by inhibiting platelet aggregation; in high doses, prolongation of the prothrombin time will contribute to the bleeding tendency. Intensive treatment can also produce unwanted nervous system effects (salicylism).

Depending on the criteria used, the incidence of aspirin hypersensitivity is variously estimated as being as low as 1% or as high as 50%, the highest frequency being found in asthmatics. The condition is characterized by bronchospasm (asthma), urticaria, angioedema, and vasomotor rhinitis, each occurring alone or in combination, often leading to severe and even life-threatening reactions. There is no clear evidence of an association with tumors, apart from the possible peripheral contribution of aspirin to the development of urinary tract neoplasms in patients with analgesic nephropathy. Indeed, some authors have suggested a role for salicylates in reducing the incidence of colorectal tumors and breast tumors.

The following are absolute contraindications to the use of aspirin:

- children under 16;
- people with hypersensitivity to salicylates, NSAIDs, or tartrazine;
- people with peptic ulceration;
- people with known coagulopathies, including those induced as part of medical therapy.

The following are relative contraindications to the use of long-term analgesic doses of aspirin:

- gout, since normal analgesic doses impede the excretion of uric acid (high doses have a uricosuric effect); an additional problem in gout is that salicylates reduce the uricosuric effects of sulfinpyrazone and probenecid;
- variant angina; a daily dose of 4 g has been found to provoke attacks both at night-time and during the day (5,6), perhaps owing to direct triggering of coronary arterial spasm; blockade of the synthesis of PGI_z, which normally protects against vasoconstriction, could be involved;
- diabetes mellitus, in which aspirin can in theory interfere with the actions of insulin and glucagon sufficiently to derange control;
- some days before elective surgery (even in coronary artery bypass grafting) or delivery, especially if extradural anesthesia is used (7), although recent data seem reassuring (8); aspirin increases bleeding at dental extraction or perioperatively;
- in elderly people, who may develop gastrointestinal bleeding;
- anorectal inflammation (suppositories);
- pre-existing gastrointestinal disease, liver disease, hypoalbuminemia, hypovolemia, in the third trimester of pregnancy, perioperatively, or in patients with threatening abortion.

Assessing the benefit-to-harm balance of low-dose aspirin in preventing strokes and heart attacks

Although there is clear evidence of benefit of acetylsalicylic acid (aspirin) in secondary prevention of strokes and heart attacks, the question of whether aspirin should also be prescribed for primary prevention in asymptomatic people is still debatable. Trials in primary prevention have given contrasting results (9,10), and aspirin can cause major harms (for example severe gastrointestinal bleeding and hemorrhagic stroke).

Furthermore, despite evidence of the efficacy of aspirin in secondary prevention, its use in patients at high risk of strokes and heart attacks remains suboptimal (11). A possible explanation for this underuse may be concern about the relative benefit in relation to the potential risk for serious hemorrhagic events. Accurate evaluation of the benefits and harms of aspirin is therefore warranted.

Two meta-analyses have provided some information. The first examined the benefit and harms of aspirin in subjects without known cardiovascular or cerebrovascular disease (primary prevention) (12). The authors selected articles published between 1966 and 2000—five large controlled studies of primary prevention that lasted at least 1 year and nine studies of the effects of aspirin on gastrointestinal bleeding and hemorrhagic stroke. The five randomized, placebo-controlled trials included more than 50 000 patients and the meta-analysis showed that aspirin significantly reduced the risk of the combined outcome (confirmed non-fatal myocardial infarction or death from coronary heart disease) (OR = 0.72; 95% CI = 0.60, 0.87). However, aspirin increased the risk of major gastrointestinal bleeding (OR = 1.7; CI = 1.4, 2.1) significantly, while the small

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increase found for hemorrhagic stroke (OR = 1.4; CI = 0.9, 2.0) was not statistically significant. All-cause mortality was not significantly affected (OR = 0.93; CI = 0.84; 1.02). Most important was the finding that the net effect of aspirin improved with increasing risk of coronary heart disease. The meta-analysis showed that for 1000 patients with a 5% risk of coronary heart disease events over 5 years, aspirin would prevent 6–20 myocardial infarctions but would cause also 0–2 hemorrhagic strokes and 2–4 major gastrointestinal bleeds. For patients at lower risk (1% over 5 years), aspirin would prevent 1–4 myocardial infarctions but would still cause 0–2 hemorrhagic strokes and 2-4 major gastrointestinal bleeds.

Therefore when deciding to use aspirin in primary prophylaxis, one should take account of the relative utility of the different outcomes that are prevented or caused by aspirin.

The other meta-analysis (13) compared the benefits of aspirin in secondary prevention with the risk of gastrointestinal bleeding. An earlier analysis of this problem included patients at various levels of risk and doses of aspirin that would currently be regarded as too high (14), and may therefore have either underrepresented the benefit or exaggerated the risk. In another analysis there was no difference in the risk of gastrointestinal bleeding across the whole range of doses used (15).

The meta-analysis reviewed all randomized, placebo-controlled, secondary prevention trials of at least 3-months duration published from 1970 to 2000. The dosage of aspirin was 50–325 mg/day. Six studies contributed 6300 patients to the analysis (3127 on aspirin and 3173 on placebo). Aspirin reduced all-cause mortality by 18%, the number of strokes by 20%, myocardial infarctions by 30%, and other vascular events by 30%. On the other hand, patients who took aspirin were 2.5 times more likely than those who took placebo to have gastrointestinal tract bleeds. The number of patients needed to be treated (NNT) to prevent one death from any cause was 67 and the NNT to cause one gastrointestinal bleeding event was 100. In other words 1.5 lives can be saved for every gastrointestinal bleed attributed to aspirin. Although the risk of gastrointestinal bleeding was increased by aspirin, the hemorrhagic events were manageable and led to no deaths. On the basis of these data we can conclude that the benefits–harm balance for low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events is highly favorable. The same conclusions have been drawn from the systematic overview published by the Antithrombotic Trialists Collaboration Group, which analysed data from 287 studies involving 135 000 patients (16).

As far as primary prevention of cardiovascular events is concerned, it appears that aspirin can reduce heart attacks and strokes but increases gastrointestinal and intracranial bleeding. The decision to use aspirin in primary prevention should therefore take into account the fact that the net effect of aspirin improves with increasing risk of coronary heart disease as well as the values that patients attach to the main favorable and unfavorable outcomes.

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Organs and Systems

Cardiovascular

Apart from rare reports of variant angina pectoris and vasculitis theoretically related to thromboxane, aspirin is not associated with adverse effects on the cardiovascular system (17,18), except an increase in circulating plasma volume after large doses.

Respiratory

The effect of aspirin on bronchial musculature is discussed in the section on Immunologic in this monograph.

Salicylates can cause pulmonary edema, particularly in the elderly, especially if they are or have been heavy smokers (19).

Chronic salicylate toxicity can cause pulmonary injury, leading to respiratory distress. Lung biopsy may show diffuse alveolar damage and fibrosis (20).

Nervous system

Salicylism is a reaction to very high circulating concentrations of salicylate, characterized by tinnitus, dizziness, confusion, and headache.

Encephalopathy secondary to hyperammonemia has been reported in those rare cases of liver failure that are associated with high doses of aspirin, and this also forms a major feature of Reye's syndrome (see the section on Liver in this monograph).

One case-control study showed no increased risk of intracerebral hemorrhage in patients using aspirin or other NSAIDs in low dosages as prophylaxis against thrombosis (21). However, intracerebral hemorrhage has been reported with aspirin, even in low doses, and in the SALT study (22) and the Physicians Health Study of 1989 (23) hemorrhagic stroke and associated deaths occurred with aspirin.

Sensory systems

Eyes

Well-documented acute myopia and increased ocular pressure attributed to aspirin has been described (24).

Ears

With the high concentrations achieved in attempted suicide, tinnitus and hearing loss, leading to deafness, develop within about 5 hours, usually with regression within 48 hours, but permanent damage can occur. Disturbed balance, often with vertigo, can develop, as well as nausea, usually with maintenance of consciousness, even without treatment. It has been postulated that in this state depolarization of the cochlear hair cells occurs, similar to the changes induced by pressure. Tinnitus is also a symptom of salicylism.

Metabolism

Aspirin lowers plasma glucose concentrations in C-peptide-positive diabetic subjects and in normoglycemic persons (25). This is of no clinical significance.

Fluid balance

NSAIDs can cause fluid retention, but this has rarely been reported with aspirin.

- Severe fluid retention, possibly due to impaired renal tubular secretion, has been reported in a 29-year-old woman taking aspirin (1.5 g/day for several days) for persistent headache (26). During rechallenge with aspirin (0.5 g tds for 3 days) a dynamic renal scintigram showed a substantial fall in tubular filtration. Withdrawal was followed by complete uneventful recovery.

Pulmonary edema is a feature of salicylate intoxication, but this patient was taking a therapeutic dosage.

Hematologic

Thrombocytopenia, agranulocytosis, neutropenia, aplastic anemia, and even pancytopenia have been reported in association with aspirin. The prospect for recovery from the latter is poor, mortality approaching 50%.

Hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase deficiency or erythrocyte glutathione peroxidase deficiency (SED-9, 128) (27–29). Whether these reports have anything more than anecdotal value (SEDA-17, 97) is not known.

Simple iron deficiency caused by occult blood loss occurs with a frequency of 1%, and upper gastrointestinal bleeding resulting from regular aspirin ingestion is the reason for hospitalization in about 15 patients per 100 000 aspirin users per year. Aspirin causes bleeding of sufficient severity to lead to iron deficiency anemia in 10–15% of patients taking it continuously for chronic arthritis. Some individuals are particularly at risk because of pregnancy, age, inadequate diet, menorrhagia, gastrectomy, or malabsorption syndromes.

Macrocytic anemia associated with folate deficiency has been described in patients with rheumatoid arthritis (30) and also in patients who abuse analgesic mixtures containing aspirin (30).

Effects on coagulation

Aspirin in high doses for several days can reduce prothrombin concentrations and prolong the prothrombin time. This will contribute to bleeding problems initiated by other factors, including aspirin's local irritant effects on epithelial cells. It is therefore very risky to use aspirin in patients with bleeding disorders. The effect will contribute to increased blood loss at parturition, spontaneous abortion, or menorrhagia, and may be linked to persistent ocular hemorrhage, particularly in older people, with or without associated surgical intervention (31,32).

By virtue of its effects on both cyclo-oxygenase isoenzymes, aspirin inhibits platelet thromboxane A_2 formation. This effect in the platelet is irreversible and will persist for the lifetime of the platelet (that is up to 10 days), since the platelet cannot synthesize new cyclo-oxygenase. It is of clinical significance that the dose of aspirin necessary to inhibit platelet thromboxane A_2 (around 40 mg/day) is much lower than that needed to inactivate the subendothelial prostacyclin (PGI_2). Hence, platelet aggregation is inhibited, with some associated dilatation of coronary and cerebral arterioles, at doses that do not interfere with prostacyclin inhibition. It is important, in considering the dosage of aspirin for prophylaxis (see below), to appreciate that prostacyclin is a general inhibitor of platelet aggregation, while aspirin, as a cyclo-oxygenase inhibitor, affects aggregation from a limited number of stimuli, for example ADP, adrenaline, thromboxane A_2. It is also worth recalling that the vascular endothelium can synthesize new cyclo-oxygenase, so that any effect on prostacyclin synthesis is of limited duration only (SEDA-12, 74) (33).

Several long-term studies have been carried out since the 1980s to determine the prophylactic usefulness of these effects on clotting. It is now clear that aspirin in dosages of around 300 mg/day can be used successfully for secondary prophylaxis in patients with coronary artery disease, in order to reduce the incidence of severe myocardial infarction, and in patients with cerebrovascular disease to reduce the incidence of transient ischemic attacks and strokes. There is some suggestion that higher doses of aspirin may be required in women. A major drawback has been the high incidence of gastrointestinal adverse effects and particularly bleeding in aspirin-treated groups (5,6,10,34). In view of the age group involved, bleeding can have serious implications. In an attempt to avoid this high proportion of ill-effects and yet retain the benefits of prophylactic antithrombotic treatment, a few trials have been conducted using aspirin in a dose of 162 mg (ISIS-2) (35) and 75 mg (RISC) (36) in symptomatic coronary heart disease, with good evidence of efficacy. Two studies have been reported in patients with cerebrovascular events, namely the Dutch TIA trial with aspirin 30 versus 283 mg (21) and the SALT study with aspirin 75 mg (22). The former did not show any difference in efficacy between the 30 and 283 mg dose groups, but there was no placebo control. The latter study showed a significant reduction in thrombotic stroke. However, intracerebral hemorrhage has been reported with aspirin, even in low doses, and in this as well as in the Physicians Health Study of 1989 (23), hemorrhagic stroke and associated deaths occurred with aspirin. On the other hand, the incidence of serious gastrointestinal events was much lower than previously described.

As nearly all of the risks seem to be dose-related (SEDA-21, 96), there is a good prospect that an even lower daily dose of aspirin may offer advantages in antithrombotic prophylaxis without an increased risk of bleeding, but the results of further such studies are still awaited (9).

Relatively few patients developed a prolonged bleeding time while taking aspirin or other NSAIDs and only few had significant intraoperative blood loss. There is variation in the response of patients for unknown reasons and so the recommendation that NSAIDs should be withdrawn before elective surgery awaits confirmation (SEDA-19, 96).

Gastrointestinal

Gastric ulceration and hemorrhage

DoTS classification

Dose-relation: collateral effect
Time-course: intermediate
Susceptibility factors: age (over 65); sex (women); disease (peptic ulceration)

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The gastrointestinal adverse effects of aspirin and the other NSAIDs are the most common. While some argue against a causative relation between aspirin ingestion and chronic gastric ulceration, the current consensus favors such a relation, while admitting that other factors, such as *Helicobacter pylori*, are likely to play a part. Patients aged over 65 years and women are more at risk, as are those who take aspirin over prolonged periods in a daily dose of about 2 g or more.

However, there is no ambiguity about the association of aspirin with gastritis, gastric erosions, or extensions of existing peptic ulcers, all of which are demonstrable by endoscopy. Even after one or two doses, superficial erosions have been described in over 50% of healthy subjects. This association is now almost universally accepted as the standard basis for comparative testing of NSAIDs and other drugs (21,37–39). Whether it is of benefit to use other drugs concomitantly to prevent the effect of gastric acid on the mucosa, and thus reduce the risk of gastric ulceration, is discussed further in this monograph.

Dyspepsia, nausea, and vomiting occur in 2–6% of patients after aspirin ingestion. Patients with rheumatoid arthritis seem to be more sensitive, and the frequency of aspirin-induced dyspepsia in this group is 10–30% (SEDA-9, 129). However, these symptoms are generally poor predictors of the incidence of mucosal damage (SEDA-18, 90).

The bleeding that occurs is usually triggered by erosions and aggravated by the antithrombotic action of aspirin. While it is reported to occur in up to 100% of regular aspirin takers, bleeding tends to be asymptomatic in young adults, unless it is associated with peptic ulceration, but it is readily detectable by endoscopy and the presence of occult blood in the feces. Hematemesis and melena are less often seen, the odds ratio being 1.5–2.0 in an overview of 21 low-dose aspirin prevention studies (40). A degree of resultant iron deficiency anemia is common. Such events are more commonly seen in older people in whom there is a significant proportion of serious bleeding and even deaths. Major gastrointestinal bleeding has an incidence of 15 per 100 000 so-called heavy aspirin users. However, the interpretation of "heavy" and of quantities of aspirin actually taken is to a large extent subjective and very dependent on the questionable accuracy of patient reporting. The risk appears to be greater in women, smokers, and patients concurrently taking other NSAIDs, and is possibly affected by other factors not yet established (41). Gastrointestinal perforation can occur without prodromes. Aspirin increases the risk of major upper gastrointestinal bleeding and perforation two- to three-fold in a dose-related manner, but deaths are rare.

Incidence

Of the estimated annual 65 000 upper gastrointestinal emergency admissions in the UK, nearly 20% (including deaths in 3.4%) are attributable to the use of prostaglandin synthesis inhibitors (42). As might be expected with an inhibitor of prostaglandin synthesis, the cytoprotective effects of prostaglandin E and prostacyclin (PGI_2) are reduced by aspirin, as is the inhibitory action on gastric acid secretion. This effect may be both direct, as is the case with aspirin released in the stomach (or the lower rectum in the case of aspirin suppositories), and indirect following absorption and distribution via the systemic circulation; attempts to reduce the problems by coating and buffering can therefore have only limited success. The indirect type of effect is shown by the fact that these adverse gastric effects can also be exerted by parenteral lysine acetylsalicylate (SEDA-10, 72). The local effects depend in part on the tablet particle size, solubility, and rate of gastric absorption, while the most important variable appears to be gastric pH. On the other hand, within-day changes in the pharmacokinetics of the analgesic compounds may be involved in the prevalence of gastrointestinal adverse effects.

The estimates of gastrointestinal complication rates from aspirin are generally derived from clinical trials (SEDA-21, 100). However, the applicability of the results of such trials to the general population may be debatable, as protocols for these studies often are designed precisely to avoid enrollment of patients who are at risk of complications. Indeed differences in benefit-to-harm balance have been found in trials using the same dose of aspirin (43,44). For this reason, a population-based historical cohort study on frequency of major complications of aspirin used for secondary stroke prevention may be of interest (45). The study identified 588 patients who had a first ischemic stroke, transient ischemic attack, or amaurosis fugax during the study period. Of these, 339 patients had taken aspirin for an average of 1.7 years. The mean age of patients who had taken aspirin was 74 years. Complications occurred within 30 days of initiation of treatment in one patient, between 30 days and 6 months in 10 patients, between 6 months and 1 year in seven patients, and between 1 year and 2 years in two patients. Estimated standardized morbidity ratio of gastrointestinal hemorrhage (determined on the basis of 10 observed events and 0.661 expected events, during 576 person-years of observation) was 15 (95% CI = 7, 28). The estimated standardized morbidity ratio of intracerebral hemorrhage (determined on the basis of only one event and 0.59 expected events) was 1.7 (CI = 0.04, 9.4). One patient had a fatal gastrointestinal hemorrhage. Unfortunately these complication rates must be considered estimates, because aspirin therapy was not consistently recorded. However, the rates of complications were similar to those observed in some randomized clinical trials. On the basis of these data and of those of a meta-analysis of 16 trials involving more than 95 000 patients (45), the overall benefits of aspirin, measured in terms of preventing myocardial infarction and ischemic stroke, clearly outweigh the risks.

Dose-relatedness

The question of whether the risk of gastrointestinal hemorrhage with long-term aspirin is related to dose within the usual therapeutic dosage range (SEDA-12, 100) (15,46) merits attention. In a meta-analysis of the incidence of gastrointestinal hemorrhage associated with

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long-term aspirin and the effect of dose in 24 randomized, controlled clinical trials including almost 66 000 patients exposed for an average duration of 28 months to a wide range of different doses of aspirin (50–1500 mg/day), gastrointestinal hemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo (OR = 1.68; 95% CI = 1.51, 1.88). In patients taking low doses of aspirin (50–162.5 mg/day; $n = 49\ 927$), gastrointestinal hemorrhage occurred in 2.3% compared with 1.45% taking placebo (OR = 1.56; 95% CI = 1.40, 1.81). The pooled OR for gastrointestinal hemorrhage with low-dose aspirin was 1.59 (95% CI = 1.4, 1.81). A meta-regression to test for a linear relation between the daily dose of aspirin and the risk of gastrointestinal hemorrhage gave a pooled OR of 1.015 (95% CI = 0.998, 1.047) per 100 mg dose reduction. The reduction in the incidence of gastrointestinal hemorrhage was estimated to be 1.5% per 100 mg dose reduction, but this was not significant.

These data are in apparent contrast with others previously reported (SEDA-21, 100) (14), which showed that gastrointestinal hemorrhage was related to dose in the usual dosage range. Many reasons may explain these contrasting results, the most important being differences in the definition of the hemorrhagic events, in study design, in the population studied, and in the presence of accessory risk factors (47–49).

The recent trends toward the use of lower doses of aspirin have been driven by the belief that these offer a better safety profile while retaining equivalent therapeutic efficacy. Despite the large number of patients enrolled in randomized clinical trials and included in meta-analyses, there is no firm evidence that dose reduction significantly lowers the risk of gastrointestinal bleeding. Patients and doctors therefore need to consider the trade-off between the benefits and harms of long-term treatment with aspirin. Meanwhile, it seems wise to use the lowest dose of proven efficacy.

A systematic review of 17 epidemiological studies conducted between 1990 and 2001 has provided further data on this topic (50). The effect of aspirin dosage was investigated in five studies. There was a greater risk of gastrointestinal complications with aspirin in dosages over 300 mg/day than in dosages of 300 mg/day or less. However, users of low-dose aspirin still had a two-fold increased risk of such complications compared with non-users, with no clear evidence of a dose-response relation at dosages under 300 mg/day, confirming previous findings (15). The study also addressed the question of whether the aspirin formulation affects gastrotoxicity. The pooled relative risks of gastrointestinal complications in four studies were 2.4 (95%; CI = 1.9, 2.9) for enteric-coated aspirin, 5.3 (3.0, 9.2) for buffered formulations, and 2.6 (2.3, 2.9) for plain aspirin, compared with non-use. These data confirm those from previous studies (SEDA-21, 100) (15), which negate any protective effect of the most frequently used aspirin formulations. Furthermore, there were higher relative risks, compared with non-use, for gastrointestinal complications in patients who used aspirin regularly (RR = 3.2; CI = 2.6, 5.9) than in patients who used it occasionally (2.1; 1.7, 2.6), and during the first month of use (4.4; 3.2, 6.1) compared with subsequent months (2.6; 2.1, 3.1).

Comparative studies

A comparative study of gastrointestinal blood loss after aspirin 972 mg qds for 4 days versus different doses of piroxicam (20 mg od, 5 mg qds, and 10 mg qds) showed that piroxicam did not increase fecal blood loss, whereas aspirin did. Gastroscopic evidence of irritation was also greater with aspirin (51).

In a randomized trial comparing ticlopidine (500 mg/day) with aspirin (1300 mg/day) for the prevention of stroke in high-risk patients, the incidence of bleeding was similar in both groups, although more patients treated with aspirin developed peptic ulceration or gastrointestinal hemorrhage (52).

Risk factors

A study of the risk factors for gastrointestinal perforation, a much less frequent event than bleeding, has confirmed that aspirin and other NSAIDs increase the risk of both upper and lower gastrointestinal perforation (OR 6.7, CI 3.1–14.5 for NSAIDs) (53). Gastrointestinal perforation has been associated with other factors, such as coffee consumption, a history of peptic ulcer, and smoking. The combination of NSAIDs, smoking, and alcohol increased the risk of gastrointestinal perforation (OR 10.7, CI 3.8–30) (SEDA-21, 97).

Associated effects

Aspirin can also play a role in esophageal bleeding, ulceration, or benign stricture, and it should be considered as a possible cause in patients, particularly the elderly, who present with any of these features. There have also been reports of rectal stricture in the elderly, associated with the use of aspirin suppositories. Effects on both these strictures emphasize the significance of a direct local action of aspirin as well as a systemic action and underlines the relevance of the involvement of oxygen-derived free radicals in the pathogenesis of mucosal lesions in the gastrointestinal tract (54–56).

A gastrocolic fistula developed in a 47-year-old woman taking aspirin and prednisone for rheumatoid arthritis (57). Other similar case reports have been published (58,59).

Long-term effects

The effects on the stomach of continued exposure to aspirin remain controversial. While in short-term use, gastric mucosal erosions may often be recurrent but transient and comparatively trivial lesions, with longer administration there seems to be an increased risk of progression to ulceration.

Prophylaxis

Intravenous administration, or the use of enteric-coated formulations or modified-release products all appear to reduce the risk both of bleeding and more particularly of erosions/ulceration. However, because of the indirect effect noted above, such formulations do not eliminate the risk, although they may reduce the incidence of

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gastric or duodenal ulcer, as may buffered aspirin (60,61).

Considerable attention in recent years has been directed toward the efficacy of using synthetic forms of PGE_2, histamine H_2 receptor antagonists, proton pump inhibitors, or antacids, either to heal peptic ulcers associated with use of prostaglandin inhibitors or more significantly to act prophylactically to protect against ulceration or bleeding associated with aspirin or the NSAIDs. With the exception of PGE_2, there is no convincing evidence to justify their prophylactic use, as they do not reduce the risk of significant gastrointestinal events. In contrast, their soothing effect on gastrointestinal symptoms may ultimately result in more severe complications (62). Since all these agents carry their own potential risks, it is more than questionable whether administration to a patient with normal gastrointestinal mucosa is justified. Generally, use of prostaglandin inhibitors should be limited to the shortest possible duration, thereby minimizing, but not eliminating, the risk of gastrointestinal damage. Only high-risk patients should be eligible for prophylactic drug therapy. Well-known risk factors for the development of mucosal lesions of the gastrointestinal tract are age (over 75 years), a history of peptic ulcer, or gastrointestinal bleeding, and concomitant cardiac disease.

Liver

Aspirin can cause dose-related focal hepatic necrosis that is usually asymptomatic or anicteric. Much of the evidence for hepatotoxicity of aspirin and the salicylates has been shown in children (63,64), usually in patients with connective tissue disorders, taking relatively high long-term dosages for Still's disease, rheumatoid arthritis, or occasionally systemic lupus erythematosus. Rises in serum transaminases seem to be the most common feature (in up to 50% of patients) and are usually reversible on withdrawal, but they occasionally lead to fatal hepatic necrosis. Severe and even fatal metabolic encephalopathy can also occur, as in Reye's syndrome (see the section on Reye's syndrome in this monograph). One can easily overload the young patient's individual metabolic capacity. The co-existence of hypoalbuminemia may be a particular risk factor; in patients with hypoalbuminemia of 35 g/l or less, close monitoring of the aspartate transaminase is advisable, especially if the concentration of total serum salicylate is 1.1 mmol/l or higher (65). Plasma salicylate concentrations in serious cases have usually been in excess of 1.4 mmol/l and liver function tests return rapidly to normal when the drug is withdrawn. Finally, a very small number of cases of chronic active hepatitis have been attributed to aspirin (66).

Reye's syndrome

First defined as a distinct syndrome in 1963, Reye's syndrome came to be regarded some years later as an adverse effect of aspirin. In fact, the position is more complex, and the syndrome still cannot be assigned a specific cause. There is general agreement that the disorder presents a few days after the prodrome of a viral illness. Well over a dozen different viruses have so far been implicated, including influenza A and B, adenovirus, *Varicella*, and reovirus. Various other factors have also been incriminated, including aflatoxins, certain pesticides, and such antioxidants as butylated hydroxytoluene. Only in the case of aspirin have some epidemiological studies been conducted, and these appeared to show a close correlation with cases of Reye's syndrome. It was these studies that led to regulatory action against the promotion of salicylate use in children. However, doubt has been thrown on the clarity of the link, and it now seems increasingly likely that while there is some association with aspirin, the etiology is in fact multifactorial, including some genetic predisposition. Studies in Japan did not support the US findings, while studies in Thailand and Canada invoked other factors.

Two characteristic phenomena are present in Reye's syndrome.

1. Damage to mitochondrial structures, with pleomorphism, disorganization of matrix, proliferation of smooth endoplasmic reticulum, and an increase in peroxisomes; mitochondrial enzyme activity is severely reduced, but cytoplasmic enzymes are unaffected. The changes first appear in single cells, but may spread to all hepatocytes. Recovery may be complete by 5–7 days. While these changes are most evident in liver cells, similar effects have been seen in cerebral neurons and skeletal muscle. There appears to be a block in beta-oxidation of fatty acids (inhibition of oxidation of NAB-linked substrates). In vitro aspirin selectively inhibits mitochondrial oxidation of medium- and long-chain fatty acids.
2. An acute catabolic state with hypoglycemia, hyperammonemia, raised activities of serum aspartate transaminase and creatine phosphokinase, and increased urinary nitrogen and serum long chain dicarboxylic acid.

Despite our lack of understanding of the syndrome, the decision taken in many countries to advise against the use of salicylates in children under 12 made an impact, in terms of a falling incidence of Reye's syndrome (SEDA-16, 96; SEDA-17, 97).

Over the last 25 years, in the USA, the incidence of Reye's syndrome has fallen significantly—from the time that the advice was introduced up to 1999 there were 25 reported cases, but 15 were in adolescents aged 12–17 years, and 8% of cases occurred in patients aged 15 years or over (67). In the UK, in view of these findings, the Commission on Safety of Medicines (CSM) amended its original statement and advised that aspirin should be avoided in febrile illnesses or viral infections in patients aged under 16 years. However, the appropriateness of this decision has been challenged (68). This is because the incidence of Reye's syndrome is already low and is falling; furthermore, restricting the use of aspirin leaves paracetamol and ibuprofen as the only available therapeutic alternatives, and their safety is not absolutely guaranteed and might be even worse than that of aspirin.

Urinary tract

Aspirin is associated with a small but significant risk of hospitalization for acute renal insufficiency (SEDA-19, 95).

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When aspirin is used by patients on sodium restriction or with congestive heart failure, there tends to be a reduction in the glomerular filtration rate, with preservation of normal renal plasma flow. Some renal tubular epithelial shedding can also occur.

Severe systemic disease involving the heart, liver, or kidneys seems to predispose the patient to the effects of aspirin and other NSAIDs on renal function (69).

Chronic renal disease

Renal papillary necrosis has been reported after long-term intake or abuse of aspirin and other NSAIDs (SEDA-11, 85) (SEDA-12, 79). The relation between long-term heavy exposure to analgesics and the risk of chronic renal disease has been the object of intensive toxicological and epidemiological research for many years (SEDA-24, 120) (70). Most of the earlier reports suggested that phenacetin-containing analgesics probably cause renal papillary necrosis and interstitial nephritis. In contrast, there was no convincing epidemiological evidence that non-phenacetin-containing analgesics (including paracetamol, aspirin, mixtures of the two, and NSAIDs) cause chronic renal disease. Moreover, findings from epidemiological studies should be interpreted with caution, because of a number of inherent limitations and potential biases in study design (71). Two methodologically sound studies have provided information on this topic.

The first was the largest cohort study conducted thus far to assess the risk of renal dysfunction associated with analgesic use (72). Details of analgesic use were obtained from 11 032 men without previous renal dysfunction participating in the Physicians' Health Study (PHS), which lasted 14 years. The main outcome measure was a raised creatinine concentration defined as 1.5 mg/dl (133 μmol/l) or higher and a reduced creatinine clearance of 55 ml/minute or less. In all, 460 men (4.2%) had a raised creatinine concentration and 1258 (11%) had a reduced creatinine clearance. Mean creatinine concentrations and creatinine clearances were similar among men who did not use analgesics and those who did. This was true for all categories of analgesics (paracetamol and paracetamol-containing mixtures, aspirin and aspirin-containing mixtures, and other NSAIDs) and for higher-risk groups, such as those aged 60 years or over or those with hypertension or diabetes.

These data are convincing, as the large size of the PHS cohort should make it possible to examine and detect even modest associations between analgesic use and a risk of renal disease. Furthermore, this study included more individuals who reported extensive use of analgesics than any prior case-control study. However, the study had some limitations, the most important being the fact that the cohort was composed of relatively healthy men, most of whom were white. These results cannot therefore be generalized to the entire population. However, the study clearly showed that there is not a strong association between chronic analgesic use and chronic renal dysfunction among a large cohort of men without a history of renal impairment.

The second study was a Swedish nationwide, population-based, case-control study of early-stage chronic renal insufficiency in men whose serum creatinine concentration exceeded 3.4 mg/dl (300 μmol/l) or women whose serum creatinine exceeded 2.8 mg/dl (250 μmol/l) (73). In all, 918 patients with newly diagnosed renal insufficiency and 980 controls were interviewed and completed questionnaires about their lifetime consumption of analgesics. Compared with controls, more patients with chronic renal insufficiency were regular users of aspirin (37 versus 19%) or paracetamol (25 versus 12%). Among subjects who did not use aspirin regularly, the regular use of paracetamol was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of paracetamol. The risk increased with increasing cumulative lifetime dose. Patients who took 500 g or more over a year (1.4 g/day) during periods of regular use had an increased odds ratio for chronic renal insufficiency (OR = 5.3; 95% CI = 1.8, 15). Among subjects who did not use paracetamol regularly, the regular use of aspirin was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of aspirin. The risk increased significantly with an increasing cumulative lifetime dose of aspirin. Among the patients with an average intake of 500 g or more of aspirin per year during periods of regular use, the risk of chronic renal insufficiency was increased about three-fold (OR = 3.3; CI = 1.4, 8.0). Among patients who used paracetamol in addition to aspirin, the risk of chronic renal insufficiency was increased about two-fold when regular aspirin users served as the reference group (OR = 2.2; CI = 1.4, 3.5) and non-significantly when regular paracetamol users were used as controls (OR = 1.6; CI = 0.9, 2.7). There was no relation between the use of other analgesics (propoxyphene, NSAIDs, codeine, and pyrazolones) and the risk of chronic renal insufficiency. Thus, the regular use of paracetamol, or aspirin, or both was associated dose-dependently with an increased risk of chronic renal insufficiency. The OR among regular users exceeded 1.0 for all types of chronic renal insufficiency, albeit not always significantly. These results are consistent with exacerbating effects of paracetamol and aspirin on chronic renal insufficiency, regardless of accompanying disease.

How can we explain the contrasting results of these two studies? A possible explanation lies in the different populations studied. In the PHS study, relatively healthy individuals were enrolled while in the Swedish study all the patients had pre-existing severe renal or systemic disease, suggesting that such disease has an important role in causing analgesic-associated chronic renal insufficiency. People without pre-existing disease who use analgesics may have only a small risk of end-stage renal disease.

Skin

Hypersensitivity reactions, such as urticaria and angioedema, are relatively common in subjects with aspirin hypersensitivity. Purpura, hemorrhagic vasculitis, erythema multiforme, Stevens–Johnson syndrome, and Lyell's syndrome have also been reported, but much less often. Fixed drug eruptions, probably hypersensitive in origin, are periodically described. In some patients they do not recur on rechallenge, that is the sensitivity disappears (74).

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Musculoskeletal

There is evidence that salicylates together with at least some NSAIDs suppress proteoglycan biosynthesis independently of effects on prostaglandin synthesis (75). Thus, prolonged use of these agents can accentuate deterioration of articular cartilage in weight-bearing arthritic joints. If this is proved, the problem will be of greatest relevance to elderly people with osteoarthritis, a condition in which this use of prostaglandin inhibitors is questionable.

Immunologic

Aspirin hypersensitivity

Of adult asthmatics 2–20% have aspirin hypersensitivity (9). The mechanism is related to a deficiency in bronchodilator prostaglandins; prostaglandin inhibition may make arachidonic acid produce more leukotrienes with bronchoconstrictor activity. Oral challenge in asthmatic patients is an effective but potentially dangerous method for establishing the presence of aspirin hypersensitivity (63).

The term "aspirin allergy" is better avoided, in the absence of identification of a definite antigen–antibody reaction. This topic has been reviewed (SEDA-17, 94) (SEDA-18, 90).

Epidemiology

Aspirin hypersensitivity is relatively common in adults (about 20%). Estimates of the prevalence of aspirin-induced asthma vary from 3.3 to 44% in different reports (SEDA-5, 169), although it is often only demonstrable by challenge tests with spirometry, and only 4% have problems in practice. Patients with existing asthma and nasal polyps or chronic urticaria have a greater frequency of hypersensitivity (76), and women appear to be more susceptible than men, perhaps particularly during the childbearing period of life (77). Acute intolerance to aspirin can develop even in patients who have taken the drug for some years without problems.

There is considerable cross-reactivity with other NSAIDs and the now widely banned food colorant tartrazine (78). Cross-sensitization between aspirin and tartrazine is common; for example, in one series 24% of aspirin-sensitive patients also reacted to tartrazine (SEDA-9, 76).

Mechanism

The current theory of the mechanism relates to the inhibition of cyclo-oxygenases (79) and a greater degree of interference with PGE_2 synthesis, allowing the bronchoconstrictor PGF_2 to predominate in susceptible individuals.

PGE_2 inhibition in macrophages may also unleash bronchial cytotoxic lymphocytes, generated by chronic viral infection, leading to destruction of virus-infected cells in the respiratory tract (80). When urticaria occurs, it may result from increased release of leukotrienes LTC_4, D_4, and E_4, which also induces bronchoconstriction, with a shunt of arachidonic acid toward lipoxygenation in aspirin-sensitive asthmatics (SEDA-18, 93). Aspirin-induced asthma patients show hyper-reactivity to inhaled metacholine and sulpyrine.

Features

The features of aspirin hypersensitivity include bronchospasm, acute and usually generalized urticaria, angioedema, severe rhinitis, and shock. These reactions can occur alone or in various combinations, developing within minutes or a few hours of aspirin ingestion, and lasting until elimination is complete. They can be life-threatening. The bronchospastic type of reaction predominates in adults, only the urticarial type being found in children. The frequency of recurrent urticaria is significantly greater in adults (3.8 versus 0.3%).

People with asthma may be particularly sensitive to acetylsalicylic acid, which may be given alone or as a constituent of a combination medicine. The association between aspirin sensitivity, nasal polyps, and rhinitis in asthma is well known.

Henoch–Schönlein purpura has been reported (81).

Life-threatening respiratory distress, facial edema, and lethargy occurred in a woman with a history of severe asthma and aspirin hypersensitivity (SEDA-22, 118).

Aspirin-sensitive subjects may have attacks induced by other NSAIDs (82).

Fish oil can also cause exacerbation of asthma in aspirin-sensitive patients (83).

Prophylaxis and treatment

Asthma induced by aspirin is often severe and resistant to treatment. Avoidance of aspirin and substances to which there is cross-sensitivity is the only satisfactory solution. Desensitization is not usually successful and repeated treatments are needed to maintain any effect (84,85).

Long-Term Effects

Tumorigenicity

Studies on the tumor-inducing effects of heavy use of analgesics, especially those that contain phenacetin, have given contrasting results (SEDA-21, 100) (86,87). There has been a case-control study of the role of habitual intake of aspirin on the occurrence of urothelial cancer and renal cell carcinoma (88). In previous studies there was a consistent association between phenacetin and renal cell carcinoma, but inconclusive results with respect to non-phenacetin analgesics. In 1024 patients with renal cell carcinoma and an equal number of matched controls, regular use of analgesics was a significant risk factor for renal cell carcinoma (OR = 1.6; CI = 1.4, 1.9). The risk was significantly increased by aspirin, NSAIDs, paracetamol, and phenacetin, and within each class of analgesic the risk increased with increasing exposure. Individuals in the highest exposure categories had about a 2.5-fold increase in risk relative to non-users or irregular users of analgesics. However, exclusive users of aspirin who took aspirin 325 mg/day or less for cardiovascular problems were not at an increased risk of renal cell carcinoma (OR = 0.9; CI = 0.6, 1.4).

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Second-Generation Effects

Teratogenicity

It is perhaps surprising that aspirin, which is teratogenic in rodents, and which by virtue of its capacity to inhibit prostaglandin synthesis would be expected to affect the development of the renal and cardiovascular systems, has shown no evidence of teratogenesis in humans, despite very widespread use in pregnant women. Perhaps increased production of prostaglandins during pregnancy overrides the effects of aspirin in the usual dosages, and the intervention of placental metabolism protects the human fetus from exposure to aspirin. Whatever the explanation, there are very few reports in which aspirin can be implicated as a human teratogen and a few studies (89,90) have provided positive reassurance.

Fetotoxicity

Because aspirin is an antithrombotic agent and can promote bleeding, it should be avoided in the third trimester of pregnancy and at parturition (91). At parturition there is a second reason for avoiding aspirin, since its prostaglandin-inhibiting capacity could mean that it will delay parturition and induce early closure of the ductus arteriosus in the near-term fetus, as other NSAIDs do (92). However, its use in low doses in pregnancy may prevent retardation of fetal growth (93).

Susceptibility Factors

Age

In view of the association with Reye's syndrome, aspirin should be avoided in children aged under 16.

Drug Administration

Drug formulations

Although the use of enteric-coated aspirin can reduce its direct adverse effect on the stomach (SEDA-10, 72), it could in principle transfer these to some extent to the intestine; modified-release NSAIDs have sometimes caused intestinal perforation.

Enteric coating reduces the rate of absorption of aspirin. In cases of severe overdosage this can cause difficulties in diagnosis and treatment, since early plasma salicylate measurements are unreliable, maximum blood concentrations sometimes not being reached until 60 or 70 hours after overdose (94,95). Another complication of the use of enteric-coated aspirin is the risk of gastric outlet obstruction and the resulting accumulation of tablets because of subclinical pyloric stenosis.

Drug overdose

Acute poisoning

Acute salicylate poisoning is a major clinical hazard (96), although it is associated with low major morbidity and mortality, in contrast to chronic intoxication (SEDA-17, 98). It can cause alkalemia or acidemia, alkaluria or aciduria, hyperglycemia or hypoglycemia, and water and electrolyte imbalances. However, the usual picture is one of hypokalemia with metabolic acidosis and respiratory alkalosis. Effects on hearing have been referred to in the section on Sensory systems in this monograph. Nausea, vomiting, tinnitus, hyperpnea, hyperpyrexia, confusion, disorientation, dizziness, coma, and/or convulsions are common. They are expressions of the nervous system effects of the salicylates. Gastrointestinal hemorrhage is frequent.

Serum salicylate concentrations above 3.6 mmol/l are likely to be toxic, and concentrations of 5.4 mmol/l can easily prove fatal.

After ingestion, drug absorption can be prevented by induction of emesis, gastric lavage, and the administration of active charcoal; drug excretion is enhanced by administering intravenous alkalinizing solutions, hemoperfusion, and hemodialysis (97). Forced diuresis is dangerous and unnecessary.

Fluid and electrolyte management is the mainstay of therapy. The immediate aim must be to correct acidosis, hyperpyrexia, hypokalemia, and dehydration. In severe cases vitamin K_1 should be given to counteract hypoprothrombinemia.

Chronic poisoning

Chronic salicylate intoxication is commonly associated with chronic daily headaches, lethargy, confusion, or coma. Since headache is a feature, it can easily be misdiagnosed if the physician is not aware that aspirin has been over-used. Depression of mental status is usually present at the time of diagnosis, when the serum salicylate concentration is at a peak. The explanation of depression, manifested by irritability, lethargy, and unresponsiveness, occurring 1–3 days after the start of therapy for aspirin intoxication, lies in a persistently high concentration of salicylate in the central nervous system, while the serum salicylate concentration falls to non-toxic values. The delayed unresponsiveness associated with salicylate intoxication appears to be closely associated with the development of cerebral edema of uncertain cause. The encephalopathy that ensues appears to be directly related to increased intracranial pressure, a known effect of prostaglandin synthesis inhibitors; it responds to mannitol (98).

Drug–Drug Interactions

Alcohol

Although ethanol itself has no effect on bleeding time, it enhances the effect of aspirin when given simultaneously or up to at least 36 hours after aspirin ingestion (99). Ethanol also promotes gastric bleeding.

The FDA has announced its intention to require alcohol warnings on all over-the-counter pain medications that contain acetylsalicylic acid, salicylates, paracetamol, ibuprofen, ketoprofen, or naproxen. The proposed warnings are aimed at alerting consumers to the specific risks incurred from heavy alcohol consumption and its interaction with analgesics. For products

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that contain paracetamol, the warning indicates the risks of liver damage in those who drink more than three alcoholic beverages a day. For formulations that contain salicylates or the mentioned NSAIDs, three or more alcoholic beverages will increase the risk of stomach bleeding (100).

Anticoagulants

The effects on coagulation are additive if aspirin is used concurrently with anticoagulants. There are also other interaction mechanisms: the effect of the coumarins is temporarily increased by protein binding displacement, and if aspirin causes gastric hemorrhages, the latter may well be more severe when anticoagulants are being given.

Aspirin should therefore generally be avoided in patients adequately treated with anticoagulants. The most relevant information on hemorrhagic complications occurring during prophylaxis with antiplatelet drugs, whether used singly or in combination, has been provided by well-controlled prospective trials with aspirin (17), aspirin combined with dipyridamole (101), or aspirin compared with oral anticoagulants (102).

Antihypertensive drugs

An increase in mean supine blood pressure has been reported with aspirin (SEDA-19, 92). Aspirin may therefore interfere with antihypertensive pharmacotherapy, warranting caution, especially in the elderly.

Captopril

Aspirin is thought to reduce the antihypertensive effect of captopril (103).

Carbonic anhydrase inhibitors

In two children, aspirin potentiated the slight metabolic acidosis induced by carbonic anhydrase inhibitors (SEDA-9, 79) (104).

Glucocorticoids

The effects of aspirin on gastrointestinal mucosa will lead to additive effects if it is used concurrently with other drugs that have an irritant effect on the stomach, notably other NSAIDs or glucocorticoids (105,106).

Heparin

Risk factors for heparin-induced bleeding include concomitant use of aspirin (107).

Intrauterine contraceptive devices

The supposed mechanisms of action of intrauterine contraceptive devices (IUCDs) include a local inflammatory response and increased local production of prostaglandins that prevent sperm from fertilizing ova (108,109). As aspirin has both anti-inflammatory and antiprostaglandin properties, the contraceptive effectiveness of an IUCD can be reduced by the drug, although the effect on periodic bleeding may prevail.

Methotrexate

Aspirin displaces methotrexate from its binding sites and also inhibits its renal tubular elimination, so that the dosage of concurrently used methotrexate should be reduced (except once-a-week low-dose treatment in rheumatoid arthritis) (110).

Nitrates

Aspirin in low dosages (under 300 mg/day) is widely used in cardiovascular prophylaxis, but its use is accompanied by an increased risk of gastrointestinal bleeding (SEDA-21, 100). Of particular interest therefore are data from a retrospective case-control study showing that nitrate therapy may reduce the risk of aspirin-induced gastrointestinal bleeding (111). As nitrates are often used in the same population of patients, such data merit further confirmation from larger prospective studies.

NSAIDs

The effects of aspirin on gastrointestinal mucosa will lead to additive effects if it is used concurrently with other drugs that have an irritant effect on the stomach, notably other NSAIDs or glucocorticoids (105,106). Salicylates can be displaced from binding sites by some NSAIDs such as naproxen, or in turn displace others such as piroxicam.

Sodium valproate

Aspirin displaces sodium valproate from protein binding sites (112) and reduces its hepatic metabolism (113).

Streptokinase

Major hemorrhagic complications, including cerebral hemorrhage, can occur with aspirin (SEDA-23, 116) and the same is also true for thrombolytic therapy of acute ischemic stroke (114). A post hoc analysis of the Multicenter Acute Stroke Trial in Italy showed a negative interaction of aspirin and streptokinase in acute ischemic stroke (115). In 156 patients who received streptokinase plus aspirin and 157 patients treated with streptokinase alone, the combined regimen significantly increased early case fatality at days 3–10 (53 versus 30; OR = 2.5; CI = 1.2, 3.6). The excess in deaths was solely due to treatment and was not explained by the main prognostic predictors. Deaths in the combination group were mainly cerebral (42 versus 24; OR = 2.0; CI = 1.3, 3.7) and associated with hemorrhagic transformation (22 versus 11; OR = 2.2; CI = 1.0, 5.0). The data suggest that aspirin should be avoided when thrombolytic agents are used for acute ischemic stroke.

Uricosuric drugs

In low dosages (up to 2 g/day), aspirin reduces urate excretion and blocks the effects of probenecid and other uricosuric agents (116). However, in 11 patients with gout, aspirin 325 mg/day had no effect on the uricosuric action of probenecid (117). In higher dosages (over 5 g/day), salicylates increase urate excretion and inhibit the effects

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of spironolactone, but it is not clear that these phenomena are of importance.

Food-Drug Interactions

Food allergens

Aspirin seems to potentiate the effects of food allergens, but this is uncertain (SEDA-10, 72).

Interference with Diagnostic Tests

Thyroid function tests

Through competitive binding to thyroid-binding globulin, salicylates in high concentrations can displace thyroxine and triiodothyronine, thus interfering with the results of diagnostic thyroid function tests (118).

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Aciclovir

General Information

Aciclovir is an acyclic purine nucleoside. Its antiviral activity depends upon intracellular phosphorylation to its triphosphate derivative. Because of its higher affinity for viral thymidine kinase, aciclovir is phosphorylated at a much higher rate by the viral enzyme. Thus, it is almost exclusively active in infected cells, fulfilling one of the selectivity principles of antiviral drugs. In addition, aciclovir triphosphate serves as a better substrate for viral than for host cell DNA polymerase and thereby causes preferential termination of viral DNA synthesis (1).

Aciclovir is active against *Herpes simplex* virus type 1 (HSV-1), HSV-2, *Varicella zoster* virus (VZV), *Herpesvirus simiae*, and to a lesser degree Epstein–Barr virus (EBV). Resistant strains of HSV can arise owing to the emergence of thymidine kinase-deficient mutants. Other forms of resistance patterns are less common (2,3).

Aciclovir is used topically or systemically, orally or intravenously. Its therapeutic potential is most impressive in active parenchymal or systemic HSV infections. The latency stage of the viral infection is not affected. Since the blood–brain barrier is well penetrated, aciclovir is the treatment of choice for HSV encephalitis.

Very few adverse effects, generally of minor importance, have been reported (4). In immunosuppressed patients abnormal liver function, encephalopathy, and myelosuppression have been observed; however, it is unclear at present whether these adverse effects are related to the drug itself or to the underlying disorder (5–7).

Comparative studies

The effects of aciclovir and valaciclovir for anogenital herpes have been studied in HIV-infected individuals in two controlled trials (8). In the first study, 1062 patients with CD4+ counts over 100×10^6/l received valaciclovir or aciclovir for 1 year and were assessed monthly. In the second study, 467 patients were treated episodically for at least 5 days with valaciclovir or aciclovir and were assessed daily. Valaciclovir was as effective as aciclovir for suppression and episodic treatment of herpesvirus infections. Hazard ratios for the time to recurrence with valaciclovir 500 mg bd and 1000 mg od compared with aciclovir were 0.73 (95% CI = 0.50, 1.06) and 1.31 (0.94, 1.82). Valaciclovir 1000 mg bd and aciclovir had similar effects on the duration of infective episodes (HR = 0.92; CI = 0.75, 1.14). The most common adverse events, which occurred at similar rates with all regimens, were diarrhea, headache, infections, rashes, nausea, rhinitis, pharyngitis, abdominal pain, fever, depression, and cough.

Organs and Systems

Nervous system

Neurotoxicity secondary to aciclovir is rare and is associated with high plasma concentrations (SEDA-18, 299), such as result from impaired renal function (9). Although the risk is greatest with intravenous administration, neurotoxicity has previously been noted with oral use.

Symptoms of neurotoxicity, which usually appear within the first 24–72 hours of administration, include tremor, myoclonus, confusion, lethargy, agitation, hallucinations, dysarthria, asterixis, ataxia, hemiparesthesia, and seizures. While aciclovir-induced neurotoxicity is most prevalent with intravenous administration, it has also been reported after oral use in patients with terminal renal insufficiency on hemodialysis.

Neurotoxicity possibly secondary to the topical use of aciclovir has also been described (10).

- A 59-year-old woman on hemodialysis was treated with oral aciclovir 200 mg/day for ophthalmic Herpes zoster. After a few days, an ophthalmic aciclovir cream was started (one application every 6 hours) because of ipsilateral *Herpes* keratitis. After 1 week of combined oral and topical treatment, she became confused, with dysarthria and audiovisual hallucinations. Aciclovir was withdrawn and hemodialysis was initiated. Complete resolution of symptoms was achieved after three hemodialysis sessions in 3 days. Aciclovir plasma concentrations before hemodialysis were high (45 μmol/l) and fell rapidly during hemodialysis.

There is no conclusive evidence for the contribution of the topically administered aciclovir to the high plasma concentrations and subsequent neurotoxicity in this case. However, the authors argued that the existence of high aciclovir plasma concentrations, in spite of careful adjustment of the oral dosage, pointed to significant topical absorption of the drug, especially since the absorption of aciclovir through the skin and mucous membranes may be unpredictable.

Coma has been attributed to oral aciclovir (11).

- A 73-year-old man with acute respiratory failure, presumed to be secondary to amiodarone toxicity, developed sepsis and acute renal insufficiency, and required intermittent hemodialysis. Following a *Herpes simplex* labialis infection he was treated with oral aciclovir (400 mg tds). The next day he became sleepy, disoriented, and agitated. Over the next 48 hours his neurological condition deteriorated and he responded to pain

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only, had uncoordinated eye movements, tremors, facial and jaw myoclonus, increased reflexes, and hypertonia. After 7 days of aciclovir he became unresponsive and comatose. Aciclovir was withdrawn and hemodialysis carried out more frequently. His neurological status improved over a period of 4 days. Trough plasma concentrations of aciclovir were well above the upper limit of the usual target range.

This appears to be the first case of coma attributable to oral aciclovir. The fact that the patient was receiving oral rather than intravenous aciclovir and was on regular hemodialysis made neurotoxicity unlikely, and this emphasizes the need to be wary of this potentially serious complication in seriously ill elderly patients.

Sensory systems

Local application of 3% ophthalmic ointment can cause mild transient stinging. Diffuse, superficial, punctate, non-progressive keratopathy can develop. This quickly resolves after withdrawal (12,13).

Psychological, psychiatric

One report described reversible psychiatric adverse effects in three dialysis patients receiving intravenous aciclovir (8–10 mg/kg/day) (14).

Hematologic

Neutropenia and thrombocytopenia occurred in an 8-year-old boy who was treated with aciclovir 200 mg bd for 5 months for "chronic cold sores" (15). After withdrawal of aciclovir, the absolute neutrophil and platelet counts normalized within days. There was no recurrence of oral herpes lesions during the ensuing month.

Urinary tract

Renal impairment has been associated with the use of intravenous aciclovir. Transient increases in serum creatinine and urea have been observed in 14% of patients treated with bolus injections (16). These are related to crystal formation in the lower renal tubules when the solubility of aciclovir in urine is exceeded. Slow (1-hour) intravenous infusion and adequate hydration are therefore mandatory. Bolus doses are to be avoided. Dosage modifications for patients with renal insufficiency are based on creatinine clearance (4).

- Crystalluria due to aciclovir occurred within 24 hours of the start of therapy with 500 mg 8-hourly in a 4-year-old African-American boy (17). Slow intravenous infusion over 1–2 hours and volume repletion avoids the problem.

Renal toxicity has not been described in infants treated with intravenous aciclovir, 5–10 mg/kg every 8 hours for 5–10 days (18) or in children receiving aciclovir 500 mg/m^2 intravenously (19) or orally (4).

Skin

Skin reactions to aciclovir are mostly mild and transitory, including pruritus, pain, rashes, contact dermatitis, and photoallergic contact dermatitis. However, serious reactions occasionally occur (20). Antiviral drugs that have been implicated include topical aciclovir, cidofovir, idoxuridine, imiquimod, lamivudine, penciclovir, podophyllin, podophyllotoxin, trifluridine, tromantadine, vidarabine, intralesional and ophthalmic solutions of interferon, intravitreal injections of fomivirsen and foscarnet, and intraocular implants of ganciclovir. Patch-testing in these cases only rarely caused positive reactions to the antiviral drug.

A case of possible aciclovir-induced Stevens–Johnson syndrome has been reported in an HIV-positive patient with mycobacterial disease (21). However, Stevens–Johnson syndrome is associated with *Herpes simplex* infection and can be prevented by aciclovir (22).

Immunologic

Although allergy to aciclovir is unusual, it can occur; in one case it resulted in a skin rash (23).

- A 38-year-old woman of African descent, with a history of atopy and mild asthma, developed a periumbilical, erythematous, maculopapular rash and generalized pruritus after starting aciclovir. The reaction resolved within a few days after withdrawal, recurred when famciclovir was used, and again resolved when famciclovir was withdrawn. She was successfully stabilized on suppressive therapy after a graded challenge with aciclovir four times a day for 5 days.

Cross-reactivity between aciclovir and famciclovir is unusual. Aciclovir desensitization may be a novel method of treating patients with aciclovir allergy.

Contact sensitization to aciclovir is rare, but frequent application to inflamed skin in relapsing *Herpes simplex* may increase the risk of allergy. Severe contact dermatitis in a teenager has been reported.

- A 16-year-old girl with an 11-year history of frequent cold sores developed an erythematous rash and severe contact dermatitis during oral and topical aciclovir therapy (24). Patch tests showed contact sensitization to aciclovir and to the related compound ganciclovir.
- In a 44-year-old woman who used topical aciclovir for genital herpes, aciclovir contact allergy was associated with a systemic contact allergic reaction with an erythematous vesiculobullous eruption in the labial and perioral skin and a rash on the upper trunk and extremities (25). Patch tests were positive to aciclovir, valaciclovir, and ganciclovir, but not to famciclovir.

Pre-existing vesicular edematous cheilitis (probably due to contact allergy to the protecting lip salve) was aggravated after application of Zovirax cream (26). Patch tests to the lip salve were positive, but in addition there were positive photopatch tests to Zovirax cream, but not to its separate constituents.

Second-Generation Effects

Pregnancy

Animal data suggest that aciclovir is probably safe in pregnancy. There are no reports of teratogenicity in

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humans, and a report of 312 pregnant women exposed to aciclovir showed no increase in the number of birth defects compared with the numbers expected in the general population (27). However, data from larger numbers of human pregnancies are not available to draw reliable conclusions about the safety of aciclovir in pregnancy.

Drug Administration

Drug administration route

Local necrosis and inflammation can occur due to extravasation of the drug at the site of injection (28).

Various local adverse effects of aciclovir eye-drops have been reported, including pruritus, burning sensations, and irritative or allergic conjunctivitis. Persistent superficial punctate keratitis, delayed epithelial healing, and epithelial dysplasia can develop (29).

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Acipimox

General Information

Acipimox (*S*-methylpyrazine-2-carboxylic acid 4-oxide) is structurally related to nicotinic acid. There were flushing and gastrointestinal disturbances in 7137 patients, of whom 15% stopped taking the drug because of adverse effects; there were no adverse effects on blood glucose or uric acid (1). Of 32 patients with hypertriglyceridemia, excessive hypertriglyceridemia, and combined hyperlipidemia, acipimox had to be withdrawn in 10 cases, because of adverse effects or absence of clinical response (2). The other 22 completed 6 months of treatment with no adverse effects. The authors claimed that acipimox is much better tolerated than nicotinic acid; it has fewer adverse effects and can therefore be used as a second-line drug.

Organs and Systems

Metabolism

In an open study, blood glucose was on average slightly lowered in 3009 type II diabetics given acipimox for at least 2 months (3).

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Acivicin

See also Cytostatic and immunosuppressant drugs

General Information

Acivicin is a cytostatic antibiotic, a glutamine analogue, which is a potent inhibitor of l-asparagine synthetase and other l-glutamine amidotransferases and has its cytotoxic action by blocking nucleotide biosynthesis.

Besides myelotoxicity, acivicin is neurotoxic, and can cause lethargy and auditory and visual hallucinations. Some patients have nystagmus, incontinence, and severe depression (1,2).

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Acoraceae

See also Herbal medicines

General Information

Acorus calamus was originally classified as a member of the arum family (Araceae), but is now designated as belonging to its own family, the Acoraceae, of which it is the only member.

Acorus calamus

Acorus calamus (calamus root, sweet flag, rat root, sweet sedge, flag root, sweet calomel, sweet myrtle, sweet cane, sweet rush, beewort, muskrat root, pine root) contains several active constituents called "asarones." The basic structure is 2,4,5-trimethoxy-1-propenylbenzene, which is related to the hallucinogen 3,4-methylenedioxyphenylisopropylamine (MDA). The amounts of the asarones in calamus rhizomes vary considerably with the botanical variety. For example, there are high concentrations in triploid calamus from Eastern Europe but none detectable in the diploid North American variety.

Acorus calamus has been used as a hallucinogen since ancient times and it has several uses in folk medicine. It may have been one of the constituents of the Holy Oil that God commanded Moses to make (Exodus 30) and is mentioned by ancient writers on medicine, such as Hippocrates, Theophrastus, Dioscorides, and Celsus (http://www.a1b2c3.com/drugs/var002.htm). Walt Whitman's 39 "Calamus poems" are to be found in his well-known collection "Leaves of Grass."

Acorus calamus has in vitro antiproliferative and immunosuppressive actions (1).

Acorus calamus contains beta-asarone [(Z)-1,2,4-trimethoxy-5-prop-1-enyl-benzene], which is carcinogenic (2). Commercial calamus preparations have mutagenic effects in bacteria (3), while calamus oil (Jammu variety) is carcinogenic in rats.

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Acrisorcin

See also Disinfectants and antiseptics

General Information

Acrisorcin (aminoacridine 4-hexylresorcinolate) has been used for induction of abortion in mid-trimester pregnancies. Abortion was produced when a 0.1% solution of acrisorcin was introduced into the extra-amniotic space in 23 women. All patients aborted after a mean induction-delivery interval of 59 hours (SEDA-11, 474) (1).

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Acrivastine

See also Antihistamines

General Information

Acrivastine is a second-generation antihistamine that has not been the subject of recent studies; earlier work was insufficient to substantiate statements that it was non-sedating.

Organs and Systems

Nervous system

Five of thirty-five patients taking acrivastine reported drowsiness compared with none in the placebo group (SEDA-14, 135). In another study acrivastine 8 mg did not impair nervous system function (SEDA-21, 172). The usual dose is 8 mg tds, which is effective in treating seasonal allergic rhinitis and has been stated to be without sedative effects (1). However, acrivastine does have a small but significant additive effect with alcohol at a dose of 8 mg (2).

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Acrylic bone cement

General Information

Local biocompatibility

Although polymerized polymethylmethacrylate is a biocompatible material, it is not biocompatible during the brief time it takes to set, during which it releases 130 calories/gram and can cause a rise in temperature up to 120°C. This temperature rise can be reduced by various techniques, although the thermal tolerance of the tissues affected is low (56°C and 72°C for coagulation of body proteins and bone collagen respectively). This is the main factor that is responsible for bone necrosis associated with acrylic bone cement. To avoid this, sucrose crystals have been added to acrylic cement. The mixture has a lower polymerization temperature and greater porosity, allowing for better ingrowth of bone into the cement pores (1); however, the resultant lower mechanical resistance limits its use (2,3). The same can be achieved by adding tricalcium phosphate, which lowers the reaction temperature. The non-polymerized monomer is cytotoxic (4), which can cause histopathological changes in soft tissues and bones.

Regional damage

Regional damage from methylmethacrylate is generally the result of poor surgical technique, whereby the cement inadvertently reaches other tissues and structures. For example, leaking methylmethacrylate cement during fixation of the acetabular cup in a total hip replacement can cause sciatic nerve compression and result in severe lasting leg pain (5).

Organs and Systems

Cardiovascular

Cardiovascular reactions to acrylic bone cement are a common complication in bone surgery. It is believed that cementation activates an adrenocortical response, increasing the blood pressure during general anesthesia (6,7); during spinal anesthesia this response is suppressed and the blood pressure falls. The mechanism is thought to be by a direct effect on the blood pressure through the kallikrein–kinin system, since aprotinin (Trasylol), an inhibitor of kallikrein, prevents the fall in arterial pressure if it is given during the application of acrylic bone cement (8).

Some investigators suggested that implantation of acrylic bone cement into the femur increases plasma histamine, which, especially in elderly patients with pre-existing cardiac diseases and/or hypovolemia, can cause serious, sometimes fatal, cardiovascular complications (9).

Respiratory

Since adverse effects in humans develop within 2–5 minutes of fixation, with features of pulmonary insufficiency, direct pulmonary damage has been

postulated, with the cardiovascular effects being a consequence of hypoxemia (10–12). This has been demonstrated by lactase dehydrogenase isomer determinations, fractions 3 and 4 being significantly raised. These isozymes are released as a result of pulmonary mitochondrial injury caused by hypoxia. Methylmethacrylate monomer vapour can irritate the respiratory tract, eyes, and skin.

Immunologic

Methylmethacrylate is essentially an immunologically inert implant material, but it induces an inflammatory mononuclear cell migration (13,14). Both cemented and cementless prostheses cause a foreign-body-type host response. A new connective tissue capsule is formed around the artificial joint, which is coarser than normal. The reaction is partly granulomatous, with a tendency to necrosis and loosening of the prosthesis. After an initial necrotic phase of 2–3 weeks repair follows, leading to stabilization within 2 years.

Sensitization can occur in patients, surgeons, and dentists and is occasionally reported (15). As most surgical gloves do not provide a reliable barrier, additional gloves are recommended. Contact dermatitis, dizziness, and nausea and vomiting occur. Ethylene oxide present in acrylic bone cement can cause acute allergic reactions in sensitized patients (16).

Infection risk

Addition of materials (for example antimicrobial drugs or radio-opaque contrast materials) to acrylic bone cement can cause mechanical weakness due to loss of homogeneity and greater water resorption. Antimicrobial drugs have been added to combat the problem of microbial adherence. However, this can lead to a considerable dead biofilm mass on the polymethylmethacrylate surface, promoting late infections by providing a surface attractive to other strains of bacteria (17).

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Activated charcoal

General Information

Activated charcoal is a standard therapy for gut decontamination after self-poisoning. It has two uses. If given within an hour or two after acute self-poisoning it can adsorb the drug and prevent it from being absorbed; in this case a single dose of activated charcoal 50 g is sufficient. However, some drugs are secreted into the gut after absorption and can be adsorbed by charcoal, preventing re-absorption; in this case repeated doses of activated charcoal 50 g 6-hourly can be used.

In a randomized study in 401 patients who had taken an overdose of oleander seeds, which contain cardiac glycosides, activated charcoal 50 g every 6 hours for 3 days was compared with sterile water. There were fewer deaths in the treatment group, 2.5% versus 8% (1). There were no important adverse effects.

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Organs and Systems

Respiratory

Pulmonary aspiration is an ever-present risk of using charcoal, especially in semi-conscious patients (2). Povidone, which is used as a suspending agent of charcoal, can cause pneumonitis, which can lead to respiratory failure and death.

Electrolyte balance

Hyponatremic dehydration has been described when charcoal was combined with sorbitol to treat theophylline overdose in a child (SED-12, 951) (3).

Gastrointestinal

- Esophageal laceration with charcoal mediastinum has been reported in a 19-year-old woman who underwent multiple attempts at orogastric lavage with isotonic saline followed by 50 g of activated charcoal and sorbitol via the orogastric tube for a drug overdose (4). She recovered after surgical intervention.

Two formulations of activated charcoal 50 g (Carbomix, made into a slurry with 400 ml of tap water, and Actidose-Aqua, which came as a 240 ml suspension) have been compared in a prospective, randomized, single-blind study in 97 patients (5). The mean total dose of Carbomix (26.5 g) was significantly higher than the mean total dose of Actidose-Aqua (19.5 g); the reasons for this difference were not stated. The rates of vomiting did not differ between patients who received Carbomix (6%) or Actidose-Aqua (8%), and were low compared with previous reports (13%).

Though usually innocuous, activated charcoal can in large or multiple doses, such as may be needed in severe poisoning, cause intestinal obstruction (3,6). Pseudo-obstruction can also occur if drugs that inhibit intestinal motility are given at the same time, and sometimes it is not clear which process has occurred (SED-12, 951) (SEDA-17, 426) (6).

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Adefovir

General Information

Adefovir is an adenine analogue reverse transcriptase inhibitor. While it has activity against both HIV and hepatitis B, its use in HIV infection is limited by nephrotoxicity due to the high doses needed (1). The dose used for treatment of hepatitis B is about one-tenth that needed to treat HIV infection, so patients with hepatitis B must have co-infection with HIV ruled out before treatment is started.

Organs and Systems

Liver

In 35 patients co-infected with hepatitis B virus and HIV given adefovir 10 mg/day plus lamivudine 150 mg bd as part of treatment for hepatitis B and followed for 48 weeks, common adverse effects included raised transaminases, particularly alanine transaminase, increased serum creatinine, and increased blood glucose (2). Concerns about the study include the small number of patients and the lack of a comparison group.

Urinary tract

Adefovir is nephrotoxic, particularly at high doses, and the possible mechanism has been investigated in a 39-year-old man, who had severe acute tubular degenerative changes mainly affecting the proximal tubule; the mitochondria were significantly enlarged, possibly as a result of depletion of mitochondrial DNA (3).

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Ademetionine

General Information

Ademetionine (*S*-adenosylmethionine) has anti-inflammatory and analgesic effects in animals. Convincing evidence of these effects in man is still lacking. In trials in osteoarthritis, as presented at a symposium organized by the manufacturers (and thus open to selection bias), ademetionine was well tolerated

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(1). In a large, uncontrolled, short-term Phase IV trial, adverse effects (moderate or severe) were reported by 21% of the patients, with withdrawal in 5.2%. Adverse effects were mainly gastrointestinal (nausea, stomachache, heartburn, diarrhea), CNS symptoms (headache, dizziness, sleep disturbances, fatigue), and skin rashes.

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Adenosine and adenosine triphosphate (ATP)

See also Antidysrhythmic drugs

General Information

Adenosine and adenosine triphosphate (ATP), its phosphorylated derivative, have been used to treat acute paroxysmal supraventricular tachycardias and adenosine has also been used in the diagnosis of narrow-and broad-complex tachycardias (SEDA-16, 176).

Several reviews of the clinical pharmacology, actions, therapeutic uses, and adverse reactions and interactions of adenosine and ATP have appeared (1–4). After intravenous administration adenosine enters cells, disappearing from the blood with a half-life of less than 10 seconds; intracellularly it is phosphorylated to cyclic AMP. Its mechanism of action as an antidysrhythmic drug is not known, but it may act by an effect at adenosine receptors on the cell membrane. Its electrophysiological effects are to prolong AV nodal conduction time by prolonging the AH interval, without an effect on the HV interval. The pharmacological and adverse effects of adenosine triphosphate are similar to those of adenosine.

Although adenosine and ATP very commonly cause adverse effects, they are generally mild and usually transient, because adenosine is rapidly eliminated from the blood (with a half-life of less than 10 seconds). Adverse effects have been reported in 81% of patients given adenosine and 94% of patients given ATP (5). Exercise reduces the non-cardiac adverse effects and the incidence of major dysrhythmias (6). Reducing the duration of adenosine infusion from 6 to 4 minutes reduced the incidence of chest discomfort and ischemic ST segment changes, but had no impact on non-cardiac effects (7).

Several studies have reported the efficacy and safety of adenosine and ATP in the treatment of tachycardias in children (8–11).

In 18 children with aortic valve disease or Kawasaki disease, adenosine stress myocardial perfusion imaging was associated with the usual adverse effects, most commonly flushing and dyspnea (12).

Exercise reduces both non-cardiac adverse effects and dysrhythmias in patients who are given adenosine for diagnostic purposes in myocardial perfusion imaging (SEDA-21, 197). This has been confirmed in two studies. In the first of these, 793 patients were given an intravenous infusion of adenosine 140 micrograms/kg/minute while exercising for 6 minutes or for a similar time without exercise (13). The rate of hypotension and dysrhythmias was significantly less in those who exercised (14 of 507) than in those who did not exercise (16 of 286). Overall reactions were more common in women than in men (5.7 versus 1.8%). All the adverse effects were transient and no specific therapy was required. The authors attributed the difference to the increase in sympathetic tone during exercise, which would have partly counteracted the hypotension and the negative chronotropic and negative dromotropic effects of adenosine. However, there was a major difference between the two groups, in that those who did not take exercise were considered unfit for exercise, which may have been associated with an increased risk of adverse effects. Nevertheless, the authors discarded that possibility, because the frequency of adverse reactions in those who did not take exercise was similar to frequencies that have previously been reported.

In the second study 19 patients received an intravenous infusion of adenosine 140 micrograms/kg/minute for 4 minutes during exercise or for 6 minutes without exercise; the patients undertook both protocols (14). Again, there were fewer adverse effects in those who took exercise, but only hypotension, chest pain, and headache were significantly different; there was a reduction in the frequency of flushing, which was almost significant. In addition, adverse effects were experienced for longer and the severity was greater in those who did not take exercise.

Organs and Systems

Cardiovascular

The most common cardiac effects are atrioventricular block, sinus bradycardia, and ventricular extra beats. Occasionally serious dysrhythmias occur (SEDA-17, 219), including ventricular fibrillation (15). ATP can cause transient atrial fibrillation (16). Chest pain occurs in 30–50% of patients and dyspnea and chest discomfort in 35–55%. Chest pain can occur in patients with and without coronary artery disease, and the symptoms are not always typical of cardiac pain.

Myocardial ischemia

Adenosine can cause cardiac ischemia by activating adenosine A1 receptors in the heart. However, in a double-blind, placebo-controlled, crossover study in eight healthy volunteers, adenosine 100 μg/kg/minute did not alter ischemic pain in an exercising arm (17). Otherwise, the usual adverse effects were noted, including facial flushing and mild chest tightness.

Hypotension

When adenosine (70 micrograms/kg/minute) was given by intravenous infusion to 45 patients with acute myocardial infarction preceding balloon angioplasty, one patient developed persisting hypotension in conjunction with a large inferolateral myocardial infarction (18). Transient hypotension in three other patients resolved with a reduction in dosage. There were no cases of atrioventricular block.

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Symptomatic hypotension has occasionally been reported in patients with myocardial infarction who have been given adenosine (SEDA-20, 174).

An infusion of adenosine, 25 micrograms/kg, in 15 women undergoing anesthesia for major gynecological procedures was effective in maintaining hemodynamic stability during operation in addition to conventional anesthesia (19). It caused a significantly greater fall in systolic blood pressure and increase in heart rate than remifentanil in a comparable group. In four cases ephedrine was required for hypotension that was refractory to intravenous fluids or a temporary reduction in the infusion rate of adenosine. Two patients also required atropine for prolonged bradycardia.

Cardiac dysrhythmias

In patients with ischemic heart disease adenosine can prolong the QT_c interval and can increase the frequency of ventricular extra beats when there is myocardial scarring. It also causes increased release of catecholamines, and this may be the mechanism whereby it causes dysrhythmias in susceptible patients. If a dysrhythmia occurs, theophylline or one of its derivatives may be beneficial (20).

Of 100 patients who received intravenous adenosine in hospital (mean dose 7.8 mg) two had a dysrhythmia other than that for which they were being treated (21).

- A 53-year-old man with a dilated cardiomyopathy was given adenosine 6 mg for a regular broad-complex tachycardia; the dysrhythmia resolved but was followed by prolonged asystole and cyanosis for about 15 seconds.
- A 64-year-old woman with atrial fibrillation was given adenosine 12 mg; she developed a non-sustained polymorphous ventricular tachycardia followed by sustained ventricular fibrillation requiring DC shock.

In the whole series, about 40% of the patients received adenosine unnecessarily, having atrial fibrillation or atrial flutter, and the authors suggested that misuse of this sort resulted in unnecessary expense and increased risks of adverse effects. Most of this misuse was attributed to misdiagnosis by house officers who thought that rapid atrial fibrillation was a paroxysmal supraventricular tachycardia. Very few thought that adenosine would be likely to terminate atrial fibrillation.

Adenosine is contraindicated in patients with aberrant conduction pathways, because it can cause cardiac dysrhythmias. Supraventricular dysrhythmias occurred in three children with Wolff–Parkinson–White syndrome who were given intravenous adenosine (22).

There have been reports of cardiac dysrhythmias in patients given either an intravenous infusion of adenosine or a single bolus dose.

- A 38-year-old man was given intravenous adenosine 6 mg for a narrow-complex tachycardia (20). Within about 1 minute his heart rate fell from 230/minute to bradycardia and then asystole. Cardiopulmonary resuscitation was ineffective. At autopsy there was a 75% occlusion of one of the coronary arteries (unspecified).

The cause of the dysrhythmia in response to adenosine was not clear. He was not known to be taking other drugs (for example dipyridamole) that might have potentiated the action of adenosine.

- A 56-year-old man was given adenosine 12 mg for a narrow-complex tachycardia on four occasions, and on each occasion developed transient atrial fibrillation for a few minutes thereafter. He had a concealed left-sided accessory pathway, which was successfully ablated (23).
- An 86-year-old woman was given adenosine 12 mg intravenously for sustained supraventricular tachycardia, which terminated but was followed by atrial fibrillation and paroxysmal ventricular tachycardia (24). Cardioversion was unsuccessful, but normal sinus rhythm was obtained with procainamide. This followed an anteroseptal myocardial infarction.
- A 75-year-old man who had had coronary bypass surgery was given an intravenous infusion of adenosine for stress testing (25). After 1 minute he developed a three-beat run of wide-complex tachycardia, followed by a 20-second run of a regular wide-complex tachycardia at a rate of 115/minute. There was left bundle branch block, and the tachycardia ended spontaneously. Adenosine infusion was continued and some ventricular extra beats with the same configuration occurred. In this case there was impaired perfusion of the left ventricle.
- In a 60-year-old woman with atrial flutter with 2:1 block and a ventricular rate of 130/minute, the ventricular rate increased paradoxically to 260/minute with 1:1 conduction after intravenous administration of adenosine 6 mg; it responded to intravenous amiodarone 300 mg (26).
- A 52-year-old woman with a wide-complex tachycardia was given adenosine 6, 12, and another 12 mg as intravenous bolus doses; immediately after the third dose she developed ventricular fibrillation (27). She recovered with cardioversion.

In the last case the authors did not discuss the possibility that the presence of digoxin (serum concentration 1.8 ng/ml) may have contributed; the risk of cardiac dysrhythmias after electrical cardioversion is increased in the presence of digoxin (SEDA-8, 174), and the same might be true of chemical cardioversion.

In a prospective study of 187 episodes of tachycardia in 127 unselected patients adenosine was given in an average dose of 9.7 mg (28). In 108 cases, adenosine induced transient ventricular extra beats or non-sustained ventricular tachycardia after successful termination of supraventricular tachycardia; more than half had a right bundle branch block morphology that suggested that the dysrhythmias had originated from the inferior left ventricular septum.

Heart block

The frequency of atrioventricular block has been studied in 600 patients who underwent stress testing with intravenous adenosine 140 micrograms/kg/minute for 6 minutes (29). The patients were young (under 49 years old; $n = 75$), middle-aged (50–65 years; $n = 214$), old (66–75 years; $n = 195$), or very old (over 75 years; $n = 116$). The respective frequencies of first-degree atrioventricular block were 15, 9.3, 14, and 17% (overall

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Table 1 The incidence of atrioventricular block with adenosine

Type of block	Baseline PR interval over 200 ms ($n = 43$)	Baseline PR interval under 200 ms ($n = 557$)
Further prolongation of PR interval	49%	10%
Second-degree block	37%	8%
Third-degree block	14%	1%

average 13%), of second-degree block 15, 7.0, 8.7, and 16% (overall average 10%), and of third-degree block 2.7, 2.3, 1.0, and 2.6% (overall average 2.0%). The differences with age were not statistically significant. All types of atrioventricular block were of short duration, were well tolerated, and did not require withdrawal of adenosine or specific treatment.

In four out of nine patients with heart transplants second-degree or third-degree atrioventricular block occurred during the administration of adenosine 140 micrograms/kg/minute over 6 minutes (30). In two patients the infusion had to be interrupted because of severe discomfort and chest pain.

The incidence of atrioventricular block has been reported in 600 consecutive patients who underwent stress myocardial perfusion imaging with adenosine (140 micrograms/kg/minute for 6 minutes), and of whom 43 had first-degree heart block before adenosine and 557 had a baseline PR interval less than 200 ms (Table 1) (31). The heart block in all cases was of short duration, was not associated with any specific symptoms, and in no case required specific treatment. The risk of atrioventricular block during adenosine infusion was not increased by the presence of other drugs that might have caused atrioventricular block (digitalis, beta-blockers, diltiazem, verapamil).

Respiratory

Adenosine can cause bronchoconstriction with asthma (32), and a history of bronchoconstriction is a contraindication to intravenous adenosine.

In 94 patients with chronic obstructive pulmonary disease who were given adenosine in an initial dosage of 50 micrograms/kg/minute, increasing to 140 micrograms/kg/minute if adverse effects did not occur, there was only a slight and insignificant fall in FEV_1 at the highest dose of adenosine (33). However, four patients had a fall in FEV_1 of 20% or more, although without shortness of breath or evidence of bronchospasm; in these the dosage of adenosine was reduced to 100 micrograms/kg/minute. Two other patients had shortness of breath with no fall in FEV_1 or bronchospasm, and the dosage was reduced to 100 micrograms/kg/minute. There was no difference in the fall in FEV_1 between patients who had a history of asthma and those who did not. Other adverse effects included light-headedness ($n = 26$), dyspnea ($n = 17$), headache ($n = 14$), flushing ($n = 8$), hypotension ($n = 7$), chest pain ($n = 6$), and nausea ($n = 2$). In a subsequent study in 117 patients, two had symptomatic bronchospasm during adenosine infusion. In two other patients in whom bronchospasm was present before treatment, bronchospasm did not develop when adenosine was infused at the highest dosage.

In another study, 63 of 122 patients had breathlessness during cardiac stress testing with adenosine but none had associated bronchospasm (34). Pre-test lung function did not predict the risk of breathlessness and neither chronic obstructive airways disease nor smoking increased the risk. The authors concluded that breathlessness during adenosine stress testing is not due to bronchospasm.

Nervous system

Adenosine has been used intrathecally to treat pain, but can itself cause backache (SEDA-23, 197) (35). In a placebo-controlled study in 40 healthy volunteers, who were given intrathecal adenosine 2 mg in 2 ml of saline, 13 had a mild headache, nine had mild to moderate backache, and one had mild aching in the thigh, compared with none of those who were given saline alone (36). No headaches or leg aches occurred later than 6 hours after the injection, but the backaches occurred at 6–24 hours; there were no later symptoms.

In a randomized, double-blind study of two doses of intrathecal adenosine in 35 volunteers with experimental hypersensitivity induced by capsaicin, intrathecal adenosine 0.5 or 2 mg in 2 ml of saline, but not saline alone, equally reduced areas of allodynia and hyperalgesia from capsaicin (37). There were adverse effects in 1, 2, and 6 of the volunteers who received saline, 0.5 mg, and 2.0 mg of adenosine respectively. The adverse effects were headache, backache, and leg or groin ache. Intravenous aminophylline 5 mg/kg, given 2 hours after the adenosine, did not reverse the effects of adenosine.

Of 12 healthy volunteers given an intrathecal injection of adenosine (500–2000 micrograms) one volunteer had transient lumbar pain lasting 30 minutes after an injection of 2000 micrograms (38). There were no adverse effects at lower doses.

Adenosine can cause increased intracranial pressure (39).

Gastrointestinal

Adenosine can cause transient epigastric pain mimicking that of peptic ulceration (40).

Immunologic

- An anaphylactic reaction has been reported in a 75-year-old woman who was given adenosine 12 mg for a supraventricular tachycardia. She developed bronchospasm and profound inspiratory stridor, her arterial blood pressure fell to 50/30 mmHg from an arterial systolic pressure of 70 mmHg, and she recovered with appropriate treatment (41).

Death

Two cases of sudden death have been reported soon after the administration of adenosine for presumed supraventricular tachycardia, which turned out to be atrial fibrillation (42). The authors thought that both patients may have been unable to cope with the sudden momentary loss of cardiac function that would have occurred

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immediately after the administration of adenosine; in one case, a patient with chronic lung disease, bronchospasm may have contributed.

Drug Administration

Drug administration route

The standard regimen for stress testing with intravenous adenosine is 140 micrograms/kg/minute for 6 minutes. However, in 599 patients a 3-minute infusion was associated with a lower frequency of some adverse effects (specifically flushing, headache, neck pain, and atrioventricular block) and had similar sensitivity in the diagnosis of coronary artery disease (43).

Intracoronary adenosine has been compared with intravenous adenosine for the measure of fractional flow reserve in 52 patients with coronary artery lesions (44). The intravenous dose was 140 micrograms/kg/minute and the intracoronary bolus dose was 15–20 micrograms to the right coronary artery and 18–24 micrograms to the left coronary artery. The two routes of administration were equally effective in measuring hyperemic flow, and adverse effects were limited to two patients who received intravenous adenosine; one patient had severe nausea and one patient with asthma had an episode of bronchospasm.

The use of intrathecal adenosine in patients with chronic neuropathic pain (35,45) has been briefly reviewed (46).

Drug–Drug Interactions

General

Adenosine does not interact with digoxin, disopyramide, flecainide, or quinidine.

Ciclosporin

Endogenous plasma adenosine concentrations were measured in 14 kidney transplant recipients taking ciclosporin and compared with five transplant recipients not taking ciclosporin, two taking sirolimus (FK506), six patients with chronic renal insufficiency, and ten controls (47). Plasma adenosine concentrations were significantly higher in those taking ciclosporin and sirolimus and in the patients taking ciclosporin the plasma adenosine concentrations correlated with serum ciclosporin concentrations. An in vitro study showed that ciclosporin inhibited the uptake of adenosine by erythrocytes. The authors concluded that since adenosine is immunosuppressant, the raised concentrations of adenosine in patients taking ciclosporin might contribute to the immunosuppressive action of ciclosporin. A further mechanism of the increase in adenosine concentration was possibly increased tissue release secondary to ciclosporin-induced vasoconstriction. The relevance of these results to the use of therapeutic intravenous adenosine in patients already taking ciclosporin is not clear.

Dipyridamole

Dipyridamole inhibits the uptake of adenosine by cells and so increases its effects; this causes a large reduction in the effective dose of adenosine (48).

Sirolimus

In two kidney transplant recipients taking sirolimus (FK506), plasma adenosine concentrations were significantly increased (47). The relevance of these results to the use of therapeutic intravenous adenosine in patients already taking sirolimus is not clear.

Xanthines

Antagonists at adenosine receptors should inhibit the action of adenosine, and indeed theophylline increases the dose of adenosine needed for conversion of supraventricular tachycardia (49).

Diagnosis of Adverse Drug Reactions

In 34 patients given midazolam or placebo in a double-blind study, midazolam significantly reduced patients' experiences of palpitation and chest pain but had no effects on other adverse events (50). These effects were probably due to amnesia rather than a true reduction in the incidence of adverse events, and it is uncertain that the benefit to harm ratio is worth while. However, the authors suggested that midazolam might be useful in patients who have previously had unpleasant adverse reactions to adenosine.

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Adiphenine

General Information

Adiphenine, in the doses generally used (up to 60 mg/day), is of disputed value. It may have a non-specific relaxant action on the gastrointestinal muscle and some local anesthetic effect on the buccal mucosa. The evidence on its effects is meager and it seems like an anticholinergic drug that has been promoted in doses that are often too low to result in either a useful therapeutic effect or in adverse effects.

Adrenaline

See also Anticholinergic drugs

General Information

Note on nomenclature

Although epinephrine is the recommended International Non-proprietary Name (rINN), there are good reasons why the name adrenaline should be preferred, based on usage, history, etymology, and, most importantly, risk of clinical errors (1).

Adrenaline is a catecholamine with agonist effects at both α- and β-adrenoceptors.

The use of adrenaline is largely limited to subcutaneous administration for the immediate relief of anaphylactic shock. Intramuscular doses of 0.1 ml of a 1:1000 solution are often given repeatedly, up to a maximum of some 2 ml in 5 minutes. Although the sensitivity of individuals to adrenaline varies considerably, the adverse reactions to such doses are generally limited to mild cardiovascular effects.

Intravenous administration of adrenaline for treatment of systemic anaphylactic shock should be undertaken with extreme caution, even in patients without a history of cardiovascular disease. At all times the patient must be monitored and emergency treatment should be available. Even the infiltration of low doses of adrenaline for local hemostasis can be attended by these risks; one patient developed ventricular tachycardia and severe hypertension after receiving 3.75 mg locally for this purpose (SEDA-17, 160), and the value of this treatment is in any case today regarded as dubious (SEDA-17, 161).

Subcutaneous adrenaline has been used to prevent the immediate adverse effects of snake antivenom, although evidence of its efficacy is scanty (2). A large clinical trial is under way in Sri Lanka.

Adrenaline was at one time a component of asthma sprays, and dilated cardiomyopathy was described after many years of use (3).

Adrenaline has been largely abandoned as an adjuvant to local anesthetics, although in a 1:80 000 concentration it is still sometimes used in dental and in epidural anesthesia.

Dipivefrin

Dipivefrin (dipivalyl epinephrine) is a prodrug of adrenaline, used topically in the treatment of glaucoma. Its potential advantages include a longer duration of action, increased local availability, greater potency, greater stability, and fewer adverse effects. The effect on pupil size is insignificant, no objective sight-threatening effects are observed, and central visual acuity and visual fields are not affected after application of a 0.1% solution of dipivefrine. However, minor sporadic and transient burning or stinging sensations can occur.

Organs and Systems

Cardiovascular

When the limits of tolerance are approached, there may be palpitation, extra beats, and a rise in blood pressure. In sensitive individuals or at high doses, ventricular fibrillation, subarachnoid hemorrhage, and even hemiplegia have been known to occur. Adrenaline can occasionally cause pulmonary edema (4,5). It is possible that in at least some of these cases the drug has been inadvertently injected intravenously.

Ventricular dysrhythmias have been reported in a case of adrenaline overdose (6).

- A 5-year-old boy was given subcutaneous adrenaline 1:1000 after a severe allergic reaction to a bee sting. Inadvertently, 10 times the correct dose was given. He developed extra beats and two brief runs of ventricular tachycardia, but recovered fully after about 20 minutes. Creatine kinase activity, both total and the MB fraction, was slightly raised in this patient (total 603 IU/l, MB fraction 161 IU/l; upper limits of the local reference range 243 and 15 IU/l), suggesting cardiac damage.

Life-threatening torsade de pointes has been observed when an epidural anesthetic was given using 20 ml of bupivacaine containing only 1:200 000 adrenaline (7).

When adrenaline 0.4 ml of a 1 mg/ml solution was inadvertently injected into the penile skin of a 12-hour-old neonate the skin blanched and the error was immediately understood (8). After repeated doses of phentolamine (total 0.65 mg) the skin regained its normal color. There were no sequelae.

Adrenaline is occasionally used as a hemostatic agent, with rare complications. However, they do occur, as noted in a report from Lyon (9).

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- A 64-year-old man with diabetes and hypertension bled from a site in the lower rectum. A local injection of adrenaline 0.2 mg successfully stopped the hemorrhage, but very soon after he became hypotensive, with rapid atrial fibrillation (ventricular rate not given), the first time he had experienced this. He reverted spontaneously to sinus rhythm within 24 hours.

The authors suggested that if this type of procedure is contemplated in elderly patients with cardiovascular disease an anesthetist should be present to monitor cardiovascular status; it may in any case be wiser to avoid adrenaline altogether in favor of other means of hemostasis.

A more unusual site of adrenaline injection has been described in a Canadian report (10).

- A 79-year-old woman developed pituitary apoplexy in an adenomatous gland and was being prepared for *trans*-sphenoidal hypophysectomy. Topical adrenaline (1:1000) was applied to both nostrils and then 1.5 ml of 1% lidocaine containing 1:100 000 adrenaline was injected into the nasal mucosa. The blood pressure immediately rose from 100/50 to 230/148 mmHg and the pulse rate from 48 to 140/minute. Although she was treated immediately with esmolol and intravenous glyceryl trinitrate, resulting in normalization of her blood pressure, subsequent investigations showed that she had had a painless myocardial infarction. She made a full recovery after pituitary surgery.

The authors suggested that if adrenaline is to be used in such cases, even lower concentrations might be advisable. This is reasonable, although one also wonders in this case whether her blood pressure may have been lowered too rapidly.

Sensory systems

Melanic conjunctivocorneal pigmentation has been reported with an incidence of 30% with adrenaline (11,12).

Cystoid macular edema has been reported to occur in 2.8% of the patients receiving adrenaline especially in aphakic or pseudophakic eyes (13). Cystoid macular edema has also been seen after the use of dipivefrine, but in the classic case described in 1982 pretreatment with timolol maleate may have predisposed the eye to this complication (14).

Central retinal vein thrombosis occurred in a 75-year-old man 20 minutes after the ipsilateral insertion of a 1% adrenaline-soaked cotton wool stick (15). Unfortunately, his visual acuity did not improve.

Metabolism

Lactic acidosis has been observed, persisting for some hours after deliberate intravenous misuse of 20 mg adrenaline by an addict (SED-12, 308). Six of 19 patients who were given adrenaline for hypotension after undergoing cardiopulmonary bypass developed lactic acidosis, though the ultimate outcome was favorable (SEDA-22, 154).

Mouth and teeth

Facial swelling due to drug-induced sialadenosis was repeatedly observed in one patient who controlled her asthma symptoms with an adrenaline inhaler (SEDA-14, 119).

Susceptibility Factors

Cardiovascular

In susceptible individuals, an attack of angina pectoris can be precipitated by adrenaline, and in any form of cardiac disease caution is indicated; at one time an attempt was made to use high doses of adrenaline for the early treatment of ventricular fibrillation, but its pharmacological effects swing the balance against its use, the immediate survival rate actually being reduced.

Hyperthyroidism

Patients with hyperthyroidism are unduly sensitive to the effects of adrenaline (SEDA-14, 179).

Drug Administration

Drug administration route

While the absorption of adrenaline from a subcutaneous injection in healthy subjects is variable (and sometimes very slow) absorption from an inhaled dose is rapid and reliable (16). The main adverse effect from the inhaled route, for example in a dose of 3–4.5 mg, is gastrointestinal discomfort, with nausea and sometimes vomiting; this seems to be a local effect since it does not occur with injections. However, both forms produce mild tremor and palpitation in some individuals.

Since adrenaline is so short acting, the metabolic and other adrenergic effects which it can produce are unlikely to be elicited unless a depot formulation is used; in the latter event, hyperglycemia may occur.

Drug–Drug Interactions

Beta-adrenoceptor antagonists

Small quantities of adrenaline, such as are present as an additive in local anesthetic formulations, can be dangerously potentiated by beta-adrenoceptor blockers; propranolol should be discontinued at least 3 days in advance of administering such products for local anesthesia. A combined infusion of adrenaline and propranolol has been used for diagnosing insulin resistance, but it can evoke cardiac dysrhythmias, even in patients without signs of coronary disease (17).

Halothane

Halothane and some other anesthetics sensitize patients to the risk of adrenaline-induced ventricular dysrhythmias and acute pulmonary edema, especially if hypoxia is present (18,19).

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Hyaluronidase

Adrenaline is physically incompatible with hyaluronidase (20).

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors have been said to potentiate the hypertensive effects of adrenaline, but there is no good clinical evidence of such an interaction (21). Nevertheless, care should be taken when contemplating the use of adrenaline in patients taking a monoamine oxidase inhibitor.

Sodium novobiocin

Adrenaline is physically incompatible with sodium novobiocin (20).

Sodium warfarin

Adrenaline is physically incompatible with sodium warfarin (20).

Tricyclic antidepressants

Tricyclic antidepressants inhibit the uptake of catecholamines, such as adrenaline, into sympathetic neurons and can enhance the cardiovascular effects, so that even the small amounts of adrenaline present as additives in some local anesthetics can have a marked effect on the cardiovascular system.

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Adrenoceptor agonists

See also Individual agents

General Information

Adrenoceptor agonists evoke physiological responses similar to those produced by stimulation of adrenergic nerves or the physiological release of adrenaline (see Table 1). For many of these responses it is currently possible to conclude that only an alpha-adrenoceptor or a beta-adrenoceptor is involved, and in some cases one can distinguish a $beta_1$ from a $beta_2$ response. In some cases, however, the distinction is not clear: most adrenoceptor agonists, however specific to a particular receptor type they are claimed to be, will for example on occasion stimulate central nervous functions, resulting in nervousness, insomnia, tremors, dizziness, or headache. In some organ systems both alpha-adrenoceptors and beta-adrenoceptors are present; thus, the nature of the response produced will depend either on the concentrations achieved or on other factors; whether, for example, the uterus contracts or relaxes in response to an adrenergic drug depends in part on the hormonal balance in the system at that moment.

Alpha-adrenoceptor agonists, such as clonidine, are little used nowadays in the treatment of hypertension or migraine. Clonidine is used epidurally, in combination with opioids, neostigmine, and anesthetic and analgesic agents, to produce segmental analgesia, particularly for postoperative relief of pain after obstetrical and surgical

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Table 1 Adrenoceptors and the effects of agonists

Organs and systems	Receptor	Response to an agonist
Cardiovascular		
Heart		
Sinoatrial node	β_1	Increased heart rate
Atria	β_1	Increased contractility and conduction velocity
Atrioventricular node and conduction system	β_1	Increased conduction velocity and automaticity
Ventricles	β_1	Increased contractility, conduction velocity, automaticity, rate of idiopathic pacemakers
Blood vessels		
Coronary	α, β_2	Constriction
Skin, mucosa	α	Constriction
Skeletal muscle	α or β_2	Constriction or dilatation
Cerebral	α	Slight constriction
Pulmonary	α or β_2	Constriction or dilatation
Abdominal viscera	α or β_2	Constriction or dilatation
Salivary glands	α	Constriction
Respiratory		
Bronchial muscle	β_2	Relaxation
Bronchial glands	α_1, β_2	Decreased or increased secretion
Nervous system		
Cerebral function	Various	Stimulation
Eyes		
Radial muscle, iris	α	Contraction (mydriasis)
Ciliary muscle	β	Relaxation for far vision (slight)
Hematologic		
Spleen capsule	α	Contraction
Salivary glands	α_1	Potassium and water secretion
	β	Amylase secretion
Gastrointestinal		
Motility and tone	α_1, β_1, β_2	Decrease (usually)
Sphincters	α	Contraction (usually)
Secretion of various substances	Various	Inhibition
Liver		
Glycogenolysis and gluconeogenesis	α_1, β_2	Stimulation
Gallbladder		
Bile ducts	β_2	Relaxation
Urinary tract		
Ureter; tone, motility	β_2	Relaxation (usually)
Bladder; detrusor	β	Relaxation (usually)
Trigone, sphincter	α	Contraction
Renal vessels	α_1, β_1, β_2	Primary contraction
Skin		
Pilomotor muscles	α	Contraction
Sweat glands	α	Slight local secretion
Musculoskeletal		
Muscle glycogenolysis	β	Stimulation
Sexual function		
Uterus	α, β_2	Variable effect[a]
Male sex function	α_1	Ejaculation

[a] Response depends inter alia on hormonal status.

procedures. Apraclonidine is available for the short-term reduction of intraocular pressure.

The drugs that were developed some 40 years ago as general beta-adrenoceptor agonists have largely fallen into disuse with the development of more selective beta$_1$-adrenoceptor agonists (for use in cardiac failure) and beta$_2$-adrenoceptor agonists (for use in airways disease and threatened premature labor).

Beta$_3$-adrenoceptor agonists

Stimulation of beta-adrenoceptors on the cell surface of adipocytes promotes lipolysis and energy expenditure. These receptors are neither beta$_1$-adrenoceptors nor beta$_2$-adrenoceptors, and they have been termed atypical or beta$_3$-adrenoceptors. Some atypical agonists (BRL 26830 A, BRL 35135, CL 316243, and D 7114) have been developed and assessed for their ability to stimulate

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these receptors and hence to induce weight loss. The BRL compounds appear to exaggerate physiological tremor, presumably through an effect on $beta_2$-adrenoceptors; the two other compounds are said to be more selective.

Ajmaline and its derivatives

See also Antidysrhythmic drugs

General Information

Ajmaline and its derivatives, prajmalium bitartrate (rINN; *N*-propylajmaline), lorajmine (rINN; chloroacetylajmaline), detajmium bitartrate (rINN), and diethylaminohydroxypropylajmaline, are *Rauwolfia* alkaloids. Their use is restricted by serious adverse effects, such as neutropenia and cardiac dysrhythmias, which have been reviewed (1). Other adverse effects include dizziness, headache, and a sensation of warmth after intravenous injection.

Organs and Systems

Cardiovascular

Ajmaline occasionally causes cardiac dysrhythmias (SEDA-17, 219). Of 1995 patients who were given ajmaline 1 mg/kg intravenously during an electrophysiological study, 63 developed a supraventricular tachydysrhythmia (atrial flutter, fibrillation, or tachycardia), and seven an atrioventricular re-entrant tachycardia (2). Those most at risk were older patients, those with underlying cardiac disease, and those with a history of dysrhythmias or sinus node dysfunction.

Two cases of torsade de pointes have been reported in association with prolongation of the QT interval (3). Polymorphous ventricular tachycardia has been reported in three cases (4–6).

- A 13-year-old boy with Brugada syndrome (right bundle branch block with persistent ST segment elevation) was given an injection of ajmaline 1 mg/kg and developed greater ST segment elevation and more marked right bundle branch block morphology (7). This was followed by short runs of non-sustained polymorphic ventricular tachycardia, gradually increasing until monomorphic ventricular tachycardia occurred. The dysrhythmia eventually resolved without further treatment.

It is unwise to give antidysrhythmic drugs to patients with Brugada syndrome.

Nervous system

Neurological effects have occasionally been reported in patients taking ajmaline derivatives; they include confusion and cranial nerve palsies (8,9).

Hematologic

Neutropenia is a relatively common and important adverse effect of ajmaline (10). Of the three main mechanisms that cause neutropenia (immune, toxic, and autoimmune) two have been associated with ajmaline: immune and autoimmune neutropenia.

Liver

Ajmaline can cause hepatitis or cholestasis. Cholestasis has been reported in association with neutropenia (11) and with fever and eosinophilia (12). Although acute liver damage due to ajmaline is usually reversible, there has been a report of persistent jaundice due to long-lasting cholestasis (13).

Immunologic

Hypersensitivity to ajmaline is rare, but there has been a report of an immune interstitial nephritis in association with fever (14).

Drug Administration

Drug overdose

In overdosage ajmaline can cause heart block and dysrhythmias, hypotension, malaise, vertigo, respiratory depression, and coma (15). In one series of 38 cases there were nine deaths (24%) (16). Treatment of overdosage includes the intravenous administration of molar sodium lactate for dysrhythmias, conduction disturbances, and circulatory failure; a pacemaker may be required.

- After an overdose of detajmium bitartrate in a dose of 18 mg/kg, a 36-year-old woman developed ventricular flutter, which responded to treatment with lidocaine, defibrillation, glucagon, noradrenaline, and sodium chloride (17). Hypokalemia responded to intravenous potassium chloride.
- A 57-year-old man took ajmaline 1000 mg with suicidal intent (18). He was unconscious and hypotensive and had serious disturbances in cardiac conduction. His serum and urine ajmaline concentrations were high. Although only 4% of the ingested dose was excreted following forced diuresis, all evidence of toxicity disappeared within 21 hours.

Various types of cardiac dysrhythmia have previously been reported after overdosage of ajmaline (SEDA-2, 162).

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Alatrofloxacin and trovafloxacin

See also Fluoroquinolones

General Information

Alatrofloxacin is a fluoronaphthyridone that is hydrolysed to the active moiety, trovafloxacin, after intravenous administration. This fourth-generation broad-spectrum fluoroquinolone has activity against Gram-positive, Gram-negative, anerobic, and atypical respiratory pathogens. Because it has significant hepatotoxicity, the list of appropriate indications for trovafloxacin has been restricted.

In a multicenter, double-blind, randomized comparison of trovafloxacin 200 mg and clarithromycin 500 mg bd in 176 subjects with acute exacerbations of chronic bronchitis, the most common adverse effects of trovafloxacin were nausea (5%), dizziness (5%), vomiting (3%), and constipation (3%) (1). Because trovafloxacin is hepatotoxic, the list of appropriate indications has been limited to patients who have at least one of several specified infections, such as nosocomial pneumonia or complicated intra-abdominal infections that are serious and life- or limb-threatening in the physician's judgement.

Trovafloxacin may down-regulate cytokine mRNA transcription in human peripheral blood mononuclear cells stimulated with lipopolysaccharide or lipoteichoic acid (2). Likewise, trovafloxacin inhibited *Salmonella typhimurium*-induced production of TNFα, HIV-1 replication, and reactivation of latent HIV-1 in promonocytic U1 cells at concentrations comparable to the plasma and tissue concentrations achieved by therapeutic dosages (3).

Organs and Systems

Cardiovascular

Phlebitis can occur during parenteral administration of trovafloxacin. High concentrations of trovafloxacin (2 mg/ml) significantly reduced intracellular ATP content in cultured endothelial cells and reduced concentrations of ADP, GTP, and GDP (4). These in vitro data suggest that high doses of trovafloxacin are not compatible with maintenance of endothelial cell function and may explain the occurrence of phlebitis. Commercial formulations should be diluted and given into large veins.

Nervous system

Alatrofloxacin can cause seizures (5).

- A 37-year-old Asian man received several antibiotics (including intravenous ceftazidime, gentamicin, meropenem, metronidazole, and vancomycin) postoperatively. After 3 weeks he was given alatrofloxacin 75 mg in 25 ml of dextrose 5% (1.875 mg/ml) and developed generalized clonus. On rechallenge, infusing at half the initial rate, the seizure recurred. A CT scan of the brain was normal.

Seizures are rare but have occurred during treatment with other fluoroquinolones. This is the first report of a case of seizures associated with slow infusion of alatrofloxacin. However, as of 21 June 2000, the manufacturers had received 53 reports of seizures through worldwide postmarketing surveillance. In rat hippocampus slices, trovafloxacin had significant convulsive potential; the underlying mechanism is hitherto incompletely understood.

Trovafloxacin has been associated with diffuse weakness due to a demyelinating polyneuropathy in a patient without an underlying neurological disorder (6).

Hematologic

Alatrofloxacin has been associated with severe leukopenia (7).

- A 79-year-old white man was treated with intravenous alatrofloxacin mesylate 200 mg bd for 5 days. His

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leukocyte count fell from 10.9 × 10^9/l to 2.2 × 10^9/l; the hemoglobin did not change. Alatrofloxacin was withdrawn, and 3 days later the leukocyte count had increased to 11.5 × 10^9/l.

The mechanism of trovafloxacin-induced leukopenia is unknown. Nevertheless, since quinolones exert their antibacterial effect by inhibiting bacterial DNA gyrase and since similar topoisomerases are involved in the organization and function of mammalian DNA, it is possible that trovafloxacin acts by modulating bone marrow stem-cell DNA production.

Alatrofloxacin has been associated with severe thrombocytopenia (8).

- A 54-year-old woman was given alatrofloxacin 300 mg intravenously qds and on day 4 developed epistaxis. Her platelet count was 7 × 10^9/l, with normal hemoglobin and white blood cell counts. Direct antiglobulin testing showed coating of erythrocytes with polyspecific immunoproteins, and platelet-associated antibody testing was positive for IgM and IgG antibodies. Alatrofloxacin was withdrawn and azithromycin was given instead. She was given methylprednisolone 125 mg intravenously bd and the platelet count fell to 2 × 10^9/l and then rose, reaching 60 × 10^9/l on day 8.

During clinical trials, thrombocytopenia occurred in under 1% of more than 7000 patients who received alatrofloxacin or trovafloxacin.

Liver

More than 100 cases of hepatotoxicity associated with trovafloxacin have been reported to the FDA.

- A 19-year-old woman developed severe acute hepatitis and peripheral eosinophilia during oral trovafloxacin therapy for recurrent sinusitis (9). Liver biopsy showed extensive centrilobular hepatocyte necrosis, probably causing veno-occlusive disease. Clinical and laboratory abnormalities resolved completely after prolonged treatment with steroids.
- A 66-year-old man had taken trovafloxacin 100 mg/day for 4 weeks for refractory chronic sinusitis (10). For several years he had also taken allopurinol, doxepin, hydrochlorothiazide, losartan, metoprolol, and nabumetone. He developed nausea, vomiting, malaise, and abdominal distension. His white cell count was 8000 × 10^9/l with 16% eosinophils; his serum aspartate transaminase was 537 IU/l, alanine transaminase 841 IU/l, direct bilirubin 17 μmol/l; total bilirubin 27 μmol/l, alkaline phosphatase 111 IU/l; blood urea nitrogen 5 μmol/l; and creatinine 190 μmol/l. Tests for hepatitis A, B, and C were negative. A biopsy of the liver showed centrilobular and focal periportal necrosis and eosinophilic infiltration; the sinusoids were dilated and contained lymphocytes and eosinophils; many hepatocytes were undergoing mitosis. After withdrawal of trovafloxacin and treatment with prednisone, his hepatic and renal function returned to normal, and the eosinophilia gradually resolved.

Skin

The photosensitizing potential of trovafloxacin 200 mg od has been compared with that of ciprofloxacin 500 mg bd, lomefloxacin 400 mg od, and placebo in 48 healthy men (aged 19–45 years) (11). Trovafloxacin had significantly less photosensitizing potential than either ciprofloxacin or lomefloxacin. Photosensitivity seemed to be induced only by wavelengths in the UVA region, was maximal at 24 hours, and had a short-term effect.

Musculoskeletal

Trovafloxacin inhibited growth and extracellular matrix mineralization in MC3T3-E1 osteoblast-like cell cultures (12). The IC_{50} was 0.5 μg/ml, which is below clinically achievable serum concentrations. The authors suggested that the clinical relevance of this observation to bone healing in orthopedic patients should be evaluated.

Second-Generation Effects

Teratogenicity

In an ex vivo study, trovafloxacin crossed the human placenta by simple diffusion and neither accumulated in the media nor bound to tissues or accumulated in the placenta (13). This implies that it should have no effects on the fetus if given during pregnancy.

Susceptibility Factors

Age

The pharmacokinetics of a single intravenous dose of alatrofloxacin have been determined in six infants aged 3–12 months and in 14 children aged 2–12 years (14). The peak trovafloxacin concentration at the end of the infusion was 4.3 μg/ml; the volume of distribution at steady state was 1.6 l/kg, clearance 2.5 ml/min/kg, and the half-life 9.8 hours, with no age-related differences. Less than 5% of the administered dose was excreted in the urine over 24 hours.

Other features of the patient

The pharmacokinetics of trovafloxacin after the administration of alatrofloxacin were not substantially altered in seven critically ill patients (three men, four women) with APACHE II scores of 27 (range 15–32) and normal or mildly impaired hepatic function (15).

Monitoring Therapy

In 17 patients aged over 18 years with severe acute community-acquired pneumonia trovafloxacin concentrations were persistently high in the sputum, bronchial secretions, bronchoalveolar lavage fluid, and epithelial lining fluid, with no significant difference between these compartments (16). The authors proposed that measurement of sputum concentrations could be used to monitor the outcome of treatment.

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Albendazole

See also Benzimidazoles

General Information

Albendazole, a benzimidazole derivative closely related to mebendazole (qv), is used in the treatment of helminth infections, such as gastrointestinal roundworms, hydatid disease, neurocysticercosis, larva migrans cutanea, and strongyloidiasis (1). Provided that an adequate concentration is attained within the cyst, it is scolicidal. In high doses given for prolonged periods or cyclically, it is effective in echinococcosis, in which it is given in a dosage of 10 mg/kg/day for 4 weeks, repeated in six cycles with 2-week rest periods between each cycle, although even with this high dose only about one-third of patients enjoy a complete cure, some 70% having a partial response. Albendazole is also active against *Pneumocystis jiroveci*, and is effective in prophylaxis and treatment in immunosuppressed mice (2). In hydatid disease a combination of albendazole and praziquantel is effective when either agent has failed when used alone (SED-12, 707) (3).

Observational studies

Ankylostomiasis

Albendazole has been used in the treatment of human hookworm and trichuriasis. In a mass-treatment report from Western Australia 295 individuals in a remote rural area were treated with albendazole 400 mg/day for 5 days because of possible *Giardia lamblia* and hookworm infections (4). The 37% prevalence of *Giardia* fell to 12% between days 6 and 9, but rose again to 28% between days 18 and 30. The effect on hookworms (*Ankylostoma duodenale*) was more pronounced and more sustained with a reduction of the pretreatment prevalence of hookworm infections from 76% before treatment to 0% after 3–4 weeks. The tolerability of the drug was judged to be excellent by 89%, good by 1%, and moderately good by 1%, while 9% gave no response. Adverse effects were reported by five individuals and consisted of mild abdominal pain ($n = 2$), mild or moderate diarrhea ($n = 2$), moderate fever ($n = 1$), and weakness ($n = 1$).

Ascariasis

The efficacy of 2 years of mass chemotherapy against ascariasis has been evaluated in Iran (5). A single dose of albendazole 400 mg was given at 3-month intervals for 2 years to every person, except children under 2 years of age and pregnant women. After 2 years of treatment the prevalences, based on 2667 post-treatment samples, had fallen (Table 1). There were no adverse effects of mass treatment with albendazole.

Echinococcosis

Hydatid disease is a common zoonosis caused by the larval cysts of *Echinococcus granulosus*. Hydatid cysts most commonly form in the liver, but can occur in any organ. The management and operative complications in 70 patients with hydatid disease aged 10–78 years have been studied retrospectively to assess the impact of albendazole and praziquantel compared with surgery (6). In all,

Table 1 Changes in prevalences of helminthic infections in patients treated with albendazole

Helminth	Number (%) of positive tests before treatment ($n = 3098$)	Number (%) of positive tests after treatment ($n = 2667$)
Ascaris lumbricoides	1198 (39%)	196 (7.4%)
Trichuris trichiura	22 (0.7%)	5 (0.2%)
Hymenolepis nana	63 (2%)	49 (1.8%)

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39 patients received albendazole and praziquantel in combination and 19 received albendazole alone; none was treated with praziquantel alone. The combined use of albendazole and praziquantel preoperatively significantly reduced the number of cysts that contained viable protoscolices. During the 12-year follow-up period an initial 3 months of drug treatment (albendazole throughout and praziquantel for 2 weeks), re-assessment, followed by either surgery or continuation with chemotherapy was found to be a rational treatment algorithm. In 11 patients albendazole, given for a median of 3 months at a dose of 400 mg bd, had adverse effects: five patients developed nausea and six had abnormal liver function tests. Therapy was withdrawn in two patients owing to altered liver function.

The efficacy of albendazole emulsion has been studied in 212 patients with hydatid disease of the liver, aged 4–82 years (7). Two regimens of albendazole were given for a variable period (3 months to more than 1 year); 67 adults received albendazole 10 mg/kg/day and 145 adults received 12.5 mg/kg/day. The overall cure rate was 75%. In the follow-up study the recurrence rate was 10%. The highest cure rate was observed in those who received albendazole 12.5 mg/kg/day for 9 months. At the start of therapy about 15% of the patients had mild pruritus, rash, and transient gastric pain, which resolved without specific therapy. Two patients had alopecia. There were frequent rises in serum transaminase activities in both groups but not to above 30–50 IU/l, except in six patients, who had values above 200 IU/l. In two patients albendazole was withdrawn because of vomiting. In one patient who took 12.5 mg/kg/day severe adverse effects, such as anorexia, jaundice, anemia, edema, and hypoproteinemia, developed, necessitating withdrawal. Reintroduction of albendazole 10 mg/kg/day was uneventful.

The use of albendazole and mebendazole in patients with hydatidosis has been evaluated in 448 patients with *E. granulosis* hydatid cysts who received continuous treatment with albendazole 10–12 mg/kg/day for 3–6 months daily orally in a total dose of (323 patients) twice or mebendazole 50 mg/kg/day (8). At the end of treatment, 82% of the cysts treated with albendazole and 56% of the cysts treated with mebendazole showed degenerative changes. During long-term follow-up 25% of these cysts showed relapse, which took place within 2 years in 78% of cases. Further treatment with albendazole induced degenerative changes in over 90% of the relapsed cysts, without induction of more frequent or more severe adverse effects, as observed during the first treatment period. Adverse effects during the first treatment period consisted of raised transaminases with albendazole (67 of 323 patients) and mebendazole (16 of 125 patients), and abdominal pain in 12 and 11% respectively. With both drugs, occasional patients experienced headache, abdominal distension, vertigo, urticaria, jaundice, thrombocytopenia, fever, or dyspepsia, but most of these are known manifestations of *Echinococcus* infection. Six of 323 patients taking albendazole withdrew because of adverse effects compared with eight of 125 patients taking mebendazole. It appears that albendazole is more effective than mebendazole in the treatment of hydatid cysts caused by *E. granulosis* and that both the intensity and frequency of the usually mild adverse effects are comparable.

Filariasis

Treatment of patients with high *Loa loa* microfilaraemia is sometimes complicated by an encephalopathy, suggested to be related to a rapid killing of large number of *L. loa* microfilariae. If the *L. loa* microfilarial count could be reduced more slowly, before ivermectin is distributed, ivermectin-related encephalopathy might be prevented. In 125 patients with *L. loa* microfilariasis the effect of albendazole (800 mg/day for three consecutive days) or multivitamin tablets on *L. loa* microfilarial load and the occurrence of encephalopathy were studied (9). *L. loa* microfilarial loads were followed for 9 months. There was no significant change in the overall microfilarial loads among those treated with albendazole, although the loads in patients with more than 8000 microfilariae/ml tended to fall more progressively during the first 3 months of follow-up. There were no cases of encephalopathy. The main adverse effects reported were itching (in eight patients taking albendazole and seven taking multivitamins), abdominal pain (two taking albendazole), and diarrhea (one taking albendazole, two taking multivitamins); overall analysis showed no significant difference in these events between the groups. Albendazole was associated with modest but significantly raised plasma transaminase activities.

Neurocysticercosis

In a report on the use of albendazole 15 mg/kg/day in two divided doses for 14 days in the treatment of persistent neurocysticercosis (10), adverse reactions were monitored in 43 patients with seizures and a solitary cysticercal cyst, who had not been treated before. In all patients CT scans confirmed the presence of a solitary cyst less than 2 cm in diameter. Antiepileptic treatment was continued. In seven patients dexamethasone 8 mg/day in four divided doses was given for the first 5–7 days after the start of treatment. Follow-up CT scans at 4–10 weeks after the start of treatment showed responses in 20 patients, with complete disappearance in seven patients and a reduction to 50% of the pretreatment size in the other 13. There were adverse effects in 15 patients, with a maximum on the fifth day after the start of treatment. Six patients had severe headaches, 11 had partial seizures, and 2 had epileptic seizures and severe postictal hemiparesis that persisted for a week or more. Because of these serious adverse effects treatment was discontinued in seven patients and dexamethasone was added in those patients who were not already taking it, although its use proved questionable. Adverse effects were seen in three of seven patients who took prophylactic steroid therapy and in 12 of 36 patients who did not.

Albendazole was effective in neurocysticercosis in an optimal dosage of 15 mg/kg/day divided in two doses every 12 hours for 8 days (11). It was generally well tolerated, although several patients had adverse reactions during the first few days after the start of treatment, consisting of headache, vomiting, and exacerbation of neurological symptoms caused by an inflammatory reaction to antigens from degenerating cysts, necessitating the concomitant use of glucocorticoids. In very large cysticerci, or cysticerci located in risky areas like the brainstem, these reactions may rarely be life-threatening.

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Protozoal infections

The efficacy of albendazole 800 mg bd for 14 days for persistent diarrhea due to cryptosporidiosis ($n = 10$), isosporiasis ($n = 54$), or microsporidiosis ($n = 23$) has been studied in 153 HIV-positive patients (12). Albendazole reduced the burden of protozoal infection and promoted mucosal recovery in 87 patients who had a complete clinical response. Two patients reported nausea and vomiting. One patient developed leukopenia (1.9×10^9/l) after treatment and four patients developed thrombocytopenia ($51–98 \times 10^9$/l).

Toxocariasis

The efficacy of albendazole plus prednisolone has been studied in five patients aged 11–72 years with ocular toxocariasis (13). All had uveitis and retinochoroidal granulomas. Their symptoms had persisted for a mean of 14 months (range 3 days to 24 months). The adults were treated with albendazole 800 mg bd for 2 weeks plus prednisolone starting at 1.5 mg/kg/day tapering over 3 months. The children were treated with 400 mg bd for 2 weeks plus prednisolone 1.0 mg/kg/day. All tolerated the therapy well without adverse effects. In particular, there were no significant hypersensitivity reactions to dying *Toxocara* larvae. The uveitis resolved in all cases and there were no relapses. After treatment, all the granulomas had disappeared, leaving heavily pigmented chorioretinal scars without loss of vision.

Comparative studies

The use of albendazole and mebendazole in patients with hydatidosis has been evaluated in 448 patients with *E. granulosis* hydatid cysts who received continuous treatment with albendazole 10–12 mg/kg/day for 3–6 months daily orally in a total dose of (323 patients) twice or mebendazole 50 mg/kg/day (8). At the end of treatment, 82% of the cysts treated with albendazole and 56% of the cysts treated with mebendazole showed degenerative changes. During long-term follow-up 25% of these cysts showed relapse, which took place within 2 years in 78% of cases. Further treatment with albendazole induced degenerative changes in over 90% of the relapsed cysts, without induction of more frequent or more severe adverse effects, as observed during the first treatment period. Adverse effects during the first treatment period consisted of raised transaminases with albendazole (67 of 323 patients) and mebendazole (16 of 125 patients), and abdominal pain in 12 and 11% respectively. Headache occurred in eight patients taking albendazole and three taking mebendazole, abdominal distension in seven and five patients, vertigo in five and one, urticaria in five and three, jaundice in one and one, thrombocytopenia in two and none, fever in three and none, dyspepsia in two and four, and tachycardia in two and none. Six of 323 patients taking albendazole withdrew because of adverse effects compared with eight of 125 patients taking mebendazole. It appears that albendazole is more effective than mebendazole in the treatment of hydatid cysts caused by *E. granulosis* and that both the intensity and frequency of the usually mild adverse effects are comparable.

In a randomized trial in Mexico (14) 622 children with *Trichuris* were randomized to either albendazole 400 mg/day for 3 days, one dose of albendazole 400 mg, or one dose of pyrantel 11 mg/kg. The aim was to study efficacy and the effects on growth. After three courses at 1 year the level of infection with *Trichuris* was reduced by 99% in the 3-day albendazole treatment group, by 87% in the single-dose albendazole treatment group, and by 67% in the pyrantel group. There were no significant differences in the increases in height, weight, or arm circumference, but contrary to expectations there was a lower increase in the thickness of the triceps skin fold in those given 3-day courses of albendazole. This was only found in the patients with lower pretreatment *Trichuris* stool egg counts. These findings suggest that although elimination of *Trichuris* may promote growth in children, albendazole in a dose of 1200 mg/kg every 4 months may have an independent negative effect on growth. In an accompanying commentary (15) it was concluded that the suggestion that relatively high doses of albendazole may affect growth deserves study, but that this possible effect must be weighed against the negative effect of prolonged helminthic infestation on children's health, growth, and cognitive function. However, it is unlikely that high-dose treatment will be standard in mass-treatment campaigns, and these results should not deter the use of single-dose albendazole in mass-treatment programs in high-risk populations.

In 110 children with ascariasis or trichuriasis the efficacy of a single dose of albendazole 400 mg has been compared with that of nitazoxanide 100 mg bd for 3 days in children aged 1–3 years and 200 mg bd for 3 days in children aged 4–11 years (16). Nitazoxanide cured 89 and 89% of the cases of ascariasis and trichuriasis respectively. Albendazole cured 91 and 58% of the cases of ascariasis and trichuriasis respectively. Abdominal pain ($n = 9$), nausea ($n = 1$), diarrhea ($n = 2$), and headache ($n = 1$) were reported as mild adverse effects in 105 patients who took nitazoxanide, and abdominal pain ($n = 1$), nausea ($n = 1$), and vomiting ($n = 1$) were reported as adverse effects in 54 patients who took albendazole. All the adverse events were mild and transient and drug withdrawal was not necessary.

Placebo-controlled studies

Albendazole has been used in the treatment and prophylaxis of microsporidiosis in patients with AIDS. In a small, double-blind, placebo-controlled trial from France (17) the efficacy and safety of treatment with albendazole was studied in four patients treated with albendazole 400 mg bd for 3 weeks and in four patients treated with placebo. Microsporidia were cleared in all patients given albendazole but in none of those given placebo. Afterwards all eight patients were again randomized to receive either maintenance treatment with albendazole 400 mg bd or no treatment for the next 12 months; none of the three patients taking maintenance treatment had a recurrence, while three of the five who took no maintenance therapy developed a recurrence. During the double-blind part of the trial there were no serious adverse effects in the patients who took albendazole, although two complained of headache, one of abdominal pain, one had raised transaminase activities, and one had

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thrombocytopenia. However, half the patients were also taking anti-HIV triple therapy, which makes it difficult to assess these abnormalities. The authors concluded that the adverse effects were not serious and did not hinder maintenance therapy. The tentative conclusion derived from these findings is that albendazole may be useful in the treatment of microsporidiosis, which in patients with AIDS often leads to debilitating chronic diarrhea and is difficult to treat.

Use in non-infective conditions

The efficacy of albendazole has been evaluated in a few patients with either hepatocellular carcinoma ($n = 1$) or colorectal cancer and hepatic metastases refractory to other forms of treatment ($n = 8$) (18). Apart from hematological and biochemical indices, the tumor markers carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) were measured to monitor treatment efficacy. One other patient with a neuroendocrine cancer and a mesothelioma was treated on a compassionate basis and only monitored for adverse effects. Albendazole was given orally in a dose of 10 mg/kg/day in two divided doses for 28 days. Albendazole reduced CEA in two patients and in the other five patients with measurable tumor markers, serum CEA or AFP was stabilized in three. In the seven patients who completed this pilot study, albendazole was well tolerated and there were no significant changes in any hematological, kidney, or liver function tests. However, three patients were withdrawn because of severe neutropenia, which resulted in the death of one. Neutropenia was more frequent than is usually experienced in the treatment of hydatid disease. The authors speculated that this may relate to reduced metabolism in patients with liver cancer or liver metastases, leading to the passage of unmetabolized drug into the circulation.

General adverse effects

As with other antihelminthic drugs, the general adverse effects of albendazole can reflect the destruction of the parasite rather than a direct action of the drug; pyrexia is likely to be seen, even in the absence of other problems. Albendazole was well tolerated in 30-day courses of 10–14 mg/kg/day separated by 2-week intervals.

Its adverse effects are similar to those of mebendazole and are possibly more common because of better and more reliable absorption.

The direct adverse effects of albendazole are few and usually minor, and consist of gastrointestinal upsets, dizziness, rash, and alopecia, which usually do not require drug withdrawal. Early pyrexia and neutropenia can also occur. Cyst rupture can also occur, as with mebendazole. About 15% of patients treated with albendazole at higher doses develop raised serum transaminases, necessitating careful monitoring and sometimes withdrawal of treatment after prolonged use. Careful monitoring of leukocyte and platelet counts is also indicated. The possibility of teratogenicity and embryotoxicity from animal studies suggests that the drug should be avoided in pregnancy.

Organs and Systems

Nervous system

Used in the treatment of neurocysticercosis, albendazole (like praziquantel) can cause a CSF syndrome characterized by fever, headaches, meningism, and exacerbation of some or many of the neurological signs of the disease; it is thought to be due to a local reaction to dying and dead larvae and can be attenuated by prednisone (SED-12, 707) (19,20).

Since neurocysticercosis is a neurological infection, it is not surprising that when treating it with any drug some of the neurological reactions to that drug (or to the death of the parasite) are particularly pronounced. For example, with a dose of 1.5 mg/kg continued for some time in cases of neurocysticercosis, a majority of patients initially develop intolerance in the form of headache, vomiting, fever, and occasionally diplopia and meningeal irritation (21). Even shorter and less intensive treatment has produced similar effects. However, all of these symptoms are probably due to the death of the parasite, and if therapy is continued they usually disappear within a few days. Nevertheless, they can be alarming and demand treatment. Data from large studies mention somnolence and even transient hemiparesis as incidental adverse effects.

Very rarely, in cases of neurocysticercosis, the reaction of the nervous system to the death of the parasite is extremely violent. In one case cerebral edema resulted in permanent neurological damage (22), while other patients have suffered hydrocephalus or acute intracranial hypertension requiring treatment, for example with glucocorticoids or mannitol (23).

Albendazole has sometimes aggravated extrapyramidal disorders or precipitated seizures in patients with prior epileptic symptoms. The risk of intracranial hypertension has led some to suggest that glucocorticoids should be given preventively when using albendazole in neurocysticercosis (24); however, dexamethasone can interact with albendazole, increasing its plasma concentrations (25), and it is not clear whether this might produce new problems.

Encephalopathy is an adverse event related to the treatment of *L. loa* with diethylcarbamazine or ivermectin, and it has also been related to albendazole (11).

- A 55-year-old woman from Cameroon took oral albendazole 200 mg bd for a symptomatic *L. loa* infection with microfilaremia of 152 microfilariae/ml and a *Mansonella perstans* infection of 133 microfilariae/ml. Three days after the start of therapy she developed an encephalopathy. Albendazole was withdrawn and she recovered without any specific treatment within the next 16 hours. On day 4, the *L. loa* microfilarial count was 29 microfilariae/ml.

The clinical presentation, the interval after starting treatment, the evolution of the episode, and the results of cerebral spinal fluid analysis and electroencephalography in this case were similar to those seen in cases of encephalopathy following treatment of *L. loa* with ivermectin or diethylcarbamazine. However, pretreatment filaremia was relatively low and *L. loa* microfilariae were not detectable in the cerebral spinal fluid. Thus, pre-existing conditions might increase the susceptibility to encephalopathy.

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Sensory systems

An allergic conjunctivitis was seen in cases of industrial occupational skin reactions to albendazole (26).

Hematologic

There have been various reports of bone marrow depression. In one study (27) two of 20 patients had a reversible drop in leukocyte count. Pancytopenia, reversible on withdrawal, has been documented in an elderly woman (28). Even with high doses neutropenia occurs in under 1% of cases. In the older literature an occasional hematological death was reported.

A megakaryocytic thrombocytopenia attributed to albendazole has been reported (29).

- A 25-year-old woman who had been taking albendazole 13 mg/kg/day for 5 months for hepatic and pulmonary echinococcosis developed fatigue, bleeding gums, and prolonged menstrual bleeding. She had ecchymoses and petechiae over her legs, marked thrombocytopenia (10×10^9/l), a mild iron deficiency anemia, and a normal leukocyte count. There was no antiplatelet immunoglobulin. A bone marrow aspiration showed absent megakaryocytes with normal granulocytes and mild erythroid hyperplasia. A cytogenetic study of the bone marrow showed normal karyotype and immunophenotype. The albendazole was withdrawn and oral iron given. At follow-up 2 months later all laboratory abnormalities had resolved.

Gastrointestinal

With a single oral dose of albendazole 400 mg, there is usually little more in the way of adverse effects than mild gastrointestinal disturbances (notably epigastric pain or dry mouth), occurring only in about 6% of patients in some large series; a few patients have abdominal pain. With higher doses, irritation of the central nervous system can lead to nausea and vomiting.

Diarrhea occurs in a few patients taking albendazole and is usually mild. However, a typical case of pseudomembranous colitis has been documented, although the patient also had AIDS and intestinal microsporidiosis and had taken a number of other drugs; the complication responded to vancomycin (30).

Liver

Even in single low doses a transient increase in transaminase activities has been repeatedly reported, generally affecting up to 13–20% of patients taking albendazole (SEDA-18, 315) (31). At the higher doses some evidence of moderate hepatitis has been claimed to be present in almost all patients, but in one series with high doses of albendazole or mebendazole for echinococcosis only 17% had a (generally slight) increase in serum transaminases, and a fair number of these had pre-existent liver disorders (32). Like various other adverse effects, the increase in transaminases may be attributable to the breakdown of liver cysts; it is almost always reversible and is usually not a reason for withdrawal; it does not become more marked during long-term treatment. A very occasional individual develops jaundice (33) or some other manifestation of hepatitis (34).

Skin

A generalized rash has sometimes been seen in patients taking albendazole (SEDA-15, 334), and skin complications (including urticaria and contact dermatitis) are a potential problem in employees in the pharmaceutical industry if they undergo heavy exposure to the drug (26).

- A 38-year-old woman with cough, eosinophilia, and pulmonary infiltrates due to visceral larva migrans from *Toxocara canis* infection took albendazole 600 mg for 8 weeks and developed slight transient skin eruptions (35).

Stevens–Johnson syndrome was reported in a man who took albendazole 400 mg/day for toxocariasis (36).

Hair

There are various well-documented reports of reversible alopecia in patients taking albendazole (SEDA-17, 358) (SEDA-22, 324), which in one study occurred in 2% of cases (SEDA-18, 315) and in another study in one case of 20 (SED-13, 913) (27).

- Severe alopecia has been described in an almost 3-year-old child who took albendazole 400 mg/d for 3 days; 2 months later alopecia developed and resolved within 1 month (37).
- When one woman took 400 mg bd for 10 months for hydatid disease, she lost much of her hair; no other likely cause could be identified, and her hair growth recovered when the drug was stopped (38).

Oddly, however, a fair proportion of patients when specifically questioned seem to remark that their hair growth has actually improved during treatment (SED-13, 913) (27).

Musculoskeletal

Myalgia and arthralgia can occur in patients taking albendazole (39). However, these symptoms are often features of the disease being treated.

Second-Generation Effects

Teratogenicity

It has been emphasized that albendazole is teratogenic in animals and should not be used in pregnancy (40).

Drug–Drug Interactions

Antiepileptic drugs

The pharmacological interactions of the antiepileptic drugs phenytoin, carbamazepine, and phenobarbital with albendazole have been studied in 32 adults with active intraparenchymatous neurocysticercosis (41):

- nine patients took phenytoin 3–4 mg/kg/day;
- nine patients took carbamazepine 10–20 mg/kg/day;
- five patients took phenobarbital 1.5–4.5 mg/kg/day;
- nine patients took no antiepileptic drugs.

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All were treated with albendazole 7.5 mg/kg every 12 hours on 8 consecutive days. Phenytoin, carbamazepine, and phenobarbital all induced the oxidative metabolism of albendazole to a similar extent in a non-enantioselective manner. In consequence, there was a significant reduction in the plasma concentration of the active metabolite of albendazole, albendazole sulfoxide.

Cimetidine

The poor intestinal absorption of albendazole, which may be enhanced by a fatty meal, contributes to difficulties in predicting its therapeutic response in echinococcosis. The effect of cimetidine co-administration on the systemic availability of albendazole has been studied in six healthy men (42). After an overnight fast, a single oral dose of albendazole (10 mg/kg) was administered on an empty stomach with water, a fatty meal, grapefruit juice, or grapefruit juice plus cimetidine. The systemic availability of albendazole was reduced by cimetidine. There were no adverse events. These results are consistent with presystemic metabolism of albendazole by CYP3A4.

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Albumin

General Information

Adverse reactions to human serum albumin are uncommon and usually mild, such as itching and urticaria. Serious reactions are rare. A patient who has reacted violently to albumin on one occasion may tolerate it well on another after being given an antihistamine such as diphenhydramine (1). Aggregates present in protein preparations may be the cause of some reactions. Another postulated cause may be the presence of antibodies against genetic variants of human albumin (2). Hypotensive reactions due to the presence of a prekallikrein activator in some batches of formulations can occur.

Albumin has been used to prevent the ovarian hyperstimulation syndrome (OHSS) associated with ovulation stimulation. In 98 women albumin had no positive effect on OHSS (3). Because of adverse effects, such as exacerbation of ascites in OHSS, nausea, vomiting, febrile reactions, allergic reactions, anaphylaxis, and the risk of pathogen transmission, albumin should not be used to prevent OHSS.

Adverse events during plasma exchanges in 28 adults with Guillain–Barré syndrome have been described in a study of 28 French and Swiss intensive care units (4). The study was based on 220 patients allocated either to plasma exchange or not. A total of 105 patients underwent 390 plasma exchanges (55 received albumin in 208 sessions as replacement fluid and 50 received fresh plasma in 182 sessions). Altogether, 253 adverse incidents were recorded, and in 15 patients plasma exchange had to be discontinued because of severe intolerance, which included bradycardia ($n = 3$), intercurrent complications (mainly infections), and technical difficulties. Fresh frozen plasma was associated with significantly more adverse incidents than albumin. The occurrence of adverse events was related to the preplasma exchange hemoglobin. Age, sex, previous history, neurological severity, and the need for mechanical ventilation did not modify the risk of adverse effects. The possibility that some of the events described in this series were attributable to the underlying disease rather than to the plasma exchange was not ruled out.

Organs and Systems

Cardiovascular

Albumin infusions can increase capillary permeability (5) and albumin infusion during resuscitation can result in hypervolemia, due to overfilling of the circulation (6).

It has been postulated that cardiac pump function can be reduced by binding of free calcium to albumin (6).

Metabolism

Acute normovolemic hemodilution to a hematocrit of 22% was performed in a prospective randomized study in 20 patients undergoing gynecological surgery (7). In one group 35% of the blood volume was replaced by 5% albumin while the other group received 6% hydroxyethyl starch solutions containing chloride concentrations of 150 and 15 mmol/l. Neither solution contained bicarbonate or citrate. After acute normovolemic hemodilution the blood volume remained constant in both groups. The plasma albumin concentration fell after hemodilution with hydroxyethyl starch and increased after hemodilution with albumin. There was a slight metabolic acidosis with hyperchloremia and a concomitant fall in anion gap in both groups. The acidosis, which was attributed to hyperchloremia and dilution of bicarbonate in the extracellular volume, was considered to be of no clinical relevance. The authors proposed that acidosis during acute normovolemic hemodilution can be avoided when the composition of electrolytes in colloid solutions is more physiological, as in lactate-buffered solutions.

Hematologic

Albumin can inhibit platelet aggregation (6). In addition, coagulation defects can result from dilution after albumin administration (6).

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Liver

Intravenous albumin formulations contain a significant amount of ammonium, with concentrations up to 800 μmol/l (8). The concentration of ammonium seems to be batch dependent and related to storage time, the highest concentration being in the oldest formulations. Ammonium is probably liberated from protein and/or amino acids during storage, enhanced in the presence of oxygen. Although this might potentially contribute to deterioration of hepatic encephalopathy in patients receiving this treatment, that was not shown in this small study.

Immunologic

Immunological reactions to human serum albumin tend to be non-IgE-mediated anaphylactic reactions (0.011% of cases treated), about a third of which are life-threatening (9). A case in which the mechanism seemed to be IgE-mediated anaphylaxis against native albumin has been reported (10).

A meta-analysis of 193 albumin-treated women versus 185 controls showed a significant reduction of severe OHSS after administration of human albumin; two cases of urticaria and one case of an anaphylactic reaction were reported (11).

Death

In July 1998, The Cochrane Injuries Group Albumin Reviewers published a meta-analysis comparing the use of albumin with the use of crystalloids or no treatment in critically ill patients (12). The review was based on 30 randomized, controlled studies, involving a total of 1419 patients with hypovolemia due to trauma, surgery, burns, or hypoalbuminemia. There was excess mortality in the albumin group of about 6%, and the authors concluded that albumin should not be used outside rigorously conducted randomized controlled trials. The review elicited numerous mostly critical comments. For example, it was commented that a meta-analysis is not exact and that in this specific studythe study had conflated three separate indications that were not comparable (5).

An Expert Working Party of the Committee on Safety of Medicines was set up to examine these findings and to advise on any necessary regulatory action. The Working Party concluded that there is insufficient evidence of harm to warrant withdrawal of albumin products from the market and that the effect of albumin on mortality can only be discovered by conducting large, purpose-designed, randomized, controlled trials (13). It was recommended that a number of changes be made to the product information for human albumin. Specifically, the Expert Working Party recommended that the indication for human albumin solutions should be focused on the use of albumin to replace lost fluids, rather than the underlying illness that resulted in hypovolemia, and that albumin deficiency in itself was not an appropriate indication. The product information should contain warnings about the risks of hypervolemia and cardiovascular overload and emphasize that hemodynamic monitoring in patients who receive albumin should be undertaken to avoid these complications. A warning that special care should be taken when administering albumin in pathological states that affect capillary integrity should also be included.

However, the validity of these findings has been questioned, because some papers chosen for meta-analysis by the Cochrane group were suggested to have been incorrectly included (14,15). The results obtained from the meta-analysis have also been challenged by another meta-analysis of albumin administration in critically ill patients, which showed no increased risk in mortality (16). This illustrates the need for high-quality, randomized, controlled trials to generate definitive evidence.

Second-Generation Effects

Pregnancy

Hypovolemic shock due to acute blood loss during delivery is one of the major causes of maternal mortality. It has been suggested that albumin may increase the risk of death, and crystalloids have been suggested to be the volume expanders of choice (17).

Drug Administration

Drug contamination

Aluminium

Contamination of albumin solutions with aluminium and consequent toxic effects have been described (18). Analysis of albumin from 20 suppliers showed aluminium contents varying from 1.03 to 1301 μmol/l depending on the batch and the manufacturer (19). Aluminium overloading is especially likely to occur in patients with impaired renal function who receive large volumes of albumin, leading to osteodystrophy and encephalopathy (20).

The source of contamination is the fractionation apparatus and can be located to containers, filters, and final product containers. The increase in aluminium content over the shelf-life period is due to the fact that the glass vial releases aluminium ions. This process is catalysed by the residual citrate content of albumin formulations and depends on the storage temperature as well as on the relation of the inner glass surface to the amount of liquid. For 10 ml bottles, stability of the aluminium content below 200 ng/ml cannot be guaranteed for the shelf life, irrespective of storage conditions.

In 50 ml and 100 ml bottles stored at temperatures below 8°C, the increase in aluminium content is sufficiently slowed down, so that it does not rise beyond 200 ng/ml within the 3-year shelf life. However, at storage temperatures exceeding 8°C, the aluminium content can increase beyond 200 ng/ml. According to stability studies, this threshold value is not passed before 12 months of storage at these higher temperatures.

An Austrian manufacturer of human albumin 20 and 25% voluntarily recalled the products because the pharmacopoeial specification for aluminium (200 ng/ml or less) for treatment of premature infants and dialysis patients cannot be guaranteed over the whole shelf life of 3 years when stored at temperatures above 8°C (21).

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The Paul Ehrlich Institut of Germany recalled certain batches of human albumin products (Human Albumin 20%, Human Albumin 20% Immuno, Human Albumin Immuno 20%, Human Albumin 25% Immuno), including batches that had exceeded 12 months of shelf life (22). This action was taken after quality assurance tests had shown that the aluminium content of these batches had exceeded the maximum acceptable concentration of 200 ng/ml.

Infections

The transmission of viral infections via albumin can be eliminated through pasteurization, and albumin treated in this way has an unblemished safety record in this regard, although there is little information on the safety of albumin with respect to hepatitis A and parvovirus (5). The production process excludes transmission of viruses such as hepatitis B and C and HIV (6). There have been no cases of HIV transmission attributed to this type of product, although many batches are known in retrospect to have been derived from HIV-contaminated pools (23).

Drug–Drug Interactions

ACE inhibitors

In a child with chronic renal insufficiency perioperative hypotension occurred after plasma volume expansion using 4% albumin (24). The fall in blood pressure was attributed to the combination of a low concentration of prekallikrein-activating factor in albumin and the use of an angiotensin-converting enzyme (ACE) inhibitor. When ACE is inhibited, the half-life of bradykinin is significantly prolonged and the concomitant administration of prekallikrein activator is likely to cause significant prolonged hypotension. To prevent this, the authors suggested withdrawing ACE inhibitors 24 hours before surgery or alternatively avoiding albumin in patients taking ACE inhibitors.

Furosemide

In children with the nephrotic syndrome, albumin in combination with furosemide carries a risk of thrombotic complications. In 12 children although antithrombin and alpha-2 macroglobulin fell, which is in accordance with a thrombotic tendency, there were no thrombotic complications (25). Furthermore, there was a fall in fibrinogen concentration, which is not consistent with a thrombotic tendency.

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Alclofenac

See also Non-steroidal anti-inflammatory drugs

General Information

While the pattern of alclofenac toxicity resembles that of other NSAIDs, the frequency of adverse effects differs widely. Allergic reactions have been reported more frequently and skin rashes have been particularly common. Hypersensitivity reactions, including anaphylactic shock, severe generalized vasculitis, hepatotoxicity, and nephrotoxicity, have been observed. Alclofenac has therefore been withdrawn in several countries (1). Blood dyscrasias and neurological symptoms are rare.

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Alcuronium

See also Neuromuscular blocking drugs

General Information

Alcuronium is a synthetic derivative of toxiferine, an alkaloid of calabash curare, and is a non-depolarizing relaxant with properties and adverse effects similar to those of D-tubocurarine. It is about twice as potent as D-tubocurarine, 0.15–0.25 mg/kg usually being adequate for abdominal relaxation, and has a similar onset time and a slightly shorter duration of action. It is bound to albumin (40%), and requirements for alcuronium are less if the plasma albumin levels are low, as may occur in hepatic disease.

Like D-tubocurarine, alcuronium does not undergo biotransformation. Excretion occurs mainly in the urine (80–85%), but, as with D-tubocurarine, some is also excreted in the bile (15–20%) (1). Persistent relaxation has been reported in renal insufficiency (2) and the drug is relatively contraindicated in this condition.

Organs and Systems

Cardiovascular

Tachycardia, hypotension, and a fall in total peripheral resistance all occur to an extent similar to that seen with D-tubocurarine, according to most studies (3–6). Others have reported that these effects are short-lived (7). Doses of 0.2 mg/kg or more may be associated with the more extreme cardiovascular effects. Blockade of cardiac muscarinic receptors (8), histamine release, and, possibly, some ganglionic blockade (although it has a very low ganglion-blocking activity in animals) (8) may all play a role in the production of the cardiovascular effects of alcuronium.

Nervous system

Two patients in intensive care treated with infusions of large amounts of alcuronium developed fixed dilated pupils. Within 6–24 hours after stopping the infusion the pupils became normally reactive again (9).

This is a very important and dangerous adverse effect, since the presence of fixed dilated pupils may lead to the mistaken diagnosis of brain death in coma patients if other neurological diagnostic procedures are not carried out.

Immunologic

Histamine release and anaphylactoid reactions occur with alcuronium (10–12). The precise incidence is not clear. Erythema is said to occur much less frequently than after D-tubocurarine (3). A retrospective study in Australia (13) showed that 37% of serious anaphylactoid reactions reported there were associated with alcuronium; alcuronium, however, at that time accounted for almost 50% of the total muscle relaxant consumption in Australia, and if this is taken into account the likelihood of a serious reaction is less than with D-tubocurarine, as others have also concluded (14). Clinical features reported range from erythema to severe hypotension and tachycardia (15) and bronchospasm (16,17). In a large prospective surveillance study (SEDA-15, 125) (SED-12, 473) involving over 1400 patients given alcuronium (initial dose 0.25 + 0.09 mg/kg), there were adverse reactions in almost 18% of the patients, with moderate hypotension (20–50% fall) in 13%, severe hypotension in 0.8%, and bronchospasm in 0.1%.

Second-Generation Effects

Fetotoxicity

Placental transfer (SEDA-6, 130) (18), occurs and is increased if alcuronium is rapidly injected (19). No complications attributable to neuromuscular block were seen in the newborn.

Susceptibility Factors

Hepatic disease

In liver cancer in children, resistance to alcuronium has been reported (SEDA-13, 104) (20).

Other features of the patient

In patients with burns, dosage requirements are increased (21).

Drug–Drug Interactions

Penicillamine

Penicillamine-induced myasthenia gravis (SED-10, 415) was probably the cause of extremely prolonged apnea

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occurring in two patients given alcuronium (SEDA-12, 111) (22,23). Patients receiving penicillamine should be treated as if they had no myasthenia; if a muscle relaxant is required, they should be given a test dose (of about one-tenth the usual dose), with monitoring of the response, before a full dose is administered.

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Aldesleukin

General Information

Aldesleukin (interleukin-2, celmoleukin, proleukin, teceleukin) is produced by activated T lymphocytes and has pleiotropic immunological effects, including the proliferation of T lymphocytes. Non-glycosylated recombinant aldesleukin has been approved for the treatment of metastatic renal cell carcinoma (1) and is also being investigated in other malignant neoplasms. Low-dose aldesleukin is a relatively safe treatment of HIV infection (SEDA-20, 334).

The adverse effects of aldesleukin include fever, chills, malaise, skin rash, nausea, vomiting (often resistant to antiemetics), diarrhea, fluid retention, myalgia, insomnia, disorientation, life-threatening hypotension, and the capillary leak syndrome (which can be preceded by weight gain) (SEDA-15, 491) (2).

In early trials, aldesleukin was given with lymphokine-activated killer (LAK) cells or tumor-infiltrating lymphocytes. However, later data showed that the addition of LAK cells does not improve the therapeutic response in renal cell carcinoma and can produce more pulmonary toxicity and hypotension (1). Compared with aldesleukin or interferon alfa alone, the combination of aldesleukin plus interferon alfa produces a significantly longer event-free survival without effect on the overall survival, but induces substantial toxicity with severe and resistant hypotension (3). The optimal safe and effective dose and schedule of administration of aldesleukin is not yet well defined, and a variety of regimens have been tested, with doses of 600 000 units/kg by intermittent bolus intravenous infusion or 18 106 units/m^2 by continuous subcutaneous or intravenous infusion.

Considerable efforts have been made to limit the toxic effects of aldesleukin, which are dose- and schedule-dependent (4). Low-dose aldesleukin, continuous infusion, and/or subcutaneous administration are preferred by various investigators, because of their reluctance to use conventional high-dose or bolus dose administration. Such regimens were considered as effective and safe for outpatients (5,6).

A thorough analysis of 255 patients from seven phase II trials treated with the currently recommended high dose of aldesleukin for metastatic renal cell carcinoma has

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been presented (7). Although severe toxicity, generally attributable to the capillary leak syndrome, was found in most patients, the problems receded promptly after withdrawal of treatment. Deaths related to aldesleukin-induced toxicity were reported in 4% of patients, and were caused by myocardial infarction, respiratory failure, gastrointestinal toxicity, or sepsis.

Use in patients with HIV infection

The use, benefits, and adverse effects of aldesleukin in HIV-infected patients have been extensively reviewed (8). Aldesleukin significantly increased the $CD4^+$ cell count without an increase in viral load. However, many questions remain unanswered. In particular, it is still not known whether immunological improvements translate into clinical benefit. Regardless of how aldesleukin is administered—intravenously, subcutaneously, or as polyethylene glycol-modified (pegylated) aldesleukin—adverse effects are generally not treatment-limiting. As the duration of adverse effects was shorter with the subcutaneous route, these patients may be treated as outpatients (9).

In two randomized, controlled studies (44 patients given subcutaneous aldesleukin, 58 given a modified-release polyethylene glycol-modified formulation, 27 given continuous intravenous aldesleukin, and 50 controls), aldesleukin was well tolerated and a minority of patients required drug withdrawal because of adverse events (10,11). The overall adverse effects profile of both routes of administration was very similar, but was substantially less severe than previously described with high-dose aldesleukin. It consisted mostly of fatigue, nasal/sinus congestion, fever above 38°C, headache, gastrointestinal disorders, stomatitis, somnolence, and mood change. Increased bilirubin and alanine transaminase activities were more frequent than in the control group. None of the patients developed the capillary leak syndrome or significant hypertension, but cardiomyopathy, attempted suicide, ulcerative colitis, and exacerbation of hepatitis B were identified in one patient each among 85 patients treated with aldesleukin (10). Erythema and injection site reactions were observed in 66–69% of patients who received subcutaneous aldesleukin, and skin biopsies showed a perivascular infiltrate with lymphocytes and some eosinophils.

Use in patients with metastatic melanoma

In an analysis of data from 270 patients with metastatic melanoma in eight clinical trials, high-dose aldesleukin (8.4–9.8 MU/kg during each cycle) produced an overall objective response rate of 16%, with 17 complete responses and 26 partial responses (12). Although the response rate was low, there was a durable response for at least 24 months in 10 of 17 complete responders. Adverse effects were primarily the same as those previously described in patients with metastatic renal cell carcinoma, and severe hypotension (64%) was the most frequent. Six patients died from bacterial sepsis, but none was taking prophylactic antibiotics.

In a randomized trial, 102 patients with metastatic melanoma had more frequent treatment-related adverse effects, particularly hematological suppression in patients treated with tamoxifen, cisplatin, and dacarbazine followed by interferon alfa and aldesleukin, than in patients treated with chemotherapy alone, but there was no increase in survival (13).

General adverse effects

The frequencies of severe adverse effects of aldesleukin (7) are listed in Table 1 and the most frequent reasons for withdrawal of high-dose intravenous aldesleukin in Table 2.

Table 1 The frequencies of severe adverse effects of aldesleukin

General symptoms	
Fever and chills	24%
Weakness	4%
Edema	2%
Sepsis	6%
Cardiovascular	
Hypotension	74%
Supraventricular dysrhythmias	3%
Myocardial damage (angina, infarction)	4%
Respiratory	
Dyspnea	17%
Adult respiratory distress syndrome	<1%
Respiratory failure	2%
Nervous system	
Coma, seizures	4%
Psychiatric	
Behavioral changes	28%
Hematologic	
Thrombocytopenia	21%
Anemia	18%
Gastrointestinal	
Nausea and vomiting	25%
Diarrhea	22%
Stomatitis	4%
Gastrointestinal bleeding	4%
Intestinal perforation	<1%
Liver	
Hyperbilirubinemia	21%
Raised transaminases	10%
Raised alkaline phosphatase	9%
Urinary tract	
Oliguria or anuria	46%
Raised blood urea nitrogen	16%
Raised serum creatinine	14%
Acidosis	6%
Skin	
Pruritus and erythema	4%
Musculoskeletal	
Arthralgia	1%
Myalgia	1%
Death	4%

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Table 2 The most frequent reasons for withdrawal of high-dose intravenous aldesleukin

Constitutional symptoms	17%
Cardiovascular	
Hypotension	19%
Atrial dysrhythmias	10%
Respiratory	
Pulmonary toxicity	12%
Nervous system	
Disorientation	10%
Hematologic	
Thrombocytopenia	7%
Gastrointestinal	
Nausea or vomiting	4%
Diarrhea	6%
Liver	
Hyperbilirubinemia	5%
Urinary tract	
Oliguria	9%
Raised creatinine concentration	13%

High-dose aldesleukin is associated with a wide range of adverse effects, and practical guidelines for their avoidance and management have been detailed (14). Constitutional symptoms (malaise, fever, chills and asthenia) are universal in patients treated with high-dose aldesleukin (4). Although they are usually suppressed by paracetamol (acetaminophen), indometacin, or pethidine, they are one of the major reasons for stopping treatment. Myalgia and arthralgia are sometimes associated with the flu-like symptoms.

A wide range of aldesleukin-induced adverse effects is associated with the capillary leak syndrome, which is characterized by an increase in vascular permeability with subsequent leakage of fluids and proteins into the extravascular space (4). This results in a third–space clinical syndrome, generalized or peripheral edema, weight gain, cardiovascular and pulmonary complications with hypotension, pericardial, and pleural effusions, ascites, oliguria, and prerenal azotemia. Symptoms usually resolve in a few days after aldesleukin withdrawal. Studies on the mechanism have raised a number of hypotheses, such as damage to the endothelial cells, release of secondary cytokines, and activation of the complement cascade (15).

Denileukin diftitox

Denileukin diftitox is a fusion protein formed by binding human aldesleukin to the cytotoxic A chain of diphtheria toxin. This product binds to the aldesleukin receptor and inhibits protein synthesis, resulting in cell death. It has been approved for treatment of persistent or recurrent cutaneous T cell lymphoma and is being evaluated in patients with severe psoriasis.

In 71 patients with cutaneous T cell lymphomas randomized to denileukin diftitox 9 or 18 μg/kg/day, flu-like and gastrointestinal symptoms were observed in 92% (16). About 60% had an acute hypersensitivity reaction, with dyspnea, back pain, hypotension, and chest pain or tightness within 24 hours of infusion. A vascular leak syndrome, as defined by the presence of at least two of edema, hypoalbuminemia, and hypotension, occurred in 25%.

A dose-escalation study in 35 patients with psoriasis confirmed that constitutional symptoms in response to denileukin diftitox were dose-related and less frequent at lower doses (below 5 micrograms/kg/day) (17). There was only one case of mild vascular leak syndrome. Skin reactions compatible with delayed hypersensitivity reactions were noted in three patients, including one case of exfoliative dermatitis.

The more severe adverse effects of denileukin diftitox consisted of acute hypersensitivity reactions during or within 24 hours of infusion in 69% of patients, and a vascular leak syndrome in 27% of patients, which was severe in 6%. In contrast to acute hypersensitivity reactions, the vascular leak syndrome was typically delayed and occurred within the first 2 weeks of infusion (18). Whether this was due to a direct action of denileukin diftitox or to tumor lysis syndrome is unknown.

Organs and Systems

Cardiovascular

Hemodynamic and cardiac complications are the major limitations of high-dose aldesleukin and have been described in both adults (19,20) and children (21). Significant hypotension requiring meticulous maintenance therapy with intravenous fluids or low-dose vasopressors was observed in most patients (22). The clinical findings were very similar to the hemodynamic pattern seen in early septic shock. Aldesleukin-induced increases in plasma nitrate and nitrite concentrations correlated with the severity of hypotension (23).

Among other cardiovascular complications, cardiac dysrhythmias were reported in 6–10% of patients, angina pectoris or documented myocardial infarction in 3–4%, and mortality due to myocardial infarction in 1–2% (4). Severe myocardial dysfunction, myocarditis, and cardiomyopathy have been seldom reported (SED-13, 1103) (SEDA-20, 334) (SEDA-22, 406).

The cardiopulmonary toxicity of high-dose intravenous bolus aldesleukin has been analysed in 199 metastatic melanoma or renal cell carcinoma patients without underlying cardiac disease (24). Cardiovascular events occurred within hours after starting infusion, persisted throughout aldesleukin therapy, and normalized within 1–3 days after treatment withdrawal. Hypotension was the most frequent adverse effect (53% of treatment courses) and resolved promptly with vasopressor treatment. Unexpectedly, the response to treatment was significantly better in patients with melanoma who had hypotension. There were cardiac dysrhythmias in 9% of patients; they mostly consisted of easily manageable atrial fibrillation or supraventricular tachycardia. Further courses of aldesleukin in 11 of these patients produced recurrent dysrhythmias in only two, and long-term treatment of dysrhythmias was never required. High-degree atrioventricular block and repetitive episodes of ventricular

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tachycardia were each observed once. Although 11% of patients had raised creatine kinase activity before or during treatment, only 2.5% had a documented rise in the MB isoenzyme fraction.

At-risk patients include those with pre-existing cardiac disease, whereas age, performance status, and sex are not significantly associated with cardiopulmonary toxicity. In view of this risk, it is reasonable to monitor cardiac function and creatine kinase activity closely in all patients, or to exclude those with significant underlying coronary or cardiorespiratory disease. Pretreatment cardiac screening has greatly reduced the incidence of myocardial infarction, ischemia, and related dysrhythmias, and two-dimensional and Doppler echocardiography was suggested to be helpful to anticipate cardiovascular toxicity (25). A reduction in systemic vascular resistance, stroke work index, and left ventricular ejection fraction are usually involved in the pathophysiology of cardiac dysfunction. Clinical, electrocardiographic, and radionuclide ventriculography monitoring in 22 patients undergoing a 5-day continuous intravenous infusion of aldesleukin for various cancers showed that reversible left ventricular dysfunction accounted for most of the observed hemodynamic changes (26). Indeed, significant coronary disease was usually not observed in patients undergoing cardiac catheterization, which argues for direct myocardial damage (24). In isolated reports, clinical and histological findings of eosinophilic, lymphocytic, or mixed lymphocytic–eosinophilic myocarditis also suggested an immune-mediated drug reaction (SED-13, 1103) (SEDA-22, 406).

Aldesleukin-induced cardiac eosinophilic infiltration has been reported (27).

- After 25 days of treatment with continuous aldesleukin infusion (up to 150 000 units/kg/day) for stage IV Hodgkin's disease, a 26-year-old woman had increased fatigue, tachycardia, hypotension, and hypothermia. Echocardiography showed bilateral intraventricular masses. Her maximal absolute eosinophil count was 11.4×10^9/l and the platelet count was 17×10^9/l. Despite aldesleukin withdrawal, her condition deteriorated and she died. Postmortem examination showed biventricular thrombi and prominent eosinophilic infiltration of the endomyocardium.

Of 10 subsequent patients who received prolonged infusions of aldesleukin and were monitored by echocardiography, one developed asymptomatic changes in cardiac function, with features suggestive of early thrombus formation and a reduced ejection fraction during weeks 6–8. The maximal absolute eosinophil count was 5×10^9/l. These abnormalities resolved on aldesleukin withdrawal.

Conjugates of aldesleukin with polyethylene glycol produce less cardiovascular toxicity (SEDA-20, 333).

Respiratory

Dose-related cough has been reported as the most frequent adverse effect of inhaled aldesleukin (28).

Among 199 patients with metastatic melanoma or renal cell carcinoma treated with high-dose intravenous bolus aldesleukin, there was severe respiratory distress in 3.2% of treatment courses, but intubation was required in only one (24). This is far less common than earlier estimates that 10–30% of patients develop respiratory distress severe enough to warrant mechanical ventilation in 5–20% of cases (4). The improvement may be related to the current strict selection criteria for the evaluation of pulmonary function, limited fluid management strategy, prophylactic antibiotics, and prompt withdrawal of treatment in patients presenting with shortness of breath, rales, or persistent hypoxemia.

Pulmonary features of the adverse effects of aldesleukin include lung opacities, diffuse pulmonary interstitial edema, pleural effusions, alveolar edema, and hypoxemia, with full and rapid recovery after treatment withdrawal (29,30).

Aldesleukin-induced increase in lung capillary permeability or direct cardiac dysfunction is thought to be a likely mechanism of this adverse effect, and a localized vascular leak syndrome, attributed to activation of eosinophils in the lung and subsequent deposition of the eosinophil major basic protein, has also been suggested, as reported in a 49-year-old woman with breast cancer (31).

There is no significant association between pre-existing clinical dysfunction and radiological interstitial edema (30). Very severe adult respiratory distress syndrome requiring double lung transplantation has been reported in one patient (32).

Nervous system

Severe pain resulting from a previously asymptomatic thoracic spine metastasis has been attributed to aldesleukin in a 64-year-old man with metastatic renal cell carcinoma (33).

Fatal acute leukoencephalopathy with brain perivascular foci demyelination (34) and delayed progressive cognitive dysfunction (35) have been reported in isolated cases.

The neurotoxicity of aldesleukin is usually dose-related and can be treatment-limiting (36).

Sensory systems

Transient episodes of amaurosis or scotomata, both of which recurred after aldesleukin rechallenge, have been described (37). Three other patients had visual phenomena, including diplopia, scotomata, and palinopsia during treatment, which resolved on withdrawal of aldesleukin (38).

Psychological, psychiatric

Aldesleukin can cause moderate impairment of cognitive function, with disorientation, confusion, hallucinations, sleep disturbances, and sometimes severe behavioral changes requiring transient neuroleptic drug administration (39–41). Some of the cognitive deficits mimicked those observed in dementias, such as Alzheimer's disease. Several studies have also shown increased latency and reduced amplitude of event-related evoked potentials in patients with cognitive impairment (41,42). Other infrequent adverse effects included paranoid delusions, hallucinations, loss of interest, sleep disturbances or drowsiness, reduced energy, fatigue, anorexia, and malaise. Coma and seizures were exceptionally noted.

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Symptoms occurred within 1 week of treatment and complete recovery was usually noted after aldesleukin withdrawal.

In 10 patients with advanced tumors, low-dose subcutaneous aldesleukin produced significant psychological changes; increased depression scores, psychasthenia, and conversion hysteria were the most common findings (43).

The short-term occurrence of depressive symptoms has been investigated by using the Montgomery and Asberg Depression Rating Scale (MADRS) before and after 3 and 5 days of treatment in 48 patients without a previous psychiatric history and treated for renal cell carcinoma or melanoma with aldesleukin alone ($n = 20$), aldesleukin plus interferon alfa-2b ($n = 6$), or interferon alfa-2b alone ($n = 22$) (44). On day 5, patients in the aldesleukin groups had significantly higher MADRS scores, whereas there were no significant changes in the patients who received interferon alfa-2b alone. Eight of 26 patients given aldesleukin and only three of 22 given interferon alfa-2b alone had severe depressive symptoms. Depressive symptoms occurred as early as the second day of aldesleukin treatment and were more severe in the patients who received both cytokines. Early detection of mood changes can be useful in pinpointing patients at risk of subsequent severe neuropsychiatric complications.

Neuropsychiatric symptoms are less frequent with subcutaneous aldesleukin (4). No predictive or predisposing factors have been clearly identified. Whether a direct effect of aldesleukin on neuronal tissues, an increased vascular brain permeability with a subsequent increased brain water content, or an aldesleukin-induced release of neuroendocrine hormones (beta-endorphin, ACTH, or cortisol), accounted for these effects, is unknown. A possible immune-mediated cerebral vasculitis has also been reported in one patient (SEDA-20, 334).

Endocrine

Various hormonal and metabolic effects of aldesleukin are temporally related to hypotension. Transient serum rises in ACTH, cortisol, beta-endorphin, adrenaline and noradrenaline have been found, whereas there were no significant changes in the plasma concentrations of several other hormones (4).

An acute episode of adrenal insufficiency secondary to adrenal hemorrhage occurred in one patient receiving aldesleukin (45).

Thyroid

Since the first reports of hypothyroidism, a number of studies have reported the occurrence of thyroid dysfunction in patients receiving aldesleukin alone or in combination with LAK cells, interferon alfa, interferon gamma, or tumor necrosis factor alfa (SED-13, 1104) (46). Symptoms were usually observed after 2–4 months of treatment (47–49), and mostly consisted of moderate hypothyroidism, which resolved after immunotherapy withdrawal or thyroxine treatment (49,50). Patients treated with aldesleukin plus interferon alfa more commonly developed biphasic thyroiditis with subsequent hypothyroidism or hyperthyroidism (50–53).

The possibility of a positive correlation between the development of thyroid dysfunction and the probability of a favorable tumor response has been debated (47,49,54). The incidence of thyroid dysfunction did not correlate with the dose or the underlying disease, but increased with treatment duration (46). In a large survey of 281 cancer patients receiving low-dose (72 000 IU/kg) or high-dose (720 000 IU/kg) aldesleukin, up to 41% of previously euthyroid cancer patients developed thyroid dysfunction (55). Combined immunotherapy was also associated with more frequent thyroid disorders. Aldesleukin plus interferon alfa produced thyroid dysfunction in 20–91% of patients (46), and the incidence of laboratory thyroid dysfunction reached 100% in patients given five or six cycles of both cytokines (51). Aldesleukin plus interferon alfa also tended to be a risk factor for the development of biphasic thyroiditis (49).

Female sex and the presence of antithyroid antibodies correlated significantly with the development of thyroid disease (49,56). This, together with the findings of strong expression of HLA-DR antigens on thyrocytes or the presence of mononuclear cell infiltrates on histological examination of the thyroid, makes an autoimmune phenomenon likely (49,52). However, a possible direct effect of immunotherapy on thyroid hormonal function has also been suggested in patients who had no detectable thyroid antibodies. There was a significant decrease in TSH concentration, while thyroid autoantibodies were not significantly raised (57).

Metabolism

Reversible insulin-dependent diabetes mellitus has been described in a predisposed patient (SEDA-20, 334).

Aldesleukin can cause lipid disorders. Recurrent and marked hypocholesterolemia with reduced high- and low-density lipoproteins, and slight increases in plasma triglycerides have been observed after high-dose aldesleukin (SEDA-21, 375) (4).

Nutrition

Severe, but reversible hypovitaminosis C was noted in patients receiving high-dose aldesleukin plus LAK cells (58).

Hematologic

Hematological adverse effects of aldesleukin typically included transient anemia, thrombocytopenia, eosinophilia, neutropenia, extreme lymphopenia, and rebound lymphocytosis (4,59). Transient suppression of hemopoiesis by secondary cytokines, peripheral platelet destruction, and increased endothelium margination of lymphocytes are possible mechanisms.

Hematological toxicity was analysed in 199 patients treated with a high-dose intravenous bolus aldesleukin regimen for metastatic melanoma or renal cell carcinoma (60). Anemia requiring transfusions was noted in 14% of all treatment courses and severe thrombocytopenia occurred in 2.2%, with three patients suffering from serious hemorrhages. Severe leukopenia was infrequent and not associated with infectious episodes. Early transient lymphopenia (93% reduction) was followed by rebound lymphocytosis up to 198% above baseline values. Except for severe thrombocytopenia, treatment withdrawal was

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not required in this study. Other investigators found that reductions in platelet count correlated with a significant increase in ex vivo platelet functional activity, but there were no episodes of bleeding or thrombosis (61).

Aldesleukin can produce sustained eosinophilia, possibly mediated by interleukin-5 or GM-CSF, but this was not associated with allergic reactions (62).

In 42 patients with advanced cancer treated with aldesleukin and lymphokine-activated killer cells from autologous lymphocytes, there were reduced numbers of circulating erythroid and granulocyte/macrophage progenitors, with recovery after withdrawal (63). Patients developed severe anemia (partly due to phlebotomy, cytopheresis, and hemodilution), thrombocytopenia, lymphopenia, and eosinophilia, with mild neutropenia and rebound lymphocytosis after treatment was stopped.

The severity of hematological disorders was not affected by previous chemotherapy for metastatic melanoma or renal cell carcinoma and there was no correlation with response to treatment (60). However, others have found that moderate to severe dose-related thrombocytopenia occurred particularly in patients previously treated with cytotoxic agents (64). Subcutaneous low-dose aldesleukin therapy reduced the frequency and intensity of hematological toxicity, and the combination of aldesleukin plus interferon alfa produced either moderate additional toxicity or no significant enhancement (65).

Most patients develop significant, but promptly reversible coagulation disorders with prolongation of the partial thromboplastin time (the most frequent effect), hypoprothrombinemia, and reduced functional concentrations of several clotting factors II, IX, X, XI, and XII (60,66,67). No clear mechanism of aldesleukin-induced coagulopathy has been identified, and the efficacy of prophylactic vitamin K has been disputed (67). Other data suggest that aldesleukin may activate the coagulation and fibrinolytic system (64,68), but the clinical relevance of these findings is not clear.

A mean splenic index increase of 64% was found on computed tomography after a mean of 66 days of aldesleukin treatment for non-hematological malignancies (69). Splenomegaly persisted after an average of 215 days after the completion of aldesleukin treatment and was not associated with tumor progression.

Mouth and teeth

Oral effects of aldesleukin include xerostomia with reversible salivary gland hypofunction, a burning sensation in the mouth, taste disorders, mucosal atrophy, mucositis, glossitis, and ulcerative lesions (70,71).

Gastrointestinal

Minor gastrointestinal adverse effects, that is anorexia, nausea, vomiting, and diarrhea, were noted in about 80% of patients (4).

Incidental case reports included symptomatic exacerbation of Crohn's disease (72) and transient painful swelling of the appendix (SEDA-21, 376).

Severe and sometimes fatal intestinal complications have been described in 1.3–7% of patients receiving aldesleukin alone or in combination with LAK cells or interferon alfa, including intestinal ischemia, bowel ulceration or perforation, and colosplenic fistula (73–75). It has been suggested that severe diarrhea may be an indicator of subsequent colonic ischemia (75).

Liver

Mild liver dysfunction, hypophosphatemia, and hypomagnesmia are the most common laboratory abnormalities caused by aldesleukin (76,77). About 20% of patients develop mild to severe intrahepatic cholestasis with reversible and dose-dependent rises in bilirubin and alkaline phosphatase while serum transaminases were only slightly increased (4,78). Recurrence of cholestasis after aldesleukin rechallenge was not always observed (79). The mechanism of aldesleukin-induced intrahepatic cholestasis is unknown, but it might be mediated by activation of Kupfer cells and the subsequent release of cytokines (SEDA-20, 335). Focal fatty infiltrates of the liver mimicking metastases were also reported in a patient receiving both aldesleukin and a short course of interferon alfa (80).

Biliary tract

Gall-bladder changes have been reported in patients given aldesleukin and should be promptly recognized to avoid unnecessary intervention in symptomatic patients (SED-13, 1105) (81). Further systematic ultrasonographic examination in 25 HIV-infected patients treated with low-dose aldesleukin (6–18 MU/day) confirmed that most patients had gall-bladder wall thickening (80%), abnormal echo texture (64%), and intramural fluid (52%) or pericholecystic fluid (20%) (82). The frequency and severity of ultrasonographic abnormalities correlated with a higher dose of aldesleukin, as did complaints of right upper quadrant pain (24%). Although these findings mimicked those observed with acute cholecystitis, clinical symptoms and ultrasonographic abnormalities rapidly reversed after aldesleukin withdrawal or between two cycles.

Aldesleukin-induced cholecystopathy has been described in patients with cancer and was fully investigated in seven of 29 HIV-infected patients (81). Right upper quadrant abdominal pain and gallbladder wall thickening at sonography developed after 4–5 days of treatment and spontaneously resolved after withdrawal or dosage reduction. Similar symptoms recurred after renewed administration of aldesleukin. Although suggestive of acalculous cholecystitis, surgery is not required because this disorder is usually benign.

Pancreas

Acute pancreatitis has been described after high-dose bolus aldesleukin therapy (83).

Urinary tract

The renal toxicity associated with aldesleukin is dose-related. It manifests as uremia, oliguria, fluid retention, and pronounced renal tubular sodium reabsorption (77). No evidence of tubular dysfunction has been found. There is reduced renal plasma flow associated with reduced renal prostaglandin synthesis and increased plasma renin activity, which may explain the mechanism (84).

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Oliguria or anuria, and increased serum creatinine concentrations occurred in over 90% of patients receiving high-dose aldesleukin (4).

Proteinuria, ranging in degree from traces to a frank, but reversible nephrotic syndrome (85,86), was sometimes observed, and a possible role of contaminants has been discussed (87).

In 199 patients with metastatic melanoma or renal cell carcinoma with high-dose intravenous bolus aldesleukin, severe oliguria, hypotension, and weight gain were frequent, and raised serum creatinine concentrations (mean peak 2.7 mg/dl) were the cause of treatment withdrawal in 13% of cycles (88). There were also various changes on urinalysis. The highest creatinine concentrations were found in patients with renal carcinoma and in elderly, male, or nephrectomized patients. There was no evidence of any long-term renal defect, and renal dysfunction was therefore not considered to be a treatment-limiting factor provided that patients were carefully managed for hypotension or oliguria.

It has been suggested that low-to-intermediate doses of aldesleukin alone or associated with interferon alfa may be safer under outpatient conditions (5). Patients over 60 years of age and individuals with previously raised serum creatinine concentrations have been thought to be likely to have longer-lasting and more severe renal impairment, but neither previous nephrectomy nor the interval between nephrectomy and initiation of aldesleukin therapy were associated with a higher risk of renal insufficiency (4).

A prerenal mechanism secondary to the vascular leak syndrome is commonly involved in the pathophysiology of acute renal insufficiency. In addition it has been suggested that a direct intrinsic intrarenal effect of aldesleukin with a higher than expected reduction in glomerular filtration rate or tubular dysfunction (85,89) is involved. Several isolated cases of acute interstitial or tubulointerstitial nephritis with predominant T lymphocyte infiltration of the kidneys (90–92) and the exacerbation of a subclinical IgA glomerulonephritis (93) suggested altered cell-mediated immunity.

Risk factors for renal dysfunction have been analysed in 72 patients with metastatic renal cell cancer treated with high-dose aldesleukin (18 MU/m^2/day), interferon alfa (5 MU/m^2/day), and lymphokine-activated killer lymphocytes (94). There was some type of renal dysfunction in 97%, of whom 69% developed renal toxicity of grade 2 (creatinine 260–525 μmol/l) or grade 3 (creatinine 525–1050 μmol/l). Although renal function commonly resolved between successive treatment courses, six patients had a persistently raised creatinine concentration (more than 20% above baseline). Among the various potential risk factors, a multivariate analysis showed that the significant risk factors for severe renal dysfunction were male sex, pre-treatment hypertension, and sepsis during treatment.

Skin

Cutaneous reactions to aldesleukin generally comprise pruritus, flushing, mild to moderate erythematous macular and desquamative eruptions, while generalized erythroderma or photosensitivity have occasionally been observed (95). The severity was not dose-dependent and did not correlate with other systemic reactions. Histological and immunopathological examination of the skin showed mild infiltrates of activated T helper lymphocytes and increased expression of HLA-DR and intercellular adhesion molecule-1 on keratinocytes and endothelial cells, and a possible role of interferon gamma has been suggested (96–98). Other adverse effects included erosions in surgical scars, multiple superficial cutaneous ulcers, and telogen effluvium (95).

Injection site reactions have been noted after subcutaneous aldesleukin (SEDA-21, 376). Localized lobular panniculitis after subcutaneous injections was further exacerbated by intravenous aldesleukin in one patient (99).

An unusually high incidence of skin erythema (70–85%) was noted in patients who received aldesleukin after autologous bone marrow transplantation. Histological examination showed features of cutaneous graft-versus-host disease or T cell epidermal infiltrates, but cutaneous toxicity was not reproduced in patients receiving low-dose aldesleukin (100,101).

The potential role of localized vertebral palliative radiotherapy before aldesleukin treatment was denied, since the area of cutaneous toxicity was broader than the irradiated field.

Aldesleukin given alone or aldesleukin plus interferon alfa produced a high incidence of vitiligo in patients with metastatic melanoma, irrespective of whether or not they had received chemotherapy (102–104). A possible correlation between aldesleukin-induced vitiligo and a favorable tumor response was found (102) but has also been disputed (103).

Some isolated reports have given rise to the suggestion that aldesleukin can exacerbate cutaneous reactions compatible with an immune-mediated phenomenon (105). Case reports included recurrence of quiescent pemphigus vulgaris, fatal dermatitis exfoliativa compatible with pemphigus vulgaris, exacerbation of localized or widespread psoriasis, acute reactivation of eczema, rapid progression of scleroderma with myositis, and leukocytoclastic vasculitis (SED-13, 1106) (SEDA-20, 335) (SEDA-21, 376).

Immunostimulation due to aldesleukin may have also played a role in the occurrence or unmasking of erythema nodosum, linear IgA bullous dermatosis, and life-threatening extensive bullous skin eruption or toxic epidermal necrolysis (SED-13, 1106) (SEDA-21, 376) (106).

Because aldesleukin stimulates T cells, it has been suggested to have favored the development of successive episodes of multifocal fixed drug eruption in response to chemically unrelated drugs (paracetamol, ondansetron, and tropisetron) in a 43-year-old patient (107).

Musculoskeletal

Joint or muscle pains have sometimes been reported in patients receiving aldesleukin, as has shoulder arthralgia with normal radiography and scintigraphic imaging consistent with bilateral synovitis (4,108).

Rare reports have suggested that aldesleukin can reactivate or cause rheumatoid arthritis (109) or cause necrotizing myositis with positive antinuclear antibodies (SEDA-20, 335).

Interstitial edema and local fluid retention resulting from increased vascular permeability has been suggested to

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cause unilateral or bilateral carpal tunnel syndrome with sensorimotor median neuropathy (SEDA-20, 334) (110).

Sexual function

A reversible reduction in testosterone concentrations has been observed in men who have received aldesleukin (4).

Immunologic

Aldesleukin was thought to be the triggering factor in the occurrence of sarcoidosis in a 36-year-old patient with AIDS stabilized for a long time by highly active antiretroviral therapy (111).

There have been very few reports of angioedema in patients receiving aldesleukin (112).

Interleukin antibodies

Recombinant aldesleukin-binding antibodies were detected in the half of 205 patients with metastatic cancer but there were neutralizing antibodies in only 7% (113). No significant difference in incidence was found between subcutaneous and continuous intravenous administration. In another study, none of the patients receiving aldesleukin alone developed neutralizing antibodies, whereas 18% of patients treated with aldesleukin and interferon alfa-2b had antibodies (114). Whatsoever, the clinical relevance of recombinant aldesleukin-neutralizing antibodies has not been accurately evaluated and a loss of response was apparently documented in only one patient (115).

Autoimmune disorders

Aldesleukin sometimes causes acute exacerbation of latent autoimmune disease, as has been further exemplified by the following description, which also included the first report of aldesleukin-induced myasthenia gravis (116).

- A 64-year-old man with non-insulin-dependent diabetes was given 14 large doses of aldesleukin (600 000 IU/kg every 8 hours) for metastatic renal cell carcinoma. One week after the completion of the first cycle he had a reversible episode of hyperosmolar, non-ketotic hyperglycemia, and insulin was started. A second cycle 3 months later was associated with hypotension, mild weakness of the right shoulder, and increased activity of creatine kinase (CK)-MB fraction. After four doses of the third cycle he again had hypotension and a raised CK-MB fraction. Two weeks later, he developed typical features of myasthenia gravis and required mechanical ventilation. Acetylcholine receptor antibodies were found and there was an inflammatory primary myositis on muscle biopsy. He gradually recovered with prednisone, pyridostigmine, and daily insulin.

In this case, which was marked by three autoimmune complications (insulin-dependent diabetes mellitus, myositis, and myasthenia gravis) in a single patient, a retrospective analysis of the patient's serum before aldesleukin therapy showed the presence of antibodies against glutamic acid decarboxylase, insulin, islet cell antigen, and striated muscle, but was negative for acetylcholine receptor antibodies. Immune stimulation by aldesleukin was therefore thought to have caused broken tolerance to self-antigens and enhanced latent autoimmunity.

Infection risk

Clinically relevant infectious complications occurred with an incidence of 10–40% after intravenous aldesleukin (4). A retrospective study showed a 13% incidence of confirmed bacterial infections during 935 treatment courses of high-dose aldesleukin; opportunistic infections were not more frequent (117). The most commonly isolated pathogens were *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli*. Documented infections affected mostly the catheter site or the urinary tract. Infections were usually noted during the first (68%) or second (21%) course of aldesleukin therapy, that is 4–9 days and 13–18 days after the start of treatment. Bacterial sepsis was mostly related to the use of central venous catheters and fatal septic shock was rarely recorded. There was also an increased incidence of infectious complications in patients receiving subcutaneous aldesleukin plus interferon alfa (118), but these findings were not confirmed in patients who received subcutaneous aldesleukin alone (119,120). Previous colonization of the skin with *S. aureus* and skin desquamation increased the risk of nosocomial bacteremia (117). Age, underlying tumor, source, dose and duration of intravenous aldesleukin, or the concomitant use of LAK cells were not risks factors, and severe neutropenia was not associated with bacteremia. The prophylactic use of antibiotics and systematic screening led to a significant reduction in the frequency of infections, from 22 to 7% of patients over 3 years (117).

The mechanism of these complications is not fully understood. A reduction in neutrophil chemotaxis, superoxide production, and/or neutrophil Fc receptor expression have been suggested to be involved. Impaired cell-mediated or humoral immune responses have also been shown after high-dose aldesleukin, but the clinical consequences of these findings are unknown.

Long-Term Effects

Tumorigenicity

Isolated case reports have described relapses of acute myeloid leukemia or the proliferation of leukemic blasts cells with phenotypic changes in a patient with acute myelocytic leukemia; a high percentage of blasts expressed the CD25 antigen in both reports (121,122). A reversible increase in peripheral monoclonal B cell lymphocyte count in a patient with B cell lymphocytic lymphoma and Hodgkin's disease in a woman receiving aldesleukin for metastatic melanoma were also documented in single reports.

Drug–Drug Interactions

General

The potential of aldesleukin to participate in drug interactions has been investigated in 18 patients who underwent surgical resection of hepatic metastases (123). Compared with seven control patients who did not

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receive aldesleukin before surgery, six patients who received 9 or 12 MU/m^2 from days 7–3 before hepatectomy had a significant fall in the activities of total cytochromes and several mono-oxygenases. No such effect was found in five patients treated with 3 or 6 MU/m^2 before hepatectomy. This suggests that high-dose aldesleukin might cause drug interactions by inhibiting hepatic drug metabolism.

Contrast media

More frequent allergic reactions to iodinated and non-ionic contrast media injection were observed when radiological examination was performed within a period ranging from 2 to 6 weeks up to 2 years after withdrawal of aldesleukin in patients who had previously tolerated contrast media well (124,125). These reactions usually appeared within 1–4 hours after contrast media injection, but delayed reactions up to 24 hours were sometimes noted. The most frequent symptoms were diarrhea, vomiting, influenza-like symptoms, skin rash, pruritus, and facial edema, and rarely included hypotension, dyspnea, and oliguria. The overall incidence was 5–15%, but as high as 28% of patients receiving aldesleukin via arterial infusion (126). This incidence is therefore about 3–4 times higher than in the general population undergoing contrast media examination. "Recall" reactions to aldesleukin have been suggested as an explanation, since these complications more closely resemble immediate adverse effects to aldesleukin than typical contrast media reactions. Putative enhancement of the immune response to iodine-containing contrast media after aldesleukin has also been suggested.

Cytotoxic drugs

An unexpected high incidence of type I allergic reactions to cisplatin and dacarbazine has been observed, several hours after administration to patients on a combination of aldesleukin and interferon alfa (127). The reactions occurred at least after the first cycle and increased in incidence thereafter, suggesting that immunotherapy can sensitize patients to several chemotherapeutic agents.

In a phase III trial in 190 patients with metastatic melanoma, sequential chemotherapy with dacarbazine, cisplatin, and vinblastine plus interferon alfa and aldesleukin modestly increased the response rates and produced considerably more frequent and severe adverse effects than chemotherapy alone (128). In particular, severe episodes of anemia and thrombocytopenia that required blood or platelet transfusions were 2–6 times more frequent in the chemotherapy group.

Morphine

Acute encephalopathy with typical signs of morphine intoxication occurred in a patient taking aldesleukin (129).

Non-steroid anti-inflammatory agents

Non-steroidal anti-inflammatory agents used to reduce fever and other aldesleukin adverse effects can theoretically potentiate aldesleukin nephrotoxicity by inhibiting prostaglandin synthesis. However this effect was deemed unlikely by several authors (85).

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Aldose reductase inhibitors

General Information

Aldose reductase inhibitors (SEDA-19, 397) (SEDA-20, 399) (SEDA-21, 447) (SEDA-22, 477) have been developed for the treatment of secondary complications in diabetes (1,2). They include alrestatin, benurestat, epalrestat, fidarestat, imirestat, lidorestat, minalrestat, ponalrestat, ranirestat, risarestat, sorbinil, tolrestat, zenarestat, and zopolrestat (all rINNs).

The aldose reductase inhibitors inhibit or reduce secondary complications induced by diabetes, specifically in tissues in which glucose uptake is not insulin-dependent (probably neural tissue, the lens, and glomeruli). Many of them (including alrestatin, imirestat, ponalrestat, and sorbinil) have been used in clinical trials, but have been withdrawn because of adverse effects or lack of effect (2). Their main adverse effects include fever, nausea, diarrhea, increases in liver enzymes, skin rashes, including toxic epidermal necrolysis and Stevens–Johnson syndrome, marked thrombocytopenia, lymphadenopathy, splenomegaly, and adult respiratory distress syndrome.

Tolrestat was withdrawn because of deaths from fatal hepatic necrosis (3) and poor efficacy in clinical trials. Sorbinil was withdrawn because of hypersensitivity reactions in more than 10% of patients.

Organs and Systems

Gastrointestinal

Nausea, vomiting, abdominal fullness, and diarrhea are reported with aldose reductase inhibitors (1).

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Alemtuzumab

See also Monoclonal antibodies

General Information

Alemtuzumab (campath-1H) is a humanized monoclonal antibody specific for the CDw52 antigen, present on cell membranes of lymphocytes and monocytes. It has been used for treatment of patients with rheumatoid arthritis and vasculitis, is being investigated for the treatment of chronic lymphocytic leukemia, and has been used to deplete circulating lymphocytes in patients with multiple sclerosis (1). In 2001, alemtuzumab was approved in Europe for the treatment of chronic B cell lymphocytic leukemia that had been treated previously with alkylating agents and was refractory to fludarabine (2). It has also been used for induction of immunosuppression/tolerance in liver transplant recipients (3,4) and kidney/pancreas transplant recipients (5).

The major adverse effects (fever, nausea, skin rash, and hypotension) may well be related to the release of cytokines as a consequence of lysis of the target lymphocytes (6). Of four patients treated with alemtuzumab, three developed antibodies against it, but without affecting the plasma concentrations and without obvious clinical consequences. Other adverse effects have included mild renal impairment and transient thrombocytopenia.

Organs and Systems

Respiratory

Of 22 patients, median age 61 years, who had received a median of three previous types of therapy for mycosis fungoides or Sézary syndrome and were given alemtuzumab in increasing doses (from 3 to 30 mg three times a week for 12 weeks), 11 had no infectious complications, one had fatal pulmonary aspergillosis 2.5 months after the end of treatment, and another contracted fatal *Mycobacterium* pneumonia 10 months after the end of treatment (7).

Endocrine

Nine of 27 patients with multiple sclerosis developed antibodies against the thyrotropin receptor and carbimazole-responsive autoimmune hyperthyroidism after a 5-day pulse of alemtuzumab, a finding that was not reported in patients treated for other disorders (1).

Hematologic

In 50 patients with advanced, low-grade, non-Hodgkin's lymphoma alemtuzumab produced marked lymphopenia and neutropenia, which were the probable cause of frequent severe infections (8). Seven patients developed opportunistic infections and nine had bacterial septicemia; three patients died from infectious complications. Severe resistant autoimmune thrombocytopenia has also been noted in one patient, but the evidence that alemtuzumab was involved was limited (9).

Immunologic

Reactivation of cytomegalovirus is a frequent complication during treatment with alemtuzumab in patients with chronic lymphocytic leukemia (10), and other organisms are occasionally described.

- A 52-year-old man with B cell chronic lymphocytic leukemia had weight loss and a steadily rising blood lymphocyte count (11). He received alemtuzumab as first-line treatment as part of a clinical trial. After 12 weeks the leukemia completely remitted. Three years later he received chlorambucil for progressive disease and had a partial remission. After another 2 years his chemotherapy regimen was change to fludarabine and cyclophosphamide. After a further year his disease became rapidly progressive, with anemia, splenomegaly, and lymphadenopathy. Alemtuzumab was reintroduced and standard prophylaxis treatment was started with co-trimoxazole, valaciclovir, and fluconazole. After 8 weeks he developed fever up to 39°C. There was no evidence of bacterial or viral infection. His general condition worsened rapidly and he showed signs of acute hepatitis, renal insufficiency, disseminated intravascular coagulation, and finally respiratory failure. He died 14 days after the start of the fever. Adenovirus 5 was recovered from the lung, spleen, liver, and blood.

Among 18 patients with chronic lymphocytic leukemia, one with a long-lasting lymphocytopenia died 3 months after treatment, owing to progressive multifocal leukoencephalopathy; papovavirus was isolated from the cerebrospinal fluid (12).

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Alfadolone and alfaxolone

See also General anesthetics

General Information

Alfadolone and alfaxolone are two steroid anesthetics that were used in combination. However, the mixture has been withdrawn because of safety considerations regarding the solvent used, polyethoxylated castor oil (Cremophor EL), which can cause non-IgE-mediated anaphylactic (anaphylactoid) reactions (SED-10, 189) (1).

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Alfentanil

General Information

Alfentanil is a potent short-acting opioid used in anesthesia. Beside its effects on opioid receptors, there is some evidence that it may affect acetylcholine, since intrathecal neostigmine produced a dose-dependent increase in the effect of alfentanil (SEDA-22, 3). Its rapid onset and short duration of action make alfentanil suitable for use in day care, although it is important to treat adverse effects before discharge.

Alfentanil is an ideal analgesic for focused and ambulatory interventions. In a prospective, uncontrolled study in three consecutive groups of outpatients undergoing shock-wave lithotripsy, group 1 (152 patients) had an induction dose of a combination of propofol 0.8 mg/kg and alfentanil 8 μg/kg; in group 2 (78 patients) and group 3 (250 patients), the induction dose was reduced by 20% (1). For all three groups the maintenance dose was a mixture of propofol 0.25 mg/kg and alfentanil 5 μg/kg given via a PCA device with a lock-out time of 5 minutes. In groups 1 and 2 the lithotripter was equipped with a standard electromagnetic shock-wave emitter (the EMSE 200), while in group 3 an upgraded EMSE F150 was used. Analgesic consumption was lower in the patients treated with the EMSE 150; groups 2 and 3, with a 20% reduction in induction dose, did not compensate by using more PCA. Groups 2 and 3 also had a significant reduction in the incidence of oxygen desaturation. The intravenous administration of a mixture of alfentanil and propofol, using the updated EMSE F150 device as in group 3, was therefore considered to be safe and reliable, with good patient tolerance and rapid recovery.

In a non-comparative study of 24 consecutive outpatients undergoing extracorporeal shock-wave lithotripsy, alfentanil (initial dose 15 μg/kg followed by 0.38 μg/kg/minute) and propofol (initial dose 1 mg/kg followed by 59 μg/kg/minute) were used for sedation (2). Both alfentanil and propofol were effective and safe, provided respiratory and cardiovascular parameters were routinely monitored.

Organs and Systems

Cardiovascular

When alfentanil 30 μg/kg was given to six healthy volunteers there were no clinical changes in respiratory or cardiovascular function (SEDA-16, 78).

Bradycardia often occurs with the combination of a potent short-acting opioid with suxamethonium during induction of anesthesia, and alfentanil has been reported to have caused sinus arrest in three patients (SEDA-17, 79) (3).

In one study alfentanil was particularly likely to cause hemodynamic instability and myocardial ischemia; however, drug interactions or the dosage regimen may have been responsible (4).

Respiratory

Significant respiratory depression occurs after alfentanil in doses in excess of 1000 μg and delayed-onset respiratory depression has been reported. Used as a general anesthetic for urgent cesarean section, alfentanil can cause marked neonatal respiratory depression, which is reversible with naloxone (SEDA-16, 78).

- A 35-year-old man developed recurrent respiratory depression after being given alfentanil 0.0125 mg/kg for vitreoretinal surgery (5). General anesthesia was induced with a combination of propofol, rocuronium, and alfentanil, subsequent inhalation of isoflurane, and three additional doses of alfentanil (total 0.04 mg/kg over 2 hours). The pulse oxygen saturation fluctuated and was as low as 89% 180 minutes after extubation.

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The severity of respiratory depression with alfentanil has been assessed in 49 patients undergoing abdominal hysterectomy under general anesthetic, who were randomly allocated to three groups (6). Group 1 did not receive alfentanil during surgery, group 2 received alfentanil 30 μg/kg, and group 3 received a bolus dose of alfentanil 10–20 μg/kg and an alfentanil infusion increasing in increments of 0.25–0.5 mg/kg/minute. In this randomized double-blind study alfentanil had respiratory depressant effects (measured by plethysmography and pulse oximetry), in one patient in group 1 and three each in groups 2 and 3, but there were no cases of clear-cut recurrent respiratory depression.

Nervous system

Increased intracranial pressure in normal pressure hydrocephalus patients has been described (SEDA-17, 79). An acute dystonic reaction has been reported in an untreated patient with Parkinson's disease (SEDA-16, 78).

Simultaneous scalp and depth electrode recordings were performed on five patients with complex partial epilepsy who underwent alfentanil anesthesia induction before depth electrode removal (7). Five equal bolus doses of alfentanil 100 μg were given to each patient at 60-second intervals (total dose 500 μg). Epileptiform activity was increased in three of the five, but without clinical evidence of seizure activity.

Gastrointestinal

Alfentanil is associated with a high incidence of nausea and vomiting. Droperidol can reduce emetic symptoms but moclobemide does not (SEDA-17, 79).

- A 30-year-old woman with multiple body injuries required five general anesthetics in under 7 days for reconstructive surgery and dressing changes. In order to avoid further general anesthesia she was given a target-controlled infusion of alfentanil in 50 ml of 0.9% sodium chloride (a total dose of 5 mg over 35 minutes). There was one self-limiting episode of nausea with no vomiting. Oxygen saturation was 93–98% on air. There were no episodes of hypotension, cardiac dysrhythmias, or sedation (8).

Musculoskeletal

Muscular rigidity involving many muscle groups has been described with alfentanil (SEDA-12, 62).

Immunologic

A possible hypersensitivity reaction to alfentanil was reported in an atopic 13-year-old girl who developed life-threatening bronchospasm and confluent urticarial wheals (9).

Second-Generation Effects

Fetotoxicity

Alfentanil 10 μg/kg in normal parturients does not reduce Apgar scores, but a higher dose (15–30 μg/kg) is recommended for attenuation of the "stress" response in nonpregnant patients. In a randomized, placebo-controlled, double-blind study alfentanil was used in 40 patients in a dose of 10 μg/kg 1 minute before induction of anesthesia in 40 uncomplicated cesarean deliveries to determine whether it would reduce the maternal stress response after tracheal intubation without subsequent neonatal depression (10). There was a small but significant improvement in maternal hemodynamic stability in the alfentanil group at the expense of early but transient neonatal depression.

Susceptibility Factors

Age

Care is needed when alfentanil is used in the elderly, in whom the elimination of alfentanil is slower (11).

Other features of the patient

Recovery times were shorter in smokers than in nonsmokers (12).

Alfentanil is 90% protein bound, and variability in protein binding can affect its actions. In 10 patients who received standardized anesthesia and alfentanil to a target concentration of 150 ng/ml for postoperative analgesia interindividual variation in plasma protein binding explained at least 39% of the interindividual variability in alfentanil requirements (13). There was a high incidence of adverse effects: seven patients had emesis and five had urinary retention.

Drug–Drug Interactions

Benzodiazepines

Muscle rigidity after high-dose opioid can be reduced by the benzodiazepines midazolam and diazepam (SEDA-19, 82).

Diltiazem

Diltiazem reduces the elimination of alfentanil and prolongs the time to tracheal extubation (SEDA-21, 86); erythromycin may do the same (14).

Fluconazole

There has been a double-blind randomized control study of the effect of the antifungal drug fluconazole 400 mg on the pharmacokinetics and pharmacodynamics of intravenous alfentanil (15). Fluconazole given either orally or intravenously 1 hour before alfentanil 20 μg/kg intravenously caused a significant doubling of the half-life, by inhibition of CYP3A4, which metabolizes alfentanil. Intravenous and oral fluconazole both increased alfentanil-induced respiratory depression by reducing the respiratory rate by 10–15% compared with alfentanil alone. Alfentanil should therefore be given cautiously to patients taking fluconazole and the authors suggested that such patients require 60% less alfentanil for maintenance of analgesia, irrespective of the mode of administration of the antifungal drug.

Ketamine

Eight healthy men participated in a 2-day study in which alfentanil was given to a constant plasma concentration of

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50 ng/ml followed by the addition of ketamine at escalating plasma concentrations of 50, 100, and 200 ng/ml (16). The resting hypoventilation induced by alfentanil was antagonized by ketamine 200 ng/ml, but not 50 ng/ml.

Reserpine

The combination of reserpine with alfentanil is reported to cause ventricular dysrhythmias (SEDA-17, 79).

Tranylcypromine

There is no interaction of alfentanil with the monoamine oxidase inhibitor tranylcypromine (SEDA-17, 79).

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Alfuzosin

See also Alpha-adrenoceptor antagonists

General Information

Alfuzosin is a uroselective alpha$_1$-adrenoceptor antagonist used to relieve the symptoms of prostatic hyperplasia (1). Its safety has been investigated in a large prospective 3-year open trial in 3228 patients with benign prostatic hyperplasia. There were no unexpected adverse effects. Only 4.2% of the patients dropped out owing to adverse effects.

In a large database of 7093 patients with lower urinary tract symptoms related to benign prostatic hyperplasia treated for up to 3 years with alfuzosin in general practice, adverse events were reported in a very complex and uninformative way (2). In another paper, the same authors reported on a subcohort of 2829 patients, with special focus on effects on quality of life. Adverse events occurred in 15% of the patients, 1.7% died during the study, and 5.2% had serious effects, which the authors did not detail, but which they stated were not related to treatment. Most adverse effects occurred during the first 3 months of treatment (3). In another database of 3095 Spanish patients taking alfuzosin 5 mg bd for 60 days, adverse events were reported in 3.3% of the patients, and led to drug withdrawal in 1.6%; postural hypotension occurred in 1.8% (4).

Organs and Systems

Nervous system

Dizziness, headache, postural hypertension, and other symptoms familiar from the older alpha-blockers occur primarily during the first 2 weeks of treatment with alfuzosin (1).

Liver

Hepatitis potentially related to alfuzosin has been reported (5).

- A 63-year-old man, who had taken amiloride and alfuzosin for 9 months for hypertension and benign prostatic hyperplasia, became jaundiced. His aspartate transaminase was 3013 IU/l, alanine transaminase 2711 IU/l, alkaline phosphatase 500 IU/l, and total bilirubin 415 μmol/l. Viral causes, autoimmune hepatitis, and biliary obstruction were excluded. After withdrawal of alfuzosin, his liver function tests gradually returned to normal within 6 months.

Immunologic

Dermatomyositis has been attributed to alfuzosin.

- A 75-year-old man, who had taken alfuzosin for 1 year, developed muscle pain and weakness over 4 days,

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accompanied by tenderness and swelling of the deltoid muscles (6). There was erythema, with rash, periungual purpura, and erythematous plaques over the finger joints. Serum CK, LDH, and transaminase activities were raised and ANA was positive. An MRI scan showed findings consistent with inflammation of muscle and a biopsy confirmed the diagnosis of dermatomyositis. Three days after drug withdrawal there was no improvement, so prednisone was started and he recovered within a few days. The temporal relation in this case was weak.

- Dermatomyositis, with typical clinical effects, biochemical tests, electromyography, and muscle biopsy, occurred in a 75-year-old man who had taken alfuzosin for 1 year (7). There was no malignancy and he recovered fully after alfuzosin withdrawal (timing not given).

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Algae

General Information

Algae are members of the kingdom Protista. They include Bacillariophyta (unicellular diatoms), Charophyta (freshwater stoneworts), Chrysophyta (photosynthetic, unicellular organisms), Cyanobacteria (photosynthetic bacteria), Dinophyta (dinoflagellates), and the various types of seaweeds.

There are three major groups of seaweeds: the green algae (Chlorophyta), the brown algae (Phaeophyta), and the red algae (Rhodophyta).

Kelp is a general name for seaweed preparations obtained from different species of Phaeophyta (such as *Ascophyllum nodosum*, *Fucus vesiculosus*, *Fucus serratus*, *Laminaria* species, and *Macrocystis pyrifera*). As kelp contains iodine, it occasionally produces hyperthyroidism (1), hypothyroidism, or extrathyroidal reactions, such as skin eruptions. It can also contain contaminants such as arsenic, and bone marrow depression and autoimmune thrombocytopenia have been described in consequence (2).

Anaphylaxis to *Laminaria* has been described (3–5).

Laminaria has been used to induce abortion and can cause uterine rupture especially in primipara.

- A 32-year-old woman in her 25th week of gestation was hospitalized for endouterine fetal death (6). She had had two previous cesarean sections. Cervical dilatation was induced with a Hagar dilator and laminaria tents, and sudden spontaneous and strong contractions led to uterine rupture.

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Alimemazine

See also Neuroleptic drugs

General Information

Alimemazine is a phenothiazine derivative with sedative antihistaminic and antimuscarinic effects.

Organs and Systems

Nervous system

Neuroleptic malignant syndrome has been reported with alimemazine (1).

- A 4-year-old girl with damage in the basal ganglia who was receiving increasing doses of alimemazine for sedative purposes developed neuroleptic malignant syndrome. The alimemazine was withdrawn and she received dantrolene and supportive measures, including

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ventilation under sedation and paralysis with midazolam and vecuronium. As her symptoms were unchanged, she was given increasing doses of bromocriptine and improved. A few days after bromocriptine withdrawal, the neuroleptic malignant syndrome recurred and was complicated by cardiorespiratory arrest.

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Aliphatic alcohols

See also Disinfectants and antiseptics

General Information

The lower aliphatic alcohols (ethanol, isopropanol, 2-propanol, *N*-propanol, and 1-propanol) are widely used for skin antisepsis. In appropriate concentrations, these alcohols are bactericidal to most of the common pathogenic bacteria, but some rare species survive and can grow, especially since these alcohols are inactive against dried spores.

Seven cases of gaseous edema were observed in the former German Democratic Republic (GDR) after intramuscular injections following rubbing of the skin with ethanol (SEDA-11, 474); this led to a national recommendation that alcohols should not be used to cleanse the skin before intramuscular injection, injection of vasoconstrictors, injections in patients with disturbed peripheral circulation, or before lumbar, paraneural, or intra-articular injection and puncture (SEDA-11, 474) (1).

Organs and Systems

Cardiovascular

Skin disinfection before insertion of peripheral infusion catheters is standard practice. Ethanol 70% has been compared with 2% iodine dissolved in 70% ethanol in a prospective, randomized trial in 109 patients who were given infusions of prednisone and theophylline (2). Phlebitis occurred six times in the ethanol group and 12 times in the iodine group. The relative risk reduction of 53% failed to reach significance, but the power of the study was only 0.55, so there was a 45% chance of missing a true difference. As vast numbers of catheters are inserted each year, a small difference in phlebitis rate could save many patients discomfort.

Skin

Skin reactions to ethanol are extremely rare, although allergic contact dermatitis due to lower aliphatic alcohols has been described (SEDA-11, 474) (3). However, in premature infants of very low birth weight, second-degree and third-degree chemical skin burns were reported after the use of isopropanol, either for conduction in electrocardiography, for the preparation of the umbilical stump for arterial catheterization, or for cleansing before herniotomy (SEDA-11, 474) (4,5). Possible causes are hypoperfusion of the skin by local pressure and general hypoperfusion derived from hypoxia, hypothermia, and acidosis. Immediate drying of the skin of small premature infants after antisepsis with alcoholic formulations and carefully avoiding that the alcohol is absorbed by the diapers is recommended.

Drug Administration

Drug administration route

When it is not possible to perform surgical treatment for omphalocele, application of ethanol is probably the safest method. However, dosage and frequency of application should be as limited, since absorption and intoxication can occur (SEDA-11, 474) (6).

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Alizapride

General Information

Alizapride is a substituted benzamide related to some neuroleptic drugs. In one study alizapride, in doses that were less effective than normal doses of metoclopramide, was equally likely to cause extrapyramidal effects and more likely to cause hypotension (SED-12, 939) (SEDA-17, 413).

In another study, doses of 5 mg/kg (but not less) caused diarrhea and orthostatic hypotension (SEDA-9, 311); the incidence of diarrhea may well be higher than with metoclopramide (1). Other recorded effects include a sensation of bodily heat and trismus (SEDA-10, 323).

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Drug–Drug Interactions

Diazepam

Alizapride increases the absorption rate of concurrently administered diazepam (2).

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Alkylating cytostatic agents — nitrosoureas

See also Cytostatic and immunosuppressant drugs

General Information

Alkylating cytostatic drugs include (all rINNs):

- Nitrosoureas: carmustine, lomustine, nimustine, streptozocin
- *N*-lost derivatives: chlormethine, cyclophosphamide, estramustine
- Others: busulfan, chlorambucil, dacarbazine, ifosfamide, melphalan, mitobronitol, mitomycin, procarbazine, thiotepa, temozolomide, treosulfan.

The first two groups (apart from cyclophosphamide) are covered in this monograph.

Nitrosoureas

Carmustine (BCNU) is used to treat myeloma, lymphomas, breast cancer, and brain tumors, Topical carmustine has been used to treat mycosis fungoides (1).

Lomustine (CCNU) is used to treat lymphomas and some solid tumors, particularly brain tumors, often in combination with procarbazine and vincristine (2).

Nimustine (ACNU) is used to treat malignant glioma (3).

Streptozocin (streptozotocin) is produced by *Streptomyces achromogenes*. It is used to treat metastatic islet cell carcinoma of the pancreas, but because of its high nephrotoxic and emetogenic potential should be reserved for patients with symptomatic or progressive disease.

N-lost derivatives

Chlormethine (mechlorethamine, mustine, nitrogen mustard) is mainly used topically in the early stages of mycosis fungoides (4).

Cyclophosphamide (see separate monograph) is used in the treatment of various solid tumors, and as an immunosuppressant in conditions such as Wegener's granulomatosis and in conditioning regimens for bone marrow transplantation.

Estramustine is a conjugated derivative of estradiol and chlormethine, mainly used to treat prostate cancer (5,6).

Organs and Systems

Respiratory

Carmustine pulmonary toxicity is well documented. Eight patients developed interstitial pulmonary fibrosis 12–17 years after exposure to carmustine in a total dose of carmustine of 770–1410 mg/m^2 (7).

Lung fibrosis has been described in a long-term follow up 13–17 years after treatment of 31 children given carmustine for brain tumors; 6 died, and of 8 still available for study, 6 had upper zone fibrotic changes of their lungs on X-ray (8).

Sensory systems

A 2.7% ocular complication rate in 112 patients treated with a cumulative dose of carmustine 370 mg/m^2 for intracranial tumors has been recorded (9).

Eye pain and blindness due to retinal and optic nerve damage are recognized hazards of intracarotid carmustine therapy reference. They are thought to be due, at least in part, to the ethanol content of the diluent. Nimustine (ACNU) is water-soluble and ethanol-free. In a study of 30 patients with malignant gliomas, 123 infusions of nimustine and 53 of carmustine were administered (10). Eye pain was experienced during all carmustine infusions but not with nimustine, and one patient developed unilateral blindness after carmustine. In another study, carmustine was administered in solution with 5% dextrose in water (11). All the patients experienced ipsilateral orbital pain and scleral erythema, suggesting that carmustine itself contributes to the toxicity. Seven additional patients were treated wearing an ocular compression device to decrease blood flow and had not experienced any ocular complications.

Mineral balance

A patient with androgen-independent prostate cancer developed hypocalcemia during treatment with estramustine (12). The total serum calcium concentrations before and after the initiation of estramustine were 2.1 and 1.1 mmol/l respectively. This prompted a retrospective survey of hypocalcemia in 135 consecutive patients taking estramustine; 20% were affected. The authors speculated that estramustine may cause hypocalcemia by inhibiting mobilization of calcium and the action of parathyroid hormone on the skeleton.

Hematologic

Of 91 patients treated with topical carmustine, three developed reversible bone marrow depression (13).

Urinary tract

Nephrotoxicity can rarely occur with lomustine, and all cases have been associated with cumulative doses of greater than 1500 mg/m^2 (14).

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Skin

Local adverse effects of topical carmustine include tender erythema, superficial denudation or bullae, contact allergy, pigment alterations, and patchy telangiectasia (1).

Reproductive system

Gynecomastia severe enough to necessitate withdrawal of therapy was the main adverse effect of estramustine 560 mg/day for more than 1 year in prostatic carcinoma (15).

Breast pain with vaginal bleeding and diarrhea were dose-limiting when estramustine 840 mg/day was given for breast cancer (16).

Immunologic

Topical carmustine can cause hypersensitivity reactions, and three previous cases have been supplemented by a fourth (17).

- A 67-year-old woman used topical carmustine for a stage-I cutaneous T cell lymphoma. A second course was started after 6 months and resulted in severe erosive inflammation at the site of treatment. Patch tests with carmustine 0.1, 0.5, and 1% in water all gave positive results; 22 controls were tested with 0.1% carmustine and lomustine and were all negative.

The most common adverse effect of chlormethine is an allergic contact dermatitis (18). Neither reducing the concentration of drug applied nor shortening the time of contact appreciably reduces the frequency of this adverse effect, which occurs in 30–80% of patients, although in one study of 203 patients with mycosis fungoides the use of chlormethine ointment was associated with contact hypersensitivity in under 10% of cases (4). In an open, prospective study in 39 patients with cutaneous T cell lymphomas or parapsoriasis, chlormethine was applied topically and then washed off after 1 hour (19). There was cutaneous intolerance in 19 patients, six of whom had an allergic contact dermatitis after a mean period of 9.3 weeks, while the other 13 developed irritant contact dermatitis after a longer period. Cutaneous intolerance did not differ significantly according to the number of applications per week or the extent of body area treated. Comparison with published studies showed no significant difference in the number of cases of cutaneous intolerance after short-term application, although their occurrence was delayed. Therapeutic response was decreased appreciably by short-term application as compared with results in the literature.

Long-Term Effects

Tumorigenicity

Chlormethine can act as a tumor promotor. In most cases squamous cell carcinomas and basal cell carcinomas have been reported. Two cases of small malignant melanoma, 3 mm in diameter, have been reported in patients with mycosis fungoides stage 1a, with latency intervals of 18 and 10 months after withdrawal of local application, which had been conducted for 18 months and almost 3 years respectively (20).

Second-Generation Effects

Fertility

In 21 boys treated with carmustine or lomustine alone or in combination with procarbazine and vincristine for brain tumors, there were 20 cases of persistent testicular damage (21). From assessment of testicular size it was thought that most those affected would remain infertile. This supports the idea that germinal epithelium is more susceptible than Leydig cells to cytostatic-induced damage.

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Alkylating cytostatic agents — *N*-lost derivatives

See also Cytostatic and immunosuppressant drugs

General Information

The *N*-lost cytostatic drugs are alkylating agents that include chlormethine (mechlorethamine, mustine, nitrogen mustard), cyclophosphamide, and estramustine (all rINNs). Chlormethine is mainly used topically in the early stages of mycosis fungoides (1). Estramustine is a conjugated derivative of estradiol and chlormethine, mainly used to treat prostate cancer (2).

Organs and Systems

Mineral balance

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Allopurinol

General Information

Allopurinol is an inhibitor of xanthine oxidase, used to lower serum uric acid concentrations in the long-term treatment of gout and in the prevention of acute gout in people who are susceptible to hyperuricemia. Allopurinol is itself metabolized to its active metabolite, oxipurinol, by xanthine oxidase.

Comparisons with antimonials in leishmaniasis

Allopurinol has an antileishmanial effect in vitro and in animals, its effect being strongly increased by the addition of antimonial compounds. Allopurinol alone as well as in combination with meglumine antimoniate has been used in clinical studies. In a small study in patients with leishmaniasis and HIV infection, clinical and parasitological cure was achieved in four of five cases treated for 4 weeks, but in only one of the six treated for 3 weeks (1).

Allopurinol and meglumine antimoniate (Glucantime) have been evaluated in a randomized controlled trial in 150 patients with cutaneous leishmaniasis (2). They received oral allopurinol (15 mg/kg/day) for 3 weeks or intramuscular meglumine antimoniate (30 mg/kg/day, corresponding to 8 mg/kg/day of pentavalent antimony, for 2 weeks), or combined therapy. There were a few adverse effects in those who used allopurinol: nausea, heartburn ($n = 3$), and mild increases in transaminases ($n = 2$). These symptoms subsided on drug withdrawal.

In an open study, 72 patients each received meglumine antimoniate (60 mg/kg/day) or allopurinol (20 mg/kg/day) plus low-dose meglumine antimoniate (30 mg/kg/day) for 20 days, and each was followed for 30 days after the end of treatment (3). Only six patients in the combined treatment group complained of mild abdominal pain and nausea; however, one patient who received meglumine antimoniate developed a skin eruption. Generalized muscle pain and weakness occurred in four patients.

Organs and Systems

Nervous system

Apart from headache and vertigo, adverse effects of allopurinol involving the nervous system are rare. Transient peripheral neuropathy has been reported (SEDA-18, 107).

Seizures, which were unresponsive to standard anticonvulsive therapy, disappeared when allopurinol was withdrawn in a patient with a primary neurological disorder (4).

In contrast, occasional reports that allopurinol may have an anticonvulsive effect prompted its use in therapy-resistant epileptic patients. Withdrawal in one of these patients precipitated a convulsive status epilepticus (SEDA-16, 114).

- A 60-year-old man developed aseptic meningitis after taking allopurinol on two separate occasions (5).

Sensory systems

Allopurinol can reportedly cause cataracts (6), but in one study there was no evidence to confirm this risk (SEDA-15, 104).

Hematologic

Eosinophilia and leukocytosis are part of a general hypersensitivity reaction to allopurinol. Leukopenia and neutropenia are sometimes associated with allopurinol. Patients taking cytostatic therapy are more susceptible to bone marrow depression if they take allopurinol as well (SED-9, 155); however, this has not been confirmed in other reports (7). Agranulocytosis is extremely rare.

Cases of aplastic anemia, some in patients with renal insufficiency, have been reported (SEDA-13, 84) (8–10), confirming the need to reduce the dose of allopurinol in patients with renal insufficiency and to monitor toxicity (SEDA-16, 114).

Liver

Hepatitis can be part of a generalized hypersensitivity reaction. Hepatotoxicity ranges from mild granulomatous hepatitis to severe hepatocellular necrosis (SED-5, 155) (SEDA-4, 70). Renal impairment seems to be a prerequisite for a severe hepatic reaction.

Urinary tract

Vasculitis due to a general hypersensitivity reaction can cause renal insufficiency and oliguria. Histological

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findings are vasculitis and tubular necrosis with fibrinoid deposits. Acute renal insufficiency due to xanthine crystals in the kidney tubules during antineoplastic chemotherapy has been reported (11).

Since allopurinol blocks xanthine conversion to uric acid, urinary xanthine excretion is increased, creating a risk of xanthine crystal formation in the urinary system or even in muscles; this can result in nephrolithiasis (12). It is still an open question whether a predisposition to renal disease or renal disease itself is required to precipitate these adverse effects. It is also not known whether increased excretion of orotic acid, due to an interaction of allopurinol with pyrimidine formation, has any consequences for these adverse effects or for its role in reducing glucose tolerance.

Granulomatous interstitial nephritis (SEDA-12, 94) and two cases of interstitial cystitis have been described during long-term treatment with allopurinol (SEDA-21, 108).

Skin

Skin reactions have a general incidence of 10%, are more common in patients with renal disorders and in those taking thiazide diuretics, and are closely correlated with persistently high serum concentrations of oxipurinol (13). The positive association of severe skin reactions with HLA haplotypes AW33 and B17 suggests a genetic predisposition to these reactions (14).

Rash, urticaria, erythematous eruptions, papulovesicular reactions, and pruritus may be the only signs of hypersensitivity or may be part of a generalized reaction.

Dangerous reactions such as exfoliative dermatitis and Lyell's syndrome rarely develop (SEDA-5, 108).

Unusual skin lesions with a benign lymphocyte infiltration have been documented (SEDA-14, 96). Toxic pustuloderma can be added to the list (SEDA-18, 108).

An allopurinol-induced fixed drug eruption was successfully treated by desensitization (SEDA-21, 108).

Allopurinol can uncover latent lichen planus (15).

Musculoskeletal

Myositis and rhabdomyolysis have been attributed to allopurinol (16).

- A 73-year-old woman with chronic renal insufficiency developed generalized muscular weakness and pain 6 days after starting to take allopurinol 200 mg/day. Her serum creatine kinase activity was increased and the diagnosis was rhabdomyolysis, attributed to severe myositis. The serum concentration of oxipurinol was also high. The muscle weakness resolved in 7 weeks with intermittent hemodiafiltration.

Fever, myalgia, and arthralgia have been reported in a patient taking captopril and allopurinol (17).

Acute gout can be exacerbated at the beginning of allopurinol treatment unless the drug is combined with colchicine or an anti-inflammatory drug (18).

Immunologic

Hypersensitivity reactions to allopurinol occur in about 10–15% of patients. Desensitization with both oral and intravenous allopurinol has been successful (SEDA-17, 114). In the allopurinol hypersensitivity syndrome, the skin is most prominently involved (19). Symptoms develop after 2–5 weeks of treatment. Hepatic involvement is present in 40% and renal involvement in 45%; 25% of patients have combined renal and hepatic lesions. The hypersensitivity syndrome has been estimated to occur in 1 in 1000 hospitalized patients. A major complication is an extensive cutaneous staphylococcal infection with septicemia and endocarditis. Gastrointestinal hemorrhage, disseminated intravascular coagulation, adult respiratory distress syndrome, cerebral vasculitis, and peripheral axonal neuropathy have also been described (SEDA-21, 109). Death occurs in 20–30% of patients with severe hypersensitivity syndrome.

One report has presented evidence of a possible association between severe drug-induced erythema multiforme and reactivation of infection with human herpesvirus 6. The reactivation is thought to have contributed in some way to the development of allopurinol hypersensitivity reactions (20).

Allopurinol has been associated, albeit rarely, with pANCA (antineutrophil cytoplasmic antibodies with a peripheral pattern) positivity. A generalized cutaneous vasculitis has been associated with the presence in the serum of pANCA and antimyeloperoxidase antibodies (21). A skin biopsy of a lesion showed leukocytoclastic vasculitis with eosinophilic infiltration. Allopurinol was withdrawn and the symptoms resolved completely. The possible drug causes of ANCA-positive vasculitis with high titers of antimyeloperoxidase antibodies in 30 new patients have been reviewed (22). The findings illustrate that this type of vasculitis is a predominantly drug-induced disorder. Only 12 of the 30 cases were not related to a drug. Allopurinol was implicated in two of the other 18 cases.

Treatment of the allopurinol hypersensitivity syndrome includes drug withdrawal and the administration of systemic corticosteroids (prednisone 40–200 mg/day) for several months. Desensitization strategies allow some patients to resume allopurinol therapy later without any further problem (23–25). The standard desensitization protocol consists of an initial allopurinol dosage of 50 μg/day, increasing every 3 days to a target of 50–100 mg/day. The interval between dosage increases can be extended to 5 days or more in elderly patients with multiple co-morbidity. Using this protocol, desensitization was successful in 25 out of 32 patients (78%); 28 patients completed the desensitization protocol and 21 did so without requiring deviation from the standard dosage schedule and without adverse effects. During the follow-up for 902 patient-months, seven of the 28 patients had recurrent skin eruptions after completing the desensitization protocol and after rechallenge with allopurinol. Desensitization to allopurinol is not recommended for all patients, but it can be useful in selected patients who have had a pruritic maculopapular eruption during treatment with allopurinol and who cannot be treated with other drugs.

Susceptibility Factors

Renal disease

Renal impairment and diuretic therapy predispose to an increased frequency of adverse effects. The exact

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mechanisms have still to be elucidated. The active metabolite, oxipurinol or alloxanthine, accumulates in renal insufficiency and also in patients taking a low protein diet (13).

Drug–Drug Interactions

Aluminium hydroxide

When aluminium hydroxide is given with allopurinol, the serum uric acid concentration can increase, probably because the antacid reduces the absorption of allopurinol (SEDA-13, 84).

Ampicillin

Concomitant administration of allopurinol with ampicillin may increase the incidence of adverse skin reactions. In one study, these occurred in 22% of patients taking the combination (26). However, this interaction was not confirmed in a later investigation (27).

Ciclosporin

Two well-documented reports have described a marked increase in ciclosporin serum concentrations when allopurinol was co-administered (SEDA-18, 108).

Cytostatic drugs

The risk of bone marrow depression by cytostatic drugs is potentiated by allopurinol, which also appears to potentiate the therapeutic effect of purine cytostatic drugs, since it competitively inhibits their metabolic breakdown. Studies in animals suggest that this reaction occurs only with oral mercaptopurine (28), although there is older evidence that the toxicity of cyclophosphamide and other cytostatic drugs can be increased by allopurinol (SED-9, 156). The danger of combining allopurinol with azathioprine has been confirmed by cases of bone marrow suppression, particularly in patients with impaired renal function (SEDA-16, 114).

Thiazides

Thiazides enhance the excretion of orotic acid, which is already increased during allopurinol treatment, but the implications for the frequency of adverse effects are not known.

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Almitrine

General Information

Almitrine is a respiratory stimulant that improves hypoxemia in about 80% of patients with severe chronic obstructive pulmonary disease (SEDA-17, 212). Oral almitrine bimesilate (100 mg/day) increased PaO_2 in patients with severe chronic obstructive pulmonary disease without altering mean pulmonary artery pressure (1). Adverse effects were rarely observed and it was concluded that long-term treatment was safe. In other studies, respiratory, digestive, and neurological symptoms have been noted but were often pre-existent (2,3).

Organs and Systems

Gastrointestinal

Mild gastrointestinal symptoms have sometimes occurred (nausea, accelerated intestinal transit) but they regress spontaneously or after symptomatic treatment (2,3).

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Aloeaceae

See also Herbal medicines

General Information

The family of Aloeaceae contains the single genus *Aloe*.

Aloe capensis and *Aloe vera*

Aloe capensis and *Aloe vera* (*Aloe barbadensis*) (Barbados aloe, burn plant, Curacao aloe, elephant's gall, first-aid plant, Hsiang dan, lily of the desert) contain several active constituents called aloins, including barbaloin, isobarbaloin, and aloe-emodin. Laxative anthranoid derivatives occur primarily in various laxative herbs (such as aloe, cascara sagrada, medicinal rhubarb, and senna) in the form of free anthraquinones, anthrones, dianthrones, and/or O- and C-glycosides derived from these substances. They produce harmless discoloration of the urine. Depending on intrinsic activity and dose, they can also produce abdominal discomfort and cramps, nausea, violent purgation, and dehydration. They can be distributed into breast milk, but not always in sufficient amounts to affect the suckling infant. Long-term use can result in electrolyte disturbances and in atony and dilatation of the colon. Several anthranoid derivatives (notably the aglycones aloe-emodin, chrysophanol, emodin, and physicon) are genotoxic in bacterial and/or mammalian test systems (SEDA-12, 409).

Aloe species contain laxative anthranoid derivatives, the main active ingredient being isobarbaloin. Large doses are claimed to cause nephritis and use during pregnancy is discouraged, since intestinal irritation might lead to pelvic congestion.

Aloes have been used on the skin to reduce the pain and swelling of burns, improve the symptoms of genital herpes and other skin conditions such as psoriasis, and to help heal wounds and frostbite. Aloe has been used orally to treat arthritis, asthma, diabetes, pruritus, peptic ulcers, and constipation. It may be effective in inflammatory bowel disease (1). It may reduce blood glucose in diabetes mellitus and blood lipid concentrations in hyperlipidemia (2).

Adverse effects

Aloe can reportedly cause muscle weakness, cardiac dysrhythmias, peripheral edema, bloody diarrhea, weight loss, stomach cramps, itching, redness, rash, pruritus, and a red coloration of the urine.

Liver

Hepatitis in a 57-year-old woman was linked to the ingestion of *A. vera*; the hepatitis resolved completely after withdrawal (3).

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Gastrointestinal

- Melanosis coli occurred in a 39-year-old liver transplant patient who took an over-the-counter product containing aloe, rheum, and frangula (4). The typical brownish pigmentation of the colonic mucosa developed over 10 months. The medication was withdrawn and follow-up colonoscopy 1 year later showed normal looking mucosa. However, a sessile polypoid lesion was found in the transverse colon. Histology showed tubulovillous adenoma with extensive low-grade dysplasia.

Skin

Four patients had severe burning sensations after the application of *A. vera* to skin that had been subjected to chemical peel or dermabrasion (5).

Aloes can cause contact sensitivity (6,7).

Urinary tract

Acute renal insufficiency been attributed to *A. capensis*.

- A 47-year-old South African man developed acute oliguric renal insufficiency and liver dysfunction after taking an herbal medicine prescribed by a traditional healer to "clean his stomach" (8). After withdrawal of the remedy and dialysis he recovered slowly, but his creatinine concentration did not fully normalize. Analysis of the remedy showed that it consisted of *A. capensis* (*Aloe ferox* Miller), which contains the nephrotoxic compounds aloesin and aloesin A.

The authors also mentioned that 35% of all cases of acute renal insufficiency in Africa are due to traditional remedies.

Drug interactions

Massive intraoperative bleeding in a 35-year-old woman has been attributed to an interaction of preoperative *A. vera* tablets and sevoflurane, since both may inhibit platelet function (9).

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Alpha$_1$-antitrypsin

General Information

Alpha$_1$-antitrypsin neutralizes the activity of neutrophil elastase and is used to treat patients with homozygous deficiency of Alpha$_1$-antitrypsin (1). Adverse effects occur only rarely (2).

Organs and Systems

Cardiovascular

Chest pain and cyanosis occurred in 14 patients but the symptoms seemed to be related to the presence of sucrose in the product (1).

Immunologic

An acute allergic reaction to alpha$_1$-protease inhibitor has been reported (3).

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Alpha-adrenoceptor antagonists

See also Individual agents

General Information

The postsynaptic alpha-adrenoceptor antagonists, indoramin, prazosin, and related quinazoline derivatives, block alpha$_1$-adrenoceptor-mediated vasoconstriction of peripheral blood vessels (both arterial and venous) and are effectively peripheral vasodilators (1,2). Qualitatively and quantitatively common adverse effects are generally similar, although indoramin has additional effects on other neurotransmitter systems and therefore tends to be considered separately. Their use in benign prostatic hyperplasia has been reviewed (3,4).

Several recent articles have reviewed the pharmacology, pharmacokinetics, mode of action, use, efficacy, and adverse effects of the selective alpha$_1$-adrenoceptor

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blockers doxazosin, prazosin, and terazosin in benign prostatic hyperplasia (5).

The frequencies and the profile of adverse effects of five major classes of antihypertensive agents have been assessed in an unselected group of 2586 chronically drug-treated hypertensive patients (6). This was accompanied by a questionnaire-based survey among patients attending a general practitioner. The percentage of patients who reported adverse effects spontaneously, on general inquiry, and on specific questioning were 16, 24, and 62% respectively. With alpha-blockers the figures were 15, 25, and 50%. The percentage of patients in whom discontinuation was due to adverse effects was 6.8% with alpha-blockers. Alpha-blockers were associated with less fatigue, cold extremities, sexual urge, and insomnia, and more bouts of palpitation than other antihypertensive drugs (RR = 2.5; CI = 1.2, 5.4). The authors did not find a significant effect of age on the pattern of adverse effects. Women reported more effects and effects that were less related to the pharmacological treatment.

The first-dose effect (profound postural hypotension and reflex tachycardia) is a well-recognized complication of the first dose of prazosin and related agents. This phenomenon is dose-related and can usually be avoided by using a low initial dosage taken at bedtime. During long-term treatment, orthostatic hypotension and dizziness is reported by about 10% of patients.

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Alpha-glucosidase inhibitors

General Information

Alpha-glucosidase inhibitors are competitive inhibitors of 1α-glucosidases, enzymes that are located in the brush border of epithelial cells, mainly in the upper half of the small intestine. The enzymes degrade complex carbohydrates into monosaccharides, which are absorbed. The alpha-glucosidase inhibitors bind reversibly in a dose-dependent manner to the oligosaccharide binding site of these enzymes and delay the degradation of polysaccharides and starch to glucose. They slow down food digestion in the gut, reducing peak blood glucose concentrations after meals. They also prevent reactive hypoglycemia, as can be seen after gastric operations, in dumping syndrome, and in idiopathic forms. When carbohydrates appear in the colon, bacterial fermentation can occur, leading to gastrointestinal adverse effects, of which flatulence and loose stools are the most frequent. During long-term treatment the colonic bacterial mass can increase. In elderly patients acarbose increases insulin sensitivity but not insulin release (1). Acarbose may reduce the incidence of colon cancer, the risk of which is 30% higher in people with diabetes than in the non-diabetic population (2).

The alpha-glucosidase inhibitors (polyhexose mimickers) in use are acarbose (rINN) (2–4), miglitol (rINN) (5–7), and voglibose (rINN), which is 20 times more potent (8).

Acarbose is not well absorbed and is mostly excreted in the feces. Miglitol is well absorbed from the gut and is almost completely excreted unchanged in the urine (9).

Observational studies

In a 2-year study of the tolerability and safety of acarbose in 2035 patients the incidence of adverse effects was 7.5% and of withdrawals 2.5% (10). Of 1907 patients, 444 (23%) reported one or more adverse events. In 143 patients the physician considered that there was a probable or possible relation between the adverse event (all gastrointestinal) and acarbose. There were 77 deaths, but none was considered to be related to acarbose; 52 stopped taking acarbose because of an adverse event and 45 were considered to be related to acarbose. Laboratory analyses were all within the reference ranges. HbA_{1c} fell by 1.92%.

The addition of metformin to acarbose in 49 patients produced a synergistic effect (11).

Of 1027 patients, 283 used acarbose as the treatment of choice (12). In 250 cases the physician was not sure of the benefit; 124 of these patients took acarbose and 126 patients took placebo besides regular therapy. In those taking acarbose HbA_{1c} fell. The adverse effects were bloating, flatulence, abdominal cramps, and diarrhea; there were moderate increases in serum transaminases.

Comparative studies

Voglibose and acarbose have been compared in 32 patients insufficiently treated by diet in an open crossover study (13). The metabolic results were identical. There were fewer adverse reactions in those who took voglibose. There was increased flatulence with acarbose in 96% and with voglibose in 57%; abdominal distension was reported in 17 and 10% respectively.

In an open study in 57 patients acarbose and gliclazide had the same effects on HbA_{1c}, blood glucose, and lipids, but the ratio of HDL to LDL cholesterol increased with acarbose (14). Acarbose caused flatulence in 30% and diarrhea in 3% and gliclazide caused at least one mild attack of hypoglycemia in 10%.

Placebo-controlled studies

The effect of adding acarbose (maximum 100 mg tds) or placebo to insulin (15) or metformin (16) has been investigated in 1946 patients with type 2 diabetes. The results were comparable with the results of the UK Prospective

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Diabetes Study (17). After 3 years, 39% were still using acarbose compared with 58% using placebo. The main reasons for stopping were flatulence (30 versus 12%) or diarrhea (16 versus 8%). After 3 years the HbA_{1c} concentration was 0.5% lower (median 8.1 versus 8.6%). Acarbose was equally effective when added to diet, sulfonylurea, metformin, or insulin.

When acarbose or placebo was given to patients with type 1 diabetes taking insulin, acarbose reduced postprandial blood glucose but there was no difference in HbA_{1c}; the only adverse effects were gastrointestinal (18).

In a double-blind, placebo-controlled study in 74 patients for 2 years, acarbose 100 mg tds, after a stepwise increase in dosage over 5 weeks, improved HbA_{1c} (–1.71%) more than placebo (19). Two patients taking acarbose withdrew with drug-related adverse effects.

In a randomized, double-blind, placebo-controlled, crossover study 12 healthy subjects took acarbose 100 mg or voglibose 0.3 mg tds (20). Postprandial glucose, the rise in plasma immunoreactive insulin, and urinary immunoreactive C-peptide were higher with acarbose than voglibose. The flatus score was higher with acarbose than voglibose, but the stool score was not different and was higher than with placebo. Voglibose before the evening meal may improve nocturnal hypoglycemia during intensive insulin therapy (21).

Acarbose reduced insulin resistance in 192 patients over 65 years of age (mean age 70) in a double-blind, placebo-controlled study (22). HbA_{1c} was significantly but modestly reduced. The most frequent adverse effect was flatulence, which caused 12 patients (9 taking acarbose and 3 taking placebo) to withdraw.

In a multicenter, double-blind, placebo-controlled study, 81 patients, in whom treatment with metformin was inadequate, received extra acarbose or placebo during 24 weeks after a 4-week run-in period to establish the optimal dose of acarbose (23). HbA_{1c} was reduced by 1.02% and fasting blood glucose by 1.13 mmol/l. Gastrointestinal adverse effects were more common in the acarbose group.

In a placebo-controlled study of 154 patients taking glibenclamide or metformin, miglitol (starting at 25 mg tds and increasing to 50 or 100 mg tds for 24 weeks) caused more meteorism, flatulence, and diarrhea (24). When miglitol was added to metformin, HbA_{1c} improved and there was weight loss. In another study in 318 patients, more of the patients taking miglitol only or miglitol plus metformin withdrew because of flatulence and diarrhea than in the other groups (25).

The effects of miglitol 25 or 50 mg tds have been compared with placebo and various doses of glibenclamide in 411 patients aged over 60 years (mean 68 years) with mild type 2 diabetes insufficiently controlled by diet for 56 weeks (26). HbA_{1c} fell after 1 year by 0.92% (glibenclamide), 0.49% (miglitol 25 mg), and 0.40% (miglitol 50 mg). Gastrointestinal events were most common in patients taking miglitol. Most (88%) of the hypoglycemic events were minor and occurred in the patients taking glibenclamide. Mean body weight increased continuously and significantly in those taking glibenclamide. In the other groups weight fell by more than 1 kg. The rate of withdrawal was the same in all groups; withdrawal was mostly occasioned by cardiovascular effects in those taking glibenclamide and by hyperglycemia, flatulence, or diarrhea in those taking miglitol.

When patients with inadequately controlled type 2 diabetes used glibenclamide plus metformin, miglitol, or placebo for 24 weeks in addition to their earlier therapy, fasting blood glucose concentrations improved with miglitol (24). Flatulence and diarrhea were significantly more common with miglitol. No patient stopped taking miglitol because of adverse effects.

General adverse effects

Acarbose and miglitol have been reviewed (13,27,28). Their major adverse effects are flatulence, abdominal discomfort, diarrhea, and bloating, particularly at the start of therapy, which sometimes prevent further use. They should not be given to patients with intestinal obstruction, malabsorption, inflammatory bowel disease, or hepatic impairment.

Organs and Systems

Sensory systems

Acarbose can cause altered taste sensation (29).

Metabolism

When acarbose is combined with insulin, the greatest effects are seen with regimens that involve only once- or twice-daily administration. The alpha-glucosidase inhibitors seem to be less effective when they are combined with intensive insulin therapy (30). In combination with insulin or oral hypoglycemic drugs the frequency of hypoglycemic episodes can increase; sucrose or higher carbohydrates are reported to be less effective, which can be understood from the mechanism of action.

Extreme weight loss has been attributed to acarbose (31).

- A 47-year-old woman weighing 59 kg took acarbose 50 mg tds. Her blood glucose improved but she lost about 1 kg/month. She had a sore tongue without oral ulcers and no evidence of malabsorption. Later she developed general weakness and iron deficiency anemia but no other evidence of malabsorption. After she had lost 7 kg in 5 months, acarbose was withdrawn. Her complaints disappeared, her weight normalized, and she had no signs of iron deficiency anemia, even without iron therapy.

Extreme weight loss due to acarbose is rare. In this case the mechanism was unclear.

In 36 Japanese patients who were relatively lean but had excess abdominal fat, glibenclamide and voglibose caused loss of weight and abdominal fat (32). The loss of abdominal fat was related to glycemic control. The ratio of subcutaneous to abdominal fat shifted toward subcutaneous fat only in those who took voglibose. Both voglibose and glibenclamide improved insulin sensitivity and the acute response to insulin.

Gastrointestinal

Abdominal pain and diarrhea with malabsorption have been described in patients taking acarbose, which can also cause carbohydrate malabsorption (33).

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A review of miglitol included data on adverse effects in 3585 patients in well-designed clinical trials (34). Only the adverse effects in the gastrointestinal tract occurred with a significantly greater incidence with miglitol 50 or 100 mg tds. The adverse effects were the same as with other drugs in this class: flatulence, diarrhea, dyspepsia, and abdominal pain. There were no differences with monotherapy or combination therapy or in relation to age or ethnicity. There were more episodes of hypoglycemia when miglitol was combined with insulin but not with oral agents. The incidence of cardiovascular events was the same as with placebo.

Long-term acarbose had a good effect on late dumping syndrome in six patients with type 2 diabetes; one patient complained of increased flatulence (35).

Although acarbose often causes abdominal complaints, dietary manipulation has not been used to reduce the complaints (36).

In 120 patients with type 1 diabetes, acarbose lowered postprandial glucose but did not reduce HbA_{1c} (17). Four patients taking acarbose withdrew because of gastrointestinal effects, which improved after withdrawal. One of the placebo group withdrew because of gastrointestinal problems and one other patient taking acarbose withdrew with a Bell's palsy, which was not considered to be related to acarbose.

Ileus has also been reported with acarbose (37–40).

Paralytic ileus with intestinal pneumatosis cystoides has been reported (39).

- An 87-year-old woman, who took acarbose, glibenclamide, and mannitol (for constipation), developed abdominal distention and loss of appetite. An X-ray showed distention of the small intestine, with pockets of small gas bubbles in the submucosal space. When her drugs were withdrawn, her symptoms subsided and the radiological evidence of ileus disappeared by 5 days. Although she had an atonic bladder, there were no signs of neuropathy. She was also hypothyroid, which could have contributed.

Acarbose may also have caused pneumatosis cystoides intestinalis in a 55-year-old woman with pemphigus vulgaris (41).

Most cases of ileus with acarbose have been reported in Japan.

- A 73-year-old man with diabetic gangrene who had used insulin and acarbose 300 mg/day for 15 months developed ileus with abdominal pain and vomiting after he took PL granules (containing salicylamide, paracetamol, anhydrous caffeine, and promethazine methylene disalicylate) for a common cold (40). The ileus subsided after acarbose and the other drugs were withdrawn.

Although the ileus in this case was not clearly related to the use of acarbose, the combination of acarbose, which can cause ileus, with the other drugs that the patient was taking, may have caused it. The anticholinergic effect of promethazine methylene disalicylate may have contributed.

Lymphocytic colitis activated by acarbose has been reported (42).

- A 52-year-old man developed watery diarrhea 6–8 times a day 2 weeks after he had started to take acarbose 100 mg. In 3 weeks he lost 3 kg. Duodenal biopsies were normal; colon biopsies showed a large increase in intraepithelial lymphocytes. The mononuclear cells expressed CD-25, and HLA-DR antigen was increased in epithelial cells. Within 4 days of acarbose withdrawal the diarrhea had disappeared, and biopsies 4 months later showed that CD-25 expression in the cells of the lamina propria was improved and HLA-DR was no longer expressed by the epithelial cells. On rechallenge the diarrhea recurred within 3 days. Biopsies showed pronounced HLA-DR in the epithelial cells and CD-25 expression in some mononuclear cells in the lamina propria.

Non-digestable sugar substitutes and alpha-glucosidase inhibitors should probably not be used in combination.

Liver

Liver damage with raised liver enzymes has been described (16,43). Four case of liver damage by acarbose have been described in women aged 52–57, three established (44) and one probable (45). All had signs of liver impairment within 2–8 months after starting to take acarbose and the changes subsidized within a month after withdrawal. The first patient was given acarbose again; her liver enzymes increased after 3 days and normalized within 10 days after withdrawal. The second and third patients had liver biopsies, which confirmed hepatic changes.

- A 45-year-old man took acarbose 50 mg tds for a year and developed an aspartate transaminase of 62 U/l and an alanine transaminase of 127 /l, with negative serology; 3 months later the alanine transaminase was 153 U/l. After withdrawal of acarbose his liver enzymes normalized (46).
- A 54-year-old woman had fatigue and dark urine after taking acarbose 50 mg tds for 5 months (46). Her aspartate transaminase was 2436 U/l, alanine transaminase 2556 U/l, γ-glutamyl transpeptidase 601 U/l, and alkaline phosphatase 174 U/l; serology was negative and she had a normal liver and gall bladder on ultrasound. Her liver enzymes normalized 5 months after withdrawal.
- A 58-year-old man taking gliclazide 80 mg/day, atenolol 100 mg/day, and pravastatin 10 mg/day started to take acarbose 150 mg/day and benazepril 10 mg/day (47). After 2 weeks he developed weakness and myalgia and 1 week later his alanine transaminase was 22 times higher and aspartate transaminase 9 times higher than the upper limits of the reference ranges. Benazepril and pravastatin were withdrawn and his hypoglycemic therapy was changed to insulin. No viral or other antibodies related to liver disease were found. He improved and was given glibenclamide and acarbose instead of insulin. His enzymes increased 3 weeks later without subjective signs and he had an eosinophilia. A liver biopsy showed intralobular and periportal necrosis of liver cells and mononuclear infiltrates. Acarbose was withdrawn and he improved.
- A 57-year-old woman developed hepatitis 2 months after starting to take acarbose 100 mg tds (48). No other causes of hepatitis were found. Liver function tests normalized 3 months after withdrawal. Acarbose was reintroduced 3 years later and she again developed acute hepatitis. Liver function tests became normal 2 months after withdrawal.

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- A 74-year-old woman who had used acarbose for 3 months developed progressive weakness and jaundice (49). Her bilirubin was 152 μmol/l (direct bilirubin 96 μmol/l). All of her liver enzymes were substantially raised. All other investigations were normal, except that she was positive for hepatitis C antigen. After withdrawal of acarbose everything became normal within 1 month.
- A 73-year-old woman who had taken acarbose 450 mg/day for 3 months became very tired and icteric (50). Her total bilirubin was 427 μmol/l (direct bilirubin 335 μmol/l) and her liver enzymes were very high. Liver biopsy showed cholestasis and cytolysis without eosinophils. Acarbose was continued for 3 days and her condition did not change. When the acarbose was withdrawn she improved rapidly.
- Another patient taking acarbose also had a serum alanine transaminase three times the upper limit of the reference range, but she had positive serology for hepatitis A (16).

Comparable reports have prompted a questionnaire investigation of 770 patients with type 2 diabetes at the start of acarbose therapy (51). Patients with one or more susceptibility factors for liver damage underwent ultrasonography and autoantibody assays. There was silent liver disease in 13% and 20 patients had a fatty liver without hepatic disease. In 15% of these patients there were slight reversible changes in transaminase activity after acarbose. This supports the supposition that severe hepatotoxic reactions to acarbose are idiosyncratic.

However, in a double-blind study in 100 patients with compensated non-alcoholic liver cirrhosis and type 2 diabetes, acarbose for 28 weeks did not alter liver function (52). The number of hypoglycemic episodes was reduced.

Skin

Erythema multiforme has been attributed to acarbose (53).

- A skin biopsy from a 58-year-old man showed necrosis of keratinocytes with lymphocytic and eosinophilic infiltration. Liver enzymes were normal. After withdrawal the rash disappeared. After 3 weeks, rechallenge with acarbose 50 mg caused the skin changes to reappear.

Second-Generation Effects

Pregnancy

In six women with gestational diabetes, acarbose 50 mg before meals normalized fasting and postprandial glucose concentrations (54). The pregnancies were uneventful and the neonates were healthy. Internal discomfort persisted during the whole pregnancy.

Drug–Drug Interactions

Colestyramine

Acarbose increases bowel motility, which reduces the effect of colestyramine.

Digoxin

Acarbose can reduce plasma concentrations of digoxin by impairing its absorption.

- An 82-year-old man with type 2 diabetes, taking digoxin and voglibose 0.9 mg/day, had digoxin serum concentrations in the target range (55). He was given acarbose 300 mg/day instead of voglibose and his digoxin concentrations fell from 0.8–2.0 ng/ml to 0.2–0.4 ng/ml. One month after restarting voglibose the digoxin concentrations were again in the target range.
- A 69-year-old woman with diabetes mellitus and heart failure repeatedly had unusual subtherapeutic plasma digoxin concentrations (56). When acarbose was withdrawn the plasma digoxin concentration rose.

In a randomized, crossover study in healthy men, acarbose 100–200 mg reduced the AUC and C_{max} of digoxin and prolonged its t_{max}, consistent with reduced absorption (57). However, in another study acarbose 50 mg tds for 12 days had no significant effect on the pharmacokinetics of a single oral dose of digoxin 0.75 mg (58).

In one study there was no interaction of voglibose with digoxin (59).

Glibenclamide

In a placebo-controlled study in six patients with type 2 diabetes, acarbose 300 mg/day for 7 days had no significant effect on the pharmacokinetics of a single dose of glibenclamide 5 mg (60).

Miglitol did not reduce the t_{max} or C_{max} of glibenclamide, but the 9-hour AUC was significantly reduced (61).

In a double-blind, crossover study in 12 healthy men, voglibose 5 mg tds for 8 days had no significant effect on the pharmacokinetics of a single dose of glibenclamide 1.75 mg (62).

Metformin

Acarbose reduces the absorption of metformin (63), as does miglitol (61).

Thioctic acid

In 24 healthy volunteers thioctic acid 600 mg orally had no significant effect on the actions of acarbose 50 mg and acarbose did not alter the pharmacokinetics of thioctic acid (64).

Warfarin

Acarbose may increase the availability of warfarin (65). However, neither miglitol (66) nor voglibose (67) has any effect.

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Alphaprodine

General Information

Alphaprodine is a synthetic opioid that is rapidly absorbed after oral submucosal injection (1). It is used in pediatric dentistry, but it has been withdrawn from the market on a number of occasions because of concerns about its safety. Problems include hypoxia, reduced respiratory rate, and generalized venodilatation with local cyanosis.

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Alpidem

General Information

Alpidem, like zolpidem, is an imidazopyridine, chemically distinct from the benzodiazepines. It binds selectively to a subset of benzodiazepine receptors (1), which may account for its apparently milder withdrawal effects and a relative dominance of anxiolytic over sedative and cognitive effects (2). Its effects are reversed by flumazenil (3). Alpidem was withdrawn in 1953 in France, the only country in which it was marketed, because of hepatotoxicity (4).

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Alprazolam

See also Benzodiazepines

General Information

Alprazolam, a triazolobenzodiazepine, has been marketed as an anxiolytic with additional antidepressant properties; an analogue, adinazolam, also has partial antidepressant activity (1) and is useful in panic disorder. Like other benzodiazepines, alprazolam is effective in acute and generalized anxiety; its efficacy in panic disorder (2,3), premenstrual syndrome (4), and chronic pain (5) is complicated by high rates of adverse effects (6). On the other hand, low-dose alprazolam (1.4 mg/day) is useful and well tolerated in the treatment of anxiety associated with schizophrenia (SEDA-19, 34).

The value of the Saskatchewan data files in an acute adverse event signalling scheme has been evaluated using two benzodiazepines (7). The first 20 000 patients taking lorazepam and the first 8525 patients taking alprazolam were followed for 12 months after the initial prescription. The most frequent adverse drug reactions associated with these benzodiazepines were drowsiness, depression, impaired intellectual function and memory, lethargy, impaired coordination, dizziness, nausea and/or vomiting, skin rashes, and respiratory disturbance. Sleep disorders, depression, dizziness and/or vertigo, respiratory depression, gastrointestinal disorders, and inflammatory skin conditions occurred significantly more often during the first 30 days after the initial prescription than during the next 6 months.

Organs and Systems

Cardiovascular

Alprazolam has been associated with hypotension (8).

- A 76-year-old woman, who had a history of hypertension, valvular heart disease (mitral regurgitation) with chronic atrial fibrillation, chronic obstructive airways disease, diverticular disease of the sigmoid colon, and generalized anxiety disorder, developed severe hypotension with a tachycardia after taking alprazolam for 7 days. She also had severe weakness, depressed mood, and impaired gait and balance, without clinical features of neuromuscular disease.

Psychological, psychiatric

Rapid and sometimes serious mood swings to mania or depression, and other adverse effects, including enuresis, aggression, impaired memory, sedation, and ataxia, can occur in patients with panic disorder treated with alprazolam (SEDA-19, 34)(SEDA-20, 31).

Disinhibition has been reported as a major problem with alprazolam, particularly in patients with borderline personality disorder (9). Several case reports have suggested that alprazolam can cause behavioral disinhibition (10), in common with other benzodiazepines that are occasionally used for recreational or criminal purposes (11). In one study, covering the period January 1989 to June 1990, the medical records of 323 psychiatric inpatients treated with alprazolam, clonazepam, or no benzodiazepine were reviewed (12). The frequencies of behavioral disturbances were not significantly different in the different groups, suggesting that alprazolam does not have unique disinhibitory activity and that disinhibition with benzodiazepines may not be an important clinical problem in all psychiatric populations. The study design did not allow the establishment of a relation between the prescription of the benzodiazepine and worsening behaviors, and the findings need to be interpreted conservatively, because it was a retrospective review of a heterogeneous population.

Agoraphobia/panic disorder occurred in 31 patients, 15 of whom had originally been treated with alprazolam and 16 with placebo, had been previously followed during an 8-week treatment period, and had alprazolam-induced memory impairment (13). These patients were reviewed 3.5 years after treatment to determine whether the memory impairment persisted. Those who had used alprazolam performed as well as those who had taken placebo on the memory task and other objective tests. The performances in both groups were similar to pretreatment values. However, there were differences in subjective ratings: those who had used alprazolam rated themselves as less attentive and clear-headed and more incompetent and clumsy. Memory impairment found while patients were taking alprazolam did not persist 3.5 years later.

Abrupt withdrawal of alprazolam after prolonged treatment of panic disorder is associated with panic attacks.

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- A 77-year-old married woman with panic attacks did not experience them while she took alprazolam 0.5 mg bd for 5 months; however, the attacks recurred after an increase in dose to 0.5 mg qds (14).

The authors suggested that the duration of action of alprazolam is too brief to prevent rebound anxiety with administration four times a day, but this explanation is highly speculative. This case illustrates the potential severity of alprazolam rebound and how its long-term use can exacerbate the symptoms for which it was originally administered.

Endocrine

Alprazolam can alter dehydroepiandrosterone and cortisol concentrations. Of 38 healthy volunteers who received a single intravenous dose of alprazolam 2 mg over 2 minutes (phase I), 15 of 25 young men (aged 22–35 years) and all 13 elderly men (aged 65–75 years) responded to alprazolam and agreed to participate in a crossover study of placebo and alprazolam infusion to plateau for 9 hours (15). Plasma samples at 0, 1, 4, and 7 hours were assayed for steroid concentrations. Alprazolam produced:

(a) significant increases in dehydroepiandrosterone concentrations at 7 hours in both the young and elderly men;
(b) significant reductions in cortisol concentrations;
(c) no change in dehydroepiandrosterone-S concentrations.

The results suggest that alprazolam modulates peripheral concentrations of dehydroepiandrosterone and that dehydroepiandrosterone and/or dehydroepiandrosterone-S may have an in vivo role in modulating GABA receptor-mediated responses.

Skin

Alprazolam, which is lipid-soluble, can cause photosensitivity after a long duration of administration.

- A 65-year-old man developed pruritic erythema on sun-exposed areas (photosensitivity) due to alprazolam (16). A photopatch test was negative, but an oral photochallenge test with UVA irradiation was positive after he had taken alprazolam for 17 days.

Long-Term Effects

Drug dependence

Dependence on alprazolam and withdrawal symptoms appear to present greater problems than with other benzodiazepines (SED-12, 98).

Drug withdrawal

Withdrawal symptoms have been described with alprazolam.

- A woman with paranoid schizophrenia developed catatonia 5 days after the abrupt withdrawal of olanzapine and alprazolam (17). The catatonic symptoms included mutism, prostration, waxy flexibility, oculogyric movements, and an inability to swallow. Her symptoms disappeared after administration of alprazolam and haloperidol, and there was no recurrence.
- A 39-year-old woman had withdrawal symptoms after her dose of alprazolam was reduced (18). Cognitive symptoms made it almost impossible for her to stop taking alprazolam or to continue psychotherapeutic treatment. The medication was stopped by means of a behavioral experiment, in which both patient and therapist were unaware of the way in which the medication was reduced, after which continuation of treatment became possible.

Pharmacological strategies for withdrawing alprazolam, by switching to a longer-acting agent, have been proposed (19).

Drug Administration

Drug overdose

The effects of alprazolam overdose have been reported (20,21).

- A 28-year-old African-American man took alprazolam 12 mg. He denied using alcohol, other prescription medications, over-the-counter medications, or illicit drugs. He denied any suicidal intent. He stated that he had taken this large dose because his usual dose of 1–2 mg had failed to relieve his anxiety. He was drowsy and his heart rate was 58/minute. He had marked first-degree atrioventricular block, with a PR interval of 500 ms.
- A 30-year-old woman, with a history of depression, was found dead after taking an unknown quantity of alprazolam, tramadol, and alcohol. At autopsy, only slight decomposition and diffuse visceral congestion were observed. Blood concentrations of alprazolam, alcohol, and tramadol were 0.21 mg/l, 1.29 g/kg, and 38 mg/l respectively.

Drug–Drug Interactions

Alcohol

In common with other benzodiazepines, alprazolam produces additional impairment of performance when it is taken together with alcohol (22). The combination can also produce behavioral disturbance and aggression (11,23).

Alosetron

In an open, randomized, crossover study in 12 healthy men and women, alosetron 1 mg bd did not affect the pharmacokinetics of a single oral dose of alprazolam 1 mg (24).

Dextropropoxyphene

Inhibition of alprazolam metabolism by dextropropoxyphene has been reported (25).

Grapefruit juice

There have been two studies of the effects of repeated ingestion of grapefruit juice on the pharmacokinetics and

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pharmacodynamics of both single and multiple oral doses of alprazolam in a total of 19 subjects (26). Grapefruit juice altered neither the steady-state plasma concentration of alprazolam nor its clinical effects.

Ketoconazole

In a double-blind, crossover, pharmacokinetic and pharmacodynamic study of the interaction of ketoconazole with alprazolam and triazolam, two CYP3A4 substrate drugs with different kinetic profiles, impaired clearance by ketoconazole had more profound clinical consequences for triazolam than for alprazolam (27).

Miocamycin

Hydroxylation of miocamycin metabolites is mainly performed by CYP3A4. Some macrolide antibiotics cause drug interactions that result in altered metabolism of concomitantly administered drugs by the formation of a metabolic intermediate complex with CYP450 or competitive inhibition of CYP450 (28). The resulting interactions can cause rhabdomyolysis (associated with the coadministration of some statins, for example lovastatin or simvastatin), hypoprothrombinemia (associated with warfarin), excessive sedation (associated with certain benzodiazepines, for example alprazolam, diazepam, midazolam, or triazolam), ataxia (associated with carbamazepine), and ergotism (associated with ergotamine).

Moclobemide

- A 44-year-old man developed the serotonin syndrome after taking moclobemide and alprazolam for 1 year (29). The symptoms developed after 4 days of extreme heat, which was thought to have contributed.

Nefazodone

Nefazodone is a weak inhibitor of CYP2D6 but a potent inhibitor of CYP3A4 and it increases plasma concentrations of drugs that are substrates of CYP3A4, such as alprazolam, astemizole, carbamazepine, ciclosporin, cisapride, terfenadine, and triazolam.

Oral contraceptives

Oral contraceptives alter the metabolism of some benzodiazepines that undergo oxidation (alprazolam, chlordiazepoxide, and diazepam) or nitroreduction (nitrazepam) (30). Oral contraceptives inhibit enzyme activity and reduce the clearances of these drugs. There is nevertheless no evidence that this interaction is of clinical importance. It should be noted that for other benzodiazepines that undergo oxidative metabolism, such as bromazepam or clotiazepam, no change has ever been found in oral contraceptive users. Some other benzodiazepines are metabolized by glucuronic acid conjugation. The clearance of temazepam was increased when oral contraceptives were administered concomitantly, but the clearances of lorazepam and oxazepam were not (31). Again, it is unlikely that this is an interaction of clinical importance.

Ritonavir

The inhibitory effect of ritonavir (a viral protease inhibitor) on the metabolism of alprazolam, a CYP3A-mediated reaction, has been investigated in a double-blind study (32). Ten subjects took alprazolam 1.0 mg plus either low-dose ritonavir (four doses of 200 mg) or placebo. Ritonavir reduced alprazolam clearance by 60%, prolonged its half-life, and magnified its benzodiazepine agonist effects, such as sedation and impairment of performance.

Sertraline

Sertraline (50–150 mg/day) had no effects on alprazolam metabolism in a randomized, double-blind, placebo-controlled study in 10 healthy volunteers (33).

Troleandomycin

Troleandomycin inhibits the metabolism of ecabapide and alprazolam by inhibition of CYP3A4 (34,35).

Venlafaxine

The effects of venlafaxine on the pharmacokinetics of alprazolam have been investigated in 16 healthy volunteers. Steady-state venlafaxine 75 mg bd did not inhibit CYP3A4 metabolism of a single dose of alprazolam 2 mg (36).

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Alprostadil

See also Prostaglandins

General Information

Alprostadil is PGE_1 available for exogenous administration. Alprostadil is widely used in neonates with cyanotic congenital heart disease to maintain the patency of the ductus arteriosus. Reported adverse effects include fever, apnea, flushing, bradycardia, and hyperostosis. Continuous chronic infusion of alprostadil via a portable pump and neuromuscular electrical stimulation help to improve the quality of life in patients with severe chronic heart failure waiting for a donor heart, as both treatments can be performed at home.

Of 15 neonates with hypoplastic left heart syndrome (nine boys and six girls; median weight 3123 g) included in a cardiac transplant program between January 1993 and August 1996, who received continuous perfusion of alprostadil from the time of diagnosis of the cardiomyopathy, 13 received transplants and 6 died in the operating room (1). All had short-term adverse effects from the continuous perfusion of alprostadil, including slight fever and irritability. However, none had apneic pauses. Cortical hyperostosis occurred in 13 and antral hyperplasia in 12, but in all transplanted cases regression of the antral hyperplasia was seen after 6 months and regression of the cortical hyperostosis was seen after 12 months.

Organs and Systems

Cardiovascular

Moderate or severe phlebitis can occur at the site of venepuncture in some patients who receive alprostadil by infusion. It is sometimes severe enough to necessitate withdrawal of therapy. The frequency and severity of

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phlebitis has been investigated in 18 men, mean age 63 (range 47–78) years, with peripheral vascular disease who received a 2-hour infusion twice daily (2). Although it is usual to dissolve 60 micrograms of alprostadil in 500 ml of fluid to avoid phlebitis, in this study 200 ml was used to prevent volume overload. The solution was neutralized to pH 7.4 with 4 ml of 7% sodium bicarbonate. Two patients had grade 0, four grade 1, 11 grade 2, and one grade 3 phlebitis (by Dinley's criteria (3)). Age correlated negatively with the severity of phlebitis. Usually, alprostadil infusion therapy is stopped when phlebitis reaches grade 4 or more, but there were no such cases in this study.

Hematologic

Investigators from the Department of Pediatrics in Johns Hopkins Hospital, after seeing a neonate who had marked leukocytosis temporally related to alprostadil, conducted a retrospective study of neonatal leukocytosis induced by alprostadil in 45 neonates (4). They concluded that alprostadil infusion is a predictable cause of leukocytosis in neonates with congenital heart disease. Alprostadil-induced leukocytosis was especially prominent in three patients with splenic disorders associated with the heterotaxy syndrome. Many of the other adverse effects of alprostadil, including respiratory depression, hypotension, fever, and lethargy, were also associated with sepsis. The authors considered that it is reasonable to look for sepsis in infants receiving alprostadil, but that it is equally reasonable to withdraw empirical therapy once infection has been ruled out. Leukocytosis associated with alprostadil infusion has not been previously reported and is not listed in the alprostadil package insert.

Skin

Penile shaft lichen sclerosus has been reported in a 63-year-old man in association with alprostadil intracavernous injection for erectile dysfunction (5). The authors suggested that the lichen sclerosus had been caused by (1) an isomorphic response to the trauma of repeated needle injection; (2) a local cutaneous response to alprostadil-induced collagen synthesis or alprostadil-induced fibroblast production of IL-6, with secondary paracrine/autocrine-induced collagen synthesis by improper skin exposure by direct injection to the skin or by retrograde flow of alprostadil through the needle puncture tract; or (3) a random occurrence of separate events.

A neonate with transposition of the great vessels developed urticaria during treatment with alprostadil (6). While flushing and peripheral edema are well recognized, urticaria has not been described before.

Allergic contact dermatitis has been attributed to latanoprost (7).

- An 85-year-old man with glaucoma developed tearing, red eyes, and pruritic, edematous, eczematous eyelids. Treatment for presumed ocular rosacea and seborrhea with oral tetracyclines, topical glucocorticoids, and metronidazole gel was unhelpful. He was using topical carboxymethylcellulose sodium 1%, propylmethylcellulose 0.3%, polyvinyl alcohol 1.4%, latanoprost, and levobunolol. Patch-testing with a standard 64-antigen patch elicited a strong reaction only to balsam of Peru. However, repeated open application of levobunolol and latanoprost for 4 days elicited a strong positive reaction to latanoprost.

Musculoskeletal

Alprostadil infusion can produce bone cortical hyperostosis. Periosteal changes have been described in 15 neonates after the administration of alprostadil for more than 1 week (8). Serum alkaline phosphatase activity was significantly raised. The long bones and clavicles were most commonly involved and symmetrically affected. The scapula was involved in two cases and the ribs in seven. The involvement of clavicles has not been previously reported.

Hypertrophic osteoarthropathy has been reported in a woman with severe chronic heart failure who was referred for cardiac rehabilitation (9).

- A 56-year-old woman with muscle weakness and severe chronic heart failure (NYHA Class III) caused by aortic coarctation received an intravenous infusion of alprostadil 5 nanograms/kg/minute. Although her hemodynamics improved, her muscle weakness and exercise intolerance persisted. Neuromuscular electrical stimulation of both thigh muscles was begun. However, during simultaneous continuous intravenous infusion of alprostadil, she developed pain in her knees and elbows. The overlying skin was warm and dusky red and the subcutaneous tissues were swollen. The discomfort was aggravated by motion. There were signs of non-inflammatory synovial effusions and X-rays showed symmetric bilateral periosteal bone deposition in the distal humerus and synovial effusions in both knees. The bone scintigram showed increased bilateral symmetrical tracer uptake in both knees, ankles, wrists, and carpal bones, and increased radionuclide uptake in periarticular regions. Secondary hypertrophic osteoarthropathy caused by continuous intravenous infusion of alprostadil was diagnosed. The dosage of alprostadil was reduced to 2.5 nanograms/kg/minute, and the signs of osteoarthropathy disappeared within 5 days.

Sexual function

Intracavernosal alprostadil was effective and well tolerated in the treatment of erectile dysfunction, according to the results of a 6-month study (funded by Pharmacia & Upjohn) in 848 men (mean age 52 years) with at least a 4-month history of erectile dysfunction (10). This is provided that the individual dose is established by titration and patients receive training in injection techniques and periodic supervision during treatment. An initial dose was established for each patient and the patients then administered the alprostadil themselves at home. Of 727 evaluable patients, 682 (94%) had at least one erectile response after the injection of alprostadil, and 88% of injections lead to a satisfactory sexual response. The most commonly reported adverse event was penile pain, reported by 44% of patients, but only after 8% of injections. In just over half of the patients who had penile pain, the condition was reported as mild.

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Prolonged erection, penile fibrosis, and priapism occurred in 8, 4, and 0.9% of patients respectively. Treatment was withdrawn because of medical events in 4% of patients, and drug-related events accounted for treatment withdrawal in 2% of patients.

There is a high dropout rate from self-injection therapy for erectile dysfunction. Of 86 patients aged 36–76 years who had been using home treatment for at least 3 months, 17 had discontinued treatment (11). The patients were evaluated by interview and clinical examination. Patients still in the program used one injection every 2 weeks, and those who had given up treatment had used one injection in 3 weeks. They were in the program for 39 and 16 months respectively, and had used a mean of 50 versus 12 injections respectively. There was no difference in the number of injections that produced unsatisfactory penile rigidity, prolonged erections, hematomas at the injection site, corporeal fibrosis, secondary penile deviation, or mean estimated duration of a drug-induced erection. Patient satisfaction, estimated partner satisfaction, increase in self-esteem, and negligible effort in performing injections were all significantly better for those still in the program. The authors commented that the reasons for dropout from self-injection therapy were not based on objective adverse effects and discomfort. Patients who leave the program are less motivated, less satisfied with the quality of drug-induced sexuality, consider the effort of giving the injections to be substantial, and have not achieved improved self-esteem.

There has been a report of a long-term follow-up program for treatment of erectile dysfunction in 32 patients who used alprostadil for a minimum of 5 years under standardized protocol conditions (12). All the patients had organic erectile dysfunction, and their mean age was 59 years. The period of observation was on average 75 months, and the mean dose of alprostadil was 14 μg. In all, 6799 injections were registered. The average number of injections was 213 per patient, 2.8 injections per month per patient. As regards adverse effects, hematomas occurred in 1.9% of the patients and there were five cases of prolonged erection (0.07%) caused by unauthorized redosing. Three patients developed reversible penile nodules. In 10 patients, the initial dosage had to be increased. Five patients dropped out after 5 years, none of them because of treatment complications.

The impact of treatment with transurethral alprostadil for erectile dysfunction on the quality of life of 249 men and their partners has been evaluated (13). The men had organic erectile dysfunction of more than 3 months' duration and self-administered transurethral alprostadil in an open, dose-escalating, outpatient study. Patients with a sufficient response ($n = 159$) were randomly assigned double-blind to either active medication or placebo for 3 months at home. Drug-related urogenital pain was reported by 12% of patients during outpatient dosing. However, this pain was usually mild, and only five patients (2%) discontinued treatment. One patient reported minor urethral bleeding/spotting. The transurethral administration of alprostadil was associated with minimal or no discomfort in 83–88% of patients. In the outpatient study, dizziness occurred in one patient and hypotension in one patient. During home treatment, drug-related urogenital pain was reported by 11 patients (14%), minor urethral bleeding/spotting by one (1.3%), and dizziness by 2 (2.6%). One patient reported prolonged erections on two occasions during home treatment, each lasting less than 5 hours.

The incidence of priapism after intracorporeal administration of alprostadil is 1%. Priapism after medicated urethral system for erection (MUSE) has been reported (14).

- A 57-year-old man with erectile impotence, who had previously been treated with intracorporeal injections of papaverine and alprostadil, resulting in recurrent episodes of priapism necessitating aspiration, decided to try intraurethral alprostadil (MUSE). The dose needed to achieve a full erection in the clinic was titrated to 1 μg, but after 5 months this was found to be inadequate unless supplemented by a hot bath before MUSE administration. The patient stated that with MUSE alone the erection lasted for 5–10 minutes but on the two previous occasions when he had had a hot bath for 20 minutes and then used MUSE, the erection had lasted 3–4 hours. However, on the third occasion, priapism lasted 20 hours and necessitated corporeal aspiration for detumescence.

Immunologic

When latanoprost was applied for 4 months to the eyes in 14 patients, there was an increase in HLA-DR expression (15). Since HLA-DR is a marker of ocular surface inflammation, these results suggested a subclinical inflammatory reaction to latanoprost. However, the clinical significance of HLA-DR expression is not clear.

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Aluminium

General Information

Aluminium is a metallic element (symbol Al; atomic no. 13), a light, silver-colored, malleable metal.

Aluminium is the most abundant of all metals and is obtained from bauxite ores by the production of alumina, which is then smelted to produce aluminium. Its abundance is demonstrated by the vast number of minerals and precious stones that contain aluminium, which include: albite, analcime, anorthite, beryl, chabazite, cimolite, dumortierite, epidote, euclase, feldspar, fuller's earth, glauconite, halloysite, harmotome, iolite, jadeite, kaolinite, kyanite, lazurite, leucite, margarite, melilite, montmorillonite, muscovite, natrolite, nepheline, noselite, penninite, phillipsite, piedmontite, pinite, prehnite, saponite, sapphirine, scapolite, scolecite, sillimanite, sodalite, spessartite, spodumene, staurolite, topaz, and vesuvianite (all of which contain salts or pure crystals of aluminium silicate); alunite (hydrous aluminium sulfate); cryolite (sodium aluminium fluoride); diaspore, gibbsite, and laterite (aluminium hydroxide); lazulite, sphaerite, turquoise, variscite, and wavellite (aluminium phosphate); scorodite and synadelphite (aluminium arsenate); and gmelinite (aluminium zeolite).

Note on nomenclature

Aluminium was first named (although not isolated) by Sir Humphry Davy, who originally called it alumium (1808) because it was found in alum, a name that had been extant since at least the 14th century. He later called it aluminum (1812), but others soon changed it to aluminium, in order to harmonize it with the many other elements whose names end in "ium" and because "aluminum" was thought not to have a particularly classical sound. For many years, both "aluminium" and "aluminum" were used in the USA, until the American Chemical Society adopted the form "aluminum" in 1925. However, "aluminium" is the official name recognized by the International Union of Pure and Applied Chemistry (IUPAC) and is the form that is used here.

Sources of exposure

Aluminium is widely used in medicine, pharmacy, food technology, and cosmetics. It is also a popular metal for making everyday objects, including kitchen utensils and other devices associated with food preparation. There is also some exposure, although generally limited, from the environment. Toxic effects of aluminium have been seen in patients treated with total parenteral nutrition contaminated with aluminium (1); high concentrations of aluminium have been detected in some intravenously administered solutions, such as human serum albumin (2) and in artificial breast milk substitutes. Exceptionally, a metallic aluminium object can become lodged in the body and give rise to aluminium toxicity (SEDA-20, 207). Additive intake from multiple medical and/or non-medical sources can prove excessive, and it can be important to recognize the many circumstances in which exposure occurs. Aluminium absorbed into the system is excreted in the bile, generally without obvious consequences (SEDA-12, 316).

Hyperaluminemia has been described in premature infants receiving prolonged intravenous alimentation, and in recipients of plasmapheresis receiving large volumes of replacement albumin solutions, which contain high concentrations of aluminium (3–4).

Many aluminium salts, including aluminium hydroxide gel, aluminium carbonate, aluminium glycinate, and aluminosilicate, are used therapeutically, and the absorption rate depends on the chemical species. Aluminium citrate is well absorbed (5), but aluminium hydroxide gel antacid is poorly absorbed (0.003%) (6). Aluminium glycinate is well absorbed and excreted in the urine. Poorly absorbed aluminium-containing formulations should be preferred for those who have poor renal function particularly elderly people.

Sucralfate is a basic aluminium salt of sucrose octasulfate.

Medical uses

The external medical uses of aluminium are many; water-soluble compounds such as alum have long been used as mild external antiseptic, astringent, antihydrotic, or styptic agents, and more recently in deodorants and antiperspirants. Metallic aluminium is also used in some wound dressings.

Internal use in medicine can exploit the alkaline nature and adsorptive capacities of aluminium compounds (as in antacid mixtures, antidiarrheal drugs, and vaccines). Aluminium is found in medications for antacid therapy and phosphate depletion; alternatives are under investigation (7). Patients on dialysis take large amounts of oral aluminium hydroxide as a means of reducing serum phosphate. Sucralfate is used to treat peptic ulceration and gastritis.

Aluminium is used as a vaccine adjuvant (8).

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General adverse effects

Topical aluminium can occasionally cause skin irritation in sensitive individuals.

The systemic availability of aluminium is normally very low, because the gastrointestinal tract, skin, and lungs are excellent barriers to its entry; furthermore, the small amounts that pass these barriers are efficiently eliminated by the kidneys. However, problems can arise if the natural protective barriers are bypassed or if there is impaired renal function. Significant systemic effects are rare unless there is a high degree of absorption.

- Acute aluminium toxicity in one reported case followed the introduction of aluminium sulfate (alum) into the urinary tract to treat hemorrhagic cystitis; there was apparently both increased absorption, due to the mucosal lesion of the bladder wall, and an increased susceptibility due to pre-existing renal insufficiency (SED-13, 585).

Aluminium is toxic in patients on chronic hemodialysis and peritoneal dialysis and in those taking oral aluminium-containing medications. Aspects of aluminium safety (9) and metabolism (10) have been reviewed. The association between aluminium in drinking water and Alzheimer's disease continues to be discussed and remains controversial (11).

Although aluminium adjuvants have proven to be safe over six decades, adverse effects, such as erythema, subcutaneous nodules, and contact hypersensitivity, sometimes occur (12). The aluminium body burden has been estimated in infants during the first year of life for a standard immunization schedule compared with breast milk and formula diets (13). The calculated body burden of aluminium from immunization exceeds that from dietary sources, but is still below the minimal risk level equivalent curve during the brief period after injection.

Organs and Systems

Respiratory

Specific chemical exposures and exposure assessment methods relating to studies in the alumina and primary aluminium industry have been reviewed (14). In aluminium smelting, exposure to fluorides, coal tar pitch volatiles, and sulfur dioxide has tended to abate in recent years, but there is insufficient information about other exposures. Published epidemiological studies and quantitative exposure data for bauxite mining and alumina refining are virtually non-existent. Determination of possible exposure–response relations for this part of the industry through improved exposure assessment methods should be the focus of future studies.

Dental technicians are potentially exposed to various occupational dusts and chemicals and pulmonary granulomatosis has been reported (15).

- A dental laboratory technician developed progressive exertional dyspnea and cough associated with pulmonary granulomatosis. Lung function studies showed a restrictive pattern with a low diffusion capacity. A high-resolution CT scan showed micronodules in both lungs, corresponding to non-caseating foreign body granulomas at histological examination. Mineralogical studies showed the presence of silica, silicates, and aluminium. The lymphocytic transformation test was positive for beryllium with the bronchoalveolar lavage.

Combined histological, mineralogical, and immunological studies led to a diagnosis of pneumoconiosis, most likely related to occupational exposure to beryllium and aluminium.

The role of aluminium in the development of occupational asthma has never been convincingly substantiated. Occupational asthma has been attributed to aluminium welding (16).

- A 32-year-old man working in a leather plant performed electric arc welding on mild steel, using manual metal arc and inert gas metal arc techniques. About once a month he welded aluminium pieces using a manual arc process with a flux-coated electrode. After 4 years of intermittent exposure to these various welding processes, he developed chest tightness and wheezing that occurred specifically on days when he was welding aluminium. His asthmatic symptoms started 1–4 hours after the end of exposure to aluminium and persisted for several hours. He never had myalgia, chills, or fever. He was treated with inhaled budesonide (400 micrograms/day) and salbutamol when necessary. Inhalation challenges combined with exposure assessment provided evidence that aluminium can cause asthmatic reactions.

A syndrome known as "pot-room asthma" occurs in around 2% of new aluminium smelters each year, with a wide range of incidences around the world (17).

- In 1529 men in two smelting factories, work-related respiratory symptoms were reported significantly more often among the ingot mill, anode, and pot-room groups in factory A after adjusting for age and smoking, while in factory B, ingot employees were more likely to report work-related wheeze and pot-room employees were more likely to report work-related rhinitis (18). Symptoms tended to increase with increasing time in the pot-rooms, but were more likely to occur in new employees in the ingot mill and anode process groups.

Nervous system

The toxicology of aluminium in the brain has been reviewed (19,20).

Since 1976, aluminium has been known to be a cause of encephalopathy, a potentially fatal condition occurring primarily in patients on chronic dialysis (21). Difficulties in speech, disturbances of consciousness, and ataxia can be followed by psychotic episodes, personality changes, myoclonic jerks, electroencephalographic abnormalities, convulsions, and dementia. Accumulation of aluminium can be demonstrated in the gray matter of the brain and in other tissues. If not too advanced, the condition can recede after reduction of aluminium intake and use of deferoxamine.

- Intravesical irrigation with 1% alum for hemorrhagic cystitis resulted in sufficient absorption to produce encephalopathic symptoms in a teenage girl (22).

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An identical condition can occur in aluminium plant workers and miners, and can be reproduced in animal experiments. However, some clinically similar encephalopathies do occur spontaneously (or possibly as a result of uremia) in children where no link with aluminium exposure can be found.

There have been reports that the use of surgical aluminium-containing bone cement can cause epileptic seizures as well as encephalopathy, at least when the cement is in direct contact with the cerebrospinal fluid, as can happen in neurosurgery (23,24) (SEDA-21, 232). In this connection it should be noted that such bone cements can produce high circulating concentrations of aluminium. One French study in six patients (25) noted mean plasma aluminium concentrations of up to 9.2 ng/ml, while up to 176 ng/ml was present in the postauricular cerebrospinal fluid (SEDA-22, 242). This aspect of aluminium cement merits further study.

Aluminium-containing antacids have been suggested to be the cause of idiopathic Parkinson's disease in a study of 200 patients and 200 age- and sex-matched controls. There was a significantly higher incidence of ulcers (diagnosed by X-ray or surgery) in the patients with Parkinson's disease compared with controls (14 versus 4%) (26,27). The ulcers typically preceded the diagnosis of Parkinson's disease by 10–20 years. Parkinson's disease occurs worldwide, suggesting perhaps that some ubiquitous toxin plays a role in its pathogenesis. Aluminium absorption resulting in raised blood concentrations has been detected in babies given "Infant Gaviscon" (which is based on aluminium alginate and is not in fact recommended by the manufacturers in the very young) and in adults given aluminium sucrose sulfate, though without apparent ill-effect.

Acute neurotoxic adverse effects of aluminium have been attributed to aluminium-containing surgical cement.

- A 52-year-old woman had a resection of an acoustic neuroma (28). Bone reconstruction was performed with an aluminium-containing cement and 6 weeks later she had loss of consciousness, myoclonic jerks, and persistent tonic-clonic seizures, effects resembling those of dialysis encephalopathy. She died 6 months later with septic complications. Light microscopy and electron microscopy of the brain showed pathognomonic aluminium-containing intracytoplasmic argyrophilic inclusions in the choroid plexus epithelia, neurons, and cortical glia. These changes are characteristic of dialysis-associated encephalopathy. Atomic absorption spectrometry showed an increase in the mean aluminium concentration in the cortex and subcortex, up to 9.3 μg/g (reference range under 2 μg/g); a laser microprobe showed increased aluminium in subcellular structures.

This case shows again the extraordinary neurotoxic potency of aluminium, which was initiated by about 30 mg and apparently caused by direct access of aluminium to the brain parenchyma via cerebrospinal fluid leakage.

Aluminium and Alzheimer's disease

The association between aluminium in drinking water and Alzheimer's disease continues to be discussed and remains controversial (11,29,30). The theory has been advanced that aluminium may be linked to the etiology of Alzheimer's disease (31), one suggestion being that the mechanism is the inhibition of tetrahydrobiopterin synthesis in the temporal cortex. This hypothesis has led to much debate (32–34), and more knowledge is accumulating regarding possible mechanisms of neurotoxicity (35).

One study has suggested that researchers looking for a connection between aluminium and Alzheimer's disease may have ignored the most important source of aluminium for the average person—foodstuffs that contain aluminium additives (36). The results implied that aluminium, added to such foods as anticaking agents, emulsifiers, thickeners, leaveners, and stabilizers, may have long-term adverse effects on health. However, the small sample size hampers any definitive conclusions, the odds ratios were very unstable, and the study had limited statistical power to rule out random errors.

The relation between different chemical forms of aluminium in drinking water and Alzheimer's disease has been studied in 68 patients with Alzheimer's disease, diagnosed according to recognized criteria and paired for age and sex with non-demented controls (37). Aluminium speciation was assessed using established standard analytical protocols along with quality control procedures (total aluminium, total dissolved aluminium, monomeric organic aluminium, monomeric inorganic aluminium, polymeric aluminium, Al^{3+}, AlOH, AlF, $AlH_3SiO_4^{2+}$, $AlSO_4$). The results suggested a possible association between monomeric aluminium exposition and Alzheimer's disease. In contrast to the results of earlier studies, this association was observed in a geographical environment characterized by low aluminium concentrations and a high pH.

However, others have suggested that the theory that aluminium plays a role in the pathogenesis of Alzheimer's disease has been largely discarded, as our understanding of the pathogenic mechanisms of Alzheimer's disease has advanced (38).

Sensory systems

Tissue lesions can be caused by local deposition of aluminium, for example in the eye (39)

- A 76-year-old man with a history of multiple melanomas noticed a gradually enlarging pigmented mass in his right eye. He had had successful pneumatic cryopexy of a retinal tear in the temporal region of the right eye 4 years before with no reported complications. Slit lamp examination showed a 4 × 2 mm elevated darkly pigmented conjunctival mass surrounding the insertion site of the lateral rectus. An excisional biopsy showed multiple foci of fine, jet-black, granular pigmentation in a perivascular distribution, with additional deposition throughout the conjunctival stroma. There were no melanocyte abnormalities or cellular atypia. Energy dispersive analysis of X-rays showed spectral peaks corresponding to heavy aluminium deposition with trace amounts of silicone.

Aluminium is often incorporated in cryoprobe tips for ophthalmic use, providing a possible source of local

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deposition. Other possibilities include a metallic foreign body and occupational exposure.

Mineral balance

The ability of aluminium gels to bind phosphate can result in clinical significant hypophosphatemia, which usually presents as myalgia, weakness, and bone pain, but can have more extreme consequences; one report described rickets with hypercalciuria after prolonged use, though the subject was an immobilized boy with spastic quadriplegia which can itself have affected the skeleton (40). Even relatively small doses of commonly used aluminium-containing liquid antacids (90–120 ml/day) can lead to adverse effects on calcium and phosphorus metabolism. During long-term therapy, a considerable loss of calcium may occur, resulting in skeletal demineralization (41). Collagen synthesis and matrix mineralization can be so seriously affected that a vitamin D-resistant osteomalacia develops (42). The adverse effects of aluminium overload on the bones respond to reduction in aluminium exposure, whether this has resulted from oral intake or use of aluminium in dialysis (43).

Metal metabolism

Severe copper deficiency has followed the intake of a gel containing bismuth, aluminium, magnesium, and sodium in a patient with pyloric stenosis (44).

Hematologic

Aluminium overload in uremic patients can lead to a microcytic hypochromic anemia (45). The mechanism is unknown, but it appears to involve inhibition of heme synthesis, either by inhibition of enzyme activity or by interference with the incorporation or utilization of iron. Exposure for 3 months is sufficient to reduce hematological values and cause significant increases in serum and urinary aluminium (46). The anemia can be reversed by lowering the aluminium intake or by chelation therapy with deferoxamine.

Gastrointestinal

Aluminium hydroxide can cause constipation, or even intestinal obstruction. Severe bowel dysfunction developed in 25 of 945 patients receiving long-term hemodialysis during 10 years (47). There was colonic perforation in 12 patients, six of whom died with peritonitis. In 10 other patients there was prolonged, severe, adynamic ileus that progressed to colonic pseudo-obstruction in eight. All had regularly taken aluminium hydroxide gel and had had chronic constipation before presentation.

Large doses of aluminium can be associated with fecal impaction and the development of intestinal obstruction in uremic patients (48). Impacted tablets have in some cases caused obstruction (SEDA-16, 417).

Aluminium hydroxide can have an aggravating effect on *Helicobacter pylori*-associated gastritis in patients with duodenal ulceration (49).

Liver

The histology and metal content of the liver have been studied in a patient with Wilson's disease (50). Copper and aluminium contents of the biopsied liver were measured simultaneously by neutron activation analysis. The copper content was markedly increased (814 μg/g dry weight) and there was an extremely high aluminium content (479 μg/g). On the other hand, macroscopically and histologically there was no evidence of cirrhosis, although there was mild fibrosis or inflammation of the liver. It is likely that toxic metals, such as aluminium, copper, and manganese, might be implicated in the pathogenesis of Wilson's disease.

Animal experiments suggest that aluminium may play a role in the pathogenesis of parenteral nutrition-induced hepatobiliary dysfunction (51).

Urinary tract

A patient who grossly overused an antacid containing aluminium and magnesium developed nephrolithiasis and bilateral ureteric obstruction as well as asymptomatic hypophosphatemia (SEDA-16, 417).

Irrigation of the urinary bladder with alum successfully controls vesical hematuria, but it can cause bladder spasm (52).

Skin

Aluminium causes histological changes at injection sites, and these stain with hematoxylin and eosin (53). Of four patients studied, one had a sclerosing lipogranuloma-like reaction with unlined cystic spaces containing crystalline material. Another presented as a large symptomatic subcutaneous swelling, which microscopically showed diffuse and widespread involvement of the subcutaneous tissues by a lymphoid infiltrate with prominent lymphoid follicles.

Contact allergy to topically applied aluminium compounds is rare but skin sensitization has been described (54). In one case the use of a cream for acne and hyperpigmentation was followed by dermatitis, and patch tests were positive to both aluminium sulfate and aluminium chloride. A more typical antecedent of sensitization is the injection of aluminium-adsorbed vaccines, and such patients may present with a granulomatous nodule at the site. Mixed contact sensitivity to nickel and aluminium has been reported to respond to antihistamine therapy (55).

Persistent skin lesions occurred in three patients after the administration of aluminium hydroxide-containing vaccines.

- A 19-year-old woman presented with multiple itchy nodules on the outer aspects of the upper arms at the sites of previous vaccine injections (56). There were several nodules, ranging from a few millimeters to 1 cm in diameter, some with overlying hyperpigmented skin. She had been receiving hyposensitization vaccines to treat recurrent extrinsic asthma and rhinitis for the previous 4 years. A skin biopsy showed a normal epidermis and upper dermis. There were multifocal unencapsulated granulomatous infiltrates in the deep dermis and subcutaneous tissues, disrupting the normal architecture of the latter. The infiltrate was predominantly composed of histiocytes with foreign body giant cells. There were also fibroblasts, fibrosis, and perivascular

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lymphocytes and plasma cells, with a few eosinophils. There was a granular basophilic material within the cytoplasm of some histiocytes. However, patch tests with aluminium chloride, nickel sulfate, and potassium dichromate were all negative. She was treated with potent topical corticosteroids and oral antihistamines, with some relief, but the nodules persisted 2 years later.

- A 37-year-old woman with a 5-year history of multiple itchy nodules on the outer aspects of the upper parts of the arms at sites of previous vaccine injections had been receiving hyposensitization vaccines to treat recurrent extrinsic asthma and rhinitis for 10 years (56). Physical examination and a biopsy of one of the nodules were identical to those of the previous case. Patch tests with aluminium chloride were negative. Symptomatic relief was obtained with topical corticosteroids and oral antihistamines. The nodules persisted for at least 3 years.
- A 52-year-old woman, allergic to wasp venom, was hyposensitized with a vaccine containing wasp venom precipitated on aluminium hydroxide (57). Each subcutaneous injection of the extract was followed by cooling of the acute local reaction at the injection site for about 1 hour. As soon as 24 hours after the second maintenance dose, she developed tender, erythematous, ill-demarcated, indurated plaques at the injection sites on both the lateral thighs. The lesions resolved spontaneously after several weeks, leaving residual hyperpigmentation and subcutaneous atrophy. They reappeared with each treatment, even after the vaccine was changed to a lyophilized, aluminium-free extract. No further lesions occurred when the injection sites were not cooled, even though the aluminium hydroxide vaccine was continued. Patch tests with the vaccine, aluminium hydroxide, human albumin, phenol, and aluminium chloride hexahydrate were all negative. A biopsy of the skin lesions showed lobular panniculitis, with lipocyte necrosis and a mixed cellular infiltrate of neutrophils, lymphocytes, and histiocytes. Ultrasound examination of the atrophic areas showed significantly thinner subcutaneous tissue than in the normal contralateral skin. Rechallenge with an ice pack alone on the upper arm caused a similar skin lesion to appear within 24 hours.

Various mechanisms were postulated to explain these persistent lesions, such as a non-allergic direct toxic effect of aluminium and a delayed hypersensitivity reaction to aluminium.

Four cases have been reported of persistent subcutaneous nodules at sites of hepatitis B vaccination due to aluminium sensitization (58). Symptoms included pruritic, sore, erythematous, and in two cases hyperpigmented, subcutaneous nodules, persisting for 8 months to 2 years. All the patients were positive for aluminium salts in patch tests, while immunization against hepatitis B was successful.

Musculoskeletal

Macrophagic myofasciitis has been reported in relation to immunization with an aluminium-based vaccine (59).

- A 5-year-old boy with chronic intestinal pseudo-obstruction required nighttime parenteral nutrition. He had abnormal pupillary reflexes and urinary retention, suggesting diffuse dysautonomia. A 3-year-old child had developed delay and hypotonia. Both children had received age-appropriate immunizations. Quadriceps muscle biopsies showed the typical patchy, cohesive, centripetal infiltration of alpha-1-antitrypsin+, alpha-antichymotrypsin+, CD68+, PAS+, CD1a–, S-100–, factor XIII– granular macrophages with adjacent atrophy of myofibers, dilated blood vessels, and mild endomysial and perimysial fibrosis. There was no myonecrosis and no discrete granulomas. There was a single aluminium peak on energy dispersive X-ray microanalysis. Most infectious causes leading to macrophage activation were ruled out, thus implicating aluminium. Both patients improved gradually with time.

Heavy chronic use of antacids containing aluminium and magnesium hydroxide can cause serious skeletal impairment (60).

- A 39-year-old female pharmacist who self-medicated with high doses of a potent antacid containing aluminium and magnesium hydroxide for peptic ulcer disease consumed over 18 kg of elemental aluminium and 15 kg of elemental magnesium over 8 years. This resulted in severe osteomalacia, due to profound phosphate depletion. Bone biopsy showed stainable aluminium deposits along 28% of the total bone surface, which is a unique observation in a patient with normal renal function. Treatment included withdrawing the antacid and supplementation with phosphate, calcium, and vitamin D. This produced marked subjective and objective improvement, including a striking increase in her bone mineral density over the next 2 years.

Osteomalacia due to aluminium-containing antacids has been associated with stainable bone aluminium in patients with normal renal function (61).

- A 39-year-old woman who took high doses of aluminium and magnesium hydroxide for peptic ulcer disease (over 18 kg of elemental aluminium and 15 kg of elemental magnesium over 8 years) developed severe osteomalacia due to profound phosphate depletion (60). Bone biopsy showed stainable aluminium deposits along 28% of the total bone surface, a unique observation in a patient with normal renal function. Treatment included withdrawal of the antacid and supplementation with phosphate, calcium, and vitamin D. Her bone mineral density increased over the next 2 years.

Unexpected persistent aluminium-related bone disease occurred after renal transplantation following earlier use of aluminium hydroxide (62).

- A 59-year-old man presented with end-stage renal insufficiency. While on hemodialysis he had used aluminium hydroxide as a phosphate binder but then used calcium lactate instead after total parathyroidectomy. Oral vitamin D was discontinued after the parathyroidectomy. However, after he had received a renal transplant he developed aluminium-related bone disease and was treated with infusions of deferoxamine.

This is the first report of worsening aluminium-related bone disease after renal transplantation.

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Hyperparathyroidism and aluminium hydroxide lead to aluminium-related bone disease; however, total parathyroidectomy does not lead to failure of aluminium mobilization after renal transplantation. This man had satisfactory graft function, and the aluminium excretion that was achieved by deferoxamine suggests that the renal transplant was not the limiting factor for the mobilization of aluminium. The most likely explanation was that he developed adynamic bone through a combination of vitamin D deficiency, hypoparathyroidism, and aluminium deposition. Vitamin D supplementation failed to prevent the osteodystrophy on its own. When aluminium chelation therapy was used, bone healing occurred and his symptoms improved.

Immunologic

Aluminium has a non-specific immunosuppressive action, which results in a lower incidence of transplant rejection in patients with high aluminium concentrations in the tissues; in the first instance one might consider this a reason for seeking to maintain a particularly high aluminium concentration in transplant patients. However, there are good reasons not to do so. Firstly, should infection occur, this immunosuppressive effect can lead to increased risk and higher mortality; work in dialysis patients has confirmed that an increased aluminium load raises the risk of infections (63). Secondly, after transplantations there already is a high aluminium concentration because of mobilization of aluminium from the storage pool. Aluminium loading before transplantation should therefore be avoided and excessive concentrations countered (64).

Aluminium salts are currently the only widely used adjuvants in human vaccines (65). Developments in the understanding of the structure, composition, and preparation of immunostimulating complexes (ISCOMs) have been reviewed and compared.

Susceptibility Factors

Renal disease

In many patients with severe renal disease there is a double risk: they are exposed to aluminium as a part of their treatment (in agents given for the control of serum phosphate concentrations, in aluminium-containing dialysis fluids and, in one case, in the form of bladder irrigation with alum) (66), and at the same time they have a reduced ability to eliminate it. Aluminium-containing phosphate binders are especially risky if used in combination with an alkalinizing citrate solution (Shohl's solution) (67,68); due to the formation of an aluminium citrate complex in the gastrointestinal tract, aluminium is absorbed more readily. In addition, aluminium citrate complex has a synergistic inhibitory action on bone growth and thus exacerbates aluminium-associated osteomalacia in chronic renal failure. Children with impaired renal function may be particularly susceptible to aluminium intoxication solely from oral aluminium loading (69).

When aluminium is used as a phosphate binder in patients on renal dialysis, absorption and accumulation can occur. Phosphate depletion accompanied by increased bone resorption and hypercalciuria (with a risk of osteomalacia) can result (70). Low phosphate diets exacerbate this risk. Concurrent use of oral citrate solutions may increase absorption of aluminium from aluminium hydroxide, resulting in high blood concentrations, especially when renal function is impaired (71).

Encephalopathy due to high serum aluminium concentrations has been reported in acute renal insufficiency (SEDA-17, 273) (72). Unsuspected intake of citrate from other sources has apparently promoted the occurrence of aluminium encephalopathy in renal insufficiency (73). Most reported instances of encephalopathy after alum irrigation have occurred in patients with compromised renal function.

- A 70-year-old man with advanced obstructive nephropathy began to hemorrhage from the bladder after decompression with a Foley catheter (74). He developed an encephalopathy after continuous irrigation with 1% alum for 2 days, associated with raised serum aluminium concentrations. Repeated treatment with deferoxamine and hemodialysis removed some aluminium, but he succumbed to bronchopneumonia. At autopsy his brain aluminium content was not excessive.

Prolonged exposure to aluminium in patients with chronic renal insufficiency can be involved in the pathogenesis of uremic pruritus, and increased calcium phosphate production seems to be an additional predisposing factor (75); certainly the incidence and intensity of pruritus in these uremic patients have been found to be related to the circulating concentrations of aluminium.

Slow accumulation of aluminium during long-term hemodialysis can cause osteomalacia (76), bone and joint pain and muscular weakness (77), iron-resistant microcytic anemia (78), and neurological disorders (79).

In 33 patients on hemodialysis, who were exposed to moderately high serum aluminium concentrations for less than 4 months, even moderately high aluminium concentrations produced significant hematological alterations and depletion of body iron stores before clinical manifestations were evident (80).

In all patients with chronic renal insufficiency, strict supervision of total aluminium intake is vital. The administration of aluminium should be stopped as soon as the serum concentration exceeds 150 μg/ml or at the appearance of the first symptoms of encephalopathy (81). According to current recommendations, dialysate solutions should contain less than 10 μg/l of aluminium (82). There is some controversy about the view that aluminium-containing medications used to control serum phosphate concentrations in uremic subjects should be replaced by calcium-containing phosphate binders (83). Another approach used to reduce the toxic risks of aluminium hydroxide may be to tailor doses to the phosphate concentration in serum, that is individualizing aluminium gel therapy (SED-12, 515).

Drug Administration

Drug overdose

Of 195 patients hospitalized after aluminium phosphide poisoning (84), 115 died. Death was related to the dose

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but not to the time between ingestion and arrival at the hospital. The non-survivors had more severe hypotension and metabolic acidosis than the survivors, who had more severe vomiting. Aluminium phosphide is highly toxic, with a fatal dose as low as 1.5 g. The dominant clinical feature in such cases is severe hypotension, and severe gastrointestinal derangement and cardiorespiratory failure can occur within a day of exposure (85).

Drug–Drug Interactions

Citrate

Citrate is included in many effervescent or dispersible tablets, and increased absorption of aluminium from the gastrointestinal tract has been reported (86–88).

Deferoxamine

Although deferoxamine is effective in treating aluminium overload, case reports have shown that it can induce an exacerbation of aluminium encephalopathy (89), possibly due to increased aluminium concentrations in the cerebrospinal fluid (90,91). During treatment with deferoxamine, plasma aluminium concentrations should be monitored, as concentrations exceeding 800–1000 μmol/l can exacerbate encephalopathy.

Diflunisal

Aluminium reduced the systemic availability of diflunisal by about 40% in healthy volunteers (92).

Prednisone

In five healthy volunteers and 12 patients with chronic active liver disease, antacids containing aluminium hydroxide and magnesium hydroxide significantly reduced the C_{max} and AUC of prednisone when administered with antacids. The systemic availability was reduced by up to 43% (93).

Silicon

Aluminium has a close chemical affinity with silicon, which may have a role in protecting against aluminium toxicity (94). Serum aluminium and silicon concentrations were measured in hemodialysis patients from four different centers. Although there was no relation across all centers combined, in one center there was a reciprocal relation in patients on home hemodialysis (who did not require reverse osmosis). Median (range) aluminium concentrations were higher, 2.2 (0.4–9.6) μmol/l when serum silicon was less than 150 μmol/l, and lower, 1.1 (0.2–2.8) μmol/l when serum silicon was greater than 150 μmol/l. In patients treated by hemodialysis without reverse osmosis, high serum silicon concentrations were associated with lower serum aluminium concentrations. Further work is needed to confirm a preventive role for silicon in the accumulation and subsequent toxicity of aluminium in dialysis patients.

Tetracyclines

The laboratory finding that aluminium hydroxide binds a variety of drugs, thus forming poorly absorbable salts or complexes, has led to a general rule of thumb that other drugs should not be taken within 1–2 hours of aluminium compounds. In most cases such interactions are clinically insignificant, but caution is advisable. The absorption of tetracyclines under these conditions can be reduced by as much as 90% (95).

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Amantadine

General Information

Amantadine is a symmetrical C10 tricyclic amine with an unusual structure (1-adamantanamine hydrochloride). It interferes with virus uncoating (1) by blocking the M2 ion channel, which is needed to affect a pH change that helps to initiate the uncoating process. Most consistent antiviral activity has been observed against influenza A virus, but amantadine has little or no activity against influenza B virus (2). However, influenza A virus can become rapidly resistant to amantadine in vitro (3). Amantadine also promotes the release of dopamine from nerve endings, but may also delay its reuptake into synaptic vesicles.

Doses of 100–200 mg/day are often used and are usually well tolerated. The best-documented adverse reactions are nausea, psychotic episodes (mania,

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hallucinations, agitation, confusion), restless legs, and convulsions. Minor adverse reactions often resemble those caused by anticholinergic agents, for example blurred vision, dryness of the mouth, insomnia, lethargy, and rash. In rare cases, photosensitization has been described. Oral or aerosol administration can be accompanied by gastrointestinal or minor neurological symptoms, such as insomnia, light-headedness, concentration difficulties, nervousness, dizziness, and headache in individuals taking 200 mg/day (4). These symptoms disappear on withdrawal. More severe but rare complications include convulsions and coma (5,6). Local nasal adverse effects of the aerosolized form can mimic the symptoms of upper respiratory tract infection. In Parkinson's disease, in which doses of 200 mg/day or more have been used, minor adverse effects resembling those caused by anticholinergic agents (for example blurred vision, dry mouth, as well as livedo reticularis, rash, and photosensitization, can occur (SED-13, 874) (7,8).

Organs and Systems

Cardiovascular

Reversible congestive cardiac failure has been attributed to amantadine (9).

Nervous system

Insomnia is common with amantadine (10).

Myoclonus, especially vocal, can occur (11).

- A 48-year-old woman with a 17-year history of Parkinson's disease developed a sensorimotor peripheral neuropathy after taking amantadine 300 mg/day for 8 years (12). She had livedo reticularis after only 1 year of treatment and this had become increasingly extensive. Attempts to withdraw the drug resulted in worsening Parkinsonian symptoms. However, after the neuropathy had been diagnosed, amantadine was withdrawn, with improvement of the neurological symptoms within 6 weeks and complete resolution after 6 months. However, the livedo reticularis was still present 18 months after withdrawal.

This is the first description of peripheral neuropathy in these circumstances, but it suggests that chronic livedo reticularis may be a forerunner of more severe problems.

Three Japanese women aged 78–87 years who had taken amantadine 100–200 mg/day for 1 month to 5 years, in two cases together with co-careldopa, developed multifocal myoclonus and two were confused (13). Amantadine concentrations were high in the two patients in whom they were measured, at over 3000 ng/ml; a concentration over 1000 ng/ml is regarded as toxic. Amantadine was withdrawn and the myoclonus disappeared within 1–2 weeks and did not recur. Cortical myoclonus has also been described with levodopa and bromocriptine, but the mechanism is not known.

Sensory systems

Rarely, amantadine causes visual impairment due to corneal abrasions, local edema, and superficial keratitis (14).

Psychological, psychiatric

The risk of mental complications seems to increase substantially if doses of 200 mg or more are given (15). Amantadine can cause mania and is contraindicated in patients with bipolar affective disorder (16).

- While taking amantadine, an elderly man developed the Othello syndrome, a severe delusion of marital infidelity, as described in Shakespeare's plays *Othello* and *A Winter's Tale*; it abated with drug withdrawal (SEDA-17, 170).
- Amantadine and phenylpropanolamine may have caused intense recurrent déjà vu experiences in a healthy 39-year-old within 24 hours of starting both drugs for influenza (17).

Fluid balance

Resistant edema of the ankles in the absence of cardiac disease has repeatedly been described and well documented by rechallenge (18).

Skin

Livedo reticularis has been stated to occur in as many as 90% of patients; it is very common in female patients especially those with antiphospholipid antibodies (19).

Long-Term Effects

Drug withdrawal

On withdrawal of amantadine after long-term therapy, acute delirium with confusion, disorientation, agitation, and paranoia occurred in three patients (20). Reintroduction of the drug returned the patients to the baseline status.

In four patients, amantadine withdrawal was associated with delirium and confusion (21). The patients, three of them women, were aged 70–83 years and all but one were considered to have early dementia. Amantadine exposure was 1–5 years and the symptoms occurred within a week of drug withdrawal. In all cases they were reversed by reintroduction. The mechanism of the withdrawal reaction is unknown, but it should obviously be borne in mind, especially in elderly patients with long exposure to the drug and with already impaired cognitive function.

Neuroleptic malignant syndrome can occur on withdrawal of amantadine (22,23).

Susceptibility Factors

Renal disease

In a case of end-stage renal insufficiency, amantadine caused coma, though drug plasma concentrations were not greatly increased (SEDA-18, 160).

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Amaranthaceae

See also Herbal medicines

General Information

The genera in the family of Amaranthaceae (Table 1) include cotton flower and rockwort.

Pfaffia paniculata and ginseng

Ginseng is an ambiguous vernacular term that can refer to *Panax* species such as *Panax ginseng* (Asian ginseng) and *Panax quinquefolius* (American ginseng), *Eleutherococcus senticosus* (Siberian ginseng), and *Pfaffia paniculata* (Brazilian ginseng). See ginseng in the monograph on Araliaceae.

Adverse effects

Respiratory

Asthma occurred in a patient who had been exposed to *Pfaffia paniculata* root powder used in the manufacturing of Brazil ginseng capsules (1). Airway hyper-reactivity was confirmed by a positive bronchial challenge to methacholine and sensitivity to the dust was confirmed by immediate skin test reactivity, a positive bronchial challenge (immediate response), and the presence of a specific IgE to an aqueous extract detected by ELISA. The bronchial response was inhibited by sodium cromoglicate. Unexposed subjects did not react to this ginseng extract with any of the tests referred to above. The same study performed with Korean ginseng (*Panax ginseng*) was negative.

Table 1 The genera of Amaranthaceae

Achyranthes (chaff flower)
Aerva (aerva)
Alternanthera (joyweed)
Amaranthus (pigweed)
Blutaparon (blutaparon)
Celosia (cock's comb)
Chamissoa (chamissoa)
Charpentiera (papala)
Cyathula (cyathula)
Froelichia (snake cotton)
Gomphrena (globe amaranth)
Gossypianthus (cotton flower)
Guilleminea (matweed)
Hermbstaedtia (hermbstaedtia)
Iresine (bloodleaf)
Lithophila (lithophila)
Nototrichium (rockwort)
Pfaffia (pfaffia)
Philoxerus (philoxerus)
Tidestromia (honeysweet)

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Amfebutamone (bupropion)

See also Antidepressants, second-generation

General Information

Amfebutamone is an amphetamine-like drug. It is structurally and pharmacologically distinct from other antidepressants, and apparently enhances both dopamine and noradrenaline function in the brain (SEDA-8, 18) (SEDA-10, 20).

Amfebutamone is used to encourage smoking cessation and in some countries as an antidepressant. In some respects its adverse effects profile is similar to that of the SSRIs: insomnia, agitation, tremor, and nausea are most often reported.

Randomized controlled trials have shown that amfebutamone is less likely to cause sexual dysfunction than SSRIs (1,2), unlike SSRIs, which gives it an important advantage in some patients.

Amfebutamone has been used as an antidepressant for many years in the USA and Canada and is now licensed in Europe for smoking cessation. There has been concern about the number of serious adverse reactions associated with amfebutamone, with particular emphasis on the risk of seizures. Deaths have also been reported from myocarditis and liver failure (3). A problem in determining the role of amfebutamone in these adverse effects is that it is prescribed for heavy smokers who are at risk of serious co-morbid disorders, particularly cardiovascular and respiratory disease. However, it has been clear for some time that the use of amfebutamone is associated with an increased risk of seizures, though this is less with the modified-release formulation (SEDA-23, 20).

Organs and Systems

Cardiovascular

The UK Committee on Safety of Medicines has received over 200 reports of chest pain in patients taking amfebutamone, and a case of myocardial infarction has been reported.

- A 43-year-old man who had smoked up to 20 cigarettes daily for several years and had a family history of heart disease was given amfebutamone and stopped smoking after reaching the recommended dose (300 mg/day) (4). Three days later he developed central chest and arm pain and 1 day later stopped taking amfebutamone. Three days after this he developed classical symptoms of acute inferoposterolateral myocardial infarction. He was treated with thrombolytic therapy and discharged taking secondary prevention therapy.

It is difficult to know how far amfebutamone might have contributed to this acute cardiac event. However, continuing vigilance and case-control studies are warranted.

Nervous system

The main concern with the use of amfebutamone is that in higher dosages it is associated with a risk of seizures (0.4%). Early in 1986, advertising began to appear in advance of the expected release of amfebutamone in the USA. Abruptly, in March, distribution was halted because of reports of seizures in patients with bulimia. Although the risk is greater than that seen with SSRIs (about 0.1%), data have suggested that amfebutamone has approximately the same seizure potential as the tricyclic compounds (SEDA-8, 30). However, a higher seizure risk for amfebutamone than for tricyclic antidepressants has been reported in patients taking amfebutamone in doses over 450 mg/day (SEDA 17, 21). Furthermore, the manufacturers have noted an increased risk of seizures in patients taking over 600 mg/day in combination with lithium or antipsychotic drugs (SEDA-10, 20).

Of 279 patients who presented to a hospital emergency service between 1994 and 1998 with a first tonic-clonic seizure, 17 (6.1%) had seizures that were thought to be drug-related (5). The most common drug-induced causes were cocaine intoxication (6/17) and benzodiazepine withdrawal (5/17) followed by amfebutamone use (4/17). While one amfebutamone-associated seizure occurred in a 26-year-old woman without any other risk factors, the three other patients (all women) had additional risk factors, such as concomitant treatment with antidepressants that also lower seizure threshold and a history of bulimia nervosa. These results suggest that amfebutamone is not an infrequent cause of de novo seizures. However, because of the time frame of the study, many of the patients would have been taking standard-release amfebutamone. It would be of interest to repeat the study now that modified-release amfebutamone is available.

Amfebutamone lowers the seizure threshold and can cause paresthesia (6).

- A 38-year-old woman who was taking olanzapine 10 mg/day and lamotrigine 200 mg/day for a schizoaffective disorder started to take amfebutamone for a depressive mood swing. After 4 weeks the dose of amfebutamone was increased to 300 mg/day, at which point she complained of a twitching pain on the left side of her face. There was hypesthesia of two branches of the left trigeminal nerve, the ophthalmic and maxillary branches, and a reduced left corneal reflex. The amfebutamone was withdrawn and the neurological signs and symptoms disappeared within 8 days. Four weeks later, because of persisting depression, the amfebutamone was reintroduced; at a dosage of 300 mg/day identical neurological symptoms recurred.

The reason for this unusual reaction is not clear. Amfebutamone may potentiate dopamine neurotransmission, and dopamine D_2 receptors modulate trigeminal nerve function (7).

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Amfebutamone has been reported to mimic transient ischemic attacks (8).

- A 67-year-old man with a strong history of ischemic heart disease, who had been smoking 20 cigarettes a day for many years, started to take amfebutamone (100 mg tds) as an aid to smoking cessation. One week later he had episodes of disorientation, a tingling sensation over his body, and roaring sounds in his ears. MRI scanning and angiography showed evidence of previous strokes. His current episodes were ascribed to transient ischemic attacks. He had stopped taking amfebutamone while in hospital and then restarted it 2 days after discharge, when the same symptoms recurred. He then stopped taking amfebutamone completely and over the next 9 months had no further neurological episodes.

It is possible that these symptoms were entirely due to amfebutamone, but more probably the amfebutamone interacted in some way with the patient's established cerebrovascular disease.

Acute dystonia is a recognized complication of treatment with antipsychotic drugs and it can also occur with SSRIs and the anxiolytic drug buspirone.

- A 44-year-old man took amfebutamone 300 mg/day and buspirone 45 mg/day for depression (9). Over 2–3 weeks he developed increasing neck stiffness, with tightening and spasm of the jaw muscles and pain in the left temporomandibular joint. He stopped taking his medications, and all his symptoms resolved over the next 3 weeks. Rechallenge with buspirone (45 mg/day) failed to reproduce the dystonic symptoms. The buspirone was withdrawn and amfebutamone 150 mg/day was started; the dystonic symptoms did not recur. However, 24 hours after the dose of amfebutamone was increased to 300 mg/day there was a return of neck stiffness and jaw spasm.

Amfebutamone has dopaminergic properties, which seem to have played a part in this dystonia. Whether the effect was initiated by concomitant buspirone therapy is unclear, but subsequently amfebutamone alone was sufficient to produce the dystonic symptoms.

Cases of visual hallucinations and tinnitus have been reported in patients taking amfebutamone (SEDA-17, 21).

Psychological, psychiatric

Amfebutamone potentiates dopamine neurotransmission and at higher doses can cause toxic delirium and psychosis, particularly in patients with a history of psychosis and those taking other dopaminergic medications (SEDA-8, 31).

- A 79-year-old man developed a paranoid psychosis with auditory hallucinations during treatment with amfebutamone (100 mg tds) (10). The symptoms remitted with reduction of the dose of amfebutamone and the introduction of haloperidol 5 mg/day.

Paranoid ideas and hallucinations can occur during the course of a severe depressive episode, but in this case the patient's mood was gradually improving, so a link with amfebutamone seems more likely. It seems prudent to dose amfebutamone conservatively in elderly patients.

In an open trial, two of 16 patients became psychotic and were withdrawn from the study (11). A more detailed report of this adverse effect described four of 13 patients who became psychotic during a trial of amfebutamone; three had a history of psychosis, but none had previously had this response to other antidepressants (12). The usual dosage range of amfebutamone is 300–750 mg/day, and the psychotic symptoms occurred at dosages of 300–500 mg/day. In two cases psychotic symptoms were absent at lower dosages, but in one case the dose was therapeutically inadequate.

Other reports of psychotic reactions and a manic syndrome associated with amfebutamone have appeared (SEDA-16, 10) (SEDA-17, 21). In two of these cases a possible drug interaction with fluoxetine, with inhibition of the metabolism of amfebutamone, could not be excluded.

Hematologic

Eosinophilia reportedly developed in a 72-year-old woman shortly after she was given amfebutamone. The eosinophil count fell rapidly after all medications (including glibenclamide and tolmetin) were withdrawn (13).

Skin

Adverse skin reactions, such as rash, urticaria, and pruritus, have been reported in 1–4% of patients taking amfebutamone (14).

Immunologic

Two cases of serum sickness-like reactions have been reported in association with amfebutamone when used as an aid to smoking cessation (15,16). Both patients developed localized swellings of the fingers and hands, urticaria, and arthralgia. In both cases treatment with antihistamines and corticosteroids produced rapid relief of symptoms.

In three other patients (two women, one man) a serum sickness-like reaction developed 6–21 days after the start of amfebutamone treatment (14). The symptoms, arthralgia, pruritus, and tongue swelling, abated within 2 weeks of treatment with oral corticosteroids. Serum sickness reactions to drugs are rare, and it will be important to find out whether amfebutamone carries an increased risk of this unusual reaction.

Death

Amfebutamone has been linked to 41 deaths (17). From the reports of suspected adverse events received by the Netherlands Pharmacovigilance Foundation, it appears that more than half concerned patients at risk of smoking-related diseases. In 15 cases there had been simultaneous use of amfebutamone with another antidepressant (10 patients), theophylline (1 patient), or insulin (4 patients). These combinations may lead to an increase in the risk of seizures. Furthermore, two patients reported having taken antiepileptic drugs, despite the fact that amfebutamone is contraindicated in patients with seizure disorders. These results suggest that the guidelines described in the product information are not being adhered to in some cases.

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Drug Administration

Drug formulations

A modified-release formulation of amfebutamone has been marketed (18). There are insufficient data yet on the risk of seizures with higher doses of the modified-release formulation, but preliminary indications suggest that it is likely to be lower than that seen with the immediate-release formulation (18).

Drug overdose

Seizure is a significant risk in amfebutamone overdose.

- An 18-year-old man attempted suicide by taking amfebutamone 7.5 g (50 × 150 mg tablets) (19). On assessment 90 minutes later he was agitated and aggressive, with a resting pulse of 160 beats/minute and a blood pressure of 142/63 mmHg. He quickly developed a persistently low blood pressure (65/40 mmHg), followed by three generalized tonic-clonic seizures, which were controlled by diazepam. He was ventilated and a metabolic acidosis was corrected with sodium bicarbonate. Despite this, his blood pressure remained persistently low (70/40 mmHg) with a sinus tachycardia (150 beats/minute). Dopamine was ineffective and adrenaline was required. After 24 hours he was extubated and made a full recovery over the next 3 days.
- A 14-year-old boy took 1.5–3.0 g of amfebutamone and had a persistent tachycardia, seizures, and brief agitation and aggression (20). He also had visual hallucinations, disorientation, and confusion but recovered about 24 hours after ingestion.

These cases show that overdose of amfebutamone can be serious.

Drug–Drug Interactions

SSRIs

Amfebutamone is sometimes used to augment the action of other antidepressant drugs, but there are few data on the pharmacokinetic effects of this strategy. In an open study in 19 consecutive patients (7 men and 12 women), amfebutamone (150 mg/day for 8 weeks) did not alter plasma concentrations of paroxetine or fluoxetine (21). Plasma concentrations of venlafaxine increased, but concentrations of its active metabolite, O-desmethylvenlafaxine, fell. Overall tolerability was good and there was a significant reduction in depression rating scales. Sexual function, particularly orgasmic function in women, improved. These data suggest that adding amfebutamone to SSRI treatment does not alter plasma concentrations of SSRIs. The addition of amfebutamone to venlafaxine seems unlikely to cause pharmacokinetic problems in practice, because the increase in plasma concentration of the parent compound was offset by a reduction in the concentration of its major active metabolite. However, there is scope for an interaction of venlafaxine with amfebutamone and the effects in individual patients might be hard to predict. This study also supports clinical suggestions that the addition of amfebutamone to SSRI treatment can enhance antidepressant efficacy and improve sexual function. However, controlled trials are needed to confirm this view.

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Amfepramone (diethylpropion)

See also Anorectic drugs

General Information

Reports on the frequency of adverse reactions to amfepramone are not entirely consistent. The number of adverse effects reported by patients taking amfepramone closely paralleled the number in those taking placebo in one study in 90 obese individuals. In another 16-week controlled study in 95 subjects who took amfepramone 25 mg tds, the main adverse effect was nervousness. In 121 obese patients who took a shorter-acting form for an average of 4.4 months, adverse effects occurred in under 9%. They were nausea, vertigo in two patients, and nervousness and palpitation in another two; treatment was discontinued in three cases because of nausea, insomnia, and paresthesia (1). With long-acting amfepramone in a double-blind 16-week crossover study in 102 Austrian patients, adverse effects included nervousness, tension, nausea, dizziness, light-headedness, and dry mouth [SED-9, 14]. The main unwanted effects in a double-blind trial of modified-release amfepramone (Tenuate Dospan) in 50 pregnant women were euphoria, sweating, irritability, and palpitation. Nervousness and insomnia were reported in another controlled study in 75 pregnant women [SEDA-8, 17]. In neither of the last two studies were the adverse reactions serious enough to justify withdrawal.

Organs and Systems

Nervous system

Altogether the effects of amfepramone on the central nervous system are much less common than those of dexamphetamine; for example, 78 patients who had to stop treatment with amphetamine and benzfetamine were able to continue therapy with amfepramone. Even insomnia is uncommon if the drug is taken early in the day.

Long-Term Effects

Drug dependence

There have been some reports of addiction and psychotic manifestations with amfepramone (2) but these are much less frequent than are those associated with amphetamine or phenmetrazole.

Drug–Drug Interactions

Diazepam

In a comparative study using a fixed combination of amfepramone 75 mg plus diazepam 10 mg the adverse effects were milder than those found with other anorexigenic drugs [SED-9, 14]. However, there were mild adverse effects (dry mouth, nervousness, and depression) in about half of the patients.

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Amikacin

See also Aminoglycoside antibiotics

General Information

Amikacin is a semisynthetic derivative of kanamycin with similar pharmacokinetic properties and dosages. It is resistant to many of the bacterial R factor-mediated enzymes that inactivate kanamycin and gentamicin. Noteworthy is its effect against *Pseudomonas aeruginosa* and against most Gram-negative aerobes that are resistant to gentamicin and tobramycin. There are strains of *Staphylococcus aureus* that inactivate amikacin by phosphorylation and adenylation. Ticarcillin or azlocillin plus amikacin is considered one of the most efficacious empiric antibiotic combinations in febrile granulocytopenia in patients with cancer. On a weight basis amikacin is less active than gentamicin, and so the usual dose is 10–20 mg/kg/day. Wherever possible, peak concentrations of 40 μg/ml and troughs of 10 μg/ml should not be exceeded during twice-daily dosing.

Organs and Systems

Respiratory

Amikacin may have been the causative agent in an apneic episode in an infant on peritoneal dialysis (1).

Sensory systems

- A 43-year-old man, who was receiving hemodialysis through a permanent catheter developed severe irreversible sensorineural hearing loss after using an amikacin–heparin lock for 16 weeks (2). He suddenly developed a high-frequency sensorineural hearing loss of 40 decibels. His condition progressed over 1 week, despite immediate withdrawal of the amikacin–heparin lock, and he developed severe irreversible hearing loss below 80 decibels for both high and low frequencies.

Retinal toxicity can occur when aminoglycosides are given intravitreally for endophthalmitis.

- Preretinal hemorrhages developed in a 58-year old man who was treated with two intravitreal injections of amikacin (0.4 mg) and cefazolin (2.25 mg) 48 hours

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apart for postoperative endophthalmitis following routine extracapsular cataract extraction (3).
- Macular toxicity followed the use of intravitreal amikacin 0.2 mg for postoperative endophthalmitis in a 69-year-old white woman (4).

Ototoxicity was observed in three of 195 patients who received amikacin (15 mg/kg/day) with either cefepime (2 g bd) or ceftazidime (2 g tds) (5). Two patients had severe loss of hearing, which persisted after drug withdrawal and resulted in permanent disability. The other had mild ototoxicity that required no action and resolved spontaneously.

Urinary tract

After administration of the recommended doses of amikacin for 10 days, renal damage probably occurs in less than 10% of cases. Limited data support the view that amikacin is less nephrotoxic than other aminoglycosides, possibly because of lower binding affinity to proximal tubular cells or reduced potential to cause phospholipidosis (SEDA-20, 236). In several prospective randomized studies the liability of amikacin to cause nephrotoxicity was no greater than that of gentamicin or tobramycin (6–8). In a prospective study there was significantly lower nephrotoxicity with amikacin 15 mg/kg/day (4% toxicity) compared with netilmicin 7 mg/kg/day (12%) (9). As with other aminoglycosides, renal toxicity is reversible in most cases (10).

Nephrotoxicity occurred in five of 195 patients who received amikacin (15 mg/kg/day) with either cefepime (2 g bd) or ceftazidime (2 g tds) (5). In two patients the deterioration in renal function was mild and resolved without withdrawal of amikacin. In the three other patients, renal insufficiency necessitated drug withdrawal; two of these patients recovered, but one died with sepsis, and renal function was still abnormal at the time of death.

Long-Term Effects

Drug tolerance

In Spain, an epidemic strain of *Acinetobacter baumannii* with resistance to amikacin was isolated in eight different hospitals (11).

Susceptibility Factors

In an open study in eight young healthy Japanese women, the pharmacokinetics of amikacin were affected by the phase of the menstrual cycle (12). In patients with hematological malignancies, bodyweight, renal function, acute myeloblastic leukemia, and hypoalbuminemia were the most important co-variates for the interindividual variability in amikacin pharmacokinetics (13).

Drug Administration

Drug formulations

The pharmacokinetics and toxicity of liposomal amikacin have been investigated in a patient treated for advanced pulmonary multidrug-resistant tuberculosis (14). The serum concentrations of amikacin obtained with the liposomal formulation were considerably greater than those obtained with the conventional formulation. Liposomal amikacin was well tolerated and led to clinical improvement, but the patient's sputum remained smear- and culture-positive during the treatment period and for 9 months.

Drug administration route

Amikacin has been tested for compatibility with a chlorhexidine-bearing central venous catheter, the ARROWg+ard Blue Plus, and did not cause a substantial increase in chlorhexidine delivery (15). The amount of amikacin sulfate that was delivered was slightly less than the amount in the infusion solution (92%), but this was considered acceptable.

Drug–Drug Interactions

Penicillins

Amikacin may be inactivated by penicillins. This inactivation occurs not only with a mixture of the agents in solution but also in vivo, particularly in patients with renal insufficiency. Amikacin offers, at least in vitro, the advantage of being much less inactivated than tobramycin or gentamicin (16).

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Amiloride

See also Diuretics

General Information

Amiloride is a potassium-sparing diuretic that acts in the distal convoluted tubule independently of the action of aldosterone, inhibiting sodium channels. It is a relatively safe drug with few reported adverse effects.

Patients with congenital nephrogenic diabetes insipidus are often treated with a combination of a thiazide and a potassium-sparing diuretic, without consensus on the preferred potassium-sparing diuretic. A Japanese adult was systematically studied to determine the renal effects of hydrochlorothiazide plus amiloride and hydrochlorothiazide plus triamterene (1). The combination with amiloride was superior to that with triamterene in preventing excessive urinary potassium loss, hypokalemia, and metabolic alkalosis. These results suggest that amiloride is the preferred add-on therapy to hydrochlorothiazide in nephrogenic diabetes insipidus.

Organs and Systems

Cardiovascular

An isolated report (2) suggests that amiloride may have prodysrhythmic potential in a small proportion of patients with inducible sustained ventricular tachycardia.

Electrolyte balance

Amiloride has a specific effect on sodium flux in the renal tubules; severe hyponatremia has been reported with the combination of a thiazide diuretic and amiloride.

As a potassium-sparing diuretic, amiloride can cause hyperkalemia (3), even in patients who are taking a potassium-wasting diuretic (4). This effect can be enhanced by concomitant therapy with ACE inhibitors or angiotensin-II receptor antagonists. In five patients with diabetes mellitus over 50 years of age who were taking an ACE inhibitor the serum potassium rose markedly 8–18 days after the addition of amiloride (5). All but one had some degree of renal impairment. In four cases potassium concentrations were between 9.4 and 11 mmol/l.

Skin

Rashes with diarrhea and eosinophilia have been reported (6).

Immunologic

Sweden's National Adverse Reaction Monitoring System called the attention of physicians to a case in which a 73-year-old woman developed anaphylactic shock after taking only a single tablet of Moduretic (7). The National System had received three other reports on anaphylactic reactions to this combination, and by 1988 the WHO center in Uppsala had received eight others from other countries. Except for mild skin reactions, hypersensitivity reactions to hydrochlorothiazide alone are highly unusual and not of this type.

Drug–Drug Interactions

ACE inhibitors

Co-administration of potassium-sparing diuretics with ACE inhibitors can cause severe hyperkalemia (SED-14, 674). In a retrospective study, five patients developed extreme hyperkalemia (9.4–11 mmol/l) within 8–18 days of starting combination therapy with co-amilozide (amiloride + hydrochlorothiazide) and an ACE inhibitor (5).

Amphotericin

Amiloride is a therapeutic option in reducing potassium losses in patients receiving amphotericin. When it was given to 19 oncology patients with marked amphotericin-induced potassium depletion mean serum potassium concentrations increased in the 5 days before and after administration (from 3.4 to 3.9 mmol/l) (8). There was also a trend toward reduced potassium supplementation (48 versus 29 mmol/day). Adverse reactions were limited to hyperkalemia in two patients who took amiloride 20 mg/day and a high potassium intake.

Carbenoxolone

Amiloride inhibits the ulcer-healing properties of carbenoxolone (9).

Lithium

Although amiloride may reduce the renal clearance of lithium, it appears to be free of the troublesome interaction with lithium that complicates the use of thiazides and loop diuretics.

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Pentamidine

Pentamidine is structurally similar to amiloride and can cause severe hyperkalemia if co-prescribed with potassium-sparing diuretics (10). This is a particularly important interaction in patients with AIDS.

Trimethoprim

Trimethoprim (SED-14, 675) is structurally similar to amiloride and can cause severe hyperkalemia if co-prescribed with potassium-sparing diuretics (10). This is a particularly important interaction in patients with AIDS.

Interference with Diagnostic Tests

Creatinine clearance

Amiloride does not alter renal function (11), but it does block the tubular secretion of creatinine, leading to falsely high measurements of creatinine clearance; inulin clearance is not affected similarly (6).

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Amineptine

See also Tricyclic antidepressants

General Information

Amineptine is a tricyclic antidepressant that selectively reduces the dopamine reuptake without affecting the uptake of noradrenaline or serotonin (5-HT) (1). In vivo, it increases striatal homovanillic acid concentrations without affecting the concentrations of other metabolites of dopamine, 3,4,dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine. However, high doses of amineptine reduced the extracellular DOPAC concentration in the nucleus accumbens but not in the striatum. Long-term treatment with amineptine causes down-regulation of beta-adrenoceptors.

Amineptine has a seven-membered carbon side-chain and is reported to have more stimulant and fewer sedative effects than other tricyclic compounds, possibly owing to differential actions on dopaminergic rather than serotonergic mechanisms. Amineptine appears to have an unusual propensity for causing hepatocellular damage, which may limit its clinical use (2).

Amineptine increases the release and reduces the re-uptake of dopamine, and it is therefore not surprising that an amphetamine-like drug dependence has been reported (3–5). A withdrawal syndrome occurs and can be improved by clonidine (SEDA-16, 8).

Organs and Systems

Liver

Of all the tricyclic antidepressants, amineptine appears to be the most likely to cause liver damage. More than 26 cases of toxic hepatitis have been reported in France (6). In most cases, hepatitis occurred within the usual dosage range and recurred on rechallenge. However, in several instances it was reported after overdosage. There are other reports of hepatotoxicity associated with amineptine (7,8).

Skin

Amineptine has been reported (9) to cause particularly active acne, occurring beyond the usual distribution on the body and beyond the usual age, especially in women. The remedy recommended is withdrawal of amineptine.

A rosacea-like eruption on the face of a 76-year-old woman was associated with amineptine; the association was confirmed by re-challenge (10).

Long-Term Effects

Drug dependence

Dependence on amineptine in a patient also taking midazolam has been reported (11).

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Aminocaproic acid

General Information

During normal fibrinolysis, inactive circulating plasminogen binds to fibrin through an active site that binds lysine. The bound plasminogen is then converted to plasmin by activators (such as tissue plasminogen activator, t-PA) and converted to plasmin, which breaks down the fibrin. Aminocaproic acid (ε-aminocaproic acid, EACA, 6-aminohexanoic acid, Amicar) and tranexamic acid (Cyklokapron) are structural analogues of lysine, which bind irreversibly to the lysine-binding sites on plasminogen, inhibiting binding to fibrin and thus the whole process of fibrinolysis (1,2). These agents inhibit the natural degradation of fibrin and so stabilize clots.

Aminocaproic acid was the first such agent to be used widely, but it has largely been superseded in clinical practice by tranexamic acid, which is about 10 times more potent. *Para*-aminomethylbenzoic acid (PAMBA) is similar to aminocaproic acid, but is about three times more active in inhibiting plasminogen activators (3). However, it is no longer used despite the fact that it is well tolerated.

Uses

Antifibrinolytic agents are of benefit in the treatment of primary menorrhagia (4–7), recurrent epistaxis (8), oral bleeding in patients with congenital and acquired coagulation disorders (9,10), hemorrhage associated with thrombolytic therapy, and to reduce blood loss associated with surgery (especially cardiac surgery, joint replacement, and orthotopic liver transplantation) (11–14). Antifibrinolytic therapy can be of value in other conditions as well (15–21). It is effective in the bleeding diathesis that can accompany acute promyelocytic leukemia (22,23), but it does not improve outcome after subarachnoid hemorrhage (24).

General adverse effects

Some adverse effects are associated with all antifibrinolytic agents, reflecting their effect on clot stability. Dissolution of extravascular blood clots may be resistant to physiological fibrinolysis. These drugs should not to be used to treat hematuria due to blood loss from the upper urinary tract, as this can provoke painful clot retention and even renal insufficiency associated with bilateral ureteric obstruction (25–31).

Well-controlled studies on aminocaproic acid in a limited number of patients showed no serious adverse effects. Minor unwanted effects have been reported in 10–20% of patients and include headache, nasal congestion, conjunctival suffusion, nausea, vomiting, diarrhea, and transient hypotension (32). Skin rashes have also been associated with aminocaproic acid, including maculopapular and morbilliform eruptions. Rarer dermatological reactions reported include purpuric rashes (33), bullous eruptions (34), and contact dermatitis with positive patch tests (35–37). Treatment with a high dose (the maximum daily dose is 36 g/day) can result in an osmotic diuresis (38).

Miscellaneous adverse reactions attributed by the authors of single case reports have included a psychotic reaction (39), convulsions after intravenous administration of aminocaproic acid in a 60-year-old man treated for bleeding esophageal varices (40), and renal insufficiency due to glomerular capillary thrombosis (31).

Aminocaproic acid used during cardiopulmonary bypass reduced mediastinal blood losses by about one-third, while transfusion requirements were unchanged (41). In one series of over 950 patients, not a single thromboembolic complication could be ascribed to aminocaproic acid. However, a few cases of muscle necrosis and rhabdomyolysis with renal insufficiency have been reported with aminocaproic acid (42,43).

Organs and Systems

Cardiovascular

Aminocaproic acid has been reported to cause acute right heart failure (44).

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Acid–base balance

Metabolic acidosis associated with a high anion gap has been reported after the administration of aminocaproic acid to a woman with renal insufficiency (45).

Hematologic

Inhibition of plasminogen by tranexamic acid and aminocaproic acid could theoretically facilitate the development of thrombosis, but whether it actually does so has been the subject of contradictory reports. Episodes of venous and arterial thrombosis have been reported in association with treatment using either tranexamic acid or aminocaproic acid. These include thrombosis at unusual sites such as mesenteric thrombosis (46), aorta (47), retinal artery occlusion (48), and intracranial arterial thrombosis (49–51), as well as deep vein thrombosis in the legs (52).

- Massive pulmonary thromboembolism was reported in a 62-year-old woman seven days after treatment with high doses for subarachnoid hemorrhage (53).

Caution should also be taken in the administration of antifibrinolytic agents in disseminated intravascular coagulation (54).

Prophylactic use of histamine H_1 and H_2 receptor antagonists, aminocaproic acid, and hyposensitization have all been proposed as means of preventing idiosyncratic reactions to radiological contrast media. Aminocaproic acid was formerly used prophylactically in France, but carried a risk of massive intravascular coagulation (SEDA-17, 536).

Skin

- A 70-year-old man taking aminocaproic acid developed dermatitis with eosinophilia and positive patch tests on days 2 and 4 (55).

Musculoskeletal

Myopathy has occasionally been reported in association with aminocaproic acid therapy in both adults and children (42,56–64).

- Myonecrosis developed in a 22-year-old man who presented with dark smoky urine and calf tenderness, with progressive weakness and difficulty in walking, after treatment with aminocaproic acid for several weeks for traumatic hematuria; after withdrawal he recovered over 3 weeks (61).

A review of published cases confirmed that this complication is very rare and is usually associated with the administration of high doses for several weeks (43). The myopathy is often painful, and associated with raised creatine kinase activity and even myoglobinuria. Full resolution can be expected once the drug is withdrawn.

Susceptibility Factors

Renal disease

Two different case reports have dealt with previously unreported adverse effects of aminocaproic acid in patients with renal insufficiency.

- A patient with underlying chronic renal insufficiency, who underwent coronary bypass artery grafting and was treated with intravenous aminocaproic acid, developed hyperkalemia (6.7 mmol/l) (65). There was no other obvious cause for the acute increase in serum potassium.

The authors suggested that the structural similarity between aminocaproic acid and lysine and arginine underlies the mechanism of hyperkalemia; intravenous arginine can cause hyperkalemia (66,67). Furthermore, aminocaproic acid infusion in anephric dogs caused a rapid rise in serum potassium (68).

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Aminoglycoside antibiotics

See also Individual agents

General Information

Eleven aminoglycosides have been, or are still, important in medical practice: amikacin (rINN), gentamicin (pINN), isepamicin (rINN), kanamycin (rINN), neomycin (rINN), netilmicin (rINN), paromomycin (rINN), sisomicin (rINN), streptomycin (rINN) and dihydrostreptomycin (rINN), and tobramycin (rINN). The following aminoglycosides are also covered in separate monographs: amikacin, gentamicin, isepamycin, kanamycin, and tobramycin.

Being chemically similar, the aminoglycosides have many features in common, in particular their mechanism of antibacterial action, a broad antibacterial spectrum, partial or complete cross-resistance, bactericidal action in a slightly alkaline environment, poor absorption from the gastrointestinal tract, elimination by glomerular filtration, nephrotoxicity, ototoxicity, a potential to cause neuromuscular blockade, and partial or complete cross-allergy (1). Aminoglycosides have a moderate capacity for diffusion into bone tissue (2).

The aminoglycosides have probably more than one mechanism of action on bacterial cells. They cause misreading of the RNA code and/or inhibition of the polymerization of amino acids.

All the aminoglycosides have similar patterns of adverse reactions, although there are important differences with regard to their frequency and severity (Table 1).

Strategies for minimizing aminoglycoside toxicity include early bedside detection of cochlear and vestibular dysfunction, which should lead to prompt withdrawal, use of short periods of treatment, dosing intervals of at least 12 hours, monitoring of serum concentrations, and awareness of relative contraindications, such as renal or hepatic dysfunction, old age, hearing impairment, and previous recent aminoglycoside exposure (3).

Observational studies

In an open, randomized, comparative study of the efficacy, safety, and tolerance of two different antibiotic regimens in the treatment of severe community-acquired or nosocomial pneumonia, 84 patients were analysed (4). Half were treated with co-amoxiclav (amoxicillin 2 g and clavulanic acid 200 mg) every 8 hours plus a single-dose of 3–6 mg/kg of an aminoglycoside (netilmicin or gentamicin), and half with piperacillin 4 g and tazobactam 500 mg every 8 hours. The patients were treated for between 48 hours and 21 days. Clinical cure was achieved in 65% of patients with co-amoxiclav/aminoglycoside and in 81% of patients with piperacillin/tazobactam. Cure or improvement was observed in 84 and 90% respectively. Treatment failures were recorded in 14 versus 7%. One patient in each group relapsed. There was only one fatal outcome in the piperacillin/tazobactam group compared with six in the co-amoxiclav/aminoglycoside group. The adverse event rate was non-significantly lower in the

Table 1 Relative adverse effects of aminoglycoside antibiotics on eighth nerve function, the nervous system, and neuromuscular function

Aminoglycoside[1]	Usual parenteral dose (mg/kg/day)[2]	Site of adverse effect[3]			
		Vestibular function	Cochlear function	Nervous system	Neuromuscular function
Amikacin	10–15	+	++	++	+
Gentamicin	3–6	++	++	++	+
Kanamycin	10–20	+	+++	++	+
Netilmicin	3–6	+	+	++	+
Sisomicin	2–4	++	++	++	+
Streptomycin	10–20	+++	+	+	++
Dihydrostreptomycin	10–20	+	+++	+++	++
Tobramycin	3–6	++	++	++	+

[1] Neomycin and paromomycin: only accidental absorption after topical or gastrointestinal use.
[2] In general, older patients require lower doses. Low doses are required during therapy of infectious endocarditis when an aminoglycoside is given with a penicillin. Monitoring serum concentrations should be considered, particularly when using dosing regimens that involve more than one dose a day and high doses for several days.
[3] The number of signs (+) indicates the relative clinical importance of each reaction.

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piperacillin/tazobactam group. In one patient given piperacillin/tazobactam, there were raised transaminases. In the co-amoxiclav/aminoglycoside group, acute renal insufficiency developed in two patients and possibly drug-related fever in one. Bacteriological efficacy was comparable (92% versus 96%). The authors concluded that piperacillin/tazobactam is highly efficacious in the treatment of severe pneumonia in hospitalized patients and compares favorably with the combination of co-amoxiclav plus an aminoglycoside.

General adverse effects

The main adverse reactions of aminoglycosides consist of kidney damage (often presenting as non-oliguric renal insufficiency) and ototoxicity, including vestibular and/or cochlear dysfunction. Neuromuscular transmission can be inhibited. Hypersensitivity reactions are most frequent after topical use, which should be avoided. Anaphylactic reactions can occur. Tumor-inducing effects have not been reported.

Pharmacoeconomics

The pharmacoeconomic impact of adverse effects of antimicrobial drugs is enormous. Antibacterial drug reactions account for about 25% of adverse drug reactions. The adverse effects profile of an antimicrobial agent can contribute significantly to its overall direct costs (monitoring costs, prolonged hospitalization due to complications or treatment failures) and indirect costs (quality of life, loss of productivity, time spent by families and patients receiving medical care). In one study an adverse event in a hospitalized patient was associated on average with an excess of 1.9 days in the length of stay, extra costs of $US2262 (1990–93 values), and an almost two-fold increase in the risk of death. In the outpatient setting, adverse drug reactions result in 2–6% of hospitalizations, and most of them were thought to be avoidable if appropriate interventions had been taken. In a review, economic aspects of antibacterial therapy with aminoglycosides have been summarized and critically evaluated (5).

Organs and Systems

Cardiovascular

Anecdotal reports refer to tachycardia, electrocardiographic changes, hypotension, and even cardiac arrest (6). In practice, effects on the cardiovascular system are unlikely to be of any significance.

Respiratory

Severe respiratory depression due to neuromuscular blockade has been observed (7). Bronchospasm can occur as part of a hypersensitivity reaction.

Neuromuscular function

The aminoglycosides have a curare-like action, which can be antagonized by calcium ions and acetylcholinesterase inhibitors (8). The mechanisms include reduced release of acetylcholine prejunctionally and an interaction with the postjunctional acetylcholine receptor-channel complex. While neomycin interacts with the open state of the receptor, streptomycin blocks the receptor (9).

Aminoglycoside-induced neuromuscular blockade can be clinically relevant in patients with respiratory acidosis, in myasthenia gravis, and in other neuromuscular diseases. Severe illness, the simultaneous use of anesthetics, for example in the immediate postoperative phase, and application of the antibiotic to serosal surfaces are predisposing factors (10).

With regard to this effect, neomycin is the most potent member of the group. Several deaths and cases of severe respiratory depression due to neomycin have been reported (11). Severe clinical manifestations are rare in patients treated with aminoglycosides that are administered in low doses, such as gentamicin, netilmicin, and tobramycin. In some cases the paralysis was reversed by prostigmine.

Sensory systems

Eyes

Collagen corneal shields pre-soaked with antibiotics are used as a means of delivering drug to the cornea and anterior chamber of the eye. Gentamicin damages the primate retina, particularly by macular infarction, and amikacin can have a similar effect; a subconjunctival injection of tobramycin causes macular infarction (SEDA-19, 245). This potentially devastating consequence suggests that care must be exercised when contemplating instillation of aminoglycosides directly into the eye. Allergic contact dermatitis causing conjunctivitis and blepharitis has been reported with topical ophthalmic tobramycin (12).

Ears

Ototoxicity is a major adverse effect of aminoglycoside antibiotics (13). They all affect both vestibular and cochlear function, but different members of the family have different relative effects (Table 1).

Differences between different aminoglycosides

Ototoxicity due to amikacin is primarily cochlear; however, in comparisons with equipotent dosages, ototoxicity was of the same order as that caused by gentamicin (14–16).

In 40 patients tobramycin had little effect on audiometric thresholds, but produced a change in the amplitude of the distortion products, currently considered an objective method for rapidly evaluating the functional status of the cochlea (17). In one case, tobramycin caused bilateral high-frequency vestibular toxicity, which subsequently showed clinical and objective evidence of functional recovery (18).

In a quantitative assessment of vestibular hair cells and Scarpa's ganglion cells in 17 temporal bones from 10 individuals with aminoglycoside ototoxicity, streptomycin caused a significant loss of both type I and type II hair cells in all five vestibular sense organs (19). The vestibular ototoxic effects of kanamycin appeared to be similar to those of streptomycin, whereas neomycin did not cause loss of vestibular hair cells. There was no significant loss of Scarpa's ganglion cells.

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Incidence

The incidence of ototoxicity due to aminoglycosides varies in different studies, depending on the type of patients treated, the methods used to monitor cochlear and vestibular function, and the aminoglycoside used (20). Clinically recognizable hearing loss and vestibular damage occur in about 2–4% of patients, but pure-tone audiometry, particularly at high frequencies, and electronystagmography show hearing loss and/or vestibular damage in up to 26 and 10% respectively, despite careful dosage adjustment (21). In patients with *Pseudomonas* endocarditis receiving prolonged high-dose gentamicin, auditory toxicity was found in 44% (22,23).

A review of nearly 10000 adults suggested rates of 14% for amikacin, 8.6% for gentamicin, and 2.4% for netilmicin. Aminoglycoside toxicity is markedly lower in infants and children, with an incidence of 0–2%. A long duration of treatment and repeated courses or high cumulative doses appear to be critical for ototoxicity, which occurs in high frequency hearing beyond the range of normal speech.

There is a discrepancy between clinical observations, in which very few patients receiving aminoglycosides actually complain of hearing loss, and the reported incidences of ototoxicity in studies of audiometric thresholds. A major reason for this discrepancy relates to the fact that aminoglycosides cause high-frequency hearing loss well before they affect the speech frequency range in which they can be detected by the patient (21).

Gentamicin also damages the vestibular apparatus at a rate of 1.4–3.7%, resulting in vertigo and impaired balance. This effect is reversible in only about 50% from 1 week to 6 months after administration.

In a retrospective study in 81 men and 29 women, hearing loss of 15 decibels at two or more frequencies, or at least 20 decibels at at least one frequency, was found in 18% of patients treated with aminoglycosides (amikacin, kanamycin, and/or streptomycin) (24). In those treated with kanamycin the rate was 16%. Age, sex, treatment duration, total aminoglycoside dose, and first serum creatinine concentration were not associated with hearing loss.

Dose-relatedness

Hearing loss was attributed to repeated exposure to aminoglycosides in 12 of 70 patients with cystic fibrosis (one child) (25). There was a non-linear relation between the number of courses of therapy and the incidence of hearing loss. The severity of loss was not related to the number of courses. Assuming that the risk of hearing loss was independent of each course, the preliminary estimate of the risk was less than 2 per 100 courses.

Presentation

Clinically, cochlear ototoxicity is more frequent and easier to detect than vestibular toxicity; combined defects are relatively rare. Symptoms of cochlear damage include tinnitus, hearing loss, pressure, and sometimes pain in the ear. The manifestations of vestibular toxicity are dizziness, vertigo, ataxia, and nystagmus. These are often overlooked in severely ill, bed-ridden patients.

Symptoms of ototoxicity can occur within 3–5 days of starting treatment, but most patients with severe damage have received prolonged courses of aminoglycosides. In some cases, hearing loss progresses after the administration of the causative drug has been interrupted. The ototoxicity is reversible in only about 50% of patients. Permanent deafness is often seen in patients with delayed onset of symptoms, progressive deterioration after withdrawal of treatment, and hearing loss of over 25 db (21).

There are interesting differences in the toxicity patterns of aminoglycosides in animals. Gentamicin and tobramycin affect the cochlear and vestibular systems to a similar extent, while amikacin, kanamycin, and neomycin preferentially damage the cochlear and streptomycin the vestibular system. Netilmicin appears to be the least toxic (26,27).

In man, differences in the ototoxic risks of the currently used aminoglycosides are difficult to evaluate (20). There have been no prospective comparisons of more than two drugs using the same criteria in similar patient populations. However, several controlled comparisons of two aminoglycosides are available and provide some information. A survey of 24 such trials showed the following mean frequencies of ototoxicity: gentamicin 7.7%, tobramycin 9.7%, amikacin 13.8%, netilmicin 2.3% (28). There was also a lower incidence of netilmicin-induced inner ear damage compared with tobramycin in two studies (29,30).

Of 20 patients with Dandy's syndrome, 15 had previously been treated with aminoglycosides (13 with gentamicin and 2 with streptomycin), of whom 10 had symptoms of pre-existing chronic nephrosis or transitory renal insufficiency. In all 13 patients who had gentamicin, peripheral vestibular function was destroyed or severely damaged, whereas there was no hearing loss (31).

Mechanism

The mechanism of ototoxicity by aminoglycosides is still not fully clarified. Most of the experimental data have been gained in the guinea-pig model, which seems to resemble man.

Animal studies

Traditionally, toxic damage is considered to be the consequence of drug accumulation in the inner ear fluids (32,33). After a period of reversible functional impairment, destruction of outer hair cells occurs in the basilar turn of the cochlear duct and proceeds to the apex. Similar changes are found in the hair cells of the vestibular system. Gentamicin was detected in the outer hair cells in the cochlea of animals receiving non-ototoxic doses of the drug and continued to increase for several days after withdrawal (34). This was followed by a third and very much slower phase of elimination (estimated half-life 6 months), and in the absence of ototoxicity gentamicin could still be detected in the outer hair cells 11 months after treatment. This may explain why patients who receive several courses of aminoglycosides in a year may be more susceptible to ototoxicity, and suggests that the cumulative dose (and by implication the duration of therapy) is the more important determinant of cochlear damage. However, it has been questioned whether

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ototoxicity correlates with plasma perilymph or whole-tissue concentrations of aminoglycosides (33).

The effects of aminoglycosides on the medial efferent system have been assessed in awake guinea-pigs (35,36). The ensemble background activity and its suppression by contralateral acoustic stimulation was used as a tool to study the medial efferent system. A single intramuscular dose of gentamicin 150 mg/kg reduced or abolished the suppressive effect produced by activation of the olivocochlear system by contralateral low-level broadband noise stimulation. This effect was dose-dependent and could be demonstrated ipsilaterally on the compound action potential, otoacoustic emissions, and ensemble background activity of the eighth nerve. Long-term gentamicin treatment (60 mg/kg for 10 days) had no effect, at least before the development of ototoxicity. Single-dose intramuscular netilmicin 150 mg/kg displayed blocking properties similar to gentamicin, although less pronounced, while amikacin 750 mg/kg and neomycin 150 mg/kg had no effect. With tobramycin 150 mg/kg and streptomycin 400 mg/kg a decrease in suppression was usually associated with a reduction of the ensemble background activity measured without acoustic stimulation, which may be a fist sign of alteration to cochlear function. There was no correlation between specificity and degree of aminoglycoside ototoxicity and their action on the medial efferent system.

Possible mechanisms and preventive strategies have also been investigated in pigmented guinea-pigs (37–39). Animals that received alpha-lipoic acid (100 mg/kg/day), a powerful free radical scavenger, in combination with amikacin (450 mg/kg/day intramuscularly) had a less severe rise in compound action potential threshold than animals that received amikacin alone. In a similar study in pigmented guinea-pigs, the iron chelator deferoxamine (150 mg/kg bd for 14 days) produced a significant protective effect against ototoxicity induced by neomycin (100 mg/kg/day for 14 days). The spin trap alpha-phenyl-tert-butyl-nitrone also protected against acute ototopical aminoglycoside ototoxicity in guinea-pigs. These studies have provided further evidence for the hypothesis that aminoglycoside ototoxicity is mediated by the formation of an aminoglycoside-iron complex and reactive oxygen species.

Aminoglycoside-induced ototoxicity may be in part a process that involves the excitatory activation of cochlear NMDA receptors (40). In addition, the uncompetitive NMDA receptor antagonist dizocilpine attenuated the vestibular toxicity of streptomycin in a rat model, further stressing that excitotoxic mechanisms mediated by NMDA receptors also contribute to aminoglycoside-induced vestibular toxicity (41). In two studies in guinea-pigs, nitric oxide and free radicals, demonstrated by the beneficial effect of the antioxidant/free radical scavenger alpha-lipoic acid, have been suggested to be involved in aminoglycoside-induced ototoxicity (38,42). In contrast, insulin, transforming growth factor alpha, or retinoic acid may offer a protective potential against ototoxicity caused by aminoglycosides. However, they do not seem to promote cochlear hair cell repair (43). In guinea-pigs, brain-derived neurotrophic factor, neurotrophin-3, and the iron chelator and antioxidant 2-hydroxybenzoate (salicylate), at concentrations corresponding to anti-inflammatory concentrations in humans, attenuated aminoglycoside-induced ototoxicity (44,45). In rats, concanavalin A attenuated aminoglycoside-induced ototoxicity, and kanamycin increased the expression of the glutamate-aspartate transporter gene in the cochlea, which might play a role in the prevention of secondary deaths of spiral ganglion neurons (46,47). Finally, 4-methylcatechol, an inducer of nerve growth factor synthesis, enhanced spiral ganglion neuron survival after aminoglycoside treatment in mice (48).

In hatched chicks repeatedly injected with kanamycin, afferent innervation of the regenerated hair cells was related more to the recovery of hearing than efferent innervation (49).

Human studies

There is evidence that the site of ototoxic action is the mitochondrial ribosome (50,51). In some countries, such as China, aminoglycoside toxicity is a major cause of deafness. Susceptibility to ototoxicity in these populations appears to be transmitted by women, suggesting mitochondrial inheritance. In Chinese, Japanese, and Arab-Israeli pedigrees a common mutation was found. A point mutation in a highly conserved region of the mitochondrial 12S ribosomal RNA gene was common in all pedigrees with maternally inherited ototoxic deafness (50). A mutation at nucleotide 1555 has been reported to confer susceptibility to aminoglycoside antibiotics, and to cause non-syndromic sensorineural hearing loss. Outside these susceptible families, sporadic cases also have this mutation in increased frequency. In patients bearing this mitochondrial mutation hearing loss was observed after short-term exposure to isepamicin sulfate (52). These findings might create a molecular baseline for preventive screening of patients when aminoglycosides are to be used (SEDA-18, 1) (50).

Differences between sera from patients with resistance or susceptibility to aminoglycoside ototoxicity have been described in vitro (53). Sera from sensitive but not from resistant individuals metabolized aminoglycosides to cytotoxins, whereas no sera were cytotoxic when tested without the addition of aminoglycosides. This effect persisted for up to 1 year after aminoglycoside treatment.

Susceptibility factors

Several factors predispose to ototoxic effects (Table 2). Drug-related toxicity is influenced by the quality of prescribing. Overdosage in patients with impaired renal function, unnecessary prolongation of treatment, and the concomitant administration of other potentially ototoxic agents should be avoided. The exact mechanism of

Table 2 Factors that increase susceptibility to the adverse effects of aminoglycosides

Patient factors	Drug-related factors
Prior renal insufficiency	High temperature
Prior abnormal audiogram	Dose (blood concentration exceeding the usual target range)
Age (mainly older patients)	Total cumulative dose
Septicemia	Prolonged duration of therapy (2–3 weeks)
Dehydration	Prior aminoglycoside exposure

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increased toxicity in patients with septicemia and a high temperature is not clear; the possible relevance of additive damage by bacterial endotoxins has been discussed (54). Dehydration with hypovolemia is probably the main reason for the increased toxicity experienced when aminoglycosides are given with loop diuretics, but furosemide itself does not seem to be an independent risk factor (55,56). Attempts have been made in animals to protect against ototoxicity by antioxidant therapy (for example glutathione and vitamin C), as well as iron chelators and neurotrophins (57).

Hereditary deafness is a heterogeneous group of disorders, with different patterns of inheritance and due to a multitude of different genes (58,59). The first molecular defect described was the A1555G sequence change in the mitochondrial 12S ribosomal RNA gene. A description of two families from Italy and 19 families from Spain has now suggested that this mutation is not as rare as was initially thought (60,61). The A1555G mutation is important to diagnose, since hearing maternal relatives who are exposed to aminoglycosides may lose their hearing. This predisposition is stressed by the fact that 40 relatives in 12 Spanish families and one relative in an Italian family lost their hearing after aminoglycoside exposure. Since the mutation can easily be screened, any patient with idiopathic sensorineural hearing loss may be screened for this and possible other mutations.

In an Italian family of whom five family members became deaf after aminoglycoside exposure, the nucleotide 961 thymidine deletion associated with a varying number of inserted cytosines in the mitochondrial 12S ribosomal RNA gene was identified as a second pathogenic mutation that could predispose to aminoglycoside ototoxicity (62). Molecular analysis excluded the A1555G mutation in this family.

The A1555G mutation in the human mitochondrial 12S RNA, which has been associated with hearing loss after aminoglycoside administration (63) and has been implicated in maternally inherited hearing loss in the absence of aminoglycoside exposure in some families, can be identified by a simple and rapid method for large-scale screening that uses one-step multiplex allele-specific PCR (64).

Using lymphoblastoid cell lines derived from five deaf and five hearing individuals from an Arab-Israeli family carrying the A1555G mutation, the first direct evidence has been provided that the mitochondrial 12S rRNA carrying the A1555G mutation is the main target of the aminoglycosides (65). This suggests that they exert their detrimental effect through altering mitochondrial protein synthesis, which exacerbates the inherent defect caused by the mutation and reduces the overall translation rate below the minimal level required for normal cellular function.

A second pathogenic mutation that could predispose to aminoglycoside ototoxicity has been identified in an Italian family, of whom five members became deaf after aminoglycoside exposure (62). In the mitochondrial 12S ribosomal RNA gene, the deletion of nucleotide 961 thymidine was associated with a varying number of inserted cytosines. Transient evoked otoacoustic emission has been suggested as a sensitive measure for the early effects of aminoglycosides on the peripheral auditory system and may be useful as a tool for the prevention of permanent ototoxicity (66).

In a case-control study in 15 children under 33 weeks gestation with significant sensorineural hearing loss and 30 matched controls, the children with sensorineural hearing loss had longer periods of intubation, ventilation, oxygen treatment, and acidosis, and more frequent treatment with dopamine or furosemide (67). However, neither peak nor trough aminoglycoside concentrations, nor duration of jaundice or bilirubin concentration varied between the groups. At 12 months of age, seven of the children with sensorineural hearing loss had evidence of cerebral palsy compared with two of the 30 controls. Therefore, preterm children with sensorineural hearing loss required more intensive care in the perinatal period and developed more neurological complications than controls, and the coexistence of susceptibility factors for hearing loss may be more important than the individual factors themselves.

Diagnosis

To recognize auditory damage at an early stage and avoid severe irreversible toxicity, repeated tests of cochlear and vestibular function should be carried out in all patients needing prolonged aminoglycoside treatment. Pure-tone audiometry at 250–8000 Hz and electronystagmography with caloric testing are the standard methods. The first detectable audiometric changes usually occur in the high-tone range (over 4000 Hz) and then progress to lower frequencies. Hearing loss of more than 15 db is usually considered as evidence of toxicity. Brainstem auditory-evoked potentials have been recommended as a means of monitoring ototoxicity in uncooperative, comatose patients (68,69). This technique is time-consuming and requires some expertise, but may become a useful tool for detecting damage at an early stage. It also provides information on pre-existing changes, which is otherwise rarely available in intensive care patients (69).

Prevention

In rats, ototoxicity caused by gentamicin or tobramycin was ameliorated by melatonin, which did not interfere with the antibiotic action of the aminoglycosides (70). The free radical scavenging agent alpha-lipoic acid has previously been shown to protect against the cochlear adverse effects of systemically administered aminoglycoside antibiotics, and in a recent animal study it also prevented cochlear toxicity after the administration of neomycin 5% directly to the round window membrane over 7 days (71).

Loss of spiral ganglion neurons can be prevented by neurotrophin 3, whereas hair cell damage can be prevented by *N*-methyl-D-aspartate (NMDA) receptor antagonists. In an animal study, an NMDA receptor antagonist (MK801) protected against noise-induced excitotoxicity in the cochlea; in addition, combined treatment with neurotrophin 3 and MK801 had a potent effect in preserving both auditory physiology and morphology against aminoglycoside toxicity induced by amikacin (72).

Metabolism

Aminoglycosides can stimulate the formation of reactive oxygen species (free radicals) both in biological and cell-free systems (73,74).

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Electrolyte balance

Aminoglycoside-induced proximal tubular dysfunction, which causes some manifestations of Fanconi's syndrome, including electrolyte abnormalities, is rare.

- A 72-year-old man was treated with ceftriaxone (2 g bd) and gentamicin (80 mg tds) for a severe urinary tract infection (75). On day 5 his serum potassium concentration was 3 mmol/l with a normal serum creatinine and urine examination. Despite treatment with oral potassium chloride plus a high potassium diet, his serum potassium fell to 2.3 mmol/l 4 days later, accompanied by inappropriate kaliuresis, hypouricemia with inappropriate uricosuria, and hypophosphatemia with inappropriate phosphaturia. There was no bicarbonate wasting, but there was proteinuria 1.2 g/day, with a predominance of low molecular weight proteins; in contrast, serum creatinine was normal and creatinine clearance was 78 ml/minute. The aminoglycoside was withdrawn with subsequent progressive improvement in renal proximal tubular function, which normalized 9 days later.

Mineral balance

Hypomagnesemia is a well-recognized adverse effect of treatment with various drugs, including aminoglycosides (SEDA-16, 279). Gentamicin-induced magnesium depletion is most likely to occur in older patients when large doses are used over long periods of time (76). Under these circumstances, serum concentrations and urinary electrolyte losses should be monitored.

Metal metabolism

Aminoglycosides can cause renal magnesium wasting and hypomagnesemia, usually associated with acute renal insufficiency. However, animal studies have shown frequent renal magnesium wasting, even in the absence of renal insufficiency and abnormalities of renal tubular morphology. In 24 patients with cystic fibrosis, treatment with amikacin plus ceftazidime for exacerbation of pulmonary symptoms by *Pseudomonas aeruginosa* resulted in mild hypomagnesemia due to renal magnesium wasting, even in the absence of a significant rise in circulating creatinine and urea concentrations (77).

In five healthy volunteers gentamicin 5 mg/kg caused immediate but transient renal calcium and magnesium wasting (78).

Reversible hypokalemic metabolic alkalosis and hypomagnesemia can occur with gentamicin, and routine monitoring has been recommended (79).

The results of an in vitro study on immortalized mouse distal convoluted tubule cells have suggested that aminoglycosides act through an extracellular polyvalent cation-sensing receptor and that they inhibit hormone-stimulated magnesium absorption in the distal convoluted tubule (80).

In children with cystic fibrosis, aminoglycosides can cause hypomagnesemia due to excessive renal loss (81).

Hematologic

In an in vitro study both gentamicin sulfate and netilmicin sulfate showed competitive inhibition of glucose-6-phosphate dehydrogenase from human erythrocytes, whereas streptomycin sulfate showed non-competitive inhibition (82).

Liver

Certain aminoglycosides affect liver function tests. Increases in alkaline phosphatase after gentamicin and tobramycin have been described.

Urinary tract

Impairment of kidney function is a major adverse effect of the aminoglycoside antibiotics. In a survey of the use of antibiotics in a surgical service, aminoglycosides were given to 26 patients, of whom four developed nephrotoxicity (83).

In patients undergoing peritoneal dialysis, intraperitoneal or intravenous aminoglycosides can increase the rapidity of the fall in residual renal function. In an observational, non-randomized study, 72 patients on peritoneal dialysis were followed for 4 years (84). Patients who had been treated for peritonitis with intraperitoneal or intravenous aminoglycosides for more than 3 days had a more rapid fall in renal creatinine clearance and a more rapid fall in daily urine volume than patients without peritonitis or patients treated for peritonitis with antibiotics other than aminoglycosides. However, the use of other nephrotoxins or agents that may improve renal function was not quantified.

Incidence

Impairment of kidney function in different studies is highly variable. It depends on the study population and the definition of toxicity, and can range from a few percent to more than 30% in severely ill patients (85,86).

In a retrospective study, the rate of nephrotoxicity at the end of treatment with aminoglycosides was 7.5% (kanamycin 4.5%) (24). Patients who developed nephrotoxicity had a longer duration of treatment and received larger total doses.

Susceptibility factors

As in the case of ototoxicity, certain susceptibility factors have been identified for nephrotoxicity (87,88). Total dose, age, abnormal initial creatinine clearance, the 1-hour post-dose and trough aminoglycoside serum concentrations, duration of treatment, and co-existent liver disease were predictors of subsequent kidney damage. However, the clinical significance and utility of predictive nomograms based on such risk factors have been challenged (89). Other factors, such as dehydration, hypovolemia, potassium and magnesium depletion, and sepsis are also important. Gentamicin nephrotoxicity is increased in biliary obstruction (SEDA-20, 235). Nephrotoxicity is potentiated by ACE inhibitors, cephalosporins, ciclosporin, cisplatin, loop diuretics (secondary to volume depletion), methoxyflurane, non-steroidal anti-inflammatory drugs, and any basic amino acid such as lysine. Additional factors, such as previous aminoglycoside exposure, metabolic acidosis, female sex, and diabetes mellitus, are less clearly associated with renal damage (90,91).

In a prospective, non-interventional surveillance study of 249 patients receiving a once-daily aminoglycoside

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(17% amikacin and 83% gentamicin), serum creatinine increased by more than 50% in 12%; none developed oliguric renal insufficiency (92). Renal damage correlated significantly with: a high aminoglycoside trough concentration (over 1.1 μg/ml); a hemoglobin concentration below 10 g/dl; hospital admission for more than 7 days before aminoglycoside treatment; and aminoglycoside treatment for more than 11 days.

Mechanism

The mechanism of nephrotoxicity has been studied in vitro, in animals, and in man. The data suggest that accumulation of aminoglycosides in the renal cortex is an important reason for functional damage. In addition, aminoglycoside-induced alterations of glomerular ultrastructure have been described (93). Tissue uptake is predominantly mediated by proximal tubular reabsorption of the filtered drug. The degree of renal injury caused by an aminoglycoside correlates with the amount of drug that accumulates in the renal cortex. However, intrinsic toxicity differs among the aminoglycosides. Endotoxins can increase intracortical accumulation (94). After the drug binds to an amino acid receptor site, there is pinocytotic entry into the tubular cells. Once the drug is within the cell, it persists there for a long time and is liberated only slowly, with a half-life of several days (95,96). Direct toxicity to tubular cells is mainly explained by inhibition of lysosomal activity, with accumulation of lamellar myeloid bodies consisting of phospholipids. Inhibition of lysosomal phospholipids can also be shown in purified liposomes in vitro (97). In renal biopsy specimens, vacuolization of the proximal tubular epithelium, clumped nuclear chromatin, and swollen mitochondria are seen. Patchy tubular cell necrosis, desquamation, and luminal obstruction are found at later stages.

The uptake of aminoglycosides into proximal renal tubular epithelial cells is limited to the luminal cell border and is saturable. Less frequent administration of doses larger than needed for saturation of this uptake may therefore reduce drug accumulation in the renal cortex (98). In vitro and in vivo data have provided evidence that partially reduced oxygen metabolites (superoxide anion, hydrogen peroxide, and hydroxyl radical), which are generated by renal cortical mitochondria, are important mediators of aminoglycoside-induced acute renal insufficiency (99).

A lipopeptide, daptomycin, which has bactericidal activity against Gram-positive bacteria by inhibition of the synthesis of lipoteichonic acid, prevents tobramycin-induced nephrotoxicity in rats. Fourier transformed infrared spectroscopy has been used to monitor the hydrolysis of phosphatidylcholine phospholipase A_2 in the presence of different aminoglycosides and/or daptomycin (100). Among the various aminoglycosides investigated there were major differences, directly related to chemical structure. The number of charges, the size, and the hydrophobicity of the substituents of an aminoglycoside determined the influence on the lag phase, on the maximal rate, and on the final extent of hydrolysis. Daptomycin alone eliminated the initial latency period, and reduced the maximal extent of hydrolysis. When daptomycin was combined with any of the aminoglycosides, the latency period also disappeared, but the phospholipase activity was higher than with the lipopeptide alone. The strongest activation of phospholipase A_2 activation was observed when daptomycin was combined with gentamicin.

Stress proteins seem to be actively involved in aminoglycoside-induced renal damage. In a study in Wistar rats, subcutaneous gentamicin caused tubular necrosis, followed by tubular regenerative changes and interstitial fibrosis (101). Both the regenerated and phenotypically altered tubulointerstitial cells were found to express heat-shock protein 47 in and around the fibrosis. Increased shedding of tubular membrane components, followed by rapid inductive repair processes with overshoot protein synthesis, can be detected by analysis of tubular marker protein in the urine of rats after administration of aminoglycosides (102).

Prevention

In a prospective, randomized, double-blind study of once-daily versus twice-daily aminoglycoside therapy in 123 patients (of whom 83 received treatment for over 72 hours), once-daily administration of aminoglycosides had a predictably lower probability of causing nephrotoxicity than twice-daily administration. In a Kaplan–Meier analysis, once-daily dosing provided a longer time of administration until the threshold for nephrotoxicity was met. The risk of nephrotoxicity was modulated by the daily AUC for aminoglycoside exposure, and the concurrent use of vancomycin significantly increased the probability of nephrotoxicity and shortened the time to its occurrence (98). In another study, once-daily aminoglycoside in 200 patients was prospectively compared with a retrospectively evaluated group of 100 patients treated with individualized traditional dosing. Patients with a baseline creatinine clearance below 40 ml/minute, meningitis, burns, spinal cord injury, endocarditis, or enterococcal infection were excluded. Clinical and microbial outcome was similar in the two groups. Nephrotoxicity occurred in 7.5% of the patients treated with once-daily aminoglycosides compared with 14% of the others. The cumulative AUC was significantly larger in patients on traditional dosing. Minimum serum concentrations, length of aminoglycoside therapy, and AUC over 24 hours were related to nephrotoxicity. Whereas vancomycin and concurrent nephrotoxic agents were independently related to toxicity, sex and age were not (103).

Careful tailoring of the dose can prevent nephrotoxicity. In 89 critically ill patients with a creatinine clearance over 30 ml/minute who were treated with gentamicin or tobramycin 7 mg/kg/day independent of renal function, with subsequent doses chosen on the basis of the pharmacokinetics of the first dose, signs of renal impairment occurred in 14%; in all survivors renal function recovered completely and hemofiltration was not needed (104).

Presentation and diagnosis

Nephrotoxicity can present as acute tubular necrosis or, more commonly, as gradually evolving non-oliguric renal failure. The time-course of toxicity is variable, but it usually develops only after several days of treatment. Early diagnosis is difficult, since there can be a reduction in glomerular filtration before a significant rise in serum

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creatinine concentration occurs (105). An increased number of casts in the urinary sediment can also precede the increase in serum creatinine (106). Measurement of phospholipids and urinary enzymes, such as beta$_2$-microglobulin or alanine aminopeptidase, has been proposed as a means of detecting early toxicity (107–109). However, data on these enzymes are not very useful, since they can be increased for various other reasons and raised concentrations do not reliably predict pending renal toxicity. Fortunately, recovery of renal function nearly always follows the withdrawal of aminoglycosides, although serum creatinine concentrations can continue to rise for several days after the last dose.

There is an increase in the urinary output of tubular marker proteins after aminoglycoside administration (102). Determination of *N*-acetyl-beta-D-glucosaminidase activity in the urine may be used as a screening test to facilitate early detection of the nephrotoxic effect of aminoglycosides (110). Urine chemiluminescence may aid in the detection of neonatal aminoglycoside-induced nephropathy (111).

Relative potency of different aminoglycosides

The nephrotoxicity of the various aminoglycosides has been compared in many animal experiments. The order of relative nephrotoxicity is as follows: neomycin > gentamicin > tobramycin > amikacin > netilmicin (112,113). However, in man conclusive data on the relative toxicity of the various aminoglycosides is still lacking. An analysis of 24 controlled trials showed the following average rates for nephrotoxicity: gentamicin 11%; tobramycin 11.5%; amikacin 8.5%; and netilmicin 2.8% (28). In contrast to this survey, direct comparison in similar patient groups showed no significant differences between the various agents in most trials (14,15,114–118). In fact, the relative advantage of lower nephrotoxicity rates observed with netilmicin in some studies may be limited to administration of low doses. In a prospective study there was significantly lower nephrotoxicity with amikacin 15 mg/kg/day (4% toxicity) compared with netilmicin 7 mg/kg/day (12%) (119). One prospective trial showed a significant advantage of tobramycin over gentamicin (120). However, these findings were not subsequently confirmed (121). Nephrotoxicity is a serious risk with all the currently available aminoglycoside antibiotics, and no drug in this series can be regarded as safe.

Skin

It is generally accepted that antibiotics that are important for systemic use should not be administered topically. This rule applies particularly to the aminoglycoside antibiotics. Even though neomycin and streptomycin are no longer often used systemically, the frequency of sensitization after topical administration of these drugs is particularly high.

Contact dermatitis due to arbekacin has been reported (122). The risk of sensitization by topically administered gentamicin seems to be smaller. Nevertheless, and in order to avoid resistance, topical use should be restricted to life-endangering thermal burns and to severe skin infections in which strains of *Pseudomonas* resistant to other antibiotics are involved.

Immunologic

In a prospective study of the results of skin patch testing in 149 patients who were scheduled for ear surgery, 14% of the patients had a positive skin reaction to one of the aminoglycosides (13% for gentamicin, 13% for neomycin) (123). In 16% of the patients with chronic otitis media and 6.7% of the patients with otosclerosis there was allergy to one of the aminoglycosides commonly found in antibiotic ear-drops. Patients who had previously received more than five courses of antibiotic ear-drops had a greater tendency to develop allergy to the aminoglycosides (35%).

Cross-reactivity between aminoglycoside antibiotics has long been known. Aminoglycoside antibiotics can be categorized in two groups, depending on the aminocycolitol nucleus: streptidine (streptomycin) and deoxystreptamine (neomycin, kanamycin, gentamicin, paromomycin, spectinomycin, and tobramycin). Another antigenic determinant is neosamine, a diamino sugar present in neomycin and, with minor changes, also in paromomycin, kanamycin, tobramycin, amikacin, and isepamicin. Streptomycin shares no common antigenic structures with the other aminoglycoside antibiotics, and cross-sensitivity with streptomycin has not been reported. Acute contact dermatitis was described in a 30-year-old man after rechallenge with gentamicin 80 mg; a patch test was positive for gentamicin, neomycin, and amikacin (124).

Occasional cases of anaphylactic shock have been reported, most of which have been due to streptomycin; other aminoglycosides have rarely been implicated, such as gentamicin (125,126) and neomycin (127).

Long-Term Effects

Drug resistance

During treatment of infections with either Gram-negative or Gram-positive bacteria, resistant subpopulations emerge, unless the peak to MIC ratio is high enough to reduce the bacterial inoculum drastically within a few hours (128). Similarly, rapid emergence of resistant subpopulations has been reported during aminoglycoside treatment in neutropenic animals. The virulence and clinical relevance of the relatively slow-growing resistant subpopulations (small colony variants) have been documented in both animal and clinical studies (129,130). Resistant subpopulations can be detected only by direct plating of specimens on aminoglycoside-containing agar plates, since resistance may be lost within one subculture. Combination therapy of an aminoglycoside plus a beta-lactam antibiotic has been successfully used to prevent selection of resistant subpopulations (131).

In a prospective surveillance study in France, the development of resistance to aminoglycosides and fluoroquinolones among Gram negative bacilli was assessed in 51 patients with a second infection due to Gram negative organisms at least 8 days after a first Gram negative infection (132). Treatment of the first infection with a beta-lactam antibiotic plus an aminoglycoside significantly reduced the susceptibility to amikacin (the most prescribed antibiotic). When the first infection was

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treated with a beta-lactam plus a fluoroquinolone, susceptibility to ciprofloxacin, pefloxacin, netilmicin, and tobramycin, but not gentamicin and amikacin, fell significantly.

A multidrug efflux system that appears to be a major contributor to intrinsic high-level resistance to aminoglycosides and macrolides has been identified in *Burkholderia pseudomallei* (133).

Out of 1102 consecutive clinical Gram negative blood isolates from Belgium and Luxembourg, 157 were "not susceptible" to aminoglycosides (134). The resistance levels were 5.9% for gentamicin, 7.7% for tobramycin, 7.5% for netilmicin, 2.8% for amikacin, and 1.2% for isepamicin. In a large European multinational study on 7057 Gram negative bacterial isolates, resistance levels were 0.4–3% for amikacin, 2–13% for gentamicin, and 2.5–15% for tobramycin among Enterobacteriaceae; 75% of *Staphylococcus aureus* isolates, but only 21% of enterococcal strains were susceptible to gentamicin (135). In a study from Spain, 9% of 1014 clinical *P. aeruginosa* isolates were resistant to amikacin or tobramycin (136). In the same country, resistance to amikacin rose from 21% to 84% and to tobramycin from 33% to 72% between 1991 and 1996 (137).

In a leading cancer center in Houston, 24% of 758 Gram negative clinical isolates were resistant to tobramycin and 12% were resistant to amikacin (138). In 3144 bacterial isolates causing urinary tract infections in Chile, 74% were identified as *Escherichia coli*; 4.2% of these strains were resistant to gentamicin, and 1.3% were resistant to amikacin (139). In contrast, the resistance levels were 30% and 17% respectively, in the other enterobacterial strains. In Brazil, all isolates of methicillin-resistant *S. aureus* were also resistant to gentamicin, amikacin, kanamycin, neomycin, and tobramycin (140), and 97% of such strains from Spain were resistant to tobramycin (141).

In mice, the bacterial neomycin phosphotransferase gene, which confers resistance to aminoglycoside antibiotics, prevented the loss of hair cells after neomycin treatment (142).

In in vitro susceptibility studies on 99 clinical isolates of *S. aureus*, 68 of 73 strains of methicillin-resistant *S. aureus* (MRSA) and two of 26 strains of methicillin-susceptible *S. aureus* were gentamicin-resistant (143). However, the combination of arbekacin plus vancomycin produced synergistic killing against 12 of 13 gentamicin-resistant MRSA isolates. Combinations of meropenem and aminoglycosides may be effective against strains of *P. aeruginosa* that are resistant to meropenem at clinically relevant concentrations; synergistic effects were observed in combinations that included arbekacin or amikacin (144).

Second-Generation Effects

Teratogenicity

During pregnancy the aminoglycosides cross the placenta and might theoretically be expected to cause otological and perhaps nephrological damage in the fetus. However, no proven cases of intrauterine damage by gentamicin and tobramycin have been recorded. In 135 mother/child pairs exposed to streptomycin during the first 4 months of pregnancy, there was no increase in the risk of any malformation (145). However, streptomycin and dihydrostreptomycin have caused severe otological damage (146).

Using the population-based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities (1980–96), which includes 38 151 pregnant women who had newborn infants without any defects and 22 865 pregnant women who had fetuses or newborns with congenital abnormalities, no teratogenic risk of parenteral gentamicin, streptomycin, tobramycin, or oral neomycin was discovered when restricted to structural developmental disturbances (147).

Susceptibility Factors

Age

In a prospective study on the prevalence of hearing impairment in a neonatal intensive care unit population (a total of 942 neonates were screened), aminoglycoside administration did not seem to be an important risk factor for communication-related hearing impairment (148). In almost all cases, another factor was the more probable cause of the hearing loss (dysmorphism, prenatal rubella or cytomegaly, a positive family history of hearing loss, and severe perinatal and postnatal complications).

Other features of the patient

The main susceptibility factors are summarized in Table 2. The most important factors are renal insufficiency, high serum drug concentrations, and a long duration of treatment (54).

Drug Administration

Drug dosage regimens

Twice-daily or thrice-daily administration was for a long time standard in aminoglycoside therapy of systemic bacterial infections in patients with normal renal function. However, in vitro, in vivo, and clinical studies have suggested that once-daily dosing of the same total daily dose might be more beneficial with respect to both efficacy and toxicity (SEDA-21, 265) (149–152).

Less frequent administration of higher doses results in higher peak concentrations. Owing to the pronounced concentration dependence of bacterial killing, higher peaks potentiate the efficacy of the aminoglycosides. The importance of a high ratio of peak concentration to the minimal inhibitory concentration (MIC) has been shown in vitro for both bactericidal activity and prevention of the emergence of resistance (153). Clinically the predictive value of the peak to MIC ratio has been documented for aminoglycoside therapy of Gram-negative bacteremia (154). Although once-daily dosing can result in prolonged periods of subinhibitory concentrations, bacterial regrowth does not occur immediately after the aminoglycoside concentration drops below the MIC. The term "post-antibiotic effect" has been suggested to describe this hit-and-run effect, in which there is persistent suppression of bacterial regrowth after cessation of

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exposure of bacteria to an active antibiotic. This phenomenon has been observed both in vitro and in vivo (155).

Various in vivo models have been used to study the effect of the dosage regimen on aminoglycoside nephrotoxicity and ototoxicity. Renal uptake of aminoglycosides is not proportional to serum concentration, because of saturation at the high concentrations achieved with once-daily regimens. The degree of renal injury increases the more often the aminoglycoside is given in humans, dogs, rabbits, guinea-pigs, and rats, as long as the total daily dose is kept constant (156,157). Early auditory alterations also occur more often, or to a greater extent, the more often the aminoglycoside is given.

Once-daily regimens have been compared with multiple-daily regimens in at least 27 randomized clinical trials and eight meta-analyses and in a mega-analysis of meta-analyses (158). In all the studies, extended-interval dosing was at least as efficacious as multiple-daily dosing, and may have been slightly better; it was no more toxic, and may have been less nephrotoxic. Extended dosing is also less expensive than multiple-daily dosing and markedly reduces costs. An analysis of 24 randomized clinical trials of amikacin, gentamicin, and netilmicin, including 3181 patients, showed superior results with once-daily regimens with respect to clinical efficacy (90 versus 85%) and bacteriological efficacy (89 versus 83%) (151). There were no statistically significant differences for toxicity. Nevertheless, both nephrotoxicity and ototoxicity occurred less often during once-daily dosing (4.5 versus 5.5% and 4.2 versus 5.8% respectively). Finally, once-daily dosing is more economical, since less nursing time and infusion material are required and drug monitoring can be reduced. In conclusion, amikacin, gentamicin, and netilmicin can be given once a day.

In a randomized trial in 249 patients with suspected or proven serious infections, the safety and efficacy of gentamicin once-daily compared with three-times-a-day was assessed in 175 patients who were treated with ticarcillin–clavulanate combined with gentamicin once-daily or three times daily or with ticarcillin–clavulanate alone (159). The achievement of protocol-defined peak serum gentamicin concentrations was required for evaluability. There were no significant differences between treatment regimens with respect to clinical or microbiological efficacy; the incidence of nephrotoxicity was similar in the three groups. In a post-hoc analysis, renal function was better preserved in those treated with gentamicin once a day plus ticarcillin + clavulanate than ticarcillin + clavulanate only.

Once-daily amikacin was as effective and safe as twice-daily dosing in a prospective randomized study in 142 adults with systemic infections (160).

In 43 patients, once-daily tobramycin (4 mg/kg/day) was at least as effective and was no more and possibly even less toxic than a twice-daily regimen (161).

The pharmacokinetics of once-daily intravenous tobramycin have been investigated in seven children with cystic fibrosis (162). All responded well. There was one case of transient ototoxicity but no nephrotoxicity.

In a prospective study, only increasing duration of once-daily aminoglycoside therapy was recognized as risk factor for toxicity in 88 patients aged 70 years and over (163).

In controlled trials of once-daily aminoglycoside regimens patients with endocarditis have often been excluded, and therefore few clinical data are available on this topic. Based on pharmacokinetic data in experimental endocarditis and integrative computer modeling, it has been hypothesized that drug penetration into vegetations would be enhanced by once-daily aminoglycoside administration, resulting in a long residence time in the vegetations and a beneficial effect in providing synergistic bactericidal action in combination with another antibiotic (164). With the exception of two early studies using enterococci, results from animal studies have been promising in once-daily aminoglycoside treatment of endocarditis. Only two human studies of once-daily aminoglycoside therapy in streptococcal endocarditis were identified. The regimen was efficacious and safe. The authors concluded that there appeared to be sufficient promising evidence to justify large trials to further investigate once-daily aminoglycoside in the treatment of endocarditis due to viridans streptococci, whereas more preliminary investigations were needed for enterococcal endocarditis.

Once-daily dosing regimens of aminoglycosides are routinely used in critically ill patients with trauma, although there is a marked variability in pharmacokinetics in these patients, eventually leading to prolonged drug-free intervals, and individualized dosing on the basis of at least two serum aminoglycoside concentrations can be recommended when once-daily dosing regimens are chosen (165).

Not all populations of patients have been included or extensively studied in published trials. Therefore, conventional multiple-daily aminoglycoside dosing with individualized monitoring should be used in neonates and children, in patients with moderate to severe renal insufficiency (creatinine clearance below 40 ml/minute), serious burns (over 20% of body surface area), ascites, severe sepsis, endocarditis, and mycobacterial disease, in pregnancy, in patients on dialysis, in invasive *P. aeruginosa* infection in neutropenic patients, and with concomitant administration of other nephrotoxic agents (for example amphotericin, cisplatin, radiocontrast agents, and NSAIDs). Extended-interval aminoglycoside dosing may be safe and efficacious in patients with mild to moderate renal insufficiency (over 40 ml/minute) and febrile neutropenia, especially where the prevalence of *P. aeruginosa* is low. In other serious Gram-negative infections warranting aminoglycoside treatment, extended-interval dosing is strongly suggested (166).

Drug administration route

Intraocular

Aminoglycosides are often used in ophthalmology to treat or to prevent bacterial infections, and they can be toxic to retinal structures if high concentrations are reached in the vitreous. Retinal ultrastructure was examined at various intervals after a single intravitreal injection of 100–4000 μg of gentamicin into rabbit eyes. Three days after injection of 100–500 μg, numerous abnormal lamellar lysosomal inclusions were observed in the retinal pigment epithelium and in macrophages in the subretinal space. These changes were typical of drug-induced lipid storage and were comparable to inclusions reported in kidney and

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other tissues as manifestations of gentamicin toxicity. One week after similar injections, focal areas of retinal pigment epithelium necrosis and hyperplasia with disruption of outer segments appeared, but the inner segments and the inner retina were intact. Doses of 800–4000 μg produced a combined picture of lipidosis of the retinal pigment epithelium and macrophages within the first 3 days, with increasing superimposed inner retinal necrosis (167).

Intratympanic

Intratympanic gentamicin therapy has gained some popularity in the treatment of vertigo associated with Menière's disease, as it offers some advantages over traditional surgical treatment. However, although the vestibulotoxic effect of gentamicin is well documented, there is no general agreement about the dose needed to control attacks of vertigo without affecting hearing. In 27 patients treated with small doses of gentamicin delivered via a microcatheter in the round window niche and administered by an electronic micropump, vertigo was effectively controlled; however, the negative effect on hearing was unacceptable (168,169).

Intraperitoneal

Bolus intraperitoneal gentamicin or tobramycin (5 mg/kg ideal body weight) is safe, achieves therapeutic blood concentrations for extended intervals, causes no clinical ototoxicity or vestibular toxicity, is cost-effective, and is convenient for patients and nurses (170).

Drug overdose

Although aminoglycoside antibiotics are dialysable, peritoneal dialysis may not remove aminoglycosides from the blood after overdosage (171). However, hemodialysis is effective (172). In one study in eight patients hemodiafiltration removed more netilmicin than conventional hemodialysis (173).

Drug–Drug Interactions

Cephalosporins

There are many reports of acute renal insufficiency from combined treatment with gentamicin (or another aminoglycoside) and one of the cephalosporins (174–176). The potential nephrotoxic effect of the combinations seems to be related mainly to the nephrotoxic effect of the aminoglycosides. In contrast, there is some evidence, both experimental (177) and clinical (178), that ticarcillin may attenuate the renal toxicity of the aminoglycosides.

Cisplatin/carboplatin

The nephrotoxic and ototoxic effects of cisplatin and carboplatin can be potentiated by concurrent administration of aminoglycosides, as shown in animals (179).

Loop diuretics

Among the agents that promote the nephrotoxic effects of the aminoglycosides, the loop diuretics furosemide and etacrynic acid are often mentioned. However, this interaction is by no means clearly established (26). These agents are not nephrotoxic in themselves. This supposed interaction may only be a consequence of sodium and volume depletion. Other types of diuretics, such as mannitol, hydrochlorothiazide, and acetazolamide, do not produce this interaction (26).

- A 60-year-old white woman developed ototoxicity after only 5 days of gentamicin therapy (500 mg, 6.8 mg/kg/day) and one dose of furosemide 20 mg (180).

Loop diuretics greatly potentiate the cochleotoxic effects of aminoglycosides (181). In pigmented guinea-pigs the effects of high-dose topical (10 μl of a 100 mg/ml solution directly on to the round window) or single-dose systemic (100 mg/kg) gentamicin and intracardiac administration of the loop diuretic etacrynic acid (40 mg/kg) on cochlear function have been studied (182). Compound action potentials were elicited at 8 kHz. All animals that received etacrynic acid had an immediate and profound rise in hearing threshold, irrespective of the method of gentamicin administration. The maximum threshold shift occurred within 30 minutes. Animals that received topical gentamicin recovered after etacrynic acid treatment; by day 20 the mean threshold shift was 7 dB. This group did not differ statistically from animals that received etacrynic acid alone. In contrast, animals that received systemic gentamicin initially recovered within 2 hours after etacrynic acid, but subsequently deteriorated over the next 24 hours. The mean threshold shift was 70 dB at day 20. Animals that received topical gentamicin had a temporary shift that resolved within 24–48 hours; by day 20, the mean threshold shift was 7 dB. Animals treated with systemic gentamicin alone did not have hearing loss. This study suggests that the potentiating effect of etacrynic acid on aminoglycoside ototoxicity is only after systematic and not topical aminoglycoside administration. This may be due to an etacrynic acid-induced increase in leakiness of the stria vascularis, thereby facilitating diffusion of aminoglycosides from the systemic circulation into the endolymphatic fluid.

Neuromuscular blocking drugs

The aminoglycosides have a curare-like action, which can be antagonized by calcium ions and acetylcholinesterase inhibitors (8). In patients who require general anesthesia, the effect of muscle relaxants, such as D-tubocurarine, pancuronium, and suxamethonium, can be potentiated by aminoglycosides (183).

Penicillins

There is an in vitro interaction between aminoglycoside antibiotics and carbenicillin or ticarcillin, leading to a significant loss of aminoglycoside antibacterial activity if these antibiotics are mixed in the same infusion bottle (184). The extent of inactivation depends on the penicillin concentration, the contact time, and the temperature. Azlocillin and mezlocillin inactivate aminoglycosides in a similar manner to that described for carbenicillin (185,186). Aminoglycosides should not be mixed with penicillins or cephalosporins in the same infusion bottle.

However, the clinical significance of the presence of both types of antibiotics in the patient is debatable. In

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patients who received a combination of gentamicin and carbenicillin the measured serum gentamicin concentrations were lower than the pharmacokinetically predicted values (187). This interaction may be especially important in patients with severe renal impairment, in whom long in vivo incubation of these drug combinations takes place before supplemental doses of the aminoglycoside drugs are given.

Vancomycin

Combined use of vancomycin and an aminoglycoside can increase the risk of toxicity (188–190).

Monitoring Therapy

Serum concentrations have often been monitored during multiple-daily dosing of aminoglycosides, particularly when high doses are used and also during prolonged therapy. The main goals of individual dosing and monitoring are to reach high bactericidal drug concentrations and to avoid drug accumulation in the serum, to minimize the risk of toxicity. Since both goals are much more likely to be met with once-daily dosing it may be feasible to reduce monitoring efforts during such dosing regimens. However, more clinical experience needs to be accumulated to establish solid guidelines for monitoring once-daily dosing regimens. Although more clinicians are nowadays switching to once-daily dosing of aminoglycosides, some continue to use multiple-daily regimens. Therefore, two separate concepts of aminoglycoside monitoring have to be considered, depending on the dosing schedule.

In a retrospective case-control study, 2405 patients received aminoglycosides in doses that were decided either by individualized pharmacokinetic monitoring or by the physician (191). Those who received individualized pharmacokinetic monitoring were significantly less likely to develop aminoglycoside-associated nephrotoxicity. Women were also less likely to develop nephrotoxicity. Age 50 years and above, high initial aminoglycoside trough concentration, long duration of therapy, and concurrent therapy with piperacillin, clindamycin, or vancomycin increased the risk.

Monitoring multiple-daily dosing regimens

Peak serum concentrations of gentamicin and tobramycin over 5–7 μg/ml and of amikacin over 20–28 μg/ml are associated with improved survival in patients with septicemia and pneumonia caused by Gram-negative bacteria (192,193). On the other hand, excessive peak concentrations (over 10–12 μg/ml) and trough concentrations (over 2 μg/ml) of gentamicin and tobramycin increase the risk of ototoxicity and nephrotoxicity (194). Dosage requirements to obtain aminoglycoside concentrations in the target range can differ considerably, even in patients with normal renal function (195). Owing to the great individual variability in pharmacokinetics, dosage adjustments with the commonly used nomograms often result in suboptimal or potentially toxic aminoglycoside concentrations (196). An individualized treatment based on serum concentration monitoring is therefore necessary to achieve maximum bactericidal efficacy without a concomitant high risk of adverse reactions. Measurements of peak and trough serum concentrations should be carried out during the first 24–48 hours in all patients and repeated after 3–5 days to detect any tendency to abnormal drug accumulation. However, one must realize that close monitoring alone cannot completely eliminate the danger of ototoxicity and nephrotoxicity, since aminoglycoside drug concentrations progressively increase in renal tissue and in the inner ear with repeated administration, even if optimum serum concentrations are maintained.

The relation between serum concentration of aminoglycosides and the two clinically important adverse effects, ototoxicity and nephrotoxicity, has been debated for many years. Whereas some authors have found a definite relation between the frequency of adverse effects and serum concentrations, others have not (194). This controversy can be partly explained by the pharmacokinetic behavior common to all aminoglycosides, which leads to drug accumulation in deep compartments, particularly in the renal cortex. Assuming that the extent of accumulation is a factor that relates to the frequency of adverse effects, it is not surprising to find a correlation between serum concentrations and toxicity in one group of patients but not in another. The amount accumulated depends not only on the dosing schedule and the serum concentration achieved during treatment, but also on the duration of drug administration. The same concentration in the same patient can be associated with a significantly different amount of drug in the body, depending on whether it was sampled during the second or the tenth day after the beginning of treatment.

In a survey of aminoglycoside treatment in 2022 patients in Saudi Arabia, 8.8%, 18%, and 12% had trough concentrations considered toxic for amikacin, gentamicin, and tobramycin respectively, whereas there were peak serum drug concentrations in the subtherapeutic range in 53%, 50%, and 57% respectively (197). Toxic concentrations were noticed mainly in patients aged over 60 years and in patients in the intensive care unit, coronary care unit, and burn unit.

Monitoring once-daily dosing regimens

In general, both peak and trough concentrations are determined during monitoring of multiple-daily dosing regimens, and doses are subsequently adjusted to achieve the target concentrations. However, peak and trough concentrations do not necessarily offer the most valuable information for dosage adjustments during once-daily dosing. The indication and frequency of monitoring and the timing of serum concentrations within the interval, along with their target ranges, have yet to be established. Different targets have been proposed and used clinically (198–200), including mid-dosage interval plasma concentration monitoring as an estimate of the AUC (201).

In one prospective study 8-hour concentrations have been considered for monitoring as an alternative to the measurement of peaks and troughs (202). In 51 adult patients given an average dose of 400 mg once a day, doses were adjusted during therapy if 8-hour concentrations were not within the target range of 1.5–6.0 μg/ml. Concentrations above or below this target range

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correlated significantly with nephrotoxicity, 24-hour trough concentrations, and AUCs. Determination of 8-hour concentrations was therefore useful for identifying patients with either low AUCs or an increased risk of nephrotoxicity. In other studies, aminoglycoside serum concentrations were determined in the second half of the dosing interval (198,200,203–205). However, trough concentrations do not allow for extrapolations of concentrations achieved in the period after infusion. Thus, patients with very low peak concentrations due to unusually high volumes of distribution cannot be identified. Similarly, very rapid elimination, as frequently happens in patients with burns or children, may not be noticed.

Depending on the goals of drug monitoring, peak 8-, 12- or 24-hour concentrations might be more important (151). Correlations of efficacy with high peak concentrations, high ratios of peak to MIC, and high AUCs suggest that drug concentrations should be determined during the first part of the dosing interval. In order to minimize toxicity, drug accumulation should be avoided. Therefore early detection of increased trough concentrations is of importance. It has been strongly suggested that the threshold values for troughs during once-daily dosing should be lowered, compared with multiple-daily dosing (203,206). To reduce the cost of aminoglycoside therapy, the indications for and frequency of monitoring serum concentrations should be minimal. Instead, serum creatinine concentrations might be used to monitor renal function. The strategy selected for monitoring aminoglycoside therapy must take a number of factors into account, including the type and severity of infection, the duration of therapy, or the presence of factors associated with increased risk of toxicity. In addition, local factors should be considered for the timing of blood samples, including the sensitivity of the drug assay available (207) and the time required for processing the specimens, in order to modify the subsequent dose, if necessary.

Major considerations in determining the appropriate dose of an aminoglycoside are its volume of distribution and rate of clearance. Concern has been raised regarding the use of the Cockcroft–Gault equation with either actual or ideal body weight, resulting in systematic errors, especially in malnourished patients (208). However, even extended-interval dosing should not obviate the need for monitoring drug concentrations. Even in patients with normal renal function in whom treatment is necessary for over 3 days, mid-interval or trough drug concentrations should be obtained once or twice a week to optimize the dosing regimen (166,209).

Economics of serum concentration monitoring

The economic impact of aminoglycoside toxicity and its prevention through therapeutic drug monitoring have been investigated in a cost-effectiveness study. It was estimated that to offset the cost of providing high-level drug monitoring, that is serum drug concentration monitoring with assessment and consultation by trained personnel using computerized resources to determine individualized pharmacokinetic parameters, for the purpose of achieving an optimum dosage regimen, by cost saving due to reducing nephropathy, the service should reduce the risk of nephrotoxicity by 6.6%. Therefore, high-level therapeutic drug monitoring is only cost-justified in populations in which high rates of nephrotoxicity would be expected. Risk factors for a high rate of nephrotoxicity include age, duration of therapy, high drug concentrations, the presence of ascites or liver disease, and the concomitant use of nephrotoxic drugs (210). The economic significance of aminoglycoside peak concentrations has been assessed in 61 febrile neutropenic patients with hematological malignancies. Since the clinical outcome and average infection-related costs depended significantly on peak aminoglycoside concentration, it was concluded that successful pharmacokinetic intervention may save money (211).

A pharmacy-based active therapeutic drug monitoring service has been examined in a prospective study (63). In the patients that were not monitored, the gentamicin dosage regimen was determined by the physician; in the patients that were monitored, the regimen was calculated using a population model and measured serum gentamicin concentrations. This resulted in significantly different mean dosage intervals: 19 hours in the monitored patients and 14 hours in the others. Active monitoring resulted in higher peak concentrations of aminoglycosides, lower trough concentrations, a reduction in the length of hospitalization, a reduced duration of aminoglycoside therapy, reduced nephrotoxicity, and a trend toward reduced mortality that was significant for patients with an infection on admission. Costs were lower with active monitoring. Although all patients treated with an aminoglycoside profited from active monitoring, it was most beneficial in patients who were admitted to the hospital with a suspected or proven Gram negative infection.

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Aminophenazone

General Information

Aminophenazone (amidopyrine) is the most toxic and most dangerous anti-inflammatory analgesic. Blood dyscrasias have been documented beyond any doubt, perhaps due to a hypersensitivity mechanism. The Committee on the Safety of Drugs of the Japanese Pharmaceutical Affairs Bureau has ordered its withdrawal because of its serious adverse effects (SEDA-12, 82) and it has been withdrawn in most developed countries. However, aminophenazone is still used in some developing countries (1).

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Hematologic

Aminophenazone causes severe bone marrow depression, usually with a fulminant course and a high mortality (SED-9, 146) (2,3). Specific antibodies and leukoagglutinins are sometimes found (4). Agranulocytosis is caused by arrest of maturation at the metamyelocyte stage (5).

Fatal thrombocytopenia has been reported in a breastfeeding infant after the administration of aminophenazone suppositories (6).

Gastrointestinal

Gastrotoxicity with aminophenazone is less common than with other analgesic/anti-inflammatory drugs, probably because of its weaker anti-inflammatory effect.

Liver

Aminophenazone is not hepatotoxic, but liver damage can occur in the course of a general hypersensitivity reaction (7).

Urinary tract

Albuminuria, hematuria, and acute renal insufficiency have been observed, and aminophenazone causes direct renal damage even at therapeutic doses. It can also contribute to analgesic nephropathy (SED-8, 211) (8,9).

Skin

Toxic epidermal necrolysis, exfoliative dermatitis, and Stevens–Johnson syndrome have been described (SED-8, 210) (10–13).

Immunologic

A range of allergic skin reactions, acute anaphylactic shock, acute bronchospasm (in predisposed patients), and cross-sensitivity to aspirin have been reported (14).

Long-Term Effects

Tumorigenicity

Aminophenazone and its derivatives may be metabolized to carcinogenic nitrosamines. The clinical importance of this is not clear (SEDA-2, 389) (15).

Drug Administration

Drug overdose

In overdose, aminophenazone mainly affects the central nervous system, causing coma and convulsions, and the liver (16). Fatal intoxication has occurred in infants (17).

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Aminorex

See also Anorectic drugs

General Information

Aminorex is an amfetamine analogue that was used as an anorectic agent, but was withdrawn from the market over 20 years ago because of its association with pulmonary hypertension, which sometimes proved fatal. Its adverse effects have been attributed predominantly to the release of noradrenaline and other catecholamines.

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Respiratory

Aminorex can cause primary pulmonary hypertension, which can be fatal (1,2). The fulminant character and rapid development of the disease (characterized by dyspnea, dysrhythmias, peripheral edema, dizziness, cyanosis, chest pain, and syncope, in the absence of usual causes of pulmonary vascular disease) suggested the possibility of its being drug-induced. Long-term follow-up of aminorex-induced primary pulmonary hypertension showed that the syndrome has a chronic course, with long-term survival possible (3). Two cases of supposedly delayed reactions to aminorex have been described (4). Both concerned pulmonary hypertension, one in a subject who had taken aminorex 6 years before. In the other there was a reaction of limited duration 8 years after aminorex treatment.

In 16 patients polymorphic hydroxylation of debrisoquine was not related to the risk of aminorex-induced pulmonary hypertension (5).

Despite the withdrawal of aminorex, work to identify the mechanism of the pathogenic effect has continued, in view of the risk that other agents might behave similarly. In smooth muscle cells taken from the small resistance pulmonary arteries of the rat lung aminorex inhibited potassium current and in isolated, perfused rat lung, it caused a dose-related increase in perfusion pressure (6). However, long-term administration of aminorex fumarate to rats failed to cause hypertensive pulmonary vascular disease (7), although in dogs there was an increase in pulmonary pressure (8).

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Aminosalicylates

General Information

The aminosalicylates that are currently available are:

- mesalazine (rINN; 5-aminosalicylic acid mesalamine);
- sulfasalazine (rINN), a compound of mesalazine and sulfapyridine, the two compounds being linked by a diazo bond that is hydrolysed by intestinal bacteria; mesalazine is therapeutically effective in inflammatory bowel disease and sulfapyridine causes adverse effects;
- olsalazine (rINN), a compound of two molecules of mesalazine, linked by a diazo bond that is hydrolysed by intestinal bacteria;
- balsalazide (rINN), a prodrug of mesalazine linked to 4-amino-benzolylanine by an azo bond that is hydrolysed by intestinal bacteria.

Mesalazine can be administered using carriers that deliver it to the large bowel or on its own in the form of a modified-release formulation (1).

The pharmacological properties of aminosalicylates and their potential value in the treatment of inflammatory bowel disease have been reviewed (2). Aminosalicylates are the drugs of first choice in the acute treatment of ulcerative colitis and in maintaining remission. Their value in Crohn's disease is more modest. The variability in clinical results is at least partly caused by the different formulations and dosages of the drug used, as well as the high variation in drug disposition and topical availability of the active drug. The popularity of aminosalicylates is most likely due to the low incidence of adverse effects and good overall safety record.

Observational studies

Mesalazine caused apoptosis and reduced cell proliferation in the colorectal mucosa in 17 patients with sporadic polyps of the large bowel (3). This may be clinically relevant in lowering the rate of polyp recurrence after polypectomy, thereby contributing to chemoprevention of sporadic colonic carcinoma.

Comparative studies

In a randomized, double-blind study, balsalazide 3 g/day and mesalazine 1.2 g/day effectively maintained remission in 99 patients with ulcerative colitis (4). Adverse events were equally common in the two groups, the most common being headache, abdominal pain and diarrhea, respiratory infections, body pains, and flu-like symptoms.

In a 12-week trial in 168 patients with mild to moderate ulcerative colitis, olsalazine 3 g/day was as effective as mesalazine 3 g/day in inducing a remission (5). There were more adverse effects in patients taking olsalazine (41 of 88) than mesalazine (29 of 80). Most of the adverse effects related to bowel disturbances: diarrhea, vomiting, abdominal discomfort, heartburn, flatulence, and nausea. Diarrhea was more common in patients taking olsalazine. One patient taking mesalazine developed a lupus-like syndrome.

The effects of mesalazine and olsalazine in delivering active mesalazine to the colon and in producing a systemic load as a basis for potential long-term toxicity have been compared in a single-blind, randomized, crossover study in 15 patients with ulcerative colitis (6). The patients took either olsalazine 500 mg bd or mesalazine 500 mg tds, with a crossover after 7 days. Plasma and urine concentrations of mesalazine and acetylmesalazine were assayed. Olsalazine caused loose stools in one patient and diarrhea in two, whereas mesalazine caused diarrhea in one. The systemic load of active mesalazine was significantly higher after mesalazine than olsalazine, based on both therapeutically recommended doses and when calculated on an equimolar basis. Some patients treated with mesalazine had very high plasma and urinary concentrations of mesalazine and acetylmesalazine, which may have long-term safety implications.

The relapse-preventing effects and safety profiles of balsalazide 1.5 g bd, balsalazide 3 g bd, and mesalazine 0.5 g tds have been studied in a multicenter, randomized, double-blind trial in 133 patients with ulcerative colitis in remission (7). High-dose balsalazide was significantly more effective in maintaining remission compared with the other two treatments. All three treatments were well tolerated.

In a double-blind, multicenter study in 182 patients with active Crohn's disease affecting the ileum and/or ascending colon, a modified-release formulation of budesonide 9 mg/day was more effective in inducing remission than mesalazine 2 g bd (8). Adverse events were similar in the two groups. Mild abnormalities of adrenal function tests were slightly more common with budesonide, but the clinical significance of these was unclear.

In a randomized, multicenter study in 94 patients, mesalazine 4 g/day for 12 weeks in a microgranular formulation was as effective as a standard dose of a glucocorticoid (6-methylpredisolone 40 mg/day) in mild to moderate Crohn's ileitis (Crohn's Disease Activity Index 180-350) (9). The group treated with methylpredisolone had a higher number of adverse events than those given mesalazine. The only adverse effect related to mesalazine was acute pancreatitis, which resolved on withdrawal.

Short-chain fatty acids, especially butyrate, are a preferred source of energy for the colonic epithelium. There is evidence to suggest that butyrate enemas are effective in the treatment of ulcerative colitis. The seeds of *Plantago ovata* (a source of fermentable dietary fiber) increase fecal concentrations of butyrate and acetate. In a randomized, open, parallel-group, multicenter study in 105 patients with ulcerative colitis, *P. ovata* seeds 10 mg bd were as effective as mesalazine 500 mg tds in maintaining remission over 12 months (10). Adverse effects were similar in the two groups, and included constipation, flatulence, nausea, and diarrhea.

Placebo-controlled studies

In an 18-month, double-blind, randomized, placebo-controlled trial in 318 patients, mesalazine 4 g/day did not significantly affect the postoperative course of Crohn's disease compared with placebo (11). There was some relapse-preventing effect in patients with isolated small bowel disease. The overall incidence of adverse effects was similar with mesalazine and placebo. Of the serious adverse effects reported, only one case of alopecia

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was considered to be possibly or probably related to mesalazine.

In a double-blind, placebo-controlled, multicenter trial in 65 patients with ulcerative proctitis in clinical and endoscopic remission, mesalazine in suppositories 500 mg/day as sole treatment was effective, well tolerated, and safe for maintenance of remission over 24 months (12). The incidence of adverse effects was similar with mesalazine and placebo. The most frequent adverse effects with mesalazine were rectal disorders, abdominal pain, and headache.

Daily mesalazine 4 g orally plus placebo enema and mesalazine 2 g orally plus mesalazine 2 g rectally as a liquid enema have been compared in the treatment of mild to moderate ulcerative colitis in a multicenter, randomized, double-blind trial in 130 patients (7). The two treatments were equally effective in inducing disease remission. Both were well tolerated, and the frequencies of adverse effects were similar in the two groups.

In a randomized, double-blind, placebo-controlled trial in 328 patients with quiescent Crohn's disease, olsalazine 2 g/day given for 52 weeks was not superior to placebo in maintaining remission (13). Gastrointestinal adverse effects were significantly more frequent in the olsalazine group; diarrhea was the most commonly reported adverse effect.

General adverse effects

Adverse reactions with sulfasalazine are frequent, and the withdrawal rate for this reason can be as high as 30% (SEDA-16, 426). Common adverse effects related to sulfapyridine include headache, nausea, anorexia, and malaise. Other allergic or toxic adverse effects include fever, rash, hemolytic anemia, hepatitis, pancreatitis, paradoxical worsening of colitis, and reversible sperm abnormalities (14). Sulfasalazine appears to cause frequent severe adverse effects in adult-onset Still's disease and systemic-onset juvenile rheumatoid arthritis, as suggested by a long-term, follow-up study of 41 patients with adult-onset Still's disease and 109 consecutive patients with rheumatoid arthritis (15). Adverse effects included abdominal pain, nausea and vomiting, urticaria, facial flushing, high fever, hypotension, severe myelosuppression, and fulminant hepatitis, which resulted in death in one patient.

Skin reactions are common with sulfasalazine, and general sensitization can occur, as with other sulfa derivatives. The clinical features, besides skin rash, include granulomatous liver disease, positive lupus phenomenon, hypocomplementemia, and fever (16). More serious skin conditions can also occur. In the case of mild reactions, patients can often be desensitized by giving small (and then progressively increasing) doses. Various complex autoimmune syndromes can occur (SEDA-17, 423); in long-term studies of the use of sulfasalazine in rheumatoid arthritis, 12–20% of evaluable patients developed antinuclear antibodies during treatment (SEDA-16, 426) (SEDA-18, 375). Tumor-inducing effects have not been described.

The role of mesalazine in the acute and long-term treatment of ulcerative colitis has been reviewed (17). Mesalazine is equivalent to or better than sulfasalazine and better than placebo in inducing remission of acute disease, and comparable to sulfasalazine and better than placebo for long-term maintenance of remission. Adverse effects are uncommon, but include idiosyncratic worsening of colitis and renal toxicity. Mesalazine is safe during pregnancy and breastfeeding. In maintenance therapy, it may reduce the risk of developing colorectal carcinoma.

Crossover studies have shown that mesalazine has about a 10-fold lower potential than sulfasalazine for inducing allergic reactions or causing intolerance. Adverse effects with all aminosalicylates include (generally more frequent with sulfasalazine) headache, nausea, abdominal pain, dyspepsia, fatigue, rash, fever, rarely exacerbation of the disease, pancreatitis, pericarditis, pneumonitis, liver disease, nephritis, and bone marrow depression. Watery diarrhea is an adverse effect unique to olsalazine, while anorexia, folate malabsorption, hemolysis, neutropenia, agranulocytosis, male infertility, and neuropathy are unique to sulfasalazine.

The adverse effects of sulfasalazine 2–3 g/day and mesalazine 1.2–2.4 g/day in 685 patients have been reviewed for a median follow-up period of 7 and 5 years respectively (18). Adverse effects were observed overall in 20% of patients taking sulfasalazine and 6.5% of those taking mesalazine. The commonest adverse effects due to sulfasalazine (reported by more than 10% of patients) were dyspepsia, rash, and headache, while the commonest due to mesalazine were rash, diarrhea, headache, fever, abdominal pain, impaired renal function, dyspepsia, and edema. Fertility was affected in all 42 male patients taking sulfasalazine who were assessed, but improved when they changed to mesalazine.

A pharmacovigilance report from France reported 128 adverse events during 15.6 million days of therapy with Pentasa in 1993 and 1994. Adverse events with a high likelihood of causality included diarrhea, pancreatitis, liver abnormalities, blood dyscrasias, renal insufficiency, and cardiac disorders, including myocarditis. Most of these rare adverse events did not appear to be dose-related in the therapeutic range (SEDA-21, 364) A meta-analysis of studies of the effectiveness of mesalazine in maintaining remission in Crohn's disease showed an adverse effect frequency of 14% in patients taking mesalazine and 15% in patients taking placebo. The most frequent adverse effect attributable to mesalazine was diarrhea (SEDA-22, 394).

The dose response relation of oral mesalazine in inflammatory bowel disease has been briefly reviewed (19). Higher doses (3 g/day) are more effective in inducing and maintaining remission than lower doses (1.5 g/day). None of the known adverse effects of mesalazine is clearly dose-related in the therapeutic range of doses.

An analysis of suspected serious adverse reactions reported to the Committee on Safety of Medicines in the UK in 1991–98 has failed to show a safety advantage for mesalazine over sulfasalazine in the treatment of inflammatory bowel disease (20). Pancreatitis and interstitial nephritis were significantly more common with mesalazine.

The adverse effects of olsalazine would be expected to be those of mesalazine, and this is largely the case. However, diarrhea has been sufficiently common to suggest that it may be a particular problem with olsalazine,

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with an incidence of some 13%; it is probably a small-intestinal secretory diarrhea (SEDA-17, 425) (21). Similarly, cholestatic hepatitis, confirmed on rechallenge, did not recur with mesalazine in similar doses (SEDA-16, 428). In one case there was a marked hypersensitivity reaction in a man previously intolerant of sulfasalazine, but the circumstances suggested a reaction to mesalazine rather than to the double molecule (SEDA-18, 376).

Organs and Systems

Cardiovascular

A single Scandinavian case report has reliably attributed a fatal myocarditis to mesalazine (22).

The time between the start of treatment and the onset of mesalazine-associated pericarditis usually ranges from a few days to 7 months. However, the delay can be longer.

- A 53-year-old man with Crohn's disease, who had taken mesalazine 500 mg/day for the past 8 years, developed pericarditis with an effusion (23). The pericarditis resolved rapidly on drug withdrawal. Investigations excluded other common causes of pericarditis.
- Pericarditis in a 16-year-old boy with inflammatory bowel disease taking mesalazine resolved on withdrawal, but recurred after starting sulfasalazine 500 mg tds (24).
- Acute pericarditis has been reported in a 17-year-old man with severe ulcerative colitis who had taken mesalazine 1.5 g/day for 2 weeks (25). The pericarditis resolved on withdrawal and recurred on rechallenge with a low dose (62.5 mg) of mesalazine 3 weeks later.
- Constrictive pericarditis has been reported in a 37-year-old woman with chronic ulcerative colitis who had taken mesalazine 2 g/day for 2 weeks (26). She recovered after radical pericardiectomy.

Bradycardia has been attributed to mesalazine.

- Severe symptomatic bradycardia has been reported in a 29-year-old woman with ulcerative colitis who was taking mesalazine (27). The bradycardia resolved on withdrawal. Six weeks later mesalazine was restarted for a relapse of her colitis, and symptomatic bradycardia recurred. Again this resolved on withdrawal.

Chest pain has been attributed to mesalazine (28).

- A 37-year-old man with ulcerative colitis developed severe retrosternal chest pain with non-specific ST–T wave changes in the inferolateral leads of the electrocardiogram after taking mesalazine 800 mg qds for 1 week. Cardiac enzymes, coronary angiography, left ventricular function, and pulmonary angiography were normal. Mesalazine was omitted and glucocorticoids were tapered. He recovered completely and his electrocardiogram normalized. Two weeks later he was given mesalazine 800 mg qds and again developed retrosternal chest pain with T wave inversion in the lateral leads. Mesalazine was withdrawn and his symptoms resolved within 24 hours. His chest pain did not recur over an 18 month follow-up period while not taking mesalazine.

Raynaud's phenomenon has been attributed to sulfasalazine (29,30).

Respiratory

"Sulfasalazine lung," fibrosing alveolitis, and eosinophilic pleurisy are variants on a well-recognized although unusual lung complication. Most commonly it presents with cough, fever, eosinophilia, dyspnea, and pulmonary infiltrates (SEDA-15, 309) (31). Sputum production, a history of allergy, rash, chest pain, and weight loss are inconsistent findings. The disease usually develops 1–9 months after the start of treatment and the fibrosing alveolitis can be fatal (32). The lung pathology is variable, the commonest change being an eosinophilic pneumonia with peripheral eosinophilia and interstitial inflammation with or without fibrosis. In case reports, the majority of patients with suspected sulfasalazine-induced lung disease improved within weeks of drug withdrawal (33). Whether the salicylate or the sulfa moiety is responsible is unclear; both can cause pulmonary eosinophilia. Differentiation from lung disease simply associated with ulcerative colitis can be difficult, particularly because the drug-induced form sometimes causes an interstitial pneumonitis without evidence of an allergic reaction (34) and rechallenge can be dangerous (SEDA-16, 427).

Peripheral lung infiltrates with blood eosinophilia are rare effects of sulfasalazine. Sulfasalazine-induced hypersensitivity lung disease with simultaneous *Legionella pneumophila* infection has been reported for the first time (35).

- A 32-year-old woman with ulcerative colitis developed bilateral pulmonary infiltrates with peripheral eosinophilia 2 weeks after starting to take sulfasalazine and mesalazine enemas, and both drugs were withdrawn. Based on a high antibody titer, legionnaires' disease was diagnosed and empirical therapy with a macrolide antibiotic was started; she improved within a few days. Three months later sulfasalazine was restarted, followed 3 days later by acute pulmonary symptoms (bilateral confluent opacities) and blood eosinophilia. The abnormalities resolved completely after drug withdrawal and prophylactic antibiotic therapy.

Various adverse respiratory effects of mesalazine have been reported.

- A patient who took mesalazine for 2 years had a symptomatic bilateral lung reaction, with interstitial infiltrates and impaired function; the condition developed insidiously but recovered within 8 months after drug withdrawal (36). The condition was not necessarily identical to the lung reaction seen with sulfasalazine.
- Pleural effusion with pulmonary infiltration has been reported in a 72-year-old woman with ulcerative colitis taking mesalazine 800 mg tds (37). The lung pathology resolved after drug withdrawal.
- An eosinophilic pleural effusion has been reported in a 35-year-old male non-smoker who had taken mesalazine 2.4 g/day orally for 2 weeks for a diarrheal illness (38). He recovered after mesalazine was withdrawn.
- A 35-year-old woman with ulcerative colitis who had taken mesalazine 1.5 g/day for about 40 days developed a low-grade fever with bilateral eosinophilic pulmonary infiltrates (confirmed by transbronchial lung biopsy) (39). Spontaneous clinical and radiological resolution

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occurred on withdrawal. A drug lymphocyte stimulation test was positive for mesalazine.

- A 29-year-old woman with ulcerative colitis taking mesalazine 1 g tds developed respiratory distress (40). Her respiratory symptoms (chest pain and respiratory distress, especially exertional dyspnea) occurred 48 hours after she started to take mesalazine and disappeared immediately on withdrawal. Similar symptoms recurred on rechallenge 3 weeks later in a lower dose of 500 mg bd. Chest X-ray and white cell count a day later were normal.
- Bronchiolitis obliterans has been reported in an 18-year-old female non-smoker with ulcerative colitis, 3 months after reintroduction of mesalazine 1.6 g/day orally (41). She recovered after mesalazine withdrawal and treatment with glucocorticoids.
- Interstitial pulmonary disease (lymphocytic alveolitis and mild interstitial pulmonary fibrosis) has been reported in a 70-year-old woman with ulcerative colitis who had taken mesalazine 2.4 g/day for 3 months (42). Halving the dose of mesalazine to 1.2 g/day led to resolution of her lung disorder without relapse of ulcerative colitis.

A limited form of Wegener's granulomatosis with a bronchiolitis obliterans organizing pneumonia-like variant has been reported in a 19-year-old man, a non-smoker, with ulcerative colitis, 6 months after the introduction of mesalazine 2.25 g tds orally (43). He recovered after mesalazine withdrawal and treatment with glucocorticoids.

Nervous system

An unusual but not unique case of transverse myelitis was reported in 1991, and other published case reports suggest links with chorea and ataxia (SEDA-16, 427).

Individual cases of other adverse effects on the nervous system have appeared.

- Vivid dreams and daytime hallucinations occurred in a woman taking sulfasalazine (44).
- Aseptic meningitis occurred in a patient with pre-existing Sjögren's syndrome; and the drug link was confirmed by positive rechallenge (45).
- In a slow acetylator, an axonal sensorimotor neuropathy could have been due to sulfasalazine (SEDA-17, 424).

Seizures with acute encephalopathy have been reported in a woman taking sulfasalazine for polyarthritis (46).

Hematologic

In a randomized, double-blind, placebo-controlled trial, 70 patients with established ankylosing spondylitis and a mean disease duration of 17 years were investigated in two centers for 26 weeks, comparing sulfasalazine 3 g/day with placebo. In the treatment group there were significantly more cases of anemia, leukopenia, eosinophilia, and thrombocytopenia (47).

Sulfasalazine causes Heinz body anemia in patients with abnormal hemoglobin and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (48).

- A 79-year-old woman who had been taking sulfasalazine for ulcerative colitis for 5 years developed a positive Coombs' test and a hemoglobin of 8.2 g/dl. Agglutination occurred when a mixture of sulfasalazine and the patient's serum was added to normal erythrocytes treated with the endopeptidase ficin, but there was no reactivity when control serum was used or when sulfasalazine was omitted. Preincubation of sulfasalazine with normal erythrocytes gave negative results on addition of the patient's serum, excluding the possibility of a penicillin-like reaction. The patient had normal glucose-6-phosphate dehydrogenase activity and there were no Heinz bodies in a blood smear.

However, about 1.7% of patients with ulcerative colitis develop immune hemolytic anemia, even in the absence of sulfasalazine, so cause and effect is not always possible to determine.

Agranulocytosis is very unusual but well described with sulfasalazine, and can occur suddenly and very early in treatment (49). The risk in sulfasalazine users with arthritic disorders (6/1000 users) was about 10 times higher than that in users with inflammatory bowel disease (0.6/1000 users) (SEDA-20, 320). Agranulocytosis is supposedly more common in slow acetylators (50). However, in one study the risk of agranulocytosis was not increased in slow acetylators (50). Leukopenia occurred in a patient taking mesalazine after a similar reaction to sulfasalazine (SEDA-17, 425).

Sulfasalazine reduces folic acid absorption, but rarely to a clinically significant extent, although megaloblastic anemia has rarely been documented (51,52).

Methemoglobinemia can occur in slow acetylators of sulfapyridine (53).

Thrombocytopenia has occasionally been attributed to mesalazine (54–56) and olsalazine (57).

- A possible association between mesalazine and pancytopenia has been reported in a 23-year-old man with Crohn's disease (58). The pancytopenia resolved after withdrawal.

Gastrointestinal

Nausea and vomiting, taste disturbances (SEDA-17, 424), anorexia, stomatitis, flatulence (59), and abdominal discomfort can occur in patients taking sulfasalazine and mesalazine. They are particularly common in slow acetylators, but symptoms remit with dosage reduction. Diarrhea is more common with olsalazine than with sulfasalazine.

Five cases of severe persistent diarrhea following the use of mesalazine in doses of 2.4–4.8 g/day have been reported (60). The diarrhea was made worse by increasing doses of the drug. Symptoms resolved on withdrawal or dosage reduction.

- Severe diarrhea that mimicked the effects expected with the use of non-steroidal anti-inflammatory drugs, associated with changes in fecal eicosanoid content, has been reported in a 57-year-old man with non-granulomatous enterocolitis who took mesalazine 4 g/day (61). The diarrhea resolved dramatically on withdrawal.

Exacerbation of existing colitis is rare but well recognized with sulfasalazine and it can also cause colitis de novo; pseudomembranous colitis with *Clostridium difficile* was reported in 1991, as was fatal neutropenic colitis with no

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evidence of *C. difficile* infection (SEDA-17, 424). Reports of exacerbation of colitic symptoms caused by intolerance of mesalazine are infrequent. Diarrhea, rectal bleeding, and weight loss have been described in three patients (aged 13, 14, and 17 years) with ulcerative colitis who were taking mesalazine 2–4 g/day (62). Their symptoms resolved dramatically after mesalazine withdrawal.

The finding of *Escherichia coli* on rectal swabs, with a range of resistance extending beyond the sulfa drugs, is difficult to evaluate. The clinical relevance is doubtful.

Liver

Exceptionally, fulminant hepatic failure with massive necrosis has been seen in patients taking sulfasalazine (63). Two fatal cases were reported in 1992 (SEDA-17, 424).

Cases of hepatitis have been observed in patients taking mesalazine; one such case was observed in a series of 103 patients taking mesalazine, and two further cases in another series of 44 patients (SEDA-20, 320).

- Severe hepatic injury with biopsy-proven cholestasis was reported in a man who had taken mesalazine in a dose of 4 g/day for 4 months (SEDA-22, 394) (64).

Mesalazine-induced chronic hepatitis and liver fibrosis, with raised serum IgG concentrations and autoantibodies, has been reported (65).

- A 57-year-old man with an unspecified abdominal complaint (later confirmed not to be inflammatory bowel disease), who was also taking simvastatin, developed abnormal liver function tests and antinuclear and anti-smooth muscle antibodies 13 months after starting to take mesalazine. Simvastatin hepatotoxicity was suspected and that drug was withdrawn, but there was no improvement in liver function. Mesalazine was withdrawn 21 months after the start of therapy, with rapid normalization of liver enzymes and serum IgG concentrations and disappearance of the autoantibodies.

Pancreas

Pancreatitis has several times been ascribed to sulfasalazine and may well be the expression of an allergic reaction; cases with positive rechallenge are on record.

Pancreatitis has been noted with mesalazine often enough to be taken seriously (66); it usually occurs within a short time of starting treatment, has occurred in children as well as adults, and has sometimes been confirmed by rechallenge (SEDA-18, 375).

- A 29-year-old man with Crohn's disease who had taken mesalazine 2 g/day for 3 days developed acute pancreatitis (67). Clinical and biochemical improvement occurred on drug withdrawal. Acute pancreatitis recurred on rechallenge.
- A 23-year-old man with ulcerative colitis developed acute pancreatitis after taking mesalazine 1.5 g/day for 4 days (68). Resolution occurred on withdrawal but rechallenge was not performed.
- A 10-year-old boy with ulcerative colitis developed acute pancreatitis 1 day after the dose of mesalazine was increased from 400 mg bd (which he has taken for 5 months without any adverse effect) to 800 mg bd for a mild relapse (69). He became asymptomatic 3 days after drug withdrawal.
- A 34-year-old woman with colitis developed pancreatitis 1 week after starting mesalazine 1 g tds; she recovered after drug withdrawal (70). She was admitted 15 months later with a relapse of colitis and was given oral prednisolone 50 mg/day and mesalazine enemas (2 g bd). Although the colitis regressed, 10 days later she again developed acute pancreatitis. She recovered 3 days after prednisolone and mesalazine enemas were withdrawn. Symptoms of pancreatitis did not recur when prednisolone was restarted.
- A patient developed pancreatitis after taking mesalazine 2 g bd; the symptoms resolved when the drug was withdrawn, but recurred when azathioprine was given (71).

Two unusual cases of delayed-onset pancreatitis occurring 3 months and 2 years after starting mesalazine have been described (SEDA-22, 394) (72).

Urinary tract

Two patients with long-standing ulcerative colitis developed what seemed to be a drug-induced chronic interstitial nephritis after taking sulfasalazine for several years, with no other detectable cause (73); the same problem has arisen with mesalazine. However, in a long-term study (mean treatment time 10 years) in 36 patients taking sulfasalazine for ulcerative colitis, there was no nephrotoxicity (74).

Proximal renal tubular proteinuria is a possible complication in patients treated with high doses of mesalazine, and it is clearly important to monitor renal function in these patients (SEDA-22, 394) (75). Two studies in 21 (76) and 95 (77) patients with ulcerative colitis and Crohn's disease have shown that proteinuria of tubular marker proteins is common and is related to disease activity rather than to treatment with mesalazine. Thus, tubular proteins are not useful predictors of an adverse renal response to the drug. Nephrotic syndrome with minimal change nephropathy has been described with sulfasalazine and mesalazine (SEDA-16, 427).

Interstitial nephritis has been well documented in patients taking mesalazine (SEDA-17, 425) (8,78–81).

- Interstitial nephritis occurred in a 29-year-woman with ulcerative colitis and a 48-year-old woman with Crohn's disease who were taking mesalazine (82).

There have been three other reports of interstitial nephritis associated with mesalazine in patients with inflammatory bowel disease, two with ulcerative colitis and one with Crohn's disease (83–85). One patient continued to be dialysis-dependent and in two patients withdrawal of the drug and treatment with glucocorticoids resulted in partial improvement in renal function.

- Acute tubular necrosis has been reported in a 49-year-old man with Crohn's disease who had taken mesalazine 4 g/day for 1 month (86). Renal function normalized rapidly after withdrawal of mesalazine.

In addition, there has been a report of a possible association between mesalazine and nephrotic syndrome due to

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minimal change nephropathy, which resolved after withdrawal (87).

Serious renal impairment occurs in under 1 in 500 recipients of enteric-coated mesalazine (88), and early recognition and withdrawal (after up to 10 months of administration) has been reported to have resulted in complete recovery of renal function in five out of six patients. Monitoring renal function in patients taking mesalazine formulations is recommended. Oral enteric-coated mesalazine should not be used in patients with renal sensitivity to sulfasalazine, a history of hypersensitivity to salicylates, severe renal impairment, and children under 2 years old.

- A 23-year-old student with ulcerative colitis who took mesalazine 1.5 g/day for 15 days developed asymptomatic renal insufficiency (89). Renal function rapidly normalized after drug withdrawal.

Two other cases of interstitial nephritis have been reported in children with Crohn's disease who were taking mesalazine (90).

Nephrotoxicity has been described during treatment with olsalazine (SEDA-21, 364). To assess the effects of 9 months of treatment with oral mesalazine 1.2 g/day and olsalazine 1 g/day on renal function, a randomized trial has been performed in 40 patients with ulcerative colitis in complete remission (91). Neither drug had a significant effect on glomerular filtration rate. Adverse effects (all mild to moderate) were more common in the mesalazine group; they included abdominal pain and distension, dyspepsia, nausea, and diarrhea.

Skin

Simple rashes are not uncommon in patients taking sulfasalazine, including maculopapular rash, pruritus, urticaria, angioedema, eczematous dermatitis, photosensitivity, skin discoloration, and oral ulceration. Raynaud's phenomenon and toxic epidermal necrolysis associated with erythroid hypoplasia and agranulocytosis have occurred; in one case of toxic epidermal necrolysis there was marked immunosuppression (SEDA-18, 375).

- Acute generalized exanthematous pustulosis occurred in a 28-year-old man with ulcerative colitis taking sulfasalazine (92). A patch test was negative, but the lymphocyte stimulation assay for sulfasalazine showed a stimulation index of 541% (controls were not mentioned).

A rare case of skin hyperpigmentation (apparently a phototoxic reaction) has been associated with sulfasalazine lung (93).

Rashes have not generally proved an important problem with mesalazine, but two cases of oral and cutaneous lichen planus which had developed during sulfasalazine treatment recurred when the patients later took mesalazine (SEDA-17, 425).

Hair

Hair loss is rare in patients taking sulfasalazine (SEDA-16, 427).

Sexual function

Erectile impotence has often been described in patients taking sulfasalazine, sometimes with positive rechallenge (94).

Immunologic

The causes of ANCA-positive vasculitis with high titers of antimyeloperoxidase antibodies in 30 new patients have been reviewed (95). The findings illustrate that this type of vasculitis is predominantly drug-induced. Only 12 of the 30 cases were not related to a drug. The most frequently implicated drug was hydralazine ($n = 10$); the others were propylthiouracil ($n = 3$), penicillamine ($n = 2$), allopurinol ($n = 2$), and sulfasalazine ($n = 1$).

Treatment with sulfasalazine was associated with lupus-like symptoms and systemic lupus erythematosus-related autoantibody production in 10% of patients with early rheumatoid arthritis; risk factors included a systemic lupus erythematosus-related HLA haplotype, increased serum interleukin-10 concentrations, and a speckled pattern of antinuclear antibodies (96).

Sulfasalazine-induced angioimmunoblastic lymphadenopathy has been reported in a patient with juvenile chronic arthritis (97).

A Kawasaki-like syndrome has been reported in a patient taking sulfasalazine, who later reacted in the same way to mesalazine (SEDA-16, 427).

The possibility of allergic reactions to mesalazine has been suggested, but they may be rather less of a problem than with sulfasalazine.

- Angioedema has been reported in a 23-year-old man with inflammatory bowel disease 48 hours after he was given mesalazine 4 g/day (98).

A lupus-like syndrome has been described on several occasions (SEDA-15, 400) (99).

Second-Generation Effects

Fertility

Oligospermia, with reduced motility and a high frequency of abnormal forms, and male infertility are well documented in patients taking sulfasalazine. Oral and rectal treatments have the same effects, which reverse on withdrawal. Male infertility caused by sulfasalazine can be reversed by switching to mesalazine.

Pregnancy

Pregnant colitic patients generally fare better if they continued to take aminosalicylates. Though sulfasalazine crosses the placenta, competes for albumin-binding sites with bilirubin, and can be detected in breast milk, no adverse effects on offspring have been detected.

Lactation

Even in women taking large doses, only very small amounts of mesalazine enter the breast milk; toxic effects are unlikely but allergic effects can occur (SEDA-18, 376).

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Susceptibility Factors

Genetic factors

Because sulfonamides are subject to polymorphic metabolism by *N*-acetyltransferase (NAT2), some of the adverse effects of sulfasalazine are more common in slow acetylators. Gastrointestinal adverse reactions occur more commonly in slow acetylators, and they should use lower doses.

Glucose-6-phosphate dehydrogenase deficiency can be associated with a tendency to hemolysis in patients taking sulfasalazine.

When chronic inflammatory bowel disease co-exists with acute intermittent porphyria, the bowel condition itself brings with it an increased risk of acute attacks of porphyria; sulfasalazine can trigger such an attack in this condition (SEDA-17, 425).

Drug Administration

Drug formulations

Oral enteric-coated mesalazine consists of ethylcellulose-coated microgranules from which mesalazine is released in the small and large intestines in a diffusion-dependent manner.

The use of oral enteric-coated mesalazine, which releases mesalazine in the terminal ileum and colon, has been reviewed (88,100). Dose-related improvements in clinical and endoscopic parameters have been reported with prolonged-release mesalazine 2–4 g/day in trials in patients with mild to moderately active ulcerative colitis. About 74% of patients with mild to moderate ulcerative colitis improve with enteric-coated mesalazine 2.4–4.8 g/day. There is a trend toward a better response with higher doses. Oral enteric-coated mesalazine 0.8–4.4 g/day appears to be as effective as sulfasalazine 2–4 g/day, modified-release mesalazine 1.5 g/day, and balsalazide 3 g/day in maintaining remission in ulcerative colitis.

Prolonged-release mesalazine also reduced disease activity in patients with mild to moderately active Crohn's disease. In Crohn's disease, mesalazine was more effective in preventing relapse in patients with isolated small bowel disease than in those with colonic involvement. Prolonged-release mesalazine appears to be as well tolerated as placebo, and the incidence of adverse effects does not appear to be dose related. Nausea/vomiting, diarrhea, abdominal pain, and dyspepsia are the most commonly reported. Reports of nephrotoxicity with this formulation are rare.

In a randomized, open trial in 227 patients with mild to moderate ulcerative colitis, mesalazine 4 g/day given as prolonged-release granules bd and qds was as effective as prolonged-release tablets given qds (101). All the treatments were well tolerated and the frequencies of adverse effects were similar in the treatment groups. The patients preferred twice-daily dosing.

In a 4-week, randomized trial in 103 patients with mild to moderate left-sided ulcerative colitis or proctosigmoiditis, mesalazine gel enema 2 g/day was as effective as mesalazine foam enema 2 g/day in inducing remission (102). Patients in the foam group had significantly more difficulty in retention and more abdominal bloating and discomfort during administration of the drug.

In an open, randomized trial in 266 patients with active distal ulcerative colitis, mesalazine foam enema 2 g/day was as effective as mesalazine standard liquid enema 4 g/day (103). The number of adverse effects attributable to medication was higher in the foam group than in the liquid enema group (14 versus 4). The most commonly reported adverse effect was flatulence.

Oral enteric-coated mesalazine is well tolerated in children aged 4–19 years and in adults who are intolerant of sulfasalazine. The most common adverse effects are headache, gas, nausea, diarrhea, and dyspepsia. The adverse effects can be severe enough to require withdrawal of the drug in up to 11% of patients.

Drug–Drug Interactions

Azathioprine and mercaptopurine

In a prospective, parallel-group study in 34 patients with Crohn's disease taking azathioprine or mercaptopurine, co-administration of mesalazine 4 g/day, sulfasalazine 4 g/day, or balsalazide 6.75 g/day for 8 weeks resulted in an increase in whole blood 6-thioguanine nucleotide concentrations and a high frequency of leukopenia (104). In 16 patients with quiescent Crohn's disease taking a stable dose of azathioprine plus sulfasalazine or mesalazine, mean 6-thioguanine nucleotide concentrations fell significantly after aminosalicylate withdrawal without significant changes in thiopurine methyltransferase activity (105).

Thiopurines are metabolized by thiopurine methyltransferase, whose activity is controlled by a common genetic polymorphism in the short arm of chromosome 6. Patients with low or intermediate activity who take azathioprine or 6-mercaptopurine are at risk of myelosuppression caused by excess accumulation of the active thiopurine metabolite 6-thioguanine nucleotide. Benzoic acid derivatives, such as mesalazine and its precursors, and prodrugs (sulfasalazine, olsalazine, and balsalazide) inhibit thiopurine methyltransferase activity in vitro. This action could explain the increase in whole blood concentrations of 6-thioguanine nucleotide, leading to leukopenia.

Digoxin

Sulfasalazine reduces the systemic availability of digoxin (106).

Ferrous sulfate

Ferrous sulfate interferes with the absorption of sulfasalazine, possibly by chelation (107). The significance of this phenomenon is doubtful, given that the beneficial effect of sulfasalazine depends on the release of mesalazine in the large intestine.

Warfarin

An interaction of mesalazine with warfarin has been reported (108).

- A 55-year-old woman taking warfarin 5 mg/day for deep venous thrombosis was also given mesalazine

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800 mg tds for a solitary cecal ulcer. Four weeks later she developed worsening of her venous thrombosis. Her serum warfarin concentrations were undetectable and the INR was 0.9. Mesalazine was withdrawn; her INR rose to 1.8 on the following day and was 2.1 five days later.

The mechanism of this interaction is not known.

Interference with Diagnostic Tests

Iron

Sulfasalazine interferes with coulometry of serum iron (109).

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Amiodarone

See also Antidysrhythmic drugs

General Information

Amiodarone is highly effective in treating both ventricular and supraventricular dysrhythmias (1). Its pharmacology, therapeutic uses, and adverse effects and interactions have been extensively reviewed (2–14).

General adverse effects

Amiodarone prolongs the QT interval and can therefore cause dysrhythmias; there have also been reports of conduction disturbances. Abnormalities of thyroid function tests can occur without thyroid dysfunction, typically increases in serum T4 and reverse T3 and a reduction in serum T3. However, in up to 6% of patients frank thyroid dysfunction can occur (either hypothyroidism or hyperthyroidism). Several of the adverse effects of amiodarone are attributable to deposition of phospholipids in the tissues. These include its effects on the eyes, nerves, liver, skin, and lungs. Almost all patients develop reversible corneal microdeposits, which can occasionally interfere with vision. There are reports of peripheral neuropathy and other neurological effects. Changes in serum activities of aspartate transaminase and lactate dehydrogenase can occur without other evidence of liver disease, but liver damage can occur in the absence of biochemical evidence. Skin sensitivity to light occurs commonly, possibly due to phototoxicity. There may also be a bluish pigmentation of the skin. Interstitial pneumonitis and alveolitis have been reported and may be fatal. Lung damage due to amiodarone may be partly due to hypersensitivity. Tumor-inducing effects have not been reported.

Studies in the prevention of dysrhythmias

In a study of the use of implantable defibrillators or antidysrhythmic drugs (amiodarone or metoprolol) in 288 patients resuscitated from cardiac arrest, the defibrillator was associated with a slightly lower rate of all-cause mortality than the antidysrhythmic drugs (15). However, the small difference was not statistically significant. There was hyperthyroidism in three of those given amiodarone. Drug withdrawal was required in nine of those given amiodarone and 10 of those given metoprolol. There were deaths in five patients fitted with a defibrillator and two patients given amiodarone. There was crossover to the other therapy in 6% in each group, usually because of recurrence of the dysrhythmia. When sudden cardiac death was analysed, the reduction in mortality with defibrillation was much larger (61%). There were no differences in all-cause mortality and sudden death rates between those given amiodarone and those given metoprolol.

Amiodarone and carvedilol have been used in combination in 109 patients with severe heart failure and left ventricular ejection fractions of 0.25 (16). They were given amiodarone 1000 mg/week plus carvedilol titrated to a target dose of 50 mg/day. A dual-chamber pacemaker was inserted and programmed in back-up mode at a basal rate of 40. Significantly more patients were in sinus rhythm after 1 year, and in 47 patients who were studied for at least 1 year the resting heart rate fell from 90 to 59. Ventricular extra beats were suppressed from 1 to 0.1/day and the number of bouts of tachycardia over 167 per minute was reduced from 1.2 to 0.3 episodes per patient per 3 months. The left ventricular ejection fraction increased from 0.26 to 0.39 and New York Heart Association Classification improved from 3.2 to 1.8. The probability of sudden death was significantly reduced by amiodarone plus carvedilol compared with 154 patients treated with amiodarone alone and even more so compared with 283 patients who received no treatment at all. However, the study was not randomized, and this vitiates the results. The main adverse effect was symptomatic bradycardia, which occurred in seven patients; two of those developed atrioventricular block and four had sinoatrial block and/or sinus bradycardia; one patient developed slow atrial fibrillation.

A meta-analysis of 13 randomized trials has shown that both total mortality and sudden death or dysrhythmic death was less common over 24 months after randomization to amiodarone than in control subjects (17).

Studies in atrial fibrillation

Cardiac glycosides such as digoxin are commonly used to treat uncomplicated atrial fibrillation. In those in whom digitalis is not completely effective or in whom symptoms (for example bouts of palpitation) persist despite adequate digitalization, a calcium antagonist, such as verapamil or diltiazem, can be added, or amiodarone used as an alternative.

The use of oral amiodarone in preventing recurrence of atrial fibrillation, for preventing recurrence after cardioversion or for pharmacological cardioversion of atrial fibrillation, has been reviewed (18). There is insufficient evidence to support its use as a first-line drug for

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preventing recurrence of atrial fibrillation or in preventing paroxysmal atrial fibrillation.

In 186 patients randomized equally to amiodarone 200 mg/day, sotalol 160–480 mg/day, or placebo, the incidence of atrial fibrillation after 6 months was higher in those taking placebo compared with amiodarone and sotalol and higher in those taking sotalol compared with amiodarone (19). Of the 65 patients who took amiodarone, 15 had significant adverse effects after an average of 16 months. There were eight cases of hypothyroidism, four of hyperthyroidism, two of symptomatic bradycardia, and one of ataxia. There were minor adverse effects in 9% of the patients, including gastrointestinal discomfort, nausea, photosensitivity, and eye problems. These patients had recurrent symptomatic atrial fibrillation. In contrast, only two patients using sotalol developed symptomatic bradycardia and one had severe dizziness.

In 208 patients with atrial fibrillation of various duration, including 50 with chronic atrial fibrillation, randomized to amiodarone or placebo, 80% converted to sinus rhythm after amiodarone compared with 40% of those given placebo (20). Amiodarone was given as an intravenous loading dose of 300 mg for 1 hour and 20 mg/kg for 24 hours, followed by 600 mg/day orally for 1 week and 400 mg/day for 3 weeks. Those who converted to sinus rhythm had had atrial fibrillation for a shorter duration and had smaller atria than those who did not convert. The shorter the duration of fibrillation and the smaller the atria the sooner conversion occurred. There was significant hypotension in 12 of the 118 patients who received amiodarone during the first hour of intravenous administration, but in all cases this responded to intravenous fluids alone. There was phlebitis at the site of infusion in 17 patients, and the peripheral catheter was replaced by a central catheter. There were no dysrhythmic effects.

In 40 patients with atrial fibrillation, some with severe heart disease (including cardiogenic shock in eight and pulmonary edema in 12), amiodarone 450 mg was given through a peripheral vein within 1 minute, followed by 10 ml of saline; 21 patients converted to sinus rhythm, 13 within 30 minutes and another 8 within 24 hours (21). There were two cases of hypotension, but in those that converted to sinus rhythm there was a slight increase in systolic blood pressure. There were no cases of thrombophlebitis. Efficacy is hard to judge from this study, because it was not placebo-controlled.

In 72 patients with paroxysmal atrial fibrillation randomized to either amiodarone 30 mg/kg or placebo, those who received amiodarone converted to sinus rhythm more often than those given placebo (22). The respective conversion rates were about 50 and 20% at 8 hours, and 87 and 35% after 24 hours. The time to conversion in patients who converted did not differ. One patient developed slow atrial fibrillation (35/minute) with a blood pressure of 75/55 mmHg. Three other patients who received amiodarone had diarrhea and one had nausea. In the control group two patients had headache, one had diarrhea, one had nausea, and two had episodes of sinus arrest associated with syncope during conversion to sinus rhythm; the last of these was thought to have sick sinus syndrome.

In a single-blind study 150 patients with acute atrial fibrillation were randomized to intravenous flecainide, propafenone, or amiodarone (23). At 12 hours there was conversion to sinus rhythm in 45 of 50 patients given flecainide, 36 of the 50 given propafenone, and 32 of the 50 given amiodarone. Thus, flecainide and propafenone were both more effective than amiodarone. There were no differences between the groups in the incidences of adverse effects; there was one withdrawal in each group, due to cerebral embolism in a patient given amiodarone, heart failure in a patient given propafenone, and atrial flutter in a patient given flecainide. There were no ventricular dysrhythmias during the study.

Amiodarone and magnesium have been compared in a placebo-controlled study to reduce the occurrence of atrial fibrillation in 147 patients after coronary artery bypass graft surgery (24). Amiodarone was given as a infusion of 900 mg/day for 3 days and magnesium by infusion of 4 g/day for 3 days. The cumulative occurrences of atrial fibrillation with placebo, amiodarone, and magnesium were 27, 14, and 23% respectively. These differences were not significant. Amiodarone delayed the onset of the first episode of dysrhythmia significantly, but the slight benefit was associated with a longer period of invasive monitoring and was not considered worthwhile. Patients who were more likely to develop atrial fibrillation were older and had a plasma magnesium concentration at 24 hours of under 0.95 mmol/l. Patients who were given amiodarone had a slightly higher rate of adverse events, including hypotension, atrioventricular block, and bradycardia; adverse events led to withdrawal in four cases.

Amiodarone, sotalol, and propafenone have been compared for the prevention of atrial fibrillation in 403 patients who had had at least one episode of atrial fibrillation within the previous 6 months; the study was not placebo-controlled (25). The rate of recurrence of atrial fibrillation was significantly higher in those given sotalol or propafenone than in those given amiodarone. During the study nine patients given amiodarone died, compared with eight given sotalol or propafenone. Four deaths were thought to be dysrhythmic, three in patients given amiodarone. There were major non-fatal adverse events in 36 of the 201 patients given amiodarone and in 35 of the 202 patients given propafenone or sotalol. These included one case of torsade de pointes in a patient who received propafenone, and congestive heart failure in 11 patients given amiodarone and nine given sotalol or propafenone. There were strokes and intracranial hemorrhages in one patient given amiodarone and nine patients given sotalol or propafenone, of whom most were taking warfarin at the time. In all, 68 of the patients who were given amiodarone and 93 of those given sotalol or propafenone withdrew from the study; 17 of those taking amiodarone withdrew because of lack of efficacy compared with 56 of those taking sotalol or propafenone; 36 of those who took amiodarone withdrew because of adverse events compared with 23 of those who took sotalol or propafenone, and this was almost statistically significant.

Amiodarone, propafenone, and sotalol have also been compared in the prevention of atrial fibrillation in 214 patients with recurrent symptomatic atrial fibrillation. They were randomized to amiodarone 200 mg/day, propafenone 450 mg/day, or sotalol 320 mg/day. There was recurrence of atrial fibrillation in 25 of the 75 patients who took amiodarone compared with the 51 of 75 who took sotalol and 24 of the 64 who took propafenone. There

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were adverse effects requiring withdrawal of treatment in 14 patients who took amiodarone, five who took sotalol and one who took propafenone while they were in sinus rhythm. These effects included symptomatic bradycardia in three patients, hyperthyroidism in six, hypothyroidism in four, and ataxia in one patient who took amiodarone. In those taking sotalol the adverse effects were bradycardia in three and severe dizziness in two. In the one patient in whom propafenone was withheld the reason was symptomatic bradycardia. Thus, amiodarone and propafenone were both more effective than sotalol, but amiodarone also caused more adverse effects requiring withdrawal (26).

In a meta-analysis of five randomized, placebo-controlled trials of amiodarone 200–1200 mg/day for 2–7 days in the treatment of postoperative atrial fibrillation and flutter in 764 patients, the incidence of adverse events with amiodarone was no greater than with placebo (27).

In a meta-analysis of five randomized, placebo-controlled trials of intravenous amiodarone about 500–2200 mg over 24 hours in the treatment of recent-onset atrial fibrillation in 410 patients, the incidence of adverse events was 27% with amiodarone and 11% with placebo (28). Intravenous amiodarone was significantly more effective than placebo in producing cardioversion. The most common adverse effects of intravenous amiodarone were phlebitis, bradycardia, and hypotension; most of these effects were not considered to be dose-limiting.

Of 85 patients with persistent atrial fibrillation after balloon mitral valvotomy given amiodarone (600 mg/day for 2 weeks and 200 mg/day thereafter), 33 converted to sinus rhythm (29). Of the other 52 patients, who underwent DC cardioversion at 6 weeks, 41 converted to sinus rhythm. Six patients had adverse effects attributable to amiodarone. Five had mild gastrointestinal symptoms, such as abdominal discomfort and nausea. One developed hypothyroidism after 3 months, which resolved when the dosage of amiodarone was reduced to 100 mg/day.

In 83 patients (27 women, 56 men; mean age 61 years) disopyramide, propafenone, or sotalol were used to prevent recurrence after elective electrical cardioversion for persistent atrial fibrillation (30). If there was recurrence cardioversion was repeated and the patient was given one of the other antidysrhythmic drugs. If there was further recurrence, amiodarone was used, a third cardioversion was performed, and, if sinus rhythm was restored, amiodarone 100–200 mg/day was continued. Patients in whom the initial cardioversion was not successful were given amiodarone and underwent repeated cardioversion. The follow-up duration was 12 months. The first electrical cardioversion was effective in 44 (53%) patients, and after 1 year 23 (52%) of them were still in sinus rhythm. None of the patients who underwent a second cardioversion and received a second antidysrhythmic drug stayed in sinus rhythm. Amiodarone as a third antidysrhythmic agent was effective in 10 (48%) patients. After 12 months of antidysrhythmic drug therapy sinus rhythm was maintained in 75% of patients in whom the first cardioversion had been effective, accounting for 40% of all the patients selected for cardioversion. In the 83 patients, sequential antidysrhythmic treatment effectively maintained sinus rhythm in 54 (65%), of whom 31 (57%) took amiodarone. The authors concluded that repeated electrical cardioversion and antidysrhythmic drug therapy enabled maintenance of sinus rhythm in 68% of patients for 1 year, that there was limited efficacy of the first antidysrhythmic drug given after a first effective electrical cardioversion, regardless of the drug used, excluding amiodarone, and that when atrial fibrillation recurred, a second antidysrhythmic drug, other than amiodarone, was completely ineffective. There were very few adverse events in this study. One patient taking amiodarone developed hyperthyroidism and two had symptomatic bradycardia.

Amiodarone 30 mg/kg orally for the first 24 hours plus, if necessary, 15 mg/kg over 24 hours has been compared with propafenone 600 mg in the first 24 hours plus, if necessary, 300 mg in the next 24 hours in 86 patients with recent onset atrial fibrillation (31). Conversion to sinus rhythm occurred faster with propafenone (2.4 hours) than amiodarone (6.9 hours). However, by 24 hours and 48 hours the same proportions of patients were in sinus rhythm; one patient given amiodarone had a supraventricular tachycardia and one a non-sustained ventricular tachycardia.

Studies in atrial flutter

Antidysrhythmic drugs have been compared with radiofrequency ablation in 61 patients with atrial flutter (32). Drug treatment was with at least two drugs, one of which was amiodarone. Of the 30 patients who took drug therapy, 19 needed to come into hospital one or more times, whereas after radiofrequency ablation that happened in only seven of 31 cases. In those who took the antidysrhythmic drugs the mean number of drugs was 3.4 and the range of drugs used was very wide. Quality-of-life and symptoms scores improved significantly in those in whom radiofrequency ablation was used, but not in those who took the antidysrhythmic drugs, apart from the symptom of palpitation, which improved in both groups, but to a greater extent in the non-drug group. Adverse effects were not discussed in this study, but it is clear that it suggests that radiofrequency ablation is to be preferred in these patients.

Studies in ventricular dysrhythmias

The effects of amiodarone in 55 patients with sustained ventricular tachycardia after myocardial infarction have been assessed in a long-term follow-up study (33). The patients underwent programmed ventricular stimulation after having been loaded with amiodarone. They were divided into those in whom ventricular tachydysrhythmias could be induced or not, and all were then given amiodarone 200 mg/day. In 11 cases a cardioverter defibrillator was implanted, because the first episode of ventricular tachycardia had been poorly tolerated or had caused hemodynamic instability. A defibrillator was also implanted in five other cases during follow-up, because of recurrence of dysrhythmias. There was a non-significant trend to a difference between the cumulative rates of dysrhythmias during long-term follow-up, with more events in those in whom a dysrhythmia had been inducible after loading. However, mortality rates in the two groups did not differ, and was around 25% at a mean follow-up of 42 months. Survival was significantly higher in patients with a left ventricular ejection fraction over 0.4, and the lower the left ventricular ejection fractions the higher the mortality. Amiodarone was withdrawn in six patients after a

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mean of 34 months because of neuropathy ($n = 1$), hypothyroidism ($n = 1$), prodysrhythmia with incessant ventricular tachycardia ($n = 2$), and non-specific adverse effects ($n = 2$). There was no pulmonary toxicity and no cases of torsade de pointes. In two patients there was evidence of hypothyroidism, mild neuropathy, and skin discoloration, but these events did not lead to withdrawal. In two patients the doses of amiodarone was reduced to 100 mg/day because of sinus bradycardia.

In a comparison of amiodarone ($n = 23$) with sotalol ($n = 22$) in patients with spontaneous sustained ventricular tachydysrhythmias secondary to myocardial infarction, sotalol was much more effective, 75% of those taking it remaining free of dysrhythmias compared with 38% of those taking amiodarone (34). Adverse effects requiring withdrawal occurred in 17% of those taking amiodarone at a median time of 3.5 months. The adverse effects included malaise, rash, headaches, flushing, and dyspnea due to pulmonary fibrosis.

Studies in myocardial infarction and heart failure

There have been reviews of the results of major trials of amiodarone after myocardial infarction (35) and in chronic heart failure (36).

- In the Basel Antiarrhythmic Study of Infarct Survival (BASIS) amiodarone significantly reduced all-cause mortality from 13 to 5%, compared with no antidysrhythmic drug therapy (37).
- In the Polish Arrhythmia Trial (PAT) amiodarone reduced all-cause mortality from 10.7 to 6.9% compared with placebo and cardiac mortality from 10.7 to 6.2% (38).
- In the Spanish Study of Sudden Death (SSD) amiodarone reduced all-cause mortality from 15.4 to 3.5% compared with metoprolol; however, the mortality in those receiving no antidysrhythmic drugs at all was only 7.7%, and in those the effect of amiodarone was not significant (39).
- In the European Myocardial Infarction Arrhythmia Trial (EMIAT) amiodarone reduced the risk of dysrhythmic deaths from 8.5 to 4.1% compared with placebo (40).
- In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) amiodarone reduced dysrhythmic deaths from 6.0 to 3.3% compared with placebo; non-dysrhythmic deaths were not affected (41).

In a meta-analysis of 10 studies of the use of amiodarone in patients with heart failure, the overall odds ratio for mortality with amiodarone compared with placebo was 0.79 (95% CI = 0.68, 0.92). The corresponding odds ratio for adverse effects was 2.29 (1.97, 2.66) (36). The benefit to risk ratio of the use of amiodarone in these patients is not yet clear. The dosage of amiodarone in these studies varied from 50 to 400 mg/day, with an average of around 250 mg/day.

Organs and Systems

Cardiovascular

The incidence of cardiac dysrhythmias with amiodarone is under 3% (42), lower than with many other antidysrhythmic drugs, and several randomized controlled trials have failed to show any prodysrhythmic effect (43).

Other cardiac effects that have been reported include sinus bradycardia, atrioventricular block, infra-His block, asystole, and refractoriness to DC cardioversion (SEDA-10, 147).

There is a risk of hypotension and atrioventricular block when amiodarone is given intravenously.

Cardiogenic shock has been reported in 73-year-old woman with a dilated cardiomyopathy who had digitalis and amiodarone toxicity (44).

Ventricular dysrhythmias

Amiodarone can prolong the QT interval, and this can be associated with torsade de pointes, although this is uncommon. This effect is potentiated by hypokalemia (45).

Ventricular dysrhythmias due to drugs can be either monomorphic or polymorphic. The class Ia drugs are particularly likely to cause polymorphic dysrhythmias, as is amiodarone (although to a lesser extent). In contrast, the class Ic drugs are more likely to cause monomorphic dysrhythmias (46).

- A 40-year-old woman developed torsade de pointes within the first 24 hours of intravenous administration of amiodarone 150 mg followed by 35 mg/hour (47). The association with amiodarone was confirmed by subsequent rechallenge.
- Three boys with congenital cardiac defects developed polymorphous ventricular tachycardia after having been given intravenous amiodarone; two died (48).
- An 8-day-old boy was given intravenous amiodarone 5 mg/kg over 60 minutes followed by 10 mg/kg/day for a postoperative junctional ectopic tachycardia after a cardiac operation. He developed ventricular fibrillation 12 hours later, but recovered with defibrillation and internal cardiac massage. His serum amiodarone concentration was 1–2.5 mg/l, within the usual target range.
- A 3-month-old boy underwent a cardiac operation and 6 hours later developed a junctional ectopic tachycardia. He was given amiodarone as a continuous intravenous infusion of 10 mg/kg/day for 3 hours and developed ventricular fibrillation, from which he was not resuscitated. The serum amiodarone concentration was 0.3 mg/l.
- A 3-month-old boy developed a postoperative junctional ectopic tachycardia 48 hours after operation and was given a continuous intravenous infusion of amiodarone 10 mg/kg/day. After 2 hours he developed ventricular fibrillation and was not resuscitated. His serum amiodarone concentration was in the target range.

It is not clear that the dysrhythmias in these cases were due to amiodarone, particularly since the doses had been very low and the serum concentrations no higher than the usual target range; QT intervals were not reported.

- A 79-year-old woman took amiodarone 4800 mg over 6 days and developed a polymorphous ventricular tachycardia; the associated precipitating factors were a prolonged QT interval and hypokalemia (49).
- A 71-year-old Japanese man with bouts of sustained monomorphic ventricular tachycardia, in whom non-sustained polymorphic ventricular tachycardia was induced by rapid pacing during electrophysiological studies, was given amiodarone and developed three different types of sustained monomorphic ventricular

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tachycardia, with slightly different cycle lengths, induced and terminated by rapid pacing (50).

The authors proposed that amiodarone had modulated the threshold of induction and/or termination of ventricular tachycardia.

Of 189 patients, five had torsade de pointes and all five had prolonged QT intervals (51). Two of the five, all women, also had raised blood glucose concentrations, and the authors suggested that hyperglycemia is a risk factor for torsade de pointes. However, the number of cases reported in this series was too small to justify such a conclusion.

It has been suggested that women are more likely to develop torsade de pointes than men in response to antidysrhythmic drugs (52), and this has been confirmed in the case of amiodarone in a study of 189 patients given intravenous amiodarone (51). This is also reminiscent of the finding that prolongation of the QT interval due to quinidine is greater in women than in men at equivalent serum concentrations (53).

T wave alternans is an occasional presentation, in association with ventricular dysrhythmias (SEDA-18, 201).

- A 65-year-old man with atrial fibrillation was given intravenous amiodarone 450 mg over 30 minutes followed by 900 mg over 24 hours (54). He reverted to sinus rhythm, but the electrocardiogram showed giant T wave alternans with a variable QT interval (0.52–0.84 seconds). He had a short bout of torsade de pointes and was given magnesium. Two days later the electrocardiogram was normal.
- In a 62-year-old man with dilated cardiomyopathy and an implantable cardioverter defibrillator for ventricular tachycardia, microvolt T wave alternans differed when amiodarone was added (55). The onset heart rate with T wave alternans was lower and the alternans voltage higher with amiodarone than without it.

The effects of amiodarone appeared to be related to exacerbations of ventricular tachycardia and an increased defibrillation threshold.

Atrial dysrhythmias

Amiodarone has been reported to cause atrial flutter in 10 patients who had been given it for paroxysmal atrial fibrillation (56). In nine of those the atrial flutter was successfully treated by catheter ablation. However, during a mean follow-up period of 8 months after ablation, atrial fibrillation occurred in two patients who had continued to take amiodarone; this was a lower rate of recurrence than in patients in whom atrial flutter was not associated with amiodarone. The authors therefore suggested that in patients with atrial flutter secondary to amiodarone given for atrial fibrillation, catheter ablation allows continuation of amiodarone therapy.

Amiodarone can sometimes cause atrial flutter, even though it is also used to treat it (SEDA-25, 180). There has been a report of seven cases (six men and one woman, aged 34–75 years) of 1:1 atrial flutter with oral amiodarone (57). Four of them had underlying cardiac disease; none had hyperthyroidism. The initial dysrhythmia was 2:1 atrial flutter ($n = 4$), 1:1 atrial flutter ($n = 2$), or atrial fibrillation ($n = 1$). One patient was taking amiodarone 200 mg/day and one was taking 400 mg/day plus carvedilol. The other five all received loading doses of 9200 (sd 2400) mg over 10 (sd 4) days. There was an adrenergic trigger factor (exertion, fever, esophageal stimulation, or a beta-adrenoceptor agonist aerosol) in five patients. One required emergency cardioversion.

Of 136 patients with atrial fibrillation treated with either amiodarone ($n = 96$) or propafenone ($n = 40$), 15 developed subsequent persistent atrial flutter, nine of those taking amiodarone and six of those taking propafenone (58). In all cases radiofrequency ablation was effective. It is not clear to what extent these cases of atrial flutter were due to the drugs, although the frequency of atrial flutter in previous studies with propafenone has been similar. Atrial enlargement was significantly related to the occurrence of persistent atrial flutter in these patients.

Bradycardia

Bradycardia has been reported to occur in about 5% of patients taking amiodarone (SEDA-20, 176).

Of 2559 patients admitted to an intensive cardiac care unit over 3 years, 64 with major cardiac iatrogenic problems were reviewed (59). Of those, 58 had dysrhythmias, mainly bradydysrhythmias, secondary to amiodarone, beta-blockers, calcium channel blockers, electrolyte imbalance, or a combination of those. Amiodarone was implicated in 19 cases, compared with 44 cases attributed to beta-blockers and 28 to calcium channel blockers. Of the 56 patients with sinus bradycardia, 10 were taking a combination of amiodarone and a beta-blocker, six were taking amiodarone alone, and three were taking amiodarone plus a calcium channel blocker.

Heart block

- In a 66-year-old woman taking amiodarone 1200 mg/week there was marked prolongation of the QT interval, to 680 ms; the succeeding P waves fell within the refractory period of the preceding beat and were unable to institute conduction (60). This resulted in 2:1 atrioventricular block. Amiodarone was withdrawn and the QT interval normalized with a time-course consistent with the long half-life of amiodarone. A subsequent rechallenge with intravenous amiodarone caused further prolongation of the QT interval.

The authors hypothesized that this patient had a silent mutation in one of the genes coding for the two major potassium channel proteins (IK_r or IK_s) that are involved in the mode of action of amiodarone. However, they did not present any genetic studies to support this hypothesis.

Respiratory

There have been reviews of the lung complications of amiodarone toxicity (61,62) and of its mechanisms (63).

Frequency

The risk of lung toxicity is about 5–6% (64) and is greatest during the first 12 months of treatment and among patients over 40 years of age. The mortality rate in those who develop respiratory involvement is about 9% (about 0.5% of the total).

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Mechanism

Amiodarone causes lung damage either by direct deposition of phospholipids in the lung tissue or by some immunologically mediated reaction. Other mechanisms have also been proposed, including oxidant-mediated damage, a direct detergent effect, and a direct toxic effect of iodide (SEDA-15, 168).

It has been suggested that the serum activity of lactate dehydrogenase (LDH) may be related to the occurrence of amiodarone-induced pneumonitis, as occurred in a 72-year-old woman in whom the serum LDH activity rose from a baseline of around 750 U/l to around 1500 U/l during acute pneumonitis and resolved with resolution of a clinical condition after withdrawal of amiodarone (65). The LDH activity in bronchoalveolar lavage fluid was also increased. The proposed mechanism was leakage of lactate dehydrogenase from the pulmonary interstitial cells into the blood. Of course, a rise in the serum LDH activity is highly non-specific, and it is not clear whether it might also rise in bronchoalveolar lavage fluid in other conditions.

Presentation

The commonest form of lung damage is an interstitial alveolitis, although pneumonitis and bronchiolitis obliterans have also been reported, as have solitary localized fibrotic lesions, non-cardiac pulmonary edema, pleural effusions, acute respiratory failure, acute pleuritic chest pain, and adult respiratory distress syndrome (SEDA-17, 220) (SEDA-18, 201) (66–68). Amiodarone has also been reported to cause impairment of lung function, even in patients who do not develop pneumonitis (69), and pre-existing impairment of lung function may constitute a contraindication to amiodarone.

Lung damage due to amiodarone usually develops slowly, but it can occasionally have a rapid onset, particularly in patients who are given high concentrations of inspired oxygen, and there is experimental evidence that amiodarone enhances the toxic effects of oxygen on the lungs (70).

- Adult respiratory distress syndrome occurred very rapidly in a 66-year-old man who took amiodarone 200 mg/day for a few weeks only (71).
- Pulmonary infiltrates occurred in a 72-year-old man after treatment with amiodarone (total dose 6800 mg) for only 7 days (72).
- Two patients with dilated cardiomyopathy developed pneumonitis after 6 weeks and 8 months while taking amiodarone 400 and 200 mg/day respectively (73).

Some cases of amiodarone-induced lung toxicity, some in patients who took very large doses, illustrate the wide variety of possible presentations.

- A 77-year-old man without a history of lung disease was given amiodarone 7 days after bypass surgery because of supraventricular dysrhythmias and non-sustained ventricular tachycardia (74). He had taken 1600 mg/day for a week followed by a maintenance dosage of 400 mg/day, and 15 days later became pale, sweaty, febrile, and tachypneic. His blood pressure was 100/60 and his heart rate 100/minute. There were reduced breath sounds and crackles throughout the lung fields. A chest X-ray showed diffuse interstitial and alveolar infiltrates and small bilateral pleural effusions. A high-resolution CT scan of the chest showed diffuse ground-glass attenuation and patchy peripheral opacities, consistent with an acute hypersensitivity pneumonitis, and other diagnoses were ruled out. He responded to gluco-corticoids.
- A 72-year-old man developed hypoxemic respiratory failure while taking amiodarone 300 mg/day (74). He had no history of lung disease. His CT scan was similar to that of the first patient. He responded to treatment with corticosteroids.
- In a 79-year-old man with emphysema taking amiodarone 200 mg/day, the diagnosis of amiodarone-induced lung toxicity was complicated by the fact that emphysema has the opposite effect on lung volumes and spirometry from interstitial lung disease (75). His FEV_1, which had been reduced, became normal and then increased. However, the combination of emphysema with amiodarone-induced lung disease led to worsening dyspnea, and a chest X-ray showed patchy mixed interstitial and airspace disease, most marked in the mid to upper lung zones bilaterally, and ground-glass opacification in the left lower lobe, suggesting an acute alveolitis. He responded to prednisone after withdrawal of amiodarone. His carbon monoxide diffusing capacity, which had fallen, returned to normal. A CT scan showed marked bullous emphysema and ground-glass interstitial changes. The FEV_1 almost doubled, from being severely reduced to within the reference range.
- A 77-year-old man who had taken amiodarone 400 mg/day for 11 months developed crackles at the lung bases and scattered respiratory wheeze (76). His leukocyte count was raised at 13.5 × 109/l and he had progressive reduction in carbon monoxide diffusing capacity, serially measured. A chest X-ray showed bilateral opacities in the upper zones, peripheral in distribution, and a CT scan showed dense bilateral lung parenchymal opacities. The symptoms of dyspnea on exertion, cough with minimal sputum, pleuritic chest pain, and low-grade fever abated after withdrawal, and the upper lobe densities resolved.
- A 62-year-old man took amiodarone 400 mg bd and developed several adverse effects, including bilateral apical opacities with left hilar lymphadenopathy (77). Amiodarone was withdrawn and he was given glucocorticoids, with good effect; there was dramatic radiographic resolution within 3 weeks and he was no longer breathless with 1 week. The lung biopsy showed typical foamy macrophages. He had fibrosis of the bronchioles and interstitium, foci of obliterative bronchiolitis, and thickening of the alveolar walls. He had an accompanying peripheral neuropathy, which improved after withdrawal, and impaired visual acuity, about which no further information was given. Biopsy of the right vastus lateralis muscle showed type II atrophy with vacuolization, which the authors suggested supported the suspicion of amiodarone toxicity.

Amiodarone can occasionally cause isolated lung masses (SEDA-15, 168). One case was associated with a vasculitis; the lesions resolved completely 4 months after amiodarone withdrawal (78). In another case an isolated mass

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was associated with multiple small nodules in both lungs; the lesions resolved completely 6 months after amiodarone withdrawal (79).

Diagnosis

Diagnosis of amiodarone-induced lung damage can be difficult. The clinical symptoms and signs, the changes on chest radiography, and abnormalities of lung function tests are all non-specific. The presence of lymphocytes and foamy macrophages in bronchial lavage fluids and of phospholipidosis in lung biopsies are all suggestive. Measurement of the diffusing capacity of carbon monoxide has been used, but is unreliable.

The sialylated carbohydrate antigen KL-6 has been reported to be a serum marker of the activity of interstitial pneumonitis in seven patients with amiodarone-induced pulmonary toxicity (80,81). The dosages of amiodarone were 200–800 mg as an oral loading dose followed by 75–200 mg/day. Pulmonary complications occurred at 17 days to 48 months of treatment. In two patients with severe dyspnea and interstitial shadows on chest X-ray the KL-6 concentrations were very high (2100 and 3000 U/ml). In one of these the concentration increased from 695 to 2100 U/ml at a time when the interstitial changes on the CT scan worsened. In contrast, in two patients in whom pneumonia resolved with antibiotic treatment and without withdrawal of amiodarone, the serum KL-6 concentrations were lower (120 and 330 U/ml). In a patient in whom congestion of the lungs due to congestive cardiac failure had been confused with interstitial shadows the KL-6 concentration was only 190 U/ml. In two patients with lung cancers the concentrations were 260 and 360 U/ml. The authors proposed that a KL-6 concentration above the reference range (more than 520 U/ml) might be useful in differentiating patients with amiodarone-induced pneumonitis from patients with similar features not associated with amiodarone.

In 25 patients, three had proven interstitial pneumonitis and KL-6 serum concentrations of 414, 848, and 1217 U/ml; in contrast, all of the other 22 patients had normal CT scans and normal KL-6 concentrations (under 500 U/ml) (82). In the same study the limitations of carbon monoxide diffusing capacity in the diagnosis of amiodarone-induced lung disease (SEDA-15, 168) were again demonstrated.

Several scanning techniques have been used in the diagnosis of amiodarone-induced lung damage.

Computed tomography

Computed tomography may show a typical pattern of basal peripheral high-density pleuroparenchymal linear opacities, although these may be absent (83). It has also been suggested that high-resolution CT scanning may be able to detect iodine deposition from the drug (84). Of 16 patients taking long-term amiodarone, eight had severe respiratory and other symptoms and eight either had no symptoms or had only mild or chronic respiratory symptoms. All eight controls had negative high-resolution CT scans with no areas of high attenuation, while all eight cases had a least one high-attenuation lesion.

^{67}Gallium scintigraphy

^{67}Gallium scintigraphy has been used to diagnose amiodarone-induced lung damage (SEDA-15, 168).

- A 75-year-old man, who had taken amiodarone 200 mg/day for 4 years, developed acute dyspnea, chest pain, fever, and sweats (85). The chest X-ray showed diffuse alveolar and interstitial infiltrates, particularly at the lung bases. No pathogenic organisms were isolated and antibiotics had no effect. There was no evidence of sarcoidosis. Pulmonary ^{67}gallium scintigraphy showed extensive uptake of tracer throughout both lungs, consistent with amiodarone pneumonitis on a background of asbestosis with interstitial fibrosis. Treatment with corticosteroids after withdrawal of amiodarone resulted in marked clinical improvement.

The authors said that the extensive changes on gallium scanning, not present on the chest X-ray, had helped them to make the diagnosis, although a high-resolution CT scan had also shown widespread changes.

^{99m}Technetium-diethylene triamine penta-acetic acid (DPTA) aerosol scintigraphy

Another scanning technique, ^{99m}Tc-diethylene triamine penta-acetic acid (DPTA) aerosol scintigraphy, has been compared with ^{67}Ga scanning in 26 patients, seven with amiodarone-induced lung damage, eight taking amiodarone without lung damage, and 11 healthy controls (86). ^{67}Ga scintigraphy was positive in four of the seven patients with lung damage but normal in the others. There was a positive correlation between ^{99m}Tc-DTPA clearance and the cumulative dose of amiodarone. The mean clearance values were 2%/minute in those with amiodarone-induced lung damage, 1.3%/minute in those without lung damage, and 0.9%/minute in the controls. The authors concluded that ^{67}Ga lung scintigraphy is useful for detecting amiodarone-induced lung damage but that ^{99m}Tc-DTPA aerosol scintigraphy is better.

Management

Although early reports suggested that glucocorticoids might be beneficial in management, this has not been subsequently confirmed (87).

Nervous system

The most common forms of neurological damage attributed to amiodarone are tremor, peripheral neuropathy, and ataxia (88). Other effects that have been reported include delirium (89), Parkinsonian tremor (90), and pseudotumor cerebri (91). Acute myolysis has recently been described at high dose (92). The peripheral neuropathy is probably due to intracellular lipidosis (93).

- Periodic ataxia has been attributed to amiodarone in a 67-year-old man taking amiodarone 200 mg/day (94). The ataxia responded to acetazolamide and eventually to withdrawal of amiodarone. It recurred with rechallenge.

Amiodarone-induced neuromyopathy has been studied in three patients by a review of their records, electromyography, and histopathology of muscle and nerve (95). Two patients had a slightly asymmetric, mixed, but primarily

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demyelinating sensorimotor polyneuropathy and the third had an acute neuropathy resembling Guillain–Barré syndrome. Creatine kinase activity did not correlate with clinical or electromyographic evidence of myopathy. In the peripheral nerves there was demyelination, some axon loss, and a variable number of characteristic lysosomal inclusions. Muscle specimens from two patients showed evidence of a vacuolar myopathy. After withdrawal of amiodarone, two patients improved and one died with a cardiac dysrhythmia.

Benign orgasmic headache has been associated with amiodarone (96).

- A 52-year-old man, who had taken amiodarone 800 mg/day for 7 months, developed acute, severe, throbbing headaches precipitated by coitus and occasionally other forms of exertion. An MRI scan of the brain was normal. When the dose of amiodarone was reduced to 200 mg/day the headaches diminished in frequency and severity. When the dose was increased again to 400 mg/day they increased in frequency and severity. The amiodarone was withdrawn and the headaches resolved.

Amiodarone was originally developed as a vasodilator, and that may have been the cause of headaches in this case.

Sensory systems

The adverse effects of amiodarone on the eyes have been reviewed (97). The most common effect is corneal microdeposits. In some cases chronic blepharitis and conjunctivitis have been reported (98), but the relation of these to amiodarone is not clear.

Keratopathy

In almost all patients (99,100) corneal microdeposits of lipofuscin occur secondary to the deposition of amiodarone. These are generally of no clinical significance, but occasionally patients complain of haloes around lights, particularly at night, photophobia, blurring of vision, dryness of the eyes, or lid irritation. Occasionally amiodarone can cause anterior subcapsular deposits, which are usually asymptomatic. In 22 patients taking long-term amiodarone there were corneal drug deposits in all of the eyes, slight anterior subcapsular lens opacities in 22%, and dry eyes in 9% (101).

Verticillate epithelial keratopathy due to amiodarone, in which there is whorl-shaped pigmentation of the cornea, has been proposed to be worsened by soft contact lenses (SEDA-15, 171). Two patients with hard contact lenses and amiodarone-associated keratopathy both complained of increased sensitivity to sunlight and were fitted with ultraviolet light-blocking lenses instead, as a precaution against further corneal damage; however, the authors did not think that the contact lenses had contributed to the damage (102).

The eyes of 11 patients (eight men and three women) taking amiodarone have been compared with those of 10 healthy sex- and age-matched controls by confocal microscopy (103). All those taking amiodarone had bright, highly reflective intracellular inclusions in the epithelial layers, particularly in the basal cell layers. In eyes with advanced keratopathy there were bright microdots in the anterior and posterior stroma and on the endothelial cell layer. Keratocyte density in the anterior stroma was lower in the treated subjects than in the controls, and there was marked irregularity of the stromal nerve fibers. The authors concluded that in some patients taking long-term amiodarone corneal damage may penetrate deeper than has previously been suspected.

Color vision disturbances

Amiodarone can cause impaired color vision associated with keratopathy (SEDA-12, 153) (104). Of 22 patients taking long-term amiodarone, two who had otherwise healthy eyes had abnormal blue color vision (101). Otherwise, color vision, contrast sensitivity, and visual fields were normal or could be explained by eye diseases such as cataract.

Optic neuropathy

A more serious effect of amiodarone on the eye is an optic neuropathy (105) (SEDA-15, 171). Although this resolves on withdrawal there can be residual field defects (106,107). Blindness has been attributed to bilateral optic neuropathy in a patient taking amiodarone (108). The incidence of optic neuropathy with amiodarone (SEDA-23, 199) has been estimated at 1.8% (SEDA-13, 141). There has been a recent review of 73 cases of optic neuropathy associated with the use of amiodarone, including 16 published case reports and 57 other reports from the National Registry of Drug-Induced Ocular Side Effects, the US FDA, and the WHO (109). Amiodarone-induced optic neuropathy is of insidious onset, with slow progression, bilateral visual loss, and protracted disc swelling, which tends to stabilize within several months of withdrawal. These features all distinguish it from non-arteritic ischemic optic neuropathy. The pathology of amiodarone-induced optic neuropathy is associated with lipid deposition, as with other forms of adverse effects of amiodarone.

- A 51-year-old man developed blurred vision after having taken amiodarone 600 mg/day for 3 months and 400 mg/day for 5 months (110). There was mild optic disc palor and edema on the right side, with a nearby flame-shaped hemorrhage; the optic disc on the left side was normal. There were accompanying corneal opacities in both eyes. Amiodarone was withdrawn and the optic neuropathy and corneal opacities improved.
- A 48-year-old man developed bilateral blurred vision and visual field changes after having taken amiodarone 400 mg/day for 2 months; 3 weeks after withdrawal of amiodarone his symptoms improved (111). There was no optic disc edema.

Other effects

The absence of optic disc edema in the last case is unusual; most cases are accompanied by some form of swelling of the optic disc.

Rare effects include raised intracranial pressure with papilledema (SEDA-12, 153) (112), retinal maculopathy (113), and retinopathy (97).

Multiple chalazia have been reported on the eyelids, due to lipogranulomata that contained a lot of amiodarone (114).

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Sicca syndrome has occasionally been reported (9,115–117).

Brown discoloration of implanted lenses has been attributed to amiodarone (118).

- A 66-year-old woman, who had had two silicone intraocular lenses inserted because of cataract, developed progressive brown discoloration of the lens while taking amiodarone (dosage not stated). The discoloration progressed markedly after vitrectomy, suggesting that it was due to leakage of the drug into the eye. She also had an amiodarone-induced keratopathy.

Psychological, psychiatric

Delirium has rarely been reported with amiodarone (SEDA-13, 140).

- A 54-year-old man with no previous psychiatric history took amiodarone 400 mg bd (119). After a few days he became depressed and paranoid, suffered from insomnia, and had rambling speech. The dosage of amiodarone was reduced to 200 mg bd and he improved. However, 3 days later he became confused, with tangential thinking, labile effect, and a macular rash on the limbs. His serum sodium was reduced at 127 mmol/l and his blood urea nitrogen was raised. A CT scan of the head was normal. Amiodarone was withdrawn and 4 days later he was alert and oriented. About a week later he started taking amiodarone again and within 4 days became increasingly agitated, confused, and paranoid. He once more recovered after withdrawal of amiodarone.
- Depression has been attributed to amiodarone in a 65-year-old woman who was taking amiodarone (dosage not stated) (120). Because the mode of presentation was atypical in onset, course, duration, and its response to antidepressant drugs, amiodarone was withdrawn, and she improved rapidly. There was no evidence of thyroid disease.

Endocrine

Testes

Amiodarone can cause endocrine testicular dysfunction, as judged by increases in serum concentrations of FSH and LH and hyper-responsiveness to GnRH (121).

Syndrome of inappropriate ADH secretion

Amiodarone-induced hyponatremia, due to the syndrome of inappropriate secretion of antidiuretic hormone, is rare (SEDA-21, 199) (122). The mechanism is unknown. Unlike other adverse effects of amiodarone, it seems to occur rapidly and to resolve rapidly after withdrawal.

- A 63-year-old man reduced his dietary sodium intake to combat fluid retention and was taking furosemide 40 mg/day, spironolactone 50 mg/day, and enalapril 2.5 mg/day (123). He then took amiodarone 800 mg/day for 7 days and his serum sodium concentration fell to 119 mmol/l; his plasma vasopressin concentration was raised at 2.6 pmol/l. The dose of amiodarone was reduced to 100 mg/day, with fluid restriction; his sodium rose to 130 mmol/l and his vasopressin fell to 1.4 pmol/l.
- An 87-year-old man reduced his dietary sodium intake to combat fluid retention and was taking furosemide 40 mg/day and spironolactone 25 mg/day (123). He then took amiodarone 200 mg/day for 7 days and 100 mg/day for 8 days and his serum sodium concentration fell to 121 mmol/l; his plasma vasopressin concentration was raised at 11 pmol/l. Amiodarone was continued, with fluid restriction; his sodium rose to 133 mmol/l and his vasopressin fell to 2.4 pmol/l.
- A 67-year-old man, who had taken amiodarone 200 mg/day for 3 months, developed hyponatremia (serum sodium concentration 117 mmol/l) (124). He was also taking furosemide 20 mg/day, spironolactone 25 mg/day, and lisinopril 40 mg/day. His urine osmolality was 740 mosmol/kg with a normal serum osmolality. Fluid restriction was ineffective, but when amiodarone was withdrawn the sodium rose to 136 mmol/l.
- A 62-year-old woman with paroxysmal atrial fibrillation who had taken amiodarone 300 mg/day had a serum sodium concentration of 120 mmol/l with a normal serum potassium and a reduced serum osmolality (240 mmol/kg); the urinary sodium concentration was 141 mmol/l and the urine osmolality 422 mmol/kg (122). There was no evident cause of inappropriate secretion of ADH and within 5 days of withdrawal of amiodarone the serum sodium concentration had risen to 133 mmol/l and rose further to 143 mmol/l 14 days later. There was no rechallenge and no recurrence of hyponatremia during the next 6 months.

In some of these cases other factors may have contributed to the hyponatremia that amiodarone seems to have caused.

Thyroid gland

The effects of amiodarone on thyroid function tests and in causing thyroid disease, both hyperthyroidism and hypothyroidism, have been reviewed in the context of the use of perchlorate, which acts by inhibiting iodine uptake by the thyroid gland (125), and there have been several other reviews (126–130).

Effects on thyroid function tests

Amiodarone causes altered thyroid function tests, with rises in serum concentrations of T4 and reverse T3 and a fall in serum T3 concentration. This is due to inhibition of the peripheral conversion of T4 to T3, causing preferential conversion to reverse T3. These changes can occur in the absence of symptomatic abnormalities of thyroid function.

Hyperthyroidism

DoTS classification

Dose-relation: collateral effect
Time-course: delayed
Susceptibility factors: genetic (unoperated or palliated cyanotic congenital heart disease; beta-thalassemia major); sex (conflicting results); altered physiology (iodine intake, conflicting results)

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Frequency

Apart from its effects on thyroid function tests, amiodarone is also associated with both functional hyperthyroidism and hypothyroidism, in up to 6% of patients. The frequency of thyroid disease in patients taking amiodarone has been retrospectively studied in 90 patients taking amiodarone 200 mg/day for a mean duration of 33 months (131). Hypothyroidism occurred in five patients and hyperthyroidism in 11. Hyperthyroidism became more frequent with time and was associated with recurrent supraventricular dysrhythmias in four of the 11 patients.

In a nested case-control analysis of 5522 patients with a first prescription for an antidysrhythmic drug and no previous use of thyroid drugs, cases were defined as all patients who had started a thyroid-mimetic or antithyroid drug no sooner than 3 months after the start of an antidysrhythmic drug and controls were patients with a comparable follow-up period who had not taken any thyroid drugs during the observation period (132). There were 123 patients who had started antithyroid drugs and 96 who had started a thyroid-mimetic drug. In users of amiodarone there was an adjusted odds ratios of 6.3 (95% CI = 3.9, 10) for hyperthyroidism compared with users of other antidysrhythmic drugs. Patients who were exposed to a cumulative dose of amiodarone over 144 g had an adjusted odds ratio of 13 (6, 27) for hyperthyroidism.

Mechanisms

Amiodarone causes two different varieties of hyperthyroidism (SEDA-23, 199), one by the effects of excess iodine in those with latent disease (so-called type 1 hyperthyroidism), the other through a destructive thyroiditis in a previously normal gland (so-called type 2 hyperthyroidism). The two varieties can be distinguished by differences in radio-iodine uptake by the gland: in type 1 hyperthyroidism radio-iodine uptake is normal or increased, whereas in type 2 it is reduced. In type 1 hyperthyroidism, thyroid ultrasound shows a nodular, hypoechoic gland of increased volume, whereas in type 2 the gland is normal.

Iodine intake may be important in determining the type of amiodarone-induced thyroid disease. In 229 patients taking long-term amiodarone hyperthyroidism was more common (9.6 versus 2%) in West Tuscany, where dietary iodine intake is low, and hypothyroidism more common (22 versus 5%) in Massachusetts, where iodine intake is adequate (SEDA-10, 148) (133). However, other factors may play a part. In a retrospective inter-regional study in France there was a greater incidence of amiodarone-induced hyperthyroidism in the maritime areas Aquitaine and Languedoc–Roussillon, and a greater incidence of amiodarone-induced hypothyroidism in Midi–Pyrenees, a non-maritime area, in which iodine intake is lower than in Languedoc–Roussillon (134).

There have also been reports of painful thyroiditis associated with amiodarone (SEDA-15, 170).

Susceptibility factors

There has been a retrospective study of the frequency of amiodarone-associated thyroid dysfunction in adults with congenital heart disease (135). Of 92 patients who had taken amiodarone for at least 6 months (mean age 35, range 18–60 years), 36% developed thyroid dysfunction—19 became hyperthyroid and 14 hypothyroid. The mean dosage was 194 (100–300) mg/day, and the median duration of therapy was 3 (0.5–15) years. Female sex (OR = 3) and unoperated or palliated cyanotic congenital heart disease (OR = 7) were significant susceptibility factors for thyroid dysfunction. The risk was also dose-related. Although the authors conceded that they may have over-estimated the risk of thyroid dysfunction, because of the selected nature of the population they studied, the risks were markedly higher than in previous studies of older patients with acquired heart disease, despite a lower maintenance dosage of amiodarone.

In contrast, it has been suggested that men are more susceptible to hyperthyroidism due to amiodarone (136). Of 122 600 patients in 12 practices in the West Midlands in the UK, 142 men and 74 women were taking amiodarone and 27 (12.5%) had thyroid disease. Of those, 11 men (7.7%) and 4 women (5.4%) had hypothyroidism, a non-significant difference; however, 12 men (8.5%) had hyperthyroidism compared with no women. This difference is particularly striking because hyperthyroidism is usually more common in women.

Patients with beta-thalassemia major have an increased risk of primary hypothyroidism. In 23 patients with beta-thalassemia amiodarone was associated with a high risk of overt hypothyroidism (33 versus 3% in controls) (137). This occurred at up to 3 months after starting amiodarone. The risk of subclinical hypothyroidism was similar in the two groups. In one case overt hypothyroidism resolved spontaneously after withdrawal, but the other patients were given thyroxine. After 21–47 months of treatment three patients developed thyrotoxicosis, with remission after withdrawal. There were no cases of hyperthyroidism in the controls. The authors proposed that patients with beta-thalassemia may be more susceptible to iodine-induced hypothyroidism, related to an underlying defect in iodine in the thyroid, perhaps associated with an effect of iron overload.

Presentation

Many examples of hyperthyroidism due to amiodarone have been published.

- A 72-year-old woman with dilated cardiomyopathy was given amiodarone for fast atrial flutter and 6 months later developed abnormal thyroid function tests, with a suppressed TSH and a raised serum thyroxine. The autoantibody profile was negative and a thyroid uptake scan showed reduced uptake (138).

Despite the fact that she was clinically euthyroid, the authors suggested that this patient had amiodarone-induced hyperthyroidism. However, amiodarone inhibits the peripheral conversion of thyroxine to triiodothyronine; it can therefore increase the serum thyroxine and suppress the serum TSH, as in this case. On the other hand, the reduced uptake by the thyroid gland is consistent with type 2 amiodarone-induced hyperthyroidism. The authors did not report the serum concentrations of free thyroxine and triiodothyronine.

- A 67-year-old man took amiodarone 200 mg/day for 20 months, after which it was withdrawn; 8 months later his serum TSH was suppressed and the free thyroxine and

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free triiodothyronine were both raised; there were no thyroid antibodies and an ultrasound scan showed a diffuse goiter with a nodule in the right lobe and reduced iodine uptake (139). Histological examination of the nodule showed a papillary cancer.

The authors attributed these changes to an effect of amiodarone, but it is not clear that amiodarone-induced changes would have taken so long to become manifest after withdrawal. However, the diagnosis of type 2 amiodarone-induced hyperthyroidism was supported by a poor response to prednisone, potassium perchlorate, and methimazole. Lithium produced temporary benefit, but thyroidectomy was required.

- In five patients who presented in Tasmania during 1 year, all of whom were taking amiodarone 200 mg/day, serum TSH was undetectable and the free thyroxine and triiodothyronine concentrations were raised (140). In one case there was a low titer of TSH receptor antibodies and in another a high titer of antithyroid peroxidase antibodies. In all cases the hyperthyroidism was severe and occurred after at least 2 years of treatment with amiodarone. In one of two patients in whom it was measured the serum concentration of interleukin-6 was raised, as has been previously shown (SEDA-19, 193). In two cases the hyperthyroidism was refractory to treatment with propylthiouracil, lithium, and dexamethasone; in these cases thyroidectomy was required. Two patients responded to propylthiouracil, lithium, and dexamethasone, and one responded to carbimazole.

Amiodarone-induced hyperthyroidism can occasionally be fatal (141).

- A 62-year-old man took amiodarone for 2 years and developed hyperthyroidism; carbimazole 40 mg/day, prednisolone, lithium, and colestyramine were ineffective and he died with hepatic encephalopathy and multiorgan failure.
- A 55-year-old man took amiodarone for 4 years and developed hyperthyroidism; carbimazole 60 mg/day, prednisolone, and lithium were ineffective and he died with septicemia and multiorgan failure.

In three other cases reported in the same paper, severe hyperthyroidism responded severally to treatment with carbimazole, carbimazole plus lithium, or propylthiouracil. In one case amiodarone therapy was restarted after prophylactic subtotal thyroidectomy.

Diagnosis

The diagnosis of amiodarone-induced thyroid disorders can be difficult, because amiodarone often alters thyroid function tests without disturbing clinical thyroid function. Although radio-iodine uptake by the thyroid gland is not helpful in making a diagnosis, the discharge of iodine from the thyroid gland in response to perchlorate is reduced in patients with hypothyroidism (142). The test is not abnormal in patients with hyperthyroidism and it is not clear how helpful it is in hypothyroidism.

Since the measurement of serum T3 and T4 concentrations may not be helpful, an alternative would be to measure metabolic status. Measurement of the serum concentration of co-enzyme Q10 may distinguish patients with clinical thyroid dysfunction from those who simply have abnormalities of thyroid function tests (143), but the value of this test remains to be established.

Color-flow Doppler sonography of the thyroid and measurement of serum interleukin-6 (IL-6) have been studied as diagnostic tools in a retrospective case-note study of patients with amiodarone-associated hyperthyroidism (144). There were 37 patients with amiodarone-associated hyperthyroidism (mean age 65, range 20–86 years), and 25 underwent color-flow Doppler sonography. Of those, 10 were classified as type 1 (based on increased vascularity) and 10 as type 2 (based on patchy or reduced vascularity); 5 were indeterminate. In those with type 1 hyperthyroidism, free serum thyroxine tended to be lower (52 versus 75 pmol/l), free serum triiodothyronine was lower (8.8 versus 16 pmol/l), the cumulative amiodarone dose was lower (66 versus 186 g), and less prednisolone was used (because the diagnosis of type 1 disease encouraged steroid withdrawal); however, carbimazole doses were not different and the time to euthyroidism was the same in the two groups (81 versus 88 days). IL-6 was raised in two patients with type 1 and in one patient with type 2 hyperthyroidism. The authors proposed that color-flow Doppler sonography could be used to distinguish the two subtypes, confirming an earlier report (145), but that IL-6 measurement was unhelpful.

Management

The treatment of amiodarone-induced hyperthyroidism is difficult. It often does not respond to conventional therapy with carbimazole, methimazole, or radio-iodine. However, corticosteroids and the combination of methimazole with potassium perchlorate have been reported to be effective (146), even if amiodarone is continued (147). Other regimens that have been used include combinations of corticosteroids with carbimazole (148), corticosteroids and benzylthiouracil (149), or propylthiouracil (SEDA-15, 170). Potassium perchlorate has also been used (SEDA-21, 199). Other forms of treatment that have been successful have been plasma exchange and in very severe cases subtotal thyroidectomy (150) or total thyroidectomy (SEDA-15, 170) (SEDA-17, 220) (151).

It has been suggested that potassium perchlorate should be used in the treatment of type 1 hyperthyroidism and glucocorticoids in the treatment of type 2 (SEDA-21, 199). Since hypothyroidism due to amiodarone tends to occur in areas in which there is sufficient iodine in the diet, it has been hypothesized that an iodinated organic inhibitor of hormone synthesis is formed and that the formation of this inhibitor is inhibited by perchlorate to a greater extent than thyroid hormone iodination is inhibited, since the iodinated lipids that are thought to be inhibitors require about 10 times more iodide than the hormone. However, there is a high risk of recurrence after treatment with potassium perchlorate, and it can cause serious adverse effects (SED-13, 1281).

When five patients with type 2 amiodarone-induced hyperthyroidism were treated with a combination of an oral cholecystographic agent (sodium ipodate or sodium iopanoate, which are rich in iodine and potent inhibitors of 5′-deiodinase) plus a thionamide (propylthiouracil or methimazole) after amiodarone withdrawal, all improved substantially within a few days and became euthyroid or hypothyroid

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in 15–31 weeks (152). Four of the five became hypothyroid and required long-term treatment with levothyroxine.

In another study, three patients with type 1 disease, two of whom had not responded to methimazole plus perchlorate, were successfully treated with a short course of iopanoic acid 1 g/day, resulting in a marked reduction in the peripheral conversion of T4 to T3 (153). Euthyroidism was restored in 7–12 days, allowing uneventful thyroidectomy. The patients were then treated with levothyroxine for hypothyroidism and amiodarone was safely restarted. The authors suggested that iopanoic acid is the drug of choice for rapid restoration of normal thyroid function before thyroidectomy in patients with drug-resistant type 1 amiodarone-induced hyperthyroidism.

However, others have suggested that the differentiation of amiodarone-induced hyperthyroidism into two types is not helpful in determining suitable therapy (154). Of 28 consecutive patients there was spontaneous resolution of hyperthyroidism in 5 and 23 received carbimazole alone as first-line therapy. Long-term euthyroidism was achieved in 11, 5 became hypothyroid and required long-term thyroxine, and 5 relapsed after withdrawal of carbimazole and became euthyroid with either long-term carbimazole ($n = 3$) or radioiodine ($n = 2$). Four were intolerant of carbimazole and received propylthiouracil, with good effect in three. One was resistant to thionamides and responded to corticosteroids. There was no difference in presentation or outcome between those in whom amiodarone was continued or stopped or between possible type 1 or type 2 disease (defined clinically and by serum IL-6 measurement). The authors concluded that continuing amiodarone has no adverse effect on the response to treatment of hyperthyroidism and that first-line therapy with a thionamide alone, whatever the type of disease, is appropriate in iodine-replete areas, thus avoiding potential complications of other drugs. However, it is not clear how good their differentiation of types 1 and 2 disease was. A previous prospective study in 24 patients showed that differentiation predicted response to treatment (155).

It is generally recommended that amiodarone should be withdrawn. However, in some cases (156,157) worsening of thyrotoxic symptoms and heart function has been reported after withdrawal of amiodarone. When withdrawal of amiodarone is not an option, near-total thyroidectomy may be preferred. If surgery is not possible plasmapheresis can be helpful.

The use of local anesthesia for total thyroidectomy in patients with amiodarone-induced hyperthyroidism and cardiac impairment has been reviewed in the context of six patients (158).

Hypothyroidism

Amiodarone-induced hypothyroidism has been reviewed in the light of a case of 74-year-old woman (148).

In a nested case-control analysis of 5522 patients with a first prescription for an antidysrhythmic drug and no previous use of thyroid drugs, cases were defined as all patients who had started a thyroid-mimetic or antithyroid drug no sooner than 3 months after the start of an antidysrhythmic drug and controls were patients with a comparable follow-up period who had not taken any thyroid drugs during the observation period (132). There were 123 patients who had started antithyroid drugs and 96 who had started a thyroid-mimetic drug. In users of amiodarone there was an adjusted odds ratios of 6.6 (3.9, 11) for hypothyroidism compared with users of other antidysrhythmic drugs.

The risk of amiodarone-induced hypothyroidism may be greater in patients who have pre-existing thyroid autoimmune disease (159). There is some evidence that the risk of hypothyroidism due to amiodarone is increased in elderly patients (160), but the data are not conclusive.

In amiodarone-induced hypothyroidism the simplest method of treatment is to continue with amiodarone and to add thyroxine as required.

Metabolism

Amiodarone can cause altered serum lipid concentrations (161). Serum cholesterol rises, as can blood glucose and serum triglyceride concentrations. The mechanisms of these effects are not known; nor is it known to what extent they are due to changes in thyroid function.

Hematologic

Although phospholipid inclusion bodies commonly occur in the neutrophils of patients taking amiodarone (162), adverse hematological effects have rarely been attributed to amiodarone. However, there have been reports of thrombocytopenia (163) and of impaired platelet aggregation, associated with gingival bleeding and ecchymoses of the legs (164). Coombs'-positive hemolytic anemia has also been reported (165).

Bone marrow granulomata have rarely been reported in patients taking amiodarone (166).

- A 53-year-old woman developed leukoerythroblastosis with giant thrombocytes in the peripheral blood and was subsequently given amiodarone. The bone marrow became hypocellular with atypical megakaryocytes and several granulomata.
- A 78-year-old woman with a raised erythrocyte sedimentation rate, a mild anemia, and a polyclonal gammopathy on serum immunoelectrophoresis. The bone marrow became hypocellular with atypical megakaryocytes and several granulomata.

In the first case amiodarone was given after the onset of the peripheral blood film abnormalities and the only change in the bone marrow was the occurrence of the granulomata. The authors proposed that the granulomata had occurred because of phospholipid accumulation.

- Bone marrow biopsy in a patient taking amiodarone 100 mg/day showed multiple non-caseating epithelioid granulomata, which resolved 3 months after the withdrawal of amiodarone in a 67-year-old man (167). Similar granulomas were found in a 77-year-old woman who had taken amiodarone 100 mg/day for many years and had thrombocytopenia; the bone marrow contained an increased number of megakaryocytes. Her platelet count normalized 1 month after

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amiodarone had been withdrawn, and after 3 months there were fewer granulomata in the bone marrow.

- A 76-year-old man, who had taken amiodarone for an unspecified time, developed a monoclonal gammopathy with bone marrow granulomata (168). After another 2 years he developed hepatic granulomata and the amiodarone was withdrawn. The bone marrow granulomata resolved within a few months. Infections were excluded and there was no evidence of sarcoidosis.

The mechanism of this effect is unknown.

Liver

Amiodarone often causes rises in the serum activities of aspartate transaminase and lactate dehydrogenase to about twice normal, without changes in alkaline phosphatase or bilirubin, and without clinical evidence of liver dysfunction (169). Changes of this kind were originally reported to be transient and dose-related, returning to normal when the dose was reduced (170).

However, amiodarone can also cause liver damage, which usually takes the form of a hepatitis associated with phospholipid deposition, and there can be changes similar to those of alcoholic hepatitis (171–173). In some cases there is progression of cirrhosis (174). The risk of hepatic impairment in patients taking amiodarone is not known, but relatively severe liver damage can occur even in the absence of symptoms and with only minor associated changes in liver function tests.

- A 40-year-old man who had taken amiodarone 400 mg/day for 6 weeks developed an acute hepatitis accompanied by clusters of light brown granular cells, which were identified as macrophages (175). There were phospholipid inclusions in the macrophages and hepatocytes.

The authors proposed that the granular macrophages represented an early marker of amiodarone-induced hepatotoxicity. Their unusual color was attributed to the deposition of a combination of phospholipid, lipofuscin, and bile breakdown products.

Other forms of liver damage that have been reported include a syndrome resembling Reye's syndrome (176). Severe hepatitis at low dosage and thought to be immunologically based has been described (177).

Chronic liver damage with amiodarone is much more common than acute hepatitis, but cholestatic jaundice is one of the relatively rare presentations (SEDA-19, 193) (178,179).

- An 84-year-old woman, who had taken amiodarone 400 mg/day for 4–5 years, developed weakness, fatigue, anorexia, and abnormal liver function tests, with an aspartate transaminase activity of 234 U/l, alanine transaminase 154 U/l, and alkaline phosphatase 316 U/l (180). She had a normal serum bilirubin and the serum concentrations of amiodarone and desethylamiodarone were both within the usual target ranges. Apart from gallstones, endoscopic retrograde cholangiography and abdominal ultrasound showed a normal biliary tree. After withdrawal of amiodarone her liver function tests improved, but 4 months later she developed a rapidly rising serum bilirubin concentration (142 mmol/l), her serum albumin concentration fell to 30 g/l, and her serum cholesterol concentration was high (11 mmol/l). She had bilirubin and urobilinogen in the urine and there was no evidence of viral or immunological hepatitis. Abdominal ultrasonography was normal, as was a liver scan, but a CT scan of the abdomen showed a diffusely hyperdense liver consistent with the effects of amiodarone. Liver biopsy also showed findings consistent with amiodarone-induced cholestatic liver damage, with distorted architecture, portal fibrosis, pericellular sinusoidal fibrosis, and focally irregular lobular sinusoidal fibrosis, but without bridging fibrosis or cirrhosis. There was ductal proliferation and a mild lymphocytic infiltrate but no cholangitis. Electron microscopy showed lamella inclusions compatible with phospholipidosis.

If amiodarone was responsible in this case, it is hard to reconcile the improvement after amiodarone withdrawal with the cholestasis that occurred 4 months later. The patient was also taking felodipine, furosemide, potassium chloride, aspirin (500 mg/day), and cisapride, but the authors argued that the changes were not consistent with liver damage due to any of those drugs. In particular they thought that the felodipine was unlikely to have caused cholestasis, although that has been previously reported, because of the presence of Mallory bodies in the liver biopsy; however, Mallory bodies have previously been reported with felodipine, and although cholestatic liver injury caused by felodipine has not been reported before, that seems as likely a candidate in this case as amiodarone.

Acute hepatitis with liver failure can occur after intravenous administration and may be due to the solvent, polysorbate (SEDA-14, 149) (SEDA-16, 178) (SEDA-18, 202) (SEDA-22, 206) (181).

- A 69-year-old man was given amiodarone intravenously 1500 mg for multiple coupled ventricular extra beats and 24 hours later developed acute hepatitis, with a 50-fold increase in serum transaminase activities and simultaneous increases in lactate dehydrogenase, gamma-glutamyl transferase, bilirubin, and prothrombin time; there was a moderate leukocytosis and mild renal insufficiency (182). No further amiodarone was given and there was full recovery within 2 weeks. Other causes of acute hepatitis were excluded.

The mechanism of this effect is not known, but the histology includes Mallory bodies, steatosis, intralobular inflammatory infiltrates, and fibrosis; electron microscopy suggests phospholipidosis.

It has been suggested that liver injury due to amiodarone is either due to a direct biochemical action or perhaps metabolic idiosyncrasy. Because there have been cases in which oral administration has not led to a recurrence, it has also been suggested that the vehicle in which amiodarone is usually dissolved, polysorbate (Tween) 80, is responsible rather than the amiodarone itself (SEDA-18, 202).

Pancreas

There have been two reported cases of pancreatitis and in one the patient died of progressive liver failure (183,184). Whether this was a direct effect of amiodarone is unclear.

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Urinary tract

Increases in serum creatinine concentrations, correlated with serum amiodarone concentrations, have been reported (185).

Skin

Amiodarone commonly causes phototoxicity reactions (186,187). The risk of phototoxicity increases with the duration of the exposure. Window glass and sun screens do not give protection, although zinc or titanium oxide formulations and narrow band UVB photo therapy can help (188–190). For most patients this adverse effect will be no more than a nuisance, and the benefit of therapy may be worthwhile. However, in a few cases treatment may have to be withdrawn. Histological examination of skin biopsies shows intracytoplasmic inclusions of phospholipids (191). There has been a single report of a severe case of photosensitivity in conjunction with a syndrome resembling porphyria cutanea tarda, resulting in bullous lesions (192).

Amiodarone can cause a cosmetically annoying bluish pigmentation of the skin (SEDA-15, 171) (SEDA-22, 207) (SEDA-23, 199) (193).

- A 54-year-old man who took the drug for 1 year developed bluish-gray discoloration of the face (194). The discoloration almost completely resolved within 9 months of withdrawal.
- A 55-year-old woman who had taken amiodarone 250 mg/day for about 10 years developed bluish-gray discoloration of the face (195). The pigmentation responded to treatment with a Q-switched ruby laser at an energy of 8 J/cm^2 and a wave length of 694 mm.

The authors suggested that the ruby laser had damaged pigment-containing cells. However, the amiodarone was continued, so presumably the laser also destroyed lipofuscin in situ.

- A 69-year-old white man who had taken amiodarone 400 mg/day for 3 years developed blue–gray discoloration of the face and other exposed areas (196). Areas that had been protected from the sun (the forehead by a broad-brimmed hat and the skin under his wrist watch) were not affected.
- A 70-year-old man developed grey–blue pigmentation on sun-exposed areas of his skin after taking amiodarone for 10 years and minocycline for 4 years (197).

Minocycline can also cause skin pigmentation and it is not clear in this last case what the interaction of amiodarone with minocycline was.

Grey–blue discoloration of the skin during amiodarone therapy has been presumed to be due to lipofucsin deposition. However, it has also been suggested that amiodarone may block the maturation of melanosomes, in view of a case of discoloration associated with a reduced number of mature melanosomes and an increased number of premelanosomes in sun-exposed areas of the skin, but normal numbers in non-exposed areas (198).

It has been suggested that the skin and mucosal toxicity of amiodarone may be enhanced by radiotherapy (SEDA-16, 178) (SEDA-17, 221). However, in a retrospective review of 10 patients who took amiodarone when having external beam radiation therapy there were no unexpected acute sequelae (199).

Other skin reactions that have been reported include iododerma (200), erythema nodosum, psoriasis (201), and exfoliative dermatitis (202).

Amiodarone can increase the risk of mucosal and skin toxicity due to radiotherapy and rarely causes hair loss (SEDA-17, 221) and vasculitis (203).

The severe form of erythema multiforme known as toxic epidermal necrolysis has rarely been attributed to amiodarone (204).

- A 71-year-old woman, who had taken amiodarone 200 mg/day for 3 months and diltiazem for 8 months, developed extensive erythema, blistering, and erosions affecting 50% of the body surface area, with a maculopapular rash on the limbs (205). She developed bilateral pneumonia and septicemia and died after 7 days.

Musculoskeletal

A proximal myopathy has occasionally been reported in patients taking amiodarone (69) and there has been a report of an acute necrotizing myopathy (206).

Sexual function

Epididymitis has been reported in patients taking high dosages of amiodarone, resolving with dosage reduction or withdrawal (SEDA-18, 203).

Reproductive system

Non-infective epididymitis has occasionally been reported in patients taking amiodarone (SEDA-10, 148) (SEDA-18, 203).

- A 25-year-old man who had taken amiodarone 200 mg bd for 1 year developed epididymitis, which resolved within 3 months of withdrawal of amiodarone and recurred within 2 months of its reintroduction (207).

This case was unusual in that it involved both testes. The mechanism of this effect is not known, but it has been reported to be dose-dependent, although anti-amiodarone antibodies have also been reported (208). The incidence is not known, but has been reported to be as high as 11%. The author of one very brief report (209) claimed to have seen 20 cases of epididymitis, some of which were bilateral, since the late 1980s. He claimed that withdrawal produced dramatic resolution of symptoms within 10–20 days, and that amiodarone in a dose of 200 mg/day did not usually cause symptoms, even in patients who had had epididymitis at higher dosages.

Immunologic

Lupus-like syndrome has rarely been attributed to amiodarone.

- A 71-year-old woman, who had been taking amiodarone 200 mg bd for 2 years, developed malaise, intermittent fever, arthralgia, and weight loss (210). She had a malar rash and hypoventilation at both lung bases. Her erythrocyte sedimentation rate was markedly raised (90 mm/hour), there was a mild normochromic

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normocytic anemia (10 g/dl), a slight lymphopenia, and otherwise normal routine tests. Her rheumatoid factor was raised in a titer of 1:320, and circulating complexes of IgG-C1q were positive. Antinuclear antibody was positive (1:640), but all other antibodies were negative. There was progressive improvement on withdrawal of amiodarone and all the biochemical tests returned to normal.

- A 59-year-old man, who had taken amiodarone 200 mg/day for 2 years, developed fever, pleuritic chest pain, dyspnea at rest, a non-productive cough, malaise, and joint pains (211). He had a verrucous endocarditis and a pleuropericardial effusion. He had raised titers of antinuclear antibodies (1:320) with anti-Ro specificity. Serum complement was normal and there were no circulating immune complexes, no cryoglobulins, and no anti-dsDNA, anti-La, anti-U1 ribonucleoprotein, anti-Sm, anti-Sc1, 70, anti-Jo 1, antihistone, antiphospholipid, anticentromere, anticardiolipin, or anticytoplasmic antibodies. Within 7 days of withdrawal of amiodarone the signs and symptoms started to resolve, and he recovered fully with the addition of prednisolone.

Angioedema has been reported in a 70-year-old woman who had taken amiodarone 200 mg/day for 8 years (212). The amiodarone was withdrawn and the symptoms disappeared. Rechallenge produced facial flush and facial angioedema within 20 minutes of a 200 mg dose.

Death

The effect of intravenous and oral amiodarone on morbidity and mortality has been studied in 1073 patients during the first hours after the onset of acute myocardial infarction (213). The patients were randomized to receive amiodarone or placebo for 6 months. The interim analysis showed an increased mortality, albeit not significant, with high-dose amiodarone (16 versus 10%) and the dose was therefore reduced from 400 to 200 mg/day. Low-dose amiodarone was associated with a reduced death rate (6.6 versus 9.9%). There were non-fatal adverse events in 108 patients taking amiodarone and 73 taking placebo. The only non-fatal adverse effect that occurred significantly more often with amiodarone was hypotension during the initial intravenous loading phase, a well-known effect. In the context of this study, it should be remembered that in several previous studies amiodarone has been shown to reduce mortality after myocardial infarction (SEDA-23, 198) (SEDA-24, 206) (214).

Second-Generation Effects

Teratogenicity

There are no major teratogenic effects of amiodarone (215).

Fetotoxicity

Exposure to amiodarone in utero has only occasionally been described.

Cardiovascular

There have been reports of sinus bradycardia (SEDA-8, 179) (SEDA-20, 176) (216,217) and prolongation of the QT interval (215).

Nervous system

Congenital nystagmus has been described (SEDA-20, 176).

Psychological

In one child there was evidence of mental delay, hypotonia, hypertelorism, and micrognathia (SEDA-20, 176), although the authors thought that the link between amiodarone and neurotoxicity was speculative. However, there has also been a retrospective study of 10 children who were exposed to amiodarone during pregnancy, compared with matched controls (218). There was no change in IQ score, but the children who had been exposed to amiodarone had impaired expressive language skills and one child had global developmental delay. However, most of the mothers were not concerned about their children's development, and so any effect of amiodarone on neurological development was probably small. One child had transient neonatal hypothyroidism, which responded to a short course of thyroxine; another had mild transient neonatal hyperthyroidism; in neither case was there any difference in development from the other children who had been exposed to amiodarone. One child was born with a congenital jerk nystagmus and had relatively poor reading and comprehension skills for both words and passages, low scores on several of the verbal subtests of the WISC-R test for information, arithmetic, and vocabulary, and below average spelling.

Endocrine

The major adverse effect on the fetus is altered thyroid function (SEDA-13, 141) (SEDA-14, 149) (SEDA-19, 194) (SEDA-20, 176). There have been individual reports of neonatal hyperthyroxinemia (219), goiter (216), and hypothyroidism (220). In the patient with goiter there was associated hypotonia, bradycardia, large fontanelles, and macroglossia (216).

Two neonates who had been given intravenous amiodarone as fetuses at 26 and 29 weeks and whose mothers had also taken it orally developed hypothyroidism (221). The authors suggested that low dietary iodine intake by the mothers may have contributed, by enhancing the Wolff–Chaikoff effect.

Susceptibility Factors

Age

The safety and efficacy of amiodarone for supraventricular tachycardia have been studied in 50 infants (mean age 1.0 month, 35 boys) (222). They had congenital heart disease (24%), congestive heart failure (36%), or ventricular dysfunction (44%). Six, who were critically ill, received a loading dose of intravenous amiodarone 5 mg/kg over 1 hour, and all took 20 mg/kg/day orally for 7–10 days, followed by 100 mg/day; if this failed to control the dysrhythmia, oral propranolol (2 mg/kg/day) was added. Follow-up was for an average of 16 months. Rhythm control was achieved in all patients. Growth and

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development were normal. The higher dose of amiodarone was associated with an increase in the QT_c interval to over 0.44 seconds, but there were no dysrhythmias. Two infants had hypotension during intravenous loading, as has previously been reported in infants (SEDA-19, 194). Aspartate transaminase and alanine transaminase activities and thyrotropin (TSH) concentrations all increased, but remained within their reference ranges. There were no adverse effects that necessitated drug withdrawal.

Young patients are more likely to develop adverse effects in the skin (223).

In children under 10 years of age the risk of adverse effects is less than in adults (224,225). It is not clear whether older children are at greater or lesser risks of adverse effects than are adults.

The safety of antidysrhythmic drugs in children has not been thoroughly studied. However, the risk of prolongation of the QT interval seems to be considerably less than that in adults (226), although it has been reported with quinidine, disopyramide, amiodarone, sotalol, and diphemanil.

Other features of the patient

Amiodarone-induced liver damage is more common in those with reduced left ventricular function (223).

Anesthesia and surgery

It has been reported that there is an increased risk of adverse reactions to amiodarone in patients undergoing anesthesia (SEDA-15, 171). However, in a retrospective survey of 12 patients who underwent anesthesia for urgent thyroidectomy due to amiodarone there were no anesthetic complications or deaths (227).

There is an increased risk of some of the adverse effects of amiodarone (including dysfunction of the liver and lungs) in patients who have had or who are having surgery (228). In addition the perioperative mortality in these patients is higher than in controls (229). The factors that increase the risks of amiodarone-associated adverse cardiovascular effects during surgery (230) include pre-existing ventricular dysfunction, too rapid a rate of intravenous infusion, hypocalcemia, and an interaction between amiodarone and both the general anesthetics used and other drugs with negative inotropic or chronotropic effects. It has therefore been recommended (230) that serum concentrations of calcium, amiodarone, and digoxin should be within the reference or target ranges before operation, and that other drugs with negative inotropic or chronotropic effects should be withdrawn before surgery.

The use of amiodarone in the prevention of atrial fibrillation after cardiac surgery has been reviewed (231). When an intravenous loading dose of amiodarone was used, bradycardia was a common adverse effect but was rarely severe enough to warrant withdrawal. When only oral amiodarone was used there were no serious adverse reactions.

Drug Administration

Drug formulations

The steady-state plasma concentrations of amiodarone and desethylamiodarone in 77 patients taking two different formulations, a new generic formulation and Cordarone, were comparable (232).

Drug administration route

In contrast to its effects during oral administration, the therapeutic and short-term unwanted effects of amiodarone during intravenous administration arise within minutes or hours (2). The reason for this is not clear; plasma concentrations after single oral and intravenous doses of 400 mg are very similar (2), but that does not rule out a pharmacokinetic explanation for the paradox. The possible role of the solvent used in the intravenous formulation, polysorbate (Tween) 80, has not been fully elucidated. Amiodarone certainly has different electrophysiological effects when it is given intravenously. For example, intravenous amiodarone prolongs the AH interval, while oral amiodarone prolongs atrial and ventricular refractory periods and the HV interval (233). Furthermore, the blocking effects of amiodarone on sodium and calcium channels and its beta-adrenoceptor blocking action occur earlier than its Class III action (234). An anecdotal report of torsade de pointes after both intravenous and oral administration of amiodarone on different occasions has underlined this difference.

- A 70-year-old woman with dilated cardiomyopathy, ventricular tachydysrhythmia, and a QT_c interval of 0.49 seconds was given intravenous amiodarone 240 mg over 15 minutes, and 30 minutes later developed a junctional escape rhythm (48/minute) with QT_c prolongation to 0.68 seconds; 8 hours later she developed torsade de pointes (235). A few years later she was given oral amiodarone 100 mg/day and 7 weeks later presented with congestive heart failure. Her QT_c interval was prolonged (0.50 seconds) and increased further to 0.64 seconds after the addition of dopamine 3 micrograms/kg/minute; torsade de pointes again developed. Amiodarone was withdrawn and the QT_c interval shortened, but she continued to have recurrent episodes of sustained ventricular tachycardia.

The authors suggested that torsade de pointes induced by intravenous amiodarone depended on heart rate during a bout of bradycardia, while that after oral amiodarone depended on increased sympathetic nervous system activity, and that therefore different electrophysiological mechanisms had been at play. However, it is by no means clear from their description of this case that that was so. They did not report plasma concentrations of amiodarone or desethylamiodarone, its active metabolite.

After rapid intravenous administration hypotension, shock, and atrioventricular block can occur and can be fatal (2). The rate of infusion should not exceed 5 mg/minute. Other adverse effects reported during intravenous infusion include sinus bradycardia (236), facial flushing, and thrombophlebitis (236–239). The risk of this last complication can be reduced by infusing the drug into as large a vein as possible and preferably via a central venous catheter, or perhaps by using a very dilute solution of the drug (240).

The use of intravenous amiodarone for atrial fibrillation has been reviewed (241). The most commonly reported adverse effects in all studies have been hypotension and bradycardia. Other effects include worsening of heart failure, thrombophlebitis at the site of infusion, non-sustained ventricular tachycardia, facial rash, and nightmares.

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A few studies have also reported the effects and adverse effects of intravenous amiodarone in patients with atrial fibrillation. Of 67 patients with atrial fibrillation, of whom 33 received amiodarone and 34 received placebo, conversion to sinus rhythm occurred in 16 of the patients who received amiodarone and in none of those who received placebo (242). In five patients the systolic blood pressure fell significantly during the first trial of intravenous drug administration. There were no cardiac dysrhythmias. Thrombophlebitis occurred in 12 patients who received amiodarone.

In a randomized, placebo-controlled trial of 100 patients with paroxysmal atrial fibrillation, intravenous amiodarone 125 mg/hour was compared with placebo (243). There were no serious adverse effects; five patients given amiodarone developed significant sinus bradycardia, in all cases after conversion to sinus rhythm. In this series there were no significant episodes of hypotension. Thrombophlebitis occurred in eight patients who received amiodarone.

Drug overdose

The features of amiodarone overdose and its management have been reviewed (244).

- There has been a report of acute self-poisoning with 8 g of amiodarone orally (245). Initially the only abnormal physical sign was profuse sweating; the electrocardiogram showed sinus rhythm with a normal QT_c interval and the blood pressure was normal. No active measures were taken. The QT_c interval subsequently lengthened on the third and fourth days after overdosage, and there was sinus bradycardia between the second and fifth days. Over 3 months of follow-up there were no effects on thyroid or liver function and no evidence of lung, skin, or corneal involvement.

Drug–Drug Interactions

Anesthetics

The risks of cardiovascular adverse effects in patients undergoing surgery may be partly related to an interaction of amiodarone with anesthetics, either directly or via some interaction with the catecholamines that are released during anesthesia (246). The risk of hypotension during cardiopulmonary bypass in patients taking amiodarone can be increased by the concurrent administration of an ACE inhibitor. There is a high incidence of lung complications when patients treated with amiodarone are ventilated with 100% oxygen, including acute adult respiratory distress syndrome.

Beta-blockers

The combination of amiodarone with beta-adrenoceptor antagonists can be beneficial in the treatment of refractory ventricular tachycardia, especially when low doses of the beta-blockers are used. However, there have also been reports of adverse interactions in these circumstances, and various correspondents have commented on the possibility that beta-blockers may enhance the effects of amiodarone in reducing mortality in patients who have had a myocardial infarction or are in heart failure (190,247,248).

In a systematic review, the beneficial interaction has been confirmed (249). Four groups of patients who had been studied in EMIAT and CAMIAT (SEDA-21, 198) were defined: patients who had taken amiodarone plus beta-blockers, patients who had taken beta-blockers or amiodarone alone, and patients who had taken neither. The relative risks for all-cause mortality and all forms of cardiac death or resuscitated cardiac arrest were lower in the patients who had taken amiodarone plus beta-blockers than in the other three groups. The results of this post hoc analysis should be regarded with caution, but in view of previous similar reports they are suggestive of a beneficial interaction of amiodarone with beta-blockers in patients who have had a previous myocardial infarction. The interaction was statistically significant for cardiac deaths and for dysrhythmic deaths or resuscitated cardiac arrest. In all other cases the relative risk was reduced, although not significantly. The risk was not affected by heart rate. This interaction has been reviewed (250).

Budesonide

The corticosteroid budesonide undergoes a high degree of first-pass elimination in the liver after oral administration, and therefore causes few systemic adverse effects. It was therefore surprising that Cushing's syndrome occurred in an 81-year-old man taking oral budesonide 9 mg/day and amiodarone 100 mg/day (251). When amiodarone was withdrawn the clinical effects of Cushing's syndrome disappeared. The authors suggested that amiodarone had inhibited the metabolism of budesonide by hepatic CYP3A.

Ciclosporin

Amiodarone can increase the blood concentrations of ciclosporin and thus impair renal function.

- A 66-year-old developed a ventricular tachycardia after kidney transplantation and was given amiodarone. Maintenance immunosuppression included prednisone, azathioprine, and ciclosporin. Ciclosporin concentrations before amiodarone initiation were stable (range 100–150 ng/ml). During amiodarone therapy, the ciclosporin concentration increased more than two-fold.

The authors proposed that changes in protein binding or metabolism might have explained this interaction.

Class I antidysrhythmic drugs

Amiodarone can potentiate the dysrhythmogenic actions of some Class I antidysrhythmic drugs (SEDA-18, 203), particularly because of the risk of QT interval prolongation (SEDA-19, 194). In 26 patients taking mexiletine plus amiodarone for 1 month and 155 taking mexiletine alone, there was no significant difference in the apparent oral clearance of mexiletine (252). However, the lack of a pharmacokinetic interaction does not reduce the risk that dangerous QT interval prolongation may occur with a combination such as this.

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Cyclophosphamide

Both amiodarone and cyclophosphamide can cause lung damage.

- Interstitial pneumonitis has been reported in a 59-year-old man, who had taken amiodarone for 18 months, 18 days after a single dose of cyclophosphamide; 1 year before he had also received six cycles of chemotherapy containing cyclophosphamide, vincristine, and prednisone, followed by four cycles of cisplatin, cytarabine, and dexamethasone (253).

The authors suggested that the lung damage had been due to the cyclophosphamide, enhanced by the presence of amiodarone, but in view of the fact that previous similar exposure on six occasions had not resulted in the same effect, it is perhaps more likely that this was a long-term adverse effect of amiodarone alone. The presence of foamy histiocytes in the lung biopsy was consistent with this interpretation (SEDA-15, 168). It is true, however, that lung damage due to amiodarone is usually of a more insidious onset than was reported in this case, although a more rapid onset can occur in patients who are given high concentrations of inspired oxygen. On the other hand, lung damage has occasionally been reported to occur rapidly (71).

Digoxin

Amiodarone reduces both the renal and non-renal clearances of digoxin and prolongs its half-life, without changing its apparent volume of distribution. It has also been suggested that amiodarone increases the extent of absorption of digoxin (SEDA-10, 144) (SEDA-12, 150). Digoxin dosages should be halved as soon as amiodarone is introduced. This interaction may also occur with acetyldigitoxin (254).

Diltiazem

Sinus arrest with hypotension has been reported in a patient with a congestive cardiomyopathy when diltiazem was added to amiodarone (255).

Indinavir

Indinavir inhibits CYP3A4, which is responsible for the de-ethylation of amiodarone to desethylamiodarone.

- A 38-year-old man, who had taken amiodarone 200 mg/day for more than 6 months, was given postexposure prophylaxis for HIV infection after a needle injury; this included zidovudine, lamivudine, and indinavir (256). During the 4 weeks of therapy his serum amiodarone concentration rose from 0.9 to 1.3 mg/l, with only a small rise in the serum concentration of desethylamiodarone from 0.4 to 0.5 mg/l. After withdrawal of the prophylactic therapy the plasma amiodarone concentration gradually fell to the pretreatment value, and there was no further change in the concentration of desethylamiodarone.

No adverse effects of this interaction were reported.

Meglumine antimoniate

A pharmacodynamic interaction has been described between amiodarone and meglumine antimoniate, both of which prolong the QT interval; the interaction resulted in torsade de pointes (257).

- A 73-year-old man with visceral leishmaniasis was given meglumine antimoniate intramuscularly 75 mg/kg/day. At that time his QT_c interval was normal at 0.42 seconds. Three weeks later his QT_c interval was prolonged to 0.64 seconds and he was given methyldigoxin 0.4 mg and amiodarone 450 mg intravenously over 8.25 hours; 12 hours later he had a cardiac arrest with torsade de pointes, which was cardioverted by two direct shocks of 300 J and lidocaine 100 mg in two bolus injections. Because he had frequent episodes of paroxysmal atrial fibrillation, he was given amiodarone 100 mg over the next 40 hours, and developed recurrent self-limiting episodes of torsade de pointes associated with QT_c interval prolongation, which responded to intravenous magnesium 1500 mg. After withdrawal of amiodarone there was no recurrence and a week later the QT_c interval was 0.48 seconds. The plasma potassium concentration was not abnormal in this case.

In view of this report it is probably wise to avoid coadministration of these two drugs.

Phenazone (antipyrine)

The clearance of phenazone (antipyrine) is reduced by amiodarone (258).

Phenytoin

Amiodarone increases the plasma concentrations of phenytoin, probably by inhibiting its metabolism (259,260), while phenytoin increases the metabolism of amiodarone and perhaps also of its metabolite desethylamiodarone (261).

Rifampicin

- In a 33-year-old woman taking amiodarone 400 mg/day the addition of rifampicin 600 mg/day resulted in paroxysms of atrial fibrillation and atrial flutter, with a very low serum amiodarone concentration and an undetectable concentration of desethylamiodarone (262). This was attributed to induction of the metabolism of amiodarone and desethylamiodarone, and after withdrawal of rifampicin the concentrations of the two compounds rose to within the target ranges.

This interaction has been demonstrated in human liver microsomes (263).

Warfarin

That amiodarone can potentiate the action of warfarin by inhibiting its metabolism is well known (SEDA-11, 156). However, potentiation of the action of warfarin has been attributed to amiodarone-induced thyrotoxicosis (264). A metabolic interaction in this case was unlikely, because the patient had taken both drugs together for 2 years before the increase in response to warfarin, coincident with the emergence of thyrotoxicosis.

In a study of this interaction in 43 patients who took both amiodarone and warfarin for at least 1 year, the interaction peaked at 7 weeks and the mean dosage of warfarin fell by 44% from 5.2 to 2.9 mg/day (265). The dosage of warfarin correlated inversely with the maintenance dose of

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amiodarone. There were minor bleeding episodes in five patients. The authors recommended reducing the daily warfarin dose by about 25, 30, 35, and 40% in patients taking amiodarone 100, 200, 300, and 400 mg/day respectively.

Interference with Diagnostic Tests

Serum creatinine

Amiodarone has been reported to cause a small and reversible increase in serum creatinine concentration (266). It is not clear whether this effect is due to true renal impairment, or to some effect on either the kinetics of creatinine or its measurement in the blood.

Thyroid function tests

Amiodarone causes altered thyroid function tests, with rises in serum concentrations of T4 and reverse T3 and a fall in serum T3 concentration (267). This is due to inhibition of the peripheral conversion of T4 to T3, causing preferential conversion to reverse T3. These changes can occur in the absence of symptomatic abnormalities of thyroid function.

Blood urea nitrogen

Amiodarone has also been reported to cause a small and reversible increase in blood urea nitrogen concentration (266). It is not clear whether this effect is due to true renal impairment, or to some effect on either the kinetics of urea or its measurement in the blood.

Diagnosis of Adverse Drug Reactions

The differences in the rates of onset of effects of amiodarone after oral and intravenous administration in the face of similar plasma concentrations suggest that there can be no simple relation between the plasma concentrations of amiodarone and its therapeutic effects. Matters are further complicated by metabolism of amiodarone to desethylamiodarone, which has pharmacological activity. However, evidence (2,268) suggests that a plasma amiodarone concentration of around 1.0–2.5 mg/ml is associated with a high likelihood of therapeutic efficacy in patients with dysrhythmias. However, adverse effects can still occur when the plasma concentration is within this range, and there is no clear limit to the concentration above which toxicity starts to become important. Similarly, the therapeutic range of concentrations for desethylamiodarone is unclear, although it has been suggested to be around 0.5–1.0 mg/ml (SEDA-10, 146).

In one careful study EC_{50} values for certain effects of amiodarone were calculated (269). The respective concentrations of amiodarone and desethylamiodarone that were associated with effects were as follows: reduction in heart rate 1.2 and 0.5 mg/ml; QT_c prolongation 2.6 and 1.4 mg/ml; corneal microdeposits 2.2 and 1.1 mg/ml.

Because amiodarone prolongs the QT_c interval, it has been suggested that this might be a useful measure of its efficacy. The percentage prolongation of the QT_c interval correlates well with both daily dose and the plasma and myocardial concentrations of amiodarone (270), although this is not a universal finding during long-term administration (237,271), and the QT_c interval is not prolonged after short-term intravenous use (2).

Since amiodarone inhibits the peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3), there is an increase in serum concentrations of reverse tri-iodothyronine (rT3). However, there have been conflicting results in studies of the relation between serum concentrations of rT3 and the therapeutic and adverse effects of amiodarone (SEDA-15, 172).

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Amiphenazole

General Information

Amiphenazole is a respiratory stimulant. It increases ventilation by accelerating the frequency at increased CO_2 partial pressures above 6 kPa (45 mmHg) (1).

Its adverse effects include restlessness, prolonged and forced expiration, nausea and vomiting, sweating, and skin reactions; the last include rashes (2), occasionally oral lichenoid eruptions (3), and ulceration (4). Muscle twitching and mental disorientation can also occur in the elderly. With large doses, convulsions can occur (5).

In a double-blind randomized study in 30 women in the recovery room a single intravenous bolus injection of amiphenazole 150 mg was compared with placebo; amiphenazole did not improve ventilation (6). However, in a double-blind study amiphenazole reversed respiratory depression and analgesia due to morphine (7).

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Amisulpride

See also Neuroleptic drugs

General Information

Amisulpride is an atypical antipsychotic drug, a benzamide derivative, which may have a low propensity to cause extrapyramidal symptoms (SEDA-22, 55).

Amisulpride 600–1200 mg/day for 3 months was effective and well tolerated in 445 patients with schizophrenia aged 18–45 years (1). During this time, 124 patients (28%) dropped out of the study; 21% reported adverse events, neurological (35%), psychiatric (15%), or endocrine (9.1%). Seven adverse events were assessed as serious: two suicides, two suicide attempts, one neuroleptic malignant syndrome, one somnolence, and one worsening of arteritis.

A lower dose of amisulpride (50 mg) has been tested in 20 healthy elderly volunteers (aged 65–79 years) (2). There were no serious adverse events, but one subject reported a moderate headache for 18 hours, a second subject vomited 9 hours after dosing, and a further subject complained of mild somnolence for 12 hours starting 4 hours after dosing; however, there were no extrapyramidal symptoms, clinically significant hemodynamic variations, or electrocardiographic abnormalities.

Comparisons with placebo and other antipsychotic drugs

In a randomized double-blind study, there were no differences in the numbers of patients with at least one adverse effect with amisulpride 100 mg (24%; $n = 18$), amisulpride 50 mg (25%; $n = 21$), or placebo (33%; $n = 27$) (3). Few patients had endocrine symptoms (2 out of 160 in the amisulpride groups).

Two narrative reviews of amisulpride have been published (4,5). The authors emphasized that amisulpride in low dosages (below 300 mg/day) causes a similar incidence of adverse effects to placebo; nevertheless, at higher dosages (400–1200 mg/day), the overall incidence of adverse events in those taking amisulpride was similar to that in patients taking haloperidol, flupenthixol, or risperidone. The most commonly reported adverse events associated with higher dosages of amisulpride were extrapyramidal

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symptoms, insomnia, hyperkinesia, anxiety, increased body weight, and agitation. The incidence of extrapyramidal symptoms was dose-related. In elderly people, amisulpride can cause hypotension and sedation. There are no systematic published data on efficacy in children aged under 15 years.

In an extensive review of 19 randomized studies for the Cochrane Library ($n = 2443$), most of the trials were small and of short duration (6). The data from four trials with 514 participants with predominantly negative symptoms suggested that low-dose amisulpride (up to 300 mg/day) was more acceptable than placebo ($n = 514$; RR = 0.6; 95% CI = 0.5, 0.8).

A meta-analysis of 10 randomized controlled clinical trials of amisulpride in "acutely ill patients" ($n = 1654$) has been published, supported in part by a grant from Sanofi-Synthélabo, the marketing authorization holder (7). Amisulpride was significantly better than conventional antipsychotic drugs by about 11 percentage points on the Brief Psychiatric Rating Scale. In four studies in patients with "persistent negative symptoms," amisulpride was significantly better than placebo ($n = 514$), but there was no significant difference between amisulpride and conventional drugs (only three trials; $n = 130$). Low doses of amisulpride (50–300 mg/day) were not associated with significantly more use of antiparkinsonian drugs than placebo ($n = 507$), and usual doses caused fewer extrapyramidal adverse effects than conventional antipsychotic drugs ($n = 1599$). In studies in acutely ill patients, significantly fewer patients taking amisulpride dropped out compared with patients taking conventional drugs, mainly owing to fewer adverse events; there were no significant differences in dropout rates between amisulpride and conventional antipsychotic drugs (three small studies).

Comparisons with antidepressants

Amisulpride has been compared with amitriptyline ($n = 250$; 6 months) (8) and with amineptine ($n = 323$; 3 months) in randomized double-blind trials in the treatment of dysthymia (9). In both trials, amisulpride was more efficacious than placebo but equal to amineptine and amitriptyline. Endocrine symptoms (such as galactorrhea and menstrual disorders) and weight gain were more frequent with amisulpride. There was galactorrhea in 8.4% and 11% respectively. In one of the studies (8), serious adverse events occurred in 13 of 165 patients taking amisulpride (15 events). Sudden death, probably secondary to myocardial infarction, occurred in a patient taking amisulpride 7 days after withdrawal. In the other cases, admission to hospital was required for fracture (two cases) and gastric pain, neuralgia, hyperglycemia, eczema, an injury, and an erythematous rash (one case each).

In a randomized, double-blind, multicenter trial for 8 weeks in 278 patients with depression, there were no differences in efficacy or tolerability between amisulpride 50 mg and SSRIs (10).

Organs and Systems

Cardiovascular

QT interval prolongation has been attributed to amisulpride.

- Sinus bradycardia and QT interval prolongation occurred in a 25-year-old man taking amisulpride 800 mg/day (11). The dosage of amisulpride was reduced to 600 mg/day and the electrocardiogram normalized within a few days.

Psychological, psychiatric

In a randomized, double-blind, crossover study in 21 healthy volunteers who took amisulpride 50 mg/day, amisulpride 400 mg/day, haloperidol 4 mg/day, or placebo, amisulpride 400 mg had several adverse effects on psychomotor performance and cognitive performance, similar to those of haloperidol, at the end of the 5-day course of treatment; however, there were no signs of mental disturbances on clinical rating scales or during a structured psychiatric interview (12).

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Amitriptylinoxide

See also Tricyclic antidepressants

General Information

Amitriptylinoxide, a metabolite of amitriptyline, has been compared with the parent drug (1). The antidepressant effects were comparable, but the metabolite was thought to have fewer adverse effects, especially cardiotoxic ones. This conclusion was based on the absence of cardiographic abnormalities in 15 patients, but this is a very small series on which to base such a conclusion.

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Amlodipine

See also Calcium channel blockers

General Information

Amlodipine is a long-acting dihydropyridine calcium channel blocker. It has an adverse effects profile similar to those of other dihydropyridines, but at a lower frequency (1). Along with felodipine (2), but unlike other calcium channel blockers, it may also be safer in severe chronic heart failure when there is concurrent angina or hypertension (3).

The effects of amlodipine and isosorbide-5-mononitrate for 3 weeks on exercise-induced myocardial stunning have been compared in a randomized, double-blind, crossover study in 24 patients with chronic stable angina and normal left ventricular function (4). Amlodipine attenuated stunning, evaluated by echocardiography, significantly more than isosorbide, without difference in anti-ischemic action or hemodynamics. Amlodipine was better tolerated than isosorbide, mainly because of a lower incidence of headache (4).

Vasodilatory calcium channel blockers have been reported to improve exercise tolerance in some preliminary studies. A multicenter, randomized, placebo-controlled trial was therefore performed in 437 patients with mild to moderate heart failure to assess the effects of amlodipine 10 mg/day in addition to standard therapy (5). Over 12 weeks amlodipine did not improve exercise time and did not increase the incidence of adverse events.

Mental stress is a risk factor for cardiovascular disease. In 24 patients with mild to moderate hypertension, amlodipine reduced the blood pressure rise during mental stress compared with placebo, but increased plasma noradrenaline concentrations (6).

Hypertension leading to cardiac dysfunction is very frequent in patients with the inherited syndrome called Ribbing's disease, which is characterized by multiple epiphyseal dystrophy. In a randomized, double-blind comparison of amlodipine (10 mg/day) and enalapril (20 mg/day) in 50 patients for 6 months, both drugs significantly reduced blood pressure, but amlodipine increased heart rate and plasma concentrations of noradrenaline and angiotensin II (7). These undesired effects make ACE inhibitors a better choice for prevention of cardiac dysfunction.

Organs and Systems

Nervous system

- A 35-year-old woman with benign intracranial hypertension and high blood pressure was given amlodipine, with good control of her blood pressure (8). However, her headache worsened and she developed papilledema. The CSF pressure was 30 cm. Her symptoms disappeared shortly after amlodipine withdrawal.

Liver

Hepatitis has been attributed to amlodipine.

- A 77-year-old man took amlodipine for 1 month and developed jaundice and raised aspartate transaminase, alanine transaminase, and bilirubin (9). A liver biopsy suggested a drug-induced hepatitis and the amlodipine was withdrawn. His symptoms and laboratory values normalized. Other drugs (metformin, fluindione, and omeprazole) were not withdrawn.
- A 69-year-old hypertensive man who had taken amlodipine for 10 months abruptly developed jaundice, choluria, raised serum bilirubin, and increased transaminases (10). After amlodipine withdrawal he progressively recovered in a few weeks without sequelae or relapses. However, after several months he presented again with jaundice and an enlarged liver, having started to take diltiazem 5 months before. He recovered completely in a few weeks after drug withdrawal.

In the second case the authors hypothesized an idiosyncratic mechanism.

Skin

Recognized skin eruptions associated with amlodipine include erythematous and maculopapular rashes, skin discoloration, urticaria, dryness, alopecia, dermatitis, erythema multiforme, and lichen planus. A granuloma annulare-like eruption has been reported (11).

- A 64-year-old Caucasian woman, with a history of ankylosing spondylitis, hypertension, and osteoporosis, took amlodipine for 13 days and developed a rash on her lower legs. Amlodipine was withdrawn, but the rash progressed to involve both of her hands. The eruption consisted of multiple erythematous pruritic papules. Histology showed focal collagen degeneration and a significant interstitial histiocytic dermal infiltrate, suggestive of granuloma annulare. Within 3 months of withdrawal of amlodipine the reaction cleared and did not recur during follow-up for 3 years.

Amlodipine can cause generalized pruritus, which usually happens within 24 hours and resolves within 24 hours of withdrawal (12).

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Photosensitivity presenting with telangiectasia can be caused by calcium channel blockers.

- A 57-year-old hypertensive man developed telangiectasia, initially on the forehead and rapidly extending to the upper back, shoulders, and chest, particularly during the summer (13). The eruption began 1 month after starting amlodipine and diminished considerably 3 months after withdrawal.
- A 3-year-old girl developed telangiectases on the cheeks and gingival hyperplasia while taking furosemide, captopril, and amlodipine for hypertension due to hemolytic–uremic syndrome (14). Both lesions disappeared on withdrawal of amlodipine.

Calcium channel blockers can cause lichen planus.

- A 56-year-old Nigerian woman, with a previous history of sickle cell trait, osteoarthritis, and non-insulin-dependent diabetes mellitus, took amlodipine 5 mg/day for hypertension for 2 weeks and developed a lichenoid eruption (15). Histological examination confirmed the diagnosis of lichen planus. Amlodipine was withdrawn and there was rapid symptomatic and clinical improvement after treatment with glucocorticoids and antihistamines.

Musculoskeletal

A patient presented with severe, generalized muscle stiffness, joint pain, and fatigue while taking amlodipine for hypertension and zafirlukast for asthma. Stopping zafirlukast did not change her symptoms; the dose of amlodipine was increased at different times up to 15 mg to control blood pressure better. The neurological symptoms worsened, in the absence of any evidence of immunological or neurological disorders, and so amlodipine was withdrawn: the symptoms disappeared within 4 days (16).

Second-Generation Effects

Pregnancy

Subcutaneous fat necrosis in a neonate has been attributed to maternal use of amlodipine during pregnancy (17).

- A boy weighing 4 kg was born by spontaneous normal delivery at 39 weeks to a 38-year-old Afro-Caribbean woman, whose pregnancy was complicated by essential hypertension treated with amlodipine. On day 1 the child developed firm, red, pea-sized nodular lesions on the face, buttocks, back, shoulders, and arms.

Subcutaneous fat necrosis of the newborn is relatively uncommon. It is said to be benign and painless and to resolve within a few weeks. However, in this case it was extremely painful and was relieved only by opiates. The skin changes persisted beyond the age of 6 months and remained extremely symptomatic until the age of 9 months, when the skin had become normal. Calcium abnormalities have often been reported in association with subcutaneous fat necrosis, and exposure to amlodipine during pregnancy may have resulted in impairment of enzyme systems dependent on calcium fluxes for their action; it may also have affected calcium homeostasis in the neonate. Since previous reports of teratogenicity in animals have been published, few women take calcium channel blockers during pregnancy and there are no reports to date of an association between these drugs and subcutaneous fat necrosis (17).

Drug Administration

Drug overdose

Amlodipine overdose has been reported (18).

- A 23-year-old woman took 60 tablets of amlodipine intentionally and developed tachycardia and severe hypotension. She did not improve with intensive therapy and developed left ventricular failure and oliguria and underwent hemodiafiltration. Her condition slowly improved over 4 days.

Drug–Drug Interactions

Chloroquine

A possible interaction of amlodipine with chloroquine has been reported (19).

- A 48-year-old hypertensive physician, who had optimal blood pressure control after taking oral amlodipine 5 mg/day for 3 months, developed a slight frontal headache and fever, thought that he had malaria, and took four tablets of chloroquine sulfate (total 600 mg base). Two hours later he became nauseated and dizzy and collapsed; his systolic blood pressure was 80 mmHg and his diastolic pressure was unrecordable, suggesting vasovagal syncope, which was corrected by dextrose–saline infusion.

There was no malaria parasitemia in this case, and hence the syncope may have resulted from the acute synergistic hypotensive, venodilator, and cardiac effects of chloroquine plus amlodipine, possibly acting via augmented nitric oxide production and calcium channel blockade. Since malaria fever is itself associated with orthostatic hypotension, this possible interaction may be unrecognized and unreported in these patients.

Ciclosporin

Ciclosporin increases the survival of allografts in man. However, it causes renal vasoconstriction and increases proximal tubular reabsorption, leading in some cases to hypertension (20). The concomitant use of calcium channel blockers can prevent most of these adverse effects of ciclosporin. However, some calcium channel blockers (verapamil, diltiazem, nicardipine) can increase plasma concentrations of ciclosporin up to three-fold through inhibition of cytochrome P450. Eight different studies have been performed on the combination of amlodipine and ciclosporin given for 1–6 months to kidney transplant recipients, and the results have been reviewed (21). In three studies, in a total of 41 patients, amlodipine increased ciclosporin concentrations, while in the others, a total of 85 patients, there was no evidence of an interaction.

In normotensive renal transplant recipients treated for 2 months with amlodipine there was a small but significant nephroprotective effect (22). Thus, amlodipine, in contrast to other calcium channel blockers, does not affect ciclosporin blood concentrations and can be safely added in transplant recipients.

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Sildenafil

The effect of sildenafil on arterial pressure has been tested in 16 hypertensive men taking amlodipine 5–10 mg/day (23). Sildenafil did not affect amlodipine pharmacokinetics, but caused a further additive fall in blood pressure. Adverse events with the combination of sildenafil and amlodipine, headache, dyspepsia, and nausea, did not require drug withdrawal.

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Ammonium chloride

General Information

Ammonium chloride, which is used as an expectorant in productive cough, can cause gastric irritation, acidosis, and hypokalemia in large doses (1).

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Ammonium tetrathiomolybdate

General Information

Ammonium tetrathiomolybdate can be used as a chelator of copper in Wilson's disease.

Organs and Systems

Hematologic

Several reports suggest that ammonium tetrathiomolybdate can cause reversible hypoplastic anemia (1,2).

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Amocarzine

General Information

Amocarzine is an antifilarial antihelminthic drug, derived from amoscanate, that is active against the adult worms of *Onchocerca volvulus*.

Although ivermectin is very effective in the treatment of onchocerciasis, a fully effective and safe macrofilaricidal drug is still lacking. In animal studies of filarial infections, amocarzine showed promise as a macrofilaricidal drug and was afterward extensively tried in humans. Promising results were obtained in the early 1990s in Ecuador with amocarzine 3 mg/kg bd for 3 days and with acceptable adverse effects, including dizziness, itching, and rash. There were reversible neurological symptoms, such as impaired coordination and a positive Romberg's sign, in 4–12% of patients (1). Amocarzine was later tried in Africa in higher doses, with less good results. In a study from Ghana (2), the combination of ivermectin and amocarzine was not more effective than ivermectin alone. Adverse effects were more severe with amocarzine alone compared with ivermectin alone or with amocarzine preceded by ivermectin. Mazzotti-type reactions, such as itching, rash, peripheral sensory phenomena, and swellings, were all more severe or frequent after amocarzine than after ivermectin. Pretreatment with ivermectin markedly reduced these adverse reactions but did not affect other symptoms, such as dizziness and gaze-evoked nystagmus, suggesting that these adverse effects were probably directly drug-related and not a reaction to dying worms.

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Amodiaquine

General Information

Amodiaquine is a Mannich base derivative related to chloroquine. While it is generally considered equivalent to chloroquine, more recent studies have shown that amodiaquine is superior to chloroquine in tackling resistant strains of *Plasmodium falciparum*, although there may be cross-resistance to chloroquine (SEDA-20, 260).

Compared with chloroquine, amodiaquine was more effective and better tolerated in outpatients with uncomplicated malaria tropica in Kenya (SEDA-20, 260).

Because of its adverse effects, amodiaquine is no longer in use in the countries of the European Union or the USA, and was dropped from malaria control programs by the WHO in 1990 (SEDA-20, 260). However, it remains in use in other areas, including Africa and Oceania (SEDA-18, 287).

Organs and Systems

Cardiovascular

Prolongation of the QT interval is a recognized effect of 4-aminoquinolines. In 20 adult Cameroonian patients with non-severe falciparum malaria treated with amodiaquine (total dose 30 mg/kg or 35 mg/kg over 3 days) there was asymptomatic sinus bradycardia ($n = 16$) and prolongation of the PQ, QRS, and QT intervals at the time of maximum cumulative concentration of drug (day 2 of treatment) (1).

Sensory systems

Corneal and conjunctival changes, which included intralysosomal membranous and amorphous inclusions in the epithelial cells, as well as abnormal retinal test responses, were reported in a man who took amodiaquine for 1 year. Follow-up over the years after withdrawal showed a reduction in the abnormalities. There are no data on possible retinal changes similar to those seen with chloroquine.

In 69 children given 35 mg/kg over 3 days (SEDA-16, 306), parasitemia was cleared in all but one case. Tolerance was good, except that there was a fairly high incidence of conjunctival hyperemia.

Hematologic

The principal reason against recommending amodiaquine for malaria prophylaxis is the reporting of agranulocytosis, occasionally associated with hepatitis (SEDA-12, 241) (SED-12, 692). Since specific IgG antibodies, which lead to leukopenia, can be detected, all this suggests that the agranulocytosis is immune-mediated.

It takes substantial doses for a couple of weeks to cause the adverse hematological effects (SEDA-16, 692) (SEDA-17, 327). If this is correct, amodiaquine could still be of use for short intensive courses of treatment in areas of chloroquine resistance.

Gastrointestinal

Gastrointestinal complaints (nausea, vomiting, diarrhea, or constipation) are not uncommon with amodiaquine (SEDA-11, 587).

Skin

Abnormal pigmentation of the palate, nail beds, and the skin of the face and neck has been reported. The duration of such pigmentation after withdrawal is unknown. The effects on the nails resemble those seen with chloroquine (SEDA-12, 692) (SEDA-12, 241).

Nails

Abnormal pigmentation of nail beds has been reported. The duration of such pigmentation after withdrawal is unknown. The effects on the nails resemble those seen with chloroquine (SEDA-12, 692) (SEDA-12, 241).

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Amopyroquine

General Information

Amopyroquine is a 4-aminoquinoline, structurally related to amodiaquine. It is not a new compound, but it is of renewed interest as a result of the extensive occurrence of resistance to chloroquine and the adverse effects of prophylactic amodiaquine. In a study in 152 patients with malaria, the efficacy of a 12 mg/kg, given as two intramuscular injections of 6 mg/kg 24 hours apart, was described as good (1). All the patients became apyrexial and there was clearance of parasites on day 7 in 143 cases; the nine who retained a low level of parasitemia were all children. In 50% of the cases, the parasite had been chloroquine-resistant. The drug was well tolerated, and there were no major adverse effects.

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Amoxapine

See also Tricyclic antidepressants

General Information

In a major review of amoxapine and its pharmacology it was concluded that it is similar in efficacy and potency to standard tricyclic compounds, with a sedative action intermediate between amitriptyline and imipramine (1).

As previously noted (SEDA-4, 21) (SEDA-5, 17), amoxapine has a tricyclic nucleus with a modified piperazine side chain and is closely related to the neuroleptic drug loxapine. In animals, amoxapine has no antiserotonergic properties and less anticholinergic activity than prototype drugs. Peak plasma concentrations are achieved in less than 2 hours, and the half-lives of the parent drug and its two active metabolites are 8, 6, and 30 hours respectively.

Overall, amoxapine appears to have some advantage over other tricyclic antidepressants: possible earlier onset of action and relative freedom from serious cardiotoxic effects. Its major drawbacks are the potential for neuroleptic adverse effects, a high incidence of seizures, deaths in overdose (2), and the possibility of long-term neurological damage.

Amoxapine is less potent than other tricyclic antidepressants, with a therapeutic dosage range of 75–600 mg/day (usually 200–400 mg/day). Clinical effects have not been consistently correlated with plasma concentrations, but amoxapine has similar efficacy to other tricyclic antidepressants in heterogeneous populations of depressed patients. Controlled comparisons have shown that its clinical profile is very similar to that of imipramine (3) and that it is somewhat less sedative than amitriptyline (4–6). In two of these studies (4,6) the results confirmed the suggestion of a somewhat earlier onset of action.

Amoxapine appears to have the same common adverse effects as other tricyclic compounds, including those attributable to anticholinergic activity. Its structural similarity to the classic neuroleptic drugs appears to confer an additional hazard of adverse effects usually found in that category of drugs, such as galactorrhea and extrapyramidal disorders (SEDA-9, 20). In a study of its potential neuroleptic properties (7), using a radioreceptor assay in vivo and using plasma drawn from patients taking neuroleptic drugs or antidepressants, amoxapine and its metabolite, 7-hydroxyamoxapine, had potent neuroleptic activity. In patients taking amoxapine, there was neuroleptic activity comparable to that in patients taking loxapine, while none of the other tricyclic antidepressants (amitriptyline, nortriptyline, imipramine, and desipramine) had this property. Further reports of adverse effects attributable to its neuroleptic profile continue to appear, including tardive dyskinesia (8,9), acute torticollis (10), and malignant neuroleptic syndrome (SEDA-16, 9) (SEDA-17, 18) (11).

Organs and Systems

Metabolism

A further reminder of the structural resemblance of amoxapine to the neuroleptic drugs has been provided by an adverse effect reported with both amoxapine and its close congener, loxapine (12).

- A 49-year-old woman with no history of diabetes was admitted in unexplained hyperglycemic coma (blood glucose 26 mmol/l) while taking lithium 1500 mg/day and loxapine 150 mg/day. She responded to insulin, but insulin responses on testing were not delayed and suggested an iatrogenic rather than a diabetic cause. The fasting glucose fell to 4.2 mmol/l after withdrawal of loxapine but continuing lithium. Two weeks later amoxapine 150 mg/day was started and she became

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acutely confused, with a serum glucose of 5.7 mmol/l. Two weeks after stopping amoxapine the serum glucose returned to normal.

The authors speculated that a common metabolite of both drugs, 7-hydroxyamoxapine, was responsible for the hyperglycemia, owing to its antidopaminergic properties.

Drug Administration

Drug overdose

A bleak picture has rapidly evolved for amoxapine with regard to its toxicity in overdosage. Over 18 months, 33 cases were reported from Washington, DC, and New Mexico Poison Centers (2). These cases included 5 patients who died and 12 who developed seizures. Thus, the mortality rate of 15% greatly exceeds that of 0.7% for other antidepressants in the same centers, and the seizure rate is 36% compared to 4.3%. The authors noted that "the striking CNS toxicity of amoxapine overdose with frequent, persistent, and poorly controlled seizure activity is disconcerting." In a retrospective comparison of deaths from antidepressant overdosage in Scotland, England, and Wales between 1987 and 1992, the number of deaths per million prescriptions of amoxapine was significantly higher than expected (13).

Renal damage has occurred in cases of amoxapine overdose.

- Acute renal insufficiency and rhabdomyolysis were reported in a 27-year-old man who took 1–2 g of amoxapine (14). The authors recommended aggressive volume expansion and diuresis with loop diuretics, because of the futility of hemodialysis.
- A 24-year-old man took 4 g of amoxapine and developed gross hematuria and a high serum uric acid concentration on the second day of hospitalization (15). As in previously reported cases, serum creatine phosphokinase was grossly raised. The patient remained obtunded and stuporose for 7 days but eventually recovered.

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Amphetamines

See also Individual agents

General Information

Note on spelling

In International Non-proprietary Names the digraph -ph- is usually replaced by -f-, although usage is not consistent, and -ph- is used at the beginnings of some drug names (for example, compare fenfluramine and phentermine) or when a name that beings with a ph- is modified by a prefix (for example, chlorphentermine). For the amphetamines we have used the following spellings: amfetamine, benzfetamine, dexamfetamine, metamfetamine (methylamphetamine), and methylenedioxymetamfetamine (ecstasy).

Pharmacology and general adverse effects

Amfetamine is a sympathomimetic compound derived from phenylethylamine. However, the word amphetamines has become generic for the entire group of related substances, including benzfetamine, dexamfetamine, metamfetamine, and methylenedioxymetamfetamine (MDMA, ecstasy). Metamfetamine, a popular drug of abuse, is also known as "speed," "meth," "chalk," "crank," "ice," "crystal," or "glass." Other amfetamine-like drugs include fenfluramine (used as an appetite suppressant) and methylphenidate (used in narcolepsy and attention deficit hyperactivity disorder (ADHD)). When it was first introduced, one of the most frequent uses of amfetamine was as an anorexigenic agent in the treatment of obesity. A number of anorectic agents, many of them related to amfetamine, have since been manufactured. Most are stimulants of the central nervous system; in descending order of approximate stimulatory potency, they are

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dexamfetamine, phentermine, chlorphentermine, mazindol, amfepramone (diethylpropion), and fenfluramine.

The amfetamine epidemic of the 1960s and early 1970s has now been superseded by cocaine abuse in the USA and many other Western countries. Realization of the risk of abuse and of dependence has led to the present attitude that there may be only a restricted place for amphetamines in medicine. Perhaps low-dose, short-term use in combating fatigue and altering depressed mood could be justified, but only for specific indications and under continuous medical supervision. However, in the USA there has been a resurgence of metamfetamine abuse on the West coast and in the Southwest and Midwest. This geographical distribution is thought to reflect the traffic from Mexico of ephedrine, a precursor for the synthesis of metamfetamine in the quick-bake method. Because primitive labs can be established in trailers, the spread to adjacent locals has been very rapid, resulting in escalation of migrating epidemics.

Adverse effects of "catecholaminergic stimulants," such as amfetamine and cocaine, fall into several categories, based on dose, time after dose, chronicity of use, and pattern of use/abuse (for example 4–5 day bingeing episodes). Adverse effects include not only responses during the period of use but also intermediate and long-term residual effects after withdrawal. For example, in some abusers once an amfetamine psychosis has developed with chronic abuse, only one or two moderate doses are required to induce the full-blown psychosis in its original form, even long after withdrawal (1). This is also evidenced by the precipitous slide to severe re-addiction in former abusers who are re-introduced to stimulants.

Even with therapeutic use of stimulants, usually in moderate doses, careful monitoring for emergent psychosis, agitation, and abuse is important. Periodic checks for monodelusional syndromes are important with doses in the mid-to-high range (2).

The use of amfetamine-type stimulants for depression, fatigue, and psychasthenia has fallen into disfavor since the early 1970s, because of the potential for abuse and the low rates of success, especially after tolerance is established. However, there have been reports and reviews of successes in carefully selected groups of patients (3–5). The underlying symptoms of patients who respond to stimulants are mild anhedonia, lack of mental and physical energy, easy fatiguability, and low self-esteem, but in the absence of the marked depressed mood disturbance, guilt, and hopelessness that are associated with major depression. Examples include patients with dysthymic disorders, medically ill patients (especially after a stroke), depressed patients, hospitalized cancer patients, and patients with significant cardiovascular disorders, all of whom can have anergia and easy fatiguability. HIV-related neuropsychiatric symptoms, including depression, respond to psychostimulants (4–6). Withdrawn apathetic geriatric patients without major dementia have positive responses (7). General adverse effects, such as tachycardia and agitation, are relatively mild and all reverse on withdrawal (SEDA-17, 1). The combination of stimulants with monoamine oxidase inhibitors in treatment-resistant depressed patients has been reported (8). However, this use should be restricted to patients in whom there is careful monitoring by specialists, because of the potential for hypertensive crisis.

The relative reinforcing effects or abuse potential of these drugs is thought to be related to their potency in releasing dopamine from nerve terminals, compared with serotonin release. Amfetamine, metamfetamine, and phenmetrazine are potent dopamine releasers with high euphoriant and stimulant properties, whereas the compounds with halide substitution in the phenol ring, for example chlorphentermine, are more potent releasers of serotonin and have greater sedative action in anorectic doses. Thus, in summary, those drugs with relatively strong serotonergic to dopaminergic releasing properties seem to provide anorectic effects without euphoria, except at high doses, and might be considered first in any patient who has potential for abuse (2,9,10).

In a study of extended treatment (15 months) of ADHD, amfetamine was clearly superior to placebo in reducing inattention, hyperactivity, and other disruptive behavioral problems. The treatment failure rate was considerably lower and the time to treatment failure was longer in the treated group; adverse effects were few and relatively mild (11).

There is an association between the illicit use of metamfetamine and traumatic accidents. A retrospective review of trauma patients in California showed that metamfetamine rates doubled between 1989 and 1994, while cocaine showed a minimal increase and alcohol a fall. Metamfetamine-positive patients were most likely to be Caucasian or Hispanic and were most commonly injured in motor vehicle collisions. The authors recommended intervention strategies, similar to those used for preventing alcohol consumption and driving, in order to minimize morbidity and mortality (12).

Traumatic shock can be complicated by metamfetamine intoxication (13). Identifying the cause of shock is a key step in the management of patients with severe injuries. This is a challenge, because shock is occasionally caused by more than one mechanism; among the many causes, metabolic derangement attributable to drug abuse should be considered, and masked metabolic acidosis may be a clue to metamfetamine intoxication (14). With the increased emergence of metamfetamine abuse, clinicians should consider it in the differential diagnosis of any patient exhibiting violence, psychosis, seizures, or cardiovascular abnormalities.

Organs and Systems

Cardiovascular

Tachycardia, dysrhythmias, and a rise in blood pressure have been described after the administration of centrally acting sympathomimetic amines. Amfetamine acutely administered to men with a history of amfetamine abuse enhanced the pressor effects of tyramine and noradrenaline, while continuous amfetamine led to tolerance of the pressor response to tyramine. As with intravenous amphetamines, cardiomyopathy, cardiomegaly, and pulmonary edema have been reported with smoking of crystal metamfetamine (15–17).

The cardiovascular response to an oral dose of *d*-amfetamine 0.5 mg/kg has been determined in 81 subjects with schizophrenia, 8 healthy controls who took amfetamine, and 7 subjects with schizophrenia

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who took a placebo (18). Blood pressure increased in both amphetamine groups, whereas placebo had no effect. However, pulse rate did not change in the schizophrenic group and only increased after 3 hours in the controls. Intramuscular haloperidol 5 mg produced a more rapid fall in systolic blood pressure in six subjects, compared with 12 subjects who did not receive haloperidol. The authors concluded that increased blood pressure due to amfetamine may have a dopaminergic component. They also suggested that haloperidol may be beneficial in the treatment of hypertensive crises caused by high doses of amfetamine or metamfetamine.

Two cases of myocardial infarction after the use of amfetamine have been reported (19,20).

- A 34-year-old man who smoked a pack of cigarettes a day took amfetamine for mild obesity. He developed an acute myocardial infarction 1 week later. Echocardiography showed inferior left ventricular hypokinesia and a left ventricular ejection fraction of 50%. Coronary cineangiography showed normal coronary arteries but confirmed the inferior left ventricular hypokinesia. Blood and urine toxicology were positive only for amfetamine.
- A 31-year-old man developed generalized discomfort after injecting four doses of amfetamine and metamfetamine over 48 hours, but no chest pain or tightness or shortness of breath. Electrocardiography showed inverted T-waves and left bundle branch block. Echocardiography showed reduced anterior wall motion.

The authors reviewed other reported cases of myocardial infarction associated with amphetamines. The patients were in their mid-thirties and most were men. The interval from the use of amphetamines to the onset of symptoms varied from a few minutes to years. No specific myocardial site was implicated. Coronary angiography in most cases showed non-occlusion. The cause of myocardial ischemia in these cases was uncertain, even though coronary artery spasm followed by thrombus formation was considered the most likely underlying mechanism. Some have suggested that electrocardiographic and biochemical cardiac marker testing should be considered in every patient, with or without symptoms suggesting acute coronary syndrome, after the use of amphetamines. Others have suggested that calcium channel blockers may play an important role in the treatment of myocardial infarction due to amfetamine use or abuse. In one patient, administration of beta-blockers caused anginal pain, suggesting that they should be avoided. All the patients except one had a good outcome.

Vertebral artery dissection has been described in a previously healthy man with a 3-year history of daily oral amfetamine abuse (21).

- A healthy 40-year-old right-handed man presented with a 3-day history of an occipital headache and imbalance. He had a 3-year history of daily oral amfetamine abuse with escalating quantities, the last occasion being 12 hours before the onset of the symptoms. He had a history of "speed" abuse and a 20-pack-year history of tobacco use. He had mild right arm dysmetria without ataxia. His brain CT scan without contrast was normal. He then developed nausea, vomiting, visual loss, and progressive obtundation. He had hypertension (160/90 mmHg), bilateral complete visual loss, right lower facial weakness, mild dysarthria without tongue deviation, divergent gaze attenuated by arousal, bilateral truncal and appendicular dysmetria with inability to stand and walk, and generalized symmetrical hyperreflexia with extensor plantar reflexes. His urine screen was positive for metamfetamine. A brain MRI scan showed infarction of both medial temporal lobes, the left posteromedial thalamus, and the right superior and left inferior cerebellum. Magnetic resonance angiography and fat saturation MRI showed reduced flow in the left vertebral artery and a ring of increased signal within its lumen, consistent with hematoma and dissection. He was treated with anticoagulants and made a partial recovery.

Since this patient had no known risk factors for vertebral artery dissection and had abused amfetamine daily for 3 years with escalating amounts, an association between metamfetamine and vertebral artery dissection cannot be excluded. The local and systemic vascular impacts of amfetamine could have contributed to initial changes (along with smoking), resulting in dissection.

Of the other central stimulants, aminorex, doxapram, fenfluramine, and fenfluramine plus phentermine can cause chronic pulmonary hypertension, as can chlorphentermine, phentermine, phenmetrazine, and D-norpseudoephedrine (SED-9, 8). A genetic predisposition may be involved (SED-9, 8). Pulmonary hypertension may develop or be diagnosed a long time after the drug has been withdrawn.

Nervous system

Metamfetamine toxicity in infants can mimic scorpion (*Centruroides sculpturatus*) envenomation (22,23). However, the neurotoxic effect of envenomation can be distinguished from amfetamine-induced toxicity by the presence of cholinergic stimulation in scorpion envenomation, producing hypersalivation, bronchospasm, fasciculation of the tongue, purposeless motor agitation, involuntary and conjugate slow and roving eye movements, and often extraocular muscle dysfunction (24). Failure of the antivenin would bring scorpion neurotoxicity into great question (25).

Concentrations of metamfetamine and its metabolite amfetamine were measured in autopsied brain regions of 14 human metamfetamine abusers (26). There was no evidence of variation in the regional distribution of amphetamines in the brain. Post-mortem redistribution of metamfetamine in the heart and lung has been reported before, although peripheral blood concentrations appear to remain constant (27,28).

Stereotyped behavior

A type of automatic behavior, which can continue for hours, has been observed in addicts who inject large doses of central nervous system stimulants. Dyskinesias can occur, with strange facial and tongue movements or jerky motions of the arms and legs and a never-ending repetition of certain actions. Such stereotyped activity is induced in laboratory animals with high doses of amfetamine.

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Amphetamines and brain damage

The question of whether amphetamines in large doses can cause permanent brain damage has repeatedly been raised by animal studies (29,30), but definitive studies in man have not been performed. Vasculitis of large elastic vessels, found in chronic animal studies, has been reported to involve the internal carotid artery in man (31); intravenous administration is secondarily implicated. In man and animals, behavioral changes continue for several months after withdrawal of amphetamines; chronic residual changes have been reported mainly in monoaminergic neurons or terminals, either as structural changes or as residual depletion of monoamines and synthesizing enzymes (32). In post-mortem studies (33,34) chronic metamfetamine abusers had significantly lower concentrations of dopamine, tyrosine hydroxylase, and dopamine transporters in the caudate and putamen. It has been suggested that the reduced dopamine concentrations (up to 50% of control), even if not indicative of neurotoxicity, are consistent with amotivational changes reported by metamfetamine abusers after withdrawal (33).

Metamfetamine-induced neurotoxicity in animals, especially involving effects on the mitochondrial membrane potential and electron transport chain and subsequent apoptotic cascade, has been comprehensively reviewed (35). Metamfetamine increases the activity of dopamine, mainly by inhibiting the dopamine transporter. However, this does not explain why psychosis persists even when the metamfetamine is no longer present in the body (36). Chronic metamfetamine use has been reported to reduce dopamine transporter density in the caudate/putamen and nucleus accumbens. However, previous studies have been criticized for not controlling for other drug use.

Dopamine transporter density in the brain has been investigated during a period of abstinence in 11 metamfetamine monodrug users and nine healthy subjects, all men (37). The dopamine transporter density of metamfetamine users was significantly lower in the caudate/putamen, nucleus accumbens, and prefrontal cortex than in the controls. The severity of psychiatric symptoms correlated with the duration of metamfetamine use. The reduction in dopamine transporter density in the caudate/putamen and nucleus accumbens was significantly associated with the duration of metamfetamine use and closely related to the severity of persistent psychiatric symptoms. The reduction in dopamine transporters may be long lasting, even if metamfetamine is withdrawn.

Only some metamfetamine users develop psychosis, not all (36). In laboratory animals, metamfetamine is toxic to dopamine terminals. In 15 subjects (six men and nine women, mean age 32 years), who met the criteria for metamfetamine abuse, and 18 healthy volunteers (12 men and six women), there was a significant reduction in the number of dopamine transporters in detoxified metamfetamine abusers compared with controls (mean values of 28% in the caudate and 21% in the putamen) (38). This was associated with poor motor and memory performance. The reductions in dopamine transporters in the metamfetamine abusers were smaller than those found in patients with Parkinson's disease and occurred in subjects who had been abstinent for 11 months. Since significant reductions in dopamine transporters occur with both age and metamfetamine use, it is possible that metamfetamine will be associated with a higher risk of parkinsonian symptoms in abusers later in life.

Glucose metabolism in the brain has been studied using positron emission tomography after administration of ^{18}F-fluorodeoxyglucose, to look for evidence of functional changes in regions other than those innervated by dopamine neurons in 15 detoxified metamfetamine abusers and 21 controls (39). Whole-brain metabolism in the metamfetamine abusers was 14% higher than in the controls. The difference was largest in the parietal cortex (20%), but there was significantly lower metabolism in the thalamus (17%) and striatum (12% caudate and 6% putamen). The authors suggested that metamfetamine, in doses abused by humans, causes long-lasting metabolic changes in brain regions connected with dopamine pathways, but also in areas that are not innervated by dopamine.

The effects of protracted abstinence on loss of dopamine transporters in the striatum in five metamfetamine abusers have been evaluated during short-term abstinence and then retested during protracted abstinence (12–17 months) (40). The dopamine transporters increased in number, providing hope for effective treatment; however, this regeneration was not sufficient to provide complete functional recovery, as measured by neuropsychological tests.

Chronic amfetamine abusers, chronic opiate abusers, and patients with focal lesions of the orbital prefrontal cortex or dorsal lateral/medial prefrontal cortex were subjected to a computerized decision-making task, in order to compare their capacity for making decisions (41). Chronic amfetamine abusers made suboptimal decisions (correlated with years of abuse) and deliberated significantly longer before making their choices. The opiate abusers had only the second of these behavioral changes. Both the suboptimal choices and the increased deliberation times were also evident in patients with damage to the orbital frontal prefrontal cortex but not other areas. These data are consistent with the hypothesis that chronic amfetamine abusers have similar decision-making deficits to those seen after focal damage to the orbital frontal prefrontal cortex.

The use of proton magnetic resonance scanning (^{1}H MRS) in detecting long-term cerebral metabolite abnormalities in abstinent metamfetamine users has been studied in 26 subjects (13 men) with a history of metamfetamine dependence (mean age 33 years) and 24 healthy subjects with no history of drug dependence (42). The neuronal marker *N*-acetylaspartate was reduced by 6% in the frontal white matter and by 5% in the basal ganglia of the abstinent metamfetamine users. *N*-acetylaspartate is a marker for mature neurons, and reduced *N*-acetylaspartate is thought to indicate reduced neuronal density or neuronal content. According to the authors, these findings suggest neuronal loss or persistent neuronal damage in the absence of significant brain atrophy in metamfetamine users. They speculated that these abnormalities may underlie the persistent abnormal forms of behavior, such as violence, psychosis, and personality changes, seen in some individuals months or even years after their last drug use. Metamfetamine users in the study also had increased concentrations of choline-containing

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compounds and myoinositol in the frontal gray matter. Myoinositol is a glial cell marker, while the increase in choline-containing compounds reflects increased cell membrane turnover. Thus, these increases in the frontal cortex in drug users may have reflected glial proliferation (astrocytosis). The authors suggested that the finding of reduced *N*-acetylaspartate accompanied by increased myoinositol, which has been observed in many active brain disorders, indicated glial proliferation in response to neuronal injury. However, they noted that neurotoxicity may not be present in subjects who use amounts of the drugs that are much lower than the amounts used by the chronic abusers they studied. They suggested that future studies should observe whether treatments or long periods of abstinence could reverse these abnormalities.

These findings have given further support to an earlier observation of long-term neurotoxicity associated with MDMA (ecstasy) in animals (SEDA-14, 3). However, it is uncertain whether the reported abnormalities suggestive of neuronal damage are reversible despite continued treatment or beyond 21 months of abstinence.

Dyskinesias

Although controversial, there is a growing consensus that stimulants can provoke, cause, or exacerbate Gilles de la Tourette's syndrome (SEDA-7, 10), based on the observation that stimulants such as the amphetamines, methylphenidate, and pemoline facilitate dopamine retention in the synaptic cleft. There is much evidence that in children with ADHD vulnerable to Tourette's syndrome, stimulants exacerbate motor and phonic tics (43). These studies suggest that Tourette's syndrome and a family history of dyskinesias should be contraindications to stimulant use. However, there is virtually no evidence that stimulants in clinically appropriate doses provoke Tourette's syndrome, and it has been suggested that dyskinesias are a function of high doses (44). Nevertheless, patients taking stimulants should be carefully examined periodically for dyskinesias. It is not known whether structural changes in the central nervous system accompany stimulant-induced dyskinesias.

Stroke

Intracerebral hemorrhage associated with amfetamine has been reported for more than five decades. Eight cases were associated with amfetamine over a period of 3.5 years (45). All had undergone head CT scans and cerebral digital subtraction angiography. Seven had a parenchymal hematoma, three in the frontal lobe and one each in the parietal lobe, frontoparietal region, temporal lobe, and brain stem. One patient had a subarachnoid hemorrhage. The time from exposure to onset of symptoms ranged from less than 10 minutes to about 2 months (median 1 day). The authors reviewed the literature and found 37 other cases. They observed that young people, mean age 28 years, were at high risk. While most were repeat abusers, one-third claimed to be first time or infrequent users. Intracerebral hemorrhage was seen with all routes of drug use, 57% from oral use, 34% from intravenous use, and 5% after inhalation. Of those who had a CT scan, 84% had a proven intracerebral hemorrhage, three had a subarachnoid hemorrhage, and one had a brainstem hemorrhage. In one patient, with a negative CT scan, the diagnosis of subarachnoid hemorrhage was confirmed by lumbar puncture. In 35 patients who had angiography, 20 were normal or showed only mass effect from a hematoma, 16 had vasculitic beading, and 1 had an arteriovenous malformation. Seven patients died and only 14 had a good recovery.

- A previously healthy 16-year-old schoolboy had mesencephalic ischemia, most probably caused by vasospasm, after combined abuse of amfetamine and cocaine (46). There was a close temporal relation between intake of the drug and the onset of symptoms. Thus, combining these drugs, even in small amounts, may be harmful.

Psychological, psychiatric

Amphetamines release monoamines from the brain and thereby stimulate noradrenergic, serotonergic, and particularly dopaminergic receptors. Under certain circumstances this leads to psychosis and compulsive behavior, as well as auditory hallucinations similar to those experienced in paranoid schizophrenia. In addition, amphetamines cause an acute toxic psychosis with visual hallucinations, usually after one or two extremely large doses (47).

When an amfetamine is taken, even in a therapeutic dose, most people experience a sensation of enhanced energy or vitality, which, with repetitive administration, follows different patterns. Most often euphoria will develop, usually with a sense of heightened function or perception, and occasionally compulsive behavior as well as hallucinogenic delusions. Dysphoria occurs in some (especially older) individuals. The euphoric effect may enhance craving for amfetamine, and repeated reinforcement can lead to conditioned drug responses, which may facilitate dependence. Progression to severe dependence depends highly on individual vulnerability, the circumstances, the setting, the pattern of use, and especially escalation to high-dose patterns of use. Although most people probably use amphetamines for the original reason they were prescribed, and do not escalate the dosage, a significant proportion do, highlighting the abuse potential. The amphetamines are sometimes used recreationally for years in moderate doses. However, once inhalation and intravenous administration or higher doses are used, a "high-dose transition" into abuse usually occurs, and the capacity for low-dose occasional use is lost, presumably, forever (see the sections on Drug abuse and Drug dependence in this monograph).

Personality degeneration

In a double-blind, placebo-controlled, short-term study there was significant deterioration of personality in five of 26 children treated with dexamfetamine (48).

Phobias

Social phobia has been attributed to amfetamine (49).

- A 26-year-old woman reported flushing, sweating, palpitation, and shortness of breath, in a range of social situations. She was described as a confident and extroverted woman, with no history of psychiatric problems.

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She reported daily oral consumption of street amfetamine 1.6 g. At the time of assessment, she had given up her work. Initially, she felt good while taking the drug, but more recently she had been using it to "get going"; there were no symptoms of psychosis or affective disorder.

The authors speculated that dopaminergic dysfunction, reported by some to underlie social phobia, could have resulted in this case from chronic amfetamine-related striatal dopamine depletion.

Psychoses

Psychotic reactions in people taking amphetamines were first reported many years ago and the question was posed whether it was due to the amphetamines or to co-existing and exacerbated paranoid schizophrenia. In one study, most of the psychotic symptoms remitted before the excretion of amines had fallen to its normal basal value (SED-9, 8). The psychotic syndrome was indistinguishable from paranoid schizophrenia, with short periods of disorientation, and could occur after a single dose (many had taken the equivalent of some 500 mg of amfetamine or metamfetamine orally) with or without simultaneous alcohol, and was most pronounced in addicts (SED-9, 9). Amfetamine psychosis was also seen in 14 people in Australia (1); the predominant hallucinations were visual, which is unusual for schizophrenia (SED-8, 11). Similarly, in contrast to schizophrenia, vision was the primary sensory mode in thinking disorders and body schema distortions in 25 amfetamine addicts (50).

In other studies, volunteers previously dependent on amphetamines were dosed to a level at which amfetamine psychosis was produced, in order to examine the mechanism of action and pharmacokinetics of amfetamine and its possible relation to schizophrenia (51,52). Psychosis was induced by moderately high doses of amfetamine and the psychotic symptoms were often a replication of the chronic amfetamine psychosis, raising the question of whether the establishment of chronic stimulant psychosis leaves residual vulnerability to psychosis precipitated by stimulants. The mechanism might be similar to that which operates in the reverse tolerance that has been seen in experimental animals (53). In some cases an underlying psychosis can be precipitated; an increase in schizophrenic symptoms (SED-8, 12) was observed in 17 actively ill schizophrenic patients after a single injection of amfetamine.

Amfetamine psychosis is relatively rare in children, even in hyperactive children taking large doses of amfetamine; amfetamine psychosis has been reported in an 8-year-old child with a hyperkinetic syndrome (SED-8, 12). Large doses of amfetamine can cause disruption of thinking, but amfetamine psychosis is not usually accompanied by the degree of disorganization normally seen in schizophrenia (SED-9, 8).

Increased sensitivity to stress may be related to spontaneous recurrence of metamfetamine psychosis, triggering flashbacks. Stressful experiences, together with metamfetamine use, induce sensitization to stress associated with noradrenergic hyperactivity, involving increased dopamine release (54,55). This hypothesis has been investigated by determining plasma noradrenaline metabolite concentrations in 26 flashbackers (patients with spontaneous recurrence of metamfetamine psychosis) (11 taking neuroleptic drugs before and during the study and 15 during the course of the study), 18 non-flashbackers with a history of metamfetamine psychosis, 8 with persistent metamfetamine psychosis, and 34 controls (23 metamfetamine users and 11 non-users). The 26 flashbackers had had stressful events and/or metamfetamine-induced, fear-related, psychotic symptoms during previous metamfetamine use. Mild psychosocial stressors then triggered flashbacks. During flashbacks, plasma noradrenaline concentrations increased markedly. Flashbackers with a history of stressful events, whether or not they had had fear-related symptoms, had a further increase in 3-methoxytyramine concentrations. Thus, robust noradrenergic hyperactivity, involving increased dopamine release in response to mild stress, may predispose to further episodes of flashbacks. The authors pointed out the limitations of their study: (a) plasma noradrenaline concentrations do not accurately reflect central monoamine neurotransmitter function; (b) raised noradrenaline concentrations may reflect heightened autonomic arousal secondary to stress or anxiety; (c) the neuroleptic drugs used may have altered the concentrations of noradrenaline and 3-methoxytyramine; and (d) the study was retrospective and carried out in women in prison.

A paranoid hallucinatory state similar to schizophrenia has been reported in women with a history of metamfetamine abuse in a study of flashbacks in 81 female inmates in Japan (56). Details of symptoms of initial metamfetamine psychosis, stressful experiences, and patterns of abuse were obtained. Plasma monoamine concentrations were also measured during flashback states and in control abusers who had never experienced them. The researchers reported that concreteness of abstract thought and impaired goal-directed thought characteristic of schizophrenia was not usually seen in metamfetamine-induced psychosis. Moreover, it was the use of metamfetamine and not a severe stressor that caused the initial psychotic state, but the flashbacks appeared to be due to mild environmental stressors. The authors described this pattern as "spontaneous psychosis due to previous metamfetamine psychosis." They also observed that plasma concentrations of noradrenaline were significantly higher in women with flashbacks both during flashbacks and during remissions. This suggests a possible role of noradrenergic hyperactivity in sensitivity to mild stress and susceptibility to flashbacks. Furthermore, these noradrenergic findings could be used to predict relapse to a paranoid hallucinatory state in schizophrenia.

Chlorpromazine has been used to treat amfetamine psychosis due to acute poisoning in children who did not respond to barbiturates (57).

Management

Reports have suggested that atypical antipsychotic drugs, such as risperidone (58–60) and olanzapine (61), can be effective in the treatment of acute and residual metamfetamine-induced psychosis. Moreover, adherence to olanzapine for about 8 weeks also effectively controlled cravings for metamfetamine. Rigorous controlled studies are needed to establish the therapeutic efficacy of atypical

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antipsychotic drugs in the treatment of the psychosis and cravings of metamfetamine addiction.

- A 76-year-old woman, who had taken dexamfetamine since the age of 28 years for narcolepsy, developed an acute schizophreniform psychosis with paranoid delusions and auditory hallucinations. She was initially treated with sulpiride while continuing to take dexamfetamine. Five months later, sulpiride was withdrawn, and her psychotic symptoms recurred. She was given risperidone 3 mg/day and continued to take dexamfetamine 15 mg/day.
- A 24-year-old man, with a history of intravenous metamfetamine abuse since the age of 19 years, developed psychotic symptoms characterized by auditory hallucinations and persecutory delusions. He had no insight and was given haloperidol and levomepromazine. His symptoms disappeared after 4 months of treatment and he then stopped using metamfetamine. A year and a half later, "odd ideas" recurred, and he became anxious but had insight. He was treated with bromperidol 9 mg/day for 6 months, but the odd ideas persisted. On referral, he was found to fulfil the criteria for obsessive-compulsive disorder according to DSM-IV. No abused substances, including metamfetamine, were identified in his urine. Risperidone 2 mg/day was started and then increased to 5 mg/day. After 3 weeks, the intrusive thoughts and symptoms of "anxious-restless state" gradually subsided and eventually disappeared. His symptoms recurred within a week of stopping risperidone and resolved on reintroduction.

Metabolism

Amphetamines can cause retardation of growth (height and weight) in hyperactive children (SED-9, 9).

Hematologic

Acute myeloblastic leukemia occurred in a 24-year-old man who had taken massive doses of amfetamine for more than 2 years (SED-8, 13).

Mouth and teeth

Dental wear has been evaluated prospectively in metamfetamine users at an urban university hospital (62). Information was collected from 43 patients (26 men, 40 tobacco smokers), mean age 39 years, who admitted to having used metamfetamine for more than 1 year. Patients who regularly snorted metamfetamine had higher "tooth-wear" scores for anterior maxillary teeth than patients who injected, smoked, or ingested metamfetamine. The authors suggested that the anatomy of the blood supply to this area possibly explained the association of the regional differences in tooth wear with snorted metamfetamine. The anterior maxillary teeth and the nasal mucosa have a common blood supply. Thus, snorting may cause vasoconstriction, impairing the blood supply both to the nasal mucosa as well as the teeth.

Skin

The severe form of erythema multiforme known as toxic epidermal necrolysis has been attributed to a mixture of dexamfetamine and ephedrine (63).

- A 27-year-old woman developed peripheral target plaques, papules, blisters, and lip erosions, consistent with erythema multiforme, 9 days after using "speed" (dexamfetamine and ephedrine), and 3 days later developed widespread lesions with large areas of blistering affecting 40% of her body surface area. She was given intravenous ciclosporin and improved within 24 hours.

Musculoskeletal

There may be an association between metamfetamine abuse and rhabdomyolysis. In a retrospective review of 367 patients with rhabdomyolysis, 166 were positive for metamfetamine (64). They had higher mean initial and lower mean peak activities of creatine phosphokinase. There was no significant difference in the incidence of acute renal insufficiency. The authors suggested screening all patients with rhabdomyolysis of unclear cause for metamfetamine and measuring creatine phosphokinase activity.

Sexual function

Reports of the effects of amfetamine on sexual behavior refer variously to unchanged, reduced, mixed, and heightened sexual performance, but long-term abusers often have sexual dysfunction (SED-9, 9).

Immunologic

An anaphylactic reaction after the injection of crushed tablets equivalent to 45 mg of amfetamine occurred in a young woman; in others injected with the same solution and at the same time there were no adverse effects (SED-9, 8). The reaction may have involved amfetamine or excipients. Scleroderma is a potential consequence of various stimulants used for appetite control (65).

Infection risk

- A 34-year-old woman who had taken intranasal metamfetamine weekly for 15 years developed osteomyelitis of the frontal bone and a subperiosteal abscess. The authors proposed that this was due to chronic abuse of metamfetamine (66).

A rare case of Pott's puffy tumor, anterior extension of a frontal sinus infection that results in frontal bone osteomyelitis and subperiosteal abscess, has been associated with metamfetamine use (67).

- A 34-year-old woman presented with a 9-day history of fever, chills, photophobia, and neck pain. Nine months earlier, she had developed a swelling on her forehead, which enlarged and spontaneously drained pus. Over the next weeks, a fistula developed at the site of the swelling, accompanied by an intermittent bloody purulent drainage that lasted for about 9 months. She had either inhaled metamfetamine or had used it intranasally weekly for 15 years and reported continued use immediately before the development of the forehead lesion. She had a sinocutaneous fistula in the midline of the forehead, with seropurulent discharge but no local erythema or tenderness. A CT scan of the head showed complete opacification of all sinuses, with a 1 cm connection between the anterior frontal sinus and the skin. Cultures grew *Streptococcus milleri* and *Candida*

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albicans. She responded to extensive medical and surgical treatment.

The authors proposed that intranasal metamfetamine had contributed to chronic sinus inflammation and subsequent complications. Furthermore, the vasoconstriction induced by metamfetamine in the mucosal vessels may have resulted in ischemic injury to the sinus mucosa, providing an environment conducive to bacterial growth.

Death

There has been a retrospective investigation of metamfetamine-related fatalities during a 5-year period (1994–1998) in Southern Osaka city in Japan (68). Among 646 autopsy cases, methamphetamine was detected in 15, most of whom were men in their late thirties. The cause and manner of death were methamphetamine poisoning ($n = 4$), homicide ($n = 4$), accidental falls and aspiration from drug abuse ($n = 4$), death in an accidental fire, myocardial infarction, and cerebral hemorrhage (one each). Blood metamfetamine concentrations were 23–170 μmol/l in fatal poisoning, 4.4–38 μmol/l in deaths from other extrinsic causes, and 14–22 μmol/l in cardiovascular and cerebrovascular accidents. The common complications were cardiomyopathy, cerebral perivasculitis, and liver cirrhosis/interstitial hepatitis. The general profile of patients reported in this series compares with that of a previous study from Taiwan (SEDA-24, 2).

Long-Term Effects

Drug abuse

The most important problem encountered with amphetamines is abuse and the development of dependence. The most rapid amfetamine epidemic occurred in Japan after World War II, where there had been little or no previous abuse (69). Although a high proportion of amfetamine users probably already have emotional and social difficulties, sustained abuse can result in serious psychiatric complications, ranging from severe personality disorders to chronic psychoses (70,71). Whereas signs of intense physical dependence are not thought to occur (SED-9, 9), withdrawal may be associated with intense depression (SED-9, 9) (72), and relapses in psychiatric disorders have often been noted. Some countries in which the problem became widespread banned amphetamines, and Australia restricted their use to narcolepsy and behavioral disorders in children. Amfetamine dependence developed into a serious problem in the USA (and to a lesser extent in the UK), where it followed the typical pattern of drug dependence (SED-9, 7, 10).

Continuing critical re-assessment of the usefulness versus the harmfulness of amphetamines has led to further restrictions in their use (SED-9, 10). They have been subjected to rigid legislative control in many countries, accompanied by recommendations that they should not be prescribed. The World Health Organization and the United Nations have also stressed the need for strict control of amphetamines (SED-9, 10) (73).

There is a high prevalence of the use of amfetamine-like drugs in Brazil, particularly among women, owing to the "culture of slimness as a symbol of beauty" (74). Of 2370 subjects in São Paulo and Brasilia, 72% had already undergone from one to more than 10 previous courses of treatment, usually with amfetamine-like anorectic drugs. Over half of them had taken amfetamine-like drugs in compound formulations containing four or more substances, such as benzodiazepines and/or laxatives, diuretics, and thyroid hormones. There were adverse reactions to the amfetamine-like drugs in 86% and 37% sought medical advice; 3.9% required hospitalization. The authors argued the need for more rigorous legislation and enforcement strategies to stop such misuse of drugs.

Further evidence concerning increased metamfetamine abuse has come from Taiwan (75). Between 1991 and 1996, of 3958 deaths with autopsies, 244 were related to metamfetamine (mean age 31 years, 73% men). The manner of death was natural (13%), accidental (59%), suicidal (11%), homicidal (14%), or uncertain (3%). Owing to the endemic problem and public hazard created by illicit metamfetamine abuse, the authors urged stronger antidrug programs.

Drug dependence

The role of dopamine in the addictive process has been explored (76). The authors raised the possibility that the orbitoprefrontal cortex is linked to compulsive drug abuse. They recruited 15 metamfetamine users and 20 non-drug user controls. The metamfetamine abusers had significantly fewer dopamine D_2 receptors than the controls. There was an association between lower numbers of dopamine D_2 receptors and metabolism in the orbitofrontal cortex in the metamfetamine users. These findings are similar to those observed in cocaine, alcohol, and heroin users. The authors suggested that D_2 receptor-mediated dysregulation of the orbitofrontal cortex could be a common mechanism underlying loss of control and compulsive abuse of drugs.

Second-Generation Effects

Pregnancy

In pregnant women who reported for prenatal care between 1959 and 1966 there was an excess of oral clefts in the offspring of mothers who had taken amphetamines in the first 56 days from their last menstrual period, but this was considered to be either a chance finding or one element in a multifactorial situation (SED-9, 9).

Teratogenicity

The possible neurotoxic effect of prenatal metamfetamine exposure on the developing brain has been studied using ^{1}H magnetic resonance spectroscopy in 12 metamfetamine-exposed children and 14 age-matched unexposed controls (77). There was an increased creatinine concentration in the striatum, with relatively normal concentrations of *N*-acetyl-containing compounds in children exposed to metamfetamine. These findings suggest that exposure to metamfetamine in utero causes abnormal

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energy metabolism in the brain of children. However, there were no differences in reported behavioral problems among metamfetamine-exposed children compared with controls.

Susceptibility Factors

Genetic factors

A study in 93 unrelated metamfetamine-dependent subjects and 131 controls did not prove any association between metamfetamine dependence in Caucasians of Czech origin and TaqI A polymorphism of the DRD2 gene, I/D polymorphism of the ACE gene, or M235T polymorphism of the AGT gene (78).

Age

Special care should be taken when using amphetamines in elderly patients, in view of the likelihood of stimulation of adrenoceptors and in particular of cardiovascular and respiratory function. Periodic users especially need to be wary of acute use under circumstances of exercise and environmental heat, owing to the risk of heat stroke.

Other features of the patient

The existence of a previous neurological disorder may be a risk factor for treatment-resistant psychosis in metamfetamine abusers (79). It is of particular interest that most of these patients sustained their disorder during childhood. It is not uncommon for metamfetamine patients to continue with psychotic symptoms despite extended periods of abstinence (80). These patients often are labeled as being schizophrenic. This study has shown the importance of considering a history of neurological disorders, especially during childhood, in such patients.

Drug Administration

Drug administration route

Injection as a method of delivery of illicit drugs carries its own special risks. Metamfetamine-dependent subjects ($n = 427$) participated in a study to detect differences between injecting metamfetamine users (13%) and non-injecting users (87%) (81). The patients entered treatment at a center in California between 1988 and 1995. Injectors reported significantly more years of heavy use. Psychological problems were more common in the injectors, more of whom reported depression, suicidal ideation, hallucinations, and episodes of feeling that their body parts "disconnect and leave." Moreover, injectors reported more problems concerning sexual functioning and more episodes of loss of consciousness. The injectors were more commonly HIV-positive and they had more felony convictions and were on parole more often than other users. Although individuals who inject metamfetamine use it more often than non-injectors, the number of grams used per week did not differ between the groups. Thus, injectors use a smaller amount of drug per dose than non-injectors. Eighty percent of the injectors were unemployed, possibly reflecting the extent of impairment related to addiction in this group. The injectors, who had more psychiatric and medical morbidity, warrant special attention and carefully designed treatment plans.

Drug overdose

Overdosage of amphetamines can cause restlessness, dizziness, tremor, increased reflexes, talkativeness, tenseness, irritability, and insomnia; less common effects include euphoria, confusion, anxiety, delirium, hallucinations, panic states, suicidal and homicidal tendencies, excessive sweating, dry mouth, metallic taste, anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually associated with hyperpyrexia, convulsions, coma, or cerebral hemorrhage. In addition, peripheral excitation of smooth muscle or blood vessels supplying skeletal muscle has been described. Excitatory actions can cause increased heart rate, palpitation, dysrhythmias, and metabolic effects, such as glycogenolysis in liver and adipose tissue.

The problem of fatal overdose is central to the problem of frequently repeated intravenous high-dose abuse of stimulants of unknown quality and quantity. Fatal overdose is less frequent among experienced chronic users than in naive or episodic high-dose users (82–84), in part because of the establishment of tolerance to hyperpyrexia and hypertension. Fatal hypertension can be potentiated by high ambient temperatures and vigorous exercise, as in the use of these drugs by athletes. Rare individuals have used up to 1–3 g/day of oral amfetamine for many years without problems of overdosing, yet acute toxic overdoses have been reported at 100–200 mg (53). Hyperpyrexia, seizures, hypertensive cerebrovascular hemorrhage, ventricular fibrillation, left ventricular failure, and complications of intravenous drug abuse have all been reported as causes of death (83–86). An autopsy study of amfetamine abusers in San Francisco showed that 54% died of drug toxicity, 10% of accidental trauma, 12% by suicide, and 10% by homicide (87).

Two deaths from metamfetamine overdose in drug dealers have been reported from Thailand, which has experienced an increase in metamfetamine abuse (88).

- A 43-year-old male drug dealer swallowed a number of metamfetamine tablets at the time of his arrest. When seen in the emergency room, he was comatose with reactive pupils. He died 6 hours after consuming the tablets. The autopsy findings were non-specific.
- Another 33-year-old female drug dealer, while at the police station, swallowed a number of metamfetamine pills that had been hidden in her undergarments. At the hospital, a gastric lavage was done but she died 10 hours after ingestion.

As described in these cases, there may be an increased risk of death in drug dealers who, in attempting to prevent arrest, may consume toxic amounts without anticipating the consequences.

Drug–Drug Interactions

Adrenergic neuron blocking drugs

Amphetamines and other stimulatory anorectic agents, apart from fenfluramine, would be expected to impair

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the hypotensive effects of adrenergic neuron blocking drugs such as guanethidine. Not only do they release noradrenaline from stores in adrenergic neurons and block the reuptake of released noradrenaline into the neuron, but they also impair re-entry of the antihypertensive drugs (89).

Alcohol

Alcohol increases blood concentrations of amphetamines (SED-9, 9).

Barbiturates

Barbiturates can enhance amfetamine hyperactivity (SED-8, 9).

Benzodiazepines

Benzodiazepines can enhance amfetamine hyperactivity (SED-8, 9).

Estradiol

Preclinical studies (as well as anecdotal clinical reports) have shown that estrogens, through effects on the central nervous system, can influence behavioral responses to psychoactive drugs. In an unusual crossover study, the subjective and physiological effects of oral D-amfetamine 10 mg were assessed after pretreatment with estradiol (90). One group of healthy young women used estradiol patches (Estraderm TTS, total dose 0.8 mg), which raised plasma estradiol concentrations to about 750 pg/ml, and a control group used placebo patches. Most of the subjective and physiological effects of amfetamine were not affected by acute estradiol treatment, but the estrogen did increase the magnitude of the effect of amfetamine on subjective ratings of "pleasant stimulation" and reduced ratings of "want more." Estradiol also produced some subjective effects when used alone, raising ratings of "feel drug," "energy and intellectual efficiency," and "pleasant stimulation." Some limitations of the study were:

(a) plasma amfetamine concentrations were not measured, so an effect of estradiol on the pharmacokinetics of amfetamine cannot be ruled out;
(b) only single doses of amfetamine and estradiol were tested;
(c) the dose of amfetamine was relatively low and that of estradiol relatively high, maximizing the chances of detecting estradiol-dependent increases in two subjective effects of amfetamine.

Monoamine oxidase inhibitors

The amphetamines should not be used together with or within 14 days of any monoamine oxidase inhibitors; severe hypertensive reactions and on occasion confusional states (for example with fenfluramine) can occur (SED-9, 9).

Ritonavir

A fatal interaction between ritonavir and metamfetamine has been described (91).

- A 49-year-old HIV-positive Caucasian man had taken ritonavir (400 mg bd), saquinavir (400 mg bd), and stavudine (40 mg bd) for 4 months. His CD4 cell count was 617×10^6 cells/l and HIV-1 RNA less than 400 copies/ml. He had previously taken zidovudine for 7 months. He self-injected twice with metamfetamine and sniffed amyl nitrite and was found dead a few hours later. At autopsy, there was no obvious cause of death. Metamfetamine was detected in the bile (0.5 mg/l) and cannabinoids and traces of benzodiazepines were detected in the blood.

Nitric oxide formed from amyl nitrite inhibits cytochrome P450 (92) and ritonavir inhibits CYP2D6 (93), which has a major role in metamfetamine detoxification (94). This interaction could have led to fatal plasma concentrations of metamfetamine. It is therefore suggested that patients who take protease inhibitors are made aware of the potential risk of using any form of recreational drugs metabolized by CYP2D6, particularly metamfetamine.

SSRIs

A man taking long-term dexamfetamine had two episodes of serotonin syndrome while taking first venlafaxine and later citalopram (95).

- A 32-year-old man, who was taking dexamfetamine 5 mg tds for adult ADHD, developed marked agitation, anxiety, shivering, and tremor after taking venlafaxine for 2 weeks (75 mg/day increased after a week to 150 mg/day). His heart rate was 140/minute, blood pressure 142/93 mmHg, and temperature 37.3°C. His pupils were dilated but reactive. There was generalized hypertonia, hyper-reflexia, and frequent myoclonic jerking. Dexamfetamine and venlafaxine were withdrawn and cyproheptadine (in doses of 8 mg up to a total of 32 mg over 3 hours) was given. His symptoms completely resolved within a few hours.

Dexamfetamine was restarted 3 days later and citalopram was started a few days later. Two weeks later he reported similar symptoms and stopped taking citalopram. He was successfully treated again with cyproheptadine.

Tricyclic antidepressants

Tricyclic antidepressants increase blood concentrations of amfetamine (96,97).

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Amphotericin

General Information

Having a broad-spectrum fungicidal activity, amphotericin remains the mainstay of treatment of most invasive fungal infections. Compared with conventional amphotericin B deoxycholate, other lipid formulations of amphotericin (amphotericin B colloidal dispersion, amphotericin B lipid complex, and liposomal amphotericin B) facilitate treatment in patients with suspected and proven invasive mycoses, who are intolerant of or refractory to conventional amphotericin.

Mechanism of action

The principal mechanism of action of amphotericin is based on its binding to lipids of the cell membrane of target cells, particularly to ergosterol, the predominant lipid in fungal cells, and cholesterol, the predominant lipid of the vertebrate cell membrane. The principle of selectivity is based on a higher affinity of amphotericin to ergosterol than cholesterol, but peroxidation of the membrane appears to be of equal importance (1–3).

Different formulations of amphotericin

Because of nephrotoxicity from amphotericin, which is common when amphotericin is given as the deoxycholate, lipid formulations have been developed. The formulations that are currently available are:

- amphotericin B deoxycholate (DAMB);
- amphotericin B colloidal dispersion (ABCD);
- amphotericin B lipid complex (ABLC);
- liposomal amphotericin B (L-Amb, AmBisome).

Pharmacokinetics

The pharmacokinetics of amphotericin are highly variable and depend on the formulation used and the infusion rate (4,5). Amphotericin, when administered as the deoxycholate complex, is highly bound to lipoproteins, mainly LDL and VLDL, and to a lesser extent to HDL (6,7) as well as to cell membranes of circulating blood cells. Binding is so avid that after spiking human plasma, no unbound amphotericin is detectable (7). Concentrations in peritoneal, pleural, and synovial fluids are usually less than half of those in serum, while cerebrospinal fluid concentrations range from undetectable to some 4% of the serum concentration, but over 40% in neonates (8). For DAMB the half-life is 1–2 days. Concentrations in bile are detectable for up to 12 days and in urine for 27–35 days. Clearance is faster and the volume of distribution smaller in neonates and infants (9) There is marked tissue storage of amphotericin, again depending on the formulation and the rate of infusion. Liver, spleen, kidneys, and lungs accumulate large amounts. Tissue storage plays a major role in the pharmacokinetics of amphotericin, which can be detected in tissues much more than a year after the completion of therapy (10–12). Up to 40% of amphotericin is ultimately excreted unchanged in urine. Elimination via the bile plays a lesser role, and metabolism appears to be unimportant. Elimination is so slow that dosages need not be altered in patients with renal insufficiency.

Lipid formulations of amphotericin have individually variable pharmacokinetics. The use of DAMB in 20% Intralipid results in marked changes, with lower antifungally active blood concentrations (13). Infusion of ABLC, ABCD, or L-Amb, AmBisome results in plasma amphotericin concentrations specific to the individual formulation. The half-life of amphotericin after lipid formulations is prolonged compared with the deoxycholate formulation (14): 4–10 days for ABCD (15) and about 5 days for ABLC (16). The importance of these differences is unknown, because they do not reflect the biologically active concentration of amphotericin, which also varies with formulation. On a weight for weight basis amphotericin in lipid formulations is less active than in the deoxycholate formulation, because of lower systemic availability (5). One factor that complicates the interpretation of blood concentrations is the sparse data

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discriminating between amphotericin bound to the original lipid formula and to plasma lipoproteins, and the minute amount of unbound amphotericin not detectable by available analytical methods (7).

The interaction of amphotericin with serum lipoproteins (6) suggests that manipulations of blood lipids and blood lipoproteins might affect the pharmacokinetics of amphotericin, and therefore also alter its activity, including toxic effects, as suggested in animal studies (17).

Observational studies

Amphotericin is highly effective in the treatment of visceral leishmaniasis (18). In a prospective study of 938 patients from Bihar, India, who received the drug in a dosage of 1 mg/kg/day infused over 2 hours for 20 days, serum creatinine values over 177 μmol/l were noted in 6.3%, and acute renal insufficiency developed in three patients. Two patients died, possibly related to amphotericin, one with renal insufficiency and one with hypokalemia and cardiac arrest. Infusion-related chills occurred in 92% and fever in 40% of patients. The parasitological cure rate (no relapse within 6 months) exceeded 99%.

Amphotericin deoxycholate

The adverse effects of amphotericin deoxycholate have been reviewed in a retrospective analysis of 102 adult patients (median age 61 years) with a variety of underlying conditions who were admitted to a small community hospital in Honolulu and who received the drug for treatment of presumed or proven fungal infections that were mostly due to *Candida* species (19). The average total dose of amphotericin deoxycholate was comparatively low at 162 (range 10–840) mg. The initial dose averaged 16 (range 1–50) mg and the total duration of therapy was 8.3 (range 1–46) days. Chills, fever, and/or nausea were noted in 25% of the patients. Hypokalemia (a serum potassium concentration below 3.5 mmol/l) occurred in 19%, and nephrotoxicity (defined as a serum creatinine concentration of at least 141 μmol/l (1.6 mg/dl) with an increase of at least 44 μmol/l (0.5 mg/dl) during amphotericin deoxycholate therapy) in 15% of the patients. Nephrotoxicity increased with increasing total dose of amphotericin, while infusion-associated toxicity decreased with advancing age. The overall response rate to therapy with amphotericin deoxycholate was 83%.

Amphotericin colloidal dispersion

The safety and efficacy of amphotericin colloidal dispersion have been evaluated in 148 immunocompromised patients with candidemia (20). ABCD was given intravenously in a median daily dose of 3.9 (range 0.1–9.1) mg/kg for a median of 12 (range 1–72) days. In the safety analysis ($n = 148$ patients), nephrotoxicity occurred in 16% of the patients, with either doubling of the baseline serum creatinine concentration or an increase of 88 μmol/l (1.0 mg/dl) or a 50% fall in calculated creatinine clearance. Severe adverse events were believed to be probably or possibly related to ABCD in 36 patients (24%), including chills and fever (9.5%), hypotension and abnormal kidney function (4%), tachycardia, asthma, hypotension (3%), and dyspnea (2%). ABCD was withdrawn in 12% because of toxicity. The overall response rate in 89 evaluable patients was 66% with candidemia alone and 14% with disseminated candidiasis.

The safety and efficacy of ABCD have been studied in 133 patients with invasive fungal infections and renal impairment due to either amphotericin deoxycholate or pre-existing renal disease (21). The mean daily dose of ABCD was 3.4 (range 0.1–5.5) mg/kg, and the mean duration of therapy was 21 (range 1–207) days. Although individual patients had increases in serum creatinine concentrations, ABCD did not have an adverse effect on renal function: the mean serum creatinine concentration tended to fall slightly with days on therapy, and increases were not dose-related. Six patients discontinued ABCD therapy because of nephrotoxicity. Infusion-related adverse events occurred at least once in 74 patients (56%); however, while 43% of patients had infusion-related toxic effects on day 1, only 18% reported these events by day 7. There were complete or partial responses in 50% of the intention-to-treat population and in 67% of the 58 evaluable patients.

The safety of ABCD has been reviewed using data from 572 immunocompromised patients refractory to or intolerant of standard therapies enrolled in five phase I/II clinical trials (22). The mean daily dose of ABCD was 3.85 (median 3.8, range 0.1–9.1) mg/kg and the mean duration of treatment was 25 (median 16, range 1–409) days. Overall, the principal adverse events associated with ABCD therapy were chills (52%), fever (39%), and hypotension (19%). These infusion-related reactions were dose-related and were the dose-limiting adverse events, defining the maximum tolerated dosage at 7.5 mg/kg. ABCD did not adversely affect renal function, as measured by overall changes in serum creatinine from baseline to the end of therapy, even in patients with pre-existing renal impairment; only 3.3% of patients discontinued therapy because of nephrotoxicity. Complete or partial responses to treatment were reported in 149 of 260 evaluable patients (57%).

The safety and efficacy of ABCD have been studied in 220 bone marrow transplant recipients enrolled in the same five phase I or phase II studies (23). The median dose in this population was 4 (range 0.4–8.0) mg/kg, and the median duration of treatment was 16 (range 1–409) days. Overall, 37 (19%) of the patients had nephrotoxicity, defined as a doubling of serum creatinine from baseline, an increase of 88 μmol/l from baseline, or at least a 50% fall in calculated creatinine clearance. There were no significant changes in hepatic transaminases, alkaline phosphatase, or total bilirubin. Fever and chills were reported by 12 and 11% of patients respectively. Other acute, severe, infusion-related adverse events were hypoxia (4.1%), hypertension (2.7%), and hypotension (2.7%).

Mucormycosis has an exceedingly high mortality rate in immunocompromised patients. In five phase I and phase II studies of ABCD, 21 patients were given ABCD (mean dose 4.8 mg/kg per infusion for a mean duration of 37 days) on the basis of pre-existing renal insufficiency, nephrotoxicity during amphotericin B therapy, or refractory infections (24). Of 20 evaluable patients, 12 responded to ABCD, and there was no renal or hepatic toxicity. However, a previous randomized, comparative trial showed an at least similar if not increased frequency

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and severity of infusion-related reactions compared with conventional amphotericin B (25).

Amphotericin lipid complex

The safety and efficacy of ABLC have been evaluated in 556 cases of proven or presumptive invasive fungal infection treated in an open, single-patient, US emergency-use study of patients who were refractory to or intolerant of conventional antifungal therapy (26). The daily dosage was either 5 mg/kg (87%) or 3 mg/kg. The investigators had the option of reducing the daily dosage as clinically warranted. Treatment was for 7 days in 540 patients (97%). During the course of ABLC therapy, serum creatinine concentrations in all patients fell significantly from baseline. In 162 patients with serum creatinine concentrations of at least 221 μmol/l (2.5 mg/dl) at baseline, the mean serum creatinine concentration fell significantly from the first week to the sixth week. The serum creatinine concentration increased from baseline to the end of therapy in 132 patients (24%). Hypokalemia (serum potassium concentration of less than 3 mmol/l) developed in 4.6%, and hypomagnesemia (serum magnesium concentration of less than 0.75 mmol/l) in 18%. There was a rise in serum bilirubin in 142/284 patients (33%); the overall increase was from 79 to 112 μmol/l (4.66–6.59 mg/dl) at the end of therapy. The mean alkaline phosphatase activity rose from 273 to 320 IU/l. There was no significant change overall in alanine transaminase activity, but the activity increased by the end of treatment in 16% of patients with initially normal values. There were complete or partial responses to therapy with ABLC in 167 of 291 mycologically confirmed cases evaluable for therapeutic response (57%).

The safety and efficacy of ABLC 5 mg/kg/day in patients with neutropenia and intolerance or refractoriness to amphotericin deoxycholate have been reported in two smaller series of 25 treatment courses from the UK. In one, the mean serum creatinine at the start of therapy was 139 μmol/l and at the end of therapy 132 μmol/l; there were no infusion-related adverse events (27). There was an increase in alanine transaminase activity in 12 of the 22 analysed treatment courses. In the other, there was an increase in serum creatinine in 5 of 18 courses (28%), and hypokalemia (less than 2.5 mmol/l) in two courses (11%); premedication for infusion-associated reactions was required in three courses (17%) (28). There were modest increases in serum alanine transaminase activities in five patients (30%).

In contrast to these reports, there was a high prevalence of adverse events with ABLC in the treatment of suspected or documented invasive fungal infections in 19 Scandinavian patients with mostly hematological malignancies (29). The mean starting dose of ABLC was 4.1 mg/kg/day, given for a median of 3 (range 1–19) days. ABLC was withdrawn because of adverse events in 14/19 patients (74%). These included rising creatinine concentrations ($n = 12$), increased serum bilirubin ($n = 7$), erythema ($n = 6$), increased alanine transaminase ($n = 6$), fever and chills ($n = 5$), hypoxemia ($n = 3$), hemolysis ($n = 2$), and back pain and increased serum alkaline phosphatase activity ($n = 1$ each). In patients with renal adverse effects, there were significantly increased serum creatinine concentration (from 85 to 199 mmol/l) and increased bilirubin concentration (from 17 to 77 μmol/l) in seven patients. The authors stated that while all the patients were very ill at the time of the start of ABLC therapy, in all cases the adverse effects had a direct and obvious correlation with the administration of ABLC. However, the reason for this unusual high rate of adverse events remains unclear.

Safety data have been published in a retrospective analysis of 551 patients with invasive fungal infections intolerant of or refractory to conventional antifungal therapy, 73 of whom received ABLC initially at 3 mg/kg/day instead of 5 mg/kg/day, as recommended in the protocol (30). There were no notable differences in adverse events (increased serum creatinine, infusion-related chills) between the two groups. Serum creatinine values were improved or stable at the end of therapy in 78 and 70% of patients respectively.

Two smaller series have addressed the safety of ABLC in immunocompromised patients (31,32). Each included about 30 patients who were treated with median dosages of 4.8 and 5.0 mg/kg for a median of 8 and 14 days. In contrast to a previous retrospective analysis that showed a 74% withdrawal rate, mostly due to infusion-related reactions (29), ABLC was well tolerated, with withdrawal rates of 6 and 0% and an overall trend for stable or improved serum creatinine values at the end of therapy. Similarly, 13 infusion-related reactions have been reported among 308 infusions in four of ten patients with hematological malignancies receiving ABLC 3 mg/kg/day (33). These reactions (fever, rigors, myalgias), occurred during the first infusions, were judged to be mild, and resolved during later infusions. ABLC was well tolerated by 30 persistently febrile neutropenic patients with hematological malignancies who received it in a low dosage of 1 mg/kg/day for a median of 7.5 (range 2–19) days (34). Seven patients (23%) had mild to moderate infusion-related reactions, and no patient had nephrotoxicity. In one patient, ABLC was discontinued owing to intolerable infusion-related fever and chills.

The safety and efficacy of low dose ABLC (1 mg/kg/day) for empirical treatment of fever and neutropenia have been studied in 69 episodes in 61 patients with hematological malignancies (35). The median duration of therapy was 8 (range 2–19) days and 13 patients had mild to moderate infusion-related adverse events. Creatinine concentrations remained stable in 42 cases, improved in 9, and deteriorated in 18. There were no other toxic effects. The response rate (resolution of fever during neutropenia and absence of invasive fungal infection) was 67%.

Fungal infection remains an important cause of morbidity and mortality in lung transplant patients. In a prospective non-comparative evaluation in lung or heart-lung transplant recipients, ventilated patients received undiluted aerosolized ABLC 100 mg, and extubated patients received 50 mg; in all, 381 treatments were given (98 in ventilated patients and 283 in extubated patients) (36). The treatment was administered by face mask jet nebulizer with compressed oxygen at a flow rate of 7–8 l/minute and inhaled over 15–30 minutes. Treatments were

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delivered once every day for four consecutive days, then once a week for 2 months. In all, 381 treatments were given to 51 patients, and ABLC was subjectively well tolerated in 98%. Pulmonary function worsened by 20% or more in under 5% of all treatments. There were no significant adverse events.

Liposomal amphotericin

The safety, tolerance, and pharmacokinetics of liposomal amphotericin have been evaluated in an open, sequential dose escalation, multiple-dose phase I/II study in 36 patients with neutropenia and persistent fever requiring empirical antifungal therapy (37). The patients received doses of 1, 2.5, 5.0, or 7.5 mg/kg/day of liposomal amphotericin for a mean of 9.2 days. Liposomal amphotericin was well tolerated: infusion-related adverse effects (fever, chills, rigor) occurred in 15 (5%) of all 331 infusions, and only two patients (5%) required premedication (dyspnea and generalized flushing; facial urticaria). Hypotension (one infusion) and hypertension (three infusions) were infrequent. One patient each had sharp flank pain and dyspnea during one infusion; these symptoms did not recur during subsequent infusions. Serum creatinine, potassium, and magnesium concentrations were not significantly changed from baseline, and there were no net increases in serum transaminases. There was, however, a significant increase in serum alkaline phosphatase activity and increase in bilirubin concentration in the overall population as well as in individual dosage groups. One patient who received concomitant L-asparaginase had increases in serum lipase and amylase activities in association with symptoms of pancreatitis while receiving liposomal amphotericin; however, as he continued to receive the drug, the serum lipase and amylase returned to baseline. Liposomal amphotericin had non-linear pharmacokinetics consistent with reticuloendothelial uptake and redistribution. There were no breakthrough fungal infections during therapy.

The efficacy of two dosages of liposomal amphotericin in the treatment of proven or probable invasive aspergillosis in neutropenic patients with cancer or those undergoing bone marrow transplantation has been studied in a prospective, randomized, open, multicenter trial in 120 patients randomized to receive either 1 mg/kg/day or 4 mg/kg/day of liposomal amphotericin; 87 patients were available for evaluation (38). There was at least one toxic event during treatment in 15 of 41 patients given 1 mg/kg/day and 25 of 46 given 4 mg/kg/day, but the numbers of events per patient were similar. These events included headache, nausea, diarrhea, rash, liver toxicity, myalgia, dyspnea, fever, chills, and back pain. Renal toxicity definitely related to liposomal amphotericin occurred in 1/41 patients treated with 1 mg/kg/day and 5/46 patients treated with 4 mg/kg/day. Only in one case was treatment permanently discontinued because of toxicity related to liposomal amphotericin (4 mg/kg/day). No patient died from liposomal amphotericin toxicity. Overall, liposomal amphotericin was effective in 50–60% of patients; however, the number of cases with proven invasive aspergillosis was too small to allow a meaningful comparison of the two dosages regarding efficacy in this life-threatening disease.

The safety and efficacy of liposomal amphotericin have been compared with that of ABLC in a retrospective analysis of 59 adult patients with hematological malignancies who received 68 courses of either liposomal amphotericin ($n = 32$) or ABLC ($n = 36$) for a variety of presumed or confirmed invasive fungal infections (39). The median daily dosages were 1.9 (range 0.7–4.0) mg/kg for liposomal amphotericin and 4.8 (range 1.9–5.8) mg/kg for ABLC. There was no statistically significant difference in the overall outcome; febrile reactions were significantly more common with ABLC (36 versus 6%), but there were no significant differences in the median creatinine concentrations at baseline and at the end of therapy or in the number of patients with urinary loss of potassium or magnesium.

In an open, sequential phase II clinical study of three different regimens of liposomal amphotericin for visceral leishmaniasis (2 mg/kg on days 1–6 and on day 10; 2 mg/kg on days 1–4 and on day 10; 2 mg/kg on days 1, 5, and 10) in Indian and Kenyan patients in three developing countries, there were few infusion-associated adverse effects (40). Of 32 Brazilian patients (15 of whom received 2 mg/kg on days 1–10 because of poor responses to the first regimen, 37% had a fever with one or more infusions, 9% had chills, and 6% had back pain; in addition, three patients had respiratory distress and/or cardiac dysrhythmias. There were different response rates to the three regimens in the different countries, leading to the recommendation of 2 mg/kg on days 1–4 and day 10 in India and Kenya, and 2 mg/kg on days 1–10 in Brazil.

In order to determine the maximum tolerated dosage of liposomal amphotericin B, a phase I/II study was conducted in 44 adult patients with proven ($n = 21$) or probable ($n = 23$) infections due to *Aspergillus* species and other filamentous fungi (41). The dosages were 7.5, 10, 12.5, and 15 mg/kg/day. The number of infusions was 1–83 with a median duration of 11 days. The maximum tolerated dosage was at least 15 mg/kg. Infusion-related reactions included fever in 8 and chills and rigors in 5 of 43 patients. Three patients developed a syndrome of substernal chest tightness, dyspnea, and flank pain, which was relieved by diphenhydramine. Serum creatinine increased two times above baseline in 32% of patients, but this increase was not dose-related. Hepatotoxicity developed in one patient. Altogether, the most common adverse events included fever (48%), increased creatinine concentration (46%), hypokalemia (39%), chills (32%), and abdominal pain (25%), with no obvious dose-dependency. Nine patients (20%) stopped taking the drug because of an adverse event. The reasons included raised serum creatinine, renal insufficiency, pancreatitis, hyperbilirubinemia, hypotension associated with the infusion, cardiorespiratory failure, multiorgan failure, and relapse of the primary malignancy. The last three events were attributed to the underlying disease process. Discontinuation was unrelated to dosage. Pharmacokinetic analysis showed dose-related non-linear kinetics at dosages of 7.5 mg/kg/day and over.

Aerosolized amphotericin

In a prospective, randomized, multicenter trial, inhalation of aerosolized amphotericin (10 mg bd) has been investigated as prophylaxis against invasive aspergillosis

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in 382 cancer patients with an anticipated duration of neutropenia of at least 10 days (42). While there was no difference in the incidence of invasive aspergillosis, infection-related mortality, and overall mortality, 31% of the patients discontinued amphotericin prophylaxis prematurely owing to adverse effects (55%; most commonly cough, bad taste, nausea), inability to cooperate further (30%), violation of the study protocol (11%), and non-adherence (4%).

Comparative studies

Comparisons of different formulations of amphotericin

Amphotericin deoxycholate in glucose versus amphotericin deoxycholate in Intralipid

The safety of two formulations of intravenous amphotericin deoxycholate has been investigated in a randomized, open comparison in neutropenic patients with refractory fever of unknown origin or pulmonary infiltrates (43). Amphotericin deoxycholate was given in a dose of 0.75 mg/kg/day either in 250 ml of a 5% glucose solution or mixed with 250 ml of a 20% lipid emulsion (Intralipid 20%) on eight consecutive days and then on alternate days as a 1–4 hour infusion. The mean number of days of treatment was 11.3 versus 9.9 days. There were no statistically significant differences between the two cohorts with respect to the incidence of infusion-related adverse events, such as fever and chills, renal impairment, or treatment failure. However, grade 3–4 acute dyspnea occurred slightly more often with the lipid emulsion formulation, and there were significantly more other severe respiratory events in patients receiving lipid emulsion, raising the possibility of a causal relation via fat overload or incompatibility between amphotericin deoxycholate and the lipid emulsion.

The efficacy and tolerability of amphotericin prepared in Intralipid 20% have been evaluated in 16 patients with HIV infection and esophageal candidiasis or cryptococcosis and compared with standard amphotericin in a matched group of 24 patients (44). While both formulations had apparently similar clinical and microbiological efficacy, fewer patients receiving the lipid emulsion formulation required premedication or symptomatic therapy for infusion-associated adverse events, and fewer patients were withdrawn because of adverse effects. Renal adverse effects (a rise in serum creatinine and/or electrolyte loss) were more common in patients who received the conventional formulation.

The efficacy and safety of amphotericin in Intralipid 20% or 5% glucose has been evaluated in a retrospective case analysis in 30 patients with AIDS and cryptococcal meningitis who received either formulation 1 mg/kg/day for 20 days with or without flucytosine ($n = 20$) or fluconazole ($n = 4$), followed by maintenance therapy with fluconazole 400 mg/day (45). Twenty patients received amphotericin deoxycholate in 500 ml 5% glucose over 5 hours, and 10 received amphotericin deoxycholate in 100 ml of 20% Intralipid given over 2 hours. Complete clinical resolution was obtained in 55 and 60% of the patients respectively. There were no differences regarding infusion-related adverse effects, nephrotoxicity, or anemia.

Amphotericin deoxycholate versus amphotericin B colloidal dispersion

Amphotericin colloidal dispersion has been compared with amphotericin deoxycholate in a prospective, randomized, double-blind study in the empirical treatment of fever and neutropenia in 213 patients (25). Patients were stratified by age and concomitant use of ciclosporin or tacrolimus and then randomized to receive ABCD (4 mg/kg/day) or amphotericin deoxycholate (0.8 mg/kg/day) for 14 days. Renal dysfunction was less likely to develop and occurred later with ABCD than with amphotericin deoxycholate. Likewise, the absolute and percentage fall in the serum potassium concentration from baseline to the end of therapy was greater with amphotericin deoxycholate than ABCD. However, probable or possible infusion-related hypoxia and chills were more common with ABCD than amphotericin deoxycholate. There was a therapeutic response in 50% of the patients who received ABCD and 43% of those who received amphotericin deoxycholate. Thus, ABCD was of comparable efficacy and less nephrotoxic than amphotericin deoxycholate, but infusion-related events were more common with ABCD.

Amphotericin deoxycholate versus liposomal amphotericin

Liposomal amphotericin 5 mg/kg/day and amphotericin deoxycholate 1 mg/kg/day have been compared in the treatment of proven or suspected invasive fungal infections in neutropenic patients in a randomized, multicenter study (46). Significantly more patients given amphotericin deoxycholate had a greater than 100% increase in baseline serum creatinine. Treatment was temporarily discontinued or the dosage reduced because of an increase in serum creatinine in 18/54 (33%) patients treated with amphotericin deoxycholate versus 2/51 (4%) treated with liposomal amphotericin. There was no statistically significant difference in the number of patients with infusion-related toxicity (fever/chills), hypokalemia, or increases in serum transaminases, alkaline phosphatase, or serum bilirubin. In 66 patients eligible for analysis of efficacy, there was a trend to an improved overall response rate and a significant difference in the rate of complete responses in favor of liposomal amphotericin; death rates were also lower in patients treated with liposomal amphotericin.

The results of a randomized, double-blind, multicenter comparison of liposomal amphotericin (3.0 mg/kg/day) with conventional amphotericin deoxycholate (0.6 mg/kg/day) for empirical antifungal therapy in patients with persistent fever and neutropenia have been reported (47). The mean duration of therapy was 10.8 days for liposomal amphotericin (343 patients) and 10.3 days for amphotericin deoxycholate (344 patients). While the composite rates of successful treatment were similar (50% for liposomal amphotericin and 49% for amphotericin deoxycholate), significantly fewer of the patients who received the liposomal preparation had

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infusion-related fever (17 versus 44%), chills or rigors (18 versus 54%), or other reactions, including hypotension, hypertension, and hypoxia. Nephrotoxicity (defined by a serum creatinine concentration twice the upper limit of normal) was significantly less frequent among patients treated with liposomal amphotericin (19%) than among those treated with conventional amphotericin deoxycholate (34%).

Amphotericin lipid complex versus liposomal amphotericin

Liposomal amphotericin and ABLC have been compared in an open randomized study in 75 adults with leukemia and 82 episodes of suspected or documented mycosis (48). The median durations of treatment and dosages were 15 days at 4 mg/kg/day for liposomal amphotericin and 10 days at 3 mg/kg/day for ABLC. Acute but not dose-limiting infusion-related adverse events occurred in 36 versus 70%. Bilirubin increased to over 1.5 times baseline in 59 versus 38%. There was no difference in the effects of either agent on renal function and drug-related withdrawals. The overall response rate to therapy in documented fungal infections (29 and 30% respectively) was not different between the two drugs.

Amphotericin deoxycholate in glucose versus amphotericin in nutritional fat emulsion

The safety of DAMB prepared in nutritional fat emulsion (a non-approved mode of amphotericin administration) has been reviewed (SEDA-21, 282) (SEDA-22, 285). It is not clear whether it has a better therapeutic index than other formulations, and methods of preparing it have not been standardized. The adverse effects of amphotericin prepared in nutritional fat emulsion have been compared with those of amphotericin prepared in 5% dextrose in two studies. While one of the studies showed a significantly lower frequency of infusion-related reactions and hypokalemia in patients receiving the fat emulsion (49), there were no differences in safety and tolerance between the two formulations in the other study (50). The safety of amphotericin prepared in nutritional fat emulsions has been reviewed (SEDA-21, 282) (SEDA-22, 285). Because of stability concerns and lack of systematic safety data, this form of amphotericin cannot be recommended.

Comparisons of amphotericin with other antifungal drugs

Antifungal azoles

Fluconazole

There has been an open, randomized comparison of amphotericin deoxycholate 0.5 mg/kg/day intravenously versus fluconazole 400 mg/day orally for empirical antifungal therapy in neutropenic patients with cancer and fever refractory to broad-spectrum antibiotics (51). Patients with abnormal hepatic or renal function were excluded, as were those with proven or suspected invasive fungal infection. The mean duration of therapy was 8.3 days with amphotericin deoxycholate and 7.9 days with fluconazole. Altogether, 32/48 patients randomized to amphotericin deoxycholate and 19/52 randomized to fluconazole had adverse affects (67 versus 36%). Two patients developed immediate hypersensitivity reactions (flushing, hypotension, bronchospasm) to amphotericin deoxycholate and had to be withdrawn. Hypokalemia was noted in 25 patients (52%), and nephrotoxicity, defined as a rise in serum creatinine of 44 μmol/l (0.5 mg/dl) or more compared with the baseline value, in nine patients (19%). The corresponding frequencies with fluconazole were 23 and 6% respectively. Treatment success rates and mortality were similar (46 versus 56% and 33 versus 27% respectively).

Fluconazole and amphotericin as empirical antifungal drugs in febrile neutropenic patients have been investigated in a prospective, randomized, multicenter study in 317 patients randomized to either fluconazole (400 mg qds) or amphotericin deoxycholate (0.5 mg/kg qds) (52). Adverse events (fever, chills, renal insufficiency, electrolyte disturbances, and respiratory distress) occurred significantly more often in patients who were given amphotericin (128/151 patients, 81%) than in those given fluconazole (20/158 patients, 13%). Eleven patients treated with amphotericin, but only one treated with fluconazole, were withdrawn because of an adverse event. Overall mortality and mortality from fungal infections were similar in both groups. There was a satisfactory response in 68% of the patients treated with fluconazole and 67% of those treated with amphotericin. Thus, fluconazole may be a safe and effective alternative to amphotericin for empirical therapy of febrile neutropenic patients; however, since fluconazole is ineffective against opportunistic molds, the possibility of an invasive infection by a filamentous fungus should be excluded before starting empirical therapy. Similarly, patients who take azoles for prophylaxis are not candidates for empirical therapy with fluconazole.

Conventional amphotericin deoxycholate (0.2 mg/kg qds) and fluconazole (400 mg qds) have been compared in a prospective randomized study in 355 patients with allogeneic and autologous bone marrow transplantation (53). The drugs were given prophylactically from day 1 until engraftment. There was no difference in the occurrence of invasive fungal infections, but amphotericin was significantly more toxic than fluconazole, especially in related allogeneic transplantation, after which 19% of patients developed toxicity compared with none of those who received fluconazole.

Itraconazole

Amphotericin and itraconazole have been compared in a multicenter, open, randomized study in 277 adults with cancer and neutropenia (54). Itraconazole oral solution (100 mg bd, $n = 144$) was compared with a combination of amphotericin capsules and nystatin oral suspension ($n = 133$). Adverse events were reported in about 45% of patients in each group. The most frequent were vomiting (14 versus 12 patients), diarrhea (12 versus 9 patients), nausea (5 versus 12 patients), and rash (2 versus 13 patients). There were no differences in liver function

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test abnormalities. Treatment had to be withdrawn because of adverse events (including death) in 34 patients who took itraconazole and 33 of those who took amphotericin plus nystatin; there were 17 deaths in each group and death was recorded as adverse event in 13 and nine patients respectively.

Intravenous amphotericin deoxycholate (0.7–1.0 mg/kg) and itraconazole (400 mg intravenously for 2 days, 200 mg intravenously for up to 12 days, then 400 mg/day orally) have been compared in 384 granulocytopenic patients with persistent fever in a randomized, multicenter trial (55). The median duration of therapy was 8.5 days. The incidence of drug-related adverse events (54 versus 5%) and the rate of withdrawal due to toxicity (38 versus 19%) were significantly higher with amphotericin. The most frequent reasons for withdrawal in patients taking itraconazole were nausea and vomiting (5%), rash (3%), and abnormal liver function tests (3%). Significantly more of the patients who received amphotericin had nephrotoxicity (24 versus 5%); however, fewer had hyperbilirubinemia (5 versus 10%). There was no difference in gastrointestinal adverse events between the two groups.

Amphotericin in capsules 500 mg qds has been compared with itraconazole elixir 2.5 mg/kg bd for the prophylaxis of systemic and superficial fungal infections in a double-blind, randomized, placebo-controlled, multicenter trial for 1–59 days (56). While itraconazole significantly reduced the frequency of superficial fungal infections, it was not superior in reducing invasive fungal infections or in improving mortality. Adverse events were reported in 222 patients taking itraconazole (79%) and in 205 patients taking amphotericin (74%). The commonest adverse events were gastrointestinal, followed by rash and hypokalemia, with no differences between the two regimens. In both groups, 5% of the adverse events were considered to be definitely drug-related. Comparable numbers of patients in the two groups permanently stopped treatment because of adverse events (including death), 78 (28%) in the amphotericin group and 75 (27%) in the itraconazole group. Nausea (11 and 9%) and vomiting (7 and 8%) were the most frequently reported adverse events that led to withdrawal. Biochemical changes were comparable in the two groups.

Echinocandins

In a randomized, double-blind comparison of amphotericin (0.5 mg/kg intravenously) and caspofungin acetate (35, 50, or 70 mg) once daily for 7–14 days in 140 patients with oropharyngeal and/or esophageal candidiasis, 63% had esophageal involvement and 98% were infected with HIV (57). Response rates were 63% with amphotericin and 74–91% with caspofungin. More patients receiving amphotericin had drug-related adverse effects (fever, chills, nausea, vomiting) than those receiving any dose of caspofungin. Two patients who took caspofungin 35 mg and one who was given amphotericin withdrew because of adverse effects. Drug-related laboratory abnormalities were also more common in patients who received amphotericin. The most common drug-related laboratory abnormalities in patients who received caspofungin were raised alanine transaminase, aspartate transaminase, and alkaline phosphatase, which were typically less than five times the upper limit of normal and resolved despite continued treatment. None of the patients receiving caspofungin and nine of those who received amphotericin developed drug-related increases in serum creatinine concentrations. No patient withdrew because of drug-related laboratory adverse effects.

Amphotericin has been compared with caspofungin in a multicenter, double-blind, randomized trial in 128 adults with endoscopically documented symptomatic *Candida* esophagitis (58). There was endoscopically verified clinical success in 63% of patients given amphotericin deoxycholate 0.5 mg/kg/day and in 74 and 89% of the patients who received caspofungin 50 and 70 mg/day respectively. Therapy was withdrawn because of drug-related adverse events in 24% of the patients who were given amphotericin and in 4 and 7% of those who were given caspofungin 50 and 70 mg/day respectively. More patients who received amphotericin had drug-related fever, chills, or nausea than those who received caspofungin. More patients who received amphotericin (91%) than caspofungin (61 and 32%) developed drug-related laboratory abnormalities. There were drug-related increases in blood urea–nitrogen concentrations in 15% of the patients who received amphotericin but none of those who received caspofungin. Likewise, serum creatinine concentrations increased in 16 patients who received amphotericin but in only one who received caspofungin. In summary, caspofungin was as effective as amphotericin but better tolerated in the treatment of esophageal candidiasis.

In a double-blind, randomized trial, amphotericin deoxycholate was compared with caspofungin for the primary treatment of invasive candidiasis (59). Patients who had clinical evidence of infection and a positive culture for *Candida* species from blood or another site were enrolled. They were stratified according to the severity of disease, as indicated by the presence or absence of neutropenia and the Acute Physiology and Chronic Health Evaluation (APACHE II) score, and were randomly assigned to receive either amphotericin (0.6–0.7 mg/kg/day or 0.7–1.0 mg/kg/day for patients with neutropenia) or caspofungin (50 mg/day with a loading dose of 70 mg on day 1). Of the 239 patients enrolled, 224 were included in the modified intention-to-treat analysis. Baseline characteristics, including the percentage of patients with neutropenia and the mean APACHE II score, were similar in the two treatment groups. The efficacy of amphotericin was similar to that of caspofungin, with successful outcomes in 62% of the patients treated with amphotericin and in 73% of those treated with caspofungin. There were significantly more drug-related adverse events (fever, chills, and infusion-related events) associated with amphotericin. Amphotericin caused more nephrotoxicity, as defined by an increase in serum creatinine of at least twice the baseline value or an increase of at least 88 μmol/l) (8.4 versus 25%). Only 2.6% of those who were given caspofungin were withdrawn because of adverse events, compared with 23% of those who were given amphotericin. Thus, caspofungin was at least as effective

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as amphotericin for the treatment of mostly non-neutropenic patients with invasive candidiasis but significantly better tolerated.

Comparisons with antimonials

Amphotericin might be useful in the treatment of leishmaniasis, as suggested by a comparative study (amphotericin in 14 doses of 0.5 mg/kg infused in 5% glucose on alternate days) against sodium stibogluconate (20 mg/kg in two divided doses daily for 40 days). All 40 patients taking amphotericin were cured, whereas in the stibogluconate group 28 of the 40 showed an initial cure but only 25 a definite cure (60).

Placebo-controlled studies

In a small randomized, double-blind, placebo-controlled study, liposomal amphotericin (2 mg/kg three times weekly) was investigated as prophylaxis against fungal infections in 161 patients undergoing chemotherapy or bone marrow transplantation for hematological malignancies (61). There were no statistically significant differences between the two study arms in the incidences of the most frequently reported adverse events or in changes in renal and hepatic laboratory parameters. Despite a sizable rate of suspected or documented fungal infections in the placebo arm, prophylactic therapy with liposomal amphotericin did not lead to a significant reduction in fungal infections or the requirement for systemic antifungal therapy.

General adverse effects

Fever, rigors, nausea, vomiting, headaches, muscle pains, and joint pains are common. The incidence and severity of these reactions are highest with rapidly increasing blood concentrations, and are frequent during the start of therapy (62). Hypersensitivity reactions have been described in case reports. Reports of rashes have been rare. The UK Committee on Safety of Medicines received 20 reports of the occurrence of rash over a 17-year period (SEDA-16, 289). However, with increased use of lipid formulations this could change (63–65). Tumor-inducing effects have not been demonstrated in animals or humans.

Organs and Systems

Cardiovascular

Electrolyte disturbances (hyperkalemia, hypomagnesemia, renal tubular acidosis) due to renal toxicity can be additional factors that precipitate cardiac reactions.

Effects on blood pressure

Changes in blood pressure (hypotension as well as hypertension) have been reported (66,67).

- A 67-year-old man with multiple intraperitoneal and urinary fungal pathogens and a history of well-controlled chronic hypertension developed severe hypertension associated with an infusion of ABLC (68). He received a 5 mg test dose, which was tolerated without incident. About 60 minutes into the infusion (5 mg/kg), his blood pressure rapidly increased to 262/110 mmHg from a baseline of 150/80 mmHg. His temperature increased to 39.8°C, and tachycardia developed (up to 121/minute). The infusion was stopped, and he was given morphine, propranolol, and paracetamol. His blood pressure returned to baseline over the next 2 hours. Rechallenge with ABLC on the next day resulted in an identical reaction despite premedication with pethidine, diphenhydramine, and morphine. ABLC was permanently withdrawn, and the infection was managed with high dosages of fluconazole.

The etiology of amphotericin-associated hypertension has not been elucidated, but it may be related to vasoconstriction. Of note, the traditional test dose appears not to identify individuals predisposed to hypertensive reactions; four of six cases of amphotericin-associated hypertension received test doses without incident.

Cardiac dysrhythmias

In 6 of 90 children given intravenous amphotericin there was a significant fall in heart rate, and monitoring of heart rate was recommended in children with underlying heart disease (69). These immediate reactions follow intravenous administration and occur particularly with excessively rapid infusion of DAMB.

Ventricular dysrhythmias have been reported after rapid infusion of large doses of DAMB (70) in patients with hyperkalemia and renal insufficiency, but not in patients with normal serum creatinine and potassium concentrations, even if they have received the drug over a period of 1 hour. Slower infusion rates and infusion during hemodialysis have been advocated in patients with terminal kidney insufficiency, in order to avoid hyperkalemia.

Chest pain

Three cases of chest discomfort associated with infusion of L-AmB at a dosage of 3 mg/kg/hour for 1 hour have been reported (71).

- The first patient had chest tightness and difficulty in breathing and the second had dyspnea and acute hypoxia (PaO_2 55 mmHg; 7.3 kPa), both within 10 minutes of the start of the infusion. The third complained of chest pain 5 minutes after the start of two infusions. In all cases the symptoms resolved on terminating therapy. Two patients were later rechallenged with slower infusions and tolerated the drug well.

A review of the literature showed that similar reactions had been reported anecdotally in several clinical trials of L-AmB, with all other formulations, and with liposomal daunorubicin and doxorubicin. While the pathophysiology of such reactions is yet unclear, the authors recommended infusing L-AmB over at least 2 hours with careful monitoring of adverse events.

Myocardial ischemia

Rare instances of cardiac arrest have been reported (72).

Vascular effects

Phlebitis occurs in over 5% of patients receiving amphotericin deoxycholate through peripheral veins, which

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limits the concentration advisable for this route of administration.

Raynaud's syndrome has been attributed to DAMB phenomenon (73).

Extravasation can cause severe local reactions, including tissue necrosis. Safe venous access, preferably via a central line is advisable. The recommendation to use sodium heparin or buffered dextrose is not supported by clinical data.

Respiratory

Inhaled DAMB, and to a lesser extent inhaled liposomal amphotericin, can provoke pulmonary reactions, including bronchospasm, cough, and dyspnea (74–77).

Original suggestions that DAMB in combination with granulocyte transfusions (78) result in pulmonary toxicity have subsequently not been confirmed in prospective observations (62,79). Pulmonary reactions, including dyspnea, hemoptysis, and new infiltrates, have also been suspected to be caused by the combined use of blood platelet transfusions and DAMB (SEDA-12, 227). It therefore appears advisable to space transfusions of blood products and amphotericin if possible (80).

Intravenous administration of DAMB has been associated with pulmonary reactions, including dyspnea, bronchospasm, fever, and chills; in contrast to rare reports of dyspnea after liposomal amphotericin (5), dyspnea was not associated with general toxic reactions. The possibility that liposome overload is the explanation of this reaction should be considered.

A life-threatening event has been reported after the use of ABLC in a patient previously treated with amphotericin deoxycholate (81).

- Tachycardia, tachypnea, dyspnea, and severe hypoxemia occurred 90 minutes after the start of the first dose of ABLC, with radiological evidence of bilateral interstitial infiltrates, and required transient mechanical ventilation. After the event, treatment was continued with amphotericin deoxycholate without undesirable effects.

Nervous system

Headache is common during the immediate infusion reaction. Neuropathy, convulsions, tremor, and paresis have also been attributed to amphotericin. It is difficult to assess these reports, because in systemic fungal infections, with the possibility of central nervous system involvement, the symptoms may be due to the underlying disease.

Reversible parkinsonism has been attributed to ABLC (82).

- A 10-year-old bone marrow recipient was given ABLC 7 mg/kg/day for prolonged periods of time. Ablation therapy before transplantation included cytosine arabinoside, cyclophosphamide, and total body irradiation. He developed progressive parkinsonian features; an MRI scan showed non-specific frontal cortex white matter abnormalities, and brain MR spectroscopy was consistent with significant neuronal loss in the left insular cortex, left basal ganglia, and left frontal white matter. He was given co-careldopa (carbidopa + levodopa) and made a slow recovery within 4 months. A follow-up MRI scan again showed frontal white matter changes, but repeat MR spectroscopy showed marked improvement in the areas previously examined.

This case shows that, regardless of the formulation of amphotericin, severe neurological adverse effects can occur, in particular in patients who receive large dosages of amphotericin after cranial irradiation. A clinical syndrome of akinetic mutism, incontinence, and parkinsonism has been described in patients who received large doses of amphotericin deoxycholate in association with central nervous system irradiation or infection (67).

Electrolyte balance

Selective distal tubular epithelial toxicity by amphotericin can cause hypokalemia, and hypokalemia can cause further tubular damage. There is some evidence that hypokalemia due to amphotericin is mitigated by both spironolactone (83) and amiloride (84).

Infusion of amphotericin deoxycholate can cause hyperkalemia, in particular in the setting of renal insufficiency (67). The primary mechanism is not known.

- Fatal cardiopulmonary arrest occurred in a 4-year-old boy with acute leukemia and disseminated invasive candidiasis after the third infusion of ABLC 5 mg/kg/day, infused over 1 hour (85). During resuscitation he had a serum potassium concentration of 16 mmol/l; there was no evidence of hemolysis or rhabdomyolysis and serum creatinine and potassium concentrations had been within the reference ranges earlier in the day. Autopsy showed numerous fungal abscesses, including several in the myocardium.
- Serum potassium concentrations were determined at the end of a 2-hour infusion of amphotericin deoxycholate (1 mg/kg/day) in a 2-year-old girl with systemic candidiasis receiving long-term hemodialysis for renal dysplasia (85). The potassium concentration was 6.7 mmol/l, despite dialysis against a 1.5 mmol/l potassium bath just before the infusion. The next dose was given during dialysis, and the serum potassium concentration was 2.6 mmol/l after the infusion.

When giving amphotericin to dialysed patients, it may be necessary to give it during dialysis in order to avoid hyperkalemia.

Hematologic

A normochromic, normocytic, usually mild anemia develops regularly during therapy with DAMB. The erythropoietin response to anemia appears to be blunted during DAMB therapy, and survival of erythrocytes may be reduced by toxic effects of amphotericin on the cell membrane (86).

Frank hemolysis has also been reported in rare instances, including, rarely, immune-mediated hemolysis (87,88).

Leukopenia has been reported (SED-12, 673).

Thrombocytopenia has been reported in several instances and also occurs with lipid formulations (89,90).

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During amphotericin therapy, the response of platelet counts to thrombocyte transfusions was reduced, as was platelet survival (91,92).

Gastrointestinal

Anorexia, nausea, and vomiting are common effects of parenteral administration of amphotericin. Gastrointestinal complaints are markedly less common with liposomal amphotericin than with ABCD(5).

Liver

Cholestasis has been reported in infants treated with amphotericin for systemic *Candida* infections (SEDA-14, 230). Most of the above reports were incidental, and amphotericin cannot be regarded as a known cause of liver damage. This does not necessarily also apply to liposomal amphotericin and other lipid formulations. Therapy with L-Amb, AmBisome was associated with a rise in alkaline phosphatase in over a third of children treated with AmBisome (93) and with hepatic dysfunction in a little under 20% of adolescents and adults. In a small retrospective study, ABLC was withdrawn in 27% of patients because of rises in serum bilirubin and alkaline phosphatase, a finding confirmed in a larger prospective study. Cholestasis has also been observed with ABCD, in contrast to reports that L-AmB does not increase transaminases (5).

Acute hepatic damage has rarely been reported with DAMB. Asymptomatic increases in hepatic serum enzyme activities were seen in one case (94).

- A 26-year-old previously healthy man with life-threatening pulmonary blastomycosis developed increased hepatic transaminases to a maximum of ten times (aspartate transaminase) and 20 times (alanine transaminase), the upper limit of the reference ranges, 10 days after the addition of amphotericin (0.5 mg/kg) to his initial itraconazole therapy (200 mg bd) (95). The serum transaminase activities returned to normal within 4 days after withdrawal of amphotericin, and the blastomycosis was successfully treated with itraconazole alone. A liver biopsy showed mild focal fatty changes but no evidence of blastomycosis.

The authors speculated that amphotericin may have facilitated the uptake of itraconazole into mammalian cells by its membrane-damaging action, leading to increased interaction of itraconazole with CYP450 enzymes and hepatocellular damage.

Pancreas

In a retrospective analysis, 5 of 31 children with cancers, who had received liposomal amphotericin in dosages of 1–3 mg/kg/day, had an isolated transient rise in the serum lipase activity during or shortly after therapy with liposomal amphotericin (96). Three of these patients had signs of pancreatitis. While the exact pathogenesis is unclear, the authors proposed fat overload or toxic damage to the pancreas by the liposomes or amphotericin itself as potential mechanisms.

Urinary tract

Amphotericin can cause both glomerular and tubular damage. Lipid-based formulations (colloidal dispersion, lipid complex, and liposomal amphotericin) are less nephrotoxic than conventional amphotericin deoxycholate (97). However, several caveats have to be kept in mind in making such comparisons. For example, there are no defined equivalent doses for amphotericin deoxycholate and its lipid-based counterparts.

Presentation

The clinical and laboratory findings include reductions in glomerular filtration rate and renal plasma flow, proteinuria, cylindruria, and hematuria; the last three are frequent but usually discrete. The reductions in renal plasma flow and filtration fraction occur early. Changes in tubular function can cause increased excretion of uric acid (an effect that can be used to monitor the tubular damage). Excessive loss of potassium, magnesium, and bicarbonate result in hypokalemia, hypomagnesemia, and renal tubular acidosis (98,99). Severe hypokalemia is common, and requires parenteral potassium replacement. Acidosis can also be severe, requiring bicarbonate. Hypomagnesemia, which may be symptomatic, can cause secondary hypocalcemia, resulting in tetany (100–102).

Amphotericin can cause an inability to form a concentrated urine (hyposthenuria) although this rarely becomes clinically important (67).

Nephrogenic diabetes insipidus, resistant to vasopressin, following damage to the distal renal tubule, may be more common than reported (103,104). Careful monitoring of electrolytes is therefore recommended in all instances of amphotericin therapy.

- A 43-year-old HIV-infected patient presented with nephrogenic diabetes insipidus associated with amphotericin deoxycholate therapy for ocular candidiasis; rechallenge was positive (105).

Mechanism

The exact mechanisms involved in amphotericin-induced uremia are not yet fully understood. Changes in tubular ion permeability have been demonstrated both in vitro and in vivo (12,100,106). The uremia can be caused by tubuloglomerular feedback, a mechanism whereby increased delivery and re-absorption of chloride ions in the distal tubule initiates a reduction in the glomerular filtration rate. Tubuloglomerular feedback is amplified by sodium deprivation and suppressed by sodium loading. Other possible mechanisms are renal arteriolar spasm, calcium deposition during periods of ischemia, and direct cellular toxicity (12). Yet other lines of research have looked at the roles of prostaglandins and TNFα, with evidence that indometacin may abate prostaglandin-mediated toxicity (107), an approach that is not practical in most patients requiring antifungal drugs.

- Renal damage due to amphotericin has also been reportedly caused by a tumor lysis-like syndrome in a 41-year-old woman with visceral leishmaniasis, with hyperkalemia, hyperphosphatemia, hyperuricemia, and acute renal insufficiency (108).

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Differences among formulations

The nephrotoxicity of lipid formulations of amphotericin varies from formulation to formulation.

Amphotericin B deoxycholate

The epidemiology of the nephrotoxicity of conventional amphotericin B has been investigated in a retrospective study in 494 adult inpatients who received two or more doses (109). Nephrotoxicity was defined as a 50–100% increase in the baseline creatinine concentration. The median cumulative dose was 240 mg and most of the patients received it for empirical therapy. Overall, 139 patients (28%) had renal toxicity, including 58 (12%) with moderate to severe nephrotoxicity. For each 10 mg increase in the mean daily dose, the adjusted rate of renal toxicity increased by a factor of 1.13. Five risk factors were defined: a mean daily dose of 35 mg or more, male sex, weight 90 kg or more, chronic renal disease, and concurrent use of amikacin or ciclosporin. The incidence of moderate to severe nephrotoxicity was 4% in patients with none of these risk factors, 8% in those with one, 18% in those with two, and 29% in those with three or more. Nephrotoxicity rarely led to hemodialysis ($n = 3$). However, at the time of discharge or death, 70% of the patients with moderate to severe nephrotoxicity had a serum creatinine concentration that was at least 44 μmol/l above baseline. This study shows dose-dependency of nephrotoxicity related to DAMB, accentuated by other nephrotoxic drugs and patient risk factors. The authors suggested that in patients with more than two risk factors alternative antifungal drugs should be considered.

The nephrotoxicity of amphotericin deoxycholate has been investigated in a retrospective multicenter study in 239 immunosuppressed patients with suspected or proven aspergillosis for a median duration of 15 days (110). The serum creatinine concentration doubled in 53% of the patients and exceeded 221 μmol/l in 29%; 15% underwent dialysis, and 60% died. Multivariate Cox proportional hazards analysis showed that patients whose creatinine concentration exceeded 221 μmol/l, and patients with allogeneic and autologous bone marrow transplants were at greatest risk of requiring hemodialysis. The use of hemodialysis, the duration of amphotericin therapy, and the use of nephrotoxic agents were associated with a greater risk of death, whereas patients who underwent solid organ transplantation were at lowest risk. The findings of this study suggest that raised creatinine concentrations during therapy with amphotericin are associated with a substantial risk of hemodialysis and a higher mortality rate, but these risks vary in different patients.

Amphotericin-associated nephrotoxicity has been studied in a retrospective analysis of 69 recipients of blood stem-cell transplants with multiple myeloma who received at least two doses of amphotericin deoxycholate during 1992–95 (111). Nephrotoxicity occurred in 30 patients (43%) and developed rapidly. Patients who developed nephrotoxicity were similar to those who did not in many aspects associated with their treatment. However, baseline-estimated creatinine clearance, ciclosporin therapy, nephrotoxic drug therapy within 30 days of starting amphotericin, and the number of concomitant nephrotoxic drugs were significant predictors of amphotericin-associated nephrotoxicity. The authors concluded that recipients of bone marrow or peripheral blood stem-cell transplants who have multiple myeloma and are receiving ciclosporin or multiple nephrotoxic drugs at the start of amphotericin therapy should be considered at high risk of amphotericin-associated nephrotoxicity.

In a retrospective study, renal function was investigated in patients receiving ciclosporin alone or in combination with amphotericin (24-hour infusion) after allogeneic stem-cell transplantation (112). Of 84 patients, 22 were treated with amphotericin. There was a statistically significant reduction in renal function compared with the 62 patients who received ciclosporin alone. However, renal insufficiency in all patients remained in a clinically acceptable range and was reversible in patients who survived to 1 year after transplantation.

Continuous infusion of amphotericin has been assessed in an open study in six lung transplant recipients with invasive or semi-invasive bronchopulmonary azole-resistant candidal infections who were treated for 40 (17–73) days by 24-hour continuous infusions of amphotericin 1 mg/kg (113). They received at least 1000 ml/day of 0.9% saline intravenously. Apart from ciclosporin, five patients received aminoglycosides for at least 2 weeks, and four received ganciclovir. Calculated creatinine clearance fell from 57 (43–73) ml/minute to a nadir of 35 (28–39) and recovered to 52 (33–60) after the end of therapy. One patient needed temporary hemofiltration for 7 days. Besides three episodes of mild hypokalemia there were no adverse effects attributable to amphotericin. Asymptomatic colonization with *Candida* persisted for 10 months in one case, but the other five patients were cured.

Amphotericin B colloidal dispersion

During ABCD therapy 8.5% of patients developed nephrotoxicity compared with 21% in those given amphotericin deoxycholate (5).

In a randomized, double-blind, multicenter trial, ABCD (Amphotec; 6 mg/kg/day) was compared with liposomal amphotericin (1.0–1.5 mg/kg/day) for the first-line treatment of invasive aspergillosis in 174 patients (114). The median duration of therapy was 13 (1–357) days in those given ABCD, and 15 (1–87) days in those given liposomal amphotericin. For evaluable patients ($n = 103$) given ABCD or liposomal amphotericin, the respective rates of therapeutic response (52 versus 51%), mortality (36 versus 45%), and death due to fungal infection (32 versus 26%) were similar. Renal toxicity was significantly lower (25 versus 49%) and the median time to onset of nephrotoxicity longer (301 versus 22 days;) in the patients who received ABCD. Rates of drug-related toxicity in the patients who received ABCD and liposomal amphotericin were respectively 53 versus 30% (chills), 27 versus 16% (fever), 1 versus 4% (hypoxia), and 22 versus 24% (toxicity requiring study drug withdrawal). Based on the results of this trial, ABCD appears to have equivalent efficacy to liposomal amphotericin, and superior renal safety in the treatment of invasive aspergillosis.

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However, infusion-related chills and fever occurred more often with ABCD.

Amphotericin B lipid complex (ABLC)

A comparison of ABLC with amphotericin deoxycholate showed significant differences, with a doubling of baseline creatinine in 28% during ABLC compared with 47% during conventional therapy (5).

There has been a retrospective comparison of the renal effects of ABLC with amphotericin deoxycholate in the treatment of invasive candidiasis and cryptococcosis in dosages of 0.6–5 mg/kg/day; most patients received 5 mg/kg/day (115). Changes in serum creatinine were evaluated in three ways: doubling of the baseline value, an increase from below 132 μmol/l (1.5 mg/dl) at baseline to over 132 μmol/l, and an increase from below 132 μmol/l at baseline to at least 177 μmol/l (2.0 mg/dl). These endpoints were achieved significantly more often with amphotericin deoxycholate than with ABLC, and the time needed to reach each of the endpoints was significantly shorter with amphotericin deoxycholate. An increased serum creatinine concentration was reported as an adverse event more often in patients receiving amphotericin deoxycholate than in patients receiving ABLC (24 versus 43%).

The rates of ABLC-associated nephrotoxicity in various clinical settings at a university hospital have been estimated retrospectively and compared with previously reported rates of nephrotoxicity (116). Data from 33 adult patients (20 men, 13 women; mean age 49 years) with and without neutropenia receiving ABLC were collected, and the degree of nephrotoxicity was determined using two definitions: (1) doubling of baseline serum creatinine concentration using the peak value within the first 7 days and (2) end-of-therapy doubling of baseline serum concentration using the end-of-therapy value. Using the selected definitions of ABLC-associated nephrotoxicity, there were only two cases. This rate was significantly below the 42% rate reported in the only large published study (95% CI = 1.7, 19.6). The median change in serum creatinine concentration was 8.9 (–97 to 380) μmol/l. The concomitant use of nephrotoxic agents was not associated with significant changes in serum creatinine concentration. The authors concluded that ABLC infrequently causes clinically significant nephrotoxicity, and that earlier data derived from a single study in febrile patients with neutropenia should be interpreted cautiously.

Liposomal amphotericin B (L-Amb, AmBisome)

In a prospective double-blind study of more than 600 patients, 0.6 mg/kg of DAMB was compared with 3.0 mg/kg of L-Amb, a dose relation at the lower limit of equivalent doses determined in an animal model (117). At these dosages, in a large prospective double-blind study, there was a doubling of serum creatinine concentration in 19% of neutropenic patients receiving empirical therapy with L-AmB and 34% receiving conventional amphotericin (47).

Liposomal amphotericin has been given to an immunosuppressed renal transplant patient with cerebral aspergillosis for almost 10 months at a cumulative dose of 42 g with no apparent changes in the function of the renal allograft, as measured by serum creatinine, creatinine clearance, and potassium concentrations (118). Therapy was ultimately successful and was discontinued after surgical resection of a residual sclerotic lesion.

Liposomal amphotericin (3 mg/kg/day) has been compared with conventional amphotericin (0.7 mg/kg/day) for induction therapy of moderate to severe disseminated histoplasmosis in a randomized, double-blind, multicenter trial in 81 patients with AIDS (119). The duration of induction was 2 weeks, to be followed by 10 weeks of itraconazole in the case of a response. Clinical success was achieved in 14 of 22 patients treated with conventional amphotericin compared with 45 of 51 patients who received liposomal amphotericin (difference, 24%; 95% CI = 1%, 52%). Culture conversion rates were similar. Three patients treated with conventional amphotericin and one treated with liposomal amphotericin died during induction. Infusion-related adverse effects were more common with conventional amphotericin (63%) than with liposomal amphotericin (25%). Nephrotoxicity occurred in 37% of patients treated with conventional amphotericin and 9% of patients treated with liposomal amphotericin. The results of this study suggest that liposomal amphotericin is less toxic than conventional amphotericin and is associated with improved survival.

Prevention

Avoidance of salt depletion and a salt load (500–1000 ml of 0.9% saline) reduce the renal toxicity of DAMB (120–126). Also the maintenance of adequate serum potassium concentrations by replacement therapy may be important and may contribute to "kidney sparing" (127). Other preventive measures, including dopamine infusion, are of no value (128).

It has been suggested that amphotericin-induced nephrotoxicity may be mitigated by increasing renal blood flow and glomerular filtration rate with low-dose dopamine (1–3 μg/kg/minute). The efficacy of low-dose dopamine in preventing nephrotoxicity associated with amphotericin deoxycholate has been evaluated in a prospective randomized study in 71 patients after antineoplastic chemotherapy for autologous bone marrow transplantation or acute leukemia (128). The patients were randomly assigned to receive low-dose dopamine by continuous infusion (3 μg/kg/minute) or no dopamine. Amphotericin deoxycholate 0.5 or 1.0 mg/kg/day was given for respectively 8 and 13 days on average. Nephrotoxicity, defined as a 1.5-fold or greater increase in baseline serum creatinine concentration, was slightly less common, but not significantly so, in those given dopamine (67 versus 80%). The grade of nephrotoxicity was the same. Ten patients developed grade IV nephrotoxicity and were withdrawn from the study. The authors concluded that dopamine offers little benefit in preventing amphotericin deoxycholate-associated nephrotoxicity.

In a randomized, controlled, single-center study, continuous infusion of amphotericin reduced nephrotoxicity and infusion-associated reactions compared with the standard infusion over 2–4 hours in patients with neutropenia, refractory fever, and suspected or proven invasive fungal infections (129). However, the concentration-dependent

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pharmacodynamics of antifungal polyenes raise concerns about the antifungal effectiveness of this mode of administration in particular, as its therapeutic efficacy has not been adequately studied in animals or in patients with documented infections.

Skin

An allergic skin reaction to amphotericin has been reported (130).

- A 3-year-old child had a severe allergic reaction during treatment with liposomal amphotericin for persistent neutropenic fever following unrelated allogeneic cord blood stem-cell transplantation. The patient developed an extensive maculopapular rash and severe itching that was unresponsive to antihistamine and glucocorticoid medication and resolved only after drug withdrawal. Continuation of therapy with conventional amphotericin for 20 days was well tolerated, suggesting that the lipid carrier was responsible for the adverse event.

Immunologic

A literature review found no support for the routine use of a test dose of amphotericin before the first therapeutic dose of amphotericin deoxycholate, as is still recommended by the manufacturers (131). The mechanism of common infusion-related adverse effects does not appear to be allergic in nature, and true allergic reactions are rare. Moreover, the absence of a reaction to a test dose does not necessarily indicate that patients will not have a severe infusion-related reaction later in the course of therapy, and the procedure of administering a test dose can lead to a detrimental delay in adequate antifungal therapy. The authors recommended starting therapy with amphotericin deoxycholate at the full therapeutic target dose, with careful bedside monitoring for infusion-related adverse events throughout therapy.

Anaphylaxis is rare with amphotericin (67). It is important to note that a patient may tolerate one formulation and respond with anaphylaxis to another.

- Anaphylaxis after ABCD occurred in a patient who had previously been treated with both amphotericin deoxycholate and ABLC without infusion-related adverse effects (65). During the first infusion of ABCD he developed spontaneously reversible severe back pain and then swelling of his lips, respiratory distress, and left-sided hemiparesis, which resolved after 24 hours. An MRI scan suggested an ischemic event in the right putamen, lending support to the hypothesis that he had had an anaphylactic reaction to ABCD, hypoperfusion, and a subsequent stroke.
- In another patient, serious adverse events (fever, severe rigors, a fall in blood pressure, worsening mental status, increasing creatinine concentration, and leukocytosis) occurred after unrecognized substitution of one amphotericin formulation (ABLC) by another (ABCD) (132). After discovery of the switch, ABLC therapy was reinstituted and tolerated without incident.

These cases underscore the need to monitor patients closely when infusing the first dose of a different formulation of amphotericin.

Second-Generation Effects

Pregnancy

Experience with amphotericin in pregnancy is limited. Amphotericin crosses the placenta and can increase creatinine concentrations in the neonate. High tissue concentrations of amphotericin persist weeks after treatment has been stopped (133).

Susceptibility Factors

Age

Neonates

The safety and efficacy of liposomal amphotericin in 40 preterm and 4 full-term neonates with invasive yeast infections have been studied retrospectively (134). The initial dosage was 1 mg/kg/day, and was increased stepwise by 1 mg/kg to a maximum of 5 mg/kg, depending on the clinical condition. There were no infusion-associated reactions. Blood pressure, hepatic, renal, and hematological indices were not altered. Hypokalemia was noted in 16 infants but was always transient and responsive to potassium supplementation. Treatment with liposomal amphotericin was successful in 72% of the children. However, 12 of the 40 preterm infants succumbed to the fungal infection; all had a birth weight of less than 1.5 kg.

Changes in serum creatinine and serum potassium have been measured in 21 neonates of very low birth weight who received amphotericin for presumed or documented yeast infections (135). The median dosage was 2.6 (range 1–5) mg/kg/day, and the median duration of therapy was 2 (11–79) days. Hypokalemia (below 3 mmol/l) was observed in 30% before treatment and in 15% during treatment. However, 21 days after the end of therapy, hypokalemia was not present in any patient. The maximum creatinine concentration fell from 121 (71–221) μmol/l to 68 (31–171) μmol/l during treatment and 46 (26–62) μmol/l at 21 days after the end of therapy. However, creatinine concentrations were available for only 10, 18, and 15 of the 21 patients respectively, and no information was provided on the number of patients who had an increase in serum creatinine during therapy. All patients responded to therapy with liposomal amphotericin, although the number of proven invasive fungal infections was small (7/21).

Infants

The safety and efficacy of ABLC in 11 neonates with systemic *Candida* infections have been reported (136). The infants were aged 3–14 (median 7) weeks and weighed 0.7–5 (median 1.4) kg. The median duration of ABLC treatment was 23 (range 4–41) days at an average dose of 4.9 (range 3.2–6.5) mg/kg/day. Nine of the eleven patients improved clinically, and eight of nine evaluable patients had a mycological cure. No infant discontinued treatment because of adverse drug reactions, and none had appreciable hepatic or hematological toxicity. Renal function improved or did not change in 8 of the 11. The median pretreatment serum creatinine concentration was 80 (range 35–522) μmol/l and the median creatinine

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concentration at the end of treatment was 44 (range 18–628) μmol/l.

Children

The disposition of liposomal amphotericin in children and adolescents is similar to that in adults. Liposomal amphotericin and conventional amphotericin have been compared in a randomized, multicenter study in 204 children with cancers, pyrexia, and neutropenia (137). There was a 2.6 times lower incidence of adverse effects with the liposomal formulation. There were severe adverse effects in 1% of those who received liposomal amphotericin and 12% of those who received the conventional formulation.

Data on the safety of amphotericin deoxycholate have been reported for 50 therapeutic courses in 44 children and adolescents with cancer and a median age of 6.8 years (range 9 months to 18 years) (50). Amphotericin deoxycholate was given in a dose of 1 mg/kg over 2 hours for a mean duration of 7.8 days. Most of the patients received the drug as empirical antifungal therapy in the setting of persistent fever and neutropenia. Nephrotoxicity, defined as a 100% increase in the serum creatinine from baseline, was observed in only one patient. Infusion-related reactions (fevers and/or rigors) occurred in 24% of treatment courses. Thus, amphotericin deoxycholate was relatively well tolerated in this population, although the mean duration of therapy was comparatively short.

The safety and efficacy of ABLC have been studied in an open, emergency-use, multicenter study in 111 treatment episodes in children with invasive mycoses refractory to or intolerant of conventional antifungal drugs (138). The mean daily dosage was 4.85 (range 1.1–9.5) mg/kg, and the mean duration of therapy was 33 (range 1–191) days. While the proportion of patients with deteriorating renal function was not mentioned, the mean serum creatinine concentration in the entire study population did not change significantly between baseline (109 μmol/l) and withdrawal of ABLC (117 μmol/l) over 6 weeks. Similarly, there were no significant differences between initial and end-of-therapy concentrations of serum potassium, magnesium, transaminases, alkaline phosphatase, and hemoglobin. However, there was a significant increase in mean total bilirubin (from 63 to 91 μmol/l) at the end of therapy. ABLC was withdrawn because of toxicity in 7 of the 111 children; adverse events leading to withdrawal included intolerable infusion-related reactions and allergic reactions. Among the 54 evaluable patients, a complete or partial therapeutic response was obtained in 38.

Drug Administration

Drug dosage regimens

By lowering the infusion rate and using continuous infusion, fewer toxic reactions have been observed. In contrast, varying the infusion time of daily doses between 1 and 6 hours made no important change in regard to toxicity (139–144). Alternatively, smaller starting doses have been suggested to reduce toxicity, a strategy that is often not advisable in acute severe mycoses. The use of lipid formulations reduces the incidence and severity of general toxic reactions and of nephrotoxicity (22,47,49). It is currently unclear, however, whether lipid formulations of amphotericin have a broader therapeutic index than conventional DAMB. It has to be borne in mind that lipid formulations, while affecting the pharmacokinetics of amphotericin, have no targeting properties that discriminate between the cell membrane of the pathogen and that of host cells. It therefore appears possible that some, if not all, of their advantages are in the avoidance of high concentrations of reactive amphotericin, an effect that could also be obtained by continuous infusion of the conventional formula (62). Monitoring of blood concentrations of amphotericin B is not practical, and there are no validated recommendations for its use, neither for avoidance of toxicity nor for monitoring of efficacy.

Drug administration route

Amphotericin given intravenously does not lead to adequate CSF concentrations, and it can rarely be given intrathecally in cases of cerebral infection. Nevertheless, amphotericin is effective even in cryptococcal meningitis, in the absence of marked meningeal inflammation. Continuous infusion may be associated with less toxicity, but experience is limited.

Delirium (145) and parkinsonism (146) have been described after intrathecal or intraventricular therapy.

Drug–Drug Interactions

Aminoglycoside antibiotics

Amphotericin prolongs the half-life of aminoglycoside antibiotics (147).

Antifungal azoles

In evaluating possible antagonism between amphotericin and antifungal azoles, details of the experimental set-up are crucial. When filamentous fungi were exposed to subfungicidal concentrations of azoles, before exposure to an amphotericin + azole combination, antagonism could always be shown both in vitro and in vivo (148–150).

In vitro studies and experiments in animals have given conflicting results relating to potential antagonism between the effects of fluconazole and amphotericin on *Candida* species (149). However, large, randomized, double-blind comparisons of fluconazole with and without amphotericin for 5 days in non-neutropenic patients with candidemia showed no evidence of antagonism, but faster clearance of the organism from the blood and a trend toward an improved outcome in those who received the combination (151).

The combination of amphotericin with ketoconazole appears to lead to antagonism (148). A study of the effects of combinations of amphotericin with fluconazole, itraconazole, or ketoconazole against strains of *Aspergillus fumigatus* in vitro showed antagonistic effects in some strains, but different effects in other strains (152). In one group of mice infected with *Candida*, combinations of amphotericin with fluconazole were more effective

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than fluconazole alone; in another group the combination showed no interaction, but was not better than either drug given alone (153).

Although there are no clinical data, it can be expected that similar antagonism occurs between amphotericin and squalene oxidase inhibitors, which also eliminate the primary target ergosterol from the fungal cell membrane.

Ciclosporin

Because ciclosporin causes a reduction in renal function, there is increased nephrotoxicity if amphotericin is also given (112,147).

Cisplatin

Amphotericin-induced hypomagnesemia may be more profound in patients who develop a divalent cation-losing nephropathy associated with cisplatin (12).

Cytotoxic drugs

Amphotericin can enhance the risk of adverse effects from cytotoxic drugs (154).

Digitalis

Hypokalemia due to amphotericin can enhance the toxicity of digitalis (12,127).

Diuretics

The concurrent use of diuretics is associated with a higher risk of nephrotoxicity from amphotericin (155).

Flucytosine

Amphotericin in combination with flucytosine results in an increased risk of hematological complications, because amphotericin often impairs renal function, causing retention of flucytosine (10).

Neuromuscular blocking drugs

Hypokalemia due to amphotericin can enhance the curariform effect of neuromuscular blocking agents (12,127,154).

Tacrolimus

Tacrolimus (FK 506), a macrolide immunosuppressant, has adverse effects similar to those of ciclosporin, including nephrotoxicity. Increased nephrotoxicity can be expected when it is given with amphotericin (156).

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Ampiroxicam

See also Non-steroidal anti-inflammatory drugs

General Information

Ampiroxicam is a piroxicam prodrug, which is completely converted to piroxicam after oral administration. Its adverse effects profile is expected to be similar to that of piroxicam. A few cases of photosensitivity have been reported (1–5).

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Amprenavir

See also Protease inhibitors

General Information

Amprenavir is an HIV protease inhibitor with an enzyme inhibitory constant of 0.6 nmol/l, similar to the inhibitory constants of other protease inhibitors. Its in vitro IC_{50} against wild-type clinical HIV isolates is 115 ng/ml. It has a long half-life (7–10 hours). It can be given twice-daily without food restrictions and had high potency when given as monotherapy in dose-finding studies (1). The recommended doses are 1200 mg bd for adults and 20 mg/kg bd or 15 mg/kg tds for children under 13 years of age or adolescents under 50 kg. Capsules and solution do not have equal systemic availability, and the recommended dose for amprenavir oral solution is 1.5 ml/kg bd or 1.1 ml/kg tds. The systemic availability increases with increasing doses. Amprenavir is about 90% bound to $alpha_1$ acid glycoprotein and 40% to albumin. It does not penetrate the brain well, because it is exported by P glycoprotein. It is mainly metabolized by CYP3A4 and its clearance is reduced in liver disease. The clinical pharmacology of amprenavir has been reviewed (2).

The use of amprenavir has been limited to patients who are highly motivated, because of the high capsule burden (16/day).

Fosamprenavir is a prodrug of amprenavir with better systemic availability. In large clinical trials the most common adverse events in patients taking fosamprenavir, with or without ritonavir, plus abacavir and lamivudine were diarrhea, nausea, vomiting, abdominal pain, drug hypersensitivity, and skin rashes (3).

Observational studies

In a monotherapy trial ($n = 37$), adverse effects were frequent but generally mild, and included rash, diarrhea or loose stools, and headache. In general, these adverse effects tend to disappear or weaken in severity within the first 2–4 weeks of treatment.

General adverse effects

The adverse effects of amprenavir in patients treated with combination therapy included nausea, vomiting, diarrhea, epigastric pain, flatulence, paresthesia, headache, rash, and fatigue (4). The contribution of a single drug to the observed adverse effects is difficult to establish. Amprenavir inhibits CYP3A4 to a greater extent than saquinavir, and to a much lesser extent than ritonavir (5). Co-administration with rifampicin and rifabutin should be avoided. Those who take

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amprenavir have complained of diarrhea, nausea, headache, and fatigue (6). The frequency of diarrhea may be as high as 50%.

Organs and Systems

Nervous system

Neurotoxicity has been attributed to amprenavir (7).

- A 61-year-old man, who had taken various antiretroviral drugs, took amprenavir 750 mg bd and after the first dose had hallucinations, disorientation, tinnitus, and vertigo. The symptoms abated within 2 hours and recurred after the next dose.

Drug–Drug Interactions

Clarithromycin

A pharmacokinetic study has shown a minor interaction of amprenavir with clarithromycin in healthy men (8). The mean AUC, $C_{max.ss}$ and $C_{min.ss}$ of amprenavir increased by 18, 15, and 39% respectively. Amprenavir had no effect on the AUC of clarithromycin, but the median $t_{max.ss}$ increased by 2 hours, renal clearance increased by 34%, and the AUC for 14-(*R*)-hydroxyclarithromycin fell by 35%. These effects were felt not to be clinically important and dosage adjustment was not recommended.

Efavirenz

Four HIV-infected children undergoing intense antiretroviral combination therapy were switched to regimens including amprenavir and efavirenz after the failure of other drugs (9). Pharmacokinetic studies suggested that combinations of these drugs can result in suboptimal concentrations of amprenavir. This was evident in two of the children taking amprenavir and efavirenz, in combination with two NRTIs, who had undetectable concentrations of amprenavir within 4 hours of administration. The addition of ritonavir to the combination restored the blood concentrations of amprenavir to those normally recorded (median 3500 ng/ml). The most probable reason for this effect is enhanced metabolism of amprenavir due to induction by efavirenz.

Indinavir

In an open, randomized study of amprenavir combined with indinavir, nelfinavir, and saquinavir (10) the amprenavir AUC increased by 35% when it was combined with indinavir, and indinavir concentrations also fell, suggesting that this protease inhibitor combination should be avoided. There was no significant interaction of amprenavir with nelfinavir.

Methadone

Amprenavir is extensively metabolized by and induces CYP3A4. Plasma methadone concentrations fell by 35% when amprenavir was used (11).

Rifamycins

Co-administration of amprenavir with rifampicin and rifabutin should be avoided (12).

Ritonavir

In attempts to lower the amprenavir capsule burden, low-dose ritonavir has been used as a pharmacokinetic booster. When ritonavir was added to amprenavir, the amprenavir AUC increased 3–4 times (13), which should allow the total daily capsule burden to be reduced. Adverse effects included diarrhea, nausea, paresthesia, rash, increased cholesterol, and increased triglycerides. The frequency of adverse events correlated with the dose of ritonavir.

Saquinavir

In an open, randomized study of amprenavir combined with indinavir, nelfinavir, and saquinavir (10), saquinavir lowered the amprenavir AUC by 32%; amprenavir did not alter the pharmacokinetics of saquinavir.

Food–Drug Interactions

Grapefruit juice

In 12 healthy volunteers, co-administration of a single dose of amprenavir 1200 mg with grapefruit juice slightly reduced the C_{max} compared with water (7.11 versus 9.10 μg/ml) and slightly increased the t_{max} (1.13 versus 0.75 hours), but did not affect the AUC (14). Thus, grapefruit juice has no clinically important effect on amprenavir pharmacokinetics.

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Amrinone

See also Phosphodiesterase type III, selective inhibitors of

General Information

Amrinone is an inhibitor of phosphodiesterase type III, and has a positive inotropic effect. Its adverse effects (1–5) include thrombocytopenia (10%), hypotension, tachydysrhythmias (sometimes resulting in syncope and death) (9%), worsening cardiac ischemia (7%), worsening heart failure (15%), gastrointestinal disturbances (39%), neurological complications (17%), liver damage (7%), fever (6%), nephrogenic diabetes insipidus, hyperuricemia, flaking of the skin, brown discoloration of the nails, and reduced tear secretions. The figures in parentheses are taken from a study of the use of amrinone in 173 patients with chronic ischemic heart disease or idiopathic cardiomyopathies (3).

Other reported adverse effects include acute pleuropericardial effusions, perforated duodenal ulcer, acute myositis and pulmonary infiltrates, vasculitis with pulmonary infiltrates and jaundice, influenza-like illnesses, chest pain, headache, dizziness, anxiety, maculopapular rash, and night sweats (6).

Organs and Systems

Cardiovascular

There has been one report of paroxysmal supraventricular tachycardia in one of 16 patients with cardiogenic shock given amrinone (7).

Hematologic

Thrombocytopenia due to amrinone has been briefly reviewed (8).

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Amtolmetin guacil

See also Non-steroidal anti-inflammatory drugs

General Information

Amtolmetin guacil (2-[2[1-methyl-5-(4-methylbenzoyl)-2-yl] acetamido] acetic acid 2-methoxyphenyl ester) is a non-acid prodrug of tolmetin. It has been introduced in various countries, and its launch was characterized by claims of better gastrointestinal tolerability than older compounds (1,2). Clinical and endoscopic comparative studies have been carried out in patients with various osteoarticular diseases (3–5). In most of these studies amtolmetin showed similar anti-inflammatory activity to other NSAIDs (diclofenac, flurbiprofen, ibuprofen, indometacin, naproxen) but less gastrotoxicity at endoscopic evaluation, with no difference in the incidence of gastrointestinal symptoms. Unfortunately, the clinical studies were small and of short duration, and the prognostic value of endoscopic studies with respect to severe gastrointestinal complications (bleeding, perforation, and obstruction) is debatable. It has been suggested that the mechanism of the gastric sparing effect of amtolmetin might be related to the local production of nitric oxide, which can counteract the damaging effects of prostaglandin inhibition (6,7).

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A renal sparing effect has also been reported, but clinical experience with this compound is limited (8).

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Amylin analogues

General Information

Amylin is a hormone produced in the beta-cells of the islets of Langerhans and is co-secreted with insulin. It has glucoregulatory effects that may complement the actions of insulin.

Pramlintide (rINN) is a non-aggregating analogue of amylin. It reduces postprandial glucose excursions, probably by reducing stomach emptying, not by stimulating the release of glucagon-like peptide (GLP-1) (1). It can only be given by injection.

The most common adverse effect of pramlintide is nausea. Hypoglycemia can occur if the dose of insulin is not reduced when pramlintide is added. In no studies was there evidence of cardiac, hepatic, or renal toxicity or hypersensitivity reactions.

Pramlintide has been studied in a double-blind, placebo-controlled, multicenter study in 480 patients with type 1 diabetes for 1 year, followed by an 1-year open extension (2). Glucose control improved with pramlintide. Hypoglycemia was less frequent with pramlintide, but nausea and anorexia doubled in frequency and constituted the most common reason for withdrawal.

In a comparable study, 656 patients with type 2 diabetes took preprandial pramlintide 60 micrograms tds, 90 micrograms bd, or 120 micrograms bd (3). Only 120 micrograms bd gave a sustained reduction in HbA_{1c}. In the first 4 weeks there was an increase in the risk of hypoglycemia, but not thereafter. Mild to moderate nausea and headache were the most frequent adverse effects; nausea abated during treatment.

Insulin + pramlintide

Pramlintide 30 micrograms was given to 16 patients using insulin pumps as an injection at meal times (4). Mealtime insulin was reduced by 17%. Serum fructosamine improved. Nausea was the most common adverse effect. There was no hypoglycemia.

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Anacardiaceae

See also Herbal medicines

General Information

The genera in the family of Anacardiaceae (Table 1) include pistachio, poison ivy, and sumac.

Rhus species

Rhus is used as a traditional remedy for gastrointestinal complaints in Korea.

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Table 1 The genera of Anacardiaceae

Anacardium (anacardium)
Buchanania (buchanania)
Campnospera
Comocladia (maidenplum)
Cotinus (smoke tree)
Dracontomelon (dracontomelon)
Gluta (gluta)
Lithrea (lithrea)
Malosma (laurel sumac)
Mangifera (mango)
Melanorrhoea (melanorrhoea)
Metopium (Florida poison tree)
Pistacia (pistachio)
Rhus (sumac)
Schinus (pepper tree)
Schinopsis (schinopsis)
Sclerocarya (sclerocarya)
Semecarpus (semecarpus)
Spondias (mombin)
Toxicodendron (poison oak)

Adverse effects

Skin

Contact dermatitis has been attributed to *Rhus* species (1,2), including a case that followed exposure to a homeopathic remedy (3).

Oral or parenteral exposure to certain contact allergens can elicit an eczematous skin reaction in sensitized individuals. This phenomenon has been called systemic contact dermatitis (SCD) and is relatively rare compared with classical contact dermatitis.

In 42 patients with systemic contact dermatitis caused by ingestion of *Rhus* (24 men and 18 women, average age 44 years, range 24–72), 14 of whom had a history of allergy to lacquer, there were skin lesions such as generalized maculopapular eruptions (50%), erythroderma (29%), vesiculobullous lesions (14%), and erythema multiforme-like lesions (7%) (4). Many patients (57%) developed a leukocytosis with a neutrophilia (74%). In some patients (5%) there were abnormalities of liver function. The lymphocyte subsets of 12 patients studied were within the reference ranges with no differences between patients with or without a history of allergy to lacquer. The authors concluded that the skin eruptions were caused by toxic reactions to *Rhus* rather than by immunological mechanisms.

In 31 patients with *Rhus* allergy over a 10-year period the clinical manifestations included maculopapular eruptions (65%), erythema multiforme (32%), erythroderma (19%) pustules, purpura, wheals, and blisters (5). All the patients had generalized or localized pruritus, and other symptoms included gastrointestinal problems (32%), fever (26%), chills, and headache. Many developed a leukocytosis (70%) with neutrophilia (88%), and some had toxic effects on the liver or kidneys. All responded to glucocorticoids or antihistamines.

Erythema multiforme in a photodistribution has been attributed to *Rhus verniciflua*, the Japanese lacquer tree (6). The rash was reproduced by challenge with the drug and sunlight. On contact with *R. verniciflua* the patient had a flare of the eruption, which was limited to the areas previously exposed to sun. Immunohistochemical studies suggested that the keratinocytes in the skin that retain the photoactivated substances may facilitate epidermal invasion of lymphocytes by persistent expression of intercellular adhesion molecules.

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Anakinra

General Information

Anakinra is an interleukin-1 receptor antagonist. It has been used to treat rheumatoid arthritis (1,2). It has been tried in graft-versus-host disease, but without success (3). According to published trial data, moderate injection site reactions were the primary adverse effect and required treatment withdrawal in under 5% of patients. An erythematous rash was seldom observed. Although a few patients have developed antibodies to anakinra, these have not so far been associated with lack of efficacy or allergic skin reactions.

Drug–Drug Interactions

Etanercept

Regulatory agencies have issued an important post-marketing warning of an increased risk of serious infections and neutropenia in patients who receive concomitant anakinra and etanercept (4). This warning was based on an analysis of a randomized clinical trial in 242 patients with rheumatoid arthritis, in which 7% of patients receiving concomitant treatment had serious infections, compared with none in those treated with etanercept alone. Concurrent administration of these two drugs was therefore not recommended.

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Androgens and anabolic steroids

See also Hormonal contraceptives—male

General Information

The classic androgen is natural testosterone, which can be given orally in micronized form, but has much more often been used as the orally active 17-methyl derivative or an injectable ester. Androgens are used to some extent in male hypogonadism, when they can promote libido and potency and increase the frequency of erections and the volume of the ejaculate (1). The use of androgens by either sex as "sexual tonics" is a matter of dispute. Some centers have used androgens to treat postmenopausal women complaining of weak libido, poor energy, or a feeling of malaise (2); workers who use this contentious approach have suggested that they should be given in association with estrogens, because of the adverse effects of androgens on serum lipids.

While some anabolic steroids are still available in the legitimate trade, others are manufactured and distributed illegally, and the contents and potency of these are unknown; some adverse effects could be due to impurities or content variation.

From about 1955 onwards, a number of so-called anabolic steroids were developed for which it was claimed, on the basis of animal experiments, that the virilizing effects had been reduced compared with testosterone, whereas the effects on tissue build-up and nitrogen retention had been maintained. These compounds were therefore promoted for such purposes as the promotion of appetite and weight increase in children and the advancement of convalescence. In fact, it has never been at all clear that these compounds are anything other than weak and expensive androgens. Even in these "tonic" doses, they can cause virilization in women and precocious development of secondary characteristics in children. In the much higher doses later developed for use in such conditions as aplastic anemia, mammary carcinoma, terminal uremia, and even hereditary angioedema (3), their androgenic effects are very pronounced indeed, and other serious complications can occur, for example in the liver (SED-12, 1038) (4–10). One formerly well-known "anabolic" steroid, metandienone (Dianabol), was withdrawn as early as 1982, and other withdrawals have followed.

When androgen therapy is used in postmenopausal women who complain of poor libido, poor energy, or a feeling of malaise (2), it should be given in association with estrogens, because of its adverse effects on serum lipids.

Hormonal contraception in men

The use of intramuscular testosterone + oral desogestrel for hormonal contraception in men is discussed in a separate monograph (Hormonal contraceptives—male).

General adverse reactions

Adverse effects of pharmacological doses of androgens include, as one would expect from male hormones, hirsutism with acne and other signs of virilization, along with adverse lipoprotein profiles, endometrial hyperplasia in women, and an increased risk of cardiovascular disease. Some compounds are particularly likely to cause liver disorders.

Male hormone replacement therapy has been reviewed (11). Hypogonadism can be accompanied by hot flushes, similar to those seen in postmenopausal women, and gynecomastia. The potential risks of testosterone replacement in adult men are precipitation or worsening of sleep apnea, hastened onset of clinical significant prostate disease, benign prostatic hyperplasia, prostatic carcinoma, gynecomastia, fluid retention, polycythemia, exacerbation of hypertension, edema, and an increased risk of cardiovascular disease.

The adverse effects of long-term testosterone therapy in HIV-positive men are irritability, weight gain, fatigue, hair loss, reduced volume of ejaculate, testicular atrophy, truncal acne, breast tenderness, and increased aggression (12).

Supraphysiological concentrations of androgen hormones can cause acne, hirsutism, and deepening of the voice.

Adverse effects of androgens in women

There are clear differences of opinion about the use of androgens in women. An Australian reviewer has argued that women may have symptoms secondary to androgen deficiency and that "prudent" androgen replacement can be effective in relieving both the physical and psychological symptoms of such insufficiency (13). The reviewer suggested that testosterone replacement for women is safe, with the caveat that doses should be restricted to the "therapeutic" window for androgen replacement in women, such that the beneficial effects on well-being and quality of life are achieved without incurring undesirable virilizing effects. The predominant symptom of women with androgen deficiency is claimed to be loss of sexual desire after a premature or natural menopause, while other indications for androgens include premenopausal iatrogenic androgen deficiency states, glucocorticoid-induced bone loss, management of wasting syndromes, and possibly premenopausal bone loss, premenopausal loss of libido, and the treatment of the premenstrual syndrome.

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Some reservations about this approach arise when one considers the possible adverse effects and the doubts that have been raised as to whether there is in fact a safe therapeutic window when treating women with androgens. This comes clearly to the fore in a thoughtful paper by another Australian author, a speech therapist (14). For women treated with androgens or related compounds for any reason, virilization of the voice, which soon becomes permanent, is a distressing complication that has not received a great deal of specific study. This review provides some pointers for clinical practice. She reports on four women aged 27–58 years who sought otolaryngological examination because of significant alterations to their voices, the primary concerns being hoarseness, lowering of habitual pitch, difficulty in projecting their speaking voices, and loss of control over their singing voices. Otolaryngological examination with a mirror or flexible laryngoscope showed no apparent abnormality of vocal fold structure or function, and the women were referred for speech pathology with diagnoses of functional dysphonia. Objective acoustic measures using the Kay Visipitch showed significant lowering of the mean fundamental frequency in each woman, and perceptual analysis of the patients' voices during quiet speaking, projected voice use, and comprehensive singing activities showed a constellation of features typically noted in pubescent men. The original diagnosis of functional dysphonia was queried, prompting further exploration of each woman's medical history. In each case the vocal symptoms had started shortly after the beginning of treatment with medications containing virilizing agents, notably danazol, nandrolone decanoate, and testosterone. Although some of the vocal symptoms abated in severity with 6 months of voice therapy and after withdrawal of the drugs, a number of symptoms remained permanent, suggesting that each subject had suffered significant alterations in vocal physiology, including muscle tissue changes, muscle coordination dysfunction, and proprioceptive dysfunction. The study showed that both the projected speaking voice and the singing voice proved highly sensitive to virilizing effects.

It has been known for more than 30 years that some 50% of women have voice changes with anabolic steroids. While it has sometimes been thought that safe doses can be identified, studies of individual patients, including one of the cases documented here, throw doubt on this. The effects can be disastrous for any woman and incapacitating to a singer; clearly the use in women of any product having any androgenic potency must be undertaken with great reticence.

Organs and Systems

Cardiovascular

Particularly when androgens/anabolics are misused to promote extreme muscular development, there is a risk of cardiomegaly and ultimate cardiac failure. Androgen-induced hypertension may be due to a hypertensive shift in the pressure-natriuresis relation, either by an increase in proximal tubular reabsorption or by activation of the renin–angiotensin system (15). This effect is not related to higher doses or longer treatment and can develop after a few months but can also be delayed for many years.

Respiratory

There has been a single published report, which could have been coincidental, of obstructive sleep apnea during use of testosterone (16).

Nervous system

Use of androgenic steroids is likely to produce a sensation of energy and euphoria, but also with a tendency to sleeplessness and irritability (1). More extreme changes in mental state can result in extreme swings in mood, ranging from depression to aggressive elation. An unusual complication in one case was a toxic confusional state and choreiform movements caused by an anabolic steroid (SED-12, 1038) (17), but it may have been due to the non-specific results of endocrine stress in a susceptible individual.

- A 40-year-old Korean woman who had taken oxymetholone for aplastic anemia (doses not stated) developed cerebral venous thrombosis accompanied by a tentorial subdural hematoma (18).

Hiccups have been classified as a neurological reaction that can be triggered by many factors. There have been a few published reports of persistent hiccups associated with oral and intravenous glucocorticoids and one of progesterone-induced hiccups, which were thought to be secondary to the glucocorticoid-like effects of progesterone on the brainstem.

- Anabolic steroid-induced hiccups have been reported in a champion power lifter (19). The hiccups occurred within 12 hours of an increase in the dose of oral methandrostenolone from 50 to 75 mg/day, and persisted for 12 consecutive hours until medical attention was sought. The hiccups abated rapidly after the dose of methandrostenolone was reduced, but he was unwilling to abandon it completely.

Psychological, psychiatric

Apart from the physical effects of exogenous anabolics and androgens, they can also have behavioral effects, including promotion of sexual behavior (which may or may not be regarded as an unwanted effect) and perhaps enhanced aggressiveness. Men who use androgenic anabolic steroids to enhance their sporting achievements seem to be more likely to have cyclic depression (20), but young men who have stopped using anabolic steroids can also develop depression and fatigue as withdrawal effects (21).

Androgens can rarely cause psychotic mania.

- A 28-year-old man with AIDS and a history of bipolar disorder was given a testosterone patch to counter progressive weight loss and developed worsening mania with an elevated mood, racing thoughts, grandiose delusions, and auditory hallucinations (22). His condition improved in hospital after removal of the patch and the administration of antipsychotic drugs. No cause for the psychosis, other than the use of testosterone, was found.

Suicide—or attempted suicide—in eight users of anabolic steroids has been described in Germany; the cases were

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related variously to hypomanic states during use of anabolic steroids or depression after withdrawal (23). Some of the users had committed acts of violence while using the drugs. In all cases, there were risk factors for suicidality and the drugs may simply have triggered the suicidal decision.

Endocrine

While both androgens and anabolic steroids have male hormone effects, resulting in virilization, they suppress endogenous secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH); the result is that on withdrawal the system is for a time deprived of sufficient amounts of male hormone (24); this can lead to hypogonadism until endogenous secretions recover. A transdermal product has a particularly marked effect on circulating concentrations of serum dehydrotestosterone, and this may prove to be the case with other forms of administration; the effects of dehydrotestosterone on the prostate and other systems do not appear to have been systematically studied.

Metabolism

Androgens alone have unfavorable effects on lipids and are atherogenic (2). However, the simultaneous administration of estrogens appears to have a protective effect on the lipid profile. Androgen implants combined with estrogens cause a fall in total cholesterol and LDL cholesterol, without significant effects on HDL cholesterol or triglycerides. There is a similar reduction in total cholesterol in postmenopausal women treated with estrogen plus methyltestosterone, with a reduction in HDL2 cholesterol and triglycerides but no change in LDL cholesterol. Testosterone replacement therapy should therefore be given to women only if they are concurrently using estrogen replacement therapy.

In sufficient doses, androgens can alter regional fat distribution, with a reduction in subcutaneous fat; despite their body-building effects they have therefore been used as part of slimming programs in men (25). In women, testosterone causes an increase in lean body mass with a reduction in total body fat (26).

One residual medical use for oxandrolone in some centers is as a growth-promoting treatment for girls with Turner's syndrome, in which it is regarded by certain workers as an acceptable supplement (in a dose of 0.06 mg/kg/day) to recombinant human growth hormone. A risk of this treatment is altered glucose metabolism, but this effect is usually transient. In a series of 18 patients, one girl developed non-ketotic hyperglycemia 50 months after the end of treatment; in the other 17 girls the effect of treatment on glucose metabolism was reversible (27). There was a moderate, but not significant, rise in fasting blood glucose throughout the course of the longitudinal study. Fasting insulin increased continuously during treatment but fell after the end of treatment; subsequent concentrations were slightly higher than before treatment, but this could have been an effect of age.

Fluid balance

Androgens, particularly oxymetholone, can lead to increased water retention (28), but it is not clear whether this occurs via a mineralocorticoid or an estrogenic effect.

Hematologic

Hemoglobin can increase with high doses of androgens (29). Severe aplastic anemia has been reported.

- A 26-year-old woman developed severe aplastic anemia, complicated by superior sagittal sinus thrombosis, while taking fluoxymesterone 30 mg/day (30).

Anabolic steroids have been reported to be thrombogenic (31–33). Stanozolol, fluomesterone, metandienone, methyltestosterone, oxymesterone, and oxymetholone all reduce the synthesis or increase the degradation of clotting factors; as a rule this effect is not clinically significant, but it can result in an interaction with anticoagulants.

Liver

Particularly because the bulk of oral treatment with androgens has been with a 17-substituted compound (methyltestosterone) there have been considerable problems with liver toxicity (5). Liver dysfunction, first indicated by a rise in alkaline phosphatase and then by increases in other enzymes, transaminases and lactate dehydrogenase, is the earliest and most common sign of dysfunction. Peliosis hepatis (characterized by blood-filled cysts in the liver), hepatomas, and hepatocellular carcinoma can follow with prolonged treatment. Large hepatocellular carcinomas have been described on various occasions (8). The anabolic steroids are as risky in this respect as more traditional androgens; a case of a liver cell adenoma in a child (9) and two cases of nodular hepatocellular carcinoma (10) have been reported in patients who took oxymetholone, metenolone acetate, or other anabolic steroids for 5–15 years. It must be stressed that the complication is not limited to the 17-substituted compounds; other anabolic steroids and androgens, if given in sufficient doses (which are likely to be in excess of physiological amounts), can also damage liver function. Early damage to liver function, for example by methyltestosterone, has been shown to be reversible (6), but longer-term effects are not. The reversibility however depends on the nature of the derangement. Patients with severe cholestasis occurring late with stanozolol recovered biochemically over 3–6 months after drug withdrawal (7).

- A Japanese girl aged 20 years, who had been legitimately treated with oxymetholone (30 mg/day) for 6 years for aplastic anemia, developed a hepatic adenoma (34). In this case, in contrast to some earlier reports, there was a predisposing factor in the form of familial adenomatous polyposis.
- Reversible hepatotoxicity, in the form of abnormal liver function tests, led to the withdrawal of stanozolol in a patient with lipodermatosclerosis (35). Since some dermatologists continue to have faith in anabolic steroids in this condition, the patient was then given oxandrolone, which is reputed to be less hepatotoxic. The

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hepatic problems did not recur, although several months later the patient developed a cardiomyopathy, which may have been coincidental.

Skin

Acne is common in patients taking androgens (36). When the effect of testosterone and anabolic steroids on the size of sebaceous glands was studied in a series of male athletes, high doses of all the products tested were found to enlarge the glands (37).

It has been claimed that testosterone implants are much less likely to cause acne than are injections of testosterone enanthate in equivalent doses; it is not clear why this might be expected and the claim seems dubious.

Multiple halo nevi have been described in a patient who took oxymetholone (SED-12, 1038) (38).

Hair

Hirsutism is common in patients taking androgens, and is often irreversible (39,40). In contrast, in women, loss of scalp hair can occur (41). Of 81 female-to-male transsexual subjects, mean age 37 years (range 21–61), treated with testosterone esters ($n = 61$; 250 mg intramuscularly every 2 weeks) or testosterone undecanoate ($n = 20$; 160–240 mg/day orally), 31 developed male-pattern baldness; thinning of the hair was related to the duration of androgen administration and was present in about half of the transsexuals after 13 years (42).

Musculoskeletal

The ability of androgens to counter osteoporosis is the basis of their use as a supplement to estrogens in one version of hormone replacement therapy. Testosterone can increase markers of bone formation (43). However, the early closure of epiphyses, with an arrest of growth, is a risk if children are exposed to these substances; this latter effect may be produced by the estrogen to which testosterone is metabolized. In some patients with excessive growth (such as Klinefelter's syndrome or Marfan syndrome) the effect is exploited therapeutically (SEDA-21, 434). Follow-up in these subjects at the age of 21–30 years showed no abnormalities of testicular function as a consequence of treatment.

A potential adverse effect of oxandrolone is acceleration of puberty and skeletal maturation (44).

- A 9-year-old boy with early puberty took oxandrolone for 22 months because of constitutional delay of growth. His height velocity increased above the 97th percentile and his bone age developed twice as fast as his chronological age. The oxandrolone was withdrawn, but his growth velocity did not decrease and his bone age continued to accelerate.

The authors hypothesized that oxandrolone could have induced early puberty. They concluded that in young children oxandrolone should be used with caution for short periods only.

Sexual function

In men, the (often desired) effects can include an increase in libido. After some time, androgenic treatment in men will lead to a reduction in the volume of the testes and azoospermia or oligospermia because of suppression of gonadotropins. Severe priapism occasionally occurs.

- A 20-year-old man with idiopathic hypogonadotrophic hypogonadism receiving a testosterone ester in a dose of 250 mg intramuscularly every 2 weeks developed priapism (46).

Reproductive system

In women and children, the main effect will be one of virilization in its various forms, ranging from hirsutism and deepening of the voice to enlargement of the female clitoris and male pattern baldness; the effect on the voice rapidly becomes irreversible because of changes in the larynx; laryngeal polyps have also been observed (46). In women, menstrual abnormalities are likely. Short-term treatment can produce increases in estradiol, dihydrotestosterone, testosterone (total and unbound), and the ratio of dihydrotestosterone to testosterone.

When ill-advisedly used to promote growth in boys by administration for some years, oxandrolone caused gynecomastia in a high proportion of subjects treated; 23 of the 33 patients affected subsequently required mastectomy (47,48).

Long-Term Effects

Drug abuse

There is a persistent illegal market in androgenic anabolic steroids, to promote physical strength. A difficulty in determining the ultimate consequences of anabolic steroid abuse for body-building or to advance sporting achievement is that individuals who are susceptible to such abuse may well have taken several different types of substance at the same time or in succession. Indeed, an analysis of the hair of seven body-builders showed what the authors termed a "complete pharmacopeia" of drug residues, ranging from glucocorticoids, anabolic steroids, and androgens to beta-adrenoceptor agonists, antidepressants, diuretics, and human chorionic gonadotropin (49).

The claimed body-building effect of the so-called anabolic compounds reflects their ability to promote muscular development, even beyond physiological limits, and this can bring with it cardiovascular complications. Surreptitious misuse by athletes remains a recurrent problem in professional sport (50); apart from the cardiovascular risks, one observes numerous physiological changes, including effects on plasma levels of enzymes, minerals and vitamins and reduced concentrations of HDL cholesterol (51).

- Poststeroid balance disorder was diagnosed in a 20-year-old Polish athlete who had been given two courses of metandienone, oxymetholone, and nandrolone phenylpropionate (52). Vertigo occurred twice just after "doping" and persisted in spite of a 1.5-year break in taking anabolic steroids. There was positional nystagmus, the eye-tracking test was abnormal, and there were abnormal responses in caloric tests. In computed

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dynamic posturography, the incidence and degree of body sway were increased and consequently the field of the outspread area was enlarged. These findings pointed to a permanent poststeroid disorder of the central part of the equilibrium organ.

- A German report of a 22-year-old male body-builder who had taken both testosterone propionate and nandrolone decanoate in rising doses over a period of 4 months detailed the emergence of fulminant acne, a sternoclavicular bone lesion, and loss of libido (53). Severe acne after excessive androgen use has been reported before, and the apparently osteoarthritic complication in this case was probably secondary to the acne.
- A Texas group observed erythrocytosis in a young body-builder taking androgens and followed up this observation by examining hematological measures in nine male competitive body-builders who admitted to using these steroids illicitly (54). Although erythropoietin concentrations were normal (and even tended to be low), six subjects had a raised hematocrit with erythrocytosis.
- Cholestasis and renal insufficiency occurred together in a German body-builder who had been taking two anabolic steroids together over a period of 80 days (55).
- A large hepatic hematoma led to intra-abdominal hemorrhage in a 24-year-old man who for 2 years had taken two anabolic steroids as well as clomiphene and human chorionic gonadotropin (56). The authors obtained information from health clubs that users commonly took some 300 mg of nandrolone weekly, whereas the recommended dose was only 50 mg monthly.

An Australian study of 41 past and present users of anabolic steroids, together with controls from a similar population (“potential users”) has vividly portrayed the risks that prolonged use of these products brings (57). Complications included alterations in libido (61%), changes in mood (48%), reduced testicular volume (46%), and acne (43%). The mean systolic and diastolic blood pressures were raised in 29% of current users, 37% of past users, and only 8% of controls, although these differences were not significant. Gynecomastia was found in 10 past users (37%), two current users (12%), and none of the controls, while mean testicular volume was significantly smaller in current users (18 ml). There were abnormal liver function tests in 20 past users (83%), eight present users (62%), and five potential users (71%).

- A partial empty sella syndrome occurred in an elite 39-year-old body-builder with a 17-year history of drug abuse involving growth hormone, anabolic steroids, testosterone, and thyroid hormone (58).

The pituitary is a hormone-responsive gland, but it has not previously been shown to suffer negative feedback in response to any of these substances. Any one of them could in principle have contributed to the effect, or it could have been an indirect consequence of drug abuse, by way of an increase in intracranial pressure, which is a known cause of empty sella syndrome.

Drug withdrawal

Withdrawal of high doses of androgens or anabolic steroids after the system has become accustomed to them can lead to menopause-like reactions, such as anxiety, chills, tachycardia, anorexia, piloerection, insomnia, sweats, hypertension, myalgia, nausea, vomiting, irritability, and hot flushes. Young men who have used these compounds can experience depression and fatigue for a time after withdrawal.

Tumorigenicity

Danazol is a weak androgen and also has a series of other hormonal and anti-hormonal properties. It inhibits pituitary gonadotropin and has been used in the treatment of endometriosis, fibrocystic disease of the breast, idiopathic thrombocytopenic purpura, and hereditary angioedema. Its hepatotoxic effects include reversible rises in serum transaminases and cholestatic hepatitis; a few cases of hepatocellular tumors have been reported.

- A 34-year-old woman who had taken danazol 400 mg/day for 13 years for hereditary angioedema developed a mass in the right hypochondrium. Her alcohol intake was under 20 g/day. She had a large heterogeneous hepatic tumor, a well-differentiated hepatocellullar carcinoma in a non-cirrhotic liver.

The hypothesis that hepatocellular carcinoma had been caused by danazol was accepted in the absence of other causes (59).

Susceptibility Factors

Age

In children, who may be exposed to androgens or anabolic steroids accidentally or in ill-advised therapy (for example to improve appetite), there will be a particular risk of virilization, premature sexual development, and early closure of the epiphyses. Virilization has even been reported after topical androgen administration (60).

Interest in the use of androgens in elderly men continues, with on the one hand the long-standing hope that potency and libido may be restored, and, on the other hand, the belief that cardiovascular prospects might be improved. The uncertainties that exist in this latter respect have been well reviewed in a paper that merits reading in full; it is best summarized in the author’s own conclusion that “· · · overall, the androgens are as likely to prevent arterial disease as they are to cause it · · ·” (61).

Other features of the patient

One possible use of anabolic agents is in the treatment of the physical wasting associated with HIV infection. Some experience has been gained, but it is still not clear whether such treatment is warranted, bearing in mind the limited benefits that can be expected and the well-documented risks of anabolic drug therapy (62). The effects and adverse effects of testosterone replacement with a non-genital transdermal system, Androderm, have been studied in 41 HIV-positive men with low testosterone concentrations (63). Nine men taking placebo and 11 taking testosterone reported adverse events. Five men taking testosterone had

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reactions at the site of administration; other adverse events in this group included problems related to resistance mechanisms ($n = 2$), gastrointestinal system ($n = 2$), and skin and appendages ($n = 1$); there was one severe adverse event (a suicidal amitriptyline overdose). There were skin reactions at the site of application of the placebo or testosterone patch in 19% of the participants. One man had blisters on one occasion, related to rupture of the patch. The mean erythrocyte count increased with testosterone and fell with placebo. Hemoglobin concentration increased with testosterone and fell with placebo.

Older data pointed to some reduction in insulin requirements when patients with diabetes mellitus received androgens, and it is wise to avoid these drugs altogether in patients with diabetes.

Drug Administration

Drug formulations

Testosterone is available as oral testosterone undecanoate, buccal testosterone, intramuscular testosterone esters, testosterone implants, and testosterone transdermal patches and gel.

After oral administration there is large variability in systemic availability, which makes this route generally unsuitable.

Buccal testosterone tablets provide sustained release of testosterone and also bypass first-pass metabolism in the liver. Common adverse effects include gum irritation, pain, and tenderness, and edema (64) and headache (65).

Intramuscular testosterone is given as a deep intramuscular injection of single testosterone esters or a mixture of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate (Sustanon), every 2–3 weeks. In one series of 551 injections, 162 were associated with pain and bleeding; injection in the gluteal site caused fewer complaints and was less susceptible to bleeding, but was painful more often than injection in the deltoid muscle or thigh (66). There were no serious adverse effects and the only systemic adverse effect was episodes of sudden non-productive cough associated with faintness after eight injections which the authors thought might have been due to pulmonary oil microembolism. Systemic availability of testosterone after intramuscular administration is variable and there can be fluctuations in mood and sexual function (67). High testosterone concentrations can cause raised lipid concentrations (68).

Topical application of testosterone, as a gel or from transdermal patches, can lead to absorption and systemic effects (SEDA-16, 158). Transdermal absorption of testosterone (usually from treatment of vulvar lichen sclerosus et atrophicus) can lead to increased libido, clitoral hypertrophy, pubic hirsutism, thinning of the scalp hair, facial acne, voice change, hirsutism, and even virilization (69).

The use of transdermal patches for administering testosterone to hypogonadal men ("Andropatch") seems logical and convenient, but a British study in 50 treated patients showed that patient acceptance was surprisingly poor (70). There were adverse effects in 84%, mostly skin problems; 72% requested a return to depot injections, and 5% returned to oral therapy. The reservoir patches, 6 cm in diameter, were, to quote the report literally, judged to be too large, uncomfortable, and visually obtrusive, while the noise they made on bodily movement distracted dogs, wives, and children; they fell off in showers and attracted ribald remarks from sports partners; they could only be removed with difficulty and left bald red marks on the body. The nature of the complaints suggests that they might be accommodated by further technical development of the product.

One unusual variant involves applying a transdermal preparation to the scrotum (71), a technique that has been claimed to mimic more closely the natural pattern of release of endogenous testosterone. It is not clear that applying it at this site has any special merit, although some work suggests that the scrotal skin is less likely than other skin areas to exhibit local reactions. Certainly topical preparations of testosterone can elicit such reactions, with pruritus and blistering being common, while induration, erythema, and allergic reactions can also occasionally occur.

Testosterone implants, like implants of other substances, can be subject to extrusion, probably in about a tenth of cases treated, and can also give rise to local irritation (72).

Drug–Drug Interactions

Anticoagulants

Many androgens and anabolic steroids reduce the dose of oral anticoagulant that a patient requires, sometimes by as much as 25% (73), and hemorrhage has sometimes resulted from their use. From the results of a study in which stanozolol reduced warfarin requirements, the investigators concluded that stanozolol increased fibrinolysis, reduced the production of vitamin K-dependent clotting factors, and increased the amount of the natural anticoagulant antithrombin III (74).

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Anesthetic ether

See also General anesthetics

General Information

Diethyl ether (SED-9, 172) is obsolete as a general anesthetic (1). It is highly inflammable and therefore incompatible with modern surgical and anesthetic techniques. It has an unpleasant smell and irritates mucous membranes; this can cause coughing, straining, laryngeal spasm, and hypersalivation. Recovery is slow and accompanied by nausea and vomiting in up to 85% of patients. Liver damage is as frequent as with halothane. Ether raises intracranial pressure and can cause convulsions. It can cause impaired immune responsiveness and contact dermatitis has been reported, together with a systemic allergic reaction (SEDA-5, 120).

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Angiotensin II receptor antagonists

See also Individual agents

General Information

Inhibition of the renin–angiotensin system by ACE inhibitors has proved efficacious in the treatment of hypertension, cardiac failure, myocardial infarction, in secondary prevention after myocardial infarction, and for kidney protection in diabetic and non-diabetic nephropathy. The development of specific antagonists to subtype 1 of the angiotensin II receptor (AT_1) has provided a new tool for inhibiting the renin–angiotensin system.

Experimental data and preliminary clinical experience have suggested that the efficacy of AT_1 receptor antagonists in the treatment of hypertension is similar to that of ACE inhibitors. However, the two drug categories also

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have potential differences, because of their different mechanisms of action. Since they have an action that is exclusively targeted at angiotensin II, the AT_1 receptor antagonists should lack the effects of ACE inhibitors that are mediated through the accumulation of bradykinin and other peptides. Furthermore, since a significant amount of angiotensin II can be generated by enzymes other than ACE, particularly the chymases, AT_1 receptor antagonists achieve more complete blockade of the effects of angiotensin than ACE inhibitors do. Nevertheless, whether these differences are clinically important is still being investigated.

The first attempt at blocking the AT_1 receptor with the peptide analogues of angiotensin II resulted in the discovery of saralasin, an antagonist that lacked oral activity and had partial agonist properties. Losartan was the first agent in the new class of orally active AT_1 receptor antagonists. Other agents with different receptor affinities and binding kinetics, such as candesartan, eprosartan, irbesartan, losartan, tasosartan, telmisartan, and valsartan, have since become available (1). Variations in chemical structure may lead to marginal but potentially clinically significant differences in the time-effect profile. Non-competitive antagonists may have longer durations of action than competitive antagonists, because they bind irreversibly to angiotensin II receptors. There have been several reviews of this class of agents (2,3). All have emphasized their remarkable tolerance profile. In double-blind, placebo-controlled trials, the type and frequency of reported adverse effects were consistently no different from placebo (4).

The angiotensin II receptor antagonists are being considered for the treatment of diseases other than hypertension (heart failure with or without left ventricular systolic dysfunction, during and after acute myocardial infarction, diabetic nephropathy, other forms of glomerulopathy, restenosis after coronary angioplasty, and atherosclerosis).

Comparative studies

The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) trial was a pilot study investigating the effects of candesartan, enalapril, and their combination on exercise tolerance, ventricular function, quality of life, neurohormone concentrations, and tolerability in congestive heart failure (5). Candesartan alone was as effective, safe, and well tolerated as enalapril. The combination of candesartan with enalapril was more beneficial in preventing left ventricular remodelling than either alone. Although the trial was not powered to assess effects on cardiovascular events, it was terminated prematurely because of a trend toward a greater number of events in the candesartan alone and combination groups compared with enalapril alone.

In the ELITE study losartan produced greater survival benefit in elderly patients with heart failure than captopril (6). ELITE II was performed in order to confirm this. It included 3152 patients aged 60 years and over with NYHA class II–IV heart failure and was powered to detect a clinically significant effect on all-cause mortality. Median follow up was 555 days. Losartan was not superior to captopril in improving survival; however, it was better tolerated. Significantly fewer patients taking losartan withdrew because of adverse effects, including effects attributed to the study drug, or because of cough. Fewer patients discontinued treatment because of adverse effects (10 versus 15%), including effects attributed to the study drug (3 versus 8%) or because of cough (0.4 versus 2.8%) (6).

The results of SPICE (The Study of Patients Intolerant of Converting Enzyme Inhibitors) and of the previously published RESOLVD led to the design of the current CHARM trial, which is investigating the effect of candesartan in 6600 patients with heart failure in three different ways: versus an ACE inhibitor in patients with preserved left ventricular function; versus placebo in patients intolerant of ACE inhibitors; and in addition to ACE inhibitors in all other patients. While waiting for the results of this trial it is advisable to continue to use ACE inhibitors as the initial therapy for heart failure. In patients with documented intolerance of ACE inhibitors (which may represent 10–20% of patients with heart failure) angiotensin receptor antagonists may be useful as a substitute to block the renin–angiotensin–aldosterone system.

Placebo-controlled studies

The SPICE was a smaller trial (270 patients, 12 weeks follow-up) which evaluated the use of candesartan versus placebo in patients with heart failure and a history of intolerance of ACE inhibitors (most commonly because of cough, symptomatic hypotension, or renal insufficiency). Titration to the highest dose of candesartan 16 mg was possible in 69% of the patients (84% in the placebo group). Death and cardiovascular events tended to be lower with candesartan (7).

The results of another trial in heart failure with another angiotensin receptor antagonist (valsartan) are now available but are still to be published. In the VAL-HeFT (Valsartan in Heart Failure Trial) valsartan 160 mg bd was compared with placebo in 5010 patients with heart failure and left ventricular systolic dysfunction receiving optimal conventional therapy, including ACE inhibitors. The results showed a non-significant effect on mortality (19% on placebo, 20% on valsartan), but a highly significant effect on the primary endpoint of all-cause mortality and morbidity (32% on placebo, 29% on valsartan). A subgroup analysis suggested that the combination of valsartan, an ACE inhibitor, and a beta-blocker was not beneficial and might even be harmful, whereas the combination of valsartan and an ACE inhibitor caused a reduction of 45% (8).

General adverse effects

The safety profile of angiotensin II receptor antagonists is so far remarkably good. Except for hypotension, virtually no dose-related adverse effects have been reported. Headache, dizziness, weakness, and fatigue are the most common adverse effects. There have been reports of raised liver enzymes (9), cholestatic hepatitis (10), and pancreatitis (11) with losartan. Several cases of angioedema have been reported but no other obvious hypersensitivity reactions.

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Organs and Systems

Cardiovascular

The action of angiotensin II receptor antagonists in interfering with the activity of the renin–angiotensin system is so similar to the action of the ACE inhibitor drugs that episodes of first-dose hypotension, renal impairment, and hyperkalemia would be anticipated. However, there have been only a few such reports to date, although this may reflect the careful screening of patients for clinical trials, from which, by inference, obviously high-risk patients may have been excluded.

Respiratory

Cough has been specifically studied, because the mechanism of action of losartan differs from the ACE inhibitors, in that there is no accumulation of kinins, which have been implicated in the non-productive cough associated with ACE inhibitors (12). In 135 patients known to have ACE inhibitor-induced cough, lisinopril, losartan, or hydrochlorothiazide were given. Of the patients rechallenged with lisinopril, 72% developed a cough compared with only 29 and 34% challenged with losartan and hydrochlorothiazide respectively (13). However, in a Prescription Event Monitoring (PEM) study in four cohorts of 9000 patients exposed to losartan, enalapril, lisinopril, or perindopril, the rate of cough was high even with losartan. The authors attributed this to a carry-over effect, since presumably patients taking losartan have previously had cough with an ACE inhibitor (14).

A compilation of three controlled trials in 1200 patients showed incidence rates of cough of 3.6% with valsartan versus 9.5% with ACE inhibitors and 0.4% with placebo (1).

In a PEM study in 9000 patients cough occurred in 3.1% of patients taking losartan, compared with 3.9, 14, and 16% in patients taking enalapril, lisinopril, and perindopril respectively (14). The unusual low rate of cough with enalapril was surprising and emphasizes the limitations of PEM studies. Worthy of remark is a possible confounding effect, discussed by the authors, related to the fact that a large number of patients were given losartan because they had had cough with an ACE inhibitor. Because of a carry-over effect, cough may still be reported, especially in the first week when patients change to losartan. This carry-over effect may have been the cause of cough reported with losartan in other cases (15).

In a multicenter controlled study in patients with hypertension and a history of ACE inhibitor-induced cough, eprosartan significantly reduced the risk of cough by 88% compared with enalapril (16).

Immunologic

Because ACE inhibitor-induced anaphylaxis is thought to be related to accumulation of bradykinin, it was assumed that angiotensin II receptor antagonists would not cause this reaction. However, angioedema has been described within 30 minutes of a first dose of losartan 50 mg in a 52-year-old man (17). The author also referred to a single case of losartan-induced angioedema mentioned in the manufacturers' package insert from among 4058 patients treated with losartan. In an international safety update report based on 200 000 patients there were 13 cases of angioedema (18). Two had also taken an ACE inhibitor and three others had previously developed angioedema when taking ACE inhibitors.

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Angiotensin-converting enzyme inhibitors

See also Individual agents

General Information

Angiotensin-converting enzyme (ACE) inhibitors inhibit the conversion of angiotensin I to angiotensin II. The ACE is also a kininase, and so ACE inhibitors inhibit the breakdown of kinins. Some of the adverse effects of these drugs are related to these pharmacological effects. For example, cough is thought to be due to the action of kinins on axon fibers in the lungs and hypotension is due to vasodilatation secondary to reduced concentrations of the vasoconstrictor angiotensin II.

Our knowledge of the use of ACE inhibitors has expanded dramatically during recent years, thanks to the publication of the results of a number of large clinical trials (1).

The Heart Outcomes Prevention Evaluation (HOPE) study showed that virtually all patients with a history of cardiovascular disease, not only those who have had an acute myocardial infarction or who have heart failure, benefit from ACE inhibitor therapy (2). The authors selected 9297 patients at increased risk of cardiovascular disease, defined as a history of a cardiovascular event or evidence of disease, such as angina. People with diabetes but no indication of heart disease were included, but they had to have an additional risk factor. They were allocated to receive the ACE inhibitor ramipril 10 mg/day or placebo. The trial was stopped early, according to the predefined rules, because of an overwhelming effect of ramipril on the primary end-point, a 22% reduction in a composite measure of myocardial infarction, stroke, and death from cardiovascular causes. Significance was also achieved on outcomes as diverse as myocardial infarction, revascularization, heart failure, cardiac arrest, and worsening angina. Patients with diabetes had a similar 25% reduction for the composite cardiovascular end-point. Moreover, patients taking ramipril had 16% less overt nephropathy (defined as urine albumin over 300 mg/24 hours, or urine total protein excretion over 500 mg/24 hours, or a urine albumin/creatinine ratio over 36 mg/mmol). They also needed 22% less laser therapy for retinopathy. Since all the patients in the HOPE study were not hypertensive, and since the cardiovascular benefit was greater than that attributable to the fall in blood pressure, the authors suggested that ACE inhibitors are cardioprotective, vasculoprotective, and renal protective, independently of their blood pressure lowering effect.

Relative to the dosage issue, the dosage–plasma concentration relation for enalaprilat (the active metabolite of enalapril) in patients with heart failure and its relation to drug-related adverse effects has been investigated (3). In patients taking enalapril for more than 3 months, in dosages of 5–20 mg bd, there were highly variable trough concentrations of enalaprilat. They were affected by serum creatinine, the severity of heart failure, and body weight. Adverse effects, such as cough and rises in serum creatinine and potassium, were more common at high enalaprilat trough concentrations. The authors concluded that these results provide a rationale for individually adjusting ACE inhibitor doses in case of adverse effects.

Use in hypertension

In hypertension, the Captopril Prevention Project (CAPPP) trial evaluated an ACE inhibitor as an alternative first-line agent in mild to moderate hypertension. It was a prospective randomized open study with blinded end point evaluation (PROBE design), comparing an antihypertensive strategy based on either captopril or conventional therapy with a beta-blocker or a diuretic in patients with mild to moderate hypertension. At the end of follow-up the incidence of cardiovascular events was equal with the two strategies. However, imbalances in the assignment of treatment resulted in a 2 mmHg higher average diastolic blood pressure at entry in the group assigned to captopril. This difference in blood pressure alone would be sufficient to confer an excess of cardiovascular risk within this group, could mask real differences between the regimens in their effects on coronary events, and could explain the greater risk of stroke among patients who took captopril. The authors claimed that the overall results support the position that from now on one should consider ACE inhibitors as first-line agents, equal to diuretics and beta-blockers (4). The CAPPP study also reported a reduced risk of diabetes with captopril, which may be explained by the fact that thiazides and beta-blockers cause changes in glucose metabolism and by favorable effects of ACE inhibition on insulin responsiveness.

The second Swedish Trial in Old Patients with hypertension, STOP-2, was designed to compare the effects of conventional antihypertensive drugs on cardiovascular mortality and morbidity with those of newer antihypertensive drugs, including ACE inhibitors, in elderly patients (5). The study was prospective, randomized, and open, but with a blinded end-point evaluation. It included 6614 patients aged 70–84 years with hypertension (blood pressure over 180 mmHg systolic, or over 105 mmHg diastolic, or both). The patients were randomly assigned to conventional drugs (atenolol 50 mg/day, metoprolol 100 mg/day, pindolol 5 mg/day, or hydrochlorothiazide 25 mg/day plus amiloride 2.5 mg/day) or to newer drugs (enalapril 10 mg/day or lisinopril 10 mg/day, or felodipine 2.5 mg/day or isradipine 2.5 mg/day). Blood pressure fell similarly in all treatment groups. There were equal incidences of the primary end-points (fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease combined) in all groups (20 events per 1000 patient years). Subgroup analyses showed that conventional therapy,

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ACE inhibitors, and calcium antagonists had similar efficacy in preventing cardiovascular mortality and major morbidity. This finding argues against the hypothesis that some classes of antihypertensive drugs have efficacy advantages over others, at least in this population of elderly hypertensive patients. Therefore, the choice of antihypertensive treatment will be related to other factors, such as cost, co-existing disorders, and adverse effects. With respect to the reported adverse effects, since the study was open, causality cannot be established. Nevertheless, the size of the study and its naturalistic design allowed accurate assessment of the incidence of adverse effects in this population of elderly hypertensive patients. With ACE inhibitors the most frequently reported adverse effects were cough 30%, dizziness 28%, ankle edema 8.7%, headache 7.7%, shortness of breath 7.3%, and palpitation 5.5%. Actually, little detail was given in the section devoted to safety in the main publication of the results of the trial.

Use in heart failure

In heart failure much debate has been generated by the observation of general "under-use" of ACE inhibitors and the use of smaller doses than have been beneficial in clinical trials. This was partly related to concern about safety with the highest doses, especially in high-risk groups, such as the elderly and patients with renal insufficiency (6). Actually, outcome trials effectively excluded elderly patients (75–80 years and over) and usually patients with renal insufficiency. As elderly patients have poorer renal function, they are more likely to have vascular disease in their renal and carotid arteries, and may be more prone to symptomatic hypotension, it cannot be assumed that the benefit to harm balance observed in younger patients will be the same, at the same doses, in elderly people. The NETWORK trial, a comparison of small and large doses of enalapril in heart failure, was poorly designed and is not conclusive. However, it suggested that apart from a trend to more fatigue with higher doses (10 mg bd), the incidence of adverse effects, including symptomatic hypotension, was similar across the three dosages (2.5, 5, and 10 mg bd) (7).

In heart failure the issue of whether it is justified to use doses of ACE inhibitors substantially smaller than the target doses used in the large-scale studies that established the usefulness of these drugs has been examined in the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial (8). This trial randomized 3164 patients with New York Heart Association (NYHA) class II–IV heart failure and ejection fractions less than 30% to double-blind treatment with either low doses (2.5–5.0 mg/day) or high doses (32.5–35 mg/day) of the ACE inhibitor lisinopril for 39–58 months, while background therapy for heart failure was continued. When compared with the low-dose group, patients in the high-dose group had a non-significant 8% lower risk of death but a significant 12% lower risk of death plus hospitalization for any reason and 24% fewer hospitalizations for heart failure. Dizziness and renal insufficiency were more frequent in the high-dose group, but the two groups were similar in the number of patients who required withdrawal of the study medication. These findings suggest that patients with heart failure should not generally be maintained on very low doses of an ACE inhibitor, unless higher doses cannot be tolerated. However, the ATLAS trial did not address this issue properly. The doses in the small-dose arm were actually very small, and much smaller than those used in routine practice, as reported in several other studies (9). The doses in the large-dose arm may have been unnecessarily high. The recommendation of using target doses proven to be effective in large-scale trials remains unchallenged.

In the studies of left ventricular dysfunction (SOLVD), adverse effects related to the long-term use of enalapril have been thoroughly investigated (10).

Use in myocardial infarction

In the acute infarction ramipril efficacy (AIRE) study, oral ramipril in 2006 patients with heart failure after acute myocardial infarction resulted in a substantial reduction in deaths within 30 days (11).

More trials during and after myocardial infarction have been published and subjected to meta-analysis (12). This very large database provides valuable information on the rate of the most common adverse effects. Of all trials of the effects of ACE inhibitors on mortality in acute myocardial infarction, only the CONSENSUS II trial did not show a positive effect. In this trial, enalaprilat was infused within 24 hours after the onset of symptoms, followed by oral enalapril. The reasons for the negative result of CONSENSUS II remain unresolved, but hypotension and a proischemic effect linked to a poorer prognosis have been suggested.

Use in nephropathy

The results of two trials in patients with chronic nephropathy have reinforced the benefit of ACE inhibitors in slowing the progression of chronic renal insufficiency due to renal diseases other than diabetic nephropathy (13–15) and have provided sufficient information on the safety profile of these agents in chronic renal insufficiency. This was found to be essentially the same as in patients with normal renal function. The current practice of avoiding ACE inhibitors in severe renal insufficiency, to prevent further renal impairment and hyperkalemia, is no longer justified, although careful monitoring should still be observed.

Ramipril has a renal protective effect in non-diabetic nephropathies with nephrotic and non-nephrotic proteinuria (14). It also improves cardiovascular morbidity and all-cause mortality in patients with some cardiovascular risk (2).

The Ramipril Efficacy in Nephropathy (REIN) trial was designed to test whether glomerular protein traffic, and its modification by an ACE inhibitor, influenced disease progression in non-diabetic chronic nephropathies (13). Patients were stratified before randomization by 24-hour proteinuria. Treatment with ramipril or placebo plus conventional antihypertensive therapy was targeted at the same bloodpressure control. At the second interim analysis, ramipril had slowed the fall in glomerular filtration rate (GFR) more than expected from the degree of blood pressure reduction. In the follow-up study GFR almost stabilized in patients who had been originally randomized to ramipril and had continued to take it for more than 36 months. The combined risk of doubling of the serum creatinine or end-stage renal insufficiency was half that found in those taking placebo plus conventional

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therapy. In patients with proteinuria of 1–3 g/day the fall in GFR per month was not significantly affected, but progression to end-stage renal insufficiency was significantly less common with ramipril (9/99 versus 18/87) for a relative risk of 2.72 (CI = 1.22, 6.08) (14); and so was progression to overt proteinuria (15/99 versus 27/87; RR = 2.40; CI = 1.27, 4.52).

The results of this trial show that ramipril was well tolerated and even protective in cases of advanced renal insufficiency. One major reason for the current practice of underprescription and of prescription of suboptimal doses of ACE inhibitors, especially in patients with heart failure, is the presence of renal insufficiency (16). In such patients, not only should ACE inhibitors no longer be avoided, they are indeed indicated for preservation of renal function.

General adverse effects

The commonest unwanted effects of ACE inhibitors are related to their pharmacological actions (that is inhibition of angiotensin-converting enzyme and kininase II): renal insufficiency, potassium retention, pronounced first-dose hypotension, cough, and the serious but less common angioedema. Skin rashes and taste disturbances are uncommon, but may be more likely with sulfhydryl-containing drugs, particularly captopril. Rare hypersensitivity reactions include rashes, bone-marrow suppression, hepatitis, and alveolitis. If administered in the second or third term of pregnancy, ACE inhibitors can cause a number of fetal anomalies, including growth retardation, renal impairment, oligohydramnios, hypocalvaria, fetal pulmonary hypoplasia, and fetal death. Neonatal anuria and neonatal death can also occur (17,18). Tumor-inducing effects have not been reported.

The frequencies and the profile of adverse effects of five major classes of antihypertensive agents have been assessed in an unselected group of 2586 chronically drug-treated hypertensive patients (19). This was accompanied by a questionnaire-based survey among patients visiting a general practitioner. The percentages of patients who reported adverse effects spontaneously, on general inquiry, and on specific questioning were 16, 24, and 62% respectively. With ACE inhibitors the figures were 15, 22, and 55%. The percentage of patients in whom discontinuation was due to adverse effects was 8.1% with ACE inhibitors (significantly higher than diuretics). Compared with beta-blockers, ACE inhibitors were associated with less fatigue (RR = 0.57; 95% CI = 0.38, 0.85), cold extremities (RR = 0.11; CI = 0.07, 0.18), sexual urge (RR = 0.52; CI = 0.33, 0.82), insomnia (RR = 0.10; CI = 0.04, 0.26), dyspnea (RR = 0.38; CI = 0.17, 0.85), and more coughing (RR = 13; CI = 5.6, 30). The authors did not find a significant effect of age on the pattern of adverse effects. Women reported more effects and effects that were less related to the pharmacological treatment.

Organs and Systems

Cardiovascular

Marked reductions in blood pressure, without any significant change in heart rate, can occur at the start of ACE inhibitor therapy. Such reductions, which are not orthostatic, are sometimes symptomatic but rarely fatal. The volume of evidence is greatest with the longer established agents, but continues to suggest that the problems of first-dose hypotension are most likely to occur in patients whose renin–angiotensin system is stimulated (renin-dependent states), such as in renovascular hypertension or other causes of renal hypoperfusion, dehydration, or previous treatment with other vasodilators (20). These conditions can co-exist, particularly in severe heart failure (21–23). Similar problems have occurred in the treatment of hypertensive neonates and infants (24), but again were particularly likely in the setting of high plasma renin activity associated with either renovascular disease or concurrent diuretic treatment.

The use of very low doses to avoid first-dose hypotension is common, although the rationale remains unclear (25). It is even less clear whether or not there are differences between different ACE inhibitors, that is whether first-dose hypotension is agent-specific or a class effect (26,27).

Respiratory

Cough

DoTS classification

Dose-relation: collateral effect
Time-course: time-independent
Susceptibility factors: genetic (polymorphisms of the bradykinin B_2 receptor gene and the ACE gene); sex (men); exogenous factors (non-smokers).

A non-productive irritant cough is associated with ACE inhibitors (28,29). The dose-relatedness of this adverse effect is not clear.

Frequency

In different studies there has been large variability in the absolute incidence of cough (0.7–48%), the discontinuation rate (1–10%), and the relative incidences with different ACE inhibitors (30). However, the placebo-controlled, randomized, HOPE study has provided a remarkable database, with the largest cohort and the longest follow-up ever reported with such therapy (over 9000 patients followed for 5 years on average). Compared with placebo, ACE inhibitor therapy with ramipril caused cough leading to drug withdrawal in 7.3% of patients (compared with 1.8% for placebo) (13).

Mechanism

The mechanism of this effect has been explored (31–33). It may be more complicated than just an increase in concentrations of bradykinin and substance P, increased microvasculature leakage, and stimulation of vagal C fibers (34). Sulindac and indometacin may abolish or reduce the intensity and frequency of cough, supposedly because of inhibition of prostaglandin synthesis (35,36). Common variant genetics of ACE, chymase, and the bradykinin B_2 receptor do not explain the occurrence of ACE inhibitor-related cough (37). In general, bronchial hyper-reactivity has been causally implicated and may also be associated with exaggerated dermal responses to

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histamine (31,33). However, in one report, airways hyperresponsiveness was not a consistent finding (38).

Susceptibility factors

Cough is more common in non-smokers (39) and in women (39,40). It has been speculated that the risk of cough is genetically predetermined. The possibility that polymorphisms of the human bradykinin B_2 receptor gene may be involved in ACE inhibitor-related cough has been investigated in a case-control study (41). The DNA of 60 subjects with and without cough who were treated with ACE inhibitors was compared with that of 100 patients with untreated essential hypertensive and 100 normotensive subjects. The frequencies of the TT genotype and T allele were significantly higher in the subjects with cough than in subjects without. These tendencies were more pronounced in women. Subjects with the CC genotype were less susceptible to cough. According to the authors, high transcriptional activity of the bradykinin B_2 receptor promoter may be related to the risk of ACE inhibitor-related cough. This is the first demonstration that a genetic variant is involved in ACE inhibitor-related cough. It may therefore be possible to predict the occurrence of cough related to ACE inhibitor use.

The genetic basis of ACE inhibitor-induced cough and its relation to bradykinin have been further explored in a study of the effect of cilazapril in two groups of healthy volunteers genotyped for ACE insertion/deletion (I/D) polymorphism (42). The cough threshold to inhaled capsaicin was significantly lower in the genotype II group than in the DD group. Skin responses to intradermal bradykinin were significantly enhanced in the genotype II group. There was no difference in responsiveness to intradermal substance P. The authors suggested that these findings provide further evidence of the link between ACE inhibitor-induced cough and I/D polymorphism of the ACE gene, and that this supports the hypothesis that ACE inhibitors cause cough by modulating tissue concentrations of bradykinin.

Chinese patients experience more cough from ACE inhibitors than Caucasians. A review of the pharmacokinetics and blood pressure-lowering efficacy of ACE inhibitors as well as of ACE and angiotensinogen gene polymorphism did not find significant differences between Chinese and Caucasians to account for the difference in cough incidence (43).

Management

ACE inhibitor-associated cough seems to be a class effect: switching to another ACE inhibitor rarely solves the problem, although there are occasional anecdotal reports (40,44). However, most patients who develop a cough related to an ACE inhibitor are able and willing to continue therapy. In a small randomized study inhaled sodium cromoglicate relieved the symptom (45). In those in whom the symptom is intolerable, a switch to an angiotensin receptor antagonist is justified.

Obstructive airways disease

It has been suggested that ACE inhibitors are also associated with an increased incidence of symptomatic obstructive airways disease, leading to bronchospasm and asthma (46). However, a prescription event monitoring study of more than 29 000 patients taking ACE inhibitors, compared with 278 000 patients taking other drugs, failed to confirm this association (47).

Endocrine

Gynecomastia has been reported in a patient taking captopril 75 mg/day; it resolved when captopril was withdrawn but recurred when the patient was given enalapril (48). This suggests that gynecomastia may not be simply attributable to the sulfhydryl group of captopril.

Metabolism

ACE inhibition has been associated with increased insulin sensitivity in diabetic patients, and it has therefore been hypothesized that ACE inhibitors can precipitate hypoglycemia in such patients. A Dutch case-control study suggested that among users of insulin or oral hypoglycemic drugs, the use of ACE inhibitors was significantly associated with an increased risk of hospital admission for hypoglycemia (49). However, a French case/non-case study from the pharmacovigilance database did not confirm this finding (50).

In a matched case-control study of 404 cases of hospitalization for hypoglycemia in diabetic patients and 1375 controls, the risk of hypoglycemia was greater in those who used insulin versus a sulfonylurea and was not influenced by the use of ACE inhibitors (51). However, the use of enalapril was associated with an increased risk of hypoglycemia (OR = 2.4; CI = 1.1, 5.3) in sulfonylurea users. Although the authors emphasized the fact that previous reports of ACE inhibitor-related hypoglycemia were more frequent with enalapril, it is unclear why only enalapril, and not ACE inhibitors as a class, was associated with a significantly increased risk of hypoglycemia, and why this occurred only in sulfonylurea users.

Conversely, it has been suggested that the protective effect of ACE inhibitors against severe hypoglycemia should be tested in high-risk patients with high ACE activity. About 10–20% of patients with type 1 diabetes mellitus have a risk of severe hypoglycemia. In 307 unselected consecutive diabetic outpatients, those with the ACE DD genotype had a relative risk of severe hypoglycemia of 3.2 (95% CI = 1.4, 7.4) compared with those with the genotype II (52). There was a significant relation between serum ACE activity and the risk of severe hypoglycemia.

Electrolyte balance

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired kidney function and/or in patients taking potassium supplements (including salt substitutes) or potassium-sparing diuretics, and especially aldosterone antagonists, hyperkalemia can occur. In two cases, hypoaldosteronism with diabetes was implicated (53,54).

Hyponatremia, defined as a plasma sodium concentration of 133 mmol/l or under, has been investigated in a prospective study of elderly patients with hip fractures. ACE inhibitors were the most frequently used drugs (five

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of 14 cases) (55). Of course, this does not prove a cause and effect relation, since in elderly people ACE inhibitors are likely to be among the most frequently prescribed drugs. However, hypoaldosteronism would be a likely mechanism.

Hematologic

ACE inhibitors are used to treat erythrocytosis, for example after transplantation (56). Efficacy in treating erythrocytosis in chronic obstructive pulmonary disease has also been described with the angiotensin II receptor antagonist losartan (57). ACE inhibitors can also lower normal erythrocyte counts and cause anemia (58). This effect has been assessed in a retrospective study of 92 patients after transplantation with and without erythrocytosis, comparing patients taking the same anti-rejection therapy (steroids plus ciclosporin or steroids, ciclosporin, and azathioprine) taking ACE inhibitors with those not taking ACE inhibitors (59). There were significantly lower hemoglobin and erythropoietin concentrations in patients taking ACE inhibitors. When enalapril was given to those who had not previously taken an ACE inhibitor, the hemoglobin concentration fell by around 10% and erythropoietin by around 40%. These effects were not affected by the presence or absence of azathioprine. Although the hemoglobin-lowering effect of ACE inhibition is not a new finding, the lack of an influence of azathioprine adds some further understanding to the effect.

Liver

Hepatic injury is a rare adverse effect of the ACE inhibitors (60,61). Both acute and chronic hepatitis and cholestatic jaundice can occur (62,63), as can cross-reactivity, as identified in a report involving enalapril and captopril (64).

Pancreas

Acute pancreatitis has been reported with both enalapril and lisinopril (65,66).

Urinary tract

The ACE inhibitors can cause reversible impairment of renal function in the setting of reduced renal perfusion, whether due to bilateral renal artery stenosis, severe congestive heart failure, volume depletion, hyponatremia, high dosages of diuretics, combined treatment with NSAIDs, or diabetes mellitus (67). Beyond treatment of the cause, preventive measures include withholding diuretics for a few days, beginning therapy with very small doses of ACE inhibitors, and cautious dosage titration. Therapy involves increasing dietary sodium intake and reducing dosages of diuretics or temporarily withdrawing them. The ACE inhibitor may have to be given in reduced dosages or withdrawn for a time. Because they prolong survival in heart failure and after myocardial infarction, if withdrawal is deemed necessary ACE inhibitors should be reintroduced after a brief respite.

The agreed mechanism of renal function impairment with ACE inhibitors is as follows: when perfusion pressure or afferent arteriolar pressure is reduced in the glomerulus, glomerular filtration is maintained by efferent arteriolar vasoconstriction, an effect of angiotensin II. Blocking the formation of angiotensin II, and perhaps increasing the formation of bradykinin, causes selective efferent arteriolar vasodilatation and results in a reduction in glomerular filtration (68).

In a retrospective study of 64 patients, mean age 71 years, with acute renal insufficiency associated with an ACE inhibitor, over 85% presented with overt dehydration due to diuretics or gastrointestinal fluid loss (69). Bilateral renal artery stenosis or stenosis in a solitary kidney was documented in 20% of cases. In seven patients dialysis was required, but none became dialysis dependent. After resolution of acute renal insufficiency, the plasma creatinine concentration returned to baseline and renal function was not significantly worsened. Two-year mortality was the highest in a subgroup of patients with pre-existing chronic renal insufficiency.

Skin

There have been numerous reports of different rashes in association with ACE inhibitors. The most common skin reaction is a pruritic maculopapular eruption, which is reportedly more common with captopril (2–7%) than with enalapril (about 1.5%). This rash occurs in the usual dosage range and is more common in patients with renal insufficiency (70). Lichenoid reactions, bullous pemphigoid, exfoliative dermatitis, flushing and erythroderma, vasculitis/purpura, subcutaneous lupus erythematosus, and reversible alopecia have all been reported (70–72).

The ACE inhibitors can worsen psoriasis by a mechanism mediated by inhibition of the activity of leukotrienes, which are implicated in the pathogenesis of psoriasis (73).

The ACE inhibitor-related pemphigus has been reviewed in the light of two cases of pemphigus attributed to fosinopril and quinapril (74). Drug-related pemphigus can be classified into two major types, based on the clinical course: induced pemphigus and triggered pemphigus, in which endogenous factors are more important and the drug plays a secondary role. The first type is usually related to thiol drugs. It is impossible to distinguish drug-related pemphigus reliably from idiopathic pemphigus on the basis of clinical findings, histopathology, or immunofluorescence. Captopril tends to be associated with pemphigus foliaceus, whereas the non-thiol ACE inhibitors are more often associated with pemphigus vulgaris, although there are exceptions. A transition from pemphigus vulgaris to pemphigus foliaceus is more common than the reverse. Several mechanisms have been proposed to be involved in the induction of pemphigus: interaction of the thiol group with sulfur-containing groups on the keratinocyte membrane, leading to acantholysis by biochemical interference with adhesion mechanisms; antigen modification resulting in antibody formation; inhibition of suppressor T cells, resulting in pathogenic autoantibody formation by B cell clones; or enzyme activation or inhibition. The maximum latency to the development of pemphigus reported for ACE inhibitors is 2 years. It can take up to 17 months for lesions to resolve after drug withdrawal. A significant proportion of cases will not improve or resolve spontaneously on drug withdrawal alone. It is important to withdraw the offending drug, treat the bullous reaction

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appropriately, and advise avoidance of ACE inhibitors, although substitution of enalapril for captopril or vice versa has been successful in some cases.

Immunologic

Angioedema

Angioedema is a potentially fatal complication that has been associated with several different ACE inhibitors, with a reported incidence of 0.1–0.5%.

Presentation

Angioedema due to ACE inhibitors can manifest as recurrent episodes of facial swelling, which resolves on withdrawal, or as acute oropharyngeal edema and airways obstruction, which requires emergency treatment with an antihistamine and corticosteroids. It may be life-threatening (75) and may need tracheostomy (76). It is occasionally fatal (77). An unusual presentation with subglottic stenosis has also been reported (78). A variant form is angioedema of the intestine, which tends to occur within the first 24–48 hours of treatment (79,80).

- Two patients presented with isolated visceral angioedema with episodes of recurrent abdominal symptoms (81). Each had undergone surgical procedures for symptoms that persisted after surgery and were ultimately relieved by withdrawal of their ACE inhibitors.
- Another similar case was diagnosed as angioedema of the small bowel after an abdominal CT scan (82). Angioedema occurred in a 58-year-old woman 3 hours after biopsy of a hypopharyngeal mass under general anesthesia and was accompanied by transient electrocardiographic features of anterior myocardial infarction with severe hypokinesis of the anterior wall regions on echocardiography but no significant change in creatinine kinase activity (83). Only T wave inversion persisted on follow-up. Repeat echocardiography showed significant spontaneous improvement and coronary angiography showed normal coronary arteries. Hypotension and hypoxemia did not seem to occur, and the authors could not therefore speculate on the mechanism of the concomitant cardiac changes.
- Recurrent episodes of tongue swelling have been reported with cilazapril (84) and perindopril (85).
- A 74-year-old man with a permanent latex condom catheter developed penile swelling that was non-pitting and involved the subcutaneous tissue of a normal scrotum, after taking lisinopril 5 mg/day for 6 days (86). Removal of the catheter had no effect. After other possible causes were ruled out, ACE inhibitor-induced angioedema was suspected and lisinopril was withdrawn. Within a few days, the swelling, which had not spread, resolved.

Time-course

Angioedema can occur within the day after the start of treatment (87) and the risk is highest within the first month of ACE inhibitor use. However, it can occur many months after the start of therapy (88,89) or even years after (90).

Susceptibility factors

Black Americans are at increased risk of angioedema (91), with an overall rate of 1.6 per 1000 person years of ACE inhibitor use.

Anaphylactoid reactions, with hypotension, and flushing, occasionally associated with abdominal cramping, diarrhea, nausea, and sweating, have been reported in patients taking ACE inhibitors undergoing hemodialysis. Angioedema can also occur in these patients; it is occasionally life-threatening and is usually associated with the concurrent use of ACE inhibitors and dialysers in which the membrane is made of polyacrylonitrile (also known as AN69) (92,93). This combination should be avoided, since well-established alternatives are available.

For unclear reasons, ACE inhibitor-induced angioedema was more prevalent among immunosuppressed patients after cardiac or renal transplantation than among other patients (94). In 156 cardiac patients and 341 patients with renal transplants, this adverse effect was observed in 4.8 and 1% respectively, that is 24 times and 5 times higher than in the general population (0.1–0.2%).

Mechanism

The exact mechanism of angioedema associated with ACE inhibitors has not been determined. Although the reaction may be immune mediated, IgE antibodies or other specific antibodies have not been detected. Some authors have speculated that it may be related to a deficiency of carboxypeptidase N and complement components, because of its parallel role with that of ACE in enzymatic inactivation of bradykinin. The involvement of high concentrations of bradykinin in the pathogenesis of angioedema related to the use of ACE inhibitors is still hypothetical, since no definitive increase in bradykinin plasma concentration during attacks of angioedema has been shown. However, kinin concentrations are difficult to measure. In a well-documented study, a newly developed reliable assay for specific measurement of plasma bradykinin, excluding other immunoreactive kinins, detected a very high concentration of bradykinin (47 pmol/l) during an acute attack of angioedema in a patient taking captopril (95).

There have been reports of a lupus-like syndrome with captopril (96) and lisinopril (97).

Second-Generation Effects

Fetotoxicity

Enalapril, captopril, and lisinopril (and presumably other ACE inhibitors) cross the placenta in pharmacologically significant amounts (17). There is clear evidence of fetotoxicity when ACE inhibitors are used beyond the first trimester of pregnancy. Since continuation of treatment beyond the first trimester carries an excess risk of low fetal birth weight and other more severe complications, it is important to withdraw the ACE inhibitor at this time. Intrauterine growth retardation, oligohydramnios, and neonatal renal impairment, often with a serious outcome, are characteristic (98); failure of ossification of the skull or hypocalvaria also appear to be part of the pattern (17). There is also evidence that persistence of a patent ductus arteriosus is also more likely to occur.

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Susceptibility Factors

Renal disease

Enalapril has been specifically studied in patients who are resistant to other drugs and intolerant of captopril (99) and in patients with collagen vascular disease and renal disease known to be at high risk of adverse effects (100). In the first study (99), the major reasons for discontinuing captopril were a low white blood cell count, proteinuria, taste disturbance, and rash. In the vast majority of the 281 patients, these adverse effects did not recur during enalapril treatment. The main adverse events that warranted withdrawal of enalapril were impairment of renal function (5%), hypotension (2%), and rashes (2%). The authors noted that patients with angioedema should not be given alternative ACE inhibitors.

In the second study (100) of 738 high-risk patients the main reasons for the withdrawal of enalapril were increases in serum creatinine (4%), hypotension (1%), and nausea (1%).

The long-term safety of enalapril in patients with severe renal insufficiency and hypertension has been evaluated in a pooled analysis of three similar, randomized, placebo-controlled clinical trials in 317 patients with renal insufficiency (101). Only patients without diabetes were included. Follow-up was for 2 and 3 years. One protocol used a fixed dose (5 mg/day) and the other two allowed titration up to 40 mg/day. Cough occurred in 18% of the patients taking enalapril and in 6.1% of those taking placebo. Hypotension (5.9 versus 1.2%) and paresthesia (7.8 versus 2.4%) were more frequent with enalapril. Angioedema (1.3 versus 0.6%) and first-dose hypotension (1.3 versus 0%) tended to occur more often with enalapril. Hyperkalemia, defined as any increase from baseline and left to the judgement of the investigators, was excessive in the enalapril-treated patients (28 versus 8.8%). Finally, the hematocrit fell more often with enalapril (7.1 versus 2.0%).

It is important to stress that although it is a risk factor, renal insufficiency is a good indication for ACE inhibitors, which slow the progression of chronic renal insufficiency (102). In trials in patients with chronic renal insufficiency (13–15,17), the safety profile was essentially the same as in patients with normal renal function. The current practice of avoiding ACE inhibitors in severe renal insufficiency, to prevent further renal impairment and hyperkalemia, seems no longer justified. However, patients with bilateral renal artery stenosis carry an excess risk of renal insufficiency when treated with ACE inhibitors. These agents are therefore contraindicated in such patients.

Drug–Drug Interactions

Aspirin

Antagonistic effects of cyclo-oxygenase inhibitors (indometacin or aspirin) have been repeatedly reported both in hypertension and in heart failure, strongly suggesting that there may be prostaglandin participation in the clinical response to ACE inhibitors (103,104). In animals, although not in all experimental models, aspirin can attenuate the beneficial effects of ACE inhibitors on ventricular remodelling after myocardial infarction. However, there are conflicting reports on the clinical significance of this interaction (105).

Positive studies

From a post-hoc analysis of the SOLVD trial, it appears that in patients with left ventricular systolic dysfunction, the use of aspirin was associated with improved survival and reduced morbidity. In aspirin users, benefit from enalapril was retained but reduced (106).

The WASH pilot study (Warfarin/Aspirin Study in Heart Failure) compared the effects on cardiovascular events of warfarin and aspirin, and on antithrombotic therapy in patients with heart failure, most of whom were also taking an ACE inhibitor. Patients taking aspirin had more events and hospitalizations related to worsening heart failure than patients in the two other groups (unpublished data, reported at the 1999 annual meeting of the European Society of Cardiology, John Cleland, personal communication). The authors speculated that this may have been related to a negative interaction between ACE inhibitor therapy and aspirin, which would counteract the beneficial effects of ACE inhibitors. The Warfarin-Antiplatelet Trial in Chronic Heart Failure (WATCH) is indirectly addressing the issue. It is based on the hypothesis that warfarin or clopidogrel (an antiplatelet agent that acts by a pathway independent of cyclo-oxygenase) may be preferred to aspirin as antithrombotic therapy in patients with heart failure. It will randomize 4500 patients, most of whom will be taking ACE inhibitors. Meanwhile, it may be advisable to avoid aspirin in patients with heart failure and no clear indication for aspirin (no evidence of atherosclerosis), and to consider substituting warfarin or clopidogrel for aspirin in patients with refractory or rapidly progressive heart failure (107). In all other cases, because each drug is clearly associated with a substantial clinical benefit, it would be excessive to deny patients aspirin or ACE inhibitors.

In a series of studies of ACE inhibitor-induced improvement in pulmonary function, treatment with aspirin 325 mg/day for 8 weeks in patients with mild to moderate heart failure due to primitive dilated cardiomyopathy did not affect ventilation and peak oxygen consumption during exercise when the patients were not taking an ACE inhibitor but worsened pulmonary diffusion capacity and made the ventilatory response to exercise (tidal volume, ventilation to carbon dioxide production) less effective in those who were, regardless of the duration of ACE inhibition (108).

A systematic overview of major ACE inhibitor trials (CONSENSUS II, AIRE, TRACE, SMILE) found a trend toward less benefit from ACE inhibitors among aspirin users (109). Although the interaction was not statistically significant, the authors concluded that the data did not "refute the hypothesis of a major aspirin interaction with ACE inhibitors," especially because patients taking aspirin had only 60% of the benefit seen in patients not taking it.

GUSTO-1 and EPILOG, two different antithrombotic trials, GUSTO-1 and EPILOG, the first in acute myocardial infarction and the second during coronary stenting, compared the event rates in patients taking aspirin, an ACE inhibitor, or both (110). In each of these trials, events

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were more frequent in patients taking the combination than in those taking aspirin alone. The authors interpreted these findings as suggesting that ACE inhibitors may reduce the benefit of aspirin in these patients, whereas the results of the ACE inhibitor trials suggested that aspirin may interfere with the effect of ACE inhibitors.

Negative studies

A post-hoc analysis of the CATS trial database in patients with acute myocardial infarction suggested that aspirin does not attenuate the acute and long-term effects of captopril (111). Because of the demonstrated benefit on morbidity and mortality with each agent, textbooks and official guidelines do not recommend withholding either aspirin or ACE inhibitors in patients with heart failure or myocardial infarction. With no sufficient proof of lack of interaction, the use of small doses of aspirin (100 mg/day or less) is recommended.

In a study of the effects of aspirin 325 mg/day, both acute (4 hours after the dose) and chronic (6 weeks), in 62 patients with mild to moderate heart failure taking enalapril (more than 10 mg/day for at least 3 months), there were no significant changes in mean arterial pressure or in forearm blood flow and vascular resistance measured by venous plethysmography (112). In another arm of the study the same results were observed with ifetroban 250 mg/day, a thromboxane A_2 receptor antagonist.

Conclusions

Two post-hoc analyses of clinical trials (110) have added to the confusion engendered by these conflicting results. GUSTO-1 and EPILOG, two different antithrombotic trials, the first in acute myocardial infarction and the second during coronary stenting, compared the event rates in patients taking aspirin, an ACE inhibitor, or both (110). In each of these trials, events were more frequent in patients taking the combination than in those taking aspirin alone. The authors interpreted these findings as suggesting that ACE inhibitors may reduce the benefit of aspirin in these patients, whereas the results of the ACE inhibitor trials suggested that aspirin may interfere with the effect of ACE inhibitors.

These conflicting results may be partly explained by the various mechanisms of the vasodilatory action of ACE inhibitors, which may differ according to the regional peripheral circulation. In none of the studies was central hemodynamics or cardiac output assessed.

However, none of the trials post-hoc analysis, which suggested that there is an interaction between aspirin and ACE inhibitors, was specifically designed to examine this question. Post-hoc and subgroup analyses may be heavily biased, and multivariate adjustment may not have been able to account fully for confounding factors. Aspirin in itself may be harmful in certain patients, such as those with heart failure, because of its antiprostaglandin activity, rather than because it interferes with the actions of ACE inhibitors, a phenomenon that would also manifest as an aspirin–ACE inhibitor interaction.

The interaction between aspirin and ACE inhibitors in patients with heart failure is probably clinically important (105). Both drugs are often prescribed for a large number of patients with a variety of cardiovascular diseases. These agents have mechanisms of action that interact at the physiological level, and there are consequently many theoretical reasons to expect important clinical consequences. In animals, although not in all experimental models, aspirin can attenuate the beneficial effects of ACE inhibitors on ventricular remodelling after myocardial infarction. Some clinical studies have suggested that there is minimal, if any, adverse peripheral hemodynamic effect. In the most recent such study, the acute (4 hours after the dose) and chronic (6 weeks) effects of aspirin 325 mg/day were investigated in 62 patients with mild to moderate heart failure treated with enalapril (more than 10 mg/day for at least 3 months) (112). This did not produce significant changes in mean arterial pressure or in forearm blood flow and vascular resistance measured by venous plethysmography. In another arm of the study the same results were observed with ifetroban 250 mg/day, a thromboxane A_2 receptor antagonist. These conflicting results may be explained by the various mechanisms of the vasodilatory action of ACE inhibitors, which may differ according to the regional peripheral circulation. In none of the studies was central hemodynamics or cardiac output assessed. There is evidence that co-administration of aspirin and ACE inhibitors can be detrimental to renal function in patients with heart failure.

Beta-lactams

Intestinal absorption of beta-lactams occurs at least in part by an active mechanism involving a dipeptide carrier, and this pathway can be inhibited by dipeptides and tripeptides (113,114), which reduce the rate of absorption of the beta-lactams. ACE inhibitors, which have an oligopeptide structure, are absorbed by the same carrier (115) and interact with beta-lactams in isolated rat intestine (116).

A second potential site of interaction between ACE inhibitors and beta-lactams is the renal anionic transport system, and concomitant administration sometimes results in pronounced inhibition of the elimination of beta-lactams (117).

Diuretics

Because of dehydration, patients taking diuretics can be particularly sensitive to the hypotensive effect of ACE inhibitors (20).

Potassium supplements, potassium-sparing diuretics, or salt substitutes

Concurrent administration of potassium supplements, potassium-sparing diuretics, or salt substitutes can precipitate hyperkalemia in ACE inhibitor-treated patients, in whom aldosterone is suppressed (SED-14, 674). Regular monitoring of serum potassium is essential in these patients, because of the risk of hyperkalemia in patients given potassium (or potassium-sparing diuretics) and ACE inhibitors or angiotensin receptor antagonists.

In a retrospective study, five patients developed extreme hyperkalemia (9.4–11 mmol/l) within 8–18 days of starting combination therapy with co-amilozide and an ACE inhibitor (118).

In eight healthy subjects, treatment with spironolactone and losartan increased mean plasma potassium

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concentration by 0.8 mmol/l (up to 5.0 mmol/l) and reduced mean urinary potassium excretion from 108 to 87 mmol/l (119).

Until more data are available, it is prudent to consider angiotensin II receptor antagonists similar to ACE inhibitors as risk factors for hyperkalemia in patients taking potassium-sparing diuretics.

Selective cyclo-oxygenase-2 (COX-2) inhibitors

Non-selective non-steroidal inflammatory drugs can attenuate the antihypertensive effects of ACE inhibitors and increase the risk of renal insufficiency. In 2278 patients taking NSAIDs, 328 taking ACE inhibitors, and 162 taking both, no nephrotoxicity was found in patients taking monotherapy, but there were three cases of reversible renal insufficiency in patients taking the combination (120).

This effect is more prominent in patients with low renin concentrations. The interaction of COX-2 inhibitors with ACE inhibitors has been much less well investigated. In a review of Phase II/III studies of COX-2 inhibitors, it was reported that the co-administration of rofecoxib 25 mg/day and benazepril 10–40 mg/day for 4 weeks was associated with an average increase in mean arterial pressure of about 3 mmHg compared with ACE inhibitor monotherapy (121).

One report has described a case of increased blood pressure in a patient taking rofecoxib and lisinopril (122).

- The blood pressure of a 59-year-old man with hypertension and normal renal function rose when rofecoxib 25 mg/day was added to lisinopril 10 mg/day (from an average of 135/80–85 to 168/98 mmHg within 5 weeks). Four days after rofecoxib was withdrawn the blood pressure was 127/78 mmHg. Rechallenge with the same dose of rofecoxib produced the same effect and the blood pressure fell when the dosage of lisinopril was increased to 20 mg/day on continuous rofecoxib. The authors did not report on the course of renal function.

The increase in blood pressure with COX-2 inhibitors from interaction with ACE inhibitors may be greater in some patients than has previously been reported.

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Animal products

General Information

Drug substances of animal origin can produce anaphylactic or anaphylactoid reactions, particularly after parenteral administration (1). Animal products can also transmit an infectious disease because of the presence of a pathogenic microbe.

The following products are covered in this monograph:

- bear bile
- bee products (bee pollen, propolis, and royal jelly)
- carp bile
- fish oils
- gangliosides (from bovine brain)
- ghee
- glycosaminoglycans (Arumalon, chitosan, chondroitin, and glucosamine)
- green-lipped mussel
- Imedeen
- Kombucha "mushroom"

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- oyster extract
- rattlesnake meat
- shark products (shark cartilage and squalene)
- Spanish fly
- toad venom

Bear bile

Bear bile contains bile acids, cholesterol, and phospholipids (phosphatidylcholine, phosphatidylethanolamine, and phosphatidylinositol). It has been used for centuries in traditional Chinese medicine to treat liver and eye complaints and convulsions, and, in combination with curcuma and capillaris, gallstones and cholecystitis. More recently it has been touted as a treatment for stroke on the basis of animal experiments. It has few or no adverse effects, but by the same token probably has little or no efficacy, although it does contain ursodeoxycholic acid, which in purified form is effective in managing gallstones.

Bee products

Bee pollen

Bee pollen products are used as general tonics. Their use has been associated with allergic reactions, including anaphylaxis (2).

Propolis

Propolis (SEDA-12, 410) (SEDA-13, 459) (SEDA-18, 4) or bee-glue is a resinous material used by bees to seal hive walls and to strengthen the borders of the combs and the hive entrance. It has antiseptic, antimycotic, and bacteriostatic properties and is found in cosmetics and "natural products" for self-treatment.

Oral mucositis with ulceration caused by propolis has been reported in an HIV-negative man (3). Infectious stomatitis is common in HIV-positive patients. Therefore, the first approach is usually the administration of antiviral therapy, antimycotic therapy, or both. However, other causes, such as contact allergy, should be suspected if the patient is exposed to a potentially allergenic substance.

Propolis can cause allergic contact dermatitis (4), and have been reported in HIV-infected patients (5–7). It has been associated with allergy after its use in cosmetics and in the self-treatment of various diseases. Although most cases involve allergic contact dermatitis arising from topical application, a few reports have described an allergic reaction after oral ingestion. Adulteration of propolis capsules with excessive amounts of lead has been reported from New Zealand (8).

Royal jelly

Royal jelly (SEDA-21, 494) is a viscous secretion produced by the pharyngeal glands of the worker bee, *Apis mellifera*. It is widely used in alternative medicine as a health tonic. Its internal use by atopic individuals can cause severe, sometimes even fatal, asthma and anaphylaxis (9–11). Topical application can lead to contact dermatitis (12).

Two patients who were sensitized to a member of the Asteraceae (Compositae) family, mugwort, had severe systemic reactions (anaphylaxis and generalized urticaria/angioedema) due to honey and royal jelly (13). Both had positive skin tests and RAST to mugwort, and in one case the RAST inhibition assay showed strong cross-reactivity between the proteins of honey and mugwort. The authors suggested that there is a link between sensitization to Asteraceae and adverse reactions to honey and royal jelly.

Of 1472 hospital employees of a teaching hospital in Hong Kong, 461 had taken royal jelly in the past (14). Nine subjects reported 14 adverse reactions to royal jelly, including urticaria, eczema, rhinitis, and acute asthma. Of 176 subjects who responded to a questionnaire, 13 (7.4%) had positive skin tests to pure royal jelly, as did 23 of 300 consecutive asthma clinic attendees (7.3%). All but one of the 36 subjects with positive royal jelly skin tests was atopic to other common allergens. There were associations between positive royal jelly skin tests and atopy (OR = 33, 95% CI = 4.5, 252) and between adverse reactions to royal jelly and a history of clinical allergy (OR = 2.88, 95% CI = 0.72, 12), but not between royal jelly symptoms and previous royal jelly intake.

Carp bile

In Asia, the raw bile of the grass carp (*Ctenopharyngodom idellus*) is believed by some to be health promoting. However, eating it can result in hepatic dysfunction and nephrotoxicity (15). The former usually resolves within a few days, but the latter is more serious, culminating in acute renal insufficiency within 2–3 days after ingestion (16). Experiments in rats have shown that the bile of the grass carp loses its lethality when treated with colestyramine, which forms insoluble complexes with bile acids (17).

Fish oils

Fish oil supplements (SEDA-13, 460) (SEDA-18, 3), rich in long-chain polyunsaturated ω-3 fatty acids (eicosapentaenoic acid, docosahexaenoic acid), can reduce plasma concentrations of triglycerides and VLDL cholesterol, reduce platelet aggregation, prolong bleeding time, reduce blood pressure, increase the fluidity of the blood, and affect leukotriene production. Reported adverse effects include fullness and epigastric discomfort, diarrhea, and a fishy taste after belching. In addition to these mild symptoms, certain areas have been identified in which problems of a more serious nature could arise:

- a potential risk that the favorable changes in plasma lipids could be offset by a deleterious increase in LDL cholesterol or LDL apoprotein B;
- the possible adverse consequence of the capacity to increase bleeding time and to reduce platelet aggregation, especially in patients with pre-existing bleeding and platelet abnormalities and in those taking other antithrombotic agents;
- preliminary evidence that a detrimental effect on patients with aspirin-sensitive asthma is possible;
- an adverse effect on the metabolic control of patients with non-insulin-dependent diabetes mellitus, when these patients are not being treated with a sulfonylurea derivative (18);
- prothrombotic effects through changes on clotting factor concentration (19);
- possible contamination.

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Gangliosides

Gangliosides extracted from bovine brain tissue (Cronassial, Sygen) have been widely used in Western Europe and South America for several neurological disorders.

Reported adverse effects of gangliosides, other than discomfort at the injection site, include a motor neuron disease-like illness, cutaneous erythema (with or without fever and nausea), and anaphylaxis. After evaluation of reported associations between the use of gangliosides and Guillain–Barré syndrome (20,21), the Committee for Proprietary Medicinal Products (CPMP) of the European Commission recommended in September 1994 that the marketing authorizations for Cronassial (a mixture of gangliosides for treating peripheral neuropathies) should be withdrawn. At the same time, the CPMP recommended that marketing authorizations for Sygen (a monosialoganglioside known as GM-1, used for the treatment of cerebral vascular insufficiency) should be suspended.

In 65 patients with ischemic stroke treated for 6 weeks with intramuscular Sygen (monosialoganglioside 40 mg/day) in a double-blind, placebo-controlled study, there were no significant differences between the groups (22). A subsequent double-blind, sequential, multicenter, randomized, placebo-controlled trial of two doses of Sygen did not provide convincing evidence of efficacy (23).

Ghee

Ghee is clarified butter from the milk of water buffaloes or cows. Although the butter is heated enough to eliminate non-sporulating organisms, the process is unlikely to kill the spores of *Clostridium tetani*. This may explain why a case-control study in rural areas of Pakistan identified its traditional use as an umbilical cord dressing as a risk factor for the development of neonatal tetanus (24).

Glycosaminoglycans

Glycosaminoglycans include chondroitin-4-sulfate, chondroitin-6-sulfate, and disaccharide polymers composed of equimolar quantities of D-glucuronic acid, *N*-acetylglucosamine, and sulfates.

Arumalon

Arumalon (Rumalon) (SEDA-14, 440) is a glycosaminoglycan-peptide complex, a "chondroprotective" agent containing a watery extract of cartilage and an extract of the red bone marrow of calves. Parenteral use has been associated with local reactions at the site of the injection and with allergic symptoms (such as fever, malaise, symptoms of pronounced inflammation, nephrotic syndrome). Polymyositis and fatal dermatomyositis are also alleged to be associated with it.

- After 18 intramuscular injections of Arumalon, a 62-year-old woman with degenerative hip-joint changes developed a severe illness, with fever up to 39°C, swellings of the finger, hand, and knee joints, a rash, leukopenia (1.9×10^9/l), thrombocytopenia (113×10^9/l), and increased transaminases and lactate dehydrogenase activity (25). There was a positive lymphocyte transformation test with Arumalon and its constituents, and Arumalon-specific antibodies in the cultured lymphocyte fluid but not the serum. She became completely free of symptoms only after 1 year while taking a maintenance dose of prednisone 15 mg/day.

Chitosan

Chitosan is a polymer of glucosamine and *N*-acetylglucosamine, obtained from crustacean shells. It has been used to lower blood lipid concentrations, for body weight reduction (26), and as an excipient in pharmaceutical formulations.

Chondroitin

Chondroitin (Arteparon) (SEDA-14, 441) is a glycosaminoglycan, a "chondroprotective" agent prepared from bovine lung and tracheal cartilage. Mucopolysaccharide polysulfuric acid ester (also known as glycosaminoglycan polysulfate), said to be its major principle, resembles heparin in its molecular structure and can have the same effect on platelet aggregation. Chondroitin has been associated with life-threatening thromboembolic complications (myocardial infarction, pulmonary embolism, hemiplegic apoplexia, cerebral hemorrhage, death). Other reported adverse effects include local reactions at the site of the injection, serious allergic symptoms, arthropathy, subcutaneous fat necrosis, and reversible alopecia.

Glucosamine

Glucosamine is 2-amino-2-deoxy-D-chitin glucopyranose, which is present in joint cartilage. It has been used to treat osteoarthritis and has a small beneficial effect (27).

Asthma has reportedly been exacerbated by the use of a glucosamine-chondroitin supplement for osteoarthritis (28).

Interactions of glucosamine with warfarin (29,30) and acenocoumarol (31) have been described.

Green-lipped mussel

An extract of the New Zealand green-lipped mussel (*Perna canaliculus*) (SED-11, 1021) has been advocated for the treatment of arthritic symptoms. Reported adverse effects include flare-up of the disease, epigastric discomfort, flatulence, and nausea. Jaundice some weeks after starting treatment has been reported.

Imedeen

Imedeen is the trade name of an oral health food product containing freeze-dried proteins from the cartilage of deep-sea fish, which is advocated as an anti-wrinkling agent. Its use has been associated with generalized skin reactions and extensive Quincke's edema (32).

Kombucha "mushroom"

Kombucha "mushroom" (SEDA-20, 430) is a symbiotic yeast/bacteria aggregate surrounded by a permeable membrane. It has no proven efficacy for any indication and has serious adverse effects (33).

Liver damage has been reported after the ingestion of Kombucha tea (34). No other cause of the liver problem could be found. The patient recovered after withdrawal of Kombucha tea.

Anti-Jo1 antibody-positive myositis, associated with pleural effusions, pericardial effusion with tamponade,

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and "mechanic's hands," was attributed to the consumption of Kombucha "mushroom" (35).

Oyster extract

A food supplement consisting of oyster extract, ginseng, taurine, and zinc (Ostrin plus GTZ 611) has been associated with Quincke's facial edema. The reaction developed immediately after intake of the food supplement, and the oyster extract was considered to be its most likely cause (36).

Rattlesnake meat

Dried rattlesnake meat (SEDA-14, 442) (SEDA-18, 2) is a well-known folk remedy that can be purchased without prescription in Mexico, El Salvador, and the South-western part of the USA. It is available as such and in the form of powder, capsules, or pills, which may be labeled in Spanish as "víbora de cascabel," "pulvo de víbora," or "carne de víbora."

All of 16 different formulations of rattlesnake powder capsules, obtained in six different cities in Mexico, were significantly contaminated with Gram-negative coliform bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter agglomerans*, *Enterobacter cloacae*, *Salmonella arizona*, and *Salmonella* of groups B, E4, and G; 81% of the capsules were contaminated with *Salmonella* species, the most frequent being *S. arizona* (37). Contamination was probably derived from both the flesh of the snake and fecal contamination during domestic preparation of the powder to produce the capsules.

Rattlesnake products can therefore cause serious systemic infections, particularly with *S. arizona*. Typical victims are Hispanic patients with an immunocompromising illness, such as systemic lupus erythematosus (38,39), AIDS (40), or cancer (41).

Of 22 Latino patients with *S. arizona* infection in Los Angeles County in 1986 and 1987, 18 reported taking snake capsules compared with two of 24 matched Latino controls with non-subgroup three salmonellosis or shigellosis (OR = 18.0, CI = 4.2, 76) (42). An average of 18 cases per year of *S. arizona* infection were reported in the county between 1980 and 1987. In this investigation most of the patients with *S. arizona* infection after snake capsule ingestion had underlying illnesses, such as AIDS, diabetes, arthritis, or cancer. The capsules were obtained primarily from Tijuana, Mexico and from Los Angeles pharmacies in Latino neighborhoods.

Although most patients respond well to intravenous therapy with ampicillin or co-trimoxazole, deaths have occurred. *S. arizona* peritonitis has been reported.

Shark products

Shark cartilage

Shark cartilage powder, prepared from cartilage from the fins of hammerhead sharks (*Sphyrna lewini*) or spiny dogfish (*Squalus acanthias*), is promoted as a treatment for arthritis and cancer (43), based on antiangiogenic properties, but crude extracts are ineffective (44), presumably because the active constituents, such as sphyrnastatins are not absorbed.

- A 38-year-old white man worked in a factory that ground shark cartilage (45). After 10 months of exposure, he reported chest symptoms at work in association with exposure to shark cartilage dust, and a physician diagnosed asthma. Six months later, he complained of shortness of breath at work and died from autopsy-confirmed asthma.

Symptomatic hypercalcemia has been reported in patients taking shark cartilage supplements (46).

There has been one report of hepatitis associated with the use of a shark cartilage product (47).

Occupational asthma has been attributed to shark cartilage dust (48).

Squalene

Squalene is a popular over-the-counter Asian folk remedy derived from shark liver oil. Oral capsules are readily available in Asian health food stores and the substance is also widely used in cosmetics.

Ingestion of squalene capsules has been associated with severe lipoid pneumonia due to aspiration; the patient also had abnormal liver function, which raised the possibility of hepatotoxicity (49). In nine patients with squalene-induced extrinsic lipoid pneumonia the most common pattern of parenchymal abnormalities on chest X-ray was areas of ground-glass opacity ($n = 9$, bilateral 6), followed by consolidation ($n = 7$, bilateral 3), and poorly defined small nodules ($n = 4$, bilateral 2) (50). The abnormalities were distributed in the right lower zone ($n = 9$), left lower zone ($n = 6$), and right middle zone ($n = 6$). Initial CT scans ($n = 8$) showed bilateral areas of ground-glass attenuation ($n = 8$), poorly defined centrilobular nodules ($n = 8$), crazy paving ($n = 6$), and consolidation ($n = 3$). The abnormalities were distributed in the right middle lobe ($n = 8$) and in both lower lobes ($n = 5$). Follow-up chest X-rays ($n = 9$) showed complete disappearance ($n = 2$) or reduction ($n = 7$) in the extent of the parenchymal abnormalities, and follow-up CT scans ($n = 3$) showed improvement ($n = 2$) or no change ($n = 1$).

Spanish fly

Spanish fly (SED-11, 1023), also known as cantharides, is the dried blistering beetle (*Cantharis vesicatoria* and related species), which contains cantharidin as a major active constituent. A related insect, which serves as an alternative source of cantharidin in the East, is the Chinese blistering beetle (*Mylabris* species). Spanish fly has gained a considerable reputation as an aphrodisiac, following observations that nearly toxic doses could cause priapism in men and pelvic congestion, occasionally with uterine bleeding, in women. These effects are due to an irritant effect on the genitourinary tract, which could be misinterpreted as increased sensuality. Cantharidin was formerly used medicinally as a counter-irritant and vesicant, but this use has been abandoned because of toxicity.

The effects of cantharidin poisoning include local vesicobullous formation, burning of the mouth, dysphagia, nausea, hematemesis, hepatotoxicity, gross hematuria, and dysuria. Mucosal erosion and hemorrhage occur in the upper gastrointestinal tract. Renal dysfunction is common and related to acute tubular necrosis and glomerular destruction. Priapism, seizures, and cardiac abnormalities are less common. Deaths have occurred (51). However, the lethal dose is not well established; one patient died after taking only 10 mg, while another survived even after taking 50 mg. Four patients with cantharidin poisoning had dysuria and dark urine, three had abdominal pain, one had flank pain, three had hematuria, two had occult rectal bleeding, and one woman had vaginal

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bleeding; there was low-grade disseminated intravascular coagulation in two patients (52).

A report from Hong Kong described a fatal case due to the ingestion of a decoction of more than 200 dried *Mylabris* beetles as an abortifacient (53).

Toad venom

The dried venom of the Chinese toad (*Bufo bufo gargarizans*) is one of the ingredients of the traditional Chinese medicine kyushin. It has been used as an aphrodisiac and contains the bufadienolides bufalin and cinobufaginal, which are structurally related to cardenolides, such as digoxin, and create the false impression of high plasma digoxin concentrations (54). Digoxin Fab fragments have therefore been used to treat toad venom poisoning (55).

Poisoning with toad venom presents like digitalis toxicity (56). A deliberate overdose of kyushin in an attempt to commit suicide resulted in nausea, vomiting, general malaise, and electrocardiographic changes (for example atrioventricular block) (57). Fatal poisoning with toad venom presented with gastrointestinal symptoms, severe bradycardia, hyperkalemia, acidosis, and cardiac dysrhythmias (58).

The Chinese medicine Ch'an su, which is derived from dried toad venom, also contains bufalin and cinobufaginal, and has repeatedly been linked with serious, even fatal, cardiotoxicity (59).

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Anorectic drugs

See also Individual agents

General Information

Anorectic drugs, which are structurally related to the amphetamines, act mainly on the satiety centre in the hypothalamus and also increase general physical activity (1). All of them, except fenfluramine, stimulate the central nervous system and can cause restlessness, nervousness, irritability, and insomnia. Adverse effects also occur through sympathetic stimulation and gastrointestinal irritation. Drug interactions can occur with monoamine oxidase inhibitors. Dexamfetamine, phenmetrazine, and benzfetamine can cause dependence. Some of them have been associated with cardiac valvulopathy and primary pulmonary hypertension (2).

Anorectic drugs act mainly on the satiety centre in the hypothalamus (1). They also have metabolic effects involving fat and carbohydrate metabolism. Most of them are structurally related to amfetamine and increase physical activity. Their therapeutic effect tends to abate after some months, and part of this reduction in effect may be due to chemical alterations in the brain. Fenfluramine commonly produces drowsiness in normal doses, but has stimulant effects in overdosage. Dexamfetamine, phenmetrazine, and benzfetamine all tend to cause euphoria, with a risk of addiction. Euphoria occasionally occurs with amfepramone (diethylpropion), phentermine, and chlorphentermine, but to a much lesser extent. Some adverse effects are due to sympathetic stimulation and gastrointestinal irritation; these may necessitate withdrawal but are never serious. There are interactions with monoamine oxidase inhibitors and antihypertensive drugs.

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Antacids

General Information

Antacids are alkalis, such as aluminium hydroxide, magnesium salts (magnesium hydroxide and magnesium trisilicate), sodium bicarbonate, and calcium hydroxide. They are generally formulated in combinations (for example magnesium hydroxide + aluminium hydroxide, known as co-magaldrox), often with other components, such as simeticone (activated dimeticone, an anti-foaming agent), alginates (anti-reflux agents), and hydrotalcite (another type of antacid, the addition of which does not improve efficacy (1).

Comparative studies

Effervescent ranitidine 150 mg bd has been compared with as-needed calcium carbonate antacids 750 mg in a randomized study in 115 subjects who frequently self-treated heartburn (2). Effervescent ranitidine was significantly more effective than antacids in reducing heartburn, healing erosive esophagitis, alleviating pain, and improving quality of life. The overall incidences of adverse events were not significantly different in the two groups; 12% in the antacid group and 3% in the ranitidine group had adverse events related to the gastrointestinal system: nausea, vomiting, diarrhea, constipation, gas, fecal incontinence; and 1% in the antacid group and 4% in the ranitidine group had adverse events related to the central nervous system: headache, dizziness, insomnia, malaise, fatigue, weakness, nervousness.

Placebo-controlled studies

In a randomized, placebo-controlled, four-way, crossover study of the effects of low-dose ranitidine and an antacid on meal-induced heartburn and acidity in 26 subjects, ranitidine 75 mg significantly reduced gastric but not esophageal acidity, calcium carbonate 420 mg significantly reduced esophageal but not gastric acidity, and ranitidine plus calcium carbonate reduced both esophageal and gastric acidity (3). Both drugs given alone reduced heartburn severity compared with placebo.

General adverse effects

When they are given in conventional doses for symptomatic relief, antacids are safe, and adverse effects seldom limit the choice of formulation, except when troublesome diarrhea occurs (4). Change of bowel habit, usually in the form of mild diarrhea, is common, especially with magnesium salts. Other adverse effects usually occur as a direct consequence of ion absorption. They include alkalosis (particularly with large doses of soluble antacids), milk alkali syndrome when calcium is included, and the consequences of absorbing individual ions, particularly sodium but also bismuth and aluminium. Heart failure can be precipitated in susceptible patients by antacids with a high sodium content (see the Cardiovascular section). Antacids can interfere with the absorption of other drugs to a clinically important extent. Allergic reactions and tumor-inducing effects have not been described.

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Alginates

The use, efficacy, and adverse effects of non-prescription alginate-containing formulations and H_2 receptor antagonists obtained from community pharmacies have been evaluated in 767 customers with dyspepsia (5). Most obtained some or complete symptom relief (75%) and were completely satisfied with the product (78%). H_2 receptor antagonists were more likely to produce complete relief of symptoms than alginate-containing formulations. Only 3% reported adverse effects: diarrhea, constipation, bloating, and flatulence from alginate formulations, and dry mouth, altered bowel habit, diarrhea, and constipation from H_2 receptor antagonists.

Simeticone

No specific adverse effects have been attributed to dimeticone and its activated form simeticone, which are commonly compounded with antacids. Its use has been associated with reduced hydrogen concentrations in the breath (6), but this has not been confirmed (7).

Organs and Systems

Cardiovascular

The sodium content of antacids varies greatly; a daily dose of some products may contain sodium equivalent to more than 1 g of salt. This may not be clear from the labeling or the name of the formulation. However, the amount can be sufficient to precipitate heart failure in predisposed individuals (8).

Nervous system

Absence seizures have been described during treatment with sodium bicarbonate (9).

Metabolism

Some antacids contain enough sugar to affect diabetic control (10). Since the sugar is not an active component, it will not be declared on the packaging in many countries.

Gastrointestinal

Formulations that contain alginates can cause gastric bezoars, as can tube-feed thickening when antacids are added (11).

With sodium bicarbonate, gastric rupture due to massive carbon dioxide release has been described, though it is very rare (12).

Second-Generation Effects

Lactation

Antacids are generally regarded as safe to use during pregnancy (13) and lactation (14), particularly those that are poorly absorbed from the gastrointestinal tract.

Table 1 The effects of aluminium-containing antacids on the absorption of some other drugs

Drug	Effect
Of probable or known clinical significance	
Diflunisal	Reduced absorption
Digoxin	Reduced absorption
Ferrous ions	Reduced absorption
Ketoconazole	Reduced absorption
Tetracycline	Reduced absorption
^{99m}TcPYP	Altered distribution[a]
Quinolone antibiotics	Reduced circulating concentrations (15)
Of dubious or unlikely clinical significance	
Aminophylline	Absorption retarded
Oral antidiabetic agents	Partly adsorbed by antacids
Cimetidine	Reduced peak concentration
Diazepam	Absorption retarded but complete
Indometacin	Reduced absorption
Isoniazid	Reduced peak concentration
Levodopa	Reduced absorption
Phenothiazines	Adsorbed in vitro
Phenytoin	Absorption retarded

[a] Accumulation of the radiopharmaceutical in the liver and reticuloendothelial system (16)

Drug–Drug Interactions

General

Concurrent antacid intake can alter the absorption of many other drugs. Antacids can reduce the peak concentration (C_{max}) by reducing the speed of absorption, and/or reduce the amount of absorption (that is the systemic availability). However, the effects are not always of clinical importance (Table 1). Interactions can be minimized by giving antacids and other medications 2–3 hours apart.

Oral anticoagulants

Since dimeticone is a surfactant, one might expect it to enhance the absorption of drugs, and there are some reports that this happens with ethyl biscoumacetate (17).

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Antazoline

See also Antihistamines

General Information

Antazoline is a first-generation antihistamine.

Organs and Systems

Hematologic

Antazoline has sometimes produced thrombocytopenic purpura when used in normal doses (1). Antibodies to antazoline were present, obviously as a result of previous, yet uneventful, use.

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- Antazoline-induced thrombocytopenic purpura occurred on three occasions in a 21-year-old woman (2). After withdrawal of the drug she recovered promptly. In vitro investigations showed the presence of an antibody in her serum, which in association with antazoline caused complement fixation when added to test platelets. Platelet agglutinins were also detected in her serum when antazoline was added.

The reactions in this case were drug specific and could still be demonstrated 9 months after the last exposure to the drug.

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Anthracyclines and related compounds

See also Cytostatic and immunosuppressant drugs

General Information

Anthracyclines form a broad group of antitumor drugs within the group of cytotoxic antibiotics. The lead compounds were doxorubicin and daunorubicin; analogues include epirubicin, idarubicin, and aclarubicin. Mitoxantrone and pixantrone are related compounds of the anthracenedione family. Amsacrine is a related compound of the aminoacridine family.

Liposomal forms of doxorubicin (Caelyx, Myocet) and daunorubicin (DaunoXome) are in use. These drugs are licensed for the treatment of a wide range of tumors (Table 1). Much information regarding the anthracyclines has been previously published in major reviews and textbooks (1,2). With this in mind, their major toxic effects are outlined here, but concentrating in more detail on new findings, such as the interaction with trastuzumab.

Table 1 Licensed indications for anthracyclines

Drug	Where licensed	Licensed for the treatment of
Doxorubicin	USA and EU	Acute leukemia, lymphomas, soft tissue and osteogenic sarcomas, pediatric malignancies, and adult solid tumors (particularly lung and breast cancers)
Epirubicin	EU	Breast, ovarian, gastric, and lung cancers; malignant lymphomas, leukemias, and multiple myeloma; superficial and in-situ bladder carcinomas
Daunorubicin	USA and EU	Acute leukemias
Idarubicin	USA and EU	Relapsed or first-line treatment refractory advanced breast cancer, acute leukemias
Liposomal doxorubicin (Caelyx, Doxil)	USA and EU	Kaposi's sarcoma in AIDS
Liposomal pegylated daunorubicin (DaunoXome)	USA and EU	Kaposi's sarcoma in AIDS
Liposomal doxorubicin (Myocet)	EU	Breast cancer

Organs and Systems

Cardiovascular

Cardiomyopathy

Anthracyclines can cause the late complication of a cardiomyopathy, which can be irreversible and can proceed to congestive cardiac failure, ventricular dysfunction, conduction disturbances, or dysrhythmias several months or years after the end of treatment (3,4). Doxorubicin can cause abnormalities of right ventricular wall motion (5). A significant number of patients receiving anthracyclines develop cardiac autonomic dysfunction (6).

Dose-relatedness

The development of anthracycline-induced cardiomyopathy is closely related to the cumulative lifetime dose of the anthracycline. The recommended maximum cumulative lifetime dose of doxorubicin is 450–550 mg/m^2 (7) and of daunorubicin 400–550 mg/m^2 intravenously in adults (1,2). About 5% of doxorubicin-treated patients develop congestive cardiac failure at this dose; however, the incidence approaches 50% at cumulative doses of 1000 mg/m^2 (7–9). These figures are derived from experience with doxorubicin administered as a bolus or by infusion of very short duration (under 30 minutes). The incidence of clinical cardiotoxicity falls dramatically with other schedules of administration (that is weekly doses or continuous infusion for more than 24 hours).

In a randomized study of adjuvant chemotherapy comparing bolus against continuous intravenous infusion of doxorubicin 60 mg/m^2, cardiotoxicity, defined as a 10% or greater reduction in left ventricular ejection fraction, occurred in 61% of patients on a bolus median dose equal to 420 mg/m^2 compared with 42% on the continuous infusion schedule with a median dose of 540 mg/m^2; the rate of cardiotoxicity as a function of the cumulative dose of doxorubicin was significantly higher in the bolus treatment arm (10).

In 11 patients with anthracycline cardiotoxicity studied by heart catheterization and endomyocardial biopsy, myocytic damage correlated linearly with cumulative dose (11). There was a non-linear relation between electron microscopic changes and the extent of hemodynamic impairment. There was pronounced fibrous thickening of

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the endocardium in most patients, especially in the left ventricle. Endocardial fibrosis may be the first morphological sign of cardiotoxicity.

Susceptibility factors

The risk of cardiotoxicity is greater in children and patients with pre-existing cardiac disease or concomitant or prior mediastinal or chest wall irradiation (12,13).

Of 682 patients, 144 who were over 65 years of age all had doses up to but not exceeding the usual cumulative dose for doxorubicin (14). The authors concluded that older patients without cardiovascular co-morbidity are at no greater risk of congestive heart failure.

The use of doxorubicin in childhood impairs myocardial growth, resulting in a progressive increase in left ventricular afterload, sometimes associated with impaired myocardial contractility (15). Of 201 children who received doxorubicin and/or daunorubicin 200–1275 mg/m^2, 23% had abnormal cardiac function 4–20 years afterwards. Of those who were followed for more than 10 years, 38% had abnormal cardiac function compared with 18% in those who were followed for less than 10 years (16,17). In another study, more than half of the children studied by serial echocardiography after doxorubicin therapy for acute lymphoblastic leukemia developed increased left ventricular wall stress due to reduced wall thickness. This stress progressed with time (18).

Predisposing factors to mitoxantrone cardiotoxicity include increasing age, prior anthracycline therapy, previous cardiovascular disease, mediastinal radiotherapy, and a cumulative dose of the drug exceeding 120 mg/m^2. In 801 patients treated with mitoxantrone, prior treatment with doxorubicin and mitoxantrone was significantly associated with risk of cardiotoxicity; however, age, sex, and prior mediastinal radiotherapy were not useful predictors (19).

Anesthesia is difficult in patients with cumulative anthracycline-induced cardiotoxicity, and it has proved fatal on occasions (20).

Comparative studies of anthracyclines

All anthracyclines have cardiotoxic potential. However, because only a few cycles of treatment are administered in most regimens, few patients reach the cardiotoxic threshold of cumulative anthracycline dose. There is therefore limited information about the comparative cardiotoxic potential of these agents.

Epirubicin is considered to cause substantially less cardiotoxicity than doxorubicin on a molar basis (4,21). This has been attributed to its more rapid clearance rather than a different action (22). In a randomized, double-blind comparison of epirubicin and doxorubicin, there was a significant reduction in left ventricle ejection fraction with doxorubicin but not with epirubicin (23). However, data from large clinical series and from morphological examination of endomyocardial biopsies in smaller series of patients suggest that the incidence and severity of cumulative cardiac toxicity associated with epirubicin 900 mg/m^2 is similar to that associated with doxorubicin 450–550 mg/m^2 (24). In 29 patients treated with epirubicin in cumulative doses ranging from 147 to 888 mg/m^2 the ultrastructural myocardial lesions were similar to those produced by doxorubicin (partial and total myofibrillar loss in individual myocytes) (25). With both drugs, severe lesions were associated with replacement fibrosis. None of the patients who received epirubicin in the study developed congestive cardiac failure.

Both mitoxantrone and the oral formulation of idarubicin have been thought to be less cardiotoxic than doxorubicin (26,27). The South West Oncology Group reported on 801 patients treated with mitoxantrone; 1.5% developed congestive cardiac failure, an additional 1.5% had a reduced left ventricular ejection fraction (LVEF), and 0.25% developed acute myocardial infarction (19). Idarubicin has been reported to cause short-term cardiac toxicity when used in high doses in leukemia, and there is no doubt that it causes cumulative dose-related toxicity as well (28). Electrocardiographic changes occurred in 7% of adults with acute leukemia receiving aclarubicin (29).

Presentation

The main effects of anthracycline-induced cardiotoxicity are reduced left ventricular function and chronic congestive heart failure. Other cardiotoxic events occur only rarely. Occasionally, acute transient electrocardiographic changes (ST–T wave changes, prolongation of the QT interval) and dysrhythmias can occur. Acute conduction disturbances, acute myopericarditis, and acute cardiac failure are also rare. In a study of the effects of anthracyclines on myocardial function in 50 long-term survivors of childhood cancer, there was cardiac failure in one patient and electrocardiographic abnormalities (non-specific ST segment and T wave changes) in two (13). In one patient with a VVI pacemaker, who received the combination of vincristine, doxorubicin, and dexamethasone, the pacemaker had to be reset after each cycle of treatment, as the pacing threshold had increased, resulting in bradycardia (30).

Hypokinetic heart wall motion abnormalities and early signs of chronic cardiomyopathy have been identified as a significant toxic effect of mitoxantrone in patients who received cumulative doses of 32–174 mg (31). Electrocardiographic T wave inversion and cardiac complications have been described from intensive therapy with mitoxantrone 40 mg/m^2 over 5 days and cyclophosphamide 1550 mg/m^2 for 4 days, given before bone marrow transplantation for metastatic breast cancer. All the patients had had previous exposure to doxorubicin in cumulative doses that did not exceed 442 mg/m^2 (19).

The authors of a study of the use of MRI scans to assess the subclinical effects of the anthracyclines concluded that increased MRI enhancement equal to or greater than 5 on day 3 compared with the baseline predicted significant reduction in ejection fraction at day 28 (32). In 1000 patients given doxorubicin chemotherapy and irradiation there were six cases of congestive heart failure and three cases of myocardial infarction; there was a cumulative cardiac mortality of 0.4% in all anthracycline-exposed patients (33).

Diagnosis

The diagnosis of anthracycline cardiomyopathy is based on the clinical presentation and investigations such as

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radionuclide cardiac angiography, which can show a reduced ejection fraction (34), and echocardiography, which can show reduced or abnormal ventricular function (35,36). Dysrhythmias can be detected by electrocardiography, and QT_c interval prolongation may offer an easy, non-invasive test to predict patients who are at special risk of late cardiac decompensation after anthracycline treatment for childhood cancer (37). Radioimmunoscintigraphy can be used to highlight damaged myocytes, and changes such as myocardial fibrosis are characteristic on endomyocardial biopsy (13,38,39).

The subtle chronic abnormalities in myocardial function that occur 10–20 years after anthracycline exposure in childhood are best detected by exercise echocardiography, since these patients may have normal resting cardiac function (40).

It has been suggested that monitoring B type natriuretic peptide concentrations after anthracycline administration can reflect cardiac tolerance, and through serial monitoring allow a picture of the degree of left ventricular dysfunction to be established (41).

Mechanisms

Several mechanisms contribute to anthracycline cardiotoxicity. The principal mechanism is thought to be oxidative stresses placed on cardiac myocytes by reactive oxygen species. Amelioration of this toxicity is possible using dexrazoxane, an intracellular metal-chelating agent of the dioxopiperazine class (3). Dexrazoxane acts by depleting intracellular iron, thus reducing the formation of cardiotoxic hydroxyl anions and radicals. In patients without heart failure, in-vivo measurements of myocardial oxidative metabolism and blood flow did not change in patients with cancer receiving doxorubicin (42).

Anthracyclines have the ability inherent in their quinone structure to form free-radical semiquinones which result in very reactive oxygen species, causing peroxidation of the lipid membranes of the heart. However, this reaction has not been demonstrated with mitoxantrone, and the mechanism of its cardiotoxicity is unknown.

Abnormalities of left ventricular ejection fraction have been described in 46% of patients ($n = 14$) treated with mitoxantrone (14 mg/m^2) and with vincristine and prednisolone (43). A history of cardiac disease or of previous anthracycline exposure was excluded. Only one patient developed clinically overt congestive cardiac failure. Other reports have described less cardiotoxicity compared with the parent compound, doxorubicin (4,44).

Management

Anthracycline cardiomyopathy, although reportedly difficult to treat, often responds to current methods used to manage congestive cardiac failure.

Severe anthracycline-induced cardiotoxicity is generally considered irreversible, and it is associated with a poor prognosis and high mortality. However, in four cases the advanced cardiac dysfunction associated with doxorubicin recovered completely after withdrawal (45). Of 19 patients with anthracycline-induced congestive cardiac failure, 12 recovered after withdrawal, although reversal was modest (46).

The prolongation of the QT interval that occurs in patients who have recently finished doxorubicin therapy is slowly reversible over at least 3 years and the degree of prolongation is related to the cumulative dose (47).

Heart transplantation has been successful in patients with late, progressive cardiomyopathy without recurrence of the underlying malignant disease (48).

Cardiac dysrhythmias

Cardiac dysrhythmias have been reported after amsacrine therapy in association with hypokalemia. Pre-existing supraventricular dysrhythmias or ventricular extra beats are not absolute contraindications to its use (49). Of 5430 patients treated with amsacrine, 65 developed cardiotoxicity, including prolongation of the QT interval, non-specific ST–T wave changes, ventricular tachycardia, and ventricular fibrillation (50). There were serious ventricular dysrhythmias resulting in cardiopulmonary arrest in 31 patients; 14 died as a result. The dysrhythmias occurred within minutes to several hours after drug administration. The cardiotoxicity was not related to total cumulative dose, and hypokalemia was possibly a risk factor for dysrhythmias.

Sensory systems

Doxorubicin can cause conjunctivitis, periorbital edema, lacrimation, blepharospasm, keratitis, and reduced visual acuity (51). There have been two reports of persistent photophobia and chronic inflammation of the eye following accidental topical exposure to doxorubicin (52).

Hematologic

Myelosuppression, principally neutropenia, occurs in 60–80% of patients who receive conventional doses of anthracyclines (single-agent standard doses: doxorubicin 60–75 mg/m^2, epirubicin 60–90 mg/m^2 given 3-weekly) (53). On an equimolar basis, in both the single-agent and combination regimens, epirubicin causes less hematological toxicity than doxorubicin (24). The incidence and severity of myelosuppression is related to dose; it has been suggested that severe neutropenia occurs in all patients who are given high-dose anthracyclines (doxorubicin 100 mg/m^2 or more and epirubicin 120 mg/m^2 or more) (54). Neutrophil nadirs occur at 7–10 days after treatment, and full neutrophil recovery usually occurs by day 21 (24). Platelets are less affected; about 35% of patients receiving epirubicin 120 mg/m^2 have grade-3 thrombocytopenia (55). Anemia occurs rarely (24).

Although the extent of leukopenia is not related to cumulative anthracycline dose, patients who have received extensive prior chemotherapy develop more severe leukopenia, possibly because of diminished bone marrow reserve (24). There was a strong correlation between dose and both leukocyte nadirs and platelet nadirs in 287 patients who received single-agent epirubicin 40, 60, 90, or 135 mg/m^2 every 3 weeks (56). Myelosuppression correlates with exposure to epirubicin, as reflected by the plasma AUC (57).

Myelosuppression is not prevented by prolonged doxorubicin infusion (53), although this can mitigate other adverse effects. Hematological toxicity associated with

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high-dose regimens can be partially ameliorated by giving hemopoietic growth factors, with or without autologous bone marrow or peripheral blood progenitor cell rescue (58–60). However, other adverse effects, mainly mucositis, then become dose-limiting. It has been suggested that mitoxantrone 14 mg/m^2 is more myelosuppressive than doxorubicin 70 mg/m^2, which in turn is more myelosuppressive than epirubicin 70 mg/m^2, each given at 3-week intervals (61).

Secondary acute myeloid leukemia, with or without a preleukemic phase, has been rarely reported in patients being concurrently treated with epirubicin or doxorubicin in association with DNA-damaging antineoplastic agents; such cases have a short latency period (1–3 years) (62,63). In one study, three of 77 patients who received epirubicin plus cisplatin and two who received other epirubicin-containing combinations developed acute myelogenous leukemia 15–33 months after the start of epirubicin treatment for advanced breast cancer (62). However, all had received prior treatment with alkylating agents and/or radiotherapy, which are recognized independent leukemogenic risk factors. Despite high mean lifetime epirubicin doses in this study (mean 800 mg/m^2), there was no relation between cumulative dose and the risk of acute myelogenous leukemia. In a second study, four of 351 patients with metastatic breast cancer who received fluorouracil + epirubicin + cyclophosphamide, but none of 359 who received cyclophosphamide + methotrexate + 5-fluorouracil, developed leukemia (three acute myelogenous leukemia, one acute lymphoblastic leukemia) (63). No secondary leukemias were documented in other large comparative studies of epirubicin-containing regimens (64,65). Nevertheless, a retrospective analysis of case reports, published in abstract form without references or methods, concluded that when epirubicin was combined with alkylating agents it was associated with an increased risk of secondary acute myelogenous leukemia in women with breast cancer (66).

Prolongation of the prothrombin time after the use of amsacrine 1200 mg/m^2 for acute myeloid leukemia was related to transient deficiency of factor X (67).

Mouth and teeth

Mucositis is a well-documented toxic effect of anthracyclines; it has been reported in 8% of combination chemotherapeutic courses including epirubicin in a dose of 180 mg/m^2 (68).

Gastrointestinal

The anthracyclines are classed as moderately to strongly emetogenic. Nausea and vomiting occurs in 21–55% of patients, but is substantially reduced by pretreatment with antiemetic drugs (53,55). In one randomized study, epirubicin 70 mg/m^2, doxorubicin 70 mg/m^2, and mitoxantrone 14 mg/m^2 were compared (61). The first cycles of epirubicin and mitoxantrone were given without antiemetic drugs, unless specifically requested, but thereafter antiemetic drugs were given as required; doxorubicin was given with antiemetic drugs from cycle one. Doxorubicin and epirubicin were significantly more emetogenic than mitoxantrone; there was grade 3 nausea and vomiting in 22% of those who received doxorubicin, 18% of those who received epirubicin, and none of those who received mitoxantrone. Oral idarubicin may cause more emesis, which is quoted as occurring in 25–86% of patients; however, these effects are said to be usually mild to moderate (27).

With the advent of the 5-hydroxytryptamine (5-HT$_3$) receptor antagonists (ondansetron, granisetron, tropisetron), used in conjunction with dexamethasone, nausea and vomiting can be ameliorated in most patients.

Mucositis and stomatitis are potentially severe and dose-limiting adverse effects of the anthracyclines. Both the frequency and the severity are dose-dependent (56,69). Their onset and recovery generally parallel the hematological toxicity, but they can occur earlier (5–10 days after treatment starts). Areas of painful erosions, mainly along the side of the tongue and on the sublingual mucosa, are common. Mucositis occurs in about 9% of patients who receive oral idarubicin in standard doses (27).

Diarrhea has also been reported with the anthracyclines. In a typical study, in which epirubicin 100 mg/m^2 was given for 1–8 cycles, one of 39 patients had grade 1/2 diarrhea and two of 39 had grade 3/4 diarrhea (70). Of patients who take oral idarubicin 10–38% are said to develop diarrhea, again generally mild to moderate (27).

Urinary tract

All anthracyclines can cause discoloration of the urine and other body fluids (that is tears) (1,2).

Skin

Anthracyclines can cause local irritant reactions. These range from erythema and phlebitis at the injection site to potentially severe vesicant reactions requiring skin grafting (24). Care appropriate to the administration of a vesicant must be observed during infusion. Various treatments have been used immediately after extravasation in an attempt to lessen the injury, including ice, steroids, vitamin E, and bicarbonate. The current recommended treatment is by intermittent cooling of the affected area, together with intermittent use of topical dimethylsulfoxide 99% (71). There is also evidence of the efficacy of intravenous dexrazoxane, and the first dose should preferably be given within 6 hours (72). In three patients who had extravasation of epirubicin or doxorubicin, healing occurred without sequelae (73,74); all three received three doses of intravenous dexrazoxane over 3 days (1000 mg/m^2 on the first two days and 500 mg/m^2 on day 3), the first dose being administered at 2–5 hours after extravasation. A fourth patient received dexrazoxane 1500 mg 1 hour after extravasation of doxorubicin and repeated 5 hours later, and 750 mg on day 2; the wound healed slowly and required surgery after 3 months (75). A fifth patient received dexrazoxane more than 6 hours after extravasation of epirubicin; the wound healed slowly and with a crusted center (76).

Reactivation of skin damage can also occur at sites of prior radiation therapy ("radiation recall") (77).

- Widespread allergic contact dermatitis occurred in a 73-year-old man after intravesical administration of epirubicin; a patch test with an aqueous solution of the drug (0.1%) was positive (78).

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A syndrome of palmar–plantar erythema (progressing in some patients to blistering and desquamation) has been reported in seven of eight patients with advanced breast or ovarian cancer who received high-dose doxorubicin (125–150 mg/m^2) (79). By contrast, in a similar dose intensification study in which patients received epirubicin 200 mg/m^2 with cyclophosphamide and growth factor support, the palmar–plantar syndrome did not occur (80).

In 60 patients receiving polyethylene glycol-coated liposomal doxorubicin (Doxil) 35–70 mg/m^2 by infusion over 1–2 hours there were four patterns of skin eruption: hand–foot syndrome (40%), a diffuse follicular rash (10%), an intertrigo-like eruption (8%), and new melanotic macules (0.5%) (81).

Hair

Complete or partial alopecia occurs in the majority (60–90%) of patients who receive anthracyclines, and although it is reversible it can be distressing (24). Scalp cooling during chemotherapy to minimize hair loss is now little used, because of limited efficacy, the discomfort of scalp cooling techniques, and concern about the potential creation of a "sanctuary" for circulating tumor cells. Alopecia is less frequent (about 35% of patients) in patients who take oral idarubicin 40–45 mg/m^2 every 3 weeks (27).

Nails

Painful onycholysis, blue discoloration of the nails (82), and reversible loss of fingernails (83) have been attributed to mitoxantrone.

Sweat glands

There has been a single report of hidradenitis associated with mitoxantrone (84).

Long-Term Effects

Mutagenicity

There was an increased number of chromosomally aberrant lymphocytes in nurses who handled cytostatic agents (doxorubicin, cyclophosphamide, vincristine, fluorouracil, and methotrexate) many years ago, before modern facilities for the preparation of chemotherapeutic drugs were in use (85). No long-term fertility problems were identified in 205 men who were treated with doxorubicin during childhood (86).

Tumorigenicity

In 604 women who were given six cycles of epirubicin after 4 years of tamoxifen, there were 12 non-breast second malignancies (87). Although the authors did not analyse these in respect to population expectation, they thought that the frequency was relatively high.

Second-Generation Effects

Teratogenicity

There is no conclusive evidence about whether anthracyclines adversely affect human fertility or are teratogenic. In 26 of 28 pregnancies, three or more chemotherapeutic agents were used to treat acute leukemia ($n = 20$), non-Hodgkin's lymphoma ($n = 3$), Ewing's sarcoma ($n = 2$), breast cancer ($n = 2$), and myoblastoma ($n = 1$) (88). The anthracyclines were introduced at various gestational ages, ranging from time of conception to 38 weeks, but in most cases chemotherapy was started in the second trimester. The outcomes were 24 normal infants, including a set of twins. Four of the five cases of infant death occurred in those with hematological malignancies (acute leukemia and non-Hodgkin's lymphoma), one each due to maternal death and therapeutic abortion and two resulting from spontaneous abortion. Neonatal pathological examination showed no congenital anomalies or organ defects, one case of marrow hypoplasia, and one case of neonatal sepsis. These findings suggest that anthracyclines have no detectable effect on the offspring up to the age of 54 months. However, bias inherent in reporting pregnancies with a successful outcome is obvious, so extreme caution must be exercised in the use of anthracyclines in pregnancy, and they should be avoided if at all possible.

Fetotoxicity

Cardiac failure occurred in a 3-day-old neonate whose mother had been given idarubicin 9 mg/m^2 as part of induction therapy for acute lymphoblastic leukemia at 22 weeks; the baby was delivered at 28 weeks (89). In the absence of another known cause, the cardiotoxicity was attributed to idarubicin exposure 6 weeks before.

Susceptibility Factors

Hepatic disease

Since the main route of metabolism and elimination of anthracyclines is via the bile, dosage reduction is recommended if there is hepatic impairment. This was first suggested after a report of increased toxicity in patients with liver metastases who received full-dose anthracycline treatment, followed by a second report that suggested that the clearance of anthracyclines is reduced in patients with hepatic metastases (90,91). These reports led to the current recommendations for anthracycline doses, based on serum bilirubin concentration or sulfobromophthalein clearance. However, the question of whether liver dysfunction significantly affects anthracycline clearance is unclear, and the dosage modifications suggested (see Table 2) have never been validated. Indeed, there is evidence that anthracycline kinetics are altered in patients with raised serum transaminases alone,

Table 2 Effects of liver function on doses of doxorubicin and epirubicin

Drug	Serum bilirubin concentration	BSP retention	Recommended dose
Doxorubicin	20–50 μmol/l	9–15%	50% of normal
	>50 μmol/l	>15%	25% of normal
Epirubicin	20–50 μmol/l		50% of normal
	>50 μmol/l		25% of normal

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which may be a better basis for dosage modification (92). In practice, many clinicians make empirical dosage modifications in patients with abnormal liver biochemistry tests (57).

Drug Administration

Drug formulations

The anthracyclines have been formulated in liposomal formulations in order to alter their pharmacokinetics and improve their therapeutic index. Examples include:

- pegylated liposomal doxorubicin (Caelyx/Doxil);
- liposomal doxorubicin (Myocet);
- liposomal daunorubicin (DaunoXome).

These formulations are dealt with in a separate monograph.

Drug administration route

The anthracyclines are most commonly given intravenously, either as bolus doses or, less often, as infusions over varying lengths of time. Alternative routes have been tried, such as the intraperitoneal, intrapleural, and intravesical routes (93,94).

Intraperitoneal

Intraperitoneal instillation of doxorubicin has been used in the early postoperative period in patients with retroperitoneal or visceral sarcoma, in an attempt to eradicate microscopic residual disease after complete macroscopic surgical excision (95). Three of 17 patients had pyrexia, one peritoneal sclerosis, one a pancreatic fistula, and two abdominal pain. There were no anastomotic disruptions or intra-abdominal hemorrhages.

Intrapleural

Adverse effects associated with the intrapleural instillation of doxorubicin in doses of 10–40 mg consist of fever (11–15%), anorexia (24–29%), nausea (20–29%), and chest pain (28–29%) (94,96). Cardiomyopathy and myelosuppression were not reported (96).

Intravesical

Intravesical epirubicin has been used to treat superficial bladder cancers. At a dose of 50 mg, the overall incidence of adverse events was 16–25% (93). The frequency of adverse events tended to increase with dose but not the number of instillations. Most adverse events were mild and transient; the commonest were localized to the bladder and included chemical cystitis (10–38%), urinary tract infection (2–13%), and hematuria (2–33%). Contracted bladder or hemorrhagic cystitis have been reported in 1–6% of patients (93).

Adverse events occurred in 31 of 194 patients who received epirubicin 80 mg intravesically compared with 12 of 205 who received placebo after transurethral resection (97). Systemic adverse events (usually cardiac or hematological adverse events or hypersensitivity) generally occurred in under 5% of patients. In two studies of intravesical epirubicin, there were reports of myocardial infarction (9%), stroke (3%), angina pectoris (3%), or atrioventricular block (2%) (98,99). There were no reports of myelosuppression in clinical trials of intravesical epirubicin, apart from thrombocytopenia in one of 37 patients in one cancer trial (98) and hemoglobinemia in two of 40 patients in another (100).

Biochemical abnormalities have been reported in trials of intravesical epirubicin. In one trial, liver function tests were impaired in seven of 40 patients who received epirubicin and in 10 of 35 patients who received epirubicin and verapamil concomitantly (101). In another study, liver function tests were impaired in one of 69 patients who received combination prophylaxis with epirubicin 50 mg and BCG 150 mg after transurethral resection (102).

Hypersensitivity has been reported in 0–8% of patients in trials of intravesical epirubicin; the symptoms included generalized skin rash, vulval irritation, or urinary frequency and dysuria, or were not stated (100,103,104). One of 34 patients developed symptoms characterized as allergic (dizziness, nausea, hypotension) 1 hour after instillation of epirubicin (105). Two patients who received epirubicin developed severe allergic reactions and one died (106,107).

Non-specific systemic adverse events (flu-like symptoms, malaise, fever, nausea, vomiting, anorexia, rash) occurred in under 5% of patients who received intravesical epirubicin (98,103,108). Alopecia was reported in one of 37 patients (98).

Intravesical epirubicin and doxorubicin appear to have similar tolerability profiles (104,109–112).

Valrubicin (a novel *N*-trifluoroacetyl, 14-valerate derivative of doxorubicin) is currently licensed in the USA for intravesical use in prophylaxis in patients with BCG-refractory carcinoma in situ after transurethral resection. It has a similar toxicity profile to that of epirubicin and doxorubicin (113).

Drug overdose

Very high single doses of anthracyclines can cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10–14 days. Treatment should aim to support the patient during this period and should include such measures as blood transfusion and reverse barrier nursing. Delayed cardiac failure can occur up to 6 months after overdosage.

Drug–Drug Interactions

Etoposide

The combination of idarubicin plus etoposide (total doses 180 mg and 5760 mg respectively) was associated with a case of acute promyelocytic leukemia (114).

Taxanes

The combination of doxorubicin plus paclitaxel is cardiotoxic.

Of 57 patients who had received at least three courses of chemotherapy with a combination of doxorubicin 50 mg/m^2 plus paclitaxel 175–225 mg/m^2, left ventricular ejection fraction did not fall overall but was significantly reduced in eight patients; it fell by more than 14% in

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three cases and by 33–48% in the other five; none of the patients developed clinical heart failure (115).

Two studies of the combination of epirubicin plus paclitaxel have shown less reduction in left ventricular ejection fraction and no clinical evidence of cardiac failure (116,117).

Clinically significant cardiac insufficiency has been reported in a patient who was given epirubicin (316 mg/m^2) followed by six cycles of docetaxel (100 mg/m^2/cycle) (118).

Trastuzumab

An interaction of doxorubicin with the anti-HER_2 receptor humanized monoclonal antibody, trastuzumab (Herceptin), has been reported. Most patients who received trastuzumab in early trials had been pretreated with anthracyclines. Despite this, preliminary information suggested that reduced systolic cardiac function was an adverse effect of trastuzumab (119). More recently, this problem has been further highlighted in a study of women with metastatic breast cancer (120). Patients who had not received prior anthracycline-containing adjuvant chemotherapy were at greater risk of cardiotoxicity when they received trastuzumab in combination with doxorubicin or cyclophosphamide (27 and 75% respectively), compared with only 11% of patients who received trastuzumab in combination with paclitaxel (120,121). The risk of cardiac events in patients treated with doxorubicin, cyclophosphamide, and trastuzumab increased markedly after a cumulative doxorubicin dose of 360 mg/m^2. This suggests synergistic cardiotoxicity with trastuzumab and doxorubicin. Trastuzumab is therefore currently licensed only for use in conjunction with paclitaxel or docetaxel and not with conventional doxorubicin.

The mechanism of trastuzumab-induced cardiotoxicity and its synergy with doxorubicin is as yet unknown. However, the cardiac failure responds to standard medical management (122).

Since trastuzumab is active as a single agent and in combination with chemotherapy in patients whose tumors overexpress HER_2, the interaction with doxorubicin is clearly of concern. Although it is possible to avoid this problem by not combining trastuzumab with doxorubicin, there are compelling reasons for further exploring its use with anthracyclines. For example, follow-up results from the CALGB 8541 study have shown that patients who received high and moderate (standard) doses of cyclophosphamide plus doxorubicin plus fluorouracil survived longer than those who received low doses (123). Moreover, examination of patients' HER_2 status in this trial showed that those whose tumors expressed large amounts of the HER_2 protein had a significantly worse survival if treated with moderate or low doses of cyclophosphamide plus doxorubicin plus fluorouracil, compared with high doses (124). These results suggest that patients whose tumors express large amounts of the HER_2 receptor protein may require high-dose anthracyclines, presenting the problem of how then to treat them with trastuzumab without causing cardiotoxicity.

In an attempt to avoid cardiotoxicity after the administration of trastuzumab with doxorubicin, alternative adjuvant regimens have been suggested. Trastuzumab could be combined with other anthracyclines (epirubicin or liposomal formulations), which are inherently less cardiotoxic, or given sequentially rather than concomitantly with the anthracycline. Alternatively, non-anthracycline combinations, such as cyclophosphamide plus doxorubicin plus fluorouracil or based around taxanes, cisplatin, and vinorelbine are being investigated (125).

Caution should of course be exercised when giving other cytotoxic drugs, especially myelotoxic agents or agents that cause significant mucositis/stomatitis, in combination with anthracyclines.

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Anthracyclines—liposomal formulations

See also Anthracyclines and cytostatic and immunosuppressant drugs

General Information

Liposomes are microscopic particles composed of a lipid bilayer membrane enclosing active drug in a central aqueous compartment (1). The aim of liposomal encapsulation of a drug is to alter its pharmacokinetics, thus improving efficacy and/or reducing toxicity (2). Current formulations of liposomal formulations of anthracyclines are as follows:

- pegylated liposomal doxorubicin (Caelyx/Doxil)
- liposomal doxorubicin (Myocet)
- liposomal daunorubicin (DaunoXome).

Sterically stabilized liposomal doxorubicin (pegylated liposomal doxorubicin; Caelyx/Doxil) is coated with polyethylene glycol (3), which results in so-called "stealth liposomes." In liposomal daunorubicin the liposome consists of a lipid bilayer of distearoylphosphatidylcholine and cholesterol in a 2:1 molar ratio (4). Both formulations have a hydrophilic outer layer, which attracts a coating of water around the liposomal shell. This increases the circulation time by making the formulation virtually invisible to the reticuloendothelial system.

The second liposome system (Myocet) was designed to preserve the antitumor effects of doxorubicin but with reduced cardiotoxicity. This type of liposome is readily recognized and phagocytosed by the mononuclear phagocyte system. In animals most of the injected cytotoxic agent is rapidly taken up by phagocytes, minimizing exposure of normal tissues, and thus diminishing some acute and chronic adverse effects (5,6). The doxorubicin is then released by the phagocytes in a controlled fashion, similar to a slow infusion.

Pharmacokinetics

The differences between liposomal doxorubicin and liposomal daunorubicin are due to the differences in their liposomal packaging.

Pegylated liposomal doxorubicin (Caelyx/Doxil) and liposomal daunorubicin (DaunoXome) produce lower peak plasma concentrations and longer circulation times than free drug (7).

Liposomal doxorubicin in Myocet has systemic availability, metabolism, and excretion similar to that of conventional doxorubicin, but at a slower rate (8). In dogs, the plasma concentrations of doxorubicin from Myocet were 1000-fold greater than conventional doxorubicin at 6 hours, but the difference diminished at 24 hours (9). This distinguishes Myocet from Doxil, which persists in the circulation for significantly longer.

Caelyx has linear pharmacokinetics and its disposition occurs in two phases, the first relatively short (5 hours) and the second prolonged (55 hours). Unlike free doxorubicin, most of the pegylated liposomal doxorubicin is

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confined to the vascular fluid volume, and its blood clearance depends on the liposomal carrier. Liposomal daunorubicin acts similarly to Caelyx, but produces a lower AUC and has a higher clearance and a shorter terminal half-life (10).

Pegylated liposomes (diameter about 70–100 nm) and liposomal daunorubicin (diameter 45 nm) are small enough to pass intact through defective blood vessels that supply tumors. This, rather than any particular affinity for tumor cells, is the reason for their accumulation in tumor tissue (2). Caelyx provides a greater concentration of doxorubicin in Kaposi's sarcoma tumors than in normal skin.

Organs and Systems

Cardiovascular

The incidence of cardiotoxicity in anthracycline-treated patients has been related to the peak plasma drug concentration (11,12). One of the aims in developing pegylated liposomal doxorubicin was to reduce plasma concentrations of free doxorubicin and restrict myocardial penetration, to minimize cardiotoxicity. Preclinical data suggested that the liposomal formulation was indeed less cardiotoxic than the free drug: about 50% more pegylated liposomal doxorubicin than free doxorubicin can be given to rabbits without producing the same frequency of cardiotoxicity (13).

Cardiac adverse events that have been considered probably or possibly related to pegylated liposomal doxorubicin have been reported in 3–9% of patients (14–16). These include hypotension, pericardial effusion, thrombophlebitis, heart failure, and tachycardia (14,15).

Left ventricular failure has been reported in a few patients, particularly those who received high cumulative lifetime doses of pegylated liposomal doxorubicin (over 550 mg/m^2) (14,15). However, cumulative doses of 450 mg/m^2 or more and 550 mg/m^2 have been administered without significant reduction in ejection fraction or the development of cardiac failure (17,18). To date, no or minimal cardiotoxicity has been observed in patients with AIDS-related Kaposi's sarcoma who received pegylated liposomal doxorubicin in high cumulative doses (19).

Both peak and overall concentrations of doxorubicin in myocardial tissue are reduced by 30–40% after Myocet relative to conventional doxorubicin (9). This reduced myocardial exposure resulted in a significant reduction in cardiotoxicity, assessed both functionally and histologically (5,6). Compared with free doxorubicin 75 mg/m^2 given 3-weekly, Myocet 75 mg/m^2 caused significantly less congestive cardiac failure (1 versus 6%) (20). However, a high dose of Myocet (135 mg/m^2, median cumulative dose 405 mg/m^2) caused a significant increase in cardiac toxicity: 38% of patients had a protocol-defined cardiac event, including 13% who developed congestive heart failure (21).

In one study there was a significant (over 20%) reduction in the shortening fraction with liposomal daunorubicin measured by echocardiography (22). In contrast, in another study there was no significant fall in cardiac function, even after cumulative doses of liposomal daunorubicin over 1000 mg/m^2 (23).

Women with metastatic breast cancer were randomized to receive either liposomal doxorubicin (Myocet) 75 mg/m^2 ($n = 108$) or conventional doxorubicin 75 mg/m^2 ($n = 116$) (24). The liposomal formulation was less cardiotoxic than the conventional one, and the cumulative doses before the onset of cardiotoxicity were 780 versus 570 mg/m^2 respectively; the liposomal formulation provided comparable antitumor activity. In another study the authors tried to define the cumulative toxic intravenous dose of daunorubicin (DaunoXome) and concluded that it may be 750–900 mg/m^2 or even higher (exceeding 1000 mg/m^2) (25).

Respiratory

Acute dyspnea, low back pain, and/or pain at the site of tumor have been described, beginning within 1–5 minutes of the start of infusion of pegylated liposomal doxorubicin (26). Three of 35 patients were described as suffering acute dyspnea, two with back pain and two with abdominal pain. In each case the symptoms resolved within 5–15 minutes of stopping the infusion, which was restarted without adverse effects. The mechanism of these symptoms was unclear. However, because the dyspnea was reminiscent of that seen in hemodialysis neutropenia, complete blood counts were obtained from four patients about 2 minutes after the onset of symptoms. All four had relative neutropenia (neutrophil counts of 3–46% of pretreatment), which resolved by the end of the infusion. In vitro, pegylated liposomal doxorubicin, in concentrations predicted to be present in the plasma during the start of treatment, stimulates neutrophil adhesion to human umbilical vein endothelial cells (26). Thus, pegylated liposomal doxorubicin may cause transient sequestration of neutrophils in the pulmonary circulation, resulting in reduced lung compliance and associated dyspnea.

Hematologic

In a phase I dose-finding study of pegylated liposomal doxorubicin, myelosuppression was not a major problem with the doses tested (20–80 mg/m^2, re-dosing every 3–4 weeks). Median nadir white cell and platelet counts were well above 2×10^9/l and 100×10^9/l respectively. In the occasional patient in whom profound granulocytopenia developed there was quick recovery of the cell counts within less than 7 days. Neutropenic fever was documented in only one patient at the top dose of 80 mg/m^2 (17). There was no significant indication of cumulative myelosuppression. Treatment-related anemia was generally mild and blood transfusions were not required. However, two patients with head and neck malignancies and extensive pretreatment were given erythropoietin to maintain hemoglobin concentrations above 9.0 g/dl (17).

Pooled data from 12 phase I or II studies, in 308 patients with solid tumors who received pegylated liposomal doxorubicin in doses of 10–80 mg/m^2, showed that there was neutropenia (neutrophil count below 1×10^9/l) in 50%, anemia in 19%, and thrombocytopenia in 9.2% (27).

Of 71 patients with metastatic breast cancer treated with pegylated liposomal doxorubicin in doses of 45–60 mg/m^2 given 3- or 4-weekly, grade 3/4 neutropenia occurred in 10% and thrombocytopenia in 1% (27).

If pegylated liposomal doxorubicin and liposomal daunorubicin are used to treat AIDS-related Kaposi's sarcoma, one has to consider additional factors that affect

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the white cell count. In patients with HIV/AIDS, myelosuppression was the most frequent dose-limiting adverse effect of liposomal anthracyclines (22,23). In one study of 30 patients with Kaposi's sarcoma given liposomal daunorubicin 40 mg/m^2, 53% developed granulocytopenia (white cell count below 1×10^9/l); 17% had a hemoglobin concentration below 8.0 g/dl, but none had thrombocytopenia (22).

In another study in 53 patients with AIDS-related Kaposi's sarcoma given pegylated liposomal doxorubicin 20 mg/m^2 every 3 weeks, 21 had leukopenia and three had thrombocytopenia (28).

At doses of 20 mg/m^2 liposomal doxorubicin, combined tolerability data from 705 patients with AIDS-related Kaposi's sarcoma showed that neutropenia (below 1×10^9/l) and anemia were the most common adverse events, affecting 50 and 19% of patients respectively (14).

In summary, myelosuppression after treatment with pegylated liposomal doxorubicin does not appear to be a major problem in patients with solid tumors and relatively intact immunological systems, but is the dose-limiting adverse effect in immunocompromised patients with HIV/AIDS.

High-dose Myocet (135 mg/m^2) caused significant hematological toxicity, namely grade 4 neutropenia in 98% and thrombocytopenia in 46 of 52 patients (21). However, Myocet 75 mg/m^2 3-weekly caused less hematological toxicity than conventional doxorubicin (20).

Gastrointestinal

Stomatitis and pharyngitis have been confirmed, along with hand–foot syndrome, as dose-limiting adverse effects of pegylated liposomal anthracyclines (17). Stomatitis was dose-limiting at high single doses over 70 mg/m^2. Similarly, 12 of 35 patients who received pegylated liposomal doxorubicin 50 mg/m^2 every 3 weeks for advanced ovarian carcinoma required dose reduction (to 40 mg/m^2) or treatment delay (to 4 weeks) because of mucositis (18). Stomatitis and mucositis are dose-dependent (29). In the treatment of Kaposi's sarcoma in patients with HIV/AIDS, mucositis and stomatitis are rarely problematic and are not dose-limiting. Presumably this is because significantly lower doses of pegylated liposomal doxorubicin are used in these patients.

Nausea and vomiting have been reported but appear to be mild and infrequent adverse effects of pegylated liposomal anthracyclines and liposomal daunorubicin (23,30). In most patients pegylated liposomal doxorubicin can be given without prophylactic antiemetics. In one study there was only mild nausea and vomiting in eight of 53 patients who had not received prophylactic antiemetics (28). Further reviews in patients with AIDS-related Kaposi's sarcoma have reported nausea and vomiting in 17 and 8% of patients respectively (29). Pooled data from 12 phase I and II studies in patients with solid tumors showed that 3.6% of patients had had grade 3/4 nausea or vomiting (27). Diarrhea has similarly been recognized as a mild and infrequent adverse effect of pegylated liposomal doxorubicin (three of 53 patients) (28).

Myocet (75 mg/m^2) causes significantly less vomiting (11 versus 23%) than conventional free doxorubicin (75 mg/m^2) (20). It also leads to lower peak-free doxorubicin concentrations in the gastrointestinal mucosa compared with conventional doxorubicin, and less gastrointestinal toxicity (5). However, high-dose Myocet (135 mg/m^2) caused grade 4 mucositis in 10 of 52 patients (21).

Liver

The authors of a case report suggested that pegylated liposomal doxorubicin was the probable cause of hepatic failure in a patient who, 2 weeks after treatment with pegylated liposomal doxorubicin 10 mg/m^2 (cumulative dose 20 mg/m^2) (15), developed jaundice and ascites (31). Despite withdrawal of other potentially hepatotoxic drugs, the patient died of hepatorenal failure 12 weeks later. This may have been an idiosyncratic effect augmented by hepatitis B viral infection (15,32), as there have been no other reports of hepatorenal failure (14,33).

Skin

Skin toxicity, manifesting primarily as palmar–plantar erythrodysesthesia or hand–foot syndrome, is one of the principal dose-limiting adverse effects of pegylated liposomal anthracyclines (for example Caelyx 50 mg/m^2 given every 4 weeks) and may warrant dosage modification, depending on the severity of the symptoms (17,18). In pooled tolerability data, grade 3/4 hand–foot syndrome was reported in 54 (17.5%) of 308 patients (27). The median time to the development of grade 3/4 hand–foot syndrome was 51 days, corresponding to the second or third cycle of treatment (27). Myocet, even when given in a high dose (135 mg/m^2), was not associated with the hand–foot syndrome characteristic of pegylated liposomal doxorubicin (20,21). This was presumed to be due to differences in the liposomal formulation. Pegylated liposomes circulate for prolonged periods and may undergo some eccrine excretion, particularly in cases of hyperhidrosis, whereas with Myocet the liposome is phagocytosed by the reticuloendothelial system and the active drug is then slowly released into the circulation, similar to a slow infusion. Severe forms of hand–foot syndrome may need acute intervention with oral dexamethasone and topical dimethylsulfoxide; oral vitamin B_6 has not been proven to be useful.

Conjunctivitis and skin pigmentation have been reported but are mild (23,27,28).

Unlike extravasation of conventional doxorubicin, which can cause severe local inflammation and tissue damage, extravasation of liposomal doxorubicin was associated with only mild transient irritation at the infusion site in the eight documented cases (34,35).

Four cases of extravasation of liposomal daunorubicin have been reported and were associated with only mild irritation and transient erythema and swelling, similar to pegylated liposomal doxorubicin (36).

In 60 patients receiving polyethylene glycol-coated liposomal doxorubicin (Doxil) 35–70 mg/m^2 by infusion over 1–2 hours there were four patterns of skin eruption: hand–foot syndrome (40%), a diffuse follicular rash (10%), an intertrigo-like eruption (8%), and new melanotic macules (0.5%) (37).

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Hair

Alopecia can occur during treatment with doxorubicin (38). It is generally mild during treatment with Caelyx and occurs in 6–9% of patients. The incidence of alopecia with single-agent Myocet is higher.

Immunologic

Acute hypersensitivity reactions have been reported with the first infusion of pegylated liposomal doxorubicin (14,15). The symptoms included flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest and throat, and hypotension. Similar reactions have been reported after the intravenous administration of colloid imaging agents and unloaded liposomes.

Acute reactions to infusion have been observed on first exposure to the drug in six of 56 patients treated with pegylated doxorubicin 20–60 mg/m^2 (17). The reactions developed at 3–25 minutes after the start of the infusion and were characterized by flushing, sensation of choking, back pain, and in one instance hypotension. All the symptoms disappeared shortly after discontinuation of the infusion. Three patients were re-treated successfully using premedication (hydrocortisone, cimetidine, and diphenhydramine) and a slower infusion rate (initial rate 1 mg/minute). Similarly, acute onset symptoms of dyspnea, back pain, and tumor site pain have been reported in other studies (26). Since this reaction generally improves on rechallenge with or without premedication, it has been termed pseudoallergic.

Long-Term Effects

Tumorigenicity

Two patients with acute promyelocytic leukemia developed therapy-related myelodysplasia 2.0–2.5 years after complete remission and then acute myeloid leukemia; both had received anthracyclines (39). In both cases the cytogenetic changes that usually occur after the use of alkylating agents were observed. There has only been one previous similar report after successful therapy with anthracyclines, but these observations suggest that anthracyclines can cause acute myeloid leukemia similar to that caused by alkylating agents.

A flare phenomenon is a well-documented effect of hormonal therapies and/or hormone-responsive tumors. A prostate-specific antigen flare occurred in four of 28 patients who received liposomal doxorubicin (Caelyx) for symptomatic androgen-independent prostate cancer (40).

Second-Generation Effects

Teratogenicity

Pegylated liposomal doxorubicin is embryotoxic in rats and embryotoxic and abortifacient in rabbits. Teratogenicity cannot therefore be ruled out, but there is no reported experience in pregnant women. Equally, it is not known if the drug is excreted into human breast milk, so breastfeeding should be discontinued before the administration of pegylated liposomal doxorubicin.

Susceptibility Factors

Since Caelyx has activity in Kaposi's sarcoma, many studies have been performed in patients with HIV/AIDS. Thus, assessment of the tolerability of Caelyx and Doxil has been complicated by underlying immune suppression, neutropenia, and co-morbidity commonly present in patients with HIV/AIDS. This has led to a difference in the dose-limiting adverse effects in patients with solid tumors compared to those with Kaposi's sarcoma. Tolerance differs in patients with HIV/AIDS (standard dose 20 mg/m^2 Caelyx every 3 weeks) and those with solid tumors (standard dose 50 mg/m^2 every 4 weeks).

Drug Administration

Drug administration route

Pegylated liposomal doxorubicin has been given to three patients via a catheter located in the hepatic artery (41). No severe adverse effects, such as nausea, vomiting, stomatitis, alopecia, or cardiotoxicity, were observed. There was mild leukopenia (2.8×10^9/l) in one patient; neither anemia nor thrombocytopenia were reported.

Drug overdose

Acute overdose with pegylated liposomal doxorubicin worsens the toxic effects of mucositis, leukopenia, and thrombocytopenia. There have been no reports of overdose of liposomal daunorubicin, but the primary anticipated toxic effect would be myelosuppression.

Drug–Drug Interactions

General

No formal drug interaction studies have been conducted with pegylated liposomal doxorubicin, liposomal daunorubicin, or Myocet. Caution should be exercised when using drugs known to interact with doxorubicin or daunorubicin. Equally, caution should be exercised when giving any other cytotoxic drugs, especially myelotoxic agents, at the same time.

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Anthrax vaccine

See also Vaccines

General Information

Inactivated anthrax vaccine is mainly used for protection against occupational anthrax exposure. A complete vaccine series consists of three 0.5-ml subcutaneous doses at 2-week intervals, followed by three additional doses 6, 12, and 18 months after the first dose. Mild local reactions occur in 30% of vaccinees, including local erythema and tenderness, which occurs within 24 hours and begins to subside within 48 hours. The reactions tend to increase in severity by the fifth injection. Systemic reactions are rare and usually characterized by malaise and lassitude, chills, and fever (1).

Until recently, there has been little research into anthrax vaccines, other than that carried out for anti-bacteriological warfare purposes by the military. Currently, three human vaccines against *Bacillus anthracis* (produced in Russia, the UK, and the USA) are commercially available. The results of two field trials of two vaccines produced in Russia and the USA have been analysed (2). The US killed vaccine was 93% effective in preventing cases of anthrax, and the Russian live attenuated vaccine afforded 75% protection when given by scarification and 84% when a jet-gun was used. The rates of local reactions (erythema, induration, and edema) and systemic reactions (fever, malaise, arthralgia, rash, headache) after the US vaccine were 5.75 and 0.4% respectively, compared with 0.54% local reactions and no systemic reactions after placebo. Adverse effects data on the Russian vaccine were not presented.

In the search for new vaccines against anthrax, manufacturers have aimed for better quality purified protective antigen vaccines with better adjuvants, vaccines made through recombinant gene technology, and mutant vaccines with altered protective antigens.

In a study by the Advisory Group of Medical Countermeasures of the UK Ministry of Defence only mild discomfort at the injection site was reported after the administration of a total of 55 000 doses of anthrax vaccine (3).

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Antianginal drugs

See also Individual agents

General Information

Drugs that are used in the treatment of angina pectoris include agents from the following groups:

- Nitric oxide donors
- Beta-blockers
- Calcium channel blockers
- Potassium channel activators.

New agents, such as L-carnitine and trimetazidine, are also being studied (1).

Safety factors that govern the choice of antianginal drug

Insights into the epidemiology, physiology, cellular biology, molecular biology, and treatment of ischemic heart disease have shown that there are three major modifiable risk factors (hypertension, hypercholesterolemia, smoking) that are the main targets of our preventive strategies. However, evidence that intervention is beneficial has been considerably strengthened.

Hypertension

In high-risk elderly people, treatment of hypertension prevents coronary events (2,3). In the Hypertension Optimal Treatment (HOT) study, which included middle-aged and elderly subjects, good blood pressure control resulted in improved outcome, the optimal blood pressure in non-diabetic subjects being about 138/82 mmHg (4). The target blood pressure was achievable but most patients required more than one drug. A further finding was that low-dose aspirin was beneficial in high-risk subjects. The HOT study found particular benefits of rigorous blood pressure lowering in diabetic subjects, findings that were confirmed by the UK Prospective Diabetes Study (UKPDS) (5), which did not find an advantage in macrovascular complications with angiotensin converting enzyme

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inhibitors compared with beta-blockers (6). The CAPPP study similarly showed no benefit of captopril over other drugs (7). This originally led to the advice that drugs other than diuretics and beta-blockers should be used infrequently (8); however, subsequent recommendations for the choice of initial therapy have been increasingly based on indications for other conditions that often co-exist with hypertension (9). The Syst-Eur study of systolic hypertension gave further prominence to isolated systolic hypertension as a treatable risk factor and provided some reassuring data on the efficacy of calcium antagonists (10). Despite rather depressing news about inadequate blood pressure control in the UK (11) and USA (12), the increased use of antihypertensive drugs appears to have resulted in less left ventricular hypertrophy (13). This may account in part for the considerable fall in mortality from cardiovascular disease observed since the late 1960s.

Hypercholesterolemia

The landmark 4S study of cholesterol-lowering therapy has convincingly shown the effectiveness of treating patients with high serum cholesterol concentrations and ischemic heart disease (14). This has largely been confirmed by subsequent studies (15–17), and the beneficial effects of lowering serum cholesterol have been extended to primary prevention (18,19). Currently, statins are recommended in all those over the age of 55 years and/or in those with pre-existing cardiovascular disease (20). Statins reduce cardiac events if begun early after acute coronary syndromes (21) and may also be indicated in any patient with aortic stenosis, regardless of severity (22).

Smoking

The risks of smoking have been highlighted (23). Evidence has emerged that changing from high-tar to low-tar cigarettes is ineffective in reducing myocardial infarction (24), and the antismoking lobby has become more vocal (25,26). The role of cigarette smoking as a major factor in myocardial infarction has been further emphasized by a study of the survivors of the ISIS studies (27). Smoking increased the risk of a non-fatal myocardial infarction five-, three-, and two-fold in the age ranges 30–49, 50–59, and 70–79 respectively. In addition, the results of this study suggested that enforcement of a European Union upper limit of cigarette tar of 12 mg will result in only a modest reduction in myocardial infarction. Preventing adolescents from smoking seems to be the only strategy, as few adults start smoking after the age of 18 (28). Passive smoking (29) and cigar smoking (30) may be associated with coronary disease, making this initiative even more important. The US ruling in July 1995 that nicotine is an addictive substance (31) was a monumental advance in fighting smoking, since cigarettes are considered to be nicotine delivery systems. If the FDA gains legal jurisdiction in regulating tobacco, active steps will be taken to reduce smoking among children.

The roles of these modifiable risks have thus become more important, and other risks interventions, such as dietary antioxidants (32) and physical activity (33), have also been highlighted. In addition, observational studies have implicated hyperhomocysteinemia as a powerful risk for premature atherosclerotic coronary artery disease (34). Whether or not treating this risk factor is beneficial in reducing cardiac events is currently being tested (35). In the USA, grain is already enriched with folic acid (140 μg/100 g) (36), and this has resulted in reduced homocysteine concentrations in the middle-aged and older population from the Framingham Offspring Study cohort (37).

In recent years, potassium channel activators have been added to the antianginal armamentarium. In addition, the line between antianginal drugs and drugs used to prevent angina has become somewhat blurred. Aspirin has now become a mainstay drug in the treatment and prevention of ischemic heart disease (38), and another antiplatelet drug, clopidogrel, has also been licensed for this indication. Lipid-lowering drugs have also been advocated for both primary and secondary prevention, and the role of beta-blockers in the secondary prevention of myocardial infarction has been extended into the treatment of systolic heart failure. The angiotensin-converting-enzyme (ACE) inhibitor enalapril has gained a licence for the prevention of coronary ischemic events in patients with left ventricular dysfunction, following the Studies of Left Ventricular Dysfunction Trials (39). More recently, evidence on lisinopril and trandolapril has suggested that these drugs prolong the lives of subjects who have a myocardial infarction, either uncomplicated or complicated by impaired ventricular function (40). The benefits of ACE inhibitors in secondary prevention are now beyond doubt, and are especially marked in diabetic patients (41).

Our view of drug therapy has subtly changed with these findings. The physician's role was to use drugs to relieve the symptoms of angina. Nowadays, drugs must not only relieve symptoms but also, when possible, improve life expectancy (20). We are also more concerned with the quality of symptomatic relief. The notion of "well-being" has become important and has been assessed in "quality-of-life" comparisons of different agents (42). Subtle effects that individually might not be detected have been highlighted in such studies and can modify our view of a drug's adverse effects profile. As the subtle adverse effects of drugs become more important, serious drug toxicity becomes even more unacceptable.

Other susceptibility factors

The roles of other modifiable susceptibility factors have become more important, and other interventions, such as dietary antioxidants (32) and physical activity (33), have also been highlighted in the past. However, a meta-analysis of the effect of vitamin E supplements has suggested that doses over 400 IU/day can increase the risk of death from any cause (43).

Pharmacoeconomics

A further consideration, the economic evaluation of drugs, has become an issue, although not without criticism (44). In its most rigorous form the cost of drug therapy is measured against the aggregate number of years of improved health that such therapy might be expected to bring (45). These so-called "quality-adjusted life years" (QUALYs) are reduced if a drug has an adverse effect, so that the net benefit of a drug that prolongs life but makes

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that life miserable may well be a negative number of QUALYs. Such studies have put a price-tag on mild adverse events as well as on beneficial effects. In time we may pay increasing attention to the price of adverse effects when choosing a drug.

The drug treatment of angina is time-consuming, empirical, and often relatively unrewarding. Drug treatment simply palliates the underlying disease, and no symptomatic treatment improves survival or prevents myocardial infarction. This is in contrast to surgical intervention, which, in good hands, prolongs survival (46) and improves its quality. The three main comparisons of coronary surgery with medical therapy (47–49) are now out of date, since both medical therapy and surgical techniques have improved considerably since they were completed. However, long-term medical therapy is now more often being reserved for patients who for one reason or another are unsuitable for surgery or percutaneous coronary angioplasty, which, at least for single-vessel disease, is superior to antianginal drug treatment (50) but may be equivalent to lipid-lowering therapy (51). Preventive therapy must now be the dominant strategy.

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Anti-CD4 monoclonal antibodies

See also Monoclonal antibodies

General Information

Anti-CD4 monoclonal antibodies are used to treat various autoimmune diseases, such as rheumatoid arthritis, asthma, and psoriasis (1–3). Keliximab (rINN) (IDEC CE9.1) is a human-cynomolgus monkey chimeric (primatized) antibody with specificity for human and chimpanzee CD4. Clenoliximab (rINN) is an immunoglobulin G4 derivative of keliximab. These antibodies induce a more than 80% down-regulation of CD4 molecules on the surface of T lymphocytes.

Observational studies

In an open, dose-escalating study, 24 patients were allocated to five consecutive daily doses of a humanized IgG1 anti-CD4 monoclonal antibody (4162W94) (4). There was at least one predefined infusion-related adverse effect (for example fever, chills/rigors, headache, nausea, vomiting, diarrhea, dyspnea, or hypotension) in 17 patients. Most of these events were mild or moderate in intensity, occurred on the first day of dosing, and resolved within 8 hours. In some patients the adverse events were associated with the

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appearance of TNF alfa in the plasma during the 3 hours after the start of antibody infusion, suggesting that they resulted from cytokine release. There was systolic hypotension, defined as a systolic pressure below 90 mmHg and a fall of at least 20 mmHg, in one patient who was given 10 mg. There were non-specific skin rashes in one patient in each of the groups who were given 10, 30, and 100 mg and in three of those given 300 mg. There were three serious adverse events: fatal rupture of an aortic aneurysm, thought to be unrelated to the drug, an episode of severe reversible airways obstruction in a patient with asthma, and an episode of unexplained collapse, presumed to be vasovagal, followed by full recovery several hours after the end of the first infusion. No opportunistic or other infections were reported.

Placebo-controlled studies

In a placebo-controlled study in 48 patients with active rheumatoid arthritis, CD4 blockade produced clinical benefit (5). Adverse events were reported in 97% of the patients, compared with 73% of those given placebo. In both groups most of the events were mild to moderate. Serious adverse events were reported in five patients who received anti-CD4; syncope/vasovagal attacks ($n = 3$), back pain ($n = 1$), abdominal pain/rectal bleeding ($n = 1$). Skin rashes occurred in 62% of the patients who received the antibody. In five cases a skin biopsy was performed, and showed a cellular infiltration centered on the blood vessels, suggesting a drug-induced vasculitis.

In a randomized, dose-ranging, placebo-controlled study of keliximab in chronic severe asthma, there were no serious adverse effects related to treatment (1).

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Anticholinergic drugs

See also Individual agents

General Information

There are many anticholinergic drugs, some structurally related to atropine, others quaternary ammonium compounds or tertiary amines. Although many of these products are claimed to have superior efficacy, specificity, or tolerance, few have ever been critically compared with others. The so-called freedom from adverse effects claimed for many of these compounds can often be traced to uncritical clinical work, the use of ineffective doses, or mere lack of activity of the compound.

General adverse effects

An indication of what may be expected in the way of adverse reactions can be obtained by fitting a drug into its structural class (see Table 1), since the pattern of effects of drugs in each class is generally very similar. The drugs closely related to atropine have the full range

Table 1 General classification of anticholinergic drugs (rINNs except where stated)

Atropine and closely related agents
Atropine
Hyoscine (BAN)
Ipratropium
Oxitropium
Tiotropium
Synthetic quaternary ammonium compounds
Clidinium
Emepronium bromide
Isopropamide
Mepenzolate
Methanthelinium (pINN)
Oxyphenonium
Poldine (pINN)
Propantheline
Tertiary amines used in visceral disorders
Adiphenine
Dicycloverine
Oxyphencyclimine
Piperidolate
Drugs with primarily anticholinergic effects used mainly in Parkinson's disease
Tertiary amines related to diphenhydramine
Chlorphenoxamine
Orphenadrine
Trihexyphenidyl-related compounds
Biperiden
Procyclidine
Trihexyphenidyl (benzhexol)
Compounds related to both atropine and diphenhydramine
Benzatropine
Etybenzatropine
Compounds used topically for pupillary mydriasis
Cyclopentolate
Eucatropine
Homatropine
Tropicamide

of antinicotinic and antimuscarinic activity of atropine itself. Of the synthetic compounds used in visceral disorders, the quaternary compounds are fully ionized in the pH range found in body fluids and are therefore less lipid-soluble than the corresponding tertiary amines. This means that they penetrate physiological barriers less readily; less drug is absorbed in the intestine, less enters the cerebrospinal fluid and aqueous humor, and less enters cells. Consequently, these drugs tend to be relatively less active by mouth and to have fewer effects on the brain and the eye than the tertiary amines. Of the latter, some have little antimuscarinic activity and indeed probably very little useful activity at all; they may have some specific relaxant effect on smooth muscle, but it seems to be of little clinical significance.

Of the drugs in this class used largely in parkinsonism, the tertiary amines related to diphenhydramine have some antihistaminic activity, as one would expect; some of these drugs are also related to atropine. The derivatives of trihexyphenidyl (benzhexol) are also pharmacologically closely similar: for example, they have some excitatory effects if given in sufficient doses.

The unwanted peripheral effects of all atropine-like drugs include flushing of the skin, dryness of the mucous membranes with fever, tachycardia, reduced salivary secretion and dryness of the mouth, drying up of the gastrointestinal secretions and decreased gastric acidity, and reduced muscle tone in the gut and constipation. Bladder tone and frequency of micturition are reduced and acute urinary retention is a risk, especially in older men with prostatic hyperplasia. Nasal, bronchial, and lacrimal secretions are reduced.

Herbal sources of anticholinergic drugs

Tropane alkaloids, such as hyoscyamine and/or scopolamine, occur in the solanaceous plants *Atropa belladonna*, *Datura stramonium*, *Hyoscyamus niger*, and *Mandragora officinarum*. These alkaloids are powerful anticholinergic agents and can elicit peripheral symptoms (for example blurred vision, dry mouth) as well as central effects (for example drowsiness, delirium). They can potentiate the effects of anticholinergic medicaments.

Organs and Systems

Cardiovascular

The potential dysrhythmogenic effect of anticholinergic drugs has been examined retrospectively in nearly 4000 patients taking flavoxate, oxybutynin, and hyoscyamine between 1991 and 1995, compared with over 10 000 patients who had no exposure to these drugs (1). All the patients were over 65 years old and they were reasonably matched for co-morbidities, although not surprisingly more women than men were taking the antispasmodic drugs (75% women in the treated group versus 67% in the control population). The encouraging conclusion was that there was no evidence that these drugs promote ventricular dysrhythmias or sudden death. However, the authors noted that more detailed analysis of these data is needed and that it may also be advisable to consider data from newer drugs.

Nervous system

Orofacial dyskinesia, though familiar with dopaminergic drugs, can apparently also occur with some anticholinergic drugs; for example, it has been described with trihexyphenidyl in a patient who did not have this reaction with levodopa (SEDA-18, 160).

Sensory systems

Anticholinergic drugs cause passive pupillary dilatation by paralysing the iridal sphincter, suppress accommodation by paralysing the ciliary muscle, and increase the vascular permeability of the iris and ciliary bodies. They are used topically for diagnostic and refractive purposes, and in combination with other drugs as part of the treatment of several serious ocular conditions, including inflammatory states. Topically applied drugs can cause local adverse effects in the eye (SEDA-23, 504) and systemic effects if sufficient drug is absorbed.

All anticholinergic drugs can cause acute closed-angle glaucoma in patients with an anatomical predisposition. They also cause photophobia and disturbances of accommodation leading to difficulties in reading and driving.

Psychological, psychiatric

Anticholinergic drugs can cause vivid and sometimes exotic hallucinations and this has led to their misuse. Plants containing atropine and related substances were used in witches' brews in the Middle Ages to conjure up the devil, but even synthetic tertiary amines given in eye-drops and depot plasters containing atropine (SEDA-13, 114) have caused hallucinations. Postoperative confusion in elderly patients has been clearly correlated with drugs that have anticholinergic properties (SEDA-13, 114), and the use of anticholinergic drugs for the treatment of Parkinson's disease has long been associated with neuropsychiatric adverse effects. Cyclopentolate is a short-acting cycloplegic with a rapid onset (and considerable intensity) of action, which particularly in children has been reported to cause hallucinations and psychotic episodes (2). It has been suggested that a partial structural affinity of the side-chain to some hallucinogens aggravates the problems associated with cyclopentolate.

Anticholinergic drugs can impair short-term memory. The effects in non-demented patients are reversible, receding within a few weeks of withdrawing treatment (3). Comparisons of dopaminergic drugs with anticholinergic drugs in healthy volunteers have shown that anticholinergic drugs caused significant impairment of memory function, more confusion, and dysphoria (SEDA-13, 115).

Immunologic

Allergic reactions to local application in the eye can occur, usually in the form of contact dermatitis and conjunctival redness and are more common with hyoscine

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than with atropine, although contact dermatitis is less likely (4).

Long-Term Effects

Drug dependence

Patients taking long-term anticholinergic drugs can develop dependence (SEDA-15, 136).

Susceptibility Factors

Anticholinergic drugs clearly may cause problems in patients with closed-angle glaucoma (or a narrow angle between the iris and cornea), paralytic ileus, pyloric stenosis, or urinary retention. Because of their effects on temperature control they may be undesirable in patients with pyrexia (especially children) and during very hot weather.

Drug Administration

Drug overdose

The clinical effects of overdosage with atropine-like drugs, as recorded in a series of 119 patients, are presented in Table 2 (5). Infrequent manifestations (less than 10% of cases) included seizures, convulsions, vomiting, rash, urinary retention, abdominal distress, paralytic ileus, and constipation. Death, when it occurs, is due primarily to the effects on the central nervous system; a stage of excitement is followed by drowsiness, stupor, and coma, with generalized central depression.

Table 2 Clinical manifestations of anticholinergic drug intoxication in 71 adults and 48 children

Adverse effect	Adults (%)	Children (%)
Pupils widely dilated and poorly reactive	79	88
Flushed face, dry mucous membranes	55	90
Tachycardia (>100)	44	65
Incoherence, confusion, or disorientation	66	56
Restlessness, hyperactivity, or agitation	39	58
Auditory or visual hallucinations	52	27
Ataxia or motor incoordination	35	48
Carphology	37	44
Hyper-reflexia, twitching, or increased muscle tone	25	35
Apprehension, fear, or paranoia	23	14
Somnolence or coma	34	16
"Toxic delirium"	14	40
Giddiness; labile or inappropriate affect	18	13
Dysarthria or slurred speech	14	14
Fever (>100°F)	18	25
Thirst or dry mouth	18	14
Blindness or blurred vision	20	13
Retrograde amnesia	18	13

Drug–Drug Interactions

Other anticholinergic drugs

Some antidepressants, neuroleptic drugs, antihistamines, antispasmodics, and antidysrhythmic drugs have anticholinergic activity, as do some herbal remedies (see the section on Herbal sources of anticholinergic drugs in this monograph). The combined use of such drugs can lead to inadvertent anticholinergic overdosage.

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Anticoagulant proteins

General Information

There are several endogenous anticoagulants proteins, antithrombin III, protein C, and protein S. Severe sepsis and septic shock are associated with activation of the coagulation system and depletion of these endogenous anticoagulants. Anticoagulant proteins prevent microthrombus formation, thereby reducing the risk of multiorgan failure.

Antithrombin III

Antithrombin III is a plasma alpha$_2$-glycoprotein that accounts for most of the antithrombin activity in plasma and also inhibits other proteolytic enzymes. Hereditary or acquired antithrombin III deficiency results in thromboembolism. The effectiveness of treatment with antithrombin III, prepared as a concentrate from human plasma, is still a matter of dispute (1,2). Apart from vasodilatation, leading to a reduction in blood pressure, remarkably few adverse effects have been noted (2,3). The fall in blood pressure seems to be related to the rate of the infusion.

High doses of antithrombin III, given to patients with severe sepsis, increased the risk of hemorrhage, particularly when it was given concomitantly with heparin, while there was no treatment benefit (4).

Protein C

The protein C pathway serves as a natural defence mechanism against thrombosis. Patients with severe sepsis have a very low concentration of activated protein C

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compared with healthy individuals. Protein C is available as either a concentrate prepared from human plasma or as recombinant human activated protein C (drotrecogin alfa). The latter increased the risk of bleeding in patients with severe sepsis (5).

Organs and Systems

Cardiovascular

In a phase III trial of drotrecogin alfa, hypertension (2.6 versus 0.6% with placebo) was one of the most frequent adverse effects (6).

Psychological, psychiatric

In a phase III trial, hallucinations occurred in 1.1% of patients treated with drotrecogin alfa versus 0.1% in the placebo group (6).

Hematologic

The predominant adverse effect of activated protein C is bleeding. In a phase III trial, in which 1690 patients with severe sepsis were treated with drotrecogin alfa or placebo, serious bleeding episodes occurred in 3.5% of patients treated with drotrecogin alfa, compared with 2.0% of those treated with placebo (7–9). It has been suggested that the risk of bleeding can be minimized by withholding drotrecogin alfa immediately after major surgery; when surgery must be performed during the treatment period, drotrecogin alfa should be temporarily withdrawn (10,11).

Drotrecogin alfa should be used with care in patients receiving heparin, thrombolytic drugs, oral anticoagulants, glycoprotein IIb-IIIa inhibitors, and aspirin or other antiplatelet drugs (6).

Immunologic

In two of 370 patients treated with drotrecogin alfa during a phase III trial, antibodies to activated protein C were found, but these were not inhibitory; no cases of neutralizing antibodies have been found (7).

Because activated drotrecogin alfa reduces inflammation, it is theoretically possible that there is an increased risk of infection. However, a phase III trial did not show an increased rate of infection in the drotrecogin alfa-treated patients compared with placebo (6).

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Antidepressants, second-generation

See also Individual agents

General Information

The newer antidepressants that have followed the monoamine oxidase inhibitors and tricyclic antidepressants are listed in Table 1. Most of them are covered in separate monographs. They have a wide variety of chemical structures and pharmacological profiles, and are categorized as "second generation" antidepressants purely for convenience. Although these drugs are widely considered to be as effective as each other and as any of the older compounds, they have different adverse effects profiles. No new antidepressant has proven to be sufficiently free of adverse effects to establish itself as a routine first line compound; some share similar adverse effects profiles with the tricyclic compounds, while others have novel or unexpected adverse effects. Complete categorization of each compound will rest on wide-scale general use beyond the artificial confines of clinical trials. This also includes the experience that accumulates from cases of overdosage, which cannot be anticipated before a new drug is released. The selective serotonin reuptake inhibitors are dealt with as a separate group, since they have many class-specific adverse effects.

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Table 1 Second-generation antidepressants (rINNs except where stated)

Compound	Structure	Comments
Amfebutamone (bupropion)	Aminoketone	Modulates dopaminergic function Increased risk of seizures in high doses
Maprotiline	Tetracyclic	Strong inhibitory effect on noradrenaline uptake Skin rashes (3%) Increased incidence of seizures in overdose Similar adverse effects profile to tricyclic compounds
Mianserin (pINN)	Tetracyclic	Sedative profile Increased incidence of agranulocytosis Possibly safer in overdose Fewer cardiac effects
Milnacipran	Tetracyclic	Inhibitor of serotonin and noradrenaline reuptake
Mirtazapine	Piperazinoazepine	Noradrenergic and specific serotonergic antidepressant (NaSSA); similar to mianserin
Nefazodone	Phenylpiperazine	Weak serotonin reuptake inhibitor Blocks 5-HT_2 receptors Chemically related to trazodone
Reboxetine	Morpholine	Selective noradrenaline reuptake inhibitor (NRI or NARI)
Trazodone	Triazolopyridine	Weak effect on serotonin uptake Blocks 5-HT_2 receptors Fewer peripheral anticholinergic properties Sedative profile
Tryptophan	Amino acid	Precursor of serotonin Eosinophilia-myalgia syndrome
Venlafaxine	Bicyclic; cyclohexanol	Serotonin and noradrenaline uptake inhibitor Nausea, sexual dysfunction, and cardiovascular adverse effects
Viloxazine	Bicyclic	Fewer anticholinergic or sedative effects and weight gain Causes nausea, vomiting, and weight loss Can precipitate migraine

Antidysrhythmic drugs

See also Individual agents

General Information

Classification

Drugs used in dysrhythmias can be classified in different ways, the usual classification being according to their effects on the cardiac action potential (1), as shown in Table 1.

Antidysrhythmic drugs with Class I activity reduce the rate of the fast inward sodium current during Phase I of the action potential and increase the duration of the effective refractory period expressed as a proportion of the total action potential duration. The action potential duration is itself affected in different ways by subgroups of the Class I drugs:

- class Ia drugs, of which quinidine is the prototype, prolong the action potential;
- class Ib drugs, of which lidocaine is the prototype, shorten the action potential;
- class Ic drugs, of which flecainide is the prototype, do not alter action potential duration.

The beta-adrenoceptor antagonists (class II) and bretylium inhibit the effect of catecholamines on the action potential.

Antidysrhythmic drugs with class III activity prolong the total action potential duration. These drugs act by effects on potassium channels, altering the rate of repolarization.

Antidysrhythmic drugs with class IV activity prolong total action potential duration by prolonging the plateau phase (phase III) of the action potential via calcium channel blockade.

Other classifications of antidysrhythmic drugs have been proposed, but the most useful clinical classification

Table 1 Electrophysiological classification of antidysrhythmic drugs

Class I	Ia Quinidine Procainamide Disopyramide	Ib Lidocaine Aprindine Mexiletine Phenytoin Tocainide	Ic Flecainide Encainide Lorcainide Propafenone (also has class II activity)
Class II	Beta-adrenoceptor antagonists Bretylium		
Class III	Amiodarone Sotalol (d-sotalol; l-sotalol has class II activity)		
Class IV	Verapamil		

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relates to the sites of action of the antidysrhythmic drugs on the various cardiac tissues, as shown in Table 2.

General adverse effects

There have been many reviews of the pharmacology, clinical pharmacology, pharmacokinetics, and adverse effects and interactions of antidysrhythmic drugs (2–13).

The patterns of adverse effects of the antidysrhythmic drugs depend on three features:

1. All antidysrhythmic drugs have effects on the cardiac conducting tissues and can all therefore cause cardiac dysrhythmias.
2. All antidysrhythmic drugs have a negative inotropic effect on the heart, and can result in heart failure. However, the degree of negative inotropy varies from drug to drug; for example, it is less marked with drugs such as lidocaine and phenytoin and very marked with the beta-adrenoceptor antagonists, verapamil, and class 1a drugs.
3. Each antidysrhythmic drug has its own non-cardiac effects, which can result in adverse effects. These are summarized in Table 3.

Table 2 Classification of antidysrhythmic drugs by their actions in different parts of the heart

Sinus node	Anomalous pathways	Atria	Ventricles	Atrioventricular node
Class Ic	Class Ia	Class Ia	Class Ia	Class Ic
Class II	Class Ic	Class Ic	Class Ib	Class II
Class IV	Class III	Class III	Class Ic	Class III
				Class IV

Table 3 Non-cardiac adverse effects of some antidysrhythmic drugs

Drug	Common non-cardiac adverse effects
Acecainide	Gastrointestinal and nervous system effects
Adenosine	Flushing, dyspnea
Ajmaline derivatives	Liver damage; agranulocytosis; nervous system effects
Amiodarone	Corneal microdeposits; altered thyroid function; lipofuscin deposition in skin, lungs, liver, nerves, muscles
Aprindine	Agranulocytosis; nervous system effects; liver damage
Cibenzoline	Gastrointestinal and nervous system effects; hypoglycemia
Disopyramide	Anticholinergic effects
Dofetilide	Nervous system effects
Encainide	Nervous system effects
Flecainide	Nervous system effects
Lidocaine	Nervous system effects
Lorcainide	Nervous system effects
Mexiletine	Nervous system effects
Moracizine	Nervous system effects
Procainamide	Lupus-like syndrome; neutropenia
Propafenone	Nervous system effects
Quinidine	Anticholinergic effects; hypersusceptibility reactions
Tocainide	Nervous system effects

Clinical studies

The efficacy of a large range of antidysrhythmic drugs in converting atrial fibrillation to sinus rhythm acutely and in maintaining it during long-term treatment has been the subject of a systematic review (14). Adverse effects were too sporadically reported to be suitable for proper review. The efficacy results are summarized in Table 4.

There is some doubt about whether conversion to sinus rhythm produces a better long-term outcome than rate control. Five randomized controlled comparisons of rhythm control versus rate control, mostly in patients with persistent atrial fibrillation ($n = 5175$ in all), have all suggested that there are no major differences in beneficial outcomes between the two strategies (15,16), although there were fewer adverse drug reactions in patients randomized to rate control in three of the studies and in all the studies rate control was associated with fewer hospital admissions. Furthermore, in an analysis of cost-effectiveness, rate control plus warfarin was much cheaper than rhythm control in preventing thromboembolism, largely because of the use of expensive modern antidysrhythmic drugs for the latter (17). Although these results suggest that rate control might be preferable to rhythm control, they do not give any information about patients in whom sinus rhythm is established permanently after pharmacological or physical conversion, since many of the patients in whom rhythm control is used as a strategy will actually have paroxysmal atrial fibrillation.

Organs and Systems

Cardiovascular

Cardiac dysrhythmias

Antidysrhythmic drugs can themselves cause cardiac dysrhythmias, their major adverse effect. The risk of antidysrhythmic-induced cardiac dysrhythmias (prodysrhythmic effects) has been estimated at about 11–13% in non-invasive studies (18,19) and at up to 20% in invasive electrophysiological studies. However, the risk varies from drug to drug and is particularly low with class III drugs. In one study the quoted risks of dysrhythmias were: flecainide 30%, quinidine 18%, propafenone 7%, sotalol 6%, and amiodarone 0% (20). However, amiodarone does cause dysrhythmias, especially when the QT_c interval is over 600 ms.

The prodysrhythmic effects of antidysrhythmic drugs have been extensively reviewed (21–36).

Dysrhythmias secondary to antidysrhythmic drugs are arbitrarily defined as either early (within 30 days of starting treatment) or late (22,23). A lack of early dysrhythmias in response to antidysrhythmic drugs does not predict the risk of late dysrhythmias (24).

Ventricular dysrhythmias due to drugs may be either monomorphic or polymorphic. The class Ia drugs are particularly likely to cause polymorphic dysrhythmias, as is amiodarone (although to a lesser extent). In contrast, the class Ic drugs are more likely to cause monomorphic dysrhythmias (25).

Class Ic antidysrhythmic drugs have been reported to cause the characteristic electrocardiographic changes of Brugada syndrome, which consists of right bundle branch block, persistent ST segment elevation, and sudden

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Table 4 The results of a systematic review of the efficacy of antidysrhythmic drugs in converting atrial fibrillation to sinus rhythm and maintaining it

Drug	Number of subjects	Efficacy in converting AF to sinus rhythm (odds ratio versus other drugs[1])	Efficacy in maintaining sinus rhythm (odds ratio versus other drugs[1])	Ventricular dysrhythmias[2] (%)	Other dysrhythmias[3] (%)	Drug withdrawal or dosage reduction (%)
Amiodarone	108	5.7		0–15	0–9	
Disopyramide	30	7.0	3.4	0	0	0–55
Dofetilide/ibutilide	530	29.0		3–9		
Flecainide	169	25.0	3.1	0–2	0–12	0–20
Propafenone	1168	4.6	3.7	0–3	0–17	0–55
Quinidine	200	2.9	4.1	0–12	0–28	0–58
Sotalol	34	0.4	7.1	0–1	2–44	4–44

[1] Digoxin, diltiazem, or verapamil
[2] Ventricular fibrillation, polymorphic ventricular tachycardia, torsade de pointes
[3] Symptomatic bradycardia, junctional rhythm, non-sustained and/or monomorphic ventricular tachycardia

cardiac death, in two patients (37). Class Ia drugs did not cause the same effect.

The prodysrhythmic effects of antidysrhythmic drugs have been reviewed in discussions of the pharmacological conversion of atrial fibrillation (38) and the relative benefits of rate control in atrial fibrillation or maintaining sinus rhythm after cardioversion (39).

Mechanisms

There are four major mechanisms whereby antidysrhythmic drugs cause dysrhythmias (21):

1. Worsening of a pre-existing dysrhythmia. For example, ventricular extra beats can be converted to ventricular tachycardia or the ventricular rate in atrial flutter can be accelerated when slowing of the atrial rate results in the conduction of an increased number of atrial impulses through the AV node.
2. The induction of heart block or suppression of an escape mechanism. For example, slowing of conduction through the AV node can impair a mechanism that allows the conducting system to escape a re-entry mechanism.
3. The uncovering of a hidden mechanism of dysrhythmia. For example, antidysrhythmic drugs can cause early or delayed afterdepolarizations, which can result in dysrhythmias.
4. The induction of a new mechanism of dysrhythmia. For example, a patient in whom myocardial ischemia has predisposed to dysrhythmias may be more at risk when an antidysrhythmic drug alters conduction.

Combinations of these different mechanisms are also possible.

The prodysrhythmic effects of antidysrhythmic drugs have been reviewed, with regard to mechanisms at the cellular level (40) and molecular level (41). As far as the cellular mechanisms are concerned, the antidysrhythmic drugs have been divided into three classes (which do not overlap with the classes specified in the electrophysiological classification).

1. Group 1 drugs have fast-onset kinetics and the block saturates at rapid rates (about 300 beats/minute).
2. Group 2 drugs have slow-onset kinetics and the block saturates at rapid rates.
3. Group 3 drugs have slow-onset kinetics and there is saturation of frequency-dependent block at slow heart rates (about 100 beats/minute).

The fast-onset kinetics of the Group 1 drugs makes them the least likely to cause dysrhythmias. Group 2 drugs, which include encainide, flecainide, procainamide, and quinidine, are the most likely to cause dysrhythmias, because of their slow-onset kinetics. Although this also applies to the Group 3 drugs, which include propafenone and disopyramide, block is less likely to occur during faster heart rates and serious dysrhythmias are therefore less likely during exercise.

The most common mechanism of dysrhythmias at the molecular level is by inhibition of the potassium channels known as IK_r, which are encoded by the human ether-a-go-go-related gene (HERG). The antidysrhythmic drugs that affect these channels include almokalant, amiodarone, azimilide, bretylium, dofetilide, ibutilide, sematilide, D-sotalol, and tedisamil (all drugs with Class III actions) and bepridil, disopyramide, prenylamine, procainamide, propafenone, quinidine, and terodiline (all drugs with Class I actions). Other drugs that affect these channels but are not used to treat cardiac dysrhythmias include astemizole and terfenadine (antihistamines), cisapride, erythromycin, haloperidol, sertindole, and thioridazine.

Susceptibility factors

There are no good predictors of the occurrence of dysrhythmias, but there are several susceptibility factors (26,27), including a history of sustained tachydysrhythmias, poor left ventricular function, and myocardial ischemia. Potassium depletion and prolongation of the QT interval are particularly important, and these particularly predispose to polymorphous ventricular dysrhythmias (for example torsade de pointes). Altered metabolism of antidysrhythmic drugs (for example liver disease, polymorphic acetylation or hydroxylation, and drug interactions) can also contribute.

The prodysrhythmic effects of antidysrhythmic drugs have been reviewed in the context of whether patients who are to be given class I or class III antidysrhythmic drugs should first be admitted to hospital for observation in the hope of identifying those who are most likely to develop dysrhythmias (20). The risk of sudden death in patients taking amiodarone was significantly increased in those who had had a prior bout of torsade de pointes. The risk of sotalol-induced torsade de pointes was higher in patients with pre-existing heart failure. Women are at a greater risk of prodysrhythmic drug effects (SEDA-18, 199). The highest risk was in women with heart failure

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who took more than 320 mg/day (22%); the corresponding figure in men was 8%. The authors delineated certain subgroups that they considered to be at specific risk of dysrhythmias, listing drugs that should be avoided in those subjects. They recommended avoiding drugs of classes Ia and III in women without coronary artery disease, drugs of class Ic in men with coronary artery disease, and drugs of classes Ia, Ic, and III in men with congestive heart failure and women with coronary artery disease.

Factors that predict atrial flutter with 1:1 conduction as a prodysrhythmic effect of class I antidysrhythmic drugs (cibenzoline, disopyramide, flecainide, propafenone, and quinidine) have been studied in 24 patients (aged 46–78 years) with 1:1 atrial flutter and in 100 controls (42). Underlying heart disease was present in nine patients. There was a short PR interval (PR < 0.13 ms) with normal P wave duration in leads V5 and V6 in nine of the 26 patients and only seven of the 100 controls. Signal-averaged electrocardiography showed pseudofusion between the P wave and QRS complex in 19 of the 26 patients and only 11 of the 100 controls. There was rapid atrioventricular nodal conduction (a short AH interval or second-degree atrioventricular block during atrial pacing at over 200 minute) in 19 of the 23 patients. Pseudofusion of the P wave and QRS complex had a sensitivity of 100% and a specificity of 89% for the prediction of an atrial prodysrhythmic effect of class I antidysrhythmic drugs.

Reducing the risk

The methods for minimizing the risks of prodysrhythmic effects of antidysrhythmic drugs (43) are as follows:

- Care in choosing those who are likely to benefit from antidysrhythmic drug therapy.
- Identification and correction, if possible, of impaired pump function and ischemic damage.
- Correction of electrolyte abnormalities.
- Exercise testing before and during the early stages of drug therapy: widening of the QRS complex during exercise predicts a high risk of ventricular tachycardia as does prolongation of the QT interval.
- Instruction of patients about the signs and symptoms that can occur with dysrhythmias.
- Monitoring renal and hepatic function in order to predict reduced drug elimination.
- Avoiding drug interactions or changing the dosage of the antidysrhythmic drug in anticipation of a change in its disposition secondary to an interaction.

Measurement of the concentrations of antidysrhythmic drugs and their metabolites in the plasma can be useful in recognizing the need for changing dosage requirements when cardiac, hepatic, or renal dysfunction occurs, in maintaining serum drug or metabolite concentrations within optimal ranges, and for predicting dosage changes required when interacting drugs are added (28). However, in most hospitals plasma drug concentration measurement is not routinely available for these drugs.

Another strategy for reducing the risk of prodysrhythmias is to use combinations of different classes of antidysrhythmic drugs in lower dosages than those used in monotherapy.

Torsade de pointes can be prevented by withholding antidysrhythmic drug therapy from patients who have pre-existing prolongation of the QT interval, and by correction of low serum potassium and magnesium concentrations before therapy. During therapy patients at risk should have frequent monitoring of the electrocardiogram and serum electrolytes.

The prodysrhythmic risks of using antidysrhythmic drugs have been mentioned in the context of a set of guidelines on the management of patients with atrial fibrillation (44,45). The recommended drugs for maintaining sinus rhythm after cardioversion vary depending on the presence of different risk factors for dysrhythmias:

- heart failure: amiodarone and dofetilide;
- coronary artery disease: sotalol and amiodarone;
- hypertensive heart disease: propafenone and flecainide.

Management

The management of drug-induced cardiac dysrhythmias includes withdrawal of the drug and the administration of potassium if necessary to maintain the serum potassium concentration at over 4.5 mmol/l and magnesium sulfate (SEDA-23, 196). Magnesium sulfate is given intravenously on a dose of 2 g over 2–3 minutes, followed by continuous intravenous infusion at a rate of 2–4 mg/minute; if the dysrhythmia recurs, another bolus of 2 g should be given and the infusion rate increased to 6–8 mg/minute; rarely, a third bolus of 2 g may be required (46). If magnesium is ineffective, cardiac pacing should be tried.

There is some anecdotal evidence that atrioventricular nodal blockade with verapamil or a beta-blocker can also be effective. However, in two cases the addition of a beta-blocker (either atenolol or metoprolol) to treatment with class I antidysrhythmic drugs (cibenzoline in one case and flecainide in the other) did not prevent the occurrence of atrial flutter with a 1:1 response (47). However, the author suggested that in these cases, although the beta-blockers had not suppressed the dysrhythmia, they had at least improved the patient's tolerance of it. In both cases the uses of class I antidysrhythmic drugs was contraindicated by virtue of structural damage, in the first case due to mitral valvular disease and in the second due to an ischemic cardiomyopathy.

Adverse hemodynamic effects of antidysrhythmic drugs

Many antidysrhythmic drugs have negative inotropic effects (48–50). This means that such drugs should be avoided in patients with a history of heart failure, a low left ventricular ejection fraction, or a cardiomyopathy. The general risk of induction or a worsening of heart failure is up to about 5%, but those who have risk factors have a risk of up to 10%. The negative inotropic effects are most marked with drugs of classes Ia, Ic, II, and IV. For drugs with class I activity there is a strong relation between their negative inotropic effect and the extent to which they block the inward sodium current (50). Thus, class Ib drugs that are associated with a short recovery time of sodium channels have a smaller negative inotropic effect than class Ia drugs, which in turn have less of an effect than class Ic drugs. However, the overall hemodynamic effects of antidysrhythmic drugs depend not only on their negative inotropic effects on the heart, but also on their effects on the peripheral circulation (51). Thus, although all drugs with class I activity have similar negative inotropic effects on the heart, disopyramide has large hemodynamic effects (because it increases

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Table 5 Some important drug–drug interactions with antidysrhythmic drugs

Object drug(s)	Precipitant drug(s)	Result of interaction
Adenosine	Dipyridamole	Increased effect
Adenosine	Theophylline	Reduced effect
Anticholinergic drugs	Disopyramide, quinidine	Potentiation
Antihypertensive drugs	Bretylium	Severe hypotension
Beta-adrenoceptor antagonists	Propafenone	Potentiation
Class I drugs	Beta-adrenoceptor antagonists	Negative inotropy
Class I drugs	Class I drugs	Potentiation
Class I drugs	Drugs that cause potassium depletion	Prodysrhythmic effects
Digoxin	Amiodarone, quinidine, verapamil	Digoxin toxicity
Disopyramide	Enzyme-inducing drugs	Increased metabolism
Neuromuscular blockers	Quinidine	Potentiation
Procainamide	Cimetidine, trimethoprim	Reduced metabolism
Quinidine	Enzyme-inducing drugs	Increased metabolism
Theophylline	Mexiletine	Cardiac dysrhythmias
Verapamil	Beta-adrenoceptor antagonists	Negative inotropy/bradycardia/asystole
Warfarin	Amiodarone, quinidine	Warfarin toxicity

peripheral resistance) and its hemodynamic effect is therefore greater than that of mexiletine, for example. Similarly the adverse hemodynamic effects of encainide and tocainide are greater than those of procainamide (52).

Death

Sudden death due to antidysrhythmic drugs has been reported in several trials in patients who have had ventricular dysrhythmias after myocardial infarction. The drugs that have been incriminated include disopyramide, encainide, flecainide, mexiletine, moracizine, procainamide, and quinidine (53–59). The class III drug d-sotalol has also been associated with an increased risk of mortality in such patients (60). This increase in mortality is thought to be due to an increased risk of cardiac dysrhythmias, perhaps as a consequence of rate-dependent conduction block and preferential slowing of conduction in the ischemic areas. Cardiac dysrhythmias of this sort may also occur through slowing of the rate of conduction around non-conducting ischemic or infracted areas in the heart.

Susceptibility Factors

Age

The safety of antidysrhythmic drugs in children has not been thoroughly studied. However, the risk of prolongation of the QT interval seems to be considerably less than that in adults (61), although it has been reported with quinidine, disopyramide, amiodarone, sotalol, and diphemanil.

Drug Administration

Drug overdose

The use of techniques of circulatory support (extracorporeal oxygenation and intra-aortic balloon pump) in seven cases of overdose with antidysrhythmic drugs (disopyramide, flecainide, prajmaline, and quinidine) has been reviewed (62).

Drug–Drug Interactions

General

Some important drug–drug interactions with antidysrhythmic drugs are summarized in Table 5.

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Antiepileptic drugs

See also Individual agents

General Information

Over 15 drugs are licensed worldwide for the treatment of epilepsy and are the subject of separate monographs. Some of them can be grouped into classes (carbamazepine and its analogue oxcarbazepine, barbiturates, hydantoins, benzodiazepines, and succinimides), while others (for example valproate, felbamate, gabapentin, levetiracetam, lamotrigine, tiagabine, topiramate, vigabatrin, and zonisamide) stand on their own. Individual drugs differ in their spectra of activity and in adverse effects profiles. For adverse effects that occur with all drugs, frequency and severity vary from one agent to another: for example, sedation is more common with barbiturates and benzodiazepines, ataxia and diplopia are more common with phenytoin and carbamazepine, and aplastic anemia is more common with felbamate. Certain adverse effects are related to specific properties shared only by certain drugs: for example, renal stones can occur with drugs causing carbonic anhydrase inhibition (acetazolamide, topiramate, zonisamide), whereas reduced efficacy of oral contraceptives can occur with inducers of isozymes that metabolize these steroids (carbamazepine, oxcarbazepine, phenytoin, barbiturates, felbamate, and topiramate).

The clinical pharmacology and adverse effects of some new antiepileptic drugs (ganaxolone, levetiracetam, losigamone, pregabalin, remacemide, rufinamide, stiripentol, and zonisamide) have been reviewed (1).

The uses and adverse effects of antiepileptic drugs in the treatment of painful peripheral neuropathy have been reviewed (2).

Clinical studies

Efficacy and tolerability data from double-blind, placebo-controlled add-on trials of new antiepileptic drugs in patients with refractory partial epilepsy have been reviewed (3). Although there were differences in adverse events profiles among the various drugs, the review identified major methodological problems, which hamper comparisons across studies and drugs. These included variability in the use of COSTART terminology, marked differences in the occurrence of specific adverse events in the placebo groups (an indication of heterogeneous evaluation procedures), and the use of non-optimal dosages or non-optimal titration schedules in many trials (3).

In a multicenter, randomized, double-blind comparison of diazepam (0.15 mg/kg followed by phenytoin 18 mg/kg), lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), and phenytoin (18 mg/kg) in 518 patients with generalized convulsive status epilepticus, lorazepam was more effective than phenytoin and at least as effective as phenobarbital

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or diazepam plus phenytoin (4). Drug-related adverse effects did not differ significantly among treatments and included hypoventilation (up to 17%), hypotension (up to 59%), and cardiac rhythm disturbances (up to 9%).

Comparisons of different antiepileptic drugs

Quality of life

The effects of carbamazepine and lamotrigine on health-related quality of life have been compared for 1 year in 260 patients with newly diagnosed epilepsy randomized to 48 weeks of treatment (5). Patients taking carbamazepine had significantly worse quality of life at week 4 but not later. They also had more cognitive adverse effects in general and more changes in energy and affect during the first 4 weeks of treatment.

Cost-effectiveness

The cost-effectiveness of four antiepileptic drugs used to treat newly diagnosed adult epilepsy has been studied by cost minimization analysis in 12 European countries (6). The analysis took account of each drug's adverse effects and tolerability profiles. Lamotrigine incurred higher costs than carbamazepine, phenytoin, and valproate, whose costs were similar.

Withdrawal of therapy

Gabapentin, lamotrigine, topiramate, and vigabatrin have been compared using Kaplan–Meier survival analysis in 61 patients to see how long they chose to keep taking each drug and, if they stopped, why they stopped (7). The results are shown in Table 1. Lamotrigine seemed to be the best tolerated of the four drugs and topiramate the least. These results have been mirrored by those of two larger retrospective studies (8,9).

Gabapentin and vigabatrin as first-line add-on treatments have been compared in 102 patients with partial epilepsy (10). The improvement rate was 48% with gabapentin and 56% with vigabatrin. There were seven withdrawals in each group because of adverse events. Of the serious adverse events only one was thought to be drug-related—depression and weight gain in a patient taking vigabatrin.

General adverse reactions

The use of antiepileptic drugs (gabapentin, lamotrigine, and topiramate) as mood stabilizers has been reviewed (11). The authors concluded that the benefit : harm ratios of these drugs have not been well enough established for their routine use in bipolar disorder.

Carbamazepine and valproic acid have been compared in a randomized study in 30 patients (12). Significantly more patients taking carbamazepine reported adverse events, including nausea and vomiting, dizziness, lethargy, and ataxia and tremors.

In a comparison of carbamazepine and lamotrigine for trigeminal neuralgia in 18 patients with multiple sclerosis, lamotrigine was more effective (13). After withdrawal of carbamazepine, drowsiness resolved in 16 patients; cerebellar signs improved partially in five patients and completely in two; brainstem signs improved partially in four patients and completely in 3; ambulation improved in 11. In one patient taking lamotrigine a skin rash forced withdrawal.

General adverse reactions

The most important adverse effects of antiepileptic drugs affect the central nervous system and include sedation, fatigue, dizziness, cognitive dysfunction, ataxia, dysarthria, nystagmus, and headache. These effects are often dose-related; they are more prominent with multiple drug therapy and they are usually reversible after dosage adjustment. Behavioral disturbances are relatively common, especially in children and in patients with pre-existing mental handicap. Exacerbation of seizures and psychiatric reactions are not uncommon. Hepatotoxic reactions have especially been reported with felbamate, valproate, carbamazepine, and phenytoin. Endocrine and metabolic changes occur with most drugs, but their clinical relevance is usually limited. Carbamazepine, phenytoin, barbiturates, and to a lesser extent felbamate, topiramate, and oxcarbazepine, are enzyme inducers, whereas felbamate and valproate are enzyme inhibitors. These effects cause significant drug interactions. Most anticonvulsants precipitate attacks in patients with acute intermittent porphyria.

Hypersusceptibility reactions

Hypersusceptibility reactions can involve any system, but they most often affect the skin, leading to drug withdrawal in up to 20% of patients. Aplastic anemia and hepatotoxicity have drastically curtailed the use of felbamate.

Table 1 Persistence with therapy with different antiepileptic drugs in different studies

	Gabapentin	Lamotrigine	Tiagabine	Topiramate	Vigabatrin
Number (Datta and Crawford; 8)	36	37	—	28	26
Median time to 50% drop out (months)	13	>43	—	9.5	29
Withdrawn owing to lack of efficacy (%)	58	24	—	25	62
Number (Lhatoo et al. 9)	146	122	88	70	37
Withdrawn owing to lack of efficacy (%)	25	16	30	30	46
Withdrawn owing to adverse effects (%)	16	15	26	42	16
Number (Lindberger et al. 10)	158	424	—	393	—
Withdrawn owing to lack of efficacy (%)	39	34	—	19	—
Withdrawn owing to adverse effects (%)	37	22	—	40	—

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Tumorigenesis
Pseudolymphoma and a condition resembling malignant lymphoma occur very rarely with phenytoin. There is no evidence of a significant increase in the incidence of other tumors.

Second-generation effects
The use of older antiepileptic drugs in pregnancy is associated with a two- to three-fold increase in the risk of fetal malformations, including facial clefts and cardiac defects. Neural tube defects, including spina bifida, are seen in 2–3% of offspring exposed to valproate and in 1% of those exposed to carbamazepine. There is some evidence that fetal exposure to barbiturates and possibly phenytoin can cause impaired postnatal mental development, but in most studies it has been difficult to discriminate the effects of drugs from those of genetic and environmental factors. There are insufficient data to assess fetal risks after exposure to the newer drugs.

Organs and Systems

Cardiovascular

Cardiac dysrhythmias induced by anticonvulsants are rare and occur mainly in patients other than those known to be at high risk of sudden death (14). Phenytoin has been rarely associated with bradydysrhythmias, almost exclusively after intravenous dosing, and some of these have been fatal. Hypotension can also complicate intravenous phenytoin. Carbamazepine can depress cardiac conduction, mostly in elderly or otherwise predisposed patients. Third-degree atrioventricular block occurred in one patient with pre-existing right bundle branch block treated with topiramate, but a cause-and-effect relation was uncertain (SEDA-21, 76).

Respiratory

Respiratory adverse effects are extremely rare, apart from respiratory depression associated with high-dose benzodiazepines or drug overdose.

Nervous system

Most major anticonvulsants can cause cerebellovestibular and oculomotor symptoms (ataxia, dysarthria, dizziness, fatigue, tremor, diplopia, blurred vision, and nystagmus), alterations in cognitive function, and disorders of mood and behavior. Less common effects include parkinsonism (almost exclusively with valproate), exacerbation of seizures, headache, dyskinesias, and dystonias. Neurophysiological evidence of peripheral neuropathy may be common, but neuropathic symptoms are relatively rare. Monoplegia, Babinski reflexes, restless legs syndrome, and retinal/optic nerve disorders are very rare (except for vigabatrin-induced asymptomatic visual field defects, which are relatively common). Neurological adverse effects are usually dose-dependent and more prominent in patients on multiple drug therapy, although it has been suggested that neurotoxicity relates more to total drug load (in terms of sum of defined daily doses for each drug) than to the actual number of drugs taken (SEDA-22, 81).

In some cases, seizure exacerbation occurs as a manifestation of drug intoxication, and is reversible on dosage reduction or elimination of unnecessary polypharmacy (15). In other cases, seizure exacerbation reflects an adverse reaction to a given drug in specific seizure types or syndromes. Carbamazepine in particular can precipitate or exacerbate a variety of seizures, most notably absence, atonic, or myoclonic seizures, especially in children with generalized epilepsies characterized by bursts of diffuse and bilaterally synchronous spike-and-wave EEG activity. Aggravation of seizures has also been reported with phenytoin and vigabatrin, particularly in children with generalized epilepsies. Gabapentin has been implicated in precipitating myoclonic jerks, while benzodiazepines occasionally trigger tonic seizures, particularly when they are given intravenously to patients with Lennox–Gastaut syndrome. Evidence that ethosuximide predisposes to tonic-clonic seizures remains inconclusive.

Experimental or clinical evidence of polyneuropathy, sometimes with paresthesia, has been found in up to 50% of patients treated chronically with carbamazepine, phenytoin, phenobarbital, and/or valproate (SEDA-18, 61), but it is usually not associated with troublesome symptoms.

The risk of aggravating juvenile myoclonic epilepsy with carbamazepine and phenytoin has been assessed in a retrospective study of 170 patients, of whom 40 had taken carbamazepine or phenytoin (16). There was aggravation of seizures in 23 patients, 6 benefited, and there was no effect in the other 11. Of the 28 patients who used carbamazepine, 19 had aggravated symptoms, including myoclonic status in 2. Of the 16 patients who used phenytoin, 6 had aggravated symptoms, including one in association with phenobarbital. Vigabatrin was given in only one case, in association with carbamazepine, and provoked mixed absence and myoclonic status.

Antiepileptic drugs have sometimes been associated with a paradoxical increase in seizures. The evidence for this comes from isolated reports and clinical impressions. Somerville asked five pharmaceutical companies responsible for the development of new antiepileptic drugs to provide data concerning increases in seizure frequency during randomized, placebo-controlled, add-on trials in patients with uncontrolled partial seizures (17). Seizure frequency in individual patients taking the active drug or placebo was compared with the baseline pretreatment seizure frequency. More than 40% of the patients in trials of tiagabine, topiramate, and levetiracetam had an increase in seizures while taking a placebo. Increased seizure frequency was no more likely to occur when they were taking any of the three drugs than when they were taking placebo. A doubling or more of seizure frequency was significantly less likely to occur with topiramate or levetiracetam than with placebo, but more likely with tiagabine. There was some evidence of a dose–response effect with tiagabine, but a negative effect with topiramate (aggravation less likely with increasing dose). Unfortunately, the author did not obtain data on gabapentin and lamotrigine. Thus, aggravation of seizures in patients using some of the new antiepileptic drugs occurs no more often than

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with placebo and probably represents spontaneous fluctuation of seizure frequency.

Retrospective studies have suggested that antiepileptic drugs can be associated with peripheral nerve dysfunction. This has been studied prospectively in 81 patients (aged 13–67 years) without polyneuropathy who took sodium valproate ($n = 44$) or carbamazepine ($n = 37$) as monotherapy in standard daily doses (18). After 2 years one patient had clinical signs of polyneuropathy and six patients had symptoms of polyneuropathy, but electrophysiology did not show significant changes or trends. Only one patient had abnormal electrophysiological findings, which were only subclinical, and eight patients had abnormal values at two subsequent visits. There were no consistent patterns, and the data were unaffected when the drugs were examined separately or when patients were grouped according to whether or not they had symptoms of polyneuropathy. The authors concluded that previously untreated young to middle-aged patients who take valproic acid or carbamazepine for 2 years are not at risk of polyneuropathy.

Sensory systems

Visual field defects associated with various antiepileptic drugs (carbamazepine, diazepam, gabapentin, phenytoin, tiagabine, and vigabatrin) have been reviewed (19). The true frequency is unknown, but in a retrospective study in 158 patients with partial epilepsy visual field defects were detected in 21 (13%); 13 patients had concentric visual field constriction without subjective spontaneous manifestations. Of these 13 patients, 9 were taking vigabatrin.

Visual-evoked potentials and brainstem auditory-evoked potentials have been measured in 58 children and adolescents taking carbamazepine, phenobarbital, or sodium valproate monotherapy and 50 sex- and age-matched controls (20). After 1 year the patients taking carbamazepine had significantly prolonged visual-evoked P100 latencies compared with both baseline and control values; they also had significantly prolonged peak latencies of auditory waves I-III-V and interpeak interval I-V. Those taking sodium valproate had significantly prolonged visual-evoked P100 latencies. In contrast, children taking phenobarbital had no changes.

In 100 epileptic patients aged 8–18 years taking carbamazepine or valproate in modified-release formulations either alone or with added vigabatrin interpeak latencies of I-III and III-V of brainstem-evoked potentials were significantly delayed and N75/P100 and P100/N145 amplitudes in the visual-evoked potentials were reduced (21). However, the addition of vigabatrin did not worsen the effects caused by the other two drugs alone.

Psychological, psychiatric

Behavioral and psychiatric disturbances are not uncommon (22). Although epilepsy is itself associated with an increased risk of such disturbances, drugs play an important role. Phenobarbital-induced behavioral disturbances, especially hyperkinesia, are especially common in children, with an incidence of 20–50% and need for drug withdrawal in 20–30% of cases, whereas it is unclear whether and to what extent adults are affected.

Psychiatric effects

Among older drugs, valproic acid and carbamazepine are least likely to cause adverse psychiatric effects, though valproate rarely causes encephalopathy and reversible pseudodementia. Phenytoin has been implicated in psychiatric adverse effects with or without other signs of toxicity, and at serum concentrations above or below the upper limit of the target range, but the actual incidence of these reactions is unknown. Benzodiazepines can cause paradoxical excitation, particularly in children and in anxious patients, and several other psychiatric symptoms can complicate the benzodiazepine withdrawal syndrome. Psychiatric or behavioral disorders have been reported with ethosuximide, but the lack of systematic studies prevents assessment of incidence and cause-and-effect relation. Among newer drugs, vigabatrin has been implicated most commonly in psychiatric adverse effects. With gabapentin, lamotrigine, and levetiracetam aggressiveness or hyperactivity can occur, especially in patients with previous behavioral problems or learning disability. Adverse psychiatric reactions to lamotrigine are uncommon, whereas with topiramate, felbamate, and other new drugs information is still insufficient.

Overall, the problem of drug-induced psychiatric disorders can be minimized by avoiding unnecessarily large dosages and drug combinations and by careful monitoring of the clinical response. In patients with a previous history of psychiatric disorders, carbamazepine and valproate are the first-line drugs, and are least likely to cause behavioral disturbances. The ideal management of such disturbances is withdrawal of the offending agent. When continuation of treatment is necessary for seizure control, psychosocial intervention and psychotropic medication can be useful.

In a retrospective study of 89 patients who developed psychiatric symptoms during treatment with tiagabine, topiramate, or vigabatrin, the psychiatric problem was either an affective or a psychotic disorder (not including affective psychoses) (23). All but one of the patients had complex partial seizures with or without secondary generalization. More than half were taking polytherapy. Nearly two-thirds had a previous psychiatric history, and there was a strong association between the type of previous psychiatric illness and the type of emerging psychiatric problem. Patients taking vigabatrin had an earlier onset of epilepsy and more neurological abnormalities than those taking topiramate.

Patients with chronic epilepsy have a higher likelihood of psychosis than the healthy population (24,25). Psychosis is especially frequent in patients with temporal lobe epilepsy (26). Antiepileptic drugs have been reported to precipitate psychosis, although the literature is confounded by the inclusion of affective and confusional psychoses in this category. Moreover, the purported association has mostly been made through isolated case reports or small non-controlled case series. In fact, most antiepileptic drugs have been associated with psychosis: phenytoin and phenobarbital (27),

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carbamazepine and valproate (28), felbamate (29), gabapentin (30), levetiracetam (31), topiramate (32), vigabatrin (33), and zonisamide (34). There have been no reports of psychosis associated with lamotrigine.

A retrospective chart review of 44 consecutive patients with epilepsy who had psychotic symptoms with clear consciousness has shown the difficulties in associating psychosis with drug effects (35). These patients were divided into two groups based on the presence or absence of changes in their drug regimen before the onset of the first episode of psychosis. In 27 patients the first episode of psychosis was unrelated to changes in their antiepileptic drug regimen, and in 23 of them the psychosis was temporally related to changes in seizure frequency. In 17 patients the first episode of psychosis developed in association with changes in their antiepileptic drug treatment, and in 12 of them the psychosis was temporally related to seizure attenuation or aggravation. This study therefore highlights the fact that psychosis can occur in relation to changes in seizure frequency, sometimes due to lack of effect of the new medication or to concomitant withdrawal of an efficacious medication.

Withdrawal of anticonvulsants with favorable mood stabilization properties, such as carbamazepine, has often been associated with acute psychosis (36,37). Moreover, the phenomenon of "forced normalization," by which complete seizure freedom in a patient with previous refractory epilepsy can lead to a psychotic state, may also contribute to the apparent association between drugs and psychosis (38).

Information from double-blind studies of psychosis as an adverse event is relatively scarce. A double-blind, randomized, add-on, placebo-controlled trial with carbamazepine showed that there was no increase in chronic psychotic symptoms in patients with suspected temporal lobe seizures (39).

The relation between psychosis and tiagabine has been assessed in an analysis of data from two multicenter, double-blind, randomized, placebo-controlled trials of add-on tiagabine therapy (32 or 56 mg/day) in 554 adolescents and adults with complex partial seizures during 8–12 weeks (40). There were psychotic symptoms (hallucinations) in 3 (0.8%) of 356 patients taking tiagabine and none of the 198 taking placebo, a non-significant difference. Thus, it appears that tiagabine does not increase the risk of psychosis, but the result is inconclusive.

An analysis of double-blind, placebo-controlled trials of vigabatrin as add-on therapy for treatment-refractory partial epilepsy showed that compared with placebo patients taking vigabatrin had a significantly higher incidence of events coded as psychosis (2.5% versus 0.3%) (17). There were no significant differences between treatment groups for aggressive reaction, manic symptoms, agitation, emotional lability, anxiety, or suicide attempts. In an open trial of topiramate, psychosis was seen in 30/1001 (3%) of the patients, and was severe enough to require withdrawal in eight (41).

Should certain antiepileptic drugs be contraindicated in patients with active psychosis? Unfortunately there is not enough solid information to answer this question. Undoubtedly, anticonvulsants that are less likely to cause psychosis (lamotrigine, carbamazepine, oxcarbazepine, valproate) should be preferred (42,43). However, patients with psychoses have been successfully treated even with drugs that are believed to be associated with psychosis, such as vigabatrin. For example, in a prospective study in 10 patients with psychosis and epilepsy to whom vigabatrin was added, there was no aggravation of the psychiatric disorder (44).

Cognitive effects

The appropriate methods and timing in assessing cognitive and behavioral adverse events during drug development programs have been thoroughly reviewed (45).

The authors of a critical review focusing on pediatric data concluded that adverse effects on learning and behavior may have been over-rated (46). Because of methodological flaws, many early studies could not discriminate between effects of drugs and the influence of heredity, brain damage, seizures, and psychosocial factors. In fact, the majority of children taking antiepileptic drugs do not experience major cognitive or behavioral effects from these medications. In some patients, however, drugs do produce detrimental effects, barbiturates and benzodiazepines being among those most commonly implicated (47). At least with some agents, such as gabapentin, behavioral adverse effects occur mainly in children with pre-existing learning disability. As to phenytoin, carbamazepine, and valproate which are the drugs most commonly recommended for first-line use, recent investigations have failed to show major differences in cognitive effects between these agents, although in some studies, patients taking phenytoin tended to have lower motor and information processing speeds (SED-13, 140) (48,49) (SEDA-19, 72) (SEDA-20, 64).

Endocrine

Although most anticonvulsants interfere with endocrine function, epilepsy may do so itself, and it is difficult to differentiate the effects of drugs from those of the disease. In any case, symptoms of endocrine dysfunction are less common than biochemical abnormalities.

Growth hormone

Normal growth hormone concentrations are found in carbamazepine-treated patients (50). Growth hormone secretion in response to levodopa stimulation was not affected by carbamazepine or phenobarbital, whereas phenytoin and anticonvulsant polytherapy caused an increase in growth hormone concentration, and valproate a fall at varying times after the administration of levodopa (51). Pubertal growth arrest has been described in a 12-year-old girl who had taken valproate for 18 months (SED-13, 152).

Adrenal–pituitary axis

Neither phenytoin, valproate, carbamazepine, nor phenobarbital altered the circadian ACTH/cortisol rhythm in epileptic patients (51). In some studies, phenytoin and carbamazepine were associated with increased serum concentrations of unbound cortisol (52), but cortisol

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concentrations were unaffected in other studies (50) and Cushing's syndrome has not been described with these drugs. Valproate can depress ACTH concentrations by inhibiting corticotrophin-releasing factor, and it has been used to treat Nelson's syndrome (53). Serum concentrations of progesterone and cortisol and the excretion of 17-hydroxycorticosteroids have been reported to be lower in untreated patients with epilepsy and to be further reduced by phenytoin (54).

Sex hormones

Carbamazepine, phenobarbital, phenytoin, and anticonvulsant polytherapy increased both basal and stimulated concentrations of prolactin, whereas valproate did not (51). However, in other studies, prolactin was unchanged (50). In boys, phenobarbital lowered baseline LH and FSH concentrations and their response to releasing hormone; baseline prolactin concentration was raised in comparison with healthy children, and the response of prolactin concentrations to stimulation was impaired (55).

Serum concentrations of bound testosterone are increased by phenytoin, carbamazepine, phenobarbital, and primidone owing to increased synthesis of the specific transport protein, sex hormone-binding globulin (SHBG), but concentrations of unbound testosterone, dehydroepiandrosterone sulfate, and 17-α-hydroxyprogesterone and the free androgen index may be reduced (50,56–58). Increased FSH in 31% of carbamazepine-treated men may reflect impairment of spermatogenesis, whereas lower concentrations of inhibin B (in 12% of men) and testosterone/LH ratio (in 50%) indicate impaired function of Sertoli cells and Leydig cells respectively (50). Sexual activity was reduced, while mean plasma concentrations of LH, FSH, PRL, and SHBG were raised in 27 epileptic patients taking phenytoin, primidone, phenobarbital, or combinations of these (59). The often-reported reduction in sexual activity and occasional reports of impotence may be related to the reduction in unbound testosterone caused by enzyme induction. Valproate has been recommended for patients with dysfunctional libido or impotence, because it apparently does not reduce unbound hormone concentrations (60).

In an assessment of the effects of antiepileptic drugs on male sexual function, men taking carbamazepine had higher plasma concentrations of SHBG and lower concentrations of dehydroepiandrosterone compared with controls (61). Patients taking phenytoin had higher total testosterone concentrations and lower dehydroepiandrosterone concentrations. Patients taking carbamazepine and phenytoin also had a lower free androgen index, but free (unbound) testosterone, a more reliable index of active androgen concentrations, did not differ from that of controls. Patients taking valproate showed no differences in hormone concentrations compared with controls. Sexual experience scales showed that treated men embraced a stricter sexual morality than untreated controls, and expressed greater satisfaction with their marriages. Most of the hormonal changes could be explained by enzyme induction, and there was no evidence of hyposexuality in this population.

Reproductive endocrine disorders and sexual dysfunction have often been attributed to epilepsy itself, but antiepileptic drugs can cause various alterations in endocrine functions. Reproductive endocrine function was prospectively evaluated in 90 men taking valproate ($n = 21$), carbamazepine ($n = 40$), or oxcarbazepine ($n = 29$) as monotherapy for epilepsy, and in 25 healthy controls (62). There were increased serum androgen concentrations in 60% of those who took valproate. Carbamazepine had an opposite effect: men had mean low serum concentrations of dehydroepiandrosterone and a high SHBG concentration. Moreover, 18% of men taking carbamazepine for epilepsy reported reduced libido, impaired potency, or both. Low daily doses of oxcarbazepine (under 900 mg/day) did not have any effects on serum concentrations of reproductive hormones, but men taking high doses of oxcarbazepine (over 900 mg/day) had increased serum testosterone, gonadotropin, and SHBG concentrations. Serum insulin concentrations were high in all patients. Thus, the three antiepileptic drugs affected the serum concentrations of reproductive endocrine hormones in men with epilepsy, but in different ways. Valproate directly affects steroid synthesis or metabolism. Oxcarbazepine and carbamazepine differ in their effects, despite their close structural homology: oxcarbazepine does not reduce the activity of androgens, whereas carbamazepine does. The relevance of these hormonal changes to reproductive or sexual function remains to be demonstrated.

In another study changes in reproductive hormones associated with valproate or carbamazepine were prospectively analysed in 17 women and 22 men with recently diagnosed epilepsy (63). There were no clinical signs of hormonal disorders or weight gain during follow-up at 1 and 3 months. Valproate and carbamazepine caused alterations in reproductive hormonal function during the first month of treatment, and these changes were stable or progressive during the next 2 months. Serum testosterone concentrations increased in half of the women taking valproate; mean serum concentrations of gonadotropins and SHBG also increased, but the concentrations of serum dehydroepiandrosterone sulfate fell. On the other hand, in men after 3 months of valproate treatment, serum FSH concentrations were low and serum progesterone and dehydroepiandrosterone sulfate concentrations were high. Carbamazepine increased serum concentrations of SHBG and dehydroepiandrosterone sulfate, while the free androgen index fell. Thus, valproate was associated with increased serum androgen concentrations, but the profiles of hormonal changes were different in men and women. On the other hand, carbamazepine was associated with reduced sex steroid function in both sexes. Although these results are of interest, the study was not randomized and a large number of statistical comparisons were performed, so that no firm conclusions can be drawn.

Thyroid hormones

Total and free (unbound) thyroxine can be reduced by phenytoin and carbamazepine, but free triiodothyronine is normal or only slightly reduced. Thyroid-stimulating hormone is normal or only slightly altered and patients remain clinically euthyroid (50,64). Reductions in the concentrations of some thyroid hormones are probably related to enzyme induction; the concentrations return to

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normal after substituting carbamazepine with oxcarbazepine, a less potent enzyme inducer (65). Hypothyroidism has been rarely described in patients taking phenytoin or carbamazepine (66). In contrast to earlier reports, there were no changes in thyroid hormones during treatment with valproate in a later study (67).

Serum thyroid hormones have been compared in 148 healthy children and 141 children with epilepsy who had been taking carbamazepine ($n = 61$), valproate ($n = 51$), or phenobarbital ($n = 29$) for at least 1 year (68). In all the groups mean thyroxine and free thyroxine concentrations were lower than in controls, and those taking carbamazepine and valproate also had lower concentrations of triiodothyronine and thyroid-binding globulin and increased mean TSH concentrations. There was subclinical hypothyroidism, defined as a TSH concentration greater than two standard deviations above the control mean, in 26% of the children taking valproate, 8.2% of those taking carbamazepine, 7.1% of those taking phenobarbital, and 3.6% of controls. However, the magnitude of the TSH increase was usually small and the children were clinically euthyroid.

The effects of antiepileptic drugs on thyroid function have also been studied in an open prospective study in 90 men with epilepsy (40 taking carbamazepine, 29 taking oxcarbazepine, and 21 taking valproate monotherapy) and 25 control subjects (69). Serum thyroxine and/or free thyroxine concentrations were below the reference ranges in 45% of men taking carbamazepine and 24% of men taking oxcarbazepine. Thyroid peroxidase and/or thyroglobulin concentrations were increased in 13% of those taking carbamazepine, 17% of those taking oxcarbazepine, and 6% of controls, but these changes were not associated with altered serum thyroid hormone concentrations. Serum triiodothyronine and thyrotropin (TRH) concentrations in those taking carbamazepine or oxcarbazepine were normal. In men taking valproate, the concentrations of thyroid hormones, thyrotropin, and antithyroid antibodies were normal. Thus, low serum thyroid hormone concentrations appear to be frequent in men taking carbamazepine or oxcarbazepine and are probably not due to liver enzyme induction or activation of immunological mechanisms. The clinical significance of these changes is uncertain: serum TSH was not affected and all the patients were clinically euthyroid. Similar results have been obtained in a retrospective study in 37 children taking valproate or carbamazepine (70).

Metabolism

Phenytoin rarely causes hyperglycemia, and the blood glucose concentration can increase in phenytoin intoxication (SED-13, 139) (71). A reduction in the insulin response to glucose has been noted with therapeutic doses of phenytoin, but glucose intolerance does not arise, probably owing to increased sensitivity to insulin.

Changes in body weight associated with anticonvulsants have been reviewed (72), including the effects of the antiepileptic drugs that have been most commonly associated with this adverse effect (valproic acid, carbamazepine, vigabatrin, and gabapentin) (73). Unlike most anticonvulsants, topiramate, felbamate, and zonisamide can cause weight loss.

Preliminary evidence suggests that certain idiosyncratic reactions to anticonvulsants are mediated by reduced free radical scavenging activity, as indicated by lower selenium concentrations and a higher lipid peroxide index in affected patients (SEDA-19, 62).

Serum lipids

Phenytoin increases high-density lipoprotein (HDL) cholesterol (74), and may also increase total cholesterol and serum triglyceride concentrations (SED-13, 143) (75). In a 5-year prospective study with carbamazepine, there was a persistent rise in total cholesterol and HDL cholesterol, whereas triglycerides and low-density lipoprotein (LDL) cholesterol increased only transiently (76). In a more recent study, total cholesterol fell when 12 patients were switched from carbamazepine to oxcarbazepine, but HDL cholesterol and triglycerides were unchanged (77). In a comparison of 101 epileptic patients with matched controls, valproate was associated with lower total and LDL cholesterol, whereas carbamazepine was associated with higher HDL cholesterol and apolipoprotein A concentrations and phenobarbital with higher concentrations of total and HDL cholesterol and apolipoproteins A and B. The ratio of total to HDL cholesterol was reduced with valproate and carbamazepine but not with phenobarbital (78).

The clinical relevance of these findings is uncertain. The increased HDL cholesterol seen with some drugs might confer some protection against atherosclerosis and coronary heart disease (SEDA-18, 63).

Porphyrin metabolism

Enzyme inducers, such as phenytoin, carbamazepine, and barbiturates, can precipitate attacks in patients with acute intermittent porphyria.

- A patient with uncontrolled posttraumatic epilepsy and acute intermittent porphyria was given phenytoin, carbamazepine, and clonazepam on successive occasions (79). Phenytoin and carbamazepine caused significant increases in porphobilinogen excretion and acute attacks of porphyria. In contrast, clonazepam caused no increase in porphobilinogen excretion.

Valproate (SED-12, 134) (80,81), ethosuximide (82), and some benzodiazepines (83) have also been implicated in the precipitation of acute attacks of porphyria, although valproate is considered safe for patients with porphyria cutanea tarda (SED-13, 150) (84).

Neither vigabatrin nor gabapentin caused porphyrin accumulation in chicken embryo cultured liver cells, whereas felbamate, lamotrigine, and tiagabine were porphyrinogenic in this model (85). For gabapentin, safety in porphyrias has been confirmed in preliminary clinical observations (SEDA-19, 70) (SEDA-20, 62).

Amino acids

Compared with healthy controls, 51 patients with epilepsy taking a variety of antiepileptic drugs (mostly carbamazepine) had higher mean plasma concentrations of homocysteine (86). This effect, which could be related to reductions in the concentrations of folate and vitamin B6, was likely to be drug-induced, but a causative role

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of the underlying disease could not be excluded. Although homocysteine is an experimental convulsant and a risk factor for atherosclerosis, the clinical relevance of these findings is uncertain.

Phenytoin can reduce blood and CSF thiamine concentrations (87).

Hyperammonemia and carnitine deficiency are adverse effects of valproate, although carnitine deficiency can also be caused by other anticonvulsants (88).

Concentrations of lipoprotein(a) were measured in 51 patients taking long-term carbamazepine, phenobarbital, phenytoin, or valproate and 51 age- and sex-matched controls (89). Lipoprotein(a) concentrations were above 450 μg/ml in 11 patients compared with only 4 controls, and the mean serum lipoprotein(a) concentrations were 330 and 169 μg/ml respectively. The epileptic patients also had a thicker intima media of the common carotid artery. These results suggest that patients taking antiepileptic drugs may be at a higher risk of atherosclerosis.

Electrolyte balance

Phenytoin inhibits the release of antidiuretic hormone (ADH), but this effect is generally clinically unimportant (SED-13, 138) (90). In contrast, both carbamazepine and, to a greater extent, its analogue oxcarbazepine produce significant dose-dependent antidiuretic effects. This is mediated by an action on hypothalamic osmoreceptors or by increased renal sensitivity to ADH, and it can cause hyponatremia and hypo-osmolality. The incidence of hyponatremia ranges from 0% to 42% in patients taking carbamazepine, and from 23% to 73% in those taking oxcarbazepine (22,91). Factors that increase the risk are high dosage (and high serum drug concentrations), old age, a history of severe head trauma or polydipsia, and possibly concomitant intake of diuretics and various psychotropic drugs. Hyponatremia is usually mild and asymptomatic, but occasionally it can cause fatigue, lethargy, drowsiness, confusion, vomiting, and neurological abnormalities, including an increased susceptibility to seizures (91,92). Demeclocycline has been used in the management of carbamazepine-induced hyponatremia (93), but a reduction in drug dosage (or no action in asymptomatic cases) is usually sufficient.

Mineral balance

Alterations in mineral balance occur in a significant proportion of patients taking antiepileptic drugs. Reductions in serum calcium and phosphate and an increase in serum alkaline phosphatase occur in up to 50% of patients treated with enzyme-inducing anticonvulsants, and there can be clinical or biochemical evidence of rickets and osteomalacia. Phenytoin is most often implicated, but similar disturbances have been reported with carbamazepine and barbiturates. The pathogenesis of these changes may involve enhanced conversion of vitamin D to inactive metabolites, but there may be other mechanisms, such as antagonism of the action of 1,25-dihydroxycholecalciferol on bone (SED-13, 139) (94). Serum calcium, phosphate, and alkaline phosphatase should be checked periodically in patients at increased risk of osteomalacia, such as those with a low intake of vitamin D, inactivity, or lack of exposure to sunlight (95). Treatment with colecalciferol may be useful in patients with evidence of vitamin D deficiency (SEDA-16, 70).

Immunoreactive parathyroid hormone concentrations may be increased by anticonvulsants, while bone mineral content is reduced. Hypocalcemia and osteopenia can occur, despite normal serum concentrations of active vitamin D metabolites, suggesting that they may be independent of drug effects on vitamin D metabolism. Bone biopsies have shown increased osteoid but normal calcification front formation, accelerated rate of mineralization, and reduced mineralization lag time, suggesting increased skeletal turnover rather than osteomalacia (96). The risk of age-related fractures in drug-treated epileptic patients is not greatly increased (97).

Valproate has not been commonly implicated in the disturbances described above. In one study, after correction for age and sex, children taking valproate had 14 and 10% reductions in bone mineral density at the axial and appendicular sites respectively; however, the significance of these findings is uncertain (SEDA-20, 69).

Transient osteosclerosis of the long bones was reported in a 15-year-old boy taking valproate with severe pain in the extremities; it disappeared after drug withdrawal (SED-13, 150) (98).

Acid–base balance

Acetazolamide, sultiame, and topiramate inhibit carbonic anhydrase and occasionally produce biochemical or clinical manifestations of acidosis.

Hematologic

Chronic treatment with phenobarbital, phenytoin, and carbamazepine is associated with reduced serum folate concentrations. Although megaloblastic anemia is rare, macrocytic changes in red cells are common in these patients. The fact that serum folate is not reduced by valproate and zonisamide, which do not induce liver enzymes, is consistent with the hypothesis that enzyme induction plays a role in the pathogenesis of folate deficiency (99).

Blood dyscrasias, ranging from mild leukopenia to fatal aplastic anemia, can occur with most anticonvulsants, but severe hematological reactions are extremely rare, except for felbamate. Thrombocytopenia, platelet dysfunction, and altered coagulation are not uncommon in patients taking valproate, but severe hemorrhagic complications are rare. Newborns of mothers treated with enzyme-inducing anticonvulsants are at risk of serious hemorrhage during the first few days of life and should receive vitamin K prophylactically.

The combination of lamotrigine with valproate has been reported to have caused the production of lupus anticoagulant (100).

- A 5-year-old boy with generalized absence seizures, who had had a moderate reduction in fibrinogen and prolonged partial thromboplastin time while taking valproate was given add-on lamotrigine (2 mg/kg). His seizures disappeared, but the partial thromboplastin time increased and tests for lupus anticoagulant and IgG anticardiolipin antibodies became positive. Serum autoantibody screen and rheumatoid factor were

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negative. The lupus anticoagulant disappeared after valproate was withdrawn.

The authors suggested that lamotrigine may have exacerbated a mild immune response initially induced by valproate, without clinical evidence of systemic disease.

In a large cohort study of the occurrence of bleeding complications in neonates exposed to maternal enzyme-inducing antiepileptic drugs in utero in 662 pregnancies in women with epilepsy, 463 had been exposed to carbamazepine, 212 to phenytoin, 44 to phenobarbital, 11 to primidone, and 7 to oxcarbazepine (101). Another 1324 "non-epileptic" pregnancies (1334 neonates) were matched for maternal age, parity, number of fetuses, and delivery date. None of the mothers had received vitamin K1 during pregnancy, but all the infants received vitamin K1 1 mg intramuscularly at birth. There were bleeding complications in five (0.7%) of the neonates exposed to maternal enzyme-inducing antiepileptic drugs and in five (0.4%) of the control subjects. Logistic regression analysis showed that bleeding was associated with premature birth and alcohol abuse, but not with exposure to enzyme-inducing antiepileptic drugs. These results contradict the widely held view, based on anecdotal evidence, that maternal enzyme-inducing antiepileptic drugs increase the risk of bleeding in the offspring. Thus, antenatal administration of vitamin K to mothers treated with enzyme-induced drugs may not be needed in most cases. However, prophylaxis may be worth considering when premature delivery is imminent in a woman who uses anticonvulsants. It is worth noting that the findings described in this article are only relevant to patients taking carbamazepine or phenytoin monotherapy. Therefore, extrapolation to individuals on polytherapy or to those taking other enzyme-inducing drugs is not possible.

Gastrointestinal

Nausea, vomiting, diarrhea, and changes in appetite can occur with all anticonvulsants, although they are usually transient and rarely require withdrawal. Felbamate and to a lesser extent valproate are the anticonvulsants that most often cause gastrointestinal adverse effects.

Liver

Virtually all of the major antiepileptic drugs can cause hepatotoxicity, although a fatal outcome is rare. Liver enzymes are increased up to three times the normal limit in up to 40% of patients treated with major antiepileptic drugs, without any additional evidence of overt hepatic disease. Repeated indiscriminate monitoring of liver function tests is not indicated in patients taking most antiepileptic drugs, and greater attention should be focused on the recognition of high-risk groups and supply of information about symptoms of incipient hepatic failure (102,103).

With phenytoin, carbamazepine, phenobarbital, primidone, and lamotrigine, hepatotoxicity usually occurs as part of a hypersensitivity reaction, with skin rashes and fever in the early weeks of treatment. More rarely, hepatic disease can develop after many years without signs of hypersensitivity. Once hepatotoxicity develops, mortality rates are 10–38% with phenytoin and about 25% with carbamazepine (104). Elderly patients may be at higher risk (105).

Fatal valproate hepatotoxicity may occur with greater frequency in children under the age of 2 years who are receiving multiple drug therapy and have additional handicaps (106).

Atrium, a proprietary mixture of phenobarbital, febarbamate, and difebarbamate, has caused several cases of hepatotoxicity, at least one of which was ascribed to the carbamates, because the patient had earlier tolerated phenobarbital (SEDA-18, 74). Atrium-induced hepatitis might be facilitated by defective CYP2C19 activity (SEDA-19, 77).

Pancreas

Pancreatitis is a rare adverse effect of valproate and can occur in isolation or in association with liver toxicity. In a review of the patients of 366 physicians, 23% of patients taking valproic acid had asymptomatic increases in serum amylase activity but there were only 39 cases of valproate-associated pancreatitis (107). Pancreatitis usually presented with epigastric pain, nausea, and vomiting, and was more common in patients aged under 20 years and with mental retardation. In most cases the pancreatitis started within the first 3 months of treatment, but in 18% the onset was after 2 years.

Pancreatitis with other antiepileptic drugs is extremely rare.

Urinary tract

Drugs that inhibit carbonic anhydrase (acetazolamide, topiramate, and zonisamide) are associated with a small risk (up to 1.5%) of nephrolithiasis. Increased excretion of *N*-acetyl-beta-glucosaminidase, a marker of renal tubular integrity, has been reported with valproate and carbamazepine, but it is probably not clinically significant (SEDA-18, 60).

Skin

All major anticonvulsants have adverse effects on the skin, ranging from a mild maculopapular rash to life-threatening Stevens–Johnson syndrome or Lyell's syndrome (toxic epidermal necrolysis), severe forms of erythema multiforme.

Mild adverse skin reactions to antiepileptic drugs include morbilliform rashes, fixed drug eruptions, bullous reactions, lichenoid-type reactions, urticaria (excluding angioedema), alopecia, pigmentation changes, and photosensitivity (108). There have been reports of positive rechallenge in some patients with exanthems, bullous eruptions, lichenoid-type reactions, and mild urticaria. Mild skin rashes during the first few weeks of treatment are among the most common causes of early withdrawal of carbamazepine, phenytoin, oxcarbazepine, barbiturates, and lamotrigine. Corticosteroids may suppress mild carbamazepine-induced eruptions, allowing continuation of treatment in a few patients.

Anticonvulsants are among the most important causative agents of serious and potentially fatal skin reactions. The management of severe reactions of any type is

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controversial, but referral to a burns center is recommended. Essential supportive care includes fluids and nutrition management. Prophylactic antibacterial drugs are not recommended. Plasmapheresis has been recommended for emergency treatment of anticonvulsant-induced toxic epidermal necrolysis (SED-13, 141) (109). Most authors advise against the use of corticosteroids, as they increase the risk of infection and sepsis.

Several reports have suggested that patients with brain tumors who undergo radiation therapy while taking phenytoin may be at increased risk of developing Stevens–Johnson syndrome. A 47-year-old black man (110) and four other patients, including one who died (111), were seen in a 24-month period in one department. A review of 20 similar reported cases showed no relation to the dosage of phenytoin or radiation, or to the histological type of the tumor (110). Isolated reports have also implicated carbamazepine and phenobarbital in causing Stevens–Johnson syndrome in patients undergoing radiation therapy. In a 53-year-old man taking phenobarbital, eruptions were limited to the sites of radiation, which were multiple (112). Conversely, a retrospective review of 289 brain tumor patients treated with cranial radiation and anticonvulsant drugs did not identify an increased incidence of severe skin rashes (113). Only one patient with Stevens–Johnson syndrome was found in this series, although the incidence of milder skin rashes was higher than expected (18 versus 5–10%). In three patients who had toxic epidermal necrolysis after taking phenytoin or carbamazepine there was an increase in CD3+CLA+ cells, paralleling the severity of the disease in both peripheral blood and skin, tending to normalize as the condition improved (114). E selectin was detected in endothelial vessels in parallel with CLA expression on lymphocytes. There was overexpression of TNF-alpha, interferon gamma, and interleukin-2 in peripheral monocytes. These results suggest an important role for T cells in the production of drug-induced toxic epidermal necrolysis.

A psoriasiform eruption has been reported in a 28-year-old woman taking carbamazepine and valproate (115). Rechallenge was not attempted, and the association with either of these drugs was not clear.

Cross-reactivity in skin reactions is relatively common, especially with anticonvulsants with an aromatic ring (116). Valproate, clonazepam, or clobazam may be safer alternatives in patients who have had a rash from aromatic anticonvulsants. However, in a 41-year-old man a fixed drug eruption that occurred after phenytoin and carbamazepine also occurred after valproate (SEDA-22, 83).

Acne can complicate treatment with phenytoin and other enzyme-inducing anticonvulsants.

Hirsutism and gingival hyperplasia are important adverse effects of phenytoin and represent a relative contraindication to first-line use of this drug in young women.

Alopecia is not uncommon with valproate, and it can also occasionally occur with phenytoin, carbamazepine, vigabatrin, and gabapentin.

Musculoskeletal

Barbiturates can cause various connective tissue disorders, including Dupuytren's contracture and frozen shoulder.

Phenytoin in young children can cause acromegalic facial features.

Osteoporosis

Epilepsy and osteoporosis are very common and frequently overlap. Nevertheless, the prevalence of low bone density appears to be disproportionately higher in patients with epilepsy, and patients with epilepsy have an excessive risk of fractures. A meta-analysis of 94 cohort studies and 72 case-control studies has shown that anticonvulsant treatment is highly associated with fractures (relative risk over 2) (117). Other risk factors were low body weight, weight loss, physical inactivity, consumption of corticosteroids, primary hyperparathyroidism, type 1 diabetes mellitus, anorexia nervosa, gastrectomy, pernicious anemia, and age over 70 years.

Bone mineral density has been measured in 59 patients and 55 age- and sex-matched controls (118). Bone mineral density in the lumbar spine (L2-4) and femurs was lower in the patients, significantly so in the former case. This reduction depended on the duration of therapy. Excretion of pyridinoline cross-links was markedly increased and 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol were significantly reduced. The proliferation rate of human osteoblast-like cells was increased by phenytoin in low doses.

Bone metabolism has been assessed in 27 children aged 3–17 years taking long-term valproate and lamotrigine (119). Valproate and lamotrigine were associated with short stature, low bone mineral density, and reduced bone formation. The effect was larger when the two drugs were used together.

The effects on bone metabolism of carbamazepine, valproate, or phenobarbital as monotherapy have been analysed in a case-control study in 118 ambulatory children with epilepsy and corresponding controls (120). Patients taking carbamazepine or phenobarbital had significantly raised alkaline phosphatase and bone and liver isoenzyme activities compared with controls. Although the authors concluded that children who take anticonvulsants may have their bone metabolism affected, this conclusion was based on abnormal values of a surrogate marker for bone disease.

There has been a prospective study of bone mineral density in patients with epilepsy (121). Femoral neck bone mineral density was analysed by dual-energy X-ray absorptiometry in 81 men with epilepsy. Bone mineral density was more than one standard deviation below normal in 47%, indicating an increased risk of fractures (122). Age and duration of therapy were the most significant risk factors associated with a low bone mineral density. Vitamin D deficiency was not a significant risk factor. Longitudinal analysis showed that only those in the youngest age group (25–44 years) had significant reductions in bone mineral density (1.8% annualized loss) while taking anticonvulsants. There was no evidence that a specific type of antiepileptic drug was more causally related to bone loss, although most patients were taking phenytoin or carbamazepine.

Markers of collagen and bone turnover in 60 children and adolescents with epilepsy taking carbamazepine monotherapy were measured at different pubertal stages after 2 years of treatment (123). Compared with

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age-matched healthy children, there was an increase in several markers of bone turnover. In particular, there was a nearly 10-fold increase in postpubertal patients of *N*-telopeptides of type I collagen excretion, indicating increased bone resorption due to excessive osteoclastic activity. These data suggest that carbamazepine can cause increased bone turnover independent of pubertal age.

Predisposing factors for bone disease

In patients with epilepsy, several factors can influence bone health, including poor mobility and anticonvulsant drug treatment. Limitations to physical activity that result from neurological deficits or cerebral palsy underlying symptomatic epilepsies clearly constitute a risk factor for osteoporosis (124). Of 117 children with moderate to severe cerebral palsy, 77% had osteopenia, but the rate was 97% among those who were unable to stand and were over 9 years old; fractures occurred in 26% of the children who were over 10 years old (125). Similarly, adults with neurodevelopmental disorders residing in long-term care facilities have a high rate of both low bone mass and skeletal fractures, especially with concomitant use of anticonvulsant drugs (126). Reduced activity and participation in sports, because of frequent seizures, might also have an impact on bone mineralization.

Certain antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, primidone) are inducers of cytochrome P450 isozymes and increase the breakdown of vitamin D (118,127). Although low vitamin D has been thought to be the cause of low bone density and osteomalacia, a reduction in bone density in the absence of vitamin D deficiency has been also found in children taking either enzyme-inducing agents (123,127) or valproate (128). Moreover, there is recent evidence that although subjects taking enzyme-inducing drugs tend to have lower bone mineral density than those taking non-inducers (clonazepam, ethosuximide, gabapentin, lamotrigine, topiramate, and valproic acid), this is not necessarily due to low vitamin D concentrations. In fact, even though 50% of patients with epilepsy have low vitamin D concentrations, there is no good correlation with bone mineral density (127).

Pathophysiology

The drug-related mechanisms that cause bone loss in patients with epilepsy are not completely understood. Although low vitamin D concentrations may play a part, a direct increase in the proliferation rate of human osteoblast-like cells (observed with phenytoin) might lead to impairment of bone formation (118).

Consequences

Low bone density leads to an increased risk of fractures. There was a 30% increased risk of non-seizure-related fractures in 348 non-institutionalized patients with epilepsy compared with a large control population (129). For non-seizure-related fractures the crude fracture rate was 1.6 fractures per 100 patient-years of observation; a similar rate (1.4) has been found in men with epilepsy (122). In addition, in children with epilepsy, treatment with valproic acid and/or lamotrigine for more than 2 years is associated with short stature, possibly in relation to a low bone mass and reduced bone formation (119).

Assessment

The results of multiple investigations suggest that patients with epilepsy and certain risk factors should be assessed for mineral loss: these include those taking enzyme-inducing agents or long-term treatment (especially polytherapy), those with low or lack of physical activity, postmenopausal women, and elderly people (118,127). Assessment should be done with dual-energy X-ray absorptiometry scanning of the hip (121) and measurement of several biochemical markers (serum total calcium, phosphate, alkaline phosphatase, gamma-glutamyltranspeptidase, aspartate transaminase, 25-hydroxycolecalciferol, and 1,25-dihydroxycolecalciferol). Patients with abnormal findings should have parathyroid hormone and sex hormone concentrations assayed or be referred to an endocrinologist for further assessment.

Despite increasing evidence of bone disease in patients with epilepsy, few pediatric (41%) and adult (28%) neurologists routinely evaluate it (130). A recent survey among neurologists showed that of those who detect bone disease through diagnostic testing, only 40% of pediatric and 37% of adult neurologists prescribed calcium or vitamin D, and about half referred patients to specialists (130). Under 10% of neurologists prescribed prophylactic calcium or vitamin D for patients taking anticonvulsants. This also reflects the fact that evidence about the indications for evaluating and treating bone disorders in patients with epilepsy is currently scarce.

Treatment

Calcium and vitamin D supplementation alone, although necessary to meet normal nutritional guidelines, may be inadequate in preventing bone loss in epilepsy. Bone loss associated with other chronic diseases and other bone-depleting medications has prompted a search for more aggressive therapy. Osteoporosis can be effectively treated with bisphosphonates, which disrupt osteoclastic bone resorption by causing apoptosis of osteoclasts. Oral bisphosphonates are typically administered daily. Third-generation intravenous agents, such as zoledronic acid, can be just as effective when administered once a year. However, there is not currently enough information to support the use of bisphosphonates in patients at risk who are taking antiepileptic drugs.

However, potential therapeutic interventions require randomized prospective studies. Variables that might be addressed in such trials include: the impact of monotherapy and polytherapy on the attainment of peak bone mass in adolescence and adulthood; bone health in women; characterization of the impact of limitations in physical activity on bone density in patients with epilepsy who have cerebral palsy or those with developmental disabilities or mental retardation; the effects of newer antiepileptic drugs on bone metabolism; standardization of the workup for bone disease in patients with epilepsy; and the effectiveness of the current recommendations for supplementation with calcium and vitamin D.

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Sexual function

See the section on Endocrine in this monograph.

Reproductive system

The risk of anovulatory cycles and its association with epilepsy syndrome and anticonvulsants has been assessed in a cross-sectional cohort study in women with epilepsy and non-epileptic controls (131). There were 59 patients with localization-related epilepsy and 35 with idiopathic generalized epilepsy. They were treated with monotherapy and followed for 6 months or more. Anovulatory cycles occurred in 11% of cycles in controls, 14% of cycles in women with focal epilepsy, and 27% of cycles in women with idiopathic generalized epilepsy. Anovulatory cycles were more frequent in women taking valproate: 38% had at least one anovulatory cycle in contrast to 11% of women not taking valproate. Predictors of ovulatory failure included generalized idiopathic epilepsy syndrome, use of valproate currently or within 3 years, high concentrations of unbound testosterone, and fewer numbers of luteinizing hormone pulses, but not polycystic-like ovaries. However, the cross-sectional design of the study did not allow firm conclusions to be drawn, especially since previous antiepileptic drug exposure was not controlled.

The incidence of polycystic ovary syndrome in women taking antiepileptic drugs has been studied in a prospective cohort analysis of premenopausal women (aged 20–53 years) with focal epilepsy (132). Of 93 women, 38 were taking one antiepileptic drug (18 valproate, 20 carbamazepine), 36 were taking more than one drug, and 19 were taking no medications. Polycystic ovary syndrome was identified in two of the 19 patients taking no medication, four of the 38 patients taking monotherapy, and one of the patients taking more than one antiepileptic drug. The incidence of polycystic ovary syndrome in patients taking valproate monotherapy (11%) was similar to that in those taking carbamazepine (10%) and those not taking antiepileptic drugs (11%). These results suggest that polycystic ovary syndrome in women with focal epilepsy is not related to valproate or carbamazepine.

Women with valproate-associated obesity have high insulin concentrations and low concentrations of insulin-like growth factor-binding protein 1. These abnormalities might play a role in the pathogenesis of hyperandrogenism and polycystic ovaries in these women (133).

Immunologic

The anticonvulsant hypersensitivity syndrome is a potentially fatal reaction to arene oxide-producing anticonvulsants, such as phenytoin, carbamazepine, and phenobarbital (14,134). It occurs in 1 : 1000 to 1 : 10 000 exposures and its main manifestations include fever, rash, and lymphadenopathy, accompanied by multisystem abnormalities. Cross-reactivity among drugs is as high as 70–80%. The reaction may be genetically determined, and siblings of affected patients may be at increased risk. Management includes rapid withdrawal of the offending agent and care of conjunctival and skin lesions; the use of steroids is controversial, as is the value of cyclophosphamide and intravenous immunoglobulin (135). Early identification is essential for proper management, and it has been suggested that Bayesian analysis, especially when coupled with a lymphocyte toxicity assay, can improve the differential diagnosis (SEDA-19, 62).

- Within 5 days of being switched to valproate after developing a rash ascribed to carbamazepine, a 55-year-old man developed anticonvulsant hypersensitivity syndrome (maculopapular rash, fever, hepatitis, and eosinophilia) and ocular manifestations consistent with bilateral anterior uveitis (136).

Although mild conjunctivitis is common in the anticonvulsant hypersensitivity syndrome, uveitis has not been reported before in this context.

Death

A nested case-control study showed that the risk of sudden unexpected death in epilepsy (SUDEP) increases with increasing number of seizures, increasing numbers of drugs taken (with a relative risk of 9.89 for polytherapy with three drugs compared with monotherapy), and a high frequency of dosage changes (137). However, these data do not necessarily implicate a role of antiepileptic drugs in the pathogenesis of SUDEP: it is possible that polytherapy and frequent dosage changes are surrogate markers for the severity of the disease. On the other hand, a possible implication of carbamazepine in SUDEP was suggested in a separate survey by the observation that 11 of 14 patients who died suddenly (79%) were taking carbamazepine, while only 38% of patients in the same clinic were taking it (138). The effects of carbamazepine on heart function were discussed as a possible mechanism, but no comment was made on the possibility that the characteristics of patients taking carbamazepine may differ from those of patients taking other drugs.

Another study implicated nitrazepam as a possible cause of increased mortality (139). Among 294 assessable children who took nitrazepam, 62 continued treatment at the last time of follow-up. There were 1.98 deaths/100 patient-years during nitrazepam treatment compared with 0.58 deaths/100 patient-years after nitrazepam withdrawal (RR=3.4). The increase in risk occurred virtually entirely in younger children: among those aged under 3.4 years, the death rate per 100 patient-years was 3.98 on nitrazepam compared with 0.26 off nitrazepam (RR=15). Causes of death differed on and off nitrazepam. Of fourteen deaths during nitrazepam treatment, seven were sudden, six were due to pneumonia, and one was due to cystinosis: nine patients had at least one contributing factor, such as dysphagia, gastroesophageal reflux, or recurrent aspiration. In the off-nitrazepam period, there were two sudden deaths and one death each caused by status epilepticus, head trauma, and shunt complication; only one patient had a contributing factor (gastroesophageal reflux). These findings were interpreted as evidence that nitrazepam increases the risk of death in young children, possibly owing to its ability to increase secretions and to cause drooling, eating difficulties, and aspiration pneumonia (140,141). Although the data suggest a role of nitrazepam in these deaths, only incomplete information was given about the distribution of other risk factors (seizure disorder, associated

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morbidity) in children who continued nitrazepam therapy. Nitrazepam should be used with caution in young children, especially those with difficulties in swallowing, aspiration pneumonia, or gastroesophageal reflux.

The risk of sudden death associated with antiepileptic drugs has been assessed in a retrospective case-control study in 6880 patients with epilepsy, from whom 57 cases of sudden death and 171 controls (living with the patients with epilepsy) were selected (142). Polytherapy, frequent dosage changes, and high carbamazepine concentrations were identified as risk factors for sudden death, all pointing to risks associated with unstable severe epilepsy. Because the study was retrospective it is difficult to know whether antiepileptic drugs in themselves are associated with sudden death, of if the higher risk is a result of uncontrolled seizures.

Long-Term Effects

Drug withdrawal

Although it has been suggested that worsening of seizures after withdrawal of non-benzodiazepine anticonvulsants may reflect loss of efficacy rather than an abstinence phenomenon (143), rapid drug withdrawal can still result in dangerous loss of seizure control and status epilepticus.

Psychiatric pathology can also occur after rapid drug withdrawal. Of 32 patients withdrawn from all anticonvulsants before a drug trial, 12 developed moderate to severe psychopathology (especially anxiety and depression) and 9 dropped out because of psychiatric symptoms (144). These findings reinforce ethical concerns about some trial designs involving withdrawal of pre-existing therapy.

Epileptic negative myoclonus status (almost continuous lapses in muscle tone associated with epileptiform discharges and interfering with postural control and motor coordination) rarely occurs after rapid withdrawal of clobazam or valproate (145).

Nausea and vomiting have been listed as withdrawal effects of anticonvulsants (146).

Tumorigenicity

Pseudolymphoma and a condition resembling malignant lymphoma occur very rarely with phenytoin (SED-13, 142). There is no evidence of a significant increase in the incidence of other tumors. There have also been reports of pseudolymphoma with other antiepileptic drugs, including carbamazepine (147–149), lamotrigine (150), phenobarbital (151), and valproic acid (151).

Second-Generation Effects

Teratogenicity

The incidence of major congenital anomalies among babies born to epileptic women is about 6–8%, compared with 2–4% in the general population. Although the disease itself and social and environmental factors may play a role, these abnormalities are related to a large extent to the effects of antiepileptic drugs (152–154).

None of the major anticonvulsants (phenytoin, carbamazepine, valproate, and phenobarbital) is free from teratogenic potential, and there is no pattern of malformations that is specific for a given drug. However, facial clefts and congenital heart defects are somewhat more common with phenytoin and barbiturates, whereas neural tube defects are more common with valproic acid (23% risk) and carbamazepine (0.5–1% risk) (SEDA-16, 72). The risk of congenital anomalies increases with increasing dosages and the number of drugs taken by the mother (SED-12, 123); with valproate, neural tube defects have also been linked to high peak serum drug concentrations. There is preliminary evidence that certain drug combinations, particularly those that include valproic acid, may be more harmful than others. In one study, the combination of phenytoin, phenobarbital, carbamazepine, and valproate was associated with the highest risk (155). In a much smaller study, the risk and severity of meningomyelocele and dysmorphic features associated with valproate seemed to be greater where a benzodiazepine had also been taken (SEDA-18, 61).

In addition to major malformations, a number of mostly craniofacial dysmorphic features, notably growth retardation, microcephaly, and mental retardation have been described as comprising a fetal antiepileptic drug syndrome. This syndrome, originally ascribed only to hydantoins and at one time known as the fetal hydantoin syndrome, has been observed in children exposed to phenytoin, barbiturates, carbamazepine, and valproate. A broad range of signs is observed in at most 5–10% of children exposed to these drugs in utero, but individual signs (for example hypertelorism) are seen in as many as 52% and digital hypoplasia in 23%. Few results from controlled studies are available, and selection criteria and methods of ascertainment are very variable. In one study the association between prenatal phenytoin exposure and digital hypoplasia or hypertelorism was confirmed, but at the age of 5.5 years none of the exposed children had all of the main characteristics of the hydantoin syndrome. The risk of developmental disturbances seemed to be lower than the 7–11% risk of the fetal hydantoin syndrome reported earlier (SED-13, 136) (156).

The rate of congenital malformations in the offspring of 517 mothers exposed to antiepileptic drugs during pregnancy has been examined in a prospective single-center study (157). The overall malformation rate was 9.7%. Malformations were classified as structurally severe (5.3%), structurally mild (2.2%), chromosomal genetic (0.4%), and deformities (1.8%). The malformation rate after exposure to polytherapy (9.6%, $n = 114$) was not higher than after exposure to monotherapy (10.5%, $n = 313$). Among monotherapy exposures, the rates for structural abnormalities were 16% with valproate ($n = 44$), 8.6% with primidone ($n = 35$), 7.1% with carbamazepine ($n = 113$), 4.8% with phenobarbital ($n = 83$), and only 3.2% with phenytoin ($n = 31$). There were no malformations in the offspring of 25 untreated patients. Among women exposed to valproate, the mothers of malformed babies took significantly higher dosages in the first trimester than mothers of non-

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malformed babies (1712 versus 1008 mg/day). These data confirm that exposure to antiepileptic drugs is associated with an increased risk of fetal malformations, and that the risk may be especially high with high-dose valproate. However, these subgroup analyses should be interpreted cautiously, especially because the numbers were small and the confidence intervals were not calculated.

In a retrospective Dutch study, the rate of major congenital anomalies among 1411 children born of mothers who had taken antiepileptic drugs during the first trimester of pregnancy was 3.7% compared with 1.5% among 2000 children born of matched controls not exposed to anticonvulsants (158). Among monotherapies with a denominator higher than 50, the relative risk (RR) was increased significantly only for carbamazepine (RR = 2.6) and valproate (RR = 4.1); for valproate there was a relation with dose. Although the risk was not increased in offspring exposed to phenobarbital monotherapy, it increased significantly (RR = 2.6) when those exposed to phenobarbital plus caffeine were combined with those who were exposed to phenobarbital alone. Caffeine intake was also associated with an increased risk among exposures to phenobarbital in combination with other anticonvulsants. Among other polytherapies, there was an increased risk for combinations that included clonazepam and for the combination of carbamazepine with valproate. Cautious interpretation of these data is required, because of the retrospective design and the small sample sizes in the subgroup analyses.

The teratogenic effects of antiepileptic drugs have been assessed through the use of a surveillance system (MADRE) in infants with malformations (159). Exposure was defined by the use of antiepileptic drugs during the first trimester of pregnancy. Of 8005 cases of malformations, 299 infants had been exposed in utero to antiepileptic drugs. Of those exposed to monotherapy, 46 were exposed to carbamazepine, 10 to methylphenobarbital, 65 to phenobarbital, 24 to phenytoin, 80 to valproic acid, and 16 to other antiepileptic drugs. The following associations were found:

(a) carbamazepine: cardiac malformations;
(b) methylphenobarbital: oral clefts and cardiac malformations;
(c) phenobarbital: oral clefts and cardiac malformations;
(d) valproate: spina bifida, cardiac malformations, hypospadias, porencephaly, and other specified anomalies of the brain, anomalies of the face, coarctation of the aorta, and limb reduction defects.

Three groups of infants born to 128 049 women were identified at time of delivery: those exposed to anticonvulsant drugs, those unexposed to anticonvulsant drugs but with a maternal history of seizures, and those unexposed to anticonvulsant drugs with no maternal history of seizures (controls) (160). The aim was to determine whether the major malformations associated with antiepileptic drugs are related to maternal epilepsy or exposure to anticonvulsant drugs. The infants were examined systematically for major malformations, signs of hypoplasia of the midface and fingers, microcephaly, and small body size. The combined frequency of anticonvulsant embryopathy was higher in 223 infants exposed to one anticonvulsant drug than in 508 controls (21 versus 8.5%; OR=2.8; 95% CI=1.1, 9.7). The frequency of anticonvulsant embryopathy was also higher in 93 infants exposed to two or more anticonvulsant drugs than in controls (28 versus 8.5%; OR=4.2; 95% CI=1.1, 5.1). The 98 infants whose mothers had a history of epilepsy but took no anticonvulsant drugs during the pregnancy did not have a higher frequency of malformations than the control infants. Thus, fetal malformations in women with epilepsy are associated with the drugs rather than the epilepsy.

The developmental outcome in children of women exposed to antiepileptic drugs has been assessed in a retrospective survey that included 150 women on monotherapy, 74 on polytherapy, and 176 not exposed to any antiepileptic drugs (161). The odds ratio of additional educational needs in children exposed to antiepileptic drugs in utero compared with those not exposed was 1.49 (95% CI=0.83, 2.67). Those exposed to valproate monotherapy had an odds ratio of 3.4 (95% CI=1.63, 7.10), significantly higher than in those exposed to carbamazepine (OR=0.26; 95% CI=0.06, 1.15). Although the authors concluded that valproate during pregnancy impairs development in children exposed in utero, the fact that this was a retrospective study means that firm conclusions are not possible.

In a prospective study of electroencephalograms, intelligence tests (Wechsler), and neurological findings (Touwen) in 67 school-age and adolescent children born to mothers with epilepsy (risk group) and in 49 controls, focal electroencephalographic changes were more common in the offspring of mothers with primary generalized epilepsy, and pathological electroencephalograms were overall more common after maternal exposure to phenobarbital or primidone (162). The prevalence of minor neurological dysfunction was also increased in the risk group, especially in the offspring of mothers who had been exposed to polytherapy. Intelligence scores were lower after maternal exposure to polytherapies in which one of the drugs was phenytoin or primidone, but socioeconomic influences also affected the scores. Higher maternal dosages of primidone were associated with lower IQ scores in the children. This study has reinforced the evidence that antenatal exposure to anticonvulsants can adversely affect postnatal intellectual development. However, it is always difficult to control for confounders, such as hereditary and social and family factors. It is also possible that prenatal drug exposure affects neural vulnerability to external influences.

A case-control study in 116 children born to epileptic women has suggested that for subjects without inherited factors the risk of developmental disorders is related to antenatal exposure to polypharmacy (OR=4.8, 95% CI=1.3, 18) and valproate monotherapy (OR = 9.4, 95% CI = 1.7, 50) (163). The findings were presented in abstract form, precluding close scrutiny of methodological aspects.

The possibility has been raised that a child who is seemingly normal at birth might later show impaired physical and/or mental development as a result of prenatal exposure to the effects of seizures or drugs. In one study, there was a correlation between seizures during pregnancy and impaired cognitive ability and psychomotor function in the child (SEDA-16, 70). In another study there were delays in height and weight gain in the

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offspring of epileptic mothers after the first month, but weight at 5.5 years of age was not affected (SED-13, 137). There was a reduction in mean head circumference without obvious intellectual impairment in children exposed to monotherapy with carbamazepine and barbiturates, but a low parental mean head circumference was a major confounding factor. In another study (164), children exposed to phenytoin in utero had lower language development scores and mean global IQ scores 10 points lower than matched controls exposed to non-teratogens; in contrast, children exposed prenatally to carbamazepine did not differ from controls. However, the validity of the statistical analysis and the comparability of groups in this study have been questioned.

Barbiturates have been most often implicated in detrimental effects on postnatal mental development. In two double-blind studies in 114 adult men exposed prenatally to phenobarbital, verbal intelligence scores were about 0.5 standard deviations lower than predicted from data in 153 matched controls (165). An exposure period that included the last trimester of pregnancy was most detrimental. Lower socioeconomic status and being the offspring of an unwanted pregnancy increased the magnitude of impairment, suggesting that adverse drug effects are magnified by interactions with environmental conditions.

Overall, the available evidence suggests that the incidence of mental deficiency in children of epileptic mothers is similar to that in the general population, although general intelligence may be lower and specific forms of cognitive dysfunction somewhat more frequent, owing to a combination of factors such as prenatal exposure to certain drugs, genetic influences, and postnatal environment.

Mechanisms

The mechanisms responsible for abnormal embryonic and fetal development in women taking antiepileptic drugs are unclear. There may be an interaction between the drugs and the underlying disease, and research has also focused on drug-induced folate or pantothenic acid deficiency, altered retinoid metabolism (SEDA-20, 59), and tissue damage caused by reactive metabolites or by embryonic hypoxia/reoxygenation. There is evidence that a genetic defect in arene oxide detoxification can increase the risk of birth defects, and epoxide hydrolase might prove useful in identifying probands at greater risk (SED-13, 137) (166).

Of the newer anticonvulsants, lamotrigine, gabapentin, tiagabine, and vigabatrin have little or no teratogenic potential in animals, whereas oxcarbazepine and topiramate are teratogenic in rodents. However, animal studies are not necessarily applicable to humans and clinical data are still insufficient to assess the effects of newer drugs on the development of the human fetus (153).

Management

Current guidelines stress the need for expert counseling, preferably before conception. Comprehensive management should include review of genetic risks, advice about contraception and interactions with oral contraceptives, information on teratogenic risks and methods for prenatal diagnosis, and integrated care by the family doctor, epileptologist, gynecologist, geneticist, and pediatrician (52,167).

Whenever possible, therapy should be optimized before pregnancy. Withdrawal of anticonvulsants can be considered after 2–5 years of seizure freedom, when other prognostic factors indicate little risk for recurrence; in that event, withdrawal should be completed at least 6 months before planning conception. In all other patients, the goal is the minimal drug load associated with acceptable seizure control. This involves selecting the most effective medication, preferably as monotherapy, at the lowest effective dosage. Control of tonic-clonic seizures before pregnancy is especially important. If possible, valproate should be avoided, especially in women with a family history of neural tube defects and in those who may object to early termination of pregnancy if a severe fetal defect should be diagnosed prenatally. If valproate is used, it should be given in two or three divided daily doses, preferably as a modified-release formulation, to minimize fluctuations in serum drug concentrations. Tobacco and alcohol should be avoided (52,167). Folate supplementation has been recommended in all women with epilepsy who plan to become pregnant and should be continued until the twelfth week of gestation. Although there is no consensus about optimal dosage, 0.4 mg/day of folic acid is a reasonable option; a larger dose (4 mg/day) is preferable if the woman has previously given birth to a child with a neural tube defect. Some authors also recommend 4 mg/day in women taking valproate or carbamazepine (168).

Because seizures themselves can adversely affect fetal outcome, and because in most patients any serious teratogenic effect will have occurred by the time pregnancy is diagnosed, changes in drug therapy during pregnancy are not recommended unless they are required by a change in the clinical response. If seizure frequency increases during pregnancy, possible non-compliance and changes in plasma drug concentration need to be considered.

Prenatal diagnosis with ultrasound at weeks 18–20 can assist in the early diagnosis of anomalies such as cleft palate, heart defects, and neural tube defects. In many patients, prenatal assessment of fetal development can be based on a combination of maternal serum alpha-fetoprotein (as screening for neural tube defect) and malformation-directed ultrasonography. Although amniocentesis at week 15–16 for alpha-fetoprotein determination can be considered for patients at high risk of neural tube defect, it carries a small risk of abortion and its use has fallen with advances in ultrasonography (including transvaginal ultrasonography).

Fetotoxicity

Contrary to early reports, which were affected by selection bias, later studies suggested that neither epilepsy nor prenatal exposure to antiepileptic drugs is associated with an increased risk of spontaneous abortion or other obstetric complications (169).

Prenatal exposure to enzyme-inducing anticonvulsants entails a risk of serious neonatal hemorrhage in the first few days after birth. To reduce the risk, some authorities recommend that pregnant women taking enzyme-inducing

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drugs be given vitamin K (20 mg/day) during the last month of pregnancy. Intramuscular vitamin K (1 mg) should be given to the neonate immediately after birth. The value of additional vitamin K orally for the first 3 months of life is controversial (168).

After delivery, the maternal response to drug treatment and, if appropriate, serum drug concentrations should be monitored, because the disposition of anticonvulsants can change. The neonate should be monitored for potential residual effects of transplacentally acquired anticonvulsants and, in the case of barbiturates and benzodiazepines, withdrawal symptoms such as irritability and feeding difficulties.

Lactation

Most anticonvulsants are excreted in the breast milk in limited amounts, and their use is not generally a contraindication to breastfeeding. Barbiturates, ethosuximide, lamotrigine, and to a lesser extent carbamazepine and benzodiazepines can reach appreciable serum concentrations in breast-fed infants, who should be carefully observed.

Susceptibility Factors

Age

Children

Febrile seizures are the most common seizure disorder in childhood, occurring in 2–5% of children, but there is no unanimity regarding the need for long-term antiepileptic drug therapy. A subcommittee of the American Academy of Pediatrics has recently concluded that there are no long-term adverse effects of simple febrile seizures, and that although there is evidence that continuous antiepileptic therapy with phenobarbital or valproate and intermittent therapy with diazepam are effective in reducing the risk of recurrence, the potential adverse effects associated with antiepileptic drugs outweigh the relatively minor risks associated with simple febrile seizures (170). They recommended that long-term treatment is not indicated.

Renal disease

Renally eliminated drugs should be used in reduced dosages in patients with renal insufficiency.

Hepatic disease

Anticonvulsants that are metabolized should be used cautiously in patients with severe hepatic disease.

Other features of the patient

Most antiepileptic drugs are contraindicated in acute intermittent porphyrias.

Case reports have suggested that the risk of serious skin reactions to phenytoin is increased in patients with brain tumors undergoing cranial irradiation, but the incidence of these reactions is unknown (113). In a retrospective study of 289 patients with brain tumors, rash occurred in 18% of exposures to antiepileptic drugs, including 22% of exposures to phenytoin, compared with an expected rate of 5–10%. Most of the rashes occurred before the start of irradiation therapy. Only one patient developed erythema multiforme. These data suggest that the risk of serious skin reactions in patients with brain tumors is actually low, even though there was an increased frequency of milder rashes. Irradiation did not appear to contribute to the risk. However, it is possible that earlier publications about the risk of serious reactions resulted in the use of lower initial dosages or earlier withdrawal of medication, before the onset of more severe manifestations. The fact that skin rashes were more common in patients with glioma than metastatic disease could be related to the effects of underlying treatments (or disease) on immune function.

Of 65 consecutive patients with malignant glioma started on anticonvulsants (mostly phenytoin), a skin rash developed in 26%; other toxic effects occurred in 14% of patients, including three who developed an encephalopathy sufficient to require hospitalization (SEDA-20, 58).

Drug Administration

Drug formulations

The rationale and use of modified-release formulations of antiepileptic drugs (carbamazepine, valproic acid, and tiagabine) have been reviewed (171). The authors concluded that modified-release formulations afford the advantages of better patient compliance, fewer adverse effects, and less fluctuation in plasma concentrations, making monitoring of drug concentrations easier. They concluded that these advantages should lead to better seizure control and improved quality of life.

Drug overdose

Accidental or deliberate overdose with anticonvulsants is common and can cause serious morbidity, even though deaths are relatively rare (172–174). Clinical manifestations vary from drug to drug, and they tend to affect mainly the central nervous system, with signs ranging from impaired consciousness to motor and coordination disturbances and seizures (for a review, see SEDA-22, 84). Metabolic, cardiac, and respiratory disturbances are seen with individual drugs. Except for flumazenil in benzodiazepine overdose, there are no specific antidotes, and management is primarily supportive. Gastric lavage is indicated within 1 hour of a major overdose with most anticonvulsants. Oral activated charcoal and hemoperfusion can be useful in individual cases of overdose with phenytoin, carbamazepine, valproate, barbiturates, and some other drugs (SEDA-22, 84). In cases of valproate overdose, naloxone has been sometimes beneficial, and carnitine supplementation has been recommended (88).

Drug–Drug Interactions

General

The interactions of anticonvulsants are summarized in Table 2, Table 3, and Table 4. Phenytoin, carbamazepine, and barbiturates are enzyme inducers and can reduce the

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Table 2 Interactions of antiepileptic drugs

Interfering drug(s) (precipitant drug(s))	Affected drug(s) (object drug(s))	Implications/comments	Mechanism
Carbamazepine	Phenytoin	Interaction inconsistent and usually of limited clinical significance	Induction and inhibition of phenytoin metabolism
Carbamazepine Phenobarbital Phenytoin Primidone	Ethosuximide Felbamate Lamotrigine Tiagabide Topiramate Valproate Zonisamide Clobazam Clonazepam Diazepam	Reduced effect of the object drug, usually compensated by the effect of the added drug; risk of toxicity when interfering drug is discontinued	Induction of metabolism of the object drug
Carbamazepine Phenytoin	Primidone	Signs of toxicity possible after addition of phenytoin owing to concomitant increase in plasma phenobarbital concentrations in some patients	Induction of primidone metabolism; phenytoin may inhibit the clearance of metabolically derived phenobarbital
Clobazam	Carbamazepine Primidone Valproate Phenytoin	Interaction inconsistent, usually of little clinical significance	Inhibition of metabolism of the object drug
Clobazam	Phenytoin Primidone	Interaction inconsistent, usually of no clinical significance	Unknown
Diazepam	Phenytoin	Interaction inconsistent, usually of no clinical significance	Inhibition of phenytoin metabolism
Ethosuximide	Valproate	Fall in valproate concentrations inconsistent; therapeutic synergism common	Therapeutic synergism due to pharmacodynamic interaction
Felbamate	Clonazepam Diazepam Phenobarbital Phenytoin Valproate	High risk of toxicity with phenytoin, phenobarbital, and valproate	Inhibition of metabolism of the affected drug
Felbamate	Carbamazepine	Risk of toxicity due to concomitant rise in carbamazepine epoxide concentration and pharmacodynamic interaction	Induction of carbamazepine metabolism, possible inhibition of epoxide hydrolase and pharmacodynamic interaction
Gabapentin	Felbamate	Interaction poorly documented; relevance doubtful	Perhaps reduced renal clearance of felbamate
Gamma-vinyl GABA	Phenytoin Phenobarbital Felbamate	Interaction inconsistent and usually of little clinical relevance	Unknown
Oxcarbazepine	Lamotrigine	Interaction less marked than that caused by carbamazepine	Induction of lamotrigine metabolism
Phenobarbital	Phenytoin	Interaction inconsistent and usually of little clinical significance	Induction and inhibition of phenytoin metabolism
Phenobarbital Phenytoin Primidone	Carbamazepine	Reduced effect of carbamazepine usually compensated by the action of the added drug; risk of carbamazepine toxicity when interfering drug is withdrawn	Induction of carbamazepine metabolism
Phenytoin	Phenobarbital	Interaction inconsistent and usually of limited clinical significance	Inhibition of phenobarbital metabolism
Tiagabide	Valproate	Effect of low magnitude, probably clinically irrelevant	Unknown
Topiramate	Phenytoin	Interaction inconsistent, usually of little clinical significance	Inhibition of phenytoin metabolism

Continued

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Table 2 *Continued*

Interfering drug (precipitant drug(s))	Affected drug(s) (object drug(s))	Implications/comments	Mechanism
Valproate	Carbamazepine epoxide Diazepam Felbamate Lamotrigine Phenobarbital	Risk of toxicity, particularly with phenobarbital including primidone-derived phenobarbital and lamotrigine	Inhibition of metabolism of the affected drug. Valproate also displaces diazepam from protein binding sites, affecting relation between total diazepam concentration and effect
Valproate	Ethosuximide	Increase in ethosuximide concentration inconsistent; synergistic therapeutic effect common	Inhibition of ethosuximide metabolism; therapeutic synergism due to pharmacodynamic interaction
Valproate	Lamotrigine	Risk of toxicity; therapeutic synergism possible	Inhibition of lamotrigine metabolism and pharmacodynamic interaction
Valproate	Phenytoin	Total serum phenytoin concentration underestimates the unbound phenytoin concentration; toxicity can occur in some patients	Displacement of phenytoin from plasma proteins, sometimes associated with inhibition of phenytoin metabolism
Valproate	Tiagabine	Interaction described in vivo remains to be clarified	Valproate displaces tiagabine from plasma binding sites in vitro
Valproate	Topiramate	Effect of low magnitude, clinically irrelevant	Unknown

Table 3 Interactions in which the serum concentration of an antiepileptic drug is modified by drugs used for other conditions

Interfering drug (precipitant drug(s))	Affected drug(s) (object drug(s))	Implications/comments	Mechanism
Analgesics			
Azapropazone	Phenytoin	Risk of phenytoin toxicity; altered relation between total phenytoin concentration and effect	Displacement from plasma proteins and inhibition of phenytoin metabolism
Bromfenac	Phenytoin	Probably of little clinical significance	Inhibition of phenytoin metabolism
Dextropropoxyphene	Carbamazepine Phenobarbital Phenytoin	Risk of toxicity, particularly with carbamazepine	Inhibition of metabolism of the affected drugs
Ibuprofen	Phenytoin	Interaction probably of little or no clinical significance	Displacement from plasma protein binding sites
Naproxen	Valproate	Interaction of little or no clinical significance	Displacement from plasma protein binding sites
Paracetamol	Lamotrigine	Interaction probably of little or no clinical significance	Unknown
Phenylbutazone	Phenytoin Valproate	Risk of toxicity, particularly with phenytoin; altered relation between total concentration and effect	Displacement from plasma protein binding sites and inhibition of metabolism of the affected drugs
Salicylic acid	Phenytoin Valproate	Altered relation between total anticonvulsant concentration and effect*	Displacement from plasma protein binding sites
Tenidap sodium	Phenytoin	Interaction poorly documented	Displacement from plasma protein binding sites
Antineoplastic drugs			
Bleomycin	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Carboplatin	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Carmustine	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Cisplatin	Carbamazepine Phenytoin Valproate	Reduced effect of phenytoin; interaction poorly documented	Unknown
Methotrexate	Phenytoin Valproate	Reduced effect of phenytoin; interaction poorly documented	Unknown

Continued

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Table 3 *Continued*

Interfering drug (precipitant drug(s))	Affected drug(s) (object drug(s))	Implications/comments	Mechanism
Vinblastine	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Vincristine	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Tegafur uracil	Phenytoin	Risk of phenytoin toxicity	Unknown
Antimicrobial drugs			
Aciclovir	Phenytoin Valproate	Reduced effect of the object drug; poorly documented	Unknown
Ceftriaxone	Phenytoin	Risk of toxicity; altered relation between total phenytoin concentration and effect	Displacement of phenytoin from binding sites and possible inhibition phenytoin metabolism
Chloramphenicol	Phenobarbital Phenytoin Primidone	Risk of toxicity of the object drugs	Inhibition of metabolism of the object drugs
Ciprofloxacin	Phenytoin	Reduced effect of phenytoin	Unknown
Fluconazole	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Isoniazid	Carbamazepine Diazepam Ethosuximide Phenobarbital Phenytoin Primidone Valproate	High risk of toxicity, especially with carbamazepine and phenytoin	Inhibition of metabolism of the object drugs
Ketoconazole	Carbamazepine Zonisamide	Risk of toxicity of the affected drugs	Inhibition of metabolism of the affected drugs
Erythromycin	Carbamazepine Phenytoin Valproate	Risk of toxicity; particularly with carbamazepine	Inhibition of metabolism of the affected drugs
Other macrolides (clarithromycin, flurithromycin, josamycin, ponsinomycin, triacetyloleandomycin)	Carbamazepine	High risk of carbamazepine toxicity	Inhibition of carbamazepine metabolism
Mefloquine	Valproate	Reduced effect of valproate; interaction poorly documented	Unknown
Metronidazole	Carbamazepine Phenytoin	Risk of toxicity; effect on phenytoin inconsistent	Inhibition of metabolism of the object drugs
Miconazole	Phenytoin Zonisamide	Risk of toxicity of the object drugs	Inhibition of metabolism of the object drugs
Nafcillin	Phenytoin	Altered relation between total phenytoin concentration and effect	Displacement of phenytoin from binding sites
Nitrofurantoin	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Oxacillin	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Panipenem-betamipron	Valproate	Reduced effect of valproate; interaction poorly documented	Unknown
Quinine	Carbamazepine Phenobarbital	Enhanced effect of the object drugs	Inhibition of metabolism of the object drugs
Rifampicin	Diazepam Ethosuximide Phenobarbital Phenytoin Valproate	Reduced effect of the object drugs	Induction of metabolism of the object drugs
Sulfadiazine	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Sulfafurazole	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Sulfamethoxazole	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Sulfamethoxazole + trimethoprim (co-trimoxazole)	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism

Continued

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Table 3 *Continued*

Interfering drug (precipitant drug(s))	Affected drug(s) (object drug(s))	Implications/comments	Mechanism
Sulfamethoxypyridazine	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Sulfametizole	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Sulfaphenazole	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Trimethoprim	Phenytoin	Enhanced effect of phenytoin	Inhibition of phenytoin metabolism
Antiulcer agents			
Antacids	Gabapentin Phenobarbital Phenytoin	Reduced effect of the object drugs	Reduced absorption of the object drugs
Cimetidine	Carbamazepine Clobazam Clonazepam Diazepam Phenytoin Valproate	Risk of toxicity, particularly with phenytoin	Inhibition of metabolism of the object drugs
Omeprazole	Diazepam Phenytoin	Risk of toxicity of the object drugs	Inhibition of metabolism of the object drugs
Ranitidine	Phenytoin	Inconsistent, probably of little clinical significance	Unknown
Sucralfate	Phenytoin	Reduced effect of phenytoin	Reduced absorption of phenytoin
Cardiovascular			
Amiodarone	Clonazepam Phenytoin	Risk of toxicity of the object drugs	Inhibition of metabolism of the object drugs
Bishydroxycoumarin	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Dicoumarol	Phenobarbital Phenytoin	Risk of toxicity, particularly with phenytoin	Inhibition of metabolism of the object drugs
Diltiazem	Carbamazepine Phenytoin	Risk of toxicity, especially with carbamazepine	Inhibition of metabolism of the object drugs
Guanfacine	Valproate	Enhanced effect of valproate; interaction poorly documented	Unknown
Phenprocoumon	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Sulfinpyrazone	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Ticlopidine	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Verapamil	Carbamazepine Phenytoin	High risk of carbamazepine toxicity; interaction with phenytoin inconsistent	Inhibition of metabolism of the object drugs
Verapamil	10-monohydroxy–carbazepine	Interaction probably of limited clinical significance	Unknown
Psychotropic drugs			
Amitriptyline	Phenytoin	Risk of phenytoin toxicity; interaction poorly documented	Inhibition of phenytoin metabolism
Chlorpromazine	Phenobarbital Phenytoin Valproate	Probably of little clinical relevance; for phenytoin, a fall in concentration has also been reported	Inhibition of metabolism of the object drugs
Ethanol	Clobazam Diazepam Phenytoin	Risk of toxicity of the object drugs; chronic ethanol can reduce serum phenytoin concentrations	Inhibition of metabolism; induction of phenytoin metabolism by chronic ethanol
Fluoxetine	Carbamazepine Diazepam Phenytoin Valproate	Risk of toxicity of the object drugs; with carbamazepine and valproate, interaction inconsistent	Inhibition of metabolism of the object drugs
Fluvoxamine	Carbamazepine Diazepam Phenytoin	Risk of toxicity of the affected drugs; with carbamazepine, interaction inconsistent	Inhibition of metabolism of the object drugs
Haloperidol	Carbamazepine	Risk of carbamazepine toxicity	Inhibition of metabolism of the object drugs
Imipramine	Phenytoin	Risk of phenytoin toxicity; interaction inconsistent	Inhibition of phenytoin metabolism
Loxapine	Carbamazepine	Risk of carbamazepine toxicity; interaction poorly documented	Unknown
Mesoridazine	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown
Methylphenidate	Phenytoin Primidone	Risk of toxicity of the affected drugs; interaction inconsistent	Inhibition of metabolism of the object drugs

Continued

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Table 3 *Continued*

Interfering drug (precipitant drug(s))	Affected drug(s) (object drug(s))	Implications/comments	Mechanism
Nefazodone	Carbamazepine	Risk of carbamazepine toxicity; interaction poorly documented	Inhibition of Carbamazepine metabolism
Sertraline	Carbamazepine Diazepam Lamotrigine Phenytoin	Risk of toxicity of the object drugs	Inhibition of metabolism of the object drugs
Thioridazine	Phenobarbital Phenytoin	Probably of little clinical relevance; an increase in serum phenytoin has also been described	Unknown
Trazodone	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Valnoctamide	Carbamazepine	Risk of carbamazepine toxicity	Inhibition of epoxide hydrolase
Viloxazine	Carbamazepine Phenytoin Oxcarbazepine	Risk of phenytoin and carbamazepine toxicity; interaction with oxcarbazepine probably of little clinical significance	Inhibition of metabolism of the object drugs
Miscellaneous			
Acetazolamide	Phenobarbital	Interaction probably of little clinical significance	Unknown
Acetazolamide	Primidone	Interaction probably of little clinical significance	Possibly reduced absorption of primidone
Activated charcoal	Carbamazepine Lamotrigine Phenobarbital Phenytoin Valproate	With some drugs can be exploited to reduce drug concentrations in overdose	Sequestration in the gastrointestinal tract
Allopurinol	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Aminophylline	Carbamazepine	Reduced effect of carbamazepine; interaction poorly documented	Unknown
Caffeine	Carbamazepine	Reduced effect of carbamazepine; interaction poorly documented	Unknown
Calcium carbide	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Chlorphenamine	Phenytoin	Risk of phenytoin toxicity	Inhibition of phenytoin metabolism
Colestyramine	Valproate	Interaction probably of little clinical significance	Reduced absorption of valproate
Danazol	Carbamazepine	Risk of carbamazepine toxicity	Inhibition of carbamazepine metabolism
Dexamethasone	Phenytoin	Interaction inconsistent	Unknown
Diazoxide	Phenytoin	Altered relation between total phenytoin concentration and effect	Displacement from plasma protein binding sites
Disulfiram	Diazepam Phenytoin	Risk of toxicity, particularly with phenytoin	Inhibition of metabolism of the object drugs
Enteral feeding formulas (some)	Phenytoin	Reduced effect of phenytoin	Reduced absorption of Phenytoin
Folic acid	Phenobarbital Phenytoin	Reduced effect of the object drug	Accelerated metabolism of the object drugs
Grapefruit juice	Carbamazepine Phenytoin unbound fraction	Risk of carbamazepine toxicity	Inhibition of carbamazepine metabolism
Halofenate	Phenytoin unbound fraction	Altered relation between total phenytoin concentration and effect	Displacement from plasma protein binding sites
Influenza vaccine	Carbamazepine Phenobarbital Phenytoin	Risk of toxicity of the affected drugs; effect on phenytoin inconsistent	Inhibition of metabolism of the object drugs
Nicotinamide	Carbamazepine Primidone	Risk of toxicity of the object drugs	Inhibition of metabolism of the object drugs
Fenyramidol	Phenytoin	Risk of phenytoin toxicity; interaction poorly documented	Unknown
Tacrolimus	Phenytoin	Risk of phenytoin toxicity	Unknown
Tamoxifen	Phenytoin	Risk of phenytoin toxicity	Unknown
Theophylline	Phenytoin	Reduced effect of phenytoin; interaction poorly documented	Unknown

Continued

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Table 3 *Continued*

Interfering drug (precipitant drug(s))	Affected drug(s) (object drug(s))	Implications/comments	Mechanism
Tolbutamide	Phenytoin	Risk of toxicity; altered relation between total phenytoin concentration and effect	Displacement from plasma protein binding sites and possibly inhibition of phenytoin metabolism

*Inconclusive evidence suggests that salicylic acid can potentiate valproate toxicity (mechanism unclear). Sulfafurazole, sulfamethoxypyridazine, possibly other sulfonamides, and sulfinpyrazone displace phenytoin from plasma protein binding sites with different affinities; total phenytoin concentrations may underestimate the concentration of unbound (pharmacologically active) drug.

Table 4 Drugs that inhibit the metabolism of antiepileptic drugs and cause intoxication

Analgesics
Bromfenac
Codeine
Dextropropoxyphene
Methadone
Paracetamol
Pethidine
Phenazone
Phenylbutazone

Anticoagulants
Dicoumarol[1]
Warfarin

Antineoplastic drugs
Aminocamptothecin
Busulfan
Cyclophosphamide
Etoposide
Ifosfamide
Methotrexate[2]
Teniposide
Topotecan
Vincristine

Antimicrobial drugs
Chloramphenicol
Delavirdine
Doxycycline
Griseofulvin[3]
Indinavir
Itraconazole
Ketoconazole
Mebendazole
Metronidazole
Misonidazole
Nelfinavir
Praziquantel
Ritonavir
Saquinavir

Cardiovascular drugs
Alprenolol
Amiodarone
Digitoxin[4]
Digoxin[5]
Disopyramide
Felodipine
Flunarizine
Lidocaine
Metoprolol
Mexiletine
Nifedipine
Nimodipine
Nisoldipine
Propranolol
Quinidine
Timolol

Glucocorticoids
Dexamethasone
Fludrocortisone
Methylprednisolone
Prednisolone
Prednisone

Immunosuppressants
Ciclosporin[6]
Tacrolimus

Neuromuscular blockers[7]
Atracurium
Metocurine
Oxacurium
Pancuronium
Pipecuronium
Rocuronium
Vecuronium

Oral contraceptives[8]

Psychotropic drugs
Alprazolam
Amfebutamone
Amitriptyline
Amoxapine
Bromperidol
Chlorpromazine
Citalopram
Clozapine
Desipramine
Doxepin
Haloperidol
Imipramine
Mesoridazine
Mianserin
Midazolam
Nefazodone
Nortriptyline
Olanzapine
Paroxetine
Protriptyline
Thioridazine[9]
Trazodone
Valnoctamide
Zotepine

Miscellaneous
Chenodeoxycholic acid
Cimetidine
Ethanol
Etretinate
Fentanyl
Folic acid
Furosemide[10]
Metyrapone
Omeprazole
Psoralens
Theophylline
Thyroxine
Tirilazad
Vitamin D analogues

[1] In addition to enzyme induction, phenobarbital can reduce dicoumarol absorption.
[2] Interaction seen only with phenytoin and mediated by displacement from plasma protein binding sites; no reduction in methotrexate activity is expected; the relation between total methotrexate concentration and effect can be altered.
[3] Some anticonvulsants can reduce griseofulvin absorption.
[4] The evidence is conflicting.
[5] In addition to enzyme induction, phenytoin can reduce digoxin absorption.
[6] With phenytoin, reduced absorption can contribute to the fall in ciclosporin concentrations.
[7] A pharmacodynamic interaction may contribute to the reduced effect of neuromuscular blocking drugs.
[8] Carbamazepine, phenytoin, phenobarbital and primidone, felbamate, oxcarbazepine, and topiramate stimulate the metabolism of oral contraceptive steroids.
[9] The concentration of the active metabolite mesoridazine falls more markedly.
[10] Phenytoin and phenobarbital reduce furosemide absorption.

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serum concentrations and clinical effects of other anticonvulsants (valproate, carbamazepine itself, including autoinduction, ethosuximide, felbamate, lamotrigine, topiramate, tiagabine, zonisamide, benzodiazepines) and a large number of other drugs that are metabolized by inducible enzymes. Examples of affected agents include oral anticoagulants, glucocorticoids, dihydropyridine calcium channel blockers and other cardioactive drugs, neuroleptic drugs, antimicrobial drugs including antiretroviral drugs, and steroid oral contraceptives. The efficacy of the contraceptive pill can also be reduced by the weaker inducers of CYP3A4, oxcarbazepine, felbamate, and topiramate.

On the other hand, felbamate and to a lesser extent valproate inhibit a range of liver enzymes and can increase the concentration of several drugs, leading to potentiation of their effects.

Similarly, drugs given for the treatment of associated disorders may inhibit the metabolism of anticonvulsants and precipitate signs of intoxication (Table 3). Examples include the increase in serum phenytoin concentrations by isoniazid and the increase in serum carbamazepine concentrations by verapamil, diltiazem, and most macrolide antibiotics (175–179).

Plasma protein binding interactions are usually clinically unimportant, but they should be recognized, because they alter the relation between serum drug concentration and the clinical response: if displacement occurs, therapeutic and toxic effects are reached at a total drug concentration lower than usual. For example, valproic acid and salicylate displace phenytoin from plasma proteins; this usually results in a fall in total phenytoin concentration without any change in the concentration of unbound (pharmacologically active) phenytoin.

Pharmacodynamic interactions also occur. In particular, the adverse effects of any drug can be increased by other drugs with similar properties. One example is the reciprocal potentiation of the neurotoxic effects of carbamazepine and lamotrigine in patients taking a combination of these drugs (180). Some drugs (for example ciclosporin, clozapine) have a proconvulsant effect and can reduce the efficacy of antiepileptic drugs.

Cisatracurium

The effect of cisatracurium on the onset, duration, and speed of recovery from neuromuscular blockade has been studied in 24 patients taking antiepileptic drugs and 14 controls (181). The onset and duration of neuromuscular blockade were not different among the groups, but the speed of recovery was significantly faster in those taking antiepileptic drugs.

Steroid neuromuscular blockers

Patients taking carbamazepine or phenytoin are resistant to steroid neuromuscular blocking drugs (181).

Diagnosis of Adverse Drug Reactions

The routine drug management of epilepsy by community health nurses without prior training in epilepsy management has been evaluated by neurologists in Zimbabwe (182). Of 114 patients (aged 8–56 years, 84% with generalized seizures), 40% had been seizure-free for at least 6 months; 72% took phenobarbital, 36% took carbamazepine, and 20% took phenytoin; 68% took monotherapy. Specialist interventions were required in 60% of consultations. Serum drug concentrations were measured in 38 patients; 58% were below the target range and 16% were above. Increased dosage was required in 29% of patients and dosage reduction or withdrawal in 18%. In several cases drug withdrawal was undertaken to convert polytherapy to monotherapy.

The use of serum antiepileptic drug concentrations has been reviewed (183). The authors suggested that there is still no evidence that specific target drug concentrations are valid in determining appropriate therapy.

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Antifungal azoles

See also Individual agents

General Information

The antifungal azoles are a class of synthetic compounds that have one or more azole rings and a more or less complex side chain attached to one of the nitrogen atoms. They are either imidazole or triazole derivatives. The imidazoles miconazole and ketoconazole were the first azoles developed for systemic treatment of human mycoses. However, severe adverse effects associated with the drug carrier (in the case of miconazole) and erratic absorption and significant interference with cytochrome P450 isozymes (in the case of ketoconazole) have limited their usefulness (1). However, the subsequently developed triazoles fluconazole, itraconazole, and voriconazole have become useful additions to the antifungal armamentarium. They have a wider spectrum of activity and greater target specificity and are generally well tolerated (1,2). Other azoles for topical use are reviewed in the monograph on Antifungal azoles and other drugs for topical use.

The azoles act by inhibiting the fungal enzyme lanosterol 14-α-demethylase, which is involved in the synthesis of ergosterol from lanosterol or 24-methylenedihydrolanosterol in the fungal cell membrane. The consequent inhibition of ergosterol synthesis originates from binding of the unsubstituted nitrogen (N-3 or N-4) of the imidazole or triazole moiety to the heme iron and from binding of their N-1 substituent to the apoprotein of a cytochrome P-450 (P-450(14)DM) of the endoplasmic reticulum (3). This inhibition interrupts the conversion of lanosterol to ergosterol, which alters cell membrane function. Itraconazole has the highest affinity for the cytochrome and is about three and ten times more active in vitro than miconazole and fluconazole, respectively (4). They also inhibit the uptake of triglycerides and phospholipids through the cell membrane.

Drug–Drug Interactions

General

Drug interactions with the antifungal azoles are common for several reasons:

- they are substrates of CYP3A4, but also interact with the heme moiety of CYP3A, resulting in non-competitive inhibition of oxidative metabolism of many CYP3A substrates; to a lesser extent they also inhibit other CYP450 isoforms;
- although fluconazole undergoes minimal CYP-mediated metabolism, it nevertheless inhibits CYP3A4 in vitro, albeit much more weakly than other azoles (5,6); however, fluconazole also inhibits several other CYP isoforms in vitro and interacts with enzymes involved in glucuronidation (7);
- interaction of antifungal azoles and other CYP3A substrates can also result from inhibition of P-glycoprotein-mediated efflux; P-glycoprotein is extensively co-localized and exhibits overlapping substrate specificity with CYP3A (7); in a cell line in which human P-glycoprotein was overexpressed, itraconazole and ketoconazole inhibited P-glycoprotein function, with 50% inhibitory concentrations of about 2 and 6 μmol/l respectively; however, fluconazole had no effect (8).
- the systemic availability of the antifungal azoles depends in part on an acidic gastric environment and the activity of intestinal CYP3A4 and P-glycoprotein.

For details of interactions with individual antifungal azoles, see individual monographs (fluconazole, itraconazole, ketoconazole, miconazole, and voriconazole).

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Antifungal azoles and other drugs for topical use

See also Antifungal azoles

General Information

All the topically used azoles can cause local irritation, burning, and, if used intravaginally, burning, swelling, and discomfort during micturition. There is cross-sensitivity between econazole, enilconazole, miconazole, and probably all other phenethylimidazoles.

Contact allergy to topical imidazoles is rare, considering how commonly they are used. The imidazole derivatives most often reported to be allergens are miconazole, econazole, tioconazole, and isoconazole. As far as cross-reactivity is concerned, in one review, there were statistically significant associations between miconazole, econazole, and isoconazole; between sulconazole, miconazole, and econazole; and between isoconazole and tioconazole (1).

Of 3049 outpatients who were patch-tested for contact dermatitis at the Department of Dermatology, Nippon Medical School Hospital from January 1984 to August 1994, 218 were patch-tested with topical antimycotic agents (2). There were 66 positive tests with imidazole derivatives, of whom 35 were allergic to the active ingredients: 16 were allergic to sulconazole, 11 to croconazole, 3 to tioconazole, 3 to miconazole, 1 to bifonazole, and 1 to clotrimazole. Exposure to croconazole occurred after a significantly shorter time with less drug than with sulconazole. Of the 35 patients who were allergic to an imidazole, 21 cross-reacted to other imidazoles.

Azoles

Bifonazole

Bifonazole has a broad spectrum of activity in vitro against dermatophytes, moulds, yeasts, dimorphic fungi, and some Gram-positive bacteria. It has been used in a strength of 1% in creams, gels, solutions, and powders, applied once a day to treat superficial fungal infections of the skin, such as dermatophytoses, cutaneous candidiasis, and pityriasis versicolor (3). In a multicenter, double-blind, randomized, parallel-group comparison with flutrimazole cream 1% in the treatment of dermatomycoses in 449 patients the overall incidence of adverse effects (mainly mild local effects such as irritation or a burning sensation) was 5% (4).

Clotrimazole

Clotrimazole was the first oral azole. While it was effective in deep mycoses, its limited absorption and induction of liver microsomal enzymes after a few days, leading to accelerated metabolism of the compound, as well as its toxicity, preclude its use for systemic therapy. Clotrimazole is therefore currently only used for topical therapy of mucocutaneous candidiasis.

Comparisons of fluconazole 200 mg/day with clotrimazole 10 mg 5 times/day in the prevention of thrush in patients with AIDS showed little difference in the occurrence of undesirable effects and abnormalities in laboratory measurements but less efficacy of clotrimazole (5,6).

Local problems can occur, including hypersensitivity reactions (1). In one case of contact allergy, patch-testing was positive with clotrimazole (5% in petroleum), itraconazole (1% in ether), and croconazole (1% in ether) (7). The authors reviewed the possible cross-reactions between the subgroups of imidazoles.

- A 71-year-old woman had a severe exacerbation of vulval dermatitis for which she had been using Canesten (clotrimazole) cream (8). There was a positive patch-test reaction with clotrimazole (1% in petrolatum) and patch tests with the other constituents of Canesten were negative.

Topical vaginal administration of even relatively high doses of clotrimazole did not result in systemic toxicity (9).

Croconazole

In one case of contact allergy, patch-testing was positive with clotrimazole (5% in petroleum), itraconazole (1% in ether), and croconazole (1% in ether) (7). The authors reviewed the possible cross-reactions between the subgroups of imidazoles.

Econazole

Econazole is used topically on the skin and also intravaginally, after which about 3–7% is absorbed. It can cause pruritus (10) and vaginal burning (11).

Enilconazole

Enilconazole is used in 10% solution/cream. Contact dermatitis has been reported (12,13).

Isoconazole

Isoconazole is mainly used for vaginal infections with *Candida albicans*. Contact dermatitis has been reported (14), including an unusual case with a papulo-pustular reaction (15).

Itraconazole

In one case of contact allergy, patch-testing was positive with clotrimazole (5% in petroleum), itraconazole (1% in ether), and croconazole (1% in ether) (7). The authors reviewed the possible cross-reactions between the subgroups of imidazoles.

Lanoconazole (latoconazole)

Used in a 1% cream, lanoconazole is effective against *Tinea*, and is more active than clotrimazole or bifonazole. Several cases of contact dermatitis have been reported (16–20).

Miconazole

See the monograph on Miconazole.

Nimorazole

Nimorazole is believed to be active against *Trichomonas vaginalis*. No specific adverse effects have been described after local use.

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Ornidazole
Complaints of dizziness (21), mild gastrointestinal symptoms (22), and headache (23) during treatment with intravaginal ornidazole have been reported, since ornidazole is relatively well absorbed after rectal and vaginal administration (23).

Terconazole
Terconazole is prepared in creams and ovules for intravaginal use. Besides local irritation it causes systemic reactions. Headache was reported in over a quarter of patients. Other effects include hypotension, fever, and chills. Terconazole is absorbed to a greater extent than other topical azoles (SED-12, 684).

Tioconazole
Tioconazole is mainly used for vaginal or inguinal *Candida* infections. It has fewer local adverse effects than some of the older imidazoles. Local irritation, burning, rash, erythema, and pruritus have been reported. In a few women there was marked burning on micturition; these women all had signs of vaginal epithelial atrophy (SED-12, 684) (24).

Other topical antifungal drugs

5-Bromo-4-chlorosalicylamide (multifungin)
5-Bromo-4-chlorosalicylamide is one of a group of local antiseptics and fungistatics that can cause photosensitization (25). There is cross-sensitization with bithionol, fenticlor, and tribromosalicylanide.

Buclosamide (N-butyl-4-chlorosalicylamide)
Photocontact dermatitis has been described with buclosamide (25). There is cross-reactivity with a number of other drugs, notably oral hypoglycemic drugs, diuretics, and sulfonamides. Because of these reactions, buclosamide is not recommended for topical use.

Captan (Orthocide-406)
Captan is one of the older fungicides. It is used for pityriasis versicolor and is included in some soaps and cosmetics to provide bactericidal and fungicidal effects. It is allergenic. It is carcinogenic in mice, and in several countries control agencies have taken steps to prohibit its use in cosmetics and non-drug products (SEDA-13, 236).

Ciclopirox
Ciclopirox, a substituted pyridone unrelated to the imidazoles, is effective against a wide variety of dermatophytes, yeasts, actinomycetes, molds, and other fungi. Ciclopirox olamine is generally well tolerated locally, and reactions occur in only 1–4% of cases (SEDA-12, 684).

Clodantoin
Contact dermatitis has been rarely reported with clodantoin.

Fluonilide (4-fluoro-3′,5′-thiocarbanilide)
Contact dermatitis has been reported with fluonilide (26).

Gentian violet
Gentian violet (27) was at one time the treatment of choice for vaginal and oral candidiasis but is now obsolete. The main problem is staining and the messiness of the application, since the purple-colored fluid has to be brushed on to the skin.

Hachimycin (trichomycin)
Contact dermatitis has been reported with hachimycin.

KP-363
KP-363, a benzylamine derivative, is used in creams and solutions in concentrations of 0.1 and 0.6%. It is reported to cause less irritation than bifonazole and tolciclate (SEDA-14, 235).

Naftitine
Naftitine is one of a series of allylamine antifungal agents, derived from heterocyclic spironaphthalenes. It is usually sold in the form of a 1% cream for topical treatment of dermatomycoses, dermatophytes, and yeasts. It is claimed to be more effective than the imidazoles. Local irritation and a burning sensation, if they occur, are only mild (SED-12, 684) (28), (SEDA-16, 297).

Natamycin (pimaricin)
No cases of contact dermatitis were described in industrial workers in frequent contact with natamycin (29).

In the Hungarian Case–Control Surveillance of Congenital Abnormalities between 1980 and 1996, of 38 151 pregnant women who delivered infants without any defects (controls) and 22 843 who had fetuses or neonates with congenital abnormalities, 62 (0.27%) and 98 (0.26%) were treated with vaginal natamycin in the two groups respectively (crude OR = 1.1; 95% CI = 0.8, 1.5). There was thus no evidence of a teratogenic effect of natamycin.

Nifuratel
Contact dermatitis, with facial edema and a generalized erythema, has been described in the partner of a woman treated with nifuratel vaginal suppositories (SED-11, 578) (30).

Niphimycin
Niphimycin, an antimycotic antibiotic derived from *Actinomyces hygroscopicus*, is effective against both dermatomycosis and onychomycosis, with a 16–26% success rate in the latter. Tolerance is reportedly good, but there is a notable lack of recent data (SEDA-12, 236).

Nystatin
See the monograph on Nystatin.

Pecilocin (Variotin)
Skin irritation has been reported in 2–6.5% of patients treated with pecilocin. Contact dermatitis has been described in a few cases (31,32). Of 44 patients treated with pecilocin who were patch-tested with pecilocin, 7 were allergic to it; in three of them the skin disease had been caused or exacerbated by pecilocin (33).

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Pyrrolnitrin (Miutrin, 3-chloro-4-(3-chloro-2-nitrophenyl) pyrrole)
Contact dermatitis with pyrrolnitrin and cross-reactivity with dinitrochlorobenzene has been reported in one case (34).

Salicylic acid 3% with benzoic acid 6% (Whitfield's ointment)
Whitfield's ointment, used for *Trichophyton rubrum*, has a keratolytic effect, and local irritation can occur (SED-12, 685) (35).

Sulbentine (dibenzthion)
Photoallergic contact dermatitis has been described with sulbentine, probably through a breakdown product, benzylisothiocyanate (36).

Tolciclate
Tolciclate, a thiocarbamate, is active against most common dermatophytes. Contact dermatitis has been reported (37).

Tolnaftate
Tolerance of tolnaftate is good. Local erythema has been described, as has allergic dermatitis (38).

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Antihistamines

See also Individual agents

General Information

Histamine is both a local hormone and a neurotransmitter in the central nervous system. It is synthesized in neurons and mast cells. There are H_1, H_2, and H_3 receptors in the central nervous system, but they differ in their localization, biochemical machinery, functions, and affinities for histamine; they are particularly important in maintaining a state of arousal or awareness (1).

The early antihistamines, H_1 histamine receptor antagonists, bore some structural resemblance to histamine and, like histamine, contained an ethylamine group. However, the structures of the many antihistamines that are available are disparate, and the traditional classification according to chemical structure (ethanolamine, ethylenediamine, alkylamine, piperazine, and phenothiazine) is outdated, since the second-generation antihistamines, such as terfenadine and astemizole, do not readily fit into the old classification system (2).

Antihistamines act as competitive antagonists of histamine at H_1 histamine receptors, thus inhibiting H_1 receptor-mediated reactions, such as vasodilatation, sneezing, and itching. Histamine release from mast cells and basophils makes a major contribution to the allergic response, and antihistamines are widely used in the treatment of certain symptoms of allergic disease.

The new second-generation antihistamines are more selective H_1 histamine receptor antagonists, and many of them have additional anti-allergic properties in vivo, for example they reduce the release of inflammatory mediators or inhibit the recruitment of inflammatory cells (3–7). They also enter the brain less well and are therefore less likely to cause central adverse effects.

The H_1 histamine receptor antagonists were discovered by Bovet and Staub at the Institut Pasteur in 1937 (8). Although the first antihistamine was too weak and toxic for clinical use, its discovery resulted in an enormous amount of research and led in 1942 to the development of the first antihistamine to be used in the treatment of allergic diseases phenbenzamine (Antegan) (9). Within a few years, three other antihistamines became available and are still in use today: mepyramine (pyrilamine) maleate (10), diphenhydramine (11), and tripelennamine (12). Despite their pronounced adverse effects, these were the first really useful drugs for the symptomatic relief of allergic disorders. During the last 25 years several compounds with greater potency, longer durations of action, and minimal sedative effects have emerged, the so-called second-generation H_1 antihistamines, as opposed to the older, or classic, first-generation antihistamines. Two papers have confirmed the safety of the second-generation antihistamines; in particular, loratadine, fexofenadine, norastemizole, and descarboxyloratadine (desloratadine) were shown not to have sedative effects (13,14).

Spontaneous reports of suspected adverse effects of antihistamines have been analysed (15). The drugs were divided into two groups, sedative and non-sedative. Adverse reactions profiles were broadly similar in the two groups.

First-generation antihistamines

Besides interacting with H_1 histamine receptors, the first-generation antihistamines also have affinity for 5-HT receptors, alpha-adrenoceptors, and muscarinic receptors. They also reduce cyclic GMP concentrations, increase atrioventricular nodal conduction, and inhibit activation of airway vagal afferent nerves. First-generation H_1 receptor antagonists easily cross the blood–brain barrier, and their consequent well-documented sedative and anticholinergic effects, together with short half-lives, greatly limit their use in the treatment of allergic symptoms. However, despite these deficiencies, first-generation drugs are still widely used, mainly as over-the-counter products, often in combination with other drugs. The incidence of adverse effects, especially sedation and antimuscarinic effects, with the first-generation antihistamines is very high, perhaps up to 50%. Although these adverse effects are rarely serious, and often disappear with continued therapy, they are often so troublesome that medication must be withdrawn.

Second-generation antihistamines

The second-generation antihistamines include acrivastine, astemizole, azelastine, carebastine, cetirizine, ebastine, loratadine, mizolastine, and terfenadine. They are used orally and some of them can be given by local application to the nose and eyes (2,16). They are relatively free from anticholinergic, antiserotonergic, and alpha-adrenergic activity. They cause markedly less sedation, perhaps because they penetrate the central nervous system less well than the first-generation antihistamines, being relatively hydrophilic (17–19).

Second-generation antihistamines have proved to be important therapeutic tools in the treatment of atopic disease, including both seasonal and perennial allergic rhinitis, urticaria, and atopic dermatitis (20). Several studies have shown that the use of second-generation antihistamines as adjunctive therapy can benefit patients whose allergic asthma co-exists with allergic rhinitis (21).

There are several novel antihistamines that are either metabolites or enantiomers of existing drugs. The aim has been to develop antihistamines with improved potency, onset and duration of action, and greater predictability and safety. Drugs of this kind that have received regulatory approval and are effective in several allergic conditions include desloratadine, fexofenadine, levocabastine, and levocetirizine. These have been developed in response to widespread concerns about the potential for cardiotoxicity and the impact of drug–drug interactions associated with some earlier second-generation H_1 receptor antagonists. Furthermore, the potential for sedation by some of the newer antihistamines still remains an issue for many. This

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is important, as many patients using antihistamines want to remain alert and active and may also use other medications.

Organs and Systems

Cardiovascular

Tachycardia and hypertension have long been known as problems arising incidentally reported with various classic antihistamines (SEDA-22, 176).

Prolonged QT interval and ventricular dysrhythmias

DoTS classification

Dose-relation: toxic effect
Time-course: time-independent
Susceptibility factors: genetic (long QT syndrome); altered physiology (hypokalemia); drug interactions (metabolism inhibitors; drugs that prolong the QT interval); diseases (liver disease; cardiac disease with prolongation of QT interval)

Several antihistamines can cause ventricular dysrhythmias of the torsade de pointes type (22), first reported with astemizole (23) and later with terfenadine (24). Astemizole and terfenadine both have a dose-dependent effect on cardiac repolarization and cause prolongation of the QT interval, which can lead to ventricular dysrhythmias (such as torsade de pointes), syncope, and cardiac arrest. Reported cases relate preponderantly to overdosage, especially in children (SEDA-12, 142) (SEDA-14, 135) (SEDA-14, 137) (SEDA-17, 196) (23–25). Terfenadine and astemizole have been described as having dysrhythmogenic actions, and deaths have been described (26,27). The effects of some antihistamines on the QT interval are listed in Table 1.

With a few exceptions, antihistamines are rapidly and completely absorbed after oral administration; peak plasma concentrations are reached after 1–4 hours and are highly variable, owing to differences in tissue distribution and metabolism (20). Many of the second-generation antihistamines (for example astemizole, ebastine, loratadine, and terfenadine) undergo extensive first-pass metabolism to pharmacologically active metabolites; as a common feature, the reaction is primarily supported by CYP3A4. Under normal circumstances this extensive metabolism leads to low or undetectable plasma concentrations of the parent drug. However, sometimes metabolism of the parent compound can be compromised. Accumulation of unmetabolized astemizole or terfenadine can result in blockade of cardiac potassium channels in the ventricular myocytes that regulate the duration of the action potential; consequent prolongation of the QT interval can result in potentially life-threatening ventricular tachycardia (28).

Dysrhythmias can also occur with therapeutic doses of these and other antihistamines, if certain other susceptibility factors are present:

- impaired hepatic metabolism due to liver disease;
- simultaneous treatment with drugs that are inhibitors of the cytochrome P450 enzyme CYP3A4 (for example macrolide antibiotics, antifungal azoles, or grapefruit juice), leading to increased plasma concentrations thereby raising the risk of cardiotoxic effects (29) (SEDA-17, 196);
- pre-existing QT prolongation caused by congenital long QT syndrome, other heart disease, or treatment with antidysrhythmic drugs, such as class I antidysrhythmic drugs, amiodarone, or sotalol;
- electrolyte imbalance; in particular, hypokalemia predisposes to Dysrhythmias.

Terfenadine is especially likely to cause torsade de pointes in patients in whom these risk factors are present (SEDA-19, 176) (SEDA-21, 176). Ventricular dysrhythmias can also occur after overdosage of antihistamines that prolong the QT interval.

The mechanism responsible for dysrhythmias has been identified as blockade of HERG potassium channels (30). The dysrhythmogenic potential of antihistamines has been evaluated in vitro using cloned human potassium channels or guinea-pig heart muscle cells, and using an in vivo guinea-pig model. Studies in humans, including the assessment of drug interactions, are considered more reliable. Investigations in human volunteers have shown that there are no significant electrocardiographic changes with azelastine, cetirizine, fexofenadine, and loratadine even at several times the therapeutic doses, which shows that cardiotoxicity is not a class effect (31) (SEDA-19, 172). Mizolastine also appears to cause no cardiac problems in humans (32). Large doses of ebastine have shown cardiac effects in guinea pigs, but QT prolongation has not occurred in human studies with up to three times therapeutic doses (33). Slight QT prolongation was seen on further increased doses to 100 mg/day and when subjects were given erythromycin or ketoconazole, but the effect was less than the effect of terfenadine and was not considered clinically relevant (33). The active metabolite of ebastine, carebastine, had no effect on the QT interval, even in large doses.

The absolute risk of antihistamine-induced dysrhythmias is low in the general population. In an epidemiological study using a general practice database, the crude incidence of ventricular dysrhythmias was 1.9 per 10 000 person-years, corresponding to a relative risk of 4.2 for all antihistamines compared with non-use. Astemizole presented the highest relative risk, whereas terfenadine was in the range of other non-sedating antihistamines. Older age was associated with greater risk. The absolute risk in this study was one case per 5300 person-years of use (34).

In the USA, terfenadine was withdrawn from the market in 1998, and in other countries terfenadine has been moved from over-the-counter to prescription-only, with only 60 mg tablets available. The active metabolite of terfenadine, fexofenadine, is marketed as an alternative. For astemizole this option was not available, since the main metabolite (desmethylastemizole) is also cardiotoxic and has a half-life of 10 days; astemizole was therefore withdrawn from the market worldwide in June 1999.

Although it is widely believed that cardiotoxicity of antihistamines is limited to second-generation compounds, both hydroxyzine and diphenhydramine can block potassium channels. Caution should therefore be exercised in prescribing first-generation antihistamines for patients with a predisposition to cardiac dysrhythmias. For example, therapeutic doses of diphenhydramine caused prolongation of the QT interval in healthy volunteers and in patients undergoing angioplasty (35), and one cannot exclude the possibility that first-generation drugs that modulate

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Table 1 The sedative, anticholinergic, and QT prolonging effects of antihistamines (all rINNs, except where stated)

Drug	Sedative effect	Anticholinergic effect	QT interval prolongation
Acrivastine	+	–	–
Alimemazine (trifluomeprazine, trimeprazine)	++++	+++	
Antazoline			
Astemizole	–		+++
Azelastine			–
Betahistine	+	++	
Brompheniramine	+	++	
Carebastine			–
Cetirizine	±	±	–
Chlorphenamine (chlorpheniramine)	++	±	–
Cinnarizine	+	+	–
Clemastine	+	+	±
Cyclizine	++	++	
Cyproheptadine	++	++	
Desloratadine	–	+	–
Dexbrompheniramine			
Dexchlorpheniramine			
Dimenhydrinate	+++	+++	
Dimetindene			
Diphenhydramine	+++	++	+
Diphenylpyraline			
Doxylamine	+		
Ebastine	–		–
Emedastine			
Fexofenadine	–	–	–
Flunarizine			
Hydroxyzine	+	–	±
Ketotifen	+		–
Levocabastine			
Levocetirizine	–		–
Loratadine	–	±	–
Mebhydrolin			
Meclozine (pINN)			
Mepyramine	++	+	
Mequitazine	+		+
Methapyrilene			
Mizolastine	–	–	–
Oxatomide			
Phenindamine			
Pheniramine			
Promethazine	++++	+++	
Terfenadine	±	+	+++
Thiazinamium			
Tripelennamine			
Triprolidine	++		

potassium channels may in some circumstances cause dysrhythmias (36). All antihistamines should be screened for cardiotoxicity, as some patients may be poor metabolizers or may be susceptible to plasma concentrations near to the usual therapeutic range. Useful information may be obtained from pharmacokinetic studies using potential inhibitors (see under Drug–Drug Interactions).

The single- and multiple-dose pharmacokinetics of ebastine (10 mg) have been determined in elderly and young healthy subjects using 24-hour Holter monitoring (37). There were no clinically relevant effects.

The incidence of ventricular dysrhythmias associated with non-sedating antihistamines (including cetirizine) has also been assessed using the UK-based General Practice Research Database (34). There were 18 cases over the period 1992–96. Astemizole was associated with the highest relative risk. The risk associated with terfenadine was no different from that with other non-sedating antihistamines, and there was no single case of ventricular dysrhythmia with the concomitant use of P450 inhibitors and terfenadine.

In a comparison of the dysrhythmogenic potential of a series of second-generation antihistamines, the antihistamines were given intravenously and electrocardiographic and cardiovascular parameters (blood pressure and heart rate) were measured. The lowest dose that produced significant prolongation of the QT_c interval

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was compared with the dose required to inhibit by 50% the peripheral bronchospasm elicited by histamine 10 micrograms/kg intravenously. Astemizole, ebastine, and terfenadine produced pronounced dose-dependent QT_c interval prolongation. In contrast, terfenadine carboxylate, norastemizole, and carebastine, the major metabolites of terfenadine, astemizole, and ebastine, and cetirizine had no effects (38).

Respiratory

Phenothiazine derivatives can aggravate asthma. The use of the first-generation antihistamines in asthma was hampered by induction of coughing when inhaled and by their sedative properties when given orally. Furthermore, the desiccating and thickening effect on the airway mucus is undesirable. However, the American Academy of Allergy and Immunology (39) has stated that antihistamines are not contraindicated in patients with asthma, unless there have been previous adverse reactions (SEDA-14, 135).

The effect of the second-generation antihistamines in treating asthma has been investigated. They have a moderate, bronchodilatory effect and an effect on exercise-induced asthma, hyperventilation, and cold-air breathing, and to a varying degree give some protection against the early and late responses to allergen (2) (SEDA-14, 135).

Antihistamines are not first-choice drugs in asthma, however, and although they can contribute to the relief of seasonal asthma symptoms and accompanying allergic rhinitis, the results of a meta-analysis do not support the general use of antihistamines in adult asthmatics (40).

Ear, nose, throat

When used for the treatment of colds and allergic upper airways disorders, antihistamines (alone or in combination with decongestants) can reduce mucociliary motility in the middle ear, thus contributing to the development of otitis media (41).

Nervous system

The sedative and anticholinergic effects of antihistamines, when known, are summarized in Table 1.

Antihistamines and drowsiness

Central nervous depression causing sedation is the most common adverse effect of the first-generation antihistamines (SEDA-21, 171) (42). The sedative effect of antihistamines is evaluated using psychometric tests, tests of driving performance, and subjective scoring or visual analogue scales, but results from studies using healthy volunteers cannot necessarily be extrapolated to patients, one difficulty being that the treated disease can itself cause sedation (43). The drowsiness has been attributed to inhibition of histamine *N*-methyltransferase and to blockade of central histamine receptors, together with actions on other receptors, in particular 5-HT receptors (2,17,19,44). Daytime drowsiness can be a problem, above all when driving or operating machinery. As with many other nervous system depressants, this effect may abate or disappear after several days of use, but co-medication with certain other agents or a short period of withdrawal of therapy may reactivate the sedative effect.

The signal characteristic of the second-generation antihistamines is their freedom from sedation (2,16). The relative lack of sedative properties in the second-generation antihistamines has been ascribed to their relative hydrophilicity. Little is known about intracerebral concentrations of antihistamines and their metabolites, but positron emission tomography has shown that the first-generation antihistamine chlorphenamine occupied a larger fraction of brain histamine H_1 receptors than terfenadine (SEDA-20, 164). Differential affinity for, or different actions on, central and peripheral H_1 receptors (SEDA-21, 171) could also explain variations in sedative effect, but differences in receptor binding have only been shown for loratadine in vitro (45).

The nervous system depressant effects of fexofenadine (46,47), loratadine (48), and mizolastine (49) appear to be no greater than those seen with placebo. However, the generality of the claim that second-generation antihistamines are free of sedative effects has been challenged (50). The issue is complicated by evidence that sedation in allergic disease (and subsequent impairment in performance and learning) can be a consequence of the condition itself, as opposed to being wholly due to antihistamines (20). This raises concerns about the purported risk-free sedation profiles of certain antihistamines, given that they are often based on objective studies in healthy volunteers (42). Another issue is the tendency of patients with allergies to self-medicate, titrating their antihistamine dosage upwards to achieve relief of symptoms; neurological impairment does in fact occur if the doses of cetirizine, loratadine, or mizolastine are increased sufficiently (20). Thus, it is more correct to describe the second-generation antihistamines as having minimal sedative effects when taken in recommended doses. A grouping of the antihistamines into those with marked, moderate, and very low sedative effect is possible. However, the dividing lines are not sharp and classification often depends on how many studies are taken into account, since results are not consistent.

The designs of protocols used in comparisons between sedative and non-sedative compounds have been questioned. They may not accurately reflect the clinical use of each drug, and the data may be misused in advice to prescribers, even though the reason a comparator was included was merely to provide an active control. Extrapolation of the results of cognitive studies in healthy volunteers to patients may be inappropriate, as a drug that is sedative in a healthy volunteer may well not be perceived to be sedative by a patient with allergic symptoms, although caution must be taken in relying on subjective assessments of performance and drowsiness. Patients with mild to moderate allergic rhinitis complain of sleep difficulties, and many who take a sedative can function reasonably well during the next day without further medication. Duration of treatment can also play a part, and certain investigations may have been too brief; in some patients, sedation is induced by the drug only after some weeks of treatment (SEDA-12, 142). Such discrepancies could explain why, despite all the investigations with positive results, some studies report sedation in 30% of the patients (SED-11, 317) (SEDA-9, 149) (SEDA-10, 135).

It is likely that the controversy will be settled by accepting the relative merits of each drug, and that sedative drugs will continue to be prescribed, at least for overnight ingestion and for some skin conditions.

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There is the special case of the use of antihistamines by individuals whose work may compromise their own safety or the safety of others, for example transport workers. Indeed, much of the support for second-generation drugs arises from safety considerations. Nevertheless, it is sometimes suggested that recommendations for the use of antihistamines by those involved in skilled activities should be based on studies of the patients themselves carrying out their day-to-day work, for example airline pilots with allergic rhinitis operating aircraft. This is an argument that lacks careful thought. In occupational medicine it is essential that controlled studies in healthy volunteers are used to establish whether an antihistamine has sedative properties, and then to choose the drug that is least likely to impair performance or cause drowsiness.

Observational studies

Antihistamines are effective and safe in preventing the symptoms of a mosquito bite; ebastine and loratadine did not cause sedation in such cases (51,52).

Comparative studies

The frequency of sedation due to acrivastine, cetirizine, fexofenadine, and loratadine has been investigated in four prescription-event monitoring studies in 43 363 patients in general practice in the UK (53). Prescriptions were obtained for each cohort in the immediate postmarketing period. Sedation and drowsiness were the main outcome measures. The odds ratios (adjusted for age and sex) for the incidences of sedation compared with loratadine were: 0.63 (95% CI = 0.36, 1.11) for fexofenadine, 2.79 (1.69, 4.58) for acrivastine, and 3.53 (2.07, 5.42) for cetirizine. There was no increased risk of accident or injury with any of the four drugs.

The effects of diphenhydramine, fexofenadine, and alcohol on driving performance have been studied in a randomized, placebo-controlled trial in the Iowa driving simulator (54). Participants had significantly better coherence after alcohol or fexofenadine than after diphenhydramine. Lane holding (steering instability and crossing the center line) was impaired after alcohol and diphenhydramine compared with fexofenadine. Mean response time to the blocking vehicle was slowest after alcohol (2.21 seconds) compared with fexofenadine (1.95 seconds). Self-reported drowsiness did not predict lack of coherence and was weakly associated with minimum following distance, steering instability, and left-lane excursion. In conclusion, the participants performed similarly when they took fexofenadine or placebo. After alcohol they performed the primary task well but not the secondary tasks, resulting in poorer driving performance. After diphenhydramine, driving performance was poorest, suggesting that diphenhydramine had a greater impact on driving than alcohol did. Drowsiness ratings were not a good predictor of impairment, suggesting that drivers cannot use drowsiness to indicate when they should not drive. Non-sedating antihistamines should therefore be preferred over sedating antihistamines in patients who drive (55).

Mequitazine has a low propensity to cause drowsiness, comparable to that of cetirizine and loratadine; it therefore differs from truly sedative antihistamines, such as dexchlorpheniramine, which cause drowsiness and fatigue in patients with atopy to a degree that is measurably different from placebo (56).

Although allergic rhinitis is not usually severe, it affects school learning performance and work productivity (57). The effects of loratadine and cetirizine on somnolence and motivation during the working day have been compared in 60 patients with allergic rhinitis in a parallel-group, double-blind study (58). Somnolence scores were similar in the two groups at baseline and at the time of dosing (0800 hours). However, cetirizine caused significantly more somnolence at 1000 hours, 1200 hours, and 1500 hours. The scores of motivation to perform activities were similar in the two groups at baseline and 0800 hours. The patients taking loratadine were relatively more motivated at 1000 hours, 1200 hours, and 1500 hours.

In a comparison of the effects over 7 days of a modified-release formulation of brompheniramine (12 mg bd) and loratadine (10 mg od), physicians' and patients' assessments were better for brompheniramine than for loratadine, but somnolence and dizziness were reported less often by those who took loratadine, although occurrences were claimed to be less frequent with brompheniramine as treatment continued (59).

The authors of a report of a comparison of the effectiveness of ebastine (10 and 20 mg) and loratadine (10 mg) for perennial allergic rhinitis claimed that ebastine provided greater symptomatic relief than loratadine, but with a similar low incidence of central effects and headache (60).

In a comparison of the incidence of drowsiness between cinnarizine (25 mg tds for 7 days, 25 mg bd for 15 days, and 25 mg daily for 15 days) and prochlorperazine (5 mg tds for 7 days, 5 mg bd for 15 days, and 5 mg od for 15 days), drowsiness was observed less often in those taking prochlorperazine (61).

In a comparison of diphenhydramine, chlorphenamine, cetirizine, loratadine, and placebo in 15 healthy elderly subjects, there were no significant differences between the first- and second-generation antihistamines (62). In another study, even the first-generation sedative drug chlorphenamine failed to cause significant sedation in a group of children (63).

In a comparison of astemizole, terfenadine, and triprolidine (positive control), only triprolidine caused reduced performance and motor incoordination (64).

In a comparison of the effects of acrivastine, terfenadine, and diphenhydramine on driving performance, there was a dose-dependent effect of acrivastine, with severely affected driving in doses of 16 and 24 mg (SEDA-19, 170). Terfenadine in doses of 60–180 mg did not affect driving performance.

In a comparison of cetirizine and loratadine, cetirizine 10 mg had acute sedative effects and impaired driving performance (65), whereas loratadine had no sedating potential; furthermore, there was an additive effect of alcohol and cetirizine but not alcohol and loratadine. However, in a study using a driving simulator cetirizine 10 mg did not affect driving ability (66). In other studies cetirizine 20 mg caused significant sedation, while in one study there was a dose-dependent sedative effect with 10 mg and 20 mg but not 5 mg (67). Pooling the available data (SEDA-16, 163) shows that cetirizine is little more sedative than loratadine and terfenadine.

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In a comparison of ebastine and triprolidine, only those taking triprolidine had impairment of several parameters of car driving performance (SEDA-18, 182).

The effects of loratadine 10, 20, and 40 mg on tests of visuomotor coordination, dynamic visual acuity, short-term memory, digit symbol substitution, and subjective assessments of mood have been studied (68). Triprolidine was used as an active control and impaired performance on all the tasks presented. Loratadine 40 mg caused a significant impairment of the Digit Symbol Substitution Test and the Dynamic Visual Acuity Test, but the 10 and 20 mg doses were without effect. Loratadine did not affect objective sleepiness, as measured by Multiple Sleep Latency Test (69). In other studies of loratadine in the normal 10 mg dose the sedation rate was no different from placebo (SEDA-12, 143) (SEDA-14, 136).

In a comparison of the initial and 5-day steady-state effects of loratadine, diphenhydramine, and placebo, using a number of psychometric tests, there was no detectable effect of loratadine compared with placebo, whereas diphenhydramine clearly reduced performance (70).

Anticholinergic effects

The marked anticholinergic properties of the first-generation antihistamines can cause dryness of the oral and respiratory mucosae. Other antimuscarinic effects are less common, but nasal stuffiness, blurring of vision, urinary retention, and constipation can all occur.

Nervous system stimulation is less frequent than nervous system depression, but when it occurs it causes insomnia, irritability, and tremor; nightmares, and hallucinations. In overt intoxication, these effects may be related to anticholinergic effects. In an analysis of 113 200 admissions to a pediatric hospital there were only two patients with excitation, insomnia, visual hallucinations, and seizures, followed by coma (71).

Antidopaminergic effects

Antidopaminergic effects of antihistamine drugs can cause extrapyramidal symptoms, including neuroleptic malignant syndrome (SEDA-19, 173) (SEDA-22, 178) (72). Prolonged use of antihistamine-containing decongestants can cause facial dyskinesias, including blepharospasm, swallowing difficulties, and dysarthria. As patients with these effects have often been taking combination products containing antihistamines, proper evaluation of interactions is needed before final assessment is possible. As a dyskinesia can be unilateral, a neurological disorder should be excluded before thinking about an adverse effect (SEDA-1, 144).

The prognosis of drug-induced parkinsonism has been discussed (73,74). Negrotri and Calzetti (73) considered that the results of Martí-Massó and Poza (74) were over-optimistic. This they ascribed to uncertainty in the collection of their data, which may not have provided adequate evidence of the course of clinical recovery, although differences in cumulative dosages and concurrent use of other drugs could also have been involved. The differences in prognosis may be attributable to the fact that the patients studied by Martí-Massó and Poza (34) were diagnosed earlier, were less severely affected, and had a good prognosis. Cinnarizine-induced extrapyramidal signs have tended to be associated with old age and prolonged treatment. However, cinnarizine-induced akathisia, parkinsonism, and depression have been reported in a 25-year-old patient after only 11 days of treatment (75).

Sensory systems

A questionnaire showed that women taking antihistamines and/or cold formulations had a tone average 9 dB higher than those not taking such medication (76). Audiography showed differences in threshold of 6.4 and 12.8 dB at 500 and 1000 Hz respectively. The medications involved were primarily meclozine for dizziness and terfenadine for allergy.

Psychological, psychiatric

In healthy volunteers promethazine caused impaired cognitive function and psychomotor performance (77). The test battery consisted of critical flicker fusion, choice reaction time, compensatory tracking task, and assessment of subjective sedation. Cetirizine and loratadine at all doses tested were not significantly different from placebo in any of the tests used.

School performance in 63 children aged 8–10 years was not impaired by short-term diphenhydramine or loratadine (78).

Comparative studies

The effects of ebastine 10 mg on cognitive impairment have been assessed in 20 healthy volunteers who performed six types of attention-demanding cognitive tasks, together with objective measurements of reaction times and accuracy (79). Ebastine was compared with placebo and a positive control, chlorphenamine (chlorphenamine, 2 mg and 6 mg). Compared with placebo, ebastine had no effect on any objective cognitive test nor any effect on subjective sleepiness. In contrast, chlorphenamine significantly increased reaction times, decreased accuracy in cognitive tasks, and increased subjective sleepiness. The effect of chlorphenamine increased with plasma concentration.

In a double-blind, placebo-controlled, randomized trial of the effects of levocetirizine 5 mg and diphenhydramine 50 mg on objective measurements (a word-learning test, the Sternberg Memory Scanning Test, a tracking test, and a divided attention test that measured both tracking and memory scanning simultaneously) in 48 healthy volunteers (24 men and 24 women). Levocetirizine had no effect, while diphenhydramine significantly affected divided attention and tracking after acute administration (80). However, on day 4 the effects of diphenhydramine did not reach significance, suggesting a degree of tolerance to this first-generation drug.

The effects of levocetirizine on cognitive function have been assessed in two comprehensive and well-controlled studies. The first analysed the effects of single and multiple doses of levocetirizine on measures of nervous system activity, using integrated measures of cognitive and psychometric performance. In a three-way crossover design, 19 healthy men took either levocetirizine 5 mg, diphenhydramine 50 mg (positive control), or placebo once-daily on five consecutive days. Critical flicker fusion tests were

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performed on days 1 and 5 at baseline and up to 24 hours after drug administration. The primary outcome was that, in contrast to diphenhydramine, levocetirizine did not have any deleterious effect on any cognitive or psychometric function compared with placebo (81). In a double-blind, crossover study levocetirizine 5 mg once-daily for 4 days was compared with cetirizine 10 mg, loratadine 10 mg, promethazine 30 mg, and placebo in terms of CNS inhibitory effects in 20 healthy volunteers (82). With the exception of promethazine none of the drugs had disruptive or sedative effects on objective measurements in a comprehensive battery of psychomotor and cognitive tests.

Metabolism

Appetite stimulation and resulting weight gain is a well-known feature of cyproheptadine, but astemizole also causes weight gain in approximately 3% of patients within weeks of treatment (16,83). Cetirizine also has been reported to cause weight gain (about 2.8%) when it is used for a prolonged time (SEDA-17, 200). Increased body weight occurred in three participants in a trial of azelastine (SEDA-21, 172).

In a double-blind, randomized, placebo-controlled study of the effect of cetirizine, clemastine, and loratadine for 7 days on blood glucose concentration in patients with allergic rhinitis, cetirizine produced a significant increase in postprandial blood glucose and a small rise in fasting blood glucose; clemastine caused a small fall in fasting and a small rise in postprandial blood glucose (84). The mechanisms of these effects are not known.

Hematologic

Blood dyscrasias are infrequent with antihistamines, but agranulocytosis, hemolytic anemia, and thrombocytopenia have been described. Thrombocytopenia has been attributed to antazoline (85), agranulocytosis to chlorphenamine (SEDA-16, 162) and mebhydrolin (86), and aplastic anemia to chlorphenamine (87).

Gastrointestinal

Antihistamines do not commonly cause gastrointestinal effects, but nausea, vomiting, gastric pain, diarrhea, or constipation can occur (88).

Liver

Repeated reports of changes in liver function may reflect coincidence, in view of the widespread use of these drugs. Occasionally, however, hepatitis (89) or cholestatic jaundice seems to have occurred.

Skin

Although antihistamines are often used in the treatment of allergic conditions, topical use often produces skin sensitization and subsequent contact dermatitis (90,91). This effect occurs more often with the use of ethylenediamines and phenothiazines; the latter also produce photoallergic cutaneous reactions (92). A photoallergic contact dermatitis followed by a persistent light reaction was attributed to topical dioxopromethazine hydrochloride incorporated into a gel in a woman with periocular pruritus (93). Photosensitivity in sun-exposed areas where she had not applied the formulation persisted for up to 500 days, with a reduced minimal erythema dose (MED) for UVA together with abnormal delayed infiltrated reactions to UVB in repeated phototests.

Cross-reactions between phenothiazine tranquillizers and first-generation antihistamines are possible, as well as reactions between antihistamines and ethylenediamine present in some creams and ointments. As local sensitization is quite common, topical use of antihistamines is not recommended. Despite these disadvantages they are still available in many countries as over-the-counter products. Topical antihistamines in sufficient doses can also cause systemic adverse effects.

Subacute cutaneous lupus-like dermatitis has been associated with cinnarizine and brompheniramine (94,95).

Long-Term Effects

Drug abuse

Some antihistamines, for example tripellenamine (often used in combination with pentazocine), have a particular abuse potential and are used by drug addicts. Psychiatric disturbances, dysphoria, depression, confusion, and hallucinations can occur while under the influence of an antihistamine or during drug withdrawal. Chronic parenteral abuse can cause skin lesions, muscular fibrosis, and vasculitis.

Drug withdrawal

Since dyskinesia can occur after withdrawal of phenothiazine neuroleptic drugs, it is not unlikely that the same problem may follow termination of prolonged antihistamine therapy.

Tumorigenicity

Tumor-inducing effects have been reported in animal studies on methapyrilene; the significance of this finding is not clear (SEDA-4, 171). An association between antihistamine exposure and accelerated tumor growth seen in experimental animal models has found no support in an epidemiological study (96).

Second-Generation Effects

Teratogenicity

Teratogenic effects have not been proven in humans, although some piperazine derivatives have teratogenic effects in laboratory animals. Some studies have suggested an association between palate malformation and antihistamines (97–99).

Teratogenic activity has been attributed to doxylamine, a constituent of many combinations with vitamin B6 and antispasmodic agents, and used in the treatment of hyperemesis gravidarum. However, extensive studies and reviews have suggested that the incidence of malformations is not higher in children whose mothers have taken formulations containing antihistamines as a group, and in particular the combination of doxylamine/pyridoxine with or without dicycloverine (100–102).

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A meta-analysis of 24 controlled studies of the association between antihistamines and major congenital malformations (more than 200 000 participating women) did not show an increased risk of malformations (103). Experience with the first-generation antihistamines is more comprehensive than with the second-generation compounds, and in a recent review it was concluded that some of the first-generation drugs can be used for allergic rhinitis in pregnancy (104). Some authors advise avoiding brompheniramine because of a supposed association with birth defects (SEDA-21, 172).

Studies with various antihistamines (105,106) have failed to provide evidence of teratogenicity. However, the samples may not have been large enough to provide adequate statistical power or to establish the true incidence of individual malformations. In study of the effect of treatment with diazepam and promethazine during pregnancy carried out in the late 1980s (minimal doses for the whole pregnancy 50 mg and 250 mg respectively), children of both sexes in the diazepam group had lower birth weights, but normal body weights at 8 months of age; there were no changes in body weight in the promethazine group (107). The incidence of major malformations with terfenadine (mean dose 30–120 mg/day) has been estimated prospectively. Rates of major malformations did not differ from matched controls amongst those exposed during the first trimester. However, birth weight was lower in babies exposed to terfenadine, but not when babies below 2500 g were compared. These findings emphasize the general value of continued studies on antihistamines during pregnancy; the findings with terfenadine may be equally applicable to its metabolite fexofenadine (108).

Cleft palate is seen more often in infants whose mothers have used antihistamines for the treatment of hyperemesis gravidarum (4.44 per 1000 births) than in infants of mothers without hyperemesis gravidarum and not treated with antihistamines (0.78 per 1000) (98). However, children of mothers suffering from hyperemesis gravidarum but not treated also showed a high incidence of cleft palate (3.14 per 1000). It is likely that cleft palate could be a consequence of the maternal condition rather than of drug teratogenicity.

Lactation

There have been no specific reports of harm resulting from the use of antihistamines during lactation, although there have been few studies. Triprolidine and loratadine would reach a breastfed infant in low concentrations (109).

Susceptibility Factors

Hepatic disease

Because sedation can lead to hepatic encephalopathy in patients with hepatic failure, sedative antihistamines should be avoided in such patients. In addition, some antihistamines are themselves hepatotoxic.

Other features of the patient

In view of their anticholinergic effects antihistamines should be avoided in cases of glaucoma and prostatism.

Antihistamines can be dangerous to drivers and people operating machinery, primarily because of their sedative effects but also because of blurring of vision.

Drug Administration

Drug overdose

- A 48-year-old woman was found dead after taking guaifenesin, diphenhydramine, and chlorphenamine, with heart blood concentrations of 27, 8.5, and 0.2 mg/l respectively (110).

Drug–Drug Interactions

Anticholinergic drugs

Drugs with anticholinergic effects (including phenothiazines, tricyclic antidepressants, quinidine, and disopyramide) will have their effects increased by antihistamines.

Cytochrome P450 isozymes

Several of the non-sedating antihistamines (astemizole, ebastine, loratadine, and terfenadine, but not cetirizine, desloratadine, fexofenadine, levocetirizine, or norastemizole) are metabolized by the cytochrome P450 isozyme CYP3A4 (SEDA-21, 177) (111). Concomitant treatment with drugs that inhibit this metabolic pathway (such as ketoconazole, itraconazole, erythromycin, clarithromycin) lead to increased plasma concentrations of the unmetabolized drug. Currently, only astemizole and terfenadine have been associated with cardiac adverse effects caused by such interactions. Terfenadine given with grapefruit juice, which also inhibits CYP3A4, resulted in higher plasma concentrations, but not QT interval prolongation (112).

Pooled human liver microsomes have been used to determine whether loratadine, desloratadine, and 3-hydroxydesloratadine are inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (113). Loratadine did not inhibit CYP1A2 or CYP3A4 at concentrations up to 3829 ng/ml, about 815 times greater than the expected maximal human plasma concentration (mean 4.7 ng/ml) after the recommended dose of 10 mg/day. Loratadine inhibited CYP2C19 and CYP2D6 with IC_{50} values of about 0.76 μmol/l (291 ng/ml) and 8.1 μmol/l (3100 ng/ml) respectively, about 60 and 660 times the expected loratadine therapeutic concentrations. Neither desloratadine nor 3-hydroxydesloratadine inhibited CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 by more than 25% at concentrations of about 3000 ng/ml. These results suggest that loratadine and its active metabolites desloratadine and 3-hydroxydesloratadine are unlikely to affect the pharmacokinetics of co-administered drugs that are metabolized by these five cytochrome P450 enzymes.

Drugs acting on the brain

Drugs that have effects on the brain (hypnotics, sedatives, narcotic analgesics, neuroleptic drugs, alcohol, lithium,

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anticonvulsants) will interact with antihistamines, especially the first-generation drugs. The second-generation antihistamines have not yet been proven to interact with drugs such as alcohol or diazepam (114–117).

Histamine

The unwanted effects of histamine injections can be partially blocked by H_1 histamine receptor antagonists, which were once used to prevent systemic adverse effects of histamine when it was used to stimulate gastric acid secretion, which is mediated by H_2 receptors.

Meglumine

When diphenhydramine was mixed with meglumine iodipamide to prevent an allergic reaction to the latter, a precipitate was formed. These two drugs should be regarded as incompatible for in vitro mixing.

Pseudoephedrine

Combinations with decongestants such as pseudoephedrine have been advocated for upper respiratory conditions, but pseudoephedrine can cause additional adverse effects, such as nervousness and raised blood pressure (118,119).

Stimulants

To counteract the sedative effects of the classic antihistamines, combinations with stimulants, such as pemoline and prolintane, have been tried. The efficacy of such combinations has not been proven, but additional adverse effects such as irritability (120) and hallucinations (121) have been observed.

D-Tubocurarine chloride

Tubocurarine can cause release of histamine by direct mast cell degranulation which can result in systemic effects, such as cutaneous flushing, local wheal and flare formation, hypotension, and occasionally bronchospasm. Preoperative oral terfenadine 60 mg + ranitidine 150 mg attenuated the reduction in blood pressure but not cutaneous flushing after the administration of tubocurarine and morphine in 60 women undergoing elective gynaecological surgery in a placebo-controlled study (122).

Interference with Diagnostic Tests

Skin testing

Since antihistamines inhibit the cutaneous response to histamine and allergens, they should be withdrawn (usually for a week, astemizole for up to 8 weeks) before skin testing for allergy is undertaken.

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Antimony and antimonials

General Information

Antimony is a brittle, bluish-white, metallic element (symbol Sb; atomic no 51). The symbol Sb comes from the Latin word stibium.

Antimony is found in such minerals as dyscrasite, jamesonite, kermesite, pyrargyrite, stephanite, tetrahedrite, and zinkenite.

The Arabic word for antimony stibnite or antimony trisulfate was kohl, from which the word alcohol ultimately derives (1). Antimonious ores were sometimes confused with lead ores, and alquifou was the name of a Cornish lead ore that looked like antimony and was used by potters to give a green glaze to earthenware. The word that the Quechua Indians of Peru use for antimony is surúcht, which gives soroche, a synonym for mountain sickness, which antimony was thought to cause.

Antimony salts have in the past found many uses in medicine, and antimony compounds, especially pentavalent ones, are still used to treat *Schistosoma japonicum* infestation and leishmaniasis (2). Antimony is also used as an emetic. Attention is being paid to the anticancer potential of antimony compounds (3,4). As with many other metals, occupational and environmental exposure is possible and can act additively with medical exposure.

Common adverse effects of antimony treatment include anorexia, nausea, vomiting, muscle ache, headache, lethargy, and bone and joint pain.

Antimony has been suggested to be a causal factor in sudden infant death syndrome, since fungal transformation of fire retardants containing antimony in cot mattresses will lead to the formation of stibine (SbH_3). However, the involvement of stibine in cot death is most unlikely (5,6).

Salts of antimony

Meglumine antimoniate

Meglumine antimoniate is a pentavalent antimonial chemically similar to sodium stibogluconate and is considered to have similar efficacy and toxicity. Meglutamine antimoniate solution contains pentavalent antimony 8.5% and stibogluconate 10%.

Sodium stibogluconate

Sodium stibogluconate is a pentavalent antimonial that contains pentavalent antimony 10%.

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Stibocaptate

Stibocaptate is a trivalent antimony compound, whose toxic effects, especially its acute adverse effects, are similar to those of the pentavalent compounds.

Uses

Antimony salts have in the past found many uses in medicine, and antimony compounds, especially pentavalent ones, are still used to treat *Schistosoma japonicum* infestation and leishmaniasis (2). The standard treatment of most South American cutaneous leishmaniasis is systemic, because of the propensity of the parasites to spread to mucous membranes. The drugs in common use remain parenteral, and are fairly toxic. Sodium stibogluconate, in a dose of 20 mg/kg for 30 days, remains the gold standard, with liposomal amphotericin a possible alternative. Both drugs are also the preferred choice for all strains of visceral leishmaniasis. Stibogluconate achieves a cure in certain cases (7,8) and is reasonably safe, although transient pancreatitis, musculoskeletal pains, and loss of appetite have been reported. Primary unresponsiveness (cure not obtained by the first course of treatment) is being increasingly reported (9) and is a particular problem in the Bihar region of North-East India, where a report documented primary unresponsiveness in 33% of cases (10). The new treatment options for visceral leishmaniasis have been reviewed (11).

Antimony is also used as an emetic. Attention is being paid to the anticancer potential of antimony compounds (3,4). As with many other metals, occupational and environmental exposure is possible and can act additively with medical exposure.

Pharmacokinetics

Antimony is excreted in the urine. Peak concentrations are seen at about 1–2 hours after an intramuscular injection of meglumine antimonate. Serum concentrations fall to about 10% of peak concentrations after about 8 hours. There is some accumulation of antimony during continued treatment. On a weight for weight basis children require a higher dose and tolerate antimony better. Toxicity is more likely in patients with impaired renal function, as would be expected for a drug that is mainly excreted in the urine.

Observational studies

The characteristics of 111 consecutive patients with visceral leishmaniasis in Sicily have been described (12). They were given intramuscular meglumine antimoniate (560 mg/m^2 of pentavalent antimony), generally for 21 days. There were adverse effects in 16 patients, including rash ($n = 3$) and dry cough ($n = 13$). All the adverse effects bar one (a severe urticarial rash) were transient and self-limiting and did not require drug withdrawal.

Comparative studies

In a prospective, open trial, conventional treatment with sodium stibogluconate ($n = 69$) was compared with meglumine antimoniate ($n = 58$) for cutaneous *Leishmania braziliensis* (13). The trial was too small and of too short a duration to compare efficacy reliably, but significantly fewer patients on meglumine antimoniate developed the myalgia/arthralgia, headache, and abdominal pain that are the most common adverse effects of the drug, and that tend to increase as treatment continues. About 30% developed significant adverse effects early in treatment and 70% late when stibogluconate was used, whereas 12% had early and 45% late adverse effects for antimoniate. Unfortunately, QT intervals were not monitored; a fatal dysrhythmia, usually preceded by increased QT dispersion, is the complication of sodium stibogluconate therapy most likely to lead to death.

There has been a further comparison of meglumine antimoniate ($n = 47$) and sodium stibogluconate ($n = 64$) (14). The trial was too small to examine the efficacy of the two drugs, but there were more adverse events with sodium stibogluconate, with a greater proportion with raised transaminase and amylase activities. There were no differences in electrocardiographic abnormalities between the two groups.

Allopurinol

Allopurinol and meglumine antimoniate (Glucantime™) have been evaluated in a randomized, controlled trial in 150 patients with cutaneous leishmaniasis (15). They received oral allopurinol (15 mg/kg/day) for 3 weeks, or intramuscular meglumine antimoniate (30 mg/kg/day, corresponding to 8 mg/kg/day of pentavalent antimony, for 2 weeks), or combined therapy. There were a few adverse effects in those who used allopurinol: nausea, heartburn ($n = 3$), and mild increases in transaminases ($n = 2$). These symptoms subsided on drug withdrawal.

In an open study, 72 patients each received meglumine antimoniate (60 mg/kg/day) or allopurinol (20 mg/kg/day) plus low-dose meglumine antimoniate (30 mg/kg/day) for 20 days, and each was followed for 30 days after the end of treatment (16). Only six patients in the combined treatment group complained of mild abdominal pain and nausea; however, one patient who received meglumine antimoniate developed a skin eruption. Generalized muscle pain and weakness occurred in four patients.

Paromomycin

In patients with visceral leishmaniasis, paromomycin (12 or 18 mg/kg/d) plus a standard dose of sodium stibogluconate for 21 days was statistically more effective than sodium stibogluconate alone in producing a final cure (17). In an open, randomized comparison of sodium stibogluconate either alone ($n = 50$) or in combination with two regimens of paromomycin ($n = 52$ and $n = 48$), there was improved parasitological cure in both groups given combination therapy (18). There were no differences in adverse events or biochemical and hematological measurements between any of the treatment arms. There was one serious adverse event (myocarditis) in the sodium stibogluconate monotherapy group. It should be noted that there were insufficient auditory examinations performed to assess any ototoxic effects of paromomycin.

Placebo-controlled studies

A randomized, double-blind, placebo-controlled study of sodium stibogluconate for 10 and 20 days has been conducted in 38 US military personnel with cutaneous leishmaniasis; 19 received sodium stibogluconate for 10

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days (and placebo for 10 days), and 19 received sodium stibogluconate for 20 days (19). Treatment withdrawal was necessary as a result of pancreatitis in seven patients (four in the 10-day treatment group and three in the 20-day group), and this occurred during the first 10 days of therapy in all seven patients. Myalgia occurred in 8 patients in the 10-day group and in 13 patients in the 20-day group. Patients in the 20-day group had myalgia on significantly more days than those in the 10-day group. Increases in amylase, lipase, and transaminases and falls in white blood cell count, hematocrit, and platelet count also differed significantly between the two groups.

General adverse effects

Common adverse effects of antimony treatment include anorexia, nausea, vomiting, muscle ache, headache, lethargy, and bone and joint pain.

Common adverse effects of meglumine antimonate are anorexia, nausea, vomiting, malaise, myalgia, headache, and lethargy. Muscle, bone, and joint pains have been described (SEDA-12, 710) (SEDA-13, 838) (20). Cardiac toxicity and electrocardiographic changes are dose-related. The general condition of the patient with visceral leishmaniasis probably plays a crucial role in these and other adverse effects. Malnutrition is common, the immune status often severely impaired, and patients are susceptible to intercurrent infections (SEDA-12, 710).

In 96 patients with visceral, mucosal, or viscerotropic leishmaniasis, who were given sodium stibogluconate 20 mg/kg/day for 20–28 days, adverse effects were common and necessitated withdrawal of treatment in 28% of cases. They included arthralgias and myalgias (58%), pancreatitis (97%), increased transaminases (67%), headache (22%), bone marrow suppression (44%), and rash (9%) (8). Arthralgias are more likely to represent reactions to the tissue of the dead or dying parasite than true allergies to the drug.

In 53 patients with dermal leishmaniasis after kala-azar, who were given sodium stibogluconate 20 mg/kg/day intramuscularly, adverse effects were changes in electrocardiographic ST segments and T waves (7%), arthralgias (11%), allergic rashes (7%), swelling at the site of injection (5%), neuralgia (4%), and a metallic taste (6%) (21).

Organs and Systems

Cardiovascular

Electrocardiographic changes are common in patients taking antimony salts; in one group there was an incidence of 7%. The most common changes are ST segment changes, T wave inversion, and a prolonged QT interval. The role of conduction disturbances in cases of cardiac failure and sudden death is not known. Cases of sudden death have been seen early in treatment after a second injection (SEDA-13, 838) (SEDA-16, 311).

Changes in the electrocardiogram depend on the cumulative dose of antimony, and sudden death can occur rarely (22).

- A 4-year-old boy with visceral leishmaniasis was given intravenous sodium stibogluconate 20 mg/kg/day (1200 mg/day) and oral allopurinol 16 mg/kg/day (100 mg tds). On day 3 he reported chest pain and a persistent cough. Electrocardiography was unremarkable. The drugs were withdrawn and 3 days later he developed a petechial rash on the legs. Sepsis and other causes of petechial rashes were ruled out. Three days after treatment was discontinued he developed ventricular fibrillation and died.

The authors suggested that patients taking antimony compounds should be observed cautiously for signs of cardiological and hematological changes.

Myocarditis with electrocardiographic changes has been well described, but the risk of dysrhythmias is usually small. There have been reports of severe cardiotoxicity, leading in some cases to death (23,24). This may largely be due to changes in physicochemical properties of the drug; one cluster of cases was associated with a high-osmolarity lot of sodium stibogluconate (23).

Because of concerns regarding the cardiac adverse effects of antimonials, it is good practice to admit patients for the duration of therapy whenever practicable. This may mean admitting otherwise fit young patients for several weeks for treatment of a non-healing ulcer. To address the safety of outpatient management, a recent small study of 13 marines in the UK showed that they could be safely managed as outpatients with daily stibogluconate injections, provided there was close monitoring of electrocardiograms and blood tests to provide early warning of bone marrow toxicity (25). Three patients developed minor electrocardiographic changes and one developed thrombocytopenia. All these adverse effects resolved when treatment was withdrawn. Patients with a predisposition to dysrhythmias (such as some with ischemic heart disease) are best treated with pentavalent antimonials as inpatients to identify and manage adverse effects early when resources allow.

The cardiac toxicity of antimony has been explored in cultured myocytes (26,27). Potassium antimony tartrate disrupted calcium handling, leading to a progressive increase in the resting or diastolic internal calcium concentration and eventual cessation of beating activity and cell death. An interaction with thiol homeostasis is also involved. Reduced cellular ATP concentrations paralleled toxicity but appeared to be secondary to other cellular changes initiated by exposure to antimony.

Even the normal dose of sodium stibogluconate can lead to both cardiotoxicity and hemotoxicity, because of its cumulative effects.

- Fatal accumulation of sodium stibogluconate occurred in a 4-year-old boy with visceral leishmaniasis treated with intravenous sodium stibogluconate 20 mg/kg (1200 mg/day) and oral allopurinol 16 mg/kg/day (100 mg tds) (22). On day 3 he reported chest pain and persistent cough, and the drugs were withdrawn. Three days later he developed a petechial rash on the legs and died with ventricular fibrillation.

Respiratory

Antimonate ore caused chronic bronchitis in 16 of 100 miners exposed (28). The chronic bronchitis was

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characterized by a mild slow course with ventilation disturbances. There were no cases of pneumoconiosis.

Nervous system

Headaches are common during treatment with antimony. Generalized neuralgia was reported in one study, with an incidence of 4% (SEDA-13, 838) (SEDA-16, 311).

Peripheral sensory neuropathy has been described after the use of sodium stibogluconate for cutaneous leishmaniasis (SEDA-21, 300).

Sensory systems

A metallic taste due to antimonials is uncommon but probably under-reported (SEDA-16, 311).

Hematologic

Autoimmune hemolytic anemia has been described with meglumine antimoniate (29).

Thrombocytopenia has been reported in a patient with *Leishmania donovani* infection and AIDS after stibogluconate therapy for 7 days (SEDA-13, 838). There have been two further reports, one involving a patient with cutaneous leishmaniasis (occurring after 19 days of treatment), the second a man with kala-azar (who became thombocytopenic 11 days after starting therapy); in kala-azar a low platelet count is common and the count normally rises with treatment (SEDA-18, 294).

Gastrointestinal

Anorexia, nausea, and vomiting are common with antimonials (30).

Liver

Hepatotoxicity has been described, but the disease itself may play an overriding role. In 16 patients with mucosal leishmaniasis treated with meglumine antimoniate 20 mg/kg intravenously for 28 days, there were raised liver enzyme in conjunction with electrocardiographic abnormalities and/or musculoskeletal complaints in three subjects (SEDA-16, 311).

Pancreas

Pancreatitis has occasionally been reported with antimonials. In 1993, four cases were described in three reports; two of the patients were immunocompromised. One was asymptomatic, while the other three complained of abdominal pain. Rechallenge with half of the standard dose was carried out in one case and resulted in a renewed increase of serum amylase activity.

Acute pancreatitis developed during treatment with meglumine antimoniate for visceral leishmaniasis in a young boy (31).

- A 2-year-old boy with a history of intermittent high-grade fever, sweating, and abdominal distension developed visceral leishmaniasis. He was given meglumine antimoniate (Glucantime®, Rhone Poulenc, France) 5 mg/kg/day, and the dose was doubled every other day to reach 20 mg/kg/day. Two days after he had reached the full dose, his temperature returned to normal, his general condition improved, and his liver and spleen began to shrink. However, the serum amylase increased to 254 U/l. Because he was asymptomatic, treatment with meglumine antimoniate was continued. However, on day 10 he complained of vomiting and abdominal pain with rebound tenderness. Acute pancreatitis was confirmed by serum amylase and lipase values up to 1557 and 320 U/l respectively and by ultrasound findings of dilatation and edema of the pancreatic ducts. Meglumine antimoniate was withdrawn and the pancreatitis was managed conservatively. Two days later his fever increased and the spleen and liver began to enlarge. He was given allopurinol (20 mg/kg/day) and ketoconazole (5 mg/kg/day) and became afebrile; the spleen and liver began to shrink, his pancytopenia improved, and the albumin:globulin ratio and serum amylase and lipase activities returned to normal. The acute pancreatitis resolved uneventfully.

The mechanism and frequency of this adverse effect are unknown. It has been suggested that immunocompromised patients may be at a higher risk (SEDA-18, 294), but pancreatitis is in any case seen more often in patients with AIDS, irrespective of drug treatment.

Urinary tract

- Septic shock with oliguria developed soon after the first intramuscular administration of meglumine antimoniate 20 mg/kg (equivalent to 510 mg of antimony) to a patient with visceral leishmaniasis and normal renal function (32). Creatinine clearance fell to 23 ml/min. Treatment was withdrawn, and antimony urinary excretion was measured. After the initial dose, 500 mg of antimony was recovered in the urine over 8 days (98% of the dose); 66% was eliminated within the first 48 hours. Nine days after the dose, meglumine antimoniate was reintroduced in a dosage of 11.7 mg/kg (equivalent to 300 mg of antimony) every 48 hours, with good tolerance. At that time creatinine clearance had returned to 88 ml/min. By day 14 of therapy the dosage interval was reduced to 24 hours and from day 17 to day 31 the dosage was increased to 16.6 mg/kg/day (equivalent to 425 mg of antimony). The patient eventually completely recovered, with normal renal function. Although there are no specific guidelines for dosage adjustment in renal insufficiency, monitoring antimony urinary excretion indicates that the kidneys are the almost exclusive route of elimination.

Musculoskeletal

Arthralgia is a common complaint during treatment with pentavalent antimonials and is usually dose-related (30). Muscle pain and bone pain have also been described.

- A palindromic arthropathy with effusion and pancreatitis occurred in association with stibogluconate treatment for kala-azar in a 30-year-old man on hemodialysis for chronic renal insufficiency (SEDA-16, 311).

Immunologic

As an industrial and environmental toxin, antimony trioxide can cause disturbances of immune homeostasis.

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Workers in antimony trioxide manufacture had reduced serum concentrations of cytokines (interleukin 2, gamma interferon) and immunoglobulin (IgG1, IgE) (33).

Death

Antimony has been suggested to be a causal factor in sudden infant death syndrome, since fungal transformation of fire retardants containing antimony in cot mattresses will lead to the formation of stibine (SbH_3). However, the involvement of stibine in cot death is most unlikely (5,6).

Sudden death has been reported during the use of stibocaptate (SEDA-11, 599) (34).

Long-Term Effects

Drug tolerance

The treatment of cutaneous leishmaniasis has been reviewed, including the use of pentavalent antimonials (35). Antimony-resistant strains continue to emerge (36), leading to the use of higher dosages of antimonials or combinations of antimonials with other compounds, such as paromomycin or gamma interferon (37).

Drug–Drug Interactions

Amiodarone

A pharmacodynamic interaction has been described between amiodarone and meglumine antimoniate, both of which prolong the QT interval; the interaction resulted in torsade de pointes (38).

- A 73-year-old man with visceral leishmaniasis was given meglumine antimoniate intramuscularly 75 mg/kg/day. At that time his QT_c interval was normal at 0.42 seconds. Three weeks later his QT_c interval was prolonged to 0.64 seconds and he was given metildigoxin 0.4 mg and amiodarone 450 mg intravenously over 8.25 hours; 12 hours later he had a cardiac arrest with torsade de pointes, which was cardioverted by two direct shocks of 300 J and lidocaine 100 mg in two bolus injections. Because he had frequent episodes of paroxysmal atrial fibrillation, he was given amiodarone 100 mg over the next 40 hours, and developed recurrent self-limiting episodes of torsade de pointes associated with QT_c interval prolongation, which responded to intravenous magnesium 1500 mg. After withdrawal of amiodarone there was no recurrence and a week later the QT_c interval was 0.48 seconds. The plasma potassium concentration was not abnormal in this case.

In view of this report it is probably wise to avoid co-administration of antimonials and amiodarone.

Amphotericin

Amphotericin can worsen stibogluconate-induced cardiotoxicity; a gap of at least 10 days between sodium stibogluconate and amphotericin is recommended (24).

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Antituberculosis drugs

See also Individual agents

General Information

Antituberculosis drugs are classified as first-line and second-line.

First-line drugs

- ethambutol
- isoniazid
- pyrazinamide
- rifampicin
- streptomycin

Second-line drugs

- capreomycin
- clofazimine
- cycloserine
- ethionamide and propionamide
- fluoroquinolones
- kanamycin
- *para*-aminosalicylic acid
- rifabutin
- thiacetazone

As a rule, a regimen of two, three, or four of the five first-line antituberculosis drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin) is used in tuberculosis (1). The 6-month short-course regimen consists of isoniazid, rifampicin, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for 4 months (1). It may be advisable to include ethambutol in the initial phase when isoniazid resistance is suspected or if the prevalence of primary resistance to isoniazid is over 4% in new cases. A 9-month regimen consisting of isoniazid and rifampicin is also highly successful (1). Treatment should always include at least two drugs to which the mycobacteria are susceptible.

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Careful monitoring and the addition of pyridoxine to isoniazid have reduced the number of adverse drug effects in tuberculosis. Awareness of potentially severe hepatotoxic reactions is vital, because hepatic failure may be a devastating and often fatal condition. Fulminant hepatic failure caused by rifampicin, isoniazid, or both has been described (2).

Treatment problems that can arise are mainly of two types: adverse reactions (collateral, toxic, or hypersusceptibility reactions), and initial or acquired resistance of *Mycobacterium tuberculosis*, *Mycobacterium bovis*, or non-tuberculous mycobacteria to one or more of the antituberculosis drugs. The latter probably only occurs when the patient has not taken the full combination or the full doses of the drugs all the time. Combination formulations are thus particularly useful. Multidrug-resistant tuberculosis, defined as resistance against at least isoniazid and rifampicin, is the most clinically relevant form of resistance to treatment worldwide.

Observational studies

An increasing number of patients with multidrug-resistant tuberculosis are being treated with second-line drugs worldwide, often in places with poor resources. The number of drugs used is large (4–7) and treatment is prolonged (1–2 years). There is justifiable concern over patients' tolerance of such regimens and their adverse effects, which determine adherence to treatment. Treatment has to be individualized according to the WHO guidelines for a DOTS-plus strategy.

It is therefore encouraging to read a report from Lima, Peru, where 60 patients from a shanty town tolerated a median of eight antituberculosis drugs fairly well for a median duration of 20 months (3). All received a parenteral aminoglycoside daily for 6 months, cycloserine, and a fluoroquinolone, and most also took *para*-aminosalicylic acid and ethionamide. Of 60 patients, 23 took clofazimine, 23 pyrazinamide, 25 isoniazid, and 3 rifampicin. Commonly encountered adverse effects included dermatological effects, including bronzing of the skin (many of these patients were taking clofazimine and fluoroquinolones), depression, anxiety, and peripheral neuropathy. All complained of mild gastritis. There were no cases of serious hepatic or renal toxicity. This may have been because only a few patients took rifampicin. Absence of eighth nerve toxicity was striking, and can be attributed to close monitoring of patients by physicians with experience of DOTS-plus regimens.

In a similar report from Turkey, adverse reactions to drugs led to withdrawal of one or more drugs in 62 of 158 patients (39%) (4). Outcomes were favorable and cultures became negative in 95% of the patients within 2 months.

General adverse reactions

Adverse reactions are often due to the combined effects of two or more drugs used simultaneously (5). Hypersusceptibility reactions can occur even to more than one agent. The incidence of adverse reactions to drugs used in the treatment of tuberculosis is higher in elderly patients, who are more likely to have intercurrent illnesses and a lower lean body mass than younger patients. In two studies from Hong Kong in patients being treated for tuberculosis with rifampicin, the incidence of adverse reactions was higher with regimens containing rifampicin; furthermore, patients taking rifampicin had a higher steady-state plasma concentration of isoniazid (1,6).

Some simple rules about which drugs are more likely to cause which reactions reflect the principle that the most probable causative agent (or agents) must be stopped.

Nervous and sensory systems

Ethambutol is the most likely drug to cause visual disturbances. Isoniazid is associated with polyneuritis and reactions of the central nervous system. Streptomycin can cause eighth nerve toxicity.

Liver

Hepatotoxicity is consistently the most common serious adverse reaction in patients taking antituberculosis drugs. Hepatic necrosis is the most important adverse effect of first-line antituberculosis drug therapy (2). Asymptomatic rises in transaminases are common and are not by themselves justification for withdrawing medication, since they settle spontaneously in most patients while treatment continues. All patients taking antituberculosis drugs should be told to report all new illnesses, especially when associated with vomiting. Hepatitis B carriers were no more likely to react adversely to antituberculosis drugs than non-carriers (7).

If liver damage occurs, isoniazid is probably an important factor and it should be stopped before rifampicin or pyrazinamide (8). Prediction of hepatotoxicity is possible (9). In a case-control study of 60 patients in India, conducted in order to identify features predicting hepatotoxicity, the body mass index was significantly lower (17.2 kg/m^2) in patients who experienced hepatotoxicity than in controls (19.5 kg/m^2) (10).

Urinary tract

In cases of renal insufficiency, streptomycin and ethambutol or second-line antituberculosis drugs with renal toxicity should be immediately withdrawn.

Skin

Adverse reactions to all types of medication are more common in HIV-positive individuals; skin reactions are especially frequent and often severe. Thiacetazone is well recognized as a cause of severe reactions, some of them fatal, but even in combination antituberculosis drug regimens that exclude thiacetazone, the incidence of adverse skin reactions is much higher in HIV-positive than HIV-negative patients: 23% against 1% in one study from Cameroon (11).

Immunologic

In allergic reactions, the drug most probably responsible can be difficult to identify, since the same kind of reaction can occur independently of the chemical nature of the drug. For evaluation of allergic drug reactions, the analysis of time relations (duration of exposure, reaction time, drug-free interval before re-exposure) is extremely

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important. Particularly in allergic reactions to rifampicin, intermittent treatment or re-exposure after a drug free-interval favors sensitization and occurrence. Depending on the severity of the adverse effects, one, two, or all drugs must be stopped until the adverse reaction has completely disappeared. The use of second-line antituberculosis drugs may sometimes be necessary. In patients with drug fever or common rashes, specific desensitization may be attempted, at least with isoniazid (12). In more severe reactions, with anaphylactic shock, agranulocytosis, thrombocytopenia, toxic epidermal necrolysis, or Stevens–Johnson syndrome, specific desensitization should not be considered and the drug should be discarded from the combination.

Organs and Systems

Liver

Hepatotoxicity is the most important adverse effect of antituberculosis drug therapy. Isoniazid, rifampicin, and pyrazinamide are the main culprits. There is wide variability in the risk of hepatotoxic reactions reported from different parts of the world or in different populations (for example African-American women in the postpartum period) (SEDA-24, 353).

Risks

The risks of hepatotoxicity differ with different antituberculosis drug combinations.

Rifampicin plus isoniazid

There are mild to moderate increases in liver transaminases during treatment with rifampicin plus isoniazid in most patients. However, biochemical hepatitis is diagnosed when transaminase activities increase to more than four times the upper limit of the reference ranges on two occasions at least 1 week apart, or more than five times on any single occasion. This calls for withdrawal of all potentially hepatotoxic drugs (rifampicin, isoniazid, and pyrazinamide) until the enzymes return to the reference ranges. During this period, streptomycin plus ethambutol, with or without cycloserine and a fluoroquinolone, is recommended in seriously ill patients.

Hepatotoxicity is generally considered to be rare among children who receive antituberculosis drugs. However, a report from Japan has suggested that this might not be the case, at least in Asia (13). The authors noted high activities of transaminases, more than five times the upper end of the reference range, in eight of 99 children aged 0–16 years who received various combinations of drugs, including rifampicin and isoniazid; 18 children were excluded because of baseline abnormalities in liver function. Age under 5 years and pyrazinamide in the drug regimen were risk factors for hepatotoxicity. There have been few other reports of the risk of hepatotoxicity in children.

Pyrazinamide plus rifampicin

There is continuing concern about the hepatotoxicity of the combination of pyrazinamide with rifampicin for the treatment of latent pulmonary tuberculosis. Among 148 who were given the combination for 2 months, grade 3 hepatotoxicity (transaminases more than 5–20 times the upper limit of the reference range) and grade 4 hepatotoxicity (transaminases more than 20 times the upper limit of the reference range) were reported in 10 and four patients respectively (14). The risk of hepatotoxicity was associated with female sex (OR = 4.1; 95% CI = 1.2, 14) and presumed recent infection (OR = 14.3; 95% CI = 1.8, 115). The investigators recommended caution in using the combination of pyrazinamide with rifampicin in populations in whom its safety has not been established.

Others consider that this combination is useful for high-risk, traditionally non-adherent patients, such as alcoholics and the homeless, but have also emphasized the need for careful monitoring for toxicity (15). This suggestion is based on the presumption that the combination regimen, although toxic, is more likely to be completed by high-risk patients than 6 months of isoniazid alone. However, others observed similar completion rates for the two regimens in a multicenter study (61% and 57%) (16), and the safety and cost-effectiveness of this combination in the treatment of latent tuberculosis has been questioned (17).

Two cases of severe and fatal hepatitis have been reported to the CDC from New York and Georgia among patients taking rifampicin and pyrazinamide for latent tuberculosis (18). Between February and August 2001, another 21 patients had severe hepatotoxicity following treatment with rifampicin plus pyrazinamide for 2 months for latent tuberculosis, as reported to the CDC; five died of fulminant hepatic failure, two of whom had recovered from isoniazid-induced hepatitis (19). This report led to revision of previous guidelines of the American Thoracic Society. According to the revised guidelines, isoniazid for 9 months is the preferred treatment for latent tuberculosis infection in HIV-negative subjects, followed by isoniazid for 6 months or rifampicin for 4 months. Rifampicin plus pyrazinamide for 2 months can be used with caution in these patients, especially if they are taking other medications that are associated with liver injury, and those who drink a lot of alcohol. This combination is not recommended for those with underlying liver disease or who have had isoniazid-associated liver damage. Liver function tests should be measured at baseline and at 2-weekly intervals thereafter for 6 weeks. Only two non-fatal cases of severe liver injury have been reported to the CDC since the publication of revised guidelines as of November 2002 (20).

Susceptibility factors

Acetylator status and other genetic factors, old age, pre-existing hepatic dysfunction, alcoholism, co-infection with hepatitis virus, and malnutrition are important potential susceptibility factors for the development of liver damage in patients taking antituberculosis drugs (21), but there have been inconsistent findings with regard to some of these risk factors in different studies.

Genetic factors

The issue of hepatic dysfunction and acetylator status during treatment with isoniazid plus rifampicin has been re-examined in 77 Japanese patients with pulmonary

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tuberculosis (22). There was a marked increase in the risk of hepatotoxicity amongst slow acetylator NAT2* genotypes (a combination of mutant alleles) compared with the rapid acetylator genotype (homozygous NAT2*4). Using Taylor's series analysis it can be calculated that the relative risk was 28 (95% CI = 4.1, 192). Despite a small sample size (seven slow acetylator genotypes, 42 intermediate, and 28 rapid) the relative risk was highly significant, which is not surprising if all seven of the slow acetylators and only one of the 28 rapid acetylators developed hepatotoxicity.

A unique feature of this study was the determination of acetylator status by genotyping rather than phenotyping. There is generally good concordance between the two methods, but in the presence of hepatic dysfunction the phenotype assessment may not reflect the genotype. Furthermore, 42 of the 77 patients were assigned to the intermediate acetylator genotype, based on heterozygosity for NAT2*4 and a mutant allele. However, phenotyping by estimation of concentrations of metabolites of the commonly used probes does not consistently result in identification of intermediate acetylators. The Japanese are mostly fast acetylators (~90%) compared with Caucasians or Indians (40–50%). It is unlikely, however, that the observed association between slow acetylator genotype and the high risk of hepatic dysfunction was affected by any of these considerations. The dose of isoniazid was rather large (~8 mg/kg/day) and this may have increased the risk of hepatotoxicity. Furthermore, hepatotoxicity was defined as an increase in transaminases to one and a half times the top of the reference range. This degree of hepatic dysfunction is not uncommon in patients taking antituberculosis drugs, and is no indication for withdrawal or modification of treatment. It is not possible to assess the risk of severe hepatotoxicity during treatment, owing to lack of detailed information in the published report.

A case-control study has suggested that there is also an increased risk of antituberculosis drug-induced hepatotoxicity in individuals with a glutathione-*S*-transferase M1 "null" mutation (23). Reduced glutathione transferase activity could theoretically predispose individuals to adverse effects of toxic metabolites and xenobiotics. These observations need to be confirmed.

Old age

Old age and the presence of hepatic dysfunction on baseline evaluation are the most consistent predictors of hepatotoxicity during antituberculosis therapy. The association between hepatotoxicity and hepatitis C virus and HIV seropositivity has been reviewed (SEDA-23, 324). A report from Hong Kong has suggested that the risk is much greater in hepatitis B virus carriers taking antituberculosis drugs (24). Even after excluding patients who had raised baseline alanine transaminase activity or with HbeAg seroconversion during the phase of hepatic dysfunction, the risk of hepatotoxicity was still significantly higher in hepatitis B carriers taking antituberculosis drugs compared with non-carriers (26% versus 8.8%). These observations are of considerable importance in regions of the world in which the prevalence of hepatitis B infection as well as tuberculosis is high, such as South-East Asia and sub-Saharan Africa.

Liver transplantation

Enhanced hepatotoxicity of conventional antituberculosis regimens has been reported in recipients of orthotopic liver transplants, which is not unexpected, because of bouts of organ rejection (25). The authors recommended ofloxacin for these patients on the basis of favorable outcome in six cases. A conventional antituberculosis induction regimen was used initially until hepatotoxicity developed in all six patients. Thereafter they were treated with a combination of ofloxacin and ethambutol, with apparent cure in all. It should be noted that most of the patients took isoniazid + rifampicin for almost 2 months, which is the usual period when hepatotoxic reactions occur. Perhaps one should evaluate substitution of rifampicin with ofloxacin from the very beginning in order to minimize hepatotoxicity, as well as interference with ciclosporin leading to graft rejection noted in an earlier study (26).

Prevention

One of the most important predictors of hepatotoxicity during antituberculosis drug therapy is an abnormal liver function test at baseline. It is reasonable to avoid potentially hepatotoxic drugs in the management of patients with pre-existing liver disease.

The use of ofloxacin instead of rifampicin in antituberculosis drug regimens for patients with underlying chronic liver disease has been reported to be associated with a significantly lower risk of hepatotoxicity (27). Similar observations have been reported among carriers of hepatitis B and liver transplant recipients by other investigators.

Management

There are four issues related to the management of patients who develop hepatotoxicity during treatment with antituberculosis drugs:

1. whatthe preferred treatment regimen should be for patients with significantly abnormal liver functions at baseline;
2. when treatment should be stopped/modified if hepatic dysfunction develops;
3. what antituberculosis treatment, if any, should be used until liver function improves;
4. what a safe regimen is for re-treatment of these patients.

Several herbal products have been claimed to mitigate drug-induced hepatitis caused by antituberculosis agents. However, few of them have undergone rigorous randomized controlled trials.

- Glycyrrhizin is widely used in Japan for the treatment of chronic hepatitis, but in a non-randomized trial in 24 patients who developed drug-induced hepatitis while undergoing antituberculosis chemotherapy, there was no difference in the time required for recovery between the patients who were treated with or without intravenous glycyrrhizin 40 ml/day (28).
- *Moringa oleifera*, commonly known as "drumstick," has been mentioned in the treatment of various illnesses in Indian folk medicine, and an ethanolic extract of the

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leaves had a hepatoprotective effect in a rat model of antituberculosis drug-induced liver injury (29).
- Russian investigators have reported a hepatoprotective effect of a plant product "Galstena" in a rat model and have extended their observations to a clinical trial, with favorable results; however, few data were given in this report (30).

It cannot be denied that there is a need for continuing research in this area, but it is necessary to undertake well-conducted scientific studies before claims of hepatoprotective effects of herbal products can be accepted.

There is a lack of consensus on the best re-treatment protocol for patients who develop hepatotoxicity during treatment with standard antituberculosis agents. Investigators from Turkey have reported a high risk of recurrence of hepatitis (in six of 25 patients) on re-introduction of all drugs in full doses after recovery from hepatitis (31). This risk was less when rifampicin and isoniazid were re-introduced sequentially in increasing doses and when pyrazinamide was replaced by streptomycin.

Long-Term Effects

Drug tolerance

Primary and secondary bacterial resistance to antituberculosis drugs represents a major problem. This can be demonstrated by resistance tests, if available. When testing is not done, primary or secondary resistance can only be suspected when drug treatment fails. The incidence of bacterial resistance varies enormously from country to country and from population to population. In Tanzania (32), where the WHO and the International Union Against Tuberculosis and Lung Diseases (IUATLD) has developed antituberculosis programs, primary resistance to isoniazid and/or streptomycin is found in 10% of cases (33). In contrast, South-East Asian and African patients harbor resistant bacteria markedly more often (SED-10, 572); resistance tests therefore remain mandatory for good epidemiological and therapeutic control. Recent reports from the WHO drug resistance surveillance network have allowed an overview of the current situation worldwide and facilitate the choice of medication according to the origin of the patients (34).

Multidrug-resistant tuberculosis generally results from inadequate therapy or lack of compliance with therapy. A strain of mycobacteria is called resistant when it is insensitive to one of the first-line drugs. It is called multiresistant when it is insensitive to both isoniazid and rifampicin. In this case other antituberculosis drugs may also be ineffective (35). In practice, at least two second-line antituberculosis drugs, selected on the basis of individual drug susceptibility, are given in combination with a fluoroquinolone (36).

Drug malabsorption may contribute to the emergence of acquired drug resistance. It has been described in HIV-infected patients with advanced disease (37), and also in immunocompetent patients (38). Thus, in addition to the use of directly observed therapy to ensure compliance, it is advisable to monitor antimycobacterial drug concentrations routinely in such patients. Practical proposals for the choice of antituberculosis drugs in special circumstances, including drug resistance, have been made (39).

Susceptibility Factors

Age

Increasing age predisposes to hepatotoxicity from antituberculosis drugs. Workers from Florida have reported a five-fold increase in the likelihood of drug-induced hepatotoxicity in patients who are hepatitis C-positive and a four-fold increase in patients who are HIV-positive, compared with seronegative patients treated for tuberculosis (40). In all, 134 patients taking antituberculosis drugs were monitored for drug-induced hepatotoxicity, defined as an increase in aspartate transaminase and/or alanine transaminase activity from normal to at least three times normal and/or an increase in bilirubin above normal. Of the 22 patients who developed drug-induced hepatotoxicity, only six developed drug-induced hepatotoxicity on re-introduction of treatment after an interval in which the abnormalities had resolved. Four of the six had liver biopsies, which showed active inflammation, attributed (at least in part) to hepatitis C. These were then treated with interferon alfa, with improvement of liver chemistry. On improvement, antituberculosis drug therapy was successfully re-introduced in the form of isoniazid and rifabutin, the latter being considered to be less hepatotoxic than rifampicin.

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Antrafenine

See also Non-steroidal anti-inflammatory drugs

General Information

Antrafenine closely resembles glafenine and floctafenine (SED-9, 153) (SEDA-7, 116) (SEDA-11, 96) (1). The same adverse effects must be expected and some have been described, for example nephrotoxicity (SEDA-4, 69) (2). Gastrotoxicity is claimed to be less than with aspirin (3), again no doubt merely because it is a weak anti-inflammatory drug.

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Apiaceae

See also Herbal medicines

General Information

The genera in the family of Apiaceae (formerly Umbelliferae) (Table 1) include a variety of spices and vegetables, such as angelica, anise, carrot, celery, chervil, coriander, cumin, dill, fennel, parsley, and parsnip.

Food allergy to spices accounts for 2% of all cases of food allergies but 6.4% of cases in adults. Prick tests to native spices in 589 patients with food allergies showed frequent sensitization to the Apiaceae coriander, caraway, fennel, and celery (32% of prick tests in children, 23% of prick tests in adults) (1). There were 10 cases of allergy related to the mugwort-celery-spices syndrome: coriander ($n = 1$), caraway ($n = 2$), fennel ($n = 3$), garlic ($n = 3$), and onion ($n = 1$).

Scratch tests with powdered commercial spices in 70 patients with positive skin tests to birch and/or mugwort pollens and celery were positive to aniseed, fennel, coriander, and cumin, all Apiaceae, in more than 24 patients (2). Spices from unrelated families (red pepper, white pepper, ginger, nutmeg, cinnamon) elicited positive immediate skin test reactions in only three of 11 patients. Specific serum IgE to spices (determined in 41 patients with a positive RAST to celery) up to class 3 was found, especially in patients with celery-mugwort or celery-birch-mugwort association. The celery-birch association pattern was linked to positive reactions (RAST classes 1,2) with spices from the Apiaceae family only.

Ammi majus and *Ammi visnaga*

Ammi majus is also known as bishop's weed or large bullwort, and *Ammi visnaga* as toothpick weed. They have numerous active ingredients, including ammirin, angenomalin, kellactone, majurin, and marmesin, furanocoumarins (psoralen, bergapten, isopimpinellin, imperatorin, umbelliprenin, xanthotoxin), and flavonol triglycosides (kaempferol, isorhamnetin). In modern times they have been used to treat vitiligo, since they contain psoralens, and have several different pharmacological effects in experimental animals, including hypoglycemic effects (3), antischistosomal effects (4), and inhibition of nephrolithiasis (5).

Table 1 The genera of Apiaceae

Aciphylla (fierce Spaniard)	*Levisticum* (levisticum)
Aegopodium (goutweed)	*Ligusticum* (licorice-root)
Aethusa (aethusa)	*Lilaeopsis* (grasswort)
Aletes (Indian parsley)	*Limnosciadium* (dogshade)
Ammi (ammi)	*Lomatium* (desert parsley)
Ammoselinum (sand parsley)	*Musineon* (wild parsley)
Anethum (dill)	*Myrrhis* (myrrhis)
Angelica (angelica)	*Neoparrya* (neoparrya)
Anthriscus (chervil)	*Oenanthe* (water dropwort)
Apiastrum (apiastrum)	*Oreonana* (mountain parsley)
Apium (celery)	*Oreoxis* (oreoxis)
Arracacia (arracacia)	*Orogenia* (Indian potato)
Berula (water parsnip)	*Osmorhiza* (sweetroot)
Bifora (bishop)	*Oxypolis* (cowbane)
Bowlesia (bowlesia)	*Pastinaca* (parsnip)
Bupleurum (bupleurum)	*Perideridia* (yampah)
Carum (carum)	*Petroselinum* (parsley)
Caucalis (burr parsley)	*Peucedanum* (peucedanum)
Centella (centella)	*Pimpinella* (burnet saxifrage)
Chaerophyllum (chervil)	*Podistera* (podistera)
Cicuta (water hemlock)	*Polytaenia* (hairy moss)
Cnidium (snow parsley)	*Pseudocymopterus* (false spring parsley)
Conioselinum (hemlock parsley)	*Pteryxia* (wavewing)
Conium (poison hemlock)	*Ptilimnium* (mock bishop weed)
Coriandrum (coriander)	*Sanicula* (sanicle)
Cryptotaenia (honewort)	*Scandix* (scandix)
Cuminum (cumin)	*Selinum* (selinum)
Cyclospermum (marsh parsley)	*Seseli* (seseli)
Cymopterus (spring parsley)	*Shoshonea* (shoshonea)
Cynosciadium (cynosciadium)	*Sium* (waterparsnip)
Daucosma (daucosma)	*Smyrnium* (smyrnium)
Daucus (wild carrot)	*Spermolepis* (scaleseed)
Dorema (dorema)	*Sphenosciadium* (sphenosciadium)
Erigenia (erigenia)	*Taenidia* (taenidia)
Eryngium (eryngo)	*Tauschia* (umbrellawort)
Eurytaenia (spreadwing)	*Thaspium* (meadowparsnip)
Falcaria (falcaria)	*Tilingia* (tilingia)
Ferula (asafetida)	*Tordylium* (tordylium)
Foeniculum (fennel)	*Torilis* (hedge parsley)
Glehnia (silvertop)	*Trachyspermum* (Ajowan caraway)
Harbouria (harbouria)	*Trepocarpus* (trepocarpus)
Heracleum (cow parsnip)	*Turgenia* (false carrot)
Hydrocotyle (hydrocotyle)	*Yabea* (yabea)
	Zizia (zizia)

Adverse effects

Injudicious use of the fruit of *A. majus* in combination with skin exposure to the sun can cause severe phototoxic dermatitis, owing to the presence of psoralens (6).

- IgE-mediated rhinitis and contact urticaria were caused by exposure to bishop's weed in a 31-year-old atopic female florist (7). A skin prick test with bishop's weed flowers gave an 8 mm wheal, and the bishop's weed-specific serum IgE concentration was 9.7 PRU/ml (RAST class 3).

Prolonged use or overdosing of the fruit of *A. visnaga* can cause nausea, dizziness, constipation, loss of appetite, headache, pruritus, and sleeping disorders.

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Angelica sinensis

Angelica sinensis, known in China as "dong quai" or "dang gui," contains antioxidants (8), inhibits the growth of cancer cells in vitro (9) and stimulates immune function in experimental animals (10). It has been used to treat amenorrhea (11) and menopausal hot flushes (12), and to reduce pulmonary hypertension in patients with chronic obstructive pulmonary disease (13).

Adverse effects

Angelica sinensis can cause hypertension (14).

- A 32-year-old woman, 3 weeks post-partum, developed acute headache, weakness, light-headedness, and vomiting. Her blood pressure was 195/85 mmHg. She had taken dong quai for postpartum weakness and said that she had not been taking any other medicines. Her 3-week-old son's blood pressure was raised to 115/69. Dong quai medication of the mother and breast-feeding of the child were discontinued and the blood pressure normalized in both patients within 48 hours.

Conium maculatum

Conium maculatum (hemlock) contains the poisonous piperidine alkaloid, coniine, and related alkaloids, *N*-methyl-coniine, conhydrine, pseudoconhydrine, and gamma-coniceine. It has well-established teratogenic activity in certain animal species.

Adverse effects

The symptoms of hemlock poisoning are effects on the nervous system (stimulation followed by paralysis of motor nerve endings and nervous system stimulation and later depression), vomiting, trembling, difficulty in movement, an initially slow and weak and later a rapid pulse, rapid respiration, salivation, urination, nausea, convulsions, coma, and death (15).

Coriandrum sativum

Coriandrum sativum (coriander) has traditionally been used as a stimulant, aromatic, and carminative, and to disguise the taste of purgatives. In experimental animals it has hypolipidemic effects (16) and hypoglycemic effects (17).

Adverse effects

Respiratory

Occupational asthma has been attributed to various spices from botanically unrelated species, including coriander.

- A 27-year-old man developed rhinitis and asthma symptoms 1 year after starting to prepare a certain kind of sausage (18). He had positive immediate skin prick tests with paprika, coriander, and mace, and specific IgE antibodies to all three. He had immediate asthmatic reactions to bronchial inhalation of extracts from paprika, coriander, and mace, with maximum falls in FEV_1 of 26, 40, and 31% respectively, but no late asthmatic reactions.

Endocrine

Adrenal insufficiency has been attributed to *C. sativum* (19).

- A 28-year-old woman took an extract of *C. sativum* for 7 days to augment lactation while breastfeeding. She developed severe stomach pain and diarrhea and 15 days later resented with dark skin, depression, dehydration, and amenorrhea. A diagnosis of adrenal dysfunction was made, the herbal remedy was withdrawn, and she was treated with dexamethasone, prednisolone, and an oral contraceptive. Her symptoms resolved within 10 days.

Skin

Contact dermatitis from coriander has been described (20).

Immunologic

An anaphylactic reaction has been described in a patient who was sensitized to coriander (21).

Ferula assa-foetida

Ferula assa-foetida (asafetida) contains coumarin sesquiterpenoids, such as fukanefuromarins and kamolonol, which inhibit the production of nitric oxide and relax smooth muscle.

Adverse effects

Methemoglobinemia occurred in a 5-week-old infant treated with a gum asafetida formulation (22).

Asafetida may enhance the activity of warfarin (23).

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Apocynaceae

See also Herbal medicines

General Information

The genera in the family of Apocynaceae (Table 1) include dogbane, oleander, and periwinkle.

Rauwolfia serpentina

The root of *Rauwolfia serpentina* (snakeroot) contains numerous alkaloids, of which reserpine and rescinnamine are said to be the most active as hypotensive agents (1).

Adverse effects

Inexpert use of *R. serpentina* can lead to serious toxicity, including symptoms such as hypotension, sedation, depression, and potentiation of other central depressants.

Table 1 The genera of Apocynaceae

Adenium (desert rose)
Allamanda (allamanda)
Alstonia (alstonia)
Alyxia (alyxia)
Amsonia (blue star)
Anechites (anechites)
Angadenia (pineland golden trumpet)
Apocynum (dogbane)
Carissa (carissa)
Catharanthus (periwinkle)
Cycladenia (waxy dogbane)
Dyera (dyera)
Echites (echites)
Fernaldia (fernaldia)
Forsteronia (forsteronia)
Funtumia (funtumia)
Hancornia (hancornia)
Haplophyton (haplophyton)
Holarrhena (holarrhena)
Landolphia (landolphia)
Lepinia
Macrosiphonia (rock trumpet)
Nerium (oleander)
Ochrosia (yellow wood)
Pentalinon (pentalinon)
Plumeria (plumeria)
Prestonia (prestonia)
Pteralyxia (pteralyxia)
Rauvolfia (devil's pepper)
Rhabdadenia (rhabdadenia)
Saba (saba)
Strophanthus (strophanthus)
Tabernaemontana (milkwood)
Thevetia (thevetia)
Trachelospermum (trachelospermum)
Vallesia (vallesia)
Vinca (periwinkle)

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Apomorphine

General Information

Apomorphine, a very potent non-selective dopamine agonist, which acts on both D_1 and D_2 receptors, has been used with some success in Parkinson's disease, particularly in patients with severe long-term adverse effects of levodopa. Because of first-pass metabolism it has to be used subcutaneously, sublingually, or intranasally. Its adverse effects resemble those of levodopa.

Yawning, somnolence, nausea, and vomiting can all result from the use of apomorphine; they respond to naloxone.

Local reactions to subcutaneous infusion of apomorphine in the nose and throat include swelling of the nose and lips, stomatitis, and buccal mucosal ulceration.

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Persistent nodules cause major problems in about 10% of patients after 3 or more years. One solution is to give the drug intravenously using an indwelling cannula. Six patients, who had responded well to subcutaneous apomorphine before nodules developed, had such cannulae inserted (1). The apomorphine was given at a mean rate of 9.0 mg/hour to a total mean dose of 257 mg/day, very similar to the subcutaneous dosage. The intravenous therapy virtually abolished "off" periods, reduced oral antiparkinsonian drug dosages by 59%, and produced a marked (but unquantified) reduction in dyskinesias and an improved quality of life. However, there were major problems. Two patients receiving high doses of apomorphine (450 and 290 mg/day, in the latter case a deliberate overdose) developed thromboembolic complications, following crystal formation, in one case to the right lung and in the other with obstruction to the superior vena cava. Both required surgical intervention. Both recovered fully, but the authors understandably commented that this therapeutic approach still needs further development.

Organs and Systems

Nervous system

A paradoxical akinetic response has been reported in a middle-aged man, probably with nigrostriatal degeneration, who became both immobile and mute 15 minutes after taking 4 mg of apomorphine; the effect was seen again on rechallenge with doses as low as 2 mg (2). The mechanism was not clear.

Psychological, psychiatric

Four men with Parkinson's disease underwent long-term treatment with apomorphine and developed dose-related psychosexual disorders (3).

Sexual function

There have been reports that apomorphine causes penile erections in both Parkinsonian and healthy men (4–6).

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Aprindine

See also Antidysrhythmic drugs

General Information

The pharmacology, clinical pharmacology, clinical uses, efficacy, and adverse effects of aprindine have been extensively reviewed (1–5).

The adverse effects of aprindine most commonly affect the central nervous system. However, other less common but serious and potentially fatal adverse effects (neutropenia and liver damage) occur, and these limit its usefulness.

Aprindine is metabolized by CYP2D6, and one would therefore expect interactions with drugs that inhibit this isozyme or are metabolized by it.

Comparative studies

In a comparison of oral aprindine and propafenone in 32 patients (25 men and 7 women, aged 43–82) with paroxysmal or persistent atrial fibrillation, aprindine was effective in five of 29 and propafenone in six of 28; adverse effects were not reported (6).

There has been a multicenter, randomized, placebo-controlled, double-blind comparison of aprindine and digoxin in the prevention of atrial fibrillation and its recurrence in 141 patients with symptomatic paroxysmal or persistent atrial fibrillation who had converted to sinus rhythm (7). They were randomized in equal numbers to aprindine 40 mg/day, digoxin 0.25 mg/day, or placebo and followed every 2 weeks for 6 months. After 6 months the Kaplan–Meier estimates of the numbers of patients who had no recurrences with aprindine, digoxin, and placebo were 33, 29, and 22% respectively. The rates of adverse events were similar in the three groups. This suggests that aprindine has a very small beneficial effect in preventing relapse of symptomatic atrial fibrillation after conversion to sinus rhythm. Furthermore, recurrence occurred later with aprindine than with placebo or digoxin (about 60% recurrence at 115 days compared with 30 days).

Organs and Systems

Respiratory

Pneumonitis has been attributed to aprindine (SEDA-16, 179).

Nervous system

Aprindine can cause adverse effects in the central nervous system (SEDA-1, 156).

Hematologic

The incidence of leukopenia has been estimated at about 2 cases per 1000 patient-years (8).

Liver

Aprindine can cause liver damage (9).

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Aprotinin

General Information

Aprotinin is a fibrinolytic agent, a naturally occurring serine protease inhibitor derived from bovine lung. It is a polypeptide of 58 amino acids, with a molecular weight of 6512, which inhibits the action of several serine proteases, including trypsin, chymotrypsin, plasmin, and kallikrein. It is extracted on a commercial basis from bovine lung. By inhibiting kallikrein, aprotinin inhibits the formation of activated factor XII indirectly. It thus inhibits the initiation of both coagulation and fibrinolysis induced by the contact of blood with a foreign surface. It does not affect platelet function. In cardiac surgery, aprotinin reduces the risk of bleeding (1,2).

Aprotinin is not effective after oral administration, but is administered intravenously as a loading dose followed by a continuous infusion. Its activity is expressed as kallikrein inactivation units (KIU). The conventional (Munich) dose regimen consists of an initial 2×10^6 KIU bolus, a similar initial dose to prime the bypass machine, and then 0.5×10^6 KIU/hour by continuous infusion thereafter. The half-life of aprotinin is about 2 hours. Plasma concentrations of 125 KIU/ml are necessary to inhibit plasmin, but a higher concentration of 300–500 KIU/ml is needed to inhibit kallikrein.

During normal fibrinolysis, inactive circulating plasminogen binds to fibrin through an active site that binds lysine. The bound plasminogen is then converted to plasmin by activators (such as tissue plasminogen activator, t-PA) and converted to plasmin, which breaks down the fibrin. Aminocaproic acid (EACA, 6-aminohexanoic acid, Amicar®) and tranexamic acid (Cyklokapron®) are structural analogues of lysine, which bind irreversibly to the lysine-binding sites on plasminogen, inhibiting binding to fibrin and thus the whole process of fibrinolysis (3,4). These agents inhibit the natural degradation of fibrin and so stabilize clots.

Uses

Aprotinin is widely used to inhibit fibrinolysis during cardiac surgery and orthotopic liver transplantation, and reduces the risk of bleeding (1,2). In addition, it is added as a constituent of several commercial formulations of fibrin sealants (“fibrin glues”), such as Quixil. The use of aprotinin in cardiopulmonary bypass surgery was pioneered by Royston, an anesthesiologist in London, who found that it reduced blood loss after both primary and repeat operations (5). It is also effective in operations normally characterized by particularly large blood losses, such as those in patients taking aspirin (6) and patients undergoing cardiac transplantation (7). It is also used to control blood loss in the setting of orthotopic liver transplantation (8,9), where accelerated fibrinolysis is an important component in the abnormalities of hemostasis, which can contribute to perioperative bleeding. Aprotinin is of value in controlling hemorrhage associated with hyperplasminemia (which can, for example, occur after thrombolytic therapy or in association with promyelocytic leukemia). A combination of aprotinin with tranexamic acid can prevent or delay rebleeding after rupture of an intracerebral aneurysm. Clinical trials have not confirmed any benefit from the use of aprotinin in acute pancreatitis.

General adverse effects

Some adverse reactions are associated with all antifibrinolytic agents, reflecting their effect on clot stability. Dissolution of extravascular blood clots may be resistant to physiological fibrinolysis. These drugs should not be used to treat hematuria due to blood loss from the upper urinary tract, as this can provoke painful clot retention and even renal insufficiency associated with bilateral ureteric obstruction (10,11).

Caution should be exercised in the administration of antifibrinolytic agents in disseminated intravascular coagulation (12,13).

Organs and Systems

Cardiovascular

The issue of whether the use of aprotinin is associated with an increased risk of vein graft thrombosis in cardiac bypass surgery has not been resolved (14,15). The use of

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aprotinin was not associated with an increased rate of early occlusion of saphenous vein or internal mammary artery grafts in controlled studies with coronary angiography (16–19).

In a randomized, placebo-controlled, multicenter study of aprotinin in coronary artery bypass surgery, there was no increase in mortality or the incidence of myocardial infarction (20).

There was no evidence of an increased risk of venous thromboembolism in patients receiving aprotinin in a small study after hip replacement (21).

Psychological, psychiatric

Psychotic reactions, including delirium, hallucinations, and confusion, have also been reported in patients given aprotinin, but it is possible that the symptoms were due to underlying pancreatitis (22).

Hematologic

It has been postulated that aprotinin potentiates a prothrombotic state (2). However, in randomized, controlled studies, there were no significant differences between aprotinin and placebo (2).

Disseminated intravascular coagulation can be aggravated by aprotinin, particularly in elderly people (13).

Urinary tract

Aprotinin has a high affinity for renal tissue; 80–90% is stored in the proximal tubule cells after 4 hours and is excreted over 12–24 hours (2). It has been hypothesized that aprotinin causes reversible overload of tubular reabsorption, resulting in transient renal dysfunction (2). It has also been postulated that aprotinin has a direct toxic effect on the proximal tubule cells or alters intrarenal blood flow, through inhibition of renin and kallikrein activity (2).

Immunologic

As might be expected with a bovine protein, allergic reactions can occur, and repeated exposure can even result in anaphylactic reactions. In view of this, some have advocated a strategy of using aprotinin only if excessive bleeding is a problem after surgery (23).

- An aphylactic reaction has been described after the use of fibrin glue as a sealant after mastectomy, probably due to the presence of bovine aprotinin (24).

In one study of 248 patients undergoing cardiac surgery, seven had allergic reactions, ranging from skin flushing to severe circulatory depression (25). Most of the reactions occurred when aprotinin was given a second time within 6 months after the first exposure. However, anaphylaxis has been documented after primary exposure (26). The reported incidence of anaphylactic reactions in other studies has ranged from 0.3 to 0.6% after a single exposure, rising to almost 5% with prior aprotinin exposure (1).

Up to 1980, 32 cases of non-fatal shock attributed to aprotinin had been reported to the Japanese Ministry of Health and Welfare, most concerning patients treated for pancreatitis (27). Although these patients survived, fatal anaphylaxis has been reported (28). Other apparently allergic reactions reported include erythema, urticaria, bronchospasm, nausea and vomiting, diarrhea, muscle pains, and blood pressure changes (29). A case of allergic pancreatitis attributed to aprotinin has also been reported (30).

There is evidence that severe allergic reactions to aprotinin are mediated by IgE, and preoperative screening for the presence of aprotinin-specific IgE antibodies can be of value in identifying patients at risk (31,32).

The sera of 150 patients who had undergone cardiac surgery and were receiving aprotinin for the first time have been studied before and after the operation. At 3.5 months after surgery, the prevalence of aprotinin-specific IgG antibodies was 33% (15/45) after local, 28% (13/46) after intravenous, and 69% (41/59) after combined exposure (33). The authors concluded that local administration of aprotinin induces a specific immune response and reinforces that of intravenous exposure; they therefore recommended that any exposure in a patient should be documented.

Allergic reactions, including anaphylaxis, can occur on re-exposure to aprotinin. The incidence rates of aprotinin-related reactions are 2.7% in re-exposed adults (5/183) and 1.2% in children (3/354), with an overall incidence of 1.8% (8/437). The following advice has been given to reduce the risk and severity of these reactions (1,2):

- give a test dose of aprotinin
- delay the first bolus injection until the surgeon starts the procedure
- give an antihistamine before re-exposure
- avoid re-exposure within the first 6 months after the last exposure.

Infection risk

Inevitably, concern has recently been expressed about the possibility of transmission of the prion believed to be responsible for bovine spongiform encephalopathy (BSE) and new variant Creutzfeldt-Jakob disease. However, the manufacturers of aprotinin have stated that the bovine lungs used as the source of aprotinin are collected in countries in South America (principally Uruguay) in which no cases of transmissible spongiform encephalopathy have been recorded. There is no evidence that any patient with new variant Creutzfeldt-Jakob disease has received aprotinin. Furthermore, in vitro experiments involving spiking of material with mouse-associated scrapie agent have demonstrated an 18-log reduction of the added prions during the manufacturing process (34).

Second-Generation Effects

Teratogenicity

There is no evidence from animal studies and clinical experience of teratogenicity or other adverse effects of aprotinin (35).

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Drug–Drug Interactions

Suxamethonium

Aprotinin slightly reduces plasma cholinesterase activity and would be expected to prolong the action of suxamethonium in combination with other factors. However, re-paralysis has been reported when aprotinin was used after operations during which suxamethonium had been given alone or in combination with normal doses of D-tubocurarine (36).

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Araliaceae

See also Herbal medicines

General Information

The genera in the family of Araliaceae (Table 1) include aralia, ginseng, and ivy.

Ginseng

Ginseng is an ambiguous vernacular term, which can refer to *Panax* species such as *Panax ginseng* (Asian ginseng) and *Panax quinquefolius* (American ginseng), *Eleutherococcus senticosus* (Siberian ginseng), *Pfaffia paniculata* (Brazilian ginseng), or unidentified material (for example Rumanian ginseng).

Asian ginseng (*P. ginseng*) contains a wide variety of flavonoids, saponins, steroids, sesquiterpenoids, and triterpenoids. These include ginsenolides and ginsenosides, protopanaxadiol, panaxadiol, panaxatriol, and panasinsene.

The botanical quality of ginseng preparations is problematic (1). For instance, when a case of neonatal androgenization was associated with maternal use of Siberian ginseng tablets during pregnancy, botanical analysis showed that the incriminated material almost certainly came from *Periploca sepium* (Chinese silk vine) (2).

Brazilian ginseng (*P. glomerata*) has been found to be contaminated with cadmium and mercury (3).

Table 1 The genera of Araliaceae

Aralia (spikenard, angelica)
Cheirodendron (cheirodendron)
Dendropanax (dendropanax)
Eleutherococcus (ginseng)
Fatsia (fatsia)
Hedera (ivy)
Kalopanax (castor aralia)
Meryta (meryta)
Munroidendron (munroidendron)
Oplopanax (oplopanax)
Panax (ginseng)
Polyscias (aralia)
Pseudopanax (pseudopanax)
Reynoldsia (reynoldsia)
Schefflera (schefflera)
Tetraplasandra (tetraplasandra)
Tetrapanax (tetrapanax)

There is no good evidence that ginseng confers benefit for any indication (4).

Adverse effects

The various adverse effects that have been attributed to ginseng formulations include hypertension, pressure headaches, dizziness, estrogen-like effects, vaginal bleeding, and mastalgia. Prolonged use has been associated with a "ginseng abuse syndrome" including symptoms like hypertension, edema, morning diarrhea, skin eruptions, insomnia, depression, and amenorrhea. However, most reports are difficult to interpret, because of the absence of a control group, the simultaneous use of other agents, insufficient information about dosage, and lack of botanical authentication (1).

The authors of a review of the adverse effects associated with *P. ginseng* concluded that it is generally safe but at high doses can cause insomnia, headache, diarrhea, and cardiovascular and endocrine disorders (5). Inappropriate use and suboptimal formulations were deemed to be the most likely reason for adverse effects of ginseng. The authors of a systematic review reached similar conclusions and showed that serious adverse effects of ginseng seem to be true rarities (6).

Cardiovascular

The WHO database contains seven cases from five countries of ginseng intake followed by arterial hypertension (7). In five of them no other medication was noted. In four cases the outcome was mentioned, which was invariably full recovery without sequelae after withdrawal of ginseng.

Nervous system

- A 56-year-old woman with previous affective disorder had an episode of mania while taking ginseng (8). She was treated with neuroleptic drugs and benzodiazepines and ginseng was withdrawn. She made a rapid full recovery.

Ginseng has also been associated with a case of cerebral arteritis (9).

Psychiatric

A woman with prior episodes of depression had a manic episode several days after starting to take *P. ginseng* (10).

Skin

Stevens–Johnson syndrome occurred in a 27-year-old man who was a regular user of *P. ginseng* (11).

Musculoskeletal

Aggravation of muscle injury has been attributed to ginseng (SED-13, 1461) (12).

Drug interactions

- A 74-year-old man had increased serum digoxin concentrations without signs of toxicity while taking Siberian ginseng (13). Common causes of increased serum digoxin were ruled out, and the association with ginseng use was confirmed by dechallenge and rechallenge. The rise in serum digoxin concentration could have been due to

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cardiac glycosides contained in *Periploca sepium*, a common substitute for *E. senticosus* (14).

Diuretic resistance has been reported in a patient consuming a formulation containing germanium and ginseng (species unspecified) (15).

Interactions of antidepressants with herbal medicines have been reported (16). Ginseng has been reported to cause mania, tremor, and headache when used in combination with conventional monoamine oxidase inhibitors.

In one case the concomitant use of *P. ginseng* and warfarin resulted in loss of anticoagulant activity (17). However, in an open, crossover, randomized study in 12 healthy men ginseng did not affect the pharmacokinetics or pharmacodynamics of *S*-warfarin or *R*-warfarin (18).

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Arecaceae

See also Herbal medicines

General Information

The genera in the family of Arecaceae (Table 1) include various types of palm.

Areca catechu

Areca catechu (areca, betel) contains piperidine alkaloids, such as guvacine, guvacoline, and isoguvacine, and pyridine alkaloids, such as arecaidine, arecolidine, and arecoline.

Many of the world's population (more than 200 million people worldwide) chew betel nut quid, a combination of areca nut, betel pepper leaf (from *Piper betle*), lime paste, and tobacco leaf. The major alkaloid of the areca nut, arecoline, can produce cholinergic adverse effects (such as bronchoconstriction) (1) as well as antagonism of anticholinergic agents (2). The lime in the betel quid causes hydrolysis of arecoline to arecaidine, a central nervous system stimulant, which accounts, together with the essential oil of the betel pepper, for the euphoric effects of chewing betel quid.

Adverse effects

Glycemia and anthropometric risk markers for type 2 diabetes were examined in relation to betel usage. Of 993 supposedly healthy Bangladeshis 12% had diabetes. A further 145 of 187 subjects at risk of diabetes (spot glucose over 6.5 mmol/l less than 2 hours after food or over 4.5 mmol/l more than 2 hours after food) had a second blood glucose sample taken; 61 were confirmed as being at risk, and had an oral glucose tolerance test; nine new diabetics were identified. Spot blood

Table 1 The genera of Arecaceae

Acoelorraphe (palm)
Acrocomia (acrocomia)
Aiphanes (aiphanes)
Archontophoenix (archontophoenix)
Calyptronoma (manac)
Caryota (fishtail palm)
Chamaedorea (chamaedorea)
Coccothrinax (silver palm)
Cocos (coconut palm)
Dypsis (butterfly palm)
Elaeis (oil palm)
Gaussia (gaussia)
Livistona (livistona)
Phoenix (date palm)
Prestoea (prestoea)
Pritchardia (pritchardia)
Pseudophoenix (pseudophoenix)
Ptychosperma (ptychosperma)
Rhapidophyllum (rhapidophyllum)
Roystonea (royal palm)
Sabal (palmetto)
Serenoa (serenoa)
Thrinax (thatch palm)
Washingtonia (fan palm)

glucose values fell with time after eating and increased independently with waist size and age. Waist size was strongly related to use of betel, and was independent of other factors such as age. The authors suggested that betel chewing may contribute to the risk of type 2 diabetes mellitus (3).

The saliva of betel nut chewers contains nitrosamines derived from areca nut alkaloids (4), and the use of areca nuts has been widely implicated in the development of oral cancers.

Serenoa repens

S. repens (American dwarf palm tree, cabbage palm, sabal, saw palmetto) has mainly been used to treat benign prostatic hyperplasia. In placebo-controlled and comparative studies its efficacy in benign prostatic hyperplasia and lower urinary tract symptoms has been demonstrated (5). Numerous mechanisms of action have been proposed, including an antiandrogenic action, an anti-inflammatory effect, and an antiproliferative influence through inhibition of growth factors.

A systematic review and meta-analysis of randomized trials of *S. repens* in men with benign prostatic hyperplasia showed that saw palmetto extracts improve urinary symptoms and flow measures to a greater extent than placebo, and similar improvements in urinary symptoms and flow measures to the 5-alpha-reductase inhibitor finasteride with fewer adverse effects (6).

Adverse effects

Hematologic

- A 53-year-old man, who had self-medicated with a saw palmetto supplement for benign prostatic hyperplasia, had profuse bleeding (estimated blood loss 2 liters) after resection of a meningioma and required 4 units of packed erythrocytes, 3 units of platelets, and 3 units of fresh frozen plasma (7). Postoperatively his bleeding time was 21 minutes (reference range 2–10 minutes), but all other coagulation tests were normal. He made an uneventful recovery.

The authors concluded that the cyclo-oxygenase inhibitory activity of saw palmetto had caused platelet dysfunction, which had resulted in abnormal bleeding.

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Aristolochiaceae

See also Herbal medicines

General Information

The family of Aristolochiaceae contains three genera:

1. *Aristolochia* (dutchman's pipe)
2. *Asarum* (wild ginger)
3. *Hexastylis* (heartleaf).

Aristolochia species

Plants belonging to the genus of *Aristolochia* are rich in aristolochic acids and aristolactams.

In the UK, the long-term (2 and 6 years) use of *Aristolochia* species in Chinese herbal mixtures, taken as an oral medication or herbal tea, resulted in Chinese-herb nephropathy with end-stage renal insufficiency (1). In reaction to these reports, the erstwhile Medicines Control Agency banned all *Aristolochia* species for medicinal use in the UK.

In June 2001, the FDA issued a nationwide alert, recalling 13 "Treasure of the East" herbal products containing aristolochic acid. Before this alert, the FDA had issued several warnings:

- On 4 April 2001 a "Dear Health Professional" letter was sent, drawing attention to serious renal disease associated with the use of aristolochic acid-containing dietary supplements or "traditional medicines." Health professionals were urged to review patients who had had unexplained renal disease, especially those with urothelial tract tumors and interstitial nephritis with end-stage renal insufficiency, to determine if such products had been used.
- On 9 April 2001 a letter was sent to industry associations, detailing the reported cases of renal disease associated with aristolochic acid.
- On 11 April 2001 the FDA cautioned consumers to immediately discontinue any dietary supplements or "traditional medicines" that contain aristolochic acid, including products with "Aristolochia," "Bragantia," or "Asarum" listed as their ingredients.

In a related action, Health Canada first issued a warning on aristolochic acid in November 1999 that this ingredient posed a Class I Health Hazard with a potential to cause serious health effects or death (2) and warned consumers not to use the pediatric product Tao Chih Pien. This Chinese product, sold in the form of tablets, is said to be a diuretic and a laxative. It is not labeled to contain aristolochic acid. However, the Chinese labeling says that it contains Mu Tong, a traditional term used to

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describe numerous herbs, including aristolochia; subsequent product analysis showed that Tao Chih Pien does indeed contain aristolochic acid. Health Canada advised individuals in possession of this product not to consume it and to return it to the place of purchase. It also issued a Customs Alert for the product to prevent the importation and sale of Tao Chih Pien and advised Canadians not to consume Longdan or Lung Tan Xi Gan products, since they may also contain aristolochic acid.

The product Longdan Qiegan Wan ("Wetness Heat" Pill) was removed from the Australian Register of Therapeutic Goods following the detection of aristolochic acid by laboratory testing by the Therapeutic Goods Administration (3).

In 2002 the Medicines Safety Authority of the Ministry of Health in New Zealand (Medsafe) ordered the withdrawal of several traditional Chinese medicines sold as herbal remedies (4). The products included Guan Xin Su He capsules, Long Dan Xie Gan Wan Pills, and Zhiyuan Xinqinkeli sachets.

In 2004 the UK's Medicines and Healthcare products Regulatory Agency, with the co-operation of Customs and Excise, seized a potentially illegal consignment of 90 000 traditional Chinese medicine tablets, Jingzhi Kesou Tanchuan, which reportedly contained *Aristolochia*.

In December 2004 the Hong Kong authorities warned the public not to take the product Shen yi Qian Lie Hui Chin, as laboratory tests showed that it contained aristolochic acid.

Adverse effects

Several review articles have covered the toxicology of *Aristolochia* (5–8).

Liver

Hepatitis has been attributed to *Aristolochia* (9).

- A 49-year-old woman developed signs of hepatitis. All the usual causes were ruled out. The history revealed that she had recently started to use a Chinese herbal tea to treat her eczema. Examination of the herbal mixture showed that it contained *Aristolochia debilis* root and seven other medicinal plants.

Like *Aristolochia fangchi*, *A. debilis* contains the highly toxic aristolochic acid and was therefore the likely cause of the toxic hepatitis.

Urinary tract

Aristolochic acid is a potent carcinogen and can cause serious kidney damage, "Chinese herb nephropathy," which can be fatal (10). Renal fibrosis has also been reported (11).

Numerous reports from many countries have confirmed that plants from the *Aristolochia* species are the cause of the nephropathy (12,13), and the toxic agent has been confirmed to be aristolochic acid (14).

- A 46-year-old Chinese woman, living in Belgium and China, developed subacute renal insufficiency (15). Her creatinine concentration had increased from 80 μmol/l (November 1998) to 327 μmol/l (January 2000). During the preceding 6 months she had taken a patent medicine bought in China "for waste discharging and youth keeping." The package insert did not list any herbs of the *Aristolochia* species. Kidney biopsy showed extensive hypocellular interstitial fibrosis, tubular atrophy, and glomerulosclerosis. Analysis of the Chinese medicine demonstrated the presence of aristolochic acid. She required hemodialysis in June 2000 and received a renal transplant 4 months later.
- A 58-year-old Japanese woman with CREST syndrome (calcinosis, Raynaud's syndrome, esophageal sclerosis, sclerodactyly, and telangiectasia) developed progressive renal dysfunction (16). Renal biopsy showed changes typical of Chinese herb nephropathy. Analyses of Chinese herbs she had taken for several years demonstrated the presence of aristolochic acid. Oral prednisolone improved her renal function and anemia.
- A 59-year-old man developed renal insufficiency after self-medication for 5 years with a Chinese herbal remedy to treat his hepatitis (17). Renal biopsy showed signs characteristic of Chinese herb nephropathy. Analysis of the remedy proved the presence of aristolochic acids I and II.

In Belgium, an outbreak of nephropathy in about 70 individuals was attributed to a slimming formulation that supposedly included the Chinese herbs *Stephania tetrandra* and *Magnolia officinalis*. However, analysis showed that the root of *S. tetrandra* (Chinese name Fangji) had in all probability been substituted or contaminated with the root of *Aristolochia fangchi* (Chinese name Guang fangji) (18,19). The nephropathy was characterized by extensive interstitial fibrosis with atrophy and loss of the tubules (20). At least one patient had evidence suggestive of urothelial malignancies (21). The same remedy was apparently also distributed in France, and two cases have been reported from Toulouse and one possible case from Nice (22).

Subsequently, Belgian nephrologists re-investigated 71 patients who were originally affected by this syndrome (23). Using multiple regression analysis, they showed that the original dose of *Aristolochia* was the only significant predictor of progression of renal insufficiency. The risk of end-stage renal insufficiency in these patients increased linearly with the dose of *Aristolochia*.

In Japan two cases of Chinese herb nephropathy were associated with chronic use of *Aristolochia manchuriensis* (Kan-mokutsu) (24). The diagnosis was confirmed by renal biopsy and the toxic constituents were identified as aristolochic acids I, II, and D.

Taiwanese authors have reported 12 cases of suspected Chinese herb nephropathy, confirmed by renal biopsy (25). Renal function deteriorated rapidly in most patients, despite withdrawal of the Aristolochia. Seven patients underwent dialysis and the rest had slowly progressive renal insufficiency. One patient was subsequently found to have a bladder carcinoma. Other cases have been reported from mainland China (26) and Taiwan (27).

Because of fear of malignancies the Belgian researchers who first described the condition have advocated prophylactic removal of the kidneys and ureters in patients with Chinese herb nephropathy. Of 39 patients who agreed to this, 18 (46%) had urothelial carcinoma, 19 of the others had mild to moderate urothelial dysplasia, and only two had normal urothelium (28). All tissue samples contained

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aristolochic acid-related DNA in adducts. The original dose of *Aristolochia* correlated positively with the risk of urothelial carcinoma.

Animal experiments have shed more light on Chinese herb nephropathy (29). Salt-depleted male Wistar rats were regularly injected with two different doses of aristolochic acid or with vehicle only for 35 days. The histological signs of Chinese herb nephropathy were demonstrated only in animals that received the high dose of 10 mg/kg. The authors presented this as an animal model for studying the pathophysiology of Chinese herb nephropathy.

Tumorigenicity

Aristolochic acid I and aristolochic acid II are mutagenic in several test systems. A mixture of these two compounds was so highly carcinogenic in rats that even homeopathic *Aristolochia* dilutions have been banned from the German market. The closely related aristolactam I and aristolactam II have not been submitted to carcinogenicity testing, but these compounds similarly show mutagenic activity in bacteria.

When 19 kidneys and urethras removed from 10 patients with Chinese herb nephropathy who required kidney transplantation were examined histologically, there were conclusive signs of neoplasms in 40% (30).

One patient who had a urothelial malignancy 6 years after the onset of Chinese herb nephropathy later developed a breast carcinoma that metastasised to the liver (31). The urothelial malignancy contained aristolochic acid-DNA adducts and mutations in the p53 gene, and the same mis-sense mutation in codon 245 of exon 7 of p53 was found in DNA from the breast and liver tumors. However, DNA extracted from the urothelial tumor also showed a mutation in codon 139 of exon 5, which was not present in the breast and liver.

Asarum heterotropoides

The Chinese herbal medicine Xu xin (32) is made from the leaves and aerial parts of *Asarum heterotropoides*. It is used for the symptomatic relief of colds, headaches, and other pains.

Adverse effects

The volatile oil of Xu xin causes the following adverse effects: vomiting, sweating, dyspnea, restlessness, fever, palpitation, and nervous system depression. Death can result from respiratory paralysis at high doses.

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Arsenic

General Information

Arsenic is a metallic element (symbol As; atomic no. 33), which exists in several allotropic forms. Various ores contain crystalline forms of arsenic salts: cobaltite contains cobalt arsenic sulfide; mispickel (arsenopyrite) iron arsenic sulfide; orpiment arsenic trisulfide; proustite (ruby silver ore) silver arsenic sulfide; realgar arsenic sulfide; and tennantite copper arsenic sulfide.

Arsenic has a long history of medicinal uses. Thomas Fowler introduced it in the form of potassium arsenite (Fowler's solution) in the late 18th century to treat ague and Sir David Bruce used it in the late 19th century to treat trypanosomiasis. In the early 20th century Paul Ehrlich synthesized and tested a large series of arsenicals, in the hope of finding one that was effective in syphilis, and emerged with arsphenamine (Salvarsan, compound 606). Subsequently other arsenicals were synthesized, such as neoarsphenamine (for syphilis) and tryparsamide and acetarsol (for trypanosomiasis).

In recent times arsenic and arsenicals have been considered obsolete in medicine, because of their limited therapeutic value, multisystem toxicity, and apparent carcinogenic properties (SED-8, 502) (SED-9, 368). However, arsenic compounds have been used to treat various types of leukemia (1–3), including acute promyelocytic leukemia, chronic myelogenous leukemia, and multiple myeloma (4). Arsenic trioxide is effective in acute promyelocytic leukemia, achieving a complete remission rate of 60–90% (5,6). It is particularly used in patients who are resistant to all-trans retinoic acid (7). Arsenic trioxide is also emerging as a therapy for multiple myeloma (8).

Reports continue to be published on incidents related to the use of traditional herbal medications from China and elsewhere that contain arsenic among other toxic substances (9,10).

There are still occasional cases of patients with late effects from obsolete formulations such as Fowler's solution or neoarsphenamine (SEDA-16, 231). As late as 1998 a case of severe chronic poisoning resulting in fatal multiorgan failure including hepatic portal fibrosis and subsequent angiosarcoma was traced back to exposure to arsenical salts used for the treatment of psoriasis many years before (11) (SEDA-22, 243). In some non-Western countries arsenic is apparently still being used in dentistry for devitalization of inflamed pulp and sensitive dentine, and cases have been described in which this has resulted in arsenical necrosis of the jaws, affecting the maxilla or mandible (12). Some exposure to arsenic may still be occurring from traditional remedies of undeclared composition, and as with other metals there may be environmental contact, notably from semiconductor materials.

General adverse effects

Chronic arsenic poisoning is marked by edema of the eyelids and face, mucosal inflammation, pruritus, anorexia, vomiting, and diarrhea. Long-term use of small doses can produce keratinization and dryness of the skin, sometimes with frank dermatitis and pigmentation; alopecia can follow, and basal cell epithelioma is a late effect (13). In the long run, as in the fatal cases noted in the introduction of this monograph, there is serious damage to internal organs.

The adverse effects of arsenic trioxide have been described in a patient with recurrent acute promyelocytic leukemia resistant to all-trans retinoic acid (14).

- A 15-year-old African American girl, with multiple recurrent acute promyelocytic leukemia that had resisted conventional chemotherapy, was given arsenic trioxide (As_2O_3) 10 mg intravenously for 28 days and again for a further 28 days after a 4-week break. She had a complete remission by morphological, cytogenetic, and molecular criteria. About 6 months later she again relapsed and had another course of arsenic trioxide, which produced a morphological, but not a cytogenetic or molecular, remission. Arsenic trioxide was well tolerated. Skin dryness was treated with topical moisturizers. Gastrointestinal upset, including mild nausea without vomiting or cramping pain, occurred only during intravenous therapy. No other toxicity was noted.

In acute promyelocytic leukemia arsenic trioxide can cause a syndrome similar to the retinoic acid syndrome (15), with fever, skin rash, edema, pleural effusion, pericardial effusion, and acute respiratory failure.

- A 37-year-old woman with acute promyelocytic leukemia was treated with all-trans retinoic acid, idarubicin, and cytosine arabinoside, with complete remission after one course. However, she had an episode of retinoic

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acid syndrome with fever, edema, and pericardial effusion, which resolved after all-*trans* retinoic acid was withdrawn. When her leukemia relapsed she was treated with arsenic trioxide 10 mg/day. Leukocytosis again developed, with symptoms (fever, skin rash, and edema) resembling the retinoic acid syndrome, which was quickly relieved by steroids. She received two courses of arsenic trioxide each for 30 days and her complete blood count returned to normal 2 weeks after the second course of treatment. The bone marrow also reached complete remission.

Organs and Systems

Cardiovascular

Atrioventricular block is very rare after arsenic trioxide treatment for refractory acute promyelocytic leukemia (16).

- A 34-year-old woman with acute promyelocytic leukemia was given arsenic trioxide solution 0.1%, 10 ml/day for 7 days. A generalized skin rash appeared, and her serum transaminases rose. An electrocardiogram was normal. A second course of arsenic trioxide was used about 3 months later. She felt palpitation and mild dyspnea and had complete atrioventricular block. Echocardiography showed a normal left ventricle. A ^{201}thallium myocardial perfusion scan did not show a perfusion defect. Arsenic trioxide was withheld. Sinus rhythm returned 3 days later. Complete atrioventricular block recurred later when arsenic trioxide was re-administered, albeit in a lower dosage for a shorter period of time.

The heart block due to arsenic trioxide in this case was reversible and did not correlate with the patient's leukemic status.

In 19 patients with hematological malignancies given arsenic trioxide 10–20 mg in 500 ml of 5% dextrose/isotonic saline over 3 hours daily for up to 60 days, there were three cases of torsade de pointes (17).

Nervous system

In a case of a rapidly progressive neuropathy with arsenic, a contributory role of thiamine deficiency was implied (18).

- A 46-year-old woman with acute promyelocytic leukemia was given arsenic trioxide 10 mg/day for 28 days. On day 33 she complained of numbness in the legs and on day 37 all four limbs were paralysed and areflexic. Her speech was inaudible and she had bulbar paralysis. Nerve conduction studies showed a generalized reduction in sensory action potentials. Thiamine deficiency was confirmed and she was given parenteral thiamine (100 mg/day). By the next day the power in her arms had dramatically improved and her speech had become audible. Over the next 5 days, she regained full power in the arms. Subsequently she was given arsenic trioxide 5 mg/day for 28 days with oral thiamine, without neurological deterioration this time. The power in her legs continued to improve.

The members of a family in India, in the business of preparing and manufacturing indigenous medicines containing arsenicals, consumed a home-made vitalizer for health which accidentally got contaminated with arsenicals (19).

- A 50-year-old woman developed severe vomiting, abdominal colic, and diarrhea, which persisted for 5–6 days and 2 weeks later developed tingling, numbness, paresthesia, and gradually progressive weakness of all four limbs. She had gross hyperpigmentation of the face, arms, and upper chest, hyperkeratosis of the palms, and transverse white lines (Mees' lines) in the finger nails. She had a symmetrical, predominantly distal, peripheral sensorimotor neuropathy in all four limbs. Meanwhile, her 52-year-old husband and her 28-year-old son developed severe gastrointestinal problems. Her husband died within 48 hours of onset and the son developed severe wasting, weakness, and a sensorimotor flaccid quadriparesis, similar to that of his mother. Two younger sons, aged 22 and 20 years, and an 18-year-old daughter were out of town but returned after the death of their father. They also developed severe diarrhea, vomiting, abdominal pain, and tingling of the hands and feet within 2–3 weeks. Arsenic concentrations were found in the hair and nails, and the concentrations were directly proportional to the severity of the illness. They were given dimercaprol, and 6 months later all had significant clinical improvement.

Arsenic-induced neurotoxicity in a child was caused by the use of an Indian ethnic remedy.

- A 5-year-old child who had been taking Indian ethnic remedies for congenital bilateral retinoblastoma became anorexic and restless, with nausea, fatigue, paresthesia, and progressive weakness of the legs (20). A year later he developed vomiting, cough, hoarseness, and a recurrent fever. Blood tests showed a severe normochromic anemia and a leukopenia with relative and absolute neutropenia. Electromyography showed a moderate distal chronic axonal polyneuropathy. The urinary arsenic concentration was not high (15 μg/g creatinine; reference range below 40 μg/g), but the hair arsenic concentration was 6.6 mg/kg (reference range below 1 mg/kg). Chronic arsenic poisoning was diagnosed. Arsenic (184 mg/g) was found in one of the ethnic remedies.

Hematologic

Leukocytosis has been commonly noted with arsenic trioxide, but this adverse effect usually resolves spontaneously and is generally not treated. However, one death has been reported.

- A 27-year-old woman (21) with acute promyelocytic leukemia was given arsenic trioxide 0.15 mg/kg/day intravenously. Her white cell count was 8.2×10^9/l; after two doses it rose to 15×10^9/l and after three doses to 21×10^9/l. The white blood cell count continued to rise to 101×10^9/l on day 7 and 213×10^9/l on day 8; the platelet count was 61×10^9/l. Arsenic trioxide was withdrawn. Later that day she became confused with slurred speech and right-sided weakness. A CT scan showed a left middle cerebral artery infarct.

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Twelve hours later she had a generalized seizure. The white blood cell count was now 292 $\times$ 10^9/l and chemotherapy with idarubicin and cytarabine was started. She continued to deteriorate and died on day 15.

Liver

Arsenic salts can cause liver damage (11).

- A 60-year-old man, a heavy drinker, with psoriasis of the palms and soles was treated with arsenical salt derivatives from 1972 to 1982. In 1984 he had an upper gastrointestinal hemorrhage. Only hyperkeratosis and palmar erythema were observed. His liver enzymes were raised. Endoscopy showed an antral ulcer with signs of recent bleeding and grade IV esophageal varices with no evidence of bleeding. Liver biopsy showed preservation of the parenchymal architecture, fibrous expansion of the portal spaces, and minimal lymphocytic infiltration. The diagnosis was portal fibrosis compatible with idiopathic portal hypertension. When he died of multiorgan failure in 1997, autopsy showed a moderately differentiated multifocal hepatic angiosarcoma with bone, gastric, and splenic metastases.

This patient had both idiopathic portal hypertension and hepatic angiosarcoma, in which the common causative factor was the chronic use of arsenical salts for the treatment of psoriasis. In a review of the literature the authors found only five other cases in which both diseases were associated, while exposure to arsenical salts was found in only one of them.

- A 50-year-old man developed upper gastrointestinal bleeding, with no history of alcohol abuse, viral hepatitis, hepatotoxic drugs, or any family history of liver disease (22). He had thalassemia minor and psoriasis, for which he had taken Fowler's solution, 2 ml/day for 5 years. Fowler's solution is a solution of potassium arsenite that contains 10 mg of arsenic trioxide. He had palmar and plantar hyperkeratosis, splenomegaly, and signs of hypovolemia, normal liver function tests, negative viral serological markers and autoantibodies, and high arsenic excretion in the urine. Abdominal ultrasonography and color Doppler showed marked wall thickening of the portal vein and its intrahepatic branches, with signs of portal hypertension and partial splenic vein thrombosis. Endoscopy showed grade III esophageal varices, with signs of recent bleeding. Liver biopsy showed venous wall hyperplasia, with signs of cellular regeneration tending toward a focal nodular pattern and terminal hepatic vein fibrosis. The wedge hepatic pressure was 12 mmHg and the free hepatic venous pressure 5 mmHg; splenoportography confirmed partial obstruction of the splenic vein.

Skin

Human papillomavirus has been implicated as a co-factor in the pathogenesis of arsenic-induced skin tumors (23).

- A 38-year-old Pakistani woman developed verrucose papules on her palms and soles 3 years after she had been treated orally with an herbal solution by a traveling Indian doctor for a period of 12 months for "white spot disease." She had widespread depigmented macules on the trunk and limbs, suggestive of vitiligo, and multiple hyperkeratotic papules on her palms and soles, some of which were coalescing into large leathery plaques. Histological examination showed compact hyperkeratosis, intermittent columns of parakeratosis, and an akanthotic epidermis with minor nuclear atypicality. Polymerase chain reaction analysis with degenerate primers identified an atypical human papillomavirus; sequencing showed an RX-variant of HPV, type 23. There were no other signs of chronic arsenic intoxication, and clinical, radiographic, and laboratory investigations showed no evidence of an internal malignancy.

Musculoskeletal

The use of arsenical paste in dental medicine can lead to severe toxicity. Severe alveolar bone necrosis has been reported as a result of leakage of an arsenical devitalization paste into the periodontium (24).

- An 18-year-old woman with dental pain had a tooth devitalized with an arsenical paste and soon after developed excruciating pain and denudation of bone. She had slightly inflamed gums and loss of the mesial papillary gingivae. The surrounding bone was exposed to a height of 3–4 mm and the exposed bone had a greyish color. The non-vital tooth was preserved by root canal treatment and flap surgery to remove necrotic bone and the associated root, and 3 months later a definitive cuspal coverage restoration was placed over the tooth. At 1 year the patient reported that the tooth was functional without any problems.

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Arsenobenzol

General Information

Arsenobenzol has been used to treat syphilis (1,2) and as a topical antiseptic in combination with cortisone and silver colloid (3). Like other compounds with an arsenic base, it can cause gastrointestinal complaints, but also polyneuritis and encephalopathy. Adrenaline prevented the development of encephalopathy and was helpful in treating hemorrhagic encephalopathy (SEDA-11, 597).

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Artemisinin derivatives

General Information

The herb Qinghaosu (*Artemisia annua*) has been known to Chinese medicine for centuries and was used in the treatment of fevers, in particular malaria fever; it is not clear why it did not become more widely used elsewhere. The plant can be grown in locations other than China, and field studies in propagating and growing the plant are being carried out in many parts of the world. In 1979 the Qinghaosu Antimalarial Coordinating Research Group reported their experience with four formulations of qinghaosu in both *Plasmodium vivax* and *Plasmodium falciparum* malaria (SEDA-13, 818) (SEDA-17, 326) (1).

Artemisinin is an antimalarial constituent isolated from Qinghao. It is a sesquiterpene lactone with an endoperoxide bridge, structurally distinct from other classes of antimalarial agents. Several derivatives of the original compound have proved effective in the treatment of *Plasmodium falciparum* malaria and are currently available in a variety of formulations: artesunate (intravenous, rectal, oral), artelinate (oral), artemisinin (intravenous, rectal, oral), dihydroartemisinin (oral), artemether (intravenous, oral, rectal), and artemotil (intravenous). Artemisinic acid (qinghao acid), the precursor of artemisin, is present in the plant in a concentration up to 10 times that of artemisinin. Several semisynthetic derivatives have been developed from dihydroartemisinin (1).

Artemether

Artemether is a methyl ether derivative of dihydroartemisinin. It is dispensed in ampoules for intramuscular injection suspended in groundnut oil and in capsules for oral use. Like artesunate and artemisinin it has been used for both severe and uncomplicated malaria. Artesunate is probably faster-acting than the other two.

Artemotil (arteether)

Artemotil is the ethyl ether derivative of dihydroartemisinin. It was the choice of the WHO for development and was considered less toxic, because one would expect it to be metabolized to ethanol rather than methanol. It is also

more lipophilic than artemether, a possible advantage for accumulation in brain tissues. The beta anomer was chosen since it is a crystalline solid and relatively easy to separate from the alpha anomer, which is liquid; it was necessary to choose a single anomer because of the more complex rules for the development of a drug with two anomers in the USA.

Artesunate

Artesunate is a water-soluble hemisuccinate derivative, available in parenteral and oral formulations. The parenteral drug is dispensed as powdered artesunic acid. Neutral aqueous solutions are unstable. Artesunate is effective by the intravenous, intramuscular, and oral routes in a dose of 10 mg/kg given for 5–7 days. The combination with mefloquine is very effective even against highly multiresistant strains of *Plasmodium falciparum*; the combination must be given for at least 3 days.

None of these medications has yet been registered for use in Europe or North America. In recent years there has been a substantial increase in our knowledge of their safety, efficacy, and pharmacokinetics. Higher cure rates are achieved when they are combined with longer-acting antimalarial drugs, such as mefloquine. After years of continued use, the sequential use of artesunate and mefloquine remains an effective treatment in areas of multidrug resistance in South-East Asia and provides an impetus for the evaluation of other artesunate-containing combination regimens for the treatment of uncomplicated malaria, such as artemether + benflumetol (2–6).

Mechanism of action

All three *Artemisia* derivatives are quickly hydrolysed to the active substance dihydroartemisinin. They produce a more rapid clinical and parasitological response than other antimalarial drugs. There are no reports of significant toxicity, and as late as 1994 there was no convincing evidence of specific resistance, but chloroquine-resistant *Plasmodium berghei* is resistant to artemisinin as well. The recrudescence rate is fairly high (1).

The mode of action is not fully known. There is strong evidence that the antimalarial activity of these drugs depends on the generation of free radical intermediates; free radical scavengers, such as ascorbic acid and vitamin E, therefore antagonize the antimalarial activity.

Drug activation by iron and heme may explain why endoperoxides are selectively toxic to malaria parasites. The malaria parasites live in a milieu of heme iron, which the parasite converts into insoluble hemozoin. Chloroquine, which binds heme, antagonizes the antimalarial activity of artemisinin.

Observational studies

Some impression of possible adverse effects in humans can be gained from a primarily pharmacokinetic study, in which artemotil solution in sesame oil was given intramuscularly. The half-life was 25–72 hours. Adverse effects in 23 subjects after the single dose included local pain in two, bitter taste and dryness of the mouth in one, and a mild but slightly itching papular rash that persisted for 14 days in another. There were no biochemical or electrocardiographic changes. Similar adverse effects were seen after 5 days of therapy in 14 of the 27 subjects; there was local pain in three, metallic taste in two, flu-like symptoms in three, and in two a maculopapular rash, which receded within 24 hours. One subject developed shivering, clammy hands and feet, dizziness, headache, nausea, and a metallic taste in the mouth, all lasting for about an hour, but the same reaction occurred after an injection of sesame oil only. Apart from some increase in eosinophil count in all groups, there were no significant hematological changes (7).

In 25 patients with acute uncomplicated *Plasmodium falciparum* malaria treated with artemotil (3.2 mg/kg followed by either 1.6 mg/kg or 0.8 mg/kg), the most frequent adverse events were headache, dizziness, nausea, vomiting, and abdominal pain; two patients complained of mild pain at the site of injection (8).

In a postmarketing surveillance study of artemotil in 300 patients, 294 (98%) were cured, five improved, and one did not show any change (9). The adverse effects were mild headache, nausea, vomiting, and giddiness.

Combination therapy

The artemisinin derivatives are limited by an unacceptable incidence of recrudescence with monotherapy, and they therefore need to be used in combination. A summary of prospective trials that looked specifically for adverse effects showed that artemisinins alone are very well tolerated (10). The same study showed no evidence of adverse interactions of artesunate with mefloquine, with an incidence of adverse effects similar to that expected from malaria and mefloquine (25 mg/kg) together. Reducing doses of mefloquine increases recrudescence rates to unacceptable levels (11). Combinations of artemisinins with quinine, co-trimoxazole, and doxycycline are well tolerated.

Artemether + benflumetol

A large trial of the first fixed-dose combination of an artemisinin derivative likely to be licensed (artemether + benflumetol) had disappointing relapse rates compared with mefloquine monotherapy (6). In the 126 patients who took artemether + benflumetol there were no adverse effects attributed to drug treatment. However, less than 70% of patients were cured at 28 days. Benflumetol may be more effective at higher concentrations (12) but toxicity studies are lacking.

Artesunate + lumefantrine

There has been a meta-analysis of 15 trials from Africa, Europe, and Asia of the use of varying doses of artesunate plus lumefantrine compared with several alternative antimalarial drugs in 1869 patients conducted by the manufacturers Novartis into its clinical safety and tolerability in the treatment of uncomplicated malaria (13). The most common adverse events were gastrointestinal—nausea (6.3%), abdominal pain (12%), vomiting (2.4%), anorexia (13%)—or central nervous—headache (21%) or dizziness (16%). There were 20 serious adverse events with artesunate plus lumefantrine, but only one (hemolytic anemia) was possibly due to artesunate plus lumefantrine. There was no QT prolongation associated with artesunate plus lumefantrine.

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Artesunate + mefloquine

Artesunate has been combined with mefloquine in areas with a high prevalence of multiresistant *Plasmodium falciparum* in Thailand and the Thai-Burmese border. In a study reported in 1992 in 127 patients who were followed for 28 days, group A took artesunate 100 mg immediately and then 50 mg every 12 hours for 5 days (total 600 mg), group M took mefloquine 750 mg and another 500 mg 6 hours later, and group AM took first artesunate and then the two doses of mefloquine (14). Fever and parasite clearance time were significantly shorter in the two groups treated with artesunate. Table 1 gives the results and adverse effects. The combination of artesunate with mefloquine was more effective than either drug alone. However, the trial design was such that the patients who took both drugs were in fact treated twice, so the findings did not prove synergism between the two drugs.

In a second Thai study, 652 adults and children were treated with artesunate plus mefloquine (15). A single dose of artesunate 4 mg/kg plus mefloquine 25 mg/kg gave a rapid response but did not improve cure rate. Artesunate given for 3 days in a total dose of 10 mg/kg plus mefloquine was 98% effective. The incidence of vomiting was significantly reduced by giving the mefloquine on day 2 of the treatment. There were no adverse effects attributed to artesunate.

Artesunate plus pyrimethamine + sulfadoxine

In Irian Jaya, a randomized, controlled trial ($n = 105$; 88 children) of oral artesunate (4 mg/kg od for 3 days) with pyrimethamine (1.25 mg/kg) + sulfadoxine or pyrimethamine + sulfadoxine alone (same dose) showed reduced gametocyte carriage and reduced treatment failure rates (RR = 0.3; 95% CI = 0.1, 1.3) in the combination group (16). Self-limiting adverse events of combination treatment were mild diarrhea (2.1%), rashes (4.3%), and itching (2.1%).

In a double-blind, randomized, placebo-controlled trial in Gambian children with uncomplicated falciparum malaria treated with pyrimethamine + sulfadoxine (25/500 mg; $n = 600$) or pyrimethamine + sulfadoxine combined with two regimens of oral artesunate (4 mg/kg, $n = 200$ or 4 mg/kg od for 3 days, $n = 200$), there were mild adverse events, such as headache, anorexia, nausea, vomiting, abdominal pain, and diarrhea, in a high proportion of children (56%) (17). Combination treatment with artesunate was associated with more rapid parasite clearance and less gametocytemia. Three-dose artesunate conferred no additional benefit over the one-dose regimen.

Artesunate + tetracycline

In a comparison between oral artesunate (700 mg over 5 days) plus tetracycline (250 mg at 6-hour intervals) and quinine (600 mg quinine sulfate at 8-hour intervals) for 7 days, artesunate was more effective and better tolerated in uncomplicated malaria (see Table 2) (18). Convulsions occurred in one case.

Dihydroartemisinin + piperaquine

The novel combination (Artekin™) of dihydroartemisinin and piperaquine has been assessed in 106 patients (76 children and 30 adults) with uncomplicated *Plasmodium falciparum* malaria in Cambodia (19). The respective doses of dihydroartemisinin and piperaquine, which were given at 0, 8, 24, and 32 hours, were 9.1 mg/kg and 74 mg/kg in children and 6.6 and 53 mg/kg in adults. All the patients became aparasitemic within 72 hours. Excluding the results in one child who died on day 4, there was a 97% 28-day cure rate (99% in children and 92% in adults). Patients who had recrudescent infections used low doses of Artekin. Adverse effects, most commonly gastrointestinal complaints, were reported by 22 patients (21%) but did not necessitate premature withdrawal.

Comparative studies

Three large clinical trials (in Kenya, the Gambia, and Vietnam) compared intramuscular artemether with intravenous quinine in severe malaria tropica (SEDA-20, 259). The treatments were similarly efficacious. There were no serious adverse effects.

Placebo-controlled studies

In a double-blind, randomized study in Vietnam ($n = 227$), extending the duration of oral artemisinin monotherapy 500 mg/day from 5 to 7 days did not reduce recrudescence rates (total 23%) (20).

Table 1 Adverse effects of artesunate with or without mefloquine in acute uncomplicated malaria tropica

	Mefloquine	Artesunate	Artesunate + Mefloquine
Total number of patients (M/F)	39/4	38/4	39/3
Number of patients with 18-day follow-up	37	40	39
Number (%) cured at 28 days	30 (81)	35 (88)	39 (100)
Fever clearance time (hours)	70	35	38
Parasite clearance time (hours)	64	36	38
Headache (%)	17 (39)	14 (33)	12 (28)
Dizziness (%)	8 (18)	6 (14)	5 (11)
Nausea (%)	9 (20)	6 (14)	9 (21)
Vomiting (%)	7 (16)	8 (19)	11 (26)
Abdominal pain (%)	1 (2)	2 (4)	1 (2)
Diarrhea (%)	1 (2)	3 (7)	1 (2)
Itching and rash (%)	0	3 (7)	1 (2)

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Table 2 Adverse effects in a comparison of artesunate plus tetracycline versus quinine

	Artesunate + Tetracycline	Quinine
Number	31	33
Parasite clearance time (hours)	37 (24–52)	73 (26–135)
Cure rate on day 27 (%)	97	10
Nausea (%)	14 (45)	20 (60)
Dizziness (%)	16 (52)	16 (48)
Vomiting (%)	9 (26)	30 (91)
Tinnitus (%)	0	29 (88)
Convulsions (%)	1 (3)	0
Bradycardia (%)	7 (23)	Not done

General adverse effects

The safety of the peroxide antimalarial drugs has been reviewed (21). In animal studies, high doses of artemotil and artemether have been associated with hemopoietic, cardiac, and nervous system toxicity. Some subclinical neurotoxicity has been reported, with a discrete distribution in the brain stems of rats and dogs after multiple (high) doses (22). Dogs given high doses (15 mg/kg artemether for 28 days) had a progressive syndrome of clinical neurological defects with terminal cardiorespiratory collapse and death. There has been no evidence of neurotoxicity in man, but the human dosage of these ethers is of course lower. Reviews of clinical trials have reaffirmed the high tolerability of the artemisinins (11,23). Adverse effects have been chiefly limited to the GI tract. Most reported adverse events were described as mild and transient and none resulted in withdrawal of treatment.

Organs and Systems

Cardiovascular

Sinus bradycardia and a reversible prolongation of the QT interval have been reported (SEDA-21, 293).

A combination of artemether + lumefantrine (co-artemether, six doses over 3 days) followed by quinine (a 2-hour intravenous infusion of 10 mg/kg, not exceeding 600 mg in total, 2 hours after the last dose of co-artemether) was given to 42 healthy volunteers in a double-blind, parallel, three-group study (14 subjects per group) to examine the electrocardiographic effects of these drugs (24). Co-artemether had no effect on the QT_c interval. The infusion of quinine alone caused transient prolongation of the QT_c interval, and this effect was slightly but significantly greater when quinine was infused after co-artemether. Thus, the inherent risk of QT_c prolongation by intravenous quinine was enhanced by prior administration of co-artemether. Overlapping therapy with co-artemether and intravenous quinine in the treatment of patients with complicated or multidrug-resistant *Plasmodium falciparum* malaria may result in a modest increased risk of QT_c prolongation, but this is far outweighed by the potential therapeutic benefit.

The effects on the QT_c interval of single oral doses of halofantrine 500 mg and artemether 80 mg + lumefantrine 480 mg have been studied in 13 healthy men in a double-blind, randomized, crossover study (25). The length of the QT_c interval correlated positively with halofantrine exposure but was unchanged by co-artemether.

Nervous system

Although in animals several of the artemisinin derivatives have produced a characteristic neurological lesion, there is no good evidence of neurotoxicity in man. A study in mice suggested that intramuscular artemether is significantly more neurotoxic than intramuscular artesunate (26).

In one case, an inadequately treated non-immune subject developed neurological symptoms after relapse and re-treatment; the symptoms were ascribed to artemether (27), although the well-recognized post-malaria neurological syndrome was much more likely, which the authors did not discuss (28).

One man developed ataxia and slurred speech after taking a 5-day course of oral artesunate (SEDA-21, 293).

A study of brain-stem auditory-evoked potentials showed no electrophysiological evidence of brain-stem damage in adults treated with artemisinin derivatives (29).

Neurotoxicity from artemether is related to drug accumulation due to slow and prolonged absorption from intramuscular injection sites. In mice, high doses of intramuscular artemether (50–100 mg/kg/day for 28 days) resulted in an unusual pattern of selective damage to certain brain-stem nuclei, especially those implicated in hearing and balance (30).

Fluid balance

Sodium artesunate inhibits sodium chloride transport in the thick ascending limb of the loop of Henle and therefore has a diuretic effect.

- In two men, aged 16 and 32 years, with falciparum malaria who were given four intravenous doses of sodium artesunate 60 mg, neither of whom had received diuretics or vasoactive drugs, there was a diuresis (6 l/day) accompanied by a natriuresis (31).

Hematologic

A transient dose-dependent reduction in reticulocyte count has been reported in healthy subjects (SEDA-21, 294).

Body temperature

Drug fever has been reported in healthy subjects taking artemether, artesunate, and artemisinin (SEDA-21, 294).

Second-Generation Effects

Pregnancy

Artemisinin derivatives (artesunate and artemether) for the treatment of multidrug-resistant *Plasmodium falciparum* malaria have been evaluated in 83 Karen pregnant women in Thailand; 55 women were treated for recrudescent infection after quinine or mefloquine, 12 for uncomplicated hyperparasitemic episodes, and 16 had not declared their pregnancy when treated (32).

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Artesunate and artemether were well tolerated and there was no drug-related adverse effect. Overall, 73 pregnancies resulted in live births, three in abortions and two in still-births; five women were lost to follow-up before delivery. There was no congenital abnormality in any of the neonates, and the 46 children followed for more than 1 year all developed normally.

Artemisinin derivatives have been studied in 461 pregnant women in a prospective cohort study in Thailand over 8 years (33). Oral artesunate monotherapy was associated with a treatment failure rate of 6.6%. Artesunate and artemether were well tolerated. The rates of abortions (including 44 first-trimester exposures), stillbirths, or congenital abnormalities were 4.8%, 1.58%, and 0.8% respectively, and were not significantly different from pregnant controls. These results are reassuring, but further information is needed before the safety of artesunate in pregnancy can be confirmed.

Drug Administration

Drug formulations

When the sesame oil vehicle in beta-artemotil was replaced by Cremophor (polyethoxylated castor oil) the total exposure in rats was 2.7-fold higher, owing to increased systemic availability (34). Anorexia and gastrointestinal toxicity from artemotil in sesame oil were significantly more severe than with artemotil in Cremophor. However, histological examination of the brain showed neurotoxic changes, which were worse with the castor oil formulation.

Drug administration route

A crossover pharmacokinetic study of single-dose rectal artesunate (10 or 20 mg/kg as a suppository) or intravenous artesunate (2.4 mg/kg) in moderate falciparum malaria in 34 Ghanaian children has been reported (35). The intravenous route gave much higher peak concentrations but more rapid elimination of artesunate and its active metabolite dihydroartemisinin than the rectal route. Rectal artesunate had higher systemic availability in the low-dose group than in the high-dose group (58% versus 23%). This is lower than published estimates of the systemic availability of oral artesunate (61–85%) (36). Parasite clearance kinetics were comparable in the two groups. There were no adverse events attributable to the drug. The results of Phase III and Phase IV studies of rectal artesunate as an alternative to parenteral antimalarial drugs in African children are awaited.

Drug–Drug Interactions

Chloroquine

Although an early report suggested antagonism between chloroquine and artemisinin (37), more recent evidence suggests the opposite, that is a synergistic effect between the two (38,39).

Deferoxamine

Co-administration of artemisinin derivatives, such as artesunate, with deferoxamine may be useful in patients with cerebral malaria, because of the combination of rapid parasite clearance by the former and central nervous system protection by the latter. Artesunate has been studied alone and in combination with deferoxamine in a single-blind comparison (40). Adverse effects were generally mild and there were no differences between the two regimens.

Omeprazole

Artemisinin induces its own elimination and that of omeprazole through an increase in CYP2C19 activity and that of another enzyme, as yet to be identified (41).

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Articaine

See also Local anesthetics

General Information

Articaine is an aminoamide that also contains an ester group, which is rapidly hydrolysed by plasma esterases. It is 4-methyl-3([2-(propylamino)propionamido)]-2-thiophenecarboxylic acid, methyl ester hydrochloride. The thiophene group increases its lipid solubility while the ester group enables it to undergo plasma esterase hydrolysis as well as hepatic enzyme metabolism. Articaine is formulated as a 4% solution with adrenaline. It is the most widely used local anesthetic agent in dentistry in some parts of Europe.

The rapid breakdown of articaine to an inactive metabolite means that it has low systemic toxicity. However, the risk of intravascular injection is high in dentistry, and articaine can cause central nervous system and cardiovascular toxicity. However, articaine is slightly more potent than lidocaine and causes less nervous system toxicity (1).

The safety of articaine has been studied in a series of three randomized trials (2). The adverse effects deemed to be related to articaine were headache, paresthesia/hyperesthesia after injection, infection, and rash. There was one case of mouth ulceration. The overall incidence of adverse effects was comparable to that of lidocaine.

Organs and Systems

Cardiovascular

The incidence of hypotension and headache after spinal anesthesia was similar to that encountered with lidocaine (SED-12, 256) (3).

Nervous system

Four cases of persistent lingual paresthesia or hyperesthesia after inferior dental block with articaine have been reported (4). Although resolution of neurological complications usually occurs within 2 weeks, the authors reported that the symptoms in their cases persisted for 6–18 months and noted that they were aware of another four cases of persistent paresthesia with articaine that had not been formally reported.

Skin

- An 11-year-old boy developed severe dermatomyositis only a few days after injection of articaine in the jaw for tooth extraction; cause and effect were not established (SEDA-10, 105).

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Artificial sweeteners

General Information

Acesulfame

Acesulfame is an artificial sweetener derived from acetoacetic acid. It is used in a wide range of non-medicinal products (1).

Aspartame

Aspartame is a dipeptide that is used as an artificial sweetener. It is completely hydrolysed in the gastrointestinal tract to methanol, aspartic acid, and phenylalanine (2).

Aspartame appears to be a safe sweetener, and despite numerous studies of its safety during the past three decades, the incidence of serious adverse effects has been difficult to determine in controlled studies. Since one of the metabolic products of aspartame is phenylalanine, excessive use of aspartame should be avoided by patients with phenylketonuria (3–5). Toxicity of another possible metabolic product, methanol, is unlikely, even when aspartame is used in extraordinary amounts (6,7).

Aspartame has reportedly caused angioedema and urticaria (SEDA-21, 526).

Cyclamates

Sodium cyclamate is a potent sweetening agent. It has been subjected to numerous safety and carcinogenicity studies. Animal data led to warning against excessive and indiscriminate use a long time ago, causing the World Health Organization in 1967 to adopt a safety limit of 50 mg/kg. However, in 1982 a joint FAO/WHO expert committee on food additives revised this recommendation to allow for a maximum daily intake of up to 11 mg/kg of sodium or calcium cyclamate (as cyclamic acid) (8). Nevertheless, since in certain climates and populations the amount of cyclamates in soft drinks and other beverages can exceed these limits, more epidemiological data are needed to evaluate, for example, a possible association with cancer of the uropoietic system (9) and with histological and radiological abnormalities of the small intestine and malabsorption (10).

Saccharin

Saccharin and its salts are potent sweeteners, about 300 times as sweet as sucrose. It is used to sweeten foods and beverages.

Sorbitol

Sorbitol, a polyhydric alcohol, is used as a sweetening agent in many oral medicinal liquids. In addition to enhancing the palatability of these liquids, it improves solution stability and reduces crystallization of syrup

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vehicles (11). It is used as a sweetener in many sugar-free food products and confectioneries. Sorbitol-containing food products are often recommended for patients with diabetes, because sorbitol does not raise blood glucose concentrations or require insulin for its metabolism (12).

Organs and Systems

Cardiovascular

Two patients with Raynaud's phenomenon (13) and one man with fibromyalgia had all used aspartame 6–15 g/day (0.12–0.16 mg/kg/day) as well as a dietary drink containing aspartame, and no other risk factors were identified. All three described regular keyboarding to the extent of 30 hours per week but had used wrist rests, "stretch breaks," and other steps to optimize their work practices. Complete resolution of symptoms occurred over 2 weeks after they had eliminated aspartame from the diet, despite no changes in the intensity of keyboarding or other work practices. Nerve conduction velocities had been within normal limits before the withdrawal of aspartame and were not repeated.

Nervous system

Headaches can follow aspartame ingestion (14). Up to July 1991 the FDA had received over 5000 reports of adverse effects in a passive surveillance program; in this and other studies the main complaints were of neurological symptoms, and headaches accounted for 18–45% of cases (15). It appears that some people are particularly susceptible to headaches caused by aspartame and may want to limit their consumption (16). In a double-blind, crossover study using volunteers with self-identified headaches after aspartame, some were particularly susceptible, and their headaches were attributed to aspartame (17).

Aspartame can alter brain wave activity in epileptic children (18). It has been associated with seizures, but only anecdotally (19).

In three non-obese individuals (two women and one man), it was suspected that heavy use of aspartame was causally related to symptoms of carpal tunnel syndrome (20). All three reported moderate pain and tingling in the hands, especially at night, using a self-administered questionnaire for the assessment of severity of symptoms and functional status (21). Given the ubiquity of aspartame—one manufacturer has stated that it is used in 5000 products—physicians may want to inquire about its use in patients who report symptoms of carpal tunnel syndrome.

Psychological, psychiatric

Aspartame has been associated with mood disturbances, but only anecdotally (19).

Gastrointestinal

Sorbitol is slowly absorbed by passive diffusion in the small intestine. After oral administration, it increases osmotic pressure in the bowel by drawing in water, and is thus an osmotic laxative, sometimes leading to diarrhea (22). Bacterial fermentation of sorbitol in the large bowel is associated with increased flatulence and abdominal cramping. Sorbitol 10 g can cause flatulence and bloating, and 20 g abdominal cramps and diarrhea.

Many healthy individuals are intolerant of sorbitol, and develop abdominal cramping and diarrhea with less than the usual laxative dose (23). It has been suggested that more than 30% of healthy adults, irrespective of ethnic origin, cannot tolerate 10 g of sorbitol (24).

Certain other patients are especially sensitive to the gastrointestinal effects of sorbitol; for example, diabetics can be prone to sorbitol intolerance, because of altered gastrointestinal transit time and motility. Some of them also have a higher consumption of sorbitol-containing dietary foods. Patients on chronic hemodialysis can be predisposed to sorbitol intolerance as a result of carbohydrate malabsorption (25).

Kayexalate (sodium polystyrene sulfonate) in sorbitol is commonly used to treat hyperkalemia in patients with renal insufficiency. Case reports have documented intestinal necrosis after the administration of kayexalate in sorbitol (26,27). In one study, there was an incidence of 1.8%, and the authors concluded that sorbitol-associated complications may not be uncommon postoperatively (28). Furthermore, it has been suggested that some cases of idiopathic colonic ulcers in patients with renal failure are due to the effects of sorbitol. While kayexalate crystals, which are purple, irregular, and jagged, can be an incidental finding and are not known to cause injury, they are a helpful histological clue to the possibility that sorbitol has been administered (29).

Five cases of extensive mucosal necrosis and transmural infarction of the colon have been reported after the use of kayexalate and sorbitol enemas to treat hyperkalemia in uremic patients (30). The authors also studied the effects of kayexalate sorbitol enemas in normal and uremic rats and concluded that sorbitol was responsible for colonic damage and that the injury was potentiated in uremic rats. When sorbitol alone or kayexalate sorbitol were given, extensive transmural necrosis developed in 80% of normal rats and in all the uremic rats.

Following reports of colonic necrosis, the Pharmaceutical Affairs Bureau of Japan has revised the product information for enemas of polystyrene sulfonate cation exchange resin suspension in sorbitol solution for potassium removal (31). Although a causal relation has not been established definitively, the Bureau has decided that sorbitol solution should not be used for enemas of sodium polystyrene sulfonate cation exchange resins.

Immunologic

The role of aspartame in hypersensitivity reactions is controversial, although there have been case reports (32). In a multicenter, randomized, double-blind, placebo-controlled, crossover study, aspartame was more likely than placebo to cause urticaria or angioedema (33).

Aspartame can cause granulomatous septal panniculitis (34).

Lobular panniculitis has been described in a 57-year-old diabetic man who ingested large amounts of aspartame as a sweetener, in soft drinks and other

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products. He stopped taking aspartame and the tender subcutaneous nodules disappeared (35).

Long-Term Effects

Tumorigenicity

Acesulfame

The studies on the basis of which acesulfame gained approval showed no evidence in animals of mutagenicity, teratogenicity, or adverse reproductive effects; a 2-year toxicology study in beagles showed no untoward adverse effects. The incidence of lymphocytic leukemia was slightly increased in high-dosed female mice, but not beyond the spontaneous variation with this strain. No other evidence of potential carcinogenicity was obtained, and it has been concluded that at the estimated level of exposure, acesulfame and its metabolites are not a health hazard (36).

Aspartame

It has been suggested that aspartame may be linked to the increase in incidence of brain tumors. Brain tumor incidence increases in the USA occurred in two distinct phases, an early modest increase that may have primarily reflected improved diagnostic technology, and a later-sustained increase in the incidence and shift toward greater malignancy that must be explained by some other factor(s) (37). Evidence potentially implicating aspartame includes an early animal study that showed an exceedingly high incidence of brain tumors in aspartame-fed rats compared with no brain tumors in concurrent controls, the finding that aspartame has mutagenic potential, and the close temporal association (aspartame was introduced into US food and beverage markets several years prior to the sharp increase in brain tumor incidence and malignancy). The authors concluded that the carcinogenic potential of aspartame needs to be reassessed.

Saccharin

Saccharin has been considered to be a possible human carcinogen on the basis of animal experiments. This suspicion has now been discredited. There is no evidence that people with diabetes, who consume larger quantities of saccharin than non-diabetics, are at greater risk of developing bladder cancer (38) or other malignancies. However, in the USA, saccharin-containing medicines are required to carry the following warning: "Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals" (39).

Susceptibility Factors

Individuals with mood disorders are thought to be particularly sensitive to aspartame, and it has been suggested that its use in such patients should be discouraged (40).

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Asclepiadaceae

See also Herbal medicines

General Information

The genera in the family of Asclepiadaceae (Table 1) include milkweed and periploca.

Asclepias tuberosa

Asclepias tuberosa (pleurisy root) contains cardenolides such as uzarigenin, coroglaucigenin, and corotoxigenin, the coumarins isorhamnetin, kaempferol, quercetin, and rutin, the steroid sitosterol, and the triterpenoids amyrin, friedelin, and lupeol.

Table 1 The genera of Asclepiadaceae

Araujia (araujia)
Asclepias (milkweed)
Calotropis (calotropis)
Cryptostegia (rubbervine)
Cynanchum (swallow-wort)
Funastrum (twinevine)
Gonolobus (gonolobus)
Hoya (hoya)
Marsdenia (marsdenia)
Matelea (milkvine)
Metaplexis (metaplexis)
Morrenia (morrenia)
Oxypetalum (oxypetalum)
Periploca (periploca)
Stapelia (stapelia)
Xysmalobium (xysmalobium)

Adverse effects

Because it contains cardenolides, *Asclepias* can have digitalis-like effects and potentiate digitalis toxicity (See monograph on Cardiac glycosides). Interference with assays of plasma digoxin concentrations is also possible (1).

Xysmalobium undulatum

Xysmalobium undulatum (xysmalobium) contains the cardiac glycoside ascleposide. It has been used topically to treat wounds (2). Its adverse effects are likely to be those of other cardiac glycosides (see monograph on Cardiac glycosides).

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Ascorbic acid (vitamin C)

See also Vitamins

General Information

The Average Requirement of ascorbic acid is 30 mg/day. The Population Reference Intake is 45 mg/day for adults. The Lowest Threshold Intake, for which considerable evidence exists, is 12 mg/day (1). These estimates have been supported by the relevant committee of the European Union. A communication from the US National Academy of Sciences, as part of the revision of US Dietary Reference Intakes, while estimating rather higher average requirements of ascorbic acid than the EU committee, does (100 mg/day) also proposed a "tolerable upper intake

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level" of less than 1 g of ascorbic acid/day (2). "Normal" plasma ascorbic acid concentrations are 60–80 μmol/l (2).

In spite of the lack of unequivocal evidence of a beneficial effect of large doses of ascorbic acid for preventing or treating the common cold, the use of ascorbic acid for this indication is still widespread.

The adverse effects of high-dose ascorbic acid have been reviewed in the context of its pharmacokinetics (3). Pharmacokinetic analysis shows that there is no justification for the use of megadoses of ascorbic acid (4). The body goes to great lengths to avoid excess accumulation of vitamin C, and has at least three ways of accomplishing this. First, absorption of vitamin C from the gut is highly saturable, ensuring that the amount that is absorbed reaches a maximum at relatively low doses. Secondly, the kidney rapidly excretes vitamin C, because its reabsorption from the renal tubules after filtration by the renal glomerulus is also highly saturable. Virtually all the vitamin C that is absorbed from the gut is thus excreted in the urine. For example, when the daily dose is increased from 200 to 2500 mg (from 1.1 to 14 mmol) the mean steady-state plasma concentration increases only from about 12–15 mg/l (from 68 to 85 mol/l)—no matter how high a dose of vitamin C you take orally there is a limit to the plasma concentration that can be reached. Thirdly, tissue uptake is also saturable. An increase in plasma concentration of vitamin C is not associated with a parallel increase in tissue concentration (5). Indeed, the tissue vitamin C concentration, measured in leukocytes, saturates at 100 mg/day (6) or plasma concentrations of 14 μg/ml (80 mol/l) (5). So no matter how much you take, all you do is increase the concentrations in your urine and gut, and that can cause adverse effects (7). Vitamin C is partly excreted as oxalate, and very high doses can lead to hyperoxaluria and kidney stones (8), particularly after intravenous use and in people with renal insufficiency. Adverse effects in the gut include nausea, abdominal cramps, and diarrhea (9).

General adverse effects

Hot flushes, headache, fatigue, insomnia, nausea, vomiting, and diarrhea have been observed with large doses, but it is difficult to tell to what extent these are real rather than placebo effects. The best evidence of problems caused by high doses relates to stone formation, mainly in patients with chronic renal insufficiency. Certain hematological and metabolic effects have been reported in premature infants; however, these have not been corroborated (10). Several cases of hemolysis have been reported. Respiratory and cutaneous allergies to ascorbic acid have been described (11). Tumor-inducing effects have not been reported.

Organs and Systems

Respiratory

Ascorbic acid 3 g/day for 6 days causes a significant loss of high altitude resistance, persisting for 2 weeks after withdrawal of treatment. High doses may therefore constitute a risk in people who take them under conditions in which the oxygen supply suddenly becomes impaired, and is also undesirable in people with pathological hypoxia, for example due to respiratory diseases (12).

A trial in 868 children showed that in those with high plasma ascorbic acid concentrations, the duration of upper respiratory infection was greater than in those with low concentrations (13). This finding, which contrasted with the optimistic expectations of other workers, requires confirmation.

Metabolism

Dehydroascorbic acid appears to have a diabetogenic effect and ascorbic acid causes increased excretion of glucose. High ascorbic acid concentrations can delay the insulin response to a glucose challenge and prolong postprandial hyperglycemia (14).

An increase in serum cholesterol has been reported in patients with atherosclerosis taking high doses of ascorbic acid (9).

Metal metabolism

Binding of zinc and copper by high doses of ascorbic acid has been reported (9).

Hematologic

Under experimental conditions, ascorbic acid 5 g/day increased the lytic sensitivity of erythrocytes to hydrogen peroxide (15). Similar doses, given with mandelamine or antibiotics, lower urinary pH and have a small effect on blood pH; in patients with sickle-cell anemia such doses can precipitate a crisis (9). The erythrocytes of premature infants can be damaged by ascorbic acid (SEDA-14, 332); reduced glutathione concentrations and increased Heinz-body formation have been seen (16). Possible explanations may be higher glucose consumption and increased glycolytic enzyme activities compared with erythrocytes in adults, accompanied by increased sensitivity to hemolysis (17).

Also at risk of hemolysis are patients with glucose-6-phosphate dehydrogenase deficiency, in whom ascorbic acid can denature hemoglobin and reduce erythrocyte glutathione concentrations; one such case proved fatal (18). This was further demonstrated by reports of hemolytic effects (19); in two young subjects with glucose-6-phosphate dehydrogenase deficiency hemolysis was induced by excessive intake of "fizzy drinks" fortified with ascorbic acid (20).

Gastrointestinal

Nausea, abdominal cramps, and diarrhea are not uncommon (9). In runners taking daily doses of 1 g of ascorbic acid for reduction of musculoskeletal symptoms, mild diarrhea is common (21). Ascorbic acid stones have been found to obstruct the ileocecal valve (22).

Urinary tract

Ascorbic acid 4 g/day increases uric acid clearance in volunteers (23), although it does not reduce protein-bound uric acid in blood. Ascorbic acid 4–12 g/day causes acidification of the urine, which can cause precipitation of urate and cystine and consequently formation of urate stones or cystinuria. Ascorbic acid is excreted largely as oxalate, and hyperoxaluria results when large doses are

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taken. In patients with pre-existing oxalosis, gram doses of ascorbic acid further increase oxalate excretion (9,24).

Whether this increased oxalate excretion has consequences in terms of stone formation depends very much on the dosage and duration of treatment. In a small study in healthy individuals short-term, high-dose ascorbic acid (4 g in 5 days) did not affect the risk factors associated with calcium oxalate kidney stone formation (8). A prospective study of the association between doses of pyridoxine and ascorbic acid and the risk of symptomatic kidney stones was undertaken in a large cohort of US nurses. Ascorbic acid was not associated with a higher risk of stone formation (25).

In a study to determine the biochemical and physicochemical risks of high doses of ascorbic acid a man with no history of nephrolithiasis took ascorbic acid 2 g qds while following his normal diet (26). The study was planned to last 9 days. However, he developed significant hematuria on the eighth day. Urinary oxalate and ascorbic acid concentrations were increased. The intestinal absorption of ascorbic acid falls from almost 100% at normal doses to 20% at a dose of 5 g/day (27), and the high concentrations of ascorbic acid in this study suggest that, irrespective of the quantity converted to oxalate, at least 35% of the ingested ascorbic acid had been absorbed. The relative supersaturation of oxalate and the Tiselius risk index both increased. Increases in the calcium oxalate relative supersaturation (28) and Tiselius index (29) are powerful physicochemical indicators of increases in the crystal-forming potential of the urine. In this case the increases in both measures were impressively substantiated by scanning electron microscopy, which showed large crystals and crystal aggregates in the urine. The authors suggested that the passage of these crystals caused irritation and epithelial injury manifesting as hematuria.

Oxalate-induced renal damage has been related to excessive doses of ascorbic acid (30).

- A 31-year-old man developed a headache, nausea, and vomiting. He had taken ascorbic acid, 2–2.5 g/day and before the onset of symptoms up to 5 g/day. He had a raised serum creatinine (1000 μmol/l). Renal ultrasound showed increased cortical echogenicity, and a renal biopsy showed acute tubular necrosis and massive oxalate deposition. He was given pyridoxine and two sessions of hemodialysis.

Various forms of renal damage, notably tubulointerstitial nephropathy, have been associated with long-term use of high dosages of ascorbic acid, for example 3 g/day (31).

Skin

Cutaneous allergy has been described with ascorbic acid (11).

Contact dermatitis has been attributed to ascorbic acid in a cosmetic anti-ageing cream (32).

- A 47-year-old woman developed eczema of the face, consisting initially of edematous lesions on the eyelids and then spreading to the rest of the face and the folds of the neck. Patch tests to a cosmetic cream she had used before the start of the eczema (Active C dry skin, La Roche Posay Laboratory) gave positive results (++D2 and D3). Subsequent patch tests with the ingredients showed positive results only to ascorbic acid. Oral provocation tests with ascorbic acid 50–2000 mg were negative. Withdrawal of the cream resulted in complete healing of the eczema without relapse over 6 months.

Musculoskeletal

In animal experiments, high doses of ascorbic acid adversely influenced skeleton stability. In chicks, supplementary ascorbic acid 220 mg/kg in the food increased mobilization of calcium and phosphate from the skeleton, as demonstrated by ^{45}Ca studies and determination of acid phosphatase activity in plasma. Increased ascorbic acid also resulted in increased oxygen consumption and decreased lactic acid production by cultured chick tibiae; in growing swine, large doses (about 1 g/day for 32 days) led to a significant increase in the excretion rate of hydroxyproline, indicating an increased rate of collagen breakdown (SED-8, 803) (33). The relevance of these old findings to humans has never been confirmed.

Immunologic

As noted above, ascorbic acid can sometimes cause immune reactions. Ascorbic acid and citric acid are used as food additives, ascorbic acid (E300) as an acidifier, an antioxidant, and an additive in wheat, and citric acid as an acidifying complex-binding agent. Because additives are widely used in foods, beverages, and drugs, people with allergies or intolerance have to be carefully instructed. Caution must also be taken when scratch tests are performed with these substances (34).

- A 62-year-old man had frequent angioedema, and a scratch test was performed with several food additives. Scratching with 1% ascorbic acid and 1% citric acid in vaseline resulted in a +3 reaction, and 20 minutes later he developed angioedema with swelling of the glottis, reddening of the face and hands, itching, vertigo, tachycardia, and hypotension. He was given a glucocorticoid and an antihistamine and recovered within half an hour.

Second-Generation Effects

Fertility

Earlier evidence that ascorbic acid in gram doses might reduce fertility was disputed; however, a case of sterility apparently due to ascorbic acid has been described (9).

Teratogenicity

Animal teratological evidence is not entirely uniform, but very high doses in rats and mice have been given without deleterious effects on the fetus (35).

Susceptibility Factors

Genetic factors

Patients with idiopathic (genetic) hemochromatosis constitute a risk group with regard to ingestion of large doses of ascorbic acid, which can lead to deterioration in cardiac function (36).

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Age

An esophageal stricture, with ulceration, inflammation, and fibrosis, has been reported in an elderly patient who had taken ascorbic acid for 2 months (37). A 500 mg tablet of ascorbic acid dissolves only slowly and is in vitro associated with a shift in saliva pH from 6.2 to 2.8. Since elderly individuals usually have less frequent esophageal contractions, it is not uncommon for this group to have a capsule lodged for a time in the esophagus (SEDA-13, 348) and it is entirely possible that cases like the above are more frequent than previously thought.

Renal disease

The use of ascorbic acid in patients with renal insufficiency should be carefully monitored to avoid accelerated development of secondary oxalosis; hyperoxalemia has been reported to be aggravated by ascorbic acid supplementation in regular hemodialysis patients (38). The pharmacological mechanism has been clarified in animal experiments (SEDA-15, 414) (39).

Other features of the patient

Ascorbic acid has been thought to precipitate widespread tumor hemorrhage and necrosis with disastrous consequences in patients with very rapidly proliferating and widely disseminating tumors. These observations suggest that ascorbic acid should be prescribed with extreme caution for persons with advanced cancer (40).

Drug–Drug Interactions

Amphetamines

Decreased renal tubular reabsorption of amphetamines can be caused by ascorbic acid (40).

Aspirin

Enhanced drug crystalluria with aspirin can be caused by ascorbic acid (40).

Fluphenazine

Ascorbic acid may lower serum fluphenazine concentrations by liver enzyme induction and by interference with absorption (41).

Iron

Ascorbic acid promotes the absorption of iron, a reason for caution in giving high doses to patients with iron overload (SEDA-9, 324). In particular, patients with hemochromatosis, polycythemia, and leukemia who present with marked iron overload should keep their intake of ascorbic acid to a minimum (42). However, ascorbic acid can also interfere with the distribution of iron in the body in these patients. One consequence is that in patients with iron overload who also have scurvy, iron tends to be deposited in the reticuloendothelial system rather than the parenchymal cells, which may reduce the risks of damage to the liver, heart, or endocrine glands. It has conversely been noted that in beta-thalassemia major with iron overload, ascorbic acid can be associated with deterioration in cardiac function (43).

Isoprenaline

Ascorbic acid in large doses (5 g/day) reduces the chronotropic effect of isoprenaline (44).

Oral anticoagulants

The effect of ascorbate in reducing prothrombin time is potentially dangerous during oral anticoagulant therapy. In one patient taking dicoumarol the prothrombin time fell from 19 seconds to normal values after intake of ascorbic acid. A similar effect was noted in a patient with thrombophlebitis given ascorbic acid 16 g/day (9). Earlier data suggested that even doses of 200 mg may have resulted in a slight increase in mortality from thromboembolism in patients in a geriatric unit (45).

Tricyclic antidepressants

Decreased renal tubular reabsorption of tricyclic antidepressants can be caused by ascorbic acid (40).

Vitamin B_{12}

Because ascorbic acid in the gastrointestinal tract can reduce the vitamin B_{12} content of food, patients with vitamin B_{12} deficiency should always be questioned about their intake of ascorbic acid (40).

Interference with Diagnostic Tests

Tests for plasma ethinylestradiol concentrations

Plasma ethinylestradiol concentrations increase when it is taken with ascorbic acid. This interaction is of significance in women taking oral contraceptives (SEDA-6, 328).

Tests for urinary glucose

The presence of high concentrations of ascorbic acid in the urine can interfere with tests for urinary glucose. With concentrations as low as 200 μg/ml, tests performed with glucose oxidase paper can be inhibited, giving a false negative result (46).

Ascorbic acid can also result in false positive tests for glucose in urine (Benedict's test, Clinitest) and blood. Any reports of glycosuria or hyperglycemia in patients taking ascorbic acid must therefore be regarded with suspicion unless a specific (for example chromatographic) test for glucose has been performed (9).

Tests for occult blood

There were false negative tests for occult blood after the ingestion of moderately high doses of ascorbic acid (250 mg) (47). Quantities in excess of this are excreted and can affect tests for occult gastric or stool blood (7,48,49). Lack of ascorbic acid can, because of its effect on iron distribution, alter laboratory indices for iron overload, causing the plasma iron or ferritin levels (or the degree of iron excretion after a challenge with deferoxamine) to be considerably less than the degree of

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severity of iron overload that would normally lead one to expect (50).

Tests for serum enzymes

Ascorbic acid interferes with the autoanalyser determination of serum transaminases and lactic dehydrogenase (7,9). Serum bilirubin concentrations may be reduced by ascorbic acid, so that the presence of liver disease may be masked (9).

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Asparaginase

See also Cytostatic and immunosuppressant drugs

General Information

Asparaginase is an enzyme that acts by breaking down the amino acid L-asparagine to aspartic acid and ammonia. It interferes with the growth of malignant cells that cannot synthesize L-asparagine. Its action is reportedly specific for the G_1 phase of the cell cycle. It is used mainly for the induction of remissions in acute lymphoblastic leukemia.

Nomenclature

Colaspase and crisantaspase are the British Approved Names of asparaginase obtained from cultures of *Escherichia coli* and *Erwinia carotovora* respectively.

Organs and Systems

Nervous system

In a review of 28 central nervous system thrombotic or hemorrhagic events and eight peripheral thromboses related to L-asparaginase, the median time from initial treatment to adverse reaction was 16–17 days (1). Most patients recovered completely, although five cases had residual neurological deficits and one died from superior sagittal sinus thrombosis. Five patients with cerebral thrombosis complicating asparaginase/prednisone/vincristine induction therapy for acute lymphoblastic leukemia were found to have a reduced platelet count after the event and, in three of them, sequential changes in von Willebrand factor multimer pattern (2). The other two patients were only studied at presentation and their multimer pattern was not appreciably different to pooled plasma from seven controls without thromboses. The findings were consistent with thrombotic complications caused by platelet agglutination by plasma Von Willebrand factor.

Metabolism

Asparaginase can reduce insulin production (3) and precipitate diabetic ketoacidosis (4,5).

Hematologic

Thrombosis and hemorrhage are well-recognized complications in 1–2% of patients receiving asparaginase. This is due to a coagulopathy, which has been variously attributed to reduced concentrations of fibrinogen, factors IX, XI, VIII complex, antithrombin III, and plasminogen (6).

In one study, 12 children in complete remission treated with daily asparaginase alone were investigated for platelet and clotting abnormalities (7). Changes in prothrombin time, partial thromboplastin time, and fibrinogen remained close to the reference range, and platelet function was normal. There were reduced concentrations of physiological inhibitors of coagulation (protein C and antithrombin III). Thrombosis was uncommon. These results are consistent with those of another study of asparaginase as a single agent in 14 children with acute lymphoblastic leukemia (8). There was severe deficiency of antithrombin III and protein C, with co-existing hypocoagulability; equilibrium between the two partly explained the lack of thromboembolic phenomena. The hypocoagulability was due to hypofibrinogenemia and reduced concentrations of vitamin K-dependent factors.

Three patients developed bilateral venous sinus thromboses after receiving asparaginase; the diagnosis and follow-up of this complication have been succinctly reviewed (9). In another patient receiving asparaginase, central nervous system thrombosis was associated with a transient acquired type II pattern of von Willebrand's disease (10).

Mouth and teeth

Acute parotitis has been attributed to L–asparaginase in association with hyperglycemia (11).

Liver

Most patients who receive asparaginase develop liver function abnormalities, which can be fatal (12). This adverse effect is of major concern in patients who are also taking other hepatotoxic drugs, such as methotrexate and mercaptopurine. Jaundice and increased serum bilirubin and transaminases occur often, and hepatomegaly and fatty deposits occur occasionally.

Pancreas

Pancreatitis has been reported in up to 16% of children receiving asparaginase for a variety of neoplasms (13). Pseudocyst formation has been described (14).

Immunologic

Asparaginase can cause allergic reactions (15), which increase with the number of doses within a cycle and the number of exposures, irrespective of drug-free intervals. There is a pegylated formulation (PEG-ASNase; Oncaspar™) with a prolonged half-life and different allergenic properties from conventional asparaginase-containing formulations. These claims have been investigated, and the authors concluded that although the hypersensitivity rate was

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lower, it was still significant; furthermore, there was no cross-sensitivity in previously treated patients (16). There were no allergic reactions to pegylated asparaginase compared with 30% with non-pegylated asparaginase in 70 children with acute lymphoblastic leukemia or non-Hodgkin's lymphoma, and other toxic effects were also less common (17).

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Astemizole

See also Antihistamines

General Information

Astemizole is a second-generation antihistamine that has been withdrawn from the market because of the association with life-threatening cardiac arrhythmias.

Organs and Systems

Cardiovascular

Astemizole is metabolized by CYP3A4 to desmethylastemizole and norastemizole, although these metabolites may not be free of the potential to prolong the QT interval.

- A 77-year-old woman with QT interval prolongation and torsade de pointes had been taking astemizole 10 mg/day for 6 months (1). She had markedly raised plasma concentrations of astemizole and was also taking cimetidine.

However, cardiac dysrhythmias in patients taking antihistamines may be related to other factors, and in this case the patient was also taking another antihistamine and had a history of hepatitis.

Nervous system

The incidence of sedation with astemizole has been reported to be similar to placebo in most studies (2–4) (SEDA-14, 136) (SEDA-18, 183).

Skin

PLEVA (pityriasis lichenoides et varioliformis) has been convincingly ascribed to astemizole by reappearance after rechallenge (SEDA-18, 4).

Stevens–Johnson syndrome has been reported with astemizole (SEDA-20, 162).

Drug Administration

Drug overdose

Two cases of overdosage with astemizole (200 mg in a 2-year-old child and 200 mg in a 16-year-old girl) were associated with cardiovascular complications (5). The

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authors recommended that patients should be observed for at least 24 hours after overdosage with astemizole.

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Asteraceae

See also Herbal medicines

General Information

The genera in the family of Asteraceae (Table 1) (formerly Compositae) include various types of asters (daisies), arnica, chamomile, goldeneye, marigold, snakeroot, tansy, thistle, and wormwood.

Table 1 The genera of Asteraceae

Acamptopappus (goldenhead)
Acanthospermum (starburr)
Achillea (yarrow)
Achyrachaena (blow wives)
Acmella (spotflower)
Acourtia (desert peony)
Acroptilon (hard heads)
Adenocaulon (trail plant)
Adenostemma (medicine plant)
Adenophyllum (dogweed)
Ageratum (whiteweed)
Ageratina (snakeroot)
Agoseris (agoseris)
Almut aster (alkali marsh aster)
Amberboa (amberboa)
Amblyolepis (amblyolepis)
Amblyopappus (amblyopappus)
Ambrosia (ragweed)
Ampel aster (climbing aster)
Amphipappus (chaffbush)
Amphiachyris (broomweed)
Anacylus (anacylus)
Anaphalis (pearly everlasting)
Ancistrocarphus (nest straw)
Anisocoma (anisocoma)
Antennaria (pussytoes)
Anthemis (chamomile)
Antheropeas (e aster bonnets)
Aphanostephus (doze daisy)
Arctium (burrdock)
Arctotheca (capeweed)
Arctotis (arctotis)
Argyroxiphium (silver sword)
Argyranthemum (dill daisy)
Argyrautia (arhyrautia)
Arnica (arnica)
Arnoglossum (Indian plaintain)
Arnoseris (arnoseris)
Artemisia (sagebrush, wormwood)
Asanthus (brickell bush)
Aster (aster)
Astranthium (western daisy)
Atrichoseris (atrichoseris)
Baccharis (baccharis)
Bahia (bahia)
Baileya (desert marigold)
Balduina (honeycombhead)
Balsamorhiza (balsam root)
Balsamita (balsamita)
Baltimora (baltimora)
Barkleyanthus (willow ragwort)
Bartlettia (bartlettia)
Bartlettina (bartlettina)
Bebbia (sweetbush)
Bellis (bellis)
Benitoa (benitoa)
Berkheya (berkheya)
Berlandiera (green eyes)
Bidens (beggar ticks)
Bigelowia (rayless goldenrod)
Blennosperma (sticky seed)
Blepharipappus (blepharipappus)
Blepharizonia (blepharizonia)
Blumea (false ox tongue)
Boltonia (doll's daisy)
Borrichia (seaside tansy)
Brickellia (brickell bush)
Brickelliastrum (brickell bush)
Buphthalmum (ox eye)
Cacaliopsis (cacaliopsis)
Calendula (marigold)
Callilepis (ox-eye daisy)
Callistephus (callistephus)
Calotis (calotis)
Calycadenia (western rosinweed)
Calycoseris (tackstem)
Calyptocarpus (calyptocarpus)
Canadanthus (mountain aster)
Carduus (plumeless thistle)
Carlina (carline thistle)
Carminatia (carminatia)
Carphephorus (chaffhead)
Carphochaete (bristlehead)
Carthamus (distaff thistle)
Castalis (castalis)
Celmisia (celmisia)
Centaurea (knapweed)
Centipeda (centipeda)
Centratherum (centratherum)
Chaenactis (pin cushion)
Chaetadelpha (skeletonweed)
Chaetopappa (least daisy)
Chamaemelum (dog fennel)
Chamaechaenactis (chamaechaenactis)
Chaptalia (sun bonnets)
Chloracantha (chloracantha)
Chondrilla (chondrilla)

Continued

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Table 1 *Continued*

Chromolaena (thoroughwort)
Chrysactinia (chrysactinia)
Chrysoma (chrysoma)
Chrysanthemum (daisy)
Chrysogonum (chrysogonum)
Chrysopsis (golden aster)
Chrysothamnus (rabbit brush)
Cichorium (chicory)
Cineraria (cineraria)
Cirsium (thistle)
Clappia (clapdaisy)
Clibadium (clibadium)
Cnicus (cnicus)
Columbiadoria (columbiadoria)
Condylidium (villalba)
Conoclinium (thoroughwort)
Conyza (horseweed)
Coreocarpus (coreocarpus)
Coreopsis (tickseed)
Corethrogyne (sand aster)
Cosmos (cosmos)
Cotula (waterbuttons)
Crassocephalum (ragleaf)
Crepis (hawksbeard)
Critonia (thoroughwort)
Crocidium (spring gold)
Croptilon (scratch daisy)
Crupina (crupina)
Cyanopsis (knapweed)
Cyanthillium (ironweed)
Cymophora (cymophora)
Cynara (cynara)
Dahlia (dahlia)
Delairea (capeivy)
Dendranthema (arctic daisy)
Dichaetophora (dichaetophora)
Dicoria (twin bugs)
Dicranocarpus (dicranocarpus)
Dimeresia (dimeresia)
Dimorphotheca (cape marigold)
Dittrichia (dittrichia)
Doellingeria (whitetop)
Doronicum (false leopardbane)
Dracopis (coneflower)
Dubautia (dubautia)
Dysodiopsis (dog fennel)
Dyssodia (dyssodia)
Eastwoodia (eastwoodia)
Eatonella (eatonella)
Echinacea (purple coneflower)
Echinops (globe thistle)
Eclipta (eclipta)
Egletes (tropic daisy)
Elephantopus (elephant's foot)
Eleutheranthera (eleutheranthera)
Emilia (tasselflower)
Encelia (brittlebush)
Enceliopsis (sunray)
Engelmannia (Engelmann's daisy)
Enydra (swampwort)
Erechtites (burnweed)
Ericameria (goldenbush)
Erigeron (fleabane)
Eriophyllum (woolly sunflower)
Erlangea (erlangea)
Eucephalus (aster)
Euchiton (euchiton)
Eupatorium (thoroughwort)
Eurybia (aster)
Euryops (euryops)
Euthamia (goldentop)
Evax (pygmy cudweed)
Facelis (trampweed)
Filago (cottonrose)
Fitchia (fitchia)
Flaveria (yellowtops)
Fleischmannia (thoroughwort)
Florestina (florestina)
Flourensia (tarwort)
Flyriella (brickell bush)
Gaillardia (blanket flower)
Galinsoga (gallant-soldier)
Gamochaeta (everlasting)
Garberia (garberia)
Gazania (gazania)
Geraea (desertsunflower)
Gerbera (Transvaal daisy)
Glyptopleura (glyptopleura)
Gnaphalium (cudweed)
Gochnatia (gochnatia)
Grindelia (gumweed)
Guardiola (guardiola)
Guizotia (guizotia)
Gundelia (gundelia)
Gundlachia (gundlachia)
Gutierrezia (snakeweed)
Gymnosperma (gymnosperma)
Gymnostyles (burrweed)
Gynura (gynura)
Haploesthes (false broomweed)
Haplocarpha (onefruit)
Haplopappus (haplopappus)
Hartwrightia (hartwrightia)
Hasteola (false Indian plaintain)
Hazardia (bristleweed)
Hebeclinium (thoroughwort)
Hecastocleis (hecastocleis)
Hedypnois (hedypnois)
Helenium (sneezeweed)
Helianthell (helianthella)
Helianthus (sunflower)
Helichrysum (strawflower)
Heliopsis (heliopsis)
Heliomeris (false goldeneye)
Hemizonia (tarweed)
Hesperevax (dwarf-cudweed)
Hesperomannia (island aster)
Hesperodoria (glowweed)
Heteranthemis (ox eye)
Heterosperma (heterosperma)
Heterotheca (false golden aster)
Hieracium (hawkweed)
Holocarpha (tarweed)
Holozonia (holozonia)
Hulsea (alpinegold)
Hymenoclea (burrobrush)
Hymenopappus (hymenopappus)
Hymenothrix (thimblehead)
Hymenoxys (rubberweed)
Hypochaeris (cat's ear)
Hypochoeris (cat's ear)
Inula (yellowhead)
Ionactis (aster)
Isocarpha (pearlhead)
Isocoma (golden bush)

Continued

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Table 1 *Continued*

Iva (marsh elder)
Ixeris (ixeris)
Jamesianthus (jamesianthus)
Jaumea (jaumea)
Jefea (jefea)
Kalimeris (aster)
Koanophyllon (thoroughwort)
Krigia (dwarf dandelion)
Lactuca (lettuce)
Laennecia (laennicia)
Lagascea (lagascea)
Lagenifera (island daisy)
Lagophylla (hareleaf)
Lapsana (nipplewort)
Lapsanastrum (nipplewort)
Lasianthaea (lasianthaea)
Lasiospermum (cocoonhead)
Lasthenia (goldfields)
Launaea (launaea)
Layia (tidy tips)
Leibnitzia (sun bonnets)
Lembertia (lembertia)
Leontodon (hawkbit)
Lepidospartum (broom sage)
Lessingia (lessingia)
Leucanthemum (daisy)
Leucanthemella (leucanthemella)
Liatris (blazing star)
Lindheimera (lindheimera)
Lipochaeta (nehe)
Logfia (cotton rose)
Luina (silverback)
Lygodesmia (skeleton plant)
Machaeranthera (tansy aster)
Madia (tarweed)
Malacothrix (desert dandelion)
Malperia (malperia)
Mantisalca (mantisalca)
Marshallia (Barbara's buttons)
Matricaria (mayweed)
Megalodonta (water marigold)
Melampodium (blackfoot)
Melanthera (squarestem)
Micropus (cottonseed)
Microseris (silver puffs)
Mikania (hemp vine)
Monolopia (monolopia)
Monoptilon (desert star)
Montanoa (montanoa)
Mycelis (mycelis)
Neurolaena (neurolaena)
Nicolletia (hole-in-the-sand plant)
Nothocalais (prairie dandelion)
Oclemena (aster)
Olearia (daisy bush)
Oligoneuron (goldenrod)
Omalotheca (arctic cudweed)
Oncosiphon (oncosiphon)
Onopordum (cotton thistle)
Oonopsis (false goldenweed)
Oreochrysum (goldenrod)
Oreostemma (aster)
Orochaenactis (orochaenactis)
Osmadenia (osmadenia)
Osteospermum (daisy bush)
Packera (ragwort)
Palafoxia (palafox)
Parasenecio (Indian plantain)
Parthenice (parthenice)
Parthenium (feverfew)
Pascalia (Pascalia)
Pectis (cinchweed)
Pentachaeta (pygmy daisy)
Pentzia (pentzia)
Pericome (pericome)
Pericallis (ragwort)
Perityle (rock daisy)
Petasites (butterbur)
Petradoria (rock goldenrod)
Peucephyllum (pygmy cedar)
Phalacroseris (mock dandelion)
Phoebanthus (false sunflower)
Picradeniopsis (bahia)
Picris (ox tongue)
Picrothamnus (bud sagebrush)
Pinaropappus (rock lettuce)
Piptocarpha (ash daisy)
Piptocoma (velvet shrub)
Pityopsis (silk grass)
Platyschkuhria (basin daisy)
Pleurocoronis (pleurocoronis)
Pluchea (camphorweed)
Polymnia (polymnia)
Porophyllum (poreleaf)
Prenanthes (rattlesnake root)
Prenanthella (prenanthella)
Proustia (proustia)
Psacalium (Indianbush)
Psathyrotes (turtleback)
Pseudogynoxys (pseudogynoxys)
Pseudelephantopus (dog's tongue)
Pseudobahia (sunburst)
Pseudoclappia (false clap daisy)
Pseudognaphalium (cudweed)
Psilactis (tansy aster)
Psilocarphus (woolly heads)
Psilostrophe (paper flower)
Pterocaulon (blackroot)
Pulicaria (false fleabane)
Pyrrhopappus (desert chicory)
Pyrrocoma (goldenweed)
Rafinesquia (California chicory)
Raillardella (raillardella)
Raillardiopsis (raillardiopsis)
Rainiera (rainiera)
Ratibida (prairie coneflower)
Rayjacksonia (tansy aster)
Reichardia (bright eye)
Remya (remya)
Rhagadiolus (rhagadiolus)
Rigiopappus (rigiopappus)
Rolandra (yerba de plata)
Roldana (groundsel)
Rudbeckia (coneflower)
Rugelia (Rugel's Indian plantain)
Sachsia (sachsia)
Salmea (bejuco de miel)
Santolina (lavender cotton)
Sanvitalia (creeping zinnia)
Sartwellia (glowwort)
Saussurea (sawwort)
Schkuhria (false threadleaf)
Sclerocarpus (bone bract)
Sclerolepis (bog button)
Scolymus (golden thistle)

Continued

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Table 1 *Continued*

Scorzonera (scorzonera)
Senecio (ragwort)
Sericocarpus (whitetop aster)
Serratula (plumeless sawwort)
Shinnersoseris (beaked skeletonweed)
Sigesbeckia (St Paul's wort)
Silphium (rosinweed)
Silybum (milk thistle)
Simsia (bush sunflower)
Smallanthus (smallanthus)
Solidago (goldenrod)
Soliva (burrweed)
Sonchus (sow thistle)
Sphaeromeria (chicken sage)
Sphagneticola (creeping ox eye)
Spilanthes (spilanthes)
Spiracantha (dogwood leaf)
Stebbinsoseris (silver puffs)
Stenotus (mock goldenweed)
Stephanomeria (wire lettuce)
Stevia (candyleaf)
Stokesia (stokesia)
Struchium (struchium)
Stylocline (nest straw)
Symphyotrichum (aster)
Synedrella (synedrella)
Syntrichopappus (Fremont's gold)
Tagetes (marigold)
Tamaulipa (boneset)
Tanacetum (tansy)
Taraxacum (dandelion)
Tephroseris (groundsel)
Tetramolopium (tetramolopium)
Tetraneuris (four-nerve daisy)
Tetradymia (horsebrush)
Tetragonotheca (nerve ray)
Thelesperma (green thread)
Thurovia (thurovia)
Thymophylla (pricklyleaf)
Tithonia (tithonia)
Tolpis (umbrella milkwort)
Tonestus (serpentweed)
Townsendia (Townsend daisy)
Tracyina (Indian headdress)
Tragopogon (goat's beard)
Trichocoronis (bugheal)
Trichoptilium (trichoptilium)
Tridax (tridax)
Tripleurospermum (mayweed)
Tripolium (sea aster)
Trixis (threefold)
Tussilago (coltsfoot)
Uropappus (silver puffs)
Urospermum (urospermum)
Vanclevea (vanclevea)
Varilla (varilla)
Venegasia (venegasia)
Venidium (venidium)
Verbesina (crownbeard)
Vernonia (ironweed)
Viguiera (goldeneye)
Wedelia (creeping ox eye)
Whitneya (whitneya)
Wilkesia (iliau)
Wollastonia (watermeal)
Wyethia (mule-ears)
Xanthisma (sleepy daisy)
Xanthium (cocklebur)
Xanthocephalum (xanthocephalum)
Xylorhiza (woody aster)
Xylothamia (desert goldenrod)
Yermo (desert yellowhead)
Youngia (youngia)
Zinnia (zinnia)

Delayed hypersensitivity reactions to the Asteraceae (Compositae) can arise from sesquiterpene lactones. To detect contact allergy to sesquiterpene lactones, a mixture of lactones (alantolactone, costunolide, and dehydrocostus lactone) is used. However, Compositae contain other sensitizers, such as polyacetylenes and thiophenes. In a prospective study, the lactone mixture was complemented with a mixture of Compositae (containing ether extracts of arnica, German chamomile, yarrow, tansy, and feverfew) to detect contact allergy to Compositae (1). Of 346 patients tested, 15 (4.3%) reacted to the mixture of Compositae, compared with eight of 1076 patients (0.7%) who gave positive results with the lactone mixture, indicating the importance of the addition of Compositae allergens to the lactone mixture. However, the authors warned that patch-testing with these mixtures can cause active sensitization.

- Compositae dermatitis occurred in a 9-year-old boy with a strong personal and family history of atopy. Positive patch test reactions were 2+ for dandelion (*Taraxacum officinale*), false ragweed (*Ambrosia acanthicarpa*), giant ragweed (*Ambrosia trifida*), short ragweed (*Ambrosia artemisifolia*), sagebrush (*Artemisia tridentata*), wild feverfew (*Parthenium hysterophorus*), yarrow (*Achillea millifolium*), and tansy (*Tanacetum vulgare*), and 1+ for *Dahlia* species and English ivy (*Hedera helix*) (2). Patch tests were negative for another 30 plants, including cocklebur (*Xanthium strumarium*), dog fennel (*Anthemis cotula*), fleabane (*Erigeron strigosus*), sneezeweed (*Helenium autumnale*), and feverfew (*Tanacetum parthenium*).

An Austrian study has re-confirmed the importance of testing with not only a mixture of Compositae and a mixture of sesquiterpene lactones, but also with additional plant extracts when there is continuing clinical suspicion of allergy to one of the Compositae (3). By using additional short ether extracts, the authors found two of five patients who had otherwise been overlooked.

Achillea millefolium

Achillea millefolium (yarrow) can cause contact dermatitis (4); a generalized eruption following the drinking of yarrow tea has also been reported (5).

- A female florist from North Germany, who ran a flower shop from 1954 to 1966 had to quit her job because of contact allergy to chrysanthemums and primrose. After a further 12 years she started to suffer occasionally from redness of the pharynx and stomachache after drinking tea prepared from yarrow and camomile. Skin tests were positive to chrysanthemum with cross-reactions to sunflower, arnica, camomile,

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yarrow, tansy, mugwort, and frullania (a lichen that does not occur in the Northern part of Germany). Patch-testing with primin showed high-grade hypersensitivity to Primula.

A. millefolium contains sesquiterpene lactones, polyacetylenes, coumarins, and flavonoids. Extracts have often been used in cosmetics in concentrations of 0.5–10%. *A. millefolium* was weakly genotoxic in *Drosophila melanogaster*. In provocative testing, patients reacted to a mix of *Compositae* that contained yarrow, as well as to yarrow itself. In clinical use, a formulation containing a 0.1% extract was not a sensitizer and alcoholic extracts of the dried leaves and stalks of the flower were not phototoxic (6). However, positive patch tests to *A. millefolium* have been reported (7).

Anthemis species and *Matricaria recutita* (chamomile)

Chamomile is the vernacular name of *Anthemis* genus and *Matricaria recutita* (German chamomile, pinhead). The former are more potent skin sensitizers (delayed-type) than the latter, presumably because they can contain a higher concentration of the sesquiterpene lactone, anthecotullid. Cross-sensitivity with related allergenic sesquiterpene lactones in other plants is possible.

Adverse effects

Internal use of chamomile tea has been associated with rare cases of anaphylactic reactions (8) and its use in eyewashes can cause allergic conjunctivitis (9).

Arnica montana

Arnica montana (arnica) contains a variety of terpenoids and has mostly been used in the treatment of sprains and bruises but is also used in cosmetics.

Ingestion of tea prepared from *Arnica montana* flowers can result in gastroenteritis reference.

- A 27-year-old woman presented with a rapidly enlarging necrotic lesion on her face and left leg together with malaise and high fever (10). She reported that she had applied a 1.5% arnica cream to her face before these symptoms had occurred. The diagnosis was Sweet's syndrome elicited by pathergy to arnica. She was treated with prednisolone and her skin lesions disappeared within 3 weeks.

Of 443 individuals who were tested for contact sensitization, 5 had a positive reaction to *A. montana* and 9 to *Calendula officinalis* (marigold); a mixture of the two was positive in 18 cases (3). Sensitization was often accompanied by reactions to nickel, *Myroxylon pereirae* resin, fragrance mix, propolis, and colophon.

Artemisia species

There are about 60 different species of Artemisia, of which the principal are *Artemisia absinthium*, *Artemisia annua*, *Artemisia cina*, and *Artemisia vulgaris*.

Artemisia absinthium

The volatile oil of *A. absinthium* (wormwood), which gives the alcoholic liqueur absinthe its flavor, can damage the nervous system and cause mental deterioration. This toxicity is attributed to thujones (alpha-thujone and beta-thujone), which constitute 0.25–1.32% in the whole herb and 3–12% of the oil. Alcoholic extracts and the essential oil are forbidden in most countries.

Artemisia annua

Artemisia annua, known in China as Qinghaosu, contains artemisinin, which has antimalarial activity. Several derivatives of the original compound have proved effective in the treatment of *Plasmodium falciparum* malaria and are currently available in a variety of formulations: artesunate (intravenous, rectal, oral), artelinate (oral), artemisinin (intravenous, rectal, oral), dihydroartemisinin (oral), artemether (intravenous, oral, rectal), and artemotil (intravenous). Artemisinic acid (qinghao acid), the precursor of artemisin, is present in the plant in a concentration up to 10 times that of artemisinin. Several semisynthetic derivatives have been developed from dihydroartemisinin (11). The artemisinin derivatives are the subject of a separate monograph.

Artemisia cina

Artemisia cina (wormseed) contains the toxic lactone, santonin, which was formerly used as an antihelminthic drug, but has now been superseded by other less toxic compounds.

Artemisia vulgaris

Artemisia vulgaris (common wormwood) contains the toxic lactone, santonin, which was formerly used as an antihelminthic drug, but has now been superseded by other less toxic compounds. Depending on the origin of the plant, 1,8-cineole, camphor, linalool, and thujone may all be major components. Allergic skin reactions (12) and abortive activity have been described.

Calendula officinalis

Calendula officinalis (marigold) contains a variety of carotenoids, saponins, steroids, sesquiterpenoids, and triterpenoids.

Of 443 individuals who were tested for contact sensitization, five had a positive reaction to *A. montana* and nine to *C. officinalis*; a mixture of the two was positive in 18 cases (3). Sensitization was often accompanied by reactions to nickel, *Myroxylon pereirae* resin, fragrance mix, propolis, and colophon.

Callilepis laureola

Callilepis laureola (impila, ox-eye daisy) contains the toxic compound atractyloside and related compounds. The plant is responsible for the deaths of many Zulu people in Natal, who use its roots as a herbal medicine.

Adverse effects

Necropsy records of 50 children who had taken herbal medicines made from *C. laureola* showed typical hepatic and renal tubular necrosis (13). In young Black children the plant causes hypoglycaemia, altered consciousness,

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and hepatic and renal dysfunction. This syndrome can be hard to distinguish from Reye's syndrome.

Acute renal insufficiency has been attributed to *C. laureola* (14).

Chrysanthemum vulgaris

Chrysanthemum vulgaris (common tansy) contains essential oils and thujone in such amounts that even normal doses can be neurotoxic (15).

Cynara scolymus

Cynara scolymus (artichoke) contains a variety of flavonoids, phenols, and sesquiterpenoids, including cynarapicrin, cynaratriol, cynarolide, and isoamberboin. It has been used to lower serum cholesterol, with little evidence of efficacy (16).

Adverse effects

Two vegetable warehouse workers developed occupational rhinitis and bronchial asthma by sensitization to *C. scolymus* (17). Skin prick tests to artichoke were positive and IgE specific for artichoke was found. Nasal challenge with artichoke extract triggered a reduction in peak nasal inspiratory flow of 81 and 85%. One patient had a reduction in peak expiratory flow rate of up to 36% after exposure to artichoke in the workplace.

Allergic contact dermatitis (18) and occupational contact urticaria (19) have also been reported.

Echinacea species

Echinacea species (coneflower, black Sampson hedgehog, Indian head, snakeroot, red sunflower, scurvy root) have become increasingly popular, particularly for the prophylaxis and treatment and prevention of cold and flu symptoms. However, the claimed efficacy of *Echinacea* in the common cold has not been confirmed in a randomized, double-blind, placebo-controlled trial (20) or a systematic review (21). *Echinacea* is claimed to have antiseptic and antiviral properties and is under investigation for its immunostimulant action. The active ingredients are glycosides (echinacoside), polysaccharides, alkamides, and flavonoids.

Adverse effects

Between July 1996 and November 1998, the Australian Adverse Drug Reactions Advisory Committee received 37 reports of suspected adverse drug reactions in association with *Echinacea* (22). Over half of these ($n = 21$) described allergic-like effects, including bronchospasm ($n = 9$), dyspnea ($n = 8$), urticaria ($n = 5$), chest pain ($n = 4$), and angioedema ($n = 3$). The 21 patients were aged 3–58 (median 31) years and 12 had a history of asthma ($n = 7$) and/or allergic rhinitis/conjuctivitis/hayfever ($n = 5$). *Echinacea* was the only suspected cause in 19 of the 21 cases. The symptoms began at variable times, within 10 minutes of the first dose to a few months, and all but two cases occurred within 3 days of starting treatment. At the time of reporting 17 of the patients had recovered, 2 had not yet recovered, and the outcome was unknown in the other two cases.

Hematologic

Possible leukopenia has been associated with long-term use of *Echinacea* (23).

Skin

Recurrent erythema nodosum has been attributed to *Echinacea*.

- A 41-year-old man, who had taken *Echinacea* intermittently for the previous 18 months, had four episodes of erythema nodosum, preceded by myalgia and arthralgia, fever, headache, and malaise (24). The skin lesions resolved within 2–5 weeks and responded to oral prednisolone. He was advised to discontinue *Echinacea* and 1 year later remained free from further recurrence.

Immunologic

Intravenous administration of *Echinacea* has been associated with severe allergic reactions. Oral ingestion can cause allergic skin and respiratory responses (25).

Five cases of adverse drug reactions have been attributed to oral *Echinacea* extracts (26). Two of the patients had anaphylaxis and one had an acute attack of asthma. The authors also tested 100 atopic subjects and found that 20 of them, who had never before taken *Echinacea*, had positive reactions to skin prick tests.

An anaphylactic reaction to *Echinacea angustifolia* has been reported (27).

- A 37-year-old woman who took various food supplements on an irregular basis self-medicated with 5 ml of an extract of *E. angustifolia*. She had immediate burning of the mouth and throat followed by tightness of the chest, generalized urticaria, and diarrhea. She made a full recovery within 2 hours.

The basis for this anaphylactic reaction was hypersensitivity to *Echinacea*, confirmed by skin prick and RAST testing. However, others have challenged the notion of a causal relation in this case (28). Nevertheless, the author affirmed his belief that *Echinacea* was the causal agent and reported that at that time *Echinacea* accounted for 22 of 266 suspected adverse reactions to complementary medicines reported to the Australian Adverse Drug Reaction Advisory Committee (28).

Sjögren's syndrome has been attributed to *Echinacea* (29).

Teratogenicity

Of 412 pregnant Canadian women who contacted a specialized information service between 1996 and 1998 with concerns about the use of *Echinacea* during pregnancy, 206 had already taken the remedy and the other 206 eventually decided not to use it (30). In the *Echinacea* group, 54% had taken it during the first trimester of pregnancy; 12 babies had malformations, six major and six minor. The figures in the control group were seven and seven respectively. Thus, there was no difference in the incidence of birth defects. However, the study lacked sufficient power to generate reliable data.

Eupatorium species

Several *Eupatorium* species, such as *Eupatorium cannabinum* (hemp agrimony) and *Eupatorium purpureum*

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(gravel root), have hepatotoxic potential due to the presence of pyrrolizidine alkaloids, which are covered in a separate monograph.

There is no evidence of pyrrolizidine alkaloids in *Eupatorium rugosum* (white snakeroot) but this plant also has poisonous properties, which are attributed to an unstable toxin called tremetol. Transfer from cow's milk to humans can produce a condition known as milk sickness, including trembles, weakness, nausea and vomiting, prostration, delirium, and even death.

Inula helenium

Large doses of the root of *Inula helenium* (elecampane) can cause vomiting, diarrhea, cramps, and paralytic symptoms.

Petasites species

Petasites species have hepatotoxic potential, owing to the presence of pyrrolizidine alkaloids, which are covered in a separate monograph. Extracts of *Petasites hybridus* (blatterdock, bog rhubarb, butterbur, butterdock) contain little in the way of these alkaloids (31). Butterbur has been used to treat allergic rhinitis and asthma and in the prevention of migraine.

Senecio species

Many species of *Senecio*, such as *Senecio jacobaea* (ragwort) and *Senecio longilobus* (thread leaf groundsel), contain hepatotoxic amounts of pyrrolizidine alkaloids (which are covered in a separate monograph). Honey made from *Senecio* plants also contains pyrrolizidine alkaloids (32).

Adverse effects

Veno-occlusive disease has been attributed to *Senecio* after chronic use (33,34).

- Hepatic veno-occlusive disease occurred in a 38-year-old woman who had occasionally consumed "Huamanrripa" (*Senecio tephrosioides*) as a cough remedy for many years (35). She had abdominal pain, jaundice, and anasarca. A hepatic biopsy showed pronounced congestion with a centrilobular predominance, foci of necrosis, and in some areas a reversed lobulation pattern. During the next 13 months she was hospitalized four times with complications of portal hypertension.
- An infant developed hepatic veno-occlusive disease after having been fed a herbal tea known as gordolobo yerba, commonly used as a folk remedy among Mexican-Americans; there was acute hepatocellular disease and portal hypertension, which progressed over 2 months to extensive hepatic fibrosis (36).

In one case hepatic damage due to *Senecio* mimicked Reye's syndrome (37).

Silybum marianum

Silybum marianum (holy thistle, lady's thistle, milk thistle, St. Mary's thistle) has been used to treat liver problems, such as hepatitis, and prostatic cancer. It contains a variety of lignans, including silandrin, silybin, silychristin, silydianin, silymarin, and silymonin.

Adverse effects

- A 57-year-old Australian woman presented with a 2-month history of intermittent episodes of sweating, nausea, colicky abdominal pain, fluid diarrhea, vomiting, weakness, and collapse (38). She was taking ethinylestradiol and amitriptyline and had taken milk thistle for 2 months. A thorough check-up showed no abnormalities. On reflection she realized that all her attacks had invariably occurred after taking the milk thistle. She stopped taking it and had no symptoms until a few weeks later, when she tried another capsule and had the same symptoms.

This idiosyncratic reaction to milk thistle seems to be a rarity. The Australian authorities knew of only two other adverse drug reactions associated with milk thistle.

Immunologic

Anaphylactic shock has been reported after the use of a herbal tea containing an extract of the fruit of the milk thistle (39).

Drug interactions

Milk thistle inhibits CYP3A4 and uridine diphosphoglucuronosyl transferase in human hepatocyte cultures (40).

In 10 healthy subjects silymarin 160 mg tds had no effect on the pharmacokinetics of indinavir 800 mg tds (41). In a similar study silymarin 175 mg tds had no effect on the pharmacokinetics of indinavir 800 mg tds (42).

Tanacetum parthenium

Tanacetum parthenium (feverfew, bachelor's buttons, motherherb) has been used in the prevention of migraine, with some benefit (43), and for rheumatoid arthritis, without (44).

Adverse effects

As *Tanacetum parthenium* is rich in allergenic sesquiterpene lactones, such as parthenolide, it is not surprising that contact dermatitis has been observed (SEDA-11, 426). The most common adverse effect of oral feverfew is mouth ulceration. A more widespread inflammation of the oral mucosa and tongue, swelling of the lips, and loss of taste have also been reported.

Feverfew inhibits platelet aggregation (45), and its concomitant use with anticoagulants such as warfarin is therefore not advised.

Tussilago farfara

Tussilago farfara (coltsfoot) has hepatotoxic potential owing to the presence of pyrrolizidine alkaloids (see separate monograph).

- An 18-month-old boy who had regularly consumed a herbal tea mixture since the 3rd month of life developed veno-occlusive disease with portal hypertension and severe ascites (46). Histology of the liver showed centrilobular sinusoidal congestion with perivenular bleeding and parenchymal necrosis without cirrhosis. The child was given conservative treatment only and recovered completely within 2 months.

The tea contained peppermint and what the mother thought was coltsfoot (*T. farfara*), analysis of which

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revealed high amounts of pyrrolizidine alkaloids. Seneciphylline and the corresponding *N*-oxide were identified as the major components, and the child had consumed at least 60 μg/kg/day of the toxic pyrrolizidine alkaloid mixture over 15 months. Macroscopic and microscopic analysis of the leaf material indicated that *Adenostyles alliariae* (Alpendost) had been erroneously gathered by the parents in place of coltsfoot. The two plants can easily be confused especially after the flowering period.

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Atenolol

See also Beta-adrenoceptor antagonists

General Information

Although atenolol, a hydrophilic cardioselective beta-adrenoceptor antagonist with no partial agonist activity, is generally regarded as one of the safest beta-blockers, severe adverse effects are occasionally reported. These include profound hypotension after a single oral dose (1), organic brain syndrome (2), cholestasis (3), and cutaneous vasculitis (4).

Organs and Systems

Nervous system

Atenolol is hydrophilic, making it less likely to cross the blood–brain barrier. However, nervous system effects are occasionally reported.

- A 54-year-old man developed progressive memory loss after taking atenolol 100 mg/day for 3 years. Four weeks after withdrawal, he completely recovered his memory (5).

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Atorvastatin

See also HMG Co-A reductase inhibitors

General Information

Atorvastatin is an HMG Co-A reductase inhibitor. Pooled data from 21 completed and 23 continuing trials representing 3000 patient-years have shown that constipation, flatulence, dyspepsia, abdominal pain, headache, and myalgia occur in 1–3% of patients. Under 2% of atorvastatin-treated patients discontinued treatment because of an adverse event (1). Serious events in this review amounted to one patient with pancreatitis and one with cholestatic jaundice (1). There were no differences in adverse effects in 177 patients randomized for 52 weeks to either simvastatin or atorvastatin (2).

Organs and Systems

Nervous system

A peripheral neuropathy has been reported with atorvastatin.

- A 60-year-old woman had painless horizontal diplopia, vertigo, blurry vision, and paresthesia in both arms after taking atorvastatin 10 mg/day (3). Neurological improvement began 2 days after drug withdrawal. Antiacetylcholine receptor antibodies were 10 times the upper limit of the reference range.

Although some features of this patient's external ophthalmoplegia were similar to myasthenia and there was a reversible rise in antiacetylcholine receptor antibody titer, a negative edrophonium test and a negative repetitive stimulation test on electromyography argued against a myasthenia-like drug reaction.

Sensory systems

In 696 patients taking atorvastatin and 235 taking lovastatin for 1 year there were no significant differences in the distribution of lenticular opacities or cortical opacities and spokes between the two drugs (4).

Hematologic

Thrombocytopenia occurred in a 46-year-old man coinciding with atorvastatin treatment; he had already tolerated simvastatin (5).

Pancreas

Pancreatitis has been observed with atorvastatin (6).

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Skin

Potentially life-threatening toxic epidermal necrolysis occurred in a 73-year-old moderately obese woman with type 2 diabetes and hypertension after she had taken 40 mg of atorvastatin (7).

- A 59-year-old man developed urticaria while taking atorvastatin for hypercholesterolemia (8). Scratch tests with his medications gave a strong positive reaction only with atorvastatin. Atorvastatin was withdrawn and his urticaria resolved over the next 10 days.

Linear IgA bullous dermatosis (9) and dermographism (10) have been described in patients taking atorvastatin.

Musculoskeletal

In one study of 133 patients there was myalgia in 3% of those taking atorvastatin, but no patient had persistent increases in creatine kinase activity above 10 times the top of the reference range (11).

Immunologic

A hypersensitivity reaction to atorvastatin has been reported.

- Antinuclear and antihistone antibodies developed in a 26-year-old man who was taking atorvastatin (12). He had constitutional symptoms and slight headaches but no definite symptoms of lupus. After some months without medication he became seronegative and asymptomatic.

This case was similar to other previous reports with other statins.

Drug–Drug Interactions

Ciclosporin

Rhabdomyolysis occurred when atorvastatin was combined with ciclosporin for 2 months in a woman with systemic lupus erythematosus and a renal transplant (13).

Terfenadine

Atorvastatin, although a substrate for CYP3A4, does not affect blood terfenadine concentrations to a clinically significant extent (14).

Warfarin

In 12 patients chronically maintained on warfarin, atorvastatin 80 mg/day for 2 weeks reduced mean prothrombin times slightly, but only for the first few days of the 2-week treatment period (15). Thus, atorvastatin had no consistent effect on the anticoagulant activity of warfarin and adjustments in warfarin doses should not be necessary.

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Atovaquone

General Information

Atovaquone is a hydroxynaphthaquinone that is effective in the prevention and treatment of murine *Pneumocystis jiroveci* pneumonitis. It also has effects against *Toxoplasma gondii* and *Plasmodium falciparum*. Food increases its absorption. The maximum serum concentration is dose-dependent, but absorption is reduced at doses above 750 mg. The maximum concentration occurs after 4–6 hours, with a second peak 24–96 hours later, suggesting enterohepatic cycling. The half-life is 77 hours.

Observational studies

In a 3-week study with test doses of 100–3000 mg/day, atovaquone was well tolerated. Three patients reported increased appetite; two of these had transient sinus arrhythmia. One of the 24 patients had a transient

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maculopapular rash that resolved without withdrawal. There were no abnormalities in hematological parameters or renal function. Two patients had slightly raised serum bilirubin concentrations and one each had raised transaminase activities. Two other patients had mildly increased transaminase activities, but both were known to have chronic hepatitis B (SEDA-13, 828).

Comparative studies

Atovaquone 250 mg tds has been compared with co-trimoxazole 320/1600 mg/day for 21 days in the treatment of *P. jiroveci* pneumonia in 408 patients. Therapeutic efficacy was similar, but atovaquone was much better tolerated, with a far lower incidence of rash, liver dysfunction, fever, nausea, and pruritus, and no neutropenia, chills, headache, renal impairment, or thrombocytopenia (1). However, pre-existing diarrhea was associated with an increased mortality in the atovaquone group.

Of 39 patients who had bone marrow transplants and who were randomized to receive either co-trimoxazole or atovaquone as prophylaxis in an open-label trial, eight taking co-trimoxazole withdrew because of presumed drug reactions, although in five of these the reported neutropenia and thrombocytopenia could have been a consequence of transplantation itself or of other drugs (2). None of 16 patients treated with atovaquone withdrew. This rate of reported adverse effects with co-trimoxazole is higher than usually reported in clinical practice with prophylactic dosages.

A study conducted by the AIDS Clinical Trials Group (ACTG) has shown that among patients who cannot tolerate treatment with co-trimoxazole, atovaquone and dapsone are similarly effective in preventing *P. jiroveci* pneumonia. Among patients who did not originally take dapsone, atovaquone was better tolerated and it might be the preferred choice for prophylaxis of *P. jiroveci* pneumonia in this setting (3). Inexplicably the rate of *P. jiroveci* pneumonia showed a greater fall in patients who discontinued the study drugs compared with those who continued to take them.

When atovaquone was compared with intravenous pentamidine in the treatment of mild and moderate *Pneumocystis jiroveci* pneumonia in an open trial, the success rates were similar. However, withdrawal of the original treatment was much more frequent with pentamidine (36%) than atovaquone (4%) (4). However, the authors' conclusion that the two approaches have a similar success rate has been challenged, and their series was small (5,6). Treatment-limited adverse effects occurred in only 7% of patients given atovaquone, compared with 41% given pentamidine. They included cases of rash and an increase in creatinine concentrations; atovaquone (unlike pentamidine) produced no vomiting, nausea, hypotension, leukopenia, acute renal insufficiency, or electrocardiographic abnormalities, but it did cause one case of dementia (4).

Combinations

Atovaquone + azithromycin

Human babesiosis has been traditionally treated with quinine plus clindamycin, a combination that has been compared with atovaquone plus azithromycin in a randomized, multicenter, unblinded study (7). The treatments were both completely effective. There were considerably fewer adverse events with azithromycin plus atovaquone than with quinine plus clindamycin.

Atovaquone + proguanil

Atovaquone acts synergistically with proguanil, and the combination of these two drugs (Malarone®) is highly efficacious in the treatment of uncomplicated malaria (8), including that against multidrug resistant forms, and in prophylaxis (9). It has not yet been widely marketed, so data on rare adverse effects are currently sparse.

An inpatient study of 79 patients given proguanil + atovaquone compared with 79 patients given mefloquine showed no malaria-independent adverse effects (10). Although there was a significant transient increase in liver enzymes, this was probably of limited clinical importance.

Prophylaxis with either one or two tablets containing atovaquone 250 mg plus proguanil hydrochloride 100 mg (one quarter or one half of the daily treatment dose), taken once-daily for 10 weeks, prevented *P. falciparum* malaria in 100% of semi-immune adults in a highly endemic area of Kenya (11). Children in Gabon taking daily Malarone at approximately one quarter of the treatment dose were similarly protected (12). Gastrointestinal adverse effects, including abdominal pain and vomiting, were relatively common in the initial parasite clearance phase of the pediatric study (when a full treatment course was given) and there was one case of repeated vomiting in the parasite clearance phase of the adult study. In both studies, the regimens were well tolerated in the prophylaxis phase (no difference from placebo). This efficacy and tolerability profile may be applicable to malaria prevention outside Africa. The use of the combination is predicted to reduce the development of resistance to each drug. Furthermore, atovaquone eliminates parasites during the hepatic phase of infection (causal prophylaxis), potentially removing the requirement to continue prophylaxis for several weeks after return from a malarious area, a period when compliance with current regimens is likely to be poor.

Proguanil plus atovaquone has been studied for chemoprophylaxis of malaria in African children (12) and in travelers (13) and is formulated as a combination of proguanil 100 mg plus atovaquone 250 mg for daily dosing. Atovaquone is a hydroxynaphthoquinone that inhibits the electron transport system (bc1 system) of parasites. Proguanil plus atovaquone is active against hepatic stages of *P. falciparum*, making it unnecessary to continue 4 weeks of prophylaxis after return from an endemic region. Current recommendations are that proguanil plus atovaquone should be continued for 1 week after returning from a malaria-endemic region.

In a comparison of proguanil plus atovaquone with proguanil (100 mg/day) plus chloroquine (155 mg base weekly) in travelers, proguanil plus atovaquone was 100% effective in the prevention of malaria (13). Those who took proguanil plus atovaquone ($n = 540$) had significantly fewer adverse events than those who took proguanil plus chloroquine ($n = 543$) (22% versus 28% respectively), particularly less diarrhea, abdominal pain, and vomiting. Only one person who took proguanil plus

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atovaquone had to discontinue prophylaxis owing to adverse events, as opposed to ten who had to discontinue proguanil plus chloroquine. There have been no other studies of similar size on the use of proguanil plus atovaquone. This combination is becoming established for the prophylaxis of malaria and the results of further phase IV studies are awaited.

The use of proguanil plus atovaquone has been reviewed (14). Neuropsychiatric adverse events were more frequent with mefloquine, whereas other adverse events occurred with similar frequencies as with chloroquine plus proguanil and mefloquine. Proguanil plus atovaquone is contraindicated in severe renal insufficiency. Co-administration of proguanil plus atovaquone with rifampicin is not recommended because of reductions in plasma atovaquone concentrations.

General adverse effects

Mild rashes are fairly common, and more serious rashes, like erythema multiforme, are rare. Gastrointestinal upsets, including abdominal pain, nausea, and diarrhea, are common. Mild nervous system disturbances have been mentioned (SEDA-18, 286) (15). Other adverse effects include fever.

Organs and Systems

Gastrointestinal

In a prospective efficacy trial of atovaquone suspension (750 mg od or 250 mg tds for 1 year) in *P. jiroveci* prophylaxis in 28 liver transplant recipients intolerant of co-trimoxazole, the adverse events reported included diarrhea ($n = 7$) and bloating or abdominal pain ($n = 3$) (16). No patient had developed *P. jiroveci* pneumonia by 37 months. This is a smaller dose than approved for *Pneumocystis* prophylaxis in HIV infection (1500 mg/day). Further studies in recipients of solid organ transplants are needed to confirm the efficacy of this prophylactic dose.

Atovaquone suspension (1500 mg orally bd) plus either pyrimethamine (75 mg/day after a 200 mg loading dose) or sulfadiazine (1500 mg qds), as treatment for acute *Toxoplasma* encephalitis (for 6 weeks) and as maintenance therapy (for 42 weeks), has been studied in a randomized phase II trial in HIV-positive patients (17). There were good responses in 21 of 28 patients who received pyrimethamine and nine of 11 who received sulfadiazine. Of 20 patients in the maintenance phase, only one relapsed. Of 40 eligible patients, 11 discontinued treatment as a result of adverse events, nine because of nausea and vomiting or intolerance of the taste of the atovaquone suspension.

Drug Administration

Drug formulations

Atovaquone suspension (750 mg bd; $n = 34$) or tablets (750 mg tds; $n = 20$) have been retrospectively compared in the treatment of *P. jiroveci* pneumonia in HIV-positive individuals (18). Efficacy was similar (74 and 70% successfully treated). Atovaquone suspension was associated with nausea in one patient and a rash in another.

Drug–Drug Interactions

Zidovudine

The metabolism of the antiviral nucleoside zidovudine to the inactive glucuronide form in vitro was inhibited by atovaquone (19,20).

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Atracurium dibesilate

See also Neuromuscular blocking drugs

General Information

Atracurium is a muscle relaxant with approximately one-fifth the potency of pancuronium (initial doses of 0.3–0.6 mg/kg and maintenance doses of 0.2 mg/kg being commonly used), an onset of action of 1.2–4 minutes (depending on the dose and the investigator), a medium duration of effect similar to (or slightly longer than) vecuronium, a rapid spontaneous recovery (slightly longer than vecuronium), and a virtual lack of accumulation. Atracurium-induced neuromuscular block is easily reversed by neostigmine.

In contrast to other non-depolarizing drugs, atracurium is completely broken down at normal blood pH and temperature by Hofmann elimination, principally (although to disputed degrees) by nucleophilic substitution and enzymatic ester hydrolysis (1–4). Four metabolites are known, laudanosine being the main biotransformation product. Of the other metabolites, the acrylate esters might possibly give rise to adverse effects. Acrylates are highly reactive pharmacologically and are potentially toxic, theoretically having the capacity to form immunogens and to alkylate cellular nucleophils (3), but so far no effects have been reported (5,6).

In animal experiments, atracurium in large concentrations, many times those providing complete neuromuscular blockade, causes vagal blockade and changes attributed to histamine release; at high dosages some hypotension is seen, possibly because of histamine release; alkalosis diminishes the neuromuscular block, and acidosis prolongs it (7). In cats, high doses of some of the breakdown products of atracurium produced dose-dependent neuromuscular blockade, hypotension, and autonomic effects (5). However, it was considered that these effects were of no pharmacological significance, in view of the low potencies of these substances and the quantities likely to be found in man. From interaction studies in cats (8) it was concluded that the action of atracurium is enhanced by D-tubocurarine, halothane, gentamicin, neomycin, and polymyxin, and antagonized by adrenaline and transiently by suxamethonium. Pretreatment with suxamethonium did not affect the subsequent block by atracurium in cats. Ciclosporin has also been reported to potentiate atracurium in cats (SEDA-12, 118) (9).

In man, histamine release by atracurium is common. The clinical significance of this is disputed, but it can cause minor transient skin reactions. Systemic effects of histamine release are much rarer than cutaneous manifestations.

Organs and Systems

Cardiovascular

There have been reports of hypotension (SEDA-15, 125) (10–12), attributed to histamine release by atracurium. A large prospective surveillance study involving more than 1800 patients given atracurium showed a 10% incidence of adverse reactions, with moderate hypotension (20–50% decrease) in 3.5% of patients (13). In one study cardiovascular stability was maintained with atracurium up to doses of 0.4 mg/kg (14). However, at higher doses (0.5 and 0.6 mg/kg) arterial pressure fell by 13 and 20% and heart rate increased by 5 and 8% respectively. These effects were maximal at 1–1.5 minutes. Since these cardiovascular effects were associated with facial flushing, it was suggested that they might have resulted from histamine release. In a subsequent study the same investigators linked significant cardiovascular changes to increased plasma histamine concentrations at a dose of atracurium of 0.6 mg/kg (15). Injecting this dose slowly over 75 seconds caused less histamine release and adverse hemodynamic effects (16). However, other investigators found no correlation between histamine plasma concentrations and hemodynamic reactions after atracurium administration (17).

Cardiovascular effects, apart from those resulting from histamine release, appear to be almost entirely limited to bradycardia. From animal studies, vagolytic (7) and ganglion-blocking (18) effects are very unlikely to occur at neuromuscular blocking doses, and these predictions appear to

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be borne out by investigations in man, cardiovascular effects being reported only at high dosages associated with signs suggestive of histamine release (14,15,19). The bradycardia (20–22) is occasionally severe, but, as with vecuronium, the explanation seems to be that the bradycardic effects of other agents used during anesthesia are not attenuated by atracurium as they are by alcuronium, gallamine, or pancuronium, which have vagolytic (or sympathomimetic) effects. The possibility that bradycardia can be caused by one of the metabolites, such as laudanosine (SEDA-12, 115), which is structurally similar to apomorphine, has yet to be excluded. An animal study has suggested that noradrenaline release from sympathetic nerve terminals can be increased by very large doses of atracurium, probably because of high concentrations of laudanosine (SEDA-14, 117) (23). Clinically, cardiovascular effects from this source would only be expected in circumstances that produced much higher than usual laudanosine concentrations.

Hypoxemia has been incidentally reported (SEDA-15, 125) (24), and most probably resulted from an increase in right-to-left cardiac shunting (in a patient with a ventricular septal defect and pulmonary atresia). Atracurium (0.2 mg/kg) may have produced a fall in systemic vascular resistance, perhaps from histamine release; pancuronium was subsequently given without incident.

Nervous system

The major metabolite of atracurium, laudanosine, can cross the blood–brain barrier (CSF/plasma ratios of 0.3–0.6 are found in dogs) (25) and produce strychnine-like nervous system stimulation, which at high plasma concentrations (around 17 ng/ml) leads to convulsions in dogs (25–27). CSF/plasma ratios of laudanosine in man have been reported to be between 0.01 and 0.14 after a 0.5 mg/kg dose of atracurium in a study in which the highest laudanosine concentration was 14 ng/ml (28). Much higher CSF laudanosine concentrations (mean 202 ng/ml, highest 570 ng/ml) were measured after larger atracurium doses (0.5 mg/kg/hour) during intracranial surgery (SEDA-15, 126) (29).

Patients in whom the blood–brain barrier is not intact, such as during neurosurgical procedures, may be at risk from exposure of the brain to unpredictable concentrations of laudanosine (and other drugs). Two patients had fits but these were not thought to be related to laudanosine (29). Under normal circumstances plasma concentrations in man will be far below those required for significant central nervous stimulation. However, the half-life of laudanosine (25) is considerably longer than that of atracurium (30), so that there is a possibility of laudanosine accumulation if many repeated doses or prolonged infusions of atracurium are given.

Skin

Minor skin reactions lasting 5–30 minutes occur in 10–50% of patients according to various studies and are not usually associated with obvious systemic effects (10,31–34). They are probably due to histamine release. A 42% incidence of cutaneous flushing has been reported in 200 patients; the effect was dose-dependent, being 18% at 0.4 mg/kg, 33% at 0.5 and 0.6 mg/kg, and 73% at 1 mg/kg (35). One patient in this study, in the 1 mg/kg group, developed generalized erythema, hypotension, tachycardia, and bronchospasm.

Immunologic

There have been reports of angioedema (10) and bronchospasm (11,36), attributed to histamine release. A large prospective surveillance study involving more than 1800 patients given atracurium showed a 10% incidence of adverse reactions, with bronchospasm in 0.2% of patients (13).

Extreme sensitivity to an intradermal skin test (0.003 mg), some 24 hours after a severe skin reaction to the intravenous administration of atracurium, has been described (37).

Severe systemic reactions after atracurium administration may be due to antibody-mediated anaphylaxis (38) rather than non-specific histamine liberation. It has been suggested that systemic effects from non-specific histamine release are dose-dependent.

Second-Generation Effects

Fetotoxicity

Placental transfer of atracurium occurs (39). In 46 patients undergoing cesarean section (SEDA-17, 18), while the Apgar scores did not differ between neonates whose mothers had received atracurium (0.3 mg/kg) or tubocurarine (0.3 mg/kg), the neurological and adaptive capacity scores (NACS) at 15 minutes (but not at 2 and 24 hours) after birth were lower after atracurium. The NACS values were normal in 83% of the babies in the tubocurarine group and in 55% of those in the atracurium group. The difference was primarily due to lower scores for active contraction of the neck extensor and flexor muscles. These results cannot be satisfactorily explained by partial curarization in some neonates of the atracurium group because the placental transfer of atracurium was lower in the atracurium group; the umbilical vein concentrations of atracurium after clamping of the umbilical cord being approximately one-tenth of the EC_{50} for block of neuromuscular transmission in neonates.

Susceptibility Factors

Age

It has been recommended that doses also be reduced in small neonates less than 3 days old, particularly if their core temperatures are less than 36°C (40), since the breakdown of atracurium is pH- and temperature-dependent.

In elderly patients atracurium infusion requirements appear not to be reduced and its effects are not prolonged (41), probably because the action of atracurium is independent of routes of elimination that are affected by age.

Other features of the patient

Temperature and pH

The breakdown of atracurium is pH-dependent and temperature-dependent. Alkalosis reduces neuromuscular blockade by atracurium, and acidosis prolongs it.

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Hypothermia, during cardiopulmonary bypass, has been reported as reducing atracurium requirements by half (42); pH changes may also have occurred.

Burns

Burns are associated with resistance to atracurium (43), as for several other non-depolarizing neuromuscular blocking agents. The EC_{50} is increased and dose requirements may be increased by up to 2–3 times. The resistance varies with the burn area and the time from injury (SEDA-12, 116), being maximal at 15–40 days in patients repeatedly anesthetized.

Dystrophia myotonica

Patients with dystrophia myotonica may be extremely sensitive to atracurium according to a case report (SEDA-10, 110) (44). Resistance to atracurium and higher than normal concentrations of acetylcholine receptors in muscle biopsies have been reported in a patient with multiple sclerosis (SEDA-13, 105) (45).

Pheochromocytoma

It has been suggested (46) that atracurium is unsuitable for use in patients with a pheochromocytoma, since increases in catecholamine concentrations, which are associated with hypertension and other unwanted cardiovascular effects, occur after the injection of relatively large doses (0.6–0.7 mg/kg). However, in an earlier report catecholamine concentrations did not increase and there were no untoward cardiovascular effects after atracurium (47). Nevertheless, considering atracurium's potential for histamine release (which can secondarily lead to increases in circulating catecholamines), vecuronium or pipecuronium are probably better choices in this condition.

Renal and hepatic insufficiency

Renal and liver dysfunction appear to have little effect on the neuromuscular blocking action of atracurium (30,48,49), although resistance has been reported in end-stage renal insufficiency (37% greater ED_{50} values and shorter duration of bolus doses) (SEDA-13, 103) (50,51).

Laudanosine metabolism may be reduced in liver disease (52), and in renal insufficiency higher plasma concentrations and an apparently delayed elimination of laudanosine have been reported (53). Prolonged infusion of atracurium in intensive care (for 38–219 hours) led to slowly increasing plasma laudanosine concentrations, which appeared to plateau after 2–3 days (54). The maximum plasma laudanosine concentrations in six patients were 1.9–5 μg/ml. There was no evidence of cerebral excitation. Nevertheless, caution is urged in patients with severe hepatic dysfunction (55,56), particularly if associated with renal insufficiency, when repeated bolus doses or an infusion of atracurium are given over a prolonged period.

Drug–Drug Interactions

Aminoglycoside antibiotics

Another interaction that has been reported not to occur in man is potentiation by the aminoglycoside antibiotics, gentamicin and tobramycin (57). In animals, however, gentamicin was found to enhance atracurium blockade (8), so further investigation is required to clarify this point.

Azathioprine

Azathioprine has been reported to reduce atracurium blockade transiently and to a clinically insignificant extent (50).

Carbamazepine

In contrast to reports on other non-depolarizing neuromuscular blocking agents, resistance to atracurium has not been found in patients taking long-term carbamazepine (SEDA-13, 104) (58).

Diisopropylphenol

The intravenous anesthetic agent, diisopropylphenol, is said to potentiate atracurium (59).

D-Tubocurarine

Small doses of D-tubocurarine (0.05 or 0.1 mg/kg) administered 3 minutes before atracurium potentiated its action synergistically (SEDA-12, 117) (60).

Halothane

From animal experiments (8) it seems likely that drug interactions with atracurium will be similar to those for other non-depolarizing neuromuscular blocking agents. Laudanosine has been reported to increase the MAC for halothane in animals (61).

In man, potentiation and prolongation of the action of atracurium by halothane (62–64) have been reported, as has potentiation after 30 minutes of isoflurane anesthesia (65). Whether the dose of atracurium should be reduced from that used during balanced anesthesia by 20, 30, or 50% when patients are anesthetized with inhalational anesthetics can only be decided in the case of an individual patient if neuromuscular monitoring is available, since many other variables, such as the tissue concentrations of the volatile anesthetic and the response of the individual patient to the neuromuscular blocking drug, will influence the overall blocking effect.

Isoflurane

A synergistic interaction between isoflurane and atracurium (high doses) has been incriminated in the causation of an increased incidence of generalized tonic-clonic seizures after neurosurgical operations (SEDA-15, 125) (66).

Ketamine

Ketamine has been shown to prolong the action of atracurium slightly (67).

Pancuronium

Small doses of pancuronium (0.5 or 1 mg) administered 3 minutes before atracurium potentiated its action synergistically (SEDA-12, 117) (60).

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Phenytoin

In contrast to reports about other non-depolarizing neuromuscular blocking agents, resistance to atracurium has not been found in patients taking long-term phenytoin (SEDA-13, 104) (68).

Suxamethonium

Prior administration of suxamethonium potentiates the action of atracurium by about 30% (69).

Tamoxifen

Tamoxifen has been associated with prolonged atracurium block in a patient with breast cancer (SEDA-12, 117) (70).

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Atropine

See also Anticholinergic drugs

General Information

Atropine is an anticholinergic drug that is mainly used today in premedication and occasionally to treat bradycardia in the acute phase of myocardial infarction.

Organs and Systems

Cardiovascular

In a classic study, more than a generation ago, of patients given atropine sulfate intravenously as premedication in a total dose of 1 mg, dysrhythmias occurred in over one-third of the subjects, and in over half of those younger than 20 years.

In adults, atrioventricular dissociation was common and in children atrial rhythm disturbances (1). In volunteers, atropine in doses of 1.6 mg/70 kg/minute causes episodes of nodal rhythm with absent P waves on the electrocardiogram (2); the episodes occurred before the heart rate had increased under the influence of the drug. In healthy men being anesthetized for dental surgery a dose of only 0.4 mg atropine intravenously 5 minutes before induction caused reductions in mean arterial pressure, stroke volume, and total peripheral resistance (3).

Second- or third-degree heart block occurred in three of 23 male heart transplant recipients given intravenous

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atropine (SEDA-22, 156). The mechanism is unknown but it appears that particular caution is needed when atropine is used in this group of patients.

The use of atropine in myocardial infarction to increase the heart rate succeeds as a rule, but in some patients with second-degree heart block the ventricular rate is slowed by atropine, resulting in bradycardia. In contrast, other patients can have tachycardia, and even ventricular fibrillation has been seen, occasionally even in doses as low as 0.5 mg (4).

Possible precipitation of acute myocardial infarction has been discussed by two American emergency medicine specialists (5).

- A 62-year-old woman developed chest pain and sinus bradycardia (41/minute). She had third-degree heart block and was given atropine 1 mg intravenously. Three minutes later, her chest pain increased and the electrocardiogram now showed an acute inferior myocardial infarction, confirmed by serum markers. Angioplasty recanalized the right coronary artery.

The authors discussed the possibility, suggested by others, that atropine can precipitate acute myocardial infarction in an ischemic setting. They concluded that while this may be true, on the whole the advantages of successfully correcting bradycardia outweigh the risks of this rare complication.

Respiratory

Atropine increases the rate and depth of respiration, probably as a reaction to the increase in the dead space resulting from bronchodilatation (5).

Sensory systems

Transient central blindness has followed an intravenous injection of atropine 0.8 mg in the course of spinal anesthesia; blink reflex and pupillary response to light and accommodation were lost; vision returned slowly after some hours after the instillation of pilocarpine (6).

Psychological, psychiatric

Atropine can cause slight memory impairment, detectable if special studies of mental function are performed (SEDA-13, 115).

Immunologic

Hypersensitivity to atropine is most usually seen in the form of contact dermatitis and conjunctivitis. One case of anaphylactic shock after intravenous injection of atropine has been reported (SEDA-14, 122).

Body temperature

Atropine was thought to have produced hypothermia in a boy aged 14 who was being treated with paracetamol (acetaminophen) and cooling blankets for hyperthermia (7). As atropine can cause hypothermia in animals, a causal relation cannot be excluded, even if a concomitant action with paracetamol is assumed.

Second-Generation Effects

Fetotoxicity

Atropine methylbromide crosses the placenta less readily than atropine; when given close to term, it has much less effect on the fetal heart rate than on the maternal heart rate (8).

Susceptibility Factors

In Down's syndrome, atropine produces an abnormally large degree of pupillary dilatation, probably because of a genetically abnormal response; there is also a much greater acceleration of the heart rate than that produced by atropine in healthy subjects.

In congenital albinism, by contrast, the duration of dilatation of the pupil is much shorter than usual; the response to homatropine, scopolamine, and pilocarpine appears to be normal.

Drug Administration

Drug formulations

A total of 1077 patients continued to take extended-release tolterodine 4 mg/day after participating in a randomized trial, about 78% of those who completed the double-blind phase of the study (9). Of the patients who took open treatment, 71% were still doing so after 12 months. The only significant adverse effect was a dry mouth in 13%, while 3.3% complained of constipation. There was no serious systemic toxicity of any kind and efficacy was judged to be at least equivalent to that of the immediate-release formulation.

Drug administration route

Atropine administered by aerosol has a selective effect on the airways because of its low systemic absorption. Adverse effects are those of atropine and atropine-like drugs, but systemic effects are unlikely after topical administration. Two patients developed the signs and symptoms of angle-closure glaucoma after receiving aerosolized atropine. Patients with shallow anterior chambers or possible prior angle-closure glaucoma are probably at greater risk (10). Atropine methylnitrate, a quaternary ammonium derivative, is more selective than atropine sulfate because it is less readily absorbed.

In a child with regular akinetic seizures, atropine sulfate eye-drops increased the frequency of seizures (11).

Drug overdose

When parasympathicolytic or anticholinergic agents are used to dilate the pupils, it is important to recognize systemic anticholinergic intoxication, because the outcome can be fatal without treatment. In patients who are confused or have difficulty speaking, large fixed pupils, and fever, anticholinergic intoxication has to be considered.

- A 3-year-old boy with amblyopia was vomiting, had difficulty in walking, had fever, was agitated, and had a warm red skin and dilated pupils that did not respond

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to light (12). An empty bottle of atropine eye-drops was found in his home, and suspected anticholinergic intoxication was confirmed. He made a full recovery following treatment with physostigmine.

It should also be remembered that there are other sources of atropine.

- A 52-year-old woman was confused and had dysarthria and difficulty in walking and swallowing (13). That same day she had eaten berries that she thought were bilberries, but were instead *Atropa belladonna* (deadly nightshade).

Drug–Drug Interactions

Paracetamol

Atropine slows the rate of absorption of paracetamol (14).

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Azapropazone

See also Non-steroidal anti-inflammatory drugs

General Information

Azapropazone is structurally related to phenylbutazone and probably shares the same adverse effects: gastrotoxicity, skin reactions, headache, vertigo, edema, and renal impairment. A review of a very large series described azapropazone adverse effects in 1724 patients (18%), causing withdrawal in 3.7%. Surprisingly, however, there were no phenylbutazone-type blood dyscrasias (SED-11, 176) (1). Azapropazone should be prescribed only for patients with active rheumatic diseases who have failed to respond to other NSAIDs (2).

Organs and Systems

Hematologic

Hemolytic anemia has been reported (SEDA-10, 79) (SEDA-12, 83). A high percentage of patients taking azapropazone had a positive direct Coombs' test, but this did not persist after treatment had been stopped for several weeks (SEDA-12, 83). Hemolytic anemia has also been described in combination with pulmonary alveolitis, which suggests an allergic or immune reaction (3). Photosensitivity is often reported: 190 reports of photosensitivity were submitted to several national drug-monitoring centers in Europe in 1985 (SEDA-10, 79) (SEDA-12, 83).

Skin

Photosensitivity is more frequent with azapropazone than with almost any other NSAID (4).

Immunologic

Patients with aspirin intolerance often also react to many other NSAIDs. Azapropazone seems to be a safe alternative in these patients, according a study that showed good tolerance of the drug in patients with aspirin intolerance (5).

Susceptibility Factors

Renal disease

Because of increases in unbound drug and reduced clearance in renal insufficiency, the dosage should be carefully adjusted in patients with renal disease (SEDA-11, 92).

Hepatic disease

Because of increases in the unbound drug and reduced clearance, the dosage should be carefully adjusted in patients with liver disease (SEDA-11, 92).

Drug–Drug Interactions

Oral anticoagulants

Azapropazone has the same pattern of interactions as phenylbutazone with oral anticoagulants (SEDA-2, 98).

Phenytoin

Azapropazone has the same pattern of interactions as phenylbutazone with phenytoin (6,7).

Tolbutamide

Azapropazone has the same pattern of interactions as phenylbutazone with tolbutamide (8).

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Azathioprine and mercaptopurine

General Information

Azathioprine, a prodrug converted to 6-mercaptopurine, is widely used as a post-transplant immunosuppressant and in various autoimmune or chronic inflammatory disorders, such as rheumatoid arthritis, dermatomyositis, systemic lupus erythematosus, skin diseases, and inflammatory bowel diseases.

Adverse effects usually occur during the first two months of treatment, do not correlate with the daily dose, and result in treatment withdrawal in 14–18% of patients, mainly because of bone marrow suppression, gastrointestinal symptoms, hypersensitivity reactions, and infections (1–3). Immediate or long-term adverse effects are of particular concern outside the field of immunosuppression where other treatment options are frequently available, but in any field of use the adverse effects of these drugs weigh heavily.

Observational studies

In a follow-up study of 157 patients receiving azathioprine or mercaptopurine for Crohn's disease, the long-term risks (mainly hematological toxicity and malignancies) over 4 years of treatment were deemed to outweigh the therapeutic benefit (4). In contrast to these findings, both drugs were considered efficacious and reasonably safe in patients with inflammatory bowel disease, provided that patients are carefully selected and regularly investigated for bone marrow toxicity (5). Similar opinions were expressed regarding renal transplant patients. Conversion from ciclosporin to azathioprine in selected and carefully monitored patients had beneficial effects, by improving renal function, reducing cardiovascular risk factors, and reducing financial costs, without increasing the incidence of chronic rejection and graft loss (6).

Experience in children with juvenile chronic arthritis or chronic inflammatory bowel disease has also accumulated, and the toxicity profile of azathioprine or mercaptopurine appears to be very similar to that previously found in the adult population (SEDA-21, 381) (SEDA-22, 410).

The "azathioprine hypersensitivity syndrome"

The complex of azathioprine-associated multisystemic adverse effects is referred to by the misnomer "azathioprine hypersensitivity syndrome." This well-characterized reaction has been described in numerous case reports and includes various symptoms which can occur separately or concomitantly; they comprise fever and rigors, arthralgia, myalgia, leukocytosis, cutaneous reactions, gastrointestinal disturbances, hypotension, liver injury, pancreatitis, interstitial nephritis, pneumonitis, and pulmonary hemorrhage (SED-13, 1121) (SEDA-20, 341) (SEDA-21, 381) (SEDA-22, 410) (7). Isolated fever and rigors are sometimes observed, and severe renal and cardiac toxicity or leukocytoclastic cutaneous vasculitis are infrequent. Symptoms usually occur within the first 6 weeks of treatment and can mimic sepsis. The initial febrile reaction is often misdiagnosed as infectious, and could be associated with acute exacerbation of the underlying disease, for example myasthenia gravis (SEDA-21, 381) (SEDA-22, 410). Hypersensitivity associated with reversible interstitial nephritis can also be mistaken for an acute rejection episode (8). This syndrome should therefore be promptly recognized to avoid unnecessary and costly investigations, and further recurrence on azathioprine rechallenge.

Organs and Systems

Respiratory

Although azathioprine-associated pulmonary toxicity mostly occurs as part of the azathioprine hypersensitivity reaction, isolated interstitial pneumonitis has been reported in a 13-year-old girl with autoimmune chronic active hepatitis (9).

Acute upper airway edema has been observed after a single dose of azathioprine (10).

- A 57-year-old woman with a history of several drug allergies underwent renal transplantation for end-stage

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polycystic kidney disease and 1 hour later was given intravenous azathioprine 400 mg. She developed profound hypotension and bradycardia within 30 minutes, reversed by sympathomimetics. Shortly after extubation, she had severe breathing difficulties with loss of consciousness. Laryngoscopy showed massive swelling of the tongue and upper airways. Later, while still taking glucocorticoids, she was rechallenged with azathioprine and had milder hypotension and edema of the airways.

Even if no clear mechanism can account for this adverse effect, positive rechallenge strongly suggested that azathioprine was the culprit.

Hematologic

Hematological toxicity is the most commonly reported severe adverse effect of azathioprine, and is marked by predominant leukopenia, thrombocytopenia, and pancytopenia (SED-13, 1120). In a 27-year survey of 739 patients treated with azathioprine 2 mg/kg for inflammatory bowel disease, dosage reduction or withdrawal of the drug because of bone marrow toxicity was necessary in 37 patients (5%) (11). There was moderate or severe leukopenia in 3.8% of patients; in three patients pancytopenia resulted in severe sepsis or death.

Leukopenia is the most serious adverse effect of azathioprine in patients with inflammatory bowel disease (12). It is variable and unpredictable and occurs 2 weeks to 11 years after the start of treatment (median 9 months); most cases recover 1 month after withdrawal.

Dual therapy with ciclosporin and prednisone has been compared with triple therapy with ciclosporin, prednisone, and azathioprine in a randomized trial in 250 renal transplant patients (13). Patients in the triple therapy group had less frequent severe episodes of acute rejection and more frequent episodes of leukopenia than the double therapy group (28% versus 4%). There were no other differences in the adverse effects profiles, in particular the incidence of infectious complications.

Macrocytic anemia and isolated thrombocytopenia without severe clinical consequences have sometimes been observed. Pure red cell aplasia can occur, but the few relevant reports concern only isolated instances involving renal transplant patients (14,15). The facts in one patient suggested that parvovirus B19 infection resulting from the immunosuppressive effects of azathioprine should also be considered as a possible indirect cause (16). Although blood cell disorders usually occur in the first 4 weeks of treatment, strict and regular surveillance of blood cell counts continuing for as long as treatment is maintained is usually recommended, since delayed hematological toxicity remains possible.

- Immune hemolytic anemia has been reported in a 67-year-old man taking mercaptopurine for chronic myelomonocytic leukemia (17). Serology showed a positive direct antiglobulin test and confirmed the presence of mercaptopurine drug-dependent antibodies. He improved and the direct antiglobulin test was no longer positive 20 days after mercaptopurine withdrawal.

Aplastic anemia due to azathioprine therapy after corneal transplantation has reportedly caused bilateral macular hemorrhage (18).

- A 38-year-old man underwent therapeutic penetrating keratoplasty for non-healing fungal keratitis in his left eye. Although the infection was controlled, he underwent a second corneal transplantation after 2 years. Since there was corneal vascularization in three quadrants, he was given oral azathioprine postoperatively. Four months later he developed gastrointestinal bleeding and a sudden reduction in vision in both eyes. His platelet count was less than 30×10^9/l, his hemoglobin 4.1 g/dl, and a bone marrow aspirate was hypocellular. There were macular hemorrhages in both eyes. The hemorrhages resolved within 2 months.

Gastrointestinal

Gastrointestinal disturbances with nausea, vomiting, and diarrhea are frequent in patients taking azathioprine or mercaptopurine. Diarrhea may be isolated or part of the azathioprine hypersensitivity syndrome. In two patients with azathioprine-induced diarrhea proven by positive rechallenge, the period of sensitization ranged from 1 week to 1 year (19).

In two cases, azathioprine caused severe gastrointestinal symptoms that could have been easily confused with an acute exacerbation of the underlying inflammatory bowel disease (20).

- A 32-year-old man with ulcerative colitis improved with prednisolone, mesalazine, and antibiotics. The dose of prednisolone was reduced and the disease flared up again. He was therefore given azathioprine and an increased dose of prednisolone, with rapid clinical improvement. After 3 weeks, he reported increasing abdominal pain, worse diarrhea, and weight loss of 3 kg. He stopped taking azathioprine and the pain improved. Because of progressive disease and active pancolitis at colonoscopy, he was given high-dose prednisolone, mesalazine, and ciprofloxacin, without improvement. He was therefore given intravenous azathioprine, but developed devastating diarrhea and weight loss of more than 6 kg in 24 hours, his CRP rose from 5 to 305 μg/ml, and he developed hypovolemic shock. He recovered after treatment with parenteral nutrition for 7 days.
- A 50-year-old woman with Crohn's disease and active disease throughout the colon was given prednisolone, mesalazine, and azathioprine 50 mg/day. After 3 weeks, the dose of azathioprine was increased to 100 mg/day, but she developed nausea, severe diarrhea, and abdominal tenderness. The symptoms subsided after azathioprine was withdrawn. She was then given mercaptopurine, without significant adverse effects.

Liver

Although rarely severe, any increase in liver enzyme activity justifies careful and regular monitoring of liver function and the results may be a reason for withdrawing treatment (SED-8, 1118) (21). In a retrospective study, hepatitis was found in 21 (2%) of 1035 renal transplant patients, and it was suggested that hepatitis B or C

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infection increases the risk of azathioprine hepatotoxicity (22). In 29 cardiac transplant recipients who had had probable azathioprine-induced liver dysfunction, cyclophosphamide was given, with improvement of liver enzyme activities and no increase in the rate of graft rejection or significant changes in the doses of other immunosuppressive drugs (23).

Azathioprine can cause reversible cholestasis (24), perhaps due to bile duct injury (25).

Direct hepatocellular injury with acute cytolytic hepatitis has been reported rarely (SEDA-21, 381).

In one patient, azathioprine-induced lymphoma with massive liver infiltration was the probable cause of fulminant hepatic failure (SEDA-21, 381).

Other histological features that have been described include lesions of the hepatic venous system (peliosis hepatis, sinusoidal dilatation, perivenous fibrosis, and nodular regenerative hyperplasia) and these can be associated with portal hypertension (SEDA-16, 520) (SED-13, 1120) (21). Particularly severe and potentially fatal veno-occlusive liver disease has been reported in patients with renal and allogeneic bone marrow transplants taking chronic treatment (26) (SEDA-12, 386), but complete histological reversal can be observed (SEDA-20, 341).

- In a 33-year-old man azathioprine-induced veno-occlusive disease was treated with a transjugular intrahepatic portosystemic shunt over 26 months, with progressive worsening 15 months after renal transplantation (27).

Four patients with renal transplants developed hepatic veno-occlusive disease after immunosuppression with azathioprine. The diagnosis was based on typical histopathological findings: perivenular fibrosis, trilobular sinusoidal dilatation and congestion, and perisinusoidal fibrosis. The patients presented with severe progressive portal hypertension followed by fulminant liver failure and death. The disease was associated with cytomegalovirus infection, and it was not related to the dose of azathioprine (26). Veno-occlusive liver disease has also been described shortly after liver transplantation (28,29). A history of acute liver rejection affecting the hepatic veins was supposedly a contributing factor in these patients, and the presence of non-inflammatory small hepatic vein lesions was a possible early indicator of hepatotoxicity. Liver biopsy should therefore be considered in liver recipients who have biological features of hepatitis, so that treatment can be withdrawn rapidly if necessary.

Azathioprine allergy can be associated with biochemical hepatitis and a normal liver biopsy, apart form marked lipofuscin deposition (30). These findings, combined with patchy isotope uptake on technetium scintigraphy, are suggestive of focal hepatocellular necrosis.

It has been suggested that there is an increased risk of azathioprine-induced liver damage in renal transplant patients with chronic viral hepatitis (SEDA-20, 341) (SEDA-23, 402).

- Fatal fibrosing cholestatic hepatitis has been reported in a 63-year-old cardiac transplant patient with acquired post-transplant hepatitis C virus infection whose immunosuppressive regimen included azathioprine (31). Histology showed several features of azathioprine hepatotoxicity, namely veno-subocclusive lesions and nodular regenerative diffuse hyperplasia, suggesting a pathogenic role of azathioprine.

In 79 renal transplant patients with chronic viral hepatitis, azathioprine maintenance treatment ($n = 34$) was associated with a poorer outcome than in 45 patients who discontinued azathioprine (32). Cirrhosis was more frequent in the first group (six versus one), and more patients died with a functioning graft (14 versus two), mostly because of liver dysfunction ($n = 5$) or infection ($n = 6$). These results suggest that azathioprine further accelerates the course of the liver disease in these patients.

- A 50-year-old woman with nodular sclerosis developed azathioprine-induced hepatotoxicity within the first weeks of treatment (33), the usual time-course. Positive rechallenge confirmed the role of azathioprine.

However, delayed occurrence of hepatitis is also possible.

- Canalicular cholestasis with portal fibrosis and ductal proliferation has been reported after 24 years of azathioprine in a 57-year-old woman with myasthenia gravis (34).

An unusual diffuse liver disease with sinusoidal dilatation (SEDA-11, 392) has been described.

Pancreas

Pancreatitis due to azathioprine or mercaptopurine has usually been reported as part of the hypersensitivity syndrome (SEDA-16, 520) (SEDA-20, 341). It has mostly been observed in patients with inflammatory bowel disease, and required withdrawal of treatment in 1.3% of patients with Crohn's disease (3). Pancreatitis was not dose-related within the therapeutic range of doses and often recurred in patients who were rechallenged with either drug (SEDA-20, 341) (35). Fatal hemorrhagic pancreatitis occurred in one patient, but a role of concomitant drugs was also possible (SEDA-20, 341). Pancreatitis or hyperamylasemia were not significantly different in renal transplant patients randomly assigned to receive azathioprine or ciclosporin, and other causative factors were found in most patients with pancreatitis (36).

In a review of definite or probable drug-associated pancreatitis spontaneously reported to the Dutch adverse drug reactions system during 1977–98, azathioprine was the suspected drug in four of 34 patients, two of whom had positive rechallenge (37). Although most of the carefully described reports of azathioprine-induced pancreatitis were found in patients with inflammatory bowel disease, transplant recipients can also suffer this complication.

- Over a year after renal transplantation, a 48-year-old man, who took azathioprine, ciclosporin, and prednisolone, developed acute necrotizing pancreatitis (38). Improvement was obtained after azathioprine withdrawal, but he again took azathioprine and had similar symptoms within 30 hours after a single dose.
- Pancreatitis has been reported after a progressive increase in dose of 6-thioguanine in a 10-year-old infant (39). She had had two previous episodes of pancreatitis after mercaptopurine.

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The chemical structure of 6-thioguanine, which results from the metabolism of azathioprine/mercaptopurine, is very similar to that of mercaptopurine. Therefore, a history of previous adverse effects with mercaptopurine should be anticipated in patients considered for 6-thioguanine treatment.

Skin

Rashes or other allergic-type cutaneous reactions are usually noted during the azathioprine hypersensitivity syndrome. Isolated but convincing reports point to the occurrence of vasculitis with microscopic polyarteritis (SEDA-21, 381) and Sweet's syndrome, which recurred after subsequent azathioprine exposure (SEDA-22, 410).

Pellagra with a photosensitivity-like rash and skin peeling syndrome has also been noted (SEDA-21, 381).

Musculoskeletal

Severe myalgia and symmetrical polyarthritis are sometimes reported in patients taking azathioprine. Eight cases of azathioprine-associated arthritis were identified in the WHO Drug Monitoring Database, including six cases with a typical hypersensitivity syndrome and two cases in whom joint involvement was the only reported symptom (40). Rhabdomyolysis has also been reported as a possible feature of the azathioprine hypersensitivity syndrome (SEDA-20, 341).

In two patients with Crohn's disease, azathioprine was suspected to have caused severe gait disorders with an inability to walk (41). Within 1 month of treatment, both had joint pains or diffuse arthralgias that were the presumed cause of pseudoparalysis of the legs. In one patient other causes were carefully ruled out and similar symptoms recurred shortly after azathioprine was re-introduced.

Immunologic

The distinction between relapse of the treated disease, systemic sepsis, and acute azathioprine allergy can be difficult, as has been shown in three patients with vasculitic disorders (42).

Allergic reactions to azathioprine were recorded in 2% of patients with Crohn's disease taking azathioprine (3), and there was no evidence to suggest that the incidence depended on the underlying disease. The more rapid recurrence and/or the severity of symptoms following rechallenge were in keeping with a putative immune-mediated reaction, but no immunological mechanism has been conclusively demonstrated (SED-13, 1121) (43,44). In one patient, progressively rising doses of azathioprine were successfully administered, despite positive skin prick tests (SEDA-21, 382). Anaphylactic shock has been occasionally reported (45). Delayed contact hypersensitivity with a positive patch test was described in a pharmaceutical handler of azathioprine (46).

Allergic reactions to mercaptopurine or azathioprine are well described, but a true immunoallergic reaction has never been convincingly demonstrated. Desensitization has been successfully performed in isolated patients (47), and this has been more extensively addressed in a retrospective analysis of the charts of patients treated for inflammatory bowel disease (48). Of 591 patients observed over a 28-year period, 16 (2.7%) developed allergic reactions, which mostly consisted of fever ($n = 14$), joint pains ($n = 6$), or severe back pain ($n = 5$). Symptoms commonly appeared within 1 month and lasted 5 days on average. All nine patients rechallenged with mercaptopurine had similar but less severe symptoms. Further rechallenge with azathioprine in six of these patients caused symptoms in five of them. Careful desensitization with mercaptopurine or azathioprine was attempted in five patients, and resulted in tolerance and therapeutic success in four. The last patient, who had a previous history of mercaptopurine-induced sepsis-like syndrome with renal insufficiency, had a similar reaction only after one-quarter of the dose of azathioprine. This study suggests that a direct switch from mercaptopurine to the parent drug azathioprine cannot be recommended in patients who developed allergic reactions to mercaptopurine, and that desensitization should not be attempted in patients with previous life-threatening hypersensitivity reactions.

A genetic predisposition is suspected, with a possible association between the hypersensitivity syndrome and the Bw4 and Bw6 phenotypes (SED-13, 1121). Mercaptopurine has sometimes been re-administered safely after a severe hypersensitivity reaction to azathioprine (49), suggesting a major role for the imidazole moiety of azathioprine. However, typical allergic reactions to mercaptopurine can also occur (SEDA-21, 381).

Infection risk

Infections, in particular bacterial and viral (cytomegalovirus, *Herpes simplex* virus, Epstein–Barr virus), and also protozoal and fungal infections, are major causes of morbidity and mortality in the post-transplantation period, whatever the immunosuppressive regimen used (50–52). Based on an analysis of medical and autopsy records, infections were found to be the cause of death in 70% of transplant patients, with bacteria (50%) or fungi (29%) the most common pathogens (53).

The frequency, course, and severity of *Herpes zoster* infection have been retrospectively evaluated in a sample of 550 patients treated with 6-mercaptopurine for inflammatory bowel disease (54). Twelve patients aged 14–73 years developed shingles after an average of 921 days, an incidence that was about two-fold higher than in the general population. Only three patients were still taking glucocorticoids at the time of onset of the shingles, and leukopenia was not associated with the occurrence of the infection. In nine patients, the course of the infection was 7–71 days and was uncomplicated. Two patients had more severe symptoms and suffered from postherpetic neuralgia. The last patient, a 14-year-old boy, had a brief episode of *H. zoster* during initial treatment and had *H. zoster* encephalitis at the age of 23 years, 16 months after 6-mercaptopurine had been restarted. From this report, it appears that 6-mercaptopurine can be restarted after brief discontinuation in patients who are expected to benefit from it.

- Fatal Epstein–Barr virus-associated hemophagocytic syndrome was reported in a young man taking azathioprine and prednisone for Crohn's disease (55).

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Donor-specific blood transfusion in the preparation for transplantation was complicated by a higher incidence of cytomegalovirus infection in patients receiving azathioprine (56).

Long-Term Effects

Tumorigenicity

Because of the varied indications for azathioprine and mercaptopurine, it is difficult to determine whether there is an increased incidence of cancer specifically related to prolonged drug exposure. Data from the Cincinnati Transplant Tumor Registry, published in 1993, helped to define comprehensively the characteristics of neoplasms observed in organ transplant recipients (57). Skin and lip cancers were the most common, and non-Hodgkin's lymphomas represent the majority of lymphoproliferative disorders, with an incidence some 30- to 50-fold higher than in controls. An excess of Kaposi's sarcomas, carcinomas of the vulva and perineum, hepatobiliary tumors, and various sarcomas has also been reported. In contrast, the incidence of common neoplasms encountered in the general population is not increased. In renal transplant patients, the actuarial cumulative risk of cancer was 14–18% at 10 years and 40–50% at 20 years (58,59). Skin cancers accounted for about half of the cases. Very similar figures were found in later studies (SEDA-20, 341).

While there is no doubt that the incidence of malignancies is increased in the transplant population, there have been controversies as to which factors (duration of treatment, total dosage, the degree of immunosuppression, or the type of immunosuppressive regimens) are the most relevant in determining risk. Partial or complete regression of lymphoproliferative disorders and Kaposi's sarcomas after reduction of immunosuppressive therapy argues strongly for the role of the degree of immunosuppression (57). The incidence of cancer was also significantly higher in renal transplant patients taking triple therapy regimens compared with dual therapy (60). Similarly, aggressive immunosuppressive therapy may account for the higher incidence of lymphomas in patients with cardiac versus renal allografts.

In a large multicenter study in more than 52 000 kidney or heart transplant patients between 1983 and 1991, the rate of non-Hodgkin's lymphomas in the first post-transplantation year was 0.2% in kidney and 1.2% in heart recipients, and fell substantially thereafter (61). Initial immunosuppression with azathioprine and ciclosporin and prophylactic treatment with antilymphocyte antibodies or muromonab were associated with a significantly increased incidence of non-Hodgkin's lymphomas compared with other immunosuppressive regimens, which confirmed the major role of the level of immunosuppression. Later studies confirmed that immunosuppression per se rather than a single agent is responsible for the increased risk of cancer (SEDA-20, 340). Finally, the most striking difference between conventional and modern immunosuppressive regimens, including ciclosporin, was the average time to the appearance of tumors, in particular skin cancers and lymphomas, which was shorter in ciclosporin-treated patients (62,63). There was an increased incidence of non-Hodgkin's lymphomas in patients receiving long-term azathioprine and prednisolone for rheumatoid disease, although the latent period was longer than in other patients, perhaps reflecting a different pathogenesis (64).

Multiple factors with complex interactions are involved in the observed pattern and increased incidence of neoplasms. They include severely depressed immunity with an impaired immune surveillance against various carcinogens, the activation of several oncogenic viruses, and a possible mutagenic effect of the drugs. Viruses, such as papillomavirus, cytomegalovirus, and Epstein–Barr virus, are believed to play an important role in the development of several post-transplant cancers. From a theoretical point of view, the use of antiviral drugs active against herpes viruses, which are commonly implicated as co-factors, can be expected to produce a reduction in the incidence of post-transplant lymphoproliferative disorders.

Long-term treatment with azathioprine has been associated with transitional carcinoma of the bladder and non-Hodgkin's lymphoma in a single case (65).

- A 59-year-old man who had had a testicular non-Hodgkin's lymphoma for 9 years, developed diplopia and ptosis due to myasthenia gravis with antibodies to the acetylcholine receptor. He was given pyridostigmine and prednisolone. After 6 months he developed pernicious anemia, and he was given vitamin B_{12} injections. An attempt to reduce the dose of prednisolone failed, and he was therefore given azathioprine and the dose of prednisone was progressively reduced. Two years later he developed a transitional carcinoma of the bladder (pTa g1), which was removed by transurethral resection. Seven years later he developed a swollen tender right testis due to a B cell lymphoma. He tolerated chemotherapy (CHOP) poorly and died 2 months later.

In renal transplant recipients, premalignant dysplastic keratotic lesions increased in frequency by 6.8% per year after the first 3.5 years after transplantation, and were ultimately observed in all 167 patients within 16 years of transplantation (66). No relation with sun exposure or skin type was found. The great majority of these patients were taking prednisolone and azathioprine, but azathioprine was considered as the main causative factor, possibly due to a carcinogenic effect rather than to immunosuppression itself.

Several isolated reports and epidemiological studies have addressed the risk of cancer in non-transplant patients treated with azathioprine. Promptly reversible Epstein–Barr virus-associated lymphomas have been reported as single cases, as have reports of acute myeloid leukemia with 7q deletion, rapidly aggressive squamous cell carcinomas, soft tissue carcinomas, or fatal Merkel cell carcinomas in patients taking long-term azathioprine maintenance (SED-13, 1122) (SEDA-20, 342) (SEDA-21, 382) (SEDA-22, 410). Although epidemiological studies allow a more accurate estimate, conflicting results have emerged and there is as yet no definite evidence that azathioprine actually increases the risk of cancer.

An increased risk of non-Hodgkin's lymphomas, possibly related to treatment duration, has been found in

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patients with rheumatoid arthritis (67). There was no evidence that azathioprine increased the overall incidence of any cancer in 259 patients with rheumatoid arthritis on immunosuppressive treatment (azathioprine in 223) and matched for age and sex (but not for disease duration and severity) with unexposed patients (68). However, death more often resulted from malignancies in those taking azathioprine.

In cases of inflammatory bowel disease, no overall increased incidence of cancer was noted after a median of 9 years follow-up in 755 patients who had taken less than 2 mg/kg/day of azathioprine over a median period of 12.5 years (69). Only colorectal cancers (mostly adenocarcinoma) were more frequent, but their incidence was also increased in chronic inflammatory bowel diseases. More specifically, there was no excess of non-Hodgkin's lymphoma, but the power of the study to detect an increased risk of this disorder was low.

Another group of investigators has estimated that the potential long-term risk of malignancies outweighs the therapeutic benefit, but this conclusion was based on the follow-up of only 157 patients treated for Crohn's disease (4).

In 626 patients with inflammatory bowel disease who had taken azathioprine for a mean duration of 27 months (mean follow-up 6.9 years), there was no increased risk of cancer (colorectal or other) (70).

In a case-control study using a database of 1191 patients with multiple sclerosis, 23 cancers (17 solid tumors, two skin tumors, and four hemopoietic cancers) were found. The relative risk of cancer was 1.3 in patients treated for less than 5 years, 2.0 in those treated for 5–10 years, and 4.4 in those treated for more than 10 years; however, none of these later changes was significant (71). Nevertheless, there was a significant association for cumulative dosages in excess of 600 g. Taken together, these results suggest a low risk of cancer in non-transplant patients, but they cannot exclude a possible dose-related increase in risk during long-term treatment.

Skin carcinoma (predominantly squamous-cell carcinoma), cancer of the lip, Kaposi's sarcoma, and carcinoma of the cervix and anus are reported to be more common following azathioprine than in the general population (72).

Mercaptopurine is not considered to be leukemogenic, but this assumption has been disputed in a study of 439 children who received mercaptopurine as part of their maintenance therapy for acute lymphoblastic leukemia (73). Five patients developed secondary myelodysplasia or acute myeloid leukemia 23–53 months after diagnosis, a consequence that was attributed to mercaptopurine. These five patients had significantly lower TPMT activity, and two were classified as heterozygous for TPMT deficiency on genotype analysis. Although the number of evaluable patients was small, the suggestion was that a subset of patients with low TMPT activity might have an increased leukemogenic risk when exposed to mercaptopurine with other cytotoxic agents. Whether these findings can be extrapolated to patients without cancers is not known.

Of 550 patients with inflammatory bowel disease treated for a mean of 8 years, 25 (4.5%) developed a malignancy, with an overall incidence of 2.7 neoplasms per 1000 years of follow-up (74). The numbers of the most commonly observed cancers, such as bowel cancers ($n = 8$), breast cancers ($n = 3$), or single cases of other cancers, did not seem to be higher than expected in the general population or in the inflammatory bowel disease population. Although mercaptopurine was suspected in two cases of testicular carcinoma, two cases of lymphoma, and one case of leukemia, the authors emphasized the small risk of malignancies compared with the beneficial results of mercaptopurine in inflammatory bowel disease.

Second-Generation Effects

Pregnancy

Even though azathioprine is teratogenic in animals, human experience allows no firm conclusions, being limited to single case reports of birth defects after first trimester exposure to azathioprine. More convincingly, there was no evidence of increased risk or of a specific pattern of congenital anomalies among hundreds of infants born to azathioprine-treated transplant patients (75–77), but large series with adequate long-term follow-up are still lacking. The absence of inosinate pyrophosphorylase, an enzyme that converts azathioprine to its active metabolites, in the fetus was suggested to account for these reassuring data. Other potential risks, that is miscarriages or stillbirths, were also within the normal range, and intrauterine growth retardation did not appear to be specifically related to azathioprine use. Potential neonatal consequences of maternal azathioprine maintenance during the whole pregnancy should be borne in mind, in view of isolated reports of immunohematological immunosuppression, pancytopenia, cytomegalovirus infection, and chromosome aberrations. Unfortunately, the extent of this risk has not been carefully evaluated.

Teratogenicity

Maternal azathioprine treatment during pregnancy is clearly teratogenic in animals, but the mechanisms are not known. A large number of reports have described the outcome of pregnancies following the use of immunosuppressant drugs, in particular in renal transplant patients, and hundreds of pregnancies have been analysed (75). The largest experience is that derived from the National Transplantation Pregnancy Registry which has been built up in the USA since 1991 (76). This registry has accumulated data on more than 900 pregnancies, of which 83% followed kidney transplantation. Overall, the immunosuppressant drug regimens commonly used in transplant patients (azathioprine or ciclosporin) do not appear to increase the overall risk of congenital malformations or produce a specific pattern of malformation. Risk factors associated with adverse pregnancy outcomes included a short time interval between transplantation and pregnancy (that is less than 1–2 years), graft dysfunction before or during pregnancy, and hypertension (78).

Possible long-term effects of in utero exposure to immunosuppressants are still seldom investigated. There have been no reports that physical and mental development or renal function are altered. In one study, there were changes in T lymphocyte development in seven children born to mothers who had taken azathioprine or

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ciclosporin, but immune function assays were normal, suggesting that development of the fetal immune system was not affected (79).

In 27 clinical series, the frequency of congenital anomalies among infants of patients who took azathioprine after renal transplantation ranged from 0 to 11% (80).

The consequences of paternal mercaptopurine exposure on the outcome of pregnancies have been retrospectively studied in 57 men with inflammatory bowel disease: 23 men had fathered 50 pregnancies and had taken mercaptopurine before conception; of these, 13 pregnancies were conceived within 3 months of paternal mercaptopurine use (group 1A) and 37 pregnancies were conceived at least 3 months after paternal mercaptopurine withdrawal (group 1B); the other 34 men, who fathered 90 pregnancies, had not been exposed to mercaptopurine before conception (group II) (81). Of the 140 conceptions, two resulted in congenital anomalies in group 1A, whereas there were no congenital anomalies in the other groups. One child had a missing thumb, and the other had acrania with multiple digital and limb abnormalities. The overall number of complications (spontaneous abortion and congenital anomalies) was significantly higher in group 1A (4/13) compared with both group IB (1/37) and group II (2/90). Although the retrospective nature of this study and the limited number of evaluable patients precluded any definitive conclusion, the observed congenital anomalies were similar to those found in the offspring of female rabbits treated with mercaptopurine during pregnancy, and suggested that paternal mercaptopurine treatment should ideally be discontinued at least 3 months before planned conception.

Whereas neutropenia and immune deficiencies can affect neonates born to transplant patients, the exact role of azathioprine is difficult to establish. A report has suggested that such effects should also be expected in neonates born to patients taking azathioprine for other conditions (82).

- A 27-year-old woman, who took azathioprine (125 mg/day) and mesalazine (3 g/day) during her whole pregnancy, delivered a normal boy who had febrile respiratory distress after 36 hours. Chest X-ray showed interstitial pneumonitis and thymus hypoplasia. There was severe neutropenia (20×10^6/l), lymphopenia (24×10^6/l), and hypogammaglobulinemia. His clinical condition improved over the next 26 days with immunoglobulin treatment and antibiotics, but B lymphocytes and IgM were still undetectable.

Lactation

Very few data on breastfed infants from azathioprine-treated mothers are available. Breastfeeding is not recommended owing to the potential risk of immunosuppression, growth retardation, and carcinogenesis.

Susceptibility Factors

Genetic factors

The complex metabolism of azathioprine and mercaptopurine is subject to a pharmacogenetic polymorphism that is relevant to the degree of efficacy and toxicity attained in a given individual. Thiopurine methyltransferase (TPMT) is one of the key enzymes regulating the catabolism of thiopurine drugs to inactive products. Owing to an inherited autosomal codominant trait, a significant number of patients have intermediate (11%) to low or undetectable (0.3%) TPMT activity (83). These patients produce larger amounts of the active 6-thioguanine nucleotides and may therefore be unusually sensitive to commonly used dosages and an increased risk of myelotoxicity (SED-13, 1120) (SEDA-21, 381).

Monitoring azathioprine therapy by measuring erythrocyte 6-thioguanine concentrations and TPMT activity is thought to ensure optimal immunosuppressive effects and to reduce the likelihood of hematological toxicity (84,85). Low or completely absent erythrocyte TPMT activity and high concentrations of erythrocyte 6-thioguanine metabolites have been found in patients with severe azathioprine-induced bone marrow toxicity, as compared to those without bone marrow toxicity (86,87). However, intracellular concentrations of thiopurine nucleotides alone did not always correlate with hematological toxicity (88). In patients in whom TPMT deficiency was not clearly demonstrated, low lymphocyte 5'-nucleotidase activity and xanthine oxidase deficiency or other factors have been postulated as possible causes of hemotoxicity, suggesting that bone marrow toxicity is probably multifactorial (87,89,90). Although not all investigators recommend systematic pretreatment screening for purine enzyme activities, evidence of deficiency of purine enzymes could well be sought when early bone marrow toxicity occurs.

In a retrospective analysis of 106 patients with inflammatory bowel disease, to evaluate the importance of thiopurine methyl transferase (TPMT) activity in the management of azathioprine therapy in inflammatory bowel disease, the relation between inherited variations in TPMT enzyme activity and azathioprine toxicity was confirmed (91).

In 3291 patients receiving azathioprine, 10% had a low TPMT activity and 15 (1 in 220 or 0.46%) had no detectable enzymatic activity at all (92), slightly more common than has been reported in other studies (1 in 300). This makes the economics of screening, to avoid myelosuppression in patients receiving azathioprine, attractive.

Of 78 patients treated with azathioprine for systemic lupus erythematosus, 10 developed azathioprine-associated reversible neutropenia (93). Only one of these patients was homozygous for TPMT deficiency, but he had the most severe episode (aplastic anemia).

In one study, 14 of 33 patients with rheumatoid arthritis had severe adverse effects (mostly gastrointestinal toxicity, flu-like reactions or fever, pancytopenia, and hepatotoxicity) within 1–8 weeks after azathioprine was started (94). The adverse effects subsided after withdrawal in all patients, but all eight patients who were rechallenged developed the same adverse effect. A baseline reduction in TPMT activity was significantly associated with the occurrence of these adverse effects in seven of eight patients, with a relative risk of 3.1 (95% CI = 1.6–6.2) compared with patients with high TPMT activity (seven of 25 patients). Another prospective evaluation in 67 patients with rheumatic disorders showed that TPMT genotype analysis is useful in identifying patients at risk of azathioprine toxicity (95). Treatment duration was

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significantly longer in patients with the wild-type TPMP alleles than in those with mutant alleles, and that was due to the early occurrence of leukopenia in the latter.

In 22 children with renal transplants, high erythrocyte TPMT activity, measured 1 month after transplantation, correlated positively with rejection episodes during the first 3 months, and this was probably due to more rapid azathioprine catabolism (96). As suggested in a study of 180 patients with acute lymphoblastic leukemia, determination of genetic polymorphisms in TMPT can be useful in predicting potential toxicity and in optimizing the determination of an appropriate dose in patients who are homozygous or heterozygous for TMPT deficiency (97).

In 30 heart transplant patients taking azathioprine, the myelosuppressive effects of azathioprine/mercaptopurine were predicted by systematic genotypic screening of thiopurine methyltransferase deficiency (98). However, myelosuppression can also be observed in patients without the thiopurine methyltransferase mutation. Of 41 patients with leukopenia or thrombocytopenia taking azathioprine/mercaptopurine for Crohn's disease, four were classified as low methylators, seven as intermediate methylators, and 30 as high methylators by genotypic analysis (99). Thus, only 27% of the patients had the typical mutations associated with enzyme deficiency and a risk of myelosuppression. The delay in bone marrow toxicity was shorter in the four homozygous patients (median 1 month) than in the others (median 3–4 months). Many other causes, including viral infections, associated drugs, or another azathioprine/mercaptopurine metabolic pathway, were suggested to account for most of the cases of late hemotoxicity. This confirmed that continuous hematological monitoring is required, even in patients with no thiopurine methyltransferase mutations.

Drug–Drug Interactions

Allopurinol

Allopurinol inhibits xanthine oxidase, which is involved in the inactivation of azathioprine and mercaptopurine, and bone marrow suppression is a well-known complication of the concomitant use of allopurinol and azathioprine (SEDA-16, 114) (SEDA-20, 342). A reduction in the dosage of azathioprine or mercaptopurine by at least two-thirds and careful hematological monitoring during the first weeks of the combination has been proposed if combined use with allopurinol is required. However, compliance with these above guidelines was observed in only 58% of 24 patients with heart or lung transplants (100). In addition, although adequate azathioprine dosage reduction reduces the incidence of cytopenias, the risk persists even after the first month of the combination.

Because of the possible risks of reduced immunosuppression if the dose of azathioprine is reduced when allopurinol is given, cyclic urate oxidase can be given instead, as has been shown in six hyperuricemic transplant patients treated with azathioprine (101).

Aminosalicylates

In vitro studies have suggested that sulfasalazine and other aminosalicylates can inhibit TPMT activity, predisposing to an increased risk of bone marrow suppression in patients taking azathioprine or mercaptopurine. This was not clinically substantiated until an extensively investigated case was reported of leukopenia and anemia in a patient treated with both olsalazine and mercaptopurine (SEDA-21, 382). A further inhibiting effect of olsalazine was suggested in this patient, who had a relatively low baseline TPMT activity.

In 16 patients with Crohn's disease taking a stable dose of azathioprine, plus sulfasalazine or mesalazine, mean 6-thioguanine nucleotide concentrations fell significantly over 3 months; withdrawal of the aminosalicylates had no effect on the clinical and biological evolution of Crohn's disease in these patients (102).

Coumarin anticoagulants

Azathioprine or mercaptopurine have been sometimes involved in reduced warfarin and acenocoumarol activity, and increased warfarin dosages may be necessary (103). Similar findings were found in a patient taking maintenance phenprocoumon (SEDA-21, 382).

- Two patients required an approximate three-fold increase in the weekly anticoagulant dosage while taking azathioprine or mercaptopurine (104,105).

A pharmacokinetic interaction is the most likely cause, but the mechanism (impaired absorption or enhanced anticoagulant metabolism) is unknown.

Isotretinoin

The combination of isotretinoin and azathioprine was reported to have a synergistic effect on the occurrence of curly hair in three transplant patients with ciclosporin-induced acne (SEDA-20, 342).

Methotrexate

In 43 patients with rheumatoid arthritis, methotrexate was thought to have increased the risk of the azathioprine-induced hypersensitivity syndrome (106).

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Azelastine

See also Antihistamines

General Information

Azelastine is a second-generation antihistamine, a phthalazinone compound with antiallergic and bronchodilator properties (SEDA-12, 375) (SEDA-15, 155) (SEDA-17, 199) (SEDA-18, 182, 184) (SEDA-19, 171–172) (SEDA-20, 162) (SEDA-21, 172) (SEDA-22, 178). It is available as a nasal spray and in oral form for the treatment of allergic rhinitis and asthma as well as dermatoses. It reduces rhinorrhea, sneezing, and nasal congestion. Azelastine is effective against exercise-induced asthma and allergen challenge in patients with extrinsic asthma. It can inhibit histamine release

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from mast cells and inhibit histamine- and leukotriene-mediated bronchospasm (1).

Comparative studies

There have been three double-blind, randomized, parallel-group comparisons of the effects of azelastine nasal spray (1.1 mg/day) with combined treatment with oral loratadine (10 mg/day) and budesonide nasal spray (336 μg/day) in 1070 patients with allergic rhinitis unresponsive to monotherapy (2). The primary outcome measure was the percentage of patients who needed additional therapy for rhinitis after 7 days of treatment, and this was 32–46% across the three studies, with no significant difference between the two treatment groups. The most common adverse event with azelastine was a transient after-taste (8% compared with 1% in the combined group) and the most common adverse event for combined treatment was headache (6% compared with 5% in the azelastine group). Rhinitis and somnolence were the other commonly reported adverse events, in 3 and 2% with azelastine, and 1 and 1% in the combined group. The authors concluded that monotherapy with azelastine is as effective and as well tolerated as combination therapy in improving symptoms in moderate to severe allergic rhinitis, and this seems to be a reasonable claim.

Azelastine has been compared with the potent antihistamine cetirizine in the treatment of pruritic dermatoses. Taste disturbance occurred in 9.7% of patients taking azelastine and headaches in 10.4% of patients taking cetirizine (3).

Similar complaints regarding taste or smell were noted in some patients when azelastine nasal spray was used alongside budesonide (4) or ebastine (5) in allergic rhinitis in equieffective doses.

General adverse effects

In controlled studies, azelastine nasal spray produced a high incidence of itching and burning of the nasal mucosa together with taste disturbance and sometimes unpleasant smell. Sedation does not seem to be frequent; in most studies, the frequency of fatigue and drowsiness was not significantly different from placebo. In an open trial in which 119 patients with various types of pruritic dermatoses were treated with oral azelastine, 27 patients reported mild adverse effects such as drowsiness (15 cases, 12.5%) and a bitter after-taste (six cases, 5%). In four patients the treatment was withdrawn because of adverse effects (SEDA-15, 2).

Organs and Systems

Sensory systems

There have been several reports of a bitter taste associated with azelastine nasal spray for the treatment of allergic and non-allergic rhinitis compared with placebo in adults and children (6–8). Azelastine has also been reported to alter taste perception for several hours after ingestion (9).

Azelastine eye drops (0.025 and 0.05%) can produce slight reactions at the site of application and a bitter or unpleasant taste (10).

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Azipranone

General Information

Azipranone is a cough suppressant claimed to have effects comparable to those of codeine (1). Limited evidence suggests that its adverse effects are no different from those of placebo (SEDA-9, 157).

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Azithromycin

See also Macrolide antibiotics

General Information

Observational studies

In 3995 patients who took azithromycin 1.5 g in divided doses over 5 days or who took 1 g as a single dose for urethritis/cervicitis adverse events occurred in 12% (1). In patients over 65 years the rate was 9.3%, and in children under 14 years of age it was 5.4%. The most common adverse effects were gastrointestinal (9.6%); central nervous system and peripheral nervous system effects were reported in 1.3%. Overall, 59% of the adverse events were considered mild, 34% moderate, and only 6% severe, involving mainly the gastrointestinal tract. Adverse events resulted in withdrawal in 0.7% of patients, lower than the rate reported with other macrolides. Treatment-related rises in liver enzymes were uncommon (under 2%), as was leukopenia (1.1–1.5%).

Phase II/III clinical trials in the USA have yielded data on 1928 children aged 6 months to 15 years who took azithromycin for infections that included acute otitis media ($n = 1150$) and streptococcal pharyngitis ($n = 754$) (2). Most took a 5-day course of azithromycin (5–12 mg/kg/day). There were adverse effects in 190 patients (9.9%): diarrhea (3.1%), vomiting (2.5%), abdominal pain (1.9%), loose stools (1%), and rash (2.5%). In three comparisons with co-amoxiclav, the overall incidence of adverse effects was significantly lower with azithromycin (7.7 versus 29%), with withdrawal rates of 0.3 versus 3.6%. However, the incidence of adverse effects was significantly greater with azithromycin than with penicillin V in comparisons in patients with streptococcal pharyngitis (13 versus 6.7%). In conclusion, it appears that the safety and tolerability of azithromycin is similar in children and adults.

In an open study, children with end-stage lung disease or chronic airflow limitation unresponsive to conventional therapy were treated with long-term azithromycin. Seven children (mean age 12 years), all of whom were colonized with *Pseudomonas aeruginosa* and who took azithromycin for more than 3 months, were studied. There was a significant improvement in FVC and FEV_1 (3). The mechanism whereby azithromycin works is unknown, but it may be other than antibacterial. It has been hypothesized that the effect may be due to upregulation of a P glycoprotein, a member of the family of multidrug resistant proteins, since erythromycin upregulates P glycoprotein expression in a monkey model. Multidrug resistance (MDR) is homologous to CFTR, and previous in vitro experiments have shown that the MDR and CFTR genes can complement each other (4). However, direct proof of this hypothesis is lacking at the moment.

Of 42 adult HIV-positive patients with confirmed or presumed acute toxoplasmic encephalitis who received azithromycin 900, 1200, or 1500 mg/day plus pyrimethamine, 28 responded to therapy during the induction period (5). Six patients withdrew during the induction period because of reversible toxic effects (three with raised liver enzymes, two with hearing loss, one with neutropenia). Treatment-terminating adverse events occurred most often among the patients who took 1500 mg/day.

In an open, prospective trial gingival hyperplasia due to ciclosporin was successfully treated with azithromycin 250 mg/day for 5 days in 30 of 35 patients, who reported esthetic satisfaction and disappearance of bleeding and pain (6). There was no change in ciclosporin concentration or renal function after azithromycin.

Comparative studies

The tolerability of azithromycin oral suspension, 10 mg/kg od for 3 days, has been assessed in children in a review of 16 multicenter studies (7). Of 2425 patients, 1213 received azithromycin and 1212 received other drugs. The incidence of treatment-related adverse events was significantly lower in those who took azithromycin, while withdrawal rates were similar. There were significantly fewer gastrointestinal events with azithromycin and their duration was significantly shorter.

Co-amoxiclav

In a multicenter, parallel-group, double-blind trial in 420 evaluable patients aged 6 months to 16 years with community-acquired pneumonia, the therapeutic effect of azithromycin (once-daily for 5 days) was similar to that of co-amoxiclav in children under 5 years and to that of erythromycin tds for 10 days. Treatment-related adverse events occurred in 11% of those given azithromycin and 31% in the comparator group (8).

Azithromycin (500 mg/day for 3 days) has been used to treat acute periapical abscesses (9). Of 150 patients treated with azithromycin 18 reported a total of 26 adverse events. Slightly more (24 out of 153) treated with co-amoxiclav reported 34 adverse events, but this difference did not reach statistical significance. Most of the adverse events (44/60) were gastrointestinal, mostly diarrhea or abdominal pain. There were no significant differences between the two groups in the severity of adverse events or in the number of withdrawals because of adverse events.

Fluoroquinolones

In a multicenter, open, randomized comparison of levofloxacin 500 mg/day orally or intravenously and azithromycin 500 mg/day intravenously for up to 2 days plus ceftriaxone 1 g/day intravenously for 2 days in 236 patients, the most common drug-related adverse events in those given azithromycin were diarrhea (4.2%), vein disorders (2.5%), and pruritus (1.7%) (10).

Other macrolides

The incidence of disseminated MAC infection has increased dramatically with the AIDS epidemic. Treatment regimens for patients with a positive culture for MAC from a sterile site should include two or more drugs, including clarithromycin. Prophylaxis against disseminated MAC should be considered for patients with a CD4 cell count of less than 50×10^6/l (11). In a randomized, open trial in 37 patients with HIV-associated disseminated MAC infection, treatment with clarithromycin + ethambutol produced more rapid resolution of bacteremia, and was more effective at sterilization of blood cultures after 16 weeks than azithromycin + ethambutol (12).

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Tetracyclines

Compared with tetracycline, azithromycin had a favorable short-term effect on childhood morbidity in a mass trial for trachoma in rural Gambian villages, and adverse effects were limited (13).

Treatment of facial comedonic and papulopustular acne with azithromycin (500 mg/day for 4 days in four cycles every 10 days) may be at least as effective as minocycline (100 mg/day for 6 weeks). Both were well tolerated and mild adverse effects were reported in 10% of patients given azithromycin and 12% of those given minocycline (14).

Placebo-controlled studies

In 169 patients with acute infective rhinitis, azithromycin (500 mg/day for 3 days) resulted in a better cure rate after 11 days than placebo; however, after 25 days the results for both improvement and cure were equal (15).

In a randomized, double-blind, placebo-controlled multicenter trial in 174 HIV-infected patients with CD4 cell counts of under 100×10^6/l, azithromycin (1200 mg once a week) was safe and effective in preventing disseminated MAC infection, death due to MAC infection, and respiratory tract infections (16).

In a triple-masked, randomized, placebo-controlled study in 1867 women, prophylaxis with azithromycin 500 mg 1 hour before IUCD insertion did not affect the rate of IUCD removal, the frequency of medical attention after insertion, or the risk of upper genital tract infection at 90 days (17). Women were at low risk of sexually transmitted disease according to self-reported medical history. Gastrointestinal adverse effects were infrequent (3% azithromycin; 2% placebo). Fewer women taking azithromycin (0.7%) than those taking placebo (1.3%) were treated with antibiotics for pelvic tenderness; however, this difference was not statistically significant. Since cervical infections increase the risk of pelvic infection in women who use IUCDs, generalization of these results may be difficult (18).

In a meta-analysis of randomized, controlled trials of 3–5 days of azithromycin or other antibiotics that are typically given in longer courses for upper respiratory tract infections, there were no significant differences in bacteriological outcomes (19). Azithromycin was withdrawn because of adverse events in only 37 (0.8%) of 4870 patients.

Organs and Systems

Cardiovascular

Torsade de pointes and cardiorespiratory arrest have been reported in a patient with congenital long QT syndrome who took azithromycin (20). In a prospective study of 47 previously healthy people, there was a modest statistically insignificant prolongation of the QT_c interval without clinical consequences after the end of a course of azithromycin 3 g/day for 5 days (21).

Sensory systems

Ears

Azithromycin can cause ototoxicity. In one study, 8 (17%) of 46 HIV-positive patients had probable ($n = 6$) or possible ($n = 2$) ototoxicity with azithromycin (22). The effects were hearing loss (88%), tinnitus (37%), plugged ears (37%), and vertigo (25%), developing at a mean of 7.6 weeks (1.5–20 weeks) after the start of long-term azithromycin therapy for *Mycobacterium avium* infection. The symptoms resolved in a mean of 4.9 weeks (2–11 weeks) after withdrawal.

Sensorineural hearing loss has been attributed to azithromycin (23).

- A 35-year old Caucasian man with AIDS and multiple opportunistic infections, including *Mycobacterium kansasii* and *Mycobacterium avium* complex (MAC) disease developed moderate to severe primary sensorineural hearing loss after 4–5 months of therapy with oral azithromycin 500 mg/day. Other medications included ethambutol, isoniazid, rifabutin, ciprofloxacin, co-trimoxazole, fluconazole, zidovudine (later switched to stavudine), lamivudine, indinavir, methadone, modified-release oral morphine, pseudoephedrine, diphenhydramine, megestrol acetate, trazodone, sorbitol, salbutamol by metered-dose inhaler and nebulizer, ipratropium, and oral morphine solution as needed. Significant improvement of the hearing impairment was documented 3 weeks after drug withdrawal.

A literature review identified several cases of ototoxicity in HIV-positive patients treated with azithromycin for *M. avium* complex infection. In four series, 14–41% of such patients had some degree of hearing loss. However, some patients were also taking other potentially ototoxic drugs, which may have contributed to the high frequency of hearing loss reported. Hearing loss improved markedly after withdrawal of azithromycin. Hearing loss may be more common and probably more severe with high-dose azithromycin than with high-dose clarithromycin.

- A 47-year-old woman who had a left lung transplantation 3 months earlier and who was taking ticarcillin + clavulanate and aztreonam for sinusitis, was given co-trimoxazole, ticarcillin + clavulanate, azithromycin (500 mg/day intravenously), and ganciclovir for presumed pneumonia (24). Other drugs included tacrolimus, mycophenolate, prednisone, lansoprazole, diltiazem, itraconazole, warfarin, alendronate, ipratropium bromide, folic acid, and nystatin. The next day, rimantadine and vancomycin were added, and co-trimoxazole was reduced. A neurological examination to assess symptoms of peripheral neuropathy noted no hearing deficit. On day 3, vancomycin, ticarcillin + clavulanate, and ganciclovir were withdrawn. On the fifth day, mild tinnitus and reduced hearing developed and gradually progressed to complete deafness. After eight doses, azithromycin was withdrawn, and 20 days later her hearing was back to baseline.

Low-dose exposure to azithromycin has been associated with irreversible sensorineural hearing loss in otherwise healthy subjects (25). Even a single oral dose of azithromycin altered the conjunctival bacterial flora of children from a trachoma endemic area (26). However, the clinical significance is not yet clear.

Psychological, psychiatric

Azithromycin can cause delirium (27).

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Hematologic

The effects of combining azithromycin and rifabutin have been studied in 50 subjects with or without HIV infection, of whom 19 took azithromycin 1200 mg/day and rifabutin 600 mg/day, and 31 took azithromycin 600 mg/day and rifabutin 300 mg/day (28). Neutropenia was the most common adverse event, in 33 of 50 subjects. Low-grade nausea, diarrhea, fatigue, and headache were also common, and most subjects had more than one type of event. There was no significant pharmacokinetic interaction between the two drugs.

Gastrointestinal

In a review of 12 clinical studies most of the adverse events in those taking azithromycin affected the gastrointestinal system, and were reported in 138 (8.5%) azithromycin-treated patients (29). Abdominal pain, diarrhea, nausea, and vomiting were the most frequently reported gastrointestinal adverse events.

Gastrointestinal symptoms were the most common adverse effects reported in a trial of azithromycin in disseminated *Mycobacterium avium* complex in 62 patients with AIDS (30). Erythromycin is a motilin receptor agonist (31–33). This mechanism may be at least partly responsible for the gastrointestinal adverse effects of macrolides. Azithromycin may act on gastrointestinal motility in a similar way to erythromycin, as it produces a significant increase in postprandial antral motility (34).

Liver

Azithromycin can cause intrahepatic cholestasis (35).

- A 33-year-old woman and a 72-year-old man developed cholestasis after they had taken a 5-day course of azithromycin. The woman was given colestyramine and underwent six courses of plasmapheresis; 2 months later, her total bilirubin and serum transaminases were back to normal (36). After withdrawal of azithromycin, the man's symptoms resolved within 1 month and his liver enzymes returned to normal (37).

Skin

- A 19-year-old man with infectious mononucleosis developed a maculopapular, non-pruritic rash after one dose of azithromycin 500 mg (38).

Immunologic

Occupational allergic contact dermatitis has been attributed to azithromycin (39).

- A 32-year-old pharmaceutical worker had been loading reactors at three different stages of azithromycin synthesis for the past 3 years and had been exposed to airborne powders. He wore overalls and latex gloves. His symptoms had persisted for 1 year in the form of pruritus, erythema, vesicles, and scaling of the face and forearms. A positive patch test and a positive workplace challenge were considered reliable in the diagnosis of occupational allergic contact dermatitis induced by azithromycin. After transfer to another work station that excluded exposure to azithromycin, he had no further work-related symptoms.

Hypersensitivity to azithromycin has been reported (40).

- A 79-year-old man developed fever, mental changes, a rash, acute renal insufficiency, and hepatitis after he had completed a 5-day course of oral azithromycin (500 mg initially then 250 mg/day). With intravenous hydration only, his fever abated and his urinary output and renal and hepatic function returned to normal over the next 4 days. His mental status improved significantly. The skin rash was followed by extensive desquamation.

Azithromycin has been associated with Churg–Strauss syndrome in a patient with atopy (41).

Second-Generation Effects

Pregnancy

In two randomized trials in pregnant women with cervical *Chlamydia trachomatis* infection, women were randomized to oral amoxicillin 500 mg tds for 7 days or oral azithromycin 1 g in a single dose (42,43). The two drugs had similar efficacy. Adverse effects were common in both groups: 40% of those who took azithromycin reported moderate to severe gastrointestinal adverse effects compared with 17% of those who took amoxicillin.

Susceptibility Factors

Renal disease

In eight patients a single 500 mg oral dose of azithromycin was not substantially removed by continuous ambulatory peritoneal dialysis in the absence of peritonitis. Azithromycin cannot be recommended for widespread use in CAPD at present. However, the successful use of azithromycin in treating peritonitis, perhaps because of an intracellular drug transport mechanism, has been reported (44).

Drug–Drug Interactions

Antacids

Owing to interference by antacids, azithromycin should be given at least 1 hour before or 2 hours after antacids. Antacids containing aluminium and magnesium reduce peak serum concentrations, but the total extent of azithromycin absorption is not altered (45).

Antihistamines

The effects of azithromycin 250 mg/day on the pharmacokinetics of desloratadine 5 mg/day and fexofenadine 60 mg bd have been studied in a parallel-group, third-party-blind, multiple-dose, randomized, placebo-controlled study (46). There were small increases (under 15%) in the mean plasma concentrations of desloratadine. In contrast, peak fexofenadine concentrations were increased by 69% and the AUC by 67%. There were no changes in the electrocardiogram.

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Carbamazepine

A retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interactions in patients who were also taking various other drugs, including carbamazepine (1,45).

Ciclosporin

When azithromycin is used concomitantly with ciclosporin, blood ciclosporin concentrations need to be monitored (47).

Cimetidine

A retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interactions in patients who were also taking various other drugs, including cimetidine (1,45).

Cytochrome P450

Azithromycin has a 15-membered ring and does not induce or inhibit cytochrome P450 in rats (48).

Digoxin

When azithromycin is used concomitantly with digoxin, serum digoxin concentrations need to be monitored (47). While data on the effects of azithromycin on the intestinal metabolism of digoxin have not been reported so far, it is likely that it will affect *Eubacterium lentum*, like other macrolides.

Methylprednisolone

A retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interactions in patients who were also taking various other drugs, including methylprednisolone (1,45).

Midazolam

In an open, randomized, crossover, pharmacokinetic and pharmacodynamic study in 12 healthy volunteers who took clarithromycin 250 mg bd for 5 days, azithromycin 500 mg/day for 3 days, or no pretreatment, followed by a single dose of midazolam (15 mg), clarithromycin increased the AUC of midazolam by over 3.5 times and the mean duration of sleep from 135 to 281 minutes (49). In contrast, there was no change with azithromycin, suggesting that it is much safer for co-administration with midazolam.

Piroxicam

In 66 patients undergoing oral surgery, treatment with azithromycin impaired the periodontal disposition of piroxicam (50).

Rifamycins

An interaction involving azithromycin with rifabutin, and less commonly rifampicin, was observed in patients with MAC infections (51).

Terfenadine

The potential interaction of azithromycin with terfenadine has been evaluated in a randomized, placebo-controlled study in 24 patients who took terfenadine plus azithromycin or terfenadine plus placebo (52). Azithromycin did not alter the pharmacokinetics of the active carboxylate metabolite of terfenadine or the effect of terfenadine on the QT interval.

Theophylline and other xanthines

A retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interactions in patients who were also taking various other drugs, including theophylline (1,45).

In two double-blind, randomized, placebo-controlled studies there was no inhibition of the metabolism of theophylline by azithromycin (53,54). However, there has been a report of reduced theophylline concentrations after withdrawal of azithromycin (55). The authors concluded that the mechanism of interaction was best explained by concomitant induction and inhibition of theophylline metabolism by azithromycin, followed by increased availability of unbound enzyme sites as azithromycin was cleared from the system.

Warfarin

A retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interactions in patients who were also taking various other drugs, including warfarin (1,45).

Zidovudine

Zidovudine does not affect azithromycin concentrations and azithromycin does not affect zidovudine concentrations (56).

Food–Drug Interactions

Owing to interference by food (57), azithromycin should be given at least 1 hour before or 2 hours after food.

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Bacille Calmette–Guérin (BCG) vaccine

See also Vaccines

General Information

Bacille Calmette–Guérin (BCG) vaccine is a suspension of living tubercle bacilli of the Calmette–Guérin strain. It is used mainly prophylactically against tuberculosis, but also as a means of stimulating the immune response in malignant disease. There are variations in the characteristics of BCG vaccines, depending on the strain of BCG derived from the original BCG strain and employed for vaccine production. BCG is generally used intradermally, except for instillation in intravesical immunotherapy. The risk of adverse effects after BCG immunization is related to the BCG strain, the dose, the age of the vaccinee, the technique of immunization, and the skill of the vaccinator.

Therapeutic uses of BCG

In addition to its use in preventing tuberculosis, BCG has been used as an immunostimulant or immunomodulator. The degree of safety of this procedure differs with the technique and the purpose for which it is used. In most areas, the use of BCG to counter cancer has proved disappointing, although it is still used to some extent, generally as an adjunct to other forms of treatment (1–7). More encouraging is the use of intravesical instillation of BCG for recurrent superficial transitional cell carcinoma of the bladder, for which it now constitutes the treatment of choice.

BCG immunotherapy in bladder tumors

Intravesical instillation of BCG has been used to treat superficial bladder carcinoma and interstitial cystitis. Many reports have confirmed the efficacy of BCG in the treatment of transitional cell bladder cancers and have delineated its adverse effects (SEDA-12, 273) (SEDA-13, 278) (SEDA-15, 344) (SEDA-16, 375) (SEDA-17, 366) (SEDA-18, 328) (SEDA-20, 287) (SEDA-21, 328) (SEDA-22, 336). The exact mechanism of its antitumor activity is unknown, but live BCG provokes an inflammatory response that includes activation of macrophages, a delayed hypersensitivity reaction, and stimulation of T and B lymphocytes and natural killer cells.

In general, BCG immunotherapy of bladder cancer is considered to be relatively safe. However, it does have adverse effects, including fever, arthritis/arthralgia, bladder irritability, bladder contracture, cytopenias, cystitis, disseminated intravascular coagulation, respiratory failure, epididymitis, hepatitis, loss of bladder capacity, miliary tuberculosis, pneumonitis, polyarthritis, prostatitis, pyelonephritis, pseudotumoral granulomatous renal mass, rhabdomyolysis, renal granulomas, renal insufficiency, skin abscess, tuberculous aneurysm of the aorta and femoral artery, ureteral obstruction, vertebral osteomyelitis, and psoas abscess. A small number of reports of life-threatening adverse effects after BCG instillation have been published, including disseminated BCG infection (8–11), some fatal. These tragic cases illustrate many points of critical importance to all urologists using BCG. BCG should never be given at the same time as tumor resection or transurethral resection of the prostate. The dose of BCG given intravesically corresponds to a potentially lethal intravenous dose. Intravasation as a result of catheterization, tumor resection or biopsy, or cystitis has occurred in two-thirds of the reported cases of systemic BCG infection.

In a review of those observed among 195 patients with bladder cancer treated with various substrains of BCG, there were frequent but mild to moderate local adverse effects, with irritative cystitis leading to frequency and dysuria in 91% of patients and hematuria in 43% (12). Low-grade fever (24%), malaise (24%), and nausea (8%) also occurred. These symptoms usually occurred after two or three instillations and lasted for about 2 days. It has been stated that these frequent adverse effects did not seriously affect the quality of life of patients (13). Additional information was obtained from a multinational retrospective survey in order to cover the whole scope of severe and/or systemic complications associated with BCG immunotherapy, and to propose guidelines for management (14). Among 2602 patients in this survey, more than 95% had no serious adverse effects. Apart from fever higher than 39°C (2.9%) and major hematuria (1%) serious adverse effects comprised granulomatous prostatitis (0.9%), granulomatous pneumonitis and/or hepatitis (0.7%), arthritis and arthralgia (0.5%), epididymo-orchitis (0.4%), life-threatening BCG sepsis (0.4%), skin rashes (0.3%), ureteric obstruction (0.3%), bladder contracture (0.2%), renal abscesses (0.1%), and cytopenias (0.1%). There was no major difference in incidence among the different substrains used. Lowering the dose of BCG in an attempt to reduce the incidence of adverse effects produced somewhat contrasting results, with a reduced incidence of various adverse effects but no significant difference (or an apparently increased incidence) in the case of pollakiuria, hematuria, fever, and headache (SEDA-20, 287) (15).

Other rare complications have been seldom reported, namely cryoglobulinemia with evidence of disseminated BCG infection (16), ruptured mycotic aneurysm of the abdominal aorta (17), bladder wall calcification (18), rhabdomyolysis (19), iritis or conjunctivitis with arthritis or Reiter's syndrome (20,21), and severe acute renal insufficiency due to granulomatous interstitial nephritis, which can occur even in the absence of other systemic complications (22).

In 1990, the US Food and Drug Administration approved the marketing of BCG Live (intravesical) for use in the treatment of primary or relapsed carcinoma in situ of the urinary bladder, with or without associated papillary tumors. BCG is not recommended for treatment of papillary tumors that occur alone. The drug is marketed by Connaught Laboratories as TheraCys and by Organon as TiceBCG. The manufacturers recommend a 6-week induction course of weekly intravesical BCG, usually starting 1–2 weeks after biopsy or after transurethral resection of papillary tumors. Follow-up

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courses of treatment at 3, 6, 12, and 24 months or monthly for 6–12 months after initial treatment are recommended.

Influence of dosage

The degree of success of different doses of BCG vaccine (100–120 mg, 20–50 mg, or a much smaller dose of 1 mg) in preventing tumor relapse has been described in patients with superficial bladder cancers (23). Adverse reactions were dose-related. The authors considered that endovesical instillation of BCG vaccine 1 mg would be the optimal dosage for prevention of relapse.

In 108 patients with bladder cancer, tumor relapse was prevented by the use of BCG vaccine 1 mg (24). Inguinal lymphadenitis and dysuria have occurred (SEDA-20, 287).

Comparison of BCG strains

In a comparison of 56 patients who received BCG instillations using Berna strain BCG and 32 patients who received Pasteur strain BCG for treatment of superficial bladder cancer, the patients who received Pasteur strain BCG had the highest tumor-free rate but had significantly more toxicity (25). The answer to another difficult question connected with the use of intravesical BCG, that is whether the treatment increases the incidence of second primary malignancies, has been sought (26,27). It was suggested that BCG immunotherapy could accelerate the growth and cause metastatic spread of a growing second primary malignancy that had remained undetected at the start of BCG therapy, and that the time relation between the starting point of second primary tumor development and the starting point of BCG treatment might be crucial in determining whether BCG eradicates the tumor or accelerates its growth. However, in 153 patients there was no evidence that intravesical BCG did increase the incidence of second primary malignancies (26). The matter is therefore still unresolved.

Comparison of different regimens for carcinoma in situ of the bladder

The efficacy and adverse effects of various alternative treatment regimens for carcinoma in situ of the bladder have been compared with those of instillation of BCG in 21 patients. All were treated initially with intravesicular instillations of Keyhole-Limpet Hemocyanin (first course: 20 mg weekly for six weeks; second course: 20 mg monthly for 1 year or bimonthly for 2 subsequent years). Patients who did not respond to two courses were treated with regular instillations of BCG Connaught strain 120 mg. Eleven patients were free from tumor tissue after the first or second course of Keyhole-Limpet Hemocyanin. Ten patients had to have a cystectomy because of persistence or progression of carcinoma after hemocyanin or hemocyanin with subsequent BCG. However, instillations of BCG caused severe dysuria in 60% and fever in 40% of patients, whereas hemocyanin treatment had only minor adverse effects (28). Combined therapy with mitomycin C and BCG was more effective in 28 patients with carcinoma in situ of the bladder than mitomycin alone (29). Compared with BCG monotherapy there were only a few adverse effects. The success rates were comparable.

Two different methods of treating superficial bladder cancer have also been compared in a randomized, multicenter trial, setting transurethral resection only against transurethral resection plus adjuvant mitomycin C and BCG instillation (30). The rate of progression was comparable in the two groups; at a medium follow-up of 20 months there was a reduction in recurrence rates with the combination therapy. Adverse effects occurred most often during or after BCG instillation. Other investigators have found the same degree of efficacy of the same regimen in reducing the incidence of recurrence of superficial urothelial cancer after transurethral bladder resection in 99 patients (31).

Treatment of adverse effects after intravesical instillation of BCG

The prompt recognition of risk factors for severe complications, namely traumatic catheterization or concurrent cystitis, that increase BCG absorption, and treatment of early adverse effects, is expected to reduce the incidence of severe adverse effects. Severe local and systemic adverse effects can be successfully treated with tuberculostatic drugs for up to 6 months (14).

Severe local and systemic adverse effects of BCG treatment can be treated successfully with tuberculostatic drugs, to most of which BCG is very susceptible, for up to 6 months (32). The effects of isoniazid on the incidence and severity of adverse effects of intravesical BCG therapy have been analysed in patients who received BCG with ($n = 289$) and without ($n = 190$) isoniazid (33). The authors concluded that prophylactic oral administration of isoniazid (300 mg/day with every BCG instillation) caused no reduction in any adverse effect of BCG. In contrast, transient liver function disturbances occurred slightly more often when isoniazid was used. The polymerase chain reaction has been used to monitor BCG in the blood after intravesical BCG instillation (22 patients) as well as after antituberculosis therapy (34). The early and fast diagnosis of BCG in the blood was considered to be potentially valuable in initiating specific early treatment of BCG complications.

General adverse effects of prophylactic BCG immunization

BCG immunization is generally well tolerated. Locally a small papule appears which scales and ultimately leaves a scar; however, abnormal reactions can occur. The most common adverse local reaction, suppurative lymphadenitis, has been reported in 0.1–10% of immunized children under 2 years of age. Faulty immunization technique is the most frequent cause of severe abnormal BCG primary reactions (35). The most serious generalized complications of BCG immunization involve disseminated infection with the BCG bacillus and BCG osteitis. Allergic reactions are unusual, but severe anaphylactic reactions can occur, especially when the product is used as an immunostimulant.

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Tuberculin

Mammalian tuberculin purified protein derivative (tuberculin PPD) is the active principle of old tuberculin. A small test dose in a healthy individual, given intracutaneously, is likely to produce only a little local pain and pruritus. If tuberculous infection is present, the local reaction is more marked, with vesiculation, ulceration, and even granuloma annulare or necrosis.

If more than a minimal dose is used in cases of tuberculous infection, a severe and even fatal generalized anaphylactic reaction can develop within about 4 hours of the injection (36).

People who are engaged in manufacturing PPD can easily become sensitized to it, and severe allergic reactions can occur if they later inhale even small quantities (37).

Lymphangitis after tuberculin testing is rare (SED-11, 686).

Acute panuveitis has been reported (38). The episodes developed after each of two tests carried out at intervals of 8 years and responded well to glucocorticoid therapy.

Organs and Systems

Cardiovascular

A mycotic aneurysm, a rare complication of intravesical BCG therapy, has been reported (17).

- A 71-year-old man with bladder carcinoma in situ received six instillations of BCG at weekly intervals followed 3 months later by three booster instillations at weekly intervals. Four months later an inflammatory aortic aneurysm, which had ruptured into a pseudoaneurysm, was diagnosed and excised. *Mycobacterium bovis* was found. After treatment with isoniazid and rifampicin he recovered. There was no sign of tumor in the bladder at cystocopy 8 months after the last BCG instillation.

Respiratory

There have been two reports of micronodular pulmonary infiltrates (BCG pneumonitis) associated with fever, chills, and night sweats following multiple instillations of intravesical BCG (39). Both patients were 71 years old. The reactions, including radiographic infiltrates, resolved spontaneously or after steroid therapy.

Nervous system

There have been two reports of tuberculous meningitis after BCG immunization in immunocompetent individuals, in two French children aged 4.5 and 5 years (40) and in a 22-year-old woman from Cambridge, UK (41).

Polyneuritis has been attributed to BCG immunization (42).

Sensory systems

Responding to the question of whether accidental inoculation of one drop of BCG vaccine into the eye of a health-care worker could be a risk, Pless (personal communication) has reported the case of a urologist who developed a corneal ulcer after a similar accident.

Endogenous endophthalmitis (SEDA-15, 344) and bilateral optic neuritis (43) have been reported after BCG immunization.

Hematologic

Clinical trials in BCG-vaccinated newborns in different countries have variously found a dose–effect relation for the risk of suppurative lymphadenitis:

- Croatia (SED-12, 799)
- French Guyana (SEDA-16, 373)
- Germany (SED-12, 798)
- Hong Kong (SED-12, 799)
- Hungary (SED-12, 798)
- India (SEDA-18, 328)

or a strain-dependent relation:

- Austria (SEDA-16, 374) (SEDA-17, 366)
- Germany (SED-12, 798)
- India (SEDA-18, 328)
- Saudi Arabia (SED-12, 799)
- Togo (SED-12, 799)
- Turkey (SED-12, 799)
- Zaire (SED-12, 799)

Since 1984, WHO's Expanded Programme on Immunization has received many reports from various countries of an increased incidence of suppurative lymphadenitis after BCG immunization. Careful investigations of risk factors have been carried out, particularly in Zimbabwe and Mozambique (1987, 1988). Those studies established a strong association between an increased risk of lymphadenitis within 6 months of immunization and both the use of the Pasteur BCG strain, and programmatic errors, such as poor injection technique, poor technique in reconstituting and mixing the freeze-dried vaccine with diluent, or an incorrectly administered dose of vaccine. The incidence of lymphadenitis was 9.9% with the suspect Pasteur strain versus 0% with two other strains used under the same conditions. Experience gained in other countries has suggested that when Pasteur strain BCG vaccine is administered properly, the rate of lymphadenitis in newborns should not exceed 1%. The increased occurrence of lymphadenitis may require both a reactogenic strain and poor technique (44). A rare case of BCG lymphangitis occurring 11 years and again 18 years after immunization has been reported (45).

Liver

Granulomatous neonatal hepatitis has been reported after BCG immunization (46).

Skin

Since the initial report of lupus vulgaris following BCG immunization in 1946, about 60 cases have been published, mostly following (multiple) revaccination.

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The risk of developing lupus vulgaris following primary immunization is extremely low.

- Lupus vulgaris occurred in a 7-year-old girl after only a single BCG immunization (47). She was treated with conventional antituberculosis therapy with an excellent response.
- Six months after BCG vaccination, an 18-year-old man developed lupus vulgaris on his right shoulder (48). He was successfully treated with rifampicin, isoniazid, and ethambutol. He had had lupus vulgaris after BCG vaccination on his left shoulder 8 years before.

Acute febrile neutrophilic dermatosis (49) and eczema vaccinatum (50) have been reported after BCG immunization.

Musculoskeletal

Arthritis and arthralgia are well-known adverse effects of intravesical BCG instillation as part of therapy of bladder cancer (SED-13, 925). The etiology and the different clinical pictures of BCG immunotherapy have been discussed (51). Considering that mycobacteria are potent stimulators of the immune system and especially of T cells, it is not surprising to observe T cell-mediated aseptic arthritis after BCG therapy. The authors suggested that the site of immune stimulation is critical, since intradermal injection produces a clinical presentation similar to reactive arthritis, and intravesical therapy causes a clinical picture identical to Reiter's syndrome.

In a large worldwide analysis of BCG adverse effects (1948–74) co-ordinated by the International Union Against Tuberculosis and Lung Disease (SED-12, 795) there were 272 cases of lesions of bones and joints, including synovial lesions. However, case reports of arthritis after BCG vaccination in healthy individuals are rare. Polyarthritis has been reported in a 33-year-old healthy woman 3 weeks after BCG vaccination (52).

Osteitis

Osteitis occurred in <0.1–30/100 000 vaccinees and has been reported mainly among infants immunized with BCG in the neonatal period in the Scandinavian countries. A retrospective study showed that BCG osteitis was present in Sweden from 1949 onwards. The reported incidence was one per 40 000 in children born between 1960 and 1969 (53,54). In Sweden, the reported incidence of osteitis rose to one per 3000 and one per 4000 for children vaccinated in the neonatal period during 1972–75. Compulsory notification of BCG adverse effects to the Swedish Adverse Drug Reaction Committee was introduced at that time.

The incidence of BCG osteitis correlates closely with the BCG vaccine used. Between 1960 and 1970, when the vaccine based on the Gothenburg strain was prepared in Sweden, the incidence of BCG osteitis was 7.3 per 100 000 vaccinees. There was a significant increase to 37 per 100 000 in the early 1970s, when the vaccine was prepared in Copenhagen using the same Gothenburg strain. Because of the increased incidence, in 1978 the vaccine was replaced by a BCG vaccine made by Glaxo, UK. Since then, the incidence has been similar to that reported in the 1960s (6.4 per 100 000 vaccinees) (55).

Following a report of 10 cases of BCG osteitis in Finland (56), the medical records of 222 children with BCG osteitis registered from 1960 to 1988 in Finland were analysed (55). The most common sites of osteitis were the metaphyses of the long bones; the legs were affected more often (58%) than the arms (14%). There was also osteitis of the sternum (15%) and ribs (11%). With adequate treatment, the prognosis for children with BCG osteitis was good, but six children were left with sequelae, with abnormalities of the limbs in five cases and pronounced cheloid formation in the other.

In Czechoslovakia, BCG osteitis was not diagnosed before 1981. However, from March 1980 onwards another BCG vaccine (Moscow strain) was introduced (57), and after 1981 12 cases of BCG osteitis were diagnosed (58). Most of the cases developed between 7 and 24 months after immunization, but some occurred later. The risk of osteitis rose to 35 per million in the period 1982–85. There were 28 cases of BCG osteomyelitis during the period from 1980 to June 1985, when Russian BCG vaccine containing a higher amount of culturable particles was used, and only 11 cases during the period from July 1985–89, by which time the dose of vaccine had been halved (59). During the last 2 years of the second period there was only one case in each immunized birth cohort. Elsewhere, an infant developed BCG osteomyelitis of the upper spine, a very rare complication described only three times before (60).

Six cases of BCG osteitis in Switzerland occurred in 1980–85 (61). Reports from various countries, for example New Zealand (62) and India (63), have emphasized the increasing knowledge of BCG osteitis. BCG osteitis has never been reported in the UK with use of the Glaxo vaccine. Table 1 shows rates of BCG osteitis in different countries (64).

Sexual function

- Following a 6-week course of intravesical BCG a 65-year-old man with carcinoma of the bladder developed a BCG-derived inflammatory infiltrate of the penis. The induration and lesions resolved after treatment with isoniazid and ethambutol (65).

Immunologic

The incidence of adverse effects after BCG immunization has been extensively investigated by the Committee on Prophylaxis of the International Union Against Tuberculosis and Lung Disease (IUATLD). Retrospective studies including 51 countries worldwide and collecting data from 1948–74, according to organ and system category, have been published (SED-12, 795) (64,66). The IUATLD carried out a second

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Table 1 Rates of BCG osteitis in different countries

Country	Number of vaccinees (all age groups) (millions)	BCG osteitis	
		Number	Rate per million vaccinees
Finland	2.79	128	45.9
Sweden	3.42	121	35.4
Denmark	2.28	4	1.75
West Germany	9.03	14	1.55
Norway	2.32	2	0.86
East Germany	8.68	5	0.58
Switzerland	2.17	1	0.46
France	16.2	6	0.37
Austria	2.86	1	0.35
Yugoslavia	17.4	2	0.11
Europe (33 countries)	498	284	0.57
Israel	1.92	3	1.56
Algeria	8.05	2	0.25
Japan	166	2	0.01

(prospective) 6-country study (1979–83) (67), using the classification system already used in the retrospective study. The mean risk of local complications and suppurative lymphadenitis was low: 0.387 per 1000 vaccinees or 0.093 per 1000 with positive bacteriological/histological findings, respectively. There were 21 cases of disseminated BCG infections and allergic manifestations recorded in four countries. The estimated risks of serious disseminated BCG infection were higher than calculated previously (except for bone and joint lesions), but very low when comparing the benefit and risks of BCG immunization, especially in infants (67).

Anaphylactic reactions

Allergy to BCG exceptionally occurs when intravesical BCG is used as an immunoenhancing agent. An anaphylactic reaction has been reported (68).

Three cases of anaphylactic reactions to BCG have been described in young children, one (in a 3-month-old girl) being fatal (69).

An acute shock-like syndrome developed 30 minutes after BCG immunization of a newborn girl.

Non-IgE-mediated anaphylactic (anaphylactoid) reactions suspected to be caused by dextran as used in BCG vaccines have been described (SEDA-16, 375).

Disseminated BCG infection

Dissemination of BCG infection occurs in under 0.1/100 000 vaccinees and is usually associated with severe abnormalities of cellular immunity. Data collected on cases immunized between 1948 and 1974 (from the retrospective IUATLD study) are shown in Table 2 (64,66).

Many authors have provided detailed reports of disseminated BCG infection after BCG immunization at birth in newborns with various underlying immunodeficiency syndromes (severe combined immunodeficiencies, cellular immunodeficiency syndromes, X-linked chronic granulomatous disease or autosomal recessive chronic granulomatous disease) (70–72) and include patients with AIDS. 108 cases of disseminated BCG infection reported worldwide since 1951, including 30 cases of disseminated infection during 1974 to 1994 in France, have been analysed (73,74). Four well-defined immunodeficiency conditions predispose to disseminated BCG infection: severe combined immunodeficiency, chronic granulomatous disease, Di George syndrome, and AIDS. About half the cases of disseminated BCG infection occur in the absence of any well-defined underlying immunological defect. However, there is little doubt that children with idiopathic BCG infection are immunodeficient, and there is good evidence

Table 2 Number of complications recorded until December 1977 in a retrospective study of adverse effects of BCG worldwide among cohorts vaccinated during 1948–74

Adverse effect	Patients in 187 countries ($n = 1\,470\,208\,160$)		Patients in 51 countries in which some cases were recorded in any category ($n = 1\,053\,402\,835$)		Cases proven bacteriologically and/or histologically	
	Number	Rate	Number	Rate	Number	Rate
1 Abnormal BCG primary complex[a]	6602	4.49	6602	6.27	1100	1.04
2 and 3. Disseminated BCG infection: generalized and/or localized lesions (non-fatal and fatal)[b]	1072	0.73	1072	1.02	561	0.53
4. Syndromes or disease clinically associated with BCG immunization[c]	1838	1.25	1838	1.74	7	0.01
All categories	9512	6.47	9512	9.04	1668	1.58

[a] Such cases have often been proven bacteriologically and/or histologically.
[b] Until now, such cases have never been proven either bacteriologically or histologically.
[c] For these seven cases, TB lesions were seen at post-mortem examination, but BCG etiology was doubtful.

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that their immunodeficient status is inherited: four pairs of siblings and one pair of cousins were found among 60 children with idiopathic disseminated BCG infection; in addition, among the 50 single-case families, parental consanguinity was found in 7 of 24 families for whom information was available.

There have been reports of disseminated BCG infection in children with chronic granulomatous disease which can result in prolonged and relapsing local complications to BCG immunization (75–77). In a series of autopsies, 26 of 36 children who had been given BCG shortly after birth showed tuberculoid granulomas at various sites. None of the infants had histological evidence of immune deficiency (SEDA-8, 301) (78).

- Recovery from BCG sepsis has been documented in a 7-year-old girl with immunodeficiency (79).
- Two other infants with severe combined immunodeficiency who had developed BCG dissemination after neonatal BCG immunization were treated successfully by bone marrow transplantation and tuberculostatic therapy (80).

However, recovery may not always be complete.

- One girl in her third year, who had been immunized against tuberculosis at birth, developed an abscess of the associated lymph nodes (which were extirpated) and some weeks later developed intestinal BCG dissemination, which appeared to be cured by tuberculostatic treatment. Despite this, at the age of 22 years she developed a left-sided hemiplegia due to aneurysms and thrombosis of cerebral arteries, and 4 years later an oculomotor nerve paralysis was diagnosed. She died at 26 from recurrent intestinal BCG dissemination, which developed at the end of a pregnancy (a healthy premature child was born).

The autopsy confirmed the diagnoses and showed acid-fast bacilli in the adventitia of the basilar artery; the paralysis of the oculomotor nerve was caused by the brain lesion. Defective function of macrophages was suggested as the possible cause of the underlying immunological abnormality (81).

- A 7-week-old infant died under circumstances reminiscent of SIDS; the histopathological examination revealed disseminated BCG infection, no abnormalities of the immune system were detected (82).
- X-ray and CT scan examinations suggested a teratoma in a 1-year-old girl who had received BCG vaccine at birth; however, histology and microbiology revealed the diagnosis of mediastinal BCGitis (83).

Histiocytosis

Cases of fatal histiocytosis have been reported in babies with immune defects immunized with BCG shortly after birth (84).

- One boy who had been immunized shortly after birth developed ipsilateral axillary lymphoma at the age of 6 months. Microscopically the picture was typical of BCG histiocytosis. The child survived. The underlying immunological disturbance was considered to be a temporary derangement of T lymphocyte function (SEDA-8, 300) (85).

Safe immunization with BCG: the WHO view

Taking into account the results of the investigations mentioned above, the WHO made the following recommendations to ensure safe and effective vaccination:

1. Pasteur BCG vaccine should be supplied only to countries using the product without problems. In no case should the vaccine be sent to a country which has been successfully using another product unless the country specifically requests this product.
2. UNICEF supplies of BCG vaccine should specify the doses to be given to infants (0.05 ml), and when possible 0.05 ml syringes should be supplied with the vaccine to reduce the likelihood of too large a dose being given.
3. WHO will supply to country programs a short protocol to assess the incidence of BCG-associated lymphadenitis using a standard case definition. Evidence of a rate greater than 1% would be the basis for investigating the problem and for reviewing the vaccine strain being used.

Additionally it is recommended that training in the technique of BCG immunization should be re-emphasized (44).

Treatment

Erythromycin for a period of 2–4 weeks resolved troublesome post-BCG-lesions in six patients (86). The effect of erythromycin on the atypical mycobacteria was described as early as 1957 (87), but its use for treatment of BCG lesions has not previously been reported. Erythromycin has been used to treat cold abscesses (88).

Neonates with suppurative lymphadenitis have been treated with isoniazid (10 mg/kg/day for 3–9 months) (89). The treatment resulted in complete resolution of the adenitis. There was no significant difference between infants with ruptured nodes and those with intact nodes.

There was no statistical difference between patients who received different forms of treatment for suppurative lymphadenitis: 36 patients received erythromycin, 21 isoniazid, and 21 isoniazid + rifampicin (90). When lymphadenitis developed rapidly (within 2 months), the incidence of spontaneous drainage and suppuration was reported to be significantly higher than in patients with slowly developing processes. Total surgical excision is recommended in these rapidly evolving cases.

Long-Term Effects

Tumorigenicity

The effects of immunization with BCG have been studied extensively (91–94) (SEDA-7, 323) (95,96). On the whole the results are inconclusive, with little good evidence of either preventive or tumor-inducing effects.

Second-Generation Effects

Pregnancy

No harmful effects of BCG vaccine on the fetus have been seen. Nevertheless, it is prudent to avoid immunization of women during pregnancy, unless there is immediate excessive risk of unavoidable exposure to infective tuberculosis (97).

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Susceptibility Factors

Disseminated BCG infection is usually associated with severe abnormalities of immunity. BCG for prevention of tuberculosis should therefore not be given to persons with impaired immune responses, such as occur in congenital immunodeficiency, leukemia, lymphoma, generalized malignancy, or AIDS, and when immunological responses have been suppressed by glucocorticoids, alkylating agents, antimetabolites, or radiation (97). The risks are greater in the debilitated or the very young.

Reports on complications after BCG immunization in HIV-positive individuals and patients with AIDS have been published. Disseminated BCGitis has been described (98–101), for example involving the spleen and mediastinal and mesenteric lymph nodes in one case and the liver and the lung in another case (100) or leading to pneumonitis (102). In one case BCG lymphadenitis occurred 30 years after BCG immunization in a 36-year-old patient with AIDS (103). Surgical excision and biopsy revealed a puriform abscess. Pathological examination established the diagnosis of Kaposi's sarcoma; no granulomatous changes were found. BCG was grown. The authors believe that the BCG lymphadenitis was due to a late reactivation of the bacillus.

BCG reactions in HIV-positive and HIV-negative children have been compared in African children. The rates of local adenitis were equal (104,105). These results have been confirmed by a number of other studies, among them one in Haiti. The Haitian investigators found that the risk of complications after BCG vaccination in HIV-infected children is low and that the risk does not outweigh the benefits of BCG vaccination in populations at high risk of tuberculosis during infancy and childhood. Mild or moderate adverse effects occurred in 19 (9.6%) of 166 infants born to HIV-seronegative mothers as compared with 4 (31%) of 13 HIV-infected infants (106).

Organisms of the *Mycobacterium avium* complex (MAC) commonly cause disseminated bacterial infection among patients with AIDS. There is evidence that immunoprophylaxis against MAC infection may be possible. A heat-killed *Mycobacterium vaccae* vaccine was given in a three-dose schedule to 12 HIV-infected adults with CD4 cell counts below 300×10^6/l (107). The vaccine was well tolerated and produced detectable immunological responses in 3 of 11 subjects who completed the trial.

The WHO has recommended that individuals with clinical (symptomatic) AIDS or other clinical manifestations of HIV-infection should not receive BCG (108). The Global Advisory Committee on Vaccine Safety has noted that there has been repeated reference to local or disseminated BCG infection several years after BCG immunization in HIV-infected persons (109). However, the Committee has not recommended a change in immunization policy (BCG immunization recommended in asymptomatic HIV-infected persons; not recommended in symptomatic HIV-infected persons), but surveillance for BCG-immunized, HIV-infected persons should be continued for 5–7 years.

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Bacitracin

General Information

Bacitracin has mostly dermatological uses. It can cause allergic reactions of the delayed type. A shock-like picture after local application has occurred in a hypersensitive individual (1). Since bacitracin is nephrotoxic, it should not be given intraperitoneally to patients with renal impairment.

Observational studies

In a randomized study of the effects of a triple antibiotic ointment (polymyxin B + bacitracin + neomycin) and simple gauze-type dressings on scarring of dermabrasion wounds, the ointment was superior to the simple dressing in minimizing scarring; the beneficial effect on pigmentary changes was especially pronounced (2).

Organs and Systems

Sensory systems

Inadvertent injection of bacitracin ointment into the orbit can cause a postoperative orbital compartment syndrome.

- Acute proptosis, chemosis, reduced vision, and ophthalmoplegia occurred after endoscopic sinus surgery in a 73-year-old woman (3). The orbit was tense and the intraocular pressure was 54 mmHg. The presence of bacitracin ointment was established by computed tomography.

Immunologic

Bacitracin is one of the most important clinical allergens (4). Anaphylaxis rarely occurs after topical administration of bacitracin ointment (5,6).

- A 45-year-old man developed a near-fatal anaphylactic reaction after he applied bacitracin ointment to an excoriated area on his foot. He had had a similar, but less severe, episode 4 years earlier. IgE antibodies to bacitracin were positive.
- A 24-year-old man injured in a motorcycle accident was treated with viscous lidocaine and bacitracin zinc ointment for extensive abrasions on the extremities. Five minutes later, he developed symptoms of severe anaphylaxis and required adrenaline, antihistamines, intravenous fluids, and glucocorticoids. Two weeks later, only the prick test to bacitracin zinc ointment was positive.

Anaphylaxis has also been reported after bacitracin nasal packing (7).

- A 48-year-old man underwent uneventful septorhinoplasty, after which his right nostril was packed with 6 ft of vaseline gauze placed in the finger of a latex glove coated with bacitracin ointment. Within seconds, his oxygen saturation fell from 97 to 94% (and increased to 97% with 100% oxygen), but blood pressure and heart rate were unchanged. After the left nostril had been packed, his oxygen saturation fell to 89%, no pulse wave was registered and an electrocardiogram showed a

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heart rate of 39/minute with first-degree atrioventricular block, and the blood pressure was not obtainable by non-invasive measurement. Cardiopulmonary resuscitation was successful, but the patient remained intubated for 2 days because of concerns about facial and upper airway edema. Later he gave a history of an episode of irritation and swelling after nasal application of polymyxin B and bacitracin ointment 2–3 weeks before surgery. Skin prick testing was positive for bacitracin but negative for latex, polymyxin, cefazolin, and saline.

Cases of anaphylaxis have also been reported after bacitracin irrigation (8,9).

- A 65-year-old man undergoing elective sternal debridement and rewiring was given a prophylactic infusion of vancomycin 1 g preoperatively. Anesthesia was induced with thiopental, suxamethonium, and fentanyl, and maintained with fentanyl, vecuronium, and isoflurane. A few minutes after wound irrigation with bacitracin (about 25 U/ml), his blood pressure fell precipitously, necessitating intravenous fluids and adrenaline. His face and arms were flushed. Afterwards, he reported having had a rash several years before after the use of an over-the-counter ointment composed of polymyxin B, bacitracin, and neomycin.
- A 9-year-old child with a repaired myelomeningocele and congenital hydrocephalus who had undergone four previous shunt revisions in the past had two episodes of anaphylaxis during insertion of the ventriculoperitoneal shunt. The shunt tubing had been soaked in a solution of bacitracin 2500 U/ml. A skin prick test was positive for bacitracin.

Thiomersal, a mercury derivative of thiosalicylic acid, is a preservative used in several types of consumer products, including cosmetics, ophthalmic and otolaryngological medications, and vaccines. In a retrospective study in 574 patients, people who were allergic to thiomersal were more likely to be allergic to bacitracin (10).

Long-Term Effects

Drug resistance

Although there is evidence of acquired resistance to bacitracin in enterococci and staphylococci isolated from animals (11), a review found no evidence that the prevalence of such resistance has increased over time or in relation to the use of bacitracin in man or in animals (in which bacitracin is used as a growth promoter) (12).

Drug Administration

Drug contamination

Commercial bacitracin comprises more than 30 different substances, but the major antibiotic isoforms A and B account for about 60% of the mixture. An impurity has been identified in some but not all bacitracin lots (13). The impurity is a powerful subtilisin-type protease capable of cleaving many proteins, including protein disulfide isomerase, myosin, and a variety of artificial substrates. Investigators using bacitracin are therefore reminded to determine whether their bacitracin is contaminated by a protease. If it is, careful reinterpretation of the results or retesting with an enzyme-free bacitracin reagent may be warranted.

Interference with Diagnostic Tests

Semen detection

In forensic medicine, the detection of semen may be critical, and identification due to Wood's lamp-induced fluorescence has been suggested to be helpful. In a study to investigate whether semen can be distinguished from other products, none of 41 physicians was able to differentiate semen from other products using a Wood's lamp; however, some ointments and creams that contained bacitracin were mistaken for semen (14).

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Baclofen

General Information

Baclofen is a chlorophenyl derivative of gamma-aminobutyric acid (GABA), a naturally occurring inhibitory neurotransmitter in the brain and spinal cord. It is of proven therapeutic value in reducing the severity of flexor or extensor spasms resulting from spinal cord injury or disease. The recommended oral dose is 5 mg tds, which can be carefully increased; however, the total daily dose should not exceed 80 mg (20 mg qds). It is also used for the treatment of intractable hiccups, especially in patients with uremia.

The most commonly reported adverse effects are drowsiness, dizziness, fatigue, confusion, hypotension, and nausea.

Organs and Systems

Nervous system

Altered consciousness is a major adverse effect of baclofen, because of its GABA-mimetic effects. While this reflects global nervous system depression, other adverse effects, such as seizures and dyskinesias, are probably better explained by selective effects on different brain areas. A case of akinetic mutism associated with baclofen might be an example of this (1).

- A 76-year-old man with a history of cognitive decline of unknown origin had severe contractures with increasing pain in his legs. He was given baclofen 10 mg tds, and 2 days later had difficulty following commands. Another 2 days later he could not speak and would not follow commands, although he was alert with his eyes open. He had no spontaneous movements, but would withdraw to painful stimuli. The electroencephalogram showed intermittent, bilateral, symmetrical, sharp waves. Computed tomography and laboratory tests showed no specific abnormalities. Baclofen was withdrawn and he improved over the next 4 days, after which there was no difference to his prebaclofen condition.

The authors explained that akinetic mutism occurs when bilateral frontal lobe or diencephalic–mesencephalic dysfunction interrupts the limbic circuitry. As symptoms were observed immediately after the start of treatment and resolved completely after withdrawal, the condition was probably caused by baclofen. It is not known why baclofen in this case impaired neuronal activity specifically in these areas. The authors found only one previous report describing the case of a 57-year-old woman with end-stage renal insufficiency, who developed akinetic mutism after a single dose of baclofen (2). In this case, the symptoms resolved after dialysis. Therefore, adverse effects of baclofen should be suspected if neuropsychiatric symptoms occur after baclofen treatment has been started. Electroencephalography and computerized tomography may be necessary to exclude other causes.

Because the systemic effects of baclofen can cause a reduced level of consciousness, intrathecal administration via a catheter is widely used to avoid systemic effects. However, because a continuous infusion is required, implantable pumps containing a very concentrated solution of baclofen are used to avoid frequent refills. Inadvertent subarachnoid bolus administration of a concentrated solution will produce cranial spread of baclofen within the CSF, resulting in cerebral effects. This is most likely to occur when a new catheter or pump is implanted or during surgical revision of a catheter or implantable pump in cases of malfunction. A report of coma after implantation of a baclofen pump in five out of nine consecutive children illustrates this (3). The authors suggested that these children should be monitored in the recovery room for 5 hours postoperatively, in order to cover both the peak effect of any baclofen bolus and the additive effects of other perioperative CNS suppressants, such as opioids, benzodiazepines, or sedative antiemetics. In another report of transient coma after perioperative intrathecal bolus administration it was shown that the management of this complication can require admission to an intensive care unit (4).

Impairment of speech, memory, and mental acuity, associated with an abnormal electroencephalogram, has been described in a young patient taking normal doses (20 mg bd); gradual withdrawal restored the patient and electroencephalogram to normal (SEDA-12, 119) (5). Abnormal electroencephalographic changes have also been reported in a patient with deteriorating multiple sclerosis who developed encephalopathy 48 hours after starting baclofen in low dosage (10 mg tds), but this patient also had renal impairment; withdrawal led to reversal of symptoms in this case (6).

Epilepsy, progressing to status epilepticus, has been ascribed to baclofen (80 mg/day); the fits stopped on gradual withdrawal of the baclofen (7). In contrast to other reports, this patient had no history of seizures.

An elderly patient with a 4-year history of Alzheimer's disease developed chorea 2 weeks after starting a trial of baclofen (SEDA-16, 23). The dosage had been gradually increased to 15 mg tds. The chorea resolved within 24 hours after the baclofen was withdrawn. The authors suggested that the chorea might have resulted from the combination of the GABA-agonist drug and deficient cholinergic function in Alzheimer's disease.

A case of aseptic meningitis after intrathecal administration of baclofen has been reported but, as viral causes could not be ruled out, the causative role of baclofen was unclear (8).

Psychological, psychiatric

Euphoria or depression can occur, and mania has been reported in a patient with schizophrenia (9).

Gastrointestinal

A possible effect of intrathecal baclofen on intestinal motility has been proposed (10). Triggered by two cases of paralytic ileus in patients receiving continuous intrathecal baclofen, the authors reviewed the case notes of 14 patients and summed the days without bowel movements before and after intrathecal baclofen therapy. Intestinal function deteriorated in 10 patients, was unchanged in one, and improved in three. They therefore

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advised that intestinal activity should be closely observed in patients receiving intrathecal baclofen. However, they felt that treatment could be continued, even in particularly sensitive patients, if prokinetic, laxative, or eubiotic drugs were used to promote peristaltic function.

Liver

Rarely, deterioration in liver function tests (increases in aspartate transaminase and alkaline phosphatase) can occur (SEDA-6, 132).

Musculoskeletal

With regard to its effects on spinal GABA receptors, intrathecal baclofen has been compared with intrathecal fentanyl for postoperative pain treatment in six children (mean age 4.2 years) with cerebral palsy undergoing bilateral dorsal rhizotomy (11). Both intrathecal baclofen and intrathecal fentanyl reduced postoperative pain. However, three of five children had severe muscle weakness after intrathecal baclofen 1–1.5 μg/kg, which prompted the authors to discontinue their study. An accompanying editorial dealt with the possible mechanisms of action of spinal GABA agonists on postoperative pain, suggesting that the effects on sensory processing probably cannot be separated from the changes in motor function (12). Therefore, this report of muscle weakness should not prompt us to close the file on intrathecal baclofen for pain treatment. More experience is needed and different dose regimens should be tested.

Sexual function

Intrathecal baclofen caused a reduction in erection rigidity and duration in eight of nine men. When ejaculation was possible before the start of baclofen treatment it disappeared or was more difficult to obtain during treatment. These effects resolved after withdrawal of baclofen (13).

Body temperature

Febrile reactions after intrathecal baclofen stopped a patient from receiving this treatment for spinal spasticity (14).

- A 33-year-old woman with spasticity caused by a myelopathy after numerous operations on her spine received a single bolus dose of baclofen 50 μg via a lumbar puncture, which resulted in complete resolution of her spasticity for almost 24 hours. However, her temperature increased to 39.0°C within 2 hours after the injection, and she had flu-like symptoms. Influenza was assumed to be the most likely explanation, as a child in her house had influenza at that time. Subsequently, an intrathecal catheter was placed and a baclofen pump implanted. However, her temperature rose again after baclofen administration had been started and the pump was halted. Subsequently, several attempts were made to restart the infusion, followed each time by spikes of fever. In the end, continuous intrathecal baclofen therapy had to be abandoned, and the fever did not recur. Several investigations to identify other causes of fever were mostly negative. However, based on bilateral hilar adenopathy on the chest X-ray and increased concentrations of angiotensin-converting enzyme, sarcoidosis was suspected.

The authors claimed that this was the first report of this problem. Referring to the observation that baclofen injection into the cerebral ventricles can produce fever in rats (15), they assumed that rostral spread of baclofen could have initiated a thermoregulatory response via the chemotrigger zone in the third ventricle. They suggested that a percutaneous subarachnoid catheter could facilitate the decision to either proceed with or abort surgical catheter or pump implantation when baclofen is associated with fever.

Long-Term Effects

Drug tolerance

Tolerance to intrathecal baclofen developed in three of 23 patients with spinal spasticity (16).

Drug withdrawal

Like many other agents that act at the GABA receptor, abrupt termination of long-term administration of baclofen can result in withdrawal symptoms, even after intrathecal administration (17,18). Patients can present with different symptoms, not all of which would be considered classical of drug withdrawal.

Clinical presentation

Common presenting features are muscular hyperactivity, hyperthermia, metabolic derangements, and rhabdomyolysis when baclofen therapy is abruptly discontinued, and several deaths have occurred (19). Clinicians should be suspicious of baclofen withdrawal if patients taking baclofen present with fever, muscle cramps, and hypotension. A case of brain death due to baclofen withdrawal with severe hypotension and hyperthermia up to 43°C has underscored the need for immediate and aggressive treatment (20).

Sudden withdrawal can cause hallucinations and grand mal convulsions or worsening of pre-existing epilepsy (SED-9, 206) (21,22).

There is a similarity between baclofen withdrawal and the neuroleptic malignant syndrome.

- A 36-year-old man with paraplegia after a spinal cord injury became disoriented (23). He had marked rigidity in both arms and legs, he was sweating and pyrexial (38°C), and his heart rate was 112/minute. His serum creatine kinase was raised at 2668 U/l and rose to 2982 U/l on day 3. At that time, baclofen was restarted. Within 3 days he was fully oriented. Over 2 weeks his creatine kinase activity gradually fell to normal and his temperature settled. It turned out that he had neglected to take any medication for several days before admission.

The authors believed that symptoms in this case resembled the neuroleptic malignant syndrome, based on the combination of muscle rigidity, pyrexia, signs of autonomic disturbance, and altered consciousness. They did not think that the raised serum creatine kinase activity was associated with rhabdomyolysis,

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stating that there was no evidence from urinalysis to suggest this. Unfortunately, they did not specify whether there was myoglobin in the urine or not. Creatine kinase activities up to 40 000 U/l have been noted during baclofen withdrawal (24), compared with which creatine kinase activity in this case was much lower, suggesting only moderate muscle damage. One might assume that muscle damage after baclofen withdrawal correlates with the duration and intensity of muscular hyperactivity. In addition, prolonged muscular hyperactivity may be expected to be followed by an increase in both body temperature and heart rate, owing to hypermetabolism and sympathetic activation. Sweating will result from sympathetic activation and a thermoregulatory response to hyperthermia and is not necessarily an autonomic disturbance. Disorientation is also an expected symptom of baclofen withdrawal. In conclusion, this patient's combination of symptoms could have been explained by baclofen withdrawal alone. Assuming that disturbances in central dopaminergic systems could have been involved, as in neuroleptic malignant syndrome, is speculative.

This is not the first report of similarities between the neuroleptic malignant syndrome and baclofen withdrawal (18,20,24). In addition, hyperthermia seems to be common in baclofen withdrawal (20).

- A 14-year-old child receiving continuous intrathecal baclofen treatment developed a fever of up to 40°C and painful muscle spasms, attributed to baclofen withdrawal due to failure of the intrathecal catheter. The symptoms resolved promptly after reintroduction of intrathecal baclofen (25).

If intrathecal baclofen has to be interrupted or cannot be restarted immediately, enteral baclofen should be given. However, finding the appropriate dose for this can be difficult and close observation of the patient is required, as illustrated in the following report (26).

- A 34-year-old man who was receiving continuous intrathecal baclofen (700 micrograms/day) for muscle spasticity after a spinal cord injury developed a fever, and infection of the implanted baclofen pump was suspected. The device was removed and he was given replacement therapy with oral baclofen (40 mg tds). He developed a tremor 12 hours after pump removal and his heart rate increased to 120/minute. Another 12 hours later he was somnolent, agitated, and confused, and had visual hallucinations. His blood pressure rose to 198/108 mmHg and his temperature to 40°C. This was followed by atrial fibrillation with a ventricular rate of 170/minute. The dose of oral baclofen was increased to 80 mg tds and he was given intravenous lorazepam 6–8 mg every 4 hours. During the following 24 hours his blood pressure, pulse, and temperature normalized and he recovered fully.

Management

Baclofen should always be withdrawn gradually. If a patient stops taking baclofen, a blood sample for baclofen serum concentration measurement should be taken if possible, to confirm the diagnosis post hoc if hyperthermia occurs. If a patient taking long-term baclofen presents with similar symptoms, baclofen withdrawal should be considered. If this is not effective and the patient deteriorates, with hyperthermia, increasing creatine kinase activity, and metabolic sequelae, dantrolene can be given.

Dantrolene is life-saving in malignant hyperthermia associated with volatile anesthetics and suxamethonium and is also the drug of choice for the treatment of neuroleptic malignant syndrome. Dantrolene has therefore been suggested as an additional therapeutic option in baclofen withdrawal (18), but there is only limited experience (24). In one case of baclofen withdrawal, dantrolene was given with success (24).

It should be stressed that baclofen withdrawal is a potentially fatal emergency. Because of the risk of rhabdomyolysis, disseminated intravascular coagulation, acute renal insufficiency, and other organ complications, patients should be transferred to the intensive care unit and given parenteral baclofen.

Since it has been hypothesized that the baclofen withdrawal syndrome might have similarities with the serotonin syndrome caused by overdose of serotonin reuptake inhibitors or amphetamines, the serotonin receptor antagonist cyproheptadine has been used in combination with oral baclofen and a benzodiazepine in four patients with baclofen withdrawal syndrome after continuous intrathecal baclofen therapy (27). The authors claimed that their patients improved significantly when cyproheptadine was given. Body temperature fell by at least 1.5°C and heart rate fell from 120–140/minute to under 100/minute. Muscular tone and myoclonus improved. Two patients also reported that itching was less intense. All this was felt to be temporarily related to the repeated administration of cyproheptadine. The authors concluded that cyproheptadine was a useful adjunct for the treatment of baclofen withdrawal syndrome. However, one of their patients suffered severe brain damage during withdrawal and subsequently died of pulmonary complications. This illustrates that early intensive care is required.

Second-Generation Effects

Fetotoxicity

Convulsions have been attributed to withdrawal of baclofen after in utero exposure (28).

- A 7-day-old baby was admitted to hospital with generalized convulsions, which did not respond to phenobarbital, phenytoin, clonazepam, lidocaine, or pyridoxine. A variety of investigations all gave negative results. Electroencephalography 4 days later showed prolonged episodes of epileptic activity. At that time baclofen withdrawal was suspected, as the paraplegic mother had been taking baclofen 20 mg tds throughout pregnancy. The baby was given baclofen 0.25 mg/kg qds and 30 minutes after the first dose the convulsions stopped. The baclofen was then slowly withdrawn over 2 weeks. An MRI scan of the brain on day 17 suggested a hypoxic ischemic insult in the perinatal period, which was considered to have been secondary to convulsions.

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As convincingly presented by the authors, baclofen withdrawal was the most likely explanation for the convulsions. In discussing the possible mechanisms of the delayed onset of convulsions the authors assumed that a secondary increase in baclofen serum concentration due to redistribution might have prevented earlier onset of the withdrawal symptoms. This is of course speculative; nothing is known about baclofen pharmacokinetics in neonates. On the other hand, the authors stated that the mother had noted some abnormal movements starting on the second day postpartum, which might have represented the first signs of withdrawal. The half-life of baclofen in adults is 3–6 hours, and adults usually become symptomatic 24–72 hours after baclofen is reduced or withdrawn (20). In conclusion, baclofen withdrawal should be suspected if postnatal convulsions occur after intrauterine exposure. The first priority in such a case is to rule out other causes, such as infections, electrolyte disturbances, and intracranial pathology, and to prevent secondary brain damage due to prolonged convulsions. Baclofen should probably be considered at an early stage, as it might be the most effective anticonvulsant in such cases.

Susceptibility Factors

Renal disease

As 70% of baclofen is excreted unchanged in the urine (29), accumulation and overdosage of baclofen can occur in patients with end-stage renal disease. Confusion, drowsiness, and coma after standard doses have been reported (30). In addition, abdominal pain was a common adverse effect of baclofen in patients with severe renal insufficiency (31). Toxic reactions characterized by a psychotic syndrome and myoclonus have also been reported (32). Patients with severely impaired renal function typically present with altered consciousness after very small doses of baclofen (31). Symptoms of overdose may resolve after hemodialysis (30,31).

- An 82-year-old man with left ventricular dysfunction and gout had worsening renal function (33). He was taking lisinopril, furosemide, naproxen, allopurinol, and baclofen 20 mg tds. As no reason could be found for the use of baclofen the dose was halved and then stopped 10 days later. The next day he had visual hallucinations, confusion, and agitation, and required sedation with diazepam. He was afebrile, with normal inflammatory markers, and a CT scan of the brain showed only cerebral atrophy. Baclofen was reintroduced, with complete resolution of neuropsychiatric symptoms within 48 hours.

Other features of the patient

Generally, patients with a history of seizures, convulsive disorders, or psychiatric disturbances, and also elderly patients with cerebrovascular disease, should be regarded as patients at risk of developing the more serious side effects (SED-9, 206).

Drug Administration

Drug administration route

Intrathecal baclofen is becoming increasingly popular for the treatment of severe spasticity in an attempt to reduce the incidence and severity of systemic adverse effects. However, hypotonia, respiratory depression, and coma can occur. Severe arterial hypotension also has been observed in two of 23 patients (16). Occasionally, nervous system suppression can be severe enough to require mechanical ventilation. Adverse effects have been seen not only with high doses (2000 micrograms/day produced flaccid quadriplegia with total areflexia) (SEDA-12, 119) (34), but also after a single bolus dose of 80 micrograms in a patient known to be very sensitive to the action of baclofen (SEDA-15, 128) (35).

Drugs injected directly into the cerebrospinal fluid have a tendency to produce unpredictable effects, their spread being influenced not only by the volume administered, but also by the concentration of the drug, its specific gravity in relation to that of cerebrospinal fluid, the positioning of the patient (head-up or head-down), and on the speed of injection of bolus doses. Truncal muscle spasms can also increase the spread of drug within the cerebrospinal fluid. All these parameters need to be taken into consideration. Standardization is required as a first step. Rapid bolus injection in particular can produce unexpectedly severe adverse effects.

Drug overdose

Overdose, which may be absolute or relative (due to impaired renal excretion or in elderly patients who develop adverse effects at lower dosages), leads to severe hypotonia, mental confusion and somnolence, respiratory depression, and eventually apnea, bradycardia, cardiac conduction abnormalities, hypotension, and coma. Convulsions can occur and hypertension has been reported. It is possible that during recovery the picture may be complicated by an acute withdrawal syndrome, with agitation, psychosis, tremor and dystonic movements, convulsions, and hallucinations (SEDA-11, 126) (36–40).

Physostigmine is rapidly effective in reversing not only the respiratory depression but also the coma and hypotonia seen in cases of intrathecal baclofen overdosage (SEDA-15, 128) (35). The doses recommended for physostigmine salicylate are 1–2 mg intravenously over 5–10 minutes, which may have to be repeated after 30–40 minutes, as the action of physostigmine is fairly short. However, physostigmine may be ineffective when large doses of baclofen are involved (41), and it also has adverse effects of its own, so that the above dosage guidelines should not be exceeded. In particular, bradycardia and cardiac conduction defects can be worsened (cardiac arrest has been reported in connection with baclofen) and it should not be used in these circumstances, respiratory support and symptomatic treatment being recommended (42).

Phaclofen is a more specific baclofen antagonist (43), but more research is required to ascertain if it can be safely used in the treatment of baclofen overdose.

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Drug–Drug Interactions

Tricyclic antidepressants

Tricyclic antidepressants can potentiate the muscle relaxant effects of baclofen, resulting in severe hypotonic weakness (44); the combination has also been incriminated in the causation of short-term memory impairment (SEDA-11, 127) (45).

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Bambuterol

See also Beta$_2$-adrenoceptor agonists

General Information

The efficacy of long-acting beta$_2$-adrenoceptor agonists in patients with chronic obstructive pulmonary disease remains unclear, but their role in treatment regimens, particularly in comparison with oral theophylline, has been reviewed (1).

Bambuterol is a beta$_2$-adrenoceptor agonist, a biscarbamate ester prodrug of terbutaline (SEDA-18, 188) (SEDA-22, 188). It is available as the hydrochloride salt in 10 and 20 mg tablets. It escapes first-pass elimination and is concentrated in lung tissue after absorption from the gastrointestinal tract. It is hydrolysed to terbutaline primarily by an enzyme, butyrylcholinesterase, found in lung tissue. Terbutaline is therefore formed preferentially in the lung, and as a result bambuterol should have a more selective effect than terbutaline. The effect of bambuterol lasts for 24 hours. Peak plasma concentrations of terbutaline occur 4–7 hours after the administration of bambuterol. Maximum therapeutic benefit occurs 1 week after starting treatment.

Except for suppression of plasma butyrylcholinesterase, the adverse effects of bambuterol are those of a beta$_2$-adrenoceptor agonist and are related to the plasma concentration of terbutaline. Plasma butyrylcholinesterase returns to control values about 2 weeks after stopping treatment (SEDA-22, 188).

Placebo-controlled studies

Oral bambuterol 20 mg at night has been compared with inhaled salmeterol 50 μg bd for persistent nocturnal symptoms in 117 asthmatics already taking inhaled corticosteroids in a randomized, double-blind, placebo-controlled trial for 6 weeks (2). The treatments resulted in significant and equivalent improvements in nocturnal and daytime asthma symptoms, peak flow, and the use of short-acting beta-adrenoceptor agonists. Drug-related adverse events included headache (six with bambuterol, two with salmeterol), tremor (three in each group), cramps (two with bambuterol), and palpitation (three with bambuterol, one with salmeterol). Four patients taking bambuterol withdrew owing to possible drug-related adverse effects (insomnia, headache, flushing, and mental excitation) compared with one patient taking salmeterol (tremor). Bambuterol appears to be a safe and effective alternative to inhaled long-acting beta$_2$-adrenoceptor agonists for poorly controlled nocturnal symptoms in asthma.

Comparative studies

The comparative safety and efficacy of oral bambuterol given once daily and oral terbutaline given three times daily in children with asthma aged 2–12 years has recently been reported in two large similar trials from the same research group. In the first study they reported results from 3 months of treatment in 155 children aged 2–6 years (3); in the second study they reported results from 12 months of treatment in 130 children aged 2–12 years (4). Both were double-blind studies with a 2:1 bambuterol:terbutaline randomization pattern. In both studies, the bambuterol and terbutaline regimens were similarly efficacious in reducing asthma symptoms and improving peak expiratory flow rate. In the 3-month study, the most commonly reported adverse event was restlessness, reported in over 85% of patients in both treatment groups; other adverse events were described as mild to moderate, and overall there was no difference in the safety profile of the two drugs. In the 12-month trial, one subject in each treatment group withdrew because of an adverse event (urticaria and dermatitis). The most commonly reported adverse events attributable to the drugs were headache and tremor, which respectively occurred in 9 and 0% with terbutaline and 6 and 2% with bambuterol. Other adverse events were not described in detail. It seems that oral bambuterol has an efficacy and safety profile similar to that of oral terbutaline, with the advantage of once-daily dosing. The caveat is that inhaled therapy has fewer systemic adverse effects and is the route of choice.

Bambuterol once a day and modified-release salbutamol bd both produced a significant reduction in the severity of nocturnal asthma, but bambuterol caused significantly less tremor (5).

Organs and Systems

Cardiovascular

A retrospective study of prescriptions from three cohort studies suggested a possible adverse effect of oral bambuterol: cardiac failure. A cohort of 12 294 patients who received at least one prescription for nedocromil acted as the control group and was compared with 15 407 patients given inhaled salmeterol and 8098 patients given oral bambuterol. Questionnaires were sent to each prescriber asking for details of significant medical events after the first prescription (prescription event monitoring). From this information, rates and relative risks of non-fatal cardiac failure and ischemic heart disease were calculated. The age- and sex-adjusted relative risk of non-fatal cardiac failure associated with bambuterol was 3.41 (CI = 1.99, 5.86) compared with nedocromil. When salmeterol was compared with nedocromil the relative risk for developing non-fatal cardiac failure was 1.1 (CI = 0.63, 1.91). The adjusted relative risks of non-fatal ischemic

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heart disease with bambuterol and salmeterol compared with nedocromil were 1.23 (CI = 0.73, 2.08) and 1.07 (CI = 0.69, 1.66) respectively. In the month after the first prescription, the relative risk of non-fatal ischemic heart disease was 3.95 (CI = 1.38, 11.31), when bambuterol was compared with nedocromil. The authors concluded that care should be exercised when prescribing long-acting oral beta$_2$-adrenoceptor agonists for patients at risk of cardiac failure.

This study at best generates the hypothesis that the oral use of a particular beta$_2$-agonist is linked to an increased risk of cardiac disease. However, the study had several flaws. The three cohorts of patients were not strictly comparable: they were not treated concurrently nor were they sufficiently matched for age and diagnosis before prescription of the study drugs. It took nearly 3 years to recruit the patients, who preferred or needed an oral agent. A smaller proportion of patients in this cohort were treated for "asthmatic wheeze"—57 versus 70% in the salmeterol cohort. More of the bambuterol patients were given the drug for other indications, such as dyspnea, bronchitis, cough, chest infection, emphysema, and bronchitis—15 versus 2.8%. The salmeterol cohort consisted mostly of patients who were changing to a longer-acting agent and those using nedocromil were mostly changing from cromoglicate. The bambuterol group was more heterogeneous. Some patients with impending or undiagnosed heart failure may have presented with dyspnea, cough, or wheeze and received bambuterol. During the first month the correct diagnosis would become evident.

A review of the preclinical studies, clinical studies, and postmarketing surveillance data has given no support to the proposed association between bambuterol and cardiac failure. The UK Committee on Safety of Medicines has received no spontaneous reports of cardiac failure due to bambuterol. Data from the WHO database, INTDIS, show no reports of cardiac failure with bambuterol, in contrast to ten reports for salmeterol.

So, there is no evidence that oral beta$_2$-adrenoceptor agonists cause cardiac failure. The epidemiological study proposing the link is inadequate, and the authors themselves have emphasized the need for prospective, randomized trials.

Drug–Drug Interactions

Mivacurium

Bambuterol has been reported to alter the metabolism of mivacurium (6). Bambuterol has a dose-dependent inhibitory effect on plasma cholinesterase activity and prolongs the effects of suxamethonium. Bambuterol 10 mg was given to 28 patients 2 hours before an elective operation requiring general anesthesia. The study was originally designed as a randomized, blinded trial, but was converted to an open study. The patients given bambuterol had a 67–97% fall in plasma cholinesterase activity, leading to reduced clearance of mivacurium. This resulted in a shorter onset and a 3- to 4-fold prolongation of action of the neuromuscular blockade produced by standard doses of mivacurium.

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Barium sulfate

General Information

Oral barium sulfate is theoretically non-toxic, but constipation and abdominal pain are not uncommon after barium meals or barium enemas (1). The main risk is that collections of barium will remain in the colon; they can persist for 6 weeks or longer in elderly patients or cases of colonic obstruction; barium fecoliths may even have to be removed surgically. Prolonged stasis of barium can occur after a barium enema into the distal loop of a colostomy. Residues in the appendix have caused appendicitis. Toxic dilatation of the colon can be aggravated by barium sulfate.

Organs and Systems

Cardiovascular

Electrocardiographic changes have been recorded during administration of barium enemas and could represent a hazard in cases of cardiac disease (2–4).

Respiratory

Aspiration of barium sulfate into the lungs during barium meal examination can cause significant respiratory embarrassment, particularly in patients with poor respiratory function. It is recommended that water-soluble low-osmolar contrast media, which are less harmful, should be

used instead of barium if there is a possibility of aspiration during examination of the upper gastrointestinal tract.

Aspiration of barium sulfate can cause obstruction of the small air passages, compromising respiratory function, and can cause inflammation in the bronchial tree and lung parenchyma (5).

- A 68-year-old woman, with a history of alcohol abuse and a leiomyoma of the stomach, aspirated barium sulfate and became dyspneic and developed hypoxia (PaO_2 46 mmHg). At bronchoscopy the bronchial mucosa was coated with barium and a chest X-ray showed heavy alveolar deposition of barium sulfate distributed over the entire lung, with some predominance in the lower zones. The patient developed a fever (39°C) and a leukocytosis (12×10^9/l) the day after aspiration. She was given cefotiam 2000 mg and metronidazole 500 mg intravenously every 8 hours. The fever resolved within 2 days and *Staphylococcus aureus* was cultured from the bronchial fluid. She was discharged 2 days later, but the chest X-ray continued to show persistent alveolar deposition of the barium sulfate with only a slight improvement compared with the initial X-ray.
- A 60-year-old man with carcinoma of the hypopharynx aspirated barium into both lower lobes. He became hypoxic (PaO_2 64 mmHg) and barium was extracted at bronchoscopy. He was given prophylactic antibiotics (cefotiam 2000 mg and metronidazole 500 mg intravenously every 8 hours for 4 days). A chest X-ray 6 days later showed residual barium deposition in the lower lobes. No further respiratory complications occurred.

The authors recommended that bronchoscopy should be performed early after aspiration to extract barium from the bronchial tree, and that prophylactic antibiotic therapy is important to prevent lung infection.

Gastrointestinal

Perforation

After a barium enema, perforation occurs rarely in children and debilitated adults or when the colon is already weakened by inflammatory, malignant, or parasitic diseases. Perforation can be triggered by manipulations involved in giving the barium enema or can result from hydrostatic pressure. In one case, perforation followed air contrast insufflation for barium enema in a patient in whom the sigmoid colon became trapped in an inguinal hernia.

At least 12 cases of perforation of the colon by barium enema, with four deaths, were reported in a series of publications (SED-12, 1165) (6–8). The incidence of perforation was about 1 in 6000 examinations. Even sterile barium sulfate can cause marked peritoneal irritation, with considerable fluid loss into the peritoneal cavity, but in practice it is usually a mixture of barium and feces that escapes and this, not surprisingly, produces severe peritonitis and dense adhesions. Mortality has been reported to be 58% with conservative treatment, and as high as 47% with surgical intervention (9). Early operation is indicated, and large volumes of intravenous fluids improve the prognosis. Patients who recover can develop fibrogranulomatous reactions and adhesions, which can lead to bowel obstruction or ureteric occlusion.

Perforation can occur elsewhere than in the colon; in one case a duodenal ulcer was apparently made to perforate. In both this and another case of perforation of a sigmoid diverticulum the complication was not immediately recognized, the duodenal perforation only being detected 5 days after administration of the barium meal (SEDA-17, 535).

In air-contrast examinations, colonic perforation can actually precede the administration of the barium enema itself. In such cases it is due to the preparatory insufflation of air if this is conducted with excessive enthusiasm in a high-risk patient (for example an elderly patient with a hitherto unrecognized epigastric hernia) (10).

Extraperitoneal perforation and leakage of barium may cause few immediate symptoms, but delayed endotoxic shock can develop some 12 hours later, often causing death. Bowel infarction can also result. Barium granulomata can occur, causing painful masses, rectal strictures, or ulcers. On proctoscopy, an ulcer with a whitish base can mimic a carcinoma. In one rare case, perforation of a barium enema into a sigmoid abscess was followed by intravasation into the portal venous system (11).

Baroliths

Baroliths are rare complications of barium contrast examinations and are usually seen in colonic diverticula. They are often asymptomatic but may be associated with abdominal pain, appendicitis, and bowel obstruction or perforation. A case of ileal obstruction by a barolith has been reported (12)

- An 83-year-old woman developed postprandial abdominal pain. Physical examination and laboratory tests were normal. She underwent gastroscopy, abdominal ultrasound, small bowel barium meal, and a double-contrast barium enema, all of which were normal, although a moderate amount of barium refluxed into the small bowel during the double-contrast examination. She continued to have postprandial abdominal pain and weight loss. A repeat abdominal X-ray 6 months after the barium enema showed an unremarkable bowel gas pattern without evidence of obstruction. However, there was a 4.5 cm triangular radio-opaque structure in the right lower quadrant, consistent with retained barium, possibly in a diverticulum. A small bowel barium meal showed that the retained barium was intraluminal within a loop of ileum. At laparotomy, a hardened short segment of ileum was resected and histology showed an intraluminal barolith adjacent to a carcinoid tumor.

In this case, narrowing of a loop of ileum secondary to a carcinoid tumor caused interference with the flow of barium and caused the development of a barolith.

Immunologic

Hypersensitivity reactions to products used during barium meal examinations are extremely rare. Barium sulfate is generally regarded as an inert and insoluble compound that is neither absorbed nor metabolized and is eliminated

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unchanged from the body. However, some studies have shown that very small amounts of barium sulfate can be absorbed from the gastrointestinal tract. Plasma and urine barium concentrations can be increased after oral barium sulfate. In addition, there are many additives in commercially prepared barium products, some of which can cause immune responses. A patient with a history of a severe reaction to barium agents should not receive barium products again (SEDA-22, 503).

Reactions to other constituents of barium sulfate enemas have been recognized (SEDA-18, 441) and could be as common as one in 1000. They vary from urticarial rashes to severe anaphylactic reactions, and can be particularly severe in patients with asthma (13). Hypersensitivity to the latex balloon catheter used in double contrast barium enemas appears to be a common mechanism (14), but hypersensitivity to glucagon, to the preservative methylparabens, or to other additives seems to be responsible in some cases. Insofar as the latex balloon is concerned, thorough washing will remove the allergen responsible for the reaction (15).

Infection risk

Transient bacteremia was recorded in 11.4% of a series of 175 patients who had undergone barium enema examination; it appeared almost at once and lasted up to 15 minutes (16). Although a second study elsewhere failed to confirm these findings, a subsequent fatal case of staphylococcal septicemia in an elderly patient with an immune deficiency suggests that the risks are not merely theoretical (17).

Drug Administration

Drug additives

Tannic acid (up to 1.5%) was at one time added to barium enemas in order to improve the quality of the radiological picture. Tannic acid is hepatotoxic and fulminant liver disease very occasionally resulted. Although it was perhaps avoidable, being apparently associated mainly with higher tannic acid concentrations, mucosal damage, or a prior tannic acid washout of the bowel, the risks have made this technique obsolete.

Drug administration route

Accidental administration of a barium enema into the vagina instead of the rectum can occur and can be very hazardous; in some of these patients there has been fatal rupture of the vagina, with venous intravasation of the barium.

Barium given orally can be inhaled, and if there is incoordination of swallowing, inhalation of thick paste can cause fatal asphyxiation (18); aspiration of barium can also cause fatal pneumonia (19).

Accidental venous intravasation of barium during administration of a barium enema usually has a high immediate mortality, due to barium embolism in the lungs, but it occasionally causes few symptoms. In one intermediate case there was hypotension and evidence of disseminated intravascular coagulation (SEDA-9, 407); the patient recovered after intensive treatment.

Drug overdose

A fatal case of poisoning resulted from the use of barium sulfide, which had been mistaken for barium sulfate (SED-8, 1022) (20). Isolated cases of barium encephalopathy have been attributed to absorption of barium after the use of barium sulfate (SEDA-15, 498).

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Barnidipine

See also Calcium channel blockers

General Information

Barnidipine is a dihydropyridine with antihypertensive activity and tolerability similar to that of other calcium antagonists of the same class. The most frequent adverse events are edema, headache, and flushing, but barnidipine does not cause reflex tachycardia (1).

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Basidiomycetes

See also Herbal medicines

General Information

Basidiomycetes are fungi that include mushrooms, puffballs, and bracket fungi.

Lentinus edodes

Lentinus edodes (shiitake) is an edible mushroom that contains a polysaccharide, lentinan. Its use is occasionally associated with skin reactions (1,2).

Adverse effects

Most adverse effects of *Lentinus edodes* occur in shiitake workers.

Respiratory

Lentinus edodes can cause an interstitial hypersensitivity pneumonitis called mushroom worker's lung, associated with IgG antibodies against shiitake spore antigens; those who cultivate white button mushrooms (*Agaricus bisporus*) or the oyster mushroom (*Pleurotus* species) have only low titers (3).

Workers at a shiitake farm developed cough and sputum production after a variable period of exposure to shiitake mushrooms (4). All four had abnormal diffusing capacity and three had abnormal spirometry. Chest X-rays showed an interstitial pattern in one case. Pulmonary function tests fell significantly during several days of work, with a more than 20% fall in forced vital capacity and/or maximal mid-expiratory flow. Antigens to shiitake spore antigens, in common with antigens from other cultivated mushrooms (*Agaricus* and *Pleurotus*), were demonstrated by ELISA.

Bronchial asthma has been attributed to shiitake (5).

Skin

Skin reactions due to *Lentinus edodes* are not uncommon (1,2).

- A 42-year-old female shiitake grower developed skin lesions while planting shiitake hyphae into bed logs (6). She complained of repeated eczematous skin lesions during the planting season, from March to July, for 10 years. Each day she handled 7000 pieces of small conic blocks made of beech, with shiitake hyphae attached to their surface, and altogether 300 000 pieces each season. Patch tests with extracts of shiitake hyphae were positive. In contrast, female shiitake growers with skin lesions associated with work other than planting, and without skin lesions, were negative on patch-testing.

Drug interactions

Lentinan inhibits CYP1A (7), but the relevance of this to drug interactions in man is not known.

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Basiliximab

See also Monoclonal antibodies

General Information

Basiliximab is a chimeric (human/mouse) anti-interleukin-2 receptor monoclonal antibody used in the prophylaxis of acute renal transplant rejection. It acts by binding the alpha chain of interleukin-2 receptors on activated T lymphocytes. Initially positive results in phase III trials have not been generally confirmed (1,2).

Compared with placebo, basiliximab was not associated with any specific adverse effects in early studies (3). However, severe hypersensitivity reactions can occur and can be associated with the cytokine release syndrome.

Organs and Systems

Respiratory

There have been reports of non-cardiogenic pulmonary edema in three adolescent renal transplant recipients, one of whom died (4).

Immunologic

Basiliximab is composed of murine sequences (30%), which can cause IgE-mediated hypersensitivity reactions. Important warnings have been released by the manufacturers regarding the possible risk of severe hypersensitivity reactions within 24 hours of initial exposure or after re-exposure after several months, based on 17 reports that included cardiac and/or respiratory failure, bronchospasm, urticaria, cytokine release syndrome, and capillary leak syndrome.

- A 42-year-old Hispanic woman, with end-stage renal disease, anemia, hypertension, and a history of an anaphylactic reaction to basiliximab, was scheduled to receive a living donor transplant and received basiliximab uneventfully (5). However, owing to donor infection the procedure was cancelled and rescheduled for 2 weeks later. Within 10 minutes after basiliximab reinduction she developed an anaphylactic reaction. In an attempt to find another induction therapy for this patient, skin testing was performed for daclizumab without response. She therefore received full-dose induction with daclizumab before her organ transplant without adverse effect.
- A child had anaphylactic shock when he received a second course of basiliximab at the time of a second renal transplantation (6). There were antibasiliximab IgE antibodies in the serum, but no IgE reactivity toward a control murine IgG_{2a} monoclonal antibody, suggesting that the IgE response was directed exclusively against basiliximab idiotypes. There was no IgE reactivity against the humanized anti-interleukin-2 receptor monoclonal antibody daclizumab. The patient's basophils harvested months after the anaphylactic shock produced leukotrienes in vitro on exposure to basiliximab.

Daclizumab, a humanized monoclonal antibody, is composed of only 10% murine antibody sequences and therefore is less immunogenic. These findings suggest that despite the similar compositions of human and mouse antibody protein sequences the IgE responsiveness is significantly different.

Drug–Drug Interactions

Ciclosporin

Basiliximab can inhibit ciclosporin metabolism transiently in children with renal transplants (7). Despite the use of lower daily doses, ciclosporin trough concentrations were significantly higher during the first 10 days after transplantation in 24 children who received basiliximab at days 0 and 4 after transplantation compared with 15 children who did not receive basiliximab. Ciclosporin dosage requirements again increased by 20% to achieve the target blood concentration at days 28–50 after transplantation. It is noteworthy that all seven acute episodes of rejection in the basiliximab group occurred during this period of time. However, these results have been debated, and there were no changes in ciclosporin dosage requirements in 54 children with liver transplants (8).

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Batanopride

General Information

Batanopride is a substituted benzamide with 5-HT_3 receptor antagonist activity. It is claimed to be free of dopaminergic properties. Clinical studies have concentrated on its use in patients suffering severe vomiting as a result of cytostatic therapy, but have run into problems because of poor tolerance at effective doses. The most important dose-limiting adverse effect is severe hypotension (1) but diarrhea and electrocardiographic changes also occur.

Comparative studies

In a randomized, double-blind comparison of intravenous batanopride 0.2–6.0 mg/kg and methylprednisolone 250 mg before cancer chemotherapy in 208 patients, the highest dose of batanopride was associated with a higher complete protection rate than the control group, but also had higher incidences of diarrhea, hypotension, and electrocardiographic abnormalities (2).

Organs and Systems

Cardiovascular

In a double-blind, randomized, crossover comparison of batanopride and metoclopramide in 21 chemotherapy-naive patients who received cisplatin at least 70 mg/m^2, the study was terminated when hypotension was observed after infusion of batanopride at other institutions testing similar drug schedules, although the authors themselves saw no cases of hypotension after treatment with batanopride (3). However, they did note asymptomatic prolongation of the QTc interval, PR interval, and QRS complex.

Susceptibility Factors

Renal disease

In 27 subjects with various degrees of renal function who were given an intravenous infusion of a single dose of batanopride 3.6 mg/kg over 15 minutes, the half-life was significantly prolonged from 2.7 hours in those with normal renal function to 9.9 hours in those with severe renal impairment (creatinine clearance below 30 ml/minute) (4). This was associated with a significant reduction in renal clearance. There were no differences in plasma protein binding or steady-state volume of distribution. There were significantly lower renal clearances of all three of the metabolites of batanopride in those with impaired renal function.

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Bemetizide

See also Diuretics

General Information

Bemetizide is chemically unrelated to the thiazides, but it shares many of their actions and adverse effects.

Susceptibility Factors

Age

The pharmacokinetics and pharmacodynamics of a fixed combination of bemetizide 25 mg and triamterene 50 mg have been evaluated in 15 elderly patients (aged 70–84 years) and 10 young volunteers (aged 18–30 years) after single doses (on day 1) and multiple doses (at steady state on day 8) (1). Mean plasma concentrations of bemetizide, triamterene, and the active metabolite of triamterene, hydroxytriamterene, were significantly higher in the elderly subjects after single and multiple doses, and urine flow and sodium excretion rates fell in tandem with the accumulation of these drugs. The glomerular filtration rate, which is reduced in elderly people, was further reduced at higher concentrations of bemetizide and triamterene, which may explain why there were limited diuretic and saliuretic effects after multiple doses. This study clearly points to a modulating effect of the degree of renal function on the diuretic actions of these compounds in elderly people.

Drug–Drug Interactions

Triamterene

In 1988 the Federal German Health Authorities issued a warning about fixed combinations of the thiazide bemetizide and triamterene that they could cause allergic vasculitis (2). Thiazides can occasionally cause allergic vasculitis and it is not clear on what basis the combination might be more likely to cause the same problem.

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Benazepril

See also Angiotensin converting enzyme inhibitors

General Information

Safety data derived from the controlled trials submitted in the benazepril New Drug Application for hypertension have been reviewed (1). In more than 100 trials involving 6000 patients with hypertension or congestive heart failure, the types and incidences of adverse effects were comparable with those of other ACE inhibitors.

Organs and Systems

Pancreas

Benazepril has been associated with pancreatitis (2).

- A 70-year old man with type II diabetes had severe epigastric pain 30 minutes after taking his first dose of 5 mg benazepril and lasting 6–8 hours. The next day he had the same pain, complicated by vomiting. Benazepril was withdrawn and he was unable to eat for 4 days. He later developed severe epigastric pain, nausea, and vomiting 30 minutes after taking a third dose. Laboratory findings confirmed pancreatitis and imaging showed a mildly edematous inflamed pancreas. He improved progressively with bowel rest and pethidine. He was symptom-free 2 months after discharge.

References

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Benorilate

General Information

Benorilate is an acetylsalicylic ester of paracetamol. It is slowly absorbed unchanged from the gastrointestinal tract but is rapidly hydrolysed to its components, aspirin and paracetamol. Thereafter its effects and kinetics are those of the two moieties. However, the delay in its metabolism reduces the incidence of direct gastric irritation, delays its onset of action, and prolongs its duration of action (1,2).

Drug Administration

Drug overdose

In cases of suspected benorilate overdosage, both salicylate and paracetamol should be assayed.

References

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Benoxaprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Since benoxaprofen, like zomepirac, provided an experience from which several lessons can be learnt, it deserves to be briefly reviewed, even though it was withdrawn 10 years ago. Some newer drugs may have some of its chemical or pharmacological characteristics and, consequently, its problems. Benoxaprofen was originally launched in 1980, with claims of a favorable adverse effects profile and "unique disease-modifying properties" in rheumatoid arthritis. These claims appeared to have been based on the fact that it was a relatively more potent inhibitor of leukotriene production and a less potent inhibitor of prostaglandin synthesis than other NSAIDs. Having passed all preclinical and clinical tests and satisfied the safety requirements set by regulatory authorities in many countries (despite rejection in several on grounds of safety), benoxaprofen was then suspended by the UK Committee on Safety of Medicines in 1982, about 18 months after marketing. Shortly afterwards it was withdrawn worldwide by its manufacturers (1). Benoxaprofen was associated with a very high incidence of adverse effects, prominent effects on the skin and nails and liver reactions, which sometimes proved fatal, particularly in elderly people.

The case led to considerable regulatory and medicolegal discussions in the 10 years after withdrawal. In the USA the company was charged by the Food and Drug Administration with misbranding the drug in press statements and associated materials, which contained a misleading headline implying that the drug was harmless, even though the company was aware of a report of deaths related to the use of benoxaprofen. The company's intense marketing campaign was heavily criticized (SEDA-8) and it was noted that the recommendation of the WHO that drugs likely to be used in elderly people should be investigated in them at an early stage had certainly been disregarded in the premarketing phases. In the UK

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the company rejected patients' demands to establish a compensation scheme and offered instead a financial settlement that the patients rejected as inadequate. The case shows how some legal systems are inadequate for dealing with mass claims of personal injury due to drugs.

Organs and Systems

Gastrointestinal

The hope of better gastric tolerance of benoxaprofen was not fulfilled, and the incidence of this type of reaction was actually higher in elderly patients.

Liver

Fatal liver damage was observed particularly in the UK and tended to occur in elderly subjects. The complication initially presented as jaundice or raised liver enzymes (including alkaline phosphatase). Surprisingly, biochemical and histological liver changes were not consistent with major hepatocellular damage. There were three reports of primary biliary cirrhosis, but a causal relation was not proven (SEDA-12, 84).

Urinary tract

All types of kidney damage were reported, ranging from a transitory fall in glomerular filtration rate and reversible renal insufficiency (part of multisystem disease with circulating LE cells) to the nephrotic syndrome.

Skin

Cutaneous adverse effects were the most frequent problem and (together with hepatic complications) the most serious: 63% of 300 patients treated for 6 months complained of one or more adverse effects (total 259 reactions); 70% were cutaneous; photosensitivity led to withdrawal in 30% of cases. Multiple subepidermal cysts (milia) on sun-exposed skin areas and onycholysis (13% of patients) were documented. Other skin reactions included rashes, hypertrichosis, erythema multiforme, and Stevens–Johnson syndrome (2). Phototoxicity persisted for many months after withdrawal (SEDA-12, 84); although a later study on persistent photosensitivity as a sequel to benoxaprofen in 42 subjects failed to confirm the link between photosensitivity and the drug (3), this was contrary to the overwhelming experience in the field. In retrospect, it seems likely that one problem was that benoxaprofen had largely been studied during the winter months, whereas in the UK it was launched in the summer.

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Bentazepam

See also Benzodiazepines

General Information

Bentazepam is a benzodiazepine with properties similar to those of diazepam.

Organs and Systems

Liver

In three cases chronic hepatocellular injury developed with oral bentazepam (1).

Reference

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Benzalkonium chloride

See also Disinfectants and antiseptics

General Information

Quaternary ammonium compounds are surface-active agents. Some of them precipitate or denature proteins and destroy microorganisms. The most important disinfectants in this group are cationic surface-active agents, such as benzalkonium chloride, benzethonium chloride and methylbenzethonium chloride, and cetylpyridinium chloride; the problems that they cause are similar.

Benzalkonium chloride is composed of a mixture of alkyldimethylbenzylammonium chlorides. The hydrophobic alkyl residues are paraffinic chains with 8–18 carbon atoms. Benzalkonium chloride is used as a preservative in suspensions and solutions for nasal sprays and in eye-drops. Depending on the concentration of the solution, local irritant effects can occur. In nasal sprays it can exacerbate rhinitis (1) and in eye-drops it can cause irritation or keratitis (2).

A total of 125 ophthalmologists in private practice located throughout France examined 919 glaucomatous patients treated with eye-drops which either did or did not contain a preservative; the proportion of patients who experienced discomfort or pain during instillation was 58% for eye-drops containing a preservative and 30% for eye-drops with no preservative (2). Moreover, the proportion of patients presenting at least one symptom of eye irritation (sensation of itching or burning, sensation of a foreign body in the eye, and flow of tears) was greater with preservative-containing eye-drops (53 versus 34%). The experience of discomfort during instillation was more often associated with problems later on. The patient's

complaints were correlated with objective signs of conjunctival damage (conjunctival redness, conjunctival follicles), or corneal damage (superficial punctate keratitis). A higher proportion of patients treated with eye-drops containing a preservative had at least one conjunctival sign (52 versus 35%) or superficial punctate keratitis (12 versus 4%). In 164 patients whose treatment was changed from eye-drops containing a preservative to eye-drops with no preservative and who were examined a second time (mean interval between visits 3.3 months) the frequency of all symptoms and objective signs fell by a factor of 3 to 4.

Organs and Systems

Respiratory

An asthmatic patient whose salbutamol formulation was replaced by another containing benzalkonium chloride as an excipient developed bronchospasm as a result (3).

Benzalkonium chloride is used as a preservative in nebulizer solutions and can cause secondary paradoxical bronchoconstriction in patients with bronchial asthma. Although nebulizers containing beta-adrenoceptor agonists may also contain benzalkonium chloride, reports are more common with anticholinergic drugs. This is probably because of the more rapid onset and larger effect of sympathomimetic-induced bronchodilatation compared with anticholinergic drugs (4).

Ear, nose, throat

Benzalkonium chloride accentuated the severity of rhinitis medicamentosa and increased histamine sensitivity in a 30-day study with oxymetazoline nasal spray in healthy volunteers (5,6).

Sensory systems

Benzalkonium chloride is used in eye-drops in concentrations of 0.033 or 0.025%. At a dilution of 1:1000 (0.1%), a drop applied to the human cornea causes mild discomfort that persists for 2 or 3 hours. Slit-lamp examination within 90 seconds shows fine grey clots (epithelial keratitis) in the corneal epithelium. Within 10 minutes, a grey haze can be seen on the corneal surface; superficial desquamation of the conjunctival epithelium can follow. The superficial irritation and disturbances disappear in a day or less.

Patients with glaucoma, dry eyes, infections, or iritis, sometimes use solutions containing benzalkonium chloride often enough and for long enough to cause damage. In these patients, there is a higher incidence of endothelial damage, epithelial edema, and bullous keratopathy, and because of the severity of the disease, additional damage from the medication can be overlooked. This is especially true in patients with defective epithelium or corneal ulcers, in whom the medication can penetrate well and who can be most vulnerable. There have been analogous results in investigations of benzethonium chloride, cetrimonium bromide, cetylpyridinium chloride, decyldodecylbromide, hexadecyl, and tetradecyltrimethylammonium bromide (SEDA-11, 490).

Immunologic

Life-threatening anaphylactic reactions that rarely occur during general anesthesia are mostly due to neuromuscular blockers. They may be due to cross-allergy mediated by drug-specific IgE antibodies to the quaternary ammonium moiety of the neuromuscular blocker molecule, perhaps with a contribution from IgE-independent mechanisms. Quaternary ammonium compounds, such as benzalkonium, in cosmetics and toiletries may play a role in sensitization (7).

Allergic reactions can occur after topical use, but are fairly rare. Allergic contact dermatitis has been reported in some cases. Allergic rhinitis on contact has also been reported.

In a study of the efficacy and acceptability of benzalkonium chloride-containing contraceptives (vaginal sponges, pessaries, and creams) in 56 women, one developed an allergic reaction with edema of the vulva (4). Non-allergic local irritation, itching, and a burning sensation were reported in nine women and nine husbands.

Infection risk

The bactericidal activity of benzalkonium chloride is limited to the Gram-positive and some of the Gram-negative bacteria, but *Pseudomonas* species are especially resistant and can cause severe infection. Too often it is not realized that the disinfectant can be contaminated with active multiplying resistant organisms.

Pseudomonas bacteremia has been attributed to the use of material in open-heart surgery that was stored in accidentally contaminated benzalkonium solutions, and after cardiac catheterization caused by inadequate disinfection of the catheters with benzalkonium solutions. In 1961, about 15 patients were reported with *Pseudomonas* infections caused by cotton pledgets kept in a contaminated aqueous solution used for skin antisepsis before intravenous and intramuscular injection (8). In 1976 there were outbreaks of *Pseudomonas cepacia* infections in two American general hospitals (9) and pseudobacteremia (*Pseudomonas cepacia* or *Enterobacter*) caused by contamination of blood cultures in 79 patients in whom contaminated aqueous benzalkonium solutions were used for skin and antisepsis before venepuncture and due to contamination of the samples (SEDA-11, 490) (10).

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Benzatropine and etybenzatropine

See also Anticholinergic drugs

General Information

Benzatropine and etybenzatropine (ethylbenzatropine) are anticholinergic drugs. They represent attempts to combine atropine-like and antihistaminic effects in single molecules. The dose is determined individually and varies from 0.5 to 6 mg/day for benzatropine and 6 to 30 mg/day for etybenzatropine. Although the adverse reactions are essentially those of the anticholinergic drugs, sedation is very likely to occur and these drugs should not be used in patients who need to drive motor vehicles. Benzatropine has also been reported to cause rash, peripheral numbness, and muscular weakness.

Organs and Systems

Cardiovascular

A paradoxical sinus bradycardia in a psychotic patient was attributed to benzatropine since it abated when benzatropine (but not others) was withdrawn (SEDA-17, 174).

Psychological, psychiatric

Benzatropine can cause slight memory impairment, detectable if special studies of mental function are performed (SEDA-13, 115) (SEDA-15, 137).

Second-Generation Effects

Teratogenicity

There have been two cases of "small left colon" in infants whose mothers had taken various psychotropic drugs, including benzatropine, late in pregnancy; the causal link was not at all clear (SEDA-6, 142).

Drug–Drug Interactions

Paroxetine

When paroxetine was introduced in a patient taking benzatropine and haloperidol, the circulating concentrations of benzatropine rose and delirium occurred (SEDA-22, 157) (1).

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Benzbromarone

General Information

Benzbromarone is a benzofuran derivative chemically related to amiodarone. It increases uric acid excretion by non-specifically inhibiting its tubular reabsorption.

It is used in patients with venous disorders to prevent, retard, or reverse varicose degenerative changes in the vessel wall.

Benzbromarone causes diarrhea (3–4% of patients), urate and oxalate stones, urinary sand, renal colic, and allergy in a small number of patients (1). Liver damage, which reverses after withdrawal, has been described (SEDA-18, 108).

Organs and Systems

Liver

After reports of several cases of acute hepatitis (SEDA-16, 205) benzbromarone was withdrawn from the market in several European countries (SEDA-17, 244). Liver damage reportedly reverses after withdrawal (SEDA-18, 108)

Drug–Drug Interactions

Anticoagulants

As benzbromarone is a coumarin derivative, it can potentiate the effects of anticoagulants, which act as vitamin K antagonists.

Reference

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Benzethonium chloride and methylbenzethonium chloride

See also Disinfectants and antiseptics

General Information

Quaternary ammonium compounds are surface-active agents. Some of them precipitate or denature proteins and destroy microorganisms. The most important disinfectants in this group are cationic surface-active agents, such as benzalkonium chloride, benzethonium chloride and methylbenzethonium chloride, and cetylpyridinium chloride; the problems that they cause are similar.

In an extensive report, the Expert Panel of the American College of Toxicology (1) has concluded that both benzethonium chloride and methylbenzethonium chloride can be regarded as safe when applied to the skin at a concentration of 0.5% or when used around the eye in cosmetics at a maximum concentration of 0.02%. In clinical studies, benzethonium chloride produced mild skin irritation at 5%, but not at lower concentrations. Neither ingredient is considered to be a sensitizer.

Drug Administration

Drug overdose

The Paris Poison Center has received reports on 45 cases of acute accidental poisoning, with 18 deaths (2). All the victims were mentally disturbed patients who had ingested Airsane HP 800, a water-soluble powder packed in a sachet; it contains a mixture of quaternary ammonium compounds and was left in the patients' rooms by hospital workers. Symptoms were corrosive burns of the mouth, pharynx, esophagus, and sometimes of the respiratory tract.

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Benzimidazoles

See also Individual agents

General Information

The benzimidazoles are a group of compounds that include albendazole, flubendazole, mebendazole, niridazole, triabendazole, and triclabendazole.

The newer broad-spectrum benzimidazoles have a wide spectrum of antihelminthic activity, killing larval and adult cestodes as well as intestinal nematodes, with generally low mammalian toxicity, apart from a potential for teratogenicity and embryotoxicity. The principal members of the group are mebendazole, its fluorine analogue flubendazole, and the better-absorbed albendazole. Mebendazole and albendazole are active orally in a single dose for a wide range of intestinal nematodes and are being used increasingly in the treatment of hydatid disease, in which experience is rapidly advancing. Flubendazole is very poorly absorbed and causes local tissue reactions at the site of injection when given parenterally.

None of the benzimidazoles is known to be safe in pregnancy and animal studies and their spectrum of toxicity suggest that they should be avoided. The absence of reports of harm in human pregnancy does not mean that no harm can occur.

The antihelminthic activity of the benzimidazoles is thought to result from selective blockade of glucose uptake by adult worms lodged in the intestine and their tissue-dwelling larvae, resulting in endogenous depletion of glycogen stores and reduced formation of adenosine triphosphate, which appears to be essential for parasite reproduction and survival. However, benzimidazole antihelminthics may also have antiparasitic activity by binding to free β-tubulin, thereby inhibiting the polymerization of tubulin and microtubule-dependent glucose uptake (1).

Uses

Ankylostomiasis

In 13 British soldiers with cutaneous larva migrans after a 2-week jungle training exercise in Belize the median incubation period was 10 (range 4–38) days; in 12 there were skin lesions on the calves or shins, and only two had foot or ankle lesions (2). Ten received oral thiabendazole, one oral mebendazole, one oral albendazole, and one topical thiabendazole. All those treated with oral thiabendazole complained of unpleasant reactions, predominantly nausea, vomiting, and dizziness. The one patient treated with topical thiabendazole returned with a new lesion 12 months later. He was then treated with systemic albendazole, with rapid resolution of symptoms. A 45-year-old woman developed larva migrans 20 days after lying on a beach in Singapore and was treated with thiabendazole 50 mg/kg in two doses for one day; she had no adverse effects (3).

The treatment of cutaneous larva migrans in 56 Italian patients aged 2–60 years has been retrospectively reviewed (4). All 13 patients treated with cryotherapy reported that it was painful, but none had recurrent disease or scarring. A further six patients were treated with oral thiabendazole 25–50 mg/kg/day for 2 days, and one had both thiabendazole and cryotherapy. In all cases there was regression of itching and skin lesions, but they had nausea, diarrhea, and dizziness while taking oral thiabendazole. No adverse effects were reported in 36 patients who were treated with albendazole 400 mg/day for 3 days (two were also treated with cryotherapy). Despite the low dose, larval migration was stopped in 1–2 days. Although a prompt and definitive cure was achieved in all 56 patients, albendazole was considered the treatment of choice given its minimal adverse effects. Until about 1980, surgery was the only treatment

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available for larval infections with *Echinococcus granulosus* or *Echinococcus multilocularis*. However, cysts are not always amenable to surgical removal, and operation is associated with the risk of rupture, leading to anaphylactic shock and re-infection; a proportion of cases are in any case not fit enough for surgery. The benzimidazoles have been used in varying high dosages over extended periods, initially to treat inoperable hydatid cysts and before surgery in attempts to sterilize cysts.

Echinococcosis

The epidemiology, clinical presentation, and treatment of alveolar echinococcosis of the liver have been described in French patients followed between 1972 and 1993 (5). From 1982 benzimidazoles were used. Of 117 patients, 72 took either albendazole or mebendazole for 4–134 months. The most common adverse effects were an increase in alanine transaminase activity to more than five times the top of the reference range (in six patients taking albendazole and in three taking mebendazole). Neutropenia (leukocyte count below 1.0×10^9/l) occurred in two patients taking albendazole. Alopecia occurred in four patients taking mebendazole. Minor adverse effects of albendazole included malaise, anorexia, and digestive intolerance in one patient each. In 13 patients treatment had to be withdrawn because of adverse effects ($n = 10$) or non-adherence to therapy ($n = 3$).

While mebendazole is used in continuous therapy of human alveolar echinococcosis, albendazole has been used in cyclic treatment. One treatment cycle consists of 28 days followed by a washout phase of 14 days without treatment, intended to reduce toxicity. Whether albendazole can also be used on a continuous basis has recently been studied in an open observational study in 35 patients with alveolar echinococcosis (in seven of 35 patients a curative operation was performed) (6). The outcome (lack of progression) was compared with the results obtained with continuous treatment with mebendazole or cyclic albendazole. Albendazole 10–15 mg/kg/day and mebendazole 40–50 mg/kg/day were equally effective. Seven patients were treated with continuous albendazole for an average of 28 (range 13–50) months. All patients taking continuous albendazole had stable or even regressive disease. The continuous dosing regimen was well tolerated without increased toxicity or higher rates of adverse reactions. Therefore, continuous dosing of albendazole is a promising alternative in cases of inoperable or progressive alveolar echinococcosis.

Prolonged cyclic albendazole treatment (for more than 9 years) was safe and effective in a patient with isolated cervical spine echinococcosis in whom surgery was performed without preoperative antihelminthic therapy because of a delay in diagnosis (7).

There have been several studies of the efficacy of albendazole in preventing recurrences of hydatid disease and cyst fluid spillage complications after surgery. In one Turkish study 22 of 36 patients with echinococcosis were treated with albendazole after surgical intervention (8). There was no significant benefit of perioperative albendazole over operation alone, although the recurrence rate of hepatic echinococcosis was lower than in historical controls. In contrast, in another study in 22 patients with hepatic echinococcosis there was a clear benefit of peri- and postoperative cyclic albendazole (12–15 mg/kg/day in four divided doses) (9). There were no cases of secondary hydatid disease or recurrence after a mean follow-up of 20 months. In two cases there were liver function abnormalities, which normalized after withdrawal.

Neurocysticercosis

Cysticercosis is caused by the larval stage of the pork tapeworm *Tenia solium*. Neurocysticercosis is the most severe and common clinical manifestation in humans and probably the most frequent parasitic infection of the central nervous system. *T. solium* is endemic in Latin America, Asia, and sub-Saharan Africa. However, with the advent of computerized neuroradiology and improved serological tests, neurocysticercosis is increasingly being diagnosed throughout the world.

Controversies in the management of neurocysticercosis have been described (10–12). The management of the neurological complications of cysticercosis and in particular the role of antiparasitic drugs are issues of debate. It is commonly believed that the use of antiparasitic drugs and steroids should be individualized, based on the presence of active or inactive disease, the location of the cysts, and the presence or absence of complications such as hydrocephalus.

Some imidazoles have been used to treat parenchymal brain cysticerci. Initially, flubendazole (40 mg/kg for 10 days) was given to 13 patients with neurocysticercosis, with promising results. However, owing to its poor intestinal absorption, the use of flubendazole is limited. Albendazole is usually well absorbed and well tolerated, and albendazole serum concentrations are not significantly affected by glucocorticoids or anticonvulsants. Albendazole was given in daily doses of 15 mg/kg for 30 days. Further studies, however, showed that a treatment course could be shortened from 30 to 8 days without affecting efficacy. Direct comparative trials have shown that albendazole usually destroys 75–90% of parenchymal brain cysts, whereas praziquantel destroys 60–70%. The advantage of albendazole over praziquantel is limited not to its better efficacy, but also to better penetration of the subarachnoid space, allowing destruction of meningeal cysticerci. It also costs less than praziquantel.

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Benznidazole

General Information

Benznidazole, a nitroimidazole, is used in the treatment of *Trypanosoma cruzi* infections and Chagas' disease, and is recommended for use in urogenital trichomoniasis, all forms of amebiasis, giardiasis, and anaerobic infections. Its adverse effects are similar to those of metronidazole (SEDA-13, 833). Drowsiness, dizziness, headache, and ataxia occur occasionally. With prolonged and/or high doses, transient peripheral neuropathy and epileptiform seizures can be seen. Other frequently mentioned adverse effects are unpleasant taste, furred tongue, nausea, vomiting, and gastrointestinal disturbances. Skin rash and pruritus can occur. One case each of erythema multiforme and of toxic epidermolysis have been reported. Benznidazole causes a disulfiram-like effect with ethanol.

Placebo-controlled studies

In a double-blind, randomized, clinical trial, benznidazole 5 mg/kg/day for 60 days was compared with placebo in children in the indeterminate phase of infection by *Trypanosoma cruzi* (1). In general, treatment was well tolerated. The treated children had a significant reduction in mean titers of antibodies against *T. cruzi* measured by indirect hemagglutination, indirect immunofluorescence, and ELISA. At 4-year follow-up, 62% of the benznidazole-treated children and no placebo-treated child were seronegative for *T. cruzi*. Xenodiagnosis after 48 months was positive in 4.7% of the benznidazole-treated children and in 51% of the placebo-treated children.

General adverse effects

The adverse effects of benznidazole can be classified into three groups (2,3):

1. symptoms of hypersensitivity—dermatitis with skin eruptions (usually occurring at 7–10 days of treatment), generalized edema, fever, lymphadenopathy, and joint and muscle pains;
2. bone marrow suppression, thrombocytopenia, and agranulocytosis being the most severe manifestations;
3. peripheral polyneuropathy, paresthesia, and polyneuritis.

In a Cochrane systematic review the incidence of adverse effects was less than 20% (4). In one study, under 5% of participants complained of a variety of minor symptoms, but rash and pruritus were reported more commonly. In children the drug was well tolerated and there were no severe adverse effects. The only study in adults reported a non-quantified variety of mild adverse effects (skin reactions, peripheral neuropathy, digestive disturbances), but it was said that they were less intense than those seen with nifurtimox.

Long-Term Effects

Mutagenicity

Like metronidazole, benznidazole is mutagenic. In tests for chromosomal aberrations and induction of micronuclei in cultures of peripheral lymphocytes from children with Chagas' disease, there were increases in micronucleated interphase lymphocytes and of chromosomal aberrations after treatment with benznidazole (4).

Drug–Drug Interactions

Disulfiram

Like metronidazole, benznidazole has a disulfiram-like effect if alcohol is taken (5).

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Benzocaine

See also Local anesthetics

General Information

Benzocaine is a poorly soluble local anesthetic, an ester of para-aminobenzoic acid. It is used in many countries as a component of some free-sale formulations for topical use, for example in skin creams, as a dry powder for skin ulcers, as throat lozenges, and as teething formulations for young children. It is also used in aerosol sprays when anesthetizing the oropharynx. Relatively high concentrations of local anesthetic are required to be effective topically, increasing tissue penetration and the risk of subsequent toxicity. Benzocaine formulations are available in concentrations of 1–20%.

Organs and Systems

Hematologic

Methemoglobinemia is a classical complication of benzocaine (SEDA-12, 256) (SEDA-21, 135) (SEDA-22, 141). The problem arises in both adults and children (1–4), and the risk has led to criticism of its free availability. It has, amongst other things, been suggested that it should be eliminated from products for use in children, that concentrations in over-the-counter products should be limited, and that there should be explicit label warnings of the hematological risk (SED-12, 256) (SEDA-17, 135) (1). Early diagnosis and treatment are crucial, as the condition is potentially fatal, particularly in neonates.

Five cases of benzocaine-induced methemoglobinemia were reported in 1998, following its use for transesophageal echocardiography (5–8). Methemoglobin concentrations over 15% can lead to cyanosis, whilst concentrations over 70% lead to circulatory collapse and death (7,8). The degree of methemoglobinemia depends on the total dose of drug and any factors that enhance systemic absorption. The elderly and neonates are particularly susceptible to methemoglobinemia, as are those with inherited methemoglobin reductase deficiency or the abnormal hemoglobin M. Adequate monitoring and observation of patients both during and after transesophageal echocardiography is essential, as this rare complication of benzocaine and other local anesthetics, such as prilocaine, is both potentially fatal and eminently treatable.

- Severe methemoglobinemia was suspected in a 1-year-old infant after topical application of 10% benzocaine ointment around an enterostomy; on postoperative day 3 the SpO_2 was 90% and arterial blood was dark red in color (9).

The authors pointed out the serious potential for toxicity in infants of a local anesthetic that is commonly used for this purpose in adults.

However, adult cases have been reported with Cetacaine (a proprietary mixture of 14% benzocaine, 2% tetracaine, and 2% butylaminobenzoate) (10–12) and with benzocaine alone (13).

Cetacaine spray used to anesthetize the oropharynx before endoscopy led to dyspnea, central cyanosis, and an oxygen saturation of 80%; methemoglobinemia was diagnosed, and the patient recovered rapidly with methylthioninium chloride 1 mg/kg over 5 minutes.

- A 77-year-old woman received two sprays of Cetacaine for an attempted emergency nasotracheal intubation. After intubation she became cyanosed. The arterial blood was chocolate-brown in color and the SaO_2 by CO oximetry was 54–58%, despite a high PaO_2. The methemoglobin concentration was 39% and she was treated with methylthioninium chloride. Three weeks later Cetacaine again caused cyanosis with a drop in SpO_2 to 76% and a methemoglobin concentration of 24%, which resolved spontaneously.
- A 74-year-old man received Cetacaine spray to his oropharynx for transesophageal echocardiography. His SpO_2 fell to 85%. He became drowsy, then unresponsive, cyanotic, and apneic, and required intubation. His PaO_2 was 37 kPa (280 mmHg), SaO_2 40%, and methemoglobin concentration 60%. Intravenous methylthioninium chloride produced an immediate improvement in the cyanosis and the methemoglobin concentration fell to 0.6%.
- A 71-year-old man received 20% benzocaine spray to the upper airway for bronchoscopy. His SpO_2 gradually fell to under 85% and he required intubation. His methemoglobin concentration was 19%, SaO_2 75%, and PaO_2 44 kPa (329 mmHg). After intravenous methylthioninium chloride the methemoglobin concentration fell to 1.8%.

Several other cases of methemoglobinemia after the administration of topical benzocaine formulations have been reported (14–19). All recovered completely without sequelae after the intravenous administration of methylthioninium chloride 1–2 mg/kg.

- A 69-year-old man developed methemoglobinemia (68%) after pharyngeal anesthesia using 20% benzocaine 15 ml (swish and swallow) for transesophageal echocardiography (20). He responded to intravenous methylthioninium chloride, but a diagnosis of non-Q wave myocardial infarction was made on the basis of raised cardiac enzymes and a normal electrocardiogram.

Whether benzocaine-induced methemoglobinemia is a hypersusceptibility or collateral reaction is controversial. There has been a retrospective review of 188 benzocaine exposures in children under 18 years of age, reported to four regional poison information centers, in 1993–96 (21). Mean and median ingested dosages were 87 and 50 mg/kg respectively and 55% patients had an exposure over 40 mg/kg. In all, 92% patients were asymptomatic. Reported symptoms included oral numbness ($n = 8$), vomiting ($n = 3$), and oral irritation, dizziness, and nausea ($n = 1$ each). Methemoglobin concentrations were measured in eight patients, seven of whom had concentrations over 1%. A child, who had

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had 5–10 applications of over-the-counter teething gel applied in 24 hours, had a methemoglobin concentration of 19% and was the only patient to have cyanosis. The authors concluded that accidental ingestion of over-the-counter benzocaine-containing products rarely causes cyanosis. The lack of dose dependence suggests that this reaction is a hypersusceptibility reaction.

Four cases of methemoglobinemia have again been described after the use of benzocaine spray for topical anesthesia of the airways.

- A 42-year-old woman had a superior laryngeal nerve block with lidocaine, topical anesthesia with benzocaine spray, and intravenous midazolam for awake fiberoptic intubation (22). Her SpO_2 fell from about 85% to about 30%, and despite high-frequency jet ventilation with 100% oxygen she had persistent SpO_2 readings in the low 80s. Her arterial blood was chocolate-brown in color, with a PaO_2 of 44 kPa (330 mmHg) and an oxyhemoglobin saturation (SaO_2) of 51%. This discrepancy between PaO_2 and SaO_2 suggested methemoglobinemia, and co-oximetry showed a concentration of 51%. Methylthioninium chloride 140 mg produced an immediate improvement in her color, and her SaO_2 improved over the next 10 minutes.
- An elderly man received benzocaine 20% spray to the throat in preparation for transesophageal echocardiography. He became unwell 1 hour later, with lethargy, central cyanosis, hypoxia, dyspnea, tachypnea, and tachycardia (23). His arterial blood was burgundy-colored and the methemoglobin concentration was 41%. He was treated with two doses of methylthioninium chloride 2 mg/kg and was weaned from oxygen within 10 hours.
- Significant methemoglobinemia occurred in a 65-year-old man on re-exposure to topical 20% benzocaine spray for anesthesia of the airways in preparation for awake fiberoptic intubation (24). This occurred despite exposure 3 days before to 14% benzocaine for the same procedure. During attempted intubation, he suddenly desaturated to 80% and had significant hypotension and bradycardia, necessitating external cardiac massage and cricothyroid puncture. His SaO_2 did not improve significantly, despite seemingly adequate resuscitation with 100% oxygen and intravenous adrenaline. His arterial methemoglobin concentration was 55%. Methylthioninium chloride 100 mg intravenously led to rapid improvement in the SaO_2, allowing surgery to continue.
- A 57-year-old man developed severe methemoglobinemia after receiving topical benzocaine spray and lidocaine jelly during awake fiberoptic intubation (25). After intubation, his oxygen saturation fell to 65% on 100% oxygen. He was cyanosed and had dark arterial blood sample with normal gas tensions. His methemoglobin concentration was 60% and treatment with methylthioninium chloride was successful.

These cases illustrate the importance of co-oximetry on grounds of clinical suspicion. Methemoglobin concentrations of 10–15% can cause dark-colored blood and cyanosis. Concentrations of 20–45% can cause lethargy, dizziness, headache, and collapse. Higher concentrations (50–70%) can cause seizures, dysrhythmias, coma, and death.

Skin

Granuloma gluteale adultorum is a rare skin condition of unknown etiology, characterized by reddish purple granulomatous nodules on the gluteal surfaces and groin areas.

- Granuloma gluteale adultorum occurred in a 40-year-old woman who presented with a 3-year history of the condition associated with the use of topical benzocaine (26).

Immunologic

Benzocaine can cause sensitization, and being a para-aminobenzoic acid derivative it can cross-react with paraphenylenediamine, sulfonamides, aniline dyes, and related local anesthetics. However, in a recent retrospective study of 5464 patients it was concluded that benzocaine allergy is not common in the UK, confirming earlier reports that benzocaine should not be used as a single screening agent for local anesthetic allergy (27).

Allergic contact dermatitis has been attributed to local benzocaine (28).

- A 72-year-old woman was treated for thoracic *Herpes zoster* with oral aciclovir and topical benzocaine 20% ointment. She subsequently developed painful pruritic erythematous dermatitis in the area of the lesions, spreading to her arm. The dermatitis was initially misdiagnosed as aciclovir resistance, but on patch testing she had a positive reaction to benzocaine.

The authors highlighted the problem in diagnosing allergic contact dermatitis in patients who have other skin lesions in that area. They emphasized the importance of patch testing to identify the causative agent.

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Benzodiazepines

See also Individual agents

General Information

The benzodiazepines typically share hypnotic, anxiolytic, myorelaxant, and anticonvulsant activity. Because their efficacy and tolerability are generally good, especially in the short term, they have been used extensively and are likely to continue to be used for many years to come. However, their less specific use in the medically or psychiatrically ill, and in healthy individuals experiencing the stresses of life or non-specific symptoms has often been inappropriate and sometimes dangerous (SEDA-18, 43). The pharmacoepidemiology of benzodiazepine use has been carefully studied in various countries (1), including the USA (2) and France, where 7% of the adult population (17% of those over 65 years) are regular users (3). In Italy, consumption of benzodiazepines remained stable (50 defined daily doses per 1000 population) from 1995 to 2003, while expenditure increased by 43% to €565M per annum (4). The need to limit spending on pharmaceutical products, as well as the very real likelihood of inducing iatrogenic disease (for example cognitive impairment, accidents, drug dependence, withdrawal syndromes), has prompted many reviews and policy statements aimed at discouraging inappropriate use. Despite this, the available evidence suggests that there continues to be expensive and inappropriate use in several countries (5).

A comprehensive review of manufacture, distribution, and use has described the rather marked international variation in use of the drugs and the role of the International Narcotics Control Board, a United Nations agency, in the restriction of these drugs (1). Most countries are signatories to the UN Convention on Psychotropic Substances 1971, and are thus obliged to implement controls on the international trade in abusable drugs, including benzodiazepines. Some countries, such as Australia and New Zealand, have imposed further stringent controls on certain drugs, such as flunitrazepam, which are thought to have particular abuse liability (6). A wide-ranging discussion of benzodiazepine regulation has pointed out both the potential merits of the approach and the fact that some restrictions in the past have turned out to be counterproductive (7).

A comprehensive review of benzodiazepine-induced adverse effects and liability to abuse and dependence, in which it was concluded that most benzodiazepine use is both appropriate and helpful (2), has been challenged (8–10). Balanced clinical reviews of benzodiazepine use (11,12) include sets of recommendations on appropriate prescribing and avoiding adverse effects, including tolerance/dependence. Similarly, guidelines for the management of insomnia and the judicious use of hypnotics have been reviewed (13,14). Benzodiazepines are often over-prescribed in hospital (SEDA-17, 42), and their continued prescription after discharge constitutes a significant source of long-term users. Anxiety symptoms and insomnia are common in the medically ill population and can be due to specific physical causes, a reaction to illness, or a co-morbid psychiatric illness, such as depression. Moreover, caffeine, alcohol, nicotine, and a variety

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of medications can cause insomnia (15). Accordingly, the systematic assessment of such patients allows remediable causes to be identified and the use of hypnosedatives to be minimized. Elderly people and medically ill patients are susceptible to the adverse effects of benzodiazepines, and alternatives are worth considering (11,16), particularly given evidence that behavioral therapies can be more effective and more durable than drug therapy (17).

The important advantages of the benzodiazepines over their predecessors are that they cause relatively less psychomotor impairment, drowsiness, and respiratory inhibition, and are consequently relatively safe in overdose. However, it must be emphasized that these advantages are relative, and that the low toxicity potential does not apply when they are combined with other agents, particularly alcohol (18) and opioids (19).

As well as the added toxicity seen in co-administration with other CNS depressants, benzodiazepines facilitate self-injurious behavior by disinhibiting reckless or suicidal impulses (20). Benzodiazepines are commonly used in both attempted and completed suicide (21). A German study has suggested that hypnosedatives are the commonest drugs used in self-poisoning, that most are prescribed by physicians, and that in nearly half of those taking them chronically, adverse effects were considered to be a possible cause of self-poisoning (22). Before prescribing any drugs of this class, clinicians are exhorted to assess both suicidality and alcohol problems; there is a quick screen for the latter, the Alcohol Use Disorders Identification Test (AUDIT), which consists of a 10-item questionnaire and an 8-item clinical procedure (23).

Hypersensitivity reactions are rare. A few cases of anaphylaxis have been described, although usually these have been with the injectable forms and may have involved the stabilizing agents (24). Serious skin reactions to clobazam (SEDA-21, 38) and tetrazepam (25) have been reported. Lesser reactions have also been reported with diazepam, clorazepate (via *N*-methyldiazepam) (26), and midazolam (SEDA-17, 44, 45).

Tumor-inducing effects have been observed in animals (SEDA-6, 39), but human reports are essentially negative.

First-trimester exposure appears to confer a small but definite increased risk (from a baseline of 0.06% up to 0.7%) of oral cleft in infants (27). However, second-generation effects are infrequent and usually reversible (28), although some doubt remains about the extent of developmental delay in children who have been exposed in utero (27). A review has emphasized that concerns about second-generation effects are mainly theoretical, and has concluded that some agents (for example chlordiazepoxide) are probably safe during pregnancy and lactation and that others (for example alprazolam) are best avoided (29).

Pharmacokinetics

As far as is currently known, benzodiazepines and similar drugs (zopiclone, zolpidem) act by a single mechanism, interacting at the GABA receptor complex to enhance the ability of GABA to open a chloride ion channel and thereby hyperpolarize the neuronal membrane. It is usual, therefore, to classify benzodiazepines, and recommend their clinical use, on the basis of their duration of action or their half-life. While this is without doubt a useful classification, it is simplistic and does not take into account other important pharmacokinetic factors.

The first factor that is considered significant is the metabolism of benzodiazepines to pharmacologically active metabolites. Many newer benzodiazepines intended for use as long-acting anxiolytic or sedative agents were in fact intended to be so metabolized to ensure stable blood concentrations over prolonged periods. Drugs with long durations of effect, attributable at least in part to the formation of active metabolites, are listed in Table 1. Individuals vary considerably in their metabolism of benzodiazepines, and interpatient variation in concentrations of the parent compounds and of (generally active) metabolites is usual. In addition, ethnicity plays a major role in determining the frequency of poor and extensive metabolizers, with notable differences between Caucasians and East Asians (30).

Another, often neglected, aspect of the pharmacokinetics of benzodiazepines is their rate of onset of action, since their properties and therapeutic benefits depend to a considerable degree on the rapidity of onset of their perceived effects. Within a given drug class, the more rapidly the hypnotic effect occurs, the greater the abuse potential. For most drugs of abuse, it is the affective and behavioral changes associated with a rapid rise in drug blood concentration that is sought, whether the drug is abused by intravenous injection, nasal or bronchial absorption, or (as with alcohol) rapid oral absorption from an empty stomach (31). Diazepam and flunitrazepam are effective hypnotics because they are rapidly absorbed and there is a quick rise in blood concentrations, even though after tissue redistribution and loss of their immediate effects they have long half-lives. It also explains the preference, and so the increased liability for abuse, for drugs like diazepam (31) and flunitrazepam, especially when the latter is snorted (32). In general, polar molecules, such as lorazepam, oxazepam, and temazepam (all of which have a hydroxyl group), gain access to the

Table 1 Benzodiazepines with active metabolites that have long half-lives; metabolism and predominant metabolite half-lives

To desmethyldiazepam*	$t_{1/2}$ (hours)	To other metabolites	$t_{1/2}$ (hours)
Lorazepate	40–100	Chlordiazepoxide	40–100
Diazepam	36	Clobazam	30–150
Halazepam	20	Flurazepam	40–120
Medazepam	2	Quazepam	40–75
Prazepam	120+		

* Half-life about 60 hours.

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Table 2 Rates of absorption and half-lives of benzodiazepines

	t_{max} (hours)	$t_{1/2}$ (hours)
Slow absorption		
Clonazepam	2–4	20–40
Loprazolam	2–5	5–15
Lorazepam	2	10–20
Oxazepam	2	5–15
Temazepam (hard capsules)	3	8–20
Intermediate absorption and elimination		
Alprazolam	1–2	12–15
Bromazepam	1–4	10–25
Chlordiazepoxide	1–2	10–25
Intermediate absorption, slow elimination (with active metabolites)		
Flurazepam	1.5	40–120
Clobazam	1–2	20–40
Chlorazepate	1	40–100
Quazepam	1.5	15–35
Rapid absorption, slow elimination, but rapid redistribution		
Diazepam	1	20–70
Flunitrazepam	1	10–40
Nitrazepam	1	20–30
Rapid absorption, rapid elimination, rapid redistribution		
Lormetazepam (soft capsules)	1	8–20
Temazepam (soft capsules)	1	8–20
Rapid absorption, rapid elimination		
Brotizolam	1	4–7
Zolpidem	1.5	2–5
Zopiclone	1.5	5–8
Rapid absorption, very rapid elimination		
Midazolam	0.3	1–4
Triazolam	1	2–5

CNS more slowly than their more lipophilic cousins. Since temazepam is much more quickly absorbed from a soft gelatin liquid-containing capsule than from a hard capsule or tablet, it is the preferred form for both hypnotic use (Table 2) and recreational use (and for this reason is restricted in some countries). Kinetic differences between drugs and between formulations partially explain why comparing equipotent doses of benzodiazepines is difficult.

The route of metabolism can also be significant, particularly in those with liver disease or who are taking concomitant hepatic enzyme inhibitors, such as erythromycin (SEDA-20, 31). The complex interaction between hepatic dysfunction and benzodiazepines has been reviewed (33); these drugs more readily affect liver function in individuals with liver disease and may also directly contribute to hepatic encephalopathy, as shown by the ability of benzodiazepine antagonists to reverse coma transiently in such patients (33). Elderly people appear to be at increased risk only if they are physically unwell, and particularly if they are taking many medications.

Rapid absorption, often followed by rapid redistribution to tissue stores with consequent falls in brain and blood drug concentrations, plays a significant role in the quick onset and cessation of perceived effects, but long-term actions, for example mild sedative and antianxiety effects, are a consequence of slow hepatic clearance, either by hydroxylation and subsequent conjugation to a glucuronide or by microsomal metabolism to other possibly pharmacologically active metabolites. Agents that are subject to microsomal metabolism and/or oxidation accumulate more rapidly in patients with reduced liver function (for example frail elderly people); only the metabolism of drugs such as oxazepam, lorazepam, and temazepam, which predominantly undergo glucuronidation, is not affected by liver function (Table 3) nor suffer from interference by drugs, such as cimetidine, estrogens, or erythromycin, which compete for the enzyme pathways (see Drug–Drug Interactions).

Pharmacodynamics

The use of techniques of molecular biology to clone the benzodiazepine receptor and the other components of the GABA receptor/chloride channel complex has shown that there are likely to be many variant forms of the receptor, owing to the multiplicity of protein subunits that constitute it. This has given rise to the hope that more selective agonist drugs, for example the "Z drugs" (zaleplon, zolpidem, and zopiclone), may produce fewer adverse effects (35,36); however, this hope appears to have been overoptimistic (10). There are also many ways in which different drugs interact with receptor sites to produce their effects, including agonism, partial agonism, antagonism, inverse agonism (contragonism), and even partial inverse agonism; this increases the complexity considerably. The

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Table 3 Predominant metabolic pathways for benzodiazepines and related agonists

Via CYP3A oxidation	Via glucuronidation
Alprazolam	Lorazepam
Anidazolam	Oxazepam
Bromazepam	Temazepam
Brotizolam	
Chlordiazepoxide	
Clobazam (also CYP2C19)	
Clonazepam	
Chlorazepate	
Diazepam (also CYP2C19)	
Estazolam	
Flunitrazepam	
Flurazepam	
Halazepam	
Loprazolam	
Lormetazepam	
Medazepam	
Midazolam	
Nitrazepam	
Prazepam	
Quazepam	
Triazolam	
Zaleplon	
Zolpidem	
Zopiclone	

NB: Drugs other than diazepam and clobazam, in particular the so-called "Z drugs" (zaleplon, zolpidem, zopiclone) (34), are also likely to have multiple oxidative pathways.

suggestion that partial agonists (such as alpidem and abecarnil) have greater anxiolytic than sedative potency (37), or that they will be less likely to give rise to abuse (35) or dependence (38), is yet to be established.

Medicolegal considerations

Medicolegal problems, especially with the use of triazolam, have been discussed (SEDA-13, 33); debate continues on the interpretation of evidence that points to an increased incidence of adverse behavioral effects with triazolam (39), flunitrazepam, and other short-acting high-potency agents (12). A review has highlighted a substantial rate (0.3–0.7%) of aggressive reactions to benzodiazepines, and the fact that a majority so affected may have intended a disinhibitory effect, with clear forensic implications (40). High rates of benzodiazepine consumption, much of it illicit, continue in prison populations.

Efforts to restrict benzodiazepines in New York State (2,7) and to ban triazolam (Halcion) in the UK (7,41) and the Netherlands (42)(SEDA-4,V) have likewise been fraught with controversy. For example, the requirement to use triplicate prescription forms in New York has been effective in reducing prescription volumes, including arguably necessary and appropriate prescriptions (43). A 1979 suspension of triazolam availability in the Netherlands was overturned in 1990, while a 1993 formal ban in the UK has remained in force (44). Two extensive reports have included recommendations for resolving the special problems posed by the Halcion controversy (44,45).

General adverse effects

Benzodiazepines have a high therapeutic index of safety, with little effect on most systems (other than the CNS) in high doses. However, their toxicity increases markedly when they are combined with other CNS depressant drugs, such as alcohol or opioid analgesics. Medically ill and brain injured patients are particularly susceptible to adverse neurological or behavioral effects (SEDA-18, 43) (SEDA-20, 30) (46).

The most frequent adverse effect which occurs in at least one-third of patients is drowsiness, often accompanied by incoordination or ataxia. Problems with driving, operating machinery, or falls can result, particularly in the elderly, and can be an important source of morbidity, loss of physical function, and mortality (47,48). Memory impairment, loss of insight, and transient euphoria are common; "paradoxical" reactions of irritability or aggressive behavior have been well documented (11) and appear to occur more often in individuals with a history of impulsiveness or a personality disorder (40), and in the context of interpersonal stress and frustration (49). Tolerance to the sedative and hypnotic effects generally occurs more rapidly than to the anxiolytic or amnestic effects (1).

Physical dependence on benzodiazepines is recognized as a major problem, and occurs after relatively short periods of treatment (50,51), particularly in patients with a history of benzodiazepine or alcohol problems. Abrupt withdrawal can cause severe anxiety, perceptual changes, convulsions, or delirium. It can masquerade as a return of the original symptoms in a more severe form (rebound), or present with additional features (SEDA-17, 42) (11). Up to 90% of regular benzodiazepine users have adverse symptoms on withdrawal. The differences between rebound, withdrawal syndrome, and recurrence have been reviewed in detail (3).

Rebound insomnia or heightened daytime anxiety can occur, particularly after short-acting benzodiazepine hypnotics (12,52,53), and constitute a major reason for continuing or resuming drug use (11).

The use of intravenous benzodiazepines administered by paramedics for the treatment of out-of-hospital status epilepticus has been evaluated in a double-blind, randomized trial in 205 adults (54). The patients presented either with seizures lasting 5 minutes or more or with repetitive generalized convulsive seizures, and were randomized to receive intravenous diazepam 5 mg, lorazepam 2 mg, or placebo. Status epilepticus was controlled on arrival at the hospital in significantly more patients taking benzodiazepines than placebo (lorazepam 59%, diazepam 43%, placebo 21%). The rates of respiratory or circulatory complications related to drug treatment were 11% with lorazepam, 10% with diazepam, and 23% with placebo, but these differences were not significant.

Intranasal midazolam 0.2 mg/kg and intravenous diazepam 0.3 mg/kg have been compared in a prospective randomized study in 47 children (aged 6 months to 5 years) with prolonged (over 10 minutes) febrile seizures (55). Intranasal midazolam controlled seizures significantly earlier than intravenous diazepam. None of the children had respiratory distress, bradycardia, or other adverse effects. Electrocardiography, blood pressure, and pulse

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oximetry were normal in all children during seizure activity and after cessation of seizures.

Organs and Systems

Cardiovascular

Hypotension follows the intravenous injection of benzodiazepines, but is usually mild and transient (SED-11, 92) (56), except in neonates who are particularly sensitive to this effect (57). Local reactions to injected diazepam are quite common and can progress to compartment syndrome (SEDA-17, 44). In one study (58), two-thirds of the patients had some problem, and most eventually progressed to thrombophlebitis. Flunitrazepam is similar to diazepam in this regard (59). Altering the formulation by changing the solvent or using an emulsion did not greatly affect the outcome (60). Midazolam, being water-soluble, might be expected to produce fewer problems; in five separate studies there were no cases of thrombophlebitis, and in two others the incidence was 8–10%, less than with diazepam but similar to thiopental and saline (61).

Respiratory

Respiratory depression has been reported as the commonest adverse effect of intravenous diazepam (56), especially at the extremes of age. Midazolam has similar effects (62). All benzodiazepines can cause respiratory depression, particularly in bronchitic patients, through drowsiness and reduction in exercise tolerance (63). Rectal administration of, for example, diazepam can offer advantages in unconscious or uncooperative patients, and is less likely than parenteral administration to produce respiratory depression.

A previous report that rectal and intravenous diazepam can cause respiratory depression in children with seizures (SEDA-24, 84) has been challenged (64,65). The authors of the second comment stated that this complication does not occur when rectal diazepam gel is used without other benzodiazepines; they also recommended that during long-term therapy families should be instructed not to give rectal diazepam more than once every 5 days or five times in 1 month.

In a prospective study of children admitted to an accident and emergency department because of seizures, there were 122 episodes in which diazepam was administered rectally and/or intravenously; there was respiratory depression in 11 children, of whom 8 required ventilation (66). The authors questioned the use of rectal or intravenous diazepam as first-line therapy for children with acute seizures.

Nervous system

Falls

The role of different types of benzodiazepines in the risk of falls in a hospitalized geriatric population has been examined in a prospective study of 7908 patients, consecutively admitted to 58 clinical centers during 8 months (67). Over 70% of the patients were older than 65 years, 50% were women, and 24% had a benzodiazepine prescription during the hospital stay. The findings suggested that the use of benzodiazepines with short and very short half-lives is an important and independent risk factor for falls. Their prescription for older hospitalized patients should be carefully evaluated.

In a case-control study using the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database, the records of 9752 patients hospitalized for fracture of the femur during the period 1992–1996 were extracted and matched by age, sex, state, and index date to the records of 38 564 control patients (68). Among older individuals, the use of benzodiazepines slightly increased the risk of fracture of the femur. Overall, non-oxidative benzodiazepines do not seem to confer a lower risk than oxidative agents. However, the latter may be more dangerous among very old individuals (85 years of age or older), especially if used in high dosages.

In a similar case-control study, 245 elderly patients were matched with 817 controls (69). Benzodiazepines as a group were not associated with a higher risk of hip fracture, but patients who used lorazepam or two or more benzodiazepines had a significantly higher risk.

Effects on performance

All benzodiazepines can cause drowsiness and sedation, and can affect motor and mental performance. Driving is one motor and mental task that is particularly likely to be impaired (SEDA-7, 46), with dangerous consequences; hypnosedatives, like alcohol, impair both actual driving performance (70) and laboratory psychomotor tests (35), and are over-represented in blood samples from delinquent drivers (71). As with alcohol, the maximal impairment occurs while the drug blood concentrations are rising (72), rather than when they have peaked, are stable, or are falling. Somewhat surprisingly, zopiclone 7.5 mg, but not triazolam 0.25 mg, produced deficits in simulated aircraft flight performance 2 and 3 hours after the dose (73). The motor and mental performance reductions induced by hypnotics, especially in elderly people (74), result in an increased incidence of falls (SEDA-21, 38) which can cause hip fractures (75). Agents with short half-lives, including the "Z drugs", were previously thought to carry a reduced risk or even none, but earlier reassuring data have been supplanted by convincing evidence of harm, particularly during the first 2 weeks of prescription (48,76).

Fit young subjects had no impairment of their exercise ability after temazepam or nitrazepam, although nitrazepam caused a subjective feeling of hangover (77).

Seizures

Benzodiazepines can provoke seizures and occasionally precipitate status epilepticus.

- A 28-year-old man with complex partial status, which lasted for 2 months, had a paradoxical worsening of seizure activity in response to diazepam and midazolam (78).

Of 63 neonates receiving lorazepam, diazepam, or both in an intensive care unit, 10 had serious adverse events, including 6 with seizures (57).

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Psychological, psychiatric

Cognition

The amnestic effects of benzodiazepines are pervasive and appear to derive from disruption of the consolidation of short-term into long-term memory (79). Amnesia appears to underlie the tendency of regular hypnotic users to overestimate their time asleep, because they simply forget the wakeful intervals (80); in contrast, the same patients underestimate their time spent asleep when drug-free. This amnestic property (SEDA-17, 42) (SEDA-19, 33) has been used to advantage in minor surgery, particularly with midazolam and other short-acting compounds (although male doctors and dentists are advised to have a chaperone present when performing benzodiazepine-assisted procedures with female patients). However, unwanted amnesia can occur, particularly with triazolam, when used as a hypnotic or as an aid for travelers (81,82). The combination of a short half-life and high potency, especially when it was used in the higher doses that were recommended when the drug was initially launched, makes triazolam particularly likely to cause this problem. Studies of low-dose lorazepam (1 mg) in healthy young adults have shown specific deficits in episodic memory (SEDA-21, 38) (SEDA-19, 35). Flurazepam and temazepam have initiated relatively few reports of adverse effects on memory, although flurazepam did cause daytime sedation. Temazepam was uncommonly mentioned in adverse reaction reports, but was also reported more often as being without adequate hypnotic effect. Ironically, temazepam produces more, and oxazepam less, sedation than other benzodiazepines in overdose (83).

The role of benzodiazepines in brain damage has been reviewed (SEDA-14, 36). Cognitive impairment in long-term users can be detected in up to half of the subjects, compared with 16% of controls, but the issue of reversibility with prolonged abstinence is unresolved. Cognitive toxicity is more common with benzodiazepines than other anticonvulsants, with the possible exception of phenobarbital (84).

Patients often have memory deficits after taking benzodiazepines and alcohol. In a study of hippocampal presynaptic glutamate transmission in conjunction with memory deficits induced by benzodiazepines and ethanol, reductions in hippocampal glutamate transmission closely correlated with the extent of impairment of spatial memory performance. The results strongly suggested that presynaptic dysfunction in dorsal hippocampal glutamatergic neurons would be critical for spatial memory deficits induced by benzodiazepines and ethanol (85).

When the relation between benzodiazepine use and cognitive function was evaluated in a prospective study of 2765 elderly subjects, the authors concluded that current benzodiazepine use, especially in recommended or higher dosages, is associated with worse memory among community-dwelling elderly people (86).

In a prospective study, 1389 people aged 60–70 years were recruited from the electoral rolls of the city of Nantes, France (Epidemiology of Vascular Aging Study) (87). A range of symptoms was examined, including cognitive functioning and symptoms of depressive anxiety, and data were also collected on psychotropic and other drugs, as well as tobacco use and alcohol consumption at baseline and thereafter at 2 and 4 years. Users of benzodiazepines were divided into episodic users, recurrent users, and chronic users. Chronic users of benzodiazepines had a significantly higher risk of cognitive decline in the global cognitive test and two attention tests than non-users. Overall, episodic and recurrent users had lower cognitive scores compared with non-users, but the differences were not statistically significant. These findings suggest that long-term use of benzodiazepines is a risk factor for increased cognitive decline in elderly people.

Delirium

Excessive anxiety and tremulousness, hyperexcitability, confusion, and hallucinations were all reported more often with triazolam than with temazepam or flurazepam, when spontaneous reporting was analysed (81). Whether this is dose-related, and perhaps related to the rapid changes in blood concentration with triazolam, is not clear. Delirium is common, particularly in elderly people, who may have impaired drug clearance, and must always be regarded as possibly drug-induced. Of considerable relevance to hospital practice is the finding of a three-fold increased risk of postoperative delirium in patients given a benzodiazepine (88). Dose- and age-related increases in adverse cognitive and other central nervous effects from benzodiazepines (82) are well documented. The use of these drugs in elderly people has been reviewed, with recommendations about maximizing the benefit-to-harm balance in this group of individuals who are susceptible to cognitive and other adverse effects (89,90).

Sleep

The benzodiazepines typically suppress REM sleep, with consequent rebound dreaming and restlessness on withdrawal, leading to poorer sleep patterns (SEDA-12, 42) (91).

The use of benzodiazepines, particularly the short-acting compounds such as triazolam, for the induction of sleep has provoked much discussion (SEDA-17, 42). The debate rages over the risks and benefits of short-acting compounds, in inducing bizarre behavior or rapid withdrawal with daytime anxiety, compared with the possibility of hangover sedation and performance deficits with longer-acting compounds (92). The treatment of sleep disorders is multifaceted, because of the complex nature of sleep and the variety of factors that can give rise to sleep disorders (82). Consequently, such treatment should be selected and proffered carefully, with due regard for all the factors, not treated cavalierly with the latest flavor-of-the-month benzodiazepine receptor agonist. Non-drug treatments are effective (17) and should be considered first; pharmacological treatment should take into consideration any pre-existing factors, for example anxiety, depression, the duration and nature of medical problems (including any painful condition), concomitant medications, and other substance use (13).

Psychoses

Depression is commonly seen (93), either during benzodiazepine treatment or as a complication of withdrawal (SEDA-17, 42). Relief of anxiety symptoms can uncover pre-existing depression, rather than causing depression

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per se. In addition to their euphoriant effects in some individuals, benzodiazepines can directly increase irritability and depression and, less commonly, lead to full-blown manic episodes (94,95).

Review of a Canadian adverse drug reactions database showed several cases of previously unreported benzodiazepine-induced adverse effects, including hallucinations and encephalopathy (96), although whether benzodiazepines alone were responsible is difficult to confirm. Visual hallucinations have also been reported in association with zolpidem (97).

Benzodiazepine withdrawal, like alcohol withdrawal, can cause schizophreniform auditory hallucinations (98).

Behavior

While they are generally regarded as being tranquillizers, benzodiazepines and related hypnosedatives can release aggression and induce antisocial behavior (99), particularly in combination with alcohol (100) and in the presence of frustration (49). Aggression can occur during benzodiazepine intoxication and withdrawal (99). Non-medical use of flunitrazepam (101) seems particularly likely to reveal paradoxical rage and aggression, with consequent forensic problems. The combination of abnormal disinhibited behavior and amnesia produced by benzodiazepines can be singularly dangerous. Anecdotal cases suggest that hypnosedatives can also disinhibit violent behavior in individuals taking antidepressants. A literature review of behavioral adverse effects associated with benzodiazepines (clonazepam, diazepam, and lorazepam) has shown that 11–25% of patients with mental retardation have these adverse effects (102). In two controlled studies, lorazepam was more likely to provoke aggression than oxazepam (103,104).

Gastrointestinal

Nausea due to benzodiazepines has been reported as being commoner in children, but the incidence does not usually greatly exceed that found with placebo. Gastrointestinal disturbances are more common with the newer non-benzodiazepine agents, for example zopiclone and buspirone (105,106).

Liver

Jaundice has been reported after benzodiazepines, although in only a few cases have they been the only drugs involved (SED-12, 97).

Sexual function

Female orgasm is inhibited by some central depressant and psychotropic drugs, including antipsychotic drugs, antidepressants, and anxiolytic benzodiazepines (107). A survey of patients with bipolar affective disorder taking lithium showed that the co-administration of benzodiazepines was associated with a significantly increased risk (49%) of sexual dysfunction in both men and women (108). Reduced libido is uncommonly reported, as is sexual inhibition, but the actual incidences of these complications may be considerably higher. Hypnosedatives, particularly flunitrazepam and gammahydroxybutyrate, are implicated in sexual assault and "date rape" (109).

Long-Term Effects

Drug tolerance

Animal studies have suggested a possible mechanism for tolerance, in that chronic treatment of rats with triazolam reduced the mRNA coding for certain GABA receptor proteins (110).

Drug dependence

The likelihood and possible severity of dependence on benzodiazepines has been discussed (50).

Drug withdrawal

The likelihood and possible severity of withdrawal from benzodiazepines has been discussed, especially with regard to the newer short-acting compounds (50).

Withdrawal symptoms occur in at least one-third of long-term users (over 1 year), even if the dose is gradually tapered (111). Symptoms come on within 2–3 days of withdrawal of a short-acting or medium-acting benzodiazepine, or 7–10 days after a long-acting drug; short-acting benzodiazepines tend to produce a more marked withdrawal syndrome (35). Lorazepam and alprazolam are particularly difficult to quit. Symptoms usually last 1–6 weeks, but can persist for many months, leaving the patient in a vulnerable state, with likely recurrence of the original disorder and of self-medication. Withdrawal symptoms can occur within 4–6 weeks of daily long-acting benzodiazepine use (112), and possibly earlier in susceptible individuals.

Symptoms on withdrawal are variable in nature and degree. Rebound insomnia can occur one or two nights after withdrawal of short-acting drugs. Anxiety is common, with both psychological and physical manifestations, including apprehension, panic, insomnia, palpitation, sweating, tremor, and gastrointestinal disturbances. Irritability and aggression also occur, notably after triazolam. Depression has been reported after benzodiazepine withdrawal (113). There may be increased or distorted sensory perceptions, such as photophobia, altered (metallic) taste, and hypersensitivity to touch and pain. Flu-like muscle aches and spasms, unsteadiness, and clumsiness are common. Perceptual distortions include burning or creeping of the skin and apparent movement or changes in objects or self (111). General malaise with loss of appetite can occur. As with alcohol, paranoid psychosis, delirium, and epileptic fits are possible on withdrawal (SED-12, 97). With careful handling, often involving psychological and sometimes adjunctive pharmacological support, motivated patients who depend on benzodiazepines can usually be successfully withdrawn. In particular, the combination of gradual dose-tapering and cognitive behavioral therapy can be helpful (114). Guidelines on the management of such patients have been concisely presented (51).

Second-Generation Effects

Teratogenicity

Benzodiazepines readily pass from the mother to fetus through the placenta (115). There may be a risk of

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congenital malformations, particularly oral cleft, if a pregnant woman takes a benzodiazepine during the first trimester, but the data are inconsistent across drugs (alprazolam having the most clearly defined risk), and any overall effect is probably small (27,28). The risk of benzodiazepine-induced birth defects thus remains uncertain (116), despite two cases of fetal-alcohol syndrome reported after benzodiazepine exposure alone (117).

The occurrence of congenital abnormalities associated with the use of benzodiazepines (alprazolam, clonazepam, medazepam, nitrazepam, and tofisopam) during pregnancy has been analysed in a matched case-control study (118). The cases and controls were drawn from the Hungarian Case-Control Surveillance of Congenital Abnormalities from 1980 to 1996. Of the 38 151 pregnant women who delivered babies without congenital anomalies, 75 had taken benzodiazepines during pregnancy, compared with 57 of 22 865 who delivered offspring with anomalies. Thus, treatment with these benzodiazepines during pregnancy did not cause a detectable teratogenic risk. However, the true relevance of these findings needs to be supported by prospective case ascertainment.

Fetotoxicity

Benzodiazepines readily pass from the mother to fetus through the placenta (115). There is a further concern about cognitive development after in utero exposure to benzodiazepines. It now appears that the slowed intellectual progress seen in some children exposed in utero will "catch up" in most cases by age 4 (28). Unfortunately, the impact of sedative-hypnotic use during pregnancy is often complicated by the abuse of multiple agents and poor maternal nutrition and antenatal care, and may be further confounded by social and environmental deprivation, which the infant often faces after birth (28,119). More definite but short-lived problems occur with benzodiazepines given in late pregnancy and during labor; here floppiness, apnea, and withdrawal in the infant can pose problems (28,120) but usually resolve uneventfully (SEDA-21, 38). Pregnant women should avoid benzodiazepines if possible, especially during late pregnancy and labor; if required, chlordiazepoxide appears to have the best established record (29). On the other hand, alprazolam should be avoided, and temazepam plus diphenhydramine appears to be a particularly toxic combination in late pregnancy, based on animal research and one case report of fetal activation followed by stillbirth (121).

Lactation

Benzodiazepines are secreted into the milk in relatively small amounts (28). During lactation, longer-acting agents are relatively contraindicated, particularly with continued administration beyond 3–5 days, owing to the likelihood of infant sedation (120,122). Short-acting benzodiazepines and zopiclone are probably safe, especially if restricted to single doses or for short courses of therapy (28,123). Zopiclone and midazolam, for example, become undetectable in breast milk 4–5 hours after a dose (124).

Susceptibility Factors

Age

The safety of benzodiazepines in neonates has been assessed in a retrospective chart review of 63 infants who received benzodiazepines (lorazepam and/or midazolam) as sedatives or anticonvulsants (57). Five infants had hypotension and three had respiratory depression. In all cases of respiratory depression, ventilatory support was initiated or increased. Significant hypotension was treated with positive inotropic drugs in two cases. Thus, respiratory depression and hypotension are relatively common when benzodiazepines are prescribed in these patients. However, both depression and hypotension could also have been due to the severe underlying illnesses and concomitant medications. Matched controls were not studied.

Other features of the patient

Benzodiazepines are more likely to cause adverse effects in patients with HIV infection and other causes of organic brain syndrome (46).

Drug Administration

Drug overdose

Overdosage of benzodiazepines alone is generally thought to be safe, but deaths have occasionally been reported (125–127). In 204 consecutive suicides seen by the San Diego County Coroner during 1981–1982, drugs were detected in 68%, and anxiolytics and hypnotics in 11% and 12% respectively; although benzodiazepines were found in under 10% of the group as a whole, they were found in one-third of those who died by overdose (128). In one series of 2827 intentional cases of poisoning, in which there were ten deaths, three were associated with benzodiazepines; death was related to a delay between ingestion and medical intervention (129), and advanced age has also been described as a risk factor (130). In other cases death has been attributed to combined overdose with other drugs, such as alcohol (126), oxycodone (131,132), tramadol (133), and amitriptyline (134).

Concomitant benzodiazepine overdose has also been reported to be an independent risk factor in the development of hepatic encephalopathy (OR = 1.91; CI = 1.00, 3.65) and renal dysfunction (OR = 1.81; CI = 1.00, 3.22) in patients who take a paracetamol overdose (135).

Drug–Drug Interactions

Antibiotics

Antibiotics (erythromycin, chloramphenicol, isoniazid) compete for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41).

Macrolides cause increases in the serum concentrations, AUCs, and half-lives and reductions in the clearance of triazolam and midazolam (136–138). These changes can result in clinical effects, such as prolonged psychomotor impairment, amnesia, or loss of

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consciousness (139). Erythromycin can increase concentrations of midazolam and triazolam by inhibition of CYP3A4, and dosage reductions of 50% have been proposed if concomitant therapy is unavoidable (140).

Antifungal imidazoles

Antifungal imidazoles (ketoconazole, itraconazole, and analogues) compete for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39, 41–43).

Antihistamines

The potentiation of sedative effects from benzodiazepines when combined with centrally acting drugs with antihistamine properties (for example first-generation antihistamines, tricyclic antidepressants, and neuroleptic drugs) can pose problems (141). Antihistamines that do not have central actions do not interact with benzodiazepines as in the case of mizolastine and lorazepam (142), ebastine and diazepam (143), and terfenadine and diazepam (141).

Calcium channel blockers

Diltiazem and verapamil compete for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41).

Central stimulants

Caffeine and other central stimulants can reverse daytime sedation from benzodiazepine use. There was a positive effect of caffeine (250 mg) on early-morning performance after both placebo and flurazepam (30 mg) given the night before (144,145), particularly in terms of subjective assessments of mood and sleepiness. However, one cannot assume that the alerting effect of caffeine necessarily reverses the amnestic, disinhibiting, or insight-impairing effects of benzodiazepines. Indeed, caffeine can actually worsen learning and performance already impaired by lorazepam (146). Other drugs with direct or indirect CNS stimulant activity (theophylline, ephedrine, amphetamine, and their analogues) have similar effects and can counteract the effects of benzodiazepines, at least subjectively. Another worrying feature of stimulant use, particularly in drug misusers, is that it commonly increases the perceived need for hypnosedatives.

Cimetidine

Cimetidine can impair benzodiazepine metabolism and lead to adverse effects (SEDA-18, 43). In contrast, a few benzodiazepines are metabolized exclusively by glucuronide conjugation (lorazepam, oxazepam, temazepam), and are therefore unaffected by concomitant therapy with cimetidine and other oxidation inhibitors (121).

Clozapine

Caution has been recommended when starting clozapine in patients taking benzodiazepines (SEDA-19, 55). Three cases of delirium associated with clozapine and benzodiazepines (147) have been reported. There have been several reports of synergistic reactions, resulting in increased sedation and ataxia, when lorazepam was begun in patients already taking clozapine (148).

- Syncope and electrocardiographic changes (sinus bradycardia of 40/minute with deep anteroseptal inverted T waves and minor ST changes in other leads) have been observed with the concurrent administration of clozapine (after the dosage was increased to 300 mg/day) and diazepam (30 mg/day) in a 50-year-old man (149).

CNS depressants

The interactions of benzodiazepines with other nervous system depressants, especially alcohol and other GABAergic drugs, have been reviewed (150). Other drugs with nervous system depressant effects (opioids, anticonvulsants, general anesthetics) also can add to, and complicate, the depressant action of benzodiazepines.

Phenothiazines and butyrophenones can counteract intoxication from lysergic acid diethylamide (LSD); benzodiazepines can inhibit this useful effect of antipsychotic drugs (151).

Disulfiram

Disulfiram competes for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41).

Enzyme inducers

Enzyme induction can be problematic with co-administration of benzodiazepines and rifampicin or certain anticonvulsants (phenobarbital, phenytoin, carbamazepine). However, despite enzyme stimulation, the net effect of adding these anticonvulsants can be augmentation of benzodiazepine-induced sedation.

Rifampicin, and presumably other enzyme inducers, reduces concentrations of zolpidem, zopiclone, and buspirone (SEDA-22, 42). Drugs that are solely glucuronidated (lorazepam, oxazepam, and temazepam) are not affected.

HIV protease inhibitors

Some protease inhibitors (saquinavir) compete for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41).

Levodopa

The question of whether starting a benzodiazepine in patients taking levodopa is followed by a faster increase in antiparkinsonian drug requirements has been studied using drug dispensing data for all the residents in six Dutch cities (152). All were 55 years old or older and had used levodopa for at least 360 days. There were 45 benzodiazepine starters and 169 controls. Antiparkinsonian drug doses increased faster in the benzodiazepine group, but the difference was not significant (RR = 1.44; 95% CI = 0.89, 2.59).

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Lithium

In 18 patients treated with benzodiazepines and/or antipsychotic drugs there were increased chromosomal aberrations and increased sister chromatid exchange, but there were no significant differences between this group and another group of 18 patients taking lithium in addition to benzodiazepines and/or antipsychotic drugs (153).

Moxonidine

Moxonidine can potentiate the effect of benzodiazepines (154).

Muscle relaxants

Laboratory investigations have shown that some benzodiazepines can produce biphasic effects on the actions of neuromuscular blocking agents (155,156), higher doses potentiating the effects (155,157); however, several human investigations have failed to show a significant effect (158–160). It has been suggested that agents that are added to commercial formulations of some benzodiazepines to render them more water-soluble may mask the benzodiazepine effect (160).

Nevertheless, some interactions of benzodiazepines with muscle relaxants used in anesthesia have been described. Diazepam has been reported to potentiate the effects of tubocurare (161) and gallamine (162) and to reduce the effects of suxamethonium (162). However, in 113 patients undergoing general anesthesia, intravenous diazepam 20 mg, lorazepam 5 mg, and lormetazepam 2 mg did not potentiate the neuromuscular blocking effects of vecuronium or atracurium (160).

In 113 patients undergoing general anesthesia, intravenous midazolam 15 mg slowed recovery of the twitch height after vecuronium and atracurium compared with diazepam. The recovery index was not altered (160). However, in another study in 20 patients, midazolam 0.3 mg/kg did not affect the duration of blockade, recovery time, intensity of fasciculations, or adequacy of relaxation for tracheal intubation produced by suxamethonium 1 mg/kg, nor the duration of blockade and adequacy of relaxation for tracheal intubation produced by pancuronium 0.025 mg/kg in incremental doses until 99% depression of muscle-twitch tension was obtained (159). Furthermore, in 60 patients undergoing maintenance anesthesia randomly assigned to one of six regimens (etomidate, fentanyl, midazolam, propofol, thiopental plus nitrous oxide, or isoflurane plus nitrous oxide), midazolam did not alter rocuronium dosage requirements (163).

Neuroleptic drugs

Because of the frequency of co-administration of benzodiazepines with neuroleptic drugs, it is important to consider possible adverse effects that can result from such combinations. In a brief review, emphasis has been placed on pharmacokinetic interactions between neuroleptic drugs and benzodiazepines, as much information on their metabolic pathways is emerging (164). Thus, the enzyme CYP3A4, which plays a dominant role in the metabolism of benzodiazepines, also contributes to the metabolism of clozapine, haloperidol, and quetiapine, and neuroleptic drug plasma concentrations can rise. Intramuscular levomepromazine in combination with an intravenous benzodiazepine has been said to increase the risk of airways obstruction, on the basis of five cases of respiratory impairment; the doses of levomepromazine were higher in the five cases that had accompanying airways obstruction than in another 95 patients who did not (165).

Omeprazole

Omeprazole can impair benzodiazepine metabolism and lead to adverse effects (SEDA-18, 43).

Opioids

Fentanyl competes for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41).

Oral contraceptives

Oral contraceptives alter the metabolism of some benzodiazepines that undergo oxidation (alprazolam, chlordiazepoxide, diazepam) or nitroreduction (nitrazepam) (166). For these drugs, oral contraceptives inhibit enzyme activity and reduce clearance. There is nevertheless no evidence that this interaction is of clinical importance. It should be noted that for other benzodiazepines that undergo oxidative metabolism, such as bromazepam or clotiazepam, no change has ever been found in oral contraceptive users. Some other benzodiazepines, such as lorazepam, oxazepam, and temazepam, are metabolized by glucuronic acid conjugation. The clearance of temazepam was increased when oral contraceptives were co-administered, but the clearances of lorazepam and oxazepam were not (167). Again, it is unlikely that this is an interaction of clinical importance.

Selective serotonin reuptake inhibitors (SSRIs)

Some SSRIs (notably fluvoxamine and to a lesser extent fluoxetine) and their metabolites inhibit hepatic oxidative enzymes, particularly CYP2C19 and CYP3A, that metabolize most benzodiazepines, as well as zaleplon, zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41) (168,169). Apart from fluvoxamine, SSRIs do not generally have a clinically prominent effect on hypnosedative effects; studies vary from those that have found that fluoxetine has a moderate but functionally unimportant impact on diazepam concentrations (170) to results that suggest significant aggravation of the cognitive effects of alprazolam when co-prescribed with the SSRI (171).

Tricyclic antidepressants

Four patients developed adverse effects attributable to combinations of benzodiazepines with tricyclic antidepressants, including exacerbations of delusional disorder (172).

Nefazodone competes for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41).

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Benzoxonium chloride

See also Disinfectants and antiseptics

General Information

Benzoxonium is a quaternary ammonium compound with antibacterial, antiviral, and antimycotic activity. It can be used in topical disinfection, disinfection of surgical instruments, inhibition of plaque formation, and in veterinary products.

Organs and Systems

Immunologic

Contact allergic reactions have been rarely reported, with potential cross-reactivity with benzalkonium chloride and domiphen bromide (1,2).

- A 37-year-old woman developed intense burning and pruritic eczema where she had applied a cream containing benzoxonium for seborrheic dermatitis for 5 months (3). The reaction disappeared on withdrawal of the cream. Patch tests were positive to benzoxonium chloride 0.1% aqueous on days 2 and 4. Patch tests with benzalkonium chloride and benzoxonium chloride in 20 controls were negative.

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Benzoyl peroxide

General Information

Benzoyl peroxide is an antimicrobial and keratolytic agent used in the treatment of acne; it is also added to some foods. It is a catalyst for cross-linking in the production of plastics and is occasionally used in acrylic resin systems (for example composite dental fillings, dental prostheses) in which it is formed during the cross-linking process.

Organs and Systems

Skin

Allergic contact dermatitis has been attributed to topical benzoyl peroxide in a variety of settings (1–4).

- An 80-year-old man developed dermatitis in his leg amputation stump. He had been using stretching tapes containing benzoyl peroxide, and a patch test showed a positive reaction to benzoyl peroxide (1% in petrolatum) on days 2 and 3 (5).

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Benzydamine

General Information

Benzydamine is 1-benzyl-3-(3-dimethylaminopropoxy)-*H*-indazole, used for medical purposes as the hydrochloride. It has analgesic, anti-inflammatory, antipyretic, and local anesthetic effects. In the past it has been especially used in the symptomatic treatment of edematous postoperative or traumatic swelling, non-specific inflammation of the upper respiratory tract, and inflammation of connective tissues and joints. Nowadays, Tantum verde is the only such formulation listed in Germany; it is used for the treatment of oral and pharyngeal inflammation from any cause, for example radiotherapy-induced mucositis, stomatitis, Vincent's angina, necrotic oropharyngeal neoplasms, after surgical operations on the mouth and

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pharynx, after intubation, and after endoscopic laryngeal surgery. It can be administered as a spray, a gargle solution, a rinsing solution, or lozenges.

Organs and Systems

Skin

Skin reactions, including photosensitivity and contact dermatitis (when used topically), have been reported (1–7).

- A 67-year-old woman with pharyngitis gargled with Tantum verde, and after 3 weeks, during a holiday, developed an erythematous rash on sun-exposed skin, worsening within the next few days (8). She had not used a sunscreen. There were mainly well-demarcated areas of eczema on the face, neck, neckline, forearms, and lower legs. After oral and topical corticosteroids, the skin lesions improved within a few days.

There have been two other case reports of photoallergic dermatitis after local pharyngeal treatment with formulations containing benzydamine (6). This presumably occurs because of oral or intestinal absorption.

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Benzyl alcohol

See also Disinfectants and antiseptics

General Information

Benzyl alcohol is commonly used as a preservative in multidose injectable pharmaceutical formulations. For this purpose, concentrations in the range of 0.5–2.0% are used and the whole amount of benzyl alcohol injected is generally very well tolerated. Concentrations of 0.9% are used in Bacteriostatic Sodium Chlorine (USP), which is often used in the management of critically ill patients to flush intravascular catheters after the addition of medications or the withdrawal of blood, and in Sterile Bacteriostatic Water for injection (USP), used to dilute or reconstitute medications for intravenous use. The content of benzyl alcohol in a lot of injectable pharmaceutical formulations needs to be considered carefully. The view still taken in many countries that the additives and excipients in medicines are trade secrets must be deplored. The duty to declare them is only realized in some countries.

The toxic effects of benzyl alcohol include respiratory vasodilatation, hypertension, convulsions, and paralysis.

Organs and Systems

Nervous system

The data on reported cases of neurological disorders after intrathecal chemotherapy with methotrexate or cytosine arabinoside that could be attributed to benzyl alcohol or to other preservatives have been reviewed in the context of a case of flaccid paraplegia after intrathecal administration of cytosine arabinoside diluted in bacteriostatic water containing 1.5% benzyl alcohol (1). Most commonly, flaccid paraparesis, with absent reflexes, developed rapidly, often with pain and anesthesia. Very often there was full recovery. The prognosis depended mainly on the concentration of the preservative and on the time of exposure. In some cases, the paralysis ascended to cause respiratory distress, cardiac arrest, and death. Only preservative-free sterile CSF substitute or saline, or preferably the patient's own CSF, should be used to dilute chemotherapeutic agents (SEDA-11, 475).

Skin

Allergic contact dermatitis, characterized by erythema, palpable edema, and raised borders, was attributed to benzyl alcohol (2). In this case, the benzyl alcohol was present as a preservative in an injectable solution of sodium tetradecyl sulfate, a sclerosing agent used for the treatment of varicose veins. The author provided a list of 151 injectable formulations (48 for subcutaneous administration) that contained benzyl alcohol as a preservative in the range 0.5–2.0%. The list included hormones and steroids, antihypertensive drugs (reserpine), vitamin formulations (vitamins B_{12} and B_6), ammonium sulfate, antihistamines, antibiotics, heparin (17 brands), tranquillizers, and sclerosing agents (sodium morrhuate and sodium tetradecyl sulfate).

- A patient with a contact allergic reaction to a topical antimycotic drug formulation that contained benzoyl alcohol had positive patch tests on day 4 and a positive repeated open application test to benzoyl alcohol 5% in petroleum jelly (3).

The authors noted that although contact allergic reactions to benzoyl alcohol are rarely reported, they can be responsible for contact allergy to topical glucocorticoid formulations.

Immunologic

Various allergic reactions have been attributed to benzyl alcohol.

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- A 55-year-old man developed fatigue, nausea, and diffuse angioedema shortly after an intramuscular injection of vitamin B12 containing benzyl alcohol (4).
- In another male patient, fever developed, and a maculopapular rash occurred on his chest and arms after an injection of cytarabine, vincristine, and heparin in a dilution solution containing benzyl alcohol (5).

Susceptibility Factors

Age

A gasping syndrome in small premature infants who had been exposed to intravenous formulations containing benzyl alcohol 0.9% as a preservative has been described (SEDA-10, 421) (SEDA-11, 475) (6–8). The affected infants presented with a metabolic acidosis, seizures, neurological deterioration, hepatic and renal dysfunction, and cardiovascular collapse. Death was reported in 16 children who received a minimum of 99 mg/kg/day of benzyl alcohol. This metabolic acidosis is caused by accumulation of the metabolite benzoic acid and is mainly related to an excessive body burden relative to body weight, so that the load of the metabolite may exceed the capacity of the immature liver and kidney for detoxification. The FDA has recommended that neither intramuscular flushing solutions containing benzyl alcohol nor dilutions with this preservative should be used in newborn infants.

In a review of the hospital and autopsy records of infants admitted to a nursery during the previous 18 months, 218 patients had been given fluids containing benzyl alcohol as flush solutions and they were compared with 218 neonates admitted during the following 18 months (9). Withdrawal of benzyl alcohol as a preservative had no demonstrable effect on mortality, but the development of kernicterus was significantly associated with benzyl alcohol in 15 of 49 exposed patients, and no cases occurred after withdrawal of the preservative. However, this apparent association was not confirmed in a 5-year study of the use of benzyl alcohol as a preservative in intravenous medications in a neonatal intensive care unit (10). In 129 neonates who died between the ages of 2 and 28 days, there was no difference in the rate of kernicterus and the exposure to benzyl alcohol between neonates who developed kernicterus and the control group of unaffected infants who were born during the same period and who were of the same birth weight and gestation age. In this study, only estimates of the extent of exposure to benzyl alcohol were given, rather than exact doses and serum concentrations.

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Bephenium

General Information

Bephenium hydroxynaphthoate is an antihelminthic drug that has been used in the treatment of hookworm infections due to *Ancylostoma duodenale* in a single dose (1). It is well tolerated, and reactions are confined to mild gastrointestinal disturbances (unpleasant taste, nausea, abdominal pain, and sometimes also vomiting and diarrhea), headache, and dizziness. It is reputed to be safe in pregnancy but is better avoided in conditions in which purgation could be dangerous; these naturally include the last few months of pregnancy, because of the risk of miscarriage.

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Bepridil

See also Antidysrhythmic drugs

General Information

Bepridil is an antidysrhythmic drug with unusual pharmacological properties in that it belongs to both class I and class IV. In other words, it blocks both the fast inward sodium current and the slow outward calcium current in excitable cardiac cells (SEDA-13, 141). It was withdrawn because of its serious prodysrhythmic effects.

Bepridil has been the subject of a brief general review (1) and its pharmacokinetics have been specifically reviewed (2). Although it is highly protein-bound, bepridil does not take part in protein-binding displacement interactions (2).

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The main adverse effect of bepridil is torsade de pointes due to QT interval prolongation. After intravenous infusion bepridil can cause local reactions (3) and phlebothrombosis (4). Other minor adverse effects that have been reported include urticaria (5), gastrointestinal disturbances (especially diarrhea) (6,7), and dizziness (6–8). Hepatic enzymes can rise (9,10).

Organs and Systems

Cardiovascular

Bepridil can cause hypotension after rapid intravenous injection (6,11), but not during long-term oral therapy (12,13).

Bepridil prolongs the QT interval (3,7,8,14), an effect that is dose-related (14). It can therefore cause dysrhythmias, including polymorphous ventricular tachycardia, the risk of which is greater in patients with potassium depletion, those with pre-existing prolongation of the QT interval, those with a history of serious ventricular dysrhythmias, and those who are also taking other drugs that prolong the QT interval (15).

Of 75 elderly patients who took bepridil 200 mg/day, 23 had prolongation of the QT interval. The factors that were associated with this were hypokalemia, bradycardia, renal insufficiency, and an increased plasma bepridil concentration (16).

Drug–Drug Interactions

Antidysrhythmic drugs

Because it prolongs the QT interval, bepridil can potentiate the effects of other drugs with the same effect (for example other Class I antidysrhythmic drugs and amiodarone).

Beta-adrenoceptor antagonists

The effect of a beta-blocker (metoprolol 30–40 mg/day or bisoprolol 2.5–5.0 mg/day for 1 month) on the change in QT interval, QT dispersion, and transmural dispersion of repolarization caused by bepridil has been studied in 10 patients with paroxysmal atrial fibrillation resistant to various antidysrhythmic drugs (17). Bepridil significantly prolonged the QTc interval from 0.42 to 0.50 seconds, QT dispersion from 0.07 to 0.14 seconds, and transmural dispersion of repolarization from 0.10 to 0.16 seconds. The addition of a beta-blocker shortened the QTc interval from 0.50 to 0.47 seconds, QTc dispersion from 0.14 to 0.06 seconds, and transmural dispersion of repolarization from 0.16 to 0.11 seconds. The authors therefore suggested that combined therapy with bepridil and a beta-blocker might be useful for intractable atrial fibrillation.

Bepridil does not interact with propranolol (8).

Digoxin

Bepridil does not interact with digoxin (18).

Phenazone

Bepridil increases the rate of clearance of phenazone (antipyrine) and might therefore be expected to enhance the rate of clearance of other drugs that are metabolized (19).

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Beraprost

See also Prostaglandins

General Information

Beraprost is a stable, orally active analogue of PGI_2. It has been tested in patients with intermittent claudication in a randomized, placebo-controlled trial (1). Beraprost improved walking distance more often than placebo. It also reduced the incidence of critical cardiovascular events, but the trial was not powered for statistical validation of this effect. As with iloprost, headache and flushing were the most common adverse effects.

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Berberidaceae

See also Herbal medicines

General Information

The genera in the family of Berberidaceae (Table 1) include lychee and soapberry.

Table 1 The genera of Berberidaceae

Achlys (achlys)
Berberis L (barberry)
Caulophyllum (cohosh)
Diphylleia (umbrellaleaf)
Epimedium (epimedium)
Jeffersonia (jeffersonia)
Mahonia (barberry)
Nandina (nandina)
Podophyllum (may apple)
Vancouveria (insideout flower)

Berberis vulgaris

Barberry (pipperidge bush) is a vernacular name for *Berberis vulgaris* (the European barberry), but it can also refer to *Mahonia aquifolium* and *Mahonia nervosa*. In the USA only the *Mahonia* species have had official status as a source of barberry, but *Berberis vulgaris* is said to serve similar medicinal purposes and to contain similar principles. Its root bark yields the quaternary isoquinoline alkaloid berberine and several other tertiary and quaternary alkaloids. Berberine is also found in *Hydrastis canadensis* (goldenseal) and *Coptis chinensis* (goldenthread).

Adverse effects

In man berberine has positive inotropic, negative chronotropic, antidysrhythmic, and vasodilator properties (1) and there is experimental evidence that it can cause arterial hypotension (2,3).

Berberine displaces bilirubin from albumin and there is therefore a risk of kernicterus in jaundiced neonates (4).

In a study of the effect of berberine in acute watery diarrhea, oral doses of 400 mg were well tolerated, except for complaints about its bitter taste and a few instances of transient nausea and abdominal discomfort. However, patients with cholera given tetracycline plus berberine were more ill, suffered longer from diarrhea, and required larger volumes of intravenous fluid than those given tetracycline alone (5).

Caulophyllum thalictroides

Caulophyllum thalictroides (blue cohosh) contains vasoactive glycosides and quinolizidine alkaloids that produce toxic effects on the myocardium in animals.

Adverse effects

Heart failure occurred in the fetus of a mother who used blue cohosh.

- A 41-week-old boy weighing 3.66 kg developed respiratory distress, acidosis, and shock shortly after a spontaneous vaginal delivery (6). His 36-year-old mother had a history of adequately controlled hypothyroidism and had taken tablets of blue cohosh for 1 month to induce uterine contractions. Subsequently she felt more contractions and less fetal activity. After delivery, the baby continued to be critically ill for several weeks and required treatment for respiratory failure and cardiogenic shock. He gradually improved and was extubated after 21 days. There were no congenital abnormalities or other reasons to explain the infant's problems. He remained in hospital for 31 days and an electrocardiogram at discharge was consistent with a resolving anterolateral myocardial infection. Two years later he had fully recovered, but cardiomegaly and impaired left ventricular function persisted.

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The authors believed that the consumption of blue cohosh by the mother had caused heart failure in the child.

Dysosma pleianthum

Dysosma pleianthum (bajiaolian), a species of May apple, is a traditional Chinese herbal medicine rich in podophyllotoxin. It has been widely used in China for thousands of years as a general remedy and for the treatment of snake bite, weakness, condyloma accuminata, lymphadenopathy, and tumors.

Adverse effects

Five people developed nausea, vomiting, diarrhea, abdominal pain, thrombocytopenia, leukopenia, abnormal liver function tests, sensory ataxia, altered consciousness, and persistent peripheral tingling or numbness after drinking infusions of bajiaolian (7). These effects were consistent with podophyllum intoxication.

Mahonia species

Barberry is a vernacular name for members of the *Berberis* species, such as *Berberis vulgaris* (European barberry), but is also used to refer to members of the *Mahonia* species, such as *Mahonia aquifolium* and *Mahonia nervosa*. In the USA only the latter species have had official status as a source of barberry, but *Berberis vulgaris* is said to serve similar medicinal purposes and to contain similar principles. Its root bark yields the quaternary isoquinoline alkaloid berberine and several other tertiary and quaternary alkaloids. It has been used to treat a variety of skin conditions (8,9). The literature sometimes cautions that barberry alkaloids can cause arterial hypotension.

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Beta$_2$-adrenoceptor agonists

See also Individual agents

General Information

Beta$_2$-adrenoceptor agonists are widely used in asthma and have inevitably been associated with a number of problems. Some of these are attributable to the drugs themselves, others to the formulations in which they are given.

Organs and Systems

Cardiovascular

Eight men with mild asthma underwent measurement of forearm blood flow, a surrogate marker for peripheral vasodilatation (1). All received in sequential order the following: normoxia plus placebo, normoxia plus inhaled salbutamol 800 micrograms, hypoxia (SpO_2 82%) plus placebo, and hypoxia plus inhaled salbutamol 800 micrograms. The period of mask breathing was 60 minutes and inhalation of salbutamol/placebo started after 30 minutes. While there were non-significant differences in blood pressure and potassium concentrations between the different treatments, forearm blood flow increased significantly by 45% in hypoxic patients inhaling salbutamol versus normoxic patients inhaling placebo. The authors concluded that the combination of hypoxia and inhalation of beta$_2$-agonists has serious systemic vascular adverse effects, potentially leading to pulmonary shunting and reduced venous return, which may be associated with sudden death. Furthermore, asthmatic patients in respiratory distress should be given beta$_2$-agonists and oxygen concomitantly whenever possible.

Intravenous and intracoronary salbutamol (10–30 micrograms/minute and 1–10 micrograms/minute respectively), and intravenous isoprenaline (1–5 micrograms/minute), a mixed beta$_1$/beta$_2$-adrenoceptor agonist, were infused in 85 patients with coronary artery disease and 22 healthy controls during fixed atrial pacing (2). Both salbutamol and isoprenaline produced large increases in QT dispersion (QT_{onset}, QT_{peak}, and QT_{end}), more pronouncedly in patients with coronary artery disease. Dispersion of the QT interval is thought to be a surrogate marker for cardiac dysrhythmia (3). The authors concluded that beta$_2$-adrenoceptors mediate important electrophysiological effects in human ventricular myocardium and can trigger dysrhythmias in susceptible patients.

In a blind, randomized study, 29 children aged under 2 years, with moderate to severe acute exacerbations of hyper-reactive airways disease, were treated with either a standard dose of nebulized salbutamol (0.15 mg/kg) or a low dose of nebulized salbutamol (0.075 mg/kg) plus nebulized ipratropium bromide 250 micrograms (4). Standard and low-dose nebulized salbutamol was given three times at intervals of 20 minutes and nebulized ipratropium bromide was given once. Clinical improvement, measured as O_2 saturation and relief of respiratory distress, was similar in both groups. QT dispersion was measured at baseline and after treatment and was

significantly increased only by the standard dose of nebulized salbutamol.

Respiratory

Beta-adrenoceptor agonists can produce or worsen hypoxia acutely in patients with asthma by increasing ventilation–perfusion inequality. It is not known whether this effect is clinically important in patients with asthma not severe enough to require hospital treatment (where supplementary oxygen is standard therapy).

Metabolism

In obstetrics, the classic effects of beta$_2$-adrenoceptor agonists on glucose metabolism can be absent or harmless in the non-diabetic, but dangerous in women with diabetes, in whom they can cause metabolic acidosis (5); the hyperglycemic effect can be aggravated if glucocorticoids are given (as they may be to prevent hyaline membrane disease in prematurity).

Immunologic

The possibility of a causal relation between the administration of beta$_2$-adrenoceptor agonists and reduced serum immunoglobulin concentrations has been raised in various studies. In one study, adults with asthma taking steroids were compared with patients taking beta$_2$-adrenoceptor agonists (6). The patients who were using beta$_2$-adrenoceptor agonists had significantly lower serum IgG concentrations, irrespective of any history of steroid use. However, in patients using both treatments this depressive effect was even more pronounced; its mechanism is unclear.

Beta$_2$-adrenoceptor agonists and the response to allergens

Following inhalation of an allergen by a sensitized asthmatic, an immediate or type I response is seen. This occurs rapidly and is characterized by dyspnea, wheeze, and a fall in the FEV_1 or peak expiratory flow. The response can be prevented or reversed by inhalation of a beta$_2$-agonist. Several hours later, however, a proportion of asthmatics develop a delayed or type III response. This response is prolonged and associated with inflammatory changes in the airways. For some time after it resolves there is an increase in non-specific reactivity of the airways. This can be quantified by measuring the PC_{20} of histamine or methacholine. This is the provocative concentration necessary to cause a 20% fall in the FEV_1 or peak expiratory flow. The delayed response is not prevented by prior inhalation of a beta$_2$-agonist. It can be prevented by prior treatment with cromoglicate or a corticosteroid.

Treatment with a beta$_2$-agonist aerosol, before allergen inhalation, allows inhalation of significantly greater amounts of allergen before the type I response occurs. In asthmatics who only have a type I response before treatment with a beta$_2$-agonist, a late response to the increased allergen dose results. In asthmatics who already have a type III response, this response is increased (7). Treatment with an oral beta$_2$-agonist for 2 weeks increases sensitivity to inhaled allergen. In addition, reversal of allergen-induced bronchoconstriction by an inhaled beta$_2$-agonist is significantly impaired (8). Treatment for 1 week with an inhaled beta$_2$-agonist increases the late (type III) asthmatic response to the same dose of inhaled allergen. The increase in airway reactivity to methacholine following the late response is also increased (9). Sufficient inhaled beta$_2$-agonist needs to be taken to produce this effect. The effect is seen with salbutamol 0.8 mg/day, but not with 0.2 or 0.4 mg/day (10). Pretreatment with an inhaled beta$_2$-agonist not only increases the response to allergen but also attenuates the protective effect of a beta$_2$-agonist against both allergen and methacholine, that is both specific and non-specific airway reactivity is increased (11).

Clearly, the combined use of a regular inhaled beta$_2$-agonist and allergen exposure can cause more airway inflammation than allergen exposure alone. It has been suggested that regular use of beta$_2$-agonists may induce dysfunction of beta-receptors on the mast cells making the mast cells more prone to release mediator (12). Regular treatment with beta$_2$-agonists alone will result in greater airway inflammation and persistent asthma. This emphasizes the importance of regular prophylactic medication with cromoglicate or inhaled corticosteroids.

Death

Increased mortality among asthmatic patients has been correlated with an increase in the use of beta-adrenoceptor agonist aerosols on two occasions, first in the UK in 1966, and then in New Zealand in the late 1970s and 1980s. On both occasions the rise in deaths correlated well with increasing use of beta-agonist aerosols. However, when the death rates subsequently fell, the use of beta-agonist aerosols did not fall to the same extent (SEDA-13, 427) (SEDA-21, 179), suggesting that the correlation may have been due to the way the aerosols were used rather than with the fact of their use.

The sharp rise in asthma mortality in 1977 in New Zealand provoked debate about the safety of beta$_2$-adrenoceptor agonists, especially the short-acting compound fenoterol. This led to the withdrawal of fenoterol in New Zealand and amendment of the American Asthma Guidelines, suggesting caution in the regular use of beta$_2$-agonists (13). Although there is evidence linking fenoterol to increased morbidity and mortality in asthma (14), the underlying mechanisms were not known. It was suggested that the increase in mortality might be linked to fatal cardiac dysrhythmias, developing under conditions of asthma-induced hypoxia and high doses of beta$_2$-adrenoceptor agonists (15).

One likely explanation for the events of 1966 and later can be found in the fact, discussed below, that with progressive use of beta-agonists the response tends to fall, as a result of which the patient takes increasing doses, without relief. An association between increasing use of beta-agonist aerosols and asthma deaths is therefore to be expected, unless this accumulation of dosage can be avoided by proper guidance. There is still a possibility that the association between the use of these products and fatal reactions could have been due to an as yet unrecognized adverse effect of

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beta-agonist aerosols that becomes prevalent only under particular conditions.

Identification of susceptible patients

An alternative explanation for the epidemic of asthma fatalities among users of beta-adrenoceptor agonist aerosols postulates the existence of a subset of asthmatic patients who are more sensitive than others to an adverse effect of beta-agonists. In this view the occurrence of a peak incidence of deaths will eliminate this subset and the overall death rate will thus fall once more without a proportionate reduction in the use of beta-agonists. A subset of asthmatic patients who develop a significant reduction in bronchodilator response to salbutamol after a short period of treatment has indeed been identified, although the number of patients studied was small. The subset developed a significant reduction in the B_{max} for beta$_2$-adrenoceptors in the lung. This was measured in vivo by PET scanning using a beta-antagonist ligand. Patients in the subset were homozygous for glycine at codon 16 on the beta$_2$-adrenoceptor gene (SEDA-21, 180).

However, another and larger study failed to identify any polymorphism or haplotype of the gene associated with fatal/near fatal asthma, and the authors concluded that the beta$_2$-adrenoceptor genotype was not a major factor in fatal or near fatal asthma (16). A third study similarly found no relation between genotype (coding for amino acids 16 and 27) and change in overall asthma control (17).

On the other hand, other workers have found that homozygotes for arginine 16 were 5.3 times (CI = 1.6, 17.7) more likely than homozygotes for glycine 16 to have a positive response to salbutamol, while heterozygotes for codon 16 on the beta$_2$-adrenoceptor gene were 2.3 times (CI = 1.3, 4.2) more likely to have a positive response to salbutamol than homozygotes for glycine 16 (18).

Finally, in a subset of patients with homozygous glycine on codon 16 of the beta$_2$-adrenoceptor gene, lymphocyte beta$_2$-adrenoceptor density was reduced after treatment for 1 week with a long-acting beta$_2$-agonist. There was also a reduction in maximal response to salbutamol (19).

The upshot of all this is that patients who are homozygous for glycine at codon 16 of the beta$_2$-adrenoceptor gene have a reduced bronchodilator response to salbutamol and this response is further reduced by repeated administration, which also causes a reduction in beta$_2$-adrenoceptor number. So far no genotype has been associated with overall asthma control or the frequency of fatal or near fatal attacks of asthma. Further documentation of the effect of the beta$_2$-adrenoceptor genotype on the response to beta$_2$-agonists may lead to the use of alternative bronchodilators in patients who are homozygous for glycine at codon 16.

Long-Term Effects

Drug tolerance

Reduced responsiveness to beta$_2$-adrenoceptor agonists

The bronchodilator effects of short-acting beta$_2$-agonists are not significantly reduced on chronic administration. However the bronchoprotective effect of beta$_2$-agonists, as measured by prevention of the response to spasmogens and exercise, becomes significantly reduced. This has been documented by measuring the PC_{20}, the concentration of methacholine or other spasmogen that provokes a 20% fall in lung function. Bronchoprotection results in a rise in PC_{20} and as bronchoprotection is lost, the PC_{20} falls.

Inhalation of salbutamol four times a day for 1 week did not affect the bronchodilator response to salbutamol, but there was a significant reduction in PC_{20} to methacholine (10).

Co-administration of a corticosteroid may mitigate the loss of bronchoprotective effect. The methacholine PC_{20} for salbutamol was significantly greater after 3 weeks treatment with the inhaled corticosteroid budesonide. However, addition of the long-acting beta$_2$-agonist salmeterol 0.05 mg bd significantly reduced the bronchoprotective effect of salbutamol, despite concurrent treatment with inhaled glucocorticoids (20). The bronchoprotective effect of salmeterol itself fell after only two doses (21). On the other hand, despite the administration of inhaled corticosteroids, the bronchodilator effect of another long-acting beta$_2$-agonist, formoterol, was reduced after treatment for 3 weeks. Administration of prednisolone 50 mg and hydrocortisone 100 mg rapidly reversed the reduction in response (22).

However, it is difficult to extrapolate PC_{20} changes after treatment with beta$_2$-agonists to the clinical outcome. There is an assumption that if PC_{20} falls, the patient is more likely to suffer acute attacks when exposed to spasmogens, allergens, and exercise. However, the loss of bronchoprotective effect has not so far been shown to increase morbidity or mortality in asthmatic patients.

Regular salbutamol has been compared with salbutamol, taken as needed, in mild asthmatics. There was no change in asthma control nor any increase in the frequency or severity of exacerbation (23). As the bronchodilator response is maintained, patients can be advised to use short-acting beta$_2$-agonists to relieve acute bronchoconstriction and if necessary to increase the dose.

The significance of stereoisomers of beta$_2$-adrenoceptor agonists

An alternative hypothesis has been proposed to explain why beta$_2$-agonists lose their bronchoprotective effect while retaining a bronchodilator effect. The beta$_2$-agonists currently available for treating asthma consist of racemic mixtures of equal amounts of two stereoisomers, the *R*-isomer (or L-isomer), which is the beta-adrenoceptor agonist, and the *S*-isomer (D-isomer) which is inactive.

In guinea-pig airways, the constrictor response to platelet activating factor (PAF), histamine, and prostaglandin $F_{2\alpha}$ are all prevented by infusion of racemic isoprenaline. After the isoprenaline is stopped, the constrictor response is markedly potentiated. Infusion of the *S*-isomer alone does not prevent the constrictor responses in contrast to the infusion of racemic isoprenaline. After infusion of the *S*-isomer is stopped there is an increase in the response to the constrictor agents, equivalent to that seen after racemic isoprenaline. This can be compared to asthma, in which prolonged exposure to racemates of beta$_2$-agonists produces a loss of the bronchoprotective effect while maintaining the immediate bronchodilator effect (24).

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Regular exposure to a racemate, especially during or after an allergic reaction, will cause hyper-reactivity to spasmogens, and this could be due to an effect of the *S*-isomer. This effect is not seen immediately, because of beta$_2$-adrenoceptor-mediated bronchodilatation by the *R*-isomer.

Most of the clinical work on this phenomenon has been undertaken with salbutamol. In one major investigation, after administration of racemic salbutamol to healthy volunteers, both the peak plasma concentration of *R*-salbutamol and the systemic availability (measured by the AUC) were higher than when *R*-salbutamol was given in an equivalent dose as the *R*-isomer alone. It was concluded that *R*-salbutamol was more efficiently metabolized in the absence of *S*-salbutamol. *S*-salbutamol is a competitive inhibitor at the active site of the phenol-sulfotransferase enzyme, and its absence allows more *R*-salbutamol to be metabolized, resulting in lower systemic availability of *R*-salbutamol when the *R*-isomer alone is administered. Although the plasma concentrations of *R*-salbutamol were lower, the rise in plasma glucose and fall in plasma potassium were greater when the pure *R*-isomer was given alone. There was also a greater increase in heart rate and finger tremor. The greater potency of *R*-salbutamol given alone suggests inhibition of the effects of the *R*-isomer by the *S*-isomer (25).

In another investigation, a single dose of 1.25 mg nebulized *R*-salbutamol, administered to asthmatics, produced equivalent bronchoprotection, bronchodilatation, tachycardia, and restlessness to that given by 2.5 mg of racemic salbutamol (26). In a further study, asthmatic patients were treated for 28 days with racemic or *R*-salbutamol administered by nebulizer three times a day. Improvement in FEV_1 was similar after *R*-salbutamol 0.63 mg and racemic salbutamol 2.5 mg and greatest with *R*-salbutamol 1.25 mg. Racemic salbutamol 1.25 mg had the least bronchodilator effect, especially after chronic dosing (27).

It is not known if this phenomenon is specific to salbutamol or is shared by other racemic beta$_2$-agonists.

Second-Generation Effects

Pregnancy

Use of beta$_2$-adrenoceptor agonists in threatened premature labor

The adverse effects of the beta$_2$-adrenoceptor agonists when given (as a rule by injection) to arrest premature uterine contractions are very similar to those experienced when the classic drug in the series (salbutamol) is used for other purposes. In the special circumstances of obstetrics, however, there are several particular safety problems.

Choice of drugs

Probably most or all beta$_2$-agonists could be used in obstetrics as well as in asthma, and some are used for both purposes; however, manufacturers have tended to develop their individual compounds for one purpose or the other. Surprisingly, one large survey suggested that when used in pregnancy, salbutamol may be less well tolerated by the mother (stimulation, cardiovascular effects) than the much less selective isoxsuprine (SED-12, 321).

In one large survey, salbutamol was less well tolerated by the mother (stimulation, cardiovascular effects) than the much less selective isoxsuprine (SED-12, 321).

Cardiovascular

None of the beta$_2$-adrenoceptor agonists used to delay delivery can be given in effective doses either orally or by injection without affecting the maternal heart rate (and to a lesser extent the fetal heart rate) in a high proportion of cases. It is not possible to say whether this effect is more likely to occur with certain drugs of this type than with others (particularly because the obstetric situation itself affects the fetal heart rate) (SEDA-17, 145), but in effective doses a maternal heart rate increase of some 30 beats/minute or more is common, with a fetal heart rate increase of up to 20 beats/minute. A substantial proportion of mothers (with intravenous use up to 30%) experience such symptoms as headache, tremulousness, tightness of the chest, palpitation, and flushing. There is clear and direct evidence that tocolytics also exert toxic effects on the myocardial tissue of the infant, especially if given for long periods (28,29). The calcium channel blocker verapamil does not protect either the maternal heart or the fetal heart against the toxic effects of tocolysis (SEDA-9, 126). Pulmonary edema is a rare but potentially life-threatening complication of beta$_2$-agonists (SEDA-10, 115) (30).

Metabolism

In obstetrics the classic effects of beta$_2$-adrenoceptor agonists on glucose metabolism can be absent or harmless in those without diabetes, but dangerous in those with diabetes, in whom they can cause metabolic acidosis (5). The hyperglycemic effect can be aggravated if glucocorticoids are also given (as they may be to prevent hyaline membrane disease in prematurity).

Susceptibility Factors

Age

The use of long-acting beta$_2$-adrenoceptor agonists in the management of asthma in children has been comprehensively reviewed (31). In children, as in adults, regular long-acting beta$_2$-adrenoceptor agonists can produce bronchodilator subsensitivity to short-acting beta-agonists and tolerance to the bronchoprotective effects of long-acting beta-agonists against challenges with exercise and methacholine. The clinical significance of these findings is unclear.

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Beta-adrenoceptor antagonists

See also Individual agents

General Information

Many beta-adrenoceptor antagonists (beta-blockers) have been developed, and their adverse effects have been comprehensively reviewed (1). The spectrum of adverse effects is broadly similar for all beta-blockers, despite differences in their pharmacological properties, notably cardioselectivity, partial agonist activity, membrane-stabilizing activity, and lipid solubility (see Table 1). The influence of these properties is mentioned in the general discussion when appropriate and is summarized at the end of the section. Individual differences in toxicity are largely unimportant but will be mentioned briefly.

Although beta-blockers have been available for many years, new members of this class with novel pharmacological profiles continue to be developed. These new drugs are claimed to have either greater cardioselectivity or vasodilatory and $beta_2$-agonist properties. The claimed

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Table 1 Properties of beta-adrenoceptor antagonists (where known)

Drug	Lipid solubility[a]	Cardioselectivity	Partial agonist activity	Membrane-stabilizing activity
Acebutolol	0.7	±	+	+
Alprenolol	31	−	+	+
Amosulalol		−		
Arotinolol				
Atenolol	0.02	+	−	
Befunolol				
Betaxolol		+	−	±
Bevantolol	Low	+	−	+
Bisoprolol		++		−
Bopindolol				
Bucindolol				
Bufetolol				
Bufuralol	+	−	+	
Bunitrolol	+	−	++	±
Bupranolol				
Butofilolol				
Carazolol				
Carteolol	−	+		
Carvedilol	++	−	−	
Celiprolol		±	+[b]	−
Cetamolol				
Cicloprolol				
Cloranolol				
Dexpropranolol				
Diacetolol				
Dilevalol				
Draquinolol				
Epanolol	Minimal	+	+	
Esmolol	−	+	−	
Flestolol	−	−	−	
Indenolol				
Labetalol	+	−	−	
Levobetaxolol				
Levobunolol		−		
Levomoprolol				
Medroxalol				
Mepindolol				
Metipranolol				
Metoprolol	0.2	+	−	±
Moprolol				
Nadolol	0.03	−	−	−
Nebivolol		+	−	−
Nifenalol				
Nipradilol				
Oxprenolol	0.7	−	+	+
Penbutolol	−	−	+	+
Pindolol	0.2	−	++	±
Practolol	0.02	+	+	−
Pronethalol				
Propranolol	4.3	−	−	++
Sotalol	0.02	−	−	−
Talinolol		+		
Tertatolol				
Tilisolol				
Timolol	0.03	−	±	±
Xamoterol		+	++	

[a] Octanol:water partition coefficient
[b] Partial beta$_2$-adrenoceptor agonist

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advantages of these new drugs serve to highlight the supposed disadvantages of the older members of the class (their adverse constrictor effects on the airways and peripheral blood vessels). Strong commercial emphasis is being placed on these new properties, and papers extolling these effects often appear in non-peer-reviewed supplements or even in reputable journals (2).

Although the toxicity of the beta-adrenoceptor antagonists has been fairly well documented, there has been a subtle change in perceptions of their potential benefits and drawbacks. The cardioprotective effect of beta-blockers after myocardial infarction and their efficacy in reducing "silent" myocardial ischemia have persuaded some clinicians to use them preferentially. On the other hand, they can significantly impair the quality of life (3) and are contraindicated in some patients. A few patients cannot tolerate beta-blockade at all. These include patients with bronchial asthma, patients with second- or third-degree heart block, and those with seriously compromised limb perfusion causing claudication, ischemic rest pain, and pregangrene.

General adverse effects

The adverse effects of beta-blockers are usually mild, with occurrence rates of 10–20% for the most common in most studies. Most are predictable from the pharmacological and physicochemical properties of these drugs. Examples include fatigue, cold peripheries, bradycardia, heart failure, sleep disturbances, bronchospasm, and altered glucose tolerance. Gastrointestinal upsets are also relatively common. Serious adverse cardiac effects and even sudden death can follow abrupt withdrawal of therapy in patients with ischemic heart disease. Most severe adverse reactions can be avoided by careful selection of patients and consideration of individual beta-blockers. Hypersensitivity reactions have been relatively rare since the withdrawal of practolol. Tumor-inducing effects have not been established in man.

Fatigue

Fatigue is one of the most commonly reported adverse effects of beta-adrenoceptor antagonists, with reported occurrence rates of up to 20% or more, particularly in those who exert themselves. It has to be viewed alongside the ability to produce fatigue and lethargy by a possible effect on the nervous system. The precise cause of physical fatigue is not known, but hypotheses include impaired muscle blood supply, effects on intermediary metabolism, and a direct effect on muscle contractility (4).

Theoretically, $beta_1$-selective drugs are less likely to alter these variables, and might therefore have an advantage over non-selective drugs. However, this has not always been shown in single-dose studies in volunteers (5,6), although in two such studies atenolol produced less exercise intolerance than propranolol at comparable dosages (7,8). For an unexplained reason, cardioselectivity impaired performance relatively less in subjects with a high proportion of slow-twitch muscle fibers than it did in those whose muscle biopsy specimens showed a high percentage of fast-twitch fibers (9). The muscle fibers of long-distance runners are predominantly of the slow-twitch type, and this probably explains the superiority of atenolol over propranolol when exercise performance was assessed in such subjects (7). The release of lactic acid from skeletal muscle cells is impaired to a greater extent by non-selective beta-blockers than by cardioselective drugs, and cardioselectivity was associated with a less marked fall in blood glucose during and after maximal and submaximal exercise (10,11). Partial agonist activity might have been the reason for the superiority of oxprenolol over propranolol in terms of exercise duration (12).

Differences among beta-blockers

Although there are now many different beta-adrenoceptor antagonists, and the number is still increasing, there are only a few important characteristics that distinguish them in terms of their physicochemical and pharmacological properties: lipid solubility, cardioselectivity, partial agonist activity, and membrane-stabilizing activity. The characteristics of the currently available compounds are shown in Table 1.

Lipid solubility

Lipid solubility (13) determines the extent to which a drug partitions between an organic solvent and water. Propranolol, oxprenolol, metoprolol, and timolol are the most lipid-soluble beta-adrenoceptor antagonists, and atenolol, nadolol, and sotalol are the most water-soluble; acebutolol and pindolol are intermediate (14).

The more lipophilic drugs are extensively metabolized in the gut wall and liver (first-pass metabolism). This first-pass clearance is variable and can result in 20-fold differences in plasma drug concentrations between patients who have taken the same dose. It also produces susceptibility to drug interactions with agents that alter hepatic drug metabolism, for example cimetidine, and can result in altered kinetics and hence drug response in patients with hepatic disease, particularly cirrhosis. Lipid-soluble drugs pass the blood–brain barrier more readily (15) and should be more likely to cause adverse nervous system effects, such as disturbance of sleep, but the evidence for this is not very convincing.

In contrast, water-soluble drugs are cleared more slowly from the body by the kidneys. These drugs therefore tend to accumulate in patients with renal disease, do not interact with drugs that affect hepatic metabolism, and gain access to the brain less readily.

Cardioselectivity

Cardioselectivity (16), or more properly $beta_1$-adrenoceptor selectivity, is the term used to indicate that there are at least two types of beta-adrenoceptors, and that while some drugs are non-selective (that is they are competitive antagonists at both $beta_1$- and $beta_2$-adrenoceptors), others appear to be more selective antagonists at $beta_1$-adrenoceptors, which are predominantly found in the heart. Bronchial tissue, peripheral blood vessels, the uterus, and pancreatic beta-cells contain principally $beta_2$-adrenoceptors. Thus, cardioselective beta-adrenoceptor antagonists, such as atenolol and metoprolol, might offer theoretical benefits to patients with bronchial asthma, peripheral vascular disease, and diabetes mellitus.

Cardioselective drugs may have relatively less effect on the airways, but they are in no way cardiospecific and they should be used with great care in patients with evidence of reversible obstructive airways disease.

The benefits of cardioselective drugs in patients with Raynaud's phenomenon or intermittent claudication have

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been difficult to prove. Because of vascular sparing, cardioselective agents may also be preferable in stress, when adrenaline is released.

Cardioselective drugs are less likely to produce adverse effects in patients with type I diabetes than non-selective drugs. At present, hypoglycemia in patients with type I diabetes mellitus is the only clinical problem in which cardioselectivity is considered important. Even there, any potential advantages of cardioselective drugs in minimizing adverse effects apply only at low dosages, since cardioselectivity is dose-dependent.

Partial agonist activity

Partial agonist activity (17,18) is the property whereby a molecule occupying the beta-adrenoceptor exercises agonist effects of its own at the same time as it competitively inhibits the effects of other extrinsic agonists. The effects of these drugs depend on the degree on endogenous tone of the sympathetic nervous system. When there is high endogenous sympathetic tone they tend to act as beta-blockers; when endogenous sympathetic tone is low they tend to act as beta-agonists. Thus, xamoterol had a beneficial effect in patients with mild heart failure (NYHA classes I and II), through a positive inotropic effect on the heart; however, in severe heart failure (NYHA classes III and IV), in which sympathetic tone is high, it acted as a beta-blocker and worsened the heart failure, through a negative inotropic effect (19).

Partial agonists, such as acebutolol, oxprenolol, pindolol, practolol, and xamoterol, produce less resting bradycardia. It has also been claimed that such agents cause a smaller increase in airways resistance in asthmatics, less reduction in cardiac output (and consequently a lower risk of congestive heart failure), and fewer adverse effects in patients with cold hands, Raynaud's phenomenon, or intermittent claudication. However, none of these advantages has been convincingly demonstrated in practice, and patients with bronchial asthma or incipient heart failure must be considered at risk with this type of compound.

Drugs with partial agonist activity can produce tremor (20).

Drugs that combine $beta_1$-antagonism or partial agonism with $beta_2$-agonism (celiprolol, dilevalol, labetalol, pindolol) or with alpha-antagonism (carvedilol, labetalol) have been developed (21). Both classes have significant peripheral vasodilating effects. Drugs with significant agonist activity at $beta_1$-adrenoceptors have poor antihypertensive properties (22).

Membrane-stabilizing activity

Drugs with membrane-stabilizing activity reduce the rate of rise of the cardiac action potential and have other electrophysiological effects. Membrane-stabilizing activity has only been shown in human cardiac muscle in vitro in concentrations 100 times greater than those produced by therapeutic doses (23). It is therefore likely to be of clinical relevance only if large overdoses are taken.

Use in heart failure

Traditionally, beta-blockers have been contraindicated in patients with heart failure. However, there are some patients with systolic heart failure who benefit from a beta-blocker (24). Early evidence was strongest for idiopathic dilated cardiomyopathy rather than ischemic heart disease (25). However, several randomized controlled trials of beta-blockers in patients with mild to moderate heart failure have been published. These include the CIBIS II trial with bisoprolol (26), the MERIT-HF trial with metoprolol (27), and the PRECISE trial with carvedilol (28). These have shown that cardiac mortality in these patients can be reduced by one-third, despite concurrent treatment with conventional therapies of proven benefit (that is ACE inhibitors).

Diastolic dysfunction can lead to congestive heart failure, even when systolic function is normal (29,30). Since ventricular filling occurs during diastole, failure of intraventricular pressure to fall appropriately during diastole leads to increased atrial pressure, which eventually leads to increased pulmonary and systemic venous pressures, causing a syndrome of congestive heart failure indistinguishable clinically from that caused by systolic pump failure (31). Diastolic dysfunction occurs in systemic arterial hypertension, hypertrophic obstructive cardiomyopathy, and infiltrative heart diseases, which reduce ventricular compliance or increase ventricular stiffness (32). As energy is required for active diastolic myocardial relaxation, a relative shortage of adenosine triphosphate in ischemic heart disease also often leads to co-existing diastolic and systolic dysfunction (33). Beta-blockers improve diastolic function in general, and this may be beneficial in patients with congestive heart failure associated with poor diastolic but normal systolic function.

Beta-blockade reduces mortality in patients with heart failure by at least a third when initiated carefully, with gradual dose titration, in those with stable heart failure (34,35). Similarly, beta-blocker prescribing should be encouraged in people with diabetes, since they have a worse outcome after cardiac events and beta-blockade has an independent secondary protective effect (36,37). The small risk of masking metabolic and autonomic responses to hypoglycemia, which was only a problem with non-selective agents in type I diabetes, is a very small price worth paying in diabetics with coronary heart disease.

Use in glaucoma

It has been more than a quarter of a century since the discovery that oral propranolol reduces intraocular pressure in patients with glaucoma. However, the use of propranolol for glaucoma was limited by its local anesthetic action (membrane-stabilizing activity).

Topical timolol was released for general use in 1978. That timolol is systemically absorbed was suggested by early reports of reduced intraocular pressure in the untreated eyes of patients using monocular treatment. About 80–90% of a topically administered drop drains through the nasolacrimal duct and enters the systemic circulation through the highly vascular nasal mucosa, without the benefit of first-pass metabolism in the liver; only a small fraction is swallowed. Thus, topical ophthalmic dosing is probably more akin to intravenous delivery than to oral dosing, and systemic adverse reactions are potentially serious. However, although patients may give their physicians a detailed list of current medications, they

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often fail to mention the use of eye-drops, about which physicians are often either unaware or do not have time to ask specific questions.

Betaxolol is a $beta_1$-selective adrenoceptor antagonist without significant membrane-stabilizing activity or intrinsic sympathomimetic activity. It may be no more effective than other drugs in reducing intraocular pressure, but it may be safer for some patients, particularly those with bronchospastic disease (but see the section on Respiratory under Drug administration route) (38).

Partial agonist activity of beta-blockers may help to prevent ocular nerve damage and subsequent visual field loss associated with glaucoma. Such damage may be related to a reduction in ocular perfusion, as might occur if an ocular beta-blocker caused local vasoconstriction. An agent with intrinsic sympathomimetic activity might preserve ocular perfusion through local vasodilatation or by minimizing local vasoconstriction. The data are sparse and inconclusive, but carteolol appears to have no effect on retinal blood flow or may even increase it, making it potentially suitable as a neuroprotective drug (38,39).

Organs and Systems

Cardiovascular

A randomized comparison of oral atenolol and bisoprolol in 334 patients with acute myocardial infarction was associated with drug withdrawal in 70 patients (21%) because of significant bradydysrhythmias, hypotension, heart failure, and abnormal atrioventricular conduction (40). Logistic regression analysis suggested that critical events were more likely to occur in patients who were pretreated with dihydropyridine calcium antagonists.

Heart failure

Beta-adrenoceptor antagonists reduce cardiac output through their negative inotropic and negative chronotropic effects. They can therefore cause worsening systolic heart failure or new heart failure in patients who depend on high sympathetic drive to maintain cardiac output. Plasma noradrenaline is increased in patients with heart failure, and the extent of this increase is directly related to the degree of ventricular impairment (41). Since the greatest effect on sympathetic activity occurs with the first (and usually the lowest) doses, heart failure associated with beta-blockade seems to be independent of dosage. Heart failure is one of the most serious adverse effects of the beta-adrenoceptor antagonists (42), but it is usually predictable and can be attenuated by pretreatment with diuretics and angiotensin-converting enzyme inhibitors in patients who are considered to be at risk.

It has been suggested that drugs with partial agonist activity (see Table 1), which have a minimal depressant effect on normal resting sympathetic tone, might cause less reduction in cardiac output (43) and thus protect against the development of cardiac decompensation (44). However, this has not been satisfactorily shown for drugs with high partial agonist activity, for example acebutolol, oxprenolol, and pindolol (45), and these drugs should therefore be given with the same caution as others in compromised patients. Xamoterol, a beta-antagonist with substantial $beta_1$ partial agonist activity, was hoped to be of benefit in mild congestive heart failure (46), but its widespread use by non-specialists in more severe degrees of heart failure resulted in many reports of worsening heart failure (47). Heart failure has also been produced by labetalol (48) and after the use of timolol eye-drops in the treatment of glaucoma (49).

Hypotension

Beta-adrenoceptor antagonists lower blood pressure, probably by a variety of mechanisms, including reduced cardiac output. More severe reductions in blood pressure can occur and can be associated with syncope (42). It has been suggested that this is more likely to occur in old people, but comprehensive studies have stressed the safety of beta-blockers in this age group (50).

- Profound hypotension, resulting in renal insufficiency, has been reported in a single patient after the administration of atenolol 100 mg orally (51); however, large doses of furosemide and diazoxide were also given in this case, and this appears more likely to have been a consequence of a drug interaction.

Cardiac dysrhythmias and heart block

Beta-blockade can result in sinus bradycardia, because blockade of sympathetic tone allows unopposed parasympathetic activity. Drugs with partial agonist activity may prevent bradycardia (52). However, heart rates under 60/minute often worry the physician more than the patient: in a retrospective study of nearly 7000 patients taking beta-adrenoceptor antagonists, apart from dizziness in patients with heart rates under 40/minute (0.4% of the total group), slow heart rates were well tolerated (53).

All beta-blockers cause an increase in atrioventricular conduction time; this is most pronounced with drugs that have potent membrane-depressant properties and no partial agonist activity. Sotalol differs from other beta-blockers in that it increases the duration of the action potential in the cardiac Purkinje fibers and ventricular muscle at therapeutic doses. This is a class III antidysrhythmic effect, and because of this, sotalol has been used to treat ventricular (54–56) and supraventricular dysrhythmias (57). The main serious adverse effect of sotalol is that it is prodysrhythmic in certain circumstances, and can cause torsade de pointes (58,59).

Acute chest pain

Worsening of angina pectoris has been attributed to beta-blocker therapy. The reports include 35 cases in a series of 296 elderly patients admitted to hospital with suspected myocardial infarction; in these 35 the pain disappeared within 7 hours of withdrawing beta-blocker therapy (60).

Worsening of angina has been reported at very low heart rates (61). Propranolol resulted in vasotonic angina in six patients during a double-blind trial, with prolongation of the duration of pain and electrocardiographically assessed ischemia. It has been suggested that this reflects a reduction in coronary perfusion as a result of reduced cardiac output, and also coronary arterial spasm provoked by non-selective agents by inhibition of $beta_2$-mediated vasodilatation

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(62). The latter explanation is controversial, and the use of beta-blockers in patients with arteriographic evidence of coronary artery spasm has not consistently caused worsening of the disorder (63).

Unstable angina has also followed treatment for hypertension with cardioselective drugs such as betaxolol (64).

Peripheral vascular effects

Cold extremities or exacerbation of Raynaud's phenomenon are amongst the commonest adverse effects reported with beta-blockers (5.8% of nearly 800 patients taking propranolol) (42); Raynaud's phenomenon occurs in 0.5–6% of patients (65). The mechanism may be potentiation of the effects of a cold environment on an already abnormal circulation, but whether symptoms can be produced de novo is more difficult to determine. However, a retrospective questionnaire study in 758 patients taking antihypertensive drugs showed that 40% of patients taking beta-blockers noted cold extremities, compared with 18% of those taking diuretics; there were no significant differences among patients taking alprenolol, atenolol, metoprolol, pindolol, and propranolol (66). Similarly, a large randomized study showed that the incidence of Raynaud's phenomenon was the same for atenolol and pindolol (67). In another study, vasospastic symptoms improved when labetalol was substituted for a variety of beta-blockers (68). On the other hand, a small, double-blind, placebo-controlled study in patients with established Raynaud's phenomenon showed that the prevalence of symptoms with both propranolol and labetalol was no greater than that with placebo (69).

Intermittent claudication has also been reported to be worsened by beta-adrenoceptor antagonists, but has been difficult to document because of the difficulty of study design in patients with advanced atherosclerosis. As early as 1975 it was reported from one small placebo-controlled study that propranolol did not exacerbate symptoms in patients with intermittent claudication (70). This has subsequently been supported by the results of several large placebo-controlled trials of beta-blockers in mild hypertension and reports of trials of the secondary prevention of myocardial infarction, in which intermittent claudication was not mentioned as an adverse effect, even though it was not a specific contraindication to inclusion (71). In addition, a comprehensive study of the effects of beta-adrenoceptor antagonists in patients with intermittent claudication did not show beta-blockade to be an independent risk factor for the disease (72). In men with chronic stable intermittent claudication, atenolol (50 mg bd) had no effect on walking distance or foot temperature (73). These findings have been confirmed in a recent meta-analysis of 11 randomized, controlled trials to determine whether beta-blockers exacerbate intermittent claudication (SEDA-17, 234).

Patchy skin necrosis has been described in hypertensive patients with small-vessel disease in the legs who were taking beta-blockers. Characteristically, pedal pulses remained palpable and the lesions occurred during cold weather and healed on withdrawal of the drugs (74–76). Three cases have been reported in which long-lasting incipient gangrene of the leg was immediately overcome when a beta-blocker was withdrawn (77,78), showing how easily these drugs are overlooked in such circumstances. In several cases of beta-blocker-induced gangrene, recovery did not follow withdrawal of therapy, and amputation was necessary (79,80). Thus, when possible, other forms of therapy should be used in patients with critical ischemia or rest pain.

It has also been suggested that beta-blockade may compromise the splanchnic vasculature. Intravenous propranolol reduces splanchnic blood flow experimentally by 29% while reducing cardiac output by only 6% (81).

Five patients developed mesenteric ischemia, four with ischemic colitis, and one with abdominal angina, while taking beta-adrenoceptor antagonists (82). Although causation was not proven, it was possible.

Respiratory

The respiratory and cardiovascular adverse effects of topical therapy with timolol or betaxolol have been studied in a randomized, controlled trial in 40 elderly patients with glaucoma (83). Five of the 20 allocated to timolol discontinued treatment for respiratory reasons, compared with three of the 20 patients allocated to betaxolol. There were no significant differences in mean values of spirometry, pulse, or blood pressure between the groups. This study confirms that beta-blockers administered as eye-drops can reach the systemic circulation and that serious adverse respiratory events can occur in elderly people, even if they are screened before treatment for cardiac and respiratory disease. These events can occur using either the selective betaxolol agent or the non-selective timolol.

Airways obstruction

Since the introduction of propranolol, it has been recognized that patients with bronchial asthma treated with beta-adrenoceptor antagonists can develop severe airways obstruction (84), which can be fatal (85) or near fatal (86,87); this has even followed the use of eye-drops containing timolol (88). Beta-blockers upset the balance of bronchial smooth muscle tone by blocking the bronchial $beta_2$-adrenoceptors responsible for bronchodilatation. They also promote degranulation of mast cells and depress central responsiveness to carbon dioxide (89,90).

Although $beta_1$-selective drugs are theoretically safer, there are reports of serious reductions in ventilatory function (91,92), even when used as eye-drops (93). However, it has been concluded that if beta-blockade is necessary in the treatment of glaucoma, cardioselective beta-blocking drugs should be preferred (94). While cardioselectivity is dose-dependent (95), and higher dosages might therefore be expected to produce adverse effects, metoprolol and bevantolol, even in dosages that are lower than those usually required for a therapeutic effect, may be poorly tolerated by patients with asthma (96).

Whether drugs with partial agonist activity confer any advantage is uncertain. Some of the evidence that patients with asthma tolerate beta-blockers is probably misleading, relating to patients with chronic obstructive airways disease who have irreversible changes and who do not respond to either bronchoconstricting or bronchodilating drugs (97). In contrast, a few patients who have never had asthma or chronic bronchitis develop severe

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bronchospasm when given a beta-blocker. Some, but not all, of these cases (98) may have been allergic reactions to the dyestuffs (for example tartrazine) that are used to color some formulations. Other patients, who need not have a history of chest disease, only develop increased airways resistance with beta-blockers during respiratory infections.

It is against this background that claims that some asthmatic subjects will tolerate certain beta-blockers (99) must be viewed. Some asthmatic patients may indeed tolerate either cardioselective beta-blockers (such as atenolol and metoprolol) or labetalol (100,101), and in patients taking atenolol $beta_2$-adrenoceptor agonists may continue to produce bronchodilatation (102), but in most instances other therapeutic options are preferable (103). Celiprolol is a $beta_1$-adrenoceptor antagonist that has partial $beta_2$-agonist activity. Small studies have suggested that it may be useful in patients with asthma (104), but worsening airways obstruction has been reported (105); it has been concluded that celiprolol has no advantage over existing beta-blockers in the treatment of hypertension (106).

Bronchospasm, which can be life-threatening, can be precipitated by beta-blocker eye-drops. Even $beta_1$-selective antagonists, such as betaxolol, can cause a substantial reduction in forced expiratory volume. Wheezing and dyspnea have been reported among patients using betaxolol: the symptoms resolved after withdrawal. A cross-sectional study has shown that ophthalmologists were more aware than chest physicians about the use of beta-blocker eye-drops by patients with obstructive airways disease; patient awareness was also poor (38,107).

Attention has also been drawn to the increased risks of the adverse effects of beta-blockers on respiratory function in old people (108).

Central ventilatory suppression

Reduced sensitivity of the respiratory center to carbon dioxide has been reported (89,109). The clinical significance of this is unknown, but lethal synergism between morphine and propranolol in suppressing ventilation in animals has been described (110).

Pneumonitis, pulmonary fibrosis, and pleurisy

Pulmonary fibrosis (111) and pleural fibrosis (112) have both been described as infrequent complications associated with practolol. Pulmonary fibrosis has also occurred during treatment with pindolol (113) and acebutolol (114,115). Pleuritic and pneumonitic reactions to acebutolol have been reported (116).

Ear, nose, throat

Nasal polyps, rhinitis, and sinusitis resistant to long courses of antibiotics and surgical intervention have been described in five patients taking non-selective beta-adrenoceptor antagonists (propranolol and timolol) (117). The symptoms resolved when the drugs were withdrawn and did not recur when $beta_1$-selective adrenoceptor blockers (metoprolol or atenolol) were given instead.

Nervous system

Some minor neuropsychiatric adverse effects, such as light-headedness, visual and auditory hallucinations, illusions, sleep disturbances, vivid dreams, and changes in mood and affect, have been causally related to long-term treatment with beta-adrenoceptor antagonists (118,119). Other occasional nervous system effects of beta-blockers include hearing impairment (120), episodic diplopia (121), and myotonia (122).

Although some migraine sufferers use beta-adrenoceptor antagonists prophylactically, there are also reports of the development of migraine on exposure to propranolol or rebound aggravation when the drug is withdrawn (123). Stroke, a rare complication of migraine, has been reported in three patients using propranolol for prophylaxis (124–126). Seizures have been reported with the short-acting beta-blocker esmolol, usually with excessive doses (117). Myasthenia gravis has been associated with labetalol (127), oxprenolol, and propranolol (128), and carpal tunnel syndrome has been reported with long-term beta-blockade, the symptoms gradually disappearing on withdrawal of therapy (129).

Propranolol and gabapentin are both effective in essential tremor. However, pindolol, which has substantial partial agonist activity, can cause tremor (130), and gabapentin can occasionally cause reversible movement disorders. A patient who developed dystonic movements after the combined use of gabapentin and propranolol has been described (131).

- A 68-year-old man with a 10-year history of essential tremor was initially treated with propranolol (120 mg/day), which was only slightly effective. Propranolol was replaced by gabapentin (900 mg/day). The tremor did not improve and propranolol (80 mg/day) was added. Two days later he developed paroxysmal dystonic movements in both hands. Between episodes, neurological examination was normal. When propranolol was reduced to 40 mg/day the abnormal movements progressively disappeared.

This case suggests that there is a synergistic effect between propranolol and gabapentin.

In addition, tiredness, fatigue, and lethargy, probably the commonest troublesome adverse effects of beta-blockers and often the reason for withdrawal (132), may have a contributory nervous system component, although they are probably primarily due to reduced cardiac output and altered muscle metabolism (65) (see also the section on Fatigue in this monograph). In general, a definite neurological association has been difficult to prove, and studies of patients taking beta-adrenoceptor antagonists for hypertension, which incorporated control groups of patients taking either other antihypertensive drugs or a placebo, appear to have shown that the incidence of symptoms that can be specifically attributed to beta-adrenoceptor antagonists is lower than anticipated (133).

The more lipophilic drugs, such as propranolol and oxprenolol, would be expected to pass the blood–brain barrier more readily than hydrophilic drugs, such as atenolol and nadolol, and there is some evidence that they do so (15). In theory, therefore, hydrophilic drugs might be expected to produce fewer neuropsychiatric adverse

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effects. A double-blind, placebo-controlled evaluation of the effects of four beta-blockers (atenolol, metoprolol, pindolol, and propranolol) on central nervous function (134) showed that disruption of sleep was similar with the three lipid-soluble drugs, averaging six to seven wakenings per night, compared with an average of three wakenings per night for atenolol and placebo. Only pindolol, which has a higher CSF/plasma concentration ratio than metoprolol and propranolol, significantly altered rapid eye movement sleep and latency (135). Patients who took pindolol and propranolol also had high depression scores.

In a placebo-controlled sleep laboratory study of atenolol, metoprolol, pindolol, and propranolol, the three lipophilic drugs reduced dreaming (equated with rapid eye movement sleep) but increased the recollection of dreaming and the amount of wakening; in contrast, although atenolol also reduced sleep, it had no effect on subjective measures of sleep (136).

The published data on the effects of beta-blockers on the nervous system have been extensively reviewed (137). The overall incidence of effects was low, and lowest with the hydrophilic drugs. However, a meta-analysis of 55 studies of the cognitive effects of beta-blockade did not show any firm evidence that lipophilic drugs caused more adverse effects than hydrophilic ones (138). Recent data confirming a correlation between lipophilicity and serum concentrations on the one hand and nervous system effects on the other (139) have fuelled this controversy.

Car-driving and other specialized skills

In view of the large numbers of people who take beta-adrenoceptor antagonists regularly for hypertension or ischemic heart disease, the question arises whether these drugs impair performance in tasks that require psychomotor coordination. The occupations under scrutiny include car-driving, the operation of industrial machinery, and the piloting of aeroplanes. The current evidence is conflicting and controversial. One report suggested that propranolol and pindolol given for 5 days impaired slalom driving in a manner comparable with the coordination defects caused by alcohol (140). In contrast, other studies have shown that driving skills were not impaired during long-term beta-blocker therapy and might even be improved (141,142). There is also a suggestion that tolerance to the central effects of these drugs can develop within 3 weeks of starting therapy, provided the dosage does not change (143). Until more information is available from well-controlled studies, it is advisable to inform patients who are starting treatment with beta-blockers that they should exercise special care in the performance of skills requiring psychomotor coordination for the first 1 or 2 weeks.

Sensory systems

Eyes

Keratopathy in association with the practolol syndrome is the major serious ocular effect ascribed to beta-adrenoceptor antagonists. Conjunctivitis and visual disturbances have also been reported, and a case of ocular pemphigoid has been described in a patient taking timolol eye-drops for glaucoma (144). Anterior uveitis has been reported in patients taking betaxolol (145) and metipranolol (146,147). Corneal anesthesia and epithelial sloughing with continuing use of topical beta-blockers have also been reported (148), as have ocular myasthenia and worsened sicca syndrome. Patients who lack CYP2D6 are more likely to have higher systemic concentrations of beta-blockers after topical application, making them susceptible to adverse effects.

- Recurrent retinal arteriolar spasm with associated visual loss has been described in a 68-year-old man with hypertension treated with atenolol (SEDA-17, 236).
- A 60-year-old man with open-angle glaucoma developed an allergic contact conjunctivitis and dermatitis from carteolol, a topical non-cardioselective beta-blocker (149). He had extensive cross-reactivity to other topical beta-blockers, such as timolol and levobunolol. Cross-reactivity among different beta-blockers is possibly due to a common lateral aliphatic chain.

Psychological, psychiatric

Disturbances of psychomotor function

Beta-adrenoceptor antagonists impair performance in psychomotor tests after single doses. These include effects of atenolol, oxprenolol, and propranolol on pursuit rotor and reaction times (150,151). However, other studies with the same drugs have failed to show significant effects (152–156), and the issue has remained controversial. A report that sotalol improved psychomotor performance in 12 healthy individuals in a dose of 320 mg/day but impaired performance at 960 mg/day (157) has been interpreted to indicate that the water-soluble beta-adrenoceptor antagonists would be less likely than the fat-soluble drugs to produce nervous system effects. Both atenolol and propranolol alter the electroencephalogram; atenolol affects body sway and alertness and propranolol impairs short-term memory and the ability to concentrate (158,159). These results suggest that both lipophilic and hydrophilic beta-adrenoceptor antagonists can affect the central nervous system, although the effects may be subtle and difficult to demonstrate.

In 27 hypertensive patients aged 65 years or more, randomized to continue atenolol treatment for 20 weeks or to discontinue atenolol and start cilazapril, there was a significant improvement in the choice reaction time in the patients randomized to cilazapril (160). This study has confirmed previous reports that chronic beta-blockade can determine adverse effects on cognition in elderly patients. Withdrawal of beta-blockers should be considered in any elderly patient who has signs of mental impairment.

In a placebo-controlled trial of propranolol in 312 patients with diastolic hypertension, 13 tests of cognitive function were assessed at baseline, 3 months, and 12 months (161). Propranolol had no significant effects on 11 of the 13 tests. Compared with placebo, patients taking propranolol had fewer correct responses at 3 months and made more errors of commission.

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Psychoses

Bipolar affective disorder

Bipolar depression affects 1% of the general population, and treatment resistance is a significant problem. The addition of pindolol can lead to significant improvement in depressed patients who are resistant to antidepressant drugs, such as selective serotonin reuptake inhibitors or phenelzine. Of 17 patients with refractory bipolar depression, in whom pindolol was added to augment the effect of antidepressant drugs, eight responded favorably (162). However, two developed transient hypomania, and one of these became psychotic after the resolution of hypomanic symptoms. In both cases transient hypomanic symptoms resolved without any other intervention, while psychosis required pindolol withdrawal.

Anxiety and depression have been reported after the use of nadolol, which is hydrophilic (163). In a study of the co-prescribing of antidepressants in 3218 new users of beta-blockers (164), 6.4% had prescriptions for antidepressant drugs within 34 days, compared with 2.8% in a control population. Propranolol had the highest rate of co-prescribing (9.5%), followed by other lipophilic beta-blockers (3.9%) and hydrophilic beta-blockers (2.5%). In propranolol users, the risk of antidepressant use was 4.8 times greater than the control group, and was highest in those aged 20–39 (RR = 17; 95% CI = 14, 22).

Organic brain syndrome

The development of a severe organic brain syndrome has been reported in several patients taking beta-adrenoceptor antagonists regularly without a previous history of psychiatric illness (165–167). A similar phenomenon was seen in a young healthy woman who took propranolol 160 mg/day (168). The psychosis can follow initial therapy or dosage increases during long-term therapy (169). The symptoms, which include agitation, confusion, disorientation, anxiety, and hallucinations, may not respond to treatment with neuroleptic drugs, but subsides rapidly when the beta-blockers are withdrawn. Symptoms are also ameliorated by changing from propranolol to atenolol (170).

Schizophrenia

A schizophrenia-like illness has also been seen in close relation to the initiation of propranolol therapy (171).

Endocrine

Prolactin

- Reversible hyperprolactinemia with galactorrhea occurred in a 38-year-old woman taking atenolol for hypertension (172).

Thyroid

Propranolol inhibits the conversion of thyroxine (T4) to tri-iodothyronine (T3) by peripheral tissues (173), resulting in increased formation of inactive reverse T3. There have been several reports of hyperthyroxinemia in clinically euthyroid patients taking propranolol for non-thyroid reasons in high dosages (320–480 mg/day) (174,175). The incidence was considered to be higher than could be accounted for by the development of spontaneous hyperthyroidism, but the mechanism is unknown.

The effect of beta-adrenoceptor antagonists on thyroid hormone metabolism is unlikely to play a significant role in their use in hyperthyroidism. Since D-propranolol has similar effects on thyroxine metabolism to those seen with the racemic mixture, membrane-stabilizing activity may be involved (176).

In one case, beta-adrenoceptor blockade masked an unexpected thyroid crisis, resulting in severe cerebral dysfunction before the diagnosis was made (177).

Metabolism

Hypoglycemia

Hypoglycemia, producing loss of consciousness in some cases, can occur in non-diabetic individuals who are taking beta-adrenoceptor antagonists, particularly those who undergo prolonged fasting (178) or severe exercise (179,180). Patients on maintenance dialysis are also at risk (181). It has been suggested that non-selective drugs are most likely to produce hypoglycemia and that cardioselective drugs are to be preferred in at-risk patients (182), but the same effect has been reported with atenolol under similar circumstances (180).

Two children in whom propranolol was used to treat attention deficit disorders and anxiety became unarousable, with low heart rates and respiratory rates, due to hypoglycemia (183). Hypoglycemia can be caused by reduced glucose intake (fasting), increased utilization (hyperinsulinemia), or reduced production (enzymatic defects). One or more of these mechanisms can be responsible for hypoglycemia secondary to drugs. Children treated with propranolol may be at increased risk of hypoglycemia, particularly if they are fasting. Concomitant treatment with methylphenidate can increase the risk of this metabolic disorder.

However, contrary to popular belief, beta-adrenoceptor antagonists do not by themselves increase the risk of hypoglycemic episodes in insulin-treated diabetics, in whom their use was concluded to be generally safe (184). Indeed, in 20 such patients treated with diet or diet plus oral hypoglycemic agents, both propranolol and metoprolol produced small but significant increases in blood glucose concentrations after 4 weeks (185). The rise was considered clinically important in only a few patients.

However, in insulin-treated diabetics who become hypoglycemic, non-selective beta-adrenoceptor antagonists can mask the adrenaline-mediated symptoms, such as palpitation, tachycardia, and tremor; they can cause a rise in mean and diastolic blood pressures, due to unopposed alpha-adrenoceptor stimulation from catecholamines, because the $beta_2$-adrenoceptor-mediated vasodilator response is blocked (186); they can also impair the rate of rise of blood glucose toward normal (187). In contrast, cardioselective drugs mask hypoglycemic symptoms less (188); because of vascular sparing, they are less likely to be associated with a diastolic pressor response in the presence of catecholamines, although this has been reported with metoprolol (189); and delay in recovery from hypoglycemia is either less marked or undetectable with cardioselective drugs, such as atenolol or metoprolol. Thus, if insulin-requiring diabetics need to be treated with a beta-adrenoceptor antagonist, a

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cardioselective agent should always be chosen for reasons of safety, while allowing that this type of beta-blocker is associated with insulin resistance and can impair insulin sensitivity by 15–30% (SEDA-17, 235), and hence increase insulin requirements.

People with diabetes have a much worse outcome after acute myocardial infarction, with a mortality rate at least twice that in non-diabetics. However, tight control of blood glucose, with immediate intensive insulin treatment during the peri-infarct period followed by intensive subcutaneous insulin treatment, was associated with a 30% reduction in mortality at 1 year, as reported in the DIGAMI study. In addition, the use of beta-blockers in this group of patients had an independent secondary preventive effect (190). The use of beta-blockers in diabetics with ischemic heart disease should be encouraged (37).

In 686 hypertensive men treated for 15 years, beta-blockers were associated with a higher incidence of diabetes than thiazide diuretics (191). This was an uncontrolled study, but the observation deserves further study.

Blood lipids

There is increasing evidence that beta-adrenoceptor antagonists increase total triglyceride concentrations in blood and reduce high-density lipoprotein (HDL) cholesterol. Comparisons of non-selective and cardioselective drugs have shown that lipid changes are less marked but still present with $beta_1$-selective agents (192). Current information suggests that $beta_1$-selective drugs may be preferable in patients with hypertriglyceridemia (193). Topical beta-blockers can cause rises in serum triglyceride concentrations and falls in serum high-density lipoprotein concentrations; this makes them less suitable in patients with coronary heart disease (38,194).

The importance of these effects for the long-term management of patients with hypertension or ischemic heart disease is unknown, but it is recognized that a high serum total cholesterol and a low HDL cholesterol are associated with an increased risk of ischemic heart disease. However, a significant reduction in HDL cholesterol after treatment for 1 year with timolol was of no prognostic significance and did not attenuate the protective effect of the drug (195). In a 4-year randomized, placebo-controlled study of six antihypertensive monotherapies, acebutolol produced only a small and probably clinically irrelevant (0.17 mmol/l) reduction in total cholesterol (196), which was not statistically different from four of the other antihypertensive drugs.

Obesity

It has been suggested that beta-blockers may predispose to obesity by reducing basal metabolic rate via beta-adrenoceptor blockade (197). Thermogenesis in response to heat and cold, meals, stress, and anxiety is also reduced by beta-adrenoceptor blockade, promoting weight gain (SEDA-16, 193). $Beta_3$-adrenoceptors have been implicated in this mechanism (198,199). Since propranolol blocks $beta_3$-receptors in vivo (200), it would be wise on theoretical grounds to avoid propranolol in obese patients; nadolol is another non-selective beta-blocker that does not act on $beta_3$-adrenoceptors.

A systematic review of eight prospective, randomized trials in 7048 patients with hypertension (3205 of whom were taking beta-blockers) confirmed that body weight was higher in those taking beta-blockers than in controls at the end of the studies (201). The median difference in body weight was 1.2 kg (range –0.4–3.5 kg). There was no relation between demographic characteristics and changes in body weight. The weight gain was observed in the first few months of treatment and thereafter there was no further weight gain compared with controls. This observation suggests that first-line use of beta-blockers in obese patients with hypertension should be considered with caution.

Electrolyte balance

Hypokalemia

Adrenaline by infusion produces a transient increase in plasma potassium, followed by a prolonged fall; pretreatment with beta-adrenoceptor antagonists results in a rise in plasma potassium (202). These effects may be mediated via $beta_2$-adrenoceptors (203), and cardioselective drugs should have smaller effects (202). In the Treatment of Mild Hypertension Study (TOMHS), acebutolol did not change serum potassium after 4 years (196).

It has been argued that drug combinations that contain a beta-adrenoceptor antagonist in combination with a thiazide diuretic minimize the hypokalemic effect of the latter; however, marked hypokalemia in the absence of primary hyperaldosteronism has been reported in a patient taking Sotazide (a combination of hydrochlorothiazide and the non-selective drug sotalol) (204). The use of a combination formulation of chlortalidone and atenolol has also produced hypokalemia (205), in one case complicated by ventricular fibrillation after myocardial infarction (206).

In addition to a rise in serum potassium, timolol increases plasma uric acid concentrations (207). In the TOMHS study, acebutolol increased serum urate by 7 μmol/l (196).

Mineral balance

A fall in serum calcium has been reported with atenolol (208), but whether this was causal has been disputed (209).

Hematologic

Thrombocytopenia has been reported in patients taking oxprenolol (210,211) and alprenolol (212,213); it can recur on rechallenge. This effect is presumed to have an immunological basis.

In the International Agranulocytosis and Aplastic Anemia Study the relation between cardiovascular drugs and agranulocytosis was examined: there was a relative risk of 2.5 (95% CI = 1.1, 6.1) for propranolol (214). Other beta-blockers did not increase risk and propranolol had no association with aplastic anemia. There are also anecdotal reports of this association (215).

Gastrointestinal

Mild gastrointestinal adverse effects, such as nausea, dyspepsia, constipation, or diarrhea, have been reported in

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5–10% of patients taking beta-adrenoceptor antagonists (42). A reduction in dosage or a change to another member of the group will usually produce amelioration. Severe reactions of this type are very infrequent, but severe diarrhea, dehydration, hypokalemia, and weight loss, recurring after rechallenge, occurred with propranolol in a single case (216).

Nausea and vomiting have been attributed to timolol eye-drops (217).

- Severe nausea and vomiting occurred in a 77-year-old woman treated with timolol eye-drops for glaucoma. Her weight had fallen by 8 kg (13%). All physical, laboratory, and instrumental examinations were negative. Gastroduodenoscopy and duodenal biopsy were unremarkable and *Helicobacter pylori* was absent. When timolol was replaced by betaxolol, her complaints disappeared and she gained 2 kg. On rechallenge 3 months later she developed severe nausea, vomiting, and anorexia after some days of treatment. She immediately stopped taking the treatment and 4 days later the symptoms disappeared.

Since timolol has been satisfactorily used by millions of patients, the incidence of serious gastrointestinal events appears to be very low. Absence of symptoms after betaxolol therapy in this patient is in agreement with its lower risk of non-cardiac adverse reactions compared with the non-selective agent timolol.

Beta-adrenoceptor antagonists can cause non-anginal chest pain because of esophagitis (218), due to adherence of the tablet mass, resulting in esophageal spasm, inflammatory change, and even perforation.

Sclerosing peritonitis and retroperitoneal fibrosis

Sclerosing peritonitis was described as part of the practolol syndrome (219–221), and it can also occur with other beta-adrenoceptor antagonists (222,223).

Retroperitoneal fibrosis has been reported in patients taking oxprenolol (224), atenolol (225), propranolol (226), metoprolol (227), sotalol (228), and timolol (including eye-drops) (229,230). However, this disorder often occurs spontaneously and has been reported very infrequently in patients taking beta-blockers (231). Thus, in the absence of any causal relation it is most likely that it reflects the spontaneous incidence in patients taking a common therapy. This conclusion has been supported by an analysis of 100 cases of retroperitoneal fibrosis (232).

Liver

Many beta-adrenoceptor antagonists undergo substantial first-pass hepatic metabolism; these include alprenolol, metoprolol, oxprenolol, and propranolol. Hepatic cirrhosis, with consequent portosystemic shunting, can therefore result in increased systemic availability and higher plasma concentrations, perhaps resulting in adverse effects. Beta-blockers may also reduce liver blood flow and cause interactions with drugs with flow-dependent hepatic clearance.

The oxidative clearance of the lipophilic drugs, metoprolol, timolol, and bufuralol, is influenced by the debrisoquine hydroxylation gene locus, resulting in polymorphic metabolism (233). This might result in an increase in the adverse effects of these beta-blockers in poor metabolizers, but to date there is no objective evidence of such an association (234).

Beta-adrenoceptor antagonists, used in the prevention of bleeding from esophageal varices in patients with hepatic cirrhosis, have reportedly caused hepatic encephalopathy in several patients (235–239). Thus, extreme caution is required, particularly because resuscitation can be difficult when beta-blockers are given to patients with gastrointestinal bleeding or encephalopathy (240).

Biliary tract

Biliary cirrhosis was reported as part of the practolol syndrome (241), but there have been no comparable reports with other beta-adrenoceptor antagonists.

Urinary tract

Propranolol reduces renal blood flow and glomerular filtration rate after acute administration, associated with, and probably partly due to, falls in cardiac output and blood pressure (242,243). There has been some argument about whether these effects persist during long-term therapy (244). Despite early suggestions that renal function might be worsened by such therapy, particularly in patients with chronic renal insufficiency (245), the clinical significance of these changes is debatable (246). Claims that nadolol increases renal blood flow and that cardioselective drugs such as atenolol reduce renal blood flow less than non-selective agents in old people (247) are thus probably relatively unimportant. The vasodilating beta-blocker carvedilol maintains renal blood flow whilst reducing glomerular filtration rate, suggesting that renal vasodilatation occurs (248), although a single case of reversible renal insufficiency has been described in a clinical trial in patients with severe heart failure (249).

Skin

Rashes were part of the practolol (oculomucocutaneous) syndrome, but are infrequent with other beta-adrenoceptor antagonists. The eruptions can be urticarial, morbilliform, eczematous, vesicular, bullous, psoriasiform, or lichenoid (250–255).

Beta-blocker eye-drops can cause skin rashes (256).

- A 70-year-old woman treated with topical timolol for glaucoma developed a papular eruption on the arms and back, consistent with prurigo. All tests were within the reference ranges. There was no improvement after 1 month of topical corticosteroids. The eruption cleared completely within 1 month of timolol withdrawal. Betaxolol eye-drops were introduced and the eruption recurred within 1 week. When beta-blocker therapy was replaced by synthetic cholinergic eye-drops (drug unspecified) the eruption cleared completely without any recurrence a year later.
- Allergic contact dermatitis due to carteolol eye drops occurred in a 61-year-old woman (257). Withdrawal of carteolol and the use of timolol instead led to improvement within 10 days, suggesting that in some cases there is no cross-reactivity between different beta-blockers.

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Although cutaneous adverse effects have been previously described after oral beta-blockers, including timolol, this observation further suggests a class effect of topical beta-blockers. This case also suggests a cross-reaction between timolol and betaxolol.

In a review of 588 patients with established psoriasis it was concluded that about two-thirds of such patients are likely to have a flare-up with a beta-adrenoceptor antagonist, regardless of the agent used (258). In patients with vitiligo, beta-blockers rarely exacerbate depigmentation (7/548 patients) (259). In a separate report, topical betaxolol used for glaucoma was associated with periocular cutaneous pigmentary changes (260).

Some patients have positive patch tests and/or a positive response to oral rechallenge. There can also be cross-sensitivity to other beta-blockers in compromised patients. The mechanisms appear to include both immunological and pharmacological effects; in the latter case the drug may modify growth regulation in the epidermis (261).

Contact allergy to topical beta-blockers can occur.

- A 68-year-old woman developed contact allergy after many years of using befunolol (262). Patch-testing showed cross-sensitivity to carteolol. Evidence of such cross-sensitivity has not previously been reported.

Sweat glands

Hyperhydrosis or sweating with beta-blockers has been reported with both oral formulations (sotalol and acebutolol) (263) and topical formulations (carteolol) (264), although the patients described in these reports were not rechallenged to ascertain the link. However, it was suggested that beta-blockade increased exercise-related sweating in healthy volunteers, more so with a non-selective beta-blocker (propranolol), than a selective one (atenolol) (265). The mechanism for this was uncertain, but was thought to be due to an imbalance between beta- and alpha-adrenergic activity. In some instances, clonidine, an alpha-adrenoceptor antagonist, was effective in treating hyperhydrosis (266), whereas in other cases, propranolol was paradoxically effective (267).

Hair

There have been single case reports of alopecia in association with propranolol (268) and metoprolol (269).

Musculoskeletal

It has been suggested that arthralgia is a not an uncommon adverse effect of beta-adrenoceptor antagonists, particularly metoprolol (270), although the association was not confirmed by rechallenge in any patient. A later case-control study in 127 patients attending a hypertension clinic who had arthropathy showed no significant relation between the arthropathy and the use of beta-blockers (271). On the other hand, five cases of metoprolol-associated arthralgia, most with negative serological tests for collagenases, have been reported to the FDA (272).

Muscle cramps have been reported in patients taking beta-blockers with partial agonist activity (273); it has been suggested (274) that this might be a $beta_2$-partial agonist effect, although this has not subsequently been supported (275). However, a crossover study in 78 hypertensive patients suggested that beta-blockers with partial agonist activity (pindolol and carteolol) caused muscle cramps in up to 40% of these patients, with an associated rise in serum CK and CK-MB, although the severity of the cramps did not correlate with the enzyme activities (276).

Sexual function

Uncontrolled studies of the effect of beta-adrenoceptor antagonists on sexual function have often shown a high incidence of absence of erections, reduced potency, and reduced libido (277). Several large controlled trials in hypertension and ischemic heart disease have provided more exact information. In a large-scale, prospective, placebo-controlled study, reduced sexual activity was an adverse effect of sufficient severity to lead to the withdrawal of some patients in the propranolol-treated group (278). In the TOMHS study, the incidence of difficulty in obtaining and maintaining an erection over 48 months was 17% with both acebutolol and placebo (196). In the TAIM study (279), a randomized, placebo-controlled study lasting 6 months, atenolol did not cause a significant increase in erectile problems in men (11%; 95% CI 2, 20%) compared with placebo (3%; 0, 9%). Loss of libido and difficulty in sustaining an erection can be induced in young healthy volunteers (134); although these effects may be more common with lipophilic drugs, such as propranolol (280) and pindolol (281), they have also been reported with atenolol (282).

Peyronie's disease

Peyronie's disease is a fibrotic condition of the penis that has been associated with beta-blockers, such as propranolol (283), metoprolol (284), and labetalol (284). However, 100 consecutive cases of Peyronie's disease included only five men who had taken a beta-blocker before the onset of the condition (285); the authors concluded that the syndrome was likely to be associated with chronic degenerative arterial disease and not with beta-adrenoceptor antagonists.

Immunologic

Leukocytoclastic vasculitis has been reported with sotalol (286).

- A progressive cutaneous vasculitis occurred in a 66-year-old man taking sotalol for prevention of a symptomatic atrial fibrillation. After 7 days he noted a petechial eruption on his wrists and ankles. This progressed during the next days to palpable purpura on the hands, wrists, ankles, and feet. A biopsy specimen showed changes consistent with leukocytoclastic vasculitis. After withdrawal of sotalol the skin rash cleared completely without any other intervention.

Other beta-blockers associated with leukocytoclastic vasculitis include acebutolol, alprenolol, practolol, and propranolol.

Antinuclear antibodies in high titers were detected in a number of patients with the practolol oculomucocutaneous syndrome. Tests in patients taking acebutolol (287,288) and celiprolol (289) have also shown a high

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frequency of antinuclear antibodies. Positive lupus erythematosus cell preparations have been observed in patients taking acebutolol (288).

The lupus-like syndrome was part of the practolol syndrome and has also been attributed to acebutolol (290,291), atenolol (SEDA-16, 194), labetalol (292), pindolol (293), and propranolol (294). However, apart from practolol, it seems to be very rare during treatment with beta-adrenoceptor antagonists.

Anaphylactic reactions have been attributed to beta-adrenoceptor antagonists only very infrequently (295). However, it appears that anaphylactic reactions precipitated by other agents can be particularly severe in patients taking beta-blockers, especially non-selective drugs, and may require higher-than-usual doses of adrenaline for treatment (296–299). The view that allergy skin testing or immunotherapy is inadvisable in patients taking beta-blockers (300) has been disputed, bearing in mind the low incidence of this adverse effect (301).

Long-Term Effects

Drug withdrawal

Interest in the possible effects of the sudden withdrawal of beta-adrenoceptor antagonists followed a 1975 report of two deaths and four life-threatening complications of coronary artery disease within 2 weeks of withdrawal of propranolol (302). Subsequent analyses did not always confirm these findings (303,304), and it has not been easy to distinguish between natural progression and deterioration caused by drug withdrawal under such circumstances. However, a case-control study in hypertensive patients showed a relative risk of 4.5 (95% CI = 1.1, 19) associated with recent withdrawal of beta-blockers and the development of myocardial infarction or angina (305).

The symptoms attributed to the sudden withdrawal of beta-adrenoceptor antagonists (severe exacerbation of angina pectoris, acute myocardial infarction, sudden death, malignant tachycardia, sweating, palpitation, and tremor) are consistent with transient adrenergic hypersensitivity. Unequivocal signs of rebound hypersensitivity have been observed after drug withdrawal in patients with ischemic heart disease (306), but not in hypertensive patients (307–309). The density of beta-adrenoceptors on human lymphocyte membranes increased by 40% during treatment with propranolol for 8 days (310), and hypersensitivity to isoprenaline can be shown in hypertensive patients after the withdrawal of different beta-adrenoceptor antagonists, including propranolol (311), metoprolol (312), and atenolol (313). This hypersensitivity occurs within 2 days of drug withdrawal, can persist for up to 14 days, and is presumed to reflect the up-regulation of beta-adrenoceptors that occurs with prolonged treatment. This phenomenon is said to be diminished by gradual withdrawal of therapy and by the use of drugs with partial agonist activity, such as pindolol (314). Whether this is directly relevant to the effects of the sudden withdrawal of beta-adrenoceptor antagonists in patients with ischemic heart disease is speculative.

Although there is evidence that abrupt withdrawal of long-acting beta-blockers is not associated with the development of the beta-blocker withdrawal syndrome (315), current information suggests that withdrawal of beta-adrenoceptor antagonists, particularly in patients with ischemic heart disease, should be accomplished by gradual dosage reduction over 10–14 days. However, even gradual withdrawal may not always prevent rebound effects (316).

Second-Generation Effects

Pregnancy

Great concern at one time accompanied the use of beta-adrenoceptor antagonists in pregnancy, particularly in the management of hypertension. On theoretical grounds beta-adrenoceptor antagonists might be expected to increase uterine contractions, impair placental blood flow, cause intrauterine growth retardation, accentuate fetal and neonatal distress, and increase the risk of neonatal hypoglycemia and perinatal mortality. There are many anecdotal reports of such complications attributed to beta-adrenoceptor antagonists, often propranolol. However, many of the adverse effects listed above are also potential complications of hypertension in pregnancy, and in the absence of a properly controlled trial of therapy, definite conclusions of cause and effect have been impossible on the basis of these anecdotes alone.

Many of the fears expressed were set aside by a double-blind, randomized, placebo-controlled trial of atenolol in pregnancy-associated hypertension in 120 women (316), which showed that babies in the placebo group had a higher morbidity, that atenolol reduced the occurrence of respiratory distress syndrome and intrauterine growth retardation, and that neonatal hypoglycemia and hyperbilirubinemia were equally common in the treated and placebo groups. Although bradycardia was more common with atenolol, it had no deleterious consequences. However, the offspring of women taking atenolol had lower body weights on follow up, the significance of which is unclear (316).

It is reasonable to consider that beta-adrenoceptor antagonists can be used in pregnancy without serious risks, provided patients are kept under careful clinical observation. Since all beta-blockers cross the placenta freely, major differences in effects or toxicity among the various drugs are unlikely, and in a review of beta-blockers in pregnancy it was concluded that no single beta-blocker is superior (317). However, in a small study in 51 women with pregnancy-induced hypertension the combination of hydralazine and propranolol was associated with lower blood glucose and weight at birth compared with the combination of hydralazine and pindolol (with partial agonist activity), despite similar blood pressure control. It was suggested that beta-adrenoceptor antagonists without partial agonist activity might reduce uteroplacental blood flow (318).

Fetotoxicity

The adverse effects of beta-adrenoceptor antagonists on the fetus have been reviewed (319). Beta blockers cross the placenta, and can have adverse maternal and fetal effects. Studies of the use of beta-blockers during pregnancy have generally been small, and the gestational age

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at the start of the study was generally 29–33 weeks, leaving substantially unanswered the possibility that treatment of more patients and/or longer treatment durations may reveal unrecognized adverse events. These observations underline the fact that the safety of beta-blockers remains uncertain and that they are therefore better not given before the third trimester.

Non-cardioselective beta-adrenoceptor antagonists

Observations derived from uncontrolled studies have shown an association between maternal use of propranolol and intrauterine growth retardation, neonatal respiratory depression, bradycardia, hypoglycemia, and increased perinatal mortality. However, in randomized, placebo-controlled studies of metoprolol and oxprenolol, there was no evidence of effects on birth weight.

- Two infants with features of severe beta-blockade (bradycardia, persistent hypotension), persistent hypoglycemia, pericardial effusion, and myocardial hypertrophy were born before term to mothers taking long-term oral labetalol for hypertension in pregnancy.

Although labetalol is considered to be generally safe in neonates, impaired urinary excretion and lower albumin binding in preterm infants can prolong the half-life of labetalol and increase its systemic availability and toxicity (320).

Cardioselective beta-adrenoceptor antagonists

There is reluctance to use atenolol in pregnancy, especially if treatment starts early. In placebo-controlled studies, birth weight was significantly lower with atenolol groups. The same was true when atenolol was compared with non-cardioselective agents: the weight of infants born to women taking atenolol was significantly lower. When atenolol was started later there was no difference in birth weight between infants born to women treated with atenolol or other beta-blockers, suggesting the relevance of the time of initiation of atenolol. Atenolol should therefore be avoided in the early stages of pregnancy and given with caution in the later stages.

- Fetal bradycardia and pauses after each two normal beats occurred at 21 weeks gestation in a 37-year-old woman using timolol eye-drops for glaucoma; when timolol was withdrawn, the fetal heart rate recovered (321).

The authors concluded that when a woman taking glaucoma therapy becomes pregnant, it is usually possible to interrupt therapy during pregnancy. Treatment may be deferred until delivery of the infant.

Lactation

The list of beta-adrenoceptor antagonists that have been detected in breast milk includes atenolol (322), acebutolol and its active *N*-acetyl metabolite (323), metoprolol (324), nadolol (325), oxprenolol and timolol (326), propranolol (327), and sotalol (328). Most authors have concluded that the estimated daily infant dose derived from breastfeeding is likely to be too low to produce untoward effects in the suckling infant, and indeed such effects were not noted in the above cases. However, in the case of acebutolol it was considered that clinically important amounts of drug could be transferred after increasing plasma concentrations were noted in two breastfed infants.

Susceptibility Factors

Genetic factors

Most beta-blockers undergo extensive oxidation (329). There have been anecdotal reports of high plasma concentrations of some beta-blockers in poor metabolizers of debrisoquine, and controlled studies have shown that debrisoquine oxidation phenotype is a major determinant of the metabolism, pharmacokinetics, and some of the pharmacological effects of metoprolol, bufuralol, timolol, and bopindolol. The poor metabolizer phenotype is associated with increased plasma drug concentrations, a prolonged half-life, and more intense and sustained beta-blockade. There are also phenotypic differences in the pharmacokinetics of the enantiomers of metoprolol and bufuralol.

Renal disease

The hydrophilic drugs atenolol and sotalol are eliminated largely unchanged in the urine; with deteriorating renal function their half-lives can be prolonged as much as 10-fold (330,331). Other beta-adrenoceptor antagonists, for example acebutolol and metoprolol, have active metabolites that can accumulate (332). Massive retention of the metabolite propranolol gluconate has also been reported in patients with renal insufficiency taking long-term oral propranolol (333); this metabolite is then deconjugated, and concentrations of propranolol can be significantly increased in these patients. Thus, in a patient with a low creatinine clearance, either dosage adjustment or a change of beta-blocker may be necessary.

Other features of the patient

Heart failure

Untreated congestive heart failure secondary to systolic pump failure is a contraindication to the use of beta-adrenoceptor antagonists. Patients in frank or incipient heart failure have reduced sympathetic drive to the heart, and acute life-threatening adverse effects can therefore follow beta-blockade. This is one of the recognized potentially serious complications of beta-blockers in the management of thyrotoxic crisis (334). However, patients with heart failure treated with ACE inhibitors and/or diuretics and digoxin may well gain long-term benefit from beta-adrenoceptor antagonists (34,35).

Heart block

Second-degree or third-degree heart block is a contraindication to beta-adrenoceptor blockade. If it is considered necessary for the control of dysrhythmias, a beta-blocker can be given after the institution of pacing.

Acute myocardial infarction

After many trials including thousands of patients, it is increasingly accepted that treatment of acute myocardial infarction with beta-adrenoceptor antagonists is

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beneficial. Given intravenously within 4–6 hours of the onset of the infarction these drugs can prevent ventricular dysrhythmias and cardiac rupture (335,336). When given orally during the first year after infarction, beta-adrenoceptors reduce mortality by about 25% (337) and probably more in diabetic subjects (37). Since heart failure, hypotension, and bradycardia are complications of both myocardial infarction and beta-adrenoceptor blockade, it might be assumed that these effects would be more common when the two are combined. However, reviews of the relevant studies (335,338–346) do not suggest that beta-adrenoceptor antagonists, given after acute myocardial infarction, either acutely intravenously or for secondary prophylaxis, increase the incidence of adverse effects or the risk of any particular adverse effect. Nevertheless, patients were rigorously selected for inclusion in these trials; less careful decisions to treat may carry increased risks.

Bronchial asthma

Beta-adrenoceptor antagonists should not be given to patients with bronchial asthma or obstructive airways disease, unless there are no other treatment options, because of the risk of precipitating bronchospasm resistant to bronchodilators. Celiprolol, a $beta_1$-antagonist with $beta_2$-agonist activity, has a theoretical but unproven advantage. Alternatively, cardioselective drugs should be chosen in the lowest possible dosages and in conjunction with a $beta_2$-adrenoceptor agonist, such as salbutamol or terbutaline, to minimize bronchoconstriction.

Smoking

Some common activities, such as mental effort (347), cigarette smoking, and coffee drinking (348,349), can produce stress associated with increased catecholamine secretion. In the presence of a non-selective beta-adrenoceptor antagonist, there can be a marked diastolic pressor response, due to mechanisms identical to those described above in hypoglycemia in diabetes. This effect may be smaller with cardioselective drugs.

Theoretically, frequent rises in diastolic blood pressure associated with smoking whilst taking a non-selective beta-adrenoceptor antagonist could be harmful; in a patient with ischemic heart disease or hypertension a cardioselective drug might offer advantages. There is no evidence of differences in morbidity or mortality in patients taking non-selective and cardioselective agents, but both the MRC and IPPPSH trials of mild hypertension showed increases in the incidence of coronary events in patients taking non-selective beta-adrenoceptor antagonists who were also cigarette smokers (350). The explanation that cigarette smoking increases the hepatic metabolism of beta-adrenoceptor blockers, reducing their effectiveness (351), does not extend to the use of cardioselective beta-blockers in smokers, as reported in the HAPPHY and MAPHY trials.

Insulin-treated diabetes

Beta-adrenoceptor antagonists may mask the symptoms of hypoglycemia, result in a catecholamine-mediated rise in diastolic blood pressure, and delay the return of blood glucose concentrations to normal. These effects are minimized or abolished by using a $beta_1$-selective drug, and this type of drug should always be used in preference to a non-selective drug in insulin-treated diabetes.

Anaphylaxis

Beta-blockers can make anaphylactic reactions more difficult to diagnose and treat (348). Even patients with spontaneous attacks of angioedema or urticaria can be at risk when given beta-blockers (352).

Drug Administration

Drug administration route

Beta-adrenoceptor antagonists are used as ocular tension-lowering drugs without notable effects on pupillary size or refraction. Their systemic effects are greater than one would expect, since there is no first-pass metabolism after ocular administration and the plasma concentration can therefore attain therapeutic concentrations (353).

The systemic adverse effects of ophthalmic beta-blockers have been reviewed (354). Symptomatic bradycardia from systemic or ophthalmic use of beta-blockers alone suggests underlying cardiac conduction disturbances. $Beta_2$-adrenoceptor blockade can exacerbate or trigger bronchospasm in patients with asthma or pulmonary disease associated with hyper-reactive airways. Occasionally, adverse systemic reactions can be severe enough to require drug withdrawal. Obtaining a careful medical history and checking pulse rate and rhythm and peak expiratory flow rate should identify the vast majority of patients with potential cardiac and respiratory contraindications.

Beta-blockers that are available as eye-drops include timolol, metipranolol, and levobunolol, which are non-selective $beta_1$- and $beta_2$-adrenoceptor antagonists, and betaxolol, a relatively cardioselective $beta_1$-adrenoceptor antagonist. Although selective $beta_1$-blockers are less likely to precipitate bronchospasm, this and other systemic effects can nevertheless occur (SED-12, 1200).

In 165 patients who used timolol 0.5% eye-drops, adverse effects were reported in 23%, including psychiatric effects (40%), cardiovascular effects (19%), respiratory effects (7%), and local effects (26%) (355).

Cardiovascular

Hemodynamic changes after the topical ocular use of beta-blockers sometimes include only small reductions in heart rate and resting pulse rate and an insignificant reduction in blood pressure. However, patients with cardiovascular disorders, especially those with an irregular heart rate and dysrhythmias, are certainly at risk (SEDA-4, 339). Bradycardia, cardiac arrest, heart block, hypotension, palpitations, syncope, and cerebral ischemia and stroke can occur (356). Rebound tachycardia has been reported after withdrawal of ophthalmic timolol (88,357). Continuous 24-hour monitoring of blood pressure has shown that beta-blocker eye-drops for glaucoma can increase the risk of nocturnal arterial hypotension (358).

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Respiratory

Beta-blockers can aggravate or precipitate bronchospasm (SEDA-4, 339) (SEDA-5, 426) and potentially life-threatening respiratory failure can occur.

- A 58-year-old patient using topical timolol maleate for open-angle glaucoma developed cough and dyspnea due to interstitial pneumonitis. Three months after withdrawal of the eye-drops, he was asymptomatic with normal lung function, chest X-ray, and thoracic CT scan (359).

Nervous system

Light-headedness, mental depression, weakness, fatigue, acute anxiety, dissociative behaviour, disorientation, and memory loss can develop a few days to some months after the start of timolol therapy (88). Central nervous system complaints are most common in patients who have the greatest reduction in intraocular pressure (SEDA-5, 426). Patients may be unaware of the symptoms until the medication is stopped.

Sensory systems

Dry eyes have been reported after the systemic or ocular use of timolol (360). A sensation of dryness in the eyes can develop and is usually transitory. There can be a reduction in the Schirmer test and tear film break-up time. Symptomatic superficial punctate keratitis in association with complete corneal anesthesia has been observed (361).

Amaurosis fugax has been reported in association with topical timolol (362).

Endocrine

Ophthalmic beta-blockers can cause hypoglycemia in insulin-dependent diabetes (363). Conversely, in diabetic patients taking oral hypoglycemic drugs, hyperglycemia can develop because of impaired insulin secretion (SEDA-21, 487).

Electrolyte balance

Severe hyperkalemia has been reported in association with topical timolol, confirmed by rechallenge (364).

Skin

Cutaneous changes secondary to instillation of betaxolol have been described (260).

Musculoskeletal

Aggravation of myasthenia gravis has been observed during ophthalmic timolol therapy (365). Bilateral pigmentation of the fingernails and toenails, marked hyperkalemia, and arthralgia after ocular timolol have all been reported (SED-12, 1200).

Sexual function

Erectile impotence can occur after ophthalmic use of beta-blockers (88).

Susceptibility factors

All of the susceptibility factors that apply to systemically administered beta-blockers also apply to eye-drops. This particularly applies to asthma (260).

Glaucoma

Eyes with potential angle closure require a miotic drug and should not be treated with beta-blockers alone. To exclude the risk of precipitating glaucoma in a susceptible individual, gonioscopy is recommended before starting topical beta-adrenoceptor antagonist therapy.

Drug tolerance

Tachyphylaxis can develop after treatment with ophthalmic beta-blockers (366). There are two forms, short-term "escape," which occurs over a few days, and long-term "drift," which occurs over months and years.

Drug overdose

The increasing use of beta-adrenoceptor antagonists appears to have resulted in more frequent reports of severe high-dose intoxication (367,368), in which beta-adrenoceptor antagonists are often taken in combination with sedatives or alcohol. There can be a very short latency from intake of the drug until fulminant symptoms occur (369). The clinical features are well established. Cardiovascular suppression results in bradycardia, heart block, and congestive heart failure, and intraventricular conduction abnormalities are common (370). Ventricular tachycardias with sotalol intoxication may reflect its class III antidysrhythmic properties, leading to prolongation of the QT interval (371) and torsade de pointes, which may respond to lidocaine (372). Bronchospasm and occasionally hypoglycemia can also occur. Coma and epileptiform seizures are often seen (370,373) and may not be secondary to circulatory changes. The outcome is seldom fatal, but 16 fatal cases of intoxication with talinolol (which is $beta_1$-selective) have been described. Deaths have also occurred with metoprolol and acebutolol. Acebutolol has membrane-stabilizing activity, and it has been suggested that drugs with this property carry greater risk when taken in overdose (374). Lipid solubility influences the rate of nervous system penetration of a drug, and overdosage with highly lipophilic drugs, such as oxprenolol and propranolol, has been associated with rapid loss of consciousness and coma (375–377).

Treatment should include isoprenaline (although massive doses may be required), glucagon, and atropine. If a $beta_1$-selective antagonist has been taken, isoprenaline may reduce diastolic blood pressure by its unopposed vasodilator effect on $beta_2$-adrenoceptors (378). The $beta_1$-selective agonist dobutamine may be preferable in such patients (379). A temporary transvenous pacemaker should be inserted if significant heart block or bradycardia occur. Seizures in overdosage with a beta-adrenoceptor antagonist respond poorly to diazepam and barbiturates; muscle relaxants and artificial ventilation may be required. In general, the lipid-soluble drugs are highly protein-bound with a large apparent volume of distribution; forced diuresis or hemodialysis are therefore unlikely to be of use.

Propranolol intoxication can cause central nervous system depression in the absence of clinical signs of cardiac toxicity.

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- A 16-year-old boy developed central nervous system depression and an acute dilated cardiomyopathy after taking 3200 mg of propranolol in a suicide attempt (380). He was treated with gastric lavage, activated charcoal, and mechanical ventilation. Echocardiography showed a poorly contracting severely dilated left ventricle. After intravenous isoprenaline hydrochloride and glucagon, echocardiography showed normal left ventricular size and function. He became fully alert 20 hours later and made a good recovery without sequelae.

Early echocardiographic evaluation is important in beta-blocker overdose and can prevent delay in the diagnosis and treatment of cardiac toxicity.

Two regional poison centers in the USA have reviewed 280 cases of beta-blocker overdose (381). All patients with symptoms developed them within 6 hours of ingestion. Four patients died as a result of overdosage. There was cardiovascular morbidity in 41 patients (15%), requiring treatment with cardioactive drugs. Propranolol, atenolol, and metoprolol were responsible for 87% of the cases and 84% of cardiovascular morbidity. Beta-blockers with membrane-stabilizing activity (acebutolol, labetalol, metoprolol, pindolol, and propranolol) accounted for 62% of beta-blocker exposures and 73% of cardiovascular morbidity. Symptomatic bradycardia (heart rate less than 60/minute) or hypotension (systolic blood pressure less than 90 mmHg) were observed in all cases classified as having cardiovascular morbidity. Beta-blocker exposure was complicated by a history of at least one co-ingestant in 73% of the cases, benzodiazepines and ethanol being the most frequent. Cardioactive co-ingestants were reported in 26% of cases: calcium channel blockers, cyclic antidepressants, neuroleptic drugs, and ACE inhibitors were the most common. Multivariate analysis showed that the only independent variable significantly associated with cardiovascular morbidity was the presence of another cardioactive drug. When patients who took another cardioactive drug were excluded, the only variable associated with cardiovascular morbidity was the ingestion of a beta-blocker with membrane-stabilizing activity.

Two fatal cases of acebutolol intoxication (6 and 4 g) have been reported (382). In both cases, the onset of symptoms was sudden (within 2 hours of ingestion), with diminished consciousness, PR, QRS, and QT prolongation, and hypotension unresponsive to inotropic drugs. In both cases there were episodes of repetitive polymorphous ventricular tachycardia.

These cases have confirmed the potential toxicity of beta-blockers with membrane stabilizing activity; they predispose the patient to changes in ventricular repolarization, which can cause QT prolongation and serious ventricular dysrhythmias. This is generally not seen in cases of propranolol intoxication.

Drug–Drug Interactions

General

Drug interactions with beta-adrenoceptor antagonists can be pharmacokinetic or pharmacodynamic (383–385).

Pharmacokinetic interactions

Absorption interactions

The absorption of some beta-adrenoceptor antagonists is altered by aluminium hydroxide, ampicillin, and food; these are interactions of doubtful clinical relevance.

Metabolism interactions

Beta-adrenoceptor antagonists that are cleared predominantly by the liver (for example metoprolol, oxprenolol, propranolol, and timolol) are more likely to participate in drug interactions involving changes in liver blood flow, hepatic drug metabolism, or both. Thus, enzyme-inducing drugs, such as phenobarbital and rifampicin, increase the clearance of drugs such as propranolol and metoprolol and reduce their systemic availability (386,387). Similarly, the histamine H_2 receptor antagonist cimetidine increases the systemic availability of labetalol, metoprolol, and propranolol by inhibiting hepatic oxidation (388–391). The disposition of drugs with high extraction ratios, such as propranolol and metoprolol, is also affected by changes in liver blood flow, and this may be the mechanism by which hydralazine reduces the first-pass clearance of oral propranolol and metoprolol (392).

Lipophilic beta-adrenoceptor antagonists are metabolized to varying degrees by oxidation by liver microsomal cytochrome P450 (for example propranolol by CYP1A2 and CYP2D6 and metoprolol by CYP2D6). These agents can therefore reduce the clearance and increase the steady-state plasma concentrations of other drugs that undergo similar metabolism, potentiating their effects. Drugs that are affected in this way include theophylline (393), thioridazine (394), chlorpromazine (395), warfarin (396), diazepam (397), isoniazid (398), and flecainide (399). These interactions are most likely to be of clinical significance when the affected drug has a low therapeutic ratio, for example theophylline or warfarin.

Beta-blockers can also affect the clearance of high clearance drugs by altering hepatic blood flow. This occurs when propranolol is co-administered with lidocaine (400), but it appears that this interaction is due more to inhibition of enzyme activity than to a reduction in hepatic blood flow (401). Atenolol inhibits the clearance of disopyramide, but the mechanism is unknown (402). Conversely, quinidine doubles propranolol plasma concentrations in extensive but not poor metabolizers (403) and oral contraceptives increase metoprolol plasma concentrations (404).

Pharmacodynamic interactions

The pharmacodynamic interactions of the beta-adrenoceptor antagonists can mostly be predicted from their pharmacology.

Blood pressure

The antihypertensive effect of beta-blockers can be impaired by the concurrent administration of some non-steroidal anti-inflammatory drugs (NSAIDs), possibly because of inhibition of the synthesis of renal vasodilator prostaglandins. This interaction is probably common to all beta-blockers, but may not occur with all NSAIDs; for example, sulindac appears to affect blood pressure less than indometacin (405–407).

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The hypertensive crisis that can follow the withdrawal of clonidine can be accentuated by beta-blockers. It has also been reported that when beta-blockers are used in conjunction with drugs that cause arterial vasoconstriction they can have an additional effect on peripheral perfusion, which can be hazardous. Thus, combining beta-blockers with ergot alkaloids, as has been recommended for migraine, can cause severe peripheral ischemia and even tissue necrosis (408).

The hypotensive effects of halothane and barbiturates can be exaggerated by beta-adrenoceptor antagonists. However, they are not contraindicated in anesthesia, provided the anesthetist is aware of what the patient is taking.

The combination of caffeine with beta-blockers causes a raised blood pressure (409).

Cardiac dysrhythmias

The bradycardia produced by digoxin can be enhanced by beta-adrenoceptor antagonists. Neostigmine enhances vagal activity and can aggravate bradycardia (410). An apparent interaction between sotalol and thiazide-induced hypokalemia, resulting in torsade de pointes (411), has prompted the withdrawal of the combination formulation Sotazide.

- The co-prescription of sotalol 80 mg bd with terfenadine 60 mg bd (both drugs that can prolong the QT interval) in a 71-year-old lady with hypertension, atrial fibrillation, and nasal congestion was complicated by recurrent torsade de pointes, causing dizzy spells and confusion after 8 days (412). She was treated with temporary pacing, but her symptoms resolved 72 hours after drug withdrawal.

Cardiac contractility

The negative inotropic effects of class I antidysrhythmic agents, such as disopyramide, procainamide, quinidine, and tocainide can be accentuated by beta-blockers; this is most pronounced in patients with pre-existing myocardial disease and can result in left ventricular failure or even asystole (413). Digoxin can obviate the negative inotropic effect of beta-blockers in patients with poor left ventricular function.

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Beta-lactam antibiotics

See also Individual agents

General Information

The beta-lactam antibiotics still comprise roughly half of the antibiotic market worldwide. The common structure that defines the whole family of beta-lactam antibiotics is the four-membered, highly reactive beta-lactam ring, which is essential for antimicrobial activity (1). The following simplifying classification is practical:

1. penicillins
2. cephalosporins
3. monobactams (containing no second ring system besides the beta-lactam ring)
4. carbapenems

In addition, beta-lactamase inhibitors also contain the beta-lactam structure.

The crucial event that initiates the antimicrobial effects of beta-lactam antibiotics is binding to and inhibition of bacterial enzymes located in the cell membrane, the so-called penicillin-binding proteins (2). This happens by

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covalent binding, through opening of the beta-lactam ring. Enzyme activities of penicillin-binding proteins are involved in the last steps of bacterial cell wall (peptidoglycan) synthesis, and their inhibition halts cell growth, causing cell death and lysis (3). Beta-lactamases are genetically and structurally closely related to penicillin-binding proteins.

Despite their chemical diversity, their adverse effects profiles share various common aspects. There are several reasons why beta-lactam antibiotics belonging to different classes can cause comparable reactions. Besides the beta-lactam ring, other structural similarities (for example side chains) or antimicrobial activity can be relevant. However, the incidence of a given reaction, and in particular instances also the severity, varies among beta-lactam classes.

Incidence and cause–effect relations

It is difficult to establish clearly the incidence and cause–effect relations of many reactions and hence to identify patients at risk. The following factors are important:

1. The range of recommended daily doses varies by more than an order of magnitude, according to clinical need. Hence, the incidence of some collateral and toxic reactions varies greatly among different populations.
2. Combinations of beta-lactam antibiotics with antimicrobial drugs from other molecular classes are often used, especially in severe infection.
3. The spectrum of potential beta-lactam-antibiotic-induced reactions is especially broad, and in most cases no test procedure is available to distinguish beta-lactam antibiotics from other causes of a reaction, in particular from the consequences of the treated infection.

Relation to dose

Many reactions to beta-lactam antibiotics are clearly not immune mediated. These include bleeding disorders, neurotoxicity, and most cases of diarrhea. In addition, many reactions, the pathogenesis of which is still being discussed, clearly depend on the daily and the cumulative dose of beta-lactam antibiotics and hence the duration of treatment. Although the rare, but well-understood, immune hemolysis after penicillin is seen mostly with high-dose and long-term treatment, dose dependency and time dependency point to direct toxicity rather than to immunological mechanisms. Indeed, direct toxic effects of beta-lactam antibiotics on eukaryotic cells and specific interactions with receptor proteins and enzymes have been shown (4) and may underlie particular reactions.

There are three lines of evidence that beta-lactam antibiotics cause a variety of reactions by toxic mechanisms:

1. Certain reactions are overwhelmingly reported to be dose-dependent and time-dependent.
2. Particular compounds cause adverse effects with unexpectedly high frequencies in certain circumstances (for example cystic fibrosis, bacterial endocarditis, and osteomyelitis) that require particularly high doses and prolonged treatment.
3. Beta-lactam antibiotics affect a variety of cultured eukaryotic cells.

For other reactions, the underlying mechanisms are less clear. The body of individual reports and some published series suggest that their incidence increases disproportionately with prolonged, high-dosage treatment, that is, with accumulation. This is particularly the case in the following reactions:

- severe neutropenia up to total agranulocytosis, as observed with virtually all beta-lactam antibiotics.
- acute interstitial nephritis, seen with methicillin but more rarely also with other beta-lactams, for example penicillin G.
- one type of hepatitis induced by isoxazolyl penicillins;
- varying combinations of symptoms positively referred to or not as "serum sickness-like syndromes."

There have been reports of high overall frequencies of adverse effects after the use of very high cumulative doses of beta-lactam antibiotics in healthy volunteers and in patients with, for example, chronic osteomyelitis, pulmonary exacerbations in cystic fibrosis, and infective endocarditis (5–9). In one series, 23% of patients treated with an average cumulative dose of carbenicillin of 925 g and 68% of those treated with ureidopenicillins 329 g developed adverse effects, including rash, fever, leukopenia, eosinophilia, thrombocytopenia, and hepatic damage, requiring change of therapy in 52% of cases in the latter group (10). Another study included a total of 292 treatment courses with five different beta-lactams for infective endocarditis (6). With a treatment duration of 9 days or less, drug was withdrawn in only 3% because of adverse reactions. However, treatment courses ranging from 10 days to 6 weeks were associated with adverse reactions in 33%, one-quarter of which consisted of neutropenia. Fourteen of 44 patients receiving piperacillin up to 900 mg/kg/day for acute pulmonary exacerbations in cystic fibrosis developed a syndrome that resembled serum sickness; the symptoms were mainly fever, malaise, anorexia, eosinophilia, and rashes (8). The reaction occurred after a minimum of 9 days and the frequency of symptoms was dose-related. All patients who developed the reaction were readmitted at 4–28 months after the initial episode and in every case re-exposure to piperacillin did not evoke the reaction.

The dose-relation of reactions to piperacillin in patients with cystic fibrosis has created a debate about its usefulness in this condition (11–15). However, comparable dose-related patterns and frequencies of adverse effects were found in other patients treated with piperacillin (15) and with other beta-lactam antibiotics (16), as well as in patients with both cystic fibrosis and other conditions (6,10,16). Three later studies showed that piperacillin more often caused fever, rash, and other reactions per treatment course in patients with cystic fibrosis compared with a large variety of other beta-lactam or non-beta-lactam antibiotics (17–19). Of particular interest is a study in which volunteers who took high doses of cefalotin or cefapirin for up to 4 weeks developed comparable syndromes, with an overall incidence of adverse effects of 100% (9). Despite these astonishingly high frequencies, these reactions were predominantly regarded as being allergic, although their pathogenesis was mostly unclear.

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Thus, a disproportionately high frequency of apparently unrelated adverse effects occurs in a relatively small group of patients, those needing high-dose prolonged treatment, who are at particular risk.

Mechanisms

Degradation products spontaneously formed in aqueous solutions, for example culture media, rather than the parent molecules themselves, may be responsible for the observed effects (4). Antiproliferative activities were generally more pronounced with cephalosporins than with penicillins, while monobactams appear to be practically free from such effects. Carbapenems have not been thoroughly studied in this respect, and some data on clavulanic acid and two other beta-lactamase inhibitors do not clearly reflect the same kind of toxicity as observed with penicillins and cephalosporins (20).

The selectivity of beta-lactam antibiotics for bacterial target proteins is not absolute. A specific interaction of modified cephalosporins with mammalian serine proteases has been shown (21) and the affinity of various penicillins for the benzodiazepine receptor may be part of the chain of events leading to neurotoxicity (22) However, most intriguing are observations made in proliferating cultured cells. Biological effects associated with proliferation were dose-dependently inhibited by a large array of beta-lactam antibiotics in a variety of cells from both man and animals (4,23). Resting cells, on the other hand, were not susceptible, even to very high concentrations.

The clinical impact of the inhibitory effects of beta-lactam antibiotics on proliferating eukaryotic cells is as yet unknown, and formal proof of a correlation with toxicity in patients is lacking. However, there are reasons for considering this type of toxicity as the cause of neutropenia and thrombocytopenia (SEDA-13, 230). In dogs, high-dose cefonicid and cefazedone for up to several months caused bone marrow damage, resembling the findings in clinical cases of neutropenia, which could explain peripheral cytopenias (24,25). In addition, mild thrombocytopenia and reticulocytopenia, which have been concomitantly found respectively in 30 and 17% of cases of neutropenia (26), are also paralleled by results in dogs. On the other hand, in the same dogs, IgG associated with erythrocytes, neutrophils, and platelets was found after high-dose treatment with cefazedone (27) Antigranulocyte IgG antibodies in beta-lactam-induced neutropenia have also been described in man (28–30). However, the relevance of these findings is unclear, since high cumulative doses of beta-lactams often induce beta-lactam-specific IgG antibodies in patients with and without adverse effects (6,31). Newer data from human and animal cell culture investigations suggest that ceftazidime-induced myelosuppression could be the consequence of multiple effects on various myeloid and non-myeloid cells in the bone marrow (32–34). They also give hints of a more rational basis for using G-CSF or other cytokines in beta-lactam-antibiotic-induced neutropenia (32,34). Hence, there is still controversy about whether beta-lactam antibiotics can cause neutropenia by both toxic and immunological mechanisms and how both mechanisms could act in concert with each other.

For evaluation of local tolerability, human peritoneal cells (35), human osteoblasts (36), and human as well as animal endothelial cells (37) have been studied in culture. The type of toxicity and rank efficacy among various compounds were congruent with the results from earlier studies on other cells (4,23). The clinical relevance of these data remains to be established.

The Jarisch–Herxheimer reaction

The Jarisch–Herxheimer reaction is a systemic reaction that occurs hours after initial treatment of spirochete infections, such as syphilis, leptospirosis, Lyme disease, and relapsing fever, and presents with fever, rigors, hypotension, and flushing (38,39). In patients with syphilis the reaction is more frequent in secondary syphilis and can cause additional manifestations, such as flare-up of cutaneous lesions, sudden aneurysmal dilatation of the aortic arch (40), and angina pectoris or acute coronary occlusion (SED-8, 559). It can easily be mistaken for a drug-induced hypersensitivity reaction. The underlying mechanism is initiated by antibiotic-induced release of spirochete-derived pyrogens. Transient rises in TNF, IL-6, and IL-8 have been detected (41). The role of TNF-alpha in the pathogenesis of the Jarisch–Herxheimer reaction is further underscored by the observation that in patients undergoing penicillin treatment for louse-borne relapsing fever, pretreatment with anti-TNF antibody Fab fragments partially protected against the reaction (42). The reaction lasts 12–24 hours and can be alleviated by aspirin. Alternatively, prednisone can be used and is recommended as adjunctive treatment of symptomatic cardiovascular syphilis or neurosyphilis.

Organs and Systems

Respiratory

Allergic bronchospasm can principally be a consequence of IgE antibody-mediated allergy to all beta-lactam antibiotics.

Nervous system

Since the first observation of convulsions after intraventricular administration of penicillin more than 50 years ago (43), neurotoxicity has been attributed to most beta-lactam antibiotics. Its manifestations are considered to be the consequence of GABAergic inhibition (44,45)and include clear epileptic manifestations as well as more atypical reactions, such as asterixis, drowsiness, and hallucinations. Epileptogenic activity of beta-lactam antibiotics has also been documented in animals and in brain slices in vitro (46). With penicillins and cephalosporins, integrity of the beta-lactam ring is a prerequisite, and epileptogenic activity is extinguished by beta-lactamase (47,48). However, this may not be true of the carbapenems, the neurotoxicity of which is differently related to their structure (49). However, clinical manifestations are always clearly dose-dependent, and brain tissue concentrations appear to be more relevant than CSF or blood concentrations (46). Accordingly, the major risk factor is impaired renal function, particularly when it is not recognized. Other risk factors are age (very young or very old),

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meningitis, intraventricular therapy, and a history of epilepsy (50).

The neurotoxic potential differs considerably among the various beta-lactam antibiotics, and experimental models have been developed for investigating this (51,52). Currently, imipenem + cilastatin appears to cause the highest frequency of neurotoxic effects (53,54) and the above-mentioned risk factors have been particularly confirmed with this compound (SEDA-18, 261) (55). Quinolone antibiotics, which themselves are proconvulsant, can potentiate excitation of the central nervous system by beta-lactam antibiotics, at least in animals (56,57).

Sensory systems

In vitro, methicillin and ceftazidime in high concentrations produced toxic effects on corneal and endothelial cells of the eye (58,59).

Metabolism

Pivaloyl-containing compounds (baccefuconam, cefetamet pivoxil, cefteram pivoxil, pivampicillin, pivmecillinam) can significantly increase urinary carnitine excretion (60,61). These compounds are esterified prodrugs, which become effective only after the release of pivalic acid, which in turn is esterified with carnitine. Carnitine loss induced by pivaloyl-containing beta-lactams was first described in children and can produce symptoms similar to other types of carnitine deficiency, for example secondary to organic acidurias (60). Carnitine is essential for the transport of fatty acids through the mitochondrial membrane for beta-oxidation. Consequences of its deficiency include skeletal damage, cardiomyopathy, hypoglycemia and reduced ketogenesis, encephalopathy, hepatomegaly, and Reye-like syndromes (62).

The administration of pivaloyl-conjugated beta-lactam antibiotics to healthy volunteers for 54 days reduced mean serum carnitine 10-fold and muscle carnitine, as measured per non-collagen protein, more than 2-fold (62). Long-term treatment of children for 12–37 months to prevent urinary tract infection resulted in serum carnitine concentrations of 0.9–3.6 μmol/l (reference range 23–60 μmol/l). In four cases, muscle carnitine was 0.6–1.4 μmol/g non-collagen protein (reference range 7.1–19) (63).

Although oral carnitine aided the elimination of the pivaloyl moiety, its simultaneous use did not fully compensate for the adverse metabolic effects of pivaloyl-containing beta-lactams (64,65). The consequences of pivaloyl-induced carnitine loss seem to be generally reversible. But as long as the risk of pivaloyl-induced urinary loss of carnitine and particular risk factors are not better defined, it is prudent to use pivaloyl-containing prodrugs only in short-term treatment.

Electrolyte balance

Since beta-lactam antibiotics contain sodium or potassium, they can cause or at least aggravate electrolyte disturbances when given in sufficiently high doses. The most frequent manifestations are hypernatremia and hypokalemia. The sodium content of injectable beta-lactam antibiotics per gram of active compound varies by up to a factor of three (66).

Hematologic

Neutropenia

While in large series of several thousands of patients, neutropenia has generally been reported as an adverse effect in under 0.1–1.0% (SEDA-13, 212), an overview in 1985 estimated that neutropenia (neutrophil count below 1.0×10^9/l) occurs in up to 15% of all patients treated with high-dose intravenous beta-lactam antibiotics for more than 10 days (26). In subsequent series of patients treated for several weeks with various beta-lactam antibiotics, up to 25% developed neutropenia (5,21,67–69).

In one series, 22 of 128 patients receiving cloxacillin for staphylococcal infections became neutropenic (67). Neutropenia appeared, on average, 23 days after the start of therapy. The same authors, in a somewhat bigger population, found neutropenia in 1.1% of patients who received cumulative doses of oxacillin below 150 g, but in 43% (22 of 51) who received more than 150 g (5). Similarly, in 132 patients, cefapirin in a cumulative dose of less than 90 g did not cause neutropenia, but did in 26% (five of 19) of those who used higher total doses (21).

In addition, for a given compound, higher daily doses increase the risk of neutropenia. In one study, seven of 14 patients became neutropenic with a mean dose of penicillin G of 17 g/day after 9–23 days (68), while in another study only 12 of 193 patients developed neutropenia with a mean dose of 11 g/day for an average duration of 20 days (69). A considerable extension of the aforementioned study (68) corroborated this: neutropenia occurred in 35% of those treated with a mean daily dose of 17 g of penicillin G for an average of 23 days, while it was found in only 8% of those who received 12 g for 22 days (6).

Epidemiological studies (7,70) as well as single cases of severe neutropenia observed with newer compounds have invariably confirmed the dose- and time-dependent pattern described above. For example, cefepime, a fourth-generation cephalosporin, possibly or probably caused neutropenia in only 0.2% of 3314 treatment courses, while 7.1% of those who received cefepime for several weeks developed neutropenia (71). Accordingly, high-dose cefepime (150 mg/kg/day) was given for 7–10 days to 43 children for bacterial meningitis without causing neutropenia (72), while there were two cases in adults after total doses of 112 g (over 28 days) and 120 g (30 days) respectively (73).

It is therefore not surprising that after consecutive or simultaneous treatment with more than one beta-lactam antibiotic, neutropenia is similarly observed, suggesting additive toxicity (6,74,75).

There is so far no clear evidence about the different risks of different compounds. The data best fit the assumption that the risk of neutropenia correlates with the cumulative dose, or probably more precisely with the area under the serum concentration versus time curve (AUC). Hence, renal insufficiency is a potential risk factor. In addition, beta-lactam-antibiotic-induced leukopenia has been associated with hepatic dysfunction (76).

Recovery in most cases is rapid and uneventful. In patients who were re-exposed to the same or other

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beta-lactam antibiotics, there was similar dependence of neutropenia on the duration of treatment and the cumulative dose (26). Whether the use of hemopoietic growth factors, and in particular G-CSF, is useful is unclear. There are case reports of positive clinical effects (77–79). However, the recovery time in these reports did not differ from that observed in a large population of untreated patients (26). Theoretically, early use of growth factors could even be counterproductive, since some toxic effects of beta-lactam antibiotics on bone marrow cells appear to be related to the S-phase of the cell cycle (4). On the other hand, G-CSF maintained the proliferative activity of bone marrow cells exposed to ceftazidime in vitro, if it was added at the beginning of the culture process (32).

Neutropenia is accompanied by fever, eosinophilia, and/or a rash in more than 80% of cases.

Hemolytic anemia

Immune hemolytic anemia was originally described with penicillin G, but subsequently also with other penicillins and cephalosporins. It is usually seen during treatment with very high doses after the so-called "drug absorption" mechanism. The beta-lactam antibiotic binds covalently to the erythrocyte surface, forming complete antigens, which can in turn bind drug-specific circulating IgG antibody. Typically, direct and indirect Coombs' tests are positive, but complement is not activated (80–82). Rarely, other immunological mechanisms have been observed, for example the so-called "innocent bystander" type of hemolysis (82), in which complement can be detected on the erythrocyte surface. Some cephalosporins, clavulanic acid, and imipenem + cilastatin can cause positive direct antiglobulin tests (83). The phenomenon is due to non-specific serum protein absorption on to the erythrocyte membrane and is not related to immune hemolytic processes. Detection of non-immunologically bound serum proteins is improved if the reagents used include additional anti-albumin activity (84). The phenomenon is a known source of difficulties in evaluating suspected immune hemolysis or routine cross-matching of blood products (85). The true frequency of the phenomenon is unclear, since it has not been positively sought.

Thrombocytosis

Thrombocytosis is frequently mentioned as an adverse effect of beta-lactam antibiotics. However, it has been suggested that this reflects healing from infection rather than toxicity (86).

Eosinophilia

Virtually all beta-lactam antibiotics can cause eosinophilia, either isolated or in the context of very different reactions.

Bleeding disorders

Treatment with beta-lactam antibiotics can result in impaired hemostasis and bleeding. The true incidence of bleeding is difficult to assess, since many non-antibiotic factors can be involved, such as malnutrition with vitamin K depletion (87), renal insufficiency (88), and serious infection (89). Cancer, the use of cytotoxic drugs, and surgery have made conclusive interpretation of coagulation disorders difficult (90). Between the different beta-lactam antibiotics, the reported incidence of clinical relevant bleeding varies widely, and was highest with moxalactam (22% of patients), now withdrawn (SED-12, 625). With other cephalosporins, bleeding was observed with frequencies ranging from 2.7% (cefazolin/cefalotin) to 8.2% (cefoxitime) (91). Two basic mechanisms have been proposed.

Altered coagulation

Both direct inhibition of the hepatic production of vitamin K-dependent clotting factors and alterations in the intestinal flora, with subsequent reduction of microbial supply of vitamin K, have been implicated (92,93). The relative role of either mechanism is difficult to assess, but experimental support for the flora theory is weak (94,95).

Several of the cephalosporins that contain either a non-substituted *N*-methylthiotetrazole (NMTT) side chain, such as cefamandole, cefamazole, cefmenoxime, cefmetazole, cefoperazone, cefotetan, and moxalactam, as well as a substituted NMTT side chain (ceforanide, ceforicid, or cefotiam), or the structurally similar *N*-methylthiotriazine ring in ceftriaxone and the 2-methyl-1,2,4-thiadiazole-5-thiol (MTD) ring of cefazolin interfere with vitamin K-dependent clotting factor synthesis in the liver (factors II, VII, IX, and X). The molecular mechanism involves dose-dependent inhibition of microsomal carboxylase function, as shown in animals (96), and inhibition of the epoxide reductase system in both animals and man (97–100). Cefoxitin, a non-NMTT compound, was implicated significantly more often than the NMTT-containing compounds cefamandole and cefoperazone (101).

The NMTT must leave the parent antibiotic to inhibit the carboxylation reaction (102). The NMTT molecule leaves the parent cephalosporin either during spontaneous hydrolysis in the blood or during nucleophilic cleavage of the beta-lactam ring by intestinal bacteria, and is reabsorbed from the gut into the portal circulation (103). Studies in healthy volunteers show compound-related differences in the ability of NMTT antibiotics to generate free NMTT, reflecting drug-specific differences in susceptibility to in vitro hydrolysis or differences in gut NMTT production, which may be a function of biliary excretion of the drug (104).

Altered platelet numbers and function

Platelet dysfunction occurs dose-dependently with carbenicillin, ticarcillin, and, infrequently, other broad-spectrum penicillins (105), but the NMTT cephalosporin moxalactam has also been associated with altered platelet function in both healthy subjects and in patients treated with standard regimens (106–110). In contrast, clinical studies including cefotaxime, ceftizoxime, cefoperazone, and ceftracone did not show platelet dysfunction attributable to these compounds (109–111). There is evidence that beta-lactam-antibiotic-induced platelet dysfunction is at least partially irreversible (112).

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From a practical point of view it can be concluded that:

1. the use of cephalosporins containing an NMTT side chain is associated with a risk of dose-dependent inhibition of vitamin K-dependent clotting factor synthesis.
2. platelet dysfunction occurs primarily with the broad-spectrum penicillins, but the NMTT cephalosporins, notably moxalactam, have also been implicated; monitoring of bleeding time should be considered in patients at risk (bleeding history, clinical bleeding, concomitant thrombocytopenia, or the use of other drugs known to interfere with platelet function.
3. the presence of non-antibiotic factors, such as therapy with vitamin K antagonists or NSAIDs, renal insufficiency, hepatic dysfunction, impaired gastrointestinal function, and malnutrition, can increase the risk of bleeding in cephalosporin-treated patients; close monitoring of homeostasis (prothrombin time, bleeding time), as well as prophylactic supplementation with vitamin K or, if necessary, therapeutic administration of fresh-frozen plasma and/or platelets is warranted according to the clinical context.

Gastrointestinal

Gastrointestinal upsets, nausea, and vomiting have been observed with virtually all beta-lactam antibiotics, both oral and parenteral. Even when comparing analogous applications and doses, no particular risk can be clearly ascribed to a given compound. Acute hemorrhagic colitis without pseudomembrane formation has been described after treatment with various penicillins and cephalosporins (SEDA-21, 261).

Antibiotic-induced diarrhea

There are three types of antibiotic-induced diarrhea:

- simple diarrhea due to altered bowel flora; this is quite common, for example it occurs in about 8% of patients who take ampicillin (113).
- diarrhea due to loss of bowel flora and overgrowth of *Clostridium difficile*, with toxin production; this is much less common.
- a rare form of diarrhea that is due to allergy.

Almost all antibacterial agents have been observed to cause diarrhea in a variable proportion of patients (114,115). The proportion depends not only on the antibiotic, but also on the clinical setting (in-patient/out-patient), age, race, and the definition of diarrhea. Severe colonic inflammation develops in a variable proportion of cases, and in some cases pseudomembranous colitis occurs (116–121). Since 1977, much evidence has accumulated that the most important causative agent in antibiotic-associated diarrhea is an anaerobic, Gram-positive, toxin-producing bacterium, *C. difficile* (122–124).

Pseudomembranous colitis was known before the introduction of antimicrobial agents and can still occur without previous antibiotic use, for example after antineoplastic chemotherapy (125) or even spontaneously. However, the number of cases has increased dramatically since antibiotics began to be used (126). Patients treated with lincomycin or clindamycin, cephalosporins, penicillinase-resistant penicillins, or combinations of several antibiotics are at especially high risk (127–130). A low risk is usually associated with sulfonamides, co-trimoxazole, chloramphenicol, and tetracyclines (116). Although few data have yet been published on this subject for the quinolones, they seldom seem to cause diarrhea and pseudomembranous colitis (131).

Presentation

In pseudomembranous colitis the stools are generally watery, with occult blood loss, which is seldom gross. Common findings include abdominal pain, cramps, fever, and leukocytosis. Especially severe forms can run such a rapid course that diarrhea does not occur; they present with symptoms of severe toxicity and shock (132). As a rare complication, marked dilatation of the colon and paralytic ileus can develop, that is, toxic megacolon.

Pseudomembranes are described as initially punctuate creamy to yellow plaques, 0.2–2.0 cm in size, which may be confluent, with "skip areas" of edematous mucosa. Histologically they are composed of fibrin, mucous, necrotic epithelial cells, and leukocytes.

An acute colitis, different from pseudomembranous colitis, was observed in five patients taking penicillin and penicillin derivatives (133). There was considerable rectal bleeding. The radiographic findings were those of ischemic colitis (spasm, transverse ridging, "thumbprinting," and punctuate ulceration). On sigmoidoscopy and biopsy, the mucosa was normal, except for an inflammatory cell infiltration in one case. Conservative treatment resulted in rapid remission.

Occurrence and frequency

Clostridium difficile has been isolated in 11–33% of patients with antibiotic-associated diarrhea, 60–75% of patients with antibiotic-associated colitis, and 96–100% of patients with pseudomembranous colitis (117,134,135). However, about 2% of the adult population are asymptomatic carriers (127). Primary symptomless colonization with *C. difficile* reduces the risk of antibiotic-associated diarrhea (136). Infants up to 2 years seem to be refractory to pseudomembranous colitis, although a high percentage may be carriers of *C. difficile* (135,137). The reasons for this are unknown. It has been speculated that infants lack receptors for the toxin.

There have been several reports of frequent diarrhea in patients treated with combinations of ampicillin or amoxicillin with beta-lactamase inhibitors, such as sulbactam or clavulanic acid (138–141). A double-blind crossover study in healthy volunteers showed disturbances of small bowel motility after oral co-amoxiclav (142).

The appearance of pseudomembranous colitis in clusters of patients (143–146) may explain the wide variation in occurrence, and suggests that the disease may result from cross-contamination among patients rendered susceptible by antibiotic treatment. This is especially true for epidemic outbreaks in hospitals, where the disease may be considered a nosocomial infection favored by serious illness, frequent and prolonged use of broad-spectrum antibiotics (especially cephalosporins), and poor compliance with the rules of hospital hygiene (147). In such an epidemic, a variable proportion of

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patients will harbor the organism as asymptomatic carriers. An additional possible explanation for the large differences in reported frequencies may be the use of different methods of detection and differences in the definition of the disease. If colonoscopy was routinely performed in all patients with diarrhea taking clindamycin, pseudomembranous colitis was found in as many as 10% (148).

Although the first antibiotics reported to cause pseudomembranous colitis were lincomycin and clindamycin, the disease was later described with all other antimicrobial drugs, even topically applied (149). Vancomycin (150) and metronidazole (151), which may be used as specific treatments, have also been implicated.

Susceptibility factors

Besides the type of antibiotic therapy, other factors such as the age of the patient, the severity of the underlying disease, colonic stasis, cytostatic therapy, surgical interventions, and gastrointestinal manipulations are predisposing factors for antibiotic-associated colitis (152–156).

It is still not established if there is a correlation between toxin production or genotype of the *C. difficile* and the clinical manifestations of the infection (157,158). Although hospital-acquired antibiotic-associated colitis is by far the major problem, community-acquired diarrhea associated with *C. difficile* has also been described (159).

Mechanism

Clostridium difficile produces two well-characterized toxins (124,160)—toxin A, an enterotoxin, and toxin B, an extremely potent cytotoxin—which are thought to be responsible for the disease. The toxigenicity of toxins A and B varies between different strains of *C. difficile* and seems to correlate with symptomatic disease (161). Pseudomembranes were found in a higher percentage of patients with stools positive for cytotoxin than in patients whose stools were positive for *C. difficile*, but toxin-negative (153) Although there is also a high association with *C. difficile* (about 20% are toxin-positive) in antibiotic-associated diarrhea without pseudomembranes, it is possible that this microorganism plays no pathogenic role in some of these usually milder forms of the disease. In these cases the diarrhea may be due to impaired metabolism of carbohydrates, altered fatty acid profiles, or the composition and deconjugation of bile acids by quantitatively and qualitatively altered fecal flora (114,115,135).

Diagnosis

The diagnosis of antibiotic-related colitis should be considered in any patient with severe diarrhea during or within 4–6 weeks after antibiotic therapy. The single best diagnostic procedure is sigmoidoscopy, although in a number of cases the typical pseudomembranous lesions may be seen only above the rectosigmoid area (162). Radiographic investigations (barium enema and air contrast) may show typical findings, but are dangerous in advanced cases and should be avoided. Computerized tomography showed typical but not pathognomonic patterns in two patients (163).

Clostridium difficile can be cultured from the stool, and toxins A and B can be assessed by different techniques (116). The most accurate method is still a cytotoxin tissue culture assay. This detects the cytopathic effect of cytotoxin B, which can be neutralized by *Clostridium sordellii* antitoxin, but it takes 24–48 hours to show a result. Alternative tests that produce faster results have been developed. A latex agglutination test lacks sensitivity and specificity, and does not distinguish toxigenic from non-toxigenic strains. An enzyme immunoassay for toxin A may be an acceptable alternative to the cell cytotoxin assay and the results are rapidly available. A dot immunobinding assay has not yet been extensively studied (164).

Management

Therapy consists of withdrawal of the antibiotic when diarrhea occurs and replacement of fluid and electrolyte losses. In less severe cases of antibiotic-associated diarrhea, no further treatment is needed. However, in patients with pseudomembranous colitis, a more intensive approach is usually required. When a toxic syndrome develops, fluid losses within the bowel can be very large. In these cases, a central venous line offers the chance to measure central venous pressure. Usually there is also loss of serum proteins and in some cases blood, which need appropriate replacement. In the rare cases with fulminant colitis and toxic megacolon, surgical intervention may be necessary (165,166).

In pseudomembranous colitis (typical endoscopic findings, positive test for *C. difficile* or its toxin), the preferred treatment is oral metronidazole, 250 mg qds or 500 mg tds (120,167). Metronidazole is as effective as vancomycin 125–250 mg qds, which is significantly more expensive (168). Oral bacitracin 25 000 U qds (169) and oral teicoplanin (170) are acceptable alternatives.

Relapses are similarly frequent after treatment with metronidazole and vancomycin (116). In 189 adult patients, a first relapse occurred in up to 24% and a second relapse in 46% (169). Relapse may be due to sporulation of *C. difficile* and not to the development of resistance. Relapses usually respond to further courses of the initial treatment. Some alternative treatments have been proposed for repeatedly relapsing cases, including the combination of vancomycin with rifampicin for 10 days (171).

The role of anion exchange resins (colestyramine and colestipol), which bind *C. difficile* toxin, is still controversial (172). If ion exchange resins are given at all, they should not be given together with vancomycin, because they also bind the antibiotic (173). Attempts to restore the intestinal flora with *Lactobacillus GG* (174), or with fecal enemas (175) from healthy volunteers have shown some favorable results in less severe cases. However, esthetic and infectious concerns may be an obstacle. It also has been suggested that treatment with *Saccharomyces boulardii* may help prevent the development of antibiotic-associated diarrhea (176). Its value in the prevention and treatment of relapses has still to be demonstrated. Antimotility agents have been associated with an increased incidence of antibiotic-related diarrhea and can worsen symptoms when the disease is already established (177). They should therefore be avoided.

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There is little evidence that re-exposure to the same antibiotic that caused pseudomembranous colitis confers a further risk for relapse. Still, it would be wise to avoid the antibiotics that are most often related to pseudomembranous colitis in a patient who has had this complication.

Liver

Increases in serum transaminases and alkaline phosphatase, largely without additional symptoms, have been reported with the majority of beta-lactam antibiotics. With different compounds the estimated frequencies vary by up to a factor of 10. However, the frequency also depends on patient-related factors; in one study only a minority of transaminase increases could not be explained by factors other than antibiotic treatment (86).

More severe liver disease, presenting as hepatitis and/or intrahepatic cholestasis, has been seen with beta-lactam antibiotics of various classes, the isoxazolyl penicillins being most frequently involved. Co-amoxiclav has repeatedly been associated with cholestatic hepatitis.

Hepatitis is accompanied by fever, eosinophilia, and/or a rash in more than 80% of cases. This hints at the possibility of overlapping pathogenetic steps and sheds some doubt on the reliability of these accompanying symptoms as indicators of immune-mediated reactions, for example serum sickness-like syndromes.

One type of hepatitis is mainly associated with oxacillin (178,179). Eight of 54 patients developed this reaction after a mean cumulative dose of oxacillin 157 g (180).

Prolonged duration of treatment and increasing age were risk factors for flucloxacillin-induced jaundice (181), and cholestatic liver injury has been described most often with flucloxacillin (182,183) and other isoxazolylpenicillins (184). Whether cholestatic hepatitis after the combination of amoxicillin with clavulanic acid (co-amoxiclav) is related to one of these categories is not yet clear.

Urinary tract

Methicillin-induced acute interstitial nephritis follows a similar pattern of dose-dependence and time-dependence to that of neutropenia (185,186). This reaction occurred in 16% of all children treated with high-dose methicillin (187). Nephritis occurred after a mean of 17 days and a mean cumulative dose of 120 g.

With other beta-lactams, mainly penicillin G, acute interstitial nephritis is rare, but it can follow the same pattern (188).

Nephritis is accompanied by fever, eosinophilia, and/or a rash in more than 80% of cases. This hints at the possibility of overlapping pathogenetic steps and sheds some doubt on the reliability of these accompanying symptoms as indicators of immune-mediated reactions, for example serum sickness-like syndromes.

Acute renal insufficiency, with or without skin rash and eosinophilia, has been reported with various beta-lactam antibiotics, most often with methicillin. Hence, the designation "methicillin-nephritis" is still sometimes used. The pathogenesis is largely unknown and is different from the nephrotoxicity of older cephalosporins (cefaloridine and cefalotin).

Skin

Rashes are among the most common adverse reactions to drugs in general and occur in 2–3% of hospitalized patients (189). Most distinct mucocutaneous reactions that can be induced by drugs have been associated with the use of individual beta-lactam antibiotics. These reactions include urticaria, angioedema, maculopapular rash, fixed drug eruption, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, allergic vasculitis, serum sickness-like syndrome, eczematous lesions, pruritus, and stomatitis (190–193). The maculopapular rash, starting on the trunk or areas of pressure or trauma, is more frequent than all other skin manifestations together (189,194). Involvement of mucous membranes, palms, and soles is variable; the eruption can be associated with moderate to severe pruritus and fever. In addition, an indistinguishable rash often accompanies various reactions in other organs.

Pustular drug eruptions due to penicillin (195), amoxicillin (196), ampicillin (197), bacampicillin (198), cefazolin (199,200), cefradine (201), cefalexin (202), cefaclor (203), or imipenem + cilastin (204) seem to form a distinct clinical entity that has to be differentiated from pustular psoriasis, which can be drug-induced as well (204). A history of drug exposure, rapid disappearance of the eruption after the drug is stopped, and eosinophils in the inflammatory infiltrate argue in favor of pustular drug eruptions.

In patients with mononucleosis, aminopenicillins, and, less so, cephalosporins evoke rashes in a much higher percentage than usual (205). The incidence of rashes in infectious mononucleosis without antibiotics is 3–15%, compared with 40–100% with ampicillin. The underlying mechanism is speculative.

Immunologic

The adverse effects of early penicillin use consisted almost exclusively of anaphylaxis. This stimulated extensive research into the immune responses associated with penicillin and made penicillin the most prominent model for immune reactions to drugs.

The pathogenesis of many presumably immunologically mediated reactions to beta-lactam antibiotics is still unknown. Reliable and standardized tests to predict hypersensitivity only exist for a minority of allergic reactions, that is, IgE-mediated reactions. The matter is further complicated by the fact that beta-lactams can readily induce immune responses that by themselves do not necessarily result in disease. This is the case, for example, when antierythrocyte antibodies directed against beta-lactam bound to the erythrocyte surface are formed. This biological property (immunogenicity) has to be distinguished from allergenicity, that is, immune responses causing disease.

Cross-reactivity, that is, hypersensitivity reactions initially induced by one compound but triggered by another, is an important and as yet unresolved problem, complicated by the fact that beta-lactams undergo structural

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modifications after administration, and that different parts of the molecule (such as the nucleus or side chains) can be involved. Data from cross-exposed patients (skin tests or drug challenge) suggest a high degree of cross-reactivity between compounds belonging to the same class and between the penicillins and carbapenems, but a low degree of cross-reactivity between penicillins and cephalosporins and between monobactams and the other beta-lactams.

Mechanisms

Drug allergy or hypersensitivity represents an acquired capacity of the organism to mount an immunologically mediated reaction to a compound. This ultimately involves covalent or exceptionally non-covalent binding to and modification of host molecules (presumably proteins) by the drug, to which the host becomes sensitized (induction phase). Re-exposure to the sensitizing drug can trigger a series of immunological effector mechanisms (effector phase). These can be defined as pathways of inflammation or tissue injury, but they also represent mechanisms of immune protection from infectious agents.

Traditionally, the classification scheme defined by Gell and Coombs (206) distinguishes four types of reactions:

- type I reactions, which are IgE-mediated immediate hypersensitivity reactions.
- type II reactions, which are mediated by cytotoxic IgM and/or IgG.
- type III reactions, which are mediated by immune complexes.
- type IV reactions, which are cell-mediated hypersensitivity responses.

However, this classification fails to account for the complex and sequential involvement of several cell types and mediators in the immune response, as recognized today (207).

IgE-antibody-mediated adverse reactions

IgE-antibody-mediated hypersensitivity can serve as a paradigm to demonstrate some important features of beta-lactam hypersensitivity. Beta-lactams are small molecules that have to combine with a host macromolecule to be recognized by the immune system. In the case of penicillin, this reaction involves coupling of reactive degradation products to a protein-containing carrier (208). There are several degradation pathways, which result in the formation of reactive compounds, most importantly penicilloyl (209), also called the major determinant. Other less abundant degradation products include penilloate, benzylpenicilloate, and benzylpenilloate, the so-called minor determinants.

The complex contains haptens, often multiple, coupled to a protein-containing carrier molecule, and can induce T cell-dependent B cell activation, leading to the formation of antihapten antibodies. The mechanisms that govern the selection of the different immunoglobulin isotypes are reviewed elsewhere (207).

The time required for sensitization is called "latency" and is variable, depending on factors such as route of exposure, hapten dose, and chemical reactivity of the drug, as well as on genetic and acquired host factors. The period between the last exposure to the drug and the first appearance of symptoms has been termed the "reaction time." It is part of the clinical description of an adverse event and may help to attribute it to a specific drug (SED-12, 594).

Once sensitivity has been established, that is, once hapten-specific IgE-producing B cells have been formed, exposure to even small amounts of hapten can induce a cascade of events that lead to immediate reactions, such as anaphylaxis (210). Briefly, preformed IgE antibodies to drug determinants recognize the hapten-carrier complex and fix to the surface of mast cells or basophils, triggering the release of a series of mediators, such as histamine, neutral proteases, biologically active arachidonic acid products, and cytokines. This ultimately leads to a clinical spectrum that ranges from a mild local reaction to anaphylactic shock.

Non-IgE-antibody-mediated immunological reactions

Modification of erythrocyte surface components due to binding of beta-lactams or their metabolic products is thought to be the cause of the formation of antierythrocyte antibodies and the development of a positive Coombs' test implicated in the development of immune hemolytic anemia (211). About 3% of patients receiving large doses of intravenous penicillin (10–20 million units/day) will develop a positive direct Coombs' test (212). However, only a small fraction of Coombs' positive patients will develop frank hemolytic anemia (213). Antibody-coated erythrocytes are probably eliminated by the reticuloendothelial system (extravascular hemolysis) (214), or less often by complement-mediated intravascular erythrocyte destruction (215). Another mechanism implicates circulating immune complexes (anti-beta-lactam antibody/beta-lactam complexes), resulting in erythrocyte elimination by an "innocent bystander" mechanism (82). Similar mechanisms have been implicated in thrombocytopenia associated with beta-lactam antibiotics (216,217).

Contact dermatitis was often observed when penicillin was used in topical formulations and still continues to be described in cases of occupational exposure to beta-lactams (218,219). The underlying mechanism is thought to involve chemical modification of antigen-presenting cells in the epidermis, leading to sensitization of drug-specific T cells (220,221).

The underlying mechanism of a series of clinical entities associated with beta-lactams, such as maculopapular rash, drug fever, eosinophilia, serum sickness-like disease, vesicular and bullous skin reactions, erythema nodosum, and acute interstitial nephritis, is suspected to be immunological but is still largely unknown.

Reactions specific to side chains

Side chain–specific allergic reactions to beta-lactams are a steadily increasing problem (SEDA-21, 260) (222–224). Apart from epitopes generated by the beta-lactam nucleus, side chains attached to it can serve as additional epitopes recognized by the host immune response. Side chain–specific antibodies can be detected in patients who are allergic to beta-lactam antibiotics, even in the absence of reactivity to the mother compound. The clinical

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importance of this is debated. Serious anaphylactic reactions to amoxicillin occurred in three patients who tolerated benzylpenicillin (225). The phenomenon is mostly relevant for patients given semisynthetic penicillins, cephalosporins, carbapenems, and monobactams: compounds derived from each of these classes of drugs share certain side chains that may be cross-recognized by preformed antibody. Diagnosis of side chain–specific allergy requires a panel of diagnostic tools available only at selected research centers.

Pseudoallergy

The term "hypersensitivity" includes both immunoallergic and pseudoallergic reactions. Immunoallergic reactions occur when highly specific mechanisms involving immunological memory and recognition are involved. Pseudoallergic reactions are reactions that mimic immunoallergic reactions, but in which a specific immune-mediated mechanism is not involved. The so-called ampicillin rash is an example of a pseudoallergic reaction. Some major mediators of pseudoallergic reactions have been reviewed (226). The roles of newer putative mechanisms, involving cytokines, kinins, and other host-derived substances, remain to be ascertained. Most important is the fact that currently there are no standardized and validated animal models for predicting pseudoallergic reactions (227).

Animal models

Guinea pigs have been used for years in studies of systemic anaphylaxis. However, variations in predictability and sensitivity limit their value (228,229). Passive cutaneous anaphylaxis is another guinea pig model, but it is no more sensitive than systemic anaphylaxis (228). Respiratory sensitization, resulting in IgE-mediated immediate hypersensitivity has been investigated in mice and guinea pigs (230,231). Most often highly reactive chemicals have been used, and the models are of limited value in testing antimicrobial drugs.

Contact sensitizers have been studied in guinea pigs and mice, and it has been stated that "these models can reasonably identify the majority of human contact sensitizers" (227).

The best approach to induce a specific immune response against substances of low molecular weights is to use hapten-carrier conjugates. This method is of value in assessing the potential for cross-reactivity between closely related compounds, such as beta-lactam antibiotics (232).

It is obvious that the development of new animal models, for example transgenic and knock-out mice, should create new possibilities for predicting the sensitizing potential of new antimicrobials. The sad fact that hypersensitivity reactions are among the most commonly occurring adverse effects when antibiotics are used underlines the urgent need for research efforts in academia and industry (227).

Incidence

The true incidence of immunologically mediated reactions to beta-lactam antibiotics is hard to evaluate. This is mainly because of problems associated with the case definition of hypersensitivity reactions. The pathogenetic mechanism for a significant number of reactions presumed to be immunological in nature has not yet been conclusively determined. Furthermore, studies that address the incidences of adverse reactions face the problem of dealing with heterogeneous patient populations, treated with different types of beta-lactams, and administered by diverse routes in various dosages. The issue can be illustrated by reviewing data derived from four pharmacoepidemiological studies.

1. The International Rheumatic Fever Study, a prospective multicenter study that recorded allergic reactions, defined as hypotension, dyspnea, pruritus, urticaria, angioedema, arthralgia, and maculopapular rash in 1790 patients treated with monthly intramuscular benzathine penicillin for prophylaxis of rheumatic fever (32 430 injections during 2736 patient years). There was a 3.2% case incidence of allergic reactions and a 0.2% case incidence of anaphylaxis (12/100 000 injections), including one death (0.05%, equivalent to 3.1/100 000 injections) (233).
2. A large national study by venereal disease clinics in the USA, including four cooperative surveys conducted at 5-year intervals (1954, 1959, 1964, and 1969). The study included data from 94 655 patients unselected with regard to a history of penicillin allergy. The frequency of anaphylaxis was 0.055%, including one death (234).
3. A retrospective analysis of allergic reactions (drug-induced fever and rash) in 90 adults with cystic fibrosis, of whom 26 developed probable allergic reactions to parenteral beta-lactams. There was drug-induced fever in 54 and skin reactions in 28 of 897 treatment courses (6 and 3.1% respectively). There was one case of non-fatal anaphylaxis. The numbers of allergic reactions per number of patients receiving specific antibiotics were: carbenicillin 4/56, mezlocillin 7/42, piperacillin 11/31, ticarcillin 1/20, cefazolin 0/24, ceftazidime 1/35, imipenem + cilastatin 4/16, and nafcillin 3/36 (17).
4. The Boston Collaborative Drug Surveillance Program. In this classic study in in-patients during 1966–82, beta-lactams headed the list of drugs causing skin reactions, presumably allergic. The overall reaction rate (the number of drug-related skin reactions per 1000 treated patients) was 51 for amoxicillin, 42 for ampicillin, 29 for semisynthetic penicillins, 16 for penicillin G, and 13 for cephalosporins (18,193).

These four sets of data illustrate a spectrum of diverse settings of beta-lactam administration: single-dose parenteral use (in venereal disease clinics), intermittent parenteral use (in rheumatic fever), and continuous high-dose parenteral use (in cystic fibrosis). Factors other than route of administration and dosing, such as drug history, underlying disease, co-administered drugs, and the risk profile of a particular compound, will be important in assessing the risk of giving a beta-lactam to a particular patient, as discussed in more detail below.

Table 1 contains a list of presumably immunologically mediated effects of beta-lactams, according to their estimated frequencies. The mechanisms of most of these reactions are not completely understood, which implies that some of the entities listed may be due to non-immunological mechanisms. The frequencies of the

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various adverse effects vary among different beta-lactams and depend on additional factors, discussed below. A compilation of reported frequencies of occurrence related to different compounds has been published and was used and extended to prepare Table 1 (194).

Presentation

The requirement for sensitization explains why a drug may be administered for a variable length of time without adverse effects. Once the organism is sensitized, the manifestation of hypersensitivity will depend on the route and dose of the allergen as well as the type of effector mechanism involved, preformed IgE being the most rapid, others evolving more slowly, typically over days. Generally much less drug is required to trigger a hypersensitivity reaction in a sensitized subject than for induction. Anaphylactic reactions have been described after ingestion of meat from penicillin-fed animals or after sexual intercourse in a penicillin-sensitive patient (269,270).

The time for sensitization to occur is often difficult to establish in a patient who develops symptoms during continuous therapy. A classification scheme that distinguishes between immediate, accelerated, and late reactions is of limited clinical use, since it will only allow distinction between IgE-mediated reactions (that is, rapid reactions) and non-IgE-mediated reactions (that is, more slowly evolving reactions) in the setting of re-exposure of a sensitized subject (80).

In contrast to hypersensitivity, other adverse reactions do not require sensitization and require similar doses of drug for recurrence. A special case is a syndrome (Hoigné's syndrome) that resembles an immediate allergic reaction combined with hallucinations, aggressive behavior, anxiety, and auditory and visual disturbances, which has been described after intramuscular procaine penicillin and benzathine penicillin. It is probably due to accidental intravascular injection and results from microembolism of the penicillin depot formulation (271–275).

Susceptibility factors

Several factors that influence hypersensitivity have been recognized and reviewed (276).

Patient-related factors

Patient-related factors include an increased incidence of allergic reactions to beta-lactams in patients with systemic lupus erythematosus (277) but not with atopic diseases (278). Genetic factors that influence drug metabolism and excretion, as well as the underlying disease of the patient and host immune reactivity, are likely to modulate the risk and severity of hypersensitivity reactions.

Table 1 Presumably immunologically mediated adverse reactions to beta-lactams

Adverse reaction	References
Expected in one or more of 100 treatment courses	
Maculopapular rash[a]	(193,194,235)
Expected once in 100–1000 treatment courses	
Urticaria, angioedema	(80,194,235,236)
Drug fever[b]	(17,237)
Eosinophilia[c]	(238–240)
Expected once in 1000–10 000 treatment courses	
Anaphylactic shock	(210,241,242)
Bronchospasm and acute severe dyspnea	(243,244)
Thrombocytopenia	(91,245)
Serum sickness-like disease	(246–249)
Vasculitis	
Expected less than once in 10 000 treatment courses	
Hemolytic anemia	(81,82,250–253)
Vesicular and bullous skin reactions (including Stevens–Johnson syndrome and toxic epidermal necrolysis)	(254,260)
Erythema multiforme[d]	(257,261)
Erythema nodosum[e]	(257,261)
Interstitial nephritis[f]	(262)
Observed after occupational exposure	
Contact sensitivity	(219,263)
Anaphylaxis	(210)
Asthma, pneumonitis	(264–268)

[a] Occurs with all beta-lactams; more often with aminopenicillins, penicillinase-resistant penicillins, and anti-*Pseudomonas* penicillins
[b] Occurs with all beta-lactams; probably more often with piperacillin + tazobactam and aztreonam
[c] Occurs with all beta-lactams; probably more often with meticillin, nafcillin, oxacillin, second- and third-generation cephalosporins, aztreonam, and imipenem
[d] Occurs with all beta-lactams; probably more often with penicillins G and V, antipseudomonal penicillins, cefaclor, cefadroxil, cefalexin, loracarbef, aztreonam, and imipenem
[e] Occurs probably with all beta-lactams, but more often with penicillins G and V, cefuroxime, cefoperazone, cefaclor, and imipenem
[f] Occurs probably with all beta-lactams; well documented for methicillin

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A history of a prior penicillin reaction increases the risk of a subsequent exposure. A classic study showed a frequency of allergic reactions to penicillin of 0.62% (155 of 24 906 treatment courses) in patients without a history of penicillin allergy compared with 13% (10 of 78 treatment courses) in patients with a history of penicillin allergy (234). Reaction rates are higher in patients with a history that suggests IgE-mediated reactions (279).

Patients with chronic lymphatic leukemia or with concurrent infection with Epstein–Barr virus or HIV have an increased frequency of ampicillin- and amoxicillin-associated rashes (280).

Drug-related factors

Drug dosage, mode of administration, and duration of treatment probably influence the frequency of allergic reactions. Topical administration has been associated with a high incidence of sensitization, in contrast to a low incidence with the oral route. For IgE-mediated reactions, a frequent and intermittent course of treatment is more likely to cause allergy than a prolonged course without a drug-free interval (208). High doses of parenteral beta-lactams are usually required for the induction of penicillin-induced hemolytic anemia (212). Similarly, it is likely that the high dosages of beta-lactams used in patients with cystic fibrosis result in a high incidence of drug fever (17).

Co-administration of beta-blockers has been associated with an increased risk of severe allergic drug reactions and reduces the effect of adrenaline in the immediate treatment of anaphylactic shock. The mechanism involves changes in the regulation of anaphylactic mediators (281).

Evidence that allopurinol potentiates skin reactions to ampicillin is controversial (192,282).

Long-Term Effects

Drug resistance

The introduction of penicillin G more than 50 years ago was one of the milestones in the treatment of infectious diseases, leading to a drastic reduction in mortality from severe infections (283–285). Two years later the emergence of the first penicillin-resistant *Staphylococcus aureus* rapidly cooled clinicians' enthusiasm. Since then microorganisms have developed various mechanisms to survive antibiotic pressure, including the following:

1. Modification of the targets of beta-lactam antibiotics, that is, the penicillin-binding proteins (286,287), resulting in a reduced affinity of the antibiotic.
2. The synthesis of new penicillin-binding proteins with very low affinity for the antibiotic, providing a high degree of resistance.
3. The production and secretion into the periplasmic space of beta-lactamases, that is, enzymes sharing structural analogies with the penicillin-binding proteins without fulfilling any function in the cell wall synthesis but hydrolysing and inactivating the beta-lactam ring. The genes encoding for these beta-lactamases are usually located on a plasmid but can also be anchored in the bacterial genome (288,289).
4. Structural modification of porines, proteins that form channels in the outer membrane of Gram-negative bacteria, preventing the antibiotics from reaching the penicillin-binding proteins by impairing their penetration through channels of the outer membrane (290,291).

All of these mechanisms are mainly based on interbacterial exchange of DNA or on point mutations (292), the predominant mechanisms for genetic exchange being transformation, transduction, and conjugation (293). Transformation is the simplest way to transfer DNA to another bacterium, provided that this is ready to accept foreign DNA (= competent bacteria). This mechanism of genetic transfer is mostly used by several human pathogens: *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, and *Bacillus subtilis*. The transduction needs a bacteriophage (a virus) as a vector to inject DNA into a bacterium. This elaborate system is limited by the restricted specificity of the vectors for few microorganisms. The most sophisticated system is conjugation. This mechanism was first observed in *E. coli* in 1952 by Hayes, who described the first transfer of genetic material (F-Factor, or fertility factor) by conjugation (294). Microorganisms use conjugation to transfer several types of genetic material, either extrachromosomal (that is, plasmids) or intrachromosomal (that is, transposons).

In summary, microorganisms can exchange and acquire genetic material in order to adapt to a changing environment, the antibiotic pressure. Furthermore, DNA exchange between prokaryotes and eukaryotic cells (yeasts) and some plants has been observed (295). A review has addressed in detail the problem of emergence and spread of resistance among clinical isolates (296). Here we shall only briefly discuss as examples the development of resistance by two major pathogens, *S. pneumoniae* and *S. aureus*.

One of the most striking features in microbiology is the rapid emergence and worldwide spread of penicillin-resistant *S. pneumoniae* (pneumococci), mainly due to the uncontrolled use of penicillin in certain countries (297). The first cases of penicillin-resistant pneumococci were reported in the 1960s in New Guinea and Australia. Penicillin-resistant pneumococci have now been registered in all continents. The highest rate was reported in 1989 in Hungary, amounting to 57% of all clinical isolates (298). Until now, pneumococci have not acquired the genes encoding for beta-lactamases. Accordingly, the underlying mechanism of penicillin resistance is structural modification of penicillin-binding proteins, leading to reduced affinity to the penicillin molecule (see above). These modifications of the penicillin-binding protein usually require several genetic steps. Moreover, horizontal transfer of pieces of penicillin-binding protein genes has been described between *Streptococcus mitis* and *Streptococcus pneumoniae* (299). Such modifications of penicillin-binding proteins lead to reduced affinity of these enzymes for their natural substrates (disaccharide-pentapeptides) (300) and eventually to the synthesis of a structurally different cell wall harboring more branched peptides. This is the biological price that pneumococci pay to survive antibiotic pressure (301). Usually in an

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epidemic area a few clones of penicillin-resistant pneumococci are responsible for the majority of the registered cases (302). Furthermore, DNA polymorphism analysis has shown that isolates have been imported from one continent to another, causing new epidemics (303–306).

Another major pathogen *S. aureus* has developed two different mechanisms of resistance:

- synthesis of beta-lactamase (nowadays more than 80% of *S. aureus* secrete beta-lactamase).
- the emergence of so-called methicillin-resistant *S. aureus* (MRSA), which can grow even in the presence of high concentrations of methicillin (up to 800 μg/ml).

The unique feature of MRSA is based on the acquisition of a low-affinity penicillin-binding protein for beta-lactam antibiotic molecules (the penicillin-binding protein 2A), which allows the bacteria to carry on synthesis of its cell wall, whereas the other penicillin-binding proteins are already inactivated by the high concentration of methicillin or other beta-lactamase-resistant beta-lactam antibiotics.

The origin of the penicillin-binding protein 2A is a matter of debate. Until now the only antibiotics that inhibit MRSA are the glycopeptides, such as vancomycin. A nightmare scenario would be the transfer of vancomycin resistance from enterococci to MRSA, which would cause a major epidemiological and therapeutic problem in the treatment of staphylococcal infections. There have been a few cases of vancomycin-resistant coagulase-negative *S. aureus* (307,308), but none of vancomycin-resistant MRSA, although transfer of vancomycin resistance to staphylococci has been achieved experimentally (309).

The continuous spread of resistance among clinical isolates, especially of multiresistant microorganisms represents a unique challenge in the treatment of infectious diseases. The detection of asymptomatic carriers of pneumococci, especially young children in day care centers, makes early detection even more difficult (310). Uncontrolled use of antibiotics in agriculture selects multiresistant fecal flora in animals, and meat can be contaminated by imperfect processing.

The problem of increasing resistance of micro-organisms is a major worldwide issue that necessitates close collaboration of clinicians, epidemiologists, and basic research laboratories. Newer and fast diagnostic tools (such as the polymerase chain reaction), routinely introduced into clinical laboratories, and better understanding at the molecular level of mechanisms of resistance of microorganisms are key prerequisites for the prevention of further spread of resistant microorganisms. Additional measures, for example broad use of vaccines and restrictions on antibiotic use imposed by health authorities, will require global cooperation and will have to be addressed by international organizations such as the WHO.

Second-Generation Effects

Teratogenicity

Since the days of the thalidomide disaster about 40 years ago, resulting in the birth of some thousands of malformed babies, it has been well recognized that drugs taken by pregnant mothers can have severe adverse effects on their unborn children. A consequence of the thalidomide disaster was worldwide awareness that drugs can cause congenital malformations and the necessity to investigate this possibility in animals. Since thalidomide, around 30 drugs have been proven to be teratogenic, not all of which are currently in clinical use (311). For most drugs, however, safety in pregnancy has still to be established. With the risk of teratogenicity and dysmorphogenesis ever present, clinicians are in general very cautious in prescribing drugs for pregnant women. Despite this, over 60% of pregnant women consume therapeutic agents not directly related to their pregnancy, and it has been estimated that about 5% of birth defects are caused by maternal drug therapy (312).

Even if a drug is generally recognized as being safe after animal experiments, it is wise to be suspicious when giving it to a pregnant woman. One major obstacle in evaluating safety in humans is the sample size required to reach sound conclusions. For example, in Europe, neural tube defects and cleft lips both occur with a prevalence of around seven per 10 000 live births (313). It has been calculated that for an uncommon drug exposure (that is, a frequency of under one per 1000 pregnant women and a background malformation prevalence of 0.001), one would have to monitor more than 1 000 000 births in order to detect a teratogenic effect, even though the relative risk associated with the drug might be as high as 20 (that is, a 20-fold increased risk of a particular malformation). In contrast, for formulations that are commonly used in pregnancy (for example by 2% of women, as was the case with thalidomide) and that are associated with an extremely high relative risk (such as 175), 1000 births would be sufficient to detect the teratogenic potential, even when the background prevalence of the malformation was as low as 0.0024 (314).

Another issue that has to be taken into consideration is the temporal relation between drug exposure and the effect on the embryo or fetus (315). Exposure to harmful drugs in the 2 weeks after conception usually leads to abortion, which may not be noticed. In the next 6–7 weeks the embryo is assumed to be extremely sensitive to teratogens (316). However, different organs and systems may be susceptible to teratogens at different times during this period. Therefore, in order to link drug use during pregnancy to a congenital malformation, drug intake must have taken place when the organ or organ system was sensitive to its harmful effects (315). It goes without saying that exact information on the timing of exposure is crucial.

In an ideal world, no drug would become available before it had been thoroughly tested for safety and effectiveness in a randomized, double-blind, placebo-controlled trial in pregnant women (317). However, because of ethical concerns about the welfare of the mother and fetus, pregnant women are traditionally excluded from drug trials. Therefore, usage is most often based on indirect measures of safety, such as in vitro studies and animal models. However, the thalidomide affair reminds us of the potential inadequacy of animal models.

In reality, most information about the safety of antimicrobial drugs in pregnancy comes from a history of long-term use with no reported adverse outcomes. As has been emphasized (317) most practitioners are happy

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to prescribe penicillin and its derivatives although there are no data from formal trials. However, there are data that show that penicillin V is safe during pregnancy (318). The study took place in Hungary between 1980 and 1996. The case group consisted of 22 865 malformed infants or fetuses, of whom 173 (0.8%) had mothers who had taken penicillin V during pregnancy. Two control neonates without malformations were matched with every case according to sex, week of birth, and the district of the parent's residence. Of the 38 151 infants in the control group, 218 had been treated with penicillin V. This difference was explained mainly by recall bias and confounders, because there was no difference in the adjusted odds ratio for medically documented phenoxymethylpenicillin treatment during the second and third months of gestation, that is, during the critical period for most major congenital abnormalities in case-matched control pairs. Thus, treatment with oral phenoxymethylpenicillin during pregnancy presents very little, if any, teratogenic risk.

There have also been two studies of the teratogenic potential of other penicillins. In the first study, in 791 women who had redeemed a prescription for pivampicillin during their first pregnancy, birth outcomes (malformations, pre-term delivery, and low birth weight) were matched with similar outcomes in 7472 reference pregnancies in which the mother had not redeemed any prescription for pivampicillin during pregnancy (319). There were no significant effects of pivampicillin. In the second study, in 78 women who took cefuroxime axetil during pregnancy, none of the 13 women who were treated in the first trimester gave birth to a malformed child, but one baby with hip dysplasia was found among 20 babies from mothers treated in their second trimester, and there was one case of hypospadias and one of imperforate anus in 47 children of mothers treated in the third trimester (320). The authors correctly concluded that the number of patients who had taken cefuroxime in the first trimester of pregnancy was small, and that cefuroxime should be used with caution in the early months of pregnancy.

Susceptibility Factors

Renal disease

Renal insufficiency is a risk factor for the toxic effects of the beta-lactams (321,322), including neurotoxic reactions (323), inhibition of platelet aggregation (324), and to some extent interaction with vitamin K-dependent synthesis of coagulation factors (325).

Drug–Drug Interactions

Antacids

Antacids increase gastric pH and can result in impaired dissolution of some cephalosporins (326–328).

Anticoagulants

Some beta-lactam antibiotics impair coagulation by inhibiting hepatic and intestinal vitamin K production and impairing platelet function.

- A patient suffered significant postoperative bleeding 4 days after dental surgery in a patient taking amoxicillin, despite the use of a tranexamic acid (4.8%) mouth rinse to control hemostasis (329).

Interactions with drugs that affect coagulation and platelet function must therefore be borne in mind.

- A 58-year-old woman developed a raised INR and microscopic hematuria while taking warfarin and co-amoxiclav (330). This was attributed to an interaction of the two drugs.

In contrast, some penicillinase-resistant penicillins (dicloxacillin, nafcillin) provoke resistance to warfarin, lasting for up to 3 weeks after withdrawal of the antibiotic (331,332).

- A patient experienced the effects of interactions of warfarin with nafcillin and dicloxacillin (333). During co-administration of nafcillin, warfarin doses were increased to as much as 4.5 times the previous amounts needed to provide adequate anticoagulation. During co-administration of dicloxacillin, warfarin doses gradually fell, but still stabilized at a higher maintenance dose than before.
- A 41-year-old man taking warfarin 22 mg/week with a prothrombin time of 20.7 seconds was given dicloxacillin 500 mg qds for 10 days (331). The prothrombin time and S- and R-warfarin concentrations fell by 17, 25, and 20% respectively after 5 days. In a retrospective review of seven other patients, the mean prothrombin time fell by 17% (range 11–26%) within 4 days of starting dicloxacillin.

This type of interaction may be due to induction of warfarin metabolism.

Digoxin

In 10% of patients taking digoxin, there is inactivation of up to 40% of the drug before absorption, by intestinal *Eubacterium lentum*. This can be reversed by antibiotics (334,335). The lack of effects of some beta-lactam antibiotics on serum digoxin concentrations in one study (336) might have been due to the small sample size or resistance of the bacteria.

Nifedipine

An active dipeptide transport system that depends on hydrogen ions takes up non-ester amino-beta-lactams (penicillin, amoxicillin, and oral first-generation cephalosporins) (337–339) and specific cephalosporins that lack the alpha-amino group (cefixime, ceftibuten, cefdinir, cefprozil) (340,341). Nifedipine increases amoxicillin and cefixime absorption, probably by stimulating the dipeptide transport system, since the serum concentrations of passively absorbed drugs and intestinal blood flow did not change (342–344).

Oral contraceptive steroids

There have been anecdotal reports that oral antibiotics reduced the efficacy of oral contraceptives. The proposed mechanism is that the antibiotics reduce the amount of gut bacteria that normally deconjugate excreted estrogens

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prior to reabsorption. However, in small formal studies this effect has not been confirmed (345–347). It is nevertheless possible that this is the mechanism, but that it occurs in too few women to be detected in small formal studies.

As early as 1971, it was observed that there was an increased incidence of intermenstrual bleeding in women who were reliably taking oral contraceptives and rifampicin for tuberculosis (348). Subsequent studies showed that pregnancy was a possible adverse effect of the combined use of antibiotics and oral contraceptives, the most commonly involved antimicrobial drugs being ampicillin, co-trimoxazole, and tetracyclines (349). In an analysis based on reports to the Committee on Safety of Medicines in the UK between 1968 and 1984, 63 pregnancies were identified in women taking this combination of drugs (345). Tetracyclines and penicillin were the drugs most often involved. However, the question of under-reporting was underlined. Over the years, there have been a few reports of the possibility of ineffectiveness of oral contraceptives during the use of antimicrobial drugs.

- A healthy 21-year-old woman, using an oral contraceptive, became pregnant while taking minocycline 100 mg/day for acne (350).

At least three different mechanisms have been proposed.

1. Antibiotics, for example rifampicin (SEDA-8, 256), interfere with the hepatic metabolism of the compounds in oral contraceptives.
2. Antibiotics increase gastric emptying and small intestinal motility. This in turn alters gastrointestinal absorption (and reabsorption) of oral contraceptives (probably both estrogens and progestogens). Increased gastrointestinal motility has been best studied in relation to macrolide antibiotics (SEDA-18, 269). However, there is no evidence of reduced efficacy of oral contraceptives through an effect of macrolides on gastrointestinal motility, which is in any case an unlikely mechanism.
3. Antibiotics interfere with the normal flora in the gastrointestinal tract, thereby also interfering with the normal enterohepatic circulation of the compounds that are included in oral contraceptives. This is a complex story. Oral contraceptives contain estrogens and progestogens. There are several different derivatives in each group and the amounts of each compound vary from formulation to formulation. However, most (if not all) of the compounds have an enterohepatic circulation—they are excreted into the bile, usually as conjugates, and are reabsorbed from the intestinal tract. The efficacy of their absorption and reabsorption depends on physicochemical factors in the gut (such as pH, conjugated versus unconjugated compounds, and adsorption to microbes and dietary constituents). In addition to this basic physiological circulation, intestinal microbes interact with the compounds, most often by splitting conjugates, but also by acting on double bonds, hydroxyl groups, and keto groups, present in the original compounds. These derivatives may have different absorption rates from the original ones. Partly because of their complexity, these microbial interactions have been very little studied. However, it is well known that microbes interfere with the enterohepatic circulation of other molecules with similar structures, such as androgens (SEDA-13, 215) (SEDA-16, 262) and bile acids (351). A similar effect can take place in patients with gastrointestinal bacterial infections. In addition, and at least from a theoretical point of view, an effect on this enterohepatic circulation may also occur in individuals with a high load of living microbes, as is the case when ingesting probiotics (products that contain live bacteria such as Bifidobacterium and Lactobacillus). This possibility has not been adequately addressed by any of the companies that sell tons of probiotics to fertile women taking oral contraceptives.

Given the problems of under-reporting, the lack of proper investigations, and the possibility of an unwanted pregnancy, the concern can be reduced to a practical one: what should women be told? An excellent recommendation has been published in the UK (352): "Your doctor has prescribed antibiotics, which are necessary to treat [your] infection. However, the antibiotics can interfere with the pill and make it less effective. This means that you may not be protected from pregnancy if you have sex, even though you are taking the pill. You are advised that you should take precautions, that is use of a condom, during the time you are taking the antibiotics, and for 7 days after completing the course of antibiotics ···" For the time being, this is the best advice. However, more investigations in this important field are needed.

Phenobarbital

There was an unexpectedly high frequency of adverse effects in a pediatric intensive care unit with the combination of high-dose phenobarbital and beta-lactam antibiotics, mainly cefotaxime (353). The reactions, which mostly affected the skin and blood, were only rarely reproduced by a single component, suggesting an interaction. However, these findings have not been confirmed, and their impact is unclear.

Probenecid

Probenecid inhibits the tubular resorption of anions and inhibits the renal excretion of most beta-lactam antibiotics (354,355).

Vecuronium

There are various conflicting reports about acute interactions of beta-lactam antibiotics, especially acylaminopenicillins (apalcillin, azlocillin, mezlocillin, piperacillin), with vecuronium, leading to prolongation of muscle blockade. Reports of clinically relevant effects (356–358) conflict with reports of no effect (359).

Food–Drug Interactions

Co-administration of acid-labile beta-lactams, such as penicillin and ampicillin, with food reduces their systemic availability by lowering gastric pH and delaying gastric emptying (360).

Food increases the systemic availability of some cephalosporin prodrug esters, possibly by improving dissolution or blocking premature hydrolysis (361,362).

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Interference with Diagnostic Tests

Aminoglycosides

Plasma aminoglycoside concentrations can be falsely low because they are inactivated by penicillins and cephalosporins. This effect occurred in plasma stored for 24 hours or longer before measurement (363–365).

Coombs' test

There are often false-positive antiglobulin tests by non-immunologically bound serum proteins, especially with cephalosporins, clavulanic acid, and imipenem + cilastin. This is a source of difficulty in cross-matching blood products.

Glycosuria

Urine samples containing beta-lactams should be tested for glucose by the glucose oxidase method, since falsely high values are observed with the copper reduction method (366,367).

Ciclosporin measurement

A retrospective study found an increased risk of ciclosporin-associated early nephrotoxicity in nafcillin-treated patients, despite the fact that ciclosporin concentrations were not different from controls (368). Possible interference of nafcillin with ciclosporin measurement, giving rise to falsely low concentrations, was considered as a possible explanation.

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Beta-lactamase inhibitors

General Information

Beta-lactamases are genetically and structurally closely related to penicillin-binding proteins. Their production by bacteria is a major mechanism of resistance to the action of beta-lactam antibiotics. Drugs have therefore been developed that inhibit beta-lactamase, as a way of overcoming this resistance (SEDA-20, 229). They are beta-lactam compounds with particularly high affinities for beta-lactamases (1,2), which therefore act as competitive inhibitors of beta-lactamases. Beta-lactamase inhibitors have no important antimicrobial activity and are only given in combination with an antimicrobial beta-lactam.

The following beta-lactamase inhibitors are in use:

- clavulanic acid (rINN), produced naturally by *Streptomyces clavuligerus*, used in combination with amoxicillin or ticarcillin; the combination clavulanic acid + amoxicillin is also called co-amoxiclav (BAN);
- sulbactam (rINN), a halogenated derivative of penicillanic acid, used in combination with ampicillin or cefoperazone;
- tazobactam (rINN), a halogenated derivative of penicillanic acid, used in combination with piperacillin.

In order to improve absorption, sulbactam has also been bound to ampicillin in the single molecule sultamicillin, which is hydrolysed to the active components after absorption.

An inherent obstacle in evaluating the adverse effects of beta-lactamase inhibitors is that they are only co-administered with antimicrobial beta-lactams, the doses of which are usually several times higher. For the most part, combinations of beta-lactam antibiotics with beta-lactamase inhibitors produce the adverse effects of the individual drugs. However, it is not always possible to say whether an adverse effect is due to one drug alone or to the combination. For example, cholestatic hepatitis occurs more often with co-amoxiclav than with ampicillin alone; however, this could be because it is primarily due to clavulanic acid or because the combination somehow increases the risk.

Organs and Systems

Respiratory

Interstitial pneumonitis has been attributed to ampicillin + sulbactam in two Japanese patients (3).

Psychological, psychiatric

Behavioral changes occurred in four children aged 1.5–10.5 years, taking co-amoxiclav (4).

Hematologic

Parallel to a well-known phenomenon seen with cephalosporins, clavulanic acid can be associated with a positive direct antiglobulin test. In three patients antibiotic courses, including intravenous ticarcillin + clavulanic acid, were associated with positive direct antiglobulin tests in over 50% of cases (5–7). Corresponding observations were made in patients taking ampicillin + sulbactam (8). In vitro studies showed that clavulanic acid and sulbactam caused non-immunological absorption of plasma proteins on to the erythrocyte surface (5,9). There seems to be no clinical impact of this phenomenon, but it can interfere with cross-matching of blood products or with the investigation of true hemolysis.

Reversible bone marrow suppression after high-dose piperacillin + tazobactam was seen in an underweight woman and was thought to be a dose-dependent and piperacillin-related effect (10).

Gastrointestinal

Two cases of hemorrhagic colitis, apparently not related to *Clostridium difficile*, have been reported after co-amoxiclav (11,12). However, the same type of colitis has repeatedly been observed with aminopenicillins alone (12).

Co-amoxiclav often causes diarrhea and other gastrointestinal problems. Oral administration was associated with motor disturbances of the small intestine (13).

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Liver

Cholestatic hepatitis

DoTS classification

Dose-relation: hypersusceptibility effect
Time-course: immediate
Susceptibility factors: genetic (DRB1*1501*DRB5-DRB5*0101-DQB1*0602 haplotypes); age over 55 years; male sex; duration of treatment

Co-amoxiclav can cause cholestatic hepatitis. The first report appeared in 1988 (14), since when several hundreds of cases have been reported, for example to health authorities (15), and over 100 cases have been described in detail (16–31). Clavulanic acid is instrumental, either alone or in combination with amoxicillin, since the risk of acute liver injury is much smaller with amoxicillin alone (32).

The relative contributions of amoxicillin and clavulanate to co-amoxiclav-induced hepatotoxicity are incompletely understood. In patients with co-amoxiclav hepatotoxicity, previous use of amoxicillin and rechallenge with amoxicillin were both uneventful, pointing to clavulanic acid as the more likely culprit (16). In a report from the UK, the incidence of liver injury with amoxicillin alone was 0.3 per 10 000 prescriptions versus 1.7 with co-amoxiclav (32). The risk increased after multiple use and with increasing age to 1 per 1000 prescriptions of co-amoxiclav. The main message is that the combination should be used with caution in elderly patients. A patient who has had documented hepatotoxicity related to co-amoxiclav should be well informed about this adverse drug reaction and any future use should be prohibited.

Ticarcillin + clavulanic acid, which is only used intravenously, has also been reported to induce a similar syndrome (33,34) and can also aggravate pre-existing hepatitis (35). One cholestatic reaction has been reported with intravenous sulbactam + ampicillin (36).

The importance of taking a careful history in patients in whom drug-related hepatitis is suspected has been underlined (37).

Incidence

Considering the large number of patients who take this very widely used combination, the risk of hepatitis was initially estimated to be very low, probably below 1/100 000 (23). Newer data, however, have suggested a risk of 1/10 000 or higher (32). In a retrospective cohort study of family practitioners' records, with a high proportion of mild cases, there was a rate of 1 per 4449 prescriptions (32). If this is the case, it is wise to reserve co-amoxiclav (and maybe also ticarcillin + clavulanate) for use in infections caused by strains producing beta-lactamases that can destroy amoxicillin (or ticarcillin).

The syndrome is practically unknown in children; only one pediatric case has been reported so far, in a 4-year-old boy with spherocytosis (16) and causality was disputed (17).

Presentation

The hepatitis usually develops acutely, although an interval of up to 4 weeks between the end of treatment and the first signs of hepatitis is frequent and can prevent rapid diagnosis. Although the clinical effects can be impressive, the condition is usually reversible within 4–6 weeks.

- A 40-year-old woman with a history of chronic sinusitis and asthma developed nausea, vomiting, abdominal pain, and diarrhea (38). Six weeks before, she had taken a 10-day course of co-amoxiclav for acute sinusitis. Her transaminase activities were markedly increased, as was total bilirubin. All drugs were withdrawn, her symptoms progressively improved, and she was discharged without a clearly identified cause of her illness. Liver function tests normalized completely within a few weeks. Two months later she had another episode of acute sinusitis and was again given co-amoxiclav. A few days later she developed nausea, vomiting, a skin rash, abdominal pain, and reduced appetite. Her alanine transaminase activity was 199 U/l (0–65), aspartate transaminase 99 U/l (0–60), and alkaline phosphatase 362 U/l (50–180). The antibiotic was withdrawn, and she completely recovered in 2 weeks and had normal liver function tests over the next several months.
- A 33-month-old boy took co-amoxiclav (dose not stated) for 10 days for otitis media (39). He had taken it twice before. One day after completing the course he developed a rash over his entire body, followed 3 days later by lethargy, jaundice, pale stools, and pruritus. The jaundice persisted, the liver was markedly enlarged, and all liver function tests were abnormal. Tests for known viral and metabolic causes of cholestasis were negative. A percutaneous liver biopsy showed centrilobular cholestasis "consistent with a drug reaction." He was given ursodeoxycholic acid (30 mg/kg/day) and vitamins A, D, and K; later prednisolone was added. However, his jaundice persisted, as did severe pruritus. He also developed extensive xanthomatosis and failure to grow. A liver transplantation was successfully performed 8 months after the onset of symptoms. His explanted liver had features of biliary cirrhosis, with ductular proliferation and ductopenia.

One fatal outcome was described in a patient who was also taking ethinylestradiol, which can itself cause cholestasis (40).

In isolated cases, Stevens–Johnson syndrome together with cholestasis and bone marrow aplasia have been associated with either amoxicillin alone (41) or with co-amoxiclav (42).

Histological features

Liver biopsy shows predominantly centrilobular or panlobular cholestasis, and occasionally granulomatous hepatitis (43).

Mechanism

The mechanism of the syndrome and its possible relation to the liver injury that other beta-lactams, particularly isoxazolylpenicillins, can cause are unclear. A slight eosinophilia has been seen in many cases (26,43,44) and some of the sporadic cases of rechallenge were positive (16). However, there is no other evidence supporting an

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immunoallergic basis. Hepatic accumulation or biliary secretion of clavulanic acid or its metabolites have not been demonstrated (45).

Two other theories have been proposed (46). One is based on the metabolic formation of neo-antigens, and subsequent recognition of these antigens as foreign by the immune system. This "immune allergic hypothesis" is supported by the strong association with an HLA class II haplotype. The authors argued that "HLA class II molecules are required for antigen presentation to CD4-positive T cells. HLA alleles may differ by a little as a single codon, and one amino acid residue difference at a critical site in the resulting polypeptide may be functionally significant, determining not only the affinity with which a given antigen is presented but also the interaction of the HLA peptide complex with the T cell receptor." Their other theory was that the liver disease may arise through linkage with another gene on chromosome 6p. This "linked-gene" hypothesis, they proposed, may explain why jaundice is rare after treatment with co-amoxiclav, although this particular HLA haplotype is common in Northern Europe, where co-amoxiclav is commonly prescribed.

Whatever the mechanisms might be, at present it is reasonable to look on clavulanate as the main contributor to the development of hepatotoxicity with co-amoxiclav. Hepatotoxicity has also been reported with clavulanate plus ticarcillin (34). So far, however, there has been no genetic evaluation of patients with hepatotoxic reactions after therapy with clavulanate and ticarcillin.

Susceptibility factors

Increasing age (over 55 years), male sex, and duration of treatment are risk factors (26,32,47), while drug dose and route of administration, other medications, previous drug allergies, or prior use of co-amoxiclav were not significantly associated with the reaction.

The importance of HLA antigens in the pathogenesis of some liver diseases (autoimmune hepatitis, primary biliary cirrhosis, primary cholangitis) is also reasonably well established (48), and there is a significant association between co-amoxiclav-induced liver damage and an HLA haplotype (49,50). HLA-class antigens have been investigated in 35 patients with biopsy-documented liver damage due to co-amoxiclav and 300 controls (volunteer bone marrow donors) (46). HLA-A and HLA-B were typed using alloantisera and HLA-DBR and HLA-DWB were typed by PCR. The patients with hepatitis were characterized by a higher frequency of the DRB1*1501*DRB5-DRB5*0101-DQB1*0602 haplotype (57 versus 12% in controls). Patients with that haplotype tended to have a cholestatic rather than a hepatocellular type of hepatitis. However, these data also suggest that other factors must act concurrently. These factors may involve heterogeneity of the formed antigens and/or polymorphism of the T cell receptor. A reaction to (unknown) metabolites of clavulanic acid also has to be kept in mind. The authors suggested that "metabolic factors may play a greater role in the pathogenesis of hepatocellular cases, whereas immunological factors may be more involved in the pathogenesis of cholestatic ones." This HLA association has been confirmed in a study in which there was an increased frequency of homozygous status for this haplotype (51). This might reflect population differences and the small sample size in both studies (46). It is reasonable to assume that HLA characterization will be implemented in a future diagnostic armamentarium.

Urinary tract

The combination of piperacillin + tazobactam was thought to have caused acute interstitial nephritis in a 51-year-old woman (52). It remains open whether the combination or one of the components was the culprit.

Immunologic

Clavulanic acid has a very low immunogenic and allergenic potential in animals. The possible impact of its co-administration with other beta-lactam antibiotics is unknown (53). Two patients with IgE-mediated hypersensitivity to oral co-amoxiclav and positive skin tests for clavulanic acid, but not for penicillins, both tolerated oral amoxicillin. One patient was also challenged with clavulanic acid and developed urticaria, conjunctivitis, and bronchial obstruction (54). Since co-amoxiclav has been widely used since its introduction in 1981, the frequency of hypersensitivity reactions is low. The clinical data available on sulbactam and tazobactam are still limited and do not allow an assessment of the frequency and pattern of associated hypersensitivity reactions (55).

Body temperature

A woman immediately developed hyperpyrexia up to 40°C after a first dose of intravenous ampicillin + sulbactam, having previously tolerated ampicillin alone for 10 days. Hyperpyrexia was repeatedly observed after six more doses of sulbactam (56).

Interference with Diagnostic Tests

Leukocyte dipstick test

Clavulanic acid caused false-positive dipstick tests for leukocytes; sulbactam and tazobactam did not (57).

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Bethanechol

General Information

Bethanechol is a quaternary ammonium compound that shares both the muscarinic and nicotinic actions of acetylcholine but it is much more slowly deactivated. It has been used to treat clomipramine-induced orgasmic dysfunction (1).

Organs and Systems

Nervous system

An acute dystonic reaction to bethanecol has been reported in a 10-month-old boy (SEDA-12, 124). This reaction was unexpected since bethanecol does not normally penetrate the blood–brain barrier; the authors assumed that the barrier may not be impenetrable to the drug in young infants.

During a controlled clinical trial of intraventricular bethanecol in patients with Alzheimer's disease, reversible drug-induced parkinsonism was observed in one patient (SEDA-15, 5). The frequent co-existence of Alzheimer's disease and Parkinson's disease presents potential problems for therapy and adverse effects when the cholinergic system is manipulated.

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Bevantolol

See also Beta-adrenoceptor antagonists

General Information

Bevantolol, a hydrophilic cardioselective beta-blocker with membrane-stabilizing activity, may have a higher incidence of fatigue, headache, and dizziness than atenolol or propranolol (1,2).

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Biguanides

General Information

Biguanides (1) and metformin (2–4) have been reviewed. Metformin (rINN) is the only biguanide commonly used; buformin (rINN) and phenformin (rINN) have been withdrawn in many countries (SEDA-4, 306) because of dangerous adverse effects. However, they are still available in a few countries, and with increasing travel, adverse effects of drugs no longer available in one country can occur if the drug is obtained elsewhere.

The biguanides have a special affinity for the mitochondrial membrane, which causes an alteration in electron transport and results in reduced oxygen consumption. Inhibition of the active transport of glucose in the intestinal mucosa, absent activation of glucose transporters, inhibition of gluconeogenesis, and inhibition of fatty

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acid oxidation and of lipid synthesis are the effects that are considered to cause lowering of the blood glucose and improving blood lipids in diabetes mellitus. The blood glucose lowering effect of metformin was comparable to that of sulfonylureas, according to a meta-analysis, but body weight increases with sulfonylureas and falls with metformin, leading to a mean weight change difference of 2.9 kg (5).

Most (70–90%) of a dose of metformin is eliminated via the kidneys with a half-life of 9 hours (6). In contrast, phenformin is mostly eliminated by metabolism; its half-life is about 11 hours (7).

Observational studies

In a large American study in 3234 non-diabetic people with a raised fasting blood glucose and a raised blood glucose 2 hours after a glucose load, diabetes occurred in 7.8 cases per 100 participants per year after a mean treatment period of 2.8 years with metformin 850 mg bd; there were 11 cases per 100 participants per year after placebo and 4.8 cases per 100 participants per year after a life-style intervention program (8). Gastrointestinal symptoms were most frequent in those who took metformin. In a later study, glucose tolerance tests were performed after a 14-day washout period of metformin and placebo in the patients who had not developed diabetes (9). Diabetes was more frequently diagnosed in the metformin group, but when the diabetes conversions during treatment and washout were combined, diabetes was still significantly less common in the metformin group.

Comparative studies

Metformin and troglitazone have been compared in 21 patients with type 2 diabetes unresponsive to glibenclamide 10 mg bd (10). Metformin stabilized weight and reduced adipocyte size, leptin concentrations, and glucose transport. GLUT1 and GLUT4 in isolated adipocytes were not changed. Insulin-stimulated whole-body glucose disposal rate increased by 20%. Troglitazone caused increases in body weight, adipocyte size, leptin concentrations, and basal and insulin-stimulated glucose transport. GLUT4 protein expression was increased two-fold and insulin-stimulated whole-body glucose disposal rate increased by 44%.

Placebo-controlled studies

In a placebo-controlled study in 40 patients with impaired glucose tolerance metformin 500 mg bd for 6 months increased insulin-stimulated glucose metabolism by 20% with minimal improvement in glucose tolerance; this effect was maintained after 12 months (11).

In 82 children aged 10–16 years with type 2 diabetes, metformin lowered HbA_{1c} and fasting blood glucose compared with placebo (12). More patients who took placebo had to drop out because more medication was necessary. Most of the adverse events (abdominal pain, diarrhea, nausea, vomiting) occurred during metformin treatment.

Combinations of oral hypoglycemic drugs

The different mechanisms of action of the various classes of hypoglycemic drugs makes combined therapy feasible: the sulfonylureas and meglitinides stimulate insulin production by different mechanisms, the biguanides reduce glucose production by the liver and excretion from the liver, acarbose reduces the absorption of glucose from the gut, and the thiazolidinediones reduce insulin resistance in fat. It is not necessary to wait until the maximal dose of one drug has been reached before starting another. However, sulfonylureas and meglitinides should no longer be used when endogenous insulin production is minimal. Combinations of insulin with sulfonylureas or meglitinides should only be used while the patient is changing to insulin, except when long-acting insulin is given at night in order to give the islets a rest and to stimulate daytime insulin secretion.

This subject has been reviewed in relation to combined oral therapy. In a systematic review of 63 studies with a duration of at least 3 months and involving at least 10 patients at the end of the study, and in which HbA_{1c} was reported, five different classes of oral drugs were almost equally effective in lowering blood glucose concentrations (13). HbA_{1c} was reduced by about 1–2% in all cases. Combination therapy gave additive effects. However, long-term vascular risk reduction was demonstrated only with sulfonylureas and metformin.

In a placebo-controlled study in 116 patients who responded insufficiently to metformin 2.5 g/day, rosiglitazone 2 or 4 mg bd was added for 26 weeks (14). HbA_{1c} and fasting plasma glucose improved and hemoglobin fell. Edema was reported in 5.2% of the patients who took rosiglitazone and two patients withdrew because of headache.

Biguanides + meglitinides

Patients with type 2 diabetes with unsatisfactory control after taking metformin for 6 months were randomized to metformin alone, repaglinide alone, or metformin + repaglinide (each 27 patients) (15). Combined therapy reduced HbA_{1c} after 3 months by 1.4% and fasting glucose by 2.2 mmol/l. Repaglinide alone or in combination with metformin increased insulin concentrations. The most common adverse effects were hypoglycemia, diarrhea, and headache. Gastrointestinal adverse effects were common in those taking metformin alone, and body weight increased in both groups taking repaglinide.

In 12 patients with type 2 diabetes, a combination of nateglinide 120 mg or placebo with metformin 500 mg before each meal on two separate days was well tolerated (16). One patient taking nateglinide had a headache. One patient was withdrawn because of a myocardial infarction and had multivessel coronary artery disease on catheterization.

In a prospective, randomized, double-blind, placebo-controlled study for 24 weeks, 701 patients took nateglinide 120 mg before the three main meals, or metformin 500 mg tds, or the combination of the two, or placebo (17). The most frequent adverse effect was hypoglycemia, and it was most common in the combination group. There were no differences between those who took nateglinide only or metformin only and there were no episodes of serious hypoglycemia. Diarrhea was more frequent in those taking metformin or the combination, but infection, nausea, headache, and abdominal pain were comparable in the two groups.

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Of 82 patients insufficiently controlled by metformin, 27 continued to take metformin with placebo, 28 took titrated repaglinide with placebo, and 27 took metformin with titrated repaglinide for 4–5 months (18). There were no serious adverse effects. Nine patients taking metformin + repaglinide reported 30 hypoglycemic events and three patients taking repaglinide reported 9 events.

Insulin + biguanides

Metformin was given as an adjunct to insulin in a double-blind, placebo-controlled study in 28 adolescents needing more than 1 U/kg/day (19). The dose of metformin was 1000 mg/day when body weight was under 50 kg, 1500 mg/day when it was 50–75 kg, and 2000 mg/day when it was over 75 kg. Metformin lowered insulin requirements. The number of episodes of hypoglycemia increased compared with placebo. There was gastrointestinal discomfort in six patients taking metformin and five taking placebo.

A comparable placebo-controlled study was reported in 353 patients with type 2 diabetes for 48 weeks. All were taking insulin, and HbA_{1c} fell in those who also took metformin. Body weight was reduced by 0.4 kg by metformin and increased by 1.2 kg by placebo. Symptomatic episodes of hypoglycemia were more common with metformin. There were mild transient gastrointestinal complaints in 56 and 13% respectively (20).

Insulin plus metformin (27 patients, 2000 mg/day) or troglitazone (30 patients, 600 mg/day) in patients with type 2 diabetes using at least 30 U/day was compared with insulin alone (30 patients) for 4 months (21). Body weight increased in the insulin and the insulin plus troglitazone groups. In the insulin plus metformin group there were significantly more gastrointestinal adverse effects but less hypoglycemia than the other groups.

In 80 patients taking metformin 850 or 1000 mg tds plus NPH insulin at bedtime, metformin was withdrawn and repaglinide 4 mg tds added in half of the patients for 16 weeks (22). In the repaglinide group the dose of insulin increased slightly and weight gain was 1.8 kg more. Mild hypoglycemia occurred more often in the metformin group; nightly episodes of hypoglycemia occurred only with repaglinide. One patient taking repaglinide had a myocardial infarction, and one had three separate hospitalizations for chest pain (myocardial infarction was excluded). No specific data were presented about gastrointestinal adverse effects or infections.

Contraindications

Contraindications to treatment with biguanides are:

1. impaired renal function (serum creatinine may not be a sufficient indicator; creatinine clearance must be estimated)
2. an increased risk of impaired renal function in intercurrent diseases with fever, congestive heart failure, or infections of the urinary tract, during treatment with diuretics, intravenous pyelography, or severe dieting
3. states associated with tissue hypoxia (respiratory insufficiency, heart insufficiency, anemia, and peripheral vascular disease)
4. hepatitis and hepatic cirrhosis
5. excessive use of alcohol
6. wasting diseases
7. preoperatively and postoperatively.

In general, biguanides should not be used in people aged over 75 years (23).

Of 308 patients 73% had contraindications, risk factors, or intercurrent illnesses necessitating withdrawal of metformin (24): 19% had renal impairment, 25% heart failure, 6.5% respiratory insufficiency, and 1.3% hepatic impairment; 51% had advanced coronary heart disease, 9.8% atrial fibrillation, 3.3% chronic alcohol abuse, 2% advanced peripheral arterial disease, and 0.7% were pregnant.

Four fatal cases in 18 months in a community hospital were reported; three had clear contraindications (25): a 45-year-old woman with liver cirrhosis, a 64-year-old man with coronary artery disease, and a 65-year-old man with peripheral arterial disease and asthma; a 74-year-old man had renal insufficiency.

In a retrospective study of 1874 patients with type 2 diabetes taking metformin, 25% had contraindications, including acute myocardial infarction, cardiac failure, renal impairment, and chronic liver disease (26). However, contraindications often did not lead to withdrawal of metformin: in 621 episodes, only 10% stopped taking it. Only 25 and 18% stopped taking metformin when they developed renal impairment or myocardial infarction, respectively. One patient developed lactic acidosis, but this may have been a consequence of myocardial infarction.

Organs and Systems

Cardiovascular

The cardiovascular effects of metformin have been reviewed (27). Metformin reduces blood pressure and has a beneficial effect on blood lipid concentrations.

In a retrospective study, cardiovascular deaths in patients using a sulfonylurea only ($n = 741$) were compared with deaths in patients taking a sulfonylurea + metformin ($n = 169$) (28). In patients taking the combination the adjusted odds ratios (95% CI) were:

- overall mortality 1.63 (1.27, 2.09);
- mortality from ischemic heart disease 1.73 (1.17, 2.55);
- stroke 2.33 (1.17, 4.63).

The patients taking the combination were younger, had had diabetes for longer, were more obese, and had higher blood glucose concentrations.

Metabolism

Biguanides cause hypoglycemia in 0.24 cases per 100 patient-years and it is more common when they are used in combination with a sulfonylurea (29). In 102 consecutive patients with drug-induced hospital-related hypoglycemic coma, 13 were taking metformin + glibenclamide and 3 were taking metformin + insulin (30).

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Lactic acidosis

DoTS classification

Adverse effect: Lactic acidosis due to biguanides
Dose-relation: toxic effect
Time-course: time-independent
Susceptibility factors: genetic (slow phenformin metabolizers); age; disease (impaired liver, kidney, or cardiac function, alcoholism)

Biguanides can cause lactic acidosis, which is fatal in 50% of cases (31).

- A 65-year-old man with a creatinine clearance of 67 ml/minute taking metformin 850 mg bd developed lactic acidosis (lactate 25 mmol/l, pH 7.13, bicarbonate 5 mmol/l) (32). Despite the relatively small dosage of metformin, he had unexplained very high metformin concentrations (61 μg/ml).

A possible explanation for the high metformin concentration in this case was that an unknown substance related to intestinal inclusion inhibited its tubular excretion. Other cases involving metformin have included the following:

- a 62-year-old woman: pH 6.60, blood lactate 45 mmol/l, creatinine 133 μmol/l (33);
- a 72-year-old woman: pH 6.84, creatinine 125 μmol/l (34);
- a 75-year-old woman: pH 6.73, lactate 18 mmol/l (34);
- a patient with creatinine 91 μmol/l, creatinine clearance 52 ml/minute, metformin concentration 61 μg/ml (target under 5 μg/ml) (35);
- a 52-year-old woman, a chronic alcohol user: pH 6.74, lactate over 30 mmol/l, creatinine 710 μmol/l (36);
- an 83-year-old woman with mild renal insufficiency (37).

All survived, but all needed hemodialysis. In all cases there were contraindications to metformin.

Five patients with metformin-associated severe lactic acidosis, seen between 1 September 1998 and 31 May 2001, have been reported (38). Two had attempted suicide. All had severe metabolic acidosis with a high anion gap and raised blood lactate concentrations. Four developed profound hypotension and three had acute respiratory failure. Three had normal preceding renal function. Three required conventional hemodialysis and two continuous renal replacement therapy.

Cases also continue to be reported with buformin and phenformin (39).

- A 67-year-old man who had taken phenformin and glibenclamide for 2 years became lethargic and confused (40). His pH was 6.91, serum lactate 25 mmol/l and later 30 mmol/l, and blood glucose very low (0.5 mmol/l), possibly because of vomiting, anorexia, and glibenclamide. Hemodialysis was advised but not performed, since he recovered spontaneously.

Incidence

In patients taking metformin, lactic acidosis is rare (3 per 100 000 patient-years) and is most often seen when contraindications to metformin (impaired kidney or liver function, alcoholism, circulatory problems, old age) are neglected or not detected (41). Although the relative risk of lactic acidosis with metformin is significantly lower than with phenformin or buformin (42), it has been repeatedly reported (SEDA-6, 371) (43), even in the absence of known contraindications (44).

Experience with metformin in a large American health organization in 9875 patients has been presented (45). There was one probable case of lactic acidosis in an 82-year-old woman who developed renal impairment while taking metformin 500 mg/day.

In 11 797 patients (22 296 person-years) in Saskatchewan who took metformin from 1980–95 there were 9 cases of lactic acidosis per 100 000 patient-years (46), a much lower incidence than the estimated rate of 40–64 cases for phenformin.

The lower frequency of lactic acidosis during treatment with metformin compared with other biguanides may be caused by its short non-polar hydrophobic side chains substituted with two CH_3 groups. This has a lower affinity for hydrophobic structures, such as phospholipids in mitochondrial and cellular membranes, than the longer monosubstituted side-chains of the other biguanides (41).

Mechanism and susceptibility factors

Biguanides in high doses inhibit the oxidation of carbohydrate substrates by affecting mitochondrial function. Anoxidative carbohydrate metabolism stimulates the production of lactate. High lactate production leads to lactic acidosis (type B) with a low pH (<6.95). Hyperlactatemia was common in patients taking buformin, even without alcoholism or impaired liver, kidney, or cardiac function (47).

In reaction to a report of lactic acidosis at a therapeutic metformin concentration (SEDA-22, 476), in which a mitochondrial defect was supposed to have increased susceptibility to metformin, it has been observed that diabetes itself may dispose to hyperlactatemia (48). Others (49) have taken issue with the opinion (SEDA-22, 476) that the association of lactic acidosis with metformin may be coincidental, as lactic acidosis can also emerge during critical illnesses (type A lactic acidosis, caused by circulatory insufficiency). However, patients with type B lactic acidosis, with high biguanide concentrations, will also develop circulatory insufficiency after some hours.

The main susceptibility factor for lactic acidosis due to metformin is renal insufficiency (33). In patients taking phenformin, poor oxidative metabolism may contribute (50).

All patients admitted to a hospital during 6 months who had taken at least one dose of metformin were retrospectively evaluated for susceptibility factors for metformin-associated lactic acidosis (8). There were 263 hospitalizations in 204 patients. In 71 admissions there was at least one contraindication, such as renal or liver disease, renal dysfunction, congestive cardiac failure, metabolic acidosis, or an intravenous iodinated contrast medium given within 48 hours of metformin. In 29 (41%) metformin was continued despite the contraindication. The most frequent contraindication was a raised serum creatinine, but in only eight of the 32 admissions was metformin withdrawn. Of nine patients using metformin who died (not necessarily directly related to metformin), six had an absolute contraindication. In two patients who

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died and in one who survived, blood lactate was increased and this was temporally related to the use of metformin.

Whether metformin in therapeutic doses can cause lactic acidosis in the absence of renal insufficiency has been investigated by studying case histories of metformin-associated lactic acidosis in various databases published from May 1995 to January 2000 (51). Overdoses and lactic acidosis caused by contrast media were excluded. There were 21 reports of 26 cases, of which five did not comply with the criteria (lactate over 5 mmol/l, pH 7.35 or less). Plasma metformin concentration was measured in only four cases. The authors distinguished between lactic acidosis precipitated by metformin, which was defined as occurring without accumulation of metformin, and lactic acidosis that occurred during primary acute or chronic renal insufficiency, with accumulation of metformin. In the first group, six of the eight patients died. In the second group, notwithstanding a mean lactate concentration of nearly 15 mmol/l, only one of the 12 patients died, having refused dialysis. They concluded that there is no relation between the use of metformin and lactic acidosis, except when metformin accumulates. This has been illustrated by the case of a 76-year-old woman taking 850 mg metformin bd who developed lactic acidosis due to metformin accumulation during deteriorating kidney function (52).

Drugs that can precipitate lactic acidosis in patients taking metformin include ACE inhibitors, thiazide diuretics, NSAIDs, and drugs such as furosemide, nifedipine, cimetidine, amiloride, triamterene, trimethoprim, and digoxin, which are all secreted in the renal tubules, compete with metformin, and can contribute to increased plasma metformin concentrations (53).

The need to follow recommended guidelines strictly in order to avoid lactic acidosis in patients taking metformin has been emphasized (54).

Presentation

The early symptoms of lactic acidosis are nausea, vomiting, and diarrhea; since these are common adverse effects of biguanides, a careful watch should be kept for their sudden onset or aggravation, which might point to lactic acidosis (55).

In retrospective studies, neither the degree of hyperlactatemia nor accumulation of metformin had prognostic significance, but mortality was linked to the underlying disease (56,57).

Management

The best therapy of metformin-induced lactic acidosis is immediate hemodialysis, but metformin in the tissues continues to produce lactate while the drug is being removed during dialysis. Sodium bicarbonate is not very effective and can paradoxically lower the pH and cause hypernatremia and fluid overload. Tracheal intubation and mechanical ventilation may be necessary (53). Theophylline and dichloroacetate have also been used. Theophylline stimulates oxygen exchange in the lungs. Dichloroacetate activates pyruvate dehydrogenase, inhibiting lactate formation, but it is neurotoxic, can cause cataract, and is mutagenic (SEDA-7, 410).

The results of hemodialysis in biguanide-induced lactic acidosis are variable. Metformin and buformin are dialysable, but phenformin is poorly eliminated. Successful continuous venovenous hemofiltration has been reported (58).

- A 68-year-old woman with type 2 diabetes and hypertension took phenformin 90 mg/day and glibenclamide 6 mg/day. She developed a urinary tract infection and oliguria followed by respiratory distress and mental confusion without neurological defects. Her pH was 6.84, serum lactate 28 mmol/l, creatinine 186 μmol/l, and glucose 10.4 mmol/l, and there were no ketone bodies. She received assisted ventilation, bicarbonate, dopamine + obutamine, glucose + insulin, and antibiotics. Her serum lactate increased to 44 mmol/l and continuous venovenous hemofiltration was started. After 5 days her lactate concentration was in the reference range (0.5–2.2 mmol/l). The serum phenformin concentration was almost 600 ng/ml (10 times the therapeutic value).

Nutrition

Vitamin B_{12} deficiency can be caused by metformin.

- A 63-year-old man with type 2 diabetes, who had taken metformin for at least 5 years, had a low serum vitamin B_{12} concentration (110 pg/ml; reference range 200–230) and a normal serum folate (59). There were no autoantibodies. A Schilling test showed malabsorption of vitamin B_{12}. Metformin was withdrawn and 2 months later a Schilling test showed no malabsorption.
- This case prompted a report of 10 metformin-associated patients with cobalamin deficiency among 162 patients with vitamin B_{12} concentrations below 200 pg/ml (60). They had taken a mean dose of metformin of 2015 mg/day for an average of 8.9 years. The mean vitamin B_{12} concentration was 140 pg/ml. All had normal serum folate and creatinine concentrations and no antibodies to intrinsic factor. In one patient there was malabsorption.

Hematologic

Megaloblastic anemia is rare with metformin, but vitamin B_{12} concentrations can be reduced by metformin and phenformin (61) because of reduced absorption, and pre-existing deficiency can be exacerbated (41).

Metformin can occasionally cause a hemolytic anemia.

- A 68-year-old woman of North African Jewish descent with a raised HbA_{1c} was given metformin 850 mg tds and repaglinide 1 mg tds, and 14 days later developed extreme weakness and anemia, her hemoglobin having fallen from 12 to 8 g/dl within 1 week (62). Her reticulocyte count was 11%, with polychromasia. The bilirubin rose to 35 μmol/l (27 μmol/l direct). The haptoglobin concentration was low and a direct Coombs' test was negative. Metformin was withdrawn. Two units of erythrocytes were transfused and the hemoglobin rose to 11 g/dl and remained stable. Glucose-6-phosphate dehydrogenase (G6PD) activity was significantly reduced. There were no other precipitating factors for hemolysis due to G6PD deficiency.

It is unclear whether metformin caused hemolysis directly in this case or via G6PD deficiency. Two other patients have been reported with normal G6PD activity (63,64); one had a positive Coombs' test (64).

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Gastrointestinal

Abdominal discomfort is frequent with metformin (15–25%), and nausea, vomiting, and diarrhea occur even in the absence of lactic acidosis. Other effects include flatulence, abdominal bloating, anorexia, and a metallic taste. Anorexia and weight loss are often seen at the beginning of treatment. Phenformin can cause hemorrhagic gastritis (65).

The gastrointestinal adverse effects of metformin can be reduced by giving the metformin during or immediately after meals, starting with a low dose and increasing it gradually (41).

In 43 patients with poorly controlled type 2 diabetes using insulin, the addition of metformin improved HbA_{1c} and reduced the dose of insulin (66). Seven patients in the metformin group and four in the placebo group had nausea; nine versus four had diarrhea.

- Three patients who had taken metformin for more than 2 years developed diarrhea (67). After withdrawal of metformin the diarrhea resolved within 1 month. A fourth patient developed diarrhea after taking metformin for 4 months, which stopped after withdrawal; rechallenge with metformin 8 months later led to recurrence. Three of these patients had bowel disease (diverticulosis, irritable bowel syndrome, and diabetic neuropathy).
- A 49-year-old woman developed chronic diarrhea after using metformin 850 mg tds and insulin for 5 years (68). After 5 months, metformin was withdrawn and the diarrhea resolved within 3 days. On rechallenge the diarrhea returned.
- A 44-year-old non-diabetic man took metformin 1700 mg/day for some weeks for obesity (69). He developed severe gastrointestinal hemorrhage needing blood transfusion. A bleeding Meckel's diverticulum was removed and he had no further hemorrhage. Coagulation studies, to investigate whether reduced platelet aggregation or altered coagulation factors (increased tissue plasminogen activator (tPA) or reduced tPA-Ag, or PAI-1) could have contributed, were not done.

Liver

Metformin can cause hepatitis (70).

- A 52-year-old woman took glipizide and enalapril and then, because of persistent hyperglycemia, metformin 1000 mg/day (71). Her liver enzymes were normal, and after 2 weeks the dosage of metformin was increased to 2000 mg/day. Two weeks later she became icteric and her bilirubin and liver enzymes were increased. Serological studies were negative. All drugs were withdrawn. A liver biopsy was consistent with toxic hepatitis. She had normal liver enzymes after a month.

Hepatitis after sulfonylureas is known, and this patient had taken glipizide for several years. The combination of glipizide and metformin may have been to blame.

- A 75-year-old man taking insulin about 40 U/day was given metformin 500 mg bd (72). He also used enteric-coated aspirin, diltiazem XR, ibuprofen, and lovastatin. Two months later his liver enzymes were raised, but he felt well. Hepatitis antibodies were negative. After withdrawal of metformin his liver enzymes became normal. He agreed to restart metformin. His liver enzymes remained normal, but he finally preferred insulin monotherapy.

It is not clear what caused the hepatitis in this case, although it seems that metformin was not to blame.

- A 64-year-old man developed cholestatic jaundice 2 weeks after starting to take metformin 500 mg bd (73). It resolved slowly over several months after withdrawal.

Pancreas

Phenformin can cause pancreatitis (74).

Skin

Urticaria and rashes are seen occasionally with metformin. Lichen ruber planus has been reported (75).

Immunologic

Leukocytoclastic vasculitis and pneumonitis have been attributed to metformin (76,77).

Death

In 2275 diabetic patients aged 45–74 years compared with 9047 non-diabetics with proven coronary artery disease, 32% of those taking metformin and 44% of those taking combined metformin and glibenclamide died during 7.7 years (78). After 4 years the risks of death with metformin alone and combined therapy were equal, but after 7 years combined therapy had a worse prognosis.

Second-Generation Effects

Lactation

Metformin is increasingly being used in the polycystic ovarian syndrome and therefore in lactating women. In seven breastfeeding mothers taking a median dose of 1500 mg/day, the mean relative infant dose transferred in the milk was 0.28% (79). Serum metformin concentrations were very low or undetectable in infants and they appeared to be healthy. A specific warning was given for children with impaired renal function (prematurity, renal insufficiency).

Susceptibility Factors

Age

The effect of age on the response to metformin has been studied in 174 patients aged over 70 years, not well-controlled on glibenclamide 7.5 mg/day or gliclazide 120 mg/day (80). They were given either maximal doses of a sulfonylurea (glibenclamide 15 mg/day or gliclazide 240 mg/day) or a sulfonylurea + metformin (1700 mg/day). Renal function and liver function were normal. There were nine cases of non-severe hypoglycemia in the first group. In the second group there were two cases of hypoglycemia after delayed meals and 35% had transient mild gastrointestinal discomfort. There were no increases in lactic acid. Lipid

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concentrations were a little lower in the second group. The authors concluded that age as such is not a contraindication to metformin, provided that contraindications, such as renal impairment, are absent and that blood glucose is measured regularly.

Drug Administration

Drug overdose

The regional poison centers certified by the American Association of Poison Control have reported 55 cases of metformin ingestion by children (81). Unintentional ingestion of 1700 mg of metformin did not pose health risks. In 21 children tested for blood glucose, lactate, or electrolytes, there was no evidence of lactic acidosis. Plasma metformin concentrations were not determined.

- A 37-year-old woman purposely took metformin 10 g (82). She did not develop hypoglycemia, but the serum lactate increased to 3.2 mmol/l (reference range under 2.1 mmol/l) and she became nauseated. She recovered.
- A healthy 21-year-old woman took metformin 45 g (53×850 mg) in a suicide attempt and developed acute pancreatitis with metabolic acidosis (pH 6.96), hypoglycemia (1.3 mmol/l), and an anion gap of 37 mmol/l (83). She was given 290 g of dextrose, and her blood glucose rose to 25 mmol/l. Other laboratory tests were normal. When later measured, serum amylase was 121 U/l, urinary amylase 97 U/l (both twice the upper limit of the reference range), and serum lipase 724 U/l (5–6 times raised). A CT scan with contrast showed stage B acute pancreatitis. Serum amylase and serum lipase rose to 368 and 1900 U/l respectively. She recovered after 8 days. A CT scan 1 month later was normal. Lactic acid and metformin were not determined. The use of alcohol or other drugs that can cause pancreatitis could not be established. Gallstones and hyperlipidemia were not present. The initial hypoglycemia could have been a direct effect of metformin; hyperglycemia is more often seen during lactic acidosis.
- A non-diabetic 25-year-old woman died after 2 days of lactic acidosis and multiple organ failure, having taken an unknown amount of her father's metformin (38,84).
- A 58-year-old woman with type 2 diabetes took an overdose of metform in 55 g plus 100 mg of glibenclamide and 3.1 g of acarbose (38,84). She developed lactic acidosis and survived with hemodialysis.

When a patient in coma has an unexplained anion gap, a suicide attempt with metformin should be considered.

Drug–Drug Interactions

Alpha-glucosidase inhibitors

Metformin can be effectively combined with miglitol (SEDA-25, 514) but metformin may accumulate in the gastrointestinal wall, and the combination of metformin with acarbose or miglitol may reduce the absorption of metformin (85,86).

Cephalexin

In a double-blind, randomized, crossover study in 12 healthy volunteers, cefalexin 500 mg increased the C_{max} and AUC of a single dose of metformin 500 mg by 34 and 24% respectively and reduced its renal clearance to 14% (87). The authors suggested that cefalexin inhibits the renal tubular secretion of metformin.

Contrast media for radiological investigations

Radiocontrast media can induce acute renal insufficiency in patients taking metformin (88,89). Metformin should be withdrawn 2 days before an iodinated contrast medium is given (SEDA-21, 445) and the following protocol has been suggested (90):

- take a blood sample for creatinine baseline estimation before giving a contrast medium;
- withdraw metformin 48 hours before the investigation;
- if the urine output is normal for 48 hours after the radiological procedure the patient can resume metformin;
- when it is discovered after a procedure that the preinvestigation creatinine was raised (since the procedure may be carried out before the creatinine is known), the patient's physician should be contacted and the creatinine must be measured again within 48 hours.

Since January 1998 the package insert approved by the FDA has stated: "Glucophage (metformin) should be discontinued at the time of or prior to the procedure and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal" (91).

Multiple drugs

The combination of metformin with other drugs that can lower the blood glucose concentration can result in severe hypoglycemia.

- A 79-year-old woman was admitted to hospital stuporose and unresponsive (92). She had taken metformin 850 mg bd for 14 days, during which time she complained of loss of appetite and consumed little starch. On that morning she had had nausea and dizziness. Her blood glucose was 2.0 mmol/l and her serum potassium 3.3 mmol/l. A CT scan of the head was normal.

The combination of metformin, which itself does not cause hypoglycemia, with an ACE inhibitor, nitrofurantoin, and an NSAID, which all have glucose-lowering effects, and poor food intake may have led to hypoglycemia in this case.

NSAIDs

Drug interactions can precipitate metformin-induced lactic acidosis, as has been reported after the addition of indometacin (93).

- A 57-year-old woman, who had taken metformin 500 mg bd for 15 years, took indometacin 50 mg qds for 2 months. She developed oliguria and acidosis (pH 6.82, serum lactate 21 mmol/l, creatinine 480 μmol/l). After stopping metformin and indometacin she

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improved and left hospital with stable impaired kidney function.

The authors reported that two other cases of metformin-associated lactic acidosis with concurrent NSAID therapy have been reported to the Committee on Safety of Medicines in the UK. Indometacin can impair kidney function and may have done so in this case. Phenformin can cause tubular damage and oliguria in animals (94) and so it is conceivable that metformin-induced renal damage may also have contributed.

Phenprocoumon

The clearance of phenprocoumon was increased by metformin, perhaps because of increased liver blood flow (95).

Rosiglitazone

In 16 male volunteers aged 22–55 years, rosiglitazone 2 mg bd had no effect on the steady-state pharmacokinetics of oral metformin 500 mg bd; there were no clinically significant episodes of hypoglycemia and blood lactic acid concentrations did not increase (96).

Warfarin

Potentiation of the anticoagulant action of warfarin by phenformin has been reported (97).

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Bile acids

General Information

The bile acids are used in the long-term treatment of cholesterol gallstones. Ursodeoxycholic acid is the 7-epimer of chenodeoxycholic acid. Tauroursodeoxycholic acid is a derivative of ursodeoxycholic acid.

Observational studies

In a retrospective review of medical records over 12 months, ursodeoxycholic acid (20 mg/kg/day) reduced serum bilirubin concentrations in four of five children with cholestasis and hyperbilirubinemia (1). No adverse effects were reported.

Placebo-controlled studies

In a randomized placebo-controlled study in 219 patients with histology-proven chronic hepatitis (44 HbsAg-positive and 149 anti-HCV antibody-positive) and persistently raised transaminases, oral ursodeoxycholic acid 300 mg bd for 6 months produced significant improvement in clinical and biochemical markers (2). Apart from diarrhea, which was reported by a few patients, it was well tolerated.

The combinations of oral ursodeoxycholic acid 13–15 mg/kg/day plus interferon (3 MU three times a week) and interferon plus placebo for 6 months have been compared in a randomized, placebo-controlled study in 91 patients with chronic hepatitis C resistant to interferon (3). Combined interferon plus ursodeoxycholic acid was more effective than interferon alone in terms of normalizing alanine transaminase at 6 months (but not at 12 months), but not in terms of virological response. The frequency of adverse effects was similar in the two groups. Diarrhea, which was reported by a few patients, was the only adverse effect attributable to ursodeoxycholic acid.

The long-term effects of ursodeoxycholic acid 14–16 mg/kg/day has been investigated in a double-blind, placebo-controlled, multicenter trial in 192 patients with primary biliary cirrhosis (4). Ursodeoxycholic acid was associated with significant improvement in liver function tests and liver histology, but it did not affect the time to death or liver transplantation. Adverse effects were mild: abdominal pain, flatulence, and diarrhea were reported in nine patients taking ursodeoxycholic acid and six taking placebo.

High-dose ursodeoxycholic acid (20 mg/kg/day) has been compared with placebo in the treatment of primary sclerosing cholangitis in a 2-year double-blind preliminary study in 26 patients (5). High-dose ursodeoxycholic acid did not influence symptoms, but

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resulted in significant improvement in liver biochemistry and a significant reduction in the progression of cholangiographic appearances and liver fibrosis, as assessed by disease staging. No significant adverse effects were reported.

Ursodeoxycholic acid 250 mg tds plus ofloxacin 200 mg bd has been compared with ursodeoxycholic acid alone in the prevention of occlusion of biliary stents in a randomized trial in 52 patients with inoperable obstructive jaundice (6). Combination treatment was not superior to ursodeoxycholic acid alone. There was no significant difference in the frequency of adverse events between the two groups.

General adverse effects

Mild diarrhea and slightly raised serum transaminases are very common with chenodeoxycholic acid, while ursodeoxycholic acid seldom causes significant diarrhea or hypertransaminasemia. This difference is puzzling, since ursodeoxycholic acid, like chenodeoxycholate, is metabolized to lithocholate, and some if not all animal studies have shown evidence of hepatotoxicity. One undesirable property of ursodeoxycholic acid is that occasionally treatment is followed by the development of resistant (and radio opaque) coatings to gallstones, thus retarding or preventing further dissolution. Neither hypersensitivity nor tumor-inducing effects reactions have been reported.

Experience with tauroursodeoxycholic acid is limited. It is less effective than ursodeoxycholic acid and causes more adverse effects. Two patients who took tauroursodeoxycholic acid for primary biliary cirrhosis developed severe right upper quadrant pain, and rechallenge with tauroursodeoxycholic acid was positive (7).

Organs and Systems

Metabolism

Although most studies have shown no consistent effects of chenodeoxycholic acid on serum cholesterol concentrations, in the National Cooperative Gallstone Study there was a 10% increase over a 2-year period in treated people compared with a 5% rise in controls (8). Low-density lipoprotein concentrations rose in association; other varieties were unaffected.

Gastrointestinal

About half of all patients given the usual dose of chenodeoxycholic acid, 15 mg/kg/day, develop diarrhea, because the unabsorbed bile acid causes water to be secreted into the large bowel (9). The symptoms remit with dosage reduction and may not recur if the dose is then slowly increased again. It is best avoided in inflammatory bowel disease.

Liver

Serum transaminases tend to double or triple in the early weeks of treatment with chenodeoxycholic acid in about one-third of patients (10). There is a hypothesis that this is due to impaired lithocholate sulfation. Lithocholic acid is formed by the 7-dehydroxylation of chenodeoxycholic acid and is ordinarily inactivated by sulfation. However, hypertransaminasemia has been detected in nearly 75% of people with a low sulfation capacity (this capacity being bimodally distributed) and in less than one in 10 of those with a high capacity. All the same, chenodeoxycholic acid is substantially, if not totally, devoid of serious hepatotoxic actions. Liver biopsy has shown no significant changes; minor changes can include fatty change and lipofuscin accumulation.

Skin

- Lichenoid skin eruptions have been reported in a 1-month-old infant with neonatal hepatitis 3 weeks after the administration of ursodeoxycholic acid (11). There was complete resolution after withdrawal of ursodeoxycholic acid and treatment with glucocorticoids.
- Lichenoid eruptions have been reported in a 61-year-old man with gallstones who took ursodeoxycholic acid 600 mg/day for a few weeks (12). The eruption improved on withdrawal, but recurred when ursodeoxycholic acid was reintroduced 3 months later.

Lichen planus developed in one patient taking a combination of chenodeoxycholic and ursodeoxycholic acid (SEDA-17, 428).

Second-Generation Effects

Teratogenicity

The clinical and biological effects and safety of ursodeoxycholic acid in intrahepatic cholestasis of pregnancy have been reported in 19 patients, 14 of whom had clinical improvement, with reduction or disappearance of pruritus, and 11 of whom had an improvement in biochemical liver function tests (13). The only birth defect reported was pyloric stenosis in a boy whose mother had taken ursodeoxycholic acid for 10 days at 34 weeks gestation.

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Bimatoprost

See also Prostaglandins

General Information

Bimatoprost is an analogue of $PGF_{2\alpha}$, used to treat glaucoma. It is believed to lower intraocular pressure by increasing the outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes.

Organs and Systems

Sensory systems

Bimatoprost can cause gradual darkening of the color of the eyes and the eyelid skin, increased thickness, numbers and darkness of eyelashes, conjunctival hyperemia, and ocular pruritus (1). Darkening of the iris occurs in 1.1% of patients (2).

Hair

Eyelash growth was reported in 36–48% of patients after 6 months of using bimatoprost (2).

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Biotin

See also Vitamins

General Information

Biotin is a water-soluble vitamin of the B complex (vitamin B_{10}, also called vitamin H), and is found in many foods, especially eggs and liver. Biotin is involved in the action of four carboxylases:

- acetyl-CoA carboxylase, which catalyses the binding of bicarbonate to acetyl-CoA to form malonyl-CoA in the synthesis of fatty acids
- pyruvate carboxylase, which is involved in gluconeogenesis
- methylcrotonyl-CoA carboxylase, which catalyses an essential step in the metabolism of leucine
- propionyl-CoA carboxylase, which catalyses essential steps in the metabolism of amino acids, cholesterol, and fatty acids.

Although biotin has been proposed as a treatment for diabetes mellitus, brittle nails, and hair loss, there is little good evidence of its efficacy in these conditions. It has also been used as a skin-conditioning agent in many cosmetic products in concentrations of 0.0001–0.6% (1).

Organs and Systems

Cardiovascular

Eosinophilic pleural effusion with eosinophilic pericardial tamponade has been attributed to concomitant use of pantothenic acid and biotin (2).

- A 76-year-old woman developed chest pain and difficulty in breathing. She had no history of allergy and had been taking biotin 10 mg/day and pantothenic acid 300 mg/day for 2 months for alopecia. Chest X-rays showed pleural effusions and cardiac enlargement. Blood tests showed an inflammatory syndrome, with an erythrocyte sedimentation rate of 51 mm/hour and an eosinophil count of $1.2–1.5 \times 10^9$/l. Pericardiotomy showed an eosinophilic infiltrate. There was no evidence of vasculitis. Serological studies were negative for antinuclear antibodies, rheumatoid factor, viruses, bacteria, and Lyme disease. Stool examination and parasitological serologies were negative. A malignant tumor was excluded by mammography, thoracoscopy, and a CT scan. Myelography, a biopsy specimen of the iliac crest bone, and the concentrations of IgE,

lysozyme, and vitamin B_{12} were also normal. A week after withdrawal of pantothenic acid and biotin she improved dramatically and her eosinophilia resolved.

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Biperiden

See also Anticholinergic drugs

General Information

Biperiden is given orally in doses rising from 2 to 6 mg/day, more being given in individual cases. Of the anticholinergic effects that biperiden can cause, drowsiness seems to be one of the most prominent, and it should not be given to patients who have to drive motor vehicles. A dose of 12 mg has been reported to precipitate involuntary movements in some cases of parkinsonism (SEDA-1, 120).

Organs and Systems

Skin

Contact dermatitis has been attributed to biperiden (1).

Long-Term Effects

Drug withdrawal

Insomnia occurred after biperiden withdrawal in two patients with schizophrenia (2).

Drug-Drug Interactions

Haloperidol

In eight healthy men volunteers biperiden 2 mg reduced the serum haloperidol concentrations increased by carteolol 10 mg (3).

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Bismuth

General Information

Bismuth is a brittle reddish-white metallic element (symbol Bi; atomic no. 83). It enjoyed great popularity up to the early 20th century, and thereafter continued to be used in the form of insoluble bismuth compounds, used for their supposed effects on the gastric wall as antacids, protective coatings, or inhibitors of proteolytic activity. The use of bismuth was particularly heavy in Australia, where bismuth subgallate was commonly used in postcolectomy or postileostomy patients, and in France, where bismuth subnitrate and other salts were widely self-administered for both gastric and intestinal conditions.

Bismuth salts are still in use. Tripotassium dicitratobismuthate and bicitropeptide (a bismuth-peptide complex) are used in the eradication of *Helicobacter pylori* in combination with antibiotics (SEDA-21, 233) (1–4), and ranitidine bismuth citrate is used to treat peptic ulcer (5). Bismuth salicylates are used in other intestinal diseases, such as microscopic colitis (6,7) and collagenous colitis (8). Bismuth subnitrate plus iodoform is used to pack surgical cavities. Bismuth oxide and bismuth subgallate are found in some topical formulations that are used for treating hemorrhoids. Bismuth is also used topically as a bacteriostatic.

Bismuth compounds are also used as hemostatic compounds (9). A uniform technique of tonsillectomy, including the use of bismuth subgallate and re-assessment of the tonsillar fossae after a 3-minute observation period, reduced the incidence of primary tonsillar hemorrhage in a retrospective study of 705 children (10). However, in a randomized study of 204 patients the evidence for the use of bismuth subgallate as a hemostatic agent in tonsillectomy was weak (11). Bismuth iodoform paraffin paste is commonly used in ear, nose, and throat surgery and in oral and maxillofacial surgery. A new area for the use of bismuth compounds may be in oncology as anticancer agents (12).

Due to the formation of an insoluble bismuth chloride complex in the gastric juice after oral administration of bismuth salts, the diffusion of the bismuth ion into the circulation is delayed. During treatment with tripotassium dicitratobismuthate, plasma concentrations of bismuth rise to 10–20 μmol/l which are not regarded as toxic. From experience over somewhat more than 20 years it would seem that the inherent risks of bismuth intoxication are relatively small if these compounds are used within the recommended ranges of dosage and length of treatment. However, they too can be abused, resulting in renal tubular damage (SEDA-18, 241) and attention has been drawn to the possible risks resulting from the ready absorption of citrate (13).

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Placebo-controlled studies

Data from 20 clinical studies in 5000 patients who had taken ranitidine bismuth citrate (200, 400, or 800 mg bd) have been reported (14). The incidence of adverse events was not different from that associated with placebo and was independent of dose. The most common events (>1% of patients) were upper respiratory tract infections, constipation, diarrhea, nausea, vomiting, dizziness, and headache, the last being the only event reported by over 2% of the patients. Adverse events considered by the clinical investigator to be adverse reactions occurred with a similar frequency amongst patients given ranitidine bismuth citrate (8%), ranitidine hydrochloride (6%), and placebo (6%). The incidence of adverse reactions was greater when amoxicillin (11%) or clarithromycin (20%) were co-prescribed.

Organs and Systems

Respiratory

There has been a single report of a lung disorder with cough, which was traced to intravenous injection of a so-called "health tonic" containing bismuth, which had resulted in bismuth-containing subpleural opacities in the lungs (15).

Two cases of respiratory complications following the use of bismuth gallate have been reported (9).

- A 19-month-old boy with reactive airways disease had a tonsillectomy and adenoidectomy and bismuth-coated sponges were used for hemostasis. Excessive bleeding was not reported. In the recovery room he developed difficulty in breathing, and required oxygen followed by bronchodilators and deep suctioning. A chest X-ray showed speckled opacities throughout the lung fields and in the oropharynx and nasopharynx, probably due to aspiration of bismuth particles. He went on to develop a pneumonitis.
- An 8-year-old girl with asthma underwent tonsillectomy and adenoidectomy; hemostasis was performed with bismuth–adrenaline paste. A small amount of bismuth was noted in the endotracheal tube before extubation, and in the recovery room she developed respiratory difficulty associated with nasal flaring and sternal retraction. A chest X-ray showed aspirated radio-opaque material outlining the tracheobronchial tree and early pulmonary infiltrates.

Both patients had a history of refractory airway disease that put them at risk of respiratory complications after bismuth aspiration. Fortunately neither developed any serious respiratory compromise immediately after aspiration or required intubation.

Nervous system

From 1973 onward many cases of an encephalopathy were reported among bismuth users. By 1979, 945 cases had been recorded in France alone, 72 of them fatal; the worldwide total exceeded 1000 cases. Bismuth encephalopathy is characterized by ataxia, confusion, speech disorder, and myoclonus. The subgallate and oxychloride have been implicated, as has the subcitrate when used in a patient with impaired bismuth clearance. The chelate tripotassium dicitratobismuthate, which contains very small amounts of bismuth, appears to be safe in this respect for normal use, as does the occasional use of more traditional bismuth products for conditions such as travelers' diarrhea. Use of bismuth subnitrate ("Roter" tablets) does not seem to lead to metal absorption (16), but such absorption does occur from bismuth salicylate (17).

- A 49-year-old woman with chronic gastric ulcers and 5 years of bismuth abuse developed bismuth encephalopathy, with progressive dementia, dysarthria, and myoclonic jerks 1 week after increasing the dosage of bismuth (18). Electroencephalography showed generalized spike-wave complexes, suggesting that the myoclonus was epileptic in nature. Bismuth was withdrawn and she was given valproate, which reduced the frequency of the myoclonic jerks. Administration of the chelator dimercaptopropane sulfonic acid (DMPS) enhanced bismuth elimination but aggravated the clinical symptoms and it was therefore withdrawn. She slowly recovered.
- An 86-year-old woman underwent partial maxillectomy for squamous cell carcinoma of the right alveolus and hard palate, and the maxillary antrum was packed with a length of bismuth iodoform paraffin paste (19). Postoperatively she developed delirium and by day 5 was exhausted, light-headed, and unsteady. She became increasingly aggressive and by day 11 was eating very little and having fainting episodes. Worsening confusion and some paranoid ideation was apparent and tremor was pronounced, but there were no focal neurological signs. The bismuth iodoform paraffin pack was removed on day 14 and 7 days later she had improved and was very cooperative and alert when she was discharged 5 days later. The bismuth serum concentration on day 14 was 146 nmol/l (reference range 0–4 nmol/l) and on day 22 was 81 nmol/l. The original peak bismuth concentration was extrapolated to over 300 nmol/l.

Three phases of the encephalopathy that bismuth can cause can be distinguished (SEDA-4 167) (20):

1. *Prodromal phase* This is characterized by such vague complaints as weakness, mental slowness, short memory, reduced working capacity, insomnia, headache, and anxiety. These symptoms can easily be dismissed as non-specific, and can persist for more than 2 years before further signs develop. In general, however, the course is gradually progressive toward the symptoms of the next phase.
2. *Acute phase* Sudden deterioration to an acute encephalopathy occurs over a period ranging from several hours to 1–2 days. Patients develop dysarthria, severe locomotor disturbances such as ataxia, difficulty in walking, intention tremor, myoclonic jerks (especially of the upper limbs, face, and trunk), incontinence due to loss of sphincter control, hyper-reflexia, and sometimes generalized convulsions. The patient may be confused, disoriented, and agitated. Excitation, hallucinations, delirium, and fluctuations of mental alertness, ranging from dizziness to loss of consciousness and coma, can occur. In about 7–9% of cases the outcome is fatal,

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owing to bronchopulmonary, cardiovascular, thromboembolic, or infectious complications.

3. *Recovery phase* After withdrawal of bismuth, the toxic symptoms usually abate rapidly, although physical and psychological weakness, depressive mood, memory impairment, intellectual deterioration, sleep disturbances, headache, and other symptoms occasionally persist for several months, and in isolated cases for more than a year. Exceptionally, psychic and intellectual capacity remain permanently impaired.

The reason for the suddenness of the outbreak of bismuth encephalopathy in the 1970s after the drug had been used for so many years is uncertain. A major French epidemiological study undertaken at the time (SEDA-6, 217) failed to detect any clear link to particular dosage habits, topographical factors, or drug interactions. Unknown environmental factors may have altered either the effects of bismuth itself or the sensitivity of the brain. It was later suggested that a change in intestinal flora converted bismuth salts into more soluble neurotoxic compounds (21), although it is not clear why this should have happened during the 1970s. Since measures were taken to counter the traditional use of bismuth, only very occasional new cases of encephalopathy have been reported since then. It is currently unresolved whether the lower doses of bismuth in gastric powders, antacids, astringents, demulcents, purgatives, and antidiarrheal formulations that are still in use are in the long run innocuous; if an unknown environmental factor did indeed lead to toxic manifestations with the older products, it might similarly modify the effects of others; watchfulness is therefore essential. In fact, one suspects something of a renaissance of bismuth encephalopathy in the 1990s; in 1993 cases were reported from several countries, associated inter alia with abuse of bismuth subsalicylate (Pepto-Bismol) (22) and the use of bismuth subgallate (23).

As late as 1994 a toxic encephalopathy, relapsing but reversible, was reported in a woman who had received a large dose of bismuth when bismuth iodoform paraffin paste was inserted extradurally (24). Elsewhere neurotoxicity has been reported (SEDA-19, 446).

Mouth and teeth

A black tongue was reportedly caused by exogenous pigment in chewable bismuth subsalicylate tablets.

- A 51-year-old white woman developed black discoloration of her tongue (25). The black substance was easily removed by scraping the surface of the tongue. She denied using tobacco products or alcohol. Her medications included alprazolam, montelukast, amitriptyline, hydroxychloroquine, triamcinolone acetonide, omeprazole, cisapride, and calcium carbonate. She had recently started to chew three to six bismuth subsalicylate tablets daily. She was advised to stop using bismuth subsalicylate and to brush her tongue with a soft-bristled toothbrush. The discoloration improved within a couple of hours and eventually disappeared completely. She continued to take hydroxychloroquine, a known cause of oral mucosal pigmentation.

Gastrointestinal

The results of a comparative trial suggested that the adverse reactions most commonly encountered during courses of treatment including bismuth and designed to eliminate *H. pylori* are vomiting, diarrhea, abdominal pain, headache, and a metallic taste in the mouth (SEDA-22, 393) (26).

Constipation is an occasional adverse effect of bismuth therapy. The feces are grey or black, and can be mistaken for melena (27).

Biliary tract

- Acute cholecystitis caused by non-O1 *Vibrio cholerae* has been described in a 55-year-old healthy traveler immediately after a vacation in Cancun, Mexico (28). During his vacation he had taken the Pepto-Bismol brand of bismuth subsalicylate 30 ml tds as prophylaxis against traveler's diarrhea. At surgery his gall bladder was acalculous, inflamed, distended, and nearly ruptured. Pathogenetic factors may have included the use of bismuth subsalicylate, distension of the gall bladder from illness-induced fasting, and bacterial toxins in the gall bladder.

The authors implied that bismuth subsalicylate could have prevented the secretory diarrhea that is seen in many infections with non-O1 *V. cholerae*. Diarrhea would result in evacuation of many organisms from the small bowel. Bismuth subsalicylate might have impaired this mechanism and increased the number of organisms with access to the common bile duct at the ampulla of Vater.

Urinary tract

Some reviewers have claimed that bismuth can cause reversible acute renal insufficiency, but if this indeed occurs it must be excessively rare; it might be part of a nephrotic syndrome.

Skin

- A man who had taken bismuth subsalicylate after heavy meals once or twice a month for the previous 4 years developed crops of small, black, carbon-like particles (size range 0.2–0.5 mm) on the skin (29). The palms and soles were not involved. These particles appeared at intervals of 15–30 days and persisted for 2 or 3 days if not removed by soap and water. They were located in follicular orifices and caused no symptoms; they tested positive for bismuth. The condition receded completely after bismuth was withdrawn (30).

Musculoskeletal

Osteoarthropathy was an associated feature in some 3% of patients with bismuth encephalopathy. However, at least one case is on record in which a bismuth osteoarthropathy developed without any manifestation of encephalopathy (31). The symptoms mainly involve one or both shoulders, of which painful restriction of movement is usually the first sign in the postacute phase of bismuth encephalopathy. This can persist for several months after bismuth has been withdrawn. X-ray examination shows an

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osteolytic deforming glenohumeral osteoarthropathy with necrosis of the humeral head. Unilateral or bilateral fractures can occur. The lesions described can regress without sequelae over several months and osteonecrosis can also proceed to complete lysis of the humeral head.

The fact that much bismuth is ordinarily stored in the skeleton may be relevant in the etiology of bismuth osteoarthropathy. In two reported cases a differing type of osteopathy occurred, associated with different localization of the pathological lesions and with unusually high bismuth concentrations in the bone: both patients had received bismuth injections for syphilis many months or even years before (SEDA-4, 169).

Immunologic

Sensitization to bismuth derivatives has been reported but is rare.

- A 33-year-old woman with atopic hand eczema and allergic rhinitis was given Noviform, an eye ointment containing bibrocathol (bismuth oxide and tetrabromocathechol), for periorbital dermatitis and noticed an exacerbation of her dermatitis (32). A patch test was positive for bismuth oxide.

Anaphylaxis to bismuth subsalicylate (Pepto-Bismol) has been observed (33).

- A 25-year-old man with symptoms of acute gastroenteritis took Pepto-Bismol, a total of eight caplets over 6 hours. About 30 minutes after the last dose, he developed generalized acute urticaria. He had previously tolerated Pepto-Bismol well, but had presumably become sensitized. He was successfully treated with intravenous fluids and histamine H_1 receptor antagonists.

Second-Generation Effects

Teratogenicity

Very little is known about the use of bismuth in pregnancy, but in documented cases mothers affected with bismuth encephalopathy during pregnancy gave birth to healthy infants.

Susceptibility Factors

Renal disease

Bismuth is predominantly excreted via the kidney and would be expected to accumulate in patients with renal insufficiency. It is not impossible that combined exposure to bismuth and other metals could render the patient more susceptible to bismuth toxicity; the parallels between the complications seen here and with other light metals (zinc, aluminium) are striking.

Drug Administration

Drug administration route

Severe systemic intoxication in the past has been observed after incautious use of bismuth salts on extensive wound areas.

Drug overdose

Renal damage has been reported in cases of bismuth overdose.

- A 17-year-old girl took 25 tablets of bismuth subcitrate 300 mg (total 7.5 g) in a suicide attempt and developed severe renal insufficiency (34). Renal biopsy showed evidence of acute tubular necrosis, with epithelial flattening, lumen widening, and atrophic changes in the convoluted tubules and mononuclear cell infiltration and edema in the interstitium. She was managed with hemodialysis and recovered.
- A 22-year-old woman took 5.4 g of colloidal bismuth subcitrate in a suicide attempt and developed Fanconi's syndrome and acute renal insufficiency (35). She received hemodialysis and intravenous sodium 2,3-mercapto-1-propanesulfonate 60 hours after intoxication. Her serum bismuth concentrations fell from 640 to 15 μg/l within 6 days, her renal function improved, and her tonsillar ulceration healed. Hemodialysis was discontinued on day 14. She had normal renal function 6 weeks later.
- Reversible bismuth nephrotoxicity was reported in a 16-year-old girl who had nausea, vomiting, and dizziness for 4–5 days and oliguria for 2 days (36). She had taken an overdose of tripotassium dicitratobismuthate tablets containing a total amount of 3.0–4.5 g of bismuth. Blood urea and serum creatinine were increased and there was proteinuria and erythrocytes in the urine. Acute tubular necrosis was observed on biopsy.

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Bisoprolol

See also Beta-adrenoceptor antagonists

General Information

Bisoprolol is a highly selective $beta_1$-adrenoceptor antagonist. Its adverse effects profile is similar to that of atenolol (1), and despite theoretical benefits there is no convincing clinical evidence that bisoprolol has an advantage (2).

Organs and Systems

Metabolism

Bisoprolol can increase serum triglycerides and reduce HDL cholesterol (3).

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Bisphosphonates

General Information

The development of bisphosphonates for clinical purposes began with the discovery that inorganic pyrophosphate is present in blood and urine and inhibits the precipitation of calcium and phosphate (1). Derivatives of pyrophosphate had been widely used for industrial purposes, because they inhibit the precipitation of calcium carbonate. Their principal use was as antiscaling additives in washing powders, water, and oil brines, to prevent deposition of calcium carbonate scale. It was then found that pyrophosphate binds strongly to calcium phosphate, prevents both the formation and dissolution of calcium phosphate crystals, and inhibits calcification in vitro. The bisphosphonates are used to treat bone diseases characterized by increased osteoclastic bone resorption (2). Long-term administration of low doses of oral bisphosphonates is considered to be valuable in patients with postmenopausal osteoporosis (3,4).

Adverse effects of the bisphosphonates include low-grade transient fever and headache; other effects are asymptomatic hypocalcemia, hypophosphatemia, and hypomagnesemia (5–7).

Alendronate

Alendronate is an aminobisphosphonate with general properties similar to those of the other bisphosphonates. It inhibits bone resorption and is used in osteoporosis and Paget's disease of bone. It has also been used in the treatment of bone metastases and hypercalcemia of malignancy.

Clodronate

Clodronate is a bisphosphonate that has demonstrated efficacy in patients with a variety of disorders of enhanced bone resorption, including Paget's disease, osteolytic bone metastases, and hypercalcemia of malignancy (8,9). In preclinical studies, clodronate prevented bone loss during immobilization (10).

Etidronate

Etidronate, an alkylbisphosphonate, was the first to be introduced for the management of bone resorption disorders. Subsequently, a cyclic regimen of etidronate followed by calcium supplementation was established in the treatment of osteoporosis.

Pamidronate

Pamidronate in the disodium form, a second-generation bisphosphonate, has an intermediate antiresorptive activity; its continuous administration produces rapid suppression of bone resorption. Unlike etidronate, it does not impair bone mineralization at therapeutic dosages in patients with Paget's disease. Pamidronate inhibits osteoclast activity primarily by binding with hydroxyapatite crystals in the bone matrix, preventing the attachment of osteoclast precursor cells. Other mechanisms of action of matrix-bound pamidronate may include direct inhibition of mature osteoclast function, promotion of osteoclast apoptosis, and interference with osteoblast-mediated osteoclast activation. In patients with osteoporosis, pamidronate increased bone mineral density by 6.8% over 2.2 years (11). The frequently observed adverse effects with pamidronate therapy were gastrointestinal: gastritis due to either a local reaction when a high concentration of the drug stays in the mucus or by chelation with calcium ions (12).

Residronate

Residronate is a pyridinylbisphosphonate with potent antiresorptive properties. In animal studies it was about 1000 times more potent than etidronate and 3-5 times more potent than alendronate (13), which enables the use of a lower dose and a shorter treatment regimen, with consequent potential minimization of adverse effects. In a randomized, double-blind, multicenter study of the efficacy, safety, and tolerability of residronate in 62 patients taking oral residronate for Paget's disease of bone, adverse effects were recorded in 29 patients (14). Twelve had upper gastrointestinal adverse events, of which three were moderate to severe. Four other patients withdrew because of adverse events, but one only was considered to be possibly drug-related (mild colitis). There was a transient reduction in serum calcium and phosphorus concentrations, greatest at 1 month after the start of treatment, and followed by a gradual return toward baseline concentrations.

Comparative studies

In 72 postmenopausal women (mean age 65 years) with established osteoporosis who took elemental calcium 1.0 g/day and vitamin D 400 U/day, etidronate and hormones were compared (15). The Hormone Replacement Therapy (HRT) group ($n = 18$) took cyclical estrogen and progesterone; the etidronate group ($n = 17$) took intermittent cyclical etidronate; and the combined therapy group ($n = 19$) took both HRT and etidronate. Three patients in the HRT group and two patients in the combined therapy group withdrew owing to estrogen-related adverse effects. One patient each from the control group and the etidronate group withdrew because of inability to tolerate the medications. Two patients each from the control and combined therapy groups, and one from the etidronate group withdrew owing to other medical problems. There was one death due to myocardial infarction in the etidronate group, and one patient in the control group was lost to follow-up. Six patients complained of nausea after etidronate, but symptoms improved with time.

In 32 women treated for postmenopausal osteoporosis for 2 years with either pamidronate or with oral fluoride, adverse effects were a transient fever with influenza-like symptoms in five patients after the first infusion of pamidronate, and rigors and mild phlebitis in one patient (16).

Placebo-controlled studies

Of 300 patients, 221 (111 pamidronate, 110 placebo) withdrew prematurely (17). The majority of withdrawals

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($n = 115$) were due to disease progression or death due to multiple myeloma. The number of patients who withdrew because of adverse experiences ($n = 30$) was small in both groups, and no deaths occurred due to the treatment. Adverse gastrointestinal events were reported in patients who received both pamidronate and placebo, but although the rates were not significantly different in the two groups, there were more cases of nausea, dysphagia/dyspepsia, and gastrointestinal ulceration in the pamidronate group.

In a long-term follow-up of two randomized, placebo-controlled trials of pamidronate in women with breast carcinoma and osteolytic bone metastases, adverse events caused premature withdrawal of therapy in 22% of 367 patients taking pamidronate 90 mg/day and 20% of 38 patients taking placebo (18).

- A 75-year-old woman was withdrawn after developing an allergic reaction in her left eye possibly related to pamidronate.
- Another patient discontinued pamidronate after an episode of symptomatic hypocalcemia.
- Two other serious and unexpected adverse events occurred in patients taking pamidronate.
- A 45-year-old woman who had been taking placebo developed an interstitial pulmonary infiltrate and dyspnea 4 days after taking pamidronate on a compassionate basis after completing the study.
- An 83-year-old woman developed increased weakness, fatigue, and dyspnea 3 weeks after her last dose of pamidronate.

These adverse events were both assessed by the treating physician as being possibly related to pamidronate. Fatigue related to the study drug was reported slightly more often by patients taking pamidronate (40%) than those taking placebo (29%). Fever related to the study drug was reported in 14% of pamidronate patients and in 5% of placebo patients.

The effect of oral pamidronate on bone mineral density and its adverse effect profile has been investigated in a double-blind, placebo-controlled study in 122 patients aged 55–75 years with established vertebral osteoporosis (19). The patients took disodium pamidronate 300 mg/day for 4 weeks every 16 weeks (group A), 150 mg/day for 4 weeks every 8 weeks (group B), or placebo (group C). All also took calcium 500 mg/day and vitamin D 400 IU/day. In groups A and B there were significant reductions in serum osteocalcin and urinary deoxypuridinoline and an excess of gastrointestinal adverse effects, particularly in group A. The authors concluded that intermittent pamidronate therapy can prevent bone loss in both the lumbar spine and femoral neck in patients with established vertebral osteoporosis, although the 300 mg dose did not appear suitable for clinical use because of gastrointestinal adverse effects.

Organs and Systems

Neuromuscular function

The efficacy and safety of amidronate in recalcitrant reflex sympathetic dystrophy have been assessed in 10 women and 13.men, mean age 44 years (20). Amidronate was given intravenously in a dose of 1 mg/kg/day for 1–3 days. There were adverse events in 14 patients: transient fever ($n = 6$), venous inflammation ($n = 2$), transient symptomless hypocalcemia ($n = 3$), nausea ($n = 1$), lymphopenia ($n = 1$), transient hypertension ($n = 1$).

Sensory systems

Eyes

Adverse effects with various forms of pamidronate included 23 cases of suspected ocular adverse drug reactions associated with the use of intravenous pamidronate disodium (21). Bilateral anterior uveitis occurred 24–48 hours after administration in six cases; three reports involved unilateral episcleritis, occurring 1–6 days after administration; and 13 patients complained of non-specific transient conjunctivitis 6–8 hours after administration.

The first case of uveitis due to pamidronate was reported in 1993 (22). A review of reports published as of 1994 (21) found 23 cases, including 7 cases of anterior uveitis, 3 of episcleritis or scleritis, and 13 of non-specific transient conjunctivitis. Since then, other cases of anterior uveitis have been reported (23,24).

Of 16 cases of pamidronate-induced anterior uveitis (23,24), 11 were bilateral and 5 unilateral. In most cases, the onset was within 24–48 hours of initiation of the pamidronate infusion, although in one patient the interval was 17 days. The severity, when specified, ranged from mild to severe. Treatment was by watchful waiting in two patients, oral glucocorticoid therapy or hospital admission in four, and topical glucocorticoids with or without cycloplegic agents in nine. The time to recovery, when specified, ranged from a few days to a month. The cumulative pamidronate dose was 30–240 mg.

Ears

Serious adverse effects of aminobisphosphonates were reported in otospongiosis. Of two patients with stapedial otosclerosis and sensorineural hearing loss one developed total bilateral deafness and the other retained minimal auditory function in the low frequencies (25). It was recommended that sensorineural deafness in selected patients with otosclerosis should be treated with sodium fluoride, and that patients with Paget's disease treated with aminobisphosphonates should be closely monitored and the drug discontinued immediately if hearing deteriorates. Elsewhere, ototoxicity has been reported (SEDA-20, 440).

Psychological, psychiatric

Olfactory hallucinations have been attributed to etidronate (26).

Endocrine

A patient who was receiving disodium pamidronate developed gynecomastia, and of another 13 patients, two more men had gynecomastia and one woman had tender swollen breasts (27).

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Mineral balance

Pamidronate can cause asymptomatic hypocalcemia (SEDA-20, 440). In a study of the use of pamidronate to treat immobilization hypercalcemia after acute spinal cord injury in nine patients, one patient had transient drug-related fever and four had asymptomatic hypocalcemia (28).

- A 39-year-old normocalcemic patient with subclinical hypoparathyroidism and bone metastases from breast carcinoma was given pamidronate 60 mg parenterally and developed hypocalcemia (1.42 mmol/l) and carpopedal spasm (29). Hypocalcemia due to latent hypoparathyroidism had been compensated by extensive osteolysis due to bone metastases.

Gastrointestinal

The aminobisphosphonates cause severe gastrointestinal adverse effects: of greatest concern is their capacity to cause esophageal lesions. A report identified three patients with severe esophagitis from alendronate (30). Four episodes of esophagitis occurred in 49 patients in a study of a new timed-release formulation of pamidronate (31). Severe esophagitis or esophageal ulceration have been reported in seven patients taking bisphosphonates (six alendronate and one etidronate); the lesions healed on withdrawal (32).

In 57 patients with advanced prostate cancer resistant to first-line hormonal therapy treated with estramustine and clodronate, the main adverse effect was nausea (33). Therapeutic efficacy was small. Reasons for premature withdrawal of clodronate in one study included refusal to continue treatment (five patients) and progressive disease of the bone (four patients) (34). One patient refused to take clodronate from the start; seven discontinued clodronate after a median of 13 (range 0.2–23) months because of adverse events. In five patients the cause was nausea, combined with vomiting in four and diarrhea in one. After 0.9, 1.0, and 1.3 months the dosage of clodronate was reduced to 800 mg/day in three patients (one had nausea, another dyspepsia, and a third had uncharacteristic sensations in the skeleton).

The safety of cyclic etidronate has been evaluated in 550 general practices in the UK in 7977 patients taking cyclic etidronate (7244 women) (35). The findings were consistent with the conclusions of several reviews of the safety and tolerability of cyclic etidronate (36,37). The most common adverse effects reported in these reviews were minor gastrointestinal events, such as diarrhea, nausea, and flatulence. Etidronate has not been associated with an increased incidence of serious gastrointestinal adverse events.

Liver

Although adverse events associated with bisphosphonates are usually gastrointestinal, raised transaminases (aspartate transaminase and alanine transaminase) have also been described in many cases. However, the frequency of such changes has been poorly investigated. The Probone study was a phase II trial in 610 osteopenic women randomized for 3 years to receive placebo or clodronate 65, 400, 800 mg/day, or 400 mg/day for 15 days out of 90 (intermittent group) (38). During the first study year, gastrointestinal adverse events were reported by 20–26% of the patients in the five study groups, but there were no differences between groups. The high-dose clodronate groups (400 and 800 mg/day) had no more hepatic adverse effects than the low-dose groups, and there were no serious adverse effects on the liver. However, these higher doses of clodronate caused a significant mean increase in alanine transaminase of 5.4–5.8 IU compared with placebo. In volunteers with initially normal transaminase activity, the risk ratio for an increase to above normal was 1.8 with clodronate 400 mg/day and 2.5 with clodronate 800 mg/day. In these groups, aspartate transaminase and alanine transaminase, respectively, rose above the top of the reference ranges in 12 and 18% of the volunteers. The respective percentages in the placebo group were 6.2 and 7.2%. All bilirubin concentrations were normal. The authors concluded that oral clodronate may increase the activity of serum transaminases, and that these enzymes most likely come from the liver.

Skin

Necrobiotic palisading granuloma has been attributed to intravenous disodium clodronate (39).

Musculoskeletal

Of 12 patients given pamidronate (seven men, mean age 25 years) with either corticosteroid-induced or postmenopausal osteoporosis, none of whom had undergone transplantation, nine reported severe bone pain, starting at about 12 hours after the infusion and lasting for up to 3 days (40). The bone pain typically started in the spine then migrated to the ribs and finally to the lower limbs. The pain was excruciating in seven patients, rendering them bed-bound and making sputum expectoration and physiotherapy difficult. Paracetamol and diclofenac were unsuccessful in preventing or relieving pain. Two of the nine patients also had febrile reactions and one developed phlebitis around the infusion site. None of the controls developed bone pain. The high incidence of bone pain after intravenous pamidronate may be a novel drug reaction specific to cystic fibrosis. The pain may be related to the abrupt reduction in bone turnover anticipated after intravenous pamidronate.

Body temperature

In a study of the use of pamidronate to treat immobilization hypercalcemia after acute spinal cord injury in nine patients, one patient had transient drug-related fever and four had asymptomatic hypocalcemia (29).

Susceptibility Factors

Age

Caution should be exercised when using pamidronate in children, since there may be an immediate calcium-lowering effect and persistence of hypocalcemia, hypomagnesemia, and hypophosphatemia, particularly when

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high doses (for example 30 mg) are given intravenously (41). The authors recommended that children be given doses of 15–20 mg.

Drug Administration

Drug administration route

Intermittent intravenous clodronate is effective in preventing and treating postmenopausal bone loss (42). In Italy, it is also available for intramuscular administration, which might be an acceptable alternative for some patients. However, intramuscular injection caused substantial pain at the site of injection, which led to withdrawal in almost 50% of the patients who received a weekly dose (43). These results suggest that intermittent intramuscular clodronate can improve skeletal bone density in osteoporotic postmenopausal women, but in situ pain may limit its extensive use.

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Bithionol

General Information

Bithionol is a chlorinated bisphenol with antihelminthic properties. It is active against most trematodes and has been recommended as preferable to praziquantel in fascioliasis and paragonimiasis, proving both effective and well tolerated. Bithionol also has antibacterial properties and was for this reason included for a time in cosmetic formulations. However, when given topically it caused photosensitivity reactions, and this form of application has been abandoned.

Organs and Systems

Gastrointestinal

An Egyptian report in 1991 on the use of bithionol in fascioliasis in doses of 30 mg/kg every other day for five doses noted that unpleasant symptoms were common, but some or most of them were certainly due to the underlying disease and actually abated with treatment (1). The only symptom the incidence of which actually increased as a result of treatment was diarrhea, which occurred in 12 of 14 users; one patient also developed urticaria with pruritus.

Liver

The effects of bithionol on the liver have been examined in an Egyptian study in 1990 (2). The pathology of human fascioliasis was studied before and after bithionol treatment using light and transmission electron microscopy. Fine needle biopsies were taken from five patients with established fascioliasis, before and after drug administration. By light microscopy the pathology of human fascioliasis was similar to that reported in experimental fascioliasis. The ultrastructural picture showed bile ductule hyperplasia, fibrosis of portal tracts, widening of the interhepatic spaces by many microvilli, and dilated Disse spaces with collagen fibers. Bile ductule hyperplasia may be the initial factor in fibrinogenesis, which subsequently enhances the development of microvilli on the surfaces of hepatocytes. Both light and electron microscopy showed regression of the picture of fascioliasis to normal after bithionol treatment, with no sign of adverse effects on the liver.

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Bitoscanate

General Information

Bitoscanate (phenylene 1,4-diisothiocyanate) enjoyed some clinical interest in the treatment of hookworm infection in around 1975 (1), but it proved highly dangerous, and deaths have occurred with as little as 300 mg. Most of the publicity that it has had in recent years relates to its listing as an "extremely hazardous substance," and the US Office of Homeland Security has actually regarded it as a possible tool for bioterrorism.

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Bleomycin

See also Cytostatic and immunosuppressant drugs

General Information

Bleomycin is a cytostatic drug that causes double-strand breaks in DNA. It has been used to treat Hodgkin's disease and a variety of solid cancers. It is often used in combination with other anticancer drugs, for example in the regimens known as ABVD (doxorubicin + bleomycin + vinblastine + dacarbazine) and BEP (bleomycin + etoposide + cisplatin). It has also been injected intrapleurally in the management of malignant effusions.

Organs and Systems

Respiratory

Bleomycin can cause diffuse interstitial pneumonitis, with significant mortality. Bleomycin is more slowly degraded in the lungs than in other tissues, such as the bone marrow or liver, because of lower bleomycin hydrolase activity. The mechanisms of lung damage include the formation of highly reactive oxygen species; lipid peroxidation of cell membranes has been suggested, but not confirmed (1). Others have suggested a role for angiotensin-converting enzyme in production of the lung damage (2), but the data are unconvincing.

Because this is a severe adverse effect it is generally recommended that a total dose of more than 400 mg of bleomycin should be avoided in patients with normal renal function. In those over 70 years of age reduced creatinine clearance makes dosage reduction necessary.

Estimates of the incidence of bleomycin pulmonary toxicity range from 11 to 23% (3). Of 99 patients previously treated with bleomycin together with other cytostatic drugs for testicular tumors, 16 developed abnormal lung function tests; amongst those who received more than 500 mg of bleomycin cumulatively, 75% had abnormal lung function tests, Raynaud's phenomenon, or both (4). Rapid progression to fatal pulmonary fibrosis has been documented previously and, in all but one instance, there had been previous or concurrent chest radiotherapy. Two cases have been reported of rapidly progressive fatal pulmonary fibrosis in patients receiving bleomycin who had had no previous lung disease, and who had not undergone radiotherapy to the chest (5). Lung toxicity can occur at low cumulative doses of bleomycin during concurrent treatment with cyclophosphamide (which independently causes pulmonary toxicity). In 19 patients (6) there was a high (26%) incidence of fatal pulmonary toxicity in patients receiving the combination of these two drugs, which warrants special caution.

Transient but significant reductions in pulmonary function tests have been reported within 8–12 months in 35 children treated with polychemotherapy who had received a cumulative dose of 120 mg/m^2 up to 12 years after diagnosis (7). However, there were no long-term abnormalities.

In 194 patients there was a fatality rate of 2.8% from pulmonary toxicity. The incidence of fatal pulmonary toxicity increased with each decade of life above 30 and the lower the glomerular filtration rate at the time of administration the greater the death rate; the death rate may exceed 10% in those over 40 years of age (8).

Bleomycin is also associated with a hypersensitivity pneumonitis. This should be considered when interpreting cytological swabs in patients treated with the drug, since the acute cytological changes can be misinterpreted (9).

A syndrome of acute chest pain occurring during bleomycin infusion has been described in 10 patients with features that could not be ascribed to pulmonary fibrosis, hypersensitivity pneumonitis, or cardiovascular toxicity (10). The pain was sudden in onset and occurred during the first or second course, usually on the second or third day. There was retrosternal pressure or pleuritic pain, in some cases severe enough to require narcotic analgesics. Stopping or slowing the infusion produced marked improvement. In two of seven patients who received a subsequent course of treatment, the pain recurred. One patient had dyspnea and two developed an erythematous rash. One had a pleural friction rub and one a pericardial friction rub. There was fever during five episodes. There were no other physical abnormalities. There were electrocardiographic changes suggestive of pericarditis in two patients; one patient developed transient blunting of a costophrenic angle on a chest X-ray, and another a transient and small retrocardiac pulmonary infiltrate. The pain resolved spontaneously with analgesics, and there were no long-term pulmonary or cardiac sequelae. Possible underlying mechanisms include pleuropericarditis due to serosal inflammation or vascular pathology.

Severe morbidity has been reported after the use of regimens containing bleomycin: 10% of patients developed adult respiratory distress syndrome and a further 9% needed prolonged ventilation (11). The authors thought that these rates were higher than expected and attributed this to a combination of the toxic effects of bleomycin on the lung and a large retroperitoneal and/or pulmonary tumor burden.

Skin

Bleomycin can occasionally cause scleroderma-like changes in the skin (12,13), an effect that may be enhanced by radiotherapy (14).

Body temperature

When bleomycin is used as a sclerosing agent in adults, a dose of up to 1 mg/kg is generally instilled into the chest through a thoracostomy tube. Bleomycin 60 mg intrapleurally caused a fever over 39°C in two of 21 patients with malignant pleural effusions; it settled without treatment and was not associated with local discomfort (15).

Drug Administration

Drug administration route

Several antineoplastic agents have been introduced into the pleural space to achieve pleurodesis, but the largest reported experience is with bleomycin. Intrapleural bleomycin has an efficacy similar to that of tetracycline and doxycycline (16). About 45% of a dose of bleomycin is

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absorbed systemically, but significant adverse events are uncommon (17). Chest pain is reported in about 28% of patients, fever in 24%, and nausea in about 11% (18). A randomized comparison of bleomycin with tetracycline in 85 patients with malignant pleural effusions showed that toxicity, predominantly in the form of chest pain and fever, was similar with the two drugs (7–17%) (19). Nearly half the patients (34) died within 90 days owing to disease progression. However, one patient died within 2 days of intrapleural bleomycin, and the investigators could not exclude a contribution from the bleomycin. In another comparison of bleomycin with doxycycline there was fever in 13%, chest pain in 11%, and chills in 4% of patients treated with bleomycin (20).

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Blood cell transfusion and bone marrow transplantation

General Information

The most common adverse effect of routine blood transfusion is an incompatibility reaction. Massive blood transfusions can cause other adverse effects (1). Human error resulting in blood group mismatching is the leading cause of transfusion-related fatalities (2,3). Although there have been major achievements in transfusion medicine to improve the safety of blood and blood products, the risks of transfusion reactions and of the transmission of infectious agents have not been eliminated. Treatment of patients with blood or blood-derived components has therefore been the subject of great public concern, mostly because of the tragic consequences of transfusion-transmitted human immunodeficiency virus (HIV).

Most patients do not react adversely to blood products. However, some have mild to severe effects immediately or delayed for 48 hours. Information on adverse reactions to blood products collected by the New Zealand Centre for Adverse Reactions Monitoring enables the identification of unusual or unpredictable adverse reactions; risk factors such as concomitant medications, underlying diseases, rate of administration; and batch problems (4).

Minimizing the risks of blood transfusion

Because of the possible complications of blood transfusion, it is constantly emphasized that unnecessary transfusions should be avoided. In most cases therapy with blood or blood components is solely a replacement therapy and should therefore be used only when a distinct deficiency of some blood component has been demonstrated; "component blood therapy" is usually preferable to

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whole blood therapy, providing more specific treatment. Also, the use of autologous transfusions, although not always feasible, seems to be a strategy that might reduce complication rates (5).

In order to reduce risks to a minimum and at the same time ensure that blood products are of high quality, three measures must be enforced.

1. Proper selection of blood donors (6).
2. Screening of individual donations (7).
3. The use of production methods specifically aimed at minimizing the risks of transmitting infectious diseases (8).

Blood donor selection

Blood donors should be non-remunerated and voluntary, and their health should be checked at regular intervals. A scheme for donor selection may include permanent exclusion criteria, such as previous episodes of jaundice (including laboratory evidence of current or previous infectious hepatitis, especially hepatitis B or C), syphilis or malaria, the presence of anti-HIV antibodies, so-called risk conduct, such as homosexual or bisexual behavior, or treatment with non-recombinant growth hormone. Time-limited exclusion criteria relating to current health status should also be used; these may also include such temporary risk factors as the taking of certain kinds of medicine, a recent blood transfusion, vaccination with live vaccines, a recent pregnancy, and travel to certain geographical areas, for example regions with malaria or a high prevalence of HIV.

In most countries, people with a history of jaundice are excluded from the donor population. However, there is a substantial geographic variation in the prevalence and detection rate of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (HCV) in donors (9,10). In addition, the type of donor involved influences the risk: commercial (paid) donors carry a much higher hepatitis risk than non-remunerated voluntary donors (11,12).

With respect to the risk of transmission of variant Creutzfeldt–Jakob disease by blood, some countries exclude from donation donors who lived in the UK for more than 6 months between 1980 and 1996 (13).

Laboratory screening of individual donations

Individual portions of donated blood should be tested for infectious risk whenever possible. The series of assays currently performed in most countries comprises tests for antibodies against HIV-I/-II, HCV, and HTLV-I/II, HBsAg, and a test for syphilis. However, screening for syphilis is no longer mandatory in all countries, as cost-benefit analysis has shown it to be of little value, at least with voluntary non-remunerated donors.

Now that hepatitis C can be tested for, the so-called surrogate tests such as alanine transaminase and antibodies to hepatitis B core antigen (HBcAb) are no longer carried out in all countries, and their relevance has been questioned (14).

Serological screening of every blood or plasma donation must be performed using the most sensitive techniques available. Screening may be unreliable in cases of HBsAg at low titers, as evidence has accumulated that blood that is HBsAg negative but strongly positive for HBcAg antibody may be infectious (15,16). However, routine screening for HBcAg antibodies is at present impracticable. There may also be a delay of 1–10 months before antibodies appear in patients infected with HIV or HCV.

In order to increase the sensitivity of screening, so as to minimize the so-called window period during which serological markers will not detect the infectivity marker, methods of detecting nucleic acids from, for example, the virus particle have been developed. Hepatitis C virus nucleic acid testing is obligatory in Europe, the USA, and Japan, and in many countries nucleic acid testing for other viruses has also been implemented. There is nevertheless no doubt that in future PCR-based methods will further increase the safety of blood and blood products.

Preparation of safe plasma-derived products

Infectivity can be reduced by introducing good manufacturing practice (GMP), both in blood banks and in plasma fractionation units. The sterility of the final products is checked and virus inactivation measures (for example heat treatment and/or chemical inactivation) are taken whenever appropriate. At present, virus inactivation procedures are most relevant to non-cellular products, although leukodepletion procedures using filtration have been used for infectious agents that are almost exclusively intracellular.

The virucidal methods currently in use (17) are based on different rationales. Heat treatment can involve heating solutions, heating lyophilized products, or heating in vapor under pressure, where the actual temperature, duration, and addition of stabilizers vary for the individual products (18,19). Chemical treatment of products with a mixture of an organic solvent and a detergent (S/D treatment) is highly effective against lipid-enveloped viruses (20,21). Other methods of removing or inactivating viruses use nanofiltration (22) or treatment with a combination of a colored photosensitizer and light (23).

Use of autologous blood transfusion

In some countries there has been a marked increase in the use of autologous blood transfusion, since it is known that blood-borne viruses, such as HIV, can be transmitted by allogeneic blood transfusion (24).

In 1997, 66 185 units of autologous blood (200 ml) were collected in Japan, 81% using preoperative collection and storage and 19% by perioperative hemodilution or blood salvage (24). The total volume of autologous blood collected accounted for 1.1% of the total number of units of whole blood donated in the same year. Of the autologous blood donated before surgery, 78% was used, while more than 70% of the blood that was collected by hemodilution, intraoperative salvage, and postoperative salvage was used. During whole blood donations adverse reactions were reported in 1.6% of cases, and ranged from mild reactions (for example dizziness) to severe reactions, such as angina and asthma. With respect to storage and transfusion, 288 errors or problems were reported, with a frequency of 1 per 455 units during production/storage, 1 per 213 transfusion problems/errors, 1 per 23 hemodilution procedures, and 1 per 54 salvage procedures. In 3.7% of the patients

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hypotension occurred during hemodilution. Clotting in blood units (0.9%) and bacterial contamination (0.4%) were the most frequent problems associated with blood salvage.

Adverse effects of massive blood transfusions

Patients who receive massive transfusions are either extremely ill and suffering from prolonged shock or are undergoing major surgery (for example organ transplantation). Patients who receive massive transfusions are exposed to several risks resulting from the addition of anticoagulant, from transfusion of cold blood, and from biochemical, hematological, and other changes in the blood during storage. The complications lead in turn to metabolic disturbances and impaired hemostasis in proportion to the transfused volume.

Acidosis

Since stored blood has a relatively low pH, transfusion can cause acidosis. Prompt and appropriate restoration of the patient's blood volume is most important, to maintain sufficient tissue and organ perfusion and to correct or avoid acidosis.

Ammonia and phosphate

Concentrations of ammonia and inorganic phosphates rise significantly during blood storage, but caution is needed only when old blood is given to patients with liver failure.

Circulatory overload

Circulatory overload with symptoms of congestive heart failure and pulmonary edema can complicate transfusion in patients with poor cardiac reserve.

Citrate toxicity

The citrate in preserved blood can cause a dangerous fall in the ionized calcium concentration in the recipient's plasma in cases of rapid and massive transfusion. The most significant warning sign of citrate intoxication is an increase in the peripheral or central venous pressure, which should be monitored during massive transfusions. An adequate intravenous dose of calcium gluconate or chloride is a reliable means of correcting dangerous hypocalcemia (25).

Coagulation factors

To correct coagulation factor deficiencies, 1–2 units of fresh frozen plasma are recommended after every 10 units of stored blood. As far as the storage lability of coagulation factors is concerned, mild falls in factors V and VIII, and occasionally fibrinogen, occur in the recipient. It must be emphasized, however, that significant coagulation disorders including disseminated intravascular coagulation (DIC) appear almost routinely during prolonged hypovolemia (26).

Hemoglobin oxygen-carrying capacity

The progressive increase in oxygen affinity of stored erythrocytes caused by a fall in the 2,3-diphosphoglycerate concentration is clinically relevant only under extreme conditions. The abnormally increased oxygen affinity of the hemoglobin is reversible in vivo within 24 hours. It is possible to restore the oxygen transport function of hemoglobin by addition of purine nucleotides to old blood (27).

Hemosiderosis

Patients who have received about 100 units of erythrocytes inevitably develop siderosis of the organs and tissues as a consequence of transfusion-induced iron overload (28). Deposition of iron results in functional damage to the heart, liver, spleen, endocrine glands, and other organs, and is often fatal. The clinical signs of iron toxicity in children are retarded growth, splenomegaly, cardiomyopathy, and endocrinopathies. Examination of the serum ferritin concentration and transferrin saturation is useful for the diagnosis of iron overload. Subcutaneous infusion of deferoxamine provides effective and relatively safe treatment by increasing iron excretion. Furthermore, ascorbic acid significantly enhances urinary iron excretion (29). Iron accumulation can be significantly reduced by transfusing young erythrocytes, since the intervals between transfusions can be extended (30,31).

Hypothermia

Transfusion of refrigerated blood, especially during massive transfusions or during exchange transfusions, can induce hypothermia, with a danger of cardiac arrest. If several units of blood are to be rapidly administered, they should be warmed, but not overheated, before transfusion (32).

Platelets

Thrombocytopenia is a well-known consequence of hemodilution. It also occurs in blood transfusions, in which thrombocytopenia constitutes a more frequent clinical problem than abnormalities of coagulation (33). If the platelet count falls below $40 \times 10^9/1$, platelet concentrates should be transfused.

In one study changes in hemostasis in surgical patients undergoing massive transfusion occurred in 93% of patients (34). The platelet count was most frequently abnormal. Well-defined hemostatic disorders, for example DIC, were detected in 48% of patients. It was suggested that the laboratory abnormalities were induced by massive transfusion. Laboratory monitoring and therapeutic measures directed at any underlying disease have been recommended.

Potassium

Hyperkalemia is an infrequent problem associated with the massive transfusion of old blood. Potassium intoxication threatens only patients with raised potassium concentrations before transfusion, for example in the crush syndrome, renal insufficiency, and extensive burns.

Cord blood

Umbilical cord blood is an alternative source of hemopoietic stem cells rather than bone marrow, especially for patients who lack an HLA-matched donor (35). Umbilical cord blood contains significantly more early and committed progenitor cells and has been used in patients with malignant and non-malignant hematological diseases. One of the advantages of cord blood is that it

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can be collected and stored in large scale in liquid nitrogen below –190°C. As the number of hemopoietic cells in umbilical cord blood is limited, current experience with this type of transplantation is predominantly restricted to children, although adults have been successfully treated with umbilical cord blood transplantation (35).

In almost all patients who receive a hemopoietic stem cell transplant, fever and neutropenia will develop (36). The median duration of fever in those given cord blood is substantially longer (27 days) than in those given allogeneic bone marrow (15 days), allogeneic peripheral blood stem cells (10 days), or autologous peripheral blood stem cells (6 days). In patients with a long period of fever, the time to engraftment and the period of neutropenia are longer. Therefore, aggressive prevention of infection will be necessary in these patients.

Exchange transfusion

Favorable results of exchange transfusion in a variety of diseases in adults, for example sickle cell disease, severe clotting disorders, hepatic failure, and acute hemolytic transfusion reactions, have been published (1). Today, however, machine apheresis procedures are more effective and safer for patients requiring exchange of cellular elements or plasma. Exchange transfusion is the most effective therapeutic procedure in the treatment of hemolytic disease of the newborn. Bilirubin removal prevents damage to the central nervous system caused by hyperbilirubinemia. In addition, sensitized erythrocytes are replaced by normally surviving cells and anemia is corrected.

The risks of exchange transfusion are essentially the same as those described above for massive transfusions, and their magnitude depends on the health of the newborn infant and its gestational age and weight. The transfused blood should be as fresh as possible and should not have been stored for more than 4–5 days. It must be free from antigens that react with antibodies in the maternal plasma. Technical errors involving perforation of the umbilical vein, wrong placement of the cannula, or air embolism are fortunately only rare complications.

Platelet transfusion

Severe thrombocytopenia is most often observed in connection with cancer chemotherapy. The availability of platelet concentrates has improved the therapeutic possibilities. Platelet concentrates are obtained by the differential centrifugation of several units of fresh blood or by apheresis from single donors using a blood cell separator. The quality of platelet concentrates obtained by apheresis deteriorates rapidly after storage for more than 24 hours. Of all blood components, platelet concentrates are the most vulnerable to bacterial contamination.

PlPlA1-negative platelets are used to treat neonatal alloimmune thrombocytopenic purpura, a rare, transient, but severe thrombocytopenia in the newborn due to platelet destruction by maternal antibody (1). The mother is usually a PlPlA1-negative person who has produced anti-PlPlA1 as a result of previous blood transfusions or pregnancy. The antibody crosses the placenta and destroys the PlPlA1-positive platelets of the neonate.

Leukocyte transfusion

Centrifugal blood cell separators and techniques for filtration leukapheresis or reversible leukoadhesion can provide a therapeutically adequate dose of granulocytes from a single donor (37), and cells separated in this way are clinically effective. Granulocyte transfusions are indicated in severely granulocytopenic febrile patients with septicemia who are not responding to antibiotics. At least 2×10^{10} granulocytes per day are considered to constitute an adequate granulocyte transfusion, but larger numbers are probably required in some cases.

Complications after granulocyte transfusions occur in about 15–20% of the recipients (38), most frequently in patients given granulocytes prepared by filtration leukapheresis. The complications are predominantly severe febrile reactions, the transmission of cytomegalovirus infection, and graft-versus-host disease. Of particular importance are respiratory reactions with pulmonary edema, which mostly occur in allo-immunized recipients. Leukocyte aggregation may be the cause, with sequestration microemboli and fluid overflow, but other causes have also been suspected. Reactions appear to be more common in patients with sepsis.

Since granulocytes prepared by centrifugation are markedly contaminated with erythrocytes, the ABO compatibility between donor and recipient will be important unless the erythrocytes can be removed before use. Some reactions, particularly allergic and febrile complications, are associated with the presence of macromolecular agents (hydroxyethyl starch, modified gelatin, dextran), used to increase the yield of centrifugal techniques. ABO incompatibility does not alter the in vivo fate of granulocytes (39).

Antibodies to "passenger B lymphocytes" can pose problems after transplantation. When kidneys from a rhesus-negative cadaveric donor, whose serum contained anti-Rho (D), were transplanted into two rhesus-positive patients, anti-Rho (D) was detected in their serum and on their erythrocytes 3.5 weeks after transplantation (40). One patient had hemolysis. The antibodies persisted for nearly 6 months, despite graft rejection and nephrectomy in one case. These antibodies presumably arose from passenger B lymphocytes in the grafts from the rhesus-immunized donor.

Leukodepleted blood products

As in several other countries, the Health Council of the Netherlands has prepared recommendations on the need for routine leukodepletion by filtration of blood. The presence of leukocytes in blood products has no beneficial effect for the recipient, except in special cases, such as patients undergoing organ transplantation (41). Apart from preventing the adverse effects associated with leukocyte transfusion, it has been postulated that the risk of transmission of new variant Creutzfeldt–Jakob disease can be prevented by using leukodepleted blood products.

The disadvantages of leukodepletion are hypotension and adult respiratory distress syndrome (42).

Red eye syndrome, which is characterized by conjunctivitis, headache, and muscle aches, with spontaneous resolution, was caused by a specific filter that is not being used any more (41).

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Organs and Systems

Cardiovascular

Bone marrow for transplantation is usually kept cryopreserved in dimethylsulfoxide (DMSO), and residual DMSO may be responsible for toxic reactions: in one report, all of a series of 10 patients had falls in heart rate and blood pressure (43). However, other factors, such as cell lysis or rapid intravenous infusion of large volumes, may be responsible.

Respiratory

Transfusion-related acute lung injury is an infrequent but life-threatening complication, clinically indistinguishable from adult respiratory distress syndrome (ARDS). It can occur after the administration of whole blood, erythrocytes, fresh frozen plasma, or cryoprecipitate, all of which contain variable amounts of plasma. In transfusion-related acute lung injury the symptoms of ARDS (dyspnea, pulmonary edema, severe hypoxia, fever, and hypotension) occur within 1–6 hours from the start of transfusion and usually subside within 1–4 days (44). These symptoms can vary from mild to severe and they lead to death in 5–10% of cases. The reaction may be more frequent than reported because confounding factors can mask the symptoms (45).

Transfusion-related acute lung injury has been associated with the presence of granulocyte antibodies, HLA antibodies, or biologically active lipids in the plasma. These agents activate granulocytes and endothelial cells and cause release of inflammatory mediators, which cause increased vascular permeability, fever, and hypotension (44). HLA class II antibodies can provoke transfusion-related acute lung injury, as observed in a 19-year-old woman, who developed transfusion-related acute lung injury after treatment with fresh-frozen plasma (46). Probably, monocytes are then involved in the pathogenesis of the acute lung injury (47).

Most of the fatal cases of transfusion-related acute lung injury have involved transfusions of fresh frozen plasma; whole blood, packed erythrocytes, cryoprecipitate, platelet concentrates, apheresis platelets, and occasionally intravenous immunoglobulin have also been implicated. The donors most often involved in fatal injury have been multiparous women who were antihuman lymphocyte antigen-positive or antigranulocyte antibody-positive; one or both of these antibody types have been found in 89% of reported cases. The factors that predispose to transfusion-related acute lung injury include surgery, active infection, massive transfusion, and cytokine therapy, which activate pulmonary endothelium and primes the patient's leukocytes. It has been hypothesized that transfusion-related acute lung injury results from a combination of two independent insults, the patient's clinical state and the presence of antileukocyte antibodies.

The FDA has issued a Dear Colleague letter, outlining the risk of transfusion-related acute lung injury with the use of blood products, particularly those that contain plasma (48). The agency has noted that since the first report of fatal transfusion-related acute lung injury in 1992, 45 more reports have been received by the Center for Biologics Evaluation and Research. Transfusion-related acute lung injury is now believed to be the third commonest cause of infusion-related deaths. The number of non-fatal cases of transfusion-related acute lung injury associated with blood products is also on the increase, but this may be due to better recognition and reporting.

A patient with acute myeloid leukemia developed pulmonary alveolar proteinosis during the period of leukopenia following an unrelated umbilical cord blood transplantation (49).

Hematologic

Hemolytic post-transfusion reactions (50) are most often caused by clerical and administrative errors involving misidentification (incorrect labeling of blood samples, erroneous identification of patients) rather than by mistakes in the laboratory (2,51). However, scrupulous care is demanded at all stages; in a review of hemolytic and other transfusion reactions, the importance of competent handling of whole blood and red cell suspensions (including the avoidance of freezing or osmotic damage) has been stressed (52).

Hemolysis mediated by immune reactions is usually avoided by routine antibody screening and cross-matching methods. Improved pre-transfusion testing has resulted in a significant decrease in the incidence of hemolytic transfusion reactions, although there are examples of transfusion reactions having occurred where no antibody was detectable either before or after transfusion (53).

Acute post-transfusion hemolytic reactions

Acute hemolytic post-transfusion reaction with measurable destruction of the donor's or recipient's erythrocytes due to incompatibility of antigens and antibodies is followed by hemoglobinemia. Hemoglobinemia occurs when the combined hemoglobin-binding capacity of the haptoglobins and hemopexin in plasma is saturated. The severity of the reaction depends on the nature of the antigen and antibody, on the binding strength of the antibody, and on the volume of transfused incompatible blood.

A severe acute hemolytic reaction immediately or soon after the transfusion of incompatible blood is characterized by classical symptoms: a feeling of heat along the vein into which the blood is being transfused, a sensation of severe pain in the lumbar region, substernal tightness, dyspnea, nausea, a fall in blood pressure, tachycardia, circulatory collapse, hemoglobinemia, hemoglobinuria, and jaundice. It is fatal in about 50% of cases, either because of hemolytic shock or hemorrhage due to intravascular coagulation, or because of acute renal insufficiency. Sometimes the clinical symptoms are poorly manifested, so that only fever with or without chills may be noted, or they are masked by signs of the primary disease, so that the reaction is not recognized. Especially in an anesthetized patient the only symptom of intravascular destruction of erythrocytes may be unexpected profuse bleeding from the operation wound and hypotension (54).

The overwhelming majority of such reactions (about 80%) are due to ABO incompatibility. Acute post-transfusion reactions can also occur in the presence of an irregular antibody in the recipient's plasma, usually

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directed against antigens of the Rh system, which can sometimes be difficult to detect; such antibodies cause hemolytic reactions only exceptionally, although several cases have been extensively described (55–59).

Delayed post-transfusion hemolytic reactions

When the signs and symptoms of a hemolytic transfusion reaction occur more than 24 hours after transfusion, the reaction is classified as a delayed reaction (60–62). It is estimated that up to 0.025% of recipients may well be at risk of delayed transfusion reactions (1); however, in one study only 1 in 10 668 transfused units cause delayed hemolysis. The severity of this type of reaction varies widely. Many of these reactions are so mild that they remain unnoticed; only a few are severe or fatal. Almost all patients with this type of complication have a history of previous transfusion and/or pregnancy, which has made sensitization possible. The symptoms comprise fever, chills, anemia, hemoglobinemia, hemoglobinuria, and reticulocytosis. Renal insufficiency can occur and the direct antiglobulin test is positive.

Delayed reactions are difficult to prevent. Incompatibility may not be demonstrable before transfusion, and at the time of the reaction the relevant antibodies may not be detectable. Post-transfusion blood samples must therefore be subjected to repeated serological testing. Delayed reactions usually occur as a result of a secondary anamnestic response within 3–21 days after the transfusion of apparently compatible blood, at a time when the antibody concentration has risen sufficiently to bring about hemolysis of the donor's erythrocytes. A primary immune response can also evoke this kind of reaction (61).

Reports of delayed transfusion reactions continue to appear and confirm the difficulty of diagnosis. Many allo-antibodies responsible for delayed reactions of various severity have been demonstrated (61,63–69). The specificities include the usual Kidd and Rh antigens/antibodies and anti-S. Delayed reactions to the Kell antigens, for example Js(a,b), have been reported (68,69), and anti-FF(b) has also been found to cause a delayed reaction (63). A delayed reaction may occur because of anti-A1 production from the group O graft and the reduction of suppressor cell activity by immunosuppressive agents (70). In sickle cell patients a more severe delayed transfusion reaction can be misdiagnosed as sickle cell crisis (71,72). This occurs particularly in patients with U variants (73).

A method for predicting the safety of transfusion is based on the use of cells labeled with radioactive chromium (74). After the administration of several milliliters of the labeled blood, the survival of erythrocytes in the recipient's circulation is examined: poor survival in vivo indicates that transfusion with these erythrocytes will be hazardous (75,76). There are two types of survival curve for incompatible erythrocytes. A curve described by a single exponential function is seen with most potent IgG antibodies that do not bind complement, including anti-D, anti-C, and anti-K, antibodies. Clearance described by more than one exponential is observed with complement-binding antibodies (77). In the latter there is a slowing of erythrocyte destruction 5–20 minutes after injection into the circulation, probably due to acquired resistance to complement activation.

The interpretation of delayed transfusion reactions can be difficult, as the occurrence of low-grade warm acquired hemolytic anemia can resemble this form of transfusion reaction (78). Careful elution of antibody, its identification, and elucidation of its relation to the transfused erythrocytes are required to establish the nature of the reaction. If the indirect antiglobulin test is negative, autoimmune hemolysis is the likely pathogenic mechanism (79).

Hemolytic reactions after transplantation

Acquired hemolytic reactions due to anti-A or anti-B can be caused by group O allografts in renal transplantation (80–83) and can be prevented by prophylactic irradiation of the kidney (84). Cases of immune hemolytic anemia have also been attributed to donor-derived red cell antibodies after allogeneic bone marrow transplantation (85,86).

Prevention of microaggregate formation

In preserved blood, microaggregates are formed during storage. Such microaggregates are identified as cellular (platelet conglomerates, leukocyte ghosts, and platelet ghosts with fibrin co-aggregates) or proteinaceous material. Blood filters with small pore sizes seem to be effective in preventing such adverse effects as febrile non-hemolytic transfusion reactions, in preventing or delaying the development of leukocyte antibodies, and in reducing the risk of respiratory distress syndrome by removing intact or disintegrating cells, debris, and microaggregates (87).

Immunologic

Sensitization to HLA antigens

Sensitization to HLA antigens (88) is undesirable in patients awaiting organ transplantation and in patients who need long-term platelet transfusion. The success of protocols based on the use of leukocyte-depleted and frozen erythrocytes may be limited, since HLA antigens may be expressed on erythrocytes. In one study the erythrocytes of 50% of blood donors contained HLA-A, HLA-B, and HLA-C antibodies (but not antibodies to class II antigens or to leukocyte-specific antigens) (89). Neither storage at 4°C for 21 days nor cryopreservation affected the expression of these antigens. The immunogenicity of HLA antigens on red cells is unknown.

Reactions due to passive transfer of allo-antibodies

Passive transfer of allo-antibodies present in donor plasma can also cause hemolytic transfusion reactions. Low-titer erythrocyte antibodies in donor blood are considered to be relatively harmless, especially when plasma-reduced or concentrated erythrocytes are transfused in a recipient whose cells carry the relevant antigen. A complication of this type provoked by high-titer anti-E antibody has been described (90). Likewise, a hemolytic transfusion reaction occurred in a Kell-negative adult when anti-Kell contained in the plasma of a unit of whole blood reacted with Kell-positive cells transfused 4 weeks before (91).

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Graft-versus-host disease

Graft-versus-host disease is a serious, potentially fatal complication of allogeneic bone marrow transplantation (92–94). It is caused by engrafted allogeneic immunocompetent T lymphocytes (passenger lymphocytes), which proliferate and react against the recipient. Graft-versus-host disease has been reported after the administration of various types of blood preparations (95), whole blood used for exchange transfusion (96), packed erythrocytes, granulocytes (97–99), and platelets (94).

Graft-versus-host disease is characterized by activated T helper cells (TH) and cytotoxic T lymphocytes (TTC) (100). Skin lesions show a reduction in antigen-presenting Langerhans cells and TTH cells and an increase in TTH/T suppressor (TTS) cells (101); these changes parallel others elsewhere in the body. Following the transfusion of blood components containing lymphocytes, graft-versus-host disease may also develop in severely immunocompromised patients, for example in patients with immunodeficiency syndrome or patients undergoing massive chemotherapy. The smallest number of lymphocytes capable of inducing graft-versus-host disease is not known, but it is known that 1 unit of blood contains a sufficient number of lymphocytes to produce graft-versus-host disease in severely immunocompromised adult patients. The finding that graft-versus-host disease is encountered more often in neonates than in adults may be explained by the immaturity of the immune defence system of neonates.

The common features of graft-versus-host disease are severe itching and persistent diarrhea. Treatment with prednisolone and, if necessary, antilymphocyte antibodies, and/or ciclosporin can help. Hepatic involvement can be mild but can progress to liver failure in spite of optimal treatment (102). Oral complications may be related to graft-versus-host disease but can also result from intensive chemotherapy/irradiation or intensive antibiotic treatment (103).

To minimize the risk of graft-versus-host disease, one can inhibit the proliferative capacity of the donor's immunocompetent lymphocytes by irradiating lymphocyte-containing blood products. A dose of 1500–3000 rads is used. A newer strategy, which seems promising, uses murine monoclonal antibodies to a pan-T cell antigen (for example CD3) to remove mature T lymphocytes from bone marrow grafts, and transplant recipients have greatly benefited from prophylactic ciclosporin (104). T cell depletion does not seem to impair (and may actually enhance) functional recovery of B cells after bone marrow transplantation (105).

The post-marrow transplantation period is followed by a period of profound immunosuppression, often complicated by life-threatening infections, for example caused by CMV (106,107).

Reactions to platelets

The major risks associated with platelet transfusion are allo-immunization and infection. Platelets rarely cause graft-versus-host disease (108,109). Allo-antibodies, especially anti-HLA antibodies, appear to be the major source of complications in patients given repeated platelet transfusions. These antibodies cause febrile reactions, but they can also be responsible for partial or complete refractoriness to platelet transfusions. It has been estimated that more than 50% of recipients become alloimmunized within 4–6 weeks after repeated platelet transfusions prepared from random donors (110,111), although there is some evidence that this problem may have been overestimated (112).

Platelet concentrates contain a considerable number of leukocytes and it is not clear whether allo-antibody formation is caused by the platelets themselves or by these contaminating leukocytes (112). There is in fact evidence that leukocyte-free platelets could prevent refractoriness to platelet transfusion (113), and also that induction of anti-HLA antibodies is reduced (114). It has also been found that that the use of HLA-matched platelets almost entirely avoids alloimmunization (114). There was severe but transient thrombocytopenia after the infusion of whole blood from a donor who was subsequently found to have a high-titer platelet-specific antibody (anti-PlA1) (115); this, however, is very rare.

Post-transfusion thrombocytopenic purpura is a rare immunological complication that develops about a week after transfusion of blood containing platelets (116–118). Most patients have been women aged 40–80 with a history of transfusions or pregnancy. The incriminated antibody in the patient's sera reacts with the recipient's own platelets. The thrombocytopenia and purpura usually last for up to 3 weeks, as the antibody disappears and the platelet count progressively rises. The responsible antibody is usually PlA1, and the patient's platelets are PlA1-negative. The precise mechanism causing this platelet destruction is uncertain, but the transient presence of an autoantibody (119) or adsorption of PlPlA1 antigen on to PlPlA1-negative platelets (120) has been suggested. There seems to be a linkage to HLA-DR3 and DRw52 (121). Anti-PlPlA2 is only seldom implicated in post-transfusion thrombocytopenia (122,123). This complication can be treated with plasma exchange, high doses of glucocorticoids, or intravenous gammaglobulin (124).

Reactions to leukocytes

Multitransfused patients often develop non-hemolytic febrile transfusion reactions. They are caused by antibodies to allo-antigens on leukocytes. The minimum number of leukocytes required to stimulate antibody production is unknown, but it is believed that these reactions occur when more than 0.5×10^9 leukocytes are transfused (125). The allo-antigens responsible for the reactions usually belong either to the HLA system, or to the granulocyte-specific antigens (126).

Allo-antibodies to these antigens can give rise to neonatal neutropenia, febrile transfusion reactions, or a poor response to granulocyte transfusions (127). The febrile reactions are usually mild, but pulmonary manifestations may be more severe. Respiratory distress may develop soon after starting the transfusion or within 24 hours. The radiologically evident pulmonary infiltrates may be associated with leukocyte aggregates and leukocyte antigen-antibody complexes. Recovery is usual.

Immune reactions to leukocytes after blood transfusion in sensitized recipients can be prevented by removing

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leukocytes from blood and packed erythrocytes (128–131). Numerous procedures for removing leukocytes have been described (132,133), including filtration through cotton wool and other more sophisticated filtering media. A reduction in leukocyte content of at least 80% must be achieved.

Reactions to cord blood

Compared with stem cells purified from bone marrow, there is no risk to donors in giving cord blood. The risk of graft-versus-host disease in recipients is lower, and the ability to reconstitute hemopoiesis and immunity after transplant is improved (35,134).

- In a 23-year-old man with severe aplastic anemia, graft-versus-host disease, characterized by localized erythematous plaques and papules, developed 10 months after transplantation of unrelated cord blood stem cells, but required no therapy (35). Microsatellite DNA fingerprinting indicated a stable and persistent donor–recipient mixed chimerism, whilst the circulating erythrocytes remained of host origin.

It has been suggested that the increased degree of tolerance of cord blood stem cells will yield a lower graft-versus-tumor effect (35), which might be associated with an increased risk of relapse of the malignancy (134). Unlike sibling marrow transplants, in which additional infusions of donor lymphocytes may be successful in inciting a graft-versus-tumor effect and salvaging relapses, there are no additional cellular therapy options for patients receiving unrelated cord units (135). However, interleukin-2 has antitumor activity and can augment cytotoxic effects after cord blood transplantation (134,135).

Susceptibility Factors

Oncology patients treated with intensive chemotherapy are usually immunosuppressed and in one study the overall incidence of reactions to blood transfusion was 0.3% of all transfused units, which is significantly lower than expected (136). Febrile non-hemolytic reactions and allergic urticarial reactions were the most frequent, and the number of delayed hemolytic post-transfusion reactions was much lower than in non-oncology patients. This probably reflects a relative inability of oncology patients to produce allo-antibodies against blood group antigens.

Drug Administration

Drug contamination

Immunological reactions due to contaminants

Allergic reactions to potentially allergenic drugs may explain some transfusion reactions that cannot be explained by the results of routine tests. In many countries donors are asked to volunteer their history of drug intake during the previous 24 hours, so that donation can if necessary be delayed. Nevertheless, in Canadian donors who had not admitted to drug intake 6–7% of the blood samples taken were found to have detectable concentrations of acetylsalicylic acid and paracetamol (137). Such drugs would be potentially capable of causing untoward reactions in the recipients. The presence of drugs in donor blood can also damage some blood components, especially platelets.

Infection risk

Transmission of infectious disease by blood and blood products has remained a serious issue, especially after the unfortunate occurrence in some countries of large-scale transmission of HIV infection by blood or blood products.

It is, however, important to consider two circumstances separately: on the one hand the risk of transmitting disease with whole blood or cellular blood components under conditions where virus inactivation or virus removal methods are scarcely available, and on the other hand the far lesser risk of transmitting disease with plasma or plasma-derived products prepared in those centers where effective virus inactivation procedures can be applied to the product.

Bacteria

Transmission of bacterial infection by transfusion to recipients of blood or blood components is a dreaded complication, but is rare when modern methods (that is closed systems) are used for the collection and preparation of blood components. Since the introduction of closed systems for blood collection and of stringent regulations regarding the storage of blood at 4°C, contamination of erythrocyte products has become very uncommon. However, platelets stored at room temperature are a potential source of bacterial infection, and there have been many reports of septic episodes associated with both erythrocyte and platelet concentrate transfusions (138). These reports suggest that such reactions may occur as often as 1 per 4000 platelet transfusions or even more often (139,140). In one study, bacterial isolates from contaminated platelets included *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Bacillus cereus* (141).

Bacterial infections transmitted by contaminated erythrocyte concentrates have been caused mainly by *Yersinia enterocolitica*. This enteric organism is capable of efficient proliferation and even selective growth at refrigeration temperatures. Of the 182 reports of transfusion-related fatalities which the US FDA received between 1986 and 1991, 29 (16%) were due to bacterial contamination, and 8 of these were caused by contamination with *Yersinia enterocolitica* (142).

Spirochetes

Syphilis is one of the oldest recognized infectious risks of blood transfusion, and blood donors have been routinely screened for syphilis by serological tests for more than 50 years. In recent times, transfusion-transmitted syphilis has become extraordinarily rare, with only very few cases reported. The general use of refrigerated blood reduces the risk of transmission as *Treponema pallidum* loses its viability within a few days in whole blood stored at 4°C.

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Viruses

The occurrence of viral hepatitis (143) and acquired immune deficiency syndrome (AIDS) after treatment with blood or blood products (6,144) underlines the importance of being aware of the risk of transmission of infections through blood products. More recently, human T cell lymphotropic viruses HTLV-I and HTLV-II and the parvoviruses have been recognized as blood-borne viruses that may compromise the safety of blood products. Cytomegalovirus may also be infective, especially in immunocompromised recipients.

Cytomegalovirus (CMV)

Up to about 70% of donors in Western countries are cytomegalovirus antibody positive (145) and about 10% have cytomegalovirus-infected leukocytes. In developing countries the percentage may be greater than 95%. Transfusion from such donors, especially leukocyte transfusions and massive transfusions of fresh blood, can result in a mild illness, with fever, splenomegaly, moderate rises in transaminases, atypical lymphoid cells in peripheral blood, and sometimes other symptoms. The syndrome usually appears about 4 weeks after transfusion and persists for 1–6 weeks. In immunocompetent individuals, infection with cytomegalovirus is transient and without serious consequences. Immunocompromised patients are at risk of serious, even fatal infections (146). Those at highest risk are premature low birth-weight neonates and bone marrow transplant recipients. Blood and platelets that have been screened for CMV-Ab are indicated in premature neonates and in CMV-Ab-negative recipients of seronegative bone marrow transplants. The use of seronegative donors has significantly reduced the risk of transfusion-induced cytomegalovirus infection in neonates (147–149). Emerging evidence suggests that leukodepletion may be effective in preventing transmission of cytomegalovirus by transfusion (150–152). The effect of leukodepletion suggests that the infective form of cytomegalovirus is intracellular.

Hepatitis viruses

Hepatitis transmitted by blood or blood products can be caused by several viruses. Hepatitis B virus (HBV) and hepatitis C virus (HCV), together with serologically unidentified hepatitis viruses that cause non-A, non-B, non-C hepatitis are leading pathological agents. Less important are hepatitis A virus (153,154), cytomegalovirus, Epstein–Barr virus, *Herpes simplex* virus, and other viruses that may cause liver damage.

Transmission of viral hepatitis continues to be a serious problem related to the transfusion of whole blood, cellular blood components, and to a lesser degree plasma-derived products (8,155). It is difficult and probably impossible to obtain complete data on the true incidence of hepatitis transmitted by blood or blood products: the incubation time is long, mild anicteric cases are not recognized, and systematic follow-up studies of transfused patients are difficult and expensive (156). In addition, the epidemiology of viral hepatitis is different in different regions.

Hepatitis A virus (HAV) Only a few reports on hepatitis A virus transmission have appeared (153,154). In 1992 an outbreak of icteric hepatitis A involving at least 83 patients with hemophilia A in Italy, Belgium, Ireland, and Germany was documented; all had been treated with a high purity factor VIII concentrate produced by one manufacturer (157,158); there was icterus in 93% and a diagnosis of hepatitis A was based on the presence of IgM anti-HA. The original source of contamination was not definitively established, but it is possible that the virus did not originate from the plasma donors.

Hepatitis B virus (HBV) Since the detection of HBsAg by Blumberg and the introduction of HBsAg screening for donors of blood and plasma in all developed countries, hepatitis B virus transmission through the use of blood and blood products has been effectively prevented. Estimates of the risk of infection, based on the sensitivities of current tests for HBsAg and for anti-HBcAg, are in the order of 1 in 200 000 per unit (159).

Passive immunization of the recipient at the time of potential exposure to hepatitis B virus is available. Prophylactic or post-exposure administration of hepatitis B immunoglobulin (HBIG) is of value in the prevention of hepatitis B. Addition of anti-hepatitis-B immunoglobulin to factor concentrates appears to abolish hepatitis B virus infectivity (160,161). Hepatitis B immunization has been used effectively in controlled trials (162,163). The prophylactic effectiveness of the vaccine administered immediately after exposure to hepatitis B virus has not been established (164).

Hepatitis C virus (HCV) Hepatitis caused by hepatitis C virus was one form of non-A, non-B hepatitis until 1989, when a test became available that identified 50–70% of acute, self-limiting cases and more than 80% of chronic cases of transfusion-related non-A, non-B hepatitis (165). In the USA 80–90% of post-transfusion hepatitis were of the non-A, non-B type (166). Post-transfusional non-A, non-B hepatitis is in general less severe than hepatitis B, and is asymptomatic and anicteric in about 60–80% of cases. However, there is evidence that non-A, non-B hepatitis tends to progress to chronic liver disease (167,168).

The test for hepatitis C was originally based on a recombinant antigen (selected from a cDNA expression library prepared from DNA) and RNA (from plasma taken from a chimpanzee infected with non-A, non-B hepatitis originating from a patient with transfusion-mediated, non-A, non-B hepatitis) (169). Although the infectious virus particle has not yet been isolated, isolation of the genome of hepatitis C virus, expression of viral proteins and synthesis of antigenic peptides of hepatitis C virus have now permitted highly sensitive tests, based on multiple antigens from the virus.

The incidence of hepatitis C among donors varies considerably (from 0.2 to 3%); among US blood donors the prevalence was 0.36% in unpaid voluntary donors, whereas it was 10% in commercial plasma donors (11). In another study, the per unit risk of hepatitis C virus infection was 0.45% before testing had been introduced, 0.19% after the introduction of so-called surrogate tests

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(alanine transaminase, anti-HBcAg), and only 0.03% after the additional implementation of anti-hepatitis C virus tests (170). Now that second- or third-generation tests are available, the risk of transmitting hepatitis C virus infection is probably as low as 1 in 6000 (171).

The availability of the hepatitis C antibody test has also emphasized the relation between chronic hepatitis C, liver cirrhosis, and hepatocellular carcinoma: in Japan, 58 patients with chronic hepatitis C were followed for 7 years; 10 of them developed hepatocellular carcinoma, 14 developed cirrhosis, 30 continued with chronic hepatitis, and in 4 there was improvement of their hepatitis (172).

Hepatitis delta When they occur with any frequency, hepatitis delta infections pose a problem, since the hepatitis tends to be more severe than hepatitis B infection alone and is more likely to progress to chronic hepatitis. Hepatitis delta virus is a defective RNA virus that can replicate only in the presence of hepatitis B virus. It has a unique hybrid structure consisting of a delta inner core encapsulated by the surface antigen of hepatitis B virus. Delta superinfection can transform asymptomatic or mild chronic hepatitis B infection to severe progressive active hepatitis and cirrhosis, and contributes substantially to fulminant hepatitis B (173,174).

Parvoviruses

Parvovirus B19 is transmissible by blood and blood products. In most cases B19 infection is of little consequence to the recipient. However, maternal infection can have serious effects on the fetus, and patients with hemolytic anemia or HIV infection may suffer an aplastic crisis as a result of B19 infection. B19 is an essentially epidemic infection and is transmitted only during the preacute phase. The virus is not lipid enveloped and is therefore not inactivated by solvent detergent treatment. Furthermore, it is highly heat-resistant. The risk of infection is generally thought to be low, perhaps in the order of 1 in 10 000 to 1 in 50 000, although a much higher frequency has been suggested by studies based on PCR (175,176).

Retroviruses

HIV-1 In the late 1970s, the human immunodeficiency virus (HIV) was spreading silently and was still undetected. By 1981, when AIDS was first recognized, cases had already occurred in several countries, but the worldwide spread of HIV infection was only fully realized in the mid-1980s. A still pertinent review dating from that period discussed transfusion-associated AIDS in great depth and also highlighted the fact that the scope of the problem widened with the recognition of other pathogenic retroviruses, such as HIV-2, HTLV-I, and HTLV-II (144). HIV can be transmitted by blood and blood products, and in most countries donated blood and plasma have been screened for the presence of HIV-1 antibodies since 1985, and subsequently for HIV-2 antibodies as well; HIV-positive units have been discarded. The overall level of HIV prevalence in blood donors fell from 0.035% in mid-1985 to 0.012% by mid-1987, primarily as a result of donor education and self-exclusion, and by eliminating seropositive donors from the donor pool (177). The prevalence of HIV positivity among donors now seems to be around 1–2 per 400 000 in countries with blood donation systems based on non-remunerated voluntary donors.

Before the screening of blood and plasma and before virus inactivation procedures were applied to coagulation factor products (for example factor VIII and factor IX), many hemophiliacs who were treated with substitution therapy were exposed to infection with HIV. In the USA about 70% of tested persons with hemophilia A (factor VIII deficiency) and 35% with hemophilia B (factor IX deficiency) were HIV-seropositive (177).

Up to 1987, 4% of all reported patients with AIDS in 28 European countries were likely to have been infected by blood transfusion. In these countries the percentages of patients with hemophilia or other coagulation disorders that develop AIDS were similar up to 1987 (178).

Transfusion of HIV-infected blood is likely to remain a public health problem, especially in parts of Africa (Central, Eastern, and Southern), Asia, and parts of the Caribbean. Non-sterile needles, syringes, and other skin-piercing instruments also play a role in HIV transmission.

People who have been infected do not develop antibodies for some weeks or months, and HIV infection of a minute number of transfusion recipients must therefore still be expected. Several recipients are reported to have seroconverted after transfusion of blood from donors who were anti-HIV negative at the time of donation (179). This window period has been estimated to last for an average of 45 days and it is probably less than 150 days in 90% of cases (180). The HIV antibody tests in current use are more sensitive and can detect seroconversion 5–15 days earlier than the tests used in the late 1980s (181). Since the frequency of positive tests among donors continues to fall, the actual risk of HIV infection should now be significantly less than the 1990 estimate.

HIV-2 HIV-2, which is closely related to HIV-1, was first reported to be associated with AIDS in 1986 in West Africa, where it is believed to be endemic. Several cases of HIV-2 infection have been reported among Europeans and West Africans residing in Europe and in the USA. The spectrum of disease and modes of transmission of HIV-2 seem to be similar to those of HIV-1 (182). However, there have been only relatively few reports of HIV-2 transmission in blood. The anti-HIV-1 EIA tests currently used for screening blood donors are estimated to detect from 42 to 92% of HIV-2 infections (183). Anti-HIV-2 assays are available and are used routinely in blood donor screening.

HTLV-1 and HTLV-2 The human T cell lymphotropic virus type I (HTLV-I) is endemic in some areas of Japan, the Caribbean, and Africa, and has been associated with adult T cell leukemia. In Japan, seroconversion has been observed when anti-HTLV-I-negative patients were transfused with seropositive blood or blood components; in one study the conversion rate was 62% (177). However, no case of transfusion-associated adult T cell leukemia has been reported to date (184,185). HTLV-II was originally isolated from a patient with hairy cell leukemia, but

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the association has not been confirmed. For both HTLV-I and HTLV-II, their natural history, their prevalence rates in blood donors, and their possible clinical consequences need to be studied further (186). In the USA the current risk of post-transfusion HTLV infection appears to be approximately 1 in 70 000 per unit (187). The risk factors for HTLV-I infection in donors are largely geographic, whereas HTLV-II infection is primarily associated with drug abuse (177). Some 97% of individuals with anti-HTLV-I show virus within their lymphocytes (179), but seroconversion has not been observed after transfusion of fresh frozen plasma or plasma-derived products from seropositive donors (177,178).

West Nile virus

A Georgia woman who died after an automobile crash was given multiple blood transfusions before she died (188). Blood samples taken at arrival in the emergency department were negative for West Nile virus, while blood samples that were taken after she had received several transfusions were positive. This finding raised concerns about transmission of West Nile virus via blood. One out of five people infected with West Nile virus will develop a mild febrile illness, lasting 3–6 days; one out of 150 people will develop meningitis or encephalitis. The West Nile virus circulates in the blood of an infected person for only a few days or weeks. Therefore, the risk of transmission of West Nile virus from transfusion of blood components is low (189).

Protozoa

Chagas' disease

In endemic areas (Central and South America), infection caused by *Trypanosoma cruzi* can be transmitted by blood. The total number of infected immigrants living in the USA has been estimated at about 50 000, and these carriers pose a risk as evidenced by reported transfusion-associated cases.

Malaria

Transfusion-induced malaria may be a life-threatening complication, especially in patients who have been repeatedly transfused, treated with immunosuppressive drugs, or splenectomized (190). The disease is readily transmitted from asymptomatic donors with latent infection. Means of preventing and treating transfusion-transmitted malaria are well defined in current literature (191,192). To prevent malaria transmission, donors from malaria-endemic areas are now only accepted after spending 3 years in a malaria-free area; this interval may well be too short.

Prion diseases

Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker syndrome, fatal familial insomnia, and kuru are fatal diseases of the central nervous system, known as transmissible subacute spongiform encephalopathies (193). Creutzfeldt–Jakob disease is the most common of these and has an incidence of 1:1 000 000 in most countries. About 10% of those involved have a familial disposition, but most cases occur sporadically. There are similar diseases in sheep (scrapie), cattle (bovine spongiform encephalopathy), and other animal species. The cause of the disease was first believed to be a "slow virus," but more and more evidence points to a protein (prion) as the causative agent (194). It appears that a normally occurring protein, located primarily in neuronal cells, changes its conformation and thereby becomes diseased. This diseased protein induces the same conformational change in otherwise healthy proteins. The diseased protein is highly resistant to proteases and accumulates intracellularly and extracellularly, thereby causing the disease.

A few cases of Creutzfeldt–Jakob disease have been transmitted by corneal transplantation, dural transplantation, surgical equipment, and human growth hormone extracted from human pituitary glands (195). This has of course raised concern that Creutzfeldt–Jakob disease might prove to be transmissible by blood and blood products (196). The concern has been further accentuated by recent fears of transmission bovine spongiform encephalopathy through food consumption by humans. Some manufacturers of plasma products have reacted by recalling products from the market (197).

To date studies have shown that patients who develop Creutzfeldt–Jakob disease do not have a history of a higher rate of transfusion or treatment with blood products. Likewise, those who have received blood from donors who subsequently prove to have Creutzfeldt–Jakob disease do not acquire an increased risk. Furthermore, animal experiments have shown that blood and blood products are very low risk materials in transfer experiments from diseased to healthy animals. All the same, certain authorities are now considering the exclusion of donors from families with known cases of classic Creutzfeldt–Jakob disease.

However, the emergence of variant Creutzfeldt–Jakob disease (vCJD) in the UK and France has raised concern about a new "theoretical" risk of infection in patients treated with blood and blood products (198). Animal experiments in which blood from sheep infected with bovine spongiform encephalopathy and natural scrapie-infected sheep into scrapie-free recipient animals have suggested disease transmission by the blood transfusion route in 2 of 24 sheep with bovine spongiform encephalopathy and in 4 of 21 sheep with scrapie (199). Many European countries have incorporated leukodepletion of all blood products, as leukocytes are believed to play a key role in the pathogenesis of variant Creutzfeldt–Jakob disease (198). In some countries, people who have lived in the UK for a period longer than 6 months between 1980 and 1996 are excluded from blood donation (13). Furthermore, it has been shown that various steps used in the manufacture of plasma-derived products also contribute to reduced infectivity by bovine spongiform encephalopathy (198).

Other Environmental Interactions

Interactions of transfusion with transplantation can occur (200). Blood transfusions, and especially donor-specific transfusions, given before kidney transplantation have beneficial effects on graft survival; the mechanism for this is not known (201–203). By contrast, pre-transplant transfusions in bone marrow recipients with aplastic anemia cause major complications, and can be responsible for graft rejection and marrow transplantation failure (204).

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Immunosuppressed patients with, for example, hematological malignancies are less likely to become sensitized to the histocompatibility antigens to which they are exposed by transfusion; restriction of transfusion in the pre-transplant period is therefore not necessary.

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Blood donation

General Information

Among the various adverse effects of blood donation, vasovagal syncope and convulsive reactions are of concern to collection centers, as they may alarm potential first-time donors. First-time donors have a higher frequency of these reactions (1.7%) than repeat donors (0.2%), and donors who have such reactions donate fewer times than those without reactions (1). Donors who react are generally of lower weight and have slightly lower blood pressure than those who do not. Of the relevant social and psychological factors that have been studied, the ingestion of caffeinated beverages and shortening the duration between registration and time of phlebotomy are associated with a reduced risk of reactions (1).

Apheresis procedures are considered to be relatively safe when performed by experienced personnel. However, they are not without dangers, and there are some health risks to both patients and donors. Not unexpectedly, the risks are greater with therapeutic plasmapheresis on account of the underlying disease, with an estimated 3 deaths per 10 000 procedures (2).

Organs and Systems

Cardiovascular

Bruising in the antecubital fossa is one of the commonest adverse effects of blood donation. The common practice of flexing the arm over a cotton wool ball or swab can aggravate bleeding, and direct compression over the puncture site and elevation of the extended arm is recommended (3).

Hematologic

The only significant drawback to repeated whole blood donation is the risk of iron deficiency. In a study in 948 menstruating and 141 non-menstruating female blood donors, menstruating donors had lower mean serum ferritin concentrations than non-menstruating donors. First-time donors had a mean ferritin concentration of 24 μg/ml and regular donors 19 μg/ml. The frequency of donations was more predictive of ferritin concentrations than the number of donations (4). The authors concluded that female donors, especially those who donate three or more times a year, should have their iron status checked at appropriate intervals and should receive iron supplements.

Immunologic

Although no important adverse effects are associated specifically with multiple blood donations, depressed cell-mediated immunity and reduced lymphocyte proliferation responses have been reported in the past (5). This fear has been allayed, for example, by a 1992 study in 27 donors who had regularly given whole blood for at least 4 years; there were no abnormalities in lymphocyte subsets, neutrophil and monocyte receptors, or molecules important for host defences (6). In 25 volunteer donors undergoing regular platelet apheresis by a discontinuous process a large number of T4 and T8 lymphocytes, a moderate number of B lymphocytes, and a smaller number of monocytes were removed (7).

Frequent donations involving apheresis procedures have been reported to cause allergic reactions (urticaria, flushing, wheezing, chest pain, and in a few cases hypotension), probably due to exposure to ethylene oxide (8). Ethylene oxide is often used for sterilizing the polyvinyl chloride tubing, and similar allergic reactions in patients undergoing chronic hemodialysis have been attributed to sensitization to the ethylene oxide used for sterilizing the dialyser. One study has shown significant concentrations of IgE antibodies to ethylene dioxide in the sera of 78% of donors with allergic reactions but in only 12% of control sera.

Susceptibility Factors

Age

It has commonly been thought that donation of blood by older people might involve health risks for themselves, and in many countries healthy potential blood donors are therefore ineligible after the age of 60. However, in a study of the growing demographic group above this age, the adverse effects were no greater than in a control group of donors aged 50–65 years when the standard volume of blood (450 ml) was taken (9).

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Blood glucose meters

General Information

There are various makes of meters used for measuring the blood glucose concentration. On occasion, some have been found to give false readings.

In early June 1998, the manufacturers of SureStep blood glucose meters (LifeScan) announced that they were going to replace some of the meters used by diabetics to test their blood sugar concentration because they were giving confusing error readings. SureStep home blood glucose meters manufactured before August 1997 may have been giving an error message ("Er-1") instead of "HI" (high) when a blood sugar concentration was very high—500 mg/dl (28 mmol/l) or greater. Such a concentration is potentially dangerous if not recognized and treated, and could result in hospitalization or death. The FDA had received reports of two deaths in people whose glucose was very high but who repeatedly got error message readings from the SureStep blood glucose meters and delayed seeking medical care. The FDA was concerned that some diabetics, wholesalers, and distributors who purchase these meters might not realize that this product replacement procedure concerns a potentially serious malfunction (1). The FDA classified LifeScan's recall as a Class I recall, that is a situation in which there is a reasonable probability that the use of the product will cause serious adverse health consequences or death.

People using the affected SureStep meters needed to know that an "Er-1" message might actually mean a very high concentration of blood glucose instead of an error. If users got an "Er-1" message, they needed to use the visual color change indicator to see if their blood glucose was too high. They had to compare the blue dot on the test strip to the color chart on the test strip bottle. If the dot on the strip was as dark as or darker than the color chart, it indicated a very high blood glucose, and they were advised to contact a health professional immediately.

People with diabetes who use the SureStep brand glucose meters were advised not to stop testing their blood glucose concentrations. They could continue to test with these meters as long as they knew that an "Er-1" message could actually mean a very high concentration. It was considered far more dangerous not to check blood glucose than to use a blood glucose meter that might give an unclear error message at high glucose concentrations.

Factors that alter measurements

High altitude

Sports like hiking and skiing at moderate high altitude make glucose estimation mandatory for people with diabetes. Changes in temperature, PaO_2, and humidity can result in errors in blood glucose determination. When tested at 3000 m (10 000 feet) the glucose meter Elite (Bayer Diagnostics) had a tendency to overestimate glucose concentrations, while the Life Scan One Touch II had a tendency to underestimate them (2). The bias was not clinically meaningful, although some care may be necessary when low or intermediate blood glucose concentrations are measured with the Glucometer Elite.

Icodextrin

Icodextrin in the dialysis fluid in continuous ambulatory peritoneal dialysis can contribute to overestimation of blood glucose (SEDA-26, 461). In a comparison of a meter using the glucose oxidation method and a meter using the glucose dehydrogenase method, only the former gave results that were comparable with the laboratory method (3). The authors concluded that meters must be cross-checked with the laboratory before they can be used to measure blood glucose in patients in contact with icodextrin.

Site of blood withdrawal

The site of blood withdrawal can give different values during acute monitoring of glucose (SEDA-26, 461). Blood was tested before and 60, 90, 120, 150, and 180 minutes after a meal from the finger tips, the arms, and the thighs with the One-Touch Ultra Blood Glucose Monitoring System (LifeScan) and an extra finger prick using a blood monitoring system. When the blood glucose concentration was rising, only the finger prick gave accurate results; the readings from the other sites were lower (even after extensive rubbing) (4).

In patients with diabetes given a 75 g oral glucose load followed by a rapid-acting insulin, producing a wide range of blood glucose concentrations, of three different devices for blood glucose estimation, only finger-prick estimations followed the changes in blood glucose (5), although patients preferred other sites for testing (6).

A subcutaneous continuous glucose monitoring system was used for 24 hours in seven strictly regulated adolescents and young adults. For comparison, blood was drawn from an intravenous cannula and determined in the laboratory, and capillary samples were measured on a glucose meter. During the night-time the readings on the continuous glucose monitoring system were on average 38% lower than the other measurements, indicating a high number of false (asymptomatic) attacks of hypoglycemia (7).

Organs and Systems

Immunologic

Finger sepsis aggressive enough to cause osteomyelitis has been reported in two women, one aged 61 years with *Staphylococcus aureus*, *Staphylococcus agalactiae*, and *Enterococcus faecalis*, and another aged 57 years with a beta-hemolytic staphylococcus, *Candida non-albicans*, and unidentified anaerobic bacteria. Antibiotic treatment and local drainage were unsuccessful and the third phalanx had to be amputated. Both patients had poorly controlled diabetes (HbA_{1c} 14% and 12% respectively); they had estimated their blood glucose six times a week using an automatic lancet without changing their disposable needle (8).

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Boraginaceae

See also Herbal medicines

General Information

The genera in the family of Boraginaceae (Table 1) include bluebells, borage, comfrey, and forget-me-nots.

Cynoglossum officinale

Cynoglossum officinale (hound's tongue) contains alkaloids with curare-like activity as well as hepatotoxic and carcinogenic pyrrolizidine alkaloids, which are covered in a separate monograph.

Symphytum officinale

Symphytum officinale (black wort, boneset, bruise wort, comfrey, knitback, knitbone, slippery root) contains pyrrolizidine alkaloids, such as lasiocarpine and symphytine, and their N-oxides, and has repeatedly been associated with hepatotoxicity.

Comfrey products have been withdrawn from the market in several countries, including the USA and the UK. The German Federal Health Office has restricted the availability of botanical medicines containing unsaturated pyrrolizidine alkaloids (1,2). Herbal medicines that provide more than 1 mg internally or more than 100 mg externally per day, when used as directed, are not permitted; herbal medicines that provide 0.1–1 mg internally or 10–100 mg externally per day, when used as directed, may be applied only for a maximum of 6 weeks per year, and they should not be used during pregnancy or lactation.

Adverse effects

Symphytum officinale contains pyrrolizidine alkaloids, which are the subject of a separate monograph. Certain representatives of this class and the plants in which they occur are hepatotoxic, as well as mutagenic and carcinogenic. They can produce veno-occlusive disease of the liver with clinical features like abdominal pain with ascites, hepatomegaly, splenomegaly, anorexia, nausea, vomiting, and diarrhea. Sometimes there is also damage to the lungs.

Liver

The main type of liver damage caused by *S. officinale* is veno-occlusive disease, a non-thrombotic obliteration of small hepatic veins leading to cirrhosis and eventually liver failure (3). Patients can present with acute or chronic signs; portal hypertension, hepatomegaly, and abdominal pain are the main features.

Table 1 The genera of Boraginaceae

Alkanna (alkanna)
Amsinckia (fiddleneck)
Anchusa (bugloss)
Antiphytum (saucerflower)
Argusia (sea rosemary)
Asperugo (German-madwort)
Borago (borage)
Bothriospermum (bothriospermum)
Bourreria (strongbark)
Brunnera (brunnera)
Buglossoides (buglossoides)
Carmona (scorpionbush)
Cordia (cordia)
Cryptantha (cryptantha)
Cynoglossum (hound's tongue)
Dasynotus (whitethroat)
Echium (vipersbugloss)
Ehretia (ehretia)
Eritrichium (alpine forget-me-not)
Hackelia (stickseed)
Harpagonella (grapplinghook)
Heliotropium (heliotrope)
Lappula (stickseed)
Lithospermum (stoneseed)
Macromeria (giant-trumpets)
Mertensia (bluebells)
Myosotis (forget-me-not)
Myosotidium (giant forget-me-not)
Nonea (monkswort)
Omphalodes (navelwort)
Onosmodium (marbleseed)
Onosma (onosma)
Pectocarya (combseed)
Pentaglottis (pentaglottis)
Plagiobothrys (popcorn flower)
Pulmonaria (lungwort)
Rochefortia (rochefortia)
Symphytum (comfrey)
Tiquilia (crinklemat)
Tournefortia (soldierbush)

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- A 23-year-old man who had taken comfrey leaves presented with hepatic veno-occlusive disease and severe portal hypertension and subsequently died from liver failure (4). Light microscopy and hepatic angiography showed occlusion of sublobular veins and small venous radicles of the liver, associated with widespread hemorrhagic necrosis of hepatocytes.

Other reports of hepatotoxicity due to *S. officinale* have appeared (5–7).

However, the author of a review of the toxicity of *S. officinale* pointed out that since 1990 no cases of adverse events have been reported and stated that comfrey has a history of effective therapeutic use in humans and that it "might not be as dangerous to humans as current restrictions indicate" (8).

Fetotoxicity

It is prudent to avoid exposing unborn or suckling children to herbal remedies containing pyrrolizidine alkaloids. Animal studies have shown that transplacental passage and transfer to breast milk are possible, and there is a human case on record of fatal neonatal liver injury, in which the mother had used a herbal cough tea containing pyrrolizidine alkaloids throughout her pregnancy.

Heliotropium species

Heliotropium species contain various pyrrolizidine alkaloids (which are covered in a separate monograph).

Adverse effects

It is prudent to avoid exposure of unborn or suckling children to herbal remedies containing pyrrolizidine alkaloids. Animal studies have shown that transplacental passage and transfer to breast milk can occur, and fatal neonatal liver damage has been reported, when the mother used an herbal cough tea containing pyrrolizidine alkaloids throughout her pregnancy.

The German Federal Health Office has restricted the availability of botanical medicines containing unsaturated pyrrolizidine alkaloids (1,2). Herbal medicines that provide over 1 mg/day internally or over 100 mg/day externally are not permitted; herbal medicines that provide 0.1–1 mg/day internally or 10–100 mg/day may be applied only for a maximum of 6 weeks per year, and they should not be used during pregnancy or lactation.

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Boric acid

See also Disinfectants and antiseptics

General Information

In the past, boric acid was falsely considered to be relatively non-toxic, and had an unwarranted reputation as a germicide. However, it is only bacteriostatic, even in a saturated aqueous solution, and can cause adverse reactions. Boric acid has often proved poisonous, either by ingestion or after local use. Cases from the world literature have been reviewed (1,2). In 172 cases of boric acid intoxication, including 83 deaths, 37 deaths occurred after external use, including 23 children with nappy rash. From 1974 to 1984, the Poison Centre in Paris recorded 134 cases of intoxication with boric acid or borates, 88 of which were accidental and 31 iatrogenic.

Boric acid penetrates even intact skin, but it is readily absorbed through inflamed or otherwise damaged skin and through mucous membranes. After the application of wet compresses of boric acid to intact and eczematous skin in 21 patients over several days, blood concentrations of boric acid were generally not raised (3). One patient, however, did have a significant rise in blood boric acid concentration, which the authors ascribed to pre-existing kidney insufficiency.

Prolonged absorption of boric acid causes anorexia, weight loss, vomiting, mild diarrhea, skin rash, diffuse alopecia, convulsions, and anemia.

On account of the high toxicity and limited therapeutic value of boric acid, the borates have been abandoned as obsolete in many countries.

Organs and Systems

Skin

The skin, which is unlikely to react unfavorably to topical boric acid, can react strongly if it is absorbed systemically; resultant redness can mimic scarlet fever, and psoriasiform lesions, bullae, and alopecia can occur.

Drug Administration

Drug overdose

In acute intoxication, symptoms develop progressively, typically beginning with persistent vomiting and diarrhea (mucous and blood, with a bluish-green color). Shortly after the onset of the gastrointestinal symptoms, in some cases even earlier, a rash appears (with macules and/or papules), beginning on the abdomen, genitalia,

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and head, and rapidly spreading, followed by excoriation and intensive desquamation after 1–2 days. Mucous membranes are often involved, especially in young infants, in whom the mouth, pharynx, and conjunctivae are often inflamed. Later, there are central nervous system symptoms, with headache and mental confusion followed by convulsions. In children there is meningism and twitching of the facial muscles and limbs followed by convulsions. Acute tubular necrosis can occur, with oliguria or anuria, hypernatremia, hyperchloremia and hyperkalemia, proteinuria, erythrocyturia, and cylindruria. Finally, hyperthermia, a fall in blood pressure, tachycardia, and shock occur.

Fourteen cases of acute boric acid ingestion were reported in New York City over 30 months. In these patients excretion of urinary riboflavin (vitamin B_2) was determined, and in about two-thirds it was significantly increased. This is not surprising, since riboflavin and boric acid are known to form a water-soluble complex. The range of lethal doses is 1–3 g for babies, 5 g for infants, and 15–20 g for adults.

- Severe acute boric acid poisoning occurred in a 3-year-old boy after the application of a boric acid-containing talcum powder (4).
- A similar case occurred in a 27-day-old baby girl (5).
- Generalized erythema and skin desquamation, fever convulsions, and diarrhea followed repeated boric acid application to a denuded umbilical stump (6).
- Fatal intoxication has followed prostatectomy and subsequent bladder irrigation with 3% boric acid (7).

Of 172 published cases of boric acid intoxication, 83 proved fatal; the series included 37 deaths after external use of boric acid, 23 of these being children who had developed diaper rashes. The actual number of cases, mostly unpublished, must have been much greater: from 1974 to March 1984, 134 cases of intoxication by boric acid or borates were recorded in France alone, 88 being accidental and 31 associated with medicinal use.

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Bornaprine

See also Adrenoceptor agonists

General Information

Bornaprine, a synthetic quaternary ammonium compound, has been used as an anticholinergic drug in treating Parkinson's disease (1). Its adverse effects are those characteristic of the anticholinergic drugs.

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Bosentan

See also Endothelin receptor antagonists

General Information

Bosentan is an endothelin-A and endothelin-B receptor antagonist. It is effective in pulmonary arterial hypertension (1,2) and has been marketed for this indication. The studies showed an improvement in exercise capacity and dyspnea and an increased time to clinical worsening. Efficacy in pulmonary hypertension has also been reported in an open study with a selective endothelin-A receptor antagonist (3).

The effects of bosentan (62.5 mg bd for 4 weeks followed by either 125 or 250 mg bd for a minimum of 12 weeks) have been studied in a double-blind, placebo-controlled trial in 213 patients with pulmonary arterial hypertension (2). The patients who took bosentan had improved exercise capacity, less dyspnea, and delayed worsening. There were similar results in 32 patients who took bosentan for a minimum of 12 weeks (62.5 mg bd for 4 weeks then 125 mg bd) (4). Bosentan significantly reduced pulmonary vascular resistance. The number and nature of adverse events were similar with bosentan and placebo.

Organs and Systems

Cardiovascular

In a dose-finding study with bosentan (100, 500, 1000, and 2000 mg/day) in 293 hypertensive patients (5) there were statistically significant falls in diastolic blood pressure with the 500 and 2000 mg/day doses. The effects were similar to that of enalapril 20 mg/day. The lowering of blood pressure was not associated with any changes in heart rate, plasma noradrenaline concentrations, plasma renin activity, or angiotensin II concentrations.

In the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) placebo-controlled study the effects of low-dose bosentan (125 mg bd) were evaluated in 1613 patients with severe heart failure

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(left ventricular ejection fraction < 35%, New York Heart Association classes IIIb-IV) (6). The primary endpoint of all-cause mortality or hospitalization for heart failure was reached in 321 of 808 patients who took placebo and 312 of 805 who took bosentan. Treatment with bosentan conferred an early risk of worsening heart failure necessitating hospitalization, because of fluid retention. These results throw doubt on the potential benefits of non-specific endothelin receptor blockade in heart failure. Preliminary data suggest that in heart failure selective endothelin-A receptor antagonists (BQ-123, sitaxsentan) may be more beneficial than non-selective antagonists, especially when there is associated pulmonary hypertension (7).

Liver

The major safety issue that has emerged with bosentan, the endothelin receptor antagonist that has been most extensively studied in man, has been dose-dependent reversible impairment of hepatic function (3% with 125 mg, 7% with 250 mg), manifesting as raised transaminases (2). The effect of bosentan on hepatocanalicular bile-salt transport has been studied in rats in conjunction with a re-examination of the safety database from two clinical trials (in hypertension and congestive cardiac failure) and measurement of bile-salt concentrations in stored blood samples from these trials (8). Hepatic injury was defined as a three-fold increase in alanine transaminase activity. In the hypertension trial there were no cases of hepatic injury with placebo or enalapril. With bosentan, the frequencies were 2, 4, 11, and 8% at dosages of 100, 500, 1000, and 2000 mg/day respectively. There was a dose-dependent increase in bile-salt concentrations. In the study in patients with heart failure (New York Heart Association classes III/IV), liver injury occurred in 4% of 126 patients taking placebo and 18% of 244 patients taking bosentan 500 mg bd. A subgroup analysis showed a higher incidence of hepatic injury in patients taking concomitant bosentan and glibenclamide. Patients with hepatic injury had raised bile-salt concentrations.

In rats, intravenous bosentan produced a dose-dependent increase in plasma bile salts. The effect was potentiated when glibenclamide was co-administered. In vitro studies in rat canalicular liver plasma membranes confirmed inhibition of bile-salt transport. Three bosentan metabolites were also investigated. The M2 metabolite was more potent than bosentan, whereas the M1 and M3 metabolites produced less inhibition of bile acid transport than bosentan. The effects of bosentan and its main metabolites, both of which are eliminated in the bile, on biliary secretion have been studied in rats with biliary fistulae and with or without a genetic defect in mrp2 (9). Intravenous bosentan 0.1–10 mg/kg caused a dose-dependent increase in biliary bilirubin excretion, and doses of 10 mg/kg or over caused a sustained increase in canalicular salt-independent bile flow, combined with significant increases in the concentrations and output of glutathione and of bicarbonate in the bile. Phospholipid and cholesterol secretion were profoundly inhibited and uncoupled from bile-salt secretion. In mrp2-deficient rats, the choleretic effect of bosentan was markedly reduced. Thus, bosentan alters canalicular bile formation mostly via mrp2-mediated mechanisms. Intermittent uncoupling of lipid from bile-salt secretion may contribute to its hepatic adverse effects.

These data suggest that bosentan causes cholestatic liver injury due to inhibition of bile-salt efflux and damage due to intracellular accumulation of bile salts.

Long-Term Effects

Drug tolerance

Despite short-term benefits of bosentan in systemic hypertension and congestive heart failure, it increases plasma concentrations of endothelin-1, probably by inhibiting its clearance via endothelin-B receptors. This may mean that its effectiveness is reduced during long-term therapy (7).

Susceptibility Factors

Renal disease

The effects of severe renal insufficiency on the pharmacokinetics and metabolism of bosentan 125 mg have been studied in an open, parallel-group study in eight patients with creatinine clearances 17–27 ml/minute and in eight healthy subjects (creatinine clearances 99–135 ml/minute) (10). The pharmacokinetics of bosentan did not differ significantly, although the concentrations of the three CYP2C9- and CYP3A4-derived metabolites increased about two-fold in the patients with renal insufficiency. It is not necessary to adjust the dosage of bosentan in patients with any grade of renal insufficiency.

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Botulinum toxin

General Information

Botulinum toxin is one of several toxins produced by the bacterium *Clostridium botulinum*. The toxin binds with high affinity to peripheral cholinergic nerve endings, such as those at the neuromuscular junction and in the autonomic nervous system, preventing the release of the neurotransmitter acetylcholine (1). This action at the neuromuscular junction can cause weakness and even paralysis of the muscles supplied by the affected nerves. Sprouting of the terminal nerves eventually results in re-innervation of the muscles and return of function. Doses are measured in mouse units (MU), 1 MU being the LD_{50} in Swiss–Webster mice.

Botulinum toxin is used in the treatment of excessive muscle contraction disorders (dystonias), such as strabismus, blepharospasm, focal dystonias, and spasticity. One of its uses is in the removal of facial wrinkles by paralysing mimic muscles. It can reduce sweat production by blocking cholinergic innervation of eccrine sweat glands.

Therapeutic studies

For blepharospasm, injections of about 12.5–25 MU are made into the periocular muscles of each eye. When so used, adverse effects are seen in 20–50% of treatments. They consist of mild ptosis, increased or reduced tear function, diplopia, and ectropion. These effects are transient, most lasting about 2 weeks, and generally well tolerated. Occasionally ptosis is so severe as to be inconvenient for the patient. The blepharospasm is relieved for 2–4 months. Systemic effects have not been reported (2).

In the treatment of spastic torticollis there is a tendency to use larger doses (up to 1000 MU) injected into the neck muscles, and weakness of the pharyngeal muscles, resulting in dysphagia and paralysis of the vocal cords, has been reported. Difficulty in swallowing and deepening of the voice were found in up to 30% of cases in one series, resolving after 2–3 weeks (3). In one case there was severe dysphagia 2 days after an injection, with unilateral vocal cord paralysis a week later; swallowing was normal again after 6 weeks (4). The possibility of appreciable effects from this neurotoxin at more distant neuromuscular junctions and the development of antibodies are potential dangers here.

Treatment of spasmodic torticollis with botulinum toxin has been reviewed retrospectively in 107 patients (SEDA-17, 45). It was efficacious in 93% but adverse effects occurred in 84%. Initially, 500 MU were injected into each muscle, but the incidence of adverse effects led to a reduction in dosage, 200–500 MU being injected depending on the muscle used and on neck thickness. The median dose per treatment was 1000 (range 200–1600) MU on the first visit and 800 MU subsequently. Dysphagia occurred after 44% of the treatments. This was severe in 2% of treatments, allowing only sips of fluid and necessitating hospitalization for two patients because of dehydration. Two patients developed stridor, two had substantial weight loss, and one developed pneumonia as a result of aspiration. According to the authors, the risk of dysphagia is 40% if a sternomastoid is injected and 25% if it is not. The risks of moderate or severe dysphagia are 7% and under 1% respectively. The authors estimated that there is a 3% chance of antibody production with reduced responsiveness during the first 15 months of treatment. They recommended antibody testing for patients who have initial but not subsequent improvement after repeated injections of botulinum toxin. The problem of immunological resistance to the effects of botulinum toxin associated with repeat injections has been reviewed elsewhere (5).

In a multicenter, randomized, placebo-controlled trial in 145 patients with axillary hyperhidrosis, refractory to treatment with topical aluminium chloride, both 100 and 200 MU of botulinum toxin reduced sweat production by about 80% (6). After 24 weeks, sweat production in the treated axillae was about 45% of baseline. Temporary adverse events during the first 14 weeks included headache, soreness of the muscles of the shoulder girdle, axillary itching, and increased facial sweating.

A multicenter, double-blind, randomized, placebo-controlled study in 320 patients with untreated hyperhidrosis showed a more than 50% reduction in sweat production at 4 and 16 weeks after treatment respectively in 94 and 82% of patients treated with botulinum toxin (50 MU per axilla) and in 36 and 21% of placebo-treated patients (7). The major treatment-related adverse effect was an increase in sweating in non-axillary sites after treatment. Open treatment with botulinum toxin A was offered to patients in whom sweat production was at least 50% of baseline values (8). Of 207 study subjects, 39% had one treatment, 45% had two treatments and 15% had three treatments. Response rates 4 weeks after treatment were 96, 91, and 83% after the first, second, and third treatments respectively. In one of 207 patients there was possible transient seroconversion from negative to positive for neutralizing antibodies to botulinum toxin, and subsequent treatment with botulinum toxin resulted in complete disappearance of axillary sweating 7 days after injection.

The long-term effectiveness of high-dose botulinum toxin (200 MU per axilla) has been evaluated in an open study in patients with axillary hyperhidrosis unresponsive to previous therapies (9). In 34 patients follow-up was for at least 12 months. Four relapsed within 12 months and two relapsed after 16 and 19 months. Mild pain and a burning

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sensation, sometimes lasting up to 1 hour after injection, were the most frequent adverse effects. No compensatory hyperhidrosis at other body sites was reported.

Organs and Systems

Nervous system

Five cases of severe headache refractory to oral analgesics have been reported in patients treated with 10–38 MU of botulinum toxin for glabella frown lines ($n = 4$) and in a patient treated with 120 MU for palmar hyperhidrosis (10). The headache lasted for 8 days to 4 weeks, did not respond to oral prednisolone, and in some patients was accompanied by photophobia, ear tenderness, or nasal congestion. Two patients had had a similar headache after a previous treatment with botulinum toxin and in another patient a similar headache occurred after the next treatment. None of the patients had a history of severe headaches.

Neuromuscular function

Muscle weakness after botulinum toxin injection is usually due to local spread of the agent. Asymptomatic systemic effects have been detected in patients with cervical dystonia after repeated botulinum toxin injections, when muscle biopsies from the vastus lateralis muscle were examined (11). However, generalized neuromuscular symptoms are rare. Patients with a reduced margin of safety with regard to neuromuscular transmission might be considered prone to systemic effects, but even in patients with myasthenia gravis symptoms distal from the injection site have been reported only occasionally (12). However, generalized muscle weakness can occur if higher doses of botulinum toxin are used, and a recent report has illustrated that this may happen in patients after many uneventful treatment sessions (13). Electrophysiological findings in these patients were suggestive of mild botulism, with doses of botulinum toxin of 600–900 units. Two similar cases had been reported previously (12). Therefore, constant long-term monitoring of patients is recommended, even if they have been receiving injections for many years without adverse effects.

Generalized muscular weakness associated with signs of systemic cholinergic autonomic impairment has been reported.

- A 25-year-old woman was treated with botulinum toxin for hyperhidrosis of the axillae and hands in one session with a total amount of 1400 MU. Six days later she complained of diffuse weakness, diplopia, mild bilateral ptosis, severe weakness in the fingers, and reduced lacrimation, salivary production, and sweating (14). She recovered completely within 2 months.

Permanent extraocular muscle damage has been reported (15).

- A 70-year-old man had increasing difficulty in maintaining binocular vision while reading. There was imbalance of his extraocular muscle activity. Botulinum toxin 2.5 MU was therefore injected into the left inferior rectus muscle under electromyography control using a 27-gauge needle. At the next visit 1 month later he complained of diplopia in all directions of gaze, in keeping with a left inferior rectus muscle palsy. Over the next 10 months there was no improvement. Magnetic resonance imaging then showed atrophy of the left inferior rectus muscle. Inferior transposition of the medial and lateral recti muscles was performed, which produced satisfactory alignment.

Botulinum-induced atrophy of extraocular muscles of the eye cannot be excluded in this case. This mechanism is supported by the observation that botulinum toxin can cause histological changes in the extraocular muscles in adult monkeys (16). The authors of the present report also suggested that intramuscular hematoma or direct damage to the nerve to the muscle may have been responsible. So far, permanent extraocular muscle damage after botulinum toxin injection seems to be rare. If additional cases are reported, patients should be informed about this possible complication before treatment.

Susceptibility Factors

In the presence of neuromuscular disorders, such as myasthenia gravis or Lambert–Eaton syndrome, botulinum toxin-induced inhibition of acetylcholine release can cause generalized weakness (17). Therefore, botulinum toxin should, if at all, be used with extreme caution in patients with neuromuscular disease, who have a reduced margin of safety with regard to neuromuscular transmission.

- An 80-year-old woman had severe difficulty in swallowing and flaccid paralysis of her cervical muscles starting 4 days after the periocular injection of botulinum toxin 120 MU for blepharospasm (12). She also developed bilateral facial nerve paralysis and slurred speech and could not fully close her eyes. Barium swallow and fluoroscopy showed signs of aspiration. The serum concentration of antiacetylcholine receptor antibodies was 6.9 units (reference range 0–0.7 units). Mestinone and prednisone improved her symptoms. She had been treated with botulinum toxin on 18 occasions over the previous 13 years without any untoward effects.

While the exact cause of muscle weakness was unclear, this case argues against the use of botulinum toxin in patients with myasthenic syndromes. When the margin of safety is reduced with regard to neuromuscular transmission, botulinum toxin can result in increased morbidity or even mortality. Generalized muscle weakness after botulinum toxin has also been reported in patients with other neuromuscular disorders (18). In addition, it should be remembered that both dysphagia and muscle weakness can occur after botulinum toxin injection, even in patients who do not suffer from generalized neuromuscular disorders (19).

Generalized weakness has been reported after botulinum toxin treatment in a patient with amyotrophic lateral sclerosis (18).

Drug Administration

Drug formulations

Pain due to injection of botulinum toxin has been reported to be less severe with botulinum toxin reconstituted in preservative-containing saline 0.9% (benzyl

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alcohol 0.9% w/v) than with botulinum toxin reconstituted in preservative-free saline 0.9% in patients with glabella-frown lines (20).

Drug–Drug Interactions

Neuromuscular blocking drugs

As botulinum toxin inhibits acetylcholine release it can interfere with neuromuscular blocking agents (21). It has been suggested that each dose of botulinum toxin may have two effects: first, a direct increase in sensitivity to neuromuscular blocking agents; second, compensatory synaptic remodeling resulting in reduced sensitivity (21). Thus, the effects of neuromuscular blocking agents on neuromuscular transmission cannot be predicted in patients receiving botulinum toxin.

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Bovine serum albumin (BSA)

General Information

Bovine serum albumin is often used as protein supplement in cell culture media, and residual bovine serum albumin in some formulations has occasionally caused adverse effects. Symptoms are usually mild, such as itching and urticaria. An anaphylactic reaction has been described in a patient undergoing bone marrow transplantation after the bone marrow cells had been kept in bovine serum albumin. As a component of sperm processing media, bovine serum albumin has caused adverse effects after intrauterine insemination (1). The risk of transmission of nvCJD by recombinant proteins is unknown, as cell cultures used for manufacturing them often contain bovine serum albumin (2).

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Brassicaceae

See also Herbal medicines

General Information

The genera in the family of Brassicaceae (Table 1) include various types of brassica (cabbage, broccoli, brussels sprouts, kale, kohlrabi, pak choi, rape, turnip), mustard, and cress.

Table 1 The genera of Brassicaceae

Alliaria (alliaria)
Alyssum (madwort)
Anelsonia (anelsonia)
Aphragmus (aphragmus)
Arabidopsis (rock cress)
Arabis (rock cress)
Armoracia (armoracia)
Athysanus (sandweed)
Aubrieta (lilac bush)
Aurinia (aurinia)
Barbarea (yellow rocket)
Berteroa (false madwort)
Brassica (broccoli, cabbage, mustard, rape)
Braya (northern-rock cress)
Bunias (warty cabbage)
Cakile (searocket)
Calepina (ballmustard)
Camelina (false flax)
Capsella (capsella)
Cardamine (bittercress)
Cardaria (whitetop)
Caulanthus (wild cabbage)
Caulostramina (caulostramina)
Chlorocrambe (chlorocrambe)
Chorispora (chorispora)
Cochlearia (scurvy grass)
Coincya (star mustard)
Conringia (hare's ear mustard)
Coronopus (swine cress)
Crambe (crambe)
Cusickiella (cusickiella)
Descurainia (tansy mustard)
Dimorphocarpa (spectacle pod)
Diplotaxis (wallrocket)
Dithyrea (shield pod)
Draba (draba)
Dryopetalon (dryopetalon)
Eruca (rocket salad)
Erucastrum (dog mustard)
Erysimum (wallflower)
Euclidium (mustard)
Eutrema (eutrema)
Glaucocarpum (waxfruit mustard)
Guillenia (mustard)
Halimolobos (fissurewort)
Hesperis (rocket)
Heterodraba (heterodraba)
Hirschfeldia (hirschfeldia)
Hutchinsia (hutchinsia)
Iberis (candytuft)
Idahoa (idahoa)
Iodanthus (iodanthus)
Ionopsidium (ionopsidium)
Isatis (woad)
Leavenworthia (gladecress)
Lepidium (pepperweed)
Lesquerella (bladderpod)
Lobularia (lobularia)
Lunaria (lunaria)
Lyrocarpa (lyrepod)
Malcolmia (malcolmia)
Mancoa (mancoa)
Matthiola (stock)
Microthlaspi (penny cress)
Moricandia (moricandia)
Myagrum (myagrum)
Neobeckia (lake cress)
Nerisyrenia (fan mustard)
Neslia (neslia)
Parrya (parrya)
Pennellia (mock thelypody)
Phoenicaulis (phoenicaulis)
Physaria (twinpod)
Polyctenium (combleaf)
Raphanus (radish)
Rapistrum (bastard cabbage)
Rorippa (yellowcress)
Schoenocrambe (plains mustard)
Selenia (selenia)
Sibara (winged rock cress)
Sibaropsis (sibaropsis)
Sinapis (mustard)
Sisymbrium (hedge mustard)
Smelowskia (candytuft)
Stanfordia (stanfordia)
Stanleya (prince's plume)
Streptanthella (streptanthella)
Streptanthus (twist flower)
Stroganowia (stroganowia)
Subularia (awlwort)
Synthlipsis (synthlipsis)
Teesdalia (shepard's cress)
Thelypodium (thelypody)
Thelypodiopsis (tumble mustard)
Thlaspi (penny cress)
Thysanocarpus (fringepod)
Tropidocarpum (tropidocarpum)
Warea (pineland cress)

Several of the Brassicaceae contain allyl isothiocyanate, which is a potent irritant and has mutagenic activity in bacteria and fetotoxic and carcinogenic effects in rats. However, as allyl isothiocyanate also occurs in ordinary mustard, it would not be realistic to ban all botanical drugs that contain it, since they commonly provide no more than a normal daily dose of mustard (for example 5 mg of allyl isothiocyanate per 5 g of mustard).

Armoracia rusticana

Armoracia rusticana (horseradish) contains 0.05–0.2% of essential oils of which 85% is allyl isothiocyanate.

Adverse effects

Abdominal discomfort and convulsive syncope occurred after the ingestion of raw horseradish that had not been properly aired before use (1).

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Brassica nigra

Brassica nigra (black mustard) contains allyl isothiocyanate. External application of preparations from black mustard has declined because of skin irritation (see *Sinapis* species).

Raphanus sativus

The root of *Raphanus sativus* var. niger (black radish) contains 0.0025% of essential oil with glycosides yielding allyl isothiocyanate and butyl isothiocyanate.

Adverse effects

The consumption of several roots of *Raphanus sativus* can produce miosis, pain, vomiting, slowed respiration, stupor, and albuminuria.

Allergic contact dermatitis has been attributed to radish (2).

Sinapis species

The *Sinapis* genus contains several different types of mustard species, including *Sinapis alba* (white mustard) and *Sinapis arvensis* (charlock mustard). Mustard has traditionally been used in heated compresses (sinapisms) to draw blood away from underlying infections and to act as a counterirritant. This can cause direct skin damage.

- A 50-year-old woman experienced a second-degree burn after applying a heated mustard compress to her chest to relieve pulmonary congestion associated with a recent episode of pneumonia (3). The injury resulted in permanent hyperpigmentation and hypertrophic scarring.

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Brequinar

General Information

Brequinar (DUP 785, NSC 368390) is a quinoline carboxylic acid derivative that inhibits pyrimidine synthesis by inhibiting dihydro-orotate dehydrogenase. It was originally developed as an anticancer drug, but has also been investigated for its immunosuppressant activity after transplantation. Some data suggest that that the immunosuppressant activity of brequinar may be partly due to inhibition of tyrosine phosphorylation in lymphocytes (1).

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Significant adverse effects of brequinar include thrombocytopenia, maculopapular dermatitis, mucositis, and gastrointestinal disorders (2).

Susceptibility Factors

In patients with renal, hepatic, and cardiac transplants the clearance of a single oral dose of brequinar was lower than expected from previous studies (3), perhaps due to an interaction with ciclosporin, as has been shown in rats (4). Overall safety results suggest that brequinar is well tolerated in stable transplant recipients (3).

Drug–Drug Interactions

Cisplatin

Brequinar was synergistic with cisplatin in preclinical models. However, co-administration of brequinar with cisplatin does not affect the pharmacokinetics of either drug (5).

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Bretylium

See also Antidysrhythmic drugs

General Information

Bretylium, originally introduced as a hypotensive agent but no longer used as such, has not been extensively used as an antidysrhythmic drug. Its clinical pharmacology, uses, efficacy, and adverse effects have been reviewed (1–4). Adverse effects have reportedly caused the need for withdrawal in about 7% of patients (3).

Organs and Systems

Cardiovascular

Postural hypotension is common, and a significant fall in arterial pressure can occur, even in patients who are supine (5).

Occasionally bretylium causes a transient rise in blood pressure after intravenous administration, due to release of noradrenaline from sympathetic nerve endings.

Ventricular tachydysrhythmias have been reported occasionally (6).

Mouth and teeth

Long-term treatment with bretylium can cause parotid pain and swelling and pain in the tongue (7).

Body temperature

Intravenous bretylium can cause severe hyperthermia (8,9).

Drug Administration

Drug administration route

Bretylium is poorly absorbed and is therefore given parenterally. Despite its poor systemic availability, bretylium was available for some years and was often combined with a tricyclic antidepressant. After intravenous administration bretylium can cause hypotension, nausea, vomiting, and diarrhea. Bretylium should be infused over 30–60 minutes to minimize these effects.

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Brimonidine

General Information

Brimonidine is a highly selective potent alpha$_2$-adrenoceptor agonist, which is distinguished from clonidine by a chemical modification that reduces its ability to cross the blood–brain barrier. Like apraclonidine, brimonidine has been used to treat glaucoma. However, unlike apraclonidine, it both reduces aqueous humor production and increases aqueous outflow through the uveoscleral pathway.

The most common adverse effects of brimonidine are dry mouth, fatigue/drowsiness, and blurring of vision, which occurred significantly more often with brimonidine 0.5% than 0.2% (1,2). It can also cause allergic conjunctivitis and ocular pruritus (3). Brimonidine causes fewer adverse effects than apraclonidine, and, because it is a highly selective alpha$_2$-adrenoceptor agonist, does not cause mydriasis, lid retraction, or conjunctival blanching/rebound hyperemia (4). It is less polar than apraclonidine and is therefore more likely to cross the blood–brain barrier. However, symptoms of fatigue can occur.

Organs and Systems

Sensory systems

In a comparison with timolol, brimonidine had similar efficacy but produced more ocular allergic reactions, oral dryness, and conjunctival follicles (5). In a comparison with betaxolol 0.25% suspension, brimonidine 0.2% solution was more effective, but with a similar overall incidence of adverse effects (6).

Susceptibility Factors

Age

Brimonidine should be avoided in children, because apnea and hypotension occur.

- A 1-month-old infant with Peters anomaly had recurrent episodes of unresponsiveness, hypotension, hypotonia, and bradycardia (7). Extensive medical evaluation showed that these episodes were caused by the ophthalmic use of brimonidine.

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Brofaromine

See also Monoamine oxidase inhibitors

General Information

Brofaromine is a selective inhibitor of monoamine oxidase (MAO) type A. In an open study in endogenous depression, adverse effects were reported in nine of 51 patients; these included dry mouth, dizziness, tremor, hypomania, anxiety, and memory problems (SEDA-17, 16).

A randomized comparison of brofaromine with imipramine in inpatients with major depression showed that brofaromine was as effective as imipramine in the treatment of major depression but had a different adverse effects profile (1). Brofaromine was more likely to cause sleep disturbances but lacked the anticholinergic and certain cardiovascular adverse effects of imipramine.

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Bromazepam

See also Benzodiazepines

General Information

Bromazepam, a moderately short-acting benzodiazepine (half-life about 12 hours), has been used in the treatment of anxiety states and has the usual effects of benzodiazepines, for example amnesia and depressed psychomotor performance, although it causes less depression than lorazepam (SED-12, 98).

Organs and Systems

Nervous system

The mechanism of rare extrapyramidal effects with bromazepam is unexplained (SEDA-18, 44).

Long-Term Effects

Drug withdrawal

Catatonia has been described as an effect of bromazepam withdrawal (1).

- A 51-year-old man who had been taking bromazepam for 9 years in a dosage that he had gradually increased to 18 mg/day abruptly stopped taking it. He initially developed psychotic symptoms and on day 5 after withdrawal became mute and was posturing. A provisional diagnosis of a catatonic syndrome was made, and he was given oral lorazepam 3 mg and risperidone 4 mg. It was later concluded that the catatonia had most probably been due to benzodiazepine withdrawal; the risperidone was withdrawn, and diazepam was substituted for lorazepam and slowly tapered. He had no recurrence of catatonic or psychotic symptoms and his fatigue improved.

Withdrawal-induced seizures have been described in a woman taking various benzodiazepines (2).

- A 43-year-old woman had had insomnia since she was a child. At the age of 15, benzodiazepine therapy improved her sleeping, but when she gradually stopped taking benzodiazepines the insomnia returned after a few days. At the age of 26 she was abusing several benzodiazepines, including diazepam and flunitrazepam. At the age of 30 she was taking high doses of bromazepam every evening before going to sleep. After 1 month, she abruptly stopped taking bromazepam and during withdrawal had an epileptic seizure. During the next few years, she had periods of relative well-being, but also two further periods of benzodiazepine abuse, both resulting in seizures after withdrawal. She later had withdrawal seizures with zolpidem.

Drug Administration

Drug overdose

A fatal overdose of bromazepam has been reported (3).

- A 42-year-old woman with a history of depression was found unconscious, lying near her car. The lower part of her body was undressed and there were multiple purple spots and excoriations on her body, suggesting a sexual assault. She was hypothermic (core temperature 28.4°C). Her plasma bromazepam concentration was 7.7 mg/l, the highest concentration reported in a case of fatal intoxication.

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Drug–Drug Interactions

Fluconazole

The interaction of bromazepam with fluconazole has been studied in 12 healthy men in a randomized, double-blind, four-way crossover study (4). The subjects took a single oral or rectal dose of bromazepam (3 mg) after pretreatment for 4 days with oral fluconazole 100 mg/day or placebo. Pharmacodynamic effects of bromazepam were assessed using self-rated drowsiness, the continuous number addition test, and electroencephalography. After rectal administration there was a higher AUC (1.7-fold) and a higher C_{max} (1.6-fold) than after oral administration; there were electroencephalographic effects and subjective drowsiness after rectal bromazepam, and the electroencephalographic effects correlated closely with mean plasma bromazepam concentrations. However, fluconazole caused no significant changes in the pharmacokinetics or pharmacodynamics of oral or rectal bromazepam.

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Bromfenac sodium

See also Non-steroidal anti-inflammatory drugs

General Information

Bromfenac sodium (2-amino-3-(4-bromo-benzoyl)-benzeneacetic acid sodium salt sesquihydrate) has a safety profile apparently similar to that of other NSAIDs (SEDA-17, 109) (SEDA-21, 104). It was approved by the FDA in 1997 for short-term management of acute pain, but was withdrawn by the manufacturers in 1998.

Organs and Systems

Liver

In June 1998 bromfenac was withdrawn from the market because of postmarketing reports of severe hepatic failure, resulting in four deaths and eight liver transplants (SEDA-22, 115). Descriptions of some cases have appeared (1–4).

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Bromhexine

General Information

Bromhexine is taken orally or by aerosol and reduces sputum viscosity as measured ex vivo. Although it is still used empirically by some physicians, there have been no controlled studies showing a significant improvement in clinical status or lung function. Administration by inhalation aerosol or nasal spray produces a local expectorant/mucolytic effect (1). Inhaled bromhexine (Paxirasol) reduces the amount of sputum, but does not reduce symptoms (SEDA-17, 208).

Organs and Systems

Gastrointestinal

Bromhexine can cause gastrointestinal intolerance and impair the mucous barrier in the stomach; it has been suggested it should not be given to patients with gastric ulceration. Reactivation of ulcers has been reported in a few patients, but hematemesis, melena, or other complications have not been described (2).

Drug–Drug Interactions

Antibiotics

Bromhexine increases the concentration of amoxicillin in the sputum (SEDA-17, 208) and promotes the diffusion of antibiotics into lung tissue (1).

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Bromocriptine

General Information

Bromocriptine is an ergot derivative. High doses (for example 30–75 mg/day orally) are used in Parkinson's disease; low doses (2.5–5.0 mg/day) are used for prostatic tumors and to suppress lactation. The adverse reactions are dose-dependent and, so far as is known, reversible, but they are frequent, being experienced in up to 50% of cases. At any dose, nausea, vomiting, and postural hypotension are problematic in some patients, especially those who take high doses from the start. The gastrointestinal symptoms tend to abate as treatment is continued, but other symptoms, for example peripheral circulatory disturbances, can occur later. Psychic and psychiatric changes can be troublesome in a proportion of patients on high doses. Constipation tends to be a frequent and persistent complication.

Organs and Systems

Cardiovascular

Occasionally, patients taking low doses have postural hypotension, leading to dizziness or syncope. Raynaud's syndrome, with blanching of the extremities in response to cold, is rare. At high doses some 30% suffer a peripheral cold reaction of this type, which may not become manifest for a time, while leg cramps occur in some 10% of cases. Under 10% of patients have flushing or erythromelalgia, and hypotension occurs in some 5%. Occasional cases of bradycardia or acute left ventricular failure have been described. Patients with angina pectoris can experience aggravation of their symptoms (SED-12, 317). Even acute myocardial infarction after coronary spasm has been reported (SEDA-12, 123) (SED-12, 317).

Bromocriptine has been associated with myocardial infarction, presumably because of coronary artery spasm.

- A 29-year-old woman took bromocriptine 5 mg/day postpartum to suppress lactation (1). Four days later she developed an acute anterior myocardial infarction. Angiography showed dissection of the left main and anterior descending arteries, with occlusion of the latter. She recovered after emergency arterial grafting.
- A 21-year-old woman had an inferior myocardial infarction, in the absence of cardiovascular risks and with normal coronary arteries on angiography (2). She made a good recovery, but with some persistent posterior-wall akinesia.

In another similar case the myocardial infarction proved fatal (3).

- A 30-year-old woman collapsed and died after a first dose of bromocriptine 2.5 mg. She had severe atheroma narrowing the right coronary artery proximal to the site of thrombosis. The only obvious risk factor was heavy smoking, 30 cigarettes per day.
- A 38-year-old woman had an acute occlusion of the right popliteal artery, which gradually resolved without surgical intervention after treatment with vasodilators, anticoagulants, and antiplatelet drugs (none of which were specified) (2). Her serum cholesterol concentration was 8 mmol/l, but she had no other risk factors.

Myocardial infarction occurred postpartum in two women taking bromocriptine (4).

- A 33-year-old woman taking bromocriptine 5 mg/day for suppression of lactation was given ergotamine 2.25 mg for acute migraine, having taken ergotamine intermittently for over 20 years. She had a myocardial infarction involving the left anterior descending coronary artery, without apparent pre-existing atherosclerosis. She made a good recovery following thrombolysis.
- A 29-year-old woman taking bromocriptine 5 mg/day postpartum had a dissection of the left anterior descending coronary artery and needed emergency bypass grafting. She made a good recovery.

These cases emphasize the potential danger of these drugs, even in young and apparently healthy individuals, although in the first case the use of two ergot derivatives simultaneously may have been ill-advised.

Edema can occur with this and other dopamine receptor agonists, the association easily being overlooked (SEDA-18, 159).

Fibrotic complications can extend to the heart, resulting in constrictive pericarditis.

Respiratory

Pulmonary reactions are rare. Pleural thickening and effusions and pleuropulmonary fibrosis have been observed in a few cases (SEDA-11, 130).

Ear, nose, throat

Nasal congestion can uncommonly occur with bromocriptine (5).

Nervous system

The high doses used in Parkinson's disease are perhaps slightly less well tolerated than equieffective doses of levodopa.

Dyskinesias can occur with bromocriptine but less often than with equieffective doses of levodopa (6).

Bromocriptine has been used successfully in patients with unilateral motor neglect, usually after a stroke.

- A 58-year-old man had a right middle cerebral artery infarction leading to, among many other neurological deficits, left-sided neglect (7). When he took bromocriptine 20 mg/day this abnormality worsened and then improved again on withdrawal.

The authors suggested that this may have been due to damage to the right putamen, while bromocriptine could still activate the striatum on the left, aggravating the hemispheric bias.

In the USA, bromocriptine has not been licensed for the suppression of lactation since 1994. Up to that time there had been no reports of intracranial hemorrhage associated with bromocriptine, but since the withdrawal

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of the license for this indication there have been 15 case reports of this disastrous adverse effect.

- Three women aged 22, 24, and 40 years took bromocriptine 2.5 mg bd for 2–5 days postpartum and complained of headache; two lost consciousness (8). One subsequently died and another had a residual neurological deficit. In all three cases intracerebral hemorrhage, confirmed by CT or MRI scans, occurred on the sixth day of administration. Maximal recorded blood pressures were 200/100, 173/120, and 180/118 mmHg.

Three cases of contractures of the extremities were possibly caused by bromocriptine (SEDA-14, 119).

Occasionally, paresthesia and bad dreams have been described.

When the manufacturers examined reports from physicians on adverse effects from bromocriptine in inhibition of lactation, there were 38 cases of seizures (9).

A cerebral angiopathy postpartum was also described (10).

Cerebrospinal fluid rhinorrhea has been described as an interesting but highly unusual sequel of bromocriptine administration (SEDA-8, 143). The reverse effect, air aspiration through a sellar-pharyngeal leak, has also been encountered (SEDA-9, 126).

Sensory systems

In one series, three of 18 patients developed blurred vision during high-dose treatment of Parkinson's disease (SEDA-3, 124). Diplopia has been incidentally reported. In three patients with chronic hepatic encephalopathy, reversible ototoxicity developed after the administration of bromocriptine (11).

Psychological, psychiatric

Up to 10% of patients have to be withdrawn from treatment because of psychiatric symptoms. Bromocriptine-induced psychosis is well known and particular caution is warranted in patients with a family history of mental disorders (12). Even very low doses of bromocriptine can cause psychotic reactions (SEDA-9, 126) (SEDA-10, 117), and well-recognized problems include confusion, hallucinations, delusions, and paranoia.

Endocrine

Inappropriate secretion of ADH has been described in a single patient (13).

Hematologic

One case of leukopenia and thrombocytopenia has been described (14).

Gastrointestinal

Nausea and vomiting are common with bromocriptine (15).

Liver

In one series, six of 18 patients taking high doses for Parkinson's disease developed isolated and asymptomatic increases in serum transaminases (SED-12, 317). Other patients have also had this reaction, which is reversible (SEDA-17, 168).

Skin

- A 28-year-old woman taking bromocriptine 5 mg/day for a microprolactinoma developed numerous nodular skin lesions (16). Skin biopsy showed a polyclonal proliferation of both B and T lymphocytes in a follicular pattern, and a diagnosis of cutaneous pseudolymphoma was made. The lesions disappeared within 8 weeks of withdrawal.

Alopecia, reversible after drug withdrawal, has been reported as a rare effect of bromocriptine (SEDA-18, 159).

Hair

Treatment with bromocriptine has very rarely been associated with reversible alopecia (17).

Serosae

Retroperitoneal fibrosis (SEDA-12, 123) (18) and pulmonary fibrosis (SEDA-11, 130) during treatment with high doses of bromocriptine have been observed. The drug's structural relation to methysergide clearly has to be kept in mind. Pleural thickening and effusions can be present in up to 6% of patients treated with bromocriptine for Parkinson's disease, and this is related to duration of exposure and cumulative dose (19). The author recommended drug withdrawal in these patients. However, withdrawal does not always lead to complete resolution of the lesions (20).

- A 63-year-old woman with Parkinson's disease developed bilateral pleural thickening and effusions with interstitial shadowing in the lungs 4 years after starting treatment with bromocriptine. After replacement of the drug by levodopa there was gradual improvement, but some pleural thickening remained nearly 3 years later.

Constrictive pericarditis has also been reported.

- Constrictive pericarditis occurred in two men aged 63 and 69 years treated respectively with bromocriptine 40 mg/day for 4 years and 30 mg/day for 2 years (21). Pericardiectomy was performed in both cases, but bromocriptine was not suspected at that time. In one case the drug was continued until a pleural effusion occurred 7 months later; in the other withdrawal of bromocriptine was prompted by an episode of confusion just before pericardiectomy.

Sexual function

Increased sexual drive in patients with Parkinson's disease is common, but bromocriptine can also cause impotence, which can respond to dosage reduction (SEDA-13, 111).

Immunologic

- An allergic reaction was attributed to bromocriptine in a 26-year-old woman with a prolactin-secreting microadenoma (22).

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Long-Term Effects

Mutagenicity

No chromosomal changes were found in 19 children born after bromocriptine-induced ovulation (23).

Tumorigenicity

In rats (but not in mice) high doses of bromocriptine induced malignant uterine tumors within 2 years (SEDA-3, 122). Tumor induction has not been seen in man, but enlargement of a non-invasive pituitary tumor has been observed on more than one occasion.

Second-Generation Effects

Fertility

Sudden induction of fertility in sterile women can occasionally be an embarrassing adverse reaction if the drug is being used for other purposes, for example Parkinson's disease.

Fetotoxicity

Because of its use in the treatment of female infertility, which inevitably involves early exposure of some embryos, the safety of bromocriptine in early pregnancy has been systematically evaluated in a large multicenter study with prolonged follow-up (SEDA-13, 112). There was no evidence that this use of bromocriptine was associated with an increased risk of spontaneous abortion, multiple pregnancy, or the occurrence of congenital malformations; nor did exposure in utero seem to have any adverse effects on postnatal development. Cervical incompetence may be a problem at the time of delivery, but this may well be due to a long history of infertility rather than to the drug itself.

Lactation

Bromocriptine suppresses lactation and the infant should not be breast-fed from the moment treatment is begun. If bromocriptine is deliberately (and successfully) used to suppress lactation, breast tenderness and milk leakage can ensue. It has been suggested that the use of bromocriptine for this purpose raises the risk of postpartum seizures, but the evidence is equivocal (SEDA-17, 146).

Susceptibility Factors

If bromocriptine is to be used to treat infertility, the presence of a pituitary adenoma must be excluded, since this can otherwise undergo suprasellar extension during pregnancy. Because of its adverse reactions profile, bromocriptine is better avoided in patients with cardiac disease or peripheral vascular disease. Acromegaly in patients with a history of gastrointestinal ulceration or bleeding should not be treated with bromocriptine; generally, however, it seems to be rather better tolerated by patients with acromegaly, as well as by postmenopausal women and patients with a raised serum prolactin concentration than by other patients.

It is thought that bromocriptine may aggravate hypertension of pregnancy (SEDA-15, 2); this has led to hesitation over the continued use of bromocriptine for suppression of lactation, especially in patients with a history of pregnancy-induced hypertension.

Cocaine abusers, it is thought, may develop cerebrovascular and cardiovascular disorders if they take bromocriptine (24,25).

Drug Administration

Drug administration route

Intravaginal administration, sometimes used to reduce gastric adverse effects, has caused a vaginal burning sensation in a few patients (26).

Drug–Drug Interactions

Griseofulvin

The response to bromocriptine, at least in acromegaly, can be blocked by griseofulvin (27).

Pseudoephedrine

Psychosis has been described in a 19-year-old postpartum woman who took bromocriptine and pseudoephedrine (28).

Sympathicomimetic drugs

Dangerous hypertensive reactions can result from interactions with the sympathicomimetic drugs isometheptene and phenylpropanolamine (SEDA-17, 168).

Tamoxifen

Tamoxifen can resolve some of bromocriptine's adverse effects, offering the possibility of bromocriptine treatment to patients who cannot otherwise tolerate it (SEDA-8, 144).

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Brompheniramine

See also Antihistamines

General Information

Brompheniramine is a first-generation antihistamine, an alkylamine derivative, with antimuscarinic and moderate sedative actions.

Long-Term Effects

Drug withdrawal

Withdrawal symptoms resembling cholinergic rebound (nausea, tremor, and sweating) have been described after long-term brompheniramine treatment (1).

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Bropirimine

General Information

Oral bropirimine is an immunostimulant that has been used in the management of transitional cell carcinoma of the bladder and upper urinary tract. It is supposedly an interferon inducer. In clinical trials, bropirimine produced mild adverse effects in about 30% of patients. Nausea or vomiting were the most common (21% of patients), and headache, transient liver enzyme rises, skin rash, and arthralgia were observed in 5–14% (1). Tachycardia or chest pain occurred in 5%. Adverse effects required drug withdrawal in 15% of patients (2).

Oral bropirimine (3 g/day thrice weekly for 1 year) has been compared with weekly intravesical Bacillus Calmette-Guérin (2 cycles of 6 weeks) in 55 patients with newly diagnosed bladder carcinoma (3). Whereas the response to treatment was not significantly different between the two groups, adverse effects resulted in more withdrawals with BCG than bropirimine (14 versus 4%). Bropirimine produced more frequent systemic reactions (in particular diarrhea, fever, flu-like syndrome, headache, nausea/vomiting) but less frequent and less severe local complications.

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Bryostatins

General Information

Bryostatins are naturally occurring antineoplastic macrocyclic lactones derived from the marine invertebrate *Bugula neritina*, different varieties being isolated from different populations of the same species. More than 13 structurally related compounds have been isolated (1,2), and there is a variety of synthetic analogues (3). The bryostatins modulate the activity of protein kinase C.

Bryostatin 1 binds to the regulatory domain of protein kinase C; short-term exposure promotes activation of protein kinase C, whereas prolonged exposure promotes significant down-regulation (4). In preclinical and phase I clinical studies it had promising antitumor and immunomodulating effects. It amplifies expansion of myeloid and erythroid progenitor cells stimulated by the cytokines GM-CSF, M-CSF, and IL-3. Similarly, it induces the production of peripheral blood mononuclear cells with enhanced lymphokine-activated killer cell activity and proliferation in the presence of IL-2 (5).

In a phase II study, 17 patients with progressive indolent non-Hodgkin's lymphoma, previously treated with chemotherapy, received bryostatin 1 (5). Phlebitis was initially due to the 60% ethanol formulation used for administration, and the subsequent use of another formulation (60% polyethylene glycol, 30% ethanol, 10% Tween 80) reduced the incidence. In one patient, bryostatin 1 was withdrawn because of grade 2 thrombocytopenia. The dose-limiting adverse effect was myalgia, which occurred in eight patients.

Other adverse effects include fatigue, nausea, headache, vomiting, dyspnea, ataxia, anorexia, anemia, and lymphopenia (6–8).

In a phase-II study, 14 patients with metastatic cervical cancer or recurrent disease not eligible for surgery or radiation received bryostatin 1 50–65 $\mu g/m^2$ + cisplatin 50 mg/m^2. The most common adverse effects were myalgia, anemia, and nausea or vomiting; one patient had a hypersensitivity reaction and one developed grade 3 nephrotoxicity (9).

Organs and Systems

Skin

Adverse effects of bryostatin 1 on the skin reported during phase I and II studies were alopecia, mucositis, non-specific rashes, bronzing, and hyperpigmentation in sun-exposed areas; a morbilliform eruption has also been reported (10).

Musculoskeletal

In a phase-I trial of bryostatin 1 as a 24-hour continuous infusion followed by bolus vincristine in 24 patients with refractory B cell malignancies other than acute leukemias, the dose-limiting adverse effect was myalgia (11).

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Bucillamine

General Information

Bucillamine (mercaptomethylpropanoylcysteine) is chemically related to penicillamine and is also used in rheumatoid arthritis. Most of the information on bucillamine comes from Japan, its country of origin (1).

The patterns of adverse reactions to sulfhydryl compounds that are used in rheumatoid arthritis (bucillamine, pyritinol, and tiopronin) show remarkable similarities to those of penicillamine (SED-12, 548) (2).

Organs and Systems

Respiratory

In 10 patients with bucillamine-associated interstitial pneumonitis, the HLA antigen DR4 was present in all 10 and a positive lymphocyte stimulation test was found in three of the six patients tested (3).

Nervous system

Myasthenia gravis has been reported during the use of bucillamine (4). However, since the disease persisted after withdrawal, the role of the drug was uncertain.

Sensory systems

A change in taste has been attributed to bucillamine in a single case, without further specification (1).

Hematologic

Among 36 Korean patients with rheumatoid arthritis agranulocytosis with high fever developed in one after 3-week use of bucillamine (dose not specified) (5).

Gastrointestinal

Stomatitis, nausea, anorexia, and epigastric discomfort are common during the use of bucillamine (5).

Hemorrhagic gastritis has been reported in a single case, without further specification (1).

Liver

Increased aminotransferase activities were found in about 5% of patients using bucillamine for rheumatoid arthritis (1,5).

Urinary tract

Proteinuria occurs in about 7% of patients using bucillamine (1). Less often, nephrotic syndrome can develop (5–9). Microscopically there is membranous glomerulonephritis, with diffuse fine granular precipitation of IgG and C3 around the capillary walls, electron-dense deposits at the subepithelial side of the basement membrane and effacement of foot processes.

Skin

Bucillamine causes skin reactions in about 5% of patients (10). Rashes and pruritus are frequent and eosinophilia can occur (1,5).

Bullous pemphigoid has been attributed to bucillamine 200 mg/day (10). The mouth, pharynx, larynx, and conjunctiva were involved, as well as the skin on the chest, abdomen, and axilla. Indirect immunofluorescence showed circulating antibodies against the basement membrane.

There have been reports of bucillamine-associated pemphigus.

- A 57-year-old woman developed a generalized itchy rash 9 months after she started to take bucillamine (11). A skin biopsy showed spongiosis, lymphocytic infiltration in the epidermis, and intercellular deposition of IgG.
- Another patient had a pemphigus foliaceus-like eruption on three different occasions, in association with penicillamine, auranofin, and bucillamine (12).

A patient taking bucillamine developed an eruption that had features of both pemphigus foliaceus and pemphigus vulgaris and was associated with glomerulonephritis (13).

- A 62-year-old man with rheumatoid arthritis developed a rash on the neck, chest, and legs after taking oral bucillamine (dose not specified) for 6 months. The lesions were of two different types: small pigmented, vesicular, erythematous macules, similar to those of pemphigus foliaceus, and skin erosions, as seen in pemphigus vulgaris. There was no mucosal involvement. Serology was positive for antinuclear antibodies (1:320, nucleolar type). A biopsy showed acantholysis in the granular, spinous, and suprabasal layers. Direct immunofluorescence showed intercellular deposits of IgG and C3 throughout the epidermis, but not in the basement membrane. Indirect immunofluorescence of donor skin showed IgG reactivity in the nuclei of keratinocytes. An enzyme-linked immunoadsorbent assay (ELISA), using baculovirus-expressed recombinant desmogleins as antigen, was positive and indifferent to circulating anti-Dsg1 and anti-Dsg3 antibodies. This patient also had the nephrotic syndrome (proteinuria 8.7 g/day, total serum protein 59 g/l, serum total cholesterol 10.2 mmol/l), probably also due to bucillamine. A renal biopsy was consistent with membranous glomerulonephritis. The skin lesions improved within 1 month of bucillamine withdrawal, but full recovery of both cutaneous and renal injury was achieved only after the use of prednisone, 40 mg/day for 2 weeks.

In 13 patients with the peculiar yellow nail syndrome, bucillamine was the suspected cause in 7 (14).

Reproductive system

Gigantism of the breasts, probably induced by bucillamine, has been reported (15).

- After attempts with chrysotherapy and lobenzarit, a 24-year-old woman was given bucillamine 300 mg/day and a glucocorticoid, predonine, for rheumatoid arthritis. After 10 months she noticed bilateral breast

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enlargement, which over 6 months progressed to extreme proportions, the left breast ultimately reaching as far as her pubis. The skin of the breasts was thin and erythematous, with marked dilatation of the superficial veins. The nipple areola complexes were elongated and poorly defined from the surrounding skin. There were no abnormalities of prolactin, sex hormones, growth hormone, or TSH (but the values were not stated). Bilateral total mastectomy was performed and the nipple-areola complexes were removed from the resected tissue and grafted on to the breasts after insertion of a tissue expander. The breast tissue removed from the right side weighed 5 kg and that from the left side 7 kg. Histologically there was increased fibrosis and duct dilatation and no malignancy.

This effect, attributed here to bucillamine, is a rare but well-established adverse effect of penicillamine. Although the patient had also taken isoniazid for pulmonary tuberculosis, that was unlikely to have played a part, since the breast enlargement started earlier and progressed after the isoniazid had been withdrawn.

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Bucloxic acid

See also Non-steroidal anti-inflammatory drugs

General Information

Bucloxic acid is an NSAID that is not widely used. The usual symptoms of gastrotoxicity, nephrotoxicity, and increased blood pressure have been reported, but the major adverse effects involve skin and allergic reactions. Quincke's edema has been observed (SED-9, 152) (1) (SEDA-1, 93).

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Bucricaine

See also Local anesthetics

General Information

Bucricaine (centbucridine) is a quinolone derivative with local anesthetic activity.

Nausea, vomiting, bradycardia, backache, shivering, and hypotension can occur with a similar incidence to that of lidocaine (SED-12, 256) (1). It has been suggested that bucricaine is more potent than lidocaine and has few cardiovascular and nervous system adverse effects in animals, at high doses. One study in humans suggested that bucricaine may be associated with fewer cardiovascular adverse effects than lidocaine, but there are insufficient data to confirm this impression (2).

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Bufexamac

See also Non-steroidal anti-inflammatory drugs

General Information

Bufexamac is intended for topical use as a cream (using iontophoresis, ultrasound, and massage). Local intolerance causes burning and irritation, attributable to components of the cream. Urticaria, folliculitis, and pyoderma can occur when occlusive dressings are used. The course of contact allergy by bufexamac was particularly protracted and refractory in most of the 24 patients observed in one hospital in 1983–1987 (1). An erythema multiforme-like rash associated with contact dermatitis has been reported (SEDA-18, 103). In children, long-term topical use of bufexamac was well tolerated with few mild local adverse effects (SEDA-20, 91).

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Buflomedil

General Information

Buflomedil hydrochloride is a vasoactive drug with a variety of actions. It is an alpha-adrenoceptor antagonist and a weak calcium channel blocker. It inhibits platelet aggregation and improves erythrocyte deformability. However, its mechanism of action in peripheral vascular disease is not known.

Buflomedil has generally been well tolerated by most patients in clinical trials (1). The most frequently reported adverse effects include flushing, headache, vertigo, gastrointestinal discomfort, and dizziness. These rarely require drug withdrawal. In controlled trials, adverse effects have occurred in 20% of patients assigned to buflomedil and 18% of those assigned to placebo; only gastrointestinal discomfort occurred more frequently in buflomedil-treated patients (3.4 versus 2%) (2).

Organs and Systems

Nervous system

Extrapyramidal symptoms have been reported in a few frail elderly women (SEDA-13, 169). A few cases of myoclonic encephalopathy have been observed at therapeutic dosages; old people, patients of low body weight, and patients with renal insufficiency due to dehydration appear to be especially vulnerable (SEDA-9, 189) (SEDA-10, 172) (SEDA-11, 179).

Psychological, psychiatric

Depression has been reported in a few frail elderly women taking buflomedil (SEDA-13, 169).

Immunologic

An anaphylactic reaction to buflomedil has been reported (3).

- A 53-year-old woman with Raynaud's phenomenon developed an urticarial rash, pruritus, and hypotension 10 minutes after the parenteral administration of buflomedil. She received corticosteroids and recovered within 6 hours. When she later underwent skin tests with buflomedil, there was an immediate positive reaction, suggesting a type I hypersensitivity mechanism.

Drug Administration

Drug overdose

Buflomedil is generally considered to be innocuous at therapeutic dosages. Acute toxicity is due to accidental or intentional overdosage. Overdosage causes generalized seizures and cardiac conduction abnormalities, eventually leading to cardiac arrest (SEDA-21, 215).

Three cases of self-poisoning with buflomedil have been reported (4–6); two were fatal.

- A 15-year-old girl took 24 tablets of buflomedil (300 mg) and had a plasma concentration of 93.7 μg/ml. She was deeply comatose and in a convulsive state. Shortly after, she developed cardiac arrest from which she did not recover despite initially successful resuscitation.
- A young girl took a single dose of buflomedil 7.5 g and a young man 18 g. Coma with convulsions occurred in both, soon followed by rhythm and conduction disturbances. Intensive resuscitation attempts could not prevent a fatal outcome in the girl.

Chronic overdose can also lead to convulsions (7).

- A 75-year-old woman had fever and convulsions. She had diabetes mellitus and angina pectoris and took buflomedil for peripheral arterial disease. No cause for her symptoms was found, but she had a high plasma concentration of buflomedil (6.3 μg/ml, usual target range 4–4.5 μg/ml). The drug was withdrawn and the symptoms did not recur. On questioning, it appeared that she had mistakenly forgotten to abandon her old commercial formulation when her pharmacist proposed a cheaper, new, generic brand, but took both at the correctly prescribed dose.

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Bumadizone

See also Non-steroidal anti-inflammatory drugs

General Information

Bumadizone is an NSAID that is metabolized to phenylbutazone and oxyphenbutazone.

In a study in 647 patients, about 15% had adverse effects (gastrointestinal, fluid retention, and hypersensitivity); treatment was stopped in 7% (1).

Reference

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Bumetanide

See also Diuretics

General Information

Bumetanide is very similar in most respects to furosemide, although it is more potent mole for mole. An oral dose of 1–4 mg often suffices for ordinary use compared with 40–160 mg of furosemide.

Most of the adverse effects of bumetanide are the same as those of furosemide. However, it is less ototoxic and can cause muscle cramps, which furosemide does not.

Organs and Systems

Respiratory

Bumetanide has been implicated in the development of pulmonary fibrosis (SEDA-16, 223), but causality could not be determined with certainty.

Sensory systems

One advantage of bumetanide is that it is less ototoxic than furosemide (1–3). It is sensible to prefer bumetanide to furosemide in patients with hearing problems or who concurrently need ototoxic drugs, such as an aminoglycoside antibiotic.

Metabolism

It has been suggested that bumetanide has a smaller effect on blood glucose than furosemide does, but that is not at all clear.

Gastrointestinal

Very high doses of bumetanide used for renal insufficiency have sometimes produced colic (SED-10, 376).

Pancreas

A patient in whom pancreatitis was induced by both furosemide and bumetanide has been documented (SEDA-14, 184).

Skin

Bullous pemphigoid induced by bumetanide has been reported (4).

- A 67-year-old man presented with an acute bullous eruption 6 weeks after starting bumetanide. He had numerous large tense bullae on erythematous skin, with superficial ulceration on the thighs, arms, and anterior trunk. Pruritus was severe. Routine laboratory tests were normal, except for blood eosinophilia. Biopsy of a blister showed subepidermal bullae associated with dermal infiltrates of neutrophils and eosinophils. Direct immunofluorescence showed continuous linear deposits of C3 and IgG at the basement membrane zone, confirmed by immunoelectron microscopy. Circulating IgG antibasement membrane antibodies were localized in the roof of the blister. Compete clinical healing and normalization of immunology occurred within 2 months of withdrawal of bumetanide.

Pseudoporphyria (SEDA-16, 222) and Stevens–Johnson syndrome have also been reported (SED-10, 376).

Musculoskeletal

Various musculoskeletal symptoms have been reported with bumetanide, including pain, cramping, and weakness (SEDA-22, 236). The symptoms are usually mild and self-limiting, with an incidence of less than 2%, but disabling reactions have occurred after oral administration and intravenous injection, and severity correlates with dose. The onset is usually 2–4 hours after dosing; the onset may be slower during infusion.

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Bupivacaine

See also Local anesthetics

General Information

Bupivacaine is a long-acting aminoamide local anesthetic with significantly more systemic toxicity than lidocaine.

Organs and Systems

Cardiovascular

Bupivacaine-induced cardiotoxicity, notably after epidural use, is a matter of concern and controversy (1–3). The risk can be greatly reduced or eliminated by careful dosage and/or the use of lower concentrations (SEDA-12, 108) (1).

All studies of the cardiotoxic effects of local anesthetics on the isolated heart published from 1981 to 2001 have been reviewed (4). Thirteen studies were identified, all of which studied bupivacaine, either alone or compared with other local anesthetics. The general conclusions were:

- Highly lipid-soluble, extensively protein-bound, highly potent local anesthetics, such as tetracaine, bupivacaine, and etidocaine, are much more cardiotoxic than less lipid-soluble, protein-bound, and potent local anesthetics, such as lidocaine and prilocaine.
- Bupivacaine has a potent depressant effect on electrical conduction in the heart, primarily via an action on voltage-gated sodium channels that govern the initial rapid depolarization of the cardiac action potential.
- The *S*(−) isomer of bupivacaine is less cardiotoxic than the *R*(+) form.
- Bupivacaine predisposes the heart to re-entrant dysrhythmias.
- The actions of bupivacaine on channels other than voltage-gated sodium channels probably contribute to the dose-dependent cardiotoxic effects of bupivacaine.

The recommended safe upper dose limit for bupivacaine is commonly 2–2.5 mg/kg. However, some authors recommend a lower dose of 1.25 mg/kg as the safe upper limit in dental practice (SEDA-20, 128) (5).

Hyperkalemia, acidosis, severe hypoxia, and myocardial ischemia increase the cardiovascular depressive effects of bupivacaine.

There has been a report of T wave changes on the electrocardiogram during caudal administration of local anesthetics (6).

- A 4.2 kg 2-month-old baby was given a caudal injection under general anesthesia for an inguinal hernia repair. A mixture of 1% lidocaine 2 ml and 0.25% bupivacaine 2 ml was injected. Every 1 ml was preceded by an aspiration test and followed by observation for 20 seconds for electrocardiographic changes. On administration of the third 1 ml dose, there was a significant increase in T wave amplitude. The aspiration test was repeated and was positive for blood. The caudal injection was stopped and the electrocardiogram returned to normal after 35 seconds. The patient remained cardiovascularly stable with no postoperative sequelae.

Previous reports have suggested that an increase in T wave amplitude could result from inadvertent intravascular administration of adrenaline-containing local anesthetics. This is the first case report of local anesthetics alone causing significant T wave changes.

Bradycardia has been reported very occasionally (7).

Bupivacaine can cause ventricular extra beats (8). Ventricular dysrhythmias and seizures were reported in a patient who received 0.5% bupivacaine 30 ml with adrenaline 5 micrograms/ml for lumbar plexus block, after a negative aspiration test (9). The patient developed ventricular fibrillation and required advanced cardiac life support for 1 hour, including 15 defibrillations, and adrenaline 40 mg before sinus rhythm could be restored. There were no neurological sequelae.

Infusions of 0.25% bupivacaine into pig coronary arteries caused ventricular fibrillation at lower rates of infusion than 0.25% bupivacaine with 1% lidocaine (10). The lidocaine/bupivacaine mixture did not have a greater myocardial depressant effect than bupivacaine alone. The authors suggested that when regional anesthesia requires high doses of local anesthetics, bupivacaine should not be used alone but in a mixture with lidocaine, and that lidocaine should be useful in the management of bupivacaine-induced ventricular fibrillation.

An animal study of the mechanism of bupivacaine-induced dysrhythmias has shown that bupivacaine facilitates early after-depolarization in rabbit sinoatrial nodal cells by blocking the delayed rectifier potassium current (11).

Inadvertent administration of bupivacaine can lead to fatal cardiovascular collapse that may be refractory to conventional resuscitation. A study in rats has suggested that in addition to its direct cardiotoxic effect, bupivacaine may have a toxic action on the brainstem, and that cardiovascular collapse may result from dysfunction of vital cardiorespiratory control systems (12).

Nervous system

Neurological symptoms subsequent to unrecognized intravascular injection are the major complications of bupivacaine: tinnitus, muscle twitching, nystagmus, and convulsions can occur. The use of vasoconstrictors is probably not advisable, as they prolong the duration of action of local anesthetics. Whether the addition of hyperbaric glucose to 0.5% bupivacaine for spinal anesthesia alters the incidence of pain from an orthopedic tourniquet is disputed; some findings suggest that it aggravates the problem (SED-12, 256) (13).

- A 13-year-old girl developed tonic-clonic seizures followed by ventricular fibrillation after subcutaneous infiltration of extensive skin abrasions with 30 mg (0.5 mg/kg) of bupivacaine over about 1 hour. She was successfully resuscitated with cardiopulmonary resuscitation and intubation, intravenous diazepam, adrenaline, and sodium bicarbonate (14).

The authors noted that although the anticonvulsant effect of diazepam is significant, some animal studies have shown that diazepam can prolong the half-life of bupivacaine. They stressed the difficulty in treating bupivacaine-induced dysrhythmias and suggested the use of phenytoin

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as a first-line agent in their management. However, this advice is based on only two case reports.

In seven children (aged 36–52 weeks) given caudal anesthesia with bupivacaine 3.1 mg/kg + adrenaline 5 micrograms/ml, there were significant electroencephalographic signs of central nervous system toxicity in six, and two had clinical signs of possible epileptic activity. The authors stopped the study early because of the high incidence of adverse effects. They felt that these were due to the fact that no sedative or anesthetic drugs that could have masked or alleviated local anesthetic toxicity were given, and also that infants have low concentrations of alpha$_1$ acid glycoprotein, leading to increased unbound plasma concentrations (15). However, it should be noted that 2 mg/kg is the usual upper dose limit recommended for bupivacaine. It is hardly surprising that such a high proportion of those studied showed evidence of systemic toxicity after the administration of a much higher dose of bupivacaine to such small children by a route that is known to result in rapid absorption of local anesthetic into the systemic circulation.

Reactions to local anesthetics often occur as a result of inadvertent overdose or accidental intravenous injection.

- A 53-year-old woman received postoperative epidural analgesia by nurse-administered bolus doses after a total knee replacement (16). She received her first epidural bolus of 0.25% bupivacaine 6 ml with morphine 2 mg 2 hours after the operation, with good effect. Six hours later she was accidentally given a second top-up dose intravenously. She became distressed and complained of tinnitus, palpitation, and dizziness. She was able to cooperate and was in sinus rhythm with a tachycardia of 120/minute. She was observed overnight on ICU and made a full recovery.

Despite correct epidural placement, this complication arose as a result of human error, and the authors believed that the low concentration and volume of the top-up had protected the patient from more serious sequelae.

Musculoskeletal

Muscular atrophy after intramuscular injection has been documented (17).

Immunologic

A non-IgE-mediated allergic reaction to bupivacaine has been reported (SEDA-21, 136).

- A 69-year-old woman with a history of bronchospasm after NSAID administration had heavy feelings in her arms and itchy eyes, without any change in hemodynamics, 30 minutes after an intradermal injection of bupivacaine. The same symptoms occurred during subsequent retesting 1 month later, with the addition of coughing and sneezing.

Second-Generation Effects

Pregnancy

Cardiotoxicity due to bupivacaine is more likely in pregnancy (18).

When epidural anesthesia was used for cesarean section, bupivacaine (with oxytocin) produced a higher frequency of neonatal jaundice than similar treatment using lidocaine (SEDA-14, 111).

Fetotoxicity

Adverse effects of bupivacaine on the fetus are uncommon (19), but fetal bradycardia has very occasionally been reported (20).

Susceptibility Factors

Genetic factors

Isovaleric acidemia (an autosomal recessive disorder of leucine metabolism causing episodes of acidosis during catabolic stress) and carnitine deficiency have been associated with a lowered threshold for bupivacaine-induced dysrhythmias (SEDA-22, 142).

Age

In the elderly, some local anesthetics (including lidocaine and bupivacaine) have longer durations of action (18).

Drug Administration

Drug formulations

A formulation of bupivacaine called Regibloc (bupivacaine HCl; Intramed, South Africa) was the only common factor in a series of serious complications after regional anesthesia (21).

- Three consecutive patients had prolonged blockade after retrobulbar block. One had not resolved after 3 months and three others had prolonged mydriasis for 2 weeks.
- Severe neuralgia developed in eight patients after interscalene blocks lasting 6–12 weeks.
- A 36-year-old woman developed supraclavicular skin necrosis, followed by sloughing of subcutaneous tissue down to the first rib, including the dorsal roots of the brachial plexus, after receiving an interscalene block followed by an infusion; 5 months later she still had complete sensory and motor paralysis of the C5 nerve root requiring nerve grafting.
- Skin sloughing after a penile ring-block required plastic reconstruction.
- A 16-year-old girl had a median nerve block followed by an area of skin and fat necrosis at the site of injection and a middle-aged patient received an interscalene block resulting in subsequent fat necrosis at the injection site.

No further complications were encountered after the authors changed to another formulation of bupivacaine and stopped using Regibloc.

Drug–Drug Interactions

Calcium channel blockers

Calcium channel blockers in combination with bupivacaine produce significant negative inotropic effects on the heart in animals, possibly due to reduced protein

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binding of the local anesthetic, as well as a generalized myocardial depressant effect (22,23).

However, bupivacaine cardiotoxicity was reduced in rats by pretreatment with low doses of calcium channel blockers (24). In vivo, the LD_{50} for bupivacaine was increased from 3.08 to 3.58 mg/kg after pretreatment with verapamil 150 micrograms/kg, and to 3.50 mg/kg after nimodipine 200 micrograms/kg. Of the rats that died, only one developed cardiac arrest first, whilst the majority developed respiratory arrest. In vitro, bupivacaine alone dose-dependently reduced heart rate, contractile force, and coronary perfusion pressure. Dysrhythmias were also noted: bradycardias, ventricular extra beats, and ventricular tachycardia were the most common. Verapamil made no difference to these adverse effects, but nimodipine significantly reduced the negative chronotropic and dysrhythmogenic effects of bupivacaine. These results, although interesting, cannot be used to reach any clinical conclusions, particularly as the mechanism of interaction between bupivacaine and calcium channel blockers has yet to be elucidated.

Clonidine

The analgesic efficacy of the addition of clonidine to an epidural solution of bupivacaine plus fentanyl has been subjected to a randomized, double-blind study in 61 parturients who received bupivacaine plus fentanyl with or without clonidine (median dose 28 micrograms/hour). There was no difference between the groups in pruritus or nausea score, but those given clonidine had less shivering and better analgesia (25).

In another randomized, double-blind study, a combination of clonidine and neostigmine was added to intrathecal bupivacaine plus fentanyl in 45 parturients (26). The combination increased the duration of labor analgesia by 83%, but was associated with significantly more nausea. However, the results were equivocal, and larger studies are needed.

Clonidine inhibits the hepatic metabolism of bupivacaine in mice (27).

Desipramine

Desipramine displaces bupivacaine from plasma proteins (28).

Mepivacaine

Bupivacaine displaces mepivacaine from protein binding sites on $alpha_1$ acid glycoprotein in vitro (29).

Pethidine

Pethidine displaces bupivacaine from plasma proteins (28). However, this interaction is probably not of clinical importance (30).

Phenytoin

Phenytoin displaces bupivacaine from plasma proteins (28).

Quinidine

Quinidine displaces bupivacaine from plasma proteins (28).

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Buprenorphine

See also Opioid analgesics

General Information

Buprenorphine is a partial agonist at OP_3 (μ) opioid receptors and an antagonist at OP_2 (κ) receptors.

In a double-blind, randomized study of three groups of 18 patients having abdominal surgery who received single doses of either intramuscular pethidine 75 mg, with sublingual buprenorphine 400 μg, or buprenorphine 300 μg alone, sedation and nausea were the most common adverse effects in all three groups. Patients who received sublingual buprenorphine were significantly less sedated in the immediate postoperative period (1).

In a 3-day randomized, placebo-controlled study, 40 patients with acute pancreatitis or acute-on-chronic pancreatitis were given either buprenorphine 2.4 mg/day or procaine hydrochloride 2 g/day by constant intravenous infusion (2). The patients who received buprenorphine had significantly lower pain scores than those given procaine and were significantly less likely to demand additional analgesia. The adverse effect profiles were similar in the two groups, with the exception of a significantly higher rate of sedation in those who were given buprenorphine. The authors suggested that intravenous buprenorphine is more effective and safer than procaine in acute pancreatitis.

Buprenorphine has been suggested to be useful for the treatment of cocaine and opiate dependence. In a study designed to assess its safety for this purpose (SEDA-18, 85) there were no adverse effects or serious interactions with a single dose of intravenous morphine or cocaine during daily maintenance on buprenorphine.

Organs and Systems

Cardiovascular

- A 27-year-old man injected a 2 mg suspension of crushed oral buprenorphine into his left ulnar artery, leading to acute ischemia of the hand; he was successfully treated with iloprost and dextran-40 (3).
- A 22-year-old man snorted an 8 mg crushed tablet of buprenorphine and 2 hours later had crushing chest pain, which resolved within a few minutes (4). The symptom recurred 3 weeks later after another inhalation of buprenorphine. An electrocardiogram suggested an acute anterior myocardial infarction caused by buprenorphine-induced coronary artery spasm.

Respiratory

Respiratory depression can occur with buprenorphine. It is not often a clinical problem, except in older and weaker subjects, in whom it can be fatal (5). When it occurs it is often prolonged and can be particularly difficult to reverse (SEDA-16, 87). Norbuprenorphine, a metabolite of buprenorphine via CYP3A4 causes dose-dependent respiratory depression, perhaps mediated by opioid receptors in the lung rather than the brain, and is 10 times more potent than buprenorphine (SEDA-22, 103).

Non-cardiogenic pulmonary edema has been reported after a single dose of buprenorphine (SEDA-19, 89).

Nervous system

Sedation and nausea are relatively frequent. When buprenorphine is used for patient-controlled analgesia, minor dysphoria or euphoria has been reported (SEDA-16, 88).

In one of three patients receiving epidural buprenorphine for the relief of pain from head and neck cancers, it was discontinued because of severe dizziness (SEDA-17, 87).

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Mouth and teeth

There have been reports of facial and lingual ulcers, the ulceration following repeated injection of buprenorphine into the left superior cervical ganglion for trigeminal neuralgia (6) and the use of sublingual buprenorphine (7).

Gastrointestinal

Impaired gastric emptying and delayed absorption after sublingual buprenorphine have also been reported (SEDA-17, 87).

Liver

- A 33-year-old man developed severe hepatitis after an oral overdose of buprenorphine tablets 112 mg over 48 hours (8). He presented with an acute confusional state, including disorientation in time and space. The condition led to anuria and hepatorenal insufficiency. He was successfully treated with hemodialysis.

With increasing use of buprenorphine in the treatment of opioid dependence, it has been confirmed that the use of buprenorphine in opioid-dependent individuals with a history of hepatitis causes significant increases in aspartate transaminase and alanine transaminase activities (9). Liver enzymes should be monitored before giving buprenorphine to patients with hepatitis.

Four former opiate-dependent individuals with confirmed hepatitis C virus were given substitution therapy with sublingual buprenorphine. After injecting buprenorphine together with their sublingual doses, they had a marked increase in serum aspartate transaminase activity (13–50 times the upper limit of the reference range), resulting in jaundice (10). Another patient who was positive for hepatitis C and HIV developed jaundice, with panlobular liver necrosis and microvesicular steatosis, after using sublingual buprenorphine and small doses of paracetamol and aspirin (10).

Intravenous buprenorphine abuse precipitated acute-on-chronic hepatitis in a 25-year-old woman who was hepatitis C positive with a history of chronic diamorphine dependence (11).

Skin

There have been reports of severe pruritus with buprenorphine (12).

Immunologic

There have been reports of anaphylactic reactions with buprenorphine (13).

Death

Two series of 39 and 78 deaths attributed to buprenorphine have respectively been reported in Strasbourg and 13 other French forensic centers between 1996 and 2000 (14). The risks incurred by the misuse of buprenorphine seem to arise through a combination of (a) the concomitant use of other psychotropic drugs (especially benzodiazepines and neuroleptic drugs) and (b) the improper use of tablets for intravenous administration and/or massive oral doses. The total recorded number of buprenorphine-related deaths is largely underestimated, because the very low concentrations require sensitive immunoassay techniques, making them difficult to detect; furthermore different cut-off points are used by different forensic pathology laboratories in diagnosing drug-related deaths.

Long-Term Effects

Drug abuse

Abuse of buprenorphine has been reported in many countries and it is now widely dealt with under psychotropic drug legislation.

Although sublingual buprenorphine has been used in the management of heroin addiction (SEDA-16, 88), widespread abuse of buprenorphine by addicts is known (SEDA-16, 88), including the snorting of crushed sublingual tablets (SEDA-16, 88).

Buprenorphine is increasingly being used as a substitute for other opioids in the treatment of opioid abuse and is generally considered to be safe because of the ceiling effect. One report from Vienna described 50 opioid-dependent subjects who received gradual (10-day) detoxification with buprenorphine, contacting the outpatient clinic daily, so that buprenorphine could be administered according to their clinical need in a free dosage scheme (15). The mean daily dosage was 2.3 mg on day 1 and the highest mean daily dose was administered on day 2, followed by daily reduction over the study period. There was 70% compliance with the regimen and withdrawal symptoms during the study period were described as moderate.

Less satisfactory outcomes have been reported from France (16–18), where acute poisoning during buprenorphine substitution has been described in three series of patients. The first included 29 opiate addicts taking high-dosage sublingual buprenorphine with non-fatal poisoning and the second included 20 addicts who died (16). Blood concentrations of buprenorphine in the first group were low (1.0–2.3 ng/ml, mean 1.4 ng/ml), but there was concomitant intake of psychotropic medication, especially benzodiazepines, in 18 cases. Blood concentrations of buprenorphine in the fatal cases were 1.1–29 (mean 8.4) ng/ml, while concentrations of its primary metabolite, norbuprenorphine, were 0.2–13 (mean 2.6) ng/ml, within or slightly over the target range. Extensive tissue distribution buprenorphine was reported (myocardium, kidney, brain, and liver) but the highest concentrations of buprenorphine and norbuprenorphine were found in the bile, and the authors suggested that this may be the sample of choice for postmortem screening. Buprenorphine was also identified in eight of 11 hair samples assayed. Intravenous injection of crushed tablets and the concomitant use of benzodiazepines were identified as the major risk factors in the fatal cases (17).

Drug dependence

Sublingual buprenorphine is an alternative to methadone in treating opiate dependence, but its opioid agonist effects pose the risk of intravenous abuse and subsequent dependence. This abuse potential may be limited by using a combination of buprenorphine with naloxone, which will precipitate opiate withdrawal when given

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intravenously but not sublingually. The effects of three combinations of intravenous buprenorphine and naloxone on agonist effects and withdrawal signs and symptoms in 12 opiate-dependent patients have been described (19). After stabilization with morphine 60 mg intramuscularly the patients were challenged with intravenous doses of buprenorphine 2 mg, either alone or in combination with naloxone in ratios of 2:1, 4:1, and 8:1, with morphine alone (15 mg), or with placebo. In those given the combination there was a naloxone dose-dependent increase in opiate withdrawal signs and a reduction in the pleasurable effects that might induce abuse liability. The authors suggested that the combination of buprenorphine with naloxone in a ratio of 2:1 or 4:1 can be useful in the treatment of opiate dependence.

There have been three studies of the use of buprenorphine to treat opiate dependence.

The authors of a randomized, multicenter, placebo-controlled, double-blind study of 72 opioid-dependent individuals, who were given either buprenorphine 8 mg/day or methadone 60 mg/day for 6 months, claimed that there were no significant differences in adverse effects during induction or maintenance (20). Buprenorphine provided an alternative to methadone, with equal improvement in quality of life, psychopathology, and compliance. The results of this study should be interpreted with care, because of the unusual experimental design, which did not reflect practices in ordinary methadone maintenance programs. However, similar observations were observed during an open, flexible-dose study involving inpatient induction and outpatient maintenance in 15 opioid-dependent pregnant women (21). Sublingual buprenorphine (1–10 mg/day) was well accepted by the women, and there was a low incidence of neonatal abstinence syndrome. Further controlled and larger studies need to be done to substantiate these observations.

In a double-blind, randomized comparison of sublingual buprenorphine tablets with oral methadone in a 6-week trial in 58 patients using a flexible dosing procedure the retention rate was significantly better in those using methadone (90 versus 50%) (22). Those who completed the study had a similar number of opioid-positive urine samples, with a mean stabilization dose of 11 mg/day of buprenorphine and 70 mg/day of methadone. This study had several limitations: 6 weeks is too short a period to determine any intermediate or long-term treatment outcomes, the sample size was too small, and the comparison of non-equivalent doses makes interpretation difficult.

Drug withdrawal

The effects of buprenorphine (sublingually or by injection) in an opioid-dependent population have been studied (23,24). There was benefit in using buprenorphine to counteract opioid withdrawal effects in patients with chronic heroin use and subsequent dependence. However, the results are limited and the benefits short-term if psychosocial support is not in place as part of an overall treatment package before buprenorphine is prescribed (25).

- A 35-year-old man with a 10-year history of heroin use was given sublingual buprenorphine 24 mg/day (26). Although it was dispensed daily by a pharmacist, he was not adequately supervised: he saved the buprenorphine tablets and continued to use heroin. He then took buprenorphine 40 mg and stopped using heroin; he immediately developed opioid withdrawal symptoms. In an attempt to relieve these symptoms, he took a further 40 or 45 mg buprenorphine in 24 hours. He subsequently came to a drug treatment clinic, where he was given another 16 mg of buprenorphine, with no effect. After 3 days, he was transferred to methadone and his withdrawal symptoms resolved.

In this case buprenorphine precipitated opioid withdrawal symptoms after heroin use. This highlights the importance of regular monitoring and supervision of community-dispensed buprenorphine.

Second-Generation Effects

Fetotoxicity

It is inadvisable to use buprenorphine during labor, as its effects on the fetus cannot be reversed.

Drug Administration

Drug formulations

A sublingual formulation that combines buprenorphine and naloxone is thought to be ideal for reducing parental buprenorphine abuse. In a small pilot study in nine opioid-dependent individuals already stabilized on buprenorphine 8 mg/day, naloxone 0, 4, or 8 mg was added (27). The addition of naloxone did not precipitate opiate withdrawal.

A transdermal therapeutic system (TTS) for rate-controlled delivery of buprenorphine is available in three strengths, with release rates of 35, 52.5, and 70 μg/hour for 72 hours. This is equivalent to daily doses of 0.8, 1.2, and 1.6 mg respectively. In a double-blind, randomized, controlled study using one of three dosage strengths of buprenorphine TTS in 445 patients with chronic pain the adverse effects were mild and typical of the opioid analgesics; they included nausea (17%), vomiting (9.3%), dizziness (6.8%), tiredness (5.6%), constipation (5.3%), and sweating (3.7%) (28). There was erythema in 25% and pruritus in 22%. More than half of the cases of erythema and one-third of the cases of pruritus resolved within 24 hours. In a single-blind, randomized study sublingual buprenorphine 0.2 mg provided an effective and convenient alternative in the treatment of acute renal colic compared with pethidine 50 mg intramuscularly (29). There was a slightly but non-significantly higher incidence of nausea, vomiting, and dizziness in those given buprenorphine.

Drug dosage regimens

Two doses (8 and 16 mg) of sublingual buprenorphine have been compared in a 6-week double-blind, placebo-controlled inpatient study of the reinforcing effects of intravenous diamorphine (30). Only eight diamorphine-dependent men were recruited and the authors could only postulate that doses over 16 mg might be more effective in blocking the reinforcing effects of diamorphine.

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Drug administration route

Adverse effects after parenteral, sublingual, and rectal use have included hypotension, bradycardia, reduced systolic blood pressure, reduced stroke volume, nausea, sweating, vomiting, vertigo, sedation, and a reduction in respiratory rate (31). In some intravenous studies nausea and vomiting have occurred in as many as 20%. Hypotension occurs in 1–5% of patients, and hypertension, tachycardia, or bradycardia in under 1%.

Drug–Drug Interactions

Benzodiazepines

Six deaths linked to misuse of buprenorphine plus benzodiazepine combinations have been described (18). The authors emphasized that blood concentrations of buprenorphine were in the target range in three subjects, although higher in three others. Exhaustive screening detected no traces of opiates in postmortem blood, but all subjects had target range concentrations of both desmethyldiazepam and 7-aminoflunitrazepam. The risk of high-dose substitution therapy (2–8 mg), if physicians do not comply with correct practices for the prescription, and use of buprenorphine were emphasized, particularly when there is a large population of patients being treated, as there was in France in 1997 (34 000 patients).

HIV-1 protease inhibitors

The metabolism of buprenorphine is inhibited by the HIV-1 protease inhibitors (32).

Naloxone

Naloxone is of limited use in reversing the effects of buprenorphine, because of its relative inability to displace it from opioid receptors. Naloxone 1 mg had little effect on the respiratory depression caused by buprenorphine 300 μg/70 kg, although both 5 and 10 μg produced consistent reversal, which was more complete with the larger dose (33). Insignificant effects on circulation and respiration have been reported at lower doses of buprenorphine (4.5–10 μg/kg) (34).

Opioid agonists

Under some conditions the antagonist action of buprenorphine can jeopardize the effect of subsequently administered pure opioid agonists, by blocking OP_3 (μ) opioid receptors so effectively that normal doses of the opioid agonist are ineffective, necessitating the administration of a higher dose, with the attendant risk of respiratory depression, from which deaths have been reported (SEDA-13, 60). Fortunately such instances appear to be rare.

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Buspirone

General Information

Buspirone, an azapirone drug, similar to its analogues ipsaperone and tandospirone, is chemically and pharmacologically dissimilar to the benzodiazepines and is useful in both generalized anxiety and depression (1). In contrast to benzodiazepines, buspirone has an antidepressant-like therapeutic latency (2), and for this reason it needs to be given with considerable education and encouragement. It is effective in children with anxiety disorders (SEDA-19, 36) and as an antidepressant adjuvant in refractory depression with (3) and without (4) obsessive-compulsive symptoms. Buspirone is also effective in treating anxious alcoholics, and in patients with agitation or aggression associated with organic brain disease (5).

Originally thought to act through a dopaminergic mechanism, buspirone is now regarded as acting as a 5-HT_{1A} receptor (partial) agonist (6) and produces dose-related adverse effects similar to those of the SSRIs (nausea, headache, insomnia, dizziness, and sexual dysfunction) (SEDA-22, 39) (7). Like them, it interacts with monoamine oxidase inhibitors and can produce the serotonin syndrome (8). An uncommon association with extrapyramidal movement disorders (SEDA-17, 46) (SEDA-18, 45) may reflect its structural relation to some dopamine receptor antagonists.

Compared with benzodiazepines, buspirone causes less sedation and memory impairment (9), has little interaction with alcohol (2,10), and is essentially devoid of problems of abuse, disinhibition, tolerance, and dependence.

These advantages are important in treating particular groups of patients, including patients with brain injury, elderly people, forensic populations, and the medically ill (11,12). On the other hand, over 50% of patients with cerebellar ataxia reported significant adverse effects, as described above (SEDA-21, 39).

Buspirone may also have advantages in treating individuals who are susceptible to problems with alcohol (13) or other hypnosedatives (10), although habitual users of benzodiazepines are often unwilling to persist with buspirone long enough for it to have a therapeutic effect (2).

Unlike carbamazepine or tricyclic antidepressants, buspirone is not helpful in the management of benzodiazepine withdrawal (14).

The safety results from two comparisons of buspirone 15 mg bd and buspirone 10 mg tds in patients with persistent anxiety have been subjected to meta-analysis (15). The incidences of adverse events were similar, except for a significantly higher incidence of bouts of palpitation in patients taking buspirone bd (5%) compared with tds (1%). The most frequently reported adverse events with both regimens were dizziness, headache, and nausea. There were no appreciable differences between treatments in vital signs, physical examination, electrocardiography, or clinical laboratory results. A change to twice-daily dosing with buspirone may offer convenience and

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possibly greater adherence to therapy in patients with persistent anxiety, without compromising the safety and tolerability profile of the drug.

The effects of hydroxyzine 50 mg/day, buspirone 20 mg/day, and placebo have been studied in 244 patients with generalized anxiety disorder in a double-blind placebo-controlled study (16). Hydroxyzine ($n = 81$) was considerably better than placebo ($n = 81$), and buspirone ($n = 82$) was intermediate. The main adverse effects were headache and migraine with buspirone (6.1 versus 4.9% with hydroxyzine and 1.2% with placebo). Somnolence occurred in 9.9% with hydroxyzine, 4.9% with buspirone, and none with placebo. Dizziness occurred in 6.1% with buspirone, none with hydroxyzine, and 2.5% with placebo.

In a 21-day, open, multicenter, dose-escalation study, 13 children and 12 adolescents with anxiety disorder and 14 healthy adults took buspirone 5–30 mg bd titrated over 3 weeks (17). Buspirone was generally safe and well-tolerated at doses up to 30 mg in adolescents and adults and in most of the children. The most common adverse events in children and adolescents were light-headedness (68%), headache (48%), and dyspepsia (20%); two children withdrew from the study at the higher doses (15 mg and 30 mg bd) owing to adverse effects. In adults, the most common adverse event was somnolence (21%); mild light-headedness, nausea, and diarrhea were also reported.

Organs and Systems

Respiratory

Because of its virtual absence of respiratory depressant effects compared with benzodiazepines (18), buspirone may be especially useful in treating anxious patients with lung disease (19).

Nervous system

The efficacy and safety of buspirone have been evaluated in the management of anxiety and irritability in 22 children with pervasive developmental disorders. One child developed abnormal involuntary movements of the mouth, cheeks, and tongue after having taken buspirone 20 mg/day for 10 months. No other drugs were prescribed. The abnormal movements disappeared completely within 2 weeks of withdrawal of buspirone. Other adverse effects in other children were minimal and included initial sedation, slight agitation, and initial nausea (20).

Long-Term Effects

Drug abuse

Despite continuing scrutiny, buspirone has shown little, if any, abuse potential (7).

Drug Administration

Drug formulations

Because of their short half-lives, buspirone and its analogues are problematic to administer (6). A single dose of buspirone ER (extended-release) 30 mg has been compared with two doses of buspirone IR (immediate-release) 15 mg given 12 hours apart to assess differences in tolerability in an open, crossover, randomized study in 18 healthy men (21). Blood samples were obtained at 22 times. Seven subjects reported a total of 13 adverse events during the study, but none of the events recorded was unexpected. All were mild and resolved by the end of the study without medical intervention. Three adverse events (rhinitis, headache, and light-headedness) were categorized as unrelated to the study drug. The other 10 adverse events included drowsiness, dizziness, depression, tinnitus, and increased blood pressure. There were no significant differences between the two formulations.

Drug–Drug Interactions

Calcium channel blockers

In a randomized placebo-controlled trial, the possible interactions of buspirone with verapamil and diltiazem were investigated. Both verapamil and diltiazem considerably increased plasma buspirone concentrations, probably by inhibiting CYP3A4. Thus, enhanced effects and adverse effects of buspirone are possible when it is used with verapamil, diltiazem, or other inhibitors of CYP3A4 (22).

Erythromycin

Erythromycin, an inhibitor of CYP3A, can increase buspirone concentrations (SEDA-22, 39).

Fluvoxamine

The effects of fluvoxamine on the pharmacokinetics and pharmacodynamics of buspirone have been investigated in 10 healthy volunteers. Fluvoxamine moderately increased plasma buspirone concentrations and reduced the production of the active metabolite of buspirone. The mechanism of this interaction is probably inhibition of CYP3A4. However, this pharmacokinetic interaction was not associated with impaired psychomotor performance and is probably of limited clinical significance (23).

Grapefruit juice

In a randomized, two-phase crossover study, the effects of grapefruit juice on the pharmacokinetics and pharmacodynamics of oral buspirone were investigated in 10 healthy volunteers. Grapefruit juice increased the mean peak plasma concentration of buspirone 4.3-fold (24). Large amounts of grapefruit juice should be avoided in patients taking buspirone.

Haloperidol

Buspirone increases haloperidol concentrations in some patients (SEDA-21, 39).

Itraconazole

Itraconazole, an inhibitor of CYP3A, can increase buspirone concentrations (SEDA-22, 39).

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Monoamine oxidase inhibitors

Buspirone interacts with monoamine inhibitors and can cause the serotonin syndrome (8).

Rifampicin

The effects of rifampicin on the pharmacokinetics and pharmacodynamics of buspirone were investigated in 10 young healthy volunteers. There was a significant reduction in the effects of buspirone in three of the six psychomotor tests used after rifampicin pretreatment. The interaction between rifampicin and buspirone is probably mostly due to increased CYP3A4 activity. Buspirone will most likely have a greatly reduced anxiolytic effect when it is used together with rifampicin or other potent inducers of CYP3A4, such as phenytoin and carbamazepine (25).

Sertraline

Serotonin syndrome has been attributed to the combination of buspirone and sertraline.

- A 49-year-old man had major adverse effects 11 days after taking a combination of sertraline, buspirone, and loxapine (26). The adverse effects were characteristic of the serotonin syndrome, which is characterized by a constellation of symptoms, including hypomania, agitation, seizures, confusion, restlessness, hyper-reflexia, tremor, myoclonus, ataxia, incoordination, anxiety, double vision, fever, shivering, variable effects on blood pressure, nausea and vomiting, sweating, and diarrhea.

St John's wort

Clinicians should inform their patients about the risks associated with taking St John's wort if they are taking psychotropic drugs that can cause the serotonin syndrome.

- A 27-year-old married woman developed symptoms of generalized anxiety disorder and was given buspirone 30 mg/day (27). During treatment she felt depressed and decided to take St John's wort. Two months later she started to have nervousness, aggressiveness, hyperactivity, insomnia, blurred vision, and very short periods of confusion and disorientation. The symptoms were consistent with serotonin syndrome. St John's wort was withdrawn and her symptoms resolved after 1 week.

Buspirone is a partial agonist at $5HT_{1A}$ receptors; St John's wort is a non-selective inhibitor of 5HT reuptake and also upregulates postsynaptic $5HT_{1A}$ and $5HT_{2A}$ receptors; it therefore causes overstimulation of $5HT_{1A}$ receptors, leading to the serotonin syndrome.

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Busulfan

See also Cytostatic and immunosuppressant drugs

General Information

Busulfan is an alkylating agent that is used to treat myeloproliferative disorders and to produce myeloablation before bone marrow or stem cell transplantation. Busulfan is metabolized by hepatic glutathione *S*-transferase, the activity of which correlates negatively with busulfan maximum and minimum concentrations and positively with busulfan clearance (1).

General adverse effects

Leukemic patients receiving marrow from HLA-identical sibling donors were randomized to either oral busulfan 16 mg/kg ($n = 88$) or total body irradiation ($n = 79$), plus cyclophosphamide 120 mg/kg (2). Over 5–9 years the following adverse effects occurred in the two groups:

- obstructive bronchiolitis (26 versus 5%).
- cataracts (6 versus 2%).
- veno-occlusive disease of the liver (12 versus 1%).
- complete or partial alopecia (28 versus 6%).
- hemorrhagic cystitis (32 versus 10%).
- acute graft-versus-host disease (cumulative incidence at 7 years, 59 versus 47%); death from graft-versus-host disease was more common with busulfan (22 versus 3%).

Organs and Systems

Cardiovascular

Pericardial fibrosis has been reported after busulfan treatment in a man with chronic myeloid leukemia (3). Endocardial fibrosis has also been reported (4).

Respiratory

Busulfan can cause interstitial fibrosing lung disease ("busulfan lung") with an estimated incidence of 6% (5). It begins gradually, causes dyspnea and cough, and is often accompanied by skin pigmentation. It usually occurs after prolonged treatment (on average 41 months, cumulative dose 2900 mg). The respiratory function pattern is characterized by reduced lung volumes with hypoxemia and hypocapnic respiratory failure. Radiology shows interstitial and predominantly basal shadows.

Various authors have discussed the differences in busulfan-induced idiopathic pneumonia syndrome, as a result of either chronic low-dose or short-course high-dose therapy. One group found that chronic low-dose therapy (even at cumulative doses of busulfan of up to 3 g) caused different lung damage from the clinical characteristics, radiological, and pathological features of the idiopathic pneumonia syndrome (6).

Three patients with busulfan-induced interstitial pneumonitis each had circulating immune complexes and alveolitis, and histology demonstrated consistent abnormalities of type I pneumocytes and depletion of type II pneumocytes (7).

Nervous system

Busulfan can cause generalized seizures (8).

High concentrations of busulfan in the cerebrospinal fluid have been correlated with development of myoclonic epilepsy and/or other electroencephalographic changes after high-dose busulfan conditioning regimens for acute leukemia (9).

- A 21-year-old woman with acute lymphoblastic leukemia underwent bone marrow transplantation after a conditioning regimen consisting of busulfan and cyclophosphamide (10). The day after starting busulfan, she had a generalized tonic-clonic seizure and electroencephalography showed diffuse polyspikes and spike-and-wave discharges, with persistent abnormalities (slowing of background activity intermixed with diffuse slow waves and isolated delta and theta bursts) for about 20 days and complete normalization 1 month after the seizure.

Phenytoin and benzodiazepines have been successfully used to prevent seizures during busulfan therapy; benzodiazepines may be preferable, because phenytoin can induce the metabolism of busulfan, reducing its efficacy. In 29 children undergoing hemopoietic stem cell transplantation who received high-dose busulfan, intravenous or oral lorazepam (median dose 0.022 mg/kg) before each dose of busulfan and for 24 hours after the last dose was used as seizure prophylaxis; drowsiness was the only significant adverse effect and there were no seizures (11). There were no tonic-clonic or myoclonic seizures in a prospective study in 16 patients with leukemia receiving busulfan before autologous bone marrow transplantation who were given phenobarbital and clonazepam, despite electroencephalographic changes in two patients after busulfan (12).

Sensory systems

Cataract due to busulfan has been reported after long-term administration (SEDA-1, 341) (13).

- A 42-year-old Japanese woman received busulfan 212 mg/day for only 4 days and developed reduced visual acuity and blurred vision in both eyes; she had a posterior polar subcapsular opacity in the lenses in both eyes (14).

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- A 49-year-old man with chronic myelogenous leukemia developed dense posterior subcapsular cataracts and punctate cortical opacities after taking busulfan for 5 years (15). Ultrastructural examination showed cortical liquefaction, with Morgagnian droplets involving primarily the region from the equator to the posterior subcapsular space, crystalloid rays, and abundant degenerate lens fiber membranes.

Hematologic

Aplastic anemia developed in 84 patients with chronic myeloid leukemia receiving busulfan; three patients died (16). The time interval until pancytopenia was detected varied considerably, ranging between 6 and 126 months. The effect did not correlate with the initial doses of busulfan.

Colony-stimulating factors have been used to treat and prevent the adverse hematological effects of busulfan (17,18).

- In a 91-year-old woman with essential thrombocythemia and marked bone marrow suppression induced by long-term busulfan, G-CSF and M-CSF increased the neutrophil and platelet counts but only transiently; there was transient eosinophilia after withdrawal of M-CSF (19).
- A 63-year-old woman with thrombocythemia was given busulfan 2 mg/day and later developed pancytopenia (20). She was given metenolone acetate 15 mg/day and G-CSF 300 μg/day, and frequent blood transfusions without effect. She was then given metenolone acetate, G-CSF 600 μg/day, and erythropoietin 24 000 units twice a week, and her pancytopenia gradually improved over several months.

One patient with busulfan-induced pancytopenia and recurrent thrombocytopenic bleeding was successfully treated prophylactically with random-donor platelet transfusions and later with HLA-matched platelets from a sibling (21).

- A patient with polycythemia vera who had undergone splenectomy received six courses of busulfan for recurrent thrombocytosis over 19 years (22). Severe pancytopenia followed and persisted for 4 months. There was marked erythroid hyperplasia in the bone marrow, with striking dyserythropoiesis, PAS-positive erythrocyte precursors, moderate numbers of circulating normoblasts, and evidence of chronic and acute hemolysis.

Of 39 patients taking busulfan 16 mg/kg/day and cyclophosphamide 120 mg/kg/day for leukemias, who received non-T cell depleted, HLA-matched sibling or unrelated donor marrow transplants 2 days after the end of chemotherapy followed by ciclosporin and methylprednisolone given to prevent graft-versus-host disease, 11 developed eosinophilia, of whom only 2 were still taking methylprednisolone (23). At the onset of eosinophilia, five of these 11 patients had graft-versus-host disease that worsened within 2 months. In the other six patients, graft-versus-host disease was not present initially but developed in all cases at a median of 4 months after the onset of eosinophilia.

Liver

In 66 patients who received busulfan in combination with cyclophosphamide, etoposide, and/or cytarabine in preparation for bone marrow transplantation, there was a higher incidence of veno-occlusive disease of the liver (sinusoidal obstruction syndrome) in those who received busulfan + cyclophosphamide (four of 10) than in those who received busulfan + cyclophosphamide + cytarabine (one of 18) or busulfan + cyclophosphamide + etoposide (seven of 38) (24). The risk of veno-occlusive disease was higher in those whose busulfan AUC was over 1500 minute.μmol/l (relative risk = 11). Other pharmacokinetic parameters, age, sex, type of bone marrow transplantation, previous therapy, or pretransplant liver function tests were not predictive of veno-occlusive disease.

In 30 patients who received oral busulfan 1 mg/kg, all six of those who developed hepatic veno-occlusive disease had a busulfan AUC greater than the mean, and five had an AUC that was greater than 1 standard deviation above the mean; veno-occlusive disease correlated with an increased AUC (25).

- Intrahepatic cholestasis has been attributed to busulfan in a 57-year-old man with chronic megakaryocytic granulocytic myelosis (26).
- Cholestatic hepatitis occurred in a 61-year-old man with chronic myelocytic leukemia who had taken busulfan for 8 years (27). He presented with fever, abdominal pain, and raised liver enzymes. A liver biopsy showed cellular cholestasis with focal liver cell necrosis accompanied by a mild inflammatory infiltrate. When busulfan was withdrawn, his liver enzymes normalized and his fever resolved.

Urinary tract

Busulfan can rarely cause hemorrhagic cystitis (28,29).

Skin

Busulfan can cause hyperpigmentation (30,31), often in combination with interstitial lung disease (5).

Hair

Of 65 patients who survived for at least 6 months after bone marrow transplantation, 31 had some degree of alopecia and 19 had extensive alopecia (32). The mean minimum busulfan concentration was 656 ng/ml in patients who developed alopecia, compared with 507 ng/ml in those who did not. Patients with more extensive alopecia had higher busulfan concentrations. In multivariate analysis, alopecia was associated with busulfan concentrations higher than the median (OR = 3.43; 95% CI = 3.04, 3.88), allogeneic transplantation (OR = 2.56; CI = 2.28, 2.88), and female sex (OR = 1.96; CI = 1.73, 2.88). There was no association between alopecia and chronic graft-versus-host disease.

Reproductive system

Busulfan can cause ovarian failure.

- A 26-year-old woman with chronic myeloid leukemia developed busulfan-induced ovarian failure, with amenorrhea, climacteric symptoms, raised plasma concentrations of luteinizing and follicle-stimulating

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hormones, and low 17 beta-estradiol concentrations (33). However, 1 year later she became pregnant, the busulfan was stopped, and amniocentesis showed a normal karyotype. The remainder of the pregnancy was unremarkable and ended with the normal delivery of a healthy child.

Of 21 girls aged 11–21 years who had received high-dose chemotherapy and autologous bone marrow transplantation without total body irradiation for malignant tumors 1.2–13 years before (median 7 years), 10 were given busulfan 600 mg/m^2 and melphalan (140 mg/m^2) with or without cyclophosphamide (3.6 g/m^2) (34). Eleven others did not receive busulfan. Twelve girls (57%) had clinical and hormonal evidence of ovarian failure. Among nine others who had had normal puberty, six had normal gonadotropin concentrations, one had raised gonadotropin concentrations, and two had gonadotropin concentrations at the upper limit of the reference range. All 10 girls who received busulfan developed severe persistent ovarian failure.

Second-Generation Effects

Teratogenicity

Retinal degeneration and microphthalmia have been described in the infants of women who have taken busulfan during pregnancy (35).

- Myeloschisis occurred in a 6-week-old human embryo whose 39-year-old mother had taken busulfan before and during the early stages of gestation for chronic lymphatic leukemia (36). Histology showed reduced mesenchymal elements together with somite disorganization in the affected area of the embryo.

Drug Administration

Drug overdose

A 4.6 kg infant with Wiskott–Aldrich syndrome received an accidental overdose of busulfan during preparation for allogeneic stem cell transplantation (37). Hemodialysis was immediately performed and resulted in accelerated clearance of busulfan. There were no acute neurological or hepatic adverse effects, and after cough and by rales for 2 months pulmonary symptoms resolved. There was stable partial donor chimerism after transplantation, but the patient was well 12 months later.

Drug–Drug Interactions

Cyclophosphamide

In bone marrow transplant recipients, prior administration of busulfan, which itself causes hemorrhagic cystitis, can increase the risk of cyclophosphamide-induced damage (38).

Busulfan reduces the clearance of cyclophosphamide to its active metabolite 4-hydroperoxycyclophosphamide (39). The first dose of high-dose cyclophosphamide should therefore be delayed for at least 24 hours after the last dose of busulfan.

Itraconazole

In 13 patients given bone marrow transplantation, the clearance of busulfan was reduced by an average of 20% in patients taking itraconazole compared with control patients and patients taking fluconazole (40).

Metronidazole

In 24 patients with graft-versus-host disease, metronidazole significantly increased busulfan plasma concentrations from 452 to 807 ng/ml (41). The authors concluded that metronidazole should not be administered simultaneously with busulfan, because of the risk of severe toxicity and/or mortality.

Phenytoin

In 17 patients given busulfan during conditioning before bone marrow transplantation, phenytoin increased the clearance of busulfan and shortened its half-life; diazepam did not have the same effect (42). There were reductions in the steady-state concentrations of busulfan in four of seven patients who took phenytoin and in only one of eight patients who took diazepam. This effect of phenytoin is probably due to induction of glutathione transferase.

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Butibufen

See also Non-steroidal anti-inflammatory drugs

General Information

Experience with the NSAID butibufen is limited. Only gastrointestinal adverse effects have been described (1).

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Butorphanol

See also Opioid analgesics

General Information

Butorphanol is a synthetic 14-hydroxymorphinan analogue with a low dependence potential and a low propensity to cause opioid adverse effects (1). It is a synthetic OP_2 (κ) receptor agonist and OP_3 (μ) receptor antagonist.

General adverse reactions

In some patients, effective doses cause troublesome effects. For example, in a randomized study of patients with sickle-cell crisis who received either butorphanol 2 mg intramuscularly or morphine 6 mg intramuscularly, adverse effects occurred in 23 and 13% respectively (2). On the other hand, a wide range of doses (4–48 mg/day) over 1 month failed to produce scores indicative of euphoric effects, and the withdrawal syndrome resembled a cyclazocine rather than a morphine abstinence effect (1).

Organs and Systems

Cardiovascular

Although cardiovascular toxicity with butorphanol is slight, raised pulmonary wedge pressure has occurred at cardiac catheterization (1).

Respiratory

Respiratory depression occurs minimally at doses of 2–4 mg (1).

Biliary tract

Butorphanol is generally believed to have a much smaller effect on biliary pressure than morphine, fentanyl, or pethidine, but 2 mg has caused biliary spasm (3).

Musculoskeletal

Fibrous myopathy has been reported in a 40-year-old woman who injected butorphanol intramuscularly (SEDA-17, 87).

Second-Generation Effects

Fetotoxicity

Two cases of sinusoidal fetal heart rhythm have been reported in which there was a significant temporal relation between the administration of butorphanol and the onset of the abnormal heart rhythm (4). In both instances the pattern reverted to normal after further analgesia was given.

Drug Administration

Drug administration route

Butorphanol has been used for epidural anesthesia in obstetric practice without adversely affecting the neonate, and no patients had pruritus (SEDA-16, 88).

As butorphanol is not orally active, reports of its transnasal administration are of interest. The most common adverse effects of transnasal butorphanol were dizziness, nausea and/or vomiting, headache, and drowsiness (SEDA-20, 83). Increased cardiac workload can also occur.

After cesarean section, transnasal butorphanol did not work quite as quickly as intravenous butorphanol. The effect lasted longer but the adverse effects were similar (SEDA-16, 88).

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Butriptyline

See also Tricyclic antidepressants

General Information

Butriptyline is the isobutyl side-chain homolog of amitriptyline. Its adverse effects, reported in two open studies, were no different from those of other tricyclic antidepressants (1,2).

References

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Butylated hydroxytoluene

General Information

Butylated hydroxytoluene is an additive used as an antioxidant in foods, such as packet cake mixes, potato crisps, salted peanuts, and dehydrated mashed potatoes. Its safety, and that of a number of other food additives, has been critically reviewed in a Danish study (1).

Organs and Systems

Immunologic

It is impossible to decide from experimental findings in animals what the result will be of prolonged human exposure to low concentrations of such substances. Butylated hydroxytoluene causes various allergies; symptoms of hay fever and asthma have been reported.

Chewing gum should be considered as a possible cause of unexplained food allergy.

- Butylated hydroxytoluene in chewing gum caused disseminated urticarial eruption in a young woman (2). An adverse drug reaction was ruled out, and the only recent dietary change had been regular use of chewing-gum containing butylated hydroxytoluene. The skin lesions showed signs of vasculitis, with a perivascular cellular infiltrate, heavy extravascular deposition of fibrinogen, and intraendothelial deposits of IgM, C'9, C3, and C9. She stopped using the gum and within a week the eruption had subsided. An oral provocation test confirmed that butylated hydroxytoluene was responsible, the cutaneous signs returning within several hours of rechallenge.

Long-Term Effects

Tumorigenicity

Although it has been suggested that butylated hydroxytoluene induces tumors in rats, others have suggested that it may protect tissues against the carcinogenic effects of many different substances.

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C1 esterase inhibitor concentrate

General Information

Hereditary angioedema, which is characterized by episodic bouts of swelling of submucosal and subcutaneous tissue, is due to a hereditary abnormality of C1 esterase inhibitor, either a deficiency of the normal enzyme or more rarely the presence of an abnormal enzyme. If C1 esterase inhibitor deficiency can be demonstrated, infusion of concentrated C1 esterase inhibitor is effective in treating the attack. In three studies, no adverse effects were recorded (1–3).

Organs and Systems

Immunologic

Allergic reactions to C1 esterase inhibitor concentrate have been observed, including possible exacerbation of angioedema (4).

Infection risk

The use of C1 esterase inhibitor concentrate has been associated with transmission of hepatitis C, but this can be prevented by heat treatment (5).

References

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Cabergoline

General Information

Cabergoline is an ergoline derivative that has been used in patients with hyperprolactinemia (SEDA-15, 133), but is used nowadays in patients with Parkinson's disease. Its adverse effects include nausea, hypotension, headache, gastric pain, dizziness, and weakness, which as a rule resolve over time.

It is almost universally accepted that directly acting dopamine receptor agonists have less efficacy than levodopa, although the reasons are not clear. Neurologists from London have sought to question this assumption by using cabergoline ($n = 11$) and pergolide ($n = 7$) at considerably higher doses than recommended (1). The actual mean doses were 8.8 and 9.4 mg/day, compared with recommended maxima of 6 and 5 mg/day respectively. The high doses were tolerated by the patients for 2.3–2.5 years; mild dyskinesias ($n = 7$), ankle edema ($n = 3$), and hallucinations ($n = 1$) were the only reported adverse effects. The authors concluded that the therapeutic window for these drugs is apparently much greater than is generally accepted, and that higher doses can be given safely with potentially enhanced efficacy.

Organs and Systems

Respiratory

- Interstitial pneumonitis occurred in a 65-year-old man who had taken cabergoline in a low dose (1 mg/day) for 4 months (2). He was given no specific therapy, but withdrawal of the drug resulted in clinical recovery after 3 weeks and radiological resolution within 2 months.

Nervous system

When cabergoline is used in patients with Parkinson's disease, the same spectrum of dyskinesias and psychiatric complications as with bromocriptine is observed (3).

The successful use of ergot derivatives to shrink macroprolactinomas can have unwanted neurological consequences, and this has been described in two case reports.

Three Italian men aged 39, 42, and 53 years with invasive prolactinomas took cabergoline 1.0–3.0 mg/week and all developed CSF rhinorrhea after 2–7 months (4). This was clearly a consequence of loss of the "stopper" effect of the tumor, owing to shrinkage, and in each case was successfully treated by endoscopic trans-sphenoidal surgery.

- A 42-year-old Spanish man took cabergoline (up to 3 mg/day) for a large prolactinoma causing hypopituitarism and symptomatic chiasmal compression (5). After 18 months there was only a minimal tumor remnant on the floor of the sella turcica, but there was chiasmal herniation. However, there were no clinical effects of this, and in particular the visual fields were normal.

Serosae

Some patients who developed retroperitoneal or pleural fibrosis from bromocriptine experienced aggravation of the condition when they switched to cabergoline. Cabergoline may share this risk with bromocriptine (SEDA-17, 169).

- A 76-year-old man taking cabergoline 10 mg/day developed constrictive pericarditis after 11 months (6). He required pericardiectomy, but cabergoline was continued and a few months later he was found to have pleuropulmonary fibrosis, which did not resolve on drug withdrawal.

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Cadmium

General Information

Cadmium is a bluish-white metallic element (symbol Cd; atomic no. 48). It is found as cadmium sulfate in a mineral called greenockite.

Cadmium is an environmental and occupational pollutant that is associated with nephrotoxicity (1) and bone toxicity (2); even low concentrations can impair renal function and/or increase bone fragility. Cadmium is also an adulterant in infant formulas and weaning foods.

Cadmium concentrations were determined in 59 baby food samples, including milk-based cereals and milk-based and soya-based formulas, recommended from 0–18 months of age. The mean weekly intake of dietary cadmium was estimated to be 0.1–3.1 μg/kg. Exposure to dietary cadmium from weaning diets can be up to 12 times higher in children fed infant formulas than in breast-fed children (3).

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Caffeine

General Information

Caffeine is a methylxanthine used to stimulate the central nervous system in combating fatigue and drowsiness. Caffeine stimulates the central nervous system, skeletal muscle contraction and gastric secretion. It acts to a lesser extent on the kidney, producing a diuresis. Most of its adverse effects result from accentuated pharmacological actions, including those described above, and they may become especially evident in pathologically or genetically predisposed individuals. Differences in the activity of *N*-acetylases in the liver, secondary to genetic polymorphism lead to differential susceptibility to caffeine (xanthine toxicity) (1). A certain degree of tolerance develops to some of the pharmacological actions of caffeine, but there is little or no tolerance to its central stimulatory effects; however, some kind of psychic habituation can develop after prolonged consumption.

The term "caffeinism" refers to a state of acute or chronic toxicity resulting from the ingestion of high doses of caffeine. An average intake of 500–600 mg/day of caffeine (about 7–9 cups of tea or 4–7 cups of coffee) is currently regarded as representing a significant health risk. The symptoms of caffeinism include behavioral, psychophysiological, and affective manifestations. They include restlessness, anxiety, irritability, agitation, muscle tremor, insomnia, headache, sensory disturbances, diuresis, cardiovascular symptoms, and gastrointestinal complaints (SEDA-10, 5). At very high doses caffeine can even produce epileptiform convulsions. Acute overdosage can occur and produce severe CNS excitation in sensitive individuals and small children (SEDA-15, 1). Tonic-clonic seizures have been reported postpartum. Maternal use of caffeine in pregnancy can cause dysrhythmias in the neonate (SEDA-14, 1). Because of a significant abuse potential and potential toxicity, formulations that contain a high content of caffeine have been made available by prescription only in some European countries.

Workers in the coffee industry often develop allergic reactions, in the form of dermatitis, rhinitis, and bronchial asthma, on exposure to dust in the process of stripping the chaff from raw beans before roasting (2). This may or may not be a reaction to caffeine itself.

The ability of caffeine to catalyse the formation of *N*-nitrosamine in the digestive tract has raised the question of its being carcinogenic (see "Pancreas" below). Caffeine has been associated with fibrocystic breast disease (3). However, a study of benign proliferative endothelial disorder of the breast did not show any association with methylxanthine consumption (SEDA-15, 1).

Organs and Systems

Cardiovascular

There is debate over the association between caffeine intake and cardiovascular disease. Increases in mean blood pressure, blood glucose and free fatty acid concentrations, and urinary catecholamine excretion have been

found after acute ingestion of 150 mg of caffeine (SEDA-4, 4). While not particularly potent, caffeine appears to produce cardiac dysrhythmias, including ventricular tachycardia. Furthermore, in non-smokers, daily consumption of five cups of percolated coffee per day (about 680 mg of caffeine) was associated with a modestly increased risk of having a cardiac arrest without a prior history of cardiovascular disease (4). In patients with pre-existing heart disease, caffeine lowers the effective and functional refractory period of the atrioventricular node (SEDA-4, 5). A two-fold increased risk of myocardial infarction has been suggested for women who drink six or more cups of coffee a day (5), and in two studies, men who drank five or more cups of coffee a day had an approximately two-fold increase in the risk of myocardial infarction (6) or coronary artery disease (7). However, prospective studies of the relation between caffeine consumption and an increased risk of coronary artery disease (or stroke) have been negative (SEDA-15, 1) or inconclusive (8,9), as has been the association between the consumption of coffee and serum cholesterol concentration assessed in 24 cross-sectional epidemiological studies (SEDA-15, 1). However, a Finnish study did show a positive-dose relation with serum cholesterol after adjustment for confounding variables, in men but not in women. It has also been suggested that the relation is seen only with boiled and not instant or filter coffee.

Guaraná is produced from the guaraná plant (*Paullina cupana*), the seeds of which contain 3.6–5.8% caffeine.

- A 25-year-old woman, who had pre-existing mitral valve prolapse and a history of having had bouts of palpitation with caffeine, developed intractable ventricular fibrillation after consuming a "natural energy" guaraná health drink containing a high concentration of caffeine (10). At autopsy, she was found to have sclerosis and myxoid changes in the mitral valve leaflets. The caffeine concentration in her aortic blood was 19 μg/ml.

This case highlights the need for more careful regulation of "natural" products, including warning patients with underlying health problems, and clear labeling to document the presence of any constituents with potentially adverse effects. It also shows the need for medical practitioners to be familiar with the more widely used "natural remedies" and their toxicological profiles. Following the death of this patient, the Western Australian Coroner recommended that Race 2005 Energy Blast should be removed from the local market, and the product was recalled nationally in August 1999.

Nervous system

Insomnia, anxiety, tachycardia, and tremor are among the symptoms most commonly reported with caffeine (11). Tenseness and irritability also occur and, with high intake, symptoms resembling those of anxiety neurosis (12). A case of "caffeine psychosis" has also been reported (13). Dose–response associations have not been particularly well studied, but some are known (SEDA-7, 6). Paradoxically, six cases have been reported of pathological sleepiness induced by caffeine (14). Tonic-clonic seizures occurred postpartum in a woman who had received 500 mg of caffeine sodium benzoate for headache after lumbar puncture; a prolonged half-life was implicated (SEDA-17, 1).

Consumption of methylxanthine-containing products can aggravate the neurological symptoms associated with the glucose transporter type 1 (Glut 1 deficiency syndrome). The human erythrocyte and the brain glucose transporters are identical, and the erythrocyte transporter has been used in four patients with individual mutations in the Glut 1 gene to demonstrate that caffeine and theophylline inhibit glucose transport (15). The Glut 1 deficiency syndrome represents impaired glucose transport across the blood–brain barrier caused by partial Glut 1 deficiency, which results in hypoglycorrhachia, seizures, and developmental delay. Identifying potential inhibitors of Glut 1 is essential in preventing further impairment of glucose transport in these patients. In addition to phosphodiesterase inhibition and adenosine A_1 receptor antagonism by methylxanthines, it is likely that inhibition of glucose transport also contributes to the convulsive effects of methylxanthines in high doses.

Psychological, psychiatric

Red Bull, a mixture of caffeine, taurine, and inositol, a widely consumed "power drink," affects mental performance and mood.

- A 36-year-old man with bipolar-I disorder had a second manic episode, after having been in remission for 5 years while taking lithium to maintain a serum lithium concentration of 0.8–1.1 mmol/l (16). One week before this episode, he drank three cans of Red Bull at night, as he needed less sleep; 3 days later he drank three more cans. After 4 days he was feeling euphoric, hyperactive, and insomniac. He gradually became more hyperactive and had increased libido and irritability. He took no more Red Bull and improved within 7 days.

Based on this report, the authors suggested that stimulant beverages that contain caffeine might cause cognitive and behavioral changes, especially in vulnerable patients with bipolar illness.

Metabolism

The major metabolic effects of caffeine are increase in free fatty acids and blood glucose concentration (17,18).

Electrolyte balance

Hypokalemia and myopathy are known effects of caffeine toxicity, and severe hypokalemia and fatigue and hypokalemia with myopathy have been described before (19).

Gastrointestinal

Large doses of caffeine can cause nausea and vomiting. Caffeine is a potent stimulant of hydrochloric acid secretion (20) and has been incriminated in exacerbating duodenal ulcers. However, decaffeinated coffee has also been reported to be as potent as instant coffee in stimulating gastric acid secretion (20).

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Pancreas

A relation between coffee consumption and pancreatic cancer was originally reported in a case-control study (SEDA-7, 8), with an unexpected increase in pancreatic cancer in coffee drinkers (relative risk in men 2.6). The same group studied differences in mortality from pancreatic cancer in different countries in relation to differences in coffee consumption and found a significant relation between increases in coffee consumption and increases in mortality from pancreatic cancer. However, the data on which the findings were based were crude.

Although the results of published epidemiological studies are compatible with a small effect of coffee consumption on pancreatic carcinogenesis, the interpretation of these findings is not clear, because of the possibility of residual confounding and other sources of bias (21). In two large cohort studies of 1 907 222 person-years of follow-up, there were 288 cases of pancreatic cancer with no evidence of an association between coffee and pancreatic cancer (22). Furthermore, there is no association between folate intake, caffeine consumption, and the risk of pancreatic cancer (23).

The relation between coffee drinking and the presence of the K-*ras* mutation in patients with exocrine pancreas cancer has been investigated in Spain in 121 cases in which tissue specimens were available (24). In exocrine pancreatic cancer, the K-*ras* gene may be activated less often among regular coffee drinkers, suggesting that caffeine, or other compounds present in coffee, or other factors with which coffee drinking is associated, may modulate K-*ras* activation. While the results of this study may have mechanistic and pathogenic relevance, they have no clinical or health policy implications.

Urinary tract

Large doses of caffeine cause diuresis. Daily consumption of caffeine citrate increased the mean urinary excretion rate of tubular cells and erythrocytes in volunteers (25). The nephrotoxicity of analgesic antipyretic drug combinations may result from a combined effect, in which aspirin, phenacetin, and caffeine all play a role (SEDA-4, 5). In 10 asymptomatic women and 20 women with confirmed detrusor instability, caffeine caused a significant increase in detrusor pressure on bladder filling in the latter, but no difference in volume at first contraction, height of contraction, or bladder capacity (26).

As up to 10% of about 42 000 dialysis patients have suffered from renal insufficiency due to analgesic nephropathy (in the postphenacetin era), German nephrologists have demanded that medications that contain fixed combinations of analgesics (paracetamol, aspirin, or propyphenazone plus caffeine) be withdrawn from the market, following the example of their US colleagues in the National Kidney Foundation (27).

Skin

Urticaria as an allergic response to caffeine has been reported (SEDA-4, 5).

Musculoskeletal

Caffeine toxicity is an uncommon cause of myopathy, but a history of excessive dietary and pharmaceutical consumption of caffeine should be sought in any patient with unexplained myopathy, particularly if there is concomitant hypokalemia (28).

- A 21-year-old woman with a 12-month history of progressive muscle weakness, nausea, vomiting, diarrhea, and weight loss had significant worsening of muscle weakness over 2 weeks, associated with exercise-induced muscle stiffness and pain. She had severe hypokalemia and metabolic acidosis. For the past 1–2 years she had been consuming about 8 liters of cola every day. She stopped drinking cola and took potassium supplements, after which her hypokalemia and muscle weakness resolved and the serum creatine kinase activity fell. Based on the concentration of caffeine in the cola, it was estimated that she had been consuming at least 1 g/day of caffeine for more than 12 months.

Long-Term Effects

Drug abuse

Abuse of analgesic combinations has been thought to be especially facilitated if they contain caffeine or codeine, reinforcing abuse. However, this has not been confirmed in an expert review, in which it was concluded that the available evidence does not support the claim that analgesics co-formulated with caffeine, in the absence of phenacetin, stimulate or sustain overuse (29). Caffeine has a synergistic effectiveness with analgesics, but although it can cause dependence, the risk is low. Withdrawal is not likely to cause increased need of analgesics. However, there is strong dependence behavior in patients using formulations containing phenacetin, antipyretics/analgesics, and caffeine. This finding may have led to the impression that caffeine stimulates overuse of analgesics.

Drug withdrawal

Restlessness, irritability, and headache are withdrawal effects attributable to caffeine. These and other symptoms can occur with lower doses of caffeine than generally supposed (30). The caffeine withdrawal headache may be responsible for the widespread practice of taking caffeine-containing analgesics habitually, since a withdrawal headache could create a vicious cycle of drug use (SEDA-5, 6).

Tumorigenicity

A possible association between the use of methylxanthine consumption and the occurrence of fibrocystic breast disease has been suggested (SEDA-6, 8) (3). It was concluded that in women who are predisposed to fibrocystic disease, methylxanthines are factors in its development. The mechanism of this effect might be an inhibitory action on the activity of cyclic AMP and cyclic GMP phosphodiesterases.

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Second-Generation Effects

Fertility

It has been suggested that the use of caffeine to improve the mobility of human sperm used in artificial insemination may be very risky, owing to the potential for chromosome damage and also possible damage to the fertilized ovum (SEDA-5, 32).

Another study suggested that a high daily intake of caffeine may predispose women to reproductive difficulties (SEDA-9, 2). Although delayed mitosis and excessive chromatid breaks have been noted in human lymphocytic cultures to which caffeine was added (31), the rapid and almost complete metabolism of caffeine in man may protect against the various deleterious effects found in human cell culture studies and animal studies.

Epidemiological studies requiring further verification have suggested a relation between caffeine intake and reduced fertility, even at a consumption as low as the caffeine equivalent of more than one cup of brewed coffee a day (SEDA-14, 1). A more recent study has suggested that this reduction in fertility is limited to non-smokers; possible acceleration of caffeine metabolism in smokers has been offered as a possible explanation for the apparent effect of smoking (32).

Fetotoxicity

In two studies (SEDA-6, 9), there was a relation between caffeine consumption and fetotoxicity. In one, a high rate of spontaneous abortions, stillbirths, and prematurity at birth was associated with ingestion of more than 600 mg of caffeine per day by either the mother or the father. In the other, a daily intake of more than eight cups of coffee by the mother increased the frequency of congenital malformations.

Concern about the possible harmful effects of caffeine on the outcome of pregnancy has evolved mainly from studies of animals which have shown a reduction in intrauterine fetal growth. However, the implications of these data for men are unclear, because of the differences in mode of exposure to caffeine, the amounts consumed, and caffeine metabolism. The possible effects of caffeine intake on the human fetus have been reviewed (SEDA-7, 8); the conclusion was that the scientific data currently available could not answer the question. In an analysis of interview and medical record data in 12 205 non-asthmatic women to evaluate the relation between coffee consumption and adverse outcomes in pregnancy, the findings were negative.

In eight pregnant women at 32–36 weeks of gestation, two cups of caffeinated or decaffeinated coffee were associated with an increase in the incidence of fetal breathing activity, and the caffeinated coffee was associated with a significant fall in baseline fetal heart rate (33). Three cases of fetal dysrhythmias resulting from excessive intake of caffeine by the mother during pregnancy have been reported (SEDA-14, 1).

Some studies have reported that a caffeine consumption of over 150 mg/day during pregnancy may be associated with a small but statistically significant increase in the risks of spontaneous abortion and low birth weight, although the authors could not rule out contributions of maternal age, smoking, ethanol use, or other confounders (34). Careful evaluation of these confounders may at least partly resolve the controversy surrounding possible adverse effects of caffeine on pregnancy outcome.

Whether the consumption of caffeine during pregnancy increases the risk of spontaneous abortion is controversial. In a nested case-control study, 591 women who had a spontaneous abortion before 140 days of gestation were compared with 2558 matched women from the same clinic who gave birth to live infants at 28 weeks' gestation and who had serum drawn on the same day of gestation as the women who had abortions (35). The women were enrolled in the Collaborative Perinatal Project from 1959 to 1966, and the serum paraxanthine concentration was measured 30 years later. Moderate consumption of caffeine was unlikely to increase the risk of spontaneous abortion; only extremely high serum paraxanthine concentrations were associated with spontaneous abortion.

Lactation

The relation between serum and breast milk concentrations of caffeine has been studied (SEDA-6, 8). Caffeine accumulation in the infant would depend on the average concentration in maternal serum and breast milk over time, the volume of milk ingested, and particularly the infant's clearance rate of caffeine.

Susceptibility Factors

Age

Infants

Xanthines have been given to infants at the risk of sudden infant death syndrome or idiopathic apnea of prematurity (see monograph on Theophylline). About 50% of 30 infants treated with caffeine (and 12 of 18 infants treated with theophylline) had significant increases in episodes of gastroesophageal reflux (36). The authors stressed that screening for reflux should precede the administration of caffeine (and theophylline) to infants at the risk of sudden infant death syndrome. As expected, the frequency of adverse effects such as tachycardia and gastroesophageal reflux is lower with lower doses of caffeine; for example 2.5 mg/kg qds (SEDA-17, 1).

Children

In healthy boys, there were increases in subjective anxiety in long-term low-caffeine users, and withdrawal symptoms in high-caffeine users. No beneficial effects of caffeine use were found (37). It has been recommended that children should take caffeine only in analgesic products and in a dose related to their age (SEDA-5, 6).

Other features of the patient

In patients who are susceptible to cardiac dysrhythmias, restriction of caffeine may be indicated. Caffeine can also add to the rise in renin and noradrenaline that occur in hepatic cirrhosis and can also considerably aggravate diarrhea in patients with irritable bowel syndrome (SEDA-15, 1).

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Drug Administration

Drug overdose

Excessive amounts (1 g or more) of caffeine can cause untoward central nervous effects, including psychotic organic brain syndrome (SEDA-5, 6).

Oral route

Oral doses that cause death are said to range from 3 to 50 g of caffeine, but death from excessive caffeine ingestion is rare, perhaps owing to its emetic effect. Death may be due to cardiovascular shock, but chronic potentially lethal toxicity, even for heavy coffee or tea drinkers, is very unlikely since 60–100 cups a day would be required.

Intravenous route

In two instances in which caffeine was given intravenously, convulsions and death were recorded at doses of 400 mg and 3.2 g (38).

The elimination of caffeine has been described in a neonate weighing 1860 g, born at 31 weeks of gestation, after the accidental administration of 160 mg/kg. The first serum concentration was 218 mg/l at 36.5 hours after dosing. The half-life was 81 hours, the clearance 0.01 l/hour (0.17 ml/minute), and the volume of distribution 1.17 liters. Toxic manifestations were hypertonia, sweating, tachycardia, cardiac failure, pulmonary edema, and metabolic disturbances such as metabolic acidosis, hyperglycemia, and raised creatine kinase activity. An unusual feature of this infant's illness was gastric dilatation. These signs resolved by day 7 at a serum concentration of 60–70 mg/l (39).

Confirmed reports of caffeine overdose are rare. Postmortem concentrations of caffeine measured in femoral blood were 220 and 190 mg/l in two adults who took unknown doses (40). In view of the extensive use of caffeine, the authors emphasized the forensic importance of measuring caffeine.

Drug–Drug Interactions

General

A comprehensive textbook has listed more than 40 drugs that interact with caffeine (41). See also the monograph on Theophylline.

Caffeine has been included in a wide variety of fixed drug combinations (for example, with non-steroidal anti-inflammatory drugs or antihistamines). The purpose of including caffeine is to increase systemic availability (for example, antipyrine), to counteract adverse effects of the other drug (for example, sedation induced by antihistamines), or to provide additional therapeutic efficacy (aspirin). The use of combination formulations complicates evaluation of caffeine's adverse effects.

Aspirin

In a comparison of a caffeine-free formulation containing aspirin 650 mg plus citric acid 60 mg and a formulation containing aspirin 650 mg plus caffeine citrate 120 mg (equivalent to 60 mg of anhydrous caffeine), caffeine significantly increased the rate of appearance as well as the maximum concentration of the salicylate in plasma by about 31 and 15% respectively; the AUC of salicylate was also significantly higher (42). The authors concluded that caffeine can increase the systemic availability of aspirin in man without any other effects on the salicylate disposition.

However, in a systematic review and meta-analysis of published randomized controlled trials, it was found that caffeine did not enhance the analgesic effect of aspirin (43).

Benzodiazepines

Caffeine and other central stimulants can reverse daytime sedation from benzodiazepine use. There was a positive effect of caffeine 250 mg on early morning performance after placebo, and flurazepam 30 mg given the night before (44,45), particularly in terms of subjective assessment of mood and sleepiness. However, one cannot assume that the alerting effect of caffeine necessarily reverses the amnestic, disinhibiting, or insight-impairing effects of benzodiazepines. Indeed, caffeine may actually worsen learning and performance already impaired by lorazepam (46).

Carbamazepine

In five children, due to receive carbamazepine for epilepsy, the caffeine breath test was carried out before the administration of carbamazepine 200–600 mg and after a minimum of 2–3 weeks therapy (47). The results suggested that carbamazepine induces the metabolism of caffeine by CYP1A2.

Clozapine

In an open, randomized, crossover study in 12 non-smoking healthy volunteers, caffeine 400–1000 mg/day reduced clozapine clearance, probably by inhibiting CYP1A2 (48). Differences in habitual caffeine intake can, therefore, explain some of the large variability in the kinetics of clozapine (49), and should be taken into consideration when clozapine is used. An earlier case report (50) also suggested that caffeine increases plasma concentrations of clozapine, causing toxic symptoms.

In seven schizophrenic patients taking clozapine monotherapy, caffeine was withdrawn for 5 days; clozapine plasma concentrations fell by 50% (51). The authors suggested that schizophrenic patients treated with clozapine should have their caffeine intake supervised, and that monitoring of concentrations of clozapine and its metabolite may be warranted.

Ephedrine

Even low doses of caffeine can, in sensitive patients, cause tremor, insomnia, and anxiety, and such problems are much more marked if ephedrine is given together with caffeine, as it sometimes is for appetite control (SEDA-17, 161).

Idrocilamide

The pharmacokinetics of caffeine is greatly altered by concomitant administration of the myorelaxant, idrocilamide, which inhibits the biotransformation of caffeine and prolongs its half-life nine-fold (SEDA-5, 7). Consequently, when idrocilamide is prescribed, partial

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or total abstinence from caffeine-containing products should be enforced.

Lithium

Caffeine increases renal lithium clearance, and it is conceivable that drastic curtailment of caffeine intake could result in an increase in serum lithium concentration.

Mexiletine

Mexiletine reduces the clearance of theophylline, and this combination has been reported to cause ventricular tachycardia (52). A similar interaction with caffeine has been reported (53).

Neuroleptic drugs

Caffeine can alter the plasma concentrations of neuroleptic drugs (SEDA-5, 6).

Excess caffeine can stimulate the CNS, which can worsen psychosis and thus interfere with the effects of neuroleptic drugs (54). Neuroleptic drugs can precipitate from solution when mixed with coffee or tea (55), but the clinical significance of this interaction is unknown (56).

Oral contraceptives

The clearance of both theophylline and caffeine is reduced in oral contraceptive users, and their half-lives are increased, probably because of inhibition of hepatic metabolism by cytochrome P450 isozymes (57). Again, caution in dosage is advisable.

Phenylpropanolamine

Phenylpropanolamine, which is available over the counter for weight loss, inhibits caffeine metabolism, leading to excessive stimulation; for example, manic psychosis (SEDA-17, 1).

Interference with Diagnostic Tests

Dexamethasone suppression test

A false-positive dexamethasone-suppression test has been associated with ingestion of caffeine equivalent to 4–5 cups of coffee (58).

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Calcipotriol

General Information

Topical calcipotriol (a vitamin D analogue) is an effective and safe treatment for mild to moderate psoriasis vulgaris. Its mode of action is identical to that of 1,25-dihydroxycolecalciferol (calcitriol).

Organs and Systems

Nervous system

Calcipotriol can cause headache (SEDA-20, 157).

Mineral balance

With the use of doses larger than the recommended maximum of 100 g/week, a few reports have documented hypercalcemia and hypercalciuria (SEDA-18, 176) (SEDA-22, 172) (1,2). However, hypercalcemia has also been reported in a few patients using no more than the recommended doses (3,4). Calcipotriol exerts its effects on systemic calcium homeostasis by increasing intestinal absorption of calcium and probably phosphate. This results in suppression of parathyroid hormone and 1,25-dihydroxycolecalciferol (5).

Skin

At recommended doses, the adverse effects of calcipotriol are limited to skin reactions. Lesional and perilesional

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irritation occurs in about 20% of patients (6). Contact dermatitis is rare. Photosensitization can occur when calcipotriol is used in patients undergoing UVB phototherapy.

Contamination of the facial skin can result in frank irritant contact dermatitis. Allergic contact dermatitis has been observed in some patients (7–10).

Hyperpigmentation due to local application of vitamin D in combination with photochemotherapy has been described. Calcipotriol may have the same potential.

- In one case, there was profound hyperpigmentation during UVB 311 nm phototherapy in combination with local calcipotriol, applied after the UVB irradiation (11). Calcipotriol-treated areas, and not the surrounding normal skin, started to show increased pigmentation after six sessions of irradiation, stabilized during therapy, and slightly decreased in intensity during the 6 months after photochemotherapy had ended. No photoallergy tests were performed.

Calcipotriol can occasionally convert psoriasis vulgaris into pustular psoriasis (SEDA-19, 165).

Immunologic

Contact allergic reactions to calcipotriol are rare. In one case patch tests with Psorcutan Salbe and calcipotriol (its active ingredient) were both positive (10).

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Calcitetracemate

General Information

The use of calcitetracemate in the treatment of lead poisoning has been described (1). Between 1993 and 2000, 45 adult patients consulted the Poison Centre of Marseilles, France after lead exposure (9 women, 36 men, average age 44, range 22–76 years). In 22 patients, a calcitetracemate provocation test was negative. Six patients with a positive test refused to be treated; the other 16 were treated with a total of 58 courses of calcitetracemate by infusion 500 mg bd for 5 days. The mean blood lead concentration in these 16 patients was 566, range 320–943 ng/ml; the mean urinary lead excretion was 3011, range 789–7229 μg/day. The mean amount of lead eliminated in the urine during chelation therapy was 30 912 μg. In 12 patients in whom lead exposure ended after the diagnosis of lead poisoning, chelation therapy reduced the blood lead concentration by 69%. In four patients in whom exposure continued during treatment, the blood lead concentration fell by only 7%. In the 16 treated patients, there was clinical improvement and no adverse effects of chelation therapy.

Drug Administration

Drug administration route

Lead poisoning in a six-week-old child was treated by adding disodium calcitetracemate to the peritoneal dialysis fluid (2).

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Calcitonin

General Information

Calcitonin inhibits osteoclastic bone resorption, increases the urinary excretion of calcium and phosphate, and reduces serum calcium. It is established in the treatment of disorders of high bone turnover, including Paget's disease and postmenopausal osteoporosis, but is less effective than the bisphosphonates. Calcitonin is less effective than other therapeutic measures in the treatment of acute hypercalcemia. Long-term administration of calcitonin reduces morbidity in cases of osteogenesis imperfecta

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and algoneurodystrophy (SEDA-13, 1307) (1,2). The role of calcitonin in treating acute pain due to osteoporotic crush fractures has been reviewed, but the mechanism of its analgesic effect is not known (3).

When used continuously in high doses, the therapeutic effect of calcitonin is sustained for only a few months, probably because of down-regulation of osteoclast receptors. The duration of the response to calcitonin can be extended by periodically interrupting treatment. A number of regimens, ranging from cycles of a few days to several months, are effective both as prophylaxis in healthy postmenopausal women and in women with established osteoporosis; however, the risk of fractures is not reduced (4). Calcitonin also has a potent analgesic effect independent of its effect on bone, possibly mediated through endogenous opioids (5). It appears to be more effective when given intranasally than subcutaneously for this indication.

Salmon- and eel-derived calcitonins are more potent than the human and porcine forms. Intranasal calcitonin has a systemic availability of only 3% of the subcutaneous form but is associated with fewer adverse effects, probably because of lower systemic availability. Antibodies against calcitonin are often found after prolonged treatment, more commonly with salmon (30–69%) or eel calcitonin than with human calcitonin. Antibodies do not usually affect the clinical effect of calcitonin and have not been reported to cause any harm to the patient. Antibody-mediated resistance is exceptional.

The adverse effects of calcitonin, although common, are usually mild and are dose-related in the therapeutic range. They include gastrointestinal effects (nausea, cramps, and vomiting), dizziness and flushing, and local reactions either at the injection site (rash, pruritus) or in the nose (rhinitis, dryness, sneezing, and rarely epistaxis). In 40 patients there was nausea and dizziness in 37% of those given rectal salmon calcitonin compared with 6% of those given placebo (6).

Observational studies

The usefulness of intranasally administered salmon calcitonin for 2 years has been evaluated in 44 glucocorticoid-dependent asthmatics (SEDA-19, 378) (7). All were taking calcium supplements (1000 mg/day), but one group also took calcitonin 100 IU every other day. Calcitonin increased spinal bone mass during the first year of treatment, and maintained bone mass in a steady state during the second year. However, the rate of vertebral fractures was similar in the two groups. The addition of salmon calcitonin did not increase the efficacy of calcium plus vitamin D in the prevention of bone loss in 48 newly diagnosed patients taking glucocorticoids for giant cell arteritis and polymyalgia rheumatica in a double-blind, randomized, placebo-controlled trial (SEDA-21, 418) (8).

Placebo-controlled studies

Salmon calcitonin nasal spray prevented bone loss in the lumbar spine of 31 patients treated with prednisone for polymyalgia rheumatica (SEDA-22, 448) (9). They were randomized to salmon calcitonin nasal spray 200 IU/day or matched placebo for 1 year. Both groups were treated with calcium supplements if their dietary intake was below 800 mg/day. With calcitonin the mean bone mineral density in the lumbar spine fell by 1.3% and with placebo by 5% after 1 year. There were no differences in the hip, including the femoral neck and trochanter, or in total body bone density.

Organs and Systems

Cardiovascular

Flushing occurs soon after administration of calcitonin in up to 20% of patients and usually settles within several minutes (10).

Respiratory

When salmon calcitonin 100 IU was given intravenously to 18 patients with atopic asthma in a randomized, double-blind, crossover study, to assess any potential anti-inflammatory effect, it significantly reduced FEV1 and FVC, but the effect lasted less than 1 hour (11). Three subjects had dyspnea that did not require specific treatment.

Ear, nose, throat

In a randomized, placebo-controlled trial 22% of 1255 postmenopausal women taking calcitonin compared with 15% of women taking placebo had rhinitis (nasal congestion, discharge, or sneezing) (12). Almost all cases were of mild to moderate severity.

Gastrointestinal

Nausea is common with calcitonin, and vomiting or diarrhea occur more rarely. These symptoms usually settle without treatment if the drug is continued and may also be reduced by giving the dose at bedtime.

In 46 patients with Paget's disease given synthetic salmon thyrocalcitonin 80 IU/day for 3 months, there were hot flushes in 35% and nausea in 24%; in only one case was it necessary to stop treatment because of intractable diarrhea (13).

Urinary tract

In postmenopausal osteoporosis treatment with calcitriol plus etidronate or calcitonin produced improvement in spinal bone mineral density, but a high rate of nephrotoxic adverse events (14).

Skin

Rash and pruritus can occur at the site of subcutaneous injections of calcitonin (15).

Immunologic

Calcitonin allergy is very rare.

- A 60-year-old woman tolerated daily intranasal calcitonin for 6 months of the year for 4 years (16). She developed nasal watering, nasal and ocular pruritus, and sweating immediately after the administration of nasal calcitonin when she restarted after a 6-month break. These symptoms recurred 2 years later, with abdominal pain and hypotension, after 10 months of

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intramuscular calcitonin, and were again reproduced by a lower dose intramuscularly.

- A 65-year-old woman, who had previously tolerated calcitonin nasal spray, developed eye and nose congestion, an itchy nose, and sneezing minutes after using intranasal salmon calcitonin (17). She was later given intramuscular salmon calcitonin and developed generalized urticaria and nasal itching within minutes. Skin testing was positive with eel and salmon calcitonins but not human calcitonin, and she was treated with human calcitonin without adverse effects.

Drug Administration

Drug formulations

Intranasal calcitonin is associated with fewer adverse effects than parenteral formulations, probably because of low systemic availability. However, a meta-analysis has confirmed that adverse events are poorly reported in clinical trials (18). The pooled relative risk for rhinitis from four trials ($n = 1663$) was 1.72, but this did not reach statistical significance.

Drug–Drug Interactions

Lithium

In four women serum lithium concentrations fell significantly within 3 days of starting calcitonin (19) because of increased renal clearance of lithium (19,20). Serum lithium concentrations should therefore be monitored in patients who start to take calcitonin.

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Calcium carbimide

General Information

Calcium carbimide has effects and uses similar to those of disulfiram, and has been used in the treatment of chronic alcoholism (1). Its alternative name, cyanamide, has also been used to designate carbimide, which is used in veterinary medicine.

Organs and Systems

Hematologic

Calcium carbimide has been linked to granulocytopenia (2) (SEDA-22, 525).

Liver

Calcium carbimide has been linked to liver damage (3) (SED-12, 1244), but caution is needed in attributing liver damage in alcoholic patients to drugs.

Skin

Calcium carbimide has been linked to skin reactions (4).

- A 37-year-old man developed itchy erythema on his trunk and legs after taking calcium carbimide (dose not specified) for 3 days. He had an eosinophilia of 22%. Patch-testing with calcium carbimide was positive. The eruption subsided after withdrawal.
- A 60-year-old man developed keratotic erythema on his trunk and extremities after taking calcium carbimide (dose not specified) for 1 month. Patch-testing with calcium carbimide was positive. The eruption subsided after withdrawal, but itch and redness persisted for 9 months.

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Calcium channel blockers

See also Individual agents

General Information

The calcium channel blockers block the movement of calcium across L-type calcium channels. The main drugs that share this action are verapamil (a phenylalkylamine), diltiazem (a benzthiazepine), and the dihydropyridines, which include amlodipine, darodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, and nitrendipine. Other agents, for example prenylamine and lidoflazine, are now rarely used, and perhexiline, having failed to reach the market at all in some countries, was withdrawn in the UK after continuing concerns about its safety (1). Mibefradil blocks T type calcium channels; it was withdrawn within 1 year of marketing because of multiple drug interactions, emphasizing the need for rigorous drug assessment before release and the importance of postmarketing surveillance of new drugs (2).

Although they are chemically heterogeneous, many adverse effects are common to all calcium channel blockers, predictable from their pharmacological actions. Calcium plays a role in the functions of contraction and conduction in the heart and in the smooth muscle of arteries; drugs that interfere with its availability (of which there are many, the calcium channel blockers being the most specific) will therefore act in all these tissues. A few idiosyncratic and hypersensitivity reactions have also been reported with individual calcium channel blockers.

The properties of these drugs vary widely (3). Nifedipine is said to have little negative inotropic effect and no effect on the atrioventricular node; verapamil is a potent cardiac depressant, with a marked effect on the atrioventricular node; and diltiazem has less cardiac depressant effect but inhibits atrioventricular nodal activity.

Controversy has surrounded the use of calcium channel blockers in the treatment of hypertension (4) and ischemic heart disease (5), with evidence for an association with unfavorable coronary outcomes compared with other therapies. Most of the evidence comes from the use of short-acting formulations, especially short-acting nifedipine. The hypothesis put forward to explain these findings was that short-acting formulations cause reflex activation of the sympathetic nervous system (6). Further observational studies showed that these drugs were also associated with gastrointestinal hemorrhage (7) and cancer (8). Claims of conflicts of interests amongst authors were published (9), often amid heated debate. Further evidence against the short-acting calcium channel blockers in hypertension has been forthcoming (10,11) and a worse than expected outcome with respect to coronary outcomes in diabetic patients has fuelled the debate (12). Further evidence of gastrointestinal bleeding has been published (13), but there is evidence against a link with cancer (14). All these scares have undoubtedly reduced the standing of this class of drugs in the eyes of physicians.

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That calcium channel blockers are effective in relieving the symptoms of angina pectoris is beyond doubt. However, the Angina and Silent Ischemia Study (15), in which nifedipine, diltiazem, and propranolol were compared with placebo in a crossover study, produced conflicting results. Only diltiazem improved treadmill exercise time and only propranolol convincingly reduced the number of silent ischemic episodes during ambulatory monitoring. These findings are hard to explain (16). Beta-blockers may be cardioprotective and therefore preferable to calcium channel blockers (17). The clinically significant deterioration seen in patients with impaired left ventricular function taking calcium channel blockers is important, as many patients with angina have previously had a myocardial infarction or have poor left ventricular function. Calcium channel blockers cannot be assumed to be safe second-line drugs for angina in patients with poor cardiac reserve, although newer agents may prove to be safer (18).

Calcium channel blockers are very effective in controlling variant angina, and are often used during coronary angioplasty and after coronary artery surgery. They are also useful in patients who are intolerant of beta-blockers (19), or who have a poor response to nitrates, or who have concurrent hypertension.

General adverse effects

Throbbing headache, facial warmth and flushing, and dizziness are minor complaints associated with the use of calcium channel blockers; these effects are believed to be caused by inhibitory actions on smooth muscle (20). Palpitation, muscle cramps, and pedal edema also occur (21–27). Dizziness, facial flushing, leg edema, postural hypotension, and constipation have been reported in up to one-third of patients. They are rarely severe and often abate on continued therapy. More serious adverse effects, mainly those affecting cardiac conduction, are much less common, and only rarely is withdrawal necessary.

Organs and Systems

Cardiovascular

Cardiac failure

Although acute hemodynamic studies have suggested that calcium channel blockers can be beneficial in cardiac failure (28), long-term treatment has been associated with clinical deterioration. Calcium channel blockers should therefore be prescribed with caution for patients with impaired cardiac function, who should be regularly reassessed; treatment should be withdrawn if the signs or symptoms of cardiac failure appear. In some cases heart failure is predictable, as in the case of a patient with aortic stenosis who developed left ventricular failure after treatment with nifedipine (29). Increased sympathetic activity can also compensate for the myocardial suppressant effects of calcium channel blockers, and the combination of these drugs (particularly verapamil) with beta-adrenoceptor antagonists has therefore given cause for concern in the past, although this combination is now considered relatively safe for the majority of patients with normal cardiac function (30–32).

Myocardial ischemia

There have been many studies of the efficacy of calcium channel blockers in early and late intervention in myocardial infarction (33). These studies have failed to show convincing benefits. Indeed, in the nifedipine intervention studies there was a consistent trend towards higher mortality in the treated patients than in those taking placebo. A study in which patients were randomized to placebo or nifedipine within 48 hours of admission was terminated after 1358 patients had been recruited, because mortality at 6 months was 15.4% on nifedipine and 13.3% on placebo (34).

It has been argued that dihydropyridine calcium channel blockers, which increase heart rate, can all increase the risk of death and reinfarction (35,36). Early beneficial results with diltiazem in patients with non-Q-wave infarction (37) were not confirmed in the Multicenter Diltiazem Postinfarction Trial (38). In patients with pulmonary congestion, diltiazem was associated with an increase in cardiac events, and there was a similar result in patients with low ejection fractions. However, verapamil does appear to reduce reinfarction (39), a benefit that is more marked in those without heart failure (40). Nifedipine may also have a detrimental effect in unstable angina; it certainly appears to offer no benefit (41).

A retrospective case-control study (4) has sparked controversy concerning the use of short-acting calcium channel blockers in treating hypertension. The study involved 623 cases of fatal and non-fatal myocardial infarction over a period of 8 years, and 2032 age- and sex-matched controls. The risk of myocardial infarction in patients taking calcium channel blockers was 16 per 1000, compared with 10 per 1000 in patients taking beta-blockers or thiazides. However, this result may have been an example of confounding by indication, since patients exposed to calcium channel blockers will have been more likely to have had peripheral vascular disease, lung disease (a low forced expiratory volume being a risk factor for cardiovascular disease), higher serum cholesterol concentrations, and diabetes mellitus. Careful statistical analysis was carried out in an attempt to control for some of the confounding factors, but such confounding can only be properly controlled for in a randomized study. A meta-analysis of 16 randomized secondary prevention studies in patients with coronary heart disease showed that the use of short-acting nifedipine is associated with an increased mortality in a dose-related manner (dose, risk: 30–50 mg, 1.06; 60 mg, 1.18; 80 mg, 2.83) (5). However, the event rates in this study were relatively small. A prospective cohort study in 906 elderly hypertensive patients showed that short-acting nifedipine is associated with a relative mortality risk of 1.7 compared with beta-blockers (42). After the publication of these studies, the FDA recommended that short-acting nifedipine should no longer be used in hypertension or unstable angina (43).

Disturbances of cardiac rhythm

Calcium channel blockers differ in their effects on the myocardial conduction system. Both verapamil and diltiazem have significant inhibitory effects on both sinoatrial and atrioventricular nodal function, whereas nifedipine has little or no effect. Nevertheless, nifedipine can on occasion cause troublesome bradydysrhythmias (44,45).

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Severe conduction disturbances can also occur if calcium channel blockers are used in hypertrophic cardiomyopathy (46), but these drugs are used in this condition (47).

Hypotension

There are many case reports of symptomatic hypotension, usually in hypertensive patients treated with large dosages of calcium channel blockers (48,49) or in patients with myocardial infarction (50). These may represent injudicious prescribing rather than true adverse drug effects. In the DAVIT II study, 1.9% of the verapamil-treated group versus 1.6% of the placebo-treated group developed hypotension or dizziness (40); the frequency of hypotension in a randomized study of diltiazem after infarction was 0.6% in the drug-treated group and 0.2% in the placebo-treated group (37).

Respiratory

Adverse respiratory effects are uncommon with calcium channel blockers. However, three cases of acute bronchospasm accompanied by urticaria and pruritus have been reported in patients taking verapamil (51), and a patient with Duchenne-type muscular dystrophy developed respiratory failure during intravenous verapamil therapy for supraventricular tachycardia (52). Recurrent exacerbations of asthma occurred in a 66-year-old lady with hypertension and bronchial asthma given modified-release verapamil (53).

In pulmonary hypertension, both verapamil and nifedipine increase mean right atrial pressure in association with hypotension, chest pain, dyspnea, and hypoxemia; the severe hemodynamic upset resulted in cardiac arrest in two patients after verapamil and death in another after nifedipine (54). A patient with pulmonary hypertension also developed pulmonary edema whilst taking nifedipine (55) and another seems to have developed this as an allergic reaction (56).

Nervous system

Calcium channel blockers can cause parkinsonism. Of 32 patients with this complication, only three had made a full recovery 18 months after withdrawal; patients under 73 years of age tended to have a better prognosis (57). It is not known if these patients would have developed parkinsonism in any case, and whether the drugs merely act as precipitants.

Calcium channel blockers can worsen myasthenic syndromes. Myasthenia gravis can deteriorate with oral verapamil (58). A patient with Lambert–Eaton syndrome and a small-cell carcinoma of the lung developed respiratory failure within hours of starting treatment with verapamil for atrial flutter, and required assisted ventilation (59). Only after verapamil had been withdrawn did breathing improve. Verapamil affects calcium channels in nerve membranes in animals, but the experimental concentrations used exceeded those found in clinical practice (59). Thus, the evidence for a drug-related effect is circumstantial. In another case, diltiazem triggered Lambert–Eaton syndrome, which improved with drug withdrawal (60).

Sensory systems

Eyes

Painful eyes occurred in 14% of patients taking nifedipine compared with 9% in captopril-treated patients in a postmarketing surveillance study (61). The mechanism is unknown but is not via ocular vasodilatation (62).

Taste

Transient disturbances of taste and smell, without other signs of neurological deficit, have been reported after nifedipine and diltiazem. The time to the onset of symptoms after nifedipine varied from days to months, and symptoms regressed within 24 hours of withdrawal (63). With diltiazem the effect gradually abated over 10 weeks, despite continuation of therapy (64).

Psychological, psychiatric

A patient taking diltiazem developed the signs and symptoms of mania (65) and another developed mania with psychotic features (66). There have also been reports that nifedipine can cause agitation, tremor, belligerence, and depression (67), and that verapamil can cause toxic delirium (68). Nightmares and visual hallucinations have been associated with nifedipine (69). Depression has been reported as a possible adverse effect of nifedipine (70).

Some reports have suggested that calcium channel blockers may be associated with an increased incidence of depression or suicide. However, there is a paucity of evidence from large-scale studies. A study of the rates of depression with calcium channel blockers, using data from prescription event monitoring, involved gathering information on symptoms or events in large cohorts of patients after the prescription of lisinopril, enalapril, nicardipine, and diltiazem by general practitioners (71). The crude overall rates of depression during treatment were 1.89, 1.92, and 1.62 per 1000 patient-months for the ACE inhibitors, diltiazem, and nicardipine respectively. Using the ACE inhibitors as the reference group, the rate ratios for depression were 1.07 (95% CI = 0.82, 1.40) and 0.86 (0.69, 1.08) for diltiazem and nicardipine respectively. This study does not support the hypothesis that calcium channel blockers are associated with depression.

Endocrine

In six hypertensive patients given nitrendipine 20 mg/day for 30 days, there was inhibition of aldosterone response but no significant change in ACTH secretion in response to corticotrophin-releasing hormone (72).

The calcium-dependent pathway of aldosterone synthesis in the zona glomerulosa is blocked by calcium channel blockers, producing a negative feedback increase in the pituitary secretion of ACTH, which in turn causes hyperplasia of the zona glomerulosa. This leads to increased production of androgenic steroid intermediate products and subsequently testosterone, which acts on gingival cells and matrix, giving rise to gingival hyperplasia (see the section on Mouth and teeth).

Metabolism

Calcium transport is essential for insulin secretion, which is therefore inhibited by calcium channel blockers (73).

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Despite this, calcium channel blockers generally have minimal effects on glucose tolerance in both healthy and diabetic subjects. Oral glucose tolerance is not affected by verapamil, and basal blood glucose concentrations were not altered during long-term verapamil administration (74). Similarly, neither nifedipine nor nicardipine produced significant hyperglycemic effects in either diabetic or non-diabetic patients (75–77). In 117 hypertensive patients nifedipine caused a significant rise in mean random blood glucose of only 0.3 mmol/l (78), an effect that was clearly of no clinical relevance. In the Treatment of Mild Hypertension Study, 4 years of monotherapy with amlodipine maleate caused no change compared with placebo in the serum glucose of 114 hypertensive patients (79). In a review (80) it was concluded that in usual dosages calcium channel blockers do not alter glucose handling. However, in a few patients diabetes appeared de novo or worsened considerably on starting nifedipine (78,81), so there may be a small risk in some individuals.

Fluid balance

Edema of the legs is a well-recognized reaction to nifedipine and also occurs with verapamil, diltiazem, and the long-acting dihydropyridines (82,83), suggesting that this is a class effect of calcium channel blockers.

Hematologic

Calcium channel blockers rarely cause hematological effects. A hemorrhagic diathesis, including impaired platelet function, develops in chronic renal insufficiency, in which calcium channel blockers are used widely as antihypertensive agents. In 156 patients with moderate to severe chronic renal insufficiency not on hemodialysis calcium channel blockers prolonged the bleeding time (OR = 3.52; 95% CI = 1.01, 12.3) (84). However, despite this effect, there were no clinically serious hemorrhagic events during the study. Among those taking calcium channel blockers, 21 patients with prolonged bleeding times were randomly assigned to two groups; in one group treatment was withdrawn and bleeding time shortened; in those who continued to take the treatment the bleeding time was unchanged.

Nifedipine has been reported to cause agranulocytosis (85) and leukopenia was attributed to diltiazem; the latter patient had scleroderma, active rheumatoid disease, and pulmonary fibrosis, but the white cell count fell after 3 weeks of diltiazem, recovered on withdrawal, and fell on rechallenge (86). Diltiazem has also been reported to cause immune thrombocytopenia in a 68-year-old man with angina (87).

Mouth and teeth

Gingival hyperplasia, similar to that seen with phenytoin and ciclosporin, is a rare but well-recognized adverse effect of nifedipine (88). It has also been reported in patients taking felodipine (89,90), nitrendipine (SEDA-16, 200), and verapamil (91), suggesting that this adverse effect is a class effect. Only one case of gingival hyperplasia related to calcium channel blockers was reported to the Norwegian Adverse Drug Reaction Committee up to 1991, despite their widespread use (92). However, subclinical gingival hyperplasia on tissue histology was found in 83 and 74% of patients taking nifedipine and diltiazem respectively (93). The reaction generally occurs within a few months of starting treatment, and in some cases drug withdrawal produces marked regression of clinical hyperplasia. The mechanism of this adverse effect is unclear, but has been proposed to involve a hormonal imbalance in the hypothalamic–pituitary–adrenal axis (94).

Periodontal disease has been assessed in 911 patients taking calcium channel blockers, of whom 442 were taking nifedipine, 181 amlodipine, and 186 diltiazem, and in 102 control subjects (95). There was significant gingival overgrowth in 6.3% of the subjects taking nifedipine, while the prevalence induced by amlodipine or diltiazem was not significantly different than in the controls. The severity of overgrowth in the nifedipine group was related to the amount of gingival inflammation and also to sex, men being three times as likely to develop overgrowth than women.

Gastrointestinal

Because of effects on smooth muscle, the calcium channel blockers (particularly verapamil (96) but also diltiazem) can cause constipation. This may be due to colonic motor activity inhibition (97). Gastroesophageal reflux can also occur, and the calcium channel blockers should be avoided in patients with symptoms suggestive of reflux esophagitis (98). Calcium channel blockers (verapamil, diltiazem, and nifedipine) can also be associated with an increased incidence of gastrointestinal bleeding, as reported in a prospective cohort study in 1636 older hypertensives, with a relative risk of 1.86 (95% CI = 1.22, 2.82) compared with beta-blockers (7). However, this finding was not confirmed in other retrospective studies (13,99,100).

Liver

Mild hepatic reactions have been observed in association with verapamil, nifedipine (101–104), and diltiazem (105,106). In some cases fever, chills, and sweating have been associated with right upper quadrant pain, hepatomegaly, and mild increases in serum bilirubin and transaminase activity; in others, patients have remained asymptomatic. One patient had granulomatous hepatitis with diltiazem (107); another had a periportal infiltrate rich in eosinophils while taking verapamil (108). The increase in liver enzyme activities is generally transient, although mild persistent abnormalities have been seen. Occasionally, extreme increases in hepatic enzyme activities have been reported (85,105). Their frequency appears to be low, and since the symptoms and signs are mild they could easily be overlooked.

Skin

Apart from minor flushing and leg erythema associated with edema, skin reactions with calcium channel blockers are infrequent; the frequency has been estimated at 1.3% for diltiazem (109).

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An erythematous rash with painful edema has been described with nifedipine (110) and also with diltiazem, but without the edematous element (109).

Mild erythema multiforme and Stevens–Johnson syndrome have been reported as probable reactions to diltiazem (85) and long-acting nifedipine (111).

Nifedipine, verapamil, and diltiazem have all been implicated as possible causes of erythema multiforme and its variants, Stevens–Johnson syndrome and toxic epidermal necrolysis, and/or exfoliative dermatitis from FDA data (112).

Psoriasiform eruptions have been reported in patients taking verapamil and nicardipine (SEDA-16, 199).

Photo-induced annular or papulosquamous eruptions due to subacute cutaneous lupus erythematosus with positive antinuclear, anti-Ro, and anti-La antibodies have been reported with verapamil, nifedipine, and diltiazem (113).

Reproductive system

Calcium channel blockers can occasionally cause menorrhagia (114) and gynecomastia (115).

Immunologic

Verapamil, nifedipine, and diltiazem have all been associated with allergic reactions, including skin eruptions and effects on liver and kidney function. Nifedipine has also been reported to cause a febrile reaction (116), and diltiazem was associated with fever, lymphadenopathy, hepatosplenomegaly, an erythematous maculopapular rash, and eosinophilia in a 50-year-old man (117).

Long-Term Effects

Drug withdrawal

The possibility of a calcium antagonist withdrawal syndrome has been raised (118–127), as it has been reported that withdrawal of verapamil, nifedipine, and diltiazem can worsen angina or even cause myocardial infarction. However, in a randomized, double-blind study of withdrawal of nifedipine in 81 patients before coronary artery bypass surgery, angina at rest occurred only in patients who had experienced similar symptoms previously, and there were no early untoward effects of drug withdrawal (120). If a withdrawal syndrome does exist, it could be due to rebound coronary vasospasm, but the present weight of evidence suggests that withdrawal results in no more than the loss of a useful therapeutic effect or the unmasking of progressive disease (127).

Tumorigenicity

A retrospective cohort study in 5052 elderly subjects, of whom 451 were taking verapamil, diltiazem, or nifedipine, showed that these drugs were associated with a cancer risk of 1.72 (95% CI = 1.27, 2.34), and there was a significant dose–response relation (8). A small risk of cancer (RR = 1.27; 95% CI = 0.98, 1.63) with calcium channel blockers was reported in a nested case-control retrospective study involving 446 cases of cancers in hypertensive patients (128). However, the authors concluded that this finding may have been spurious, as there was no relation between the cancer risk and the duration of drug use. Another study did not show any excess cancer risk with short-acting nifedipine after myocardial infarction in patients followed up for 10 years, although there were only 22 cancer deaths in 2607 patients (129). Neither did the much larger Bezafibrate Infarction Prevention (BIP) Study, which reported cancer incidence data in 11 575 patients followed for a mean period of 5.2 years, with 246 incident cancer cases, 129 among users (2.3%) and 117 (2.1%) among non-users of calcium channel blockers (130). Others also failed to find a positive link between calcium channel blockers and cancer (14,131). However, elderly women taking estrogens and short-acting calcium channel blockers had a significantly increased risk of breast carcinoma (hazard ratio = 8.48; 95% CI = 2.99, 24) (132). This controversy can perhaps only be resolved by prospective studies with longer follow-up periods (133), although ideal studies are unlikely ever to be conducted.

Second-Generation Effects

Pregnancy

The calcium channel blockers have had very limited use in pregnancy. The absence of reports of fetal deaths, malformations, or other maternal or neonatal adverse effects cannot therefore be construed as indicating safety. However, a comparison of nifedipine and hydralazine in 54 patients with severe pre-eclampsia showed that nifedipine is more effective, allowing delivery of more mature infants (134).

- Modified-release nifedipine 40 mg tds caused marked hypotension when used to delay preterm labor in a previously healthy 29-year-old woman who started contracting at 29 weeks; the hypotension may have precipitated an uncomplicated non-Q-wave myocardial infarction (135).

When nifedipine is combined with intravenous magnesium to delay preterm labor, colonic pseudo-obstruction can occur (136).

Lactation

Both verapamil (137) and diltiazem (138) are excreted in breast milk, but the risk to the suckling infant is unclear.

Susceptibility Factors

Patients with impaired function of the sinus node or impaired atrioventricular conduction can develop sinus bradycardia, sinus arrest, heart block, hypotension and shock, and even asystole, with verapamil (139) or diltiazem. These drugs should not be given to patients with aberrant conduction pathways associated with broad-complex tachydysrhythmias, and they can cause severe conduction disturbances in hypertrophic cardiomyopathy.

Similarly, verapamil should be used with caution in patients with heart failure, and both diltiazem and nifedipine can cause problems in patients with poor cardiac reserve. However, the PRAISE study (18) suggested that amlodipine may be used safely, even in the presence of severe heart failure optimally treated with diuretics,

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digoxin, and ACE inhibitors. In this study, amlodipine significantly reduced cardiac mortality by more than a third in non-ischemic dilated cardiomyopathy, without significantly affecting mortality in ischemic cardiomyopathy (140).

Calcium antagonists should be avoided when possible in the peri-infarction period.

The use of calcium channel blockers in patients with pulmonary hypertension has been associated with cardiac arrest and sudden death.

Caution should be exercised in using verapamil in patients with hepatic cirrhosis, as its metabolism is reduced, leading to high plasma concentrations and potential toxicity (SEDA-16, 198). Similarly, lower starting and maintenance doses of other calcium channel blockers should be used in the presence of liver impairment. This also applies to patients with chronic renal insufficiency, especially those taking the modified-release formulation of verapamil (SEDA-17, 238).

Drug Administration

Drug overdose

The treatment of overdosage with calcium channel blockers has been reviewed (141); other reports have reviewed poisoning with verapamil (142–144), and other calcium channel blockers (145,146).

The features appear to be arterial hypotension, bradycardia due to sinus node depression and atrioventricular block, and congestive cardiac failure and angina (147–149). Although the therapeutic effects are different according to the drug, in overdosage the effects are similar (145). Severe metabolic acidosis (usually lactic acidosis) and generalized convulsions can also occur (150) and hypoglycemia has been reported (151). Non-cardiogenic pulmonary edema has been reported with diltiazem (152) and verapamil (153). Several deaths have occurred with verapamil.

- An overdose of nifedipine 280 mg produced marked vasodilatation in a young patient with advanced renal insufficiency; it was successfully treated with intravenous calcium (154).

Treatment consists of gastric lavage, activated charcoal, and cathartics. Contrary to popular belief, significant overdosage of immediate-release verapamil can be associated with delayed absorption, as suggested by a case report, the authors of which suggested the use of repeated doses of activated charcoal (142). In severe cases total gut lavage should be considered. Intravenous calcium gluconate (155), glucagon (156), pressor amines (isoprenaline, adrenaline, or dobutamine), artificial ventilation, and cardiac pacing may all be required. Hemoperfusion does not appear to influence the clinical course, but 4-aminopyridine reversed the features of a modest accidental overdose of verapamil in a patient on maintenance hemodialysis (157). The rationale for the use of aminopyridine, an antagonist of non-depolarizing neuromuscular blocking agents, supported by prior animal experiments, was the enhancement of transmembrane calcium flux and the facilitation of synaptic transmission. This is of potential value, in view of the apparent unresponsiveness of some patients to supportive measures.

Five cases of overdose of calcium channel blockers have been reported (158):

- a 34-year-old woman who took amlodipine 0.86 mg/kg;
- a 48-year-old man who took an unknown amount of modified-release diltiazem;
- a 5-month-old girl inadvertently given nifedipine 20 mg;
- a 14-year-old girl who took modified-release verapamil 30 mg/kg;
- a 31-year-old man who took modified-release verapamil 71 mg/kg.

All were successfully treated with hyperinsulinemia/euglycemia therapy. The authors described the mechanism of action of this form of therapy, which is mainly related to improvement in cardiac contractility and peripheral vascular resistance and reversal of acidosis. They proposed indications and dosing for this therapy consisting in most cases of intravenous glucose with an intravenous bolus dose of insulin 1 U/kg followed by an infusion of 0.5–1 U/kg/hour until the systolic blood pressure is over 100 mm/Hg and the heart rate over 50/minute. Hyperinsulinemia/euglycemia therapy is currently reserved as an adjunct to conventional therapy and is recommended only after an inadequate response to fluid resuscitation, high-dose calcium salts, and pressor agents.

Drug–Drug Interactions

Beta-adrenoceptor antagonists

The greatest potential for serious mishap arises from interactions between calcium channel blockers (especially verapamil and related compounds) and beta-adrenoceptor antagonists (159,160). This combination can cause severe hypotension and cardiac failure, particularly in patients with poor myocardial function (161–163). The major risk appears to be associated with the intravenous administration of verapamil to patients who are already taking a beta-blocker (164), but a drug-like tiapamil, which closely resembles verapamil in its pharmacological profile, might be expected to carry a similar risk (165). Conversely, intravenous diltiazem does not produce deleterious hemodynamic effects in patients taking long-term propranolol (166). However, there have been instances when the combination of diltiazem with metoprolol caused sinus arrest and atrioventricular block (167).

The concurrent use of oral calcium channel blockers and beta-adrenoceptor antagonists in the management of angina pectoris or hypertension is less likely to result in heart block or other serious adverse effects (168), and these two drug groups are commonly used together. However, caution is still advised, and nifedipine or other dihydropyridine derivatives would be preferred in this type of combination (26,169,170). Nevertheless, the combination of nifedipine with atenolol in patients with stable intermittent claudication resulted in a reduction in walking distance and skin temperature, whereas either drug alone produced benefits (171).

Carbamazepine

A pharmacokinetic interaction has been described between carbamazepine and the calcium channel blockers

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verapamil (172) and diltiazem (173). With both drugs, inhibition of the hepatic metabolism of carbamazepine resulted in increased serum carbamazepine concentrations and neurotoxicity, with dizziness, nausea, ataxia, and diplopia. Adding nifedipine to carbamazepine was not associated with alterations in steady-state carbamazepine concentrations (173).

Cardiac glycosides

Calcium channel blockers interact with cardiac glycosides. The main mechanism is inhibition of digoxin renal tubular secretion by inhibition of P glycoprotein. In a review of the interactions of calcium channel blockers with digoxin, in which their clinical relevance was assessed, it was concluded that serious consequences can be prevented by careful monitoring, especially in patients whose serum digoxin concentration is already near the upper end of the therapeutic range (174).

Verapamil suppresses renal digoxin elimination acutely, but this suppression disappears over a few weeks (175). However, inhibition of the extrarenal clearance of digoxin persists, and the result of this complex interaction is an increase in steady-state plasma digoxin concentrations of less than 100%. Patients taking both drugs should be carefully monitored. However, the pharmacodynamic effects of digoxin are apparently reduced by verapamil (176), so that dosage adjustment may be unnecessary. Cardiovascular collapse and/or asystole has followed the use of intravenous verapamil in patients taking oral digoxin alone (177) or in combination with quinidine, propranolol, or disopyramide (165).

The interaction of digoxin with nifedipine increases plasma digoxin concentrations by only about 15% (178,179) and is less important.

Diltiazem increases digoxin concentrations by 20–50% (180,181).

Interactions of digoxin with nitrendipine (182) and bepridil (183) have also been described.

Verapamil and diltiazem, but not nifedipine, increase steady-state plasma digitoxin concentrations (184).

Ciclosporin

Calcium channel blockers are given to transplant patients for their protective effect against ciclosporin-induced nephrotoxicity and to optimize ciclosporin immunosuppression in order to reduce early rejection of renal grafts. Nifedipine has been used to treat ciclosporin-induced hypertension, although amlodipine may be just as effective (185).

However, some calcium channel blockers have pharmacokinetic interactions: diltiazem, verapamil, nicardipine, and amlodipine increase ciclosporin concentrations, whereas nifedipine, felodipine, and isradipine do not (SED-14, 604) (SEDA-21, 210) (SEDA-21, 212) (SEDA-22, 216). Two confirmations of these observations have been published. In a retrospective study of 103 transplant patients verapamil and diltiazem, but not nifedipine or isradipine, caused a significant increase in plasma ciclosporin concentrations (186). The effect of verapamil and diltiazem on ciclosporin concentrations was independent of dosage. In a crossover comparison between verapamil, felodipine, and isradipine in 22 renal transplant recipients, verapamil interacted pharmacokinetically with ciclosporin but felodipine and isradipine did not (187).

Nine kidney transplant recipients had an increase in trough whole blood ciclosporin concentrations of 24–341% after introduction of nicardipine (188). A similar interaction has been reported with diltiazem (189) and verapamil (190).

Cimetidine

The histamine H_2 receptor antagonist cimetidine increases plasma concentrations of nifedipine and delays its elimination by inhibition of hepatic mono-oxygenases. Maximum plasma nifedipine concentrations and AUC can be increased by as much as 80%, and this results in a significant increase in the antihypertensive and antianginal effects of nifedipine and also toxicity (191,192).

Cimetidine also increases plasma concentrations of nitrendipine and nisoldipine (182,193).

Ranitidine, which inhibits the microsomal mono-oxygenase system only slightly, does not alter plasma dihydropyridine concentrations to the same extent (194).

Combinations of calcium channel blockers

Paralytic ileus has been attributed to the combined use of diltiazem and nifedipine (195).

- A 62-year-old man with chest pain underwent cardiac catheterization. The diagnosis was vasospastic angina and he was given nifedipine 20 mg bd; when his angina attacks persisted he was also given oral diltiazem 100 mg bd. After 2 days, although his angina was well controlled, abdominal distension and vomiting occurred, and an X-ray suggested intestinal ileus. The drugs were withdrawn and the ileus resolved. It recurred when the treatment was resumed and gradually resolved again after withdrawal.

The disorder was suspected to be due to enhanced pharmacodynamic effects caused by the combination of the two calcium channel blockers. However, plasma concentrations of nifedipine have also been reported to increase about three-fold when it is combined with diltiazem (196).

Dantrolene

Dantrolene interacts with verapamil and with diltiazem, causing myocardial depression and cardiogenic shock (SEDA-16, 199).

Grapefruit juice

The ability of grapefruit to increase the plasma concentrations of some drugs was accidentally discovered when grapefruit juice was used as a blinding agent in a drug interaction study of felodipine and alcohol (197). It was noticed that plasma concentrations of felodipine were much higher when the drug was taken with grapefruit juice than those previously reported for the dose of drug administered. In other studies concurrent administration of grapefruit juice and felodipine increased the AUC, causing increased heart rate, and reduced diastolic blood pressure (198), or caused increased blood pressure and heart rate, headaches, flushing, and light-headedness (199). Grapefruit increases plasma concentrations of

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nifedipine (200) and nisoldipine (201) by increasing their systemic availability (202); with nisoldipine or nitrendipine there was an increase in heart rate.

Prazosin

An interaction of prazosin with nifedipine or verapamil resulted in acute hypotension (203,204). The mechanism appears to be partly kinetic (the systemic availability of prazosin increasing by 60%) and partly dynamic.

Theophylline

Theophylline toxicity has been reported in several patients, apparently stabilized on theophylline, after the introduction of verapamil (205) or nifedipine (206).

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Calcium dobesilate

General Information

Calcium dobesilate is an antioxidant that has been used to treat diabetic retinopathy, in which it slows progression of the disease during long-term oral treatment by reducing microvascular permeability, leading to improved visual acuity (1). It not only acts as an antioxidant but also stimulates endothelial production of nitric oxide.

In early studies the most common adverse effects of calcium dobesilate after oral administration were gastrointestinal disturbances and, occasionally, nervousness and fever (SEDA-3, 181) (SEDA-16, 204).

In a systematic review of the published literature from 1970 to 2003, a postmarketing surveillance report covering the period 1974–1998, and periodic safety update reports covering the period 1995–2003 from the French regulatory authorities pharmacovigilance database, the following adverse effects were reported: fever (26%), gastrointestinal disorders (12.5%), skin reactions (8.2%), arthralgia (4.3%), and agranulocytosis (4.3%) (2).

Organs and Systems

Hematologic

Agranulocytosis associated with calcium dobesilate has occasionally been reported (3). Although the risk has been calculated at 121 cases per million per year from case-control and case-population studies (4), there have been many fewer spontaneous reports than are consistent with this relatively high figure, and the true incidence is unknown (5).

Drug Administration

Drug administration route

Intramuscular calcium dobesilate can be painful (SEDA-3, 181).

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Calcium salts

General Information

Calcium is a soft grayish-white metallic element, one of the alkaline earth metals (symbol Ca; atomic no. 20). It is found in sources such as lewisite (calcium antimonate), colemanite and pandermite (calcium borates); ankerite, aragonite, calcite, chalk, dolomite, and stromatolite (calcium carbonates); hydrophilite (calcium chloride); powellite (calcium molybdate); whewellite (calcium oxalate); autunite (calcium phosphate); anorthite, apophyllite, chabazite, datolite, epidote, eudialite, feldspar, gyrolite, hornblende, margarite, melilite, monticellite, nephrite, pectolite, phillipsite, piedmontite, prehnite, scapolite, scawtite, scolecite, thaumasite, titanite, vesuvianite, wollastonite, and zeolite (calcium silicates); glauberite, gypsum, and polyhalite (calcium sulfates); perovskite (calcium titanate); and scheelite (calcium tungstate). Calcium phosphate is a major constituent of bones (apatite).

Uses

Salts of calcium are used as a source of calcium:

- to treat hypocalcaemia (for example calcium gluconate);
- to treat hyperphosphatemia (for example calcium acetate, calcium carbonate);
- to treat hyperkalemia (calcium polystyrene sulfonate; see monograph on Polystyrene sulfonates);
- to treat and prevent osteomalacia and osteoporosis (in combination with vitamin D or a bisphosphonate);
- as antacids (for example calcium hydroxide and calcium carbonate).

However, although calcium salts can produce short-term relief from dyspepsia, calcium ions stimulate antral gastrin release, and hence gastric acid secretion, making them unsuitable for long-term treatment of peptic disorders (1).

Other uses of calcium salts incidental to the calcium they contain include:

- in wound dressings (calcium alginate);
- to prevent methotrexate toxicity (calcium folinate and levofolinate);
- in lead poisoning (sodium calcium edetate).

Organs and Systems

Mineral balance

In one study of the use of calcium carbonate as a phosphate binder in patients on chronic hemodialysis, there was a low incidence of hypercalcemia at daily doses below 6 g (2), whereas in another report on 26 dialysis patients who used calcium carbonate for 3 years, 42% developed new calcification (3).

Calcium edetate can cause mild transient hypercalcemia (4) and hypercalciuria (5).

Acid–base balance

Long-term use of calcium salts can cause the milk-alkali syndrome and alkalosis in conjunction with hypercalcemia and renal insufficiency (6). It presents acutely with headache, nausea, irritability, and weakness, or chronically with uremia, alkalosis, and hypercalcemia. Sustained high dosage and/or concurrent renal disease are common antecedents (7).

Gastrointestinal

There is an unsubstantiated belief that calcium-containing antacids cause a rebound increase in gastric acid secretion that is more intense than with other antacids. This was thought to be due to absorption of calcium, the resultant hypercalcemia leading to increased acid secretion. This has been investigated in two trials. One (8) was an open, randomized, crossover study in 12 healthy volunteers who were given calcium carbonate and magnesium carbonate (Rennie) and hydrotalcite (Talcid). The other (9) was a double-blind, crossover trial in 12 healthy volunteers who were given placebo, Maalox liquid, and Rennie liquid. All the antacids had similar efficacy and there was no evidence of acid rebound with calcium carbonate.

Urinary tract

In general, there is an increased risk of nephrolithiasis with prolonged high calcium intake. Studies aimed at determining whether high calcium intake increases the risk of nephrolithiasis have shown that in patients at risk of nephrolithiasis or with a history of nephrolithiasis, calcium can be safely given for osteoporosis, provided there is careful monitoring (10,11).

In a French analysis of 22 510 urinary calculi performed by infrared spectroscopy, drug-induced urolithiasis was divided into two categories: first, stones with drugs physically embedded ($n = 238$; 1.0%), notably indinavir monohydrate ($n = 126$; 53%), followed by triamterene ($n = 43$; 18%), sulfonamides ($n = 29$; 12%), and amorphous silica ($n = 24$; 10%); secondly, metabolic nephrolithiasis induced by drugs ($n = 140$; 0.6%), involving mainly calcium/vitamin D supplementation ($n = 56$; 40%) and carbonic anhydrase inhibitors ($n = 33$; 24%) (12). Drug-induced stones are responsible for about 1.6% of all calculi in France. Physical analysis and a thorough drug history are important elements in the diagnosis.

Second-Generation Effects

Pregnancy

In a pregnant woman, calcium-containing antacids raised the calcium concentration to the point where hemodialysis was required (SEDA-17, 413).

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Campanulaceae

See also Herbal medicines

General Information

The genera in the family of Campanulaceae (Table 1) include lobelia and Venus' looking glass.

Table 1 The genera of Campanulaceae

Asyneuma (harebell)
Brighamia (brighamia)
Campanula (bell flower)
Campanulastrum (bell flower)
Canarina (canarina)
Clermontia (clermontia)
Cyanea (cyanea)
Delissea (delissea)
Downingia (calico flower)
Gadellia (gadellia)
Githopsis (bluecup)
Heterocodon (heterocodon)
Hippobroma (hippobroma)
Howellia (howellia)
Jasione (jasione)
Legenere (false Venus' looking glass)
Legousia (legousia)
Lobelia (lobelia)
Nemacladus (threadplant)
Parishella (parishella)
Platycodon (platycodon)
Porterella (porterella)
Rollandia (rollandia)
Trematolobelia (false lobelia)
Triodanis (Venus' looking-glass)
Wahlenbergia (wahlenbergia)

Lobelia inflata

Lobelia inflata (Indian tobacco) contains lobeline and other pyridine alkaloids. It has been used as an emetic, antidepressant, respiratory stimulant, an aid to smoking cessation, and a treatment for metamfetamine abuse (1).

Adverse effects

Lobeline has peripheral effects similar to those of nicotine, whereas its central activity may be different. It has been associated with nausea, vomiting, headache, tremors, and dizziness. Symptoms caused by overdosage include profuse sweating, paresis, tachycardia, hypertension, Cheyne-Stokes respiration, hypothermia, coma, and death. Large doses are convulsant.

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Camphor

General Information

The symptoms of systemic camphor poisoning have been reviewed (1).

Organs and Systems

Nervous system

Systemic nervous system adverse reactions after cutaneous contact with camphor have been reported (2).

- A 15-month-old child had crawled through spirits of camphor containing 10% camphor. Over the next 48 hours he became progressively ataxic and had several brief generalized motor seizures. The seizures persisted for 2 days despite appropriate therapy. Over 15 days he slowly improved; recovery in motor and mental function was eventually complete. The child had no further seizures until 1 year later, when a camphorated vaporizer containing 4.81% camphor was administered by the mother. During inhalation there was a brief major motor seizure.

Breathing difficulties, convulsions, and coma have been reported after repeated topical application of camphor-containing agents (3).

Skin

- A woman developed severe eczema of the ears, neck, and upper chest after having applied Earex ear drops. Patch tests with rectified camphor oil were positive on days 2 and 4 (4).

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Candesartan cilexetil

See also Angiotensin II receptor antagonists

General Information

Candesartan cilexetil is the prodrug of candesartan, an angiotensin II type 1 (AT_1) receptor antagonist. Absorbed candesartan cilexetil is completely metabolized to candesartan. Candesartan has a half-life of about 9 hours (slightly longer in elderly people).

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In an open study of 4531 hypertensive patients, the total incidence of adverse effects of candesartan was 6.1% (1). Individual adverse effects did not occur in more than 0.8% and were mainly dizziness and headache.

Susceptibility Factors

Renal disease

In patients undergoing chronic hemodialysis, the safety profile did not differ from that reported in other populations, except for some rare cases of hypotension during hemodialysis. Hemodialysis does not affect the kinetics of candesartan. Because of the variability of oral clearance and the pronounced influence of hemodialysis-induced volume contraction on the hemodynamic effects of candesartan, careful monitoring is recommended (2).

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Cannabaceae

See also Herbal medicines

General Information

The family of Cannabaceae contains two genera:

1. *Cannabis* (hemp)
2. *Humulus* (hop).

The cannabinoids are covered in a separate monograph.

Humulus lupulus

Humulus lupulus (hop) contains a variety of sesquiterpenoids, diterpenoids, and triterpenoids, phytoestrogens, and the flavonoid xanthohumol, which has some in vitro anti-HIV activity (1). Apart from their use in brewing beer, hops have been used for sedative purposes, but evidence of efficacy is poor.

Adverse effects

Hop farmers are exposed to air that can contain dust, endotoxin, and micro-organisms. In one study of 19 farms in Poland Gram-positive bacteria formed 22–96% of the total count; among them, corynebacteria and endospore-forming bacilli were prevalent (2). Fungi constituted 3.7–65% of the total count; the dominant species were *Penicillium citrinum*, *Alternaria alternata*, and *Cladosporium epiphyllum*. Thermophilic actinomycetes and Gram-negative bacteria were detected in the air of only 10 and six farms respectively. The concentrations of endotoxin were 313–6250 μg/g. The hop growers seem to be exposed to lower concentrations of dust, micro-organisms, and endotoxin than other branches of agriculture, which the authors partly attributed to antimicrobial properties of *H. lupulus*.

Eight of twenty-three hops farmers, who had been exposed to organic dust from *H. lupulus*, reported symptoms of chronic bronchitis and five reported work-related symptoms, including dry cough and dyspnea (3).

After 30 years of working with hop without any health problems a 46-year-old farmer developed erythema of the face, neck, and upper chest, edema of the eyelids, conjunctivitis, and dermatitis of the hands (4). Her symptoms were provoked by both fresh and dried hops, appeared after half-an-hour of working, and persisted over 1–2 days. Skin tests yielded the following results: hop leaves (saline extract)—prick positive, patch negative; hop leaves (glycerol extract)—prick positive, patch negative; hop cones (saline extract)—prick positive, patch negative; hop cones (glycerol extract)—prick negative, patch positive after 48 and 72 hours. Despite discontinuing work, the patient had several relapses attributed to other sources of hop allergens: a beauty cream, a herbal sedative, and her husband, also a hop farmer.

Systemic urticaria has been reported in patients who had been exposed to *H. lupulus* (5), in one case with arthralgia and fever (6).

Flavonoids in hops that persist in beer can inhibit certain isoforms of cytochrome P450 in vitro (7). At a concentration of 10 μmol/l xanthohumol almost completely inhibited CYP1A1 and other hop flavonoids inhibited it by 27–91%. At a concentration of 10 μmol/l xanthohumol completely inhibited CYP1B1 and other hop flavonoids inhibited it by 2–99%. The most effective inhibitors of CYP1A2 were the two prenylated flavonoids, 8-prenylnaringenin and isoxanthohumol, which produced over 90% inhibition in concentrations of 10 μmol/l. However, the flavonoids were poor inhibitors of CYP2E1 and CYP3A4 and so in vivo drug interactions are unlikely to be of importance.

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Cannabinoids

General Information

Cannabis is the abbreviated name for the hemp plant *Cannabis sativa*. The common names for cannabis include marijuana, grass, and weed. Other names for cannabis refer to particular strains; they include bhang and ganja. The most potent forms of cannabis come from the flowering tops of the plants or from the dried resinous exudate of the leaves, and are referred to as hashish or hash.

Cannabis is one of the oldest and most widely used drugs in the world. In different Western countries the possible therapeutic use of cannabinoids as antiemetics in patients with cancer or in patients with multiple sclerosis has become an issue, because of the prohibition of cannabis, and has polarized opinion about the seriousness of its adverse effects (1,2).

Pharmacology

The primary active component of cannabis is Δ9-tetrahydrocannabinol (THC), which is responsible for the greater part of the pharmacological effects of the cannabis complex. Δ8-THC is also active. However, the cannabis plant contains more than 400 chemicals, of which some 60 are chemically related to Δ9-THC, and it is evident that the exact proportions in which these are present can vary considerably, depending on the way in which the material has been harvested and prepared. In man, Δ9-THC is rapidly converted to 11-hydroxy-Δ9-THC (3), a metabolite that is active in the central nervous system. A specific receptor for the cannabinols has been identified; it is a member of the G-protein-linked family of receptors (4). The cannabinoid receptor is linked to the inhibitory G-protein, which is linked to adenyl cyclase in an inhibitory fashion (5). The cannabinoid receptor is found in highest concentrations in the basal ganglia, the hippocampus, and the cerebellum, with lower concentrations in the cerebral cortex.

When cannabis is smoked, usually in a cigarette with tobacco, the euphoric and relaxant effects occur within minutes, reach a maximum in about 30 minutes, and last up to 4 hours. Some of the motor and cognitive effects can persist for 5–12 hours. Cannabis can also be taken orally, in foods such as cakes (for example "space cake") or sweetmeats (for example hashish fudge) (6).

Many variables affect the psychoactive properties of cannabis, including the potency of the cannabis used, the route of administration, the smoking technique, the dose, the setting, the user's past experience, the user's expectations, and the user's biological vulnerability to the effects of the drug.

Animal and in vitro toxicology

Δ9-tetrahydrocannabinol, the active component in herbal cannabis, is very safe. Laboratory animals (rats, mice, dogs, monkeys) can tolerate doses of up to 1000 mg/kg, equivalent to some 5000 times the human intoxicant dose. Despite the widespread illicit use of cannabis, there are very few, if any, instances of deaths from overdose (7).

Long-term toxicology studies with THC were carried out by the National Institute of Mental Health in the late 1960s (8). These included a 90-day study with a 30-day recovery period in both rats and monkeys and involved not only Δ9-THC but also Δ8-THC and a crude extract of marijuana. Doses of cannabis or cannabinoids in the range 50–500 mg/kg caused reduced food intake and lower body weight. All three substances initially depressed behavior, but later the animals became more active and were irritable or aggressive. At the end of the study the weights of the ovaries, uterus, prostate, and spleen were reduced and the weight of the adrenal glands was increased. The behavioral and organ changes were similar in monkeys, but less severe than those seen in rats. Further studies were carried out to assess the damage that might be done to the developing fetus by exposure to cannabis or cannabinoids during pregnancy. Treatment of pregnant rabbits with THC at doses up to 5 mg/kg had no effect on birth weight and did not cause any abnormalities in the offspring (8).

A similarly detailed toxicology study was carried out with THC by the National Institute of Environmental Health Sciences in the USA, in response to a request from the National Cancer Institute (9). Rats and mice were given THC up to 500 mg/kg five times a week for 13 weeks; some were followed for a period of recovery over 9 weeks. By the end of the study more than half of the rats treated with the highest dose (500 mg/kg) had died, but all of the remaining animals appeared to be healthy, although in both species the higher doses caused lethargy and increased aggressiveness. The THC-treated animals ate less food and their body weights were consequently significantly lower than those of untreated controls at the end of the treatment period, but returned to normal during recovery. During this period the animals were sensitive to touch and some had convulsions. There was a trend towards reduced uterine and testicular weights.

In further studies rats were treated with doses of THC up to 50 mg/kg and mice with up to 500 mg/kg 5 times a week for 2 years in a standard carcinogenicity test (9). After 2 years, more treated animals had survived than controls, probably because the treated animals ate less and had lower body weights. The treated animals also had a significantly lower incidence of the various cancers normally seen in aged rodents in testes, pancreas, pituitary gland, mammary glands, liver, and uterus. Although there was an increased incidence of precancerous changes in the thyroid gland in both species and in the mouse ovary after one dose (125 mg/kg), these changes were not dose-related. The conclusion was that there was "no evidence of carcinogenic activity of THC at doses up to 50 mg/kg." This was also supported by the failure to detect any genetic toxicity in other tests designed to identify drugs capable of causing chromosomal damage. For example, THC was negative in the so-called "Ames test,"

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in which bacteria are exposed to very high concentrations of a drug to see whether it causes mutations. In another test, hamster ovary cells were exposed to high concentrations of the drug in tissue culture; there were no effects on cell division that might suggest chromosomal damage.

By any standards, THC must be considered to be very safe, both acutely and during long-term exposure. This probably partly reflects the fact that cannabinoid receptors are virtually absent from those regions at the base of the brain that are responsible for such vital functions as breathing and blood pressure control. The available animal data are more than adequate to justify its approval as a human medicine, and indeed it has been approved by the FDA for certain limited therapeutic indications (generic name = dronabinol) (7).

Respiratory

There have been several attempts to address this question by exposing laboratory animals to cannabis smoke. After such exposure on a daily basis for periods of up to 30 months, extensive damage has been observed in the lungs of rats (10), dogs (11), and monkeys (12), but it is very difficult to extrapolate these findings to man, as it is difficult or impossible to imitate human exposure to cannabis smoke in any animal model.

Nervous system

Animal studies on neurotoxicity have yielded conflicting results. Treatment of rats with high doses of THC given orally for 3 months (13) or subcutaneously for 8 months (14) produced neural damage in the hippocampal CA3 zone, with shrunken neurons, reduced synaptic density, and loss of cells. But in perhaps the most severe test of all, rats and mice treated on 5 days each week for 2 years had no histopathological changes in the brain, even after 50 mg/kg/day (rats) or 250 mg/kg/day (mice) (9). Although claims were made that exposure of a small number of rhesus monkeys to cannabis smoke led to ultrastructural changes in the septum and hippocampus (15,16), subsequent larger-scale studies failed to show any cannabis-induced histopathology in monkey brain (17).

Studies of the effects of cannabinoids on neurons in vitro have also yielded inconsistent results. Exposure of rat cortical neurons to THC shortened their survival: twice as many cells were dead after exposure to THC 5 μmol/l for 2 hours than in control cultures (18). Concentrations of THC as low as 0.1 μmol/l had a significant effect. The effects of THC were accompanied by release of cytochrome c, activation of caspase-3, and DNA fragmentation, suggesting an apoptotic mechanism. All of the effects of THC could be blocked by the antagonist AM-251 or by pertussis toxin, suggesting that they were mediated through CB1 receptors. Toxic effects of THC have also been reported in hippocampal neurons in culture, with 50% cell death after exposure to THC 10 μmol/l for 2 hours or 1 μmol/l for 5 days (19). The antagonist rimonabant blocked these effects, but pertussis toxin did not. The authors proposed a toxic mechanism involving arachidonic acid release and the formation of free radicals. On the other hand, other authors have failed to observe any damage in rat cortical neurons exposed for up to 15 days to THC 1 mmol/l, although they found that this concentration killed rat C6 glioma cells, human astrocytoma U373MG cells, and mouse neuroblastoma N18TG12 cells (20). In a remarkable study, injection of THC into solid tumors of C6 glioma in rodent brain led to increased survival times, and there was complete eradication of the tumors in 20–35% of the treated animals (21). A stable analogue of anandamide also produced a drastic reduction in the tumor volume of a rat thyroid epithelial cell line transformed by K-ras oncogene, implanted in nude mice (22). The antiproliferative effect of cannabinoids has suggested a potential use for such drugs in cancer treatment (23).

Some authors have reported neuroprotective actions of cannabinoids. WIN55,212-2 reduced cerebral damage in rat hippocampus or cerebral cortex after global ischemia or focal ischemia in vivo (24). The endocannabinoid 2AG protected against damage elicited by closed head injury in mouse brain, and the protective effects were blocked by rimonabant (25). THC had a similar effect in vivo in protecting against damage elicited by ouabain (26). Rat hippocampal neurons in tissue culture were protected against glutamate-mediated damage by low concentrations of WIN55,212-2 or CP-55940, and these effects were mediated through CB1 receptors (27). But not all of these effects seem to require mediation by cannabinoid receptors. The protective effects of WIN55,212-2 did not require either CB1 or CB2 cannabinoid receptors in cortical neurons exposed to hypoxia (24), and there were similar findings for the protective actions of anandamide and 2-AG in cortical neuronal cultures (28). Both THC and cannabidiol, which is not active at cannabinoid receptors, protected rat cortical neurons against glutamate toxicity (29) and these effects were also independent of CB1 receptors. The authors suggested that the protective effects of THC might be due to the antioxidant properties of these polyphenolic molecules, which have redox potentials higher than those of known antioxidants (for example ascorbic acid).

Pregnancy

In animals, THC can cause spontaneous abortion, low birth weight, and physical deformities (30). However, these were only seen after treatment with extremely high doses of THC (50–150 times higher than human doses), and only in rodents and not in monkeys.

Tolerance and dependence

Many animal studies have shown that tolerance develops to most of the behavioral and physiological effects of THC (31). Dependence on cannabinoids in animals is clearly observable, because of the availability of CB_1 receptor antagonists, which can be used to precipitate withdrawal. Thus, a behavioral withdrawal syndrome was precipitated by rimonabant in rats treated for only 4 days with THC in doses as low as 0.5–4.0 mg/kg/day (32). The syndrome included scratching, face rubbing, licking, wet dog shakes, arched back, and ptosis, many of the signs that are seen in rats undergoing opiate withdrawal. Similar withdrawal signs occurred when rats treated chronically with the synthetic cannabinoid CP-55940 were given rimonabant (33). Rimonabant-induced withdrawal after 2 weeks of treatment of rats with the cannabinoid HU-120 was accompanied by a marked increase in release of the stress-related neuropeptide corticotropin-releasing factor in the

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amygdala, a result that also occurred in animals undergoing heroin withdrawal (34). An electrophysiological study showed that precipitated withdrawal was also associated with reduced firing of dopamine neurons in the ventral tegmental area of rat brain (35).

These data clearly show that chronic administration of cannabinoids leads to adaptive changes in the brain, some of which are similar to those seen with other drugs of dependence. The ability of THC to cause selective release of dopamine from the nucleus accumbens (36) also suggests some similarity between THC and other drugs in this category.

Furthermore, although many earlier attempts to obtain reliable self-administration behavior with THC were unsuccessful (31), some success has been obtained recently. Squirrel monkeys were trained to self-administer low doses of THC (2 μg/kg per injection), but only after the animals had first been trained to self-administer cocaine (37). THC is difficult to administer intravenously, but these authors succeeded, perhaps in part because they used doses comparable to those to which human cannabis users are exposed, and because the potent synthetic cannabinoids are far more water-soluble than THC, which makes intravenous administration easier. Mice could be trained to self-administer intravenous WIN55212-2, but CB_1 receptor knockout animals could not (38).

Another way of demonstrating the rewarding effects of drugs in animals is the conditioned place preference paradigm, in which an animal learns to approach an environment in which it has previously received a rewarding stimulus. Rats had a positive THC place preference after doses as low as 1 mg/kg (39).

Some studies have suggested that there may be links between the development of dependence to cannabinoids and to opiates (40). Some of the behavioral signs of rimonabant-induced withdrawal in THC-treated rats can be mimicked by the opiate antagonist naloxone (41). Conversely, the withdrawal syndrome precipitated by naloxone in morphine-dependent mice can be partly relieved by THC (42) or endocannabinoids (43). Rats treated chronically with the cannabinoid WIN55212-2 became sensitized to the behavioral effects of heroin (44). Such interactions can also be demonstrated acutely. Synergy between cannabinoids and opiate analgesics has been described above. THC also facilitated the antinociceptive effects of RB 101, an inhibitor of enkephalin inactivation, and acute administration of THC caused increased release of Met-enkephalin into microdialysis probes placed into the rat nucleus accumbens (45).

The availability of receptor knockout animals has also helped to illustrate cannabinoid–opioid interactions. CB_1 receptor knockout mice had greatly reduced morphine self-administration behavior and less severe naloxone-induced withdrawal signs than wild type animals, although the antinociceptive actions of morphine were unaffected in the knockout animals (38). The rimonabant–precipitated withdrawal syndrome in THC-treated mice was significantly attenuated in animals with knockout of the pro-enkephalin gene (46). Knockout of the μ opioid (OP_3) receptor also reduced rimonabant-induced withdrawal signs in THC-treated mice, and there was an attenuated naloxone withdrawal syndrome in morphine-dependent CB_1 knockout mice (47,48).

These findings clearly point to interactions between the endogenous cannabinoid and opioid systems in the CNS, although the neuronal circuitry involved is unknown. Whether this is relevant to the so-called "gateway" theory is unclear. In the US National Household Survey of Drug Abuse, respondents aged 22 years or over who had started to use cannabis before the age of 21 years were 24 times more likely than non-cannabis users to begin using hard drugs (49). However, in the same survey the proportion of cannabis users who progressed to heroin or cocaine use was very small (2% or less). Mathematical modeling using the Monte Carlo method suggested that the association between cannabis use and hard drug use need not be causal, but could relate to some common predisposing factor, for example "drug-use propensity" (50).

Tumorigenicity

THC does not appear to be carcinogenic, but there is plenty of evidence that the tar derived from cannabis smoke is. Bacteria exposed to cannabis tar develop mutations in the standard Ames test for carcinogenicity (51), and hamster lung cells in tissue culture develop accelerated malignant transformations within 3–6 months of exposure to tobacco or cannabis smoke (52).

General adverse effects

A review has summarized the evidence related to the adverse effects of acute and chronic use of cannabis (53). The effects of acute usage include anxiety, impaired attention, and increased risk of psychotic symptoms. Probable risks of chronic cannabis consumption include bronchitis and subtle impairments of attention and memory.

The adverse effects of cannabis can be considered under two main headings, reflecting psychoactive and autonomic effects, in addition to which there are direct toxic effects. The most frequently reported psychoactive effects include enhanced sensory perception (for example a heightened appreciation of color and sound). Cannabis intoxication commonly heightens the user's sensitivity to other external stimuli as well, but subjectively slows the appreciation of time. In high doses, users may also experience depersonalization and derealization. Various forms of psychomotor performance, including driving, are significantly impaired for 8–12 hours after using cannabis. The most serious possible consequence of cannabis use is a road accident if a user drives while intoxicated.

Adverse reactions have been reported at relatively low doses and principally affect the psyche, leading to anxiety states, panic reactions, restlessness, hallucinations, fear, confusion, and rarely toxic psychosis. These effects appear to be reversible (54). Ingestion of cake with cannabis by people who seldom use or have never used cannabis before can result in mental changes, including confusion, anxiety, loss of logical thinking, fits of laughter, hallucinations, hypertension, and/or paranoid psychosis, which can last as long as 8 hours.

The autonomic effects of cannabis lead to tachycardia, peripheral vasodilatation, conjunctival congestion, hyperthermia, bronchodilatation, dry mouth, nystagmus, tremor, ataxia, hypotension, nausea, and vomiting, that is a spectrum of effects that closely resembles the consequences

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of overdosage with anticholinergic agents. Some individuals have sleep disturbances. Increased appetite and dry mouth are other common effects of cannabis intoxication.

Hypersensitivity reactions are rare, but a few have been reported after inhalation. Delayed hypersensitivity reactions, particularly affecting vascular tissue, have been recorded with chronic systemic administration. Tumor-inducing effects are difficult to attribute to cannabis alone. Animal studies have shown neoplastic pulmonary lesions superimposed on chronic inflammation, but such pathology may be primarily associated with the "tar" produced by burning marijuana. The most serious potential adverse effects of cannabis use come from the inhalation of the same carcinogenic hydrocarbons that are present in tobacco, and some data suggest that heavy cannabis users are at risk of chronic respiratory diseases and lung cancer.

The effects of oral cannabinoids (dronabinol or *Cannabis sativa* plant extract) in relieving pain and muscle spasticity have been studied in 16 patients with multiple sclerosis (mean age 46 years, mean duration of disease 15 years) in a double-blind, placebo-controlled, crossover study (55). The initial dose was 2.5 mg bd, increasing to 5 mg bd after 2 weeks if the dose was well tolerated. The plant extract was more likely to cause adverse events; five patients had increased spasticity and one rated an adverse event of acute psychosis as severe. All physical measures were in the reference ranges. There were no significant differences in any measure of efficacy score that would indicate a therapeutic benefit of cannabinoids. This study is the largest and longest of its kind, but the authors acknowledged some possible shortcomings. The route of administration could affect subjective ratings, since the gastrointestinal tract is a much slower and more inefficient route than the lungs. Another possibility is that the dose was too small to have the desired therapeutic effects.

Organs and Systems

Cardiovascular

Marijuana has several effects on the cardiovascular system, and can increase resting heart rate and supine blood pressure and cause postural hypotension. It is associated with an increase in myocardial oxygen demand and a decrease in oxygen supply. Peripheral vasodilatation, with increased blood flow, orthostatic hypotension, and tachycardia, can occur with normal recreational doses of cannabis. High doses of THC taken intravenously have often been associated with ventricular extra beats, a shortened PR interval, and reduced T wave amplitude, to which tolerance readily develops and which are reversible on withdrawal. While the other cardiovascular effects tend to decrease in chronic smokers, the degree of tachycardia continues to be exaggerated with exercise, as shown by bicycle ergometry.

Marijuana use is most popular among young adults (18–25 years old). However, with a generation of post-1960s smokers growing older, the use of marijuana in the age group that is prone to coronary artery disease has increased. The cardiovascular effects may present a risk to those with cardiovascular disorders, but in adults with normal cardiovascular function there is no evidence of permanent damage associated with marijuana (54,56,57), and it is not known whether marijuana can precipitate myocardial infarction, although mixed use of tobacco and cannabis make the evaluation of the effects of cannabis very difficult.

Ischemic heart disease

Investigators in the Determinants of Myocardial Infarction Onset Study recently reported that smoking marijuana is a rare trigger of acute myocardial infarction (58). Interviews of 3882 patients (1258 women) were conducted on an average of 4 days after infarction. Reported use of marijuana in the hour preceding the first symptoms of myocardial infarction was compared with use in matched controls. Among the patients, 124 reported smoking marijuana in the previous year, 37 within 24 hours, and 9 within 1 hour of cardiac symptoms. The risk of myocardial infarction was increased 4.8 times over baseline in the 60 minutes after marijuana use and then fell rapidly. The authors emphasized that in a majority of cases, the mechanism that triggered the onset of myocardial infarction involved a ruptured atherosclerotic plaque secondary to hemodynamic stress. It was not clear whether marijuana has direct or indirect hemodynamic effects sufficient to cause plaque rupture.

Cardiac dysrhythmias

Paroxysmal atrial fibrillation has been reported in two cases after marijuana use (59).

- A healthy 32-year-old doctor, who smoked marijuana 1–2 times a month, had paroxysmal tachycardia for several months. An electrocardiogram was normal and a Holter recording showed sinus rhythm with isolated supraventricular extra beats. He was treated with propranolol. He later secretly smoked marijuana while undergoing another Holter recording, which showed numerous episodes of paroxysmal atrial tachycardia and atrial fibrillation lasting up to 2 minutes. He abstained from marijuana for 12 months and maintained stable sinus rhythm.
- A 24-year-old woman briefly lost consciousness and had nausea and vomiting several minutes after smoking marijuana. She had hyporeflexia, atrial fibrillation (maximum 140/minute with a pulse deficit), and a blood pressure of 130/80 mmHg. Echocardiography was unremarkable. Within 12 hours, after metoprolol, propafenone, and intravenous hydration with electrolytes, sinus rhythm was restored.

The authors discussed the possibility that Δ9-THC, the active ingredient of marijuana, can cause intra-atrial re-entry by several mechanisms and thereby precipitate atrial fibrillation.

Sustained atrial fibrillation has also been attributed to marijuana (60).

- A 14-year-old African-American man with no cardiac history had palpitation and dizziness, resulting in a fall, within 1 hour of smoking marijuana. After vomiting several times he had a new sensation of skipped heartbeats. The only remarkable finding was a flow murmur. The electrocardiogram showed atrial fibrillation. Echocardiography was normal. Serum and urine

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toxicology showed cannabis. He was given digoxin, and about 12 hours later his cardiac rhythm converted to sinus rhythm. Digoxin was withdrawn. He abstained from marijuana over the next year and was symptom free.

The authors noted that marijuana's catecholaminergic properties can affect autonomic control, vasomotor reflexes, and conduction-enhancement of perinodal fibers in cardiac muscle, and thus lead to an event such as this.

Arteritis

A case of progressive arteritis associated with cannabis use has been reported (61).

- A 38-year-old Afro-Caribbean man was admitted after 3 months of severe constant ischemic pain and numbness affecting the right foot. The pain was worse at night. He also had intermittent claudication after walking 100 yards. He had a chronic history of smoking cannabis about 1 ounce/day, mixed with tobacco in the early years of usage. However, at the time of admission, he had not used tobacco in any form for over 10 years. He had patchy necrosis and ulceration of the toes and impalpable pulses in the right foot. The serum cotinine concentrations were consistent with those found in non-smokers of tobacco. Angiography of his leg was highly suggestive of Buerger's disease (thromboangiitis obliterans).

Remarkably, this patient, despite having abstained from tobacco for more than 10 years, developed a progressive arteritis leading to ischemic changes. While arterial pathology with cannabis has been reported before, it has been difficult to dissociate the effects of other drugs.

Respiratory

Acute inhalation of marijuana or THC causes bronchodilatation, but with chronic use resistance in the bronchioles increases (62,63). Prolonged use of cannabis by inhalation can cause chronic inflammatory changes in the bronchial tree, in part related to the inhalants that accompany the smoke. In some cases attacks of asthma and glottal and uvular angioedema can occur. Reduced respiratory gas exchange has been reported in long-term smokers, and under experimental conditions THC can depress respiratory function slightly and act as a respiratory irritant. In fact, chronic marijuana cigarette smoking and chronic tobacco cigarette smoking produce very similar changes, but these occur after smoking fewer cigarettes when marijuana is smoked, compared with tobacco-smoking. With marijuana inhalation, when a filter is never used, inhalation is deeper and the smoke is held in the lungs for longer than when smoking commercially produced tobacco-based cigarettes (64). There is therefore a greater build-up of carbon monoxide, reduction in carboxyhemoglobin saturation, and alveolar cellular irritation with depression of macrophages (SEDA-13, 25). Pneumothorax, pneumopericardium, and pneumomediastinum have been reported when positive pulmonary pressure is applied or a Valsalva maneuver used, as often happens (65,66).

A possible role of marijuana use in the formation of large lung bullae has been discussed (67). Four men, who smoked both tobacco and marijuana, developed large, multiple, bilateral, peripheral bullae at their lung apices, with normal parenchymal tissue elsewhere. Three patients with large bullae in the upper lung lobe have been reported (68). All had been heavy marijuana smokers over 10–24 years. However, they all had at least nine pack-years of cigarette exposure and so marijuana may not have been the only cause of their lung bullae. Nevertheless, the authors recommended that all those who present with upper lung bullae should be screened for cannabis use.

While Δ9-THC may not contribute directly to lung bullae, it is possible that the respiratory dynamics of smoking the drug explains it. Typically, a draw on a marijuana joint has, on average, a depth of inspiration that is one-third greater, a volume two-thirds greater, and a breath-holding time four times longer than a draw on a cigarette. The marijuana joint lacks a filter tip, and the practice of smoking "leads to a fourfold greater delivery of tar and a five times greater increase in carboxyhemoglobin per cigarette smoked" (62). Smoking three to four joints of marijuana per day is reported to produce a symptom profile and damage to the respiratory airways similar to that caused by smoking 20 tobacco cigarettes daily.

Nervous system

Marijuana can interact with the neurotransmitter dopamine, and the effects of marijuana on the brain in schizophrenia have been studied by single photon emission computerized tomography (SPECT) (69).

A 38-year-old man with schizophrenia secretively smoked marijuana during a neuroimaging study. A comparison of two sets of images, before and after marijuana inhalation, showed a 20% reduction in the striatal dopamine D_2 receptor binding ratio, suggestive of increased synaptic dopaminergic activity.

On the basis of this in vivo SPECT study, the authors speculated that marijuana may interact with dopaminergic systems in brain reward pathways.

Sensory systems

Eyes

No consistent effects of cannabinoids on the eyes have been reported, apart from a reduction in intraocular pressure (70). The initial reduction in intraocular pressure is followed by a rebound increase associated with increased prostaglandin concentrations.

Ears

The effect of THC, 7.5 mg and 15 mg, on auditory functioning has been investigated in eight men in a double-blind, randomized, placebo-controlled, crossover trial (71). Blood concentrations of THC were measured for up to 48 hours after ingestion, and audiometric tests were carried out at 2 hours. There were no significant differences across treatments, suggesting that cannabis does not affect the basic unit of auditory perception.

Psychological, psychiatric

The psychological effects of cannabis vary with personal and social factors. However, some guidance to the essential

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effects of the drug can be derived from investigations with THC and marijuana in non-user volunteers. Blood concentrations of THC over 75 μg/ml under these conditions are associated with euphoria, and somewhat higher concentrations with dissociation of events and memory and impairment of psychomotor tasks lasting over 24 hours (54).

Through random urine testing of draftees to the Italian army, 133 marijuana users were identified, tested, and interviewed (72). Among these marijuana users, 83% of those with cannabis dependence, 46% with cannabis abuse, and 29% of occasional users had at least one DSM-IIIR psychiatric diagnosis. With greater cannabis use, the risk of associated psychiatric disabilities tended to increase progressively.

Occasional and regular users can suffer panic attacks, paranoia, hallucinations, or feelings of unreality (depersonalization and derealization).

Psychosis

The causal relation between cannabis abuse and schizophrenia is controversial. Cannabis abuse, and particularly heavy abuse, can exacerbate symptoms of schizophrenia and can be considered as a risk factor eliciting relapse in schizophrenia (74). Chronic cannabis use can precipitate schizophrenia in vulnerable individuals (75).

Four cases in which psychosis developed after relatively small amounts of marijuana were smoked for the first time have been reported (76). All required hospitalization and neuroleptic drug treatment. Each had a mother with manic disorder and two had psychotic features. The authors noted that marijuana is a dopamine receptor agonist, and mania may be associated with excessive dopaminergic neurotransmission. The use of marijuana may precipitate psychosis or mania in subjects who are genetically vulnerable to major mental illness.

Marijuana abuse and its possible associated risks in reinforcing further use, causing dependence, and producing withdrawal symptoms among adolescents with conduct symptoms and substance use disorders has been investigated in 165 men and 64 women selected and then interviewed from a group of 255 consecutive admissions to a university-based adolescent substance abuse treatment program (77). All had DSM-IIIR substance dependence, 82% had conduct disorder, 18% had major depression, and 15% had attention-deficit/hyperactivity disorder. Most (79%) met the criteria for cannabis dependence. Two-thirds of the cannabis-dependent individuals admitted serious drug-related problems and reported associated drug withdrawal symptoms according to the Comprehensive Addiction Severity Index in adolescents (CASI). For the majority, progression from first to regular cannabis use was as rapid as tobacco progression and more rapid than that of alcohol.

Cognitive effects

Long-term heavy use of cannabis impairs mental performance, causes defects in memory (especially short-term memory), and leads to impairment of memory, attention, and organization and integration of complex information (78). Adolescents with pre-existing disabilities in learning and cognition have experienced serious aggravation of their problem from regular use of cannabis (79).

The effects of chronic marijuana smoking on human brain function and cognition have been further investigated (62). Normalized regional brain blood flow and regional brain metabolism, measured using PET scanning with ^{15}O, were compared in 17 frequent marijuana users and 12 non-users. Testing was performed after at least 26 hours of monitored abstinence in all subjects. Marijuana users had hypoactivity or reduced brain blood flow in a large region of the posterior cerebellum compared with controls. This is consistent with what was reported in the only previous PET study of chronic marijuana use (80). The cerebellum is hypothesized to have input to aspects of cognition, specifically timing, the processing of sensory information, and attention and prediction of real-time events. Users often report that marijuana smoking is followed by alterations in the sense of time and less efficient cognitive processing.

The safety and possible benefits of long-term marijuana use have been studied in four seriously ill patients in the Missoula Chronic Clinical Cannabis Use Study with a quality-controlled sample of marijuana (73). They were evaluated using an extensive neurocognitive battery.

- A 62-year-old woman with congenital cataracts smoked marijuana illicitly for 12 years (current use 3–4 g/day smoked and 3–4 g/day orally). She had mild-to-moderate difficulty with attention and concentration and minimal-to-mild difficulty with acquisition and storage of very complex new verbal material. Her executive functioning was not affected.
- A 50-year-old man with hereditary osteo-onychodysplasia had smoked marijuana since 1974 to alleviate muscle spasms and pain (current use 7 g/day of 3.75% THC). He had mild-to-moderate impairment of attention and concentration and reduced ability to acquire new verbal material. He scored poorly on the California Verbal Learning Test (CVLT), a measure of short-term memory recall, and had difficulty with motor tasks.
- A 48-year-old man with multiple congenital cartilaginous exostoses had smoked marijuana since the late 1970s (current use 9 g/day of 2.7% THC). His neurocognitive scores suggest mild difficulty in sustaining attention and a minimal-to-mild deficit in the acquisition of new verbal material.
- A 45-year-old woman with multiple sclerosis had smoked cannabis since 1990 to control pain and muscle spasms (current use marijuana cigarettes containing 3.5% THC 10/day). She had impairment of concentration, learning, and memory efficiency. Her ability to acquire new verbal information was also impaired.

The authors attributed these cognitive deficits not to marijuana use but rather to the patients' illnesses, arguing that it is difficult for patients with painful debilitating diseases to concentrate on neurocognitive tasks. Any abnormalities in MRI imaging and electroencephalography were attributed to age-related brain deterioration. There were no significant abnormalities of respiratory function, apart from a "slight downward trend in FEV_1 and FEV_1/FVC ratios, and perhaps an increase in FVC" in three patients, interpretation of these findings being complicated by concomitant tobacco smoking. One patient had mild polycythemia and a raised white cell count. None had abnormal endocrine tests. This was a comprehensive study of the long-term effects of cannabis,

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but concomitant illnesses and use of tobacco made the results difficult to interpret.

Concerns have been raised about the possible adverse effects of acute as well as chronic medicinal and recreational use of cannabis on cognition and the body (81). The author, while acknowledging the therapeutic role of cannabinoids in the management of pain and other conditions, expressed concern that in recent years the prevalence of recreational cannabis use (especially in the young) and the potency of the available products have markedly increased in the UK.

An unusual account of transient amnesia after marijuana use has been reported from Europe (82).

- A 40-year-old healthy man with a long history of cannabis use was hospitalized with an acute memory disturbance after smoking for several hours a strong type of marijuana called "superskunk." After smoking, he had difficulty recollecting recent events and would ask the same questions repeatedly. While his routine laboratory results were within the reference ranges, his urine and blood toxic screens had very high concentrations of cannabinoids (and no other drugs). He was alert and oriented to his name, address, date, and place of birth, but could not recall his marital status, whether he had children, or the nature of his job. He was disoriented in time. He performed normally in tests of general cognitive functioning (for example Raven's matrices, word fluency, Rey's complex figurecopy) and short-term memory (for example digit span, verbal cues), but showed severe impairment in verbal and non-verbal long-term components of anterograde memory tests. He had a severe retrograde memory defect mainly affecting autobiographical memory, with a temporal gradient such that remote facts were preserved. These memory impairments lasted 4 days and then rapidly improved, leaving amnesia for the acute episode. Electroencephalography during the amnestic episode was normal, except for brief trains of irregular slow activity in the frontal areas bilaterally. A SPECT scan of his brain was normal. A week later, repeat neuropsychological examination showed normal memory and a normal electroencephalogram and MRI scan of the brain with enhancement. One year later, he had stopped using marijuana and had no further amnestic episodes.

The authors found similarities between the memory disorder seen here and transient global amnesia, which consists of anterograde amnesia and a variably graded retrograde amnesia. Such amnesia has been previously reported with a number of substances and medications, but not with marijuana. The authors stated that although memory impairment has been reported with marijuana before, it has never involved retrieval of already learned material. They wondered if the memory impairment was due to marijuana-induced changes in cerebral blood flow and ischemia through vasospasm. However, their SPECT data did not support this theory. They considered the possibility that cannabinoid receptors, which are dense in the hippocampus, could have been occupied by marijuana, resulting in such memory loss. They cautioned that the effects of marijuana on memory may be more severe than previously thought.

Endocrine

In animals (particularly monkeys), cannabis depresses ovarian and testicular function. In man, chronic use has been associated with reduced serum FSH and LH concentrations in a few people, often accompanied by reduced serum testosterone, oligospermia, reduced sperm motility, and gynecomastia (83). There is no evidence of impairment of male fertility; no studies have been carried out on female fertility. There is evidence of slightly shortened gestation periods in chronic users (84). There are variable non-specific effects on serum prolactin and growth hormone and a rise in plasma cortisol concentrations has been recorded in one study.

Hematologic

Of the hematological changes very occasionally noted, polycythemia appears to be secondary to reduced pulmonary oxygen exchange (see the Respiratory section in this monograph).

Immunologic

Tetrahydrocannabinol depresses lymphocyte and macrophage activity in cell cultures, while in rats in vivo it directly suppresses natural killer cell activity and impairs T lymphocyte transformation by phytohemagglutinin in concentrations of cannabinoids achievable with the usual doses (85). Variable results have been obtained in man in tests of circulating T cells and hormonal immunity (86).

In animals and man, chronic use often suppresses the immune system's response to inhaled bacterial or fungal material. In this connection it is relevant to note that a contaminant mould (*Aspergillus*) found in cannabis can predispose immunocompromised cannabis smokers to infection. It has been suggested that baking the cannabis (at 300°F for 15 minutes) before smoking will kill the fungus and reduce the potential risk (87).

The effects of marijuana on immune function have been reviewed (88). The studies suggest that marijuana affects immune cell function of T and B lymphocytes, natural killer cells, and macrophages. In addition, cannabis appears to modulate host resistance, especially the secondary immune response to various infectious agents, both viral and bacterial. Lastly, marijuana may also affect the cytokine network, influencing the production and function of acute-phase and immune cytokines and modulating network cells, such as macrophages and T helper cells. Under some conditions, marijuana may be immunomodulatory and promote disease.

A severe allergic reaction after intravenous marijuana has been reported (89).

- A 25-year-old man with intermittent metamfetamine use developed facial edema, pruritus, and dyspnea 45 minutes after injecting a mixture of crushed marijuana leaves and heated water. He was anxious, and had tachypnea, respiratory stridor, wheezing, edema of the face and oral mucosa, and truncal urticaria. There was mild pre-renal uremia and urine toxicology was positive for metamfetamine and marijuana. Skin testing was not done. With appropriate medical intervention there was resolution of symptoms within a day.

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The authors noted that marijuana may have contaminants, including *Aspergillus*, *Salmonella*, herbicides, and mercury, which can trigger allergic reactions.

Long-Term Effects

Drug tolerance

Tolerance develops with heavy chronic use in individuals who report problems in controlling their use and who continue to use cannabis despite adverse personal consequences (53).

Drug withdrawal

Withdrawal symptoms occur after chronic heavy use (53). Abrupt withdrawal of high-level use of cannabinoids causes irritability, restlessness, and insomnia, with a rebound increase in REM sleep, tremor, and anorexia lasting up to a week (90–92). Occasional use does not appear to be associated with major consequences.

Second-Generation Effects

Pregnancy

Behavioral anomalies have been identified in the offspring of monkeys and women exposed to cannabis during pregnancy (93,94). These include reduced visual responses, increased auditory responses, and reduced quietude. Most of the effects resolved within 4–5 weeks postpartum and there were no abnormalities at 1 year.

Teratogenicity

In animals, THC crosses the placenta and is excreted in breast milk. There is conflicting evidence concerning teratogenicity in animals, but no definitive evidence in man. However, there have been many anecdotal reports of abnormalities. Although these were without consistent characteristics, the descriptions would readily fit the fetal alcohol syndrome (95–98) and clinical evaluation of the use of cannabis during pregnancy is complicated by the frequent concomitant use of alcohol and tobacco.

Fetotoxicity

The effect of maternal and prenatal marijuana exposure on offspring from birth to adolescence is being investigated (99). The Ottawa Prenatal Prospective Study (OPPS), a longitudinal project begun in 1978, recently reported its findings in 146 low-risk, middle-class children aged 9–12 years. Their performances on neurobehavioral tasks that focus on visuoperceptual abilities (ranging from basic skills to those requiring integration and cognitive manipulation of such skills) were analysed. Performance outcomes were different in children with prenatal exposure to cigarette smoking and those with prenatal exposure to marijuana. Maternal cigarette smoking affected fundamental visuoperceptual functioning. Prenatal marijuana use had a negative effect on performance in visual problem-solving, which requires integration, analysis, and synthesis. In a second prospective study, the effects of prenatal marijuana exposure and child behavior problems were studied in 763 subjects aged 10 years (100). Prenatal maternal marijuana exposure was associated with increased hyperactivity, impulsivity, and inattention in the children. There was also increased delinquency and externalizing problems. The authors suggested a possible pathway between prenatal marijuana exposure and delinquency, which may be mediated by the effects of marijuana exposure on symptoms of inattention.

Susceptibility Factors

Age

Children

In young children, accidental ingestion leads to the rapid onset of drowsiness, hypotonia, dilated pupils, and coma. Fortunately, gradual recovery occurs spontaneously, barring accidents. Passive inhalation of marijuana in infants can have serious consequences.

- A 9-month-old girl presented with extreme lethargy and a modified Glasgow coma scale of 10, after having been exposed to cigarette and cannabis smoke at the home of her teenage sister's friend (101). The physical examination and laboratory results were unremarkable. Cannabinoids were detected in a urine screen.

While chronic adult users can display apathy and impaired concentration, these effects are possibly in part associated with other factors. No permanent organic brain damage has been demonstrated (101,102).

Other features of the patient

People with pre-existing coronary artery disease may have an increased incidence of attacks of angina (103). In individuals who are vulnerable to schizophrenia, cannabis can precipitate psychoses or aggravate schizophrenia. The control of epilepsy may be impaired. Users undergoing anesthesia may react unexpectedly and may have enhanced nervous system depression. Because of impairment of judgement and psychomotor performance, users should not drive or operate machinery for at least 24 hours after administration.

Drug–Drug Interactions

Alcohol

Additive psychoactive effects sought by users may be achieved by combinations of cannabis and alcohol, but at the same time the ability of THC to induce microsomal enzymes will increase the rate of metabolism of alcohol and so reduce the additive effects (90).

Anticholinergic drugs

The anticholinergic effects of cannabis (90) may result in interactions with other drugs with anticholinergic effects, such as some antidysrhythmic drugs.

Barbiturates, short-acting

Additive psychoactive effects sought by users may be achieved by combinations of cannabis and short-acting

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barbiturates, but at the same time the ability of THC to induce microsomal enzymes will increase the rate of metabolism of barbiturates and so reduce the additive effects (90).

Disulfiram

Concurrent administration with disulfiram is associated with hypomania (104).

Lysergic acid diethylamide

"Flashbacks," or the return of hallucinogenic effects, occur in almost a quarter of those who have used LSD, particularly if they have also used other CNS stimulants, such as alcohol or marijuana. They can experience distortions of perception of objects, space, or time, which intrude without warning into reality, resulting in delusions, panic, and unusual images. A "trailing phenomenon" has also been reported, in which the visual perception of objects is reduced to a series of interrupted pictures rather than a constant view. The frequency of these events may slowly abate over several years, but in a significant number their incidence later increases (105,106).

Psychotropic drugs

Cannabis alters the effects of psychotropic drugs, such as opioids, anticholinergic drugs, and antidepressants, although variably and unpredictably (90).

Sildenafil

Myocardial infarction has been attributed to the combination of cannabis and sildenafil.

- A 41-year-old man developed chest tightness radiating down both arms (107). He had taken sildenafil and cannabis recreationally the night before. His vital signs were normal and he had no signs of heart failure. However, electrocardiography showed an inferior evolving non-Q-wave myocardial infarct and his creatine kinase activity was raised (431 U/l).

Cannabis inhibits CYP3A4, which is primarily responsible for the metabolism of sildenafil, increased concentrations of which may have caused this cardiac event.

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Capparaceae

See also Herbal medicines

General Information

The genera in the family of Capparaceae (Table 1) include caper and stinkweed.

Capparis spinosa

The leaf and fruit of *Capparis spinosa* (caper plant) both contain isothiocyanates, in addition to the flavonoid rutinoside and the quaternary alkaloid stachydrine.

Adverse effects

Allergic contact dermatitis can follow the application of *C. spinosa* in the form of wet compresses (1).

Table 1 The genera of Capparaceae

Atamisquea (atamisquea)
Capparis (caper)
Cleome (spiderflower)
Cleomella (stinkweed)
Forchhammeria (forchhammeria)
Koeberlinia (allthorn)
Morisonia (morisonia)
Oxystylis (oxystylis)
Polanisia (clammyweed)
Wislizenia (wislizenia)

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Capreomycin

See also Antituberculosis drugs

General Information

Capreomycin has been abandoned for the treatment of tuberculosis and replaced by first-choice drugs. In rare cases, it has been administered in infections with non-tuberculous mycobacteria when there is multiple drug resistance to the first-line antituberculosis drugs (1).

Organs and Systems

Electrolyte balance

Marked renal loss of sodium, chloride, potassium, and magnesium with progressive metabolic alkalosis and hyper-reninemia have been reported (2).

Urinary tract

A Bartter-like syndrome has been reported in a 25-year-old man taking prolonged capreomycin for drug-resistant pulmonary tuberculosis (2).

Drug–Drug Interactions

Streptomycin

Capreomycin should never be combined with streptomycin or other aminoglycosides because of nephrotoxicity and ototoxicity (3).

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Captopril

See also Angiotensin converting enzyme inhibitors

General Information

Captopril is a sulfhydryl-containing ACE inhibitor used in the management of hypertension and heart failure, after myocardial infarction, and in diabetic nephropathy.

Organs and Systems

Respiratory

Two cases of alveolitis have been reported with captopril, one associated with eosinophilia (1) and the other with a lymphocytic pulmonary infiltrate (2).

Sensory systems

A report from the Australian Drug Evaluation Committee has confirmed that dysgeusia (taste disturbance and taste loss) is more likely to complicate treatment with captopril than with other ACE inhibitors; captopril accounted for more than half the cases of taste loss (3). Taste loss was dose-related, in that more than 90% of reports detailed a daily dose of 50 mg or more. Most cases recovered on withdrawal, although the sense of taste had not returned 7 months after withdrawal in one case, and in two of the reports there was associated anosmia. Although there was no significant difference between captopril and lisinopril

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(4), it appears that captopril, presumably via its sulfhydryl group, is more likely to provoke dysgeusia.

Hematologic

Anecdotal reports of a bone-marrow suppressant effect of captopril have been published, but not since 1989. Cases of neutropenia and agranulocytosis (5–8) have also been reported, although in some of these there were complicating issues, making a clear association difficult to establish. Usually the incidence is higher in patients with renal insufficiency or collagen vascular disease. In few cases the white cell count returned to normal when captopril was withdrawn. Although agranulocytosis has been attributed to the presence of the sulfhydryl group in captopril, it has also been reported with enalapril (9).

Agranulocytosis has also been reported in association with toxic epidermal necrolysis (10).

- A 59-year-old woman with long-standing hypertension took captopril 200 mg bd plus hydrochlorothiazide 50 mg od and 3 days later developed nausea, vomiting, malaise, and a severe, pruritic, erythematous rash, with severe dehydration and orthostatic hypotension. The diuretic was withdrawn and intravenous fluids and diphenhydramine were given. She recovered within 1 week and remained asymptomatic for 4 weeks. She then developed fever, malaise, a new rash, orthostatic hypotension, and diffuse erythroderma. Her posterior pharynx was erythematous. She had neutropenia (900×10^6/l) and captopril was withdrawn. She was treated empirically with antibiotics and intravenous fluids and subcutaneous granulocyte colony-stimulating factor (G-CSF) for 5 days. The erythroderma progressed to large coalescing blisters, which then ruptured, producing large areas of weeping skin over all her limbs. The bone-marrow and skin recovered fully within 2 weeks.

Autoimmune thrombocytopenia, gradually reversible on withdrawal of captopril, was reported in three patients taking captopril (11).

Pancreas

Two new cases of pancreatitis with captopril have been reported (12,13). It has been suggested that early detection of raised serum amylase and lipase activities can prevent the development of full-blown pancreatitis (13).

Urinary tract

Acute renal insufficiency with tubular necrosis has been described (14). It occurred within 24 hours of the first dose of captopril and required hemodialysis for 8 weeks. The diagnosis of ischemic tubular necrosis was confirmed by renal biopsy. Few previous cases of ACE inhibitor-induced nephropathy have been documented by renal biopsy.

Immunologic

Lupus–like syndrome has been reported with captopril (15). The authors believed their patient to be the fifth such published case.

- A 54-year-old Caucasian man presented with a 4-week history of chills, fever, malaise, and generalized arthralgia. Following an aortic valve replacement, he had taken aspirin, coumadin, and captopril 25 mg tds for 1 year. He was febrile (temperature 39.4°C), normotensive, with diffuse livedo reticularis, and the physical signs of aortic valve disease. Infective endocarditis was ruled out by appropriate investigations. He had a raised erythrocyte sedimentation rate (142 mm/hour) and a positive antinuclear antibody test (FANA 1:2560) with a negative antinative DNA test. Captopril was withdrawn and he was given prednisone for 5 days. His symptoms resolved rapidly and the livedo reticularis cleared within 2 days. The FANA and ESR returned to normal and remained so at follow-up 6 months later.

During early drug development, the occurrence of antinuclear antibodies in 10 of 37 patients taking high doses of captopril was described (16).

Drug–Drug Interactions

General anesthesia

The hazards of general anesthesia in the presence of ACE inhibitors have been recognized and reviewed (17). It has generally been accepted that ACE inhibitors should be continued up to the time of surgery. Patients should be monitored aggressively and hemodynamic instability treated appropriately.

- An 86-year-old man, who was taking captopril 25 mg bd and bendroflumethiazide 25 mg/day for hypertension, had a transurethral resection of the prostate under spinal anesthesia, and developed profound bradycardia and hypotension with disturbances of consciousness during transfer to the recovery room (18). Initial treatment with atropine produced rapid improvement in cardiovascular and cerebral function. A further hypotensive episode, without bradycardia, occurred about 1 hour later, but responded rapidly to methoxamine. He made a full recovery overnight.

The authors suggested that the concomitant administration of captopril may have contributed to the adverse effect, since the renin–angiotensin system is important in maintaining blood pressure during anesthesia. Because of a protective effect of angiotensin II in the presence of sympathetic blockade by presynaptic stimulation of adrenergic neurons, the authors hypothesized that hypotension and bradycardia in this patient may have been magnified by suppression of the renin–angiotensin system, resulting in an enhanced negative Bainbridge effect.

Iron and other transition metals

Captopril has been reported to react with iron and other transition metals. This interaction has been investigated in vivo in seven healthy adults (19). Co-administration of ferrous sulfate and captopril resulted in a 37% decrease in the AUC of unconjugated captopril, with no significant changes in C_{max} or t_{max}. The plasma AUC of total captopril was not altered. The authors suggested that the interaction may be specific to captopril among ACE inhibitors, because it contains a sulfhydryl group. Therefore, if iron salts were to be taken by a patient requiring an ACE inhibitor, an agent other than captopril might be considered.

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Interference with Diagnostic Tests

Legal reaction

Like other sulfhydryl-containing compounds, captopril can cause false-positive ketonuria when assessed with the Legal reaction (sodium nitroprusside reacting with acetoacetic acid and possibly with acetone). It has therefore been suggested that in patients with diabetes taking such drugs ketonuria should be assessed with the Acetest (20). Alternatively, a blood ketone test with Acetest and/or enzymatic detection of beta-hydroxybutyric acid can be performed for confirmation.

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Carbachol

General Information

Carbachol is a quaternary ammonium compound that shares both the muscarinic and nicotinic actions of acetylcholine but is much more slowly deactivated. Carbachol has been used topically in ophthalmology and systemically (subcutaneously, for example in doses of 2 mg/day) for urinary retention. Severe cholinergic effects can result. In one instance they primarily involved the gastrointestinal tract and the patient died of esophageal rupture (1). In other cases patients have experienced extreme bradycardia with hypotension, requiring treatment with intravenous atropine. As carbachol is not destroyed by cholinesterase, a cumulative effect is possible in patients who receive regular doses at short intervals; in one case, hypotension only developed on the third treatment day (2).

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Carbamazepine

See also Antiepileptic drugs

General Information

Carbamazepine is usually regarded as the drug of choice for partial seizures (with or without secondary generalization) and it can also be valuable in preventing primary generalized tonic-clonic seizures.

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General adverse reactions

Cerebellovestibular and oculomotor dysfunction (with dizziness, diplopia, nystagmus, ataxia), fatigue, and sedation (usually transient) are relatively common. Nausea, vomiting, cognitive dysfunction, headache, myoclonus (including non-epileptic myoclonus), exacerbation of seizures, movement disorders, behavioral or psychiatric disturbances, hyponatremia, and altered cardiac conduction are less common.

Hypersusceptibility reactions

Hypersusceptibility reactions to carbamazepine are relatively common and range from cutaneous reactions (including Stevens–Johnson syndrome and toxic epidermal necrolysis, severe forms of erythema multiforme) to systemic reactions with fever, lymphadenopathy, and/or involvement of the bone marrow, the liver, the heart, the gastrointestinal system, the lungs, and other organs.

In ten children with chorea (eight girls and two boys; aged 7–16 years), nine with rheumatic fever, carbamazepine (4–10 mg/kg/day; plasma concentrations 12–34 μmol/l) produced improvement within 2–14 days (1). The chorea disappeared within 2–12 weeks. There were no adverse effects.

Organs and Systems

Cardiovascular

Carbamazepine can depress the cardiac conducting system (SEDA-16, 71). There have been a few reports of reversible atrioventricular block (SED-12, 130) (2–4), and asystole has been described in a patient with Guillain–Barré syndrome (SEDA-18, 62).

In one patient carbamazepine caused pacemaker failure until the pacemaker was adjusted, no doubt because of its effects on cardiac conduction (SEDA-18, 62).

Three cases of carbamazepine-induced Stokes–Adams attacks caused by intermittent total atrioventricular block, sinoatrial block with functional escape rhythm, and intermittent asystole have been described; it was suggested that cardiac conduction should be assessed if syncope or changes in seizure type occur in patients taking carbamazepine (5).

Bradydysrhythmias of different types and severity have also been reported, especially in the elderly, but they do not seem to be common.

There has been a report of carbamazepine-induced hypertension (6).

- A 33-year-old man with complex partial seizures was switched from phenytoin to carbamazepine. His blood pressure was 118/70, but 4 months later, while he was taking carbamazepine 600 mg bd, his blood pressure was 150/112 and 1 month later 142/110. He was taking no medications beside carbamazepine. Secondary causes of hypertension were ruled out. Carbamazepine was withdrawn and gabapentin prescribed. One month later his blood pressure was normal, and it remained so at subsequent follow-up appointments over the next 2 years.

A case of congestive heart failure possibly caused by carbamazepine has been described (SED-12, 130) (7), but there have been no subsequent reports.

Potentially fatal eosinophilic myocarditis may be a manifestation of carbamazepine hypersensitivity (SEDA-22, 86).

Four additional cases of carbamazepine-induced sinus node dysfunction ($n = 3$) and atrioventricular block ($n = 1$) were described in elderly Japanese women taking 200–600 mg/day. In two of the three patients rechallenged, sinus arrest recurred within 48 hours (8).

In 12 patients in whom carbamazepine was withdrawn, power-spectrum analysis of RR interval variability was used to investigate changes in sympathetic/parasympathetic autonomic equilibrium (9). Abrupt withdrawal of carbamazepine altered the sympathovagal balance during non-REM sleep, shifting the sympathovagal balance toward sympathetic predominance. However, analysis of the before and after withdrawal cardiac Holter recordings showed no serious cardiac dysrhythmias in any patient.

Respiratory

Acute hypersensitivity reactions involving the lung or the bronchi have been reported, but are rare (SEDA-16, 71) (SEDA-18, 62).

Nervous system

Most central nervous system adverse effects are mild, transient, and reversible on dosage adjustment. Those reported more commonly (in 10–50% of patients, depending on dosage and assessment method) include somnolence, which is usually transient, diplopia, nystagmus, dizziness, fatigue, headache, ataxia, and cognitive dysfunction. These effects may be intermittent and related to high peak concentrations of the drug. Dividing the total daily dose or switching to a modified-release formulation can minimize these effects (SEDA-19, 64). Patients with MRI evidence of cerebellar atrophy may be more prone to nystagmus, dizziness, and ataxia when they take carbamazepine (SEDA-21, 69).

Carbamazepine can precipitate or aggravate myoclonic, atonic, and absence seizures, especially in children and adolescents with a history of bilaterally synchronous spike-and-wave discharges in the electroencephalogram; both generalized and partial seizures can be worsened (10). In children, the new appearance of generalized paroxysmal discharges after treatment may be predictive of seizure exacerbation or suboptimal control (11). Tonic seizures are occasionally aggravated by carbamazepine (SEDA-22, 85). Non-epileptic myoclonus occurs rarely.

A mild reduction in motor and sensory conduction velocities, possibly related to folate deficiency, has been found in patients taking long-term treatment (SED-13, 146) (12), but symptoms of peripheral neuropathy are uncommon.

Asterixis, dystonias, and dyskinesias (including motor tics, orofacial and lingual dyskinesias, and oculogyric crises) are uncommon, as are auditory disturbances (SED-13, 146) (13–15), (SEDA-20, 60) (SEDA-21, 69).

Neuroleptic malignant syndrome occurred in a middle-aged man who had previously experienced the same

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reaction to tiotixene (SEDA-17, 72). A 54-year-old man who had been taking neuroleptic drugs for about 30 years developed neuroleptic malignant syndrome within 3 days of taking add-on carbamazepine (400 mg/day) (16). It was speculated that the pathogenesis could have involved rebound cholinergic activity after a reduction in plasma neuroleptic drug concentrations by carbamazepine.

Aseptic meningitis reversible on drug withdrawal has been described at least three times (17).

Retrospective studies have suggested that antiepileptic drugs can be associated with peripheral nerve dysfunction. This has been prospectively studied in 81 patients (aged 13–67 years) without polyneuropathy who took sodium valproate ($n = 44$) or carbamazepine ($n = 37$) as monotherapy in standard daily doses (18). After 2 years one patient had clinical signs of polyneuropathy and six had symptoms of polyneuropathy, but electrophysiology did not show significant changes or trends. Only one patient had abnormal electrophysiological findings, which were only subclinical, and eight patients had abnormal values at two subsequent visits. There were no consistent patterns, and the data were unaffected when the drugs were examined separately or when patients were grouped according to whether or not they had symptoms of polyneuropathy. The authors concluded that previously untreated young to middle-aged patients who take valproic acid or carbamazepine for 2 years are not at risk of polyneuropathy.

Combined phonic and motor tics occurred in a 7-year-old boy with Down's syndrome when he took carbamazepine 19 mg/kg for suspected focal epilepsy (19). Carbamazepine concentrations were within the usual target range. The symptoms resolved completely after withdrawal.

Carbamazepine can cause altered visual evoked potentials and brainstem evoked potentials (20). In 100 epileptic patients aged 8–18 years taking carbamazepine in a modified-release formulation, interpeak latencies of I-III and III-V of brainstem evoked potentials were significantly delayed and N75/P100 and P100/N145 amplitudes in the visual evoked potentials were reduced.

Relatively low doses of carbamazepine (300–600 mg/day) have been reported to cause serious worsening of disability in five patients with multiple sclerosis (21). The authors suggested that this effect was due to blockade of sodium channels by carbamazepine.

Sensory systems

There was abnormal color perception in 28% of 18 patients taking carbamazepine monotherapy; in one case there was an abnormality in the blue-yellow (tritan) axis (22). In the same patients carbamazepine had no effect on contrast sensitivity or glare sensitivity (23).

Auditory disturbance is rarely associated with carbamazepine.

- A 25-year-old woman had falsely higher pitch perception after starting carbamazepine for schizoaffective disorder (24). Her serum carbamazepine concentration was in the usual target range. The symptom resolved on withdrawal.

Psychological, psychiatric

Behavioral and psychiatric disturbances are less common with carbamazepine than with other anticonvulsants.

- A 9-year-old boy with seizures developed intermittent complex visual hallucinations during therapy with fosphenytoin and, on a separate occasion, carbamazepine (25).

In 10 children with rolandic epilepsy, carbamazepine impaired memory and possibly visual search tasks (26). Evaluation of individual data suggested that some children were especially vulnerable to the adverse effects of carbamazepine on cognition. The authors did not comment on the fact that rolandic epilepsy is regarded as a syndrome for which treatment in most cases is not indicated.

The cognitive effects of carbamazepine and gabapentin have been compared in a double-blind, crossover, randomized study in 34 healthy elderly adults, of whom 19 withdrew (15 while taking carbamazepine, probably because of excessively rapid dosage titration) (27). The primary outcome measures were standardized neuropsychological and mood state tests, yielding 17 variables. Each subject had cognitive testing at baseline (before drug treatment), at the end of the first drug phase, the end of the second drug phase, and 4 weeks after completion of the second drug phase. Adverse events were frequently reported with both anticonvulsants, although they were more common with carbamazepine. There were significant differences between carbamazepine and gabapentin for only one of 11 cognitive variables, with better attention/vigilance for gabapentin, although the effect was modest. Both carbamazepine and gabapentin can cause mild cognitive deficits in elderly subjects, and gabapentin has a slightly better profile.

Endocrine

Carbamazepine therapy in eight women was associated with increased serum concentrations of sex hormone binding globulin (SHBG) and a reduced serum ratio of 17-α-estradiol and estradiol to SHBG. Of 56 women who had been taking carbamazepine for over 5 years, 14 had menstrual disturbances, which tended to be associated with raised SHBG and reduced serum concentrations of 17-α-estradiol (28). Carbamazepine may also reduce serum LH, progesterone, dehydroepiandrosterone, and the free androgen index (29,30), and some of these changes may be associated with anovulatory cycles and menstrual irregularities.

Men taking carbamazepine had mean low serum concentrations of dehydroepiandrosterone and a high SHBG concentration. Moreover, 18% of men taking carbamazepine for epilepsy reported reduced libido, impaired potency, or both.

Metabolism

Changes in body weight have been evaluated in 349 patients taking carbamazepine, phenytoin, or tiagabine. Carbamazepine add-on therapy caused significant mean weight gain of 1.5% (31). Tiagabide add-on therapy

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caused no significant weight change when added to either phenytoin or carbamazepine.

Some antiepileptic drugs have been associated with low serum and erythrocyte folate concentrations and high total plasma homocysteine concentrations in some patients. The concentrations of folate and homocysteine have been measured in 42 patients taking carbamazepine and 42 matched healthy controls (32). Patients taking carbamazepine had significantly lower serum and erythrocyte folate concentrations. There was hyperhomocystinemia (over 15 μmol/l) in 24% of the patients and 5% of the controls.

Nutrition

Concentrations of plasma homocysteine, plasma pyridoxal 5′-phosphate (active vitamin B6), serum folate, erythrocyte folate, and serum vitamin B12 have been measured both during fasting and after methionine in 60 epileptic patients (aged 14–18 years) and 63 sex- and age-matched controls before therapy and after 1 year of therapy with valproate or carbamazepine (33). After 1 year the patients who took valproate and carbamazepine had significantly increased plasma homocysteine concentrations compared with both baseline and control values and there was a significant fall in serum folate and plasma pyridoxal 5′-phosphate. Serum vitamin B12 and erythrocyte folate were unchanged.

The genetic determinants of this effect on homocysteine have been determined in 136 epileptic children taking carbamazepine or valproate as monotherapy (34). Nutritional determinants (folate and vitamins B6 and B12) and genetic determinants (MTHFR 677CT) of plasma homocysteine were studied in a random sample of 59 of those children. Total homocysteine concentrations were significantly increased and folate and vitamin B6 concentrations were significantly reduced. Carbamazepine lowered folate concentrations in association with hyperhomocysteinemia, which seemed to be related to the homozygous MTHFR 677CT mutation. Valproate, although also associated with hyperhomocysteinemia, only reduced vitamin B6 concentrations, independent of the MTHFR genotype.

Electrolyte balance

Carbamazepine can cause hyponatremia due to stimulation of antidiuretic hormone secretion (35,36). In a boy who developed hyponatremia it also seems to have caused fluid retention and cardiomegaly (SEDA-18, 62).

Symptomatic cases are relatively rare, but two cases have been reported (37).

- A 72-year-old woman developed somnolence and continuous sharp waves over the left hemisphere when carbamazepine was added to primidone and a diuretic. Her serum sodium concentration was initially 130 mmol/l and fell further to 100 mmol/l.
- In a 65-year-woman, carbamazepine-induced hyponatremia (127–130 mmol/l) led to serial tonic-clonic seizures, somnolence, confusion, and an electroencephalographic misdiagnosis of non-convulsive status.

Both patients recovered with normalization of the serum sodium when the carbamazepine dose was tapered.

In 117 patients with chronic epilepsy taking carbamazepine in residential care the retrospective prevalence of hyponatremia was 42% compared with 9.4% in controls (38). Higher doses and serum concentrations of carbamazepine were associated with a higher risk of hyponatremia.

Hematologic

In view of the very low incidence of serious blood dyscrasias, such as pancytopenia and agranulocytosis, indiscriminate continuous hematological monitoring is of little value (SED-13, 145) (39). Leukopenia occurs in up to 21% of patients, usually during the first 3 months of treatment, with a higher risk in those with a low or low-normal pretreatment white blood cell count. Although it may reverse during continuation of treatment (SED-12, 131) (40), (SEDA-20, 60), high-risk cases should be monitored. Bone-marrow aspirates need not be performed routinely in patients with chronic leukopenia and continuation of treatment is probably safe, although caution is required if the neutrophil count is consistently below 1.0×10^9/l (SEDA-19, 66). Other authors have recommended a reduction in dose or withdrawal of treatment if white cell counts are below 3.0×10^9/l or if neutrophil counts are below 1.0×10^9/l.

Some 15 cases of thrombocytopenia, reversible after withdrawal of carbamazepine, have been published (SED-13, 147) (41,42). There have also been single case reports of reticulocytosis (SED-13, 147) (43), leukopenia with thrombocytopenia with Henoch-Schönlein purpura (SEDA-18, 63), hemolytic anemia, and pure red cell aplasia (SED-13, 147) (44).

Serious blood dyscrasias from carbamazepine can be accompanied or preceded by a rash.

- A 66-year-old man had severe leukopenia a few days after a generalized rash appeared on the 36th day after he started to take carbamazepine (45).
- A 69-year-old woman had severe leukopenia and thrombocytopenia about a month after the onset of a rash and 2 months after she started to take carbamazepine (45).

In both patients, the abnormalities resolved after withdrawal, except for the platelet count, which increased but did not fully normalize over 6 weeks. This report suggests that patients developing a rash on carbamazepine should be monitored for the possible risk of associated blood dyscrasias.

Increased concentrations of PIVKA-II (prothrombin-induced by vitamin K absence for factor II) were found in four of six samples of cord blood collected at parturition from the placenta in 12 mothers exposed to carbamazepine during pregnancy (46). Prothrombin concentrations were also reduced in the whole group. High PIVKA-II concentrations were also recorded in cord blood from a newborn exposed prenatally to phenytoin and vigabatrin, but not in two exposed to phenytoin alone and one exposed to valproate alone. These results are consistent with evidence that enzyme-inducing anticonvulsants, particularly carbamazepine, interfere with vitamin K metabolism during pregnancy and can result in bleeding disorders in the newborn. Administration of vitamin K is recommended in these newborns at time of birth or in the mother toward the end of pregnancy. The authors also discussed the possibility that vitamin K supplementation in early pregnancy might reduce the risk of fetal

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facial dysmorphisms caused by enzyme-inducing anticonvulsants.

Gastrointestinal

Nausea, vomiting, and gastric intolerance are relatively uncommon and mild. However, there have been reports of severe diarrhea requiring drug withdrawal. Eosinophilic colitis (47) and lymphocytic colitis (SEDA-22, 85) are rare reactions.

A report of two cases has suggested that carbamazepine can cause colitis as part of the anticonvulsant hypersensitivity syndrome (48).

- A 47-year-old man developed fever, lymphadenopathy, flu-like symptoms, facial edema, a skin rash, and diarrhea after taking carbamazepine 200 mg/day for 3 weeks. Laparotomy because of severe abdominal pain 2 weeks later showed severe colitis with perforations.
- A 41-year-old woman had diarrhea, fever, and a skin rash after taking carbamazepine 300 mg/day for 4 weeks. Colitis was confirmed at colonic biopsy.

Both patients also had raised liver enzymes, peripheral eosinophilia, and eosinophils in the colonic infiltrate. Persistent recovery occurred after carbamazepine was withdrawn.

Lymphocytic colitis has been attributed to carbamazepine in a 77-year-old man, who had taken it for 6 months (49).

Liver

There have been several reports of fatal hepatic failure (SED-12, 132) (50), granulomatous hepatitis (SED-12, 132) (51–53), cholestatic hepatitis (SEDA-16, 71), and cholangitis ascribed to carbamazepine. Most acute hepatotoxic reactions caused by carbamazepine are accompanied by fever, rash, eosinophilia, and other signs of hypersensitivity, although they have also occurred without rash and eosinophilia (SEDA-19, 66).

Urinary tract

Carbamazepine-induced renal insufficiency has been described, but has not been firmly documented (SEDA-18, 63). Two diabetic patients who developed urinary retention on low doses (400–600 mg/day) were confirmed by rechallenge; there have been earlier reports, and pre-existing autonomic dysfunction may be a predisposing factor (54).

Skin

A skin rash occurs in 5–20% of patients started on carbamazepine, and is a common cause of early drug withdrawal. The rash is usually erythematous or maculopapular and may accompany systemic manifestations of hypersensitivity. Exfoliative dermatitis, Stevens–Johnson syndrome, and toxic epidermal necrolysis are relatively rare (SED-13, 148) (55,56).

There has been one case of toxic pustuloderma and two cases of lichenoid eruption attributed to carbamazepine (SEDA-16, 71) (SED-13, 148) (57–59). Patch testing for carbamazepine allergy tends to be positive only in some cases (60,61). A desensitization procedure, using gradually increasing dosages of carbamazepine over 6 weeks, has been described (SEDA-18, 64).

- A 58-year-old man developed stomatitis and widespread edematous erythema with papules and pustules after taking a combination of carbamazepine and paracetamol for 2 days, a most unusual treatment for headache and fever (62). The stomatitis improved but the eruption persisted for 2 months and was diagnosed as eosinophilic pustular folliculitis, a disorder that is rarely drug-induced. Recovery was achieved with glucocorticoid therapy.

A role of carbamazepine was suggested by reoccurrence of eosinophilic folliculitis after patch testing and low-dose (2 mg) oral rechallenge.

- A 17-year-old girl developed Stevens–Johnson syndrome after using carbamazepine 400 mg/day for 2 weeks (63). She was treated with intravenous immunoglobulin and intravenous methylprednisolone and recovered completely.

Immunologic

Hypersensitivity reactions are relatively common with carbamazepine. Most affect the skin, but systemic reactions with fever, lymphadenopathy, and/or involvement of the bone-marrow, the liver, the heart, the gastrointestinal system, the lungs, and other organs have been described. Severe serum sickness associated with immunoblastic lymphadenopathy has been reported in one case (SED-13, 148) (64). Occasional cases of systemic lupus erythematosus have occurred within the first few months, although an unusual case with onset after 8 years has been described (SEDA-22, 83).

- A 44-year-old woman, who was allergic to phenytoin, developed fever, lymphadenopathy, pneumonitis, hepatitis, and a morbilliform eruption after taking carbamazepine for 1 month (65). A skin biopsy of the dermis showed atypical lymphocytes that were CD3+, CD30+, and L26–. She improved quickly after carbamazepine was withdrawn.

This seems to have been the first report of carbamazepine-induced histological features of cutaneous pseudolymphoma, including CD30+ cells.

Cervical lymphadenopathy, fever, and a maculopapular skin rash developed in a 17-year-old boy after he had taken carbamazepine for 3 weeks (up to 600 mg/day) (66). Lymph node biopsies showed features typical of Kikuchi disease, a rare and self-limited immune-mediated lymphadenopathy that affects mostly the cervical region. The condition cleared rapidly after withdrawal.

- A 40-year-old man who had taken carbamazepine since childhood suffered for over 10 years from a lupus-like illness with hypocomplementemia, pancytopenia, and splenomegaly (67). He later developed cryoglobulinemia with membranoproliferative glomerulonephritis and raised ANA and pANCA titers. A causative role of carbamazepine in the latter syndrome was suggested by the observation that after withdrawal the antibodies fell and cryoglobulinemia resolved.

The carbamazepine hypersensitivity syndrome has been reviewed (68). Some of the following cases are examples of the different manifestations of this syndrome.

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- A 12-year-old boy developed a maculopapular rash on two occasions after taking carbamazepine (69). A patch test was positive, but an in vitro lymphocyte transformation test was negative. However, T cells incubated with carbamazepine produced an excess of interferon-gamma.

The author proposed that this had been a delayed hypersensitivity response, perhaps mediated by a reactive metabolite.

- A 45-year-old man developed acute cardiac tamponade due to systemic lupus erythematosus associated with carbamazepine, which he had taken for 8 months (70).
- An 11-year-old girl developed a skin rash, fever, lymphadenopathy, and arthralgia after taking carbamazepine (plasma concentration 21 μmol/l) for 3 weeks (71). She had a lymphocytosis, mild thrombocytopenia, marked eosinophilia, and high transaminases. She was given betamethasone, and carbamazepine was gradually withdrawn. The fever and rash gradually abated and all the laboratory tests normalized by 2 weeks after the disappearance of the skin rash.

Long-Term Effects

Tumorigenicity

Carbamazepine and phenytoin have previously been associated with lymphoproliferative disorders, including dermatopathic lymphadenitis, atypical lymphoid proliferation, and cutaneous pseudolymphoma. In most reported cases, regression follows withdrawal of treatment with the causative drug. However, rarely true lymphoma can develop.

- A 13-year-old girl who had taken carbamazepine for about 8 months developed multiple painless reddish skin nodules, which grew and quickly ulcerated (72). The nodules were on the neck, trunk, and arms and varied in size. Neither lymphadenopathy nor splenomegaly was detected. Histology showed a CD30, primary, cutaneous, anaplastic, large-cell lymphoma. Carbamazepine was withdrawn, she received radiotherapy, and the lesions regressed. At 3 years after diagnosis she was still in complete remission.

Second-Generation Effects

Teratogenicity

Data from various studies in 1255 patients exposed to carbamazepine have been analysed to evaluate its potential teratogenicity (73). There was an increased rate of congenital anomalies, mainly neural tube defects, cardiovascular and urinary tract anomalies, and cleft palate. The combination of carbamazepine with other antiepileptic drugs was more teratogenic than carbamazepine monotherapy. Because this study was retrospective, the conclusions should not be seen as definitive.

There is an association of carbamazepine with cardiac malformations.

The Israeli Teratogen Information Service has prospectively followed 210 pregnancies with exposure to carbamazepine in the first trimester (74). The outcomes were compared with those in two overlapping groups of matched controls ($n = 629$) who had been exposed to non-teratogens. There was a two-fold increase in the rate of major congenital anomalies in the women who had used carbamazepine (12/160 on carbamazepine versus 18/560 controls; RR = 2.24; 95% CI = 1.10, 4.56) and a reduction in birth weight of about 250 g after in utero exposure to carbamazepine. There were no neural tube defects. These results are to be interpreted with caution, as they were obtained from a questionnaire in 87% of cases.

Fetotoxicity

Increased concentrations of PIVKA-II (prothrombin-induced by vitamin K absence for factor II) were found in four of six samples of cord blood collected at parturition from the placenta in 12 mothers exposed to carbamazepine during pregnancy (46). Prothrombin concentrations were also reduced in the whole group. High PIVKA-II concentrations were also recorded in cord blood from a newborn exposed prenatally to phenytoin and vigabatrin, but not in two exposed to phenytoin alone and one exposed to valproate alone. These results are consistent with evidence that enzyme-inducing anticonvulsants, particularly carbamazepine, interfere with vitamin K metabolism during pregnancy and can cause bleeding disorders in the newborn. Administration of vitamin K is recommended in these newborns at time of birth or in the mother toward the end of pregnancy. The authors also discussed the possibility that vitamin K supplementation in early pregnancy might reduce the risk of fetal facial dysmorphisms caused by enzyme-inducing anticonvulsants.

Lactation

In seven lactating women the mean concentrations of carbamazepine in milk and plasma samples were 15 and 26 μmol/l respectively; the concentrations of carbamazepine 10,11-epoxide were 5 and 8 μmol/l respectively (75). The mean milk/plasma ratios were 0.64 and 0.79 respectively. The amounts of carbamazepine and carbamazepine 10,11-epoxide that a breast-feeding child is likely to consume are thus very small.

Susceptibility Factors

Age

The elderly appear to be at increased risk of blood dyscrasias and liver reactions (39). Age above 55 years was associated with a greater risk of toxicity after rapid switch-over to a carbamazepine dosage designed to yield a plasma concentration of 10 μg/ml (76). Moderately severe to severe adverse effects in the 11 patients in either subgroup included sedation, ataxia, and confusion.

Hepatic disease

Because of the reactions described above, and because carbamazepine is mostly metabolized in the liver, it should be used with caution in patients with hepatic disorders.

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Other features of the patient

Because of the reactions described above, carbamazepine should be used with caution in patients with cardiac disorders.

Alcohol abusers may represent a high-risk group for serious skin reactions (SED-13, 145) (39).

Carbamazepine is porphyrogenic (SED-12, 131) (77), (SED-13, 147) (78), and should not be used in patients with acute intermittent porphyria.

The presence of a static encephalopathy (defined as focal or diffuse structural brain lesions associated with mild to moderately severe cognitive dysfunction) was associated with a greater risk of toxicity after rapid switch-over to a carbamazepine dosage designed to yield a plasma concentration of 10 μg/ml (76). Moderately severe to severe adverse effects in the 11 patients in either subgroup included sedation, ataxia, and confusion.

Drug Administration

Drug formulations

When 14 patients taking a brand-named modified-release formulation of carbamazepine were switched to a generic modified-release formulation, nine developed adverse effects such as dizziness, nausea, ataxia, diplopia, and nystagmus, despite the fact that the two formulations met pharmacokinetic criteria for bioequivalence (79). Mean AUC and C_{max} values were about 10% higher with the generic formulation. The authors suggested that standard bioequivalence criteria (90% confidence limits of 80–125% for AUC and 70–143% for C_{max}) may be too broad for carbamazepine, which has a relatively narrow therapeutic ratio. While this may be correct, the findings could have been biased by the lack of a control group, lack of randomization in the sequence of the two treatments, and the use of a non-blinded design.

The suitability of a modified-release formulation of carbamazepine (Carbatrol) for administration through feeding tubes in six children has been assessed (80). Carbatrol was administered as follows: first, the tube was flushed with 10 ml of water, then the granular contents of a capsule of Carbatrol were added to 15 ml of water and administered via the tube; this was followed by an additional flush with 10 ml of water. Two of the six children had to be withdrawn from the study because of frequent tube occlusions, attributed to the Carbatrol granules.

Drug dosage regimens

The relations between plasma concentrations of carbamazepine and its two major metabolites, carbamazepine-10,11-epoxide and carbamazepine-10,11-diol, and antimanic efficacy and adverse effects in patients with schizoaffective disorder have been studied in 10 patients (81). There were positive relations between plasma concentrations of the epoxide and the degree of clinical improvement and adverse effects, but not with plasma concentrations of carbamazepine or its diol.

Drug overdose

Acute interstitial pneumonia or diffuse alveolar damage in the context of other manifestations of overdose has been described (SEDA-22, 84).

There was impaired neuromuscular transmission at high frequency repetitive nerve stimulation in two children who presented in coma with diffuse hypotonia and areflexia after carbamazepine overdose (82). Both recovered with supportive care.

Acute massive carbamazepine intoxication has been reported in a 27-year-old man (83). The plasma concentration was 147 μmol/l. He had a sinus tachycardia and a leukocytosis.

In 14 children under the age of 5 years with peak serum carbamazepine concentrations of 76–134 μmol/l after acute accidental overdose there was nystagmus in 12, drowsiness in 10, ataxia in four, and mild tachycardia in two (84). None died.

Three drug dispensing errors causing carbamazepine overdose have been reported (85). In each case carbamazepine was given instead of another drug with a similar name—Tegretol instead of Trental (pentoxifylline, two cases) and carbamazepine–Neuroxpharm instead of piracetam–Neuraxpharm. All three developed mild cerebellar symptoms and all had high carbamazepine concentrations (50–55 μmol/l).

The postmortem blood concentration of carbamazepine has been reported in a case of suicide attributed to "mixed drug toxicity" with carbamazepine, lamotrigine, paroxetine, and thioridazine (86). It was 76 μmol/l.

Drug–Drug Interactions

General

Carbamazepine is an enzyme inducer, and its own metabolism can be induced or inhibited by other drugs, particularly those affecting cytochrome CYP3A4.

Antiretroviral protease inhibitors

Some antiretroviral protease inhibitors inhibit CYP3A4, which is mostly responsible for the metabolism of carbamazepine.

- Failure of antiretroviral drug therapy has been attributed to an interaction of carbamazepine with indinavir in a 48-year-old man taking indinavir, zidovudine, and lamivudine; his HIV-RNA viral load became undetectable after less than 2 months and he developed a Herpes zoster infection (87). Lower doses of carbamazepine are also required during co-administration of ritonavir, as has been shown in two recent cases.
- Within 4 days of the introduction of ritonavir in a 49-year-old woman taking carbamazepine 600 mg/day the serum carbamazepine concentration rose from 29 to 84 μmol/l and ataxia occurred (88). The dosage of carbamazepine was reduced to 300 mg/day and the serum concentration fell but then rose again. Finally, a serum carbamazepine concentration in the target range was achieved with a dosage of 100 mg/day.

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- The serum carbamazepine concentration rose from 27 to 76 μmol/l after ritonavir was introduced in a 36-year-old man (89). Dizziness and a gait disorder resolved when carbamazepine was withdrawn. The serum phenytoin concentration was unaffected by ritonavir.

Clobazam

Negative myoclonus and more typical signs of carbamazepine intoxication (fatigue, ataxia, clumsiness) occurred in a 66-year-old man after he took add-on clobazam (10 mg/day) for 4 weeks (90). Plasma concentrations of carbamazepine (58 μmol/l) and carbamazepine-10, 11-epoxide (19 μmol/l) were higher than before clobazam therapy, and his symptoms resolved quickly when carbamazepine dosage was reduced and clobazam was withdrawn. The interaction was confirmed on rechallenge; however, it does not occur in most patients.

Coumarin anticoagulants

Carbamazepine reduces the effects of coumarin anticoagulants (SED-14, 1185) (91,92), including phenprocoumon (SEDA-22, 86), by inducing cytochrome P450 enzymes, and another case has been reported (93).

- A 53-year-old woman taking phenprocoumon had a large reduction in prothrombin time when carbamazepine was added. After withdrawal of carbamazepine, the prothrombin time returned to target values. Valproate had no effect on phenprocoumon.

Dextropropoxyphene

Dextropropoxyphene inhibits the oxidative metabolism of carbamazepine, leading to clinically significant rises in carbamazepine concentrations (94).

Fluconazole

In a 33-year-old man stabilized on carbamazepine, the addition of fluconazole (150 mg/day) led to severe carbamazepine toxicity associated with high carbamazepine concentrations (104 μmol/l) (95). The condition cleared after withdrawal of both drugs, and carbamazepine was then readministered without recurrence of toxicity. This interaction is likely to be mediated by inhibition of the CYP3A4-mediated metabolism of carbamazepine by fluconazole.

Grapefruit juice

In 10 patients grapefruit juice 300 ml taken with the morning dose of carbamazepine resulted in an approximate 50% increase of plasma carbamazepine concentrations (96). The interaction was ascribed to inhibition of cytochrome CYP3A4 by components of the juice.

Inhibitors of epoxide hydrolase

Clinically significant interactions can be caused by inhibitors of epoxide hydrolase, such as valpromide and valnoctamide, which increase the serum concentrations of the active metabolite carbamazepine-10,11-epoxide.

Lamotrigine

In dogs concurrent administration of lamotrigine had no significant effect on the pharmacokinetics of carbamazepine or the plasma concentration ratio of carbamazepine epoxide to carbamazepine (97).

In a retrospective study, in which 376 samples from 222 patients were analysed, carbamazepine reduced lamotrigine concentrations by 54% (98).

Lithium

A 42-year-old woman developed sinus node dysfunction during lithium toxicity (serum concentration 3.4 mmol/l) (99). The authors suggested that concomitant carbamazepine therapy (serum concentration 22 μmol/l) had exacerbated the effect of lithium on the sinus node.

Mianserin

In 12 patients, carbamazepine (400 mg/day for 4 weeks) markedly reduced the plasma concentrations of concomitantly administered mianserin, probably through enzyme induction (100). The concentration of *S*-mianserin, the more potent of the enantiomers of mianserin, fell by 45%, while the plasma concentrations of desmethylmianserin changed only slightly. These data suggest that patients co-medicated with carbamazepine may require higher dosages of mianserin.

Monoamine oxidase inhibitors

Carbamazepine is contraindicated in patients taking monoamine oxidase inhibitors (101,102). The combination can cause sudden high body temperature, extremely high blood pressure, and severe convulsions; at least 14 days should be allowed between stopping treatment with one medicine and starting the other.

Nefazodone

The pharmacokinetic interaction of nefazodone 200 mg bd with steady-state carbamazepine has been investigated in 12 healthy men (103). Nefazodone increased the steady-state plasma AUC of carbamazepine by 23% and reduced the AUC of active carbamazepine-10,11-epoxide by 20%. The steady-state AUC of nefazodone fell 14-fold and the AUCs of its metabolites (hydroxynefazodone, metachlorophenylpiperazine, and triazoledione) also fell significantly. Thus nefazodone had a small inhibitory effect on carbamazepine metabolism, while carbamazepine greatly increased the metabolism of nefazodone.

Olanzapine

In 11 healthy volunteers carbamazepine (400 mg/day for 2 weeks) reduces by about 30% the AUC of olanzapine, presumably by induction of olanzapine metabolism (104). Although the interaction was considered of little relevance, it cannot be excluded that some patients on carbamazepine may require higher olanzapine dosages than usual.

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Rifampicin

Serum carbamazepine concentrations were reduced in a 44-year-old woman who also took rifampicin (105), presumably through induction of metabolism.

Risperidone

Risperidone significantly increases serum carbamazepine concentrations (106) and carbamazepine significantly reduces serum risperidone concentrations (107). The clinical relevance of these changes is uncertain.

Steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone have been measured in 23 patients taking risperidone alone and in 11 patients co-medicated with carbamazepine (108). Carbamazepine markedly reduced the concentrations of both compounds, although the difference was significant only for the metabolite.

Sertraline

Loss of antidepressant activity of sertraline can occur at usual therapeutic doses when depressed patients have also taken drugs that induce CYP3A4, including carbamazepine, as has been reported in two cases, a 33-year-old woman and a 25-year-old man (109).

St. John's wort

St. John's wort contains an enzyme inducer that can reduce the plasma concentrations of drugs that are substrates of CYP3A4, such as indinavir and ciclosporin. However, in eight healthy volunteers aged 24–43 years, St. John's wort 300 mg/day (0.3% hypericin standardized tablet) for 14 days had no effect on the pharmacokinetics of carbamazepine (110).

Trazodone

In one case trazodone increased serum carbamazepine concentrations by about 30% (111). However, only one sample was taken after adding trazodone, and the rise in carbamazepine concentration might have been caused by random fluctuation.

Ziprasidone

In 25 healthy subjects, carbamazepine (up to 400 mg/day for 25 days) reduced the steady-state AUC of ziprasidone (40 mg/day) by about 35%, presumably through induction of the CYP3A4-mediated metabolism of the neuroleptic drug (112). Although the interaction was considered clinically insignificant, the dosage of carbamazepine was relatively low and a greater effect might occur at higher dosages.

The effect of steady-state carbamazepine administration on the steady-state pharmacokinetics of ziprasidone has been studied in 25 healthy young adults, in a randomized, placebo-controlled study (112). Carbamazepine caused small reductions in ziprasidone $AUC_{0\rightarrow12}$ and C_{max} (36% and 27% respectively). The authors concluded that carbamazepine had increased ziprasidone clearance by induction of CYP3A4.

Diagnosis of Adverse Drug Reactions

The usual target range for plasma carbamazepine concentrations is 17–42 μmol/l (4–10 μg/ml).

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Carbapenems

See also Beta-lactam antibiotics

General Information

Carbapenems differ from penicillins and cephalosporins by a methylene substitution for sulfur in the five-membered beta-ring structure. Imipenem and meropenem belong to this class of compounds.

In the last 25 years, various natural carbapenems have been discovered (1). However, their potential is limited by chemical instability. Imipenem (*N*-formimidoylthienamycin), the first carbapenem in use, is therefore a stabilized synthetic compound. To overcome a second difficulty, namely inactivation by a kidney dehydropeptidase, imipenem has to be combined with cilastatin, a competitive inhibitor of that enzyme. Meropenem has better stability in the presence of renal dehydropeptidase I (2). The antibacterial spectrum of carbapenems is among the broadest of all beta-lactam antibiotics, and they have good stability against many beta-lactamases.

General adverse reactions

The safety profile of the carbapenems is comparable to that of other beta-lactam antibiotics, in particular with regard to laboratory abnormalities, the most common ones being those related to liver function (3,4). In patients with pre-existing nervous system disease or who take dosages above the recommended limits (for example in renal impairment) seizures appear to be more common with imipenem + cilastatin.

Organs and Systems

Nervous system

Seizures associated with imipenem + cilastatin have repeatedly been reported (5–7). As with other beta-lactam antibiotics, it is difficult to assess clearly the cause of a seizure in patients with a cluster of other predisposing factors for neurotoxicity (8) and hence to reach clear estimates of frequency. In a review of 1754 patients there was a similar incidence of seizures with imipenem + cilastatin as with other antibiotic regimens usually containing another beta-lactam (9). In rabbits imipenem + cilastatin and another carbapenems were more neurotoxic than benzylpenicillin (10). In mice, ataxia and seizures were seen, with much lower blood concentrations of imipenem than cefotaxime or benzylpenicillin (1900 μg/ml versus 3400 μg/ml and 5800 μg/ml) (11). In mice imipenem also lowered the convulsive threshold of pentetrazol (pentylenetetrazole) more than cefazolin or two other carbapenems (12). Cilastatin alone was not proconvulsant, but it increased the effects of co-administered imipenem.

Imipenem is a more common cause of seizures than other beta-lactam antibiotics, particularly when high doses are given (13–15). In one study, seven of 21 children developed seizure activity while receiving imipenem + cilastatin for bacterial meningitis, a recognized risk factor (13). However, computer-assisted monitoring of imipenem + cilastatin dosages in relation to renal function resulted in a reduced incidence of seizures (16).

In animals, meropenem (17) and other carbapenems (18,19) were less epileptogenic than imipenem. In 403 children there was no meropenem-associated neurotoxicity (20) and meropenem was well tolerated in children with bacterial meningitis (21). In summary, a larger dose range of meropenem than imipenem appears to be tolerated, but when strictly observing known risk factors for seizure propensity the difference between the two compounds is very small (22,23).

Sensory systems

Taste alterations were seen in some early patients who were treated with carbapenems (24); these observations have not subsequently been confirmed.

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Hematologic

As with some cephalosporins and clavulanic acid, the Coombs' test was positive in a number of patients taking carbapenems, but without hemolysis (25).

Mouth and teeth

Yellowish-brown staining of the teeth was related to imipenem in several cases (26,27). Staining was mostly removable with dental assistance.

Urinary tract

In animals, the tubular toxicity of imipenem was completely prevented by cilastatin. Accordingly, definite nephrotoxicity of this combination has not been documented in patients (25) or in healthy volunteers (28). The cilastatin component may even reduce the nephrotoxic effects of ciclosporin after kidney transplantation (29) or bone marrow transplantation (30).

Skin

Of all the drugs that have been implicated in drug-induced toxic epidermal necrolysis, antimicrobial drugs account for 29–42% (now more than 100 in number) (31,32), and almost all antimicrobial drugs have been implicated, including meropenem (33).

- A 75-year-old woman developed acute pneumonia. She was first given oral co-amoxiclav, fluconazole, and ciprofloxacin for 10 days, followed by cefotaxime and amikacin, both intravenously. Six days later, she developed a progressive erythematous rash, soon involving 40% of her body surface. The antibiotics were withdrawn and she was rehydrated and given intravenous immunoglobulins 0.75 g/kg for 5 days, but not systemic glucocorticoids. She then developed severe septic shock because of a combination of two very resistant bacterial strains and was given meropenem 1 g and teicoplanin 800 mg bd. However, within 2 days her skin lesions recurred, extending to previously uninvolved skin areas and including over 60% of her body. A biopsy showed typical features of toxic epidermal necrolysis. Meropenem was withdrawn and replaced by aztreonam. However, she died 5 days later.

Imipenem, which is related to meropenem, has also been reported to cause toxic epidermal necrolysis (34). The authors stated that to the best of their knowledge, this was the first report of a possible cross-reaction between two classes of antibiotics in causing toxic epidermal necrolysis. The time between first administration and the occurrence of epidermal necrolysis is considerably shorter in recurrence or provocation testing (35,36). They also claimed that it is likely that the beta-lactam ring is responsible for this hypersensitivity reaction, citing the evidence that the patient had been given amoxicillin 15 days before the cephalosporin, and that could have served as the sensitizing event. They did not discuss whether aztreonam, a monobactam, also could have caused a cross-reaction; however, it has been involved in two cases of fatal toxic epidermal necrolysis (37).

A pustular rash, as repeatedly observed with cephalosporins, has been described in one case (38). The frequencies of rash, urticaria, and pruritus were similar to those seen with other beta-lactam antibiotics (25).

Meropenem can cause occupational allergic contact dermatitis (39).

- A 45-year-old nurse presented with a 6-month history of recurrent periorbital erythema with itching and runny eyes. Each episode lasted about 5–6 days and settled on withdrawal from her place at work, where she handled a large number of drugs, including meropenem. She was patch-tested with the European standard series, and was negative to all except meropenem. She had complete remission after quitting her workplace.

The authors assumed that the localization to the periorbital region was due to involuntary contact with her hands or airborne contact.

Immunologic

There was a high degree of cross-reactivity between imipenem determinants, analogous to the penicillin determinants in penicillin-allergic patients. Nine of twenty patients with positive penicillin skin tests had positive skin reactions to analogous imipenem determinants (40). In view of this appreciable cross-reactivity, imipenem should not be given to patients with penicillin allergy.

Immediate hypersensitivity related to imipenem has been reported in a patient allergic to penicillin and aztreonam (41).

Drug–Drug Interactions

Ciclosporin

The addition of imipenem + cilastatin to long-term ciclosporin provoked seizures in patients without a corresponding history (42). In general, nervous system toxicity occurred shortly after the start of the antibiotic therapy and drug concentrations were stable, suggesting a synergistic effect.

Ciclosporin-induced acute nephrotoxicity was reduced by cilastatin, an inhibitor of active tubular resorption (30,43). Reduced renal parenchymal accumulation of the drug may account for this effect. Serum ciclosporin concentrations were unchanged or insignificantly reduced. A similar protective effect against tacrolimus is possible, but unproven (44).

GABA receptor antagonists

Carbapenems (imipenem more than meropenem) are believed to increase central nervous system excitation by inhibition of GABA binding to receptors. Combinations with other GABA inhibiting drugs such as theophylline or quinolones have been reported to provoke seizures (45,46).

Valproic acid

Two carbapenems, meropenem and panipenem + betamipron, reduced serum valproic acid concentrations, and increased the risk of seizures (47,48). The mechanism of the interaction was unclear. Accelerated

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renal elimination of valproic acid is probable, since the almost immediate fall in serum drug concentrations and low protein binding of carbapenems argue against enzyme induction or protein binding displacement (49).

Interference with Diagnostic Tests

Leukocyte urine dipstick test

Imipenem caused positive dipstick tests for leukocytes in patients with agranulocytosis and normal urinary sediments. This phenomenon was reproducible in vitro with imipenem, meropenem, and clavulanic acid. Sulbactam, tazobactam, three penicillins, three cephalosporins, and the basic structures of penicillins, cephalosporins, and monobactams tested negative (50).

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Carbenoxolone

General Information

Liquorice owes its ulcer-healing properties to glycyrrhizin and glycyrrhizic acid; carbenoxolone is related to the latter. All these substances have unwanted mineralocorticoid-like effects. Deglycyrrhizinated liquorice and lauryl glycyrrhetinic acid, which are also used in some countries for their ulcer-healing effects, do not have mineralocorticoid-like effects. It should be noted that liquorice is sometimes present in laxatives, for example those prepared by herbalists, and that hyperaldosteronism can occur unexpectedly in such cases when liquorice consumption has gone unrecognized (SEDA-16, 425). For example, hypokalemia and hypertension has been associated with the use of liquorice flavored chewing gum (1).

Organs and Systems

Endocrine

- Hyperprolactinemia occurred in a woman with secondary amenorrhea and hypertension who was taking large amounts of liquorice; all the abnormalities reversed on withdrawal (2).

This effect could have reflected involvement of prolactin in adrenal steroidogenesis or salt and water homeostasis.

Electrolyte balance

The mineralocorticoid properties of carbenoxolone are probably exerted by displacement of aldosterone from non-specific receptor sites in cells, thus making it more available to affect mineral metabolism. What this means in practice is that in normal doses carbenoxolone can cause salt and water retention, with occasional hypokalemia. These effects are common but usually mild; they are detected more often during treatment if patients are weighed, their blood pressure measured, and serum potassium concentrations checked. Those who take prolonged courses, elderly patients, and those with hepatic, cardiac, or renal impairment are at special risk; severe effects, with serious hypertension, heart failure, and hypokalemia of sufficient degree to induce myopathy and tubular necrosis, can usually be ascribed to ill-advised treatment of people in whom carbenoxolone is contraindicated, to its use in elderly patients, or to prolonged intake without supervision.

Liquorice-induced pseudohyperaldosteronism can cause hypokalemic myopathy (3).

- A 65-year-old man, diabetic and alcoholic, developed pseudohyperaldosteronism with hypokalemia, myopathy, and a reversible dilated cardiomyopathy associated with a small dose of liquorice-containing stomachics (0.06 of liquorice extract in total granules of 3 g/day) over a few years for gastritis and a total of 800 mg of glycyrrhizin intravenously over 2 months for worsening liver dysfunction.

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Drug–Drug Interactions

Amiloride

Amiloride inhibits the ulcer-healing action of carbenoxolone (SEDA-6, 317).

Antihypertensive drugs

Because of its mineralocorticoid fluid-retaining properties, carbenoxolone opposes the therapeutic effects of diuretics and other drugs used to treat hypertension.

Spironolactone

Spironolactone inhibits the ulcer-healing action of carbenoxolone (SEDA-6, 317).

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Carbocisteine

General Information

Carbocisteine is a mucolytic that is administered orally or from a metered dose inhaler. Its adverse effects include headache, nausea, vomiting, gastric discomfort and bleeding, diarrhea, and skin rash. It has, however, been shown to be an effective mucolytic which is generally well tolerated with few adverse effects (SEDA-17, 208).

The place of mucolytic drugs in respiratory disease has recently been reviewed (1). The authors suggested that they have been inappropriately used in the past. As mucolytic agents do not improve lung function tests in COPD, the European Respiratory Society and the American Thoracic Society guidelines discourage their use in the treatment of COPD. Future trials should evaluate clinical symptoms and quality of life as well as lung function tests. Mucolytic agents should be evaluated earlier in the natural history of COPD, when mucus hypersecretion is the major feature and before lung function has deteriorated.

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Carbon dioxide

General Information

Alternatives to iodinated X-ray contrast agents have been sought for cases in which they are contraindicated. One such agent is carbon dioxide (CO_2), a highly soluble gas, which is therefore relatively safe to inject into the circulation, where it displaces blood and reduces X-ray absorption, acting as a negative contrast agent (SEDA-20, 423) (1). No complication of any kind was reported with the use carbon dioxide in aortography or peripheral angiography (SEDA-20, 423).

In a UK study the safety and diagnostic efficacy of carbon dioxide as an arterial contrast agent have been investigated in 63 patients (36 men and 27 women, aged 46–86 years) who underwent angiographic examinations with carbon dioxide via an automated injector and iodinated contrast medium (2). There were adverse effects in 15 patients, including nausea ($n = 4$), abdominal pain ($n = 8$), and leg and groin pain ($n = 8$). All the symptoms were directly related to the injection of carbon dioxide and resolved within 1–2 minutes of injection. No arteriogram had to be abandoned because of adverse effects, and the incidence of adverse reactions was less with selective studies. Although it has been reported that carbon dioxide is well tolerated, with minimal discomfort, in this study there was a variety of mild to severe unpleasant symptoms, but no serious complications. The abdominal symptoms were related to the passage of a large volume of carbon dioxide into the mesenteric vessels. The catheter was above the mesenteric vessels in most of the patients with abdominal symptoms. These symptoms can be reduced by placing the tip of the catheter in non-selective studies at the aortic bifurcation to reduce the amount of carbon dioxide that passes into the superior or inferior mesenteric arteries. The symptoms are also reduced by injecting smaller volumes. The authors concluded that when iodinated contrast media are contraindicated carbon dioxide provides a diagnostic alternative.

The safety of carbon dioxide in vena cavography has been investigated in 119 patients (aged 17–89 years, 65 men). Patients with intracardiac shunts, severe pulmonary compromise, or non-dialysis-dependent renal insufficiency were excluded. Two patients developed mild adverse effects: one had nausea that resolved spontaneously and the other vomited several minutes after the administration of carbon dioxide but needed no treatment. The diagnostic quality of the venography was comparable to that with iodinated contrast media. The authors concluded that carbon dioxide cavography is well tolerated and is especially valuable in patients with a history of a reaction to iodinated contrast material or renal insufficiency.

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Carbonic anhydrase inhibitors

General Information

The carbonic anhydrase inhibitors, of which acetazolamide (rINN), a non-competitive inhibitor, is the prototype, are not suitable for normal diuretic use, because tolerance soon develops. However, they are well suited to brief intermittent use, particularly in the relief of glaucoma and in the prevention of acute mountain sickness. Acetazolamide and methazolamide (rINN) should be used with caution in the long-term control of glaucoma because of its serious systemic adverse effects. However, brinzolamide (rINN) and dorzolamide (rINN) are available for long-term topical administration.

The safety profile and efficacy of 2% dorzolamide hydrochloride (Trusopt) eye-drops have been evaluated. It was as effective as pilocarpine 2% and its ocular hypotensive efficacy was comparable with that of betaxolol 0.5%. The patients reported less interference with quality of life with dorzolamide than pilocarpine, particularly in regard to limitations in their ability to drive, read, and perform moderate activities. Long-term use was not associated with important electrolyte disturbances or the systemic effects commonly observed with oral carbonic anhydrase inhibitors (1–3).

In a 3-month prospective study of the adverse effects and efficacy of topical dorzolamide in 39 patients intolerant of systemic carbonic anhydrase inhibitors, the effect on mean intraocular pressure was similar to that of acetazolamide, and health assessment scores improved significantly in seven of the eight categories of the SF-36 health assessment questionnaire used to evaluate changes in well-being and quality of life (4). There were no adverse effects with the switch in medication.

General adverse effects

The incidence and severity of many adverse reactions to carbonic anhydrase inhibitors are dose-related and the problems usually abate when the dose is reduced or the drug is withdrawn. Symptoms of depression, confusion, fatigue, impotence, irritability, malaise, nervousness, and weight loss are often present to some extent in patients on long-term acetazolamide or methazolamide therapy. These symptoms may be related to systemic metabolic acidosis (due to renal excretion of bicarbonate), which is often accompanied by a reduction in serum potassium concentration (5). Gastrointestinal intolerance, manifested as abdominal cramping, dyspepsia, and nausea, with or without diarrhea, is another common problem. Carbonic anhydrase inhibitors reduce the urinary excretion of citrate and uric acid, which may lead to renal calculi and gouty arthritis. Pulmonary edema, taste disorders, and alopecia have also been reported. The most serious adverse effect of carbonic anhydrase inhibitors is bone-marrow depression.

Organs and Systems

Cardiovascular

Anaphylactic shock has been reported after a single oral dose of acetazolamide (6).

- A 70-year-old man was given acetazolamide 250 mg to control postoperative intravascular pressure 5 hours after cataract removal under local anesthetic. Thirty minutes later he complained of nausea, became cyanotic, and had an acute respiratory arrest. His systolic blood pressure was 70 mmHg, his heart rate was 180/minute, and there was tachypnea (40 breaths/minute). Arterial gases confirmed hypoxemia (PaO_2 6.34 kPa, 47 mmHg). Pulmonary embolism and high-pressure pulmonary edema were excluded by perfusion lung scanning and right-sided heart catheterization. Management was with ventilatory support, vasopressors, intravenous hydrocortisone, and diphenhydramine. Clinical improvement occurred over 12 hours. After stabilization, sulfonamide hypersensitivity was confirmed by skin testing, suggesting cross-sensitivity with a sulfonamide derivative (acetazolamide).

Physicians should be aware of the risk of anaphylaxis to acetazolamide, particularly in patients with a history of allergy to sulfonamides.

Nervous system

A case of possible Gerstmann syndrome has been attributed to acetazolamide (7).

- A 60-year-old woman became acutely confused 2 days after the removal of a cataract. She had long-standing diabetes mellitus, hypertension, and ischemic heart disease. There had been a minor stroke with complete recovery 2 years before. Her medication included aspirin, indapamide, enalapril, and oral hypoglycaemic agents. Acetazolamide 500 mg bd was added shortly after her eye operation. Neurological examination showed finger agnosia, nominal and receptive dysphasia, acalculia, astereognosis, and left–right disorientation. Other systems were normal. Withdrawal of acetazolamide resulted in rapid improvement with no residual neurological signs two days after admission.

Acetazolamide toxicity was suspected, because of the temporal association between drug treatment and the onset of the neurological symptoms, together with metabolic acidosis. Gerstmann syndrome is usually due to an acute stroke. Although a brain CT scan was negative, such an event was likely in this patient, who had a history of cerebrovascular disease and multiple risk factors, and a causal relation to acetazolamide must be considered tenuous.

Sensory systems

Eyes

In a multicenter, double-blind, prospective, parallel-group comparison of brinzolamide 1.0% bd or tds, dorzolamide 2.0% tds, and timolol 0.5% bd in 572 patients with

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primary open-angle glaucoma or ocular hypertension, the three drugs were equally effective (8). Brinzolamide 1.0% caused less ocular discomfort (burning and stinging) (bd 1.8%; tds 3.0%) than dorzolamide (16%).

- A 68-year-old woman developed bilateral marginal keratitis 2 weeks after starting to use dorzolamide eye-drops (9). One week after withdrawal she was asymptomatic, with complete resolution of her corneal infiltrates.

In this case the allergic reaction was caused by dorzolamide hydrochloride and not the preservative, benzalkonium chloride, since therapy was uneventfully continued with timolol maleate, which also contains benzalkonium chloride as a preservative. This is the first report of this phenomenon with a carbonic anhydrase inhibitor.

Taste

Acetazolamide can cause altered taste perception of carbonated drinks. The mechanism is unknown, but carbonic drinks may be a source of high concentrations of carbonic acid, which are reduced by carbonic anhydrase activity (SEDA-15, 219).

Endocrine

Thyrotoxic periodic paralysis occurs only occasionally in Caucasians, but for unknown reasons it can be worsened by acetazolamide (SEDA-15, 219).

Electrolyte balance

The carbonic anhydrase inhibitors are the most kaliuretic of all diuretics and can cause severe hypokalemia during the first few days of administration. However, hypokalemia is not a problem during long-term administration, because of compensatory potassium retention secondary to acidosis (10).

- A 46-year-old man with hypokalemic periodic paralysis and diabetes mellitus had worse muscle weakness after taking acetazolamide, possibly because of reduced muscle uptake of potassium (11).

Acid–base balance

Acetazolamide can produce severe lactic acidosis, with an increased lactate:pyruvate ratio, ketosis with a low beta-hydroxybutyrate:acetoacetate ratio, and a urinary organic acid profile consistent with pyruvate carboxylase deficiency. The acquired enzymatic injury that results from inhibition of mitochondrial carbonic anhydrase V, which provides bicarbonate to pyruvate carboxylase, can damage the tricarboxylic acid cycle.

Four preterm neonates with posthemorrhagic ventricular dilatation developed severe metabolic acidosis after being given acetazolamide (12). The acidosis suddenly disappeared after a transfusion of packed erythrocytes, which was attributed to the citrate contained in the blood.

Acetazolamide can cause a metabolic acidosis in 50% of elderly patients (SEDA-11, 199); occasionally (particularly if salicylates are being given or renal function is poor) the acidosis can be severe. It does this by inhibiting renal bicarbonate reabsorption. This effect is of particular use in treating patients with chronic respiratory acidosis with superimposed metabolic alkalosis. Life-threatening metabolic acidosis is rarely observed in the absence of renal insufficiency and/or diabetes mellitus. In three patients with central nervous system pathology alone conventional doses of acetazolamide resulted in severe metabolic acidosis (13). After withdrawal it took up to 48 hours for the metabolic acidosis and accompanying hyperventilation to resolve.

Metabolic acidosis has also been described with the topical carbonic anhydrase inhibitor dorzolamide.

- A 5-day-old boy, weighing 2.3 kg, developed a metabolic acidosis after receiving topical dorzolamide for 1 week for bilateral Peter's anomaly (a congenital corneal disorder characterized by a central leukoma and adhesions at the periphery of the corneal opacity) (14). The maximum base deficit was 20.2 mmol/l. On withdrawal of topical dorzolamide his acidosis resolved within 1 day.

Factors that may have contributed to this metabolic acidosis included low birth weight, renal tubular immaturity, and impaired renal function, which may have resulted in systemic accumulation with repetitive dosing. This case stresses the fact that topical medications can cause systemic effects if a sufficient amount of drug is absorbed in a susceptible subject.

Hematologic

Aplastic anemia occurs in about one in 18 000 patient-years of exposure to oral carbonic anhydrase inhibitors. Most cases occur within the first 6 months, and peak at 2–3 months.

Eleven cases of acetazolamide-associated aplastic anemia were reported in Sweden during a 17-year period (15). The median dose was 500 mg/day and the median duration of therapy was 3 (2–71) months. Ten of the eleven patients died within 8 weeks of diagnosis. The relative risk of aplastic anemia with acetazolamide was 13.3 (95% CI = 6.8, 25) and the estimated frequency was 1 in 18 000. These findings suggest that acetazolamide is associated with a substantially increased risk of aplastic anemia.

However, the National Registry of Drug-Induced Ocular Side Effects has not received a report of blood dyscrasias in patients who have taken oral carbonic anhydrase inhibitors for less than 2 weeks (16). Since there is generally some time before abnormal blood counts progress to bone-marrow failure, seeking a symptomless "early window" is precisely the point of routine hematological screening; thus, patients taking long-term oral carbonic anhydrase inhibitors should have erythrocyte, leukocyte, and platelet counts bimonthly during the first 6 months of therapy and then every 6 months thereafter. Routine hematological surveillance should always be accompanied by patient education about warning signs and symptoms of progressive marrow failure.

Urinary tract

In a French analysis of 22 510 urinary calculi performed by infrared spectroscopy, drug-induced urolithiasis was divided into two categories: first, stones with drugs

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physically embedded ($n = 238$; 1.0%), notably indinavir monohydrate ($n = 126$; 53%), followed by triamterene ($n = 43$; 18%), sulfonamides ($n = 29$; 12%), and amorphous silica ($n = 24$; 10%); secondly, metabolic nephrolithiasis induced by drugs ($n = 140$; 0.6%), involving mainly calcium/vitamin D supplementation ($n = 56$; 40%) and carbonic anhydrase inhibitors ($n = 33$; 24%) (17). Drug-induced stones are responsible for about 1.6% of all calculi in France. Physical analysis and a thorough drug history are important elements in the diagnosis.

Skin

Two Japanese-American women developed clinical features that satisfied the criteria for Stevens–Johnson syndrome during methazolamide treatment (18). Methazolamide is a sulfonamide, the most common group of drugs associated with Stevens–Johnson syndrome.

Topical dorzolamide caused severe periorbital dermatitis after an average exposure time of 20 weeks in 14 patients (19). Although dermatitis due to dorzolamide can resolve when it is withdrawn, this does not always occur, and in some patients all topical medications containing benzalkonium chloride must be withdrawn. Allergic contact blepharoconjunctivitis has also been reported with dorzolamide in a 72-year-old man (20).

Musculoskeletal

Chronic acetazolamide therapy is associated with greater spinal bone mineral density. This is probably the result of metabolic acidosis; urine calcium is increased and serum phosphate reduced. Osteomalacia has been reported during long-term therapy in combination with barbiturates in two patients.

Immunologic

Fatal anaphylactic shock with massive pulmonary edema has been reported in a 66-year-old woman who was taking acetazolamide for glaucoma (21). She had a history of sulfonamide allergy, and acetazolamide is a sulfonamide derivative. Sulfonamide allergy should be regarded as a contraindication to acetazolamide.

- Non-fatal anaphylactic shock with acute pulmonary edema has been reported in a 79-year-old woman after a first dose of acetazolamide (22). There was no history of sulfonamide allergy and she had been taking hydrochlorothiazide for some time.

Anaphylactic shock with acetazolamide should be recognized to occur as a first-dose phenomenon with no prior demonstrable sulfonamide allergy.

Long-Term Effects

Drug tolerance

Acetazolamide alkalinizes the urine and increases its volume. Urinary sodium, potassium, and bicarbonate concentrations rise, and chloride concentration falls. These effects are due to inhibition of carbonic anhydrase in the nephron, mainly in the proximal convoluted tubule, which reduces the number of protons available for Na/H antiporter exchange. Consequently, the concentration of bicarbonate in extracellular fluids falls, causing a metabolic acidosis, which itself limits the diuretic response to acetazolamide. Thus, the initial kaliuretic effect is lost within a few weeks.

Second-Generation Effects

Teratogenicity

Possible teratogenicity due to acetazolamide resulted in one case of congenital glaucoma, microphthalmia, and patent ductus arteriosus and one case of sacrococcygeal teratoma. One child was born with acidosis, hypercalcemia, and hypomagnesemia; these features resolved rapidly, but at 8 months there was mild hypotonicity of the legs. It has been suggested that acetazolamide should be avoided in the first trimester of pregnancy (SEDA-21, 228).

Fetotoxicity

The use of acetazolamide in pregnancy is ill-advised.

- Renal tubular acidosis occurred in a preterm boy shortly after birth (23). His mother had taken oral acetazolamide during pregnancy for glaucoma. When renal tubular acidosis developed, acetazolamide was detected in his serum, demonstrating transplacental passage of acetazolamide.

Susceptibility Factors

Carbonic anhydrase inhibitors should be used with caution in patients with respiratory acidosis or those with severe loss of respiratory capacity, and in patients with diabetes mellitus. They are contraindicated in patients with hepatic disease or insufficiency, reduced serum concentrations of sodium or potassium, adrenocortical insufficiency, hyperchloremic acidosis, or severe renal disease or dysfunction. They should also be avoided in patients taking salicylates.

Drug Administration

Drug administration route

Brinzolamide eye-drops can cause transient blurred vision (24).

Dorzolamide eye-drops can cause irreversible corneal edema in glaucoma patients with endothelial compromise (25).

Drug overdose

Overdosage with acetazolamide can destroy the gastric mucosal barrier, by interfering with prostaglandin and bicarbonate release, and can cause thrombocytopenia by bone marrow suppression, eventually leading to hemorrhagic gastritis. Although acetazolamide binds strongly to plasma proteins, and clearance by hemodialysis is generally poor, this approach and hemoperfusion (without heparin) appears to be effective (SEDA-22, 236).

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Acetazolamide overdose has been reported in a child.

- A 12-month-old girl, weighing 10 kg, developed metabolic acidosis after taking 500–1250 mg of acetazolamide (26). The maximum base deficit recorded was 11.6. She was treated with sodium bicarbonate and recovered completely.

Accidental poisoning with acetazolamide should be included in the differential diagnosis of metabolic acidosis.

Drug–Drug Interactions

Furosemide

Acetazolamide inhibits cerebrospinal fluid production, and its effects are augmented by furosemide, suggesting a role for this combination in infants with ventricular dilatation resulting from severe periventricular hemorrhage. The International Posthaemorrhagic Ventricular Drug Trial Group has reported the results of a randomized, controlled trial of standard therapy alone or with the addition of acetazolamide plus furosemide in the first 151 of 177 randomized patients (27). The addition of acetazolamide plus furosemide was not only ineffective but also worsened the already poor outcome in these infants. At 1 year, death and the need for shunt placement were substantially commoner in the diuretic-treated group. There were adverse events (for example acidosis, nausea, anorexia, and diarrhea) in 37% of those given acetazolamide plus furosemide; in addition, 27% developed nephrocalcinosis (SEDA-21, 228). Altered cerebral blood flow due to acetazolamide may have caused additional brain injury.

In a commentary on this trial (28) it was pointed out that the use of acetazolamide alone or with furosemide in the treatment of posthemorrhagic hydrocephalus is another example of the use of untried therapy in neonatal care. The safety and efficacy of acetazolamide in children has never been established.

Salicylate

Two elderly patients developed lethargy, confusion, and incontinence, attributed to an interaction between acetazolamide and salicylate (29). Salicylate may reduce acetazolamide clearance by inhibiting its renal tubular secretion. Analgesic doses of salicylates should probably be avoided in elderly patients taking acetazolamide.

- A 50-year-old woman with chronic renal insufficiency treated with acetazolamide for simple glaucoma developed confusion, cerebellar ataxia, and metabolic acidosis 2 weeks after starting to take aspirin for acute pericarditis (30). A diagnosis of salicylism was made despite low serum salicylate concentrations.

The authors suggested that acetazolamide-induced acidosis increases the concentration of the unionized form of salicylate, which crosses membranes more rapidly, and hence explains the cerebral toxicity associated with low serum concentrations of salicylate. However, an increase in the plasma or erythrocyte concentrations of acetazolamide (not measured) is a much more convincing explanation for this patient's symptoms.

Other Environmental Interactions

Ketogenic diet

A ketogenic diet is sometimes used to control intractable seizures. Acetazolamide should be discontinued before starting the diet, because of the potential risk of severe secondary metabolic acidosis (31). Acetazolamide can be reintroduced once the acid–base status of the patient has stabilized.

Interference with Diagnostic Tests

HPLC assays for theophyline

Acetazolamide interferes with certain HPLC assays for theophylline, leading to spuriously increased theophylline concentrations (SEDA-21, 228).

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Carboprost

See also Prostaglandins

General Information

Carboprost is a 15-methylated analogue of $PGF_{2\alpha}$. It is used in termination of pregnancy, in the management of labor, and to treat postpartum hemorrhage and uterine atony.

Organs and Systems

Respiratory

Pulmonary edema has been attributed to carboprost (1).

- An 18-year-old woman at 37 weeks gestation was given prostaglandin E_2 gel for cervical ripening followed by oxytocin. After delivery by cesarean section uterine atony, which did not respond to oxytocin and methylergometrine maleate, was treated with intramyometrial 15-methyl-prostaglandin $F_{2\alpha}$ 0.25 mg. After 5 minutes, her SpO_2 fell to 89 and she had dyspnea and sinus tachycardia due to acute pulmonary edema.

Gastrointestinal

Vomiting is a common adverse effect of $PGF_{2\alpha}$ (2).

Reproductive system

Uterine rupture has been reported after intramuscular injection of carboprost to terminate a mid-trimester pregnancy (3).

Drug Administration

Drug overdose

A neonate was accidentally given a large dose of carboprost and recovered (4).

- A full-term neonate was accidentally given carboprost 250 μg intramuscularly in an error for hepatitis vaccine. Within 15 minutes, he became tachypneic and hypertensive and then developed bronchospasm and dystonic movements and/or seizure activity in the arms. He was hyperthermic and had diarrhea. He recovered within 18 hours.

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Cardiac glycosides

General Information

Many aspects of the pharmacology, clinical pharmacology, and adverse effects and interactions of cardiac glycosides have been reviewed (1–12).

Note on nomenclature

The most commonly used cardiac glycosides, digoxin and digitoxin, are derived from foxgloves, respectively *Digitalis lanata* and *Digitalis purpurea*. For this reason they are generally known as "digitalis." Most other cardiac glycosides, such as ouabain and proscillaridin, do not come from foxgloves but are nevertheless also commonly called "digitalis." Thus, the terms "cardiac glycoside" and "digitalis" are used interchangeably.

The cardiac glycosides that have been used therapeutically are listed in Table 1.

Mechanisms of digitalis toxicity

There is a large amount of evidence that the mechanisms of action of cardiac glycosides are mediated directly or indirectly by inhibition of the sodium/potassium pump enzyme, Na/K-ATPase (13). Their toxic effects on the myocardium may be due to excessive inhibition of cardiac Na/K-ATPase, although there is also evidence that effects on the nervous input to the heart may be involved (14), and it is not clear to what extent such an effect is mediated by inhibition of Na/K-ATPase. However, color vision disturbances associated with cardiac glycosides are due to inhibition of Na/K-ATPase (15).

Table 1 Cardiac glycosides that have been used therapeutically

Drug	Source	Main route of elimination
Acetyldigoxin	Semisynthetic derivative of digoxin	Renal
Digitoxin	*Digitalis purpurea*	Hepatic
Digoxin	*Digitalis lanata*	Renal
Gitoformate	*Digitalis purpurea*	Hepatic
Gitoxin	*Digitalis purpurea*	Hepatic
Lanatoside C	*Digitalis lanata*	Renal
Metildigoxin (betamethyldigoxin)	Semisynthetic derivative of digoxin	Hepatic/ renal
Ouabain (strophanthin-g)	*Strophanthus gratus, Acokanthera schimperi, Acokanthera ouabaio*	Renal
Peruvoside	*Nerium peruviana*	Hepatic
Proscillaridin	*Drimia maritima*	Hepatic
Strophanthin-k	*Strophanthus kombe*	Renal

Epidemiology of digitalis toxicity

Digitalis toxicity is common, since all cardiac glycosides have a low therapeutic index. Estimates vary widely from study to study, but in large prospective studies of hospital inpatients the frequency of digitalis toxicity has been as high as 29% (16). In outpatients the figure may be as high as 16% (7). The lower frequency in outpatients may be due partly to poor compliance and partly to digitalis toxicity being a reason for admission to hospital, thus increasing the numbers of toxic inpatients. The risk of toxicity may be lower with digitoxin than with digoxin (4), but when toxicity occurs it lasts longer, because of the very long half-life of digitoxin.

The overall mortality from digitalis toxicity also varies widely, having been reported as low as 4% and as high as 36% (7). However, it varies with dysrhythmias, and for paroxysmal supraventricular tachycardia with block may be as high as 50% (7).

In a study of serum digoxin concentrations in 1433 patients admitted to hospital, 115 had a raised concentration (17). Of the 82 in whom the blood sample had been taken at an appropriate time, 59 had electrocardiographic or clinical features of digoxin toxicity. The patients whose serum digoxin concentrations were over 3.2 nmol/l (2.5 ng/ml) were slightly older (78 versus 73 years) and had higher serum creatinine concentrations (273 versus 123 μmol/l) than those whose plasma concentrations were below 3.1 nmol/l. Of 47 patients with raised digoxin concentrations on admission, 21 were admitted because of digoxin toxicity, and impaired or worsening renal function contributed to high concentrations in 37 patients. A drug interaction was a contributory factor in 10 cases. These results suggest that digoxin toxicity is still very common and confirms the increased risk in elderly patients, patients with renal impairment, and patients taking drugs that may interact with digoxin. Serum potassium concentrations were not reported in this study.

In another study of this sort, serum digoxin concentrations were measured in 2009 patients (18). The concentration was over 2.6 nmol/l in 320 cases (9.3%) but in 51 of those the sample had been drawn too soon after the dose. When other results were omitted in cases in which the sampling time was not known, there were 138 evaluable patients, of whom 83 had clinical evidence of digoxin toxicity, an overall incidence of 4.1%. The authors concluded that digoxin toxicity was less common in their series than has previously been reported. There were no differences between the groups in serum potassium, calcium, or magnesium concentrations, but the serum creatinine concentration was significantly higher in those who had definite and possible toxicity. The mean age of the patients was 69 years. It is likely that the differences across studies of this sort are largely due to differences in renal function and age in the population being studied.

In a multicenter survey, conducted between 1988 and 1997, of 28 411 patients aged 70 (s.d. 16) years admitted to

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81 hospitals throughout Italy, 1704 had adverse drug reactions (19). In 964 cases (3.4% of all admissions), adverse reactions were considered to be the cause of admission. Of these, 187 were regarded as severe. Gastrointestinal complaints (19%) were the most common, followed by metabolic and hemorrhagic complications (9%). The drugs most often responsible were diuretics, calcium channel blockers, non-steroidal anti-inflammatory drugs, and digoxin. Female sex (OR = 1.30; 95% CI = 1.10, 1.54), alcohol use (OR = 1.39; 95% CI = 1.20, 1.60), and number of drugs (OR = 1.24; 95% CI = 1.20, 1.27) were independent predictors of admission for adverse reactions. For severe adverse reactions, age (for age 65–79, OR = 1.50; 95% CI = 1.01, 2.23; for age 80 and over, OR = 1.53; 95% CI = 1.00, 2.33), co-morbidity (OR = 1.12; 95% CI = 1.05, 1.20 for each point on the Charlson Comorbidity Index), and number of drugs (OR = 1.18; 95% CI = 1.11, 1.25) were predisposing factors. Of the 28 411 patients, about 6700 were taking digoxin, and they suffered 82 adverse effects, either gastrointestinal ($n = 28$) or unspecified dysrhythmias ($n = 44$), or presumably both (data not given); of those, 11 were graded as severe (two gastrointestinal and nine dysrhythmias).

Of 603 adults aged 79 years, of whom 59% were women and 18% African-American, 376 patients (62%) were discharged taking digoxin, and 223 (37%) had no indication for its use, based on the absence of left ventricular systolic dysfunction or atrial fibrillation (20). After adjustment for various factors, prior digoxin use (OR = 11; 95% CI = 5.7, 23) and pulse over 100/minute (OR = 2.33; 95% CI = 1.1, 4.9) were associated with inappropriate digoxin use. Unfortunately, the authors did not report the frequency of adverse effects, and it is not therefore clear whether patients in whom digoxin is used inappropriately are more or less likely to suffer adverse reactions.

General adverse effects

The adverse effects of cardiac glycosides can be cardiac or non-cardiac. They mostly occur through toxicity and are time-independent (DoTS classification); susceptibility factors include electrolyte abnormalities (particularly hypokalemia), renal insufficiency, and age.

Frequent non-cardiac reactions include gastrointestinal effects (anorexia, nausea, vomiting, and diarrhea), central nervous system effects (drowsiness, dizziness, confusion, delirium), and less commonly visual effects (color vision abnormalities, photophobia, and blurred vision). Hypersensitivity reactions are rare and include thrombocytopenia and skin rashes. Tumor-inducing effects have not been reported.

Frequent cardiac adverse effects include heart block and ectopic dysrhythmias (ventricular extra beats, other ventricular tachydysrhythmias, and paroxysmal supraventricular tachycardia). The combination of heart block with an ectopic dysrhythmia, for example paroxysmal supraventricular tachycardia with block, is particularly suggestive of toxicity due to cardiac glycosides. Any other dysrhythmia can occasionally be caused by cardiac glycosides.

Of 332 residents of a nursing home, 52 had to be admitted to hospital because of adverse drug reactions (21). The drugs most commonly associated with adverse effects were non-steroidal anti-inflammatory drugs ($n = 30$), psychotropic drugs ($n = 14$), and digoxin ($n = 5$).

Individual cardiac glycosides

There are major pharmacokinetic differences among the different cardiac glycosides, the principal difference being between those that are mainly excreted via the kidneys (for example digoxin, metildigoxin, beta-acetyldigoxin, ouabain, and k-strophanthin) and those that are mainly excreted via hepatic metabolism (including digitoxin, gitoxin, pengitoxin (16-acetyldigoxin), and gitoformate).

It has also been suggested that there may be some pharmacodynamic differences among different cardiac glycosides (22), but these may at least partly be determined by differences in tissue distribution.

It is debatable whether any of these differences makes any particular cardiac glycoside preferable to another. The most strongly argued case is that digitoxin is preferable to digoxin in patients with renal insufficiency, since digitoxin is metabolized and digoxin is excreted by the kidneys. However, digitoxin has a much longer duration of action, and if toxicity occurs it will take longer to resolve. Furthermore, determining the effective dose of digitoxin is much more difficult, since there is great interindividual variability in the extent to which digitoxin is metabolized, and hepatic metabolic function cannot be directly measured. Although digoxin excretion also varies from patient to patient, it can at least be gauged by measurement of creatinine clearance. The arguments for and against these preferences have been outlined (4,23) and it is probably best to choose a particular drug according to individual patient requirements.

Herbal formulations

Numerous plants worldwide contain cardiac glycosides that have been used both therapeutically as herbal formulations and for the purposes of self-poisoning. Details are given in Table 2.

- A 59-year-old man developed third-degree atrioventricular block after using an extract of *Nerium oleander* transdermally to treat psoriasis (24). A fatality due to drinking a herbal tea prepared from *N. oleander* leaves, erroneously believed to be eucalyptus leaves, has been reported (25).

Poisoning from ingestion of the seeds of *Thevetia peruviana* (yellow oleander) can be treated with oral multiple-dose activated charcoal (26).

In a Turkish case, the ingestion of two bulbs or *Urginea maritima* as a folk remedy for arthritic pains was sufficient to result in fatal poisoning (27).

Organs and Systems

Cardiovascular

Cardiac dysrhythmias and heart block

Percentage incidence figures for digitalis-induced dysrhythmias were given by Chung in his review of 726 patients (5). The commonest dysrhythmias are ventricular extra beats (54% of all dysrhythmias), coupled ventricular

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Table 2 Some plants that contain cardiac glycosides

Plant	Common name(s)	Cardiac glycoside(s)	Comments
Adonis vernalis	False hellebore, pheasant's eye	Adonitoxin, strophanthidin	
Antiaris toxicaria	Upas tree	Antiarin	A Javanese tree of the mulberry family, used as an arrow poison
Convallaria majalis	Lily of the valley	Convallamarin	
Erysimum helveticum	Wallflower	Helveticoside	
Helleborus niger	Black hellebore, Christmas rose	Helleborcin	Also called melampodium after the Greek physician Melampus, who used it as a purgative
Nerium oleander	Pink oleander	Neriifolin	
Periploca graeca	Silk vine	Periplocin	
Tanghinia venenifera	Ordeal tree	Tanghinin	At one time used in Madagascar to test the guilt of someone suspected of a crime
Thevetia peruviana	Yellow oleander	Peruvoside, thevetins	Seeds widely used for self-poisoning in Southern India and Sri Lanka
Urginea (Scilla) maritima	Squill	Proscillaridin	Squill was a common remedy for dropsy in ancient times and up to the 19th century

extra beats (25%), and supraventricular tachycardia (33%). Sinus tachycardia was not common (3.4%). Atrial fibrillation (1.7%) or atrial flutter (1.8%) can cause difficulty in diagnosis, since digitalis is often used to treat those dysrhythmias.

Atrioventricular block was common (42%): first-degree, 14%; second-degree, 17%; and complete, 11%). However, first-degree heart block (that is prolongation of the PR interval) without higher degrees of atrioventricular nodal block can occur in the absence of digitalis intoxication.

Digitalis-induced dysrhythmias can be classified according to their sites of origin in the sinus node, the atria and atrioventricular node, and the ventricles.

Sinoatrial node

Digitalis can cause sinus bradycardia as a toxic effect, although patients with sinus bradycardia at rest often have no other evidence of digitalis toxicity, and this effect may simply represent increased vagal tone (28). Digitalis inhibits conduction through the sinoatrial node and has been reported to cause a syndrome mimicking that of the sick sinus syndrome (29–31); however, it is not clear whether or not it can impair sinus node function in patients who have previously normal sinoatrial nodes (32,33). Digitalis can certainly worsen sinus node function that has been otherwise impaired, for example by hyperthyroidism (34) or endotracheal suction (35).

Atria and atrioventricular node

Digitalis can cause supraventricular extra beats or tachycardia. The combination of such dysrhythmias with atrioventricular block is particularly suggestive of digitalis toxicity and carries a high mortality rate (3,36). Rarely atrial fibrillation (37) and atrial flutter (38) may be attributed to digitalis toxicity. The frequency of atrioventricular nodal block is mentioned above.

Paroxysmal atrial tachycardia with Wenckebach (Mobitz type I) atrioventricular block has been reported in a patient with a serum digoxin concentration of 3.2 ng/ml (39) and in a patient who in error took three times the recommended dose (40).

Ventricles

Ventricular extra beats, including coupled beats (that is ventricular bigeminy), are the most common cardiac effects of digitalis toxicity, although they are not specific. In more severe cases ventricular tachycardia, bidirectional tachycardia, and ventricular fibrillation can occur. There have also been reports of accelerated idioventricular rhythm (41,42).

Digoxin can cause ventricular fibrillation in children with Wolff–Parkinson–White syndrome (43,44).

- A male infant, whose narrow-complex tachycardia at birth had responded to adenosine, was treated with digoxin and 1 week later, during transesophageal electrophysiology with isoprenaline, developed coarse ventricular fibrillation after the induction of a supraventricular tachycardia (45). The serum digoxin concentration was not measured. The isoprenaline was withdrawn and the dysrhythmia resolved spontaneously at 160 seconds.

The effects of digoxin, isoprenaline, and transesophageal stimulation may have combined in this case to cause ventricular fibrillation.

Effects of digitalis on the electrocardiogram

Digitalis can prolong the PR interval and cause shortening of the QT interval, depression of the ST segment, and asymmetrical T wave inversion. These effects are non-specific and can occur in the absence of toxicity. However, there is evidence that the effects on the ST segment and T wave may be more common in patients with co-existing ischemic heart disease (46). Digitalis can also rarely cause both left (47) and right (48) bundle branch block.

The electrocardiographic effects of cardiac glycoside toxicity in 688 patients have been reviewed in the context of three cases of digoxin toxicity (49). The three cases featured bidirectional tachycardia in a 50-year-old man with a plasma digoxin concentration of 3.7 ng/ml, junctional tachycardia in a 59-year-old man with a plasma digoxin concentration of 4.3 ng/ml, and complete heart block in a 90-year-old woman whose postmortem digoxin concentration was 5.0 ng/ml.

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Heart failure

In toxic doses digitalis impairs myocardial contractility and can cause or worsen heart failure. In one series of 148 patients with digitalis intoxication, worsening heart failure was diagnosed in 7.5% (50). In some cases worsening heart failure may be attributable to a cardiac dysrhythmia (51).

Vasoconstrictor and hypertensive effects

Giving a cardiac glycoside rapidly intravenously causes a transient increase in blood pressure, which has been attributed to an increase in peripheral resistance (52). However, digitalis does not seem to increase blood pressure during long-term treatment.

Myocardial ischemia

Subacute digitalis intoxication in dogs causes myocardial damage (53), and after intravenous administration there is increased creatine kinase activity in the plasma in man (54), suggesting ischemic damage.

There has been a report of coronary vasoconstriction in patients who were given acetyldigoxin 0.8 mg intravenously at angiography (55). Pretreatment with nisoldipine 10 mg, 2 hours before angiography, prevented the digoxin-induced vasoconstriction. These patients all had pre-existing coronary artery disease, but the vasoconstrictor effect occurred in both normal and abnormal coronary segments. However, the effect on high-grade stenoses was more pronounced. There is other evidence that ischemic damage can occur in patients who have been given digoxin intravenously, including an increase in the activity of serum creatinine kinase (54) and impaired left ventricular function after acute myocardial infarction (56).

- A 26-year-old woman who had taken a herbal supplement for stress relief which contained *Scutellaria lateriflora*, *Pedicularis canadensis*, *Cimifuga racemosa*, *Humulus lupulus*, *Valeriana officinalis*, and *Capsicum annuum* developed chest pain of 7 hours duration (57). Her medical history was otherwise unremarkable. Examination of her heart showed no abnormality, but during monitoring her heart rate fell to 39/minute and her blood pressure to 59/36 mmHg. Her serum digoxin concentration was 0.9 ng/ml. The authors therefore concluded that the herbal remedy contained digoxin-like factors that had caused digitalis toxicity.

Long-term use and cardiovascular adverse effects of cardiac glycosides

There have been many studies of the long-term efficacy of digitalis in patients in heart failure in sinus rhythm and also in patients with atrial fibrillation. These have been reviewed (SEDA-4, 123) (SEDA-14, 145) (SEDA-18, 196). The following is a brief resumé.

Atrial fibrillation is not necessarily an indication for long-term therapy with digitalis. In patients with controlled atrial fibrillation whose plasma digitalis concentration is below the lower limit of the target range (0.8 ng/ml for digoxin and 10 ng/ml for digitoxin) withdrawal rarely if ever results in deterioration. However, in those who have plasma digitalis concentrations within the target range withdrawal should not be attempted, since the risk of worsening atrial fibrillation outweighs the risk of toxicity, if there is careful monitoring of the plasma concentration.

In patients with heart failure in sinus rhythm there is no way of predicting which patients will benefit from long-term therapy, but the following recommendations can be made:

1. If the plasma digitalis concentration is below the therapeutic range (0.8 ng/ml for digoxin and 10 ng/ml for digitoxin) withdrawal is very unlikely to produce deterioration.
2. If a patient's condition is stable, and the plasma digitalis concentration is in the therapeutic range, with little risk of toxicity, withdrawal is probably not worthwhile because of the risk of deterioration.
3. If there is an increased risk of toxicity (for example because of renal impairment or if potassium balance is difficult to maintain) careful withdrawal of digitalis may be worth attempting.
4. In patients who have evidence of poor left ventricular function it may be better to continue therapy, even if there is an increased risk of toxicity, since these patients are very likely to deteriorate following withdrawal. In these cases careful monitoring of therapy will help to reduce the risk of toxicity.

The long-term adverse cardiovascular effects of digitalis have been reviewed (SEDA-10, 142) (SEDA-11, 153) (SEDA-15, 165). Briefly, in a number of retrospective studies, although mortality in the digitalis-treated patients was generally higher than in those not treated with digitalis, the difference was reduced when allowance was made for other confounding factors, such as the degree of heart failure, a history of dysrhythmias, and the use of other drugs. There may also be a higher mortality rate in patients who take long-term digitalis therapy after coronary artery bypass graft surgery (58), in patients who have had a cardiac arrest (59), and in those without evidence of heart failure or atrial fibrillation (60). In the first two studies the risk was increased further among those who were taking digitalis with diuretics, and it may be that these effects are due to digitalis toxicity secondary to potassium depletion, although it may simply indicate a greater prevalence of hypertension or heart failure among those treated with digitalis and diuretics.

Despite these earlier results, in the Digitalis Investigation Group (DIG) study (61) digoxin had no overall impact on mortality in patients with heart failure in sinus rhythm and with left ventricular ejection fractions equal to or less than 0.45.

It produced a small reduction in hospitalizations due to heart failure (nine per 1000 patients-years) balanced by a significant increase in deaths from presumed dysrhythmias. Digitalis is therefore indicated for a small number of patients who have severe heart failure associated with sinus rhythm after treatment with diuretics, vasodilators, beta-blockers, and spironolactone. It remains the drug of first choice in patients with heart failure accompanied by fast atrial fibrillation, especially if due to myocardial or mitral valve disease. A trial of withdrawal of digitalis therapy can be considered in some cases (as noted in point 3 above).

Of course, there are alternatives to digitalis in the long-term treatment of heart failure in sinus rhythm. It is not

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clear that any of these offers any particular advantage over digitalis in terms of therapeutic efficacy, although there may be fewer problems with toxicity. The comparative studies have been reviewed (SEDA-14, 141).

Sinus rhythm

The question of whether digoxin should be used to treat patients with mild to moderate heart failure in sinus rhythm, in the wake of randomized, controlled trials of its efficacy, including PROVED, RADIANCE, and DIG (SEDA-18, 196) (SEDA-20, 173), has been reviewed (62). The authors concluded that digoxin is effective in producing symptomatic improvement in patients with mild or moderate heart failure, but that because of concerns about its safety careful consideration must be taken in each case before using it.

Other positive inotropic drugs carry no extra benefit, and can increase mortality during long-term administration. There is no evidence that the combination of two drugs with positive inotropic actions is beneficial in chronic congestive heart failure. Vasodilators are as efficacious as digitalis, but there is a rationale for combining digitalis and a vasodilator, since by doing so it is possible to affect simultaneously the three important factors determining cardiac output (contractility, pre-load, and afterload). Furthermore, a vasodilator will oppose the small effect that digitalis has in increasing peripheral resistance, and which may reduce the beneficial effect of digitalis on cardiac output.

Of 2254 elderly patients, 724 were being treated with digoxin, of whom 187 had congestive heart failure, 90 had atrial fibrillation, and 447 were both free from heart failure and in sinus rhythm (60). Among those who did not have heart failure or atrial fibrillation, cardiovascular and total mortality were significantly higher among those taking digoxin. Digoxin was a predictor of mortality in those subjects. In addition, the incidence of non-fatal heart failure was higher among those taking digoxin. This is yet another non-randomized study purporting to show deleterious effects of digoxin during long-term use, in this case in patients in whom it was not indicated in the first place. Since similar non-randomized studies in patients with heart failure, which also showed deleterious effects (SEDA-20, 173), have since been contradicted by proper prospective randomized studies, this result should be ignored.

Atrial fibrillation

In uncomplicated atrial fibrillation a cardiac glycoside such as digoxin remains the drug of first choice. However, in those in whom digitalis is not completely effective or in whom symptoms (for example bouts of palpitation) persist despite adequate digitalization, a calcium antagonist, such as verapamil or diltiazem, can be added, or amiodarone used as an alternative. In patients with atrial fibrillation due to hyperthyroidism, a beta-adrenoceptor antagonist should be used in preference to digitalis, but digitalis can be added if there is an incomplete effect. In patients with atrial fibrillation secondary to an anomalous conduction pathway (for example Wolff–Parkinson–White syndrome), in most of whom digitalis is contraindicated, a calcium antagonist would be the treatment of choice. Paroxysmal atrial fibrillation generally does not respond to digitalis, and digitalis may in fact prolong the duration of a paroxysmal attack when it occurs. The treatment of paroxysmal atrial fibrillation is problematic, but many use amiodarone. Sotalol, propafenone, and flecainide are options, but there are doubts about the long-term safety of flecainide and sotalol, particularly in those who have had an acute myocardial infarction.

There has been a multicenter, randomized, placebo-controlled, double-blind comparison of aprindine and digoxin in the prevention of atrial fibrillation and its recurrence in 141 patients with symptomatic paroxysmal or persistent atrial fibrillation who had converted to sinus rhythm (63). They were randomized in equal numbers to aprindine 40 mg/day, digoxin 0.25 mg/day, or placebo, and were followed every 2 weeks for 6 months. After 6 months the Kaplan-Meier estimates of the numbers of patients who had no recurrences while taking aprindine, digoxin, and placebo were 33%, 29%, and 22% respectively. The rates of adverse events were similar in the three groups. This confirms that digoxin does not prevent relapse of symptomatic atrial fibrillation after conversion to sinus rhythm.

Cardioversion and digitalis

The presence of digitalis increases the risk of serious dysrhythmias after electrical cardioversion, even in the absence of frank toxicity (64). In order to minimize the risk of dysrhythmias in these circumstances digitalis should be withdrawn if possible a day or two before cardioversion and potassium depletion should be corrected. If cardioversion is required acutely, it has been recommended that low energies (for example 10 J) should be used initially (65).

Nervous system

Toxic effects of digitalis on the nervous system occur relatively often. Although in severe toxicity the incidence may be as high as 65% (66), in most series it has been below 25% (67).

Anorexia, nausea, and vomiting are mediated by the central nervous system. Other common nervous system effects of digitalis include confusion, dizziness, drowsiness, bad dreams, restlessness, nervousness, agitation, and amnesia.

Epilepsy occurs rarely and can be accompanied by electroencephalographic changes (68–70).

Other reported effects include transient global amnesia (71), trigeminal neuralgia (72,73), nightmares (74), organic brain syndrome (including impairment of long-term and short-term memory) (75), impairment of learning and memory (23), and a clinical syndrome resembling herpes encephalitis (76).

- Progressive stupor has been reported in an 85-year-old woman with mild renal insufficiency who was given digoxin 0.25 mg/day (77). The plasma digoxin concentration was 7.8 nmol/l. She recovered within 2 weeks after digoxin withdrawal, consistent with the likely half-life of digoxin. A 24-hour electrocardiogram showed one period of asystole for 4 seconds, but that is unlikely to have explained her symptoms.

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Chorea has occasionally been reported in adults taking digitalis (SEDA-13, 138) (78), and also in a child (79).

- A 7-year-old girl with severe congenital heart disease who was given digoxin 0.125 mg bd developed chorea and had a serum digoxin concentration of 3.8 ng/ml. When digoxin was withheld and the serum concentration fell to 1.5 ng/ml her symptoms resolved. They recurred 4 days after rechallenge when her digoxin concentration was 2.5 mg/ml and again resolved after it had fallen to 1.3 mg/ml.

The authors hypothesized that digoxin caused chorea by virtue of an estrogenic effect in the basal ganglia, similar to the effect that is occasionally produced by oral contraceptives.

Sensory systems

Color vision abnormality is a well-known adverse effect of digitalis (SEDA-20, 173), and particularly occurs in patients with digitalis toxicity.

There have been two cases of digoxin-related visual disturbances in patients whose blood concentrations were in the usual target range (319).

- A 68-year-old woman had shimmering lights in her field of vision in both eyes when in sunlight, and a 63-year-old woman complained of blurring of vision in both eyes. The serum digoxin concentrations were 2.2 and 1.3 nmol/l (1.7 and 1.0 ng/ml) respectively. Withdrawal of digoxin caused resolution of their symptoms within 1–2 weeks.

Unfortunately the authors did not report serum electrolyte concentrations, and it is not clear in these cases whether the effect of digoxin was potentiated by potassium depletion.

In 30 patients (mean age 81 years) taking digoxin and an age-matched control group there was no correlation between color vision impairment and serum digoxin concentration (80). There was slight to moderate red-green impairment in 20–30% of those taking digoxin, depending on the test used; about 20% had a severe tritan defect. The authors suggested that color vision testing in elderly patients would have limited value in the detection of digitalis toxicity. However, this conclusion was based on using the digoxin concentration as a standard, while the point of pharmacodynamic tests, such as color vision measurement, is that they are supposed to reflect the effect of the drug better than the serum concentration.

Psychological, psychiatric

Acute psychosis and delirium can occur in digitalis toxicity, particularly in elderly people (81–83), and can be accompanied by visual or auditory hallucinations (84,85).

- Acute delirium occurred in a 61-year-old man whose serum digitoxin concentration was 44 ng/ml (86).

Digitalis toxicity can occasionally cause depression (87).

- A 77-year-old woman developed extreme fatigue, anorexia, psychomotor retardation, and social withdrawal 1 month after starting to take digoxin 0.5 mg/day for congestive heart failure (88). She did not respond to intravenous clomipramine 25 mg/day for 7 months. Her serum digoxin concentration was 3.2 ng/ml. Digoxin was withdrawn, and 12 days later, when her serum digoxin concentration was 0.5 ng/ml, she had improved, but was left with a memory disturbance, which was attributed to background dementia.

Endocrine

Digitalis has effects on sex hormones. It causes increased serum concentrations of follicle-stimulating hormone (FSH) and estrogen and reduced concentrations of luteinizing hormone (LH) and testosterone (89–92). These effects are probably not related to any direct estrogen-like structure of digitalis (despite structural similarities), but rather to an effect involving the synthesis or release of sex hormones. There are three possible clinical outcomes of these effects.

Gynecomastia in men and breast enlargement in women

Effects of cardiac glycosides in the breasts can be associated with demonstrable histological changes (93,94).

Stratification of the vaginal squamous epithelium in postmenopausal women

This can cause difficulty in the pathological interpretation of vaginal smears for cancer diagnosis (95).

A possible modifying effect on breast cancer

Digitalis can reduce the heterogeneity of breast cancer cell populations and reduce the rate of distant metastases (96). There is also evidence that the 5-year recurrence rate after mastectomy is lower in women who have been treated with digitalis (97). Early studies suggested that when breast tumors occurred in women with congestive heart failure taking cardiac glycosides, tumor size was significantly smaller and the tumor cells more homogeneous (SEDA-7, 194). It was originally thought that this action was due to an estrogen-like effect of cardiac glycosides, but more recent evidence suggests that it occurs because inhibition of the Na/K pump is involved in inhibiting proliferation and inducing apoptosis in various cell lines (98–101). Cardiac glycosides have different potencies in their effects on cell lines such as those of ovarian carcinoma and breast carcinoma (order of potency: proscillaridin A > digitoxin > digoxin > ouabain > lanatoside C) (102).

Metabolism

In three patients with diabetes mellitus, withdrawal of digoxin improved blood glucose control, implying that digoxin had impaired glucose tolerance (103). The authors conceded that the effect might have occurred coincidentally, but in one case glucose tolerance deteriorated again after rechallenge. Insulin increases the cellular uptake of glucose and stimulates the sodium/potassium pump, and it may be that inhibition of the sodium/potassium pump by digoxin has the opposite effect.

In 14 patients with morbid obesity, who were being given digoxin in the hope that reduced production of cerebrospinal fluid, with the consequent reduction in pressure, might be associated with weight reduction, the dosage of digoxin (Lanacrist 0.13 mg, equivalent to 0.065 mg of digoxin) was titrated to produce a minimum serum digoxin concentration of 1.0 nmol/l (104). One patient was already diabetic, and five developed fasting

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blood glucose concentrations greater than 5.0 mmol/l on three consecutive occasions, with accompanying glycosuria. Another had fasting blood glucose concentrations of 6.0–8.5 mmol/l. There was a significant relation between the dose of digoxin and the risk of impaired glucose tolerance. However, the diabetes mellitus did not abate after digoxin withdrawal, and since all these patients were obese, the occurrence of diabetes was probably coincidental.

Hematologic

Thrombocytopenia has been reported in patients taking digitoxin, acetyldigoxin, and digoxin (105–108).

There have been rare reports of eosinophilia in patients taking cardiac glycosides (109).

Gastrointestinal

Gastrointestinal symptoms are common in digitalis toxicity. These include anorexia, nausea, and vomiting (110), probably as a result of stimulation of the chemoreceptor trigger zone in the brain.

Diarrhea occurs occasionally (111).

Dysphagia has been rarely reported (112,113).

Other rare events include intestinal ischemia (SEDA-17, 215) (114), and hemorrhagic intestinal necrosis (115).

- A 79-year old woman with a serum digoxin concentration of 4.9 ng/ml had a mesenteric infarction (116). At postmortem no other causes were discovered.

Intestinal ischemia responds to verapamil and to antidigoxin antibody (115).

Death

In a retrospective, non-randomized study of 484 patients, 90 of whom were taking digoxin, there was an increased death rate (RR = 2.12, CI = 1.21, 3.74) in those taking digoxin (117). In another non-randomized, retrospective analysis of the effects of digoxin in patients with acute myocardial infarction there was a higher rate of mortality in the 243 patients taking digoxin compared with the 1743 patients who were not (118). The results of these studies are reminiscent of the results of previous similar retrospective analyses. However, the prospective DIG study clearly showed no increase in mortality (SEDA-20, 173), and the results of these more recent non-randomized retrospective studies should be ignored.

In 345 patients with heart failure randomized to either digoxin ($n = 175$) or captopril ($n = 170$) and followed for a median of 4.5 years the death rate at 48 months was lower with captopril (21%) than with digoxin (32%), although this did not reach conventional significance (119). Since there was no placebo group for comparison it is not clear whether digoxin altered mortality in this study. Of the numerous adverse effects that were reported, the only one that differed between the two treatments was cough, which was significantly more frequent with captopril. In the absence of a placebo comparison it is impossible to say whether any of the other adverse effects were drug-related.

Despite the fact that the prospective study called DIG clearly showed that there was no increase in mortality in patients in taking long-term digoxin therapy (SEDA-20, 173), retrospective, non-randomized studies continue to be reported (SEDA-24, 201). In 180 patients with idiopathic dilated cardiomyopathy the overall mortality was 19% in those taking digoxin and 10% in those not taking digoxin (120). However, when the use of digoxin was adjusted for several predictive variables it no longer predicted cardiac death. This finding is reassuring, but results of studies like this, whatever their results, should be ignored, in view of the evidence that is currently available from the one large prospective, randomized study.

When interpreting the evidence presented in other accounts of the association between drug therapy and death it is important to remember that the current evidence suggests that digoxin does not cause excess mortality. For example, digoxin was the second most commonly encountered medication in an investigation of 2233 deaths reported to an American County Medical Examiner's office, with a medication history available in 775 cases (121). Furosemide was mentioned 181 times, digoxin 131 times, and glyceryl trinitrate 103 times. All other drugs were mentioned less than 100 times each. The authors suggested that the presence of digoxin at a death scene should suggest heart failure or a cardiac dysrhythmia, but they did not go further and stress that in such a case digoxin need not necessarily be implicated in the death. Postmortem diagnosis of digoxin toxicity is exceptionally difficult, but measurement of digoxin in the vitreous fluid can be helpful.

In a survey of 2 312 203 deaths in the USA in 1995, 206 (0.009%) were attributed to adverse drug reactions on death certificates (122). At the same time in the MedWatch program, 6894 deaths were reportedly attributed to adverse drug reactions, representing 6.3% of the 108 735 reports of adverse drug reactions. In the death certificate study 18 deaths were attributed to cardiac glycosides and in the MedWatch survey 15 deaths. This compares with figures of 289 and 782 from antimicrobial drugs, 449 and 280 from hormones, and 947 and 477 from drugs that affect the constituents of the blood (for example anticoagulants).

Sex-based differences in the effect of digoxin have been explored in a post-hoc analysis of the data from the DIG) study (SEDA-20, 173) (123). There was an absolute difference of 5.8% (95 CI = 0.5, 11) between men and women in the effect of digoxin on the case fatality rate from any cause. Women who were randomly assigned to digoxin had a significantly higher fatality rate than women who were randomly assigned to placebo (33 versus 29%), while the fatality rate was similar among men randomly assigned to digoxin or placebo (35% versus 37%). However, serum digoxin concentrations were higher in the women at 1 month, and this may have contributed to the increased risk of death (124).

In another post-hoc analysis of the data from the DIG study the patients who had been randomized to digoxin were divided into three groups, according to serum digoxin concentration, 0.5–0.8 ng/ml, 0.9–1.1 ng/ml, and 1.2 ng/ml and over (125). Higher concentrations were associated with higher all-cause fatality rates: 30%, 39%, and 48% respectively.

Both of these studies suggest that lower serum concentrations of digoxin (0.5–1.0 ng/ml) may be beneficial for

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routine therapy of heart failure than have traditionally been recommended (0.8–2.0 ng/ml), and this has been discussed in a brief review (126).

Second-Generation Effects

Pregnancy

Digoxin has been used to cause fetal death before termination of pregnancy (127). However, in a double-blind study in 126 women who had terminations by dilatation and evacuation at 20–23 weeks gestation intra-amniotic injection of digoxin 1 mg did not alter blood loss or pain; nor did it reduce difficulties with or the complications of the procedure (128). Significantly more women vomited after intra-amniotic digoxin. Digoxin given by this route is slowly absorbed into the systemic circulation, with a peak plasma concentration of 0.8 ng/ml at 11 hours (129).

Fetotoxicity

Digoxin crosses the placenta and enters the neonatal circulation (130). It has therefore been used, for example, to improve fetal cardiac function (131). In normal circumstances there seem to be no adverse effects on the neonate, and neonatal plasma concentrations are below those generally considered to be therapeutic. There has been one report of fatal toxicity in the fetus of a woman who took an overdose of digitoxin (132).

Susceptibility Factors

Age

Elderly people

The risk of digoxin toxicity is increased in old people, partly because they have poor renal function and lower body weight, factors that tend to increase the concentration of drug at the active site during steady-state therapy, and partly because they are liable to electrolyte imbalances, such as hypokalemia, which tend to increase the response of the tissues to a given concentration. Other factors, such as altered Na/K pump activity, may also contribute to increased tissue sensitivity. This means that the serum digoxin concentration that is associated with an increased risk of toxicity is slightly lower in elderly people than in younger people, and this has been confirmed in a recent study of 899 patients taking digoxin for heart failure or atrial fibrillation (133). No patients with serum digoxin concentrations below 1.4 ng/ml had evidence of digoxin toxicity. All patients who had a concentration of 3.0 ng/ml or more had severe toxicity. However in the range 1.4–2.9 ng/ml there were patients with and without evidence of toxicity, and the overlap was age-dependent. In patients aged 51–60 there was more evidence of toxicity with concentrations of 2.4–2.9 ng/ml; in patients aged 61–70 the range was 1.8–2.9 ng/ml, in patients aged 71–80 it was 1.4–2.7 ng/ml, and in those aged over 80 it was 1.4–2.6 ng/ml. The authors therefore suggested that serum digoxin concentrations should be no greater than 1.4 ng/ml during routine steady-state therapy. The incidences of toxicity were 16% in patients over 70 years of age and 7.3% in the whole group. The risk of toxicity was increased in the presence of renal insufficiency.

Because digitoxin is metabolized rather than being renally eliminated, the effects of renal impairment in elderly patients may not be so important in precipitating digitoxin toxicity. In 80 patients hospitalized 147 times, toxicity with digitoxin occurred in 7.6% of 92 admissions and digoxin toxicity occurred in 18.3% of 55 admissions (134). On the basis of these results the authors suggested that digitoxin is safer than digoxin in elderly patients. This is an old debate, and there are arguments in favor of both digoxin and digitoxin (135). However, there is currently no information on the long-term toxicity of digitoxin, and in particular its effects on mortality in patients with heart failure. Neither the severity of toxicity nor its duration was reported in this study.

A retrospective Bayesian analysis in 60 patients confirmed that age is a major factor in digoxin toxicity (136). However, an analysis of the data from the DIG study (SEDA-20, 173) has shown that while mortality in heart failure increases with age, the actions of digoxin are independent of age (137).

Children

Matters are also more complicated in young people. The pharmacokinetics of cardiac glycosides are different (138): the apparent volume of distribution of digoxin is higher in neonates, infants, and older children than in adults, and renal digoxin clearance is lower in children under 4–6 months. However, there may also be increased resistance to the effects of digoxin in infants because of changes in digitalis tissue receptors (139). Seriously ill children of low birth weight may be particularly at risk, even when low dosages of digitalis are used (140).

The risk of digitalis toxicity during the therapeutic use of cardiac glycosides is similar in children to that in adults, ranging in 12 separate published series from 12 to 50% (median 21%) (141). The most common non-cardiac effects are vomiting and feeding problems, and the most common cardiac effects are conduction defects, particularly atrioventricular block and ectopic rhythms, although (as in adults) any dysrhythmia can occur.

The pharmacokinetics of digoxin have been studied in 181 neonates and children with and without congestive heart failure (142). The clearance rate was lower in premature neonates than in neonates born at full term. Children with congestive heart failure also had lower digoxin clearance.

A population pharmacokinetic study in 172 neonates and infants showed that the clearance of digoxin is affected significantly by total body weight, age, renal function, and congestive heart failure (143).

Other features of the patient

Several factors increase patient susceptibility to digitalis intoxication. They can be considered in two groups (144).

Factors that alter the amount of digitalis that accumulates in the body or the plasma concentration at a fixed dose (pharmacokinetic factors)

Pharmacokinetic factors affect different cardiac glycosides differently.

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Altered tissue distribution
The apparent volume of distribution of digoxin is reduced in hypothyroidism (145) and in renal insufficiency (146). This leads to increased plasma concentrations after a loading dose and hence an increased risk of toxicity, but does not affect the plasma concentration at steady state. The opposite occurs in hyperthyroidism.

Altered renal elimination
The effects of renal insufficiency on the pharmacokinetics of cardiac glycosides have been reviewed (146). The most important effect of renal failure is a reduced rate of elimination of digoxin, leading to increased accumulation during steady-state treatment. The same applies to some other glycosides, including beta-methyldigoxin, beta-acetyldigoxin, ouabain, and k-strophanthin, but not to glycosides that are mostly metabolized, such as digitoxin, the proscillaridins, and peruvoside (4). Drug interactions can also lead to reduced digoxin renal elimination.

A retrospective Bayesian analysis in 60 patients confirmed that renal impairment is a major factor in digoxin toxicity (136).

A population pharmacokinetic study in 172 neonates and infants showed that the clearance of digoxin is affected significantly by renal function (143).

Altered non-renal elimination
See Drug–Drug Interactions.

Factors that alter the clinical response to digitalis at a fixed amount of digitalis in the body and a fixed plasma concentration (pharmacodynamic factors)
Pharmacodynamic factors affect all cardiac glycosides in the same way.

Electrolyte disturbances
Of electrolyte disturbances that alter the response to a cardiac glycoside, hypokalemia is the most important. It has been estimated that a fall in plasma potassium concentration from 3.5 to 3.0 mmol/l is associated with a 50% increase in sensitivity to digoxin (144). Total body potassium depletion, even in the absence of hypokalemia, has a similar effect (147).

There is evidence that hypomagnesemia has the same effect as hypokalemia (148).

Hypercalcemia has the same effect as hypokalemia; hypocalcemia has the opposite effect, that is it causes resistance to the effects of digitalis.

Hypoxia and acidosis increase the risk of digitalis intoxication.

Renal insufficiency
In addition to its effect in reducing the elimination of digoxin, renal insufficiency may be associated with an increased sensitivity to the actions of digitalis (149).

Thyroid disease
Apart from the pharmacokinetic differences in thyroid disease (mentioned above), there may also be changes in tissue responsiveness, with reduced sensitivity in hyperthyroidism and the reverse in hypothyroidism (145). The reasons for these changes are not known, but they may be related to differences in tissue Na/K-ATPase activity.

Cardiac disease
All cardiac glycosides are best avoided in patients with acute myocardial infarction, since they increase oxygen demand in ischemic tissue, increase peripheral vascular resistance, and carry an increased risk of dysrhythmias, especially in the presence of tissue hypoxia and acidosis. Furthermore, there is evidence that digitalis is of little value in patients with acute myocardial infarction and either left ventricular failure or cardiogenic shock (150). The evidence that mortality in patients who take digitalis after an acute myocardial infarction is increased is discussed in the section Death in this monograph.

Cardiac glycosides are contraindicated in conditions in which there is obstruction to ventricular outflow, for example hypertrophic obstructive cardiomyopathy, constrictive pericarditis, and cardiac tamponade. Acute myocarditis may also increase the risk of toxicity.

Direct current cardioversion increases the risk of digitalis-induced dysrhythmias, but digitalis treatment is not a contraindication to cardioversion (151).

Hypercalcemia
The effects of digitalis are enhanced in the presence of hypercalcemia.

- An 81-year-old woman with congestive heart failure and hypercalcemia secondary to squamous cell carcinoma of the bronchus developed first-degree heart block and symptomatic sinus pauses when her serum digoxin concentration was only 1.5 mg/ml (152).

Drug Administration

Drug contamination

Digoxin toxicity has been reported in two patients who took herbal remedies (153). *D. lanata* was found as a contaminant.

Drug administration route

Intramuscular injection of digitalis can be painful and can cause local muscle necrosis, sometimes with pyrexia (154). The systemic availability of digitalis after intramuscular injection is poor (155), and this route of administration should be avoided if possible.

Digoxin has a rapid onset of action after oral administration, and there is rarely any justification for giving digoxin intravenously. This route of administration should be restricted to those who have severe atrial fibrillation that requires rapid treatment and in whom cardioversion or other drug therapy is not possible or indicated. If digoxin is given intravenously it should be infused over at least half-an-hour, since there is a risk of hypertension if it is infused faster.

There has been a randomized, double-blind comparison of intravenous diltiazem and digoxin in 40 patients with atrial fibrillation and a ventricular rate of over 100/minute (156). One patient given intravenous digoxin had a burning sensation at the site of injection.

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Drug overdose

The most important complication of overdosage of digitalis in all age groups is disturbance of cardiac conduction, but in addition any dysrhythmia can occur. Death can result from asystole or ventricular fibrillation. Hyperkalemia is common, and the higher the plasma potassium concentration the poorer the prognosis (157).

Other common effects of overdosage are nausea, vomiting, and central nervous system and visual disturbances (66).

- Accidental overdose of digoxin in a 22-month-old boy caused vomiting, lethargy, and dehydration. The plasma digoxin concentration was 12 mg/ml. There was a relative bradycardia of 90/minute and Mobitz type 1 second-degree heart block on the electrocardiogram (158).

The pharmacokinetics of digoxin are altered after overdosage, the half-life being reportedly rapid, but there is too little information to define the kinetics precisely (157).

- Plasma glycoside concentrations have been documented after an overdose with purple foxglove in a 36-year-old woman (159). Apart from gitaloxin, which peaked on the fifth day at 113 ng/ml, all the glycosides detected peaked on the first day (gitoxin 13 ng/ml, digitoxin 113 ng/ml, digitoxigenin 3.3 ng/ml, and digitoxigenin monodigitoxoside 8.9 ng/ml). There was a second peak of digitoxin at about 70 hours, and this is consistent with the known enterohepatic recirculation of digitoxin.

Treatment of toxicity and overdosage

The treatment of digitalis toxicity and overdose have been reviewed (SEDA-5, 172) (SEDA-12, 149). In summary, the following measures should be taken.

Remove digitalis from the stomach

If the patient is seen within 1 hour of overdosage try to remove whatever drug still remains in the stomach by gastric lavage, although the risk of dysrhythmias may be increased. There is no evidence that emesis is beneficial.

Give activated charcoal

The use of activated charcoal in the treatment of digitalis overdose has been reviewed (160). The rationale for its use is that after absorption into the systemic circulation digitoxin is secreted into the bile and digoxin (161) (and probably other cardiac glycosides) is secreted into the gut lumen by the action of the P glycoprotein. Activated charcoal in the gut binds this secreted digoxin and encourages further secretion. To be fully effective charcoal should be given at regular intervals (for example 50 g 4-hourly).

In pigs, repeated doses of activated charcoal reduced the half-life of intravenous digoxin significantly from 65 to 17 hours and increased the clearance from 2.3 to 7.1 ml/minute/kg (162).

There is evidence of the efficacy of charcoal in healthy volunteers. In six adult volunteers repeated doses of activated charcoal significantly reduced the half-life of digoxin from 23 to 17 hours without a significant increase in clearance; the half-life of digitoxin was also reduced from 110 to 51 hours, and this was accompanied by a significant increase in clearance from 0.24 to 0.47 l/hour (163). In a volunteer with chronic renal insufficiency charcoal reduced the digoxin half-life from 93 to 29 hours and increased the clearance from 3.6 to 10 l/hour (163). Similarly, during maintenance therapy in six individuals, daily activated charcoal significantly reduced the mean plasma digoxin concentration by 31% and serum digitoxin concentration by 18% (164). In 10 healthy volunteers given intravenous digoxin 10 μg/kg repeated doses of activated charcoal significantly increased the total body clearance from 12 to 18 l/hour and reduced the half-life from 37 to 22 hours (161).

There have also been reports of the value of multiple doses of activated charcoal in patients with digoxin and digitoxin poisoning. In 23 patients with plasma digoxin concentrations over 2.5 ng/ml multiple doses of activated charcoal increased the mean clearance of digoxin to 98 ml/minute compared with 55 ml/minute in 16 patients who were not treated, and reduced the half-life from 68 to 36 hours (165). Anecdotal reports have also appeared.

- In a 69-year-old man the plasma digoxin concentration of 8.3 ng/ml fell with a half-life of 14 hours (166).
- In a 71-year-old woman with chronic renal insufficiency and a plasma digoxin concentration of 9 ng/ml charcoal shortened the half-life from 7.3 to 1.4 days (167).
- In a 66-year-old man with chronic renal insufficiency whose serum digoxin concentration did not respond to daily hemodialysis, multiple doses of activated charcoal caused a rapid reduction in the serum concentration (168).
- In a patient with a peak plasma digoxin concentration of 264 ng/ml multiple doses of activated charcoal reduced the half-life of digitoxin from 162 hours to 18 hours (169).
- In a patient on hemodialysis, activated charcoal caused a fall in the plasma digoxin concentration with a half-life of 29 hours (170).
- In another patient there was convincing evidence of a change in the digoxin half-life after repeated doses of activated charcoal (166).
- In a 73-year-old woman who took 12.5 mg of digoxin, gastric lavage and activated charcoal tided the patient over until antibodies became available (171).

However, the best evidence of the usefulness of repeated oral doses of activated charcoal in cardiac glycoside poisoning comes from the results of a randomized, placebo-controlled study in 402 individuals who took overdoses of the seeds of the yellow oleander tree in Sri Lanka. Repeated doses of activated charcoal reduced mortality from 8.0% to 2.5% (26).

Thus, the use of repeated doses of activated charcoal in patients with digitalis toxicity is a cheap way of increasing the rate of cardiac glycoside clearance.

Colestyramine has been used for the same purpose. In two elderly patients with congestive heart failure and raised serum digoxin concentrations it enhanced the elimination of digoxin (172). In one case the half-life of digoxin was 20 hours and in the other 24 hours.

Correct electrolyte disturbances

Hypokalemia should be treated with potassium chloride.

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Hyperkalemia carries a poor prognosis and is usually an indication for antidigoxin antibody. The suggestion that intravenous calcium should be used to treat the hyperkalemia that can occur in digitalis intoxication (173) has been challenged, on the grounds that it can increase the risk of cardiac dysrhythmias in such cases (174).

Give antidigoxin antibody

Antidigoxin antibody (Fab fragments) is the treatment of choice in patients with severe digitalis toxicity due to any cardiac glycoside. It is effective after self-poisoning with digitoxin, lanatoside C, and acylated forms of digoxin, as well as digoxin itself (175). It should be used when there are life-threatening dysrhythmias or heart block, and when the plasma potassium concentration is above 5.0 mmol/l or is rising, since hyperkalemia is evidence of serious toxicity and carries a poor prognosis. Evidence of the efficacy of antidigoxin Fab antibody fragments in reducing the risk of cardiac dysrhythmias in the treatment of intoxication due to oleander poisoning, previously only anecdotally reported (176,177), has come from a prospective study (178), although the study was too small to assess the effect on mortality. The role of antidigoxin antibody fragments in treating milder forms of digitalis toxicity has not been fully assessed.

In a systematic review of 250 publications no controlled, randomized trials were found, and the authors concluded that there was little or no scientific evidence of efficacy, because there are no randomized, controlled trials (179). However, this is one case in which the cumulative anecdotal evidence is overwhelmingly convincing, and there can be no doubt that antidigoxin antibodies are highly effective in the treatment of digoxin intoxication and of intoxication with other cardiac glycosides. The important question is whether there are cases in which the antibodies need not be used, and guidelines have yet to be developed.

- Overdose of digoxin in a neonate caused complete atrioventricular block and cardiogenic shock, which were completely reversed within 4 hours after administration of the first dose of antidigoxin antibody; a second dose was given 48 hours later, when first-degree atrioventricular block occurred (180).

However, it is not known whether antidigoxin antibody reduces mortality after digitalis poisoning; one randomized, controlled study (178) was too small to detect an effect on mortality after self-poisoning with seeds of the yellow oleander, which contains cardiac glycosides such as peruvoside. Another study that suggested reduced mortality (181) was confounded by being retrospective and inferential, based on changes in death rates as antibody was introduced and reintroduced; furthermore, the change in mortality that was attributed to the use of antibody occurred at the same time as multiple-dose activated charcoal was introduced, and that has definitively been shown to reduce mortality.

The dose of antidigoxin antibody should be based on the dose of digitalis taken and, when possible, the plasma digitalis concentration. The recommended doses for cases of poisoning with digoxin and digitoxin are given in Table 3. Although the clearance of the fragments is reduced in patients who also have severe renal impairment (182,183), there is no need to reduce the dose of antibody in such patients (184–187).

Different formulations of antidigoxin antibody are available. Digibind is an ovine antibody to digoxin, whose production is stimulated by the administration of digoxin conjugated to human albumin. In contrast, DigiFab, also ovine, is stimulated by injecting a conjugate of digoxin to keyhole-limpet hemocyanin (188). In 15 adults with digoxin toxicity who were given DigiFab, electrocardiographic abnormalities resolved within 4 hours in 10 patients and the signs of toxicity completely resolved within 4 hours in seven patients and within 20 hours in 14 patients. In one patient loss of the effect of digoxin resulted in pulmonary edema, pleural effusions, and renal insufficiency. The half-life of DigiFab is slightly shorter than that of Digibind (15 versus 23 hours), but their pharmacodynamic properties are similar. It is said that DigiFab may be preferred in patients who are allergic to sheep proteins, papain, chymopapain, or bromelains.

Antidigoxin antibody fragments cause adverse events in about 7% of cases. These include allergic responses, possible recurrence of digitalis toxicity after treatment, and some effects attributable to the withdrawal of digitalis, such as worsening of heart failure. In one series allergic reactions occurred in only six of 717 patients reviewed, and consisted of pruritic rash and flushing or facial swelling (189). The risk of an allergic reaction was increased in patients who had a history of previous allergy or asthma. Recurrence of digitalis toxicity after treatment was usually due to inadequate treatment with the antibody.

Plasma exchange has been used to enhance the rate of removal of antidigoxin antibody Fab fragments in a

Table 3 Methods for calculating the required dose of antidigoxin antibody fragments in cases of digoxin or digitoxin intoxication

Digoxin

(1) When the ingested dose is known:

(a) Tablets	dose in mg x 40
(b) Elixir	dose in mg x 48
(c) Capsules	dose in mg x 55
(d) Intravenous	dose in mg x 60

(2) When the plasma or serum concentration is known:
ng/ml x lean body weight x 0.34
or
nmol/l x lean body weight x 0.26

Example: Plasma digoxin concentration = 24 ng/ml in a 75 kg patient
Dose of antibody = 24 x 75 x 0.34 = 612 mg
Give 640 mg (for example 16 ampoules of Digibind)

Digitoxin

(1) When the ingested dose is known (all formulations):
Dose in mg x 60

(2) When the plasma or serum concentration is known:
ng/ml x lean body weight x 0.034
or
nmol/l x lean body weight x 0.026

Example: Plasma digitoxin concentration = 280 ng/ml in a 70 kg patient
Dose of antibody = 280 x 70 x 0.034 = 666 mg
Give 680 mg (for example 17 ampoules of Digibind)

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46-year-old man with renal insufficiency (190). Removal of the digoxin-Fab complexes in this case prevented their subsequent dissociation and a further increase in the unbound concentration of digoxin. The authors proposed that plasma exchange is best used in these cases within the first 3 hours after the administration of antidigoxin antibodies.

Treat dysrhythmias

Cardiac dysrhythmias in digitalis overdose should be treated only if they are life-threatening. Phenytoin is probably the treatment of choice for ventricular tachydysrhythmias, but lidocaine or a beta-adrenoceptor antagonist, such as propranolol, are options. After an overdose of 300 tablets of digoxin (plasma digoxin concentration 50 ng/ml), recurrent ventricular fibrillation was successfully treated with bretylium tosylate (191). Sinus bradycardia may respond to atropine.

Treat or anticipate heart block

Heart block is the most serious consequence of digitalis poisoning and should be anticipated by the insertion of a temporary pacemaker. If this is postponed until heart block or dysrhythmias occur, there may be difficulty in inserting the pacemaker (because of ventricular excitability), and delay in treatment can be deleterious.

Other measures

Because digoxin has a large apparent volume of distribution, plasma exchange, hemodialysis, and hemoperfusion are not effective methods of removing digoxin from the body.

Hemoperfusion

Hemoperfusion has been used to treat digitalis overdose (SEDA-5, 174) but once a cardiac glycoside has been distributed to the body tissues hemoperfusion is unlikely to be of benefit. For digitoxin, which has a lower apparent volume of distribution than digoxin, charcoal hemoperfusion may be more valuable.

- In an 88-year-old woman whose serum digoxin concentration was 6.4 ng/ml, hemoperfusion with an adsorption column containing beta$_2$-microglobulin caused a fall in serum concentration from 6 ng/ml to 2.3 ng/ml, with improvement in gastrointestinal symptoms (192). The serum digoxin concentration then rose again to 3.5 ng/ml over the next 3 days, and a further hemoperfusion treatment reduced it to 1.7 ng/ml, after which the serum concentration gradually fell and the patient improved. Because of chronic renal insufficiency, she also had repeated hemodialyses on alternate days, which also contributed to the reduction in serum digoxin concentrations.

The clearance of digoxin was measured in eight patients receiving hemodialysis during the use of a beta$_2$-microglobulin column (193). After 240 minutes of hemoperfusion the serum digoxin concentration fell from 1.11 to 0.57 ng/ml and digoxin clearance was about 145 ml/minute. However, this clearance rate cannot have been the true total body clearance, since it merely reflected the change in plasma concentration during hemoperfusion, which would have been almost entirely due to removal of digoxin from the plasma only and not from the tissues. This method cannot be recommended as a substitute for the use of antidigoxin antibodies in the treatment of digitalis toxicity.

Hemofiltration

Hemofiltration has been used to treat digitalis poisoning (SEDA-12, 149), but there is no convincing evidence of its efficacy.

Exchange transfusion

There have been reports of the use of exchange transfusion to remove Fab antibody fragment-digoxin complexes in patients with acute anuric renal insufficiency (194).

- Plasma exchange was used to enhance the rate of removal of antidigoxin antibody Fab fragments in a 46-year-old man with renal insufficiency (190). Removal of the digoxin-Fab complexes in this case prevented their subsequent dissociation and a further increase in the unbound concentration of digoxin.

The authors proposed that plasma exchange is best used in these cases within the first 3 hours after the administration of antidigoxin antibodies.

- A 70-year-old man with alcoholic cirrhosis was given amiodarone and digoxin for atrial fibrillation after a hemicolectomy for adenocarcinoma (195). He developed acute renal insufficiency and digoxin toxicity, with a serum concentration of 4.4 ng/ml. A dose of Fab antidigoxin antibody fragments was followed 16 hours later by exchange transfusion and another dose was followed by two exchanges. He recovered slowly over the next few days. The total digoxin concentration (antibody bound and unbound) rose after the first dose of Fab fragments but did not fall until after the second plasma exchange (after the second dose of Fab fragments).

In this case digoxin was recovered from the plasma collection bags, but the total amount recovered seems to have been less than 100 μg, so the efficacy of plasma exchange was not clear.

Drug–Drug Interactions

General

Drug interactions with cardiac glycosides can be subdivided into six types, according to mechanism. Interactions with digoxin have been reviewed (SEDA-6, 173) (196–198). Drug interactions with digitoxin have been briefly reviewed in the context of its use in the treatment of congestive heart failure (199).

Absorption

Absorption interactions with digitalis are probably not of great clinical importance, since (a) the dosages of drugs that reduce the absorption of digitalis are usually larger than those used clinically, and (b) the major effect on absorption probably occurs only if the two drugs are taken together.

The effect of activated charcoal in reducing digitalis absorption is mentioned under the treatment of

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poisoning, and binding resins such as colestyramine and colestipol have similar actions (200,201).

Certain combinations of cytotoxic drugs (cyclophosphamide, vincristine, and prednisone, with and without procarbazine) reduced plasma digoxin concentrations by about 50% during treatment with beta-acetyldigoxin, perhaps through impaired absorption of beta-acetyldigoxin (202); digitoxin was not affected (203).

Absorption interactions involving altered gastrointestinal motility have been described. These include interactions of digoxin with propantheline (204), metoclopramide (204), and cisapride (205). However, the clinical relevance of these interactions is unclear and they are probably unimportant.

Some antacids, such as magnesium trisilicate, reduce the absorption of digoxin slightly, but these interactions are probably of no clinical importance (206).

Protein-binding displacement

Interactions of this kind are of no importance for digoxin, which is only about 20% bound and has a high apparent volume of distribution.

An interaction of heparin with digitoxin has been described and ascribed to altered protein binding, secondary to changes in fatty acid concentrations, but the clinical relevance, for example in patients undergoing hemodialysis, is unclear (207).

Renal clearance

Digoxin is cleared by the kidneys by glomerular filtration and active secretion, and retained by passive reabsorption, the last two roughly balancing each other, so that clearance is usually proportional to creatinine clearance. A major mechanism for drug interactions with digoxin is inhibition of its renal tubular secretion by inhibition of P glycoprotein. This mechanism has been reviewed in relation to an in vitro tissue culture model, consisting of confluent polarized renal tubular cell monolayers (208). This model has confirmed the action of several drugs that can inhibit the renal tubular secretion of digoxin in this way, including amiodarone, ciclosporin, itraconazole and ketoconazole, mifepristone, propafenone, quinidine, spironolactone, verapamil, and vinblastine and vincristine.

In three large studies using either population pharmacokinetic analysis or Bayesian techniques, drugs that inhibit the transport of digoxin by inhibiting P glycoprotein significantly increased the serum digoxin concentration (143,209,210). These drugs included quinidine, spironolactone, and the calcium channel blockers diltiazem, nicardipine, nifedipine, and verapamil. The effects varied from about 22% to about 36%.

Vasodilators may increase the active secretion of digoxin, which is a high clearance process and is therefore affected by renal blood flow.

Uptake by the end-organ

The interaction of quinidine with digoxin involves displacement of digoxin from tissues.

Hyperkalemia, due to potassium chloride, potassium-retaining diuretics, ACE inhibitors, or angiotensin-receptor antagonists, reduces the apparent affinity of digitalis for Na/K-ATPase and thereby reduces its tissue binding.

Response of the end-organ

Interactions involving changes in the response of the end-organ to digitalis are the most common of all interactions with cardiac glycosides.

Potassium depletion, for example due to diuretics or corticosteroids, potentiates the effects of cardiac glycosides on the myocardium and may also have a small effect in reducing the renal tubular secretion of digoxin (211,212).

Magnesium depletion may have a similar effect (213), but the data are not as clear-cut as those for potassium.

Anecdotal reports suggest that intravenous infusion of calcium salts in patients taking digitalis can result in dangerous cardiac dysrhythmias. This may also be the basis of reports that edrophonium and suxamethonium enhance the actions of digitalis, since both of these drugs might cause altered disposition of calcium. Conversely, there is good anecdotal evidence that hypocalcemia causes reduced plasma responsiveness to digoxin (214).

Alpha-glucosidase inhibitors

Acarbose

In patients taking steady-state digoxin therapy the addition of acarbose reduced the plasma digoxin concentration (215,216). The association was confirmed in both cases by withdrawal of acarbose. The likely mechanism of this interaction is inhibition of the absorption of digoxin by acarbose, although the authors also suggested that acarbose might interfere with the hydrolysis of digoxin before absorption, thus altering the pattern of metabolites in the blood; however, this is a much less likely mechanism. The authors recommended that if acarbose be used in conjunction with digoxin, the doses should be separated by about 6 hours. This absorption interaction has previously been highlighted (217,218).

However, in a formal study of the pharmacokinetics of a single dose of digoxin 0.75 mg before and after the administration of acarbose 50 mg tds for 12 days in healthy volunteers, apart from a small increase in C_{max}, the pharmacokinetics of digoxin were unaffected by acarbose (219). It is not uncommon for anecdotal reports of a possible interaction to be unconfirmed by formal kinetic studies, and it is possible in such cases that there is a subset of patients who are susceptible to the interaction who have not been included in the formal study. In this case, for example, it may be that the interaction occurs in people with diabetes and not in healthy subjects. There may also be a difference in the effect of acarbose on a single dose of digoxin, compared with steady-state therapy. Advice that acarbose and digoxin should be administered 6 hours apart is still reasonable.

Voglibose

In eight healthy men voglibose, another inhibitor of alpha-glucosidase, had no effect on the pharmacokinetics of digoxin (220). This result suggests that inhibition of alpha-glucosidase is not the mechanism whereby acarbose alters the absorption of digoxin; however, acarbose also inhibits alpha-amylase and such inhibition cannot be ruled out as a mechanism of the interaction with acarbose, perhaps by altered gastrointestinal motility.

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Amiodarone

Amiodarone inhibits the renal tubular secretion of digoxin (SEDA-22, 201) and it has also been suggested that it increases its absorption (SEDA-10, 144) (SEDA-12, 150). This interaction has also been reported with acetyldigoxin (SEDA-18, 198) (221).

Amiodarone also interacts with digitoxin (222). In two cases the half-life of digitoxin was prolonged, but there was no other information that suggested a mechanism. The author suggested that amiodarone might displace digitoxin from tissue sites, but that would have led to a shortening of the half-life rather than a prolongation. It seems more likely that amiodarone inhibits the clearance of digitoxin by inhibiting renal and gut P glycoprotein and perhaps by inhibiting its metabolism.

Antacids

Although digoxin is not extensively metabolized in most patients, it is metabolized before its absorption from the gut by two mechanisms, hydrolysis by gastric acid and hydrogenation by intestinal bacteria. In patients who have hypochlorhydria presystemic metabolism is reduced and increasing concentrations of digoxin are achieved systemically. This means that drugs that reduce gastric acid secretion, such as cimetidine, ranitidine, other histamine H_2 receptor antagonists, and omeprazole would be expected to increase the systemic availability of digoxin, and there is some supporting evidence (223,224), although this is not conclusive (SEDA-17, 216).

Antidysrhythmic drugs

Digoxin does not interact with a variety of antidysrhythmic drugs, including ajmaline, aprindine, lidocaine, lidoflazine (225), and moracizine (226). Other drugs that may have minor and clinically unimportant interactions include captopril, carvedilol, disopyramide, and flosequinan.

Antifungal imidazoles

Itraconazole increases steady-state serum digoxin concentrations, perhaps by inhibiting the renal tubular secretion of digoxin (SEDA-22, 202) (227–229). An alternative proposed mechanism is inhibition of CYP3A (SEDA-21, 196), and this has been reported in rats with ketoconazole (230), although an effect on P glycoprotein was also possible. Whatever the mechanism, ketoconazole increased the systemic availability of digoxin from 0.68 to 0.84 and reduced the mean absorption time from 1.1 hours to 0.3 hours. The increased systemic availability could have been explained by inhibition of CYP3A or P glycoprotein in the gut, but the increased rate of absorption could only be explained by inhibition of the P glycoprotein. Since the t_{max} was unaffected, the authors hypothesized that inhibition of P glycoprotein increased the absorption rate, which would have tended to reduce the t_{max}, while inhibition of CYP3A, which would have reduced the elimination rate of digoxin, would have tended to increase the t_{max}. Thus a combination of these two effects would have had no effect on t_{max}. It should be noted that CYP3A is an important route of metabolism of digoxin in rats, but not in man.

Digoxin toxicity sometimes accompanies this interaction.

- A 62-year-old woman who was taking digoxin took itraconazole 400 mg/day for 3 days developed nausea, anorexia, and lethargy; the symptoms improved within 48 hours after withdrawal of itraconazole (231). The serum digoxin concentrations were not reported.
- In a 75-year-old man who took itraconazole in a low dose (200 mg/day) the steady-state serum digoxin concentration only rose from 0.8 to 1.1 ng/ml after 8 days (232).
- Two renal transplant patients developed digoxin toxicity when they also took itraconazole (233).

Itraconazole increases the digoxin $AUC_{0–72}$ by about 50%, and reduces its renal clearance by about 20% (234). Apart from inhibition of the renal secretion of digoxin, which is probably mediated by inhibition of P glycoprotein, a study in guinea pigs also showed significantly reduced biliary excretion of digoxin by itraconazole, suggesting that the interaction between itraconazole and digoxin may be due not only to a reduction in renal clearance, but also to a reduction in the metabolic clearance of digoxin by itraconazole (235).

Argatroban

The thrombin inhibitor argatroban had no effect on the steady-state pharmacokinetics of oral digoxin 0.375 mg/day in 12 healthy volunteers; the argatroban was given as an intravenous infusion of 2 micrograms/kg/minute on days 11–15 (236).

Bosentan

In a randomized study in 18 young men, bosentan caused a small (12%) reduction in the AUC of digoxin, without changing either the C_{max} or the C_{min} (237). This was a steady-state study, with plasma concentration measurements for only 24 hours, and so the half-life of digoxin was not measured. Bosentan is an antagonist at endothelin type 1 receptors and could therefore have increased renal blood flow by pre- and postglomerular vasoconstriction, increasing the elimination of digoxin. Furthermore, bosentan is a substrate for P glycoprotein, which mediates the renal tubular secretion of digoxin, and may induce its expression, increasing digoxin renal clearance. However, whatever the mechanism of this putative interaction, it is clearly unlikely to be of clinical significance.

Calcium channel blockers

Calcium channel blockers have varying effects on the disposition of digoxin. The calcium channel blockers for which varying amounts of information are available include cinnarizine, diltiazem, felodipine, fendiline, gallopamil, isradipine, lidoflazine, mibefradil, nicardipine, nifedipine, nitrendipine, tiapamil, and verapamil (238).

Diltiazem

Studies of the effects of diltiazem on the pharmacokinetics of digoxin have yielded variable results. In one study, diltiazem reduced the steady-state total body clearance of beta-acetyldigoxin in 12 healthy men, perhaps because of reduced renal and non-renal clearances (SEDA-10, 145). In some studies diltiazem 120–240 mg/day increased steady-state plasma digoxin concentrations by about 20–40% (SEDA-14, 146) (239), although not in other

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studies (SEDA-14, 146), and reduced the total body clearance of digoxin, with changes in both renal and non-renal clearances (SEDA-11, 154), although others did not find this (240). In at least one case digoxin toxicity was attributed to this interaction (SEDA-17, 216). In eight patients with chronic heart failure taking digoxin 0.25 mg/day, diltiazem 180 mg/day increased the AUC and mean steady-state serum concentrations of digoxin by 50% and reduced its total clearance (241).

Mibefradil

In 40 healthy subjects mibefradil 50 or 100 mg/day for 6 days had no significant effects on the steady-state pharmacokinetics of digoxin, apart from a very small increase in the C_{max} (242).

Tiapamil

Tiapamil reversed digoxin-induced splanchnic vasoconstriction in healthy men (243), but this has no direct effect on systemic hemodynamics.

Verapamil

Verapamil increases plasma digoxin concentrations at steady state by inhibiting the active tubular secretion and non-renal clearance of digoxin (244,245). There is only anecdotal evidence that this can result in digitalis toxicity (245,246).

Verapamil reversed digoxin-induced splanchnic vasoconstriction in healthy men (243), but this has no direct effect on systemic hemodynamics.

Captopril

There have been contradictory results in studies of the effects of captopril on digoxin pharmacokinetics. In some cases, captopril increased steady-state plasma digoxin concentrations (247), while in others there was no evidence of an interaction (248–251). In eight patients with NHYA Class IV congestive heart failure, captopril 12.5 mg tds for 1 week increased the peak digoxin concentration, reduced the time to peak, and increased the AUC during a single dosage interval at steady state; trough digoxin concentrations did not change (252). There are two possible explanations for these findings: that captopril reduced the clearance of digoxin or that it increased both the rate and extent of absorption of digoxin; unfortunately, the authors did not measure either the mean steady-state concentration or the half-life, which would have clarified this. On the whole, however, it is unlikely that this interaction is of any clinical significance, since in no study has there been evidence of digoxin toxicity during concomitant captopril therapy, and in one formal study (251) there was evidence of no pharmacodynamic interaction.

Cilomilast

In 12 healthy young adults the phosphodiesterase inhibitor cilomilast 15 mg bd for 5 days had no effect on the steady-state pharmacokinetics of digoxin, apart from a small reduction in the maximal concentration and a small increase in the time to peak (253). This was consistent with a small effect on the rate of digoxin absorption, which is unlikely to be of clinical significance. Digoxin had no effect on the disposition of cilomilast.

Cisapride

- In a 90-year-old woman the addition of cisapride 5 mg bd reduced the mean steady-state digoxin concentration from 0.9 ng/ml to 0.6 ng/ml and 5 mg tds reduced it to 0.4 ng/ml, with recurrence of her severe biventricular failure (254). When the doses of digoxin and cisapride were separated, the serum digoxin concentration rose again. The mechanism of this effect is thought to be increased gastrointestinal motility, although in this case the effect of separating the doses suggests that there might be a direct chemical interaction between the two drugs.

Citalopram

In 11 healthy adults citalopram 40 mg/day had no effect on the pharmacokinetics of a single oral dose of digoxin 1 mg (255). Digoxin did not affect citalopram pharmacokinetics.

Clopidogrel

In 12 healthy men steady-state clopidogrel 75 mg/day had no effect on the steady-state plasma concentrations of digoxin (256).

Dihydroergocriptine

The effect of dihydroergocriptine on the pharmacokinetics of a single oral dose of digoxin has been studied in 12 healthy men aged 23–39 years (257). There was no interaction.

Dofetilide

In 14 healthy men dofetilide 250 μg bd for 5 days had no effect on the pharmacokinetics of digoxin at a steady-state trough concentration of 1.0 ng/ml (258). However, in a placebo-controlled study in patients with atrial fibrillation or atrial flutter, conversion to sinus rhythm in patients given dofetilide was more likely if they were also given digoxin (259), so there may be a pharmacodynamic interaction.

Fondaparinux

Fondaparinux sodium, a selective inhibitor of coagulation factor Xa, is eliminated by the kidneys. In a randomized, crossover study in 24 healthy volunteers the pharmacokinetics and pharmacodynamics of digoxin 0.25 mg/day orally for 7 days were unaffected by fondaparinux sodium 10 mg/day subcutaneously for 7 days (260).

Hydralazine

The vasodilator hydralazine increases the renal clearance of digoxin, perhaps by increasing renal blood flow and therefore renal tubular secretion (261). This causes a small fall in plasma digoxin concentration the clinical significance of which is unclear.

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Indometacin

Indometacin increased plasma digoxin concentrations in premature neonates with a patent ductus arteriosus (262), but a formal study in healthy adults showed no interaction (263). It may be that pre-existing impairment of renal function is required for this interaction, but this remains to be elucidated.

Levetiracetam

In 11 healthy adults in a double-blind, placebo-controlled study levetiracetam had no effect on the steady-state pharmacokinetics of digoxin or the actions of digoxin on the electrocardiogram (264).

Macrogol

Macrogol 20 g/day for 8 days caused a 30% reduction in the AUC and a 40% reduction in the C_{max} of a single dose of digoxin in 18 healthy volunteers; the t_{max} and half-life were not affected (265). This interaction was probably due to reduced absorption of digoxin, perhaps by a physicochemical interaction between the two compounds.

Macrolide antibiotics

Although digoxin is not extensively metabolized in the majority of patients, in some it is metabolized before its absorption from the gut, by two mechanisms: hydrolysis by gastric acid and hydrogenation by intestinal bacteria, mainly *Eubacterium lentum*. The macrolide antibiotics and tetracycline increase the systemic availability of digoxin, by inhibiting its breakdown by intestinal bacteria (266,267).

Macrolides have also been suggested to interact with digoxin by inhibiting P glycoprotein (SEDA-26, 200). However, in a study of this mechanism in nine healthy Japanese men, clarithromycin 200 mg bd and erythromycin 200 mg qds did not alter the plasma concentration versus time curve of a single intravenous dose of digoxin 0.5 mg, but increased its renal clearance (268). This contrasts with an observation of reduced renal clearance of digoxin in two patients taking clarithromycin (SEDA-23, 194). That inhibition of renal P glycoprotein may not reduce the renal clearance of digoxin has also been suggested by studies with talinolol (SEDA-25, 172) and atorvastatin (269). Other transport mechanisms for digoxin, including the organic anion-transporting polypeptides, have not been well studied and may play a role in digoxin disposition and hence drug interactions.

Azithromycin

- In a 31-month-old boy with Down's syndrome and Fallot's tetralogy during a 5-day course of azithromycin 5 mg/kg/day the serum digoxin concentration rose and the child had anorexia, diarrhea, and second-degree atrioventricular block with junctional extra beats (270).

The mechanism was not investigated.

Clarithromycin

- In a 72-year-old woman taking digoxin 0.25 mg/day, the addition of clarithromycin caused a rise in the serum digoxin concentration to 4.6 ng/ml (271).

In two other cases in which clarithromycin increased serum digoxin concentrations there was an associated reduction in the rate of renal digoxin clearance, which may be another mechanism for this interaction (272). The authors hypothesized that clarithromycin inhibited P glycoprotein. This was supported by the observation of a concentration-dependent effect of clarithromycin on in vitro transcellular transport of digoxin.

There is anecdotal evidence that this interaction may be clinically important. Digoxin toxicity occurred in a patient taking clarithromycin (273).

Erythromycin

- Digoxin toxicity occurred in a neonate who was also given erythromycin (274). She had bradycardia and coupled extra beats. Digoxin and erythromycin were withdrawn and she was given antidigoxin antibodies. Her plasma digoxin concentration, which had previously been 1.8 ng/ml, had risen to 8.0 ng/ml.

Meglitinides

In 12 healthy volunteers aged 19–36 years nateglinide had no effects on the pharmacokinetics of a single dose of digoxin (275). Similarly, in 14 healthy adults, repaglinide 2 mg three times had no effect on the steady-state pharmacokinetics of digoxin (276). These results suggest that the meglitinides do not affect P glycoprotein.

Nitrates

The effects of nitrates on the pharmacokinetics of digoxin are probably small.

In eight patients with chronic heart failure taking digoxin 0.25 mg/day, isosorbide dinitrate 10 mg tds caused only a small increase in C_{max} (15%) and had no effect on the mean steady-state serum concentration or AUC (241).

Nitroprusside increased the renal clearance of digoxin, perhaps by increasing renal blood flow and therefore renal tubular secretion (261). This caused a small fall in plasma digoxin concentration, the clinical significance of which is unclear.

Phenobarbital

The metabolism of digitoxin can be increased, with resulting increasing dosage requirements, by enzyme-inducing drugs (200). For example, phenobarbital 100 mg daily reduces steady-state serum digitoxin concentrations by 50%.

Propafenone

Propafenone causes a small increase in plasma digoxin concentrations by an unknown mechanism (277,278). Although this effect is perhaps not clinically significant, in patients with dysrhythmias it was accompanied by an increase in PR interval (214).

Quinidine

Digoxin

The quinidine–digoxin interaction has been reviewed (SEDA-6, 173) (SEDA-7, 195) (SEDA-9, 159) (SEDA-10, 145) (SEDA-15, 166) (SEDA-18, 198).

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Although the major mechanism of the interaction is probably inhibition of the active tubular secretion of digoxin by quinidine, other mechanisms are involved, including reduced non-renal clearance and displacement of digoxin from the tissues. The reduction in non-renal clearance is at least partly due to a reduction in biliary clearance. This interaction affects most patients and on average causes a two-fold increase in steady-state plasma digoxin concentrations. Because both clearance and apparent volume of distribution are reduced, the half-life of digoxin is either unaffected or perhaps slightly prolonged.

In addition to the pharmacokinetic interaction, there may be a pharmacodynamic interaction, since there is some evidence that quinidine reduces the positive inotropic effect of digoxin on the heart, in addition to having a negative inotropic effect of its own. Thus, the outcome of the interaction is a 24-fold increased risk of digoxin toxicity and a reduction in its beneficial effect on the heart, at least in sinus rhythm. If the two drugs are used together, the initial digoxin dosage should be halved and adjusted subsequently on the basis of the patient's clinical condition and the plasma digoxin concentration.

Lanatoside C and metildigoxin are theoretically likely to be similarly affected by quinidine, and there is anecdotal evidence of this (279).

The pharmacokinetic interaction of quinidine with digoxin also occurs with quinine (280,281) and hydroxychloroquine (282). However, the effects of these drugs are smaller than those with quinidine. Quinine reduces the extrarenal clearance of digoxin, perhaps by altering its biliary secretion (283).

Digitoxin

In five healthy adults quinidine prolonged the half-life of a single dose of digitoxin from 174 to 261 hours and reduced its total body clearance from 1.54 to 1.09 ml/hour/kg and renal clearance from 0.65 to 0.46 ml/hour/kg. Digitoxin volume of distribution and protein binding were unaffected. Quinidine caused a rise in serum digitoxin concentrations (284).

In eight healthy subjects steady-state digitoxin plasma concentrations and renal excretion increased from 13.6 ng/ml and 16.1 μg/day before dosing to 19.7 ng/ml and 23.4 μg/day respectively during quinidine dosing for 32 days (285). Renal digitoxin clearance was not noticeably changed by quinidine, but total and extrarenal digitoxin clearances fell by 32% and 41% respectively. The half-life of digitoxin was prolonged from 150 to 203 hours. There were corresponding pharmacodynamic effects, as assessed by electrocardiography and systolic time intervals.

Quinolone antibiotics

The quinolone antimicrobial drugs gemifloxacin, levofloxacin, and sparfloxacin do not interact with digoxin.

In a crossover study in 14 healthy elderly individuals gemifloxacin 320 mg/day had no effect on the steady-state pharmacokinetics of digoxin (286).

Levofloxacin 500 mg bd for 6 days in 12 healthy volunteers did not interact with digoxin (287).

The interaction of sparfloxacin with digoxin, both at steady state, has been studied in a double-blind, placebo-controlled, crossover study in 24 healthy men aged 20–49 years. Sparfloxacin had no effect on the steady-state mean plasma concentration, C_{min}, t_{max}, or AUC of digoxin (288). Conversely digoxin did not alter the steady-state pharmacokinetics of sparfloxacin.

Rifampicin

The metabolism of digitoxin can be increased, with resulting increasing dosage requirements, by rifampicin (289).

Rifampicin also induces P glycoprotein and should therefore increase the clearance of digoxin by that mechanism. Some reports (290,291) have suggested that rifampicin reduces the steady-state concentration of digoxin. Another study in eight healthy men has shown that steady-state rifampicin significantly reduced the AUC of oral digoxin but had less of an effect on intravenous digoxin (292). The authors attributed this to induction of P glycoprotein in the intestine, with increased secretion of the drug into the gut lumen. Rifampicin has previously been reported to reduce steady-state plasma digitoxin concentrations, an effect that was attributed to induction of the metabolism of digitoxin to digoxin (289); however, in that study plasma digoxin concentrations were not measured separately, and it may be that rifampicin also increases the secretion of digitoxin into the gut lumen.

Ropinirole

In 10 patients with Parkinson's disease steady-state ropinirole treatment caused small reductions in the AUC and C_{max} of digoxin at steady state (10% and 25% respectively) (293). However, the C_{min} was unaffected and overall there was probably no significant effect of ropinirole on digoxin disposition.

Sevelamer

Sevelamer, a non-absorbed phosphate-binding polymer, in a dose of 2.4 g, had no effect on the pharmacokinetics of single doses of digoxin in 19 healthy volunteers (294).

Spironolactone

Spironolactone inhibits the active tubular secretion of digoxin by about 25% and in some cases digoxin dosages may have to be reduced (295).

St. John's wort (*Hypericum perforatum*)

St. John's wort (*Hypericum perforatum*) had no effect on the pharmacokinetics of digoxin after a single dose in 25 healthy volunteers, but during steady-state therapy it reduced the AUC of digoxin by 25% (296). There were also significant reductions in C_{max} and C_{min} (26% and 33% respectively). This effect was attributed to induction of P glycoprotein.

In Japan enough patients take St. John's wort with a cardiac glycoside to make this interaction potentially important; of 741 outpatients taking St. John's wort, 171 had been given a prescription for either digoxin or metildigoxin (297).

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Statins

The effects of statins on the pharmacokinetics of digoxin have been variable. There is no simple explanation that reconciles the disparate findings.

- A 52-year-old man developed rhabdomyolysis while taking simvastatin, digoxin, ciclosporin, and verapamil (298). The authors proposed that this had been due in part to inhibition of the biliary secretion of simvastatin by digoxin; however, it is likely that the major mechanism of the interaction was inhibition of CYP3A4 by ciclosporin.

Atorvastatin

Atorvastatin 80 mg/day increased the AUC and C_{max} of digoxin 0.25 mg/day by 15% and 20% respectively during steady-state therapy, without affecting renal digoxin clearance (269).

Cerivastatin

In 20 healthy men, cerivastatin had no effect on the steady-state pharmacokinetics of digoxin (299). Digoxin had no significant effect on the pharmacokinetics of cerivastatin.

Fluvastatin

A single dose of fluvastatin increased the steady-state C_{max} of digoxin 0.125–0.5 mg/day by 11% and renal clearance by 15%, without changing AUC or t_{max} (300).

Rosuvastatin

Rosuvastatin 40 mg/day had no effect on the pharmacokinetics of a single oral dose of digoxin 0.5 mg in 18 healthy men (301).

Talinolol

The effects of talinolol on the pharmacokinetics of digoxin have been studied in 10 healthy volunteers aged 23–30 years in a crossover study (302). Oral talinolol 100 mg increased the AUC of digoxin significantly, but the renal clearance and half-life of digoxin were unchanged. Intravenous talinolol 30 mg had no effect on the pharmacokinetics of oral digoxin. The authors concluded that the change in AUC after oral talinolol was due to increased systemic availability of digoxin, through inhibition of intestinal P glycoprotein. They did not discuss the possibility that talinolol had also reduced the non-renal clearance of digoxin by inhibiting its biliary secretion, and indeed there was a small, albeit non-significant reduction in non-renal clearance of digoxin after both oral and intravenous talinolol. In contrast, digoxin did not affect the kinetics of talinolol.

Tamsulosin

The alpha$_1$-adrenoceptor antagonist tamsulosin 0.4 and 0.8 mg/day had no effect on the pharmacokinetics of a single intravenous dose of digoxin 0.5 mg in 10 healthy men (303).

Tegaserod

In 12 healthy subjects the 5-HT$_4$ receptor partial agonist tegaserod 6 mg bd for 3 days had a small effect on the pharmacokinetics of a single oral dose of digoxin 1 mg, reducing the mean AUC by 12% and the C_{max} by 15% (304). There was a small delay in the time to peak, which was not significant. These results suggest that tegaserod slightly reduces the systemic availability of digoxin, perhaps because it increases gastrointestinal motility, but that the effect is of no clinical significance.

Telmisartan

Multiple-dose telmisartan 120 mg/day administered with digoxin 0.25 mg/day resulted in higher serum digoxin concentrations (305). Digoxin AUC rose by 22% and C_{max} by 50%; the rise in C_{min} (13%) was not significant. These results suggest that telmisartan reduces the clearance of digoxin. The magnitude of this effect is comparable to that observed with calcium channel blockers, carvedilol, captopril, amiodarone, quinidine, and propafenone. Monitoring serum digoxin concentrations should be considered when patients first use telmisartan and when the dosage of telmisartan is changed.

Tetracycline

Although digoxin is not extensively metabolized in the majority of patients, in some it is metabolized before its absorption from the gut, by two mechanisms: hydrolysis by gastric acid and hydrogenation by intestinal bacteria, mainly *E. lentum*. Tetracycline increases the systemic availability of digoxin, by inhibiting its breakdown by intestinal bacteria (252).

Tiagabine

Tiagabine, which is principally metabolized by CYP3A, had no effect on the steady-state pharmacokinetics of digoxin in 13 healthy volunteers (306). This is evidence that CYP3A is not important in the metabolism of digoxin.

Warfarin

It has been claimed that digoxin potentiated the effects of warfarin in a 66-year-old man (307). However, the discussion of the possible mechanisms of this observation was flawed, and there is no reason to expect such an interaction, which probably does not occur (308).

Zaleplon

The effects of zaleplon on the pharmacokinetics and pharmacodynamics of steady-state digoxin have been studied in 20 healthy men aged 18–45 years (309). There was no interaction.

Interference with Diagnostic Tests

Digoxin radioimmunoassays

Spironolactone interferes with some digoxin radioimmunoassays, because it and its metabolites, such as canrenone and 7-alpha-thiomethylspironolactone, are

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immunoreactive with some forms of antidigoxin antibody (310–312). However, in contrast to this there has been a recent report that canrenoate, the main metabolite of spironolactone, interfered with the immunoassay of digoxin (313). The effect was largest with the AxSym MEIA II assay, and there was also some interference with the EMIT assay. However, the TDx assay did not show any interference. Spironolactone also caused some interference in the AxSym assay but less than canrenoate. In this case the failure to measure high digoxin concentrations resulted in clinical toxicity in a 71-year-old man who was given 3.8 mg over 11 days.

In a study of the use of the TDx II assay in 80 children and adults, there was apparent digoxin immunoreactivity in 3.7% of healthy subjects ($n = 80$), 3.6% of pregnant women ($n = 28$), 10% of patients with renal transplants ($n = 31$), and 23% of immature infants ($n = 40$) (314).

In nine assays (AxSYM, IMx, TDx, Emit, Dimension, aca, TinaQuant, Elecsys, and Vitros) interference by spironolactone, canrenone, and three metabolites was sought in vitro, and all routine digoxin measurements using the AxSYM system over 16.5 months ($n = 3089$) were reviewed (315). There was a reduction in the expected concentrations by canrenone (3125 ng/ml) in the following assays: AxSYM (42% of expected), IMx (51%), and Dimension (78%). There was positive bias in aca (0.7 ng/ml), TDx (0.62 ng/ml), and Elecsys (>0.58 ng/ml). Of 669 routinely monitored patients, 25 had falsely low results and 19 of them actually had potentially toxic digoxin concentrations; this was attributable to concurrent therapy with spironolactone, canrenone, hydrocortisone, or prednisolone. However, standard doses of spironolactone (up to 50 mg/day) in patients with heart failure produced less than 11% inhibition.

Monitoring Therapy

The use of plasma digitalis concentrations in monitoring therapy has been reviewed (133,316).

In a retrospective analysis of 210 randomly selected digoxin plasma concentration determinations in inpatients, the indications were considered to have been inappropriate in 67, appropriate in 81, and unevaluable in 4 (317). Timing of the blood sample was wrong in 17 cases (samples should be taken at least 6 hours and preferably about 11 hours after the dose). Of the measurements whose indications were considered to have been inappropriate, most (52) were performed as part of "routine" monitoring.

The following are the main uses of plasma digitalis concentration measurements.

Individualizing therapy

In the absence of factors that alter the response to digitalis it may be worth measuring the plasma concentration during the initial stages of therapy to ensure that a reasonable concentration has been achieved (1.0–1.5 ng/ml for digoxin, 10–15 ng/ml for digitoxin). In cases where there is still a poor response to treatment it is justifiable to increase digitalis dosages cautiously, but the risk of toxicity starts to rise markedly at plasma concentrations above 2.0 and 20 ng/ml respectively. If there are subsequent changes in the patient's condition, for example renal impairment, then plasma concentration measurement may help in readjusting dosages.

Monitoring adherence

The commonest cause of a low plasma digitalis concentration in a patient taking a cardiac glycoside is poor adherence to therapy.

Making decisions about long-term therapy

If the plasma digitalis concentration is below the target range in a patient whose condition is stable (for example atrial fibrillation with a ventricular rate of 80/minute) digitalis can usually be withdrawn safely.

Diagnosis of toxicity

The underlying principles in using plasma digitalis concentrations to diagnose toxicity are as follows:

1. The plasma digitalis concentration must be considered in conjunction with other clinical information, that is symptoms, the signs of possible intoxication, the stability of the underlying condition, age, renal function, the dosage, and biochemical measurements such as the plasma potassium concentration.
2. At plasma digitalis concentrations above 3.0 ng/ml (digoxin) or 30 ng/ml (digitoxin) toxicity is highly likely. At concentrations below 1.5 or 15 ng/ml, respectively, toxicity is unlikely. However, toxicity can occur even with low concentrations and should be suspected particularly if there is hypokalemia.
3. Certain factors increase the risk of digitalis toxicity at a given plasma concentration (see Susceptibility Factors). These factors will alter the interpretation of the plasma digitalis concentration and should lower the threshold for suspicion.
4. When in doubt it is far better to withhold digitalis and monitor progress than to continue treatment, thereby running the risk of perpetuating toxicity.

In patients whose condition is satisfactory and stable and whose plasma digoxin concentration is low (below 0.8 ng/ml), withdrawal of digoxin is recommended and is highly unlikely to affect the patient's condition (discussed in the section Making decisions about long-term therapy). Probably the same applies for digitoxin at concentrations below 8.0 ng/ml, although that has not been demonstrated.

It has yet again been confirmed that the serum digoxin concentration distinguishes between patients with and without digoxin toxicity, but with considerable overlap (318). Of 99 patients, 41 with toxicity had mean serum digoxin concentrations of 3.1 ng/ml compared with 1.6 ng/ml in 58 non-toxic patients. However the digoxin concentration was below 2 ng/ml in 10 patients with toxicity and higher than 2 ng/ml in 16 patients without. There were no significant differences in serum electrolyte concentrations between the toxic and non-toxic patients, and the authors therefore concluded that such abnormalities are less important than they have usually been considered to be. However, this study does not demonstrate that at all; rather it shows that even if serum electrolyte concentrations are well controlled it may not be possible to avoid digitalis toxicity for other reasons. Indeed, in this study

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the patients with toxicity had significantly worse renal function, which would have explained their increased risk.

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Carisoprodol

General Information

Carisoprodol is a precursor of meprobamate, an oral anxiolytic with similarities to benzodiazepines. The spasmolytic effect of carisoprodol is thought to be due to interruption of neuronal communication within the reticular formation and spinal cord. Major adverse effects are sedation and drowsiness.

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Organs and Systems

Nervous system

In 104 cases carisoprodol and its metabolite meprobamate were detected in the blood of car drivers who were either involved in accidents or arrested for impaired driving (1). In many of these cases, either alcohol or other nervous system depressants were also found. In 21 cases carisoprodol/meprobamate were the only drugs detected. Symptoms and reported driving behavior were similar in all cases. Impairment of driving ability appeared to be possible at any concentration of these two drugs. However, the most severe driving impairment and most overt symptoms of intoxication were noted when the combined concentration of carisoprodol and meprobamate exceeded 10 mg/l.

Long-Term Effects

Drug dependence

Because of its relation to benzodiazepines, dependence on carisoprodol can be a problem. Among patients who had taken carisoprodol for 3 months or more, up to 40% had used it in amounts larger than prescribed, and up to 30% had used it for an effect other than that for which it was prescribed (2). A significant percentage of physicians were unaware of the potential of carisoprodol for abuse and of its metabolism to meprobamate. Patients with carisoprodol withdrawal can present with agitation, restlessness, hallucinations, seizures, anorexia, and vomiting.

Drug Administration

Drug overdose

Carisoprodol overdose is reportedly rarely fatal. However, a review of the deaths examined at the Jefferson County Medical Examiner Office from 1986 to 1997 revealed 24 cases of carisoprodol overdosage (3). In all 24 cases other co-intoxicants were involved. Since the mechanism of death was respiratory depression in 82% of the cases, the authors suggested that carisoprodol had contributed to the fatal outcome. Carisoprodol overdosage should be regarded as potentially fatal if other respiratory depressants add to its effect.

Carisoprodol intoxication can also be associated with symptoms of nervous system overactivity rather than depression. Agitation and myoclonic movement disorders have been observed (4).

As carisoprodol and its metabolite meprobamate are GABA receptor agonists, the use of the benzodiazepine receptor antagonist flumazenil might be considered in some cases of carisoprodol toxicity (5).

- A 51-year-old woman took 87 tablets of carisoprodol (350 mg each) over 13 days and developed lethargy and abnormal speech. She was confused and her Glasgow Coma Score was 9/15. Her pupils were small and reactive. Two boluses of naloxone 2 mg were administered with no effect. After flumazenil 0.2 mg she became more alert but was still mildly somnolent. After a second dose of flumazenil 0.2 mg all signs of intoxication were reversed within 2 minutes. Her blood concentrations at admission were 7.4 μg/ml for carisoprodol and 30.7 μg/ml for meprobamate.

This suggests that flumazenil may be an effective therapeutic option if carisoprodol intoxication results in nervous system depression. However, carisoprodol overdose can also produce myoclonic movements or agitation (4), in which case it is questionable if flumazenil should be used.

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Carnidazole

General Information

Carnidazole is an imidazole derivative, less potent than most other similar compounds (1). In early studies, its adverse effects were mild; nausea and vomiting, abdominal discomfort, dry mouth, dizziness, headache, and tiredness were reported (SEDA-6, 264). Metronidazole-like adverse effects should be anticipated.

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Carprofen

See also Non-steroidal anti-inflammatory drugs

General Information

The main adverse effects of the NSAID carprofen are cutaneous and hepatic. Photoreactions are being increasingly reported and its chemical similarity to benoxaprofen is worth noting (SEDA-12, 84). The photosensitivity mechanism is either toxic or allergic.

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Other cutaneous symptoms, such as burning, pruritus, dermatitis, and skin redness, have also been reported (1). In trials in the USA, 14% of 1500 patients had slight transient rises in liver function tests, the significance of which is unclear (SEDA-13, 79). Headache, dizziness, gastrointestinal discomfort, and dysuria have also been described (1). Asthma can be precipitated in aspirin-sensitive patients.

Susceptibility Factors

Other features of the patient

Although carprofen is reported to be well tolerated by patients with peptic ulcers taking ranitidine (2), it cannot be presumed to be without risk in patients with ulcer disease.

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Carvedilol

See also Beta-adrenoceptor antagonists

General Information

Carvedilol is a highly lipophilic non-selective beta-adrenoceptor antagonist with alpha$_1$-blocking action, promoting peripheral vasodilatation. It also has free radical scavenging and antimitogenic effects.

The safety and tolerability profile of carvedilol in heart failure appears to be reassuring (1). In trials in patients with congestive heart failure, carvedilol was withdrawn in only about 5% (2). The most common adverse reactions were edema, dizziness, bradycardia, hypotension, nausea, diarrhea, and blurred vision. The rate of drug withdrawal was not different among patients under 65 years and among older ones.

The largest trial of carvedilol in patients with heart failure documented only a 5% withdrawal rate in 1197 patients during the open phase that preceded randomization. The major reasons for withdrawal were worsening heart failure (2%), dizziness (1.1%), bradycardia (0.2%), and death (0.5%). Overall, 78% of the patients who entered the trial and were randomized to carvedilol achieved the target dose of 50 mg/day, and withdrawal rates were comparable with carvedilol and placebo (11–14% over 6.5 months of treatment).

The issue of tolerability is particularly important in patients with severe heart failure (NYHA class IV). Unfortunately, so far all trials with carvedilol have failed to recruit a large number of such patients. A retrospective analysis of the tolerability profile of carvedilol in 63 patients with NYHA class IV heart failure showed that non-fatal adverse events while taking carvedilol were more frequent than in patients with class II-III heart failure (43 versus 24%) and more often resulted in permanent withdrawal of the drug (25 versus 13%) (3). However, 59% of the patients with class IV heart failure improved by one or more functional class after 3 months of treatment. The conclusion was that carvedilol is a useful adjunctive therapy for patients with NYHA class IV heart failure, but these patients require close observation during the start of treatment and titration of the dose.

In patients with heart failure, amiodarone is often required for the treatment of serious ventricular dysrhythmias. The beneficial effects of carvedilol on left ventricular remodeling, systolic function, and symptomatic status were not altered by amiodarone in 80 patients with heart failure. Adverse effects that necessitated withdrawal of carvedilol were no more frequent in patients taking amiodarone than in those taking carvedilol alone (26 versus 25%) (4).

In 10 patients with gastroesophageal varices, none having bled, treated with oral carvedilol 12.5 mg/day for 4 weeks, hemodynamic measurements were performed before the first administration and at 1 hour and 4 weeks after (5). After acute administration, the hepatic venous pressure gradient was significantly reduced by 23% (from 16.4 to 12.6 mmHg), with a significant reduction in heart rate. After 4 weeks, the hepatic venous pressure gradient was further significantly reduced to 9.3 mmHg. Carvedilol was well tolerated, and only one patient had asymptomatic hypotension. The results of this study suggest that low-dose carvedilol significantly reduces portal pressure without significantly systemic hemodynamic effects. The reduction in portal pressure with carvedilol was larger than that obtained with propranolol, encouraging specific trials of carvedilol for the primary prevention of variceal hemorrhage.

Organs and Systems

Cardiovascular

Since the adrenergic system is activated to support reduced contractility of the failing heart, the administration of a beta-blocker in a patient with heart failure can cause myocardial depression. This effect is more marked with non-selective first-generation beta-blockers, such as propranolol. Carvedilol has an acceptable tolerability profile, reducing after-load and thus counteracting the negative inotropic properties of adrenoceptor blockade. While these vasodilatory properties can play a favorable role at the start of treatment, it is less likely that vasodilatation can make a substantial contribution to the long-term effects of third-generation beta-blockers.

As with other alpha-blockers, postural hypotension is quite common with carvedilol, especially in elderly people (6). In a comparison of carvedilol with pindolol in elderly patients, postural hypotension occurred even with small doses of carvedilol (12.5 mg) (7). The authors concluded

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that lower starting doses should be used in elderly people, in patients taking diuretics, and in patients with heart failure.

Liver

Liver function abnormalities in trials of carvedilol occurred in 1.1% of patients taking carvedilol compared with 0.9% in patients taking placebo (2). However, in all trials the patients with pre-existing liver disease were excluded, and so information on the effects of carvedilol in these patients is not available.

Urinary tract

Renal insufficiency can occur in patients with heart failure treated with carvedilol, usually when pre-existing renal insufficiency, low blood pressure, or diffuse vascular disease are present (2). Patients at high risk of renal dysfunction should be carefully monitored, particularly at the beginning of treatment, and the drug should be withdrawn in case renal function worsens.

Skin

- Stevens–Johnson syndrome occurred in a 71-year-old man with stable ischemic cardiomyopathy taking carvedilol (8).

Sexual function

In a comparison of carvedilol with valsartan in 160 patients with hypertension (mean age 46 years) each treatment was continued for 16 weeks, with crossover after 4 weeks of placebo (9). Blood pressure was significantly lowered by both drugs (48% normalization with valsartan and 45% with carvedilol). In the first month of treatment, sexual activity (assessed as the number of episodes of sexual intercourse per month) fell with both treatments compared with baseline, although the change was statistically significant only with carvedilol. After the first month of treatment, sexual activity further worsened with carvedilol, but it improved or recovered fully with valsartan. The results were confirmed by the crossover. This confirms that beta-blockers can cause chronic worsening of sexual function.

Drug Administration

Drug overdose

Overdosage of carvedilol results mainly in hypotension and bradycardia (2). For excessive bradycardia, atropine has been used successfully, while to support ventricular function intravenous glucagon, dobutamine, or isoprenaline have been recommended. For severe hypotension, adrenaline or noradrenaline can be given.

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Catheters

General Information

Adverse effects can arise from physical effects of catheters used for intravenous, intra-arterial, urinary, or spinal access. Adverse reactions can also occur from the latex that some catheters contain or from the antiseptics with which they are sometimes combined.

Central venous catheters are reluctantly used as blood access for hemodialysis because of safety concerns and frequent complications, for example sepsis, thrombosis, and vessel stenosis. Nevertheless, 20% or more of all patients rely on atrial catheters for chronic dialysis because of lack of other access. Potentially fatal risks related to central venous catheters include air embolism (1), severe blood loss (2), and electric shock (3). These specific risks have been substantially eliminated by the inherent design and implantation of Dialock (Biolink Corporation, USA). Dialock is a subcutaneous device consisting of a titanium housing with two passages with integrated valves connected to two silicone catheters. The system is implanted subcutaneously below the clavicle. The tips of the catheters are placed in the right atrium. The port is accessed percutaneously with needle cannulas.

The results of a study of Dialock/CLS have been reported in 70 patients (29 men, 41 women; mean age at implantation 63 (range 30–88) years), of whom 42 had no infection (45 when infections occurring within 30 days after implantation were omitted) (4). Excluding these early events, 25 patients had a total of 30 infections. The majority (22 events in 20 patients) were pocket infections. The first seven of these pocket infections caused loss of the Dialock. After local treatment with gentamicin no further devices were lost through pocket infection. No infections were recorded during the last 3 months, although the expected rate calculated on the basis of

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previous occurrences would have been about four. This may have been related to increased nursing care.

Fracture of a central venous catheter due to compression between the clavicle and the adjacent first rib has been reported (5). A "pinched-off sign" on X-ray indicates the need to remove the catheter, because of a significant risk of subsequent fracture, which has an incidence of 0.9%. Catheters lying anterior to the subclavian vein between the clavicle and the first rib are liable to be compressed and to fracture subsequently. This is a potentially life-threatening complication that can be averted by correct placing of the central venous catheter and by immediate chest radiography to search for evidence of catheter kinking or compression.

Totally implantable venous devices are being increasingly used in patients who require long-term continuous parenteral drug therapy, especially in cancer chemotherapy. Inevitably there have been complications, including catheter fracture, as a consequence of "pinched-off" syndrome (6).

- A 67-year-old woman was provided with a totally implantable venous device in the right subclavian vein by the Seldinger technique with a peel-away sheath. The device was used for a course of chemotherapy. After about 1 month there was subcutaneous extravasation of the drug. A chest X-ray showed that the silicone catheter had fractured below the clavicle and the distal portion of the catheter had embolized into the right atrium. The fragments were removed.

This "pinched-off" effect appears to be due to narrowing of the catheter as it passes over the first rib and beneath the clavicle, when using the Seldinger technique, but it is usually only observed after long-term use. The authors recommended that the cephalic cut-down (Seldinger) technique is best avoided.

Continuous venous access for extended periods is commonly required in patients with cancer for chemotherapy delivery. Transcutaneously tunnelled central venous lines provide one means for the administration of such therapy, although they account for significant costs and morbidity (7). In a prospective study, 923 central venous tunnelled catheters in 791 patients were evaluated for devise-specific events. The most important adverse events included 11 insertion complications. Subsequent to placement, a proven or suspected devise-specific complication occurred in 540 lines. For every 10 000 catheter days there were 17.6 episodes of infection, 8.1 thrombotic complications, 6.9 instances of catheter breakage, 3.5 accidental or inadvertent cases of catheter displacement, and 0.6 device leaks. The devices were in position for a median of 365 days, but the median duration of device-specific complications was 167 days, reflecting a highly significant device salvage rate after complications. The authors concluded that central lines can be placed safely for use in long-term administration of cancer chemotherapy. Factors determining outcome are related to where the device is placed as well as the patient's disease.

Migration of a catheter caused failure of parenteral nutrition in a baby (8).

- A premature small-for-dates girl (34 weeks gestation, birth weight 1000 g) received parenteral nutrition for necrotizing enterocolitis. On day 7, among several septic spots that developed on the skin, an abscess developed on the left shoulder and ruptured spontaneously, leaving a superficial ulcer with purulent discharge. This was cleaned daily with isotonic saline and covered with gauze. On day 11, the blood glucose fell to 1.3 mmol/l and 10% glucose was given. Four further episodes of hypoglycemia during the next 12 hours were similarly treated. Over the next 12 hours the baby became lethargic, hypothermic, and apneic. Her blood glucose remained low (0.9–1.6 mmol/l). Several hours later she became bradycardic and hypotensive. It was then noticed that her bed linen was wet, and some fluid was seen trickling from the ulcer on her shoulder. A chest X-ray showed that the catheter tip had migrated to the left cephalic vein adjacent to the site of the ulcer. Despite rigorous resuscitation she died.

The authors speculated that the catheter tip had spontaneously migrated because the ulcer on the left shoulder had eroded deeply to form a venocutaneous fistula with the left cephalic vein. Continuous leakage of parenteral nutrition fluid through the fistula was soaked up by the gauze pads used to cover the ulcer, preventing early recognition of the problem.

In a systematic review of randomized studies of the use of different catheter materials for umbilical catheterization in newborn infants of any birth weight or gestation, there were no significant differences between heparin-bonded polyurethane catheters and polyvinyl chloride (PVC) catheters (9).

Organs and Systems

Cardiovascular

A major complication of intravenous infusion is thrombophlebitis, which is a principle limitation of peripheral parenteral nutrition. Its precise pathogenesis is unclear, but venospasm has been proposed as the most likely cause. However, in a study with ultrasound techniques to monitor vein caliber, there was no evidence to support this hypothesis, although thrombophlebitis was observed (10). The author suggested that the initiating event may be venous endothelial trauma, caused by the venepuncture itself, abrasion at the catheter tip, or the delivery of the feeding solution.

Venous reactions could also theoretically be influenced by the composition of the fat emulsion, because long-chain triglycerides, in particular, generate prostaglandin synthesis which can in turn effect vein tolerance. This potentially important issue has been assessed in a randomized, comparative trial of peripheral parenteral nutrition regimens with fat emulsions containing either long-chain triglycerides alone or in equal proportions with medium-chain triglycerides (11). All other factors were standardized. Long-chain triglyceride-based fat emulsions significantly prolonged the life of the peripheral vein, compared with mixtures of medium-chain and long-chain triglycerides. The authors hypothesized that this effect was due to a reduced reaction of the venous epithelium to the irritating nutritional mixture.

Superior vena cava thrombosis has been described after frequent central venous catheterization and total parenteral nutrition, with eventual partial recovery (12).

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The possible etiological factors included the catheter material, catheter-related sepsis, endothelial trauma, osmotic injury, and hypercoagulability. Although thrombosis of the great veins of the thorax is rare, it is life-threatening, characterized by swelling of the head, upper limbs, and torso, and on chest X-ray by mediastinal widening. Confirmation of thrombosis is best achieved by contrast venography or contrast-enhanced CT scan.

Cardiac tamponade is a serious complication of central venous catheterization. A classical case history has been described with detailed discussion of prevention and management (13). Most serious complications, including air embolism, pneumothorax, hemothorax, chylothorax, chylopericardium, rupture of the right atrium, ventricular dysrhythmias, and cardiac tamponade, are essentially mechanical injuries relating to catheter insertion. Cardiac tamponade can be caused by acute perforation of the superior vena cava during insertion. Alternatively, a delayed event may be due to catheter-related erosion of the vascular wall, either in the vena cava or in the ventricular wall. The consequences are impairment of diastolic filling and a dramatic decrease in cardiac output, with a very high death rate (about 70%).

- A 63-year-old man with cancer of the esophagus developed severe dysphagia. A central venous catheter was introduced for presurgical parenteral nutrition and 3 hours later he reported severe epigastric and retrosternal pain. His condition deteriorated rapidly, with loss of consciousness, a weak pulse, hypotension, distant heart sounds, and jugular venous distension. A chest X-ray showed an enlarged mediastinal shadow and an electrocardiogram showed reduced voltage. The catheter was promptly removed. An emergency laparotomy showed only hepatic engorgement and about 100 ml of ascites, but at thoracotomy the pericardial sac was distended by about 500 ml of clear fluid. There was no apparent injury to the right subclavian artery or evidence of pleural hemorrhage.

The authors concluded that the right ventricle had been perforated by the catheter and they pointed out that these events can be insidious, and can take several months before symptoms suddenly start, requiring quick diagnosis and immediate intervention. This includes immediate removal of the catheter and often also emergency surgical intervention.

Respiratory

Lung transplant patients appear to be at increased risk of air embolism from catheters perhaps because of the considerable negative intrathoracic pressure that can develop when the diseased lung is replaced with a normal lung. Lung transplant patients are often also emaciated and have little subcutaneous tissue, allowing for a short tract from the central venous line insertion site to the opening of the central vein.

- A 53-year-old woman developed a serious air embolism from the central venous catheter tract after lung transplantation, at the time of removal of the catheter (14).

The authors referred in their report to four other cases of air embolism in lung transplant patients.

Nervous system

Complications have been described after the insertion of 157 intrathecal catheters in 142 patients (15). In most cases problems were related to the placement procedure, with subsequent neurological complications. Clinically unsuspected degeneration of the posterior columns, perhaps related to intraspinal infusion of morphine or to a paraneoplastic effect, has been observed postmortem in two patients with implanted pumps (16).

Paraplegia has been reported 2 months after morphine infusion by intrathecal catheter (17). Another case of paraplegia was reported in a 73-year-old man with an intrathecal catheter and a spinal cord stimulator (18).

Fluid balance

Umbilical venous catheters are commonly used in neonatal care for drug administration and parenteral nutrition. However, many risks are associated with their use. Ascites associated with parenteral nutrition have been reported (19).

- A girl weighing 1488 g was born by emergency cesarean section at 28 weeks gestation. An umbilical venous catheter was inserted as sole venous access. An abdominal X-ray showed that the catheter was at the level of T11/T12 in the midline. Owing to complications with oral feeding, parenteral nutrition was begun on day 2. The baby developed necrotizing enterocolitis and had to be ventilated. An abdominal X-ray suggested abdominal ascites. A diagnostic paracentesis produced 90 ml of bloodstained opalescent fluid, which settled to show a white layer on the surface (presumed to be fat emulsion). Following this procedure, respiratory status improved. Ultrasound and aerated saline tests on the umbilical venous catheter suggested that it had not migrated to the peritoneal cavity. However, it was removed and the abdominal distension resolved. The baby was extubated 3 days later and subsequently thrived with no further abdominal problems.

Hematologic

Heparinization of the fluid infused through an umbilical arterial catheter with heparin 0.25 units/ml reduces the likelihood of catheter occlusion; heparinization of flushes without heparinizing the infusate is ineffective (20).

Immunologic

Anaphylaxis to a central venous catheter (ARROWg+ard Blue Catheter) coated with chlorhexidine and sulfadiazine has been reported in a 50-year-old man (21).

Infection risk

Systemic catheter-related infections and local infections at catheter exit sites have been studied in relation to 479 central venous catheters in a prospective study in 311 patients in a general hospital in Australia (22). Local infections developed in association with 54 catheters (11%) and systemic infections with 32 (6.7%). Local

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infections predicted systemic infections, but the absence of a local infection did not exclude the possibility of systemic infection. Local complications included entry-site abscesses, cellulitis, and septic thrombophlebitis. Hemodialysis catheters were responsible for a higher rate of systemic infections than other types. Of all cases of bacteremia (33/160) detected in the hospital, 20% occurred in patients with a central venous catheter, and 24 of these (73%) were definitely or probably due to the catheter. The most common organism responsible was methicillin-resistant *Staphylococcus aureus*, and 40% of cases were due to catheter-related infection. Infection complications were few: three patients developed local abscesses, one developed endocarditis, and two died. In other surveys infective endocarditis has complicated 20% of systemic catheter-related infections, but it occurred only once in this study. It is possible that the short duration of this study (5 months) resulted in an underestimate of the real incidence of late complications of catheter-related infections. Innocuous in situ catheters can apparently be responsible for systemic infections. In other studies the risk of infection depended mainly on the duration of catheter therapy (23,24).

Catheter-related bacteremia due to *Pseudomonas paucimobilis* has been reported in two patients with cancer-associated neutropenia (25). This organism has rarely been implicated in community-acquired and nosocomial infections. Both patients had been undergoing intensive chemotherapy, and both required removal of the catheter to eradicate the infection.

There is some disagreement as to whether infectious complications differ with the use of different types of chronic central venous access devices in patients with cancer. In one study there was no significant difference in the risk of infection between subcutaneous ports and external catheters (26). However, this has been disputed by other workers, who found that in children with cancer there was a lower infection rate when subcutaneous ports were used compared with external catheters (27). The differences between the studies and the conclusions reached may be the result of their size and design, rather than real differences.

In 55 patients, continuous lumbar sympathetic blockade with local anesthetics administered via a catheter to treat sympathetic pain caused a psoas abscess in two patients, both of whom were treated with a continuous infusion of 0.25% bupivacaine (28). It was assumed that the catheter had been dislodged and that the drug had been injected into the psoas muscle or the psoas sheath. Another reason for this complication could have been local trauma due to a hematoma around the vertebrae during the insertion of the needle. The main drawbacks of the technique were the high incidences of infections and displacement of the catheters.

Infective endocarditis is a serious complication of centrally placed venous access devices. The successful treatment in situ of a large thrombus associated with the tip of the catheter has been described (29). The antibiotic regimen was gentamicin and vancomycin, both delivered via the venous access device; vancomycin was allowed to remain in situ between each 8-hourly dosing. This regimen successfully eradicated the thrombus within 3 weeks, without removal of the line.

In a prospective, double-blind study, the use of either vancomycin + heparin + ciprofloxacin or vancomycin + heparin flush solution, compared with heparin alone, significantly reduced the infective complications associated with tunnelled central venous lines in immunocompromised children. Neither antibiotic could be detected after flushing and there were no adverse events (30).

The incidence and types of complications related to central venous catheters in 71 patients with AIDS have been studied and compared with two control groups of patients without AIDS (65 immunocompromised patients and 14 immunocompetent patients receiving home total parenteral nutrition) (31). Three groups of patients requiring permanent venous access for administration of virustatics and/or total parenteral nutrition were investigated retrospectively. The Port-A-Cath system of implantation was used in all cases. Catheter-related mortality was low in all the groups (0–1%). Infectious complications could not be related to the degree of immunosuppression (CD4+ lymphocyte counts or white blood cell count). The incidence of both infectious and non-infectious complications was significantly higher in the immunocompetent subjects than in the others, probably because of the type of medium used and/or differences in handling of the catheter. The overall conclusions were that central venous catheters are safe and well tolerated by patients with AIDS and that they present no greater risk to them than they do to other categories of patients, regardless of degrees of immune competence. This conclusion should be regarded with some caution, given the retrospective nature of the study and the imbalance in the number of subjects studied in each category. However, it appears that totally implantable central venous catheters are safe and well tolerated by patients with AIDS, no differently to other immunocompromised patients and immunocompetent patients.

Total parenteral nutrition

Catheter sepsis rates in total parenteral nutrition are variable, depending on several patient factors. These include immunosuppression or associated critical illness, multiple intravascular catheters, and bacterial transfer from another source in the body. Catheter-related sepsis can present as fever, chills, change in mental status, hypotension, and leukocytosis. In patients with suspected catheter-related infection whose peripheral blood cultures do not grow the same organism as a culture drawn directly from the catheter, a guide wire exchange of the catheter may be effective. However, this is a surgical procedure which can become complicated by catheter malposition, air embolism, dislodgement of a septic thrombus, or cardiac dysrhythmias (32).

In a study of catheter infection in patients treated with total parenteral nutrition a distant septic focus was present in 165 of 244 patients (188 of 269 catheters: 70%). There was a colonization rate of 19% of the catheters of the patients with a distant septic focus, compared with 7.4% in patients without a distant septic focus. There was a high mortality rate in patients with a distant septic focus and a colonized catheter; sepsis was responsible for 33 of the 48 deaths (69%) in this group (33).

If a centrally placed venous catheter is required, tunnelling of the catheter under the skin from the entry point to the appropriate vein minimizes the risk of infection,

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and the inclusion of an internal cuff on the catheter provides a more reliable subcutaneous anchor point. The purpose of the cuff is to fibrose to the wall of subcutaneous tissue, helping to prevent dislodgement of the catheter and reduce the risk that infection will migrate from the entrance site in the skin. Cuffed catheters can be composed of polyurethane or silicone. It has been suggested that the former is better, because they are theoretically less thrombogenic. However, in a prospective study there was no difference between the two types (34). Mean catheter lifespans were similar, as were complication rates (including sepsis, obstruction, dislodgement, and thrombosis). However, fractures were entirely associated with the detachable flow-control devise. The authors therefore concluded that there was little evidence to support the hypothesis that polyurethane catheters offer more security in long-term parenteral nutrition.

Catheter infections in recipients of parenteral nutrition are of particular concern in children and can result in line removal, deep vein thrombosis, or an increased risk of liver disease. The incidence of catheter-related infections in 47 children receiving long-term parenteral nutrition has been studied retrospectively, one goal being to identify potential risk factors (35). The children had 125 catheters and 207 catheter-years. The average infection rate was 2.1/1000 parenteral nutrition days. The only factor identified was that early onset of infection after starting parenteral nutrition appeared to predict a poor prognosis.

HIV-positive subjects are expected to be at even greater risk of line-related infection. A prospective study of 212 subjects with HIV infection with 327 central venous catheters has provided evidence of this enhanced risk (36). Over the period 1994–97, 33% were suspected as being infected, although only 61 episodes were diagnosed as catheter-related sepsis. Three variables affected the rate of sepsis: parenteral nutrition, low numbers of circulating CD+ cells, and a high Apache score.

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Celastraceae

See also Herbal medicines

General Information

The genera in the family of Celastraceae (Table 1) include bittersweet and khat.

Table 1 The genera of Celastraceae

Canotia (canotia)
Cassine (cassine)
Catha (khat)
Celastrus (bittersweet)
Crossopetalum (crossopetalum)
Euonymus (spindle tree)
Gyminda (false box)
Lophopyxis
Maytenus (mayten)
Mortonia (saddlebush)
Pachystima (pachystima)
Paxistima (paxistima)
Perrottetia (perrottetia)
Pristimera (pristimera)
Salacia
Schaefferia (schaefferia)
Torralbasia (torralbasia)
Tripterygium

Catha edulis

Chewing the leaves of *Catha edulis* (khat, qat) results in subjective mental stimulation, increased physical endurance, and increased self-esteem and social interaction. Until recently, this habit was confined to Arabian and East African countries, because only fresh leaves are active, but because of increased air transportation, khat is now also chewed in other parts of the world. Although cathine (norpseudoephedrine) is quantitatively the main alkaloid, the amphetamine-like euphorigenic and sympathomimetic cardiovascular effects of khat are primarily attributed to cathinone (1). In Yemen chewers of khat produced in fields where chemical pesticides are used regularly have more symptoms than chewers of khat produced in fields where chemical pesticides are rarely or never used (2).

The toxicologist Louis Lewin described the effects of chewing khat in his monograph *Phantastica* (1924): "The khat eater is happy when he hears everyone talk in turn and tries to contribute to this social entertainment. In this way the hours pass in a rapid and agreeable manner. Khat produces joyous excitation and gaiety. Desire for sleep is banished, energy is revived during the hot hours of the day, and the feeling of hunger on long marches is dispersed. Messengers and warriors use khat because it makes the ingestion of food unnecessary for several days."

Adverse effects

Tachycardia and increased blood pressure, irritability, psychosis, and psychic dependence have been described as acute adverse effects of khat.

The long term adverse effects were well described by Louis Lewin: "Those organs functions which are incessantly subjected to the influence of the drug finally flag or are diverted into another channel of activity ... The khat eater is seized with a restlessness which robs him of sleep. The excited cerebral hemispheres do not return to their normal state of repose, and in consequence the functions of the peripheral organs, especially those of the heart, suffer to such a degree that serious cardiac affectations have been ascertained in a great number of khat eaters. The disorders of the nervous system in many cases also give rise to troubles of general metabolism partly due to the chronic loss of appetite from the consumption of khat ... In Yemen it was openly stated that inveterate eaters of khat were indifferent to sexual excitation and desire, and did not marry at all, or for economic reasons waited until they had saved enough money. The lost of libido sexualis has been also observed in other inhabitants of these countries."

Cardiovascular

When 80 healthy volunteers chewed fresh khat leaves for 3 hours there were significant progressive rises in systolic and diastolic blood pressures and heart rate, without return to baseline 1 hour after chewing had ceased (3).

Of 247 chronic khat chewers 169 (62%) had hemorrhoids and 124 (45%) underwent hemorrhoidectomy; by comparison, of 200 non-khat chewers 8 (4%) had hemorrhoids and one underwent hemorrhoidectomy (4).

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Nervous system
Of 19 khat users suspected of driving under the influence of drugs, three had impaired driving and 10 had marked impairment of psychophysical functions with effects on the nervous system (slow pupil reaction to light, dry mouth, increased heart rate), trembling, restlessness/nervousness, daze/apathy/dullness, and impaired attention, walking, and standing on one leg; however, the concentrations of the khat alkaloids assayed in blood did not correlate with the symptoms of impairment (5).

A leukoencephalopathy has been associated with khat (6).

Psychiatric
Khat has amphetamine-like effects and can cause psychoses (7–13), including mania (14) and hypnagogic hallucinations (15). Two men developed relapsing short-lasting psychotic episodes after chewing khat leaves; the psychotic symptoms disappeared without any treatment within 1 week (16).

In 800 Yemeni adults (aged 15–76 years) symptoms that might have been caused by the use of khat were elicited by face-to-face interviews; 90 items covered nine scales of the following domains: somatization, depression, anxiety, phobia, hostility, interpersonal sensitivity, obsessive-compulsive, hostility, interpersonal sensitivity, paranoia, and psychoticism (17). At least one life-time episode of khat use was reported in 82% of men and 43% of women. The incidence of adverse psychological symptoms was not greater in khat users, and there was a negative association between the use of khat and the incidence of phobic symptoms.

Psychological
In 25 daily khat-chewing flight attendants, 39 occasional khat-chewing flight attendants, and 24 non-khat-chewing aircrew members, memory function test scores were significantly lower in khat chewers than non-chewers and in regular chewers than occasional chewers (18).

Sensory systems
Bilateral optic atrophy occurred in two patients who were long-standing users of khat leaves and had chewed larger quantities than usual (19).

Metabolism
Chronic khat chewing increased plasma glucose and C-peptide concentrations in people with type 2 diabetes mellitus (20).

Mouth
In 20 volunteers who chewed khat regularly (10–160 g/day), there was an eight-fold increase in micronucleated buccal mucosa cells compared with 10 controls (21). Among heavy khat chewers, 81% of nuclei had a centromere signal, suggesting that khat is aneuploidogenic. The effects of khat, tobacco, and alcohol were additive. The highest frequency of abnormality occurred during the fourth week after consumption.

Of 2500 Yemeni citizens (mean age 27 years) 1528 (61%) were khat chewers; of them, 342 cases (22%) had oral keratotic white lesions at the site of khat chewing, while only 6 (0.6%) non-chewers had such lesions; the prevalence and severity of these lesions increased as duration and frequency of use increased (22).

However, in a case-control study in 85 khat-chewing Kenyans and 141 matched controls, smoking unprocessed tobacco (Kiraiku) and smoking cigarettes were the most significant factors for oral leukoplakia; traditional beer, khat, and chili peppers were not significantly associated with oral leukoplakia (23).

A 30-year-old immigrant from Somalia developed a plasma-cell gingivitis in the mandibular gums, probably caused by chewing khat (24).

Chewing khat can cause a generalized mousy brown pigmentation of the gums (25).

Gastrointestinal
In 12 healthy volunteers who chewed Khat leaves or lettuce for 2 hours gastric emptying was significantly prolonged by khat (26).

Chewing khat is said to be a risk factor of duodenal ulceration. (27).

Urinary tract
In 11 healthy men khat chewing produced a fall in average and maximum urine flow rate; this effect was inhibited by the alpha$_1$-adrenoceptor antagonist indoramin (28).

Sexual function
Chewing khat lowers libido and can also lead to erectile impotence after long-term use (29).

Fertility
In 65 Yemeni khat addicts (mean duration of addiction 25 years; mean age 40 years), semen volume, sperm count, sperm motility and motility index, and percentage of normal spermatozoa were lower than in 50 controls (30). There were significant negative correlations between the duration of khat consumption and all semen parameters. On electron microscopy, about 65% of the spermatozoa were deformed, with different patterns of deformation, including both the head and flagella in complete spermatozoa, aflagellate heads, headless flagella, and multiple heads and flagella. Deformed heads had aberrant nuclei with immature nuclear chromatin and polymorphic intranuclear inclusions; these were associated with acrosomal defects.

Fetotoxicity
In pregnant women, consumption of khat affects fetal growth by inhibiting placental blood flow (29), and birth weights are reduced (31). In 1141 consecutive deliveries in Yemen, non-users of khat ($n = 427$) had significantly fewer low birth-weight babies (less than 2500 g) than occasional users ($n = 223$) and regular users ($n = 391$) (32). Khat-chewing mothers were older, of greater parity, and had more surviving children than the non-chewers. Significantly more khat-chewers had concomitant diseases. There was no difference in rates of stillbirth or congenital malformations.

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Lactation
Khat chewing by a breastfeeding mother can lead to the presence of cathine in the urine of the suckling child.

Drug interactions
The speed and extent of ampicillin systemic availability were reduced significantly by khat chewing in eight healthy adult Yemeni men, except when they took it 2 hours after the khat (33).

Euonymus species

The fruit of *Euonymus europaeus* (the European spindle tree) and the bark of *Euonymus atropurpureus* (Wahoo bark) have cathartic and emetic activity, due to sesquiterpenoids and cardiac glycosides that they contain.

Adverse effects
IgE-mediated type I allergy to *E. europaeus* wood has been described in a 44-year-old goldsmith who developed rhinitis and conjunctivitis after having worked with dust from the wood for 15 years (34).

Tripterygium wilfordii

Extracts from the root of *Tripterygium wilfordii* (Lei gong teng) are used in China for the treatment of various disorders, such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and glomerulonephritis. The potential benefits in such serious diseases should be carefully weighed against a substantial risk of adverse reactions, including gastrointestinal disturbances, skin rashes, amenorrhea, leukopenia, and thrombocytopenia (35).

Adverse effects
Cardiovascular

- A previously healthy young man developed profuse vomiting and diarrhea, leukopenia, renal insufficiency, profound hypotension, and shock after taking an extract of *T. wilfordii* (36). Serial electrocardiograms, cardiac enzymes, and echocardiography showed evidence of coexisting cardiac damage. He died of intractable shock 3 days later.

Gastrointestinal
In a double-blind, placebo-controlled study in 35 patients with long-standing rheumatoid arthritis in whom conventional therapy had failed, an extract of *T. wilfordii* was used in either a low-dose (180 mg/day) or a high-dose (360 mg/day) for 20 weeks, followed by an open extension period (37). Only 21 patients completed the study, of whom one in each group withdrew because of adverse events. The most common adverse effect of *T. wilfordii* was diarrhea, which caused one patient in the high-dose group to withdraw.

Reproductive system
In men, prolonged use of *T. wilfordii* can cause oligospermia and azoospermia, and a reduction in testicular size (38–40).

In 14 women with rheumatoid arthritis *T. wilfordii* caused amenorrhea associated with increased FSH and LH concentrations, which began to rise after 2–3 months and reached menopausal values after 4–5 months; estradiol concentrations began to fall after 3–4 months and reached very low concentrations at 5 months, suggesting an effect on the ovary (41).

Immunologic
The immunosuppressive properties of Lei gong teng can promote the development of infectious diseases (42).

Teratogenicity
A boy whose mother had taken *T. wilfordii* for rheumatoid arthritis early in her pregnancy was born with an occipital meningoencephalocele and cerebellar agenesis, which the authors attributed to the herb (43).

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Celecoxib

See also COX-2 inhibitors

General Information

Celecoxib is a selective COX-2 inhibitor.

Organs and Systems

Psychological, psychiatric

A 78-year-old woman had auditory hallucinations while taking celecoxib for osteoarthritis (1). Her symptoms occurred after she had taken celecoxib 200 mg bd for 48 hours and progressed over the next 8 days. Celecoxib was withdrawn and her hallucinations gradually disappeared over the next 4 days. Rechallenge with a lower dose (100 mg bd) caused recurrence.

There have been two reports of visual hallucinations in patients taking celecoxib.

- A 79-year-old woman presented to her optometrist with a 2-day history of seeing orange spots in both visual fields 2 months after starting to take celecoxib 100 mg/day (2). Physical examination and a CT scan were normal. Celecoxib was withdrawn and her symptoms resolved within 3 days.
- An 81-year-old woman took celecoxib 100 mg/day, and over the next 2 weeks developed delirium and auditory and visual hallucinations (3). Celecoxib was withdrawn and her symptoms resolved over several days. She took a few doses of rofecoxib 12.5 mg/day 6 months later without any problem. She began to take rofecoxib regularly again 2 months later, and after 1 month developed agitation, confusion, and hallucinations. Physical examination suggested no cause of the delirium other than rofecoxib. A CT scan was negative. The rofecoxib was withdrawn, and over the next 2 days her symptoms resolved

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Auditory hallucinations have been previously reported in a patient taking celecoxib (SEDA-25, 134) but are probably uncommon.

Hematologic

A report has raised the possibility that patients with a known prothrombotic state and raised platelet thromboxane A_2 production may be at high risk of thrombosis when selective COX-2 inhibitors are used (4).

Thrombosis occurred during celecoxib therapy (400 mg/day) in four women (aged 37–56 years) with connective tissue diseases and conditions that predisposed them to thrombosis, including Raynaud's phenomenon, raised anticardiolipin antibody titers, and a previous history of thrombosis. Peripheral artery thrombosis (three patients) and pulmonary embolism (one patient) were documented after starting celecoxib. Symptoms of thrombosis began to appear within 1 week of starting celecoxib in three patients and 2 months after starting celecoxib in the fourth patient.

A causal relation between celecoxib and these thrombotic events cannot be established with certainty on the basis of the available evidence. However, the temporal relation between the start of treatment and the thrombotic event was impressive, at least in three patients, and the findings were consistent with the hypothesis that thrombosis is an adverse consequence of reduced production of systemic prostaglandin I_2 brought about by COX-2 inhibition. Reduced synthesis of prostaglandin I_2 may act in concert with other thrombotic risk factors (such as those occurring in this series of patients) to precipitate acute vascular occlusion.

Gastrointestinal

Celecoxib reportedly exacerbated inflammatory bowel disease in two patients (5).

- An 80-year-old woman with ulcerative colitis started taking celecoxib for arthritic pain, and 3 days later developed abdominal pain and diarrhea. Celecoxib was withdrawn and her symptoms improved.
- A 35-year-old woman with ileal and perianal Crohn's disease took four doses of celecoxib for an orthopedic injury, and had rectal bleeding, severe abdominal pain, and worse diarrhea. Celecoxib was withdrawn and her symptoms returned to baseline within 5 days.

The possible association of NSAIDs with inflammatory bowel disease is a matter of controversy (SEDA-25, 131), and there is little clinical experience with the selective COX-2 inhibitors. Coxibs should not be prescribed for patients with chronic inflammatory bowel disease until more experience has accumulated.

Liver

A 67-year-old woman developed acute hepatocellular and cholestatic liver damage after taking celecoxib 100 mg/day for 1 week (6). Celecoxib was withdrawn and the liver function tests normalized within 2 weeks.

There have been three case reports of acute cholestatic hepatitis in patients taking celecoxib.

- A 55-year-old non-alcoholic obese woman, who was allergic to sulfa drugs, presented with a 5-day history of jaundice, malaise, and a pruritic rash that began 3 weeks after she started to take celecoxib 200 mg/day for radicular pain (7). There were marked increases in liver enzymes and bilirubin and a peripheral eosinophilia. Liver biopsy showed marked intrahepatocyte cholestasis with eosinophil-rich inflammation, consistent with a drug reaction. Her symptoms and laboratory abnormalities completely resolved after withdrawal of celecoxib but took a long time (4 months) to normalize.
- A 54-year-old woman took celecoxib 200 mg/day for sacroiliac pain (8). After 4 days her pain resolved, but she developed generalized pruritus, which resolved when celecoxib was withdrawn. A week later, the pain recurred and celecoxib was restarted; 2 days later she again developed pruritus associated with dark urine, and 5 days later jaundice and raised bilirubin and liver enzymes. Her eosinophil count was raised. On withdrawal of celecoxib her liver function tests improved and her symptoms resolved.
- A 49-year-old man with alcoholic cirrhosis developed jaundice, fatigue, and choluria after he started to take celecoxib 200 mg/day for musculoskeletal pain (9). There were increases in transaminases, alkaline phosphatase, and bilirubin (to 547 μmol/l). Liver biopsy showed cirrhosis and marked hepatocellular cholestasis. On withdrawal of celecoxib the bilirubin began to fall very slowly; 1 year later he was well, with a total bilirubin concentration of 44 μmol/l.

The histories, clinical findings, and laboratory tests in these cases all suggested celecoxib-induced acute cholestatic hepatitis. The first case suggested that a sulfonamide-like allergic reaction was the pathogenic mechanism, and the same mechanism cannot be excluded in the other two patients, as sulfonamide allergy is often ignored and is discovered only when an adverse reaction occurs. Celecoxib should not be given to patients who are allergic to sulfa drugs.

Urinary tract

As more experience accumulates it appears clear that COX-2 inhibitors have a nephrotoxic potential similar to that of the non-selective NSAIDs. Sixteen cases of tubulointerstitial nephritis were reported to the manufacturers of celecoxib between the time when it was launched in 1999 and July 2001, but the diagnosis was not confirmed in 12 of these cases (10). Most of these renal adverse reactions occur in patients with susceptibility factors associated with prostaglandin-dependent renal function (11–13).

Skin

Skin reactions, including rashes, urticaria, and other allergic reactions, are not uncommon, according to data reported to the Australian Adverse Reactions Advisory Committee (14) and other reports (15–17).

Stevens–Johnson syndrome occurred in a 58-year-old man taking celecoxib (18). He recovered promptly after withdrawal. The reaction recurred 1 month later, after one dose of celecoxib.

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Sweet's syndrome can be associated with several drugs. A case involving celecoxib has been reported (19).

- A 57-year-old man developed the typical cutaneous erosions and plaques of Sweet's syndrome after taking celecoxib 100 mg bd for 1 week for bursitis. Celecoxib was withdrawn and the mucocutaneous lesions began to clear. However, the bursitis recurred and he restarted celecoxib. The cutaneous lesions worsened dramatically. After withdrawal of celecoxib for the second time the lesions cleared completely.

Drug–Drug Interactions

Clopidogrel

Co-administration of celecoxib and clopidogrel can increase the hemorrhagic potential of clopidogrel, possibly by a pharmacokinetic interaction involving CYP2C9 (20). However, this possibility requires confirmation, as serious, sometimes fatal, hemorrhage has been reported during the postmarketing use of clopidogrel alone (21).

Warfarin

Celecoxib can potentiate the anticoagulant effects of warfarin. Although concomitant administration of celecoxib and warfarin had no significant effect on prothrombin time or the steady-state pharmacokinetics of *S*-warfarin or *R*-warfarin in 24 healthy volunteers (22), serious bleeding complications have been reported to adverse drug reactions monitoring systems (23) and in journals (24–26). These data suggest that celecoxib potentiates the anticoagulant effects of warfarin in some patients. Patients taking warfarin must be fully monitored when celecoxib is adding, changed, or withdrawn.

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Celiprolol

See also Beta-adrenoceptor antagonists

General Information

Celiprolol is a beta$_1$-selective antagonist with partial beta$_2$-agonist activity. In healthy volunteers it caused "particularly unpleasant" subjective adverse effects, including headache, sleepiness, and feeling cold and generally unwell (1). However, it has beneficial effects on lipids, reducing total cholesterol by 6% and low-density lipoproteins by 10% (SEDA-17, 235). Whether this translates into clinical benefit is not known, and celiprolol has no convincing advantages over other beta-blockers (2).

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Organs and Systems

Respiratory

There has been a report of hypersensitivity pneumonitis secondary to celiprolol (3).

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Cephalosporins

See also Beta-lactam antibiotics

General Information

The cephalosporins represent a family of beta-lactam antibiotics originally derived from the naturally occurring cephalosporin C. Isolation of the cephalosporin C nucleus, 7-aminocephalosporanic acid, made it possible to introduce new groups into this molecule to obtain the current variety of compounds (1). Cephalosporins vary widely in their antibacterial properties, beta-lactamase stability, and pharmacokinetic behavior, but there is as yet no unequivocal classification (2). For reasons more practical than pharmacological, cephalosporins are often classified into first-, second-, third- and fourth-generation compounds, as shown in Table 1.

General adverse effects

Reactions that parallel those observed with penicillins include local reactions to parenteral administration, epileptogenicity, effects on sodium and potassium balance, autoimmune hemolytic anemia, neutropenia, thrombocytopenia, and altered platelet function.

More specifically associated with cephalosporins are false-positive Coombs' tests (also seen with clavulanic acid and imipenem + cilastatin), impaired vitamin K-dependent clotting factor synthesis with cephalosporins that contain the *N*-methylthiotetrazole side chain, biliary sludge formation with ceftriaxone, tubular nephrotoxicity of some older compounds (cefaloridine, cefaloglycin, and cefalotin), and disulfiram-like interactions with alcohol. Anaphylactic shock and other IgE antibody-mediated reactions are rare, but analogous to those experienced with the penicillins. Sufficiently reliable tests to predict or prove these reactions are still lacking for the cephalosporins. Other hypersensitivity reactions include acute interstitial nephritis, the majority of drug-inducible mucocutaneous manifestations, and various combinations of symptoms often referred to as "serum sickness-like reactions."

Table 1 Some cephalosporins and cephamycins (all rINNs except where stated)

Orally active cephalosporins	Injectable cephalosporins
Cefaclor[2] (pINN)	Cefamandole[2] (pINN)
Cefadroxil[3] (pINN)	Cefazolin[3] (pINN)
Cefalexin[2] (pINN)	Cefotaxime[3]
Cefetamet[3]	Cefoxitin[2]
Cefixime[3]	Ceftazidime[3]
*Cefradine[1]	Ceftizoxime[3]
*Cefuroxime[2]	Ceftriaxone[3]
	Cefuroxime[2]
	Latamoxef[3] (pINN)

[1]First-generation drugs
[2]Second-generation drugs
[3]Third-generation drugs
*Can also be given by injection

Organs and Systems

Cardiovascular

In isolated cases, cefalotin (3) and cefaclor (4) have been suspected to cause hypersensitivity myocarditis.

Respiratory

Diffuse pulmonary inflammation, as documented by gallium scanning in one case, was possibly caused by ceftriaxone (5). Cefotiam and in another case cefotiam followed by ceftazidime have been suspected to have caused pulmonary hypersensitivity (6,7).

Cefotetan-induced hiccup recurred after each cefotetan infusion and disappeared immediately after withdrawal; it did not recur after administration of another antibiotic (8). Intractable hiccups in a boy were attributed to ceftriaxone-induced pseudolithiasis (9).

Nervous system

In rats, intracerebroventricular injection of various cephalosporins produced markedly different responses in epileptogenic potential (10), later confirmed with a total of 15 compounds (11). Compounds with two heterocyclic rings at both position 3 and position 7 of the cephalosporin molecule, for example ceftriaxone, cefoperazone, and ceftazidime, were even more epileptogenic than benzylpenicillin, while others, with only one heterocyclic ring at position 7, for example cefotaxime and cefonicid, were less potent. Cefazolin, a tetrazole derivative, similar to the convulsant phenyltetrazole, was most potent.

Neurotoxicity has been reported with intracerebroventricular cefazolin (12) and with systemic cefazolin (13–15), cefepime (16), cefotaxime (17–19), ceftazidime (20,21), and cefuroxime (22). Ceftazidime also caused truncal asterixis (23) and absence status and toxic hallucinations (24). Even the least epileptogenic of 15 cephalosporins, namely cefonicid (11), caused seizures (25), although this effect was disputed (26). As expected, seizures after systemic treatment were predominant in uremic patients, and neurotoxicity has been associated with intraperitoneal ceftazidime therapy in a patient

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undergoing CAPD (27). Of practical interest was a patient treated with intravenous cefmetazole in whom the CSF concentration was twice as high as the corresponding blood concentration (236 versus 103 μg/ml) (28). Uremia may have contributed to this unusual distribution pattern.

- A 66-year-old woman had several episodes of recurrent aseptic meningitis associated with cefalexin, cefazolin, and ceftazidime (29). Intrathecal ceftazidime-specific IgG antibodies were isolated and a skin test with cefazolin provoked recurrence of the aseptic meningitis.

Two patients developed status epilepticus during treatment with cefepime for *Pseudomonas aeruginosa* sepsis (30).

- A 44-year-old man, who had previously had bilateral lung transplantation and who was on hemodialysis for chronic renal insufficiency, was given cefepime 2 g/day. Within 24 hours he started to become confused and developed diffuse hyper-reflexia. Two days later an electroencephalogram showed nearly continuous, generalized sharp-wave/slow-wave activity. After lorazepam 2 mg the status epilepticus resolved, but he remained confused. A follow-up electroencephalogram showed recurrence of generalized sharp-wave activity. Cefepime was withdrawn, and within hours he rapidly recovered his mental status. An electroencephalogram showed absence of epileptiform discharges.
- A 28-year-old woman with a thoracic spina bifida was given cefepime 1 g bd for an infection with *P. aeruginosa*. After a time (not stated) an electroencephalogram showed a continuous generalized spike and wave pattern. She was given lorazepam 2 mg, which resulted in resolution. Cefepime was withdrawn and she promptly recovered.

In the first case the dose was inappropriate for the degree of renal impairment and in the second case the dose was inappropriate for the patient's body weight. The authors underlined the importance of giving cefepime with great care, especially to patients with renal impairment and low body weight.

Five patients developed severe symptoms after receiving cefepime (31). The patients, three men and two women, aged 16–75 years, received 2 g/day ($n = 3$) 4 g/day ($n = 1$) or 9 g/day ($n = 1$). The symptoms started 12–16 days after the start of therapy. In all cases, the initial neurological symptoms (disorientation, confusion, and reduced consciousness) were progressive and were attributed to the infection. Facial or multifocal myoclonic movements occurred subsequently and were rapidly followed by convulsive or non-convulsive status epilepticus. The dose of cefipime had not been adjusted for renal function in any of the patients. Cefepime serum concentrations were measured in three cases, and were 72, 73, and 134 μg/ml. All the patients underwent hemodialysis, and the serum concentrations of cefepime fell to 4.3, 21, and 25 μg/ml respectively. In the other two patients, the serum concentrations after dialysis were 14 and 54 μg/ml, suggesting high concentrations before dialysis. There was complete recovery in four of the patients. One, a 73-year-old woman, died of multiorgan failure with refractory status epilepticus and coma. The authors referred to four other reports of cefepime-induced generalized seizures. They seriously questioned whether the actual frequency of this complication might not be underestimated, owing to insufficient knowledge, underreporting, and/or lack of specificity of clinical features.

- An 82-year-old man on chronic hemodialysis had pneumonia, for which he was given intravenous cefepime 1 g/day (32). After 4 days he developed a seizure and cefepime was withdrawn. Hemodialysis was started and his conscious level improved. On the next day, after a second hemodialysis, he recovered completely.

The authors recommended that in elderly patients with severe renal impairment, other agents than cefepime should be considered.

Psychological, psychiatric

It has long been known that intramuscular procaine penicillin can cause some peculiar psychological adverse reactions, and that other penicillin derivatives, such as amoxicillin, can cause psychiatric reactions, such as hallucinations (SEDA-21, 259). In a report from the Netherlands, neuropsychiatric symptoms occurred in six patients who received cefepime for febrile neutropenia (33). The patients, two men and four women, aged 32–75 years, received 6 g/day ($n = 5$) or 3 g/day ($n = 1$). The symptoms started 1–5 days after the first dose and varied from nightmares, anxiety, agitation, and visual and auditory hallucinations to coma and seizures. After withdrawal of cefepime, they recovered within 1–5 days. The causality between their neuropsychiatric symptoms and cefepime was considered as probable (WHO criteria) because of the temporal relation, lack of other causal neurological explanations, and positive rechallenge in five patients.

The mechanisms of these adverse effects are unknown, although it might be of value to take a closer look at the theory that drug-induced limbic kindling may be the principal pathogenic factor (SEDA-21, 259).

Hematologic

Since the days when chloramphenicol was more commonly used, it has been recognized that many antimicrobial drug are associated with severe blood dyscrasias, such as aplastic anemia, neutropenia, agranulocytosis, thrombocytopenia, and hemolytic anemia. Information on this association has come predominantly from case series and hospital surveys (34–36). Some evidence can be extracted from population-based studies that have focused on aplastic anemia and agranulocytosis and their association with many drugs, including antimicrobial drugs (37,38). The incidence rates of blood dyscrasias in the general population have been estimated in a cohort study with a nested case-control analysis, using data from a General Practice Research Database in Spain (39). The study population consisted of 822 048 patients aged 5–69 years who received at least one prescription (in all 1 507 307 prescriptions) for an antimicrobial drug during January 1994 to September 1998. The main outcome measure was a diagnosis of neutropenia, agranulocytosis, hemolytic anemia,

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thrombocytopenia, pancytopenia, or aplastic anemia. The incidence was 3.3 per 100 000 person-years in the general population. Users of antimicrobial drugs had a relative risk (RR), adjusted for age and sex, of 4.4, and patients who took more than one class of antimicrobial drug had a relative risk of 29. Among individual antimicrobial drugs, the greatest risk was with cephalosporins (RR = 14), followed by the sulfonamides (RR = 7.6) and penicillins (RR = 3.1).

Hemolytic anemia

Autoimmune hemolytic anemia has rarely been reported with the older cephalosporins, including cefalexin (40), cefalotin (41,42), cefazolin (43), and cefaloridine (44). The main laboratory findings correspond to the "drug adsorption" mechanism classically found in benzylpenicillin-induced immune hemolysis. Antibodies cross-reacting with cefalotin and benzylpenicillin were found in both benzylpenicillin-induced and cefalotin-induced hemolysis (43,45) Cases have also been reported with cefamandole (46), cefalexin (47), ceftriaxone (48), cefotaxime (49,50), cefotetan (51,52) and ceftazidime (53).

Cefotetan-induced hemolytic anemia has been discussed in a review of 35 cases, eight of which were discussed in greater detail (54). All eight cases were associated with the prophylactic use of cefotetan in gynecological or obstetric procedures. The patients had received 1–4 doses of cefotetan, and they left hospital in good shape, but all were re-admitted with hemolytic anemia within 2 weeks after the last dose. All needed several blood transfusions and two underwent plasmapheresis twice. They all survived, but the authors underlined the seriousness of this adverse effect. Of 43 cases of drug-induced hemolytic anemia that had been referred to their laboratory in the previous 8 years, 35 had been caused by cefotetan and three by ceftriaxone; 11 had a fatal outcome, eight and three caused by cefotetan and ceftriaxone respectively.

Hemolytic anemia has also been attributed to ceftizoxime (55).

- A 76-year-old Japanese man, who had been given 23 courses of intravenous antibiotic therapy over 2 years for chronic bronchitis, was given intravenous ceftizoxime 1 g/day. He developed anaphylactic shock and hemolysis. Despite very extensive therapy he died 2 weeks later.

The patient's serum was tested for antibodies against five penicillins and 30 different cephems (that is all types of cephalosporins), using protocols to detect drug adsorption as well as immune-complex mechanisms. His serum contained an IgM antibody that formed immune complexes with 10 of the 30 cephems. The 10 drugs were classified as oxime-type cephalosporins, that is they had a common structural formula at the C7 position on 7-aminocephalosporinic acid. This antibody did not show any cross-reactivity with five kinds of penicillins (ampicillin, aspoxicillin, carbenicillin, piperacillin, sulbenicillin). The authors asked a difficult question: Why did anaphylactic shock accompany acute hemolysis? Their answer was that the complex of ceftizoxime with IgM anti-ceftizoxime might act like anti-A or anti-B. This hypothesis will surely be further tested. In the meantime, it would be wise not to use the newer cephalosporins too freely.

Ceftriaxone has been associated with autoimmune hemolytic anemia, erythroblastocytopenia, and acute hepatitis (56). The ceftriaxone in this case was given intravenously and not orally, as erroneously published (written communication from the authors). Other cases of hemolysis have been reported after ceftriaxone (57).

- A 38-year-old man with no known disease rapidly developed disturbed consciousness 4 days after having taken co-amoxiclav for sinusitis (58). On admission, he was given intravenous ceftriaxone 2 g bd for purulent meningitis. On the 10th day of therapy, he developed icterus and hemolytic anemia. Despite vigorous resuscitative efforts, he died with evidence of multiple organ failure on day 5.
- A 48-year-old woman who had been given ceftriaxone 2 g/day intravenously for 7 days for Lyme disease developed severe hemolytic anemia (59). She had previously been given ceftriaxone twice without any adverse effects. An immune complex mechanism was suggested.
- A 14-year-old girl, perinatally infected with HIV, had a medical history of recurrent infections that had been treated with several antibiotics, including ceftriaxone. She was given ceftriaxone (60 mg/kg intravenously) for pneumonia and 30 minutes later complained of severe back pain, became nauseated, vomited, and collapsed. Despite intensive medical care she died within a few hours with massive intravascular hemolysis and disseminated intravascular coagulopathy. Autopsy was refused.

Of 10 patients with hemolysis due to ceftriaxone, seven died, six of them children (48,57,60–62).

- A 5-year-old girl, who had taken co-trimoxazole prophylaxis for recurrent urinary tract infections since the age of 1 year, received ceftriaxone intramuscularly for 7 days at the age of 5 years, uneventfully (63). Six months later she was given intramuscular ceftriaxone 50 mg/kg/day and amikacin 20 mg/kg for a new urinary tract infection. After 3 days she became unexpectedly ill and had a generalized seizure 30 minutes after the administration of both drugs. A day later, her seizures recurred, she rapidly became worse, and she was referred to an ICU for ventilatory support. There, she had two cardiac arrests and was resuscitated successfully. Her hematocrit and reticulocyte count were eight and 0.2% respectively. A direct antiglobulin test was strongly positive. She was given methylprednisone 5 mg/kg/day and three units of red blood cells. The direct antiglobulin test became negative on day 3, and the dose of methylprednisone was reduced to 3 mg/kg/day but then had to be increased again to 5 mg/kg/day because of recurring hemolysis. The steroid was withdrawn uneventfully after 8 weeks. She remained well and had no neurological deficit.

The authors stated that in children, hemolysis usually starts within minutes to some few hours after the administration of the drug, whereas in adults it starts after a period of days.

Mechanism

In addition to the "drug-adsorption" mechanism, the findings in some instances of anemia associated with cephalosporins were consistent with concomitant formation of

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auto-antibodies (51) or the so-called "innocent bystander" mechanism, leading to acute intravascular hemolysis, one with ceftriaxone being fatal (48). After this, another six cases were reported, of which five were fatal (57,60,61,64–66). All were due to ceftriaxone and all were in children aged 2–14 years, who were immunocompromised and/or had a hematological disease. All had been previously exposed to ceftriaxone and in some instances also to other cephalosporins. The hemolysis occurred abruptly within 5–54 minutes. However, it is not settled whether the risk reflected by those observations is specific to ceftriaxone or occurs with all cephalosporins. Ceftriaxone has a large share of the cephalosporin market, and three of the reports (61,65,66) were stimulated by a foregoing one (60), which may point to publication bias. Cross-reactivity of ceftriaxone antibodies with other cephalosporins was not studied. The significance of the underlying immunological or hematological diseases and the youth of the patients is also uncertain. Cefalotin and other cephalosporins can cause a positive direct antiglobulin test (67,68). This phenomenon is due to non-specific serum protein adsorption on to the erythrocyte membrane and is not related to immune hemolytic processes. Detection of non-immunologically bound serum proteins improves if reagents used in the direct antiglobulin test include additional antialbumin activity (69). The phenomenon is a known source of difficulties in evaluating suspected immune hemolysis or in routine cross-matching of blood products (70). The true frequency with many individual cephalosporins is unclear, since it has not been positively sought. However, it may depend on daily doses and in particular on the duration of treatment. For example, in a study with cefepime there were positive direct antiglobulin tests in 43% (71). The mean duration of treatment was 19 days and positive direct antiglobulin tests were principally seen in patients taking long-term treatment for osteomyelitis (mean duration of treatment 32 days). On the other hand, ceftazidime given for 9 days induced positive direct antiglobulin tests in 12% of patients (72). Positive direct antiglobulin tests can turn negative again while treatment with cephalosporins continues (71).

In a case of hemolysis associated with ceftriaxone the causative antibodies appeared to be stimulated solely by a degradation product of ceftriaxone (62).

- A 16-year-old girl with craniofacial dysplasia was given ceftriaxone 4 g/day for pneumococcal meningitis. On the seventh day of therapy she developed neck muscle spasms, dizziness, and tachypnea immediately after the administration of ceftriaxone. On the next day, the same symptoms occurred about 30 minutes after the end of the infusion of ceftriaxone. Her plasma was red and her hemoglobin had fallen to 2.4 g/dl. A direct antiglobulin test was positive only for C3d and no ceftriaxone-dependent antibodies were detected. Her serum reacted strongly with erythrocytes in the presence of ex vivo antigen related to ceftriaxone (urine samples from patients receiving ceftriaxone). All therapeutic attempts were unsuccessful and she developed renal insufficiency and died.

The authors concluded that this was the first reported case in which the causative antibodies appeared to be stimulated solely by a degradation product of ceftriaxone. Unfortunately, they were not able to characterize the degradation products. They ended their report by advising that degradation products should be taken into account in all suspected cases of drug-dependent hemocytopenia in which the antibody remains undetectable.

Neutropenia

Virtually all cephalosporins can cause neutropenia and agranulocytosis (73). This has been associated with cefapirin (74), cefepime (75), cefmenoxime (76), cefmetazole (77), ceftriaxone (78–81), moxalactam (82), and others. All of these cases were seen after high cumulative doses given in one treatment course. In one series, cefapirin-induced neutropenia occurred in five of 19 patients who took a total of 90 g or more, but not in 113 patients who took smaller cumulative doses (74). It has not been settled whether toxic mechanisms, immunological mechanisms, or both are involved.

Thrombocytopenia

Thrombocytopenia has rarely been reported, always associated with cefalotin (83–85). In one case there were drug-dependent antibodies. In two other cases the role of drug-dependent antibodies was further evaluated. In one case the antibodies only reacted with platelets in the presence of exogenous cefotetan, but not with cefotetan-coated platelets (86). In another case associated with cefamandole, antibodies cross-reacted with two cephalosporins that had a thiomethyltetrazole group at position 3 but not with other cephalosporins (87). In an additional case, cefuroxime has been implicated (88). In about one-third of cases with cephalosporin-induced neutropenia, slight concomitant thrombocytopenia has been found (73).

Impaired hemostasis

As with other beta-lactam antibiotics, cephalosporins can cause impaired hemostasis and bleeding by altering coagulation and platelet function.

Pseudolymphoma

Pseudolymphoma leukemia (Sézary syndrome) has been reported to occur mainly after the use of phenytoin and other anticonvulsant drugs (89,90), but cefixime has also been implicated (91).

- A 48-year-old woman developed fever and cough, for which she was given oral cefixime. After 48 hours she developed an itchy diffuse erythematous maculopapular rash all over her body. Her white blood cell count was 20×10^9/l, with 8% eosinophils; 5 days later it was 12.5×10^9/l, with atypical, so-called Sézary-like, cells and 64% eosinophils. A bone marrow aspirate showed 20% atypical lymphocytes with a Sézary-like appearance, having large cerebriform nuclei. An increase in eosinophil precursors was also noted. Cefixime was withdrawn, and as she continued to be febrile with a rash and her eosinophil count increased to 72% she was given corticosteroids. Her fever fell to 37.5°C, the rash improved, and her white cell count fell. At follow-up 12 months later her leukocytosis and eosinophilia had

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completely resolved and she did not have any other problems.

The authors stressed that, like patients with phenytoin-induced pseudolymphoma, this patient will need long-term follow-up to differentiate true prelymphoma. This case can be taken as a reminder that every new beta-lactam coming on the market may have an adverse effects profile of its own.

Mouth and teeth

Three children receiving cefaclor developed intraoral ulcers covered with a thick pseudomembrane together with various skin lesions, suggesting a viral disease at first sight (92).

Gastrointestinal

Acute hemorrhagic colitis without pseudomembranes has been reported after oral cefuroxime (SEDA 21, 261). In mice, some cephalosporins accelerated gastric emptying, in some instances even more effectively than erythromycin or metoclopramide (93). The relevance of this to the gastrointestinal adverse effects of cephalosporins, such as nausea and vomiting, is uncertain.

Liver

As with all beta-lactam antibiotics, slight increases in serum transaminases and alkaline phosphatase have been reported with cephalosporins. However, in contrast to the isoxazolylpenicillins and co-amoxiclav, only very sporadic cases with more severe liver disease have occurred (94–98). Very prolonged cholestasis was reported in isolated cases with cefmenoxime (99) and ceftibuten (98).

Biliary tract

Ceftriaxone has been associated with mostly asymptomatic and reversible biliary sludge. The condition is defined by the presence of low amplitude echoes with absent postacoustic shadows in the gallbladder on ultrasonography and has also been called "biliary pseudolithiasis" (100). Findings consistent with the presence of cholelithiasis (high amplitude echoes with acoustic shadowing) have also been reported (101).

The frequency of biliary sludge in 37 children treated for serious infections was 40% and was lower in adults (about 20%) (100,102,103). The condition usually runs a benign course and ultrasound becomes normal after withdrawal of ceftriaxone within a mean of 15 days (100). However, clinical evidence of cholecystitis has been reported (104). Gallstones containing mostly ceftriaxone have been described (105). In a case-control study of patients treated with ceftriaxone for Lyme disease, more serious biliary complications (cholecystitis and cholelithiasis) were observed in 2%. Age over 18 years and female sex were risk factors (106).

Ceftriaxone does not seem to predispose to subsequent gallbladder stone formation, as assessed 6 and 12 months later (107). The pathogenesis relates to ceftriaxone's high rate of biliary excretion and the subsequent formation of calcium-containing precipitates (108). Thus, apart from the risk factors mentioned above, the risk of biliary sludge may increase with the use of high doses, rapid bolus injection, gall bladder stasis, and renal insufficiency associated with enhanced biliary excretion. Routine ultrasound scans are not required in patients taking ceftriaxone. In the presence of symptoms possibly due to ceftriaxone-associated sludge or cholelithiasis, confirmed by ultrasonography, the drug should be withdrawn. Surgery is mostly unnecessary.

Pancreas

Ceftriaxone has been reported to have caused pancreatitis (109).

- A 13-year-old boy received long-term intravenous ceftriaxone after surgical drainage of a right frontal subdural empyema secondary to sinusitis. After about 5 weeks he developed abdominal pain with profuse emesis; his serum amylase was 1133 U/l and lipase 3528 U/l. Abdominal ultrasound showed cholelithiasis, and he had an uncomplicated cholecystectomy. The material in the gallbladder was 100% ceftriaxone.

The authors ended by stating that patients taking long-term ceftriaxone may be at risk of cholelithiasis and pancreatitis. Ultrasound screening might be useful for monitoring such patients.

Urinary tract

Two of the older cephalosporins, cefaloridine and cefalotin, are nephrotoxic and have often caused renal dysfunction (110,111). The nephrotoxicity of cefaloridine is related to its unusual renal transport, resulting in higher intracellular concentrations in the proximal tubular cells than with other cephalosporins (112). Since less toxic cephalosporins are available, the clinical use of cefaloridine is no longer justified.

Cefalotin can cause two types of renal disease in man (111): acute tubular necrosis, similar to that seen with cefaloridine, although less often; and acute interstitial nephritis, often accompanied by a rash, fever, or eosinophilia, resembling the same disorder as that caused by methicillin.

Beta-lactam nephrotoxicity has been reviewed, particularly considering structure-activity relations (112). Acute proximal tubular necrosis as a consequence of beta-lactam toxicity develops in proportion to:

- uptake by the cupular cell
- acylation inactivation of mitochondrial substrate transporters
- in the case of cefaloridine, lipid peroxidation.

For example, cefaloglycin, which is no longer used, is highly nephrotoxic because of its reactivity, while cefalexin, being comparably sequestered in the tubular cells, is not (112).

Broad clinical use of second- and third-generation cephalosporins has not produced clear evidence of significant nephrotoxicity. In two groups of 10 and 17 patients treated with ceftazidime 3 or 4 g/day, falls in glomerular filtration rate of about 10 ml/minute were seen after treatment courses of 4–9 days or 7–31 days respectively (113,114). For many other cephalosporins comparable data are lacking. Furthermore, an increase

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in aminoglycoside nephrotoxicity have only been documented with cefalotin and cefaloridine when used in combination (110,115). Nevertheless, adjustment of cephalosporin dosages in renal insufficiency is justified, and acute tubular necrosis can occur with very high doses of cephalosporins other than cefaloridine and cefalotin (116). Isolated cases of acute interstitial nephritis with newer compounds have been related to cefaclor (117), cefamandole (118), cefotaxime (119,120), cefotetan (121), cefoxitin (122), ceftazidime (123), ceftriaxone (124), and cefuroxime (125). Ceftriaxone, on the other hand, protects against tobramycin nephrotoxicity in rats (126). In addition to biliary sludge and stone formation with ceftriaxone, occasional patients developing urinary stones have been described (127,128).

In a report of acute tubulointerstitial nephritis in a patient receiving cefdinir, it was stated that among 41 kinds of cephalosporins available in Japan, this complication has been reported with 12 (129).

- A 58-year-old woman developed acute renal insufficiency soon after a 7-day course of cefdinir 300 mg/day for acute bronchitis. Renal histology showed tubular atrophy and interstitial fibrosis accompanied by moderate lymphocyte infiltration. A lymphocyte stimulation test with cefdinir was positive. Serum creatinine concentrations continued to rise even after withdrawal of cefdinir, but steroid therapy normalized renal function.

The outcome of drug-induced acute tubulointerstitial nephritis can be life-long dialysis or renal transplantation if it is not adequately treated in time. The authors therefore concluded that it is important to look out for this complication when using any cephalosporin.

Skin

Generalized pustular eruptions, histologically presenting as leukocytoclastic vasculitis with neutrophils forming subcorneal pustules, have been reported with different cephalosporins, such as cefaclor (130), cefazolin (131,132), cefalexin (133), and cefradine (134).

Isolated cases of the following syndromes have been reported more recently in connection with cephalosporins:

- pseudolymphoma leukemia syndrome after cefixime presenting with itchy rash, atypical Sézary-like cells, and lymphadenopathy (91);
- pemphigus vulgaris with cefadroxil (135) and cefalexin (136);
- erythema multiforme with cefotaxime (137) and cefalotin (138);
- adult linear IgA disease associated with an erythema multiforme-like reaction with cefamandole (139);
- Stevens–Johnson syndrome with cefalexin (140);
- toxic epidermal necrolysis with cefsulodin (141) and cefazolin (142);
- photosensitivity due to intravenous ceftazidime in a patient with cystic fibrosis (143);
- fixed drug eruption with cefalexin (144);
- occupational contact allergy with ceftiofur (145).

The frequencies of rashes have been retrospectively investigated in 5923 children (146). All the children who developed a rash after treatment with one or more of the commonly used oral antibiotics were identified, 472 in all. Significantly more rashes were documented with cefaclor (4.79%) compared with sulfonamides (3.46%), penicillins (2.72%), and other cephalosporins (1.04%). Based on the numbers of patients for whom the antibiotics were prescribed, the frequencies of rashes were 12.3% for cefaclor, 8.5% for sulfonamides, 7.4% for penicillins, and 2.6% for other cephalosporins.

Telangiectasiae in a light-exposed distribution have rarely been reported with cephalosporins.

- An otherwise healthy 57-year-old man developed telangiectatic skin lesions after receiving intramuscular cefotaxime 1 g bd for 7 days for a urinary tract infection (147). He had used no other medications, and there was no history of photosensitivity or rosacea. He had several asymptomatic telangiectasiae widely distributed on the forehead and on the backs of both hands. Antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative. Skin biopsy showed dilated capillaries without signs of vasculitis. A light provocation test produced telangiectatic lesions at 36 hours. Because of the relation between the administration of cefotaxime and the onset of the telangiectasiae, confirmed by light testing, cefotaxime was withdrawn, with progressive improvement and complete resolution after 2 months; rechallenge was not performed.

Iatrogenic telangiectasis is a poorly understood dermatological adverse effect of several drugs, including cephalosporins (143,148). Telangiectasiae localized to light-exposed areas, as in this case, have been described with some calcium channel blockers (149,150).

Immunologic

Type I reactions

Immediate hypersensitivity reactions, mediated through IgE antibodies to cephalosporin determinants, are a major factor limiting their use. Early cases of anaphylaxis to cephalosporins were probably due to contamination with trace amounts of penicillin (151). These studies may therefore have over-reported cross-sensitivity.

In a retrospective study the frequency of systemic anaphylaxis to cefaloridine, cefalotin, or cefalexin was two out of 9388 patients (0.02%) without a history of penicillin allergy, and two out of 450 patients (0.4%) with a history of penicillin allergy (152). In the first group, two of the 1983 patients treated with cefalotin accounted for the adverse event.

Two of 178 prospective patients, of whom 151 had a history of penicillin allergy but were negative on penicillin skin testing, had reactions to a cephalosporin (153). There were 27 who had a positive penicillin skin test but did not react to a cephalosporin. Similar results were found by others (154).

However, a history of penicillin allergy is often vague, and many studies have suggested that it is an unreliable indicator, which has been confirmed (155). In 62 penicillin skin-test-positive patients, cephalosporins produced only one reaction of mild urticaria and bronchospasm (156).

Primary cephalosporin allergy in patients not allergic to penicillin has been reported, but the exact frequency is

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not known (157,158). The true incidence of allergic reactions may differ among the cephalosporins. Several reports implicating particular compounds have been published (159–163).

An accurate molecular definition of cephalosporin allergy is not currently available. Relevant determinants of cephalosporin-induced anaphylaxis may not reside in the bicyclic core, but rather in the side chain (164,165).

Neither in vitro tests nor skin tests reliably predict cephalosporin allergy (166). The true frequency of allergic reactions in penicillin-allergic patients exposed to cephalosporins has been estimated to be 1 or 2% (167). Nevertheless, when there is a history of penicillin anaphylaxis or other severe IgE-mediated reactions, it is wise to avoid cephalosporins.

An acute, life-threatening, anaphylactic reaction has been described in a child who received his first intravenous injection of ceftriaxone (168).

- A 3-year-old boy developed a high fever and a petechial rash. In the past he had been treated four times with amoxicillin for upper respiratory tract infections without allergic reactions. At presentation he had multiple petechiae over the trunk and limbs. There were no signs of meningeal irritation. He was given intravenous ceftriaxone 100 mg/kg and after 1 minute developed excitation and a generalized papular urticarial rash. His heart rate increased to 160/minute and the blood pressure was not measurable. He was given subcutaneous adrenaline 0.15 mg plus intravenous clemastine fumarate 2 mg, dexamethasone 3 mg, and fluids. Within 15 minutes his circulation was restored and the urticarial rash abated. Instead of ceftriaxone, he was given chloramphenicol for 7 days, and no further allergic reaction was observed. *Neisseria meningitidis*, sensitive to chloramphenicol and ceftriaxone, was cultured from his blood and spinal fluid. He was discharged well 12 days after admission. One month later, skin tests for ceftriaxone and benzylpenicillin were negative, as was a test for ceftriaxone-specific IgE. Because hypersensitivity could not be demonstrated, a controlled intravenous challenge with ceftriaxone 100 mg/kg was performed, and 20 seconds later there was again excitation and a generalized papular urticarial rash. He was treated as before and recovered within 15 minutes.

According to the authors, anaphylaxis after a single injection of ceftriaxone without previous exposure to the drug is very rare, and they referred to only one previous report (169). However, despite the fact that hypersensitivity could not be demonstrated by skin testing or the presence of ceftriaxone-specific IgE, the outcome of the challenge to ceftriaxone very clearly pointed to an anaphylactic reaction.

An anaphylactic reaction to a subconjunctival injection of cefazolin has been described.

- A 70-year-old white woman with a history of penicillin allergy underwent an uncomplicated eye operation, at the end of which she received a subconjunctival injection of cefazolin 50 mg (170). About 90 minutes postoperatively she developed acute respiratory distress and an erythematous macular rash over the face, neck, chest, forearms, and lateral thighs. The rash became urticarial without pruritus. She was given bronchodilators and intravenous glucocorticoids, with little improvement, but repeated subcutaneous injections of adrenaline gave some improvement in breathing. However, she had to be intubated, and was weaned from the ventilator only after some hours.

The main lesson from this case is that a small amount of a beta-lactam antibiotic anywhere in the body can cause life-threatening anaphylaxis.

Type III reactions

Serum sickness was first described by von Pirquet and Schick in 1905 and was regarded as a syndrome resulting from the administration of heterologous serum or other foreign proteins. The immunopathology of classic serum sickness results from antigen-antibody complex formation with a foreign protein as the antigen. Characteristic symptoms include fever, cutaneous eruptions, edema, arthralgias, and lymphadenopathy. The incidence of classical serum sickness has fallen secondary to the refinement of foreign proteins. However, a serum sickness-like reaction that is clinically similar to classical serum sickness can result from the administration of a number of non-protein drugs, such as tetracyclines, penicillins, cephalosporins (171). The reaction typically occurs within 1 month of the start of therapy and resolves after withdrawal.

Most cephalosporins have sporadically been reported to cause reactions closely resembling classical serum sickness (172,173), and intriguingly comparable syndromes were seen in the majority of a series of volunteers treated for up to 4 weeks with high doses of cefalotin and cefapirin (174). There is so far no clear evidence of drug-specific antibodies. The outcome has always been benign. Earlier suspicions that cefaclor increases the risk of serum sickness-like syndromes (175) have subsequently been confirmed (176–181). The true incidence is still a matter of debate. Data suggest that it is several-fold higher than with other cephalosporins or comparator antimicrobials, such as amoxicillin-containing products, penicillin, flucloxacillin, trimethoprim, and others (182,183). More children are affected, which might at least in part reflect preferential use of cefaclor in this age group (184,185).

Serum sickness has been attributed to cefaclor (186).

- A 2-year-old girl was given cefaclor for an infection, having been given it on one previous occasion without any adverse effects. However, on this occasion, after 6 days she developed a rash, edema, and joint swelling. Her symptoms were thought to be due to serum sickness caused by cefaclor, which was withdrawn. The rash resolved within 2 days and the arthralgia settled within 1 week.

It is still uncertain whether cefaclor-associated serum sickness-like reactions correspond to true hypersensitivity. It has indeed been suggested that they may result from inherited defects in the metabolism of reactive intermediates and may be a unique adverse reaction requiring biotransformation of the parent drug (187). A lymphocyte-based cytotoxicity assay has shown that cefaclor metabolites, as generated by murine hepatic microsomes, mediated cytotoxicity among patients with

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cefaclor-induced serum sickness-like disease, but not with other immediate or delayed hypersensitivity reactions (188). The positive tests were not shared with loracarbef, a carbacephem with a methylene (instead of a sulfur) substituent at position 5, but otherwise structurally identical to cefaclor. It is not known whether the chemical degradation of cefaclor in vivo (189) contributes to the pathophysiology of serum sickness-like reactions.

Second-Generation Effects

Teratogenicity

Sporadic reports of findings in cell cultures (190) and animals (191) have suggested potential second-generation effects of cephalosporins; however, no such effects are known in man.

Drug Administration

Drug administration route

Thrombophlebitis is a common reaction to the administration of cephalosporins into peripheral veins. The use of buffered solutions mitigated the reaction with cefalotin (192). Published trials have mainly compared older cephalosporins, but the overall results are still contradictory (193,194). Pain and inflammatory reactions after intramuscular injection are also common. Ceftriaxone is probably given more often intramuscularly now than any other cephalosporin. Its local tolerability does not differ from that of other compounds (195).

Drug–Drug Interactions

ACE inhibitors

Intestinal absorption of beta-lactams occurs at least in part by an active mechanism involving a dipeptide carrier, and this pathway can result in interactions with dipeptides and tripeptides (196,197), which reduce the rate of absorption of the beta-lactams. In particular, angiotensin-converting enzyme (ACE) inhibitors, which have an oligopeptide structure, are absorbed by the same carrier (198) and interact with beta-lactams in isolated rat intestine (199). However, there might be a second site of interaction between ACE inhibitors and beta-lactams. Both groups of substances are excreted by the renal anionic transport system, and concomitant administration of both drugs sometimes results in pronounced inhibition of the elimination of beta-lactams (200). In the case of cefalexin, it may not lead to toxic effects. However, when more toxic beta-lactams are used, the possibility of this interaction has to be kept in mind.

In rats, ACE inhibitors reduced renal cefdinir excretion, probably by competition at the tubular anionic carrier (201).

Alcohol

Cephalosporins that contain a methyltetrazole-thiol side chain (as in cefamandole, cefmenoxime, cefmetazole, cefonizid, cefoperazone, ceforanide, cefotetan, cefotiam, latamoxef, and moxalactam) and chemically similar structures (cefepime, ceftriaxone) co-administered with alcohol can produce a disulfiram-like syndrome by inhibiting aldehyde dehydrogenase (195,202,203).

Transient toxic reactions to cefepime and alcohol in the inner ear have been reported (204). Alcohol intolerance needs some time to build up and has been described for up to 5 days after the ingestion of the antibiotic (205,206). It has to be kept in mind that many pharmacological formulations contain alcohol.

Sudden but reversible bilateral labyrinthine hearing loss occurred after cefepime therapy for one-sided otitis and simultaneous intake of alcohol (204). An abortive form of the acetaldehyde syndrome was assumed.

Ciclosporin

Ceftriaxone reportedly increases ciclosporin blood concentrations (207).

Iron

There was a more than 10-fold reduction in AUC when cefdinir was given concomitantly with iron (208). Since the formation of a chelation complex is believed to account for this effect, similar interactions with aluminium- and magnesium-containing antacids are likely.

Vancomycin

Ceftazidime formed microprecipitates when it was mixed with vancomycin (209).

Verapamil

Competitive albumin binding of drugs with high serum protein affinity can increase pharmacologically active unbound concentrations and enhance the metabolism of low clearance drugs. Acute verapamil toxicity with ceftriaxone and clindamycin may be explained by this mechanism (210).

Interference with Diagnostic Tests

Galactose absorption

Some cephalosporins non-competitively inhibited the active absorption of D-galactose by reducing the activity of Na/K-ATPase (211). Theoretically, this effect might interfere with galactose tolerance testing.

Jaffee Test

Certain cephalosporins (cefoxitin, cefpirome, cefacetrile, cefaloglycin, cefaloridine, cefalotin) react with alkaline picrate solution, forming a chromogen with the same spectrum of absorbance as that formed by creatinine and alkaline picrate, producing falsely high serum

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creatinine values (212,213). This reaction occurs at therapeutic concentrations. Other cephalosporins (cefamandole, cefazolin, cefoperazone, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, latamoxef) do not interfere with this assay (214).

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Cerivastatin

See also HMG Co-A reductase inhibitors

General Information

Weight for weight, cerivastatin is the most potent statin. Like other statins, the chance of rhabdomyolysis increases when cerivastatin is taken together with certain other drugs (1). Although cerivastatin is degraded by two different isoforms of P_{450} in the liver, and therefore should be less likely to take part in drug interactions than most of the other statins, clinically important interactions do occur, and reports of drug interactions in 2001 triggered its withdrawal, after 31 people in the USA taking cerivastatin, 12 of whom had also taken gemfibrozil, died of severe rhabdomyolysis (2).

In other respects, the adverse effects of cerivastatin are similar to those of other statins (3), and a pooled analysis of studies of cerivastatin 100–400 micrograms/day taken for at least 8 weeks showed no differences in drug-related adverse events between cerivastatin and placebo (4). There was no association between plasma transaminase or creatine kinase activities and cerivastatin dosages. Cerivastatin 800 micrograms/day for 4 weeks had only mild transient adverse effects (5).

Organs and Systems

Liver

There were increases in serum transaminase activities to more than three times the top end of the reference range in under 1% of patients taking cerivastatin, which is similar to findings with other statins (6).

Musculoskeletal

There were no cases of myalgia in 94 patients taking cerivastatin 50–300 micrograms/day for 72 weeks, whereas in the same study, two of 59 patients taking simvastatin had myalgia (7). At dosages of 300–400 micrograms/day for 8 weeks in 349 patients there were no rises in creatine kinase activity above 10 times the upper limit of the reference range, and asymptomatic increases (to over three times the upper limit of the reference range) occurred more often with placebo (2.8%) than with cerivastatin (1.4% with 0.4 mg; none with 0.3 mg) (8).

Drug–Drug Interactions

Ciclosporin

Cerivastatin 0.2 mg/day was well tolerated when given together with ciclosporin, although there were 3- to 5-fold increases in the plasma concentrations of cerivastatin and its metabolites when single-dose cerivastatin was given to 12 kidney transplant recipients taking ciclosporin 200 mg bd and to 12 healthy controls (9). Ciclosporin may have affected both the distribution of cerivastatin and its biotransformation in the liver.

Gemfibrozil

Cerivastatin was withdrawn in 2001 after 31 people in the USA taking cerivastatin, 12 of whom had also taken gemfibrozil, died of severe rhabdomyolysis (2).

- Myalgia and a marked increase in creatine kinase was precipitated in a 74-year-old woman with normal renal function who took gemfibrozil 1200 mg/day 3 weeks after she had started to take cerivastatin 300 μg/day (10).

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Ceruletide

General Information

Ceruletide is a synthetic decapeptide that resembles cholecystokinin and causes contraction of the gallbladder. It has sometimes been used instead of the traditional "fatty meal" in cholecystography. After intramuscular injection, nausea, vomiting, diarrhea, and cramps have been reported.

Intravenous injection can cause spasm of the gall-bladder neck and severe pain with tingling sensations, sweating, and mild hypotension (1).

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Cetirizine

See also Antihistamines

General Information

Cetirizine is a non-sedating metabolite of hydroxyzine (SEDA-18, 181) (SEDA-19, 172) (SEDA-21, 172) (SEDA-22, 178). There is only minor hepatic metabolism of cetirizine (1), which is excreted unchanged in the urine. It has not been associated with dysrhythmias. Skin reactions have been reported, and the anticoagulant activity of acenocoumarol may be potentiated (SEDA-22, 178).

Seasonal allergic rhinitis affects about 10% of school-age children, and there is evidence of a significant impact of the disease on health-related quality of life. The effect on health-related quality of life of once-daily of cetirizine syrup 10 mg/day for 4 weeks has been studied in 544 children with seasonal allergic rhinitis in a multicenter, open, non-comparative study (2). In addition to improvements in symptom scores the authors also reported significant improvements in health-related quality of life, with good tolerability of the drug. Treatment-related adverse effects were reported in 22 subjects, of which somnolence was the most frequent problem, reported by six of the subjects. Only 12 of subjects discontinued treatment owing to an adverse effect.

Health-related quality of life and clinical outcomes in 865 adult patients with seasonal allergic rhinitis treated with cetirizine or placebo for 2 weeks have been evaluated in a double-blind, randomized, parallel-group study (3). Cetirizine significantly improved both symptoms and health-related quality of life, while treatment-related adverse effects were comparable with those in the placebo group.

Organs and Systems

Cardiovascular

In a prospective, double-blind, parallel-group study for 18 months in 817 children with atopic dermatitis aged 12–24 months, cetirizine 0.25 mg/kg bd had no effect on the QT_c interval (4).

In a double-blind, randomized, placebo-controlled study in 85 infants aged 6–11 months there were no differences in the frequencies of adverse events between those who were given cetirizine or placebo, and no electrocardiographic changes, particularly in the QT interval (5).

Nervous system

Oculogyric crisis has been described in nine patients treated with cetirizine; eight cases occurred in children (6).

The effects of cetirizine (5, 10, and 15 mg) on sleep latency, subjective sleepiness, and performance from 0.5 to 7.5 hours after ingestion have been studied (7). Cetirizine produced shortened sleep latencies, increased subjective sleepiness, and impaired tracking. The authors considered that cetirizine should not be used by personnel involved in critical occupations.

Psychological, psychiatric

In a double-blind, crossover study levocetirizine 5 mg once daily for 4 days was compared with cetirizine 10 mg, loratadine 10 mg, promethazine 30 mg, and placebo in terms of nervous system inhibitory effects in 20 healthy volunteers (8). With the exception of promethazine, none of the drugs had disruptive or sedative effects on objective measurements in a comprehensive battery of psychomotor and cognitive tests.

The Early Treatment of the Atopic Child (ETAC) Study has provided evidence that cetirizine may be able to halt the progression to asthma in high-risk groups of young children and infants with atopic dermatitis (9). However, the study involved giving relatively high doses of cetirizine to very young children (aged 1–2 years at study entry) over a long period of time. Therefore, the impact of prolonged use of high-dose cetirizine (0.25 mg/kg bd over 18 months) on behavior and cognitive ability in young children and infants has been assessed in a double-blind, randomized, placebo-controlled study (10). Well-validated and standardized assessments of behavior or cognition were used, and the ages at which psychomotor milestones were attained were established. The authors concluded that, compared with placebo, cetirizine had no significant effects on behavior, cognition, or psychomotor milestones in young children with atopic dermatitis.

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Liver

Severe hepatitis has been reported in a 23-year-old man taking cetirizine (11) and cholestasis in a 28-year-old man who had taken cetirizine for 2 years (12). However, a causal relation between these uncommon events and cetirizine was difficult to confirm.

Skin

Cutaneous reactions have been reported with cetirizine (13).

- A man taking cetirizine developed a multifocal fixed drug eruption (14).
- In a 45-year-old man cetirizine caused multiple fixed erythematous lesions on the trunk (15). Cetirizine was withdrawn for 15 days and an oral challenge test was performed. The same skin lesions developed in the previously affected skin sites when cetirizine was taken.
- A 14-year-old girl with house dust mite allergy had generalized skin eruptions after taking cetirizine. She also had symptoms of acute hepatitis, which also resolved after withdrawal of cetirizine (16).
- A 73-year-old man had skin eruptions associated with cetirizine and hydroxyzine therapy, which healed after drug withdrawal (17).

There have been several case reports of urticaria due to cetirizine.

- Generalized urticaria developed in a woman 2 hours after she took cetirizine (18).
- Acute generalized urticaria occurred in a 42-year-old woman taking cetirizine for seasonal allergic rhinitis and conjunctivitis, which had previously been treated with loratadine (19).
- A 32-year-old woman with recurrent idiopathic urticaria, asthma, and metal-induced contact dermatitis had 5–10 episodes of urticaria a year, with pruritic wheals of less than 24 hours duration (20). Cetirizine 10 mg/day was associated with the appearance of pruritic wheals on her neck, forehead, and arms. The symptoms resolved on drug withdrawal and reappeared on rechallenge. Double-blind challenge tests with mizolastine, loratadine, fexofenadine, dexchlorphenamine, ebastine, ketotifen, and placebo were negative, whereas hydroxyzine and its active metabolite, cetirizine, reproduced the urticaria.
- A 36-year-old woman noted intense exacerbation of urticarial wheals and facial edema 3–4 hours after taking cetirizine 10 mg (21). Skin tests with cetirizine produced an urticarial reaction 5 hours after challenge. Placebo-controlled oral challenge resulted in generalized urticaria, edema of the hands, and intense pruritus 90 minutes after administration of cetirizine, with symptoms lasting up to 12 hours. Skin biopsies showed inflammation typical of urticaria.

Susceptibility Factors

Age

The long-term safety of cetirizine (0.25 mg/kg bd) has been studied in children with atopic dermatitis (22). The mean duration of exposure to cetirizine in 399 children was 17 months. The frequency of dropouts and serious events did not differ between cetirizine and placebo. There were no clinically important differences in neurological or cardiovascular events, growth, or behavioral or cardiovascular assessments between the groups. No child taking cetirizine had prolongation of the QT_c interval.

The effects of cetirizine 0.25 mg/kg bd for 18 months have been investigated in a prospective, double-blind, parallel-group study in 817 children with atopic dermatitis aged 12–24 months (4). Dropouts and serious events, including hospitalization, were infrequent and were less common in the children who took cetirizine, although the differences were not statistically significant. Most of the adverse events were mild and were not related to medication.

Drug–Drug Interactions

Alcohol

Cetirizine did not potentiate the effects of ethanol on psychomotor and driving performance (SEDA-20, 163), but did affect tracking speed and performance in divided attention tests.

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Cetrimonium bromide and cetrimide

See also Disinfectants and antiseptics

General Information

Cetrimonium bromide and cetrimide are quaternary ammonium antiseptics, trimethylammonium derivatives, with similar structures. Cetrimonium bromide is hexadecyltrimethylammonium. Cetrimide is a mixture of tetradecyltrimethylammonium (mostly), dodecyltrimethylammonium, and hexadecyltrimethylammonium. They dissociate in aqueous solution, forming a relatively large and complex cation, which is responsible for their surface activity, and a smaller inactive anion. They are emulsifiers and detergents and have bactericidal activity against Gram-positive and, at higher concentrations, some Gram-negative bacteria.

In three hospitals, 378 patients with hydatid cysts were treated surgically, including irrigation with cetrimide solutions in concentrations between 0.05 and 1% (1). No adverse effects were observed.

Organs and Systems

Sensory systems

Accidental use of cetrimide solution 0.1% as an irrigation solution during cataract surgery in two cases resulted in immediate corneal edema, which in turn resulted in a severe bullous keratopathy (2).

Acid–base balance

Severe metabolic acidosis without signs of peritonitis occurred after more than 1 liter of 1% cetrimide was instilled into hydatid cysts (SEDA-11, 490) (3).

Hematologic

Severe methemoglobinemia has been reported after excision of hydatid cysts and liberal irrigation of the cysts in the liver with a 0.1% solution of cetrimide (4).

Skin

Eighteen cases of an ichthyosiform contact dermatitis caused by antiseptic solutions containing 3% cetrimide and 0.3% chlorhexidine have been reported (5,6). Biopsies showed hyperkeratosis with striking vesiculation of lamellar bodies in the granular cells and upper spinous cells, premature secretion of lamellar bodies, and abundant remnants of lamellar bodies and retention of desmosomes between corneocytes. Cetrimide, and not chlorhexidine, was said to be the cause of the dermatitis.

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Chenopodiaceae

See also Herbal medicines

General Information

The genera in the family of Chenopodiaceae (Table 1) include beet and spinach.

Table 1 The genera of Chenopodiaceae

Allenrolfea (allenrolfea)
Aphanisma (coastalcreeper)
Arthrocnemum (arthrocnemum)
Atriplex (saltbush)
Axyris (Russian pigweed)
Bassia (smotherweed)
Beta (beet)
Ceratoides (winterfat)
Chenopodium (goosefoot)
Corispermum (bugseed)
Cycloloma (cycloloma)
Dysphania (dysphania)
Endolepis (endolepis)
Grayia (hopsage)
Halogeton (saltlover)
Kochia (molly)
Krascheninnikovia (winterfat)
Microtea (jumby pepper)
Monolepis (povertyweed)
Nitrophila (niterwort)
Polycnemum (polycnemum)
Proatriplex (proatriplex)
Salicornia (pickleweed)
Salsola (Russian thistle)
Sarcobatus (greasewood)
Sarcocornia (swampfire)
Spinacia (spinach)
Suaeda (seepweed)
Suckleya (suckleya)
Zuckia (zuckia)

Chenopodium ambrosioides

Chenopodium ambrosioides (American wormseed) contains the diterpenoid aritasone and the toxic principle ascaridole, which was formerly used as an antihelminthic drug, but has now been superseded.

Chloral hydrate

General Information

Chloral hydrate, which was synthesized by Justus Liebig in 1832, continues to be used for sleep disorders and for sedation before surgery or radiology, especially in children (1). As an alternative to the benzodiazepines, it has essentially similar properties and problems, but is associated with perhaps rather more frequent gastrointestinal disturbances, up to 7% in one large sample of children. Chloral hydrate had a reputation for safety, which has been challenged by data that suggest that it and short-acting barbiturates are particularly lethal when taken in overdose (2). Liver damage and cardiac toxicity, consistent with the chemical similarities between trichloroethanol, chloroform, and alcohol, can occur.

Organs and Systems

Cardiovascular

A single dose (1.2 g) in a 4-year-old girl gave rise to a reversible ventricular dysrhythmia (SEDA-21, 39).

Nervous system

Two generalized seizures occurred in a 2-year-old boy after he was sedated before echocardiography (SEDA-22, 42).

Gastrointestinal

A 78-year-old woman and a 45-year-old man developed pneumatosis cystoides coli. Both were taking chloral hydrate (3). It was speculated that chloral hydrate had caused the abdominal symptoms in these patients.

- A 69-year-old man had daily loose stools with mucous discharge. Repeated stool cultures were negative. Histology confirmed the appearances of pneumatosis cystoides coli. Various treatments had little effect on his symptoms. He had taken chloral hydrate for insomnia for 10 years. Subjectively, his symptoms were worse while taking the drug and resolved after withdrawal. With his consent, an unblinded controlled challenge with chloral hydrate was performed. The results, recorded meticulously in a symptoms diary, were dramatic. Before chloral hydrate, his bowels opened 18 times per week and only two motions contained mucus. After one tablet of chloral hydrate on days 1, 2, 5, and 7 he passed 49 stools in one week, 35 containing mucus. Two weeks later his bowel habit had returned to normal, with 15 movements per week, and only one stool contained mucus. Subsequently his bowel frequency fell to 8–10 times per week with considerable colonoscopic improvement.

Liver

Hyperbilirubinemia in neonates associated with chloral hydrate (4) may be due to the more prolonged half-life of trichloroethanol in newborns compared with adults (37 versus 14 hours).

Skin

Allergic skin reactions continue to be reported (5).

Immunologic

Several reports have highlighted the importance of gelatin allergy in young children, with some deaths due to anaphylaxis.

- A 2-year-old boy and a 4-year-old boy developed anaphylactic symptoms after being given a chloral hydrate suppository, which contained gelatin, for sedation before electroencephalography (6).

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Chloral hydrate suppositories are often used to sedate children during various examinations and the authors suggested using gelatin-free formulations.

Long-Term Effects

Drug dependence

Chloral hydrate dependence can occur (7), the most famous case being that of Anna O. (Bertha Pappenheim), who was treated by Breuer from 1880 to 1882, and whose pathology was discussed by him and Freud in 1895 (8).

Tumorigenicity

Concerns about carcinogenicity are not supported by its persisting and generally successful therapeutic use.

Drug Administration

Drug formulations

Several reports have highlighted the importance of gelatin allergy in young children, with some deaths due to anaphylaxis. Some formulations of chloral hydrate contain gelatin.

- A 2-year-old boy and a 4-year-old boy developed anaphylactic symptoms after being given a chloral hydrate suppository, which contained gelatin, for sedation before electroencephalography (6).

Chloral hydrate suppositories are often used to sedate children during various examinations and the authors suggested using gelatin-free formulations.

Drug overdose

Chloral hydrate toxicity can cause a number of dysrhythmias, including supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, and torsade de pointes.

- A 27-year-old man with a history of psychiatric illness became unconscious after taking about 20 g of chloral hydrate, 1000 mg of loxapine, and 180 mg of fluoxetine (9). He became unresponsive and hypotensive and had intermittent episodes of ventricular tachycardia, which was successfully treated with intravenous propranolol.

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Chloramphenicol

General Information

Chloramphenicol is one of the older broad-spectrum antibiotics. It was introduced in 1948 and grew in popularity because of its high antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria, *Rickettsiae*, *Chlamydia*, and *Mycoplasma* species. It is particularly useful in infections caused by *Salmonella typhi* and *Haemophilus influenzae*. It is mainly bacteriostatic. It readily crosses tissue barriers and diffuses rapidly into nearly all tissues and body fluids.

The main route of elimination of chloramphenicol is metabolic transformation by glucuronidation. The microbiologically inactive metabolites are excreted rapidly and only a small proportion of unchanged drug is excreted in the urine. The usual daily dose is 50 mg/kg for adults and children over 2 months. The total dose should not exceed 3.0–3.5 g/70 kg. The statement that neither the dose nor the interval of chloramphenicol administration needs to be adjusted in patients with significant renal dysfunction (1) probably has to be modified in view of recent findings (2).

By 1950 it became evident that chloramphenicol could cause serious and fatal blood dyscrasias. Its use has therefore steadily fallen during the past 50 years. Since the risk of serious chloramphenicol toxicity is so small (1:18 000 or probably less) it is of more than historical interest. There are still many areas in which its benefits outweigh its risks. These include:

- typhoid and paratyphoid fever;
- other septic forms of *Salmonella* infections;
- meningitis due to *H. influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* when the patient is allergic to beta-lactam antibiotics or when the strains (*H. influenzae*, Enterobacteriaceae) are resistant to aminopenicillins and cephalosporins;
- brain abscess;
- serious infections caused by *Bacteroides fragilis* (as an alternative to clindamycin or metronidazole).

Since chloramphenicol is still one of the cheapest antibiotics, this list of indications is longer in developing

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countries, where chloramphenicol may be more readily available than newer expensive antibiotics. However, most infections can be readily, safely, and effectively treated with alternative drugs. Therefore, the role of chloramphenicol in the treatment of infectious diseases is likely to diminish further.

Chloramphenicol and its metabolites act primarily on the 50S ribosomal subunit, with suppression of the activity of the enzyme peptidyltransferase. It inhibits mitochondrial membrane protein synthesis, leading to suppression of mitochondrial respiration and ultimately to cessation of cell proliferation (3). Analogous mechanisms may operate in the production of the reversible type of bone marrow depression, which is the most prominent toxic effect in patients taking chloramphenicol. Its potency to induce toxic effects on mitochondria in maturing or rapidly proliferating eukaryotic cells is very close to that for inhibiting prokaryotic cells (bacteria and blue-green algae). However, little progress has been made in elucidating the pathogenesis of irreversible bone marrow aplasia (3–5).

Observational studies

The response to chloramphenicol has been assessed in cases of bacteremia due to vancomycin-resistant enterococci, of whom 65% received chloramphenicol (6). Among those in whom a response could be assessed, 61% had a clinical response and 79% had a microbiological response. Mortality was non-significantly lower in patients treated with chloramphenicol. In cases with central line-related bacteremia, there was no difference in mortality among those treated with chloramphenicol, line removal, or both. No adverse effect could be definitely attributed to chloramphenicol.

General adverse effects

Chloramphenicol has been associated with two serious but rare toxic effects, each with a high mortality. One is the "gray syndrome," vasomotor collapse in neonates caused by excessive parenteral doses. The second is bone marrow aplasia, which is a hypersusceptibility reaction. Prolonged use can result in neuropathies. Mild gastrointestinal disturbances are common. Chloramphenicol can cause a Jarisch–Herxheimer reaction, for example in patients with louse-borne relapsing fever (7). Hypersensitivity reactions are commonly mild and more frequent with topical use (allergic contact dermatitis, rashes, glossitis). The late, severe type of bone marrow reaction may be of allergic origin. Tumor-inducing effects have not been described; a statement that chloramphenicol might cause cancer in the fetus appears to have been purely speculative.

Organs and Systems

Cardiovascular

The "gray syndrome" is the term given to the vasomotor collapse that occurs in neonates who are given excessive parenteral doses of chloramphenicol. The syndrome is characterized by an ashen gray, cyanotic color of the skin, a fall in body temperature, vomiting, a protuberant abdomen, refusal to suck, irregular and rapid respiration, and lethargy. It is mainly seen in newborn infants, particularly when premature. It usually begins 2–9 days after the start of treatment.

Inadequate glucuronyl transferase activity combined with reduced glomerular filtration in the neonatal period is responsible for a longer half-life and accumulation of the drug. In addition, the potency of chloramphenicol to inhibit protein synthesis is higher in proliferating cells and tissues. The most important abnormality seems to be respiratory deficiency of mitochondria, due, for example to suppressed synthesis of cytochrome oxidase. The dosage should be adjusted according to the age of the neonate, and blood concentrations should be monitored. In most cases of gray syndrome, the daily dose of chloramphenicol has been higher than 25 mg/kg (8,9). Occasionally, treatment of older children and teenagers with large doses of chloramphenicol (about 100 mg/kg) has resulted in a similar form of vasomotor collapse (10).

Nervous system

Peripheral neuropathy has been seen after prolonged courses of chloramphenicol (11).

Retrobulbar optic neuritis and polyneuritis have been attributed to prolonged chloramphenicol therapy (12).

Sensory systems

Eyes

Optic neuropathy has been seen after prolonged courses of chloramphenicol (13). Alterations in color perception and optic neuropathy, in some cases resulting in optic atrophy and blindness, have been observed, especially in children with cystic fibrosis receiving relatively high doses for many months (12,14). Most of these complications were reversible and were attributed to a deficiency of B vitamins.

Ears

Local application of chloramphenicol can cause hearing defects. Asymmetrical hearing loss with lowered perception of high tones has been documented after treatment of chronic bilateral otitis media with chloramphenicol powder (15). Propylene glycol is often used as a vehicle for chloramphenicol ear-drops, and ototoxicity may be due to chloramphenicol and/or propylene glycol, which is itself strongly ototoxic. Ototoxic effects can also occur after systemic drug administration (16).

Hematologic

The first death resulting from bone marrow aplasia induced by chloramphenicol eye-drops was described in 1955 (17). Chloramphenicol causes two types of bone marrow damage (18).

- A frequent, early, dose-related, reversible suppression of the formation of erythrocytes, thrombocytes, and granulocytes (early toxicity).
- A rare, late type of bone marrow aplasia, a hypersusceptibility reaction, which is generally irreversible, and has a high mortality rate (aplastic anemia) (19–21).

Chloramphenicol inhibits mRNA translation by the 70S ribosomes of prokaryotes, but does not affect 80S eukaryotic ribosomes. Most mitochondrial proteins are encoded by

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nuclear DNA and are imported into the organelles from the cytosol where they are synthesized. Mitochondria retain the capacity to translate, on their own ribosomes, a few proteins encoded by the mitochondrial genome. True to its prokaryotic heritage, mitochondrial ribosomes are similar to those of bacteria, meaning that chloramphenicol inhibits protein synthesis by these ribosomes. Chloramphenicol-induced anemia is believed to result from this inhibition (22). Chloramphenicol can also cause apoptosis in purified human bone marrow CD34+ cells (23).

Dose-related bone marrow suppression

The early, dose-related type of chloramphenicol toxicity is usually seen after the second week of treatment, and is characterized by inhibited proliferation of erythroid cells and reduced incorporation of iron into heme. The clinical correlates in the peripheral blood are anemia, reticulocytopenia, normoblastosis, and a shift to early erythrocyte forms. The plasma iron concentration is increased. Early erythroid forms and granulocyte precursors show cytoplasmic vacuolation. After withdrawal, complete recovery is the rule. Leukopenia and thrombocytopenia are less frequent.

Although there is no evidence that these abnormalities progress to frank bone marrow aplasia, continuation of chloramphenicol after the appearance of early toxicity is thought to be hazardous. Pre-existing liver damage (for example due to infectious hepatitis or alcoholism) and impaired kidney function can lead to reduced elimination of chloramphenicol and its metabolites, thereby aggravating marrow toxicity. As a rule, this is not the irreversible type.

Aplastic anemia

Although bone marrow aplasia has not been related with certainty to either the daily or the total dose of chloramphenicol or to the sex or age of the patients, it has occurred almost exclusively in individuals who were taking prolonged therapy, particularly if they were exposed to the drug on more than one occasion (24). The condition is rare, occurring about once in every 18 000–50 000 subjects in various countries. These variations may in part depend on ethnic factors (25,26). For example, there have been very few cases reported in blacks (27). Bone marrow aplasia due to chloramphenicol has usually resulted in aplastic anemia with pancytopenia; other forms, such as red cell hypoplasia, selective leukopenia, or thrombocytopenia, are less common.

When bone marrow aplasia was complete, the fatality rate approached 100%. As a rule, it has been found that the longer the interval between the last dose of chloramphenicol and the appearance of the first sign of a blood dyscrasia, the more severe the resulting aplasia. Nearly all patients in whom the interval was longer than 2 months died as a result of this complication. However, fatal aplastic anemia can also occur shortly after normal doses of chloramphenicol (28).

The pathogenesis of bone marrow aplasia after chloramphenicol is still uncertain. Compared with normal cells, bone marrow aspirates from patients with bone marrow aplasia are relatively resistant to the toxic effects of chloramphenicol in vitro. This has been explained by the hypothesis that during treatment with chloramphenicol, chloramphenicol-sensitive cells were eliminated, leaving behind only a chloramphenicol-insensitive population of blood cell precursors with poor proliferative capacity (29). Chloramphenicol can induce apoptosis in purified human bone marrow CD34+ cells; however, there was no protection from a variety of antioxidants on chloramphenicol-induced suppression of burst-forming unit erythroid and colony-forming unit granulocyte/monocyte in vitro (30). In contrast, a caspase inhibitor ameliorated the apoptotic-inducing effects of chloramphenicol.

Since thiamphenicol, which causes very few cases of aplastic anemia, differs from chloramphenicol by substitution of the para-nitro group by a methylsulfonyl group, interest has been focused on the para-nitro group and metabolites of that part of the molecule, nitrosochloramphenicol and chloramphenicol hydroxylamine. In human bone marrow, nitrosochloramphenicol inhibited DNA synthesis at 10% of the concentration of chloramphenicol required for the same effect, and proliferation of myeloid progenitors was irreversibly inhibited. The covalent binding of nitrosochloramphenicol to marrow cells was 15 times greater than that of chloramphenicol (31). This has lent support to the hypothesis that abnormal metabolism may contribute to the susceptibility to bone marrow aplasia. The production of reduced derivatives by intestinal microbes may contribute to toxicity, but oral administration of chloramphenicol is not essential for the development of aplastic anemia (32). There is evidence that genetic predisposition may play a role (33,34). The wide geographical variations in the incidence of aplastic anemia may also reflect environmental factors.

For many years it had been said that there were no cases of aplastic anemia after parenteral administration of chloramphenicol; however, a few cases of aplastic anemia have been reported (35). There have also been reports of bone marrow hypoplasia after the use of chloramphenicol eye-drops (36,37).

There is controversy about the risk of aplastic anemia with topical chloramphenicol. In a prospective case-control surveillance of aplastic anemia in a population of patients who had taken chloramphenicol for a total of 67.2 million person-years, 145 patients with aplastic anemia and 1226 controls were analysed. Three patients and five controls had been exposed to topical chloramphenicol, but two had also been exposed to other known causes of aplastic anemia. Based on these findings, an association between ocular chloramphenicol and aplastic anemia could not be excluded, but the risk was less than one per million treatment courses (38). In another study, a review of the literature identified seven cases of idiosyncratic hemopoietic reactions associated with topical chloramphenicol. However, the authors failed to find an association between the epidemiology of acquired aplastic anemia and topical chloramphenicol. Furthermore, after topical therapy they failed to detect serum accumulation of chloramphenicol by high performance liquid chromatography. They concluded that these findings support the view that topical chloramphenicol was not a risk factor for dose-related bone marrow toxicity and that calls for abolition of treatment with

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topical chloramphenicol based on current data are not supported (39).

In a study using general practitioner-based computerized data, 442 543 patients were identified who received 674 148 prescriptions for chloramphenicol eye-drops. Among these patients, there were three with severe hematological toxicity and one with mild transient leukopenia. The causal link between topical chloramphenicol and hematological toxicity was not further evaluated in detail (40).

Leukemia

In a small fraction of patients who survive the chronic type of bone marrow damage, myeloblastic leukemia develops (41,42). In most instances this complication has appeared within a few months of the diagnosis of aplasia and was considered to be a sequel of chloramphenicol treatment. Sometimes the delay was shorter. The majority were either children or adults aged 50–70 years.

The occurrence of acute leukemia has been studied in relation to preceding use of drugs (before the 12 months preceding the diagnosis) in a case-control study of 202 patients aged over 15 years with a diagnosis of acute leukemia and age- and sex-matched controls (43). Among users of chloramphenicol or thiamphenicol the odds ratio for any use was 1.1 (0.6–2.2) whereas the odds ratio for high doses was 1.8 (0.6–5.3). Other systemic antibiotics showed no substantial relation with the occurrence of leukemia.

Gastrointestinal

Mild gastrointestinal disturbances are common in patients taking chloramphenicol. In 51 children with Mediterranean spotted fever randomized for 7 days to either clarithromycin, 15 mg/kg/day orally in two divided doses, or chloramphenicol, 50 mg/kg/day orally in four divided doses, the two drugs were equally well tolerated and there were no major adverse effects; there was vomiting in two patients treated with clarithromycin and in one treated with chloramphenicol (44). None of the patients required drug withdrawal.

Skin

Hypersensitivity occurs about four times more often after topical than after oral use (45). In fact, there has been a continuous increase in chloramphenicol hypersensitivity, owing to the use of dermatological formulations (46). Allergic contact dermatitis and macular or vesicular skin rashes are usually limited to skin areas previously exposed to the drug. Contact conjunctivitis has also been reported.

A case of a facial contact dermatitis due to chloramphenicol with cross-sensitivity to thiamphenicol has been reported (47).

Immunologic

Systemic reactions with collapse, bronchospasm, angioedema, and urticaria occur rarely (48,49).

Infection risk

The number and types of microorganisms that constitute the normal microflora of the alimentary, respiratory, and genital tracts change during therapy with chloramphenicol. Superinfections can then develop with *Staphylococcus aureus*, *Pseudomonas*, *Proteus*, and fungi. The changes in intestinal flora may be partly responsible for a reduction in the synthesis of vitamin K-dependent clotting factors, especially in patients with severe illnesses and malnutrition or during the administration of oral anticoagulants.

Long-Term Effects

Drug tolerance

There have been reports of chloramphenicol-resistant *H. influenzae* from various countries, but there have been few cases (50). Outbreaks of chloramphenicol-resistant *S. typhi* have been observed in several countries (51,52).

High-level chloramphenicol-resistant strains of *N. meningitidis* serogroup B were isolated from 11 patients in Vietnam and one patient in France. Resistance was due to the presence of the catP gene on a truncated transposon that has lost mobility because of internal deletions (53).

Salmonella typhimurium DT104 is usually resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An outbreak of 25 culture-confirmed cases of multidrug-resistant *S. typhimurium* DT104 has been identified in Denmark (54). The strain was resistant to the above-mentioned antibiotics and nalidixic acid and had reduced susceptibility to fluoroquinolones. A swineherd was identified as the primary source (54). The DT104 strain was also found in cases of salmonellosis in Washington State, and soft cheese made with unpasteurized milk was identified as an important vehicle of its transmission (55).

A high rate of resistance of non-typhoid *Salmonella* to commonly used antimicrobial agents was found in Taiwan; 67% of the isolated strains were resistant to chloramphenicol (56).

Streptococcus pneumoniae was isolated in 30% of 40 HIV-infected and 50% of 162 HIV-negative children living in a Romanian orphanage (57). Multidrug-resistant streptococci were highly prevalent, and 21% of the isolates were resistant to chloramphenicol.

Esterases in serum from rabbits and to a lesser extent humans can convert diacetyl chloramphenicol back to an active antibiotic. Therefore, in vitro findings may not accurately reflect the level of chloramphenicol resistance by chloramphenicol acetyltransferase-bearing bacteria in vivo, when growth media supplemented with serum are used (58).

The flo gene that confers resistance to chloramphenicol and the veterinary antibiotic florfenicol have previously been identified in *Photobacterium piscicida* and *Salmonella enterica serovar typhimurium* DT104 (59). Florfenicol-resistant isolates of *Escherichia coli* were tested and found to contain large flo-positive plasmids, suggesting that several of these isolates may have a chromosomal flo gene. The *E. coli* flo gene also specifies non-enzymatic cross-resistance to both florfenicol and chloramphenicol (60). Florfenicol resistance has emerged among veterinary isolates of *E. coli* incriminated in bovine diarrhea.

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Second-Generation Effects

Teratogenicity

In the large population-based dataset of the Hungarian Case Control Surveillance of Congenital Abnormalities, of 38 151 pregnant women who had babies without any defects and 22 865 pregnant women who had neonates or fetuses with congenital abnormalities, 51 and 52 had been treated with oral chloramphenicol respectively. Treatment during early pregnancy presented little, if any, teratogenic risk to the fetus (61).

Fetotoxicity

Chloramphenicol penetrates the fetal circulation and should therefore be avoided during the last phase of pregnancy (62,63). The gray syndrome has been observed in babies born to mothers who had received chloramphenicol in the final stage of pregnancy.

Lactation

Chloramphenicol has been found in relatively large amounts in breast milk. It should therefore be avoided during breast-feeding (62,63).

Susceptibility Factors

Age

In children, a high cumulative dose seems to be an important risk factor. As leukopenia can occur in the early phase of treatment, a complete blood count every third day is recommended (SEDA-15, 267).

Renal disease

Impaired kidney function, with reduced clearance of chloramphenicol, may be a risk factor for toxicity.

Hepatic disease

Liver damage, with reduced clearance of chloramphenicol, may be a risk factor for toxicity.

Other features of the patient

In a retrospective study of 30 consecutive children with sepsis treated with oral chloramphenicol, weight, albumin, and white blood cell count were the most important determinants for chloramphenicol distribution volume, whereas age, white blood cell count, and serum creatinine were most important for drug clearance (64). A preexisting blood dyscrasia is generally considered to be an absolute contraindication to the use of chloramphenicol.

Drug Administration

Drug administration route

In 1993 the American National Register of Drug Induced Ocular Side Effects received reports of 23 patients with blood dyscrasias that could have been related to topical ocular administration of chloramphenicol (65).

Of the two types of bone marrow toxicity that chloramphenicol can cause, it may cause the late type only in genetically predisposed patients. The overall risk of aplastic anemia after oral administration of chloramphenicol is 1:30 000 to 1:50 000, which is 13 times greater than the risk of idiopathic aplastic anemia in the population as a whole. Since topical administration achieves systemic effects by absorption through the conjunctival membrane or through drainage down the lacrimal duct, with eventual absorption from the gastrointestinal tract, the risk may be similar to that after oral administration. However, based on two case-control studies and a cohort study, the incidence of blood dyscrasias due to chloramphenicol eye-drops was estimated to be somewhat lower, namely 1:100 000 treated patients (40,66).

It is difficult to justify subjecting patients to this small potential risk, in view of the availability of other antibiotics for use in the eye. In the USA the Physician's Desk Reference emphasizes with repeated warnings the importance of not using ocular chloramphenicol unless there is no alternative, and this warning should be respected on both sides of the Atlantic (67,68).

Allergic reactions to chloramphenicol eye-drops include conjunctivitis, keratitis, and palpebral and periocular eczema (47).

Erythema multiforme caused by local treatment with chloramphenicol eye-drops has been described (47). The possible role of an allergic mechanism in this reaction was suggested, based on a positive mast cell degranulation test (69).

Drug–Drug Interactions

Ciclosporin

A possible interaction between ciclosporin and chloramphenicol has been observed (70).

- A morbidly obese 17-year-old Hispanic girl, who had a cadaveric renal transplantation 5 years before, took ciclosporin and prednisone for stabilization. She was treated with chloramphenicol 875 mg qds and ceftazidime 2 g tds for vancomycin-resistant enterococcal sinusitis. There was a substantial and sustained increase in ciclosporin concentrations after chloramphenicol was added. Normalization was achieved after withdrawal of chloramphenicol.

Cyclophosphamide

Chloramphenicol inhibits the biotransformation of cyclophosphamide (71).

Cytochrome P450

Chloramphenicol can interfere with the elimination of drugs that are inactivated by hepatic metabolism, probably through a mechanism involving inhibition of microsomal enzymes. The mechanism has been claimed to be inactivation of microsomal enzymes via an intermediate reactive metabolite that binds covalently to the protein moiety of cytochrome P450 (71). Assuming such a mechanism, chloramphenicol would be expected to interact with the metabolism of other drugs dealt with by cytochrome P450.

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Oral anticoagulants

Chloramphenicol inhibits the biotransformation of oral anticoagulants (71).

Paracetamol (acetaminophen)

Paracetamol altered the pharmacokinetics of chloramphenicol in some studies but not in others.

In six adults the half-life of chloramphenicol, 1 g intravenously was increased from 3.3 to 15 hours by paracetamol 100 mg intravenously (72).

In contrast, in five children aged 2.5–5 years paracetamol 50 mg/kg/day for several days significantly lowered the C_{max} of chloramphenicol, increased its apparent volume of distribution and clearance, and slightly shortened its half-life (73).

Other studies have failed to show any interaction in children (74) or adults (75).

Phenobarbital

Phenobarbital can increase the rate of chloramphenicol metabolism and so lead to abnormally low serum chloramphenicol concentrations. In 17 children receiving chloramphenicol succinate alone, mean peak and trough serum concentrations were 25 and 13 μg/ml respectively. In six patients phenobarbital reduced these concentrations to 17 and 7.5 μg/ml respectively (76).

Phenytoin

The ability of chloramphenicol to inhibit the biotransformation of phenytoin is well established and clinically relevant (77).

Conversely, phenytoin can increase the rate of chloramphenicol metabolism and so lead to abnormally low serum chloramphenicol concentrations, as has been anecdotally reported (78). However, contrary to expectation, in another study serum chloramphenicol concentrations rose during concomitant phenytoin therapy (76).

Rifampicin

Rifampicin can increase the rate of chloramphenicol metabolism and so lead to abnormally low serum chloramphenicol concentrations (79,80).

Tacrolimus

Inhibition of tacrolimus clearance has been observed in an adolescent renal transplant recipient who was treated with standard doses of chloramphenicol for vancomycin-resistant enterococci. Toxic concentrations of tacrolimus were observed on the second day of chloramphenicol treatment, requiring an 83% reduction in the dose of tacrolimus (81).

A significant interaction has also been reported in an adult (82).

- A 47-year-old white man with a cadaveric liver transplant took chloramphenicol for a urinary tract infection due to a vancomycin-resistant *Enterococcus* and inadvertently received 1850 mg qds (roughly twice the maximum recommended dose). On day 4 he had a 12-hour trough tacrolimus concentration of over 60 ng/ml, and complained of fatigue, lethargy, headache, and tremor, symptoms consistent with tacrolimus toxicity.

It was suggested that the underlying mechanism might be inhibition of CYP3A4 by chloramphenicol.

Tolbutamide

Chloramphenicol inhibits the biotransformation of tolbutamide (71).

Warfarin

An interaction of warfarin with ocular chloramphenicol (5 mg/ml; 1 drop qds in each eye), which led to an increase in INR, has been suspected in an 83-year-old white woman (83). The authors suggested that the effect may be due to chloramphenicol inhibition of hepatic microsomal CYP2C9, since the pharmacologically active enantiomer *S*-warfarin is metabolized by this enzyme).

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Chlordiazepoxide

See also Benzodiazepines

General Information

Chlordiazepoxide, which has a long duration of action ($t_{1/2}$ = 10–25 hours), is useful for the management of alcohol withdrawal and is arguably better tolerated than other benzodiazepines when used for this indication. As with diazepam, loading doses are possible and simplify clinical management.

Organs and Systems

Metabolism

A San Francisco woman with a history of diabetes and high blood pressure was hospitalized in January 2001 with a life-threatening low blood sugar concentration after she consumed Anso Comfort capsules (1). The authors conjectured that hospitalization may have been necessitated by a drug interaction of chlordiazepoxide with medications that she was taking for other medical conditions.

Hematologic

- A 68-year-old man, who had been taking lorazepam, perphenazine, and amitriptyline for many years, developed acute thrombocytopenic purpura after combination therapy of chlordiazepoxide 5 mg and clidinium 2.5 mg tds for irritable bowel syndrome (2). His disease

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improved after withdrawal of chlordiazepoxide and clidinium and treatment with intravenous prednisolone.

In this case it was not clear which of the two compounds caused the purpura; it is possible that it was due to the combination.

Drug Administration

Drug formulations

The California State Health Director has warned consumers to stop using the herbal product Anso Comfort capsules immediately, because the product contains the undeclared prescription drug chlordiazepoxide (1). Anso Comfort capsules, available by mail or telephone order from the distributor in 60-capsule bottles, are clear with dark green powder inside. The label is yellow with green English printing and a picture of a plant. An investigation by the California Department of Health Services Food and Drug Branch and Food and Drug Laboratory showed that the product contains chlordiazepoxide. The ingredients for the product were imported from China and the capsules were manufactured in California. Advertising for the product claims that the capsules are useful for the treatment of a wide variety of illnesses, including high blood pressure and high cholesterol, in addition to claims that it is a natural herbal dietary supplement. The advertising also claims that the product contains only Chinese herbal ingredients and that consumers may reduce or stop their need for prescribed medicines. No clear medical evidence supports any of these claims. The distributor, NuMeridian (formerly known as Top Line Project), has voluntarily recalled the product.

Drug–Drug Interactions

Heparin

In normal non-fasting subjects, 100–1000 IU of heparin given intravenously caused a rapid increase in the free fractions of diazepam, chlordiazepoxide, and oxazepam (3,4), but no change in the case of lorazepam (3). The clinical implications of this finding are not known.

Oral contraceptives

In 7 healthy young women who had taken oral contraceptives for more than 6 months the protein binding of chlordiazepoxide was reduced and its volume of distribution increased (5). The clearance of chlordiazepoxide is also reportedly reduced by oral contraceptives (6).

Mid-cycle spotting occurred in a large proportion of 72 women taking oral contraceptives and chlordiazepoxide; however, there were no pregnancies (7).

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Chlorhexidine

See also Disinfectants and antiseptics

General Information

Chlorhexidine (1,1′-hexamethylene-*bis*[5-(*p*-chlorophenyl) biguanide]) is a widely used antibacterial agent with activity against Gram-positive bacteria, Gram-negative bacteria (less against *Pseudomonas* species), and yeasts. It was introduced as an antiseptic in the early 1950s. It has been primarily used for topical antisepsis, for example in preoperative skin disinfection, and for disinfection of materials, mainly in combination with cetrimide. Long-term experience has shown a low incidence of sensitization and a low irritant potential (SEDA-11, 480).

Unwanted effects have resulted from undue reliance on the disinfecting properties of chlorhexidine. Hospital-acquired infections have been caused by infected chlorhexidine used for bladder irrigation and for storage or disinfection of catheter spigots and needles (SEDA-11, 480) (1,2). A microbiological analysis of chlorhexidine-cream tubes, repeatedly used by patients with indwelling urethral catheters, showed high contamination with potential pathogens in 32% of cream samples and in 35% of swabs taken from the outside of the tubes beneath the screw cap (SEDA-11, 480) (3).

Use of chlorhexidine in dentistry

Chlorhexidine has been used as an adjuvant for plaque control and in the treatment of gingival inflammation. It is generally considered to be effective in the control of plaque and can be helpful in the treatment of gingivitis. It can be applied in the form of a solution, used as a mouth rinse or with a toothbrush, in dentifrice or as a gel. The concentrations used are 0.05–2%.

It is very difficult to summarize the effect of chlorhexidine on oral hygiene, since studies differ markedly as regards the population studied, the occurrence of gingival lesions, the use of other oral hygiene regimens, previous scaling, and polishing of the teeth. The most frequently reported adverse effects of oral use are discoloration of the teeth, tongue, and buccal mucosa, taste disorders, and desquamation of the oral mucosa. A mild increase in

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gingival bleeding was reported after the use of chlorhexidine mouthwash compared with mechanical cleaning methods.

Use of chlorhexidine in neonatal skin care

The withdrawal of hexachlorophene-containing products for routine neonatal skin care stimulated investigations into the possible use of chlorhexidine in this field. Its activity range includes effectiveness of high dilutions against Gram-positive and Gram-negative bacteria, yeasts, and molds. In studies of nursery populations, chlorhexidine appears to be as effective as hexachlorophene in preventing staphylococcal colonization and infection. However, there is no evidence that chlorhexidine promotes Gram-negative colonization in neonates bathed in water-containing chlorhexidine (SEDA-11, 482).

Data presented in three studies have provided substantial evidence that there is very low percutaneous absorption in full-term infants and also in excessively exposed newborn rhesus monkeys. However, traces of chlorhexidine were found in adipose tissue (two of five monkeys), kidneys (five of five), and liver (one of five), suggesting some absorption percutaneously or by oral ingestion, following the rigorous bathing procedure in the above study. The grooming habits of the monkeys could have played a role (SEDA-12, 578) (4).

Use of chlorhexidine in routine neonatal cord care

About 0.2 ml of undiluted 4% chlorhexidine solution with a detergent was included in the daily routine of rubbing the dry cord stump and the surrounding skin, which were then rinsed and dried. No chlorhexidine was detectable in the blood samples of the neonates, taken on the fifth day (5).

Use of chlorhexidine in spermicides

The use of chlorhexidine in spermicides has been promoted as a strategy for protecting against sexually transmitted diseases, including HIV infection. However, both the claim of protection and the cytotoxicity of chlorhexidine, with a risk of damage to the epithelia of the vagina, cervix, and glans penis due to chronic exposure, have to be further validated (6).

Vaginal use of chlorhexidine

Five studies of the prophylactic intravaginal use of chlorhexidine vaginal suppositories before delivery and in obstetrics have been reviewed (7). No severe adverse reactions were reported.

Accidental ingestion

A newborn had cyanotic spells associated with sinus bradycardia but not with apnea on the third day of life(8). The mother had used a chlorhexidine spray on her breasts from the third feed onwards. Bradycardia became less frequent and less severe from day 4 after the spray was stopped, and had abated completely by day 6.

Five healthy newborn breast-fed babies were accidentally fed a dilute antiseptic solution containing chlorhexidine 0.05% with cetrimide 1% instead of sterile water (9). They developed caustic burns of the lips, mouth, and tongue within minutes. One baby became severely ill due to acute pulmonary edema, but all survived without sequelae.

Organs and Systems

Respiratory

Chlorhexidine gluconate when ingested usually causes relatively mild symptoms, with poor gastrointestinal absorption, and is considered relatively safe. However, a rare fatality, with acute respiratory distress syndrome, has been reported (10).

- An 80-year-old woman with dementia accidentally took about 200 ml of chlorhexidine gluconate 5%. She aspirated her gastric contents and despite intensive treatment died of acute respiratory distress syndrome 12 hours later. The serum concentration of chlorhexidine gluconate was markedly high (25 μg/ml).

It is possible that in this case, although chlorhexidine was poorly absorbed from the gastrointestinal tract, absorption occurred through the pulmonary alveoli.

Occupational asthma caused by chlorhexidine alcohol disinfectant spray was well documented in three nurses (11).

Ear, nose, throat

Reversible hyposmia occurred after Hardy's operation for pituitary adenomas following preoperative disinfection of the nasal cavity with chlorhexidine (12). The olfactory disturbance improved after 3–7 weeks. Degeneration of the olfactory epithelium was also seen in guinea pigs when the nasal cavities were irrigated 3 times with 5 ml 0.5% chlorhexidine solution; regeneration of the epithelium started after 14 days and the surfaces appeared normal after 1 month.

Nervous system

The middle ear should be carefully protected against chlorhexidine solutions in preoperative skin disinfection in otolaryngology. Severe sensorineural deafness occurred in 14 of 97 patients who underwent myringoplasty (13). The only common factor in all these patients was the preoperative skin disinfection of the ear with 0.5% chlorhexidine in a 70% alcoholic solution.

In extensive investigations of the ototoxicity caused by chlorhexidine after introducing it into the middle ear of guinea pigs, the extent of severe vestibular and cochlear damage was related to the concentration of chlorhexidine, to the duration of exposure, and to the time-lapse after exposure (14–16).

Sensory systems

Eyes

Accidental contamination of the eye with chlorhexidine can cause adverse effects. Care should be taken during preoperative skin preparation to keep chlorhexidine out of the eye and to flush copiously with sterile saline solution or sterile water if contact accidentally occurs.

- Accidental use of chlorhexidine solutions (1:666 and 1:1000) as irrigation during cataract surgery resulted in

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immediate corneal edema, which resulted in a bullous keratopathy (17).
- Chlorhexidine disinfectant was accidentally used to irrigate the eyes of four patients; despite immediate treatment, corneal burns occurred in all (18).
- In four patients, accidental corneal exposure to Hibiclens (4% chlorhexidine formulated with a detergent) resulted in keratitis, with severe and permanent corneal opacification (19).
- Epithelial and stromal edema of the cornea and a diffuse bullous keratopathy developed in a 39-year-old woman 2 weeks after a preoperative disinfection of the face with an alcoholic chlorhexidine solution. This led to penetrating keratoplasty 10 months later (20).

The histopathological findings in the cornea have been described in such cases; they include epithelial edema with bullous changes, marked loss of keratocytes, thickening of Descemet's membrane, and an attenuated disrupted cell layer (21).

Chlorhexidine has also been accidentally irrigated into the anterior chamber of the eye, instead of balanced salt solution, during cataract surgery (22). Later in the operation, a decrease in corneal clarity was noted and an epithelial abrasion had to be performed. The inadvertent use of chlorhexidine in this patient resulted in reduced endothelial function and loss of corneal clarity.

Progressive ulcerative keratitis related to the use of chlorhexidine gluconate 0.02% eye-drops has been reported (23).

- A 45-year-old woman was treated for presumed *Acanthamoeba* keratitis with chlorhexidine gluconate 0.02% and propamidine 0.1% eye-drops. After using the eye-drops for 8 weeks she developed a near total loss of the corneal epithelium and progressive ulcerative keratitis, which eventually required penetrating keratoplasty. Histopathological examination of the corneal button showed ulceration and loss of Bowman's membrane, massive loss of keratocytes with apparent apoptosis, and loss of endothelial cells, with inflammatory cells adherent to the remaining cells. These findings were similar to those seen in chlorhexidine 4% keratopathy. No organisms were seen in stained sections and immune histochemistry showed no significant findings.

Taste

Taste impairment and/or disturbance is especially seen with chlorhexidine mouthwashes (SEDA-11, 481) (SEDA-12, 577) (24). It occurs in about one-third of subjects and is perhaps the main complaint. Symptoms include a burning sensation, a feeling of soreness, a dry mouth, and a bitter aftertaste lasting from a few minutes up to several hours. However, these types of symptoms also occur, albeit to a lesser extent, in placebo or control groups.

Mouth and teeth

Desquamation and ulceration of the oral mucosa has been observed after the use of chlorhexidine mouthwashes. The frequency of this adverse effect must be very low. Histological and histochemical examination of mucosal biopsies taken after 18 months of daily exposure to chlorhexidine did not show any adverse effect on the oral mucosa. There was increased keratinization of human gingival cells in vitro in cell cultures if the chlorhexidine concentration exceeded 25 μg/ml, and the same acceleration of keratinization of human gingival cells in gingival swabs occurred after rinsing with 0.025, 0.05, and 0.1% chlorhexidine solutions (25). In one case there was excessive impairment of wound healing after daily rinses with a 0.1% chlorhexidine solution after oral surgery.

Staining of the teeth was the first and principal adverse effect observed with the dental use of chlorhexidine. In a 4-month study of soldiers who used chlorhexidine mouthwashes in concentrations of 0.1 and 0.2%, 15% of the interproximal surface and 62% of the fillings, especially the old and porous ones, were discoloured (26,27). The stain intensity seems to be directly correlated to the concentration of the chlorhexidine and to the frequency and duration of use. The type of administration (0.2% mouthwash, 0.2% spray, or 1% gel) does not seem to influence the amount of tooth-staining. The initial discoloration is yellow-brown, but prolonged use and stronger concentrations result in a dark-brown color. Extensive investigations have been performed to evaluate factors that influence tooth-staining and the possibility of avoiding it. The cause of extrinsic tooth discoloration is not fully understood. However, the available evidence suggests that browning and formation of pigmented metal sulfides are the most likely causes, while dietary factors (such as beverages or red wine) and smoking may play an aggravating role only (SEDA-10, 427).

A discoloration of the dorsum of the tongue occurs in up to one-third of subjects using chlorhexidine mouth rinses. It does not occur during the use of chlorhexidine-containing dentifrices or gels (SEDA-11, 481) (27,28).

Reversible swelling of the parotid glands has been reported occasionally after the use of chlorhexidine mouthwashes; this is probably due to mechanical obstruction of the parotid duct by over-rigorous rinsing (SEDA-11, 481) (29).

Gastrointestinal

- Atrophic gastritis was reported in a 72-year-old man with Parkinson's disease who had used a 4% chlorhexidine solution as a daily mouthwash but had also swallowed it. Gastroscopy showed multiple erosions in the lower part of his stomach and the first part of the duodenum (30).

Skin

Of 551 patients with venous or traumatic ulcers of the leg who were patch-tested with chlorhexidine, 10 developed severe dermatitis and 4 developed skin infections on the face and/or scalp (31).

Serosae

Sclerosing peritoneal disease occurred in peritoneal dialysis patients in whom the tubing connection had been disinfected with chlorhexidine (32–34); 214 cases were

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reported from 112 centers in European countries up to 1984 (SEDA-15, 250).

Musculoskeletal

Chlorhexidine is not normally used in arthroscopy, but it is a common irrigating fluid for surgical wounds. In three of five patients with pain, swelling, crepitus, and loss of range of movement following arthroscopy of the knee, there had been accidental irrigation with 1% aqueous chlorhexidine. Histological examination showed partial necrosis of the cartilage, with slight non-specific inflammation and fibrosis of synovial specimens (35). This shows that particular care is needed in checking irrigation fluids.

Even very dilute solutions of chlorhexidine can cause marked chondrolysis of articular cartilage, leading to severe permanent damage of the knee (36).

- A 20-year-old woman, a 30-year-old man, and a 62-year-old woman all had arthroscopic reconstruction of the anterior cruciate ligament performed by the same surgeon. The only difference in technique in these three cases, compared with the rest of his cases, was the use of chlorhexidine 0.02% for irrigation throughout the procedure. All had good immediate postoperative recovery with no sign of infection, and none had preceding rheumatoid or other inflammatory joint disease, systemic disease, or chronic use of drugs. However, they all developed pain, swelling, stiffness, and loud crepitus at 2–4 months after the procedure and had radiological evidence of loss of joint space, especially in the medial compartment. Arthroscopy in all three cases showed a large amount of loose chondral material, a "snowstorm" appearance, which could be washed out. Severe erosion of the articular cartilage and a mild synovitis were also demonstrated. The ligaments were all intact and culture of the synovial fluid was sterile. Histopathology of the fragments of cartilage showed non-viable chondrocytes, with an absence of acute inflammatory cells and very few chronic inflammatory cells. The synovial biopsies showed evidence of fibrosis. All three patients had severely damaged knees which required total knee replacement.

These cases of chondrolysis did not result from accidental use of relatively concentrated solutions of chlorhexidine, but from the use of a very low concentration, 0.02%, which is widely used as an irrigation solution during surgical procedures. Chlorhexidine has a damaging effect on the articular cartilage of the knee, and should not be used, even in low concentrations, to irrigate exposed articular cartilage.

Immunologic

Allergic reactions, including anaphylaxis, from chlorhexidine are reported with all types of use and are well documented. However, chlorhexidine may still not be suspected as a possible cause of anaphylaxis when several agents are used in the anesthetized surgical patient, and hypersensitivity to chlorhexidine may not be tested for (37). If a reaction occurs during anesthesia, there is often doubt about the exact agent responsible; patch-testing will help if there is doubt about causality.

Mechanism

The molecular basis of the recognition of chlorhexidine in a sensitive patient has been examined (38).

- A 75-year-old man had three anaphylactic events after the use of chlorhexidine. The first occurred in September 1995 during general anesthesia for coronary artery bypass grafts. Ten minutes after induction he developed a marked fall in blood pressure, bronchospasm, tachycardia, and increased pulmonary artery pressure. In July 1996, a transurethral resection of the prostate was performed under spinal anesthetic. At cystoscopy he developed a headache, a rash, and bronchospasm, which settled after treatment. He had a further cystoscopy in February 1998, during which he became flushed, wheezy, and hypotensive, and had a cardiac arrest. He was successfully resuscitated. He had raised serum tryptase activities (60.4 and 26.6 μg/l at 3.5 and 9.5 hours after the event), suggesting a true anaphylactic reaction. Since the only pharmacological agent common to all three procedures was urethral jelly containing lidocaine 2% and chlorhexidine 0.05%, he subsequently had skin prick tests, intradermal tests, and sequential subcutaneous challenges to lidocaine without any positive or adverse effects. Because he had developed profound anaphylaxis with cardiac arrest after the topical administration of chlorhexidine, skin tests were deemed unethical, and an in vitro method for detecting sensitivity to chlorhexidine was pursued. Detailed quantitative hapten inhibition studies were carried out with chlorhexidine-reactive IgE antibodies identified in the serum of the patient.

The authors concluded that unlike most drug allergic determinants the whole chlorhexidine molecule is complementary to the IgE antibody combining sites and that the 4-chlorophenol, biguanide, and hexamethylene structures together comprise the allergenic component.

Frequency and susceptibility factors

In a collaborative Danish study, 2061 patients were patch-tested with chlorhexidine gluconate 1% in water. There was a positive reaction in 2.3% of the patients. This was more common in patients with leg eczema (6.8%) or leg ulcer (10.6%) than in those with eczema of the hands (1.9%) or at other sites (1.6%). Of the 14 patients who were retested with chlorhexidine, only one was positive to the 1% solution and none to a solution of 0.01%. This apparent loss of sensitivity may be due to irritable skin at the initial testing, the so-called excited skin syndrome. This study suggests that the sensitizing potential of chlorhexidine is very low, but that it should be used with caution in dressings for leg ulcers.

In 1063 consecutive eczema patients tested with the ICDRG standard series, supplemented with chlorhexidine gluconate 1% in water and 1% in petrolatum, the frequency of positive reactions was similar to that in the collaborative study (39).

Application to the skin

In a report of generalized urticaria after skin cleansing with and urethral instillation of chlorhexidine-containing products, the authors suggest that there is under-reporting

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of such reactions and that alternative antiseptics should be considered in urological and gynecological procedures (40).

- Life-threatening anaphylactic reactions with generalized urticaria, dyspnea, and shock occurred in six patients after the use of 0.05, 0.5, or 1% chlorhexidine (41), and in one patient after topical use of an alcoholic 0.5% chlorhexidine digluconate solution (42). A severe systemic allergic response was observed in a patient in whom the large donor area of skin graft was dressed with Bactigras, which contains 0.5% chlorhexidine acetate (43).
- An acute anaphylactic reaction occurred in a 19-year-old man after cleaning of burns on the left arm (44). A scratch test with chlorhexidine acetate 0.05% was positive.
- Anaphylaxis occurred in four surgical patients after the use of chlorhexidine as a skin disinfectant. All four had a history of minor symptoms, such as rashes or faints, in connection with previous surgery or invasive procedures (45).
- Following disinfection of a drain insertion site with chlorhexidine digluconate 2% solution, a 43-year-old man had severe anaphylaxis, manifest as dyspnea, shock, and ST segment elevation (46). In the past he had had two episodes of contact dermatitis with chlorhexidine antiseptics.
- A 14-year-old girl had combined delayed and immediate types of allergy, with urticarial rash and syncope, after long-term use of an antiacne formulation containing chlorhexidine in an unknown concentration.
- When chlorhexidine was used as a skin disinfectant in a 53-year-old man undergoing lung resection for adenocarcinoma, anaphylaxis was complicated by coronary artery spasm (47). He had two anaphylactic reactions accompanied by severe myocardial ischemia. Immunological testing indicated chlorhexidine as the causative substance.

In the last two cases, epicutaneous tests with 1% chlorhexidine gluconate and acetate, and prick tests with 0.05 and 0.01% of the acetate solution were positive (48).

Local hypersensitivity reactions to chlorhexidine-impregnated patches occur in neonates (49). In a randomized comparison of povidone-iodine and a chlorhexidine gluconate impregnated dressing for the prevention of central venous catheter infections in neonates, the risk of local contact dermatitis limited the use of the chlorhexidine dressing (50).

Application to mucous membranes

Anaphylaxis has been reported after nasal application of chlorhexidine.

- Anaphylactic circulatory arrest occurred in a 53-year-old man with acromegaly when his nasal mucosa was cleaned with an aqueous solution of chlorhexidine gluconate 0.05% (51).

A report to the Japanese Ministry of Welfare about reactions observed between 1967 and 1984 included 22 cases with a fall in blood pressure, 13 with dyspnea, 9 with anaphylactic shock, 4 with cyanosis, 19 with erythema, 11 with urticaria, 9 with pruritus, and 7 with facial wheals; following this report, in 1984, the Japanese Ministry of Welfare recommended that the use of chlorhexidine on mucous membranes be prohibited because of the evidence of the risk of anaphylactic shock (41).

Application to wounds

Application of chlorhexidine to wounds is generally safe, but it should be used at the lowest bactericidal concentration of 0.05% (41).

Application to the urethra

Anaphylaxis after cystoscopy or urinary catheterization has been reported repeatedly (SEDA-18, 255) (SEDA-19, 235) (SEDA-20, 225) (52).

- A 64-year-old man had severe anaphylaxis induced by intraurethral chlorhexidine gel 0.05% (53). Previous hypersensitivity reactions during urethral dilatation had been thought to be due to lidocaine. Chlorhexidine-specific IgE antibodies were demonstrated, and the chlorhexidine gel had been used in all the preceding urological procedures the patient had undergone.

Severe allergic reactions occurred in five patients after the insertion of an intra-urethral lidocaine jelly containing chlorhexidine gluconate and instrumentation of the urethra (54). All had a positive response to chlorhexidine gluconate (0.0005%) and a negative response to lidocaine (0.2%).

Impregnated intravenous catheters

Chlorhexidine-coated catheters have been developed in the hope of reducing the incidence of central venous line sepsis. Package inserts warn that these should not be used in individuals who are thought to be sensitive to chlorhexidine.

It is possible that the potential benefit of reducing the incidence of central venous sepsis by using chlorhexidine-coated catheters is outweighed by the risk of sudden and profound anaphylaxis. Certainly a high degree of suspicion of chlorhexidine allergy should be exercised and skin tests performed.

In a randomized clinical study of the efficacy of catheters impregnated with antiseptics for the prevention of central venous catheter-related infections in intensive care units in 204 patients with 235 central venous catheters between November 1998 and June 1999, a standard triple-lumen polyurethane catheter and a catheter impregnated with chlorhexidine and silver sulfadiazine were indistinguishable from each other (55). Compared with standard polyurethane catheters, antiseptic catheters were less likely to be colonized by micro-organisms when they were cultured at removal (8 versus 20 colonized catheters per 100 catheters; relative risk 0.34 (95% CI = 0.15, 0.74). There were no significant differences between the groups in catheter-related infections (0.9 versus 4.9 infections per 100 catheters; relative risk 0.17 (95% CI = 0.03, 1.15)). Gram-positive cocci and fungi were more likely to colonize the standard polyurethane catheters than antiseptic catheters. Two of the cases in the control group died because of catheter-related candidemia. There were no adverse reactions such as hypersensitivity or leukopenia with the antiseptic catheters. The authors concluded that central venous catheters with antiseptic coating are safe and carry less risk of

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colonization of bacteria and fungi than standard catheters in critically ill patients.

However, although randomized studies have failed to show an association between hypersensitivity reactions and chlorhexidine-impregnated central venous catheters, there have been reports of anaphylaxis after insertion of these catheters (SEDA-22, 262) (56,57), and two life-threatening episodes of anaphylaxis in the same patient were attributed to a central venous catheter that had been impregnated with chlorhexidine and sulfadiazine (58).

- In a 51-year-old man, two episodes of pronounced, refractory cardiovascular collapse accompanied the insertion of a chlorhexidine-coated central venous catheter (59). Sensitivity to chlorhexidine was not at first suspected, but 5 months later, a skin prick test with chlorhexidine resulted in a characteristic sustained wheal and flare response, strongly suggesting IgE-mediated sensitivity. The patient subsequently underwent uneventful surgery following strict avoidance of chlorhexidine exposure.

Bronchospasm was not a feature in any of these cases.

The FDA has issued a public health notice to inform health-care professionals about the potential for serious hypersensitivity reactions to medical devices impregnated with chlorhexidine. The Agency is also seeking information and reports to better evaluate the potential health hazard these products might pose, and to decide on what action, if any, should be taken. Devices that incorporate chlorhexidine that the FDA has cleared for marketing include intravenous catheters, topical antimicrobial skin dressings, and implanted antimicrobial surgical mesh. The notice describes non-US reports of systemic reactions to chlorhexidine-impregnated gels or lubricants used during urological procedures and similarly impregnated central venous catheters. It also describes other types of reactions that have been reported in the USA, including localized reactions to impregnated patches in neonates and occupational asthma in nurses exposed to chlorhexidine and alcohol aerosols (49).

A meta-analysis of the clinical and economic effects of chlorhexidine and silver sulfadiazine antiseptic-impregnated catheters has been undertaken (60). The costs of hypersensitivity reactions were considered as part of the analysis, and the use of catheters impregnated with antiseptics resulted in reduced costs. The analysis used the higher estimated incidence of hypersensitivity reactions occurring in Japan, where the use of chlorhexidine-impregnated catheters is still banned (61).

Polyhexanide

Caution also seems to be warranted concerning polyhexanide, a chlorhexidine polymer, used in disinfectants for a relatively short time.

- Polyhexanide caused severe anaphylaxis in two young patients (62). Both were exposed to the disinfectant Lavasept®, containing polyhexanide, on surgical wounds during orthopedic interventions. They had never been exposed to polyhexanide before, but had been exposed to chlorhexidine. However, skin prick tests were positive for polyhexanide in both cases, while chlorhexidine was negative. Negative skin prick tests to polyhexanide were obtained from controls.

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Chlormezanone

General Information

Chlormezanone is a tranquillizer with central muscle relaxant effects. In reaction to some case reports of serious, sometimes fatal, cutaneous toxicity and after intervention by drug regulatory authorities in some European countries, all major manufacturers have stopped production of chlormezanone. It may still be available in combination products in some Asian countries.

For the most part chlormezanone causes only minor adverse effects, such as sedation, dizziness, nausea, and headache, which clear on stopping the drug.

Organs and Systems

Hematologic

Rarely, thombocytopenia can occur in a patient taking chlormezanone (1).

Liver

Rarely, cholestatic hepatitis can occur with chlormezanone.

- A 46-year-old woman with rheumatoid arthritis developed cholestatic liver disease while taking chlormezanone and paracetamol (2).
- Fulminant liver necrosis requiring liver transplantation occurred in a young pregnant woman who had taken chlormezanone 600 mg/day for 3 weeks (SEDA-17, 157).

Skin

Toxic epidermal necrolysis and Stevens–Johnson syndrome have been attributed to chlormezanone (3).

Drug–Drug Interactions

Paracetamol

The concomitant use of paracetamol may increase the chance of adverse effects, especially erythema and urticaria (4).

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Chloroform

See also General anesthetics

General Information

Chloroform (SED-8, 250) should no longer be used, because of its toxic effects on the heart, liver, and kidneys, although the exact nature and extent of these complications has been debated (1). The very serious adverse effects of chloroform anesthesia when poorly administered have been briefly reviewed (2).

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Chloroprocaine

See also Local anesthetics

General Information

Chloroprocaine is a local anesthetic, an aminoester of para-aminobenzoic acid. Its systemic toxicity is low, owing to rapid hydrolysis by plasma pseudocholinesterases (1).

Organs and Systems

Cardiovascular

Of 25 patients who received epidural chloroprocaine for various day procedures, 23 had a fall in arterial blood pressure of 15%, and in two it fell by 25% (2).

Neuromuscular function

Prolonged neuromuscular blockade has been reported after epidural chloroprocaine (3).

- A 29-year-old woman in labor was given an epidural infusion of bupivacaine 0.04% plus fentanyl 1.66 micrograms/ml, running at 15 ml/hour for 7 hours. She then required an urgent cesarean section and 15 ml of chloroprocaine 3% was given, followed 20 minutes later by 12 ml of 2% lidocaine. Half an hour later she showed signs of high epidural blockade with dyspnea followed by unresponsiveness, and required immediate intubation with suxamethonium. She then developed prolonged neuromuscular blockade with a first-twitch response occurring after 1.75 hours. It took 3.75 hours before she could be extubated. Her plasma cholinesterase activity was low immediately postpartum, with a concentration of 1.3 U/ml (reference range 2.8–11), returning to normal within 7 weeks.

The authors believed that the high epidural blockade and the prolonged neuromuscular block had resulted from reduced pseudocholinesterase activity.

Second-Generation Effects

Pregnancy

Reduced pseudocholinesterase activity has been described both in pregnancy and with magnesium therapy. As most ester local anesthetics (with the exception of cocaine) are metabolized by this enzyme, caution should be exercised when using ester local anesthetics in pregnancy, especially with the increasing use of magnesium sulfate in this field.

Susceptibility Factors

Genetic factors

When there is an atypical pseudocholinesterase, complications can occur, notably convulsions (1).

Drug Administration

Drug formulations

Chloroprocaine does not itself appear to be neurotoxic at clinical concentrations. However, formulations that contain EDTA can cause burning back pain when used in epidurals (SEDA-22, 142).

Local neural irritation can occur when large doses of formulations containing sodium bisulfate as a preservative are used epidurally or intrathecally, probably because of the low pH and the sodium bisulfate content rather than the local anesthetic (SEDA-14, 111). Prolonged neural deficits have been described, the pathophysiology of which is controversial (SEDA-10, 105).

Drug–Drug Interactions

Suxamethonium

Because it is hydrolysed by plasma cholinesterase, chloroprocaine may competitively enhance the action of suxamethonium (4).

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Chloroquine and hydroxychloroquine

General Information

Chloroquine is rapidly and almost completely absorbed from the intestinal tract, peak serum concentrations being reached in 1–6 hours (average 3 hours). It is extensively distributed and redistribution follows. It is slowly metabolized by side-chain de-ethylation. The half-life is 30–60 days. Elimination is mainly via the kidney. Malnutrition can slow down the rate of metabolism.

Comparative studies

Amodiaquine and chloroquine have been compared in an open, randomized trial in uncomplicated falciparum malaria in Nigerian children (1). The doses were amodiaquine ($n = 104$) 10 mg/kg/day for 3 days and chloroquine ($n = 106$) 10 mg/kg/day for 3 days. After 28 days, the cure rate was significantly higher with amodiaquine than chloroquine (95% versus 58%). The rates of adverse events, most commonly pruritus (10%) and gastrointestinal disturbances (3%), were similar in the two groups. Cross-resistance between the two aminoquinolines is common, and there are concerns regarding toxicity of amodiaquine with repeated use.

General adverse effects

There are relatively few adverse effects at the doses of chloroquine that are used for malaria prophylaxis and standard treatment doses. However, the use of higher doses than those recommended, for example because of problems with resistance, can cause problems. Infants are very easily overdosed (SEDA-16, 302). In the treatment of rheumatoid arthritis and lupus erythematosus, larger doses are used, often for long periods of time, and with this use the incidence of adverse effects is high. Neuromyopathy, neuritis, myopathy, and cardiac myopathy can cause serious problems. Retinopathy can lead to blindness. Chloroquine has a long half-life and accumulates in the tissues, including the brain. Concentrations in the brain can have a bearing on mental status and psychotic syndromes. Chloroquine interferes with the action of several enzymes, including alcohol dehydrogenase, and blocks the sulfhydryl–disulfide interchange reaction. Allergic reactions are generally limited to rashes and pruritus.

Organs and Systems

Cardiovascular

Electrocardiographic changes, comprising altered T waves and prolongation of the QT interval, are not uncommon during high-dose treatment with chloroquine. The clinical significance of this is uncertain. With chronic intoxication, a varying degree of atrioventricular block can be seen; first-degree right bundle branch block and total atrioventricular block have been described. Symptoms depend on the severity of the effects: syncope, Stokes–Adams attacks,

and signs of cardiac failure can occur. Acute intoxication can cause cardiovascular collapse and/or respiratory failure. Cardiac complications can prove fatal in both chronic and acute intoxication.

Third-degree atrioventricular conduction defects have been reported in two patients with rheumatoid arthritis after prolonged administration of chloroquine (2,3).

Intravenous administration can result in dysrhythmias and cardiac arrest; the speed of administration is relevant, but also the concentration reached: deaths have been recorded with blood concentrations of 1 μg/ml; concentrations after a 300 mg dose are usually 50–100 μg/ml (SEDA-13, 803).

Long-term chloroquine can cause cardiac complications, such as conduction disorders and cardiomyopathy (restrictive or hypertrophic), by structural alteration of the interventricular septum (4). Thirteen cases of cardiac toxicity associated with long-term chloroquine and hydroxychloroquine have been reported in patients with systemic autoimmune diseases. The cumulative doses were 600–2281 g for chloroquine and 292–4380 g for hydroxychloroquine.

- A 64-year-old woman with systemic lupus erythematosus took chloroquine for 7 years (cumulative dose 1000 g). She developed syncope, and the electrocardiogram showed complete heart block; a permanent pacemaker was inserted. The next year she presented with biventricular cardiac failure, skin hyperpigmentation, proximal muscle weakness, and chloroquine retinopathy. Coronary angiography was normal. An echocardiogram showed a restrictive cardiomyopathy. A skeletal muscle biopsy was characteristic of chloroquine myopathy. Chloroquine was withdrawn and she improved rapidly with diuretic therapy.
- Chloroquine cardiomyopathy occurred during long-term (7 years) treatment for rheumatoid polyarthritis in a 42-year-old woman, who had an isolated acute severe conduction defect, confirmed by histological study with electron microscopy (5).

Regular cardiac evaluation should be considered for those who have taken a cumulative chloroquine dose of 1000 g, particularly elderly patients.

More than one mechanism may underlie the cardiac adverse effects of chloroquine. Severe hypokalemia after a single large dose of chloroquine has been documented, and some studies show a correlation between plasma potassium concentrations and the severity of the cardiac effects (6).

Light and electron microscopic abnormalities were found on endomyocardial biopsy in two patients with cardiac failure. The first had taken hydroxychloroquine 200 mg/day for 10 years, then 400 mg/day for a further 6 years; the second had taken hydroxychloroquine 400 mg/day for 2 years (SEDA-13, 239). A similar case was reported after the use of 250 mg/day for 25 years (SEDA-18, 286).

Respiratory

Respiratory collapse can occur with acute overdosage.

Acute pneumonitis probably due to chloroquine has been described (7).

- A 41-year-old man with chronic discoid lupus erythematosus was given chloroquine 150 mg bd for 10 days followed by 150 mg/day. After 2 weeks he developed fever, a diffuse papular rash, dyspnea, and sputum. A chest X-ray showed peripheral pulmonary infiltrates. He improved on withdrawal of chloroquine and treatment with cefpiramide and roxithromycin. No organism was isolated. A subsequent oral challenge with chloroquine provoked a similar reaction.

Nervous system

The incidence of serious nervous system events among patients taking chloroquine for less than a year has been estimated as one in 13 600.

Chloroquine, especially in higher doses, can cause a marked neuromyopathy, characterized by slowly progressive weakness of insidious onset. In many cases this weakness first affects the proximal muscles of the legs. Reduction in nerve conduction time and electromyographic abnormalities typical of both neuropathic and myopathic changes can be found. Histologically there is a vacuolar myopathy. Neuromyopathy is a rare adverse effect and is usually limited to patients taking 250–750 mg/day for prolonged periods. The symptoms can be accompanied by other manifestations of chloroquine toxicity (SEDA-11, 583). An 80-year-old woman developed symptoms after taking chloroquine 300 mg/day for 6 months (8), once more demonstrating that a standard dosage can be too much for elderly people.

A spastic pyramidal tract syndrome of the legs has been reported. In young children the features of an extrapyramidal syndrome include abnormal eye movements, trismus, torticollis, and torsion dystonia.

Chloroquine can cause seizures in patients with epilepsy. The mechanism is uncertain, but it may include reductions in inhibitory neurotransmitters and pharmacokinetic interactions that alter anticonvulsant concentrations. Tonic–clonic convulsions were reported in four patients in whom chloroquine was part of a prophylactic regimen. Antiepileptic treatment was required to control the seizures. None had further seizures after withdrawal of the antimalarial drugs (9).

Chloroquine and desethylchloroquine concentrations have been studied in 109 Kenyan children during the first 24 hours of admission to hospital with cerebral malaria (10). Of the 109 children 100 had received chloroquine before admission. Blood chloroquine and desethylchloroquine concentrations were no higher in children who had seizures than in those who did not, suggesting that chloroquine does not play an important role in the development of seizures in malaria.

- A 59-year-old woman had a generalized convulsion 24 hours after returning from a trip to Vietnam (11). She had a history of partial complex seizures (controlled with carbamazepine) due to a previous ruptured cerebral aneurysm. For the preceding 3 weeks she had been taking chloroquine 100 mg/day and proguanil 200 mg/day. A blood film was negative for malaria. A CT scan of the brain showed changes compatible with the previous hemorrhage. She was successfully treated

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with clobazam (dose not stated) until withdrawal of chemoprophylaxis.

The interaction between chloroquine and carbamazepine was not examined. Chloroquine should not be given to adults with a history of epilepsy.

Neuromuscular function

Severe neuromyopathy has been reported in patients taking chloroquine (SEDA-21, 295).

Chloroquine-induced neuromyopathy is a complication of chloroquine treatment of autoimmune disorders or long-term use of chloroquine as a prophylactic antimalarial drug (12).

Sensory systems

Eyes

Chloroquine and its congeners can cause two typical effects in the eye, a keratopathy and a specific retinopathy. Both of these effects are associated with the administration of the drug over longer periods of time.

Keratopathy

Chloroquine-induced keratopathy is limited to the corneal epithelium, where high concentrations of the drug are readily demonstrable. Slit lamp examination shows a series of punctate opacities scattered diffusely over the cornea; these are sometimes seen as lines just below the center of the cornea, while thicker yellow lines may be seen in the stroma. The keratopathy is often asymptomatic, fewer than 50% of patients having complaints. The commonest symptoms are the appearance of halos around lights and photophobia. Keratopathy can appear after 1–2 months of treatment, but dosages of under 250 mg/day usually do not cause it. Dust exposure can lead to similar changes. The incidence of keratopathy is high, occurring in 30–70% of patients treated with higher dosages of chloroquine. The condition is usually reversible on withdrawal and does not seem to involve a threat to vision (SEDA-13, 805). There are differences in incidence between chloroquine and hydroxychloroquine. In a survey of 1500 patients, 95% of the patients taking chloroquine had corneal deposition of the drug, while less than 10% of patients taking hydroxychloroquine showed any corneal changes (SEDA-16, 303).

Retinopathy

The retinopathy encountered with the prolonged use of chloroquine or related drugs is a much more serious adverse effect and can lead to irreversible damage to the retina and loss of vision. However, it is not possible to predict in which patients and in what proportion of patients an early retinopathy will progress to blindness. The typical picture is that of the "bull's eye," an intact foveal area surrounded by a depigmented ring, the whole lesion being enclosed in a scattered hyperpigmented area. At this stage the retinal vessels are contracted, there are changes in the peripheral retinal pigment epithelium, and the optic disk is atrophic. In the early stages there are changes in the macular retinal pigment epithelium. However, the picture is not always clear, and peripheral retinal changes may appear as the first sign. Another sign may be unilateral paramacular retinal edema. The macular changes and the "bull's eye" are occasionally seen in patients who have never been treated with chloroquine or related drugs (SED-13, 805). Retinopathy can occur after chloroquine antimalarial chemoprophylaxis for less than 10 years: the lowest reported total dose was 110 g (13). A case of hydroxychloroquine-induced retinopathy in a 45-year-old woman with systemic lupus erythematosus has illustrated that maculopathy can be associated with other 4-aminoquinolines (14).

The resulting functional defects are varied: difficulty in reading, scotomas, defective color vision, photophobia, light flashes, and a reduction in visual acuity. Symptoms do not parallel the retinal changes. By the time that visual acuity has become impaired, irreversible changes will have taken place.

Testing of visual acuity, central fields (with or without the use of red targets), contrast sensitivity, dark adaptation, and color vision provides no early indication of chloroquine retinopathy. Careful ophthalmoscopic examination of the macula can be a sensitive index when visual acuity remains intact. More sophisticated tests, such as the measurement of the critical flicker fusion frequency and the Amsler grid test (detection of small peripheral scotoma), can be useful. It is important to trace, if at all possible, the results of a pretreatment ophthalmological examination after dilatation of the pupils, thus reducing the possibility of confusing senile degenerative changes with chloroquine-induced abnormalities.

Despite the fact that the retinopathy has been known for many years, it is still not clear why certain patients develop these changes while others do not. There is a clear relation to daily dosage: the retinopathy is rarely seen with daily doses below 250 mg of chloroquine or 400 mg of hydroxychloroquine; the daily dose seems to be more important than the total dose. Nevertheless, cases of retinopathy have been described after the use of small doses for relatively short periods of time, while prolonged treatment and total doses of a kilogram or more have been used in many other patients without any evidence of macular changes. In the published cases there is usually no information about other treatments given previously or concomitantly. More cases are seen in older people. Patients with lupus erythematosus are more susceptible than patients with rheumatoid arthritis. The presence of nephropathy increases the likelihood of retinopathy, as does the concomitant use of probenecid. Exposure to sunlight may be of importance, since light amplifies the risk of retinopathy. The retinopathic changes are probably connected with the concentrating capacity of the melanin-containing epithelium. Chloroquine inhibits the incorporation of amino acids into the retinal pigment epithelium.

Little is yet known about the development of the retinopathy after withdrawal of treatment. Retinal changes in the early stages are probably reversible if the drug is withdrawn, and progression of a severe maculopathy to blindness seems to be less frequent than feared. In 1650 patients with 6/6 vision and relative scotomas there was no further decline in visual acuity after drug withdrawal, but 63% of patients who presented with absolute scotomas lost further vision over a median period of 6 years.

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This suggests that withdrawal of chloroquine at an early stage halts progression of the disease (SEDA-17, 327).

Three patients with chloroquine retinopathy have been studied with multifocal electroretinography (15). All three had been taking chloroquine for rheumatological diseases and all had electroretinographic changes that were more sensitive than full field electroretinography. It may be that multifocal electroretinography will be a useful technique in the assessment of suspected cases of subtle chloroquine retinopathy.

The need for routine ophthalmological testing of all patients who take chloroquine is under discussion, an obvious element being the cost/benefit ratio. The best current opinion seems to be that at doses not exceeding 6.5 mg/kg/day of hydroxychloroquine, given for not longer than 10 years and with periodic checking of renal and hepatic function, the likelihood of retinal damage is negligible and ophthalmological follow-up is not required (SEDA-16, 303) (SEDA-17, 327). However, patients taking chloroquine or higher doses of hydroxychloroquine should be checked.

Other adverse effects on the eyes

Rhegmatogenous retinal detachment and bitemporal hemianopsia have both been seen in association with chloroquine retinopathy. Bilateral edema of the optic nerve occurred in a woman who took chloroquine 200 mg/day for 2.5 months. Diplopia and impaired accommodation (characterized by difficulty in changing focus quickly from near to far vision and vice versa) also affect a minority of patients (SEDA-13, 806).

Ears

Ototoxicity has been mentioned occasionally over the years; tinnitus and deafness can occur in relation to high doses; symptoms described after injection of chloroquine phosphate include a case of cochlear vestibular dysfunction in a child (16). However, there is insufficient evidence to attribute ototoxicity to chloroquine in humans, except as a rare individualized phenomenon. In guinea pigs given chloroquine 25 mg/kg/day intraperitoneally, one of the first signs of intoxication was ototoxicity (SEDA-11, 586).

- Unilateral sensorineural hearing loss occurred in a 7-year-old girl with idiopathic pulmonary hemosiderosis after she had taken hydroxychloroquine 100 mg bd for 2 years (17).

Taste

Disturbances of taste and smell have been attributed to chloroquine (18).

Psychological, psychiatric

Many mental changes attributed to chloroquine have been described, notably agitation, aggressiveness, confusion, personality changes, psychotic symptoms, and depression. Acute mania has also been recognized (SEDA-18, 287). The mental changes can develop slowly and insidiously. Subtle symptoms, such as fluctuating impairment of thought, memory, and perception, can be early signs, but may also be the only signs. The symptoms may be connected with the long half-life of chloroquine and its accumulation, leading to high tissue concentrations (SEDA-11, 583). Chloroquine also inhibits glutamate dehydrogenase activity and can reduce concentrations of the inhibitory transmitter GABA.

In some cases with psychosis after the administration of recommended doses, symptoms developed after the patients had taken a total of 1.0–10.5 g of the drug, the time of onset of behavioral changes varying from 2 hours to 40 days. Most cases occurred during the first week and lasted from 2 days to 8 weeks (SEDA-11, 583).

Transient global amnesia occurred in a healthy 62-year-old man, 3 hours after he took 300 mg chloroquine. Recovery was spontaneous after some hours (SEDA-16, 302).

In one center, toxic psychosis was reported in four children over a period of 18 months (SEDA-16, 302). The children presented with acute delirium, marked restlessness, outbursts of increased motor activity, mental inaccessibility, and insomnia. One child seemed to have visual hallucinations. In each case, chloroquine had been administered intramuscularly because of fever. The dosages were not recorded. The children returned to normal within 2 weeks.

Metabolism

Hypoglycemia was reported in a fatal chloroquine intoxication in a 32-year-old black Zambian male (SEDA-13, 240). Hypoglycemia has also been seen in patients, especially children, with cerebral malaria (SEDA-13, 240). Further studies have shown that the hypoglycemia in these African children was usually present before the antimalarial drugs had been started; in a study in Gambia hypoglycemia occurred after treatment with the drug had been started, although it was not necessarily connected with the treatment (SEDA-13, 240). Convulsions were more common in hypoglycemic children. This commonly unrecognized complication contributes to morbidity and mortality in cerebral *Plasmodium falciparum* malaria. Hypoglycemia is amenable to treatment with intravenous dextrose or glucose, which may help to prevent brain damage (SEDA-13, 804).

Although hydroxychloroquine has been used to treat porphyria cutanea tarda (19), there are reports that it can also worsen porphyria (20,21).

Electrolyte balance

Severe hypokalemia after a single large dose of chloroquine has been documented, and some studies show a correlation between plasma potassium concentrations and the severity of the cardiac effects. In a retrospective study of 191 consecutive patients who had taken an overdose of chloroquine (mean blood chloroquine concentration 20 μmol/l; usual target concentration up to 6 μmol/l), the mean plasma potassium concentration was 3.0 mmol/l (0.8) and was significantly lower in those who died than in those who survived (6). Plasma potassium varied directly with the systolic blood pressure and inversely with the QRS and QT intervals. Plasma potassium varied inversely with the blood chloroquine.

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Hematologic

Chloroquine inhibits myelopoiesis in vitro at therapeutic concentrations and higher. In a special test procedure, a short-lasting anti-aggregating effect could be seen with chloroquine concentrations of 3.2–32 μg/ml (SEDA-16, 303). These effects have clinical consequences. Chloroquine and related aminoquinolines have reportedly caused blood dyscrasias at antimalarial doses. Leukopenia, agranulocytosis, and the occasional case of thrombocytopenia have been reported (SEDA-13, 804) (22). There is some evidence that myelosuppression is dose-dependent. This is in line with the hypothesis that 4-aminoquinoline therapy merely accentuates the cytopenia linked to other forms of bone marrow damage (SEDA-11, 584) (SEDA-16, 302).

Some studies have pointed to inhibitory effects of chloroquine on platelet aggregability. In an investigation, this aspect of chloroquine was studied in vitro in a medium containing ADP, collagen, and ristocetin. There was a highly significant effect at chloroquine concentrations of 3.2–32 μg/ml. However, there were no significant differences in platelet responses to ADP or collagen 2 or 6 hours after adding chloroquine, compared with pre-drug values. The investigators believed that these data provided no cause for concern in using chloroquine for malaria prophylaxis in patients with impaired hemostasis (SEDA-16, 303).

Mouth and teeth

Pigmentation of the palate can occur as a part of a more generalized pigmentation in patients taking chloroquine (23).

Several patients seen with chloroquine retinopathy in Accra have been observed to present with depigmented patches in the skin of the face. This may be associated with a greyish pigmentation of the mucosa of the hard palate. Two such cases are reported here to illustrate the condition. Stomatitis with buccal ulceration has occasionally been mentioned (SEDA-11, 584).

Gastrointestinal

Gastrointestinal discomfort is not unusual in patients receiving chloroquine, and diarrhea can occur. Changes in intestinal motility may be to blame; intramuscular injection of chloroquine caused a shortened orofecal time in the five cases in which this was measured. Overdosage can cause vomiting.

Skin

Skin lesions and eruptions of different types have been attributed to chloroquine, including occasional cases of epidermal necrolysis (24).

The most common dermatological adverse event associated with chloroquine is skin discomfort (often called pruritus). It is much more common in people with darker skins and has been ascribed to chloroquine binding to increased melanin concentrations in the skin. In a pharmacokinetic study, the ratio of $AUC_{0–48}$ for chloroquine and its major metabolite desethylchloroquine was significantly higher in the plasma and urine of 18 patients with chloroquine-induced pruritus than in that of 18 patients without (25). These results imply that differences in metabolism and higher chloroquine concentrations may be partly responsible for chloroquine-induced pruritus.

Pruritus begins about 10 hours after the start of treatment, with a maximum intensity at about 24 hours. These times correspond to maximum serum concentrations of chloroquine and its metabolites after oral ingestion. In many cases, the itch is confined to the palms of the hands and the soles of the feet. In a study in Nigeria, the incidence of pruritus was 60–75%; the itch was considered unbearable in 40%, and 30% refused further chloroquine (26). In a second study, there was an even higher incidence. In a study elsewhere, the incidence of pruritus was 27% (SEDA-16, 304). Not surprisingly, pruritus is a major cause of non-adherence to treatment, and it may contribute largely to the emergence and spread of resistant *P. falciparum* (SEDA-16, 304). Pruritus is more often seen in black-skinned than in white-skinned people in Africa, a difference that has been ascribed to the binding of chloroquine to melanin, and hence a racial predisposition. No such reports have come from America (SEDA-11, 584) (SEDA-16, 303) (SEDA-17, 327) (SEDA-18, 288). Antihistamine treatment can have a preventive effect on pruritus. Other treatments that have been mentioned include prednisone and niacin, but the results were not impressive (27).

A few cases of psoriasis, or severe exacerbation of psoriasis shortly after the start of treatment, have been reported (SEDA-13, 804) (SEDA-16, 304) (SEDA-17, 327).

Photosensitivity and photo-allergic dermatitis have been seen, particularly during prolonged therapy with high doses.

Blue–black pigmentation involving the palate and facial, pretibial, and subungual areas occurs rarely, but it has been associated with retinopathy (SEDA-11, 584). The nail bed can turn blue–brown and the nail itself may develop longitudinal stripes and show a blue–grey fluorescence (SEDA-11, 584).

Chloroquine can cause vitiligo (SEDA-17, 327).

Fatal toxic epidermal necrolysis has been associated with hydroxychloroquine (28).

- A 39-year-old woman with rheumatoid arthritis took hydroxychloroquine 200 mg bd for painful synovitis, in addition to meloxicam, co-dydramol, and Gaviscon. She inadvertently took twice the prescribed dose of hydroxychloroquine, but stopped it after 2 weeks because of nausea. The next day she developed a widespread blotchy erythema and 2 weeks later was admitted to hospital with clinical and histological toxic epidermal necrolysis and deteriorated rapidly with multiorgan failure; she died 1 week later.

There have been only a few isolated reports of Stevens–Johnson syndrome associated with hydroxychloroquine. Recently, a clear temporal relation to the start of treatment with hydroxychloroquine has been documented in a patient with rheumatoid arthritis (29).

An increased frequency of skin reactions to hydroxychloroquine was noted in 11 patients (seven of whom had systemic lupus erythematosus, two discoid lupus, and two a lupus-like syndrome) when a coloring agent (sunshine yellow E110) was removed from the formulation; the authors were unable to explain this unexpected finding (30).

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There have been four case reports of photosensitivity associated with hydroxychloroquine (31) which has an estimated incidence of about 10 per 1000 patient-years (32).

Hydroxychloroquine causes skin reactions such as urticaria. There is some support for the contention that hydroxychloroquine causes skin reactions more often than chloroquine.

Nails

Chloroquine can turn the nail bed blue–brown and the nail itself can develop longitudinal stripes and show a blue–grey fluorescence (SEDA-11, 584).

Immunologic

- Allergic contact dermatitis, which progressed to generalized dermatitis and conjunctivitis, followed later by severe asthma, occurred in a 60-year-old worker in the pharmaceutical industry after exposure to hydroxychloroquine (33). Patch-testing showed delayed sensitivity to hydroxychloroquine. Equivalent tests in five healthy volunteers were negative. The patch test reactions were pustular, and a biopsy was interpreted as multiform contact dermatitis. Bronchial exposure to hydroxychloroquine dust produced delayed bronchial obstruction over the next 20 hours, progressing to fever and generalized erythema (hematogenous contact dermatitis).

Long-Term Effects

Drug tolerance

Chloroquine-resistant falciparum malaria was first reported in 1960. As of 1996, chloroquine resistance became widespread throughout the world and in many areas there is multidrug resistance. Preventive administration of drugs such as chloroquine, primaquine, and pyrimethamine, as well as the use of various sulfonamide mixtures and combinations of sulfonamides with trimethoprim, has progressively lost its usefulness. Currently, hardly half a century after the therapeutic breakthroughs occurred, quinine is once more one of the most valuable drugs in the treatment of malaria and there is a desperate need for other effective drugs.

Alongside the well-known development of resistance by *P. falciparum* to chloroquine, the emergence of chloroquine-resistant *Plasmodium vivax* is now clear (SEDA-13, 801). An increased frequency of cerebral malaria appears to coincide with the growing emergence of the chloroquine-resistant strains in Francophone Africa.

Second-Generation Effects

Pregnancy

Chloroquine inactivates DNA, and crosses the placenta in animals. Caution has generally been advised with respect to the use of chloroquine and related compounds during pregnancy, but except for one (perhaps coincidental) case, there have been no reports of complications to mother or child from treatment with chloroquine during pregnancy (SEDA-14, 239) (SEDA-17, 326).

An observational comparison in a rural Ghanaian hospital of 2083 pregnant women and 3084 historical controls showed no serious adverse events with chloroquine chemoprophylaxis (300 mg/week), but a high rate of pruritus (34). There was a decrease in anemia in pregnancy but no increase in perinatal mortality or birth weight in the chloroquine-treated mothers, although this was only in comparison with historical controls.

Susceptibility Factors

Genetic factors

Mutations in the ABCR gene (a photoreceptor-specific ATP-binding cassette transporter gene) have been associated with Stargardt disease, which has some features similar to chloroquine-induced retinopathy. In a case-control study of eight cases of chloroquine-induced retinopathy, five of the eight cases had mis-sense mutations in the ABCR gene, two of which have been associated with Stargardt disease (35). It may be that polymorphisms in the ABCR gene predispose to chloroquine-induced retinopathy.

Age

Small children have usually been considered as being relatively more sensitive to the effects of overdosage, but it has been calculated that on a mg/kg body weight basis, adults are in fact equally sensitive. Young children seem to be truly more susceptible to gastric irritation. Patients with a history of mania or epilepsy should be careful in taking chloroquine (9). The hypoxemic effects of chloroquine, reflecting cardiac and respiratory toxicity, pose a particular problem in the newborn, in whom existing malarial infection may not become clinically manifest until some months after birth (SEDA-16, 302).

Compared with adults, mortality in children after acute chloroquine poisoning is extremely high. Although the clinical presentation is mostly similar to that in adults (apnea, seizures, cardiac dysrhythmias), a single 300 mg chloroquine tablet was enough to kill a 12-month-old female infant (SEDA-16, 302).

Other features of the patient

Skin reactions to hydroxychloroquine occur more often in patients with dermatomyositis than in patients with systemic lupus erythematosus, as has been shown in a retrospective, age-, sex-, and race-matched case-control study in 78 patients (36). Twelve of 39 patients with dermatomyositis developed a skin reaction to hydroxychloroquine, compared with only one of 39 patients with lupus erythematosus.

Drug Administration

Drug formulations

Chloroquine has a bitter taste, which can deter children from taking it, so a sweet effervescent formulation of chloroquine phosphate has been compared with chloroquine tablets in a pharmacodynamic study (37). However,

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sweet-tasting medications carry a risk of accidental overdose in children.

Drug administration route

If given intravenously, chloroquine should be diluted and infused slowly, since rapid injection causes toxic concentrations. Toxicity and even death have been reported after intramuscular administration of larger doses; this is probably connected with rapid absorption in such cases (SEDA-17, 327).

Drug overdose

Acute intoxication, either accidental or in attempted suicide, can cause headache, drowsiness, vision disturbance, vomiting and diarrhea, cardiovascular collapse, and respiratory failure. Deaths have been recorded at blood concentrations of 1 μg/ml (SEDA-11, 586) (38,39). Compared with adults, mortality in children after acute chloroquine poisoning is extremely high. Although the clinical presentation is mostly similar to that in adults (apnea, seizures, cardiac dysrhythmias), a single 300 mg chloroquine tablet was enough to kill a 12-month-old female infant (SEDA-16, 302).

Deaths from chloroquine overdose have been reported with doses as low as 2–3 g in adults, and the death rate is as high as 25%. The effects of chloroquine overdose include cardiac effects (such as dysrhythmias, reduced myocardial contractility, and hypotension) and central nervous system complications (such as confusion, coma, and seizures).

There have been three reports of chloroquine overdose, two from Oman (40) and one from the Netherlands (41). The two reports from Oman were similar to previously published reports of chloroquine overdose associated with cardiac dysfunction, confusion, and coma; both patients had standard treatment with activated charcoal, diazepam infusions, and positive inotropic drugs, and both survived. The single case report from the Netherlands gave pharmacokinetic measurements performed before, during, and after hemoperfusion. This showed that hemoperfusion extracted very little chloroquine and was unlikely to be of any use in chloroquine overdose, as would be expected from the high protein binding and large volume of distribution of chloroquine.

In Zimbabwe, 544 cases of poisoning by a single agent were identified in a retrospective hospital record review (42). Antimalarial drugs accounted for the largest proportion of admissions (53%), and chloroquine accounted for 96% of these (279 cases). The median length of hospital stay in those who took chloroquine was significantly shorter (1 versus 2 days) and more patients took chloroquine deliberately (80% versus 69%). The mortality rate from chloroquine poisoning was significantly higher than from poisoning with other drugs (5.7% versus 0.7%).

Overdose with hydroxychloroquine is far less common than with chloroquine. Three of eight patients died (43). Life-threatening symptoms, such as hypotension, conduction disturbances, and hypokalemia can occur within 30 minutes of ingestion and are similar to those seen in chloroquine overdose. The lethal plasma concentration of hydroxychloroquine is not well established. Therapeutic drug concentrations are usually less than 1 μmol/l. Serious toxicity has been reported at plasma concentrations of 2.1–29 μmol/l.

Management of hydroxychloroquine overdose is similar to that of chloroquine overdose, including the use of charcoal for drug adsorption, diazepam for seizures and sedation, early intubation and mechanical ventilation, and potassium replacement for severe hypokalemia.

Drug–Drug Interactions

Amlodipine

Syncope occurred in a hypertensive 48-year-old man who took oral chloroquine sulfate (total 600 mg base) while also taking amlodipine 5 mg/day (44). Chloroquine and amlodipine both cause vasodilatation, perhaps by release of nitric oxide, and the syncope in this case was probably due to a synergistic mechanism. Malaria itself can also provoke orthostatic reactions, which may be why syncope is not a reported adverse effect of chloroquine. However, in this patient malaria had been excluded.

Antibiotics

Studies of chloroquine used in combination with antibiotics showed an antagonistic effect with penicillin but a synergistic effect with chlortetracycline. Urinary tests after single doses of ampicillin 1 g and chloroquine 1 g showed a significant reduction in the systemic availability of the ampicillin.

Chlorphenamine

Chlorphenamine enhances the efficacy of chloroquine in acute uncomplicated falciparum malaria, but the disposition of chloroquine in these circumstances is unpredictable. Chloroquine (25 mg/kg) was given orally over 3 days in combination with chlorphenamine to Nigerian children with parasitemia (45). The peak whole blood chloroquine concentration was increased and the time to peak concentration shortened. In small trials there seemed to be an increase in QT interval with this combination, but less than with halofantrine (46). However, in other studies, the addition of chlorphenamine to chloroquine did not amplify the cardiac effects of chloroquine (46).

Ciclosporin

Chloroquine can increase ciclosporin blood concentrations (47).

Cimetidine

Cimetidine enhanced the susceptibility of *P. falciparum* to chloroquine in vitro in 60% of isolates (48).

Digoxin

The pharmacokinetic interaction of quinidine with digoxin also occurs with quinine and hydroxychloroquine (49).

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Fansidar (sulfadoxine + pyrimethamine)

The combined use of Fansidar (sulfadoxine + pyrimethamine) with chloroquine has been reported to result in more severe adverse reactions (50). However, an increased risk has not been reported in recent studies (51).

Halofantrine

There is an increased risk of dysrhythmias, including torsade de pointes, when halofantrine is combined with quinine/quinidine or chloroquine and any other drug that prolongs the QT interval (52).

Insulin

There may be an interaction of chloroquine with insulin. An oral glucose load given to healthy subjects and to patients with non-insulin-dependent diabetes mellitus, before and during a short course of chloroquine, showed a small but significant reduction in fasting blood glucose concentration in the control group and improvement in glucose tolerance in the patients (SEDA-12, 240). The response seems to reflect reduced degradation of insulin rather than increased pancreatic output.

Quinine

Chloroquine antagonizes the action of quinine against *P. falciparum* in vivo. However, no such evidence of antagonism was found in a study in which Malawian children with cerebral malaria were treated with quinine. There was no difference in survival and rate of recovery in patients who had also been given chloroquine compared with those who had not (SEDA-13, 816).

Thyroxine

A marked increase in serum TSH occurred in the same patient on two occasions after several weeks of antimalarial prophylaxis with chloroquine and proguanil, the likely mechanism being enzyme induction and increased thyroxine catabolism (SEDA-22, 469).

Vaccines

Chloroquine 300 mg/week adversely affected the antibody response to human diploid-cell rabies vaccine administered concurrently. The mean rabies-neutralizing antibody titer was significantly reduced on each day of testing (SEDA-13, 806) (8). In contrast, retrospective studies of the response to pneumococcal polysaccharide in patients with systemic lupus erythematosus taking chloroquine or hydroxychloroquine, and of the response to tetanus–measles–meningococcal vaccine in a region of Nigeria where malaria is endemic, did not show an effect on antibody production. However, it was pointed out that the altered immune status of patients with systemic lupus erythematosus makes it difficult to compare their response to that of young healthy adults receiving rabies vaccine. Illness and nutritional state could have influenced the findings in the Nigerian study (SEDA-13, 807) (53).

Verapamil

Verapamil completely reversed pre-existing in vitro resistance to chloroquine to below the cut-off point of 70 nmol/l (48).

Smoking

Antimalarial drugs (chloroquine, hydroxychloroquine, or quinacrine) were given to 36 patients with cutaneous lupus, of whom 17 were smokers and 19 non-smokers (8). The median number of cigarettes smoked was one pack/day, with a median duration of 12.5 years. There was a reduction in the efficacy of antimalarial therapy in the smokers. Patients with cutaneous lupus should therefore be encouraged to stop smoking and consideration may be given to increasing the doses of antimalarial drugs in smokers with refractory cutaneous lupus before starting a cytotoxic agent.

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Chlorotrianisene

General Information

Chlorotrianisene is a non-steroidal triphenylethylene with estrogen and antiestrogen activity. Diethylstilbestrol and other non-steroidal estrogens came into vogue at a time when the cost of producing steroidal estrogens, whether synthetic or of natural origin, was still prohibitive. They have fallen out of favor, in view of the association between diethylstilbestrol in pregnancy and second-generation injury. There is no reason for believing that the short-term acute adverse reactions to these non-steroidal compounds differ from those of estrogenic steroids.

Chlorotrianisene does not bind in vitro to the uterine estrogen receptor but has potent estrogenic and antiestrogenic actions in vivo, suggesting that it is a prodrug. Its antiestrogenic activity has been proposed to be due to a reactive intermediate (1).

Organs and Systems

Hematologic

In 50 postpartum women who took chlorotrianisene for lactation suppression in a double-blind, randomized, placebo-controlled study, antithrombin III concentrations were significantly lower on the third day postpartum compared with placebo (2).

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Chloroxylenol

See also Disinfectants and antiseptics

General Information

Since the withdrawal of hexachlorophene from the nonprescription drug market in the USA, the antiseptic chloroxylenol, which is less antigenic, has been a substitute in a large number of products.

Organs and Systems

Skin

Topical exposure can cause rashes.

- A 10-day-old baby who was given a bath in a 25% solution of Dettol containing 1.2% chloroxylenol became dehydrated and developed diffuse erythema and vesicles, and afterwards exfoliative dermatitis (1). There was a good response to therapy with systemic glucocorticoids and supportive measures.

Immunologic

Allergic contact dermatitis can occur after sensitization to chloroxylenol, for example in medicated Vaseline or in electrocardiographic paste (2).

In a retrospective analysis of patch tests in 951 patients 1.8% had positive reactions to chloroxylenol (3). Most of the patients had been sensitized by popular proprietary formulations containing chloroxylenol (SEDA-11, 221).

Drug Administration

Drug overdose

There have been many cases of intoxication with oral Dettol liquid, a widespread household disinfectant that contains chloroxylenol 4.8%, pine oil, and isopropyl alcohol (4–8). Dettol was involved in 10% of hospital admissions related to self-poisoning in Hong Kong. In a retrospective study of 67 cases, serious complications were relatively common (8%) and these included aspiration of Dettol with gastric contents, resulting in pneumonia, cardiopulmonary arrest, bronchospasm, adult respiratory distress syndrome, and severe laryngeal edema with upper airway obstruction. Of 89 patients, five developed minor hematemesis, in the form of coffee-colored or blood-stained vomitus (6). One patient had a gastroscopy performed on the day after admission, which showed signs of chemical burns in the esophagus and stomach. Gastroscopy in another patient on day 11, done to rule out an esophageal stricture, showed no abnormality. All patients with hematemesis recovered completely. The authors suggest that upper gastrointestinal hemorrhage after Dettol ingestion tends to be mild and self-limiting. Gastroscopy, which may increase the risk of aspiration in patients with impaired consciousness, is not required unless other causes of gastrointestinal bleeding are suspected. Furthermore, Dettol poisoning can be associated with an increased risk of aspiration, possibly caused by the use of gastrointestinal lavage in 88% of the patients and vomiting in 62% (6,7).

Of 121 patients who ingested Dettol 200–500 ml, three developed renal impairment, as evidenced by raised plasma urea and creatinine (7). Two of these patients also had serious complications, including aspiration leading to pneumonia and adult respiratory distress syndrome; one died. Renal impairment only appears to be observed when relatively large amounts of Dettol are ingested (7).

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Chlorphenamine maleate

See also Antihistamines

General Information

Chlorphenamine (chlorpheniramine) is a first-generation antihistamine, an alkylamine derivative, with sedative and antimuscarinic activity.

Organs and Systems

Psychological, psychiatric

Functional neuroimaging of cognition was impaired by chlorphenamine (1).

Skin

Lichen-planus-like contact dermatitis after topical use of chlorphenamine has been described in one case report, with positive patch-testing (2).

Drug–Drug Interactions

Chloroquine

Chlorphenamine enhances the efficacy of chloroquine in acute uncomplicated falciparum malaria, but the disposition of chloroquine in these circumstances is unpredictable. Chloroquine (25 mg/kg) was given orally over 3 days in combination with chlorphenamine to Nigerian children with parasitemia (3). The peak whole blood chloroquine concentration was increased and the time to peak concentration shortened. However, in further studies the addition of chlorphenamine to chloroquine did not amplify the cardiac effects of chloroquine (4).

Ranitidine

In the same way that pharmacokinetic studies have been used to ascertain whether co-administration of an inhibitor of CYP3A4 can lead to cardiotoxicity, similar studies have been carried out to indicate whether the co-administration of an inhibitor can enhance a limited sedative effect. Healthy subjects took a single dose of racemic chlorphenamine 4 mg on two separate occasions; the second occasion coincided with the sixth day of dosing with ranitidine 75 mg bd for 8 days. Serum concentrations and urinary excretion of chlorphenamine were not altered, and so it was considered unlikely that co-administration with ranitidine would enhance the potential of chlorphenamine to cause drowsiness (5).

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Chlorphenoxamine

General Information

Chlorphenoxamine is an antihistamine closely related to diphenhydramine with a similar metabolic pathway (1). It appears to have been developed in the hope of producing a greater effect in Parkinson's disease by combining both anticholinergic and antihistaminic effects in a single molecule (2).

In the doses commonly used well-recognized anticholinergic effects can occur (3). Some patients become drowsy, whilst others are stimulated; with increasing dosages, some patients go into coma; others have agitation, convulsions, and marked euphoria, perhaps with hallucinations and disorientation.

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Chlorphentermine

See also Anorectic drugs

General Information

Chlorphentermine is an anorectic sympathomimetic amine, with actions and adverse effects similar to those of amfepramone (diethylpropion).

Organs and Systems

Respiratory

Pathological changes in the lungs were produced with chlorphentermine in laboratory animals (SED-9, 14). Pulmonary complications might therefore occur in humans, which puts in doubt the wisdom of continuing to recommend chlorphentermine as an anorectic drug until more definitive information is available.

Nervous system

Much less stimulation of the central nervous system has been reported in patients taking chlorphentermine than in those taking dexamphetamine; less frequent too were complaints of light-headedness, tremors, restlessness, nervousness, and insomnia; patients taking chlorphentermine can paradoxically become drowsy (1).

Gastrointestinal

In 25 patients who had taken chlorphentermine, constipation and dryness of the mouth were more frequent than with other appetite depressants. In another comparative study with phenmetrazine in volunteers, constipation and dry mouth were again among the more frequent adverse reactions, along with sleepiness and increases in motor activity and urinary urgency (SED-8, 16).

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Chlorpromazine

See also Neuroleptic drugs

General Information

Chlorpromazine is a phenothiazine with a large range of pharmacological actions; it is a dopamine receptor antagonist, an alpha-adrenoceptor antagonist, a muscarinic antagonist, and an antihistamine.

Organs and Systems

Cardiovascular

The possibility that some of the cardiac effects of chlorpromazine may be related to metabolites as well as the parent compound has been explored (1,2).

Some cases of sudden death in apparently young healthy individuals may be directly attributable to cardiac dysrhythmias after treatment with thioridazine or chlorpromazine (3).

Nervous system

In 15 schizophrenic inpatients aged 16–55 years, there was a 50% probability that a patient would have a tremor when the plasma concentration of chlorpromazine was 46 ng/ml or more, corresponding to the minimum plasma concentration that has been associated with a good clinical response (4).

Skin

Chlorpromazine most often causes photosensitivity reactions (incidence around 3%), which may result from formation of a cytotoxic by-product after exposure to ultraviolet light. Patients should be advised to avoid prolonged exposure to strong indoor light, to wear protective clothing, and to use a combined para-aminobenzoic acid plus benzophenone sunscreen when exposure to strong sunlight is unavoidable.

Toxic epidermal necrolysis has been reported in association with chlorpromazine (5).

Chlorpromazine is thought to have caused an immunologically mediated contact urticaria (6–10).

Sexual function

Two cases of priapism have been attributed to chlorpromazine: a 65-year-old man who took a single dose of chlorpromazine 25 mg and a 27-year-old man who took chlorpromazine 200 mg for agitation after a suicide attempt (11).

Drug–Drug Interactions

Amfetamine

Chlorpromazine has sometimes been used to treat amfetamine psychosis, for example due to acute poisoning in children who did not respond to barbiturates (12).

Beta-adrenoceptor antagonists

Lipophilic beta-adrenoceptor antagonists are metabolized to varying degrees by oxidation by liver microsomal cytochrome P450 (for example propranolol by CYP1A2 and CYP2D6 and metoprolol by CYP2D6). They can therefore reduce the clearance and increase the steady-state plasma concentrations of other drugs that undergo similar metabolism, potentiating their effects. Drugs that interact in this way include chlorpromazine (13).

- A schizophrenic patient experienced delirium, tonic-clonic seizures, and photosensitivity after the addition of propranolol to chlorpromazine, suggesting that chlorpromazine concentrations are increased by propranolol (14).

Although high dosages of propranolol (up to 2 g) have been used in combination with chlorpromazine to treat schizophrenia, the combination of propranolol or pindolol with chlorpromazine should be avoided if possible (15).

Haloperidol

- A 40-year-old man with schizophrenia developed a raised plasma concentration of haloperidol in combination with chlorpromazine and during overlap treatment with clozapine (16).

Like haloperidol, chlorpromazine is a competitive inhibitor of CYP2D6; however, clozapine appears to be largely metabolized by CYP1A2.

Monoamine oxidase inhibitors

Hyperthermia and labile blood pressure occurred in a patient taking chlorpromazine, phenelzine, and clomipramine (17).

Smoking

Chlorpromazine concentrations were reduced by 36% in smokers (18). Of factors that can affect chlorpromazine concentrations, smoking may be second in importance only to dosage (19).

Interference with Diagnostic Tests

Cholesterol

Chlorpromazine can cause overestimation of cholesterol (Zlatkis–Zak reaction) (20).

CSF protein

Chlorpromazine can cause falsely increased CSF protein (Folin–Ciocalteau method) (20).

Haptoglobin

Chlorpromazine can cause falsely reduced serum haptoglobin concentrations (20).

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Chlorprothixene

See also Neuroleptic drugs

General Information

Chlorprothixene is a thioxanthene neuroleptic drug.

Organs and Systems

Immunologic

Rare disorders of connective tissue resembling systemic lupus erythematosus have been reported with chlorpromazine, perphenazine, and chlorprothixene (1).

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Chlortalidone

See also Diuretics

General Information

Chlortalidone (chlorthalidone) is chemically unrelated to the thiazide diuretics but shares many of their actions and adverse effects.

It is so closely similar to the thiazide diuretics in most respects that data have generally been regarded as interchangeable.

Comparative studies

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), over 40 000 participants aged 55 years or older with hypertension and at least one other risk factor for coronary heart disease were randomized to chlortalidone, amlodipine, doxazosin, or lisinopril (1,2). Doxazosin was discontinued prematurely because chlortalidone was clearly superior in preventing cardiovascular events, particularly heart failure (2). Otherwise, mean follow-up was 4.9 years. There were no differences between chlortalidone, amlodipine, and lisinopril in the primary combined outcome or all-cause mortality. Compared with chlortalidone, heart failure was more common with amlodipine and lisinopril, and chlortalidone was better than lisinopril at preventing stroke.

Organs and Systems

Electrolyte balance

In the past chlortalidone was thought to carry a greater risk of hypokalemia and hyponatremia (SED-8, 488), but this probably reflected relative overdosage with accumulation, because of its long half-life. With the much lower dosages now in use there appears to be no clear difference from the thiazides.

Skin

Pseudoporphyria has been attributed to chlortalidone (3).

Body temperature

Drug fever has been attributed to chlortalidone (4).

- A 58-year-old woman presented with intermittent nocturnal fever (up to 39.5°C) for 4 weeks beginning 2 weeks after the introduction of chlortalidone for hypertension. Otherwise, physical examination was normal. Investigations showed a normochromic normocytic anemia and a raised erythrocyte sedimentation rate and C-reactive protein. Other biochemical tests, blood cultures, and serological and immunological tests were negative. Chest radiography, lung scintigraphy, and abdominal ultrasound were unremarkable. There was no further fever after chlortalidone was withdrawn, and all biochemical tests became normal. The lymphocyte transformation test showed stimulation by chlortalidone.

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Chlorzoxazone

General Information

Chlorzoxazone is a centrally acting benzoxazole derivative with a weak muscle relaxing effect (1). It is usually used in combination with paracetamol for the treatment of painful muscle spasms. The usual dose is 500 mg tds. Drowsiness, weakness, dizziness, and gastrointestinal complaints are the most frequent unwanted effects.

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Organs and Systems

Nervous system

A spasmodic torticollis-like syndrome, repeatedly evoked after the ingestion of chlorzoxazone, is an unusual adverse effect of the drug. Benzatropine mesilate 1 mg intravenously led to resolution of the symptoms within 10 minutes (2).

Liver

The most serious adverse effect of chlorzoxazone, which fortunately occurs only rarely, is hepatotoxicity.

In one case jaundice occurred and rechallenge with a single tablet of Parafon Forte (chlorzoxazone plus paracetamol) resulted in a dramatic reaction after 5 hours, with fever, chills, nausea, vomiting, and recurrence of icterus. Paracetamol on its own had no adverse effect in this case.

The authors reviewed some 23 other cases (SEDA-12, 119) (3).

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Cholera vaccine

See also Vaccines

General Information

Cholera vaccines consist of live attenuated or heat-killed *Vibrio cholerae* organisms. They can be given orally or parenterally.

Following the administration of live oral cholera vaccine (containing the attenuated strain *V. cholerae* CVD 103-HgR, prepared from *V. cholerae* 01 strain 569B), there were significant rises in serum antitoxin concentrations and only few mild adverse effects (SED-13, 925). There was protective efficacy in 82–100% of healthy adult volunteers and no difference in adverse effects between 25 recipients of the vaccine and 26 controls (1).

A randomized, double-blind, placebo-controlled trial using a live oral cholera vaccine (strain CVD 103, derived from the *V. cholerae* 01 classical Inaba strain 569B by deletion of the genes encoding the A subunit of cholera toxin) was conducted in 50 healthy Swiss adults. There was a significant rise in serum antitoxin titers in 76% of the volunteers. Two vaccinees reported watery stools after immunization (2).

When an oral single-dose cholera vaccine against *V. cholerae* 0139 was given to ten volunteers there was 83% protective efficacy and the only adverse effect, in one volunteer, was mild diarrhea (3).

The results with an oral cholera vaccine consisting of the immunogenic but completely non-toxic B subunit of cholera toxin in combination with heat- and formalin-killed *V. cholerae* represent an improvement compared with previous parenteral vaccines (4). The frequency of adverse effects (pain at the injection site, nausea, diarrhea) was low (5).

Severe complications connected with cholera (or combined) immunization are extremely rare and the causal relation is always doubtful. However, when they do occur they constitute a contraindication to further administration. There are occasional reports of neurological and psychiatric reactions (SED-8, 706) (SEDA-1, 246), Guillain–Barré syndrome (SEDA-1, 246), myocarditis (6,7), myocardial infarction (SEDA-3, 261), a syndrome similar to immune complex disease (8), acute renal insufficiency accompanied by hepatitis (9), and pancreatitis (10).

Drug Administration

Drug formulations

A parenteral cholera vaccine consisting of a heat-killed, phenol-preserved, mixed suspension of the Inaba and Ogawa subtypes of *V. cholerae*, Serovar 01, has been used subcutaneously or intramuscularly, or for booster doses intradermally. About 1% of vaccinees develop mild local skin lesions comprising transitory soreness at the injection site within 5-7 days after injection, characterized by erythema, swelling, pain, and induration, and rarely resulting in ulceration. More general reactions are allergic: as a rule, these amount at most to slight pyrexia, headache, and malaise. However, considering the low protective efficacy and high reactogenicity of this vaccine, the World Health Organization and many national health authorities do not recommend it anymore and most manufacturers have stopped producing it.

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Choline

General Information

Choline has been given in the past as an acetylcholine precursor to raise acetylcholine concentrations in the brain and thus enhance cholinergic neurotransmission. There is evidence that the symptoms of tardive dyskinesia can be reduced by choline or lecithin (1).

Organs and Systems

Psychological, psychiatric

Occasionally, doses of choline up to 9 g/day have been found to produce severe depression, presumably by altering the adrenaline/acetylcholine balance (2).

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Choline alfoscerate

General Information

Choline alfoscerate increases cerebral acetylcholine synthesis and release (1). In the light of animal studies it has been investigated as a possible treatment for vascular dementia (2). Adverse effects have been few, notably headache and flushing.

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Chromium

General Information

Chromium is a metallic element (symbol Cr; atomic no. 24) that occurs naturally in minerals such as fuchsite and picotite.

Certain salts of radioactive chromium (1) are used as radiopharmaceutical tracers in various hematological procedures. Chromium compounds are also used in oral and parenteral nutrition and in artificial hip and knee joints. Chromium picolinate has been promoted as a nutritional supplement and has received a great deal of interest because of its possible beneficial effects on muscle strength and body composition.

Trivalent chromium is supposedly an essential trace element, but its essentiality continues to be discussed (2). The biochemistry of chromium has been reviewed (3), as have the mechanisms of its toxicity, carcinogenicity, and allergenicity (4) and its general toxicology (5).

Trivalent chromium compounds (chromium chloride, chromium nicotinate, and chromium picolinate) are used by patients to enhance weight loss, to increase lean body mass, or to improve glycemic control. Drug histories should include attention to the use of over-the-counter nutritional supplements often regarded as harmless by the public and lay media. The recommended daily allowance of chromium picolinate is 50–200 micrograms, but information about its toxicity is limited.

The quest for the molecular mechanisms of chromium in relation to diabetes continues (6,7). Chromium picolinate may aid muscle insulin sensitivity, and initial reports suggest that it is an effective therapy for type 2 diabetes (8). Chromium picolinate supplementation alone does not improve insulin sensitivity (9).

- In a 28-year-old woman with an 18-year history of type 1 diabetes mellitus the glycosylated hemoglobin fell from 11.3 to 7.9% and her blood glucose concentration was 1.7–3.3 mmol/l lower after she had taken chromium picolinate (200 micrograms tds for 3 months) (10). There were no adverse effects.

Chromium in metal implants and prostheses

Complications from the use of metal implants and prostheses can arise because of biochemical and histological reactions to some of the materials used (SEDA-22, 250). These include titanium, stainless steel (10–14% nickel, 17–20% chromium), and cobalt chrome alloys (27–30% chromium, 57–68% cobalt, and up to 2.5% nickel). All of these metals can produce sensitization or elicit toxic reactions when they are solubilized and come into contact with tissues; it can be difficult or even impossible to differentiate between hypersensitivity and toxic reactions.

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Metals from prostheses can continue to be released into the system for many years. The development of hypersensitivity takes time, and allergic reactions are usually delayed for weeks, months, or 1–2 years. The symptoms can assume a variety of forms. Local reactions can cause loosening of the device or local pain. Dermatological reactions include eczema, bullous pemphigoid, urticaria, and "muscle tumors."

Attempts continue to predict metal sensitivity in the individual patient so that the choice of material can be made accordingly. In vitro tests for metal allergies have been developed on the basis of lymphokine (MIF) release from sensitized T lymphocytes exposed to metal-protein complexes (11). About 6% of patients without a previous metal implant had positive reactions to nickel, chromium, or cobalt. However, it is still not clear whether such a positive reaction is a reliable predictor of clinical problems. In practice few patients have either local or systemic reactions; when symptoms occur and other causes are ruled out, the implant should be removed. Some workers recommend removal of an implant whenever there is both a positive MIF test and a positive skin test, even in the current absence of a serious reaction. Allergic dermatitis will clear up as soon as the metal has begun to be cleared from the tissue. The type of metal and the amount released into the tissue will affect the time taken for the disappearance of toxic dermatological phenomena.

Organs and Systems

Psychological, psychiatric

There have been three reports of the efficacy of chromium in depression, with adverse effects that included dizzy spells and vivid dreams (12).

- A 50-year-old man developed bipolar II disorder with the onset of a major depressive episode in his late twenties. His mood stabilized with lithium, but he continued to have periods of irritability and breakthrough depression. He started to take chromium picolinate 400 micrograms/day and within 2 days felt more relaxed and stable than he had since the onset of his disorder. He stopped taking lithium. Several months later he forgot to take his chromium, and within a few days his symptoms returned. In order to catch up he took 800 micrograms/day and developed sweating each morning and a mild hand tremor. After reducing the dosage to 600 micrograms/day he again went into complete remission. After more than 1 year of chromium treatment he developed uric acid kidney stones. One year after switching to a different chromium salt (the polynicotinate), there was no recurrence of kidney stones.
- A 38-year-old man with bipolar II disorder took chromium polynicotinate 400 micrograms/day. Shortly after the first dose his mood started to improve, but he had unusually vivid intense dreams. The dose of chromium was increased to 600 micrograms/day. He then developed intermittent brief dizzy spells due to orthostatic hypotension. After switching to chromium picolinate his dizzy spells did not recur.
- A 47-year-old man with a dysthymic disorder and intermittent panic attacks and rage outbursts took chromium 400 micrograms/day, and after 1 day had strikingly vivid dreams. Over the next several days there was a dramatic improvement in his mood and behavior. The efficacy of chromium was later confirmed by a double-blind, placebo-controlled, *n*-of-1 trial.

Liver

Hepatic injury is a risk that is associated primarily with occupational exposure to chromium, in this case among chromium platers (13), an occupation that has an increased incidence of chronic hepatitis or liver cirrhosis. There also appears to be a trend toward a significantly increased risk of lung cancer.

- A 35-year-old woman complained of nausea, fatigue, pruritus, dark urine, pale stools, and jaundice after taking a supplement containing chromium picolinate for weight loss (14). Infectious hepatitis was excluded and a liver biopsy was consistent with toxic liver damage. Hepatic chromium concentrations were more than 10 times normal. The chromium supplement was withdrawn and she received supportive treatment with a suspension containing "natural products," colestyramine 1 g qds, and hydroxyzine 25 mg tds. She fully recovered in 3 months.

Skin

Allergic contact dermatitis has apparently been most commonly due to occupational exposure of building workers to a form of cement containing a water-soluble form of chromium (SEDA-20, 208) (15). Such reactions to medical exposure have not been described but could in principle occur.

Chromium has been reported to cause dermatitis when ingested (16).

- A 35-year-old man developed a subacute dermatitis with scattered patches of erythema and scaling on the lower legs, ankles, hands, and wrists. He had no history of atopy but a prior history of allergy to a leather watchstrap. He had taken various oral vitamin and mineral formulations for several weeks. Patch-testing showed reactions to potassium dichromate at 48 and 96 hours.

Chromium picolinate has caused acute generalized exanthematous pustulosis (17).

- A 32-year-old previously healthy man developed an extensive rash of sudden onset associated with a low-grade fever (37.4°C), a sore throat, and malaise after taking chromium picolinate 1 mg/day for 4 days. He had a confluent symmetrical erythematous eruption with numerous non-follicular 1–2 mm pustules on the trunk and proximal limbs. The eruption was most prominent in the antecubital and popliteal fossae bilaterally. There was mild pharyngeal erythema and bilateral tender cervical adenopathy, but no tonsillar enlargement or exudate. Chromium picolinate was withdrawn and he was treated with oral prednisone 60 mg/day tapered over 15 days. The acute eruption resolved within 1 week, followed by post-inflammatory desquamation. It did not recur during follow-up for 15 months.

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Musculoskeletal

- Rhabdomyolysis has been attributed to chromium picolinate in a 24-year-old body builder who took 1200 micrograms over 48 hours (18).

Long-Term Effects

Tumorigenicity

Hexavalent chromium compounds have no medical uses and are known as mutagens and carcinogens (19). In an in vitro study the coordination of chromium by picolinate ligands made chromium picolinate more toxic to cultured cells, leading to enhanced apoptosis (20). These observations support the hypothesis that chromium picolinate is a human carcinogen.

A mortality study among workers engaged in producing chromium compounds from chromite, performed using retrospective data (21), showed a significantly increased risk of lung cancer, despite cessation of exposure. The risk of nasal cavity/sinus cancer was also significantly increased.

Drug Administration

Drug overdose

Toxicity secondary to chronic ingestion of 6–12 times the recommended daily allowance of over-the-counter chromium picolinate has been reported (22).

- A 33-year-old white woman presented with weight loss, anemia, thrombocytopenia, hemolysis, liver dysfunction (transaminase activities 15–20 times normal, total bilirubin three times normal), and renal insufficiency. She had taken chromium picolinate 1200–2400 micrograms/day for the previous 4–5 months to enhance weight loss. Her plasma chromium concentrations were 2–3 times normal. After withdrawal of chromium picolinate, she was managed with supportive measures, blood transfusions, and hemodialysis. The hemolysis stabilized and her liver and renal function eventually recovered.

Drug–Drug Interactions

Sertraline

Chromium can potentiate antidepressant pharmacotherapy for manic-depressive disorder. In five patients taking sertraline, supplementation with chromium picolinate and chromium polynicotinate led to enhanced remission of dysthymic symptoms (23).

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Chymotrypsin

General Information

The enzyme chymotrypsin has been used for enzymatic zonulolysis during operations for cataract (1). Its possible role in precipitating postoperative intraocular hypertension has been studied, but the use of enzymatic

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zonulolysis does not seem to increase significantly the risk of glaucoma (2).

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Cianidanol

General Information

Cianidanol is an antioxidant flavonoid that occurs especially in woody plants. It is one constituent of green tea. It has immunomodulatory properties, including effects on T lymphocytes and killer cells (1).

Of 40 patients with chronic active hepatitis, 22 took cianidanol 3 g/day and 18 took placebo (2). Adverse effects of cianidanol were fever ($n = 4$), hemolysis ($n = 1$), and urticaria ($n = 1$).

Serious adverse effects were not observed when cianidanol was used to treat HBe-antigen-positive chronic hepatitis in 338 patients (3). The only adverse effect of note that appeared to be drug-related was transient pyrexia in 13, necessitating withdrawal of therapy in eight. Four patients also had a skin eruption.

Organs and Systems

Hematologic

Nine cases of acute intravascular hemolysis, severe enough to cause death in one and to necessitate hemodialysis in two others, were attributed to cianidanol on the basis of a close temporal relation and serological tests (4).

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Cibenzoline

See also Antidysrhythmic drugs

General Information

Cibenzoline is an antidysrhythmic drug of Class Ia, with some additional properties of drugs of Class III and Class IV. Its pharmacology, electrophysiological effects, therapeutic effects and indications, pharmacokinetics, and adverse effects have been reviewed (1,2). Prolongation of the QT interval, leading to cardiac dysrhythmias, is the major adverse effect. Other effects include gastrointestinal disturbances, effects on the central nervous system, and hypoglycemia, perhaps related to inhibition of ATP-dependent potassium channels in the pancreas.

Comparative studies

Cibenzoline and flecainide have been compared in the prevention of recurrence of atrial tachydysrhythmias in 139 patients (3). During the study, 27 patients withdrew, in 13 cases with adverse effects, seven of which were due to cibenzoline. Overall there were 26 adverse effects in 23% of the patients taking cibenzoline; these included one case of ventricular dysrhythmia, four minor cardiac events, four cases of nausea or epigastric pain, eight cases of weakness, four cases of depression or insomnia, one skin rash, and one case of hypoglycemia. The QRS complex was prolonged by more than 13% in 14 patients, but the QT interval was not prolonged. Although this was not a placebo-controlled study, the incidence of adverse effects with cibenzoline was probably as one would expect in such a population.

Organs and Systems

Cardiovascular

Cibenzoline prolongs the PR interval, the QRS interval, and the QT_c interval (4–7). It also prolongs the AH and HV intervals (5,8) and shortens the sinus cycle length (5–8). Because of these effects it can cause dysrhythmias (4,6,7,9).

- Cardiac dysrhythmias have been attributed to cibenzoline in a 60-year-old man with hypertrophic cardiomyopathy (10).
- In a 72-year-old woman cibenzoline was associated with left bundle branch block and heart failure (11). Excess cibenzoline accumulation was suspected, because of reduced renal function, but plasma cibenzoline concentrations were not reported.

Right bundle branch block has also been reported (6).

In three patients in whom cibenzoline had caused sinus node dysfunction, normal sinus node recovery time was restored by cilostazol (12).

Cibenzoline has a negative inotropic effect and can therefore cause hypotension (6,7,13,14) and worsening heart failure (4).

Nervous system

Various nervous system complaints have been reported in occasional patients, including headache (15), disturbances of visual accommodation (15), and tremulousness (16). Dizziness and light-headedness have more commonly been reported, sometimes in association with hypertension (7,17).

There have been frequent reports of anticholinergic adverse effects, including dry mouth (7,9,13), blurred vision (4,9), and difficulty in micturition (18).

- Choreiform movements associated with persistent orofacial dystonia have been attributed to cibenzoline in a 77-year-old woman who took 260 mg/day for 1 week (19). When cibenzoline was eventually withdrawn the effects resolved within 1 month.

The authors proposed that the effect was due to inhibition of potassium channels.

A myasthenia-like syndrome has occasionally been attributed to cibenzoline (SEDA-21, 199) (20).

- A 57-year-old man with chronic renal insufficiency treated by continuous and ambulatory peritoneal dialysis took cibenzoline 150 mg/day for a ventricular dysrhythmia. Four days later he developed proximal muscle weakness, progressing to generalized muscle weakness, with dysphagia and dysarthria. Hemodiafiltration on six occasions caused complete improvement and cibenzoline was withdrawn. There was no further recurrence, even when other drugs that he had been taking were restarted.

The authors suggested that cibenzoline may have inhibited ATP-dependent potassium channels in skeletal muscle. The plasma cibenzoline concentration at the height of this patient's symptoms was very high at 1890 μg/ml (usual target range 300–600) and the authors counselled caution in patients with renal insufficiency (SEDA-15, 174).

Metabolism

Several cases of hypoglycemia have been attributed to cibenzoline (21–23) (SEDA-18, 204). In a case-control study of 14 156 outpatients, 91 had hypoglycemia, and each was matched with five controls (24). Eight of those with hypoglycemia were taking cibenzoline and three were taking disopyramide. In contrast, only seven of the controls were taking cibenzoline, a significant difference. However, 20 of the controls were taking disopyramide, which was not significant from the patients with hypoglycemia, although disopyramide is known to cause hypoglycemia. Insulin was also associated with hypoglycemia, but sulfonylureas were not. Furthermore, there was a positive association with what were termed "thyroid agents." All of these features cast some doubt on the validity of these results in relation to cibenzoline.

- A 65-year-old woman developed hypoglycemia while taking cibenzoline and alacepril (25).

It is possible that hypoglycemia due to cibenzoline can be enhanced by ACE inhibitors, which can increase insulin sensitivity (SED-14, 640).

Gastrointestinal

Various gastrointestinal adverse effects have been reported not infrequently, including nausea (15), sometimes in association with abdominal pain (7,9,13), vomiting, and diarrhea (7,8,14,16).

Liver

Hepatotoxicity with cibenzoline has been rarely reported. There has been a report of slight rises in the activities of serum transaminases (16), and one of ischemic hepatitis (26).

- A 67-year-old woman, who also had mild thrombocytopenia developed markedly abnormal liver function tests, which normalized within 3 months of withdrawal (27).

Susceptibility Factors

Renal disease

Cibenzoline is 60% eliminated by the kidneys (14,28,29). Its renal clearance falls with age (28); this is attributable to renal impairment.

- Three patients with severe renal insufficiency (creatinine clearance 10–16 ml/minute) had increased plasma cibenzoline concentrations during treatment with 300 mg/day (30). They developed prolonged QTc intervals, widened QRS complexes, dysrhythmias, hypotension, and hypoglycemia. Their plasma cibenzoline concentrations were 1944–2580 μg/l, 5–10 times higher than the usual target range. The half-lives of cibenzoline immediately after withdrawal were 69, 116, and 198 hours, 3–10 times longer than reported in patients with end-stage renal insufficiency (about 20 hours).

Drug Administration

Drug overdose

Overdose of cibenzoline has been reported.

- An 80-year-old woman who took an unknown number of 300 mg tablets had impaired consciousness, a low blood pressure (58/30 mmHg), coarse crackles in the lung, and a prolonged QT_c interval (0.64 seconds) (31). There was mild left ventricular global hypokinesia with a 50% left ventricular ejection fraction, severe mitral regurgitation, and left atrial dilatation. There was a mild partially compensated metabolic acidosis and hypoglycemia (2.9 mmol/l). The plasma concentration of cibenzoline was 2580 ng/ml. She was treated with sodium bicarbonate, dopamine, and noradrenaline. A pre-existing right ventricular pacemaker was not functioning, and the amplitude was increased from 2.5 to 7.5 volts at a rate of 90 per minute. Charcoal perfusion for 5 hours caused a dramatic fall in the plasma cibenzoline concentration in association with a reduction in the QT_c interval to 0.48 seconds and improvement in the pacing threshold.
- Fatal intoxication with cibenzoline has been reported in an 83-year-old man (32).

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Diagnosis of Adverse Drug Reactions

It has been suggested that plasma concentrations of 100–200 mg/ml are necessary for efficacy and that at concentrations over 400 mg/ml there is an increased risk of adverse reactions (7). In most studies plasma cibenzoline concentrations have been around 200–400 mg/ml (4,6,8,17). Plasma concentrations correlate well with electrophysiological effects (6), its hemodynamic effects (33), and reduction in ventricular extra beats (34). In one study, patients who had adverse effects had a mean concentration of 913 mg/ml compared with 312 mg/ml in those who did not (8).

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Ciclosporin

General Information

Ciclosporin is an immunosuppressant drug that primarily inhibits T cell activation, therefore down-regulating the T cell responses that mediate graft rejection. Myelotoxic effects are therefore not expected. Ciclosporin has also been used in a wide range of chronic inflammatory or autoimmune diseases.

Considerable efforts have been devoted to defining the optimal dose to ensure minimal toxicity while retaining efficacy. In transplant patients, the daily maintenance dose is 2–6 mg/kg/day. In non-transplant patients, daily doses of 2.5 mg/kg up to a maximum of 4 mg/kg are usually recommended.

In renal transplantation, ciclosporin maintenance monotherapy can be effectively achieved in a subset of patients with the aim of reducing adverse effects associated with glucocorticoids or azathioprine, but this should be carefully balanced against the risks of acute or chronic allograft rejection. This approach was again emphasized, based on data from 100 adults and a review of the most recent literature (1). According to the authors, clinical predictors of successful ciclosporin maintenance therapy included compliant patients over 25 years old with a donor age younger than 40 years, patients with later azathioprine withdrawal, patients with serum creatinine concentrations of 125 μmol/l or less, patients without a history of rejection (or one rejection episode responding favorably to glucocorticoids), and patients who have successfully discontinued glucocorticoids 6 months before.

Comparative studies

Although the pattern of long-term toxicity of ciclosporin and tacrolimus is remarkably similar for most serious adverse effects (particularly nephrotoxicity), a higher incidence of several minor adverse effects with ciclosporin, namely hirsutism, gingivitis or gum hyperplasia, has been thought to underlie a moderate but significant decrease in the quality of life with ciclosporin compared with tacrolimus (2).

General adverse effects

As regards long-term toxicity, particularly nephrotoxicity, and frequent drug interactions, the benefit-to-harm balance of ciclosporin is still debatable. Whereas the adverse effects have generally been deemed acceptable, although occasionally treatment-limiting in patients with rheumatoid arthritis given low-dose ciclosporin rather than conventional antirheumatic drugs, conflicting opinions have been expressed on the acceptability of the risks in patients with psoriasis (SEDA-20, 343).

Of 20 patients with chronic idiopathic thrombocytopenic purpura refractory to glucocorticoids or splenectomy treated with ciclosporin, six withdrew owing to toxicity (3). The target blood concentration range was identical to that aimed at in the first 3 months after kidney transplantation. The most common adverse effects were hypertension, headache, and severe myalgia.

The antileukemic effect of ciclosporin has been harnessed in the treatment of cytopenias associated with chronic lymphatic leukemia. In 31 patients the most common adverse effect was a raised serum creatinine concentration of grade 2 or worse in six patients (19%); three patients developed opportunistic infections (4).

Drug interactions with ciclosporin have been comprehensively reviewed (5).

Organs and Systems

Cardiovascular

Compared with azathioprine, hypertension has been considered one of the main long-term risks in patients taking ciclosporin, with major concerns about the post-transplantion increase in cardiovascular morbidity and mortality. However, there are many susceptibility factors for cardiovascular disease in transplant patients (6), and it is difficult to take into account their complex interplay. Ciclosporin-associated hypertension appears to be dose-related, and higher whole-blood ciclosporin concentrations were found during the preceding months in patients who had thromboembolic complications compared with patients who did not (7).

De novo or aggravated hypertension is very common in patients taking ciclosporin, with the highest incidence in cases of heart transplant (71–100%) and the lowest incidence in bone marrow transplant recipients (33–60%) (8). In addition, 30–45% of patients with psoriasis, rheumatoid arthritis, or uveitis had hypertension, suggesting that ciclosporin is a significant cause of hypertension in organ transplantation. Ciclosporin-associated hypertension can cause acute vascular injury, with microangiopathic hemolysis, encephalopathy, seizures, and intracranial hemorrhage.

The incidence, clinical features, consequences, and management of ciclosporin-induced hypertension have been reviewed (9). The prevalence was 29–54% in non-transplant patients and 65–100% in heart and liver transplant patients also taking glucocorticoids. Disturbed circadian rhythm with a loss of nocturnal blood pressure fall was the main characteristic, and patients therefore had higher risks of left ventricular hypertrophy,

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cerebrovascular damage, microalbuminuria, and other target organ damage.

The pathophysiology of ciclosporin-induced hypertension is complex and not yet fully elucidated. Increased systemic vascular resistance subsequent to altered vascular endothelium function, renal vasoconstriction with reduced glomerular filtration and sodium-water retention, and/or increased activity of the sympathetic nervous system were suggested, while only a minor role or none was attributed to the renin–angiotensin system (10). However, hypertension often occurs before changes in renal function or sodium balance can be demonstrated, and ciclosporin nephrotoxicity alone does not explain ciclosporin-associated hypertension (8,11).

The effects of antihypertensive agents have been evaluated in patients taking ciclosporin. Collectively, dihydropyridine calcium channel blockers that do not affect ciclosporin blood concentrations substantially or at all (felodipine, isradipine, and nifedipine) are usually considered to be the drugs of choice. However, the risk of gingival hyperplasia with nifedipine, which ciclosporin also causes, should be borne in mind. Combination therapy with angiotensin-converting enzyme inhibitors or beta-blockers, or the use of other calcium channel blockers (verapamil or diltiazem) should also be considered, but careful monitoring of ciclosporin blood concentrations is recommended with the latter because they inhibit ciclosporin metabolism.

A possible role of ciclosporin in the exacerbation or development of Raynaud's disease has been suggested on one occasion; such an effect could be linked to endothelial damage or changes in platelet function (12).

A capillary leak syndrome with subsequent pulmonary edema has also been reported after intravenous ciclosporin (SEDA-21, 383).

Infusion phlebitis has been attributed to intravenous ciclosporin (13).

Respiratory

Adult respiratory distress syndrome has been described after intravenous ciclosporin. It was thought that a high concentration of the drug in the pulmonary vasculature due to administration through a central vein was responsible for capillary leakage, but in one patient the pulmonary capillary leak resolved rapidly when the intravenous ciclosporin was changed to oral (14). This suggested that Cremophor (polyoxyethylated castor oil), the solvent for parenteral ciclosporin, was responsible. However, there has been a report of an adult who developed respiratory distress syndrome in association with oral ciclosporin given after renal transplantation (15).

Hypersensitivity pneumonitis has been attributed to ciclosporin (16).

- A 35-year-old woman taking glibenclamide and mesalazine for Crohn's colitis was given ciclosporin for severe disease exacerbation. Within 6 weeks, she developed arthralgia and moderate thrombocytopenia, and ciclosporin was discontinued. Acute fever (41°C) and dyspnea were noted several days later, and a chest X-ray showed diffuse bilateral infiltrates. Bronchoalveolar lavage showed neutrophil preponderance and plasma cells, and a lung biopsy strongly suggested an acute hypersensitivity pneumonitis. All her symptoms subsided after a short course of prednisolone and oxygen.

Both the absence of an infectious cause and the rapid improvement without withdrawal of other drugs suggested that ciclosporin was the likely cause.

Nervous system

Neurological adverse effects of ciclosporin have been reported in up to 39% of all transplant patients. Most are mild. The most frequent is a fine tremor, the mechanism of which is not known. From many case reports or studies in transplant patients, the pattern of ciclosporin neurotoxicity ranges from common and mild to moderate symptoms, such as headaches, tremors, paresthesia, restlessness, mood changes, sleep disturbances, confusion, agitation, and visual hallucinations, to rare but severe or life-threatening disorders, including acute psychotic episodes, cerebellar disorders, cortical blindness (permanent in one report), spasticity or paralysis of the limbs, catatonia, speech disorders or mutism, chorea, seizures, leukoencephalopathy, and coma (SED-13, 1124) (SEDA-16, 516) (SEDA-17, 520) (SEDA-20, 343) (SEDA-21, 383) (17–19).

A 19% incidence of central nervous system toxicity with ciclosporin has been reported in pediatric renal transplantation patients; the symptoms included seizures, drowsiness, confusion, hallucinations, visual disturbances, and mental changes (20).

Neurological symptoms were observed in 12–25% of liver-transplant patients and in 29% of bone marrow transplant patients, but severe neurotoxicity occurred only in about 1% (18,19,21). They usually appeared within the first month of treatment, but were sometimes delayed (19). Particular attention should be paid to prompt recognition of severe neurotoxicity, because abnormalities of the white matter can occur. Patients usually improved rapidly after temporary ciclosporin withdrawal or dosage reduction, and tacrolimus has sometimes been used successfully instead (SEDA-21, 383) (18). However, recurrence of seizures and persistent electroencephalographic abnormalities were found in 46 and 70% of pediatric transplant patients respectively who had had ciclosporin acute encephalopathy and seizure syndrome and who were followed-up for 49 months (22).

Although the role of many other factors should be considered when neurological symptoms occur in transplant recipients, isolated reports of neurotoxicity in non-transplanted patients are in keeping with a causal role of ciclosporin. There are many susceptibility factors in ciclosporin neurotoxicity. Blood ciclosporin concentrations are sometimes raised, but severe neurological symptoms have been observed in some patients with concentrations in the usual target range (18). Other possible susceptibility factors for ciclosporin neurotoxicity include hypocholesterolemia, hypomagnesemia, aluminium overload, concomitant high-dose glucocorticoid therapy, hypertension, and concomitant microangiopathic hemolytic anemia (SED-13, 1124) (SEDA-21, 383). Acute graft-versus-host disease or HLA-mismatched and unrelated donor transplants were also potential susceptibility factors in recipients of bone marrow transplants (SEDA-22, 383) (19).

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Ciclosporin-induced vasculopathy, with endothelial injury and derangement of the blood–brain barrier, is the postulated mechanism of neurological damage. Transient cerebral perfusion abnormalities, demonstrable in SPECT scans of the brain, have been suggested as a reliable indicator of ciclosporin neurotoxicity (SEDA-20, 344). Clinical symptoms as well as CT and/or MRI scans were very similar to those observed in hypertensive encephalopathy, with predominant and reversible white-matter occipital lesions (23). There was complete neurological recovery in most patients after blood pressure was normalized, and deaths due to intracranial hemorrhage are reported only exceptionally.

A retrospective study identified a significantly higher incidence of central nervous system symptoms in patients with Behçet's disease (24). Headache, fever, paralysis, ataxia, dysarthria, or disturbed consciousness occurred in 12 of 47 ciclosporin-treated patients compared with nine of 270 patients not treated or taking other drugs. CT and/or MRI scans were abnormal in all 12. As the clinical findings were very similar to the neurological effects of Behçet's disease, it was suggested that ciclosporin can promote the development of neurological complications in this population.

Ciclosporin neurotoxicity is particularly frequent in liver and bone marrow transplant patients, who usually recover after temporary dosage reduction or withdrawal. However, a fatal outcome has been reported (25).

- A 54-year-old man was given ciclosporin and methotrexate after allogeneic bone marrow transplantation. He noted blurred vision during several days and became confused 11 weeks after transplantation. Generalized tonic-clonic seizures occurred the day after and he was given phenytoin and antibiotics. His neurological condition deteriorated during the next 5 days, despite ciclosporin withdrawal, and he died from respiratory failure. Postmortem examination showed white matter edema and astrocyte injury without demyelination.

Most studies have focused on the central nervous system adverse effects of ciclosporin, and there have been few reports of peripheral neuropathy.

- In two patients, ciclosporin was suggested as a possible cause of an entrapment neuropathy, and surgery was required in both (26).

However, the report did not provide sufficient evidence to assess the causal relation fully.

- Another patient developed a symmetric polyneuropathy with flaccid paraplegia while her ciclosporin serum concentrations were about twice normal (27). Electromyography showed features of axonal degeneration in the peripheral nerves and neurological symptoms improved on ciclosporin dosage reduction.

Migraine associated with ciclosporin is sometimes resistant to classical treatment and the consequences can be even more severe.

- Three young adult renal transplant patients, including two with a previous history of moderate migraine, had severe attacks of unilateral throbbing migraine associated with vomiting during ciclosporin treatment (28). In two patients, vomiting was severe enough to reduce compliance with the immunosuppressive regimen, and both subsequently lost their grafts. The same sequence of events was again observed after retransplantation.

Substitution by tacrolimus may be beneficial in such cases.

Severe ciclosporin neurotoxicity has mostly been reported in transplant patients, but should also be considered in non-transplanted patients.

- An 87-year-old patient with resistant nodular prurigo was successfully treated with ciclosporin (3 mg/kg/day) and prednisone (10 mg/day) (29). Bilateral numbness and distal limb weakness developed after 18 months. Clinical examination, electromyography, and nerve conduction studies confirmed a diffuse axonal neuropathy which rapidly progressed over the next 2 months. Ciclosporin alone was withdrawn and complete remission was observed within 3 months.

Unfortunately, ciclosporin blood concentrations and renal function at the time of diagnosis were not reported.

Very severe or fatal neurotoxicity has been reported in isolated patients only.

- Based on postmortem findings in a 32-year-old woman who died with an acute encephalopathy (30) and another report of two patients investigated with transcranial Doppler ultrasound and MRI for symptoms of ciclosporin neurotoxicity (31), vascular changes with vasospasm and dissection of the vascular intima strongly suggest that vasculopathy is a possible mechanism of ciclosporin-induced encephalopathy.

Prolonged confusion is a recognized complication of ciclosporin, and can be due to non-convulsive status epilepticus (32). Three patients who developed neurotoxicity following treatment with ciclosporin manifested with generalized tonic-clonic seizures and dysarthria. The plasma ciclosporin concentration in these patients increased as the neurological signs appeared, and the signs resolved quickly after dosage reduction (33). Tonic-clonic seizures have been reported in a child taking ciclosporin (34).

- A 13-year-old boy with severe Crohn's disease developed hematochezia and required blood transfusion. He was given ciclosporin on day 22 because of persistent rectal bleeding and diarrhea, despite high-dose intravenous glucocorticoids. After 6 days he developed multiple episodes of generalized tonic-clonic seizures, with MRI findings typical but not pathognomonic of ciclosporin: prominent meningeal enhancement, bifrontal, bitemporal, biparietal, and bioccipital cortical and subcortical white matter high-signal changes, and swelling of the gyri, which obliterated the sulci.

This case illustrates that severe ciclosporin neurotoxicity can develop in patients with predisposing factors, such as hypomagnesemia, hypocholesterolemia, hypertension, and glucocorticoid therapy.

There is still debate about whether ciclosporin crosses the blood–brain barrier and enters the cerebrospinal fluid. Ciclosporin could not be identified in cerebrospinal fluid

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from 14 patients with liver transplants who had various neurological complications (35). Ciclosporin metabolites were measurable in the cerebrospinal fluid in only four patients, who had evidence of acute renal insufficiency, cholestasis, and raised blood concentrations of ciclosporin metabolites but identical ciclosporin parent drug blood concentrations compared with 10 patients with undetectable concentrations of ciclosporin metabolites in the cerebrospinal fluid. Ciclosporin metabolites enter the cerebrospinal fluid, and direct neurotoxicity is therefore possible in at least some patients with renal or hepatic dysfunction.

Endogenous ligands for ciclosporin and tacrolimus, known as immunophilins, are found in very high concentrations in the basal ganglia, and ciclosporin can alter dopamine phosphorylation in the medium-sized neurons in the striatum. Changes in basal ganglia glucose metabolism have been studied in a patient with severe ciclosporin-related tremor (36).

- A 37-year-old man received ciclosporin after bone marrow transplantation for chronic myelogenous leukemia. Soon afterwards he developed a severe tremor, which persisted despite dosage reduction. A brain MRI scan was normal. After 22 months he developed a personality change. A high resolution PET scan showed symmetrical increases in ^{18}F-deoxyglucose uptake in both caudate and putamen.

These results confirm that ciclosporin can modulate dopaminergic transmission in the striatum, presumably by inhibition of calcineurin.

- A 16-year-old girl with end-stage renal insufficiency underwent successful renal transplantation and was given ciclosporin on day 1 (37). On day 10 she complained of tinnitus and tremor and had a right facial nerve palsy. An MRI scan showed areas of increased signal in the white matter of the periventricular region. The dose of ciclosporin was reduced, since no other cause could be determined. Her tremor and tinnitus resolved, but the facial nerve palsy persisted. She was given tacrolimus, but the tremor and tinnitus recurred. She was then given mycophenolate mofetil and prednisone, and the tremor and tinnitus disappeared, although the facial nerve palsy persisted. The MRI scan 3 months later was normal.

The serum magnesium concentration was below the reference range in this case, which may have favored the development of neurotoxicity.

Sensory systems

Controversial reports of ocular symptoms have been published in patients taking oral ciclosporin, with ptosis and diplopia attributed to unilateral or bilateral sixth nerve palsies in four patients (who had also taken ganciclovir), and nystagmus in one patient (SEDA-21, 383). Peripheral optic neuropathy, with visual loss, nystagmus, and ophthalmoplegia, has also been reported (38). Acute cerebral cortical blindness complicating ciclosporin therapy in a 5-year-old girl (39) and transient cortical blindness and occipital seizures with visual impairment (40,41) have also been reported in association with ciclosporin.

Bilateral optic disc edema is sometimes associated with ciclosporin given for bone marrow transplantation, but unilateral papilledema with otherwise asymptomatic raised intracranial pressure can occur (42). Eight cases of optic disc edema have been reported in bone marrow transplant patients taking ciclosporin. In two of the patients there were other possible explanations, but in all cases withdrawal of ciclosporin resulted in resolution of the papilledema (43).

Ciclosporin eye-drops have been used after keratoplasty, in high-risk cases, to prevent graft rejection and to treat severe vernal conjunctivitis, keratoconjunctivitis sicca, and various immune-related corneal disorders. Despite its severe adverse effects after systemic use, topical ciclosporin can generally be used without serious adverse reactions (44,45).

Ciclosporin oil-in-water emulsion has been used in the local treatment of moderate to severe dry eye disease. Chronic dry eye disease results from inflammation mediated by cytokines and receptors for autoimmune antibodies in the lacrimal glands. It affects the lacrimal gland acini and ducts, leading to abnormalities in the tear film, and ultimately disrupting the homeostasis of the ocular surface. Topical ciclosporin reduces the cell-mediated inflammatory response associated with inflammatory ocular surface diseases.

In two large, randomized controlled trials in 977 patients, the adverse effects associated with ciclosporin ophthalmic emulsion for the treatment of dry eye disease were minimal and consisted mostly of mild ocular burning and stinging (46). However, topical application of ciclosporin eye-drops was the suspected cause of severe visual loss with bilateral white corneal deposits in a 45-year-old patient with dry eye syndrome caused by graft-versus-host disease (47). Infrared spectroscopy and X-ray analysis suggested that the deposits contained ciclosporin. A reduction in tear clearance and compromised epithelial barrier function caused by the concomitant use of oxybuprocaine may have precipitated this adverse effect.

The efficacy, safety, tolerability, and optimal dose of ciclosporin eye-drops have been studied in a randomized, double-masked, vehicle-controlled multicenter trial in 162 patients with keratoconjunctivitis sicca with or without Sjögren's disease and refractory to conventional treatment (48). Ciclosporin ophthalmic emulsion 0.05, 0.1, 0.2, or 0.4%, or the vehicle alone was instilled twice daily into both eyes for 12 weeks, followed by a 4-week observation period. There was no clear dose–response relation; ciclosporin 0.1% emulsion produced the most consistent improvement in objective and subjective endpoints and ciclosporin 0.05% gave the most consistent improvement in symptoms. The vehicle also performed well, perhaps because of its long residence time on the ocular surface. There were no significant adverse effects, no microbial overgrowth, and no residence time of the vehicle emulsion on the ocular surface. All treatments were well tolerated and the highest ciclosporin blood concentration detected was 0.16 ng/ml.

To study the efficacy and safety of ciclosporin 0.05 and 0.1% ophthalmic emulsions and their vehicle in patients with moderate to severe dry eye disease, two identical multicenter, randomized, double-masked, vehicle-controlled trials have been performed in 877 patients for

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6 months (46). More than 76% completed the course. Ciclosporin 0.05 or 0.1% eye-drops gave significantly greater improvement than the vehicle in two objective signs of dry eye disease (corneal staining and Schirmer values). Ciclosporin 0.05% also gave significantly greater improvement in three subjective measures (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). There was no dose–response effect and there were no topical or systemic adverse findings.

Corneal deposition of ciclosporin can occur (47).

- A 45-year-old woman with dry eye syndrome caused by graft-versus-host disease after bone marrow transplantation for acute leukemia was given systemic ciclosporin and topical 0.1% sodium hyaluronate, 0.3% ofloxacin, 0.1% fluorometholone, and isotonic saline. She was also given 0.4% oxybuprocaine for the relief of severe ocular pain. The bilateral corneal epithelial defects persisted even after the application of punctal plugs, and 2% ciclosporin in olive oil was added as eye-drops three times a day bilaterally. Five days later she complained of severe visual loss in association with bilateral corneal opacities, which covered the pupil and the punctal plugs bilaterally. As she did not agree to keratectomy, infrared spectroscopy and X-ray analysis were conducted on the deposits on the plugs. The spectroscopic pattern and X-ray analysis showed that the deposits had the properties of ciclosporin.

As the corneal deposits did not abate after withdrawal of the ciclosporin eye-drops, the systemic ciclosporin as well as its topical use may have contributed to the deposits. One should be aware that precipitation of ciclosporin on a compromised cornea can lead to severe visual impairment.

Metabolism

Diabetes mellitus

Diabetes mellitus after transplantation is recognized as an important adverse effect of immunosuppressants, and has been extensively reviewed (49). However, the use of ciclosporin in immunosuppressive regimens is not associated with diabetes mellitus after transplantation (10–20%) (50).

Hyperlipidemia

Ciclosporin is potentially more toxic in patients with altered LDL concentrations or a low total serum cholesterol (51). Ciclosporin therapy itself significantly raises plasma lipoprotein concentrations by increasing the total serum cholesterol; this is due to an increase in LDL cholesterol, demonstrated in a prospective, double-blind, randomized, placebo-controlled trial in 36 men with amyotrophic lateral sclerosis (52). In 22 patients there were significant increases in mean serum triglycerides and cholesterol 2 weeks after they started to take low-dose ciclosporin (53). Hypertriglyceridemia developed in seven patients taking ciclosporin 2.0–7.5 mg/kg/day for psoriasis during the first month of therapy; the values were greater than the upper limit in age- and sex-matched controls (54).

The pathology of hyperlipidemia after transplantation is multifactorial, but it is clearly dose-dependently related to immunosuppressive therapy (55). This results in cardiovascular disease, which is one of the most common causes of morbidity and mortality in long-term survivors of organ transplantation (56). Hyperlipidemia can also cause renal atheroma, resulting in graft rejection. The possible impact of ciclosporin on lipids includes an increase in total cholesterol, LDL cholesterol, and apolipoprotein B concentrations, and a reduction in HDL cholesterol (SED-13, 1124). The influence of ciclosporin on lipoprotein(a) concentrations has been debated (SEDA-21, 383) (57). Post-transplant hyperlipidemia is multifactorial and can be affected by impaired renal function, diuretics and beta-blockers, increased age, and female sex. A combination of lipid-lowering drugs and optimization of immunosuppressive regimens compatible with long-term allograft survival is probably required to reduce post-transplantation hyperlipidemia.

Whereas azathioprine is considered to play no role, glucocorticoid use correlates positively with increased serum cholesterol concentrations. It is uncertain whether these lipid changes reflect primarily an effect of ciclosporin alone or an additive/synergistic effect of the drug plus glucocorticoids. Ciclosporin has been considered as a possible independent susceptibility factor by several investigators, but others were unable to find an association between hyperlipidemia and ciclosporin (SEDA-20, 344). There was indirect evidence for a causal role of ciclosporin in several studies; hyperlipidemia developed in non-transplant patients taking ciclosporin alone; there was a transient reduction in hyperlipidemia after ciclosporin withdrawal; there was a significant correlation between ciclosporin blood concentrations and lipid abnormalities; and there was a higher incidence of lipid abnormalities in patients taking ciclosporin alone compared with patients taking azathioprine and prednisolone (SED-8, 1131) (SEDA-17, 524) (SEDA-21, 383) (55,58). Other studies have provided striking evidence that hyperlipidemia is more frequent in patients taking ciclosporin than in those taking tacrolimus, with more patients classified as having high cholesterol concentrations in the ciclosporin group or a significant fall in total cholesterol or LDL cholesterol in patients switched from ciclosporin to tacrolimus (59,60). Although the glucocorticoid-sparing effect of tacrolimus may account for these differences, the concept that the glucocorticoid dose is a confounding factor has been disputed (SEDA-22, 412). Whether these differences translate to a higher risk of cardiovascular complications in patients taking ciclosporin has not been carefully assessed. The treatment of hyperlipidemia in transplant patients may represent a major dilemma, because of several drug interactions, with an increased risk of myopathy and rhabdomyolysis after the combined use of ciclosporin and several lipid-lowering drugs.

Hyperuricemia

Significant hyperuricemia has been observed in as many as 80% of patients taking ciclosporin (61). In one series, hyperuricemia occurred in 72% of male and 82% of

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female patients taking ciclosporin after cardiac transplantation; there was also an increased incidence of gouty arthritis in these patients (62). Episodes of gout developed mostly in men taking diuretics, but the incidence was lower than in the hyperuricemic population. In renal transplant patients, the incidence of gout was 5–24% and tophi sometimes developed rapidly after the onset of gout (63). The potential mechanisms of hyperuricemia include reduced renal function and impaired tubular secretion of acid uric, with hypertension and diuretics as confounding factors (SEDA-21, 383).

Nutrition

Higher plasma homocysteine concentrations, which may contribute to atherosclerosis, have been found in patients taking ciclosporin, compared with both transplant patients not taking ciclosporin and non-transplant patients with renal insufficiency (SEDA-20, 344).

Electrolyte balance

Mild and uncomplicated hyperkalemia is commonly observed in patients taking ciclosporin and is generally prevented by a low potassium diet. A reduction in distal nephron potassium secretion and tubular flow rate, with insensitivity to exogenous mineralocorticoids, and leakage of cellular potassium into the extracellular fluid are possible mechanisms (SED-13, 1124) (64).

Mineral balance

Hypomagnesemia and hypercalcemia occur infrequently during ciclosporin treatment (SED-13, 1124).

- In a 43-year-old renal transplant patient, hypomagnesemia was associated with muscle weakness and a near four-fold increase in serum creatine kinase activity (65). Both disorders resolved after magnesium supplementation, and ciclosporin was continued.

Renal magnesium wasting occurred in 24% of a series of renal transplant patients taking ciclosporin; other indicators of renal function were normal (66,67).

Hypomagnesemia in the early post-transplant period has been cited as a possible risk factor for acute ciclosporin neurotoxicity. Ciclosporin-induced sustained magnesium depletion has been investigated in 109 ciclosporin-treated patients with renal transplants who had been stable for more than 6 months (68). Total and ionized plasma magnesium concentrations were significantly lower than in 21 healthy volunteers and in 15 patients with renal transplants who were not taking ciclosporin. Ciclosporin-treated patients who were also taking hypoglycemic drugs had lower plasma magnesium concentrations, but patients taking diuretics did not.

Hematologic

A very few cases of ciclosporin-induced immune hemolytic anemia have been reported (SED-13, 1125) (69,70), but a direct causal relation with ciclosporin is difficult to establish. Ciclosporin-induced hypercoagulability was suggested in patients with aplastic anemia (SEDA-20, 344). Higher whole-blood ciclosporin concentrations were found during the preceding months in patients who experienced thromboembolic complications compared with patients who had not.

Ciclosporin-associated thrombotic microangiopathy occurs in 3–14% of patients with a renal transplant and can cause allograft loss. Renal impairment, reflected by an increase in serum creatinine concentration, is often the only change found, and hemolysis is not always present. Plasmapheresis has been used to treat this complication (71).

- A 47-year-old multiparous Hispanic woman received a living-unrelated kidney transplant for end-stage renal disease secondary to polycystic kidney disease. On the day of transplantation she received intravenous daclizumab 1 mg/kg plus methylprednisolone 300 mg and mycophenolate mofetil 3 g/day, and on day 3 ciclosporin emulsion 4 mg/kg/day. On day 8 she developed thrombotic microangiopathy without evidence of rejection. Ciclosporin was withdrawn. Plasmapheresis with fresh frozen plasma was started. Daclizumab on day 14 was postponed for 24 hours and plasmapheresis was stopped to avoid clearance of daclizumab. Thereafter she was given tacrolimus, without recurrence of hemolysis.

Mouth and teeth

Ciclosporin-induced gingival hyperplasia was noted in the early 1980s, and subsequent studies investigated the prevalence and pathophysiology of this adverse effect (SED-13, 1127). The reported incidence was 7–70%, and clinically significant gingival overgrowth, that is to say requiring treatment or surgical excision, affected about 30% of patients within the first 6 months of treatment (72). Clinical and histological features are similar to those associated with phenytoin or nifedipine. Compared with control specimens, ultrastructural gingival examinations in patients taking ciclosporin showed many fibroblasts, abundant amorphous substance, and marked plasma cell infiltration (73). Although an imbalance between the production and removal of collagen is supposed to account for gingival hyperplasia, the mechanism of ciclosporin-induced gingival overgrowth has not yet been clearly established. Possible local lymphocyte resistance to ciclosporin resulting in an increasing number of several inflammatory cells in the gingival lamina propria and ciclosporin-induced inhibition of prostaglandin I_2 synthesis have also been suggested (74,75).

There are many susceptibility factors for ciclosporin-induced gingival hyperplasia. The duration of treatment and the cumulative dose during the first 6 months play a major role. Accordingly, reduction of the ciclosporin dose can lessen the risk, and the use of lower doses is thought to reduce the overall incidence (76,77). There is also a positive correlation between the degree of gingival hyperplasia and changes in renal function (78). There are conflicting findings regarding the effects of blood concentrations on the incidence of gingival hyperplasia, and no clear relation between saliva and blood ciclosporin concentrations has been found. Lower age correlated significantly with the presence of gingival hyperplasia and children under 6 years of age are more susceptible to the complication in severe form (76,79). Male sex is a predisposing factor, a finding supported by the report of an

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increased androgen metabolism in gingival hyperplasia induced by ciclosporin (80). There has been also speculation concerning genetic differences in the susceptibility to develop these changes (72) (SEDA-21, 384). Finally, the combination of ciclosporin and nifedipine is additive with an increased prevalence and/or severity of gingival hyperplasia (SED-13, 1127) (76,77,80–82). As several other calcium channel blockers can produce gingival overgrowth, more frequent gingival hyperplasia should be expected, at least theoretically, when these drugs are combined with ciclosporin.

It is not yet clearly established whether bacterial plaque, gingival bleeding index, or inflammation are the cause or result of gingival hyperplasia. Certainly, poor oral health with subsequent local inflammation appears to be a contributing factor. Consequently, careful dental hygiene with plaque control is often sufficient to improve or resolve hyperplasia, but surgical treatment is sometimes necessary. Preliminary case reports have suggested that azithromycin or metronidazole can improve ciclosporin-induced gingival hyperplasia (SEDA-19, 350). This has been confirmed for azithromycin, with no indication that ciclosporin blood concentrations are modified during a short course of azithromycin (SEDA-22, 414).

Gastrointestinal

Gastrointestinal symptoms due to ciclosporin are usually mild and transient. In rheumatoid arthritis, gastrointestinal intolerance has been reported in 50% of patients, being the main cause for withdrawal of ciclosporin in 8% (83). Whereas worsening colitis did not occur in patients with inflammatory bowel disease, ciclosporin was involved in the development of acute colitis in isolated reports (SED-13, 1125).

Liver

There was at least one episode of hepatotoxicity in 228 of 466 patients (49%) with renal transplants who took ciclosporin; 110 (48%) had hyperalbuminemia, 108 (47%) a raised aspartate transaminase, and 167 (59%) a raised alkaline phosphatase (84). Ciclosporin dosage reduction resulted in resolution of hepatotoxicity in 185 patients (81%), while 32 (14%) had recurrent or persistent liver function abnormalities. Eleven (2.4%) developed biliary calculous disease. The serum ciclosporin concentration was high among the patients with hepatotoxicity. Pharmacokinetic studies showed an increased AUC in the patients with hepatotoxicity, probably due to reduced drug clearance.

A causal association has been shown between the hepatotoxicity of ciclosporin and cold ischemic liver damage that can occur during preservation before liver transplantation (85). This presents a problem when ciclosporin is used after liver transplantation. In more than 1000 patients there was an incidence of mild reversible hepatotoxicity of 40% in patients taking 5-fluorouracil and levamisole as adjuvants for more than 1 year; the incidence of mild hepatotoxicity in those taking levamisole alone and amongst those receiving no treatment at all was the same, a little over 16% (86).

Experiments with isolated human hepatocytes have shown that ciclosporin competitively inhibits the uptake of cholate and glycocholate bile acids; the biological features of ciclosporin-associated hepatotoxicity are therefore mostly those of cholestasis, with reduced bile excretion (87). The presence of underlying chronic viral hepatitis can increase the severity of ciclosporin-induced cholestasis (88).

Ciclosporin can cause cholestasis and cellular necrosis by an inhibitory effect on hepatocyte membrane transport proteins at both sinusoidal and canalicular levels. It induces oxidative stress by accumulation of various free radicals. Ademetionine (*S*-adenosylmethionine) is a naturally occurring substance that is involved in liver detoxification processes. The efficacy of ademetionine in the treatment and prevention of ciclosporin-induced cholestasis has been studied in 72 men with psoriasis (89). The patients who were given ciclosporin plus ademetionine had low plasma and erythrocyte concentrations of oxidants and high concentrations of antioxidants. The authors concluded that ademetionine may protect the liver against hepatotoxic substances such as ciclosporin.

A possible consequence of bile acid abnormalities and cholestasis associated with ciclosporin is the development of cholelithiasis in liver transplant patients when the donor has pre-existing susceptibility for cholesterol gallstone formation or abnormalities of bile composition.

- A young patient who received a liver from a 78-year-old donor subsequently developed cholesterol gallstones (SEDA-21, 383).

In a retrospective study in 50 consecutive patients who received both parenteral nutrition and glucocorticoids, with or without the addition of ciclosporin, at some stage in their management, there was no evidence that ciclosporin caused more liver dysfunction than that associated with parenteral nutrition (90).

Urinary tract

The renal toxicity of ciclosporin has been described as being an adverse effect of the drug on the compensatory mechanisms of the kidney, without effects on proximal tubular function (urea and sodium reabsorption) (91). A rise in serum creatinine concentration may be adequate to identify acute-onset ciclosporin nephrotoxicity, but it is not suitable for identification of chronic, late-onset ciclosporin nephrotoxicity (92).

Presentation

Acute renal impairment

Acute ciclosporin-induced nephrotoxicity, causing reduced renal function, develops within the first month, and includes a dose-related rise in serum creatinine concentrations and hyperkalemia. Fatal acute tubular necrosis has also been noted after very high intravenous doses (SEDA-19, 345). Although it is clinically often difficult to differentiate from acute allograft rejection in renal transplant patients, the alteration in renal function promptly resolves on ciclosporin withdrawal or dosage reduction, and initial acute renal insufficiency is not clearly associated with the development of subsequent chronic renal dysfunction (93). Several conditions, such as pre-existing hypovolemia, concomitant diuretic treatment, or renal artery stenosis, are susceptibility factors.

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Hypothyroidism was thought to be involved in one patient (94), and the transplanted kidney itself rather than interindividual differences between recipients was thought to play a role (SEDA-21, 384).

Hemolytic–uremic syndrome and thrombotic microangiopathy

Hemolytic–uremic syndrome, with histological findings of thrombotic microangiopathy and possible evolution to graft loss or death, is another instance of very severe acute nephrotoxicity (SED-13, 1125). It usually occurs at between the second and fourth weeks after transplant, with associated fever, thrombocytopenia, erythrocyte fragmentation, neurotoxicity, and renal impairment. Uncommon clinical features have been reported.

- In two women, hemolytic–uremic syndrome was apparently revealed by an episode of severe acute depression (95).
- In another patient, a single injection of ciclosporin may have induced the development of fibrin thrombi seen in the perioperative graft biopsy (96). Later on, she was confirmed to have clinical and biological features of hemolytic–uremic syndrome, which reversed after ciclosporin withdrawal.

Hemolyti–uremic syndrome has also been reported during ciclosporin treatment for Behçet's disease (SEDA-21, 384). Both early and delayed hemolytic–uremic syndrome can occur after transplantation, and its actual incidence may have been underestimated. Thrombotic microangiopathy with clinical features of hemolytic–uremic syndrome was found in 3.5–5% of renal transplant patients (97,98). Graft loss was mostly found in patients who developed hemolytic–uremic syndrome early after transplantation, and the clinical distinction from acute rejection can be very difficult. Hemolytic–uremic syndrome does not recur after initial withdrawal and further ciclosporin reintroduction, once renal function has normalized, or even despite ciclosporin maintenance with dosage reduction (SED-13, 1125) (SEDA-20, 345). In some cases, the patient was successfully switched to tacrolimus, and only one case of hemolytic–uremic syndrome with recurrence on ciclosporin rechallenge has been reported (SEDA-21, 384). In contrast, both ciclosporin and tacrolimus were significant susceptibility factors for recurrence of hemolytic–uremic syndrome in patients who had undergone renal transplantation for end-stage renal disease (99).

The factors that contribute to the development of thrombotic microangiopathy have been retrospectively investigated in 50 of 188 patients with kidney or kidney + pancreas allografts who underwent graft biopsies and in 19 control patients who had never had renal graft dysfunction or a biopsy (100). There were definite histological features of thrombotic microangiopathy 4 days to 6 years after transplantation in 26 patients, of whom 24 were taking ciclosporin and two were taking tacrolimus, showing that this complication can occur at any time after transplantation. Eight patients had graft loss, but only two had associated systemic evidence of microangiopathy, that is thrombocytopenia and intravascular hemolysis, suggesting that thrombotic microangiopathy should be considered in any patients with renal graft dysfunction, even if there are no suggestive systemic symptoms. Although the more frequent use of the microemulsion form of ciclosporin (Neoral) in patients with confirmed thrombotic microangiopathy than in controls suggested a possible role of this formulation, this issue remains to be further investigated, because the number of evaluable patients was small. None of the other investigated variables (age, sex, race, living-related or cadaveric donor status, the degree of HLA mismatch, the type of allograft, or the incidence of urinary tract infections after transplantation) was significantly associated with the occurrence of thrombotic microangiopathy compared with patients without thrombotic microangiopathy. Finally, the most successful strategy was a switch from ciclosporin to tacrolimus, which resulted in normalization of graft function in 81% of these patients.

Chronic renal insufficiency

Chronic renal impairment, as first reported in cardiac transplant patients (101), is of major concern, because of possible irreversible renal dysfunction. A considerable amount of work has subsequently accumulated on the development of progressive renal dysfunction in patients receiving long-term ciclosporin for organ transplantation or chronic inflammatory disease (SED-13, 1125) (SEDA-20, 345) (SEDA-21, 384) (SEDA-22, 413), and there have been several comprehensive reviews (102–105). About one-third of all patients have increased serum creatinine concentrations and reduced glomerular filtration rate during ciclosporin maintenance therapy. The histopathological features of chronic nephropathy consist mostly of non-specific tubular atrophy and interstitial fibrosis (106); arteriolar lesions are considered very suggestive of ciclosporin nephrotoxicity. The prevalence of renal damage due to ciclosporin has fallen considerably since the use of lower doses. Arteriolopathy sometimes improves after reducing or withdrawing ciclosporin. Morphological features in patients with autoimmune diseases are non-specific, and include a wide range of lesions, mostly characterized by tubulointerstitial changes and arteriolopathy. There is no significant correlation between histological findings and ciclosporin dose. Severe histological lesions can be identified in some patients with normal renal function (107); the severity of tubulointerstitial lesions has been deemed to be a better index than the glomerular filtration rate for predicting the occurrence of chronic nephropathy, but in one study there was no correlation between histological renal findings and various measures of renal function (108).

Because the possibility of irreversible renal dysfunction is a major problem in ciclosporin maintenance in both transplant and non-transplant patients, this issue continues to receive attention. Even though many studies have been performed, the long-term prognosis is a source of conflicting opinions, and the initial assumption that long-term use of ciclosporin will sooner or later cause irreversible chronic nephropathy is hotly debated. It is still unclear to what extent long-term ciclosporin contributes to progressive renal insufficiency and whether chronic ciclosporin nephropathy is irreversible or improves after dosage reduction. A retrospective analysis

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of more than 12 000 renal transplant patients showed that long-term maintenance with a glucocorticoid-free ciclosporin regimen (ciclosporin alone or with azathioprine) significantly increased renal graft and patient survival, compared with patients taking other immunosuppressive regimens (109). This allowed the use of higher doses of ciclosporin without increasing the frequency of nephrotoxicity. In contrast, several investigators have considered a change to a ciclosporin-free regimen in 40% of patients, because of progressive renal deterioration with histological signs of nephrotoxicity (110). The incidence of end-stage renal insufficiency requiring dialysis or renal transplantation ranges from 1% in renal transplant patients to 3–6% in heart-transplant patients (111–114). Nevertheless, several investigators have shown that despite an initial reduction in renal function, serum creatinine concentrations stabilized with no strong evidence of progressive nephropathy after several years of surveillance in various organ transplant patients (93,112,115–117).

The potential long-term consequences of ciclosporin nephrotoxicity constitute a major disadvantage in non-transplant patients. Renal function was assessed 7 years after the end of a 1-year ciclosporin treatment period in 36 young patients from a randomized, placebo-controlled trial of ciclosporin in diabetes mellitus, 19 taking ciclosporin, and 17 taking placebo (118). Blood pressure did not differ between the groups. Compared with baseline values, urinary albumin excretion rate was significantly higher and estimated glomerular filtration rate significantly lower with ciclosporin. The results in the placebo group showed no change or increases. In addition, there was progression to micro- or macro-albuminuria in four patients taking ciclosporin, and two of five patients who underwent renal biopsy had arteriolar hyalinosis. It is not known whether these changes will translate to an increased risk of nephropathy, but they suggest that ciclosporin might enhance it. Of 91 consecutive patients with renal transplants with a minimum graft survival of 1 year who were followed for 7–8 years, 65% had stable renal function despite ciclosporin serum concentrations of 200–250 ng/ml (119). In addition, none of the 26 patients with worsening renal function had features of ciclosporin nephrotoxicity on renal biopsy.

Frequency

In a meta-analysis of 18 trials involving ciclosporin doses below 10 mg/kg/day for at least 2 months in autoimmune diseases, the weighted percentage increase in serum creatinine concentrations was 17% in ciclosporin-treated patients and 1.7% in controls (120). The corrected risk difference for an increase of more than 50% of pretreatment serum creatinine concentrations between the two groups was 21% (95% CI = 12, 30) (120). This meta-analysis did not fully consider the long-term outcome, but clinical and histological evidence of sustained or progressive ciclosporin nephropathy in this population continues to accumulate. Unfortunately, some of the findings are discordant (107,121–130).

In a retrospective study of 106 patients following renal transplantation who had been treated with ciclosporin, 85% were hypertensive compared with 54% of patients taking azathioprine (131). Renal function was significantly better in hypertensive patients treated with nifedipine than with other antihypertensive medication (beta-blockers and vasodilators), and it was similar to that of normotensive patients treated with ciclosporin.

Pathophysiology

The pathogenesis of chronic ciclosporin nephrotoxicity is not fully understood (105). Intrarenal afferent arteriolar vasoconstriction may play an important part, particularly in acute nephrotoxicity (132), in which a marked reduction in renal blood flow associated with an increase in renal vascular resistance, probably due to postglomerular vasoconstriction, has been demonstrated (133,134). The supposed mechanism is primarily an imbalance between several regulatory mechanisms of renal vasodilatation and vasoconstriction, leading to increased renal vasoconstriction, and the explanations that have been proposed include activation of the renin–angiotensin system, prostaglandin inhibition, and sympathetic nervous system activation (135). However, it is unclear whether a continuous increase in renal vascular resistance can account for chronic renal dysfunction in patients taking long-term ciclosporin. There are many possible mediators of renal vasoconstriction, for example nitric oxide, the renin–angiotensin and kallikrein–kinin systems, endothelin-1 release, and stimulation of sympathetic nervous system activity. A major effect of ciclosporin is to promote calcium accumulation in the mitochondrial matrix, which in turn reduces ATP synthesis (136). The main morphological abnormality that has been demonstrated in the kidneys of patients taking long-term ciclosporin is interstitial fibrosis. Vascular lesions, predominantly arteriolar, with arterial intimal fibrosis have been noted in renal biopsies from patients with chronic ciclosporin nephrotoxicity (137).

Renal morphology has been studied in 17 patients who received ciclosporin for sight-threatening uveitis. Most had not received other potentially nephrotoxic drugs. Variable interstitial fibrosis, frequently associated with tubular atrophy, was noted in all 17. The extent of the pathological changes did not correlate with the age, treatment duration, or average cumulative dose (138). Ciclosporin nephrotoxicity mimics the histological features of acute allograft rejection and tubular necrosis. It is important to be able to distinguish clinically between ciclosporin toxicity on the one hand (necessitating a reduction in dose) and rejection (requiring an increase in dose) on the other.

The long-term effects of ciclosporin on renal function in 11 liver transplant recipients were evaluated over a follow-up period of 6–26 months (135). Immediately postoperatively, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) fell by 60%, subsequently settling at 45–60% of normal. There were additional toxic effects on renal tubular function. Histopathological findings were mild to moderate; notably, arterial and arteriolar nephrosclerosis. Renal function improved as the dose of ciclosporin was reduced, despite continued administration of the drug. This suggests a persistent, potentially reversible, functional component to chronic ciclosporin nephrotoxicity.

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The respective roles of organ preservation and ciclosporin in the pathogenesis of post-transplant renal damage have been studied in an in vitro model that simulates the hypothermic kidney preserved before surgery in Collins' solution and exposed after transplantation to ciclosporin (139). The results showed that preservation sensitizes the kidney to ciclosporin injury, which is consistent with clinical experience (140). If the preserved kidney cells were given a period of repair before administration of ciclosporin, further injury did not happen. In animal experiments, prolonged cold preservation causes progressive deterioration in the renal cortical microcirculation; concentration of ciclosporin in the renal cortex of hypoperfused kidneys markedly potentiates the vascular damage caused by cold preservation (131).

Large-scale studies with long periods of follow-up have emphasized the major role of graft arteriopathy (chronic graft rejection) rather than chronic ciclosporin nephrotoxicity as the primary cause of graft failure (111,116,141). Severe ciclosporin nephropathy was the cause of renal transplant failure in less than 1% of patients.

Susceptibility factors and prediction

Many factors have been postulated as being relevant to ciclosporin nephrotoxicity. Whereas in several studies initial high doses of ciclosporin increased the risk of chronic nephrotoxicity (115,121), others suggested that patients maintained on relatively high ciclosporin concentrations had no more chance than others of developing toxic nephropathy (116). Neither the daily dose nor the duration of ciclosporin treatment reasonably predicts the risk of chronic renal insufficiency. Chronic renal dysfunction can be observed, despite the maintenance of ciclosporin blood concentrations below 400 ng/ml. However, age, sustained hypertension, hypertriglyceridemia, low HDL cholesterol concentrations, and recurrent episodes of severe acute nephrotoxicity increase susceptibility to chronic ciclosporin nephrotoxicity (122,142).

From a prospective study in 36 heart transplant patients with stable renal function for at least 6 months after transplantation, it was suggested that high urinary retinol-binding protein concentrations may indicate tubulointerstitial damage and therefore detect patients who are at risk of ciclosporin nephrotoxicity (143). At the start of the study, 13 patients had high urinary retinol-binding protein concentrations and 23 had normal concentrations. After 5 years of follow-up, five of the 13 patients developed end-stage renal insufficiency requiring dialysis, whereas none of the 23 other patients had terminal renal insufficiency. Although these data await confirmation, the authors suggested that ciclosporin dosage reduction should be considered in patients with high urinary retinol-binding protein concentrations, in order to limit renal damage.

Ciclosporin can cause tubulointerstitial lesions, the pathogenesis of which is unclear. In 37 patients, the duration of ciclosporin treatment and of heavy proteinuria were independent risk factors for ciclosporin-induced tubulointerstitial disease (144).

Management

The possible risk of precipitating end-stage renal insufficiency should not be regarded as a major limitation to ciclosporin treatment in organ-transplant patients, and no matter how defective our knowledge of the susceptibility factors is, attempts must be made to prevent or manage ciclosporin nephrotoxicity. Delaying the introduction of ciclosporin until post-transplant renal function has returned to normal and reducing the dose of ciclosporin when increases in serum creatinine concentrations are more than 30% above baseline values are measures that may well reduce the risk of acute nephrotoxicity. In the long term, switching patients from ciclosporin to azathioprine, reducing ciclosporin doses, or even electively withdrawing ciclosporin have been suggested as helpful measures, but they should be regarded cautiously and set against the risk of rejection (145–149). Once-daily dosing of ciclosporin in the morning improves glomerular filtration rate and renal blood flow compared with half the dose taken twice daily (150). Despite evidence for a very similar profile of nephrotoxicity, conversion from ciclosporin to tacrolimus has been used successfully (SEDA-20, 347).

Finally, several drugs have been investigated in experimental and clinical studies to prevent ciclosporin nephrotoxicity. Calcium channel blockers, such as nifedipine, diltiazem, or verapamil, have repeatedly been proposed as reliable adjunctive drugs to minimize the long-term nephrotoxic effects of ciclosporin in renal transplant patients. Among anti-ischemic drugs, trimetazidine might be a good choice, because it prevents the loss of ATP synthesis caused by ciclosporin in rat kidney cells. S-15176 and S-16950 are trimetazidine derivatives that antagonize the mitochondrial toxicity of ciclosporin without changing its immunosuppressive effects.

Viewing the evidence as a whole, it appears that the use of lower doses of ciclosporin is probably the most important factor accounting for the fact that the majority of patients on long-term ciclosporin do not today have evidence of progressive nephrotoxicity.

Skin

Mild flushing often occurs during ciclosporin treatment, but more severe extensive erythema is uncommon.

- Recurrent episodes of diffuse flushing of the arms, the face, and the trunk reportedly occurred about 2 hours after each dose of ciclosporin in a 24-year-old man who had received a renal transplant 6 years before (151). These episodes were noted from the beginning of treatment, but worsened after he changed to Neoral, the microemulsion form of ciclosporin, and completely resolved after ciclosporin was replaced by tacrolimus.

Ciclosporin sometimes causes chronic inflammatory dermatitis, and there have been two reports of four male transplant recipients who developed clinical and histopathological features of keloid acne of the posterior scalp or neck (152,153). *Staphylococcus aureus* infection was identified in three. Ciclosporin-induced hypertrichosis was suggested as a possible cause, with local bacterial infection and immunosuppression as trigger factors.

- Multiple, large epidermoid cysts have been described in a 23-year-old man taking ciclosporin (154).

Acute generalized pustular psoriasis occurred 1 week after ciclosporin withdrawal in a 32-year-old woman

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who had taken ciclosporin for 12 weeks for chronic plaque psoriasis (155). This is in keeping with a similar phenomenon sometimes observed after glucocorticoid withdrawal.

Coarsening of facial features and a possibly more frequent occurrence of acne vulgaris and keratosis pilaris have been described in children taking ciclosporin (SED-8, 1125) (156). In 19 children who took ciclosporin and prednisone after renal transplantion, there was coarsening of facial features with thickening of the nares, lips, and ears, puffiness of the cheeks, prominence of the supraorbital ridges, and mandibular prognathism; this was found in all the children who had been treated for 6 months (157). Although the concurrent use of glucocorticoids may play a role in the development of acne, resolution of severe acne was in one reported case attained only after ciclosporin withdrawal (SEDA-20, 345). Convincing but anecdotal evidence of the worsening of subcutaneous sarcoidosis has been reported (SEDA-22, 384).

Sebaceous glands

Juxtaclavicular beaded lines are unique malformation of sebaceous glands or a variant of sebaceous hyperplasia.

- A 63-year-old man developed small, asymptomatic, linear papules over the neck and clavicles. He had taken prednisone and ciclosporin for 30 months after kidney transplantation (158). A skin biopsy showed sebaceous hyperplasia.

The pathogenesis of juxtaclavicular beaded lines is unclear. Some authors have reported a prevalence of 16% in heart transplant patients, but only in men. Because ciclosporin is highly lipophilic, it has many adverse effects associated with alterations of pilosebaceous follicles, such as hypertrichosis and acne. In this case the authors postulated that the combined effect of prednisone and ciclosporin may have induced sebaceous gland hyperplasia.

Hair

Widespread hypertrichosis is one of the most common complications of ciclosporin, and distichiasis (accessory eyelashes) has been reported in one patient (SEDA-20, 345). Ciclosporin-associated soft tissue proliferation with an abnormal hyperplastic reaction has been suggested to account for the development of hyperplastic pseudofolliculitis barbae (159).

Alopecia areata or alopecia totalis has been noted in isolated cases (SEDA-21, 384).

A white-headed man noted progressive darkening of the hair while taking ciclosporin (160).

Nails

Several nail changes (excess granulation tissue or ingrowing toenails) have been attributed to ciclosporin (SED-13, 1127).

- Marked pitting with Mees' lines (homogeneous transverse white lines in the nail plates) in the fingernails, a disorder that has not been previously reported, was attributed to ciclosporin-associated kidney dysfunction in a 41-year-old man who inadvertently took ciclosporin 300 mg/day for psoriasis (161).

Musculoskeletal

Muscle disorders attributed to ciclosporin have been mostly described in anecdotal case reports (SED-14, 1291). In an analysis of published or spontaneous case reports, the manufacturers found 29 cases of muscle disorders in patients taking ciclosporin; the complications fell into two categories (162). Myopathic symptoms, that is myalgia and muscle weakness without rhabdomyolysis, were reported in 0.17% of patients and abated after dose reduction or treatment withdrawal. Rhabdomyolysis occurred in under 0.05% of patients and was mostly observed in patients taking other drugs, such as lovastatin or colchicine.

This topic has been re-analysed in a systematic review of published papers, in which relevant information from a total of 34 patients was identified (163). All but two patients were also taking concomitant drugs known to affect the muscles, among which glucocorticoids, simvastatin, lovastatin, colchicine, and pyrazinamide were the most frequently cited. Ciclosporin is therefore difficult to implicate in most patients, but at least one case with positive ciclosporin re-administration supported a causative role. The clinical picture was non-specific, with myalgia, cramps, and muscle weakness, sometimes associated with raised serum creatine kinase activity, and heterogeneous histopathology. Finally, skeletal muscle abnormalities have rarely been described in patients without muscle symptoms.

Ciclosporin is increasingly cited as a possible cause of severe bone and joint pain (164). Acute bilateral deep bone pain, mostly involving the legs, has been retrospectively identified in 19% of patients taking ciclosporin, with the highest prevalence in renal transplant recipients (165). In addition, about half of the patients with osteonecrosis had a history of episodic bone pains. Another study showed features of acute bone marrow edema on MRI in six patients who had bone pain, including one patient who further developed avascular necrosis (SEDA-21, 385). Calcium channel blockers dramatically improved bone pain in prospectively evaluated transplant patients, suggesting a possible vascular etiology (165).

Osteopenia is another potential adverse effect after renal transplantation, but the possible contribution of ciclosporin to bone loss and subsequent osteoporosis is controversial (SEDA-19, 350) (SEDA-20, 345). Moreover, ciclosporin did not appear to have a negative influence on post-transplantation growth in prepubertal children (166).

Both ciclosporin and tacrolimus cause increased bone turnover and significant reductions in bone mass, more marked with tacrolimus (FK506). As most transplantation regimens include glucocorticoids, the individual effects of ciclosporin and tacrolimus are uncertain. As tacrolimus is the more potent immunosuppressant, theoretically, its use after transplantation should allow reduction in glucocorticoid doses, which would be associated with higher bone mineral density. Preliminary data suggest that there is a lower rate of vertebral fractures in patients taking tacrolimus compared with those taking ciclosporin. In 18 men who underwent liver transplantation and took ciclosporin and seven patients who took tacrolimus, bone mineral density in the lumbar spine and proximal femur was

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prospectively measured before and at 6, 12, and 24 months after transplantation (167). Serum concentrations of parathyroid hormone and 25-hydroxycolecalciferol were determined at the same time. Although the two groups had the same pattern of rapid early bone loss, tacrolimus was associated with lower doses of glucocorticoids and a trend to faster lumbar bone mass recovery. This may have a favorable effect on long-term bone mass evolution, especially in the femoral neck.

Reproductive system

Benign mammary hyperplasia occurs in 0.7% of women taking ciclosporin (168). The mechanism is poorly understood, but it may be related to trophic effects in the breast through ciclosporin receptors on fibroblasts (169), to an effect of ciclosporin on the hypothalamic-pituitary axis (170), or to antagonism at prolactin receptor sites on B and T (171,172).

Immunologic

Anaphylactoid reactions can occur with intravenous ciclosporin, sometimes after the first dose. Reported symptoms included pruritic rash, respiratory symptoms, chest pain, and, rarely, cardiopulmonary arrest. The presence of Cremophor EL, polyoxyethylated castor oil used as a solvent, is likely to account for this life-threatening reaction. The mechanism is still unclear, and results of skin tests were available in only three of 22 previously published patients.

In a report of an anaphylactic reaction, positive intradermal tests suggested a possible IgE-mediated reaction, most probably directed against Cremophor EL, as the patient subsequently tolerated the corn-oil-based soft gelatin formulation (173).

During a Phase I/II trial of high-dose intravenous ciclosporin, there was a high incidence of anaphylactoid reactions associated with improper mixing during preparation of the infusions, perhaps due to large initial bolus infusions of the vehicle, Cremophor EL (174).

Infection risk

Infections, in particular bacterial and viral (cytomegalovirus, *Herpes simplex* virus, Epstein–Barr virus), and also protozoal and fungal infections, are major causes of morbidity and mortality after transplantation, whatever the immunosuppressive regimen used (175–177). Based on an analysis of medical and autopsy records, infections were found to be the cause of death in 70% of transplant patients, with bacteria (50%) or fungi (29%) the most common pathogens (178).

Body temperature

Recurrent episodes of fever, which disappeared after ciclosporin withdrawal, have only been reported in one patient (SEDA-22, 414).

Long-Term Effects

Mutagenicity

An increase in chromosomal abnormalities correlated with serum ciclosporin concentrations in one study (179).

Tumorigenicity

Because of the varied indications for azathioprine and mercaptopurine, it is difficult to determine whether there is an increased incidence of cancer specifically related to prolonged drug exposure. Data from the Cincinnati Transplant Tumor Registry, published in 1993, helped to define comprehensively the characteristics of neoplasms observed in organ transplant recipients (180). Skin and lip cancers were the most common, and non-Hodgkin's lymphomas represent the majority of lymphoproliferative disorders, with an incidence some 30- to 50-fold higher than in controls. There is also an excess of Kaposi's sarcomas (181), carcinomas of the vulva and perineum, hepatobiliary tumors, various sarcomas, and renal cell carcinomas (182–184). In one case, complete regression of Kaposi's sarcoma followed withdrawal of ciclosporin (185). In contrast, the incidence of common neoplasms encountered in the general population is not increased. In renal transplant patients, the actuarial cumulative risk of cancer was 14–18% at 10 years and 40–50% at 20 years (186,187). Skin cancers accounted for about half of the cases. Very similar figures were found in later studies (SEDA-20, 341).

In patients with transplanted organs ciclosporin is associated with a small but significant risk of Epstein–Barr virus-associated lymphoproliferative disorders.

- A 39-year-old man with atopic eczema was given ciclosporin for an exacerbation, which responded well (188). After 2 years he developed a large ulcerated erythematous nodule, a CD30+ lymphoma of the skin. Ciclosporin was withdrawn and the lesion resolved within 2 months.

Of all transplant-related lymphomas 15% are of T cell origin and are unrelated to Epstein–Barr virus infection. Cutaneous T cell lymphomas are rare and carry a good prognosis, with a 90%, 4-year survival rate. Regression is often observed when immunosuppression is withdrawn or reduced.

While there is no doubt that the incidence of malignancies is increased in the transplant population, there has been controversy as to which factors (namely duration of treatment, total dosage, the degree of immunosuppression, or the type of immunosuppressive regimens) are the most relevant in determining risk. Partial or complete regression of lymphoproliferative disorders and Kaposi's sarcomas after reduction of immunosuppressive therapy argues strongly for the role of the degree of immunosuppression (180). The incidence of cancer was also significantly higher in renal transplant patients taking triple therapy regimens compared with dual therapy (189). Similarly, aggressive immunosuppressive therapy may account for the higher incidence of lymphomas in patients with cardiac versus renal allografts.

In a large, multicenter study in more than 52 000 kidney or heart transplant patients between 1983 and 1991, the rate of non-Hodgkin's lymphomas in the first post-transplantation year was 0.2% in kidney and 1.2% in heart recipients, and fell substantially thereafter

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(190). Initial immunosuppression with azathioprine and ciclosporin, and prophylactic treatment with antilymphocyte antibodies or muromonab was associated with a significantly increased incidence of non-Hodgkin's lymphomas compared with other immunosuppressive regimens, which confirmed the major role of the level of immunosuppression. Later studies confirmed that immunosuppression per se rather than a single agent is responsible for the increased risk of cancer (SEDA-20, 340). Finally, the most striking difference between conventional and modern immunosuppressive regimens, including ciclosporin, was the average time to the appearance of tumors, in particular skin cancers and lymphomas, which was shorter in ciclosporin-treated patients (191,192).

Multiple factors with complex interactions are involved in the observed pattern and increased incidence of neoplasms. They include severely depressed immunity with an impaired immune surveillance against various carcinogens, the activation of several oncogenic viruses, and a possible mutagenic effect of the drugs. Viruses, such as papillomavirus, cytomegalovirus, and Epstein–Barr virus, are believed to play an important role in the development of several post-transplant cancers. From a theoretical point of view, the use of antiviral drugs active against herpes viruses which are commonly implicated as co-factors can be expected to produce a reduction in the incidence of post-transplant lymphoproliferative disorders.

In an in vitro and in vivo experiment, ciclosporin promoted tumor growth by a direct cellular effect (193). This was suggested to be due to increased synthesis of transforming growth factor beta (TGF beta); anti-TGF beta antibodies blocked the increased spread of cancer cells. The clinical relevance of these data awaits further careful clinical confirmation. Continuing analysis of clinical experience has not provided clear evidence for a ciclosporin-specific effect and has instead supported an immunosuppressive effect (194).

Fibroadenomata are the most common solid breast masses in young women. Between 1997 and 2000, five women who had had transplant surgery and who were taking ciclosporin developed new breast masses, which were histologically confirmed to be fibroadenomata (195).

Ciclosporin-associated soft tissue proliferation with an abnormal hyperplastic reaction has been suggested to account for the development of eruptive angiomatosis (196).

Second-Generation Effects

Pregnancy

Pregnancies in women who took ciclosporin resulted in live neonates in 68%; half were premature while the other half were of low birth weights (197). Reduced renal graft function during pregnancy was associated with greater risks of neonates of lower birth weights and graft loss. In another study, a ciclosporin-based regimen was associated with more frequent miscarriage, preterm birth and intrauterine growth retardation, compared with previous experience (198).

It has been suggested that ciclosporin is more likely to induce maternal renal dysfunction or pre-eclampsia than tacrolimus, but this view was based on a comparison involving only a small number of patients (SEDA-22, 414).

Teratogenicity

Maternal azathioprine treatment during pregnancy is clearly teratogenic in animals, but the mechanisms are not known. A large number of reports have described the outcome of pregnancies following the use of immunosuppressant drugs, in particular in renal transplant patients, and hundreds of pregnancies have been analysed (199). The largest experience is that derived from the National Transplantation Pregnancy Registry which has been built up in the USA since 1991 (200). This registry has accumulated data on more than 900 pregnancies, of which 83% followed kidney transplantation and in this and other studies there was no difference in the rate of malformations when comparing ciclosporin with other immunosuppressive regimens (197,198,201). Ectopic pregnancies and miscarriages seemed to occur at a similar rate as in the general population. The most common complications were frequent prematurity and more frequent intrauterine growth retardation with low birthweight. Risk factors associated with adverse pregnancy outcomes included a short time interval between transplantation and pregnancy (that is less than 1–2 years), graft dysfunction before or during pregnancy, and hypertension (202).

There have been no reports that physical and mental development or renal function are altered. In one study, there were changes in T lymphocyte development in seven children born to mothers who had taken azathioprine or ciclosporin, but immune function assays were normal (203). Thus, development of the fetal immune system is not affected by ciclosporin (204).

Renal function in 14 children born to women with transplants treated throughout pregnancy with a ciclosporin-based regimen has been extensively investigated at a mean of 2.6 years after delivery (205). No renal function abnormalities were found. In particular, glomerular filtration rate was within the reference range. Renal function was found to be normal in 22 children evaluated after a mean of 39 months after birth (206), and no adverse effects on the immune function were identified in the few infants examined in this respect (203).

In a meta-analysis of the effects of exposure to ciclosporin during pregnancy, 15 studies (total 410 patients; 6 studies with control groups who were not given ciclosporin) met inclusion criteria for malformations, 10 for preterm delivery, and five for low birth weight (207). Ciclosporin did not appear to be a major human teratogen, but was associated with increased rates of prematurity.

Lactation

Ciclosporin is excreted into human breast milk and because of potential immunosuppression, breastfeeding is usually regarded as contraindicated. Reassuring reports are now however available (SEDA-21, 385). After follow-up for 12–36 months in seven breast-fed infants (duration 4–12 months) whose mothers were treated with ciclosporin, none of them experienced renal or other long-term adverse

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consequences (208). Although ciclosporin concentrations measured in breast milk from six mothers were close to those measured in blood samples, it was calculated that the infants ingested less than 300 μg/day, and ciclosporin was not detectable in random blood samples.

Drug Administration

Drug formulations

In an attempt to overcome the poor and unpredictable absorption of the standard oral formulation, a microemulsion-based formulation (Neoral) has been developed. The benefit-to-harm balance of conversion from the standard to the microemulsion formulation have been discussed at length and guidelines for conversion have been proposed (209).

From the results of a retrospective study of 227 liver transplant patients who took Neoral as the primary immunosuppressant, it was suggested that this formulation may reduce the risk of severe neurotoxicity (210). Mild-to-moderate symptoms, that is headache ($n = 24$), mild hand tremor ($n = 13$), and paresthesia ($n = 5$), were the most frequent, whereas generalized seizures were reported in only two patients.

In one large study in 1097 patients, there was a significantly higher incidence of neurological complications, gastrointestinal disturbances, and increased serum creatinine concentrations during the first month of treatment with Neoral, compared with conventional ciclosporin (211). However, a meta-analysis showed that the adverse events profile was similar with the two formulations, while primary immunosuppression with Neoral produced significant benefit in terms of a lower incidence of rejection (212). In particular, in liver transplant patients treated with Neoral from the start, the incidence of adverse events was halved. All the same, because dosage adjustments were often required and often hazardous, owing to the risk of adverse effects and transplant rejection, other investigators concluded that switching to Neoral may be of little benefit, at least in previously stable liver transplant patients (213).

As the data from this meta-analysis were subject to many potential biases, the same authors reanalysed their results, taking into account only randomized, prospective studies (214). The incidence of adverse effects was higher with Sandimmune in open-label studies (840 patients) and higher with Neoral in blinded studies (3006 patients). In accordance with other investigators, these authors concluded that de novo immunosuppression with Neoral is beneficial, without significant differences in the incidence of adverse effects, whereas conversion from Sandimmune to Neoral in previously stable patients is associated with significantly more adverse effects with Neoral.

Drug dosage regimens

Several authors were unable to find convincing evidence that ciclosporin specifically increases the risk of tumors in transplant patients compared with previously used immunosuppressive regimens, and some even suggested a possibly lower incidence in ciclosporin-treated patients (191,192,215). However, in analyses from Japan and France (3454 patients), the average time that elapsed until the occurrence of cancer was significantly shorter in patients treated with ciclosporin compared with those taking conventional immunosuppressive treatment, that is 43–452 months versus 92–96 months (216,217). In addition, French authors found a higher cumulative risk of cancer after 10 years in ciclosporin-treated patients (14 versus 8.4%), and this was mostly due to an increased incidence of skin carcinomas (216). Other significant risk factors included age, a shorter duration of pretransplant dialysis and the combination with azathioprine treatment. The occurrence of cancer in ciclosporin-treated patients is thought to be dose-related, and one study found a significantly higher frequency of cancer in the normal than in the low-dose group (218). These positive findings were limited by the more frequent occurrence of acute rejection in the low-dose group.

Long-term ciclosporin also carries the risk of malignancies in non-transplant patients, and the overall incidence of lymphoma was estimated to be 0.14% among 3700 patients treated for autoimmune disease (219). However, the available studies are again conflicting. They are mostly based on a limited number of patients or a short duration of follow-up. Patients with rheumatoid arthritis receiving ciclosporin had an increased relative risk of malignancies compared with those given glucocorticoids, but it was similar to the risk in patients treated with disease-modifying antirheumatic drugs (220). Another study showed no increased risk of malignancies in ciclosporin-treated patients compared with controls who had never received ciclosporin (221). The spontaneous occurrence of cancers unrelated to the treatment cannot be excluded, and an increased risk of lymphomas has been repeatedly found in patients with rheumatoid arthritis. In patients with psoriasis and as compared to the expected incidence rate of cancer in this population, the relative risk of malignancies was 5.6 (95% CI = 3.9, 8.0) in a cohort of 1223 ciclosporin-treated patients (222). This was comparable to the increased risk of cancer in patients treated with other immunosuppressants.

Drug overdose

Experience with ciclosporin overdose has been reviewed by the manufacturers using published data or cases spontaneously reported (223). Accidental overdose was the most common, with doses of 20–400 mg/kg. In adults, no serious clinical consequences were observed with doses up to 100 mg/kg, and there were only minor clinical or biological effects (transient hypertension, tachycardia, headache, gastrointestinal symptoms, or slight increases in serum creatinine concentrations). However, life-threatening reactions occurred in three neonates, of whom one died after severe metabolic acidosis and renal insufficiency. Subchronic ciclosporin overdose over 8 days did not appear to cause any additional risk (224).

Taken together, the available data suggest that the acute toxicity of ciclosporin is low in adults, but that more severe intoxication could be expected in neonates. However, two reports, including one fatal case, have shown that accidental intoxication sometimes produces severe complications in adults (225,226).

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- A 29-year-old man received a double lung transplantation for end-stage cystic fibrosis. After uneventful surgery, he was accidentally given ten times the intended dose of ciclosporin (30 instead of 3 mg/kg) and 18 hours later became anuric. His blood ciclosporin concentration was 4100 ng/ml. Hemodialysis was required for 6 weeks. A renal biopsy 7 weeks later showed typical features of acute tubular necrosis and lesions that resembled chronic nephrotoxicity. Renal function was still abnormal when he died from another cause 14 weeks after the accidental overdose.
- A 51-year-old man underwent double lung transplantation for pulmonary fibrosis, accidentally received an infusion of ciclosporin 30 mg/hour instead of 3 mg/hour, and 3 hours later had bilateral reactive mydriasis and absence of tendon reflexes. A CT brain scan showed diffuse cerebral edema, and massive intracranial hypertension rapidly developed. He died 5 hours later from brainstem compression, and pathological examination showed diffuse cerebral edema with neuronal necrosis.

The first of these cases suggested that acute renal dysfunction secondary to acute overdose can lead to renal sequelae. In the second patient, an isolated neurotoxic effect of ciclosporin was suggested because no predisposing factor except overdose was identified.

Drug–Drug Interactions

Acetazolamide

The interaction of ciclosporin with acetazolamide was previously supported by a single case report only. In three further patients, the addition of acetazolamide produced a near seven-fold increase in ciclosporin blood concentrations within 3 days (227).

Aciclovir

In an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, aciclovir altered ciclosporin pharmacokinetics (228).

The coadministration of ciclosporin with drugs with nephrotoxic effects carries a risk of increased renal dysfunction. Although a possible enhancement of nephrotoxicity has been suggested in patients also taking aciclovir (229), there were no such findings in a retrospective analysis of a double-blind study (230).

Aminoglycoside antibiotics

Severe nephrotoxicity has been reported in three renal transplant patients who received ciclosporin and gentamicin, and in others receiving both drugs before surgical procedures, even though toxic serum concentrations of either drug were not reached (231).

Angiotensin receptor blockers

In an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, losartan and valsartan altered ciclosporin pharmacokinetics (228).

Bisphosphonates

In an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, alendronic acid altered ciclosporin pharmacokinetics (228).

Calcium channel blockers

A large amount of data has accumulated on the effects of various calcium channel blockers on ciclosporin metabolism or a possible renal protective effect. Diltiazem, nicardipine, or verapamil inhibit ciclosporin metabolism, and this has been investigated as a potential beneficial combination for ciclosporin-sparing effects, particularly for diltiazem or verapamil (232,233). Any change in the formulation of calcium channel blockers in patients previously stabilized should be undertaken cautiously because unpredictable changes in ciclosporin concentrations can occur (234). In contrast, nifedipine, isradipine, or felodipine do not significantly affect ciclosporin pharmacokinetics (SED-13, 1129). Results obtained with amlodipine are conflicting; some studies have shown no effect, while others indicate an increase of up to 40% in ciclosporin blood concentrations (SEDA-19, 351) (SEDA-20, 345). Co-administration of calcium channel blockers is also regarded as a valuable option in the treatment of ciclosporin-induced hypertension, or to prevent ciclosporin nephrotoxicity.

There are conflicting results from studies on the protective role of calcium channel blockers in patients taking ciclosporin in regard to blood pressure and preservation of renal graft function. In a multicenter, randomized, placebo-controlled study in 131 de novo recipients of cadaveric renal allografts, lacidipine improved graft function from 1 year onwards, but had no effect on acute rejection rate, trough blood ciclosporin concentrations, blood pressure, number of antihypertensive drugs, hospitalization rate, or rate of adverse events (235).

The combination of ciclosporin with nifedipine produces an additive on gingival hyperplasia, with an increased prevalence and/or severity (SED-13, 1127) in both children (77,81) and adults (76,80,82). In contrast, verapamil had no significant additional effects on the prevalence or severity of ciclosporin-induced gingival overgrowth (SEDA-21, 385).

Chloramphenicol

Chloramphenicol was suspected of causing a dramatic increase in ciclosporin blood concentrations in a single patient (236). However, multiple concomitant confounding factors made this interaction purely speculative.

Clindamycin

In two lung-transplant patients aged 39 and 48 years, blood ciclosporin concentrations fell after the addition of oral clindamycin (1.8 g/day), and both patients required temporary increases in daily ciclosporin dose until clindamycin withdrawal (237).

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Colchicine

The combination of colchicine with ciclosporin increased the risk of myopathy. In a retrospective study of 221 renal transplant patients, five of 10 patients who took both drugs developed acute or chronic proximal myopathy, whereas none of the 30 controls matched for age, sex, transplant duration, ciclosporin use, and cumulative dose of glucocorticoids had similar symptoms (238).

Cytotoxic drugs

High-dose chemotherapy with cyclophosphamide, vincristine, prednisolone, and intrathecal methotrexate given for post-transplant lymphoproliferative disease was suggested to have favored the occurrence of acute ciclosporin neurotoxicity (headache, fever, seizures, and visual agnosia) in a 9-year-old cardiac transplant patient (239). Ciclosporin serum concentrations were normal and a further similar episode occurred on ciclosporin readministration.

In 27 patients, ciclosporin caused a marked increase in the AUC of idarubicin and its main metabolite idarubicinol, perhaps due to inhibition of the multidrug transporter P-glycoprotein (240).

There was a dramatic increase in the systemic availability of paclitaxel when ciclosporin was administered concomitantly (241) and in a phase I study of the pharmacokinetics of twice-daily oral paclitaxel 60–160 mg/m^2 in 15 patients in combination with ciclosporin (15 mg/kg) there was a seven-fold increase in the systemic exposure to paclitaxel; the plasma concentration increased from negligible to therapeutic concentrations (242). The inhibitory effect of ciclosporin on the gastrointestinal multidrug transporter P-glycoprotein was suggested to account for these interactions.

Several studies have shown that ciclosporin reduces the clearance or increases the AUC of dactinomycin, etoposide, mitoxantrone, and vincristine (5,243).

Digoxin

In an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, digoxin increased ciclosporin systemic availability (228).

Doxorubicin

High-dose ciclosporin increased the AUC of doxorubicin and doxorubicinol and produced greater doxorubicin-related myelotoxicity (244).

Fibrates

A possible synergistic risk of muscle disorders should be considered in patients taking ciclosporin with fibric acid derivatives (SEDA-19, 351).

Fluoroquinolones

Although ciprofloxacin was initially thought to increase ciclosporin blood concentrations and enhance ciclosporin nephrotoxicity, no definite evidence to support this interaction has been found (245). A norfloxacin-induced increase in ciclosporin blood concentrations has been reported in children (5,246), while ofloxacin did not appear to alter ciclosporin metabolism (247).

Foscarnet

Foscarnet (248), but not ganciclovir (249), has also been involved in reversible renal insufficiency after concomitant use with ciclosporin.

Grapefruit juice

Following the observation that grapefruit juice ingestion can increase the systemic bioavailability of ciclosporin, there was considerable interest in its possible use to reduce ciclosporin doses (SEDA-19, 351). However, this has been strongly criticized and considered hazardous because of large interindividual variability and the commercial availability of different formulations of grapefruit juice with potentially different effects on ciclosporin pharmacokinetics (250).

Histamine H_2 receptor antagonists

The available data on a possible interaction between histamine H_2 receptor antagonists and ciclosporin are inconclusive. Whereas neither cimetidine nor ranitidine significantly altered ciclosporin pharmacokinetics, there was an increase in serum creatinine concentration in patients taking both ciclosporin and cimetidine, but not ranitidine. The clinical significance of this interaction is probably limited, and it has been attributed to competition of cimetidine with creatinine for tubular secretion (251).

HMG-CoA reductase inhibitors

Dosages of statins should be reduced in patients taking ciclosporin, because of pharmacodynamic and pharmacokinetic interactions.

Pharmacodynamic interactions

Patients taking ciclosporin with conventional dosages of lovastatin or simvastatin can develop acute muscle toxicity (SED-14, 1296) (SEDA-19, 351). Among 110 ciclosporin-treated patients with heart transplants, four of 18 patients taking simvastatin 20 mg/day developed rhabdomyolysis, whereas none of the patients taking simvastatin 10 mg/day (26 patients) or pravastatin 20 mg/day (66 patients) had similar symptoms (252). Inhibition of CYP3A by ciclosporin was the most likely mechanism. In another study, there was a five-fold higher AUC of lovastatin (10 mg/day for 10 days) in 16 patients taking ciclosporin compared with 13 patients not taking ciclosporin (253).

- The addition of atorvastatin (10 mg/day) to a multidrug regimen including ciclosporin in a 40-year-old patient with a renal transplant resulted in rhabdomyolysis within 2 months (254).

Similar interactions are expected with other HMG-CoA reductase inhibitors such as cerivastatin and rosuvastatin.

Pharmacokinetic interactions

Plasma concentrations of lovastatin- or simvastatin-active metabolites were increased in several patients and in a

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pharmacokinetic study, suggesting that ciclosporin can inhibit their metabolism (255–257). Lower doses of lovastatin and simvastatin can be safely administered (258). Fluvastatin or pravastatin may offer some advantages, as no significant drug interactions have been documented with ciclosporin, at least for pravastatin (259).

From an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, atorvastatin, fluvastatin, pravastatin, and simvastatin were found to affect ciclosporin pharmacokinetics (228).

In a study of the safety and efficacy of simvastatin in hyperlipidemia after renal transplantation in 15 patients, the C_{max} and AUC of simvastatin were increased seven-fold by ciclosporin (260). In contrast, in 17 patients, tacrolimus had no effect. Although there were no complications, such as myopathy or rhabdomyolysis, creatine kinase activity must be monitored during co-administration of simvastatin and ciclosporin.

Ciclosporin produced a three- to five-fold increase in the plasma concentrations of cerivastatin and its metabolites in 12 patients with renal transplants who took cerivastatin 0.2 mg/day for 7 days compared with a single dose in 12 healthy controls (261).

Hypericum perforatum (St. John's wort)

Hypericum perforatum (St. John's wort), which is used for mild depression, is an inducer of cytochrome P-450. It caused a rapid dramatic fall in ciclosporin blood concentrations, resulting in acute heart transplant rejection in two patients aged 61 and 63 years (262). It produces an average 50% reduction in ciclosporin blood concentrations (263). At least three other case reports have clearly confirmed that St. John's wort is dangerous in transplant patients, because it produced a rapid and dramatic reduction in blood ciclosporin concentration and resulted in acute organ rejection in two patients (264–266). Induction of CYP3A4 and/or P-glycoprotein was the most likely mechanism.

- A 44-year-old black woman with a living-related renal transplant had an acute rejection within 3 months and was given muromonab but was from then on stable. She was later given oral ciclosporin (Neoral 2 mg/kg bd), mycophenolate mofetil 1000 mg bd, and prednisolone 7.5 mg/day. Over 6 months her ciclosporin blood concentrations were consistently below the target concentration of 200 ng/ml. It was then discovered that she had also been taking 2–3 tablets/day of St. John's wort (Your Life, Leiner Health Products, Carson CA, 300 mg standardized to 0.3% hypericin). The St. John's wort was withdrawn and her blood ciclosporin concentrations reached the target within 2 weeks.
- A 29-year-old white woman with cadaveric kidney and pancreas transplants had two early rejection episodes but then stabilized on ciclosporin 100 mg bd and prednisolone 5 mg/day. Her blood ciclosporin concentration was consistently 200–350 ng/ml. She then started to take St. John's wort and over the next 30 days her blood ciclosporin concentration fell to 155 ng/ml and 3 weeks later to 97 ng/ml. Her serum creatinine rose to 1.3 mg/dl (115 μmol/l) and her serum amylase rose from a baseline of 60–90 to 314 U/l; this was associated with abdominal pain. Renal biopsy confirmed acute rejection, which was treated. She subsequently developed chronic rejection, confirmed by renal biopsy.

Imidazoles

Among the imidazole derivatives, numerous case reports or studies have shown that ketoconazole, fluconazole, and itraconazole can inhibit ciclosporin metabolism and increase blood ciclosporin concentrations (267). Ketoconazole, which is undoubtedly the most potent inhibitor, has been used to reduce the dose, and therefore the cost or adverse effects, of ciclosporin (268–270). There was also a beneficial effect on the rate of rejection or infection. In contrast, interactions with metronidazole and miconazole have only been described in isolated case histories (SEDA-19, 351) (5).

In a double-blind, randomized, placebo-controlled study in renal transplant patients taking ciclosporin, voriconazole increased the mean ciclosporin AUC 1.7-fold (271). The authors therefore recommend halving the dose of ciclosporin in these patients and carefully monitoring ciclosporin blood concentrations.

Imipenem/cilastatin

In contrast to what has previously been stated, there was no significant increase in the frequency of seizures among 77 patients with bone marrow transplants who were taking ciclosporin alone (three seizures), 45 patients taking ciclosporin plus imipenem/cilastatin (two seizures), and 44 patients taking imipenem/cilastatin alone (no seizures) (272).

Inducers, inhibitors, or substrates of 3A

Ciclosporin is absorbed to a variable extent from the gastrointestinal tract and almost completely metabolized in both the liver and small intestine by CYP3A, which metabolizes a large number of drugs. Inducers, inhibitors, or substrates of CYP3A therefore have the potential to interact with ciclosporin. In addition, ciclosporin has wide pharmacokinetic variability and a narrow therapeutic index. Conversely, ciclosporin can inhibit the hepatic metabolism of other drugs that share the same CYP3A metabolic pathway.

Drugs that increase the systemic availability of ciclosporin do not always have negative effects, and several ciclosporin-sparing agents have indeed been used for the purpose of improving efficacy while reducing the cost of treatment. However, use of such combinations should be balanced against their potential risks (273).

Table 1 lists drugs that have proven or possible clinically relevant drug interactions with ciclosporin.

Macrolide antibiotics

Erythromycin increases ciclosporin blood concentrations, and increased serum creatinine concentrations have been consistently demonstrated; isolated reports have also suggested possible interactions with clarithromycin, josamycin, midecamycin, or pristinamycin (SEDA-21, 385) (274). A two-fold increase in ciclosporin concentrations has been

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Table 1 A summary of major interactions with ciclosporin

Pharmacokinetic	Pharmacodynamic
Anticonvulsants	**Increased risk of nephrotoxicity**
Carbamazepine*	ACE inhibitors
Phenobarbital*	Aciclovir (see text)
Phenytoin*	Aminoglycosides
Primidone*	Amphotericin
Antidepressants	Co-trimoxazole
Fluoxetine (unproven; see text)	Diuretics
Fluvoxamine	Foscarnet (see text)
Nefazodone	Melphalan
St. John's wort	Nafcillin (see text)
Antimicrobial drugs	NSAIDs (unproven, see text)
Antifungal drugs	**Increased risk of muscle toxicity (see text)**
Ketoconazole, fluconazole, itraconazole, metronidazole	Colchicine
Chloramphenicol (unproven)	Fibric acid derivatives
Clindamycin*	HMG CoA reductase inhibitors (statins)
Fluoroquinolones	Pyrazinamide (SEDA-20, 346)
Griseofulvin*	**Increased risk of gingival hyperplasia**
Macrolides or related drugs (see text)	Nifedipine
Clarithromycin, erythromycin, josamycin, midecamycin, miocamycin, pristinamycin	**Increased risk of neurotoxicity**
Protease inhibitors	Imipenem/cilastatin
Ritonavir, saquinavir	**Increased risk of hepatotoxicity**
Pyrazinamide*	Androgens
Quinupristin/dalfopristin (SEDA-21, 386)	Norethandrolone, oxymetholone
Rifamycins*	Parenteral nutrition (see text)
Sulfadiazine*	**Increased risk of hyperkalemia**
Terbinafine* (SEDA-21, 386)	Potassium salts
Cardiovascular drugs	Potassium-sparing diuretics
Amiodarone	
Calcium channel blockers	
Amlodipine, diltiazem, nicardipine, verapamil	
Carvedilol (SEDA-22, 415)	
Clonidine	
Propafenone	
Hypoglycemic drugs	
Glibenclamide	
Glipizide	
Troglitazone*	
Miscellaneous drugs	
Acetazolamide	
Allopurinol	
Bezafibrate	
Bile acid resin*	
Chloroquine	
Danazol	
Glucocorticoids	
Grapefruit juice	
Modafinil*	
Muromonab (SEDA-21, 386)	
Octreotide*	
Oral contraceptives (unproven)	
Orlistat*	
Probucol*	
Sulfasalazine*	
Sulfinpyrazone*	
Tacrolimus	
Ticlopidine*	
Vitamin E (water-soluble) (SEDA-20, 346)	

*These drugs reportedly reduce ciclosporin blood concentrations; the rest increase them

reported in patients receiving miocamycin. In contrast, spiramycin or roxithromycin did not significantly affect ciclosporin concentrations, and a single report involving azithromycin (SEDA-19, 351) was not substantiated by several prospective studies.

Mycophenolate mofetil

The interaction of ciclosporin with mycophenolate mofetil was investigated in 52 renal transplant patients taking triple therapy (ciclosporin, mycophenolate mofetil, and prednisone), who continued taking the same treatment ($n = 19$) or underwent elective ciclosporin withdrawal ($n = 19$) or prednisolone withdrawal ($n = 14$) 6 months after transplantation (275). Median mycophenolate mofetil trough concentrations 3 months later were about two-fold higher in patients who had discontinued ciclosporin compared with patients who continued to take triple therapy and patients who had discontinued prednisone. No clear mechanism readily explains these changes.

Nefazodone

Nefazodone can alter blood ciclosporin concentrations (276,277). In one case there was nearly a 10-fold increase in whole-blood ciclosporin concentrations in a cardiac transplant patient shortly after the addition of nefazodone (278).

NSAIDs

Based on the theoretical possibility of additive nephrotoxic effects, the combined use of NSAIDs with ciclosporin is expected to reduce renal function and therefore to increase ciclosporin-induced nephrotoxicity.

- In an 8-year-old girl with rheumatoid arthritis, the combination of ciclosporin with NSAIDs (indometacin and diclofenac) was suggested to have caused biopsy-proven, non-specific colitis, because her symptoms occurred only when the combination was used (279).

From several studies performed in healthy volunteers, repeated doses of diclofenac, aspirin, indometacin, or piroxicam did not significantly alter ciclosporin single-dose pharmacokinetics, but the AUC of diclofenac was increased by ciclosporin (280). In a further study of 20 patients with rheumatoid arthritis who took ciclosporin for 4 weeks, there was a two-fold increase in diclofenac AUC, and a small but significant increase in serum creatinine concentrations (281). Changes in renal function were easily managed by dosage titration of both drugs. In another study of 32 patients who received a 4-week course of paracetamol, indometacin, ketoprofen, or sulindac, changes in the calculated creatinine clearance were minimal (282). There were no striking differences among different NSAIDs. Taken together, the results of these studies and previous findings suggested that the clinical relevance of this interaction is limited.

Orlistat

Orlistat reduces plasma ciclosporin concentrations.

- A 29-year-old woman with increased body weight after renal transplantation was unable to adhere to a low-fat

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diet and took orlistat, which gave her severe diarrhea (283). Her plasma ciclosporin concentrations fell to subtherapeutic, even though she took the orlistat 2 hours before the ciclosporin and even though the daily dose of orlistat was reduced to 240 mg/day.
- There was a two-fold reduction in blood ciclosporin concentrations 2 weeks after orlistat was given to a 61-year-old patient with a heart transplant (284).

The FDA has received six reports of subtherapeutic blood ciclosporin concentrations soon after transplant recipients started to take orlistat (285). Reduced absorption of ciclosporin is the most likely mechanism (286,287) by reduction in fat absorption rather than by a direct drug–drug interaction.

Oxycodone

In an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, oxycodone reduced ciclosporin systemic availability (228).

Parenteral nutrition

Cholestasis from other causes can increase the accumulation of ciclosporin or its metabolites, which in turn worsens hepatic cholestasis. This mechanism has been suggested in patients with bowel diseases who experienced an aggravation of hyperbilirubinemia or an increased incidence of hepatotoxicity from the combination of total parenteral nutrition and ciclosporin (SEDA-19, 348) (288).

Protease inhibitors

Interactions of ciclosporin with protease inhibitors should be expected, particularly with ritonavir, a potent inhibitor of CYP3A.

- Despite a prophylactic reduction in the dose of ciclosporin (100 mg/day) before antiretroviral treatment, a 40-year-old woman had an acute increase in ciclosporin trough concentrations (over 1000 ng/ml) and serum creatinine concentration (from 84 to 228 μmol/l) after taking zidovudine (600 mg/day), saquinavir (800 mg/day), and ritonavir (800 mg/day) for 11 days (289). Despite ciclosporin withdrawal, ciclosporin and creatinine blood concentrations remained high for over 10 days until triple drug therapy was withdrawn. Ritonavir was the most likely suspect.

Proton pump inhibitors

Conflicting data have emerged on the interaction of omeprazole with ciclosporin, with isolated case reports suggesting that omeprazole can increase or reduce ciclosporin concentrations, whereas no effect of omeprazole was demonstrated in a controlled trial (290–292).

Quinidine

In an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, digoxin increased ciclosporin systemic availability (228).

Saquinavir

A reciprocal interaction between ciclosporin and saquinavir has been reported in an HIV-positive kidney transplant patient (293). Whereas ciclosporin concentrations were previously acceptable, there was a three-fold increase in ciclosporin trough concentrations after 3 days of saquinavir (3600 mg/day). In addition, the saquinavir AUC was four times higher than that usually observed in patients taking similar dosages.

Selective serotonin reuptake inhibitors

Fluvoxamine and fluoxetine have been involved in isolated cases of increased blood ciclosporin concentrations, but fluoxetine was not confirmed to affect ciclosporin concentrations significantly in 13 patients (SEDA-20, 345) (SEDA-22, 385–386). In an analysis of changes in ciclosporin clearance and systemic availability obtained from the medical records of 100 transplant patients, sertraline altered ciclosporin pharmacokinetics (228).

Sulfasalazine

In a 51-year-old woman with a renal transplant who had been stable for the past 13.5 months with ciclosporin (9.6 mg/kg) and sulfasalazine (1.5 g/day) for ulcerative colitis, sulfasalazine withdrawal resulted in an almost two-fold increase in ciclosporin blood concentrations over the next 10 days (294).

Sulfinpyrazone

In 120 heart transplant patients, sulfinpyrazone (200 mg/day) for ciclosporin-associated hyperuricemia was associated with lowered blood ciclosporin concentrations despite an increase in the daily dose (295). The authors cited evidence (296) that sulfinpyrazone induces ciclosporin metabolism.

Sulfonylureas

Both glipizide and glibenclamide increase ciclosporin concentrations significantly (297).

Ticlopidine

Although there was no interaction between ciclosporin and ticlopidine in a pharmacokinetic study, a 64-year-old patient with a renal transplant had a reduction in the concentration:dose ratio of ciclosporin after each of two successive courses of ticlopidine (298).

Troglitazone

Case reports and a retrospective evaluation of seven renal transplant patients showed that troglitazone can increase ciclosporin metabolism with a subsequent reduction of 15–45% in ciclosporin trough concentrations (299). The interaction of ciclosporin with troglitazone has been confirmed in four heart transplant patients with a 30–60% fall in ciclosporin concentrations within days of taking troglitazone 200 mg/day (300).

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Monitoring Therapy

Ciclosporin pharmacokinetics vary considerably between patients, and even in an individual patient from time to time, with changes in the clinical condition and treatment, particularly with administration of other drugs (301). Inadequate exposure to ciclosporin is a key factor in acute rejection and contributes to the development of chronic rejection and graft failure. Monitoring of ciclosporin concentrations is widely adopted as an accurate and practical measure of drug exposure (302).

In an open, randomized, parallel-group study in 307 patients, ciclosporin blood concentrations measured 2 hours after a dose were compared with conventional trough ciclosporin blood concentrations (303). The traditional predose blood concentration did not correlate well with drug exposure, and the 2-hour concentration was superior in preventing acute rejection. This is important, because data derived from the database of the United Network for Organ Sharing Scientific Liver Transplant Registry has shown that moderate and more severe grades of rejection are associated with poor graft function and outcome in liver transplant recipients.

Of 53 bone marrow transplant recipients in whom ciclosporin was used to suppress graft-versus-host disease, 63% developed acute nephrotoxicity (304). These patients had significantly higher plasma ciclosporin concentrations during the first month after transplantation than those who did not develop acute nephrotoxicity, even though they received the same cumulative dose. Children received a higher cumulative dose, but their plasma concentrations did not differ significantly from the adults, and they suffered less nephrotoxicity.

Although a correlation between early post-transplantation whole-blood concentrations of ciclosporin and the occurrence of ciclosporin-induced toxicity has been suggested, blood concentrations in most patients are in the target range, and the identification of patients susceptible to adverse effects has yet to be achieved (305).

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Cidofovir

General Information

Cidofovir (*S*-1-3-hydroxy-2-phosphonylmethoxypropylcytosine), also known as HPMPC, is a nucleotide analogue with potent activity against cytomegalovirus (CMV) in vitro and in vivo.

Observational studies

Cidofovir has been used to treat 14 patients with cytomegalovirus infection after stem-cell transplantation; no adverse effects were reported in this small study (1).

In an open study of the use of intralesional cidofovir in treating laryngeal papilloma, 14 adults received monthly injections of cidofovir (maximum dose 37.5 mg per injection in 6 ml of saline; mean 22.5 mg) (2). Remission was achieved in all cases with an average of six injections and without additional laryngeal scarring, vocal cord damage, or systemic adverse effects.

Organs and Systems

Sensory systems

In a placebo-controlled study of the efficacy of cidofovir 1% eye-drops with and without ciclosporin 1% eye-drops four or ten times a day for acute adenovirus keratoconjunctivitis in 34 patients, the frequency of severe corneal opacities was lower with cidofovir (3). However, cidofovir caused conjunctival pseudomembranes, conjunctivitis, and erythematous inflammation of the skin of the eyelids, and the trial was stopped as a result.

Two cases of iritis shortly after intravenous administration of cidofovir have been reported (4). Intravitreal administration of cidofovir delays the progression of CMV retinitis, but can be associated with reduced intraocular pressure or vitreitis (5). In two cases the drug association with the iritis was demonstrated by withdrawal and rechallenge (6). These patients had also taken probenecid, but it is not clear whether or not that was involved. The evidence is that in such cases the cidofovir should be withdrawn; treatment should be with a mydriatic and glucocorticoids.

In a study of compassionate use of intravenous cidofovir in AIDS patients with CMV retinitis, iritis developed in 21 of 51 individuals (7). The appearance of this inflammatory process did not fit the characteristics of the vitritis associated with immune reconstitution, or with HIV-induced vitritis. The high rate in this cohort (compared with a 5–7% incidence in randomized trials) was associated with severe CMV retinitis, and the authors suggested that breakdown of the blood–ocular barrier in these patients may promote higher intraocular concentrations of cidofovir and thus enhance local toxicity. Previous correlations of prior use of HIV protease inhibitors with iritis were not confirmed in this study, although patients with iritis had better immunological and virological status than those without the disease.

Uveitis (8) and cystoid macular edema (9) are recognized risks associated with cidofovir treatment for cytomegalovirus retinitis. The latter is almost certainly an immune recovery phenomenon, since it is apparently encountered only in eyes with inactive CMV retinitis; the unaffected contralateral side never develops cystoid macular edema. The time range of appearance (3–48 weeks after administration) also makes a direct toxic effect of cidofovir unlikely.

In a retrospective record review of 18 HIV-infected patients (30 eyes) who were being treated with intravenous cidofovir for complicated cytomegalovirus retinitis, eight patients developed anterior uveitis after a median of four (range 2–8) doses of cidofovir or a median of 55 (20–131) days after the start of therapy (10). While they were receiving treatment with cidofovir, none of the patients showed any evidence of progression of CMV retinitis. Five of the eight had symptoms of photophobia and blurred vision at the onset of uveitis, and the other three were asymptomatic. There was no difference in the use of HIV-1 protease inhibitors between the patients who did or did not develop anterior uveitis. Baseline intraocular pressure measurements were available for 11/18 patients. With the introduction of cidofovir there was a fall in mean intraocular pressure, and a trend for this fall to be more pronounced in those who developed anterior uveitis. Withdrawal of cidofovir was necessary in only one patient, after which all symptoms and signs disappeared and vision returned to baseline within 1 month. In two of the seven other patients, cidofovir had to be withdrawn because of nephrotoxicity. In the other five patients, cidofovir was continued and the uveitis was controlled with topical therapy, consisting of corticosteroids with or without a cycloplegic agent.

During long-term follow-up of patients with AIDS treated with parenteral cidofovir for CMV retinitis, the median time to discontinuation for intolerance was 6.6 months (11). Cidofovir-associated uveitis occurred in 10 of 58 patients and ocular hypotony (a 50% fall in intraocular pressure from baseline to below 5 mmHg) occurred at a rate of 0.16 per person-year. There were 51 episodes of proteinuria in 30 of the 58 patients and 82% of these episodes resolved on withdrawal (median time to resolution 20 days). No nephrotoxic events required dialysis.

Urinary tract

The main adverse effect associated with intravenous cidofovir is renal tubular damage (12), although it is usually mild. However, cases of acute renal insufficiency leading to end-stage disease have been reported (13,14). Acute renal insufficiency has also been attributed to topical cidofovir (15).

- A 28-year-old bone marrow transplant recipient with chronic renal insufficiency developed genital condylomata resistant to standard therapy. After application of topical cidofovir (1% daily for 5 days, then 4% for 12 days) the lesions improved but local erosions appeared. He developed acute renal insufficiency with features of tubular acidosis on day 19. He recovered after cidofovir withdrawal.

It was not clear whether this effect was due to the cidofovir or to its vehicle, propylene glycol. The authors suggested that topical cidofovir should be avoided on abraded skin and should be carefully monitored.

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The risk of renal toxicity was higher in patients with established CMV infections than in those who were taking it prophylactically, and there was no relation between dosage and nephrotoxicity; toxicity occurred early in therapy, usually within the first 3 weeks (16). Proteinuria seems to be an early indicator of this adverse effect. Other laboratory abnormalities associated with nephrotoxicity are glycosuria, reduced serum phosphate, uric acid, and bicarbonate, and an increased serum creatinine. Serious and potentially irreversible nephrotoxicity can generally be prevented by the concomitant administration of intravenous saline and oral probenecid, monitoring the blood and urine immediately before each infusion of cidofovir, and withdrawing the drug for low-threshold increases in either urinary protein or serum creatinine concentrations (17). Concomitant use of other nephrotoxic drugs should be avoided.

In a rare cytomegalovirus comparison trial, a ganciclovir insert (an intraocular implant) plus oral ganciclovir was compared with intravenous cidofovir (18). Based on data from 61 patients (the trial was stopped early owing to low recruitment), cidofovir was associated with a raised serum creatinine concentration of 142 μmol/l (1.6 mg/dl) or greater (0.48 per person-year), 3+ or greater proteinuria (0.29 per person-year), uveitis (0.35 per person-year), and neutropenia (0.11 per person-year).

Prophylactic cidofovir treatment for CMV antigenemia has been investigated in a prospective study in patients with transplants (19). Renal toxicity, occasionally with proteinuria, was reported, as was nausea. The renal toxicity was mild and reversible.

Susceptibility Factors

Renal disease

The pharmacokinetics of cidofovir were studied in 24 subjects with varying degrees of renal insufficiency, who were given a single intravenous dose of cidofovir 0.5 mg/kg over 1 hour (20). Those who were not receiving dialysis were given intravenous hydration and concomitant oral probenecid. Mean cidofovir clearance in control subjects (normal renal function; $n = 5$) was 1.7 ml/minute/kg, and this fell markedly with falling renal function. The mean steady-state volume of distribution did not change significantly in those with kidney disease, but the half-life of cidofovir was significantly prolonged in those with severe renal insufficiency. Cidofovir was not significantly cleared during continuous ambulatory peritoneal dialysis, but high-flux hemodialysis resulted in the removal of 52% of the dose. The authors concluded that very considerable aggressive dosage reduction of cidofovir would be necessary in subjects with kidney disease to ensure comparable drug exposure in terms of serum concentrations.

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Cilazapril

See also Angiotensin converting enzyme inhibitors

General Information

Cilazapril is a non-sulfhydryl ACE inhibitor (1). Like enalapril and ramipril it is a prodrug and is hydrolysed after absorption to cilazaprilat, which has a long half-life allowing once-daily administration (2).

Organs and Systems

Skin

Many cases of pemphigus have been reported with ACE inhibitors, related to the amide group they contain. This is the case for cilazapril.

- A 69-year-old white woman developed skin lesions of pemphigus foliaceus after she had taken cilazapril for 3 months; they resolved on withdrawal and the addition of prednisone and azathioprine (3).
- Pemphigus vulgaris possibly triggered by cilazapril has been reported (4).

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Cilostazol

General Information

Cilostazol is a phosphodiesterase inhibitor that suppresses platelet aggregation and also acts as a direct arterial vasodilator. Small studies in Japan suggested that it might be useful for treating chronic arterial disease and symptoms of intermittent claudication. A trial in 81 patients with claudication substantiated this claim: claudication distance was improved by 35% for initial and 41% for absolute claudication distance.

Placebo-controlled studies

The efficacy and safety data of cilostazol in placebo-controlled clinical trials have been repeatedly subjected to meta-analysis, with the same conclusion (1,2). Cilostazol is well tolerated; headache, bowel complaints, and palpitation are the most common but mild adverse effects.

Six multicenter placebo-controlled trials have been conducted in the USA (3,4). They involved more than 2000 patients with intermittent claudication and established the efficacy of cilostazol in improving walking distance in these patients.

Cilostazol was approved by the FDA in January 1999 for the treatment of symptoms of intermittent claudication; from 1984 to 1999 pentoxifylline was the only drug approved in the USA for this indication. The two drugs have been compared with placebo in a large, randomized, double-blind, placebo-controlled trial (5). After 24 weeks of treatment the mean increase in maximal walking distance was 54% with cilostazol and only 30% with pentoxifylline and 34% with placebo. Headache, diarrhea, abnormal stools, and bouts of palpitation were significantly more common with cilostazol. They were reported as generally mild to moderate and self-limiting and have been previously recognized as being related to cilostazol.

The efficacy of antithrombotic prophylaxis with cilostazol for the secondary prevention of cerebral infarction has been studied in a Japanese, placebo-controlled trial in 1095 patients (6). There was a 42% relative risk reduction compared with placebo. As in the trials in patients with peripheral arterial disease, mild to moderate headache and palpitation were the most commonly observed symptomatic adverse events attributed to cilostazol; they respectively occurred in 13 and 5.3%. Headache with cilostazol is attributed to cerebral vasodilatation induced by relaxation of vascular smooth muscle.

In another placebo-controlled trial, there were gastrointestinal complaints in 44% of the cilostazol-treated patients and in 15% of the placebo group. The most commonly reported adverse effects included diarrhea, loose stools, flatulence, and nausea; they were usually mild and transient but persisted in some patients. Headache occurred in 20% of cilostazol-treated patients but also in 15% of those given placebo (7).

Safety data relating to the use of cilostazol in 2702 patients who participated in eight USA–UK placebo-controlled trials have been re-analysed (8). The most frequently recorded adverse events were headache (32%), diarrhea (17%), and abnormal stools (14%).

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Palpitation, tachycardia, and dizziness were additional events that occurred more often in cilostazol-treated patients and were considered to be probably related to treatment. Headache led to withdrawal of cilostazol in 3.5% of patients, and palpitation and diarrhea led to withdrawal in another 1%. All adverse events quickly resolved after withdrawal. Cardiovascular and all-cause mortality were similar with cilostazol and placebo.

Organs and Systems

Cardiovascular

Ventricular tachycardia has been reported during cilostazol therapy (9).

- A 92-year-old woman developed sudden runs of ventricular tachycardia, a few days after she started to take cilostazol because of subacute leg ischemia. She was known to have atrial fibrillation and intraventricular conduction delay. The runs did not respond to empirical magnesium therapy but subsided shortly after withdrawal of cilostazol.

The phosphodiesterase III inhibitors have no known direct dysrhythmogenic effects. However, the authors speculated that raised concentrations of cAMP may have contributed to the ventricular tachycardia, mainly because ventricular dysrhythmias have been mentioned with other agents of the same family in patients with heart failure. Whether some populations are particularly vulnerable is unknown.

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Cimetidine

See also Histamine H_2 receptor antagonists

General Information

Cimetidine is a histamine H_2 receptor antagonist.

General adverse effects

The main varieties of adverse effects attributed to cimetidine relate to its antiandrogenic properties and its actions in sufficient concentrations on the central nervous system. There is also a spectrum of drug interactions, mainly attributable to inhibition of hepatic CYP isoforms, but they only have clinical consequences under special circumstances. Occasional adverse effects, which are generally minor, include bradycardia and conduction defects, thrombocytopenia, neutropenia, interstitial nephritis, mild hepatic dysfunction, and headache. Intestinal infection due to loss of the gastric acid barrier also occurs, and myalgia, fever, monoamine oxidase-like interactions, and neuropathies have been well documented occasionally. Allergic reactions, such as bronchospasm, have rarely been described. Anaphylaxis with recurrence on rechallenge is on record, as are asthma and skin effects.

Organs and Systems

Cardiovascular

Rapid infusion of cimetidine causes an increase in plasma histamine concentration, and this could be one reason for its cardiac effects. A marked degree of bradycardia (for example a 30% reduction in heart rate) is uncommon although well recognized (SEDA-17, 417); sinoatrial and atrioventricular conduction effects and dysrhythmias of every possible type have occasionally been noted, particularly after infusion but also with oral therapy. It has been suggested that if a patient is particularly at risk (for example because of poor renal function) the electrocardiogram should be monitored (SEDA-15, 394).

Symptoms of vasodilatation have been attributed to cimetidine (1).

- A 31-year-old white man taking maintenance hemodialysis had frequent episodes of hot flushes, sweating, palpitation, and dizziness, which started after about 1 month of treatment with cimetidine 400 mg/day. When the drug was temporarily discontinued and later when it was totally withdrawn, he noted marked improvement in 2–5 days.

Respiratory

Bronchospasm is occasionally reported, reflecting the possibility of allergy to cimetidine, and the need for some caution with its initial use in any patient with

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asthma (SEDA-15, 394). In pre-existing atopic asthma, H_2 receptor antagonists can enhance bronchial reactivity (SEDA-16, 421). Central nervous system effects can lead to respiratory depression, although this is rare.

Loss of the gastric acid barrier can predispose to intestinal infection, and pulmonary aspiration of infected gastrointestinal secretions can very occasionally cause pneumonia after anesthesia or during intensive care (2). Interstitial lung disease can occur under these conditions.

Nervous system

Cimetidine crosses the blood–brain barrier and its adverse events include central respiratory depression and extrapyramidal and cerebellar disturbances. There have been convincing isolated reports of choreiform movements (3,4).

Severe central neurological problems are not common with cimetidine. In one intensive survey of nearly 10 000 patients followed for 3 months there were only five cases of confusion, though there were 34 with sensations of dizziness, 23 with headache, and 74 with other milder central nervous effects (5). The overall incidence of adverse neurological effects reported to the US public health authorities (which naturally represent only a small proportion of those that actually occur) was 8.6 per million prescriptions for cimetidine and virtually the same for ranitidine. Healthy elderly people are probably not at particular risk.

Occasionally, neuropathies have been documented (6). The fear that cimetidine or ranitidine might increase the incidence of motor neuron disease was raised in the light of case-control work, but seems to have been allayed by data from the Oxford Record Linkage Study published in 1993 (7).

A dystonic reaction has been attributed to cimetidine (8).

- A 39-year-old woman developed a dystonic reaction (masseter spasm, lip smacking, oculogyric crisis, and mild neck spasm) within 5 minutes of intravenous administration of cimetidine 300 mg for epigastric pain. She had epilepsy and had not taken her antiepileptic medication regularly. She had developed a similar dystonic reaction to prochlorperazine 1 week before. She recovered within 5 minutes of treatment with intravenous diphenhydramine and lorazepam.

Psychological, psychiatric

Cimetidine crosses the blood–brain barrier and can cause confusion, particularly in elderly or sick individuals with compromised hepatic or renal function, and especially after intravenous treatment. Very rarely an acute confusional psychosis has been seen in a younger person (9). Delirium has been thought to be a particular problem with intravenous use, but this is more likely to be a reflection of patient selection. Depression has occasionally been attributed to cimetidine (10,11).

Metabolism

In the earlier years of cimetidine use there were scattered (although well-documented) reports of the drug having destabilized severe diabetes, resulting in impaired control (12); however, most people with diabetes are unlikely to be affected.

Modest increases in serum high-density lipoproteins have occasionally been noted in patients taking cimetidine (SED-12, 942) (13).

Hematologic

There was concern during the first years of cimetidine therapy that it might produce severe blood dyscrasias, but most of those that have been described have occurred in patients who were already severely ill or exposed to other toxic influences (SED-12, 942) (SEDA-15, 394).

Thrombocytopenia has been attributed to cimetidine, with recurrence on rechallenge, and neutropenia has also been documented as an occasional adverse effect, possibly related to inhibition of granulocyte colony growth (SEDA-10, 325). These effects appear to occur with all H_2 receptor antagonists in an incidence roughly proportional to their sales. Exceptionally, thrombocytopenia and leukopenia have occurred together (SEDA-17, 417). In one case of pancytopenia there was cimetidine dose-related inhibition of normal human CFU-GM colon formation (SEDA-16, 422).

Mouth and teeth

Parotitis with positive rechallenge has been documented in one case (14).

Gastrointestinal

An early concern was the possibility that H_2 receptor antagonists could predispose to gastric carcinogenesis, but this seems to have been allayed, as was the fear once expressed that ulcers might be more liable to perforate after cimetidine had been given and withdrawn.

Liver

The rate of acute liver injury due to cimetidine 800 mg/day in the UK has been estimated at over 10 per 100 000 users. The increased risk was seen mainly in the first 2 months of use. The risks of liver injury due to ranitidine and omeprazole were much lower (SEDA-22, 391) (15).

Cimetidine has rarely been reported to cause hepatic encephalopathy.

- Cimetidine-induced hyperammoniacal encephalopathy has been reported in a previously healthy 44-year-old man who had taken cimetidine 400 mg/day for 4 days; he recovered completely after drug withdrawal (16).

Pancreas

Pancreatitis has several times been suggested as a complication of treatment (17), but this is unconfirmed.

Urinary tract

Minor rises in serum creatinine concentrations reflect interference with tubular function; this seems to be clinically unimportant and fully reversible. There were two early reports of reversible acute renal insufficiency, one of them with positive rechallenge and a biopsy finding of interstitial infiltrates of inflammatory cells (18).

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Skin

Allergic skin reactions to cimetidine include urticaria (19), exfoliative dermatitis (20), and the various forms of erythema multiforme (21–23).

Several cases of psoriasis have been precipitated or aggravated by cimetidine, and ranitidine has the same rare effect (24).

Xerosis and asteatotic dermatitis are among the rare cutaneous effects that can occur with cimetidine; they may be of antiandrogenic origin (25).

Hair

A possibly unique case of alopecia affecting the entire body was described in 1981; in that case the temporal association was convincing and there was a correlation with an antiandrogenic effect on hormone concentrations (26).

Musculoskeletal

A small proportion of patients develop troublesome myalgia when taking cimetidine (27). There have been incidental reports of polymyositis and a form of myopathy probably of motor neuron origin. Myalgia can also be associated with arthritis and joint effusion, but this is extremely unusual (SED-12, 942) (28).

Sexual function

Mild antiandrogenic properties, which are dose-related, are associated with binding of cimetidine to androgen receptors. Reduced sperm counts have been reported, as have modestly raised serum prolactin levels after intravenous treatment (SEDA-9, 313). Some slight degree of male breast enlargement is not uncommon (for example in one series of 25 men, five had it) (29), but it can regress with continued treatment; it is very rarely massive and unilateral; there is no strict parallel between the effects on the breasts and the blood prolactin concentration. In 81 535 men aged 25–84 years, the relative risk of gynecomastia among users of cimetidine compared with non-users was 7.2. The period of maximum risk lay between the 7th and the 12th months of treatment (SEDA-19, 313).

Erectile impotence has been suggested in the light of some case experiences; this type of effect is always difficult to prove but it has been described repeatedly with various H_2 receptor antagonists.

One well-documented case suggested that in an infant girl reversible premature puberty was induced, but it must be noted that domperidone was also being given (SEDA-15, 394); in another instance an 18-month-old infant had marked enlargement of one breast (SEDA-16, 421–422), but this is probably similar to the effect sometimes seen in adult men rather than a true endocrine effect.

Body temperature

Fever is occasionally noted with cimetidine (30).

Long-Term Effects

Drug withdrawal

A complex neurobehavioral and gastroenteric withdrawal syndrome has been seen with both cimetidine and ranitidine. The characteristics included anxiety, sleeplessness, anorexia with weight loss, irritability, tachycardia, diarrhea, nausea and vomiting, abdominal pain, headache, and vertigo. The syndrome virtually disappeared when the drugs were given again, but reappeared when they were withdrawn once more. The syndrome may be related to a fall in prolactin concentrations; it responded well to domperidone (31).

Susceptibility Factors

Age

Neurological adverse effects are more likely to occur in elderly patients with impaired hepatic or renal function.

Sex

It has been suggested that women with spinal cord injuries may be at increased risk of galactorrhea due to H_2 receptor antagonists, since such injuries can themselves cause galactorrhea (SEDA-17, 417).

Drug–Drug Interactions

General

The many drug interactions described with cimetidine are largely attributable to inhibition of CYP isozymes or renal clearance of other drugs. Cimetidine also reduces hepatic blood flow and so can, for example, reduce the clearance of lidocaine. In the kidneys cimetidine interferes with the tubular excretion of procainamide and quinidine. Both effects are small, and the long list of drugs for which interference is demonstrable (Table 1) is out of all proportion to the number for which interference is of clinical significance.

Table 1 Groups of drugs interacting with cimetidine

Drug	Effect	References
Analgesics		
Methadone	Potentiation	(32)
Anticoagulants		
Acenocoumarol	Potentiation	(33,34)
Phenindione	Potentiation	(33)
Warfarin	Potentiation	(35,36)
Antiepileptic drugs		
Carbamazepine	Transient rise in concentrations	(37,38)
Phenytoin	Increased steady-state concentrations Small reduction in to clearance	(39)
Valproate		(40)
Antidepressants		
Tricyclics		
Amitriptyline	Reduced metabolism	(41)

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Drug	Effect	References
Desipramine	Reduced metabolism in extensive hydroxylators	(42)
Doxepin	Reduced metabolism	(43)
Imipramine	Reduced metabolism	(44,45)
Nortriptyline	Reduced metabolism	(45)
SSRIs		
Fluoxetine	Parkinsonism	(46)
Paroxetine	Reduced metabolism	(47)
Antidysrhythmic drugs		
Cifenline	Increased serum concentrations	(48)
Encainide	Increased serum concentrations	(49)
Flecainide	Increased serum concentrations	(50)
Lidocaine	Toxic concentrations	(51)
Moracizine	Reduced metabolism	(52)
Procainamide	Increased plasma concentrations	(53)
Quinidine	Increased plasma concentrations	(54,55)
Tocainide	Reduced oral systemic availability	(56)
Anti-inflammatory to drugs		
Indometacin	Reduced serum concentrations	(57)
Benzodiazepines		
Adinazolam	Increased plasma concentrations	(58)
Alprazolam	Increased plasma concentrations	(59,60)
Chlordiazepoxide	Increased plasma concentrations	(61)
Clobazam	Increased plasma concentrations	(62)
Clorazepate	Prolonged elimination	(63)
Diazepam	Increased plasma concentrations	(64,65)
Flurazepam	Increased plasma concentrations	(66)
Nitrazepam	Increased plasma concentrations	(67)
Triazolam	Increased plasma concentrations	(59,60)
Beta-blockers		
Atenolol	Slightly prolonged half-life	(68)
Labetalol	Increased systemic availability; toxicity	(69,70)
	Increased plasma concentrations	
Metoprolol	Increased plasma concentrations	(71)
Propranolol		(72)
Bronchodilators		
Theophylline	Increased plasma concentrations; toxicity	(73,74)
Calcium channel blockers		
Diltiazem	Increased plasma concentrations	(75)
Felodipine	Increased plasma concentrations	(76)
Nifedipine	Increased plasma concentrations	(77)
Nimodipine	Increased systemic availability	(78)
Nisoldipine	Increased systemic availability	(79)
Nitrendipine	Increased systemic availability	(80)
Verapamil	Increased systemic availability	(81)
	Reduced clearance	(82)
Cytotoxic drugs		
Fluorouracil	Increased plasma concentrations	(83)
	Increased antiproliferative effect	(84)
Diuretics		
Furosemide	Increased AUC	(85)
Hypoglycemic drugs		
Gliclazide	Hypoglycemia	(86)
Immunosuppressants		
Ciclosporin	Increased plasma concentrations; toxicity	(87)
Neuromuscular blockers		
Suxamethonium	Delayed recovery (not confirmed)	(88,89)
Vecuronium	Delayed recovery	(90,91)

In most cases the slowing of the metabolism of other drugs, by a third at most, is only likely to be troublesome for drugs with a narrow margin between the therapeutic and toxic dose, such as theophylline, phenytoin, and warfarin; the clearance of theophylline may be reduced by up to 22% and the half-life increased by 50% (SEDA-16, 421).

Alcohol

Cimetidine slightly reduces the rate of metabolism of alcohol and alters its absorption (92–94), but it is doubtful if these effects are clinically significant.

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Cimetropium bromide

See also Anticholinergic drugs

General Information

Cimetropium bromide is an anticholinergic drug that belongs to a series of scopolamine quaternary salts with strong antimuscarinic effects (1).

Reference

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Cinchocaine

See also Local anesthetics

General Information

Cinchocaine (dibucaine) is an aminoamide local anesthetic. It is ten times more potent than lidocaine and potentially very toxic. It is available in a number of over-the-counter topical formulations, such as antihemorrhoidal drugs.

Organs and Systems

Nervous system

Low concentrations of cinchocaine (0.003 and 0.03% respectively) caused irreversible neurotoxicity in A_β and C rabbit vagus nerve preparations (1). Cinchocaine had the greatest neurotoxic effect and the lowest safety margin compared with tetracaine and bupivacaine.

Cauda equina syndrome has been reported after a spinal anesthetic using cinchocaine (2).

- A 64-year-old man with a history of borderline diabetes who had undergone two previous operations uneventfully under spinal anesthetic received a spinal anesthetic with hyperbaric 0.24% dibucaine 2.2 ml and then a general anesthetic because of unilateral block. The next day he complained of difficulty in defecation and urination, with abnormal anal sensation. A diagnosis of cauda equina syndrome was made. He made a gradual recovery, but mild hypesthesia remained after 4 months.

A possible cause for this adverse event may have been maldistribution in the intrathecal space of the high concentration of cinchocaine, affecting the cauda equina and resulting in nerve damage; the incomplete block achieved in this case is suggestive of this. Elderly patients undergoing urological surgery often have risk factors for cauda equina syndrome, such as intraoperative lithotomy position, frequent spinal anesthetics, old age, and diabetes mellitus. The authors suggested that cinchocaine should be avoided for spinal anesthesia in these patients, because of its high neurotoxicity compared with other local anesthetics.

Hematologic

Cinchocaine inhibits ADP-mediated platelet aggregation (3); it is not known whether this has any clinical significance.

Skin

Two cases of contact dermatitis have been reported after the use of Proctosedyl and Ruscens Llorens, both of which contain cinchocaine. After patch testing, the first case was found to be allergic in origin and the second was due to photosensitivity. Neither showed cross-sensitivity to other local anesthetics (4).

Two cases of allergic contact dermatitis have been described after the use of cinchocaine formulations.

- A 71-year-old Japanese man, who was using an over-the-counter formulation, Makiron, for minor wounds, developed an itchy rash with seropapules and erosions on his right leg at the site of application (5). Makiron contains 0.1% cinchocaine hydrochloride and chlorphenamine maleate as well as naphazoline hydrochloride and benzethonium chloride. On patch testing, he was positive to both chlorphenamine and cinchocaine.
- A 79-year-old man presented with a 10-day history of weeping dermatitis affecting the perianal skin, buttocks, and proximal thighs (6). He had used Proctosedyl ointment topically for the preceding 3 weeks. Proctosedyl is an over-the-counter topical formulation for use as an antihemorrhoidal agent. It contains cinchocaine 5%, hydrocortisone, and lanolin. Patch testing was strongly positive to cinchocaine.

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The authors highlighted the potential limitations of the International Contact Dermatitis Research Group (ICDRG) standard series for topical anesthetics. Benzocaine is the only topical anesthetic in the series and it will not detect contact allergy to amide agents; cross-sensitivity can also exist. They suggested that patch testing should include agents from both groups.

DoloPosterine N is an ointment for topical application in the treatment of hemorrhoids. Its active ingredient is cinchocaine. Although cinchocaine is a known contact sensitizer, as described above, systemic contact dermatitis is rare.

- A 62-year-old woman, who had applied DoloPosterine N ointment topically to the perianal skin and rectal mucosa for several days, developed erythematous vesicular lesions in the perianal area and an erythematous edematous rash of the face, axillae, elbow flexures, and inner thighs (7). This abated on withdrawal of the drug and the administration of oral prednisolone for 10 days. Patch testing was positive with cinchocaine.

Immunologic

An anaphylactic reaction to cinchocaine has been described.

- A 71-year-old man received intrathecal anesthesia using 0.3% cinchocaine 2 ml for a transurethral prostatectomy (8). He had a history of allergic rhinitis, and 2 months before had had an uneventful prostate biopsy and cystoscopy, also under spinal anesthesia with isobaric bupivacaine. Within 45 minutes of the spinal injection he complained of periorbital itching, started to shake, and developed muscle rigidity. He rapidly became unconscious, with a systolic blood pressure of 40 mmHg and widespread erythema. He was treated with hydrocortisone and antihistamines and required an infusion of adrenaline. Intradermal testing after full recovery was positive with cinchocaine.

Death

Three deaths after seizures and cardiac arrest have been reported in toddlers who accidentally ingested small amounts of cinchocaine (SEDA-21, 135).

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Cinchophen

General Information

Cinchophen is a uricosuric drug that was formerly used in the treatment of gout (1). In 1991 the Spanish authorities withdrew cinchophen. It had been known for some time that it can cause severe hepatitis (SEDA-17, 114).

Reference

1. Cutrin Prieto C, Nieto Pol E, Batalla Eiras A, Casal Iglesias L, Perez Becerra E, Lorenzo Zuniga V. Hepatitis toxica por cincofeno: descripcion de tres enfermos. [Toxic hepatitis from cinchophen: report of 3 cases.] Med-Clin-(Barc). 1991;97(3):104–6.

Cinmetacin

See also Non-steroidal anti-inflammatory drugs

General Information

Cinmetacin is an NSAID related to indometacin. There has been little experience with its use. In one study, gastrointestinal adverse effects developed in 13 of 30 patients (1).

Reference

1. Lucietti MV, Banchieri G. Studio clinico sulla efficacia e tollerabilita di un nuovo antiflogistico non-steroideo, la cinmetacina. [Clinical study of the efficacy of and tolerance for a new nonsteroidal anti-inflammatory agent, cinmetacin.] G Clin Med 1980;61(7):545–52.

Cinnarizine and flunarizine

See also Antihistamines

General Information

Cinnarizine and flunarizine are piperazine derivatives with antihistaminic properties and calcium channel blocking activity (SEDA-13, 131) (SEDA-14, 136) (SEDA-22, 178). Flunarizine is the difluoro derivative of cinnarizine. Cinnarizine is used to treat motion sickness.

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A few controlled clinical trials of flunarizine in patients with intermittent claudication have suggested significant improvements in subjective signs and some objective measurements. Its effectiveness in patients with cerebrovascular insufficiency has not been clearly shown, but its use in the prevention of migraine and other forms of common headache has been studied extensively. Several double-blind controlled studies have suggested that flunarizine in a dosage not over 10 mg/day reduces the frequency of headaches (SEDA-11, 179). Clinical studies of the antiepileptic efficacy of flunarizine have been equivocal (SEDA-20, 191).

With a maintenance dosage of 10 mg/day, the main adverse effects of flunarizine are somnolence, sedation, fatigue, and drowsiness during the first few days in up to 10% of patients. During prolonged treatment some patients note difficulty in sleeping, lethargy, and reduced motivation. A dosage of 20 mg/day or more can cause drowsiness, increased sweating, peripheral edema, and fatigue (SEDA-7, 229).

Organs and Systems

Nervous system

A study in young volunteers has established the effects of cinnarizine 15–45 mg on daytime sleepiness and performance (1). Doses of 30 mg or more caused impaired performance and increased sleepiness. The authors therefore advised that cinnarizine should not be used in aircrew involved in tasks that demand attention.

Insomnia has been described with cinnarizine (SEDA-22, 178).

Blepharospasm has been attributed to flunarizine in an elderly woman (SEDA-22, 178).

Extrapyramidal adverse effects

Several reports have described extrapyramidal reactions and depression associated with the use of cinnarizine and flunarizine (SEDA-14, 136) and worsening of motility in parkinsonian patients (SEDA-13, 391).

In a Spanish study there were 70 reports of tremor and parkinsonism in patients taking cinnarizine and 11 reports of tremor and parkinsonism in patients taking flunarizine (2).

In a Brazilian study carried out to establish whether there are geographic differences in the cause of parkinsonism, the diagnosis of drug-induced parkinsonism was made in 45 of 338 patients (3). Cinnarizine and flunarizine were two of the three most commonly prescribed drugs.

In a retrospective study in 74 patients with cinnarizine-induced parkinsonism over 15 years, cinnarizine-induced parkinsonism was more frequent in women; most of the patients (66/74) recovered completely within 16 months after withdrawal (4). This suggests that cinnarizine-induced parkinsonism is reversible in most cases, but there is still a question of whether cinnarizine predisposes to permanent Parkinson's disease in a few patients. Cinnarizine-induced parkinsonism is a warning against prolonged use of an apparently harmless drug, especially in elderly people.

Parkinsonism, tardive dyskinesia, and depression have been described in some mostly elderly patients taking flunarizine (SEDA-12, 170) (SEDA-13, 169) (SEDA-14, 167) (SEDA-15, 198). These symptoms are resistant to anticholinergic drugs, levodopa, and bromocriptine, but regress within a few weeks to months after withdrawal of flunarizine; however, mild rigidity and bradykinesia persist in some patients. The recommended dosage of 10 mg/day should never be exceeded, and in elderly patients dosages higher than 5 mg/day can lead to an increased risk of extrapyramidal symptoms. Patients who take flunarizine to prevent migraine are usually some 25–30 years younger than those with cerebrovascular and peripheral vascular disease and appear to be at less risk of developing extrapyramidal symptoms with flunarizine (5).

Liver

Drug-induced cholestasis has rarely been reported in patients taking cinnarizine.

- An 87-year-old man took cinnarizine 75 mg/day for tinnitus and developed jaundice 7 weeks later, with dark urine and pale stools (6). He had taken no other drugs. Bile duct obstruction was ruled out and serological tests for viral hepatitis were negative. A liver biopsy 6 weeks later showed distinct centrilobular cholestasis and a slight lymphocytic infiltrate. He recovered completely and the liver tests were normal after another 3 months without cinnarizine. Rechallenge was not performed.

Skin

Various skin lesions have been attributed to cinnarizine and flunarizine.

- A 32-year-old woman developed subacute cutaneous lupus erythematosus after exposure to the sun while taking cinnarizine and thiethylperazine for vertigo (7). A similar eruption had occurred 10 years before, after exposure to the sun, while she was taking cinnarizine only. The problem did not occur when she was not taking the drug.
- A 78-year-old woman developed generalized lichen pemphigoides while taking cinnarizine (225 mg/day) and recovered after withdrawal of the drug and anti-inflammatory drug treatment (8).
- A lichen planus pemphigoides-like eruption following the use of cinnarizine has been reported in a Japanese woman (SEDA-11, 146).

Immunologic

Subacute cutaneous lupus erythematosus has been attributed to cinnarizine.

- A 32-year-old woman developed an erythematous, papulosquamous, annular, polycyclic skin eruption on her neck, trunk, and lateral parts of the limbs after sunbathing while taking cinnarizine and thiethylperazine (a phenothiazine) for vertigo. She had positive antinuclear antibodies (nucleolar pattern, anti-Ro/SSA). The lesions cleared without residual scars within a few weeks after stopping both drugs and starting steroids and chloroquine.

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Phenothiazines can induce photosensitivity, but cinnarizine does not. The authors' arguments that cinnarizine was to blame in this case were its structural resemblance to piperazine and a similar episode of skin eruption in the same patient after sunbathing many years before while she was taking cinnarizine only but for which she did not seek medical advice (7).

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Ciprofloxacin

See also Fluoroquinolones

General Information

Ciprofloxacin is a fluoroquinolone antibacterial drug with a wider spectrum of activity than nalidixic acid.

Observational studies

Antimicrobial prophylaxis to prevent inhalational anthrax has been recommended for people potentially exposed to *Bacillus anthracis* as a result of recent bioterrorist attacks. Of 3428 people taking ciprofloxacin, 666 (19%) reported severe nausea, vomiting, diarrhea, or abdominal pain; 484 (14%) reported fainting, lightheadedness, or dizziness; 250 (7%) reported heartburn or acid reflux; and 216 (6%) reported rashes, hives, or an itchy skin. Of those taking ciprofloxacin, 287 (8%) stopped taking it, 116 (3%) because of adverse events, 27 (1%) because of fear of possible adverse events, and 28 (1%) because they "did not think it was needed" (1–4).

The imaging of inflammation/infection with ^{99m}Tm-labeled ciprofloxacin in 96 patients had a sensitivity of 81% and specificity of 87%. The positive and negative predictive values were 90 and 75% respectively. No adverse effects were reported (5).

Comparative studies

In a multicenter, double-blind study of 234 patients with acute bacterial exacerbations of chronic bronchitis, ciprofloxacin (500 mg bd) was associated with a trend toward a longer infection-free interval and a significantly higher bacteriological eradication rate compared with clarithromycin (500 mg bd) after 14 days (6).

In a double-blind study, ciprofloxacin (500 mg bd) was associated with an infection-free interval and clinical response that were similar to those achieved with cefuroxime axetil (500 mg bd), but the bacteriological eradication rate associated with ciprofloxacin was significantly higher (7).

Organs and Systems

Cardiovascular

Ciprofloxacin causes prolongation of the QT interval (8,9).

Nervous system

Headache was recorded in 8% of patients taking ciprofloxacin (10)

Ciprofloxacin can cause confusion and general seizures (11,12).

Ciprofloxacin can cause facial dyskinesia (13,14).

Two cases of generalized painful dysesthesia associated with ciprofloxacin have been reported (15).

Sensory systems

Eyes

Bilateral acute visual loss, possibly due to toxic optic neuropathy, was observed after 4 weeks of treatment with ciprofloxacin 1.5 g/day and improved after withdrawal (16).

Ciprofloxacin 0.3% ophthalmic drops can cause microprecipitates of pure ciprofloxacin in the corneal epithelium (17). In four corneal transplantation patients treated preoperatively with ciprofloxacin 0.3% ophthalmic drops, there were microprecipitates associated with damaged corneal epithelium in two patients; another developed a macroprecipitate in a corneal ulcer (18). The crystalline precipitates were pure ciprofloxacin.

Ears

Topical 0.2% ciprofloxacin (0.2 ml od for 7 days) did not significantly affect the auditory brainstem response thresholds of guinea pigs, whereas 4% gentamicin (0.2 ml od for 7 days) resulted in total hearing loss (19).

Topical 0.2% ciprofloxacin solution was effective and well tolerated in 232 patients with chronic suppurative otitis media; the most frequently reported adverse events were pruritus, stinging, and earache. Audiometric tests did not show changes attributable to ciprofloxacin (20).

In children with tympanic membrane perforation, topical ciprofloxacin caused no signs of local intolerance or

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ototoxicity and did not result in significant serum concentrations (21).

Psychological, psychiatric

The administration of ciprofloxacin has been associated with psychosis (22,23) and hypoactive delirium (24,25).

- A 27-year-old woman developed an acute psychotic reaction following the use of ciprofloxacin eye-drops (1 drop hourly to each eye) (26).

Hematologic

Ciprofloxacin has been associated with hemolysis in combination with a severe skin reaction in a young adult (27).

Fatal ciprofloxacin-associated thrombotic thrombocytopenic purpura (28) and thrombocytopenia (29) have been reported.

Gastrointestinal

In a randomized, double-blind comparison of prulifloxacin 600 mg/day and ciprofloxacin 500 mg bd in 235 patients with acute exacerbations of chronic bronchitis, the most common treatment-related adverse event was gastric pain of mild or moderate intensity, reported in 8.5% of the patients taking prulifloxacin and 6.8% of those taking ciprofloxacin (30).

Ciprofloxacin has been associated with diarrhea due to *Clostridium difficile* (31–33). In 27 patients the only significant risk factor for nosocomial *C. difficile*-associated diarrhea was the use of ciprofloxacin (34).

Liver

Ciprofloxacin causes a mild reversible rise in liver enzymes in 2–3% of patients. Acute hepatitis is rare, but has been reported in a 32-year-old man (35).

Pancreas

A report has suggested that ciprofloxacin can cause pancreatitis (36).

Urinary tract

Two cases of acute renal insufficiency due to necrotizing vasculitis associated with ciprofloxacin were reported in elderly patients (37). In two patients who underwent high-dose chemotherapy with autologous stem cell rescue, acute renal insufficiency developed while they were taking prophylactic ciprofloxacin; withdrawal resulted in prompt reversal of renal insufficiency (38). Ciprofloxacin-induced acute renal insufficiency has been reported in cancer patients undergoing high-dose chemotherapy and autologous stem cell rescue (38). A case report has suggested that ciprofloxacin overdose can lead to acute renal insufficiency characterized by acute tubular necrosis with distal nephron apoptosis (39).

- An 18-year-old woman with cystic fibrosis had pronounced impairment of renal function after taking oral ciprofloxacin 750 mg tds (30 mg/kg/day) for 3 weeks; withdrawal led to normalization of renal function within 10 days (40).

Hemolytic-uremic syndrome has been attributed to ciprofloxacin (41).

- A 53-year-old white man was given chemotherapy for acute lymphoblastic leukemia and after 4 weeks recovered his blood cell count but developed a fever and was given oral ciprofloxacin 500 mg bd. After four doses he developed the typical features of hemolytic–uremic syndrome with microangiopathic hemolytic anemia. The ciprofloxacin was withdrawn, and he received five sessions of plasma exchange. He recovered completely.

Bilateral hydronephrosis and acute renal insufficiency due to urinary tract stones predominantly composed of ciprofloxacin has been reported (42).

Skin

Ciprofloxacin can cause a fixed drug eruption (43,44), purpuric skin lesions (44,45), bullous pemphigoid (46), cutaneous vasculitis (45–47), and ultraviolet recall-like phenomenon (48).

Musculoskeletal

Tendinopathy

Ciprofloxacin can be associated with partial or complete tendinitis. Of 72 lung transplant recipients who received ciprofloxacin, 20 had Achilles tendon involvement (tendinitis 15, rupture 5) (49). Tendon rupture occurred at a lower dosage of ciprofloxacin than tendinitis and the mean recovery duration was significantly longer.

- Achilles tendon rupture without any sudden pain occurred in a 45-year-old female runner who developed bilateral tendinopathy of the Achilles tendon after repeated treatment with ciprofloxacin; histological analysis showed cystic changes with focal necrosis (50).

Arthropathy

The available data suggest that the incidence of arthrotoxicity in children taking ciprofloxacin is the same as in adults; the use of other fluoroquinolones is too rare to obtain clear information about the risks in children (51). In 12 children with sickle cell disease treated successfully for acute osteomyelitis with oral ciprofloxacin, transient bilateral Achilles tendon tendinitis occurred in one 5-year old (52). Another case was reported in a hemodialysis patient with a ciprofloxacin-associated Achilles tendon rupture (53).

In 75 children with typhoid fever, aged under 6 years (mean age 32 months), ciprofloxacin had no adverse effects on growth or joints (54). In another study only 2 of 219 children treated with ciprofloxacin developed arthropathy, in one case transiently (55). In a necropsy study on children treated with ciprofloxacin 20–40 mg/kg/day for an average of 148 days, there were no chondrotoxic effects; however, synovial membranes showed signs of subacute synovitis, which had not been noted in life (56).

Data on more than 1500 children treated with ciprofloxacin suggest that the safety profile of ciprofloxacin in children and adolescents is similar to the profile in adults (57). Adverse events, mostly involving the gastrointestinal tract, were noted in 5–15% of patients. Reversible

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arthralgia occurred in 36 of 1113 patients, but there was no radiographic evidence of cartilage damage.

An acute reversible arthropathy has been described in a child with cancer treated with a short course of ciprofloxacin for febrile neutropenia (58).

Immunologic

Anaphylactoid reactions occurred in 3 of about 3200 students who took ciprofloxacin 500 mg for chemoprophylaxis of meningococcal meningitis; two had no history of atopic illness (59). Additional adverse reactions were mild skin rashes in three students and nausea and vomiting in two.

Angioimmunoblastic lymphadenopathy is a rare disorder characterized by generalized lymphadenopathy, fever, hepatosplenomegaly, immune hemolytic anemia, and polyclonal hypergammaglobulinemia. Biopsy-proven angioimmunoblastic lymphadenopathy has been reported in a 79-year-old man who had received ciprofloxacin (60).

A Jarisch–Herxheimer reaction to ciprofloxacin has been reported (61).

- A 14-year-old girl developed tachycardia, hypotension, and disseminated intravascular coagulation after her first dose of oral ciprofloxacin 500 mg for presumed pyelonephritis. A peripheral blood smear showed spirochetes consistent with *Borrelia* species.

Susceptibility Factors

Age

Children

In 36 premature infants, delivered at 25–35 weeks and with birth weights of 750–2050 g, ciprofloxacin (13.8 mg/kg/day in two or three divided doses for 3–20 days) had good efficacy in 66% of cases (62). Thrombocytopenia (five cases), raised transaminases (three cases), hyperbilirubinemia (three cases), and raised creatinine concentration (two patients) were reported as adverse events; one child developed femoral osteitis.

In a Russian study of children with cystic fibrosis, the adverse effects of ciprofloxacin were chiefly gastrointestinal (nausea, stomach pain, diarrhea) and increased transaminase activity (63). One episode of arthrotoxicity was transient. There were no negative effects on growth and no chondrotoxicity.

Oral ciprofloxacin (10 mg/kg bd) was as safe and effective as intramuscular ceftriaxone (50 mg/kg/day) in the treatment of acute invasive diarrhea in 201 children (aged 6 months to 10 years) (64). Possible drug-related adverse events occurred in 8% and were mild and transient. Joints were normal during and after the completion of therapy in all patients.

Elderly people

In a retrospective analysis there were no clinically important differences in the safety profile of ciprofloxacin in patients aged under or over 65 years (65). The incidence of drug-related adverse events was higher in those under 65 years (25%) than in those aged 65 years or more (17%); the most common adverse events affected the gastrointestinal and central nervous systems.

Other features of the patient

Ten patients with peripheral arterial occlusive disease were scheduled to undergo elective percutaneous transluminal angioplasty after a single dose of ciprofloxacin 400 mg (66). Antibiotic concentrations were significantly reduced in ischemic lesions compared with healthy adipose tissue. However, improvement of arterial blood flow in the affected limb was associated with increased cure rates of soft tissue infections.

The pharmacokinetics of intravenous ciprofloxacin have been studied in intensive care unit patients during continuous venovenous hemofiltration ($n = 5$) or hemodiafiltration ($n = 5$) (67). Ciprofloxacin clearance was not altered. A dosage of 400 mg/day was sufficient to maintain effective drug plasma concentrations in patients undergoing continuous renal replacement therapy.

Drug Administration

Drug administration route

In a comparison of intravenous and oral ciprofloxacin in children, treatment associated adverse events were reported in 11% of children taking oral ciprofloxacin, compared with 19% of the children who were treated intravenously (68). In 31 children (1.5%) arthralgia occurred, but it was generally mild to moderate and resolved spontaneously.

Drug overdose

A patient developed acute renal insufficiency after ciprofloxacin overdose. This was mediated by tubulointerstitial nephritis with distal nephron apoptosis, as evidenced by renal biopsy (39).

Drug–Drug Interactions

Ciclosporin

In 42 patients who had received a kidney transplant, cases were treated with ciprofloxacin in the first 1–6 months after transplantation, and matched controls (two per case) were not. The proportion of cases with at least one episode of biopsy-proven rejection 1–3 months after transplantation (45%) was significantly higher than in the controls (19%). The authors speculated that ciprofloxacin increases rejection rates in renal transplant recipients by antagonizing ciclosporin-dependent inhibition of interleukin-2 production (69).

Clozapine

Ciprofloxacin can alter plasma clozapine concentrations, perhaps by inhibition of cytochrome P450 enzymes (70).

Didanosine

Didanosine one enteric-coated capsule/day (400 mg/day) did not affect the absorption of ciprofloxacin in 16 patients (71).

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Glibenclamide

Hypoglycemia and raised serum concentrations of glibenclamide, which is metabolized by CYP2C9, occurred after treatment with ciprofloxacin for 1 week in a patient taking long-term glibenclamide (72).

Insulin

Hypoglycemia occurred in a patient treated with insulin and ciprofloxacin 500 mg bd (29).

Methadone

Ciprofloxacin, given to a patient who had been successfully treated with methadone for more than 6 years, caused profound sedation, confusion, and respiratory depression (73). This may have been due to inhibition of CYP1A2 and CYP3A4, two of the isozymes involved in the metabolism of methadone.

Methotrexate

Methotrexate elimination can be delayed by ciprofloxacin. Two adolescents with malignant diseases had reduced elimination of methotrexate (12 g/m^2 4-hourly) when they took ciprofloxacin 500 mg bd (74).

Oral contraceptives

Some antibiotics can reduce the efficacy of oral contraceptives. However, there is pharmacokinetic evidence that plasma concentrations of oral contraceptive steroids are unchanged by co-administration of ciprofloxacin (75). Furthermore, ciprofloxacin (500 mg bd) did not interfere with the ovarian suppression produced by the oral contraceptive Marvelon (30 micrograms of ethinylestradiol plus 150 micrograms of desogestrel) in 24 healthy women in a randomized, double-blind, placebo-controlled, crossover trial (76).

Phenytoin

Ciprofloxacin may interact with phenytoin reducing phenytoin concentrations (77).

- A lower than expected phenytoin serum concentration has been measured in a 78-year-old white woman with a grade III astrocytoma of the right parieto-occipital region treated with ciprofloxacin (500 mg bd) (78).

Increased renal excretion has been suggested to be at least partly responsible for the increased clearance.

Besides this kinetic interaction, the possible epileptogenic potential of ciprofloxacin itself may contribute to the development of seizure activity.

Probenecid

The renal excretion of ciprofloxacin was reduced and plasma concentrations increased by probenecid (79).

Quinidine

Serum quinidine concentrations rose during concomitant administration of ciprofloxacin (80). The authors speculated that the mechanism was inhibition of cytochrome P450 by ciprofloxacin.

Rifamycins

Rifampicin-induced lupus-like syndrome is associated with combination therapy with ciprofloxacin, since rifampicin is metabolized by (among others) CYP3A4, which is inhibited by ciprofloxacin, and combined usage may lead to higher rifampicin blood concentrations (81).

Ropinirole

During co-administration of ciprofloxacin with ropinirole in 12 patients there was an increase in the plasma ropinirole concentration, which is metabolized by CYP1A2 (82).

Warfarin

Ciprofloxacin can occasionally cause an exaggerated hypoprothombinemic response and bleeding in patients taking warfarin. In 66 patients (median age 72 years, range 36–94), the mean time to detection of the coagulopathy after ciprofloxacin challenge was 5.5 days (83). Hospitalization was reported in 15 cases, bleeding in 25, and death in one. The median INR was 10.0. Patients in their seventh decade and those requiring polypharmacy were most at risk.

Food–Drug Interactions

The systemic availability of ciprofloxacin is reduced by 30–36% when it is taken with dairy products (84).

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Ciramadol

General Information

Data on the incidence of adverse effects after usual doses of oral ciramadol are conflicting. In one study there was a low incidence of mild adverse effects (1), but in another, in which ciramadol 60 mg was more effective than codeine 60 mg or placebo, there was a high incidence of opioid adverse effects (2); some other workers have had the same experience.

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Cisapride

General Information

Cisapride is structurally similar to metoclopramide, but has no dopamine receptor antagonist activity and hence no central antiemetic effect. However, because it stimulates the release of acetylcholine in the gastrointestinal tract it is effective in conditions such as reflux esophagitis and gastroparesis. During clinical trials, the most frequent unwanted effects were diarrhea (5–11%) and abdominal pain (16% with 20 mg bd).

Observational studies

The effect of cisapride 20 mg bd for 7 days in preventing symptoms of gastro-esophageal reflux disease induced by a provocative meal has been assessed in 122 patients who had had symptoms suggestive of gastro-esophageal reflux for at least 3 months (1). Cisapride prevented or reduced the symptoms of heartburn and related symptoms, such as belching and regurgitation. Mild to moderate diarrhea was the main adverse effect.

Comparative studies

In a randomized, double-blind study in 106 patients with non-ulcer dyspepsia, cinitapride 1 mg tds was as effective as cisapride 5 mg tds in relieving symptoms (2). Adverse events, mainly gastrointestinal, were transient and did not require drug withdrawal. In another randomized study in 28 children (aged 5–17 years) with diabetic gastroparesis, domperidone 0.9 mg/kg/day for 8 weeks was superior to cisapride 0.8 mg/kg/day in reversing gastric emptying delay and gastric electrical abnormalities, as well as in improving dyspeptic symptoms and diabetic control (3). No potentially drug-related adverse effects were reported.

Placebo-controlled studies

The effect of cisapride 10 mg qds for 5 days on the frequency of nocturnal transient lower esophageal sphincter relaxation and esophageal acid exposure has been studied in a double-blind, placebo-controlled, crossover study in 10 patients with gastro-esophageal reflux disease (4). Cisapride significantly reduced the frequency of transient lower esophageal sphincter relaxation during sleep and increased lower esophageal sphincter pressure without changing gastric emptying. However, in a larger double-blind, placebo-controlled, crossover study in 30 patients with gastro-esophageal reflux disease, cisapride 20 mg bd for 4 weeks (despite adequate plasma concentrations) had no significant effects on swallow-induced esophageal peristaltic activity, the basal tone of the lower esophageal sphincter, or the number of transient lower esophageal sphincter relaxations induced by gas distension of the stomach (5). Adverse effects were similar in the two treatment sequences, although there were a few more episodes of abdominal cramps, nausea, and headache with cisapride.

General adverse effects

A comparison of data from prescription event monitoring in over 13 000 recipients of cisapride and from a further 9726 recipients involved in a controlled study showed that diarrhea, in about 2–4% of patients, was the commonest adverse effect reported. Other relatively common adverse effects are headache, abdominal pain, nausea and vomiting, and constipation, all in about 1–1.5% of patients.

A thorough review of the effects of cisapride in patients in intensive care suggested that adverse reactions are not likely to be severe or problematical (6). However, cisapride has been withdrawn because of the risk of prolongation of the QT interval and consequent ventricular dysrhythmias.

Organs and Systems

Cardiovascular

The FDA reported that between September 1993 and April 1996 it received reports of prolonged QT intervals in 23 patients and torsade de pointes or ventricular fibrillation in 34. Some proved fatal (SEDA-21, 361).

Several later studies confirmed the finding of QT interval prolongation during cisapride therapy in children (7).

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The effects of cisapride on the QT_c interval, heart rate, and cardiac rhythm were reported in a controlled study of 83 infants aged 2–54 months who received cisapride for a minimum of 4 days for gastro-esophageal reflux and 77 controls, using continuous bipolar limb lead electrocardiography for 8 hours (8). The QT_c interval was significantly prolonged by cisapride in infants under 3 months old. There was no significant difference in heart rates and there were no dysrhythmias. None of the infants was receiving drugs that inhibit the hepatic metabolism of cisapride via CYP3A4.

The effect of cisapride 0.8 mg/kg/day for 14 days on the QT_c interval has been studied prospectively in 50 infants with feeding intolerance, apnea, and bradycardia episodes secondary to gastro-esophageal reflux and gastrointestinal dysmotility (9). In 15 infants there was prolongation of the QT_c interval at some time during the 14 days. Infants with a QT_c interval on day 3 at least two standard deviations above the mean baseline QT_c interval were more likely to develop a prolonged QT_c interval.

Over 30 drugs (for example clarithromycin, erythromycin, and troleandomycin; nefazodone; fluconazole, itraconazole, and ketoconazole; indinavir and ritonavir) and other substances (for example grapefruit juice) can interact with cisapride and enhance its dysrhythmogenic effect. Despite regulatory action, including strengthened warnings in the product information, reports of dysrhythmias have repeatedly appeared. For example, in the UK the Medicines Control Agency received 60 reports of serious cardiac adverse events between 1988 and 2000; five were fatal (10). The corresponding worldwide figures were 386 serious ventricular dysrhythmias with 125 deaths and 50 unexplained deaths.

- An 81-year-old woman, who had a permanent pacemaker for complete heart block with symptomatic bradycardia-dependent torsade de pointes, had breakthrough torsade de pointes during therapy with cisapride 10 mg tds for 22 days and paroxetine for 9 days (11). She made a good recovery on withdrawal of the drugs.

In some countries therefore the product licence was suspended (10) and cisapride was subsequently withdrawn from the market by Janssen Cilag in 2003 (12).

Before its withdrawal in the UK cisapride was specifically contraindicated in premature babies for up to 3 months after birth, because of the risk of QT interval prolongation (10). Between 1988 and 2000 the Medicines Control Agency received 64 reports of suspected adverse effects of cisapride in children under 13 years, of which two were cases of QT prolongation and two were sudden unexplained deaths. Another 106 cardiovascular events were reported from other countries, including 30 cases of QT prolongation, six cases of ventricular fibrillation or tachycardia, and four sudden unexplained deaths.

Electrocardiographic changes and predisposition to cardiac dysrhythmias were investigated in 63 children (mean age 29 months) with gastro-esophageal reflux who had taken cisapride 0.2 mg/kg tds for at least 15 days and 57 control children (mean age 27 months) who were hospitalized for other reasons and were not given cisapride or other oral treatment (13). All the children had an electrocardiogram performed at inclusion, and 24-hour Holter recording was performed in all children with prolonged QT intervals. When a prolonged QT interval was detected cisapride was withdrawn and a new electrocardiogram was recorded. Five children in the treatment group and six controls had prolonged QT intervals, which normalized in three of the five children after cisapride was withdrawn. Holter recording was normal in all children.

The effect of cisapride 0.2 mg/kg tds for 8 weeks on cardiac rhythm was studied in a placebo-controlled, double-blind trial in 49 children aged 0.5–4 years with gastro-esophageal reflux resistant to other medical therapy (14). None had underlying cardiac disease or electrolyte imbalance. Cisapride had no effect on cardiac electrical function. However, in a prospective study cisapride 2 mg/kg qds given for 72 hours to 10 premature infants caused a significant increase in the QT_c interval compared with pretreatment values (15).

The relation between cisapride plasma concentrations, QT_c interval, and cardiac rhythm was evaluated in a controlled study in 211 infants undergoing routine 8-hour polysomnography (16). Cisapride was given for at least 4 days. At comparable doses of cisapride and comparable plasma concentrations, the QT_c was significantly higher in infants below 3 months of age.

In a postmarketing study of the safety of cisapride during 1993–9, 341 patients had cardiac effects, of whom 80 (23%) died, the deaths being directly or indirectly associated with a dysrhythmic event (17). The cardiac effects included QT interval prolongation, torsade de pointes, polymorphous ventricular tachycardia, ventricular fibrillation, ventricular tachycardia, cardiac arrest, unspecified "serious" dysrhythmias, and sudden death. In most instances the dysrhythmia occurred in the presence of risk factors such as other drugs or medical conditions.

Nervous system

Despite the fact that cisapride is not a dopamine receptor antagonist, tardive dyskinesia has been reported.

- Tardive dyskinesia with involuntary movement of muscles of mastication and the tongue has been reported in a 76-year-old man who took cisapride 10 mg tds, with complete resolution on withdrawal (18).

Psychological, psychiatric

In 16% of children given cisapride for intestinal pseudo-obstruction, treatment was followed by mild irritability and hyperactivity (SEDA-18, 370). In one adult, aggressive behavior seemed to be a direct complication of treatment (19).

Gastrointestinal

The effect of cisapride 10 mg bd on gastroduodenal reflux and gall bladder motility has been assessed in 77 patients with gallstones in a double-blind, placebo-controlled study (20). Cisapride increased gallbladder motility but did not have any effect on gastroduodenal reflux. Diarrhea, abdominal cramps, and increased bladder frequency were common adverse effects.

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A multicenter trial in 353 patients assessed the efficacy and tolerance of sodium alginate (four 10 ml sachets a day) compared with cisapride (5 mg qds) in the symptomatic treatment of uncomplicated gastro-esophageal reflux without severe esophagitis (21). Sodium alginate, which costs less than cisapride, was more effective in relieving symptoms. Adverse effects were rare and not serious. Constipation was the most common adverse effect of alginate while diarrhea was the commonest adverse effect of cisapride.

Liver

In one elderly man receiving cisapride, hepatitis occurred and resolved rapidly on drug withdrawal; there was no detectable cause other than the use of cisapride (22).

Urinary tract

Cisapride can cause functional changes in the urinary tract because of increased pressure in the bladder, which may be a problem in individuals with hyperactive bladders. In individuals who had complete traumatic spinal cord injury, the increase in reflex bladder contractions was sufficient to reduce compliance markedly (23).

Six cases of pollakiuria have been published (24), reversible when treatment was withdrawn (SEDA-19, 325).

Susceptibility Factors

Age

Children

The use of cisapride and its benefit to harm balance in children has been reviewed (25). Overall it is well tolerated. The most common adverse effects are diarrhea, abdominal cramps, borborygmi, and colic. Serious adverse events are rare and include isolated cases of extrapyramidal reactions, seizures in epileptic patients, cholestasis, QT interval prolongation and ventricular dysrhythmias, anorexia, and enuresis. Interactions of cisapride with other drugs are similar to those reported in adults. Co-administration of drugs that inhibit CYP3A4, such as imidazoles, macrolide antibiotics, the antidepressant nefazodone, and protease inhibitors such as ritonavir, are contraindicated. Furthermore, co-administration of anticholinergic drugs can compromise the beneficial effects of cisapride.

A systematic review of randomized, controlled trials of cisapride for gastro-esophageal reflux in children has been reported (26). Seven comparisons of cisapride with placebo (286 children in all) were included. The reflux index was significantly reduced by cisapride. However, there was no clear evidence that cisapride reduced symptoms of gastro-esophageal reflux. Adverse events (mainly diarrhea) were not significantly more common with cisapride.

The effects of cisapride 0.2 mg/kg tds on acid gastro-esophageal reflux in 32 formerly preterm infants receiving respiratory stimulation with caffeine have been studied using 24-hour esophageal pH monitoring (27). Cisapride significantly reduced the reflux index and the frequency of reflux without impairing the systemic availability or therapeutic effects of caffeine.

The effects of cisapride 0.2–0.3 mg/kg tds on chronic constipation were studied in a double-blind, placebo-controlled trial in 36 children (28). Cisapride was effective in the treatment of chronic constipation without major adverse effects.

The effects of low-dose cisapride (0.1 mg/kg tds) on gastric emptying and the QT interval were studied in a double-blind, placebo-controlled, crossover trial in 20 infants of low birth weights (29). Low-dose cisapride significantly improved gastric emptying without prolonging the QT interval.

Elderly patients

The pharmacokinetics of cisapride have been studied in eight elderly patients (mean age 85 years) (27). There were no adverse effects, apart from a slight increase in stool frequency. There were no changes in the corrected QT interval. However, plasma cisapride concentrations were higher than expected. Thus, in extremely elderly patients cisapride should be given once or twice a day rather than three times.

Other features of the patient

Cisapride should not be prescribed for patients with a history of disturbances of cardiac rhythm or who are at risk of developing frank dysrhythmias, especially individuals with hypokalemia or hypomagnesemia (SEDA-22, 389).

Cisapride should not be used in cases of intestinal obstruction, perforation, or hemorrhage (SEDA-22, 389).

Drug–Drug Interactions

Cimetidine

In eight healthy volunteers oral cimetidine 400 mg tds increased the steady-state C_{max} and AUC of oral cisapride 10 mg tds. Cisapride shortened the t_{max} and reduced the AUC of cimetidine (30). The authors concluded that cimetidine inhibits the metabolism of cisapride, and cisapride enhances the gastrointestinal absorption of cimetidine.

Digoxin

A possible interaction between cisapride and digoxin has been reported (31).

- A 90-year-old woman took cisapride, first in a dose of 5 mg bd and then 5 mg tds. She had been taking digoxin for a long time, but the serum digoxin concentration began to fall gradually after cisapride was given, from 1.1 nmol/l in January to 0.7 nmol/l in March and 0.5 nmol/l in August. The digoxin tablets were of reportedly high dissolution rate, with an onset of action at 30–60 minutes and a peak effect at 4–6 hours after a single dose. The onset of action of cisapride is 30–60 minutes, but the duration of its promotility effect during multiple dose therapy is not clear. The drugs were then separated by 4 hours, with the aim of reducing the promotility effect of cisapride on digoxin absorption, and there was an improvement in both clinical response and digoxin concentration.

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The authors speculated that cisapride reduced digoxin absorption by accelerating bowel transit time.

Diltiazem

A possible interaction of cisapride 20 mg/day with diltiazem has been reported in a 45-year-old woman who developed near syncope and had QT interval prolongation (32). The QT interval returned to normal after withdrawal of cisapride. Rechallenge was not attempted. Diltiazem inhibits CYP3A4, and should therefore probably be avoided in combination with cisapride.

Oral anticoagulants

The absorption of the anticoagulants warfarin and phenprocoumon is unaffected by cisapride (SEDA-21, 361).

Propranolol

The absorption of propranolol is unaffected by cisapride (SEDA-21, 361).

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Cisatracurium besilate

See also Neuromuscular blocking drugs

General Information

Cisatracurium is one of the ten isomers of atracurium. With an ED_{95} of 0.05 mg/kg it is about three times more potent than atracurium (1–3). The duration of action of cisatracurium tends to be slightly longer than that of atracurium. Less cisatracurium is required to achieve a given degree of neuromuscular blockade and so less laudanosine is produced.

Cisatracurium and atracurium share the same metabolic pathways, but Hofmann elimination may have a greater role in the elimination of cisatracurium than in atracurium (2,4–7). Spontaneous in vivo degradation accounts for 77% of total body clearance of cisatracurium (6). Organ clearance is 23% of total body clearance. Major metabolites of cisatracurium are laudanosine and a monoquaternary acrylate.

Clinical problems due to histamine release after bolus administration of cisatracurium have not been observed, even with very large doses up to 0.4 mg/kg (3,8), but in some patients there were considerable increases in plasma histamine concentrations (8–10).

Organs and Systems

Cardiovascular

With doses up to eight times the ED_{95} no cardiovascular adverse effects were observed (8) and in other studies cisatracurium had only minor cardiovascular adverse effects (9,11,12). Patients with coronary artery disease undergoing myocardial revascularization tolerated cisatracurium doses up to several fold the ED_{95} well; hemodynamic changes from pre- to postinjection were minimal (13,14).

Immunologic

Anaphylactic reactions have been reported (15–17).

Susceptibility Factors

Age

In line with its non-organ-dependent elimination pathways, neither the plasma clearance nor the duration of action of cisatracurium differed between young and elderly patients (18).

Renal disease

In patients with or without renal failure, there was no difference in the duration of action of cisatracurium (19).

Hepatic disease

In patients with hepatic failure neither the half-life nor the duration of action of cisatracurium was prolonged when compared with controls (20). In another study, however, the volume of distribution was increased and the plasma clearance reduced in patients with end-stage liver disease (21). Recovery times were not statistically different but the variability was greater in patients with liver disease (21).

Drug–Drug Interactions

General anesthetics

The action of cisatracurium is potentiated by isoflurane, sevoflurane, and enflurane (22).

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Citalopram and escitalopram

See also Selective serotonin re-uptake inhibitors (SSRIs)

General Information

Citalopram is a racemic bicyclic phthalane derivative and is a highly selective serotonin re-uptake inhibitor with minimal effects on noradrenaline and dopamine neuronal reuptake. Inhibition of 5-HT re-uptake by citalopram is primarily due to the *S*-enantiomer (escitalopram). Its most frequent adverse events (nausea, somnolence, dry mouth, increased sweating) are mainly transient and mostly mild to moderate (1).

The single and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in the range 10–60 mg/day. Citalopram is metabolized to demethylcitalopram, didemethylcitalopram, citalopram-N-oxide, and a deaminated propionic acid derivative. Citalopram has a mean half-life of about 35 hours (2). Racemic citalopram is several times more potent than its metabolites in inhibiting serotonin reuptake (3).

In a systematic review of clinical trials the therapeutic efficacy of citalopram was significantly greater than that of placebo and comparable with that of other antidepressants (4).

Escitalopram oxalate is the *S*-enantiomer of citalopram (5). The therapeutic activity of citalopram resides in the *S*-isomer and escitalopram binds with high affinity to the human serotonin transporter; *R*-citalopram is about 30-fold less potent. The half-life of escitalopram is 27–32 hours. Citalopram and escitalopram have negligible effects on CYP isozymes.

Escitalopram was efficacious in patients with major depressive disorder in short-term, placebo-controlled trials, three of which included citalopram as an active control, and in a 36-week study in the prevention of relapse in depression (5). It has also been used to treat generalized anxiety disorder, panic disorder, and social anxiety disorder. Results also suggest that, at comparable doses, escitalopram demonstrates clinically relevant and statistically significant superiority to placebo treatment earlier than citalopram. The most common adverse events associated with escitalopram include nausea, insomnia, disorders of ejaculation, diarrhea, dry mouth, and somnolence. Only nausea occurred in more than 10% of patients taking escitalopram.

A meta-analysis of 20 short-term studies of five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) has been published (6). There were no overall differences in efficacy, but fluoxetine had a slower onset of action. Citalopram and sertraline were least likely to cause drug interactions, but citalopram was implicated more often in fatal overdoses.

Organs and Systems

Cardiovascular

There has been some concern about the cardiovascular safety of citalopram, mainly because of animal studies showing effects on cardiac conduction. These most commonly occur in large overdoses, in which a variety of cardiac abnormalities, including QT_c prolongation, have been noted. However, this can occur with therapeutic doses too.

- Bradycardia (34/minute) with a prolonged QT_c interval of 463 ms occurred in a patient taking citalopram 40 mg/day (7). The bradycardia resolved when citalopram was withdrawn. The patient also had alcohol dependence and evidence of cardiomyopathy; presumably this may have potentiated the effect of citalopram on cardiac conduction.
- A 21-year-old woman developed QT_c prolongation (457 ms) after taking a fairly modest overdose (400 mg) of citalopram (usual daily dose 20–60 mg) (8). The QT_c prolongation resolved uneventfully over the next 30 hours.

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This suggests that even modest overdoses of citalopram can cause QT_c prolongation and that cardiac monitoring should be considered. Based on the pharmacokinetic profile of citalopram and the temporal pattern of QT_c change, the authors suggested that the effect of citalopram on the QT_c interval was mediated by one of its metabolites, dimethylcitalopram.

Prolongation of the QT_c interval has been reported in five patients who made non-fatal suicide attempts by taking large amounts of citalopram. Their electrocardiograms showed other conduction disorders, including sinus tachycardia and inferolateral repolarization disturbances (SEDA-21, 12).

Nervous system

SSRIs can infrequently cause extrapyramidal movement disorders and can also worsen established Parkinson's disease (SEDA-22, 23) and another case has been reported (9).

- A 68-year-old woman developed major depression. A neurological assessment excluded neurological diseases, including Parkinson's disease. After treatment with citalopram, 20 mg/day for 7 days, she developed severe parkinsonism, with rigidity, tremor, and bradykinesia, and became unable to walk. The citalopram was withdrawn after a further week and nortriptyline was substituted; however, 10 days later parkinsonism was still present. Her symptoms eventually responded to cobeneldopa.

The authors concluded that the citalopram had probably precipitated latent Parkinson's disease. Citalopram is the most highly selective SSRI and, in anecdotal accounts, has been implicated somewhat less often than other SSRIs in extrapyramidal movement disorders. However, this case, together with another report of citalopram-induced worsening of pre-existing Parkinson's disease (10), suggests that it should be used with caution in patients with this disorder.

Psychological, psychiatric

Mania has been reported in six patients, five of whom were taking citalopram and one paroxetine (SEDA-22, 12).

Electrolyte balance

Hyponatremia can sometimes cause severe disturbances of consciousness.

- A 47-year-old woman with multiple sclerosis took citalopram 20 mg/day for 4 weeks and was found unconscious in her apartment (11). The main finding was a low plasma sodium (108 mmol/l). As a result of prolonged coma, she had rhabdomyolysis and required intubation for 3 days as well as sodium replacement therapy. She eventually made a full recovery.

It is possible in this case that the underlying demyelinating disease may have made the patient more susceptible to the sodium-lowering effects of the SSRI.

- A 45-year-old woman developed hyponatremia complicated by rhabdomyolysis while taking citalopram and the antipsychotic drug chlorprothixene for depressive psychosis (12). The hyponatremia became apparent 2 weeks after the dose of citalopram was increased to 40 mg/day, when she complained of weakness and lethargy.

SSRI-induced hyponatremia is unusual in non-geriatric populations, but the chlorprothixene may have played a role in this case.

Gastrointestinal

Gastrointestinal adverse effects are one of the major disadvantages of SSRIs. The most common is nausea, and the incidence is said to be 20% or more for citalopram (13,14).

Sexual function

Citalopram has a relatively modest effect in delaying ejaculation (15).

Sexual disinhibition has been reported in five patients, four of whom were taking citalopram; they had an unusual increase in sexual interest, with preoccupation with sexual thoughts, promiscuity, and excessive interest in pornography (16). In some of the cases symptoms such as diminished need for sleep suggested the possibility of a manic syndrome.

Long-Term Effects

Drug withdrawal

Reports of withdrawal symptoms after citalopram withdrawal are rare, but it is uncertain whether this reflects a truly lower propensity to cause withdrawal symptoms.

- A 30-year-old man with a history of major depression and panic disorder had been in remission for a year with citalopram 20 mg/day, valproate 600 mg/day, and alprazolam 3 mg/day (17). The citalopram was tapered over 3 weeks to 5 mg/day and then withdrawn. The day after the last dose he experienced anxiety and irritability together with frequent short-lasting bursts of dizziness, not having had the latter previously panic and depression did not recur and after a week the symptoms resolved spontaneously.
- A 45-year-old woman achieved remission from an episode of major depression within 2 weeks of taking citalopram (40 mg/day). After about 3 months of treatment she missed her daily dose of citalopram, and 3 hours later had a sudden episode of dizziness while driving. A similar episode occurred 2 weeks later again after a missed dose of citalopram. The dizziness remitted about 1 hour after the citalopram was taken.

These symptoms, particularly dizziness, are characteristic of SSRI withdrawal, and suggest that citalopram, like other SSRIs, can cause a withdrawal syndrome in some patients, despite slow tapering of the dose.

Withdrawal symptoms in the 2 weeks after sudden discontinuation of citalopram have been examined in a double-blind, placebo-controlled study (18). Withdrawal symptoms were overall mild, but neurological and psychiatric disturbances were 2–3 times as common in patients randomized to placebo than in those randomized to continue with citalopram. The authors pointed out that withdrawal symptoms were particularly common in

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patients who were randomized to placebo who also had depressive relapses. This shows the difficulty of disentangling the effects of depressive relapse from those of pure treatment withdrawal. However, it is also possible that acute withdrawal of medication induces an abnormal neurobiological state, in which both depression and abstinence symptoms are more likely to occur. It would be wise to warn patients about the possible effects of missing doses of the shorter-acting SSRIs.

Second-Generation Effects

Lactation

Citalopram has been reported to cause sleep disturbance in a breast-fed infant (19).

- A 29-year-old woman took citalopram (40 mg/day) while breast feeding her 5-week-old daughter. The maternal citalopram concentrations were 99 ng/ml in the serum and 205 ng/ml in the breast milk. The serum concentration in the infant was 13 ng/ml, and the child's sleep was fitful and disturbed. The dosage of citalopram was reduced to 20 mg/day and the two feeds after each daily dose were replaced by artificial nutrition. One week later the infant was sleeping normally, and the serum citalopram concentrations in mother and infant had fallen to 35 ng/ml and 2 ng/ml, respectively.

These data suggest that although breast feeding during citalopram treatment is possible, careful dosing and close observation of mother and infant are necessary.

Drug Administration

Drug overdose

Six deaths have been reported after overdosage of citalopram. Although five of the six had also taken other substances, these were not thought to have contributed significantly (SEDA-20, 8). Of five patients who made non-fatal suicide attempts by taking large amounts of citalopram (up to 5200 mg), four developed generalized seizures and all had prolonged QT_c intervals. Other conduction disorders included sinus tachycardia and inferolateral repolarization disturbances. Two patients developed rhabdomyolysis and one hypokalemia. These data suggest that citalopram overdose can cause seizures and disturbances of cardiac conduction that might predispose to fatal dysrhythmias (SEDA-21, 12) (20,21).

In another case prolonged sinus bradycardia occurred (22).

- A 32-year-old woman took 800 mg of citalopram, 20 times her usual daily dose, in a suicide attempt. On admission to hospital she had a sinus bradycardia (41/minute) but the electrocardiogram was otherwise normal, with a QT interval of 430 ms. Treatment with atropine failed to increase her heart rate and she had hypotension and syncope. A temporary pacemaker was inserted and was required for the next 6 days before it could be safely removed.

There are concerns that citalopram may be less safe in acute overdose than other SSRIs (SEDA-21, 12). Among all fatal poisonings in one forensic district of Sweden, citalopram was the fourth most commonly used drug (22 of 358 cases) (23). However, when correction was made for prescription rate, citalopram was less toxic than amitriptyline, dextropropoxyphene, or nitrazepam. This study has confirmed that citalopram is less toxic than tricyclic antidepressants such as amitriptyline. However, whether it is more toxic than other SSRIs is still uncertain.

Drug–Drug Interactions

General

Of all the SSRIs citalopram has the least inhibitory effect on cytochrome P450 enzymes and has not been associated with clinically significant interactions with other CNS drugs.

It has been used successfully in combination with the tricyclic antidepressant desipramine in a 45-year-old woman who had previously suffered tricyclic toxicity when desipramine had been combined with paroxetine (24).

Acenocoumarol

When a drug has a relatively narrow therapeutic index, such as acenocoumarol, pharmacokinetic interactions can have serious clinical consequences.

- A 63-year-old woman taking acenocoumarol 18 mg/week (INR 1.8) started to take citalopram 20 mg/day and 10 days later noted spontaneous bleeding from her gums; the INR had risen to more than 15 (25). She was treated with two units of whole blood and the citalopram was withdrawn. Five days later the INR had returned to the target range.

Citalopram is said to be less likely than other SSRIs to cause drug interactions, because it is a relatively weak inhibitor of CYP isozymes. However, even slight inhibition may have produced serious consequences in this case.

Clozapine

The effect of citalopram on plasma concentrations of clozapine have been prospectively studied in 15 patients with schizophrenia taking clozapine 200–400 mg/day (26). The addition of citalopram 40 mg/day did not alter plasma clozapine concentrations.

However, in a 39-year-old man with a schizoaffective disorder, citalopram 40 mg/day appeared to increase plasma clozapine concentrations and increased adverse effects (27). The adverse effects settled within 2 weeks of a reduction in citalopram dosage to 20 mg/day, with a corresponding 25% fall in clozapine concentrations. It is possible that at higher doses, citalopram can increase clozapine concentrations, perhaps through inhibition of CYP1A2 or CYP3A4.

Digoxin

Citalopram 40 mg/day for 4 weeks did not alter the pharmacokinetics of digoxin 1 mg orally (28). Digoxin is not a CYP substrate, so an interaction with SSRIs is unlikely, but the authors cited a report that fluoxetine increased plasma digoxin concentrations (29).

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Risperidone

The effect of citalopram on plasma concentrations of risperidone has been prospectively studied in 15 patients with schizophrenia (26). The addition of citalopram did not alter plasma risperidone concentrations.

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Citric acid and citrates

General Information

Citric acid is used in effervescing mixtures and granules. Formulations that contain citric acid are used in the management of dry mouth and to dissolve renal calculi, alkalinize the urine, and prevent encrustation of urinary catheters. Citric acid is also an ingredient of citrated anticoagulant solutions.

Uses

Urinary calculi

Treatment of complex and large urinary calculi secondary to infection can be difficult, and complete removal of the stone may not always be possible. Residual stone fragment rates are 37% (range 10–57%) after percutaneous nephrolithotomy and 20% after anatrophic nephrolithotomy (1). Technical advances in the management of urinary calculi have resulted in improved stone clearance rates in these cases. Owing to a combination of factors, such as large stone mass, associated infection, abnormal renal anatomy, and poor general health of the patient, infection stones can still pose a difficult treatment problem. This has resulted in the use of alternative (and minimally invasive) treatment options. Dissolution treatment, either alone or as adjuvant therapy, has been used. Citric acid, in various concentrations, has been used in dissolution treatment (2). Citric

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acid, being a urinary acidifier, inhibits the formation of precipitates of calcium phosphate, calcium carbonate, and magnesium ammonium phosphate, and allows dissolution of stones. It may also help to reduce the size of calculi, allowing spontaneous elimination.

Citric acid has been used to treat 22 patients (10 men and 12 women, mean age 45, range 15–60 years; 23 affected kidneys) with kidney stones (14 staghorn calculi, four partial staghorn calculi, and five large-burden calculi) (3). They underwent irrigation with solution R (citric acid monohydrate 6 g, magnesium carbonate 2.8 g, glucolactone 0.6 g, and water 100 ml) following debulking of the stone with percutaneous nephrolithotomy ($n = 20$), ureteroscopy, and shock wave lithotripsy ($n = 2$) combined with open procedures ($n = 4$). Irrigation was performed through a nephrostomy tube ($n = 20$) or in a retrograde fashion ($n = 3$) using a closed infusion pump system (40 ml/hour). The response to treatment was checked using a nephrostogram and/or plain X-ray. In six kidneys irrigation had to be abandoned because of loin pain, leak, or sepsis after an average duration of 2 (1–5) days. The average duration of irrigation was 6 (1–20) days. At the end of irrigation, four kidneys had complete radiographic clearance, and the stone was reduced to calyceal dust in three. There was a partial response in 11 and no response in five. Following alternative interventions in six cases (four with a partial response and two with no response), further clearance was achieved in three and calyceal dust in three. The response was better if the stone was reduced to less than 10 mm before irrigation. At the mean follow-up of 2.4 (1–4) years, of 13 kidneys with stone clearance or calyceal dust, nine suffered recurrence or re-growth, five of which required further interventions. Only four of the 23 kidneys remained stone-free.

In patients with complex stone disease, adjuvant solution R irrigation can reduce the stone burden, although the overall success rate is limited. However, there is a considerable potential for adverse effects, necessitating close monitoring for sepsis and electrolyte abnormalities.

Anticoagulation

In 2000 the FDA issued an urgent warning to all hospital pharmacies and hemodialysis units that triCitrasol, an unapproved formulation of sodium citrate that has been used as an anticoagulant to keep intravascular lines open, can cause death after intravenous infusion. triCitrasol is marketed in individual sterile 30 ml glass vials, distributed both individually and in hemodialysis kits (4). A patient died of cardiac arrest shortly after the injection of triCitrasol 46.7% into a permanent hemodialysis blood access catheter that had just been implanted. Rapid or excessive infusion of citrate solutions can cause fatal cardiac dysrhythmias, seizures, or bleeding due to sequestration of blood calcium.

triCitrasol is manufactured by Cytosol Laboratories, and is distributed by Medcomp (previously by Citra Anticoagulants, Inc). Both Cytosol Labs and Medcomp have voluntarily recalled triCitrasol for use with blood access catheters. On 9 April 2000, Medcomp announced in a letter to its customers that it was recalling its kits (or trays) containing triCitrasol and the Medcomp Ash Split Catheter II for hemodialysis or apheresis, a blood separation and re-transfusion process. About 3000 Medcomp catheter kits with triCitrasol were distributed nationwide. They were also distributed in Puerto Rico and Canada.

The FDA urged hospital pharmacies and hemodialysis units across the USA to stop using the product. Alternative 4% solutions of citrate are available for use in these and most other medical settings.

Organs and Systems

Cardiovascular

Citric acid toxicity has been reported previously, but only after intravenous administration. It was originally seen with massive transfusion of blood products with citrate as the anticoagulant. Two case reports have described accidental intravenous administration of citrate or citric acid; at a maximum serum concentration of citrate (4.1 mmol/l) there were profound alterations in blood pressure and QT interval; these were reversed by calcium infusion (5).

Metabolism

Although there is a long list of causes of metabolic acidosis with an increased anion gap (6,7), clinical clues can help diagnosis. A case report has illustrated the acute metabolic and hemodynamic effects of ingestion of a massive load of oral citric acid. The principal findings included a metabolic acidosis accompanied by an increase in the plasma anion gap, not due to lactic acidosis, hyperkalemia, and the abrupt onset of hypotension (8).

- A 42-year-old previously healthy male prisoner drank a large volume of a commercial solution of unknown composition. His medical history was non-contributory, except for severe epigastric pain. Within an hour, his condition deteriorated; he was ashen, his blood pressure was 80/40 mmHg, and his pulse rate was 102/minute. His neck vessels were flat and his breath sounds were equal bilaterally, with occasional expiratory wheezes at both bases. There were no cardiac murmurs. The abdomen was soft and the bowel sounds were active. His extremities were warm with no cyanosis or edema. There were no neurological abnormalities. Fortuitously, because of therapy to avoid cardiac complications of hyperkalemia, he was given 1 g of calcium chloride, 50 mmol of sodium bicarbonate, 25 g of glucose, and 10 units of regular insulin intravenously. His blood pressure immediately increased to 116/76 mmHg and his pulse rate fell to 90/minute. By the next morning his plasma acid–base balance was normal, as was his ionized calcium concentration (1.1 mmol/l).

Because of the short duration and severity of the metabolic acidosis, together with a near-normal lactate concentration, acid ingestion was the most likely cause for his acid–base disorder. This diagnosis was confirmed once the composition of the ingested fluid was known.

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Clarithromycin

See also Macrolide antibiotics

General Information

Clarithromycin is a commonly used macrolide antibiotic and is a regular part of regimens for the eradication of *Helicobacter pylori*, often in combination with a nitroimidazole antibiotic as well, in addition to a proton pump inhibitor. Variable rates of adverse events (4–30%) have been reported with clarithromycin.

Comparative studies

In a double-blind, multicenter trial in 328 patients with *H. pylori* infection and non-ulcer dyspepsia, omeprazole 20 mg bd, amoxicillin 1 g bd, and clarithromycin 500 mg bd were compared with omeprazole alone. The rate of success and quality of life were similar in both groups. There were no serious adverse events. However, there were 12 withdrawals in the group given omeprazole and antibiotics and two in the group given omeprazole alone. Diarrhea occurred in 63 patients in those given omeprazole and antibiotics and in ten patients given omeprazole alone (1). In another double-blind, placebo-controlled trial eradication of *H. pylori* (omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg bd) in long-term users of NSAIDs with past or current peptic ulcer or troublesome dyspepsia led to impaired healing of gastric ulcers and did not affect the rate of peptic ulcers or dyspepsia over 6 months (2).

Beta-lactam antibiotics

In a multicenter, double-blind, randomized comparison of cefprozil, 500 mg bd for 5 days and clarithromycin 500 mg bd for 10 days in 295 subjects with an acute exacerbation of chronic bronchitis, the most common adverse effects of clarithromycin were nausea (8%), diarrhea (12%), taste disturbance (8%), and dry mouth (5%) (3).

Clarithromycin (250 mg bd for 10 days) was as effective as cefuroxime axetil (250 mg bd for 10 days) in the treatment of acute maxillary sinusitis in a randomized, double-blind, multicenter study in 370 patients; 10% of patients in each group had adverse events (4).

Other macrolides

The incidence of disseminated *Mycobacterium avium* complex (MAC) infection has increased dramatically with the AIDS epidemic. Treatment regimens for patients with a positive culture for MAC from a sterile site should include two or more drugs, including clarithromycin. Prophylaxis against disseminated MAC should be considered for patients with a CD4 cell count of less than 50 x 10^6/l (5). In a randomized, open trial in 37 patients with HIV-associated disseminated MAC infection, treatment with clarithromycin + ethambutol produced more rapid resolution of bacteremia, and was more effective at sterilization of blood cultures after 16 weeks than azithromycin + ethambutol (6).

In a direct comparison of clarithromycin with erythromycin stearate, the rate of adverse events was 19% in 96 patients taking clarithromycin and 35% in 112 patients taking erythromycin (7). Most of the adverse events associated with clarithromycin affect the gastrointestinal tract (7%).

In a prospective, single-blind, randomized study of a 7-day course of clarithromycin (7.5 mg/kg bd) and a 14-day course of erythromycin (13.3 mg/kg tds) in 153 children with pertussis, the incidence of treatment-emergent drug-related adverse events was significantly higher with erythromycin than with clarithromycin (62 versus 45%) (8). Three subjects given erythromycin withdrew prematurely because of adverse events: one because of a rash; one with vomiting and diarrhea; and one with vomiting, abdominal pain, and rash.

Quinolones

In a multicenter, double-blind, randomized comparison of trovafloxacin 200 mg and clarithromycin 500 mg bd in 176 subjects with acute exacerbations of chronic bronchitis, the most common adverse effects of clarithromycin were nausea (3%), diarrhea (4%), and taste disturbances (4%) (9).

Tetracyclines

Clarithromycin (0.75–2 g/day), minocycline (200 mg/day), and clofazimine (100 mg/day) for 15 months were investigated as treatment of MAC lung disease in 30 HIV-negative patients. Eight patients did not complete the study owing to deviations from protocol or adverse effects. Persistently negative cultures were found in 14 of the other patients. There were three cases of hepatic disturbances and three of ototoxicity, which required a reduction in clarithromycin dosage after a short interruption of treatment (10).

Organs and Systems

Cardiovascular

- QT interval prolongation and a ventricular dysrhythmia occurred in an HIV-positive 30-year-old man at the start of intravenous clarithromycin therapy 500 mg 12-hourly (11).

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Intravenous clarithromycin caused thrombophlebitis in four patients when it was given inappropriately as a rapid bolus injection instead of a short infusion; the manufacturers have received other reports of similar reactions, even with infusions, but the incidence seems to be considerably lower than with erythromycin (12). In a prospective, non-randomized study, phlebitis occurred in 15 of 19 patients treated with intravenous erythromycin (incidence rate of 0.40 episodes/patient-day) and in 19 of 25 patients treated with intravenous clarithromycin (0.35 episodes/patient-day) (13).

Respiratory

Bronchospasm with clarithromycin occurred in a 44-year-old woman who had no history of respiratory allergies but had had adverse drug reactions to general and regional anesthetics and to ceftriaxone (14). After the administration of a quarter of the therapeutic dose the patient had dyspnea, cough, and bronchospasm throughout the lung.

Nervous system

Adverse events on the nervous system due to clarithromycin have been observed in 3% of patients.

- Progressive loss of strength and difficulty in swallowing and eye opening after the first dose of clarithromycin (2 g/day) occurred in a patient with cerebral toxoplasmosis and AIDS (15). This myasthenic syndrome resolved within 6 hours of withdrawal of clarithromycin and administration of pyridostigmine.

The authors postulated that this adverse effect may have been the consequence of neuromuscular blockade, through inhibition of the presynaptic release of acetylcholine.

Sensory systems

Eyes

Topical clarithromycin can cause self-resolving corneal deposits (16).

Ears

- Ototoxicity was attributed to clarithromycin in a 76-year-old man 4 days after he started to take clarithromycin for atypical pulmonary tuberculosis (17). When the clarithromycin was withdrawn his hearing improved subjectively, but it worsened again on re-exposure.

Taste

Abnormal taste developed in 17 of 175 patients treated with clarithromycin 250 mg bd for 10 days for community-acquired pneumonia, compared with 3 of 167 patients treated with sparfloxacin (18). Mild to moderate gastrointestinal disturbances were the most common adverse events and were reported in 13 and 11% respectively.

Psychological, psychiatric

Two patients, a man aged 74 and a woman aged 56 years, developed delirium after taking clarithromycin (19).

Two patients (aged 21 and 33 years) with late-stage AIDS had acute psychoses shortly after taking clarithromycin (2 g/day) for MAC bacteremia (20). In both cases the psychosis resolved on withdrawal but recurred on rechallenge. In one case treatment with azithromycin was well tolerated.

Of cases of mania attributed to antibiotics and reported to the WHO, 28% were due to clarithromycin (21).

- A 77-year-old man who was HIV-negative developed mania after 6 days treatment with clarithromycin 1 g/day for a soft tissue infection; his mental state resolved on withdrawal (22).
- A 53-year-old Canadian lawyer taking long-term fluoxetine and nitrazepam developed a frank psychosis 1–3 days after starting to take clarithromycin 500 mg/day for a chest infection (23). His symptoms resolved on withdrawal of all three drugs, and did not recur with erythromycin or when fluoxetine and nitrazepam were restarted in the absence of antibiotics.

The symptoms may have been due to a direct effect of clarithromycin or else inhibition of hepatic cytochrome P450 metabolism, leading to fluoxetine toxicity.

Clarithromycin occasionally causes hallucinations.

- Visual hallucinations with marked anxiety and nervousness occurred after the second dose of oral clarithromycin 500 mg in a 32-year-old woman (24). Clarithromycin was withdrawn and the symptoms disappeared a few hours later.
- Visual hallucinations developed in a 56-year-old man with chronic renal insufficiency and underlying aluminium intoxication maintained on peritoneal dialysis 24 hours after he started to take clarithromycin 500 mg bd for a chest infection, and resolved completely 3 days after withdrawal (25).

Hematologic

- Thrombotic thrombocytopenic purpura was reported in a 42-year-old man with no past medical history after he had just completed a 30-day course of clarithromycin 250 mg bd (26).

Gastrointestinal

Erythromycin acts as a motilin receptor agonist (27–29). This mechanism may be at least partly responsible for the gastrointestinal adverse effects of macrolides. Clarithromycin may act on gastrointestinal motility in a similar way. In dogs, clarithromycin caused contractions and discomfort, as did erythromycin (30). In healthy volunteers, oral clarithromycin 250 mg bd caused a statistically significant increase in the number of postprandial antral contractions and antral motility (31). A single oral dose of clarithromycin 3000 mg resulted in severe abdominal pain within 1 hour of administration in two patients (32).

Based on observations made in dogs and rabbits, clarithromycin is significantly less potent than azithromycin and erythromycin as an agonist for stimulation of smooth muscle contraction (33). Therefore, a lower rate of gastrointestinal adverse events would be expected with clarithromycin.

Pseudomembranous colitis is relatively rarely seen with macrolides, but has been reported with clarithromycin (SED-12, 597) (34,35).

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Liver

Abnormal liver function tests and hepatomegaly have been described with clarithromycin; in 4291 patients, the frequency of increased alanine transaminase activity was 5% (36). Clarithromycin was also associated with cholestatic hepatitis (30). To date, at least nine cases of hepatotoxicity have been described in HIV-negative patients taking clarithromycin 1–2 g/day for chronic lung disease due to *M. avium* or *Mycobacterium abscessus* (37). The pattern of liver enzyme abnormality was primarily cholestatic, and the patients were typically elderly (all but one aged over 60 years), or of low weight. Only three patients were symptomatic, and the liver function abnormalities resolved on withdrawal. Subsequent rechallenge was successful in four patients, unsuccessful in one, and not performed in four. There was some dispute as to whether toxicity was dose-related or not, but it is wise to recommend that elderly patients should receive an initial daily dose of 1 g in this disease setting.

Although cholestatic hepatitis has been typically described in association with erythromycin, newer macrolides are not totally free of this risk. A gradual increase in bilirubin and transaminases has been reported during treatment of a *Mycobacterium chelonae* infection with clarithromycin. These alterations were quickly reversible after withdrawal, but re-appeared on re-exposure to clarithromycin 1 g (38).

- Fatal drug-induced cholestasis associated with clarithromycin 500 mg bd for 3 days has been reported in a 59-year-old woman with diabetes mellitus and chronic renal insufficiency (39).
- Idiosyncratic drug-induced fatal fulminant hepatic failure has been reported in a 40-year-old woman with end-stage renal insufficiency taking clarithromycin 500 mg bd (40).

Skin

Clarithromycin has been associated with fixed drug eruptions and hypersensitivity reactions (41,42). In one case a clarithromycin-induced fixed drug eruption was reproduced by oral provocation, whereas patch tests on both unaffected and residual pigmented skin were negative (43).

- A 31-year-old woman developed Stevens–Johnson syndrome after she had taken oral erythromycin 333 mg tds for otitis media (44). After two doses she developed oral ulcers, tongue swelling, and a generalized erythematous rash. The diagnosis was confirmed histologically. She recovered slowly after withdrawal of erythromycin.
- Roxithromycin-induced generalized urticaria and tachycardia with a positive prick test and a cross-reaction to erythromycin and clarithromycin has been reported in a 31-year-old woman (45).

Clarithromycin can cause phototoxicity (46).

Drug–Drug Interactions

Antifungal imidazoles

In three patients with pulmonary MAC and aspergillosis infections, itraconazole was suggested to increase the plasma concentration of clarithromycin as well as the clarithromycin:14-hydroxyclarithromycin ratio (47). This effect may have been due to inhibition of CYP3A4 by itraconazole.

Antihistamines

Toxic effects of terfenadine and astemizole have been reported in patients taking concomitant macrolides, especially clarithromycin (48–51), typically resulting in prolongation of the QT interval and cardiac dysrhythmias (torsade de pointes) (52).

Cisapride

Cisapride can prolong the QT interval, with a risk of ventricular dysrhythmias (53,54). Clarithromycin increases serum concentrations of cisapride (55). This potentially dangerous interaction can result in QT interval prolongation and dysrhythmias such as torsade de pointes.

- Torsade de pointes occurred in a 77-year-old woman taking cisapride and clarithromycin (56).

Warnings have been issued by the manufacturers to avoid concomitant administration.

Colchicine

- Fatal colchicine intoxication occurred in a 67-year-old man who had taken clarithromycin 500 mg bd for 4 days (57).

Clarithromycin may have inhibited colchicine metabolism and caused a rise in colchicine concentration.

Digoxin

Clarithromycin has been reported to cause digoxin toxicity (58). Two different mechanisms are involved, inhibition of the renal excretion of digoxin and alteration of intestinal flora, which reduces the presystemic hydrolysis of digoxin.

- A 70-year-old woman taking digoxin for atrial fibrillation developed nausea, vomiting, and dizziness 2 days after starting to take clarithromycin (59). Her serum digoxin concentration was 3.9 ng/ml (target range 0.5–2.0).

Disulfiram

Fatal toxic epidermal necrolysis and fulminant hepatitis occurred shortly after the start of treatment with clarithromycin in a 47-year-old man who was taking disulfiram (60).

- A 47-year-old man with a history of chronic alcoholism took disulfiram 250 mg/day for 1 month. He then took clarithromycin 500 mg bd and paracetamol 500 mg tds and 1 week later noticed non-pruritic cutaneous maculopapular lesions on his legs, extending to the rest of his body, excluding the palms and soles. Previous drug therapy was withdrawn. A skin biopsy showed toxic epidermal necrolysis. During the next several days the skin lesions worsened. Cutaneous blisters became evident, initially covering less than 10% of the body surface, but then extending all over the body. The serum

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bilirubin concentration was 359 μmol/l (direct bilirubin 213 μmol/l), the partial thromboplastin time longer than 200 seconds, and the prothrombin time 26 seconds. He developed septic shock and, despite supportive measures, died.

Ergot alkaloids

In patients with ergotamine toxicity, vasoconstriction can lead to frank ischemia. Clarithromycin interferes with ergotamine metabolism.

- A 41-year-old woman developed worsening lower leg pain, pallor, and a sensation of coolness aggravated by exertion; there was severe vasospasm in the legs (61). She had taken a caffeine + ergotamine formulation for migraine for many years and had recently been given clarithromycin 500 mg bd for flu-like symptoms.

HIV nucleoside reverse transcriptase inhibitors

Clarithromycin reduced the peak concentration and AUC of zidovudine at steady state by about 12% (32), possibly as a result of reduced zidovudine absorption (62). However, if the two drugs were taken at least 2 hours apart, the pharmacokinetics of zidovudine were unaffected.

In 12 HIV-positive patients there was no statistically significant difference in concentrations of didanosine when clarithromycin was added (63).

Midazolam

In an open, randomized, crossover, pharmacokinetic and pharmacodynamic study in 12 healthy volunteers who took clarithromycin 250 mg bd for 5 days, azithromycin 500 mg/day for 3 days, or no pretreatment, followed by a single dose of midazolam (15 mg), clarithromycin increased the AUC of midazolam by over 3.5 times and the mean duration of sleep from 135 to 281 minutes (64). In contrast, there was no change with azithromycin, suggesting that it is much safer for co-administration with midazolam.

Omeprazole

In 21 healthy volunteers, clarithromycin (400 mg bd) for 3 days before omeprazole (20 mg/day) significantly inhibited the metabolism of omeprazole (65).

Pimozide

Clarithromycin inhibits the metabolism of pimozide, pimozide plasma concentrations increase, and there is an increased risk of cardiotoxicity through prolongation of the QT interval and fatal ventricular dysrhythmias (66).

Rifamycins

Clarithromycin is one of the core drugs for MAC infections in both HIV-infected and non-infected patients. For this indication, doses of up to 2000 mg/day are used, typically in combination with other drugs.

The interaction of clarithromycin with the rifamycins is complex. Clarithromycin inhibits CYP3A4, while both rifampicin and rifabutin induce P450 cytochromes, including CYP3A4, resulting in enhanced metabolism of drugs. The changes in serum concentrations of clarithromycin and its metabolite in the presence of the enzyme inducers rifampicin and rifabutin suggest that metabolism of clarithromycin by CYP3A4 is increased (67).

After the addition of rifampicin, peak serum concentrations of clarithromycin fell markedly, from a mean of 5.8–2.5 μg/ml (67). At the same time the ratio of the serum concentrations of clarithromycin and its 14-OH metabolite was reversed from 3.3:1 to 1:2.7. There were similar, although less marked, changes after the addition of rifabutin 600 mg/day to a regimen that included clarithromycin 1000 mg/day.

Whether these changes in serum clarithromycin concentrations are relevant to its antimicrobial activity is unknown, since prediction of clinical efficacy based on serum concentrations of clarithromycin is probably not justified, given that the macrolides accumulate to a large degree in tissues and macrophages.

In patients with MAC infections taking rifabutin or rifampicin the addition of clarithromycin resulted in rifamycin-related adverse events in 77% of patients (68). These included uveitis (69–72), especially at rifabutin doses of 600 mg/day or more, neutropenia, nausea, vomiting, diarrhea, and abnormal liver enzyme activities. In addition, diffuse polyarthralgia (19%) was observed. Since inhibition of cytochrome P450 by clarithromycin can interfere with rifabutin metabolism, as illustrated by a report of a significant increase in the AUC of rifabutin during treatment with clarithromycin (68), the authors recommended using rifabutin in a dosage of 300 mg/day in regimens that include a macrolide.

The effects of fluconazole and clarithromycin on the pharmacokinetics of rifabutin and 25-*O*-desacetylrifabutin have been studied in ten HIV-infected patients who were given rifabutin 300 mg qds in addition to fluconazole 200 mg qds and clarithromycin 500 mg qds (73). There was a 76% increase in the plasma AUC of rifabutin when either fluconazole or clarithromycin was given alone and a 152% increase when both drugs were given together. The authors concluded that patients should be monitored for adverse effects of rifabutin when it is co-administered with fluconazole or clarithromycin.

Sulfonylureas

- Severe hypoglycemia occurred in two elderly men with type 2 diabetes mellitus and mild to moderate impaired renal function, who took clarithromycin 1000 mg/day for respiratory infections, in addition to a sulfonylurea (glibenclamide 5 mg/day in one case and glipizide 15 mg/day in the other) (74). Both developed severe hypoglycemia within 48 hours of starting clarithromycin.

Tacrolimus

Clarithromycin can increase the steady-state concentrations of drugs that depend primarily on CYP3A metabolism.

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- Steady-state tacrolimus concentrations rose in a 32-year-old African-American man who took clarithromycin 500 mg bd for 4 days (75).
- In two women aged 37 and 69, acute and reversible tacrolimus nephrotoxicity developed after the addition of clarithromycin for an upper respiratory tract infection (76).

Theophylline and other xanthines

Inhibition of cytochrome P450 activity by clarithromycin affects the metabolism of theophylline. However, the results of several studies of the effect of clarithromycin on theophylline concentrations are conflicting. While the total body clearance of theophylline fell (77) and plasma theophylline concentrations increased by 18% (78), mean theophylline concentrations remained within the target range (78). Based on these data it is wise to monitor serum theophylline concentrations in patients taking high dosages of theophylline or in patients with theophylline concentrations in the upper target range who start to take clarithromycin (36).

Warfarin

Increases in International Normalized Ratio (INR) have been detected in patients who have previously been stabilized on warfarin when they were simultaneously given clarithromycin. In one case this caused a suprachoroidal hemorrhage (79).

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Clebopride

General Information

Like alizapride, clebopride is a prokinetic dopamine receptor antagonist that has extrapyramidal effects. These effects were initially overlooked, but a warning was eventually issued in 1988 (1). The problem has continued to be reported, the incidence at effective doses probably being as high as 25%.

In a 1991 report on a crossover trial, a third of the participants had to withdraw because of adverse effects, among which drowsiness, dizziness, tremors, and anxiety were prominent (2).

Organs and Systems

Nervous system

Clebopride can cause extrapyramidal syndromes (3,4). They range from transient dyskinesia to persistent parkinsonism, tardive dyskinesia (5,6), and tardive dystonia (7).

Extrapyramidal symptoms associated with clebopride have been reported in two 17-year-old patients within 10–16 hours of taking clebopride 0.5 mg tds (3).

In one case respiratory dyskinesia, which can easily be mistaken for psychogenic hyperventilation, was described (SEDA-17, 414).

Progressive supranuclear palsy has also been described (8).

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Clemastine

See also Antihistamines

General Information

Clemastine (SEDA-7, 172) (SEDA-21, 173) belongs to the benzhydryl ether group and was developed in the hope of lessening sedative effects. There was no significant difference compared with other first-generation antihistamines.

Organs and Systems

Nervous system

Clemastine caused sedation in 9–50% of patients (1).

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Reference

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Clenbuterol

See also Beta$_2$-adrenoceptor agonists

General Information

Clenbuterol may cause somewhat more adverse effects than some other beta$_2$-adrenoceptor agonists and its long half-life could perhaps explain this.

Organs and Systems

Cardiovascular

Induction of physiological cardiac hypertrophy has important implications in various clinical settings, particularly in training of the left ventricle in operations for certain types of congenital heart disease. Positive effects of beta$_2$-adrenoceptor overexpression on cardiac function have been shown in experiments in mice (1).

The hypothesis that clenbuterol improves right ventricular systolic function in large mammalian species when given at the time of induction of pressure-overload cardiac hypertrophy has been tested in 15 open-chest operated sheep before and after 6 weeks of pulmonary artery banding (2). The animals were randomly assigned to either saline solution or clenbuterol. There was a highly significant improvement in the slope of the end-systolic pressure–volume loops in the clenbuterol-treated animals, without detrimental hemodynamic effects. No predictions can be made as to the lasting effects of clenbuterol's ability to augment systolic function in a chronically pressure-overloaded, thin-walled ventricle beyond 6 weeks, or the potential for tachyphylaxis.

Nervous system

Dyskinetic movements have been reported in one elderly patient taking clenbuterol (SEDA-17, 164).

Drug Administration

Drug overdose

The effects of overdose with clenbuterol have been described (3).

- A 28-year-old woman developed a sustained sinus tachycardia (140/minute), hypokalemia (2.4 mmol/l), hypophosphatemia (0.29 mmol/l), and hypomagnesemia (0.76 mmol/l) after accidentally ingesting a reportedly small quantity of clenbuterol. She was treated with metoprolol and potassium. Her serum clenbuterol concentration was 2.93 ng/ml 3 hours after ingestion, well above the maximal peak serum concentration of 0.087 ng/ml 2.4 hours after administration of a therapeutic dose of 20 μg of clenbuterol (4).

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Clidinium bromide

See also Anticholinergic drugs

General Information

The anticholinergic drug clidinium is best known as a component of Librax (chlordiazepoxide 5 mg plus clidinium bromide 2.5 mg); the dose used is sufficient to produce typical anticholinergic adverse effects. Since here it is combined with a benzodiazepine, it is most unwise to allow patients taking Librax to drive motor vehicles or to ingest alcohol.

Clobazam

See also Benzodiazepines

General Information

Clobazam, a 1,5-benzodiazepine, differs in its chemical structure from most other benzodiazepines. It has been claimed to have less sedative effects for its effective anticonvulsant and anti-anxiety effects (SED-12, 98). Whether because of tolerance or not, clobazam tends to be less sedative than clonazepam. Both the therapeutic and adverse effects of clobazam have been related to its major metabolite *N*-desmethylclobazam, the formation of which depends on CYP2C19 activity. Mutant alleles that confer high CYP2C19 activity, and are therefore associated with high concentrations of the metabolite, are particularly common (30–40%) in Asian populations (1).

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Comparative studies

In a randomized double-blind comparison of clobazam, carbamazepine, and phenytoin monotherapy in children with epilepsy, there were no differences in tests of intelligence, memory, attention, psychomotor speed, and impulsivity between clobazam and the other drugs after 6 and 12 months of therapy, suggesting that the adverse effects of clobazam on cognition and behavior may be less common than generally thought (2). However, the authors did not discuss a trend for some scores, particularly items in the Wechsler Intelligence Scale for Children–Revised, to improve significantly only in children taking non-benzodiazepine anticonvulsants. Moreover, many children withdrew from the study before completion of the follow-up, resulting in potential bias.

In a prospective multicenter double-blind comparison of clobazam with phenytoin or carbamazepine monotherapy in children with partial or generalized tonic-clonic seizures, the retention rate after one year did not differ, but exit due to inefficacy tended to be more common with clobazam (19 versus 11% for the other drugs combined), while exit due to adverse effects tended to be more common with carbamazepine or phenytoin (15 versus 4% for clobazam) (3). Although all treatments were claimed to have similar efficacy, detailed descriptions of the changes in seizure frequency and the proportion of patients who gradually achieved seizure control in each treatment group were not given. Behavioral and mood problems tended to be more common with clobazam than with the other drugs (38/119 versus 29/116). Drooling was more common with clobazam (7/119 versus 2/116), whereas rash or vomiting were more common with the other treatments (9/116 versus 4/119 and 10/116 versus 4/119 respectively). Tolerance was reported in 7.5% of patients taking clobazam, in 4.2% of those taking carbamazepine, and in 6.7% of those taking phenytoin; however, the definition of tolerance (no seizures for 3–6 months, followed by seizures sufficiently numerous to require a switch to another drug) was questionable, and no information was given about patients with seizure relapses who required an increase in dosage. Although these results suggest that clobazam is a valuable alternative to phenytoin and carbamazepine in childhood epilepsy, more precise characterization of responses would have been desirable.

Organs and Systems

Respiratory

Patients receiving intravenous benzodiazepines must be monitored for respiratory depression, and may need artificial ventilation during intensive treatment.

Nervous system

Clobazam is better tolerated than other benzodiazepines used in epilepsy (4). Its most common adverse effects are mild and transient drowsiness, dizziness, or fatigue; rather less common are muscle weakness, restlessness, aggressiveness, weight increase, ataxia, mood disorders, psychotic and behavioral disturbances, vertigo, hypotonia, hypersalivation, and edema (SED-13, 152). There may be a loss of therapeutic response over time.

Akathisia has been rarely seen with benzodiazepines (SED-13, 152).

Psychological, psychiatric

Of 63 children with refractory epilepsy given add-on clobazam (mean dosage 0.8 mg/kg/day) and followed for 15–64 months, 15 (24%) had to discontinue treatment owing to adverse effects, which included severe aggressive outbursts, hyperactivity, insomnia, and depression with suicidal ideation (5). Likewise, there were behavioral or mood problems in 38 of 119 children taking clobazam monotherapy over one year of follow-up, while drooling was reported in seven children (3). In another study, 7 of 63 children treated with clobazam developed aggressive agitation, self-injurious behavior, insomnia, and incessant motor activity. All the affected children were relatively young (mean age 6 years) and mentally disabled (6).

In controlled trials with clonazepam, adverse events were recorded in 60–90% of cases, and led to withdrawal rates as high as 36% (7). The most common effects were drowsiness, ataxia, and behavioral and personality changes. Other problems were hypersalivation, tolerance, and sometimes a paradoxical increase in seizure frequency.

Skin

Toxic epidermal necrolysis has been associated with clobazam (SEDA-21, 48). Bullae with sweat gland necrosis rarely complicate coma, but have recently been reported in association with clobazam, used as adjunctive therapy for resistant epilepsy in a 4-year-old girl (8).

Long-Term Effects

Drug tolerance

Clobazam has similar effects on anxiety to other benzodiazepines, but may be better tolerated (SEDA-20, 31). Used as an anticonvulsant, clobazam is generally well tolerated in epileptic patients, many showing little evidence of tolerance (4). On the other hand, children with epilepsy appear unusually prone to adverse behavioral reactions when taking clobazam (SEDA-19, 34).

Drug withdrawal

Withdrawal effects can be troublesome. Of 13 patients taken off clonazepam 0.01–0.5 mg/day because of adverse effects, 8 had withdrawal seizures and 5 had other withdrawal symptoms (SEDA-19, 63). Choreoathetosis was described in one patient completing withdrawal of clonazepam (SED-13, 152).

Epileptic-negative myoclonus status (almost continuous lapses in muscle tone associated with epileptiform discharges and interfering with postural control and motor coordination) rarely occur after rapid withdrawal of clobazam or valproate (9).

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Drug–Drug Interactions

Antiepileptic drugs

Several metabolic interactions between clobazam and other antiepileptic drugs have been reported, in particular phenytoin intoxication after the addition of clobazam (SED-12, 98).

Carbamazepine

Negative myoclonus and more typical signs of carbamazepine intoxication (fatigue, ataxia, clumsiness) occurred in a 66-year-old man after he took add-on clobazam (10 mg/day) for 4 weeks (10). Plasma concentrations of carbamazepine (58 μmol/l) and carbamazepine-10,11-epoxide (19 μmol/l) were higher than before clobazam therapy, and his symptoms resolved quickly when carbamazepine dosage was reduced and clobazam was withdrawn. The interaction was confirmed on rechallenge.

This interaction does not occur in most patients.

Stiripentol

After the addition of stiripentol (50 mg/kg) in 20 children treated with clobazam, mean serum clobazam concentrations increased about twofold and norclobazam concentrations increased about threefold; a mean 25% reduction in clobazam dose was required because of adverse effects (11). Serum concentrations of concomitantly administered valproic acid rose by about 20%. These findings are in agreement with evidence that stiripentol is a potent metabolic inhibitor.

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Clobuzarit

See also Non-steroidal anti-inflammatory drugs

General Information

Clobuzarit, a methylpropionic acid derivative, thought to have a penicillamine-like effect, was withdrawn from the market in the 1980s because of several reports of Stevens–Johnson syndrome (1).

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Clofazimine

See also Antituberculosis drugs

General Information

Clofazimine is weakly bactericidal against *Mycobacterium leprae*. It is active in chronic skin ulcers (Buruli ulcer) and partly against *Mycobacterium avium* intracellulare. The usual adult dosage is 50–100 mg/day. At higher doses, its anti-inflammatory effect seems to prevent the development of acute reactions, such as erythema nodosum leprosum.

Clofazimine is a strongly lipophilic dye and accumulates in tissues, especially fat, bile, macrophages, the reticuloendothelial system, and skin. This is the basis of adverse reactions, including skin discoloration (1). Lymphedema (2), diminished sweating, and reduced tearing have been observed (3).

Observational studies

In 84 patients with leprosy who took clofazimine, the most common adverse effect was a dark red skin pigmentation of varying intensity, which appeared within 10 weeks of the start of therapy (4). The intensity of the colour was proportional to the density of the infiltration. There was ichthyosis in 56 patients. Adverse effects such as anorexia, diarrhea, lymph gland enlargement, liver enlargement, corneal drying, and loss of weight were self-correcting, but nine patients had severe gastrointestinal effects (severe abdominal pain, vomiting, and diarrhea).

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Organs and Systems

Respiratory

Clofazimine crystals were observed in macrophages in the respiratory alveoli of a patient with AIDS; this is considered harmless (5).

Nervous system

Intraneural deposition of a ceroid-like pigment has been seen after treatment of lepromatous leprosy with clofazimine (6). This pigment does not affect the healing process. Treatment can be continued, provided that the dose is not too high.

Sensory systems

In 76 patients taking multidrug therapy, including clofazimine, for at least 6 months, 46% had conjunctival deposition, 53% had deposition in the cornea, and crystals were found in the tears of 32% (7). Conjunctival pigmentation has been reported, as well as reversible linear brownish corneal streaks. Two cases of macular pigmentation have also been described (SEDA-5, 294).

Gastrointestinal

Nausea, vomiting, diarrhea, abdominal pain, and anorexia have been reported with clofazimine (8).

Clofazimine can accumulate and precipitate in tissues, such as the wall of the small bowel, after prolonged administration. Enteropathy can develop if crystals are stored in the lamina propria of the jejunal mucosa and the mesenteric lymph nodes. These effects depend on the dosage and duration of therapy. When this complication is suspected jejunal biopsy is indicated. At laparotomy, all organs can have an orange–yellow color (SEDA-9, 272) (1,9). On drug withdrawal, the enteropathy progressively improves. Recognized for the first time in 1967, only 14 cases of this complication have so far appeared in the English-language literature (10). Acute or chronic abdominal pain was the main symptom. In most patients, the diagnosis was made after exploratory laparotomy. Barium meal follow-through or CT scanning of the abdomen showed mucosal thickening in the small intestine. Mesenteric lymph node enlargement was present in the index case. Characteristic eosinophilic clofazimine crystals were demonstrated in the histiocytes of all patients except three. The authors proposed the term "clofazimine-induced crystal-storage histiocytosis" to emphasize causes other than B cell neoplasms for crystal-storage histiocytosis. Awareness of this complication of clofazimine can avoid unnecessary surgical exploration.

Liver

Clofazimine can inhibit the liver damage that is associated with lepromatous leprosy and the leprosy reaction; it has only minimal or no deleterious effects on liver function (11).

Skin

Pigmentation and purple skin discoloration are the most frequent adverse effects of clofazimine. It is therefore unacceptable to most light-skinned patients (12).

Ichthyosis is very frequent at dosages of clofazimine over 100 mg/day (SEDA-8, 290).

Nails

Nail changes, such as brown discoloration of the nail plate and onycholysis, have been described in patients taking high doses (300 mg/day) of clofazimine (13). Clofazimine crystals were demonstrated in the nails and nail beds.

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Clofedanol

General Information

Clofedanol is a centrally acting cough suppressant with mild local anesthetic properties. In an open study 30 patients were treated with clofedanol for 14 days. Two were withdrawn from the study because of tiredness and vomiting. These adverse effects disappeared immediately after treatment was withdrawn (1).

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Cloforex

See also Anorectic drugs

General Information

Cloforex is similar in structure to chlorphentermine. It produces adverse effects similar to those of other appetite suppressants. Outstanding among them are sleeplessness or tiredness, headache, diarrhea, increased sweating, and dryness of the mouth; there may also be tolerance to its effects (1).

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Clometacin

See also Non-steroidal anti-inflammatory drugs

General Information

The NSAID clometacin is an indometacin derivative.

Because of the risk of long-term or repeated use of clometacin, the French authorities restricted its use to prescriptions for no more than 8 days. It seems wise to recommend that it be no longer used.

Organs and Systems

Hematologic

Thrombocytopenia has been attributed to clometacin (SEDA-6, 94).

Liver

The hepatotoxic potential of clometacin was first reported in France in 1978. Since then many cases of hepatotoxic effects have been described (SEDA-7, 109). In two retrospective studies the clinical, biochemical, immunological, and histopathological features were outlined in detail (1,2). The patients had jaundice and/or hepatomegaly (90%), weakness (60%), fever (30%), and abdominal pain (20%), with or without diarrhea, nausea, and vomiting, usually presenting after long-term use or shortly after a rechallenge. The biochemical disorders were hepatocellular hepatitis and cholestatic hepatitis. High titers of antitissue antibodies and hypergammaglobulinemia were also present in most patients. Histological findings were characteristic of acute hepatitis or chronic active hepatitis. There was a high prevalence of HLA-antigen B8. These immunological features suggest an autoimmune pathogenesis.

Urinary tract

A retrospective analysis of acute renal insufficiency related to NSAID therapy in France showed that clometacin was most frequently implicated. Cases of functional renal insufficiency and interstitial nephritis with nephrotic syndrome were reported (SEDA-12, 84).

Skin

Skin eruptions, generalized pruritus, and weight loss have been reported (1).

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Clomethiazole

General Information

Clomethiazole is a sedative-hypnotic that has been used extensively in the treatment of alcohol withdrawal, as well as for inducing sedation and sleep in the elderly. In addition to GABA enhancement, which it shares with the benzodiazepines, clomethiazole also enhances the activity of another inhibitory amino acid, glycine. Whether this property is clinically important is uncertain. As well as the expected effects of sedation and memory impairment, it produces nasal irritation, especially in younger patients, in whom it has a shorter half-life. Its use in alcohol withdrawal is becoming less common, possibly owing to the demonstrated safety and efficacy of longer-acting benzodiazepines, such as chlordiazepoxide, and alternatives such as carbamazepine.

Hypotension, phlebitis, and respiratory depression can occur after intravenous use. While effects in the elderly may be increased, the incidence of adverse effects is similar to that seen in younger subjects (1).

Clomethiazole, like the benzodiazepines, has an additive effect with other CNS depressants, and can cause profound bradycardia when combined with beta-adrenoceptor antagonists.

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Organs and Systems

Nervous system

In a double-blind, double-dummy, placebo-controlled comparison of clomethiazole and gammahydroxybutyrate in ameliorating the symptoms of alcohol withdrawal, alcohol-dependent patients were randomized to receive either clomethiazole 1000 mg or gammahydroxybutyrate 50 mg/kg (2). There was no difference between the three treatments in ratings of alcohol withdrawal symptoms or requests for additional medication. After tapering the active medication, there was no increase in withdrawal symptoms, suggesting that physical tolerance did not develop to either clomethiazole or gammahydroxybutyrate during the 5-day treatment period. The most frequently reported adverse effect of gammahydroxybutyrate was transient vertigo, particularly after the evening double dose.

The effect of clomethiazole on cerebral outcome in patients undergoing coronary artery bypass surgery has been investigated in 245 patients, who were randomized double-blind to placebo or clomethiazole (1800 mg over 45 minutes followed by 800 mg/hour until the end of surgery) (3). A battery of eight neuropsychological tests was administered preoperatively and repeated 4–7 weeks after surgery. There were no differences between the clomethiazole and placebo groups in postoperative neuropsychological tests scores. Thus, clomethiazole did not improve or worsen cerebral outcome after coronary artery bypass surgery.

The efficacy and safety of clomethiazole (75 mg/kg by intravenous infusion over 24 hours), as a neuroprotective drug, were studied in a double-blind, placebo-controlled trial (CLASS, the Clomethiazole Acute Stroke Study) in 1360 patients with acute hemispheric stroke (4). Clomethiazole was generally well tolerated and safe. Sedation was the most common adverse event, leading to treatment withdrawal in 16% of patients compared with 4.2% of placebo-treated patients.

In a small subset of CLASS (95 patients) mortality at 90 days was 19% in the clomethiazole group and 23% in the placebo group (5). Sedation was the most common adverse event (clomethiazole 53%, placebo 17%), followed by rhinitis and coughing. The incidence and pattern of serious adverse events was similar between the groups.

A report has illustrated the dangers of driving a motor vehicle whilst taking clomethiazole (6).

- A 53-year-old male car driver was followed by the police for about 2 km, while he drove in an unsafe manner, until the car crashed into the owner's garage. Analysis of his blood showed a clomethiazole concentration of 3.3 μg/ml. Neither alcohol nor any other drug could be detected. One day later he committed suicide by swallowing at least 60 capsules of clomethiazole.

Liver

Reversible cholestatic jaundice has been attributed to clomethiazole (SEDA-21, 39).

Long-Term Effects

Drug abuse

As with other GABA enhancers, clomethiazole is highly abusable in susceptible individuals and should not be used for outpatient detoxification (7).

Drug dependence

Clomethiazole maintains its efficacy with apparently less dependence than temazepam during prolonged use (7).

Drug–Drug Interactions

Alteplase

The safety of the thrombolytic drug alteplase (tPA) plus clomethiazole in patients with acute ischemic stroke has been assessed in a randomized, double-blind study (8). All received alteplase 0.9 mg/kg, beginning within 3 hours of stroke onset, and then either intravenous clomethiazole 68 mg/kg ($n = 97$) over 24 hours, or placebo ($n = 93$) beginning within 12 hours of stroke onset. During follow-up for 90 days the number of serious adverse event reports was 47 in the clomethiazole group and 48 in the placebo group. There were 15 deaths in those given clomethiazole and nine in those given placebo, but this was not significantly different. Sedation was also greater with clomethiazole (42%) than with placebo (13%).

Cimetidine

Cimetidine can reduce clomethiazole clearance by 60–70% (9).

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Clomiphene

General Information

Clomiphene is a very weak non-steroidal estrogen; it blocks the feedback effect of endogenous estrogens on the pituitary, promoting the further secretion of gonadotropins. The primary use of clomiphene in women is in the induction of ovulation. In men, it has been used to treat infertility in view of its ability to increase endogenous production of testosterone (1).

General adverse effects

In one large study, some adverse reactions in treated women were due to its ovulatory effects and others were direct reactions to the substance itself (2). The most common problem was ovarian enlargement (14%), followed by hot flushes (11%), abdominal and pelvic discomfort (7.0%), and nausea and vomiting (2.1%). Incidental symptoms were breast discomfort, vaginal changes, psychological symptoms, headache, heavier menses, and increased urinary frequency. Sporadic case-reports on clomiphene in the literature relate to fetal ovarian dysplasia or maternal psychosis (SEDA-7, 391), either of which may have been coincidental. However, it must be borne in mind that the substance is related structurally to triparanol, an obsolete drug that produced a series of disastrous adverse effects some 40 years ago.

In another study, the adverse effects of the antiestrogenic effects of clomiphene citrate were hot flushes (10%), mood swings, depression, headaches (1%), pelvic pain (5.5%), nausea (2%), breast tenderness (2–5%), dryness and loss of hair (0.3%), visual symptoms, halos and streaks around lights (particularly at night), blurring, and scotoma (1.5%) (3).

Organs and Systems

Nervous system

In a multicenter WHO study, two men withdrew because of visual disturbances, dizziness, and headaches (4).

Reproductive system

In some men taking clomiphene in the hope of improving subfertility, a non-bacterial pyospermia developed and could well have had an adverse effect on the outcome; it appeared more commonly in clomiphene users than controls (5).

Long-Term Effects

Tumorigenicity

Mammary cancer in the mother has been suspected as a risk of clomiphene, but specific investigations into the matter have not supported this suspicion (SED-12, 1034) (6).

A case of testicular seminoma in a man receiving both clomiphene and mesterolone for 15 months for oligospermia has been described (7), but it is unlikely that the drug was responsible.

Malignant melanoma

Concern that the drug treatment of female infertility might predispose the user to malignant melanoma was first engendered by a US study published in 1995 (8). Among women who had used clomiphene citrate for infertility, the incidence of melanoma was higher (RR = 1.8; 95% CI = 0.8, 3.5) than among American women in general. However, in a case-cohort study of nearly 4000 infertile women there was a similar increase in the incidence of melanoma among those who had been treated with human chorionic gonadotropin compared with the rest; there was no association with the use of clomiphene.

Quite apart from the inherent discrepancy in these findings, several pieces of evidence have confused the debate. In the first place, the cohort of melanoma cases was small—barely a handful. In the second place, some earlier papers had suggested that infertility in women might of itself have an association with melanoma. The same impression came from various studies, in which the incidences of cancers in infertile women were examined (9–11). If that were true, it could affect the initial findings in either direction: a high spontaneous incidence might mask a real drug effect, or it might provide a predisposition to melanoma, which the drugs might then more readily trigger.

In the meantime, data from Australia have shown no greater incidence of melanoma among women who had used fertility drugs and undergone in vitro fertilization than in the country's general female population (12). Since then there has been one more significant paper, again from Australia, using data from a specialized fertility clinic in Queensland, relating to all women who attended the center over a decade (13). Whenever possible, the women were traced and their subsequent history noted. Originally intended as a retrospective case-cohort study using a subcohort, the approach had to be amended because no cases of melanoma were found in the subcohort. The work therefore proceeded as a matched case-control study; all the data were taken and set against publicly available figures on melanoma in Queensland. After some necessary exclusions, 3186 women were included; care was taken to minimize recall bias. Fourteen women developed melanoma after fertility treatment, eight cases being invasive. The expected incidence in the general population would have been 15.8

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cases in the same period. The incidence actually observed was therefore only 0.89 of that anticipated (95% CI = 0.54, 1.48). The numbers of women who had used clomiphene or human menopausal gonadotropin were too small to make more differentiated calculations, but the incidence of melanoma seemed to correspond to that in the general population.

On current evidence there seems no reason to discourage fertility-promoting drug treatments because of any risk of melanoma; they may even reduce it to some extent. However, this does not alter the fact that the data are deficient in various ways. Quite apart from the small numbers of melanoma cases that have been recorded, all the work to date has been performed in relatively sunny parts of the world; it is not known what would happen in other climates. Within countries there are sharp differences in melanoma figures; in the USA, where about 32 000 new cases of skin melanoma were projected for 1994 (14), the highest melanoma rates occur among light-skinned populations in areas of intense sunlight, for example Arizona; the same applies to Queensland, Australia. In the USA as a whole there is a melanoma incidence among whites of 12.4 per 100 000 (15), while mortality rates vary inversely with latitude (16). Furthermore, in whites, there has been a recent increase in the incidence of melanoma, during the precise period that this type of treatment has become popular, but probably for entirely different reasons, which may be associated with lifestyles and holiday habits; the reported incidence in whites rose by no less than 102% from 1973 to 1991 (16). Finally, as the Australian authors themselves stressed, the fact that the Queensland clinic was a private institution specializing in IVF/GIFT therapy means that women with endocrine-associated or ovulation-associated infertility may not have been referred to it so readily.

All this makes it very difficult to find a baseline incidence for melanoma with which cases treated for infertility can be compared. It is to be hoped that data of this type will continue to arrive from other centers, so that a definitive judgement will become possible.

Second-Generation Effects

Teratogenicity

Suspicions that clomiphene might adversely affect a fetus that has developed as a result of successful ovulation induction are difficult to confirm or allay, since the condition for which clomiphene is being used, that is subfertility, might itself be associated with a risk of malformation. The fear originally arose after 18 cases of trisomy had been reported in the USA; later data on a large series of clomiphene-induced pregnancies (17) indicated that if there was indeed such risk it must be very small; a study of 200 instances of Down's syndrome showed that none of them had been exposed to the drug (SEDA-6, 357). Another report concerned a case of congenital retinopathy (SEDA-7, 391).

Cornel and colleagues concluded in 1989 that there was a relative risk of at least two of an association between disturbed fertility and neural tube defects (18), but others found no evidence for an association between maternal clomiphene use and such defects. The authors of a pooled analysis of all published work concluded that any increase in neural tube defects is likely to be less than two-fold and that there may in fact be no increase at all (1).

One unusual possibility is a change in the sex ratio; in one study the ratio of boys to girls among infants conceived after induction of ovulation with clomiphene was 0.85, significantly different from the normal human sex ratio at birth, which is about 1.06 (19).

An unusual condition that has been tentatively ascribed to clomiphene is persistence of the hyperplastic primary vitreous, that is fetal ophthalmic tissue that normally resolves before birth. If more than a trace of the material persists, ocular complications, including cataract and retinal detachment, can result. In a case reported from Canada, there had been an estimated 3 weeks of exposure to high doses of clomiphene (100 mg/day) after gestation, and the child's vision was severely impaired (20). This is probably not a mere chance association, since several cases of visual defects of various types after exposure to clomiphene have been described before, and in some animal studies the drug does adversely affect ocular development.

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Clomipramine

See also Tricyclic antidepressants

General Information

Clomipramine is the imipramine analogue of chlorpromazine. However, while the difference between chlorpromazine and promazine is large, adding a chloride atom to imipramine hardly affects its actions. Most trials have failed to show any superiority of the chlorinated compound over imipramine. The adverse effects profile is similar (1), but drowsiness, confusion, and "feeling awful" are commonly reported (2).

In a controlled comparison between clomipramine and amitriptyline, the former caused adverse effects more often, especially drowsiness (3). Overdose toxicity is the same as with other tricyclic antidepressants (4); fatal interactions with monoamine oxidase (MAO) inhibitors have been reported (SEDA-18, 16) (5). Altogether, toxic effects are not substantially different.

Besides depression, clomipramine is also widely used in the treatment of phobic and obsessive-compulsive disorders (6–8) and in panic disorders (9).

Organs and Systems

Cardiovascular

Venous thrombosis is a recognized complication of tricyclic antidepressants. Thrombosis of the cerebral veins occurred in a 61-year-old woman after intravenous clomipramine, and the authors suggested that the risk may be greater when the intravenous route is used (10).

Intravenous administration invariably produced electrocardiographic changes, sometimes slow to reverse, in elderly patients (11).

At therapeutic doses, tricyclic antidepressants can cause postural hypotension, but they are regarded as being safe in patients who require general anesthesia. However, hypotension during surgery has been associated with clomipramine (12).

- A 57-year-old man due to undergo mitral valve surgery took clomipramine (150 mg at night) up to the night before surgery. His blood pressure before induction with thiopental (250 mg) and fentanyl (250 μg) was 105/65 mmHg, with a heart rate of 70 beats/minute. Anesthesia was maintained with isofluorothane, and 45 minutes after induction, his systolic blood pressure fell to 90 mmHg. Ephedrine (30 mg total), phenylephrine (500 μg total), or dopamine (10 μg/kg/minute) did not increase the blood pressure. After sternotomy, his systolic blood pressure fell to 55 mmHg and his pulse rate to 60 beats/minute, and he had third-degree atrioventricular block. Further ephedrine, phenylephrine, and adrenaline were without effect. During cardiopulmonary bypass, a noradrenaline infusion was started (0.2 μg/kg/minute) and isofluorothane was withdrawn. After he had been weaned from bypass the noradrenaline infusion was continued at a dose of 0.2–0.8 μg/kg/minute, sufficient to maintain the systolic blood pressure at 90–100 mmHg. After the operation, clomipramine was withheld and the noradrenaline infusion tapered off, and 3 days later the hypotension had resolved.

The hypotension in this case was severe and refractory to noradrenergic stimulation, perhaps because of the alpha$_1$-adrenoceptor antagonist properties of clomipramine. The fall in systolic blood pressure was accompanied by a paradoxical fall in heart rate, perhaps because the anticholinergic effect of clomipramine removed the effect of vagal tone on the resting heart rate. It seems likely that the hypotensive effect of clomipramine was potentiated by general anesthesia; however, such a reaction is rare and the underlying cardiac problem may have contributed to this severe adverse reaction. This case reinforces current advice that tricyclic antidepressants are best avoided in patients with significant cardiac disease.

Nervous system

Use of the intravenous route is fraught with danger and without any demonstrable advantages.

- A 31-year-old woman who received clomipramine intravenously 300 mg/day developed seizures and cardiac arrest on the 15th day; she was successfully resuscitated (13).

Seizures occurred in four of 50 patients receiving intravenous treatment. Those vulnerable to this complication were not identified in advance by prescreening electroencephalography (14).

Endocrine

Clomipramine has also aroused interest because of an action on prolactin release, which occurs with major tranquillizers but not with other tricyclic antidepressants (15). This action of clomipramine is related to its chemical structure and reflects a greater effect on dopamine

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metabolism and serotonin uptake compared with other antidepressants.

Sexual function

Delayed or complete abolition of ejaculation is attributed to strong 5-HT re-uptake blockade but perhaps with additional alpha-adrenoceptor-blocking activity (16). Impotence may be due to a ganglionic blocking action.

Four patients taking up to 100 mg/day developed uncontrollable yawning, in three cases (two men and one woman) associated with sexual arousal, in two instances with spontaneous orgasm (17). In all four patients the symptoms disappeared after withdrawal.

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Clonazepam

See also Benzodiazepines

General Information

Clonazepam is a benzodiazepine that is used predominantly in epilepsy, panic disorder, and mania, and also appears to be effective in relieving antipsychotic drug-induced akathisia (1). The use of clonazepam in psychiatric disorders is complicated by significant drowsiness in a majority of patients, and additional behavioral problems in children (SEDA-19, 34).

Although they are commonly used in the adjunctive management of chronic pain, benzodiazepines are generally not analgesic per se. One exception may be the stabbing/lancinating neuropathic pain that often responds to anticonvulsants, including clonazepam. Nevertheless, the use of benzodiazepines in pain syndromes is generally contraindicated, and clonazepam, although often effective, should be used with caution (SEDA-17, 42). This is because of the availability of other agents with comparable or superior efficacy and the significant incidence of adverse effects of clonazepam, including depression, self-poisoning, cognitive impairment, and dependence (2), as well as the potential for diversion.

Organs and Systems

Nervous system

In controlled trials with clonazepam, adverse events were recorded in 60–90% of cases and led to withdrawal rates as high as 36% (3). The most common effects were drowsiness, ataxia, and behavioral and personality changes. Other problems were hypersalivation, tolerance, and sometimes a paradoxical increase in seizure frequency.

Psychological, psychiatric

The addition of clonazepam to clomipramine has been reported to have caused acute mania (4).

- A 48-year-old Japanese man with a history of bipolar affective disorder became depressed again. He was already taking lithium carbonate 800 mg/day and carbamazepine 800 mg/day. Clomipramine was added, and the dose was increased to 225 mg/day over 2 months and then maintained for 2 months. Because clomipramine had little effect, clonazepam 3 mg/day was added. On the first day after he took clonazepam, symptoms of hyperthymia, haughtiness, talkativeness, and flight of ideas suddenly appeared once more. Drug-induced delirium was excluded, because orientation was not disrupted and the symptoms did not fluctuate over time. Clomipramine and clonazepam were withdrawn. Because the symptoms were similar to the previous manic episode, the same prescription was reinstated, with the addition of sodium valproate 800 mg/day. After 3 months, he was discharged in remission and

had no recurrence. He had not taken other benzodiazepines throughout the treatment.

This report suggests that clonazepam induced a switch to mania, possibly in combination with an effect of clomipramine.

Mouth and teeth

A sensation of a burning mouth has been attributed to clonazepam (5).

- A 52-year-old white woman developed a burning mouth. She had previously taken alprazolam for anxiety, but this was changed to clonazepam because of increased anxiety and panic. Clonazepam relieved her symptoms, but after 4 weeks of therapy she continued to have a constant, mild, oral burning sensation. Examination of the mouth was normal and laboratory tests were unremarkable. The dose of clonazepam was reduced and her symptoms abated but remained intolerable. Clonazepam was withdrawn and her symptoms completely resolved. Since no other medications relieved her anxiety and panic she took clonazepam again, but again developed an intolerable burning mouth. Clonazepam was again withdrawn and her symptoms resolved.

Long-Term Effects

Drug withdrawal

Withdrawal effects can be troublesome. Of 13 patients taken off clonazepam at a rate of 0.016–0.5 mg/day because of adverse effects, 8 had withdrawal seizures and five had other withdrawal symptoms (SEDA-19, 63). Choreoathetosis was described in one patient completing withdrawal of clonazepam (SED-13, 152).

- A 43-year-old man underwent an incomplete transcranial removal of a pituitary growth-hormone-secreting macroadenoma (6). His daily insulin dose was reduced from more than 300–104 U/day and he was given hydrocortisone and levothyroxine replacement therapy, together with lanreotide injections. A month after discharge, he was given high-dose clonazepam. Three months later, the clonazepam was withdrawn abruptly and he developed hypoglycemic coma.

The author concluded that interruption of benzodiazepine treatment had caused reduced growth hormone secretion and insulin requirements.

Drug–Drug Interactions

Carbamazepine

The mutual interaction of clonazepam and carbamazepine has been investigated in 183 children and adults with epilepsy during routine clinical care (7). Carbamazepine increased the clearance of clonazepam by 22% and clonazepam reduced the clearance of carbamazepine by 21%.

The effects of concomitant carbamazepine, phenytoin, sodium valproate, and zonisamide on the steady-state serum concentrations of clonazepam have been investigated in 51 epileptic in-patients under 20 years of age (8). Serum concentrations of clonazepam correlated positively with the dose of clonazepam and negatively with the doses of carbamazepine and valproic acid, but not with phenytoin or zonisamide. These results confirm that as the oral doses of carbamazepine and sodium valproate increase, the serum concentration of clonazepam falls, but there is no interaction with either phenytoin or zonisamide. In the case of carbamazepine the mechanism of action is thought to be enzyme induction, increasing the metabolism of clonazepam. It is not known what the mechanism is with sodium valproate. In patients with epilepsy, the co-administration of either sodium valproate or carbamazepine will reduce the serum concentration of clonazepam and increase the risk of a seizure. When clonazepam is used in the treatment of epilepsy, sodium valproate and carbamazepine should be avoided; phenytoin and zonisamide would be safer alternatives.

Phenelzine

A flushing reaction has been associated with an interaction of phenelzine with clonazepam (SEDA-17, 17).

Sertraline

In a randomized, double-blind, placebo-controlled, crossover study in 13 subjects, sertraline did not affect the pharmacokinetics or pharmacodynamics of clonazepam (9).

Valproate

The effects of concomitant carbamazepine, phenytoin, sodium valproate, and zonisamide on the steady-state serum concentrations of clonazepam have been investigated in 51 epileptic in-patients under 20 years of age (8). Serum concentrations of clonazepam correlated positively with the dose of clonazepam and negatively with the doses of carbamazepine and valproic acid, but not with phenytoin or zonisamide. These results confirm that as the oral doses of carbamazepine and sodium valproate increase, the serum concentration of clonazepam falls, but there is no interaction with either phenytoin or zonisamide. In the case of carbamazepine the mechanism of action is thought to be enzyme induction, increasing the metabolism of clonazepam. It is not known what the mechanism is with sodium valproate. In patients with epilepsy, the co-administration of either sodium valproate or carbamazepine will reduce the serum concentration of clonazepam and increase the risk of a seizure. When clonazepam is used in the treatment of epilepsy, sodium valproate and carbamazepine should be avoided; phenytoin and zonisamide would be safer alternatives.

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Clonidine and apraclonidine

General Information

The presynaptic alpha-adrenoceptor agonists, particularly methyldopa and clonidine, are agonists at presynaptic alpha$_2$-adrenoceptors. Guanabenz, guanfacine, and tiamenidine appear to be qualitatively similar to clonidine; clear evidence of quantitative differences remains to be confirmed.

The mechanism of action of these drugs depends on reducing sympathetic nervous outflow from the nervous system by interference with regulatory neurotransmitter systems in the brainstem. Because none of the drugs was selective or specific for circulatory control systems, the hypotensive effects were invariably accompanied by other nervous system effects. However, the identification of imidazoline receptors has suggested that it may be possible to develop drugs, such as moxonidine and relminidine, with greater selectivity for circulatory control mechanisms and a reduced likelihood of unwanted nervous system depressant effects (1).

Clonidine has been used to treat hypertension and migraine. It ameliorates the opioid withdrawal syndrome by reducing central noradrenergic activity. Its role in the treatment of psychiatric disorders has been the subject of an extensive review, but without new information on its safety (2). Clonidine is also used epidurally, in combination with opioids, neostigmine, and anesthetic and analgesic agents, to produce segmental analgesia, particularly for postoperative relief of pain after obstetrical and surgical procedures.

The use of clonidine in children has been comprehensively reviewed (3,4).

Apraclonidine (*para*-aminoclonidine) is a relatively nonspecific alpha$_1$- and alpha$_2$-adrenoceptor agonist, which is less likely to cross the blood–brain barrier than clonidine. Apraclonidine suppresses aqueous humor flow by 39–44% and lowers intraocular pressure by 20–23% (5).

Organs and Systems

Cardiovascular

Clonidine causes sinus bradycardia and atrioventricular block, as illustrated by two cases, one a 10-year-old boy (6) and the other a 71-year-old woman (7), who developed Wenckebach's phenomenon. Clonidine was also studied in seven patients subjected to electrophysiological studies after 5 weeks of therapy (8). It slowed the sinus rate and increased the atrial pacing rate, producing Wenckebach's phenomenon, indicating depressed function of the sinus and AV nodes.

In three patients with chronic schizophrenia and primary polydipsia given clonidine in doses of up to 800 micrograms/day for 2–5 months, blood pressure and pulse fell significantly in a dose-dependent manner, but fluid intake, as assessed by measurements of weight and 24-hour urine volume, was not affected (9). Hypotension and bradycardia limited the extent to which the dose of clonidine could be increased. The lack of effect of clonidine on polydipsia in this small sample and the inconsistent results of two other recent studies have provided little overall support for using clonidine to treat primary polydipsia associated with schizophrenia.

Clonidine-induced hypertension has been reported in a patient with autonomic dysfunction (10).

- A 39-year-old quadriplegic man with poorly controlled pain had many features consistent with autonomic dysfunction (for example a C4 spinal lesion, orthostatic hypotension, hypertension). He routinely used transdermal clonidine and transdermal glyceryl trinitrate as needed for control of acute hypertensive episodes. The clonidine was discontinued, after which his blood pressure fell (maximum systolic and diastolic pressures by about 50 and 25 mmHg respectively).

Because clonidine relies on central alpha$_2$-adrenoceptor agonist activity for its hypotensive effects, it can cause hypertension in patients with autonomic dysfunction. It should therefore be used with great caution when autonomic dysfunction is suspected.

The effect of intrathecal clonidine has been evaluated in a prospective randomized study in 45 children aged 6–15 years, who were randomized to receive either 0.5% hyperbaric bupivacaine or 0.5% hyperbaric bupivacaine plus clonidine 2 micrograms/kg (11). Clonidine was associated with non-significant prolongation of motor block, from an average of 150–190 minutes. Postoperative analgesia was significantly longer with clonidine (490 versus 200 minutes). Clonidine was associated with higher incidences of hypotension (54 versus 36%) and bradycardia (30 versus 0%).

Respiratory

The effects of clonidine and other alpha$_2$-adrenoceptor agonists on respiratory function in asthmatics have been

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reviewed (12). Inhaled alpha$_2$-adrenoceptor agonists reduce the bronchial response to allergens, and if ingested they can aggravate the bronchial response to histamine.

Nervous system

Treatment with centrally acting agents is characterized by a relatively high incidence (up to 60% in some studies) of nervous system depressant effects (dizziness, drowsiness, tiredness, dry mouth, headache, depression), particularly during the initial period of treatment or after dosage increments. Sedation, lethargy, and tiredness are common with clonidine, particularly at the start of treatment (13).

In a placebo-controlled study of a single oral dose of clonidine 0.25–3 mg in 18 healthy men aged 18–21 years, clonidine caused more sleepiness than placebo; it significantly reduced stage 1 and rapid-eye-movement (REM) sleep and increased stage 2 sleep (14).

Clonidine 300 micrograms was given orally to 30 patients 60 minutes before intrathecal anesthesia with lidocaine 40 mg or 80 mg, and 60 other patients received either plain lidocaine 100 mg or lidocaine 40 mg or 80 mg with clonidine 100 micrograms intrathecally (15). Clonidine, both intrathecally and orally, prolonged the duration of spinal block and allowed a reduction in the dose of lidocaine needed for a given duration of block, but prolongation of motor block, exceeding the duration of sensory block, was a drawback with both routes and doses of clonidine. The smallest hemodynamic changes were seen with lidocaine 40 mg + clonidine 100 micrograms intrathecally, which provided adequate anesthesia for operations lasting up to 140 minutes. All doses of clonidine caused sedation.

Endocrine

Clonidine stimulates the release of growth hormone and has been used as a provocation test of growth hormone reserve (16).

Clonidine reduces plasma renin activity and urinary aldosterone and catecholamine concentrations (17).

Mouth

Dry mouth is common with clonidine, and investigation of the mechanism has come from an experimental study in which the direct effect of clonidine on salivary amylase excretion from rat parotid dispersed cells was measured in vitro (18). Clonidine stimulated calcium influx into the cells and inhibited postsynaptic alpha$_1$-adrenoceptor responses.

Gastrointestinal

Constipation is frequent with clonidine, and one case of pseudo-obstruction of the bowel has been reported (19).

Urinary tract

Epidural clonidine is less likely to produce urinary retention than epidural opioids (20,21).

Skin

Rashes occur in about 4% of patients taking clonidine (22).

Transdermal clonidine formulated in adhesive skin patches has been used for long-term treatment with once-weekly application. When transdermal clonidine is used to lower blood pressure systemic adverse effects seem to be fewer than with oral clonidine (23). However, localized skin reactions are common, and the incidence increases with the dose and duration of use. Common signs include erythema, scaling, vesiculation, excoriation, and induration. Allergic contact dermatitis is less frequent but still common. Hyperpigmentation and depigmentation also occur. Pretreatment with 0.5% hydrocortisone is associated with less skin irritation and higher blood concentrations.

Immunologic

During long-term treatment of glaucoma with apraclonidine allergic reactions can occur. In a retrospective analysis of 64 patients who used apraclonidine 1% for more than 2 weeks, 31 (48%) developed an allergic reaction that led to withdrawal of treatment, with a mean latency of 4.7 months (24). Those who had allergic reactions tended to be older and female.

- A 46-year-old woman, who took clonidine 25 mg bd for menopausal flushing, developed depigmentation and swelling of her forearms (25). A skin biopsy showed a pattern consistent with immune complex disease, with IgG, IgM, Clq, C2c, and C4 complement between muscle fibers and at the dermo-epidermal junctions. All of these abnormalities disappeared after withdrawal.

Long-Term Effects

Drug tolerance

During long-term treatment of glaucoma, apraclonidine 0.5% is effective in reducing intraocular pressure, both in the short term and for up to 24 months. However, efficacy is lost in some patients. Of 174 patients followed for up to 24 months apraclonidine was ineffective in 38 patients (21%), at some point during the study (26).

Drug withdrawal

A withdrawal syndrome with marked rebound hypertension (attributed to increased sympathetic nervous activity as a result of drug-modified receptor responses) is an occasional but well-recognized complication of the abrupt withdrawal of alpha$_2$-adrenoceptor agonists, particularly with clonidine. In its most florid form, the clonidine withdrawal syndrome is characterized by a pronounced increase in blood pressure, tachycardia, tremulousness, and sweating (27). There is an associated marked increase in catecholamine output and the features are reminiscent of pheochromocytoma or accelerated hypertension. Milder cases can pass unnoticed, unless the patient is being carefully monitored. The syndrome begins within 48 hours of withdrawal, and although the exact incidence is unknown it is more likely if the patient has been taking a high dosage. There has even been a case report of rebound hypertension in association with transdermal clonidine (28). Treatment is by combined alpha- and beta-blockade, and it is important to avoid monotherapy with a beta-blocker, since this may exacerbate the syndrome by promoting unopposed alpha-adrenergic effects.

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There have been two case reports of other serious complications arising from the acute withdrawal of clonidine. Neuropsychiatric disturbance with self-injury occurred in a child (29) and myocardial infarction developed in a patient with no history of ischemic heart disease (30).

Drug Administration

Drug formulations

Transdermal clonidine (clonidine TTS) has been used with some success for the treatment of mild hypertension. Systemic adverse effects are similar to those seen after oral administration, but are less frequent and milder. They include dry mouth, drowsiness, headache, sexual disturbance, cold extremities, obstipation, and fatigue (31–33). These adverse effects rarely necessitate withdrawal of clonidine TTS.

A high percentage of patients who take clonidine (up to 38%) (34) develop contact allergic reactions, usually due to the active ingredient, at the patch application site (35). This has been reported with a frequency of 15% in 357 African–American hypertensive patients. It can lead to drug discontinuation in 4.2% of patients.

Recurrent maculopapular rash due to both topical and systemic administration of clonidine has been reported (36).

- A 47-year-old woman was given transdermal, oral, and intravenous clonidine at different times, separated by several months. The patches were withdrawn after 2 months because of pruritic erythematous vesiculation at the site of application. Oral clonidine (0.3 mg/day) had to be withdrawn when a generalized maculopapular rash appeared on the third day, and was promptly exacerbated by each dose. Intravenous clonidine 0.150 mg was followed within 30 minutes by a severe, generalized, maculopapular reaction requiring systemic steroids and antihistamines.

The authors interpreted these reactions as being allergic. A patch test was very positive to the commercial formulation. Clonidine is a weak sensitizer, but occlusion and prolonged skin contact during transdermal application can cause delayed hypersensitivity.

Drug administration route

The most common ocular adverse effects of topical apraclonidine are conjunctival hyperemia, itching, foreign body sensation, and lacrimation. The most frequent systemic adverse effects are dry mouth and unusual taste perception (37–39). With *para*-aminoclonidine, headaches, attributable to ocular vasoconstriction, as well as anxiety, vomiting, dry mouth, tremor, and pallor, have been reported (40).

Drug overdose

The effects of exposure to clonidine hydrochloride in children, as reported to US poison centers from 1993 to 1999, have been retrospectively reviewed (41). There were 10 060 reported exposures, of which 57% were in children under 6 years, 34% in children aged 6–12 years, and 9% in adolescents aged 13–18 years. In 1999 there were 2.5 times as many exposures as in 1993. Clonidine was the child's medication in 10% of those under 6 years, 35% of those aged 6–12 years, and 26% of the adolescents. Unintentional overdose was most common in those under 6 years, while therapeutic errors and suicide attempts predominated in those aged 6–12-years and the adolescents. In 6042 symptomatic children (60%), the most common symptoms were lethargy (80%), bradycardia (17%), hypotension (15%), and respiratory depression (5%). Most of the exposures resulted in no effect (40%) or minor effects (39%). There were moderate effects in 1907 children (19%), major effects in 230 (2%), and one death in a 23-month-old child.

- A hypertensive crisis and myocardial infarction occurred in a 62-year-old woman after a combined injection of hydromorphone 48 mg and clonidine 12 mg subcutaneously in an attempt to refill an implanted epidural infusion pump (42). She was immediately treated with naloxone, but she subsequently had accelerated hypertension, a brief tonic-clonic seizure, and an anteroseptal myocardial infarction. Cardiac catheterization showed no coronary narrowing or blockage, but an anterior infarct was confirmed.

It is believed that the reaction was secondary to the vasoconstricting effects of high-dose clonidine through stimulation of peripheral alpha-adrenoceptors.

Drug–Drug Interactions

Mianserin

Mianserin has alpha-adrenoceptor activity and so might interact with clonidine (43). In healthy volunteers, pretreatment with mianserin 60 mg/day for 3 days did not modify the hypotensive effects of a single 300 mg dose of clonidine. In 11 patients with essential hypertension, the addition of mianserin 60 mg/day (in divided doses) for 2 weeks did not reduce the hypotensive effect of clonidine. The results of this study appear to have justified the authors' conclusion that adding mianserin to treatment with clonidine will not result in loss of blood pressure control.

Mirtazapine

Hypertension has been reported with mirtazapine plus clonidine (44).

- A 20-year-old man had had Goodpasture's syndrome for 2.5 years, end-stage renal disease on chronic hemodialysis for 15 months, and hypertension controlled with metoprolol, losartan, and clonidine. He developed dyspnea and hypertension (blood pressure 178/115 mmHg) 2 weeks after his psychiatrist first gave him mirtazapine 15 mg at bedtime to treat depression. His blood pressure did not fall significantly, despite the addition of losartan and minoxidil and the use of intravenous glyceryl trinitrate and labetalol. Only after emergency dialysis and intravenous nitroprusside did his blood pressure fall to 150–180/80–100 mmHg. When mirtazapine was withdrawn, his blood pressure was controlled with minoxidil 5 mg, clonidine 0.1 mg, and metoprolol 10 mg, all bd.

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The authors recognized that mirtazapine alone could have caused the hypertensive event. In postmarketing surveillance of mirtazapine, hypertension occurred in at least 1% of patients. However, it is likely that the patient lost antihypertensive control because mirtazapine antagonized the antihypertensive effect of clonidine. Mirtazapine, a tetracyclic antidepressant, stimulates the noradrenergic system through antagonism at central alpha$_2$ inhibitory receptors, which is precisely opposite to the effect of clonidine.

Neostigmine

Clonidine increases the analgesic effect of intrathecal neostigmine without enhancing its adverse effects (45).

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Clopidogrel

General Information

Clopidogrel is a thienopyridine compound, structurally related to ticlopidine, which inhibits ADP-induced platelet aggregation (1). Its efficacy in stroke, myocardial infarction, and other vascular causes of death has been demonstrated in the CAPRIE Study (2), a large trial in which 9599 patients were treated with clopidogrel. The most frequent adverse effects were gastrointestinal symptoms, although they were not significantly more frequent than with aspirin. Bleeding disorders were as common with clopidogrel as with aspirin (9.3% with each). More patients withdrew from treatment because of rashes from clopidogrel (0.9%) than from aspirin (0.4%). Neutropenia and thrombocytopenia occurred very rarely and with similar rates in the two groups.

The adverse effects of clopidogrel have been reviewed (3).

Organs and Systems

Hematologic

During active surveillance by medical directors of blood banks, hematologists, and the manufacturers of clopidogrel, 11 patients were identified in whom thrombotic thrombocytopenic purpura developed during or soon after treatment with clopidogrel (4). Of these 11 patients, 10 had taken clopidogrel for 14 days or less before the onset. From this study it is not possible to calculate the frequency of thrombotic thrombocytopenic purpura, since the size of the population from which the 11 cases were drawn is unknown.

- Fatal aplastic anemia has been reported in two patients taking clopidogrel (5,6). Aplastic anemia was diagnosed 5 months after starting clopidogrel in the first patient and after 3 months in the second. Both died from infection (sepsis and pneumonia). Except for allopurinol in the first case, these patients did not take any medications associated with aplastic anemia.

Major bleeding is uncommon with clopidogrel. In a randomized, double-blind, placebo-controlled, 18-month study of the effects of aspirin 75 mg/day in 7599 high-risk patients with recent ischemic stroke or transient ischemic attacks and at least one additional vascular risk factor who were already taking clopidogrel 75 mg/day, life-threatening bleeding was more common in the group who took aspirin and clopidogrel compared with clopidogrel alone: 96 (2.6%) versus 49 (1.3%); absolute risk increase 1.3% (95% CI 0.6, 1.9) (7). Episodes of major bleeding were also more common in those taking aspirin plus clopidogrel, but there was no difference in mortality.

Acquired autoimmune hemophilia has been attributed to clopidogrel (8).

Skin

Clopidogrel can cause pruritus and urticaria (9).

Immunologic

A severe allergic reaction has been associated with clopidogrel (10).

- A 57-year-old man took clopidogrel after a myocardial infarction and after 5 days developed a fever, rash, pruritus, and abdominal pain. Three days later he developed shock. He had thrombocytopenia, lymphopenia, aseptic leukocyturia, and raised serum activities of transaminases, amylase, and gamma-glutamyl transpeptidase. Blood cultures were negative. Clopidogrel was withdrawn and within 1 week he had completely recovered and all blood tests had returned to normal. One month later, he took clopidogrel again; 4 hours later the same symptoms

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reappeared, with aseptic leukocyturia and raised transaminases and gamma-glutamyl transpeptidase. Drug allergy was suspected and clopidogrel was withdrawn. All the symptoms disappeared within a few days and did not recur during the following year.

It is highly probable that this reaction was provoked by clopidogrel because of the positive rechallenge and because the patient did not take any other drug.

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Clortermine hydrochloride

See also Anorectic drugs

General Information

Clortermine, an alpha-dimethylphenethylamine chlorine derivative, suppresses food-reinforced behavior without concomitant stimulation or depression of the central nervous system. Headache was the main characteristic complaint in 49 obese people taking clortermine 50 mg/day; in four subjects it was severe enough to stop treatment. In all cases, the complaints were drug-related and not placebo-related (SED-9, 17) (1).

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Clotiapine

See also Neuroleptic drugs

General Information

Clotiapine is a dibenzothiazepine neuroleptic drug.

Organs and Systems

Pancreas

Pancreatitis has been attributed to clotiapine (1).

- A 49-year-old woman started to take clotiapine 200 mg/day for a severe psychotic episode. On the second day, she complained of abdominal pain and nausea, followed by vomiting. Increased activities of serum amylase (1490 U/ml), serum lipase (3855 U/ml), and urinary amylase (3417 U/ml) suggested pancreatitis. There was no evidence of gallstones or tumor. She was given perphenazine instead, and her amylase and lipase activities fell to normal. Six months later, when she had a psychotic relapse, she was again treated with clotiapine and 2 days later had a rapid rise in amylase activity (887 U/ml). When switched to perphenazine, she had new peaks in amylase and lipase. A year later, her amylase and lipase were normal and her psychiatric disorder was stabilized with pimozide.

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Cloximate

General Information

Cloximate is approved in only a few countries, so experience with its use is limited. The usual adverse effects of NSAIDs (headache, insomnia, drowsiness, anorexia, gastrointestinal symptoms, a transient increase in blood urea, leukopenia, thrombocytopenia, and rashes) have been reported (1).

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Clozapine

See also Neuroleptic drugs

General Information

Clozapine is a dibenzodiazepine, an atypical neuroleptic drug with a high affinity for dopamine D_4 receptors and a low affinity for other subtypes (1). It is also an antagonist at alpha-adrenoceptors, 5-HT_{2A} receptors, muscarinic receptors, and histamine H_1 receptors.

Observational studies

Rates of hospitalization with clozapine have been analysed by Novartis, the manufacturers, based on two retrospective studies of hospitalization among patients with treatment-resistant schizophrenia (2). All the patients who began clozapine treatment in Texas State psychiatric facilities during the early 1990s ($n = 299$) were compared with controls who received traditional neuroleptic drugs ($n = 223$), matched for severity, age, and sex. More patients in the latter group required continuous hospitalization: at 4 years, four times as many patients taking a traditional medication had a 6-month period of continuous hospitalization.

In a study in Ohio, patients with chronic borderline personality disorder who were in hospital for an average of 110 days/year were given clozapine (mean daily dosage at time of discharge 334 mg; range 175–550 mg) (3). None stopped taking clozapine and few adverse effects were reported. Among the seven patients who were taking clozapine when they were discharged, hospitalization fell to a mean of 6.3 days per patient per year. There was no control group in this study.

- Of 10 adolescent inpatients (aged 12–17 years) with severe acute manic or mixed episodes, who did not improve after treatment with conventional drugs and who were given clozapine (mean dose 143 mg/day), all responded positively after 15–28 days and adverse effects (increased appetite, sedation, enuresis, sialorrhea) were frequent but not severe enough to require reduced dosages (4). Mean weight gain after 6 months was 7 kg (11%), and neither reduced white cell counts nor epileptic seizures were reported during follow-up for 12–24 months.

In a case series in which clozapine was used as add-on medication, two patients with bipolar disorder and one with schizoaffective disorder had marked reductions in affective symptoms after clozapine had been added to pretreatment with a mood stabilizer; transient and moderate weight gain and fatigue were the only adverse effects (5).

In a retrospective open study of 46 patients taking clozapine for 4 years, clozapine had to be discontinued in 10 patients (21%) and serious adverse effects were rare; no patient had agranulocytosis (6). The most troublesome adverse effects were drooling, sedation, and weight gain, and three patients had seizures.

Experiences in uncontrolled open studies in Chinese patients have been summarized (7). The most common adverse effect of clozapine was hypersalivation, followed by sedation. Mandatory blood monitoring is considered an obstacle in persuading some patients to undergo a trial of clozapine, mainly for cultural reasons, summed up by the Chinese proverb that "a hundred grains of rice make a drop of blood."

Clozapine has been used in some special groups of patients, including patients with severe borderline personality disorder (8), patients with aggressive schizophrenia (9), and mentally retarded adults (10).

Of 12 in-patients with borderline personality disorder treated with clozapine for 16 weeks, 10 developed sedation, which disappeared during the first month of treatment; 9 had hypersialorrhea, and 6 had falls in white blood cell counts, which never reached unsafe values.

Patients with aggressive schizophrenia ($n = 29$) improved when treated with clozapine; one was withdrawn after the development of leukopenia. In 10 mentally retarded patients taking clozapine for 15 days to 46 months improvement was observed. Half of the patients developed sedation and hypersalivation, and one discontinued the drug after 2 weeks because of neutropenia. The putative neurotoxicity of clozapine in moderately to profoundly retarded patients (that is, those with an accentuation of cognitive deficits due to the drug's anticholinergic and sedating properties) was not observed. Fifty special hospitalized patients with schizophrenia associated with serious violence were treated with clozapine (mean dose at 2 years 465 mg) (11). The most frequent adverse effects were hypersalivation ($n = 14$), sedation ($n = 10$), and weight gain ($n = 6$); two patients had tonic-clonic seizures, two others developed mild neutropenia, and in one case treatment was stopped owing to agranulocytosis.

In a retrospective review, 33 mentally retarded patients were evaluated; adverse effects were mild and transient, constipation being the most common ($n = 10$) (12). There were no significant cardiovascular adverse effects and no seizures; no patient discontinued treatment because of agranulocytosis. Small sample sizes, short durations of treatment, and lack of controls in these studies preclude definite conclusions.

A 37-item survey covering a variety of somatopsychic domains has been administered to 130 patients with schizophrenia taking a stable clozapine regimen (mean dose 464 mg/day; mean duration 34 months) (13). Most of them reported an improvement in their level of satisfaction, quality of life, compliance with treatment, thinking, mood, and alertness. Most reported worse nocturnal salivation (88%); weight gain (35%) came second; fewer patients reported a worsening of various gastrointestinal and urinary symptoms.

Clinical predictors of response have been examined in 37 partially treatment-refractory outpatients who

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had been assigned to clozapine in a double-blind, haloperidol-controlled, long-term (29-week) study (14). Clozapine responders were rated as less severely ill, had fewer negative symptoms, and had fewer extrapyramidal adverse effects at baseline compared with non-responders.

Combination therapy

Of 656 Danish patients who were taking clozapine, 35% were taking concomitant neuroleptic drugs, 28% benzodiazepines, 19% anticholinergic drugs, 11% antidepressants, 8% antiepileptic drugs, and 2% lithium (15). The rationale for supplementing clozapine treatment in refractory schizophrenia in this way has been thoroughly reviewed following a bibliographic search covering 1978–1998 (16). In all, 70 articles were retrieved but only a few were controlled studies, most being case reports/series. Among the many possible drug combinations, the evidence suggests that clozapine plus sulpiride is the most efficacious combination. The combined use of benzodiazepines and clozapine can cause cardiorespiratory collapse; valproate can cause hepatic dysfunction and more so with clozapine; lithium can cause neurotoxicity and seizures and more so with clozapine; and at least some serotonin reuptake inhibitors (SSRIs) appear to raise plasma clozapine concentrations to above the usual target range.

Organs and Systems

Cardiovascular

Clozapine has been associated with cardiomyopathy (SED-14, 142) (SEDA-21, 52) (17), changes in blood pressure (SEDA-21, 52) (SEDA-21, 52) (SEDA-22, 57) (18,19), electrocardiographic changes (SEDA-22, 57) (20–22), and venous thromboembolism (SEDA-20, 47).

Hypertension

Several cases of hypertension have been associated with clozapine (SEDA-22, 57), and alpha$_2$-adrenoceptor blockade has been proposed as a possible mechanism (18). Four patients developed pseudopheochromocytoma syndrome associated with clozapine (23); all had hypertension, profuse sweating, and obesity. The authors suggested that clozapine could increase plasma noradrenaline concentrations by inhibiting presynaptic reuptake mediated by alpha$_2$-adrenoceptors.

Hypotension

Hypotension is the most commonly observed cardiovascular adverse effect of neuroleptic drugs, particularly after administration of those that are also potent alpha-adrenoceptor antagonists, such as chlorpromazine, thioridazine, and clozapine (24). A central mechanism involving the vasomotor regulatory center may also contribute to the lowering of blood pressure.

- A 51-year-old man taking maintenance clozapine developed profound hypotension after cardiopulmonary bypass (19).

Cardiac dysrhythmias

A substantial portion of patients taking clozapine develop electrocardiographic abnormalities; the prevalence was originally estimated at 10% (SEDA-20, 47) (SEDA-22, 57). However, although the prevalence may be higher, most of the effects are benign and do not need treatment. In 61 patients with schizophrenia taking clozapine, in whom a retrospective chart review was conducted to identify electrocardiographic abnormalities, the prevalence of electrocardiographic abnormalities in those who used neuroleptic drugs other than clozapine was 14% (6/44), while in the neuroleptic drug-free patients it was 12% (2/17); when treatment was switched to clozapine, the prevalence of electrocardiographic abnormalities rose to 31% (19/61) (25).

The correlation between plasma clozapine concentration and heart rate variability has been studied in 40 patients with schizophrenia treated with clozapine 50–600 mg/day (21). The patients had reduced heart rate variability parameters, which correlated negatively with plasma clozapine concentration.

Clozapine can cause prolongation of the QT interval (26).

- In a 30-year-old man taking clozapine there were minor electrocardiographic abnormalities, including a prolonged QT interval. A power spectrum analysis of heart rate variability showed marked abnormalities in autonomic nervous system activity. When olanzapine was substituted, power spectrum analysis studies showed that his heart rate had improved significantly and that his cardiovascular parameters had returned to normal. Serial electrocardiograms showed minimal prolongation of the QT interval.

Tachycardia is the most common cardiovascular adverse effect of clozapine, and atrial fibrillation has also been reported (SEDA-22, 57) (20).

The reports of sudden death associated with clozapine and the possibility that it may have direct prodysrhythmic properties have been reviewed (27).

A patient developed ventricular fibrillation and atrial fibrillation after taking clozapine for 2 weeks (22).

- A 44-year-old man with no significant cardiac history was given clozapine and 12 days later had bibasal crackles in the chest and ST segment elevation in leads V2 and V3 of the electrocardiogram. He then developed ventricular tachycardia and needed resuscitation. He also developed atrial fibrillation for 24 hours, which subsequently resolved.

Cardiomyopathy

Cardiomyopathy has been associated with neuroleptic drugs, including clozapine (28–30), and partial data initially suggested an incidence of 1 in 500 in the first month.

A thorough study of the risk of myocarditis or cardiomyopathy in Australia detected 23 cases (mean age 36 years; 20 men) out of 8000 patients treated with clozapine from January 1993 to March 1999 (absolute risk 0.29%; relative risk about 1000–2000) (17). All the accumulated data on previous reports of sudden death, myocarditis, or cardiac disease noted in connection with clozapine treatment were requested from the Adverse Drug Reactions

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Advisory Committee (ADRAC); there were 15 cases of myocarditis (five fatal) and 8 of cardiomyopathy (one fatal) associated with clozapine. All cases of myocarditis occurred within 3 weeks of starting clozapine. Cardiomyopathy was diagnosed up to 36 months after clozapine had been started. There were no confounding factors to account for cardiac illness. Necropsy results showed mainly eosinophilic infiltrates with myocytolysis, consistent with an acute drug reaction.

The manufacturers analysed 125 reports of myocarditis with clozapine and found 35 cases with fatal outcomes (31). A total of 53% occurred in the first month of therapy, and a small number (4.8%) occurred more than 2 years after the start of treatment. In this series, 70% of the patients were men.

Taking into account the results from an epidemiological study of deaths in users and former users of clozapine (32), the cardiovascular mortality risk related to clozapine may be outweighed by the overall lower mortality risk associated with its beneficial effects, since the death rate was lower among current users (322 per 100 000 person years) than among past users (696 per 100 000 person years). The reduction in death rate during current use was largely accounted for by a reduction in the suicide rate compared with past use (RR = 0.25; CI = 0.10, 0.30).

Since cardiomyopathy is potentially fatal, some precautions must be taken. If patients taking clozapine present with flu-like symptoms, fever, myalgia, dizziness or faintness, chest pain, dyspnea, tachycardia or palpitation, and other signs or symptoms of heart failure, consideration should always be given to a diagnosis of myocarditis. Suspicion should be heightened if the symptoms develop during the first 6–8 weeks of therapy. It should be noted, however, that flu-like symptoms can also occur during the titration period, supposedly as a result of alpha-adrenoceptor antagonism by clozapine. Patients in whom myocarditis is suspected should be referred immediately to a cardiac unit for evaluation.

Clozapine rechallenge after myocarditis has been described (33).

- A 23-year-old man with no history of cardiac disease was given clozapine 12.5 mg/day, increasing to 200 mg/day over 3 weeks; 5 weeks later he complained of shortness of breath and non-specific aches and pains in his legs and body. There was marked ST-segment depression and T wave inversion in the lateral and inferior leads of the electrocardiogram. There was no eosinophilia, and creatine kinase activity was not raised. An echocardiogram showed a hyperdynamic heart and left ventricular size was at the upper limit of normal. The heart valves were normal. Clozapine was withdrawn, but his mental state and quality of life deteriorated, and 2 years later clozapine was restarted because other drugs had not produced improvement. The dose of clozapine was built up to 225 mg at night and he remained well and free from cardiac adverse effects.

In this case a consultant cardiologist diagnosed myocarditis secondary to clozapine, as no other confounding co-morbidity was identified. However, the negative rechallenge suggests either that the clozapine was not responsible or that there was tolerance to the effect.

Pericarditis

Serositis (pericarditis and pericardial effusion, with or without pleural effusion) has been reported in patients taking clozapine (34–36).

- A 43-year-old man developed a pericardial effusion after taking clozapine for 7 years. The condition resolved when the drug was withdrawn.
- A 16-year-old girl developed pericarditis associated with clozapine. There were electrocardiographic changes and serial rises in serum troponin I, a highly sensitive and specific marker of myocardial injury.

The latter is said to be the first reported case of pericarditis due to clozapine demonstrating rises in troponin I, which resolved despite continuation of therapy. The authors suggested that troponin I is the preferred marker for monitoring the cardiac adverse effects of clozapine.

Venous thromboembolism

Typical neuroleptic drugs have been associated with an increased risk of venous thromboembolism (37). Data from the Swedish Reactions Advisory Committee suggested that clozapine is also associated with venous thromboembolic complications (38). Between 1 April 1989 and 1 March 2000, 12 cases of venous thromboembolism were collected; in 5 the outcome was fatal. Symptoms occurred in the first 3 months of treatment in eight patients; the mean clozapine dose was 277 mg/day (75–500). Although during the study total neuroleptic drug sales, excluding clozapine, accounted for 96% of all neuroleptic drug sales, only three cases of thromboembolism associated with those neuroleptic drugs were reported. The reported risk of thromboembolism associated with clozapine is estimated to be 1 per 2000–6000 treated patients, the true risk being higher owing to under-reporting. These conclusions were consistent with those from an observational study (32).

Between February 1990, when clozapine was first marketed in the USA, and December 1999 the FDA received 99 reports of venous thromboembolism (83 mentioned pulmonary embolism with or without deep vein thrombosis and 16 mentioned deep vein thrombosis alone) (39). In 63 cases death had resulted from pulmonary embolism; 32 were confirmed by necropsy. Of 36 non-fatal cases, only 7 had been documented objectively by such diagnostic techniques as perfusion-ventilation lung scanning and venography. Thus, in 39 of the 99 reports there was objective evidence of pulmonary embolism or deep vein thrombosis. The median age of the 39 individuals was 38 (range 17–70) years and 20 were women. The median daily dose was 400 (range 125–900) mg. The median duration of clozapine exposure before diagnosis was 3 months (range 2 days to 6 years). Information on risk factors for pulmonary embolism and deep vein thrombosis varied; however, 18 of the 39 patients were obese. The frequency of fatal pulmonary embolism in this study is consistent with that described in the labelling for clozapine in the USA.

As of 31 December 1993, there were 18 cases of fatal pulmonary embolism in association with clozapine therapy in users aged 10–54 years. Based on the extent of use recorded in the Clozapine National Registry, the mortality rate associated with pulmonary embolism was 1 death per 3450 person years of use. This rate was about 28 times

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higher than that in the general population of a similar age and sex (95% CI = 17, 42). Whether pulmonary embolism can be attributed to clozapine or some characteristic(s) of its users is not clear (40).

Fatal pulmonary embolism occurred in a 29-year-old man who was not obese, did not smoke, and had not had recent surgery, after he had taken clozapine 300 mg/day for 6 weeks (41).

Nervous system

Clozapine has been used to treat benign essential tremor refractory to the usual drugs (propranolol, primidone, alprazolam, phenobarbital, and botulinum toxin) in a randomized, double-blind, crossover study in 15 patients with essential tremor (42). Responders with more than 50% improvement after a single dose of clozapine 12.5 mg, compared with placebo, subsequently received 39–50 mg unblinded for a mean of 16 months. Tremor was effectively reduced by a single dose of clozapine in 13 of 15 patients; sedation was the only adverse effect reported.

Sleep

In a study of the effects of clozapine on the electroencephalogram, 13% of patients developed spikes with no relation to dose or serum concentration of clozapine; 53% developed electroencephalographic slowing. Compared with plasma concentrations below 300 ng/ml, a clozapine serum concentration of 350–450 ng/ml led to more frequent and more severe electroencephalographic slowing (43). There were considerable differences in the electroencephalographic patterns between classical neuroleptic drugs and clozapine (44). Clozapine-treated patients showed significantly more stage 2 sleep, more stable non-REM sleep (stages 2, 3, and 4), and less stage 1 than patients treated with haloperidol or flupentixol. In a longitudinal study, clozapine significantly improved sleep continuity and significantly increased REM density, but did not affect the amount of REM sleep (45).

Seizures

Clozapine has a proconvulsant effect. Factors that increase the likelihood of seizures include high doses of clozapine, rapid dose titration, the concurrent use of other epileptogenic agents (such as antidepressants, neuroleptic drugs, and mood stabilizers) and a previous history of neurological abnormalities (46).

The prevalence of seizures with clozapine is higher than average (about 5%) and is dose-dependent (SED-14, 142) (47,48).

- A tonic-clonic seizure occurred in a 30-year-old man 4 weeks after he started to take clozapine 400 mg/day (49). This was followed by a large increase in liver enzymes, which had been normal the week before.

Seizure characteristics and electroencephalographic abnormalities in 12 patients taking clozapine have been identified; there was a surprisingly high incidence of focal epileptiform abnormalities (50). Seizures associated with clozapine are dose-dependent (SEDA-21, 53) (SEDA-22, 57). However, there have been reports of seizure activity in patients taking therapeutic or subtherapeutic doses of clozapine (47,48). Seizures have occasionally been reported in patients taking low doses.

- A 28-year-old woman, with no history of prior seizures and not taking concomitant medication, had seizures while taking clozapine 200 mg/day (48).
- A 75-year-old patient developed seizures while taking clozapine 12.5 mg/day.

However, in the second case the seizure was unlikely to have been due to clozapine, given the very low dose and non-recurrence with rechallenge at higher dosages (51).

Despite the risk of seizures in patients without pre-existing epilepsy, six patients with epilepsy and severe psychosis taking clozapine had no increases in seizure frequency, and three had a substantial reduction (52).

Several anticonvulsants have been shown to be helpful in the prevention and treatment of clozapine-induced seizures.

- A 15-year-old boy with refractory schizophrenia had seizures with clozapine; he was given gabapentin, and several years later was free of seizures (53).

The addition of lamotrigine to clozapine therapy has been associated with rapid improvement of psychiatric symptoms (54); this has been observed in three cases of poor response or resistance to clozapine monotherapy.

Stuttering has been associated with clozapine (SEDA-22, 58). The pathogenesis of developmental stuttering, as well as acquired or neurogenic stuttering, is unclear. However, since clozapine-induced stuttering can precede a seizure (SEDA-25, 64) it may be related to an effect on the brain rather than to a dystonic syndrome, as previously suggested.

- A 28-year-old man taking clozapine 300 mg/day developed severe stuttering and subsequently had a generalized tonic-clonic seizure while taking 425 mg/day (55). There were electroencephalographic abnormalities, especially left-sided slowing.
- A 49-year-old woman had prominent stuttering before a generalized epileptic seizure and recovered after antiepileptic treatment (56).

Extrapyramidal effects

Clozapine has a more favorable extrapyramidal effects profile than other neuroleptic drugs (57) and little or no parkinsonian effect (58).

Akathisia

The low prevalence of akathisia in patients taking clozapine has led to the proposal that clozapine should be used to treat patients with neuroleptic drug-induced chronic akathisia (59,60).

Parkinsonism

The efficacy and safety of treatment with clozapine in patients with Parkinson's disease have been discussed (SEDA-22, 57), and a multicenter retrospective review of the effects of clozapine in 172 patients with Parkinson's disease has been published (61). The mean duration of clozapine treatment was 17 (range 1–76) months. Low-dose clozapine improved the symptoms of

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psychosis, anxiety, depression, hypersexuality, sleep disturbances, and akathisia. Of the 40 patients, 24% withdrew as a result of adverse events, mostly sedation ($n = 19$). Sedation was reported in 46%, sialorrhea in 11%, and postural hypotension in 9.9%. Neutropenia was detected in four patients (2.3%).

Six patients who met the criteria for a diagnosis of HIV-associated psychosis, and who had previously developed moderate parkinsonism as a result of typical neuroleptic drugs, were treated with clozapine (62). Parkinsonism improved by an average of 77%, but one patient did not complete the trial because of a progressive fall in leukocyte count.

Clozapine has been used to treat psychosis related to Parkinson's disease (SEDA-22, 57) (61). In a randomized, double-blind, placebo-controlled trial of low doses of clozapine (6.25–50 mg/day) in 60 patients (mean age 72 years) with idiopathic Parkinson's disease and drug-induced psychosis, the patients in the clozapine group had significantly more improvement after 14 months than those in the placebo group in all measures used to determine the severity of psychosis (63). Clozapine improved tremor and had no deleterious effect on the severity of parkinsonism, but in one patient it was withdrawn because of leukopenia.

In a randomized, double-blind, placebo-controlled, 4-week trial in 60 patients with similar drug-induced psychosis in Parkinson's disease, assigned to clozapine ($n = 32$) or placebo ($n = 28$), the initial clozapine dose of 6.25 mg/day was titrated over at least 10 days to a maximum of 50 mg/day and was rapidly effective (64). Somnolence and worsening of parkinsonism were significantly more frequent in the clozapine group, seven of whom reported worsening of Parkinson's disease, usually mild or transient, which was confirmed by aggravation of the Schwab and England score by 10–20% in three patients; however, no-one withdrew for this reason.

Tardive dyskinesia

It is said that clozapine causes less tardive dyskinesia than haloperidol and even that it can improve pre-existing tardive dyskinesia (65–69).

Patients with schizophrenia with ($n = 15$) and without ($n = 11$) tardive dyskinesia differed markedly in their dopaminergic response to haloperidol, assessed by means of plasma homovanillic acid variations, which increased, whereas this difference was not observed after clozapine (70).

Nevertheless, 46 patients taking clozapine had higher tardive dyskinesia scores compared with 127 taking typical neuroleptic drugs (71). In a multiple regression analysis, there was a significant relation between the total score on the Abnormal Involuntary Movement Scale (AIMS) as a dependent variable and current neuroleptic drug dose, duration of treatment, age, sex, diagnosis, current antiparkinsonian therapy, and illness duration. There was no beneficial effect of clozapine on the prevalence of tardive dyskinesia, and the authors' conclusion was that certain patients develop tardive dyskinesia despite long-term intensive clozapine treatment; however, since most clozapine users were past users of typical neuroleptic drugs, this conclusion must be regarded with caution.

- A 45-year-old woman developed tardive dyskinesia while taking clozapine (72). She had never had any of the symptoms before she started to take 223 mg/day and first experienced involuntary tongue movements and akathisia 5 months after the start of treatment.
- Tardive dyskinesia has been attributed to clozapine in a 44-year-old man, who had discontinued haloperidol 24 days before the event (73).

Tardive dystonia

It is generally considered that clozapine has little or no potential to cause tardive dystonia; it has even been speculated that it may be an effective therapy for this adverse effect (SEDA-21, 53). The efficacy of clozapine in severe dystonia was therefore assessed in an open trial in five patients (74). All had significant improvement; nevertheless, all had adverse effects, such as sedation and orthostatic hypotension: in one case persistent symptomatic orthostatic hypotension and tachycardia limited treatment.

However, there was no evidence of a beneficial effect of clozapine in primary dystonia, the most common form of dystonia and a difficult disorder to treat, until the report of a 56-year-old woman with severe and persistent primary cranial dystonia (Meige's syndrome), who responded to clozapine (50–100 mg) (75).

Tardive dystonia, probably associated with clozapine, has been described (76).

- A 37-year-old man, who had taken numerous neuroleptic drugs from 1975 to 1990, was switched to clozapine because of breakthrough psychosis. Clozapine was effective and was his only neuroleptic drug treatment from that time. In 1996, when his clozapine dosage was 825 mg/day, he had left torticollis of 60–70°, mild left laterocollis, and superimposed spasmodic head movements jerking his head to the left. He had difficulty rotating his head to the right past the midline.

Tardive tremor

Tardive tremor is a hyperkinetic movement disorder associated with chronic neuroleptic drug treatment. It was first described in 1991 as a symmetrical tremor, of low frequency, present at rest and during voluntary movements but most prominent during maintenance of posture, and often accompanied by tardive dyskinesia. Tetrabenazine is the current treatment. Sequential responsiveness to both tetrabenazine and clozapine has been reported (77).

- A 55-year-old man with a 15-year history of schizophrenia treated with various neuroleptic drugs developed a tremor and was given tetrabenazine 75 mg/day, with complete regression of the tremor. Three months later he developed depression, a known adverse effect of tetrabenazine, which was discontinued, with subsequent partial improvement of his depressive symptoms but reappearance of the tardive tremor. Clozapine 25 mg/day was started and increased to 75 mg/day; his tardive tremor again disappeared.

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Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with clozapine (SEDA-22, 58) (78), although some doubts were expressed about the features of earlier cases. In the light of two cases, a 35-year-old man and a 62-year-old woman, the literature was comprehensively reviewed and the characteristics of neuroleptic malignant syndrome due to clozapine and typical neuroleptic drugs were compared (79). Causation with clozapine was deemed highly probable in 14 cases, of medium probability in 5 cases, and of low probability in 8 cases. The most commonly reported clinical features were tachycardia, changes in mental status, and sweating. Fever, rigidity, and raised creatine kinase activity were less prominent than in the neuroleptic malignant syndrome associated with typical neuroleptic drugs. This suggests that the presentation of clozapine-induced neuroleptic malignant syndrome may be different from that of typical neuroleptic drugs. Two other cases have also illustrated that possibility (80,81).

Neuroleptic malignant syndrome and subsequent acute interstitial nephritis has been reported in a 44-year-old woman (82). This patient met the main criteria for neuroleptic malignant syndrome, although she did not develop rigidity or a rise in creatine kinase activity. On the other hand, abnormal creatine kinase activity and signs of myotoxicity were respectively found in 14% and 2.1% of patients who took clozapine for an average of 18 months ($n = 94$) (83).

Delirium

Toxic delirium caused by neuroleptic drugs with potent anticholinergic properties has been widely reported (SED-11, 107), and has been reported with low-dose clozapine (84).

Psychological, psychiatric

Suicide, suicidality, and suicidal ideation are very serious problems in patients with schizophrenia. Based on general observations that 1–2% of patients with schizophrenia complete suicide within 1 year after initial attempts, the authors of a retrospective study of 295 neuroleptic drug-resistant patients with schizophrenia who had taken clozapine monotherapy for at least 6 months would have expected as many as 10 or 11 successful suicides or suicide attempts, but none was observed (85).

Obsessive-compulsive symptoms during clozapine therapy have been suggested to be more common than first reported (SEDA-21, 54). In a retrospective cohort study, new or worse obsessiveness has been analysed in 121 consecutive young patients with recent-onset schizophrenia or other psychotic disorders taking clozapine and other neuroleptic drugs (86). More clozapine-treated subjects (21%) had new or worse obsessiveness than subjects treated with other neuroleptic drugs (1.3%). However, there was no information on comparability of the groups.

Panic disorder has been attributed to clozapine (87).

- A 34-year-old woman taking clozapine 400 mg/day for psychiatric symptoms had recurrent attacks of sudden chest pressure, dizziness, fear of dying, and intense anxiety; reducing the dose of clozapine to 250 mg/day led to modest improvement. Olanzapine 10 mg/day was then substituted, without recurrence, and her panic symptoms progressively improved.

Metabolism

Diabetes mellitus

Several cases of de novo diabetes mellitus or exacerbation of existing diabetes in patients taking neuroleptic drugs have been reported, including patients taking clozapine (88–91). There was no significant relation to weight gain.

- A 49-year-old man taking olanzapine developed diabetes mellitus and recovered after withdrawal (92).
- Diabetic ketoacidosis occurred in a 31-year-old man who had taken clozapine 200 mg/day for 3 months for refractory schizophrenia (93). Clozapine was withdrawn and he remained metabolically stable. Two months later, clozapine was restarted, and only 72 hours after drug re-exposure he had increased fasting glycemia and insulinemia, suggesting insulin resistance as the underlying mechanism. Apart from slight obesity, he had no predisposing factors.

Hyperglycemia occurs at 2 weeks to 3 months after the start of clozapine treatment and occurs without predisposing factors. Clozapine-induced hyperglycemia can be serious, leading to coma, but it is reversible if clozapine is withdrawn. In some cases, continuation of clozapine is possible by controlling blood glucose concentrations with hypoglycemic drugs. This approach can be useful in refractory schizophrenia responsive to clozapine. All patients should be advised to report altered consciousness, polyuria, or increased thirst.

Glucose metabolism has been studied in 17 patients taking clozapine (94). Six had impaired glucose tolerance and eight had a glycemic peak delay.

Diabetes was also more common in 63 patients taking clozapine than in 67 receiving typical depot neuroleptic drugs (95). The percentages of type 2 diabetes mellitus were 12% and 6% respectively. Nevertheless, the mechanism is not known. In six patients with schizophrenia, clozapine increased mean concentrations of blood glucose, insulin, and C peptide (96). The authors concluded that the glucose intolerance was due to increased insulin resistance.

However, opposite data have been found in a case-control study in 7227 patients with new diabetes and 6780 controls, all with psychiatric disorders (97). Clozapine was not significantly associated with diabetes (adjusted OR = 0.98; 95% CI = 0.74, 1.31) and there was no suggestion of relations between larger dosages or longer durations of clozapine use and an increased risk of diabetes. Among individual non-clozapine neuroleptic drugs, there were significantly increased risks for two phenothiazines: chlorpromazine (OR = 1.31; 95% CI = 1.09, 1.56) and perphenazine (OR = 1.34; 95% CI = 1.11, 1.62). The authors suggested that, in contrast to earlier reports, these results provided some

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reassurance that clozapine does not increase the risk of diabetes. However, cases of diabetes were identified by the new use of antidiabetic drugs, and it is therefore possible that clozapine was associated with less pronounced glucose intolerance that did not require drug therapy.

Weight gain

Weight gain is often associated with clozapine (SEDA-21, 54). In 42 patients who took clozapine for at least 1 year, men and women gained both weight and body mass, which is more directly related to cardiovascular morbidity (98). Over 10 weeks, leptin concentrations, which correlate with body mass index, increased significantly from baseline in 12 patients taking clozapine (99).

The association between clozapine-related weight gain and increased mean arterial blood pressure has been examined in 61 patients who were randomly assigned to either clozapine or haloperidol in a 10-week parallel-group, double-blind study, and in 55 patients who chose to continue to take clozapine in a subsequent 1-year open study (100). Clozapine was associated with significant weight gain in both the double-blind trial (mean 4.2 kg) and the open trial (mean 5.8 kg). There was no significant correlation between change in weight and change in mean arterial blood pressure.

There were no significant associations between cycle length and weight change during clozapine treatment in 13 premenopausal women with psychoses (101).

Sleep apnea associated with clozapine-induced obesity has been reported (102).

- A 45-year-old woman with schizophrenia who took clozapine 300 mg/day for 16 months gained 18 kg and had hypertriglyceridemia and glucose intolerance. She had daytime sedation, difficulty in sleeping at night, loud snoring, and periods of apnea during sleep.

Nasal continuous positive airway pressure produced improvement.

Phenylpropanolamine 75 mg/day did not promote weight loss in a randomized, placebo-controlled study in 16 patients with schizophrenia who had gained at least 10% of their body weight while taking clozapine (103).

- A 29-year-old man taking clozapine 800 mg/day gained 46 kg in weight after 25 months, and had myoclonic jerks in the hands, arms, and shoulders on both sides (104). He was treated with topiramate (which causes weight loss). The myoclonic jerks disappeared completely. He lost 21 kg over 5 months, with no significant change in eating habits or food consumption, and felt more energetic, more active, and more motivated to exercise.

Hematologic

Neutropenia and agranulocytosis

DoTS classification (BMJ 2003; 327:1222–1225)
Dose-relation: hypersusceptibility effect
Time-course: intermediate or delayed
Susceptibility factors: genetic; age

Incidence

Clozapine-induced agranulocytosis was originally determined to be 0.21% in a selected Finnish population (SED-9, 83) (105), and the drug was withdrawn, only to be cautiously reintroduced in some countries a decade later, with hematological monitoring. With mandatory hematological monitoring by the Clozaril Patient Management System in the USA, the cumulative incidence of agranulocytosis was 0.8% at 1 year and 0.9% at 1.5 years of treatment; the risk was not related to dosage (SEDA-18, 54) (106). In France, the incidences of agranulocytosis and neutropenia in clozapine-treated patients from December 1991 were 0.46 and 2.1% respectively (107). Some of the available postmarketing data on clozapine-induced agranulocytosis are presented in Table 1 (108).

Mechanism

The underlying mechanisms of agranulocytosis are unknown, but hemopoietic cytokines, such as granulocyte colony-stimulating factor (G-CSF), are likely to be involved (109).

- In a 26-year-old woman who developed granulocytopenia twice, first when taking clozapine and again when taking olanzapine, G-CSF concentrations, but not those of other cytokines, closely paralleled the granulocyte count.
- In a 73-year-old patient who developed granulocytopenia while taking clozapine, G-CSF and leukocyte

Table 1 Reported incidences of clozapine-induced agranulocytosis

Country	Period	Number of patients	Incidence (mortality) (%)	Reference
Finland	1975	2260	0.70 (0.35)	(SED-9, 83) (105)
USA	1990–1991	11382	0.80 (0.02)	(SEDA-18, 54)
France	1992	2834	0.46 (ND)	(SEDA-21, 54)
USA	1990–1994	99502	0.38 (0.01)	(SEDA-22, 59)
UK and Ireland	1990–1994	6316	0.80 (0.03)	(SEDA-22, 59)
New Zealand	1988–1995	963	1.15 (0.00)	(SEDA-22, 59)
Australia	1993–1996	4061	0.90 (0.00)	(99)
Spain	1993–1999	6354	0.16 (0.02)	Agencia Española del Medicamento (personal communication)
Total		133402	0.44 (0.018)	

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counts were reliable indicators of the evolution of the condition, showing an abortive form of toxic bone-marrow damage with subsequent recovery (110).

Immune-mediated mechanisms of clozapine-induced agranulocytosis have been reviewed in the context of agranulocytosis in a 46-year-old woman (111). Immune and toxic mechanisms have also been explored in patients taking clozapine, three who developed agranulocytosis, seven who developed neutropenia, and five who were asymptomatic. There was no evidence of antineutrophil antibodies in the blood of patients shortly after an episode of clozapine-induced agranulocytosis, and an antibody mechanism seems unlikely, in view of the delay in onset of clozapine-induced agranulocytosis on re-exposure to the drug (112).

Susceptibility factors

Some of the genetic aspects of clozapine-induced agranulocytosis have been evaluated (113). Polymorphisms of specific clozapine metabolizing enzyme systems were determined in 31 patients with agranulocytosis and in 77 without. Genotyping of a recently discovered G-463 A polymorphism of the myeloperoxidase gene and CYP2D6 showed no evidence of an association.

Because of the unusually high incidence of agranulocytosis in Finnish and Jewish patients (SEDA-20, 49), an ethnic susceptibility factor for agranulocytosis has been suggested. Human leukocyte antigen (HLA) B38 phenotype was found in 83% of patients who developed agranulocytosis and in 20% of clozapine-treated patients who did not develop agranulocytosis (114). Gene products contained in the haplotype may be involved. In an open study in 31 German patients with clozapine-induced agranulocytosis and 77 controls with schizophrenia, agranulocytosis was significantly associated with HLA-Cw*7, DQB*0502, DRB1*0101, and DRB3*020 (115). No other antigens were associated with agranulocytosis, but age was another major susceptibility factor. In another study in two groups of Finnish patients (19 "clozapine responders" and 26 patients with a history of non-fatal clozapine-induced granulocytopenia or agranulocytosis), the frequency of the HLA-A1 allele in the latter was low (12%), whereas HLA-A1 was associated with a good therapeutic response at an allele frequency of 58% (the frequency of HLA-A1 being 20% in the Finnish population) (116).

Concordant clozapine-induced agranulocytosis in monozygotic twins also suggested a genetic susceptibility; in both twins there was a low leukocyte count after 9 weeks of treatment (117). Serological typing of the HLA system showed identical patterns in the twins: HLA-A: 28, 26; HLA-B: 49, 63; DR: 2 (versus 16), 12, 52; DQ: 1. The authors pointed out that these data suggest that genetic factors may participate not only in the time of onset of schizophrenia, but also in the emergence and timing of agranulocytosis in response to clozapine.

Clinical features

Careful attention should be paid to possible early warnings of agranulocytosis, such as fever, sore throat, and lymphadenopathy.

Circadian variation in white cell count, with a dip in the morning, has been misdiagnosed as clozapine-induced neutropenia (118).

- A 31-year-old man with resistant schizophrenia took clozapine 500 mg/day. Although this was effective, the granulocyte count fell to 1.2×10^9/l (total count not given) and clozapine was withdrawn. During the subsequent year, several neuroleptic drugs were used, with unsatisfactory results. Careful monitoring showed a pronounced diurnal variation in both total white cell count ($2.9–4.2 \times 10^9$/l in the morning and $3.6–7.1 \times 10^9$/l in the afternoon) and granulocytes ($0.8–1.4 \times 10^9$/l in the morning and $2.9–5.5 \times 10^9$/l in the afternoon).

Thus, an apparently low white cell count may simply reflect the nadir of the diurnal variation and may not indicate a need to withdraw clozapine.

In over 11 000 patients the risk of agranulocytosis was higher in the first 3 months of treatment and is greater among women and elderly patients (119).

Agranulocytosis after very long-term clozapine therapy has been reported (120).

- A 41-year-old man suddenly developed agranulocytosis after taking clozapine nearly continuously for 89 months. During this time, his white blood cell and granulocyte counts remained stable. The white blood cell and granulocyte counts returned to baseline shortly after withdrawal of clozapine and administration of sargramostim.

Rechallenge

Cases of negative or positive rechallenge in patients with agranulocytosis have been reported (SEDA-20, 54) (SEDA-22, 59).

- A 58-year-old man developed agranulocytosis during a second trial of clozapine, despite a successful previous trial (121).
- A 17-year-old boy with severe clozapine-induced neutropenia had a negative rechallenge; because he had had an unsatisfactory response to traditional neuroleptic drugs, clozapine was continued despite a fall in white blood cell count, since concomitant treatment with granulocyte colony-stimulating factor was followed by rapid normalization of the white blood cell count (122).
- A 29-year-old woman developed agranulocytosis after taking clozapine 300 mg/day for 5 years; 4 months after withdrawal, the clozapine was reintroduced (500 mg/day), and after 8 months the leukocyte count was still within the reference range (123).

Monitoring therapy

Over 10 000 patients have been treated with clozapine in Australia since its introduction in 1993, and the Clozaril monitoring system has ensured that since that time there have been no deaths from agranulocytosis in patients taking clozapine (124).

An increase in white blood cell count of at least 15% above previous counts is a sensitive, although not specific, predictor for the development of agranulocytosis within 75 days (119). Clozapine dosage and baseline white cell count do not appear to predict agranulocytosis.

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Monitoring G-CSF concentrations, if available, may be useful in following patients in whom clozapine-induced marrow damage is suspected.

An example of a false sense of security gained by relying on monitoring monthly blood counts in patients taking clozapine has been published (125).

- A 61-year-old man who had taken clozapine for 3 years had normal blood counts. However, one day, his hemoglobin was 8.5 g/dl, having previously been 13 g/dl, following a steady asymptomatic fall over 6 months that had been documented but had gone unnoticed. He subsequently underwent investigation and treatment for anemia.

However, it is not clear in this case that clozapine was responsible for the anemia.

Treatment

Withdrawal of clozapine can lead to resolution of agranulocytosis, but not always. Granulocytopenia, presumably induced by clozapine, persisted in a 53-year-old woman after she switched from clozapine to quetiapine (126).

Treatment with granulocyte colony-stimulating factor and granulocyte macrophage colony stimulating factors was helpful in a case of sepsis and neutropenia induced by clozapine (127) and in a case of agranulocytosis in a 45-year-old man (128).

Lithium can be used in combination with clozapine, and in these patients the possibility of inducing leukocytosis and increasing the total leukocyte count and the granulocyte count has been considered (SEDA-20, 50). Lithium has even been used to prevent clozapine-induced neutropenia (SEDA-22, 59). It has also been used in a patient with clozapine-induced neutropenia and in another with complete agranulocytosis: in both cases lithium increased the neutrophil count to within the reference range within 6 days (129). In the patient who had neutropenia, clozapine was restarted in the presence of lithium and the neutrophil count did not fall thereafter. Five other patients who took combined clozapine and lithium had a significant improvement with this combination and there were no cases of agranulocytosis, neuroleptic malignant syndrome, or other adverse effects (130).

Eosinophilia

Clozapine-induced eosinophilia and subsequent neutropenia has been reported (131). As the patient had a high IgE concentration, an allergic cause was proposed. In a previous study in 70 patients there was no predictive value of eosinophilia for clozapine-induced neutropenia (132). Eosinophilia associated with clozapine treatment has been reported in 13% of treated patients in a study in Australia (28).

Platelet count

Thrombocytosis and thrombocytopenia have both been reported.

- Thrombocytosis (774×10^9/l) occurred in a middle-aged man taking clozapine (133).
- A 43-year-old man developed thrombocytopenia (platelet count 60×10^9/l), which persisted for 40 months after clozapine treatment (134). There was increased in vitro platelet serotonin release in the presence of clozapine (135).

In the second case, the authors suggested an immune mechanism and pointed out that the manufacturers recommend withdrawing clozapine when the platelet count falls below 100×10^9/l.

Mouth and teeth

Hypersalivation is a common adverse effect of clozapine (136), which has been estimated to occur in 10–23% of patients (SEDA-20, 49). Salivary gland swelling has been reported in patients treated with clozapine (SEDA-20, 49) (137).

There is evidence implicating alpha-adrenoceptors in hypersalivation caused by clozapine, and it has been hypothesized that a biallelic polymorphism in the promoter region of the alpha$_2$-adrenoceptor gene confers susceptibility to schizophrenia, which is associated with a clozapine-induced favorable therapeutic response and/or clozapine-induced hypersalivation (138). However, the results in 97 patients showed that the alpha$_2$-adrenoceptor gene polymorphism did not play a major role in susceptibility to hypersalivation or the therapeutic response of patients with schizophrenia.

A comprehensive review has been published on the evidence of the benefit of using antimuscarinic agents, adrenoceptor antagonists, and adrenoceptor agonists in treating clozapine-induced hypersalivation (139). There is a lack of good-quality controlled trials, most papers having reported series of uncontrolled cases dependent on subjective measures of improvement reported by patients; however, the authors suggested that the most effective treatment may be a combination of terazosin and benzhexol (140). Ten patients with sialorrhea associated with clozapine, who did not respond to anticholinergic or adrenergic drugs, received intranasal ipratropium bromide; at 6 months, six patients maintained improvement (141).

Gastrointestinal

Reflux esophagitis has been reported in patients taking clozapine (142). It has been speculated that reduced esophageal motility was the mechanism (143).

Constipation is an adverse effect that has often been associated with clozapine; it can be serious and even fatal (SEDA-22, 60).

- A 49-year-old man taking clozapine developed a perforated colon and peritonitis (144). He survived, albeit with a markedly reduced quality of life.

The authors suggested that diet modification and regular exercise should be encouraged in patients taking clozapine, in order to prevent constipation.

- A 43-year-old man took clozapine 750 mg/day for 6 years and developed vomiting and epigastric pain (145). He had ulcerative esophagitis, and a CT scan was reportedly normal "apart from constipation." He was given omeprazole 20 mg/day and twice-daily psyllium. Six months later he developed abdominal

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pain with feculent vomiting. Emergency laparotomy revealed large-bowel obstruction secondary to severe fecal impaction. He died 3 weeks later with septic shock and progressive multisystem organ failure.

Liver

Transient asymptomatic liver enzyme rises are common with clozapine (146).

Hepatitis associated with clozapine has been reported (SEDA-20, 49) (SEDA-22, 59).

- A 49-year-old woman (147) took clozapine 300 mg/day and developed lethargy, anorexia, fever, eosinophilia, leukocytosis, and abnormal liver function tests. The serum clozapine concentration was 8595 nmol/l. Clozapine was withdrawn and after 8 days her condition stabilized and low-dose clozapine treatment was successfully restarted with serum monitoring.

Obstructive jaundice has been described (148).

- A 48-year-old man with schizophrenia started taking clozapine 12.5 mg/day, increasing over the next 18 days to 150 mg/day. By that time he was icteric, with mild distress and fever and raised bilirubin 149 μmol/l (reference range 5–26), direct bilirubin 92 μmol/l, gamma-glutamyl transpeptidase 446 IU/l (<65), alanine transaminase 100 IU/l (<40), and aspartate transaminase 56 IU/l (<40). Hepatitis serology showed positive hepatitis B surface antibodies, and HBs antigen was negative, as were hepatitis A, hepatitis C, Epstein-Barr virus, and cytomegalovirus. He also had hyperglycemia, pleural effusion, eosinophilia, hematuria, and proteinuria, which also resolved on clozapine withdrawal.

A case of fatal liver failure has been reported (149).

Pancreas

Occasional cases of pancreatitis have been related to clozapine therapy (SEDA-17, 63).

- A 73-year-old woman with a 4-year history of Parkinson's disease developed hallucinations and delusions that were interpreted as secondary effects of levodopa (150). She was given clozapine 25 mg/day and continued to take levodopa. Four days later she complained of abdominal pain. She had raised activities of serum amylase 806 IU/l (reference range <220 IU/l), lipase 2598 IU/l (<190 IU/l), and creatine kinase 464 IU/l (<190 IU/l), and normal concentrations of total and direct bilirubin. Other causes of pancreatitis were ruled out.

Two other cases have been reported in patients with no prior history of alcohol abuse or gallstones (151,152). The authors recommended monitoring serum amylase activity during slow increases in the dosage of clozapine if there is leukocytosis or eosinophilia, which may be associated with asymptomatic pancreatitis.

Urinary tract

Enuresis has been rarely associated with clozapine (0.23% of patients) (SEDA-19, 54) (153), and has been successfully treated with benzatropine in patients taking a variety of psychotropic medications (154).

In a retrospective study, 27 of 61 Chinese patients who took clozapine for more than 3 months developed urinary incontinence, persistent in 15 cases (155). The reaction could not be related to age, sex, clozapine dosage, duration of clozapine use, duration of hospitalization, duration of illness, age at onset of schizophrenia, or concurrent treatment with other psychiatric drugs.

Polymorphisms of the alpha 1a adrenoceptor gene were found to play no major role in the pathogenesis of schizophrenia or in clozapine-induced urinary incontinence (156).

Acute interstitial nephritis has been attributed to clozapine (157).

- A 38-year-old woman developed anorexia, lethargy, and vomiting, and noticed a profound reduction in urine output about 11 days after starting clozapine (125 mg bd). Severe renal insufficiency was confirmed (blood urea 33 mmol/l and creatinine 1200 μmol/l). There was no history of pre-existing renal or other systemic disease.

Musculoskeletal

Clozapine-induced myokymia (weakness and reduced muscle tone, with undulating movements of the muscle and skin, accompanied by involuntary repetitive firing of grouped motor unit action potentials) has been reported (158).

- A 33-year-old woman developed muscle twitching and spasms of the legs and back after having taken clozapine for 3 years (158). Neurological examination showed myokymia in both thighs, calves, and the lower lip. The myokymia disappeared 1 week after withdrawal of clozapine.

In an open study in 41 patients, strength control was evaluated before the start of clozapine therapy and again at the end of the titration period (on average 9 weeks later). The results suggested that the strength deficit was primarily due to clozapine and that there were two distinct effects: an initial transient stage characterized by "drowsiness" and a subsequent stage with dose-dependent myoclonic features (159).

- Rhabdomyolysis occurred in two men, aged 21 and 42 years, taking clozapine (160,161). The first had no risk factors, but calcium-dependent potassium efflux, normally responsible for membrane hyperpolarization and muscle refractoriness, was severely impaired in his erythrocytes. The second had marked hyponatremia, due to psychogenic polydipsia, and developed a marked rise in creatine kinase activity (62 730 U/l) after correction of hyponatremia with hyperosmolar fluids.

Sexual function

The frequency and course of sexual disturbances associated with clozapine have been studied in a prospective open study in 75 men and 25 women, mean age 29 years, and compared with the effects of haloperidol in 41 men and 12 women, mean age 26 years (162). There were no statistically significant differences between the patients

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taking haloperidol and those taking clozapine. During 1–6 weeks of treatment with clozapine, the most frequent sexual disturbances among women were diminished sexual desire (28%) and amenorrhea (12%), while among men they were diminished sexual desire (57%), erectile dysfunction (24%), orgasmic dysfunction (23%), ejaculatory dysfunction (21%), and increased sexual desire (15%). The mean daily doses were haloperidol 16 mg and clozapine 261 mg.

Retrograde ejaculation has been associated with clozapine (163).

Immunologic

Allergic reactions associated with clozapine are uncommon; however, a case of rash (SEDA-21, 55) and a case of pleural effusion (SEDA-22, 60) have previously been reported. Both rash and pleural effusion have been reported in a 37-year-old woman about 1 week after starting clozapine (164).

Body temperature

Clozapine often causes a benign transient increase in body temperature early in treatment (165).

Long-Term Effects

Drug withdrawal

Rebound psychosis or delirium or both have been reported after withdrawal of clozapine (166–171). Clozapine withdrawal has also been associated with nausea, vomiting, diarrhea, headache, restlessness, agitation, and sweating (172,173), which occur as the result of cholinergic rebound and which may respond to anticholinergic drugs (174), and with dystonias and dyskinesias. Delirium and the return of dyskinetic movements can occur within days after clozapine withdrawal.

Four patients had severe dystonias and dyskinesias on abrupt withdrawal of clozapine (175), and another two had obsessive-compulsive symptoms during withdrawal; resumption of clozapine led to the complete disappearance of the obsessive-compulsive symptoms (176).

Second-Generation Effects

Pregnancy

Clozapine caused no serious complications or developmental abnormalities during pregnancy in two cases (177).

Susceptibility Factors

Age

Data from an open study ($n = 329$) have suggested that patients aged 55–64 years may have a better response to clozapine than those aged 65 and older, but there were no significant differences between the two age groups in the number of patients remaining on clozapine therapy and the number in whom therapy was discontinued ($n = 134$) (178). The mean duration of clozapine therapy was 278 days. The most common adverse effects that required withdrawal were sedation ($n = 12$), hematological adverse effects ($n = 7$), and cardiovascular adverse effects ($n = 6$).

In over 11 000 patients the risk of agranulocytosis was greater among elderly patients (119).

Sex

In over 11 000 patients the risk of agranulocytosis was greater among women (119).

Other features of the patient

Patients with Lewy body dementia may be more intolerant of neuroleptic drugs, including atypical drugs, than other patients with neurodegenerative dementia. However, because hallucinations are common in this form of dementia, it is likely that people with Lewy body dementia will be exposed to neuroleptic drugs. Two patients with Lewy body dementia taking clozapine developed confusion and behavioral symptoms (179).

Drug Administration

Drug formulations

Since clozapine is expensive, it is interesting that generic clozapine (given as 25 and 100 mg tablets) behaves like Clozaril, the branded formulation; bioequivalence has been observed in 30 patients with schizophrenia (180).

Drug dosage regimens

Since up to 17% of patients must discontinue clozapine because of adverse effects, strategies for minimizing and managing the adverse effects of clozapine have been reviewed (181,182). Treatment should begin with a low dosage, 12.5–25 mg/day.

The optimal plasma concentration of clozapine is 200–350 ng/ml, which usually corresponds to a daily dose of 200–400 mg (183,184). A nomogram to predict clozapine steady-state plasma concentrations has been generated using data from 71 patients (185). Clozapine steady-state plasma concentrations and demographic variables were obtained. The model explained 47% of the variance in clozapine concentrations. Two equations were obtained to predict steady-state plasma concentrations, one for men and one for women:

$$\text{clozapine (ng/ml)} = 0.464D + 111S + 145 \text{ (men)}$$
$$\text{clozapine (ng/ml)} = 1.590D + 111S - 149 \text{ (women)}$$

where D = dosage (mg/day), S = 1 for smokers, and S = 0 for non-smokers.

A further model for optimizing individual dosage regimens using Bayesian methods has been proposed (186).

Drug overdose

Fatal overdoses have been reported with clozapine (187).

Seven patients who took large doses of clozapine (mean 3 g, range 0.4–16 g) have been reported (188). All made a full recovery and toxicokinetic modelling suggested that

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norclozapine was formed by a saturable process but that clozapine kinetics were linear over the estimated doses.

- Clozapine overdose (2.5 g) in a 67-year-old woman resulted in seizures, loss of consciousness, metabolic acidosis, prolonged sedation, and aspiration pneumonia (189). By 9 days after intoxication she had recovered completely.
- A 40-year-old man who took 3–4 g of clozapine became unconscious, with constricted pupils, sinus tachycardia, and twitching; peak clozapine and norclozapine concentrations were 3.5 mg/l and 0.7 mg/l respectively, with secondary peaks at about 36 hours (190). Recovery was uneventful, and he was well 2 days after admission.
- A 41-year-old woman took 12.5 g of clozapine (125 tablets of 100 mg each) in a suicide attempt (191). She developed agitation, hallucinations, diminished distrust, and lethargy; she was given physostigmine 2 mg and recovered completely within 1 week.

Drug–Drug Interactions

Benzodiazepines

Caution has been recommended when starting clozapine in patients taking benzodiazepines (SEDA-19, 55). Three cases of delirium associated with clozapine and benzodiazepines (192) have been reported. There have been several reports of synergistic reactions, resulting in increased sedation and ataxia, when lorazepam was begun in patients already taking clozapine (193).

Hypotension, collapse, and respiratory arrest occurred when low doses (12.5–25 mg) of clozapine were added to a pre-existing diazepam regimen in several patients (SEDA-22, 41).

- A 50-year-old man developed syncope and electrocardiographic changes (sinus bradycardia with deep inverted anteroseptal T waves and minor ST changes in other leads) with the concurrent administration of clozapine (after the dosage was increased to 300 mg/day) and diazepam (30 mg/day) (194).

Caffeine

Caffeine has been associated with changes in the metabolism of clozapine (SEDA-20, 50) (SEDA-22, 61). Seven schizophrenic patients taking clozapine monotherapy participated in a study of the effects of caffeine withdrawal from the diet (195). After a caffeine-free diet for 5 days, clozapine plasma concentrations fell by 50%. The authors suggested that schizophrenic patients treated with clozapine should have their caffeine intake medically supervised, and that monitoring of concentrations of clozapine and its metabolite may be warranted.

Ciprofloxacin

A possible pharmacokinetic interaction between ciprofloxacin, which inhibits CYP1A2, and clozapine, with moderately increased serum concentrations of clozapine, has been reported (196).

Cisplatin

There is a potentially dangerous interaction with cancer treatment in patients with schizophrenia taking clozapine, because of the unpredictable risk of myelotoxicity. However, a 37-year-old patient taking clozapine for schizophrenia was given full-dose cisplatin and concomitant radiotherapy for an undifferentiated nasopharyngeal carcinoma, without significant neutropenia (197).

Cocaine

An interaction between clozapine and cocaine, causing near syncope, has been reported (198).

Erythromycin

Increased clozapine serum concentrations have been reported with erythromycin (199,200) and can cause adverse effects (SEDA-21, 55). However, in 12 healthy men who took a single dose of clozapine 12.5 mg alone or in combination with a daily dose of erythromycin 1.5 g, the metabolism of clozapine was not altered (201). This confirms that CYP3A4 is a relatively minor pathway for clozapine metabolism, in contrast to CYP1A2.

In a case of neutropenia the authors suggested that an interaction of clozapine with erythromycin had been the precipitating factor (202).

Interferon alfa

Agranulocytosis was observed after patients taking clozapine were given interferon alfa (SEDA-22, 404) (203). In one case, agranulocytosis occurred after 7 weeks of combined therapy in a 29-year-old patient who had been taking clozapine for more than 5 years without developing hematological abnormalities (203). Even so, it was not clear in these cases whether the agranulocytosis was due to the combination of clozapine with interferon-alfa or the clozapine alone.

Lithium

Seizures and other neurological effects have been described in a few cases when lithium was added to clozapine (204), but in other instances the combination was beneficial in overcoming treatment resistance or attenuating clozapine-induced leukopenia.

Modafinil

Clozapine toxicity occurred in a 42-year-old man after he was given modafinil 300 mg/day, a central stimulant, to combat sedation associated with clozapine (450 mg/day) (205). He complained of dizziness, had an unsteady gait, and fell twice. His serum clozapine concentration was 1400 ng/ml, which suggested a metabolic interaction between clozapine and modafinil. The authors suspected that inhibition of CYP2C19 by modafinil had reduced clozapine clearance.

Perphenazine

Perphenazine doubled clozapine concentrations in a 46-year-old male smoker, with paradoxical myoclonus, hypersalivation, and worsening of psychosis (206). The mechanism of this effect is not known; perphenazine is a

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substrate for CYP2D6, but that is not important in the metabolism of clozapine.

Phenobarbital

Phenobarbital can stimulate the metabolism of clozapine, probably by inducing its N-oxidation and demethylation. Seven patients taking clozapine in combination with phenobarbital had significantly lower plasma clozapine concentrations than 15 controls taking clozapine only (207).

Risperidone

Clozapine plasma concentrations increase when risperidone is introduced. The effects of risperidone 3.25 mg/day on cytochrome P450 isozymes have therefore been assessed in eight patients by determination of the metabolism of caffeine (for CYP1A2), dextromethorphan (for CYP2D6), and mephenytoin (for CYP2C19) (220). The results suggested that risperidone is a weak in vivo inhibitor of CYP2D6, CYP2C19, and CYP1A2. The authors concluded that inhibition by risperidone of those isozymes is an unlikely mechanism to explain increased clozapine concentrations.

SSRIs

Some SSRIs increase clozapine plasma concentrations (SEDA-20, 50) (SEDA-21, 55) (SEDA-22, 62) by inhibiting its metabolism.

Citalopram

Citalopram had no effect on plasma concentrations of clozapine ($n = 8$), risperidone ($n = 7$), or their active metabolites over 8 weeks (208). However, a possible interaction of clozapine with citalopram has been reported, with increased serum clozapine concentrations, perhaps dose-related (209).

Fluoxetine

In 10 patients stabilized on clozapine (200–450 mg/day) who took fluoxetine (20 mg/day) for 8 weeks, mean plasma concentrations of clozapine, norclozapine, and clozapine N-oxide increased significantly by 58%, 36%, and 38% respectively (210).

In two cases ingestion of clozapine and fluoxetine had a fatal outcome (211). The blood fluoxetine concentration was 0.7 μg/ml, which would be considered a high therapeutic concentration (usual target range 0.03–0.5 μg/ml). The blood clozapine concentration was 4900 ng/ml, which is within the lethal concentration range (1600–7100 ng/ml).

Dual effects were observed in a 44-year-old schizophrenic patient taking clozapine with both fluoxetine and sertraline for mood stabilization (212). Clinical and motor status improved with both fluoxetine and sertraline; cognitive function improved with clozapine and fluoxetine, but was not sustained with sertraline.

Fluvoxamine

Fluvoxamine increases clozapine plasma concentrations (210,213). In 16 patients taking clozapine monotherapy, fluvoxamine 50 mg was added in the hope of ameliorating the negative symptoms of schizophrenia (214). At steady state the serum concentrations of clozapine and its metabolites increased up to five-fold (average two- to three-fold). However, adverse effects were almost unchanged in frequency and severity, in spite of the pharmacokinetic interaction.

In another study there were similar increases in plasma clozapine concentrations and adverse reactions in 18 patients taking fluvoxamine 50 mg (week 5, mean dose 97 mg) (215).

In nine men who were given a single dose of clozapine 50 mg on two separate occasions with a 2-week interval, fluvoxamine increased clozapine plasma concentrations, and the total mean clozapine AUC was increased by a factor of 2.6; all the patients were sedated during combined therapy (216).

Combined therapy with clozapine and fluvoxamine ($n = 11$) and clozapine monotherapy ($n = 12$) have been monitored before and during the first 6 weeks of medication (217). The co-administration of fluvoxamine attenuated and delayed the clozapine-induced increase in plasma concentrations of tumor necrosis factor-alpha, enhanced and accelerated the clozapine-induced increase in leptin plasma concentrations without a significant effect on clozapine-induced weight gain, and reduced granulocyte counts.

In two studies of short duration (18 patients each) there were benefits of using low doses of clozapine plus fluvoxamine, and the authors suggested taking advantage of this interaction (218). Patients taking fluvoxamine required relatively low doses of clozapine and had clinically significant reductions in the symptoms of their illness while avoiding the sedative adverse effects associated with the usual doses of clozapine.

Paroxetine

The effect of paroxetine on steady-state plasma concentrations of clozapine and its metabolites has been studied in 17 patients taking clozapine (200–400 mg/day), nine of whom took additional paroxetine (20–40 mg/day) (219). Paroxetine, a potent inhibitor of CYP2D6, inhibited the metabolism of clozapine, possibly by affecting a pathway other than N-desmethylation and N-oxidation. After 3 weeks of paroxetine, mean plasma concentrations of clozapine and norclozapine increased significantly by 31% and 20% respectively, while concentrations of clozapine N-oxide were unchanged.

Sertraline

Dual effects were observed in a 44-year-old schizophrenic patient taking clozapine with both fluoxetine and sertraline for mood stabilization (212). Clinical and motor status improved with both fluoxetine and sertraline; cognitive function improved with clozapine and fluoxetine, but was not sustained with sertraline. However, sertraline did not affect steady-state plasma concentrations of clozapine and its metabolites in 17 patients taking clozapine (200–400 mg/day), 8 of whom took additional sertraline (50–100 mg/day) (219).

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Tricyclic antidepressants

Nefazodone had minimal effects on clozapine metabolism when co-administered in six patients: mean clozapine concentrations rose by 4% and norclozapine concentrations by 16% (221).

Valproate

Clozapine inhibits the metabolism of valproate (222). Valproic acid has been reported to increase the sedative effects of clozapine (SEDA-20, 50) and alter serum concentrations of clozapine.

- In a 33-year-old woman taking clozapine and valproic acid, the serum concentrations of clozapine fell significantly (223).

The authors suggested that valproic acid had induced the metabolism of clozapine.

However, one study showed only small effects on plasma clozapine concentrations, which were thought to be unlikely to be clinically significant (224).

Smoking

Smoking is highly prevalent among patients with schizophrenia, of whom 70–80% smoke tobacco. In a before-and-after study, 55 smokers smoked less when treatment was switched to clozapine than when they were taking typical neuroleptic drugs (225). Nevertheless, it is probable that heavy smoking can induce CYP1A2, the main enzyme involved in the metabolism of clozapine, and plasma concentrations of clozapine are lower in smokers than in non-smokers. Conversely, sudden cessation of smoking can cause a rise in plasma clozapine concentrations. In one case, seizures have been reported as a result (226).

- A 35-year-old schizophrenic man successfully treated with clozapine 700–725 mg/day for more than 7 consecutive years abruptly stopped chronic heavy cigarette smoking and 2 weeks later suddenly developed tonic-clonic seizures followed by stupor and coma. After recovery, he successfully reduced the daily dose by about 40% before he stopped smoking.

Diagnosis of Adverse Drug Reactions

In an open study in 37 patients (27 men and 10 women; mean age 35 years) with treatment-resistant schizophrenia treated with clozapine for 18 weeks, there was no correlation between plasma clozapine concentrations and percentage improvement on the Positive and Negative Syndrome Scale (227). Plasma clozapine concentrations were not significantly different between those who responded to clozapine ($n = 19$) and those who did not ($n = 18$), nor between patients who smoked ($n = 28$) and those who did not ($n = 9$). Dosages were adjusted according to clinical response, and plasma concentrations of clozapine and its metabolites were measured weekly. The mean endpoint clozapine dosage was 487 mg/day and there was a significant correlation between the daily dosage of clozapine and the plasma concentrations of clozapine and its metabolites. Three patients dropped out of the study owing to adverse effects (two because of significant sedation and one because of hypersalivation); there were no cases of agranulocytosis.

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Clusiaceae

See also Herbal medicines

General Information

The genera in the family of Clusiaceae (Table 1) include St. John's wort.

Hypericum perforatum

Hypericum perforatum (devil's scourge, goat weed, rosin rose, St. John's wort, Tipton weed, witch's herb) contains the naphthodianthrones hypericin and pseudohypericin, flavonoids, such as hyperoside, isoquercitin, and rutin, and phloroglucinols, such as adhyperforin and hyperforin. It is effective in mild to moderate depression (1).

Adverse effects

A meta-analysis of 23 randomized, controlled trials of St. John's wort showed that the herbal extract is more effective than placebo for mild to moderate depression, but that current evidence was inadequate to establish whether St. John's wort is as effective as standard antidepressants (2). In clinical trials, St. John's wort appeared to have fewer short-term adverse effects than some conventional antidepressants, but information on long-term adverse effects is lacking.

Two reviews have systematically addressed the safety of St. John's wort. One showed that the most common adverse events were gastrointestinal symptoms, dizziness, confusion, tiredness, sedation, and dry mouth (3). A second review compared the adverse effect profile of St. John's wort with those of conventional antidepressants (4). The adverse effects of St. John's wort were fewer and less serious than those associated with conventional antidepressant drugs.

A review of all reported adverse effects associated with St. John's wort has shown that it has an encouraging safety profile (3). Adverse effects reported in clinical trials were invariably mild and transient: gastrointestinal symptoms (8.5%), dizziness/confusion (4.5%), tiredness/sedation (4.5%), and dry mouth (4.0%). Synthetic drugs used in comparative trials were burdened with significantly higher rates of adverse effects. Data obtained from the WHO Collaborating Center for International Drug Monitoring are summarized in Table 2.

Cardiovascular

A 41-year-old man who had taken St. John's wort had a hypertensive crisis after taking cheese with red wine (5).

Table 1 The genera of Clusiaceae

Calophyllum (calophyllum)
Clusia (attorney)
Garcinia (sap tree)
Hypericum (St. John's wort)
Mammea (mammea)
Pentadesma (pentadesma)
Platonia (platonia)
Triadenum (marsh St. John's wort)

Table 2 Reports of adverse effects of formulations of St. John's wort (up to May 1998)

System	Number of cases
Cardiovascular (edema)	2
Cardiovascular (bradycardia)	1
Respiratory	4
Nervous system	5
Nervous system (stroke)	1
Psychiatric	15
Hematological (coagulation)	4
Gastrointestinal	2
Liver	4
Urinary tract (interstitial nephritis)	1
Skin (allergic reactions)	16
Skin (conjunctivitis)	1
Reduced therapeutic response	1

St. John's wort is a monoamine oxidase inhibitor, and the authors believed that this explained how the concomitant use of a tyramine-rich food with St. John's wort had caused this problem.

Nervous system

The mechanism of action of St. John's wort in depression is not understood, but serotonin re-uptake inhibition is one possibility, for which evidence is increasing. In one case this may have led to the serotonin syndrome in a 33-year-old woman who developed extreme acute anxiety after taking only three doses of extracts of St. John's wort and recovered after withdrawal (6).

- A 40-year-old man with a history of anxiety disorder and depression presented with flushing, sweating, agitation, weakness of the legs, dry mouth, tightness in the chest, and inability to focus (7). He was taking clonazepam (0.5 mg bd) and had started to take St. John's wort 10 days before. He had previously had two similar episodes after having taken sertraline.

The authors concluded that self-medication with St. John's wort, which has SSRI activity, had caused the serotonin syndrome.

Psychiatric

Delirium has been attributed to St. John's wort.

- A 76-year-old woman began taking an extract of St. John's wort (75 mg/day) and developed delirium and psychosis 3 weeks later (8). She had no relevant medical history and did not take any other medications. She was given risperidone and donepezil hydrochloride, and her paranoid delusions and visual hallucinations improved.

The final diagnosis was acute psychotic delirium associated with St. John's wort in a woman with underlying Alzheimer's dementia.

Hypomania has been reported with St. John's wort (9).

- A 47-year-old woman with an 8-year history of nocturnal panic attacks and a recent history of major depression had a poor response to SSRIs and instead took a 0.1% tincture of St. John's wort. After 10 days she

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noted racing and distorted thoughts, increased irritability, hostility, aggressive behavior, and a reduced need for sleep. After discontinuing the herbal treatment, her symptoms resolved within 2 days.

The author suggested that St. John's wort had caused this episode of hypomania.

Two cases of mania have been associated with the use of St. John's wort (10). The authors pointed out that St. John's wort, like all antidepressants, can precipitate hypomania, mania, or increased cycling of mood states, particularly in patients with occult bipolar disorder. Alternatively, the mania experienced by these patients could simply be the expression of the natural cause of their psychiatric illness.

Endocrine

In a retrospective case-control study, 37 patients with raised TSH concentrations were compared with 37 individuals with normal TSH concentrations (11). Exposure to St. John's wort during the previous 3–6 months increased the odds of a raised TSH concentration by a factor of 2.12 (95% CI = 0.36, 12). The authors concluded that an association between St. John's wort and raised TSH concentrations is probable.

Skin

Photosensitivity has been attributed to St. John's wort (12).

- A 35-year-old woman took ground whole St. John's wort (500 mg/day) for mild depression. After 4 weeks she developed stinging pain on her face and the backs of both hands, which worsened with sun exposure. She was seen after the area of pain had spread following exposure to the sun. After withdrawal of St. John's wort, the symptoms gradually disappeared during the next 2 months.

The authors thought that photoactive hypericins had caused demyelination of cutaneous nerve axons. If they are correct, then this would be the first human case of photosensitivity after St. John's wort, a condition previously only reported in animals.

Of 43 users of St. John's wort surveyed by telephone, 47% reported adverse effects that they related to the remedy (13). The only potentially serious complaint was photosensitivity, which was noted by four individuals.

An Australian dermatologist has reported three cases of phototoxic reactions to St. John's wort (14). The patients were fair-skinned and had had significant exposure to ultraviolet light. In two cases St. John's wort was applied topically. In all cases complete recovery occurred after withdrawal of St. John's wort and cessation of exposure to ultraviolet light.

Hair

Alopecia has been attributed to St. John's wort.

- A 24-year-old woman with schizophrenia who self-medicated with St. John's wort while also taking olanzapine (5–10 mg/day) developed hair loss on her scalp and eyebrows 5 months later; it persisted for 12 months (7). Her medical history was otherwise unremarkable.

The authors speculated that, like SSRIs, St. John's wort can cause hair loss.

Pregnancy

Like all herbal remedies, there is insufficient evidence that it is safe to take St. John's wort during pregnancy. Two women who took St. John's wort during pregnancy in order to avoid potential harmful effects of synthetic antidepressants to the fetus also discontinued their prescribed medications and did not discuss their decisions with their doctor (15). Although the effects of St. John's wort on the fetus are not known, the authors cautioned against using it under these circumstances and argued that tricyclic antidepressants or fluoxetine would be safer.

Drug interactions

Interactions of St. John's wort with prescribed drugs are due to its ability to induce the activity of both CYP3A4 and the P glycoprotein transporter system (16). Prescribed drugs that interact with St. John's wort include ciclosporin, digoxin, HIV protease inhibitors, oral contraceptives, serotonin re-uptake inhibitors, theophylline, and warfarin (17).

The mechanism of hepatic enzyme induction by St. John's wort has been intensively researched (18,19). Treatment of human hepatocytes with extracts of St. John's wort or with hyperforin (one of its active constituents) resulted in induction of CYP3A4 expression (20).

Following reports about the potential for herb–drug interactions, many national regulatory agencies issued warnings about the use of St. John's wort and its safety was reviewed (21,22).

Ciclosporin

St. John's wort is a hepatic enzyme inducer (23) and can lower the plasma concentrations of various prescribed drugs, including oral anticoagulants and ciclosporin.

In 30 patients a fall in ciclosporin concentrations by 33–62% after self-medication with St. John's wort necessitated a gradual increase in the dose of ciclosporin of 187% (range 84–292%) (24). No patient suffered any permanent consequences as a result.

There have also been anecdotal reports of interactions of ciclosporin with St. John's wort.

- A 29-year-old woman, who had received a cadaveric kidney and pancreas transplant, had stable organ function with ciclosporin when she decided to take St. John's wort (25). Subsequently her ciclosporin concentrations became subtherapeutic and she developed signs of organ rejection. St. John's wort was withdrawn and her ciclosporin concentrations returned to the target range. However, she developed chronic kidney rejection and had to return to dialysis.
- A 63-year-old patient with a liver allograft developed severe acute rejection 14 months after transplantation (26). Two weeks before he had taken St. John's wort, which significantly reduced his ciclosporin concentration. The dose of ciclosporin was doubled, at the expense of adverse effects. He recovered fully after St. John's wort was withdrawn.
- A 55-year-old woman, who had received a kidney transplant and had stable organ function with ciclosporin, took St. John's wort and 4 weeks later her ciclosporin concentration fell sharply (27). The concentration rose again on withdrawal of St. John's wort and fell on

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rechallenge. As the problem was identified early enough, the patient incurred no serious consequences.
- Two patients who took ciclosporin after kidney transplantation self-medicated with St. John's wort, and their ciclosporin concentrations became subtherapeutic (28). One subsequently had an acute transplant rejection. Withdrawal of St. John's wort resulted in normalization of ciclosporin concentrations.
- After a kidney transplant for end-stage renal insufficiency a 58-year-old man was given ciclosporin, azathioprine, and prednisolone (29). Four years later he started to take St. John's wort (300 mg bd) for depression, and 2 weeks later his previously stable ciclosporin concentrations had halved. Withdrawal of the St. John's wort resulted in normalization of his ciclosporin concentrations.

In a systematic review of all reports of interactions of St. John's wort with ciclosporin, 11 case reports and two case series were found (30). In most cases there was little doubt about causality.

Digoxin

In a randomized, placebo-controlled, double-blind study volunteers with steady-state digoxin concentrations took either placebo, a standardized extract of St. John's wort, encapsulated St. John's wort powder, St. John's wort tea, or an encapsulated fatty oil formulation of St. John's wort (31). The extract and the powder caused marked reductions in digoxin concentrations but the tea and the fatty oil formulation did not. The mechanism was not discussed, and it is not clear why the different formulations had different effects.

Irinotecan

In a randomized, crossover study five patients with cancer taking irinotecan were given St. John's wort (32). The plasma concentrations of irinotecan significantly fell in the presence of the herbal remedy. The authors pointed out that this is likely to reduce the effectiveness of the anticancer drug.

Oral contraceptives

- A 36-year-old woman became pregnant whilst taking an oral contraceptive, ethinylestradiol/dienogest (doses not stated) (33). She had also taken St. John's wort extract.

As no other cause for contraceptive failure could be identified, the authors concluded that the St. John's wort had been responsible.

Selective serotonin re-uptake inhibitors

Inhibition of serotonin re-uptake by St. John's wort can lead to interactions with SSRIs (34).

- A 28-year-old man without a previous psychiatric history was given sertraline 50 mg/day for depression after bilateral orchidectomy. Against medical advice, he also took St. John's wort and subsequently became manic.

The authors suggested that inhibition of serotonin re-uptake by sertraline had been potentiated by the use of St. John's wort.

Warfarin

In an open, crossover, randomized study in 12 healthy men St. John's wort significantly induced the apparent clearance of both *S*-warfarin and *R*-warfarin (by 29 and 23% respectively), which in turn resulted in a significant reduction in the pharmacological effect of racemic warfarin (35).

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Coagulation proteins

See also Individual agents

General Information

The major coagulation and fibrinolytic proteins are listed in Table 1.

Coagulation protein concentrates became available in the 1970s, a significant step in the prevention and management of bleeding. The factors that are currently available are factor VII, factor VIIa, factor VIII, factor IX, factor XI, and factor XIII. There is also a factor VIII inhibitor bypassing factor, activated prothrombin

Table 1 Proteins involved in coagulation and fibrinolysis

Protein (synonym)	Function
Coagulation proteins	
Factor I (fibrinogen)	Activated to fibrin
Factor II* (prothrombin)	Activated to thrombin
Factor III (tissue thromboplastin)	Extrinsic pathway
Factor IV (calcium)	Co-factor
Factor V (Ac-globulin; proaccelerin)	Converts prothrombin to thrombin
Factor VI (unassigned)	
Factor VII* (proconvertin)	Extrinsic pathway
Factor VIII (antihemophilic factor)	Intrinsic pathway
Factor IX* (Christmas factor)	Intrinsic pathway
Factor X* (Stuart–Prower factor)	Extrinsic pathway
Factor XI (plasma thromboplastin antecedent)	Intrinsic pathway
Factor XII (Hageman factor)	Intrinsic pathway
Factor XIII (fibrin stabilizing factor)	Stabilizes fibrin
Von Willebrand factor (factor VIII-related antigen; vWF)	
High molecular weight kininogen (Fitzgerald factor)	Intrinsic pathway
Prekallikrein (Fletcher factor)	Intrinsic pathway
Fibrinolytic proteins	
Plasminogen	Converted to fibrinolysin
Prourokinase	Precursor of urokinase
Tissue plasminogen activator	Activates plasminogen
Antithrombin III	Inhibits thrombin, IXa, Xa, XIa, XIIa
Protein C*	Inhibits factors Va, VIIIa
Protein S*	Co-factor for protein C
α_2-Antiplasmin	Inhibits binding of fibrinolysin

*Vitamin K-dependent factor; the intrinstic and extrinsic pathways converge with the activation of factor X to Xa by factor VIII and IX.

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complex concentrate. Fresh frozen plasma and prothrombin complex concentrate, which contain mixtures of coagulation proteins, are also available.

Two major classes of complications in the use of these proteins have emerged (1). First, transfusion-related infections with various blood-borne viruses, such as hepatitis B and C and human immunodeficiency virus (HIV). Secondly, alloimmune antibodies (inhibitors) against the deficient coagulation factors.

Organs and Systems

Cardiovascular

Two factor XI products, both containing antithrombin III and heparin, have been associated with evidence of coagulation activation and thrombotic events in patients with pre-existing vascular disease (2). It has been recommended that doses of more than 30 U/kg and factor XI peak concentrations in severely deficient patients of more than 500–700 U/l should be avoided. In addition, the concurrent use of tranexamic acid or other antifibrinolytic drugs should be avoided.

Immunologic

Patients with bleeding disorders are at risk of developing antibodies against the protein that is absent, present in reduced amounts, or present in an inactive form in their blood. Such coagulation inhibitors make treatment very difficult. Inhibitors of factor VIII are the most common and develop in 5–20% of patients with hemophilia A. Inhibitors of factor IX develop in 1–4% of patients with hemophilia B (3,4). Patients with factor VIII inhibitors present clinically either as "high responders" who show a strong anamnestic response and a sharp rise in inhibitor concentrations after exposure to factor VIII, or "low responders," who show little or no anamnestic response (5).

Because of the difference in prevalence of inhibitors in hemophilia B and hemophilia A, it has been postulated that there is a correlation between mutation type and inhibitor risk (6). Of the patients with gross deletion, nonsense, or frameshift mutations, 11% developed inhibitors compared with 0% and 0.36% of patients with hemophilia B with mis-sense or other mutations.

Recombinant and high-purity coagulation factor products appear to have a greater tendency to induce inhibitors than human-derived concentrates of intermediate or low purity (7). These intermediate-purity or low-purity human-derived concentrates are probably more suitable for inducing immune tolerance in patients with hemophilia with inhibitors. It has been suggested that for immune tolerance a high content of Von Willebrand factor in factor VIII concentrates is required, although direct comparisons of different products have not been made (8).

Risk factors for developing an inhibitor are the severity of the hemophilia, age (under 30 years), genetic predisposition, antigenicity of factor replacement therapy, and race (increased prevalence among black people) (9). In addition, it has been suggested that changing from one product to another can also stimulate the development of inhibitors (10).

Inhibitor formation has been observed in only a few patients with factor XI deficiency. Like patients with hemophilia A and B, these patients may be treated with prothrombin complex concentrates or recombinant factor VIIa (2).

Drug Administration

Drug contamination

In the past, plasma factor VIII products have exposed patients with hemophilia to foreign proteins as well as blood-borne viruses, including hepatitis B, hepatitis C, human parvovirus B19, and human immunodeficiency virus (11,12). Before the introduction of heat-treated concentrates in 1985, about 20% of patients with hemophilia in the UK became infected with HIV (13) and virtually all patients with hemophilia who were exposed to large-pool coagulation factor concentrates before the introduction of viral inactivation procedures developed hepatitis C (14). Studies using a second-generation enzyme-linked immunosorbent assay showed 89% anti-HCV positivity in a heterogeneous group of patients in the USA and in 98% of Dutch patients with hemophilia who had been exposed to large-pool, non-virally inactivated coagulation factor concentrates (14). In the UK and the Netherlands increased mortality due to liver disease in patients with hemophilia has been reported (14). In patients co-infected with HIV, liver disease was more severe, probably because of higher amounts of hepatitis C viral RNA (13). In addition, patients infected with hepatitis C virus genotype 1 had a more rapid course of disease due to HIV (14).

Since viral inactivation methods, such as solvent detergent and heat pasteurization, were implemented in the production process, the risks of HIV and hepatitis have virtually been eliminated. Dry heating at 60°C is insufficient to eliminate all hepatitis C virus, which requires dry heating at 80°C, pasteurization, or treatment with mixtures of solvents and detergents (14). Nevertheless, many viral inactivation methods currently used do not completely eliminate certain (non-enveloped) viruses, for example parvovirus and hepatitis A (11,15); removal of the small, non-lipid-enveloped parvovirus B19 requires 15 nm nanofiltration. HIV appears to progress more rapidly in patients co-infected with hepatitis B and cytomegalovirus (11). In addition, hepatitis C replicated more rapidly in patients infected with HIV (11).

In a mortality study amongst patients with hemophilia in the UK in 1977–91, AIDS was far the commonest cause of death, and liver disease ranked as the third commonest cause of death (15).

It has been postulated that transfusion-transmitted virus (TT virus) can be transmitted through heat-treated blood products (16). Transfusion-transmitted virus is a common DNA virus in healthy Japanese, and it lacks a lipid envelope, similar to parvovirus B19 (16,17). Transmission of transfusion-transmitted virus often occurs with blood transfusion and it can cause post-transfusion hepatitis with high postoperative peak alanine transaminase activity (17). No patients with hepatitis due to transfusion-transmitted virus have clinically apparent hepatitis (17). The incidence of transfusion-transmitted virus viremia in patients with hemophilia

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was 43% of those who received only virus-inactivated concentrates and 78% in those who received non-inactivated products before 1984 (16).

Bacterial growth in infusion bags has not been detected, and complications such as infections during the postoperative period have not been observed (18).

Although transmission of classic Creutzfeldt–Jakob disease has never been observed, manufacturers have withdrawn plasma-derived products prepared from plasma obtained from donors who were subsequently found to have classic Creutzfeldt–Jakob disease (19). Although leukocytes are believed to play a key role in the pathogenesis of variant CJD, there may also be a theoretical risk of transmission by plasma products. However, various steps used in the manufacture of plasma-derived factors also contribute to reduced infectivity by bovine spongiform encephalopathy (20). The risk of transmission of nvCJD by recombinant products is unknown, as the cell cultures used for manufacturing them sometimes contain bovine proteins (21).

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Cobalt

General Information

Cobalt is a metallic element (symbol Co; atomic no. 27). It is an important constituent of the cobalamins (vitamin B_{12}) and is found as arsenates and arsenides in naturally occurring minerals such as erythrite, skutterudite, and smaltite.

Cobalt has been used in the treatment of anemia, because of its erythropoietic action. However, it is toxic to many organs, and its medicinal benefits have repeatedly been questioned. In most countries the use of cobalt in anemia has been abandoned, although it is possible that in very rare cases there may be a need for it. If it is still to be used at all, the administration of cobalt ought to be entrusted to an experienced clinical hematologist.

Occupational exposure is mainly due to cobalt powders. Its main other uses are in metal alloys and medical devices (for example aneurysm clips) (1).

The toxicity of cobalt has been reviewed (SEDA-1, 185) (SED-9, 370) (2).

One tragic case in 1989 concerned a 13-month-old baby treated with a commercial iron–cobalt formulation that was still on sale, resulting in hypothyroidism, cardiomyopathy, polycythemia, and hypertrichosis (SEDA-16, 231).

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Cobalt in metal implants and prostheses

Complications from the use of metal implants and prostheses can arise because of biochemical and histological reactions to some of the materials used (SEDA-22, 250). These include titanium, stainless steel (10–14% nickel, 17–20% chromium), and cobalt chrome alloys (27–30% chromium, 57–68% cobalt, and up to 2.5% nickel). All of these metals can produce sensitization or elicit toxic reactions when they are solubilized and come into contact with tissues; it can be difficult or even impossible to differentiate between hypersensitivity and toxic reactions.

Nickel plays a major role in sensitization of patients. Even the small amount present in cobalt chrome alloys often suffices to elicit allergic reactions. Reactions to cobalt are more generally toxic in nature (3). An increased rate of allergy to cobalt and nickel has been found in those patients bearing metallic implants who have developed bone infection in the surroundings of osteosynthesis material.

Metals from prostheses can continue to be released into the system for many years. The development of hypersensitivity takes time, and allergic reactions are usual delayed for weeks, months, or 1–2 years. The symptoms can assume a variety of forms. Local reactions can cause loosening of the device or local pain. Dermatological reactions include eczema, bullous pemphigoid, urticaria, and "muscle tumors."

Attempts continue to predict metal sensitivity in the individual patient so that the choice of material can be made accordingly. In vitro tests for metal allergies have been developed on the basis of lymphokine (MIF) release from sensitized T lymphocytes exposed to metal–protein complexes (4). About 6% of patients without a previous metal implant had positive reactions to nickel, chromium, or cobalt. However, it is still not clear whether such a positive reaction is a reliable predictor of clinical problems. In practice few patients have either local or systemic reactions; when symptoms occur and other causes are ruled out, the implant should be removed. Some workers recommend removal of an implant whenever there is both a positive MIF test and a positive skin test, even in the current absence of a serious reaction. Allergic dermatitis will clear up as soon as the metal has begun to be cleared from the tissue. The type of metal and the amount released into the tissue will affect the time taken for the disappearance of toxic dermatological phenomena.

Catastrophic failure of two cemented cobalt-containing femoral stems that had been used in conjunction with the impacting bone-grafting technique has been reported in two cases (5).

- A-59-year-old woman with degenerative arthritis of the hip was managed with bipolar arthroplasty and later with total hip replacement. A long-stem component, manufactured from forged cobalt-chromium, was later used for revision. She developed acute pain in the thigh and buttock, with tenderness and swelling in the thigh and hip and pain on movement. Hip X-rays showed catastrophic failure of the femoral component of the prosthesis, and at operation the prosthesis and the femur were fractured at the same level.
- A 51-year old woman sustained a fracture of the left femoral neck, later treated by total hip arthroplasty, which was revised several times with the impaction bone grafting technique and insertion of a prosthesis with cement. She developed a persistent weakness of the hip in flexion and abduction. Later the left hip buckled and she fell while walking. X-rays showed a periprosthetic fracture with bending of the femoral component.

It was thought that the mechanism of failure had been cantilever bending secondary to good distal fixation in the presence of poor proximal bone support resulting from poor proximal incorporation of the impacted allograft. In essence, a fatigue fracture had occurred in a forged cobalt–chromium stem that did not have an obvious manufacturing defect at the site of failure. Both failures were apparently related to implant design and operative technique rather than to defects introduced during the manufacturing process.

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Cocaine

General Information

Cocaine is an alkaloid derived from the plant *Erythroxylon coca* and other *Erythroxylon* species in South America. The leaves contain cocaine as the principal alkaloid, plus a variety of minor alkaloids. Only decocainized coca products are legal in the USA, but some commercially available tea products have been found in the past to contain cocaine in a concentration normally found in coca leaves (about 5 mg of cocaine per 1 g tea-bag). This results in only mild symptoms when package directions to drink a few cups per day are followed, but massive overdosing can result in severe agitation, tachycardia, sweating, and raised blood pressure.

Cocaine, as the leaf or as an extracted substance in different forms, has been used for different purposes. Andean Indians have long chewed leaves of the coca plant to reduce hunger and increase stamina. Pure cocaine was first extracted from coca in the 19th century; it was used to treat exhaustion, depression, and morphine

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addiction and was available in many patent medicines, tonics, and soft drinks. In the USA, after the Harrison Narcotic Act of 1914 and the Narcotic Drugs Import and Export Act of 1922, the use of cocaine fell, and the National Commission on Marihuana and Drug Abuse in 1973 reported that cocaine was little used. Since then, however, use has grown and there is now an epidemic in many countries. There may be about 5 million regular cocaine users in the USA, and users who have significant difficulties, including serious as well as fatal medical complications, continue to be reported frequently (1,2). Deaths occur not only from overdosage but also from drug-induced mental states, which can lead to serious injuries (3).

Cocaine was also the first aminoester local anesthetic, and its adverse effects differ from those of other local anesthetics. Owing to its rapid absorption by mucous membranes, cocaine applied topically can cause systemic toxic effects. There is a wide variation in the rate and amount of cocaine that is systemically absorbed. This variability can be affected by the type and concentration of vasoconstrictor used with cocaine and also accounts for the differences in cocaine pharmacokinetics in cocaine abusers (SEDA-20, 128).

As a recreational drug cocaine can be snorted (sniffed), swallowed, injected, or smoked. The street drug comes in the form of a white powder, cocaine hydrochloride. The hydrochloride salt and the cutting agents are removed to create the free base, which is smoked. The inexpensive widely available crack formulation is prepared by alkalinizing cocaine hydrochloride and precipitating the resultant alkaloidal free-base cocaine, which, unlike the hydrochloride, is not destroyed by heat when smoked. Smoking crack provides a rapid effect, comparable to that of intravenous injection. Intense euphoria, followed within minutes by dysphoria, leads to frequent dosing and a greater potential for rapid addiction (4). As with amphetamines, the euphoric effect can enhance craving, and repeated reinforcement can lead to conditioned drug responses, which facilitate dependence. Facilitated conditioned effects with cocaine may be due to its rapid elimination and the development of acute tolerance. Frequent repeated dosing becomes necessary to sustain euphoria, thereby promoting a tight temporal juxtaposition of euphoria with recent drug-taking (5).

Rapid intravenous or inhalational administration of cocaine can cause very high concentrations in areas of high vascular perfusion, for example the heart and brain, before eventual distribution to other tissues. Under these conditions there is a catecholaminergic storm in the heart and a local anesthetic effect, with prolongation of conduction. Once beyond the immediate period of vulnerability, accumulation (for example through frequent overdosing or accidents from body packing of condom-filled stimulants to avoid detection) leads to a different cascade of events over a period of hours, leading to death. This cascade includes a catecholaminergic hypermetabolic state, with hyperpyrexia and acidosis, anorexia, and repeated seizures, usually ending in cardiac collapse (1,6). On the other hand, chronic dosing can cause catecholaminergic cardiomyopathy, for example contraction bands, cardiomegaly (7,8), and repeated vasospastic insults to cerebral and coronary arteries (9). Whether these chronic effects predispose to increased sensitivity to acute toxicity has not been systematically explored, but autopsy studies suggest that they do.

In addition to other chronic changes in abusers, personality deterioration carries a significant association with high-risk behaviors, which are a source of physical and psychiatric morbidity and mortality. These include suicide, violent trauma and aggressive behavior, high-risk methods of drug use (for example needle sharing), and high-risk sexual behavior, with increased risks of HIV, hepatitis B, and other infections.

The stimulant properties of cocaine are similar to those of amphetamines, although the differences are notable, in part because of the very short half-life of cocaine. However, cocaine has the same problem of abuse potential as other stimulants, and at high doses causes stimulant psychosis (10). In addition, even when it is used as a local nasopharyngeal anesthetic, it has toxic, even fatal, effects in high doses.

Death from cocaine often occurs within 2–3 minutes, suggesting direct cardiac toxicity, fatal dysrhythmias, and depression of medullary respiratory centers as common causes of death (11,12). Thus, cocaine's local anesthetic properties can contribute additional hazards when high doses are used, reminiscent of deaths reported in the era when it was used as a mucous membrane paste for nasopharyngeal surgery (13).

Periods of increased cocaine use, especially intravenous administration, inhalation of the free base, and high-dose use, are associated with cocaine-related deaths. For example, according to the Drug Abuse Warning Network, there was a three-fold increase in such deaths from 195 to 580 per year in the USA between 1981 and 1985. Despite the importance of these mortality data, relatively little is known of the types of pathophysiological sequences involved in the cascade of events leading to death. More important, there is a paucity of guidelines to appropriate diagnostic and treatment strategies for the various prefatal conditions.

General adverse effects

Cocaine has a spectrum of pharmacological effects. It initially causes excitement and euphoria; later, with higher doses, lower centers become involved, producing reduced coordination, tremors, hyper-reflexia, increased respiratory rate, and at times nausea, vomiting, and convulsions. These symptoms are eventually followed by CNS depression.

Cardiovascular effects include tachycardia, hypertension, and increased cardiac irritability; large intravenous doses can cause cardiac failure. Cardiac dysrhythmias have been ascribed to a direct toxic effect of cocaine and a secondary sensitization of ventricular tissue to catecholamines (14), along with slowed cardiac conduction secondary to local anesthetic effects. Myocardial infarction has increased as a complication of cocaine abuse (7,8). Dilated cardiomyopathies, with subsequent recurrent myocardial infarction, have been associated with long-term use of cocaine, raising the possibility of chronic effects on the heart (15). Many victims have evidence of pre-existing fixed coronary artery disease precipitated by cocaine (SEDA-9, 35) (16–18). However, myocardial

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infarction has been noted even in young intranasal users with no evidence of coronary disease (19), defined by autopsy or angiography (20,21). If applied to mucous membranes, cocaine causes local vasoconstriction, and, with chronic use, necrosis.

As a general rule, mortality is higher when cocaine is used intravenously or as smoked free base than if taken nasally or orally (22). The symptoms of acute cocaine poisoning include agitation, sweating, tachycardia, tonic-clonic seizures, severe respiratory and metabolic acidosis, apnea, and ventricular dysrhythmias. Seizures occur at high doses, and may be a major determinant of fatal outcomes; their control with sedatives is important to reduce lethality (23). Associated hyperthermia can contribute as a primary cause in cases of fatal hyperpyrexia, and can potentiate the hypoxic cardiovascular events in cardiac deaths in those who survive the initial acute dose (24,25). A study of a very large number of cocaine deaths showed that the morbidity rate increased by four times on days on which the ambient temperature rose above 31.1°C (26). The final agonal events in cocaine deaths involve the combination of sympathomimetic myocardial responses and/or cardiac conduction slowing, secondary to cocaine's local anesthetic effect, leading to dysrhythmias (27). In reported fatal overdoses, convulsions and death have usually occurred within minutes. Most patients who have survived for the first 3 hours after an initial acute overdose have been likely to recover. Treatment includes respiratory and cardiovascular resuscitative measures. Short-acting barbiturates, benzodiazepines, beta-blockers, and phentolamine have all been used with some success (20,28). Because of a possible risk of coronary vasodilatation with the use of propranolol to manage dysrhythmias in cocaine overdose, the use of labetalol for this indication is recommended, if a beta-blocker is required (29,30). In one study of 60 cocaine-related deaths, autopsy findings were non-specific but typical of those found in respiratory depression of central origin (31).

Organs and Systems

Cardiovascular

Cocaine abuse is a risk factor for myocardial ischemia, infarction, and dysrhythmias, as well as pulmonary edema, ruptured aortic aneurysm, infectious endocarditis, vascular thrombosis, myocarditis, and dilated cardiomyopathy (32). Acutely, cocaine suppresses myocardial contractility, reduces coronary caliber and coronary blood flow, induces electrical abnormalities in the heart, and increases heart rate and blood pressure. These effects can lead to myocardial ischemia (33,34). However, intranasal cocaine in doses used medicinally or recreationally does not have a deleterious effect on intracardiac pressures or left ventricular performance (35).

Tachycardia and vasoconstriction from cocaine can exacerbate coronary insufficiency, complicated by dysrhythmias and hypertensive and vascular hemorrhage (1). Sudden deaths have been reported in patients with angina (36). Chronic dosing includes cardiomyopathy and cardiomegaly; other chronic conditions include endocarditis and thrombophlebitis. Crack smoking has led to pneumopericardium (37).

The cardiac effects of intracoronary infusion of cocaine have been studied in dogs and humans (38). The procedure can be performed safely and does not alter coronary arterial blood flow. The effects of direct intracoronary infusion of cocaine on left ventricle systolic and diastolic performance have been studied in 20 patients referred for cardiac catheterization for evaluation of chest pain. They were given saline or cocaine hydrochloride (1 mg/minute) in 15-minute intracoronary infusions, and cardiac measurements were made during the final 2–3 minutes of each infusion. The blood cocaine concentration obtained from the coronary sinus was 3.0 μg/ml, which is similar in magnitude to the blood–cocaine concentration reported in abusers who die of cocaine intoxication. Minimal systemic effects were produced. The overall results were that cocaine caused measurable deterioration of left ventricular systolic and diastolic performance.

Possible predictors of cardiovascular responses to smoked cocaine have been studied in 62 crack cocaine users (24 women and 38 men, aged 20–45 years) who used a single dose of smoked cocaine 0.4 mg/kg (39). Physiological responses to smoked cocaine, such as changes in heart rate and blood pressure, were monitored. The findings suggested that higher baseline blood pressure and heart rate, a greater amount and frequency of current cocaine use, and current cocaine snorting predicted a reduced cardiovascular response to cocaine. By contrast, factors such as male sex, African-American race, higher body weight, and current marijuana use were associated with a greater cardiovascular response.

Fatal pulmonary edema developed in a 36-year-old man shortly after injecting free-base cocaine intravenously (40).

Symptoms of cardiac ischemia

Cocaine users often present with complaints suggestive of acute cardiac ischemia (chest pain, dyspnea, syncope, dizziness, and palpitation). Two studies have shown that the risk of actual acute cardiac ischemia among cocaine users with such symptoms was low. The first study reviewed the clinical database from the Acute Cardiac Ischemia–Time Insensitive Predictive Instrument Clinical Trial, a multicenter prospective clinical trial conducted in the USA in 1993 (41). Among 10 689 enrolled patients, 293 (2.7%) had cocaine-associated complaints. This rate varied from 0.3% to 8.4% in the 10 participating hospitals. Only six of these patients had a diagnosis of acute cardiac ischemia (2.0%), four with unstable angina and two with acute myocardial infarction. The cocaine users were admitted to the coronary care unit as often as other study participants (14 versus 18%), but were much less likely to have confirmed unstable angina (1.4 versus 9.3%). A second study also suggested that cocaine users who present with chest pain have a very low risk of adverse cardiac events (42). Emergency departments have instituted centers for the evaluation and treatment of patients with chest pain who are at low to moderate risk of acute coronary syndromes. In this particular study, patients with a history of coronary artery disease or presentations that included hemodynamic instability, electrocardiographic changes consistent with ischemia, or clinically unstable

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angina were directly admitted to hospital. In a retrospective study of 179 patients with reliable 30-day follow-up in chest pain centers, there was one cardiac complication due to cocaine use.

Coronary artery disease

By one estimate, since the first report in 1982, over 250 cases of myocardial infarction due to cocaine have been reported, mostly in the USA. The first report from the UK was published in 1999 (43).

In a review of 114 cases, coronary anatomy, defined either by angiography or autopsy, was normal in 38% of chronic cocaine users who had had a myocardial infarction (20). The authors of another review concluded that "the vast majority of patients dying with cocaine toxicity, either have no pathological changes in the heart, or only minimal changes" (21). There can be a delay between the use of cocaine and the development of chest pain (44). The results of a study of 101 consecutive patients admitted with acute chest pain related to cocaine suggested that it commonly causes chest pain that may not be secondary to myocardial ischemia (45). The use of intranasal cocaine for therapeutic purposes (to treat epistaxis) was associated with myocardial infarction in a 57-year-old man with hypertension and stable angina (46).

In a review of the literature, 91 patients with cocaine-induced myocardial infarction were identified (47). Myocardial infarction occurred in 44 patients after intranasal use, in 27 after smoking, and in 19 after intravenous use. Almost half had a prior episode of chest pain. Two-thirds had their myocardial infarction within 3 hours of use. There were acute complications related to the myocardial infarction in 18 patients. Of 24 patients followed up, 58% had subsequent cardiac complications. Two-phase myocardial imaging with ^{99m}Tc-sestamibi can be helpful in the definitive diagnosis of cocaine-induced myocardial infarction in patients with a history of cocaine use, chest pain, and a non-diagnostic electrocardiogram (48). Damage to the myocardium associated with cocaine can be unrecognized by the abuser (49). Major electrocardiographic findings (including myocardial infarction, myocardial ischemia, and bundle branch block) were recorded during a review of 99 electrocardiograms of known cocaine abusers. None of the 11 patients with major electrocardiographic changes had a past history of cardiac disease or had complained of chest pain. The mechanism by which cocaine causes acute myocardial damage is unclear. Of 20 healthy cocaine abusers given intravenous cocaine, in doses commonly self-administered, or placebo, none developed myocardial ischemia or ventricular dysfunction on two-dimensional echocardiography during the test (50).

Myocardial infarction has been documented in 6% of patients who present to emergency departments with cocaine-associated chest pain (51,52). Treatment of cocaine-associated myocardial infarction has previously generally been conservative, using benzodiazepines, aspirin, glyceryl trinitrate, calcium channel blockers, and thrombolytic drugs. In the context of 10 patients with cocaine-associated myocardial infarction, who were treated with percutaneous interventions, including angioplasty, stenting, and AngioJet mechanical extraction of thrombus, the authors suggested that percutaneous intervention can be performed in such patients safely and with a high degree of procedural success (53). Patients with cocaine-associated chest pain and electrocardiographic ST-segment elevation should first undergo coronary angiography, if available, followed by percutaneous intervention. Alternatively, thrombolytic drugs can be used. However, the relative safety and efficacy of thrombolytic drugs compared with percutaneous intervention is undefined in patients with cocaine-associated myocardial infarction.

Other vascular disease

Dissection of the aorta has been reported during cocaine use (54,55). The authors of these two reports noted that all six cases of this rare complication reported in the past 5 years were in men with pre-existing essential hypertension. In a review of emergency visits to a hospital during a 20-year period, 14 of 38 cases of acute aortic dissection involved cocaine use; 6 were of type A and 8 of type B (56). Crack cocaine had been smoked in 13 cases and powder cocaine had been snorted in one case. The mean time of onset of chest pain was 12 hours after cocaine use. The chronicity of cocaine use was not known in most of the cases. The cocaine users were typically younger than the non-cocaine users. Chronic untreated hypertension and cigarette smoking were often present.

- A 43-year-old man with untreated hypertension developed transient mild chest pressure followed by shortness of breath for 4 hours (57). He had long used tobacco, alcohol, and cocaine and admitted to having used cocaine within the last 12 hours. He had a tachycardia with a pansystolic murmur suggesting mitral regurgitation. Urine drug screen was positive for cocaine metabolites. A chest X-ray showed mild cardiomegaly and prominent upper lobe vasculature. An electrocardiogram showed atrial flutter at a rate of 130/minute and non-specific T wave changes. The diagnoses were myocardial infarction due to cocaine, with mild congestive heart failure, mitral regurgitation and atrial flutter. However, transesophageal echocardiography showed severe aortic insufficiency and a dissection flap in the ascending aorta. He underwent emergency repair of the aortic root and resuspension of the aortic valve.

Intramural hematoma of the ascending aorta has been reported in a cocaine user (58).

- A healthy 39-year-old man developed retrosternal chest pain radiating to the back with nausea and sweating. About 10–15 minutes before, he had inhaled cocaine for 2 hours and then smoked crack cocaine. He had an aortic dissection, which was repaired surgically.

The authors identified hypertension secondary to the use of cocaine as the risk factor for this complication.

Coronary artery dissection associated with cocaine is rare. The first case was reported in 1994 (59) and two other cases have been reported (60,61).

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- A healthy 33-year-old man with prior cocaine use had a small myocardial infarction and, 36 hours later, having inhaled cocaine, developed a dissection of the left main coronary artery, extending distally to the left anterior descending and circumflex arteries. There was marked anterolateral and apical hypokinesis.
- A 23-year-old man with a history of intravenous drug abuse and hepatitis C was found unconscious, hypoxic, and hypotensive. A urine drug screen was positive for cocaine metabolites, benzodiazepines, and opiates. An electrocardiogram suggested a myocardial infarction, verified by raised troponin I and the MB fraction of creatine kinase. He had severe hypokinesia with a left ventricular ejection fraction of 10%, falling to less than 5%. He became septic, developed multiorgan system failure, and died. The postmortem findings included dissection of the left anterior descending artery with complete occlusion of the true lumen and thrombosis of the false lumen. The left ventricle showed extensive transmural myocardial necrosis with adjacent contraction band necrosis. He also had deep vein thromboses in veins in the neck and abdomen and multiple pulmonary infarctions.

Peripheral vascular disease in the fingers has been attributed to cocaine.

- A 48-year-old man who smoked cigarettes and used cocaine developed ischemia of the right index finger due to occlusion of the distal ulnar artery (62). He had a history of recurrent deep vein thrombosis. A venous bypass graft was performed. Two years later he had non-healing gangrene of the left index finger. His blood pressure was normal in both arms. Urine toxicology was positive for cocaine. Angiography of the left arm showed small-vessel vasculitis.
- A healthy 36-year-old man, who had used intranasal crack cocaine daily in increasing doses for 2 weeks, developed pain, numbness, swelling, and cyanosis of the fingers and toes aggravated by cold and an ulcer on one finger (63). Ultrasound Doppler of the hand confirmed ischemic finger necrosis. He was treated unsuccessfully with aspirin, diltiazem, and heparin, but responded to intravenous infusions of iloprost for 5 days.

Another less common complication of cocaine use is cerebral vasculitis (64), and benign cocaine-induced cerebral angiopathy has been reported (65). (Stroke is discussed under the section Nervous system in this monograph).

Cardiac dysrhythmias

Dysrhythmias seem to be the most likely cause of sudden death from cocaine, but cardiac conduction disorders are more common in patients with acute cocaine toxicity. Severe cocaine toxicity also causes acidemia and cardiac dysfunction (66). Four patients developed seizures, psychomotor agitation, and cardiopulmonary arrest; two of these are briefly summarized here.

- A 43-year-old man injected a large dose of cocaine in a suicide attempt and had a seizure and cardiopulmonary arrest, from which he was resuscitated. His arterial blood pH was 6.72 and his electrocardiogram showed a wide complex tachycardia. An infusion of sodium bicarbonate maintained the blood pH at 7.50 and the electrocardiogram became normal. The bicarbonate infusion was discontinued after 12 hours.
- A 25-year-old man had a cardiac arrest after taking one "knot" or sealed bag of crack cocaine (2.5 g) and was resuscitated. His arterial blood pH was 6.92 and an electrocardiogram showed sinus rhythm, QRS axis 300°, and terminal 40 msec of the QRS axis 285°. After an infusion of sodium bicarbonate, his blood pH was 7.30, his QRS axis 15°, and the terminal 40 msec QRS axis 30°. He passed the bag of cocaine rectally within 12 hours of admission.

These patients' initial laboratory values showed acidosis, prolongation of the QRS complex and QT_c interval, and right axis deviation. Appropriate treatment included hyperventilation, sedation, active cooling, and sodium bicarbonate, which led to correction of the blood pH and of the cardiac conduction disorders. The authors suggested that when intracellular pH is lowered, myocardial contractility is depressed as a result of reduced calcium availability. During acidosis, there are abnormalities of repolarization and depolarization, which potentiate dysrhythmias.

The electrocardiographic PR interval increased with increasing abstinence from crack cocaine in a study of 441 chronic cocaine users who had smoked at least 10 g of cocaine in the 3 months before enrollment (67). The authors suggested that this may have reflected the normalization of a depolarization defect. Chronic cocaine users have shortened PR intervals, indicative of rapid cardiac depolarization.

Cardiovascular effects of cocaine as a local anesthetic

Cardiovascular effects due to enhanced sympathetic activity include tachycardia, increased cardiac output, vasoconstriction, and increased arterial pressure. Myocardial infarction is the most common adverse cardiac effect (39), and there is an increased risk of myocardial depression when amide-type local anesthetics, such as bupivacaine, levobupivacaine, lidocaine, or ropivacaine are administered with antidysrhythmic drugs.

- A woman who inappropriately used cocaine on the nasal mucosa to treat epistaxis had a myocardial infarction (49).
- A patient who was treated with intranasal cocaine and phenylephrine during a general anesthetic had a myocardial infarction and a cardiac arrest due to ventricular fibrillation (SEDA-20, 128).
- Myocardial ischemia was reported in a fit 29-year-old patient after the nasal application of cocaine for surgery. No relief was gained from vasodilators or intracoronary verapamil, and there were no other signs of cocaine toxicity. Although coronary vasoconstriction and platelet activation are systemic effects of cocaine, pre-existing thrombus may also have played a part (SEDA-22, 142).

Previous cocaine abuse has also been implicated in increasing the risk of myocardial ischemia when other local anesthetics are used.

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Cardiac dysrhythmias have also been described in patients after the use of topical cocaine for nasal surgery (SEDA-20, 128).

- A patient who was treated with intranasal cocaine and submucosal lidocaine during general anesthesia developed ventricular fibrillation (SEDA-17, 142).

These events do not appear to have been related to the concomitant use of a vasoconstrictor, but more to excessive doses of cocaine.

Substantial systemic absorption of cocaine can cause severe cardiovascular complications (68).

- An 18-year-old man had both nasal cavities prepared with a pack soaked in 3–5 ml of Brompton solution (3% cocaine, about 3 mg/kg, plus adrenaline 1:4000) 2 hours preoperatively. In the anesthetic room he was anxious and withdrawn, with a mild tachycardia. Ten minutes later the nasal pack was removed and polypectomy was begun, with immediate sinus tachycardia and marked ST depression on lead II of the electrocardiogram. Increasing the depth of anesthesia and giving fentanyl had little effect, and the procedure was terminated. After extubation a further electrocardiogram showed T wave flattening in leads II, III, aVF, and aVL. Further cardiac investigations ruled out a myocardial infarction, an anatomical defect, or other pathological or metabolic processes. On day 4 a stress electrocardiogram showed no ischemic changes.

Absorption of cocaine from the nasal mucosa in eight patients using cotton pledglets soaked in 4 ml of 4% cocaine and applied for 10 or 20 minutes resulted in an absorption rate four times higher than expected, but was not associated with any cardiovascular disturbance; however, one of four patients who received 4 ml of 10% cocaine for 20 minutes developed intraoperative hypertension and another transient ventricular tachycardia (69). The authors advised against topical use of 10% cocaine.

Respiratory

The respiratory effects of cocaine are well known (70). In healthy crack cocaine users, there is evidence of cocaine-related injury to the pulmonary microcirculation, from fiberoptic bronchoscopy and examination of the bronchoalveolar fluid in 10 cocaine-only smokers, six cocaine-plus-tobacco smokers, 10 tobacco smokers, and 10 non-smokers, all with normal respiratory function (71). The percentages of hemosiderin-positive alveolar macrophages (a marker of recent alveolar hemorrhage) were markedly increased in the cocaine smokers compared with the others. Furthermore, the concentrations of endothelin (ET-1), an indicator of cell damage, were significantly raised in the cocaine smokers and to a lesser extent in the cocaine-and-tobacco smokers. These findings suggest that many asymptomatic healthy crack users have chronic alveolar hemorrhage that is not clinically evident.

In 177 heavy cocaine users (compared with 75 non-cocaine users), some of whom were also tobacco or marijuana users, cocaine use was associated with a higher prevalence of acute respiratory symptoms, including black sputum and chest pain. However, chronic respiratory symptoms occurred at similar frequencies in both groups. In cocaine-only smokers, mild impairment in carbon monoxide diffusing capacity suggested pulmonary capillary membrane damage, and abnormal airway conductance suggested injury to the upper airway or the large intrathoracic bronchi. Reported pulmonary complications of crack cocaine range from acute symptoms (coughing, chest pain, and palpitation) to acute syndromes (end-stage lung disease, eosinophilic infiltrates of the lung, and pulmonary infarction). The single-breath carbon monoxide diffusing capacity after the use of crack cocaine was reduced in three of six reports (70). If confirmed, a reduced carbon monoxide diffusing capacity after crack may signify damage to the alveolar capillary membrane or the pulmonary vasculature. It has been suggested that a well-designed controlled study to investigate the true impact of crack on the lung is necessary, since several confounding factors may account for the discrepancy in results (72).

Reports of acute pulmonary syndromes after the inhalation of cocaine have long been familiar.

- A 32-year-old woman rapidly developed progressive deterioration of respiratory function leading to end-stage lung disease (73). An open lung biopsy showed an inflammatory process with extensive accumulation of free silica.

The authors cautioned that some cocaine may contain silica, which could lead to severe pulmonary complications after smoking.

- A 27-year-old man twice developed inflammatory lung disease (with a predominance of eosinophils) after inhaling crack cocaine (74). Glucocorticoid treatment led to prompt resolution on both occasions.
- A 23-year-old woman developed pulmonary infarction associated with the use of crack (75).

Passive inhalation of free-base cocaine in small children can lead to serious consequences.

- A previously healthy 3-week-old boy developed pulmonary edema and autonomic manifestations of cocaine exposure from passive use (76). The urinary drug screen was positive for benzoylecgonine, a cocaine metabolite.
- Fatal pulmonary edema developed in a 36-year-old man shortly after he injected free-base cocaine intravenously (43).

A case of severe bullous emphysema in a cocaine smoker has been described (77).

- A 40-year-old man with cough, shortness of breath, and fever progressed to respiratory failure. He had smoked cocaine for the previous 17 years. His tobacco history was not known. His medical history included recurrent respiratory tract infections. A chest X-ray and CT scan showed findings consistent with bilateral bullous emphysema with a right lung abscess. He was ventilated and given antibiotics but died from respiratory failure secondary to pneumonia. Sputum cultures were positive for *Enterobacter cloacae* and *Streptococcus* species. Alpha-1 antitrypsin deficiency was ruled out.

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Spontaneous pneumomediastinum has been reported (78).

- A 20-year-old obese Hispanic man awoke with severe, continuous retrosternal chest pain radiating to the neck and back (79). The pain was aggravated by deep breathing and local chest pressure. He denied substance abuse and gave a history of a flu-like illness 2 months before. His respiratory rate was 19/minute. He had a two-component pericardial rub. Laboratory blood testing ruled out myocardial infarction. His arterial blood gases and pH, electrocardiogram, chest X-ray, and echocardiogram were unremarkable. A later chest X-ray showed air in the mediastinum and chest CT confirmed the diagnosis of pneumomediastinum. Urine toxicology was positive for cocaine and cannabinoids. On further questioning, he admitted to substance use and performing a Valsalva maneuver during inhalation.

Handling cocaine pipes can cause thermal injury to the fingertips. The presence of bilateral thumb burns raised suspicion of crack lung in a young woman with suspected community-acquired pneumonia (80). When confronted with urine toxicology positive for cocaine, she admitted to having smoked large quantities of free-base cocaine only a few hours before the onset of symptoms.

Pneumothorax and pneumomediastinum

Two cases of spontaneous pneumothorax in intranasal cocaine users have been reported from Italy (81).

- A 30-year-old man, a cocaine sniffer, who had used cocaine more than five times a month for 4 years, complained of shortness of breath and acute chest pain. He had episodic cough and bloody sputum. A chest X-ray showed an 80% pneumothorax on the left side. On thoracoscopy the entire lung visceral pleura seemed to be covered by fibrinous exudate. After yttrium aluminium garnet (YAG) laser pleurodesis surgery, which abrades the pleura, he made a full recovery within 4 days.
- A 24-year-old man who had been inhaling cocaine nasally 4–5 times a month for a year developed respiratory distress and chest pain 2 days after the last use, because of a right-sided pneumothorax. He underwent video-assisted thoracoscopic surgery with laser pleurodesis and responded rapidly.

In both cases, pneumothorax occurred with a delay after cocaine inhalation. The authors suggested that it was therefore unlikely that these cases of pneumothorax were due to direct traumatic effects of the drug powder inhaled, to barotrauma due to exaggerated inspiration, or to a Valsalva maneuver. Histological examination in both cases showed small foreign body granulomas with polarized material in the subpleural parenchyma. The authors proposed that the pleural damage could have been directly caused by a filler substance known as mannite (a fine white powder comprised of insoluble cellulose fibers).

Spontaneous pneumomediastinum has been reported with the inhalation of free-base cocaine (78).

Asthma

Cocaine can cause exacerbation of asthma. All adult visits to an urban emergency room for an asthma attack during a 7-month period were reviewed (82). Of 163 patients (aged 18–55 years), 116 agreed to participate in a facilitated questionnaire and 103 provided urine samples for drug screening. African-Americans made up 89% of the group and 35% were cigarette smokers. Urine toxicology was positive for cocaine in 13% and for opiates in 5.8%. The severity of the exacerbation of asthma was greatest in the cocaine-positive group, 38% of whom were admitted to hospital (compared with 20% of the non-cocaine users). The length of stay was significantly longer in the cocaine-positive patients. Most of the patients did not use inhaled corticosteroids according to the treatment guidelines.

Ear, nose, throat

Intranasal use, a common method of cocaine abuse, can damage the sinonasal tract, causing acute and chronic inflammation, necrosis, and osteocartilaginous erosion (SEDA-17, 36). These conditions occur secondary to the combined effects of direct trauma from instrumentation, vasoconstriction of small blood vessels with resultant ischemic necrosis, and chemical irritation from adulterants. Intranasal cocaine users can develop septal perforation, saddle-nose deformities, and sinonasal structural damage.

- A 43-year-old woman with a past history of chronic heavy cocaine use and osteomyelitis of the hard palate and nasal cavity 10 years before had required continuous follow-up for recurrent ethmoid and sphenoid sinusitis (83). Endoscopy showed an absent nasal septum, middle turbinates, anterior two-thirds of the inferior turbinates, and lateral nasal wall.
- Pott's puffy tumor, a subperiosteal infection of the frontal bone, has been described in a 34-year-old man with a history of chronic intranasal cocaine use (84).

This rare complication of frontal sinusitis appeared to develop secondary to the insertion of foreign bodies into the nose to facilitate inhalation of cocaine. Local trauma plus cocaine-induced vasoconstriction may have led to the complication.

Midline nasal and hard palate destruction have been reported in two chronic users of intranasal cocaine (85). The pathophysiology of these lesions is multifactorial, including ischemia secondary to vasoconstriction, chemical irritation from adulterants, impaired mucociliary transport, reduced immunity, and infection secondary to trauma.

In another case there was progression of septal perforation to secondary bone infection in a chronic cocaine user (86).

- A 56-year-old chronic intranasal cocaine abuser with a visible nasal defect presented with a hole in the roof of his mouth. He had been reportedly drug free for 2 weeks. He had an oronasal fistula with adjacent black necrotic areas and erosive destruction of the nasal septum, turbinates, and antrum, with mucoperiosteal thickening of the sphenoid and maxillary sinuses. Treatment included antibiotics and a prosthesis plate construction

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to cover the defect. Two years later, having continued to inhale cocaine, he had progressive destruction of his sinonasal tract, a fistula between his oral and nasal cavity, a saddle-nose deformity with total cartilage loss, and a complete palatal defect. Biopsy of the nasal septum showed acute osteomyelitis and extensive bacterial overgrowth (including anerobic *Actinomyces*-like organisms). He was given intravenous antibiotics for 6 weeks followed by long-term oral antibiotics.

Cocaine-related erosion of the external nasal structures has been described (87).

- A 43-year-old woman with a T12 paraplegia due to a car accident 24 years earlier and a sublabial abscess 2 years before developed progressive erosion of both the internal and external portions of her nose over 6 months, with nasal crusting and nose bleeds. Several antibiotics were unhelpful. There was partial destruction of the external nasal structure and two oronasal fistulae in the upper gingival sulcus. Intranasal biopsy showed acute and chronic inflammation. On two occasions urine drug screening was positive for cocaine, although she denied using cocaine.

Nervous system

Research in 21 cocaine users and 13 non-drug-using, age-matched controls has suggested that chronic cocaine use may be associated with specific neurochemical changes in the brains of habitual users (88). All the subjects underwent a spectral brain scan in a proton MRS scanner. The significant finding was that the concentration of *N*-acetylaspartate in the left thalamus (but not in the basal ganglia) was significantly lower (17%) in the chronic cocaine users than in the controls. *N*-acetylaspartate is found in adult neurons and not in glia; it is often used as a marker of neuronal viability; a reduction suggests neuronal damage and/or loss.

Assessment of smooth pursuit eye movements has been used in the study of neurophysiological effects of a variety of clinical and subclinical disorders. In 126 patients who met DSM-IIIR criteria for dependence on alcohol, cocaine, or heroin, or dual alcohol and cocaine abuse, there was a significant reduction in tracking accuracy in the heroin-dependent and the dually-dependent subjects relative to controls (89). However, eye movement dysfunction in the drug-dependent groups was not detectable when the effects of antisocial personality disorder were statistically removed. The magnitude of the dysfunction correlated significantly with several antisocial personality-related features, including an increased number of criminal charges, months of incarceration, increased problems associated with drug abuse, and lower intellectual functioning. The findings suggested that there may be an association between premorbid personality traits and eye movement impairment.

Cocaine use has been associated with a reduced inhibitory response of the P50 auditory evoked response, attributed to increased catecholaminergic and reduced cholinergic neurotransmission secondary to cocaine (90). In a double-blind, placebo-controlled study, 11 cocaine users in the first and third weeks of detoxification had electrophysiological testing 10 minutes before and 30 minutes after taking nicotine gum 6 mg. Nicotine briefly reversed the inhibitory deficit.

Chronic substance use has been associated with long-lasting changes in brain function (91). Five brain regions that may be affected (the orbitofrontal gyrus, rectal gyrus, anterior cingulate gyrus, basal ganglia, and thalamus) were selected for analyses of cerebral glucose metabolism by positron emission scanning in controls, cocaine users, and alcoholics (17 in each group), who performed the Stroop test, which assesses cognitive interference and response inhibition. In controls, higher brain glucose metabolism in the orbitofrontal gyrus correlated with poorer performance. In contrast, in substance users, higher brain glucose metabolism was associated with better performance. Chronic abuse appears to be associated with altered function of the orbitofrontal gyrus.

Cerebellar dysfunction

Cocaine has been associated with movement disorders, such as acute dystonias, choreoathetosis, and akathisia. Chronic pancerebellar dysfunction occurred in a cocaine user with schizophrenia treated with risperidone (92).

- A 38-year-old man was found comatose in a crack house. The ambient temperature was 13°C. He had earlier abused cocaine. His temperature was 43°C, heart rate 115, blood pressure 144/89 mmHg, and oxygen saturation 97% on air. His general muscle tone was flaccid. He had a mild leukocytosis and hypophosphatemia. Urine toxicology was positive for benzoylecgonine, a cocaine metabolite. He was mechanically ventilated, cooled, and given intravenous fluids. His temperature fell to 38°C, but he later developed acute disseminated intravascular coagulation and rhabdomyolysis. After 5 days he developed nystagmus, intention tremor, truncal ataxia, dysarthria, ocular dysmetria, and dysmetria of the arms and legs. There were no sensory or motor deficits. Finger-to-nose and heel-to-knee tests were slowed and uncoordinated. He could not stand. Brain imaging studies (CT and MRI scans) were unremarkable. He was given thiamine, propranolol, clonazepam, primidone, and baclofen every 8 hours without improvement. After 1 year he still had nystagmus, intention tremor, ataxic gait, and dysmetria. He could walk short distances slowly.

Cocaine and neuroleptic drugs can both cause hyperthermia and the authors proposed that the combination of cocaine and risperidone may have caused this problem.

Migraine

About 60–75% of chronic cocaine abusers report severe headaches (93), which can resemble migraine; migraine-like symptoms can include auras, visual field changes, and paraphasia (94). About 60–75% of chronic cocaine abusers report severe headaches (93,94). Of 21 patients who were admitted to hospital from January 1985 to December 1988 for acute headache associated with cocaine intoxication 15 had headaches with migrainous features in the absence of neurological or systemic complications (93). None had a history of cocaine-unrelated headaches or a family history of migraine, and all had a

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favourable outcome. The authors discussed three possible mechanisms of cocaine-related vascular headaches, depending on the interval between cocaine ingestion and development of the headache. They postulated that acute headaches after cocaine use may relate to the sympathomimetic or vasoconstrictive effects of cocaine, while headaches after cocaine withdrawal or exacerbated during a cocaine binge may relate to cocaine-induced effects on the serotoninergic system.

Movement disorders

The effects of cocaine or its withdrawal on neurotransmitter activity have been evaluated in several studies. Although changes in dopaminergic activity appear to be associated with early cocaine abstinence, extrapyramidal symptoms (due to alterations in dopamine functioning) have only infrequently been reported in cocaine users. However, in a recent report, extrapyramidal symptoms of classic muscle stiffness and cogwheel rigidity at the elbow occurred during the "crash" phase of a 40-year-old man's cocaine withdrawal (95).

Cocaine can cause other movement disorders (96). Motor and vocal tics, pre-existing tremors, and generalized dystonia were induced or exacerbated by drug use, and continued even after cocaine use ended. Lastly, dopamine dysregulation (that is reduced dopamine receptor availability in association with reduced frontal metabolism) was demonstrated by positive emission tomography in 20 chronic cocaine abusers (97). The findings were prominent in the orbitofrontal, cingulate, and prefrontal cortex 3–4 months after detoxification. The author hypothesized that dysregulation of these brain areas may result in compulsive drug-taking behavior.

Dystonia has been described shortly after the use of cocaine (SEDA-16, 24). In a retrospective study of 116 patients taking neuroleptic drugs, 42% of cocaine users versus 14% of non-users developed dystonia (98). This suggests that the use of cocaine may be a major risk factor for acute dystonic reactions secondary to the use of neuroleptic drugs.

Cocaine-induced chronic tics have been reported (99), and cocaine has reportedly exacerbated Gilles de la Tourette syndrome (100).

Myasthenia gravis

A 24-year-old woman developed myasthenia gravis during cocaine use (101). The authors speculated that while cocaine did not cause impairment of motor axons for neuromuscular transmission, a reduction in the number of acetylcholine receptors per neuromuscular junction (as occurs in myasthenia gravis) could have increased the susceptibility to an effect of cocaine.

A rare case of polysubstance abuse, which unmasked myasthenia and caused complete external ophthalmoplegia, has been reported (102).

- A 29-year-old woman, who used cocaine 2 g/day, heroin 1 g/day, and methadone 40 mg/day, developed abscesses caused by drug injection. She had had generalized weakness, difficulty in swallowing, and lagging eyelids for 1 week. There was bilateral ptosis, and a diagnosis of myasthenia was made. Edrophonium 10 mg relieved the ptosis and improved ocular movements.

Seizures

Cocaine lowers the seizure threshold and may therefore be dangerous to patients already at risk of seizures (40). Exacerbation of generalized tonic-clonic seizures (which occurred initially during the use of crack but later continued independently of the drug) has been described, with progressive electroencephalographic abnormalities (103). In this case, the development of the seizures suggested that cocaine can stimulate kindling, with progressive intensification of after-discharges and the eventual emergence of seizure activity.

Cerebrovascular vasoconstriction and a sudden increase in blood pressure probably underlie the many reports of cocaine-induced strokes, CNS hemorrhage, and migraine (SEDA-17, 1).

Three cases of generalized seizures occurring shortly after the intravenous use of cocaine (104).

Sleep disturbance

The disruption of normal sleeping patterns during cocaine withdrawal may be related to effects on the cholinergic system. In a study of nine patients undergoing cocaine withdrawal, rapid eye movement (REM) latency was markedly shortened, REM sleep percentage was increased, REM density was very high, and the total sleep period was long during the first week (105). Changes in REM sleep are thought to be related to changes in cholinergic activity. At week 3, characteristic chronic insomnia was observed.

Stroke

Cocaine has been associated with cerebrovascular events, such as transient ischemic attacks (SEDA-24, 24), cerebral hemorrhage (106,107), and cerebral infarction (SEDA-22, 23) (SEDA-20, 26) (SEDA-20, 21).

Regional cerebral blood flow was assessed using single photon emission computed tomography (SPECT) and tracer HMPAO in 10 cocaine abusers within 72 hours of last cocaine use and then after 21 days of abstinence (108). Compared with controls, recent cocaine abusers had significantly reduced cerebral blood flow in 11 of 14 brain regions, with the largest reductions in the frontal cortex and parietal cortex and greater cerebral blood flow in the brain stem. These perfusion defects appeared to be primarily due to combined abuse of alcohol and cocaine. Frontal but not parietal defects appeared to resolve partially during 21 days of abstinence.

In a review of ischemic stroke in young American adults (aged 15–44 years) admitted to 46 regional hospitals between 1988 and 1991, illicit drug use was noted in 12% and was the probable cause of stroke in 4.7% (109). Multidrug use was common among users: 73% used cocaine, 29% used heroin, and 14% used phencyclidine. Drug-associated stroke in these young adults appeared to be related to vascular mechanisms (such as large and small vessel occlusive disease) rather than to hypertension or to diabetes. Cerebral infarction is significantly more common among users of cocaine alkaloid (crack) than cocaine hydrochloride (110).

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Ischemic stroke has been attributed to combined use of cocaine and amphetamine (111).

- A previously healthy 16-year-old man developed an unsteady gait and double vision. His symptoms began 5 minutes after intranasal "amfetamine" (actually amfetamine cut with cocaine). He had a left-sided internuclear ophthalmoplegia, an incomplete fascicular paresis of the left oculomotor nerve, and saccadic vertical smooth pursuit. Cranial MRI showed a left-sided hyperintense lesion near the midline of the mesencephalon. A repeat MRI scan 9 days later showed that the lesion was much smaller. He made a full recovery within 3 weeks.

The cause of cocaine-related stroke and transient ischemic attacks has been studied by transcranial Doppler sonography, a continuous measure of cerebral blood flow velocity, to monitor the course of cerebral hemodynamic changes during acute intravenous injection of placebo, and of cocaine 10, 25, and 50 mg in seven cocaine abusers (112). There was a significant increase in mean and systolic velocity (lasting about 2 minutes) with all doses of cocaine but not with placebo. Cocaine produced an immediate brief period of vasoconstriction (as demonstrated by an increase in systolic velocity) in the large arteries of the brain.

"Spontaneous" acute subdural hematoma related to cocaine abuse has been described (113).

- A 38-year-old man with a 10-year history of cocaine use became comatose. He had had an acute severe headache and progressive deterioration after abusing cocaine. His Glasgow Coma Scale was 3 and his pupils were dilated but reactive to light. He had hypertension and bradycardia. Routine toxicology was positive for cocaine. Blood tests, including coagulation profile, were normal. A CT scan of the brain showed a left acute subdural hematoma with midline shift and obliteration of the basal cisterns. During emergency craniotomy the source of the bleed was identified as a pinhole rupture of a parietal cortical artery. The patient had no history of head injury and there were no intraoperative findings of head injury. He died 24 hours later without evidence of clot reaccumulation. An autopsy was not performed.

Hypertensive encephalopathy can follow the use of cocaine (114).

Brown–Séquard syndrome after esophageal sclerotherapy and recent crack cocaine abuse has been reported (115).

- A 44-year-old man with hepatitis C and cirrhosis, esophageal varices, and poorly controlled hypertension, who was also a chronic alcoholic and crack cocaine abuser, had his varices injected at endoscopy and developed right-sided weakness and numbness up to T4. There was flaccid right leg weakness, right T4-6 hypalgesia, left leg hypalgesia up to L1, and reduced sweating on the left up to T4-6. An MRI scan of the thoracic spine showed a lesion at T4-6 involving the anterior and central portions of the spinal cord. A urine screen was positive for cocaine. He recovered spontaneously 2 weeks later.

Cocaine-induced ischemia was the most likely cause of this adverse outcome.

Subarachnoid hemorrhage

There is an association between cocaine use and aneurysmal subarachnoid hemorrhage (SEDA-18, 36) (SEDA-21, 26) (116). Subarachnoid hemorrhage was temporally related to cocaine abuse in 12 young adult abusers who had underlying cerebral aneurysms; hypertension was a probable contributing factor (117) and cocaine is a risk factor for cerebral vasospasm after aneurysmal subarachnoid hemorrhage (118). In a retrospective analysis of the medical records of 440 patients who presented to a neurosurgery unit between 1992 and 1999 with aneurysmal subarachnoid hemorrhage, 27 patients (6.1%) had either a positive urine screen for cocaine metabolites ($n = 20$) or a history of cocaine use within 72 hours of subarachnoid hemorrhage ($n = 7$). Cocaine users were more likely to have cerebral vasospasm from 3 to 16 days after subarachnoid hemorrhage than non-exposed patients (63 versus 30%). They were also more likely to be younger and to have aneurysms of the anterior circulation than the control group (97 versus 84%).

Sensory systems

Ophthalmic effects associated with cocaine can occur during both active drug use and early abstinence. Cocaine abuse has been associated with ophthalmic complications, including ulceration of the cornea, vasoconstrictor effects on the retinal vasculature, irregularities in oculomotor performance, and secondary optic neuropathy.

Corneal ulceration secondary to smoking crack cocaine has been reported in a 27-year-old woman (119).

Cases of the "crack eye syndrome" continue to be reported. Of 14 crack cocaine users with corneal problems, 10 had corneal ulcers infected with both bacterial and fungal organisms; 4 had corneal epithelial defects (120). All were actively smoking crack daily. The authors suggested that crack smoking predisposes users, through an unknown mechanism, to corneal epithelial changes, infection, and perforation. Typical presentations include loss of vision with or without pain.

- A 29-year-old woman with a painful corneal ulcer related to cocaine abuse was found to be putting cocaine powder directly into the affected eye to reduce the pain (121). Her history included prior corneal perforations.

Such topical use of cocaine may aggravate the condition.

Acute iritis has been reported after intranasal use (122).

There has been a report of retinal changes in 60 users of crack (123). Microtalc retinopathy and retinal nerve fiber layer "rake" or "slit" defects were detected by threshold visual field testing and fundus photography.

Orbital infarction has been described after cocaine use (124).

- A 36-year-old woman drank alcohol and snorted cocaine and heroin at a party. She lost consciousness, with her head positioned down with her left face pressed against a desk. She awoke 3 hours later with severe left orbital pain. Her right eye was normal but there was complete visual loss in the left eye and a nearly complete left ptosis. The left pupil did not react to light but reacted consensually. Movements in the right eye were full, but movements in the left eye

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were severely limited in all directions. In the left fundus there was retinal edema and retinal pigment epithelium disruption. An orbital MRI scan showed diffuse swelling of all the extraocular muscles in the left orbit. A week later the pain had abated and there was mild improvement in the eye movements and ptosis, but no change in vision. She was instructed to wear protective polycarbonate lenses at all times.

Central retinal artery occlusion has previously been reported in cases of intravenous and intranasal cocaine abuse and has also been reported in a man who smoked crack cocaine (125).

- A 42-year-old man smoked crack and developed sudden painless loss of vision in his right eye for 9 hours. He had smoked cigarettes for 20 years and crack cocaine twice a week for the previous 4 years. Visual acuity in the right eye was counting fingers at one meter, and in the left eye 6/4. There was a right relative afferent papillary defect. In the right fundus there was evidence of central retinal artery occlusion and the left fundus was unremarkable. Treatment included intravenous acetazolamide, intermittent ocular massage, and rebreathing into a paper bag. He was found to have sickle cell trait, a risk factor for central retinal artery occlusion.

Psychological, psychiatric

Single photon emission computerized tomography (SPECT) has suggested that some psychiatric symptoms in cocaine users are associated with changes in blood flow (126). Multiple scalloped areas of reduced cerebral blood flow (especially periventricular regions and deep portions of the brain) have been seen. Hypoperfusion has also been noted in the frontal lobes of cocaine users with mania.

Cognitive function

The effects of cocaine on cognitive functions have been measured in controlled studies. The preliminary results of a study of 20 heavy cocaine abusers and a group of matched controls showed impaired function on neuropsychological tests in 50% of the abusers compared with 15% of the controls (127). There were problems with concentration, memory, problem-solving, and abstract thinking in the cocaine users. The heavy users had the greatest loss of memory. Recent cocaine use was associated with poorer oral fluency and arithmetic scores.

The effect of cocaine on cognitive functioning has been studied in 20 crack users, 37 crack and alcohol users, and 29 controls at 6 weeks and 6 months of abstinence (128). The two substance-dependent groups had significant cognitive impairment in a range of neuropsychological tests compared with the controls at both times. Drug dose was strongly associated with the extent of impairment. Abstinent substance users were more depressed than controls during the test period, but depression had only a slight effect on neuropsychological performance.

Neuropsychological performance was examined in 355 incarcerated adult male felons, who were classified by DSM-IV criteria into four subgroups: alcohol dependence or abuse ($n = 101$), cocaine dependence or abuse ($n = 60$), multisubstance dependence or abuse ($n = 56$), and no history of drug abuse ($n = 138$) (129). The cocaine and control groups had similar neuropsychological test scores. However, both the multisubstance and alcohol groups performed significantly worse on nearly all measures. The multisubstance group had worse short-term memory, long-term memory, and visuomotor ability. Correlations between neuropsychological performance and length of abstinence from drug use showed that after abstinence the alcohol group had the greatest improvement on tests. Although the cocaine group had the least amount of improvement with abstinence, their overall performance was not significantly different from controls.

Even after 4 weeks of abstinence, chronic heavy cocaine users have poor cognitive functioning compared with non-drug-using controls (130). A battery of neuropsychological tests was administered to 30 abstinent chronic cocaine abusers and 21 non-drug-using matched controls. Decrements in areas such as executive functioning, visuoperception, psychomotor speed, and manual dexterity were associated with heavier use of cocaine. Neither frequency nor duration of cocaine use was a strong predictor of performance.

Neurolinguistic functioning has been assessed in six African-American male cocaine abusers undergoing drug rehabilitation (131). A test battery to assess language, cognition, and memory skills was administered at 1 week and 1 month of cocaine abstinence. Participants' performances were compared with the normative data for each test. There was reduced ability for general language knowledge, memory, and verbal learning ability during the period of early abstinence. However, the sample size was small and the duration of study short.

Mood disorders

The rate of co-morbidity has been studied in 208 female African-American crack cocaine users; 148 were in treatment, 54 were active crack users, and 61% reported a history of sexual abuse (132). Many had co-morbid depression (48%) and eating disorders (11%).

Delirium

Cocaine-induced delirium with severe acidosis has been reported (133).

- A 25-year-old man with agitation and paranoia who had consumed a lot of alcohol with cocaine the night before had a clonic seizure lasting 1 minute. In the emergency room, he responded to pain and made incomprehensible sounds. His pulse rate was 116/minute, blood pressure 100/40 mmHg, respiratory rate 28/minute, and temperature 38.3°C. He was acidotic (pH 6.53), with a $PaCO_2$ of 13.1 kPa, a base deficit of 36 mmol/l, a serum potassium concentration of 7 mmol/l, and sodium 153 mmol/l. He was hyperventilated and given sodium bicarbonate, dantrolene, and passive cooling. His acidosis quickly corrected and his temperature fell to 37.6°C within 1 hour.

Obsessive-compulsive disorder

Suspected risk factors for obsessive-compulsive disorder were investigated in a prospective epidemiological study,

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using data from the Epidemiologic Catchment Area surveys (1980–1984) (134). Users of both cocaine and marijuana were at increased risk of obsessive-compulsive disorder compared with non-users of illicit drugs, but cocaine use alone was not associated with an increased risk, within the limited sample size.

Panic disorder

As with several other drugs, for example marijuana, PCP, and LSD, cocaine can precipitate panic disorder, which continues long after drug withdrawal (135). Among 280 patients in a methadone maintenance clinic, the prevalence of panic disorder increased from 1% to 6% over a decade (136). A marked rise in the frequency of cocaine abuse coincided with this outbreak. The authors suggested that episodes of panic occurring in cocaine users can result in hospitalization for either psychiatric or medical illnesses.

Paranoid psychoses

Of 55 individuals with cocaine dependence, 53% reported transient cocaine-induced psychotic symptoms (137). Paranoid delusions (related to drug use) and auditory hallucinations were often reported. In addition, almost one-third (all of whom also described psychotic symptoms) reported transient behavioral stereotypes.

Paranoid psychosis has also been described in a 64-year-old man who had first begun to use crack cocaine 6 months before. The paranoid symptoms continued for 3 weeks after he stopped using crack.

The author suggested that the man's age may have made him particularly sensitive to the psychiatric effects of cocaine (138).

The possible genetic basis of cocaine-induced paranoia has been studied in 45 European Americans with cocaine dependency (139). Low activity of the enzyme dopamine β-hydroxylase (the enzyme that catalyses the conversion of dopamine to noradrenaline) in the serum or cerebrospinal fluid was positively associated with the occurrence of positive psychotic symptoms in several psychiatric disorders. The activity of dopamine β-hydroxylase is a stable, genetically determined trait that is regulated by genes located at the DBH locus. The haplotype associated with low dopamine β-hydroxylase activity, Del-a, occurred more often in 29 subjects with cocaine-induced paranoia than in 16 without. These findings may have implications for the pharmacological treatment of cocaine dependence.

Endocrine

Blood sugar concentrations can become labile in people with diabetes mellitus who use cocaine, not only because their diet changes, but also because adrenaline concentrations affect the mobilization of glucose (36).

In a prospective study, endocrine responses to hyperthermic stress were assessed in 10 male cocaine users after 4 weeks of abstinence and again after 1 year of abstinence (140). They sat in a sauna for 30 minutes at a temperature of 90°F and a relative humidity of 10%. At the end of the sauna, they rested for another 30 minutes at room temperature. Sublingual temperature, pulse rate, and blood pressure were recorded just before and immediately after the sauna and 30 minutes after the period at room temperature. Venous β-erythropoietin, ACTH, metenkephalin, prolactin, and cortisol were also measured. There were no significant differences between the two groups in heart rate and blood pressure. At baseline and after 1 year of abstinence, plasma prolactin concentrations were higher in the cocaine users than in the controls. Moreover, the hormonal responses in the cocaine users were different from those in controls. Concentrations of all the hormones, except for metenkephalin, were significantly lower in the cocaine users than in the controls at the end of the sauna; the cocaine users did not have significant hormonal changes to hyperthermia after either 4 weeks or 1 year of abstinence. The authors concluded that cocaine abuse produces alterations in the hypothalamic-pituitary axis, which persist during abstinence.

Electrolyte balance

Cocaine-induced periodic paralysis with hypokalemia has been reported (141).

- A healthy 33-year-old man suddenly developed generalized weakness and became unable to walk or lift his limbs; he also had mild chest pain. He had had similar episodes 10 days and 5 years before, with spontaneous resolution. He had no spontaneous motor activity and his strength was 2/5 in all major muscle groups with a very mild left upper limb predominance. Cardiac enzymes and neuroimaging of the brain and spinal cord were normal. Creatinine kinase was raised (395 IU/l). Acetylcholine receptor antibodies were in the reference range. His serum potassium concentration was 1.9 mmol/l. Urine toxicology screen showed cocaine, cannabinoids, and benzodiazepines and he admitted to cocaine binge use the previous night and also before the previous two episodes. With potassium supplements his strength gradually improved.

Such severe generalized weakness and hypokalemia may be due to intracellular shift of potassium due to adrenergic stimulation by cocaine or a direct effect on potassium channels.

Hematologic

In an attempt to replicate the conclusions of an earlier study, there was no association between cocaine use during pregnancy and acute thrombocytopenia in 326 patients (142). There were similar prevalences of thrombocytopenia in cocaine-using women (13/160) and non-using women (11/160) during pregnancy. Thrombocytopenia occurred more often in the third trimester in both groups.

Gastrointestinal

Gastrointestinal symptoms, especially diarrhea, occur after cocaine use. Cases of more severe abdominal distress have required surgical intervention and have been due to bowel infarction (1,143) or pneumoperitoneum (144).

Esophageal damage

The esophagus can undergo thermal injury, in which the inner esophageal wall has a "candy-cane" appearance

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(alternating pink and white linear bands), when boiling-hot liquids are consumed. This reversible condition is associated with chest pain, difficulty in swallowing, odynophagia, and abdominal pain. Candy-cane esophagus secondary to smoking crack cocaine has been reported (145).

- A 55-year-old man accidentally sucked into his mouth and swallowed a portion of boiling water during his last smoke of free base cocaine and 2 days later developed sudden constant pain in the left shoulder and arm accompanied by sweating. He had melena, a hematocrit of 30%, a blood urea nitrogen of 35 mmol/l, and a serum creatinine of 1.1 mmol/l. The initial electrocardiogram showed sinus rhythm, left atrial enlargement, and borderline left ventricular hypertrophy. However, 2 hours later he started to sweat and became hypotensive (blood pressure 85/50 mmHg). An electrocardiogram showed new biphasic T waves and T wave inversion. Urgent cardiac catheterization showed patent coronary arteries. Esophagogastroduodenoscopy within the hour showed a candy-cane appearance in the distal esophagus, patchy erythema and erosions in the gastric antrum, and an ulcer in the base of the duodenal bulb. Biopsies of the esophagus tissue showed parakeratosis, squamous hyperplasia with regeneration, and minimal inflammation. Biopsies of the stomach showed chronic gastritis and bacteria consistent with *Helicobacter pylori*. Later that day, the electrocardiogram normalized.

The most likely cause of the chest pain was microvascular spasm of the epicardial coronary arteries, due to either thermal injury to the esophagus or a direct effect of cocaine.

Peptic ulceration

There is a higher incidence of gastric ulcers in cocaine users, both perforated ulcers and giant gastroduodenal ulcers, thought to be due to localized ischemia secondary to vasoconstriction (146,147). Two reports have afforded data on gastrointestinal ulcers and cocaine. In one study the authors observed that since the advent of crack cocaine they had seen more than 70 cases of crack-related perforated ulcers (146). They suggested that an ischemic process rather than an acid-producing mechanism was to blame. They described three patients, all of whom had laparoscopic omental patches for ulcers, with good results. In a longitudinal assessment of patients with endoscopically diagnosed gastric ulcers ($n = 98$) or duodenal ulcers ($n = 116$) users of cocaine or metamfetamine were nearly 10 times more likely to have giant gastric or duodenal ulcers (over 2.5 cm) compared with non-users (147). The authors speculated that cocaine and amfetamine-induced catecholamine stimulation of α-adrenoceptors may cause intense vasoconstriction and thus a reduced blood supply to an ulcer, resulting in a giant ulcer.

Five cases of gastric perforation (rather than the more common duodenal perforation) have been reported in young male smokers of crack, all of whom had only brief histories of prodromal symptoms and none of whom had long-standing peptic ulcer disease (148).

Intestinal ischemia

Two women developed chronic mesenteric ischemia, successfully managed by revascularization (149). The authors concluded that in both cases chronic mesenteric ischemia had been caused by intravenous cocaine abuse.

Ischemia of the small bowel and colon after the use of cocaine has been reported (SEDA-22, 33).

- A 38-year-old man presented with a 2-day history of severe abdominal pain and bloody stools after smoking cocaine 48 hours earlier (150). He had abdominal pain, guarding, rebound tenderness, and high-pitched, hypoactive bowel sounds. His white blood cell count was 31×10^9/l. Radiography showed thumb-printing in the transverse colon. Endoscopy showed friable edematous mucosa with submucosal hemorrhage and patches of yellowish fibrinous material. He recovered fully with intravenous nutrition and supportive measures after 30 days.
- A 36-year-old man who had injected cocaine the day before admission and who occasionally sniffed, smoked, or injected cocaine, presented with a 3-day history of severe abdominal pain and bloody diarrhea (151). His mid-abdomen was very tender, with rebound tenderness and guarding; bowel sounds were absent. Radiography showed a dilated transverse colon and dilated small bowel loops. He underwent emergency surgery and an edematous dilated transverse colon was removed. The pathology was consistent with ischemic colitis. The blood vessels were dilated but showed no structural abnormalities or thrombosis.

Liver

Cocaine has been associated with liver toxicity (SEDA-14, 32) (SEDA-13, 27).

- A 23-year-old man became unresponsive and had a seizure after taking cocaine and alcohol (152). Severe liver necrosis developed and hepatocellular damage was documented with ^{99m}Tc-PYP imaging.

Acute hepatitis induced by intranasal cocaine, with transient increases in liver enzymes, has been reported in three HIV-positive patients (153). All had non-active chronic viral hepatitis with normal immunological status; one was seropositive for hepatitis B virus and two were positive for hepatitis C virus. A few days after intranasal cocaine use, serum transaminases rose to high values, and two of the patients had fever, stiffness, sweats, and hepatomegaly. Alcohol and hepatotoxic agents were ruled out. Within a few days, the clinical and laboratory signs of hepatitis improved in all three cases.

Urinary tract

Cocaine can cause acute renal insufficiency (SEDA-21,19) (SEDA-24, 38). Acute renal insufficiency, with malignant hypertension, apparently precipitated by cocaine-induced vasoconstriction, has been described in a 33-year-old woman who had pre-existing scleroderma and normal renal function (154). She was successfully treated with hemodialysis.

Cocaine can also cause chronic renal insufficiency (155). Of hemodialysis patients from an urban center in California, 55 who reported a history of significant

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cocaine use were compared with 138 non-users. A diagnosis of hypertension-related end-stage renal disease was reported in 49 of the 55 cocaine users (89%) and 64 of the 138 non-users (46%). Of 113 patients with end-stage renal disease, 49 had a history of cocaine use. The patients who had used cocaine had hypertension for a shorter duration (5.3 versus 12.7 years). They were also younger (41 versus 54 years). The authors proposed that this outcome had been caused by several mechanisms: renal vasoconstriction or stenosis, resulting in ischemic nephropathy and secondary hypertension, direct renal damage with progressive renal insufficiency, and recurrent episodes of accelerated hypertension, vasculitis, acute tubular necrosis, and rhabdomyolysis.

Chronic cocaine use can exacerbate pre-existing hypertension, when renal blood vessels narrow secondary to cocaine-induced intimal fibrosis. Acute renal insufficiency with concomitant rhabdomyolysis after cocaine use has been reported (156,157), but it can also occur, albeit rarely, in the absence of rhabdomyolysis (158).

- A healthy 31-year-old man developed acute renal insufficiency 18 hours after inhaling cocaine 5 g. His blood pressure was 150/100 mmHg, his serum creatinine 177 μmol/l, creatine phosphokinase activity 107 U/l, and serum potassium concentration 3.8 mmol/l. The urinary sodium concentration was 30 mmol/l and there was a trace of protein and 1–2 red blood cells per high-power field. Immunological studies were unremarkable. Ultrasound showed kidneys of normal size with hyperechogenity of the right kidney. Over the next 10 days he recovered spontaneously.

The authors suggested that intense cocaine-induced renal vasoconstriction had been the likely underlying mechanism.

Renal infarction is an uncommon adverse effect of cocaine (159).

- After using intranasal cocaine, a 25-year-old African man developed fever and progressive right flank pain over 4 days. He had a temperature of 38.3°C, a blood pressure of 106/54 mmHg, and severe tenderness in the right flank and right lower quadrant of the abdomen. His urine contained cocaine. A CT scan showed reduced uptake in the lower pole of the kidney, confirming renal infarction. Other causes were ruled out.

Sexual function

The practice of trading sex for drugs in places where there is a high prevalence of cocaine abuse has been noted in both metropolitan areas and smaller communities along major interstate highways. In Baltimore, there was a 97% increase in the number of primary and secondary cases of syphilis from 1993 to 1995 (160).

Priapism has been reported in men who have used cocaine by inhalation or applied it topically to the glans penis or intraurethrally (SEDA-19, 26).

- Three men developed priapism and delayed seeking treatment (161). Cocaine use within the previous 24 hours was the singular contributing factor in all three cases. Two of the men had had previous episodes of priapism, which had resolved spontaneously. Initial duplex ultrasonography confirmed low penile blood flow. Manual aspiration and irrigation failed in all three cases. Surgical shunting failed in the first two cases. One man required partial penile amputation for infected, gangrenous, distal penile tissue; one responded to angiographic embolization; and one had only a partial response to angiographic embolization, but then refused further intervention; his erection resolved during the next 24 hours.

The authors suggested that acute sexual excitement during cocaine intoxication can cause penile erection, with impaired detumescence. Cocaine can inhibit the reuptake of noradrenaline (by blocking transport in presynaptic sympathetic neurons), thus preventing sinusoidal contraction and the efflux of penile blood.

- A 44-year-old black man developed priapism 2 hours after having overdosed on 30–40 trazodone tablets 50 mg and 10 Tylenol No. 3 (paracetamol plus codeine) tablets (162). Toxicology analysis was positive for cocaine and opiates. The priapism required detumescence twice, on initial presentation and then 6 hours later, and 8 hours after presentation he again developed painless priapism, which resolved spontaneously after 1.5 hours.

Trazodone-induced priapism may be mediated by alpha-adrenoceptor antagonism. While the mechanism for cocaine-induced priapism is unclear, it may result from vasospasm, venous pooling, and sludging of blood in the penis. The authors proposed that the two drugs may act in an additive or synergistic manner, posing a greater hazard than either alone.

Priapism associated with intracavernosal injection of cocaine has also been reported.

- A 43-year-old man developed persistent painful erection after intracavernosal injection of cocaine (163). He had previously administered cocaine in this way to prolong erections. Cavernosal aspiration resulted in partial detumescence, but the condition recurred. Urine screen was positive for cocaine. Aspiration and irrigation fully alleviated the condition.

During penile erection, nitric oxide is released from the endothelium of the cavernous spaces and from nerve endings (non-adrenergic and non-cholinergic). Nitric oxide stimulates guanylate cyclase, which is involved in the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP); the latter relaxes the smooth muscle in the corpora cavernosa, allowing influx of blood for erection. The authors suggested that cocaine directly applied to the cavernosal endothelium can cause nitric oxide production.

Immunologic

The prevalence of infection with the human immunodeficiency virus (HIV) among drug abusers, including cocaine users, is increasing (164). Two separate reports have suggested that cocaine may compromise immunological function. In one study, human mononuclear cells were stimulated in vitro with mitogens in the presence and absence of cocaine; cocaine inhibited the proliferation of the mononuclear cells (165). In a second study, cocaine

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amplified HIV-1 replication in co-cultures containing cytomegalovirus-activated peripheral blood mononuclear cells (166).

Two cases of connective tissue disease have been reported (167).

A case of urticarial vasculitis, a type III hypersensitivity reaction, has been reported after cocaine use (168).

- A 24-year-old man with acute malaise and fever had a pruritic rash with multiple erythematous circumscribed weals on the trunk, arms, legs, neck, and scalp. He admitted to using intranasal cocaine 6 months, 4 days, and 1 day before the onset of the symptoms. His temperature was 39°C. His erythrocyte sedimentation rate was 80 mm in the first hour, C-reactive protein was 283 mg/l (reference range below 10), and the white blood cell count was 12.4×10^9/l with 89% neutrophils. A biopsy of an urticarial lesion showed a perivascular inflammatory infiltrate in the upper and middle dermis. Bed rest, oral prednisone, oral hydroxyzine, and topical polidocanol led to improvement within 24 hours.

Two cases of cocaine-induced type I hypersensitivity reactions, have been reported (169).

- A 23-year-old woman developed tongue swelling and difficulty in breathing immediately after having sniffed cocaine. The anterior half of her tongue was edematous with bleeding lesions caused by her fingernails. There were cocaine metabolites in the urine. The diagnosis was angioedema of the tongue induced by cocaine or its contaminants, and it resolved with subcutaneous adrenaline, H_1 receptor antihistamines, and intravenous glucocorticoids.
- A 19-year-old man developed generalized urticaria, intense pruritus, and mild bronchospasm 30 minutes after injecting cocaine for the third time. He had weals on the face, neck, arms, and chest, and scattered wheezing in the lungs. Urine toxicology screen was positive for cocaine metabolites. His symptoms resolved several hours after the administration of H_1 receptor antihistamines and intravenous glucocorticoids.

Body temperature

Cocaine can cause hyperthermia, primarily in hot weather, perhaps through a hypermetabolic state; impaired heat dissipation may be another contributing factor. Seven healthy, cocaine-naïve subjects participated in tests of progressive passive heat stress, during which each received intranasal cocaine or lidocaine as placebo (170). Esophageal temperature, skin blood flow, sweat rate, and perceived thermal sensation were measured. Cocaine augmented the temperature increase during heat stress and also increased the temperature threshold for the onset of both cutaneous vasodilatation and sweating. It also impaired the perception of heat. This study elicited commentary, in which it was pointed out that measured effects of small doses of cocaine may not be reflective of true cocaine poisoning (171). Also, the subjects in the study did not have psychomotor agitation, which is often prominent in cocaine toxicity and which improves with sedatives.

Death

Poisoning can occur with doses of cocaine as low as 20 mg (10 drops of cocaine 4%). Victims generally collapse and die after associated cardiovascular abnormalities, dysrhythmias, and respiratory failure. Signs and symptoms of intoxication include excitement, restlessness, headache, nausea, vomiting, abdominal pain, convulsions, and delirium.

In a retrospective study of 48 men who suffered cocaine-related deaths and a control group of 51 male cocaine users who died of trauma, the blood cocaine concentrations measured in the two groups were similar (172). However, concentrations of the cocaine metabolite benzoylecgonine were higher in those with cocaine-related deaths. This group also had a significantly lower body mass index, with larger hearts and heavier lungs, livers, and spleens than the control subjects. Reduced body weight, an adverse effect of long-term cocaine use, is probably related to its effects on the serotonergic system and therefore appetite. Cardiomegaly is thought to result from chronic cocaine-induced excessive catecholamine stimulation, with circulatory overload, and increased organ weight is a result of passive visceral congestion in cocaine-induced heart failure. Cardiac alterations may explain why similar blood cocaine concentrations can be lethal in some cases but benign in others. This study shows that isolated measurements of postmortem cocaine and benzoylecgonine blood concentrations cannot be used to assess or predict cocaine toxicity.

The increasing prevalence of multisubstance abuse can influence morbidity and mortality (173).

- An 18-year-old man experienced sudden and severe chest pain while drinking alcohol. He vomited, collapsed, and died. On postmortem examination, thrombosis of the left coronary artery, dilated cardiomyopathy with congestive heart failure, and pulmonary embolism were noted. Blood analysis showed raised cocaine and marijuana concentrations and a trace of alcohol.

The author's opinion was that although multidrug use had played a part, the high blood concentration of cocaine had been the main cause of death. He also noted that marijuana can interact with cocaine to produce pronounced sympathomimetic effects.

The smuggling of illicit drugs by the technique called "body packing" carries medical risks. Drug packages can rupture and digestive secretions can seep into packets and allow drug absorption. Consequently, drug intoxication, intestinal obstruction, peritonitis, and death can occur. A man carrying 99 cocaine powder packages weighing 10 g died as a result (174), and the death of a drug dealer has been reported (175).

- A 17-year-old man swallowed a small plastic bag of cocaine in order to avoid arrest. After 1 hour he complained of a headache and 30 minutes later developed palpitation and agitation and collapsed. Histological examination of his heart showed myocardial necrosis. The blood concentration of cocaine was high at 98 μg/ml. The tissue concentrations of cocaine and its metabolites in various organs and fluids were recorded; the highest concentrations of cocaine and metabolites were detected in the liver, lungs, brain, and blood (in descending order).

The cause of sudden death in this case was probably a cardiac dysrhythmia.

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Long-Term Effects

Drug tolerance

Chronic cocaine exposure and long-term adaptation at the molecular level have been investigated; changes in transcription factor gene expression may be involved (176). NURR1 is a key factor that regulates transcription of the gene that encodes the cocaine-sensitive dopamine transporter and functions in the development of dopamine neurons. In a recent study, postmortem human midbrain specimens from cocaine users and controls underwent various analyses. Human NURR1 gene expression was markedly reduced in dopamine neurons in the cocaine users and normal in the controls. NURR1-deficient cocaine abusers also had dopamine neurons with markedly reduced dopamine transporter gene expression. NURR1 appears to have a critical role in the brain's adaptation to repeated cocaine exposure and in maintenance of dopamine neurons.

Drug dependence

There has been considerable interest in evaluating drugs such as amfepramone (diethylpropion) for attenuating the negative emotional state induced by craving for cocaine, in the hope of finding a drug for long-term treatment of cocaine dependence. However, in 50 cocaine-dependent patients amfepramone was ineffective and caused significant adverse effects (177). Of the patients who took amfepramone 25–75 mg/day, 12% were withdrawn from the study: one developed coronary vasospasm and another atrial fibrillation. These poor results are comparable to those of earlier studies with methylphenidate in cocaine addicts (178,179).

Drug withdrawal

There have been reports of the effects of cocaine withdrawal on cognition. There was impairment of memory, visuospatial abilities, and concentration in 16 cocaine abusers during the first 2 weeks of abstinence (55). Measured deficits were independent of withdrawal-related depression.

Tumorigenicity

Chronic cocaine use, which is associated with immunosuppression, may be carcinogenic. The possible association between chronic cocaine exposure and pancreatic adenocarcinoma has been investigated (180,181). A study of hospital records in Brazil for the years 1986–1998 showed that of 198 patients with pancreatic adenocarcinoma, 13 (6.5%) were younger than 40 years; of these, five had a history of chronic cocaine inhalation and one had abused marijuana.

Second-Generation Effects

Pregnancy

Some of the risks run by the pregnant cocaine-using mother and her child (such as preterm labor and premature delivery) have been reported (182). However, the literature on maternal cocaine use and its possible outcomes is problematic, because many studies have been methodologically flawed (183).

A retrospective study of data from a large perinatal registry showed that there was an increased risk of placenta previa among women who used cocaine, compared with those who did not use drugs or alcohol (184).

Another apparent obstetric risk of cocaine use is rupture of a uterine scar (from a previous cesarean section).

- There was extensive laceration of the maternal urinary bladder after a vaginal birth in a 34-year-old woman whose urine tested positive for cocaine (185).

The authors postulated that the injury may have resulted from a cocaine-augmented contractile response of the pregnant uterus.

A "pre-eclampsia–like" syndrome has been described, characterized by acute hypertension and a low platelet count, in a 33-year-old cocaine user; her 20-week-old fetus died (186).

One of the serious medical conditions linked with cocaine use during pregnancy is premature delivery, with an incidence in cocaine users of 17–27%. The mechanism of the effect of cocaine on both spontaneous and agonist-induced contractility of pregnant human myometrium has been evaluated (187). Myometrium samples from 42 women who were undergoing cesarean section at term were examined after exposure to various pharmacological probes in combination with cocaine. The results suggested that cocaine augments the contractility of uterine tissue by both adrenergic and non-adrenergic mechanisms. Cocaine increased spontaneous myometrial contractility over three-fold. Prazosin, an alpha-adrenoceptor antagonist, blocked this effect, but only for the first 35 minutes. Cocaine increased both the sensitivity and maximal tissue response to the alpha-adrenoceptor agonist methoxamine. The maximal response to oxytocin, but not sensitivity, was increased by cocaine; prazosin did not inhibit this effect.

Cocaine has been associated with both preterm delivery and premature rupture of the membranes (188). Among 85 of 604 expectant mothers with premature rupture of the membranes with documented cocaine exposure compared with women with no drug exposure for six conditions of major neonatal morbidity, cocaine users were older and of higher parity. The non-cocaine users had more morbidity, in particular neonatal infection and sepsis. The authors proposed that the mechanism of premature rupture of the membranes in the presence of cocaine may not be related to infection. Instead, cocaine may have a direct effect on the myometrium, stimulating uterine contractility.

The Maternal Lifestyle Study has reported that the prevalence of adverse perinatal complications associated with the use of cocaine or opiates during pregnancy was lower than has been previously reported (189). In 11 811 mother–infant pairs followed prospectively, 11% of the exposed and non-exposed groups were hospitalized at least once. However, violence was a factor (20%) in admissions among the cocaine-exposed women.

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Teratogenicity

The data suggest that cocaine-exposed infants may be at increased risk of congenital malformations (190). However, it is unclear by what mechanism cocaine affects the fetus. Interruption of the intrauterine blood supply, with subsequent destruction of fetal structures, may account for some of its effects (191).

There are frequent reports of intrauterine growth retardation, neurobehavioral abnormalities, cerebral injury, and cardiac anomalies in "coke babies" (SEDA-14, 15) (SEDA-21, 4) (SEDA-21, 129) (192,193). Brain hemorrhages (194) and asymmetrical growth retardation (195) associated with maternal cocaine abuse have been discussed.

In 500 neonates ankyloglossia, a defect in the attachment of the tongue within the mouth, was 3.5 times more common in cocaine-exposed neonates than in others (196). Other facial, vertebral, and cardiovascular defects have been described (SEDA-17, 4) (19).

Two other clinical syndromes involving anomalies of multiple organ systems in fetuses of cocaine-abusing women have been described.

- An infant with Pena–Shokeir phenotype (including facial, musculoskeletal, pulmonary, and cardiac malformations accompanied by extensive brain damage) was born to a cocaine-abusing mother (197). The infant died shortly after birth.
- An infant exposed to cocaine in utero had a combination of facial, ear, eye, and vertebral anomalies, accompanied by cardiac, central nervous system, and other malformations (198).

In contrast, in 34 light-to-moderate cocaine users compared with 600 non-users attending a public prenatal care clinic, pronounced untoward effects on the fetus were reportedly less common than in other studies (199). In all cases the cocaine had been taken intranasally, and the majority of users reduced their intake during pregnancy; none had been referred for drug abuse counseling and none was taking drug treatment. There was no significant difference in obstetric complications among these mild cocaine users compared with non-users, and no significant differences in infant growth, morphology, or behavior. However, the cocaine users had histories of more fetal losses and during pregnancy they suffered more infectious diseases, such as hepatitis, *Herpes simplex*, and gonorrhea.

Fetal growth

Among the adverse outcomes of prenatal cocaine exposure, low birth weight and reduced length and head circumference have been reported. In a prospective study in New York City, 386 pairs of cocaine- and crack-using mothers and their infants and 130 matched control pairs were followed during the course of pregnancy and delivery (200). The neonates were assessed by physical and neurological examination, the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), and the Neonatal Stress Scale during the first 48 hours of life. The results corroborated earlier findings of reduced fetal growth in cocaine-exposed infants. Significantly more (17%) of the babies of cocaine users had a head circumference less than the tenth percentile compared with the controls (3%). They performed less well on the BNBA Scale and had higher measures on the Neonatal Stress Scale. They had clinically significant neurological impairment, with jitteriness, increased tone, and an exaggerated Moro reflex. However, some of these findings may have reflected a direct neurotoxic effect of cocaine, since testing was done during the first 48 hours of life. The authors observed that crack had a more adverse outcome than cocaine. They concluded that the most important predictor of neonatal outcome may be the frequency, quantity, and type of cocaine used.

The effect of maternal cocaine use on infant outcome has been prospectively assessed in 224 women, of whom 105 were cocaine users and 119 were controls (201). The infants were of gestational age 34 weeks or more and were not asphyxiated. The infants exposed to cocaine were more likely to be admitted to the newborn intensive care unit, to be treated for congenital syphilis or presumed sepsis, to have a greater length of stay, to have lower birth weight and head circumference, and to be discharged to the care of someone other than the mother. However, the two groups were similar in the incidence of abnormal cranial and renal ultrasonography and abnormal pneumocardiography. Moreover, when controlled for cigarette use and other confounders, there were no significant differences in the groups on growth retardation factors.

Cardiovascular

Intrauterine cocaine exposure is associated with neonatal cardiovascular dysfunction and malformations. The long-term effects of cocaine on the neonate's cardiovascular system and development are unknown. The effect of cocaine on the infant's autonomic function and subsequent development has been reported (202). Heart rate variability, a non-invasive test of autonomic function, was evaluated in 77 prenatally cocaine-exposed infants, 77 healthy controls, and 89 infants who had been exposed prenatally to drugs other than cocaine (alcohol, marijuana, and/or nicotine). Within the first 72 hours of life, the cocaine-exposed infants were asymptomatic but had lower heart rate variability and lower vagal tone than the two comparison groups. At follow-up, the cocaine-exposed infants had recovered at 2–6 months of age and now had higher heart rate variability and vagal tone than the two non-exposed groups. Most of the increase in heart rate variability and vagal tone was seen in the infants who had had light cocaine exposure and was not apparent in those who had had heavy exposure.

The same researchers have published two reports on the cardiovascular effects of intrauterine cocaine. In the first study, 82 healthy neonates with intrauterine cocaine exposure, 108 exposed to drugs other than cocaine, and 87 healthy controls were evaluated for global and segmental systolic and diastolic cardiac function (203). During the first 48 hours of life, the neonates with intrauterine cocaine exposure had significant left ventricular diastolic segmental abnormalities. They had a higher index of asynchrony and global and segmental fractional area changes in contrast to the other two groups. The degree of abnormality in the index of asynchrony was greater in the neonates with

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heavier cocaine exposure. In a second study at 2–6 months of age, 56 cocaine-exposed infants were compared with 72 who had been exposed to drugs other than cocaine and 60 healthy controls (204). The cocaine-exposed infants had recovered left ventricular diastolic function. Only in infants with heavy cocaine exposure was there an alteration in septal wall diastolic filling.

- A 6-month-old fetus who had been exposed to cocaine had a single-ventricle heart; the authors suggested that coronary spasm, resulting in infarction, may have destroyed the right ventricle (205).

Nervous system

In two reports it was suggested that brain hemorrhage (194) and asymmetrical growth retardation (195,206) can occur.

Cognitive effects

The influence of exposure to cocaine in utero on the developing human nervous system is not yet clearly understood (SEDA-22, 21). Prenatal cocaine exposure has been associated with neurobehavioral effects in infancy, ranging from no effect to effects on arousal and state regulation, as well as on neurophysiological and neurological functions. A prospective controlled study in 154 cocaine-using pregnant mothers and suitable matched controls from a rural community produced neurobehavioral effects that supported those from previous controlled studies (207). The mothers underwent drug testing and medical examination during each trimester. Their infants were assessed as near to 40 weeks after conception as possible, using the BNBA Scale. When controlled for the effects of marijuana, alcohol, and tobacco use, the use of cocaine in the third trimester was negatively related to state regulation, attention, and responsiveness among the exposed infants. Twice as many cocaine-exposed infants as controls failed to come to and maintain the quiet alert state required for orientation testing.

It is unclear whether abnormalities in early infancy are associated with neurodevelopmental impairment at a later age. Several studies have suggested that the findings are limited to early childhood. The possible effects of prenatal cocaine exposure on later cognitive functioning and difficulties have been reported in three studies. In the first, 236 infants at 8 and 18 months of age were evaluated; 37 had heavy exposure to cocaine in utero, 30 had light exposure, and 169 had no exposure (208). Cognitive functioning was assessed with the Bayley Scales of Infant Development. Information processing was tested with an infant-controlled habituation procedure. At 8 months, cocaine-exposed infants and controls had no differences in cognitive functioning. Their abilities to process information indexed by habituation and response to novelty were comparable. However, at 18 months the infants with high cocaine exposure performed poorly on the Mental Development Index (MDI). The 18-month index covers a wider range of cognitive tasks requiring integrated learning, responsiveness to environmental cues, and memory than the 8-month index. These results suggest that the effects of cocaine are more likely to show up when more challenging measures are used. Infants raised in high-risk environments, with stressors and low support, scored lower at both 8 and 18 months.

In a second study, intellectual functioning at 6–9 years was measured in 88 cocaine-exposed children and 96 unexposed children in New York City (209). The participants were interviewed and underwent medical and neurological examination and psychological assessment. Child intelligence was measured with the Wechsler Intelligence Scale for Children-III (WISC-III). Intelligence quotient scores did not differ between the two groups of children, even when adjustments for co-variables were made.

In a third study the Robert Wood Johnson database of published literature on prenatal cocaine exposure and child outcome was examined (210). Only 8 of 101 studies focused on school-age children. Intelligence quotient (IQ), receptive language, and expressive language were measured. This meta-analysis showed an average difference of 3.12 IQ points between cocaine-exposed and control groups. When the IQ distribution is shifted downwards by this amount, there is a 1.6-fold increase in the number of children with IQs under 70. The authors noted that the calculated decrement in IQ in exposed children is subtle and does not include the possible effect of the drug on domains of function such as language abilities.

Research on the relation between prenatal cocaine exposure and childhood behavior also continues. In a pilot study, 27 children exposed to cocaine in utero and 75 control children were assessed (211). The children had a mean age of 80 months and most were first-grade students. The child's first-grade teacher (blinded to exposure status and study design) rated the children's behavior with the Conners' Teacher Rating Scale (CTRS) and the Problem Behavior Scale (PROBS 14), an investigator-developed scale that measures behaviors associated with cocaine exposure. The drug-exposed children had higher CTRS scores (that is more problematic behavior), but the difference was not significant. On subscales of the PROBS 14, the drug-exposed group had significantly more problematic behavior. These results appear to substantiate teachers' reports of problematic behavior in children with prenatal cocaine exposure.

The effects of prenatal cocaine exposure on information processing and developmental assessment have been studied in 108 infants aged 3 months, 61 of whom had been exposed to cocaine, and 47 controls using an infant-control habituation and novelty responsiveness procedure in a developmental assessment using the Bayley Scales of Infant Development (212). Infants exposed to cocaine prenatally were significantly more likely than controls to fail to start the habituation procedure, and those who did were significantly more likely than controls to react with irritability early in the procedure. Cocaine-exposed infants had a comparatively depressed performance on the motor but not the mental Bayley scales. This information was obtained by raters blind to the history and was controlled for both perinatal and sociodemographic factors. Most of the infants in both groups reached the habituation criteria, and among those who did there were no significant differences between cocaine-exposed and non-exposed infants in habituation or in recovery to a novel stimulus. Thus, differences in reactivity to novelty, but not information processing, between cocaine-exposed and

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non-cocaine-exposed infants suggested that the effects of prenatal cocaine exposure may be on arousal and attention regulation, rather than on early cognitive processes.

Developmental correlates have been assessed in three groups of children aged 4–6 years (213). In 18 children there had been prenatal exposure to cocaine and the mothers had continued to use crack. Another 28 children had had no prenatal exposure but their mothers had used crack after the children were born. The control group were 28 children whose mothers had never used cocaine. Prenatally exposed children performed significantly worse than the others in tests of receptive language and visual motor drawing. Prenatal crack exposure was associated with poor visual motor performance, even after controlling for intrauterine alcohol and marijuana exposure, age, birth weight, and duration of maternal crack use.

There have been two studies of the neurodevelopmental effects of cocaine during the first 48 hours of life. In the first, 23 cocaine-exposed and 29 non-exposed infants were prospectively assessed within the first 48 hours of life; infant meconium was used to detect cocaine and the BNBA Scale was used for clinical assessment (214). One-third of the cocaine-exposed neonates were born to women who denied cocaine use. In six of the seven clusters assessed, cocaine-exposed infants fared badly compared with control infants. The cocaine-exposed infants had poor autonomic stability and there was a dose–response relation between meconium cocaine concentration and poor performance in relation to orientation and so-called "regulation of state," which refers to how the infant responds when aroused. The authors concluded that cocaine exposure is independently related to poor behavioral performance in areas that are central to optimal infant development. They emphasized the value of the identification and quantification of cocaine in infants.

In another blinded study, neurodevelopmental and neurobehavioral performance were prospectively assessed in 131 neonates (mean age 43 hours) exposed in utero to cocaine, with or without other drugs (215). Cocaine-exposed neonates were developmentally at risk in the tests compared with infants exposed to other drugs alone or in combination. As in the previous study, larger amounts of cocaine were associated with higher neurobehavioral risk scores.

In a study of immediate and late dose–response effects of cocaine exposure in utero on neurobehavioral performance, 251 full-term urban neonates were examined by blinded raters at 2 and 17 days (216). The babies were classified as having been heavily exposed, lightly exposed, or not exposed to cocaine. After controlling for covariates, in contrast to the studies mentioned above (211,215), there were no neurobehavioral effects of exposure at 2 days of age. However, at 17 days there was a significant dose-related effect: heavily exposed infants had poorer state regulation and greater excitability, implying impairment of their ability to modulate arousal. The authors postulated that these late effects might be expected if cocaine exposure in utero is associated with evolving neuroanatomical damage or disruption of the monoaminergic neurotransmitter systems. These effects did not appear to be related to intrauterine growth retardation, as has been suggested by others.

Arousal and attention have been investigated in 180 healthy nursery infants before hospital discharge and at 1 month of age (217). Cocaine-exposed infants showed a lack of arousal-modulated attention and preferred faster frequencies of stimulation, regardless of arousal condition compared with non-exposed infants. There were similar differences 1 month after birth, showing that these effects persisted beyond the period of presence of cocaine or its metabolites at birth. These effects were independent of absence of prenatal care, alcohol use, minority status, or sex, suggesting a direct and even chronic effect of intrauterine cocaine exposure on arousal-modulated attention and presumably on the developing nervous system of the infants.

The behavioral and hormonal responses in 30 preterm cocaine-exposed infants were compared with the responses in 30 non-cocaine-exposed infants of similar gestational age (218). The mothers of cocaine-exposed infants were more often single, had higher parity and more obstetric complications, and were less likely to visit, touch, hold, and feed their infants than the other mothers. Cocaine-exposed infants had smaller head circumferences at birth, spent more time in the neonatal intensive care unit, and had a greater incidence of periventricular or intraventricular hemorrhages. They also had poorer state regulation and difficulty in maintaining alert states and in regulating their own behavior. They spent more time in indeterminate sleep (suggesting nervous system immaturity), with reduced periods of quiet sleep and increased amounts of agitation, tremulousness, mouthing, multiple limb movements, and clenched fists. There were higher urinary noradrenaline, dopamine, and cortisol concentrations and lower plasma insulin concentrations in the cocaine-exposed infants, suggesting that they may have experienced a high degree of stress in the perinatal period.

In a study of 464 inner-city black infants, whose mothers were recruited prenatally based on alcohol and cocaine use during pregnancy, gestational age of less than 38 weeks was significantly correlated with cocaine use in the mothers (219). The infants were tested at 6.5, 12, and 13 months of age; the cocaine-exposed infants were more excitable, preferred faster frequencies of stimulation, had more difficulty habituating, were more reactive, and showed a greater startle response to noise. Moreover, these effects of cocaine on cognitive function were documented beyond the neonatal period, thus eliminating effects from acute cocaine exposure or withdrawal. The authors suggested that two separate mechanisms may underlie the effects of cocaine on gestational age and cognition. The nervous system deficits, poorer cognitive performance, and faster reactivity are probably mediated by a direct action of cocaine (requiring heavy exposure) on neurotransmitters, whereas shortened gestation may be mediated by vasoconstriction, which occurs at lower exposure. Timing of exposure during pregnancy may also play a critical role in determining the type of deficits.

The effects of prenatal maternal cocaine use on neurobehavior have been reported in 2-week old infants (220). The BNBA Scale was administered to the infants of mothers who had a reported high frequency of cocaine use during pregnancy: ($n = 23$, >75th percentile reported days of use) or a low frequency ($n = 32$, <75th percentile).

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Infants with high intrauterine exposure had higher scores on the BNBAS excitability cluster than infants with low exposure. Infants with a high BNBAS excitability score had poorer tone and motor movement, were more irritable and hard to console, and had difficulties in self-quieting.

In a meta-analysis of 18 published reports (1985–1988, 13 of which failed to meet the inclusion criteria and were excluded) on the effect of in utero exposure to cocaine on infant neurobehavioral outcome, cocaine-exposed infants were compared to non-exposed infants on BNBAS cluster scales at birth and at 3–4 weeks of age (221). Although the sample size was large enough to detect statistical significance in most of the tests of difference between the two groups, the magnitude of all the effects was small. This was true for differences in the motor performance and abnormal reflex clusters in the infant groups (with a slight trend toward increasing standard differences over time) and in the orientation and autonomic regular clusters (with a trend toward a reduced effect size over time). However, the main finding of the study was the small magnitude of the neurobehavior dysfunction at both times. The authors cautioned that these data may not be generalizable, since polydrug exposure, the amount of cocaine exposure, and other variables could have confounded the data.

In 158 cocaine-exposed (82 heavily and 76 lightly exposed) and 161 non-cocaine exposed infants, neurobehavioral function was assessed at 43 weeks after conception (222). Mediating factors (the timing and amount of drug exposure) and maternal psychological distress as a confounding factor were considered in the design and statistical analysis. The infants with heavy cocaine exposure had significantly more jitteriness and attentional difficulties. They were also more likely to be identified with an abnormality and less likely to cooperate with testing procedures than infants in the other groups. Higher concentrations of cocaine metabolites, cocaethylene and benzoylecgonine, were associated with a higher incidence of movement and tone abnormalities, jitteriness, and the presence of any abnormality. Higher cocaethylene concentrations were associated with attentional abnormalities; higher concentrations of metahydroxybenzoylecgonine were associated with jitteriness.

Cognitive, motor, and behavior development, as measured by the Mullen Scales of Early Learning and the Bayley Scales of Infant Development-II, were compared in 56 prenatally cocaine-exposed infants and toddlers (aged 1–3 years) and 56 non-exposed matched controls (223). There were developmental problems in expressive and receptive language areas in those who had been exposed prenatally.

The effect of intrauterine cocaine exposure on visual attention, cognition, and behavior has been investigated in 14 cocaine-exposed children and 20 controls aged 14–60 months (224). The cocaine-exposed children were slower in tests of disengagement and sustained attention. They also had greater difficulties in behavioral regulation.

Research on the effects of prenatal cocaine exposure on development in the first 2 years of life has been reported in 203 full-term infants (225). The infants, who were defined as having had no cocaine exposure, light exposure, or heavy exposure, were tested with the Bayley Scales of Infant Development at 6, 12, and 24 months. Assays of neonatal meconium for cocaine metabolites along with mothers' self-reports were used to evaluate the dose–response relation. There were no significant adverse effects due to cocaine exposure on scores in the major tests up to 24 months of age. Cocaine-exposed infants with the lowest 10th percentile birth weight and those placed with kinship caregivers had less optimal development. Cocaine-exposed infants who participated in child-focused early intervention programs scored higher than the others.

The behavioral effects of prenatal cocaine exposure at age 5 years have been studied in 140 children exposed to cocaine, 61 exposed to alcohol, tobacco, and/or marijuana, and 120 not exposed to any drugs (226). They were evaluated with the Achenbach Child Behavior Checklist. There was no association between behavior and intrauterine cocaine exposure. However, the current behavioral health of the mother, including recent drug use and psychological functioning, did affect the child's internalizing and externalizing behavior.

Gastrointestinal

Cocaine exposure in utero can affect various fetal organs. Gastrointestinal disorders, including ten cases of necrotizing enterocolitis (227), one of intestinal atresia, and one of spontaneous colonic perforation, have been reported (228).

Reproductive system

An increased incidence of genital malformations has often been noted (229).

Fetotoxicity

The prevalence rate of cocaine use during pregnancy is 10–45% in some centers in North America. As cocaine use is increasing and widespread, information on the possible adverse effects secondary to fetal cocaine exposure continues to amass in case reports and studies.

However, in a prospective, large-scale, longitudinal study there was no association between prenatal cocaine exposure and congenital anomalies in 272 offspring of 154 cocaine-using mothers and 154 non-using matched controls (230). The cocaine-exposed group had significantly more premature infants, who were significantly smaller in birth weight, length, and head circumference than the control infants. However, there were no differences in the type or number of abnormalities.

The impact of prenatal exposure to cocaine on fetal growth and fetal head circumference has been studied in 476 African-American neonates, including 253 full-term infants prenatally exposed to cocaine (with or without alcohol, tobacco, or marijuana) and 223 non-cocaine exposed infants (147 drug-free, 76 exposed to alcohol, tobacco, or marijuana) (231). The cocaine-associated deficit in fetal growth was 0.63 standard deviations and for gestational age 0.33 standard deviations. There were also cocaine-associated deficits in birth weight and length, but no evidence of a disproportionate effect on head circumference.

The relation between prenatal cocaine exposure and early childhood outcome has been reviewed (232). Prospective longitudinal studies of perinatal cocaine exposure and associated outcomes were studied in a

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survey of 36 of 74 reports, published from 1984 to October 2000, in which the examiners were blinded to cocaine exposure. Prenatal cocaine exposure did not alter physical growth, developmental test scores, or receptive and expressive language among children aged 6 years or less. The authors concluded that there is no convincing evidence that prenatal cocaine exposure is associated with effects on a child's physical or behavioral development, and that many findings once thought to be specific effects of in utero cocaine exposure instead correlated with factors such as the quality of the child's environment and prenatal exposure to tobacco, marijuana, or alcohol.

This review generated responses from other authorities in the field. Some commented that the conclusions may be premature, given the age of the subjects, and drew attention to several studies that have shown subtle but consistent deficits in cognitive and attentional processes in 6- and 7-year-old children (233). These effects may become more prominent as development continues and may persist into adulthood. Others criticized the attempt to isolate cocaine exposure from all other associated risk factors; from a public health perspective, prenatal cocaine exposure clusters with other risk factors, such as poor caregiving, child maltreatment, domestic violence, and prenatal exposure to other substances (234). Furthermore, the selection criteria narrowed the total articles reviewed to under half of the 74 articles found. Others suggested that the study had been misinterpreted (235).

The effects of prenatal cocaine exposure have been assessed prospectively in 217 infants, 95 (44%) of whom had benzoylecgonine, a cocaine metabolite, in their meconium (214). Among these infants, benzoylecgonine concentration was inversely related to fetal growth (birth weight, length, and head circumference), whereas maternal self-report of days of cocaine use did not correlate with either fetal growth or meconium benzoylecgonine concentration. The report suggested a dose–response relation between the magnitude of prenatal cocaine exposure and impaired fetal growth.

In 39 cocaine-exposed infants and 39 control infants aged 35 weeks or older, head size was smaller and birth weight tended to be lower in the cocaine-exposed infants (236). Moreover, the head circumference of the cocaine-exposed infants was significantly smaller at any given birth weight than in the control infants. The behavioral scores were significantly higher (on days 1 and 2) in the cocaine-exposed infants; the higher scores were most frequently attributed to increased jitteriness, a hyperactive Moro response, and excessive sucking. Lastly, cocaine-exposed infants had an increase in flow velocity in the anterior cerebral arteries between days 1 and 2; however, there was no increased propensity to ischemic and/or hemorrhagic cerebral injury in the infants exposed to cocaine. The blood flow changes on the second day may have reflected falling infant cocaine concentrations after birth.

In a longitudinal evaluation of 28 infants exposed to cocaine in utero and 22 unexposed controls for 15 months, the cocaine-exposed infants weighed significantly less at birth than the control infants, but not subsequently (237). Compared with controls, motor development was compromised in the cocaine-exposed infants at 4 and 7 months, but not at 1 and 15 months, suggesting that compromised motor performance in the exposed group normalized for later milestones, probably through a self-righting process. A disturbing aspect of this study was the extremely poor performance in all-motor assessments at every age by every infant (including the controls). The investigators postulated that in an inner-city population (such as that studied here), once an infant accumulates three or more risk points (as most infants in the study did), additional risk factors (including exposure to cocaine) have little further negative impact on their development.

The complex interplay between the relative effects of prenatal cocaine exposure and the perinatal and environmental factors on development has been evaluated, using a structural model to describe the direct and indirect effects of prenatal drug exposure on developmental outcome from birth to age 6 months (238). Key variables included prenatal drug exposure, perinatal medical characteristics, maternal/caregiver/family characteristics, the home environment, and neurobehavioral outcomes. The study was based on 154 predominantly crack-using women and 154 control subjects matched for pregnancy risk, parity, race, and socioeconomic status. Prior exclusion criteria included age under 18 years, a major illness diagnosed before pregnancy, chronic use of legal drugs, and any use of illicit drugs other than cocaine and marijuana. Urine specimens were collected at two unanticipated times and positive serum samples were confirmed by gas chromatography/mass spectroscopy. Measures analysed by blinded evaluators included medical assessment at birth and developmental assessments at birth, 1 month, and 6 months, as well as caregiver characteristics and environmental factors at birth and 1 month.

Exposure to cocaine affected development at birth. Increasing exposure was significantly related to poor developmental outcomes, as measured by the Brazelton qualifier scores. Although no direct effects of cocaine were found at either 1 month or 6 months analysed separately, time-dependent analysis showed an effect on development at 6 months. The indirect effects of cocaine exposure were mediated through maternal psychosocial well-being at delivery and birth head circumference. In addition, indirect effects of prenatal cocaine exposure were also related to concomitant alcohol and tobacco use and the birth head circumference. Neither maternal nor caregiver factors at 1 month was directly related to developmental outcome at any time. These findings support previous findings (239–241) that suggest that cocaine is a mild teratogen with regard to neurodevelopmental outcome.

The presence of cocaine during the prenatal period disrupts the development of neural systems involved in mediating visual attention. Of 14 cocaine-exposed children and 20 control children aged 14–60 months, whose visual attention, cognition, and behavior were assessed, the cocaine-exposed children had slower reaction times, supporting the hypothesis that impairment in disengagement and sustained attention are associated with prenatal cocaine exposure (242). There was a trend to slower reaction times to targets presented in the right visual field, but not the left visual field. Cocaine-exposed children also had greater difficulties in behavioral regulation, especially related to an ability to cope with heightened levels of positive and negative emotions (243).

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An association between prenatal cocaine exposure and deficits in total language functioning was found in 236 cocaine-exposed and 207 non-cocaine exposed full-term children (244). The link between prenatal cocaine exposure and language deficits during early childhood was not related to cocaine-associated deficits in birth weight, length, or head circumference. Three different but potentially interacting mechanisms whereby maternal cocaine use might affect early language development have been proposed (245):

- subtle dysregulation of attentional systems, with potential for disrupting an infant's ability to extract and process available linguistic information;
- disruptions in parent–child linguistic interactions due to cocaine and other drug use;
- impoverished, unstable, and endangering social and care-giving environments.

Early detection of language deficits allowed ameliorative intervention aimed at improving academic performance and social adaptation in preschool and school-aged children.

Cardiovascular

In a retrospective review of all dysrhythmias in children with prenatal cocaine exposure, 18 cases were detected in 554 infants who had positive urine screens for cocaine (246). In 13 neonates the dysrhythmia occurred beyond the period of direct cocaine exposure and six of the children had dysrhythmias after the neonatal period. Most of the dysrhythmias were supraventricular extra beats. Overall, the rate of consultations for dysrhythmias was higher among cocaine-exposed neonates than expected. Some cocaine-exposed children had symptomatic dysrhythmias that were persistent or recurrent and required treatment to maintain cardiac output and restore normal cardiac rhythm. Children who were exposed prenatally to cocaine appeared to be at increased risk of abnormal responses to stress, manifested by symptomatic dysrhythmias beyond the period of cocaine exposure.

- A child presented at 12 months of age with status epilepticus, sustained ventricular tachycardia, and a positive urine screen for cocaine. At 22 months he returned with a cardiac arrest, a history of a fall, a head injury, and a positive test for cocaine in the urine. He died soon after.

There has been a recent report of a myocardial infarct in a full-term infant born to a 28-year-old woman who had used cocaine 2–3 times per week and methadone 40 mg/day (247).

Respiratory

Respiratory rates in the 3-week-old babies of mothers who had used cocaine during pregnancy were higher than expected; in addition newborn babies who had been exposed prenatally to both cocaine and narcotic analgesics had abnormal control of breathing (following hypercapnia challenge) during the first few months of life (248). The preliminary results of another study are also of some interest; this prospective study of maternal drug abuse showed a reduced incidence of respiratory distress syndrome among premature infants prenatally exposed to cocaine (249). The authors noted that while this finding needs to be confirmed, it may suggest that fetal lung maturation can be accelerated by exposure to cocaine.

Prenatal cocaine exposure appears to have short-term effects on respiratory function in very low birth weight infants. In a retrospective study of 149 such infants, 48 cocaine-exposed and 101 non-exposed, the cocaine-exposed infants had transiently improved respiratory status at time of delivery; they needed surfactant treatment in lower doses and at a lower frequency and intubation less often (250). At 24 and 48 hours there was no significant difference between the treatment requirements in the two groups. The development of bronchopulmonary dysplasia was also similar. The authors suggested that prenatal cocaine exposure affects the fetus by two mechanisms: indirectly through reduced uterine blood flow with placental insufficiency and directly through an adrenergic effect on the fetus. The fetus may experience cocaine as a stressor that leads to accelerated fetal lung maturity.

Nervous system

Fetal microcephaly has been attributed to cocaine abuse during pregnancy (251). Urine toxicology confirmed the presence of morphine, benzoylecgonine, barbiturates, paracetamol, and propoxyphene. Analyses of amniotic fluid, placenta, and fetal serum and urine were also positive for these substances. The authors suggested that vascular disruption was the likely major mechanism of anomalies, both behavioral and malformative, due to prolonged exposure to cocaine in utero.

- An infant born at 37 weeks gestation to a mother who had engaged in discontinuous cocaine abuse during the first and second trimesters of pregnancy had microcrania (below the 10th percentile), a closed anterior fontanelle, and overlapping of all sutures (252). The infant was of low birth weight (2290 g; 25th percentile). There were deep scalp rugae, a prominent occipital bone, and normal hair pattern. An MRI scan of the brain showed enlargement of the lateral ventricles and pericerebral spaces, with severe reduction of the cerebral and cerebellar parenchyma and white matter abnormalities.

These findings are part of the recognizable pattern of defects in the rare condition termed fetal brain disruption sequence. The presence of a normal hair pattern suggests normal brain development during the first 18 weeks of gestation. At a later stage partial destruction of the brain results in reduced intracranial pressure and subsequent collapse of the fetal skull.

Prenatal cocaine exposure has been associated with subependymal hemorrhage and subependymal cyst formation in term neonates and more recently in preterm neonates (<36 weeks of gestation) (253). Medical records and cranial sonograms obtained during 1 year on 122 premature infants showed an increased incidence of subependymal cysts in preterm cocaine-exposed infants (8 of 18) compared with non-exposed infants (8 of 99). There was no increase in the incidence of major structural abnormalities. All subependymal cysts resolved by 4 months of age. The authors noted

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that the neurodevelopmental implications of such cyst formation are unknown.

An unusual congenital malformation, the cloverleaf skull, has been associated with cocaine exposure in utero (254). In this condition, the cranium is trilobed, with severe brain deformity and hydrocephalus, because of premature fusion of the coronal and lambdoid sutures.

- A girl born by cesarean section at 38 weeks gestation weighed 3515 g and measured 54 cm in length and needed cardiopulmonary resuscitation. She had feeding and respiratory problems. Cranial sonography on day 11 showed a trilobed cranial mass with ventricular enlargement. She was discharged on day 35. The mother, a 24-year-old cocaine user, had engaged in active drug use for the 2 years before and during the first 2 months of pregnancy; she had also used alcohol (three units per day) and smoked marijuana (1–2 joints per day) during the first 5 months, and she had smoked 10 joints per day throughout the entire pregnancy. The father was also a marijuana smoker. The infant failed to thrive (body weight at 6 months 3120 g, height 57 cm), developed sepsis, and died. Autopsy showed adrenal infarction secondary to systemic infection.

Psychological

A study in 105 African-American infants suggested that infants exposed prenatally to cocaine are at a high risk of significant problems in arousal and attention (255). The 8-week-old infants had their heart rates recorded when presented with a series of stimuli. The order of the stimuli was as follows: auditory (rattle), visual (red ring), and social (examiner's face and voice). There were four groups of infants: preterm drug-exposed ($n = 25$), full-term drug-exposed ($n = 32$), preterm non-exposed ($n = 22$), and full-term non-exposed ($n = 26$). Preterm infants' ages were corrected to match those of the full-term infants. There were significant differences in the responses to social stimuli. Drug-exposed infants had an accelerated heart rate (indicating distress or arousal), whereas non-drug exposed infants had a slowed response (indicating focused attention). However, there were no heart rate differences among the groups in the auditory or visual conditions.

There have been two studies of the adverse effect of prenatal cocaine on behavior of the offspring. In the first, 31 cocaine-exposed, very low birth weight infants and matched very low birth weight controls followed longitudinally were assessed at 3 years (256). The cocaine-exposed children had delayed cognitive, motor, and language development compared with the controls. Of the exposed children 45% scored in the range of mental retardation compared with 16% of the controls. Infants in the exposed group during the neonatal period were less responsive in their interactions and their mothers were less nurturing and less emotionally available.

In contrast, in a second study there were few differences in interactive behaviors between prenatally cocaine-exposed and non-exposed 12-month-old infants and their mothers (257). Videotapes recorded African-American infants and their mothers engaged in interactions (49 cocaine-exposed, 63 non-exposed). Children who were prenatally exposed to cocaine ignored their mother's departure during separation significantly more often than controls. Mothers who abused cocaine used more verbal behavior with their children than non-abusers.

The effects of prenatal cocaine exposure on later learning abilities, including language, have been further investigated in 265 infants aged 1 year (134 cocaine-exposed and 131 matched non-exposed), who were tested using the Preschool Language Scale-3 (PLS-3) by blinded examiners (258). The infants were assigned to three cocaine exposure groups (as defined by maternal self-report and infant meconium assay): non-exposure ($n = 131$), heavier exposure ($n = 66$), and lighter exposure ($n = 68$). Fetal cocaine exposure was associated with deficits in developmental precursors of speech/language skills. At 1 year of age, more heavily exposed infants had poorer auditory comprehension than the non-exposed infants and worse total language performance than lighter and non-exposed infants. The more heavily exposed infants were also more likely to be classified as mildly delayed than non-exposed infants. Moreover, the degree of cocaine exposure had an inverse relation to auditory comprehension.

Drug Administration

Drug administration route

With the use of cocaine eye-drops, poisoning can occur with doses as small as 20 mg (10 drops of cocaine 4%). Victims generally collapse and die after associated cardiovascular abnormalities, dysrhythmias, and respiratory failure. Signs and symptoms of intoxication include excitement, restlessness, headache, nausea, vomiting, abdominal pain, convulsions, and delirium.

Drug overdose

Body packing, the act of swallowing packets holding illegal drugs in order to hide the evidence from legal authorities, can cause symptoms of drug intoxication or overdose (SEDA-22, 44) (259). In an analysis of all cases of cocaine body packers reported to a metropolitan poisons control center from January 1993 to May 1994, 34 of 46 individuals were symptom-free. Eight had mild symptoms (hypertension and tachycardia) that resolved with decontamination (activated charcoal or whole body irrigation) or tranquilizers (one received benzodiazepines). Two had severe symptoms, including seizures and cardiac dysrhythmias, and both died.

An increase in the number of deaths of all body packers in New York has been associated with an increase in deaths among opiate body packers: of 50 deaths among body packers from 1990 to 2001, 42 were due to opiates (260). Four were related to cocaine and four to both opiates and cocaine. In 37 cases open or leaking drug packets in the gastrointestinal tract resulted in acute intoxication and death. Five cases involved intestinal obstruction or perforation, one a gunshot wound, one an intracerebral hemorrhage due to hypertensive disease,

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and one was undetermined. The number of packets recovered was 1–111 (average 46).

- A 49-year-old man became ill during a plane flight (261). He admitted to having swallowed 102 latex packages of cocaine 5 g each and 20 tablets of activated charcoal 125 mg. After stabilization in an emergency room, he suffered a seizure. After restabilization he had not defecated and was given a laxative of a mineral oil liquid paraffin. During the next 24 hours his condition worsened. His serum cocaine concentration increased from 1.95 to 2.2 μg/ml. During preparation for surgery he developed an untreatable dysrhythmia and died. Autopsy showed cocaine packages in the gut, 71 ruptured and 95 intact.

The reported lethal oral dose of cocaine is 1–3 g. In this case, paraffin may have contributed to rupture of the packages by dissolving the latex.

In another cocaine body packer, non-surgical management was followed by the development of a giant gastric ulcer (262).

- A 35-year-old man presented to the emergency room 5 days after swallowing 35 latex-wrapped packages of cocaine. He was asymptomatic but concerned that only 10 of the 35 packets had passed in his stools. He was treated with laxatives and passed only 8 packages during the next 8 days. Radiography showed that 10–15 foreign bodies remained clustered in the stomach 14 days after ingestion. Several fragments of latex wrapping were found in his stools. On exploratory laparotomy, 15 latex packages were found impacted in the antrum just proximal to the pylorus. Beneath the packages there was a giant gastric ulcer, 2.5 cm in diameter. He had an uneventful postoperative course.

Fatal crack cocaine ingestion has been reported in an infant (263).

- A 10-month-old girl developed apnea, ventricular fibrillation, and a metabolic acidosis, and died shortly afterwards. Her 2-year-old brother had fed her crack cocaine. At autopsy the brain had a thinned corpus callosum, ranging in thickness from 0.2 to 0.5 cm. There were two pieces of crack cocaine in the duodenum and high concentrations of cocaine in the blood and other tissues.

The authors noted that the thinned corpus callosum suggested that the infant had been exposed to cocaine in utero or during the early postnatal period.

Drug–Drug Interactions

Alcohol

Cocaine abusers have reported that alcohol prolongs the euphoriant properties of cocaine, while ameliorating the acutely unpleasant physical and psychological sequelae, primarily paranoia and agitation. It may also lessen the dysphoria associated with acute cocaine abstinence. It has also been proposed that concurrent alcohol abuse may be an integral part of cocaine abuse. The combination of cocaine with alcohol can cause enhanced hepatotoxicity and enhanced cardiotoxicity (264). Trauma in patients who use cocaine plus alcohol has been reported (265). Those who use cocaine plus alcohol are 3–5 times more likely to have homicidal ideation and plans; this is particularly prominent in patients with antisocial personality disorder (266). A large high school survey by the Centers for Disease Control and Prevention showed that illicit substance abuse, prevalence of weapon carrying, and physical fighting were higher among the adolescents who reported recent use of cocaine, marijuana, alcohol, and corticosteroids. Among 215 female homicide offenders, 70% had been regular drug users at some time before imprisonment. Alcohol, crack, and powdered cocaine were the drugs most likely to be related to these homicides (267).

In a double-blind study, subjects meeting DSM-IV criteria for cocaine dependence and alcohol abuse participated in three drug administration sessions, involving intranasal cocaine with oral alcohol, cocaine with oral placebo alcohol, and cocaine placebo with oral alcohol (268). Cocaine plus alcohol produced greater euphoria and increased perception of well-being than cocaine alone. Heart rate was significantly higher with cocaine plus alcohol than with either alone. Cocaine concentrations were higher after cocaine plus alcohol than after cocaine alone. Metabolism of cocaine to cocaethylene was observed only during administration of cocaine plus alcohol. The authors concluded that enhanced psychological effects during abuse of cocaine plus alcohol may encourage the ingestion of larger amounts of these substances, placing users at increased risk of toxicity than with either drug alone.

The adverse effects of the combined use of alcohol and cocaine have been reviewed (269). There is little evidence that this combination acts synergistically or that either drug enhances the negative effects of the other. However, the combination leads to the formation of cocaethylene, which may potentiate cardiotoxic effects and the combination has a greater than additive effect on heart rate. Lastly, cocaine antagonizes the learning and psychomotor performance deficits and driving impairment caused by alcohol.

Reports of liver complications after cocaine use are infrequent. However, fulminant hepatitis with acute renal insufficiency requiring liver transplantation occurred after the use of cocaine and alcohol (270).

- A 33-year-old chronic alcoholic with hepatitis C developed acute liver and renal insufficiency with grade III encephalopathy. Hemodialysis was begun and emergency liver transplantation was performed. The explanted liver showed marked diffuse macrovesicular steatosis with massive coagulative-type necrosis. The postoperative course included a persistently raised gamma-glutamyltransferase, but he recovered fully after 60 days.

Macrovesicular steatosis can be attributed to alcohol or cocaine, but massive liver necrosis is more probably due to cocaine. The mechanisms of cocaine hepatotoxicity, such as increased lipid peroxidation, free radical activity, and impaired calcium sequestration, may be potentiated by alcohol.

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Atropine

Anticholinergic poisoning involving adulterated cocaine has been reported (271).

- A 39-year-old man who was a recreational user of alcohol and cocaine presented with agitation, hallucinations, and delirium. He had a dry flushed skin, tachycardia, dilated, minimally reactive pupils, urinary retention, and absent bowel sounds. He was treated with intravenous fluids and a sedative. There were cocaine metabolites in the urine. Reanalysis of a urine sample by thin layer chromatography confirmed the presence of the anticholinergic drug atropine.

Clozapine

An interaction of clozapine with cocaine has been reported (272). Eight male cocaine addicts underwent four oral challenges with increasing doses of clozapine (12.5, 25, and 50 mg) and placebo, followed 2 hours later by cocaine 2 mg/kg intranasally (273). Subjective and physiological responses, and serum cocaine concentrations were measured over 4 hours. Clozapine pretreatment increased cocaine concentrations during the study and significantly increased the peak serum cocaine concentrations dose-dependently. Despite this rise in blood concentrations, clozapine pretreatment significantly reduced subjective responses to cocaine, including "expected high," "high," and "rush" effects, notably at the 50 mg dose. There were also significant effects on "sleepiness," "paranoia" and "nervousness." Clozapine caused a significant near-syncopal episode in one subject, requiring withdrawal. Clozapine had no significant effect on baseline pulse rate or systolic blood pressure, but it attenuated the significant pressor effects of a single dose of intranasal cocaine. These data suggested a possible therapeutic role for clozapine in the treatment of cocaine addiction in humans, but also suggest caution due to the near-syncopal event and the increase in serum cocaine concentrations.

Diamorphine

Rhabdomyolysis and ventricular fibrillation has been attributed to cocaine plus diamorphine (heroin) ingestion (274).

- A 28-year-old man went into cardiorespiratory arrest after using intravenous cocaine and diamorphine. He was intubated and ventilated and given adrenaline, naloxone, and sodium bicarbonate. During a thoracotomy he developed ventricular fibrillation and was electrically converted to sinus rhythm. He had hyperkalemia and myoglobinuria. He developed acute renal insufficiency, disseminated intravascular coagulopathy, and a right leg compartment syndrome. There were cocaine metabolites and opioids in his urine. Hemodialysis and fasciotomy were performed, but he died 2 months later with a complicating bronchopneumonia.

The authors discussed the possibility that naloxone, an effective opioid antidote, may have been harmful in this case.

Ephedrine

Chronic cocaine use sensitizes coronary arterial α-adrenoceptors to agonists (SEDA-22, 154).

Indometacin

Cocaine combined with indometacin in a 23-year-old pregnant woman at 34 weeks gestation may have caused fetal anuria and neonatal gastric hemorrhage (275).

Monoamine oxidase inhibitors

The combination of monoamine oxidase inhibitors with cocaine can cause hyperpyrexia (270).

Neuroleptic drugs

Cocaine-abusing psychiatric patients significantly more often develop neuroleptic drug-induced acute dystonia according to a 2-year study carried out on the island of Curaçao, Antilles, where cocaine and cannabis are often abused (277). The sample consisted of 29 men with neuroleptic drug-induced acute dystonia aged 17–45 years who had received high potency neuroleptic drugs in the month before admission; nine were cocaine users and 20 non-users. Cocaine use was a major risk factor for neuroleptic drug-induced acute dystonia and should be added to the list of well-known risk factors, such as male sex, younger age, neuroleptic drug dosage and potency, and a history of neuroleptic drug-induced acute dystonia. The authors suggested that high-risk cocaine-using psychiatric patients who start to take neuroleptic drugs should be provided with an anticholinergic drug as a prophylactic measure to prevent neuroleptic drug-induced acute dystonia.

Nimodipine

It has been suggested that calcium channel blockers can be used to treat cocaine dependence, and some studies have shown reductions in cocaine-induced subjective and cardiovascular responses with nifedipine and diltiazem. The cardiovascular and subjective responses to cocaine have been evaluated in a double-blind, placebo-controlled, crossover study in five subjects pretreated with two dosage of nimodipine (278). Nimodipine 60 mg attenuated the rise in systolic, but not diastolic, blood pressure after cocaine. In three subjects nimodipine 90 mg produced greater attenuation than 60 mg. The subjective effects of cocaine were not altered by either dose of nimodipine.

Suxamethonium

Procaine and cocaine are esters that are hydrolysed by plasma cholinesterase and may therefore competitively enhance the action of suxamethonium (succinylcholine) (279). Chloroprocaine may have a similar action. Lidocaine also interacts, although the mechanism is not clear unless very high doses are used (280).

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Cocamidopropyl betaine

General Information

Cocamidopropyl betaine is the most commonly used amphoteric surfactant in shampoos, bath products, and other cosmetic products. It is popular because of its relatively low irritation potential.

Organs and Systems

Immunologic

Contact allergic reactions are infrequent and have been attributed to sensitizing intermediates rather than cocamidopropyl betaine itself. Of 30 patients who were allergic to cocamidopropyl betaine, all reacted to 3-dimethylaminopropylamine (1). Two studies have shown that cocamidopropylamine is the more relevant impurity (2,3).

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Codeine

See also Opioid analgesics

General Information

The pharmacodynamic and adverse effects of codeine are mainly due to *O*-demethylation by CYP2D6 to morphine or a metabolite of morphine (SEDA-21, 86) (SEDA-22, 5). Poor metabolizers may lack the analgesic effect of codeine.

In a retrospective study of patients with chronic rheumatological conditions, 290 of 644 clinic patients had received either codeine or oxycodone analgesia, of whom 137 had been given opioids for a continuous period of over 3 months (1). Adverse effects were described in 38% of both long-term and short-term opioid users, of which the most common were constipation, nausea, and sedation. Headache, dizziness, rash or itching, confusion, insomnia, depression, diarrhea, and myoclonic jerking were also reported. No significant differences in the adverse effects profile were reported between the groups and no subjects discontinued medication because of adverse effects. There were opioid abuse behaviors in 3% of the long-term users, but no association with a history of substance misuse was established.

A prospective double-blind, randomized study in 184 patients with cancers involved three treatment regimens (2): diclofenac alone (50 mg qds), diclofenac plus codeine (40 mg qds), or diclofenac plus imipramine (10–25 mg tds). There was no significant difference between the different treatments in terms of their analgesic effects, as measured on a visual analogue scale after 4 days. However, 10 of 61 subjects taking codeine withdrew because of adverse effects, compared with three taking imipramine group and two taking diclofenac alone. Gastrointestinal disturbances, dry mouth, and central nervous system disturbances were all more frequent in those taking codeine. These results suggest that the addition of a low-potency opioid to diclofenac fails to give enhanced analgesia while the frequency of opioid-related adverse effects increases.

Organs and Systems

Nervous system

Patients with migraine who use daily codeine or other opioids can be more susceptible to chronic daily headaches; this is evident in opiate overuse. In a pilot questionnaire study of 32 patients who used codeine or other opioids for control of their bowel motility after colectomy, chronic daily headaches occurred in those who were misusing opioids, but only if they had pre-existing migraine (3). The study had significant limitations, including the small sample size, diagnosis by means of a mailed questionnaire, a short duration of overuse of opioids, and the fact that it was uncontrolled.

Twelve cases of analgesic-related headache have been reported in children aged 6–16 years, half of whom were taking paracetamol in combination with codeine (4). Headaches occurred on at least 4 days per week and analgesic withdrawal led to symptom resolution in 50% and some improvement in the other cases.

Sensory systems

Reduced pupil size has been related to plasma codeine concentration (5).

Pancreas

Acute pancreatitis has been attributed to codeine (SEDA-21, 86), in one case in a patient taking co-codamol (paracetamol plus codeine) (6).

- A 20-year-old woman, who had previously taken paracetamol without adverse effects, took paracetamol 1 g and codeine 60 mg for a headache. After 3 hours she developed severe upper abdominal pain radiating to the back. The abdominal pain resolved within 24 hours of the administration of phloroglucinol and tiemonium. Her serum amylase activity was raised 3-fold and the serum lipase 15-fold. Other biochemical parameters, abdominal ultrasound, and an MRI scan were normal. Contrast-enhanced computed tomography showed pancreatic edema.

The previous use of paracetamol without adverse reactions supports the theory that the reaction was linked to the addition of codeine.

Four other cases of acute pancreatitis related to codeine have been reported (7).

- A 65-year-old man presented with severe abdominal pain 90 minutes after taking codeine and low-dose paracetamol. Serum amylase and lipase were significantly raised. Liver function tests were moderately abnormal. Abdominal ultrasound and CT scan showed edematous pancreatitis. Endoscopic retrograde cholangiography showed a papilla with a spastic appearance and an abnormal bile duct. He recovered completely, but 3 months later took codeine and paracetamol after a hemorrhoidectomy; abdominal pain recurred 1 hour later and acute pancreatitis was confirmed.
- A 26-year-old woman developed abdominal pain 2 days after taking codeine for a respiratory tract infection. Three hours later she complained of epigastric pain and vomiting. Her serum amylase and lipase were raised. Her symptoms resolved and the diagnosis was mild idiopathic pancreatitis. One week later she took codeine for similar respiratory symptoms. Two hours later she developed similar symptoms and a CT scan showed an enlarged and heterogeneous pancreas, with necrosis of the tail of the pancreas involving the left kidney. She responded to conservative treatment.
- A 53-year-old woman developed severe central abdominal and epigastric pain 90 minutes after taking codeine for migraine. Pancreatic amylase, lipase, and liver function tests were mildly raised. Abdominal ultrasound was consistent with acute pancreatitis.
- A 57-year-old woman developed severe abdominal pain 2 hours after taking codeine. She had had two similar episodes in the past, once with loperamide and once with codeine. An abdominal CT scan showed edematous acute pancreatitis.

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In three of these cases unintentional rechallenge with codeine resulted in recurrence of the symptoms, and the diagnosis was confirmed radiologically and biochemically. All the patients had previously had a cholecystectomy, suggesting that this may increase the likelihood of codeine-induced pancreatitis. The authors speculated that codeine could cause a rise in biliary and/or pancreatic sphincter pressure in cholecystectomized patients, either by exacerbating pre-existing disease of the sphincter of Oddi or as a consequence of reduced storage capacity of the biliary tract, initiating acute pancreatitis. They cautioned that codeine-associated acute pancreatitis can be misconstrued—it may seem as if patients are taking codeine for pancreatic pain when in fact the codeine is producing the pain.

Skin

Rashes have been attributed to codeine.

- A 72-year-old man developed a generalized maculopapular rash 12 hours after taking co-codamol (codeine 10 mg plus paracetamol 500 mg) (8). The lesions persisted for 7 days, became scaly, and disappeared. He later reported a similar skin condition after having taken a combination of acetylsalicylic acid, codeine, and caffeine. Patch tests gave a positive result for codeine, suggesting a type IV allergic reaction.
- A 58-year-old man developed a maculopapular rash on the dorsal aspects of the hand and upper body 6 days after taking codeine as an analgesic for hemoptysis secondary to tuberculosis; on withdrawal of codeine, the rash subsided after 48 hours (9).

Two reports have highlighted the importance of using an oral provocation test and not a patch test to determine if codeine is the causative agent in non-urticarial skin lesions (10,11).

- A 58-year-old man developed a pruritic rash on the body and face, with periorbital swelling 3 hours after taking codeine 20 mg, acetylcysteine 600 mg, and acetylsalicylic acid 500 mg. An oral provocation test over 2 hours with codeine phosphate (1 mg, 4 mg, and 8 mg) precipitated a pruritic scarlatiniform rash for 24 hours, with swelling of the arms, starting 7 hours after the 8 mg dose. A rechallenge test confirmed the effect of codeine. Throughout this period, histamine release tests (CAST-ELISA with codeine) were negative.
- A 57-year-old patient presented with generalized malaise, fever, pruritus, and palpebral and labial angioedema 6 hours after taking a tablet containing paracetamol 500 mg, saccharin 10 mg, and codeine phosphate 30 mg. There was complete resolution in 8 hours, after treatment with prednisolone, hydroxyzine, and metamizole. Later a patch test with 1% codeine and an oral provocation test with paracetamol were both negative. Following an oral provocation test with codeine 5 mg, the patient developed similar symptoms.

Immunologic

True allergy to opioids is extremely rare. However, a near anaphylactic reaction in a patient taking codeine has been reported; the management of true codeine allergy was discussed and agents with different structures, such as phenylpiperidines or methadone-like compounds, are recommended (SEDA-17, 80).

Long-Term Effects

Drug abuse

Recreational use and abuse of codeine cough syrup is becoming more frequent. In a literature search of scientific journals and news media, complemented with in-depth interviews of 12 professionals working in the law enforcement or treatment aspects of drug abuse and 25 adults who reported using codeine syrup in the 30 days before their interview, the information provided useful insights into the different types of cough formulations, the reported reasons for their use, and the various types of administration (12). The effects of cough syrup, including their adverse effects, were reported. The most frequently mentioned negative effects included taste disturbance, prolonged sedation beyond the desired effect, loss of co-ordination, lethargy, constipation, and urinary retention. This qualitative study cannot be described as authoritative or representative, because of its limited nature, involving as it did only a small number of individuals living in the Houston area.

Drug dependence

In an exploratory survey among long-term codeine users recruited via newspaper advertisements in Toronto, Canada, more than 300 individuals who used codeine on at least 3 days per week for a minimum of 6 months and were older than 16 years were studied (13). Those who used codeine for pain related to malignancy were excluded. The mean age of the respondents included in the final analysis ($n = 339$) was 44 years and 51% were women. On average, the total number of years of regular codeine use was 12, with a current mean daily dose of 115 mg. About 60% ($n = 213$) had sought help for mental health problems, most commonly for depression (70%), followed by generalized anxiety (55%) and panic attacks (24%). One-third of the subjects ($n = 339$) identified at least one family member as having a mental health problem, with depression as the most frequent. Current antidepressant use was reported by 14% of the whole sample. Men used significantly higher doses of codeine than women; they also used the drug for a longer period and more commonly took it for pleasurable effects and under social pressure. Regular codeine users, in addition to having high rates of drug dependence, had raised scores on general measures of psychological distress and depressive symptoms. From the survey it was not clear to what extent these symptoms preceded codeine use and may have initiated the use and to what extent they were caused by codeine. The authors speculated that many respondents used codeine to modulate mood, particularly dysphoria, in the absence of more appropriate interventions. They suggested that understanding long-term codeine use and its relation to dysphoria may be

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important in designing both preventive and secondary treatment interventions.

The same investigators further analysed the data according to codeine abuse/dependent and non-dependent status (14). There was codeine abuse/dependence in 41% of the subjects. The most common psychological and physical problems attributed to codeine use in the dependent/abuse group ($n = 124$) were depression (23%), anxiety (22%), gastrointestinal disturbances (15%), constipation (6%), and headache/migraine (5%). The codeine-dependent subjects were younger than those who were not dependent. The mean age of the respondents when they first started using codeine was 26 (range 2–78) years. A total of 563 codeine products had been used on a regular basis; the most common combination involved codeine with paracetamol (70%). Codeine was used for headaches (41%), back pain (22%), and other types of pain (25%). Those in the dependent group were more likely to have used codeine initially for other reasons, for example for pleasure and to relax or reduce stress. Most subjects said that they had obtained their codeine from one physician (66%) or by purchasing it over the counter (54%). Subjects in the dependent group also obtained codeine from friends (32%), from family (11%), "off the street" (19%), and through prescriptions from more than one physician (11%). Overall, more subjects in the dependent group considered themselves to have problems with a larger number of substances (3.3: range 0–15) compared with those in the non-dependent group (1.2: range 0–8). In the dependent group, more subjects said that their physical or mental health problems interfered with normal social activities at least "quite a bit." Significantly more subjects in the dependent group had sought help for a mental health problem, had had an inpatient psychiatric admission, or had sought help for a substance-use disorder, especially alcohol and stimulants. A larger number of subjects in the dependent group identified at least one family member (usually male) with substance-use problems compared with those in the non-dependent group.

This study suggests that codeine dependence may be more common in the general population than has been previously thought. The authors suggested that it is important to identify those with codeine abuse or codeine dependence, since they may be using substantial doses of codeine for apparently little benefit compared to the risks. Furthermore, there are also health risks of associated chronic use of paracetamol and a potential for analgesic rebound headache.

Drug Administration

Drug dosage regimens

In a comparison of the adverse effects of 30, 60, and 90 mg codeine the most frequent adverse effects, headache, drowsiness, nausea, thirst, and a feeling of strangeness, occurred after 60 and 90 mg doses only. Visuomotor co-ordination was altered with 60 and 90 mg and dynamic visual acuity with 90 mg only (15).

Drug–Drug Interactions

Amitriptyline

There were signs of opiate toxicity, reversible with naloxone, in an 80-year-old woman after concomitant treatment with amitriptyline and co-codamol (codeine plus paracetamol) (SEDA-18, 79).

Inhibitors of CYP2D6

Inhibitors of CYP2D6 can reduce or abolish the analgesic effects of codeine (16).

Quinidine

Quinidine inhibits the hepatic metabolism of codeine to morphine. Whether this diminishes or abolishes the analgesic effect of codeine is uncertain (17,18).

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Co-dergocrine

General Information

Co-dergocrine is the British Approved Name for a formulation that contains a combination of dihydrogenated ergot alkaloids: dihydroergocornine mesilate, dihydroergocristine mesilate, and (in the ratio 2:1) α- and β-dihydroergocryptine mesilates. It has been used for its supposed therapeutic effects on mood depression, confusion, and lack of self-care in the elderly, and purportedly acts by improving cerebral blood flow. The basis of these indications has been reviewed and has not been fully validated (1)(2)(3).

Surprisingly few adverse effects have been reported. They include sinus bradycardia, nausea, and a single report of vasospastic angiitis (4).

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Colchicine

General Information

Colchicine is an antimitotic agent, highly effective in the treatment of gout, but associated with considerable toxicity. Diarrhea is used as a criterion for adequate dosage. Accidental overdosage occurs relatively often and can be dangerous. For these reasons, NSAIDs (except aspirin) are often used in acute gout instead of colchicine.

There is controversy about the long-term toxicity of colchicine. In familial Mediterranean fever, low dosages of colchicine (1–2 mg/day) for 15–18 years have been well tolerated, even by young patients (SEDA-16, 114).

Organs and Systems

Nervous system

Neuropathy, polyneuritis, toxic encephalitis, delirium, and coma have occurred only in severe colchicine intoxication. During prolonged treatment, neuritis, muscular weakness and myopathy occur more commonly than was previously thought in patients with impaired renal function. In some cases the neuromyopathy was part of multiorgan system failure, but in others the syndrome was not accompanied by other features of colchicine toxicity. Patients taking long-term colchicine should take low dosages (probably no more than 0.6 mg/day) and have their serum creatine kinase monitored (SEDA-12, 94).

Metabolism

Transient diabetes and hyperlipidemia have been reported. Metabolic acidosis is probably a consequence of heavy, cholera-like diarrhea. Progressive reduction of libido was attributed to colchicine in patients with familial Mediterranean fever (1).

Electrolyte balance

Water and electrolyte disturbances, including inappropriate antidiuresis, can occur in patients who have taken high doses of colchicine (2,3), including hypernatremia and polyuria (4).

Hematologic

Bone marrow depression is common after colchicine overdose and intoxication and less common in therapeutic doses. Fatal cases of agranulocytosis are more often associated with bone marrow aplasia (SEDA-4, 70) (5). Bone marrow depression usually occurs between the third and sixth days of acute intoxication. Cytoplasmic inclusions in neutrophils and megaloblastic anemia have been described. Administration of therapeutic doses intravenously and orally to two patients with reduced renal function caused profound prolonged neutropenia complicated by septicemia, which ended in death (SEDA-13, 84).

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Gastrointestinal

Gastrointestinal symptoms often develop after therapeutic doses and are even used for dose titration. Diarrhea is often followed by nausea, vomiting, and abdominal pain. Long-term therapy can provoke steatorrhea, malabsorption, and defects in intestinal enzyme activity (6).

Urinary tract

Acute renal insufficiency has been associated with colchicine intoxication (7).

Skin

Blood dyscrasias are associated with ecchymosis and purpura. Allergic skin changes are rare. Alopecia is common after acute intoxication and prolonged treatment (SEDA-5, 109). A fixed drug eruption has been reported (SEDA-21, 109).

Musculoskeletal

Acute rhabdomyolysis with fever, muscle cramps, rises in creatine phosphokinase and lactic acid dehydrogenase activity, phlebitis at the injection site, and transitory leukopenia and thrombocytopenia have been reported (8).

Second-Generation Effects

Fertility

Reversible azoospermia (later not confirmed) was observed after long-term treatment with colchicines (9).

Pregnancy

Owing to its antimitotic properties, colchicine should not be given during pregnancy (SED-9, 158) (10).

Susceptibility Factors

Renal disease

The dosage of colchicine should be adjusted according to creatinine clearance during long-term use to avoid the risk of myoneuropathy (SEDA-16, 114). Colchicine should not be used in patients undergoing hemodialysis, since it cannot be removed by either dialysis or exchange transfusion (11).

Drug Administration

Drug administration route

Intravenous administration is potentially much more toxic than oral administration; because of its unfavorable benefit to harm, balance and the availability of less dangerous treatments, colchicine should not be given intravenously (SEDA-5, 109) (SEDA-13, 84) (SEDA-16, 115).

Drug overdose

Acute intoxication with colchicine occurs relatively often, because the therapeutic dose is close to the toxic dose. Gastrointestinal, hematological, and neurological reactions are the most frequent effects (SEDA-7, 118). An accidental overdose of colchicine by nasal insufflation has been reported in a young male drug abuser who had mistaken it for metamfetamine. The effects included gastrointestinal distress, myalgia, thrombocytopenia, hypocalcemia, and hypophosphatemia (12). Electrolyte disturbances can occur (2–4). Deaths have been reported (3).

Drug–Drug Interactions

Ciclosporin

Acute reversible ciclosporin toxicity occurred in a renal transplant patient a few days after colchicine was administered for an acute attack of gout (SEDA-16, 115). Other potential adverse effects of combining colchicine with ciclosporin include diarrhea, increases in serum liver enzymes, bilirubin, and creatinine, and less often severe myalgia (SEDA-19, 101). Acute myopathy, associated with neuropathy in one case, has been observed in two young renal transplant recipients (SEDA-22, 119).

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Collagen and gelatin

General Information

Collagen is a natural fibrous protein found in human cartilage, connective tissue, and bone. Glutaraldehyde cross-linked bovine collagen is a sterile, biocompatible, biodegradable, purified bovine dermocollagen cross-linked with glutaraldehyde, mixed in a phosphate-buffered saline solution.

Purified solubilized bovine collagen is used as biomaterial for the treatment of soft tissue defects and has been used for the treatment of stress urinary incontinence since the late 1980s (1). Injected material precipitates at body temperature, forming a matrix allowing fibroblastic infiltration and formation of new tissue. It has been used for cosmetic purposes by injection in the dermis to correct scars and other contour deformities of the skin.

Urethral injection of bovine collagen under local anesthesia is considered safe and effective, with minimal complications (2,3). It has low antigenicity and is associated with a minimal inflammatory response, although foreign body reactions have occasionally been reported (4). However, antibody formation is not impossible (5). Patients with a history of allergic reactions to bovine collagen-derived products should be investigated because of the widespread use of collagen-derived therapeutic devices, the potential for immunological cross-reactivity with dietary collagen (gelatin), and the potential for anaphylaxis.

Gelatin is an important constituent of many drug formulations, including capsules and suppositories. It is also found in some volume replacement solutions (for example Gelofusine). Gelofusine is a colloidal plasma volume expander used in the treatment of hypotension. It is prepared from bovine collagen. Severe anaphylactoid reactions after gelofusine occur with an incidence that has been reported at between 0.066 and 0.345% of cases. They are more common in those with known drug allergy and in men. The mechanism may be triggering of non-immune complement C3 activation by colloid particles in the gelatine formulation or by combination with components in the patient's blood (6).

Organs and Systems

Cardiovascular

Hypotension has been described in a patient who received 500 ml of gelofusine during surgery for an infrarenal abdominal aneurysm (7). Within 5 minutes there was a significant fall in blood pressure, in the absence of surgical bleeding and ischemic changes on the electrocardiogram. There was no change in oxygenation. A further 500 ml of gelofusine was rapidly infused, with an additional fall in blood pressure to 50/30. Subsequently, after recovery, a small test dose (100 ml) of gelofusine reproduced the transient hypotension.

A patient undergoing anesthesia for coronary artery bypass surgery developed a probable anaphylactic reaction to Gelofusine (8). The principal feature of the reaction was cardiovascular depression. An infusion of the angiotensin analogue angiotensinamide was effective in treating the reaction.

Urinary tract

Few complications of urethral injection of collagen have been reported, including urinary tract infection, bleeding, and transient urinary retention. During a prospective, cohort study in 337 women to determine the effectiveness of and adverse effects associated with transurethral collagen injection for treatment of stress urinary incontinence, there were three cases of delayed allergic reactions at the skin test site associated with arthralgia (9). Delayed reactions at the skin test site occurred in three patients (0.9%), and were associated with arthralgias in two. The incidence and systemic nature of this type of reaction led the authors of the study to conclude that glutaraldehyde cross-linked collagen injection is not as innocuous as previously believed, and clinicians were advised to consider double skin testing before treatment. The overall risk of complications in any given individual of this study population was 20% (1), although irritating lower urinary tract symptoms after collagen injection could be related to local inflammatory changes, persistence and eventually worsening of these symptoms should suggest the presence of iatrogenic bladder outlet obstruction (10). Urethral prolapse (11) and unusually long collagen persistence (12) after periurethral collagen injection have also been reported.

Immunologic

Bovine collagen is contraindicated in patients with immunological disorders and reports of delayed allergic reactions underline the need for adequate follow-up when collagen implants are used. Patients should be tested with bovine collagen and reassessed at 4 weeks. About 3% of the patients tested in this way developed hypersensitivity reactions to collagen, whereas 1% of treated patients have symptoms of hypersensitivity at treatment sites (13). In this series, erythema was the sole symptom in 24%, and erythema and induration occurred in an additional 42%. Of the patients with complications, 45% reported an onset of symptoms within 10 days while in 22% the onset was more than 30 days following treatment with collagen. Abscesses as a manifestation of hypersensitivity to bovine collagen occur rarely (four in 10 000 cases), but the possibility of contamination should always be considered. Local tissue necrosis occurs rarely after implantation (nine reported in 10 000 cases) and this is thought to be the result of local vascular interruption rather than a hypersensitivity reaction. The incidence varies widely according to the site of implantation, but more than one-half of the cases involve the glabellar region, probably because of its special vascular distribution (14).

Anaphylactic reactions to collagen have been described (15). Despite pretreatment collagen testing, anaphylactic shock has been reported in one patient, necessitating adrenergic agents and glucocorticoids.

An allergic rash has been described after collagen injection (16).

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Delayed hypersensitivity reactions after bovine collagen injection for stress urinary incontinence have been reported.

- A 50-year-old woman had a negative collagen skin test for 4 weeks (9). After an injection of transurethral collagen, she developed a flare-up at the skin test site and subsequently had recurrent flares at 21–26 day intervals for six cycles, which corresponded to her menses and were thought to be hormone-related.
- A 64-year-old woman with recurrent urinary leakage elected to undergo conservative therapy with collagen injection, had no reaction to a collagen skin test, and had an uneventful transurethral injection of collagen 30 days later (17). Her postoperative course was complicated by urethritis, trigonitis, severe urge, bilateral leg arthralgias, leg pain relieved by massage, and leg edema at 6 weeks. She had a total voided volume of 300 ml and a postvoid residual of 180 ml, and was started on intermittent self-catheterization for urinary retention. Induration at the skin injection test site was noticeable 9 weeks after the injection. Her severe urge, leg edema, and pain gradually resolved after 13 months, but her stress incontinence continued without relief.
- A 50-year-old woman with stress urinary incontinence chose a trial of transurethral injection of collagen (18). A skin test showed no evidence of allergy at 1 month and collagen 2.5 ml was injected transurethrally without problems but with little improvement. A second injection of 2.5 ml 5 weeks later was again uneventful, but 2 weeks later she began to have difficulty in emptying her bladder, with a poor stream and a sense of incomplete emptying. At the same time she noticed redness and firmness at the initial skin test site on her arm, which had previously been benign.

Several reports have highlighted the importance of gelatin allergy in young children, with some deaths due to anaphylaxis. Elsewhere, anaphylactoid reactions have been reported to gelatin-containing injectables (SEDA-20, 310).

- A 2-year-old and a 4-year-old boy developed anaphylactic symptoms after being given a chloral hydrate suppository, which contained gelatin, for sedation before electroencephalography (19).

The authors suggested using gelatin-free formulations in children.

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Complementary and alternative medicine

General Information

Complementary and alternative medicine (also referred to as "non-orthodox," "unconventional," "holistic," and "integrative" medicine) comprises a heterogeneous array of treatments, from acupuncture to spinal manipulation

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and from herbal medicine to homeopathy. The techniques covered in this monograph are:

- Acupuncture
- Aromatherapy
- Cell therapy
- Homeopathy
- Hypnosis
- Manipulation
- Massage.

Herbal products and animal products are covered in separate monographs.

Complementary medicine continues to be a growth area (1). A survey conducted in South Australia showed that almost half of the 3004 respondents had used at least one type of complementary remedy in the previous 12 months and that one-fifth had consulted a practitioner of complementary medicine (2). In European countries for which estimates on the annual utilization of complementary medicine are available, estimates range from 20 to 50% of the population (3). In the UK, retail sales of complementary medicines (licensed herbal medicines, homoeopathic remedies, essential oils used in aromatherapy) were estimated to be £72 million in 1996, an increase of 36% in real terms since 1991 (4). This, however, is likely to be a gross underestimate as popular products sold as food supplements, including *Ginkgo biloba* and garlic, were not included. According to a detailed analysis of the herbal medicines market in Germany and France, total sales of herbal products in those countries in 1997 were US$1.8 billion and US$1.1 billion respectively (5). In 1994, annual retail sales of botanical medicines in the US were estimated to be around US$1.6 billion; in 1998, the figure was closer to US$4 billion (6).

Some of the most useful data on trends in complementary medicine use come from two surveys of US adults carried out in 1991 and 1997/8, which involved over 1500 and over 2000 individuals respectively (7,8). The use of at least one form of complementary therapy in the 12 months preceding the survey increased significantly from 34% in 1990 to 42% in 1997 (8) and in November 1998 all 10 journals of the American Medical Association published theme issues on the subject.

The reasons for the popularity of complementary medicine are many and diverse. It appears that complementary medicine is not usually used because of an outright rejection of conventional medicine, but more because users desire to control their own health (9) and because they find complementary medicine to be more congruent with their own values, beliefs, and philosophical orientations toward health and life (10). Also, users may consult different practitioners for different reasons (9). An important reason for the increase in use is that consumers (often motivated by the lay press) consider complementary medicine to be "natural" and assume it is "safe." Of all patients attending an emergency department in the USA 43% had used at least one complementary therapy at some time and 24% were current users (11). All complementary treatments were considered to be safe by 16% of the patients and 33% of all users failed to tell their physicians. Furthermore, 15% of the women and 7% of the men believed that complementary therapies do not interact with other medications. As the popularity of complementary medicine rises, so does the research interest in this subject (12), including research into direct and indirect risks (13–15).

However, this notion is dangerously misleading; adverse effects have been associated with the use of complementary therapies (16). Furthermore, complementary therapies may not only be directly harmful (for example adverse effects of herbal formulations), but like other medical treatments have the potential to be indirectly harmful (for example through being applied incompetently, by delaying appropriate effective treatment, or by causing needless expense) (17).

The efficacy of many complementary therapies is largely unknown, and more definitive evidence is urgently needed (18). Like any other interventions, complementary therapies are associated with adverse effects, and for responsible therapeutic decision-making, the balance of benefits and harms must be considered (19).

Incidence of adverse effects

Most of the data on adverse effects associated with complementary therapies is anecdotal, and assessment and classification of causality is often not possible. Likewise, there have been few attempts to determine systematically the incidence of adverse effects of non-orthodox therapies.

Two prospective interview surveys have generated incidence figures for adverse effects associated with chiropractic treatment. In a Norwegian investigation (20), 102 chiropractors were asked to monitor 1058 new patients. At least one adverse effect was reported by 55% of the patients at some time during the course of a maximum of six treatments. The most common adverse effects were local discomfort (53% of total), headache (12%), tiredness (11%), or radiating discomfort (10%). A Swedish survey used similar methods to monitor 1858 chiropractic consultations and demonstrated an incidence rate for adverse effects of 44% (21). In both studies, all effects noted were mild and transient; no serious effects were recorded.

In a prospective Japanese survey of adverse effects of acupuncture, 55 291 treatments were monitored between 1992 and 1997 (22). There were 64 adverse events in all; none was serious or led to permanent damage.

General adverse effects

Even a perfectly safe remedy (mainstream or unorthodox) can become unsafe when used incompetently. Medical competence can be defined as doing everything in the best interest of the patient according to the best available evidence. There are numerous circumstances, both in orthodox and complementary medicine, when competence is jeopardized:

- missed diagnosis
- misdiagnosis
- disregarding contraindications
- preventing/delaying more effective treatments (for example misinformation about effective therapies, loss of herd immunity through negative attitude towards immunization)

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- clinical deterioration not diagnosed
- adverse reaction not diagnosed
- discontinuation of prescribed drugs
- self-medication.

The most obvious danger is that some patients (or their parents) may elect to abandon conventional therapies for serious diseases in favor of alternative approaches. This can have fatal consequences (23). Survey data suggest that a sizeable proportion of complementary practitioners advise their clients to reduce their prescribed medication (24).

Diagnostic techniques can also cause serious risks; an example is the apparent over-use of X-rays by chiropractors (25). Although this practice seems to be in decline, it can put patients at risk through the mutagenic effects of X-rays.

The attitude of consumers towards complementary medicine may also constitute a risk. When 515 users of herbal remedies were interviewed about their behavior vis-a-vis adverse effects of herbal versus synthetic over-the-counter drugs, a clear difference emerged. While 26% would consult their doctor for a serious adverse effect of a synthetic medication, only 0.8% would do the same in relation to an herbal remedy (26). A further risk might lie in the plethora of lay books on complementary medicine now available in every High Street bookstore. A pilot project has attempted to evaluate the value of a random selection of such books and concluded that the lay literature on complementary medicine is far from adequate and has the potential to put the health of the reader at risk (27).

The fear has been expressed that "with the increased interest in alternative medicine, we [shall] see a reversion to irrational approaches to medical practice" (28). The only way to minimize incompetence is proper education and training, combined with responsible regulatory control. While training and control are self-evident features of mainstream medicine they are often not fully incorporated in complementary medicine. Thus the issue of indirect health risk is particularly pertinent to complementary medicine. Whenever complementary practitioners take full responsibility for a patient, this should be matched with full medical competence; if on the other hand, competence is not demonstrably complete, the practitioner in question should not assume full responsibility (29).

Misinformation

More and more patients seek advice on complementary medicine via the Internet. It is therefore important to monitor the validity of such advice. In one survey, most of the 13 most popular websites on complementary medicine for cancer recommended cancer therapies for which there was no evidence of efficacy (30). Three of the sites overtly discouraged cancer patients from using conventional therapies. When the study was repeated, this time focussing on HIV instead of cancer, the results were virtually identical (31). These findings were similar to those of another study of 61 popular websites on herbal medicines for cancer (32). Most of these sites were commercial by nature and claimed cancer cures through herbal medicines, with little regard for current regulations.

Herbalists readily volunteer advice about the administration of herbal medicines during pregnancy, but the nature of their advice is misleading at best and dangerous at worst (33). Others have studied the impact of herbal medicine on the use of conventional treatments (34). Their results showed that 32% of female patients in internal medicine delayed obtaining conventional care while waiting for an herbal medicine to work.

Attitudes to immunization

The indirect risks of complementary medicine are grossly under-researched, and at present we can but guess the size of the problem (35). There are, however, particular aspects on which some data do exist. One is the attitude of practitioners towards immunization. The majority of homeopaths (36–38) and chiropractors (39) are unconvinced of the benefit of immunization. They claim that it causes more illness than it prevents disease and advise, in many instances successfully, their patients against it (40).

When 1593 visitors to a "health fair" were surveyed on their use of complementary medicine, it emerged that elderly users were significantly less likely to use influenza immunization (41). Students of a Canadian chiropractic college were questioned about whether they agreed with immunization in general. The longer they had attended college, the less favorable their attitude toward immunization became (42). An analysis of the contents of 22 leading anti-immunization websites showed that about 70% of these sites claimed that homeopathy represented an alternative to conventional vaccination (43). In a similar study it was found that 39% of the anti-immunization websites claimed that natural lifestyle conveys immunity to infections, thus allegedly rendering immunization unnecessary, and 45% claimed that "alternative health" is superior to immunization (44). In another study homeopaths and chiropractors were specifically asked about their advice regarding MMR immunization; 40% of the homeopaths and 19% of the chiropractors admitted advising mothers against it (45).

This attitude not only exposes individual patients to unjustifiable risks, but also jeopardizes herd immunity, thus representing a threat to public health. A homeopathic remedy might be totally safe, but the homeopath might not be (46).

Acupuncture

On a global basis, acupuncture is one of the most commonly used forms of complementary and alternative medicine. It is used predominantly to alleviate pain, but many other indications have been proposed. Contrary to prevailing public opinion it is not entirely risk free (47). Several review articles have addressed this issue, and it has been pointed out that tissue trauma (for example pneumothorax) and infections (for example hepatitis B) are the most common complications of acupuncture (48). Both are rare and both could be avoidable with adequate training and experience of acupuncturists.

Acupuncture can cause various minor adverse effects (49) and there have been many reports of serious complications (Table 1). The authors of a review of the risks

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Table 1 The most common serious complications of acupuncture

Condition	Number of cases in the world literature
Cardiac trauma	<10
Contact dermatitis	<10
Drowsiness	~100
Endocarditis	<10
Erythema	<10
Hepatitis	~130
Perichondritis	~10
Peripheral nerve injury	<10
Pneumothorax	>90
Renal injury	~20
Retained needle	~10
Septicemia	<10
Spinal cord injury	~20
Syncope	~50

associated with acupuncture mentioned pneumothorax (more than 90 cases on record), cardiac tamponade ($n = 6$), injuries of the spinal cord ($n = 10$), and infections ($n = 126$), particularly hepatitis (50).

Some reports of complications after acupuncture are summarized in Table 2.

Acupuncture keeps being associated with serious adverse events (61), and several attempts to define the size of this problem more closely have been published.

In a prospective investigation of the adverse effects of Japanese acupuncture, all adverse effects experienced by patients in an acupuncture clinic seen between November 1992 and October 1997 were recorded (22). There were 64 adverse events. Failure to remove the needles, dizziness, discomfort, and sweating were the most frequent adverse reactions. There were no serious adverse events. These data suggest that superficial needling as used in Japanese acupuncture is relatively safe.

A Japanese survey of 391 patients who received acupuncture in 1441 treatment sessions involving a total of 30 338 needle insertions showed the following systemic adverse effects: tiredness (8.2%), drowsiness (2.8%), aggravation of the presenting condition (2.8%), itching in the punctured region (1.0%), dizziness or vertigo (0.8%), faintness or nausea during treatment (0.8%), headache (0.5%), and chest pain (0.3%) (62). The incidences of local reactions were: minor bleeding after withdrawal of the needle (2.6%), pain on insertion of the needle (0.7%), petechiae or ecchymoses (0.3%), local pain after treatment (0.1%), subcutaneous hematomas (0.1%).

Norwegian researchers sent questionnaires about acupuncture to a random sample of the Norwegian general population (63). Of the 653 respondents, 7% claimed to have had adverse effects. The most common were dizziness, fatigue, and pain from the needles. No serious adverse effects were reported.

In a prospective UK survey of members of the medical and physiotherapy acupuncture organizations in Britain the preliminary data included 25 500 treatments given by 77 acupuncturists (64). There were 29 major events, including four episodes of loss of consciousness and one tonic-clonic seizure. The most common minor events were bleeding or hematoma (3%), aggravation of symptoms (1%), and pain during needling (0.9%).

In a survey of 1100 Australian providers of traditional Chinese medicine the adverse events of acupuncture were also monitored (65). There were 3222 events, including 64 cases of pneumothorax and 80 convulsions. No deaths were recorded.

A systematic review of case reports from the Japanese literature yielded 105 cases of suspected acupuncture adverse effects not previously reported in Western publications (66). These included 21 spinal lesions, 21 cases of pneumothorax, 19 infections, 15 cases of foreign bodies in organs, 10 instances of argyria, 10 neural injuries, and 11 other adverse events, including two cases of cardiac tamponade.

A systematic review of all prospective studies of adverse effects associated with acupuncture included nine primary investigations (67). The most commonly reported adverse events were needle pain (1–45%), tiredness (2–41%), and bleeding (0.03–38%). Pneumothorax was the only serious complication in these studies; it was reported twice in about 250 000 patients.

Table 2 Reports of adverse events associated with acupuncture

Indications	Adverse event	Site of acupuncture	Causality	Reference
Presumably local pain	A closed ankle fracture was converted to an open fracture and open joint by acupuncture	Local	Likely, but insufficient details reported	(51)
Intermittent claudication	Occlusion of the popliteal artery	Local	Likely	(52)
Back pain	Rupture of a pseudoaneurysm	Local	Likely	(53)
Arthritis	Pneumothorax	The neck	Likely	(54)
Shoulder stiffness	High cervical epidural abscess and vertebral osteomyelitis	Posterior nuchal region	Fairly certain	(55)
Not stated	Peritemporomandibular abscess	Local	Fairly certain	(56)
Back pain	Unilateral septic sacroileitis	Local	Likely	(57)
Arthritis	Death due to streptococcal toxic shock-like syndrome	Right shoulder	Probable	(58)
Back pain	Argyria 10 years after acupuncture with a silver needle	Ear	Possible	(59)
Stroke (2 cases)	Angina pectoris during electroacupuncture	Scalp	Possible	(60)

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Two prospective UK studies with a total of about 70 000 consultations have confirmed that serious adverse events of acupuncture are true rarities in Britain (68,69). Bleeding and needle pain were the most frequent adverse events, with a prevalence of about 1:1000.

A systematic review of all adverse events associated with acupuncture in the Japanese medical literature located 124 cases (70). These included 25 cases of pneumothorax, 18 cases of spinal cord injury, 11 cases of hepatitis B, and 10 cases of localized argyria.

- An 82-year-old woman was scheduled for gastrectomy with an epidural anesthetic (71). She had previously had many acupuncture treatments with a Japanese technique (okibari), in which small needles are left in situ. Her preoperative chest and abdominal X-rays showed hundreds of needles around the vertebrae. The anesthesiologists feared that an epidural anesthetic might lead to spinal cord injury or pneumothorax, and general anesthesia was chosen instead.

Cardiovascular

Acupuncture has been associated with hemopericardium due to ventricular puncture (72).

- An 83-year-old Austrian woman developed syncope and cardiogenic shock shortly after acupuncture over the sternum. Echocardiography showed cardiac tamponade and pericardiocentesis revealed hemopericardium. At operation a small bleeding perforation of the right ventricle was found and closed. The acupuncture at the point "Ren 17" was above a sternal foramen, which allowed the needle to penetrate the heart.

A case in which acupuncture was apparently responsible for cardiac dysrhythmias has been reported (73).

Respiratory

Pneumothorax has been reported in association with acupuncture (74,75).

- A 28-year-old Chinese woman developed bilateral pneumothoraces after receiving acupuncture in the upper thoracic and paraspinal regions (75). She was treated conservatively and was discharged after 2 days.
- A 30-year-old woman developed bilateral chest pain and dyspnea after paraspinal acupuncture resulted in bilateral pneumothorax; she recovered fully within 2 days (76).

Nervous system

Acupuncture has been associated with subarachnoid hemorrhage due to arterial puncture (77).

- A 44-year-old Chinese man had severe occipital headache, nausea, and vomiting during acupuncture in the posterior neck. A CT scan showed hemorrhage in the third, fourth, and lateral ventricles, and blood was found in the lumbar fluid. The problem was due to puncture of a branch of the vertebral artery at the "feng fu" point, which coincides with the site for performing cisternal puncture. The patient made a spontaneous full recovery within 28 days.

Convulsions, inadvertent anesthesia, loss of co-ordination, and tinnitus have been associated with acupuncture (78).

Endocrine

Galactorrhea has been associated with acupuncture.

- A 41-year-old woman with breast cancer was treated with acupuncture for pain control (79). She had an episode of galactorrhea 6 days after the first treatment and also during the second acupuncture treatment. No reason for this unusual phenomenon other than acupuncture could be found.

The authors pointed out that in Chinese medicine acupuncture at the points used in this patient promotes lactation.

Skin

Acupuncture needles can cause local reactions (80).

- A 55-year-old Japanese woman developed papules at sites where she had had acupuncture 4 years and 3 weeks before. Histological examination showed that the papules were silicone granulomas.

The authors postulated that the papules were reactions to the silicone from the coating of the acupuncture needles.

Skin malignancy (78) and Koebner phenomenon (81) have been associated with acupuncture.

- A 52-year-old man received acupuncture in the backs of both hands for chronic back pain and subsequently developed bilateral swelling of both hands and fingers (82).

No reason for this adverse effect could be found, and the authors considered infection or allergy as the most likely cause, but without finding strong evidence of either.

- A 59-year-old woman presented with a 1-month history of non-pruritic papules on the dorsa of both feet (83). During the previous year she had repeatedly received acupuncture in this area. A biopsy showed mixed lichenoid, spongiotic, and granulomatous dermatitis. Ultrastructural examination showed macrophages containing silicone. At follow-up new lesions on her mid calves were noted, and again she explained she had recently received acupuncture at these sites.

It was discovered that the acupuncturist used silicone-coated needles and silicone deposition was thus caused by acupuncture.

Immunologic

Allergies to the various metals used in acupuncture needles have been described (84).

Infection risk

Acupuncture needles must be handled meticulously to guarantee sterility of the needle on insertion. If such safety rules are not strictly adhered to, there is a high risk of transmitting infectious diseases. In principle one can assume that any blood-borne infection is transmittable through the misuse of acupuncture needles.

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Bacterial infections

Osteomyelitis (85), endocarditis (86,87), or generalized *Staphylococcus aureus* infections (88) have been associated with acupuncture.

- A 67-year-old Japanese man was treated with "depot acupuncture," an unusual technique involving the implantation of a sheep gut thread through a spinal anesthesia needle into the abdomen (89). He subsequently developed intractable pain, high fever, and other signs of infection. A CT scan showed a low density mass in the left psoas muscle and the ventral portion of the distal aorta, corresponding to an abscess and a false infected aneurysm. The affected part of the aorta was replaced with a Gore-Tex graft and the patient was treated with antibiotics. He eventually made a full recovery.

In a review of serious complications there were three cases of infection, one of auricular perichondritis that resulted in permanent disfigurement, one of bacterial meningitis with full recovery, and one of pyarthrosis also with full recovery (90).

Microbiologists from Hong Kong have reported four cases of mycobacterial infections within 2 years (91). All the patients had lesions at acupuncture points. Acid-fast bacilli were present in two cases. Gene sequencing identified the strain from two patients as *Mycobacterium chelonae* and from two patients as *Mycobacterium nonchromogenium*.

- A 37-year-old man with diabetes had septicemia and compartment syndrome of the leg after acupuncture in the calf area (92). Decompression fasciotomy was performed and Gram-positive cocci were grown from the wound swab and group A streptococci from blood cultures. He required intensive care, including intravenous antibiotics, and eventually recovered.
- Endophthalmitis occurred in a patient from Singapore (93). Group B streptococci were isolated from the blood. Despite aggressive intravitreal antibiotic therapy the affected eye lost its light perception.
- A 79-year-old woman presented with induration of the right leg three months after receiving acupuncture in this area (94). Radiography showed a focal dystrophic calcification at this point and histological studies showed suppurative granulomatous inflammation with microabscesses and caseous necrosis due to infection with *Mycobacterium chelonae*. She made a full recovery after antibiotic treatment.
- A 42-year-old woman with Marfan's syndrome, who had previously had an aortic root and valve replacement, presented with fever and polyarthralgia 6 days after receiving acupuncture for back pain (95). Examination of the valve showed no abnormalities, but *S. aureus* was grown from blood cultures. Extensive investigations did not identify a cause for the infection. Her condition deteriorated despite antibiotic therapy, and emergency aortic root and valve replacement became necessary. She eventually made a full recovery.

Virus infections

In at least three published case reports, acupuncture was the only plausible explanation for infections with HIV (96,97).

Hepatitis infections may be transmitted in this way (98–100). A retrospective cohort serological study identified five confirmed cases of acute hepatitis B virus infection within 3.5 years related to one London acupuncture clinic (101). The acupuncturist was hepatitis B-positive and the strain of his virus was identical to that from the patient. Nine further patients of his had antibodies to the hepatitis B core antigen but had other risk factors for hepatitis B infection.

After a patient of a London doctor (who practiced an unusual acupuncture technique involving re-injection of native blood) acquired hepatitis B, 352 of his patients treated by this method were investigated; 33 were positive for hepatitis B antigen and 30 showed complete nucleotide identity in the DNA segments derived from the surface and core genes (102). Contaminated saline used in the treatment was identified as the probable vehicle of transmission.

An epidemiological screening program in 2231 subjects in Japan was aimed at defining the risk factors of hepatitis C infection (103). It showed that the relative risk was increased (1.30, CI = 0.65, 2.61) in those participants who had received acupuncture. A newspaper article reported that 21 confirmed cases of hepatitis B were related to a London-based physician who practiced an obscure variation of acupuncture (104).

A nationwide community-based survey in Taiwan has been carried out in seven locations in a total of 11 904 men tested for antibodies against hepatitis C virus. Exposure to acupuncture was a risk factor for hepatitis C positivity (105).

Korean epidemiologists have studied the prevalence of hepatitis C virus infection in a rural population ($n = 1033$) with a high incidence of liver cancer (106). They noted that the strongest associations in a multivariate analysis were with anti-HCV positivity and the use of acupuncture (OR = 2.2, 95% CI = 1.0, 4.7).

French investigators have evaluated the presence of serum markers of hepatitis A, B, and C viruses in a rural population of 303 volunteers (107). The main risk factors for positivity were past hospitalizations (72%), acupuncture (18%), conjugal unfaithfulness (11%), blood transfusion (9.4%), tattoos (5.8%), homosexuality (1.1%), and intravenous drug addiction (0.73%).

Trauma

If acupuncture, which entails tissue trauma, is performed properly and on the correct acupuncture points, trauma will affect only the skin and the connective tissue below. If, however, acupuncture needles are inserted at the wrong site or penetrate too deeply, other tissues or organs can be affected. Traumatic complications of acupuncture have been reviewed (108). They have been described in relation to the thoracic and abdominal viscera, in the peripheral and central nervous systems, and in blood vessels. Several deaths have been reported from pneumothorax and cardiac tamponade. The anatomical tissues at several acupuncture points are such that needles can injure vulnerable structures. Thus, good knowledge of anatomy is an essential precondition for acupuncturists.

One review identified 32 cases of pneumothorax and two of hemothorax (109). Damage to the middle ear

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(following auriculoacupuncture), injury to the spinal cord (49), and cardiac tamponade have been other serious traumatic complications (110,111). Needles can also break while in situ, and parts of acupuncture needles have been found in patients' kidneys (112), carpal tunnel (113), cervical spine (114), spinal cord (115), and heart (116). Petechiae and other forms of bleeding have also been reported (109). If a nerve is punctured the patient might experience unnecessary pain and even sustain minor nerve damage, which in extreme cases can be persistent. In another case there was a delayed traumatic effect of an acupuncture needle fragment (117).

- A 43-year-old man developed a false aneurysm of the popliteal artery after a penetrating injury from an acupuncture needle (118). The aneurysm ruptured spontaneously, but the patient was successfully managed by vascular surgery.

A review of serious complications included one case of cardiac tamponade (with full recovery of the patient after surgery), one case of peripheral nerve damage (foot drop with residual weakness after 6 years), and three cases of pneumothorax (all with full recovery) (90).

A further case of pneumothorax has been reported (119).

- A 60-year-old woman was treated by a non-medically qualified acupuncturist for chronic rib pain. About 15 needles were inserted along either side of her back, and one (in the right lower thoracic region) caused immediate discomfort. After removal of the needle she noted pain and breathlessness. A chest X-ray 2 days later confirmed a small right pneumothorax, which resolved spontaneously within one week.

Pregnancy

Abortion and miscarriage (49) have been associated with acupuncture.

Fetotoxicity

Acupuncture in pregnant women might carry a risk for the fetus, since it is postulated that acupuncture can increase oxytocin release in the mother, which might harm the unborn child (120).

Aromatherapy

Aromatherapy is a highly popular form of complementary medicine usually entailing the application of essential plant oils to the skin by gentle massage. It has been shown to have relaxing effects but other claims have not been substantiated by reliable trial evidence (121). Allergic airborne contact dermatitis occurred in a patient who had previously used several essential oils for aromatherapy (122). The toxicity of essential oils has been reviewed (123).

Four cases of allergic contact dermatitis caused by essential oils used in aromatherapy have been described (124). A survey of UK aromatherapists (no details provided) yielded 11 reports of adverse effects (125). Most of these cases seemed to relate to allergic reactions to the essential oils. A therapist also reportedly developed an allergy to ylang-ylang oil used in aromatherapy (126).

Japanese dermatologists have reported an increase in positive patch tests to lavender oil from 1.1% in 1990 to 14% in 1998 (127). The authors argued that this rise coincided with a similar increase in the use of lavender aromatherapy in Japan and that the latter had caused the former.

See also monographs on substances that affect the skin.

Cell therapy

Cell therapy consists of the parenteral or enteral administration of cells or parts of cell obtained from animal organs and/or tissues from cattle, sheep, pigs, or rabbits. Two different types of cell preparations are in use: fresh cells, which are administered in fresh form, and dried cells or so-called sicca cells, which are prepared for later use. The most prevailing risks of cell therapy are local and generalized allergic reactions (fever, nausea, vomiting, urticaria, and anaphylactic shock). Other untoward consequences include fatal and non-fatal encephalomyelitis, polyneuritis, Landry–Guillain–Barré syndrome, fatal serum sickness, perivenous leukoencephalitis, and immune-complex vasculitis.

Homeopathy

Most, although not all, homeopathic remedies are too dilute to cause toxic effects. However, potentially toxic concentrations of arsenic (128) and cadmium (129) in homeopathic remedies have been described. Concern has also been voiced about potentially carcinogenic effects of low potencies of *Aristolochia* (130). Acute pancreatitis has been reported after the administration of a complex homeopathic formulation containing 19 different ingredients (131). Low potencies can also cause allergic reactions (132,133) and cases of severe allergic and anaphylactic reactions have been reported. In cases of concomitant drug treatments, interactions are conceivable, even though there is no published evidence on this matter. Generally speaking, adverse reactions to homeopathic medications are probably rare. However, we cannot at present tell their true incidence, as no definitive study of this has been carried out.

A systematic review of all data on the safety of such medicines has challenged the view that because homeopathic remedies are often highly dilute they are therefore devoid of adverse effects (134). It showed that in placebo-controlled trials the mean incidence of adverse effects of homeopathic remedies was 9.4%, higher than that of placebo (6.1%). All the adverse effects were minor and transient. Anecdotal reports of more serious adverse effects mainly related to aggravation of presenting symptoms, which, from the homeopathic point of view, can be looked on as confirmation that the optimal remedy has been found, and thus interpreted as a positive event. Since the homeopathic principle is that like cures like, exacerbation of symptoms by what can be presumed to be toxic doses of a supposed remedy confirms that the remedy causes the problem and will therefore cure it if given in homeopathic doses.

Harm can also be done when an ineffective homeopathic intervention replaces an effective conventional one (135).

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- A 40-year-old woman travelling to a malaria-infested region took her homeopath's advice and was "immunized" with homeopathic remedies (*Ledum palustre* 5CH and *Malaria officinalis* 4CH) instead of taking conventional protection. She contracted malaria and had to be treated for 2 months in intensive care for multiple organ system failure due to *Plasmodium falciparum*.

Seven Israeli children were seriously harmed when their parents used homeopaths and other providers of complementary medicine instead of conventional doctors; four died (136). Similarly, it has been reported that seeing a traditional healer in Kenya increased the risk of dying from an acute pneumonia by 5.3 times (137).

The author of a review of the safety of homeopathic products concluded that they are usually safe, but that continued vigilance is in order, not least because of the currently high popularity of homeopathy (138). In response, it was pointed out that under-reporting is high, that homeopathic products are often mistaken for herbal medicines, and that the main risks of homeopathy relate to the prescriber rather than the medicine (139).

Hypnosis

Hypnosis is not usually seen as a treatment burdened with adverse effects. However, an authoritative review has reminded us that it is by no means completely safe (140). Complications include amnesia, catharsis, paralysis, disorientation, literalness of response, accelerated transference, and memory contamination. A further unwanted effect of hypnosis is an inability to dehypnotize the patient. A review of the literature has shown several such cases and has contributed two new such incidents (141).

Manipulation

Manipulative therapies (chiropractic and osteopathy) are amongst the most prevalent of complementary treatments. Spinal manipulation is carried out by chiropractors, osteopaths, physiotherapists, and other healthcare professionals to treat back and neck pain as well as other (predominantly musculoskeletal) disorders.

A literature review has provided reassurance about the relative safety of spinal manipulation (142). When the serious adverse effects of non-steroidal anti-inflammatory drugs were compared with those of spinal manipulation, both used for neck pain, manipulation emerged as being safer by more than two orders of magnitude. However, these procedures can be associated with serious complications, particularly when they involve the cervical spine (143).

In a survey of UK physiotherapists trained in spinal manipulation, 19% reported having encountered complications of spinal manipulation (144). These related mostly to the upper spine and were mostly not serious. A further survey of 686 general practitioners in the UK disclosed 28 serious adverse effects related to spinal manipulation (145).

An authoritative summary of all cases of complications of spinal manipulation of the cervical spine published since 1925 has appeared (146). There were 177 cases of severe injury. The most common injuries involved arterial dissection or spasm and brain stem lesions. In 32 instances (18%) they were fatal. The author concluded that high velocity thrusts of the cervical spine are not demonstrably associated with more benefit than harm and should therefore be avoided.

In the UK 108 consecutive patients of chiropractors were asked to complete a questionnaire, which 80% of them returned (147). Of the questionnaires 68% were suitable for analysis. Adverse effects at 1 hour after treatment were reported by 28 patients and eight had adverse effects the morning after treatment. The most common adverse effects were extra local pain or radiating pain. No serious adverse effects were reported.

Some chiropractors tend to advise clients against any type of immunization. The basis of this attitude seems to lie in early chiropractic philosophy. Eschewing the germ theory of infectious disease, this philosophy considered any disease to be the result of spinal nerve dysfunction caused by misalignment of vertebrae (148). When 150 US chiropractors were questioned about their attitude towards immunization, only 30% reported recommending childhood immunizations (149).

A systematic review of all prospective studies of the risks associated with spinal manipulation included five primary investigations (150). The most valid studies suggested that about half of all patients who see a chiropractor will have adverse effects, which are usually mild and transient. No reliable data about serious adverse events were uncovered. However, a review of recent case reports has shown that spinal manipulation was associated with several serious adverse effects, including dissection of the vertebral and internal carotid arteries, resulting in strokes and at least one death (151). Other instances relate to epidural hematoma, intracranial aneurysm, cauda equina syndrome, contusion of the spinal cord, myelopathy, radiculopathy, and palsy of the long thoracic nerve.

A report on malpractice suits in the USA has shown that in 1990–96 claims against chiropractors have been constant (between 2.3 and 3.0 claims per 100 policy holders per year) (152). There were about four times more claims against primary care physicians. The percentage of claims paid varied between 46 and 57% for the chiropractors and 29 and 33% for the physicians. The three most frequent reasons for the claims against chiropractors were disc herniation, failure to diagnose, and bone fractures produced through treatment.

The frequency with which chiropractors use radiology of the spine might be a cause for concern. Among Dutch chiropractors 40% have been reported to use X-rays "often or always" (153). In the USA, 96% of chiropractors use X-rays routinely on all new patients, and 80% use them in follow-up (154).

Cardiovascular

The Stroke Council of the American Heart Association registered 359 cases of vascular accidents until 1981 (155). In Switzerland 1255 such incidents were recorded in 1 535 000 manipulations (156). Others estimated the incidence of reported vascular accidents at 1–4 per million treatments (157–159). The mortality/severe long-term

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impairment rate is 28% (160). The incidence is higher if minor symptoms are included and specifically searched for: out of a total of 75 500 procedures applied, 25 such cases were reported (161). The reported incidence rates are probably a gross under-estimation of the true figures; in a series of 13 cases of clinically and radiologically verified vertebral artery dissection, eight were spontaneous, two occurred after manipulation, and three occurred after minor injury (162).

The mechanisms of vascular complications of cervical manipulations involve vertebral artery dissection, intramural bleeding or pseudo-aneurysm leading to thrombosis or embolism (160) as well as transient cerebral ischemia through mechanical artery compression during cervical rotation (163) and vasospasm (164). The vertebral artery at the C1/C2 segment is most often affected. Combined rotation, extension and traction movements apparently create the highest risk, particularly when executed forcefully (165). The most frequent clinical findings are Wallenberg's syndrome (28%), other brain stem syndromes (49%), cerebellar syndromes (8%), occipital lobe syndromes (5%) and unclassified syndromes (160). They usually occur during or promptly after the intervention, but delays of hours or days have also been observed (159,166,167). Symptoms can start as headache and neck pain, which are frequent reasons for applying manipulative therapies in the first place. In at least one case neck pain was the first sign of dissection, which was treated by manipulation, resulting in a fatal stroke (168).

- Two patients had oculosympathetic palsy after self-treatment with a "shiatsu massager" (169). A thorough diagnostic work-up, including MRI and MRA scans, identified dissection of the carotid artery as the cause of the problem. In the absence of other causes, the authors believed that the self-treatment had caused dissection.
- A 32-year-old woman who had seen a traditional American "bone-setter" for shoulder problems was subjected to a "sudden thrusting of the head upward and to the right" (170). She had neck discomfort immediately afterwards. The pain persisted for 6 days, when she noted vertigo and left-sided ataxia. An MRI scan showed acute infarction in the middle left cerebellar hemisphere and vermis. An MRA scan showed left vertebral artery dissection with a probable embolus.

When all 26 cases of vertebral artery dissection during the period 1989–99 were retrospectively analysed in a tertiary Canadian academic center, possible precipitating factors were identified in 14 patients (171). Chiropractic spinal manipulation and sporting activity were the most common factors (11% and 15% respectively).

Nervous system

Several reports of nervous system adverse effects after spinal manipulation have been published (172–174). They are summarized in Table 3.

Of 13 consultant neurologists in the Republic of Ireland 11 had seen a total of 16 patients with neurological complications after chiropractic spinal manipulation within 5 years; strokes were the most frequently reported problem, and in 13 cases had led to persistent neurological deficits (175).

A survey of 177 members of the American Academy of Neurology aimed to find out how many adverse events related to chiropractice had been noted by these doctors within a 2-year period. Chiropractic interventions were associated with 55 strokes, 16 cases of myelopathy, and 30 cases of radiculopathy (176).

A Ukrainian doctor has reported a series of 49 additional cases with neurological complications after spinal manipulation (177).

Swedish authors have summarized cases reported to three Swedish insurance companies within 2 years (178). They found 21 cases associated with the cervical spine, six associated with the thoracic spine, 13 with the lumbar spine, and 14 with the sacro-iliac joints. Cervical spinal manipulation had caused damage to the vertebral artery with subsequent paralysis in three cases and disk herniation in three cases. Lumbar spinal manipulation had caused disk herniation in six cases, three of whom suffered severe and persistent problems.

German neurologists have reported 10 cases of ischemic stroke due to either vertebral arterial dissection ($n = 8$) or internal carotid artery dissection ($n = 2$) after chiropractic spinal manipulation (179). There were no identifiable predisposing factors. In three cases the dissections were bilateral. The onset of symptoms was immediate ($n = 5$) or delayed by up to 2 days. Neurological deficits developed during up to 3 weeks. In five patients the eventual clinical outcome was good while marked deficits persisted in three patients. One patient continued to suffer from a locked-in syndrome and another was in a persistent vegetative state.

- A 34-year-old woman had pain, dizziness, vomiting, and diplopia immediately after cervical spinal manipulation (180). An MRI scan showed a left cerebellar infarction, and duplex sonography showed dissection of both vertebral arteries leading to 50% occlusion on the right side and total occlusion on the left side.
- A 46-year-old man consulted a traditional Chinese "bone setter" for persistent neck pain (181). The healer had "forcefully rotated his head to one side and then to the other side." The patient immediately developed numbness of the whole body and dyspnea. An MRI

Table 3 Reports of adverse events associated with spinal manipulation

Indication	Adverse event	Site of manipulation	Therapist	Causality	Reference
Back pain	Cauda equina syndrome	Lumbar	Traditional healer	Likely	(172)
Cervical pain	Brown–Séquard syndrome due to contusion of the spinal cord	Cervical	Chiropractor	Fairly certain	(173)
Neck pain	Vertigo, profuse vomiting	Cervical	Chiropractor	Certain	(174)

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scan showed incomplete cervical cord injury with mild cervical cord swelling. He was treated with high-dose methylprednisolone and made a good recovery with only minimal persistent deficits.

- A 67-year-old woman had spinal manipulation for neck pain and experienced severe pain (182). She subsequently noted weakness of her left side, which worsened rapidly and also affected bladder function. She had a left-sided ptosis, all sensation was impaired below C6, and she had urinary incontinence. An MRI scan showed an epidural hematoma in the left posterolateral aspect of the spinal cord at C3–C5. Laminectomy was performed and a large epidural hematoma was removed. She subsequently made a full recovery.
- A 34-year-old man with a whiplash injury consulted a chiropractor for his neck pain, and 36 hours after one particularly painful treatment he experienced throbbing, positional headache, dizziness, diplopia, otorrhea, and rhinorrhea (183). After thorough neurological examination the author concluded that the patient had suffered a dural tear due to cervical manipulation.
- A 34-year-old woman had memory loss, ataxia, and poor co-ordination of the right arm associated with right neck pain after consulting a chiropractor (184). An MRI scan confirmed a right cerebellar infarct, most probably caused by upper spinal manipulation. She made a full recovery within 1 month.
- A 41-year-old man with neck pain sought chiropractic care and the evening after felt unable to breathe in the recumbent position (185). Diaphragmatic paralysis was attributed to phrenic nerve injury during cervical manipulation. He remained short of breath and had persistent difficulties breathing in the supine position.

A highly unusual case of thoracic epidural hematoma after spinal manipulation of the lumbar spine has been reported (186).

- A 64-year-old woman experienced acute severe pain and progressive neurological defects for the first time during spinal manipulation. Swift surgical intervention was initiated and a thoracic epidural hematoma was evacuated. This resulted in complete recovery.

A survey of 323 UK neurologists disclosed 35 previously unreported cases of serious neurological complications of spinal manipulation (187). This means that in this particular series, under-reporting of adverse events had been 100%.

Musculoskeletal

Dislocations and fractures of vertebrae have also been reported and are not confined to the upper spine (188,189). Patients with osteoporosis are at high risk; manipulation is therefore contraindicated in these individuals. Nerve lesions range from plexus paralysis and ophthalmoplegia to tetraplegia, disk herniation, and phrenic nerve palsy (188,190). A review of the English language literature included 89 neurological complications after manipulation; the number of unreported cases could be considerably higher.

Massage

There are many different forms of massage therapy, which are not normally associated with serious adverse effects. However, trauma can occur (191).

- A 39-year-old woman with an unremarkable medical history underwent deep body massage, including the abdomen. Within 24 hours she experienced discomfort and nausea and after 72 hours she had a CT scan, which showed a large hematoma in the right hepatic lobe. There was no evidence of a plausible cause for this. In spite of adequate medical treatment, her recovery was slow and she had nausea and low-grade fever for about 6 months.
- An 80-year-old Japanese man with a recent history of cerebral infarction received a shiatsu massage in the neck area to relieve a headache (192). Immediately after he had right visual field impairment. Thorough ophthalmological and neurological show multiple branch occlusions of the central retinal artery and multiple small infarctions in the right frontoparietal lobe. He was given urokinase for 7 days, and made an almost complete recovery.

The authors of the second report concluded that forceful neck massage had caused the problem.

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Conorfone

See also Opioid analgesics

General Information

Conorfone is an opioid analgesic, a codeine derivative, with mixed agonist–antagonist activity (SED-11, 150). It has adverse effects similar to those of codeine, but causes more drowsiness (1).

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Contact lenses and solutions

General Information

There are two types of contact lenses, soft and hard; most are manufactured from methacrylate polymer (http://www.eyecarecontacts.com/contact_lenses_reports.html).

Soft lenses are made of hydrophilic hydrogel polymers that contain 36–74% water. Other plastics and copolymers are added to alter the physical characteristics of the lens. The diameter is 10.5–15.5 mm and the thickness at the center 0.03–20 mm. Soft lenses can correct most optical defects, including myopia, hyperopia, and astigmatism. Bifocal lenses are also available. They can be colored with either transparent hues or opaque patterns to change apparent eye color or to mask malformations of the cornea or iris. They are available for daily, weekly, and twice-weekly disposable use, 1–3 months frequent replacement, and annual replacement.

Hard lenses are made from gas-permeable materials that contain silicon and fluorine. They can correct most optical defects and have diameters of 8–10 mm.

Some lenses combine soft and hard materials, including hard lenses with soft surfaces and lenses with a hard center and a soft periphery.

The ocular risks related to the use of contact lenses are due not only to the lenses themselves, but also to the toxic or allergic effects of cleaning solutions (1) and the preservatives that they contain. The latter are also found in various eye-drops. Preservatives have adverse effects on the corneal epithelium and endothelium. Eye-drops that contain preservatives should not be used during surgery or in patients with ocular surface disease, in cases of perforating injury.

Organs and Systems

Sensory systems

Ulcerative keratitis is considered the most serious adverse effect of the use of soft contact lenses.

The risk can be greatly reduced by avoiding overnight wear of the lenses (2,3). In one study extended wear was associated with a 5–6 times higher risk of keratitis than daily wear was (4).

Soft contact lenses, especially extended-wear lenses, carry a significantly higher risk of keratitis than hard lenses do. In a case-control study, the relative risk for overnight wear soft lenses was 21, for daily-wear soft lenses 3.6, and for polymethylmethacrylate hard lenses 1.3, as compared with gas-permeable hard lenses (5).

Microorganisms can infiltrate into soft hydrophilic lenses, causing infection and possibly corneal ulcers. *Acanthamoeba* is the most common cause. In a case-control study there was an increased risk of *Acanthamoeba* infection largely attributable to lack of disinfection or the use of chlorine-based disinfection (the latter having little protective effect against the organism). Around 80% of cases of *Acanthamoeba* keratitis could have been avoided by the use of lens disinfection systems that are effective against this organism (6). *Pseudomonas aeruginosa* adherence to corneal epithelial cells was also enhanced in those who used extended-wear soft contact lenses (7). Because acanthamoebae are more commonly found in stagnant water tanks, contact lens wearers should be advised to use water from downstairs kitchen taps rather than upstairs bathroom taps.

Oxygen deficiency can occur under the lens. The dimension of the lens, duration of wear, and hygiene are determining factors. Tolerance is individual, and less hydrophilic materials produce a higher degree of corneal hypoxia. This is manifested by edema, and sometimes by vascularization and even limbus hyperemia and pannus corneae (8,9). Tear-film disruption can be a contributing factor.

Cases of allergic conjunctivitis and blepharitis have been reported with the preservatives benzalkonium chloride and mercurial salts, although benzalkonium at the commonly used concentration of 0.01% produces no evident damage. These adverse reactions can be prevented by rinsing hard lenses in clean water before insertion in the eye and by boiling soft lenses in normal saline after cleaning.

Chlorhexidine digluconate is a biguanide surfactant with low toxicity, but it is a strong contact sensitizer. Its mucus-binding capacity limits its use: it binds to hydrophilic (soft) contact lenses. Build-up of proteinaceous debris in lenses may greatly increase the binding of chlorhexidine to the lens.

The use of chlorobutanol is limited to pHs below 6. It is subject to thermal degradation and can be adsorbed on to the walls of containers. However, it has no major adverse effects. Chlorobutanol has no effect on wetting of the cornea or contact lenses, as surface-active agents do. When tested with soft lenses, chlorobutanol, concentrated in the lenses, causes mild conjunctivitis.

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Continuous ambulatory peritoneal dialysis

General Information

One complication of long-term CAPD is peritoneal calcification. The cause is unclear, but it may be associated with multiple bouts of peritonitis combined with hyercalcemia. In one case there was evidence that the effect may be reversible (1).

- A 48-year-old woman undergoing CAPD had several bouts of peritonitis, with four admissions for treatment between 1988 and 1993. In 1993, moderate amounts of calcification surrounding the small bowel were identified by CT scan, and this progressively increased over the following year. CAPD was discontinued and hemodialysis with a low dialysate calcium concentration was used instead. After a further admission 4 months later, parenteral nutrition was begun. Over the following three years, CT scans showed a progressive reduction in the extent of peritoneal calcification surrounding the small bowel.

The authors speculated that hemodialysis and long-term parenteral nutrition may result in reversal of peritoneal calcification caused by CAPD.

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Convolvulaceae

See also Herbal medicines

General Information

The genera in the family of Convolvulaceae (Table 1) include bindweed and morning glory.

Table 1 The genera of Convolvulaceae

Aniseia (aniseia)
Argyreia (argyreia)
Bonamia (lady's nightcap)
Calystegia (false bindweed)
Convolvulus (bindweed)
Cressa (alkaliweed)
Dichondra (pony's foot)
Evolvulus (dwarf morning glory)
Ipomoea (morning glory)
Jacquemontia (cluster vine)
Merremia (wood rose)
Operculina (lidpod)
Poranopsis (poranopsis)
Stictocardia (stictocardia)
Stylisma (dawn flower)
Turbina (turbina)
Xenostegia (morning vine)

Convolvulus scammonia

Convolvulus scammonia (Mexican scammony) contains alkaloids that are drastic purgatives with irritant properties. It has now been superseded.

Ipomoea purga

Ipomoea purga (jalap) is a drastic cathartic with irritant action, which has been superseded by less toxic laxatives.

Copper

General Information

Copper is a reddish metallic element (symbol Cu; atomic no. 29). Its symbol derives from the Latin word cuprum, because it was originally discovered in Cyprus. It is widely found as different salts in minerals such as atacamite (chloride); azurite and malachite (carbonates); bornite, chalcocite, chalcopyrite, stannite, tennantite, and tetrahedrite (sulfides); chalcanthite (sulfate); dioptase (silicate); erinite and olivenite (arsenates); tenorite (oxide); torbernite (phosphate); and zorgite (selenide). Copper is an essential constituent of several enzymes. It is carried in the blood by a specific copper-binding protein, ceruloplasmin.

The bulk of publications on copper deal with its metabolism as an essential trace element, its role in

Menkes' disease (associated with copper deficiency) and Wilson's disease (associated with copper excess) (1,2), and its possible role in Alzheimer's disease (3), prion disease (4), and familial amyotrophic lateral sclerosis (5). Copper metabolism and toxicity have been reviewed (6). The potential use of novel chelating agents for copper isotopes with short half-lives in radiopharmacy has been discussed (7).

Copper histidine is increasingly being used in Menkes' disease and allows survival into adolescence (8). The neurological abnormalities respond better than the connective tissue abnormalities.

A boy with Menkes' disease and low plasma concentrations of copper (3.6 μmol/l) and ceruloplasmin (50 mg/l) received copper histidine and died aged 10. Postmortem examination showed significant pathology of the mesenchymal tissues, including skeletal abnormalities, vascular degeneration, and bladder diverticula. The central nervous system, in contrast, showed minimal pathology of copper metabolism compared with classical Menkes' disease.

The differential sensitivity of central nervous system and mesenchymal tissues to copper histidine may be due to heterogeneity in the responses of different copper-dependent enzymes.

There is also contact with copper in daily life. When copper comes into contact with biological materials it becomes corroded, and the compounds that are formed can produce irritation and other reactions.

Some copper compounds have been used therapeutically in the past. Small quantities of copper salts enhance the physiological utilization of iron and are thus often present in hemopoietic formulations. Copper chloride and copper sulfate are used in parenteral nutrition solutions. The artificial radioactive copper isotope ^{64}Cu has been used in mineral metabolic studies. Excess accumulation of copper can occur due to an abnormality of ceruloplasmin and causes Wilson's disease and Menkes' disease, which are both characterized by copper accumulation (SEDA-22, 244) (9).

Copper-containing intrauterine contraceptive devices

Copper-containing intrauterine contraceptive devices (10–12) became popular because local inflammatory reactions in the endometrium are more marked and the contraceptive effect is thus more pronounced (SEDA-21, 234) (13). In addition, copper ions released from intrauterine contraceptive devices reach concentrations in the luminal fluids of the genital tract that are toxic to spermatozoa and embryos. The ability of copper to induce the generation of free radicals and the formation of malonaldehyde may be involved in its contraceptive effect.

There is a positive correlation between high copper loss from an intrauterine contraceptive device and the development of menorrhagia or pathological lesions, such as cervical dysplasia and endometrial cytopathology (14). Evidence of endometrial carcinoma was not found in endometrial aspirates from 189 women who had used Copper-T-200 devices for 1–10 years, but five cases of endometrial hyperplasia (2.67%) were encountered in women in the series, all of whom had worn copper devices for 6 years or more. Inflammatory changes in the endometrial cells were found in 12 cases (6.2%), 11 of 12 having worn the device for over 3 years. It is possible that constant exposure to copper may be responsible for persistence of chronic inflammatory changes in endometrial cells, which could be the precursors of hyperplastic changes. It is not clear whether the dissolved copper is also responsible for the temporarily increased predisposition to bacterial contamination and the somewhat increased risk of pelvic inflammatory disease, seen especially in young nulliparous women using this type of contraceptive method.

Migration of intrauterine contraceptive devices is relatively rare, although they have been found in the omentum, rectosigmoid, peritoneum, bladder, appendix, small bowel, adnexa, and iliac vein. Most authors have recommended removal of copper-containing devices, because of the potential for inflammatory reactions, which can cause bowel obstruction and perforation (15). Two cases of migration of intrauterine contraceptive devices to the bowel have been reported.

- A Copper-T intrauterine contraceptive device migrated to the rectal lumen in a 36-year-old woman with menorrhagia for 3 months and a history of Copper-T insertion 6 years before (16).
- A 28-year-old pregnant woman developed an ileal perforation 4 weeks after the insertion of a Multiload-Cu 375 intrauterine contraceptive device (17).

The second report documents the shortest interval between insertion and proven bowel injury by an intrauterine contraceptive device.

Immunological and hypersensitivity reactions beyond the uterus are uncommon, but they can occur. Rashes, including generalized urticaria and eczematoid eruptions, have occurred as a result of allergy to the copper released from intrauterine contraceptive devices, although they are extremely rare (SEDA-11, 204) (SEDA-12, 186) (SEDA-21, 235). One woman who had worn a copper-containing device for 12 months developed widespread urticaria and angioedema of the eyelids and the labia majora and minora for about 6 months (18). She also had persistent symptoms of premenstrual and postmenstrual spotting and leukorrhea for about 6 months. A patch test was positive with 1% copper sulfate, as was an in vitro lymphocyte stimulating test with copper. An endometrial biopsy showed vulvovaginitis, with hyperplasia of the cervical canal and T cell and eosinophilic granulocyte infiltration. Removal of the device caused complete remission.

Genital tract actinomycosis has come increasingly to the fore (19,20). In one study in Britain, the pelvic smears of nearly one-third of women using plastic devices were positive for *Actinomyces*-like organisms, compared with two of 165 women using copper-loaded IUCDs and none in a series of oral contraceptive users. There was a highly significant correlation between the presence of these organisms on smear and pain and other symptoms of pelvic inflammatory disease.

- A 32-year-old woman, who had had a copper intrauterine contraceptive device for more than 5 years,

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developed acyclic menstrual bleedings and had a uterine biopsy after removal of the intrauterine device (21). Histology of the abraded tissue showed an actinomycotic endometritis, with brown to black deposits in or around typical *Actinomyces druses*, but there was no carcinoma. Electron microscopy showed copper deposits in the shell and matrix of the druses and inside the bacteria. Electron-dense accumulations showed high signals for copper and sulfur, and to a lesser extent also for phosphorus and oxygen.

Copper accumulation in this case may have been caused by active uptake and concentration by the *Actinomycetes*.

If copper-containing fragments of intrauterine contraceptive devices perforate the uterine wall and enter the peritoneal cavity, acute inflammatory reactions and peritoneal adhesions can occur. Laparoscopic removal is then not only as a rule impossible but may also be dangerous because of the marked peritoneal reaction surrounding the copper part of the device. Laparotomy has therefore been suggested as the primary measure in such cases. Whether copper devices result more commonly in perforation than non-copper devices is not entirely clear, nor is the question answered whether copper increases the risk of extrauterine pregnancies, although older evidence suggested this as a risk (SED-9, 371).

Although copper-containing intrauterine contraceptive devices are very effective, pregnancies do occur and the question of possible second-generation effects has to be considered. In one case the neonate showed significantly increased copper and ceruloplasmin concentrations, whereas maternal concentrations were within the reference range. Whether such exposure to copper can cause harm is not clear; because of the pharmacological effects of copper, it has been suspected of having mutagenic and carcinogenic potential. Until now, there is no clear evidence that harm is actually done. Five published cases scattered throughout the literature in which incomplete closure of the neural tube was found (22) could have been coincidental, bearing in mind the large number of pregnancies in which exposure to copper must occur in this way. In various species of animals which have been studied (rat, rabbit, hamster, sheep) no teratogenicity of intrauterine copper was detected (SED-11, 442).

Organs and Systems

Nervous system

It has been suggested that copper-mediated toxicity in some neurodegenerative diseases (Alzheimer's disease and familial amyotrophic lateral sclerosis) may contribute to neurodegeneration (23). It should be borne in mind that similar but unproven theories have been raised regarding other metals, notably aluminium.

Sensory systems

Penetration of the eye by copper wire has been reported to produce a recurrent chronic uveitis (24).

Ocular chalcosis has been attributed to injury with a copper-containing foreign body (25).

- After having suffered an open-globe injury, presumably due to a small foreign body after a grenade explosion, a 30-year-old man presented 6 years later with ocular chalcosis, including sunflower cataract, a multitude of tiny brownish particles in the anterior vitreous, fibrillar degeneration of the posterior vitreous, and brilliant patches overriding the foveal region. The patches were measured by confocal scanning laser tomography and optical coherence tomography. Besides acquired cyandyschromatopsia, psychophysical and electrophysiological tests were unremarkable. Vision was 20/20. The central patches measured 200–700 μm in diameter and 150–200 μm in height above the inner retinal surface. With the exception of a Kayser–Fleischer ring of the cornea the patient presented all the morphological signs of ocular chalcosis. Since signs of inflammation were absent no further therapy was planned.

This man had probably suffered from a penetrating damage of the left eye caused by a copper-containing body, which had eventually dissolved. Although the observed patches on the central retina in ocular chalcosis have previously been described, their nature is not known.

Hematologic

The effects of combined oral contraceptives, depot medroxyprogesterone acetate injections, levonorgestrel subdermal implants (Norplant), copper-containing intrauterine contraceptive devices (IUCDs), and Chinese stainless steel ring IUCDs on hemoglobin and ferritin have been studied in 2507, non-pregnant non-lactating women, aged 18–40 years, in seven countries (Bangladesh, Chile, China, the Dominican Republic, Pakistan, Thailand, and Tunisia) (26). In 1295 current users of the contraceptive methods hemoglobin and ferritin concentrations were higher than in 1212 women who were starting to use contraceptives. The current users of copper IUCDs had higher hemoglobin concentrations (difference in mean concentrations of 0.3 g/dl), but lower ferritin concentrations (difference of 10 g/l) than non-users. Current use of the stainless steel ring had an adverse effect on both hemoglobin and ferritin. In 285 anemic women there were significant mean increases of hemoglobin at 12 months among the users of the hormonal contraceptives, but not among users of copper or stainless steel ring IUCDs. The authors concluded that hemoglobin and ferritin concentrations are affected by contraceptives and that the hormonal contraceptives included in this study have a beneficial effect, while the effects of copper IUCDs should be studied further.

Liver

Copper poisoning can cause hepatic cirrhosis in Wilson's disease (SEDA-21, 234) (27), but no cases appear to be known in which this resulted from medicinal exposure. Apart from Wilson's disease and Menkes' disease, much attention has been given to copper-associated liver disease in infancy and childhood, in which excessive dietary copper overload and a genetic predisposition can lead to high liver copper concentrations and progressive liver disease (28).

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Skin

Perimenstrual dermatitis has been attributed to a copper-containing intrauterine contraceptive device (29).

- A 41-year-old woman had a 2-year history of a recurrent, self-healing skin rash associated with abdominal pain. She had had cholinergic urticaria since 1995 and had had a copper-containing intrauterine contraceptive device inserted 12 years before. The eruption followed a cyclical pattern, invariably appearing 3–7 days before the menses and tending to improve spontaneously with the onset of bleeding. This non-itchy rash was associated with abdominal distension and cramps that followed a similar course. She had multiple non-itchy symmetrical erythematous papules on the upper trunk, neck, and arms. Patch-testing was positive for copper sulfate. The intrauterine contraceptive device was removed and the abdominal symptoms subsided at the following cycle. Progressive resolution of the dermatitis was observed. No cutaneous eruption was observed after 8 months and no new lesions developed after a further 5 months.

Hair

A remarkable (although non-medical) case reported in 1996 concerned a man who developed green hair as a result of drinking tap water with a high copper concentration (30). The discoloration disappeared promptly after the use of a shampoo containing penicillamine.

Reproductive system

The fibrinolytic activity of menstrual blood in wearers of Lippes loops exceeds that of patients with menorrhagia, while the values in users of the Cu-T (200) are in the same range as in normally menstruating and untreated women. In users of Lippes loops no fibrin was found in the endometrial stroma. This may explain the increased blood loss associated with the use of the Lippes loop, which can be severe enough to cause anemia (31).

Susceptibility Factors

Hepatic disease

In primary sclerosing cholangitis there is increased hepatic retention of both copper and selenium (32)

Drug Administration

Drug overdose

Overdose of copper sulfate can cause nephrotoxicity.

- A 21-year-old pharmacist developed acute renal insufficiency (33). Three days before he had dissolved a small quantity of copper sulfate in 5 ml of tap water and injected it intravenously in a suicide attempt. The serum copper concentration was 1.950 μg/ml (31 μmol/l). He was dialysed and gradually improved over 6 weeks. His serum copper concentration a month after the incident was 0.5 μg/ml (8 μmol/l). At 8 weeks a renal biopsy showed marked patchy tubular atrophy with interstitial fibrosis and mild focal chronic interstitial inflammation. Some tubules showed regenerating epithelial cells with multilayering and mitosis, with a predominant loss of proximal tubules. The findings were suggestive of chronic tubulointerstitial nephritis.

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Coriariaceae

See also Herbal medicines

General Information

The family of Coriariaceae contains the single genus *Coriaria*.

Coriaria species

Coriaria arborea (tutu) plant is a traditional Maori medicine. It contains various sesquiterpenoids, including a toxin, tutin, that is allied to picrotoxin (1).

Adverse effects

Ingestion of portions or concoctions of *Coriaria* plants can result in tonic-clonic seizures, respiratory arrest, and death.

Three sisters who ate berries of *Coriaria myrtifolia* (redoul) suffered from acute poisoning; the adverse effects affected the gastrointestinal tract (nausea, vomiting, abdominal pain), the nervous system (obnubilation, convulsions, and their complications), and respiratory function (hyperpnea, apnea, short and superficial respiration), together with myositis of the pupils; one died (2).

Of 25 children who ate the fruits of *C. myrtifolia*, 13 had gastrointestinal digestive symptoms and nine had nervous system toxicity, including seizures and coma (3).

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Corticorelin (corticotropin-releasing hormone (CRH))

General Information

For complete functional evaluation of the hypothalamic–hypophyseal–adrenal axis one can use synthetic corticorelin (corticotropin-releasing hormone), which is available in both human (hCRH) and ovine (oCRH) forms (1).

Single bolus injections in standard doses (for example 200 μg of hCRH or oCRH), whether given on a single occasion or at fixed intervals, have a very low rate of complications. At higher doses adverse effects occur in

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almost 40% of patients (2). At a dose of 1 mg/kg they mainly comprise flushing or a feeling of warmth (30%), a sensation of discomfort (5%), palpitation (3%), and dyspnea (1%). Higher doses (more than 200 mg) can cause hypotension or coronary ischemia. Patients with brain injury are more susceptible to adverse reactions (2). No serious allergic reactions have been reported. Continuous infusions of hCRH or oCRH for several hours have also been well tolerated, but adverse effects occurred with cumulative doses of 200–300 μg/hour.

High doses can provoke marked adverse effects in patients with neurological disorders, coronary heart disease, or disorders of the pituitary–adrenal axis, especially if the blood–brain barrier has been damaged (for example by a head injury or during intracranial surgery). Nonstandard doses should only be used in experimental work with well-designed safety precautions.

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Corticosteroids—glucocorticoids

General Information

Nomenclature

The two main classes of adrenal corticosteroids are properly known as glucocorticoids and mineralocorticosteroids. The former are often known by shorter names and are commonly referred to as "glucocorticoids", "corticosteroids", "corticoids", or even simply "steroids"; the latter are often referred to as "mineralocorticoids". Here we shall use the terms "glucocorticoids" and "mineralocorticoids". When referring to both we shall use the term "corticosteroids".

Relative potencies

The main human anti-inflammatory corticosteroid, the glucocorticoid cortisol (hydrocortisone), as secreted by the adrenal gland, has generally been replaced by related glucocorticoids of synthetic origin for therapeutic purposes. These Δ^1-dehydrated glucocorticoids are designed to imitate the physiological hormone. They have marked glucocorticoid potency but only minor effects on sodium retention and potassium excretion; the relative glucocorticoid and mineralocorticoid potencies of the best-known compounds, insofar as these potencies are agreed, are compared in Table 1.

Over many years, a great deal of research has been devoted to producing better glucocorticoids for therapeutic use. Those endeavors have succeeded only in part; from the start the mineralocorticoid effects were sufficiently minor to be nonproblematic; the fact that successive synthetic glucocorticoids had an increasing potency in terms of weight was not of direct therapeutic significance; and the most hoped-for aim, that of dissociating wanted from unwanted glucocorticoid effects has not been achieved (1). Most untoward effects, such as those due to the catabolic and gluconeogenic activities of the glucocorticoid family, probably cannot be dissociated entirely from the anti-inflammatory activity (2) it is possible that myopathy and muscle wasting are actually more common when triamcinolone or dexamethasone are used, but this may merely reflect overdosage of these potent drugs. However, some progress in achieving a dissociation of effects has been made. Beclomethasone does have a relatively greater local than systemic effect. Deflazacort, one of the few new glucocorticoids to have been developed in recent years, originally promised reduced intensity of adverse effects, for example on bone mineral density, but the early promise has not held up (SEDA-18, 389). Cloprednol seems to affect the hypothalamic–pituitary–adrenal axis much less than other glucocorticoids, and to cause less excretion of nitrogen and calcium (3).

Uses

Most patients who are treated therapeutically with glucocorticoids do not have glucocorticoid deficiency. Adverse

Table 1 Relative potencies of glucocorticoids

Compound	Glucocorticoid potency relative to hydrocortisone	Mineralocorticoid potency	Equivalent doses (mg)
Cortisone	0.8	++	25
Hydrocortisone	1.0	++	20
Prednisone	4	+	5
Prednisolone	4	+	5
Methylprednisolone	5	0	4
Triamcinolone	5	0	4
Paramethasone	10	0	2
Fluprednisolone	10	0	1.5
Dexamethasone	30	0	0.75
Betamethasone	30	0	0.6

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almost 40% of patients (2). At a dose of 1 mg/kg they mainly comprise flushing or a feeling of warmth (30%), a sensation of discomfort (5%), palpitation (3%), and dyspnea (1%). Higher doses (more than 200 mg) can cause hypotension or coronary ischemia. Patients with brain injury are more susceptible to adverse reactions (2). No serious allergic reactions have been reported. Continuous infusions of hCRH or oCRH for several hours have also been well tolerated, but adverse effects occurred with cumulative doses of 200–300 μg/hour.

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Fluprednisolone	10	0	1.5
Dexamethasone	30	0	0.75
Betamethasone	30	0	0.6

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reactions to glucocorticoids depend very largely on the ways in which, and the purposes for which, they are used. There are four groups of uses.

(1) Substitution therapy is used in cases of primary and secondary adrenocortical insufficiency; the aim is to provide glucocorticoids and mineralocorticoids in physiological amounts, and the better the dosage regimen is adapted to the individual's needs, the less the chance of adverse effects (1).
(2) Anti-inflammatory and immunosuppressive therapy exploits the immunosuppressive, anti-allergic, anti-inflammatory, anti-exudative, and anti-proliferative effects of the glucocorticoids (2). The desired pharmacodynamic effects reflect a general influence of these substances on the mesenchyme, where they suppress reactions that result in the symptoms of inflammation, exudation, and proliferation; the non-specific effects of glucocorticoids on the mesenchyme are part of their physiological actions, but they can only be obtained to a clinically useful extent by using dosages at which the more specific (and unwanted) physiological effects also occur. High doses sufficient to suppress immune reactions are used in patients who have undergone organ transplantation.
(3) Hormone suppression therapy can be used, for example, to inhibit the adrenogenital syndrome (3). Higher doses are used. The treatment of the adrenogenital syndrome is only partly substitutive and has to be adapted to the individual case, but doses are needed at which various hormonal effects of the glucocorticoids and mineralocorticoids are likely to become troublesome.
(4) Massive doses of glucocorticoids, far exceeding physiological amounts, are given in the immediate management of anaphylaxis, although their beneficial effects are delayed for several hours. This is because, in severely ill patients, early administration of hydrocortisone 100–300 mg as the sodium succinate salt can gradually enhance the actions of adrenaline (4). Glucocorticoids have been used as an adjunct to the use of inotropic and vasopressor drugs for septic shock. Their efficacy, as well as their proposed mechanisms of action, is controversial; inhibition of complement-mediated aggregation and resultant endothelial injury, and inhibition of the release of beta-endorphin are current theories of their mechanism of action. However, controlled studies have not indicated a beneficial effect of high-dose glucocorticoid therapy in treating septic shock (5,6). Hence, there is no established role for glucocorticoids in the treatment of shock, except shock caused by adrenal insufficiency.

Routes of administration

Glucocorticoids can be given by the following routes:

- oral
- rectal
- intravenous
- intramuscular
- inhalation
- nasal
- topical (skin, eyes, ears)
- intradermal
- intra-articular and periarticular
- intraspinal (epidural, intrathecal)
- intracapsular (breast)

All of these routes are covered in this monograph, except the inhalation route, which is the subject of a separate monograph.

Therapeutic studies

Although there have been several trials of early dexamethasone to determine whether it would reduce mortality and chronic lung disease in infants with respiratory distress, the optimal duration and adverse effects of such therapy are unknown. The purpose of one study was: (a) to determine if a 3-day course of early dexamethasone therapy would reduce chronic lung disease and increase survival without chronic lung disease in neonates who received surfactant therapy for respiratory distress syndrome and (b) to determine the associated adverse effects (7). This was a prospective, placebo-controlled, multicenter, randomized study of a 3-day course of early dexamethasone therapy, beginning at 24–48 hours of life in 241 neonates, who weighed 500–1500 g, had received surfactant therapy, and were at significant risk of chronic lung disease or death. Infants randomized to dexamethasone received a 3-day tapering course (total dose 1.35 mg/kg) given in six doses at 12-hour intervals. Chronic lung disease was defined by the need for supplementary oxygen at a gestational age of 36 weeks. Neonates randomized to early dexamethasone were more likely to survive without chronic lung disease (RR = 1.3; CI = 1.0, 1.7) and were less likely to develop chronic lung disease (RR = 0.6; CI = 0.3, 0.98). Mortality rates were not significantly different. Subsequent dexamethasone therapy was less in early dexamethasone-treated neonates (RR = 0.8; CI = 0.70, 0.96). Very early (before 7 days of life) intestinal perforations were more common among dexamethasone-treated neonates (8 versus 1%). The authors concluded that an early 3-day course of dexamethasone increases survival without chronic lung disease, reduces chronic lung disease, and reduces late dexamethasone therapy in high-risk, low birthweight infants who receive surfactant therapy for respiratory distress syndrome. The potential benefits of early dexamethasone therapy in the regimen used in this trial need to be weighed against the risk of early intestinal perforation.

In another randomized trial, the effects and adverse effects of early dexamethasone on the incidence of chronic lung disease have been evaluated in 50 high-risk preterm infants (8). The treated infants received dexamethasone intravenously from the fourth day of life for 7 days (0.5 mg/kg/day for the first 3 days, 0.25 mg/kg/day for the next 3 days, and 0.125 mg/kg/day on the seventh day). The incidence of chronic lung disease at 28 days of life and at 36 weeks of postconceptional age was significantly lower in the infants who were given dexamethasone, who also remained intubated and required oxygen therapy for a shorter period. Hyperglycemia, hypertension, growth failure, and left ventricular hypertrophy were the transient adverse effects associated with early

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glucocorticoid administration. Early dexamethasone administration may be useful in preventing chronic lung disease, but its use should be restricted to preterm high-risk infants.

A systematic review of randomized controlled trials has been performed to determine whether dexamethasone therapy in the first 15 days of life prevents chronic lung disease in premature infants (9). Studies were identified by a literature search using Medline (1970–97) supplemented by a search of the Cochrane Library (1998, Issue 4). Inclusion criteria were: (a) prospective randomized design with initiation of dexamethasone therapy within the first 15 days of life; (b) report of the outcome of interest; and (c) less than 20% crossover between the treatment and control groups during the study period. The primary outcomes were mortality at hospital discharge and the development of chronic lung disease at 28 days of life and 36 weeks postconceptional age. The secondary outcomes were the presence of a patent ductus arteriosus and treatment adverse effects. Dexamethasone reduced the incidence of chronic lung disease by 26% at 28 days (RR = 0.74; CI = 0.57, 0.96) and 48% at 36 weeks postconceptional age (RR = 0.52; CI = 0.33, 0.81). These reductions were more significant when dexamethasone was started in the first 72 hours of life. The 24% relative risk reduction of deaths was marginally significant (RR = 0.76; CI = 0.56, 1.04). The 27% reduction in patent ductus arteriosus and the 11% increase in infections were not statistically significant, nor were any other changes. The conclusion from this meta-analysis was that systemic dexamethasone given to at-risk infants soon after birth may reduce the incidence of chronic lung disease. There was no evidence of significant short-term adverse effects.

Although dexamethasone is commonly associated with transient adverse effects, several randomized trials have shown that it rapidly reduces oxygen requirements and shortens the duration of ventilation. A randomized study was designed to evaluate the effects of two different dexamethasone courses on growth in preterm infants (10). The first phase included 30 preterm infants at high risk of chronic lung disease, of whom 15 (8 boys) were given dexamethasone for 14 days, from the tenth day of life; they received a total dose of 4.75 mg/kg; 15 babies were assigned to the control group (8 boys). The second phase included 30 preterm infants at high risk of chronic lung disease, of whom 15 babies (7 boys) were treated with dexamethasone for 7 days, from the fourth day of life; they received a total dose of 2.38 mg/kg; 15 babies were assigned to the control group (9 boys). Infants given dexamethasone had significantly less weight gain than controls, but they caught up soon after the end of treatment. At 30 days of life, the gains in weight and length in each group were similar to those in control infants, but those given dexamethasone had significantly less head growth. There were no differences between the groups at discharge. The longer-term impact of postnatal dexamethasone on mortality and morbidity is less clear. Better data, from larger clinical trials with longer follow-up, will determine whether this kind of treatment enhances lives, makes little difference, causes significant harm, or does several of these things (11).

General adverse effects

The incidence and severity of adverse reactions to glucocorticoids depend on the dose and duration of treatment. Even the very high single doses of glucocorticoids, such as methylprednisolone, which are sometimes used, do not cause serious adverse effects, whereas an equivalent dose given over a long period of time can cause many long-term effects.

The two major risks of long-term glucocorticoid therapy are adrenal suppression and Cushingoid changes. During prolonged treatment with anti-inflammatory doses, glucose intolerance, osteoporosis, acne vulgaris, and a greater or lesser degree of mineralocorticoid-induced changes can occur. In children, growth can be retarded, and adults who take high doses can have mental changes. There may be a risk of gastroduodenal ulceration, although this is much less certain than was once thought. Infections and abdominal crises can be masked. Some of these effects reflect the catabolic properties of the glucocorticoids, that is their ability to accelerate tissue breakdown and impair healing. Allergic reactions can occur.

Anyone who prescribes long-term glucocorticoids should have a checklist in mind of the undesired effects that they can exert, both during treatment and on withdrawal, so that any harm that occurs can be promptly detected and countered. The main groups of risks arising from long-term treatment with glucocorticoids are summarized in Table 2.

The adverse reactions that were reported in a study of 213 children are listed in Table 3 (12).

Table 2 Risks of long-term glucocorticoid therapy

1. Exogenous hypercorticalism with Cushing's syndrome
Moon face (facial rounding)
Central obesity
Striae
Hirsutism
Acne vulgaris
Ecchymoses
Hypertension
Osteoporosis
Proximal myopathy
Disorders of sexual function
Diabetes mellitus
Hyperlipidemia
Disorders of mineral and fluid balance (depending on the type of glucocorticoid)
2. Adrenal insufficiency
Insufficient or absent stress reaction
Withdrawal effects
3. Unwanted results accompanying desired effects
Increased risk of infection
Impaired wound healing
Peptic ulceration, bleeding, and perforation
Growth retardation
4. Other adverse effects
Mental disturbances
Encephalopathy
Increased risk of thrombosis
Posterior cataract
Increased intraocular pressure and glaucoma
Aseptic necrosis of bone

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Table 3 Adverse reactions in 213 children given intravenous methylprednisolone

Adverse effect	Number
Behavioral changes	21
Abdominal disorders	11
Pruritus	9
Urticaria	5
Hypertension	5
Bone pain	3
Dizziness	3
Fatigue	2
Fractures	2
Hypotension	2
Lethargy	2
Tachycardia	2
Anaphylactoid reaction	1
"Grey appearance"	1

Drug interactions that affect the efficacy of glucocorticoids have been reviewed (13).

Organs and Systems

Cardiovascular

The considerable body of evidence that glucocorticoids can cause increased rates of vascular mortality and the underlying mechanisms (increased blood pressure, impaired glucose tolerance, dyslipidemia, hypercoagulability, and increased fibrinogen production) have been reviewed (14). In view of their adverse cardiovascular effects, the therapeutic options should be carefully considered before long-term glucocorticoids are begun; although they can be life-saving, dosages should be regularly reviewed during long-term therapy, in order to minimize complications.

Hypertension

The secondary mineralocorticoid activity of glucocorticoids can lead to salt and water retention, which can cause hypertension. Although the detailed mechanisms are as yet uncertain, glucocorticoid-induced hypertension often occurs in elderly patients and is more common in patients with total serum calcium concentrations below the reference range and/or in those with a family history of essential hypertension (SEDA-20, 368) (15).

Hemangioma is the most common tumor of infancy, with a natural history of spontaneous involution. Some hemangiomas, however, as a result of their proximity to vital structures, destruction of facial anatomy, or excessive bleeding, can be successfully treated with systemic glucocorticoids between other therapies. The risk of hypertension is poorly documented in this setting. In one prospective study of 37 infants (7 boys, 17 girls; mean age 3.5 months, range 1.5–10) with rapidly growing complicated hemangiomas treated with oral prednisone 1–5 mg/kg/day, blood pressure increased in seven cases (16). Cardiac ultrasound examination in five showed two cases of myocardial hypertrophy, which was unrelated to the hypertension and which regressed after withdrawal of the prednisone.

Myocardial ischemia

Cortisone-induced cardiac lesions are sometimes reported and electrocardiographic changes have been seen in patients taking glucocorticoids (17). Whereas abnormal myocardial hypertrophy in children has perhaps been associated more readily with corticotropin, it has been seen on occasion during treatment with high dosages of glucocorticoids, with normalization after dosage reduction and withdrawal.

Fatal myocardial infarction occurred after intravenous methylprednisolone for an episode of ulcerative colitis (18).

- A day after a dose of intravenous methylprednisolone 60 mg a 79-year-old woman developed acute thoracic pain and collapsed. An electrocardiogram showed signs of a myocardial infarction and her cardiac enzyme activities were raised. She died within several hours. Autopsy showed an anterior transmural myocardial infarction and mild atheromatous lesions in the coronary arteries.

This report highlights the risk of cardiovascular adverse effects with short courses of glucocorticoid therapy in elderly patients with inflammatory bowel disease, even with rather low-dosage regimens. Acute myocardial infarction occurred in an old man with coronary insufficiency and giant cell arteritis after treatment with prednisolone (SEDA-10, 343) but could well have been coincidental.

Myocardial ischemia has been reportedly precipitated by intramuscular administration of betamethasone (SEDA-21, 413) (19). It has been suggested that long-term glucocorticoid therapy accelerates atherosclerosis and the formation of aortic aneurysms, with a high risk of rupture (SEDA-20, 369) (20).

Patients with seropositive rheumatoid arthritis taking long-term systemic glucocorticoids are at risk of accelerated cardiac rupture in the setting of transmural acute myocardial infarction treated with thrombolytic drugs (21).

- Two women and one man, aged 53–74 years, died after they received thrombolytic therapy for acute myocardial infarction. All three had a long history of seropositive rheumatoid arthritis treated with prednisone 5–20 mg/day for many years.

Cardiomyopathy

Postnatal exposure to glucocorticoids has been associated with hypertrophic cardiomyopathy in neonates. Such an effect has not previously been described in infants born to mothers who received antenatal glucocorticoids. Three neonates (gestational ages 36, 29, and 34 weeks), whose mothers had been treated with betamethasone prenatally in doses of 12 mg twice weekly for 16 doses, 8 doses, and 5 doses respectively, developed various degrees of hypertrophic cardiomyopathy diagnosed by echocardiography (22). There was no maternal evidence of diabetes, except for one infant whose mother had a normal fasting and postprandial blood glucose before glucocorticoid therapy, but an abnormal 1-hour postprandial glucose after 8 weeks of betamethasone therapy, with a normal HbA_{1C} concentration. There was no family history of hypertrophic cardiomyopathy, no history of maternal intake of other relevant medications, no hypertension,

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and none of the infants received glucocorticoids postnatally. Follow-up echocardiography showed complete resolution in all infants. The authors suggested that repeated antenatal maternal glucocorticoids might cause hypertrophic cardiomyopathy in neonates. These changes appear to be dose- and duration-related and are mostly reversible.

Transient hypertrophic cardiomyopathy is a rare sequel of the concurrent administration of glucocorticoid and insulin excess (SEDA-21, 412) (23). The heart is also almost certainly a site for myopathic changes analogous to those that affect other muscles.

Transient hypertrophic cardiomyopathy has been attributed to systemic glucocorticoid administration for a craniofacial hemangioma (24).

- A 69-day-old white child presented with a rapidly growing 2.5 × 1.5 cm hemangioma of the external left nasal side wall. He was normotensive and there was no family history of cardiomyopathy or maternal gestational diabetes. Because of nasal obstruction and possible visual obstruction, he was given prednisolone 3 mg/kg/day. After 10 weeks his weight had fallen from 7.6 to 7.1 kg and 2 weeks later he became tachypneic with a respiratory rate of 40/minutes. A chest X-ray showed cardiomegaly and pulmonary venous congestion. An echocardiogram showed hypertrophic cardiomyopathy. The left ventricular posterior wall thickness was 10 mm (normal under 4 mm), and the peak left ventricular outflow gradient was 64 mmHg. He was given a beta-blocker and a diuretic and the glucocorticoid dose was tapered. The cardiomyopathy eventually resolved.

Dilated cardiomyopathy caused by occult pheochromocytoma has been described infrequently.

- A 34-year-old woman had acute congestive heart failure 12 hours after administration of dexamethasone 16 mg for an atypical migraine (25). The authors postulated that the acute episode had been induced by the dexamethasone, which increased the production of adrenaline, causing $beta_2$-adrenoceptor stimulation, peripheral vasodilatation, and congestive heart failure.

In an addendum the authors reported another similar case.

Cardiac dysrhythmias

Serious cardiac dysrhythmias and sudden death have been reported with pulsed methylprednisolone. Oral methylprednisolone has been implicated in a case of sinus bradycardia (26).

- A 14-year-old boy received an intravenous dose of methylprednisolone 30 mg/kg for progressive glomerulonephritis. After 5 hours, his heart rate had fallen to 50/minute and an electrocardiogram showed sinus bradycardia. His heart rate then fell to 40/minutes and a temporary transvenous pacemaker was inserted and methylprednisolone was withdrawn. His heart rate increased to 80/minutes over 3 days. After a further 3 days, he was treated with oral methylprednisolone 60 mg/m^2/day and his heart rate fell to 40/minutes in 5 days. Oral methylprednisolone was stopped on day 8 of treatment and his heart rate normalized.

Hypokalemia, secondary to mineralocorticoid effects, can cause cardiac dysrhythmias and cardiac arrest.

Recurrent cardiocirculatory arrest has been reported (27).

- A 60-year-old white man was admitted for kidney transplantation. Immediately after reperfusion and intravenous methylprednisolone 500 mg, he developed severe bradycardia with hypotension and then cardiac arrest. After resuscitation, his clinical state improved quickly, but on the morning of the first postoperative day directly after the intravenous administration of methylprednisolone 250 mg, he had another episode of severe bradycardia, hypotension, and successful cardiopulmonary resuscitation. A third episode occurred 24 hours later after intravenous methylprednisolone 100 mg, again followed by rapid recovery after resuscitation. Two weeks later, during a bout of acute rejection, he was given intravenous methylprednisolone 500 mg, after which he collapsed and no heartbeat or breathing was detectable; after cardiopulmonary resuscitation he was transferred to the intensive care unit, where he died a few hours later.

If patients at risk are identified, glucocorticoid bolus therapy should be avoided or, if that is not possible, should only be done under close monitoring.

Pericarditis

- Disseminated *Varicella* and staphylococcal pericarditis developed in a previously healthy girl after a single application of triamcinolone cream 0.1% to relieve pruritus associated with *Varicella* skin lesions (SEDA-22, 443) (28).

Vasculitis

Long-term treatment with glucocorticoids can cause arteritis, but patients with rheumatoid arthritis have a special susceptibility to vascular reactions, and cases of periarteritis nodosa after withdrawal of long-term glucocorticoids have been reported (29).

Respiratory

Local adverse effects are common in patients with asthma who use inhaled glucocorticoids, as suggested by a survey of the prevalence of throat and voice symptoms in patients with asthma using glucocorticoids by metered-dose pressurized aerosol (SEDA-20, 369) (30).

There have been no reports of an increased frequency of lower respiratory tract infections. However, patients with aspiration of gastric material who were treated with glucocorticoids did not have improved survival but had a higher incidence of pneumonia (SED-12, 982).

In cases of pneumothorax with closed thoracotomy tube drainage, chronic glucocorticoid treatment has been reported to delay and impede re-expansion of the lung (SED-8, 820).

Hiccup is a rare complication of glucocorticoid therapy; five cases have been published at various times (31).

- A 59-year-old man had intractable hiccups during treatment with dexamethasone for multiple myeloma (32).
- Persistent hiccupping has been described in a 30-year-old man after the administration of a single

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intravenous dose of dexamethasone (16 mg) (33). The symptom was resistant to metoclopramide and resolved spontaneously after 4 days. On rechallenge, the hiccups recurred within 2 hours and disappeared after 36 hours.

Low-dose metoclopramide can be effective and may allow a patient to continue beneficial therapy without the discomfort and exhaustion that can accompany intractable hiccups.

Ear, nose, throat

Atrophic changes and fungal and other infections can alter the nasal mucosa after aerosol treatment (34), and since most systematic published documentation on these intranasal products is limited to 1–2 years of experience (although they have been in use for a far longer period), some reserve is warranted with respect to their long-term safety and the wisdom of continual use.

Nervous system

Cerebral venous thrombosis associated with glucocorticoid treatment has rarely been reported. A relation between glucocorticoids and venous thrombosis has already been suggested but has never been clearly understood. Three young patients, two women (aged 28 and 45) and one man (aged 38 years), developed cerebral venous thrombosis after intravenous high-dose glucocorticoids (35). All presented with probable multiple sclerosis according to clinical, CSF, and MRI criteria. All had a lumbar puncture and were then treated with methylprednisolone 1 g/day for 5 days. All the usual causes of cerebral venous thrombosis were systematically excluded. The authors proposed that glucocorticoids interfere with blood coagulation and suggested that the administration of glucocorticoids after a lumbar puncture carries a particular risk of complications.

Dexamethasone is widely used for the prevention and treatment of chronic lung disease in premature infants, in whom follow-up studies have raised the possibility of an association with alterations in neuromotor function and somatic growth. In 159 survivors (mean age 53 months) of a previous placebo-controlled study, the children who had received dexamethasone had a significantly higher incidence of cerebral palsy (39/80 versus 12/79; OR = 4.62; 95% CI = 2.38, 8.98) (36). The most common form of cerebral palsy was spastic diplegia. Developmental delay was more frequent in the dexamethasone group (44/80 versus 23/79; OR = 2.9; CI = 1.5, 5.4).

Long-term treatment with glucocorticoids can cause cerebral atrophy (37).

Severe organic brain syndrome has been seen in six patients taking long-term glucocorticoids (SEDA-3, 304). The manifestations included confusion, disorientation, apathy, confabulation, irrelevant speech, and slow thinking; the symptoms occurred abruptly.

Latent epilepsy can be made manifest by glucocorticoid treatment. Seizures in patients with lung transplants were related to glucocorticoids, which had been used in high dosages to prevent organ rejection. There was an increased risk of seizures in younger patients (under 25 years) and with intravenous methylprednisolone (SEDA-21, 413) (38).

Long-term glucocorticoid treatment can result in papilledema and increased intracranial pressure (the syndrome of pseudotumor cerebri or so-called "benign intracranial hypertension"), particularly in children.

- Benign intracranial hypertension occurred in a 7-month-old child after withdrawal of topical betamethasone ointment and in a 7-year-old boy treated with a 1% cortisol ointment in large amounts.
- A 6-year-old girl, who had taken prednisone for 2.5 years for nephrotic syndrome with seven relapses in 3 years, developed symptoms of benign intracranial hypertension after oral glucocorticoid dosage reduction over 10 months from 30 mg/day to 2.5 mg/every other day (39). Laboratory studies and head CT scan were normal, but there was bilateral papilledema and the cerebrospinal fluid pressure was increased. She was given prednisone 1 mg/kg/day initially, with acetazolamide, and 25 ml of cerebrospinal fluid was removed. All her symptoms resolved and treatment was gradually withdrawn. She developed no further visual failure.

The symptoms can simulate those of an intracranial tumor. All patients taking large doses of glucocorticoids who complain of headache or blurred vision, particularly after a reduction in dosage, should have an ophthalmoscopic examination to exclude this complication. Paradoxically, cerebral edema occurring during a surgical procedure can be partly prevented by glucocorticoids (40).

An encephalopathy can occur at any age (SEDA-18, 387), not necessarily in association with intracranial hypertension.

There have been repeated reports of epidural lipomatosis, which can lead to spinal cord compression (41,42) or spinal fracture (43); in one instance, the excised lipomata contained brown fat, a phenomenon that may prove to be not unusual in glucocorticoid-induced lipomata (SEDA-16, 451).

- A 40-year-old woman with ulcerative colitis took cortisone 20 mg/day and developed progressive paraplegia (43). There was kyphosis of the thoracic spine from T7 to T9, with pathological fractures. An MRI scan showed massive epidural fat extending from T1 to T9. She recovered 3 months after surgical removal of the epidural fat.
- A 78-year-old man was given methylprednisolone (60 mg/day reducing to 8 mg/day) for temporal arteritis (44). After 4 months, he developed numbness and paresis of the legs and hyperalgesia at dermatomes T3 and T4. After 10 months he had marked disturbance of proprioception combined with spinal ataxia and an increasing loss of motor bladder control. There was an intraspinal epidural lipoma in the dorsal part of the spine from T1-10. The fat was removed surgically and within 4 weeks his gait disturbance and proprioception improved, the sensory deficit abated, and the bladder disorder disappeared completely.
- A 57-year-old man took prednisone 20–30 mg/day for 13 years for rheumatoid arthritis (45). He had been treated unsuccessfully with gold, azathioprine, hydroxychloroquine, and sulfasalazine; tapering his glucocorticoid dosage had been unsuccessful. He developed worsening back pain in his thoracic spine and lateral

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leg weakness. He was unable to walk. He was Cushingoid and had marked thoracic kyphosis associated with multiple vertebral body fractures in T5-8. An MRI scan at T5-6 showed displacement and compression of the spinal cord by high-signal epidural fat, which had caused anterior thecal displacement and total effacement of cerebrospinal fluid.

The authors of the last report commented on the high dose of prednisone used.

In the past there was reason to think that glucocorticoids might precipitate multiple sclerosis. However, this has not been confirmed, and there is evidence that a special glucocorticoid regimen can actually be capable of retarding deterioration in multiple sclerosis (SEDA-18, 387).

A Guillain–Barré-like syndrome occurred in a patient receiving high-dose intravenous glucocorticoid therapy (SEDA-16, 449). Although glucocorticoids have been used successfully to treat weakness due to chronic inflammatory demyelinating sensorimotor neuropathy, other types of acquired chronic demyelinating neuropathies can be impaired by these drugs.

- In four patients with a pure motor demyelinating neuropathy treated with oral prednisolone (60 mg/day) motor function rapidly deteriorated within 4 weeks of starting prednisolone (SEDA-19, 375) (46). Intravenous immunoglobulin some months later in two of them produced clear improvement in strength and motor nerve conduction.

Sensory systems

The eye can be involved in generalized adverse reactions to systemically administered glucocorticoids. For example, conjunctivitis can occur as part of an allergic reaction and infections of the eye can be masked as a result of anti-inflammatory and analgesic effects. Ophthalmoplegia can occur as one of the consequences of glucocorticoid myopathy (SEDA-16, 450). Two complications that require special discussion are cataract and glaucoma.

Cataract

Oral glucocorticoid treatment is a risk factor for the development of posterior subcapsular cataract. A review of nine studies including 343 asthmatics treated with oral glucocorticoids showed a prevalence of posterior subcapsular cataracts of 0–54% with a mean value of 9% (47). In a 1993 study in children taking low-dose prednisone there were cataracts in seven of 23 cases (48). Some studies have shown a clear correlation with the duration of treatment and total dosage, others have not (SEDA-17, 449). The use of inhaled glucocorticoids was associated with a dose-dependent increased risk of posterior subcapsular and nuclear cataracts in 3654 patients aged 49–97 years (SEDA-22, 446) (49). Data on glucocorticoid use were available for 3313 of these patients; glucocorticoid use was classified as none in 2784 patients, inhaled only in 241, systemic only in 177, and both inhaled and systemic in 111. Compared with nonuse, current or prior use of inhaled glucocorticoids was associated with a significant increase in the prevalence of nuclear cataracts (adjusted relative prevalence = 1.5; 95% CI = 1.2, 1.9) and posterior subcapsular cataracts (1.9; 1.3, 2.8), but not cortical cataracts. The increased prevalence of posterior subcapsular cataracts was significantly associated with current use of inhaled glucocorticoids (2.6; 1.7, 4.0); there was no association with past use. Current use of inhaled glucocorticoids was also associated with an increased prevalence of cortical cataracts (1.4; 1.1, 1.7). The highest prevalences of posterior subcapsular and grade 4 or 5 nuclear cataracts were found in patients who had taken a cumulative dose of beclomethasone over 2000 mg.

It has been suggested that the risk of cataract is higher in patients with rheumatoid arthritis than in patients with bronchial asthma, and it is also higher in children. The reversibility of the lenticular changes has often been discussed (50,51), but even without glucocorticoid withdrawal regression has been found in children taking long-term treatment (52). Nevertheless, some 7% of the patients who develop cataract caused by glucocorticoid treatment have to be operated on. A change in permeability of the lens capsule, followed by altered electrolyte concentrations in the lens and a change in the mucopolysaccharides in the lens have been advanced as reasons for the development of cataract.

Increased intraocular pressure and glaucoma

Ocular hypertension and open-angle glaucoma are well-known adverse effects of ophthalmic administration of glucocorticoids (SEDA-17, 449).

Frequency

A total of 113 patients with angiographically proven subretinal neovascularization were enrolled into a prospective study of the effects of intravitreal triamcinolone (53). About 30% developed a significant rise in intraocular pressure (at least 5 mmHg) above baseline during the first 3 months.

A large case-control study, in which 9793 elderly patients with ocular hypertension or open-angle glaucoma were compared with 38 325 controls, has shown an increased risk of these complications with oral glucocorticoids (SEDA-22, 446) (54). The risk of ocular hypertension or open-angle glaucoma increased with increasing dose and duration of use of the oral glucocorticoid. There was no significant increase in the risk of ocular hypertension or open-angle glaucoma in patients who had stopped taking oral glucocorticoids 15–45 days before. The authors estimated that the excess risk of ocular hypertension or open-angle glaucoma with current oral glucocorticoid use is 43 additional cases per 10 000 patients per year. However, in patients taking over 80 mg/day of hydrocortisone equivalents, the excess risk is 93 additional cases per 10 000 patients per year. Monitoring of intraocular pressure may be justified in long-term users of oral glucocorticoids, as it is in long-term users of topical glucocorticoids.

Prolonged use of high doses of inhaled glucocorticoids also increases the risk of ocular hypertension and open-angle glaucoma (SEDA-22, 446) (55). In a case-control study of the records of 9793 elderly patients with ocular hypertension or open-angle glaucoma over a 6-year period, there was a significantly increased risk of ocular hypertension and open-angle glaucoma in patients who had taken high doses of inhaled glucocorticoids

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(1500–1600 micrograms) for 3 months or longer (OR = 1.44; 95% CI = 1.01, 2.06). Both a high dosage of inhaled glucocorticoid and prolonged continuous duration of therapy had to be present to increase the risk.

Glaucoma and ocular hypertension have been reported after dermal application of glucocorticoids for facial atopic eczema (SEDA-19, 376) (56), and after treatment with beclomethasone by nasal spray and inhalation (SEDA-20, 373) (57).

The effects of topical dexamethasone on intraocular pressure have been compared with those of fluorometholone (SEDA-22, 446) (58). The ocular hypertensive response to topical dexamethasone in children occurs more often, more severely, and more rapidly than that reported in adults. It should be avoided in children if possible and it is desirable to monitor the intraocular pressure when it is being used. Fluorometholone may be more acceptable.

Pathogenesis

The pathogenesis of glucocorticoid-induced glaucoma is still unknown, but there is reduced outflow, and excessive accumulation of mucopolysaccharides may be a major factor. An association with cataract and papilledema has often been observed. The rise in intraocular pressure is variable: in the pediatric study of low dose cited above there was a reversible effect in only two of 23 subjects compared with controls, but in other studies serious increases in pressure have occurred, with a risk of blindness.

There is almost certainly a genetic predisposition to glucocorticoid-induced glaucoma, as there is to glaucoma in general.

Chorioretinopathy

Systemic glucocorticoid treatment can cause severe exacerbation of bullous exudative retinal detachment and lasting visual loss in some patients with idiopathic central serous chorioretinopathy (SEDA-20, 374) (59). The atypical presentation of this condition can include peripheral retinal capillary nonperfusion and retinal neovascularization. The treatment of choice in patients with idiopathic central serous chorioretinopathy is laser photocoagulation.

Keratopathy and keratitis

Band-shaped keratopathy is caused by the deposition of calcium salts in the basement membrane of the corneal epithelium and superficial stroma. It is typically a chronic process that develops over a period of months and years, and is associated with chronic corneal or intraocular inflammation.

- Infectious crystalline keratopathy developed in a 73-year-old woman with noninsulin-dependent diabetes mellitus after the use of topical prednisolone 1% eye-drops, for conjunctival injection over 12 months (SEDA-20, 372) (60).
- Acute-onset calcific band keratopathy has been reported in a woman using topical prednisolone (SEDA-20, 372) (61).

Patients with severe keratoconjunctivitis sicca are at definite risk of this complication, and the addition of phosphate-containing eye-drops tilted the precariously balanced situation toward precipitation of calcium in the cornea and bandage contact lens. Acetate-containing rather than phosphate-containing glucocorticoid eye drops may be a safer alternative in patients with such predisposing factors.

Bacterial keratitis is one of the most frequent ophthalmic infections. In a meta-analysis of publications from 1950 to 2000, the use of a topical glucocorticoid before the diagnosis of bacterial keratitis significantly predisposed to ulcerative keratitis in eyes with pre-existing corneal disease (OR = 2.63; 95% CI = 1.41, 4.91). Previous glucocorticoid use significantly increased the risk of antibiotic failure or other infectious complications (OR = 3.75; 95% CI = 2.52, 5.58). The use of glucocorticoids with an antibiotic for the treatment of bacterial keratitis did not increase the risk of complications, but neither did it improve the outcome of treatment.

Retinal damage

An apparent association between severe retinopathy of prematurity and dexamethasone therapy has been shown in a retrospective study (SEDA-20, 372) (62). Infants treated with dexamethasone required longer periods of mechanical ventilation (44 versus 26 days), had a longer duration of supplemental oxygen (57 versus 29 days), had a higher incidence of patent ductus arteriosus (28/38 versus 18/52), and required surfactant therapy more often for respiratory distress syndrome (17/38 versus 11/52). Prospective, randomized, controlled studies are needed to correct for differences in severity of cardiorespiratory disease. Until such studies are available, careful consideration must be given to indications, dosage, time of initiation, and duration of treatment with dexamethasone in infants of extremely low birthweight.

Retinal hemorrhage occurred in four women after they had received epidural methylprednisolone for chronic back and hip pain (SEDA-20, 373) (63). Retinal and choroidal vascular occlusions are a serious and sometimes lasting complication of periocular and facial injections of glucocorticoids (SEDA-21, 416).

Toxic optic neuropathy

Toxic optic neuropathy can occur and may underlie various reports of sudden blindness in patients taking glucocorticoids. In one case, transient visual loss occurred on several occasions, each time after administration of a glucocorticoid (SEDA-17, 447). In another case, blindness occurred suddenly and paradoxically after glucocorticoid injections into the nasal turbinates (64). Although glucocorticoids are sometimes used successfully to relieve pre-existing optic neuritis, a number of such patients react adversely with increased episodes of visual loss.

Exophthalmos

Exophthalmos has been described incidentally as a complication of long-term glucocorticoid therapy and there has been a series of 21 cases (65).

Psychological, psychiatric

The psychostimulant effects of the glucocorticoids are well known (66), and their dose dependency is recognized (SED-11, 817); they may amount to little more than

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euphoria or comprise severe mental derangement, for example mania in an adult with no previous psychiatric history (SEDA-17, 446) or catatonic stupor demanding electroconvulsive therapy (67). In their mildest form, and especially in children, the mental changes may be detectable only by specific tests of mental function (68). Mental effects can occur in patients treated with fairly low doses; they can also occur after withdrawal or omission of treatment, apparently because of adrenal suppression (69,70).

- A 32-year-old woman developed irritability, anger, and insomnia after taking oral prednisone (60 mg/day) for a relapse of ileal Crohn's disease (71). The prednisone was withdrawn and replaced by budesonide (9 mg/day), and the psychiatric adverse effects were relieved after 3 days. A good clinical response was maintained, with no relapse after 2 months of budesonide therapy.

Development

Dexamethasone has been used in ventilator-dependent preterm infants to reduce the risk and severity of chronic lung disease. Usually it is given in a tapering course over a long period (42 days). The effects of dexamethasone on developmental outcome at 1 year of age has been evaluated in 118 infants of very low birthweights (47 boys and 71 girls, aged 15–25 days), who were not weaning from assisted ventilation (72). They were randomly assigned double-blind to receive placebo or dexamethasone (initial dose 0.25 mg/kg) tapered over 42 days. A neurological examination, including ultrasonography, was done at 1 year of age. Survival was 88% with dexamethasone and 74% with placebo. Both groups obtained similar scores in mental and psychomotor developmental indexes. More dexamethasone-treated infants had major intracranial abnormalities (21 versus 11%), cerebral palsy (25 versus 7%; OR = 5.3; CI = 1.3, 21), and unspecified neurological abnormalities (45 versus 16%; OR = 3.6; CI = 1.2, 11). Although the authors suggested an adverse effect, they added other possible explanations for these increased risks (improved survival in those with neurological injuries or at increased risk of such injuries).

Behavioral disorders

Children have marked increases in behavioral problems during treatment with high-dose prednisone for relapse of nephrotic syndrome, according to the results of a study conducted in the USA (73). Ten children aged 2.9–15 years (mean 8.2 years) received prednisone 2 mg/kg/day, tapering at the time of remission, which was at week 2 in seven patients. At baseline, eight children had normal behavioral patterns and two had anxious/depressed and aggressive behavior using the Child Behaviour Checklist (CBCL). During high-dose prednisone therapy, five of the eight children with normal baseline scores had CBCL scores for anxiety, depression, and aggressive behavior above the 95th percentile for age. The two children with high baseline CBCL scores had worsening behavioral problems during high-dose prednisone. Behavioral problems occurred almost exclusively in the children who received over 1 mg/kg every 48 hours. Regression analysis showed that prednisone dosage was a strong predictor of increased aggressive behaviour.

Intravenous methylprednisolone was associated with a spectrum of adverse reactions, most frequently behavioral disorders, in 213 children with rheumatic disease, according to the results of a US study (12). However, intravenous methylprednisolone was generally well tolerated. The children received their first dose of intravenous methylprednisolone 30 mg/kg over at least 60 minutes, and if the first dose was well tolerated they were given further infusions at home under the supervision of a nurse. There was at least one adverse reaction in 46 children (22%) of whom 18 had an adverse reaction within the first three doses. The most commonly reported adverse reactions were behavioral disorders (21 children), including mood changes, hyperactivity, hallucinations, disorientation, and sleep disorders. Several children had serious acute reactions, which were readily controlled. Most of them were able to continue methylprednisolone therapy with premedication or were given an alternative glucocorticoid. The researchers emphasized the need to monitor treatment closely and to have appropriate drugs readily available to treat adverse reactions.

Large doses are most likely to cause the more serious behavioral and personality changes, ranging from extreme nervousness, severe insomnia, or mood swings to psychotic episodes, which can include both manic and depressive states, paranoid states, and acute toxic psychoses. A history of emotional disorders does not necessarily preclude glucocorticoid treatment, but existing emotional instability or psychotic tendencies can be aggravated by glucocorticoids. Such patients as these should be carefully and continuously observed for signs of mental changes, including alterations in the sleep pattern. Aggravation of psychiatric symptoms can occur not only during high-dose oral treatment, but also after any increase in dosage during long-term maintenance therapy; it can also occur with inhalation therapy (74). The psychomotor stimulant effect is said to be most pronounced with dexamethasone and to be much less with methylprednisolone, but this concept of a differential psychotropic effect still has to be confirmed.

Memory

The effects of prednisone on memory have been assessed (SEDA-21, 413) (75). Glucocorticoid-treated patients performed worse than controls in tests of explicit memory. Pulsed intravenous methylprednisolone (2.5 g over 5 days, 5 g over 7 days, or 10 g over 5 days) caused impaired memory in patients with relapsing-remitting multiple sclerosis, but this effect is reversible, according to the results of an Italian study (76). Compared with ten control patients, there was marked selective impairment of explicit memory in 14 patients with relapsing-remitting multiple sclerosis treated with pulsed intravenous methylprednisolone. However, this memory impairment completely resolved 60 days after methylprednisolone treatment.

Glucocorticoids can regulate hippocampal metabolism, physiological functions, and memory. Despite evidence of memory loss during glucocorticoid treatment (SEDA-23, 428), and correlations between memory and cortisol

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concentrations in certain diseases, it is unclear whether exposure to the endogenous glucocorticoid cortisol in amounts seen during physical and psychological stress in humans can inhibit memory performance in otherwise healthy individuals. In an elegant experiment on the effect of cortisol on memory, 51 young healthy volunteers (24 men and 27 women) participated in a double-blind, randomized, crossover, placebo-controlled trial of cortisol 40 mg/day or 160 mg/day for 4 days (77). The lower dose of cortisol was equivalent to the cortisol delivered during a mild stress and the higher dose to major stress. Cognitive performance and plasma cortisol were evaluated before and until 10 days after drug administration. Cortisol produced a dose-related reversible reduction in verbal declarative memory without effects on nonverbal memory, sustained or selective attention, or executive function. Exposure to cortisol at doses and plasma concentrations associated with physical and psychological stress in humans can reversibly reduce some elements of memory performance.

Prednisone, 10 mg/day for 1 year, has been evaluated in 136 patients with probable Alzheimer's disease in a double-blind, randomized, placebo-controlled trial (78). There were no differences in the primary measures of efficacy (cognitive subscale of the Alzheimer Disease Assessment Scale), but those treated with prednisone had significantly greater memory impairment (Clinical Dementia sum of boxes), and agitation and hostility/suspicion (Brief Psychiatric Rating Scale). Other adverse effects in those who took prednisone were reduced bone density and a small rise in intraocular pressure.

In healthy individuals undergoing acute stress, there was specifically impaired retrieval of declarative long-term memory for a word list, suggesting that cortisol-induced impairment of retrieval may add significantly to the memory deficits caused by prolonged treatment (79).

Sleep

The effects of acute systemic dexamethasone administration on sleep structure have been investigated. Dexamethasone caused significant increases in REM latency, the percentage time spent awake, and the percentage time spent in slow-wave sleep. There were also significant reductions in the percentage time spent in REM sleep and the number of REM periods (SEDA-21, 413) (80).

Psychoses

Mania has been attributed to glucocorticoids (81).

- A 46-year-old man, with an 8-year history of cluster headaches and some episodes of endogenous depression, took glucocorticoids 120 mg/day for a week and then a tapering dosage at the start of his latest cluster episode. His headaches stopped but then recurred after 10 days. He was treated prophylactically with verapamil, but a few days later, while the dose of glucocorticoid was being tapered, he developed symptoms of mania. The glucocorticoids were withdrawn, he was given valproic acid, and his mania resolved after 10 days. Verapamil prophylaxis was restarted and he had no more cluster headaches.

The authors commented that the manic symptoms had probably been caused by glucocorticoids or glucocorticoid withdrawal. They concluded that patients with cluster headache and a history of affective disorder should not be treated with glucocorticoids, but with valproate or lithium, which are effective in both conditions. Lamotrigine, an anticonvulsive drug with mood-stabilizing effects, may prevent glucocorticoid-induced mania in patients for whom valproate or lithium are not possible (82).

Glucocorticoids can cause neuropsychiatric adverse effects that dictate a reduction in dose and sometimes withdrawal of treatment. Of 32 patients with asthma (mean age 47 years) who took prednisone in a mean dosage of 42 mg/day for a mean duration of 5 days, those with past or current symptoms of depression had a significant reduction in depressive symptoms during prednisone therapy compared with those without depression (83). After 3–7 days of therapy there was a significant increase in the risk of mania, with return to baseline after withdrawal.

The management of a psychotic reaction in an Addisonian patient taking a glucocorticoid needs special care (SED-8, 820). Psychotic reactions that do not abate promptly when the glucocorticoid dosage is reduced to the lowest effective value (or withdrawn) may need to be treated with neuroleptic drugs; occasionally these fail and antidepressants are needed (SEDA-18, 387). However, in other cases, antidepressants appear to aggravate the symptoms.

- Two patients with prednisolone-induced psychosis improved on giving the drug in three divided daily doses. Recurrence was avoided by switching to enteric-coated tablets.

This suggests that in susceptible patients the margin of safety may be quite narrow (SED-12, 982). It is possible that reduced absorption accounted for the improvement in this case, but attention should perhaps be focused on peak plasma concentrations rather than average steady-state concentrations.

In one case, glucocorticoid-induced catatonic psychosis unexpectedly responded to etomidate (84).

- A 27-year-old woman with myasthenia gravis taking prednisolone 100 mg/day became unresponsive and had respiratory difficulties. She was given etomidate 20 mg intravenously to facilitate endotracheal intubation. One minute later she became alert and oriented, with normal muscle strength, and became very emotional. Eight hours later she again became catatonic and had a similar response to etomidate 10 mg. Glucocorticoid-induced catatonia was diagnosed, her glucocorticoid dosage was reduced, and she left hospital uneventfully 4 days later.

The effect of etomidate on catatonia, similar to that of amobarbital, was thought to be due to enhanced GABA receptor function in patients with an overactive reticular system.

A case report has suggested that risperidone, an atypical neuroleptic drug, can be useful in treating adolescents with glucocorticoid-induced psychosis and may hasten its resolution (85).

- A 14-year-old African-American girl with acute lymphocytic leukemia was treated with dexamethasone

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24 mg/day for 25 days. Four days after starting to taper the dose she had a psychotic reaction with visual hallucinations, disorientation, agitation, and attempts to leave the floor. Her mother refused treatment with haloperidol. Steroids were withdrawn and lorazepam was given as needed. Nine days later the symptoms had not improved. She was given risperidone 1 mg/day; within 3 days the psychotic reaction began to improve and by 3 weeks the symptoms had completely resolved.

Obsessive-compulsive disorder

Obsessive-compulsive behavior after oral cortisone has been described (86).

- A 75-year-old white man, without a history of psychiatric disorders, took cortisone 50 mg/day for 6 weeks for pulmonary fibrosis and developed severe obsessive-compulsive behavior without affective or psychotic symptoms. He was given risperidone without any beneficial effect. The dose of cortisone was tapered over 18 days. An MRI scan showed no signs of organic brain disease and an electroencephalogram was normal. His symptoms improved 16 days after withdrawal and resolved completely after 24 days. Risperidone was withdrawn without recurrence.

Endocrine

The endocrine effects of the glucocorticoids variously involve the pituitary–adrenal axis, the ovaries and testes, the parathyroid glands, and the thyroid gland.

Pituitary gland

Empty sella syndrome occurred in a boy who developed hypopituitarism after long-term pulse therapy with prednisone for nephrotic syndrome (87).

- A 16-year-old Japanese boy's growth and development was normal until the age of 2 years. He then developed nephrotic syndrome and was treated with pulsed glucocorticoid therapy nine times over the next 14 years. After the age of 3 years, his rate of growth had fallen. At 16 years, when he was taking prednisone 60 mg/m^2/day he was given prednisone on alternate days and the dose was gradually tapered. The secretion of pituitary hormones, except antidiuretic hormone, was impaired and an MRI scan of his brain showed an empty sella and atrophy of the pituitary gland.

When markedly impaired growth is noted in patients treated with glucocorticoids long-term or in pulses, it is necessary to assess pituitary function and the anatomy of the pituitary gland. Children who receive glucocorticoid pulse therapy may develop an empty sella more frequently than is usually recognized.

Pituitary–adrenal axis

Raised glucocorticoid plasma concentrations usually result, after 2 weeks, in the first signs of iatrogenic Cushing's syndrome. The characteristic symptoms can occur individually or in combination. Whereas in Cushing's disease or corticotropin–induced Cushing's syndrome, the predominant symptoms are in part determined by hyperandrogenicity and tend to comprise hypertension, acne, impaired sight, disorders of sexual function, hirsutism or virilism, striae of the skin, and plethora, Cushing's syndrome due to glucocorticoid therapy is likely to cause benign intracranial hypertension, glaucoma, subcapsular cataract, pancreatitis, aseptic necrosis of the bones, and panniculitis. Obesity, facial rounding, psychiatric symptoms, edema, and delayed wound healing are common to these different forms of Cushing's syndrome.

It has been said that Cushing-like effects are to be expected if the function of the adrenal cortex is suppressed by daily doses of more than 50 mg hydrocortisone or its equivalent. However, pituitary–adrenal suppression has been described at lower dosage equivalents, for example during prolonged intermittent therapy with dexamethasone (88). The secondary adrenal insufficiency caused by therapeutically effective doses can be observed even after giving prednisone 5 mg tds for only 1 week; after withdrawal, adrenal suppression lasts for some days. If one continues this treatment for about 20 weeks, maximal atrophy of the adrenal cortex results, and lasts for some months. This effect begins with inhibition of the hypothalamus, and culminates in true atrophy of the adrenal cortex. It can occur even with glucocorticoids given by inhalation (89). Inhaled fluticasone is associated with at least a twofold greater suppression of adrenal function than inhaled budesonide microgram for microgram, according to the results of a crossover study (SEDA-21, 415) (90). Patients with liver disease may experience adrenal suppression with lower doses of glucocorticoids (91). It is advisable to use alternate-day therapy to avoid suppression of corticotropin secretion in patients who will need long-term therapy; it will produce the same therapeutic effect as daily dosage. It can be helpful to measure the degree of suppression of corticotropin secretion during long-term glucocorticoid treatment of asthmatic children, as a means of optimizing therapy and avoiding excessive dosage (92). The period of time during which the patient should be considered at risk of adrenal insufficiency after withdrawal of oral prednisolone treatment in childhood nephrotic syndrome is still controversial. A study in such patients has suggested that adrenal insufficiency may occur up to 9 months after treatment has ended (SEDA-19, 376) (93).

Many protocols for treating children with early B cell acute lymphoblastic leukemia involve 28 consecutive days of high-dose glucocorticoids during induction. The effect of this therapy on adrenal function has been prospectively evaluated (94) in 10 children by tetracosactide stimulation before the start of dexamethasone therapy and every 4 weeks thereafter until adrenal function returned to normal. All had normal adrenal function before dexamethasone treatment and impaired adrenal responses 24 hours after completing therapy. Each child felt ill for 2–4 weeks after completing therapy. Seven patients recovered normal adrenal function after 4 weeks, but three did not have normal adrenal function until 8 weeks after withdrawal. Thus, high-dose dexamethasone therapy can cause adrenal insufficiency lasting more than 4 weeks after the end of treatment. This problem might be avoided by tapering doses of glucocorticoids and providing supplementary glucocorticoids during periods of increased stress.

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Tolerance to glucocorticoids in this, as in some other respects, varies from individual to individual; some patients tolerate 30 mg of prednisone for a long time without developing Cushing's syndrome, while others develop symptoms at 7.5 mg; the doses recommended today to avoid Cushing's syndrome in most patients are usually equivalent to hydrocortisone 20 mg. Cushing's syndrome and other systemic adverse effects can occur not only from oral and injected glucocorticoids, but also from topical and intranasal treatment (95) and intrapulmonary or epidural administration (SEDA-19, 376) (SEDA-20, 370) (96,97).

- Two patients developed hypopituitarism and empty sella syndrome during glucocorticoid pulse therapy for nephrotic syndrome (SEDA-22, 444) (98).

Glucocorticoid-treated patients with inadequate adrenal function who have an intercurrent illness or are due to undergo surgery will have an inadequate reaction to the resulting stress and need to be temporarily protected by additional glucocorticoid (99).

Pseudohyperaldosteronism has been reported even after intranasal application of 9-alpha-fluoroprednisolone (SEDA-11, 340).

Parathyroid function

There is antagonism between the parathyroid hormone and glucocorticoids (100). Latent hyperparathyroidism can be unmasked by glucocorticoids (101).

Thyroid function

Even a single dose of corticotropin briefly inhibits the secretion of thyrotrophic hormone. The uptake of radioactive iodine is also suppressed by corticotropin and by glucocorticoids, but this has no clinical relevance. Pathological changes in thyroid function induced by glucocorticoid treatment are reportedly rare.

Metabolism

Glucose metabolism

All glucocorticoids increase gluconeogenesis. The turnover of glucose is increased, more being metabolized to fat, and blood glucose concentration is increased by 10–20%. Glucose tolerance and sensitivity to insulin are reduced, but provided pancreatic islet function is normal, carbohydrate metabolism will not be noticeably altered. So-called "steroid diabetes," a benign diabetes without a tendency to ketosis, but with a low sensitivity to insulin and a low renal threshold to glucose, only develops in one-fifth of patients treated with high glucocorticoid dosages. Even in patients with diabetes, ketosis is not to be expected, since glucocorticoids have antiketotic activity, presumably through suppression of growth hormone secretion.

Glucocorticoid treatment of known diabetics normally leads to deregulation, but this can be compensated for by adjusting the dose of insulin. The increased gluconeogenesis induced by glucocorticoids mainly takes place in the liver, but glucocorticoid treatment is especially likely to disturb carbohydrate metabolism in liver disease.

When hyperglycemic coma occurs it is almost always of the hyperosmolar nonketotic type. After termination of glucocorticoid treatment, steroid diabetes normally disappears. An apparent exception to these findings is provided by the case of a patient in whom glucocorticoid treatment was followed by severe diabetes with diabetic nephropathy, but this was a seriously ill individual who had already undergone renal transplantation (SEDA-17, 449). Gestational diabetes mellitus was more common in women who had received glucocorticoids with or without beta-adrenoceptor agonists for threatened preterm delivery compared with controls (SEDA-22, 445) (102).

Glucocorticoids probably have more than one effect on carbohydrate metabolism. An increase in fasting glucagon concentration has been observed in volunteers given prednisolone 40 mg/day for 4 days, and this effect may be involved, alongside gluconeogenesis, in glucocorticoid-induced hyperglycemia. Some newer glucocorticoids have been claimed to have smaller effects on blood glucose (as well as less salt and water retention), but further studies are needed to confirm whether this interesting therapeutic approach has been successful (SEDA-13, 353).

Deflazacort, an oxazoline derivative of prednisolone, was introduced as a potential substitute for conventional glucocorticoids in order to ameliorate glucose intolerance. In a randomized study in kidney transplant recipients with pre- or post-transplantation diabetes mellitus, 42 patients who switched from prednisone to deflazacort (in the ratio 5:6 mg) were prospectively compared with 40 patients who continued to take prednisone (SEDA-22, 445) (103). During the mean follow-up period of 13 months, neither graft dysfunction nor acute rejection developed in the conversion group, and there was improvement in blood glucose control. When the conversion group was stratified into those with pre- or post-transplantation diabetes, there were promising effects in the patients with post-transplantation diabetes. More than a 50% dosage reduction of hypoglycemic drugs was possible in 42% of those with post-transplantation diabetes.

The risk of hyperglycemia requiring treatment in patients receiving oral glucocorticoids has been quantified in a case-control study of 11 855 patients, 35 years of age or older, with newly initiated treatment with a hypoglycemic drug (SEDA-19, 375) (104). The risk for initiating hypoglycemic therapy increased with the recent use of a glucocorticoid. The risk grew with increasing average daily glucocorticoid dosage (in mg of hydrocortisone equivalents): 1.77 for 1–39 mg/day, 3.02 for 40–79 mg/day, 5.82 for 80–119 mg/day, and 10.34 for 120 mg/day or more.

Lipid metabolism

High-dose glucocorticoid therapy can cause marked hypertriglyceridemia, with milky plasma (SEDA-15, 421) (SEDA-16, 450). It has been suggested that this is caused by abnormal accumulation of dietary fat, reduced postheparin lipolytic activity, and glucose intolerance (105). An association between glucocorticoid exposure and hypercholesterolemia has been found in several studies (106) and can contribute to an increased risk of atherosclerotic vascular disease.

Most premature neonates need intravenous lipids during the first few weeks of life to acquire adequate energy

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intake and prevent essential fatty acid deficiency before they can tolerate all nutrition via enteral feeds. Dexamethasone is associated with multiple adverse effects in neonates, including poor weight gain and impairment of glucose and protein metabolism. In ten neonates (four boys, mean age 17.3 days) taking dexamethasone for bronchopulmonary dysplasia, intravenous lipids (3 g/kg/day) caused hypertriglyceridemia in the presence of hyperinsulinemia and increased free fatty acid concentrations (107). Because of concomitant hyperinsulinemia, the authors speculated that dexamethasone reduced fatty acid oxidation, explaining poor weight gain.

Altered fat deposition has been repeatedly reported. Fat can be deposited epidurally and at other sites. Adiposis dolora, which involves the symmetrical appearance of multiple painful fat deposits in the subcutaneous tissues, has on one occasion been attributed to glucocorticoids (SEDA-16, 451).

Tumor lysis syndrome

Acute tumor lysis syndrome is a life-threatening metabolic emergency that results from rapid massive necrosis of tumor cells. There have been repeated reports of an acute tumor lysis syndrome when glucocorticoids are administered in patients with pre-existing lymphoid tumors (108).

- A 60-year-old woman took dexamethasone 4 mg 8-hourly for dyspnea due to a precursor T lymphoblastic lymphoma-leukemia with bilateral pleural effusions and a large mass in the anterior mediastinum (109). She developed acute renal insufficiency and laboratory evidence of the metabolic effects of massive cytolysis. She received vigorous hydration, a diuretic, allopurinol, and hemodialysis. She recovered within 2 weeks and then underwent six courses of CHOP chemotherapy. The mediastinal mass regressed completely. She remained asymptomatic until she developed full-blown acute lymphoblastic leukemia, which was resistant to treatment.

Electrolyte balance

The severity of potassium loss due to glucocorticoids depends partly on the amount of sodium in the diet; the most widely used synthetic glucocorticoids cause less potassium excretion than natural hydrocortisone does. Prednisone and prednisolone have a glucocorticoid activity 4–5 times that of hydrocortisone, but their mineralocorticoid activity is less (see Table 1); even at high dosages they do not cause noteworthy sodium and water retention. Of the major synthetic glucocorticoids, dexamethasone has the strongest anti-inflammatory, hyperglycemic, and corticotropin-inhibitory activity; sodium retention is completely absent; the degree of glucocorticoid-induced metabolic alkalosis may also be less with dexamethasone than with hydrocortisone or methylprednisolone (SEDA-10, 343).

Mineral balance

There can be increases in calcium and phosphorus loss because of effects on both the kidney and the bowel, with increased excretion and reduced resorption (110). Tetany, which has been seen in patients receiving high-dose long-term intravenous glucocorticoids, has been explained as being due to hypocalcemia, and there are also effects on bone. Tetany has also been reported in a patient with latent hyperparathyroidism after the administration of a glucocorticoid (101).

Hypocalcemic encephalopathy occurred in a 35-year-old woman with hypoparathyroidism. It was believed that the administration of methylprednisolone intramuscularly had precipitated severe hypocalcemia, which had led to a metabolic encephalopathy (SEDA-20, 371) (111).

The administration of large doses of glucocorticoids to patients with major burns presenting with low cardiac output has been reported to produce a reversible drop in serum zinc, which might lead to impaired tissue repair (SED-8, 824), but it is not clear whether this has clinical effects.

Metal metabolism

Glucocorticoids increase chromium losses and glucocorticoid-induced diabetes can be reversed by chromium supplementation (112). Doses of hypoglycemic drugs were also reduced by 50% in all patients when they were given supplementary chromium.

Hematologic

Erythrocytes

Polycythemia is a symptom of Cushing's syndrome, and conversely anemia correlates with Addison's disease, but polycythemia is not generally encountered as a consequence of treatment with glucocorticoids, perhaps because there is no increased secretion of androgens; an increase in hemoglobin was nevertheless the most frequent adverse effect observed in a study over 8 years of 77 patients treated for hyperergic-allergic reactions. At the beginning of treatment more than 40% (and during continuous therapy more than 70%) of patients showed this change in erythrocytes (113). There was leukocytosis in more than 60% in the early phases and in more than 40% later (113). Thrombocytosis occurred in 5–10% during continuous treatment. This report agrees fairly well with some older publications, but it has been noted in the past that in the long run very high-dose glucocorticoid treatment can result in suppression of the activity of the bone marrow with fatty infiltration replacing hemopoietic tissue.

Leukocytes

Not all classes of leukocytes are affected by glucocorticoids in the same way. The total leukocyte count is increased, but the number of eosinophilic leukocytes falls, as does the lymphocyte count. The number of monocytes is reduced, as is their capacity to perform phagocytosis.

In children, a leukemoid reaction has been induced by betamethasone treatment (114); this possibility must always be borne in mind, since glucocorticoids can actually be used to treat leukemia or its complications. A case of very high white blood cell count with neutrophilia in a preterm infant whose mother had received two doses of betamethasone prenatally to enhance fetal lung maturation is one of a short list of leukemoid reactions possibly attributable to antenatal glucocorticoid treatment (115).

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It is possible that in children with acute lymphoblastic leukemia, glucocorticoid therapy adversely affects the duration of remissions, and it has therefore been suggested that leukemia should be ruled out in children before starting long-term therapy with glucocorticoids (SEDA-11, 340). Depression of the lymphocyte count seems to be a general and direct action of the glucocorticoids (116), but the mechanism is still incompletely understood; certainly, lymphocytolysis seems to be increased by glucocorticoids. Studies of lymphocyte subpopulations show a preferential reduction in T cells, while B cells are constant or slightly reduced. B lymphocyte function (measured as immunoglobulin synthesis) falls, suppressor T lymphocyte activity is suppressed, and helper T lymphocyte function is unaffected by glucocorticoids (SEDA-3, 308) (117).

- Fever and leukopenia with methylprednisolone and prednisolone has been reported in a 29-year-old woman with systemic lupus erythematosus (118).

The authors commented that fever associated with glucocorticoids occurs frequently, whereas leukopenia is rare. Fever and leukopenia are important signs of an exacerbation of systemic lupus erythematosus, and it would be difficult to distinguish between an exacerbation of the disease and an adverse effect of glucocorticoids.

Platelets and coagulation

In heart transplant recipients, intramuscular glucocorticoids can impair fibrinolysis, producing susceptibility to thrombotic disease (SEDA-22, 443) (119). They can also increase the platelet count. In one patient the blue toe syndrome occurred repeatedly when glucocorticoids were used to increase the platelet count (SEDA-16, 451).

Mouth and teeth

Oral candidiasis is seen in some 5–10% of patients who use inhaled glucocorticoids, particularly when oral hygiene is poor, but is rarely symptomatic. The risk can be reduced by the use of a large-volume spacer (120,121).

Hypertrophy of the tongue has been attributed to inhaled beclomethasone and may have been related to edema of the buccal mucosa and tongue from direct contact with the glucocorticoid, infection, glossitis caused by glucocorticoid therapy, a direct effect of glucocorticoids on the tongue muscle, or excess localized deposition of fat, as is seen in patients given systemic glucocorticoids (SEDA-20, 371) (122).

Gastrointestinal

Peptic ulceration

It is no longer seriously believed that glucocorticoid treatment in adults markedly increases the risk of peptic ulceration (123,124). However, the symptoms of an existing peptic ulcer can certainly be masked. There may also be a genuine risk of ulcerative disorders in premature children. The issue has often been complicated by the simultaneous (sometimes unrecorded) use of ulcerogenic non-steroidal anti-inflammatory agents. A meta-analysis of whether glucocorticoid therapy caused peptic ulcer and other putative complications of glucocorticoid therapy was negative: peptic ulcers occurred in nine of 3267 patients in the placebo group (0.03%) and 13 of 3335 patients in the glucocorticoid group (0.04%).

Peptic ulcer should not be considered a contraindication when glucocorticoid therapy is indicated (SEDA-19, 376) (125). However, the risk of a fatal outcome due to ulcer complications was increased about fourfold in a previous case-control study. Gastrointestinal hemorrhage occurred more often in glucocorticoid-treated patients (2.25%) than in controls (1.6%) (126). The frequency of gastrointestinal bleeding in these studies compares well with earlier observations in the Boston Collaborative Surveillance Program's 1978 report, according to which 0.5% of a large series of medical inpatients taking glucocorticoids had gastrointestinal bleeding sufficiently severe to require transfusions and 28% had minor bleeding (SED-12, 986).

- A 47-year-old woman developed a gastrocolic fistula during treatment with aspirin (dosage and duration of therapy not stated) and prednisone for chronic rheumatoid arthritis (127).

The author commented that 50–75% of gastrocolic fistulas are related to benign gastric ulcers secondary to the use of NSAIDs. The use of aspirin plus prednisone, as in this patient, increases the risk of complication of peptic ulcer disease two- to fourfold.

The mechanism of whatever harm glucocorticoids may do to the stomach is not clear; cortisol neither consistently increases acid or pepsinogen secretion, nor reduces the protective production of mucin by the gastric mucosa. Serum gastrin concentrations are raised in Cushing's syndrome and in patients taking prolonged glucocorticoid treatment. On the other hand, the secretion of prostaglandin E_2 in gastric juice in response to pentagastrin was impaired during glucocorticoid therapy in children. Since PGE_2 has a cytoprotective effect on the gastric mucosa, impaired secretion in response to increased acid secretion during glucocorticoid therapy may be related to the development of peptic ulcer (SEDA-19, 376) (128).

Some reports suggest that people with hepatic cirrhosis or nephrotic syndrome are particularly at risk. Whatever the degree of risk, patients taking long-term glucocorticoids should be regularly checked to detect peptic ulcers, which can bleed and even perforate without producing pain. There do not seem to be differences in gastric tolerance between the various synthetic glucocorticoids.

Regional ileitis

While glucocorticoids may have a beneficial effect on regional ileitis, perforation of the ileum, lymphatic dilatation, and microscopic fistulae have been observed after treatment.

Ischemic colitis

Glucocorticoids should be used with caution in progressive systemic sclerosis, and concomitant administration of anticoagulants to prevent ischemic colitis is recommended when administering glucocorticoids in high doses, especially by pulse therapy (SEDA-21, 415) (129).

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Ulcerative colitis

A possible risk of glucocorticoid treatment of ulcerative colitis is the development of toxic megacolon or colonic perforation. A change from ulcerative colitis to Crohn's disease may have been induced by prolonged treatment with glucocorticoids (SEDA-19, 376) (130). This case provides further evidence for the view that ulcerative colitis and Crohn's disease may represent a continuous spectrum of inflammatory bowel disease and raises the possibility that reduced polymorphonuclear leukocyte function caused by glucocorticoids may have provoked the development of granulomata.

Diverticular disease

Existing diverticula can perforate during glucocorticoid therapy (SEDA-18, 387). Abdominal tenderness is the most common and often the only early sign of perforated diverticula in patients taking glucocorticoids. However, in some cases, even abdominal tenderness is absent (SEDA-22, 445) (131).

- Perforation of the sigmoid colon occurred in a 61-year-old Caucasian man with colonic diverticular disease and rheumatoid arthritis treated with pulses of methylprednisolone 1 g (132).

The authors suggested that methylprednisolone pulses should be used carefully in patients over 50 years of age and/or people with demonstrated or suspected diverticular disease.

Liver

The process of gluconeogenesis, which is promoted by glucocorticoids, takes place mainly in the liver. The glycolytic enzymes of the liver are also activated by these glucocorticoids. The synthesis of ribonucleic acid and of enzymes involved in protein catabolism is increased, but the process of protein catabolism takes place outside the liver as well, for example in the muscles. There is experimental evidence for glucocorticoid-induced enhancement of hepatic lipid synthesis (SEDA-3, 308), but the main effect of glucocorticoids in this connection is lipid mobilization from adipose tissue. The influence of long-term glucocorticoid treatment on liver function is still unknown. If pathological changes are diagnosed, the possible influence of the disease which is being treated has to be borne in mind.

Liver damage from glucocorticoids is rarely severe, but fatal liver failure has been reported.

- A 71-year-old white woman with a compressive optic neuropathy was given five cycles of intravenous methylprednisolone 1 g/day for 3 days followed by tapering oral cortisone for 10–14 days (133). The intervals between cycles were 14 days to 6 weeks. She was otherwise healthy and had no history of liver disease. Her liver function tests were normal or only slightly raised during the first five cycles. She then developed raised liver enzymes, a prolonged prothrombin time, and fatal liver failure. Postmortem examination showed necrosis of the liver parenchyma. Hepatitis serology (A, B, and C) was negative as was in situ hybridization for immunohistochemical proof of hepatitis Bs and Bc or delta virus antibodies in the liver.
- A 53-year-old woman who took prednisolone 20 mg/day for systemic lupus erythematosus for 38 days developed increased aspartate transaminase and alanine transaminase activities (175 and 144 IU/l respectively on day 38 and 871 and 658 IU/l on day 69) (134). She denied taking hepatotoxic drugs. Serological tests for hepatitis viruses were all negative. Autoantibodies against mitochondria and smooth muscle were not detected. Ultrasound and CT scan were consistent with fatty infiltration. Histology showed macrovesicular fat infiltration, periportal cell infiltration with fibrosis, and a few Mallory bodies. The glucocorticoid was gradually tapered and the transaminases gradually fell.
- A 67-year-old teetotaler was given intravenous prednisolone 25 mg tds for primary dermatomyositis and 8 days later developed painless icteric hepatitis, with daily progressive marked deterioration of liver biochemistry (135). She had not taken any other hepatotoxic drugs, and serological tests for hepatitis and hepatotropic viruses were all negative. Antinuclear, antimitochondrial, and smooth muscle autoantibodies were negative. Ultrasound and CT scan of the upper abdomen showed liver fatty infiltration. Prednisolone was tapered gradually, and she gradually improved. However, on day 26 she developed pneumonia and died 6 days later.

Glucocorticoid treatment in the early phase of acute viral hepatitis carries the risk of transition to chronic active hepatitis (SEDA-3, 308).

Three children developed hepatomegaly and raised liver enzymes after receiving high-dose dexamethasone therapy (0.66–1.09 mg/kg/day) (136).

Pancreas

Pancreatitis and altered pancreatic secretion can occur at any time during long-term glucocorticoid treatment (SED-12, 986) (SEDA-14, 339) (137). Necrosis of the pancreas during glucocorticoid treatment has been described and can be lethal. Impairment of pancreatic function can predispose to glucocorticoid-induced pancreatitis. Two other cases of glucocorticoid-induced pancreatitis have been reported (138).

- A 74-year-old woman with seronegative rheumatoid arthritis was given sulfasalazine followed by methotrexate, both of which were withdrawn because of adverse effects. She also took prednisone 10 mg/day. She developed acute abdominal pain and fever (38.7°C) with no chills. Her serum amylase was 269 IU/l, serum lipase 300 IU/l, and urinary amylase 2895 IU/l. There was no evidence of tumor, hypertriglyceridemia, or lithiasis. In addition to prednisone, she was taking amlodipine, bromazepam, and omeprazole, none of which have been reported to cause pancreatitis. A marked improvement was noted after prednisone withdrawal.
- A 68-year-old woman who had taken prednisone 30 mg/day for polymyalgia rheumatica for 6 months developed sharp stabbing abdominal pain, fever (39°C), and vomiting. Her serum amylase was 310 IU/l, serum lipase 340 IU/l, and urinary amylase 1560 IU/l.

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Other causes of pancreatitis were ruled out. She had been taking a thiazide diuretic therapy for the past 10 years. Her symptoms improved noticeably after prednisone withdrawal.

Although the literature suggests a causal relation between glucocorticoid therapy and these various pancreatic complications there is still no certainty; glucocorticoid treatment is, after all, often given simultaneously with other forms of therapy which can cause pancreatitis (SED-11, 82). The strongest evidence that there is a causal relation is provided by a Japanese report on 52 autopsies, which showed marked changes in pancreatic histology in glucocorticoid-treated patients compared with controls (SEDA-17, 449).

Urinary tract

Urinary calculi are more likely during glucocorticoid treatment because of increased excretion of calcium and phosphate (110).

Prednisolone can cause an abrupt rise in proteinuria in patients with nephrotic syndrome. A placebo-controlled study in 26 patients aged 18–68 years with nephrotic syndrome has clarified the mechanisms responsible for this (139). Systemic and renal hemodynamics and urinary protein excretion were measured after prednisolone (125 mg or 150 mg when body weight exceeded 75 kg) and after placebo. Prednisolone increased proteinuria by changing the size–selective barrier of the glomerular capillaries. Neither the renin–angiotensin axis nor prostaglandins were involved in these effects of prednisolone on proteinuria.

Changes resembling diabetic nodular glomerular sclerosis have been seen in glucocorticoid-treated nephrosis.

Treatment with glucocorticoids can result in minor increases in the urinary content of leukocytes and erythrocytes without clear renal injury (140).

The use of high doses of glucocorticoids to counter rejection of renal transplants is still a matter of intensive study; the optimal dose to ensure an effect without undue risk of complications has yet to be agreed on (141).

Vasopressin-resistant polyuria induced by intravenous administration of a therapeutic dose of dexamethasone has been reported (SEDA-20, 370) (142) and nocturia is fairly common during glucocorticoid treatment (143).

The administration of glucocorticoids should be undertaken with caution in progressive systemic sclerosis and the concomitant administration of anticoagulants to prevent scleroderma renal crisis is recommended when administering glucocorticoids in high doses, especially by pulse therapy (SEDA-21, 415) (129).

Skin

Acne is common during treatment, particularly after topical application, and is said to be correlated with the use of compounds that have a particularly strong local effect (144), although this is not proven.

Leukoderma can occur, accompanied by normal melanocyte function but reduced phagocytic activity of the keratinocytes to eliminate the melanosomes (145). Depigmentation can occur at the site of injection of glucocorticoids.

Three cases of severe lipoatrophy, one also with leukoderma, occurring within the same family after intramuscular injection of triamcinolone, suggested genetic susceptibility to this adverse effect (SEDA-3, 303).

Inhibition of the function of the sebaceous glands in the skin is caused by glucocorticoids whilst androgens stimulate their function (146).

A delayed hypersensitivity reaction, characterized by a skin rash, due to dexamethasone has been reported (147). These kinds of reactions to systemic glucocorticoids are rarely reported.

- A 59-year-old woman, who had not used glucocorticoids before, developed an exfoliative rash on her face, upper chest, and skin folds after 3 days treatment with oral dexamethasone (dosage not stated) for an acute episode of encephalomyelitis disseminata. Dexamethasone was immediately withdrawn and her skin lesions resolved over several days. Patch tests were positive to dexamethasone, betamethasone, and clobetasol, but negative to other glucocorticoids, including prednisolone, hydrocortisone butyrate, methylprednisolone, and triamcinolone. Prick tests with all of these glucocorticoids were negative. She tolerated oral methylprednisolone without adverse effects.

Reduced skin thickness and bruising

The glucocorticoids reduce subcutaneous collagen and cause atrophic changes in the skin (148). Subcutaneous atrophy after intramuscular and intra-articular injection has often been reported. Ecchymosis and paper-thin skin folds recall those seen in old people. An increased incidence of subcutaneous ecchymosis in older women has been observed during treatment with triamcinolone acetate (149). Purpura has been observed during glucocorticoid treatment and an increased fragility of the capillaries is thought to occur in about 60% of these patients. There have been reports of cutaneous bruising after the use of high doses of inhaled glucocorticoids (budesonide and beclomethasone), suggesting systemic absorption (SEDA-21, 416) (150).

Prednicarbate is a topical glucocorticoid that seems to have an improved benefit–harm balance, as has been shown in 24 healthy volunteers (7 men, 17 women, aged 25–49 years) in a double-blind, randomized, placebo-controlled study of the effects of prednicarbate, mometasone furoate, and betamethasone 17-valerate on total skin thickness over 6 weeks (151). On day 36, total skin thickness was reduced by a mean of 1% in test fields treated with vehicle; the relative reductions were 13, 17, and 24% for prednicarbate, mometasone furoate, and betamethasone 17-valerate respectively. There were visible signs of atrophy or telangiectasia in two subjects each with betamethasone 17-valerate and mometasone furoate, but not with prednicarbate or its vehicle.

Contact allergy

Topical glucocorticoids are well-known contact sensitizers. Immediate allergic or allergic-like reactions to systemic glucocorticoids also occur, but less often. Two atopic patients developed urticaria, possibly IgE-mediated, from a hydrocortisone injection or infusion (152) and other reactions have been reported.

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- A 50-year-old woman developed contact dermatitis on her legs after she applied hydrocortisone aceponate cream (Efficort) to psoriatic lesions on her lower back (153). Similar lesions also occurred on her legs after she used topical betamethasone cream (Diprosone). However, no eczema developed on or around the site of application. Patch tests were negative to a range of glucocorticoids, including Efficort and Diprosone creams. However, a repeated open application test was positive with Efficort cream, hydrocortisone aceponate 0.127% in petroleum, and tixocortol pivalate 1% in petroleum.
- A 42-year-old woman developed a nonpigmented fixed drug eruption after skin testing and an intra-articular injection of triamcinolone acetonide, which has not been previously reported (154).

Contact allergy to glucocorticoids was evaluated in 7238 patients in a multicenter multinational study of five drugs: budesonide, betamethasone-17-valerate, clobetasol-17-propionate, hydrocortisone-17-butyrate, and tixocortol-21-pivalate. There was a positive patch-test reaction to at least one of the glucocorticoids in 189 patients (2.6%). The incidence ranged from 0.4% in Spain to 6.4% in Belgium. Positive reactions were more frequent with budesonide (100 results) and tixocortol (98 reactions) (SEDA-21, 415) (155). Contact allergic reactions to intranasal budesonide and fluticasone propionate have been described. Many of these cases were characterized by perinasal eczema, often with vesicles, and edema as the initial symptoms. Lesions sometimes spread to the upper lip, cheeks, and eyelids. For fluticasone propionate, analysis of data on adverse events from the Spontaneous Reporting System of the US FDA Division of Epidemiology and Surveillance showed that, in the first 5 months after its introduction into the USA in 1995, 46 patients reported 89 adverse events suspected to be caused by fluticasone propionate intranasal spray. Central nervous system symptoms occurred in 46%, cardiac symptoms in 28%, dermatological symptoms in 39%, and epistaxis in 6.5%. These numbers may underestimate the problem, since no cases reported by the drug manufacturer were included. These results suggest that safety issues may differentiate budesonide and fluticasone propionate from other intranasal glucocorticoids, such as beclomethasone dipropionate (SEDA-21, 415) (156).

Budesonide is advocated as a marker molecule for glucocorticoid contact allergy. When patch testing glucocorticoids, one must consider both their sensitizing potential and their anti-inflammatory properties, as well as the possibility of different time courses of such properties. The dose–response relation for budesonide has therefore been investigated with regard to dose, occlusion time, and reading time in 10 patients (ages not stated) who were patch tested with budesonide in ethanol in serial dilutions from 2.0% down to 0.0002%, with occlusion times of 48, 24, and 5 hours (157). Readings were on days 2, 4, and 7. The 48-hour occlusion detected most positive reactors (8/10) at a reading time of 4 days and 0.002% detected most contact allergies. The "edge effect" (reactions with a peripheral ring due to suppression of the allergic reaction under the patch because of the intrinsic anti-inflammatory effect of the glucocorticoid itself) was noted with several concentrations at early readings. That lower concentrations can detect budesonide allergy better at early readings and that patients with an "edge reaction" can have positive reactions to lower concentrations can be explained by individual glucocorticoid reactivity, the dose–response relation, and the time-courses of the elicitation and the anti-inflammatory capacity.

- A 36-year-old man, who had a long history of atopic dermatitis of the neck, chest, and arms, developed allergic contact dermatitis after topical administration of clobetasone ointment 0.05% (Kindavate) and prednisolone ointment 0.3% (Lidomex) (158). Patch tests with both ointments showed a positive reaction only to Kindavate. Further testing with the separate ingredients of Kindavate showed positive reactions to 0.05, 0.01, and 0.005% clobetasone on day 7.
- A 40-year-old woman had a flare-up of her eczema (159). She had had previous negative patch tests 10 years before. She had taken topical glucocorticoids and emollients for a few months, but had not used budesonide. Patch testing with the European standard series showed a positive reaction to budesonide 0.1% at 3 days. All other allergens were negative. The only antecedent exposure was that she had three children with asthma, all of whom regularly used inhaled budesonide and occasionally nebulizers. She had not used the inhaler but had helped her children to manage the devices. A subsequent patch test with powdered budesonide from the inhaler was positive.
- A 14-year-old girl with newly diagnosed systemic lupus erythematosus developed a pruritic bullous eruption while taking prednisone 20 mg/day (160). She was given a single daily dose of intravenous methylprednisolone 60 mg with rapid improvement. In preparation for discharge, the glucocorticoid was changed to oral prednisone 60 mg/day, to which she developed a pruritic bullous eruption consistent with erythema multiforme. She underwent immediate and delayed hypersensitivity tests. Intradermal and patch tests to liquid prednisone were positive. She was given oral methylprednisolone 48 mg/day and has not had recurrence of the skin lesions.
- A 27-year-old woman, a pharmacist, had dermatitis on three separate occasions a few hours after she started to take oral deflazacort 6 mg for vesicular hand eczema (161). On each occasion, her symptoms included a widespread macular rash mainly on the inner aspects of her arms and legs and buttocks. She also had severe scaling, fever, nausea, vomiting, malaise, and hypotension. A skin biopsy was consistent with erythema multiforme, and direct immunofluorescence showed granular deposits at the dermoepidermal junction. Patch tests to the commercial formulation of deflazacort 6 mg (1% aqueous solution) and to pure deflazacort (1% aqueous solution) were positive, but there were no cross-reactions to other glucocorticoids.

The author of the last report commented that the patient probably developed hypersensitivity to deflazacort as a result of occupational exposure.

Other cases of erythema multiforme-like contact dermatitis after topical budesonide have been reported (SEDA-21, 415) (162). In a large case-control study, potential cases of severe forms of erythema multiforme,

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toxic epidermal necrolysis and Stevens–Johnson syndrome, were collected in four European countries (France, Portugal, Italy, and Germany) (SEDA-20, 371) (163). There was a significant relation with glucocorticoid use in the preceding week (multivariate analysis relative risk = 4.4; 95% CI = 1.9, 10), or when prescribed for long-term therapy (crude relative risk for use less than 2 months = 54; 95% CI = 23, 124). The estimates of excess risks associated with glucocorticoids or sulfonamides (which are well-known to cause these syndromes), expressed as the number of cases attributable to the drug per million users in 1 week, were 1.5 and 4.5 respectively.

Cross-reactivity between glucocorticoids and progestogens has been described (164).

- A 68-year-old woman, with a prolonged history of pityriasis lichenoides chronica treated with topical glucocorticoids, including hydrocortisone, took a formulation containing conjugated estrogens 0.625 mg and hydroxyprogesterone acetate 5 mg (frequency of administration not stated) for late menopausal syndrome. Years later she started to have pruritus, a maculopapular rash, and flu-like symptoms for several days before menstruation. On this occasion, she presented with a severe, pruritic, papulovesicular eruption on her chest, back, abdomen, and legs. The eruption had developed after treatment for 7 days with the estrogen–progestogen formulation; she had developed similar symptoms on several previous occasions after taking the same medication. She was treated with antihistamines and her skin eruption resolved within a few days. Patch tests were positive to 17-OH-progesterone, tixocortol pivalate, and budesonide.

The authors hypothesized that this patient, who had taken topical glucocorticoids for several years, had become sensitive and that the recurrent episodes of autoimmune progestogen dermatitis were related to endogenous progestogen sensitivity following cross-sensitivity to glucocorticoids. This hypothesis was supported by the development of recurrent eczema several times after she took an estrogen–progestogen preparation.

Musculoskeletal

Osteoporosis

The use of glucocorticoids is associated with reduced bone mineral density, bone loss, osteoporosis, and fractures. This has been described during the long-term use of glucocorticoid by any route of administration (SEDA-19, 377) (SEDA-20, 374). The effects of glucocorticoids on bone have been reviewed (SEDA-21, 417) (165). Biochemical markers of bone mineral density are listed in Table 4. In patients with secondary hypoadrenalism, hydrocortisone 30 mg/day for replacement produced a significant fall in osteocalcin, indicating bone loss. Lower doses of hydrocortisone (10 mg and 20 mg) produced similar efficacy in terms of quality of life but smaller effects on osteocalcin concentrations and therefore a reduction in bone loss (166).

The fluorinated glucocorticoids are said to have relatively more catabolic activity than others and might have a greater effect on the skeleton but such impressions may merely reflect the general potency of some newer glucocorticoids and a tendency to use them in inappropriate doses. A relatively new glucocorticoid, deflazacort, has been proposed to have less effect on bone metabolism, but a double-blind study has failed to show an advantage compared with prednisolone (SEDA-21, 417) (167).

Osteoporosis induced by chronic glucocorticoid therapy has been reviewed in patients with obstructive lung diseases (168) and patients with skin diseases (169).

Table 4 Biochemical markers of bone mineral density

Bone formation
Blood
Alkaline phosphatase (bone-specific)
Osteocalcin
Procollagen type I carboxy-terminal propeptide (PICP)
Procollagen type I amino-terminal propeptide (PINP)
Procollagen type III amino-terminal propeptide (PIIINP)
Bone resorption
Blood
Acid phosphatase (acid-resistant)
Type I collagen carboxy-terminal telopeptide (ICTP)
Urine
Calcium
Hydroxyproline
Cross-linked peptides (pyridinium and deoxypyridinoline)

Presentation

Of the effects of glucocorticoids on the skeleton, osteoporosis is the most important clinically; manifestations can include vertebral compression fractures, scoliosis resulting in respiratory embarrassment, and fractures of the long bones. The risk of vertebral fractures is not different in patients taking or not taking glucocorticoids in whom bone mineral density is similar (170).

Glucocorticoids can even cause osteoporosis when they are used for long-term replacement therapy in the Addison's disease, as has been shown by a study of 91 patients who had taken glucocorticoids for a mean of 10.6 years, in whom bone mineral density was reduced by 32% compared with age-matched controls (SEDA-19, 377) (171). However, these results contrasted with the results of a Spanish study in patients with Addison's disease, in which no direct relation was found between replacement therapy and either bone density or biochemical markers of bone turnover of calcium metabolism (alkaline phosphatase, osteocalcin, procollagen I type, parathormone, and 1,25-dihydroxycolecalciferol) (SEDA-19, 377) (172).

Atraumatic posterior pelvic ring fractures that simulate the form of presentation of metastatic diseases can be produced by glucocorticoid administration (SEDA-19, 377) (173).

Accelerated bone loss, with an increased risk of first hip fracture, occurred in elderly women taking oral glucocorticoids (174). At baseline, 122 (1.5%) women were taking inhaled glucocorticoids only (median dose equivalent to inhaled beclomethasone 168 micrograms/day), 228 (2.8%) were taking oral glucocorticoids (median dose equivalent to prednisone 5 mg/day) with or without inhaled glucocorticoids, and 7718 were not taking any glucocorticoids. The women who were taking oral glucocorticoids had lower mean bone mineral density at 3.6 years than nonusers, with an interim fall that was twice as fast. First hip fracture

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occurred in 4.8% of the women who were taking oral glucocorticoids and in 2.8% of the women who were not (RR = 2.1; CI = 1.0, 4.4). The researchers said that the power of the study was not sufficient to determine the relative risk of hip fracture in women taking inhaled glucocorticoids.

A reduction in bone mineral density has been described in 23 patients (19 men) with chronic fatigue syndrome taking low-dose glucocorticoids in a double-blind, randomized, placebo-controlled study (175). The patients took hydrocortisone 25–35 mg/day or matched placebo for 3 months. Mean bone mineral density in the spine fell by 2% with hydrocortisone and increased by 1% with placebo.

A group of 367 patients with lung disease taking oral glucocorticoids (177 women, mean age 68 years, 190 men, mean age 70 years) and 734 matched controls completed a questionnaire about lifestyle, fractures, and other possible adverse effects of glucocorticoids (176). The cumulative incidence of fractures from the time of diagnosis was 23% in patients taking oral glucocorticoids and 15% in the controls (OR = 1.8; 95% CI = 1.3, 2.6). Fractures of the vertebrae were more likely (OR = 10; 95% CI = 2.9, 35). The adverse effects were dose-related, with a higher risk of all fractures (OR = 2.22; 95% CI = 1.04, 4.8) and vertebral fractures (OR = 9.2; 95% CI = 2.4, 36) in those who took the highest compared with the lowest cumulative doses (61 versus 5 g).

Systemic glucocorticoids are often prescribed for rheumatoid arthritis. Even in low doses they can have clinical benefits and can inhibit joint damage, but they can cause osteoporotic fractures. In a 2-year double-blind, randomized, placebo-controlled trial in 81 patients (29 men, mean age 62 years) with early active rheumatoid arthritis who had not been treated with disease-modifying antirheumatic drugs, 41 were assigned to oral prednisone 10 mg/day and 40 to placebo. NSAIDs were allowed in both groups and after 6 months, sulfasalazine (2 g/day) could be prescribed as rescue medication. Those who took prednisone had more clinical improvement with less use of concomitant drugs. After month 6, radiological scores had progressed significantly less in those who took prednisone. After 24 months, seven patients had new vertebral fractures, five in the prednisone group and two in the placebo group (177).

Mechanisms

Several mechanisms underlie the effect of glucocorticoids on bone, both biochemical and cellular. Effects on calcium are:

(a) increased excretion of calcium into the bowel and inhibition of its absorption;
(b) inhibition of the tubular re-absorption of calcium in the kidney;
(c) increased mobilization of calcium from the skeleton.

When calcium homeostasis cannot be maintained, the resulting hypocalcemia can have serious consequences (SEDA-18, 388) (178,179). This so-called "glucocorticoid hyperparathyroidism" was the explanation traditionally most prominently advanced for glucocorticoid osteoporosis, but it is not the only one and may not be the most central. Other biochemical effects include:

(a) a catabolic effect on protein metabolism, causing a reduction in the bone matrix;
(b) altered vitamin D metabolism, with reduced concentrations of vitamin D metabolites (180);
(c) a dose-dependent reduction of serum osteocalcin, a bone matrix protein that appears to correlate with bone formation.

Measurement of serum osteocalcin is a useful marker for glucocorticoid-induced osteoporosis, and can be used alongside other measures noted below.

Various cellular mechanisms are involved in the production of glucocorticoid-induced osteoporosis (SEDA-20, 375) (181). The major change is a reduction in osteoblast activity that results in a reduced working rate (mean appositional rate), and a reduced active lifespan of osteoblasts. The cellular mechanism seems to be related to diminished production of cytokines and other locally acting factors. Increased bone resorption and reduced calcium absorption have also been described. A sophisticated mathematical model has been used to describe changes in calcium kinetics in patients treated with glucocorticoids (SEDA-20, 375) (182). Plasma calcium concentrations were higher than in controls, with a marked reduction in calcium flow into the irreversible stable bone compartment in glucocorticoid-treated patients. The authors concluded that prednisone has direct effects on osteoblast function.

Osteoprotegerin (osteoclastogenesis inhibitory factor, OCIF) has been identified as a novelly secreted cytokine receptor that plays an important role in the negative regulation of osteoclastic bone resorption. There are reports that suggest that glucocorticoids promote osteoclastogenesis by inhibiting osteoprotegerin production in vitro, thereby enhancing bone resorption. However, there are only a few clinical reports in which the regulatory functions of osteoprotegerin have been explored. In order to clarify the potential role of osteoprotegerin in the pathogenesis of glucocorticoid-induced osteoporosis, Japanese investigators have measured serum osteoprotegerin and other markers of bone metabolism before and after glucocorticoid therapy in patients with various renal diseases (183). The findings suggested that short-term administration of glucocorticoids significantly suppresses serum osteoprotegerin and osteocalcin. This might be relevant to the development of glucocorticoid-induced osteoporosis via enhancement of bone resorption and suppression of bone formation. Further long-term studies are needed to elucidate the mechanism of the glucocorticoid-induced reduction in circulating osteoprotegerin and its participation in the pathogenesis of osteoporosis.

Although glucocorticoids can cause changes in trabecular microarchitecture, loss of bone (reduced bone density) seems to be the major determinant of osteoporosis (184).

Although glucocorticoid use seems to be an important factor for low mineral density, sex hormones have also been suggested as an important determinant of bone mineral content. Bone mineral density and sex hormone status have been studied in 99 men with rheumatoid arthritis and 68 age-matched controls (SEDA-20, 375) (185). There were significant reductions in lumbar and

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femoral density, and salivary testosterone, androstenedione, and dehydroepiandrosterone in the patients. Salivary testosterone correlated with femoral density. By multiple regression analysis, weight, serum testosterone concentrations, and cumulative dose of glucocorticoid were significant predictors of lumbar bone density. Weight, age, androstenedione concentrations, and cumulative dose of glucocorticoids were significant predictors of femoral bone density.

Dose relation

Lumbar spine bone mineral density has been assessed in 76 prepubertal asthmatics (mean age 7.7 years, 26 girls) using glucocorticoids (186). After stratification for dose and route of administration, the children who used over 800 micrograms/day of inhaled glucocorticoids, with or without intermittent oral glucocorticoids, had a significant lower weight-adjusted bone density than children who used 400–800 micrograms/day of inhaled glucocorticoids (mean difference –0.05 g/cm^2; 95% CI = –0.02, –0.09). Bone mass was similar in children who did not use inhaled glucocorticoids and those who used 400–800 micrograms/day.

In kidney transplant recipients, lumbar bone loss was significantly higher in 20 patients who took daily prednisone (5.9%, mean dosage 0.19 mg/kg/day) than in 27 patients who used alternate-day prednisone (1.1%, mean dosage 0.15 mg/kg/day) (187).

Time course

The loss of bone mineral after organ and tissue transplant associated with immunosuppressive therapy follows a delayed time course. The long-term effects of immunosuppressive therapy on bone density have been determined in 25 cardiac transplant patients (SEDA-20, 375) (188). As expected, there was bone loss in the spine during the first year, but this was not maintained during the second and third years after transplantation, despite continuing maintenance immunosuppression with prednisolone. Only four patients, all of whom were hypogonadal, continued to lose bone.

Susceptibility factors

The overall effect of glucocorticoids on bone mineral content differs between patients on comparable treatments, which suggests that some patients are more predisposed than others (SEDA-3, 306), and probably also that the standards of evaluation used in different clinics are not comparable. This variability and the wide range of products and dosage schemes used mean that one does not have a clear impression of what constitutes a safe regimen as far as the skeleton is concerned (SEDA-20, 374), or whether any regimen is safe in this respect. Certainly, in a series of men with rheumatoid arthritis, even a very low dose of glucocorticoids (for example 10 mg or less of prednisolone daily) has proved to have a significant effect on bone mineral density (189); other work has provided similar results (SEDA-20, 374) (190). In another published study, patients who took 1–4 mg/day had the same density as those who were not taking glucocorticoids. Patients who took 5–9 mg/day and those who took more than 10 mg/day had significantly lower bone density (84 and 81% of control values respectively) (SEDA-20, 374) (191).

Glucocorticoid-related complications have been described in 748 adult kidney transplant recipients, followed for at least 1 year. For bone/joint complications, the multivariate analysis showed that the only significant variable was the cumulative duration of glucocorticoid therapy. For avascular necrosis, no variables were significant (SEDA-19, 377) (192).

In a similar study of 65 renal transplant patients treated with immunosuppressive drugs for at least 6 months, multivariate analysis showed that cumulative glucocorticoid dose and female sex were the major predictors of low vertebral bone density (SEDA-19, 377) (193).

In another study, the loss of bone density correlated with the cumulative dose of prednisolone (21 g total dose at 11.4 mg/day) and renal function (SEDA-21, 417) (194).

In a review of renal transplantation during 1974–94, 166 patients were classified into those with osteonecrosis of the femoral head (22 patients) and those without (47 patients) (SEDA-21, 417) (195). The total dose of methylprednisolone was higher in those with osteonecrosis. All five patients who had received intravenous pulse doses over 2000 mg had osteonecrosis.

The risk of vertebral deformity is increased by the combination of an oral glucocorticoid and advanced age, according to the findings in 229 patients (69% women) taking long-term oral glucocorticoids (prednisone equivalents of 5 mg/day or more) and 286 untreated controls (196). The duration of treatment was 0.5–37 (median 4.8) years. More than 60% of the treatment group were aged over 60 years, and most (62%) had been treated for rheumatoid arthritis. Bone mineral density data were analysed in 194 patients. The researchers identified at least one vertebral deformity (defined as a more than 20% reduction in anterior, middle, or posterior vertebral height) in 65 (28%) of the patients in the treatment group, and two or more fractures were identified in 25 (11%). In the treatment group, vertebral deformities were significantly more common in men than in women, and the prevalence of deformities increased with age. Compared with patients aged under 60 years, glucocorticoid-treated patients aged 70–79 years had a five-fold increased risk of vertebral deformity (OR = 5.1; 95% CI = 2.0, 13). The prevalence of vertebral deformities increased significantly with age in the glucocorticoid group. While the mean spine and femoral bone mineral density scores were lower in the glucocorticoid group, logistic regression analysis showed that bone mineral density was only a modest predictor of deformity. Age is an important independent risk factor, with very high prevalence rates in those over 70 years. Increasing duration of glucocorticoid use may increase the risk of fracture.

Comparisons of glucocorticoids

Bone loss induced by glucocorticoids has been assessed in three different populations. A group of 374 subjects (mean age 35 years, 55% women) with mild asthma taking beta-adrenoceptor agonists only, were randomized to inhaled glucocorticoids (budesonide or beclomethasone) or non-glucocorticoid treatment for 2 years (197). Bone mineral density was measured blind after 6, 12, and 24 months. Mean doses of budesonide and beclomethasone were 389 micrograms/day and 499 micrograms/day,

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respectively. At the end of follow-up, the subjects who had used glucocorticoids had better asthma control. The mean changes in bone density over 2 years in the budesonide, beclomethasone, and control groups were 0.1%, –0.4%, and 0.4% for the lumbar spine and –0.9%, –0.9%, and –0.4% for the neck of the femur. The daily dose of inhaled glucocorticoid was related to the reduction in bone mineral density only at the lumbar spine. Low to moderate doses of inhaled glucocorticoids caused little change in bone mineral density over 2 years and provided better asthma control.

Diagnosis

Several techniques are used to measure bone density. Cortical bone can be assessed in peripheral sites by single-photon absorptiometry and a combination of cortical and trabecular bone in central sites by dual X-ray absorptiometry. Trabecular bone can be assessed by quantitative computer tomography scanning of the lumbar spine. Since single-photon absorptiometry and dual X-ray absorptiometry give a negligible dose of radiation, they are useful for population screening. However, these two techniques are not sensitive enough to show subtle changes in bone density over short periods of time. Quantitative computed tomography gives a significant dose of radiation (of the order of one-tenth of a lateral X-ray of the spine) but can focus on trabecular bone, which has a tenfold greater turnover, compared with cortical bone. Quantitative computed tomography is more sensitive to changing bone density over time.

Other methods, such as the fasting urinary hydroxyproline/creatinine ratio, alkaline phosphatase activity, dual-absorption photometry of the hip, and serum osteocalcin measurements, can also be used, depending on an individual clinic's equipment and experience (SEDA-17, 447).

Management

The prevention and treatment of glucocorticoid bone loss in patients with skin diseases have been reviewed (169). Strategies for the management of this problem have been discussed (SEDA-22, 184) and the clinical implications of trials in the management of glucocorticoid-induced osteoporosis have been reviewed (198). Provided no fractures have occurred, loss of bone mineral density seems to be reversible when treatment is withdrawn (SEDA-18, 389). The management of glucocorticoid-induced osteoporosis has been revised by the UK Consensus Group Meeting on Osteoporosis (SEDA-20, 376) (183) and by the American College of Rheumatology (SEDA-21, 417) (199).

Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis have been published (200). Although there are several consensus statements and recommendations for prophylactic measures against glucocorticoid-induced osteoporosis in patients with rheumatoid arthritis, prophylaxis is commonly underprescribed. In two recent studies of 191 and 92 patients taking long-term glucocorticoids, relatively few were taking primary prevention, although some were taking vitamin D and calcium tablets. Around 65–68% of all those who qualified for prophylaxis for glucocorticoid-induced osteoporosis did not receive therapy, and only 9% of those in one study and 21% in the other were taking bisphosphonates (201,202).

Low availability compounds

Bone loss in patients taking oral budesonide has been evaluated in a longitudinal study in which bone mineral density was measured annually for 2 years in 138 patients (67 men, mean age 36 years old) with quiescent Crohn's disease (203). They took budesonide (8.5 mg/day; $n = 48$), prednisone (10.5 mg/day, $n = 45$), or non-steroidal drugs ($n = 45$). After 1 year, the bone mineral density in the lumbar spine fell by 2.36% in those who took budesonide, by 0.61% in those who took prednisone, and by 0.09% in those who took non-steroidal drugs. In the second year, the largest fall occurred in those who took budesonide (1.97%), but the differences between the groups were not significant. After 2 years, bone mineral density in the femoral neck fell by 2.94% with budesonide, 0.36% with prednisone, and 1.05% with the non-steroidal drugs. These results suggest that budesonide can cause bone loss, but the non-randomized design of the study limits conclusions about the comparison between budesonide and prednisone.

Pulse administration

The administration of glucocorticoids in sporadic pulses has been shown not to reduce bone density in patients with multiple sclerosis. In a prospective study, 30 patients were given 1000 mg/day of methylprednisolone intravenously for 3 days, followed by oral prednisone in tapering dosage for 2 weeks. Bone density was determined in the lumbar spine and femoral neck before and at 2, 4, and 6 months after therapy. At baseline, the patients had a reduced bone mass compared with controls; this reduction did not correlate with previous exposure to glucocorticoids. Ambulant patients during follow-up after glucocorticoid pulse therapy had an increase in lumbar bone density (+1.7% at 6 months). Average femoral density did not change; however, in patients who required a walking stick or other aid, femoral density fell (–1.6%), while in those with better ambulation it increased (+2.9%). These results suggest that inactivity is the main factor causing bone loss in patients treated with sporadic pulses of glucocorticoids (SEDA-21, 417) (204).

Calcium and vitamin D

Infusion of ionic calcium has sometimes been used to counteract the malabsorption of calcium in patients taking long-term glucocorticoids, particularly in patients who develop secondary hypoparathyroidism (SEDA-3, 306). There is also evidence that in amenorrheic or menopausal women requiring glucocorticoids, the adverse effects on the vertebrae can be countered by hormonal replacement therapy with estrogen and progesterone (205); progestogens similarly seem to have a promising effect in men, and while they cause a fall in serum testosterone they apparently do not undermine the desired effects of glucocorticoids (SEDA-16, 449).

The administration of calcium and vitamin D3 can prevent bone loss induced by glucocorticoids, and trials have confirmed its efficacy when given for 2 years. Patients taking prednisone and placebo lost bone density in the

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lumbar spine at a rate of 2% per year. Those taking prednisone and calcium plus vitamin D3 gained bone mineral density at a rate of 0.72% per year. Calcium plus vitamin D3 did not improve bone mineral density in patients who were not taking prednisone (SEDA-21, 417) (206).

In a similar randomized double-blind study, the effects of vitamin D (50 000 units/week) and calcium (1000 mg/day) were evaluated in 62 patients with different rheumatic diseases treated with prednisone (10–100 mg/day) (SEDA-21, 418) (207). The primary outcome was bone mineral density in the lumbar spine at 36 months. Patients taking placebo had reductions of 4.1, 3.8, and 1.5% at 12, 24, and 36 months respectively. Patients taking calcium and vitamin D had reductions of 2.6, 3.7, and 2.2% respectively. The results suggested that preventive therapy could be beneficial early in the prevention of glucocorticoid-induced bone loss, but there was no evidence of long-term beneficial effects. In kidney transplant patients, the preventive administration of 25-hydroxycolecalciferol and calcium reduced bone loss in the spine and femoral neck and the number of new vertebral crush fractures (SEDA-21, 418) (208). In children with rheumatic diseases taking glucocorticoids, calcium and vitamin D supplementation improved spinal bone density, although osteocalcin concentrations remained low (SEDA-19, 378) (209).

Calcitonin

Less clear are the results observed after the administration of salmon calcitonin. The usefulness of intranasally administered salmon calcitonin for 2 years has been evaluated in 44 glucocorticoid-dependent asthmatics (SEDA-19, 378) (210). All were taking calcium supplements (1000 mg/day), but one group also took calcitonin (100 IU every other day). Calcitonin increased spinal bone mass during first year of treatment, and maintained bone mass in a steady state during the second year. However, the rate of vertebral fractures was similar in the two groups. The addition of salmon calcitonin did not increase the efficacy of calcium plus vitamin D in the prevention of bone loss in 48 newly diagnosed patients taking glucocorticoids for temporal arteritis and polymyalgia rheumatica in a double-blind, randomized, placebo-controlled trial (SEDA-21, 418) (211). However, salmon calcitonin nasal spray prevented bone loss in the lumbar spine of 31 patients treated with prednisone for polymyalgia rheumatica (SEDA-22, 448) (212). They were randomized to salmon calcitonin nasal spray (200 IU/day) or matched placebo for 1 year. Both groups were treated with calcium supplements if their dietary intake was below 800 mg/day. With calcitonin, the mean bone mineral density in the lumbar spine fell by 1.3% and with placebo by 5% after 1 year. There were no differences in the hip, including the femoral neck and trochanter, or in total body bone density.

Bisphosphonates

There have been several studies of the use of bisphosphonates in preventing glucocorticoid-induced osteoporosis.

Intermittent cyclical etidronate prevented bone loss induced by prednisone in 10 postmenopausal women with temporal arteritis (SEDA-19, 378) (213). Cyclical etidronate (400 mg/day for 2 weeks every 3 months) plus ergocalciferol (0.5 mg/week) was given to 15 postmenopausal women (mean age 63 years) starting glucocorticoid therapy (prednisone 5–20 mg/day). A control group of 11 postmenopausal women (mean age 60 years) with glucocorticoid-induced osteoporosis were treated with calcium supplements only (1 g/day). During the first year, the cyclical regimen significantly increased lumbar and femoral neck bone density compared with placebo (7 and 2.5% for spine and femur respectively). After the second year of cyclical therapy, femoral neck bone density continued to increase while lumbar spine density remained stable (SEDA-20, 376) (214). The effect of intermittent cyclical therapy with etidronate has been investigated in the prevention of bone loss in 117 patients taking high-dose glucocorticoid therapy (a mean daily dose of at least 7.5 mg for 90 days followed by at least 2.5 mg/day for at least 12 months) (215). The patients were randomized to oral etidronate 400 mg/day or placebo for 14 days, followed by 76 days of oral calcium carbonate (500 mg elemental calcium), cycled over 12 months. The mean lumbar spine bone density changed 0.30% and –2.79% in the etidronate and placebo groups respectively. The mean difference between the groups after 1 year (3.0%) was significant. The changes in the femoral neck and greater trochanter were not different between the groups. There was a reduction in pyridinium cross-links, significant from baseline at both 6 and 12 months, in the etidronate group. Osteocalcin increased in the placebo group, and the differences between the groups at 6 and 12 months were –25% and –35% respectively. There was no significant difference between the groups in the number of adverse events, including gastrointestinal disorders. In a placebo-controlled study of the effects of 104 weeks of intermittent cyclical etidronate therapy in 49 patients, the same dose and cycles were used as in the previous study, but calcium (97 mg/day) was given with vitamin D (400 IU) (216). Intermittent cyclical etidronate therapy with vitamin D supplementation significantly increased lumbar spine bone mineral density by 4.5 in patients with osteoporosis resulting from long-term treatment with glucocorticoids.

Contradictory results have been published about the prophylactic use of two other bisphosphonates in patients treated with glucocorticoids. There were no bone losses after therapy, and no differences in bone density or biochemical bone markers between placebo and clodronate (SEDA-22, 447) (217).

Pamidronate disodium has been compared with calcium supplementation in an open trial of primary prevention of glucocorticoid-induced osteoporosis in 27 patients with different rheumatic conditions, randomly assigned to pamidronate (90 mg intravenously every 3 months) plus calcium (800 mg calcium carbonate) or calcium only for 1 year (SEDA-22, 448) (218). The glucocorticoids were given in a starting dosage of 10–80 mg/day. With pamidronate there was a significant increase in bone density (3.6% lumbar, 2.2% femoral neck), but there was a significant reduction with calcium (–5.3% in both spine and femoral neck).

The effects of risedronate on bone density and vertebral fracture have been studied in 518 patients (mean age 59 years, 40% with rheumatoid arthritis, 56% men, 64% of the women postmenopausal) taking moderate to high

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doses of oral glucocorticoids (equivalent to prednisone 7.5 mg/day or more) (219). The patients were randomized double-blind to placebo, or risedronate 2.5 or 5 mg/day for 1 year. All took elemental calcium 1000 mg/day and vitamin D 400 IU/day. The mean density of the lumbar spine fell by 1% in the placebo group and increased by 1.3% and 1.9% with risedronate 2.5 and 5 mg respectively. There was a significant reduction of 70% in the risk of vertebral fracture with risedronate 5 mg compared with placebo. There were similar incidences of adverse effects in all the groups.

Similar results have been reported in a clinical trial in 290 patients (38% men, 55% of the women postmenopausal) taking high-dose glucocorticoid therapy (prednisone over 7.5 mg/day or equivalent) (220). The subjects were randomized to receive placebo or risedronate 2.5 or 5 mg/day for 1 year. All took elemental calcium 1000 mg/day and vitamin D 400 IU/day. Risedronate 5 mg increased bone mineral density at 1 year by a mean of 2.9% in the lumbar spine, 1.8% in the femoral neck, and 2.4% in the trochanter. The values for placebo were 0.4%, –0.3%, and 1.0% respectively. The results for risedronate 2.5 mg were positive but not significant compared with placebo. The incidence of spinal fractures was reduced by 70% in the combined risedronate treatment groups compared with placebo. Risedronate and placebo caused similar adverse effects.

In a 1-year extension of a previous double-blind, randomized, placebo-controlled study, two doses of alendronate (5 and 10 mg/day) were compared in 66 men and 142 women taking glucocorticoids (at least 7.5 mg/day of prednisone or equivalent) (221). The extension was also double-blind, but those who had taken alendronate 2.5 mg/day in the previous study were given 10 mg/day. All the patients took supplementary calcium and vitamin D. The primary end-point was the mean percentage change in lumbar spine bone mineral density from baseline to 2 years. In those who took alendronate 5, 10, and 2.5/10 mg/day, bone mineral density increased significantly by 2.8, 3.9, and 3.7% respectively, and fell by –0.8% with placebo. There were significantly fewer patients with new vertebral fractures in the alendronate group compared with placebo (0.7 versus 6.8%). Adverse events were similar across the groups.

Fluoride

Fluoride is a potent stimulator of trabecular bone formation. Sodium monofluorophosphate was given to 48 patients with osteoporosis due to glucocorticoids (more than 10 mg of prednisone equivalents/day). Patients were randomly allocated to 1 g of calcium carbonate (control) or 200 mg of sodium monofluorophosphate plus 1 g of calcium carbonate for 18 months. At the end of the study lumbar spine bone density had increased by 7.8% in the fluoride group versus 3.3% in the controls. There were no changes in femoral neck density (SEDA-20, 376) (222).

Growth hormone

Growth hormone is a potent anabolic agent that stimulates protein synthesis, cell growth, and osteoblast activity. Recombinant human growth hormone has been used in patients taking long-term glucocorticoid treatment with suppressed endogenous growth hormone responses to GH-releasing hormone (SEDA-20, 376) (223). A single daily dose of 0.1 IU/kg of human growth hormone was given subcutaneously to nine nonobese patients. There was a significant increase in nitrogen balance, osteocalcin, carboxy-terminal propeptide of type I procollagen, and carboxy-terminal telopeptide of type I collagen. Growth hormone also lowered total high density lipoprotein, and low density lipoprotein cholesterol. These preliminary data suggest that growth hormone could ameliorate some adverse effects induced by long-term glucocorticoids.

Others

Other agents are effective in special populations. Vitamin K prevented bone loss in 20 patients with chronic glomerulonephritis treated with prednisolone (224) and ciclosporin 4.8 mg/kg/day prevented glucocorticoid-induced osteopenia in 52 patients taking prednisone 10 mg/day after kidney transplantation (225).

Avascular necrosis

Avascular aseptic necrosis of bone (SEDA-19, 377) (226,227) is a well-recognized adverse effect related to high-dose glucocorticoid therapy (equivalent to more than 4000 mg of prednisone) for extended periods (3 months or longer) but can occur after short-term glucocorticoid therapy. It occurs in a wide range of patients with many different disorders and is particularly likely to involve the femoral and humeral heads. The first lesions are often localized small osteolytic areas in the subchondral bone, where they can be diagnosed early by X-radiography. Magnetic resonance imaging (MRI) is one of the more sensitive techniques to diagnose avascular necrosis of the femoral head. The development and changes in avascular necrosis of the femoral head had been studied by MRI in patients with systemic lupus erythematosus treated with long-term prednisolone administration (SEDA-19, 377) (SEDA-19, 164). MRI abnormalities could be detected soon after the start of glucocorticoid therapy or were associated with increased dosages for treating exacerbation of the disease. Normal hips are rarely involved in avascular osteonecrosis. However, aseptic osteonecrosis of the femoral head is often seen in young patients; the lunate, capitate, and patella are their locations. Usually only one joint is involved, although lesions can be multiple. Whether intra-articular injections of glucocorticoids can cause necrosis of bone is still uncertain.

Femoral head necrosis in kidney transplant recipients who receive postoperative immunosuppression with prednisone can be prevented, at least to some extent, by minimizing the dosage of prednisone whenever feasible (228). Of 750 patients (445 men and 305 women) who had undergone kidney transplantation in 1968–95, 374 had received an average of 12.5 g of prednisone during the first year after surgery (high-dose prednisone group) and 276 had received an average of 6.5 g during this time (low-dose prednisone group) plus ciclosporin. Femoral head necrosis occurred in 42/374 patients (11%) in the high-dose prednisone group, an average of 26 months

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after transplantation. In contrast, femoral head necrosis occurred in only 19/376 patients (5.1%) in the low-dose group an average of 21 months after transplantation. The difference between the high- and low-dose groups was highly significant.

The risk of avascular necrosis has been assessed in a nested case-control study using computer records (229). There were 31 cases during 720 000 person-years Avascular necrosis was strongly associated with glucocorticoid exposure (RR = 16). When total prednisone exposure over 35 months was stratified into three levels (under 440 mg, 440–1290 mg, and over 1290 mg), there was no excess risk for cumulative doses of up to 440 mg (RR = 0; 95% CI = 0, 5). The relative risk was increased for doses between 440 and 1290 mg (RR = 6; CI = 1, 43) and indeterminately increased at doses over 1290 mg (CI = 26, infinity).

In 15 men with osteonecrosis of the femoral head after short-term therapy the mean duration of therapy was 21 (range 7–39) days and the mean dose in milligram equivalents of prednisone was 850 (range 290–3300) mg (230). The time from administration of glucocorticoids to hip pain was 17 (range 6–33) months. A new case of bilateral avascular necrosis of the femoral heads after high-dose short-term dexamethasone therapy as an antiemetic in cancer chemotherapy has been reported (231).

Myopathy

The presence of physiological amounts of glucocorticoids is necessary for the normal functioning of muscle. Excessive glucocorticoid concentrations, in contrast, result in protein catabolism and a reduced rate of muscle protein synthesis (232), and hence in muscle atrophy and fibrosis. The molecular and biochemical basis of myopathy has been widely studied, and the mechanism has been attributed to impairment of glycogen synthesis. Muscle glycogen synthase protein content and activity was measured in samples from 14 patients taking glucocorticoids after kidney transplantation and from 20 healthy subjects (SEDA-21, 418) (233). The patients had impaired activation of glycogen synthase and reduced enzyme activity. Muscular weakness can of course also result from glucocorticoid-induced hypokalemia. In spontaneous Cushing's syndrome, there is muscle involvement in some 50% of cases (234).

Among reports of myopathy in patients taking glucocorticoids, involvement of the respiratory muscles is often mentioned (235,236), possibly because this is particularly likely to have clinical consequences. Patients on mechanically assisted ventilation may be particularly at risk of myopathy (SEDA-18, 390). However, any muscle can be affected; one often sees weakness and atrophy of the hip muscles and (in about half the cases) the shoulder muscles and the proximal muscles of the limbs.

The myopathy usually develops gradually, without pain, and symmetrically. However, a single epidural injection of a glucocorticoid for lumbar radicular pain has caused Cushing's syndrome and myopathy (SEDA-20, 370) (97).

There is a suggestion that the incidence of myopathy is greatest during treatment with compounds that are fluorinated at the 9-alpha position, such as triamcinolone, but this may simply reflect its general potency. In children, the risk of effects on muscles is relatively high.

Biopsy is not justified as a routine, but it is useful as a diagnostic tool in distinguishing suspected corticoid myopathy from diseases of the muscles or vascular system with inflammation that may have been the indication for giving glucocorticoids in the first place; electromyographic measurements cannot confirm the diagnosis.

After termination of treatment the myopathy normally improves over a period of several months.

Damage to tendons and fascia

Tendons can be injured by glucocorticoids and can rupture (237). Ten cases of Achilles tendon rupture were seen in a single clinic over a 10-year period (SEDA-17, 448). The risk seems to be greater if local (for example intra-articular) injections are used.

Rupture of the plantar fascia induced by glucocorticoids has usually been reported in athletes. However, a case of spontaneous degenerative rupture has been reported in a 72-year-old man who had received four glucocorticoid injections over 1 year for plantar fasciitis (SEDA-21, 418) (238).

Growth in children

The possibility that inhaled glucocorticoids may impair growth in children is of concern, but difficult to assess, as severe chronic asthma can impair growth. If not adequately controlled, asthma modifies the prepubertal growth spurt, the pubertal growth spurt, and the catch-up phase, which allows the child to attain adult height. There is a wide range of individual responses and some children have adverse effects with relatively small doses of glucocorticoids. It is still not clear whether this is a transient phenomenon, causing a slowing of growth and maturational delay with no adverse effect on adult height, or whether growth can be permanently impaired. Ideally studies should establish the effect of asthma treatments on final adult height (compared with predicted values for sex and parental height). Such studies pose considerable logistic problems. For this reason most studies have measured growth over shorter time spans. Outcome measures have been expressed as the height velocity or growth rate, that is changes in height over a defined time. Alternatively height is measured and compared with that of age- and sex-matched controls. Such relatively short-term studies do not necessarily predict the effects of treatment on eventual adult height.

The growth-inhibiting effects of glucocorticoids in children are related not only to inhibition of growth hormone secretion, but also to the sensitivity of the peripheral tissues to the effects of growth hormone. By means of overnight profile analysis it was shown that glucocorticoid treatment reduces the amplitude but not the number of pulses of the physiological growth hormone secretion (SEDA-14, 335) (239).

Effects on growth occur early in treatment: with sensitive testing methods they can be detected in growing children within a few weeks of starting therapy. The effects can be produced by any route of administration, including even inhalation therapy (at least with

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dexamethasone) (SEDA-18, 391). Comparisons of attained heights with expected heights in children who have used inhaled or oral glucocorticoids have been summarized in a meta-analysis (SEDA-19, 375) (240). There was a significant but small tendency for glucocorticoid therapy in general to be associated with reduced final height. However, this effect varied according to the route of administration. As expected, there was significant impairment of growth with prednisone and other oral glucocorticoids. On the other hand, inhaled beclomethasone dipropionate was associated with normal stature, even when it was used in higher dosages, for longer durations, or in patients with more severe asthma. In another study in 94 children aged 7–9 years, beclomethasone in a dosage taken by many children with mild asthma (400 micrograms/day) significantly reduced growth (SEDA-20, 369) (241). In children with growth suppression during therapy with inhaled beclomethasone or budesonide (200–400 micrograms/day) there was catch-up growth when they switched to equipotent dosages of inhaled fluticasone (100–200 micrograms/day) (SEDA-21, 414) (242). However, in six children with severe asthma, treatment with inhaled high-dosage fluticasone 1000 micrograms/day was associated with growth retardation and adrenal insufficiency (SEDA-21, 414) (243). In one child, growth rate and adrenal function normalized 9 months after the fluticasone dosage was reduced to 500 micrograms/day.

It is generally agreed that the use of single doses of prednisone on alternate mornings minimizes growth retardation but does not avoid it; in children it has been shown that biochemical markers of growth are lower in patients receiving daily glucocorticoid therapy than in patients treated with an alternate-day regimen or not receiving glucocorticoids (SED-12, 988) (244).

It has long been thought by some physicians that the impairment of growth caused by glucocorticoids can be lessened by switching to corticotropin, but this is uncertain. Compensatory treatment with anabolic hormones is definitely not recommended today, since they do not stimulate growth but actually impede it by promoting closure of the epiphyses. Recombinant growth hormone (rGH) treatment of poorly growing children with glucocorticoid-dependent renal disease has often been observed to improve linear growth. However, the dosage of prednisone has been reported to be a critical factor in determining the efficacy of rGH therapy in glucocorticoid-dependent children (SEDA-19, 375) (245). When the dose of prednisone was greater than 0.35 mg/kg/day, rGH did not increase the linear growth rate. At lower doses, the response was inversely related to the amount of prednisone.

Provided glucocorticoid treatment is terminated before the end of puberty, total growth may catch up with the physiological norm (SEDA-17, 448). Concern has been expressed that fear of growth retardation can result in unjustifiable denial of glucocorticoid therapy. It does, however, seem highly advisable to keep doses as low as possible and to switch to a therapeutic regimen that excludes glucocorticoids as children approach the expected onset of puberty (SEDA-14, 335).

Serum osteocalcin determinations appear to be a helpful marker to evaluate the effects of glucocorticoids on growth in children.

One unanswered question is whether the growth suppression that occurs in children during glucocorticoid treatment persists after treatment is withdrawn and affects final adult height. In an attempt to answer this question, growth 6–7 years after withdrawal of alternate-day prednisone has been evaluated in children (aged 6–14 years) with cystic fibrosis who had participated in a multicenter trial from 1986 to 1991 (246). Of 224 children, 161 had been randomized to prednisone (1 or 2 mg/kg) and 73 to placebo. At the time of the study, 68% were aged 18 years or more. Height fell during prednisone therapy, but catch-up growth began 2 years after withdrawal. However, the heights of the boys treated with prednisone remained significantly lower by 4 cm than those who took placebo. In contrast, in the girls there were no differences in height at 2–3 years after prednisone withdrawal.

Reproductive system

Reduced sperm count and motility and inhibition of the secretory function of the testicles during glucocorticoid treatment have been reported and discussed in relation to the suppression of adrenal androgen production. These reports still await confirmation.

Since amenorrhea is a symptom of Cushing's syndrome, disorders of menstruation are common in fertile women taking higher doses of glucocorticoids (SEDA-3, 305). On the other hand, plasma cortisol concentrations in normally menstruating women have marked circadian variation, the extent of which can reach 200% or more (247), with the peak of the cortisol plasma concentrations at mid-cycle and near its end. Inhibition of ovulation by triamcinolone 25 mg has been reported when the drug is given on day 1 or 2 of the cycle. How glucocorticoids interfere with the hormonal control of the menstrual cycle is still unknown (248).

Women should be warned about the possibility of menstrual disorders after local triamcinolone injections (249). When premenopausal women received their first injection of triamcinolone intra-articularly ($n = 46$), injected into soft tissue ($n = 24$), or epidurally ($n = 7$) they were specifically asked to report flushing or menstrual irregularities during a mean follow-up period of 6 weeks. Of the 77 women in the study, 39 reported menstrual disorders. The onset of menstruation was later than expected in ten women and earlier in 16 women. There was reduced loss of blood and/or a shorter duration of menstruation in four women and increased loss of blood and/or a longer duration of menstruation in 18. Also, 22 women had flushing. Menstrual disorders occurred significantly less often in women who were taking oral contraceptives.

Immunologic

Since the glucocorticoids have immunosuppressive and anti-inflammatory properties, one would not expect allergic reactions to be a problem, except when excipients act as allergens. Nevertheless, allergic reactions to glucocorticoids themselves have been reported (SEDA-21, 419) (250). Urticaria after glucocorticoid treatment has been explained as a reaction of the mesenchyme. Also, an increase in eosinophilic leukocytes (which normally are diminished by glucocorticoids) has been reported as a first reaction to treatment with glucocorticoids.

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Class I immune reactions

Anaphylactic shock has been described after intranasal hydrocortisone acetate, intramuscular methylprednisolone (SEDA-21, 419) (251), intravenous methylprednisolone (SEDA-22, 448) (252), intramuscular dexamethasone (SEDA-22, 448) (253), and intra-articular methylprednisolone (SEDA-22, 449) (254). A life-threatening anaphylactic-like reaction to intravenous hydrocortisone has been described in patients with asthma (255). Acute laryngeal obstruction has been described for the first time after the intravenous administration of hydrocortisone (SEDA-22, 449) (256). There is some reason to believe that sodium succinate esters are more likely to cause hypersensitivity reactions (SEDA-17, 449), but unconjugated glucocorticoids can definitely produce allergy in some cases (SEDA-16, 452).

- A 64-year-old woman with a history of bronchial asthma developed increasing shortness of breath after an upper respiratory tract infection (257). Her medication included inhaled salbutamol as necessary, theophylline 300 mg bd, and aspirin 325 mg/day. She was given nebulized salbutamol and ipratropium and hydrocortisone 200 mg intravenously. Within 30 minutes, she developed a generalized rash, fever (38.3°C), and respiratory distress. She was promptly intubated and mechanical ventilation was started. No further doses of glucocorticoid were given. Skin testing with various parenteral formulations of glucocorticoids produced a 5 mm wheal at the site of hydrocortisone and methylprednisolone injections. She was subsequently given a challenge dose of triamcinolone using a metered-dose inhaler with no reaction, and was therefore continued on this medication.
- An anaphylactoid reaction (angioedema, generalized urticaria, worsening bronchospasm, and marked hypotension) occurred in a 35-year-old man with multiple sclerosis who became allergic to methylprednisolone (dose not stated) after starting treatment with interferon beta-1b (258). He had previously been treated with different courses of methylprednisolone. Clinicians should be aware that the complexity of the effects of interferon beta-1b on the immune system can lead to unexpected outcomes. It is uncertain whether the sequence of events here was due to an effect of interferon beta-1b or to coincidence.
- A 17-year-old boy, with an 11-year history of asthma, had anaphylaxis with respiratory distress shortly after he received intravenous methylprednisolone for an exacerbation of asthma while taking a tapering course of oral prednisone 15 mg/day (259). He had been glucocorticoid-dependent for at least 1 year. He reported having received intravenous glucocorticoids previously. He was treated with inhaled salbutamol and then intravenous methylprednisolone 125 mg over 15–30 seconds, and 3–4 minutes later became flushed and dyspneic, and developed diffuse urticarial lesions on his trunk and face and an undetectable blood pressure. He was treated with adrenaline, but required intubation. Sinus bradycardia developed and then asystole. He was successfully resuscitated and a 10–15 seconds period of generalized tonic-clonic activity was treated with diazepam. He remained unresponsive to stimulation for 30 minutes. However, he awoke 1 hour after his respiratory arrest and was extubated and discharged the following day taking a tapering dosage of prednisone.
- An anaphylactoid reaction occurred in a 68-year-old woman after treatment with intravenous methylprednisolone for asthma. She had developed urticaria with methylprednisolone 1 year earlier, but the reaction had been thought to be related to the solvent in the formulation (260).
- Forty minutes after a first dose of prednisone 25 mg, a 17-year-old girl with a history of aspirin intolerance had generalized flushing, hives, hypogastric pain, and abdominal cramps, followed by vomiting and diarrhea (261). She lost consciousness and developed arterial hypotension. She responded to intravenous diphenhydramine and hydrocortisone. Intradermal skin tests were positive for prednisone and negative for methylprednisolone and hydrocortisone. An oral challenge test with prednisone led to flushing, nausea, dizziness, tachycardia, and hypotension and responded to intravenous diphenhydramine and hydrocortisone. Challenge tests with intravenous methylprednisolone and hydrocortisone were negative.
- A 30-year-old man with recurrent atopic eczema of the head and neck, generalized xerosis, keratosis pilaris of the arms, and a history of dyshidrosis was initially treated with prednisolone-21-acetate ointment (262). His skin eruption became worse. He was given oral prednisolone 25 mg, and 5 hours after the first dose developed intense generalized pruritus with erythema and swelling of the face. After 24 hours there was generalized erythema with disseminated partly follicular papules. There was an eosinophilia (1.1×10^9/l). Total IgE was not raised. Patch tests showed delayed reactions to hydrocortisone 1%, prednisolone 1%, prednisolone-21-acetate ointment, and prednisolone 2.5%. Prick and intradermal tests with methylprednisolone succinate, hydrocortisone succinate, betamethasone, and triamcinolone acetonide in concentrations up to 1 : 10 were negative at 15 minutes. However, 4 hours after intradermal testing, generalized pruritus developed and 24 hours later there was a disseminated partly follicular eczematous reaction with involvement of the flexural areas. Biopsy of the eruptions caused by prednisolone and of the positive skin reaction to methylprednisolone succinate showed superficial dermatitis with a perivascular infiltration consisting predominantly of CD4+ cells and some eosinophils. Immunofluorescence showed increased expression of HLA-DR molecules on the CD4+ and CD8+ cells. During the exanthema caused by prednisolone, interleukin-5 (14 pg/ml), interleukin-6 (38 pg/ml), and interleukin-10 (26 pg/ml) were detected in the blood; 2 months after recovery these cytokines were not detectable.

The authors of the last report commented that generalized delayed type hypersensitivity to systemic administration of a glucocorticoid is rare. Despite the potent immunosuppressive effect of glucocorticoids on immunocompetent cells, the clinical features, the skin biopsy specimen, and the positive delayed skin test reactions strongly suggested an immunological mechanism: T cells were clearly involved and the high concentrations of

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interleukins 5, 6, and 10 were consistent with a T helper type 2 reaction. The raised concentrations of interleukin-5 were probably responsible for the blood and tissue eosinophilia.

Budesonide has been marketed in oral form for intestinal inflammatory disease. An non-IgE-mediated anaphylactic reaction has been associated with oral budesonide (263).

- A 32-year-old woman with Crohn's disease, who had taken prednisone 20 mg/day and azathioprine 150 mg/day, switched to budesonide 9 mg/day because of weight gain, and 5 minutes after the first capsule her tongue and throat swelled, accompanied by wheeziness and diarrhea. She was given clemastine and recovered after 4 ays. Intracutaneous tests with diluted budesonide suggested a non-IgE-mediated reaction. She had a previous history of a similar reaction to mesalazine. One year later her tongue and throat swelled after intravenous dexamethasone.

Urticaria with angioedema has been described in a patient taking deflazacort (264).

- A 64-year-old woman with allergic alveolitis caused by parakeet feathers improved with intravenous methylprednisolone, and was given oral deflazacort 60 mg/day, to be reduced progressively. After 30 days she developed generalized itchy blotches and lip edema. At that time she was mistakenly taking deflazacort in a dose of 120 mg/day. She was given an antihistamine, without any improvement. Deflazacort was then replaced by prednisolone and her symptoms disappeared immediately. Skin tests (a prick test and an epicutaneous test) were positive with deflazacort. Oral provocation with deflazacort 30 mg was positive, with the immediate appearance of the same symptoms as in the initial episode.

Vasculitis

Exacerbation of giant cell arteritis, with clinical signs of an evolving vertebrobasilar stroke, has been attributed to prednisolone (265).

- A 64-year-old man with giant cell arteritis was given prednisolone 60 mg/day. Within 5 days he developed double vision and agitation and became drowsy and confused. A cranial MRI scan showed recent cerebral lesions and a Doppler scan showed high-resistant blood flow in both vertebral arteries. He had an episode of complete loss of vision and was given dexamethasone and intravenous heparin followed by warfarin. He gradually improved over the next few weeks but was left with cognitive and memory deficits.

Immunosuppression

Glucocorticoids inhibit the formation of antibodies. Of 111 consecutive heart transplant recipients taking oral prednisone (mean 13.8 months), 57% developed hypogammaglobulinemia (IgG below 7 g/l) (266). Those with severe hypogammaglobulinemia (IgG below 3.5 g/l) were at increassed risk of opportunistic infections compared with those with IgG concentrations over 3.5 g/l (55 versus 5%, OR = 23). Parenteral glucocorticoid pulse therapy was associated with a significantly increased risk of severe hypogammaglobulinemia (OR = 15).

With long-term treatment, IgG subclass deficiencies can become marked (267). There is suppression of the antigen–antibody reaction, and since this reaction itself normally results in liberation of kinins, the latter is also suppressed. Failure of kinin liberation leads in turn to inhibition of invasion of sensitized leukocytes and reduced production and maturation of phagocytes. Undoubtedly, it is true that using minimal effective doses will avoid the most serious consequences, but the problem cannot be fully circumvented, since the anti-inflammatory effects themselves involve some inhibition of the migration of leukocytes and phagocytosis.

Dexamethasone significantly affected the antibody response of preterm infants with chronic lung disease to immunization against *Haemophilus influenzae* (268). Serum samples were obtained before and after immunization from an unselected cohort of 59 preterm infants (30 boys; gestational age 175–208 days). *Haemophilus influenzae* antibodies were measured using ELISA. IgG antibody concentrations in 16 infants who received no dexamethasone were 0.16 and 4.63 microgram/ml before and after immunization respectively. The corresponding values for those who received dexamethasone were 0.10 and 0.51 microgram/ml.

Infection risk

The consequence of this interference with immune responses can be multiplication of bacteria and an increased risk of bacterial intoxication when infection does occur; hence, the frequency and severity of clinical infections tend to increase during glucocorticoid therapy. Aggravation of existing tuberculosis and reactivation of completely quiescent cases of this infection are classic consequences demanding prophylactic measures; atypical mycobacteria have also caused tissue infections (SEDA-17, 449). Other bacterial infections, some severe and proceeding to sepsis, have followed glucocorticoid treatment. There is little evidence that glucocorticoids, even in high dosages and early in the course of infection, significantly alter the ultimate outcome (269). Use of glucocorticoids in the treatment of septic shock is not recommended in the absence of adrenal suppression.

It has been suggested that there are some differences between drugs. The use of fluticasone nasal spray to control polyp recurrence after functional endoscopic sphenoethmoidectomy should be viewed with caution, as it has been said to be associated with a high incidence of severe postoperative infection compared with beclomethasone (SEDA-21, 375) (270).

Acute generalized exanthematous pustulosis due to a glucocorticoid has been reported (SEDA-21, 416) (271).

Bacterial infections

Infections with *Clostridium difficile*, *Pseudomonas aeruginosa*, and *Listeria monocytogenes* (SEDA-22, 450) (272) have occasionally been precipitated or aggravated by glucocorticoids, as has tuberculous peritonitis (SEDA-20, 377) (273).

The cumulative and mean daily dosages of glucocorticoids in patients with systemic lupus erythematosus,

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inflammatory myopathy, overlap syndrome, or mixed connective tissue disease were the most important risk factors for the development of tuberculosis, according to a study conducted in Korea (274). Records were analysed from 269 patients who had been hospitalized during a 5-year period. In 21 patients active tuberculosis developed after a mean duration of 27 months from diagnosis of their rheumatic disease, an incidence rate of 20 cases per 1000 patient-years. The mean cumulative and daily dosages of prednisolone during the follow-up period were 31 594 and 25 mg respectively in patients who developed tuberculosis, compared with 17 043 and 18 mg in patients who did not. Glucocorticoid pulse therapy was a risk factor for the development of tuberculosis.

- A 43-year-old woman developed cavitary lung tuberculosis after she received methotrexate and glucocorticoid pulse therapy for rheumatoid arthritis (275).

The authors commented that the onset of the lung infection appeared to be closely related to methotrexate and glucocorticoid pulse therapy, because of the interval between drug administration and the onset of tuberculosis, and the lack of other risk factors for opportunistic infections.

In a retrospective study, the use of glucocorticoids during *Pneumocystis jiroveci* pneumonia (mean total dose methylprednisolone 420 mg, mean treatment duration 12 days) did not increase the risk of development or relapse of tuberculosis or other AIDS-related diseases (SEDA-20, 377) (276). The study included 129 patients (72 who took glucocorticoids and 57 who did not) who were followed up at 6, 12, 18, and 24 months of glucocorticoid therapy. The rates of infections were similar in both groups, and the cumulative rate of tuberculosis at 2 years was 12–13%.

Mycobacterium avium septic arthritis has been reported in two patients with pre-existing rheumatic disease (scleroderma and polymyositis) who were taking prednisolone and azathioprine; the infection was in the left shoulder in one patient and in the knee in the other (277).

The use of glucocorticoids in patients with hematological diseases is a factor that facilitates the occurrence of *Legionella pneumophila* pneumonia, and 10 episodes of this infection were possibly related to glucocorticoids in a series of 67 cases of Legionnaires' disease diagnosed in a single institution during 2.5 years (278).

Viral infections

Infections such as chickenpox can have serious consequences, including death, in patients taking systemic glucocorticoids (SEDA-19, 378) (SEDA-20, 377) (279,280). It has been suggested that *Varicella zoster* immunoglobulin should be given to patients in contact with chickenpox if they have taken glucocorticoids in dosages over 0.5 mg/kg/day during the preceding 3 months, in the context of near-fatal chickenpox in a child receiving prednisolone (SEDA-20, 377) (281). Smallpox vaccination has in the past resulted in vaccinia gangrenosum in patients taking glucocorticoids, and the current type of *Varicella* vaccine is much more likely to produce rashes in children who are already taking glucocorticoids than in controls (SEDA-16, 452).

Herpes simplex virus encephalitis after myxedema coma has been described in an 81-year-old man treated with hydrocortisone (100 mg 8-hourly) and levothyroxine (282). In renal transplantation, two cases of death from *Herpes simplex* as a result of glucocorticoid treatment are on record (SED-8, 827) (SEDA-17, 449).

Fungal and yeast infections

Fungal and yeast infections (including cases of fulminant fungal pericarditis, mucormycosis, *Aspergillus fumigatus* infection, and cutaneous alternariosis) can be precipitated or aggravated by glucocorticoid treatment (SEDA-17, 449) (SEDA-18, 390) (SEDA-20, 377) (SEDA-21, 418) (SEDA-22, 449) (283–286).

Primary esophageal histoplasmosis must be considered in patients who have a history of gastroesophageal reflux disease and are immunosuppressed by long-term glucocorticoids (SEDA-22, 450) (287). Oropharyngeal candidiasis is a well-described adverse effect of inhaled glucocorticoids. However, few cases of esophageal candidiasis have been reported (SEDA-22, 179).

Invasive pulmonary aspergillosis with cerebromeningeal involvement has been described after short-term intravenous administration of methylprednisolone (SEDA-22, 449) (288). Of 473 HIV-infected children, 7 (1.5%) developed invasive aspergillosis during the study period (1987–95) (SEDA-22, 449) (289). Sustained neutropenia or glucocorticoid therapy as predisposing factors for invasive aspergillosis were found in only two patients.

- Fatal pulmonary infection with *Aspergillus fumigatus* and *Nocardia asteroides* has been described in a patient who took prednisone 1 mg/kg/day for 1 month for bronchiolitis obliterans (290).
- Fatal *Aspergillus* myocarditis, probably related to short-term administration of glucocorticoids, has been described in a 58-year-old man, who had an acute exacerbation of his chronic obstructive pulmonary disease and received oxygen, bronchodilators, omeprazole, co-amoxiclav, and intravenous methylprednisolone 40 mg 8-hourly; he died 5 days later and postmortem examination showed a fungal myocarditis (291).
- Fatal aspergillosis with a thyroid gland abscess occurred in a 74-year-old man after treatment with prednisolone for polymyalgia rheumatica (292).

Scedosporium apiospermum infection occurred in the left forearm of an 81-year-old man who was taking chronic oral prednisone (increased to 40 mg/day 1 month before presentation) for lung fibrosis (293).

Cutaneous alternariosis (infection with *Alternaria alternata*) has been described in a 78-year-old farmer with idiopathic pulmonary fibrosis taking oral prednisone 20 mg/day (294).

The effect of dexamethasone has been assessed in a retrospective chart review study in neonates weighing less than 1200 g, both with ($n = 65$) and without ($n = 269$) *Candida* sepsis; dexamethasone therapy and prolonged antibiotic therapy were associated with *Candida* infection (295).

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Helminth infections

Strongyloidiasis (SEDA-20, 377) (SEDA-21, 419) (SEDA-22, 449) (296–298) has been precipitated or aggravated by glucocorticoids.

Protozoal infections

Toxoplasmosis has been precipitated by glucocorticoids (299,300).

Pneumocystis jiroveci pneumonia has been precipitated or aggravated by glucocorticoids (SEDA-20, 377) (SEDA-22, 450) (272,301,302). There is some concern about the use of glucocorticoids as adjunctive therapy in patients with AIDS who develop *Pneumocystis jiroveci* pneumonia. The immunosuppressant properties of glucocorticoids have been reported to enhance the risk of tuberculosis and other AIDS-related diseases (for example Kaposi's sarcoma or cytomegalovirus infection).

Amebic dysentery has been precipitated by glucocorticoids (303).

Death

Mortality associated with glucocorticoid has been retrospectively studied in 556 patients with chronic obstructive pulmonary disease admitted to a rehabilitation center (304). Median survival was 38 months and 280 patients died during follow-up. On multivariate analysis, oral glucocorticoid use at a prednisone equivalent of 10 mg/day without inhaled glucocorticoid was associated with an increased risk of death (RR = 2.34; 95% CI = 1.24, 4.44), and 15 mg/day increased the risk further (RR = 4.03; 95% CI = 1.99, 8.15). The risk of death was not increased in those using 5 mg/day or when patients used any oral dose in combination with inhaled glucocorticoids.

Long-Term Effects

Drug withdrawal

Suppression of adrenocortical function is one of the consequences of repeated administration of glucocorticoids; after termination of treatment a withdrawal syndrome can occur. In many cases this is unpleasant rather than acutely dangerous; in such instances the patients may have headache, nausea, dizziness, anorexia, weakness, emotional changes, lethargy, and perhaps fever; in some cases severe mental disorders occur and there are repeated reports of benign intracranial hypertension (305). The glucocorticoid withdrawal syndrome also seems to underlie the "glucocorticoid pseudorheumatism" that can occur when the drugs are withdrawn in rheumatic patients.

Withdrawal symptoms disappear if the glucocorticoid is resumed, but as a rule they will in any case vanish spontaneously within a few days. More serious consequences can ensue, however, in certain types of cases and if adrenal cortical atrophy is severe. In patients treated with corticoids for the nephrotic syndrome and apparently cured, the syndrome is particularly likely to relapse on withdrawal of therapy if the adrenal cortex is atrophic (SEDA-3, 305). In some cases, acute adrenocortical insufficiency after glucocorticoid treatment has actually proved fatal. It is advisable to withdraw long-term glucocorticoid therapy gradually so that the cortex has sufficient opportunity to recover. Table 5 lists methods of withdrawing prednisolone after long-term therapy in different circumstances (306).

Table 5 Suggested methods of withdrawing prednisolone

Circumstances	Change in daily dose
The problem has resolved and treatment has been given for only a few weeks	Reduce by 2.5 mg every 3 or 4 days down to 7.5 mg/day; then reduce more slowly, for example by 2.5 mg every week, fortnight, or month
There is uncertainty about disease resolution and/or therapy has been given for many weeks	Reduce by 2.5 mg every fortnight or month down to 7.5 mg/day then reduce by 1 mg every month
Symptoms of the disease are likely to recur on withdrawal (for example rheumatoid arthritis)	Reduce by 1 mg every month

Anorexia nervosa has been precipitated by withdrawal of oral prednisolone for asthma (SEDA-21, 414) (307).

A case of papilledema as a manifestation of raised intracranial pressure has been reported following withdrawal of topical glucocorticoids (SEDA-3, 305).

Panniculitis, which causes erythematous, firm, warm subcutaneous nodules, can occur within 2 weeks of withdrawal of large doses of glucocorticoids, but case reports confirm that resolution without scarring is the rule and that reintroduction of glucocorticoids is not necessary for improvement (308).

Churg–Strauss syndrome has come into prominence with the introduction of the leukotriene receptor antagonists, because they allow glucocorticoid-dependent asthmatics to discontinue their oral prednisolone. Five patients developed Churg–Strauss syndrome when their oral glucocorticoids were withdrawn (309). The duration of oral glucocorticoid therapy was 3–216 months and the dosage of prednisolone was 2.5–25.5 mg/day. The diagnosis of Churg–Strauss syndrome was made from 6 to 83 months after withdrawal of the oral glucocorticoids. These case reports support the hypothesis that it is the withdrawal of glucocorticoids that unmasks the underlying systemic vasculitis in these patients with asthma, rather than an effect of the new therapeutic agents that permits the reduction (and withdrawal) of prednisolone. Case-control studies are needed to determine the respective roles of the new therapeutic agents, prednisolone withdrawal, or other factors in the emergence of Churg–Strauss syndrome in these asthmatic patients

Tumorigenicity

Direct tumor-inducing effects of the glucocorticoids are not known, but the particular risk that malignancies in patients undergoing immunosuppression with these or other drugs will spread more rapidly is a well-recognized problem.

- Progressive endometrial carcinoma associated with azathioprine and prednisone therapy has been reported (310).

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- Rapid progression of Kaposi's sarcoma 10 weeks after combined treatment with glucocorticoids and cyclophosphamide has been described; marked improvement of the skin lesions was noted after discontinuation of prednisone therapy (311).

Patients (mean age 39 years, $n = 1862$) who underwent 1924 renal transplantations from March 1995 to May 1997 were followed for 3–150 months. They received one of the following regimens: prednisolone plus azathioprine (group 1; $n = 100$); prednisolone plus azathioprine plus ciclosporin (group 2; $n = 1464$); and the same therapy as group 2 plus either muromonab-CD3 or antithymocyte globulin as induction or antirejection therapy (group 3; $n = 298$). The mean time to appearance of neoplasia after renal transplantation was 48 months. Malignancies developed earlier in group 3 patients (mean time to appearance 31 months) than in group 2 (39 months) and in group 1 (90 months). Seven of the patients who developed malignancies had also received pulse methylprednisolone for acute rejection. The authors concluded that the treatment of acute rejection with pulsed methylprednisolone and the use of muromonab-CD3 and antithymocyte globulin may lead to an increased incidence of malignancies after renal transplantation. They recommended that strategies be implemented for the early detection of malignancy (312)

In seven patients, accelerated growth of Kaposi's sarcoma lesions during glucocorticoid therapy suggested that glucocorticoids can alter the biological behavior of this malignant disease (313). Hydrocortisone accelerates the growth of cell lines derived from Kaposi's sarcoma cells cultured in vitro and this may partially explain these findings. Reports continue to point to the reversibility of the condition when glucocorticoids are withdrawn (314).

Kaposi's sarcoma has been associated with prednisolone therapy in two elderly women (315).

- An 84-year-old woman with polymyalgia rheumatica and a 79-year-old woman with undifferentiated connective tissue disease and leukocytoclastic vasculitis were given prednisolone 20 mg/day with subsequent dosage reductions. The first patient developed a raised purpuric rash and lymphedema of the left leg within 5 months and the second developed large purple nodules on the soles of her feet and the backs of her hands accompanied by periorbital and peripheral edema. Skin biopsies showed Kaposi's sarcoma, and both patients had raised IgG antibody titers to human herpesvirus-8.

Prior infection with herpesvirus-8 is a requisite for the development of Kaposi's sarcoma. The question arises as to how glucocorticoid treatment alone can lead to the emergence of this malignancy. In vitro evidence supports the hypothesis that glucocorticoids have a direct role in stimulating tumor development and the activation of herpesvirus-8.

A possible relation between systemic glucocorticoid use and a risk of esophageal cancer has been described in a population-based study in Denmark, in which the prescriptions database and the Danish cancer registry were linked (316). There was an increase in the number of cases observed ($n = 36$) compared with the number expected ($n = 19$), with a standardized incidence ratio of 1.92 (95% CI = 1.34, 2.65).

Second-Generation Effects

Pregnancy

In a statement, the American Academy of Pediatrics and the Canadian Paediatric Society did not recommend the routine use of systemic dexamethasone for the prevention or treatment of chronic lung disease in infants with very low birthweights, because it does not reduce overall mortality and is associated with impaired growth and neurodevelopment delay (317,318).

In an analysis of 595 preterm infants born at 26–32 weeks gestation during a randomized controlled trial for the prevention of lung disease, glucocorticoids given to women at risk of preterm delivery promoted fetal lung maturation, reduced the incidence of respiratory distress syndrome, and reduced neonatal morbidity and mortality (319). Dexamethasone was given as either two doses of 12 mg 24 hours apart or four doses of 6 mg every 6 hours. Mortality was 9.2% after three or more courses, compared with 4.8% after one or two courses. This association was not explained by other factors (maternal or other common preterm morbidities).

The effects of glucocorticoids on uterine activity and preterm labor in high-order multiple gestations have been retrospectively reviewed (SEDA-20, 377) (320). In 15 women with triplet or quadruplet pregnancies, 17 out of 57 courses of betamethasone were associated with episodes of significant contractions requiring tocolytic intervention; 11 of these episodes were associated with cervical change and four resulted in premature delivery. The authors did not recommend the use of glucocorticoids if patients have more than 3.5 contractions per hour.

Prenatal glucocorticoid therapy to enhance fetal lung maturation reduces neonatal morbidity and mortality. However, adverse effects of serial courses of betamethasone on mother and fetus can occur.

Endocrine

Maternal hyperadrenalism occurred after five courses of betamethasone to enhance fetal lung maturation (321).

- A 26-year-old woman was given intravenous salbutamol 0.3 mg/hour for preterm labor, and intramuscular betamethasone 12 mg/day for 2 days. Daily oral tocolysis (salbutamol 2 mg every 6 hours plus nicardipine 50 mg every 12 hours) and betamethasone every week were continued at home for 3 weeks. The mother developed amyotrophy, acne on the face and trunk, moon face, hirsutism with whiskers, and thin skin. Free urinary cortisol was less than 5 micrograms/day (reference range 25–90), plasma cortisol was less than 10 ng/ml (100–200), and the salivary cortisol was less than 0.6 ng/ml (2.3–4.7). One hour after intramuscular tetracosactide 250 micrograms, her plasma cortisol was 102 ng/ml (reference range over 210) and the salivary cortisol was 3.1 ng/ml (13–25), indicating no adrenocortical response. She was given hydrocortisone 20 mg/day, and 2 months later adrenocortical insufficiency persisted, with a plasma cortisol of

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152 ng/ml after corticotropin stimulation. One year later, she still required hydrocortisone 10 mg/day.

Hyperadrenalism has never otherwise been reported after the sequential use of glucocorticoids for fetal lung maturation.

A study in 10 women has been conducted to determine whether betamethasone administered at risk of preterm delivery causes adrenal suppression (322). After adrenal stimulation with corticotropin 1 microgram at 24–25 weeks, each woman received two intramuscular doses of betamethasone 12 mg 24 hours apart; 1 week later, another corticotropin test was followed by another two doses of betamethasone; a third corticotropin stimulation test was carried out 1 week later. All the women had normal baseline and stimulated cortisol concentrations during the first corticotropin stimulation test. Mean baseline serum cortisol concentrations fell with each corticotropin stimulation test (from 700 nmol/l (254 micrograms/l) before betamethasone to 120 nmol/l (43 micrograms/l) 1 week after the second course of betamethasone). The mean stimulated cortisol concentrations also fell significantly, from 910 nmol/l (330 micrograms/l) to 326 nmol/l (118 micrograms/l). There was evidence of adrenal suppression in four patients after the first course of betamethasone and in seven patients after the second course. There was no evidence of Addisonian crisis antepartum or intrapartum.

Musculoskeletal

Osteonecrosis of the femoral head can occur with glucocorticoids in nonpregnant individuals, but has not previously been reported in pregnancy (323).

- A 37-year-old white woman was given betamethasone, two doses of 12 mg over a day, at 24 weeks of a twin pregnancy, because of a history of growth restriction in her first pregnancy. At 25 weeks Doppler of the umbilical vessels suggested a reduction in end-diastolic flow in one twin. Betamethasone was prescribed again and was repeated weekly to a total of six courses because of the high risk of preterm delivery. At 30 weeks she complained of pain in the right hip exacerbated by weight bearing, which increased over the following 7 days until standing was impossible. An MRI scan showed avascular necrosis of the femoral head.

Infection risk

The use of betamethasone for the treatment of premature rupture of membranes during pregnancy is associated with an increased prevalence of maternal and neonatal infections. Two reports have described the risk of infections associated with the use of glucocorticoids during pregnancy. Of 374 patients with preterm premature rupture of membranes, 99 received a single course of glucocorticoids, 72 received multiple courses, and 203 were not treated with glucocorticoids (324). Only multiple courses of betamethasone increased the incidence of early-onset neonatal sepsis, chorioamnionitis, and endometritis in mothers. A single course of glucocorticoid was not significantly associated with any maternal or neonatal infectious complications. The incidence of maternal infections in 37 patients who received three or more courses of betamethasone (median 6, range 3–10) because of the risk of preterm delivery has been evaluated, with 70 healthy pregnant women as controls (325). Of those treated with betamethasone, 65% developed infectious diseases compared with 18% of controls. Symptomatic lower urinary tract infections (35 versus 2.7%) and serious bacterial infections (24 versus 0%) were more frequent in treated mothers. Eight of nine serious infections occurred in patients exposed to five or more courses of glucocorticoids.

Singleton pregnancies delivered at 24–34 weeks after antenatal betamethasone exposure have been prospectively analysed, in order to study the incidence of perinatal infection (326). There were 453 patients, 267 of whom took a single course of betamethasone (two doses of 12 mg in 24 hours), and 186 of whom took a multiple course (more than two doses in the 24 hours after the initial course). Multiple courses were significantly associated with early-onset neonatal sepsis (OR = 5.0; 95% CI = 1.0, 23), neonatal death (OR = 2.9; CI = 1.3, 6.9), chorioamnionitis (OR = 10; CI = 2.1, 65), and endometritis (OR = 3.6; CI = 1.7, 8.1). Respiratory distress and intraventricular hemorrhage were similar in the two groups. Although the study was non-randomized the results suggest an increased risk of neonatal infection and death after multiple courses of dexamethasone during pregnancy.

In a retrospective study in 609 mothers and their 713 infants who were treated with 1–12 courses of antenatal glucocorticoids, data from 369 singleton preterm infants born at 34 weeks or later, 210 multiple gestations, and 134 infants delivered at 35 weeks or later were analysed (327). The incidence of respiratory distress syndrome was 45% for single courses and 35% for multiple courses of glucocorticoids (OR = 0.44; 95% CI = 0.25, 0.79). The multiple-course group also had significantly less cases of patent ductus arteriosus (20 versus 13%). The incidences of death before discharge and other neonatal morbidities were similar. The multiple-course group had a significant reduction of 0.46 cm in head circumference at birth when adjusted for gestational age and pre-eclampsia. The two groups had similar birthweights. Infants born at more than 35 weeks, multiple-gestation infants, and infants who were born more than 7 days after the last dose of glucocorticoid had similar outcomes, regardless of the number of courses they had received. Mothers treated with multiple courses compared with a single course had a significantly higher incidence of postpartum endometritis, even though they had a lower incidence of prolonged rupture of membranes (24 versus 33%) and similar cesarean delivery rates. In conclusion, antenatal exposure to multiple courses of glucocorticoids compared with a single course resulted in a significant reduction in the incidence of respiratory distress syndrome in singleton preterm infants delivered within a week of the last glucocorticoid dose. This was associated with a reduction in head circumference at birth and an increased incidence of maternal endometritis. Whether the potential benefits of repeated therapy outweigh the risks will ultimately be determined in randomized controlled trials.

Teratogenicity

Teratogenic effects of glucocorticoids, which have been demonstrated in animal experiments since 1950, have not generally been confirmed in man. The question whether a

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disease that has had to be treated with glucocorticoids in pregnancy or the glucocorticoid treatment itself may have caused congenital anomalies reported anecdotally usually cannot be answered in any individual case. Dexamethasone, for instance, given in a suppressive dosage, seems to have been therapeutically effective in endocrine abnormal pregnancy with congenital adrenogenital syndrome (328); how is one to distinguish cause and effect here? Cleft lip and palate, seen in animal studies, have not been encountered more often in the offspring of glucocorticoid-treated women than in those of untreated women. In several small series of patients in whom glucocorticoids were used before and during pregnancy, no congenital abnormalities were seen on follow-up, but material on which to base a firm judgement is lacking. Certainly, the evidence to date does not suggest that on teratological grounds one should hesitate to administer glucocorticoids for therapeutic reasons during pregnancy (SEDA-3, 306).

However, first trimester in utero exposure to a glucocorticoid was associated with a small risk of major neonatal malformations, according to the results of a Canadian meta-analysis (329). Six cohort studies and one case-control study were analysed, and the results showed that women who had taken long-term glucocorticoid therapy during pregnancy were more likely to have a baby with a major malformation than women who had not (OR = 2.46; 95% CI = 1.41, 4.29).

Glucocorticoids have been used in cases of hyperemesis gravidarum when standard antiemetics are ineffective. In an observational comparison of women with complicated hyperemesis gravidarum and weight loss, over 5% of prepregnant weight treated with ($n = 30$) or without ($n = 25$) glucocorticoids, gestational evolution and singleton birthweights were not different in the two groups (330).

A hydatidiform mole during pregnancy may have been due to the glucocorticoids used in an immunosuppressive regimen (331).

- A 33-year-old woman took immunosuppressive therapy after renal transplantation: ciclosporin (dosage adjusted to achieve blood concentrations of 120–160 ng/ml), azathioprine 1 mg/kg (frequency of administration not stated), and methylprednisolone 40 mg/day from day 1 after transplantation, tapered weekly by 4–8 mg/day. Because of rejection symptoms at weeks 1, 4, and 7, she received three cycles of intravenous methylprednisolone 250 mg/day, each cycle lasting 5–7 days; she also received a bolus dose of methylprednisolone 500 mg on day 0. Pregnancy was diagnosed on day 12 after transplantation (9 weeks after conception). At week 6 after transplantation she had a missed abortion. Curettage was performed and a partial hydatidiform mole was detected. She was discharged at week 10 and immunosuppressive therapy was tapered.

The teratogenic effects of prednisone have been evaluated in a placebo-controlled study in 372 women and a meta-analysis (332). There was no statistical difference in the rate of major anomalies between the glucocorticoid-exposed women and the controls. The meta-analysis included 10 studies (six cohort and four case-control studies), with data from 535 exposed and 50 845 nonexposed women. The odds ratios for major malformations were 1.5 (95% CI = 0.8, 2.6) for the cohort studies and 3.4 (CI = 2.0, 5.7) for the case-control studies. The results suggest that although prednisone does not represent a major teratogenic risk in humans in therapeutic doses, it does increase the risk of oral cleft defects by an order of 3.4-fold.

Fetotoxicity

The effect of prolonged antenatal betamethasone (three or more weekly administrations) has been studied in 414 fetuses (333). Multidose betamethasone was not associated with higher risks of antenatal maternal fever, chorioamnionitis, reduced birthweight, neonatal adrenal suppression, neonatal sepsis, or neonatal death.

The effects of antenatal dexamethasone on birthweight have been studied in 961 infants and matched controls (334). Dexamethasone-treated infants had significantly lower birthweights (after adjustment for week of gestation). The average differences from controls were 12 g at 24–26 weeks, 63 g at 27–29 weeks, 161 g at 30–32 weeks, and 80 g at 33–34 weeks. In the case of preterm rupture of membranes, the data were not conclusive.

Betamethasone, two doses of 12 mg a day apart, in 40 pregnant women (27–34 weeks) caused important changes in fetal physiology (335). Fetal breathing (the number of breathing episodes and the total breathing time in 30 minutes) fell by 83% and fetal limb and trunk movements fell by 53% and 49% respectively. These changes were transient and returned to the range of normality 96 hours after administration. There were no changes in Doppler velocimetry of the umbilical and middle cerebral arteries. Awareness of these effects may prevent unnecessary iatrogenic delivery of preterm infants who present abnormal biophysical profile scores 2 days after glucocorticoid exposure.

Retardation of intrauterine growth by glucocorticoids has been reported not only in animals but also in man. In a 1990 case from France, dwarfism (as well as Cushing's syndrome) was recorded in a child whose mother had received high-dose glucocorticoids during pregnancy.

It has been suggested that the risk of stillbirth may be increased by glucocorticoid treatment; the figures are suggestive, but the possibility that the disorder that led to the use of the glucocorticoid was itself responsible for the less favorable outcome cannot be excluded (336).

Prevention of the respiratory distress syndrome in anticipated prematurity has become a widely accepted (though not uncontroversial) indication for glucocorticoids in late pregnancy, the compound most often used being dexamethasone. The timing of such treatment in late pregnancy seems to be of crucial importance (SEDA-3, 306); the possible adverse effects on the mother and child are still being discussed. The issue has been extensively reviewed (SEDA-17, 445). A meta-analysis of 15 trials, involving 1780 patients treated with glucocorticoids and 1780 controls, has shown a lower risk of the syndrome, and a substantial reduction in neonatal mortality (OR = 0.60; 95% CI = 0.48, 0.76),

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without a higher risk of infection in the mother or maternal pulmonary edema (SEDA-20, 377) (337). In the mother, labor can be delayed by such glucocorticoid therapy (SEDA-3, 306); the combination of this treatment with sympathomimetic drugs may put the mother at risk of fluid retention with pulmonary edema (SED-12, 990), although it is not clear whether this problem only occurs when both drugs are used.

As far as the child is concerned, there may be only moderate adrenal suppression (338), although in some cases substitution treatment with glucocorticoids can be necessary in such babies; short-term treatment with betamethasone shortly before birth generally does not inhibit the infant's adrenal capacity to react to corticotropin (339). A single case of a leukemoid reaction in a preterm infant has been observed, after the mother was given betamethasone shortly before delivery (SEDA-3, 306).

On the other hand, there are many reports of hypertension (340), and electrocardiographic and other studies have often confirmed the presence of a disproportionately serious and bilateral hypertrophic obstructive cardiomyopathy, which unless it proves fatal is, in general, reversible once the glucocorticoids are withdrawn (SEDA-18, 386). Although the issue is confounded by the possibility that infants with bronchopulmonary dysplasia may be innately hypertensive, there seems no doubt as to the effect.

Most babies treated with glucocorticoids for lung dysplasia also show an appreciable rise in blood urea nitrogen, due almost entirely to an increase in structural protein catabolism (341). Serious gastrointestinal complications can occur. In one typical series of premature neonates treated in this way there were three such instances (perforated duodenal ulcer, perforated gastric ulcer, and upper gastrointestinal hemorrhage, the last two proving fatal) (342); the symptoms are apparently not masked by the glucocorticoid, as one would expect in adults. Treated infants also tend to have a low pH, which is unusual in premature babies (SEDA-18, 445).

Clearly, the duration of such treatment after delivery should be as brief as possible, but there is no reason for such concern as would lead to withholding therapy; one Dutch study with a 10-year follow-up detected no problems with exposed children's intellectual, motor, or social functioning compared with controls (114).

A meta-analysis, including 15 controlled trials and involving more than 1400 women, has shown that antenatal glucocorticoids in women with ruptured membranes may be beneficial in reducing the risks of neonatal death (RR = 0.68; 95% CI = 0.43, 1.07) and respiratory distress syndrome (RR = 0.56; CI = 0.46, 0.70), with no increase in the risk of infection in either the mother (RR = 0.88; CI = 0.61, 1.20) or baby (RR = 1.05; CI = 0.66, 1.68) (343).

A reduction in fetal response to vibroacoustic stimulation (vibroacoustic startle reflex) has been reported during 48 hours after the administration to pregnant women of two doses of betamethasone (12 mg 2 days apart) (344). The authors recommended that this test should not be used to evaluate well-being in fetuses exposed to glucocorticoids.

Susceptibility Factors

Genetic factors

Significant differences in the pharmacokinetics of methylprednisolone have been described in black and white renal transplant patients. Black patients had a slower clearance rate and a lower apparent volume of distribution. They had higher cortisol concentrations throughout the day, with higher nadir concentrations. Some of them had glucocorticoid-associated diabetes, and no white patients did. Further studies are needed to define the differences between the races (SEDA-20, 377) (345).

Age

Children

Inhaled glucocorticoids are recommended as first-line therapy for persistent asthma in children, to reduce both asthma symptoms and inflammatory markers. Treatment should be begun early in the course of the disease, because inhaled glucocorticoids can preserve airway function and prevent airway remodelling and subsequent irreversible airway obstruction (346). Because asthma is a chronic disease requiring long-term treatment, it is very important to balance the safety and efficacy of inhaled glucocorticoids to achieve optimal long-term results. Major safety concerns in children are the potential adverse effects on growth, adrenal function, and bone mass. Overall, the benefits of inhaled glucocorticoids clearly outweigh their potential adverse effects and the risks of poor asthma control. However, high doses of inhaled glucocorticoids in children are still of concern (347). It is of utmost importance to use the lowest effective dose, to limit systemic availability by selecting drugs with high first-pass hepatic inactivation, and to instruct patients on proper inhalation technique. Moreover, the use of adjuvant asthma medications acting by different mechanisms can help to reduce inhaled glucocorticoid dosages (346,347). These add-on therapies include leukotriene modifiers, long-acting beta$_2$-agonists, cromoglicate and nedocromil, and in selected cases theophylline. These agents should be added to, but should not in any case replace, inhaled glucocorticoid therapy (346,347).

The use of postnatal glucocorticoids in very premature infants is controversial; although dexamethasone reduces bronchopulmonary dysplasia, it has been associated with severe adverse effects (348). In 220 infants with a birthweight of 501–1000 g randomized to placebo or dexamethasone (0.15 mg/kg/day for 3 days and tapering over a period of 7 days) the relative risk of death or chronic lung disease compared with controls was 0.9 (95% CI = 0.8–1.1) at 36 weeks of gestational age (304). Infants treated with dexamethasone were less likely to need supplementary oxygen. Dexamethasone was associated with increased risks of hypertension (RR = 7.4; 95% CI = 2.7, 20.2), hyperglycemia (RR = 2.0; 95% CI = 1.1, 3.6), spontaneous gastrointestinal perforation (13 versus 4%), lower weight, and a smaller head circumference.

Elderly people

Prolonged use of glucocorticoids in elderly people can exacerbate diabetes, hypertension, congestive heart failure, and osteoporosis, or cause depression. In a retrospective,

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controlled study, the risks of high-dose intravenous or oral glucocorticoid therapy were assessed in 55 patients with Crohn's disease who were over the age of 50 years (350). They had a higher risk of developing hypertension, hypokalemia, and changes in mental state.

Hepatic disease

In patients with acute hepatitis and active hepatitis, protein binding of the glucocorticoids will be reduced and peak concentrations of administered glucocorticoids increased. Conversion of prednisone to prednisolone has been reported to be impaired in chronic active liver disease (351). However, although plasma prednisolone concentrations were more predictable after the administration of prednisolone than of prednisone to a group of healthy subjects (352), there was no difference in patients with chronic active hepatitis. There was also impaired elimination of prednisolone in these patients. In a review of the pharmacokinetics of prednisone and prednisolone it was concluded that fear of inadequate conversion of prednisone into prednisolone was not justified (353). Patients with hepatic disease suffer adrenal suppression more readily (91).

Other features of the patient

Menopause

Significant differences in the pharmacokinetics of prednisolone amongst menopausal women have been described (SEDA-21, 419) (354). The postmenopausal women had reduced unbound clearance (30%), reduced total clearance, and an increased half-life. Similar results are seen in the postmenopausal women who took estrogen or estrogen–progestogen therapy.

Protein binding

The association between low serum albumin concentrations and complications of prednisone has been long recognized, and it is an elementary pharmacokinetic principle that concentrations of unbound drug in plasma (the fraction that can reach the tissues) will be increased when binding of a drug to serum albumin is reduced (355).

Systemic lupus erythematosus

In 539 patients with systemic lupus erythematosus, organ damage was associated with glucocorticoid therapy compared with controls (356). Oral prednisone 10 mg/day for 10 years (cumulative dose 36.6 g) was significantly associated with osteoporotic fractures (RR = 2.5; 95% CI = 1.7, 3.7), symptomatic coronary artery disease (RR = 1.7; CI = 1.1, 2.5), and cataracts (RR = 1.7; CI = 1.4, 2.5). Avascular necrosis was associated with high-dose prednisone (at least 60 mg/day for at least 2 months; RR = 1.2; CI = 1.1, 1.4). Intravenous pulses of methylprednisolone (1000 mg for 1–3 days) were associated with a small increase in the risk of osteoporotic fractures (RR = 1.3; CI = 1.0, 1.8).

Drug Administration

Drug contamination

Unregulated Chinese herbal products adulterated with glucocorticoids have been detected (357). Dexamethasone was present in eight of 11 Chinese herbal creams analysed by UK dermatologists. The creams contained dexamethasone in concentrations inappropriate for use on the face or in children (64–1500 micrograms/g). The cream with the highest concentration of dexamethasone was prescribed to treat facial eczema in a 4-month-old baby. In all cases, it had been assumed that the creams did not contain glucocorticoids. The authors were concerned that these patients received both unlabelled and unlicensed topical glucocorticoids. They wrote that "greater regulation and restriction needs to be imposed on herbalists, and continuous monitoring of side effects of these medications is necessary."

Drug dosage regimens

Daily or alternate-day administration

The unwanted effects of the glucocorticoids can be reduced to some extent by altering the dosage routine, for example by giving them on alternate days or giving the total daily dose every morning.

Because of circadian variation in endogenous glucocorticoid secretion, the pituitary–adrenal axis is suppressed more easily in the night than during the day (358). Thus, administration of the total dose as a single dose in the morning is preferable to twice daily dosing or administration in the evening alone.

Alternate-day therapy (giving twice the daily dose on alternate days) can in some cases maintain the therapeutic efficacy of oral glucocorticoids, while reducing their adverse effects (359–361).

Use in fixed combinations

Fixed combinations of oral glucocorticoids with nonsteroidal anti-inflammatory analgesics or broncholytic drugs that have to be given repeatedly during the day are undesirable, since their pattern of administration is determined in part by the demands of the other components; the glucocorticoid is thus likely to be given in such a way that it alters the circadian rhythm of endogenous glucocorticoids.

Pulse or megadose therapy

Extremely large intravenous doses of glucocorticoids given at longer intervals can sometimes be effective when a patient does not respond to conventional high doses. Systemic lupus erythematosus, various rheumatic diseases, and the treatment of renal graft rejection are indications for this type of use (SEDA-6, 331). High doses of glucocorticoids also have an antiemetic effect in patients with cancers.

No adverse effects are to be expected after a single injection of a high dose of a glucocorticoid, but some serious complications have been observed with repeated use, including both infections and the known direct adverse effects of glucocorticoids. Cases of ventricular dysrhythmias and atrial fibrillation have been reported (SEDA-18, 391). With pulse therapy, the nature of the injected glucocorticoid seems to be important; for

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example, hydrocortisone, which is more rapidly metabolized, seems to be better tolerated than dexamethasone (SEDA-6, 331).

Drug administration route

Most knowledge of the adverse effects of glucocorticoids has been acquired in connection with their use as oral products. However, various other routes of administration have been developed, sometimes specifically in the hope of securing a local therapeutic effect while avoiding systemic adverse reactions. Although experience has shown that the latter cannot be eliminated in this way, they can be diminished in some cases. In other cases, new problems arise. Administration by inhalation is covered in the monograph on inhaled glucocorticoids.

Topical administration to the skin

The percutaneous absorption of high-potency topical glucocorticoids has been documented, but hypothalamic–pituitary–adrenal axis suppression, leading to clinically significant adrenal insufficiency or Cushing's syndrome, is infrequent. Two patients developed adrenal suppression after the unregulated use of betamethasone dipropionate 0.05% ointment (about 80 g/week) or clobetasol 0.05% ointment (up to 100 g/week), obtained without prescription to treat psoriasis (362).

Although glucocorticoids are used to treat eczema, they can sometimes exacerbate it (363).

- A 74-year-old man developed worsening eczema 24 hours after he applied clobetasol (Decloban) to treat chronic eczema of his external ear. Twelve years earlier he had noted exacerbation of a cutaneous lesion after he had applied a topical glucocorticoid. He had also had generalized erythema after an intra-articular injection of paramethasone. Patch tests to a series of glucocorticoids were positive for all drugs except flupametasone, fluocortine, and tixocortol. In addition, intradermal tests were positive to hydrocortisone and prednisolone, despite negative patch tests.

The authors commented that most glucocorticoid-sensitized patients react to several of the same group and less frequently of different groups. No case of hypersensitivity to glucocorticoids of all four classes has previously been reported.

- Chronic lichenified eczema has been attributed to prolonged use of topical methylprednisolone aceponate and budesonide (strength and duration of therapy not stated) in a 26-year-old woman (364). Patch tests were positive for methylprednisolone aceponate and budesonide cream, but negative for all other topical glucocorticoids.

The effects of exposure to topical glucocorticoids during pregnancy have been evaluated in a population-based follow-up study in 363 primigravida exposed to topical glucocorticoids during pregnancy and 9263 controls who received no prescriptions at all (365). The prevalence of malformations was 2.9% among 170 infants exposed to glucocorticoids during the first trimester and 3.6% among the controls. There were no increases in the risks of low birthweight, malformations, or preterm delivery in the offspring of women who were exposed to topical glucocorticoids during pregnancy.

Topical administration to the eye

Glucocorticoids that have been used for local ophthalmic treatment include medrysone, fluorometholone, tetrahydroxytriamcinolone, and clobetasone. Loteprednol etabonate 0.5% increases intraocular pressure less than dexamethasone. Studies on animal models of uveitis and two randomized double-masked trials showed that loteprednol etabonate 0.5% was less potent than dexamethasone, prednisolone acetate 1%, or fluorometholone, which may partly explain the improved toxicity profile of loteprednol etabonate (366).

Clinicians should not prescribe glucocorticoid-containing eye-drops unless they have performed a slit-lamp examination with tonometry, have assurance of appropriate follow-up, and understand the differential diagnosis, evaluation, and treatment. Unless clearly indicated, prescribing volumes larger than 5 ml or providing refillable prescriptions should be avoided. It should be stressed that excessive use of glucocorticoids can result in corneal Herpes infection and mycosis.

Since glucocorticoids reduce the immunological defences of the body to most types of infection, their use in the eyes should be monitored carefully. When long-term use is necessary, even with oral or inhalation therapy, eye examination should be performed every 6 months. The ophthalmological follow-up of patients using topical glucocorticoids should include tonometry at least twice a year, careful slit-lamp examination for early signs of herpetic or fungal keratitis and for changes in the equatorial and posterior subcapsular portions of the lens, examination of pupillary size and lid position, and staining of the cornea to detect possible punctate keratitis. Blood glucose concentrations should be checked if there are symptoms that suggest hyperglycemia.

Sensory systems

Ocular adverse effects of local or systemic administration of glucocorticoids include cataracts, glaucoma, papilledema, pseudotumor cerebri, activation of corneal infections, superficial keratitis, ptosis, pupillary dilatation, conjunctival palpebral petechiae, uveitis, and scleromalacia. Topical ocular application and facial application can cause high glucocorticoid concentrations in the anterior compartment of the eye. Serious visual loss can occur owing to the development of cataract in patients using glucocorticoid creams.

Glucocorticoid creams applied topically to the skin are routinely used in the treatment of many skin disorders, and their use on the face in severe atopic eczema is relatively common. Three patients developed advanced glaucoma while using topical facial glucocorticoids. Two other patients developed ocular hypertension secondary to topical facial glucocorticoids (367).

The use of a combination of a glucocorticoid with an antimicrobial drug is illogical and should generally be avoided because of the possibility of the emergence of resistant bacterial strains. It would be highly preferable if prescriptions for these drugs were issued by

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ophthalmologists only, at least in those parts of the world where adequate medical services are available.

Three vision-threatening complications have been described due to the indiscriminate use of glucocorticoid-containing eyedrops (368).

- A 31-year-old man noted a blind spot in his right eye. He had worn contact lenses for 10 years to correct his myopia. He had applied Tobradex ointment (tobramycin 0.3% and dexamethasone 0.1%) to each eye every evening for the past 4 years because of irritation due to contact lenses, and continuous refills of this prescription were obtained through an acquaintance who was employed in a pharmacy. With spectacle correction his visual acuity was 20/25 in each eye. The intraocular pressure was 52 mmHg in his right eye and 37 mmHg in his left eye. The optic discs showed glaucomatous cupping in each eye. Automated visual field testing showed superior and inferior arcuate defects typical of glaucoma in both eyes. Slit-lamp biomicroscopy showed mild papillary conjunctivitis bilaterally due to contact lenses. The antibiotic + glucocorticoid ointment was withdrawn and his bilateral glucocorticoid-induced open-angle glaucoma was treated with antiglaucomatous drugs.
- A 15-year-old boy felt a foreign body sensation in his right eye after he had been raking hay. His local physician prescribed a suspension of tobramycin 0.3% + dexamethasone 0.1% tds, but 6 days later referred him for evaluation of a suspected fungal keratitis. He had a corneal epithelial defect with an underlying dense inflammatory infiltrate. Corneal scrapings contained fungal hyphae and *Fusarium* species was identified. Natamycin 5% was administered topically every hour, the infection resolved, and his visual acuity returned to 20/20 despite a dense corneal scar.
- A 56-year-old woman had bilateral primary open-angle glaucoma without visual field loss, which was well controlled with a long-term topical beta-blocker in each eye. She underwent a left dacryocystorhinostomy for nasolacrimal duct obstruction, but developed persistent tearing and irritation of the left eye several months postoperatively. A suspension of tobramycin 0.3% + dexamethasone 0.1% was prescribed, which she continued to use as needed for 6 months. Pain and reduced vision persisted in her left eye. Corrected visual acuity was 20/20 in her right eye and 20/60 in her left eye. The intraocular pressures were 18 mmHg in her right eye and 68 mmHg in her left eye. Automated visual field testing showed a normal field in her right eye, but only a central island and a crescent of temporal visual field in her left eye. External examination showed persistent nasolacrimal duct obstruction on the left side with mild conjunctival injection. The diagnosis was primary open-angle glaucoma in both eyes, which was exacerbated by topically applied glucocorticoids in her left eye. The antibiotic + glucocorticoid suspension was withdrawn, and a topical ocular hypotensive therapeutic regimen was initiated in her left eye.

Susceptibility factors

Local and systemic adverse effects of ophthalmic glucocorticoids occur in children more often, more severely, and more rapidly than in adults, for unknown reasons. It could be that children have relatively immature chamber angles, giving rise to a rapidly increasing intraocular pressure (369).

Glaucoma has been reported after the use of a glucocorticoid ointment in a young boy (369).

- A 6-year-old boy underwent a resection of levator palpebrae superioris for congenital blepharoptosis. Postoperatively, an ointment containing 0.1% dexamethasone and neomycin (Maxitrol) was applied to the operated eyelid three times a day to reduce lid edema. Four days later the surgical correction was satisfactory and there were no symptoms, but the intraocular pressure was raised to 44 mmHg in the operated eye, although normal in the other eye. The glucocorticoid was withdrawn and topical ocular hypotensive agents were prescribed. The intraocular pressure returned to normal the next day, and the antiglaucoma treatments were maintained for 1 week and tapered over the next 2 weeks. Subsequent follow-up confirmed normal intraocular pressure and no glaucomatous damage.

The ocular hypertensive response in this case could have been due to systemic absorption of glucocorticoid through the skin of the eyelid, especially when there was a surgical wound. Alternatively, a sufficient amount of ointment could have seeped over the eyelid margins, causing the rise in intraocular pressure, similar to the application of eye-drops, as has been reported in another child, who also had Cushing's syndrome, a rare result of ophthalmic glucocorticoids (370).

- An 11-year-old boy with iridocyclitis developed Cushing's syndrome, a posterior subcapsular cataract, and increased intraocular pressure in both eyes after the topical administration of prednisolone acetate 1% eyedrops bilaterally for 6 months. The Cushing's syndrome was aggravated when periocular methylprednisolone acetate was started while bilateral posterior subtenon injections of 80 mg of suspension were continued every 6 weeks for 6 months. He had not used systemic glucocorticoids before.

Topical administration to the nose

The local application of glucocorticoids for seasonal or perennial rhinitis often results in systemic adverse effects. The use of nasal sprays containing a glucocorticoid that has specific topical activity (such as beclomethasone dipropionate or flunisolide) seems to reduce the systemic adverse effects, but they can nevertheless occur, even to the extent of suppression of basal adrenal function in children (371). Local adverse effects include *Candida* infection, nasal stinging, epistaxis, throat irritation (372), and, exceptionally, anosmia (373).

Nervous system

Benign intracranial hypertension with nasal glucocorticoids has been reported (374).

- A 13-year-old boy with Crohn's disease in remission, who had taken fluticasone aqueous nasal spray 50 micrograms to each nostril od regularly for 5 days, gave a 10-day history of head and back pain. He had a

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right sixth nerve palsy with bilateral swelling of his optic discs. An unenhanced computer tomogram was normal and magnetic resonance imaging excluded cavernous sinus thrombosis. The cerebrospinal fluid was clear with no cells, and protein and glucose concentrations were normal.

Although there was no clear temporal relation between the onset of the symptoms and the regular use of fluticasone, the authors proposed that the fluticasone was responsible, because the symptoms resolved after drug withdrawal. The association remains unproven but it does highlight the possibility of an association.

Sensory systems

Nasal budesonide or beclomethasone 100 micrograms bd for 3–9 months had no effect on the eyes in 26 patients who had undergone endoscopic sinus surgery (375). Ophthalmologic examination, tonometry, visual field testing, and biomicroscopic studies showed no evidence of ocular hypertension or posterior subcapsular cataract.

Ear, nose, and throat

The use of intranasal glucocorticoids in the treatment of allergic and vasomotor rhinitis in Sweden has doubled over a period of 5 years, and the number of reported cases of nasal septum perforation increased over the same time (376). The most common risk factor in 32 patients with nasal septum perforation (21 women, 11 men) was glucocorticoid treatment. Information from the Swedish Drug Agency showed that 38 cases of glucocorticoid-induced perforation had been reported over 10 years. The number of adverse effects per million Defined Daily Doses averaged 0.21. The risk of perforation was greatest during the first 12 months of treatment and most cases were in young women.

Endocrine

Aqueous nasal triamcinolone spray 220 or 440 micrograms od for the treatment of allergic rhinitis reportedly had no measurable adverse effects on adrenocortical function in 80 children (aged 6–12 years) in a placebo-controlled, double-blind study (377). Plasma triamcinolone concentrations measured over 6 hours fell rapidly and there was little or no accumulation during 6 weeks.

There have been reports of Cushing's syndrome after prolonged use of intranasal betamethasone 0.1% for chronic catarrh in two boys (378) and from an interaction of nasal fluticasone with ritonavir (379).

- A 30-year-old man who was using an intranasal formulation of fluticasone (therapeutic indication not stated), developed Cushing's syndrome about 5 months after starting ritonavir 600 mg bd, zidovudine, and lamivudine for HIV infection. His plasma cortisol concentrations were undetectable, his corticotrophin was low (under 2 pmol/l), and his 24-hours urinary cortisol excretion was under 30 nmol/l. Further investigations were consistent with secondary adrenal failure or with glucocorticoid use. He admitted to having used a topical glucocorticoid cream for 2 months. However, 6 weeks after he stopped using this cream, his plasma cortisol concentrations were still undetectable. It was then established that he had used nasal fluticasone propionate 200 micrograms/day for about 1 year before starting ritonavir. Ritonavir was replaced by nevirapine, and he continued to use fluticasone nasal spray. Three weeks later, his plasma cortisol concentration had increased to 290 nmol/l. Ritonavir was then added and his plasma cortisol concentration fell rapidly. Ritonavir was stopped again and his cortisol concentration normalized and his Cushingoid facies improved.

The authors thought it likely that inhibition of cytochrome P-450 by ritonavir increased the systemic availability of fluticasone and thus caused Cushing's syndrome in this patient.

Intralesional injection

Intralesional triamcinolone acetonide has been used extensively for the treatment of hypertrophic and keloid scars. Complications are few, usually being local skin color changes, prominent vascular markings, or subcutaneous atrophy. Cushing's syndrome after intralesional administration of triamcinolone acetate has been described in two adults and two children (aged 10 years and 21 months) after treatment of hypertrophic burn scars with intralesional triamcinolone acetonide (SEDA-21, 419) (350). These two children may have had a form of hypersensitivity to triamcinolone acetonide, as Cushing's syndrome was not the result of overdosage.

- Acute anaphylaxis occurred in an 18-year-old man after the third course of intradermal injections of triamcinolone suspension ("Kenalog" 10 mg per treatment) for alopecia areata (380). Subsequent rechallenge with intradermal triamcinolone 1 ml resulted in the same anaphylactic reaction as before and his serum IgE concentration was increased.

Immediate hypersensitivity reactions to paramethasone acetate, causing widespread eruptions, have been described in at least four cases. Delayed allergic reactions are less common.

- A woman had received intralesional paramethasone and other topical glucocorticoids several times for alopecia between the ages of 7 and 18 years (381). When she was 30 she was again treated with intralesional paramethasone for a relapse of alopecia. She developed pruritus after the first intralesional injection and erythema, edema, and vesicles 6–8 hours later. A biopsy showed spongiform lymphocytic folliculitis with spongiosis and exocytosis in the sweat gland ducts and in the pilosebaceous unit. She was treated with triamcinolone cream and her skin lesions resolved. Patch tests were positive for paramethasone, with cross-reactivity to tixocortol pivalate, hydrocortisone, and hydrocortisone butyrate.

Intraspinal injection

Intrathecal

The effects of intrathecal administration, both wanted and unwanted, are still much debated (382). The question as to whether oral glucocorticoid therapy should be preferred to intrathecal injections is raised by the harmful effects that have sometimes occurred after the latter,

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although some of these may have been caused by irritative substances in the injection fluid (SEDA-6, 331). The same local glucocorticoid concentrations can probably be attained with fewer problems with oral administration. Epidural injection of glucocorticoids seems to be safer than intrathecal injection, but injection of high doses can cause the same systemic adverse effects as seen with oral treatment. Facial flushing and erythema after lumbar epidural glucocorticoid administration have been reported (SEDA-20, 378) (383).

Glucocorticoids given intrathecally can cause a rise in cerebrospinal fluid protein and carry the risk of arachnoiditis (SED-8, 820). Chemical meningitis has been reported after two intrathecal injections of methylprednisolone acetate (384) and after lumbar facet joint block (SEDA-17, 450). Intraspinal injections of hydrocortisone for multiple sclerosis apparently led in one case to a cauda equina syndrome, with subsequent ulceromutilating acropathy (SEDA-17, 450). Intra-discal injections of triamcinolone acetonide in a number of French cases led to disk or epidural calcification, sometimes symptomless (SEDA-17, 450).

Postlumbar puncture syndrome with abducent nerve palsy followed the use of intrathecal prednisolone for the treatment of low back pain and sciatica (385).

- A 38-year-old woman received intrathecal prednisolone 3 ml (strength not stated) and 1 day later developed a postural headache, nausea, and dizziness. She was treated with intravenous fluids and analgesics. Eight days later she suddenly developed a complete palsy of the right abducent nerve. An MRI brain scan showed contrast meningeal enhancement typical of postlumbar puncture syndrome. She was treated with oral glucocorticoids and blood patching was performed. Her headache began to resolve a week later. Four months later she had almost completely recovered function of her abducent nerve and a repeat MRI scan was normal.

Epidural

The indications, rationale, techniques, alternatives, contraindications, complications, and efficacy of lumbar and caudal epidural glucocorticoid injections have been reviewed (SEDA-21, 420) (386).

Bilateral posterior subcapsular cataracts have been reported after treatment with epidural methylprednisolone for low back pain secondary to degenerative joint disease and disk protrusion (387).

- A 42-year-old man had received 15 epidural injections of methylprednisolone 80 mg over 10 years. About 6 weeks after his last injection, he developed progressively worsening cloudy vision. He had bilateral posterior subcapsular cataracts and subsequently underwent bilateral cataract removal.

The authors commented that it is possible that multiple epidural glucocorticoid injections had contributed to cataract formation. The patient also had several other risk factors for cataracts (cigarette smoking, alcohol consumption, exposure to ultraviolet radiation, low socioeconomic class, and low intake of antioxidant vitamins). However, the role of these other risk factors was speculative.

Symptoms consistent with complex regional pain syndrome have been reported after a cervical epidural glucocorticoid injection (SEDA-22, 451) (388).

Spinal epidural lipomatosis secondary to exogenous administration of glucocorticoids is a rare condition that has been reported almost exclusively in association with systemic treatment. However, local epidural administration has also been implicated (389).

One case of *Staphylococcus aureus* meningitis, a rare complication of epidural analgesia, has been published. The same patient developed a cauda equina syndrome of uncertain etiology, although neural ischemia as a result of meningitis secondary to immunosuppression was possible (SEDA-21, 420) (390). A unique case of transient profound paralysis after epidural glucocorticoid injection (acute paraplegia) has now been reported (SEDA-22, 451) (391). Diplopia associated with the peridural or intrathecal infiltration of prednisolone have not been previously reported (SEDA-22, 451) (392).

Of 31 patients who received 1 ml (40 mg) of methylprednisolone epidurally at the end of microdiscectomy, three developed epidural abscesses (393). These results were compared with a historical series of 400 patients not taking glucocorticoids, who had no deep infection. Although the data were limited, epidural glucocorticoids after discectomy should not be recommended.

Cervical epidural glucocorticoid injection is often used for the treatment of cervical radiculopathy. Subjective patient satisfaction has been reported, but controlled trials have not yet delineated the effectiveness of this procedure. Three cases of severe pain consistent with nerve injury have been reported immediately after cervical epidural glucocorticoid injection, bringing into question the benefit–harm balance of this technique (394).

Intra-articular and periarticular administration

Local injections of glucocorticoids into and around the joints can have a dramatic therapeutic effect, but the catabolic effect can have serious consequences, including adverse effects on joint structure (395) and on local tendons, subcutaneous atrophy, and possibly osteonecrosis. Provided the state of the joint is carefully inspected before any new injection is given, and the interval between the injections is not less than 4 weeks, the risk seems to be small enough to justify treatment in invalidating cases (SEDA-3, 307).

Neuropsychiatric effects of glucocorticoids, like hallucinations, can result from intra-articular administration (SEDA-22, 444) (396).

An acute adrenal crisis occurred in a woman who received an intra-articular glucocorticoid for pseudogout of the knee (397).

- An 87-year-old woman received intra-articular betamethasone (Diprophos) 7 mg on three occasions for painful knee joints over 6 months. Six weeks after the last injection she developed diffuse pain and contractures in the legs, fatigue, nausea, abdominal pain, and weight loss of 6 kg. Both knee joints were tender but there was no effusion. Her serum sodium concentration was 123 mmol/l, serum osmolality 254 mosmol/kg, urine sodium 136 mmol/l, and urinary osmolality

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373 mosmol/kg. The syndrome of inappropriate antidiuretic hormone secretion was diagnosed, but despite treatment she remained drowsy and hyponatremic. About a week later, she developed hypotension and symptoms of an acute abdomen. Further investigations showed that her basal cortisol concentration was low (36 nmol/l) but it increased to 481 nmol/l after a short tetracosactide test, consistent with acute adrenal crisis. She recovered rapidly after treatment with oral hydrocortisone, but still required glucocorticoid substitution several months later.

An erythema multiforme-like eruption has been reported after intra-articular triamcinolone in the right knee, with cross-sensitivity to budesonide (398).

- A 70-year-old man had received three intra-articular injections of triamcinolone (dose not stated) into the same knee over 3 months without any allergic reactions. However, 12–24 hours after the last injection he developed pruritus and erythema at the injection site. This eruption was treated with topical budesonide, but within the next few hours, acute eczema developed. The lesions spread to his legs and abdomen, and were erythematous, edematous, and resembled erythema multiforme. He was treated with boric acid solution dressings, emollients, and oral antihistamines. His lesions gradually resolved and did not recur during 8 months of follow-up. A month after the lesions had resolved, he underwent patch testing, which was positive to triamcinolone 1% and budesonide 1% in petrolatum, but negative to other glucocorticoids.

Hiccups have been reported after intra-articular administration (399).

- A 38-year-old man had an intra-articular injection of betamethasone dipropionate (dose not stated) into his right ankle, and the day after had hiccups that lasted for 24 hours and then resolved without treatment. Some months later, because of persistent arthritis, he received a further injection of betamethasone dipropionate into his right ankle. Once again, he had hiccups the following day. On this occasion, the hiccups resolved after 2 weeks, following treatment with levomepromazine.

Anaphylaxis occurred in two women after intra-articular administration of paramethasone plus mepivacaine 2% (400).

- A 44-year-old woman developed generalized pruritus 10 minutes after intra-articular paramethasone and mepivacaine and 30 minutes later developed generalized urticaria, tachycardia, and dyspnea. She received emergency treatment and her condition initially improved. However, her symptoms recurred after 6 hours and she was treated again and then discharged taking oral dexchlorpheniramine. She had a history of allergic contact dermatitis due to nickel sulfate sensitization, and 7 years before had had generalized urticaria and dyspnea after intra-articular administration of a glucocorticoid.
- A 31-year-old woman developed generalized pruritus and urticaria, facial edema, and dyspnea 2 hours after the intra-articular administration of paramethasone and mepivacaine. She was treated with an intramuscular glucocorticoid and antihistamines, with worsening of her symptoms. She received intravenous fluids and dexchlorpheniramine, but her symptoms recurred after 1 hour, when she was given subcutaneous adrenaline, intravenous fluids and dexchlorpheniramine. She was later discharged taking oral diphenhydramine. She had a history of a systemic reaction after the administration of a glucocorticoid and a local anesthetic.

Skin prick tests were positive for isolated paramethasone in both patients, but negative for mepivacaine. There has only been one previous report of anaphylaxis in association with paramethasone.

Osteomyelitis after three glucocorticoid injections for tennis elbow has been reported; the second injection was given 3 months after the first and the third 2 days later (401). This case illustrates the need for vigilance, even after common procedures, and that exacerbation of symptoms after local glucocorticoid injections should prompt the doctor to review the diagnosis and consider the need for further investigation.

Inadvertent intra-arterial injection

Particularly when injecting glucocorticoids locally, for example to relieve arthritis of the wrist, accidental injection into an artery is possible. Severe local ischemia can result (SEDA-17, 450).

Intracapsular injection

The use of implants for augmentation of the breast can lead to capsular contracture. Patients with intractable capsular contracture are treated with intracapsular injection of triamcinolone. Major complications included three cases of major atrophy requiring surgical correction. This problem appeared to have been eliminated by reduction of the dose of triamcinolone from 50 to 25 mg. There was one implant puncture (SEDA-19, 379) (402).

Rectal administration

Systemic absorption of glucocorticoids can occur after rectal administration.

- A 48-year-old woman developed avascular necrosis 9 months after she had completed a 3-month course of hydrocortisone 100 mg retention enemas once or twice daily for ulcerative proctitis (403). An MRI scan showed multiple bony infarcts in her distal femora, proximal tibiae, and posterior proximal right fibular head, extending from the diaphysis to the epiphysis, consistent with avascular necrosis.
- Cushing's syndrome occurred in a 65-year-old woman with ulcerative colitis who received a daily betamethasone enema (404).

The authors of the second report reported the pharmacokinetics of betamethasone after rectal dosing, with plasma concentrations of betamethasone high enough to cause Cushing's syndrome. Suppression of the hypothalamic–pituitary–adrenal axis disappeared after the dosage schedule was changed from daily to three times a week. These findings suggest that a considerable amount of betamethasone is absorbed after rectal dosing.

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Occupational exposure

Occupational exposure to glucocorticoids can cause adverse effects. Facial plethora has been found in workers manufacturing synthetic glucocorticoids, some of them having grossly abnormal responses to tetracosactide.

- A 58-year-old woman, who had been involved in the manufacturing of glucocorticoid creams and ointments for over 10 years, developed occupational contact sensitization to topical glucocorticoids (405). Patch tests were positive to hydrocortisone, hydrocortisone butyrate, and tixocortol pivalate. Intradermal tests were positive to hydrocortisone succinate, methylprednisolone, and prednisolone. An oral challenge with betamethasone 0.75 mg, 2.5 mg, and 8 mg on three consecutive days resulted in no adverse reactions.

It has been recommended that all workers manufacturing potent glucocorticoids should be screened regularly for glucocorticoid overdosage and should be moved regularly to units processing other drugs (406).

Drug overdose

High doses of glucocorticoids in patients with cancers can increase the risk of metastases, for example in breast cancer; this has been attributed in some cases to immunosuppression (407). These hormones should therefore only be used in patients with those types of tumors for which they are known to improve the efficacy of the cancer treatment.

A curious reaction to intravenous high-dose dexamethasone, used as an antiemetic agent in cancer chemotherapy or for other purposes, is sudden severe itching, burning, and constrictive pain in the perineal region, which has been described in several published reports (SEDA-11, 336) (408).

Drug–Drug Interactions

Albendazole

Dexamethasone reduced the clearance of albendazole and increased its half-life; plasma concentrations almost doubled (SEDA-22, 450) (409).

Amiodarone

Budesonide for collagenous colitis caused Cushing's syndrome in a patient with chronic renal insufficiency taking amiodarone for paroxysmal atrial fibrillation (410).

- An 81-year-old man with persistent diarrhea was given oral budesonide 9 mg/day, following unsuccessful treatment with mesalazine and prednisone. He was also taking amiodarone 100 mg/day. His diarrhea resolved within 6 weeks, and attempts to reduce the dosage of bzudesonide resulted in recurrent diarrhea. After 11 months he developed Cushing's syndrome, which persisted despite a reduction in dosage to 3 mg/day. His mild diarrhea recurred and the dosage of budesonide was increased to 6 mg/day with worsening of Cushing's syndrome; the dosage was reduced to 3 mg/day. Four weeks later amiodarone was withdrawn. The symptoms of Cushing's syndrome resolved within 4 weeks.

The authors suggested that the development of Cushing's syndrome and its persistence at a low dosage of budesonide was caused by inhibition of the metabolism of budesonide by amiodarone.

Anticoagulants

Intravenous methylprednisolone (1 g/day for 3 days) has been reported to inhibit the metabolism of oral anticoagulants (acenocoumarol and fluindione) in 10 patients, increasing the INR by 8 (range 5–20) (411).

Glucocorticoids can also alter the response to anticoagulants. A raised tolerance to heparin has been reported and a fall in fibrinolytic activity has been seen during glucocorticoid treatment (SED-8, 816). The entire clotting mechanism and particularly the prothrombin time should therefore be checked periodically in patients taking glucocorticoids concomitantly with anticoagulants, particularly if the glucocorticoid dose is changed. In addition there is an increased risk of gastric bleeding in patients taking both glucocorticoids and anticoagulants.

Antifungal azoles

Itraconazole 200 mg/day markedly increased plasma methylprednisolone concentrations and reduced morning plasma cortisol concentrations by over 80% in 10 healthy volunteers (412). The C_{max}, AUC, and half-life of methylprednisolone were increased 1.9, 3.9, and 2.4 times respectively.

Itraconazole 200 mg/day orally for 4 days markedly reduced the clearance and increased the half-life of intravenous methylprednisolone from 2.1 to 4.8 hours in a double-blind, randomized, two-phase, crossover study in nine healthy volunteers (SEDA-23, 430) (413). The volume of distribution was not affected. The mean morning plasma cortisol concentration during the itraconazole phase, measured 24 hours after methylprednisolone, was only 9% of that during the placebo phase (11 versus 117 ng/ml).

The authors of these two reports recommended that care be taken when methylprednisolone is prescribed in combination with itraconazole or other potent inhibitors of CYP3A4.

Itraconazole, given orally increased oral prednisolone concentrations by only 24% (414) but increased intravenous dexamethasone concentrations 3.3-fold and oral dexamethasone 3.7-fold (415).

In another study, ketoconazole was given orally as 200 mg od for 4 days, following a single oral dose of budesonide 3 mg either at the same time as ketoconazole or 12 hours before (416). Ketoconazole increased budesonide concentrations (C_{max} and AUC) 6.8- to 7.6-fold when the two drugs were co-administered; with a 12-hour separation, budesonide concentrations increased only 1.7- to 2.1-fold.

Calcium channel blockers

Methylprednisolone concentrations increased with the co-administration of diltiazem (2.6-fold) and mibefradil (3.8-fold) (417).

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Ciclosporin

Glucocorticoids cause additive immunosuppression when they are given with other immunosuppressants, such as ciclosporin (SEDA-22, 451) (418).

Clarithromycin

Clarithromycin inhibits CYP3A4, which is responsible for the metabolic clearance of prednisolone, the biologically active metabolite of prednisone. Clarithromycin (500 mg bd for 2 days) reduced the clearance of methylprednisolone by 65% and significantly increased its plasma concentrations; clarithromycin did not influence the clearance or plasma concentrations of prednisone (419). Acute mania has been reported to be related to inhibition of the metabolic clearance of prednisone by clarithromycin (SEDA-22, 444) (420).

Cyclophosphamide

The effect of prednisone 1 mg/kg on the pharmacokinetics of cyclophosphamide and its initial metabolites 4-hydroxycyclophosphamide and aldophosphamide (the acyclic tautomer of 4-hydroxycyclophosphamide) has been studied between the first and sixth cycles in seven patients (two men) with systemic vasculitis receiving intravenous cyclophosphamide 0.6 g/m^2 as a 1-hour intravenous infusion every 3 weeks for six cycles (421). Prednisone reduced the clearance of cyclophosphamide from 5.8 to 4.0 l/hour, reducing the amount of initial metabolites formed. Although the clinical significance of this interaction is unclear, 4-hydroxycyclophosphamide and aldophosphamide are probably responsible for the cytotoxic activity of cyclophosphamide, and increased cyclophosphamide dosages should be considered in patients taking prednisone.

Diuretics

Glucocorticoids with mineralocorticoid activity potentiate potassium loss when they are given with potassium-wasting diuretics (422).

Grapefruit juice

Methylprednisolone concentrations increased with the coadministration of grapefruit juice (1.75-fold) (423).

Leukotriene receptor antagonists

In a probable pharmacodynamic interaction, severe peripheral edema followed treatment with montelukast and prednisone for asthma (424).

- A 23-year-old man, with a history of asthma, house dust mite allergy, and rhinoconjunctivitis, presented with acute respiratory symptoms. He was given oral cetirizine, inhaled salmeterol, and fluticasone propionate, and oral prednisone 40 mg/day for 1 week and 20 mg/day for 1 week. His asthma recurred when prednisone was withdrawn and he took oral prednisone 60 mg/day for 1 week and 40 mg/day for 1 week. He also took montelukast 10 mg/day. He then developed severe peripheral edema with a gain in weight of 13 kg. Prednisone was withdrawn and his edema resolved. Montelukast was continued.

The author commented that the patient had tolerated prednisone without montelukast and montelukast without prednisone. However, he had severe edema when both drugs were used together. Montelukast may have potentiated glucocorticoid-induced renal tubular sodium and fluid retention. Both have been associated with edema.

Oral contraceptives

Oral contraceptives increased budesonide concentrations by only 22%, but prednisolone concentrations increased by 131%, suggesting a clinically important interaction (425).

Phenobarbital

Phenobarbital increases the metabolism of glucocorticoids, reducing the half-life by some 50% (426).

Phenytoin

Phenytoin increases the metabolism of glucocorticoids, reducing the half-life by some 50% (426).

Rifampicin

Rifampicin and other drugs that induce liver enzymes increase the metabolism of glucocorticoids (427), sufficient to reduce their therapeutic effects, for example in asthma (428).

Salicylates

Glucocorticoids reduce the plasma concentrations of salicylates (429). If they are given with aspirin or other anti-inflammatory drugs, there may be an additive effect on the gastric wall, leading to an increased risk of bleeding and ulceration (430–432).

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Corticosteroids—glucocorticoids, inhaled

See also Corticosteroids—glucocorticoids *and* Inhaler propellants

General Information

Treatment with inhaled glucocorticoids reduces the need for oral glucocorticoids in the treatment of severe asthma. The compounds used for inhalation have high local activity and low systemic availability when delivered to the lung. However, if sufficient amounts of glucocorticoids reach the bronchioles be absorbed, systemic effects will occur. Furthermore, a proportion of the dose intended for inhalation is actually swallowed and is absorbed from the gastrointestinal tract. The consequence is that if sufficiently high doses are used, enough drug will be absorbed from the respiratory and gastrointestinal surfaces to result in systemic effects.

Systemic availability of inhaled glucocorticoids can be reduced in two ways. First, by using esters that reduced local absorption; in the case of beclomethasone the dipropionate is used. Secondly, by using glucocorticoids that are extensively metabolized in the liver after absorption from the gut, such as fluticasone and budesonide. These strategies can be combined: fluticasone is given as the ester fluticasone propionate.

When a patient switches from oral or parenteral therapy to inhalation therapy, the systemic effect is reduced, just as if the dose of systemic glucocorticoid is reduced, and precautions should be taken to avoid withdrawal symptoms.

Systemic availability of inhaled glucocorticoids

The systemic availability of an inhaled glucocorticoid represents the additive and complex combination of pulmonary and gastrointestinal drug absorption. Absorption is influenced by many factors, including delivery device, the use of a spacer, the particle size of the inhaled drug, and the absorption and metabolism of the swallowed drug (1).

In healthy volunteers, high doses of both budesonide and fluticasone were readily absorbed after inhalation from a metered-dose aerosol (2). Fluticasone is extensively metabolized by the liver, so measurable concentrations of parent drug in the systemic circulation reflect efficient absorption across the lung. Lower doses of these inhaled glucocorticoids also result in some systemic absorption, reflected in effects on the hypothalamic–pituitary–adrenal axis (3).

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The extent of absorption of inhaled glucocorticoids tends to be less in asthmatic subjects than in healthy volunteers. In a study of fluticasone (500 micrograms via a dry powder device) in asthmatic patients with a wide range of severity, there was a highly significant linear correlation between lung function (expressed as percentage predicted FEV_1) and the absolute magnitude of adrenal suppression (4). In 11 patients with moderately severe asthma (mean FEV_1 54% predicted), who took fluticasone 1000 micrograms/day via a metered-dose inhaler with a spacer, the systemic availability of fluticasone was significantly less (10%) than in 13 healthy controls (21%). The plasma fluticasone concentrations (expressed as AUC) correlated positively with gas transfer (5). In contrast, there was no difference in plasma concentrations of fluticasone and budesonide between 15 mild asthmatics (mean FEV_1 81% predicted) and healthy volunteers after inhalation of 1000 micrograms of either drug with single or repeated dosing (6). Taken together, these studies suggest that patients with severe asthma are protected from the systemic adverse effects of high doses of inhaled glucocorticoids, owing to airways obstruction and reduced lung availability. However, as their lung function improves with continued use of the inhaled glucocorticoids, it is likely that the lung availability of inhaled glucocorticoid will increase. This likely outcome is a compelling argument for reducing the dose of inhaled glucocorticoids to a lowest dose that maintains optimal control of asthma and optimal lung function.

Plasma concentrations have been measured in 13 healthy subjects and eight patients with mild asthma using inhaled fluticasone propionate 1000 micrograms bd via Diskus or pressurized metered-dose inhaler and of budesonide 1000 micrograms bd daily via Turbuhaler for 7 days. Twenty-four-hour plasma cortisol concentrations were determined to assess the systemic activity of fluticasone propionate and budesonide. At steady state, the systemic availability of budesonide via Turbuhaler (39%) was significantly higher than that of fluticasone propionate via Diskus (13%) or inhaler (21%). Fluticasone propionate had a larger distribution volume and slower rates of absorption and clearance. Despite a significantly higher pulmonary availability of budesonide via Turbuhaler, plasma cortisol suppression was less than that of fluticasone propionate via inhaler and similar to that of fluticasone propionate via Diskus. There were no differences between healthy subjects and patients with mild asthma in subgroup analyses. However, this study had some limitations as the doses of fluticasone propionate and budesonide were not equipotent, fluticasone being twice as potent as budesonide (7).

The effects of fluticasone 1500 micrograms/day and budesonide 1600 micrograms/day, both by dry powder inhalation, on three systemic markers (urinary concentrations of total cortisol metabolites, morning serum cortisol, and osteocalcin concentrations) have been investigated in 46 healthy and 31 asthmatic subjects (8). Urinary total cortisol metabolite concentrations represented the most sensitive marker of the systemic effects of inhaled glucocorticoids, and were lower in healthy subjects treated with fluticasone than in asthmatic patients, suggesting greater systemic availability of fluticasone in healthy subjects. A similar correlation was not found for budesonide. Fluticasone impaired the hypothalamic–pituitary–adrenal axis more than budesonide, while budesonide significantly lowered serum osteocalcin concentrations, which reflect osteoblastic activity. The authors suggested that different inhaled glucocorticoids have different effects on the hypothalamic–pituitary–adrenal axis and bone metabolism. This study also had its limitations given that the fluticasone and budesonide doses were not equipotent (9).

The safety and efficacy of fluticasone, beclomethasone dipropionate, and budesonide have been compared in a randomized trial in 133 patients with chronic severe asthma who required at least 1750 micrograms/day of beclomethasone/budesonide (10). The patients were randomized to their regular beclomethasone/budesonide or to fluticasone at about half the dose for 6 months. The patients who used fluticasone had a better safety profile, especially with regard to adrenocortical function and bone turnover, while maintaining asthma control. There were significant increases in morning serum cortisol concentrations, the urine cortisol:creatinine ratio, serum osteocalcin, and the serum (deoxy)-pyridinoline:creatinine ratio only with fluticasone, suggesting less suppression of the hypothalamic–pituitary–adrenal axis. The 2:1 potency ratio for clinical efficacy of fluticasone and budesonide/beclomethasone seems to be maintained even at doses of 2000 micrograms/day or higher.

Since many patients with allergic asthma also have rhinitis, they may be taking both inhaled glucocorticoids for their asthma and intranasal formulations for their hay fever. The total systemic availability of glucocorticoids has been studied after the addition of intranasal therapy in patients already taking inhaled glucocorticoids (11) in 12 moderately severe asthmatic subjects (mean FEV_1 84% predicted), who were randomized in a placebo-controlled, two-way, crossover comparison of inhaled fluticasone (880 micrograms bd) plus intranasal fluticasone (200 micrograms od), inhaled triamcinolone (800 micrograms bd) plus intranasal triamcinolone (220 micrograms od), and respective placebos. Both the inhaled glucocorticoids caused significant suppression of adrenocorticoid activity, although the addition of intranasal formulations did not produce further significant suppression. There were more individual subjects with abnormally low cortisol values when intranasal fluticasone was added. These findings suggest that the dose of intranasal glucocorticoids should be taken into account (particularly if used in the long term) when considering the systemic availability of glucocorticoids used in the treatment of asthma and hay fever.

The concept of the L:T ratio in inhalation therapy is a useful one, where L represents the local or lung availability of an inhaled drug and T the total systemic availability. This ratio will be affected by differences in first-pass metabolism. Another important variable that determines the L:T ratio is the inhalation device. The L:T ratio for budesonide is 0.66–0.85, depending on the method of inhalation (12).

Another way of describing the L:T ratio concept is that of "pulmonary targeting." Drug properties that improve pulmonary targeting include slow absorption from the lungs, low oral systemic availability, and rapid systemic clearance.

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Differences in delivery devices can also produce differences in pulmonary targeting by altering the dose of drug deposited in the lungs. Allowing for both drug and inhaler differences, the relative potencies of the commonly used drugs are as follows: fluticasone propionate > budesonide = beclomethasone dipropionate > triamcinolone acetonide = flunisolide. Potency differences can be overcome by giving a larger dose of the less potent drug. However, comparisons between glucocorticoids must measure the systemic effects as well as the lung effect of each dose (13).

Inhalation devices

The importance of the inhalation device has been shown in studies of beclomethasone. Pressurized metered-dose inhalers containing chlorofluorocarbons produce relatively large particles that deposit less than 10% of the delivered dose in the lungs, primarily in the large airways, more than 90% being deposited in the oropharynx. A hydrofluoroalkane beclomethasone multidose aerosol (Qvar 3M Pharmaceuticals) delivers a smaller particle size. More than 50% is deposited in the lungs in animal and mechanical models. This has been confirmed using radiolabelled Qvar in patients with asthma and in healthy volunteers. In these subjects, 50–60% of the dose is deposited throughout the airways and about 30% in the oropharynx. The breath-activated Autohaler provides lung deposition equivalent to an optimally used Qvar inhaler, by automatically delivering drug early in the inhalation. Neither of these devices is improved by the addition of a spacer (14).

Both inhaled and swallowed fractions cause significant systemic activity, the degree of which depends on the inhaler device used. In one study, systemic activity was greater using a dry power inhaler (52%) than a pressurized metered-dose inhaler with a large volume spacer (28%) (15). It was recommended that when high-dose beclomethasone is used, a pressurized metered-dose inhaler with a large volume spacer would help in limiting potential adverse effects.

The systemic availability of inhaled budesonide has been measured in 15 healthy volunteers, using an open crossover design. Each subject was given three treatments, intravenous budesonide 0.5 mg, inhaled budesonide (from a metered-dose inhaler with a Nebuhaler) 1 mg (200 micrograms × 5) plus oral charcoal, and inhaled budesonide 1 mg without oral charcoal. The treatment order was randomized. The mean systemic availability of inhaled budesonide compared with intravenous budesonide was 36% with charcoal and 35% without charcoal, indicating that the absorption of budesonide from the gastrointestinal tract did not contribute to its systemic availability. Pulmonary deposition was 36% with charcoal and 34% without. When the inhaler was used incorrectly, that is, the canister was shaken only before the first of the five inhalations, systemic availability fell by 50%. This shows that the performance of each inhaler is very dependent on proper use (16).

The available studies suggest that fluticasone is more effective than beclomethasone, triamcinolone, or budesonide. However, budesonide delivered by Turbuhaler has equivalent efficacy to fluticasone delivered by metered-dose inhaler or Diskhaler, and is more effective than beclomethasone. When comparative safety is considered, budesonide and triamcinolone delivered by metered-dose inhaler have less systemic activity than fluticasone. Beclomethasone and fluticasone delivered by metered-dose inhaler are equivalent. Budesonide delivered by Turbuhaler has less systemic activity than fluticasone delivered by Diskhaler (17).

The equivalence of inhaled glucocorticoids based on equipotent (cortisol suppression) effects has been studied by the Asthma Clinical Research Network (ACRN). Six different inhaled glucocorticoids and matched placebos (beclomethasone chlorofluorocarbon, budesonide dry powder inhaler, fluticasone dry powder inhaler, fluticasone chlorofluorocarbon metered-dose inhaler, flunisolide chlorofluorocarbon, and triamcinolone chlorofluorocarbon) were compared by measuring their systemic effects (18). Glucocorticoid-naïve patients with asthma ($n = 156$) were enrolled at six centers and a one-week doubling dose design was used for each of the six inhaled glucocorticoids and matched placebos to a total of four doses. The best outcome variable for the reliable assessment of a systemic effect was the 12-hour AUC of the hourly overnight plasma cortisol measurements from 8 p.m. to 8 a.m. Microgram comparisons of the glucocorticoids could only be performed at 10% cortisol suppression, because fluticasone did not cause higher suppression. The following equipotent doses (that is, doses producing equal systemic cortisol suppression) were found: flunisolide 936 micrograms; triamcinolone 787 micrograms; beclomethasone 548 micrograms; fluticasone dry powder: 445 micrograms; budesonide 268 micrograms; and fluticasone metered-dose inhaler 111 micrograms. The ranking of systemic effects was very similar to that found earlier in a large meta-analysis (19).

Dry powder inhaler and pressurized metered-dose inhaler for administration of low-dose budesonide (400 micrograms/day) have been compared (20). Only the dry powder caused suppression of the hypothalamic–pituitary–adrenal axis. As effective inhaled glucocorticoid therapy is expected to cause detectable reductions in the physiological secretion of cortisol (1), low-dose budesonide by pressurized metered-dose inhaler is probably not effective. In another study, budesonide inhalation suspension, developed for nebulization to meet the specific needs of infants and young children, did not cause significant suppression of hypothalamic–pituitary–adrenal axis function (basal plasma cortisol concentrations and corticotropin test) in doses from 0.25 to 1.0 mg (21). However, inhaled fluticasone propionate by pressurized metered-dose inhaler with a spacer in 62 children resulted in abnormal morning cortisol concentrations in 36% (17 using a low dose of 176 micrograms/day; 43 using a high dose, over 880 micrograms/day) (22).

In a randomized, double-blind study, adult asthmatic patients took budesonide 800 micrograms/day over 12 weeks either by Easyhaler ($n = 103$) or by Turbuhaler ($n = 58$) dry powder inhaler. The Easyhaler was equivalent to the Turbuhaler with regard to safety and efficacy, but was more acceptable to the patients (23).

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Therapeutic studies

Budesonide

Inhaled budesonide has been studied in the management of moderately severe, acute asthma in children (24). After treatment with nebulized terbutaline, 11 children were randomly allocated to receive one dose of either budesonide 1600 micrograms by Turbuhaler or prednisolone 2 mg/kg. There was no significant difference in the improvement of the pulmonary index score or peak expiratory flow rate. Children treated with budesonide had an earlier clinical response than those given prednisolone. Prednisolone caused a fall in serum cortisol concentration. The authors concluded that children with moderately severe asthma attacks could be effectively treated with a short-term course of inhaled budesonide, starting with a high dose and reducing over the following week.

In 81 patients with acute asthma, mean age 38 years, inhaled budesonide 1600 micrograms bd via Turbuhaler was compared with oral prednisolone (40 mg on day 1, reducing to 5 mg by day 7) in a randomized, double-blind, parallel-group design (25). The mean increase in FEV_1 from baseline to day 7 was 17% with budesonide and 18% with prednisolone. Mean values of morning peak expiratory flow rate increased from day 1 to day 7 by 67 l/second with budesonide and by 57 l/second with prednisolone. There were no statistically significant differences between the groups in either symptoms or the number of doses of rescue medication. The authors concluded that high-dose inhaled budesonide may be a substitute for oral therapy in the treatment of an acute attack of asthma.

The effect of supplementary inhaled budesonide in acute asthma has been evaluated in a randomized, double-blind comparison with standard treatment in 44 children aged 6 months to 18 years with a moderate to severe exacerbation of asthma (26). Prednisone 1 mg/kg orally and nebulized salbutamol (0.15 mg/kg) every 30 minutes for three doses and then every hour for 4 hours were given to all children. In addition, each child was given 2 mg of nebulized budesonide or nebulized isotonic saline. There was a more rapid discharge rate in the budesonide group. There were no adverse effects. The authors concluded that nebulized budesonide may be an effective adjunct to oral prednisone in the management of moderate to severe exacerbations of asthma.

Fluticasone

Inhaled fluticasone 500 micrograms bd from a pressurized metered-dose inhaler for 6 months has been compared with placebo in a randomized, double-blind trial in 280 patients with COPD, aged 50–75 years (27). There was no significant difference in the number of patients who suffered one or more exacerbations. Moderate or severe exacerbations occurred significantly more often with placebo than with fluticasone. Diary-card scores, morning peak expiratory flow rate, clinic FEV_1, FVC, and mid-expiratory flow all improved significantly with fluticasone. Scores for median daily cough and sputum volume were significantly lower with fluticasone than with placebo. At the end of treatment, patients using fluticasone had increased their 6-minute walking distance significantly more than those using placebo. Fluticasone propionate was tolerated, as well as placebo, with few adverse effects and no clinically important effect on mean serum cortisol concentration. The authors suggested that inhaled glucocorticoids may have an important place in the long-term management of patients with COPD.

Local adverse effects

The local adverse effects of inhaled glucocorticoids have been studied in a prospective, cross-sectional, cohort study in 639 asthmatic children using beclomethasone (721 micrograms/day) or budesonide (835 micrograms/day) for at least one month (28). The local adverse effects included cough (40%), thirst (22%), hoarseness (14%), dysphonia (11%), oral candidiasis (11%), perioral dermatitis (2.9%), and tongue hypertrophy (0.1%). A spacer doubled the incidence of coughing.

Potent glucocorticoids in high local doses increase the risk of local infection and even promote atrophy of the bronchial mucosa. The latter effect has not proved clinically important, but there is an increased incidence of oropharyngeal candidiasis. The incidence varies depending on the population studied and the criteria used to make the diagnosis; candidiasis can affect 13–71% of patients, the highest incidence being seen with doses up to 0.8 mg. Candidiasis rarely requires treatment or withdrawal of the drug. Local measures, such as gargling immediately after inhalation of the aerosol, and the use of a large-volume spacer are effective in reducing the incidence of this complication. However, candidiasis can result in dysphonia.

A local myopathy caused by inhaled glucocorticoids can also cause dysphonia. However, patients with asthma have more dysphonia and vocal fold pathology than healthy controls and inhaled glucocorticoids can improve the voice in some patients (SEDA-21, 188).

In some patients, the propellant used in certain aerosols can cause acute bronchoconstriction (SEDA-6, 332).

Organs and Systems

Sensory systems

Cataract

In a population-based cross-sectional study of vision and common eye diseases in 3654 people, 49–97 years of age, inhaled glucocorticoid use was reported by 370 subjects, of whom 164 reported current use and 206 previous use. Subjects who reported using inhaled glucocorticoids had a higher prevalence of nuclear cataracts (OR = 1.5; CI = 1.2, 1.9) and posterior subcapsular cataracts (OR = 1.9; CI = 1.3, 2.8). The highest prevalence (27%) was in patients whose lifetime dose was more than 2000 mg (relative prevalence 5.5) (SEDA-22, 187).

In 3677 patients undergoing cataract extraction over 2 years compared with a matched control group of 21 868 people, the patients were more likely to undergo cataract extraction if they had used inhaled glucocorticoids for more than 3 years (OR = 3.06; CI = 1.53, 6.13). This risk was not significant in patients who used low to medium doses (1000 micrograms/day or less) when the OR was 1.63 (CI = 0.85, 3.13) after 2 years. The OR was

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higher in patients using average daily doses of beclomethasone dipropionate or budesonide (over 1000 micrograms) (OR = 3.40; CI = 1.49, 7.76) after more than 2 years of treatment (29).

In a nested case-control analysis based on a retrospective, observational, cohort study, 103 289 asthmatic patients using inhaled glucocorticoids were identified from the UK General Practice Database and were compared with 98 527 asthmatic patients with no history of glucocorticoid use (30). There was a slightly increased risk of cataract in those who used inhaled glucocorticoids (RR = 1.3; 95% CI = 1.1, 1.5). The relative risk of cataract was 2.0 in oral glucocorticoid users relative to glucocorticoid non-users (95% CI = 1.5, 2.2). The risk ratio increased with extensive use of inhaled glucocorticoids, but not with moderate use. The association of extensive use with cataract was most pronounced in those aged 70 years and over, and there was no effect in those aged under 40. The increased risk of cataract in patients aged 70 years and over persisted after controlling for cataract risk factors, such as smoking, diabetes mellitus, hypertension, and sex.

In another study, treatment for 2 years with fluticasone propionate (500 micrograms bd) had no significant effect on ophthalmic parameters (glaucoma and posterior subcapsular cataracts) (31). Slit lamp examinations were carried out in 157 asthmatic children treated with inhaled budesonide at a mean daily dose of 504 (range 189–1322) micrograms for 3–6 years (mean 4.4 years). Posterior subcapsular cataract due to budesonide was not detected (32).

Glaucoma

A case-control study compared 9793 patients with open-angle glaucoma or ocular hypertension to 38 325 randomly selected controls (33). There was no association between the use of inhaled or intranasal glucocorticoids and the risk of open-angle glaucoma or ocular hypertension. In patients who were currently using high doses, there was a small but significant increase in risk (OR = 1.44; CI = 1.01, 2.06).

Endocrine

Hypothalamic–pituitary–adrenal axis function provides one of the most sensitive markers of the systemic activity of inhaled glucocorticoids (34), and suppression can be used as a surrogate marker for adverse effects of inhaled glucocorticoids in other tissues.

The different methods of assessing hypothalamic–pituitary–adrenal axis activity in patients using inhaled glucocorticoids have been compared (35). The AUC of serum cortisol concentrations was the most reliable method. There were significant positive correlations between AUC and the 8 a.m. serum and salivary cortisol concentrations. The authors favored the non-invasive method of salivary concentration measurement. However, 24-hour urine collection is not recommended, as it correlated only moderately well. This finding is consistent with the results of other studies. Urinary free-cortisol estimation based on immunoassay after inhaled glucocorticoids may be an unreliable surrogate marker of adrenal suppression, and studies using this method should be interpreted with caution (36).

In a randomized, placebo-controlled study, the activity of the hypothalamic–pituitary–adrenal axis was assessed at baseline and after 21 days by determining 22-hour time-integrated serum cortisol concentrations, 24-hour urinary cortisol (corrected for creatinine), and morning salivary cortisol concentrations in 153 patients with mild to moderate asthma, randomly assigned to either inhaled flunisolide (500 or 1000 micrograms bd), inhaled fluticasone (110, 220, 330, or 440 micrograms bd), oral prednisone (7.5 mg/day), or placebo (19). Flunisolide and fluticasone caused dose-dependent suppression of the hypothalamic–pituitary–adrenal axis, and fluticasone was significantly more potent. However, the lowest fluticasone dose (110 micrograms/day) had no effect. These findings are consistent with those of a previous meta-analysis, which showed that fluticasone caused a greater dose-related suppression of the hypothalamic–pituitary–adrenal axis than other inhaled glucocorticoids (37). Fluticasone is more lipophilic than flunisolide and therefore has a larger volume of distribution and a longer half-life (34), but it is not clear how this might be associated with the larger effect described here.

The effect of fluticasone aqueous nasal spray on the hypothalamic–pituitary–adrenal axis has been compared with that of oral prednisone and placebo, using a 6-hour tetracosactide infusion test in a 4-week, randomized, double-blind, placebo-controlled study in 105 adults with allergic rhinitis randomly assigned to receive fluticasone 200 micrograms od, fluticasone 400 micrograms bd, oral prednisone 7.5 mg od, oral prednisone 15 mg od, or placebo (38). Fluticasone 400 micrograms bd and both doses of prednisone caused a significant reduction in the morning plasma cortisol concentration. The two fluticasone treatments produced no significant change in the hypothalamic–pituitary–adrenal axis response to co-syntropin. This contrasted with oral prednisone 7.5 or 15 mg od, which significantly reduced both plasma cortisol concentrations after co-syntropin and 24-hour urinary cortisol excretion.

A review of the literature from 1 January 1966 to 31 July 1998 identified 27 studies in which the effects of inhaled glucocorticoids on adrenal function were measured. A meta-regression of adrenal suppression in these 27 studies showed that adrenal suppression occurred with high doses of inhaled glucocorticoids (above 1500 micrograms/day; 750 micrograms/day for fluticasone propionate). However, there is a considerable degree of interindividual susceptibility. Meta-analysis showed significantly greater potency for dose-related adrenal suppression with fluticasone propionate compared with beclomethasone dipropionate, budesonide, or triamcinolone acetonide. Prednisolone and fluticasone propionate were approximately equivalent in a dose ratio of 10:1 (19).

Adrenal suppression by inhaled glucocorticoids in children

Inhaled glucocorticoids are being prescribed more and more in younger children at an earlier stage of their disease and for longer periods; children with severe asthma are also treated with larger doses than licensed.

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Therefore, considerations of their systemic effects are of importance. Symptomatic adrenal insufficiency has been reported in children after various regimens of inhaled glucocorticoids.

- Four boys 4–8 years old with symptomatic adrenal insufficiency had all used consistent high doses of fluticasone propionate 1000–1500 micrograms/day over extended periods (16 months to 5 years) (39). They presented with acute hypoglycemia secondary to iatrogenic adrenal suppression, with abnormal corticotropin tests, although none had Cushingoid features.
- A 33-year-old man and three children (two girls, one boy, 7–9 years) presented with symptomatic adrenal insufficiency (40). All three children had seizures because of hypoglycemia, and the man had a low blood pressure, nausea, and fatigue. In all cases, corticotropin tests were abnormal, showing adrenal insufficiency. The children had used fluticasone propionate 500–2000 micrograms/day and the man had recently switched from fluticasone propionate 1000–2000 micrograms/day to budesonide dry powder inhaler 800 micrograms/day. Only one of the children had used oral glucocorticoids in the previous year.
- A 21-month-old boy had a hypoglycemia-induced seizure in the setting of adrenal suppression (41). He had been given increasing doses of budesonide up to 2000 micrograms qds and oral glucocorticoids until the age of 15 months.
- A 32-month-old girl developed hypoglycemic seizures (42). She had been given fluticasone propionate 440–880 micrograms/day and up to 5 months before the incident oral glucocorticoids.
- Two girls aged 11 and 16 years, one boy aged 12 years, and one woman aged 54 years developed hypothalamic–pituitary–adrenal axis suppression during treatment with inhaled fluticasone propionate 220–880 micrograms bd for long-term control of asthma; however, two of the patients also took oral prednisone or prednisolone (43). Because of poor growth, an 8-year-old girl's asthma medication was changed from budesonide to fluticasone propionate 250 micrograms/day (44). However, 5 months later she had developed a round face. Her early morning cortisol concentration was less than 30 nmol/l (reference range 140–720) and her growth had been no more than 0.5 cm during the past 5 months. Fluticasone propionate was discontinued. After 1 month, her Cushingoid features had resolved and her fasting morning cortisol concentration was 310 nmol/l.
- A 32-year-old woman's asthma regimen was changed from budesonide to fluticasone propionate 500 micrograms/day and salmeterol (44). Eight months later, she was evaluated because of excessive bodyweight gain; her serum cortisol concentration was 16 nmol/l. Fluticasone propionate was replaced with nedocromil and 1 month later her serum cortisol concentration had normalized.

In addition to these case reports, there has been a survey of symptomatic adrenal suppression associated with inhaled glucocorticoids in the UK (45). Only 24% of the questionnaires were returned (709 responses), and there were 28 cases of symptomatic adrenal suppression reported in children and five in adults (including the 10 cases discussed above). The children presented mostly with hypoglycemia and coma, whereas the adults mainly had lethargy and nausea. No obvious precipitating cause was found in 65% of the cases. In four children, diagnosis was delayed by 3 months to 2 years. All but three patients had been treated with fluticasone propionate alone, but at high daily doses (children 500–2000 micrograms, adults 1000–2000 micrograms). One child had used both fluticasone propionate and budesonide, and one adult and one child used beclomethasone dipropionate.

A series of cases has illustrated the unexpected occurrence of symptomatic adrenal insufficiency in eight asthmatic children using inhaled glucocorticoids (46). The authors concluded that therapeutic doses of inhaled glucocorticoids can provoke paradoxical symptoms of adrenal insufficiency. Very high doses (calculated according to body surface area) may partly explain marked suppression of the hypothalamic–pituitary–adrenal axis. The need to taper inhaled glucocorticoid doses and to recognize the possibility of life-threatening acute adrenal insufficiency is of utmost importance.

In a double-blind, randomized pilot study of the efficacy and adverse effects of inhaled fluticasone in 25 newborn preterm infants who required mechanical ventilation for treatment of respiratory distress syndrome, the infants were randomized to receive inhaled fluticasone 1000 micrograms/day or placebo (47). The hypothalamic–pituitary–adrenal axis was assessed by the response to corticotropin-releasing factor. All basal and post-stimulation plasma corticotropin and serum cortisol concentrations were significantly less with inhaled fluticasone than placebo. Cumulative high-dose inhaled glucocorticoids caused moderately severe suppression of both the pituitary and the adrenal glands. This systemic activity is probably associated with pulmonary vascular absorption that avoids hepatic first-pass metabolism.

Chronic inhalation of beclomethasone dipropionate (up to 1000 micrograms/day) can produce adrenal suppression in some children. This effect is reduced by the attachment of a large volume spacer to the aerosol (SEDA-21, 188). Budesonide inhaled from the Turbuhaler, at doses of 800 or 1600 micrograms/day), did not produce any statistically significant suppression of the hypothalamic–pituitary–adrenal axis compared with placebo. The reduction was significant only after 3200 micrograms/day of budesonide when suppression equivalent to 10 mg/day oral prednisone was seen (48). Fluticasone propionate powder, 500 micrograms bd, given using a Diskhaler, for 104 weeks caused only minimal changes in the hypothalamic–pituitary–adrenal axis (31). Inhaled fluticasone propionate 400 micrograms/day for 8 weeks did not cause adrenal suppression in asthmatic children. In children, the benefit/risk ratio generally decreases at doses above 400 micrograms/day of fluticasone propionate (49). Hypothalamic–pituitary–adrenal axis suppression has been reported with inhaled fluticasone propionate at doses in excess of 1000 micrograms/day (SEDA-21, 188).

Different inhaled glucocorticoids have been compared for their suppressing effects on the hypothalamic–pituitary–adrenal axis (18). In a large meta-analysis, budesonide or beclomethasone dipropionate in doses of over 1500 micrograms/day was associated with adrenal

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suppression in adults (19). In children, fluticasone propionate 200 micrograms/day or budesonide 400 micrograms/day caused detectable adrenal gland suppression (50). For interpretation of the different studies, it is very important to distinguish between detectable indicators for systemic drug action (that is, reduced morning cortisol) and true suppression of the hypothalamic–pituitary–adrenal axis, as determined by adrenal function tests (standard-dose or low-dose corticotropin test), which are more predictive of possible systemic adverse effects (1).

The fact that fluticasone propionate is involved in the vast majority of the published cases should be discussed further. The systemic concentration of an inhaled glucocorticoid depends on the absorbed fraction of the drug in the gut and in the lung. Swallowed fluticasone propionate is almost completely metabolized in the liver by CYP3A4 (first-pass effect over 99.9%) before reaching the systemic circulation; however, its metabolic clearance can be altered in patients with low CYP3A4 expression and activity (51). Pulmonary absorbed fluticasone propionate is very potent; because of its pronounced lipophilicity, it binds with higher affinity to glucocorticoid receptors and has a larger distribution volume and a longer half-life than other inhaled glucocorticoids (52). These characteristics give it the potential of accumulating with multiple doses.

Other factors that determine the absorbed fraction of inhaled glucocorticoids include the age of the child, as lung deposition of inhaled drugs increases with age (53). Therefore, the minimum effective dose may fall as the child becomes older. Moreover, it is reasonable to hypothesize that systemic absorption will increase once asthma control is established (54). Furthermore, patient adherence and inhaler technique are two factors that can have a large influence on the amount of glucocorticoid inhaled and absorbed.

However, the most important factor is the dose. The safety and efficacy of fluticasone propionate in children in daily doses of 100–200 micrograms have been demonstrated in many studies (55). The doses in the case reports of symptomatic adrenal suppression have to be considered as being excessively high. These reports reflect excessive dosing of inhaled glucocorticoids, and in some cases a residual effect of previous oral glucocorticoid treatment cannot be excluded. The use of excessive doses is empirical and not supported by the literature. All inhaled glucocorticoids have a flat dose–response curve (56). Extensive clinical experience with inhaled glucocorticoids over the past 20 years has suggested that the risk of adrenal insufficiency with inhaled glucocorticoids alone is very low when recommended doses are used (57). To avoid symptomatic adrenal suppression, the lowest effective dose should always be used. Before automatically increasing the dose in refractory patients, the diagnosis should be reconsidered. Furthermore, a reduction in the dosage of inhaled glucocorticoid can also be achieved with the addition of adjuvant therapies, such as leukotriene receptor antagonists and long-acting β_2-adrenoceptor agonists (58).

Monitoring children using inhaled glucocorticoids has been discussed (1). Children using low to moderate doses of inhaled glucocorticoids (up to 200 micrograms of fluticasone propionate or budesonide) do not require routine hypothalamic–pituitary–adrenal axis measurement. In children using consistently higher doses (up to 400 micrograms of fluticasone propionate or budesonide) or using glucocorticoids by other routes, morning plasma cortisol should be monitored periodically because of the increased risk of clinically significant adrenal suppression. If cortisol concentrations are below 276 μmol/l (100 ng/ml), functional testing of the hypothalamic–pituitary–adrenal axis should be considered.

Metabolism

Impaired diabetic control has been reported with high doses of inhaled glucocorticoids.

- A 67-year-old man with asthma and non-insulin-dependent diabetes mellitus, taking glibenclamide 5 mg/day and metformin 1700 mg/day, had glycated hemoglobin concentrations of 7.0–7.3% (59). For asthma, he used nebulized ipratropium bromide 0.5 mg and salbutamol 5 mg qds. He was given inhaled fluticasone propionate 2000 micrograms/day by metered-dose inhaler through a Volumatic spacer device, with beneficial effect. In the third week he developed persistent glycosuria and the dose of fluticasone was reduced stepwise to 500 micrograms/day. He was then rechallenged by increasing his daily dose of fluticasone from 500 to 1000 micrograms. Within a week he had glycosuria, which again resolved on reduction of the dose of fluticasone. His glycated hemoglobin concentration rose to 7.8% after 1000 micrograms/day and to 8.2% after 2000 micrograms/day.
- Deterioration in glucose control occurred in a 64-year-old man with non-insulin-dependent diabetes mellitus (60). High doses of both fluticasone (2000 micrograms/day) and budesonide (2000 micrograms/day) had produced glycosuria despite treatment with glibenclamide and metformin 1700 mg/day. On reducing the dose of budesonide, there was a commensurate fall in glycosylated hemoglobin and glycosuria. There was no glycosuria at a daily maintenance dose of 800 micrograms and the glycosylated hemoglobin fell from 8.2 to 7.2%.

The association between inhaled glucocorticoids and the risk of diabetes mellitus in elderly people (over 65 years) has been investigated in two Canadian studies. In a nested case-control study of the association between current use of inhaled glucocorticoids and the risk of using antidiabetic drugs among 21 645 subjects the risk of diabetes was not statistically significant (61). Moreover, there was no statistically significant increase in risk among users of high-dose beclomethasone compared with non-users. In a retrospective population-based cohort study using administrative databases, the association between oral and inhaled glucocorticoid use and the onset of diabetes mellitus in the elderly was quantified (62). Users of proton pump inhibitors ($n = 53\ 845$) were the controls. Relative to controls, oral glucocorticoid users ($n = 31\ 864$) were more likely to develop diabetes mellitus, but there was no association between the use of inhaled glucocorticoids ($n = 38\ 441$) and diabetes mellitus. These results suggest that the use of inhaled glucocorticoids in elderly people does not significantly increase the risk of diabetes mellitus.

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Skin

Reduced skin thickness

Skin thickness (measured with ultrasound) was not significantly different from controls in patients taking low-dose beclomethasone dipropionate (200–800 micrograms/day). There was a reduction in skin thickness of 15–19% in patients using high dose beclomethasone dipropionate (1000–2500 micrograms/day), and 28–33% in patients using long-term oral prednisolone (5–20 mg/day). Bruising occurred in 12% of controls, 33% of patients using low-dose beclomethasone dipropionate, 48% of patients using high-dose beclomethasone dipropionate, and 80% of patients using oral prednisolone (63). Other workers have concluded that patients using beclomethasone dipropionate who report bruising are older (61 versus 52 years), take higher daily doses (1388 versus 1067 micrograms), and have been on treatment longer (55 versus 43 months) (64). The number of bruises seems to be inversely related to the concentration of urinary cortisol (SEDA-21, 188). In children using budesonide (189–1322 micrograms/day) for 3–6 years, there was no increase in bruising (32).

The effect of long-term inhaled glucocorticoids (800–1000 micrograms/day of either budesonide or beclomethasone) on skin collagen synthesis and thickness has been prospectively investigated in 27 consecutive new asthmatic patients (65). Asthma was treated with a moderate dosage of inhaled glucocorticoids. Skin thickness was measured before treatment and at 3 and 6 months using ultrasound on the abdomen and the upper right arm. Suction blisters were induced on the abdominal skin using a disposable suction blister device. Blister fluid was collected and kept frozen for radioimmunoassay of PINP and PIIINP. Skin punch biopsies were taken from the abdominal wall for the determination of skin hydroxyproline. After 1–2 years, 20 subjects attended for a further measurement of skin thickness. Control data were obtained in 14 healthy women who were followed for 6 months. PINP and PIIINP concentrations in blister fluid were followed in eight male volunteers for 1 year. There was no significant change in abdominal skin thickness after 6 months of inhaled glucocorticoids. In the upper arm there was a small, significant reduction from 1.64 to 1.50 mm after 6 months. After 1–2 years the skin thickness in the abdomen and upper arm was unchanged in 14 subjects who had used only inhaled glucocorticoids, but in six patients who had taken supplementary oral glucocorticoids for one to several weeks there was thinning of the skin in the upper arm but not the abdomen. The procollagen propeptides were markedly reduced in blister fluid at 3 and 6 months. There was no significant change in skin collagen expressed as hydroxyproline. Thus, despite evidence of a reduction in collagen synthesis, skin thickness and collagen did not change, possibly because the degradation and turnover of collagen slowed down. However, in the six patients who subsequently used oral glucocorticoids, skin thickness decreased.

Bruising

Since the original observation of the association between high-dose glucocorticoids and purpura and dermal thinning, easy bruising of the skin has become recognized as a systemic adverse effect of inhaled glucocorticoids (63). In a double-blind crossover study 69 asthmatic subjects received either the usual dose of beclomethasone dipropionate or fluticasone (at half the dose of beclomethasone) both for 4 months (66). The frequency and severity of skin bruising were assessed by questionnaire, and the numbers of bruises were assessed by direct examination. The dose of fluticasone was selected on the basis of previous studies that showed that it had comparable efficacy when given in half the dose of beclomethasone. This dose of fluticasone had comparable efficacy with respect to the control of asthma, but there was no skin bruising. These findings suggest that the systemic availability of equieffective doses of fluticasone is less than that of beclomethasone.

Contact allergy

Nasal glucocorticoids and inhaled glucocorticoids can have adverse effects on the nose and mouth, including pruritus, burning, dryness, erythema, edema, dry cough, and odynophagia; less commonly, they can cause eczema and urticaria, particularly on the face. Contact dermatitis to glucocorticoids can be facilitated by impaired epithelial barriers, and has been found in 4.7% of patients receiving topical hydrocortisone (67). Inhaled glucocorticoids can cause hypersensitivity reactions, especially in patients with chronic eczema who have been sensitized to local glucocorticoids.

Tixocortol pivalate is a marker for glucocorticoid contact allergy, as a positive patch test suggests established contact allergy to hydrocortisone, prednisolone, and their derivatives (68). A literature search via Medline from 1966 to May 2000 revealed only one patient hypersensitive to tixocortol pivalate and budesonide in a pilot study in 34 patients (10 with asthma, 13 with rhinitis, 11 with both) (69). From case reports, the prevalence of glucocorticoid-induced contact allergy has been estimated at 2.9–5%.

Based on these observations it has been concluded that patients who use inhaled glucocorticoids and develop unprecedented skin reactions during therapy should be tested for glucocorticoid-related contact allergy (70). Switching from one of the four main glucocorticoid groups to another might prove successful in these cases.

Two cases of perioral dermatitis have been associated with the use of inhaled glucocorticoids (71).

- A 38-year-old woman who had used inhaled beclomethasone daily (dosage not stated) during the winter for the past 5 years for mild asthma, developed a perioral rash with numerous small pustules and papules. She stopped using beclomethasone and was treated with oral erythromycin and topical tretinoin. Her rash resolved within 4 weeks. One year later, she restarted beclomethasone and her rash reappeared after 2 weeks. There was no recurrence of her perioral dermatitis during subsequent treatment with monthly intramuscular injections of betamethasone.
- A 46-year-old woman, who had used inhaled budesonide (dosage not stated) for 8 years for vasomotor rhinitis, developed a recurrent perioral rash, which responded to treatment with oral erythromycin 1 g/day for 6 weeks. One year later, she had a recurrence, which resolved with oral erythromycin. She continued to use inhaled budesonide.

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As cross-reactivity within glucocorticoid groups may be clinically relevant, skin patch testing has been proposed in cases of suspected glucocorticoid allergy, to identify the substances that can be safely administered (72). The prevalence of glucocorticoid allergy has been studied by skin patch testing in 30 patients using inhaled or intranasal glucocorticoids (73). Four patients had a positive patch test (three allergic reactions and one irritant reaction). Eight different glucocorticoids were used, but allergic reactions occurred only with budesonide. The authors therefore suggested that budesonide is more likely to cause contact hypersensitivity, but also referred to the possible relevance of allergic or irritant reactions to preservatives.

Contact allergy to glucocorticoids is not rare in patients with atopic dermatitis. In patients with known contact allergy to budesonide, allergic skin reactions can also occur when inhaled forms of the drug are used, as shown by a randomized, double-blind, placebo-controlled study in 15 non-asthmatic patients with budesonide hypersensitivity on patch testing (74). In four of seven patients who used inhaled budesonide, there was reactivation of the 6-week-old patch test sites and they had new distant skin lesions. No flare-up reactions were observed in the other 11 patients (three had used inhaled budesonide and eight placebo for 1 week). None of the patients developed respiratory symptoms; spirometry and peak expiratory flow rates remained normal.

Musculoskeletal

Bone

Studies of the effects of inhaled glucocorticoids have used biochemical markers of bone function and imaging techniques to assess bone mineral density. Some of the biochemical markers are summarized in Table 1. Initial, short-term studies caused concern about the effect of inhaled glucocorticoids on bone metabolism. Beclomethasone dipropionate 2000 micrograms/day reduced serum osteocalcin concentrations at 1 and 2 weeks, and they returned to normal at 1 and 2 weeks after withdrawal. Nebulized budesonide (2000 micrograms bd) produced a similar increase in FEV_1 to oral prednisolone 30 mg/day given over 5 days. Serum osteocalcin was significantly higher: 2.3 (0.9–3.7) ng/ml with budesonide compared with 0.6 (0–1.2) ng/ml with prednisolone. The 24-hour urinary calcium to creatinine ratio was significantly lower in patients treated with nebulized budesonide (SEDA-22, 183). After 4 weeks on beclomethasone dipropionate or budesonide 800 micrograms/day, there were significant but paradoxical changes in osteocalcin and PICP (both markers of bone formation). Osteocalcin concentrations fell, but PICP concentrations rose. Patients on beclomethasone dipropionate 800 micrograms/day followed for 30 months showed no change in markers of resorption (ICTP) or formation (PICP) (SEDA-22, 183).

While biochemical markers of bone metabolism may be sensitive to the effects of glucocorticoids in the short term, the relation between changes in these markers and intermediate measures, such as bone mineral density, and the more important clinical outcomes of fractures, is unknown. In a random stratified sample of 3222 women in the perimenopausal age range (47–56 years), including 119 women with asthma, bone mineral density was measured to determine whether asthma was a risk factor of osteoporosis and to investigate the effect of inhaled glucocorticoids (75). The subjects had predominantly adult-onset asthma, as the age at diagnosis was over 40 years. There were 26 patients who were treated mainly with inhaled glucocorticoids (average daily dose 1000 micrograms). The asthmatic women in this general perimenopausal population had slightly reduced spinal and femoral neck bone mineral density compared with non-asthmatic women. These differences were more prominent in women who were not taking hormone replacement therapy. The reduction in bone mineral density may be due to glucocorticoids, and hormone replacement therapy appears to be protective against bone loss in asthmatics as well as healthy subjects. Cross-sectional studies such as this provide information about association but do not imply causality, for which longitudinal studies are required. Studies of the effects of inhaled glucocorticoids on markers of bone mineral density have provided conflicting data (76).

Table 1 Biochemical markers of bone mineral density

Bone formation	Bone resorption
Blood	*Blood*
Alkaline phosphatase (bone-specific)	Acid phosphatase (acid-resistant)
Osteocalcin	Type I collagen carboxy-terminal telopeptide (ICTP)
Procollagen type I carboxy-terminal propeptide (PICP)	*Urine*
Procollagen type I amino-terminal propeptide (PINP)	Calcium
Procollagen type III amino-terminal propeptide (PIIINP)	Hydroxyproline
	Cross-linked peptides (pyridinium and deoxypyridinoline)

Effects on bone mineral density

Bone mineral density has been measured in a 3-year prospective study in 109 premenopausal asthmatic women, aged 18–45 years, all of whom used inhaled triamcinolone acetonide (77). They were grouped according to their inhaled glucocorticoid use at base line (no glucocorticoids and triamcinolone less than 800 micrograms/day or more than 800 micrograms/day). Therapy with triamcinolone was associated with a dose-related fall in bone mineral density at the hip overall and the trochanter. There was no effect at the femoral neck or the spine. None of the measured serum or urinary markers of bone turnover predicted the degree of bone loss. The dose-related loss of bone mineral density was suggested to be clinically related to prolonged treatment with inhaled glucocorticoids, and periodic bone mineral density assessment in patients taking high-dose inhaled glucocorticoids was proposed.

The effect of beclomethasone on bone mineral density has been examined over 1 year in 36 premenopausal and

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early postmenopausal women with asthma using inhaled glucocorticoids (beclomethasone at a mean dose of 542 micrograms/day) compared with 45 healthy matched controls (78). In early postmenopausal asthmatic women using beclomethasone, bone mineral density was significantly lower than in the controls, but not in premenopausal asthmatic women using inhaled beclomethasone. Serum osteocalcin concentrations were lower in the early postmenopausal asthmatic women using inhaled glucocorticoids than in the healthy controls, suggesting reduced bone formation, which leads to more pronounced bone loss. Ovarian hormones were suggested to offset the bone-depleting effects of inhaled beclomethasone in premenopausal women by maintaining or stimulating osteoblastic function.

There were significant reductions in bone mineral density in the lumbar spine and femur in 32 asthmatic women taking long-term inhaled beclomethasone (750–1500 micrograms/day) compared with 26 healthy controls (79). Control subjects and asthmatic patients were matched for age, sex, menopausal status, body-mass index, calcium intake, and physical activity. Loss of bone mass was more pronounced in the postmenopausal women. The authors identified several risk factors for accelerated bone loss in the lumbar spine, including postmenopausal status, low body-mass index, long duration of disease, long-term inhaled glucocorticoid therapy, and higher average daily and cumulative inhaled glucocorticoid doses.

The effects of inhaled budesonide 800 micrograms/day and fluticasone 400 micrograms/day on bone metabolism, morning cortisol concentrations, and clinical parameters have been studied in eight asthmatic patients (80). There were no changes in serum and bone alkaline phosphatase, osteocalcin, carboxyterminal propeptide of type 1 procollagen, and urinary calcium and deoxypyridinoline concentrations over 6 months. The authors concluded that fluticasone is as effective as twice the dose of budesonide in controlling asthmatic symptoms, without adverse effects on bone metabolism.

In a prospective comparison of the changes in bone mineral density in adults with mild asthma, 374 subjects with mild asthma (mean FEV_1 86% predicted; mean age 35 years; 55% women) were randomized to receive inhaled budesonide, inhaled beclomethasone, or non-glucocorticoid treatment (the control group) for 2 years (81). Bone mineral density was measured blind after 6, 12, and 24 months. The median daily doses of budesonide (87 subjects) and beclomethasone (74 subjects) were 389 and 499 micrograms respectively. The mean changes in bone density over 2 years in the budesonide, beclomethasone, and control groups were 0.1, –0.4, and 0.4% in the lumbar spine and –0.9, –0.9, and –0.4% in the neck of the femur. The mean daily dose of inhaled glucocorticoid was related to the reduction in bone mineral density only in the lumbar spine. Low to moderate doses of inhaled glucocorticoids caused little change in bone mineral density over 2 years and provided better asthma control.

In a retrospective cohort comparison of patients using inhaled glucocorticoids or bronchodilators with controls, there was an increased risk of fractures, particularly at the hip and spine, in those using inhaled glucocorticoids. There were no differences in relative fracture risks with different drugs, for example fluticasone, budesonide, beclomethasone (82). In an earlier retrospective study, there was a dose-dependent increase in bone fracture risk with oral glucocorticoids (83).

The effects of inhaled glucocorticoids on bone mineral density (measured using dual X-ray absorptiometry of the spine and hip) and biochemical parameters were followed over 18 months. Mean serum osteocalcin concentrations were significantly lower in patients taking beclomethasone dipropionate or budesonide at doses of 800 micrograms/day and more. However, bone mineral density of the lumbar spine and hip was not affected. The normal advancement of bone mineral density expected in growing children was not affected by inhaled glucocorticoids taken for 7–16 months (SEDA-22, 184).

Treatment with beclomethasone dipropionate 1500 micrograms/day for 6 weeks significantly reduced markers of bone formation (osteocalcin and PICP), whereas fluticasone propionate 750 micrograms/day had no effect. Neither drug affected biochemical markers of bone resorption. There was no significant change in bone density (SEDA-22, 183).

Effects on bone mineral density in children

A cross-sectional study in children (84) showed no significant difference in total and anteroposterior spine bone mineral density between children with asthma treated with long-term budesonide (200–800 micrograms for at least 6 months; $n = 52$) and asthmatic children who had never used inhaled glucocorticoids ($n = 22$). These results are in agreement with those of a larger cross-sectional study of the effects of long-term treatment (3–6 years, mean 4.5 years) with inhaled budesonide on total bone mineral density in children with asthma ($n = 157$). The results provided evidence that long-term treatment with inhaled glucocorticoids in moderate dosages is unlikely to affect bone mineral density adversely in children with asthma (85). However, a study of the association of clinical risk factors and bone density with fractures in 324 prepubertal children, of whom 32 had a fracture, suggested that for total fracture risk bone mineral density may be less important than clinical risk factors (86). In a multivariate model incorporating age, weight, height, breast-feeding history, sports participation, and the use of inhaled glucocorticoids, these factors accounted for 10% of the variability in the risk of fracture. Surprisingly, bone mineral density in the lumbar spine, femoral neck, and total body bone did not differ between those with and without fractures.

In a small cross-sectional study, bone mineral density was studied in 20 prepubertal asthmatic patients treated with moderate to high doses of inhaled glucocorticoids (under 400 micrograms/day beclomethasone or budesonide or over 200 micrograms/day fluticasone) (87). Volumetric trabecular bone mineral density of the lumbar spine and distal radius were measured using dual energy X-ray absorptiometry and were within the reference ranges.

Bone mineral density (measured by dual X-ray absorptiometry) did not change significantly in asthmatic children treated for 3–6 years with a mean daily dose of 504 micrograms (189–1322 micrograms) budesonide (85).

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In 23 children, randomized to either fluticasone 100 micrograms bd or beclomethasone 200 micrograms bd for 20 months, there was a significant increase in bone mineral density in the lumbar spine with time, following the normal growth pattern (88).

Comparisons with placebo

More data on the effect of inhaled glucocorticoids on bone mineral density in adults have been generated by the large randomized, multicenter, double-blind, placebo-controlled EUROSCOPE (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease) study of 912 patients with chronic obstructive pulmonary disease randomly assigned to treatment for 3 years with budesonide 800 micrograms/day or placebo (89). There were no significant differences in bone mineral density at L2–4 vertebrae, the femoral neck, trochanter, or Ward's triangle; nor did the fracture rate between budesonide-treated and placebo-treated patients differ. These findings are in contrast to recent data from the Lung Health Study, which showed that triamcinolone 1200 micrograms/day for 4 years was associated with a statistically significant 2% reduction in bone mineral density in the femoral neck compared with placebo (90).

Comparisons of glucocorticoids

In a 12-month, multicenter comparison of fluticasone propionate 250–500 micrograms/day with beclomethasone dipropionate 500–1000 micrograms/day, the two drugs had an equal therapeutic effect. Fluticasone propionate treatment resulted in a higher bone mineral density (assessed at the hip) and higher serum osteocalcin concentrations.

In a prospective randomized comparison of the effects of fluticasone propionate 1000 micrograms/day and budesonide 1600 micrograms/day, over 1 year, bone mineral density measured in the spine was normal at the start of the study and increased slightly with time in both groups, as did serum osteocalcin concentration.

Fluticasone propionate 1000 micrograms/day or beclomethasone dipropionate 2000 micrograms/day taken for 2 years caused no change in biochemical markers of bone metabolism. Bone mineral density, measured by dual X-ray absorptiometry or single-photon absorptiometry, showed no consistent change. However, when bone mineral density was measured using quantitative computed tomography of the lumbar spine, beclomethasone dipropionate was associated with a small fall in bone mineral density, which stabilized by 24 months. It is doubtful that a small fall in bone density seen only on quantitative computed tomography is clinically relevant (SEDA-22, 184).

The efficacy and safety of fluticasone 750 micrograms/day and beclomethasone 1500 micrograms/day delivered by a spacer device have been compared in 30 asthmatic children in a 12-week, randomized, double-blind, crossover study (91). All of the children had persistent asthma requiring 1000–2000 micrograms/day of inhaled glucocorticoids before the trial. There was no significant difference in efficacy, as judged by daytime and nighttime symptom scores and PEFR. There was a minimal reduction in serum cortisol in both groups. Both groups had identical height gain velocities. At the doses used in this trial, the authors were unable to show a safety advantage of fluticasone over beclomethasone, as assessed by cortisol concentrations.

In a 1-year prospective, randomized, open comparison of inhaled fluticasone 500 micrograms bd with budesonide 800 micrograms bd delivered by metered-dose inhaler and large volume spacer, bone mineral density was measured in 29 patients in the lumbar spine and femoral neck (92). Bone mineral density in the spine increased slightly in both groups over the 12 months. Serum osteocalcin concentrations increased from baseline in both treatment groups (fluticasone +17%, budesonide +14%). The percentage change from baseline in bone mineral density of the spine correlated with the increase in serum osteocalcin. Mean serum cortisol concentrations remained in the reference range after both inhaled glucocorticoids.

It can be hypothesized that different glucocorticoids have different systemic effects, and therefore different effects on bone metabolism. An alternative hypothesis is that these effects are dose dependent (58), support for which comes from a population-based case-control study of 16 341 older patients with hip fractures (mean age 79 years) and 29 889 controls; recent use of an inhaled glucocorticoid was associated with a small dose-dependent increase in the risk of hip fracture (93).

Comparisons with other drugs

Bone mineral density was measured after 7.4 months in 49 asthmatic children, 38 of whom took inhaled beclomethasone, average daily dose 276 micrograms, and 11 sodium cromoglicate, average daily dose 30 mg (94). Children who had used beclomethasone had grown as much as those who used sodium cromoglicate. Trabecular and cortical bone mineral density in the proximal forearm and lumbar spine increased to the same extent in both groups.

The effects of fluticasone 50 micrograms bd or sodium cromoglicate 20 mg qds on growth over 12 months have been studied in 122 asthmatic children aged 4–10 years (95). The mean height velocity was 6 cm/year with fluticasone and 6.5 cm/year with sodium cromoglicate. There was no significant treatment difference in the mean 24-hour urinary-free cortisol concentrations at 6 or 12 months. Mean predicted peak expiratory flow rate improved over 1 year in both groups, but to a greater extent with fluticasone. The authors concluded that growth was normal in mildly asthmatic children using fluticasone (50 micrograms bd) for 1 year. Fluticasone was more effective than sodium cromoglicate, with fewer withdrawals and greater improvement in lung function.

Dose relation

Current evidence suggests that the changes in bone mineral density in asthmatic patients who take inhaled glucocorticoids occur within the high therapeutic range of doses. In patients with mild asthma who are well maintained on low doses of inhaled glucocorticoids, the benefits derived from good control of the asthma appear to

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outweigh any concerns about minor changes in bone mineral density. The picture is less clear in patients with other risk factors, such as estrogen deficiency and advancing years.

No adverse effect on bone has been shown with beclomethasone dipropionate or budesonide at doses less than 1000 micrograms/day or fluticasone propionate less than 500 micrograms/day. Most patients obtain a good therapeutic response at these doses. Higher doses may be required in some patients. Aerosols delivering doses of beclomethasone dipropionate 250 and 500 micrograms, budesonide 400 micrograms and fluticasone propionate 250 and 500 micrograms should be reserved for patients in whom the requirement for a high dose has been demonstrated in an adequate trial of therapy.

In an uncontrolled study, 56 women with asthma taking long-term inhaled glucocorticoids had bone mineral density measurements of the lumbar spine and hip (96). Women who had taken more than three short courses of systemic glucocorticoids per year over the preceding 3 years were excluded. Data on duration of use and dose of inhaled glucocorticoids were obtained from the patients' medical records. Doses of inhaled glucocorticoids were arbitrarily classified as low (under 500 micrograms/day), medium (500–1000 micrograms/day), and high (over 1000 micrograms/day). More than half the women (61%) had reduced bone mineral density at either the hip or lumbar spine. Amongst the postmenopausal women in the study, 17% of those aged under 65 years had osteoporosis compared with 43% of those aged over 65 years. These figures exceeded those from a national sample of estrogen-deficient women, in which 5.7% under the age of 65 and 29% over the age of 65 years had osteoporosis. Bone mineral density loss increased with higher doses of inhaled glucocorticoids, from 5% in the low-dose group to 50% in the high-dose group. Whilst this is a potentially important finding in women at risk of osteoporosis because of the menopause, there are some aspects of the design of the study that limit the applicability of the findings. There was no appropriate age- and ethnicity-matched control group, and the contribution of nasal glucocorticoids was not accurately assessed.

In a large cross-sectional study, patients aged 20–40 years with asthma who had taken inhaled glucocorticoids for a median of 6 years were studied (97). Patients were excluded if they had taken a course of oral or parenteral glucocorticoids in the past 6 months or more than two courses ever, or if they had had more than 10 inhalers of nasal glucocorticoids or more than 10 prescriptions of a dermal glucocorticoid. Computerized records of general practices were used to identify patients for the study. Bone mineral density was measured at the lumbar spine (L2–L4) and the left femur (neck, Ward's triangle, trochanter). The cumulative dose of inhaled glucocorticoid was expressed as a product of the mean daily dose and time (mg days). This information was obtained from a patient questionnaire and validated against general practice computer and paper records. More than half of the patients (119/196) were women and the median cumulative dose of inhaled glucocorticoid was 876 mg (range 88–4380 mg). There was a significant inverse relation between the cumulative dose of inhaled glucocorticoid and bone mineral density at the spine and hip in both men and women. A doubling of cumulative dose was associated with a 0.16 times SD reduction in bone mineral density. Extrapolation from cross-sectional data such as these requires confirmation in longitudinal studies, since bone loss with oral glucocorticoids is more rapid in the first 12–24 months of therapy.

Bone mineral density has been measured at 3-year intervals in 51 patients taking inhaled glucocorticoids for asthma (98). The patients were divided into a high-dose group taking over 800 micrograms/day of beclomethasone or budesonide ($n = 28$, mean dose 983 micrograms/day) and a control group taking no inhaled glucocorticoid or less than 500 micrograms/day ($n = 23$, mean dose 309 micrograms/day). Whilst there were statistically significant reductions in bone markers, such as serum calcium and phosphorus and osteocalcin, over the 3-year period in each group, there was no significant reduction in bone mineral density in either group of asthmatic patients. Although the change in bone mineral density in the high-dose group was small over the 3-year period and not statistically significant, there was a correlation between bone loss and the daily dose of inhaled glucocorticoids. There was no significant correlation between the changes in bone density and either the initial bone density or biomarkers of bone turnover for the level of physical activity. This longitudinal study has shown the unreliability of biomarkers of bone turnover in predicting changes in bone density (and presumably relevant clinical outcomes, such as risk of fracture) and shows the need for measurement of bone mineral density in asthmatic patients who are deemed to be at risk of bone loss. Such patients include those taking oral glucocorticoids, perimenopausal women not taking hormone replacement therapy, and patients who need high doses of inhaled glucocorticoids. Whilst patients in this study did not have significant changes in bone mineral density over 3 years, the effects of higher doses remain uncertain, so it would be prudent to measure bone mineral density in patients who need higher doses.

Time course

The time course of changes in bone mineral density with inhaled glucocorticoids has yet to be determined. Longitudinal studies will be required to determine whether bone loss is most rapid in the first 12–24 months after initiating inhaled glucocorticoid therapy, as is the case with oral glucocorticoids (99) and whether the risk of fracture falls towards baseline after withdrawal of treatment, as was suggested by the GPRD (General Practice Research Database) study (87).

In older women with asthma, who have an increased risk of osteoporosis, there was no significant change in bone mineral density after 1 year of treatment with beclomethasone dipropionate 1000 micrograms/day (100).

Bone mineral density, bone turnover markers, and adrenal glucocorticoid hormones have been measured in 53 patients (34 women, 19 men) with chronic bronchial asthma who took either inhaled beclomethasone or budesonide in doses of at least 1500 micrograms/day for at

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least 12 months (101). The patients were divided into those who had taken oral glucocorticoids for more than 1 month and those who had not. Bone mineral density was measured at the lumbar spine and the proximal femur. The values were about one standard deviation lower in men and women taking oral glucocorticoids or very high doses of inhaled glucocorticoids. The reduction in bone mineral density was enough to a double the risk of fracture at these sites. There was suppression of both endogenous glucocorticoid and adrenal androgen production in all subjects. Adrenal androgen suppression may increase the susceptibility of postmenopausal women treated with an oral glucocorticoid to bone loss.

Risk of fracture

Although studies in which biochemical markers of bone turnover are measured for periods of 1–2 months do not predict the development of bone thinning, osteoporosis, or fracture, they can be useful in comparing the potential effects on bone of different glucocorticoids. Studies of bone mineral density over longer time periods relate more directly to osteoporosis and fracture risk.

Whilst there have been several studies of the effects of inhaled glucocorticoids on bone mineral density, there are few data on the effects of inhaled glucocorticoids on the risk of fracture. In a retrospective cohort study the risk of fracture was established by examining the General Practice Research Database (GPRD), which is run by the Medicines Control Agency in the UK (87). Users of inhaled glucocorticoids were defined as permanently registered patients aged 18 years or more who received one or more prescriptions for inhaled glucocorticoids during the time from enrolment in the GPRD until the end of data collection. Patients who received a prescription for oral glucocorticoids for a period of 6 months before to 91 days after the last prescription for an inhaled glucocorticoid were excluded. There were two comparison groups: a bronchodilator group, which included adults who received prescriptions for non-systemic glucocorticoids and bronchodilators, and a second control group who received non-systemic glucocorticoids but never inhaled systemic glucocorticoids or bronchodilators. The database included over 440 000 patients and all patients who had fractures were identified from their medical records during the follow-up period, which was 91 days after the last prescription for an inhaled glucocorticoid. The relative rates of non-vertebral, hip, and vertebral fractures during inhaled glucocorticoid treatment compared with controls were 1.15 (95% CI = 1.10, 1.20), 1.22 (CI = 1.04, 1.43), and 1.51 (CI = 1.22, 1.85) respectively. There were no differences between inhaled glucocorticoids and bronchodilators (non-vertebral fracture relative rate = 1). The authors concluded that users of inhaled glucocorticoids may have an increased risk of fracture, particularly at the hip and spine, but that this excess risk may be related more to the underlying respiratory disease than to the inhaled glucocorticoids.

There were no major differences between the three groups in baseline fracture history. About 1% in each cohort recorded a history of non-vertebral fractures in the year before baseline. During the follow-up, the incidence of non-vertebral fractures was 1.4 fractures per 100 persons with inhaled glucocorticoids, 1.4 with bronchodilators, and 1.1 in the control group. Comparing inhaled glucocorticoid users with a control group, there was a dose response for hip and vertebral fractures. For a standardized daily dose of under 300 micrograms/day of budesonide, hip fracture was 0.95, rising to 1.06 at doses of 300–700 micrograms/day and 1.77 at doses of 700 micrograms/day or more. There was no consistent trend in the rate of fractures amongst users of inhaled glucocorticoid compared with bronchodilators.

This is a noteworthy study because it has examined the most important clinical outcome of change in bone mineral density: the risk of fracture. The results point to an increased risk of fracture, especially at the hip and the vertebral bodies, amongst patients who use inhaled glucocorticoids as well as those using bronchodilators, when compared with patients not using these drugs. Fracture risk tended to fall after withdrawal of inhaled glucocorticoids or bronchodilators. These findings suggest that low-dose inhaled glucocorticoids are not associated with an increased risk of fracture and that patients with chronic respiratory disease who use any inhaled therapy are at risk compared with a control population. There were no differences in fracture risk between the various types of bronchodilators, suggesting that the underlying lung disease itself was the basis of risk rather than any particular type of bronchodilator. The authors noted that 1.9% of patients were using doses of budesonide equivalents of over 1500 micrograms/day and that the possibility of a more pronounced increased fracture risk at these high doses cannot be excluded. The age- and sex-specific incidence of fracture in the control group was similar to that of the general population in the GPRD.

Estimates of the important outcome of bone fracture have shown a small increased risk with inhaled glucocorticoids, but this may well be a feature of the disease rather than the therapy, because comparisons with treatment with bronchodilator drugs show no difference between risk factors in patients taking glucocorticoids or bronchodilators.

Prevention of osteoporosis with bisphosphonates

The effect of high-dose inhaled glucocorticoids and antiresorptive therapy with sodium etidronate has been studied for 18 months in 38 Chinese patients (24 men and 14 premenopausal women aged 30–50 years), of whom 28 were asthmatics who had already been treated for at least 12 months with high-dose inhaled glucocorticoids (beclomethasone or budesonide over 1.5 mg/day), and 10 healthy controls (102). The patients were randomly allocated to (1) no supplement, (2) a calcium supplement 1000 mg/day, or (3) cyclical sodium etidronate 400 mg/day for 14 days followed by calcium 1000 mg/day for 76 days. All three groups continued to take inhaled glucocorticoids. Bone mineral density was measured at the lumbar spine and hip. Bone mineral density in the group one patients fell by about 1% over 18 months and rose by about 1.5% in the healthy controls, neither change being significant. In groups 2 and 3 bone mineral density rose significantly at 12 and 18 months by 2 and 3% respectively. Serum osteocalcin concentrations fell significantly in all three groups of asthmatic patients but not in the controls. There were no significant changes in serum

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alkaline phosphatase or parathyroid hormone. In the patients taking calcium, with or without etidronate, mean serum calcium increased. The authors suggested that calcium supplementation and cyclical etidronate work by reducing bone resorption, and hence reduced bone turnover, rather than by increasing bone formation. This is consistent with the fall in serum osteocalcin.

The efficacy of clodronate in treating glucocorticoid-induced bone loss in asthmatic subjects has been evaluated in a double-blind study in 74 adults (41 women and 33 men, mean age 57 years) with a long history (mean 8.1 years) of oral and inhaled glucocorticoid use, randomized to clodronate 800, 1600, or 2400 mg/day or placebo (103). There was no increase in bone mineral density with placebo or clodronate 800 mg/day, but a significant dose-related increase with clodronate 1600 and 2400 mg/day. The most common adverse effect was gastric irritation in the patients who took the highest dose of clodronate.

Growth

Oral glucocorticoids inhibit growth by blunting pulsatile growth hormone secretion, by decreasing insulin-like growth factor-1 activity, and by directly inhibiting collagen synthesis (104). Although inhalation reduces systemic exposure, concerns have been raised regarding the potential effects on growth and final height in children, especially when inhaled glucocorticoids are used for long periods.

Uninterrupted administration of moderate-dose inhaled glucocorticoids (for example 400 micrograms/day of budesonide equivalents) has been associated with a suppressed growth rate in some children with asthma. Budesonide reduced the growth by 1 and 1.4 cm over 7 and 12 months, respectively (105). Consequently, in the USA, a class label warning for inhaled glucocorticoids about growth retardation in children was introduced in 1998, when the FDA decided to alter the class labeling for all inhaled and nasal glucocorticoids in children, to indicate that the use of recommended doses might be associated with a reduction in growth velocity (19). However, the available studies suggest that in children, the major advantages of adequate asthma control with inhaled glucocorticoids outweigh any potential adverse effects on growth.

However, results from trials in asthmatic children can be flawed by confounding variables. Severe asthma can itself have a negative effect on growth and adversely affect adult height, as with any chronic disease. Even in well-controlled asthma, children typically show retardation in pubertal growth spurt and attain normal adult height later. As growth in children is non-linear over time, trials over short periods are likely to capture short-term effects of inhaled glucocorticoids rather than the long-term outcome. Furthermore, the growth-retarding effect of inhaled glucocorticoids is more pronounced at the start of treatment.

Long-term studies have suggested that a temporary short-term or medium-term reduction in growth velocity is normally compensated for later on, and individuals attain normal adult height (106,107). The effects of inhaled glucocorticoids on growth rate over weeks and months are dose-dependent, and dose-response curves of pulmonary and adverse systemic effects differ widely, so that individual titration of the inhaled glucocorticoid dose according to the severity of the disease is strongly recommended, and the lowest dose of inhaled glucocorticoids that controls the disease should always be preferred. In conclusion, accumulating evidence shows that children with asthma, even when treated with inhaled glucocorticoids for years, attain normal adult height. However, close growth monitoring during inhaled glucocorticoid therapy is recommended, as idiosyncratic responses can occur, probably owing to individual glucocorticoid receptor polymorphism (108).

A two-part review was published in 2002, addressing the difficulties of assessing the effects of asthma therapy on childhood growth and reviewing the published literature based on the authors' recommendations (109,110). In the first part (109), a simple classification system for growth studies was developed:

- comparisons with placebo (type 1 studies);
- comparisons with non-steroidal asthma therapy (type 2 studies);
- comparisons with another inhaled glucocorticoid (type 3 studies);
- comparisons with "real life" asthma therapy (type 4 studies).

In the context of these different study types, the authors also discussed the choice of end-point, key trial design issues, the selection and numbers of subjects in the active and control groups, the duration of assessments, and methods for measuring height and data analysis. They also elaborated specific recommendations regarding study duration, age/sexual maturity of the patients, exclusion criteria for height and growth velocity, permitted therapy during the study, the protocol for height measurement, the numbers of patients for adequate statistical power, and methods for statistical analysis (109).

In the second part, they selected 18 growth studies that included minimal criteria, such as selected control group, measured height by stadiometry, and at least a 12-month duration; they compared the design attributes of these studies with the described recommendations (110). Of the 18 selected studies, 17 were susceptible to one or more important confounding factors; nevertheless, the outcomes of all 18 studies were considered to be consistent. In summary, impaired growth velocity was found with budesonide and beclomethasone dipropionate compared with placebo, non-steroidal treatment, and fluticasone propionate during 1–2 years of therapy, but none of the inhaled glucocorticoids appeared to affect final height (110). Growth in children treated with low-dose fluticasone propionate (up to 200 micrograms/day) for 1 year is similar to growth in those treated with placebo or non-steroidal therapy. Standard pediatric doses of inhaled glucocorticoids (less than 800 micrograms of budesonide and less than 400 micrograms of budesonide or fluticasone) are considered not to affect growth adversely (57,111). The risk of growth suppression depends on the dose, the administration regimen, and the delivery device.

An important confounding factor is the influence of non-adherence to inhaled glucocorticoid treatment (112). Sensitive and reliable measures of adherence

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should be applied when evaluating long-term effects on height.

The time of dosing can influence the effect of inhaled glucocorticoids on growth suppression in the prepubertal child, since growth hormone secretion is generally confined to nighttime. Therefore, once-daily morning dosing could be advantageous (113).

For clinical practice, the lowest effective dose should be achieved, and all children using inhaled glucocorticoids should have their growth measured every 6 months, as this is a sensitive method of detecting significant systemic effects (57,113).

These results apply to children over 4 years of age; for younger children only assumptions can be entertained and age-specific studies are needed (113).

Dose relation

Lumbar spine bone mineral density has been assessed in 76 prepubertal asthmatics (mean age 7.7 years, 26 girls) using glucocorticoids (114). After stratification for dose and route of administration, the children who used over 800 micrograms/day of inhaled glucocorticoids, with or without intermittent oral glucocorticoids, had a significant lower weight-adjusted bone density than children who used 400–800 micrograms/day of inhaled glucocorticoids (mean difference –0.05 g/cm^2; 95% CI = –0.02, –0.09). Bone mass was similar in children who did not use inhaled glucocorticoids and those who used 400–800 micrograms/day.

The authors of a review concluded, from short-term and intermediate-term growth studies, that there are no clinically significant adverse effects on growth with inhaled glucocorticoids at normal pediatric doses (100–200 micrograms/day budesonide equivalents), but that growth retardation can occur with all inhaled glucocorticoids at higher doses (115). Individual idiosyncratic adverse reactions are rare. Long-term studies and studies that have examined the effect on final adult height have been consistent in showing significantly reduced growth rates during the first months and up to 2 years of treatment with inhaled glucocorticoids. However, children treated with inhaled glucocorticoids attain their predicted adult height to the same extent as their healthy peers. It is important to note that changes in growth rate during the first year of inhaled glucocorticoid treatment cannot be used to predict final adult height.

Growth velocity measured over a 12-month period in prepubertal children with asthma was reduced by prior treatment with inhaled glucocorticoids for an average of 2.7 years. However, measurement of biochemical markers (Table 1) gave conflicting results. Osteocalcin concentrations were reduced, but alkaline phosphatase did not change. PINP and PIIINP were reduced, but PICP increased. ICTP, a marker for collagen I degradation, fell.

Comparisons of glucocorticoids

Fluticasone propionate 400 micrograms/day or budesonide 800 micrograms/day were administered for 20 weeks to children with moderate to severe asthma aged 4–12 years. Fluticasone propionate was superior to budesonide in improving peak expiratory flow and comparable in controlling symptoms. Growth was reduced with budesonide treatment compared with fluticasone propionate treatment mean difference, 6.2 mm (CI = 2.9, 9.6). There was no difference in serum cortisol suppression (116).

Comparisons with other drugs

Beclomethasone dipropionate 400 micrograms/day and salmeterol 50 micrograms bd were compared in asthmatic children treated for 12 months. Beclomethasone dipropionate treatment resulted in better overall asthma control. Over 12 months, linear growth was 3.96 cm/year in the children using beclomethasone dipropionate, compared with 5.40 cm/year in those who used salmeterol and 5.04 cm/year in a placebo group (SEDA-22, 186).

The long-term effects of inhaled glucocorticoids on growth in children have been recently assessed. In the so-called CaAMP Study (117), children aged 5–12 years with mild to moderate asthma were randomized to budesonide 200 micrograms bd (n = 311), nedocromil 8 mg bd (n = 312), or placebo (n = 418). At the end of the 4–6 year treatment period, the mean increase in height in the budesonide group was 1.1 cm less than in the placebo group. The difference between budesonide and placebo in the rate of growth was evident primarily within the first year but did not increase thereafter, and all the groups had similar growth velocity by the end of the treatment period.

Comparisons with oral glucocorticoids

A meta-analysis of 21 studies in which 810 asthmatic children were treated with oral prednisolone (8 trials) and/or beclomethasone dipropionate, dosage range 200–900 micrograms/day (12 trials) has been reported. Significant suppression of growth occurred with oral glucocorticoids but not with beclomethasone dipropionate (118).

Reversibility

Growth data obtained in 50 children who used beclomethasone dipropionate over 7 months suggested that any growth suppression is temporary and that growth velocity recovers during continuing treatment. Growth velocity fell most in the first 6 weeks of treatment, from 0.140 to 0.073 mm/week (0.067 mm/week; 95% CI = 0.015, 0.120). There were similar reductions at 12 and 18 weeks. After this, growth velocity increased to rates seen before treatment began: 0.138 mm/week at 24 weeks and 0.120 mm/week at 30 weeks (119).

Long-term use of beclomethasone dipropionate 400–600 micrograms/day was reported to delay the onset of puberty. However, subsequent catch-up growth was unaffected and subjects reached their normal predicted adult height (120).

Children taking budesonide (mean daily dose 412 micrograms, range 110–877 micrograms) for periods of 3–13 years have been followed to adulthood to determine their final height (107). These 142 budesonide-treated children were compared with 18 control patients with asthma who had never taken inhaled glucocorticoids

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and 51 healthy siblings of the patients in the budesonide group. These children, who had taken long-term inhaled glucocorticoids, attained normal adult height. There was no evidence of a dose–response relation between the mean daily dose of budesonide, the cumulative dose, or the duration of treatment with budesonide and the difference between the measured and target adult heights.

These studies are important, because several previous reports of growth during a period of 1 year after beginning treatment with inhaled glucocorticoids (in daily doses of about 400 micrograms of budesonide) identified growth retardation of about 1.5 cm. The mechanism for the termination after 1 year of the effects on growth is uncertain.

Immunologic

Hypersensitivity to inhaled glucocorticoids is rare.

- An asthmatic patient using inhaled budesonide and salbutamol developed an acute asthma attack. Despite emergency treatment the patient deteriorated, requiring endotracheal intubation and assisted ventilation, and there was no improvement until the glucocorticoid was withdrawn, after which there was steady improvement. Skin prick tests with prednisolone, sodium hemisuccinate, and 6-methylprednisolone-sodium hemisuccinate were positive. Thirty minutes after intradermal 6-methylprednisolone-sodium hemisuccinate 4 mg, the patient developed a dry cough, dyspnea, and wheezing and a 17% fall in FEV_1.
- A 37-year-old woman who was pregnant developed Churg–Strauss syndrome after withdrawal of her usual high-dose inhaled glucocorticoid therapy (drug not stated) that she had used for 3 years for bronchial asthma (121).

The authors of the second report commented that activated eosinophils and their cytotoxic products, such as eosinophil catatonic protein, may play a part in the pathogenesis of Churg–Strauss syndrome. Measuring serum concentrations of eosinophil catatonic protein may be useful in monitoring disease activity, since concentrations were increased before treatment and normalized afterwards.

Infection risk

Inhaled or topical immunosuppressive and anti-inflammatory glucocorticoids increase the risk of oral candidiasis (122). Patients who harbor oral *Candida* before they use inhaled glucocorticoids may have an increased risk. The location and degree of oral candidiasis seems to be related to dosage, administration frequency, and inhalation technique. Preventive measures include using a spacer, lowering the dosage, and rinsing the mouth after use.

Invasive aspergillosis occurred after high-dose inhaled fluticasone (440 micrograms qds) and zafirlukast 20 mg/day in a 44-year old man with moderately severe asthma; this is the first report of invasive pulmonary aspergillosis associated with an inhaled glucocorticoid (123).

Second-Generation Effects

Teratogenicity

Congenital malformations that may be associated with inhaled budesonide in pregnancy have been evaluated using the Swedish Medical Birth Registry (124). Of 2014 infants whose mothers started to use inhaled budesonide in early pregnancy, 75 (3.7%) had a congenital malformation; the corresponding rate among all infants born in 1995–97 was 3.5%. Five infants had chromosomal anomalies that were unlikely to have been caused by drugs. This study did not identify teratogenic properties of inhaled budesonide.

Drug–Drug Interactions

Itraconazole

Interactions with other drugs can increase plasma concentrations of inhaled glucocorticoids. Itraconazole, a potent inhibitor of CYP3A4, markedly increased plasma concentrations of inhaled budesonide (125).

Ritonavir

Ritonavir, a potent inhibitor of CYP3A4, caused Cushing's syndrome in a patient using fluticasone propionate 1000 micrograms/day (126).

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Corticosteroids—glucocorticoids, topical

See also Glucocorticosteroids

The local adverse effects of topical glucocorticoids (1,2) are listed in Table 1. They include transient local erythema, calcinosis cutis, cramps (due to injection of crystals into a vessel), amaurosis (a dubious report), depigmentation, skin atrophy, and skin necrosis (3,4). The systemic adverse effects of topical glucocorticoids (5–8), which are those to be expected from systemic use, are also listed in Table 1.

Table 1 Local adverse effects of topical glucocorticoids

Effects on the pilosebaceous unit
Perioral dermatitis (SEDA-5, 151)
Steroid rosacea or rosacea-like dermatitis; cannot be differentiated from perioral dermatitis and can be identical
Steroid acne
Exacerbation of pre-existing rosacea
Hypertrichosis of the face
Atrophic changes
Cigarette-paper wrinkling of the skin
Telangiectasia (SEDA-6, 153)
Petechiae, ecchymoses
Striae rubrae distensae, mainly in the inguinal and axillary region (occlusion effect)
Susceptibility of the skin to minor trauma
Fragile skin in surgery
Delayed wound healing
Worsening of existing ulceration
Photosensitivity of atrophic skin
Effects on the immune system
Aggravation of pre-existing folliculitis
Development of extensive, but unrecognized dermatophytic infections ("tinea incognito")
Perpetuation of masked infections with *Candida albicans*
Conversion of scabies into the Norwegian type
Widespread lesions of molluscum contagiosum
"Galloping" impetigo
(Possibly) exacerbation or dissemination of viral skin infections
Generalized pustular psoriasis
Generalized urticaria
Spreading of malignant skin lesions
Suppression of pruritus
Allergic contact dermatitis* (SEDA-15, 139)
Ocular effects
Ocular hypertension
Open-angle glaucoma (9)
Uveitis
Posterior subcapsular cataracts (9)
Nasal effects
Nasal septal perforation (steroid aerosols)
Skin lesions
Acne
Hirsutism
Ecchymoses
Milia
Granuloma gluteale infantum
Pseudocicatrices stellaires spontanées
Eczema craquelatum after withdrawal
Elastoidosis cutanée nodulaire à cystes et à comedones Favre-Raacouchot
Erythrosis interfollicularis colli
Cutis punctata linearis colli or "stippled skin"
Effects on skin color
Hypopigmentation
Hyperpigmentation
Striae
Miscellaneous effects
Tachyphylaxis to the vasoconstrictor effect of topical glucocorticoids
Systemic adverse effects of topical administration
Cushing's syndrome
Suppression of the hypothalamic–pituitary–adrenal axis
Growth retardation (SEDA-6, 151)
Hyperglycemia
Benign intracranial hypertension after withdrawal
Subcapsular cataract
Pancreatitis
Bony avascular necrosis (9)
Psychiatric symptoms
Fluid retention
Hypertension (SEDA-7, 167)

*Cross-allergy between glucocorticoids is infrequent (10–12).

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Corticosteroids—mineralocorticoids

General Information

Aldosterone is the principal physiological salt-retaining mineralocorticoid, but it is unsuitable for routine medical use since it is rapidly inactivated when given orally. Desoxycorticosterone (DCA, DOCA, desoxycortone) was used for a long time, but it had to be taken sublingually (or implanted or injected) to avoid inactivation during passage through the liver. Overdosage of desoxycorticosterone, leading to hypertensive encephalopathy and permanent brain damage, has been described (SED-8, 820).

The approximate potency of various mineralocorticoids relative to cortisone is shown in Table 1.

Fludrocortisone is the compound that is most often used at present for long-term mineralocorticoid treatment. The dose of fludrocortisone needed in chronic adrenocortical insufficiency varies very widely, from 0.05 to 1.0 mg/day. In salt-losing forms of the congenital adrenogenital syndrome up to 0.2 mg/day may be needed. In doses appropriate to the individual's needs, adverse reactions to the glucocorticoid effects of fludrocortisone rarely prove problematic; the main problem is to adjust the dosage (as well as salt intake) to these needs, since the adverse effects that can be experienced mainly reflect relative overdosage; if high doses are to be used, meticulous monitoring is required.

Table 1 Approximate potency of various mineralocorticoids relative to cortisone

Compound	Route of administration	Mineralocorticoid effect	Glucocorticoid effect
Cortisone	Oral	1	1
Desoxycorticosterone	Sublingual	50	Negligible
Fludrocortisone	Oral	150	10–20
Aldosterone	Injected	500	None

Organs and Systems

Cardiovascular

Edema, hypertension, and cardiac hypertrophy can occur with fludrocortisone (1). Hypertension is the most common reason for reducing the dosage.

Fluid retention due to mineralocorticoid effects can cause cardiac failure (1).

- Congestive heart failure occurred in a 47-year-old woman after she had taken fludrocortisone 100 micrograms/day for 2 weeks for Addison's disease (2). Ten months later, fludrocortisone 25 micrograms/day was restarted, and the dosage was increased to 100 micrograms/day over 2 months. At follow-up after 4 months she was well, without fluid retention or electrolyte abnormalities.

Electrolyte balance

Hypokalemia due to fludrocortisone can cause muscle weakness (3).

Drug–Drug Interactions

Phenytoin

In two patients with adrenal insufficiency, phenytoin increased fludrocortisone dosage requirements (4).

Potassium-sparing diuretics

Potassium-sparing diuretics, such as prorenoate and spironolactone, can prevent the potassium-losing effects of fludrocortisone (5).

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Corticotrophins (corticotropin and tetracosactide)

General Information

The adrenocorticotrophic hormone ACTH (corticotropin) stimulates the adrenal cortex to secrete the glucocorticoids hydrocortisone (cortisol) and corticosterone, the mineralocorticoid aldosterone, and a number of weakly androgenic substances, as well as a small amount of testosterone. Aldosterone synthesis is also regulated by renin and angiotensin.

This monograph should be read in conjunction with the monograph on glucocorticoids. It is not always clear which adverse effects are specific to corticotrophins and which simply result from the secretion of the glucocorticoids that they induce; conversely, almost any adverse effect associated with glucocorticoids can in principle also occur with corticotrophins.

Structures and nomenclature

Natural ACTH (corticotropin) is a polypeptide consisting of 39 amino acids. Its hormonal activity is related to the first 24 amino acids in a sequence that is found in both animal and human pituitary glands. The differing sequences of the remaining 15 amino acids in animals can lead to antibody formation and hence to allergic reactions when animal hormones are injected into humans. From 1970 onwards, therefore, even highly purified corticotropin preparations of animal origin were largely displaced by the so-called "synthetic ACTH" or "synthetic corticotropin," better known by its generic name of tetracosactide (rINN), which contains only the first 24 amino acids, hence avoiding much of the antigenicity of the complete molecule. Collectively, corticotropin and tetracosactide are known as the corticotrophins.

Since the development of tetracosactide, other modifications to the corticotropin molecule have been made, and some clinical work has been done with products containing fewer than 24 amino acids, for example 1–18. However, none has proved more usable than tetracosactide. The replacement of some naturally occurring amino acids by others may intensify or prolong the effect of the polypeptide.

Production and elimination

Fluctuations in the rates of secretion of glucocorticoids from the adrenal cortex are determined by variations in the rate of release of corticotropin from the anterior pituitary, and this in turn is controlled by the hypothalamic corticotropin-releasing hormone (CRH). Since release of CRH is affected by circulating glucocorticoid concentrations, a negative-feedback control operates to keep the system in balance. It follows from this that if glucocorticoids are administered exogenously they will operate through this feedback to suppress adrenal function.

The mode of inactivation and excretion of corticotropin is still almost completely unknown; its biological half-life has been variously assessed as several minutes or several hours.

Uses

Corticotrophins can be used diagnostically to investigate adrenocortical insufficiency. Corticotropin has also been used therapeutically in most of the conditions for which systemic glucocorticoids are indicated, although such use is now fairly limited. However, corticotropin is used in certain neurological disorders, such as infantile spasms and multiple sclerosis. The main indications for corticotropin and tetracosactide are thus diagnostic rather than therapeutic; for the latter purpose they are being increasingly replaced by CRH.

General adverse effects

Corticotrophins share all the adverse effects of glucocorticoids, including impaired immunity, but they do not depress adrenocortical function. In addition, the melanocyte-stimulating hormone (MSH) sequence in the corticotropin molecule can result in hyperpigmentation, and induction of androgen secretion can lead to virilization. Corticotrophins also have additional unwanted effects of their own, such as myoclonic encephalopathy and adrenal hemorrhage. Hypersensitivity reactions occur occasionally, but have become less frequent since older preparations of animal origin were phased out. Tumor-inducing effects have not been observed.

Organs and Systems

Cardiovascular

Corticotropin has been reported to cause enlargement of cardiac tumors in tuberous sclerosis (1).

- A female infant with tuberous sclerosis had multiple large cardiac tumors in the left and right ventricles. Corticotropin was given (dose not stated; once a day for 2 weeks, tapering over 3 months) at 4 months for infantile spasms. At 6 months a heart murmur was detected. Echocardiography showed pronounced enlargement of the tumors in both ventricles and a small tumor extending from the upper portion of the interventricular septum into the left ventricular outflow tract. An electrocardiogram showed 2–3 mm ST segment depression in leads I, aVL, and V4-6. Gated single photon emission CT showed low perfusion at the lateral and inferior regions of the left ventricle, indicating myocardial ischemia.

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Corticotropin was withdrawn and 3 months later the patient was asymptomatic. An echocardiogram showed that the tumors had reduced in size, and there was concomitant improvement in the electrocardiogram.

There is a risk of myocardial hypertrophy in children on prolonged treatment with ACTH (2), an effect that could reflect increased androgen secretion and thus be more likely to occur than with glucocorticoids.

Hypertension, with or without simultaneous hypertrophic myopathy, is a common feature of adrenal stimulation that seems to be common with depot tetracosactide but not simple tetracosactide (3). During treatment for infantile spasms, hypertension occurred more often in those treated with high doses (SEDA-19, 374) (4), and changes in cardiac function, such as left ventricular shortening fraction, can occur early and sometimes before systolic hypertension (SEDA-19, 374) (5).

Respiratory

Corticotropin and to a lesser extent tetracosactide can cause asthma in sensitive subjects (6). The question as to whether tetracosactide or glucocorticoids should be preferred for the treatment of chronic asthmatic bronchitis has been discussed mainly with respect to adverse effects, particularly adverse endocrine effects and effects on growth. An earlier belief that corticotropin might be more effective in children has not been confirmed.

Nervous system

In 138 Japanese patients with West syndrome treated with low-dose tetracosactide, the initial effects on seizures and long-term outcome were not related to dose (daily dose 0.005–0.032 mg/kg, 0.2–1.28 IU/kg; total dose 0.1–0.87 mg/kg, 4–35 IU/kg) (7). There were moderate or severe adverse effects in 30% of the patients. There was slight loss of brain volume on CT/MRI scans in 64% of the patients, moderate loss in 23%, and severe loss in 4%. The severity of adverse effects correlated with the total dose of corticotropin, and the severity of brain volume loss due to corticotropin correlated well with the daily and total doses. The authors recommended a reduction in the dose of corticotropin in order to avoid serious adverse effects.

Brain shrinkage has been described as a possible adverse effect of corticotropin treatment of infantile spasms, and this has been confirmed using magnetic resonance imaging (SEDA-20, 368) (8,9). Changes in midline structures (volume reductions in the pons, corpus callosum, and cerebellum) seem to show that the beneficial effect of corticotropin in infantile spasms could be due to a direct effect on the brainstem. Cerebral shrinkage and subdural hematoma occurred after the administration of high doses of corticotropin for West syndrome (total dose 4.5–6.75 mg) and subdural hematoma occurred in two children (aged 2 and 5 months) during the administration of low doses of tetracosactide (0.01 mg/kg/day; total dose 0.24–0.26 mg) (10).

Drowsiness, hypotonia, and irritability were observed in 37% of infants given corticotropin in a randomized comparison of corticotropin with vigabatrin in the treatment of infantile spasms (SEDA-22, 442) (11).

Myoclonic encephalopathy appears to be a specific, if rare, complication of corticotropin, not seen with the glucocorticoids (12).

Sensory systems

Bilateral subcapsular cataracts and glaucoma have been reported as possible risks (13), but they presumably reflect glucocorticoid effects.

Bilateral macular degeneration has been described with tetracosactide (13), but presumably reflects glucocorticoid effects.

Central serous retinopathy has been linked to the therapeutic use of corticotrophins or glucocorticoids or to endogenous corticotropin hypersecretion. Bilateral central serous retinopathy has been reported in a woman treated with tetracosactide intramuscularly (SEDA-22, 442) (14).

Psychological, psychiatric

Mood changes continue to be reported in association with corticotropin (15). Emotional instability or psychotic tendencies can be aggravated, while euphoria, insomnia, and personality changes such as hypomania and depression can be precipitated, sometimes even with psychotic manifestations. Although it seems reasonable to assume that one is dealing here mainly with an effect of the glucocorticoids secreted in response to corticotropin, it should be recalled that segments of the corticotropin molecule themselves have effects on brain function and could conceivably play a role.

Endocrine

Corticotropin can promote the development of a more or less pronounced Cushingoid state. Corticotropin also increases the metabolic clearance rate of cortisol, aldosterone, and desoxycorticosterone (SEDA-1, 282).

Prolonged stimulation by corticotropin leads to adrenocortical cell hyperplasia and an increase in the size and weight of the adrenal glands; massive enlargement can be demonstrated by computerized tomography as well as clinical examination (16).

Acute adrenal hemorrhage, either unilateral (17) or bilateral (18), has been observed repeatedly after corticotropin administration, and causes an acute abdominal crisis. Although it is usually seen in children, hemorrhage can also occur in adults (SEDA-17, 451).

Even a single dose of corticotropin can cause inhibition of thyrotrophic hormone secretion (19), although the effect is brief. Conversely, thyroid hormones increase the sensitivity of adrenocortical cells in vitro to corticotropin (20) and hyperthyroidism increases sensitivity to corticotropin (21,22).

Corticotropin suppresses the growth hormone response to hypoglycemia (23).

Androgen secretion due to corticotropin can cause virilization in women (24).

Fluid balance

Corticotropin affects mineral and fluid balance in varying degrees, as would be expected from its effect on mineralocorticoid secretion.

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Hematologic

Marked leukocytosis has been described, despite the absence of infection, in a patient treated with tetracosactide (SED-12, 980); the effect may well have been due to glucocorticoid secretion rather than to tetracosactide itself.

Gastrointestinal

A relative indication for corticotropin is the occasional gastrointestinal intolerance that occurs with oral glucocorticoids. In these cases, however, only the local effects of the glucocorticoids can be avoided, and not their systemic effects on the gastrointestinal tract (25).

Urinary tract

Renal calcinosis can develop as a result of hypercalciuria and is a major concern in the treatment of infantile spasms with corticotropin. In 16 infants, corticotropin, often associated with anticonvulsants, results in increased urinary excretion of calcium and phosphate, with increased parathormone serum concentrations and in some cases generalized aminoaciduria (26). This makes it imperative that the dose of corticotropin and the duration of treatment be kept to the minimum required to ensure efficacy. In one case in which calcified stones were removed surgically, recurrence was apparently prevented, despite the presence of a Cushingoid state, by long-term chlorothiazide (27).

Skin

Allergic skin reactions, for example urticaria, can occur. Since the first 13 amino acids in the corticotropin peptide are the same as in MSH, treatment with corticotropin can occasionally cause hyperpigmentation. The shorter peptide chain in tetracosactide can even cause rather more pronounced melanocyte-stimulatory effects. Long-term treatment with depot tetracosactide has itself caused melanoderma (SED-12, 980) and, in one series of 41 patients, there was hyperpigmentation in 3 of them (SEDA-1, 281).

Immunologic

Although the incidence of severe allergic reactions to natural corticotropin of animal origin fell as progressively purer products were introduced, the problem remained for a small minority of patients. Exact figures are difficult to cite, but hypersensitivity reactions have sometimes even been described in patients with no history of corticotropin treatment, presumably sensitized by other animal material. Hypersensitivity to corticotropin generally causes only dizziness, nausea and vomiting, or cutaneous hypersensitivity reactions, but in several instances shock with circulatory failure has been observed (28). In a number of patients who were allergic to porcine corticotropin, no such problems were observed when tetracosactide was given. This suggests that the absence of most of the antigenic part of the original molecule reduces the risk of hypersensitivity reactions. However, the smaller synthetic molecule can still stimulate the formation of antibodies in some individuals (SEDA-12, 979) (29).

However, allergic reactions and anaphylactic shock have been observed during treatment with tetracosactide and have even proved fatal. Local reactions have even been seen after the administration of small doses for intracutaneous testing. In the early years of tetracosactide use, the frequency of local and general reactions to a long-acting acetylated tetracosactide was estimated at as little as one in 30 000 (SED-12, 979), but it is doubtful whether this figure can be supported today, unless one interprets it as referring only to major calamities. Indeed, subclinical immune reactions to both natural and tetracosactide appear to be fairly common during long-term treatment of patients with asthma, with an incidence of intradermal reactions of about 50%, a prevalence of IgE antibodies that is significantly higher than in controls, and a high incidence of low-titer agglutinating antibodies to corticotropin. The antibodies can result in a gradual loss of effect.

Infection risk

Pneumonia due to *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) has been attributed to high-dose corticotropin (30).

- An infant girl was given corticotropin 80 U/day for infantile spasms. After 5 weeks she became increasingly lethargic, with reduced oral intake, cough, an increased respiratory rate (50 breaths/minute), and a fever of 38.6°C. Investigations were consistent with pneumonia and she was given intravenous ceftriaxone. She initially improved, but 36 hours later her respiratory distress worsened and she required intubation and mechanical ventilation. The diagnosis of *P. jiroveci* pneumonia was confirmed and she was given intravenous co-trimoxazole and glucocorticoids. Her respiratory distress resolved and she was extubated 10 days later. Immunological testing after the withdrawal of corticotropin did not show any abnormalities that could have predisposed her to *P. jiroveci* pneumonia.

The authors commented that a transient immunodeficiency related to corticotrophin may have predisposed to the development of *P. jiroveci* pneumonia.

Long-Term Effects

Drug withdrawal

Relative adrenocortical insufficiency can follow withdrawal of corticotropin treatment (presumably because the cortex has adapted itself to a constant high level of stimulation) and can persist for some months. Glucocorticoid substitution has to be provided during this period. The risk of this effect can be reduced by keeping the dose of corticotropin as low as possible.

Second-Generation Effects

Pregnancy

There are no firm data on the use of corticotropin in pregnancy; both glucocorticoid and androgenic effects might be expected to affect the fetus.

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Susceptibility Factors

Age

Although it has been stated in reviews that treatment with corticotropin inhibits growth much less than glucocorticoid treatment does, the growth hormone response to stimuli is reduced, and since growth hormone secretion is impaired during corticotropin treatment, claims for the greater safety of this therapy in children with asthma must be treated with reservations.

Other features of the patient

Susceptibility factors for adverse effects are as for glucocorticoids. In addition, patients with a known allergic tendency should preferably not receive these substances, unless sufficient supervision is possible to cope with unexpected allergic reactions, at least until tolerance has been demonstrated.

Drug–Drug Interactions

Coumarin anticoagulants

In 10 of 14 patients taking dicoumarol or phenindione who also took corticotropin for 4–9 days, there was a small increase in the effects of the anticoagulants (31). One patient taking ethyl biscoumacetate developed bleeding after taking corticotropin 20 mg/day for 3 days (32). However, in contrast, reduced efficacy of ethyl biscoumacetate has been described (33).

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Corynebacterium parvum

General Information

Inactivated *Corynebacterium parvum* has been tried as an adjuvant in patients with cancer and in the treatment of malignant pleural effusions. Fever and chills were frequent, with sustained fever and chest or abdominal pain in several patients (1,2).

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Coumarin

General Information

The plant lactone coumarin (not to be confused with coumarin anticoagulants) is a constituent of some plants, including:

- *Alyxia lucida*
- *Dalea tuberculata*
- *Dipteryx odorata*
- *Dipteryx oppositofolia*
- *Levisticum officinale*
- *Melilotus officinalis*
- *Scabiosa comosa.*

Organs and Systems

Hematologic

Coumarin is devoid of anticoagulant activity, but the molding of sweet clover can give it hemorrhagic potential by transforming coumarin to the anticoagulant dicoumarol. This transformation could explain a case of abnormal clotting function and mild bleeding after the drinking of an herbal tea prepared from tonka beans, sweet clover, and several other ingredients. Unfortunately, this possibility was not investigated, as the reporting physician was not aware of the exact phytochemistry and pharmacology of coumarin-yielding plants.

Liver

Coumarin has hepatotoxic potential in man, when taken in daily doses of 25–100 mg (1). Bile-duct carcinomas have been reported to occur in rats fed coumarin, but the correctness of this diagnosis has been seriously criticized.

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Coumarin anticoagulants

General Information

The coumarins were first discovered in Wisconsin, when bleeding in cattle was found to be due to the consumption of bruised sweet clover in the 1920s (1). The causative agent, dicoumarol, was isolated in 1940, and a range of related compounds was then synthesized, the most popular of which proved to be warfarin (named after the Wisconsin Alumni Research Foundation). Other coumarins that have been used are acenocoumarol (nicoumalone), bishydroxycoumarin, dicoumarol, ethyl biscoumacetate, and phenprocoumon.

The coumarins act as competitive inhibitors of vitamin K epoxide reductase, which is responsible for regenerating reduced vitamin K from vitamin K epoxide after it has been consumed as a co-factor in the synthesis of coagulation factors II, VII, IX, and X.

Uses

The main use of the coumarins is in the treatment and prevention of thromboembolic disease, including deep vein thrombosis, pulmonary embolism, and cerebral embolism from cardiac and other sources.

Protein C, another vitamin K-dependent serine protease zymogen in plasma, is a regulatory protein that, when activated, limits the activity of two activated procoagulant co-factors, factors Va and VIIIa. Heterozygotes for hereditary isolated protein C deficiency tend to develop a thrombotic disease which has been successfully treated with long-term coumarins (2,3). Apparently, the

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balance between the activities of protein C and the procoagulant factors (II, VII, IX, and X), which is disturbed in protein C-deficient patients, is restored during long-term treatment with coumarins.

Non-anticoagulant uses

Warfarin reduces calcium deposition in spontaneously degenerated bioprosthetic valves (4).

Both direct and indirect antitumor actions of anticoagulants have been postulated on the basis of experimental findings in animals (5). Warfarin given alone or in combination with cytostatic drugs reduces the size of fibrosarcomas in animals (5,6) and of osteosarcomas in man (7), and consequently prolongs survival times in both. The Cooperative Studies Program of the Veterans Administration Medical Research Service suggests that, among patients with various tumors, those with small-cell carcinoma of the lung had a significantly longer survival (about 4 years instead of 2) when warfarin was added to standard treatment (8). There were no differences in survival between warfarin-treated and control groups for advanced non-small-cell lung cancers, colorectal, head and neck, and prostate cancers (9). However, the contention that cancer morbidity and/or mortality is reduced in anticoagulated patients is not substantiated by the results of a retrospective study of 378 patients who had been taking anticoagulants for about 10 years on average (10).

It has been suggested that warfarin may have a specific effect on tumor-cell growth via the inhibition of protein synthesis (11). Another explanation of the effect of the drug is a reduction in the co-adherence of tumor cells, which renders them more vulnerable to the actions of defence mechanisms. The reduction in co-adherence is thought to be caused by an inhibitory action of anticoagulants on the fibrin network that is vital for tumor cell growth. This hypothesis, which is supported by dose dependence of the inhibitory effect of both heparin and warfarin (12), has been studied in a controlled randomized trial of the use of streptokinase after surgery for tumors of the large bowel (6).

Supercoumarins

Resistance to warfarin emerged soon after its original use as a poison for rodents. Second-generation anticoagulants, termed "superwarfarins," were subsequently developed and are sold as rodenticides for pest control. These include agents such as brodifacoum and difenacoum, which typically have much longer half-lives than warfarin. There have been several published case reports of accidental or intentional poisoning due to these drugs (13,14), which can result in prolonged coagulopathy (15,16).

In 10 762 children aged 6 years and under who unintentionally took single doses of brodifacoum, there were no deaths or major adverse effects, although 67 reported evidence of coagulopathy (17). There were minor and moderate adverse effects in 38 and 54 children, respectively. About half of the children received some form of gastrointestinal decontamination, which had no effect on the distribution of outcomes but caused adverse effects in 42 patients.

Ingestion of a small amount of a superwarfarin does not require specific therapy (18,19). However, if the coagulopathy due to a superwarfarin is severe, large doses of vitamin K may be required (15). Recombinant activated factor VII has been successfully used to treat superwarfarin poisoning (20).

When cases of unexplained acquired coagulopathy and selective deficiency of vitamin K-dependent clotting factors occur in patients in the absence of liver disease or inhibitors, physicians should consider the possibility of superwarfarin poisoning as a cause.

General adverse effects

The major adverse effect of the coumarins is hemorrhage and, exceptionally, hemorrhagic skin necrosis. Administration during pregnancy can cause an embryopathy. Allergic reactions are extremely rare. Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Vasodilatory effects on the coronary arteries, peripheral veins, and capillaries, with purple toes as one of the most obvious consequences (21,22), have been reported. Sensations of cold may be due to increased loss of body heat caused by peripheral vasodilatation (23).

Cholesterol embolization, which promptly improves after the drug is withdrawn (24), may explain the purple-toe phenomenon.

Nervous system

Apart from cerebral hemorrhage, coumarins have no direct adverse effects on the nervous system.

Endocrine

An antithyroid effect of bishydroxycoumarin has been suspected (25).

Metabolism

Dicoumarol has been reported to have a uricosuric effect (26).

Hematologic

Hemorrhage

Bleeding is the major complication of coumarin anticoagulants. The annual incidence of major bleeding among 4060 patients in the AFFIRM trial, who were followed for an average of 3.5 years, was about 2% per year (27).

Dose-dependency

The intensity and stability of treatment, in addition to the beneficial effect of the coumarins, determine the rate and severity of bleeding complications. The average annual frequencies of fatal, major, and major and minor bleeding during warfarin therapy were 0.6, 3.0, and 9.6% respectively (28). The relationship between the intensity of anticoagulant therapy and the risk of bleeding is very strong, both in patients with deep vein thrombosis tissue and in those with mechanical heart valves. In randomized trials for these indications, the incidence of major bleeding in patients randomly assessed to less intense warfarin therapy (targeted INR 2.0–3.0) has been less than half the incidence found in patients randomly assigned to more

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intense anticoagulation (INR more than 3) (29). The bleeding risk increases dramatically when the INR is higher than 4.0 (30), especially the risk of intracranial hemorrhage. Less intense warfarin therapy has been used in patients with non-rheumatic atrial fibrillation, with only a very slight increase in major bleeding compared with placebo. In such patients, an INR of 2.5 (range 2.0–3.0) minimizes both hemorrhage and thromboembolism (31).

Time-dependency
Although bleeding can occur at any time, if the effective dose of drug increases, whether because of a change in dose or an interaction, most studies have reported higher frequencies of bleeding soon after the start of treatment. In one study the incidence of major bleeding fell from 3.0% per month during the first month of outpatient warfarin therapy to 0.8% per month during the rest of the first year of therapy and to 0.3% per month thereafter (32). Increased variation in anticoagulant effect, as reflected by time-dependent variation in the INR is associated with an increased frequency of hemorrhage independent of the mean INR (33,34).

Susceptibility factors
Important susceptibility factors include age, endogenous coagulation defects, thrombocytopenia, hypertension, cerebrovascular disease, thyroid disease, renal insufficiency, liver disease, tumors, cerebrovascular disease, alcoholism, a history of gastrointestinal bleeding (peptic ulcer disease alone without past bleeding is not associated with an increased risk of bleeding), and an inability to adhere to the regimen.

Management
The management of coumarin toxicity depends on the INR and whether there is bleeding.

- INR more than 0.5 over the target but under 5.0: reduce the dose
- INR 5.0–8.0: withhold the drug and restart once the INR is below 5.0
- INR over 8.0 and no bleeding: withhold the drug and restart once the INR is below 5.0
- INR over 8.0 with bleeding: withhold the drug and give vitamin K_1 (phytomenadione) 0.5 mg intravenously or 5 mg orally
- INR over 8.0 with life-threatening hemorrhage: withhold the drug and give a prothrombin complex concentrate (such as Beriplex-P/N or Prothromplex-T) 50 U/kg (35); if this is not available, give fresh frozen plasma 15 ml/kg.

If rapid and complete reversal is required (for example before a procedure such as a liver biopsy), vitamin K_1 (phytomenadione) 5–10 mg can be given slowly (1 mg/minute).

Other effects
Blood and plasma viscosity fall by 5–10% during the administration of coumarins in healthy volunteers and in patients with coronary artery disease (36). This may also explain, at least partly, the antianginal effect of coumarins. The mechanism might be related to changes in the protein composition of the plasma.

A reversible increase in white cell count has been reported with long-term use of acenocoumarol (37).

Hemolytic anemia thought to be related to warfarin has been reported (38).

Gastrointestinal

Gastrointestinal complications due to coumarins are limited to hemorrhage.

Liver

Only a few cases of hepatic injury have been documented in patients taking coumarins. In some of them, rechallenge caused a relapse (39). The usual presentation was with a cholestatic illness, beginning about 10 days after the coumarin anticoagulant was started, sometimes associated with eosinophilia. In Switzerland, oral anticoagulants were involved in only 11 of 674 reports of drug-induced liver disease collected during 1981–95. Seven cases were due to phenprocoumon and three to acenocoumarol. The severity ranged from asymptomatic rises in liver enzymes to cholestatic hepatitis. The interval between administration and onset of symptoms varied from 2 days to several weeks or months (40).

Subacute liver failure necessitating orthotopic liver transplantation has been reported with phenprocoumon (41).

- A 39-year-old woman developed idiopathic thrombosis of the posterior tibial vein. Oral contraceptives and resistance to activated protein C were identified as risk factors. After initial treatment with intravenous heparin, she was given phenprocoumon and the oral contraceptive was withdrawn. After 4 months she developed subacute liver failure and phenprocoumon was withdrawn immediately. Autoimmune disease, viral hepatitis, toxic causes, and Budd–Chiari syndrome were excluded. Despite symptomatic treatment, she deteriorated further and orthotopic liver transplantation was performed. Histopathology of the explanted liver further excluded ischemic liver cell necrosis and Budd–Chiari syndrome.

Urinary tract

In one case, multisystem abnormalities, including renal insufficiency, were caused by cholesterol embolization. Withdrawal of the anticoagulant resulted in dramatically improved renal function (24).

Skin

Maculopapular rashes with cross-sensitivity between coumarin derivates have been reported (42). Non-pruritic purpuric skin eruptions, histologically presenting as vasculitis and reappearing on rechallenge with warfarin or acenocoumarol, have been described (43).

Skin necrosis
Skin necrosis is a rare but serious complication of oral anticoagulation, seen typically during induction of therapy and occurring in about 0.01–0.1% of patients (44). It is conceivable that this condition is more common than is generally recognized, because many formes frustes can occur, presenting as painful cellulitis without hemorrhagic necrosis. Severe skin necrosis in a patient taking an oral

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anticoagulant was first described in 1943, but not documented in a series of patients until 11 years later (45). The morbidity of this complication is high and, despite treatment, about 50% of patients ultimately require surgical intervention and in some cases skin grafting.

There is convincing evidence that skin necrosis occurs exclusively in patients with excessively severe initial coumarin-induced hypocoagulability (46). As a rule, excessive doses have been given, resulting in severe and rapid reductions in the concentrations of factor VII and protein C (47,48).

Time-course

Familiarity with the clinical and histological pictures is essential, because the earliest signs and symptoms must be recognized if necrosis is to be prevented. The lesion does not usually occur before the second day of treatment or after the second week of treatment has started; most commonly it appears between the third and fifth day (49,50). There are occasionally exceptions to this rule; warfarin-induced skin necrosis can occur several days after discontinuation of warfarin (51) and some cases have been reported during long-term treatment (52,53). However, as a general rule, when skin necrosis occurs after 10 days of warfarin therapy, another cause must be sought.

Presentation

The lesion often appears symmetrically or at a pair of unrelated sites, with a predilection for parts of the body rich in fatty tissue, such as the breasts, abdomen, buttocks, thighs, and calves (54). Feet and toes are seldom affected, male genitalia only rarely (45,55,56), and the vagina and uterus very exceptionally (57).

The lesion begins with an evanescent, painful, slightly raised, more or less clearly demarcated erythematous patch. Histological examination at this stage reveals slight round-cell perivascular infiltration of the corium, edema, and swelling of the capillary endothelium, particularly at the cutis/subcutis boundary (the dermovascular loop), with fibrin thrombi in the small venules. Patches of necrotic fatty tissue, slight polymorphonuclear perivascular infiltration, and patchy interstitial edema as well as bleeding are present at this stage. Very soon, petechiae appear and become confluent within 24 hours, forming purple ecchymotic lesions surrounded by a sharply defined zone of hyperemia. During the next 24 hours, thrombotic occlusion of the veins causes infarction with necrosis of the skin, subcutaneous fat, and sometimes also of deeper anatomical structures. Hemorrhagic blisters characterize the onset of irreversible necrosis of the skin. Laboratory investigation may reveal diffuse intravascular coagulation and even hemolytic anemia (58).

Mechanism

The pathogenesis is still not completely elucidated, but data suggest that transient protein C deficiency may be causative.

Hemorrhagic skin necrosis has been described with all coumarins and indanediones. During the initial phase of oral anticoagulant treatment with these agents, the plasma concentration of protein C falls rapidly in parallel with factor VII. The half-lives of protein C and factor VII are much shorter than those of factors II, IX, and X, and during this initial phase of oral anticoagulation, there is therefore a striking imbalance between procoagulant factors (factors IX, X, and II) and anticoagulant vitamin K-dependent factors (protein C).

Susceptibility factors

Probably because of the sites of predilection, women account for about 80% of cases (49).

Patients with hereditary protein C deficiency (59,60) or acquired functional protein C deficiency (61) are particularly susceptible to the development of hemorrhagic skin necrosis. However, skin necrosis has also been reported in patients with deficiency of protein S (a co-factor for protein C), in patients at high thrombogenic risk linked to a constitutional antithrombin III deficit, and in patients with antiphospholipid antibodies associated with systemic lupus erythematosus (62,63).

Prevention

Prevention of coumarin-induced skin necrosis can be achieved by avoiding initial overshooting of the coumarin effect. A primary cautious initial dosage is mandatory (60), especially in elderly people, who require a smaller dose than younger age groups (one-third less on average) (64). Secondly, adequate patient surveillance is essential. The development of full-blown skin necrosis can usually be prevented by the administration, at the first signs of a developing lesion, of vitamin K_1 (46). If the lesions progress, the oral anticoagulant should preferably be withdrawn.

Prevention of recurrence of coumarin necrosis in patients with protein C deficiency, if treatment is necessary, could consist of transient simultaneous infusion of fresh frozen plasma (leading to a constant concentration of protein C) and heparin both before and at the first time of administration of an oral anticoagulant, associated or not with protein C concentrate (65,66).

Musculoskeletal

Preliminary results that suggested coumarin-associated reduction in bone density have not been confirmed. In a study from the Osteoporotic Fractures Research Group, 6201 postmenopausal women who were either users ($n = 149$) or non-users of warfarin were assessed for fractures and bone mineral density. Over 2 years, the two groups had similar age-adjusted heel and hip bone mineral density measurements. During an average of 3.5 years, non-traumatic, non-vertebral fractures occurred in 10% of warfarin users and 9.3% of non-users (67).

However, bones that fracture during oral anticoagulant therapy require more time to form adequate amounts of callus. This may be explained by an anticoagulant-induced increase in the size of fracture hematoma. However, the observation that warfarin inhibits calcification inside artificial hearts implanted in calves adds to the body of evidence indicating that coumarin depresses not only coagulation factors, but also other (Gla)-containing proteins, for example osteocalcin, a shortage of which may also delay skeletal calcification (68). Osteocalcin is a non-collagenous bone matrix protein containing gamma-carboxyglutamic acid, the synthesis of which is vitamin K-dependent. During oral

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anticoagulation with phenprocoumon, osteocalcin concentrations were lower than in control subjects, whereas the proportion of non-carboxylated osteocalcin was significantly higher than in healthy subjects (69). Since osteocalcin concentrations reflect bone formation, but not bone resorption activity, the reduced serum total osteocalcin concentrations during oral anticoagulation do not necessarily imply that bone loss occurs in these patients. However, reduced bone formation and impaired gamma-carboxylation of osteocalcin in patients treated with phenprocoumon can be clinically important in circumstances such as fracture healing or when there is pre-existing bone disease. It has been suggested that vitamin D regulates the synthesis of vitamin K-dependent bone protein, but no significant effect of the duration of phenprocoumon therapy on parathormone and vitamin D concentrations has been observed (69).

Immunologic

Skin-test reactivity, that is induration and tissue factor generation by monocytes, is reduced by therapeutic doses of oral anticoagulants, but lymphocyte transformation activity is not. This constitutes the rationale for the use of oral anticoagulants in the treatment of immune diseases characterized by fibrin deposition, such as allograft rejection and lupus nephritis (70).

Second-Generation Effects

Pregnancy

Antithrombotic treatment during pregnancy carries a well-established and substantial risk for both mother and fetus (71). The mother has an increased chance of abortion and of perinatal bleeding complications.

Contraceptive counselling must be given to all women who need anticoagulants. Recommendations for the use of anticoagulants during pregnancy have been reassessed in various publications (72–75). In cases of previous venous thrombosis and/or pulmonary embolism, two reasonable approaches are possible. One can either use low-dose heparin throughout pregnancy followed by an oral anticoagulant postpartum for 4–6 weeks, or one can choose to initiate clinical surveillance combined with periodic venous non-invasive tests followed by an oral anticoagulant postpartum for 4–6 weeks. If venous thrombosis occurs, heparin should be used until term, withdrawn immediately before delivery, and then both heparin and an oral anticoagulant can be started postpartum. When pregnancy is planned in patients who are taking long-term oral anticoagulants, the physician should either replace the oral anticoagulant with heparin before conception is attempted, or perform frequent pregnancy tests and substitute oral anticoagulant for heparin when pregnancy is achieved.

In patients with artificial heart valves, management in pregnancy is problematic, because the efficacy of heparin has not been established. Two approaches have been recommended. One can use heparin in a therapeutic dosage throughout pregnancy or use heparin until the 13th week, followed by an oral anticoagulant until the middle of the third trimester, and then heparin until delivery.

Teratogenicity

Vitamin K antagonists, including hydroxycoumarin derivatives and indan-1,3-dione-derived drugs, can be teratogenic and can also induce bleeding in the fetus (71,72,76–79). Adverse fetal outcomes occur in about one-third of pregnancies after either oral anticoagulants or heparin (77). This surprisingly high figure, which is often quoted, should be tempered by the consideration that these data are largely (if not exclusively) derived from women with heart valves taking relatively large doses of warfarin in order to maintain the INR at around 4. Some have suggested that the risk of fetal embryopathy is lower in women taking lower doses for prophylaxis or treatment of deep venous thrombosis (80).

The pattern of teratogenicity of congeners of the vitamin K antagonist group is generally known as warfarin embryopathy, also referred to as the fetal-warfarin syndrome and Conradi–Hünermann syndrome, although the latter term also covers an identical hereditary disorder. The pattern is now considered to represent a specific group of malformations occurring in some fetuses exposed to a vitamin K antagonist during the first trimester, with a critical period during the sixth to twelfth weeks of gestation. The minimal criteria for the diagnosis include either nasal hypoplasia or stippled epiphyses. In severe cases the forehead is bossed and the nose is sunken, with deep grooves between the alae nasi and the tip of the nose; other skeletal deformities can also be present. Half the affected children have upper airway obstruction, secondary to underdeveloped cartilage. Radiography shows stippling (caused by abnormal focal calcification of the epiphyseal regions), preferentially in the axial skeleton, for example the proximal femur, and in the calcanei. Children with milder defects can show catch-up growth, and stippling can disappear after the first year of life; however, in severe cases the nose remains small and sunken. It is questionable whether mental retardation is part of the syndrome, since it has only been observed in cases of exposure for at least two trimesters.

The belief that the incidence of the overt syndrome is of the order of 5% seems to have been confirmed by a review of 186 studies: among 1325 pregnant women who took anticoagulant drugs, 970 were allocated to warfarin and the incidence of warfarin embryopathy was 4.6% (81). However, in a prospective survey of 72 pregnant women with cardiac valve prostheses, the incidence of coumarin embryopathy was 25% in the 12 pregnancies in which heparin was not substituted for acenocoumarol until after the 7th week, and 30% in the 37 pregnancies in which acenocoumarol was given throughout pregnancy. There were no signs of coumarin embryopathy when acenocoumarol was withdrawn from the sixth to the twelfth weeks of gestation and the women were treated instead with heparin (82).

Oral anticoagulation may cause warfarin embryopathy by inhibiting post-translational carboxylation of proteins needed in the normal ossification process. Intensity of treatment appears to be of importance, since there were no cases of warfarin embryopathy in 44 consecutive children of 42 mothers exposed in the first trimester, but who had prothrombin times prolonged by 40–60% (83,84). Experiments in rats in which highly intensive long-term

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anticoagulant therapy produced excessive mineralization disorders favor this causal relation (85).

Another possible adverse reaction is the occurrence of central nervous system anomalies in fetuses exposed to vitamin K antagonists at any time during pregnancy. The anomalies may result from fetal intracerebral hemorrhage with scarring. There are two patterns: one consists of dorsal midline dysplasia, expressed as agenesis of the corpus callosum, Dandy-Walker malformation, midline cerebral atrophy, or possible encephalocele; the other consists of ventral midline dysplasia, characterized by optic atrophy. The patients are never completely normal on follow-up, and the resulting personal and social burdens are considerable. According to a review (81), there were central nervous system anomalies in 26 (2.7%) of 970 pregnancies in which warfarin was used. Neonates can also have hemorrhagic complications if a pregnant mother takes an oral anticoagulant near term. The neonatal liver is immature, and concentrations of vitamin K-dependent coagulation factors are low. Although maternal warfarin concentrations are in the therapeutic range, bleeding can occur in neonates. Warfarin in particular should be avoided beyond 36 weeks of gestation (86).

Other consequences of oral anticoagulation during pregnancy are spontaneous abortion, stillbirth, and premature birth (87).

Lactation

In contrast to heparin, coumarins are secreted into the breast milk, but it has long been known that prothrombin activity in the plasma of neonates whose mothers take coumarins is not significantly reduced (88–90) and that warfarin does not have anticoagulant effects in breast-fed infants when given to nursing mothers (89,91). These conclusions are subject to the reservation that in some of the studies the dose of anticoagulant was low (89). Acenocoumarol-treated breastfeeding mothers can as a rule safely breastfeed their infants (92,93); nevertheless, it is prudent to check the infant's prothrombin time in such cases.

There are differences between infants in their sensitivity to coumarins. Some experts therefore recommended weekly oral administration of 1 mg of vitamin K_1 to the child if the mother is taking a coumarin and breastfeeding (94).

Susceptibility Factors

Genetic factors

There is a strong association between CYP2C9 variant alleles and warfarin dosage requirements (95), and the CYP2C9*2 and CYP2C9*3 variant alleles, which are associated with reduced enzyme activity, have been associated with significant reductions in mean warfarin dosage requirements (96). The possession of a variant allele may also be associated with an increased risk of adverse effects (97). The CYP2C9 genotype is also relevant to acenocoumarol (98). Other polymorphisms, such as those that affect CYP3A4 or CYP1A2, may also be important (96). The molecular basis of warfarin resistance is unclear but could be due to unusually high CYP2C9 activity (pharmacokinetic resistance) or to abnormal activity of vitamin K epoxide reductase (pharmacodynamic resistance) (96).

There is also a rare ala-10 mutation in the propeptide of factor IX, which leads to an increased risk of bleeding when starting anticoagulation with coumarin anticoagulants (99,100).

Age

Age is generally considered as an important susceptibility factor for bleeding during oral anticoagulant treatment (101). The frequency of bleeding was higher in elderly patients in four of five cohort studies of warfarin-related bleeding, published over a 10-year period (29,33). In one study (30), age was the only significant independent risk factor for subdural hemorrhage, apart from the intensity of anticoagulation, whereas age was only of borderline significance for intracerebral hemorrhage. Various explanations could account for the effect of age: co-medication, co-morbidity, increased sensitivity to warfarin, and impaired vascular integrity. Elderly patients, especially those with moderate hypertension, cerebral thrombosis, or a latent gastrointestinal ulcer, should be supervised closely (102).

Other features of the patient

Susceptibility factors for bleeding with oral anticoagulants, apart from age, include (29):

- endogenous coagulation defects
- thrombocytopenia
- hypertension
- cerebrovascular disease
- thyroid disease
- renal insufficiency
- liver disease
- tumors
- cerebrovascular disease
- alcoholism
- a history of gastrointestinal bleeding (peptic ulcer disease alone without past bleeding is not associated with an increased risk of bleeding)
- an inability to adhere to the regimen.

Patients with hypothyroidism and hyperthyroidism should all be carefully monitored because the response is greatly reduced in hypothyroidism and greatly enhanced in hyperthyroidism (103). The increased warfarin sensitivity is said to be related to increased degradation of clotting factors. When the thyroid disease is treated, the susceptibility of these patients to coumarins gradually normalizes.

Since vitamin K is one of the vitamins whose absorption is significantly affected by diarrhea, a raised INR and bleeding can occur during episodes of diarrhea (104). Therefore, patients who have diarrhea or reduced food intake should have their INR evaluated more often and their anticoagulant doses adjusted appropriately.

For oral anticoagulant prophylaxis, the overall number of bleeding patients with organic lesions exceeds 50%. Most have prothrombin times within the usual target range. It is therefore clear that all cases of major (or recurrent mild) internal hemorrhagic complications should be investigated for possible underlying organic disease. In one study, patients with hemorrhagic complications, despite a

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prothrombin time within the target range, were more likely to have an underlying pathological lesion as a direct cause of bleeding than patients whose bleeding occurred when the prothrombin time was above the target range (105).

Drug–Drug Interactions

General

Commonly prescribed drugs can potentiate or antagonize the anticoagulant effect of coumarin drugs in several ways:

- by interfering with the absorption of the drug
- by inhibiting intestinal bacterial production and absorption of vitamin K_2
- by inhibiting the absorption of vitamin K_1 present in food
- by altering the binding of the coumarins to plasma proteins
- by altering the metabolism of the drug by liver microsomes.

Competition for metabolic pathways (for example cytochrome P_{450} isozymes) could lead to an increase in the anticoagulant effect, and/or the pharmacological effects of a drug whose active metabolites are produced by the same metabolic pathway. Hence, any patient taking an oral anticoagulant who has another drug added to or withdrawn from the regimen must have prothrombin time carefully monitored to avoid important changes in the intensity of treatment.

The information on interactions given in Table 1 is mainly based on well-documented prospective studies and, in a few instances, on anecdotal reports. A given interaction may hold for one but not for another coumarin congener.

Alcohol

Alcoholics can drink ethanol in amounts large enough (200 g) to inhibit warfarin clearance as an acute effect. However, daily consumption of ethanol for a period of 3 weeks in the form of wine taken with meals in moderate amounts (28 g/day) or even in liberal amounts (56 g/day) had no effect on the hypoprothrombinemia induced by warfarin (256).

Although long-term alcohol can induce some cytochrome P_{450} isozymes, such as CYP1A1, CYP1A2 (257), CYP2B1, and CYP2E1 (258), these effects are not relevant to the coumarins, which are mostly metabolized by CYP2C9.

A report of ethanol potentiation of aspirin-induced prolongation of bleeding time (259) is of importance, in view of a putative increase, due to alcohol intake, of the hemorrhagic risk accompanying outpatient oral anticoagulation.

Co-amoxiclav

In a case-control study in 300 previously stable outpatients taking phenprocoumon or acenocoumarol with INR values of 6.0 or more and 302 matched controls with INR values within the target range, potentially interacting drugs were predominantly antibacterial drugs (260). A course of co-amoxiclav was associated with a small increase in risk (OR = 2.4; 95% CI = 1.0, 5.5). Of 87 potentially interacting drugs, 45 were not used during the 4-week study and only 15 drugs were used by at least 10 patients. The authors concluded that unless no therapeutic alternative is available, co-amoxiclav should be avoided in patients taking coumarins. If no therapeutic alternative is available, increased monitoring of INR values is warranted to prevent overanticoagulation and potential bleeding complications.

Co-trimoxazole

In a case-control study in 300 previously stable outpatients taking phenprocoumon or acenocoumarol, with INR values of 6 or more, and 302 matched controls with INR values within the target range, potentially interacting drugs were predominantly antibacterial drugs (260). A course of co-trimoxazole was associated with a large increase in the risk of excess anticoagulation (adjusted OR = 24; 95% CI = 2.8, 209). Of 87 potentially interacting drugs 45 were not used during the 4-week study and only 15 drugs were used by at least 10 patients. The authors concluded that unless no therapeutic alternative is available, co-trimoxazole should be avoided in patients taking coumarins. If no therapeutic alternative is available, increased monitoring of INR values is warranted to prevent overanticoagulation and potential bleeding complications.

Danshen

- Potentiation of the effect of warfarin by danshen (the root of *Salvia miltiorrhiza*), a widely used traditional Chinese herbal medicine, particularly for cardiovascular complaints, has been described in a 62-year-old man with a mechanical mitral valve prosthesis (159).

Fluoroquinolones

A series of cases of coagulopathy due to an interaction of warfarin with ciprofloxacin has been extracted from the FDA's Spontaneous Reporting System database, including all cases reported from 1987 to 1997, combined with two of the author's own cases (261). Soon after the introduction of ciprofloxacin in 1987, hemorrhagic events from hypoprothrombinemia were reported in patients taking warfarin. However, several prospective studies of combining ciprofloxacin and other fluoroquinolones with warfarin failed to show a significant change in INR (Table 2). Although it is impossible to estimate the frequency of the ciprofloxacin/warfarin interaction from these or other descriptive data, it can be concluded that potentiation of anticoagulant effect by ciprofloxacin occurs most often in older patients and those taking multiple medications.

Methylprednisolone

Potentiation of the effects of vitamin K antagonists by high-dose intravenous methylprednisolone has been prospectively studied in 10 consecutive patients and 5 controls after the observation of a sharp increase in the International Normalized Ratio (INR) in a patient taking oral anticoagulation after concomitant administration of methylprednisolone (1 g/day for 3 days) (262). The mean INR was 2.8 (range 2.0–3.8) at baseline and increased to 8.0 (5.3–20). The maximum increase in INR occurred after a mean of 93 (29–156) hours. The coumarins taken by these patients were fluindione in eight and acenocoumarol in two. The prothrombin time in the controls

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Table 1 Important drug–drug interactions with coumarin anticoagulants

Drug	Effect on anticoagulant response	Mechanism	Comment
Acetylsalicylic acid and other salicylates	Potentiation (106,107) (at doses over 1.5 g/day) even with topical application (108)	Unknown	Avoid concurrent use: can also impair platelet aggregation and cause peptic erosion and ulceration
Allopurinol	Potentiation (109)	Inhibition of microsomal enzymes (110)	Adjust dosage
Aminoglutethimide	Reduction possible (111)	Unknown	Adjust dosage
Aminoglycoside antibiotics	Potentiation possible (112)	Reduced availability of vitamin K (113)	Monitor INR
Amiodarone	Potentiation (114–117)	Reduced warfarin and acenocoumarol clearances (114,117)	Adjust dosage
Anabolic steroids and androgens (C17-alkylated)	Potentiation (118)	Unknown	Adjust dosage
Antacids containing magnesium	Potentiation possible (119) (only documented for dicoumarol)	Increased absorption (119)	Of no practical importance
Azapropazone	Potentiation (120)	Displacement from binding sites on plasma proteins (121); inhibition of metabolism causes peptic ulceration	Avoid concurrent use
Azathioprine	Reduction (122,123)	Unknown	
Azithromycin	Potentiation (124)	Inhibition of microsomal enzymes possible	Monitor INR or avoid concurrent use
Barbiturates	Reduction (125)	Induction of microsomal enzymes (126)	Adjust dosage
Benziodarone	Potentiation (127)	Unknown	Adjust dosage
Bezafibrate	Potentiation (128,129)	Unknown	Adjust dosage
Carbamazepine	Reduction (130,131)	Induction of microsomal enzymes (131)	Adjust dosage
Carbimazole	Reduction (132)	Decreased catabolism of vitamin K-dependent clotting	Adjust dosage
Cetirizine	Potentiation (133)	Unknown	Anecdotal
Cephalosporins	Potentiation possible (134,135)	Inhibition of hepatic vitamin K metabolism (136)	Monitor INR
Chloral hydrate and related compounds	Minor potentiation during initial phase of anticoagulation therapy, not during maintenance therapy (108,137)	Displacement from binding sites on plasma proteins	Usually of no practical importance
Chloramphenicol	Potentiation (138,139) even with ocular administration (140)	Unknown	Adjust dosage Monitor INR
Chlortalidone	Pseudoreduction	Hemoconcentration (141)	No practical importance
Colestyramine	Reduction (142,143)	Reduced absorption and interruption of enterohepatic circulation (142,143)	Adjust dosage: separate dosage of these two drugs by a long time interval
Cimetidine	Potentiation (144); not documented for phenprocoumon (145)	Stereoselective inhibition of warfarin metabolism (146)	Adjust dosage
Ciprofloxacin	Potentiation possible (147,148)	Unknown	Monitor INR
Cisapride	Potentiation (149)	Inhibition of microsomal enzymes possible	Monitor INR
Clarithromycin	Potentiation (150–152)	Inhibition of microsomal enzymes possible	Monitor INR or avoid concurrent use
Clofibrate	Potentiation (153)	Unknown	Adjust dosage
Co-trimoxazole	Potentiation (154,155)	Unknown	Adjust dosage
Cyclophosphamide	Reduction possible (156)	Unknown	Anecdotal
Ciclosporin	Reduction possible (157)	Unknown	Adjust dosage
Danazol	Potentiation (158)		
Danshen	Potentiation (159)	Unknown	Anecdotal
Dicloxacillin	Reduction (160)	Unknown	Monitor INR
Diflunisal	Potentiation possible (161)	Can impair platelet aggregation and cause peptic ulceration	Avoid concurrent use

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Drug	Effect on anticoagulant response	Mechanism	Comment
Disulfiram	Potentiation (162,163)	Inhibition of microsomal enzymes (162)	Adjust dosage
Erythromycin	Potentiation possible (164,165)	Reduced warfarin clearance (166)	Monitor INR
Etacrynic acid	Potentiation possible (167)	Unknown	Anecdotal
Fenofibrate	Potentiation (168)	Displacement from binding sites on plasma proteins	Adjust dosage Monitor INR
Floctafenine	Minor potentiation (169)	Unknown	Monitor INR
Fluconazole	Potentiation possible (170–172)	Unknown	Monitor INR
Fluorouracil	Potentiation possible (173)	Unknown	Monitor INR
Fluoxetine	Potentiation (174)	Unknown	Adjust dosage or avoid concurrent use
Flurbiprofen	Potentiation possible (175,176)	Unknown	Monitor INR
Fluvastatin	Potentiation possible (177)	Unknown	Monitor INR
Furosemide	Reduction (178)	Hemoconcentration	Monitor INR
Ginseng	Reduction (179)	Unknown	Anecdotal
Glucagon	Potentiation (180)	Unknown	Avoid concurrent use
Glucocorticoids	Ambiguous (181,182)		No practical importance
Glutethimide	Reduction (183)	Induction of microsomal enzymes (183)	Adjust dosage
Griseofulvin	Reduction (184)	Unknown	Adjust dosage
Haloperidol	Reduction possible (185)	Unknown	Anecdotal
Indometacin	Potentiation possible (186)	Unknown	Monitor INR
Isoniazid	Potentiation possible (187)	Unknown	Anecdotal
Itraconazole	Potentiation possible (188)	Unknown	Monitor INR
Ketoconazole	Potentiation possible (189)	Unknown	Monitor INR
Lovastatin	Potentiation possible (190)	Unknown	Monitor INR
Mefenamic acid	Potentiation possible (191)	Fibrinolysis	No clinical importance
Mercaptopurine	Reduction (192)	Unknown	Adjust dosage
Mesalazine	Reduction (193,194)	Unknown	Monitor INR
Metronidazole	Potentiation (195)	Stereoselective inhibition of metabolism (warfarin) (195)	Adjust dosage
Miconazole	Potentiation possible (196–198) even with topical application (197,199,200)	Inhibition of metabolism (201)	Avoid concurrent use or contraindicated
Nafcillin	Reduction possible (202,203)	Unknown	Anecdotal
Nalidixic acid	Potentiation possible (204,205)	Unknown	Anecdotal
Norfloxacin	Potentiation (147)	Unknown	Monitor INR
Nutritional formulations	Reduction (206)	Increased availability of vitamin K (206)	Adjust dosage
Ofloxacin	Potentiation (207)	Unknown	Monitor INR
Omeprazole	Potentiation (208)	Unknown	Monitor INR
Oral contraceptives	Ambiguous (209,210)	Unknown	No practical importance
Paracetamol	Potentiation during long-term administration (211,212)	Unknown	Use paracetamol for limited periods Monitor INR
Phenylbutazone	Potentiation (213)	Displacement from binding sites on plasma proteins; stereoselective inhibition of metabolism (warfarin); causes peptic ulceration (214,215)	Avoid concurrent use
Phenytoin	Reduction (216); warfarin may give potentiation (217,218)	Unknown	Adjust dosage
Piracetam	Potentiation possible (219)	Unknown	Anecdotal
Piroxicam	Potentiation (220)	Unknown	Monitor INR
Pravastatin	Potentiation (221)	Unknown	Monitor INR
Proguanil	Potentiation (222)	Unknown	Monitor INR
Propafenone	Potentiation (223)	Unknown	Monitor INR
Propranolol	Potentiation (224)	Inhibition of metabolism	Monitor INR
Quinidine	Potentiation possible (225,226)	Pharmacodynamic interaction	Monitor INR

Continued

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Table 1 Continued

Drug	Effect on anticoagulant response	Mechanism	Comment
Ranitidine	Possible potentiation at high dosages (227)	Unknown	Monitor INR if high dosage
Rifampicin	Reduction (228)	Induction of microsomal enzymes (229,230)	Adjust dosage
Ritonavir	Reduction (231)	Unknown	Monitor INR
Saquinavir	Potentiation (232)	Inhibition of microsomal enzymes	Monitor INR
Simvastatin	Potentiation (233,234)	Unknown	Adjust dosage Monitor INR
Spironolactone	Pseudoreduction (235)	Hemoconcentration	No practical importance
Sucralfate	Reduction possible (236,237)		Anecdotal
Sulfinpyrazone	Potentiation possible (238–241) (not documented with phenprocoumon) (240)	Inhibition of microsomal enzymes (242)	Adjust dosage
Sulfonamides	Potentiation possible (243,244)	Unknown	Anecdotal
Sulindac	Potentiation possible (245,246)	Unknown	Monitor INR
Tamoxifen	Potentiation possible (247,248)	Unknown	Adjust dosage
Tetracyclines	Potentiation possible (139,154)	Reduced availability of vitamin K (113)	Monitor INR
Thiouracils	Reduction	Reduced catabolism of vitamin K-dependent clotting factors	Adjust dosage
Thyroid hormones	Potentiation (148,249)	Increased catabolism of vitamin K-dependent clotting factors (132)	Adjust dosage
Tramadol	Potentiation possible (250,251)	Inhibition of microsomal enzymes	Monitor INR
Ubidecarone	Reduction (252)	Unknown	Adjust dosage
Vitamin E	Potentiation possible (253)	Unknown	Anecdotal
Zafirlukast	Potentiation possible (254)	Unknown	Monitor INR
Zileuton (255)	Potentiation	Unknown	Adjust dosage Monitor INR

Table 2 Prospective interaction studies of fluoroquinolones with warfarin

Study design	N	Source of subjects	Drug	Coagulation effect	Reference
Single arm	9	Warfarin clinic	Ciprofloxacin	None	(264)
Single arm	16	Warfarin clinic	Ciprofloxacin	*R*-warfarin	(265)
Placebo-controlled[a]	36	Warfarin clinic	Ciprofloxacin	*R*-warfarin	(266)
Randomized crossover[b]	6	Healthy volunteers	Enoxacin	*R*-warfarin	(267)
Randomized crossover[c]	10	Healthy volunteers	Ofloxacin	None	(268)
Single arm	7	Healthy volunteers	Ofloxacin	None	(269)
Single arm	10	Healthy volunteers	Temafloxacin	None	(270)

[a]Randomized, double-blind, placebo-controlled study
[b]Randomized, double-blind, placebo-controlled, multicenter study
[c]Randomized, two-way, crossover study

remained stable. A similar rise in INR was described in two patients with multiple sclerosis taking warfarin (263).

The mechanism of the interaction of methylprednisolone with oral anticoagulants has not been elucidated, but it might be due to inhibition of anticoagulant catabolism. In the three patients in whom the authors assayed fluindione concentrations, these increased in parallel with the INR. The administration of high-dose methylprednisolone to patients taking oral anticoagulants is not rare; daily monitoring of INR or even reducing the anticoagulant dose before administering methylprednisolone is advised.

Miconazole

Interactions between coumarins and miconazole have been reported, although the mechanism of the interaction is not known. There have been two separate reports of potentiation of the anticoagulant effect of acenocoumarol by non-systemic administration of miconazole. Three patients taking long-term acenocoumarol who used miconazole gel for oral candidiasis had significant rises in INR (197). In two other patients vaginal miconazole potentiated the anticoagulant effect of acenocoumarol (198).

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NSAIDs

The COX-2 selective non-steroidal anti-inflammatory drug celecoxib did not alter the pharmacokinetics or the hypoprothrombinemic effect of warfarin in 24 healthy subjects (30). However, there have been at least two reports of increased INR in patients taking stable warfarin therapy and celecoxib (31,101).

Another COX-2-selective non-steroidal anti-inflammatory drug, rofecoxib, increased plasma concentrations of the biologically less active isomer, *R*(+) warfarin, which accounted for an approximately 8% increase in INR at steady state in healthy volunteers (33).

Standard monitoring of INR in patients taking warfarin should be performed when therapy with celecoxib or rofecoxib is begun or changed.

Paracetamol

In a prospective, case-control study, designed to determine causes of INRs over 6.0 in an outpatient anticoagulant unit, there was a clear dose-dependent association between the use of paracetamol (acetaminophen) and having an INR greater than 6.0 (212). The authors studied 93 patients with INRs over 6.0 (cases) and 196 patients with INRs of 1.7–3.3 (controls) during warfarin therapy. The likelihood of an INR greater than 6.0 increased from an odds ratio of 3.5 for doses of 2275–4549 mg per week, to 6.9 for doses of 4550–9099 mg per week, to a 10-fold increase at a dose of over 9100 mg per week.

Paracetamol also potentiates the effects of acenocoumarol (211) and although a study with phenprocoumon showed no interaction (271), the study was too small and not well designed to detect an effect of the sort that has been shown in case-control studies.

Ribavirin

Inhibition of the effect of warfarin by ribavirin has been described.

- In a 61-year-old man, who was taking long-term warfarin after a heart valve replacement, the dose of warfarin had to be increased by 40% after the introduction of ribavirin for chronic hepatitis C; the inhibition of the effect of warfarin was reproduced on rechallenge (272).

The mechanism of this effect was not clear.

Ritonavir

Inhibition of the effect of acenocoumarol by ritonavir has been described.

- A 46-year-old man with two prosthetic heart valves taking acenocoumarol started to take ritonavir 600 mg/day. Despite a progressive increase in the dose of acenocoumarol to three times the original dose, it was impossible to achieve a therapeutic INR, and the ritonavir was withdrawn (273).

The authors proposed that ritonavir had induced CYP1A2, CYP1A4, and CYP2C9/19 activity, leading to increased metabolism, at least of acenocoumarol. However, this effect was the opposite of what was expected, since ritonavir is a potent inhibitor of most hepatic isoenzymes.

Salicylates

Salicylates can interact with warfarin in different ways. They displace warfarin from albumin binding sites, and this can result in a transient increase in anticoagulant activity, which is usually clinically unimportant. They can also cause peptic ulceration and reduce platelet aggregation, making bleeding more likely and slower to stop when it occurs.

There was a rise in INR from 2.8 to 12 when a topical pain-relieving gel containing methylsalicylate was applied to the knees of a 22-year-old white woman taking stable warfarin anticoagulation (274).

Other similar cases have been reported (275).

Food–Drug Interactions

Cranberry juice

Cranberry juice has been reported to enhance the action of warfarin (276).

- After a chest infection, a man in his 70s had a poor appetite for 2 weeks and ate next to nothing, taking only cranberry juice as well as his regular drugs (digoxin, phenytoin, and warfarin) (277). Six weeks later his international normalised ratio was over 50, having previously been stable. He died of gastrointestinal and pericardial haemorrhage. He had not taken any over-the-counter preparations or herbal medicines, and he had been taking his drugs correctly.

The Committee on Safety of Medicines has received several other reports through the yellow card reporting scheme about a possible interaction between warfarin and cranberry juice. In one case, this effect was suggested to have been due to contamination with salicylic acid, which displaces warfarin from protein binding sites (278).

Smoking

Cigarette smoking altered the clearance and apparent volume of distribution of warfarin, although the net effect on anticoagulant activity was negligible both in volunteers (279) and patients (280).

Monitoring Therapy

There are no clear guidelines about how often the INR should be measured in patients taking coumarins. However, it should be done quite frequently at the start of therapy when the risk of bleeding is higher (32). Monitoring anticoagulant therapy is greatly improved by the use of anticoagulation clinics or anticoagulation management services in which the management is conducted by registered nurses, pharmacists, or physicians using dosage adjustment protocols developed by experts in the field (281).

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COX-2 inhibitors

See also Individual agents

General Information

The cyclo-oxygenase (COX) that is responsible for prostaglandin synthesis exists in two isoforms, COX-1 and COX-2, which differ in their structure, regulation, expression, and function. COX-1 is expressed normally in a constant amount in almost all body tissues and produces prostaglandins important for the maintenance of normal homeostasis. In particular, among other important functions, they help to protect the gastrointestinal mucosa against ulceration and regulate renal function and platelet activity. COX-1 appears to be largely unaffected by inflammatory stimuli. In contrast, the COX-2 isoform is constitutively expressed only in the brain, in bone (associated with osteoblast activity), in the female reproductive tract (associated with both the ovulatory cycle and implantation of fertilized ova), and in the kidney, where it may play an important role in regulating renal function. In many other cells COX-2 is expressed at very low levels or is undetectable, but it is readily induced by inflammatory cytokines, mitogens, and endotoxins. Therefore, prostaglandins generated by COX-2 mediate pain and inflammation in many tissues and probably also have a role in renal, brain, and reproductive physiology, and in tissue repair (1–4).

Traditional NSAIDs inhibit both COX-1 and COX-2, providing benefit at sites of inflammation, but at the cost of potential adverse effects related to COX-1 inhibition, particularly in areas such as the gastrointestinal mucosa, platelets, and the kidney. The development of a drug that inhibits only COX-2 would offer the promise of relieving pain and inflammation without some, if not all, of these adverse effects. However, the concept that selective inhibition of COX-2 is only a positive event and inhibition of COX-1 a bad one may be simplistic, as it is flawed by many experimental data that have also implicated COX-2 as an integral component in the maintenance of physiological homeostasis (3). In particular, COX-2 may reduce inflammation by generating anti-inflammatory prostanoids (5); COX-2, like COX-1, may be present in normal gastric mucosa (6,7) and can play a physiological role there in defense mechanisms (8,9), and there is evidence that prostaglandins derived from COX-2 may be important in the healing of gastric ulcers (9–12). Furthermore, COX-2 inhibition alone may be insufficient to resolve inflammation and pain (13), suggesting that COX-1 inhibition may play a role in reducing inflammation as well (14). Although the relevance of these experimental observations to the possible beneficial role of COX-2 activity is uncertain, they cannot be simply dismissed.

Nearly all of the traditional NSAIDs are predominantly COX-1-selective. In fact, only two of them, meloxicam and nimesulide (1,2), have been shown to have some COX-2 selectivity in humans. Two other NSAIDs, etodolac and nabumetone, may be COX-2 preferential inhibitors, but the evidence is less convincing than for meloxicam or nimesulide. Unfortunately, despite their wide use, clinical and epidemiological evidence that supports the claim of better tolerability of these preferential inhibitors with respect to other NSAIDs, is scanty and even controversial (1,4). Furthermore, for both meloxicam and nimesulide there are data consistent with reduced COX-2 selectivity at high doses, those usually used in clinical practice. These considerations have prompted research for more selective COX-2 inhibitors, and three compounds, celecoxib, parecoxib, and rofecoxib, have become available. These compounds are much more selective than previous preferential inhibitors and they have no effect on COX-1 (COX-1 sparing drugs) over the whole range of doses used and concentrations achieved in clinical use. In particular, they have been shown in humans to spare gastric COX-1 to a much greater extent than traditional NSAIDs.

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Is there convincing evidence that COX-2-selective NSAIDs offer a distinct therapeutic advantage over non-selective ones? To prove the usefulness of these compounds, clinical studies should show:

- whether the COX-2 selective inhibitors are as effective as older NSAIDs in the relief of pain and/or inflammation;
- whether in the effective dosage range there is evidence of less damage to the mucosa of the upper gastrointestinal tract than with conventional NSAIDs;
- whether there are any effects on platelet in effective doses;
- whether unexpected adverse drug reactions compromise the safety of these compounds.

As far as the last of these criteria is concerned, the finding that rofecoxib increases the risk of cardiovascular disease (heart attacks and strokes) during long-term therapy has led to a reappraisal of the role of the COX-2 inhibitors. Furthermore, both rofecoxib and valdecoxib have been withdrawn by their manufacturers, the former because of its adverse cardiovascular effects and the latter because of an increased risk of cardiovascular events after coronary artery bypass surgery and reports of potentially fatal skin reactions.

Clinical studies

Both celecoxib and rofecoxib have been evaluated in large randomized trials lasting from weeks to 1 year, for the relief of the signs and symptoms of osteoarthritis or rheumatoid arthritis in adults (1,15–21). In all of these studies both compounds have been shown to be more effective than placebo and at least as effective as traditional NSAIDs (that is ibuprofen, diclofenac, nabumetone, naproxen). However, there is less information about their efficacy as analgesics. A few randomized, double-blind trials have shown that both compounds are more effective than placebo; rofecoxib was as effective as non-selective NSAIDs (ibuprofen, naproxen) in relieving the pain of osteoarthritis or after dental surgery, but celecoxib was less effective (22–26). Rofecoxib was also analgesic in patients with primary dysmenorrhea (27). However, there are no published data on the usefulness of COX-2-selective NSAIDs in other types of acute pain, such as that related to acute gout, migraine, cancer, or biliary or ureteric colic.

General adverse effects

Although the scientific literature has been flooded by articles and reviews on the use of selective COX-2 inhibitors (coxibs), the safe prescribing and use of these compounds is controversial (28–31).

COX-2 selectivity may be a double-edged sword. Because the cardiovascular risk outweighs the gastrointestinal risk in adults with rheumatoid arthritis or osteoarthritis, the harm would outweigh the benefits in most clinical settings. This means that the total number of serious adverse events would be increased by COX-2-selective NSAIDs compared with non-selective NSAIDs. COX-2 selectivity, which is an appealing theoretical concept, might be a clinical failure (30).

Much information on celecoxib and rofecoxib has come from two large pivotal randomized clinical trials, the Celecoxib Long-term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcomes Research (VIGOR) studies, in which the efficacy and safety of the two coxibs and various non-selective NSAIDs were compared (32,33).

Summary

The COX-2-selective inhibitors are as efficacious as traditional NSAIDs in treating inflammation and pain due to osteoarticular diseases. However, there are questions to be addressed before COX-2-selective inhibitors can be considered to be definitely safer than traditional NSAIDs (4). Among these questions the most important relate to the possibility that COX-2 inhibitors may cause complicated ulceration in some subgroup of patients and may retard ulcer healing in others. Therefore, whether the COX-2 inhibitors in place of non-selective NSAIDs will prove to be cost-effective by reducing ulcer-related morbidity remains to be demonstrated. Moreover, it is likely that such drugs can cause the same renal problems as traditional NSAIDs do. Finally, the effect of COX-2 inhibitors on the incidence of vascular disease will need strict scrutiny, since vascular disease is a commoner cause of death than ulcer perforation or bleeding and since some of them clearly increase the long-term risk of heart attacks and strokes. Only their continuing use and postmarketing surveillance studies will demonstrate their strengths and weaknesses with respect to non-selective NSAIDs.

Organs and Systems

Cardiovascular

Prothrombotic effects

COX-2 inhibitors inhibit the synthesis of prostacyclin in the vascular wall but not platelet thromboxane production. They could therefore theoretically increase the risk of cardiovascular events by shifting the hemostatic balance toward a prothrombotic state. However, it is not clear that theory has much impact on reality.

Information about this topic comes from the two large studies, CLASS and VIGOR, from a pooled cardiovascular safety analysis using individual patient data derived from all rofecoxib phase IIb to V trials conducted by the manufacturer that lasted at least 2 weeks, and from the adverse events reporting system in the USA (34). As a result of these and other studies the COX-2 inhibitors, rofecoxib and valdecoxib, have been voluntarily withdrawn from the market by their manufacturers, and other COX-2 inhibitors are under scrutiny.

In VIGOR, rofecoxib 50 mg/day was associated with a higher rate of non-fatal myocardial infarction (0.4%) than the non-selective COX-2 inhibitor naproxen 500 mg bd (0.1%) (RR = 0.2; CI = 0.1, 0.7) (33). In CLASS there was no difference in the rates of myocardial infarction in patients taking celecoxib (0.5%) and those taking ibuprofen or diclofenac (0.4%). However, the protocols of the two studies differed substantially with respect to the use of aspirin. In VIGOR, the patients were not allowed to take aspirin or any other antiplatelet drug, while in

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CLASS one-fifth of the patients took aspirin. A re-analysis of CLASS for cardiovascular thromboembolic events, including myocardial infarction, stroke, cardiovascular deaths, and peripheral events, showed no significant increase with celecoxib versus NSAIDs (35).

The results of VIGOR might be explained by a significant prothrombotic effect of rofecoxib and/or an antithrombotic effect of naproxen, which may have a significant antiplatelet effect. To clarify this, the annualized myocardial infarction rates in both VIGOR and CLASS were compared with those found in placebo-treated patients with similar cardiac risk factors enrolled in three meta-analyses of four aspirin primary prevention trials (34,36). The analysis showed 0.24 and 0.30% increases over placebo in cardiovascular events for rofecoxib and celecoxib respectively, suggesting a prothrombotic potential of both COX-2 inhibitors. However, these results have been heavily criticized (37–43), because of many potential pitfalls in the comparisons of patient populations in different trials. The results from a recently reported pooled analysis of individual patient data combined across rofecoxib phase IIb to phase V trials seem to be more reliable (44). Cardiovascular events were assessed across 23 studies. Comparisons were made between patients taking rofecoxib and those taking placebo, naproxen, or other non-selective NSAIDs (diclofenac, ibuprofen, and nabumetone). The major outcome measure was the combined end-point used by the Anti-platelet Trialist Collaboration, which includes cardiovascular death, hemorrhagic death, death of unknown cause, non-fatal myocardial infarction, and non-fatal stroke. More than 28 000 patients, representing more than 14 000 patient-years at risk, were analysed. The relative risk for an end-point was 0.84 (95% CI = 0.51, 1.38) when comparing rofecoxib with placebo; 0.79 (95% CI = 0.40, 1.55) when comparing rofecoxib with non-selective NSAIDs; and 1.69 (95% CI = 1.07, 2.69) when comparing rofecoxib with naproxen. These data provide no evidence for an excess of cardiovascular events for rofecoxib relative to either placebo or the non-selective NSAIDs that were studied. Instead, the difference between rofecoxib and naproxen showed that naproxen was associated with a reduced risk of cardiovascular events.

The cardiovascular results in VIGOR may have occurred simply by chance, given the low number of events, or because naproxen may have a cardioprotective effect similar to that of aspirin, or because rofecoxib 50 mg/day could have prothrombotic effects, especially in the absence of concomitant COX-1 inhibition in patients at increased risk of cardiovascular thromboembolic events. Because there was no untreated group in VIGOR, we do not know whether this finding suggests a protective effect of naproxen or a harmful effect of rofecoxib. All three explanations are plausible, and they are not mutually exclusive.

It has been suggested that the increase in thrombotic cardiovascular events in rofecoxib-treated patients probably represents the antiplatelet effect of naproxen (34,45,46). Naproxen has a long pharmacodynamic half-life and inhibits platelet aggregation by 88% for up to 8 hours (47).

In VIGOR (30,33), the incidence of confirmed thrombotic cardiovascular events was 0.6% higher with rofecoxib than with naproxen (RR = 2.4; 95% CI = 3.9, 4.0).

Some data may help to answer the important question of whether the relative difference in the incidence of myocardial infarction in VIGOR was due to a harmful effect of rofecoxib or a beneficial effect of naproxen. Although contrasting data have been published (48), the hypothesis that naproxen has a cardioprotective effect has gained wider support (49). Only one of the four most recently published studies negated a potential cardioprotective effect of naproxen.

However, an analysis of FDA data suggested an increase in serious cardiac events with celecoxib (30). The incidence of serious cardiac adverse events (myocardial infarction, combined anginal events, and atrial dysrhythmias) was 0.6% higher with celecoxib than with other NSAIDs (RR = 1.55; CI = 1.04, 2.30). The reasons for these inconsistencies are not clear.

In an 11-year observational study in new users of non-selective, non-aspirin NSAIDs (n = 181 441) and an equal number of non-users there was no evidence of a protective effect of naproxen (50). During 532 634 person-years of follow-up there were 6382 cases of serious coronary heart disease (11.9 per 1000 person-years). Multivariate-adjusted rate ratios for current and former use of non-aspirin NSAIDs were 1.05 (95% CI = 0.97, 1.14) and 1.02 (0.97, 1.08) respectively. Rate ratios for ibuprofen, naproxen, and other NSAIDs were 1.15 (1.02, 1.28), 0.95 (0.82, 1.09), and 1.03 (0.92, 1.16) respectively. There was no protection in long-term users with uninterrupted use; the rate ratio among current users with more than 60 days of continuous use was 1.05 (0.91, 1.21). When naproxen was directly compared with ibuprofen, the rate ratio in current users was 0.83 (0.69, 0.98). This study therefore seems to have shown no cardioprotective effect of naproxen. However, the study had a number of important limitations, including: lack of information about some important confounders (smoking, obesity), possible exposure misclassification, and lack of information about over-the-counter use of aspirin.

Opposite evidence has emerged from three case-control studies from the USA, Canada, and the UK, which showed that the rates of myocardial infarction in patients taking naproxen were lower than in patients not taking any NSAIDs (51,52) and those taking other NSAIDs (53).

In the first study, 4425 patients hospitalized with acute myocardial infarction who used NSAIDs were compared with 17 700 controls in a large health-care database in the USA (51). Multivariate models were constructed to control for potential confounders. A quarter of the cases and controls had also filled a prescription for an NSAID in the 6 months before the study. Overall, the NSAID users had the same risk of acute myocardial infarction as non-users, but naproxen users had a significantly lower risk of acute myocardial infarction compared with those who were not taking NSAIDs (adjusted OR = 0.84; 95% CI = 0.72, 0.98). The cardioprotective effect of naproxen was very modest compared with aspirin (a 44% reduction in the risk of acute myocardial infarction in the Physician Health Study (54)).

The second study was a case-control study sponsored by Merck & Co (the manufacturers of celecoxib), in which the risk of acute thromboembolic cardiovascular events among 16 937 patients aged 40–75 years with rheumatoid arthritis using naproxen was examined using the British General Practice Research Database (52). Each patient with a first

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thromboembolic event ($n = 809$: 435 myocardial infarctions, 347 strokes, 27 sudden deaths) was matched with four controls. The results suggested that patients with rheumatoid arthritis who currently use naproxen have a significantly lower risk of thromboembolic events relative to those who have not used naproxen in the past year (RR = 0.61; 0.39, 0.94). However, the risk was not lower with previous use of naproxen, suggesting that any effect of naproxen is likely to be short-lived. Moreover, the significantly lower risk of myocardial infarction with current naproxen was not found when myocardial infractions were analysed separately (RR = 0.57; 0.3, 1.06). There was no protective effect for thromboembolic events with current use of non-naproxen NSAIDs.

The third study was also sponsored by Merck & Co and was designed to examine the association between the use of naproxen and other non-selective NSAIDs and hospitalization for acute myocardial infarction (53). In a database of 14 163 patients aged 65 years or older who were hospitalized for acute myocardial infarction and an equal number of age-matched controls, concurrent exposure to naproxen had a protective effect against myocardial infarction compared with the other non-selective non-aspirin NSAIDs (RR = 0.79; CI = 0.63, 0.99). This effect was present only with concurrent naproxen exposure and was stronger in long-term users. However, this study also had several limitations: some important risk factors, such as smoking and obesity, could not be assessed, patients who died of myocardial infarction before reaching the hospital were not included, and there was uncertainty about concurrent use of over-the-counter drugs, especially aspirin.

In conclusion, although these three studies suggest that patients who take naproxen have a lower incidence of myocardial infarction than those who take other NSAIDs or who do not take NSAIDs, the data do not provide definitive evidence that naproxen is cardioprotective. The data therefore raise a cautionary flag about the risk of severe cardiovascular events with COX-2 inhibitors and again call for more studies.

Hypertension

The shift in hemostatic balance toward a prothrombotic state might not be the only mechanism by which COX-2 inhibitors could increase the risk of cardiovascular adverse effects. In fact, non-selective NSAIDs can raise blood pressure and antagonize the hypotensive effect of antihypertensive medications to an extent that may increase hypertension-related morbidity (55,56). The problem is clinically relevant, as arthritis and hypertension are common co-morbid conditions in elderly people, requiring concurrent therapy.

Information on the effect of COX-2-selective inhibitors on arterial blood pressure is scanty. In VIGOR, more patients developed hypertension with rofecoxib than naproxen. For rofecoxib, the mean increase in blood pressure was 4.6/1.7 mmHg compared with a 1.0/0.1 mmHg increase with naproxen (34). Previous work has shown that a 2 mmHg reduction in diastolic blood pressure can result in about a 40% reduction in the rate of stroke and a 25% reduction in the rate of myocardial infarction (57). The effect of celecoxib on blood pressure was evaluated in a post hoc analysis using the safety database generated during the celecoxib clinical development program in more than 13 000 subjects (58). The incidence of hypertension after celecoxib was greater than that after placebo but similar to that after non-selective NSAIDs. Hypertension and exacerbation of pre-existing hypertension occurred, respectively, in 0.8 and 0.6% of patients. Furthermore, there was no evidence of interactions between celecoxib and other antihypertensive drugs.

The safety profiles of celecoxib (200 mg/day) and rofecoxib (25 mg/day) have recently been compared in a 6-week, randomized, parallel-group, double-blind trial in 810 patients with osteoarthritis aged 65 years or over taking antihypertensive drugs (59). The primary endpoints were edema and changes in systolic and diastolic blood pressures, measured at baseline and after 1, 2, and 6 weeks. Systolic blood pressure rose significantly in 17% of rofecoxib-treated patients ($n = 399$) compared with 11% of celecoxib-treated patients ($n = 411$), a statistically significant difference, at any time in the study. Diastolic blood pressure rose in 2.3% of rofecoxib-treated patients compared with 1.5% of celecoxib-treated patients, a non-significant difference. At week 6, the change from baseline in mean systolic blood pressure was +2.6 mmHg for rofecoxib compared with –0.5 mmHg for celecoxib, a highly significant difference. Nearly twice as many rofecoxib-treated than celecoxib-treated patients had edema. Despite some limitations, this study provides some evidence that COX-2-selective inhibitors may differ in their ability to alter arterial blood pressure.

Cardiac dysrhythmias

There have been reports of celecoxib-associated torsade de pointes in three patients who had never had any complaints before celecoxib administration; the dysrhythmia did not recur after the drug was withdrawn (60). However, all three patients had cardiac abnormalities that might have predisposed them to the development of torsade de pointes, and the follow-up period was too short to evaluate possible spontaneous recurrence. The hypothesis that celecoxib is dysrhythmogenic requires confirmation.

Respiratory

Most people tolerate aspirin well, but not patients with asthma, of whom there is a subgroup in whom aspirin precipitates asthmatic attacks (61,62). This is a distinct clinical syndrome, called aspirin-induced asthma, which affects about 10% of adults with asthma (63). Aspirin-induced asthma is usually accompanied by naso-ocular symptoms and can be triggered not only by aspirin, but by several NSAIDs, a fact that makes immunological cross-reactivity most unlikely. The propensity of an NSAID to precipitate an attack of asthma is probably related to inhibition of COX (63). There is evidence that potent inhibitors of COX-1 (such as ibuprofen, indometacin, and naproxen) are more likely to precipitate bronchoconstriction than NSAIDs that inhibit COX-2 preferentially (such as meloxicam and nimesulide) (64,65). A widely accepted hypothesis is that in patients with asthma and aspirin intolerance, NSAID-induced COX inhibition results in increased products from the 5-lipoxygenase pathway, the leukotrienes, which are both potent bronchoconstrictors and also inducers of

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mucous hypersecretion and airway edema. The leukotrienes implicated in aspirin intolerance are cysteinyl leukotrienes (61,63), but leukotriene release is probably not the only pathogenic mechanism.

The hypothesis that in aspirin-induced asthma the attacks are triggered by inhibition of COX-1 and not COX-2 has been tested in three small studies, two of which were double-blind and placebo-controlled (66–68). In the first study (66) 12 patients with aspirin-induced asthma were challenged with increasing doses of rofecoxib (1.25–25 mg/day for 5 days); no patients had any adverse symptoms, and biochemical markers that reflect intolerance to aspirin in asthma (urinary leukotriene E4 and 9α-11β-PGF-2) were unchanged.

In the second study, 60 aspirin-sensitive asthmatics were challenged with oral rofecoxib (12.5 and 25 mg/day for 2 days) (67). There were no signs or symptoms of asthma in any patient and no reductions in FEV_1.

In the third study, 27 patients with stable chronic asthma in whom inhalation of lysine aspirin caused a 20% fall in FEV_1 were challenged with increasing doses of oral celecoxib (from 10 to 200 mg/day); they do not develop bronchoconstriction or other extrapulmonary reactions (68).

So, is the safety of COX-2 inhibitors in patients with aspirin-induced asthma sufficiently well documented? Avoidance of NSAIDs is crucial in patients with asthma who have aspirin sensitivity, and hitherto two alternative analgesic options have been available: paracetamol and non-acetylated salicylates. Paracetamol is a generally safe substitute; however, it is a weak COX inhibitor and, albeit very rarely, patients who are sensitive to aspirin have an adverse reaction to high-dose paracetamol (69). Choline magnesium salicylate and salicylic acid are also weak COX inhibitors and should therefore be used with care in these patients. The results of the above-mentioned studies suggest that rofecoxib and celecoxib can be taken safely by patients with aspirin-induced asthma. However, this conclusion must be treated with caution, as only a few patients were studied and this does not exclude COX-2 inhibitors from participating in other types of reactions, including immune recognition after prior treatment.

Nervous system

Aseptic meningitis is a rare complication of NSAID therapy. Five serious cases of aseptic meningitis associated with rofecoxib have been reported (70).

- A 55-year-old woman who had taken rofecoxib for 1 month reported numbness and tingling on the left side of the tongue and left hand (71). The association between paresthesia and rofecoxib was supported by the time-course of the reaction and resolution after withdrawal.

Because this patient was using other medications (paroxetine, zolpidem, and sumatriptan), which can have a similar effect, this report requires confirmation.

Hematologic

Platelets have only the COX-1 isoform for generating thromboxane to precipitate platelet aggregation. Therefore, selective COX-2 inhibitors have no effect on platelet aggregation or bleeding time (3,72). On the other hand, COX-2 plays a role in the production of endothelial PGI2. In vitro studies have shown that COX-2 expression is up-regulated in endothelial cells by laminar shear stress (73). Furthermore, selective COX-2 inhibitors reduce systemic PGI-2 production in healthy volunteers (74). The clinical implications of these observations are unknown. In theory, COX-2 selective NSAIDs might increase the risk of thromboembolic cardiovascular events because of preferential inhibition of endothelial prostacyclin synthesis without corresponding inhibition of platelet thromboxane synthesis, but no reliable data are available on the occurrence of cardiovascular events in patients treated with COX-2 selective or non-selective NSAIDs.

Gastrointestinal

Gastric damage

Evidence that the COX-2 selective agents cause less damage to the gastrointestinal mucosa than traditional NSAIDs is still limited. Gastrointestinal tolerability has been evaluated by measuring the frequency and severity of gastrointestinal adverse effects during randomized comparative efficacy trials, by performing microbleeding or endoscopic studies, and by evaluating the incidence of severe ulcer complications. Evidence from efficacy trials suggests an incidence of unwanted gastrointestinal effects (dyspepsia, epigastric abdominal pain, nausea, or diarrhea) similar to that caused by the traditional NSAIDs (1,15–17,20,75). The withdrawal rate from clinical trials because of unwanted effects (gastrointestinal or as a whole) was also similar, the only exception being one study in which fewer patients with rheumatoid arthritis stopped taking celecoxib than stopped taking diclofenac (16). However, the clinical importance of the frequency and severity of symptoms is uncertain. In fact, it is well known that symptoms do not necessarily predict the presence of mucosal damage, and it is still unclear if patients who have dyspeptic symptoms associated with NSAIDs are at greater or lesser risk of serious gastrointestinal complications (SEDA-15, 92) (SEDA-17, 103), the crucial question in evaluating these drugs.

In endoscopic comparisons of the new compounds with placebo or older NSAIDs, in both healthy volunteers and patients with rheumatoid arthritis or osteoarthritis, endoscopically observed lesions (erosions, ulcers) in the stomach and duodenum were undoubtedly fewer with the two COX-2-selective compounds than with non-selective NSAIDs (16,75–78) and were similar to those found with placebo (1).

However, the clinical significance of endoscopically detected erosions and ulcers is debatable (SEDA-14, 79) (SEDA-20, 97), as there is much controversy about whether endoscopic ulcers are surrogates for clinical outcomes such as perforation, obstruction, and gastrointestinal bleeding (78). Thus, although endoscopic studies are an important step in the evaluation of COX-2-selective inhibitors, large-scale, prospective, randomized outcome studies are necessary before we can definitively determine if these drugs will indeed represent significantly safer alternatives to the older NSAIDs. Unfortunately, these prospective comparative complication trials are difficult to perform, as the absolute rate of serious gastrointestinal complications (perforation, obstruction, and bleeding) is

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low (about 2% per year) (78) and so a large number of patients must be studied.

Suggestions for improved gastrointestinal safety of COX-2-selective inhibitors have come from two studies, which addressed the problem of sample size by pooling published and unpublished randomized, double-blind trials of varying design and duration, comparing celecoxib, rofecoxib, non-selective NSAIDs (diclofenac, ibuprofen, nabumetone), and placebo in patients with osteoarthritis and/or rheumatoid arthritis.

In the first study the results of eight studies were pooled (79). The sample size of 5435 patients was large enough to detect even small differences in rates of complicated ulcers (perforation, symptomatic ulcers, and bleeding ulcers). Over 12 months complicated ulcers occurred at a rate of 1.33 per 100 patient-years with rofecoxib and 2.60 per 100 patient-years with non-selective NSAIDs. The analysis of confirmed upper gastrointestinal perforations, symptomatic ulcers, and upper gastrointestinal bleeding showed a relative risk (RR) with rofecoxib versus NSAIDs of 0.51 (95% CI = 0.26, 1.00). The difference between rofecoxib and the usual NSAIDs in the incidence of perforation, symptomatic ulcers, and bleeding ulcers became statistically significant as early as 6 weeks and remained so up to 12 months. However, this study has some limitations: first, it was not a prospective analysis or a properly conducted meta-analysis; secondly, there were only enough patient-years of exposure to compare rofecoxib with pooled traditional NSAIDs rather than individual drugs; thirdly, the confidence intervals were wide and compatible with no difference between the two treatment groups; fourthly, the time to exposure with any selective drug or placebo was too short to give a good prediction of actual complication rates with typical use.

In the second analysis, data from 14 studies of the efficacy of celecoxib in osteoarthritis or rheumatoid arthritis in 11 007 patients were pooled (80,81). Gastrointestinal complications (bleeding, obstruction, or perforation) occurred in 0.2% of the patients per year of exposure to celecoxib and in 1.7% per year of exposure to traditional NSAIDs. The absolute risk reduction was 1.5% (CI = 0.4, 2.6). This study, too, had some limitations. In fact, ulcer complication was not the specified end-point of the studies that were pooled, and about 15% of celecoxib-treated patients took a dose below that indicated for arthritis.

Assuming that a COX-2-selective inhibitor will prevent complicated ulcers in 50% of patients, it has been calculated that the NNT for avoiding one complicated ulcer each year in low-risk patients with rheumatoid arthritis (that is with a 0.4% risk of ulcer complications) is 500. On the other hand, in patients at higher risk (that is a 5% risk for ulcer complications) the NNT is 40 (82). It is therefore of paramount importance that studies currently under way confirm the same benefit from COX-2-selective agents in patients with a high risk of ulcer complications (that is aged 75 years or older, with a prior history of ulcer and gastrointestinal tract bleeding, taking low-dose aspirin for cardiovascular disease).

Two large trials have addressed the efficacy of COX-2 selective inhibitors and the associated risk of gastrointestinal complications: the CLASS and the VIGOR trial (32,33).

The CLASS consisted of two separate studies, in which celecoxib was compared with ibuprofen and diclofenac; the results obtained from the two traditional NSAIDs were pooled for analysis. Overall, 3987 patients with osteoarthritis and rheumatoid arthritis took celecoxib (400 mg bd), 1985 patients took ibuprofen (800 mg tds), and 1996 took diclofenac (75 mg bd). The study lasted 13 months, but only the data from 6 months of follow-up were published initially.

There was no statistically significant difference between the two groups in the incidence of the primary end-point of complicated ulcers (upper gastrointestinal bleeding, ulcer perforation, gastric outlet obstruction); the annualized incidence of complicated ulcers in patients taking celecoxib was 0.76% (11 events per 1441 patient-years) versus an incidence of 1.45% (20 events per 1384 patient-years) in patients taking the non-selective NSAIDs, a non-significant difference. However, for the composite end-point of upper gastrointestinal ulcer complications plus symptomatic gastroduodenal ulcers, celecoxib was significantly better tolerated than traditional NSAIDs; the annualized incidence was 2.08% (30 events per 1441 patient-years) with celecoxib versus 3.54% (49 events per 1384 patient-years) for patients taking traditional NSAIDs, significantly different.

The lack of difference in the rate of ulcer complications between the two treatments appeared to be a function of the higher-than-expected rate of complicated ulcers in those taking celecoxib compared with previous studies (81). Further analysis showed that this increase in complications was likely to be attributable to concurrent low-dose aspirin; the annualized incidence of upper gastrointestinal tract ulcer complications and of symptomatic gastroduodenal ulcers in patients not taking low-dose aspirin was significantly lower with celecoxib than with non-selective NSAIDs (0.44% or 5 events per 1143 patient-years versus 1.27% or 14 events per 1101 patient-years respectively). In patients taking aspirin, the annualized incidence of upper gastrointestinal complications and symptomatic ulcers were not significantly different (4.7% or 14 events per 298 patient-years in patients taking celecoxib versus 6.0% or 17 events per 283 patient-years in those taking traditional NSAIDs).

Moreover, the overall incidence of gastrointestinal symptoms in patients taking celecoxib was only slightly lower than that of patients taking the traditional NSAIDs, as was the rate of withdrawal due to gastrointestinal intolerance in both users and non-users of low-dose aspirin.

This subgroup analysis shows what might be called "competing co-morbidity"; that is, in the subgoup of patients taking aspirin as prophylaxis against ischemic heart disease, the gastrointestinal safety advantage of celecoxib over traditional NSAIDs was almost totally wiped out by the use of aspirin (83).

Despite that, the authors of CLASS concluded by stating that celecoxib caused fewer symptomatic ulcers and ulcer complications than ibuprofen or diclofenac at 6 months.

However, these conclusions were not only contradicted by the published data (32), but were also called into question by subsequent information on the trial available to the FDA (84,85). As was first

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described on the FDA website, the published account of CLASS differed from the original protocol in many respects (in primary outcomes, statistical analysis, and trial duration). In particular, the published article represented selective reporting of the combined analysis of only the first 6 months of two separate protocols of longer duration: the first a 12-month comparison of celecoxib with diclofenac and the other a 16-month comparison of celecoxib with ibuprofen. The unpublished data show that by week 65 celecoxib was associated with a similar number of ulcer complications as diclofenac and ibuprofen and that the relative risks of both complicated ulcers and all serious gastrointestinal adverse events were higher at 12–16 months than they were at 6 months, suggesting an increased risk of serious adverse events with celecoxib long-term therapy.

Serious criticism was therefore aimed at the authors on the grounds of design, data analysis, and misleading presentation of the results. They were charged with having published and circulated overoptimistic short-term pooled data from different protocols, and of omitting disappointing long-term data. They replied to these criticisms, but their explanations were not considered to be convincing (86–88). Furthermore, Pharmacia, the manufacturers of celecoxib, continue to present inappropriately pooled short-term results from different protocols performed in different continents with different comparator drugs for the SUCCESS 1 trial, the successor to CLASS (86–88).

In the VIGOR study, 8076 patients with rheumatoid arthritis were randomly assigned to receive rofecoxib 50 mg/day or naproxen 500 mg bd. The primary endpoint was a confirmed clinical upper gastrointestinal event (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcer).

Overall, confirmed upper gastrointestinal events occurred in 177 patients, 56 with rofecoxib ($n = 4047$), and 121 in those taking naproxen ($n = 4029$). In 53 of these patients (16 taking rofecoxib and 37 taking naproxen) the event was complicated. That means that during a median follow-up of 9.0 months, there were 2.1 confirmed gastrointestinal events per 100 patient-years with rofecoxib compared with 4.5 per 100 patient-years with naproxen (RR = 0.5; 95% CI = 0.2, 0.8). The respective rates of complicated ulcers (perforation, obstruction, and bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (RR = 0.4; 95% CI = 0.2, 0.8).

It is also worth noting that the most common adverse events that led to withdrawal of treatment, excluding the primary gastrointestinal end-points, were dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn and that significantly fewer patients discontinued treatment as a result of any one of these five upper gastrointestinal symptoms in the rofecoxib group (3.5%) than in the naproxen group (4.9%).

Problems have also occurred in interpreting the results of VIGOR (33). There were significantly fewer upper gastrointestinal adverse events with rofecoxib compared with naproxen, but an unexpected substantial excess of serious cardiovascular events, making the overall safety of rofecoxib uncertain. When the complete data from VIGOR were presented and all serious adverse events were included (not just gastrointestinal events) the patients who took naproxen had fewer overall serious events: 9.3% of the patients who took rofecoxib had a serious adverse event, compared with 7.8% of those who took naproxen (RR = 0.81; 95% CI = 0.62, 0.97).

The reasons for the discrepancy between celecoxib and rofecoxib in the frequency of upper gastrointestinal complications are not clear, but some hypotheses have been proposed. First, aspirin was used concomitantly with celecoxib (20% of patients) in CLASS but not in VIGOR, increasing the risk of gastrointestinal damage. Secondly, diclofenac (which has greater COX-2 selectivity than naproxen) was used as a comparator in CLASS. Thirdly, the dosages of celecoxib were too high and at the doses studied in CLASS celecoxib might not have had true selectivity for COX-2. Finally, the selectivity of celecoxib for COX-2 is probably lower than that of rofecoxib. Therefore, given major differences in study design and data analysis between the two trials, a valid comparison of the two coxibs is not possible from these data alone; a head-to-head comparison in a large outcome study is needed (89).

Two recently published articles have helped to clarify this point: a systematic review of randomized clinical trials on the upper gastrointestinal safety of celecoxib (90) and a population-based retrospective cohort comparison of the rate of upper gastrointestinal hemorrhages in over 40 000 NSAID-naïve elderly users of non-selective NSAIDs, celecoxib, or rofecoxib with the rate in 100 000 patients who had not been exposed to NSAIDs (91).

In the systematic review, all published and unpublished randomized clinical trials that compared at least 12 weeks of celecoxib treatment with placebo or a traditional NSAID (diclofenac, ibuprofen, naproxen) were analysed. Nine of 17 trials fulfilled the inclusion criteria (a total of 15 187 patients). Withdrawals because of drug-related gastrointestinal adverse effects, ulcers detected at endoscopy, and complicated ulcers were used as measures of gastrointestinal tolerability. Compared with those taking non-selective NSAIDs, the patients who took celecoxib had a lower rate of withdrawals because of adverse gastrointestinal effects at 12 weeks (3.2 versus 6.2%), but there was no significant difference between celecoxib and NSAIDs in the incidence of withdrawals for all adverse events. The incidence of ulcers detected at routine endoscopy at 12 weeks was also lower in patients who took celecoxib compared with those who took non-selective NSAIDs (6.2 versus 23%). In four trials that provided information on the incidence of ulcers detected by endoscopy according to whether or not patients were taking concomitant aspirin up to 325 mg/day, the benefit provided by celecoxib was greater in patients not taking aspirin. The incidences of ulcers were as follows:

- celecoxib alone 6.2%;
- celecoxib + aspirin 12%;
- non-selective NSAID alone 25%;
- non-selective NSAID + aspirin 26%.

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However, these results must be treated with great caution, as the total number of patients who took prophylactic aspirin was small (150 taking celecoxib and 140 taking non-selective NSAIDs) and the largest number of patients came from a single trial (CLASS).

The same warning applies to evaluation of the incidence of complicated ulcers (bleeds, perforation, and obstructions). The incidence of these serious events with celecoxib was 2.7% (11 events) versus 5% (20 events) in patients taking diclofenac or ibuprofen, a non-significant difference.

This meta-analysis has provided further evidence that celecoxib has better upper gastrointestinal tolerability that some traditional NSAIDs when withdrawal from trials due to drug-related adverse effects or ulceration detected during routine endoscopy are used as measures of tolerability. However, not all ulcers detected by endoscopy progress to a serious event, and many probably heal spontaneously; the clinical relevance of this measure is therefore controversial. On the other hand, there is a consensus that ulcer complications, the prime cause of concern with NSAIDs, should be the primary end-point of outcome studies aimed at evaluating the gastrointestinal toxicity of NSAIDs. Unfortunately, this consensus is counterbalanced by the problems of doing such studies, as they need to be very large to achieve even marginal power and there are also problems in evaluating the clinical outcomes (89).

Another study that deserves attention was an observational study of upper gastrointestinal hemorrhage in over 40 000 elderly patients taking COX-2-selective drugs (celecoxib, rofecoxib) or non-selective NSAIDs with and without misoprostol, compared with 100 000 non-NSAID users (91). Of about 1.3 million potential subjects aged 65 years and over, 364 686 (28%) were given an NSAID during the study period (about 1 year). From the total elderly population, the authors identified 5391 users of non-selective NSAIDs, 5087 users of diclofenac plus misoprostol, 14 583 users of rofecoxib, 18 908 users of celecoxib, and 100 000 controls. Most of the users of non-selective NSAIDs were taking naproxen (32%), ibuprofen (23%), or diclofenac (20%). During over 55 000 person-years of follow-up, there were 187 hospitalizations for upper gastrointestinal hemorrhage. Relative to the non-users, there was a significantly greater risk of upper gastrointestinal hemorrhage in the patients who took non-selective NSAIDs (adjusted risk ratio 4.0; 95% CI = 2.3, 6.9), diclofenac plus misoprostol (3.0; 1.7, 5.6), or rofecoxib (1.9; 1.3, 2.6), but not celecoxib (1.0; 0.7, 1.6). There were also significant differences in the risks of upper gastrointestinal hemorrhage. Relative to celecoxib users, there was a higher risk of hospitalization for upper gastrointestinal hemorrhage, not only among users of non-selective NSAIDs and diclofenac plus misoprostol but also among users of rofecoxib.

This study has provided further evidence that the risk of upper gastrointestinal hemorrhage with COX-2 inhibitors is significantly lower than with conventional NSAIDs, whether or not they are taken with misoprostol. The apparently greater risk of gastrointestinal hemorrhage with rofecoxib than with celecoxib needs confirmation, as the study had some limitations, of which the most important were the low absolute number of events in the study group and the retrospective design.

What are the implications of these data on the use of the coxibs? Overall they suggest that COX-2 selective inhibitors are less likely to cause upper gastrointestinal damage than some traditional NSAIDs. This advantage is measured by a lower number of events that represent a composite end-point of gastrointestinal toxicity, such as endoscopically detected symptomatic ulcers and serious ulcer complications (perforation, obstruction, bleeding). However, this may not be true in all patients, especially in those who simultaneously take aspirin. This question is of major clinical importance, as many patients with osteoarthritis or rheumatoid arthritis use low-dose aspirin for cardiovascular prophylaxis. We do not know whether gastrointestinal safety is preserved with the use of such combinations, nor whether a proton pump inhibitor should be added in this situation. Furthermore, the data on which of the coxibs has better gastrointestinal tolerability are inconclusive. Large outcome studies will be necessary to solve these questions.

A final consideration is worthwhile. To focus attention only on gastrointestinal events may provide an incomplete picture of the benefit/harm profile of the COX-2 inhibitors. Meta-analysis of mortality and morbidity outcomes from CLASS and VIGOR has suggested that total mortality was higher with coxibs than with non-selective NSAIDs, although the difference was not statistically significant (30). Moreover, if one takes into account the incidence of serious adverse events (including death, admission to hospital, and any life-threatening event or events leading to serious disability) as a combined measure of harm, the incidence was significantly higher with COX-2 selective compounds than with other NSAIDs, and complicated gastrointestinal ulcers accounted for only a small proportion of total serious adverse events. Non-gastrointestinal serious adverse events call for more attention.

Two other aspects of gastrointestinal toxicity have yet to be studied. First, the use of COX-2 inhibitors in patients with inflammatory bowel disease, in whom it is likely that COX-2 activity is upregulated (92) and in whom traditional NSAIDs may exacerbate the disease. Experimental colitis has been induced both in COX-2-deficient mice and in rats treated with COX-2-selective inhibitors (93). However, in healthy volunteers, rofecoxib did not alter intestinal permeability, in contrast to indometacin, which increased it (94). Studies in patients with inflammatory bowel disease are necessary before considering COX-2 selective inhibitors to be safe in these patients (95).

Secondly, a possible beneficial role of COX-2 on the stomach should also be taken into account. In mice, COX-2 is expressed at the borders of gastric ulcers and has been implicated as a critical factor in promoting repair (11). Whether these experimental data have any clinical relevance is unknown, but this issue raises the possibility that individuals with pre-existing peptic ulcers who take COX-2 selective drugs may be at risk of delayed ulcer healing and potential complications. This issue may be of particular concern in patients with ulcers due to *Helicobacter pylori* infection.

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In conclusion, clinical trials have shown that COX-2-selective NSAIDs seem to be less toxic to the gastrointestinal mucosa than traditional ones. However, life-threatening ulcer complications have been reported in patients taking both celecoxib (81,96,97) and rofecoxib (79). The FDA and other regulatory authorities require that drug information sheets for celecoxib and rofecoxib carry gastrointestinal ulcer warnings similar to those for older NSAIDs.

Large bowel damage

Little is known about the effects of COX-2 inhibitors on the colon, although animal evidence suggests that they can worsen or precipitate acute colitis. Features similar to those seen in cases of ischemic colitis have been reported in a patient taking rofecoxib (98).

- A 52-year-old woman with a colostomy for a tumor of the sigmoid colon developed low back pain that radiated to the legs. A bone scan showed no evidence of tumor. She was given rofecoxib 25 mg/day and 4 days later noticed bloody diarrhea from the colostomy. At colonoscopy a large portion of the transverse colon was seen to be hemorrhagic, with nodularity, a superficial exudate, and mucosal edema, with a well-demarcated transition to normal areas. Despite extensive investigations, no plausible cause of the bloody diarrhea and colitis were found, except the possible involvement of rofecoxib. She stopped taking it and was given intravenous fluids. After 4 days the colostomy stopped oozing blood; colonoscopy showed no evidence of hemorrhage and the mucosa was regenerative. Bleeding did not recur.

Pancreas

Two case reports have suggested a potential association between the sulfonamide group in celecoxib and the development of acute pancreatitis (99,100). The cause of acute pancreatitis in patients taking celecoxib is speculative, but sulfonamides are known to cause pancreatitis, and one of these patients reported an allergy to sulfa medication. Thus, the reaction might have been allergic in nature.

Urinary tract

Kidneys

Renal dysfunction after therapy with COX-2 inhibitors is not unexpected. COX-2 is expressed in the normal human kidney, especially in endothelial and smooth muscle cells of the vasculature and glomerular epithelial cells. Angiotensin II and endothelin induce and upregulate COX-2 and prostaglandin synthesis. Furthermore, it seems reasonable to hypothesize that intrarenal dependence on COX-2-synthesized prostaglandins increases in heart failure, liver failure, volume depletion, and chronic renal disease (101). It is thought that in healthy kidneys COX-2 plays an important role in the balance of water and electrolytes, and its activity is upregulated in patients with reduced left ventricular filling pressure, to help maximize renal blood flow.

As experience with COX-2-selective inhibitors accumulates, it appears that the pattern of nephrotoxicity is similar to that of traditional NSAIDs (102,103). Non-selective NSAIDs can cause hemodynamically mediated acute renal insufficiency in predisposed patients and can cause sodium and water retention, causing peripheral edema and hypertension. Efficacy trials have shown a similar incidence of pedal edema, renal adverse effects, and hypertension with COX-2 selective and non-selective NSAIDs (18,75).

- A 43-year-old woman with rheumatoid arthritis developed dizziness having taken celecoxib 200 mg/day for 2 weeks. At the start of treatment she had normal renal function (104). Her serum creatinine was 670 μmol/l (7.4 mg/dl) and blood urea nitrogen 30 mmol/l (90 mg/dl). Creatinine clearance was 16 ml/minute. Urinalysis was normal and casts were not present. Urinary chemical analysis showed a sodium concentration of 18 mmol/l, a fractional excretion of sodium of 0.3, and a renal failure index of 0.493, consistent with prerenal acute renal insufficiency. Celecoxib was withdrawn. Although her renal function then improved, her serum creatinine was still abnormal (4.7 mg/dl) 1 month later.

In a randomized comparison of celecoxib and diclofenac plus omeprazole, renal adverse events, including hypertension, peripheral edema, and renal insufficiency, were common and similar in the two groups (105). They occurred in the 24% of the patients who took celecoxib and in 31% of those who took diclofenac plus omeprazole. Among patients with renal impairment at baseline, 51% of those who took celecoxib and 41% of those who took diclofenac plus omeprazole had renal adverse events. Careful monitoring of renal function in patients taking COX-2 inhibitors or traditional NSAIDs is mandatory, especially in high-risk subjects (for example those with pre-existing renal disease, diabetes, or heart failure).

Two studies in healthy volunteers have shown that the effects of COX-2 inhibitors on renal function are similar to those of traditional non-selective NSAIDs (106,107). The first was a short-term crossover study on renal function in healthy elderly subjects treated with rofecoxib and naproxen. Although there was a greater fall in glomerular filtration rate with naproxen, reductions in the urinary excretion of sodium, prostaglandin E-2, and 6-keto-prostaglandin F-1α were similar with the two compounds (106). In the second study in elderly people taking a low-salt diet, rofecoxib and indometacin significantly lowered the glomerular filtration to a similar extent (107).

However, these data are limited and must be interpreted with caution, since NSAIDs have significant toxic effects on the kidney only in patients at risk (that is those with volume depletion, heart failure, cirrhosis, intrinsic renal disease, and hypercalcemia), in whom the secretion of vasodilator prostaglandins is increased in an attempt to counteract the effect of increased renal vasoconstrictors, such as angiotensin II.

The incidence of adverse effects related to renal function in CLASS and VIGOR was low and similar (0.9% with celecoxib and 1.2% with rofecoxib). The incidence of increased creatinine and urea nitrogen concentrations was slightly lower in patients taking celecoxib than in those taking ibuprofen or diclofenac. Similar results have been documented in two other clinical trials. The

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first compared celecoxib with diclofenac in long-term management of rheumatoid arthritis in 430 patients (16). There were only small increases in serum creatinine concentration (from 93 μmol/l at baseline to 96 μmol/l at the final visit) and serum urea concentration (from 6.0 to 6.4 mmol/l). There was a similar increase in patients taking diclofenac. The second trial, in 1149 patients, compared celecoxib with naproxen; serum creatinine concentrations were not affected by either celecoxib or naproxen (75). However, data from these clinical trials must be interpreted with caution, as patients at major risk of renal adverse events were likely to be excluded.

In contrast, published case reports and case series have provided more insight into the potential nephrotoxicity associated with COX-2-selective inhibitors. Taken together, these case reports suggest that COX-2 inhibitors, like non-selective NSAIDs, produce similar and consistent renal adverse effects in patients with one or more risk factors that induce prostaglandin-dependent renal function (that is patients with renal and cardiovascular disease and taking a number of culprit medications, such as diuretics and ACE inhibitors). Acute renal insufficiency, disturbances in volume status (edema, heart failure), metabolic acidosis, hyperkalemia, and hyponatremia have been commonly described. The duration of treatment with COX-2 inhibitors before the development of clinically recognized renal impairment ranged from a few days to 3–4 weeks. Withdrawal of COX-2 inhibitors and supportive therapy most often resulted in resolution of renal dysfunction, but in some patients hemodialysis was required (102,108–112).

The renal safety of rofecoxib and celecoxib has been studied using the database of spontaneous reports of adverse drug reactions in the WHO Monitoring Center in Uppsala (113). Disproportionality in the association between COX-2 selective inhibitors and renal-related adverse drug reactions was evaluated using a Bayesian confidence propagation neural network method, in which a statistical parameter (the information component: IC) was calculated for each drug-reaction combination. In this method an IC value significantly greater than 0 implies that the association of a drug-reaction pair is stronger than background; the higher the IC value, the more the combination stands out from the background. As with non-selective NSAIDs, both COX-2 selective inhibitors were associated with renal-related adverse drug reactions. IC values were significantly different for the following comparisons: water retention, abnormal renal function, renal insufficiency, cardiac failure, and hypertension. However, the adverse renal impact of rofecoxib was significantly greater than that of celecoxib. Renal-related events for rofecoxib were two- to four-fold higher than for celecoxib and the severity of these reported adverse reactions was also more serious. Studies based on spontaneous reports have many limitations and their results must therefore be confirmed by additional epidemiological studies that can provide more accurate information on incidence rates and risk factors.

Rare reports of acute reversible renal impairment have been recorded in patients with predisposing factors (109).

Whether selective COX-2 inhibitors can cause the other types of renal toxicity that are associated with non-selective NSAIDs (that is acute interstitial nephritis, nephrotic syndrome with or without renal insufficiency) is not known.

Bladder

The use of NSAIDs to treat and prevent bladder spasms has been documented in clinical trials (114) and their role in relaxing bladder smooth muscle has experimental support (115). Three elderly patients who used rofecoxib or celecoxib developed acute but reversible urinary retention (116). Each had co-morbidities likely to cause bladder dysfunction, and the administration of a COX-2 inhibitor may have caused further relaxation of the detrusor muscle, resulting in urinary retention.

Skin

There have been reports of maculopapular rash (117) and severe erythema multiforme (toxic epidermal necrolysis) (118) with celecoxib. Three patients developed erythema multiforme while taking rofecoxib (119). All were well documented, and oral rechallenge with rofecoxib, positive in two of them, confirmed the role of rofecoxib in the pathogenesis of this adverse reaction.

- Swelling and wrinkling of the palms soon after exposure to water occurred in an 18-year-old-woman taking rofecoxib for mixed connective tissue disease (120). The swelling followed exposure for 1 to a few minutes to water at any temperature. The swelling developed rapidly and was accompanied by symptoms of mild pain and discomfort. Over the following 2 hours, the palms would return to normal. Because of the temporal correlation with the use of rofecoxib, it was withdrawn, and 3 weeks later her symptoms had almost completely resolved.

The authors speculated that this phenomenon might have been due to increased salt content of the skin caused by the rofecoxib, resulting in increased water-binding capacity of keratin.

Musculoskeletal

An in vitro experiment on cartilage explants from patients with osteoarthritis showed upregulation of COX-2 activity, which may be linked to cartilage repair (121). If this is true, long-term use of COX-2 inhibitor NSAIDs could have harmful effect on joints. Preliminary data suggest that these drugs are efficacious in osteoarthritis, at least in the short term.

Reproductive system

Many reproductive processes (ovulation, fertilization, implantation, decidualization, and parturition) depend on prostaglandin ligand–receptor interactions. It is therefore not surprising that selective COX-2 inhibition has a negative local effect on ovulation, resulting in delayed follicular rupture and infertility, without affecting peripheral hormonal cyclicity (122,123).

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There have been several case reports that non-selective NSAIDs (diclofenac, naproxen, piroxicam) can cause infertility, attributed to "luteinized unruptured ovarian follicles" syndrome (124–126). Now the syndrome has been documented in a double-blind, randomized, placebo-controlled study, in which women were assessed over two menstrual cycles while taking rofecoxib (123). Women who are trying to become pregnant should avoid taking any NSAIDs if possible, and those who need one for a chronic rheumatic disorder should be aware of possible infertility; in such cases further investigation is not required, as withdrawal of the drug restores fertility.

Immunologic

There is considerable difficulty and controversy in identifying and classifying allergic reactions to NSAIDs, for many reasons (127). First, the difficulty in making a definite diagnosis in patients who have these reactions without provocative challenge with the suspected drug and other NSAIDs. Secondly, reactions are characterized by a large spectrum of target organ responses to NSAIDs, and the same drug can cause different types of reactions in different organs in the same or different individuals. Thirdly, a patient can have a similar reaction to a structurally different NSAID. Finally, reports of these reactions include different, often imprecise, terms, making interpretation difficult. It is worth evaluating the safety of new coxibs in patients who cannot tolerate non-selective NSAIDs.

Anaphylaxis due to celecoxib has been described (SEDA 26, 121). Life-threatening anaphylaxis, with urticaria, angioedema, and bronchospasm, has also been described 30 minutes after a dose of celecoxib for arthritis of the hip (128).

Allergic vasculitis has been reported in association with various NSAIDs, and has been attributed to celecoxib (129,130), including one case with a fatal outcome (131).

Whether allergic reactions to celecoxib occur more often in patients who report a previous reaction to sulfonamides, and should therefore be contraindicated in such patients, is still unknown (132).

Angioedema has been attributed to rofecoxib (SEDA-26, 121).

- A 60-year-old man developed angioedema after taking two doses of rofecoxib 12.5 mg 18 and 12 hours before (133). Despite intensive treatment he developed pulmonary hemorrhagic edema and died a day later. He had fibrotic lung disease, which may have predisposed him to the lethal event.

The tolerability of rofecoxib in patients with cutaneous allergic and pseudoallergic adverse reactions to non-selective NSAIDs has been confirmed in a study in 139 patients with NSAID-induced adverse reactions: 60 with urticaria alone (43%), 34 with angioedema (25%), 34 with angioedema plus urticaria (2.9%), and 2 with Stevens–Johnson syndrome (1.4%) (134). They all underwent a single-blind, placebo-controlled oral challenge with increasing doses of rofecoxib, and 138 of them tolerated it without adverse reactions. Only one had mild urticaria on the arms. Rofecoxib may be a useful alternative in patients with NSAID hypersensitivity.

Anaphylaxis

Among the anaphylactic reactions to NSAIDs that result in different types of reaction (urticaria, angioedema, asthma, or hypotension), there have been very few reports of anaphylactic shock. However, anaphylaxis has been described in patients taking celecoxib (135,136) or rofecoxib (137). Rofecoxib caused anaphylaxis in a patient who had had a similar reaction to diclofenac, suggesting that COX-2 inhibitors may be not safe in all individuals who have adverse reactions to non-selective COX inhibitors. It also suggests that different mechanisms may be involved in patients with asthma and in those with anaphylactoid reactions to NSAIDs.

Sulfonamide-like allergic adverse reactions

Concerns that COX-2 inhibitors may be associated with an increased risk of allergic reactions in patients with a history of sulfonamide hypersensitivity arise from the molecular structures of these compounds (SEDA-24, 119) (138).

A sulfur component is necessary for the receptor binding of both celecoxib and rofecoxib, but their structures differ and they have different potentials for causing allergic reactions. Consequently, celecoxib is thought to be contraindicated in patients with a history of allergy to sulfonamides. The available data on the immunological tolerability profile of celecoxib and rofecoxib are scanty but merit attention.

Sulfonamide-like adverse drug reactions seem to occur more frequently with celecoxib than with rofecoxib, according to a report from Sweden (139). The investigators identified a profile of 19 typical sulfonamide-like adverse reactions from published papers and the WHO Adverse Drug Reactions database from 1968 to 2000, and compared this profile with reported adverse drug reactions associated with celecoxib and rofecoxib. The WHO database contained 11 514 reports about celecoxib describing 21 292 suspected adverse drug reactions and 10 200 reports about rofecoxib describing 18 585 suspected drug reactions. The relative reporting rate of sulfonamide-like adverse drug reactions was almost twice as high for celecoxib as for rofecoxib (RR = 1.8; 95% CI = 1.6, 1.9) for all reports and for reports that listed a COX-2 inhibitor as the only suspected drug. The reporting rate for 15 of the 19 sulfonamide-like adverse drug reactions was higher for celecoxib than for rofecoxib, with significant differences for rash (RR = 2.3; CI = 2.0, 2.6), urticaria (RR = 2.0; CI = 1.6, 24), Stevens–Johnson syndrome (RR = 3.6; CI = 1.4, 12), and photosensitivity (RR = 2.4; CI = 1.5, 4.0). Fatal adverse drug reactions fitting the typical sulfonamide profile also occurred more often with celecoxib than with rofecoxib (1.8; CI = 0.9, 4.0).

Even though serious sulfonamide reactions are rare, their clinical impact warrants close monitoring as more data become available, and physicians should be aware of possible sulfonamide allergy when prescribing COX-2 inhibitors, in particular celecoxib.

There have been single case reports of sulfonamide-like allergic reactions in patients taking celecoxib; in two cases sulfonamide allergy was ignored and was discovered only after an adverse reaction to celecoxib (140) or rofecoxib (141) had occurred.

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Urticaria and angioedema

Of 110 patients with a history of urticaria and angioedema triggered by one or more non-selective NSAIDs, who were submitted to 184 single-blind, placebo-controlled oral challenges with the suspected NSAID, patients with a positive challenge underwent further oral challenge with various COX-2 inhibitors (celecoxib and rofecoxib, and also nimesulide and meloxicam, which are relatively selective COX-2 inhibitors) (142). The maximal challenge doses were celecoxib 200 mg, rofecoxib 25 mg, meloxicam 15 mg, and nimesulide 100 mg. Reactions (expressed as a percentage of tested patients with a positive test) varied among the COX-2 inhibitors: 33% (10/30) for celecoxib, 21% (16/75) for nimesulide, 17% (8/46) for meloxicam, and 3% (1/33) for rofecoxib. This suggests that the degree of cross-reactivity of COX-2 inhibitors was related to the degree of in vitro COX-1 inhibition, since meloxicam, nimesulide, and celecoxib inhibit COX-1 to a similar extent (143). The results also suggested that the most selective COX-2 inhibitor (rofecoxib) might be relatively safe in a patient with NSAID-induced urticaria/angioedema.

In another study, 34 patients with a history of urticaria and/or angioedema after ingestion of at least two chemically unrelated non-selective NSAIDs, 22 of whom also had chronic urticaria, all underwent a single-blind, placebo-controlled oral tolerance test with rofecoxib (12 and 25 mg 1 hour apart) (144). Rofecoxib caused urticaria and/or angioedema in 6/34 patients (18%), with no difference between patients with or without a history of chronic urticaria.

There was even better tolerability of rofecoxib in another study in 33 patients with documented urticaria/angioedema after ingestion of two different NSAIDs (145). The patients underwent provocative tests with increasing doses of rofecoxib (from 6.25 to 25 mg); at the end of the challenge all tolerated rofecoxib 25 mg.

Other single case reports have supported the evidence of better tolerability of COX-2-selective inhibitors (in particular rofecoxib) in patients with a history of urticaria/angioedema (64,146). However, contrasting data have shown cross-reactivity of celecoxib with other NSAIDs and between celecoxib and rofecoxib (147).

Why are COX-2-selective drugs better tolerated? The mechanisms underlying intolerance to chemically unrelated NSAIDs are unknown, but it has been hypothesized that intolerant patients may have exaggerated sensitivity to the effects of leukotrienes, which are more active than histamine in inducing wheal and flare reactions. Blockade of both COX-1 and COX-2 by non-selective NSAIDs increases the production of leukotrienes by the lipoxygenase pathway, whereas COX-2-selective agents do not increase the production of LTB_4 or cysteinyl LTS. However, this may not be the only pathogenic mechanism, as some drugs probably trigger histamine release from mast cells and basophils non-specifically, and others may trigger immunological cross-reactivity. Overall, the above-mentioned studies and clinical experience suggest that urticaria and angioedema can occur with COX-2 inhibitors, albeit with a lower frequency than with non-selective NSAIDs.

Second-Generation Effects

Fetotoxicity

A single case report supports the hypothesis that a COX-2-selective NSAID might have the efficacy of indometacin as a tocolytic agent without its adverse effects in the fetus (148).

Drug–Drug Interactions

Lithium

A possible interaction of rofecoxib with lithium has been reported (149).

- A 73-year-old man with manic-depressive illness, who had taken lithium for 40 years, underwent coronary bypass surgery and was given long-term warfarin. He developed signs of lithium intoxication (confusion, irritability, tremor, and gait disturbance) after having taken rofecoxib 12.5 mg/day for 9 days for arthritis. Rofecoxib had been chosen in order to avoid a possible drug interaction with warfarin. Lithium and rofecoxib were withdrawn and the signs resolved within 1 week. His serum lithium concentration was 1.5 mmol/l and his serum creatinine 1430 μmol/l.

Both lithium and rofecoxib have been associated with nephrotoxicity, and it is likely that lithium intoxication was caused by concomitant administration of rofecoxib, causing a reversible reduction in renal function.

Propofol

A single perioperative dose of parecoxib did not alter the disposition or the clinical effects of a bolus of propofol (150).

Sex hormones

Rofecoxib did not cause any clinically important changes in ethinylestradiol and norethindrone pharmacokinetics in 18 subjects (151).

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Cremophor

General Information

Cremophor is a non-ionic solubilizer and emulsifier that is made by reacting ethylene oxide with castor oil (1). It is a pale yellow oily liquid consisting of a mixture of components, primarily polyethylene glycol conjugates. Fatty acid esters of polyethyleneglycol are also present, as well as hydrophilic polyethylene glycols and ethoxylated glycerol. It is present in intravenous formulations of the anticancer drugs teniposide and paclitaxel. The paclitaxel formulation consists of 6 mg/ml in 50% ethanol and 50% Cremophor. Thus, a patient receiving paclitaxel in the widely used dose of 175 mg/m^2 will also receive about 14 ml/m^2 of Cremophor.

Anaphylactoid reactions can occur after the intravenous administration of Cremophor (SEDA-22, 526) when it is used as a diluent of alfadolone/afaxolone (SED-11, 211) (2), ciclosporin (3), paclitaxel (4), propanidid (SED-11, 211) (5,6), teniposide (7), and vitamin K (8,9). Cardiorespiratory arrest after intravenous miconazole has been attributed to the histamine-releasing properties of Cremophor (10).

In a study of the effects of Cremophor after 74 cycles of doxorubicin in Cremophor in 39 patients, there were no major hypersensitivity reactions to Cremophor, and no patients had their infusion discontinued or modified (11). Adverse effects that were considered to be potentially related to Cremophor were cutaneous (pruritus, flushing, or rashes), hypotension or dizziness, and headache. Because of the subjective nature of some of these symptoms, they were classified as grade 1 (mild and not requiring treatment or interfering with function), grade 2 (moderate, causing some impairment of function but not requiring hospitalization), or grade 3 (severe, requiring hospitalization or causing significant interference with function). No grade 2 or 3 toxicity was recorded at the first three doses. One patient at level 4A had grade 2 dizziness, one patient at level 5 had grade 2 rash, one patient at level 5 had grade 3 headache and grade 3 pruritus, and one patient at level 6 had grade 3 hypotension and grade 3 rash. In no patient did these symptoms occur with doxorubicin alone, confirming their relation to Cremophor. These symptoms began several hours to days after Cremophor and persisted for 1–2 weeks, with the exception of the patient at level 5, whose pruritus gradually resolved over 3 months after discontinuing Cremophor.

Organs and Systems

Hematologic

The hematological toxicity of Cremophor has been evaluated after 74 cycles of doxorubicin in Cremophor in 39 patients (11). The principal effect was neutropenia. The incidence of grade 4 neutropenia increased with increasing doses of Cremophor from 1 to 60 ml/m^2. Grade 4 neutropenia occurred in zero of three patients at 1 ml/m^2, one of four patients at 7.5 ml/m^2, four of six patients at 15 ml/m^2, and 11 of 16 patients at 30 ml/m^2. When the dose of doxorubicin was reduced, grade 4 neutropenia occurred in one of six patients at 45 ml/m^2 and two of four patients at 60 ml/m^2. Febrile neutropenia occurred in one patient at 15 ml/m^2, three patients at 30 ml/m^2, one patient at 45 ml/m^2, and one patient at 60 ml/m^2. There was one death from neutropenic sepsis at 30 ml/m^2.

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Cromoglicate sodium

General Information

Cromoglicate disodium salt (cromoglicate sodium) is available as a powder for inhalation. Each capsule contains 20 mg. The usual dose is 1 capsule inhaled four times daily. It is also dispensed in a multidose-pressurized aerosol delivering 1 or 5 mg per actuation. A 1.0% nebulizer solution (20 mg dissolved in 2 ml of distilled water) is also available. It is nebulized over 15 minutes and has the same effect as 20 mg given as a powder (1). Cromoglicate is taken regularly in chronic asthma and when it is effective it improves symptoms and lung function and reduces the need for bronchodilators. It has a steroid-sparing effect and should be tried before inhaled steroids are used,

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especially in children. It is a prophylactic drug and is not effective in acute asthma.

A liquid form is also available for use in rhinitis and ocular conditions. When applied topically to the eye cromoglicate is effective in the treatment of vernal keratoconjunctivitis (vernal catarrh, spring catarrh), allergic conjunctivitis, and hay fever.

Cromoglicate inhibits mast-cell degranulation and histamine release induced by phospholipase A2, but does not interfere with the interaction of antigen and reaginic antibodies. Evidence is accumulating that it has an important stabilizing action on leukocytes, apart from mast cells, such as neutrophils, eosinophils, and monocytes, and that it also affects nerve reflexes in the lung (2).

The overall incidence of adverse effects was about 2% when using inhaled cromoglicate (3). Most of the observed adverse effects are mild and transient and do not require withdrawal of therapy. Adverse effects such as laryngeal edema, swollen parotid glands, bronchospasm, joint swelling, nausea, cough, headache, nasal congestion, rash, and urticaria have been reported in only one in 10 000 patients (SEDA-12, 142). The American Academy of Allergy and Immunology reported two 10-year safety reports involving 424 and 85 patients. These emphasized the safety of long-term treatment with cromoglicate. The only serious adverse effects were three cases of pulmonary infiltration and eosinophilia (SEDA-6, 171). In another series of 375 patients, only eight experienced adverse reactions; these included dermatitis with pruritus, myositis, and gastroenteritis (SEDA-4, 120).

While no systemic or severe adverse reactions have been attributed to ocular cromoglicate even after as long as 8 months of therapy, transient local stinging and burning have been reported in 13–77% of patients who used the original formulation of this drug, which contained 2-phenylethyl alcohol as a preservative. These effects regressed during continued treatment and can vary greatly depending on both the individual and the underlying disease. Ocular cromoglicate without 2-phenylethyl alcohol has been reported to be more effective than formulations that contain this preservative; stinging, leading to increased lacrimation, dilutes the drug and reduces the time for which it is retained in the conjunctival sac. The desired topical effects of cromoglicate are therefore reduced if it is formulated with 2-phenylethyl alcohol.

Organs and Systems

Cardiovascular

- A woman developed peripheral eosinophilia and pericarditis with cardiac tamponade after using cromoglicate (SEDA-4, 120). Cellular and humoral sensitivity to cromoglicate were demonstrated and she recovered following pericardiocentesis.

Respiratory

Initial bronchospasm, seen in some patients, is thought to be due to the irritant effect of the dry powder. This can be prevented by prior inhalation of a beta$_2$-adrenoceptor agonist. In one case, a severe asthmatic reaction occurred and was thought to be reflexogenic in origin (SEDA-4, 120). Inhalation of nebulized cromoglicate by asthmatic children causes a reduction in forced mid-expiratory flow rate equivalent to that seen with distilled water (SEDA-17, 205). Bronchospasm and breathlessness as a result of hypersensitivity are rare, but do occur.

Rarely, a hypersensitivity reaction can cause bronchospasm or aggravation of existing asthma and a progressive fall in FEV_1, resulting in dyspnea (4).

Three cases of pulmonary infiltration with eosinophilia were reported among a total of 509 patients treated with cromoglicate (SEDA-6, 171).

- A 7-year-old asthmatic child, sensitive to timothy grass, used inhaled cromoglicate for 1 week and developed cyanosis, hypotension, and cardiopulmonary arrest. IgE involvement was demonstrated by passive transfer of the patient's serum to the mother (5).

Ear, nose, throat

Intranasal use of cromoglicate can cause sneezing and nasal congestion. There is nasal irritation in 35% of patients, swollen sore eyes in 17%, and a sore throat in 21%. The sensitive nasal mucosa can be susceptible to irritation by any nasal spray (6).

Nervous system

Most investigators have referred to headaches, but no clear relation to cromoglicate has been seen in any study. Dizziness has been reported, but may be connected with hyperventilation during the inhalation of the powder.

Sensory systems

The irritant effect of cromoglicate can cause lacrimation and inflammatory changes in the eye.

An allergic reaction to cromoglicate eye drops has been reported. After application of the eye-drops intense itching, burning, redness, and severe swelling of both conjunctivae developed immediately. Skin prick tests and conjunctival provocation with pure cromoglicate were positive. Circulating IgE-specific antibodies to cromoglicate were demonstrated by RAST (7).

Gastrointestinal

Nausea can occur. Esophagitis following inhalation of cromoglicate has been reported. It was much improved by prophylactic antacids given before each inhalation (SEDA-5, 169). In a patient with lactose intolerance, cromoglicate disodium capsules with lactose produced nausea, bloating, and flatulence. Lactose-free formulations produced no such symptoms (SEDA-13, 135).

Liver

Minor abnormalities of liver function have been described when cromoglicate is used orally for ulcerative colitis (8).

- A 45-year-old woman developed liver disease, vasculitis, and peripheral eosinophilia (SEDA-4, 120). Liver

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biopsy showed inflammatory changes with infiltration of eosinophils. Withdrawal of the drug markedly improved the symptoms.

Skin

Skin reactions including dermatitis with pruritus have been reported in patients using cromoglicate. Urticaria or maculopapular rashes occur rarely.

Musculoskeletal

Bone mineral density was measured after 7.4 months in 49 asthmatic children, 38 of whom took inhaled beclomethasone, average daily dose 276 μg, and 11 sodium cromoglicate, average daily dose 30 mg. Children who had used beclomethasone had grown as much as those who used sodium cromoglicate. Trabecular and cortical bone mineral density in the proximal forearm and lumbar spine increased to the same extent in both groups.

The effects of fluticasone 50 μg bd or cromoglicate 20 mg qds on growth over 12 months have been studied in 122 asthmatic children aged 4–10 years (9). The mean height velocity was 6 cm/year with fluticasone and 6.5 cm/year with sodium cromoglicate. There was no significant treatment difference in the mean 24-hour urinary free cortisol concentrations at 6 or 12 months. Mean predicted peak expiratory flow rate improved over 1 year in both groups, but to a greater extent with fluticasone. Fluticasone was more effective than sodium cromoglicate, with fewer withdrawals and greater improvement in lung function.

Immunologic

Immunological reactions to cromoglicate can involve the pericardium, the lung, the eye, the nasal mucosa, the skin, the joints, and the liver. Rarely, a hypersensitivity reaction can cause fever (4). A survey of the world literature up to 1982 found 13 cases of facial rash, urticaria, and/or generalized dermatitis, and one of nasal congestion. In 19 patients there was bronchospasm and/or pulmonary edema, eventually culminating in shock. Four cases of eosinophilic or granulomatous pulmonary infiltration, one of liver disease and vasculitis, one of pericarditis, and three of polymyositis were reported.

IgE and/or specifically reactive lymphocytes do not mediate many of the adverse reactions to cromoglicate, which mimic allergic processes of the immediate or delayed type. These reactions fulfilled the criteria that characterize pseudo-allergic reactions (3,10). There is a much higher incidence of such adverse reactions when cromoglicate is used orally in the treatment of food allergy, as high as 29% of cases treated (3,10).

The US Food and Drug Administration has issued a report (SEDA-7, 1) on a suspected case of cromoglicate-induced lupus-like syndrome. Treatment with cromoglicate for 6 months resulted in arthritis, positive LE cells, and a positive antinuclear factor. After withdrawal of cromoglicate, the signs and symptoms regressed. Although this does not prove cause and effect, the report suggests a similarity between lupus-like syndrome and some of the adverse reactions that were listed earlier in the US data sheet (SEDA-3, 48).

Second-Generation Effects

Teratogenicity

Cromoglicate probably does not reach the fetus after inhalation, as systemic blood concentrations are extremely low (11). Animal testing did not show any teratogenic effects.

A critical review of drug therapy for allergic rhinitis during pregnancy has been published (12). Mast cell stabilizers are not teratogenic and can be considered as excellent first-line choices to treat allergic conjunctivitis and rhinitis. However, any recommendation should be accompanied by informed consent.

Drug Administration

Drug administration route

No systemic or severe adverse reactions have been attributed to ocular sodium cromoglicate, even after as long as 8 months of therapy. However, transient local stinging and burning were reported in 13–77% of patients who used the original formulation of this drug, which contained 2-phenylethyl alcohol as a preservative. These effects regressed during continued treatment and varied greatly depending on the individual and the underlying disease. Ocular sodium cromoglicate without 2-phenylethyl alcohol has been reported to be more effective; stinging, leading to increased lacrimation, dilutes the drug and reduces the time it is retained in the conjunctival sac. The desired topical effects of sodium cromoglicate are therefore reduced if it is formulated with 2-phenylethyl alcohol.

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Crotetamide

General Information

Crotetamide is a mixture in equal parts by weight of cropropamide and crotethamide. It has similar actions to doxapram hydrochloride and has been used as a respiratory stimulant in man as well as illicitly in racehorses. When crotetamide was given intravenously, the incidence of adverse effects was 25% (1–3).

Organs and Systems

Nervous system

Flushing, paresthesia, headache, restlessness, muscle twitching, tremor, and dyspnea have been ascribed to crotetamide. Convulsions have been reported but are rare.

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Crystalloids

General Information

Potassium and sodium salts are given intravenously in solutions to replace body fluids and electrolytes. Adverse effects are rare and usually limited to the effects of overtransfusion.

Microwave heating of crystalloid fluids has been recommended as a method of correcting hypothermia during resuscitation. Severe full-thickness burns and venous thrombosis occurred after infusion of over-heated crystalloid fluid in the management of a ruptured aortic aneurysm in a 75-year-old man (1). Measuring the temperature of the fluid before starting the infusion is necessary to avoid this complication.

Organs and Systems

Nervous system

Central pontine myelinolysis has been reported in patients given intravenous saline (2). Pontine and extrapontine myelinolysis are generally considered to be linked with rapid correction of severe hyponatremia, for example in the treatment of hyponatremia in patients with so-called hyperosmolar non-ketoacidotic hyperglycemia reference. Neurological deterioration is likely to result. It is not certain what rate of sodium repletion is safe. The best data available suggest that correction should not exceed 12 mmol/l per day, although more rapid correction may be safe. The duration of treatment also seems to be important: 12 mmol/l per day may be excessive if continued for more than 2 or 3 days.

Accurate control of the serum sodium is a major difficulty in the setting of severe hyponatremia. The administration of an amount of hypertonic saline calculated to raise the sodium to mildly hyponatremic concentrations can result in serum sodium in the normonatremic or even hypernatremic range. The serum sodium should not be allowed to raise more that 12 mmol/l over the first 24 hours, and even less over each subsequent 24-hour period. It is clear that an amount of saline calculated to raise the serum sodium by a given amount affects individuals differently. This makes frequent monitoring of serum sodium mandatory.

Gastrointestinal

Gastric and upper small bowel necrosis have been described after oral ingestion of massive amounts of concentrated saline (1 kg of sodium chloride in 660 ml of water) as an emetic.

Second-Generation Effects

Pregnancy

The value of intravenous crystalloid administration in preventing hypotension developing during spinal anesthesia in parturition has been questioned (3). Moreover, the association between increasing crystalloid volume and reducing postpartum colloid osmotic pressure raises concerns about the risks of maternal and fetal pulmonary edema. In a comparative study of the dose–response effects of crystalloid fluids before spinal anesthesia, all groups had a fall in mean arterial blood pressure and systemic vascular resistance index, measured using non-invasive thoracic impedance monitoring (3). The extent of the fall did not differ according to the volume given. There were no differences in neonatal colloid osmotic pressure with varying preload. No apparent benefit is to be gained in healthy parturients by giving crystalloid in volumes up to 30 ml/kg.

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Cucurbitaceae

See also Herbal medicines

General Information

The genera in the family of Cucurbitaceae (Table 1) include cucumbers, gourds, and melons.

Bryonia alba

Bryonia alba (white bryony) contains toxic triterpenoids called cucurbitacins.

Adverse effects

Cucurbitacins are drastic laxatives and emetics and can cause the symptoms of food poisoning (1).

Citrullus colocynthis

The dried pulp of the fruit of *Citrullus colocynthis* (colocynth) is a drastic laxative, which contains toxic cucurbitacins.

Table 1 The genera of Cucurbitaceae

Apodanthera (apodanthera)
Benincasa (benincasa)
Brandegea (starvine)
Bryonia (bryony)
Cayaponia (melonleaf)
Citrullus (watermelon)
Coccinia (coccinia)
Ctenolepis (ctenolepis)
Cucumis (melon)
Cucumeropsis (cucumeropsis)
Cucurbita (gourd)
Cyclanthera (cyclanthera)
Doyerea (doyeria)
Ecballium (squirting cucumber)
Echinocystis (echinocystis)
Echinopepon (balsam apple)
Fevillea (fevillea)
Hodgsonia (hodgsonia)
Ibervillea (globeberry)
Lagenaria (lagenaria)
Luffa (luffa)
Marah (manroot)
Melothria (melothria)
Momordica (momordica)
Psiguria (pygmymelon)
Sechium (sechium)
Sicana (sicana)
Sicyos (burr cucumber)
Sicyosperma (sicyosperma)
Telfairia (telfairia)
Thladiantha (thladiantha)
Trichosanthes (trichosanthes)
Tumamoca (tumamoca)

Adverse effects

A man experienced vomiting, colicky pain, and bloody diarrhea after self-medication with *C. colocynthis* (2). Hemorrhagic colitis secondary to ingestion of colocynth has been reported (2). In three cases of toxic acute colitis 8–12 hours after ingestion of colocynth for ritual purposes, the prominent clinical feature was dysenteric diarrhea; colonoscopic changes included congestion and hyperemia of the mucosa with abundant exudates but no ulceration or pseudopolyp formation; there was rapid recovery within 3–6 days, with normal endoscopy at day 14 (3).

Ecballium elaterium

Ecballium elaterium (squirting cucumber) contains toxic cucurbitacins, which are violent purgatives. It is used in the Mediterranean as a purgative and in treating sinusitis.

Adverse effects

Intranasal use of *E. elaterium* has been associated with Quincke's edema (4) and with fatal cardiac and renal failure (5).

A report from a poisons unit in Israel included 13 patients who had used the juice of the squirting cucumber, either orally or topically, for unreported reasons (6). They subsequently had edema of the pharynx, dyspnea, drooling, dysphagia, vomiting, and conjunctivitis. With symptomatic treatment they recovered within a few days.

In a retrospective chart analysis in a Greek ENT department 42 patients with allergic reactions to *E. elaterium*, including upper airway edema, were identified (7). Treatment with glucocorticoids and antihistamines resulted in full recovery in all cases.

Momordica charantia

Oral formulations of *Momordica charantia* (karela fruit, bitter melon) have hypoglycemic activity in non-insulin dependent diabetes mellitus (8,9), and can interfere with conventional treatment with diet and chlorpropamide (10). In 15 patients aged 52–65 years a soft extract of *M. charantia* plus half doses of metformin or glibenclamide or both in combination caused hypoglycemia greater than that caused by full doses during treatment for 7 days (11). Subcutaneous injection of a principle obtained from the fruit may lower blood glucose concentrations in juvenile diabetes.

Adverse effects

Metabolism

M. charantia can cause hypoglycemic coma and convulsions in children (12).

Drug interactions

M. charantia inhibits P glycoprotein in vitro and drug interactions can therefore be expected (13).

Sechium edule

The tuber of *Sechium edule* (chayote) is valued as a potent diuretic by Latin American populations. Its use as a decoction by a pregnant woman suffering from pedal edema may have been the cause of a severe case of hypokalemia (14).

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Cuprammonium cellulose

General Information

Cuprammonium cellulose is a constituent of some dialysis membranes (1).

Organs and Systems

Immunologic

Anaphylaxis as an adverse effect of hemodialysis has been analysed from records of about 260 000 courses of dialysis treatment, at three centers. There were 21 severe reactions over the 10.5-year period of the survey, all highly suggestive of anaphylaxis (2). Reactions occurred within minutes of initiating dialysis and were characterized by cardiopulmonary, mucocutaneous, and/or gastrointestinal tract symptoms. Four respiratory arrests occurred and there was one death. When the individual histories and treatments were analysed, there was strong evidence that hollow-fiber dialysers made of cuprammonium cellulose were responsible. No obvious factors could be found to identify predisposed patients; suboptimal rinsing of the cuprammonium cellulose hollow-fiber dialysers before use may have been responsible for some of the reactions. Repeated dialysis anaphylaxis in one patient has been reported (3).

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Cupressaceae

See also Herbal medicines

General Information

The genera in the family of Cupressaceae (Table 1) include cedar, cypress, and juniper.

Juniperus communis

Extracts of *Juniperus communis* and other species are used in cosmetics, as hair conditioners, and in fragrances (1). The volatile oil distilled from the berries of *Juniperus communis* (juniper) can act as a gastrointestinal irritant. It is said that excessive doses can cause renal damage, and use during pregnancy is discouraged because of a fear that this might also stimulate the uterus.

Table 1 The genera of Cupressaceae

Callitris (cypress pine)
Calocedrus (incense cedar)
Chamaecyparis (cedar)
Cupressus (cypress)
Cupressocyparis
Juniperus (juniper)
Platycladus (platycladus)
Tetraclinis (tetraclinis)
Thuja (red cedar)

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Cyanoacrylates

General Information

Cyanoacrylate (Histoacryl) is a tissue adhesive used in duraplasty. The sites at which it is used should be carefully chosen. Cyanoacrylates are also in use for embolization of arteriovenous malformations in the brain. The risk of this procedure is the creation of pulmonary emboli after acrylate glue injection, particularly when delivery systems without flow arrest are used in high-flow vascular brain lesions. Techniques using acetic acid to delay polymerization time and "sandwich" techniques, in which glue is pushed with dextrose, appear to be more likely to cause this complication (1).

Organs and Systems

Immunologic

Infection can develop in the frontal area and at the lateral base of the skull after the use of cyanoacrylates, even after a symptom-free interval of several years; the lesions can be characterized by infected granular nodules, chronic sinusitis, or otogenic meningitis (2).

References

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Cycadaceae

See also Herbal medicines

General Information

The family of Cycadaceae contains the single genus *Cycas*.

Cycas circinalis

The seeds of *Cycas circinalis* (false sago palm, queen sago) contain the non-protein amino acid beta-*N*-methylamino-L-alanine, which is similar to the neurotoxic amino acid beta-*N*-oxalylamino-L-alanine. Monkeys fed this amino acid develop a syndrome that closely resembles the disease that is known by the Chamorros of Guam as lytico-bodig, a complex of amyotrophic lateral sclerosis parkinsonism dementia that occurs in Guam, where the seeds of *C. circinalis* are a traditional staple of the indigenous diet (1). Consumption of flying foxes may also generate sufficiently high cumulative doses of *Cycas* neurotoxins, since the flying foxes forage on cycad seeds (2). The risk may be increased by the use of poultices prepared from cycad seeds as a topical cure for skin lesions in Eastern Irian Jaya (New Guinea), Indonesia.

Adverse effects

In a retrospective chart review at the Poison Control Center in Taiwan from 1990 to 2001 there were 21 cases of *Cycas* seed poisoning (3). The patients had taken 1–30 seeds for cosmetic use (5%), as edible food (70%), or for health promotion (10%), cancer prevention (10%), and gastrointestinal discomfort (5%). All had eaten the seeds after washing and cooking them. The time from ingestion to the onset of symptoms ranged from 30 minutes to 7 hours (mean 2.8 hours). All the patients except one presented with gastrointestinal disturbances, and 90% sought medical care at the emergency department. Severe vomiting was the most striking symptom. There was no respiratory depression. Within 24 hours all had recovered. Six patients had blood cyanide or thiocyanate concentrations measured, and although they were higher than normal, they did not reach the toxic range.

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Cyclandelate

General Information

The spasmolytic action of cyclandelate, an ester of mandelic acid, was described as early as 1959, but only in later years have its properties been more fully investigated. It appears to act as a calcium channel blocker in smooth muscle and platelets, this effect being partly due to inhibition of phosphodiesterases. It also produces increased deformability of erythrocytes, the mechanism of which is so far unknown, although phosphodiesterase inhibition may again be responsible. Cyclandelate also reduces the activity of the rate-limiting enzyme in the biosynthesis of cholesterol (HMG-CoA), and its "antidiabetic" properties may be due to inhibition of aldose reductase.

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Cyclandelate is mainly given to elderly patients with mild to moderate cognitive impairment; it is also used in the prophylaxis of migraine. Its efficacy is not impressive (SEDA-21, 215) (1).

Major adverse effects have not been reported with dosages of 1.6 g/day. Gastrointestinal upset, flushing, and tingling are rare and minor complaints. Even elderly patients apparently tolerate 3.2 g/day without problems (SEDA-9, 189).

Reference

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Cyclazocine

General Information

Cyclazocine is an agonist at OP_2 (κ) opioid receptors and it is its affinity for these receptors that is thought to account for disruption of the normal sleep pattern, urination, and sustained arousal that it causes (1). Visual disturbances and racing thoughts have also been reported and are subject to tolerance (2).

Long-Term Effects

Drug withdrawal

Abrupt withdrawal resulted in a classical withdrawal syndrome, but without drug-seeking behavior (2). Adverse effects could be minimized by gradual increments in daily dosage over 3 weeks.

References

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Cyclizine

See also Antihistamines

General Information

Cyclizine is a first-generation antihistamine, a piperazine derivative, with sedative and antimuscarinic activity, although its sedative effects are not marked.

Organs and Systems

Nervous system

Four cases of dystonic reactions caused by single doses of cyclizine have been reported (1–4).

Long-Term Effects

Drug abuse

Abuse of cyclizine in teenagers has been described (5).

References

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Cyclobenzaprine

General Information

Cyclobenzaprine is a centrally acting skeletal-muscle relaxant, claimed to be effective in providing relief of muscle spasm, pain and tenderness, and in reducing the limitations imposed thereby on normal daily activities. The recommended total oral daily dose is 10–30 mg (1). It is structurally similar to the tricyclic antidepressants and adverse effects similar to those seen with the tricyclic antidepressants are therefore to be expected.

The most common adverse effects of cyclobenzaprine are somnolence, dry mucous membranes, dizziness, and confusion. Less commonly, tachycardia, dysarthria, disorientation, and hallucinations have been reported (2).

Organs and Systems

Cardiovascular

Cyclobenzaprine can occasionally cause marked arteriolar spasm due to increased adrenergic tone, precipitating Raynaud's syndrome (SEDA-6, 132).

Psychological, psychiatric

Rarely, manic psychosis can be activated in patients with bipolar affective disorders (3).

First-onset paranoid psychosis has also been reported (4).

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- A 36-year-old woman with no past psychiatric problems took 23 tablets of cyclobenzaprine (10 mg each) over 6 weeks to ease back pain resulting from a back injury. She developed insomnia, reduced appetite, poor concentration, irritability, disorganized thoughts, persecutory delusions, and auditory hallucinations. Cyclobenzaprine was withdrawn and a course of loxapine was started, leading to rapid and complete resolution of her agitation and psychotic symptoms within 72 hours. Loxapine was subsequently quickly withdrawn with no ill effects and she recovered fully.

The authors thought that this psychotic episode was related to cyclobenzaprine, in view of the temporal relation of the symptoms to the administration of cyclobenzaprine and their rapid resolution after withdrawal.

Drug Administration

Drug overdose

Common effects of cyclobenzaprine overdose were lethargy, agitation, sinus tachycardia, and both hypertension and hypotension (5).

References

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Cyclofenil

General Information

Cyclofenil is a weak non-steroidal estrogen related to diethylstilbestrol. For a number of years it was used for inducing ovulation, but has lost favor; more recently there have been studies of its possible effects in Raynaud's phenomenon secondary to scleroderma (1).

Up to 2% of patients taking cyclofenil complain of nausea, vomiting, hot flushes, or headache. Mild abdominal pain has been reported in up to 18%, ovarian enlargement without cysts in 3%, and galactorrhea in 4%. There have been a few case reports of hemolytic anemia (SED-12, 1034) (2).

Organs and Systems

Liver

Cyclofenil can cause reversible mild cholestatic jaundice. The authors of a review of 30 patients with hepatic reactions to cyclofenil concluded that liver derangement due to cyclofenil is probably related to metabolic hypersusceptibility rather than to a direct toxic effect (3). There is a surprising lack of such reports from countries where cyclofenil was widely used: in France, at least, the number of cases of hepatitis occurring is known to have been much greater than that reported in print, and the drug was abandoned in that country in 1988.

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Cyclopentolate hydrochloride

General Information

Cyclopentolate is an anticholinergic drug used as a mydriatic.

Organs and Systems

Skin

Contact urticaria has been reported with cyclopentolate (1).

- A 72-year-old man, with a history of adverse reactions to sulfonamides, had erythema, edema, itching, burning of the eye, and an urticarial rash on his right cheek after the administration of several drugs to his right eye. Patch testing was performed and the cyclopentolate hydrochloride patch showed erythema after 15 minutes and an itching wheal after 30 minutes. No immediate or delayed reaction was observed with any of the other eye-drops. Patch tests with cyclopentolate hydrochloride in eight healthy volunteers were negative.

Reference

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Cyclophosphamide

General Information

Cyclophosphamide is an alkylating nitrogen mustard derivative mainly used in oncology patients (1) or in conditioning regimens for bone marrow transplantation. Its immunosuppressant properties have been used in organ transplantation and more often in chronic inflammatory disorders or autoimmune diseases.

Observational studies

Cyclophosphamide has been investigated in a wide range of diseases, but results in aplastic anemia and idiopathic pulmonary fibrosis have been disappointing. In a low dose (2 mg/kg/day), it produced minimal efficacy in 19 patients with idiopathic pulmonary fibrosis who had failed to respond to a glucocorticoid or who had had adverse effects (2). Moreover, 13 patients had cyclophosphamide-induced adverse effects, which required drug withdrawal in 9. The most frequent were severe gastrointestinal effects, leukopenia, and skin rashes. In another study, high-dose cyclophosphamide plus ciclosporin (50 mg/kg/day for 4 days) was compared with antithymocyte globulin plus ciclosporin in patients with severe aplastic anemia, but the trial was prematurely stopped after only 31 patients had been enrolled because of three early deaths in patients taking cyclophosphamide (3). Subsequent analysis showed excess morbidity and mortality in patients taking cyclophosphamide, with six proven or suspected cases of systemic fungal infection (including the three deaths) compared with no cases in the other group, but no significant difference in the hematological response rates between the groups. In addition, the durations of hospital stay, neutropenia, and antibacterial treatment were longer with cyclophosphamide. Based on these results, the authors concluded that cyclophosphamide should not be used in aplastic anemia.

General adverse effects

Common adverse effects observed at low doses of cyclophosphamide are similar to, but less frequent than, those observed in oncology patients. They include gastrointestinal disturbances (mostly nausea), hematological toxicity (mostly leukopenia), alopecia, and infectious complications (4,5).

Organs and Systems

Cardiovascular

Cardiac toxicity can be observed at high doses of cyclophosphamide (usually over 1.5 g/m^2/day), and acute myocardial necrosis or severe cardiac failure have been anecdotally reported after smaller dosages (SEDA-21, 386).

High-dose cyclophosphamide (120–200 mg/kg) can cause lethal cardiotoxicity, and severe congestive heart failure can develop 1–10 days after the first dose. Severe congestive heart failure is accompanied by electrocardiographic findings of diffuse voltage loss, cardiomegaly, pulmonary vascular congestion, and pleural and pericardial effusions. Pathological findings include hemorrhagic myocardial necrosis, thickening of the left ventricular wall, and fibrinous pericarditis.

Of 80 patients who received cyclophosphamide 50 mg/kg/day for 4 days in preparation for bone marrow grafting 17% had symptoms consistent with cyclophosphamide cardiotoxicity (6). Six died from congestive heart failure. Older patients were at greatest risk of developing cardiotoxicity.

In six patients who developed heart failure after high-dose conditioning therapy before stem cell transplantation, cyclophosphamide was suspected, despite the possible involvement of four drugs (7). The authors suggested monitoring high-risk patients.

Corrected QT dispersion was a predictor of acute heart failure after high-dose cyclophosphamide chemotherapy (5.6 g/m^2 over 4 days) in 19 patients (8).

Respiratory

Cyclophosphamide-induced pneumonitis has been described in 29 cases (9). Considering the widespread use of this drug over many years, this is a rare adverse effect. It does not clearly correlate with dosage (SED-8, 1112) (SED-13, 1122). From a review of 12 case reports and a retrospective analysis of six other patients (including four with Wegener's granulomatosis), in whom cyclophosphamide was thought to be the only causative factor, two distinct clinical patterns of pneumonitis with different prognoses were identified (10). Early-onset pneumonitis ($n = 8$) occurred acutely within 1–8 months of treatment, and complete recovery was noted after cyclophosphamide withdrawal and prednisone treatment. In contrast, late-onset pneumonitis ($n = 10$) developed insidiously over several months (eventually after cyclophosphamide withdrawal) in patients maintained taking low daily doses for months to years. These patients had progressive pulmonary fibrosis unresponsive to glucocorticoid therapy, and six died of respiratory failure. Radiological pleural thickening may be an early sign of late-onset lung toxicity.

Nervous system

Progressive multifocal leukoencephalopathy is sometimes associated with Wegener's granulomatosis, but one case occurred in a patient who was taking low-dose cyclophosphamide, with subsequent significant improvement on withdrawal of the drug (SEDA-19, 347).

Sensory systems

Blurred vision is sometimes reported after high intravenous doses of cyclophosphamide, and there has been one report of transient myopia that recurred after each monthly intravenous pulse (11).

Endocrine

Even low-dose intravenous cyclophosphamide can cause a syndrome that resembles inappropriate secretion of antidiuretic hormone, with severe hyponatremia and symptoms of water intoxication (SEDA-19, 347) (SEDA-21, 386). A direct effect on the renal tubules is likely, but no other nephrotoxic effects have been documented.

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Hematologic

Leukopenia, and less commonly thrombocytopenia or anemia, due to cyclophosphamide are typically dose-related in the therapeutic range. Cyclophosphamide-induced anemia has led to retinopathy presenting as striated hemorrhage of the retina (12).

Relative eosinophilia and increased interleukin-4 secretion were found in one study, suggesting that an immune deviation toward a type-2 T helper cell (Th2) response can occur (13). The clinical relevance of these findings as regards hypersensitivity reactions is unknown.

The idea that the degree of leukocyte suppression can be used to predict the success of adjuvant chemotherapy has been applied to combined treatment with cyclophosphamide, methotrexate, and 5-fluorouracil for breast cancer; the lower the nadir leukocyte count, the greater the incidence of metastatic disease-free survival (14).

Mouth and teeth

Unilateral necrosis of the tongue has been attributed to cyclophosphamide (15).

- A 62-year-old woman with invasive ductal carcinoma of the breast was treated with epirubicin and cyclophosphamide. She rapidly developed swelling and necrosis of the tongue and consequent airway obstruction necessitating tracheostomy. After excision of the necrosis, the swelling of the tongue and the airway obstruction resolved.

Because of the temporal connection between the necrosis and the chemotherapy, the authors suspected an adverse effect, although they could not exclude a paraneoplastic pathogenesis.

Gastrointestinal

Nausea and vomiting are infrequent with daily low-dose cyclophosphamide (4).

Two-thirds of patients treated with cyclophosphamide orally for 4 months plus intravenous 5-fluorouracil and methotrexate for breast cancer developed Barrett's epithelium (16), perhaps as a result of esophagitis, rather than through mucosal re-epithelialization by undifferentiated stem cells (17).

Toxic megacolon occurred after five cycles of epirubicin 70 mg/m^2, 5-fluorouracil 500 mg/m^2, and oral cyclophosphamide 75 mg/m^2 for 14 days (18). The clinical presentation included a raised erythrocyte sedimentation rate and a colonic diameter of greater than 9 cm; the outcome can be fatal.

Liver

Cyclophosphamide-induced, dose-related liver damage is probably caused as a result of impaired clearance of its metabolite acrolein (19). This causes raised serum transaminases (20) and can be aggravated by prior exposure to azathioprine.

Acute reversible cytolytic or cholestatic jaundice can also occur after low-dose cyclophosphamide in adults and children (SED-13, 1122) (SEDA-19, 347) (SEDA-20, 342) (SEDA-21, 386). Acute liver failure required liver transplantation in one patient (21). Although glucocorticoids were given concomitantly in most of these patients, no data are available to indicate a possibly increased hepatotoxic potential of this drug combination.

Hepatic veno-occlusive disease was attributed to low-dose cyclophosphamide in a 2-year-old child, and in repeated episodes of serum transaminase fluctuations in a patient with hepatitis C virus infection (SEDA-19, 347).

Late hepatotoxicity has also been reported with low-dose cyclophosphamide (22).

- A 67-year-old man with Sjögren's syndrome took cyclophosphamide for 2 years, a cumulative dose of 40.5 g. He then developed severe progressive jaundice due to acute hepatocellular injury. Gallstones and acute viral hepatitis were excluded, and only anti-smooth muscle antibodies were weakly positive. Liver histology showed marked ballooning of the hepatocytes and cell loss, cytoplasmic and canalicular cholestasis, and infiltration of the portal tract with inflammatory cells. Complete resolution occurred 6 weeks after cyclophosphamide withdrawal.

The authors emphasized this was the first case suggesting a cumulative hepatotoxic effect of low-dose cyclophosphamide. Previous rare cases of low-dose cyclophosphamide-induced acute hepatitis have usually occurred within the first 2 months.

Urinary tract

Hemorrhagic cystitis and bladder cancer are well-known complications of cyclophosphamide. The damage to the urinary bladder epithelium is caused by acrolein, a metabolite of cyclophosphamide that is excreted in the urine. In bone marrow transplant recipients, prior administration of busulfan, which itself causes hemorrhagic cystitis, can increase this risk (23). Mesna (2-mercaptoethane sodium sulfonate) is used to prevent this adverse effect. It is excreted by the kidney, and it binds and detoxifies acrolein in the urine; mesna also prevents the breakdown of acrolein precursors. Intravesical prostaglandin E_2 has been suggested as an alternative treatment (23).

The incidence of cystitis and/or dysuria was only 8% in 531 women with breast cancer who were given oral cyclophosphamide 60 mg/m^2/day for 1 year; the majority of cases were only grade 1 (24).

Upper renal tract disorders with ureteric reflux and bilateral hydronephrosis has been briefly reported in a patient with a history of cyclophosphamide-induced cystitis (SEDA-22, 410–411).

In 155 patients with Wegener's granulomatosis, of whom 142 took daily oral cyclophosphamide, the most frequent long-term cyclophosphamide-related adverse effects were cystitis despite mesna therapy (12%) and myelodysplasia (8%) (25). Patients who took a cumulative dose of over 100 g had a two-fold greater risk of cystitis and/or myelodysplasia than patients who took under 100 g. The authors emphasized that cyclophosphamide therapy should be as short as possible, with mesna and close surveillance in order to reduce treatment-associated morbidity.

Cyclophosphamide was thought to have favored the development of emphysematous cystitis in a 73-year-old man (26).

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Skin

High doses of cyclophosphamide can cause the erythrodysesthesia syndrome, that is erythema of the hands and feet (27).

Stevens–Johnson syndrome developed in two patients, including one with positive rechallenge (SEDA-20, 342).

Five of thirty-two patients treated with the alternating drug regimen CAMBO-VIP (cyclophosphamide, doxorubicin, methotrexate, bleomycin, vincristine, etoposide, ifosfamide, and prednisolone) for non-Hodgkin's lymphoma developed blisters under the thickened skin of the palms and/or soles, followed by desquamation (28).

Discrete cutaneous hyperpigmentation occurred in two patients after high-dose chemotherapy with cyclophosphamide, etoposide, and carboplatin (29).

Hair

Alopecia occurs in patients taking cyclophosphamide, but it is less common and less severe in patients taking low doses. Mild to moderate alopecia was observed in 17% of patients with Wegener's granulomatosis (4).

Nails

Beau's lines (transverse ridging of the nails) developed after multiple drug therapy for Hodgkin's disease, including cyclophosphamide (30).

Reproductive system

In autoimmune diseases cyclophosphamide can cause menstrual disorders (oligomenorrhea or sustained amenorrhea) and ultimately sterility or premature menopause. This has been particularly exemplified in lupus erythematosus, and several studies have shown a high prevalence of menstrual disorders or premature ovarian failure in cyclophosphamide-treated patients, or a significantly higher incidence of both complications compared with other immunosuppressive regimens or healthy controls (31–33).

Of 17 adult men who had been treated before puberty for sarcoma with high-dose pulse cyclophosphamide (median dose 20.5 m/m^2) as part of regimens containing vincristine, dactinomycin, and cyclophosphamide, with or without doxorubicin, 10 had azoospermia, five had oligospermia, and only two had normal sperm counts (34). The authors concluded that a previous suggestion that puberty acts as a protection to infertility was not borne out and that the risk of infertility was proportional to the cumulative dose of cyclophosphamide.

Susceptibility factors have been investigated in a large retrospective study of 274 patients aged under 45 years, of whom 70 had received cyclophosphamide, 84 azathioprine but not cyclophosphamide, and 88 either no drug or hydroxychloroquine alone (35). The overall incidence of ovarian failure, defined as sustained amenorrhea for at least 12 months and documented by reduced estradiol concentrations, was 26, 1, and 0% respectively. The mean delay to onset of the first missed menses was 4.4 months. A higher age at the start of treatment and cumulative dose were independent risk factors for cyclophosphamide-induced ovarian failure. The incidences were 14, 28, and 50% in patients aged under 30 years, 30–39 years, and over 40 years respectively, and 4, 26, 31, 70% for cumulative doses of under 10, 10–20, 20–30, and over 40 g, respectively.

Immunologic

Type I hypersensitivity

Anaphylactic reactions have very rarely occurred after intravenous cyclophosphamide (SED-8, 1126) (SEDA-17, 522) (36), and positive skin tests to the parent drug and/or 4-hydroxycyclophosphamide were found in several well-documented case reports (SEDA-19, 347). Although other mechanisms could be considered, a possible IgE antibody-mediated reaction was substantiated by the positivity of immediate skin tests to cyclophosphamide metabolites in five patients, and the recurrence of symptoms following intravenous or oral rechallenge in several of them (37).

Cyclophosphamide reportedly caused a type I hypersensitivity reaction in a patient with systemic lupus erythematosus (38).

- A 17-year-old Chinese girl with systemic lupus erythematosus developed acute angioedema over the neck, chest, and larynx, and required mechanical ventilation. She had received two previous courses of cyclophosphamide without incident. She developed urticaria 30 minutes after an infusion of cyclophosphamide, without angioedema, stridor, wheezing, or hypotension. Skin prick testing with cyclophosphamide was negative. Four weeks later, 15 minutes after the start of an infusion of cyclophosphamide, she developed generalized urticaria. Further infusions were given with diphenhydramine premedication.

In the absence of drug-induced angioedema or anaphylaxis, monthly therapy with cyclophosphamide can be continued with antihistamine premedication in patients who have allergic reactions.

Infection risk

Owing to its effects on cellular and humoral immune responses, and independently of leukopenia, cyclophosphamide can induce more frequent and more severe infectious complications (SED-13, 1123) (SEDA-20, 343). Older age and total cumulative dose are possible susceptibility factors for severe infectious episodes. More specifically, an increased risk of severe, life-threatening *Pneumocystis jiroveci* pneumonia has been identified, particularly in patients with lymphopenia (39,40). There was also a 10- to 20-fold increase in *Herpes zoster* infections (41,42). Fatal aspergillosis and disseminated cryptococcosis have been sometimes reported (SEDA-20, 343) (43). Infections were mostly reported in patients who were also taking glucocorticoids, and a synergistic effect with glucocorticoids is likely to be relevant in causation (41,44); all the same, there is direct evidence that cyclophosphamide itself is involved. Its role was investigated in a retrospective study of 100 patients with systemic lupus erythematosus: 45% developed serious bacterial infections (58%), opportunistic infections (24%), or *H. zoster* infections (18%), compared with 12% in 43 patients taking high-dose glucocorticoids alone (45). Infections were more frequent with sequential intravenous and oral cyclophosphamide (68%) than with intravenous

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cyclophosphamide (39%) or oral cyclophosphamide (40%), and leukopenia was an additional risk factor. Other investigators have similarly adduced evidence of more frequent infections, particularly *P. jiroveci* pneumonia, in patients receiving cyclophosphamide plus glucocorticoids daily rather than alternate-day glucocorticoids (41).

- A 72-year-old man with autoimmune thrombocytopenia had taken prednisone (30 mg/day) for 1 year, when he was found to have systemic lupus erythematosus (46). Prednisone was continued and he started to take chloroquine (250 mg/day) and monthly cyclophosphamide (0.75 g/m^2). Three weeks after the first bolus of cyclophosphamide, he complained of fever and dyspnea, and chest X-rays showed bilateral pulmonary infiltrates. Despite prompt medical management, he died 5 days after admission with cytomegalovirus-induced interstitial pneumonia.

In addition to cyclophosphamide, this patient had several susceptibility factors for fatal infection, namely age (older than 50 years) and a low leukocyte nadir (2900×10^6/l) after treatment with cyclophosphamide and prednisone.

Long-Term Effects

Tumorigenicity

Although tumor induction has mostly been documented in patients treated for cancer, long-term cyclophosphamide treatment for non-neoplastic conditions can also increase the incidence of certain neoplasms. Whether this oncogenic effect is a consequence of drug-induced chromosomal aberrations rather than immunosuppression is unclear. An increased incidence of bladder cancers, skin cancers, and myeloproliferative disorders was found in a 20-year follow-up study of 119 patients with rheumatoid arthritis, and a high dose of cyclophosphamide (mean total dose of 80 g) was the main susceptibility factor (47).

In another study in patients with Wegener's granulomatosis there was an 11-fold increase in the incidence of lymphomas compared with the general population (41). In contrast, previous exposure to cyclophosphamide did not appear to be associated with a significantly higher risk of cancer in patients with systemic lupus erythematosus, but the number of cases was very low (48).

Myelodysplastic syndromes

Cyclophosphamide can cause myelodysplastic syndromes, particularly after prolonged treatment. The type of myelodysplastic syndromes and cytogenetic abnormalities that developed after treatment with alkylating agents for rheumatic diseases have been described in eight patients (mean age 57 years), of whom seven had taken oral cyclophosphamide and one chlorambucil (49). The mean cumulative dose of cyclophosphamide was 118 g for a mean cumulative duration of 4.4 years, and the myelodysplastic syndrome was diagnosed 0–4 years (mean 2.4 years) after the end of treatment. Concomitant immunosuppressive drugs were given in four of seven cyclophosphamide-treated patients. Cytogenetic abnormalities of chromosome 5 and/or 7, which are characteristic of treatment-related myelodysplastic syndromes, were found in all patients. Only two patients were still alive at the time of the report, and the outcome was remarkably poor in patients with chromosome 5 deletion. This study suggested that a high cumulative dose of cyclophosphamide is a risk factor for hematological malignancies, and that patients require long-term surveillance.

Urinary tract tumors

Squamous cell carcinoma of the bladder has been reported 4 years after pulsed cyclophosphamide therapy (50). However, the authors noted that other susceptibility factors, such as bladder diverticula and human papilloma virus infection, occurred in the intervening period and they speculated on the cumulative risk.

- A 72-year old woman who received 1400 mg cyclophosphamide over 2 weeks for Wegener's granulomatosis had gross hematuria and dysuria (51). Cystoscopy was normal, but there was marked irregularity of the mucosa of the upper ureteric mucosa, the renal pelvis, and the renal calyces on retrograde ureteropyelography. Nephroscopy showed a gray necrotic uroepithelium with dystrophic calcification.

The risk of bladder cancer persists for as long as 20 years after cyclophosphamide withdrawal. In a retrospective analysis, half of the 145 patients on long-term treatment for Wegener's granulomatosis had microscopic or gross hematuria, among whom 70% had cystoscopic features compatible with cyclophosphamide-induced bladder injury (52). Seven patients (5%) developed bladder cancer, a 31-fold higher incidence than in the general population. As previous episodes of hematuria were found in all seven patients and the drug was the only significant risk factor for bladder cancer, prompt cystoscopy should be done in any patient who develops gross hematuria, even after treatment withdrawal. Another study showed an excess in the incidence of bladder cancer in patients with multiple sclerosis who received cyclophosphamide and who also had an indwelling catheter (53).

Renal adenocarcinoma has been reported in a 50-year-old man after 3 years of cyclophosphamide treatment for hepatic sarcoidosis (54).

Other tumors

It has been suggested that cyclophosphamide can contribute to the risk of cervical dysplasia. In a retrospective study of 110 patients with systemic lupus erythematosus, cervical dysplasia was significantly more frequent in patients who had received intravenous cyclophosphamide (10 of 61) than in a control group who did not receive cyclophosphamide (two of 49) (55). In addition, cervical pathology worsened during cyclophosphamide therapy in all four patients with pre-existing cervical dysplasia, and one patient developed in situ cervical carcinoma.

- A 54-year-old man with polyarteritis nodosa developed hepatic angiosarcoma after taking cyclophosphamide for 13 years (56). Although this may have been coincidental, the authors found two other published reports of this very rare tumor in patients taking long-term cyclophosphamide.

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To determine the frequency and types of malignancies that occur in children with end-stage renal insufficiency who required renal replacement therapy, data from 249 patients were analysed retrospectively (57). There were 22 malignancies in 21 patients; skin cancers accounted for 59% and non-Hodgkin's lymphomas for 23%. At 25 years after first renal replacement therapy, the probability of developing a malignancy was 17%. The incidence of cancers overall was 10-fold higher than in the general population. For cancers other than melanoma and non-Hodgkin's lymphoma, the standardized risks were 222 and 46 respectively. The use of more than 20 mg/kg cyclophosphamide was associated with an increased risk of malignancy. Six patients died as a result of their malignancy, accounting for 9.5% of overall mortality. The long-term risk of certain malignancies is significantly increased in children who have undergone renal replacement therapy, especially after treatment with cyclophosphamide.

Second-Generation Effects

Fertility

Cyclophosphamide, or testicular and cranial irradiation, in the treatment of childhood malignancies can lead to small testicular size and decreased sperm production in adulthood (58). Of 17 adult male survivors of childhood sarcomas treated before puberty with high-dose cyclophosphamide, only two had normal sperm counts, 10 had azoospermia, and five had oligospermia (34). The two patients with normal sperm counts had taken the lowest doses of cyclophosphamide.

Gonadal toxicity has been documented in both men and women receiving cyclophosphamide (4). In men, the incidence of transient or permanent oligospermia/azoospermia is 50–90%, and in prepubertal patients spermatogenesis will more readily return to normal than adults. In one study, testosterone prophylaxis given at the same time as cyclophosphamide reduced the incidence of disorders of spermatogenesis and accelerated spermatogenesis recovery after cyclophosphamide discontinuation, but few patients were evaluable (59).

Of 23 men treated with either cyclophosphamide or non-alkylating agent combinations, there was a dose-related disturbance of gonadotrophin secretion in the cyclophosphamide group (60). The chances of maintaining normal gonadal function after combined treatment of Hodgkin's disease are significantly greater among girls than boys at 9-year follow-up (61). Pre- and post-pubescent boys were affected by six cycles of MOPP, whether or not pelvic radiation was administered; on the other hand, in girls similarly treated, ovarian function was directly affected by the number of courses of chemotherapy and the ovarian radiation dose (62). In a study of male gonadal function at 9 years follow-up after regimens containing cyclophosphamide, mechlorethamine, vincristine, or procarbazine, there was azoospermia, whereas regimens containing dactinomycin and vinblastine did not have a toxic effect on spermatogenesis (63). Testicular volume and sperm count in 18 patients, 1–3 years after chemotherapy, showed that all those who had received chemotherapy that did not include cisplatin had normal testicular size and sperm counts, whereas of seven who had received cisplatin, six had small testes and azoospermia and one was oligozoospermic with normal-sized testes (64).

The risk of ovarian failure and infertility has been studied in 84 women with an underlying inflammatory disease receiving intravenous cyclophosphamide (65). The incidence of sustained amenorrhea was 22% and was independent of the underlying inflammatory disease. After treatment with cyclophosphamide following bone marrow transplantation, ovarian function can occasionally recover, resulting in a successful pregnancy up to 7 years after treatment (66). No specific factors correlated with recovery of normal ovarian function. However, recovery was rare if the patient had undergone concurrent total body irradiation (67).

Pregnancy

Cyclophosphamide crosses the placenta and reaches an amniotic fluid concentration of 25%. Six pregnancies occurred in women taking cyclophosphamide; three had induced abortions, one had a spontaneous abortion, and two had normal pregnancies. After withdrawal of cyclophosphamide, 16 women became pregnant; three had induced abortions for severe morphological anomalies, three had spontaneous miscarriages, and 10 delivered healthy infants. Contraception during intravenous cyclophosphamide therapy is recommended, and after withdrawal, pregnancy is possible, with a favourable outcome in two-thirds of cases.

Teratogenicity

The FDA has classified cyclophosphamide as a pregnancy risk factor D drug: it is teratogenic in animals, but population studies have not conclusively shown teratogenicity in humans. However, in a study of in utero first-trimester exposure to four doses of cyclophosphamide 20 mg/kg it was concluded that cyclophosphamide is a human teratogen, that there is a distinct embryopathic phenotype, and that there are serious doubts about the safety of cyclophosphamide in pregnancy (68). The congenital malformation rate has been estimated at 10–44% (69).

Reported congenital abnormalities are many and include facial and palate defects, skin and skeletal anomalies, and visceral malformations. Based on one case and a review of six previous reports of malformations after in utero exposure to cyclophosphamide in the first trimester, a distinct embryopathy due to cyclophosphamide has been suggested (68). The proposed phenotype included growth deficiency, developmental delay, craniosynostosis, blepharophimosis, flat nasal bridge, abnormal ears, and distal limb defects; chromosomes were normal.

In one case of first-trimester exposure to cyclophosphamide in a woman pregnant with twins, the male twin was born with multiple congenital abnormalities and developed papillary thyroid cancer at 11 years of age and stage III neuroblastoma at 14 years of age; the female twin was unaffected (70).

Most cases have been reported in patients with cancer who were also exposed to other antineoplastic drugs or to irradiation. The potential for congenital abnormalities in the offspring of men treated with cyclophosphamide is yet unknown.

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Fetotoxicity

The effects of second- or third-trimester exposure to cyclophosphamide are poorly documented, although normal children have been described (71). However, in other cases growth retardation and neutropenia have been reported (72).

Drug Administration

Drug dosage regimens

In inflammatory or autoimmune diseases, both daily oral and cyclic pulse intravenous cyclophosphamide regimens are used, but it is unclear whether one route of administration should be preferred to another. The cumulative dose obtained in those given an intravenous pulse regimen is consistently lower than in those given daily oral administration, and the incidence of bladder cancer or infection is expected to be lower in the former. However, the choice of the maintenance regimen remains a dilemma as regards efficacy and toxicity (73). For example, in one study in 50 patients with Wegener's granulomatosis there was a similar overall incidence of adverse effects in patients treated with prednisone plus oral cyclophosphamide compared with those who received prednisone plus intravenous pulse cyclophosphamide (74). Patients in the oral group had a higher incidence of severe or fatal infectious complications, but a lower incidence of cumulative relapse rates at 4.5 years.

In 47 patients intravenous pulsed cyclophosphamide was as effective as daily oral cyclophosphamide, but caused fewer adverse effects (75). The patients were randomized to receive monthly intravenous pulses of cyclophosphamide (0.75 g/m^2, $n = 22$) or daily oral cyclophosphamide (2 mg/kg/day, $n = 25$) for at least 1 year. Both groups received glucocorticoids. Whereas efficacy end-points did not show significant differences between the two groups, leukopenia (18 versus 60%) and severe infections (14% with no deaths versus 40% with three deaths) were significantly less frequent with intravenous pulsed cyclophosphamide. As a result, the probability of freedom from adverse effects (no deaths, severe infections, leukopenia, or thrombocytopenia) over a 12-month period was only about 25% in the oral group, compared with 70% in the intravenous group. In addition, and based on the findings of a significantly lower serum follicle-stimulating hormone concentration at 3 and 6 months and a 57% reduction in the total dose in the intravenous pulse group, the intravenous pulse regimen was expected to produce fewer adverse gonadal effects and a reduced risk of malignancies.

Drug–Drug Interactions

Cisplatin

A 4-year follow-up of comparison of a combination of cyclophosphamide with either 50 mg/m^2 or 100 mg/m^2 of cisplatin in ovarian cancer has been reported (76). Peripheral neuropathy was dose-limiting and persistent. Ten of thirty-one patients had significant toxicity in the high-dose group compared with one of 24 in the low-dose group.

Fluconazole

Cyclophosphamide is a prodrug that requires cytochrome P_{450}-dependent hepatic activation to produce alkylating species and several inactive by-products. However, very few metabolic interactions involving cyclophosphamide have been reported. In a retrospective study of 22 children treated with cyclophosphamide for cancer or bone marrow transplantation, cyclophosphamide clearance was significantly lower in nine patients taking fluconazole compared with 13 patients not taking it (77). In vitro studies in human liver microsomes confirmed that the rate of 4-hydroxylation of cyclophosphamide was inhibited by fluconazole.

Prednisolone

Daily prednisolone significantly reduced the total clearance of cyclophosphamide and the peak concentration and AUC of 4-hydroxycyclophosphamide (78). It is not known whether this interaction has clinical consequences.

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Cyclopropane

See also General anesthetics

General Information

Cyclopropane is an inhalational anesthetic gas. Its minimum alveolar concentration (MAC) is 9.2%. Because of the risk of explosion, it is usually administered by closed circuit (1).

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Organs and Systems

Cardiovascular

Cardiac dysrhythmias, which can be ventricular, can complicate the use of cyclopropane (2), and the risk is increased in patients who have also been given catecholamines (3).

Nervous system

Delirium can occur in patients given cyclopropane (4).

Gastrointestinal

Nausea and vomiting are fairly frequent after recovery from cyclopropane anesthesia (5,6).

Liver

Liver dysfunction due to cyclopropane, as judged by effects on indocyanine green clearance, has been reported (7).

Urinary tract

Cyclopropane has an antidiuretic effect that is partly reversed by alcohol (8).

Body temperature

There has been a report of malignant hyperthermia in a patient who was given cyclopropane during cesarean section (9), consistent with the in vitro effect of cyclopropane on caffeine-induced muscle contraction (10).

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Cycloserine

See also Antituberculosis drugs

General Information

Cycloserine is an aminoisoxazolidone that shows no cross-resistance with other tuberculostatic agents (1). Because of its high toxicity, it should only be used when microorganisms are resistant to other drugs (relapse or primary resistance). It is usually given orally.

Organs and Systems

Nervous system

Cycloserine can cause headache, somnolence, and tremor (2). In mice, L-cycloserine protects against auditory-invoked seizures by binding to pyridoxal phosphate in the presence of zinc ions (3). The addition of a fluoroquinolone can increase the risk of nervous system effects (4).

Psychological, psychiatric

Cycloserine can cause altered mood, cognitive deterioration, dysarthria, confusion, and even psychotic crises (2).

Susceptibility Factors

Renal disease

Cycloserine accumulates to toxic concentrations in patients with renal insufficiency (5).

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Cyproheptadine

See also Antihistamines

General Information

Cyproheptadine is a first-generation antihistamine with antiserotoninergic effects (SEDA-12, 142). It has been used because of its appetite-stimulating capacity.

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Drowsiness and other adverse effects common to the first-generation antihistamines are common.

Organs and Systems

Psychological, psychiatric

A central anticholinergic syndrome with psychotic symptoms in a 9-year-old boy on therapeutic doses has also been described (1).

Cyproheptadine (6 mg/day) was considered to be the most likely cause of aggressive behaviour in a 5-year-old boy (2).

Long-Term Effects

Drug dependence

A case of cyproheptadine dependence has been reported (SEDA-12, 142).

Drug Administration

Drug overdose

Cyproheptadine caused a reversible toxic psychosis in a patient with renal impairment and low body weight after an incidental overdose of 24 mg within 24 hours (SEDA-2, 150).

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Cytarabine

See also Cytostatic and immunosuppressant drugs

General Information

Cytarabine is a pyrimidine nucleoside that is used to treat acute myelogenous leukemia and lymphocytic leukemias. It is activated intracellularly by deoxycytidine kinase to phosphorylated nucleotides that interfere with DNA synthesis in the S phase of the cell, and is rapidly deaminated intracellularly to the inactive metabolite uracil arabinoside.

Organs and Systems

Respiratory

Two cases of respiratory failure occurred during induction chemotherapy for acute myelomonocytic leukemia with cytarabine and all-*trans*-retinoic acid (1). The authors attributed this to a manifestation of the retinoic acid syndrome. Both patients developed acute respiratory failure with widespread pulmonary infiltrates about 60 hours after starting chemotherapy. Both were managed successfully using high-dose dexamethasone and ventilation.

Nervous system

Central nervous system disturbances, especially impaired cerebellar function, limit doses of cytarabine, and age is an important predictive factor. Of 418 patients who received 36–48 g/m^2 only 35 (8%) had severe cerebellar toxicity, which was irreversible or fatal in 4 (1%) (2). Patients over 50 years of age were significantly more likely to develop cerebellar problems than younger patients (26/137, 19%, compared with 9/281, 3%); a second course did not increase the incidence, implying that it is the individual rather than the cumulative dose that is important.

The cerebellar syndrome is the most common complication of high-dose cytarabine therapy. In a study of the cerebellar syndrome caused by cytarabine (3), in which it was found in seven of 30 patients treated, symptoms of toxicity appeared between the third and seventh days of chemotherapy, manifesting first as lethargy and confusion (3). Within the next 24 hours there were signs of cerebellar dysfunction, including dysarthria, ataxia, tremor, nystagmus, and dysmetria. In most patients in whom neurotoxicity developed, liver function worsened during chemotherapy. Abnormal liver function at the start of therapy and the development of neurotoxicity appear to be linked. The symptoms of neurotoxicity resolved within 4–49 days.

Aseptic meningitis can also occur in patients given cytarabine (4,5), and signs of cerebellar dysfunction after the administration of cytarabine 24 g/m^2 have been reported in association with aseptic meningitis (6).

Sensory systems

Keratoconjunctivitis is a complication of cytarabine therapy, with a reported incidence of 30–100% and commonly associated with high doses (3 g/m^2). Corneal and conjunctival toxicity have been described after therapy for 4 days with 235 mg (100 mg/m^2) daily (7).

Gastrointestinal

The addition of cytarabine 10 mg/m^2/day subcutaneously for 10 days to interferon monotherapy more than doubled the incidence of gastrointestinal toxicity in the treatment of chronic myeloid leukemia in 139 patients (8).

Skin

Acute, painful, swollen, and self-limiting erythema of the hands and soles has been reported after induction therapy for acute myeloid leukemia and attributed to cytarabine (9).

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Immunologic

A hypersensitivity reaction has been ascribed to cytarabine (10).

Drug Administration

Drug administration route

The safe intrathecal administration of a long-acting formulation of cytarabine has been reported (11).

Drug–Drug Interactions

Daunorubicin

Hepatotoxicity, with either hyperbilirubinemia or increased alkaline phosphatase activity, occurred in five of 14 patients in a trial of cytarabine 200 mg/m^2/day for 9 days by continuous infusion and daunorubicin 70 mg/m^2/day for 3 days (12).

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Cytostatic and immunosuppressant drugs

See also Individual agents *and* Alkylating cytostatic agents

General Information

Cytostatic drugs generally have both anticancer and immunosuppressive properties, while immunosuppressant drugs have more specific immunosuppressive effects, although this is a somewhat arbitrary distinction. The following list of drugs is based on the classification used in the *British National Formulary*. Monoclonal antibodies and corticosteroids are not included in this list.

A. Cytostatic drugs

1. Alkylating drugs
   Nitrosoureas: carmustine (BCNU), lomustine (CCNU), nimustine (ACNU), streptozocin.
   N-lost derivatives: chlormethine (mechlorethamine, mustine, nitrogen mustard), cyclophosphamide, estramustine.
   Others: busulfan, chlorambucil, dacarbazine, ifosfamide, melphalan, mitobronitol, mitomycin, procarbazine, thiotepa, temozolomide, treosulfan.
2. Antimetabolites
   Folic acid antagonists: methotrexate, raltitrexed.
   Purine derivatives: cladribine (2-chlorodeoxyadenosine), fludarabine, mercaptopurine, pentostatin (deoxycoformycin), tioguanine.
   Pyrimidine derivatives: capecitabine, cytarabine, fluorouracil (SEDA-23, 476), gemcitabine, tegafur.
3. Cytostatic antibiotics
   Anthracyclines (SEDA-25, 533): aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin.
   Others: acivicin, amsacrine, bleomycin, dactinomycin (actinomycin D), mitoxantrone.
4. Photodynamic drugs: porfimer, temoporfin.
5. Platinum compounds (SEDA-26, 490): carboplatin, cisplatin, oxaliplatin.
6. Taxanes: docetaxel, paclitaxel (SEDA-21, 463).
7. Topoisomerase inhibitors (SEDA-27, 477)
   Inhibitors of topoisomerase type 1: irinotecan, topotecan.
   Inhibitors of topoisomerase type 2: etoposide, teniposide.
8. Vinca alkaloids (SEDA-28, 538): vinblastine, vincristine, vindesine, vinorelbine.
9. Others: bexarotene, bortezomib, colaspase and crisantaspase (asparaginases), hydroxycarbamide (hydroxyurea).

B. Immunosuppressant drugs

1. Antiproliferative immunosuppressants: azathioprine, mycophenolate mofetil.

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2. Calcineurin inhibitors: ciclosporin, everolimus, pimecrolimus, sirolimus, tacrolimus, temsirolimus.

General adverse effects

There are several types of adverse effects that the cytostatic drugs have in common. These include hyperuricemia (as a result of tumor lysis syndrome), bone marrow suppression, oral mucositis, gastrointestinal discomfort, and alopecia. These are dealt with under the relevant headings below.

Individual drugs also have specific adverse effects. However, one of the difficulties in attributing adverse effects to individual cytostatic and immunosuppressant drugs is the common use of multidrug or multiintervention studies. A good example of this is the Phase I Study of Foscan-Mediated Photodynamic Therapy and Surgery in Patients with Mesothelioma, in which the authors could not separate the adverse effects, which included local effects, cardiotoxicity, and hepatotoxicity, according to causative drug or procedure (1).

Extravasation of cytostatic drugs

Extravasation is leakage of intravenous drugs from a vein into the surrounding tissues. This can cause local pain accompanied by burning or stinging, erythema, swelling, and tenderness. Not all cytostatic drugs are harmful to the tissues after extravasation. The different types of drugs are classified in Table 1.

The management of extravasation of cytostatic drugs has been reviewed (2–5) and guidelines have been suggested (http://www.ucht.n-i.nhs.uk/pubinfo/Extravasation_of_intravenous_drugs).

Local extravasation

- Stop administering the drug and explain to the patient that extravasation may have occurred.
- Put on gloves and goggles.
- Leave the cannula in place.
- Attach a 20 ml syringe and try to withdraw residual drug.
- Give specific antidotes for specific cytostatic drugs (Table 2).
- Remove the cannula.
- Do not apply pressure, which increases the area of extravasation.
- Apply a thermal pack (for vesicant, exfoliant, and irritant drugs only) (Table 2).
- Raise the limb for 48 hours for vesicant drugs.
- Review vesicant extravasation in 24 hours.
- Consult a plastic surgeon if necessary.

Extravasation from a central venous catheter

If the patient complains of altered sensation, pain, burning, or swelling at the central venous catheter site or in the ipsilateral chest, or if there is a change in intravenous flow rate, extravasation may have occurred.

- Stop administering the drug and explain to the patient that extravasation may have occurred.
- Put on gloves and goggles.
- Attach a 20 ml syringe and try to withdraw residual drug from the line.
- If the reason for extravasation is needle dislodgement, and if aspiration through the needle was unsuccessful, remove the needle and try to aspirate subcutaneously in the pocket and surrounding tissues.
- Give specific antidotes for specific cytostatic drugs (Table 2).
- If a needle is still in situ it should be removed after instillation of the antidote; the antidote can also be injected into the surrounding tissues if needed.
- Do not apply pressure, which increases the area of extravasation.
- Apply a thermal pack (for vesicant, exfoliant, and irritant drugs only) (Table 2).

Table 1 Classification of cytostatic drugs according to their ability to cause tissue damage after extravasation (from http://www.ucht.n-i.nhs.uk/pubinfo/Extravasation_of_intravenous_drugs)

Vesicants[a]	Exfoliants[b]	Irritants[c]	Inflammatory agents[d]	Neutral agents[e]
Amsacrine	Aclarubicin	Carboplatin	Etoposide phosphate	Asparaginase
Chlormethine	Carmustine	Daunorubicin liposomal	Fluorouracil	Bleomycin
Dactinomycin	Cisplatin	Doxorubicin liposomal	Methotrexate	Cladribine
Daunorubicin	Dacarbazine	Etoposide	Raltitrexed	Cyclophosphamide
Doxorubicin	Docetaxel	Irinotecan		Cytarabine
Epirubicin	Floxuridine	Teniposide		Fludarabine
Idarubicin	Mitoxantrone			Gemcitabine
Mitomycin	Oxaliplatin			Ifosfamide
Streptozocin	Paclitaxel			Interleukin-2
Vinca alkaloids	Topotecan			Melphalan
	Treosulfan			Pentostatin
				Thiotepa
				Interferon alfa

[a]Vesicants cause pain, inflammation, and blistering of the skin and underlying tissues, leading to tissue death and necrosis
[b]Exfoliants cause inflammation and shedding of the skin, but are less likely to cause tissue death
[c]Irritants cause inflammation and irritation, but rarely cause tissue damage
[d]Inflammatory agents cause mild to moderate inflammation and flare in local tissues
[e]Neutral agents do not cause inflammation or tissue damage

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Table 2 Specific antidotes for cytostatic drugs after extravasation

Drug	Antidote	Instructions	Comments
Anthracyclines	Dimethylsulfoxide Dexrazoxane	Apply dimethylsulfoxide 99% topically Give intravenous dexrazoxane 1000 mg/m^2 on days 1 and 2 and 500 mg/m^2 on day 3; most effective if the first dose is given within 6 hours	Apply a cold pack for 15 minutes, four times a day. Inspect after 24 hours and 7 days. If there are signs of erythema or ulceration after 7 days, discuss with a plastic surgeon
Chlormethine	Sodium thiosulfate	Dilute 0.6 ml of sodium thiosulfate 50% with 9.4 ml of water for injection. Inject 4 ml through the cannula, then remove the cannula. Infiltrate with 0.2 ml subcutaneously over and around the affected area	Apply a cold pack for 15 minutes, four times a day. Inspect after 24 hours and 7 days. If there are signs of erythema or ulceration after 7 days, discuss with a plastic surgeon
Cisplatin[a,b]	Sodium thiosulfate	Dilute 0.6 ml of sodium thiosulfate 50% with 9.4 ml of water for injection. Inject 4 ml through the cannula, then remove the cannula. Infiltrate with 0.2 ml subcutaneously over and around the affected area	Apply a warm pack for 15 minutes, four times a day. Inspect after 24 hours and 7 days. If there are signs of erythema or ulceration after 7 days, discuss with a plastic surgeon
Vinca alkaloids	Hyaluronidase	Mix 1500 units of hyaluronidase with 1 ml of sodium chloride 0.9% for injection. Inject 0.5 ml through the cannula. Remove the cannula. Infiltrate with 0.2 ml subcutaneously over and around the affected area	Apply a warm pack for 15 minutes, four times a day. Inspect after 24 hours and 7 days. If there are signs of erythema or ulceration after 7 days, discuss with a plastic surgeon

[a]High concentration only
[b]Sodium thiosulfate should only be used if a large volume (greater than 20 ml) of concentrated cisplatin (that is a concentration over 0.5 mg/ml) has extravasated

- Review vesicant extravasation in 24 hours.
- Extravasation in the deep part of a central venous catheter will require referral to a plastic surgeon.

Review articles

Some review articles on the adverse effects of cytostatic drugs and related topics are listed in Table 3.

Organs and Systems

Nervous system

Neurological symptoms occur in more than 20% of patients with cancer and can be increased by cytostatic drugs. Acute and late neurotoxic syndromes involve a number of cytostatic agents (Table 4).

The late nervous system effects in survivors 7 years after treatment for childhood acute lymphoblastic leukemia include impaired concentration, attention, and memory (32).

The late effect of chemotherapy and radiotherapy for nervous system lymphoma has been studied in 15 patients; 10 had severe symptomatic diffuse changes in the white matter within 8 months of completing treatment (33).

Endocrine

Combined cytostatic drug therapy for Hodgkin's disease in childhood often results in abnormal endocrine function, particularly increases in follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone (34).

Metabolism

Hyperglycemia was reported in 21 of 56 patients who received weekly paclitaxel with oral estramustine and carboplatin (4-weekly); under 10% required pharmacological intervention (35). There was mild hyperphosphatemia in 24.

There was fasting hypoglycemia in 19 of 35 children with acute lymphoblastic leukemia receiving maintenance therapy of daily oral mercaptopurine and weekly oral methotrexate; all the children improved on withdrawal of chemotherapy and 10 of 15 normalized (36).

There have been cases of acute tumor lysis syndrome in patients with melanoma (37) and light-chain amyloidosis (38). The authors reviewed the incidence of acute tumor lysis syndrome in these diseases, which are less typically associated with it.

Hematologic

The authors of a study in 101 patients concluded that in addition to the dose of chemotherapy and the administration of hemopoietic growth factors, poor performance status and a high concentration of soluble p75-R-TNF can predict the occurrence of chemotherapy-induced myelosuppression in lymphoma (39).

In 43 patients, raised plasma concentrations of FLT3-L (an fms-like tyrosine kinase) in patients who had previously received chemotherapy predicted the stage of recovery of the bone-marrow compartment (40). FLT3-L seems to identify the likelihood that the patient will have severe thrombocytopenia if additional cytostatic therapy is given. Knowledge of bone-marrow activity

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Table 3 Some review articles in cytostatic drug therapy

	Topic	Reference
Adverse effects	The relation between a drug's adverse effects spectrum and its pharmacological action	(6)
	Adverse effects profiles of individual drugs	(7)
	Prognostic factors	(8)
	Anemia	(9)
	Nausea and vomiting	(10)
	The relation between toxicity and efficacy	(11,12)
Treatment of specific cancers	Colorectal cancers	(13)
	Lymphomas	(14)
	Melanoma	(15)
	Metastatic breast cancer	(16)
	Prostate cancer	(17)
	Soft tissue sarcomas	(18)
	Testicular carcinoma, non-seminomatous	(19)
Administration	The relation between a drug's adverse effects spectrum and its dosage regimen	(20–22)
	Effects of dosage regimens in combined therapy	(23,24,25)
	Effects of the route of administration	(26,27)
	Dose-finding techniques	(28)
	Preventing dose-limiting adverse effects in patients with nasopharyngeal carcinoma	(96)
	Oral versus intravenous therapy in small cell lung cancer	(29)
Susceptibility factors	Effects of sex	(30)
	The expression and prognostic significance of P glycoprotein in adult solid tumors	(31)

should permit more aggressive therapy, by establishing the earliest possible time for dosing with any cytostatic agent for which myelosuppression is the dose-limiting toxic effect.

Mouth and teeth

Cytostatic drugs can cause oral mucositis, which characteristically affects the whole buccal mucosa (41). It is caused by damage to the oropharyngeal epithelium which has a rapid turnover. The oral mucosa can also be affected by infection. Susceptibility factors include age, nutritional status, tumor type, oral hygiene, and neutrophil count.

Oral mucositis causes pain, interferes with nutrition, and can lead to systemic infection and other complications that increase morbidity and mortality (42). Interventions that have been used to prevent oral mucositis or reduce its severity and sequelae include meticulous pretransplantation and continuing mouth care, calcium phosphate solution, treatment with near-infrared light and lower-energy laser light, interleukin-11, sucralfate, oral glutamine, rinsing with granulocyte-macrophage colony-stimulating factor, tretinoin, keratinocyte growth factor, and amifostine. However, very few interventions have been shown to be effective compared with placebo.

Table 4 Neurotoxic effects of cytostatic drugs

Drug	Neurotoxicity
Asparaginase	Acute encephalopathy
Bortezomib	Peripheral neuropathy
Busulfan	Seizures
Carmustine	Brain damage in conventional doses when combined with radiation
Chlorambucil	Disorientation, cognitive dysfunction
Chlormethine	Rare encephalopathy following high doses
Cisplatin	Peripheral neuropathy, deafness, cerebral cortical blindness, seizures
Cytarabine	Cerebellar ataxia in high doses
Fluorouracil	Cerebellar ataxia in high doses
Ifosfamide	Mild memory disturbances
Methotrexate	Acute meningitis; acute fatal cerebral dysfunction; chronic leukoencephalopathy
Oxaliplatin	Acute and chronic sensory neuropathy
Taxanes	Peripheral neuropathy
Vinblastine	Jaw pain, myopathy, inappropriate ADH secretion
Vincristine	Peripheral neuropathy, abdominal pain, constipation
Vindesine	Overdose or accidental intrathecal injection is usually fatal
Vinorelbine	Sensorimotor distal symmetrical axonal neuropathy

In a retrospective analysis over 13 years of cytostatic therapy for various conditions, six doses of etoposide each of 250 mg/m^2 caused grade 4 mucositis and 50% of patients who received epirubicin 120 mg/m^2 developed grade 2 or 3 mucositis (43). Severe stomatitis complicated epirubicin 1250 mg/m^2 (44).

A scoring system for mucositis has been proposed and validated (45) and multivariate analysis has been used to identify contributory factors (46). A diagnosis of leukemia, the use of total body irradiation or allogenic transplantation in treatment, or delayed neutrophil recovery were associated with an increased incidence of oral mucositis.

It has been proposed that a change in serum diamine oxidase activity is a very sensitive surrogate for early signs of upper gastrointestinal tract mucositis (47).

Gastrointestinal

Nausea and vomiting are common adverse effects of cytostatic drugs (48). They can be acute (occurring within 24 hours of therapy), delayed (persisting for 6–7 days after therapy), or anticipatory (occurring before chemotherapy) (49). Their treatment has been reviewed (50,51).

Diarrhea can also occur (52) and is particularly problematic with some drugs, such as irinotecan (53). Its management has been reviewed (54).

In a retrospective analysis over 13 years of cytostatic therapy for various conditions there were 12 cases in which chemotherapy had caused gastrointestinal perforation (43). Six doses of etoposide each of 250 mg/m^2 induced an advanced stage (grade 4) of mucositis. Fifty percent of patients receiving epirubicin 120 mg/m^2

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developed grade 2 or 3 mucositis. Severe stomatitis complicated epirubicin 1250 mg/m^2 (44).

Increased intestinal permeability has been shown in children receiving low-dose methotrexate therapy (44).

Liver

Of 54 patients with non-small-cell lung cancers treated with a combination of gemcitabine 1000 mg/m^2 on days 1 and 8 and paclitaxel 200 mg/m^2 on day 1, six had abnormal but significantly raised transaminases (55). The authors believed that this was drug-induced, but could not rule out underlying liver disease.

Urinary tract

Hemolytic-uremic syndrome in association with thrombotic thrombocytopenic purpura has been reported in a patient receiving pentostatin (deoxycoformycin) after exposure to only 15 mg/m^2 given over 3 days (56).

Skin

There has been a report of six cases of a variant of the palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), in which patients who had previously reported the syndrome developed it again when they were treated with completely different chemotherapeutic drugs (57). The recall syndrome was of mild to moderate intensity, less severe than the primary syndrome, and self-limiting in all cases.

Four cases of hyperkeratotic seborrheic warts appearing over a 2-year period, 25 years after the patients had been started on azathioprine 2.5 mg/kg, have been reported (58).

Calciphylaxis is a rare, often fatal disease, characterized clinically by progressive cutaneous necrosis and ulceration and histologically by vascular calcification and thrombosis. It has been described in association with end-stage renal disease and hyperparathyroidism.

- A 64-year-old woman who 3 months before had finished a course of cyclophosphamide, doxorubicin, and fluorouracil chemotherapy for breast carcinoma developed calciphylaxis (59). She had no renal disease and had normal renal function and parathyroid hormone concentrations.

The authors speculated that the cause may have been chemotherapy-induced functional deficiency of protein C and protein S.

Musculoskeletal

Bone mineral density has been used to help predict which children who have had chemotherapy may subsequently develop osteoporosis (60).

Reproductive system

Gynecomastia is frequent in men with testicular tumors that produce large amounts of human chorionic gonadotrophin (HCG), and its appearance after completion of chemotherapy may indicate residual or recurrent disease. However, not uncommonly, gynecomastia is a harmless, although troubling, late adverse effect of chemotherapy. In 16 patients who developed gynecomastia 2–9 months after treatment, and who were in complete remission, estradiol concentrations were raised; follicle-stimulating hormone (FSH) produced a higher estradiol/testosterone ratio than similarly treated patients without gynecomastia (61). It is likely that this was due to increased secretion of testicular estrogen in response to a compensatory increase in pituitary gonadotrophins after cytostatic damage to Leydig cells and spermatogenesis.

The gonadal effects of MOPP (mechlorethamine + Oncovin (vincristine) + procarbazine + prednisone/prednisolone) and MVPP (mustine + vinblastine + procarbazine + prednisone/prednisolone) in patients with Hodgkin's disease have been described (SEDA-11, 397) (SEDA-11, 403). Similar studies have been conducted in patients treated with ABVD (adriamycin + bleomycin + vinblastine + dacarbazine) and COPP (cyclophosphamide + vincristine + procarbazine + prednisone) (62). The results suggested that all men have irreversible sterility with preservation of normal Leydig cell function after COPP, which is more spermatotoxic than MOPP and much more so than ABVD. Ovarian failure was age-related after COPP, occurring in 86% of those over 24 years of age at the time of therapy, compared with 28% in women patients less than 24 years old. In contrast to men, sterility in women was always associated with ovarian endocrine failure requiring estrogen replacement. Pregnancies and normal births did occur: 14 women became pregnant and five healthy children were born. It has been proposed that analogues of gonadotropin-releasing hormone preserve gonadal function during the administration of anticancer drugs to premenopausal women.

Infection risk

Infections are major causes of morbidity and mortality in the period after transplantation, whichever immunosuppressive regimen is used, in particular bacterial infections and viral infections (cytomegalovirus, *Herpes simplex* virus, Epstein–Barr virus), but also protozoal and fungal infections (63–65). Based on an analysis of medical and autopsy records, infections were the cause of death in 70% of transplant patients, with bacteria (50%) or fungi (29%) as the most common pathogens (66).

Long-Term Effects

Mutagenicity

An increased incidence of gene aberration is to be expected in the offspring of men being treated at the time of conception with chemotherapy for testicular tumors (67). Various drug regimens for Hodgkin's disease and high-grade non-Hodgkin's lymphoma produce different patterns of changes in sister chromatid exchange frequency, and the changes may reflect the potential of the drugs concerned to induce second malignancies (68).

Tumorigenicity

Malignant tumors have been documented with increasing frequency over the last 35 years as a long-term complication of cytostatic and immunosuppressant therapy.

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Alkylating agents have been implicated in the causation of secondary tumors, including acute myeloid leukemia, myelodysplastic syndromes (69), solid tumors (70,71), Hodgkin's disease (72,73), ovarian cancer (74,75), and gastric cancer (69). Survival from the time of diagnosis of secondary malignancies is usually very short (69).

Risks in patients with Hodgkin's disease

The actuarial risks of developing secondary malignancies and/or myelodysplastic syndrome at 5, 10, and 15 years after treatment for Hodgkin's disease have been calculated (76).

In a multicenter, case-control study, the incidence of acute myeloid leukemia in treated Hodgkin's disease was 64 times higher than in the general population, the risk being greater in men. There was also a significant association between the development of acute myeloid leukemia in those patients and the use of extensive radiotherapy, vincristine + procarbazine, splenectomy, and the dose of chlormethine (73). The problem is thought to be the result of chromosomal aberrations developing in patients treated with alkylating agents (77), although there is no general agreement about this (75).

Among 679 patients receiving chemotherapy for advanced Hodgkin's disease, there were four deaths due to secondary malignancies (78). There were 75 deaths in all during 3 years, of which the vast majority were related to disseminated Hodgkin's disease.

The increased incidence of breast cancer after treatment of Hodgkin's disease may be related to supradiaphragmatic irradiation, but the risk was higher in patients with ovarian cancer, which is consistent with a common predisposition to breast and ovarian cancer. However, cytostatic drugs may have contributed to the risk.

Risks in patients with leukemias

The nucleoside analogues fludarabine, pentostatin, and cladribine have not traditionally been associated with secondary malignancies. Long-term follow-up for 5–7.5 years of 2014 patients who had received these agents for chronic lymphoid leukemia and hairy cell leukemia has been reviewed (79). Of 111 malignancies that were detected, the three most common were lymphoma ($n = 25$), prostate cancer ($n = 19$), and lung cancer ($n = 15$). While these incidences suggested significant additional risks beyond those in the normal population, the authors could not conclude beyond a reasonable doubt that the increased risks were greater than expected.

Chemotherapy-related myelodysplastic syndrome has been reported in association with adult T cell leukemia (80).

Risks in patients with Wilms' tumor

The National Wilms' Tumor Study Group has reported the incidence of second malignant neoplasms in 5278 patients treated over 22 years (81). There were 43 second malignant neoplasms, whereas only five were expected. Fifteen years after the diagnosis of Wilms' tumor, the cumulative incidence of a second malignant neoplasm was 1.6% and increasing steadily. Abdominal irradiation, given as part of the initial therapy, increased the risk, and doxorubicin potentiated the radiation effect. Among 234 patients who received doxorubicin and over 35 Gy of abdominal radiation, eight second malignant neoplasms were observed, whereas only 0.22 were expected. Treatment for relapse further increased the risk by a factor of 4–5.

Risks in patients with other tumors

Lymphoblastic leukemia has been described after treatment of a malignant germ cell tumor; it was suggested that this was related to the etoposide component of the treatment, and that development of secondary leukemia after etoposide may not be confined to the myeloid cell lineage (82).

A large international collaborative study by cancer registries has published the incidence of second malignancies following testicular cancer, ovarian cancer, and Hodgkin's disease (83): 3157 second cancers were observed among 133 411 patients diagnosed between 1945 and 1984. Patients with Hodgkin's disease were at particular risk, having an 80% excess of cancers. It confirms the high incidence of this complication noted in other reports involving smaller numbers of patients (84,85).

Other conclusions deriving from the international collaborative study (83) include the following:

- patients with testicular cancer had a 30% greater probability of developing cancers than the general population, and those with ovarian cancer 20%;
- leukemia, previously linked to alkylating agents, occurred in excess after testicular cancer, ovarian cancer, and Hodgkin's disease (relative risk 6.1), as did non-Hodgkin's lymphoma (relative risk 1.8) (the latter particularly after Hodgkin's disease);
- other cancers with significant excesses were lung cancer following Hodgkin's disease (relative risk 1.9), breast cancer following Hodgkin's disease (relative risk 1.4), and bladder cancer following ovarian cancer and Hodgkin's disease (relative risks 1.7 and 2.2 in women, respectively);
- a marked excess in incidence of secondary malignancies was found in the salivary gland, thyroid, bone, and connective tissue (there was a smaller excess for colorectal cancers following ovarian cancer).

It is likely that there is a casual relation between treatment of a first malignancy and development of a second. Alkylating agents are strongly implicated in the pathogenesis of the leukemias. Non-Hodgkin's lymphoma occurred after a 10-year latency in patients with ovarian cancer, suggesting a possible radiation effect, but early in patients with testicular tumors or Hodgkin's disease, possibly related to the immunosuppressive effect of cytostatic drugs. The excess of bladder cancers in patients with Hodgkin's disease and ovarian cancer may be related to radiotherapy (subdiaphragmatic in the former), and/or cyclophosphamide, which is widely used in the treatment of both and is a human bladder carcinogen.

Risks in transplant recipients

Although the risk of secondary malignancy clearly outweighs that of under-treatment in transplant patients,

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increasing periods of survival extend the importance of this problem and the need for close monitoring. Considerable amounts of data are accumulating based on multicenter or single-center experience, but they reflect the use of various immunosuppressive regimens and prophylactic antiviral treatments, and use different approaches to the calculation of risk incidence. Estimates of risk therefore vary widely between studies and no direct comparison is as a rule possible. However, updated data from the Cincinnati Transplant Tumor Registry, published in 1993, have helped to define comprehensively the characteristics of neoplasms observed in organ transplant recipients (86). Skin and lip cancers were the most common, and non-Hodgkin's lymphomas represent the majority of lymphoproliferative disorders with an incidence some 30- to 50-fold higher than in controls. An excess of Kaposi's sarcomas, carcinomas of the vulva and perineum, hepatobiliary tumors, and various sarcomas is also reported. By contrast, the incidence of common neoplasms encountered in the general population is not increased. In renal transplant patients, the actuarial cumulative risk of cancer is 14–18% at 10 years and 40–50% at 20 years (87,88). Skin cancers accounted for about half of the cases.

There is controversy about which factors (duration of treatment, total dosage, the degree of immunosuppression, or the type of immunosuppressive regimen) are the most relevant to determining risk. Partial or complete regression of lymphoproliferative disorders and Kaposi's sarcomas after reduction of immunosuppressive therapy argues strongly for the role of the degree of immunosuppression (86). The incidence of cancer was also significantly higher in renal transplant patients receiving triple therapy regimens compared with double therapy (89). Similarly, aggressive immunosuppressive therapy may account for the higher incidence of lymphomas in cardiac versus renal allograft patients. In a large, multicenter study involving more than 52 000 kidney or heart transplant patients between 1983 and 1991, the rate of non-Hodgkin's lymphomas in the first year after transplantation was 0.2% in kidney recipients and 1.2% in heart recipients, and fell substantially thereafter (90). Initial immunosuppression with azathioprine and ciclosporin, and prophylactic treatment with antilymphocyte antibodies or muromonab was associated with a significantly increased incidence of non-Hodgkin's lymphomas compared with other immunosuppressive regimens, which confirmed the major role of the degree of immunosuppression. Other studies have confirmed that immunosuppression per se rather than a single agent is responsible for the increased risk of cancer (SEDA-20, 340). Finally, the most striking difference between conventional and modern immunosuppressive regimens, including ciclosporin, was the average time to the appearance of tumors, in particular skin cancers and lymphomas, which was shorter in ciclosporin-treated patients (91,92).

The risk of malignant disease in renal transplant recipients increases with time after the transplant. The commonest cancers in this setting are squamous carcinoma of the skin and lip, in situ carcinoma of the cervix, and non-Hodgkin's lymphoma. An increased incidence of hepatocellular carcinoma has been reported (93). In Australia and New Zealand tumors of the urogenital tract, especially of the kidney and bladder, are the commonest non-cutaneous tumors encountered in renal transplant recipients (94). Severe metaplastic and dysplastic changes, suggestive of premalignancy, have been found in the lining epithelium of collecting ducts and tubules of cadaveric renal transplants in two patients receiving azathioprine and prednisolone (95).

Second-Generation Effects

Fertility

A reduced chance of paternity has been reported in 67% of patients who had been treated with MOPP/ABVD for Hodgkin's disease. This included oligospermia, asthenozoospermia, and/or teratozoospermia. The recovery of spermatogenesis was documented in only 40% (97).

Teratogenicity

The outcomes of pregnancies after the use of immunosuppressive drugs, in particular in renal transplant patients, have been reported, and hundreds of pregnancies have been analysed (98). The largest experience is that derived from the National Transplantation Pregnancy Registry, which has been built up in the USA since 1991 (99). This registry has accumulated data on more than 900 pregnancies, of which 83% followed kidney transplantation. Overall, the immunosuppressive regimens commonly used in transplant patients (that is azathioprine-based or ciclosporin-based programmes) do not appear to increase the overall risk of congenital malformations or to produce a specific pattern of malformation. There was no difference in the rate of malformations when comparing ciclosporin to other immunosuppressive regimens or to the baseline risk of malformations (100,101). Ectopic pregnancies and miscarriages seemed to occur at a similar rate as in the general population. The most common complications were frequent prematurity and more frequent intrauterine growth retardation with low birth weight. Susceptibility factors associated with adverse pregnancy outcomes included a short interval between transplantation and pregnancy (less than 1–2 years), graft dysfunction before or during pregnancy, and hypertension (102). Possible long-term effects of in utero exposure to immunosuppressive drugs are still seldom investigated. There is no evidence that physical and mental development or renal function are altered in children. In one study, there were changes in T lymphocyte development in seven children born to mothers who had taken azathioprine or ciclosporin, but immune function assays were normal, suggesting that fetal immune system development is not affected (103).

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Dabequine

General Information

Dabequine is a 4-aminoquinoline derivative, the adverse reaction pattern of which is unknown. The WHO Scientific Group's report concerning this drug dates from 1984 and there seems to be little or no later information on it in humans.

Dacarbazine and temozolomide

See also Cytostatic and immunosuppressant drugs

General Information

Dacarbazine is converted to an active metabolite that is thought to be an alkylating agent. It has been used to treat metastatic melanoma and, in combination regimens, soft-tissue sarcomas and Hodgkin's disease.

Temozolomide is structurally related to dacarbazine and is thought to act via the same active metabolite. It has been used to treat malignant gliomas and malignant melanoma.

Organs and Systems

Hematologic

- Temozolomide-related myelodysplastic syndrome has been reported in a 44-year-old woman with recurrent anaplastic astrocytoma in association with a cytogenetic deletion in chromosome 3 (1).

Liver

Hepatotoxicity has been reported with single-dose dacarbazine (2,3), presenting as acute liver necrosis with hepatic venous thrombosis, which can be fatal.

- Severe hepatic insufficiency in a 69-year-old man after two courses of dacarbazine, 250 mg/m^2/day for 5 days, was successfully treated with intravenous hydrocortisone 300 mg/m^2/day (4).

Fatal hepatotoxicity has also been associated with dacarbazine 500 mg/day for 5 days (5). The cause of this effect is unclear; an allergic hepatic vasculitis with thrombosis is possible.

Skin

Phototoxic reactions occurred in 10 patients with malignant melanoma when they were given dacarbazine (6). In five patients who were tested there was increased sensitivity to ultraviolet A; patch-testing in six showed no type IV allergies. In five patients oral temozolomide did not cause phototoxicity.

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Daclizumab

See also Monoclonal antibodies

General Information

Daclizumab, a humanized antibody directed against the alfa chain of the interleukin-2 receptor, has been used for initial immunosuppression in transplant patients. In a phase III trial in 275 patients who received ciclosporin, glucocorticoids, and daclizumab or placebo, there were no specific adverse effects associated with daclizumab (1). In particular, the cytokine-release syndrome did not occur, and there was no difference in the incidence of fungal or cytomegalovirus infections between the two groups.

Organs and Systems

Immunologic

The efficacy of daclizumab in acute and chronic glucocorticoid-refractory graft-versus-host disease has been studied in 16 patients, of whom nine responded (2). However 14 developed infectious complications during treatment, with a high incidence of cytomegalovirus reactivation; there were three infection-related deaths.

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Dactinomycin

See also Cytostatic and immunosuppressant drugs

General Information

Dactinomycin is used to treat cancers in children, in particular Wilms' tumor. It has similar adverse effects to doxorubicin.

Organs and Systems

Respiratory

Dactinomycin increases the pulmonary toxic effects of radiation by an estimated 30%, and reduces the radiation tolerance of the lung by at least 20% (1).

Liver

Several cases of hepatotoxicity have been reported in children receiving dactinomycin for Wilms' tumor (2–5). The hepatotoxicity of dactinomycin is dose- and schedule-related; mild hepatotoxicity is described in up to 12% of patients (6).

Five of 40 patients, who received a pulsed regimen of 60 μg/kg of dactinomycin every 3 weeks up to and including week 15, developed severe hepatotoxicity, with sharp rises in liver function test values, ascites, and liver enlargement. One child with complicating factors died and the others recovered. All five had possible contributing factors, such as repeated anesthesia (3).

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Danaparoid sodium

General Information

Danaparoid is a low molecular heparinoid consisting of a mixture of sulfated glycosaminoglycans (heparan, dermatan, and chondroitin sulfates). It has an antithrombotic effect via antithrombin III-mediated inhibition of factor Xa and to a lesser extent through inhibition of factor IIa. The ratio of antifactor Xa to antifactor IIa is over 20.

Danaparoid is as effective as heparins in inhibiting the formation of thrombi. Its major advantage over low molecular weight heparins is its low rate of cross-reactivity with heparin-associated antibodies from patients with heparin-induced thrombocytopenia (1). It is therefore indicated in patients with heparin-associated thrombocytopenia who require further anticoagulation after withdrawal of heparin. However, it should not be used if there is in vitro cross-reactivity between heparin and danaparoid. Cross-reactivity is uncommon but can result in thrombotic complications, as reported in a case with a fatal outcome (2).

Organs and Systems

Hematologic

Severe bleeding is uncommon with danaparoid but was 3.1% in one series (3).

Immunologic

Delayed hypersensitivity reactions have been reported in patients given danaparoid (4).

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Dantrolene

General Information

Dantrolene, a hydantoin derivative, is well established in clinical practice, being of greatest value for the reduction of clonus and involuntary muscle spasms (1,2). The recommended oral doses for the treatment of spastic conditions are 75–400 mg/day.

Dantrolene (1,2) is the agent of choice for treatment of malignant hyperthermia and greatly reduces the mortality to under 10% if given in time (3) together with general supportive measures.

Dantrolene differs from the centrally acting muscle relaxants in that its site of action is beyond the muscle cell membrane. It interferes with the excitation–contraction coupling mechanism of striated muscle, presumably

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by inhibition of calcium release from the sarcoplasmic reticulum.

The most common adverse reactions, seen in up to 75% of patients, are weakness, fatigue, drowsiness, and dizziness. Nausea, vomiting, and diarrhea or constipation are also common, but all these adverse reactions tend to disappear as treatment continues. In general, by adjusting the dose a satisfactory effect can be achieved with acceptable adverse effects.

Rare, but occasionally very serious, adverse effects include hepatotoxicity, respiratory depression, seizures, pleuropericardial reaction, and lymphocytic lymphoma (SEDA-5, 137).

Organs and Systems

Respiratory

Muscle weakness associated with the oral prophylactic use of dantrolene in a patient with compromised respiratory function is reported to have exacerbated postoperative respiratory depression to such an extent that artificial ventilation was required (SEDA-14, 114) (4).

Pleuropericardial reactions, with sterile effusions and eosinophilia, have also rarely been reported in patients taking 225–400 mg/day for 3 months to 4 years (5). There is no proof of a causal relation, but the chemically related nitrofurantoin has also been associated with pulmonary reactions. Patients taking dantrolene should be screened periodically.

Nervous system

Numbness of the hands and feet has been reported (6); long-term use of the structurally related phenytoin has been incriminated in causing polyneuropathy.

Exacerbation or precipitation of seizures has been reported in children with cerebral palsy taking long-term treatment with high doses of dantrolene (4–12 mg/kg) (7).

Sensory systems

Deafness occurred after 5 days' treatment with dantrolene 25 mg/day in a patient who was also taking long-term baclofen and diazepam (8). This may have been coincidental, but the authors suggested that dantrolene may have caused the effect by interfering with the release of calcium from the sarcoplasmic reticulum. It is therefore interesting that one hypothesis that explains the ototoxicity of aminoglycoside antibiotics involves disturbance of calcium ion binding and phosphorylation processes (SED-11, 549).

Hematologic

Fatal lymphocytic lymphoma has been described during high-dose dantrolene therapy (600 mg/day over 3 years) (9). Although the association was only circumstantial, another hydantoin derivative, phenytoin, is known to cause pseudolymphoma.

Liver

Hepatotoxicity from dantrolene consists mainly of minor liver function disturbances (in 1% of patients), with symptoms in 0.35–0.5% and fatal hepatitis in 0.3% (10,11). The risk of severe liver damage is greater with doses above 300–400 mg/day, with prolonged treatment (more than 60 days), in women and in patients older than 35 years.

Reproductive system

Dantrolene may have contributed to uterine atony, with resulting excessive hemorrhage when given prophylactically after a cesarean section (12).

Drug–Drug Interactions

Calcium channel blockers

The combination of dantrolene with calcium channel blockers, such as verapamil, can result in severe cardiovascular depression and hyperkalemia (SEDA-12, 113) (13,14), so that extreme care is required.

Metoclopramide

The absorption of oral dantrolene can be significantly increased by metoclopramide (15). As the risk of hepatotoxicity has been related to the dosage of dantrolene, increased clinical surveillance is necessary to avoid toxicity of dantrolene during concurrent treatment with metoclopramide.

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Dapsone and analogues

General Information

Dapsone is 4,4-diaminodiphenylsulfone (DDS, avlosulfone, disulfone) (SEDA-17, 352). It is a bacteriostatic antileprosy drug with a sulfonamide-like structure. The dosage should be 50–100 mg/day in adults (1). In children aged 3–5 years, the dosage should be reduced according to weight to, for example, 25 mg/day (2).

Studies of patients with borderline leprosy have suggested that dapsone has mild immunosuppressive effects (SEDA-18, 30). Thus, it has been given with some success to patients with dermatitis herpetiformis, subcorneal pustular dermatosis, bullous dermatoses, relapsing polychondritis, thrombocytopenic purpura (3), giant cell arteritis (4), rheumatoid arthritis, and systemic lupus erythematosus (5).

Dapsone is an alternative drug for *Pneumocystis jiroveci* pneumonia prophylaxis in individuals who cannot tolerate co-trimoxazole, and although this has become less of a problem since the advent of highly active antiretroviral drug therapy in countries able to afford these regimens, further data on the toxicity of dapsone in children are welcome. In a multicenter study from the USA daily and weekly dapsone regimens have been compared in 94 HIV-infected children, monitoring hematological and liver toxicity and the incidence of skin rashes, *P. jiroveci* pneumonia, or death (6). They concluded that the weekly regimen produced less hematological toxicity, but that this advantage was offset by a trend toward higher breakthrough rates of *P. jiroveci* pneumonia.

Dapsone analogues

The sulfone acedapsone (rINN) (4,4′-diacetyldiaminodiphenylsulfone, DADDS) is the diacetyl derivative of dapsone with a long half-life (7). However, its plasma concentrations are much lower than those of dapsone and it could enhance the emergence of resistant strains of *Mycobacterium leprae*. Its adverse effects are similar to those of dapsone, which it can replace if gastrointestinal symptoms become severe. It is available in an enteric-coated formulation, given in a dosage of 330 mg/day.

General adverse effects

The adverse effects of dapsone have been comprehensively reviewed (8). The most common untoward effect is hemolysis of varying degree; it is usually mild, except in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Methemoglobinemia and Heinz body formation also occur and methemoglobinemia can be a problem at doses over 200 mg/day. Agranulocytosis is rare but potentially fatal. Mild gastrointestinal complaints and neurological effects of dapsone are not uncommon. Under 0.5% of the patients taking prolonged dapsone therapy develop the dapsone syndrome (SEDA-16, 347). Other rare adverse effects include peripheral neuropathy, psychosis, hepatitis, nephritic syndrome, and renal papillary necrosis. Hypoalbuminemia has been seen after prolonged dapsone therapy of dermatitis herpetiformis (9). Erythema nodosum leprosum may be due to an immune complex mechanism; the antigen is provided by the bacteria and their degeneration products, possibly as a kind of Jarisch–Herxheimer reaction (10). Anaphylactic shock and tachycardia are rare. Rashes, serious cutaneous reactions, and erythema nodosum may have an immunological basis. Tumor-inducing effects have not been reported.

In France, dapsone is available in combination with ferrous oxalate as Disulone (Aventis), and in 1983–98, 249 adverse reactions were reported to French pharmacovigilance centers, mainly blood dyscrasias (often neutropenia and agranulocytosis, rarely hemolysis and anemia) (11). Five patients died; three of them had septicemia secondary to agranulocytosis. There were 29 cases of dapsone syndrome, 39 skin reactions, 27 cases of liver damage, and 27 cases of neurological and psychiatric adverse effects. Patients taking dapsone need to be under close medical supervision for early recognition of adverse reactions.

Organs and Systems

Cardiovascular

Signs of heart failure with edema, ascites, and severe hypoalbuminemia have been described in the treatment of dermatitis herpetiformis with dapsone (9).

Respiratory

Two cases of pulmonary eosinophilia attributed to dapsone were reported in 1998. Four cases had previously been reported, in which the fixed combination of dapsone and pyrimethamine (a malaria prophylactic) had been implicated, but only one previous report had implicated dapsone alone.

- A French woman with chronic urticaria (12) and an Indian man with lepromatous leprosy (13) developed fever, wheezing, and breathlessness. Both had peripheral eosinophilia and chest X-rays showed infiltrates. The woman's symptoms began 2 weeks after she started to take dapsone but recurred a few hours after a subsequent rechallenge. The man's symptoms occurred a few hours after each daily dose. Symptoms in both cases resolved within a few days of stopping dapsone.

Nervous system

Dapsone-induced neuropathy is not common (14), in spite of its widespread use in a variety of unrelated disorders. It has not been reported in patients with leprosy, but it would be easy to miss, since worsening neuropathy would readily be attributed to the underlying disease.

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Neuropathy has not been reported in patients with leprosy taking the usually recommended dosage of 100 mg/day. Isolated cases of dapsone-induced peripheral neuropathy, including motor and minor sensory defects, have been published (15,16). The clinical characteristics include a motor neuropathy affecting the extremities with onset within 5 years after the start of dapsone therapy in doses of over 300 mg/day. Complete recovery from the neuropathy almost always occurs after the dose is reduced or the drug is withdrawn.

Infection with *M. leprae* affects the peripheral nerves and the dermis, causing an accumulation of macrophages and other immune cells at the infected site (17).

Sensory systems

Ocular toxicity is rare with dapsone. Reduced visual acuity has been described after overdosage (18).

Psychological, psychiatric

Dapsone-induced psychosis has rarely been reported (SEDA-15, 331) (19).

Hematologic

The most common adverse effect of dapsone therapy is hemolysis (SEDA-15, 331). In varying degrees, it develops in nearly all patients taking dapsone in dosages of 200–300 mg/day. Even with the usual dose of 100 mg/day in normal persons and 50 mg/day in patients with G6PD deficiency, there can be some degree of hemolysis (20,21). Red cell survival can be reduced by dapsone, depending on the dose of the sulfone and its oxidizing activity, but hemolytic anemia generally does not occur without a preexisting disorder of the erythrocytes or bone marrow. The hemolysis can be so severe that manifestations of hypoxia become striking (20).

- Mild hemolytic anemia occurred in a breast-fed infant and his mother, who had continuously been taking 100–150 mg/day; dapsone and its metabolite, monoacetyldapsone, were identified in the infant's serum (SEDA-8, 290).

Dapsone is an oxidant and can trigger methemoglobinemia and delayed sulfhemoglobinemia (SEDA-8, 289) (22). Methemoglobinemia remains subclinical in most cases. However, it can be accurately inferred by a discrepancy between the oxygen saturation measured by pulse oximetry and the concentration of oxygen in the arterial blood (22). Methemoglobinemia at concentrations over 10% produces a visible lavender-colored cyanosis, and concentrations over 35% result in weakness and shortness of breath. Methemoglobinemia can be minimized by the administration of an antioxidant, such as vitamin C or vitamin E (23). Methemoglobinemia disappears after withdrawal of dapsone (SEDA-10, 273).

- A patient who had been taking dapsone inappropriately instead of an antispasmodic that had been prescribed for a spinal condition, because of incorrect labeling in a pharmacy, developed methemoglobinemia (24). Methylene blue was given intravenously and may have contributed to the severe hemolysis that followed.

Agranulocytosis is a rare complication of dapsone treatment (25).

Liver

Jaundice and hepatitis can occur as part of the sulfone syndrome with dapsone (26). Previous liver damage can predispose to serious hepatic or other adverse effects.

Urinary tract

Renal insufficiency can be associated with severe hemolysis due to dapsone (27).

Skin

Pruritus and various forms of rash can occur with dapsone. In 17 cases of dapsone syndrome, the symptoms developed on average 27 days after the start of treatment. The skin lesions took the form of erythematous papules and plaques ($n = 13$), eczematous lesions ($n = 4$), and associated bullous lesions ($n = 2$) (28). The other manifestations were: fever ($n = 16$), pruritus ($n = 15$), lymphadenopathy ($n = 14$), hepatomegaly ($n = 10$), icterus and oral erosions ($n = 5$ each), photosensitivity ($n = 4$), and splenomegaly ($n = 2$).

Serious cutaneous reactions, such as exfoliative dermatitis, toxic epidermal necrolysis, and erythema multiforme bullosum are extremely rare. Erythema nodosum leprosum has been described during dapsone therapy, mostly in the lepromatous type of leprosy (10). If erythema nodosum develops before the start of therapy, the drug should be withheld until the reaction has disappeared. Severe erythema nodosum can be controlled by short-term glucocorticoid therapy. Desensitization to dapsone in patients with hypersensitivity reactions has been proposed (29).

Immunologic

The sulfones occasionally exacerbate lepromatous leprosy, the so-called sulfone syndrome or dapsone syndrome, which resembles acute infectious mononucleosis (SEDA-16, 347) (30), and can develop 3–6 weeks after the start of treatment in malnourished patients. It appears to be an allergic reaction. It includes fever, malaise, pruritus, exfoliative dermatitis, photosensitivity, polyarthritis (31), jaundice and even hepatic necrosis, hepatosplenomegaly, lymphadenopathy, methemoglobinemia, and anemia. The syndrome is accompanied by the formation of atypical T lymphocytes with markedly increased spontaneous thymidine uptake (SEDA-8, 289). The full syndrome is probably rare, but it is important to recognize its partial expression (5,32,33). It has been suggested that it has become more common since the introduction of multidrug therapy (34), especially with rifampicin plus dapsone. The syndrome usually resolves rapidly after withdrawal of dapsone and with glucocorticoid treatment (for example prednisolone 30–60 mg/day). However, it can also end in a fatal allergic reaction (SEDA-12, 259).

Anaphylactic shock and tachycardia are among the most severe allergic reactions to dapsone (34).

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Second-Generation Effects

Pregnancy

The use of antileprosy drugs during pregnancy depends upon the severity of the disease and the relative need for treatment. Even though untoward effects on the fetus have not been reported, treatment of leprosy during pregnancy probably predisposes to erythema nodosum leprosum; if this occurs during pregnancy, clofazimine is considered the best drug available (35).

Lactation

Dapsone passes into the breast milk, with a milk to plasma AUC ratio of 0.22:0.45 (36). Assuming a daily milk ingestion of 1 liter by the infant, the maximum percentage of the maternal dose in milk was 14% over 9 days. Usually no adverse effects are noted in the newborn, unless there is G6PD deficiency.

Susceptibility Factors

Genetic factors

Glucose-6-phosphate dehydrogenase deficiency is a risk factor for hemolytic anemia (37–39).

To what extent phenotype (fast versus slow acetylators) affects the metabolism of dapsone is controversial. Since dapsone is acetylated in the liver, an effect might be anticipated (SEDA-4, 217) (40), but has not been demonstrated.

Hepatic disease

Previous liver damage predisposes to adverse effects during dapsone therapy (41).

Other features of the patient

Malnutrition predisposes to adverse effects during dapsone therapy (42).

Drug Administration

Drug administration route

Aqueous or oily suspensions of dapsone for intramuscular injection can be used to ensure adherence and to prevent resistance due to irregular drug intake. The therapeutic efficacy of intramuscular formulations lasts 3–4 weeks (43).

Drug overdose

Several reports of accidental poisoning with dapsone in children have appeared since the early 1980s. Two reports (44,45) have emphasized the persistence of the problem, although the number of childhood cases has fallen over the years. Poisoning with dapsone results in cyanosis due to methemoglobinemia, vomiting, mental confusion, tachycardia, and dyspnea. It has been suggested that treatment with multiple doses of activated charcoal may be sufficient for less severely poisoned children (methemoglobin concentration below 30%) and that a single dose of methylthioninium chloride (methylene blue) should be given to those with higher concentrations (45).

Drug–Drug Interactions

Clofazimine

In 28 patients with lepromatous leprosy, clofazimine did not influence the urinary excretion of dapsone, except in one case (46).

Rifamycins

When rifampicin was given, dapsone blood concentrations were lowered and urinary excretion was increased during the first 2 days; however, blood concentrations remained in the therapeutic range (47).

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Daptomycin

General Information

Daptomycin is a novel lipopeptide antibiotic, an inhibitor of lipoteichoic acid synthesis, with potent bactericidal activity against most clinically important Gram-positive bacteria, including resistant strains (1,2).

When daptomycin 4 mg/kg was given intravenously to seven healthy men the mean peak concentrations in plasma and inflammatory fluid were 78 and 28 μg/ml respectively; the mean half-lives were 7.7 and 13 hours respectively; the overall penetration of total drug into the inflammatory fluid was 68% and the mean urinary recovery over 24 hours was 60% (3).

Organs and Systems

Musculoskeletal

Daptomycin may have adverse effects on skeletal muscle, since it increases serum creatine kinase activity. To find the dosing regimen that has the least effects on skeletal muscle, dogs were given repeated intravenous daptomycin every 24 hours or every 8 hours for 20 days (4). The results suggested that adverse effects on skeletal muscle are primarily related to dosing frequency but not peak plasma concentrations, and once-daily administration appeared

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to minimize the potential for daptomycin-related skeletal-muscle effects, possibly by allowing more time between doses for repair of subclinical effects.

Long-Term Effects

Drug tolerance

The activity of daptomycin against both vancomycin-sensitive and vancomycin-resistant *Enterococcus faecalis* was greater than that of quinupristin + dalfopristin (5). Daptomycin was as active as quinupristin + dalfopristin but more active than linezolid. At concentrations four times the MIC, daptomycin and vancomycin achieved 99.9% killing of methicillin-resistant *Staphylococcus aureus* after 8 hours, which was greater than the killing seen with linezolid and quinupristin + dalfopristin. However, the antibacterial activity of daptomycin strongly depended on the calcium concentration of the medium.

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Decamethonium

See also Neuromuscular blocking drugs

General Information

Decamethonium, a depolarizing neuromuscular blocker, is little used nowadays. A dose of 3 mg provides adequate relaxation for intra-abdominal surgery for about 15 minutes, supplements being required at intervals of 10–30 minutes. It is not as rapid in onset of action as suxamethonium. It is not hydrolysed by plasma cholinesterase, but is eliminated by the kidneys (1).

Tachyphylaxis occurs and a phase II block develops readily (2). In high doses, muscarinic actions can be seen and histamine release can occur.

Organs and Systems

Cardiovascular

Cardiovascular effects are less frequent than with suxamethonium; a reduction in heart rate sometimes occurs after a second dose.

Nervous system

Fasciculation occurs, with similar consequences to those described with suxamethonium.

Myotonia has been precipitated by decamethonium in patients with myotonia congenita and dystrophia myotonica (3).

Susceptibility Factors

Decamethonium depends on renal excretion for the termination of its effects and is therefore contraindicated in renal insufficiency (1).

The action of decamethonium is prolonged by hypothermia (4).

Drug–Drug Interactions

Hexafluorenium and decamethonium are antagonistic. Potentiation of decamethonium block has been reported with ketamine, and can occur with neostigmine.

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Deferiprone

General Information

Deferiprone is an alpha-ketohydroxypyridine compound with metal-chelating properties (1). It is absorbed within minutes after oral administration and reaches maximum blood concentrations within 1 hour. It has a half-life of 1–2 hours, and is almost completely undetectable in blood within 5–7 hours after a single dose. Deferiprone is mostly metabolized to a glucuronide conjugate that reaches maximum blood concentrations within 1.0–1.5 hours. Deferiprone, its iron complex, and its glucuronide conjugate are detectable in the urine, and in most instances the total amount of all three accounts for almost 100% of the

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Table 1 Metal stability constants of deferiprone, deferoxamine, and diethylenetriaminepentaacetic acid (DTPA)

Ion	Deferiprone	Deferoxamine	DTPA
Fe^{3+}	35.0	30.6	28.6
Cu^{2+}	19.6	14.0	21.0
Zn^{2+}	13.5	11.1	18.4
Ni^{2+}	12.1	10.0	20.2
Co^{3+}	11.7	11.0	19.0

dose. Deferiprone is not excreted in the feces. However, there is much interindividual variation in its metabolism. The order of metal binding by deferiprone at pH 7.4 is iron > copper > aluminium > zinc (1) (see Table 1).

Deferiprone has a concentration-dependent affinity for iron, with a higher binding constant than deferoxamine or diethylenetriaminepentaacetic acid (DTPA). However, it takes three molecules of deferiprone to bind one molecule of iron, whereas deferoxamine binds iron in a 1:1 ratio. For this reason, deferiprone must be present in very high concentrations, close to toxic concentrations, to be effective (2). Deferiprone dissociates from iron when its concentration in body fluids falls to the concentration achieved just a few hours after oral administration (3). Deferiprone is effective in excreting iron in iron storage diseases and aluminium in patients on hemodialysis (1).

Iron chelation treatment has dramatically improved the prognosis of patients with beta-thalassemia (4). Parenteral deferoxamine reduces tissue iron stores, prevents iron-induced organ damage, and reduces morbidity and mortality. However, the burden of prolonged subcutaneous portable pump infusions, adverse reactions, patient non-compliance, and high cost are limiting factors, which have stimulated the development of orally active compounds. Combinations of chemically different types of chelators, which have different iron-carrying capacities and access different iron compartments, may work synergistically and result in increased efficacy, whereas lower doses of individual drugs may be less toxic (5). Examples are parenteral deferoxamine with oral deferiprone or 2,3-dihydroxybenzoic acid (2,3-DHB), or oral deferiprone with oral *N,N′-bis*(2-hydroxybenzyl)ethylenediamine-*N,N′*-diacetic acid (HDEB). Iron bound to a "shuttle," an oral agent that mobilizes tissue iron, is exchanged in the blood stream with a "sink," such as parenteral deferoxamine, and excreted via the kidneys, while the shuttle is reused. Combinations of different iron chelators can enhance iron excretion, target specific iron compartments, minimize adverse effects, increase treatment options, improve adherence to therapy, and facilitate individualization of therapy. Increasing understanding of the kinetics of iron metabolism, iron overload, and the complexity of chelation should further improve therapeutic strategies.

Observational studies

Since the controversy about the safety of deferiprone (SEDA-18, 250), its position as a therapeutic agent has been clarified (1). In the absence of iron storage, deferoxamine is undoubtedly toxic. However, it has been accepted, in spite of serious toxicity, because of the great need of an effective iron chelator for oral use (SEDA-18, 250). In this context, two studies are important, because they cast doubt on the efficacy of deferiprone (6,7). In the first, a long-term study in 51 transfusion-dependent iron-overloaded patients, 19 withdrew because of adverse events: arthropathy (stiffness, crepitus, effusion; $n = 5$), gastrointestinal symptoms (severe nausea, anorexia, vomiting; $n = 5$), granulocytopenia ($n = 3$), renal insufficiency ($n = 1$), and tachycardia ($n = 1$) (6). In the second study, in 26 patients who continued to use the drug, there was generally no satisfactory reduction in iron stores. On the other hand, deferiprone caused fewer adverse effects and was more effective in patients who were previously well-chelated and had lower initial ferritin concentrations. Also, in the long run deferiprone did not adequately control the body iron burden. In addition, in this study the alarming suspicion was raised that deferiprone can paradoxically worsen hepatic fibrosis in patients with thalassemia major, based on hepatic biopsies in 19 patients (7).

In contrast, studies in Italy and the USA have reached more positive conclusions. Of 187 patients with thalassemia who were unable or unwilling to use deferoxamine, 162 completed 1 year of treatment with deferiprone (75 mg/kg/day) (8). One patient developed agranulocytosis and another nine had various degrees of neutropenia (altogether 5%). Other reasons for withdrawal were nausea and vomiting ($n = 4$; total frequency 24% of patients), thrombocytopenia below 100×10^9/l ($n = 2$), and a fall in serum alanine transaminase ($n = 2$). Arthralgia developed in 11 patients (6%). In 29 patients who had not adhered well to deferoxamine and who took deferiprone (70 mg/kg/day) with a minimum follow-up of 1 year, adverse effects were pain in the knees in three patients, reversible neutropenia in one, and gastric intolerance in one (9). A repeat liver biopsy in 20 patients showed a reduction in the grade of liver siderosis and of iron content in seven. Worsening of hepatic fibrosis was not mentioned.

In 11 Greek patients who took deferiprone 75–100 mg/kg/day for 6 months, there were no serious adverse events of any kind (10).

In a Lebanese study in 17 patients, mainly with thalassemia major, there were no serious adverse reactions to deferiprone 50–75 mg/kg/day (11). Joint pain, stiffness, or swelling occurred in six patients; the symptoms were severe in two and mild in four patients. Seven patients had nausea, especially in the first month of treatment, and two had a reduced appetite. Headache developed in four patients. Mouth ulcers, sore throat, bitter taste, and fatigue occurred in single cases. In one patient there was a weakly positive ANF after 6 months. There were no cases of granulocytopenia and in none of the patients did adverse effects require drug withdrawal. The authors suggested that environmental or hereditary factors might have influenced the results.

In a large-scale program for the controlled use of deferiprone, established in 1997 by the Italian Ministry of Health, 86 centers collected information about 532 patients (12). In 187 patients, 269 events led to interruption of treatment, often transient. Permanent withdrawal because of adverse events occurred in 47 patients (8.9%). Reasons for withdrawal of treatment in 64 patients included

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non-compliance ($n = 30$), a serum ferritin concentration above 4000 ng/ml ($n = 14$), and a ferritin concentration below 500 ng/ml ($n = 3$). The most common adverse events were mild to severe granulocytopenia (4.3%), arthralgia (3.9%), gastrointestinal discomfort (3.2%), including nausea, vomiting, and abdominal pain, and transient increases in alanine transaminase activity (2.8%); however, the alanine transaminase results were not clearly presented in the report. Adverse events that were not established as adverse effects were urticaria, erythema, dermatitis, fever, flu-like symptoms, and "infectious episodes"; the authors did not comment on these.

Comparative studies

Deferiprone and deferoxamine have been compared in Lebanese patients, mainly with thalassemia major, of whom 17 used oral deferiprone 75 mg/kg/day and 40 received subcutaneous deferoxamine 20–50 mg/kg/day on 5 days a week; the patients were followed for 2 years (13). All those who took deferiprone did so because deferoxamine had not been suitable, due to either non-compliance or adverse reactions. One of those taking deferiprone withdrew for unknown reasons (and was excluded from the study). Deferiprone was commonly associated with orange discoloration of the urine. Six patients complained of joint pains, mainly in large joints (moderate to severe in two and mild in four), not requiring drug withdrawal. Seven patients reported nausea, four had headaches, two rashes, and two fatigue. Abdominal discomfort, mouth ulcers, and sore throat each occurred in one patient. Although two patients had transient falls in neutrophil count (to 1.3×10^9 and 1.44×10^9/l), presumably secondary to a viral infection, there were no cases of agranulocytosis.

Organs and Systems

Cardiovascular

Since circulating deferiprone-iron complexes can easily dissociate, deferiprone can redistribute iron in the body (14). Although this might theoretically lead to the precipitation or aggravation of heart failure (14), no such cases have as yet been reported.

Sensory systems

Eight patients with deferoxamine-related hearing loss were switched to deferiprone (dose not specified). In five there was deterioration in hearing (15).

Metal metabolism

Zinc deficiency was detected in 12 out of 84 patients, but withdrawal of deferoxamine was not needed (16). In another study, zinc excretion was moderately increased in three of 16 patients, and two had reduced serum zinc concentrations (17). None had clinical signs of zinc deficiency.

Hematologic

Agranulocytosis is a major limitation to the use of deferiprone and has an estimated frequency of 1.6% (16–21). Moderate leukopenia is more common.

Oxidation of deferiprone with hypochlorous acid, the major oxidant of neutrophil leukocytes, results in the formation of a chemically reactive species, consistent with the quinone metabolite of deferiprone. Deferiprone-related agranulocytosis presumably results from a T cell-mediated immunological reaction, induced by a reactive metabolite of deferiprone (18). In one case agranulocytosis and systemic vasculitis (with arthritis, palpable purpura of the legs, erythema of the palms and soles, and desquamation of the skin over the distal phalanges) occurred in association with deferiprone (22).

In 51 children with thalassemia studied in the All India Institute of Medical Sciences some degree of granulocytopenia developed in 12, 7 of whom were taking a low dose (50 mg/kg/day) and 5 a high dose (75 mg/kg/day) (23). Four had neutrophil counts well below 1×10^9/l; one developed a serious infection. Deferiprone was restarted in nine of the 12, leading to a relapse of granulocytopenia after 5 months in only one. The mechanism may be different for moderate and severe granulocytopenia. The authors suggested that the high prevalence of granulocytopenia in the Indian study could have been secondary to conditions such as poor transfusion schedules, poor nutritional status, higher serum ferritin concentrations, or genetic factors. In another study, five of 13 patients were re-challenged and granulocytopenia recurred (18).

In a large-scale program for the controlled use of deferiprone, established in 1997 by the Italian Ministry of Health, 86 centers collected information about 532 patients (12). Agranulocytosis developed in five patients, three of whom had previously had transient episodes of granulocytopenia, while using deferiprone; deferiprone was permanently withdrawn and all five recovered. There were episodes of less profound neutropenia in 18 other patients. In eight patients with neutropenia deferiprone was restarted; in one case agranulocytosis recurred and in three there was a relapse of less severe neutropenia; in the other four patients rechallenge was uneventful. Granulocytopenia occurred predominantly in patients with an intact spleen and in the younger age group (under 18 years); however, splenectomy was more frequent in the older patients. The risk of agranulocytosis is higher during the first months of exposure and probably falls with time.

In a patient with sickle cell anemia there was an increase in the frequency of sickle cell crises during the use of deferiprone (17).

Gastrointestinal

Nausea, occasionally with vomiting, occurred in six out of 20 children taking deferiprone (21). In another study, in 38 patients with transfusional iron overload, three withdrew because of severe nausea and another three had mild gastrointestinal complaints (17). The daily doses were 3–6 g (50–100 mg/kg).

Liver

In 84 patients receiving deferiprone, there were transient increases in liver enzymes in 44%, but persistent

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liver dysfunction leading to withdrawal occurred in only one (16).

Deferiprone paradoxically worsened hepatic fibrosis in patients with thalassemia major, based on hepatic biopsies in 19 patients (7). On the other hand, in another study of 20 liver biopsies, worsening of hepatic fibrosis was not mentioned (9).

In view of the suspicion that deferiprone can cause hepatic fibrosis, experience at the Sydney Children's Hospital in Australia has been reviewed, encompassing two liver biopsies in 14 patients taking deferiprone and 22 receiving deferoxamine (SEDA-23, 240) (24). The liver iron concentrations in the two groups, both at initial biopsy and subsequent biopsy, were not significantly different. Fibrosis progressed in five of 14 deferiprone users and in eight of 22 deferoxamine users. Progression greater than 1 unit occurred in four of 14 deferiprone users and two of 22 deferoxamine users. In those with positive hepatitis C serology, fibrosis showed progression in one of three patients using deferiprone and two of nine deferoxamine users; these findings were not significantly different. Pericellular fibrosis and Councilman bodies were seen in some patients: four of 11 deferiprone users and one of 20 deferoxamine users, a significant difference. However, errors in the presentation of the data hindered interpretation of the findings.

A further study has provided some reassurance. Three pathologists evaluated 112 coded liver biopsies obtained from 56 patients before and after deferiprone treatment (median duration 3.5 years). They found no evidence that deferiprone had worsened hepatic fibrosis (25). In view of the history of this problem, it is worth noting that "The International Safety Monitoring Committee that commissioned this study [was] an independent body of scientists," and that "The members of the Safety Monitoring Committee and the authors [had] no financial interest in the development of deferiprone."

Skin

In 38 patients with transfusional iron overload, deferiprone had to be withdrawn in one case because of a rash (17). Another patient developed a systemic vasculitis with arthritis, palpable purpura of the legs, erythema of the palms and soles, and desquamation over the distal phalanges. This patient had also had agranulocytosis in association with deferiprone (22).

Musculoskeletal

Deferoxamine commonly causes arthropathy of the knees, hips, shoulders, wrists, and fingers (1,17,26–32). Symptoms range from pain to inflammation and restriction of movement. Knee radiographs in one patient showed thalassemic changes, joint effusions, and minor degenerative changes in the patellofemoral joint. Magnetic resonance imaging confirmed effusions, with no evidence of synovial hypertrophy or cartilage abnormalities. The synovial fluid was a sterile transudate without inflammatory cells and low concentrations of deferiprone uncomplexed to iron. Arthroscopy showed mild synovial hypertrophy and hyperplasia, with iron staining. Synovial biopsy showed mild synovial lining cell proliferation and extensive iron deposition, without evidence of an inflammatory or allergic reaction. Since circulating deferiprone-iron complexes can easily dissociate, iron redistribution might play a role in the development of arthropathy (14). High concentrations of iron relative to deferiprone were detected in synovial fluid, suggesting that iron is shifted by deferiprone from body stores to the joints and that incomplete complexation may result in the formation of catalytic iron.

A joint effusion developed in one of 14 children using deferiprone (24).

Immunologic

A few observations have suggested that deferiprone can cause a lupus-like syndrome, with antinuclear and antihistone antibodies (33,34), but this suspicion is still unproven (29,35).

Infection risk

- An 82-year-old woman with a myelodysplastic syndrome died of *Escherichia coli* septicemia after 5 months of treatment with deferiprone (17). There was no granulocytopenia.

Death

The preliminary results of adding deferiprone to conventional treatment in order to reduce mortality from acute *Plasmodium falciparum* malaria suggest benefit (36). In 24 patients who were given deferiprone there were two deaths, compared with four in the control group of 21 patients. One patient who was given deferiprone died of unexplained pneumonia.

Second-Generation Effects

Fetotoxicity

Deferiprone inhibits intracellular ribonucleotide reductase, a rate-limiting enzyme in DNA synthesis, and in animal experiments it is toxic to proliferating tissues, especially the bone marrow. It has a pattern of adverse effects similar to those of cytotoxic drugs and is teratogenic and embryotoxic in animals (14,37).

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Deferoxamine

General Information

Deferoxamine is a polyhydroxamine acid with specific affinity for iron and, less strongly, aluminium. It is a naturally occurring siderophore produced by *Streptomyces pilosus*.

Uses

Deferoxamine is used in the treatment of acute iron poisoning and in iron storage diseases, notably beta-thalassemia (1). The usual regimen is 40 mg/kg/day as a subcutaneous infusion over 10–12 hours, starting at an early age (3 years). During erythrocyte transfusion,

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deferoxamine 300 mg/kg can be given intravenously over 24 hours. Vitamin C 100 mg/day can also be given orally to facilitate mobilization of stored iron. With such a regimen the duration and quality of life in thalassemia can be greatly improved (2,3). Another indication for deferoxamine is aluminium storage in patients on hemodialysis.

Iron chelation treatment has dramatically improved the prognosis of patients with beta-thalassemia (4). Parenteral deferoxamine reduces tissue iron stores, prevents iron-induced organ damage, and reduces morbidity and mortality. However, the burden of prolonged subcutaneous portable pump infusions, adverse reactions, patient non-compliance, and high cost are limiting factors, which have stimulated the development of orally active compounds. Combinations of chemically different types of chelators, which have different iron-carrying capacities and access different iron compartments, may work synergistically and result in increased efficacy, whereas lower doses of individual drugs may be less toxic (5). Examples are parenteral deferoxamine with oral deferiprone or 2,3-dihydroxybenzoic acid (2,3-DHB), or oral deferiprone with oral *N,N′-bis*(2-hydroxybenzyl)ethylenediamine-*N,N′*-diacetic acid (HDEB). Iron bound to a "shuttle," an oral agent that mobilizes tissue iron, is exchanged in the blood stream with a "sink," such as parenteral deferoxamine, and excreted via the kidneys, while the shuttle is reused. Combinations of different iron chelators can enhance iron excretion, target specific iron compartments, minimize adverse effects, increase treatment options, improve adherence to therapy, and facilitate individualization of therapy. Increasing understanding of the kinetics of iron metabolism, iron overload, and the complexity of chelation should further improve therapeutic strategies.

Comparative studies

Deferiprone and deferoxamine have been compared in Lebanese patients, mainly with thalassemia major, of whom 17 used oral deferiprone, 75 mg/kg/day for 2 years, and 40 received subcutaneous deferoxamine 20–50 mg/kg/day on 5 days a week (6). Those who received deferoxamine had done so for 4–24 years and were followed for 2 years. Infusion site reactions occurred in 34 patients, including pain, tenderness, itching, burning, erythema, swelling, induration, and lipodystrophy. Five patients had disturbances of vision and hearing, three had growth retardation. Six patients had increased heart rates, four had dizziness, and one had leg cramps.

General adverse effects

Deferoxamine is only used parenterally. It is more toxic when used in patients with a low iron burden. After subcutaneous infusion many patients have some local irritation and swelling. Rapid intravenous injection can be followed by flushing, wheals, tachycardia, hypotension, acute adult respiratory distress, and renal insufficiency; shock or convulsions can also occur. Headache, blurred vision, dysuria, diarrhea, and leg or hand cramps have been reported. Intramuscular injection can be painful. Hypersensitivity reactions occasionally occur, with rash, fever, and edema; anaphylactic shock has been encountered (SEDA-7, 262) (7,8). As a test dose in patients with aluminium storage disease, a low dose (500 mg in 100 ml of 0.9% saline) is usually effective and safe (9). At the higher doses used in treatment, nausea, itching, dizziness, or more serious reactions can occur. When deferoxamine is given early in childhood, osteopathy and growth impairment can occur.

Withholding iron is an important protection strategy of the body against microbial and neoplastic cells, and cellular iron depletion plays a prominent role in cell-mediated immune defence (10). The use of deferoxamine is associated with an increased risk of life-threatening opportunistic infections, notably yersiniosis and mucormycosis; such infections can affect various organ systems and pose diagnostic problems. Hypersensitivity reactions can occur but are infrequent. Rare cases of anaphylactic shock, thrombocytopenia, and bone marrow failure have been described. Tumor-inducing effects have not been reported. Deferoxamine is teratogenic in animals.

Organs and Systems

Cardiovascular

Although rarely described, hypotension can be a significant problem in patients receiving deferoxamine, especially when it is given too rapidly by intravenous injection (11); it is possibly due to histamine release (12). Dose reduction alleviates the hypotension. Anaphylactic shock has only rarely been reported (SEDA-7, 262).

In a single report, soft-tissue swelling around the elbow and localized mild pitting edema were thought to have been induced by deferoxamine (13). Although the clinical features suggested a deep-vein thrombosis, this was ruled out by a phlebogram.

In iron storage disease, ascorbic acid should be given only after adequate serum concentrations of deferoxamine have been attained, in order to prevent serious cardiac arrhythmia (14). Opportunistic fungal infections associated with deferoxamine may also involve the heart muscle and usually have a fatal outcome (15–17).

There was severe phlebitis in cancer patients receiving deferoxamine (50 mg/kg/day by intravenous infusion over 72 hours) and iron sorbitol citrate in an attempt to enhance doxorubicin activity (18). Dilution of the drug in large volumes of saline did not prevent this adverse effect.

Respiratory

Deferoxamine by continuous infusion can cause life-threatening acute adult respiratory distress syndrome, with respiratory failure, hypoxia, pulmonary edema, low pulmonary compliance, and a reduced pulmonary capillary wedge pressure (19,20). Respiratory distress can start 32–72 hours after the infusion. Lung biopsy shows diffuse abnormalities with alveolar damage, interstitial fibrosis, and inflammatory infiltration with lymphocytes, eosinophils, mast cells, and some erythrocytes. It is therefore recommended that deferoxamine should not be given as a continuous infusion for more than 24 hours (21). Although the mechanism is unknown, it has been suggested that deferoxamine causes lung damage by paradoxically increasing the production of free radicals, as a result of extended exposure of the

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lungs to ferrioxamine (21). However, others have emphasized that pulmonary endothelial cells are sensitive to macrophage-generated oxidants, and have proposed that in chelating, intracellular iron deferoxamine may acutely reduce the synthesis of catalase and heme, and that readily available extracellular heme subsequently enters cells, is broken down, and releases iron in the presence of low concentrations of catalase, which catalyses oxidant damage (22).

- In one patient, pulmonary symptoms occurred after 7 days of continuous deferoxamine infusion (dyspnea, tachypnea, tachycardia, pleuritic chest pain, and fever) and were diagnosed as pulmonary microemboli (23).

Respiratory distress and interstitial infiltrates have also been reported in children receiving deferoxamine for iron poisoning or refractory cancers (24,25).

Lung damage was attributed to high doses of deferoxamine in 17 patients with beta-thalassemia major who were given 33 courses by continuous intravenous infusion of 10 days duration in doses up to 10 mg/kg/hour (26). Respiratory dysfunction developed in two girls given the highest doses (aged 11 and 15 years). The symptoms were dyspnea, tachypnea, tachycardia, and low-grade fever. Arterial blood gas measurements showed hypoxemia and hypercapnia. Chest X-rays showed bilateral interstitial infiltrates. In one patient, mechanical ventilation was needed for 2 weeks and it took 8 months before pulmonary function returned to normal. In both patients deferoxamine was reintroduced later on without relapse.

The lungs can also be involved in deferoxamine-associated infections, such as systemic mucormycosis, which often runs a fatal course (16,17,27,28).

- Pneumonia during treatment with high doses of deferoxamine (2–2.5 g by continuous infusion) in a patient with thalassemia major was found to be caused by *Pneumocystis jiroveci* (29).

Nervous system

The use of deferoxamine to reduce aluminium overload in hemodialysis patients can exacerbate aluminium encephalopathy and precipitate dialysis dementia (30–34). Confusion, disorientation, agitation, aggression, abnormal behavior, speech arrest, myoclonus, hallucinations, and seizures can occur. Some patients are very sensitive to this effect, and a test dose of deferoxamine is advisable in order to ascertain whether aluminium is excessively mobilized (35).

Deferoxamine can modify the electroencephalogram, with progressive slowing and bilateral paroxysms (36).

Nausea and vomiting often develop in patients with rheumatoid arthritis after 4–12 days of treatment with deferoxamine, presumably as a result of chelation of iron from the central nervous system (37). Two patients who took the phenothiazine derivative prochlorperazine during treatment of rheumatoid arthritis with deferoxamine lost consciousness for 48–72 hours, possibly because this combination of drugs removed essential iron from the nervous system (38).

Headache, loss of vision, disturbed consciousness, and various other neurological symptoms can be alarming signs of deferoxamine-associated systemic mucormycosis with cerebral involvement, a condition that is usually fatal (15–17).

Sensorimotor neurotoxicity, with paresthesia, areflexia, reduced vibration and position sense, muscle weakness of the arms, and concomitant disturbances of vision and hearing, has been described in two thalassemia patients during the intravenous administration of high dosages of deferoxamine (120 mg/kg/day) (28).

Neurophysiological evaluation of 40 patients with beta-thalassemia major showed abnormal findings in brainstem-evoked potentials: auditory (25%), visual (15%), and somatosensory (7.5%); some had abnormal nerve conduction velocity (25%) and 15% had involvement of multiple neural pathways (39). Subclinical involvement of the auditory pathway was statistically associated with a higher mean daily dose of deferoxamine and a longer duration of treatment. Abnormalities of the somatosensory pathways were related to old age, a long duration of deferoxamine use, and low serum copper concentrations. Multiple neural pathway involvement was related to the duration of treatment. However, deferoxamine is only partly responsible for the subclinical abnormalities of neural pathways often found in patients with beta-thalassemia major.

Sensory systems

The reported frequency of sensorineural toxicity of deferoxamine varies. Some degree of visual and auditory toxicity can occur in about one-third of patients (40), and impairment of vision and hearing can occur simultaneously (41).

- A 25-year-old woman with beta-thalassemia, who had received subcutaneous deferoxamine 2 g/day (50 mg/kg) for 7 days a week for 3 years, developed visual loss. Her best-corrected visual acuity was 20/60 bilaterally. Automated perimetry showed bilateral central scotomata, and a Farnsworth Panel D-15 test showed an irregular pattern of errors. There were no lens opacities, and fundoscopy and fluorescein angiography were normal. Audiometry showed a bilateral high-frequency sensorineural deficit. Two days after withdrawal of deferoxamine and oral administration of zinc sulfate 20 mg/day, the central scotomata disappeared and her color vision and audiographic abnormalities reversed completely. The serum ferritin concentration was 656 ng/ml.

Since the serum ferritin concentration was relatively low, the original dose of deferoxamine may have been too high. Although zinc concentrations were not measured before treatment, the rapid and complete improvement in 48 hours after starting zinc sulfate suggested that deferoxamine-induced zinc deficiency may also have played a role.

Eyes

In aluminium-overloaded dialysis patients, acute visual impairment can occur after only the first or second intravenous test dose of 40 mg/kg deferoxamine (42–44). Visual symptoms are of retinal origin and include impairment of color vision, night blindness, and reduced visual acuity; serious and persistent visual loss can occur

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(42,45–48). Color blindness is of the tritan type, involving the blue–yellow axis (49). A light- and electron-microscopic study showed loss of microvilli from the apical surface, patchy depigmentation, vacuolation of the cytoplasm, swelling and calcification of mitochondria, and thickening of Bruch's membrane (50). Optic neuritis and pigmentary retinal degeneration can develop (51–55).

In one prospective study in 17 patients with hemolytic anemia (aged 5–25 years) lens opacities were found in 41%, changes in the retinal pigment epithelium in 35%, tortuosity of retinal vessels in 24%, dilatation and sheathing of retinal vessels in 18%, defects in color vision in 29%, and abnormal dark adaptation in 18% (56). In many other studies much lower frequencies were found. Perhaps retinal injury is related to the depletion of metals such as zinc, copper, and/or iron (57). On the other hand, ocular and auditory disturbances are not infrequent in patients with thalassemia, iron storage diseases (58,59), or uremia (45), and may be coincidental in patients receiving deferoxamine (60).

The sensorineural toxicity of deferoxamine is much more pronounced in patients without iron storage disease (for example rheumatoid arthritis). Ocular toxicity was also apparent in cancer patients receiving deferoxamine and iron sorbitol citrate in an attempt to enhance doxorubicin activity (18). Careful estimation of the necessary doses of deferoxamine and regular ophthalmological monitoring can often prevent serious injury. Visual evoked potentials can be used to monitor patients receiving high doses of deferoxamine (61). It is of great diagnostic and prognostic importance to keep in mind that a sudden loss of vision or other neurological events in a patient receiving deferoxamine can also be the first sign of life-threatening cerebral mucormycosis (62).

Cataract has been observed in animals, but even after prolonged use of deferoxamine it has only rarely been reported in humans (63,64).

- Two patients with transfusion-related hemochromatosis, who received deferoxamine 9 g/week and 10 g/month to a total dose of 39 g, and one with hemodialysis-related aluminium storage, who received 9 g/week, experienced gradual loss of visual acuity (65). There was pigmentary mottling near the maculae and electroretinography was abnormal in the two patients studied.

Acute loss of visual acuity has been described after a single test dose of deferoxamine (66).

- A 58-year-old patient with proliferative glomerulonephritis suddenly suffered loss of visual acuity (320/200 in both eyes) and disturbance of color vision 2 hours after hemodialysis, during which deferoxamine 10 mg/kg had been given to test for aluminium storage. Computerized campimetry showed bilateral central scotomata. Recovery was good but slow: within 3 months visual acuity had increased to 20/30, but bilateral pigmentary macular changes persisted.

In a study in China, electroretinographic responses and dark adaptation visual thresholds showed subtle but significant retinal dysfunction in elderly chronically transfused patients with thalassemia receiving deferoxamine (67). The authors concluded that the findings suggested that iron accumulation and not deferoxamine toxicity played a major role in these patients.

Ears

Ototoxicity due to deferoxamine ranges from a subclinically abnormal audiogram, through mid- to high-frequency neurosensorial hearing loss of the cochlear type, to acute deafness (SED-12, 552) (46). The ototoxic effects of deferoxamine have been studied in 70 adult transfusion-dependent patients (40). Characteristically there was high-frequency sensorineural hearing loss; tinnitus was less frequent. In five of eight patients with deferoxamine-related hearing loss who were switched to deferiprone there was a deterioration of hearing (40).

There are two risk factors: a high total cumulative deferoxamine dose and a low serum ferritin concentration. In order to prevent deferoxamine ototoxicity, a therapeutic index has been proposed, defined as the daily dose of deferoxamine (in mg/kg/day) divided by the serum ferritin concentration (ng/ml) (SED-12, 552) (68). A therapeutic index of 0.027 is considered to be associated with a low risk of deterioration of hearing. Regular audiometric follow-up, with special attention to the frequencies of 3 and 6 kHz, can help to detect and prevent permanent hearing loss.

Of 75 adults with thalassemia major (age range 17–32 years) 50 had normal audiography (69). Of the other 25, 13 had a sensorineural deficit of 35 dB or less, with high frequency losses, and two had a deficit of 35–75 dB. There was no association between hearing loss and age, ferritin concentration, or therapeutic index. The authors concluded that their findings were not different from those in a healthy population of the same age and were not suggestive of an ototoxic effect of deferoxamine.

In an Iranian study, the incidence of sensorineural hearing impairment in 128 patients taking deferoxamine was assessed by otological examination and pure tone audiometry (70). Patients who received deferoxamine subcutaneously every other day were compared with those who received it for 6 days a week. In both groups the average daily dose was the same, 21–39 mg/kg/day, since the alternate-day group received double doses. Of the patients in the once-a-day group there was hearing loss at a frequency of 8000 Hz in the right ear in 28% and in the left ear in 23%. In the alternate-day group, hearing loss was more common: 45% and 42% respectively. It appears that the maximum plasma deferoxamine concentration is a determinant of sensorineural toxicity. There was no relation between ototoxicity and either the serum ferritin concentration (which was meticulously controlled) or the duration of deferoxamine treatment.

Mineral balance

The administration of deferoxamine to dialysis patients in order to chelate aluminium is often associated with asymptomatic hypocalcemia, which can in turn aggravate hyperparathyroidism (12). Deferoxamine-induced hypocalcemia can be corrected with supplements of vitamin D and calcium carbonate.

- In an 8-month-old child the administration of deferoxamine for chelation of aluminium, which had accumulated as a result of total parenteral nutrition, caused sustained hypocalcemia without concomitant hypercalciuria (71).

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Presumably, the reduced calcium concentrations in this case reflected bone regeneration following the disappearance of aluminium from the bone.

Hematologic

Deferoxamine has a strong depressant effect on proliferation of bone marrow cultures in vitro (72). On the other hand, deferoxamine improves hemopoiesis in patients with anemia, for example in rheumatoid arthritis, hemolysis, or myelodysplastic syndromes, and reduces transfusion dependency (73–78). The mechanism is unknown, but increased erythropoietin responsiveness secondary to iron chelation may play a role (77).

In 11 hemodialysis patients who also received recombinant human erythropoietin for anemia secondary to renal failure, deferoxamine increased the proliferation of erythroid precursor cells and had a synergistic in vivo effect on erythropoietin (79,80).

When used in patients without iron overload, deferoxamine can cause iron deficiency (12). In 20 patients, there were falls in ferritin concentrations in six, requiring withdrawal of deferoxamine and parenteral administration of iron dextran (12). Monitoring ferritin concentrations is therefore recommended in patients receiving deferoxamine for aluminium overload. On the other hand, the administration of deferoxamine (500 mg/day by subcutaneous infusion) improves chronic anemia in patients with rheumatoid arthritis (77). This effect is thought to be achieved through increased erythropoietin responsiveness, secondary to iron chelation. Iron chelation with deferoxamine also improves hemopoiesis in patients with myelodysplastic syndromes and can reduce transfusion dependency (78). Exactly how deferoxamine works in these patients remains to be explained.

There have been rare reports of thrombocytopenia and aplastic anemia with pancytopenia, attributed to deferoxamine (81,82). Deferoxamine can accumulate in renal insufficiency if repeated doses are given, and it has been advised that platelet counts should be monitored in such patients (81).

Gastrointestinal

Gastrointestinal upsets are frequent after parenteral administration of deferoxamine (12). In addition to nausea, vomiting, and abdominal cramps, passage of black stools can occur, perhaps because of increased stool iron content. Nausea, anorexia, and vomiting often occur when deferoxamine is used in rheumatoid arthritis or Alzheimer's disease (32,83).

Urinary tract

The iron–deferoxamine complex gives the urine a reddish-brown color.

In 27 patients with thalassemia, subcutaneous deferoxamine caused a clinically significant reduction in renal glomerular filtration rate in 40% and a mild reduction in another 40% (84). In all cases of severe reductions the glomerular filtration rate tended to return to baseline on withdrawal of deferoxamine. There was also a significant increase in urine volume during deferoxamine therapy.

Deferoxamine has occasionally been reported to cause renal insufficiency (85,86) and adequate hydration and repeated measurements of renal function are recommended in patients receiving intravenous deferoxamine. Perhaps the inability to reabsorb sodium and to concentrate urine during administration of deferoxamine is due to a diuretic effect of ferrioxamine (87).

Skin

Subcutaneous deferoxamine often causes local irritation, pruritus, and swelling of the skin at infusion sites (11,88–90). Dilution of the deferoxamine solution reduces the frequency, and the addition of 1–2 mg hydrocortisone to the solution can alleviate the problem. Occasionally, severe local reactions with fever occur, leading to withdrawal (89). Disfiguring lumps can develop and can serve as foci for bacterial infection. Proper needle placement in deep subcutaneous sites and rotation of sites around the lower abdomen, thighs, buttocks, and arms usually allow sufficient time for one area to heal before it is used again.

Rapid intravenous infusion of deferoxamine (more than 25 mg/kg over 30 minutes) can cause vertigo, hypotension, diffuse erythema, and generalized pruritus (11). Such reactions reverse on withdrawal of the infusion, although occasionally a fluid bolus and/or an antihistamine may be needed to reverse the symptoms more rapidly. This reaction is considered to be due to histamine release and not to be immunological in nature; patients can be safely treated later at a lower rate of infusion.

- An edematous, erythematous, itchy rash developed on the legs of a 62-year-old woman within 48 hours after infusion of deferoxamine (91).
- Porphyria cutanea tarda-like skin lesions on the dorsum of the hands and forearms, worsening with sun exposure, has been described in association with penicillamine (12).

In another study, deferoxamine was used successfully as a treatment for hemodialysis-related porphyria cutanea tarda (92).

Skin lesions imitating vasculitis or cutaneous infarction can be the first manifestation of life-threatening mucormycosis (93,94).

Musculoskeletal

Bone dysplasia

In children, deferoxamine can cause bone dysplasia, especially when it is started at a young age (95–100). Injury to the metaphyseal growth plate cartilage affects the development of tubular bones and vertebrae. The lesions are reminiscent of scurvy, but the mechanism is uncertain. Perhaps a combination of mechanisms is involved, of which the most relevant seem to be defective function of iron-dependent enzymes and chelation of other metals, such as zinc, copper, and aluminium. Deferoxamine-induced bone dysplasia can cause reduced body height and spinal deformities. Metaphyseal changes can be detected at an early stage by serial radiography. When they are found, the nightly dose of deferoxamine should be reduced to the lowest dose that results in a negative iron balance, and growth rate should be carefully observed.

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The issue of deferoxamine osteochondropathy is even more complex, because thalassemia itself is also associated with growth impairment and body disproportionality with truncal shortening, whether puberty is induced or spontaneous (101).

Presentation

Of 476 patients in a multicenter study 40% had a short trunk and 18% short stature; in 14% there was disproportion between the upper and lower body segments (102). Spinal growth deficit starts early in infancy and is progressive. Deferoxamine-induced bone dysplasia has been identified as a contributing factor, in addition to thalassemia, hypogonadism, and siderosis. In addition to a short trunk, platyspondylosis and signs of bone dysplasia are characteristic features of bone lesions due to deferoxamine (102). The same group studied three children with beta-thalassemia (one girl aged 7 and two boys aged 6 and 12) (103). The ages of first exposure to deferoxamine were 2.5, 2, and 1.5 years and the mean daily doses were 48, 49, and 55 mg/kg/day respectively (route not stated). All three had short stature, a short trunk, and reduced growth velocity. One had protrusion of the sternum and another had genu valgum. Radiographs of the spine and long bones showed various degrees of osteopenia, platyspondylosis, cupped metaphysis of the distal femur, and pseudocystic cavities with sclerotic borders at distal and proximal metaphyses of the tibia. A reduction in the dosage of deferoxamine was followed by improvement in the bone lesions and growth velocity but not height. The authors concluded that in all children receiving deferoxamine, regular radiological and growth evaluation is needed, in order to limit bone dysplasia and short stature.

Another patient had pain and swelling at the anterior ends of the eighth and ninth ribs (104). This patient had been treated with subcutaneous deferoxamine since the age of 3 years with 37–66 mg/kg/day for 6 days a week. Radiologically there were rickets-like "rosary" lesions of the costochondral junctions. The pain disappeared within a few days after withdrawal of deferoxamine and reappeared after readministration. The mechanism underlying rickets-like changes due to deferoxamine is not known.

In a long-term evaluation of 29 patients with transfusion-dependent thalassemia major there were deferoxamine-induced skeletal changes in 15 patients: metaphyseal and spinal changes in five and spinal changes alone in 10 (105). After a reduction in the dosage of deferoxamine, the metaphyseal changes regressed in two but progressed in three, whereas the spinal changes were unchanged or progressed. Two patients required surgical intervention for marked valgus knee deformities. Of a further 21 patients with growth retardation and skeletal dysplasia, secondary to deferoxamine, four underwent surgery to correct genu valgum (106). Bone histology showed abnormal chondrocytes, alteration of staining pattern of cartilage, irregular columnar cartilage, and lacunae in the cartilaginous tissue. Bone microfractures were sometimes present. Bone microstructure showed varying degrees of impaired mineralization and the hardness of bone tissue was reduced. Bone apatite was quantitatively reduced.

Two Chinese studies in 35 consecutive patients with thalassemia on a hypertransfusion scheme plus chelation therapy have confirmed that deferoxamine-induced bone dysplasia was associated with height reduction and occurred at doses below 50 mg/kg/day (107,108).

In the first study, the patients had radiography of the left hand for bone age determination, and 12 had deferoxamine-induced long bone dysplasia (107). There was irregularity at the physeal–metaphyseal junction of the distal ulna (the site most frequently affected) and radius; metaphyseal sclerosis was also common, especially of the ulna, but also of the radius, metacarpals, and phalanges. Radiolucent lesions occasionally accompanied metaphyseal sclerosis. In six patients with relatively mild lesions, the dysplastic changes had been missed or not mentioned.

In another study, probably in the same 35 patients, coronal T1-weighted MRI scanning of the femur was performed, and in 11 patients also of the patella (108). In the distal but not proximal femurs of 11 of the 35 patients the following abnormalities were seen (in decreasing frequency): blurred physeal–metaphyseal junction, distal metaphyseal areas of hyperintensity, physeal widening, metadiaphyseal lesions, and (in only two) patellar lesions. Patients with MRI evidence of bone dysplasia had a significantly greater reduction in height than patients without.

Of 180 thalassemic patients receiving chelation therapy with subcutaneous deferoxamine, five had deferoxamine-induced serious rickets-like lesions of the long bones; two more had vertebral compression without long bone involvement (109). A microstructural analysis was made of tibia biopsy specimens taken in six patients during orthopaedic surgery and a biopsy of the iliac crest in one. With microradiography and X-ray diffraction there was irregular and reduced mineralization in all seven patients, compared with autopsy bone tissue. Apparently the osteochondrodystrophic lesions in deferoxamine osteopathy are areas with poor mineralization. The bone tissue does not reach maturity, and reduced microhardness leads to an increased risk of microfractures.

In a separate study, apparently in the same seven patients, the histological findings were presented (110). All the bone specimens showed a similar pathological pattern, with irregular columnar cartilage, lacunae in the cartilaginous tissue, abnormal chondrocytes, and impaired mineralization. Microfractures were common and were a likely explanation for the pain experienced by the patients.

Of 41 patients in Hong Kong with transfusion-dependent homozygous beta-thalassemia, who received subcutaneous infusion of deferoxamine in doses not exceeding 50 mg/kg/day, 16 had radiographic evidence of deferoxamine-induced bone dysplasia (111). All 16 had metaphyseal sclerosis of long bones (arms, hands, legs, and/or ribs); three had irregular sclerosis at the costochondral junction; one had platyspondyly. There was osteoporosis (unrelated to deferoxamine), as indicated by thinning of the metacarpal cortex, in 17 patients, eight with and nine without deferoxamine dysplasia. Two patients had evidence of medullary expansion; however, they were from mainland China and had had irregular blood transfusions and no chelation therapy, and it was unrelated to deferoxamine.

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Diagnosis

The use of sonography as a cheap and easy tool in the assessment of deferoxamine-induced bone dysplasia of the knee has been studied in 32 patients with thalassemia major (112). Characteristic lesions were notching at the metaphyseal corner, a blurred or irregular peripheral juxtaphyseal–metaphyseal contour, and widening of the peripheral juxtaphyseal–metaphyseal echogenic interface. There were 14 true positive results, 10 true negative, 7 false negative, and 1 false positive. Thus, sonography is specific but not sensitive in the diagnosis of deferoxamine-induced dysplasia. Because of its high specificity, low cost, and non-invasiveness, sonography may have a role in the longitudinal monitoring of deferoxamine-induced bone dysplasia.

Mechanism

The mechanism underlying the effect of deferoxamine on bone formation has not been identified. In one study in 21 thalassemic patients with growth retardation and skeletal dysplasia secondary to deferoxamine, there were reduced concentrations of growth hormone in 72% of patients with bone dysplasia, compared with 41% of patients without (106). Four patients with growth hormone deficiency were treated with human recombinant growth hormone. Growth velocity doubled in two patients and one patient had a partial response; the fourth patient did not respond. There was a fall in growth velocity after 1 year of treatment with growth hormone in the partial responder and in one of the responders.

Management

The following strategy may be helpful in preventing bone dysplasia during treatment with deferoxamine (105,106):

- Chelation therapy should be started after the age of 3 years and when iron accumulation has become established.
- The dosage of deferoxamine should be established on the basis of iron balance and dose–response curves.
- Deferoxamine dosages above 50 mg/kg/day subcutaneously should be avoided.
- The deferoxamine dosage should be reduced if serum ferritin values are consistently below 1500–1000 ng/ml, or if the patient has reduced growth velocity.
- It is important to detect bone changes as early as possible, since a timely reduction in deferoxamine dosage or a switch to deferiprone can prevent serious skeletal injury.

A change from deferoxamine to deferiprone led to general improvement in a 14-year-old boy with deferoxamine-induced osteochondropathy (113). Unfortunately, the patient's sitting height had deteriorated, illustrating the irreversibility of platyspondylosis.

Sexual function

Repeated monilial vaginitis was reported in patients receiving deferoxamine for dialysis-related aluminium overload (12).

Immunologic

Generalized hypersensitivity reactions and anaphylactic shock can occur but are infrequent. Hypersensitivity reactions to deferoxamine may require permanent withdrawal, worsening the prognosis in thalassemia. However, successful desensitization has been achieved in three patients with previous deferoxamine hypersensitivity, enabling continued administration of deferoxamine (8,114,115).

Infection risk

In many species, from mammals to microbes, iron is essential, and the extremely low free iron content of the blood is an important antimicrobial factor. Many microorganisms do not produce siderophores and are entirely dependent on the iron content of their direct environment; usually their inability to produce siderophores is associated with low infectivity. In the case of increased availability of iron, for example in iron storage diseases, patients may have increased susceptibility to infectious diseases (116–118). Furthermore, iron impairs granulocyte function (119,120) and monocytic function (94). An abundance of publications has shown that the use of deferoxamine in iron storage disease, dialysis patients, or acute iron poisoning (121) can promote the development of infections, notably with microorganisms that are iron-dependent and are known to be otherwise only slightly infective (SED-12, 553) (122–126). Besides providing iron to these microorganisms by acting as a siderophore, deferoxamine can deplete the pool of iron available to the macrophage cytotoxic system (127), and adversely influence the immune system (29,35).

Yersinia enterocolitica or *Yersinia pseudotuberculosis*, *Pneumocystis jiroveci* (29), *Staphylococcus aureus* (128), *Cunninghamella bertholletiae* (127), and *Rhizopus* spp. have been involved. The diagnosis of these spontaneously rare infections may be even more difficult, because the deferoxamine-associated form can have an unusual and atypical course.

Mucormycosis

Many reports of fatal cases of mucormycosis have underlined the danger of acquiring disseminated fungal infection in patients receiving deferoxamine (15–17,93,94,129–135). Boelaert and co-workers of the International Registry of Mucormycosis in Dialysis Patients (Algemeen Ziekenhuis Sint Jan, B-8000 Brugge, Belgium) collected data on a total of 62 cases of mucormycosis, of which 59 were studied in detail (136); 78% of these patients were receiving deferoxamine. The infection presented as disseminated mucormycosis in 44%, rhinocerebral in 31%, and other forms in 25%, and ran a fatal course in 52 patients (86%). The fungus (cultured in only 36%) was always *Rhizopus* (in spite of the fact that human mucormycosis can be caused by various other fungal genera (for example *Mucor*, *Absida*, and *Cunninghamella*). The finding that the species was *R. microsporus* in all identified cases is at variance with the usual predominance of *R. oryzae* in patients with diabetes mellitus. Patients using deferoxamine who present with fever, sinusitis, dry cough, hemoptysis (28), acute loss of vision (62), or neurological symptoms should undergo evaluation for mucormycosis.

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Occasionally, such conditions can start with skin lesions imitating vasculitis (93) or cutaneous infarction (94), or present with cavernous sinus or carotid arterial thrombosis (131). Although mucormycosis often has a fatal course, it can have a favorable prognosis if diagnosed early and treated aggressively with surgery and antifungal drugs (28). Many patients have several risk factors for mucormycosis in addition to deferoxamine (for example hemochromatosis, diabetes mellitus, splenectomy, immune suppression) and the contribution of deferoxamine can be difficult to prove or quantify in individual cases.

Yersinia enterocolitica

Infections with *Y. enterocolitica*, a Gram-negative aerobic and facultatively anaerobic, non-spore-forming bacterium, can occur in immunocompromized patients, and enteritis and lymphadenopathy are characteristic. However, in deferoxamine-treated patients septicemia predominates, and peritonitis and intestinal perforation (123) have been reported; the fatality rate is high (119,121,126,137–143). In all patients receiving deferoxamine, children and adults, the appearance of fever and other non-specific signs of infection should be a reason to think of yersiniosis. Children with acute iron poisoning are also at risk. In view of the severity of *Yersinia* sepsis, the prophylactic use of antibiotics has been advised whenever deferoxamine is administered to children from areas with a high incidence of yersiniosis (121). There have been single case reports of neck abscess (*Salmonella choleraesuis*) and of osteomyelitis of the ilium (*S. aureus*) during the use of deferoxamine (144,145). In the latter case bacterial contamination was considered to have occurred during insertion of the needle or during the preparation or infusion of the deferoxamine solution.

Long-Term Effects

Tumorigenicity

Deferoxamine is used experimentally in a variety of diseases, including Kaposi's sarcoma, and in vitro tests have suggested that it inhibits the growth of sarcoma-derived cells (146). Unfortunately, the intralesional injection of deferoxamine led to paradoxical exacerbation of Kaposi's sarcoma of the skin and the development of numerous sarcomatous papules in the area of injection, whereas there were no changes in untreated lesions (147).

Second-Generation Effects

Teratogenicity

Deferoxamine is teratogenic in animals, but experience in humans is not so far suggestive of deferoxamine-related malformations (148–150).

Susceptibility Factors

Age

The administration of high subcutaneous doses of deferoxamine to young children with thalassemia before iron overload has been established and is associated with a significant reduction in mean body length (151,152). Impairment of growth is associated with a rickets-like syndrome and joint stiffness. Metabolic studies have shown reduced hair and leukocyte zinc concentrations and leukocyte alkaline phosphatase activity. Retardation of growth may be related to chelation of trace elements (for example zinc), to a direct toxic effect of unchelated deferoxamine by inhibiting critical iron-dependent enzymes, or to both. It is advised that in thalassemia major, treatment with deferoxamine be started only after iron accumulation is established, that is at around 3 years of age, after 20–30 blood transfusions, when ferritin concentrations are in the range 800–1000 ng/ml. Deferoxamine doses should be established on the basis of studies of iron balance and dose–response curves, and longitudinal growth monitoring is warranted.

Children are also susceptible to opportunistic infection, notably *Y. enterocolitica* sepsis (142). In 10 children receiving intravenous deferoxamine (25 mg/kg) there were unexpected infections in four; three had episodes of fever and *S. aureus* in blood cultures, and one had *Y. enterocolitica* sepsis (128). Because of the possibility of septicemic dissemination secondary to digestive *Y. enterocolitica* infection, the occurrence of febrile diarrhea in a child with thalassemia is a reason for immediate withdrawal of deferoxamine and the administration of antimicrobial therapy (co-trimoxazole) (142).

Other features of the patient

A possible relation has been suggested between toxicity and the ratio of metabolite B of deferoxamine to unmetabolized deferoxamine (SEDA-18, 250) and there is a relation between regular deferoxamine treatment in respect to the degree of iron overload, as defined by the therapeutic index, that is the daily dose of deferoxamine in mg/kg/day divided by the serum ferritin concentration in ng/ml (SED-13, 621), and the ratio of metabolite B to total deferoxamine (deferoxamine plus ferrioxamine) in the plasma or urine (153). This is consistent with the hypothesis that metabolite B of deferoxamine, which is a product of the intercellular metabolism of iron-free but not iron-bound deferoxamine, inversely reflects the availability of iron in the plasma compartment. In patients who receive a high amount of chelation (measured as mean daily dose of deferoxamine in mg/kg) in relation to iron stores (as reflected by serum ferritin in ng/ml), the proportion of iron-free deferoxamine that is available for metabolism is greater. Therefore, the proportion of metabolite B is higher in the urine or blood of patients who are relatively well chelated. These findings suggest that the ratio of metabolite B/ferrioxamine, expressed either as plasma AUCs or urine concentrations, reflects the availability of chelatable iron, and hence the risk from excess deferoxamine administration at the time the measurement is taken, but that there is unlikely to be an inherent qualitative difference in deferoxamine metabolism in at-risk patients. Further study is needed to determine whether this is of value in identifying patients with increased risk of adverse effects prospectively.

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Drug Administration

Drug administration route

Intravenous deferoxamine can be indicated in gross iron overload, serious cardiomyopathy, or intolerance of or non-adherence to subcutaneous administration. The results of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in 17 patients (25 intravenous lines) have been presented (154). The doses of deferoxamine were calculated with reference to the serum ferritin concentration, with a view to maintaining the therapeutic index (mean daily dose in mg/kg divided by the serum ferritin concentration in ng/ml) below 0.025. The usual regimen was 6 or 7 days of continuous treatment. Only eight patients received mean daily deferoxamine doses exceeding 50 mg/kg at any time. The mean number of catheter days per patient was 697 and the median follow-up was 54 months (the longest study reported to date). The main catheter-related complications were infection (1.15 events per 1000 catheter days) and thromboembolism (0.48 events per 1000 catheter days). There were 10 episodes of bacteremic infection (with a variety of species) and 11 of port or exit-site infections (mainly coagulase-negative staphylococci). Line thrombosis occurred in four instances, pulmonary embolism in two, superior vena cava thrombosis in one, and internal jugular thrombosis in one. Since deferoxamine is a risk factor for acquiring bacterial and fungal infections (SED-14, 717), it is noteworthy that the observed rate of infection was similar to that in other patient groups. During this study, audiometric abnormalities were not observed. Only one of the 17 patients, while the therapeutic index was briefly exceeded (mean daily dose of deferoxamine 80 mg/kg), had manifestations of deferoxamine toxicity, with visual field and acuity defects (retinopathy). In this patient full resolution occurred over 9 months after dosage reduction.

The local tolerability of subcutaneous bolus injections of deferoxamine has been studied in 27 patients; deferoxamine was given 12-hourly into the abdominal wall on 5 days per week (30 mg/kg/day) (155). The patients had iron overload due to multiple transfusions and were treated for a mean period of 20 months. All had mild transient painless swelling during injection, disappearing within 10–15 minutes. Two also had pain at the injection site, with redness in one case.

Drug–Drug Interactions

Artemisinin derivatives

Co-administration of artemisinin derivatives, such as artesunate, with deferoxamine can be useful in patients with cerebral malaria, because of the combination of rapid parasite clearance by the former and central nervous system protection by the latter. Artesunate has been studied alone and in combination with deferoxamine in a single-blind comparison (156). Adverse effects were generally mild and there were no differences between the two regimens.

Ascorbic acid

There is a complex interaction between ascorbic acid, iron, and deferoxamine (157). Ascorbic acid appears to be essential for the mobilization of stored iron into a labile pool, available for chelation therapy. As a result, the administration of deferoxamine to patients with ascorbic acid deficiency will have a limited effect. On the other hand, ascorbic acid increases the toxic effects of iron, especially on the heart. In order to prevent serious cardiac dysrhythmias, ascorbic acid should only be given after deferoxamine infusion has been started and adequate serum concentrations of deferoxamine have been reached (SEDA-8, 239) (158). Ascorbic acid reduces ferric to ferrous iron, and it is the reduced iron that is responsible for the generation of highly reactive free radicals, causing tissue injury (157). Ascorbic acid up to 2 g/day stimulates deferoxamine-mediated urinary iron excretion, probably without adverse cardiac results (159). However, a report of the precipitation of cardiomyopathy with a dose of 1 g/day of ascorbic acid in a patient with hemochromatosis not receiving deferoxamine provides reason for caution in this respect (160). Interestingly, this patient later had a rapid beneficial response to deferoxamine on the heart, even before significant iron chelation could have been established. Presumably deferoxamine detoxifies iron by the inhibition of Fe^{2+}-induced hydroxyl radical generation and lipid peroxidation.

Methotrexate

In 21 children the liberation of "catalytic iron" in acute myeloid leukemia appeared to aggravate the adverse effects of high-dose methotrexate chemotherapy (161). This finding suggests that the toxicity of chemotherapy might be reduced by the co-administration of iron chelators.

Prochlorperazine

The combination of prochlorperazine and deferoxamine can cause loss of consciousness (38).

Interference with Diagnostic Tests

Iron-binding capacity

In the presence of deferoxamine, misinterpretation of the measurement of the iron-binding capacity can occur (125).

Radioactive ^{67}gallium scanning

Experience in a patient with a cerebral hemorrhage showed that chelation of gallium by deferoxamine can interfere with the diagnostic value of a ^{67}Ga scan (162).

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Defibrotide

General Information

Defibrotide is a polydeoxyribonucleotide extracted from mammalian organ. Its antithrombotic activity is partly ascribed to enhancement of eicosanoid metabolism, in particular increased release of prostacyclin, with ensuing vasodilatation and inhibition of platelet aggregation. An additional mechanism is activation of the fibrinolytic system, primarily increased activation of tissue plasminogen in the vessel wall.

The antithrombotic potential of defibrotide has been reported in patients with hepatic veno-occlusive disease after stem cell transplantation. In a randomized, placebo-controlled trial in 310 patients with claudication there was significant improvement in walking distance with defibrotide, but no difference in efficacy between the two doses of the drug tested (800 and 1200 mg/day) (1). Twenty patients stopped taking the drug because of cardiovascular events, the preset endpoints of the study. Seven others stopped because of adverse drug reactions, mainly gastrointestinal intolerance and skin reactions. They were equally distributed among the placebo and the two defibrotide groups.

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Delavirdine

See also Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

General Information

Delavirdine is a non-nucleoside reverse transcriptase inhibitor, which is dosed three times daily. No food restrictions apply. It is metabolized mainly by CYP3A, and so interactions with other drugs that use this metabolic pathway can occur.

Organs and Systems

Skin

The most frequent adverse effect of delavirdine is a rash, which usually occurs during the first 3 months of therapy in up to 50% of individuals. It is usually mild and resolves spontaneously in most patients or can be treated successfully with a short course of antihistamines. Interruption of treatment is required in less than 4% of patients (1,2).

Immunologic

Severe hypersensitivity reactions, including anaphylaxis, can occur and may necessitate drug withdrawal (3).

Drug–Drug Interactions

Antacids

Antacids interfere with the absorption of delavirdine and should therefore not be given concomitantly (4).

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Administration of antacids and buffered formulations of didanosine should be separated from that of delavirdine by at least 1 hour.

Didanosine

Didanosine interferes with the absorption of delavirdine and should therefore not be given concomitantly (5).

Enzyme inducers

Concomitant use of inducers of cytochrome P450, such as rifampicin, rifabutin, phenytoin, phenobarbital, or carbamazepine, should be avoided, since they significantly reduce delavirdine plasma concentrations (4).

HIV protease inhibitors

By inhibiting their metabolism, ritonavir potentiates the actions of other protease inhibitors. The addition of delavirdine instead of another NNRTI in three patients taking protease inhibitors plus ritonavir further increased the exposure to the protease inhibitors (6). Combining delavirdine with indinavir removes the food restrictions during indinavir administration (4). The superior virological response observed in antiretroviral regimens containing delavirdine and protease inhibitors has been attributed in part to the pharmacokinetic interaction.

Statins

- Rhabdomyolysis with acute renal insufficiency has been reported in a 63-year-old man who was taking atorvastatin 20 mg/day and delavirdine 400 mg 8-hourly (7).

The authors suggested that delavirdine had inhibited the metabolism of atorvastatin by inhibiting CYP3A4.

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Desflurane

See also General anesthetics

General Information

Desflurane is identical in structure to isoflurane, except that it is halogenated completely with fluorine instead of fluorine and chlorine. Desflurane is a volatile anesthetic that combines low blood gas solubility with moderate potency and high volatility. Its pharmacology has been reviewed (1,2).

Compared with volatile anesthetics in current use, desflurane has the advantages of being practically inert and of having a low blood-gas partition coefficient (0.4), making its onset and offset of action rapid. Its disadvantages include its low boiling point (close to room temperature) and the fact that it requires a specially heated vaporizer for delivery. It is also irritating to airways, precluding its use for induction of anesthesia and making the safety of mask anesthesia questionable. It also has excitatory effects on the sympathetic nervous system, causing tachycardia and mydriasis, which can make it difficult to judge the adequacy of anesthetic depth.

When desflurane is used with the proper equipment, alveolar concentrations can be adjusted more rapidly and precisely during administration, and recovery is quicker in both the short and long term than with other agents (3).

In a prospective, randomized study of 120 patients undergoing day-surgery, desflurane and sevoflurane were associated with shorter times to awakening, extubation, and orientation than propofol by infusion (4). Average times to awakening at the end of anesthesia were 5, 5, and 8 minutes respectively.

Organs and Systems

Cardiovascular

Desflurane increases the heart rate and reduces both mean arterial pressure and systemic vascular resistance while maintaining cardiac output (5,6). In high concentrations it can cause transient activation of the sympathetic nervous system, predisposing to hypertension and dysrhythmias (7).

Despite some coronary vasodilatation in dogs, there is no evidence of coronary steal in man. Desflurane may benefit elderly patients by allowing more rapid recovery from anesthesia (8).

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Respiratory

Desflurane is a mild respiratory irritant (6). Moderate to severe laryngospasm and moderate to severe coughing occurred often (50% of cases) during induction of anesthesia with desflurane in 206 children aged 1 month to 12 years; the authors concluded that the high incidence of these airway complications during induction limit the use of desflurane in children, but that anesthesia could be safely maintained with desflurane after induction with another anesthetic (9).

Nervous system

Increasing doses of desflurane caused no demonstrable fall in cerebral blood flow. Consequently, it can be advocated for patients undergoing neurosurgical procedures (10).

Neuromuscular function

Depression of neuromuscular function occurred 10 minutes after the introduction of desflurane 1.3% in a 32-year-old man who had previously received midazolam, fentanyl, and thiopental for induction. On withdrawal his neuromuscular function returned to baseline (11).

Liver

Poorly metabolized gases are generally safer than those that undergo extensive metabolism. Desflurane is poorly metabolized, and appeared to have no toxic effects on the liver and kidneys in 13 young men (12).

However, a case of severe hepatotoxicity after desflurane anesthesia has been reported (13).

- An obese 37-year-old woman with a past history of allergy to penicillin, nickel, and cobalt, and unexplained mild hepatitis 6 weeks after halothane anesthesia 9 years before, was given an anesthetic including etomidate, alcuronium, metamizole, piritramizide, fentanyl, nitrous oxide, and desflurane. Ten days later she developed the symptoms and signs of hepatitis, an eosinophilia, and raised hepatic enzymes, including alanine transaminase 1776 IU/l, aspartate transaminase 1258 IU/l, gamma-glutamyl transpeptidase 48 IU/l, and bilirubin 503 μmol/l. After exclusion of common causes of hepatitis, a liver biopsy confirmed acute hepatitis. There were increased titers of antitrifluoroacetylated IgG antibodies, which peaked at 0.159 on day 25 postoperatively. She eventually recovered.

This patient had multiple risk factors for anesthesia-induced hepatitis, including obesity, middle age, female sex, a history of drug allergies, and multiple exposures to fluorinated anesthetic agents. Desflurane has a very low rate of hepatic oxidative metabolism (0.02 versus 20% for halothane), and is considered to be one of the safest volatile agents as far as hepatotoxicity is concerned. Nevertheless, this case shows that it can cause severe hepatotoxicity.

Urinary tract

The effects of sevoflurane, isoflurane, and desflurane on macroscopic renal structure have been studied in 24 patients undergoing nephrectomy (14). All the anesthetics were administered using a fresh gas flow of 1 l/minute and a sodium hydroxide absorber and had an average duration of 3 hours. No injury to nephrons was observed by pathologists blinded to which anesthetic agent had been used. Postoperative creatinine concentrations and urine volumes did not differ significantly between the groups.

Body temperature

- Malignant hyperthermia has been described in a 10-year-old boy who received thiopental and suxamethonium for induction of anesthesia, followed by desflurane for maintenance of anesthesia (15).

The role of suxamethonium must also be considered in this case.

Susceptibility Factors

Age

In old people, the MAC of desflurane, with or without nitrous oxide, was less than that in patients aged 18–65 years. Doses of desflurane must therefore be reduced in older people, as with all other inhalation agents (16).

Drug–Drug Interactions

Adrenaline

Adrenaline used during anesthesia can cause ventricular dysrhythmias. The threshold dose of adrenaline for dysrhythmias is reduced by halothane, but not by desflurane; the dose of adrenaline required to produce dysrhythmias in 50% of patients was three times that needed when anesthesia was with halothane (17).

Fentanyl

The MAC of desflurane was significantly reduced 25 minutes after a single dose of fentanyl (18).

Propofol

Desflurane-based anesthesia, with and without prophylactic ondansetron, to reduce the incidence of postoperative nausea and vomiting, has been compared with a propofol infusion in 90 women of ASA grades 1 and 2 undergoing outpatient gynecological laparoscopic surgery (19). The incidence of postoperative nausea and vomiting was 80% with desflurane alone, 40% with desflurane plus ondansetron, and 20% with propofol. Postoperative antiemetic requirements were larger and times-to-home readiness longer with desflurane alone, but sedation and analgesic requirements were similar. The high incidence of postoperative nausea and vomiting suggests that routine antiemetic prophylaxis should be considered in outpatients receiving desflurane-based anesthesia.

Rocuronium

Both desflurane and sevoflurane significantly increase the neuromuscular blocking effects of rocuronium compared with isoflurane or propofol (20,21).

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Desloratadine

See also Antihistamines

General Information

Desloratadine is the primary metabolite of loratadine, with superior H_1 receptor binding, potent antihistaminic activity compared with the parent compound, and proven efficacy in allergic disease (1). It is effective and well tolerated in seasonal allergic rhinitis, including relief of nasal congestion (2–4).

In a randomized, open, four-way, crossover study in 20 healthy men desloratadine was given as single doses (5, 7.5, 10, and 20 mg) in four different treatment periods with 14 days between each dose. The C_{max} for all doses occurred at 4 hours after administration, with a half-life of 21–24 hours. There were no dose-related differences in drug absorption rate, and even the 20 mg dose was well tolerated (5). The systemic availability of desloratadine was unaffected by food in healthy adult volunteers (6).

Organs and Systems

Cardiovascular

In a large, multicenter, double-blind, placebo-controlled, parallel-group study of the efficacy and tolerability of desloratadine in 346 patients with seasonal allergic rhinitis, the symptoms improved significantly and there was no significant effect on the QT_c interval (7).

In a multicenter, randomized, double-blind, placebo-controlled study in 190 patients, desloratadine was effective in the treatment of moderate to severe chronic idiopathic urticaria, with no adverse electrocardiographic effects (8).

In healthy volunteers, 12 men and 12 women, there was no prolongation of the QT_c interval after co-administration of desloratadine with erythromycin (9).

Nervous system

Desloratadine appears to be minimally sedative, given that several studies, published in abstract, have shown no impairment in terms of wakefulness or psychomotor performance (10–12). Moreover, in a study in which desloratadine was effective and well tolerated in patients with seasonal allergic rhinitis there were no clinically significant sedative effects (7).

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Psychological, psychiatric

The results of several studies suggest that desloratadine has minimal or no effects on cognitive functions and psychomotor performance (13–15).

Susceptibility Factors

Genetic factors

The effect of race on desloratadine pharmacokinetics at steady state has been examined (16). The authors concluded that no dosage adjustments for desloratadine were required.

Age

The effect of age on desloratadine pharmacokinetics at steady state has been examined (17). The authors concluded that no dosage adjustments for desloratadine were required.

Sex

The effect of sex on desloratadine pharmacokinetics at steady state has been examined (16). The authors concluded that no dosage adjustments for desloratadine were required.

Drug–Drug Interactions

Azithromycin

The effect of co-administration of azithromycin on plasma concentrations of desloratadine has been examined in a randomized third-party-blind, placebo-controlled, parallel-group study in 90 healthy volunteers (18). An initial loading dose of azithromycin (500 mg) was given on day 3, followed by 250 mg od for 4 days. Concomitant azithromycin had little effect (<15%) on either the C_{max} or AUC of desloratadine, and there were no statistically significant increases in the PR, QT, QT_c interval, QRS complex duration, or ventricular rate after administration of desloratadine with or without azithromycin.

Erythromycin

There was no clinically relevant interaction between desloratadine and erythromycin (9).

Fluoxetine

Co-administration of desloratadine with fluoxetine did not result in clinically relevant changes in the pharmacokinetics of either drug in 54 healthy volunteers (19).

Grapefruit juice

In an unblinded, randomized, single-dose, crossover study in 24 healthy adults, grapefruit juice had no effect on the systemic availability of oral desloratadine (20). There were no clinically significant electrocardiographic changes after co-administration of grapefruit juice with desloratadine compared with desloratadine alone.

Ketoconazole

The electrocardiographic safety of desloratadine in combination with the CYP3A4 inhibitor ketoconazole has been assessed in a randomized, two-way, crossover, third-party-blind, multiple-dose, placebo-controlled study over 10 days in 24 healthy volunteers (21). Compared with desloratadine alone there were no significant or clinically important changes in QT_c, QT, PR, or QRS intervals when desloratadine (7.5 mg/day, that is 50% higher than the recommended dose) was co-administered with ketoconazole (200 mg bd). There was a 1.3-fold increase in desloratadine C_{max} when it was co-administered with ketoconazole, but this was judged not to be clinically important. The authors concluded that co-administration of desloratadine with ketoconazole has no clinically relevant electrocardiographic or pharmacodynamic implications. There was no clinically relevant interaction between desloratadine and ketoconazole (21).

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Desmopressin

See also Vasopressin and analogues

General Information

Desmopressin (*N*-deamino-8-D-arginine vasopressin, dDAVP) is a longer acting analogue of vasopressin. It has very little vasoactive effect but is antidiuretic by an action on vasopressin V_2 receptors in the renal tubule and is used to treat central diabetes insipidus and nocturnal enuresis.

At higher doses desmopressin also has significant hematological effects and can significantly boost concentrations of factor VIII and von Willebrand factor (VWF) in the blood. Desmopressin is therefore a valuable agent for the treatment of mild and moderate hemophilia A (congenital or acquired) and type 1 von Willebrand disease, in which the VWF protein structure is normal but the plasma concentration is reduced (1). By contrast with conventional coagulation factor concentrates, desmopressin is cheap and is free from the risk of transmission of viral infections, which have proved such a problem in the past. It is also very useful in the treatment of carriers of hemophilia A, many of whom have significant reductions in the baseline concentration of factor VIII. By contrast, desmopressin has no effect on the concentration of factor IX, and is thus of no value in hemophilia B (Christmas disease). It is also of little value in type 2 (abnormal VWF structure) von Willebrand's disease, which accounts for about 15–20% of all cases. The administration of desmopressin to patients with type 2B von Willebrand's disease can be hazardous, as it is likely to cause thrombocytopenia (2). The use of desmopressin in bleeding disorders has been reviewed (3). Tachyphylaxis develops if desmopressin is used for prolonged periods to control bleeding disorders, because desmopressin causes release of stored factor VIII and von Willebrand factor, after which it takes time for them to accumulate again.

Intravenous injection is the most common route although subcutaneous injection may also be used. A concentrated nasal spray formulation has been proved to be efficient for home treatment of patients with bleeding episodes or even minor surgical procedures and has also been used prophylacticly (4). The nasal spray used to treat diabetes insipidus (Desmospray) is too dilute for use in disorders of hemostasis. Similarly, desmopressin in tablet form (Desmotabs) is intended for treatment of nocturnal enuresis in children and is of no use in the treatment of hemostatic disorders.

Desmopressin also shortens the prolonged skin bleeding time in patients with renal insufficiency (5,6), hepatic cirrhosis (7,8), and congenital or acquired defects of platelet function (9–11), including aspirin-induced platelet dysfunction (12).

Desmopressin reduces blood loss in patients without bleeding disorders during surgical procedures, including cardiac surgery (13,14). However, similar benefits have also been observed with other agents, including aprotinin, tranexamic acid, and aminocaproic acid. Meta-analyses have confirmed the efficacy of these agents and have shown that aprotinin is the most effective of these agents in reducing blood loss, while desmopressin was the least effective (15,16).

Children with nocturnal enuresis treated with desmopressin have fewer wet nights per week, but this effect does not persist after therapy is stopped. A meta-analysis showed an overall rate of 7.1 adverse events per 100 children (17). These were almost all local nasal reactions, including nasal irritation and epistaxis.

In an open trial of high-dose desmopressin 1.5 mg intranasally to control bleeding in 278 patients with congenital bleeding disorders, headache occurred in 3.6% and flushing in 3.2% of patients (18). Dizziness and nausea were reported in 1–1.5% and edema in 0.3% of patients.

General adverse effects

The adverse effects of desmopressin include headache, tachycardia, facial flushing, abdominal pain, tremor, and

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sweating during or shortly after intravenous administration (1). These symptoms are quite common but are usually simply the consequence of rapid intravenous infusion, and symptoms usually quickly subside after slowing, or even temporarily stopping, the infusion. The incidence of these relatively minor adverse effects increases with the dose of desmopressin.

Organs and Systems

Cardiovascular

Facial flushing occurred in two of 25 children with either hemophilia or von Willebrand disease given high-dose intranasal desmopressin (150 micrograms) in a single-dose open study (19).

Marked hypotension with circulatory collapse has occasionally been reported with desmopressin (20,21), although both of these reports related to patients with pre-existing cardiac conditions.

Thrombotic disorders

Desmopressin stimulates the release from endothelial cells of all the multimeric forms of von Willebrand factor found in normal plasma, including large forms that are not normally present (22). These abnormal multimers can aggregate platelets, particularly at the high levels of fluid shear stress that occur at sites of arterial stenosis.

Myocardial thrombosis

There have been several reports of arterial thrombosis associated with the use of desmopressin, including myocardial infarction (23–27). One of these reports concerned a case of fatal myocardial infarction in a blood donor in excellent health, with no risk factors and no signs of vascular disease (25).

- A 59-year-old woman with hemolytic–uremic syndrome and a recent history of atypical chest pain was given prophylactic desmopressin 0.4 micrograms/kg immediately before a renal biopsy (28). Within 30 minutes she developed chest pain and bradycardia due to myocardial infarction.

Three other cases of myocardial infarction in the absence of desmopressin have been reported in patients with hemolytic–uremic syndrome, who already have an increased risk of thrombosis.

A meta-analysis of placebo-controlled trials of desmopressin in 702 cardiac surgery patients showed a significantly increased risk of myocardial infarction in treated patients (RR = 2.39, CI = 1.02, 5.60) (29). Overall mortality was not different from placebo. Desmopressin was less efficacious in reducing perioperative blood loss than either aprotinin or lysine analogues.

Cerebral thrombosis

Cerebral infarction has also been reported in association with the use of desmopressin in children (30,31). One of these cases involved a 7-month-old child with congenital nephrotic syndrome who developed a cerebral infarction after surgery (30). One child developed cerebral ischemia after *Varicella* infection and desmopressin for enuresis (31).

Thromboembolism

There are isolated reports of thromboembolic complications in recipients of desmopressin; most occurred in patients with pre-existing vascular disease. However, in nine trials of the hemostatic efficacy of desmopressin in reducing blood and transfusion requirements in 763 patients, there were no significant differences between the frequencies of thromboembolism in subjects treated with desmopressin and controls (32). An analysis of 31 clinical trials of desmopressin in patients undergoing cardiac, vascular, orthopedic, or other major surgery showed that desmopressin did not increase the incidence of thrombosis (33).

Most of the reported thromboembolic complications occurred in elderly patients and desmopressin should not be used in patients with documented arterial disease or even in elderly patients, in whom some degree of latent arterial disease may be assumed to be present (33). Concomitant use of antifibrinolytic agents, such as tranexamic acid, should also be avoided.

Ear, nose, throat

Nasal irritation and rhinitis are common adverse effects of nasal desmopressin: treatment does not normally have to be altered as a result (34,35).

Fluid balance

A potential risk of desmopressin is of water intoxication with resultant hyponatremia (36), and rapid falls in serum sodium concentration can result in seizures. The risk is increased in infants and patients receiving hypotonic intravenous fluids, and such patients need to be carefully monitored.

- A 37-year-old woman with primary enuresis continued her customary daily fluid intake (2 liters) when she started intranasal desmopressin 30 micrograms at night. Within 2 days she became severely hyponatremic, with loss of consciousness, generalized seizures, and cerebral edema.
- An 80-year-old woman with a high baseline fluid intake developed severe hyponatremia, with loss of consciousness and seizures, after a single dose of desmopressin 0.2 mg (37).
- An 89-year-old woman, who had previously been stable on desmopressin, developed severe hyponatremia and became confused and unresponsive after an increase in fluid intake (37).
- A 47-year-old woman with von Willebrand disease, who was given desmopressin and intravenous fluids perioperatively, developed hyponatremia and seizures, which resolved after water restriction (38).

In a double-blind study of desmopressin, 10 of 224 adult men had serum sodium concentrations below 130 mmol/l during a 3-week, open, dose-titration period. Men aged

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65 years and over were more likely to develop hyponatremia (39).

In another open study of elderly men and women, one of 30 subjects developed generalized weakness in association with a serum sodium concentration of 125 mmol/l and a serum potassium concentration of 3.1 mmol/l (40).

In a double-blind, crossover study, 20 men aged 52–80 years were given desmopressin for nocturia. Three of them had symptoms due to fluid retention, particularly bloating, headache, and reversible weight gain, and two of these had a significant fall in plasma sodium (41). In a meta-analysis of 14 studies of serum sodium in 529 patients treated with desmopressin there was mild asymptomatic hyponatremia in up to 10% of patients (42).

Fluid balance and plasma electrolytes should be monitored to prevent this complication, particularly if repeated doses are required. Children seem to be particularly vulnerable to this complication (43). In a long-term, open study of 245 Swedish children given intranasal desmopressin 20–40 micrograms at night for enuresis, five had an asymptomatic fall in plasma sodium (34). Mild hyponatremia, which did not cause symptoms, was found in five of 399 children in an open, multicenter trial (44).

Convulsions have been reported after desmopressin administration, some associated with excessive fluid intake.

- In a 12-year-old boy taking desmopressin for nocturnal enuresis, hyponatremia and cerebral edema developed after high fluid intake before a urodynamic procedure (45).
- A 13 kg 3-year-old boy given 40 micrograms of desmopressin intravenously and 1.6 liters of hypotonic fluid over 12 hours had convulsions and a respiratory arrest: his plasma sodium fell to 114 mmol/l (46).

There have been several reports of seizures in association with hyponatremia after intravenous administration of desmopressin to cover surgery in young children with congenital bleeding disorders such as mild hemophilia A or von Willebrand's disease (46–48). Hyponatremia and convulsions have occurred in children without congenital bleeding disorders who received desmopressin for urine concentration tests or to treat nocturnal enuresis (42,49,50).

Pulmonary edema associated with fluid retention occurred in a 27-year-old man after the administration of desmopressin to reduce blood loss during surgery (51).

Excess water intake during desmopressin therapy was implicated in seven cases of cerebral edema in children, which occurred over a 5-year period in the Czech Republic (52). A non-metered dropper was used for the desmopressin, so overdosage may have contributed.

Hematologic

Thrombocytopenia is rarely reported in patients who receive desmopressin, and is probably due to increased platelet aggregation (SEDA-13, 1310) (53).

- In a 50-year-old woman with uremia the platelet count fell from 149×10^9/l to 45×10^9/l after an abdominal hysterectomy with prophylactic desmopressin, and she developed a fatal subdural hemorrhage (53).
- A 38-year-old man with von Willebrand disease type 2B developed severe thrombocytopenia after a single dose of desmopressin (54).

Desmopressin also stimulates fibrinolysis (55), and this may have contributed to the outcome in the first patient.

In four patients with von Willebrand disease, desmopressin caused a significant but transient reduction in platelet count without an increase in plasma glycocalicin concentrations nor enhanced expression of P selectin, suggesting that acute thrombocytopenia after the administration of desmopressin in type 2B von Willebrand disease is not related to platelet activation and consumption (56).

In 224 adult men, mean age 65 (range 37–88) years, thrombocytopenia developed in one man during a 1-week washout period after dose titration to up to 0.4 mg of oral desmopressin daily over the preceding 3 weeks; thrombocytopenia did not recur on rechallenge (39).

Second-Generation Effects

Pregnancy

There is growing evidence that desmopressin can be used safely in pregnant women and no adverse effects have been reported in either mothers with diabetes insipidus or their babies (57), or in women with clotting factor deficiencies (58). However, the manufacturers advise that it should be used with caution in women with bleeding disorders, who require high doses.

One report described adverse reactions in two pregnant women with von Willebrand disease (59). One went into premature labor after a single dose (attributed to the oxytocic effect of desmopressin) and the other had severe hyponatremia associated with seizures after repeated administration of desmopressin to cover a cesarean section.

Lactation

Insignificant quantities of desmopressin pass into breast milk (60), and so breastfeeding is not contraindicated in association with desmopressin administration to a nursing mother.

Drug–Drug Interactions

Carbamazepine

Carbamazepine increases the release of endogenous antidiuretic hormone and can therefore potentiate the antidiuretic effect of desmopressin. Of 103 children with cranial diabetes insipidus included in a retrospective analysis, 10% became hyponatremic (61). The risk of hyponatremia was three-fold higher when desmopressin and carbamazepine were given in combination.

Chlorpromazine

Chlorpromazine increases the release of endogenous antidiuretic hormone and can therefore potentiate the antidiuretic effect of desmopressin (62).

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Lamotrigine

In 103 children with cranial diabetes insipidus, 3 children who started or had an increase in dose of lamotrigine needed a larger dose of desmopressin, suggesting an effect on the renal tubule or on drug clearance (61). Lamotrigine also increased desmopressin dosage requirements in two other children with cranial diabetes insipidus (63).

Tricyclic antidepressants

Tricyclic antidepressants increase the release of endogenous antidiuretic hormone and can therefore potentiate the antidiuretic effect of desmopressin. A hyponatremic convulsion occurred in a child who was given desmopressin and imipramine (64).

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Dexamfetamine

See also Amphetamines

General Information

Dexamfetamine or (+)-amfetamine is significantly more potent than (−)-amfetamine. The use of dexamfetamine as an appetite suppressant has rapidly declined, because of appreciation of its potential for abuse and addiction. These arise mainly from euphoria, which may be followed by depression as the effect of the drug wears off. Stimulant effects were reported in 23% of 347 patients using dexamfetamine as an appetite suppressant (SED-9, 10).

Dexamfetamine is extremely variable in its effects, and can even produce drowsiness in a small proportion of subjects. Postmenopausal women are more prone to drowsiness, anger, and sadness than euphoria (1). Adverse effects due to sympathetic overactivity are fairly common but not usually serious. However, in view of dexamfetamine's addiction potential, other anorectic drugs should be considered first.

When it was first introduced, one of the most frequent uses of amfetamine was as an anorexigenic agent in the treatment of obesity. A number of anorectic

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agents, many of them related to amfetamine, have since been manufactured. Most are stimulants of the central nervous system. In descending order of approximate stimulatory potency, they are dexamfetamine, phentermine, chlorphentermine, mazindol, diethylpropion, and fenfluramine. The last of these has a stimulatory effect only in overdosage. One of the problems that has concerned clinicians over the use of anorectic drugs for the treatment of weight reduction is that despite 6 weeks to 3 months of weight reduction efficacy, the effect begins to wear off and on withdrawal weight gain rebounds.

The anorectic agents produce adverse effects mainly of the central nervous system sympathomimetic type. Therapy should therefore only be allowed under strict medical supervision, to ensure the earliest possible detection of any signs of drug abuse. Long-term drug treatment of obesity should be avoided altogether.

Organs and Systems

Metabolism

Hyperinsulinemia secondary to chronic administration of dexamfetamine, with a fall in fasting blood sugar after a few weeks of use, has been described (SED-9, 10).

Drug Administration

Drug formulations

Introduction of modified-release formulations has provided some improvement in the use of anorectic drugs. Steady release of the drug permits a constant concentration in the blood throughout the entire day. Thus, a sudden excess of physiological hunger is prevented, and adverse effects involving the central nervous system are diminished.

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Dexbrompheniramine

See also Antihistamines

General Information

Dexbrompheniramine is the dextrorotatory isomer of the first-generation antihistamine brompheniramine.

Drug Administration

Drug overdose

Marked dyskinesia in an 18-month-old girl followed an overdose of a combination of dexbrompheniramine and pseudoephedrine (1).

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Reference

1. Barone DA, Raniolo J. Facial dyskinesia from overdose of an antihistamine. N Engl J Med 1980;303(2):107.

Dexchlorpheniramine

See also Antihistamines

General Information

Dexchlorpheniramine maleate (SED-13, 417) is the dextrorotatory isomer of chlorphenamine.

Organs and Systems

Sensory systems

In healthy volunteers dexchlorpheniramine caused impaired selective auditory attention in the absence of subjective awareness of this impairment (1).

Hematologic

Dexchlorpheniramine caused hemolytic anemia in a 47-year-old woman who took 4 mg/day for 3 days. The direct antiglobulin test was positive, and circulating antibodies were detected in the serum, which reacted in vitro with other antihistamines as well (2).

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Dexibuprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Dexibuprofen is the dextrorotatory isomer of ibuprofen.

Organs and Systems

Nervous system

Meningoencephalitis has been attributed to dexibuprofen in a 22-year-old woman with systemic lupus

erythematosus (1). Patients with systemic lupus erythematosus have increased susceptibility to NSAID-induced aseptic meningitis or encephalitis.

Reference

1. Obermoser G, Bellmann R, Pfausler B, Schmutzhard E, Sepp N. Aseptic meningo-encephalitis related to dexibuprofen use in a patient with systemic lupus erythematosus: a case report with MR findings. Lupus 2002;11(7):451–3.

Dexindoprofen

See also Non-steroidal anti-inflammatory drugs

General Information

The NSAID dexindoprofen has a similar adverse effect pattern to the parent drug, indoprofen. Gastrointestinal, nervous system, and skin reactions are the most frequent (1).

Reference

1. Fornasari PA, Mattara L. Efficacia e tollerabilità del dexindoprofen in confronto con il diclofenac sodico nel trattamento di patienti osteoartrosici. [Efficacy and tolerance of dexindoprofen compared with diclofenac sodium in the treatment of osteoarthrosis patients.] Clin Ter 1985;113(2):125–33.

Dextrans

General Information

Dextrans are mixtures of polymerized glucose molecules, mostly alpha-1,6-glucans, of variable molecular weight from 1 to 110 kDa. Infused dextran is mainly eliminated unmodified by the kidney at a rate of 50% in the first 24 hours and 20% in the following 48 hours. The remaining 30%, which is made up of the molecules with the highest molecular weights, is partly eliminated by the gastrointestinal tract, where it is thought to be hydrolysed by coliform bacteria, and partly metabolized by splenic and hepatic dextranase (dextrano-alpha-1,6-glucosidase).

Uses

Dextran 70, so-called because its molecules have an average weight of 70 kDa, is used as a plasma substitute, as is dextran 40. Dextran 40 has been used to improve blood flow in ischemic limbs. Dextran 40 and dextran 70 have been used to prevent deep venous thrombosis. Dextran 1 is used as a desensitizer to prevent allergic reactions to dextrans of larger molecular weight. After reproductive surgery 32% dextran 70 is sometimes administered intraperitoneally in an attempt to reduce the formation of adhesions.

Dextran deposition in tissues

In biopsy and autopsy studies 32 patients treated with regular hemodialysis for an average of 61 months, who had also received dextran 40 as a plasma expander because of hypotension during hemodialysis, were compared with a control group of 11 hemodialysed patients who were given other plasma expanders. In 11 of the former who had received the largest dose of dextran 40 (0.38 g/kg/week), particles were found in the cytoplasm of macrophages in various organs, which were PAS-positive and diastase-resistant on light microscopy and birefringent on polarization. Electron microscopy showed a fibrillar structure, but ionic analysis by electronic sampler on scanning electron microscopy excluded silicone. No intracellular inclusions were observed in the control group, or in the patients given dextran 40 in doses lower than 0.08 g/kg/week. There was a linear relation between the number of particles and dose of dextran 40 that had been given, leading the authors to suggest that the material demonstrated in the macrophages was dextran that had been structurally modified and conglomerated by macrophage activity to a water-insoluble form (1).

Organs and Systems

Cardiovascular

High output left ventricular failure has been described after hysteroscopic lysis of adhesions using dextran as a distension medium. Prolonged surgical dissection of the uterine wall (the precise duration of the operation was not stated in the report) and the large volume of dextran and fluid (2 liters of 5% dextrose and an additional 800 ml of dextran) probably caused the dextran to enter into the systemic circulation, inducing a significant shift of fluid into the intravascular compartment (2).

Respiratory

Pulmonary edema and coagulopathy following intrauterine instillation of 700 ml of 32% dextran 70 has been reported (3). The volume exceeded that recommended by the manufacturer (500 ml), and the installation time (2 hours) was in excess of that recommended (45 minutes). The authors pointed out that hyperosmolarity of the agent is such that if it enters the intravascular compartment, volume overload can result, since 100 ml of intravascular dextran 70 will osmotically expand the intravascular volume by 860 ml, by drawing interstitial fluid into the central compartment. This can further aggravate the risks of pulmonary edema and dilutional coagulopathy.

Dextrans can also cause non-cardiogenic pulmonary edema and/or respiratory distress syndrome.

- Adult respiratory distress syndrome occurred after the intravenous infusion of dextran 40 in a 30-year-old woman, a smoker with a history of insulin-dependent diabetes mellitus, who had sustained an acute inferior myocardial infarction; the dextran was given in

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preparation for possible stent placement after angioplasty of the right coronary artery (4).

- A 43-year-old woman underwent delayed breast reconstruction 9 months after modified radical mastectomy and received 4 liters of crystalloid intraoperatively (5). Postoperatively she was given an infusion of dextran 40 preceded by a small dose of dextran 1. On the next 2 days she was febrile, with no respiratory symptoms, although her oxygen saturation was 83%. On the third day, she was febrile and dyspneic, with a respiratory rate of 29 breaths per minute. Her oxygen saturation fell to 70%. A chest X-ray showed diffuse alveolar infiltration. Dextran was withdrawn. Her lungs worsened, and on day 6 she required intubation for worsening hypoxia, dyspnea, and tachypnea. A chest X-ray showed bilateral alveolar consolidation and other signs consistent with respiratory distress syndrome. Her oxygenation slowly improved and extubation was possible on day 11.
- Acute pulmonary edema developed in a healthy patient after elective microsurgery for treatment of a malignant tumor of the forearm (6). The patient was in good physical condition before the operation, and there was no sign of volume overload perioperatively. Cardiac enzymes, electrocardiogram, and echocardiogram were normal. No other medications were likely to have caused the pulmonary edema. The gradual response to diuretics suggested a non-cardiogenic cause.

Although thromboprophylaxis of microvascular anastomoses seems advisable theoretically, there is little clinical evidence to support the use of dextran for this purpose. The pulmonary edema in these cases was thought to be non-cardiogenic, similar to that caused by heroin, methadone, propoxyphene, and salicylates, due to a direct adverse effect on the pulmonary vasculature, rather than anaphylaxis, cardiac pump failure, or volume overload.

Severe pulmonary edema developed in a patient who underwent breast reconstruction in whom dextran was used to improve the deterioration of flap perfusion during the postoperative period (7).

- A 48-year-old white woman underwent right modified radical mastectomy for infiltrative ductal carcinoma. She was given dextran 40, 10 ml/kg, on the second postoperative day because of partial ischemic changes in the flap. She then had nausea, vomiting, and fever, and 10 hours later developed dyspnea and chest pain, which worsened on the following day. Chest radiography showed bilateral pleural effusions and bilateral reticulonodular opacities that were interpreted as pneumonic infiltration. She did not have hemoptysis or pleuritic chest pain, and there were no signs of heart failure. She had a leukocytosis (16.4×10^9/l). Cultures of sputum and fluid aspirate were negative. On postoperative day 4, her dyspnea worsened, her PO_2 fell, and her pH rose to 7.53. Lymphangitic carcinomatosis was considered, but this was not supported by cytology of the effusion fluid or tumor markers. Her history of allergic reactions suggested the possibility of dextran-induced severe pulmonary edema leading to respiratory distress syndrome. Dextran was withdrawn and she was given an intravenous bolus dose of prednisolone 250 mg. Her symptoms rapidly improved and she recovered gradually over the following week.

Although severe pulmonary edema with respiratory failure is not a typical allergic reaction to dextrans, this case illustrates that it cannot be discounted.

Acid–base balance

Arterial blood gases and acid–base balance were evaluated in 50 patients with dextran-induced anaphylactic reactions. Metabolic acidosis was consistently present in severe cases, leading to cardiac arrest. Acidosis was also found in patients with less severe reactions and only slight impairment of the circulation. Bronchospastic respiratory signs were common, but acidosis also developed in the absence of these symptoms and in patients with mild or no circulatory problems. The severity of the acidosis was often underestimated during treatment. Arterial PO_2 and PCO_2 were not significantly affected during these reactions. It was suggested from this study that the circulation is unlikely to be normalized until the metabolic acidosis is corrected, despite other therapeutic efforts that may be made (8).

Liver

In a retrospective study of the adverse effects of various drugs in 197 patients who underwent infertility surgery under general anesthesia and simultaneous intraperitoneal administration of 32% dextran 70, there were increases in postoperative transaminases in 86. The use of 32% dextran 70 in combination with glucocorticoids or halothane (or other halogenized drugs) resulted in an increased risk of temporarily disturbed liver function. Of 31 patients followed after discharge from hospital, the transaminases returned to normal within 6 months in 29. The authors suggested that hepatocytes may be damaged by enhanced glycogen deposition and/or lipid accumulation in patients who receive dextran. Glucocorticoids potentially increase the risk of liver function disturbance (9).

Urinary tract

Of 207 patients with ischemic stroke, stages III or IV, treated with an intravenous infusion of dextran 40 over 4 days, 9 (4.3%) developed acute renal insufficiency attributable to the dextran. Oliguria occurred after a mean time of 4 (range 3–6) days. The incidence of dextran-induced renal insufficiency was higher in patients with pre-existing impaired kidney function. The high risk of death in the patients who developed renal insufficiency was due to non-renal complications, notably pneumonia and pulmonary embolism (10).

Of 211 patients with acute ischemic stroke, stages III or IV, treated with daily intravenous dextran 40, 500–1000 ml for 4 days, 10 (4.7%) developed acute renal insufficiency associated with dextran infusion (11). Oliguria developed after a mean time of 4 (range 3–6) days. The incidence of dextran-induced acute renal insufficiency was significantly higher in patients with pre-existing reduction of glomerular filtration rate below 30 ml/minute/1.73 m^2. Five of the patients with acute renal insufficiency died within 4–12 days after hemodilution therapy with dextran 40; this high mortality was attributable to non-renal complications.

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In a report of two cases of anuric acute renal insufficiency induced by dextran 40, diuresis and renal function were quickly restored to normal after plasmapheresis (12). Renal biopsy showed normal kidneys, except for swelling and vacuolation of renal tubules suggestive of osmotic nephrosis.

Cases of acute renal insufficiency, apparently representing a hypersensitivity reaction, have been reported from Australia (SED-11, 726) (13), and elsewhere (14,15). On the basis of these observations it has been suggested that the pathogenesis of renal dysfunction during treatment with dextran 40 involves mainly intraluminal hyperviscosity, reduced tubular flow, and pinocytic uptake of colloid into tubular cells (16). Direct injury to the renal tubular epithelium cannot be ruled out (17).

- During surgery for an avulsed pinna, an 18-year-old Chinese man was given 500 ml of 10% dextran 40 infused over 2 hours at 12-hourly intervals (18). On day 3 he developed nausea and abdominal pain. The dextran infusion was stopped. His serum creatinine was 1092 μmol/l. Total anuria followed within 24 hours and he developed acute pulmonary edema. Renal biopsy was compatible with osmotic nephrosis caused by dextran.

Dextran is widely used in plastic surgery, but acute renal insufficiency is rare; according to one source only 60 cases have been reported (19). These patients were usually either critically ill or had pre-existing renal impairment. The authors presumed that acute renal insufficiency had occurred as a result of increased plasma oncotic pressure, reducing the filtration pressure in the glomerulus; alternatively, some dextran 40 polymers may have been filtered into the tubules, causing obstruction. The amount of dextran required before acute renal insufficiency develops varies from 50 to 1000 g. One patient received 300 g over 3 days, although renal function deterioration was not recognized until uremia developed. The authors suggested that care be taken when using dextran 40, especially in patients with pre-existing renal impairment or vascular disease. Regular monitoring of urine output, electrolytes, and renal function in all dextran recipients is recommended. Administering replacement fluids before checking renal function could lead to life-threatening fluid overload. Withdrawal of dextran should be considered if there is persistent oliguria or a rise in creatinine or urea concentrations. Treatment of dextran-induced acute renal insufficiency should comprise temporary hemodialysis alternating with plasmapheresis, to remove dextran molecules from the blood.

- A 45-year-old man with insulin-dependent diabetes associated with nephropathy, neuropathy, and retinopathy was given dextran 40 (25 ml/hour) after orthopedic surgery (20). His urine output fell from 2 to 3 liters on postoperative day, 1–40 ml/day on day 2, and his creatinine clearance fell from 54 to 32 ml/minute. There were many casts in the urine. Dextran was withdrawn, but his creatinine clearance fell to 12 ml/minute on day 5. On day 6 a large hematoma in the rectus sheath was drained, followed by plasmapheresis (to remove dextran) and hemodialysis. Over the next 24 hours, his urine output increased to 2.2 l/day and his creatinine clearance increased to 20 ml/minute. Plasmapheresis was repeated. Nine days later, his renal function had improved.

This is another case of dextran-induced renal insufficiency in a patient with pre-existing renal insufficiency, in this case caused by insulin-dependent diabetes mellitus of more than 30 years duration. The authors recommended that dextran should not be used in patients with chronic renal insufficiency and a creatinine clearance below 40 ml/minute. If dextran-induced renal insufficiency develops, dextran should be withdrawn and if renal function does not recover, plasmapheresis should be used to remove the dextran load.

Acute renal insufficiency due to dextran has rarely been reported after microsurgery (21).

- An 81-year-old woman underwent commando resection and supraomohyoidal lymphadenectomy for recurrent squamous cell carcinoma of the right inferior alveolar process. Preoperatively, she was given intravenous gentamicin 120 mg and clindamycin to be continued twice-daily postoperatively. During surgery and the first 5 postoperative days, she was given dextran 40, 1 l/day, as an antithrombotic and rheological agent. On the second postoperative day she became increasingly dyspneic. Despite furosemide her urine production fell and she became anuric on day 4. Gentamicin was stopped on day 3. On day 5, she was reintubated and artificially ventilated; thrice-weekly plasmapheresis was started. Three days later spontaneous diuresis recurred and she was extubated on postoperative day 10. On day 25, she refused further plasmapheresis and diuresis returned to normal.
- A 69-year-old man underwent radical resection, supraomohyoidal lymphadenectomy, and radial forearm flap reconstruction for squamous cell carcinoma of the oropharynx. Preoperatively, he was given intravenous gentamicin 320 mg/day and clindamycin 600 mg bd, to be continued for 5 days. He was given dextran 50, 500 ml/day. Despite extra intravenous hydration combined with dopamine and furosemide, his urine output fell to 40 ml/hour on the first postoperative day and he became anuric on day 2. Gentamicin and dextran were withdrawn, he was artificially ventilated, and thrice-weekly plasmapheresis was started. Renal biopsy showed hydropic swelling and vacuolation of the tubular epithelium and narrowing of the tubular lumen. After 6 days, he was extubated and his renal function recovered only marginally. One month after surgery, he died of respiratory failure.

The authors suggested that acute renal insufficiency had been caused by dextran rather than gentamicin, because both patients developed anuria, which is commonly present in dextran-induced acute renal insufficiency, rather than the initial non-oliguric course characteristic of aminoglycosides. Further evidence for this conclusion was the renal biopsy in the second patient, while negative immunofluorescence and the rapid return of kidney function in the first patient suggested a non-structural effect of dextran on the kidney. The authors have stopped using dextran as an antithrombotic agent in microsurgery.

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Immunologic

Anaphylactic reactions to dextrans have been reported, for example within 10 minutes after exposure to dextran in hysteroscopy (22). It can be fatal (23).

- A 54-year-old man developed generalized pruritus, dyspnea, and sudden hemodynamic shock, with cardiac and respiratory arrest 8 hours after the resection of a hepatic hydatid cyst, while being given dextran 40. He had no prior history of atopy or adverse drug reactions. Despite intensive resuscitation he remained unconscious and hemodynamically unstable. During the succeeding days he became septic with progressive renal function impairment and died on day 5. A range of serum tests for antibodies detected dextran-reactive antibodies. In addition, there was evidence of complement protein consumption within 6–24 hours of the clinical reaction.

The authors suggested that dextran-reactive antibodies had formed immune complexes with dextran, leading to complement activation and release of mediators of anaphylaxis. There was also evidence of mast cell degranulation. They therefore recommended that titration of dextran-reactive antibodies before administration of dextrans could provide a method of identifying those who are at risk of dextran-induced anaphylactic reactions.

- A 24-year-old healthy volunteer was given 10 ml of 6% dextran 60 during a preliminary examination (24). After about 5 minutes the first clinical symptoms of anaphylactic shock were evident, with a reduction in systolic blood pressure to 90 mmHg and an increased heart rate to over 90/minute. These returned to normal after therapy in the head-down position with clemastine 2 ml (2 mg), hydrocortisone 200 mg, and etherified starch 500 ml over about 8 minutes. During this period, responsiveness was unsatisfactory although he complained of warming of the skin, paresthesia, and nausea.

The authors suggested that this reaction had been due to a dextran-induced anaphylactic reaction, but were uncertain as to the cause of these observations, as they were not accompanied by immediate symptoms of shock. It is unclear if this case was caused by an antibody reaction.

Frequency and susceptibility factors

A large-scale prospective study was carried out in 49 public and private hospitals throughout France between June 1991 and October 1992, aimed at discovering the frequency and severity of anaphylactoid reactions to colloid plasma substitutes, looking for possible risk factors, and determining the mechanisms involved (25). In all, 19 593 patients were evaluated; 48% were given gelatins, 27% starches, 16% albumin, and 9% dextrans. There were 43 anaphylactoid reactions, an overall frequency of 0.22%, or one reaction per 456 patients. The frequency differed according to the plasma substitute used: 0.35% for gelatins, 0.27% for dextrans, 0.10% for albumin, and 0.06% for starches. The reactions were serious (grades III and IV) in 20% of cases.

Multivariate analysis showed four independent susceptibility factors: the administration of gelatins (OR = 4.81), the administration of dextrans (OR = 3.83), a history of drug allergy (OR = 3.16), and being male (OR = 1.98). The relative risks of anaphylactoid reactions due to one type of plasma substitute with respect to another were estimated to be six times less with starches than with gelatins and 4.7 times less than with dextrans. The relative risk of albumin was 3.4 times less than that of gelatins, and almost identical to that of the starches. An immunological assessment was carried out in 15 patients who had been given a gelatin (Plasmion); in seven cases an IgE-dependent reaction was proved. It was concluded that gelatins and dextrans should be avoided in patients with a known history of drug allergy; when a reaction does occur, an immunological assessment should be carried out, as the reaction may be due to specific antibodies, in which case that particular plasma substitute would be contraindicated for the rest of the patient's life.

Prevention

Severe anaphylactic reactions only occur in patients with preformed dextran-reactive antibodies. Infusion of dextran causes the formation of large immune complexes that trigger activation of a cascade of enzyme systems, leukocytes, and platelets. It is possible to prevent or minimize these effects by blocking the reactive sites on the antibodies with small dextran fragments; this is hapten inhibition. The method used is to inject very low-molecular weight dextran (dextran 1, molecular weight 1 kDa) intravenously before an infusion of dextran is started; this blocks access to the antigen-combining sites by preformed circulating dextran-reactive antibodies.

In Sweden, there was a reduction in the reports of severe reactions to dextran from 22 per 100 000 units of dextran administered between 1975 and 1979 to 1.2 per 100 000 units between 1983 and 1985 (26). The number of reported fatal reactions fell over the same period from 23 to 1. More than 600 000 units of dextran were used during each period. This represented a nearly 20-fold reduction in the reported incidence of severe dextran-induced adverse reactions in the country in the 3 years following the introduction of dextran 1 for the purpose of desensitization. During the same periods the incidence of grade I reactions (which are not considered to be antibody-mediated) did not change, suggesting that the reduced incidence of severe reactions after introduction of dextran-1 was not explained by a general reduction in the reporting of adverse reactions. It was emphasized that pre-injection of dextran 1 does not eliminate completely the risk of severe reactions to dextran.

The incidence of anaphylactoid reactions to dextran was studied in 5745 patients over 63 months from January 1981 to March 1986 (27). A total of 12 646 half-liter units of dextran 70 had been administered to these patients. The average number of dextran units transfused was 2.2 per patient. There were 15 reactions, a rate of one reaction per 383 patients treated (0.26%). Seven of these reactions were potentially life-threatening (grade III or IV), giving a combined incidence of severe reactions of one in 821 patients treated (0.12%). The remaining eight reactions were less severe (grade I or II), and the combined incidence of the milder reactions was 1:718 patients treated (0.14%).

Pre- and post-reaction titers of dextran-reactive antibodies have been analysed in most Scandinavian studies (28). The incidence of severe dextran-induced anaphylactic

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reactions to clinical dextran after the prophylactic use of hapten inhibition was approximately 1/200 000 patients receiving dextran 1. In Sweden, where reporting of severe adverse drug reactions is mandatory, the incidence was about one in 70 000, indicating a 35-fold reduction. Only two fatal reactions were reported, an incidence of one per 2.5 million doses, indicating a 90-fold reduction. Both occurred in patients with extremely high titers of dextran-reactive antibodies. Adverse reactions to dextran 1, mostly mild, were reported in about one per 100 000 doses. These adverse effects were not antibody-mediated. The author concluded that dextran with hapten inhibition has arguably become the safest plasma substitute in current clinical practice. These conclusions were reached on the basis of a postmarketing surveillance study, and were confirmed in another publication from the same center (29).

It is possible for a severe dextran-induced anaphylactic/anaphylactoid reaction to develop despite prophylaxis with monovalent hapten dextran (30). This has been reported in a 60-year-old patient with multiple trauma, who received a dextran infusion for prophylaxis of thrombosis due to severe thrombocytosis in the late postoperative period. The causal relation to dextran was considered likely, although no serum sample was taken before the reaction, due to the close time relation to the infusion of dextran 60. In addition, there were high titers of dextran-reactive antibodies in the blood drawn immediately after the reaction occurred.

Second-Generation Effects

Pregnancy

Three cases of severe allergic reactions to dextran 70 (including one pregnant woman at the time of delivery) have been reported (31). All three had received previous hapten prophylaxis. Although the pregnant woman recovered, the baby had evidence of serious brain damage at birth. Another patient with a very high titer of dextran-reactive antibodies died from myocardial infarction, which happened at the same time. The third patient recovered without sequelae. The authors concluded that dextran 70 should be avoided in pregnancy until the baby is born, and that even in the presence of immune prophylaxis, these complications of dextran 70 can develop. Vigilant observation and resuscitation facilities are necessary in all cases.

An anaphylactoid reaction in a pregnant woman occurred immediately after the administration of dextran 40 solution (32). The baby was delivered rapidly by cesarean section after the event, and was apparently dead at birth but successfully resuscitated. The case has prompted Barbier and colleagues to report on the safety in general of dextran administered during pregnancy (32). They found information on 32 moderate anaphylactoid reactions associated with severe fetal distress and they advised avoiding preventive fluid preload with dextran in pregnancy.

Drug Administration

Drug administration route

After reproductive surgery 32% dextran 70 is sometimes administered intraperitoneally as adjuvant treatment for reducing adhesion formation. Dextran is thought to keep the raw peritoneal surfaces apart and prevent adhesion formation. However, the scientific evidence in support of the use of intraperitoneal dextran as an anti-adhesion adjuvant is scant. The complications of this procedure have been described in five patients (33). In one, a right pleural effusion was detected on the third postoperative day and resolved within 4 days. In the other four cases bilateral vulvar edema developed on the first or second postoperative day, and resolved in each case at 5–9 days after surgery. One patient had combined vulvar and leg edema, not previously reported. It is thought that this edema is due to extravasation of dextran along fascial planes, increasing the colloid-oncotic pressure in these spaces and promoting movement of a large amount of fluid from the vascular into the extravascular space. The right pleural effusion was thought to be due to movement of dextran through the diaphragmatic lymphatics or through small openings in the diaphragm, the majority of which are in the right hemidiaphragm.

In 139 consecutive patients who underwent major gynecological surgery and in whom 32% dextran 70 had been used as an anti-adhesion adjuvant (the mean amount of dextran used was 183 ml), there was an acceptably low rate of complications (34). Adverse effects involved 11 patients and included postoperative ileus (2.9%), pleural effusion (2.2%), allergic reactions (1.4%), wound infection (1.4%), and labial swelling (0.7%). There was no evidence of an increased infection rate.

The complications of repeated postoperative intraperitoneal instillation of 6% dextran 60 (given for 5 days to 32 patients) have been monitored and compared with the outcome in 15 control patients. In the dextran-treated subjects abdominal pain and dyspnea occurred significantly and more frequently than in the controls. During intraperitoneal irrigation with dextran there was a significant increase in body weight and an increased central venous pressure. Bradycardia developed between the third and sixth postoperative days. Blood pressure remained unchanged. Of the patients given dextran, 75% developed pleural effusions containing dextran by the fifth postoperative day. It was concluded that the uncertain advantages of dextran in the prevention of adhesions do not offset undesired adverse effects (35).

The syndrome of acute hypotension, adult respiratory distress syndrome, non-cardiogenic pulmonary edema, anemia, coagulopathy, and anaphylactic reactions after the administration of dextran 70 is referred to as the "dextran syndrome" (36–39). Factors other than acute volume overload due to intravascular absorption of dextran are thought to account for the syndrome. A combination of diverse pathophysiological factors may be responsible, namely direct pulmonary toxicity, activation of the coagulation cascade, release of vasoactive mediators, hypotension, pulmonary edema, intravascular intravasation of fluids, dilution of blood, and impaired renal and hepatic clearance. Cases of pulmonary edema are described under the section Respiratory.

Pulmonary hemorrhage after dextran use has also been described in hysteroscopy (40).

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Drug–Drug Interactions

Radiocontrast media

- Acute anuric renal insufficiency has been described after administration of dextran 40 and radiocontrast to a 59-year-old woman (41).

Radiocontrast-induced renal ischemia may have contributed to the pathogenesis of the dextran-induced renal insufficiency, as has been shown in animal studies. The mechanism of dextran-induced acute renal insufficiency may be multifactorial, with elements of hyperoncotic acute renal insufficiency, tubular obstruction, and direct tubular toxicity. Radiocontrast-induced acute renal insufficiency is unusual in patients with normal baseline creatinine concentrations. The ischemic effect of radiocontrast seemed to be important in this case. Renal function should be carefully monitored if the simultaneous administration of dextran and radiocontrast is necessary. If renal function deteriorates and oliguria or anuria occurs, plasmapheresis may be an appropriate and effective approach for clearing dextran.

Three cases of acute renal insufficiency occurred after low molecular weight dextran infusion; two of the patients had only received standard therapeutic doses (total 450 and 650 g) (42). In both of these cases a contrast medium was co-administered, and the authors suggested that this could have predisposed to acute renal insufficiency.

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Dextromethorphan

General Information

Dextromethorphan is the dextrorotatory isomer of the synthetic opioid levorphanol and is thought to act as a central nervous system antitussive (1). It binds to CNS sigma opioid binding sites and increases 5-HT concentrations by inhibiting uptake and by enhancing the release of 5-HT. It is also an antagonist at NMDA receptors.

Dextromethorphan is metabolized by CYP2D6 to dextrorphan, which binds to phencyclidine receptors and is thought to account for the toxic effects of hallucinations, tachycardia, hypertension, ataxia, and nystagmus (2,3).

Drug studies

Pain relief

The role of dextromethorphan in acute and chronic pain control has been reviewed (4). There is a clear beneficial role of oral dextromethorphan (in doses of 30–90 mg) in acute pain management; it has no or few adverse effects and even reduces the need for analgesic adjuncts.

Three double-blind, crossover, randomized, placebo-controlled studies of the role of dextromethorphan in neurological pain conditions in 40 adults with diabetic neuropathy, postherpetic neuralgia, and non-specific neuropathic pain syndromes have been reviewed (5). Dextromethorphan dosages varied from 13.5 mg tds on alternate days to 120 mg qds. High-dose dextromethorphan significantly reduced pain in diabetic neuropathy with no effect in postherpetic neuralgia. Sedation (58%) and dizziness (25%) were the most commonly reported adverse effects.

In a randomized, placebo-controlled study in 60 patients given dextromethorphan 10, 20, or 40 mg intramuscularly before abdominal surgery, there was a dose-dependent effective postoperative analgesic effect, with lower total consumption of rescue morphine during the 3-day observation period (6). There were no opioid-related adverse effects in those who were given dextromethorphan 40 mg.

The effect of dextromethorphan premedication on postoperative analgesic requirements, pain scores, and adverse effects has been examined in two double-blind, randomized studies (7,8). In the first study, 60 adults scheduled for elective upper abdominal surgery were randomly allocated to three equal groups (7). One group received intramuscular dextromethorphan 120 mg 30 minutes before skin incision (preincisional group); the second group received placebo (intramuscular saline) 30 minutes before skin incision and intramuscular dextromethorphan 120 mg 30 minutes before the end of surgery (postincisional group); and the third group received placebo 30 minutes before skin incision and 30 minutes before the end of surgery (control group). Preincisional intramuscular dextromethorphan 120 mg provided pre-emptive analgesia, reduced the need for postoperative analgesic supplements, and had a minimal and non-significant adverse effects profile. In the second study, oral dextromethorphan 90 mg was compared with placebo given 90 minutes preoperatively to patients undergoing laparoscopic cholecystectomy or inguinal hernioplasty under general anesthesia (8). Pain intensity and sedation were significantly reduced in the experimental group, with sparing of postoperative analgesics for up to 24 hours. Dextromethorphan 90 mg also abolished postoperative thermal-induced hyperalgesia and hyperpathia. No adverse effects were recorded in either group.

A randomized, double-blind, placebo-controlled study of oral dextromethorphan and PCA morphine has been performed in 66 patients undergoing knee surgery (9). The study was in two parts. The first was a dose escalation study in 25 postoperative patients to determine the maximum tolerated oral dose of dextromethorphan. The second involved giving less than the maximum tolerated dose divided into three increments at 8-hour intervals. The maximum tolerated dose of dextromethorphan was 750 mg. One patient, who was given 800 mg of dextromethorphan, had adverse effects, including severe slurred speech and light-headedness followed by deep sedation. In the second part of the study 66 patients were intended to receive dextromethorphan 800 mg in three doses of 400, 200, and 200 mg. The treatment group was subsequently reduced to 22 patients, compared with 34 in the

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placebo group, because of unexpected nausea and vomiting in five patients given dextromethorphan 400 mg. Dextromethorphan 200 mg 8-hourly caused a significant increase in nausea 2–24 hours after the first dose. One patient given dextromethorphan had mild hallucinations on one occasion only. There was an associated modest reduction in postoperative morphine consumption (29%), with no other benefits. The study failed to provide evidence that the maximum tolerated dose of dextromethorphan 200 mg 8-hourly is useful in the treatment of postoperative pain after knee surgery.

Neuropathic pain

In a double-blind, placebo-controlled, crossover pilot study in three patients with cancer-associated postamputation phantom limb pain, oral dextromethorphan 60–90 mg bd or placebo were given for 1 week each, followed by dextromethorphan or placebo again (10). Dextromethorphan satisfactorily improved phantom limb pain at a dosage of 60 mg bd in two patients and 90 mg bd in the third. Even though a relatively high total dose of dextromethorphan was used, there were no adverse effects.

There have been two randomized, placebo-controlled, double-blind trials in 19 patients with painful diabetic neuropathy and 17 with postherpetic neuralgia (11). In the first trial dextromethorphan was compared with memantine and/or lorazepam. Among the patients with diabetic neuropathy, dextromethorphan (median dose 400 mg/day) reduced pain intensity by a mean of 33% from baseline; memantine reduced pain by a mean of 17% and lorazepam by 16%, showing no significant difference to placebo. Among the patients with postherpetic neuralgia, dextromethorphan (median dose 400 mg/day) reduced pain intensity by a mean of 6.5%, which was not different from the effects of memantine and lorazepam. In the second trial the 10 patients with diabetic neuropathy who had responded to dextromethorphan shared a significant dose–response effect on pain intensity; the highest dose was significantly better than that of lorazepam. The median dose was 520 (range 240–920) mg/day. The adverse effects profiles were uneventful. These results confirm the long-term safety of high-dose dextromethorphan for selected patients with painful diabetic neuropathy (5).

Non-ketotic hyperglycinemia

A review of *N*-methyl-D-aspartic acid (NMDA) antagonist interventions in the treatment of non-ketotic hyperglycinemia included six cases in which dextromethorphan was used (3). Non-ketotic hyperglycinemia is an autosomal recessive disorder in which there is failure of the glycine cleavage enzyme system, leading to impaired oxidative decarboxylation of glycine and a toxic accumulation of this amino acid. Antagonism at NMDA receptors is hypothesized to offer partial relief to the effects of this inborn error of metabolism. Of the six cases, adverse effects were described in three. Patient 1 had profound sedation in response to a dose of 7.5 mg/kg of dextromethorphan administered as a single dose when the infant was 5 days old. The same daily dosage split into three doses relieved symptoms without sedation, but doses in excess of 7.5 mg/kg resulted in somnolence, agitation, and involuntary movements. Patient 4 developed apnea, hypotonia, nystagmus, and seizures at 38 days of age and was given dextromethorphan 1 mg/kg/day at the age of 10 months, resulting in anorexia. In patient 5 an increase in dextromethorphan dosage to 10 mg/kg/day was associated with lethargy, apnea, and a return of seizure activity. Further trials are required for clarification of the use of dextromethorphan in the treatment of non-ketotic hyperglycinemia.

Parkinson's disease

In a trial of dextromethorphan in Parkinson's disease only one-third of the initial sample entered the double-blind, placebo-controlled phase (12). One-third of the sample had a reduction in the benefits of levodopa when dextromethorphan 30 mg/day was given. A further one-third withdrew because of failure to gain clinical benefit from the highest tolerated dose of dextromethorphan. Adverse effects included drowsiness, increased dystonia, increased impotence, light-headedness, sweating, and nausea.

Huntington's disease

Of 11 patients with Huntington's disease adverse effects were reported in seven. These included eczematoid rash, clumsiness, dysarthria, drowsiness, and worsening rigidity (13).

Organs and Systems

Nervous system

Although generally safe, dextromethorphan can in some individuals cause nervous system adverse effects, including hyperexcitability, increased muscle tone, and ataxia. Respiratory depression can occur with excessive doses.

Dextromethorphan has been implicated in a case of movement disorder (14).

- An 8-year-old boy complained of abnormal facial movements and hallucinations. One day before these symptoms, he had been given his sister's Cordec DM droplets (carbinoxamine maleate 2 mg, pseudoephedrine hydrochloride 25 mg, and dextromethorphan 4 mg) for a cold. He had facial dyskinesia, dilated pupils, pyrexia, tachycardia, and reduced bowel sounds and responded to a benzodiazepine.

Psychological, psychiatric

Dextromethorphan-induced psychotic and/or manic-like symptoms have been reported.

- A 2-year-old child developed hyperirritability, incoherent babbling, and ataxia after being over-medicated with a pseudoephedrine/dextromethorphan over-the-counter combination cough formulation for upper respiratory symptoms (15). The symptoms abated after withdrawal of the product.

In another three cases (girls aged 10, 13, and 15 years) severe acute psychosis was associated with the use of an over-the-counter formulation containing ephedrine or pseudoephedrine and dextromethorphan combined with

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other compounds (16). The psychopathology included agitation, depressed mood, flat affect, pressure of speech, visual and auditory hallucinations, and paranoia. All three improved dramatically, with residual symptoms of irritability, 2–4 days after withdrawal of the mixture and treatment with risperidone 0.5–2.0 mg/day.

- An 18-year-old student had dissociative phenomenon, nihilistic and paranoid delusions, vivid visual hallucinations, thought insertion, and broadcasting after having consumed 1–2 bottles of cough syrup (dextromethorphan 711 mg per bottle) every day for several days (17). The psychotic symptoms remitted completely without any treatment 4 days after withdrawal of dextromethorphan. He was hospitalized twice more over the next 2 months with similar symptoms; each time he had consumed large doses of dextromethorphan.

Cautious use of over-the-counter formulations is recommended in patients with a predisposition to affective illness (SEDA-21, 87).

Cognitive deterioration has been reported from prolonged use of dextromethorphan (18).

Endocrine

During a double-blind, placebo-controlled study of the effect of high doses of dextromethorphan in children with bacterial meningitis, two of four patients developed type 1 diabetes mellitus; they had received dextromethorphan and the other two placebo (19).

- A 10-year-old boy received dextromethorphan 36 mg/kg/day by nasogastric tube. He developed hyperglycemia with ketoacidosis after 5 days and required insulin. The dose of dextromethorphan was reduced over the next 4 days and withdrawn. Insulin was withdrawn 4 days later.
- A 14-year-old girl received dextromethorphan 26 mg/kg/day by nasogastric tube. She developed hyperglycemia after 2 days and needed insulin for 6 days. A later glucose tolerance test was normal.

Pancreatic beta cells in rats express NMDA receptors, stimulation of which leads to insulin secretion (20). The authors postulated that dextromethorphan inhibits insulin secretion by blocking NMDA receptors and thus impairs glucose tolerance. Both patients had reduced insulin concentrations, implying that peripheral insulin resistance was unlikely to have been the cause of diabetes.

Skin

On two occasions, a fixed drug eruption occurred on the arm of a 45-year-old woman after using dextromethorphan as an antitussive (SEDA-16, 79). Worsening of urticaria pigmentosa has been attributed to dextromethorphan (SEDA-21, 87).

Sexual function

Spontaneous ejaculation occurred in a 64-year-old man who took dextromethorphan for a common cold (21). His sexual activity normalized 7 days after stopping the dextromethorphan. He had had a similar episode 5 months before, when spontaneous ejaculation had started 3 days after he took dextromethorphan and abated 4 days after withdrawal of the drug.

Immunologic

Dextromethorphan-induced anaphylactic symptoms have been reported (22).

- A 40-year-old woman suffered repeated hives, lip swelling, and shortness of breath on taking cough suppressants containing dextromethorphan. None was sufficient to require emergency medical intervention. On challenge with dextromethorphan 1 mg, mild transient pruritus occurred. After dextromethorphan 30 mg, hives and nasal and conjunctival congestion occurred. Vital signs and peak flow remained stable. There was no bronchospasm or angioedema. No reaction occurred to hydrocodone or codeine.

The authors noted that many opioids are potent histamine releasers and most reactions to opioids are anaphylactoid rather than IgE-mediated. It was of particular interest that the patient was able to tolerate the opioids hydrocodone and codeine.

Second-Generation Effects

Teratogenicity

In 184 pregnancies exposed to dextromethorphan (128 exposures in the first trimester) there were 172 live births, 10 spontaneous abortions, one therapeutic abortion, and one stillbirth (23). There were three major malformations and seven minor malformations in the children of women who had used dextromethorphan in the first trimester. In the control group there were 174 live births, 8 spontaneous abortions, and 2 therapeutic abortions; there were 5 major and l8 minor malformations. This small study did not show that dextromethorphan used during pregnancy increases the rates of major malformations above the expected baseline rate of 1–3%.

Susceptibility Factors

Genetic factors

Individuals who are poor CYP2D6 metabolizers are at increased risk of serotonergic adverse effects, as well as the narcotic adverse effects of coma and respiratory depression (24).

Other features of the patient

Individuals who take long-acting dextromethorphan formulations are at increased risk of adverse effects.

Drug Administration

Drug formulations

Individuals who take long-acting dextromethorphan formulations are at increased risk of serotonergic adverse effects, as well as the narcotic adverse effects of coma and respiratory depression (24).

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Drug overdose

Intentional dextromethorphan overdose has caused two deaths (SEDA-17, 210). Dextromethorphan toxicity occurred in a 3-year-old child who ingested up to 270 mg. The effects were reversed by naloxone (2).

Drug–Drug Interactions

Monoamine oxidase inhibitors

A possible interaction between dextromethorphan and the monoamine oxidase inhibitor isocarboxazid has been described, with myoclonic jerks, choreoathetoid movements, and marked urinary retention (25).

Individuals who take monoamine oxidase inhibitors are at increased risk of serotonergic adverse effects, as well as the narcotic adverse effects of coma and respiratory depression (25,26)

Four subjects had markedly reduced *O*-demethylation of dextromethorphan after they had taken moclobemide 300 mg bd for 9 days (27). *N*-demethylation was not affected. This result supports the hypothesis that moclobemide or a metabolite reduces the activity of the cytochrome enzyme CYP2D6. The clinical implications of this particular interaction remain to be clarified.

Morphine sulfate

Morphi Dex contains morphine sulfate and dextromethorphan in a 1:1 ratio. Double-blind, single-dose analgesic efficacy studies in over 800 patients with postsurgical pain have shown superior analgesic activity for the combination (60:60 mg) than separate doses of the individual components (28,29). In double-blind, multiple-dose studies in 321 patients with chronic pain the combination provided satisfactory pain control with a significantly lower mean daily dose of morphine sulfate. Other studies have shown similar responses (28) and an adverse events profile similar to that of a similar dose of morphine sulfate (30). The most common adverse events seen in a multiple-dose, non-placebo-controlled study in 1400 subjects were nausea, dizziness, vomiting, somnolence, confusion, and pruritus. There was a significant trend toward lower incidence of constipation with the combination than with morphine sulfate alone (31,32).

Quinidine (sulfate)

The effects of quinidine sulfate, 50 mg orally, an inhibitor of cytochrome CYP2D6, on the metabolism of dextromethorphan 50 mg have been studied in seven healthy volunteers in a randomized, double-blind, crossover, placebo-controlled study (24). Quinidine suppressed the conversion of dextromethorphan to dextrorphan in extensive metabolizers to the extent seen in poor metabolizers. The increased concentrations of dextromethorphan increased subjective and objective pain thresholds by 35 and 45% respectively. This result suggests that debrisoquine/sparteine-type polymorphisms account for important differences in the effect of dextromethorphan and the balance between the analgesic effect of dextromethorphan and the hallucinogenic effect of dextrorphan. Concomitant use of quinidine or other inhibitors of CYP2D6 could further affect this balance, increasing the risk of serotonergic- and narcotic-related adverse effects.

Serotonin reuptake inhibitors

Those who take serotonin reuptake inhibitors are at increased risk of adverse effects because of inhibition of CYP2D6 and pharmacodynamic potentiation; hallucinations and the serotonin syndrome have been reported (33,34).

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Dextropropoxyphene

General Information

The most frequent adverse effects of dextropropoxyphene are dizziness, sedation, and nausea and vomiting. Other reported effects include constipation, abdominal pain, skin rashes, light-headedness, headache, weakness, euphoria, dysphoria, minor reversible visual disturbances, and liver dysfunction (1).

A systematic review of single-dose dextropropoxyphene for postoperative pain identified 130 published articles (2). Of these, 11 placebo-controlled studies met the inclusion criteria for the review, 6 of dextropropoxyphene (65 mg) and five of the same dose of dextropropoxyphene plus paracetamol (650 mg) (co-proxamol). Pooled data from the studies showed that the incidence of nausea, drowsiness, and headache with dextropropoxyphene alone was not significantly different from placebo. Previous reports have suggested that dextropropoxyphene is significantly associated with dizziness, sedation, and nausea and vomiting. However, co-proxamol caused significantly increased dizziness (relative risk 2.2, 95% CI = 1.1, 4.3) and drowsiness (2.1, 1.5, 2.9). The relative risk of headache was reduced to 0.5 (0.3, 0.9). Analgesic effect was greater with co-proxamol than with dextropropoxyphene alone.

Organs and Systems

Cardiovascular

Dextropropoxyphene-induced cardiogenic shock has been described (3).

- A 32-year-old man became deeply comatose, with intraventricular conduction disturbances, after taking dextropropoxyphene 4.6 g. Treatment-resistant seizures lasted for hours. He was treated with an intra-aortic balloon pump and a continuous infusion of milrinone for 7 days and recovered fully.

The mechanism of cardiotoxicity of dextropropoxyphene is unknown, but the membrane-stabilizing effect of its major metabolite, norpropoxyphene, seems to play a central part. The cardiac effects are not reversed by naloxone (4), but dopamine may be effective.

Respiratory

Hypersensitivity pneumonitis has been associated with co-proxamol (paracetamol plus dextropropoxyphene) (5).

- A 61-year-old man, who was taking prednisolone 20 mg and co-proxamol as required for cranial arteritis, presented with a 2-month history of increasing breathlessness. His chest X-ray showed vague shadowing in both lower zones, consistent with an interstitial abnormality, and a lung biopsy confirmed focal interstitial hypersensitivity pneumonitis. After a diffuse rash appeared, the co-proxamol was withdrawn and then reintroduced. The rash recurred and the breathlessness deteriorated. A subsequent challenge with paracetamol did not produce the same symptoms. The dosage of prednisolone was not altered.

Sensory systems

Nerve deafness in a 44-year-old woman, dependent on co-proxamol (dextropropoxyphene plus paracetamol), has been reported (SEDA-17, 80).

Metabolism

Severe hypoglycemia has been reported in the elderly (SEDA-17, 80).

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Hematologic

Hemolytic anemia has been attributed to dextropropoxyphene (6).

Gastrointestinal

Four cases each of necrotizing anorectitis and proctitis have been reported after long-term (2–24 months) use of suppositories containing dextropropoxyphene and paracetamol (SEDA-10, 62). Perineal ulceration can also occur (7).

Liver

Various forms of hepatotoxicity, sometimes involving jaundice or mimicking biliary tract disease, have been reported by the UK Committee on Safety of Medicines (8). In most, but not all, cases the drug had been taken with paracetamol. In some cases, rechallenge caused hepatotoxicity within a few hours, and an immunologically based mechanism has been suggested.

Dextropropoxyphene has been implicated in hepatic injury in four patients taking co-proxamol (dextropropoxyphene plus paracetamol) (9). The cases were recorded at the Regional Centre of Pharmacovigilance in St Etienne, France between 1985 and 2000 and were similar to 29 cases published in the international literature between 1971 and 1994. The risk factors identified in the confirmed cases included age over 50 years, female sex, and a history of excessive alcohol consumption or previous pathology that might have caused liver damage. Drug withdrawal produced good outcomes.

Skin

Acute generalized pustulosis attributed to dextropropoxyphene has been reported (10).

- A 43-year-old woman, who had taken antibiotics and analgesics, including dextropropoxyphene, for parotitis, developed generalized erythema with numerous pustules on the trunk followed by a pyrexia. Patch testing was positive with dextropropoxyphene only and negative with paracetamol, spiramycin, aspirin, and tenoxicam.

Musculoskeletal

Fibrous myopathy has been reported after long-term dextropropoxyphene injections (SEDA-18, 85).

Long-Term Effects

Drug dependence

In common with other opioids, dextropropoxyphene can produce dependence (11). However, it has also been used to withdraw patients from morphine (12).

Susceptibility Factors

Age

Acute respiratory failure predominated in patients under 30 years of age whilst cardiotoxic effects predominated in the elderly.

Renal disease

Severe hypoglycemia has been reported in a patient with chronic renal insufficiency (13).

Drug Administration

Drug overdose

Dextropropoxyphene is widely prescribed in combination with aspirin or paracetamol. It is particularly dangerous when taken in overdose (14). A mortality rate of 8% was described in a series of 222 self-harm patients (15).

Drug–Drug Interactions

Alcohol

Cardiorespiratory arrest can occur only 15 minutes after drug ingestion (16). This risk is enhanced if ethanol is taken concomitantly.

Alprazolam

Inhibition of alprazolam metabolism by dextropropoxyphene has been reported (17).

Carbamazepine

Dextropropoxyphene inhibits the oxidative metabolism of carbamazepine, leading to clinically significant rises in carbamazepine concentrations (18).

Severe carbamazepine toxicity can occur if dextropropoxyphene is taken concurrently (19).

Nortriptyline

Inhibition of nortriptyline metabolism by dextropropoxyphene has been reported (20).

Warfarin

Prolongation of the prothrombin time was observed in a patient concurrently taking warfarin and a compound analgesic containing dextropropoxyphene (21).

Smoking

Heavy smoking can increase the elimination of dextropropoxyphene (22).

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Dezocine

General Information

Dezocine is structurally related to pentazocine (1). It reacts primarily with OP_3 (μ) receptors, but also has some affinity for OP_1 (δ) and OP_2 (κ) receptors. It is slightly more potent than morphine, but with similar adverse effects at effective doses (2.5–10 mg). The most common adverse effects (3–9%) are nausea and vomiting, sedation, or local injection site reactions; dizziness/vertigo have also been reported (1–3%) (SEDA-16, 88). However, in some trials nausea and/or vomiting were reported in 5–22%, while headache was the most common CNS complaint (16–35%). Other adverse effects reported in 1% of patients involve the cardiovascular system, respiratory system, urogenital system, CNS, gastrointestinal system, and visual senses.

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Diacerein

General Information

Diacerein (diacetylrhein), an anthraquinone derivative, is said to be effective in the treatment of osteoarthritis. Its active metabolite is rhein, about which there are very few clinical data. Diacerein does not affect arachidonic acid metabolism and might be better tolerated than other NSAIDs with regards to renal and gastric toxicity. Epigastric or abdominal pain and diarrhea are the most frequent adverse effects. Diarrhea occurred in 37% of patients with osteoarthritis taking diacerein (1). Acute hepatitis has been described (SEDA-22, 119), as have skin reactions.

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Dialysis fluids

General Information

Dialysis fluids are solutions of electrolytes formulated in concentrations similar to those of extracellular fluid or plasma. They contain, or may contain:

- sodium
- chloride
- bicarbonate or lactate
- calcium
- magnesium
- potassium
- glucose
- amino acids
- icodextrin

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Dialysis fluids are provided in a sterile concentrated form for dilution with water before use; the water used need not be sterile.

Icodextrin

Icodextrin (rINN) is a maltodextrin glucose polymer with a mean molecular weight of 20 kDa, which is broken down to maltose. It is used as an alternative to glucose as the active osmotic agent for peritoneal dialysis. Icodextrin is similar in structure to dextran, but has improved ultrafiltration properties, because it is less well absorbed than glucose.

Organs and Systems

Skin

The manufacturers have reported from pharmacovigilance data that the incidence rate of all skin reactions with icodextrin is of the order of 2.5%; in most cases the symptoms are mild, often not requiring withdrawal (1).

The adverse effects associated with icodextrin in patients with renal insufficiency over 12 months have been reviewed (2). There were three cases of exfoliative skin reactions in 102 patients. Each was acute and started within 3 days of icodextrin exposure. All resolved promptly on withdrawal. There were two acute blistering reactions on sun-exposed areas, occurring within 3–6 months after icodextrin. Both responded slowly to withdrawal, taking 6–8 weeks to resolve completely. Nine further patients reported some form of minor skin problem (itching, dryness, rash, and blistering).

- A 48-year-old woman with a long history of insulin-dependent diabetes mellitus developed a severe cutaneous reaction to icodextrin (3). This happened 10 days after changing over to 7.5% icodextrin in order to improve ultrafiltration. The rash was maculopapular and it affected most parts of her body. It was associated with severe pruritus. By the 13th day after it first appeared the rash had become exfoliative and erythrodermic. There was rapid improvement in the first few days after the icodextrin dialysate had been withdrawn and she reverted to conventional glucose peritoneal dialysate.

Allergy to icodextrin was the most likely explanation for the severe cutaneous reaction. The epitope(s) for allergic reactions to dextrans have not been defined, although they are undoubtedly immunogenic. It is possible that the same or a similar epitope may be responsible for allergic reactions to icodextrin.

- A 50-year-old woman with insulin-dependent diabetes developed end-stage renal insufficiency secondary to diabetic nephropathy, and was treated with standard CAPD containing glucose (4). About 20 months later she was given 2 liters of icodextrin 7.5% postoperatively and 11 days later complained of pruritus on the lateral aspects of the thigh with erythroderma, which quickly spread to the back, abdomen, arms, hands, and head, followed by a widespread pruritic erythematous maculopapular rash, which became exfoliated and psoriasiform. Icodextrin was withdrawn 5 days later and there was rapid healing of the dermatitis, almost completely within 7 days. Rechallenge resulted in recurrence within 2 days.

The authors pointed out that in previous cases scaly and exfoliative rashes occurred several days after starting icodextrin but regressed without the need to withdraw icodextrin, except in one case. They concluded that, given the therapeutic advances made possible by icodextrin, and the extreme rarity of such adverse events, there should be no hesitation in using it in CAPD. The possibility of cutaneous adverse events 10–12 days after starting peritoneal exchange should be borne in mind, although the normal transient nature of such reactions rarely requires withdrawal.

Serosae

Giant and atypical mesothelial cells can develop in the peritoneum in response to irritation caused by peritoneal dialysis solutions. Mesothelial hyperplasia without an increase in mesothelial cell size, cytological atypia in mesothelial cells, polynucleate cells with nucleoles, and enlarged mesothelial cells with a flat small nucleus and without evident nucleoles have all been described (5). These giant cells are not found unless there is peritonitis. During peritonitis mesothelial cells detach en masse from the basal lamina.

Continual exposure of the peritoneum over a period of years to conventional peritoneal dialysis fluids contributes to loss of membrane function in two ways: (i) by compromising peritoneal host defences mediated by resident and infiltrating leukocytes and the resident cells of the peritoneal membrane and (ii) by directly contributing to structural changes in the peritoneal membrane (6). Peritoneal dialysis fluids have significant modulatory and, in some cases, toxic effects on peripheral and peritoneal cell functions. The impact of long-term exposure of the peritoneum to peritoneal dialysis fluids and how its function as a dialysing organ is affected are less well understood. From a comprehensive review of the literature it has emerged that lactate-buffered peritoneal dialysis fluids inhibit many leukocyte and peritoneal cell functions, even when exposure times are short. This suggests the need for more biocompatible peritoneal dialysis fluids. Neutral pH bicarbonate- or bicarbonate/lactate-buffered fluids are superior in all test systems to lactate-buffered fluids, irrespective of the concentration of glucose present in the solution. The cell inhibitory and stimulatory effects of high glucose concentrations remain, and this issue will have to be addressed before the perfect biocompatible alternative is produced. It is not clear whether long-term use of bicarbonate-containing fluids will improve patient outcome by reducing infection rates and better preserving the integrity of the peritoneal membrane.

The adverse effects of peritoneal dialysis fluids on the peritoneum have been succinctly summarized by authors arguing the case for a new, less toxic, and less acidic fluid for peritoneal dialysis (7). A low pH, high osmolality and lactate concentration, and the presence of several toxic contaminants may all contribute to impaired cellular function in the peritoneal membrane. In conventional peritoneal dialysis pH is deliberately lowered to 5.0–5.6

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in order to prevent caramelization of the glucose (that is the production of glucose degradation products) during heat sterilization and storage. Low pH, especially in combination with tissue fluid hyperosmolality and high lactate concentrations, will cause vasodilatation and recruitment of capillaries in microvascular beds. In the peritoneal membrane, acidic solutions cause an increased "effective" vascular surface area and more rapid loss of glucose gradient than a neutral solution. Thus, a neutral solution would theoretically behave more favorably with regard to transperitoneal ultrafiltration (glucose-induced osmosis) than a conventional acidic solution. This is because the glucose osmotic gradient will be better preserved over time with neutral solutions. Even neutralized peritoneal dialysis solutions seem to be cytotoxic in vitro. This cytotoxicity is related less to hyperosmolality and the presence of lactate in the fluid than the toxicity occurring at a low pH. Glucose degradation products formed during heat sterilization and storage include acetaldehyde, methylglyoxal, 2-furaldehyde, formaldehyde, 5-hydroxymethylfurfural, and formic acid. All may, in the long term, affect the peritoneum adversely and lead to a deterioration of peritoneal membrane function. The risk of losing ultrafiltration capacity after 6 years of continuous ambulatory peritoneal dialysis is as high as 31%. Glucose degradation products can also cause abdominal discomfort and pain, and can be responsible for acute losses in ultrafiltration capacity.

Infection risk

Infectious peritonitis contributes to death in 5% of patients receiving peritoneal dialysis (8). The common organisms that cause peritonitis are *Staphylococcus epidermidis*, *Staphylococcus aureus*, streptococci, Gram-negative bacilli, and fungi. Predisposing factors are exit-site infections leading to tunnel infections, catheter infections, and nasal carriage of *S. aureus*, which is associated with exit-site and tunnel infections and peritonitis. Coagulase-negative staphylococci are often resistant to methicillin, and methicillin-resistant *S. aureus* was the cause of 13% of all peritonitis episodes and 30% of catheter infections in one study (8). Vancomycin is required for treatment (but not prophylaxis) of such cases.

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Diamorphine

See also Opioid analgesics

General Information

Heroin is a potent opioid that offers no substantial advantages over morphine. In the UK it is the preferred parenteral opioid for subcutaneous administration to cachectic cancer patients, because of its high solubility.

In a randomized, double-blind study, 14 patients who underwent elective surgery for correction of bilateral arthritic deformities of the feet received 15 ml of 0.9% saline containing diamorphine 2.5 mg into the cannula in one foot and 15 ml of saline into the other foot (1). Intravenous regional diamorphine did not improve postoperative pain relief or secondary hyperalgesia. There were no significant adverse effects.

High-dose diamorphine has been compared with morphine in a double-blind, crossover, randomized study in 39 intravenous opioid users who were allocated to either morphine 3% solution or diamorphine 2% solution, gradually increasing up to an individual maintenance dose adjusted to meet the patient's subjective needs (2). Those who started with diamorphine and subsequently switched to morphine terminated prematurely owing to excessive histamine reactions, all of which occurred during crossover to morphine. Symptoms included severe pruritus, flushing, swelling, urticaria, severe headaches, nausea, general malaise, hypotension, and tachycardia. Only 44% of the original cohort finished the 6-week study (14 getting diamorphine at the end and three getting morphine). Average daily doses were 491 mg for diamorphine and 597 mg for morphine. These results suggest that diamorphine produces fewer adverse effects than morphine and may be preferable for high-dose maintenance prescription. However, the study was very small and the subject selection was biased, as were the variables used to determine a successful outcome. The result was contrary to all the well-established pharmacological facts, and the authors did not mention the risks associated with high doses of short-acting opioids.

In a randomized, double-blind study, 64 patients undergoing total knee arthroplasty received either intrathecal morphine 0.3 mg or intrathecal diamorphine, 0.3 mg in 0.3 ml, with 2–2.5 ml of 0.5% heavy spinal bupivacaine (3). The patients given morphine had significantly greater analgesia at 4, 8, and 12 hours postoperatively. The incidence of opioid-related adverse effects was not significantly different between the groups.

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In a single-blind, randomized, controlled study, 70 patients scheduled for elective cesarean section under spinal anesthesia using hyperbaric bupivacaine 0.5% received intrathecal fentanyl 20 µg, intrathecal diamorphine 300 µg, or 0.9% saline (4). Significantly less intraoperative and postoperative "analgesic control" was required in the opioid groups, especially in those given diamorphine. Diamorphine produced longer-lasting analgesia than fentanyl (12 hours versus 1 hour). Nausea, vomiting, and pruritus occurred relatively infrequently, with no differences between the groups; sedation was more frequent with fentanyl.

Organs and Systems

Respiratory

"Chasing the dragon," or inhaling heroin vapor through a straw, is a technique by which heroin users avoid the risks of injection. In Amsterdam, 85% of heroin users smoke or chase the drug. Pulmonary function can be affected by heroin inhalation. It can depress the respiratory center, release histamine (which can trigger asthma), result in septic emboli, and increase susceptibility to infectious diseases, such as tuberculosis and pneumonia. In 100 methadone maintenance users, lung function and shortness of breath were evaluated using spirometry and clinical history (5). Impaired lung function and shortness of breath correlated with chronic heroin smoking.

Heroin-induced pulmonary edema, or "heroin lung" (SEDA-19, 29) (SEDA-25, 39), is a serious complication, which may be due to release of histamine, with increased pulmonary lymph flow and capillary permeability. There have been 27 reports of non-fatal heroin overdose associated with non-cardiogenic pulmonary edema (6). In a retrospective case-control study there were 23 heroin fatalities and 12 controls with sudden cardiac deaths (7). The authors tried to verify that defects of the alveolar capillary membranes and/or an acute anaphylactic reaction can lead to pulmonary congestion, edema, and hemorrhages. There were defects of the epithelial and endothelial basal laminae of the alveoli in both groups. There was an insignificant increase in IgE-positive cells in the heroin group. The findings suggested that heroin-associated lung edema is generally not caused by an anaphylactic reaction.

Bilateral pulmonary edema associated with heroin abuse has been reported several times (8). Bronchospasm has been noted following the use of street heroin, perhaps due to contaminants (9).

Nervous system

Delayed onset oculogyric crisis and generalized dystonia occurred in a 19-year-old man after intranasal heroin use, possibly due to bilateral hypoxic infarction of the pallidum and pallidothalamic tracts (10).

There has been one report of mixed transcortical aphasia attributed to heroin (11).

Myoclonic spasm has been reported about 24 hours after withdrawal of an epidural infusion of diamorphine (SEDA-16, 81).

Demyelination has been attributed to diamorphine (12).

- A 41-year-old chronic diamorphine user developed an unsteady gait and dysarthria over 2 weeks, followed by severe cerebellar ataxia and moderate dysmetria of the arms and legs. An MRI scan suggested myelin damage, with symmetrical involvement of the cerebellar hemispheres and decussation of the superior cerebellar peduncles, the corticospinal tracts, and the centrum semiovale, suggesting spongiform leukoencephalopathy. Two years later having taken no more diamorphine he was improved, with minor regression of the MRI lesions, especially the white matter lesions.

Myelopathy has been reported after intranasal insufflation of diamorphine (13).

- A 52-year-old man with a history of diamorphine abuse presented with sudden paraplegia a few hours after intranasal insufflation. He had flaccid paralysis of both legs, acute urinary retention, and reduced rectal tone. Deep tendon reflexes were absent and plantar responses were extensor. An MRI scan of the spine and an immunoglobulin profile supported the conclusion that this was a case of acute myelopathy with an immunopathological cause, involving a protein specific to spinal cord parenchyma, triggering acute local inflammation, ischemia, and tissue damage. Seven weeks later he recovered normal neurological function.

This case of heroin myelopathy is similar to other reported cases, except that this case occurred with intranasal rather than intravenous use. The MRI findings were consistent with a transverse myelitis. The authors suggested that hypersensitivity and an immune-mediated attack on the spinal cord was the likely mechanism of injury.

Reflex sympathetic dystrophy, in which there is an excessive or abnormal sympathetic nervous system response in a limb, has been associated with rhabdomyolysis secondary to heroin abuse (14).

- A 37-year-old male heroin smoker developed tea-colored urine and pain, swelling, and tenderness in both feet. He had acute renal insufficiency and rhabdomyolysis and was treated with hemodialysis. Urine toxicology was negative. He also had persistent, burning pain in both feet, with cool, pale, thin skin on both legs, a mild reduction in sensation on the lateral aspects of the lower legs and diminished bilateral knee and ankle reflexes. Walking was restricted, with limited range of movement owing to the severe pain. His feet would swell and redden after a 5-meter walk, suggesting loss of sympathetic regulation. Nerve conduction velocity studies of the tibial, peroneal, and sural nerves were abnormal. Radiographs showed mildly reduced bone mineralization in the legs. Three-phase bone scintigraphy showed diffusely increased radiotracer accumulation over both feet in all three phases, as found in reflex sympathetic dystrophy. The diagnosis was confirmed by local anesthetic sympathetic blockade. Nasal calcitonin spray led to pain relief 2 months later. A follow-up three-phase bone scintigram showed less radiotracer uptake, consistent with a good response to calcitonin therapy.

Progressive spongiform leukoencephalopathy

A rare consequence of inhaling heated heroin ("chasing the dragon") is a progressive spongiform

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leukoencephalopathy. The first three cases in the USA were reported in 1996 (SEDA-22, 35). The presentation includes apathy, bradyphrenia, motor restlessness, and progressive cerebellar ataxia. Another report has provided more details from physical assessments and laboratory and radiological (MRI and MRS) data, and more information about the course of this heroin-related effect (15). The three cases showed raised concentrations of intracerebral lactate (reflecting mitochondrial dysfunction), which suggests a conversion of aerobic to anaerobic metabolism seen in hypoxic-ischemic conditions, including stroke. One patient recovered quite well after antioxidant therapy, supporting a metabolic effect of the heroin-related toxin; a similar response to co-enzyme Q has been found in other mitochondrial disorders with a high CSF lactate. Thus, the authors recommended that although the role of antioxidant therapy in this condition is unclear, it may be prudent to administer oral co-enzyme Q supplemented with vitamins C and E to patients with this syndrome.

Intravenous administration of pure heroin did not cause a leukoencephalopathy in a patient in whom inhalation had caused it (16), and toxicity in these cases may have been due to the heating of the heroin. This might have implications for young heroin users who, because of the known increased risk of HIV infection, prefer to "chase" (smoke) the drug, rather than to inject it intravenously.

- A 23-year-old pregnant woman at 39 weeks of gestation developed tonic-clonic seizures and hypothermia after taking excessive heroin intravenously (17). She developed Cheyne-Stokes respiration needing intubation and a cesarean section was performed, after which she developed inappropriate secretion of antidiuretic hormone and acute renal insufficiency. She made a complete recovery.

The etiology of this leukoencephalopathy is unclear. Because cases occur in clusters, even though many others who inhale heroin do not get this effect, there is suspicion about the possible role of contaminants of small batches of drug by an unknown substance. In addition, some have suggested that heating could be important, since leukoencephalopathy has not been reported with other means of heroin use (until this year, as reported in the next case). The authors of the report postulated that there might be a relation between the amount of heroin inhaled and the severity of the illness. Once symptoms develop, progression continues, usually for 2–3 weeks, but in some individuals it progresses for up to 6 months after exposure. "Coasting," or the phenomenon of symptom progression after cessation of exposure to toxins, has been observed with other toxins, and it is proposed to result from the storage of toxin in lipid-rich neural or non-neural body tissues, with subsequent release into the bloodstream. Although the "toxin" involved in this condition is unknown, progression could be due to "coasting." Alternatively, oxidative damage could be initiated by the toxin and produce persistent metabolic changes in the affected white matter. Whatever the mechanism, the illness is extremely grave, with no known treatment and with progression to akinetic mutism and death in about 20% of reported cases.

- A 37-year-old male cocaine abuser was admitted with intoxication, mutism, and substupor (18). His toxicological screening was positive for heroin and cocaine. There was spasticity of all limbs and Babinski reflexes. The CSF contained some erythrocytes. The electroencephalogram showed generalized slowing, and a CT scan showed bifrontal confluent hypodensities in the deep white matter. The cranial MRI scan showed diffuse bihemispheric white matter lesions dominantly in the frontal lobe on T2-weighted images. There were abnormal hyperintense lesions in the pyramidal tracts and the corpus callosum. He gradually improved and made a complete recovery within 6 months, as confirmed by neurological and neuropsychological examination.

The findings of toxic leukoencephalopathy in this patient's brain-imaging studies were similar to those reported in patients who have inhaled impure heroin. However, he had used intravenous heroin and cocaine. This is therefore the first case report of leukoencephalopathy after intravenous use of these drugs. However, it should be noted that the authors did not indicate how the route of drug use was confirmed. They noted that lipophilic substances, such as hexachlorophene or triethylthin, were likely impurities in the abused substances.

- A 53-year-old man with a 7-year history of heroin abuse presented with confused speech and unsteady gait (19). A CT scan showed low attenuation in the white matter tracts and an MRI scan showed increased signal intensity in the white matter tracts extending from the centrum semiovale, corpus callosum, corona radiata, posterior limbs of the internal capsules, cerebral and cerebellar peduncles, and pyramidal tracts, suggestive of spongiform demyelination. He became bed-bound and tetraplegic and died of a chest infection.
- A 37-year-old man, with a short history of heroin and cocaine use, presented with spasticity of all limbs, a confusional state, and mutism (18). The electroencephalogram, CT scan, and MRI scan showed predominantly positive frontal pathology, with other lesions in the pyramidal tracts and corpus callosum. The diagnosis was leukoencephalopathy. The symptoms gradually abated after 4 weeks, and repeat tests after 6 months shown to be normal.

Three cases of toxic and progressive spongiform leukoencephalopathy have also been reported as a result of vapor inhalation of heroin (15). There were generalized white matter abnormalities and pathology in the cerebellum, internal capsule, corpus callosum, and brain stem.

Heroin-induced leuckoencephalopathy has been misdiagnosed as psychiatric illness (20).

- A 47-year-old woman, with a history of amphetamine abuse, depression, and paranoia, smoked heroin for 4 weeks after stopping amphetamines, and 10 days later became drowsy and confused with increased paranoia and depression. She was disoriented and restless. Her speech was garbled. She had frequent non-purposeful movements and an unsteady gait. A CT brain scan was normal. She was given chlorpromazine, doxepin, and diazepam, but her ataxia and incontinence worsened, her speech and all her

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movements slowed, with increased tone in all limbs and cogwheel rigidity. Her power and sensation were normal. Truncal ataxia impaired walking. An MRI brain scan showed diffuse high-intensity signals in both cerebral hemispheres, and review of the CT scan showed hypodensities in the same regions. She was treated with co-enzyme Q and regained mobility and continence, but with no improvement in cognitive impairment.

Sensory systems

Profound reversible deafness with vestibular dysfunction has been attributed to heroin abuse (21).

- A 47-year-old intravenous opiate user, after a period of abstinence, injected about 0.25 g of illicit diamorphine during a period of 24 hours and developed bilateral symmetrical sensorineural hearing loss, ear fullness, and loud tinnitus 20 minutes later. His symptoms gradually subsided with no sequelae after 3 weeks.

The authors pointed out that bilateral deafness after heroin relapse after prolonged abstinence had been reported in previous two cases, suggesting resensitization of a tolerized opioid system or prolonged hypersensitization of a system in withdrawal.

Endocrine

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been attributed to heroin (17).

- A 23-year-old pregnant woman developed antepartum bleeding at 35 weeks and a tonic-clonic convulsion and hypothermia at 39 weeks, having used heroin 4 hours before. She had further tonic-clonic seizures, became obtunded, and required intubation. She had occasional runs of ventricular bigeminy. A cesarean section was performed. The neonate had poor respiratory effort and required ventilation. Blood chemistry suggested inappropriate secretion of antidiuretic hormone, acute renal insufficiency, and acute pancreatitis. She and the baby recovered after 2 weeks.

Urinary tract

Following an observation that many patients develop acute renal insufficiency after using heroin, the authors identified 27 patients (mostly men, average age 29 years) who developed renal insufficiency after intravenous heroin use (22). Rhabdomyolysis was the likely cause of renal insufficiency in all cases. Twelve had a history of polydrug abuse and all had a history of intravenous diamorphine use in the 24 hours before presentation. Eight patients required renal dialysis for an average of 14 days. Patients who required dialysis had a higher admission creatine kinase, a higher peak creatine kinase, and a lower urine output in the initial 24 hours. They also had a longer hospital stay. Some had positive tests for hepatitis B (10%), hepatitis C (74%) and HIV (5%); viral infections can compound rhabdomyolysis and subsequent renal impairment through glomerulonephritis. No patient died and all patients recovered normal renal function. Rhabdomyolysis is a recognized cause of renal insufficiency, but its pathogenesis after heroin use is not fully understood.

In most of 19 renal specimens from autopsies of intravenous diamorphine users there was severe lymphomonocytic glomerulonephritis as a result of activation of the classical pathway of the complement binding system (23). This could have been a result of diamorphine itself, adulterants, or active hepatitis B and/or C infection.

Heroin was presumed to be the cause of reversible nephrotic syndrome in patients dependent on heroin (24).

Renal amyloidosis can be a late effect (24).

Skin

A traumatic skin lesion with blisters and sweat gland necrosis was described in a 24-year-old man who was comatose as a result of heroin overdose; immunofluorescence showed deposits of immunoglobulin and C3 in dermal vessels (25).

Musculoskeletal

Focal myopathy has been reported after intramuscular diamorphine (26).

- A 36-year-old man developed progressive, painless stiffness of both knee joints over 3 months. It had started 4 weeks after he began to give himself heroin injections two to three times a day in alternate thigh muscles. He had a broad-based stiff gait, and he walked without bending his knees. Because of contractures of the quadriceps muscles, which were indurated, active and passive knee flexion was limited to an angle of 5–10 degrees. Electromyography of the right quadriceps muscle showed firm fibrous resistance to needling without insertional activity. Ultrasound showed a preserved but enlarged muscle structure and thickening of the connective tissue. A muscle biopsy showed variation in fiber size with scattered collection of atrophic fibers and perivascular and endomysial infiltrates comprised chiefly of lymphocytes and macrophages. The serum creatine kinase activity was normal. After 7 weeks of physiotherapy, MRI of the thighs showed severe fibrosis of the muscle, suggesting a possible inflammatory component. Following treatment with prednisone and D-penicillamine, he was entirely normal, except for slightly limited knee flexion on both sides.

This patient's main symptom was progressive stiffness, due to contractures of the quadriceps muscles induced by chronic heroin injections. The findings made it very likely that heroin caused a primarily vascular lesion leading to non-specific inflammatory changes and subsequent fibrosis. Clinically, weakness was minimal and there was painless contracture. This presumably reflects the predominantly fibrotic process within muscle tissue. Combination therapy with prednisone and D-penicillamine led to significant improvement. The regenerating process was confirmed by the second muscle biopsy, and electromyography showed reinnervation. The second biopsy did not show inflammatory cells, indicating absence of the inflammatory component. Thus, this case suggests that heroin-induced fibrotic myopathy is reversible.

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Long-Term Effects

Drug abuse

Smoking heroin by heating the free base over tin foil and inhaling the vapors is known as "chasing the dragon," a method that probably originated in Southeast Asia. Some are using this to reverse the stimulant effects of ecstasy. In 102 patients (55 men and 47 women, mean age 21 years) interviewed at four clinics in Dublin, Ireland, three subgroups of opiate users were identified: (a) those who had ever used opiates to come off ecstasy, who were compared with those who had never used opiates for this purpose, (b) those whose first use of opiates had been to come off ecstasy, and (c) those who had started opiates by "chasing" and then did or did not move to injecting (27). Of the 102 patients, 92 reported having taken ecstasy, 68 of whom reported having taken opiates to come off it, and the remaining 24 of whom had not. The 68 patients who reported taking opiates to come off ecstasy had significantly heavier ecstasy use, in terms of the number of nights per week and number of tablets taken per night. Of 36 who reported that their first ever experience of using opiates was in the context of "chasing" to come off ecstasy, 28 reported this as their main reason for starting to use opiates and the other eight reported that they would probably have tried opiates independent of their ecstasy use. Of the 86 patients whose initial route of using heroin was "chasing," 61 reported changing to injecting, 23 continued to smoke heroin, and two switched to an oral formulation of methadone or morphine. When those who came to inject heroin were compared with those who did not (61 versus 23), the injectors had begun illicit drug use earlier, had started heroin at a younger age, were younger at the time of interview, and had been more likely to have a history of ecstasy use. Despite the younger age of onset of illicit drug use in those who came to inject, they had not been using illicit drugs for longer at the time of interview. This study confirmed the authors' previous findings that heroin smoking was associated with ecstasy use.

The Swiss government has developed a program called PROVE, which provides prescriptions of injectable opioids for the treatment of heroin-dependent patients. This program has generally been viewed to be successful in terms of retention in treatment, morbidity and mortality, legal behavior, and cost-effectiveness. However, during the 26-month observation period, epileptic seizures occurred in 11% of the 186 patients treated. This finding, along with previous reports of reduced regional blood supply to the brains of opioid users, led the authors to study cerebral deoxygenation after intravenous opioid administration in ten opioid-dependent subjects and to compare it with intravenous saline in ten matched controls using Near Infrared Spectroscopy (NIRS) (28). Heroin and methadone produced a rapid and dramatic reduction in both respiratory rate and cortical hemoglobin oxygenation, while saline had no effects. The authors suggested that opioid-induced acute deoxygenation of cortical hemoglobin was probably associated with respiratory depression. In one in three subjects, oxygen saturation after intravenous heroin fell rapidly, a finding that has not previously been described in humans.

The authors suggested two possible mechanisms for this phenomenon. They discounted the possibility that opioids increase the utilization of oxygenated hemoglobin in the CNS, because PET data from other studies suggest decreased utilization of glucose (indicating reduced brain activity) following opioids. They believed that it was more likely that the increase in cortical-reduced hemoglobin was related to opioid-induced respiratory depression, with carbon dioxide retention and resulting vasodilatation. Although preliminary, these data have potential implications for treatment programs involving intravenous opioid maintenance. The authors suggested that intravenous opioids may produce both systemic and cerebral hypoxia, which may at least in part account for the hyperexcitability (as measured by electroencephalography) found after intravenous opioids in other studies. Furthermore, hypoxia may mediate or contribute to the rush sensation, similar to that seen with high altitude or in cases of asphyxiophilia.

Drug withdrawal

The relation between the severity of opiate withdrawal and the dose, duration, and route of administration of heroin has been assessed in a retrospective analysis of heroin withdrawal in 22 patients (29). Abrupt withdrawal from opiates resulted in increased symptom severity, peaking on day 2 and then abating after that until day 7. Both the dose and the route of administration were related to the withdrawal score: intravenous heroin was linked to greater total and maximum withdrawal severity than smoking heroin. The authors speculated that the effect of the route of administration may have been due to lower systemic availability of smoked compared with injected heroin. Their data suggested that even the duration of the withdrawal symptoms seemed to increase with higher doses and intravenous use. However, there were several limitations to this study. It was retrospective and the period of observation lasted only 7 days although the withdrawal symptoms lasted much longer. In addition, many subjects took doxepin and benzodiazepines during the observation phase, which may have reduced or suppressed their withdrawal symptoms.

Second-Generation Effects

Fetotoxicity

A report of death associated with intravenous heroin use has provided insights about the distribution of heroin and its metabolites in the fetus (30).

- A 17-year-old girl with a history of heavy drug abuse for 2 years was found dead in a public restroom, with fresh needle puncture marks. She was 18–20 weeks pregnant with a male fetus, and had massive brain and lung edema from acute intoxication. Analysis of her hair showed that she had used heroin over the previous few months. Drug screening of body fluids showed only opiates (high concentrations of 6-monoacetylmorphine and morphine) in the maternal and fetal circulation at the time of death. Unexpectedly high amounts of morphine, 6-monoacetyl-morphine, and

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morphine-3-glucuronide were also found in the amniotic fluid. Only morphine-3-glucuronide was detected in the fetus, whereas both morphine-3-glucuronide and morphine-6-glucuronide were detected in the mother, in the body fluids, and in all investigated organ tissues except the brain.

The authors noted that heroin is considered a "prodrug," with 6-monoacetyl-morphine, morphine, and morphine-6-glucuronide accounting for most of its narcotic activity. In blood, diamorphine is rapidly converted to the active metabolite 6-monoacetyl-morphine, which is presumably converted to morphine in the liver. The majority of the morphine is converted to morphine-3-glucuronide and small amounts are converted to morphine-6-glucuronide, which is pharmacologically active. They concluded that morphine-3-glucuronide can cross the placenta and that high concentrations of heroin and its metabolites can be found in fetal compartments during heroin abuse by the mother. Lastly, heroin and its pharmacologically active metabolites appear to be present in the fetal central nervous system for much longer than in the maternal circulation, because of low fetal drug-metabolizing capacity as well as minimal drug elimination from the amniotic fluid in advancing pregnancy.

Drug Administration

Drug dosage regimens

High-dose intrathecal diamorphine for analgesia after elective cesarean section has been studied in 40 women who were randomized to diamorphine 0.5 or 1 mg (31). All also received diclofenac 100 mg at the end of the cesarean section and morphine via a patient-controlled analgesia system. Postoperative analgesia was more prolonged and reliable in those who were given diamorphine 1 mg, who needed significantly less morphine. There was postoperative nausea in just under half of the patients in each group, and most of the patients (93%) had mild to moderate pruritus. There were no cases of excessive sedation or oxygen desaturation.

Drug administration route

Nasal diamorphine is as effective as intramuscular morphine and is much better tolerated by children, with no apparent increased risk of adverse effects (32,33). In a multicenter, randomized, controlled study, 404 children aged 3–16 years with a fracture of an arm or leg were given either nasal diamorphine 0.1 mg/kg or intramuscular morphine 0.2 mg/kg. The onset of pain relief was faster with nasal diamorphine, and there were no serious adverse effects. The frequencies of opioid-related mild adverse effects were similar in the two groups.

In a randomized, placebo-controlled, double-blind study of the relative efficacies of patient-controlled analgesia (PCA) regimens (34), 60 patients undergoing elective total hip or knee replacement were randomly allocated to receive epidural diamorphine 2.5 mg followed by a PCA bolus 1 mg with a 20-minute lockout (group 1), subcutaneous diamorphine 2.5 mg followed by a PCA bolus 1 mg with a 10-minute lockout (group 2), or epidural diamorphine 2.5 mg in 4 ml of 0.125% bupivacaine followed by a PCA bolus of 1 mg diamorphine in 4 ml 0.125% bupivacaine with a 20-minute lockout (group 3). Diamorphine demands were significantly higher in group 2 in the first postoperative 24-hour period, but pain scores were only significantly higher in group 2 in the first 3 hours postoperatively compared with group 3 and group 1. There were also fewer opioid-related adverse effects in group 2, and group 3 reported higher incidences of various adverse effects. The conclusion was that PCA diamorphine given with or without bupivacaine provides analgesia of similar efficacy once adequate pain relief has been achieved. Taking the incidences of adverse effect profiles into account, diamorphine subcutaneous PCA was a simple and effective method of providing analgesia.

In 62 women who asked for regional analgesia in labor and who were randomized to an intrathecal injection of either bupivacaine 2.5 mg with fentanyl 25 μg or bupivacaine 2.5 mg with diamorphine 250 μg, the diamorphine provided longer analgesia (35). There were significant differences in adverse effects between the groups. There were no instances of nausea or vomiting, but pruritus was more common in those who received fentanyl. The dose of diamorphine was deliberately low, and more studies are needed to confirm these findings.

Drug overdose

The main life-threatening complications of heroin intoxication include acute pulmonary edema and delayed respiratory depression with coma after successful naloxone treatment. In a prospective study of the management of 160 heroin and heroin mixture intoxication cases treated in an emergency room in Switzerland between 1991 and 1992, there were no rehospitalizations after discharge from the emergency room and there was only one death outside the hospital due to pulmonary edema, which occurred at between 2.25 and 8.25 hours after intoxication (36). A literature review found only two reported cases of delayed pulmonary edema, which occurred 4 and 6 hours after hospitalization. The authors recommended surveillance of a heroin user for at least 8 hours after successful opiate antagonist treatment.

Among heroin users, the annual rate of mortality is 1–4%; overdose and HIV infection being the leading causes. The effect of the frequency and route of heroin administration on the occurrence of non-fatal heroin overdose has been studied (37). Among 2556 subjects with heroin dependence, 10% had taken overdoses requiring emergency care in the prior 12 months. The cumulative risk of overdose increased as the frequency of heroin use fell. Among daily heroin users, the risk was greater with increased frequency of heroin injection, but not among non-daily users. The risk of overdose was greater with injection than with other routes of administration.

Drug–Drug Interactions

Alcohol

Many heroin users use heroin and alcohol together. There has been an evaluation of the pharmacokinetic interaction between heroin and alcohol and the role of

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that interaction in the cause of 39 heroin-related deaths that were attributed to either heroin or heroin + ethanol (38). The cases were arbitrarily divided into two groups according to blood ethanol concentration (low-ethanol group, under 1000 μg/ml, and high ethanol group, over 1000 μg/ml. The high-ethanol group was associated with reduced hydrolysis of 6-acetylmorphine to morphine, and there was an inverse correlation between blood ethanol concentration and hydrolysis of 6-acetylmorphine to morphine. The concentration of total morphine was lower in the high-ethanol group. High blood ethanol concentrations were also associated with an increased ratio of unbound to total morphine and with reduced excretion of unbound and total morphine. The relative concentrations of conjugated heroin metabolites were reduced in the presence of a high blood ethanol concentration. The authors hypothesized that alcohol inhibits the glucuronidation of morphine, resulting in less conjugated morphine in the blood. Thus, in patients with high blood ethanol concentrations the additional depressant effects of unconjugated heroin metabolites may contribute to a more acute death.

Anticholinergic drugs

Combining opiates with anticholinergic drugs is a common practice in recreational abuse (SEDA-21, 34). Heroin mixed with hyoscine (scopolamine) is nicknamed "polo" and "point on point." Mixed drug toxicity, with atypical signs and symptoms of opiate abuse, has been reported (39).

- A 41-year-old woman who had taken 11 alprazolam tablets and heroin mixed with an unknown substance developed slurred speech and a staggering gait. She was also taking paroxetine. Her pupils were dilated, her skin warm and dry. Electrocardiography showed a sinus bradycardia. She was given intravenous naloxone 2.0 mg and became acutely agitated and combative. She was delirious, agitated, and disoriented, and was given an intravenous sedative and intubated. Her urine contained codeine, morphine, and atropine.

This case exemplifies the difficulty in identifying anticholinergic drugs such as atropine, and unfortunately the finding of dilated pupils did not raise the suspicion of mixed drug toxicity. The use of naloxone uncovered florid agitation due to anticholinergic drug toxicity.

Interference with Diagnostic Tests

Blood glucose

Diamorphine flattens the glucose tolerance curve and increases glycosylation of HbA_1 (40).

Antithrombin III

Diamorphine depresses the biological activity of antithrombin III (41).

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Diazepam

See also Benzodiazepines

General Information

Diazepam produces less sedation in cigarette smokers, and higher (not lower, as stated in SEDA-20) doses may be required for the same sedative or anxiolytic effect. Owing in part to its continued widespread use, several unusual adverse effects of diazepam continue to be reported. These include cases of urinary retention and compartment syndrome, which are not explicable by its pharmacology. On the other hand, accumulation of diazepam and attendant complications of obtundation and respiratory depression may be understood in terms of its long half-life, particularly in elderly people and medically ill patients. Caution about the intravenous use of diazepam comes from a study that showed cardiac dysrhythmias (mainly ventricular extra beats) in a quarter of oral surgery patients; midazolam and lorazepam were much safer (1).

Organs and Systems

Cardiovascular

Cases of inadvertent intra-arterial injection of diazepam have been reported.

- A 51-year-old woman with an acute claustrophobic anxiety attack developed gangrene of the fingers after she was inadvertently given diazepam 10 mg intra-arterially (2).
- Inadvertent intra-arterial injection of diazepam (2.5 mg in 0.5 ml) has been reported in an 8-year-old girl (3). Gangrene resulted and amputation of the 4th and 5th fingers was required.

Gangrene has been previously reported with intra-arterial injection of diazepam and is also well known with other classes of drugs, such as barbiturates and phenothiazines. It appears to be caused by the drug rather than the solvent used in the intravenous formulations.

Respiratory

Respiratory difficulties are a major potential adverse effect of rectal diazepam (4).

Of 94 children who presented with seizures, 11 had respiratory depression after intravenous or rectal diazepam (5). However, this finding was challenged (6,7). The authors of the second comment stated that this complication does not occur when rectal diazepam gel is used without other benzodiazepines; they also recommended

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that during long-term therapy families should be instructed not to give rectal diazepam more than once every 5 days or five times in 1 month.

Patients receiving intravenous benzodiazepines must be monitored for respiratory depression, which may demand artificial ventilation during intensive treatment. Diazepam may cause more respiratory depression than lorazepam at equieffective dosages (SEDA-20, 59) and is contraindicated in neonates for this reason and because it produces unacceptably prolonged sedation (8).

Nervous system

In an open study in 104 patients with acute stroke, diazepam 10 mg bd for 3 days was well tolerated (9).

In a multicenter, double-blind study, 310 patients with generalized anxiety disorder were treated for 6 weeks with abecarnil (mean daily dose 12 mg), diazepam (mean daily dose 22 mg), or placebo in divided doses for 6 weeks (10). Those who had improved at 6 weeks could volunteer to continue double-blind treatment for a total of 24 weeks. Slightly more patients who took diazepam (77%) and placebo (75%) completed the 6-week study than those who took abecarnil (66%). The major adverse events during abecarnil therapy were similar to those of diazepam, namely drowsiness, dizziness, fatigue, and difficulty in coordination. Abecarnil and diazepam both produced statistically significantly more symptom relief than placebo at 1 week, but at 6 weeks only diazepam was superior to placebo. In contrast to diazepam, abecarnil did not cause withdrawal symptoms. The absence of a placebo control makes it difficult to interpret the results of another study of the use of abecarnil and diazepam in alcohol withdrawal, which appeared to show comparable efficacy and adverse effects of the two drugs (11).

The mechanism of rare extrapyramidal effects with diazepam is unexplained (SEDA-18, 44).

Seizures

In a randomized trial, seizures occurred in 14 (16%) of 86 patients with gliomas undergoing contrast CT examinations; however, in 83 other patients with gliomas receiving diazepam prophylaxis, seizures occurred in only two patients (2.2%).

Six patients had untoward effects from excessive rectal diazepam (12). In three cases, seizures reappeared and were interrupted by rectal diazepam, followed by sedation and gradual awakening; the intervals were about 4 days. The other three patients had variable and complex symptoms, with serial seizures and alternating states of tension, apathy, and sleepiness. The plasma concentrations of diazepam and desmethyldiazepam showed rapid fluctuations.

- A 20-year-old man with complex partial seizures presented with exacerbation of his disease (13). He was taking phenytoin and sodium valproate, with plasma concentrations in the target ranges. During a video electroencephalogram recording he was given diazepam 10 mg, and the partial seizures developed into frequent generalized seizures. The same response was seen on a subsequent occasion.

The authors commented that although paradoxical reactions to benzodiazepines are rare, they should be considered in cases of refractory epilepsy.

- A 28-year old man with complex partial status, which lasted for 2 months, had a paradoxical worsening of seizure activity in response to diazepam and midazolam (13).

Neuromuscular function

Muscle rigidity after high-dose opioids can be reduced by the benzodiazepines midazolam and diazepam (SEDA-19, 82).

Psychological, psychiatric

A fugue-like state with retrograde amnesia has been associated with diazepam (14).

- A 23-year-old military officer on active duty took diazepam 5 mg tds and ibuprofen for back spasms. Three days later he was found sitting in a church, having assumed a previous role from his past life. He identified the date as 14 months before and his memory before that time was intact. However, he had no memory of events during the previous 14 months. There were no symptoms suggesting a schizophrenic disorder and his mental function was normal. His symptoms resolved within 24 hours of withdrawal of diazepam, except for amnesia of the event. He assumed his correct identity and was aware of the correct date. He had taken ibuprofen in the past with no adverse effects and this was his first exposure to a benzodiazepine. No other medications were involved and a full medical review found no cause for his symptoms other than diazepam use.

Endocrine

Gynecomastia, with raised estradiol, has been reported in men taking diazepam (15).

Skin

Cutaneous adverse effects of diazepam are rare. The incidence was 0.4 per 1000 in the Boston Collaborative Surveillance Program (16).

- A 50-year-old woman was referred to hospital for chronic depression with alcohol dependence (17). There was no history of drug allergy. She was given oral thioridazine 100 mg/day and diazepam 10 mg qds. After 2 days she noticed an erythematous eruption on her ankles. Thioridazine was withdrawn, but the eruption became more erythematous and affected both extremities and flanks within a few hours. She was given methylprednisolone 80 mg/day. The next day the eruption became bullous and she became pyrexial (39.4°C). Urea and creatinine concentrations were normal. Blood cultures were negative. A skin biopsy showed bullous vasculitis with numerous eosinophils in the dermis. Diazepam was then withdrawn, the pyrexia resolved, and the skin lesions healed, although post-inflammatory ulcers persisted on both ankles for 2 months. A lymphocyte blast transformation test was positive for diazepam.

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Sweet's syndrome has been attributed to diazepam (18).

- A 70-year-old white man, with no significant preceding medical history, developed an acute painful rash, a fever (38.4°C), and severe arthralgia 5 days after starting to take diazepam 10 mg bd for lumbar muscular contracture due to hard physical exercise. He had taken no other medications. There were well-defined purple-red skin plaques, surmounted by vesicular and hemorrhagic blisters. He had a leukocytosis. Sweet's syndrome was confirmed by punch biopsy of a lesion. Diazepam was withdrawn, and prednisolone 30 mg/day was given for 2 weeks and then tapered. The patient improved quickly and the eruption cleared in 10 days.

Immunologic

Hypersensitivity reactions after diazepam are very rare and usually mild. However, some severe reactions have been reported.

- A 50-year-old woman with chronic depression or dysthymic disorder and alcohol dependence was given oral thioridazine 100 mg/day and diazepam 10 mg qds (19). She had no history of drug allergy. Two days later she noticed an erythematous eruption on her ankles. Thioridazine was withdrawn, but the eruption became more widespread over a few hours. She was given methylprednisolone 80 mg/day, but the following day the eruption progressively became bullous and her condition worsened. She developed a fever of 39.4°C, felt ill, and had a neutrophilia, but blood cultures were sterile and her renal function was normal. A skin biopsy showed bullous vasculitis with numerous eosinophils in the dermis. Diazepam was then withdrawn, which led to resolution of pyrexia and gradual healing of the skin lesions over the next 2 months. The lymphocyte blast transformation test was positive for diazepam.
- A 28-year-old nurse had generalized urticaria and collapsed while she was undergoing a gastroscopy for suspected *Helicobacter pylori* infection (20). Before the start of the procedure she was given lidocaine oral spray and intravenous diazepam 10 mg, and at the end intravenous flumazenil 1 mg. Skin prick tests and intradermal tests with diazepam 5 mg/ml produced a weal-and-flare reaction; flumazenil 0.1 mg/ml and lidocaine 2% had no effect.

Although in the second case, for safety reasons, a challenge test was not performed, it was suggested that the reaction had been IgE-mediated.

Second-Generation Effects

Fetotoxicity

Postnatal, longitudinal, somatic, neurological, mental, and behavioral development has been studied at birth and at 8, 15, and 24 months of life in children whose mothers had been treated during pregnancy with diazepam ($n = 126$) or promethazine ($n = 127$) and in children whose mothers had not been exposed (21). The children in the diazepam group weighed less at birth but not at 8 months or subsequently.

Diazepam has been reported to cause inappropriate ADH secretion in a neonate (22).

- A female infant was delivered vaginally at 41 weeks. Her 30-year-old mother had taken diazepam for epilepsy and hysterical attacks throughout the pregnancy. The pregnancy and delivery were uneventful. The baby was admitted to the neonatal ward in anticipation of neonatal drug withdrawal syndrome. On the first day of life, milk feeding was stopped because of poor sucking, vomiting, and increased gastric aspirate volume. On the same day oliguria was reported and the urine osmolality was increased. Secretion of antidiuretic hormone was suspected as the cause of the oliguria, and so fluid intake was restricted and a diuretic was given. Subsequently the urine output increased and the urine osmolality gradually fell. The baby's condition became stable and she was discharged on day 16.

Susceptibility Factors

Age

Five neonates who suffered an unexpected long period of respiratory failure, muscular hypotonia, and drowsiness were retrospectively investigated (8). Unusually high doses of diazepam had been given by intravenous bolus injection and serum concentrations of diazepam and its active metabolites were high. The authors emphasized the persistence of the very long-acting *N*-desmethyldiazepam, particularly in neonates and even more exaggeratedly in premature infants, owing to reduced capacity of hepatic uridine diphosphate glucuronyl transferase activity (8).

Drug Administration

Drug administration route

Although intravenous diazepam is the preferred route, the undiluted intravenous solution of diazepam can be given rectally, and is effective in the emergency management of seizures in children (23). Rectal gel is an alternative, and can be given by non-medical personnel (24). Adverse effects of rectal diazepam are rare and mild. Animal studies and clinical experience have not shown damage to the rectal mucosa.

Drug overdose

- A 54-year-old man took 2 g of laboratory-grade diazepam and was treated with activated charcoal, diuresis, and flumazenil infusion (25). He wakened, but had drowsiness, dysarthria, diplopia, and dizziness for 9 days. Blood concentrations of diazepam and its main metabolite, *N*-desmethyldiazepam, remained high for over 4 weeks.

Of 149 patients, 10 received an overdose of rectal diazepam indicated for acute repetitive seizures (51 overdoses in total) (26). There were no untoward events in 40 cases, and the adverse events were most often not drug-related. No patient had bradypnea or apnea.

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Drug–Drug Interactions

Antihistamines

Drugs that depress the CNS, such as the benzodiazepines, have their effects increased by interaction with the classic antihistamines. However, the second-generation antihistamines have not yet been proven to interact with CNS depressants such as alcohol or diazepam (27–30).

Antiepileptic drugs

Some interactions of diazepam with antiepileptic drugs are listed in Table 2 in the monograph on antiepileptic drugs.

Beta-adrenoceptor antagonists

Lipophilic beta-adrenoceptor antagonists are metabolized to varying degrees by oxidation by liver microsomal cytochrome P450 (for example propranolol by CYP1A2 and CYP2D6 and metoprolol by CYP2D6). They can therefore reduce the clearance and increase the steady-state plasma concentrations of other drugs that undergo similar metabolism, potentiating their effects. Drugs that interact in this way include diazepam (31).

Bupivacaine

Animal studies have shown that diazepam can prolong the half-life of bupivacaine (32).

Caffeine

At least 40 drugs interact with caffeine, including benzodiazepines (for example diazepam, whose sedative effect is counteracted by caffeine) (33).

Cholinesterase inhibitors

Although diazepam does not have anticholinergic properties, it is possible to reverse diazepam-induced delirium by the use of cholinesterase inhibitors, such as physostigmine; however, physostigmine can on occasion induce severe arterial hypertension, especially if the dose exceeds 2 mg intravenously. In healthy volunteers sedated with diazepam, an increase in awareness was established with the use of physostigmine, but there was also a reduction in ventilatory drive (SEDA-10, 119).

Cisapride

Cisapride increases the absorption of diazepam (34).

Clozapine

Hypotension, collapse, and respiratory arrest occurred when low doses (12.5–25 mg) of clozapine were added to a pre-existing diazepam regimen (SEDA-22, 41).

- A 50-year-old man with symptoms of chronic paranoid schizophrenia resistant to typical neuroleptic drugs had a brief syncopal attack with significant electrocardiographic changes (sinus bradycardia and deep anteroseptal inverted T waves and minor ST segment changes) after the dosage of clozapine was increased to 300 mg/day while he was taking diazepam 30 mg/day (35).

The mechanism of this presumed interaction is unknown.

Disulfiram

Disulfiram inhibits hepatic drug metabolism and can prolong the effects of substances that are normally metabolized in the liver. This has been studied for various benzodiazepines. The clearances of chlordiazepoxide and diazepam were significantly reduced and their half-lives prolonged by disulfiram (36).

Heparin

In healthy non-fasting subjects, 100–1000 IU of heparin given intravenously caused a rapid increase in the unbound fractions of chlordiazepoxide, diazepam, and oxazepam (37,38), but no change in the case of lorazepam (37). The clinical implications of this finding are not known.

Ibuprofen

The effect of diazepam on the pharmacokinetics of ibuprofen has been studied in eight healthy subjects, who took ibuprofen or ibuprofen plus diazepam at 10.00 or 22.00 hours in a randomized, crossover study (39). Diazepam significantly prolonged the half-life of ibuprofen at 22.00 hours but not at 10.00 hours. The mean clearance of ibuprofen was therefore reduced by diazepam at night. This time-dependent effect of diazepam on the pharmacokinetics of ibuprofen may be due to circadian variation in the pattern of protein production in the liver and/or competitive protein binding of the two drugs during the night.

Lithium

There has been a well-documented case of profound hypothermia in a patient taking lithium and diazepam; it did not occur with either drug alone (40). Otherwise, benzodiazepines and lithium are compatible.

Naltrexone

The effects of naltrexone on diazepam intoxication were investigated in 26 non-drug-abusing subjects who received either naltrexone 50 mg or placebo and 90 minutes later oral diazepam 10 mg in a double-blind, crossover trial (41). Naltrexone was significantly associated with negative mood states, such as sedation, fatigue, and anxiety, compared with placebo, while positive states (friendliness, vigor, liking the effects of diazepam, feeling high from diazepam) were significantly more common with placebo. Naltrexone significantly delayed the time to peak diazepam concentrations (135 minutes) compared with placebo (75 minutes), but there were no significant differences in the concentrations of nordiazepam, the main metabolite of diazepam, at any stage in the study.

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Omeprazole

In human liver microsomes, the metabolism of diazepam was mainly to 3-hydroxydiazepam (90%); omeprazole inhibited this conversion (42).

In a double blind, placebo-controlled, crossover study in eight white and seven Chinese men who were extensive metabolizers of debrisoquine and mephenytoin, omeprazole 40 mg/day reduced the oral clearance of diazepam by 38% and increased desmethyldiazepam AUC by 42%. In contrast, in the Chinese men the oral clearance of diazepam fell by only 21% and desmethyldiazepam AUC by 25%. The authors concluded that the extent of the inhibitory effect of omeprazole on diazepam metabolism depends on ethnicity (43). Differences between Caucasians and Asians may account for such effects.

Penicillamine

In one patient the use of penicillamine led to exacerbation of phlebitis that had been caused by intravenous diazepam (44).

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Diazoxide

General Information

Diazoxide is a direct vasodilator that acts on vascular smooth muscle to produce systemic vasodilatation. As a result there is baroreceptor-mediated activation of the sympathetic nervous system and the renin–angiotensin system.

Vasodilators (as monotherapy) are associated acutely with flushing, headache, dizziness, reflex tachycardia, and palpitation. Chronic treatment can be complicated by fluid retention.

Organs and Systems

Cardiovascular

Rapid administration of diazoxide intravenously can cause severe hypotension. In some cases this has resulted in abnormal neurological signs associated with ischemic damage (1).

Metabolism

Diazoxide can cause hyperglycemia and diabetes mellitus and has been used to treat hyperinsulinism in infancy, although its use may be hazardous (2,3).

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Dibenzepin

See also Tricyclic antidepressants

General Information

Dibenzepin is a 6,7,6 tricyclic compound of the dibenzodiazepine type. A comparison with imipramine was said to show equal efficacy; adverse effects were comparable in type and degree (1).

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Dibromopropamidine

General Information

Dibromopropamidine in a cream base is used to treat herpesvirus skin lesions.

Organs and Systems

Immunologic

Contact allergy is infrequently reported with dibromopropamidine.

- A 40-year-old man with genital herpes and an acute edematous vesicobullous dermatitis on his penile shaft had a positive patch test with dibromopropamidine and not the other ingredients of the cream (1).

Reference

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Dichloralphenazone

General Information

Dichloralphenazone is a complex of phenazone (antipyrine) and chloral hydrate, which dissociates in aqueous solution. It has been used as a hypnotic but is obsolete. Its adverse effects are those of its components (1,2).

Drug Interactions

Phenytoin

The phenazone component of dichloralphenazone is an enzyme inducer and hastens the metabolism of phenytoin (3).

Warfarin

The phenazone component of dichloralphenazone is an enzyme inducer and hastens the metabolism of warfarin (4).

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Dichlorophen

General Information

Dichlorophen is an antihelminthic drug that was used in the treatment of tapeworm infections but has been superseded by praziquantel and niclosamide. It also has antifungal and antibacterial activity and has been used topically in the treatment of fungal infections and as a germicide in soaps and cosmetics (1).

During the first few hours after taking a single oral dose one-third of patients have nausea, diarrhea, or abdominal pain, and some experience vomiting. Urticaria, contact allergic dermatitis, and photosensitivity can occur. In the past, with larger doses, jaundice and even hepatic necrosis have been described.

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Diclofenac

See also Non-steroidal anti-inflammatory drugs

General Information

The overall incidence of adverse reactions to diclofenac is about 30%, but less than 1% of patients have to have treatment withdrawn for this reason. The manufacturers' analysis of 1966 adverse effects in 987 patients over about 6 years, when over 30 million patients had been treated, provided some interesting quantitative data. Of the total number of adverse reactions, 34% were gastrointestinal and 16% hematological. Worldwide experience with diclofenac showed that the incidences of serious adverse drug reactions in phase III short-term trials (1227 patients) and long-term trials (1173 patients) in the USA were respectively as follows (1):

- peptic ulcer 0.16 and 0.34%;
- gastrointestinal bleeding 0.16 and 0.17%;
- hepatitis 0 and 0.26%;
- thrombocytopenia 0 and 0.17%.

Organs and Systems

Respiratory

Diclofenac caused eosinophilic pneumonitis in a 67-year-old man (SEDA-18, 103).

Nervous system

The frequency of central nervous system adverse effects is 1–9%. Headache, dizziness, vertigo, insomnia, drowsiness, and agitation have been reported. Hallucinatory symptoms and generalized tonic-clonic seizures have also been described (SEDA-16, 109). Toxic encephalitis can be part of a general toxic reaction (2). Diclofenac provoked aseptic meningitis in patients with systemic lupus erythematosus (SEDA-17, 109).

Sensory systems

Hyperemia, burning of the eyes, eyelid allergic contact dermatitis, and conjunctivitis can occur in patients who use diclofenac eye-drops (SEDA-20, 92) (SEDA-21, 104).

Diclofenac can cause reduced corneal sensitivity, starting from 15 minutes after instillation and measurable after 1 hour (3). This corneal hypesthesia can be useful in reducing pain and discomfort in ocular inflammation and after surgery. In chronic treatment, however, the effect of diclofenac on corneal nerves can cause either increased healing time of the corneal epithelium or a neurotrophic epitheliopathy in patients with conditions that predispose to epithelial damage, such as dry eyes. In contrast, flurbiprofen, indometacin, and ketorolac tromethamine did not cause corneal hypesthesia.

Electrolyte balance

Severe hyponatremia developed in an elderly woman treated with intramuscular diclofenac (SEDA-13, 80).

NSAIDs can cause hyperkalemic acidosis and should be used with caution in the presence of renal impairment (4).

- A 76-year-old woman developed quadriparesis associated with hyperkalemia after taking diclofenac 100 mg/day for 10 months for gouty arthritis. She had a metabolic acidosis with a normal anion gap and mild renal impairment. Her weakness resolved after withdrawal of diclofenac and correction of the hyperkalemia.

Mineral balance

At least three reports of severe hyponatremia have been described (SEDA-12, 85) (SEDA-13, 80) (SEDA-18, 103). In the last case the withdrawal of diclofenac and fluid restriction led to normal fluid and electrolyte balance within 10 days, despite concomitant treatment with nabumetone.

Hematologic

In an analysis of 447 adverse effects in 194 patients worldwide (5), 20 had blood abnormalities, including two cases of agranulocytosis and one of granulocytopenia. One of these patients, who was sensitive to pyrazolone, had taken a pyrazolone compound as well. Immune-mediated agranulocytosis and thrombocytopenia have been reported (SEDA-16, 110).

Reversible hemolytic anemia (SEDA-4, 69) (6), two cases of severe immune hemolytic anemia with acute renal insufficiency (SEDA-20, 92) (SEDA-22, 115), and fatal hemolytic anemia have occurred (7).

Diclofenac can cause panmyelopathy (8). Data from the International Agranulocytosis and Aplastic Anemia Study showed an increased risk of aplastic anemia (multivariate rate-ratio 8.8) (9). Fatal aplastic anemia has also been described (SEDA-4, 69) (10), as have purpura and thrombocytopenia, although not always with certainty. Spontaneous bleeding (subcutaneous bruises, hematoma, greater wound drainage) has been associated with diclofenac (SEDA-15, 100).

Gastrointestinal

Gastrointestinal adverse effects are particularly frequent, and affect some 14–25% of patients; the incidence of the most serious, peptic ulcer and bleeding were 0.16–0.34% and 0.16–0.17%, respectively (1). A prospective 12-week endoscopic study documented better gastrointestinal tolerability with diclofenac than naproxen (SEDA-20, 92). Upper gastrointestinal hemorrhage has been associated with transdermal application of diclofenac, with massive bleeding in two of four patients (SEDA-21, 104).

Perforation of the terminal ileum occurred in one patient who had taken a high dose (400 mg/day) of modified-release diclofenac (11).

Colonic stricture, similar to ileum "diaphragm" disease, developed in a patient during prolonged administration of modified-release diclofenac (12). Pseudomembranous colitis and colonic ulceration, with or without a diaphragm-like colonic stricture, have been reported (SEDA-16, 110) (SEDA-17, 109). Dispersible diclofenac is a formulation from which absorption is more rapid than the usual formulation, but gastrointestinal adverse events still occur (SEDA-20, 92).

Rectal administration caused adverse effects in 16% of patients (13); anorectal lesions (erosions, ulcers, stenosis of the anal margin) occurred after a relatively short period of suppository use (14).

Liver

Liver function can be impaired during diclofenac treatment, and liver damage may be more common than previously thought (SEDA-10, 83) (15). The risk is the same as with the few other NSAIDs that have been adequately studied. Biopsy-proven hepatitis with positive rechallenge and dechallenge has been described (16) and confirmed (17,18). The usual clinical presentation is acute hepatitis, but chronic active hepatitis has been described (17–20). Although recovery is usually rapid in the acute form after drug withdrawal, fatal cases have occurred (SEDA-11, 93) (SEDA-12, 85) (SEDA-13, 80) (21). Diclofenac-induced fulminant hepatic failure has been successfully treated with liver transplantation (22). Patients who developed combined reversible hepatorenal damage have also been reported (23–25) (SEDA-20, 91).

In a retrospective study, two-thirds of cases were detected by symptoms (jaundice, anorexia, nausea, vomiting, with or without fever) (26). The illness developed more than 5 weeks after starting diclofenac in more than 75% of patients, and within six months in 85%. Liver injury was classified as hepatocellular in 54% of patients and the histology was acute hepatocellular injury (nine patients) and chronic hepatitis (six patients). Factors affecting the susceptibility to diclofenac liver damage were sex (female) and type of disease (osteoarthritis). The mechanism of diclofenac-induced liver injury is unknown, but since the incidence is very low an idiosyncratic mechanism rather than intrinsic toxicity of the drug seems likely. In view of the rarity of hallmarks of hypersensitivity, the delayed development of injury and the delayed response to rechallenge, a metabolic effect rather than immunological idiosyncratic mechanism seems probable in most cases. The usefulness of monitoring serum enzymes is unknown, but it might be prudent to do so in the first 6 months of treatment.

Urinary tract

Renal papillary necrosis and interstitial nephritis with the nephrotic syndrome have been documented (27,28). Other cases of the nephrotic syndrome, with or without renal insufficiency, which were apparently due to minimal-change nephropathy (which is relatively more common in NSAID users), have been reported (29,30). The unusual feature of diclofenac-associated renal interstitial mucinosis has been described (SEDA-17, 109). Functional renal insufficiency after the use of diclofenac in a patient with burns has been described (SEDA-20, 92).

Skin

Allergic skin rashes, serous bullous dermatitis with positive rechallenge, and linear IgA deposits along the basal membrane in lesional and perilesional skin have all been reported (31). A patient who developed Stevens–Johnson

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syndrome died (SEDA-5, 103). Contact dermatitis and a generalized maculopapular eruption caused by delayed hypersensitivity to diclofenac have been reported with topical and oral diclofenac (SEDA-18, 104). Photosensitivity after topical application has been described (SEDA-22, 115). Diclofenac triggered pemphigus vulgaris, an uncommon manifestation of NSAID toxicity (SEDA-22, 115).

- Contact dermatitis on the eyelids developed in a 70-year-old-woman after she had used eye-drops containing diclofenac. Patch tests were positive to both diclofenac and indometacin, suggesting possible cross-reactivity between the two compounds (32).
- Staphylococcal scalded skin syndrome developed in a 68-year-old man after he had taken diclofenac for knee arthritis subsequently diagnosed as septic arthritis due to *Staphylococcus aureus* (33).

NSAIDs can predispose to severe infections (SEDA-22, 112).

Nicolau syndrome (embolia cutis medicamentosa) is a very rare complication of intramuscular injections, in which there is extensive necrosis of the injected skin area, perhaps due to accidental intra-arterial and/or para-arterial injection; it usually occurs in children (34). Of the NSAIDs with which it has been reported, diclofenac is the most common (35–38).

Musculoskeletal

Massive rhabdomyolysis resulting in renal insufficiency with complete recovery after withdrawal has been described in a man who took diclofenac for 2 weeks (SEDA-21, 104).

Immunologic

Acute allergic reactions were reported in 48 patients, and included anaphylactic or anaphylactoid reactions and angioedema without shock. Two anaphylactic reactions, one fatal, to parenteral diclofenac have been reported (SEDA-18, 104). Hepatorenal damage (SEDA-15, 100), thrombocytopenia, and hemolytic anemia mediated by an immune mechanism have been reported (SEDA-16, 110).

Skin tests with diclofenac were not useful in diagnosing hypersensitivity in a series of 12 non-atopic patients who had severe symptoms of hypersensitivity (39). However, oral challenge in patients who had had only cutaneous symptoms was diagnostic.

Second-Generation Effects

Fertility

Three cases of infertility have been reported with diclofenac (SEDA-21, 104).

Fetotoxicity

As inhibitors of cyclo-oxygenase, NSAIDs given during pregnancy can cause adverse maternal and fetal effects (SEDA-22, 112).

- Premature closure of the ductus arteriosus occurred in a fetus who was exposed in utero to diclofenac at 34–35 weeks of gestation (40). Emergency cesarean section was performed and the baby girl required cardiorespiratory support and multiple medications. She gradually improved and further development was normal.

Susceptibility Factors

The Japanese Health Authority has sent a "Dear Doctor" letter warning against the use of diclofenac in patients with encephalitis or encephalopathy related to influenza, which may be associated with higher mortality (41).

Drug Administration

Drug administration route

Aseptic tissue necrosis after intramuscular injection (Nicolau syndrome) has been reported after accidental intra-arterial injection. Antirheumatic drugs are often involved in these reactions and diclofenac has also been implicated (42). Other consequences of intramuscular administration of diclofenac are asymptomatic high serum creatine kinase activity or damage to muscle, nerve, or blood vessels (SEDA-17, 109).

Necrotizing fasciitis was reported in three patients, two of whom died as a consequence of severe local reactions associated with intramuscular diclofenac (43).

If appropriately diluted and infused intravenously, diclofenac is usually well tolerated, although local venous thrombosis has been described (SEDA-17, 109).

Drug–Drug Interactions

Ciclosporin

The risk of ciclosporin-induced nephrotoxicity can be increased when NSAIDs are also used (44,45). Diclofenac in particular should be avoided, because it is more likely to cause deterioration of renal function in patients taking ciclosporin (SEDA-15, 100) (SEDA-17, 107). There is also a pharmacokinetic interaction, which may be caused by inhibition by ciclosporin of the first-pass metabolism of diclofenac (SEDA-21, 104).

In 16 healthy volunteers there were no important pharmacokinetic changes when a single dose of ciclosporin was taken during steady-state administration of aspirin, indometacin, or piroxicam, but there was an interaction with diclofenac, whose AUC was doubled in the presence of ciclosporin (46).

In patients with rheumatoid arthritis, steady-state coadministration of diclofenac with ciclosporin was associated with a significant rise in serum creatinine concentration.

Lithium

Diclofenac increases serum lithium concentrations by impairing its renal excretion (47).

Triamterene

The interaction between diclofenac and triamterene causes renal impairment (48).

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Interference with Diagnostic Tests

Thyroid hormone tests

Diclofenac alters thyroid hormone tests, causing a fall in total serum triiodothyronine, principally by interfering with its serum protein binding (SEDA-19, 98).

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Dicycloverine

See also Anticholinergic drugs

General Information

Dicycloverine, in the doses generally used (up to 450 mg/day), is of disputed value. It may have a non-specific relaxant action on the gastrointestinal muscle. The evidence of its effects is meager and it seems to be an anticholinergic drug that which has been promoted in doses that are often too low to result in either a useful therapeutic effect or in adverse effects.

Second-Generation Effects

Teratogenicity

Dicycloverine was formerly combined with doxylamine succinate and sometimes with pyridoxine in Debendox (Bendectin) tablets, which were used in certain countries for the treatment of nausea and vomiting in pregnancy. There has been a widely discussed suggestion that Debendox might cause a range of fetal malformations, but numerous studies have failed to confirm this (1).

For example, in a survey of 22 977 pregnant women in Great Britain 620 of whom had been given Debendox and 743 other women had been given agents other than Debendox containing pyridoxine during the first 13 weeks of gestation, the rates for all abnormal outcomes among women given Debendox and those not given it were 5.0 and 5.4% respectively (2).

However, the sporadic reports of such problems sometimes involved women who took the product in high doses for long periods in early pregnancy and there is some doubt as to the dosage schedule used in the larger studies. Particularly since the pattern of supposed malformations was highly variable, and they were of types which tend to occur spontaneously, the point cannot be considered settled. However, any teratogenic effect must have been very slight.

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Didanosine

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Didanosine (2′,3′-dideoxyinosine, ddI) is a purine analogue reverse transcriptase inhibitor. The major clinical adverse effects reported during the first years of use of didanosine were acute pancreatitis and a painful neuropathic syndrome (due to a peripheral neuropathy), which appeared to be related to both dosage and cumulative dose (SEDA-17, 340) (1). However, the incidence of acute pancreatitis and peripheral neuropathy in these studies was lower than in earlier studies with didanosine (2,3). This may be related to the fact that treatment was started earlier or to the use of lower dosages (200–400 mg/day) in these studies compared with earlier studies. In the latter studies, gastrointestinal symptoms, most notably nausea and vomiting, were the most commonly reported adverse effects in patients taking didanosine. Minor adverse effects include insomnia, headaches, anxiety, irritability, rash, increased plasma uric acid concentration, and increased hepatic transaminase activities combined with a rash (4). There were no toxic effects of didanosine on hematological laboratory indices (5).

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Observational studies

The use of didanosine 125–200 mg bd plus interferon alfa-2b in AIDS-associated Kaposi's sarcoma has been studied in 68 patients (6). Withdrawal of didanosine was required in cases of peripheral neuropathy, rises in serum amylase activity, and hypertriglyceridemia.

Organs and Systems

Sensory systems

Eyes

Retinal depigmentation has been described in children taking didanosine (7).

Ears

Hearing loss attributed to didanosine has been reported in an HIV-infected adult (8).

- A 37-year-old HIV-infected man developed bilateral deafness while taking didanosine (400 mg/day), which had been started about 4 years before. He was also taking azithromycin, ciprofloxacin, and myambutol for about 1 month for a *Mycobacterium avium* infection. Otoscopic examination and tympanometry were normal. Audiometry showed a bilateral sensorineural hearing deficit of 40–60 dB. There were no other neurological abnormalities. An MRI scan of the brain was normal. Didanosine was withdrawn and replaced by alternative antiretroviral agents. All other medications were continued. His hearing improved progressively and returned to normal after 2 months.

In the absence of rechallenge, there was no conclusive evidence for a causative role of didanosine in the development of hearing loss in this case. However, the authors argued that the improvement on discontinuation of didanosine, which is known to cause neuritis, implicated the drug.

Extensive serial audiological studies in an HIV-infected child showed high-frequency hearing loss after 19 months of combined treatment with zidovudine and didanosine (dosages unknown), which were started at 24 months of age (9). Normal tympanograms indicated that this hearing loss was sensorineural.

While no conclusive evidence was given for a causative role of either antiretroviral drug, the authors concluded that children taking antiretroviral therapy need to be monitored for possible ototoxicity.

Hematologic

Thrombocytopenia has been observed in patients using didanosine (10,11).

Musculoskeletal

There is no evidence that didanosine contributes to the development of myopathy in patients taking didanosine and zidovudine in whom this adverse event occurs (12).

Multiorgan failure

There has been a report of a patient in whom pancreatitis, fulminant hepatic failure, and persistent lactic acidosis occurred, culminating in death from liver failure (13).

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Diethyl sebacate

General Information

Diethyl sebacate is an emulsifier used in cosmetics and topical medicaments. In contrast to the emulsifying agents stearyl alcohol, stearic acid, and glyceryl stearate, diethyl sebacate is considered to be a rare sensitizer.

Organs and Systems

Immunologic

There were positive patch tests to diethyl sebacate (10 and 30% in ether and 1 and 10% in petrolatum) in a 48-year-old woman who had been using a topical antimycotic ointment (1).

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Diethylcarbamazine

General Information

Diethylcarbamazine is an antihelminthic drug used in the treatment of filarial infections. With some infecting species it is effective in both the adult and microfilarial stages, whilst with others it is active only against the microfilarial stages and does not eradicate the infection.

Pharmacokinetics

Diethylcarbamazine is extensively metabolized, the half-life being 6–12 hours; the remainder enters the urine within 48 hours. Over the initial period the dosage should be increased slowly to avoid or reduce allergic responses as a result of destruction of parasites and liberation of antigen, and then maintained at 3 mg/kg tds for 34 weeks. Not all of its adverse effects are necessarily due to destruction of the parasite; weakness, lethargy, anorexia, and nausea can be due to the drug itself.

The pharmacokinetics, safety, and tolerability of co-administered diethylcarbamazine and albendazole have been investigated in a double-blind, randomized, placebo-controlled trial in 42 subjects (aged 18–52 years, weighing 46–67 kg) living in a lymphatic filariasis endemic region but without detectable microfilariae (1). Three groups of 14 patients received diethylcarbamazine 6 mg/kg alone, albendazole 400 mg alone, or diethylcarbamazine 6 mg/kg plus albendazole 400 mg. Both diethylcarbamazine and albendazole were well tolerated alone and in combination. In contrast to a study in patients with lymphatic filariasis (2), there were no adverse events in amicrofilaremic individuals. In all three treatment groups the drugs were rapidly absorbed from the gastrointestinal tract, although there was marked interindividual variation. The pharmacokinetics of diethylcarbamazine, albendazole, and albendazole sulfoxide were similar.

Observational studies

Brugia malayi and *Wuchereria bancrofti*

When treating *Brugia malayi* and *Wuchereria bancrofti* infections, reactions include headache and fever, sometimes accompanied by malaise, nausea, and vomiting. Urticarial skin rashes can occur, and subsequently lymphangitis and lymphadenopathy often appear (SEDA-17, 357). Abscess formation can occur in association with adult worms. Major systemic complications of therapy include proteinuria and severe pruritus; proteinuria has even been seen in some patients using the drug topically. Circulating immune complexes have been found to be increased in many cases. Those with CIq binding greater than 3% are at significantly increased risk of developing visual field constriction and proteinuria.

In lymphatic filariasis diethylcarbamazine can cause systemic reactions, such as fever, arthralgia, headache, and malaise, and local reactions such as swollen and painful lymph nodes. All of these reactions are thought to be caused by an allergic reaction to antigens from the dying microfilaria and not to a toxic effect of the drug itself. This causal relation is further emphasized by a study from Indonesia, in which adverse reactions to treatment with diethylcarbamazine were studied in patients with *B. malayi* filariasis—26 microfilaria-positive patients (mean 235 mf/10 ml), 12 "endemic" controls (from the endemic area, but microfilaria counts negative), and 17 patients with elephantiasis, of whom three had with high microfilaria counts (3). Adverse effects, mainly fever, headache, and body aches, started 2–24 hours after the administration of diethylcarbamazine 6 mg/kg/day for 12 days. Of the patients with positive pretreatment microfilaria counts 15% had severe adverse reactions, 19% moderate reactions, and 65% mild reactions. There was a direct relation between the severity of the adverse effects and the height of pretreatment microfilaria counts, and the more severe adverse effects occurred in the patients with the highest pretreatment microfilaria counts. In the endemic controls there were no reactions or only mild ones. In the patients with elephantiasis there were no reactions or only mild ones in all but two patients, both of whom had moderate reactions and had high pretreatment microfilaria counts.

That diethylcarbamazine may still be the more effective drug in *B. malayi* infections, despite these adverse effects, is suggested in a study from India, in which the efficacy and safety of several single-dose drug combinations, including albendazole, diethylcarbamazine, and ivermectin were compared in 51 microfilaria-positive patients with *B. malayi* and in which diethylcarbamazine was more effective in reaching a sustained reduction in microfilaria counts after 1 year than ivermectin, although the study was small (4). Adverse reactions (fever, headache, myalgia, and chills) occurred in all of the 16 patients treated with a combination of ivermectin (200 micrograms/kg as a single dose) and diethylcarbamazine (6 mg/kg as a single dose), in 15 of the 16 patients treated with albendazole (400 mg as a single dose) and diethylcarbamazine (6 mg/kg as a single dose),

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and in 12 of the 16 patients treated with ivermectin and albendazole.

In order to assess the effects of re-treatment in *B. malayi* infections, 35 asymptomatic microfilaremic patients were re-treated at the end of the first year with an additional single dose of the combination they had previously received (5). Eleven patients received ivermectin 200 micrograms/kg plus diethylcarbamazine 6 mg/kg, nine patients received ivermectin 200 micrograms/kg plus albendazole 400 mg, and 15 patients received diethylcarbamazine 6 mg/kg plus albendazole 400 mg. The best suppression of brugian microfilaremia 1 year after re-treatment was obtained with combinations that included diethylcarbamazine. Whatever the drug regimen, both the frequency and intensity of adverse reactions after re-treatment were less than after initial treatment. The greatest difference was in patients who received ivermectin plus diethylcarbamazine, who also had the lowest mean microfilarial counts immediately before re-treatment. None of the adverse reactions after re-treatment was severe. Most of them, including fever, headache, and myalgia, were easily controlled with paracetamol. Postural hypotension and the "string sign" (dilated painful and inflamed lymphatic channels) did not occur with re-treatment.

In another study the cost-effectiveness of a revised mass annual single-dose regimen of diethylcarbamazine 6 mg/kg was estimated for large-scale control of lymphatic filariasis in a pilot program launched in Tamil Nadu (6). This regimen gave good coverage (90% of the population studied) and high compliance of 82%. Adverse effects occurred in 22% of patients and most were non-specific (giddiness in 54%, vomiting in 11%, nausea in 1%, fever in 14%, and headache in 20%).

Loa loa

In loiasis both adult and microfilariae are susceptible to diethylcarbamazine. However, encephalitis is a major risk in patients with heavy infestation (SEDA-17, 356) (7), and ivermectin should be preferred. Severe allergic reactions can need treatment with antihistamines and glucocorticoids. The risk of encephalitis has led to the recommendation that prophylactic use of diethylcarbamazine against *Loa loa* should only be contemplated when the chance of infection is considerable.

Onchocerca volvulus

In onchocerciasis, severe reactions can occur in the initial stages of therapy, particularly since diethylcarbamazine only kills the microfilariae of *Onchocerca volvulus* (resulting in the release of toxins) and does not eradicate the infection. The Mazzotti reaction, a Herxheimer-like response, can be severe and even fatal; it comprises a pruritic papular dermatitis, urticaria, fever, malaise, and postural hypotension; asthma and respiratory distress can occur and the hypotension can be associated with irreversible collapse. There can be painful lymphadenopathy.

Ocular complications are of particular importance: iritis can be induced by dying microfilariae and may call for topical or systemic glucocorticoid treatment. Associated complications include chorioretinitis, anterior uveitis, and punctate keratitis. Changes can also occur in the posterior segment (8), with visual field defects; there can be transient retinal pigment epithelial lesions at the posterior pole, globular infiltrates at the limbus, and optic disk leakage (9) with visible pallor. Similar ocular lesions can develop after topical diethylcarbamazine (SEDA-7, 316). Visual field defects are not reversible and they limit the clinical value of diethylcarbamazine in this disease.

Mass treatment with diethylcarbamazine is a key measure for control of the transmission of bancroftian filariasis. However, severe adverse reactions can occur in patients with onchocerciasis treated with high doses of diethylcarbamazine, which may limit the prospects for the use of common salt medicated with diethylcarbamazine in many parts of Africa. However, the daily dose of diethylcarbamazine-medicated salt is considerably lower than that of conventional tablets (25–50 mg od for the first 1 or 2 days followed by 100 mg bd for 5–7 days).

The adverse effects of diethylcarbamazine-medicated salt in patients with *O. volvulus* has been assessed in a double-blind, placebo-controlled trial in four groups of ten men (10). Groups I and II had *O. volvulus* microfilariae only, group III had both *O. volvulus* and *W. bancrofti* microfilariae, and group IV had *W. bancrofti* microfilariae only. Groups I, III, and IV received diethylcarbamazine-medicated salt. Group II served as a control group and received cooking salt. The medicated salt (0.33% w/w) originated from a batch previously produced for control trials. Each individual was given a total daily dose of 5.8 g of salt for 10 days, corresponding to the average daily salt intake for individuals aged over 15 years in the area. The salt supplement was spaced over three daily meals: 0.5 g, 2.5 g, and 2.8 g at breakfast, lunch, and dinner respectively. Hence, the daily dose of diethylcarbamazine was 19.1 mg. Diethylcarbamazine-medicated salt had no significant effect on *O. volvulus* microfilarial counts, but *W. bancrofti* microfilarial counts were significantly reduced in groups III and IV. The most pronounced adverse reactions occurred in groups I and III and were mild to moderate itching and rash. They were observed on days 3–4 and lasted for the remaining medication period, but did not interfere with normal daily activities. At day 30, all the reactions had abated. There were no severe adverse events, perhaps because of low pre-existing microfilarial counts and the short duration of therapy. There was no evidence that patients with *O. volvulus* and *W. bancrofti* double infection had a different adverse reaction pattern than individuals with *O. volvulus* infection only. Thus, diethylcarbamazine-medicated salt may be an important drug for the control of bancroftian filariasis in Africa. Salt with an even lower concentration of diethylcarbamazine may still have microfilaricidal properties in bancroftian filariasis without inducing microfilarial killing and adverse reactions in onchocerciasis, which may further improve treatment compliance and ease of use.

Wolbachia

In 15 Indonesian patients with *B. malayi* infection, the release of *Wolbachia* bacteria was studied in relation to adverse events after diethylcarbamazine treatment (6 mg/kg orally for 12 days) (11). Three patients had severe reactions and six patients had moderate reactions. In all samples from the three patients with severe reactions

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and in one of the six with moderate reactions, *Wolbachia* PCR products were detected from 4 hours after treatment, and persisted for 8–20 hours. These data suggest that release of *Wolbachia* bacteria into the blood may be associated with severe inflammatory reactions after diethylcarbamazine. Adverse reactions associated with increases in proinflammatory cytokines have also been reported in bancroftian filariasis and onchocerciasis, suggesting that similar events can also occur in these filarial infections.

Comparative studies

Filariasis

The efficacy of new treatment strategies for lymphatic filariasis using a single dose of diethylcarbamazine or a combination of diethylcarbamazine plus albendazole has been studied in 30 people (aged 11–52 years, weighing 25–63 kg) infected with *Brugia timori* and compared with the results of 27 people (aged 13–52 years, weighing 27–73 kg) infected with *W. bancrofti* (2). All were allocated at random to diethylcarbamazine (100 mg on day 1 and up to a total dose of 6 mg/kg on day 3) or diethylcarbamazine plus albendazole group (placebo on day 1 and diethylcarbamazine 6 mg/kg plus albendazole 400 mg on day 3). There was no difference in adverse reactions between diethylcarbamazine alone and diethylcarbamazine plus albendazole. Headache ($n = 15$), myalgia ($n = 13$), itching ($n = 8$), and adenolymphangitis ($n = 8$) were the most common adverse effects; none were severe or life-threatening. The microfilaricidal effect of the drugs was achieved more rapidly for *B. timori*, which is associated with more adverse reactions than *W. bancrofti* filariasis. As previously shown, there was a strong correlation of microfilarial density with the frequency and severity of adverse reactions. The addition of albendazole resulted in no additional adverse reactions compared with diethylcarbamazine alone.

General adverse effects

Adverse reactions to treatment with diethylcarbamazine vary with the infecting filarial species and are most severe in onchocerciasis. Minor reactions include malaise, nausea, and headache, but diethylcarbamazine also depresses the central nervous system in some individuals, resulting in dizziness and somnolence; reversible coma has been reported in patients in poor physical condition. Nicotine-like properties can produce autonomic effects. A degree of eosinophilia during treatment is usual.

Although over 120 million individuals have lymphatic filariasis, it may be eradicable. Newer strategies for the elimination of lymphatic filariasis aim at transmission control through the use of annual doses of combinations of ivermectin, diethylcarbamazine, or albendazole, and disease control through individual patient management. Mass chemotherapy appears to be essential in the control of lymphatic filariasis. However, drug availability and the co-endemicity of onchocerciasis and loiasis play crucial roles. Although a single annual dose of diethylcarbamazine may be an effective approach toward long-term suppression of brugian and bancroftian microfilaremia, repeated multidrug chemotherapy is the preferred approach for control of lymphatic filariasis, as in other chronic infections, such as tuberculosis and leprosy. In addition, combining diethylcarbamazine with albendazole has the advantage of controlling intestinal parasites.

Organs and Systems

Immunologic

Brugia malayi is more susceptible to diethylcarbamazine than *W. bancrofti*. A study of the former, undertaken to explain the very severe effects often associated with diethylcarbamazine treatment of lymphatic filariasis, provided evidence of the involvement of the cytokine interleukin-6 (IL-6), concentrations of which were raised during treatment (12).

The involvement of inflammatory mediators in the development of adverse events has recently been studied in 29 patients with *B. malayi* microfilaremia treated with diethylcarbamazine (13). Before and at serial time points after the start of treatment, plasma concentrations of the inflammatory mediators interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor-alfa, and lipopolysaccharide-binding protein were measured in relation to diethylcarbamazine concentrations and adverse events. The adverse effects of diethylcarbamazine correlated well with pretreatment microfilariae counts, consistent with previous experience with diethylcarbamazine in lymphatic filariasis and onchocerciasis. Concurrent measurements of diethylcarbamazine concentrations failed to establish a clear relation between diethylcarbamazine concentrations and adverse events. Detailed kinetic studies showed the strongest association of the severity of symptoms with interleukin-6 and lipopolysaccharide-binding protein. Concentrations of interleukin-6 started to rise as early as 2–4 hours and reached a maximum after about 8 hours. Fever also occurred at 4–8 hours, consistent with the pyrogenic activity of interleukin-6. In addition, interleukin-6 plays a central role in the induction of the acute phase proteins involved in inflammatory reactions. Indeed, concentrations of the acute phase protein, lipopolysaccharide-binding protein, started to rise at 8 hours (that is after interleukin-6), and also peaked later than interleukin-6, at 24–48 hours after diethylcarbamazine. These observations suggest that the adverse effects of diethylcarbamazine result from an exaggerated host inflammatory response stimulated by a high load of antigen released from killed or degenerating microfilariae.

Susceptibility Factors

Renal disease

The clearance of diethylcarbamazine is reduced in renal insufficiency (14), and dosages should be reduced.

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Diethylenetriamine penta-acetic acid

General Information

Diethylenetriamine penta-acetic acid (DTPA) is a chelating agent that has been used in radiolabeled form as a tracer. It has been used in the following combinations:

- DTPA: to assess iron body stores (1–3);
- ^{111}indium-DTPA: to label proteins, such as albumin (4) and monoclonal antibodies (5), for the radiodetection of cancers;
- ^{99m}technetium-DTPA: for scanning organs such as the kidneys (6), lungs (7), and brain (8);
- dysprosium-DTPA: in experimental imaging of cerebral ischemia (9);
- ^{97}ruthenium-DTPA: to label cerebrospinal fluid (10);
- gadolinium-DTPA: as a contrast agent in computed tomography (11) and magnetic resonance imaging (12).

In a study of the use of $^{117m}Sn^{4+}$-DTPA for palliative pain reduction in 15 patients with bone metastases, there were no myelotoxic or other adverse effects (13).

Organs and Systems

Hematologic

In nine patients with advanced breast carcinoma, administration of a ^{90}Y-DTPA-BrE-3 complex was associated with transient and uncomplicated thrombocytopenia in four patients and leukopenia in two patients (14).

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Diethylstilbestrol

General Information

For a complete account of the adverse effects of estrogens, readers should consult the following monographs as well as this one:

- Estrogens
- Hormonal contraceptives—emergency contraception
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens
- Hormone replacement therapy—estrogens + androgens
- Hormone replacement therapy—estrogens + progestogens.

Diethylstilbestrol and other non-steroidal estrogens came into vogue at a time when the cost of producing steroidal estrogens, whether synthetic or of natural origin, was still prohibitive. They have largely fallen out of favor, in view of the association between the use of diethylstilbestrol in pregnancy and second-generation injury. There seems to be no reason for believing that the short-term acute adverse reactions to these non-steroidal compounds differ from those of estrogenic steroids.

Diethylstilbestrol continues to be recommended in some centers as one of the agents of last resort when prostate cancer proves refractory to steroid hormones or androgen deprivation therapy has done all it can (1). In a Japanese study in which 16 patients were given a daily intravenous injection of diethylstilbestrol diphosphate 250 mg for 28 days, the short-term response was favorable and the drug was well tolerated (2).

Organs and Systems

Cardiovascular

In a randomized study of men treated hormonally for prostatic cancer (3), cardiovascular adverse effects were reported more often in patients treated with diethylstilbestrol than in those treated with cyproterone acetate. The risk was highest during the first 6 months of treatment.

Mineral balance

Profound hypocalcemia occurred in a patient with osteoblastic metastatic carcinoma of the prostate after treatment with diethylstilbestrol 15 mg/day for 7 days (SED-12, 1032) (4).

Immunologic

In 13 women exposed to diethylstilbestrol in utero compared with similar control subjects with respect to the in vitro T cell response to the mitogens phytohemagglutinin, concanavalin A, and interleukin-2, incorporation of tritiated thymidine into T cells from diethylstilbestrol-exposed women was increased three-fold over a range of concentrations in response to concanavalin A, increased by 50% over a range of concentrations in response to phytohemagglutinin, and increased two-fold in response to the endogenous mitogen interleukin-2 (5). This in vitro evidence of a change in T cell-mediated immunity clearly raises questions about the clinical consequences.

Long-Term Effects

Tumorigenicity

Exposure to diethylstilbestrol during pregnancy in 4836 women has been reported to carry a relative risk of 1.27 of breast cancer later in life. However, the authors found no evidence to support the link between diethylstilbestrol exposure and ovarian, endometrial, or other cancers.

In a 25-year follow-up study there were very slightly more breast tumors in women using diethylstilbestrol in pregnancy and significantly more cancer deaths (6).

In one study there was a six-fold risk of endometrial cancer among estrogen users compared with non-users; long-term users (over 5 years) had a 15-fold risk; there were excess risks for both diethylstilbestrol and conjugated estrogens (7).

Diethylstilbestrol can cause hepatic adenomas and carcinomas in experimental animals (8), and hepatocellular carcinoma has been reported in a man who took a total of 668 g over 12 years for suspected carcinoma of the prostate (9).

Second-Generation Effects

Teratogenicity

Diethylstilbestrol was used extensively in pregnancies between 1940 and about 1975, in the belief that it could protect threatened pregnancies and counter the risk of spontaneous abortion. Toward the end of that period, increasingly clear evidence emerged that diethylstilbestrol could have an adverse effect on the second generation that

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did not become apparent until puberty or adulthood, and perhaps could also appear in the third generation (10). It appears to be the only estrogen with this effect, but it is naturally not excluded that some structurally related non-steroidal estrogens might carry the same risk, although these have never been used in the same way in pregnancy.

History

Diethylstilbestrol provides several illustrations of how societies cope with the risks of harm from a drug. Under different brand names diethylstilbestrol has been given to a wide range of patients over many years, mostly pregnant women and aging men with prostate cancer. The history of iatrogenic disease as a result of the use of diethylstilbestrol in pregnant women shows that patients can play an important role in securing legitimacy for research and the publication of data on the harmful effects of a drug.

Diethylstilbestrol was given to pregnant women in many countries, mainly in the 1940s to 1970s, in the mistaken belief that it would prevent miscarriage and provide strong healthy babies (11,12). The application to market diethylstilbestrol in the USA was the first new drug application submitted to the FDA shortly after the 1938 Food, Drugs, and Cosmetics Act had been passed; permission was granted, although diethylstilbestrol had already been identified as a carcinogen in animals (13). Diethylstilbestrol was especially popular in some maternity clinics in North America, serving middle-class and upper-middle class women, and in the Netherlands, where the Queen's gynecologist promoted it. In other countries it was dispensed through public health maternity centers.

In the USA, evidence showing that it was ineffective for its intended purpose appeared by the 1950s. However, conclusions based on animal experiments, as well as a major double-blind, controlled clinical trial (14), remained unheeded, partly because prescribing physicians trusted their collegial loyalty more than data that implicitly threw doubt on their practice.

In 1971, a rare form of aggressive cancer in the vagina of young girls was attributed to the girls' exposure to diethylstilbestrol in utero in a report that was based on a case-control study of eight young women, two of whom had died, at the Massachusetts General Hospital (15). It was already clear from this small study that monitoring young women exposed to diethylstilbestrol would save lives. However, months and even years were to pass before the discovery led to any public action, at different times in different countries. Only after 5 months, when the risk of cancer in patients exposed to diethylstilbestrol was featured at hearings in the US Congress, did the FDA react. The FDA's Administrator then announced that diethylstilbestrol products were to be labelled with a warning that diethylstilbestrol was contraindicated in pregnancy and should not be given to pregnant women because of risk of the cancer in the offspring (16).

Drug regulatory agencies in other countries in which diethylstilbestrol had also been commonly used in pregnancy delayed taking action. In the Netherlands, the first change of labelling to include a warning to physicians that diethylstilbestrol given to pregnant women might harm the fetus was implemented in 1972. A similar change in labelling was introduced in France in 1977. In many other countries, the news that some daughters of women who had taken diethylstilbestrol while pregnant were at risk of developing a potentially lethal cancer was passed over in silence.

In Britain, the medical community was alerted to the risks by an editorial in the British Medical Journal in 1971, but it was only in 1973 that the Committee on Safety of Medicines advised against the use of diethylstilbestrol during pregnancy (17). In Britain, drugs were commonly not labelled with information about their contents, nor with warnings of risk until well into the 1990s; thus, patients were kept in ignorance. No measures have yet been taken in Britain to alert the public to the need for medical surveillance of women who have been exposed to diethylstilbestrol in utero.

It is estimated that in the USA, the Netherlands, and France, diethylstilbestrol was given to over 5.3 million pregnant women, and it is known that it has been given to pregnant women in most parts of the world. Single cases of clear-cell vaginal carcinoma from many countries are known, but systematic studies have not been conducted everywhere.

One in a thousand young women exposed to diethylstilbestrol before birth have been estimated to be at risk of developing clear-cell vaginal adenocarcinoma (18). Exposure to diethylstilbestrol in utero also has a range of other effects on exposed women, including malformations of the reproductive organs and difficulties in conception and carrying a pregnancy to term. Some of the men exposed to diethylstilbestrol in utero have urogenital malformations and an increased risk of testicular cancer (19).

Most of the women who suspected that they had taken diethylstilbestrol were to learn of the problems from the media, and they had to guess that their daughters might be at risk of developing cancer. When they tried to discover whether they had been given diethylstilbestrol during pregnancy, many of the women found that their obstetricians were not willing to give them access to their own medical records. In a report from a nationwide US survey intended to locate pregnant women who had been given diethylstilbestrol during 1940–72, the investigators complained that at some clinics they had encountered extreme difficulties in getting access to the records (20). Women who have been exposed to diethylstilbestrol sometimes say that never have so many medical files reportedly been lost through fire and inundation, as when they asked for access to records that might document the use of diethylstilbestrol during pregnancy.

Many doctors did not notice or did not heed warnings in the early 1970s about the risks of giving diethylstilbestrol to pregnant women. As late as 1974, according to one writer, some 11 000 prescriptions for diethylstilbestrol to be used during pregnancy were written in the USA (21). In 1976, it was observed that diethylstilbestrol was given to unsuspecting pregnant women in several Latin-American countries (21). In other countries, prescribing physicians' responses to reports that linked the use of diethylstilbestrol during pregnancy with cancer risks in their daughters were even slower. The latest documented prescription of diethylstilbestrol in Europe was in Spain in 1983 (22).

The first batches of educational material for physicians, with warnings and advice regarding health care for women who had been exposed to diethylstilbestrol, were distributed in the USA in 1971, in the Netherlands in

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1974, and in France in 1989. No such material has been distributed in Britain.

Mothers in the USA who had taken diethylstilbestrol formed an organization, DES Action, to inform the public about the risks and to alert exposed mothers that their daughters needed regular medical examinations, so that potential tumor development would be detected early. Through DES Action they also gave each other mutual support during litigation against the manufacturers and acted politically to ensure that health care would be available for their daughters. DES Action groups outside the USA were formed in Australia, Belgium, Canada, France, Great Britain, Italy, Ireland, and the Netherlands. DES Action was still in the 1990s a prime mover in securing resources for research and follow-up of women who had been exposed to diethylstilbestrol, and in promoting educational programs for those women and for medical professionals.

Initiatives by medical researchers, by DES Action, and by the Public Citizen's Health Research Group secured funding in the USA for medical research on the prevalence of cancer and other effects in the young women who had been exposed in utero, and eventually also the men. The US National Institute for Environmental Health Sciences (NIEHS) has been one of the centers for toxicological studies of the effects of diethylstilbestrol. A substantial amount of research on the effects of diethylstilbestrol—animal experiments as well as epidemiological studies—has produced a valuable body of knowledge about how hormones affect the development of the fetus and prime the individual for disease later in life.

As in the case of thalidomide, the emotional engagement evoked by the harm caused by diethylstilbestrol in pregnancy led to committed action. Some physicians have devoted a major part of their careers to finding out why and how diethylstilbestrol produced adverse effects. The anger over the harm caused by diethylstilbestrol inspired patients to a commitment to prevent further harm by engaging in political action and achieving an effective response from legislators and governmental administrators. Despite the abandonment of diethylstilbestrol in pregnancy for habitual or threatened abortion, its late effects continue to be reported. Essentially, the female offspring of these pregnancies tend to develop vaginal changes (adenosis, with cervical ectropion) when reaching adolescence or adulthood and these can subsequently give rise to a clear-cell adenocarcinoma. Whereas carcinomas are a late and infrequent event, even in exposed subjects, cervical vaginal adenosis is common, the incidence probably being some 30% (23). The estimated tumor risk is only 0.14–1.4 per 1000 diethylstilbestrol-exposed subjects, but since up to 6 million fetuses were exposed to diethylstilbestrol between 1940 and 1970 the total number affected in some way may be very high indeed. There is also a high incidence of fertility disturbances among these daughters, and their own pregnancies apparently stand a high chance of not going normally to term (SED-12, 1023) (24). Analogous changes were found in male offspring (25). As in the case of thalidomide, an important element in determining cause and effect was the characteristic nature of the defect: the vaginal pathology does occur spontaneously but is highly unusual. A major problem has been the fact that the defect is as a rule only recognizable so many years after birth, by which time the history of the original treatment may be difficult or impossible to reconstruct. Even today the material is not homogeneous and strict statistical analysis of some of the epidemiological data has been claimed to point to a series of shortcomings. This does not undermine the clear conclusion that the drug is indeed responsible for the effects described (26).

Epidemiological studies on the complications of the use of diethylstilbestrol in pregnancy will certainly produce new data as time goes on: most of the data will probably continue to come from the USA and the Netherlands, where diethylstilbestrol was much more widely used to treat habitual or threatened abortion than elsewhere. In France 150 000–200 000 pregnancies were involved; in the Netherlands, with a much smaller population, 180 000–380 000 pregnant women were treated with diethylstilbestrol up to 1976.

Vaginal adenosis and adenocarcinoma

Second-generation (and possible third-generation) effects of diethylstilbestrol continue to be reported (27,28). Typical is a 1987 update analysing 519 cases of clear-cell carcinoma of the vagina and cervix identified by the Registry for Research on Hormonal Transplacental Carcinogenesis of the University of Chicago (18); in 60% of all cases the patient's mother could be shown to have used diethylstilbestrol during pregnancy. The median age at diagnosis was 19 years. The authors argued that in view of the relative rarity of the tumors, even in exposed women, one could consider that diethylstilbestrol is not a complete carcinogen and that some other factor is also involved in the pathogenesis of this type of carcinoma. The particular question of third-generation injury has actually been the subject of judicial proceedings in the USA (27,28); on the balance of evidence it seems that it can occur, although the mechanism is not clear.

Evidence has also emerged on long-term survival in young women with a clear-cell adenocarcinoma of the vagina, 20% of whom had been exposed to diethylstilbestrol and 80% had not (29). The probabilities of survival at 5 and 10 years for diethylstilbestrol-associated cases were 84 and 78% respectively, compared with 69 and 60% for those not associated with diethylstilbestrol. These differences were not due to differences in clinical prognostic factors, but suggest differences in tumor behavior for as yet undetermined reasons.

Although it is more than 30 years since the full extent of the injury to offspring by the ill-advised use of diethylstilbestrol during pregnancy became clear, details of that injury are still being filled in as the individuals concerned grow older. The picture will continue to develop as long as this generation of individuals lives, and it is even possible that findings in the third generation will throw light on the persisting injury to the family.

Psychological research among "DES daughters" has shown how traumatic it can be for a woman to learn of her prenatal exposure to diethylstilbestrol, and the extent to which this creates persistent uncertainty about her health; the failure of a physician to provide reliable information and continuing support can severely undermine her faith in health care (30).

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Table 1 Outcomes in pregnancies exposed and not exposed to diethylstilbestrol

Outcome	Exposed (%)	Non-exposed (%)
Full-term delivery	64	85
Spontaneous abortion	19	10
Preterm delivery	12	4.1
Ectopic pregnancy	4.2	0.8

Long-term studies of the pregnancy experiences of women exposed to diethylstilbestrol in utero, compared with unexposed women, now include one in the US National Collaborative Diethylstilbestrol Adenosis cohort and one in the Chicago cohort and their respective non-exposed comparison groups. A review of questionnaire replies from 3373 exposed daughters and from controls has confirmed that diethylstilbestrol-exposed women were less likely than unexposed women to have had full-term live births and more likely to have had premature births, spontaneous pregnancy losses, or ectopic pregnancies (31). The data are shown in Table 1. Second-trimester spontaneous pregnancy losses were much more common in diethylstilbestrol-exposed women.

Other cancers

Long-term data are also accumulating on the actual incidence of genital cancer in women exposed to diethylstilbestrol in utero (32). In the Netherlands, a country in which diethylstilbestrol was used intensively in pregnancy, there is evidence that the risk of cervical cancer in these women is trebled, rather than doubled as was previously supposed (33).

- A diethylstilbestrol-exposed woman developed concurrent primary cancers of both the vagina and the endometrium at the age of 39 (34).

However, it is important to bear in mind that cases occur in which there is no history of the mother's having taken diethylstilbestrol during pregnancy. In one such case, HIV/AIDS infection was also a predisposing factor for vaginal carcinoma and this could explain a proportion of new cases that are being reported today (35).

A further follow-up and analysis of 3879 women, taken from two earlier US studies, who had been exposed to diethylstilbestrol during pregnancy has been presented (36). The results showed a modest association between diethylstilbestrol exposure and the risk of breast cancer (RR = 1.27; 95% CI = 1.07, 1.52). The increased risk was not further aggravated by a family history of breast cancer, by use of oral contraceptives, or by HRT. There was no evidence that diethylstilbestrol was associated with a raised risk of ovarian, endometrial, or other hormone-associated cancers.

Sensory systems

A study in the USA has produced some evidence that in people with amblyopia, those who were exposed to diethylstilbestrol before birth may be more likely to develop myopia (37).

Menstrual and vaginal disturbances

The effects of in-utero exposure to diethylstilbestrol on the menstrual cycle have been studied prospectively in 198 women and in 162 unexposed controls (38). A major limitation of this study was the exclusion of women with a severe menstrual abnormality. Exposure to diethylstilbestrol was associated with a statistical significantly lower duration of menstrual bleeding but not with dysmenorrhea. For most women exposed to diethylstilbestrol, any effects on reproductive hormonal function are in all probability minor, if present at all.

Even the classic genital manifestations of diethylstilbestrol in women who have been exposed to it in fetal life may be overlooked unless one is alert to them; vaginal discharge with ectropion should cause one to enquire as to possible prenatal diethylstilbestrol exposure (39).

Autoimmune disease

During the last 15 years, various additional aspects of the diethylstilbestrol problem have given rise to concern. One emerged in 1988 from a large multicenter epidemiological cohort study established by the US National Cancer Institute (DESAD Project), in which it was found that women exposed in utero to diethylstilbestrol had a 50% increased incidence of autoimmune disease (40).

Drug Administration

Drug formulations

The parenteral formulation diethylstilbestrol diphosphate is less commonly used than the oral formulation. In Japan, 24 elderly patients with advanced relapsed prostatic cancer were treated with high doses supplemented with ethinylestradiol (doses unclear); there was some slight therapeutic effect, but there were gastrointestinal symptoms and fluid retention (41). Also in Japan, a few patients with advanced disease were treated using intravenous diethylstilbestrol diphosphate 500 mg/day for 20 consecutive days to a total dose of 10 g; the authors' conclusion was more positive but adverse events were not specified (42).

Drug contamination

Contamination of isoniazid tablets with diethylstilbestrol was the cause of several cases of precocious puberty in a children's tuberculosis ward (43).

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Diethyltoluamide

General Information

Diethyltoluamide is an insect repellent.

Organs and Systems

Nervous system

Toxic encephalopathy has been reported in children sprayed repeatedly with diethyltoluamide 10–15% (1).

Psychological, psychiatric

Acute manic psychosis has been attributed to percutaneous absorption of diethyltoluamide (SEDA-12, 138).

Reference

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Difenpiramide

See also Non-steroidal anti-inflammatory drugs

General Information

Difenpiramide, a phenylacetic acid derivative, is less efficacious but has fewer adverse effects than indometacin or phenylbutazone. The most frequent reactions are in the gastrointestinal tract and skin (1). However, gastrointestinal tolerance is, as one would expect, better (2).

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Difetarsone

General Information

Difetarsone is a pentavalent arsenical that often causes minor adverse effects, such as rashes, nausea, vomiting, and abdominal discomfort. Transient increases in transaminase activities can occur (SEDA-13, 834) (1).

Organs and Systems

Immunologic

Generalized angioedema occurred in a patient taking difetarsone 500 mg tds for *Entamoeba histolytica* infection (SEDA-11, 597) (2).

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Diflunisal

General Information

Diflunisal is a fluorinated salicylic acid derivative, which is absorbed unchanged from the gastrointestinal tract, reaching peak concentrations after about 2 hours, and is metabolized by glucuronidation (1). Its adverse effects and other characteristics are those of aspirin, although gastrointestinal haemorrhage may be less common (2).

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Diftalone

General Information

Because of hepatotoxicity and carcinogenicity (hepatoma) detected in preclinical studies, and hemotoxicity and gastrointestinal adverse effects in man, diftalone has been withdrawn by its manufacturer (1).

Reference

1. Anonymous. Dow Lepetit drops diftalone. Scrip 1977; October 15;22.

Dihydrocodeine

See also Opioid analgesics

General Information

Dihydrocodeine is an opioid analgesic related to codeine, in which the double bond in the 7th position is saturated. It is about one-tenth as potent as morphine and 2–3 times more potent than codeine. It is similar to codeine in other respects. The most common adverse effects are nausea, vomiting, and drowsiness (SEDA-16, 79) (SEDA-17, 80) (SEDA-18, 79).

In a randomized, double-blind comparison of the antitussive effect of dihydrocodeine 10 mg tds with levodropropizine 75 mg tds in 140 adults with primary lung cancer or metastatic cancer there was no significant difference between the two drugs as far as cough severity and the numbers of night wakings were concerned, both drugs leading to significant improvement (1). However, dihydrocodeine caused significantly more somnolence, which was reported by 11% and in some cases was continuous. Other adverse effects reported by those taking dihydrocodeine included erythema of the abdomen and epigastric pain, although constipation, a potential adverse effect of codeine derivatives, was not reported.

Organs and Systems

Sensory systems

Severe narcosis after therapeutic doses (2) has been reported.

Urinary tract

Acute renal insufficiency after therapeutic doses (2) has been reported.

Dihydrocodeine was implicated in cases of granulomatous interstitial nephritis (3).

Immunologic

Anaphylaxis has been reported with dihydrocodeine (4).

Susceptibility Factors

Age

There is a risk in giving dihydrocodeine to the elderly (2).

Renal disease

There is a risk in giving dihydrocodeine to those with renal insufficiency (2).

Drug Administration

Drug formulations

A modified-release formulation extends the duration of action of dihydrocodeine from 2–4 hours to 12 hours. In 12 volunteers who took modified-release dihydrocodeine 60 mg or 120 mg and 120 minutes later lactulose 40 mg diluted in 100 mg of water, the orocecal transit time was significantly prolonged by dihydrocodeine compared with placebo (5). Dihydrocodeine also significantly suppressed the pupillary light reflex. Both dosages caused similar adverse effects. Tiredness and dry mouth were reported in 80%, vertigo in 5%, and headache in 1%.

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Dilevalol

See also Beta-adrenoceptor antagonists

General Information

Dilevalol is one of the four enantiomers of labetalol. It was withdrawn from the market by its manufacturers in early 1991 because of an unacceptably high incidence of liver damage (1).

Reference

1. Harvengt C. Labetalol hepatoxicity. Ann Intern Med 1990;114:341.

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Diloxanide

General Information

Diloxanide often causes flatulence and, occasionally, nausea, vomiting, diarrhea, urticaria, and pruritus. It is an excellent luminal amebicide and is indicated after treatment with the 5-nitroimidazole compounds, which have relatively weak activity on the cyst stage. Experience over 14 years has been summarized by the Centers for Disease Control and Prevention (CDC, Atlanta), confirming the minimal toxicity of diloxanide. Fewer adverse effects were reported in patients aged 20 months to 10 years than in those aged over 10 years. There is no record of interactions between diloxanide and either metronidazole or tinidazole (SEDA-13, 830) (SEDA-17, 333).

Diltiazem

See also Calcium channel blockers

General Information

Diltiazem is a benzthiazepine calcium channel blocker.

Organs and Systems

Cardiovascular

Diltiazem can be associated with heart block (1,2). In a randomized trial in patients with non-Q-wave myocardial infarction, 38 of 287 patients who took diltiazem developed some degree of atrioventricular block at some time. Of these episodes, 32 were first-degree, eight were second-degree, and only two were third-degree. In the placebo-treated group there were 10 events in 289 patients; eight were first-degree, two second-degree, and none third-degree.

Atrioventricular block has been reported in three patients taking therapeutic doses of diltiazem; one died (3).

- A 47-year-old man taking furosemide for hypertension was given diltiazem 300 mg/day to achieve better blood pressure control; 1 month later he developed atrioventricular block, resolved by atropine.
- A 62-year-old hypertensive man with renal artery stenosis, an adrenal adenoma, peripheral artery disease, and an abdominal aortic aneurysm developed a hypertensive crisis with chest pain. He was treated with nitrates, heparin, aspirin, and nicardipine, which were afterwards replaced by diltiazem 200 mg/day, because of persistent chest pain. He developed atrioventricular block 2 hours after the second dose of diltiazem, and was successfully treated with a pacemaker.
- A 59-year-old woman with a previous myocardial infarction, hypertension, diabetes, and uterine cancer developed angina. She was treated with nitrates, aspirin, and heparin; diltiazem 200 mg/day was then added because of persistent chest pain. She developed atrioventricular block 72 hours later, and despite resuscitative efforts died in electromechanical dissociation.

Following the publication of a report of heart block (4), further cases (junctional bradycardia, sinoatrial block) have been reported (5).

Nervous system

Paresthesia of the hands and feet has been reported with diltiazem (SEDA-17, 237). Akathisia has been attributed to diltiazem (6). Parkinsonism associated with diltiazem has been reported (7).

- A 53-year-old man with hypertension took diltiazem 60–120 mg/day for 5 years and then developed parkinsonism. His neurological symptoms were treated without success and only after the substitution of diltiazem with an ACE inhibitor did his parkinsonian symptoms begin to regress, with eventual complete recovery.

Urinary tract

Diltiazem was associated with the development of acute renal insufficiency in a patient being treated for severe retrosternal chest pain who had neither primary kidney disease nor urinary tract obstruction (8,9).

Acute interstitial nephritis has been attributed to diltiazem (9).

- A 53-year-old man was given diltiazem for precordial pain and about 2 hours later developed an erythematous maculopapular rash mainly on the trunk and lower limbs. Four days later he developed abdominal pain radiating to both renal angles, accompanied by dysuria and tenesmus and followed 6 days later by acute renal insufficiency associated with raised liver function test results.

In this case, the self-limiting resolution in 4–5 days without relapse, the presence of the skin rash, and the liver sequelae suggested a common immunoallergic mechanism. The clinical symptoms, the time relation between drug administration and the occurrence of the syndrome, the inability to explain the syndrome otherwise, and its disappearance on withdrawal of diltiazem support an association with the drug.

A retrospective analysis of postoperative renal function in patients undergoing cardiac operations has been conducted to evaluate whether the use of prophylactic intravenous diltiazem, in order to reduce the incidence of ischemia and dysrhythmias, was associated with increased renal dysfunction (10). The incidence of acute renal insufficiency requiring dialysis was 4.4% with diltiazem versus 0.7% in the controls. Logistic regression analysis suggested that the risk of acute renal insufficiency was strongly associated with intravenous diltiazem, age, baseline serum creatinine, the presence of left main coronary disease, and the presence of cerebrovascular disease.

Skin

Skin reactions ranging from exanthems to severe adverse events have been reported in association with diltiazem

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(SED-13, 513) (SEDA-18, 215) (SEDA-22, 216). Three cases of skin reactions (hypersensitivity syndrome reaction, pruritic exanthematous eruption, and acute generalized exanthematous pustulosis) possibly induced by diltiazem have been described and the literature on skin reactions associated with calcium antagonists has been reviewed. The number of diltiazem-induced cutaneous events was significantly greater than those induced by either nifedipine or verapamil. However, there was no difference in the proportion of serious cutaneous adverse events due to any of these three drugs (11).

Cutaneous vasculitis (12) and angioedema (13,14) have been reported with diltiazem. In 1988, the Federal German Health Authorities imposed a warning of dermal hypersensitivity reactions (including erythema multiforme) with diltiazem.

- Acute generalized exanthematous pustulosis in an 82-year-old woman was confirmed as being due to diltiazem by a positive patch test (15).
- Exfoliative dermatitis with fever occurred in a 69-year-old man with ischemic heart disease treated with mexiletine and diltiazem for three weeks; the rash resolved after withdrawal of both drugs and systemic corticosteroid therapy. Patch tests with mexiletine and diltiazem were positive. In addition to this case, 39 cases of drug eruption due to diltiazem have been reported in Japan (16).
- Lichenoid purpura of 6 months' duration occurred in a 65-year-old man with hypertension who had taken diltiazem for 1 month. Topical therapy with a very potent glucocorticoid was not effective and the eruption began to regress only after diltiazem withdrawal, after which it disappeared 3 weeks later (17).

Four cases of photodistributed hyperpigmentation associated with long-term administration of a modified-release formulation of diltiazem hydrochloride have been reported (18). All the patients were African-American women, mean age 62 (range 49–72) years. The duration of diltiazem administration before the development of hyperpigmentation was 6–11 months. The hyperpigmentation was slate-gray and reticulated. Phototesting during diltiazem therapy showed a reduced minimal erythema dose to UVA in one patient. Histological examination showed lichenoid dermatitis with prominent pigmentary incontinence. Electron microscopy showed multiple melanosome complexes. Withdrawal of diltiazem resulted in gradual resolution of the hyperpigmentation.

Acute generalized exanthematous pustular dermatitis has been reported after diltiazem (19).

Drug Administration

Drug overdose

Several cases of accidental or deliberate self-poisoning with calcium antagonists have been described (SED-12, 452) (SEDA-16, 198) (SEDA-20, 186) and different approaches to the management of these patients have been proposed.

- A 52-year-old woman with essential hypertension erroneously took a 7-day supply of modified-release diltiazem, enalapril, and trichlormethiazide, and 30 minutes later complained of nausea (20). She was treated with gastric lavage, calcium gluconate, activated charcoal, and polyethylene glycol. Her blood pressure and heart rate fell progressively to 120/62 mmHg and 40/minute respectively, 14 hours after ingestion. Afterwards, her hemodynamic status gradually normalized without further treatment.
- A 54-year-old man with severe triple vessel coronary artery disease took six modified-release diltiazem tablets 180 mg following an episode of severe angina, and 10 hours later developed bradycardia, hypotension, and severe pulmonary edema, but was free of chest pain (21). After intensive hemodynamic monitoring and noradrenaline treatment, his renal, respiratory, and cardiac problems recovered to baseline over the next 48 hours. Diltiazem overdose was confirmed by a diltiazem serum concentration of 1230 ng/ml (usual target range 40–160 ng/ml).
- A 15-year-old woman intentionally took 10 modified-release tablets of diltiazem 200 mg. She developed hypertension, oliguria, pulmonary edema, and respiratory distress syndrome, and required mechanical ventilation for 3 days, besides intravenous calcium, dopamine, and noradrenaline. After 5 days in an intensive care unit, she was transferred to a psychiatric hospital in good physical condition (22).
- A 50-year-old man took 28 modified-release tablets of diltiazem 240 mg and 28 tablets of hydrochlorothiazide and 12–14 hours later became lethargic but oriented and complaining of nausea and dizziness; he had bradypnea, hypotension, and second-degree heart block with bradycardia (23). He was given activated charcoal, oxygen, atropine, glucagon, and calcium gluconate by prolonged infusion. His heart rate, blood pressure, and electrocardiogram recovered to baseline over the next 24 hours, with no further episodes of dysrhythmias or hypotension.
- A 38-year-old white man with a history of coronary artery disease, myocardial infarction, coronary artery by-pass, alcoholism, and depression took a combined massive overdose of diltiazem and atenolol (24). He underwent cardiopulmonary resuscitation because of cardiac arrest; bradycardia, hypotension, and oliguria followed and were resistant to intravenous pacing and multiple pharmacological interventions, including intravenous fluids, calcium, dopamine, dobutamine, adrenaline, prenalterol, and glucagon. Adequate mean arterial pressure and urine output were restored only after the addition of phenylephrine and transvenous pacing. He survived despite myocardial infarction and pneumonia.

Drug–Drug Interactions

Ciclosporin

Many studies have shown an interaction of ciclosporin with diltiazem: concomitant administration allows reduction of the daily dose of ciclosporin. However, according to a study in eight renal transplant recipients, the low systemic availability and high degree of variation in

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diltiazem metabolism within and between patients can give unpredictable results (25).

Diltiazem abolishes the acute renal hypoperfusion and vasoconstriction induced by ciclosporin in renal transplant patients. Plasma endothelin-1 may be a mediator of ciclosporin-induced renal hypoperfusion, but is not affected by diltiazem (26). This interaction has been confirmed with a new microemulsion formulation of ciclosporin in nine patients with renal transplants who took diltiazem 90–120 mg bd for 4 weeks (27). Diltiazem caused a 51% increase in the AUC of ciclosporin and a 34% increase in peak concentration, without altering the time to peak concentration. However, the ciclosporin microemulsion did not significantly affect the pharmacokinetics of diltiazem.

- Ciclosporin-induced encephalopathy was precipitated by diltiazem in a 76-year-old white woman with corticosteroid-resistant aplastic anemia and thrombocytopenia, type 2 diabetes, and coronary artery disease, who was taking diltiazem for hypertension (28). She became comatose after 13 days of therapy with ciclosporin, and clinical examination and electroencephalography showed diffuse encephalopathy of moderate severity. Ciclosporin was withdrawn and she regained consciousness after 36 hours.

Concomitant diltiazem without proper dosage adjustment of ciclosporin can cause adverse neurological events.

Methylprednisolone

Co-administration of diltiazem with methylprednisolone increased plasma concentrations of methylprednisolone and its adrenal suppressant effects in nine healthy volunteers (29). Care should be taken when these two drugs are co-administered for a long period, even if the clinical relevance of this pharmacokinetic interaction still needs to be evaluated.

Sildenafil

Sildenafil is metabolized predominantly by CYP3A4, which diltiazem inhibits. An interaction of diltiazem with sildenafil has been reported (30).

- A 72-year-old man, who regularly took aspirin, metoprolol, diltiazem, and sublingual glyceryl trinitrate for stable angina, reported chest pain during elective prognostic coronary angiography, which resolved with half of a sublingual tablet of glyceryl trinitrate. Within 2 minutes he developed severe hypotension, with an unchanged electrocardiogram and no evidence of anaphylaxis. He had taken sildenafil 50 mg 48 hours before angiography.

The interval after which even short-acting nitrates can be safely given after the use of sildenafil is likely to be substantially longer than 24 hours when elderly patients are concurrently taking a CYP3A4 inhibitor, such as diltiazem.

Sirolimus

The pharmacokinetic interaction of a single oral dose of diltiazem 120 mg with a single oral dose of sirolimus 10 mg has been studied in 18 healthy subjects, 12 men and 6 women, 20–43 years old, in an open, three-period, randomized, crossover study (31). The whole-blood sirolimus AUC increased by 60% and the C_{max} by 43% with diltiazem co-administration; the apparent oral clearance and volume of distribution of sirolimus fell by 38 and 45% respectively, consistent with the change in half-life from 79 to 67 hours. Sirolimus had no effect on the pharmacokinetics of diltiazem or on the effects of diltiazem on either diastolic or systolic blood pressures or the electrocardiogram. Single-dose diltiazem co-administration leads to higher sirolimus exposure, presumably by the inhibition of first-pass metabolism. Because of pronounced intersubject variability in this interaction, whole-blood sirolimus concentrations should be monitored closely in patients taking the two drugs.

Statins

Atorvastatin

Rhabdomyolysis and acute hepatitis have been reported in association with the co-administration of diltiazem and atorvastatin (32).

- A 60-year-old African-American man developed abdominal pain, a racing heart, and shortness of breath over 24 hours. He had also noticed increasing fatigue and reduced urine output over the previous 2–3 days. He had been taking several medications, including atorvastatin, for more than 1 year, but diltiazem had been added 3 weeks before for atrial fibrillation. On the basis of laboratory findings and physical examination, a diagnosis of acute hepatitis and rhabdomyolysis with accompanying acute renal insufficiency was made. His renal function gradually normalized and his CK activity reached a maximum of 2092 units/l on day 1 and fell to 623 units/l on discharge. His liver function tests returned to normal by 3 months.

While rhabdomyolysis from statins is rare, the risk is increased when they are used in combination with agents that share similar metabolic pathways. Atorvastatin is metabolized by CYP3A4, which is inhibited by diltiazem.

Lovastatin

The effects of co-administration of oral diltiazem, a potent inhibitor of CYP3A, on the pharmacokinetics of lovastatin have been evaluated in a randomized study in 10 healthy volunteers (33). Lovastatin is oxidized by CYP3A to active metabolites. Diltiazem significantly increased the oral AUC and maximum serum concentration of lovastatin, but did not alter its half-life. The magnitude of the increase of plasma concentration of lovastatin suggested that caution is necessary when co-administering diltiazem and lovastatin.

In another study by the same investigators, 10 healthy volunteers were randomized in a two-way, crossover study either to oral lovastatin or to intravenous diltiazem followed by oral lovastatin. Intravenous diltiazem did not significantly affect the pharmacokinetics of lovastatin (oral AUC, C_{max}, t_{max}, or half-life), suggesting that the interaction does not occur systemically and is primarily a first-pass effect (34). Drug interactions with diltiazem may therefore become evident when a patient is changed from intravenous to oral dosing.

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Pravastatin

The effects of co-administration of diltiazem, a potent inhibitor of CYP3A, on the pharmacokinetics of pravastatin have been evaluated in a randomized study in 10 healthy volunteers (33). Pravastatin is active alone and is not metabolized by CYP3A. Diltiazem did not alter the oral AUC, maximum serum concentration, or half-life of pravastatin.

Simvastatin

The interaction of diltiazem with simvastatin has been investigated in 135 patients attending a hypertension clinic (35). Cholesterol reduction in the 19 patients taking diltiazem was 33% compared with 25% in the other 116 patients (median difference 8.6%; 95% CI = 1.1, 12). Multivariate analysis showed that concurrent diltiazem therapy, age, and the starting dose of simvastatin were independent predictors of percentage cholesterol response. The authors concluded that patients who take both diltiazem and simvastatin may need lower doses of simvastatin to achieve the recommended reduction in cholesterol.

Results from two clinical studies of the interaction of diltiazem with simvastatin showed that diltiazem increased the C_{max} of simvastatin (36) and enhanced its cholesterol-reducing effect (35).

In 10 healthy volunteers taking oral simvastatin 20 mg/day, diltiazem 120 mg bd for 2 weeks significantly increased the simvastatin C_{max} 3.6-fold, the AUC 5-fold, and the half-life 2.3-fold (36). There were no changes in the t_{max} of simvastatin or simvastatin acid.

Of 135 patients attending a hypertension clinic who were taking simvastatin for primary or secondary prevention of coronary heart disease, 19 were also taking diltiazem (35). The cholesterol reduction in the 19 patients taking diltiazem was significantly higher than in the other 116 (33 versus 25%), with less interindividual variability. Concurrent diltiazem therapy, age, and the starting dose of simvastatin were significant independent predictors of the percentage cholesterol response.

Rhabdomyolysis due to an interaction of simvastatin with diltiazem has been reported (37).

- A 75-year-old-man taking simvastatin 80 mg/day and diltiazem 240 mg/day developed extreme weakness and diffuse muscle pain. All drugs were withdrawn and he underwent hemodialysis. Within 3 weeks his muscle pain disappeared and he regained function in his legs. The activities of creatine kinase and transaminases gradually returned to normal, but he continued to need hemodialysis.

Tacrolimus

Diltiazem can increase the blood concentration of the macrolide immunosuppressant tacrolimus (38).

- A 68-year-old man developed diarrhea, dehydration, and atrial fibrillation 4 months after liver transplantation. He was taking tacrolimus (blood concentration 13 ng/ml) and was given a continuous infusion of diltiazem for 1 day followed by oral therapy. Three days later he became delirious, confused, and agitated, and the blood concentration of tacrolimus was 55 ng/ml. His mental status gradually improved after withdrawal of both drugs.

The mechanism of this interaction is likely to be the inhibition of tacrolimus metabolism in the intestine and liver by the inhibition of CYP3A4 and P glycoprotein.

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Dimenhydrinate

See also Antihistamines

General Information

Dimenhydrinate (SEDA-21, 173) is an antihistamine, the diphenhydramine salt of 8-chlorotheophylline.

Organs and Systems

Sensory systems

Dimenhydrinate altered color discrimination, night vision, reaction time, and stereopsis in healthy volunteers (1).

Skin

Diphenhydramine has been associated with a fixed drug eruption, but only three such cases have been published with dimenhydrinate. In one such case patch tests were conducted; there was a positive response to the dimenhydrinate patch, but negative responses to separate patches containing either dimenhydrinate or 8-chlorotheophylline.

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Dimercaprol

General Information

Dimercaprol or British Anti-Lewisite (BAL) was originally developed to counteract arsenic-containing war gases (1). It is now used for the treatment of poisoning with heavy metals, such as arsenic, gold, lead, or mercury, and is administered by intramuscular injection. Its adverse effects include nausea, vomiting, a burning sensation in the mouth, throat, eyes, and sometimes limbs, muscle pain and spasms, lacrimation, rhinorrhea, and hypersalivation. Of importance are a raised blood pressure and tachycardia. Pain in head, teeth, or abdomen can occur. The symptoms develop soon after injection and subside within about 2 hours. Injections can be painful and give rise to sterile abscesses. Fever can occur.

Susceptibility Factors

Genetic factors

Dimercaprol is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, because of the risk of hemolysis (2,3).

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Dimercaptopropane sulfonate

General Information

Dimercaptopropane sulfonate (2,3-dimercapto-1-propanesulfonate) is a water-soluble and possibly less toxic derivative of dimercaprol, used in poisoning with arsenic, bismuth, mercury, and other heavy metals.

- Dimercaptopropane sulfonate is the treatment of choice for acute arsenic poisoning and has been used safely in high doses (15.25 g in 12 days, first intravenously and later orally) in a 21-year-old man who swallowed about 1000 mg or more of arsenic trioxide (1). There were no adverse effects. A modest transient increase in serum transaminases was thought to have been due to the arsenic.

In a UK study, single oral doses of dimercaptopropane sulfonic acid or succimer in different combinations with or without acetylcysteine and potassium citrate were given to 191 patients considered to have mercury toxicity from amalgam dental fillings (2). After a single dose, about 5% of patients complained of mild gastrointestinal discomfort, fatigue, mental fuzziness, headache, and diuresis. These usually cleared within 6 hours of the dose and were considered to be due to heavy metal mobilization. There were no cases of hypersensitivity.

Reported adverse effects of dimercaptopropane sulfonate include nausea, vertigo, headache, weakness, pruritus, and allergic reactions, such as rashes (3–6). Nausea can occur after both oral and intravenous administration.

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Dimetacrine

See also Tricyclic antidepressants

General Information

Dimetacrine is a 6,6,6 tricyclic acridine derivative. In a double-blind study, dimetacrine was less effective than imipramine and produced more weight loss and abnormal liver function tests more often (1).

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Dimethylsulfoxide

General Information

Dimethylsulfoxide is an agent with a wide spectrum of pharmacological effects, including membrane penetration, anti-inflammatory effects, local analgesia, and weak bacteriostasis. The principal use of dimethylsulfoxide is as a vehicle for other drugs, thereby enhancing the effect of the drug, and aiding penetration of other drugs into the skin. Dimethylsulfoxide has been given orally, intravenously, or topically for a wide range of indications. It is also given by bladder instillation in the symptomatic relief of interstitial cystitis, and is used as a cryoprotectant for various human tissues.

In preparation for bone marrow transplantation, autologous hemopoietic stem cells are normally frozen in liquid nitrogen after harvesting. However, a cryoprotective agent is required, and dimethylsulfoxide is normally used. During and immediately after stem cell infusion, many adverse effects, which may be severe or life-threatening, have been reported. They include hypotension and hypertension, anaphylactic reactions, and cardiac and respiratory failure, all possibly due to dimethylsulfoxide, hemolysis induced by cryopreservation and thawing, and fluid overload.

In a retrospective study, 30 children were reviewed after bone marrow or peripheral autologous hemopoietic transplantation (1). At the time of infusion, hydrocortisone, chlorphenamine, and hyperhydration were administered to all patients, and furosemide and tropisetron to most. Vital signs and symptoms were monitored for 6 hours after the infusion. Thawing was performed rapidly at the bedside in a 42°C water-bath, and the cells were infused through a central venous catheter at 10 ml/minute. All 32 procedures were well tolerated; there were infusion-related adverse effects in 15 of 32 infusions, but none required specific therapy. There was mild bradycardia in nine patients, one reported abdominal pain, two reported headache, and three had hemoglobinuria. The authors concluded that a single-step cryopreservation technique aimed at limiting the total

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amount of dimethylsulfoxide is effective in avoiding most toxicity while not compromising post-thawing viability.

The efficacy and safety of dimethylsulfoxide are still relatively unclear; few studies have been performed in such a way as to permit reliable conclusions. Dimethylsulfoxide penetrates quickly through the tissues, and there are no great differences between its effects after different routes of administration. Adverse reactions are common, but can be avoided in large part by using more dilute solutions (2). Although the systemic toxicity of dimethylsulfoxide is considered to be low, it can potentiate the effect of simultaneously administered drugs. Combinations of dimethylsulfoxide with other toxic agents probably constitute its greatest toxic potential (3).

Organs and Systems

Nervous system

The infusion of dimethylsulfoxide-cryopreserved autologous peripheral blood stem cells has been associated with a number of infusion-related adverse effects (4). Severe reversible encephalopathy was experienced by two patients after infusion of peripheral blood stem cells cryopreserved in 10% dimethylsulfoxide. In one patient, reduction of the plasma dimethylsulfoxide concentration by plasmapheresis resulted in marked improvement in encephalopathy (5). The presence of renal insufficiency may have predisposed to the development of neurological toxicity by delaying the excretion of dimethylsulfoxide and its metabolites. Other cases of dimethylsulfoxide-induced encephalopathy have been described (6–8).

Sensory systems

Animal studies have documented a characteristic change in the ocular lens, resulting in myopia, which becomes more severe with long-term administration or high concentrations of dimethylsulfoxide. However, studies and clinical experience have not shown similar effects in humans (9,10)

Hematologic

Intravenous dimethylsulfoxide poses the greatest problems and causes transient systemic hemolysis with hemoglobinuria, but without gross hematuria. The hemolysis is dose-dependent and appears within several minutes after infusions of dimethylsulfoxide 20–40% (11). There was no evidence of kidney damage because of handling higher amounts of hemoglobin after hemolysis.

Sulfhemoglobinemia has been reported after transdermal administration of dimethylsulfoxide (12).

Gastrointestinal

Dimethylsulfoxide caused gastrointestinal discomfort in volunteers who used a topical 80% solution (1 g/kg/day). Nausea developed in 32%, vomiting in 6%, diarrhea in 5%, constipation in 3%, and anorexia in 2% (6).

A garlic-like breath occurs in almost all patients who use topical dimethylsulfoxide (13) and probably by any other route of administration.

Skin

Dimethylsulfoxide has also been used to treat extravasation of vesicant drugs (14). However, dimethylsulfoxide can itself cause redness and blistering at the site of application in high concentrations (90–100%); this effect can be reduced by using it sparingly or in lower concentrations (70%).

Drug Administration

Drug formulations

A formulation of dimethylsulfoxide (RIMSO 100) has introduced a problem since, when it is diluted with water, a strong exothermic reaction results. This caused thermal injury on intracystic instillation unless one waits until the mixture cools (15).

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Dimethyltryptamine

General Information

Dimethyltryptamine is inactive by mouth and is only used by inhalation or injection. Its effects are similar to those of lysergic acid diethylamide (LSD) (1,2).

References

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Dimetindene

See also Antihistamines

General Information

Dimetindene (SEDA-21, 174) is a first-generation antihistamine. The limited published material does not suggest that the adverse reactions to dimetindene when given orally are significantly different to those of others (1). It has also been used as a nasal spray in cases of allergy (2); some local irritation can occur, as is usual with this type of administration of antihistamines.

References

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Dinitrochlorobenzene

General Information

Dinitrochlorobenzene is a potent sensitizer that has been applied topically in the evaluation of delayed hypersensitivity. It has also been used as an immunostimulant in conditions such as leprosy, HIV infection, and some forms of cancer, and to treat alopecia and warts.

Generalized urticaria, pruritus, and dyspepsia developed in a previously healthy individual who used dinitrochlorobenzene for alopecia totalis; all the symptoms disappeared within 10 days after the drug was withdrawn, but returned after reintroduction (1).

Organs and Systems

Skin

A woman developed an itchy brownish patch on the right upper arm, in the same place where she had previously been sensitized by dinitrochlorobenzene 2% in acetone (2). A diagnosis of lymphadenosis benigna cutis was made.

References

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Dinoprostone

See also Prostaglandins

General Information

Dinoprostone is PGE_2 available for exogenous administration.

Organs and Systems

Reproductive system

Uterine rupture occurred after labor had been induced with dinoprostone at 10 days after term; the baby was born dead (1).

- A 26-year-old woman, whose first child had been delivered by elective cesarean section at 38 weeks of gestation because of a breech presentation, was given two doses of dinoprostone vaginal gel 1 mg 6 hours apart; 8 hours after the second dose her cervix was soft, fully effaced, and dilated to 3 cm. Since her uterine contractions were only mild and irregular, she underwent amniotomy and an infusion of oxytocin was begun. Fetal tachycardia occurred 4 hours later, with recurrent decelerations. Prolonged deceleration of the fetal heart then occurred and there was fresh vaginal bleeding. Uterine rupture was suspected and the neonate was delivered by emergency cesarean section, but could not be resuscitated. The mother required a blood transfusion, but subsequently made a good recovery.

The authors commented that induction with prostaglandins in women with a previous lower segment cesarean scar is associated with a risk of symptomatic scar rupture no greater than 0.6%, and the vaginal delivery rate is about 75%, that is similar to rates quoted for spontaneous labor in women with a cesarean scar. At present, faced with the lack of comparative evidence, clinicians can only

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provide women with the best estimate of risk based on uncontrolled observational data.

Reference

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Dioxium

General Information

Dioxium is obsolete. Accounts of its adverse effects will be found in earlier volumes in this series (SED-10, 213) (SEDA-6, 131).

Diphencyprone

General Information

Diphencyprone is a potent sensitizing chemical used to induce a contact dermatitis of the scalp in the topical immunotherapy of alopecia areata.

Organs and Systems

Immunologic

- Pressure-induced urticaria and widespread severe dermographism developed after the first application to the scalp of a 0.003% solution of diphencyprone in a 19-year-old Japanese man (1). Diphencyprone was withdrawn, but the symptoms persisted for almost 3 months.

An IgE-mediated hypersensitivity reaction was suggested by the authors, but skin tests were not performed and neither was specific IgE measured. A similar case has been described and the adverse events of diphencyprone reviewed (2).

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Diphenhydramine

See also Antihistamines

General Information

Diphenhydramine is a typically sedating first-generation antihistamine. It is still widely used, mainly in over-the-counter products, often in combination with other drugs.

Diphenhydramine inhibits CYP2D6 and can cause clinically important interactions with many CYP2D6 substrates, particularly those with a narrow therapeutic index.

Organs and Systems

Nervous system

Diphenhydramine can cause significant daytime neurological impairment comparable to intoxication with alcohol (1). In a study of injury rates in 12 106 patients taking diphenhydramine compared with 24 968 patients taking loratadine, using a health-care claims database that included employees, dependents, and retirees who filed claims from January 1991 to December 1998, there was a strong association between the use of diphenhydramine and the occurrence of injuries: 55% of all injuries were associated with its use. The loratadine and diphenhydramine groups had similar predrug intake injury rates. The authors concluded that a substantial number of excess injuries and costs had been incurred as the result of the use of diphenhydramine (2).

Neuroleptic malignant syndrome has been attributed to diphenhydramine (3).

- A 39-year-old man presented with a gait disturbance confusion, hyperthermia (38.2°C), and hyperhidrosis after massive ingestion of a formulation containing diphenhydramine. With intensive support, including bromocriptine, he recovered within 12 days. The estimated dose of diphenhydramine was 40 mg × 60 tablets, and each tablet included 26 mg of diprophylline, a xanthine derivative.

The genesis of this case was not clear. Atropine-like effects occur with diphenhydramine, although signs such as muscle rigidity, akinesia, and hyperhidrosis, cannot be ascribed to anticholinergic activity. However, the patient had also taken sulpiride, which is a potent dopamine receptor antagonist.

Diphenhydramine can cause extrapyramidal symptoms as part of an acute dystonic reaction (SEDA-19, 173).

Psychological, psychiatric

Use of diphenhydramine, mainly as a sleeping aid, has been associated with cognitive impairment in elderly people without dementia (4).

Diphenhydramine has been associated with acute delirium in elderly patients with mild dementia, even in single doses of 25 mg (SEDA-19, 173).

Children and adolescents who are given diphenhydramine as premedication, often intravenously as a bolus,

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to prevent the adverse effects of blood transfusion, can develop drug-seeking behavior. It is recommended that in these circumstances antihistamines should be given orally or infused slowly (5).

Skin

- A 56-year-old woman developed itchy erythematous lesions on sun-exposed areas when she used diphenhydramine ointment 1% for 6 months; the condition gradually subsided with a glucocorticoid ointment (6).

Long-Term Effects

Drug abuse

Abuse of antihistamines in Scandinavia has been found in schoolchildren, and particularly involved diphenhydramine (alone or in combination with caffeine). As a consequence such formulations were changed from over-the-counter to prescription-only status (7,8). Abuse of diphenhydramine with drug-seeking behavior and anticholinergic adverse effects have been reported in five children and adolescents with chronic hematological or oncological diseases (5).

Reinforcing, subjective, and performance effects have been compared between oral diphenhydramine and the benzodiazepine lorazepam in men with a history of recreational abuse, and the results suggested that the two drugs have similar abuse potential (SEDA-21, 174).

Drug tolerance

In 15 healthy men tolerance to diphenhydramine developed rapidly in a randomized, placebo-controlled, crossover study (9). Diphenhydramine 50 mg or placebo was given twice a day for 4 days and tests of objective and subjective sleepiness together with computer-based tests of psychomotor performance were carried out. Compared with placebo on day 1, diphenhydramine caused significant impairment. However, by day 4 sleepiness and impairment of performance were indistinguishable from placebo.

Drug Administration

Drug administration route

Topical application of diphenhydramine can cause systemic toxicity.

- Acute anticholinergic toxicity with fever, hallucinations, and tachycardia occurred in a 2.5-year-old boy from applications of calamine + diphenhydramine lotion (10).
- A 5-year-old child who used a topical lotion containing 1% diphenhydramine for pruritic vesicular exanthema developed disorientation, agitation, dilated pupils, and ataxia (SEDA-13, 132).

Drug overdose

A total of 136 cases of self-poisoning with diphenhydramine (with suicidal intent) have been evaluated. The most common symptom was impaired consciousness, followed by psychotic behavior resembling catatonic stupor. Other symptoms included hallucinations, mydriasis, tachycardia, and less often diplopia, respiratory insufficiency, and seizures (SEDA-13, 132).

Although the clinical features of diphenhydramine overdose are well known, information about dose-dependent toxicity is still scarce. This has been investigated in patients with acute diphenhydramine poisoning in retrospective and prospective studies in 232 and 50 patients respectively (11). Mild symptoms (somnolence, anticholinergic signs, tachycardia, nausea/vomiting) occurred in 55–64% of patients, moderate symptoms (isolated and spontaneously resolving agitation, confusion, hallucinations, and electrocardiographic disturbances) in 22–27%, and severe symptoms (delirium/psychosis, seizures, coma) in 14–18%. Moderate symptoms occurred at doses over 0.3 g. For severe symptoms the critical dose limit was 1.0 g. Coma and seizures were significantly more frequent in those who took over 1.5 g compared with those who took 1.0–1.5 g. These data showed clear dose-dependent acute toxicity of diphenhydramine and suggested that only patients who take over 1.0 g are at risk of severe symptoms.

- A 35-year-old woman took diphenhydramine 16 g and developed hypertension and QRS prolongation; charcoal hemoperfusion and hemodialysis were used successfully (12).
- A 28-year-old died after an overdose of diphenhydramine. He developed hyperpyrexia and tachycardia and died from a cardiac arrest (13). Hemorrhagic pulmonary edema and renal shock were the most prominent findings. At the time of death, the plasma concentration of diphenhydramine was 5 μg/ml and there were particularly high concentrations in the lungs (55 mg/kg) and kidneys (50 mg/kg).

Rhabdomyolysis has been reported after overdose with diphenhydramine (SEDA-21, 175).

Drug–Drug Interactions

Metoprolol

Diphenhydramine inhibits the metabolism of metoprolol in extensive metabolizers, thereby prolonging its negative chronotropic and inotropic effects (14).

Prolintane

- Visual hallucinations occurred in an otherwise healthy 19-year-old man who took the stimulant prolintane and diphenhydramine (15). The psychiatric complications occurred 2 months after he started to take the two drugs and resolved quickly once they were withdrawn.

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Venlafaxine

CYP2D6 is the major enzyme involved in the metabolism of venlafaxine, and diphenhydramine alters the disposition of venlafaxine, increasing plasma concentrations and predisposing to cardiovascular adverse effects (16).

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Diphenoxylate

General Information

Diphenoxylate is a synthetic compound designed to have the antidiarrheal effects of the opiates, but it also retains some less desirable opiate effects. It is generally combined with atropine, as co-phenotrope, which was originally added to the formulation in the hope of preventing misuse, although it can itself cause problems, especially if the combination is intentionally or accidentally used to excess.

In one instance keratoconjunctivitis occurred in a patient taking co-phenotrope, confirmed by rechallenge but not with diphenoxylate alone (SEDA-16, 425). Adverse effects are rare during ordinary use in adults, but children can be particularly sensitive to the adverse effects of both components, and in cases of poisoning complex and prompt measures may be needed, particularly since respiratory depression can be delayed until a day after ingestion and can recur even after a good response to opioid antagonists.

Drug Administration

Drug overdose

Only six of 36 children who took overdoses of co-phenotrope had signs of atropine overdose (central nervous system excitement, hypertension, fever, flushed dry skin) (1). Opioid overdose (central nervous system and respiratory depression with miosis) predominated or occurred without any signs of atropine toxicity in 33 cases (92%). Diphenoxylate-induced hypoxia was the major problem and was associated with slow or fast respiration, hypotonia or rigidity, cardiac arrest, and in three cases cerebral edema and death. Respiratory depression recurred 13–24 hours after the ingestion in seven cases and was probably due to accumulation of difenoxine, an active metabolite of diphenoxylate. Recommended treatment is an intravenous bolus dose of naloxone, followed by a continuous intravenous infusion, prompt gastric lavage, repeated administration of activated charcoal, and close monitoring for 24 hours.

Drug–Drug Interactions

Nitrofurantoin

Co-phenotrope, and other drugs that reduce intestinal motility, can interact with other drugs by affecting their absorption. For example, the absorption of nitrofurantoin can be doubled (2).

References

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Diphenylpyraline

See also Antihistamines

General Information

Diphenylpyraline is an antihistamine, a piperadine derivative, with antimuscarinic and sedative properties.

Organs and Systems

Skin

Cutaneous reactions have been reported with diphenylpyraline hydrochloride (1).

Reference

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Diphtheria vaccine

See also Vaccines

General Information

Diphtheria vaccine contains diphtheria toxoid carried on aluminium hydroxide or calcium phosphate. Single antigen products are available only for cases in which combined antigens should not be used. The formulations used in most countries are a childhood formulation containing 25–30 Lf (flocculating units) of diphtheria toxoid (D) and an adult formulation containing 2 Lf of diphtheria toxoid (d). The formulations of choice in routine immunization are DTP (diphtheria and tetanus toxoids combined with pertussis vaccine), DT (diphtheria and tetanus toxoids) for pediatric use, and Td (tetanus and diphtheria toxoids with a limited amount of diphtheria antigen) for use in older children and adults.

Combined diphtheria + tetanus immunization

In a prospective cohort study in Italy, 380 children aged 6 years were randomly assigned to receive either the DT or the Td vaccine as a booster dose in order to determine whether a booster dose of Td (diphtheria–tetanus vaccine with a reduced amount of diphtheria toxoid, adult formulation) would produce comparable diphtheria antibody titers but lower reactogenicity than DT (childhood formulation). The frequencies of symptoms within 3 days of vaccine administration were similar in the two groups, except for local redness and swelling, which were significantly more common in the children who received DT vaccine: redness 31% versus 16%, and swelling 36% versus 26%. The mean duration of local symptoms was 3.3 days in the diphtheria–tetanus group and 2.6 days in the Td group. After booster immunization, 97% of children in the DT group and 91% of those in the Td group had antibody concentrations of at least 1 IU/ml ("long-term" protection titer) (1).

There have been comparisons of the immunogenicity and reactogenicity of different diphtheria vaccines. They have involved single or combined administration of diphtheria and/or tetanus toxoids (SEDA-13, 279) (SEDA-15, 345), booster immunization using Td vaccines including either aluminium hydroxide or calcium phosphate as adjuvant (SEDA-20, 288), or either plain or adsorbed formulations (SEDA-21, 328).

Adverse events after diphtheria–tetanus vaccine in the USA in 1982–84 have been reviewed in detail (SEDA-13, 273). The usual types of local intolerance can be seen. For example, some 5% of schoolchildren develop redness and swelling, whilst some older children develop enlargement of the regional lymph nodes. Such reactions are much less common in young children, and much more common in children given combined vaccines.

General reactions (seen in some older children and adults) are usually limited to brief fever; sustained fever and other systemic reactions are uncommon unless the person has been hyperimmunized. After the administration of DT vaccine, local reactions, generally erythema and induration, with or without tenderness, can occur. In hyperimmunized cases, Arthus-type hypersensitivity reactions can occur. These characteristically severe local reactions generally start 2–8 hours after an injection. People who have such reactions usually have very high serum antitoxin concentrations and one should be careful not to administer a booster more than once every 10 years.

The occurrence of epidemic diphtheria in Eastern Europe led to the recommendation in the UK that those aged 15–18 years should receive a combined tetanus and low-dose diphtheria toxoid vaccine instead of a tetanus booster alone. In March 1995, 220 children aged 14–16 years were inadvertently given high-dose diphtheria and tetanus toxoid vaccine, and their parents were sent a questionnaire; 153 replied. A total of 141 (92%) of adolescents reported one or more reactions, most of which were classified as mild or moderate and lasted less than 1 week. However, 47 (31%) reported at least one severe local or systemic reaction (2).

In a study of adverse events after immunization in New Zealand in 1990–95 (3), reactions at the injection site after adult tetanus–diphtheria vaccine (68 reports per 100 000 immunizations) were reported five times more often than with tetanus vaccine.

Combined diphtheria + tetanus + pertussis immunization

An overview of clinical trials with a special diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine has been published (4). The vaccine contains as pertussis components purified filamentous hemagglutinin, pertactin, and genetically engineered pertussis toxin. The vaccine induces high and long-lasting immunity and is at least as efficacious as most whole-cell pertussis vaccines and similar in efficacy to the most efficacious DTaP vaccines that contain three pertussis antigens. The vaccine is better tolerated than whole-cell vaccines and has a similar reactogenicity profile to other acellular vaccines.

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A vaccine containing diphtheria and tetanus toxoids and DTaP with reduced antigen content for diphtheria and pertussis (TdaP) has been compared with a licensed reduced adult-type diphtheria–tetanus vaccine and with an experimental candidate monovalent DTaP vaccine with reduced antigen content (ap) (5). A total of 299 healthy adults (mean age 30 years) were randomized into three groups to receive one dose of the study vaccines. The antibody responses (antidiphtheria, antitetanus, antipertussis toxin, antipertactin, antifilamentous hemagglutinin) were similar in all groups. The most frequently reported local symptom was pain at the injection site (62–94%), but there were no reports of severe pain; redness and swelling with a diameter of 5 cm or more occurred in up to 13%. The incidence of local symptoms was similar after TdaP and Td immunization. The most frequently reported general symptoms were headache and fatigue (20–50%). The incidence of general symptoms was similar in the TdaP and Td groups. There were no reports of fever over 39°C. No serious adverse events were reported.

Data from the Third National Health and Nutrition Survey (1988–94) have been used to analyse the possible effects of DTP or tetanus immunization on allergies and allergy-related symptoms among 13 944 infants, children, and adolescents aged 2 months to 16 years in the USA (6). The authors concluded that DTP or tetanus immunization increases the risk of allergies and related respiratory symptoms in children and adolescents. However, the small number of non-immunized individuals and the study design limited their ability to make firm causal inferences about the true magnitude of effect.

Tetravalent, pentavalent, and hexavalent immunization

DTaP or DTwP vaccine can be combined with other antigens, such as *Haemophilus influenzae* type b (Hib), inactivated poliovaccine (IPV), and hepatitis B vaccine. In children DTaP or DTwP vaccines are the basis for such combinations, while in adults it is mostly Td or Tdap vaccine combined with inactivated poliovaccine (IPV). Current safety concerns regarding combination vaccines have been defined and reviewed (7). The author concluded that there is no evidence that adding vaccines to combination products increases the burden on the immune system, which can respond to many millions of antigens. Combining antigens usually does not increase adverse effects, but it can lead to an overall reduction in adverse events. Before licensure, combination vaccines undergo extensive testing to assure that the new products are safe and effective.

The frequency, severity, and types of adverse reactions after DTP-Hib immunization in very preterm babies have been studied (8). Adverse reactions were noted in 17 of 45 babies: nine had major events (apnea, bradycardia, or desaturation) and eight had minor reactions (increased oxygen requirements, temperature instability, poor handling, and feeding intolerance). Babies who had major adverse reactions were significantly younger at the time of immunization than the babies who did not have major reactions. Of 27 babies immunized at 70 days or less, nine developed major reactions compared with none of those who were immunized at over 70 days.

The Hexavalent Study Group has compared the immunogenicity and safety of a new liquid hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and Hib (DTP + IPV + HB + Hib vaccine, manufactured by Aventis Pasteur MSD, Lyon, France) with two reference vaccines, the pentavalent DTP + IPV + Hib vaccine and the monovalent hepatitis B vaccine, administrated separately at the same visit (9). Infants were randomized to receive either the hexavalent vaccine ($n = 423$) or (administered at different local sites) the pentavalent and the HB vaccine ($n = 425$) at 2, 4, and 6 months of age. The hexavalent vaccine was well tolerated (for details, see the monograph on Pertussis vaccines). At least one local reaction was reported in 20% of injections with hexavalent vaccine compared with 16% after the receipt of pentavalent vaccine or 3.8% after the receipt of hepatitis B vaccine. These reactions were generally mild and transient. At least one systemic reaction was reported in 46% of injections with hexavalent vaccine, whereas the respective rate for the recipients of pentavalent and HB vaccine was 42%. No vaccine-related serious adverse event occurred during the study. The hexavalent vaccine provided immune responses adequate for protection against the six diseases.

Organs and Systems

Cardiovascular

Myopericarditis has been attributed to Td-IPV vaccine (10).

- A 31-year-old man developed arthralgia and chest pain 2 days after Td-IPV immunization and had an acute myopericarditis. He recovered within a few days with high-dose aspirin.

The authors discussed two possible causal mechanisms, natural infection or an immune complex-mediated mechanism. Infection was excluded by negative bacterial and viral serology and the favorable outcome within a few days without antimicrobial treatment.

Nervous system

Supposed neurological adverse effects of diphtheria immunization have been reported, but a causal connection was unclear (11). Of five cases of neurological complications after diphtheria or diphtheria-tetanus immunizations two were classified as vaccine-induced poliomyelitis; the other three could be traced back to a hyperergic reaction to diphtheria toxoids in the cerebral vessels (12).

Guillain–Barré syndrome (13) and polyradiculoneuritis (14,15) have rarely been reported. In a national surveillance study of Guillain–Barré syndrome in the USA, 31 of 998 cases developed the illness within 8 weeks after immunization. Of these 31 cases, 5 had been immunized with DT or DPT vaccine (16).

The bioelectric activity of the brain after DT immunization was studied in healthy children. Electroencephalography showed significant changes in 13 of 17 children, which resolved within 3 weeks (17). The question has arisen of whether this is of more than experimental significance: between 1980 and 1982 in the

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Campana region of Italy, several cases of encephalopathy in children who had been given DT immunization 1 week before were reported to the health authorities. However, summarizing the results of a case-control study, Greco pointed out that the statistical association that he found between the incidence of encephalopathy and DT administration did not imply a causal association (18).

Sensory systems

Optic neuritis has been attributed to Td-IPV vaccine (19).

- Ten days after receiving Td-IPV vaccine a 56-year-old woman developed acute unilateral optic neuritis. Complete remission occurred within 6 weeks of prednisolone treatment. No other causes were found.

Skin

Erythema multiforme developed 8 hours after diphtheria–tetanus immunization in a 9-month-old infant (20). There have also been reports of erythema multiforme after hepatitis B vaccine, MMR vaccine, and DPT vaccine.

Bullous pemphigoid has been attributed to DTP-IPV vaccine (21).

A previous healthy 3.5-month-old infant developed bullous pemphigoid 3 days after receiving a first dose of DTP-IPV vaccine. *Staphylococcus aureus* was isolated from purulent bullae. The lesions resolved rapidly after treatment with antibiotics and methylprednisolone.

The authors mentioned 12 other cases of bullous pemphigoid, reported during the last 5 years, that had possibly been triggered by vaccines (influenza, tetanus toxoid booster, and DTP-IPV vaccine).

Immunologic

- A six-year-old child had anaphylaxis 30 minutes after a fifth dose of DT vaccine (22). Skin tests, in vitro determination of specific IgE antibodies, and immunoblotting assays showed that the IgE response was directed against tetanus and diphtheria toxoids. Cross-reactivity between the two toxoids was not demonstrated, indicating the presence of co-existing but non-cross-reacting IgE and IgG antibodies.

Susceptibility Factors

Other features of the patient

The only contraindication to administering single diphtheria toxoid or combined diphtheria and tetanus toxoids is a history of a severe hypersensitivity or neurological reaction after a previous dose.

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Dipyridamole

General Information

Dipyridamole inhibits platelet aggregation by inhibiting platelet cyclic AMP phosphodiesterase, potentiating adenosine inhibition of platelet function by blocking adenosine reuptake by vascular and blood cells and breakdown of adenosine, and by potentiating prostaglandin I_2 antiaggregatory activity and enhancement of its synthesis. These independent processes inhibit platelet aggregation by increasing platelet cyclic AMP through a reduction in enzymatic breakdown of cyclic AMP and stimulation of cyclic AMP formation by activation of adenyl cyclase by adenosine and possibly prostaglandin I_2 (1).

Dipyridamole is also a potent coronary arteriolar vasodilator, perhaps by opening of vascular K_{ATP} channels (2). However, the Food and Drug Administration withdrew conditional approval for certain drug products containing dipyridamole, because of a lack of sufficient evidence of effectiveness in the long-term therapy of angina pectoris (3).

Observational studies

The incidence of major adverse reactions to dipyridamole was determined in a multicenter retrospective study, involving 73 806 patients who underwent intravenous dipyridamole stress imaging in 59 hospitals and 19 countries (4). The main conclusion was that the risk of serious dipyridamole-induced adverse effects is very low, a conclusion that is in line with other reports (5), and comparable to that reported for exercise testing in a similar patient population. Combined major adverse events among the entire patient population included 7 cardiac deaths (0.95 per 10 000), 13 nonfatal myocardial infarctions (1.76 per 10 000), 6 nonfatal sustained ventricular dysrhythmias (0.81 per 10 000) (ventricular tachycardia in 2 and ventricular fibrillation in 4), 9 transient cerebral ischemic attacks (1.22 per 10 000), 1 stroke, and 9 severe cases of bronchospasm (1.22 per 10 000). Minor non-cardiac adverse effects were less frequent among the elderly and more frequent in women and patients taking maintenance aspirin.

Placebo-controlled studies

The efficacy and safety of dipyridamole have been assessed in patients with chronic stable angina in a large-scale, international, randomized, placebo-controlled, parallel-group study, in which 400 patients with chronic stable angina pectoris and a positive treadmill exercise test were randomized to receive either modified-release dipyridamole (200 mg bd orally; $n = 198$) or placebo ($n = 202$) for 24 weeks as an add-on to conventional antianginal therapy and for 4 additional weeks as monotherapy, the latter after withdrawal of standard treatment with calcium channel blockers and/or beta-blockers and/or long-acting (prophylactic) nitrates (6). Of the 198 patients randomized to dipyridamole, 134 completed the add-on phase but only 12 completed the monotherapy phase. Of the 202 patients randomized to placebo, 162 reached the add-on phase but only 12 reached the monotherapy phase. There were serious adverse events in 15 patients who took dipyridamole and 12 who took placebo (7.6 versus 6.0%). These included chest pain, angina pectoris, and non-cardiac adverse effects, such as diarrhea, nausea, and headache.

Organs and Systems

Cardiovascular

Dipyridamole is used with ^{201}thallium imaging in the detection of coronary artery disease, but can cause dysrhythmias.

- A 41-year-old man with hypertension was investigated for chest tightness by dipyridamole–thallium single-photon emission computed tomography (7). A standard dose of dipyridamole (0.56 mg/kg) was infused intravenously over 4 minutes, during which his heart rate increased from 68 to 88/minute and his blood pressure fell slightly (from 160/80 to 140/76 mmHg). He had no subjective symptoms, such as palpitation, dizziness, or chest tightness, but had ventricular extra beats 40 seconds after completion of the dipyridamole infusion, followed 1 minute later by a sustained ventricular tachycardia. His blood pressure fell to 80/50 mmHg and he complained of dizziness. Intravenous aminophylline 125 mg was given immediately. About 30 seconds later, the ventricular tachycardia terminated and his hemodynamics stabilized. The ventricular extra beats persisted for another 30 seconds.
- Two cases of severe bradydysrhythmias (one complete heart block, one sinus bradycardia) occurred after intravenous dipyridamole (8).

Dipyridamole can also cause myocardial ischemia.

- A 43-year-old man had an acute myocardial infarction immediately after exercise and pharmacological stress echocardiography with dipyridamole + atropine 1 month after successful stent implantation (9).
- A 59-year-old man developed unstable angina 1 month after coronary artery bypass surgery (10). During dipyridamole scintigraphy, 2 minutes after the beginning of dipyridamole infusion, ST segment elevation occurred in the inferior electrocardiographic leads and there

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were two marked anteroseptal and inferior defects on myocardial scintigraphy.

A patient with aorto-iliac occlusive vascular disease and hypertension suffered a stroke 6.5 minutes after administration of intravenous dipyridamole during a ^{201}thallium myocardial study (11). Aminophylline did not reverse its progression.

Respiratory

The practicability of dipyridamole ^{13}N-ammonia myocardial positron emission tomography for perioperative risk assessment of coronary artery disease in patients with severe chronic obstructive pulmonary disease undergoing lung volume reduction surgery has been studied in 13 men and 7 women (mean age 57 years) without symptoms of coronary artery disease (12). Nine patients had intolerable dyspnea due to bronchoconstriction and required intravenous aminophylline. Dipyridamole cannot be recommended as a pharmacological stress in this setting.

Fatal respiratory insufficiency after dipyridamole–thallium imaging has been described in patients with a history of chronic obstructive lung disease (13,14). The authors of these reports concluded that patients with a history of chronic obstructive lung disease may have an increased risk of bronchospasm after dipyridamole infusion, and caution is advised in such patients.

Nervous system

Dipyridamole in combination with aspirin was more effective in preventing secondary stroke than low-dose aspirin or dipyridamole alone in only one of several studies (15). There is some evidence that dipyridamole can sometimes cause transient ischemic attacks (16).

- A 74-year-old woman had a 3-year history of mild dysarthria, dizziness, and gait ataxia, accompanied by two transient ischemic attacks with involuntary ballistic movements of her left arm lasting several seconds each, and another transient ischemic attack with a right homonymous hemianopia lasting 30 minutes. About 45 minutes after her first-ever oral administration of dipyridamole plus aspirin she developed a transient cerebellar deficit that reproduced features of previous vertebrobasilar ischemic events, as well as severe headache, flushing, and diarrhea.

The acute onset, the pattern of the cerebellar deficit, and the absence of features of epilepsy suggested that the episode was a transient ischemic attack. Aspirin is not known to cause transient ischemic attacks, and only rarely causes headache, flushing, and diarrhea. Since headache, flushing, and diarrhea, which can be caused by dipyridamole, occurred at the same time as the transient ischemic attacks and did not recur after withdrawal, dipyridamole may have caused the transient ischemic attacks. However, it was not clear whether the attacks occurred despite treatment rather than because of it.

In the Second European Stroke Prevention Study, headaches associated with dipyridamole (in 8% of patients taking dipyridamole or dipyridamole + aspirin versus 2% of patients taking aspirin alone or placebo) often led to withdrawal of therapy.

The predictive factors for headaches were explored in a study of the bioequivalence of two formulations of dipyridamole 200 mg in a modified-release combination with aspirin 25 mg (17). The conclusion was that the rapid fall in the incidence of headaches over time implied that most patients quickly develop tolerance to dipyridamole-associated headaches. However, in the European Stroke Prevention Study 2, headache was the most common adverse event, and it occurred more often in dipyridamole-treated patients (18).

Biliary tract

Recurrent drug-containing gallstones, 18 months after a previous stone had been removed endoscopically, were attributed to dipyridamole (19).

Immunologic

Infusion of dipyridamole caused an acute allergic reaction during myocardial scintigraphy (20).

- A 56-year old man with a history of allergy to aspirin, tetracycline, and penicillin, including angioedema and dyspnea, was given a dipyridamole stress test. About 1 minute after the infusion was started he reported periorbital pruritus. The infusion was completed uneventfully with the administration of ^{99m}technetium sestamibi at 7 minutes. Twenty minutes later he had tightness in the neck, dyspnea, and generalized facial swelling. He was given oxygen and intravenous promethazine hydrochloride and hydrocortisone. He improved over the next 2 hours, with residual periorbital edema but complete recovery from the respiratory symptoms. The cardiac study was completed without further events. The result was normal.

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Direct thrombin inhibitors

General Information

The class of direct thrombin inhibitors includes the hirudins, lepirudin and bivalirudin, and the tripeptide or peptidomimetic compounds argatroban, efegatran, inogatran, napsagatran, melagatran, and ximelagatran. They act by binding to the active site on thrombin and inhibiting its enzymatic activity. They thus inhibit fibrin formation, activation of anticoagulant factors V, VIII, and XIII, and protein C, and platelet aggregation. The antithrombin action occurs rapidly and is quickly reversible.

In a meta-analysis of individual patients' data from 11 randomized comparisons of direct thrombin inhibitors (hirudin, bivalirudin, argatroban, efegatran, or inogatran) with heparin, 35 970 patients were treated for up to 7 days and followed for at least 30 days (1). Compared with heparin, the direct thrombin inhibitors were associated with a lower risk of death or myocardial infarction at the end of treatment (OR = 0.85; 95% CI = 0.77, 0.94) and at 30 days (OR = 0.91; CI = 0.84, 0.99). There was no excess of intracranial hemorrhages with the direct thrombin inhibitors.

Hirudin

Hirudin is the principal anticoagulant of the medicinal leech (*Hirudo medicinalis*). Though long known in its natural form, this is now produced by recombinant DNA techniques and characterized by a high affinity for thrombin, whether it is free in the plasma or absorbed onto the fibrin clot. The high incidence of hemorrhagic strokes in patients treated with both thrombolytic drugs and hirudin led to the redesign of three major trials (GUSTO-IIA, TIMI-9A, HIT III) of the effect of these antithrombotic agents in myocardial infarction (2–4). Hirudin is now regarded as the treatment of choice for heparin-induced thrombocytopenia. It is not recommended for use in pregnancy as it can cross the placenta; however, its safe use has been reported (5).

There is no specific antidote for the direct thrombin inhibitors: they are not neutralized by protamine sulfate.

Desirudin

Desirudin, similarly produced by recombinant techniques, has been used to prevent venous thromboembolism. It has been investigated in studies in patients with total hip replacements. In a large comparison of desirudin and low molecular weight heparin (enoxaparin), desirudin produced better prophylaxis against proximal deep vein thrombosis after total hip replacement (6) with no differences between the two groups with respect to perioperative, postoperative, and total blood loss. There were no cases of thrombocytopenia associated with desirudin.

Argatroban

Argatroban has been approved in the USA and Canada for the prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia, and in Japan and Korea for various thrombotic disorders. Its effects can be monitored using the activated partial thromboplastin time for low doses and the activated clotting time for high doses. Its pharmacology, clinical pharmacology, and uses have been reviewed (7–14).

Organs and Systems

Immunologic

The effects on activated partial thromboplastin time and the incidence and clinical relevance of antihirudin antibodies in patients treated with lepirudin have been studied using data from two prospective multicenter studies, in which patients with heparin-induced

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thrombocytopenia received one of four intravenous lepirudin dosage regimens (15). Of 196 evaluable patients, 87 (44%) had IgG antihirudin antibodies. The development of antihirudin antibodies depended on the duration of treatment (antibody-positive patients 18.6 days versus antibody-negative patients 11.6 days). Antihirudin antibodies were not associated with increases in clinical endpoints (limb amputation, new thromboembolic complications, or major bleeding). In 23 of 51 evaluable patients in whom antihirudin antibodies developed during treatment with lepirudin, the antibodies enhanced the anticoagulatory effect of lepirudin. During prolonged treatment with lepirudin, anticoagulatory activity should be monitored daily.

Desirudin has a very low immunogenic potential. During repeated administration to 263 healthy volunteers, there were no signs or symptoms directly attributable to desirudin and only three volunteers exposed to a second course had allergic reactions with pruritic erythema attributable to desirudin in one case (16). In this study, specific antibodies directed against desirudin were detected in only one subject.

Drug–Drug Interactions

Digoxin

The pharmacokinetics of intravenous argatroban 1.5–2.0 μg/kg/minute were unaffected by co-administration of oral digoxin in healthy volunteers (17).

Erythromycin

Argatroban is metabolized by CYP3A4/5, and its pharmacokinetics might therefore be expected to be altered by inhibitors of CYP3A. However, in 14 healthy men erythromycin 500 mg qds had no effects on the pharmacokinetics of argatroban 1 μg/kg/minute infused over 5 hours (18).

Lidocaine

The pharmacokinetics of intravenous argatroban 1.5–2.0 μg/kg/minute were unaffected by co-administration of intravenous lidocaine in healthy volunteers (17).

Paracetamol

The pharmacokinetics of intravenous argatroban 1.5–2.0 μg/kg/minute were unaffected by co-administration of oral paracetamol in healthy volunteers (17).

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Dirithromycin

See also Macrolide antibiotics

General Information

Adverse effects of dirithromycin were studied in 4263 patients (1). There was abdominal pain in 5.6%, diarrhea in 5.0%, and nausea in 4.9%. Headache was relatively common (4.5%). In 63% of cases the adverse events were considered mild, in 31% moderate, and in 6.3% severe. Adverse events resulted in withdrawal in 3.1%, mainly because of gastrointestinal symptoms such as nausea and abdominal pain.

Organs and Systems

Respiratory

Adverse events involving the respiratory system (dyspnea, increased cough, or asthma) were reported in about 2% of patients taking dirithromycin (1).

Drug–Drug Interactions

Ciclosporin

Dirithromycin has a small effect on ciclosporin concentrations but to a clinically insignificant extent (2).

Oral contraceptives

Oral dirithromycin reduced the mean ethinylestradiol 24-hour AUC and increased its oral clearance in women using an oral contraceptive (3). However, since there was no effect on inhibition of ovulation, the clinical importance of this interaction may be negligible.

Theophylline and other xanthines

Drug interactions with dirithromycin have rarely been reported, since it does not interact with cytochrome P450. Nevertheless, in 13 healthy volunteers 500 mg/day for 10 days caused a significant 18% fall in the average steady-state plasma theophylline concentration and a 26% fall in peak concentration, with a 14–15% increase in clearance (4). In contrast, the steady-state pharmacokinetics of theophylline did not change in 14 patients with chronic obstructive airways disease who took dirithromycin for 10 days (5).

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Disinfectants and antiseptics

See also Individual agents

General Information

Antimicrobial drugs are widely used in topical medicaments, cosmetics, household products, and industrial biocides. Depending on their concentrations, they can function as disinfectants, antiseptics, or preservatives. The prevalence and rank order of sensitization to antimicrobial allergens in Europe have been reviewed (1,2). The most frequent antimicrobial allergens in 8521 patients who were patch-tested between 1985 and 1997 in Belgium are given in Table 1 (2).

In the multicenter study of the Information Network of Departments of Dermatology, sensitization rates of preservatives in the standard series were all over 1% in the test population of 11 485 patients. Thiomersal was rating highest (5.3%), chloromethyl-isothiazolinone/methyisothiazolinone, formaldehyde, and methyl-dibromoglutaronitrile/phenoxyethanol were next at about 2%, and parabens rating lowest at 1.6%. Glutaral, a biocide

Table 1 Most frequent antimicrobial allergens in Belgium out of 8521 patients in 1985–97

Rank	Allergen	Number
1	Methyl(chloro)isothiazolinone	143*
2	Thiomersal	136
3	Merbromine	94
4	Iodine	89
5	Cetrimide	88
6	Formaldehyde	80
7	Parabens	71
8	Chloramine	43
9	Quaternium-15	32
10	Nitrofurazone	29
11	Quinoline mix	28
12	Benzyl alcohol	25
	Benzoic acid	25
	Thiocyanomethylbenzothiazole	25
	Chlorhexidine	25
13	Glutaral (glutaraldehyde)	22
	Methyldibromoglutaronitrile + phenoxyethanol	22
14	Chloroacetamide	20
	Diazolidinyl urea	20

*Methyl (chloro) isothiazolinone was not tested until 1987

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mainly used as a disinfectant, showed a remarkable increase in sensitization from less than 1% in 1990 up to more than 4% at the end of 1994. Health personnel and cleaning personnel were often affected and showed a sensitization rate of 10% (1,3).

The individual compounds that are covered in separate monographs are:

- Acrisorcin
- Aliphatic alcohols
- Benzalkonium
- Benzethonium
- Benzoxonium
- Benzyl alcohol
- Boric acid
- Cetrimonium bromide and cetrimide
- Chlorhexidine
- Chloroxylenol
- Ethacridine
- Ethylene oxide
- Formaldehyde
- Glutaral (glutaraldehyde)
- Hexachlorophene
- Hexetidine
- Parabens
- Peroxides
- Phenols
- Polyhexanide
- Polyvidone
- Salicylanilides
- Sodium hypochlorite
- Sulfites
- Tosylchloramide
- Triclocarban.

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Disopyramide

See also Antidysrhythmic drugs

General Information

The use, clinical pharmacology, and adverse effects of disopyramide have been reviewed thoroughly (1,2).

Comparative studies

Disopyramide (by intravenous infusion of 2 mg/kg/minute up to a maximum total dose of 100 mg) has been compared with pilsicainide (in a single oral dose of 100–150 mg) in the treatment of paroxysmal atrial fibrillation in 72 patients (3). Conversion to sinus rhythm occurred in 29 of the 40 patients given pilsicainide and 18 of 32 patients given disopyramide, a non-significant difference. However, the mean time to conversion was faster with disopyramide (23 versus 60 minutes). No adverse effects were observed with either drug.

General adverse reactions

The adverse effects of disopyramide are mostly mediated by its effects on the cardiovascular system and by its anticholinergic effects. Disopyramide has a strong negative inotropic effect on the myocardium and can cause heart failure and hypotension. It prolongs the QT interval and can cause serious ventricular tachydysrhythmias. Anticholinergic effects can cause dry mouth, blurred vision, urinary retention, glaucoma, and erectile impotence. Hypoglycemia can also occur. Disopyramide can cause uterine contractions and should not be used during pregnancy. Angioedema has been reported rarely. Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Disopyramide has three effects that can lead to cardiovascular complications (4).

1 *Anticholinergic* The anticholinergic effects of disopyramide on the vagus have been reported to cause tachycardia with bundle branch block or conversion to 1:1 conduction of a supraventricular tachycardia with block.
2 *QTc interval prolongation* There have been several reports of ventricular dysrhythmias (for example polymorphous ventricular tachycardia, ventricular fibrillation, ventricular tachycardia) in association with a prolonged QTc interval (SEDA-5, 180).
3 *Negative inotropic effect* Disopyramide can worsen cardiac failure and occasionally causes hypotension.

The risk of adverse cardiac effects of disopyramide during intravenous administration relates to the speed of its administration rather than to the total dose given (SEDA-10, 149).

Torsade de pointes due to disopyramide is well described (SEDA-4, 180). This effect is associated with prolongation of the QT interval. There has been a study of the effects of disopyramide on the QT interval in patients with pre-existing QT interval prolongation (5). In eight patients with QT interval prolongation during bradycardia and five patients without QT interval prolongation, disopyramide significantly prolonged the QT interval; however, the change was more pronounced in those with pre-existing bradycardia (78 versus 35 ms). The authors proposed that this difference might be due to an underlying abnormality of potassium channels in those with pre-existing bradycardia. Thus, those who are genetically predisposed to cardiac dysrhythmias may be at greater risk of the prodysrhythmic effects of antidysrhythmic drugs.

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The risk of myocardial depression with consequent hypotension is greatest when disopyramide is infused rapidly intravenously (SEDA-10, 149). Loading doses of disopyramide should therefore be infused slowly (over 30–60 minutes).

Respiratory

- Pneumonitis has been attributed to disopyramide in a 72-year-old man; the symptoms began soon after the first dose (6). Bronchoalveolar lavage fluid contained a high percentage of lymphocytes (65%) and a high CD4:CD8 ratio (69:1).

The results of a lymphocyte stimulation test suggested that disopyramide had been responsible.

Nervous system

Through its anticholinergic effects disopyramide causes dry mouth and blurred vision and can occasionally cause serious adverse effects, including glaucoma and acute urinary retention (1).

Neuropathy has rarely been attributed to disopyramide (7).

- A 71-year-old woman, who had taken disopyramide 500 mg/day for 4 years, developed fatigue, paresthesia, pain, and cramps in her legs (8). She had proximal weakness in all four limbs and an unsteady gait. Electrophysiology showed a sensorimotor polyneuropathy, with reduced motor conduction velocity and muscle denervation. All antibodies were negative. The symptoms did not respond to prednisone but improved in the months after disopyramide withdrawal.

Psychological, psychiatric

Acute psychosis has been attributed to disopyramide (9,10).

Metabolism

Disopyramide can cause hypoglycemia (SEDA-6, 180) (SEDA-17, 222) (11), perhaps due to increased secretion of insulin, and can also potentiate the effects of conventional hypoglycemic drugs (12). This effect may be due to its chief metabolite mono-*N*-dealkyldisopyramide, since many of the reported cases of hypoglycemia have been in patients with renal impairment, in which the metabolite accumulates. In six subjects who were being considered for treatment with disopyramide, serum glucose concentrations were measured at 13, 15, 17, and 19 hours after supper, with no further food, with and without the added administration of two modified-released tablets of disopyramide 150 mg with supper and 12 hours later (13). Disopyramide significantly reduced the serum glucose concentration at all measurement times by an average of 0.54 mmol/l. The fall in serum glucose concentration was not related to the serum concentration of disopyramide or the serum creatinine concentration; it was greater in older patients and in underweight patients.

- Hypoglycemia has also been reported in a 70-year-old woman with type 2 diabetes mellitus taking disopyramide (14).

Hematologic

Disopyramide has caused neutropenia (15) and a coagulopathy (16).

Liver

Liver damage was reported in 22 (0.35%) of 6294 patients given disopyramide, with jaundice in 6 (0.09%) (17). Liver damage due to disopyramide can be associated with direct hepatocellular damage (18) and intrahepatic cholestasis (19,20). However, it can also occur indirectly, because of heart failure and hepatic congestion (21). Thus, the incidence of direct liver damage quoted above may be an overestimate.

Sexual function

Erectile impotence has been attributed to disopyramide (22,23).

Immunologic

Angioedema has been attributed to disopyramide (24).

Second-Generation Effects

Pregnancy

Disopyramide can cause uterine contractions (SEDA-3, 156) (25), and has been reported to have caused the onset of uterine contractions in eight of 10 patients at term (25).

- A 26-year-old woman with Wolff–Parkinson–White syndrome was given two doses of disopyramide at 36 weeks and shortly afterwards went into active labor with prepartum hemorrhage (26). The child was delivered by cesarean section and the woman made a full recovery.

In view of these reports disopyramide should be avoided in pregnancy.

Lactation

Although disopyramide and its *N*-monodesalkyl metabolite are both excreted in breast milk, the amounts are probably too small to be of importance (27).

Susceptibility Factors

Renal disease

In renal insufficiency there are complex changes in the pharmacokinetics of disopyramide, but the overall effect is accumulation of it and its active metabolite, due to reduced renal clearance (28).

Other features of the patient

Because of the anticholinergic effects of disopyramide, care should be taken both in patients with symptoms of prostatic hyperplasia (because of the risk of urinary retention) and in patients with glaucoma.

Disopyramide is highly bound to plasma proteins and this binding is saturable within the therapeutic range. Thus, at high dosages there may be an increase in the

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unbound fraction of drug in the plasma with proportionately greater effects. However, this is probably of no clinical relevance.

Drug Administration

Drug overdose

Overdosage of disopyramide is associated with apnea, loss of consciousness, loss of spontaneous respiration, hypotension, and cardiac dysrhythmias (29,30). Suggested treatment (31) includes arterial blood pressure monitoring, correction of acidosis and hypokalemia, and the intravenous infusion of a pressor agent for severe hypotension. Cardiac depressant drugs (for example class I antidysrhythmic drugs) should not be used to treat dysrhythmias, and the use of pyridostigmine to reverse the anticholinergic effects of disopyramide (32) is not recommended (SEDA-10, 149).

Drug–Drug Interactions

Class I antidysrhythmic drugs

There is an increased risk of dysrhythmias if disopyramide is used in conjunction with other drugs that prolong the QT interval, for example class I or class III antidysrhythmic drugs (33).

Macrolide antibiotics

Some of the macrolide antibiotics have been reported to inhibit the clearance of disopyramide (SEDA-21, 200) (SEDA-22, 207), resulting in serious dysrhythmias or hypoglycemia. The mechanism of this interaction is presumed to be inhibition of dealkylation of disopyramide to its major metabolite, mono-*N*-dealkyldisopyramide. For example, in human liver microsomes the macrolide antibiotic troleandomycin significantly inhibited the mono-*N*-dealkylation of disopyramide enantiomers by inhibition of CYP3A4 (34). This interaction can result in serious dysrhythmias or other adverse effects of disopyramide.

- A 76-year-old woman developed torsade de pointes 5 days after starting to take clarithromycin 200 mg bd in addition to disopyramide 100 mg tds (35). Her serum potassium concentration was 2.8 mmol/l and the QT_c interval was prolonged to 0.71 seconds. The plasma disopyramide concentration was in the usual target range (3.2 μg/ml). The disopyramide and clarithromycin were withheld and potassium was given; 14 hours later the serum potassium concentration was 4.3 mmol/l and there was no further dysrhythmia, despite prolongation of the QT_c interval to 0.67 seconds, falling to 0.45 seconds 10 days later.
- A 35-year-old woman taking disopyramide phosphate modified-release capsules 150 mg qds was given azithromycin 500 mg initially and 250 mg/day thereafter (36). In 11 days she developed malaise, light-headedness, and urinary retention. After the insertion of a urinary catheter she developed a monomorphic ventricular tachycardia with left bundle branch block. She was successfully cardioverted and the electrocardiogram showed a markedly prolonged QT interval of 560 ms and T wave inversion in the anterolateral leads. Her serum disopyramide concentration, which had previously been 2.6 μg/ml, was 11 μg/ml.
- In a 59-year-old man taking disopyramide 50 mg/day the addition of clarithromycin 600 mg/day caused hypoglycemia, and the serum disopyramide concentration rose from 1.5 to 8.0 μg/ml (37). The ratio of plasma insulin concentration to blood glucose concentration was greatly increased, suggesting that hypersecretion of insulin was responsible, confirming the likelihood that the hypoglycemia was due to disopyramide intoxication secondary to inhibition of its metabolism by clarithromycin. There was also slight prolongation of the QT_c interval, but no cardiac dysrhythmias. After withdrawal of clarithromycin and disopyramide both the blood glucose concentration and the QT_c interval returned to normal.
- An 86-year-old woman presented with severe hypoglycemia after clarithromycin 500 mg/day had been added for 3 days to her other therapy, which included disopyramide 500 mg/day (38). The hypoglycemia resolved completely after withdrawal of disopyramide.

Potassium-sparing drugs

Hyperkalemia has been reported to increase the risk of dysrhythmias in patients taking disopyramide (39), and disopyramide should therefore be used with caution in patients who are taking drugs that can increase body potassium, such as potassium-sparing diuretics and ACE inhibitors.

Practolol

The combination of disopyramide and practolol can cause profound sinus bradycardia and asystole (40,41).

Warfarin

Disopyramide can potentiate the effects of warfarin (42), although it is not known whether this is of any importance (43).

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Disulfiram

General Information

Disulfiram (tetraethylthiuram) has been widely used since the late 1940s to facilitate abstinence from alcohol (1). Concomitant use of alcohol during disulfiram therapy results in an autonomic symptom complex that can involve headache, flushing, nausea and vomiting, sweating, tachycardia, hypotension, and confusion. The mechanism of action of disulfiram is inhibition of aldehyde dehydrogenase; alcohol is metabolized to acetaldehyde, which accumulates (2).

Sulfiram

Sulfiram is similar in structure to disulfiram, but has one less sulfur atom in its central chain. It is a much weaker inhibitor of aldehyde dehydrogenase than disulfiram and is used in the topical treatment of scabies.

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General adverse effects

Several adverse effects of disulfiram itself (as opposed to the aldehyde that it allows to accumulate) have been described. They include neurological reactions and skin reactions, but hepatotoxicity is the only previously reported life-threatening reaction, and it is rare (3).

Disulfiram modifies the metabolism of many drugs by inhibiting the cytochrome CYP2E1. Adverse reactions to disulfiram occur with a frequency of 1 in 200 to 1 in 2000 per treatment-year (4). The death rate is about one per 25 000 patients per year, and hepatic failure accounts for most of these (4). Allergic reactions can occur. Tumor-inducing effects have not been described.

Organs and Systems

Cardiovascular

Disulfiram in a dose of 250–300 mg/day does not affect pulse rate, blood pressure, or plasma noradrenaline concentrations, but 500 mg/day causes an increase in plasma noradrenaline, increased systolic blood pressure both recumbent and erect, and an increased erect pulse rate. The raised blood pressure does not reach hypertensive values, but the results suggest increased sympathetic nervous system activity in patients who take disulfiram. Caution should therefore be exercised in using disulfiram in hypertensive patients. Close monitoring of blood pressure is advised, and the dose of disulfiram should preferably be reduced to 250 mg/day (5).

Cardiac dysrhythmias occurred during a disulfiram + alcohol test in a 48-year-old man who had been an alcoholic for 5 years (6). After drinking a test amount of alcohol, he developed flushing, nausea, vomiting, sweating, dyspnea, and hyperventilation, palpitation, tremor, confusion, and syncope. The electrocardiogram showed atrial fibrillation and non-sustained bouts of ventricular tachycardia of 7–8/minute. He also had severe hypotension.

Nervous system

Disulfiram can cause a polyneuritis (7), which can occasionally be fulminant and irreversible.

- A 39-year-old woman developed a severe sensori motor polyneuritis after taking ethanol and disulfiram in high doses (8). The disorder was similar to other cases of disulfiram neuropathy, but was acute and more severe.

The neurotoxic effects of disulfiram have been compared with those of carbon disulfide, a disulfiram metabolite (9). The results suggested that carbon disulfide may be responsible for the behavioural and neurological adverse effects of disulfiram. If so, other toxic effects of carbon disulfide might follow administration of high doses of disulfiram, such as parkinsonism, psychotic behaviour, and encephalopathy.

Disulfiram-induced neurotoxicity caused parkinsonism in a man who had been an alcoholic for 10 years (10).

- A 52-year-old alcoholic stopped drinking in August 1996 and started to take disulfiram 500 mg/day. His usual medications had been aspirin 300 mg/day and levothyroxine 100 µg/day. He had had severe loss of visual acuity (2/10) in the left eye 3 months before admission. He was admitted to hospital because of drowsiness. Neurological examination showed severe hypophonia, difficulty in swallowing, and mild rigidity of the limbs. Disulfiram was withdrawn but the other medications were maintained. His drowsiness improved over 5 days, but he remained bradykinetic, with extrapyramidal hypertonia, facial hypomobility, and abnormal posture. His gait was slow and shuffling.
- A 20-year-old woman was referred for implantation of an intrathecal baclofen pump (11). She had had severe dystonia and spasticity following a suicide attempt with disulfiram at age 14 years. T1-weighted MRI scanning of her brain showed bilateral globus pallidus infarction. She had profound relief of spasticity after intrathecal test injections of baclofen and underwent implantation of an intrathecal baclofen pump. Her spasticity subsequently improved.

Sensory systems

Retrobulbar neuritis can be part of a disulfiram-induced polyneuritis, with dramatic reduction in visual acuity and impaired colour perception (SEDA-10, 349) (12). This complication is rare but serious. It occurs at dosages of 500 mg/day, and there is a latent period of 2–36 months. Tobacco abuse is thought to be a predisposing factor.

Disulfiram can cause optic neuropathy (13,14).

Psychological, psychiatric

Disulfiram can cause distressing neuropsychiatric effects including paranoia, impaired memory and concentration, ataxia, dysarthria, and frontal release signs (signs that can be indicative of permanent structural damage or temporary metabolic or infectious changes to the brain's frontal lobes), such as snout and grasp reflexes (2,15). The mechanisms are not properly understood, but adverse effects develop more frequently in subjects with low plasma dopamine beta-hydroxylase activity. In one study, a research subject with low dopamine beta-hydroxylase activity developed a schizophrenic reaction to disulfiram; it would be useful to know whether determining blood dopamine beta-hydroxylase activities predicts the risk of adverse reactions to disulfiram (16).

Of 52 patients with alcohol dependence/abuse who were given disulfiram 250 mg bd after food, six developed psychotic symptoms; all had a mood disorder but no thought disorder (17). The psychotic symptoms remitted completely after withdrawal and a short course of antipsychotic therapy, except in one patient who had to be given lithium.

- A 47-year-old man with alcohol abuse took disulfiram (18). He developed a psychosis while taking it and for 2 weeks after. He stated that he had not taken alcohol. He was successfully treated with antipsychotic drugs. Afterwards it was discovered that his family history was positive for schizophrenia; it is therefore possible

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that he was more vulnerable to develop psychosis due to disulfiram.

Prolonged toxic delirium related to disulfiram and alcohol intake has been reported (19). The predominant presenting feature was neuropsychiatric rather than autonomic symptoms.

- A 50-year-old woman with a history of bipolar disorder type I and alcohol dependence taking disulfiram had a 4-day history of a change in mental status, including visual hallucinations and deficits in orientation and concentration. Other features included a tachycardia and non-focal neurological signs. Extensive metabolic, infectious, and neurological investigations revealed no abnormalities that alone could explain her acute confusional state. It was subsequently discovered that she had drunk alcohol on at least two separate occasions while taking disulfiram before her change in mental status, and that a similar, although shorter, episode had occurred previously.

Gastrointestinal

In a colostomy patient, the smell of the colostomy was present only so long as disulfiram exposure continued (20). The cause was obscure.

Liver

About 25 cases of disulfiram-induced liver damage (apparently as a result of an immunological mechanism) have been reported, some fatal. The cause is not known, since many alcoholic patients who use disulfiram have pre-existing liver damage. Nevertheless, it is believed that disulfiram does sometimes trigger serious liver damage (SEDA-10, 438); severe hepatitis, sometimes fatal, has been reported (21–24). Liver function should be checked before giving disulfiram, especially since there may be a long history of alcohol abuse (25).

The Swedish adverse drug reactions register, SWEDIS, received 149 case reports of 157 adverse reactions associated with disulfiram from 1971 to 1999, of which 63 cited disorders of the liver and biliary tract (26). Of these 63 reports, seven were classified as serious. In three cases of severe liver damage with a fatal outcome, disulfiram was suspected to have caused the reaction. If signs of liver damage appear, it is recommended that disulfiram be withdrawn and liver function tests performed.

Skin

A fatal rash has been attributed to disulfiram.

- A 47-year-old man developed a generalized rash and malaise (27). He had chronic alcoholism and had taken disulfiram 250 mg/day for 1 month. He denied previous liver disease, blood transfusions, or having taken hepatotoxic drugs or alcohol. He was given clarithromycin 500 mg bd and paracetamol 500 mg tds and 1 week later noticed non-pruritic cutaneous maculopapular lesions on the legs, which spread to the rest of his body, excluding the palms and soles. His temperature was 41°C, his blood pressure 90/60 mmHg, and his heart rate 130/minute. There were no signs of encephalopathy. His conjunctivae were yellow. There was furfuraceous desquamation on his face and confluent erythematous annular lesions with a purpuric component on the groins, thighs, and the undersides of his arms. There was edema of the hands and feet. During the next several days the skin lesions worsened. He developed blisters, initially covering less than 10% of the body surface, but then extending all over the body. He developed septic shock and, despite supportive measures, died.
- A 49-year-old woman developed pruritic erythema 2 weeks after the implantation of a modified-release formulation of disulfiram, Esperal, in her left buttock (28). Three months later she started drinking alcohol and developed generalized erythema with numerous papules on her face and limbs; the dermatitis at the site of the implant became more severe. The serum ethanol concentration was 270 mg/dl. Methanol was not detected.
- A 55-year-old man developed yellow palms and soles while taking disulfiram (29).

The authors speculated that the mechanism was inhibition of carotene metabolism by disulfiram.

Immunologic

Allergic reactions to disulfiram tend to be limited (30). However, the possibility of hypersensitivity should be borne in mind in patients who have had allergic reactions in the past, regardless of the allergen concerned.

Second-Generation Effects

Pregnancy

Disulfiram should not be used in women who may become pregnant because of potential teratogenicity (31).

Drug–Drug Interactions

Alcohol

The interaction of disulfiram with alcohol, the metabolism of which is interfered with at the aldehyde stage, is the basis for its therapeutic use; disulfiram renders alcohol intake unpleasant, and dangerous if much alcohol is taken.

Sulfiram is related to disulfiram, and after repeated topical treatment the ingestion of alcohol can rarely cause a similar reaction, with generalized flushing, malaise, and rhinorrhea (32).

Amitriptyline

Amitriptyline potentiates the disulfiram reaction (33).

Benzodiazepines

Disulfiram inhibits the hepatic metabolism of other drugs and can prolong their effects. The half-lives of chlordiazepoxide and diazepam increase significantly after disulfiram, while the clearances are reduced, with accumulation. No change in half-life or clearance has been noted for oxazepam (which is not metabolized in

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the liver) (34). The benzodiazepines reduce the disulfiram reaction to alcohol.

Caffeine

Disulfiram reduces caffeine clearance (35).

Cocaine

Simultaneous abuse of cocaine and alcohol is common and alcohol reduces negative stimulant effects and potentiates "highs." Disulfiram has therefore also been used to treat cocaine dependence, with the rationale that an inability to modulate the effects of cocaine with alcohol may reduce cocaine use.

Six volunteers with cocaine dependence and alcohol abuse or dependence, mean age 32 years, took disulfiram 250 mg/day or placebo (36). After 3 days they participated in cocaine administration sessions (one session daily for 3 days). The study drugs were separated by at least 5 days, based on the time needed for enzyme regeneration (37). After disulfiram, cocaine significantly increased heart rate and blood pressure, and they remained high when plasma cocaine concentrations were falling at later times, and were greatest for cocaine 2 mg/kg. These findings contrast with those obtained when multiple doses of cocaine alone have been given to healthy volunteers, in whom there was evidence of acute tolerance to the cardiovascular effects of cocaine (38,39). Disulfiram therefore has potential as a treatment for cocaine + alcohol abuse, but could also increase the risk of toxicity as a result of its pharmacokinetic interaction with cocaine.

Warfarin

Bad breath has been reported in patients taking disulfiram concurrently with warfarin (40).

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Diuretics

See also Individual agents

General Information

Diuretics are among the most widely used drugs, particularly for the treatment of hypertension and of various conditions associated with sodium retention.

Considering the widespread use of diuretics over a long period (chlorothiazide was introduced in 1957) their safety record is remarkable, and reports of adverse effects of any significance with the best-known drugs of this type are uncommon.

When problems do arise they usually reflect either interactions, which with caution could have been avoided, or relative overdosage. In the course of time the recommended antihypertensive doses of diuretics have been reduced, and some adverse effects that were noted in the early years are now of less significance; these include hypotension, dehydration, reduction of the glomerular filtration rate, and severe hypokalemia. Continued use of thiazides in excessive doses may reflect ignorance of their very flat dose–response curve (1). At currently recommended low doses, diuretics improve overall quality of life, even in asymptomatic patients with mild hypertension (2). The large HANE study (3) provided no evidence of superior efficacy or tolerability of new classes of antihypertensive drugs.

Uses

Hypertension

The popularity of thiazide diuretics in the management of hypertension reflects three major factors (4):

- recognition of the effectiveness of much lower dosages than those used previously, thereby providing good antihypertensive efficacy with fewer adverse effects (SED-13, 558);
- the excellent reductions in morbidity and mortality that have been achieved by low-dosage diuretic-based therapy in multiple randomized, controlled trials (SED-13, 558);
- the increasing awareness that some diuretic-induced shrinkage of effective blood volume is essential for adequate treatment of most patients with hypertension.

The Seventh Joint Committee Report on Detection, Evaluation, and Treatment of High Blood Pressure (5) concluded that a diuretic should be the first-step drug of choice, unless there are specific indications for other drugs. Although there may be theoretical advantages of certain newer types of drugs, the data thus far have not consistently shown that these drugs are more effective in reducing morbidity and mortality than therapy based on diuretics or beta-blockers (6). Emphasis is correctly placed on the important role of ACE inhibitors in retarding progression of renal insufficiency in diabetic and other nephropathies (7). However, in these circumstances, ACE inhibitors are added to a background of other antihypertensive therapies, commonly including a diuretic. Therefore, the renal protective action of ACE inhibitors is in the context of combination regimens. The ability of low doses of diuretics to enhance efficacy has been demonstrated for all other classes of drugs (8). Moreover, the tendency for increased retention of sodium by the hypertensive kidney when non-diuretic drugs cause the blood pressure to fall has long been recognized to contribute to loss of antihypertensive efficacy, which can be restored immediately by the addition of a diuretic.

Clinical trials

The LIVE (Left ventricular regression, Indapamide Versus Enalapril) study was a 1-year, prospective, randomized, double-blind comparison of modified-release indapamide 1.5 mg and enalapril 20 mg in reducing left ventricular mass in 411 hypertensive patients with left ventricular hypertrophy (9). For equivalent reductions in blood pressure, indapamide was significantly more effective than enalapril in reducing left ventricular mass index.

The effectiveness of specific first-line antihypertensive drugs in lowering blood pressure and preventing adverse outcomes has been systematically quantified in a meta-analysis of randomized controlled trials that lasted at least 1 year, and compared one of six possible first-line antihypertensive therapies either with another of the six drug therapies or with no treatment (10). Of 38 trials identified, 23 in 50 853 patients met the inclusion criteria. Four drug classes were evaluated: thiazides (21 trials), beta-blockers (5 trials), calcium antagonists (4 trials), and ACE inhibitors (1 trial). In five comparisons of thiazides with beta-blockers, thiazides were associated with a significantly lower rate of withdrawal because of adverse effects (RR = 0.69; 95% CI = 0.63, 0.76). In the trials that had an untreated control group, low-dose thiazide therapy was associated with a significant reduction in the risk of death (RR = 0.89; CI = 0.81, 0.99), stroke (RR = 0.66; CI = 0.56, 0.79), coronary heart disease (RR = 0.71, CI = 0.60, 0.84), and cardiovascular events (RR = 0.68; CI = 0.62, 0.75). Low-dose thiazide

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therapy reduced the absolute risk of cardiovascular events by 5.7% (CI = 4.2, 7.2); the number needed to treat (NNT) for approximately 5 years to prevent one event was 18. High-dose thiazide, beta-blocker, and calcium antagonist therapy did not significantly reduce the risk of death or coronary heart disease. Thiazides were significantly better than the other drugs in reducing systolic pressure, but antihypertensive efficacy did not differ between the high- and low-dose thiazide trials.

In the UK Medical Research Council (MRC) trial, the outcome of antihypertensive treatment based on diuretics was compared with placebo in a very large number of hypertensive subjects (11). Treatment based on a thiazide did not increase the incidence of coronary events or sudden death; indeed, thiazide-based treatment reduced the incidence of strokes by 67% and of all cardiovascular complications by 20%. It should be noted that the dose of bendroflumethiazide used in the MRC trial (10 mg/day) is now known to be unnecessarily high and that it was used without prophylaxis against hypokalemia. Even so, a subgroup analysis of data from the MRC Trial provided no evidence that the association between major electrocardiographic abnormalities and an increased likelihood of a clinical event was strengthened by bendroflumethiazide treatment (12).

A series of trials in elderly hypertensive subjects has shown a very pronounced reduction in cardiac events as a result of treatment based on thiazide diuretics. In the European Working Party on Hypertension in the Elderly (EWPHE) trial (13), total cardiovascular deaths were reduced by 38%, all cardiac deaths by 43%, and deaths due to myocardial infarction by 60%. Benefits in the Systolic Hypertension in the Elderly Program (SHEP) included a reduction in fatal and non-fatal myocardial infarction of 25% and major cardiovascular events of 32% (14) and were seen in those with and without electrocardiographic abnormalities at entry. The risk of heart failure was also reduced in patients taking chlortalidone-based therapy (15). Relative risk was similar in patients with and without non-insulin dependent diabetes mellitus; absolute risk reduction was twice as great in the diabetic subjects (16). The Swedish Trial of Old Patients with Hypertension (STOP-Hypertension) reported a significant reduction in myocardial infarction and all-cause mortality (17). In the MRC Trial in elderly adults (18), diuretic treatment reduced coronary events by 44% and fatal cardiovascular events by 35%.

In the MRC trials (11,18), the IPPPSH trial (19), and the HAPPHY trial (20), antihypertensive treatment based on a thiazide diuretic was compared with treatment based on a beta-blocker. The results with diuretic treatment were no less favorable as regards cardiac events than those when using a "cardioprotective" beta-blocker (20). In the IPPPSH trial, the group using no beta-blockers (but with a higher incidence of diuretic use and of hypokalemia) showed no excess of cardiac events, even in patients who had an abnormal electrocardiogram when they entered the study. The MRC trial in elderly adults (18) showed a significantly lower risk of cardiovascular events with the diuretic compared with the beta-blocker, raising the possibility that diuretics confer benefit through a mechanism other than the reduction of blood pressure.

In the MAPHY study (21), total mortality was significantly lower for metoprolol than for thiazide, because of fewer deaths from coronary heart disease and stroke. However, the MAPHY study population comprised a subgroup of about half of the patients from the HAPPHY trial followed for an extended period. The difference in mortality between metoprolol and diuretics did not emerge during this extended follow-up, but was present during the first period of observation (that is during the HAPPHY trial), when there was no overall difference between beta-blockers and thiazides. Therefore, patients treated with atenolol in the HAPPHY trial must have fared worse than those treated with thiazides and much worse than those treated with metoprolol. Since there was no prior hypothesis for a difference between atenolol and metoprolol (and no plausible explanation for it), it seems reasonable to conclude that the apparent advantage of metoprolol was a chance finding produced by post-hoc subgroup analysis. The MAPHY study should be interpreted with extreme caution.

A review of the large trials has shown that the reduction in the incidence of events with usual thiazide-based treatment is 16% (95% CI = 8, 23%) against the prediction from epidemiological studies of 20–25% (22). This shortfall in benefit could easily be due to chance.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), over 40 000 participants aged 55 years or older with hypertension and at least one other risk factor for coronary heart disease were randomized to chlortalidone, amlodipine, doxazosin, or lisinopril (23,24). Doxazosin was discontinued prematurely because chlortalidone was clearly superior in preventing cardiovascular events, particularly heart failure (24). Otherwise, mean follow-up was 4.9 years. There were no differences between chlortalidone, amlodipine, and lisinopril in the primary combined outcome or all-cause mortality. Compared with chlortalidone heart failure was more common with amlodipine and lisinopril, and chlortalidone was better than lisinopril at preventing stroke. The authors concluded that diuretics are superior to other antihypertensive drugs in preventing one or more major form of cardiovascular disease and are less expensive. They should therefore be used as the preferred first-step treatment of hypertension. Although the design, conduct, and analyses of ALLHAT can be criticized (25), it was a huge, prospective, randomized study and its results suggest that diuretic-based therapy is unsurpassed in the management of hypertension.

Adverse effects

The frequencies and the profile of adverse effects of five major classes of antihypertensive agents have been assessed in an unselected group of 2586 chronically drug-treated hypertensive patients (26). This was accompanied by a questionnaire-based survey among patients attending a general practitioner. The percentages of patients who reported adverse effects spontaneously, on general inquiry, and on specific questioning were 16, 24, and 62% respectively. The percentage of patients in whom discontinuation was due to adverse effects with diuretics was 2.8%. The authors did not find a significant effect of age on the pattern of adverse effects. Women reported more effects and effects that were less related to the pharmacological treatment.

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Heart failure

Loop and thiazide diuretics

Loop and thiazide diuretics have been the mainstay of treatment for symptomatic heart failure (27), relieving symptoms and improving cardiovascular hemodynamics. However, despite their widespread use, they have not been shown to improve survival in patients with heart failure. As it is not feasible to conduct such a trial in patients with pulmonary edema due to heart failure, the place of diuretic therapy in the management of heart failure appears secure.

Aldosterone receptor antagonists

Although they are widely used in the management of heart failure, loop and thiazide diuretics have not been shown to prolong survival. However, spironolactone and eplerenone must be added to the list of medications that offer improved survival for patients with heart failure.

In the Randomized Aldactone Evaluation Study (RALES) in 1663 patients with New York Heart Association (NYHA) class III (70%) or IV (30%) symptoms and an ejection fraction less than 35%, the addition of spironolactone 25 mg/day to conventional treatment (an ACE inhibitor, a loop diuretic, in most cases digoxin, and in 11% a beta-blocker) for an average of 24 months lowered the risk of all-cause mortality by 30% (from 46% to 35%), death from progressive heart failure, and sudden death (28). There were similar reductions in hospital admissions for worsening heart failure and for all cardiac causes. The magnitude of the overall effect was similar and additional to the proven benefit from ACE inhibition in severe heart failure.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), in 6632 patients with an acute myocardial infarction complicated by left ventricular dysfunction and heart failure, the addition of eplerenone 25–50 mg/day to optimal medical therapy significantly reduced all-cause mortality by 15% and cardiovascular mortality by 17% over a mean follow-up period of 16 months; hospitalization rates were also reduced (29).

Mechanisms

Several mechanisms have been postulated to underlie the benefits of aldosterone receptor antagonists in heart failure (30). Aldosterone-induced cardiac fibrosis may reduce systolic function, impair diastolic function, and promote intracardiac conduction defects, with the potential for serious dysrhythmias. Aldosterone may also increase vulnerability to serious dysrhythmias by other mechanisms. The diuretic and hemodynamic effects of spironolactone in RALES and EPHESUS were subtle, and there were no significant changes in body weight, sodium retention, or systemic blood pressure.

Clinical use

The safe and effective dose of spironolactone remains uncertain (30). Pilot data from RALES showed that the frequency of hyperkalemia and uremia increased with doses of spironolactone above 50 mg/day (SEDA-20, 202). Doses up to 50 mg/day are appropriate, with adequate monitoring of serum electrolytes and renal function. The optimum strategy in the face of hyperkalemia, uremia, or symptomatic hypotension (reduction in frequency of spironolactone to alternate-day dosing, reduction in dose of ACE inhibitor, and/or increased dose of loop diuretics) is unclear, and how frequent such dose adjustments were necessary in RALES was not stated (28).

Adverse effects

The only frequent adverse effects were gynecomastia, breast pain, or both in 10% of men. The rate of discontinuation because of these events was 2%. The risk of gynecomastia should not be an argument against the use of spironolactone in men with severe heart failure, since it reduces both morbidity and death.

At the dose of spironolactone used in RALES (28), there was serious hyperkalemia, defined as a serum potassium concentration over 6.0 mmol/l, in 2% (compared with 1% of controls) and uremia was rare. However, a serum potassium concentration over 5 mmol/l and a serum creatinine concentration over 220 µmol/l were exclusion criteria. Although 29% of patients in the spironolactone group used potassium supplements, the benefit of spironolactone in these patients was similar to that in patients who did not.

In EPHESUS, as in RALES, the exclusion criteria included a serum potassium concentration over 5 mmol/l and a serum creatinine concentration over 220 µmol/l. There was serious hyperkalemia (a serum potassium concentration of 6.0 mmol/l or over) in 5.5% of those who took eplerenone and in 3.9% of those who took placebo. In each treatment group the incidence of hyperkalemia was higher among patients with the lowest baseline creatinine clearances.

The use of diuretics in patients with renal insufficiency

About 84% of the patients in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL) required diuretic therapy to effect blood pressure control (31). Although not specifically reported, a similarly high proportion of patients were likely to have required diuretic therapy to reach the target blood pressure in the Irbesartan Diabetic Nephropathy Trial (IDNT) (32). These studies remind us once again of the importance of targeting volume control in order to reduce blood pressure in patients with chronic renal insufficiency.

In a cohort study of 552 patients with acute renal insufficiency studied from 1989 to 1995 diuretic use was associated with a significant increase in the risk of death or non-recovery of renal function (33). This increased risk was largely borne by patients who were relatively unresponsive to diuretics. Although this study was observational, which prohibits causal inference, it is unlikely that diuretics afford any material benefit in the setting of acute renal insufficiency.

Thiazide and loop diuretics

Various factors influence the choice of a diuretic in patients with renal insufficiency. First, it is widely believed that thiazide diuretics are ineffective once renal

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function falls below a creatinine clearance of 40–50 ml/minute. Diuretics need to enter the renal tubule to reach their luminal sites of action. In renal insufficiency, higher diuretic doses are required to overcome disease-related impediments to drug delivery to their sites of action. In the case of the loop diuretics the common practice is to titrate the dose of the diuretic until the desired response occurs (34). No such titration generally occurs with thiazide-type diuretics; consequently they are likely to fail, although for no reason other than their not being titrated to a truly effective dose. The true basis for "failure" of thiazide-type diuretics in patients with renal insufficiency resides in the fact that these diuretics are not of sufficient maximal efficacy to produce adequate volume control in these typically volume-expanded patients (35).

However, resistance to loop diuretics can occur by various mechanisms (36). These include poor adherence to therapy, poor absorption, progressive worsening of heart failure, excess volume loss, renal insufficiency, secondary hyperaldosteronism, and hypertrophy of the tubular cells of the distal nephron. Resistance due to inadequate drug absorption—either its speed or extent—is common with furosemide, which is poorly absorbed (34). Once recognized, this hurdle to response can be overcome by using loop diuretics that are predictably well absorbed, such as bumetanide and torasemide or by giving intravenous furosemide (37).

If loop diuretics fail to produce the desired diuretic response, combination diuretic therapy can be considered by adding a thiazide or a thiazide-like diuretic, such as metolazone. Such combinations are generally quite successful in both advanced congestive heart failure and late-stage chronic renal insufficiency, although excessive diuresis is a constant risk with such combinations. An excess diuresis with combination loop plus thiazide diuretic therapy is best managed by temporarily withdrawing both diuretics. Generally, diuretic doses are reduced when therapy is resumed (38).

An alternative in the diuretic-resistant patient is the use of continuous infusions of loop diuretics rather than bolus diuretic therapy. Such infusions can also be given with a small volume of hypertonic saline, with good effect (39). The reasons why continuous infusions of loop diuretics work when bolus doses have failed may relate to a more efficient time-course of diuretic delivery and/or less activation of the renin–angiotensin system (40). Furosemide and torasemide may be the safest loop diuretics to be given as infusions, in that infusion of bumetanide has been associated with severe musculoskeletal symptoms (41).

The importance of volume control in patients with renal insufficiency extends beyond its effect on blood pressure. Accordingly, the addition of hydrochlorothiazide can overcome the blunting by a high sodium intake of the therapeutic efficacy of ACE inhibition on proteinuria (42). This presumably relates to volume-related activation of the renin–angiotensin system.

Finally, loop diuretics reduce the metabolic demand of tubular cells, reducing oxygen requirements and thereby, in theory, increasing resistance to ischemic insults and perhaps other toxic circumstances. This property has been advanced as the basis for using diuretics in acute renal insufficiency. Although an attractive hypothesis to date, there is no compelling evidence to suggest any benefit from loop diuretics in established acute renal insufficiency. Alternatively, loop diuretics can convert oliguric to non-oliguric acute renal insufficiency, thereby easing the fluid restriction that would otherwise be necessary in such patients (43).

Aldosterone receptor antagonists

It is no longer appropriate to consider the endocrine or paracrine properties of aldosterone as being restricted to the classical target cells. Hemodynamic and humoral actions of aldosterone have important clinical implications for the pathogenesis of progressive renal disease, and may therefore affect future antihypertensive strategies. Initially, one might anticipate that the adverse effects of aldosterone could be attenuated merely by blocking aldosterone release with either an ACE inhibitor or angiotensin-II receptor antagonists. However, this appears not to be the case. Several investigators have now shown that ACE inhibitors acutely reduce aldosterone concentrations, but that with continued use this suppression fades. Thus, the presumption that ACE inhibitors would suppress the production of both aldosterone and angiotensin-II was incorrect. So, although ACE inhibitors and angiotensin-II receptor antagonists are individually very effective in retarding disease progression, additional benefit may be realized with a concurrent aldosterone receptor antagonist. As observed in clinical studies of congestive heart failure, as well as in animals with renal disease, antagonism of aldosterone receptors protects against end-organ damage through a combination of both hemodynamic and direct cellular actions (44).

An important consideration regarding the feasibility of aldosterone receptor antagonist therapy in chronic renal insufficiency is the risk of provoking hyperkalemia. Many patients with chronic renal insufficiency are already taking an ACE inhibitor or an angiotensin-II receptor antagonist, with the attendant risk of hyperkalemia. Despite such concerns, the results of the RALES and EPHESUS trials have been reassuring (28). In those studies, patients taking an ACE inhibitor who were randomized to spironolactone or eplerenone 25–50 mg/day had only small increases in potassium concentrations. Although the differences between those who took aldosterone receptor antagonists and those who took placebo were statistically significant, the mean increases were not clinically important, and serious hyperkalemia was uncommon. However, in clinical practice the risk of hyperkalemia may be greater (45), and close laboratory monitoring and judicious use of these drugs is necessary to minimize the risk.

Although it is an effective aldosterone receptor antagonist, spironolactone is limited by its tendency to cause undesirable sexual adverse effects. At standard doses, impotence and gynecomastia can occur in men, and premenopausal women can have menstrual disturbances. These adverse effects, caused by the binding of spironolactone to progesterone and androgen receptors, are substantial causes of drug withdrawal. In the RALES study there was a 10% incidence of gynecomastia or breast pain in men, compared with 1% with placebo, and significantly more patients discontinued treatment (2 versus 0.2%).

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Although troublesome, these adverse effects are reversible and dose-related. The advent of selective aldosterone receptor antagonists, such as eplerenone, should reduce these adverse effects and thereby improve patient compliance. In EPHESUS there was no increase in the incidence of gynecomastia, breast pain, or impotence in men or menstrual irregularities in women who took eplerenone.

Organs and Systems

Cardiovascular

Cardiac dysrhythmias

Changes in potassium metabolism supposedly cause electrical instability in the heart, cardiac dysrhythmias, and increased mortality; replacement of potassium has been said to eliminate the risk of dysrhythmias (46–48). Mild hypokalemia might be expected to cause dysrhythmias in patients with serious organic heart disease (cardiomegaly, an abnormal electrocardiogram, frequent ventricular extra beats before treatment). However, the evidence suggests that hypokalemia after myocardial infarction is not the cause of dysrhythmias, but that both are the result of excess catecholamines. Furthermore, although hypertensive patients with left ventricular hypertrophy have an increased frequency of ventricular dysrhythmias, extra beats do not increase in frequency during diuretic treatment, even in the face of profound hypokalemia (49).

Early evidence linking thiazide-induced hypokalemia with dysrhythmias and sudden death was indirect and tenuous at best (50,51). One study suggested that diuretics are not responsible for the relation between hypokalemia and ventricular fibrillation in acute myocardial infarction (50). Chronic preoperative hypokalemia due to diuretics was not a risk factor for intraoperative dysrhythmias (52). Two large studies using 24-hour electrocardiographic monitoring failed to show a relation between diuretic-induced hypokalemia and ventricular dysrhythmias (53,54).

However, a retrospective analysis of 6797 patients with ejection fractions below 0.36 enrolled in the Studies Of Left Ventricular Dysfunction (SOLVD) was conducted to assess the relation between diuretic use at baseline and the subsequent risk of dysrhythmic death (54). Patients who were taking a diuretic at baseline ($n = 2901$) were significantly more likely to have such an event than those not taking a diuretic ($n = 2896$): 3.1 versus 1.7 per 1000 person-years. On univariate analysis and after controlling for important co-variates, the relation remained significant (relative risks 1.85 and 1.37 respectively). However, the association was seen only with non-potassium-sparing diuretics ($n = 2495$; relative risk 1.33); for potassium-sparing diuretics, alone or in combination with a non-potassium-sparing diuretic ($n = 406$), the relative risk was 0.90.

These data suggest that diuretic-induced potassium disturbances can cause fatal dysrhythmias in patients with left ventricular systolic dysfunction. SOLVD were not randomized trials of the risk of dysrhythmic death caused by diuretics. On average, patients retaking diuretics not only had lower serum potassium concentrations, but were also older, had more severe heart failure and were more likely to be taking antidysrhythmic drugs at baseline, although they had fewer indicators of ischemic heart disease. Even controlling for bias in multivariate analysis does not exclude the influence of unrecognized confounders. It is unknown whether diuretics were continued or changed during the 3 years of the trial. Thus, it remains uncertain that diuretic therapy is related to a risk of sudden dysrhythmic death in patients with heart failure.

Diuretic-induced hypokalemia is undoubtedly associated with a risk of serious ventricular dysrhythmias if diuretics are co-administered with drugs that prolong the QT interval (SED-13, 563). Diuretics increase the risk of torsade de pointes during antidysrhythmic drug therapy, independent of serum potassium concentration (54). The list of cardiac and non-cardiac drugs that prolong the QT interval continues to lengthen (54). It includes various antidysrhythmic drugs, including ibutilide, almokalant, and dofetilide; antimicrobial drugs, including clarithromycin, clindamycin, co-trimoxazole, pentamidine, imidazoles (such as ketoconazole), some fluoroquinolones, and antimalarial drugs (quinine, halofantrine); histamine H_1 receptor antagonists (terfenadine and astemizole); the antidepressant zimeldine; antipsychotic drugs (pimozide and sertindole); tricyclic/tetracyclic antidepressants; and cisapride. Particular care should be taken to avoid diuretic-induced hypokalemia when any of these agents is co-prescribed.

Coronary heart disease

There is no valid evidence that diuretics contribute to myocardial infarction, sudden death, or a failure of antihypertensive treatment or other risk factor interventions to prevent coronary deaths (50). An association between diuretics and sudden death has been suggested only in selected subset analyses, which allow no valid conclusions. Even in subjects with electrocardiographic abnormalities before treatment, there is no sound or consistent evidence to support the suggestion that diuretics predispose to sudden death.

Two retrospective case-control studies have reported an increased risk of cardiac arrest in hypertensive patients treated with thiazide-type diuretics (55,56). The risk was less among those treated with low-dose thiazides (equivalent to hydrochlorothiazide 25 mg/day) or with thiazides plus potassium-sparing drugs. The case-control design lacks one of the major advantages of randomized clinical trials, a tendency to equalize unknown, but important, differences between the comparison groups. Underadjustment is usual in case-control studies; for example, patients with more severe hypertension were more likely to have been treated with higher doses and less likely to have received potassium-sparing drugs because of renal dysfunction. Failure to randomize treatment tends to exaggerate differences between groups. Data from the prospective observational Gothenburg study suggested that metabolic changes during long-term treatment with antihypertensive drugs (predominantly beta-blockers and thiazides) are not associated with increased risk of coronary heart disease (57).

Metabolism

Despite their safety record, speculation persists that the metabolic effects of long-term diuretic treatment

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predispose to myocardial infarction or sudden death, and that diuretic treatment may therefore be hazardous. It is worth noting that much of this speculation is found outside the columns of the legitimate medical press (SEDA-10, 185). The supposed risks of diuretics are broadcast in countless symposium proceedings, monographs, and such like, sponsored by pharmaceutical companies with a vested interest in diverting prescriptions from diuretics to other drugs. Needless to say, these publications do not present a balanced view. Studies of dubious quality are published repeatedly without ever appearing in refereed journals, and eventually come to be cited in independent reviews and articles. There can be no doubt that these publications have a large impact on prescribing practices.

It is relatively easy to foster these concerns, particularly since antihypertensive therapy would be expected to prevent myocardial infarction and sudden death, but in selected studies does not appear to do so. To explain this, it is suggested that the beneficial effects of lowering blood pressure are offset in part by adverse effects related to thiazide-induced biochemical disturbances. Hypokalemia and hypomagnesemia might, for example, be dysrhythmogenic and cause sudden death; or hyperlipidemia and impaired glucose tolerance might be atherogenic and promote myocardial infarction. Some authors have suggested that thiazides should certainly be avoided in left ventricular hypertrophy and coronary heart disease, because of an increased risk of ventricular extra beats (58,59), and that diuretics are not appropriate options in those who already have hyperglycemia, hyperuricemia, or hyperlipidemia (60). The argument has been taken ad absurdum by a suggestion that the use of diuretics as first-line treatment of hypertension is illogical (27). Others have argued effectively that we should not be impressed by such speculations and that treatment should be based on long-term experience (61), a conclusion similar to that reached in volumes of SEDA, from SEDA-9 to SEDA-19.

Impaired glucose tolerance and insulin resistance

There is little doubt that high dosages of diuretics carry an appreciable risk of impairing diabetic control in patients with established diabetes mellitus. However, their role in causing de novo glucose intolerance is not clear (63). Long-acting diuretics are more likely to alter glucose metabolism. Impaired glucose tolerance is a relatively rare complication with loop diuretics, although isolated cases of non-ketotic hyperglycemia in diabetics have been described (SED-9, 350).

The effects of thiazide-type diuretics on carbohydrate tolerance cannot be ignored (50). There is a definite relation between diuretic treatment, impaired glucose tolerance, and biochemical diabetes, and a possible relation with insulin resistance (64). It is well established that the effect of thiazides on blood glucose is dose-related, probably linearly, while the antihypertensive effect has little relation to dose (65–67). There is relatively little information on the time-course; numerous short-term studies have shown that the blood glucose concentration increases in 4–8 weeks (68). The evidence that current low dosages impair glucose tolerance in the long term is not entirely consistent, perhaps because of differences between studies in dosages, diuretics used, durations of treatment, and types of patient (68,69). In SHEP, low-dosage chlortalidone in elderly patients for 3 years resulted in a non-significant excess of diabetes (8.6 versus 7.5%) compared with placebo (70). The apparent differences between diuretics may be due to comparisons of dosages that are not equivalent (71). Important differences between individual diuretics will be established only when their complete dose–response relations for metabolic variables and blood pressure have been defined (68).

In contrast to the wealth of evidence on impaired glucose tolerance in diabetics, sound clinical trials of the effect on insulin resistance are difficult to find, considering the amount of comment and speculation on the topic (SEDA-15, 216). It is not known whether insulin resistance is completely or even partly responsible for the changes in glucose tolerance that occur during long-term thiazide treatment; impaired insulin secretion may also have a role (72). Hypokalemia or potassium depletion may contribute to impaired glucose tolerance, by inhibiting insulin secretion rather than by causing insulin resistance, but is not the only or even the main cause of impaired glucose tolerance during long-term diuretic treatment (68,69). The routine use of potassium-sparing diuretics with relatively low dosages of thiazides does not prevent impaired glucose tolerance.

Diuretics worsen metabolic control in established diabetes, but it is not known whether this adversely affects prognosis (68). Disturbances of carbohydrate homeostasis have been detected by detailed biochemical testing, but their clinical importance is uncertain (64). The major clinical trials have not shown a major risk of diabetes mellitus. The incidence of diabetes mellitus in diuretic-treated subjects is only about 1%, even when large dosages are used (73). In ALLHAT, among patients classified as non-diabetic at baseline, the incidence of diabetes after more than 4 years was 12% with chlortalidone compared with 9.8% (amlodipine) and 8.1% (lisinopril). Despite these trends, there was no excess of cardiovascular events or mortality from chlortalidone in the entire population or among patients with diabetes. Although these data are reassuring, observational data suggest that diuretic-induced new-onset diabetes carries an increased risk of cardiovascular morbidity and mortality, but that this may take 10–15 years to become fully apparent (74).

Since changes in glucose balance after diuretics tend to be reversible on withdrawal, measures of carbohydrate homeostasis should be assessed after several months of thiazide treatment to detect those few patients who experience significant glucose intolerance (75). With this approach, the small risk of diabetes mellitus secondary to diuretic therapy can be minimized.

Hyperuricemia

Most diuretics cause hyperuricemia. Increased reabsorption of uric acid (along with other solutes) in the proximal tubule as a consequence of volume depletion is one reason; however, diuretics also compete with uric acid for excretory transport mechanisms. There is a small increased risk of acute gout in susceptible subjects (73). In the large outcome trials, about 3–5% of subjects treated with diuretics for hypertension developed clinical gout

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(76). In those with acute gout during diuretic treatment, attacks were more strongly related to loop diuretics than to thiazides (77). Gout was significantly associated with obesity and a high alcohol intake in the subgroup taking only a thiazide diuretic. About 40% of cases of acute gout may have been prevented by avoiding thiazides in those 20% of men who weighed over 90 kg and/or who consumed more than 56 units of alcohol per week.

Well-conducted studies have shown that diuretic-induced changes in serum uric acid are dose-related (66,78). In low-dosage regimens, as currently recommended, alterations are minor, and other than the risk of gout the long-term consequences of an increased serum uric acid are unknown.

The issues of whether hyperuricemia is an independent risk factor for cardiovascular disease and the clinical relevance of the rise in serum uric acid caused by diuretic treatment are controversial (SED-14, 660) (50). In the Systolic Hypertension in the Elderly Program (SHEP), diuretic-based treatment in 4327 men and women, aged 60 years or more, with isolated systolic hypertension was associated with significant reduction in cardiovascular events (SED-14, 657). Serum uric acid independently predicted cardiovascular events in these patients (79). The benefit of active treatment was not affected by baseline serum uric acid. After randomization, however, an increase in serum uric acid of less than 0.06 mmol/l (median change) in the active treatment group was associated with a hazard ratio (HR) of 0.58 (CI = 0.37, 0.92) for coronary heart disease compared with those whose serum uric acid rose by 0.6 mmol/l or more. This was despite a slight but significantly greater reduction in both systolic and diastolic blood pressures in the latter. Those with serum uric acid increases of 0.6 mmol/l or more in the active group had a similar risk of coronary events as those in the placebo group.

This analysis of the SHEP database confirms the findings of a systematic worksite hypertension program (80). In 7978 treated patients with mild to moderate hypertension, cardiovascular disease was significantly associated with serum uric acid (HR = 1.22; CI = 1.11, 1.35), controlling for known cardiovascular risk factors. The cardioprotective effect of diuretics increased from 31% to 38% after adjustment for serum uric acid.

These observations suggest that persistent elevation of serum uric acid during diuretic-based antihypertensive therapy may detract from the benefit of blood pressure reduction. However, the relation between serum uric acid and cardiovascular disease was independent of the effects of diuretics. Furthermore, low-dose thiazide regimens have a smaller impact on serum uric acid (SED-14, 660).

Lipid metabolism

Reviews of the influence of diuretics on serum lipids (81–84) are in broad agreement as regards short-term effects. Thiazide and loop diuretics increase low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, total cholesterol, and triglycerides. The effect on high-density lipoprotein (HDL) cholesterol has been variable. The ratio of LDL/HDL or total cholesterol/HDL is generally increased, but not in all studies. Spironolactone 50 mg bd caused modest falls in HDL cholesterol and triglycerides (85). The effects of other potassium-sparing drugs on lipid metabolism have not been well documented. The possible mechanisms of these various short-term effects have been discussed (84).

Diuretic-induced effects on lipid metabolism are dose-related (66,67): at low dosages of thiazides, changes are very slight while antihypertensive efficacy is well maintained. Diuretic-induced lipid changes have not been prominent in studies lasting one year or longer (11,20,81,84,86). An association between thiazide use or antihypertensive treatment and changes in serum lipids has been shown in some population surveys (87,88) but not in others (89).

Most studies of the effects of diuretics on serum lipids have lacked a placebo control to allow identification of time-dependent or environmental changes, or have been confounded intentionally or unknowingly by life-style interventions, including weight loss, diet, and exercise (69). The argument that the effects of diuretics on lipids may limit the beneficial effect of blood pressure reduction is difficult to sustain (50). The effect of thiazides is largely transient, and in the long term total cholesterol and LDL cholesterol are raised only slightly and HDL cholesterol is unchanged. It is not known whether diuretic-induced changes in cholesterol carry the same prognostic significance as naturally occurring hyperlipidemia (50,90). Attempts to calculate a potential impact of diuretic-induced increases in total cholesterol and LDL cholesterol on coronary prognosis are premature. Observations have so far been limited largely to serum concentrations. However, binding of lipids to vascular cells, rather than in the bloodstream, is decisive for atherogenesis, and the effect at the cellular level remains to be investigated.

It has been suggested that even small changes in lipids might be clinically significant (91). However, the study was underpowered to show statistical significance of minor effects. Since under 50% of the patients in each group were followed for 1 year, selection bias may also have been introduced. It should be remembered that lipid changes are subsidiary to mortality. In this respect, diuretics are the best established of the antihypertensive drug classes.

There is little or no evidence that thiazides should be avoided in patients with hyperlipidemia (75), although some physicians continue to make this recommendation. Serum lipids should be checked within 3–6 months of starting thiazides to detect the very few patients who have an increase in total cholesterol or LDL cholesterol. This should not add to the cost of care, since serum chemistry need only be obtained once or twice a year and is no reason to avoid the use of these drugs as initial monotherapy.

Electrolyte balance

Potassium-wasting diuretics can cause sodium and potassium depletion with hyponatremia and hypokalemia. Potassium-retaining diuretics can cause hyperkalemia.

Hyponatremia

Treatment with thiazide diuretics is one of the most common causes of hyponatremia (92). Patients can present with variable hypovolemia or apparent euvolemia,

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depending on the magnitude of sodium loss and water retention.

Two major surveys have reviewed the features of diuretic-induced hyponatremia (93,94). Thiazide-like diuretics alone or in combination with potassium-sparing diuretics are responsible for more than 90% of cases. Hyponatremia occurs mainly in elderly women, although the relation with age probably merely reflects the widespread use of diuretics in older subjects. In most cases, the interval between starting thiazide and clinical presentation is less than 2 weeks; serum sodium may fall by 5 mmol/l or more in 24 hours or less in patients who develop severe hyponatremia. In contrast, when loop diuretics cause hyponatremia, the lag period is usually several months. Hypertension is the indication for diuretics in over 80% of cases. The patient is clinically euvolumic, but in the majority excess antidiuretic hormone (ADH) activity, hypokalemia, excess water intake, and increased free water clearance singly or together appear to contribute to the development of hyponatremia. The urine is inappropriately concentrated and contains moderately large amounts of sodium. The findings may be clinically indistinguishable from those of the syndrome of inappropriate ADH secretion. Severe neurological complications are seen in about 60%; seizures (30%), stupor or coma (30%), and death (5–10%). The extent of irreversible loss of intellectual function is unknown. Serum sodium concentration is usually in the range 105–120 mmol/l. If diuretics are withdrawn, the serum sodium concentration returns to normal, but hyponatremia is reproducible on rechallenge.

Comprehensive accounts of the pathophysiology, etiology, and management of hyponatremia have stressed the care required in correction of symptomatic hyponatremia (95). Neurological signs are an indication for active sodium replacement using hypertonic saline. Correction should be planned over 24–48 hours to increase serum sodium by 1 mmol/l each hour with a target increase of 20–25 mmol/l, a serum sodium concentration of 130 mmol/l or abolition of symptoms. If onset is within 24 hours of starting diuretics, correction should be rapid but within a total increase of 20 mmol/l in the first 24 hours. If the onset is over several days or longer, correction should be slower, aiming for 12–15 mmol/l in 24 hours. There is concern that rapid correction of hyponatremia and a relatively high total correction (more than 20 mmol/l in the first 24 hours) can be associated with higher morbidity or a demyelinating syndrome (94), but the rate of correction does not appear to be important to the outcome if the absolute increase is limited to 25 mmol/l over 48 hours (95). An extensive review of the literature suggested that rate of correction is not a factor in the genesis of hyponatremic brain syndrome (95).

The use of fixed combination of a thiazide and a potassium-sparing drug, often Moduretic (hydrochlorothiazide 50 mg with amiloride 5 mg), has been consistently implicated in diuretic-induced hyponatremia. Treatment with chlorpropamide (200–800 mg/day) along with Moduretic has precipitated hyponatremia in several cases (96). Simultaneous use of Moduretic with trimethoprim has also been reported to increase the risk (97). The mechanism appears to be impairment of the clearance of free water, resulting in dilutional hyponatremia. Whether data such as these point to a special risk of Moduretic as a product or merely reflect its extraordinarily widespread use in old people is not clear. In a survey of electrolyte disturbances in 1000 geriatric admissions, the incidence of hyponatremia with the combination of hydrochlorothiazide and amiloride was twice that with other diuretics, although the difference failed to reach statistical significance (98).

Management

There is no consensus about the optimal treatment of symptomatic hyponatremia. The authors of a comprehensive review recommended a targeted rate of correction that does not exceed 8 mmol/l on any day of treatment (92). Remaining within this target, the initial rate of correction can still be 1–2 mmol/l/hour for several hours in patients with severe symptoms (SED-13, 562). They suggested the following formulae for calculating the effect of giving 1 liter of infusate on serum sodium.

- Solutions containing sodium only:
  Change in serum sodium concentration (mmol/l)
  $= (\text{infusate } Na^+ - \text{serum } Na^+)/(\text{total body water} + 1)$
- Solutions containing sodium and potassium:
  Change in serum sodium concentration (mmol/l)
  $= (\text{infusate } Na^+ + \text{infusate } K^+ - \text{serum } Na^+)/(\text{total body water} + 1)$

Estimated total body water (in liters) is calculated as a function of body weight: 0.6 l/kg in children; 0.6 and 0.5 l/kg in non-elderly men and women respectively; 0.5 and 0.45 l/kg in elderly men and women respectively.

Loop diuretics can cause hypernatremia by increasing free water clearance (net water loss in the form of hypotonic fluid) (99). Over-rapid correction should be avoided.

Hypokalemia

The loss of potassium caused by diuretics is their most intensively debated adverse effect, and the extent and significance of the problem has long been disputed. The effect of diuretics on potassium balance and their clinical consequences have been reviewed extensively (50–52,65,100–102). The risks of diuretic-induced hypokalemia have been greatly exaggerated (50,65,102). A fall in plasma potassium is common, but sound studies have consistently showed that diuretics do not deplete body potassium or cause potassium deficiency during long-term therapy in hypertensive patients (50).

Susceptibility factors

In most patients, routine monitoring of serum potassium and routine administration of potassium-sparing diuretics is unnecessary (65,102), although patients at special risk require particular attention. Routine administration of potassium-sparing diuretics may have some justification in such patients. The following postulates seem to summarize the present position:

- When there is severe hypokalemia, it should not be attributed immediately to diuretic treatment. It may well be due to primary hyperaldosteronism, occult chronic liver disease, or abuse of licorice or laxatives.

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- Relatively mild degrees of hypokalemia can be dangerous in patients taking cardiac glycosides, because their effects on the myocardium are potentiated in the absence of potassium (51).
- Diuretic-induced hypokalemia should also be avoided in patients taking drugs that prolong the QT interval, for example some antidysrhythmic drugs (quinidine, procainamide, disopyramide, encainide, sotalol, amiodarone), some psychotropic drugs (thioridazine, imipramine, phenothiazines), the lipid lowering drug probucol, the antibiotic erythromycin, and the 5-HT_2 receptor antagonist ketanserin.
- The risk of a clinically important degree of hypokalemia is increased in patients with liver cirrhosis and those with severe cardiac failure complicated by secondary hyperaldosteronism.
- In heart failure, depletion of potassium can provoke fatigue and lethargy and can cause ventricular dysrhythmias in the failing heart (102). Potassium depletion can occur in cardiac failure when neurohumoral systems are stimulated by diuretics and can be especially profound when skeletal muscle wasting is advanced (101). However, since heart failure itself, independent of diuretic treatment, is associated with loss of total body potassium, it is difficult to assess the independent contribution of diuretic treatment to this potassium deficit.

Critical reviews have concluded that in most patients (that is in the absence of the occasional risk factors listed above) diuretics can be prescribed alone, and that there is no need to take precautions against hypokalemia (63,103). Precautions, including the monitoring of serum potassium, have to be taken when there are risk factors or when symptoms (for example muscle pain) occur, or in patients who require aggressive treatment with both a thiazide and a loop diuretic; such a combination is indeed likely to provoke considerable falls in serum potassium, even to concentrations below 2.5 mmol/l (104). An observational study in 43 738 American men aged 40–75 years and without cardiovascular disease or diabetes showed that stroke was less likely in those with high potassium intake and that use of potassium supplements was related inversely to stroke in men taking diuretics (105). Diuretic-based treatment was associated with a significant mean reduction in serum potassium in SHEP (70). Although there were notable reductions in stroke in SHEP (14), potassium supplements were used if the serum potassium fell below 3.5 mmol/l. Therefore, avoidance of hypokalemia may be important in ensuring the cardiovascular benefits of thiazides in the management of hypertension.

Well-conducted studies (66,78) have underlined the fact that the dose–response curves for lowering blood pressure and lowering plasma potassium during diuretic treatment are dissociated. There is little if any loss of antihypertensive effect with low doses of diuretics, whereas hypokalemia is much less prominent. Although low dosages of diuretics are to be preferred in uncomplicated hypertension, very low dosages of thiazides may not be as effective as higher dosages (106).

Management

In patients in whom hypokalemia needs to be prevented or corrected, potassium-sparing diuretics should be preferred to potassium supplements, which are relatively ineffective, even in high dosages (SEDA-14, 180) (SEDA-15, 214).

The National Council on Potassium in Clinical Practice has provided guidelines on potassium replacement (107). In hypertensive patients with drug-induced hypokalemia, an effort should be made to achieve and maintain the serum potassium concentration at 4.0 mmol/l or over. Potassium replacement should be considered routinely in patients with congestive heart failure, even if the initial potassium determination is normal. Regular monitoring of serum potassium is essential in these patients, because of the risk of hyperkalemia in patients given potassium (or potassium-sparing diuretics) and ACE inhibitors or angiotensin receptor antagonists. Maintenance of optimal potassium concentrations (4.0 mmol/l or over) is critical in patients with cardiac dysrhythmias, and again routine potassium monitoring is obligatory.

Angiotensin-converting enzyme inhibitors are widely believed to attenuate diuretic-induced falls in plasma potassium. However, captopril 25 mg bd had no effect on plasma potassium in hypertensive patients treated with bendroflumethiazide 5 mg/day (108).

Hyperkalemia

All potassium-sparing diuretics can cause hyperkalemia. Several groups of patients are at particularly high risk of developing hyperkalemia if they take potassium-sparing diuretics (109). These include patients with moderate to severe chronic renal insufficiency, hypoaldosteronism, and diseases associated with impaired response to the potassium secretory effects of aldosterone. Hypoaldosteronism is often seen in elderly patients, those with chronic renal impairment or diabetic nephropathy, those with AIDS, or those with primary adrenal disease. In addition, patients with sickle cell disease, obstructive uropathy, systemic lupus erythematosus with nephropathy, and renal transplants may have tubular resistance to the effects of mineralocorticoids. Spironolactone 300 mg can significantly increase the serum potassium concentration in hemodialysis patients, suggesting that aldosterone may affect the cellular handling and gastrointestinal excretion of potassium. Commonly forgotten is the patient for whom these diuretics are prescribed as a precautionary measure and who for many years has been flavoring a low-salt diet with "salt substitutes," which are often based on potassium chloride (110).

Life-threatening hyperkalemia has been observed in patients receiving potassium-sparing diuretics (111). The most distressing finding in this study was that these agents were far more often prescribed in patients with abnormal kidney function than were other diuretics. Combining potassium-sparing diuretics with potassium supplements borders on malpractice; regular monitoring of serum potassium is mandatory in all patients treated with potassium-sparing diuretics, particularly if they are elderly or have abnormal renal or hepatic function.

Mineral balance

Thiazide and thiazide-like diuretics reduce the renal clearance of calcium by inhibiting the tubular secretion

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of calcium ions. In contrast, furosemide (which does not promote reabsorption of calcium in the distal tubule) causes transient hypercalciuria, an effect that has been exploited on occasion in the treatment of hypercalcemia (SED-9, 346) (112).

Metal metabolism

Diuretic-induced magnesium loss has been heavily stressed both by some independent investigators and by those seeking for commercial reasons to discredit the diuretics; there are far more reviews on the subject than sound original studies. It has been declared (113) that diuretic-induced magnesium deficiency "positively contributes" to myocardial infarction, delayed infarct healing, coronary and cerebral arterial spasm, hyperlipidemia, and cardiac dysrhythmias, with the addition of a horrific catalog of clinical manifestations, including ataxia, delirium, convulsions, coma, and ventricular fibrillation. Ramsay has remarked that this review, and others like it, belongs to the category of science fiction rather than that of serious medical writing (SEDA-10, 187).

Most reviews of the effects of diuretics on magnesium metabolism are uncritical and extrapolate wildly from the little sound evidence that is available (50). Several uncontrolled studies and very few controlled studies have suggested that long-term thiazide treatment causes a small fall in serum magnesium within the reference range. The complex relation between intracellular free and total magnesium content remains to be clarified, and there is absolutely no evidence that diuretic treatment reduces intracellular magnesium, and the few competent investigations have suggested that it does not. Diuretic-induced disturbances of magnesium balance do not cause depletion of intracellular potassium. The clinical significance of the small diuretic-induced alterations in magnesium balance, if any, is obscure. There is no satisfactory evidence that diuretic-induced magnesium disturbances cause or predispose to cardiac dysrhythmias, either in general or specifically after myocardial infarction (114).

A balanced account (115) concluded that the controlled trials, of which there are few, do not substantiate a role of diuretics in causing magnesium deficiency. Consequently, the vast majority of patients taking conventional doses of thiazides do not need magnesium supplements. On balance, potassium-sparing diuretics tend to increase serum and intracellular magnesium content, but this should not be taken as evidence of prior magnesium deficiency. It remains theoretically possible that large doses of loop diuretics given more than once-daily for long periods could induce negative magnesium balance and magnesium deficiency. However, it is difficult to conduct appropriately controlled trials in heart failure, in which such treatment is needed, and until more reliable information becomes available no absolute recommendation can be made. Magnesium depletion should be regarded as no more than a possible, as yet unproven, risk factor for cardiovascular morbidity and mortality (116).

In ordinary practice, serum magnesium need not be monitored in patients taking diuretics, and potassium-sparing drugs should not be used to prevent non-existent magnesium problems (SEDA-10, 190).

Gastrointestinal

Potassium, given separately or in combination with a diuretic, introduces the risk of esophageal injury; attempts to provide potassium in modified-release formulations have simply transposed the site of injury from the esophagus to the small bowel (SEDA-10, 187).

Urinary tract

Since diuretics act primarily on the kidney, it is hardly surprising that renal damage can occur including interstitial nephritis (117,118). However, toxic damage is very rare in relation to the number of patients treated. Renal damage due to interstitial nephritis is more likely to occur in patients with pre-existing glomerular disease. It tends to present 4–10 weeks after starting treatment, with non-oliguric acute renal insufficiency and in some cases pyrexia and eosinophilia. This complication probably always recovers spontaneously and completely, although some consider it prudent to give high doses of glucocorticoids.

Sexual function

The adverse effects of thiazide and thiazide-like diuretics on male sexual function include reduced libido, erectile dysfunction, and difficulty in ejaculating. The exact incidence of sexual dysfunction in patients taking diuretics is poorly documented, perhaps because of the personal nature of the problem and the reluctance of patients and/or physicians to discuss it. However, these abnormalities have been reported with incidence rates of 3–32%. The true incidence of sexual dysfunction probably lies closer to the lower end of this range (119). In a meta-analysis of 13 randomized, placebo-controlled trials conducted over a mean of 4 years the NNH (number needed to harm) for erectile impotence with thiazide diuretics in hypertension was 20 and the relative risk was 5.0 (120).

The mechanisms by which thiazides affect erectile dysfunction or libido are unclear, but it has been suggested that they have a direct effect on vascular smooth muscle cells or reduce the response to catecholamines. Sexual dysfunction does not appear to be mediated by either a low serum potassium concentration or a low blood pressure. Since sexual dysfunction can adversely affect the quality of life of hypertensive patients, physicians or health-care providers should take an accurate baseline sexual history and monitor sexual status for changes during therapy. If there are significant changes in sexual function, diuretic therapy can be withdrawn and an alternative drug class substituted. However, not uncommonly sexual dysfunction will persist despite withdrawal of the diuretic, suggesting that elements of the hypertensive state itself contribute to the process.

Analysis of the risk of erectile impotence has been hampered by the fact that impotence is common in men beyond middle age and is likely to be even more common in hypertension, treated or otherwise. The UK MRC trial (11) was the first to provide quantified evidence of a link with diuretics; in men taking bendroflumethiazide 10 mg/day, the withdrawal rate for impotence was 19.6 cases per 1000 treatment years, compared with 0.9 cases with placebo. However, these figures may exaggerate the effect, since the trial was single-blind. A questionnaire

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pointed to a less striking difference; after 3 months impotence was noted in 16% of diuretic-treated patients and 9% of those taking placebo, and the roughly 2:1 ratio was again noted after 2 years. Later studies (16,86,121–123), pointed to a similar effect, even when low-dosage regimens were used (16,86). Some studies (123) but not others (86) have suggested that weight reduction ameliorates diuretic-induced sexual dysfunction. Erectile dysfunction occurs early and is often tolerable; onset after 2 years is unlikely (86).

Erectile impotence is particularly common in men with diabetes (16), who are likely to have difficulties because of autonomic dysfunction. It is unclear whether younger men and women are similarly affected and whether normotensive men have fewer such problems (124). Most investigations of the effects of diuretics on sexual function have been characterized by poor study design (125); the majority had no placebo control and relied on comparisons with baseline. The best studies have suggested an increase in erectile dysfunction in thiazides users compared with placebo. Bearing in mind all the confounding factors, it can be concluded that diuretics will sometimes cause impotence, but that in the population as a whole the effect is slight compared with other causes (SEDA-11, 197) (SEDA-11, 198).

Sexual problems due to diuretics are very rare in women (16,86).

Long-Term Effects

Drug abuse

When diuretics are abused it is mostly in the course of a misguided attempt to lose weight; in the past, various "slimming remedies" offered for sale outside normal trading channels have been found to contain diuretics, sometimes with components such as thyroid extract. The unnecessary use of diuretics by a healthy individual, perhaps in excessive doses, can lead to dehydration, hypokalemia, and hypotension; when furosemide is abused, even tetany can occur because of hypocalcemia (126). The weight loss achieved by using diuretics in this way is purely due to dehydration and will soon be annulled by extra fluid intake.

One complication of long-term diuretic therapy in otherwise healthy individuals is edema, and it has been suggested that surreptitious use of diuretics can explain some otherwise paradoxical cases of idiopathic edema; presumably the diuretic induces a persistent increase in plasma renin activity and secondary hyperaldosteronism, and attempts to stop the diuretic intake can at first actually aggravate the condition (127). However, three studies have furnished strong evidence that diuretic abuse is not an important cause of idiopathic edema (128–130).

In some patients the covert use of diuretics leads to a complete replica of Bartter's syndrome, characterized by hypokalemia and hyper-reninemia without hypertension (131,132). In a patient who denies having taken diuretics, the true diagnosis may only be made by finding the drug or its metabolites in the urine, although challenge with diuretic may provoke the syndrome, while withdrawal leads to weight gain and the resolution of metabolic alkalosis.

The dangers of diuretic abuse among athletes have been discussed (SEDA-21, 228). Diuretics are used illegitimately by many athletes and amount for 6% of all drugs abused. They are taken by body builders to dehydrate the tissues, giving better definition to muscle shape, as well as to offset the fluid retaining effect of concomitant anabolic steroids and growth hormone, used to increase muscle mass. Diuretics are used in other sports to reduce weight, allowing competition in lower body weight classes, and to dilute the urine, reducing its specific gravity and making difficult the detection of other banned drugs. This practice is not only unethical but also hazardous.

Tumorigenicity

There is an association between diuretic use and renal cell carcinoma (133). Some of the studies that support this association can be dismissed, since the epidemiological data on which they were based were not suitably adjusted for confounding variables, including obesity, hypertension, age, and cigarette smoking. However, other case-control studies have shown a small risk of renal cell carcinoma in patients taking long-term diuretics after adjustment of the data for potentially confounding variables.

The carcinogenic mechanism of diuretics is not known, but could be related to a carcinogenic action of *N*-nitroso metabolic derivatives of thiazide and loop diuretics or structural changes in the transporting tubular epithelia, which provoke different stages of apoptosis. Rats and mice treated with diuretics have been reported to develop nephropathies and renal adenomas. Renal cell carcinoma arises in renal tubular cells, which are the principal site of action of diuretics. Contact over years or decades may have a low-grade carcinogenic effect. However, most prospective randomized trials provide too short a period of observation to assess the potential for carcinogenicity unequivocally. Furthermore, the findings may have been confounded by other risk factors for renal cell carcinoma. Adjustment for confounders greatly attenuated the risk (to non-significance) in one study, and in another the association with diuretic use disappeared completely. Therefore, the findings from these observational studies may have resulted from uncontrolled confounding by known or unrecognized risk factors.

The relation between diuretic therapy and the risk of malignancies has been examined in a review of pertinent publications between 1966 and 1998 (134). In nine case control studies (4185 cases), the odds ratio for renal cell carcinoma in patients treated with diuretics was 1.55 (95% CI = 1.42, 1.71) compared with non-users of diuretics. In three cohort studies of 1 226 229 patients (802 cases), patients taking diuretics had a more than two-fold risk of renal cell carcinoma compared with patients not taking diuretics. Women had an odds ratio of 2.01 (CI = 1.56, 1.67) compared with 1.96 (CI = 1.34, 2.13) in men. Thus, the cumulative evidence suggests that long-term use of diuretics may be associated with renal cell carcinoma.

The findings linking diuretic therapy with renal cell carcinoma need careful scrutiny. The strength of evidence provided by observational studies is limited, and such studies have yielded contradictory and controversial results in the past. An accompanying editorial (135)

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pointed out that some of the studies reviewed appear to have been designed to evaluate predictors of renal cell carcinoma without an a priori hypothesis that diuretics might be implicated. Statistical significance (set at $P < 0.05$) may have emerged merely by chance if 20 risk factors were examined.

Another commentary (136) emphasized the potential bias of observational studies and also publication bias in meta-analysis. The contemporary relevance of the findings is further reduced, since many of the studies included patients taking very high doses of thiazides. It is difficult to disentangle a drug-related effect from the association between hypertension and renal cell carcinoma.

Since renal cell carcinoma is rare, the practical importance of these observations is small: one extra case of renal cell carcinoma in 1500 patients treated for 20 years. If the hypothesis is correct, antihypertensive therapy with diuretics will prevent 20–40 strokes, 3–28 heart attacks, 3–10 cardiovascular deaths, and 4–14 deaths overall for every extra case of renal cell carcinoma. Even middle-aged women would be spared six strokes for each potential case of renal cell carcinoma. If a low grade carcinogen is involved, most patients will not live long enough for its effect to be expressed. The available information does not support a change in current prescription practices for diuretics in the treatment of hypertension and cardiac failure. Physicians should be more concerned about controlling blood pressure rather than concerning themselves with what at best might be a small risk of renal cell carcinoma.

Other cancer types have been evaluated for their association with diuretic therapy. The development of colon cancer has been studied in 14 166 patients aged 45–74 years with a previous myocardial infarction and/or stable angina, screened for participation in the Bezafibrate Infarction Prevention Study (137). Of these, 2153 used diuretics and 12 013 did not. Multivariate analysis identified diuretics as an independent predictor of an increased incidence of colon cancer (hazard ratio 2.0) and colon cancer mortality (hazard ratio 3.7). However, the association between diuretic therapy and a higher incidence of colon cancer was observed only among non-users of aspirin. There was a relatively lower incidence of colon cancer in furosemide users and a higher incidence in the small combined subgroup of those who took amiloride and/or hydrochlorothiazide. Further studies to test the association between diuretics and colon cancer, as well as the potential protective effects of aspirin, are needed. Until these data become available, physicians should be aware of the potential effects of diuretics, especially when choosing long-term treatment for young patients with mild hypertension.

Second-Generation Effects

Pregnancy

Diuretics have been used for the treatment of both hypertension and edema in pregnancy. While regimens including thiazides have improved the outcome in hypertension developing during the first 20 weeks of pregnancy, the situation in later pregnancy seems to be different. Some controlled studies have shown that the thiazides do not influence the development of pre-eclampsia (138) and can even aggravate it.

Edema is a relatively frequent finding in normal pregnancy. It appears to be benign and can even be associated with improved obstetric performance (139). Edema, even in the presence of hypertension or proteinuria, is not a useful predictor of obstetric complications (140). These observations are important, in view of the finding that treatment with thiazide diuretics is associated with a reduced birth weight in normotensive pregnant subjects (141).

In a review of eight large-scale trials, four well-controlled studies did not show any benefit, whereas four others, which showed some benefit, were judged to be totally unsatisfactory, either because control was not strict enough or because inclusion and exclusion criteria were either not sufficiently well-defined or were scientifically unacceptable (142). The general consensus in earlier publications was that diuretics are useless, because they reduce the already lowered cardiac output in pre-eclamptic toxemia and so further reduce placental and uterine perfusion (143,144); diuretics do not alter the incidence of pre-eclamptic toxemia and eclampsia and they do not improve perinatal mortality or birth weight. Both the maternal adverse effects (hypokalemia, metabolic acidosis, hyperglycemia, hyperuricemia, hemorrhagic pancreatitis, and even death due to abuse) and the fetal and perinatal adverse effects (hyponatremia, fetal dysrhythmias induced by hypokalemia, thrombocytopenia, and jaundice) preclude the use of diuretics in pre-eclamptic toxemia.

Nine randomized, controlled studies of the use of diuretics in pre-eclampsia have been analysed (145). There were almost 7000 subjects in whom thiazides had been compared with placebo or no treatment. In the pooled analysis, diuretic treatment was associated with a non-significant reduction in perinatal mortality (about 10%) and stillbirths (about 33%). There was no excess of serious adverse reactions, either in the mothers or the neonates. These findings thus give no support to the belief that diuretics are harmful in pregnancy. It should not be concluded that diuretics ought to be used in pre-eclampsia in preference to other well-established agents, but they certainly can be used with confidence when they are really needed, for example in patients with severe hypertension that predates pregnancy and in heart failure.

Nevertheless, substantial numbers of pregnant women use these agents during pregnancy. In a Swedish study (146), 11% of 341 women took diuretics in the third trimester, while in a Tennessee Medical study (147) diuretics were prescribed as frequently as hypnotics and minor tranquilizers (7% for each category of drug). On the other hand, a study based on a University obstetrics programme in Florida (148) found that diuretics had been prescribed for only 2.4% of the patients.

Obviously treatment with any drug during pregnancy will affect both mother and fetus, and two aspects of such therapy are important: the adverse effects of the drug and the potential for teratogenicity.

Chlorothiazide readily crosses the placenta (149), but there have been few studies of the effects of diuretic treatment on the fetus. There are case reports of abnormalities of glucose handling (150) and severe electrolyte disturbances (151) in pregnant women taking diuretics,

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but these reports generally do not mention the metabolic values in the neonate. There has been one report of chronic fetal bradycardia associated with a low serum potassium in the diuretic-treated mother (152). Infusion of potassium restored maternal electrolytes and fetal heart rate. Normal delivery followed later, and electrolyte values in the child were normal. With regard to glucose handling, Senior and others (153) have raised the possibility that thiazide treatment of the mother can lead to neonatal hypoglycemia. In the absence of other predisposing factors, thiazides had been given to the mothers of 57% of their affected children, and, in the general population, the risk of neonatal hyperglycaemia was increased five-fold by thiazide treatment of the mother.

Hematological effects in the neonate have also been ascribed to maternal diuretic treatment. Seven cases of neonatal thrombocytopenia attributed to chlorothiazide have been described (154) and one case in which hydrochlorothiazide may have played a role (155). None of the mothers had thrombocytopenia. There was one death among the affected infants. Neonatal hemolysis occurred in two infants and was attributed to maternal thiazide therapy (156).

There is no evidence of a teratogenic effect of diuretics in humans, although one case of teratoma has been reported in the offspring of a woman treated for the first 19 weeks of pregnancy with acetazolamide (157), which is teratogenic in experimental animals. The lack of evidence of teratogenicity is not surprising. Assuming a basic malformation rate of 0.1% and that a drug that is used by 2% of pregnant women increases the malformation rate six times, it would require more than 100 000 women to be sure of detecting such an effect (146).

Susceptibility Factors

Age

There has been much discussion about the safety or risks of diuretics in elderly people. Although diuretic use has been implicated as a cause of urinary incontinence, no evidence has been presented to confirm this. An epidemiological survey of 1956 respondents aged at least 60 years showed no significant difference between diuretic-users and non-users in the prevalence of incontinence (158).

Orthostatic hypotension, although often loosely referred to in older literature (SED-10, 370) (159), is in fact only likely to become a problem in very old subjects, aged 90 years or more, even if a potent loop diuretic is used; this was the clear conclusion of a good prospective study published in 1978 (159). In 843 independent living men and women aged 60–87 years, postural fall in systolic blood pressure was not related to treatment with diuretics, after correction for initial blood pressure (160). At currently recommended doses, older subjects do not generally experience particular problems from hypokalemia and do not appear to be at special risk of cardiac dysrhythmias in the face of diuretic-induced hypokalemia (SEDA-15, 218).

Reviews of the age-related effects of diuretics in hypertensive subjects (161,162) have concluded that symptomatic adverse reactions are not more frequent in older patients and some trials have suggested a lower frequency than in younger subjects. Although the elderly may be susceptible to some metabolic effects of diuretics, the evidence for cardiotoxic potential is not conclusive.

The best overall evidence of the safety of diuretics in old people comes from the large-scale outcome trials in hypertensive patients (11,13,15,17,18). These studies in over 10 000 subjects aged over 60 years showed clearly that thiazide-based treatment reduces the risk of stroke, coronary heart disease events, and cardiovascular events in older hypertensive patients. A meta-analysis (163) of randomized trials lasting at least 1 year and involving 16 164 individuals aged at least 60 years showed that diuretics were superior to beta-blockers with regard to all endpoints (stroke, coronary heart disease events, cardiovascular mortality, and all-cause mortality). The beneficial effects noted in these trials should dispel any doubts about the safety and efficacy of diuretics in old people.

Drug Administration

Drug formulations

Fixed combinations of thiazides and loop diuretics with potassium and of thiazides with beta-blockers serve little useful purpose and can in fact do harm. Combinations of thiazides and loop diuretics with potassium-sparing diuretics serve the needs of the small minority of patients who develop clinically significant hypokalemia when given diuretics alone, or in whom hypokalemia is particularly risky. In fact, these combinations are much too widely used, and since individual needs vary so much there is a spectrum of risk, ranging from hypokalemia to hyperkalemia (SEDA-10, 370) (SEDA-10, 371).

Drug–Drug Interactions

Antidysrhythmic drugs

Hypokalemia due to diuretics potentiates the dysrhythmogenic actions of antidysrhythmic drugs that prolong the QT interval, such as Class I and Class III antidysrhythmic drugs, increasing the risk of torsade de pointes (164). This can also happen with other drugs that prolong the QT interval, such as phenothiazines (165).

Beta-blockers

Interaction of thiazides with beta-blockers can cause a greater risk of hyperglycemia than if either component is given separately (166,167).

Cardiac glycosides

Hypokalemia due to diuretics potentiates the actions of cardiac glycosides and can result in digitalis toxicity. In 67 patients taking a maintenance dose of digoxin, 42 with digoxin toxicity and 25 without, the mean serum digoxin concentration was significantly higher in the former and the mean serum potassium concentration was significantly lower (168). Among the patients with toxicity, 24% had hypokalemia due to diuretics. The mean serum digoxin concentration in those with hypokalemia and toxicity was significantly lower than in those with normokalemia and toxicity.

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Dobutamine

General Information

Dobutamine is a relatively selective $beta_1$-adrenoceptor agonist with only slight $beta_2$- and alpha-adrenoceptor activity. It has been developed as a positive inotropic agent that is less vasoconstrictive than high doses of dopamine.

Organs and Systems

Cardiovascular

Dobutamine stress testing, particularly combined with echocardiography, is a very widely used tool in cardiological investigation, and its safety continues to be examined in great detail. In a review of 37 publications, each reporting on 100 or more patients, with a total of over 26 000 tests, 79 life-threatening complications were described, including acute myocardial infarction, a variety of cardiac dysrhythmias, and severe hypotension (1). The authors also referred to 29 isolated case reports of severe complications, including two deaths. They concluded that there must be a clear indication for the procedure, informed consent must be obtained, a physician should be present during the test, and patients should be carefully followed as outpatients in case of delayed problems.

An Israeli group has reviewed the hemodynamic and adverse effects of dobutamine in 400 patients, of whom 187 were aged 65–79 years and 49 were 80 years or older (2). They found a very low incidence (1.5%) of serious adverse effects, even at high doses of up to 50 micrograms/kg/minute, and noted that most problems occur transiently at a lower dose and then resolve. Hypotension and dysrhythmias were the most common adverse effects, and their incidence was not related to age.

Acute subaortic left ventricular outflow tract obstruction has been described during dobutamine infusion in a patient who had no evidence of this at rest but developed severe obstruction when his pulse rate exceeded 105/minute (3). The subaortic gradient eventually reached the very high figure of 182 mmHg, even though the patient remained asymptomatic and there was no clear reason why this occurred in this particular patient.

In 47 consecutive patients (mean age 64 years, 46 men) with three or more cardiovascular risk factors, intravenous dobutamine was given at a rate of 40 micrograms/kg/minute until the target heart rate was achieved, which took a mean of 11.6 minutes (4). Subjective sensations occurred in 49% of the patients (palpitation 21%, chest pain 6%, nausea 6%, headache 6%, dizziness 13%), while half the patients had abnormal cardiac rhythms (ventricular extra beats 38%, supraventricular tachycardia 10%, and non-sustained ventricular tachycardia 2%). The authors concluded that the safety and tolerability of this procedure is comparable to that of standard dobutamine stress testing, although its specificity and selectivity are still uncertain.

The value and safety of dobutamine stress echocardiography have been studied in 135 patients aged 70 years or older (mean age 74 years; 58% men) soon after

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myocardial infarction (5). A diagnostic end-point was reached in 83% of patients, a figure comparable to younger populations. No major complications were reported. The procedure was terminated prematurely because of symptomatic hypotension ($n=8$), non-sustained ventricular tachycardia ($n=2$), systolic hypertension ($n=2$), atrial fibrillation ($n=1$), or bladder discomfort ($n=1$). All of these problems resolved rapidly after the procedure was stopped. At the time of discontinuation, seven of these 16 patients had objective evidence of myocardial ischemia.

Cardiac dysrhythmias

Dobutamine increases cardiac output after acute myocardial infarction without exacerbating myocardial infarction or ventricular dysrhythmias. However, a mild increase in heart rate often occurs, and occasionally a more marked tachycardia.

Cardiac dysrhythmias of various types (including occasional ventricular dysrhythmias) when dobutamine is used as a stress-inducing agent during echocardiography have been described (SEDA-18, 158).

- A 56-year-old woman with dilated cardiomyopathy developed QT interval prolongation and torsade de pointes during infusion of dobutamine in a low dose (2.5 micrograms/kg/minute). She had no previous documented dysrhythmias (6). She was hypokalemic and when her plasma potassium concentration was restored to normal the dysrhythmia disappeared and the QT interval normalized. The authors observed that this was the first case of its kind and emphasized the importance of normokalemia in dobutamine-treated patients.
- A 55-year-old man with stable angina was admitted for dobutamine stress testing (7). He had been taking metoprolol, but this was withdrawn 2 days before the test. During the lowest dose of the dobutamine infusion (5 micrograms/kg/minute) his heart rate rose to 143/minute and he developed chest pain and ST segment depression in the lateral chest leads of the electrocardiogram. The drug was stopped and metoprolol and glyceryl trinitrate were given immediately, but a few minutes later he developed torsade de pointes followed by ventricular fibrillation. Resuscitation was unsuccessful. There was no evidence of acute myocardial infarction at autopsy.
- A 74-year-old man with idiopathic dilated cardiomyopathy was given dobutamine (5 micrograms/kg/minute) to determine whether it would produce a positive inotropic effect (8). After 14 minutes he developed asymptomatic pulsus alternans, which resolved within 20 minutes of withdrawal.

A much more serious complication of dobutamine therapy is ventricular dysrhythmias. Of 305 patients with acutely decompensated congestive heart failure, 58 were given dobutamine (although it is difficult to ascertain the dose), 44 were given other standard inotropic drugs such as milrinone, and 203 were treated with brain natriuretic peptide (nesiritide, 0.015 or 0.03 micrograms/kg/minute) (9). Of those given dobutamine 7% had sustained ventricular tachycardia, 17% had non-sustained ventricular tachycardia, and 5% had a cardiac arrest. In contrast, the figures for nesiritide were 1, 11, and 0% respectively. There was no analysis of other outcomes but these results certainly do not encourage the use of dobutamine in these very vulnerable patients.

A study from Rotterdam, has examined the consequences of adding atropine to dobutamine in 200 patients with impaired left ventricular function (ejection fraction less than 35%) (10). There were cardiac dysrhythmias in 6% of patients and significant hypotension in 11%, figures comparable to those in other published studies. In the 36 patients who required atropine to achieve target heart rates the incidence of adverse effects was not increased. The same group has studied over 1000 consecutive patients undergoing dobutamine stress scintigraphic imaging of the myocardium (11). In these patients the incidence of dysrhythmias was about 8%, of whom about half had transient ventricular tachycardia, but only about 3% had significant hypotension (defined as a fall in systolic blood pressure of 40 mmHg). Atropine was required in nearly 40% of the patients in order to achieve target heart rates, but it is difficult to determine whether this had any influence on the occurrence of adverse effects.

A report from the Mayo Clinic has described 27 elderly patients (mean age 71 years) with aortic stenosis in whom dobutamine stress hemodynamic testing was used to assess the severity of the stenosis (12). There were no severe adverse effects, but relatively minor problems occurred in 16 patients, including chest pain and ventricular extra beats ($n=9$ each) and atrial dysrhythmias ($n=4$). The authors concluded that the procedure appears to be safe in these high-risk patients, although its diagnostic value may be limited.

There are variants of the standard procedure that do not appear to be associated with increased risk. An accelerated high-dose protocol, in which a constant infusion of 50 micrograms/kg/minute was given for up to 10 minutes in 100 patients, has been compared with the standard stepwise procedure in a similar number (13). The cumulative dose was somewhat lower in the accelerated protocol, while the duration of the test was halved. Dysrhythmic adverse effects occurred in 28 patients on the accelerated protocol and in 39 of those tested by the standard method: this difference was said to be non-significant. In another study, transesophageal was compared with transthoracic dobutamine stress echocardiography in 63 and 100 patients respectively (14). Baseline pulse and blood pressure were higher in the transesophageal group. The authors noted that there were no cases of ventricular tachycardia or fibrillation in either group, or of myocardial infarction. They also stated that the incidence of less serious dysrhythmias was similar in the two groups; however, no figures were quoted.

In the PRECEDENT study, dobutamine was compared with nesiritide (B natriuretic peptide) in patients with acutely decompensated congestive heart failure (15). The primary objective of the study was to assess the risk of ventricular dysrhythmias with the two therapies. Altogether 255 patients (mean age 61 years, 67% men) were randomized to receive dobutamine 5 micrograms/kg/hour or one of two doses of nesiritide 0.015 or 0.03 micrograms/kg/hour. Dobutamine significantly

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increased the number of episodes of ventricular tachycardia by 48/day, ventricular extra beats by 69/hour, and overall heart rate by 5/minute. These parameters were unchanged or improved by nesiritide. Since the two drugs had similar effects on the hemodynamic features of heart failure and its symptoms, the authors concluded that nesiritide should be considered as an alternative to dobutamine in this type of patient.

Myocardial ischemia

Angina and coronary artery spasm (16) have also occurred under these and other conditions. Some 10% of patients require treatment for angina occurring during stress testing, but up to a quarter have ischemic changes on the electrocardiogram (SEDA-17, 163), while others have headache, palpitation, anxiety, nausea, tingling, and flushing.

Myocardial ischemia has also been reported in susceptible patients. A Japanese group carried out dobutamine stress echocardiography in 51 patients with a presumptive diagnosis of variant angina (17). All had coronary vasospasm in response to intracoronary acetylcholine and seven also had chest pain and reversible ST segment elevation. One must incidentally wonder whether this procedure was entirely advisable.

In 47 patients in Mannheim (mean age 61 years, 34 men) dobutamine echocardiography was carried out, with blood sampling immediately before and after the procedure and then at 1, 2, 4, 6, and 12 hours (18). Assays were carried out for creatine kinase-MB, troponins I and T, myoglobin, and fibrin monomer antigen. There were no significant increases in these markers of myocardial damage and coagulation, regardless of the outcome of the stress test. These findings have confirmed those of an earlier study, although the data do not absolutely exclude abnormal findings in a minority of individuals (19).

Hypotension

In one study 38% of patients undergoing dobutamine stress echocardiography developed hypotension. Increases in blood pressure are more in line with what one would expect. Although dobutamine does not as a rule cause a marked increase in systolic blood pressure in normotensive patients, hypertensive patients can develop marked systolic hypertension during an infusion of the drug. When stress echocardiography with dobutamine is performed in subjects who prove to be entirely healthy, an audible Still's-like vibratory systolic ejection murmur is nevertheless produced.

Severe peripheral ischemia (even leading to dermal necrosis) can occur, as with dopamine (20).

Urinary tract

Urinary urgency can occur during infusion of a relatively high dose (15 micrograms/kg/minute) of dobutamine (21).

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Docetaxel

See also Cytostatic and immunosuppressant drugs

General Information

Docetaxel is a taxane that is used in combination with doxorubicin in the treatment of metastatic breast cancer and as a single agent in metastatic lung cancer.

Organs and Systems

Respiratory

Interstitial pneumonitis has been attributed to docetaxel in four cases (1). None of the patients had lung disease and they all had normal liver function. Within 8–14 days of receiving a second cycle of docetaxel (75 mg/m^2 in three cases and 60 mg/m^2 in the other), all developed acute dyspnea and fever, which progressed until they needed ventilation; two died. In contrast, in a study of 33 patients treated with paclitaxel and carboplatin, only one had reduced diffusion capacity for carbon monoxide, with no accompanying clinical or radiological changes (2).

Fluid balance

Fluid retention has previously been reported with docetaxel. Some believe that this effect depends on the dose and the duration of infusion (3,4) and that high concentrations of M4, the cyclized oxazolidinedione metabolite of docetaxel, cause more pronounced fluid retention.

Hematologic

In 46 chemotherapy-naive patients, docetaxel had an important but reversible non-specific lymphopenic effect, thought to be associated with an increased risk of non-neutropenic infections (5).

Gastrointestinal

Three of 14 patients in a phase 1 study of docetaxel plus vinorelbine for metastatic breast cancer developed colitis (6). A further three patients were identified in other studies of docetaxel.

Skin

Of 99 patients who received low-dose docetaxel (60 mg/m^2 every 3 or 4 weeks), 25 had skin toxicity, mainly erythema and nail changes (7). Of a subset of 25 patients who received irradiation before docetaxel, four had recall dermatitis during their first infusion of docetaxel. All had previously received doxorubicin, which may in part have explained some of the toxicity.

Maculopapular eruptions and desquamation of hands and/or feet occurred in 35% of patients with non-small cell lung cancers given docetaxel (8).

Four cases of fixed plaques of erythrodysesthesia have been attributed to intravenous docetaxel (9). There had been no extravasation or previous skin injury. While this was a new presentation, the authors did not explain why the lesions were not just late presentations of small-volume extravasation injuries.

Nails

Onycholysis has been reported in patients receiving docetaxel (10).

Immunologic

A 25% incidence of grade 2 or more severe immunological reactions to docetaxel has been reported after the use of oral prednisone (100 mg orally before treatment and 50 mg once on the morning of treatment and the following 2 days) in 20 patients with non-small-cell lung cancers (8). No other premedications were given routinely. If infusion-related symptoms occurred, the infusion was interrupted and diphenhydramine was given. On subsequent cycles those patients then were routinely premedicated with diphenhydramine 25 or 50 mg intravenously and cimetidine 300 mg intravenously.

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Dofetilide

See also Antidysrhythmic drugs

General Information

Dofetilide is a pure Class III antidysrhythmic drug, without actions of any other class. It was developed following the observation that bis(arylalkyl)amines with methanesulfonamido moieties on both aryl groups prolong the cardiac action potential without significantly altering the maximum rate of depolarization (1). The pharmacology, clinical pharmacology, uses, adverse effects, and interactions of dofetilide have been reviewed (2–8). Cardiovascular adverse effects of dofetilide are the most troublesome. Other common effects have included mild headache, dizziness, dyspepsia, nausea, and vomiting (9).

Pharmacology

Dofetilide is a highly selective blocker of the rapidly activating component of the inward rectifier potassium channel, IK_r (10–16). It therefore delays ventricular repolarization, which becomes less heterogeneous (17), and prolongs the action potential duration and effective refractory period (14,18,19); it has the same effects in ventricular muscle in dilated cardiomyopathy and chronic ischemic cardiomyopathy (10). It has greater affinity for atrial than ventricular tissues in animals (20), but probably not in man (14,18). It preferentially blocks open channels and has Group 3 actions (SEDA-25, 209), with slow-onset kinetics (21) and an increased likelihood of being prodysrhythmic at slower heart rates (22).

Dofetilide causes a dose-related and plasma concentration-related prolongation of the QT_c interval (14,18,19,23–27), and either reduces QT_c dispersion (26) or has no effect on it (28,29). The effects on the QT_c interval are rate-dependent, being greater at slower heart rates (30). Dofetilide does not usually broaden the QRS complex, but this was reported (and published twice) in a single patient with atrial fibrillation, in whom it was attributed to aberrant conduction (31,32).

During repeated oral administration of dofetilide 1.0–2.5 mg/day for 5 days the effect on the QT interval was slightly greater on day 1 than on day 5 at a range of plasma concentrations of about 1–4 ng/ml; this observation suggests the occurrence of tolerance, but in that case one would have expected a clockwise hysteresis loop in the effect concentration curve, and no hysteresis was seen either after a single dose or at steady state (25).

Dofetilide has a small positive inotropic effect in animal hearts (15,33). In a double-blind, placebo-controlled study of oral dofetilide 125, 250, or 500 mg bd for the maintenance of sinus rhythm after cardioversion of sustained atrial fibrillation or flutter in 201 patients, there were small changes in echocardiographic measures of atrial contractility, but no changes in stroke volume or cardiac output (34).

Clinical pharmacology

The pharmacokinetics of dofetilide are linear after single oral doses of 2–10 micrograms/kg (24,35) and repeated doses of 1.0–2.5 mg/day (25). Dofetilide is well absorbed (about 90%) after oral administration (24,35,36). Its absorption is relatively slow and peak concentrations are not reached for 1–2.5 hours; absorption is slower after food. It is a low clearance drug, with a clearance rate of about 6 ml/minute/kg, and has a volume of distribution of about 3 l/kg (23,36). It is mostly excreted unchanged by the kidneys, with a half-life of about 8 hours. Its clearance is therefore roughly proportional to creatinine clearance, particularly at high rates of clearance. A small proportion is metabolized in the liver by CYP3A4 to inactive metabolites (37).

In a pharmacokinetic–pharmacodynamic study in 10 healthy volunteers intravenous dofetilide 0.5 mg caused a mean maximum prolongation of the QT_c interval of 121 ms and the mean plasma concentration associated with half-maximal effect was 2.2 ng/ml (36).

Uses

Dofetilide has been used to convert atrial fibrillation and atrial flutter to sinus rhythm, in maintaining sinus rhythm thereafter, in suppressing paroxysmal supraventricular tachycardia, inducible atrioventricular nodal re-entry tachycardia, and inducible sustained ventricular tachycardia, in suppressing the dysrhythmias of the Wolff–Parkinson–White syndrome, and in facilitating conversion of ventricular fibrillation.

Open clinical studies

In 19 patients with atrial fibrillation and five with atrial flutter, dofetilide 2.5–8.0 micrograms/kg caused conversion to sinus rhythm in 14 (10 with atrial fibrillation and four with atrial flutter) (38).

In patients with sustained monomorphic ventricular tachycardia inducible by programmed electrical stimulation, who had previously been unsuccessfully treated with

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0–7 other drugs, intravenous dofetilide 3–15 micrograms/kg suppressed or slowed inducible ventricular tachycardia in 17 of 41 patients, compared with none of nine patients who received only 1.5 micrograms/kg (19).

Intravenous dofetilide 2.5–5.0 micrograms/kg produced sinus rhythm in seven patients with paroxysmal atrial fibrillation of recent onset (under 7 days) and terminated paroxysmal supraventricular tachycardia in four of six patients (39).

In patients with electrically inducible atrioventricular re-entrant tachycardia intravenous dofetilide 1.5–15 micrograms/kg had no effect on tachycardia inducibility at two lower doses but prevented the re-induction of tachycardia at three higher doses in 11 of 31 patients (40).

Placebo-controlled studies

Conversion of atrial fibrillation and flutter

In a crossover, placebo-controlled study in 16 patients with recent onset atrial fibrillation, cardioversion was achieved in two of six patients who received dofetilide 8 micrograms/kg and in two of nine who received 12 micrograms/kg (41). None cardioverted with placebo. However, the average duration of atrial fibrillation was 35 days in those who cardioverted with dofetilide and 83 days in those who did not. The authors concluded that dofetilide had only limited effect in cardioverting atrial fibrillation of moderate duration.

In a double-blind, placebo-controlled study 98 patients, who developed atrial fibrillation/flutter within 1–6 days after coronary artery bypass graft surgery, were given dofetilide 4 or 8 micrograms/kg intravenously over 15 minutes (42). Eight of 33 patients converted to sinus rhythm after placebo, 12 of 33 after dofetilide 4 micrograms/kg, and 14 of 32 after dofetilide 8 micrograms/kg.

In a double-blind, placebo-controlled study in patients with sustained atrial fibrillation ($n = 75$) or atrial flutter ($n = 16$), dofetilide 8 micrograms/kg terminated the dysrhythmia in nine of 29 patients, compared with only four of 32 who received 4 micrograms/kg and none of 30 who received placebo (43). Patients with atrial flutter had a greater response to dofetilide (six of 11) than those with atrial fibrillation (five of 49).

In a placebo-controlled study in patients with atrial fibrillation or atrial flutter with a median dysrhythmia duration of 62 (range 1–180) days, there was conversion to sinus rhythm in 20 of 66 patients given dofetilide, compared with one of 30 patients given placebo (44). The conversion rate was higher in atrial flutter (seven of 11 patients) than in atrial fibrillation (13 of 55).

In a double-blind, placebo-controlled study in 325 patients with atrial fibrillation or flutter cardioversion, rates for dofetilide 125, 250, and 500 micrograms bd were 6.1, 9.8, and 30% respectively, compared with 1.2% with placebo (45). The probabilities of remaining in sinus rhythm at 1 year with dofetilide 125, 250, and 500 micrograms bd were 0.40, 0.37, and 0.58 respectively, and 0.25 for placebo.

In a double-blind, placebo-controlled study in 69 patients with atrial fibrillation or flutter, intravenous dofetilide 2–8 micrograms/kg caused conversion to sinus rhythm in 16 of 51 patients, compared with one of 18 who were given placebo; conversion of atrial flutter occurred in five of seven who were given dofetilide compared with none of three who were given placebo (46).

In a randomized, placebo-controlled, crossover study in 15 men, mean age 34 (range 18–63) years, with Wolff–Parkinson–White syndrome and atrial fibrillation or atrioventricular re-entrant tachycardia induced electrophysiologically, six of ten patients who were given dofetilide converted to sinus rhythm, compared with one of five who were given placebo (47). There were no dysrhythmias.

Ventricular tachydysrhythmias

In a placebo-controlled study, sustained ventricular tachycardia or fibrillation, reproducibly inducible electrophysiologically, was no longer inducible in eight of 18 patients who were given intravenous dofetilide 0.1–8.0 ng/ml, compared with one of six patients who received placebo (48).

In a randomized, double-blind, placebo-controlled study in 32 patients with ventricular extra beats (more than 30/hour on two consecutive 24-hour Holter recordings while drug free and more than 50/hour during 2-hour telemetric electrocardiography), dofetilide 7.5 micrograms/kg produced an 83% and placebo a 2.9% median reduction in ventricular extra beats (49).

Sudden death

The Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) study comprised two studies in patients at high risk of sudden death: one in patients with congestive heart failure and one in patients with acute myocardial infarction within the previous 7 days (50).

In the congestive heart failure study, 1518 patients with symptomatic congestive heart failure and severe left ventricular dysfunction were recruited at 34 Danish hospitals; 762 were randomized double-blind to dofetilide and 756 to placebo (51). After 1 month, 22 of 190 patients with atrial fibrillation at baseline had sinus rhythm restored by dofetilide, compared with only three of 201 who took placebo. Dofetilide was also significantly more effective than placebo in maintaining sinus rhythm (hazard ratio for the recurrence of atrial fibrillation = 0.35; CI = 0.22, 0.57). Dofetilide significantly reduced the risk of hospitalization for worsening congestive heart failure (risk ratio = 0.75; CI = 0.63, 0.89). During a median follow-up of 18 months, 311 patients taking dofetilide and 317 patients taking placebo died (hazard ratio = 0.95; CI = 0.81, 1.11).

In the corresponding myocardial infarction study, 1510 patients with severe left ventricular dysfunction after myocardial infarction were recruited in 37 Danish coronary-care units; 749 were randomized double-blind to dofetilide and 761 to placebo (52). There were no significant differences between dofetilide and placebo in all-cause mortality or total dysrhythmic deaths. Dofetilide was significantly better than placebo at restoring sinus rhythm in patients with atrial fibrillation or flutter.

Comparative studies with other antidysrhythmic drugs

Amiodarone

In a comparison of intravenous dofetilide (8 micrograms/kg; $n = 48$), amiodarone (5 mg/kg; $n = 50$),

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or placebo ($n = 52$) in converting atrial fibrillation or flutter to sinus rhythm in 150 patients, sinus rhythm was restored in 35, 4, and 4% respectively (53).

Flecainide

In a non-randomized comparison of flecainide (2 mg/kg; $n = 11$) and dofetilide (8 micrograms/kg; $n = 10$) in patients with atrial flutter, only one patient given flecainide converted to sinus rhythm compared with seven of the 10 patients given dofetilide (54).

Propafenone

In a randomized, placebo-controlled, parallel-group comparison of oral dofetilide 500 micrograms bd, propafenone 150 mg tds, or placebo in preventing the recurrence of paroxysmal supraventricular tachycardia in 122 symptomatic patients, the respective probabilities of remaining free of episodes of paroxysmal supraventricular tachycardia were 50, 54, and 6%; both dofetilide and propafenone also reduced the frequency of episodes (median numbers 1, 0.5, and 5 respectively) (55).

Sotalol

In a double-blind, randomized, crossover comparison of oral dofetilide 500 micrograms bd with sotalol 160 mg bd in 128 patients with ischemic heart disease and inducible sustained ventricular tachycardia, 46 patients responded to dofetilide and 43 to sotalol; however, only 23 patients responded to both dofetilide and sotalol (9).

The hemodynamic effects of dofetilide 500 micrograms bd and sotalol 160 mg bd for 3–5 days have been studied in 12 patients with ischemic heart disease and sustained ventricular tachycardia (56). There were significant reductions in heart rate, mean systemic pressure, and cardiac index (–13%) with sotalol, but cardiac index increased significantly with dofetilide (11%) with no effect on heart rate or systemic blood pressure. The authors suggested that oral dofetilide could be useful in patients with ventricular tachydysrhythmias associated with impaired left ventricular function. One patient taking dofetilide reported mild dizziness and there were no cardiac dysrhythmias.

Organs and Systems

Cardiovascular

Because dofetilide prolongs the QT interval, there is a risk of ventricular tachydysrhythmias, which have often been reported, after both intravenous and oral administration.

In 154 patients with implantable cardioverter-defibrillators randomly assigned to dofetilide or placebo, there were pause-dependent runs of polymorphic ventricular tachycardia in 15 of the 87 patients who received dofetilide and in only five of the 87 who received placebo (57). There were five early events (at less than 3 days of therapy), all torsade de pointes in patients taking dofetilide. There were 15 late events, 10 with dofetilide and five with placebo. The median time to a late event was 22 (range 6–107) days for dofetilide and 99 (34–207) days for placebo.

In the DIAMOND study in congestive heart failure, there were 25 cases of torsade de pointes in the dofetilide group (3.3%) compared with none in the placebo group (51). In the DIAMOND myocardial infarction study there were seven cases of torsade de pointes (0.93%), all in those who were given dofetilide (52).

In a double-blind, placebo-controlled study in 325 patients with atrial fibrillation or atrial flutter randomized to dofetilide 125, 250, or 500 micrograms bd or placebo, there were two cases of torsade de pointes, one on day 2 and the other on day 3 (0.8% of all patients given the active drug); there was one sudden cardiac death, classified as prodysrhythmic, on day 8 (0.4% of all patients given the active drug). The authors recommended that dosage adjustment based on QT_c interval and renal function would minimize the small but not negligible prodysrhythmic risk of dofetilide.

In 128 patients who received dofetilide and sotalol in a crossover study, there were treatment-related adverse events in 2.3% of the patients who received dofetilide and 8.6% of those who received sotalol (9). Three patients who took dofetilide had torsade de pointes.

In a comparison of intravenous dofetilide (8 micrograms/kg; $n = 48$), amiodarone (5 mg/kg; $n = 50$), or placebo ($n = 52$) in converting atrial fibrillation or flutter to sinus rhythm in 150 patients, two patients given dofetilide had non-sustained ventricular tachycardias; four had torsade de pointes, in one case requiring electrical cardioversion (53).

- In one of 10 healthy men given intravenous dofetilide 0.5 micrograms/kg there was prolongation of the QT_c interval from 451 to 808 ms 5 minutes after the end of the infusion; this was associated with five beats of polymorphic ventricular tachycardia, several multifocal ventricular extra beats, and ventricular couplets and triplets, all within 10 minutes after the end of the infusion (24).
- In a 37-year-old woman with atrial flutter with 1:1 conduction and partial right bundle branch block, intravenous dofetilide 5 micrograms/kg given over 5 minutes not only suppressed the atrioventricular nodal block to 2:1 or 3:1 but also caused complete right bundle branch block and QT interval prolongation (58).
- Self-limiting torsade de pointes developed in a 67-year-old man who was given 12.8 micrograms/kg (plasma concentration 7.1 ng/ml) in an open study; the QT_c interval was prolonged to over 600 ms (19).

This patient had stopped taking amiodarone 1 month before the administration of dofetilide, and that may have contributed to the prolongation of the QT_c interval.

- A woman with atrial fibrillation developed torsade de pointes after receiving intravenous dofetilide 6 micrograms/kg (plasma concentration 26 ng/ml) (41).
- A patient with atrial fibrillation received intravenous dofetilide 8 micrograms/kg and developed torsade de pointes before reverting to sinus rhythm (41).
- One of 18 patients with sustained ventricular tachycardia or fibrillation, reproducibly inducible electrophysiologically, developed torsade de pointes after receiving intravenous dofetilide 8 micrograms/kg (plasma concentration 5.3 ng/ml) (48).
- Short episodes of aberrant ventricular conduction and ventricular tachycardia occurred in three of 32

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patients with atrial fibrillation who were given dofetilide 8 micrograms/kg (42).

- Torsade de pointes occurred in two of 62 patients with atrial tachydysrhythmias who received dofetilide 4 or 8 micrograms/kg; two other patients had ventricular extra beats associated with prolongation of the QT_c interval (43).
- In a placebo-controlled study of the effect of dofetilide 8 micrograms/kg in converting atrial fibrillation or flutter, transient torsade de pointes occurred in two men, aged 57 and 67, with prolongation of the QT_c interval from 370 and 420 ms to 450 and 510 ms respectively (44).
- A 58-year-old woman developed torsade de pointes with prolongation of the QT_c interval to 490 ms after receiving intravenous dofetilide 4.3 micrograms/kg; she responded to intravenous magnesium sulfate plus isoprenaline (46).

Other cardiac dysrhythmias that have been reported have included episodes of junctional rhythm with bundle branch block, spontaneous atrioventricular re-entrant tachycardia, and sustained supraventricular tachycardia (40).

Hypotension occasionally occurs after intravenous dofetilide (40).

Death

The risk of death in patients with supraventricular dysrhythmias taking dofetilide has been studied in a systematic review of randomized controlled trials (59). After adjusting for the effects of dysrhythmia diagnosis, age, sex, and structural heart disease, the hazard ratio was 1.1 (CI = 0.3, 4.3).

Drug–Drug Interactions

Digoxin

In 14 healthy men dofetilide 250 micrograms bd for 5 days had no effect on the pharmacokinetics of digoxin at a steady-state trough concentration of 1.0 ng/ml (60). However, in a placebo-controlled study in patients with atrial fibrillation or atrial flutter, conversion to sinus rhythm in patients given dofetilide was more likely if they were also given digoxin (44), suggesting that there may be a pharmacodynamic interaction.

Histamine (H_2) receptor antagonists

In a randomized, placebo-controlled study of the effects of cimetidine and ranitidine on the pharmacokinetics and pharmacodynamics of a single dose of dofetilide 500 micrograms in 20 healthy men, ranitidine 150 mg bd did not affect the pharmacokinetics or pharmacodynamics of dofetilide, but there was a dose-dependent increase in exposure to dofetilide with cimetidine (61). With cimetidine 100 and 400 mg bd the AUC of dofetilide increased by 11 and 48%, the maximum plasma dofetilide concentration increased by 11 and 29%, renal clearance fell by 13 and 33%, and non-renal clearance by 5 and 21%; dofetilide-induced prolongation of the QT_c interval was increased by 22 and 33%. The authors suggested that cimetidine inhibited renal tubular dofetilide secretion, an effect that is specific to cimetidine in its class. Cimetidine should be avoided in patients taking dofetilide.

Verapamil

Pharmacokinetic and pharmacodynamic interactions between dofetilide 0.5 mg bd and verapamil 80 mg tds have been studied in 12 healthy men (62). At steady state verapamil increased the peak plasma concentration of dofetilide from 2.40 to 3.43 ng/ml, without other pharmacokinetic effects. This was accompanied by a small increase in the prolongation of the QT_c interval produced by dofetilide alone, from 20 to 26 ms. Although this small effect is unlikely to be of clinical significance, it would be wise to avoid verapamil in patients taking dofetilide.

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Domperidone

General Information

Domperidone is a neuroleptic antiemetic, a dopamine receptor antagonist. It produces the expected range of dystonic and extrapyramidal adverse effects (1), which seem, as with metoclopramide, to be more likely to occur in children (2). It is difficult to accept that claims for lower frequencies than with metoclopramide are justified, particularly when one reads a report of neuroleptic malignant syndrome (3). Like its congeners, domperidone has repeatedly been shown to cause symptoms attributable to hyperprolactinemia (galactorrhea, amenorrhea, and breast tenderness), despite claims that there is a lower incidence of effects on prolactin concentrations. However, a study in patients with Parkinson's disease using domperidone did not suggest that the adverse effects are especially problematical in these patients (4).

Observational studies

The mechanism of action and clinical use of domperidone and its specific use in diabetic gastroparesis have been reviewed (5,6). Domperidone is generally well tolerated and has a low incidence of adverse effects. Adverse effects after oral administration include headache, dry mouth, diarrhea, itching, muscle cramps, and anxiety. Galactorrhea, breast tenderness, and pseudopregnancy can occur in women because of a dopamine-induced increase in serum prolactin concentration.

Comparative studies

The efficacy and adverse effects of domperidone and metoclopramide have been compared in a double-blind, multicenter, randomized trial in 93 insulin-dependent diabetics with symptomatic gastroparesis (7). Domperidone 20 mg qds and metoclopramide 10 mg qds, for 4 weeks, were equally effective in alleviating symptoms of gastroparesis. Somnolence, akathisia, anxiety, and depression were more

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severe with metoclopramide. Of the spontaneously reported adverse effects, nausea, vomiting, headache, insomnia, and diarrhea occurred in 6–10% of patients treated with domperidone and in up to 4% of patients treated with metoclopramide. The incidence of prolactin-related adverse effects was similar in the two groups (6%).

Organs and Systems

Cardiovascular

Intravenous infusion of domperidone, withdrawn some years ago, has caused convulsions and cardiac arrest (8–10).

Nervous system

- A 9-year-old child developed dysphagia and involuntary movements of the facial muscles after being treated with domperidone 0.25 mg/kg/day (11). There was complete recovery after withdrawal.

Drug–Drug Interactions

Anticholinergic drugs

Concomitant administration of anticholinergic drugs can antagonize the beneficial effects of domperidone (12).

Azole antifungals

Because domperidone is metabolized mainly by CYP3A4, interactions of azole antifungals with domperidone can occur. In human liver microsomes domperidone underwent hydroxylation to 5-hydroxydomperidone and N-dealkylation to 2,3-dihydro-2-oxo-1H-benzimidazole-1-propionic acid and 5-chloro-4-piperidinyl-1,3-dihydro-benzimidazol-2-one (13). The rate of domperidone metabolism correlated with the activity of CYP3A. Ketoconazole 1 μmol/l inhibited the metabolism of domperidone 5 μmol/l by 87%.

Cimetidine and antacids

Since cimetidine and antacids can interfere with the systemic availability of domperidone (SEDA-22, 389), they should not be co-administered.

Troleandomycin

In human liver microsomes domperidone underwent hydroxylation to 5-hydroxydomperidone and N-dealkylation to 2,3-dihydro-2-oxo-1H-benzimidazole-1-propionic acid and 5-chloro-4-piperidinyl-1,3-dihydro-benzimidazol-2-one. The rate of domperidone metabolism correlated with the activity of CYP3A. Troleandomycin 50 μmol/l inhibited the metabolism of domperidone 5 μmol/l by 64%.

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Donepezil

General Information

The approval of donepezil in several countries in America and Europe has been hailed as a major milestone, because it has met regulatory guidelines for the approval of antidementia drugs (1). Donepezil belongs to a piperidine class of reversible acetylcholinesterase inhibitors, chemically unrelated to either tacrine or physostigmine. It is highly specific for acetylcholinesterase and does not inhibit butyrylcholinesterase. The incidence of adverse effects with donepezil is comparable to that of placebo in controlled trials, and unlike tacrine, liver enzyme monitoring is not required. The long-term effectiveness of donepezil in large populations is yet to be established. Moreover, while it improves cognitive symptoms, it does not alter the course of the disease. Based on a limited number of studies, support for the use of donepezil in Alzheimer's disease has emerged (2–5).

Clinical trials of donepezil were funded by the manufacturer and appear to have been methodologically sound, although the absence of caregiver quality-of-life measures

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and outcomes related to activities of daily living is difficult to reconcile. An earlier 12-week study showed no improvement in caregiver quality of life with donepezil (4). As with most phase 3 studies, extrapolation of these results to routine practice is hampered by the fact that study populations are likely to be healthier than patients seen in routine clinical practice. Whether the results would be any different in a more heterogeneous population remains to be seen (6).

In a more recent 12-week double-blind, placebo-controlled, parallel-group study, aimed at establishing the efficacy and safety of donepezil in patients with mild to moderately severe Alzheimer's disease, donepezil (5 and 10 mg od) was well tolerated and efficacious (7). Adverse events significantly more common with donepezil were nausea, insomnia, and diarrhea, which appeared to be dose related and did not require treatment. Seven patients treated with placebo and six in each of the donepezil groups had serious adverse events during the trial. Three had events that were considered possibly related to donepezil. These included gastric ulceration with hemorrhage, syncope and a transient ischemic attack, nausea, aphakia, tremor, and sweating. Both groups of patients treated with donepezil had falls in mean heart rate that were larger than with placebo. Two patients treated with donepezil had electrocardiographic changes: one developed an intraventricular conduction defect and ventricular extra beats, while the other had sinus arrhythmia, left axis deviation, and increased QRS voltage, possibly secondary to left ventricular enlargement. Neither reported cardiovascular adverse events. Two patients taking placebo also had electrocardiographic abnormalities: one with bundle branch block, the other with sinus bradycardia and ventricular extra beats.

The launch of donepezil has attracted intense interest among both the scientific community and the public. The debate regarding "lessons for health care policy" (8) has been summarized:

(1) Licensing trials in highly selected patients may provide insignificant information on which to base clinical decisions, especially when the effect sizes are small and comorbidity is common.
(2) All trial evidence should be published before new drugs are marketed, and medical journals should not carry advertisements referring to unpublished data.
(3) Communication of benefits and risks should emphasize clinical effect sizes rather than statistical significance.
(4) Claims about effects on populations or services should be based on evidence.
(5) Secrecy surrounding licensing should be ended, and data from trials should be available for independent analysis.
(6) Overvaluation of new technology could threaten funding for vital but more mundane care.

There was intense debate in response to the above publication, as reflected by several letters to the Editor of the *British Medical Journal* (9–14).

Further evidence that donepezil is effective and well tolerated in treating symptoms of mild to moderately severe Alzheimer's disease has emerged from a multinational trial (15). Common adverse effects were nausea, vomiting, diarrhea, anorexia, dizziness, and confusion, consistent with previous findings.

A meta-analysis of various drugs approved for treating Alzheimer's disease in the USA and Canada has suggested that donepezil can delay cognitive impairment and deterioration in global health for at least 6 months in patients with mild-to-moderate Alzheimer's disease (16). Patients taking active treatment will have more favorable Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) scores for at least 6 months, after which their scores will begin to converge with those who are taking placebo. The cost-effectiveness data were inconclusive.

Although once-daily donepezil is effective and well tolerated for the symptoms of mild-to-moderate Alzheimer's disease (17), two practical questions arise:

(1) Which patients are too severely affected to be treated with donepezil?
(2) At what point should donepezil be discontinued if the patient continues to deteriorate?

The current status of donepezil in the management of Alzheimer's disease has been comprehensively reviewed (18). Several recent studies have confirmed the efficacy and tolerability of donepezil using different doses, study designs, and durations of treatment (19–23). Some relevant conclusions were the following:

(1) Younger patients should be targeted for assessment and treatment (24).
(2) Of the patients 6% discontinued medication owing to adverse events (23).
(3) Sleep disturbances were more common in trials with bedtime dosing of donepezil (22).
(4) Long-term safety and realistic improvement were observed over a period of up to 4.9 years (25).
(5) The presence of the apolipoprotein E4 allele did not predict donepezil failure (20).

Seven elderly patients with psychotic or non-psychotic behavioral symptoms in Lewy body dementia had some benefit from donepezil (26). Donepezil was withdrawn prematurely in three patients owing to poor response and/or adverse events. The adverse events were sedation, somnolence, worsening of chronic obstructive pulmonary disease, syncope, sweating, and bradycardia. These results have to be confirmed in controlled trials.

In two patients with Alzheimer's disease, donepezil provided some benefit in relieving cognitive symptoms, but there were increased behavioral problems, such as anxiety, agitation, irritability, and lack of impulse control; these were then successfully controlled by adding gabapentin (27).

The adverse effects of donepezil in general practice have been evaluated in a post-marketing pharmacovigilance study in 1762 patients in the UK (28). This observational cohort study used the technique of prescription-event monitoring for a minimum period of 6 months. The commonest adverse events were nausea, diarrhea, malaise, dizziness, and insomnia. Aggression, agitation, and abnormal dreams were uncommonly associated with the drug. There were no causally associated cardiac rhythm disturbances or liver disorders. The authors suggested that the abnormal dreams and psychiatric disturbances were possible adverse drug reactions that require further confirmation.

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The beneficial effect of donepezil on global ratings of dementia symptoms, cognition, and activities of daily living has been confirmed (29,30). Donepezil was to be well tolerated for periods up to 1 year, and adverse events were usually mild and transient, lasted only an initial few days, and typically resolved without the need for dosage modification. It has been suggested that patients with Alzheimer's disease do best while taking donepezil 10 mg/day and when the dosage is maintained at that level without interruption. Donepezil treatment effects that are lost after prolonged withdrawal do not fully recover when the drug is restarted (31).

Organs and Systems

Cardiovascular

Symptomatic sinus bradycardia is a possible adverse effect of treatment with donepezil in Alzheimer's disease (32).

- An 84-year-old patient with hypertensive cardiomyopathy developed bradycardia, fainting, and left-sided heart failure 3 weeks after starting treatment with donepezil. When donepezil was withdrawn, the sinus bradycardia disappeared; 24-hour electrocardiography showed no signs of sinus node disease, and no episodes of this type recurred during the next 6 months.

It is important to emphasize that disorders of cardiac rhythm associated with the use of donepezil are extremely unusual.

Nervous system

Convulsions have been reported during treatment with donepezil (33).

- A patient with mild Alzheimer's disease taking donepezil, 5 mg/day for 2 weeks and then 10 mg/day for 23 days, was admitted with convulsions. His only other medication was aspirin 100 mg/day. Blood analysis was normal, and a computerized tomographic (CT) scan showed a mild degree of cortical atrophy with no structural lesions. Donepezil was withdrawn, and no other drug treatment was given. Six weeks later, donepezil 5 mg/day was restarted. On day 52, he developed loss of consciousness and convulsions, necessitating withdrawal of donepezil.

Convulsions in Alzheimer's disease are very rare until late in the illness, and the authors attributed this patient's convulsions to donepezil.

Restless legs, mumbling, and stuttering have been reported in a patient taking donepezil (34). According to the Naranjo probability scale, the causality was probable, since rechallenge was positive.

Extrapyramidal effects have been reported in three patients taking donepezil; in two cases, the effects disappeared when donepezil was withdrawn (35).

Psychological, psychiatric

Behavioral worsening in seven patients with Alzheimer's disease after the start of donepezil therapy has been described (36). Their mean age was 76 years, and their mean score on the Mini-Mental State Examination was 18. Five patients had had dementia-related delusions and irritability before taking donepezil, one had had a history of major depression, and another had had a history of somatization disorder. At the start of treatment with donepezil, four were taking sertraline, one paroxetine, one venlafaxine, and four risperidone. All took donepezil 5 mg/day, and after 4–6 weeks the dosage in five patients was increased to 10 mg/day. In the other two cases, donepezil was discontinued after 5 weeks: in one case because of gastrointestinal symptoms and in the other because of increasing agitation. After an average of 7.3 (range 1–13) weeks after starting donepezil, all seven patients had a recurrence of previous behavioral problems. Five became agitated, one became depressed, and the other became more anxious and somatically preoccupied. The pattern of behavioral change involves regression to an earlier behavioral problem.

Violent behavior has been described with donepezil (37).

- A 76-year-old man who was taking oxybutynin 3 mg tds for bladder instability took donepezil 5 mg/day for presumed Alzheimer's disease and 5 days later became very paranoid, believing that his wife had been stealing his money. He beat her and held her hostage in their house with a knife until their daughter intervened. He was given haloperidol 0.5 mg bd, and donepezil and oxybutynin were withdrawn. His paranoid ideation resolved within a few days and did not recur despite withdrawal of haloperidol.

Although a causal relation between this violent incident and donepezil cannot be proved, the temporal relation was suggestive.

Liver

Donepezil has not been associated with hepatotoxic effects, which is a distinct advantage over tacrine. Donepezil treatment benefit persisted over 98 weeks, with no evidence of hepatotoxicity (38).

Urinary tract

Urinary incontinence may often be disregarded as a manifestation of dementia, but it has also been attributed to donepezil.

Of 94 patients with mild-to-moderate disease treated with recommended dosages of donepezil (3 mg/day during the first week and then 5 mg/day), 7 developed urinary incontinence (39). In five of them, the incontinence was transient, and there was no need to change the prescription. Incontinence occurred in both sexes, in relatively young and old patients, and in those with very mild-to-moderate dementia. In six patients the incontinence occurred at the higher dosage of 5 mg/day, in one patient it disappeared when donepezil was withdrawn, and in another an increase in dosage caused the reappearance of incontinence, suggesting a likely causal, dose-dependent relation between donepezil and urinary incontinence.

Urinary incontinence in patients with Down syndrome treated with donepezil has been described before (40). Urinary incontinence can be a major concern and a source of distress, not only for patients but also for caregivers. Clinicians should be alert to the possibility of urinary incontinence when prescribing donepezil for individuals

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with Alzheimer's disease. The authors emphasized that the incontinence may often be transient and not serious, but it could limit a patient's activities and quality of life and could also affect therapeutic adherence.

Skin

A purpuric rash associated with donepezil has been reported (41).

- An 82-year-old woman with hypertension, taking long-term atenolol and doxazosin, developed moderate cognitive impairment attributed to Alzheimer's disease. She was given donepezil 5 mg/day and, after 4 days, developed diarrhea, vomiting, and a purpuric rash on her trunk, arms, and legs. Platelet counts were 119–157 $\times$ 10^9/l. Donepezil was withdrawn, with resolution of the gastrointestinal symptoms.

Donepezil was the probable cause of this rash, because of the temporal association with treatment and its recurrence on rechallenge.

Susceptibility Factors

Other features of the patient

Three patients with Alzheimer's disease associated with Down syndrome were treated with donepezil (40). One became agitated and aggressive; the other two developed urinary incontinence. In all three cases donepezil was withdrawn. These results are important, because many individuals with Down syndrome develop clinical and neuropathological evidence of Alzheimer's disease after the age of 40 years. Also, patients with Down syndrome were excluded from donepezil clinical trials. Therefore, lesser data on the efficacy or safety of donepezil are available for this population.

Drug Administration

Drug overdose

Two cases of donepezil overdose have been reported (42,43).

- A 79-year-old nursing home patient was given donepezil 50 mg in error. She developed nausea, vomiting, and persistent bradycardia—typical cholinergic adverse effects. She was treated with atropine, 0.2 mg as needed, for bradycardia (total dose 3 mg over 18 hours) and was discharged on the second day.
- A 74-year-old woman with a history of stroke, myocardial infarction, hypothyroidism, and probable multi-infarct dementia took nine donepezil tablets (a total dose of 45 mg). She developed nausea and vomiting 2 hours later. She fell asleep for 4–5 hours but remained rousable. About 9 hours after ingestion, she became flushed and had a bout of diarrhea. Donepezil was withdrawn for 3 days, and there were no adverse effects when it was reintroduced.

Drug–Drug Interactions

Neostigmine

An additive inhibitory effect of donepezil and neostigmine on acetylcholinesterase has been proposed to explain prolonged neuromuscular blockade during anesthesia in an 85-year-old woman taking donepezil (44).

Paroxetine

A possible interaction between donepezil and paroxetine has been described (45).

- Two elderly patients with Alzheimer's disease and a mood disorder were treated with donepezil 5 mg/day and paroxetine 20 mg/day. One of them became agitated, confused, and aggressive, and donepezil was withdrawn after 8 days. On reintroduction of donepezil she again became rapidly confused, irritable, and verbally aggressive. In the other case, while the patient was taking paroxetine, donepezil 5 mg/day resulted in severe diarrhea, flatulence, and insomnia. The dosage of donepezil was reduced to 5 mg on alternate days, but the diarrhea and flatulence persisted. The symptoms resolved when donepezil was stopped.

Donepezil is metabolized in the liver by CYP2D6 and CYP3A4. Selective serotonin re-uptake inhibitors (SSRIs), such as paroxetine, are potent inhibitors of CYP2D6. Mood disorders are common in patients with Alzheimer's disease, and SSRIs are used in these patients and can increase the plasma concentration of donepezil, increasing the risk of severe adverse reactions.

Risperidone

Extrapyramidal effects occurred in a patient who took donepezil and risperidone concurrently (46). Although risperidone is less likely than conventional antipsychotic drugs to cause extrapyramidal effects, and is therefore particularly useful for older patients who are very susceptible to developing extrapyramidal disturbances, an increase in brain acetylcholine resulting from donepezil, along with dopamine receptor blockade by risperidone, would have led to an imbalance between cholinergic and dopaminergic systems. Although a clinically significant interaction between donepezil and risperidone seems to be rare, clinicians should be alert to such a possibility.

Tiapride

Parkinsonism has been reported in a patient concurrently taking donepezil and tiapride, probably through a pharmacodynamic interaction (47).

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Dopamine

General Information

Dopamine is a naturally occurring catecholamine and central neurotransmitter capable of raising cardiac output, reducing peripheral resistance, and specifically increasing renal blood flow. Infusions (generally up to 10 micrograms/kg/hour) have proven valuable in shock and congestive heart failure.

Common adverse reactions during infusion include extra beats, tachycardia, and palpitation. Angina pectoris, bradycardia, altered cardiac conduction, nausea and vomiting, headache, and dyspnea can occur. Piloerection and uremia have been reported and blood pressure can either rise or fall.

Organs and Systems

Cardiovascular

The major risk during dopamine treatment is that of severe peripheral ischemia, particularly in patients in whom the peripheral circulation is already impaired, since dopamine is converted to noradrenaline; gangrene has repeatedly resulted. In some of the reported cases the error lay in extravasation of dopamine from a peripheral venous infusion site; in others the dosage had been high and prolonged, or ergometrine had also been given. In cases of pre-existing vascular damage from arteriosclerosis, diabetes, Raynaud's disease, or frostbite, particular care must be taken. If discoloration appears, the infusion should be stopped and phentolamine 5–10 mg given intravenously. Nitroprusside may fail to prevent the onset of gangrene.

Nervous system

In one case, dopamine was considered to have produced myoclonic encephalopathy (1).

Hematologic

When used to treat low-output congestive heart failure, dopamine can inhibit platelet aggregation, in contrast to the platelet-aggregating properties of many catecholamines (2).

Susceptibility Factors

Other features of the patient

For obvious reasons, the use of dopamine may be dangerous in cases of coronary or peripheral vascular disorders. Dopamine used for hypotension during percutaneous transluminal angioplasty (PTCA) can be associated with diffuse coronary spasm, and it should therefore be used with caution, particularly if high doses are required. When dopamine aggravates pulmonary hypertension and right ventricular failure, isoprenaline should be considered as an alternative inotropic drug.

Drug–Drug Interactions

Alkali

Dopamine is unstable in the presence of alkalis (3). It should not be infused in bicarbonate solutions.

Cyclopropane and halogenated hydrocarbon anesthetics

In the nucleus accumbens of rats the dopamine concentration was increased by both cyclopropane and halothane anesthesia; cyclopropane, but not halothane, also increased the dopamine concentration in the caudate nucleus halothane, but not cyclopropane, significantly reduced the dopamine concentration in the ventral nucleus of the thalamus (4). It has been suggested that potentiation of the actions of dopamine could occur with cyclopropane or halogenated hydrocarbon anesthetics, but there is no direct evidence that this interaction occurs in humans.

Monoamine oxidase inhibitors

The hypertensive effect of dopamine is potentiated by monoamine oxidase inhibitors.

- A 75-year-old man who was taking selegiline 5 mg bd for Parkinson's disease was given an intravenous infusion of dopamine for reduced urine output and hypotension (5). Within minutes of starting the infusion, his systolic blood pressure rose from 105 to 228 mmHg. Similar reactions occurred during two subsequent rechallenges.

The authors proposed that selegiline may have caused this effect by inhibiting dopamine metabolism, and that selegiline may not be as specific an inhibitor of monoamine oxidase type B as previously thought.

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Dopexamine

General Information

Dopexamine, which is related structurally to dopamine, is a potent beta$_2$-adrenoceptor agonist (1). Its reported adverse effects include cases of atrial fibrillation and single instances of supraventricular tachycardia and hypotension.

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Dornase alfa

General Information

Dornase alfa is human recombinant deoxyribonuclease. Daily therapy with dornase alfa in patients with cystic fibrosis can reduce the frequency of respiratory infections and improve lung function in patients with bronchiectasis.

Therapeutic studies

The role of dornase alfa in modifying bronchial secretions in patients with cystic fibrosis has been evaluated in 54 subjects aged 5 years or over (1). They were treated for 12 months with mesna by nebulizer bd and oral ambroxol (30 mg bd). Dornase alfa was then given once daily by aerosol 2.5 mg for 12 months. Mesna and ambroxol caused reductions in FEV_1 and FVC (FEV_1 fell by 11%, FVC by 13%). After 12 months of dornase alfa, FEV_1 had increased by 7.7% and FVC by 5.3%. The patients found treatment with dornase alfa more acceptable than mucolytic therapy. Hemoptysis was the only reported adverse effect, but it occurred frequently in only one patient.

The effect of daily nebulized dornase for 24 weeks has been studied in a randomized, double-blind, placebo-controlled trial in 349 patients with idiopathic bronchiectasis (2). Three patients withdrew from the trial; two in the placebo group (hemoptysis and sinusitis) and one in the treatment group (increased sputum production, probably an adverse event). The primary outcome measures were the number of infective exacerbations and a fall in FEV_1. There were more exacerbations in the treatment group, with a relative risk of 1.35 (not statistically significant). The rate of fall in FEV_1 and FVC was significantly higher in the treatment group than in the placebo group, and the treatment group required more days of antibiotics and corticosteroids. Four patients died during the study, three in the treatment group. No deaths were considered to have been due to the treatment. Adverse events occurred equally in both groups, the commonest being non-specific respiratory disorders (10% in the placebo group and 15% in the treatment group). No other adverse events were detailed. These results suggest that dornase is not effective in patients with idiopathic bronchiectasis and may even be detrimental. Dornase should not be used in these patients.

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Dosulepin

See also Tricyclic antidepressants

General Information

Dosulepin (dothiepin) is a tricyclic antidepressant that has been available in Europe for over 30 years and is particularly popular in the UK. Its animal and clinical pharmacology has been described in an extensive review (1). It appears to be equivalent to amitriptyline, although few studies have reported dosages above 225 mg/day. Dosulepin is as effective and sedative as amitriptyline, with somewhat fewer anticholinergic adverse effects in several studies. However, it does not appear to have been compared with other less sedative or anticholinergic tricyclic compounds or second-generation drugs. Although it is claimed to have fewer cardiovascular effects, this has not been well substantiated in controlled comparative studies, and the cardiovascular and other effects of overdosage appear to be identical for all tricyclic compounds. Fetal tachydysrhythmias were believed to be caused by maternal ingestion of dosulepin (2).

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Doxacurium chloride

See also Neuromuscular blocking drugs

General Information

Doxacurium chloride is a long-acting non-depolarizing neuromuscular blocking agent. It is a bisquaternary benzylisoquinolinium derivative (a diester). It is subject to minimal hydrolysis by plasma cholinesterase (at about 6% of the rate of hydrolysis of suxamethonium when incubated with purified pooled human plasma cholinesterase) (1). Antagonism by edrophonium (1 mg/kg) was considered inadequate in one study, whereas no difficulties were experienced with neostigmine (0.05 mg/kg) (2).

Organs and Systems

Cardiovascular

No rise in plasma histamine concentration was found with bolus doses up to 0.08 mg/kg (1), but in one case there was transient hypotension 1 minute after a bolus dose of 0.05 mg/kg via a pulmonary artery cannula, with cutaneous flushing at 2 minutes, suggesting that histamine release can occur on occasion (3). There was no tachycardia or bronchospasm, but the mean arterial pressure fell from 88 to 40 mmHg and recovered with therapy within 3 minutes, by which time the skin flushing was fading.

In a study of 54 patients, plasma histamine concentrations increased by 200% following doxacurium in two patients, but there were no changes in heart rate or blood pressure (4). Indeed, cardiovascular stability has been reported in several studies (1,4) and only minor clinically insignificant changes have been seen with doses up to 0.08 mg/kg, even in cardiac patients (AHA classes III–IV) (5,6).

Bradycardia is occasionally seen (2), but this may be due to co-administration of vagotonic drugs with atracurium, vecuronium, and pipecuronium.

Susceptibility Factors

Renal disease

Renal excretion is the main route of elimination of doxacurium, and its duration of action would be expected to be prolonged in patients with renal dysfunction. There have been two reports of the use of doxacurium in patients with chronic renal insufficiency. In the first it was reported that the action of doxacurium (0.025 mg/kg bolus dose) was "markedly but not statistically prolonged"; the mean time to 25% recovery of the twitch height was 121 minutes in the group of patients with renal insufficiency as opposed to 67 minutes in the control group, with great interindividual variation in both groups (7). The second was a study of the pharmacokinetics and pharmacodynamics of doxacurium in patients undergoing cadaveric kidney or liver transplantation (8). The duration of action of doxacurium was more variable and greatly prolonged in patients with end-stage renal insufficiency, although once again the results were clinically but not statistically significant, because of the small numbers of patients and large variability. Plasma clearance was significantly slower and mean residence time significantly greater in the renal transplant group than in control patients. In the patients with liver disease there were no significant pharmacokinetic changes, but the duration of action of the low dose used (15 mg/kg) did tend to be somewhat prolonged.

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Doxapram

General Information

Generalized stimulation of the central nervous system has been observed with doxapram, particularly in large doses. Adverse reactions have included hyperactivity, tachycardia, increased deep tendon reflexes and muscle twitching, and laryngospasm. Raised blood pressure can also occur.

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Doxapram is contraindicated in epilepsy and other convulsive disorders and in hypertension. Doxapram has been used to treat post-anesthetic shivering; in one study it was effective (1).

Adverse effects of doxapram are not long-lasting, because of its short half-life of 2–4 hours.

In seven patients treated with doxapram after anesthesia, the adverse effects were not serious and comprised excessive coughing, weeping, muscle tremor, nausea, and hysterical reactions to dreams. However, sweating, excessive salivation, and vomiting were noted in the control patients, and the authors concluded that recovery was smoother with doxapram.

There was a very high incidence of adverse reactions, such as hot flushes, sweating, hyperventilation, tremor, nausea, and vertigo, in postoperative analgesia combined with doxapram 1 mg/kg (2).

In a controlled study of the use of doxapram infusion for late postoperative hypoxemia (3) three of nine patients who received doxapram had an adverse event, compared with none of the placebo patients. In 18 patients there was a significant trend toward higher mean oxygen saturation in the doxapram group and a significantly higher minimum oxygen saturation and reduced number of hypoxemic events on the first postoperative night. The authors concluded that although the results were promising, continuous nocturnal postoperative doxapram infusion should be postponed until there is more information about its pharmacokinetics in this condition.

The effects of doxapram given enterally or intravenously have been studied in a prospective randomized trial in 15 infants with apnea of prematurity who had not responded to caffeine (4). Of the nine infants randomized to receive enteral treatment, five had to be changed to intravenous treatment, largely owing to doxapram-induced upper gastrointestinal symptoms (vomiting and large gastric residuals). Doxapram significantly reduced the frequency of attacks of apnea and associated bradycardia and hypoxia in 82% of the infants. The major adverse event was feeding intolerance in one-third of infants given enteral treatment. This resolved when doxapram was given intravenously. Importantly, some infants responded to and could tolerate enteral treatment, thus avoiding the need for an intravenous line.

Organs and Systems

Cardiovascular

Dysrhythmias consisting of self-limiting or single ventricular extra beats were observed after doxapram was given by injection; it was suggested that electrocardiographic dysrhythmias occurring in anesthesia could be associated with analeptic drug administration (5).

Doxapram is used to treat idiopathic apnea in premature infants. Second-degree atrioventricular heart block developed after its administration to three neonates (6).

- Thirty-six hours after an infusion of doxapram was started, the first infant developed second-degree AV block, with QT interval prolongation and an increase in the QRS interval. There was no hypotension. Sinus rhythm returned 92 hours after stopping the infusion.
- Doxapram was given orally, every 6 hours, to the second infant. After 43 hours second-degree AV block with a prolonged QT interval was noted. Echocardiography showed a normal heart. Doxapram was discontinued and 8 hours later sinus rhythm returned.
- The third infant was given aminophylline orally and doxapram by intravenous infusion; 5 days later cisapride was added to treat suspected gastro-esophageal reflux. The next day the infant had developed second-degree AV block, with a prolonged QT interval. Doxapram was withdrawn and sinus rhythm returned 36 hours later.

Heart block did not occur in the third case until cisapride, which can prolong the QT interval, was added.

There has been another report of three cases of second-degree atrioventricular block and QT interval prolongation associated with doxapram; sinus rhythm returned after withdrawal (7).

The mean pulmonary arterial pressure was significantly, but not severely, increased in 10 patients receiving intravenous infusions of doxapram (8).

There have been two studies of doxapram in very low birth weight infants before extubation. In one it was concluded that doxapram did not increase the likelihood of successful extubation. In the other there was an increase in systolic blood pressure along with much higher plasma doxapram concentrations than expected (9,10).

Nervous system

Of 20 patients, mean age 72, treated with low doses of doxapram by infusion, four developed violent restlessness, confusion, and hallucinations (SED-9, 5). Of these, three were known to drink excessive alcohol and two had abnormal liver function. The reactions were relatively brief and occurred at the beginning and end of doxapram administration.

In a controlled study of the use of doxapram infusion for late postoperative hypoxemia (3) the drug was withdrawn because of brainstem infarction in a 90-year-old woman.

In 285 surgical patients, respiratory stimulation was safely performed with doxapram, especially with small, frequently repeated doses. Adverse effects included neuromuscular signs of excessive central nervous system stimulation in a very few patients at 1 mg/kg. Seven patients had excitement and there was tremor in three and rigidity in two. Coughing, laryngospasm, and salivation are probably physiological manifestations of the return of protective reflexes secondary to arousal (11).

Liver

Reversible hepatotoxicity has been attributed to doxapram (12).

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Doxazosin

See also Alpha-adrenoceptor antagonists

General Information

The alpha$_1$-adrenoceptor antagonist doxazosin has similar adverse effects to those of prazosin. In a review of its clinical pharmacology and therapeutic uses, reports of tolerability included an update from previously unpublished pooled data on file (1). In 339 patients treated with doxazosin for hypertension compared with 336 treated with placebo, adverse effects were essentially the same as those reported in 665 patients being treated for benign prostatic hyperplasia compared with 300 treated with placebo. Dizziness (19 versus 9% and 16 versus 9%) and fatigue (12 versus 6% and 8 versus 2%) were reported significantly more often than with placebo (figures for patients with hypertension and benign prostate hyperplasia respectively, versus placebo). However, in hypertensive patients somnolence was reported more often than with placebo (5 versus 1%). In patients with benign prostatic hyperplasia the following adverse effects were reported significantly more often than with placebo: hypotension (17 versus 0%), edema (2.7 versus 0.7%), and dyspnea (2.6 versus 0.3%).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (2) was a multicenter comparison of drugs from each of three classes of antihypertensive agents (amlodipine, lisinopril, and doxazosin) with chlortalidone as an active control, in 24 335 adults with hypertension and at least one other coronary heart disease risk factor. In an interim analysis (median follow-up 3.3 years) there was no significant difference in the rates of fatal coronary heart disease or non-fatal myocardial infarction, or in total mortality between doxazosin and chlortalidone, but doxazosin was associated with higher rates of stroke (RR = 1.19; CI = 1.01, 1.40) and combined cardiovascular disease (RR = 1.24; CI = 1.17, 1.33). Considered separately, the risk of congestive heart failure was doubled (RR = 2.04; CI = 1.79, 2.32). Mean systolic blood pressure with doxazosin was about 2–3 mmHg higher than with chlortalidone and mean diastolic pressure was similar in the two groups. The authors concluded that the difference in blood pressure control did not account for the differences in cardiovascular end-points.

Doxazosin, and perhaps the whole class of alpha-blockers, should no longer be considered as first-line antihypertensive therapy. Doxazosin can still be used for symptom relief in patients with nocturia secondary to prostatic hyperplasia, although it should probably be avoided in patients with manifest or latent congestive heart failure (3). This issue has been intensely debated (4).

Phenoxybenzamine and doxazosin have been compared in 35 patients with pheochromocytoma (5). Hemodynamic, pharmacological, and biochemical indicators of alpha- and beta-adrenoceptor blockade were measured before, during, and after anesthesia and surgery in eight patients pretreated with phenoxybenzamine and in 27 patients pretreated with doxazosin. Doxazosin (2–16 mg/day) was as effective as phenoxybenzamine in controlling arterial blood pressure and heart rate before and during surgery and it caused fewer adverse effects.

Organs and Systems

Cardiovascular

Hypotension is a risk with doxazosin and has been reported to cause stroke (6).

- A 64-year-old man developed a right hemiparesis after taking one dose of doxazosin 4 mg for prostatic symptoms. A CT scan of the brain and carotid ultrasound studies were normal. He recovered most of his neurological function within a few days. Ambulatory blood pressure monitoring after treatment with doxazosin 2 mg showed striking blood pressure reduction during sleep.

Psychological, psychiatric

Doxazosin, 16 mg/day, has been reported to have caused an acute psychosis.

- A 71-year-old woman with type II diabetes and hypertension began to hear voices and to have auditory hallucinations. Doxazosin was progressively withdrawn over the next 14 days and by the time the dosage had been reduced to 8 mg a day the psychosis was much less severe; it disappeared completely after withdrawal (7).

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Drug Administration

Drug formulations

Doxazosin can cause a sharp fall in blood pressure at the start of therapy, and a modified-release formulation has been developed in an attempt to obviate this. In an open, non-comparative, sequential study in primary care, the ordinary formulation (1–16 mg/day for 3–6 months) was replaced by the modified-release formulation (4–8 mg/day for 3 months) in 3537 patients (8). The most common reasons for withdrawal from the study were loss to follow-up (37%) and adverse events (28%). Blood pressure fell from 160/95 to 139/82 mmHg with the ordinary formulation and to 135/79 mmHg when the modified-release formulation was used instead. The most common adverse events were weakness, headache, dizziness, and hypotension, all of which were more common with the ordinary formulation. However, these differences could have been due to a healthy survivor effect, in which those who had an adverse event early on (that is while taking the ordinary formulation) dropped out before taking the modified-release formulation, which would therefore appear to be safer. Thus, the lack of crossover in this study makes the results hard to interpret, although it appears that the two formulations were at worst no different from each other.

Drug overdose

A case of doxazosin overdose has been reported.

- Hypotension, bradycardia, and ST segment elevation on the electrocardiogram occurred in a patient who took doxazosin 40 mg (9). His blood pressure was 90/60 mmHg and his heart rate fell to 50/minute. Eight hours after aggressive saline infusion and gastric lavage the patient was awake, but his hypotension and bradycardia were corrected only after 96 hours and the administration of intravenous atropine 0.5 mg.

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Doxepin

See also Tricyclic antidepressants

General Information

Doxepin is a tricyclic antidepressant that has also been used topically in the treatment of atopic dermatitis and other forms of eczematous dermatitis. It causes the adverse effects that one would expect, and systemic effects can result from absorption after topical administration.

Organs and Systems

Nervous system

Short-term treatment with 5% doxepin cream caused mild transient drowsiness in 16–28% of patients, severe enough to necessitate withdrawal in about 2% (1). In addition, 5% of treated patients noted a dry mouth. Excessive use in children can result in intoxication, with seizures, respiratory depression, electrocardiographic abnormalities, and coma (2).

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Doxifluridine

See also Cytostatic and immunosuppressant drugs

General Information

Doxifluridine is a derivative of 5-fluorouracil. It has been used to treat a variety of solid tumors, including cancers of the breast, pancreas, stomach (1), and large bowel.

Organs and Systems

Nervous system

In a neurological evaluation of 17 patients treated with doxifluridine 3 or 5 g/m^2/day for 5 days every 4 weeks for 3 months, 10 developed symptoms of central nervous system toxicity. The neurological symptoms, cerebellar and encephalopathic, developed simultaneously and were commonly first noted during the second week of the first cycle. The neurotoxicity was dose-related and worsened during subsequent treatment. The symptoms of cerebellar disease ranged from a subjective feeling of unsteady gait to disability, while the encephalopathy resulted in difficulties with concentration and memory. Patients with marked weight loss and with generalized electrocardiographic dysrhythmias are at greatest risk of developing neurotoxicity with doxifluridine (2).

Gastrointestinal

Anorexia has been reported with doxifluridine in the absence of nausea or vomiting (3).

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Doxycycline

See also Tetracyclines

General Information

Doxycycline and minocycline are more lipophilic tetracyclines. They are well absorbed after oral administration. Their half-lives are 16–18 hours. Their higher affinity for fatty tissues improves their effectiveness and changes their adverse effects profile. Local gastrointestinal irritation and disturbance of the intestinal bacterial flora occur less often than with the more hydrophilic drugs, which have to be given in higher oral doses for sufficient absorption.

Nevertheless, their toxic effects are similar to those of other tetracyclines and arise from accumulation in fatty tissues. Accumulation in a third compartment and the resulting long half-life may contribute to an increased incidence of various toxic adverse effects during long-term treatment, even if lower daily doses are used. This seems also to be the case for pigmentation disorders and possibly for neurological disturbances (1).

Minocycline and doxycycline are predominantly eliminated by the liver and biliary tract (70–90%). Therefore, no change in dose is needed in patients with impaired renal function. However, it should be considered that hepatic elimination of doxycycline or minocycline might be accelerated by co-administration of agents that induce hepatic enzymes.

Organs and Systems

Nervous system

Peripheral neuropathy from doxycycline has been reported (2).

- A 61-year-old doctor with recurrent bronchopneumonia took two courses of doxycycline. During the first course he had persistent numbness in his feet. During the second course, a few months later, he noticed after only 2 or 3 days that the numbness accelerated markedly and was associated with a low threshold for muscle cramps in the feet. He stopped taking doxycycline and during the following weeks noticed slight improvement. However, some symptoms persisted and he had neurological investigations. A wide range of clinical and laboratory tests showed no cause for his neuropathy.

A search for an association between doxycycline and polyneuropathy failed to identify any documented cases. An inquiry to the Swedish Adverse Drug Reactions Advisory Committee elicited information about three cases of "paresthesia," two cases of "sensitivity disturbance," and one case of "neuropathy." The last was a man who had had pain and paresthesia in the feet, arms, and face after taking doxycycline 100 mg/day for 2 weeks for prostatitis. The symptoms began to wane 1 week after treatment was stopped, and disappeared completely 1 week later.

Metabolism

Doxycycline can cause hypoglycemia.

- A 70-year-old man with type 2 diabetes mellitus presented with sudden confusion, which rapidly progressed to loss of consciousness (3). The only drug he had taken during the previous 2 months was doxycycline (100 mg/day), which he had taken for 5 days for an upper respiratory tract infection. Urine tests for sulfonylureas were negative. Routine hematological and biochemical tests and an electrocardiogram were normal. He improved with intravenous glucose and withdrawal of doxycycline and had no further episodes of hypoglycemia over the next 3 months.

Plasma insulin was not measured in this case, so the mechanism of hypoglycemia was unclear.

Hypoglycemia has also been attributed to doxycycline in a non-diabetic patient (4).

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Gastrointestinal

Esophageal ulcers have been described in association with oral doxycycline or tetracycline. Acute onset of substernal burning pain and dysphagia was noted within hours of taking the drug (5–9). Remaining parts of the ingested capsule were identified by esophagoscopy.

Thirty centers for pharmacovigilance in France have reported 81 cases of esophageal damage after treatment with tetracyclines collected between 1985 and 1992 (10). There were 64 ulcers, eight cases of dysphagia, and nine of esophagitis. Most (96%) of the cases were caused by doxycycline and 73% of the patients were female, mean age 29 years. Prescriptions were for dermatological (54%), urogenital (23%), and ENT diseases. In one patient, a 71-year-old man, an esophagobronchial fistulation required esophagectomy. In 92% the drugs were not taken correctly, that is at bedtime or without a sufficient quantity of fluid. Treatment with sucralfate 1 g tds did not change the outcome of tetracycline-induced esophageal ulcers (11).

Two cases of esophagitis in children have been reported (12).

- A 12-year-old boy developed lower chest pain, having taken doxycycline for 7 days for presumed epididymitis. He had a normal chest X-ray and electrocardiogram and no signs of infection. Doxycycline was withdrawn, but the chest pain persisted. After 4 days endoscopy showed two very large ulcerated craters measuring about 5×12 mm in the distal esophagus.
- A 15-year-old girl developed chest pain and difficulty in swallowing after having taken five doses of doxycycline. Physical examination was normal and she had a normal chest X-ray and electrocardiogram. Doxycycline was withdrawn and she was given sucralfate 10 ml tds, omeprazole having been ineffective. Gastroscopy was not performed. Her pain began to improve 2 days later.

The authors stated that it is important to inquire about the use of tetracyclines in children with chest pain, and to consider them as a possible cause of the pain.

Esophageal ulceration occurred in two adults taking doxycycline as malaria chemoprophylaxis (13).

- A 20-year-old woman, who had been taking doxycycline malaria prophylaxis, took a doxycycline capsule (dose not given) before going to bed and awoke hours later with the feeling that the capsule was stuck in her esophagus. Over the next 4 days she developed worsening dysphagia. Esophagoscopy showed an esophageal ulcer over 20% of the esophageal surface. She was treated with ranitidine and sucralfate and improved over the next 2 days.
- A 27-year-old man with an 8-day history of dysphagia and retrosternal pain was taking doxycycline prophylaxis and occasional terfenadine (doses not stated). He recalled no problems with taking any of his doxycycline prophylaxis. He had an esophagoscopy, which showed a 1 cm esophageal ulcer. He improved with ranitidine.

Liver

Doxycycline-induced liver injury has been reported (14). The patient took oral doxycycline 200 mg/day for 8 days and had markedly altered liver function. The liver enzyme activities normalized only 109 days after withdrawal.

Skin

Fixed drug eruptions have been attributed to doxycycline (15).

Immunologic

Renal small-vessel vasculitis related to doxycycline has been reported (16).

Second-Generation Effects

Teratogenicity

Doxycycline has not been shown to be teratogenic (17).

Susceptibility Factors

Renal disease

Doxycycline is almost completely eliminated via the liver and the biliary tract and is therefore safe in patients with pre-existing renal insufficiency. However, for intravenous administration, doxycycline is solubilized with polyvinylpyrrolidone, the clearance of which is less than that of doxycycline. In patients with a serum creatinine concentration of more than 250 μmol/l (3 mg/dl), it is therefore advisable to limit the duration of treatment to a few days.

Drug Administration

Drug administration route

When intravenous tetracycline became no longer available, many centers began to use doxycycline as a sclerosant. In one review (18), chest pain was the most frequent adverse event with doxycycline, occurring in about 40% of the 60 patients in whom it had been used, and fever occurred in about 7%. In a more recent controlled trial in 106 patients treated with either doxycycline or bleomycin, there was chest pain in 20% of the patients treated with doxycycline, and nausea in one patient (19).

Drug–Drug Interactions

Methotrexate

Doxycycline can be added to the long list of drugs (SEDA-18, 262) (SEDA-23, 253) that can interact with methotrexate (20).

- A 17-year-old girl with a femoral osteosarcoma received her 11th cycle of methotrexate and simultaneously oral doxycycline 100 mg bd for a palpebral abscess. As in previous cycles, pharmacokinetic monitoring of methotrexate was performed. On this occasion the half-life of methotrexate was more than doubled. She developed hematological and gastroenterological toxicity.

The authors recommended that in patients receiving methotrexate an alternative to doxycycline should be used.

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Warfarin

There has been a report of bleeding and prolonged international normalized ratio in a 69-year-old man given warfarin and doxycycline (21).

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Doxylamine

See also Antihistamines

General Information

Doxylamine is an antihistamine, a monoethanolamine derivative, with antimuscarinic and pronounced sedative effects.

Second-Generation Effects

Teratogenicity

The mixture of doxylamine succinate and pyridoxine (at one time combined with dicycloverine), known under the brand names of Bendectin and Debendox, was withdrawn after a campaign had incriminated it as a teratogen. Used mainly in some English-speaking countries, it was used primarily to treat nausea and vomiting during pregnancy in circumstances in which, in other countries, dietary measures and/or low doses of antihistamines alone are more customary. No consistent picture of the congenital defects that it was alleged to produce (for example pyloric stenosis) ever emerged, and reviews have never concluded otherwise than that it was at most a low-grade teratogen (SEDA-9, 311) or entirely innocent. A review of the literature (1) and a meta-analysis failed to detect any evidence that Bendectin has a teratogenic effect (2).

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Droperidol

See also Neuroleptic drugs

General Information

Droperidol is a butyrophenone with actions similar to those of haloperidol.

Of 20 volunteers who took droperidol 5 mg orally in orange juice, none had a neutral or pleasant experience (1). All reported restlessness, 17 felt sedated, and 11 reported dysphoria, the onset being relatively immediate; one subject broke down in tears within an hour of taking droperidol. Suicidal feelings emerged acutely in two subjects and were entertained in two more subjects. Among other adverse events were skin hypersensitivity ($n = 5$), aching in the muscles ($n = 6$), wheezing consistent with respiratory dyskinesia ($n = 1$), change in voice quality ($n = 1$), and marked rhinorrhea ($n = 1$). Mental effort

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was difficult, and all subjects reported some problems with concentration.

Droperidol 5–7.5 mg given during induction of anesthesia was associated with impaired well-being scores 6 hours postoperatively in a randomized double-blind comparison of similar doses of droperidol ($n = 78$) and midazolam ($n = 72$) for preventing postoperative nausea and vomiting (2).

Organs and Systems

Cardiovascular

Droperidol has been associated with QT interval prolongation (SED-14, 141) (3–5) and torsade de pointes has been reported (6).

- A 59-year-old woman with no history of cardiac problems, except for hypertension, who was taking amlodipine 5 mg qds, cyclobenzaprine 10 mg qds, and co-triamterzide 37.5 + 25 mg qds, and who had a QT_c interval of 497 ms, was given intravenous droperidol 0.625 mg and metoclopramide 10 mg 45 minutes before surgery. About 1.75 hours after surgery she developed a polymorphic ventricular tachycardia with findings consistent with torsade de pointes, which resolved with defibrillation.

Nervous system

Intramuscular droperidol 2.5 mg was used to treat 23 consecutive patients with acute migraine who had not responded to other drugs (7). If no relief was achieved by 30–60 minutes after treatment, and no significant adverse effects were reported, a second dose of droperidol 2.5 mg was given. Varying degrees of akathisia after treatment were reported by six patients. Similarly, in a retrospective series of 37 patients who received droperidol 2.5 mg for migraine, 3 developed mild akathisia and 5 had drowsiness (8).

Balance disturbances have been described with droperidol in 120 women undergoing gynecological dilatation and curettage, who were randomly assigned to receive either 0.9% saline (placebo) or droperidol 0.625 mg intravenously before surgery (9). The change in body sway from the baseline before anesthesia was significantly greater after droperidol (61%) than after placebo (33%).

Drug–Drug Interactions

Fentanyl

An exception to the relatively safe use of high-potency agents has been noted in the combination of droperidol with the narcotic fentanyl, which can cause marked hypotension (10).

Neuromuscular blocking agents

Animal studies suggest that large doses of pethidine and droperidol can augment the myoneural effects of neuromuscular blocking agents (11).

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Droseraceae

See also Herbal medicines

General Information

The family of Droseraceae contains two genera:

1. *Dionaea* (Venus flytrap)
2. *Drosera* (sundew).

Dionaea muscipula

The expressed sap of *Dionaea muscipula*, a fly-catching plant (Venus flytrap), was once available in Germany as an herbal oncolytic in the form of ampoules and oral drops (1). However, when it became apparent that intramuscular administration could produce shivers, fever, and anaphylactic shock, the health authorities banned the ampoules. They also ruled that the product information on the oral drops should warn against use in pregnancy and should list reddening of the face, headache, dyspnea, nausea, and vomiting as adverse effects.

Reference

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Droxicam

See also Non-steroidal anti-inflammatory drugs

General Information

Droxicam, a piroxicam prodrug, has similar adverse effects (SEDA-16, 113) (1). Because of many Spanish reports of non-fatal liver damage, according to the CPMP the Summary of Product Characteristics should state that serious hepatic damage can occur (SEDA-17, 113). Owing to its hepatotoxicity, droxicam has been withdrawn in many countries (SEDA-19, 99).

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Dryopteraceae

See also Herbal medicines

General Information

The genera in the family of Dryopteraceae (Table 1) include various types of fern.

Table 1 The genera of Dryopteraceae

Arachniodes (holly fern)
Athyrium (ladyfern)
Bolbitis (creeping fern)
Ctenitis (lacefern)
Cyclopeltis (cyclopeltis)
Cyrtomium (netvein hollyfern)
Cystopteris (bladderfern)
Deparia (false spleenwort)
Diplazium (twinsorus fern)
Dryopteris (wood fern)
Elaphoglossum (tongue fern)
Fadyenia (dotted fern)
Gymnocarpium (oak fern)
Hemidictyum (hemidictyum)
Hypoderris (hypoderris)
Lastreopsis (shield fern)
Lomagramma (lomagramma)
Lomariopsis (fringed fern)
Matteuccia (ostrich fern)
Megalastrum (megalastrum)
Nephrolepis (sword fern)
Nothoperanema (island lace fern)
Oleandra (oleander fern)
Olfersia (island fern)
Onoclea (sensitive fern)
Phanerophlebia (phanerophlebia)
Polystichum (holly fern)
Rumohra (rumohra)
Tectaria (halberd fern)
Triplophyllum (triplophyllum)
Woodsia (cliff fern)

Dryopteris filix-mas

The rhizome of *Dryopteris filix-mas* (male fern) was formerly used as an antihelminthic drug (1), but it is highly toxic and has been superseded by other less-dangerous agents. In spite of poor absorption, serious poisoning can occur, for example when absorption is increased by the presence of fatty foods. Poisoning is characterized by vomiting, diarrhea, vertigo, headache, tremor, cold sweats, dyspnea, cyanosis, convulsions, mental disturbances, disturbed vision, and even blindness, which in a few instances is permanent.

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Ebastine

See also Antihistamines

General Information

Ebastine is a second-generation antihistamine with proven efficacy in the treatment of allergic disease (1). It is rapidly absorbed after oral administration, and undergoes extensive first-pass metabolism by CYP3A4 to its active carboxylic acid metabolite, carebastine.

Organs and Systems

Cardiovascular

Cardiac effects were reported from early experimental work using very high doses of ebastine, but they are not believed to be clinically relevant in normal use. In one study serial electrocardiograms showed no changes with doses up to the maximum used (30 mg). Ebastine in doses up to five times the recommended therapeutic dose did not cause clinically relevant changes in QT_c interval in healthy subjects (2). Co-administration of ebastine with ketoconazole or erythromycin did not lead to significant changes in the QT_c interval (3,4).

Psychological, psychiatric

The effects of ebastine 10 mg on cognitive impairment have been assessed in 20 healthy volunteers who performed six types of attention-demanding cognitive tasks, together with objective measurements of reaction times and accuracy (5). Ebastine was compared with placebo and a positive control, chlorphenamine 2 mg and 6 mg. Compared with placebo, ebastine had no effect on any objective cognitive test nor any effect on subjective sleepiness. In contrast, chlorphenamine significantly increased reaction times, reduced accuracy in cognitive tasks, and increased subjective sleepiness. The effect of chlorphenamine increased with plasma concentration.

Susceptibility Factors

Age

The effect of age on the pharmacokinetics of ebastine and carebastine has been studied (6). Ebastine can be safely given to elderly subjects and there are no clinically important age-related differences in the pharmacokinetics of ebastine/carebastine.

Sex

The effect of sex on the pharmacokinetics of ebastine and carebastine has been studied (6). There were no clinically important sex-related differences in the pharmacokinetics of ebastine/carebastine.

Food–Drug Interactions

Like other antihistamines that rely on activation by metabolism, the systemic availability of ebastine can be affected by food. In a double-blind, placebo-controlled, parallel-group study, 215 patients with seasonal allergic rhinitis took ebastine with solid food (immediately after breakfast), while 218 took it 1–2 hours after breakfast (7). Food taken at the time of dosing did not alter the therapeutic or adverse effects of ebastine for 2 weeks in seasonal allergic rhinitis. Although carebastine steady-state concentrations were 15% higher when ebastine was taken with food this was not considered clinically important.

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Echinocandins

General Information

The echinocandins are a class of semisynthetic antifungal lipopeptides that are structurally characterized by a cyclic hexapeptide core linked to a variably configured lipid side chain. The echinocandins act by non-competitive inhibition of the synthesis of 1,3-α-D-glucan, a major polysaccharide component of the cell wall of many pathogenic fungi, which plays a key role in cell division and cell growth and is absent from mammalian cells. In concert with chitin, the rope-like glucan fibrils are important in maintaining the osmotic integrity of

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the fungal cell and play a key role in cell division and cell growth.

The currently available echinocandins are anidulafungin (rINN; Versicor Inc, Freemont, CA), caspofungin (rINN) (Merck & Co, Inc, Rahway, NJ), and micafungin (rINN; Fujisawa Inc, Deerfield, IL). They have relatively similar pharmacological properties. All three have potent and broad-spectrum antifungal activity against *Candida* species and *Aspergillus* species without cross-resistance to existing agents. They have prolonged post-antifungal effects and fungicidal activity against *Candida* and they cause severe damage to *Aspergillus* at the sites of hyphal growth. Their efficacy against these organisms in vivo has been demonstrated in animals (1,2). Their activity against other fungal pathogens in vitro is variable (3).

Pharmacokinetics

The echinocandins are currently available only for intravenous administration. They have dose-proportional plasma pharmacokinetics, with half-lives of 10–15 hours, which allows once-daily dosing. All echinocandins are highly protein-bound (over 95%) and distribute into all major tissues, including the brain; concentrations in non-inflammatory CSF are low. The echinocandins are eliminated by degradation and/or hepatic metabolism, and are slowly excreted as inactive metabolites in the urine and feces; only small fractions are excreted unchanged in the urine. As a class they are generally well tolerated and lack significant potential for drug interactions mediated by CYP450 isozymes (1–4). In vitro biotransformation studies of caspofungin have shown that it is not a substrate of P-glycoprotein and is a poor substrate and a weak inhibitor of cytochrome P450 enzymes (5). However, other in vitro studies have shown that it may inhibit CYP3A4 (6).

Observational studies

The clinical efficacy of anidulafungin, caspofungin, and micafungin against *Candida* species has been documented in phase II or phase III studies in immunocompromised patients with esophageal candidiasis. All achieved therapeutic efficacy at least comparable with standard agents. Phase III efficacy studies of caspofungin for esophageal candidiasis, invasive candidiasis, and empirical antifungal therapy in persistently febrile neutropenic patients have been completed. Caspofungin had no serious adverse effects and had therapeutic efficacy that was at least as good as standard agents (7–9). It is approved in the USA and the EU for second-line therapy of definite or probable invasive aspergillosis and for primary therapy in non-neutropenic patients with invasive *Candida* infections (3,5).

Caspofungin has been studied in a multicenter, open, non-comparative phase II trial in 83 patients with definite or probable invasive aspergillosis refractory to or intolerant of standard therapies (10,11). Common underlying conditions included hematological malignancies (48%), allogeneic blood and marrow transplantation (25%), and solid organ transplantation (11%). Caspofungin was administered in a dose of 70 mg on day 1, followed by 50 mg/day for a mean duration of 34 (range 1–162) days. There was a favorable response to caspofungin in 37 patients, including 32 of 64 with pulmonary aspergillosis and 3 of 13 with disseminated aspergillosis. Caspofungin was generally well tolerated. One serious adverse event was reported as possibly drug-related. Infusion-related reactions, nephrotoxicity, and hepatotoxicity were uncommon. Two patients discontinued caspofungin because of adverse effects.

The safety and tolerability of caspofungin have been studied in 623 patients, including 295 who received at least 50 mg/day for at least 1 week in clinical studies. In 263 patients who received caspofungin in randomized, double-blind, active-control trials, there were no serious clinical or laboratory drug-related adverse events; caspofungin was withdrawn in 2% of these patients because of drug-related adverse effects (12).

Comparative studies

Amphotericin

Caspofungin (Cancidas; 50 and 70 mg/day for 14 days; $n = 74$) has been compared with conventional amphotericin (0.5 mg/kg/day for 14 days; $n = 54$) in the treatment of esophageal candidiasis in a randomized, double-blind, multicenter trial in South America (13). Most of the patients (over 75%) were HIV-infected and about half of them had CD4+ lymphocyte counts of under 50×10^6/l. Caspofungin was well tolerated: eight patients in the amphotericin group and one patient in the combined caspofungin group developed a raised serum creatinine of over 176 μmol/l (2 mg/dl) during treatment. Of the patients who received caspofungin, 4.1% withdrew prematurely owing to drug-associated adverse effects, compared with 22% in the amphotericin arm. There was a clinical response (symptoms plus endoscopy) in 85% of the patients in the combined caspofungin group versus 67% in the amphotericin group.

Caspofungin has been compared with amphotericin in a multicenter, double-blind, randomized trial in 128 adults with endoscopically documented symptomatic *Candida* esophagitis (7). There was endoscopically verified clinical success in 74 and 89% of the patients who received caspofungin 50 and 70 mg/day respectively, and in 63% of patients given amphotericin deoxycholate 0.5 mg/kg/day. Therapy was withdrawn because of drug-related adverse events in 24% of the patients who were given amphotericin and in 4 and 7% of those who were given caspofungin 50 and 70 mg/day respectively. The most frequent adverse events with caspofungin were fever, phlebitis, headache, and rash. Fewer patients who received caspofungin had drug-related fever, chills, or nausea than those who received amphotericin. More patients who received amphotericin (91%) than caspofungin (61 and 32%) developed drug-related laboratory abnormalities, the most common in the caspofungin groups being hypoalbuminemia and increased serum activities of alkaline phosphatase and transaminases. There were drug-related increases in blood urea nitrogen concentrations in 15% of the patients who received amphotericin but in none of those who received caspofungin. Likewise, serum creatinine concentrations increased in 16 patients who

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received amphotericin but in only one who received caspofungin. In summary, caspofungin was as effective as amphotericin but better tolerated in the treatment of esophageal candidiasis.

In a double-blind, randomized trial, caspofungin was compared with amphotericin deoxycholate for the primary treatment of invasive candidiasis (9). Patients who had clinical evidence of infection and a positive culture for *Candida* species from blood or another site were enrolled. They were stratified according to the severity of disease, as indicated by the presence or absence of neutropenia and the Acute Physiology and Chronic Health Evaluation (APACHE II) score, and were randomly assigned to receive either caspofungin (50 mg/day with a loading dose of 70 mg on day 1) or amphotericin (0.6–0.7 mg/kg/day or 0.7–1.0 mg/kg/day for patients with neutropenia). Of the 239 patients enrolled, 224 were included in the modified intention-to-treat analysis. Baseline characteristics, including the percentage of patients with neutropenia and the mean APACHE II score, were similar in the two treatment groups. The efficacy of caspofungin was similar to that of amphotericin, with successful outcomes in 73% of the patients treated with caspofungin and in 62% of those treated with amphotericin. There were significantly fewer drug-related adverse events associated with caspofungin: fever, chills, and infusion-related events were less frequent with caspofungin. Caspofungin caused less nephrotoxicity (as defined by an increase in serum creatinine of at least twice the baseline value or an increase of at least 88.4 μmol/l: 8.4 versus 25%). Only 2.6% of those who were given caspofungin were withdrawn because of adverse events, compared with 23% of those who were given amphotericin. Thus, caspofungin was at least as effective as amphotericin for the treatment of mostly non-neutropenic patients with invasive candidiasis but significantly better tolerated.

The safety, tolerability, and efficacy of caspofungin in patients with oropharyngeal and/or esophageal candidiasis have been investigated in a phase II dose-ranging study (14). The patients were randomized, double-blind to either caspofungin acetate (35, 50, or 70 mg) or amphotericin (0.5 mg/kg intravenously) once daily for 7–14 days. Of 140 patients, 63% had esophageal involvement and 98% were infected with HIV. Response rates with caspofungin groups were 74–91%, and 63% with amphotericin. Fewer patients receiving any dose of caspofungin had drug-related adverse effects (fever, chills, nausea, vomiting). Two patients who took caspofungin 35 mg and one who was given amphotericin withdrew because of adverse effects. Drug-related laboratory abnormalities were also more common in patients who received amphotericin. The most common drug-related laboratory abnormalities in patients who received caspofungin were raised alanine transaminase, aspartate transaminase, and alkaline phosphatase, which were typically less than five times the upper limit of normal and resolved despite continued treatment. None of the patients receiving caspofungin and nine of those who received amphotericin developed drug-related increases in serum creatinine concentrations. No patient withdrew because of drug-related laboratory adverse effects.

Antifungal azoles

Caspofungin and fluconazole have been compared in adults with *Candida* esophagitis in a double-blind, randomized trial (8). Eligible patients had symptoms compatible with esophagitis, endoscopic mucosal plaques, and microscopic *Candida*. They were randomized to receive caspofungin (50 mg) or fluconazole (200 mg) intravenously once a day for 7–21 days. Most of them (154/177) had HIV infection, with a median CD4 count of 30×10^6/l. Favorable response rates were achieved in 66 of the 81 patients in the caspofungin arm and in 80 of the 94 patients in the fluconazole arm; symptoms had resolved in over 50% of the patients in both groups by the fifth day of treatment. Drug-related adverse effects were reported in 41% of patients given caspofungin and 32% of those given fluconazole; the most common events in both groups were phlebitis, headache, fever, nausea, diarrhea, abdominal pain, and rashes. Drug-related laboratory abnormalities developed in 29% of patients given caspofungin and in 34% of those given fluconazole. The most frequent laboratory abnormalities included reduced white blood cell count, hemoglobin concentration, and serum albumin concentration, and increased alkaline phosphatase and transaminases. No patient given caspofungin developed a serious drug-related adverse effect; therapy was withdrawn in only one patient (who was receiving fluconazole), because of an unspecified adverse effect.

Drug–Drug Interactions

Amphotericin

There were no pharmacokinetic interactions of caspofungin with amphotericin deoxycholate in healthy volunteers (5).

Antifungal azoles

In rats, caspofungin did not alter the plasma pharmacokinetics of ketoconazole, a potent inhibitor of CYP3A4 (5). Co-administration of caspofungin 50 mg/day and itraconazole 200 mg/day to healthy subjects for 14 days did not alter the pharmacokinetics of either drug (15).

Ciclosporin

Ciclosporin increased the AUC of caspofungin by about 35%, but caspofungin did not increase the plasma concentrations of ciclosporin. Because of transient rises in hepatic transaminases not exceeding 2–3 times the upper limit of the reference range in single-dose interaction studies, concomitant use of caspofungin with ciclosporin should be undertaken with care (5), although limited experience in patients studied by the manufacturers suggests that it may be safe.

Enzyme inducers

Regression analysis of pharmacokinetic data from patients has suggested that co-administration of caspofungin with inducers of drug metabolism and mixed inducer/inhibitors, namely carbamazepine,

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dexamethasone, efavirenz, nelfinavir, nevirapine, phenytoin, and rifampicin, can cause clinically important reductions in caspofungin concentrations. However, no data are currently available from formal interaction studies, and it is not known which clearance mechanisms of caspofungin are inducible. The manufacturer currently recommends considering an increase in the daily dose of caspofungin to 70 mg in patients who are taking these drugs concurrently and who are not responding (5).

Indinavir

In rats, caspofungin did not alter the plasma pharmacokinetics of indinavir, a substrate and competitive inhibitor of CYP3A2 (5).

Tacrolimus

While tacrolimus had no effect on the plasma pharmacokinetics of caspofungin, chronic caspofungin reduced the AUC of tacrolimus by about 20% (5).

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Edetic acid and its salts

General Information

Edetic acid is a metal chelator. The effect of an intravenous dose of 1 g of calcium disodium edetate on the urinary excretion on the elements aluminium, boron, barium, calcium, copper, iron, lead, magnesium, manganese, phosphorus, potassium, silicon, sodium, strontium, sulphur, and zinc was measured in healthy volunteers. The ratio of the increase of urinary elimination was about two for iron, five for aluminium, lead, and manganese, and 15 for zinc (1).

Salts of edetic acid are still used in intravenous "chelation therapy" as an alternative treatment for atherosclerotic disease in several countries (SEDA-10, 225) (2–7). Many of the data on their adverse effects are derived from older studies. There is some evidence of efficacy, although the dangers are obvious (SED-14, 722) (8,9).

Urea edetate (with methylhexyl ether) has been used for the dissolution of calcified gallbladder stones, without adverse effects (10).

Adverse effects of disodium edetate include hypocalcemia, tetany, convulsions, cardiac dysrhythmias, respiratory arrest, and renal insufficiency. Other possible symptoms include nausea, vomiting, diarrhea, fever, headache, and urinary urgency. Pain and phlebitis at the site of injection can occur (11). The sodium load in "chelation therapy" can precipitate heart failure. Renal tubular necrosis can occur (2).

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Sodium calcium edetate can cause the same adverse effects as the disodium salt, with the exception of hypocalcemia.

In children receiving disodium ethylenediaminetetraacetate by intravenous infusion, an influenza-like syndrome developed, characterized by lacrimation, rhinorrhea, sneezing, and cough (12). Other symptoms included malaise, fatigue, nausea, and vomiting; one patient had a fever of 39.2°C.

Five patients became ill shortly after chelation therapy at an out-patients clinic, where they had received an infusion of Na_2EDTA 3 g, MgCl 2 g, vitamin B_1 100 mg, vitamin B complex 1 ml, and vitamin C 15 g in sterile water at a rate of 180 ml/hour (13). One patient also received 10 ml of 50% dimethylsulfoxide. All initially had gastrointestinal and musculoskeletal symptoms (trembling, muscle spasms) and complained of dry mouth or excessive thirst. All had fever and hypotension, four had tachycardia and sweating. Laboratory data were collected in four patients, all of whom had varying degrees of thrombocytopenia, leukopenia, and lymphocytopenia, reflecting transient bone marrow suppression. Subsequent measurements showed leukocytosis with early cell forms. Urinalysis showed transient proteinuria (in four), microscopic hematuria (in three), hyaline casts (in two), and ketonuria (in four). Three had mild transient rises in serum urea and creatinine concentrations. Three had hypocalcemia, requiring supplementation in one (probably accounting for the muscular symptoms). In these patients, acute edetate toxicity appeared to be related to errors in dosage or the rate at which the formulation was administered.

Organs and Systems

Respiratory

Additives to drug for inhalation, such as disodium edetate or benzalkonium chloride, can cause bronchoconstriction (14). This can lead to reduced therapeutic effectiveness of bronchodilators, for example salbutamol or ipratropium. Some products do and others do not contain these additives and an unexpected reduction in response to a bronchodilator may be the result of a casual change of product.

- In one case, paradoxical bronchoconstriction and laryngospasm necessitated emergency admission after the use of salbutamol in a metered-dose inhaler, which also contained edetate disodium as a preservative (15). Although there was prompt relapse on re-exposure, there were no positive findings demonstrating the role of edetate disodium.

Sensory systems

In two patients with atypical band keratopathy, the combined use of the preservatives sodium edetate, boric acid, and benzalkonium chloride in eye-drops for glaucoma treatment was identified as the cause (16).

Metal metabolism

Salts of edetic acid have been reported to cause symptomatic zinc deficiency, with abnormalities of the skin, including crusted lesions of the mouth and eyelids, leukokeratosis of the tongue, stomatitis, and a papular, pustular, erosive rash of the face and perianally, alopecia, and white bands on the nails (17,18).

Hematologic

For pseudothrombocytopenia, pseudoneutropenia, and pseudoleukocytosis caused by the use of edetic acid as an in vitro anticoagulant, see the section on "Interference with diagnostic tests" in this monograph.

Urinary tract

Intravenous administration of disodium edetate can cause renal insufficiency and acute tubular necrosis (2). In children with subclinical lead poisoning, the administration of sodium calcium edetate and dimercaprol together was associated with mild and transient biochemical evidence of renal damage in 13% of patients, whereas another 3% had acute renal insufficiency (19).

Edetate-induced renal damage is associated with vacuolization of the proximal tubules, loss of the brush border, and eventually degeneration of the proximal tubular cells. A possible mechanism underlying this renal toxicity is an interaction between edetate and endogenous metals in the proximal tubule (13).

Skin

Disodium edetate can cause contact dermatitis, for instance when used in local anesthetics (20).

Immunologic

Derivatives of edetic acid are allergenic and can cause allergic reactions, with rashes, fever, edema, and arthralgia. There can be cross-allergy to ethylenediamine, which is a constituent of various drug formulations (for example aminophylline, some ointments) (SED-8, 538). In addition, disodium edetate is found in small amounts in certain drugs, as a result of the removal of trace quantities of heavy metals. However, ethylenediaminetetraacetate was administered for lead poisoning without ill effects to a child with a proven allergy to ethylenediamine hydrochloride (21).

Second-Generation Effects

Teratogenicity

Salts of edetic acid are teratogenic in animals, probably by causing zinc deficiency (22,23). However, there is no evidence of teratogenicity in humans.

Drug–Drug Interactions

Phenylmercuric preservatives

The activity of phenylmercuric preservatives can be reduced by interaction with disodium edetate (24).

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Warfarin

Reduced anticoagulation has been reported in a patient taking warfarin when he was given chelation therapy (25).

- A 64-year-old man with coronary artery disease taking atenolol, lisinopril, atorvastatin, glyceryl trinitrate, triamterene, hydrochlorothiazide, omeprazole, nizatidine, enteric-coated aspirin, and a liquid multivitamin formulation containing spinach and broccoli extracts was given warfarin for bilateral pulmonary embolism. About 3 weeks later he received chelation therapy with a cocktail including sodium edetate 3 g and heparin 2500 units. The next day his INR had fallen from 2.6 to 1.6. He denied having missed a dose of warfarin, having taken other drugs, or having made dietary changes. The dose of warfarin was increased and the INR reached the target range.

The authors did not propose a mechanism for this interaction, although the rapidity of the effect suggests protein binding displacement of warfarin; nor did they comment on the possible role of the extract of broccoli, which contains vitamin K.

Interference with Diagnostic Tests

Cell counters

A major unwanted effect of edetic acid, related to its use as an in vitro anticoagulant in blood samples, is the phenomenon of pseudothrombocytopenia by interference with electronic cell counters, which occurs in 0.1–2.0% of blood samples (26–36). It is assumed that about 15–30 minutes after collecting blood, edetic acid, presumably by extraction of calcium, causes changes in the platelet membrane, exposing a hidden glycoprotein antigen (28). An already circulating immunoglobulin — mostly IgG, but sometimes IgM or IgA — behaves as a drug-dependent antibody and reacts with glycoproteins in the cell membrane, resulting in the agglutination of platelets and falsely low platelet counts (26,30,35). It is more frequent in hospital patients with significant concurrent illnesses, suggesting that the antibody involved is acquired. A variety of disorders, including viral infections, neoplastic diseases, autoimmune disorders, liver disease, trauma, atherosclerosis, and thrombotic disorders, are thought to be risk factors (26). Sometimes the use of a medicine, for example mexiletine (37), is involved in the development of edetic acid-induced pseudothrombocytopenia. Pseudothrombocytopenia is more likely to occur when there is a delay between taking and testing the blood samples. The agglutinin crosses the placenta and can cause transient pseudothrombocytopenia in neonatal blood samples (26).

The clinical importance of edetic acid as a cause of pseudothrombocytopenia can be illustrated by the following findings. In a retrospective study, 15% of patients thought to have true thrombocytopenia were found to be cases of edetic acid-induced pseudothrombocytopenia (28). In another study, there were eight cases of pseudothrombocytopenia, compared with only three patients with Werlhof's disease (idiopathic thrombocytopenic purpura) during the same period (26). Among pregnant women with isolated thrombocytopenia, 7% had edetic acid-mediated pseudothrombocytopenia (38). Although it is rarer, pseudothrombocytopenia can also occur in connection with other anticoagulants, such as citrate or heparin. Sometimes different anticoagulants cause pseudothrombocytopenia in one and the same patient (26). Moreover, similar antibodies can occur that are not edetate dependent (39). Obviously, pseudothrombocytopenia deserves a place in the differential diagnosis of thrombocytopenia.

Failure to recognize pseudothrombocytopenia can lead to diagnostic errors, unnecessary invasive procedures (for example bone marrow puncture), delayed surgery, and wrong treatments (for example unnecessary withdrawal of wrongly suspected drugs, unnecessary transfusions, the use of potentially harmful drugs, splenectomy). Confusion can arise when pseudothrombocytopenia develops during hospitalization, especially in patients with pre-existing or expected (true) thrombocytopenia.

Artefactual pseudothrombocytopenia is typically an error of automated cell counters. When platelet clumps are mistaken for leukocytes this can result in pseudoleukocytosis (30,36). Edetic acid can also cause agglutination of granulocytes, and confusing findings such as combined pseudothrombocytopenia, pseudoneutropenia, and pseudolymphocytosis can occur (28).

Whenever pseudothrombocytopenia is suspected, for example in the case of unexpected thrombocytopenia without signs of bleeding, the diagnosis can be confirmed by finding normal platelet counts immediately after drawing the blood specimen or by examination of a blood smear. When serial counts are made, the number of platelets falls linearly with time. Pseudothrombocytopenia is usually associated with a normal mean platelet volume, whereas true thrombocytopenia is associated with a reduced mean platelet volume (28).

A case report from Germany has underlined the clinical importance of early recognition of edetate-induced pseudothrombocytopenia (SEDA-21, 250) (40). In this case, artefactual thrombocytopenia led to a bone marrow puncture and treatment with high doses of glucocorticoids, with severe Cushing's syndrome as a result. In such patients, concomitant bleeding disorders (without true thrombocytopenia), for example menorrhagia due to an intrauterine contraceptive device, can add to the confusion.

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Edrecolomab

See also Monoclonal antibodies

General Information

Edrecolomab (17-1A antibody), a mouse monoclonal antibody, has been used in the adjuvant treatment of colorectal cancer.

Organs and Systems

Immunologic

Severe exacerbation of Wegener's granulomatosis with multiorgan involvement has been reported after the first infusion of edrecolomab (500 mg over 2 hours) in a 64-year-old man (1).

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Hypersensitivity and anaphylactic reactions have been noted, and urticaria prolonged over a 4-month period was reported in one patient (2).

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Efavirenz

See also Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

General Information

Efavirenz is a non-nucleoside reverse transcriptase inhibitor with excellent inhibitory activity against HIV-1. Its most frequent adverse effects involve the central nervous system and the skin (1). At the start of therapy, dizziness, insomnia, or fatigue is observed in most patients, and headache and even psychotic reactions have also been observed. A maculopapular rash is seen in about 10%. These adverse effects usually vanish within the first 2–4 weeks of therapy (2). About 1–2% of individuals stop taking efavirenz because of neurological or dermatological adverse events. Administration of efavirenz at bedtime reduces the incidence of severe adverse effects, and the rash can be managed by short-term antihistamines or topical corticosteroids (1). Nausea and vomiting are less often observed than in patients treated with zidovudine, lamivudine, or indinavir.

There is other evidence that efavirenz is in some respects better tolerated than certain of the alternatives used in HIV infection. However, comparisons are difficult, since efavirenz will generally be used with drugs of other types in order to avoid the rapid development of resistance. Combined efavirenz with nucleoside analogues reduces toxicity (3). Efavirenz-induced adverse effects often begin on the first day of therapy and resolve within 14–28 (median 13) days (4).

Because efavirenz is metabolized by cytochrome P450, several clinically significant interactions have been described. Efavirenz induces CYP3A4 (5); there was 55% mean induction at a dose of 400 mg/day and 33% at 200 mg/day. However, no significant interaction was noted with co-administration of nelfinavir, zidovudine, lamivudine, fluconazole, or azithromycin (2).

Observational studies

In 77 HIV-positive subjects randomized to switch from protease inhibitors to nevirapine or efavirenz or to continue taking protease inhibitors, quality of life significantly improved among those who switched (6). In those who took efavirenz there was an increase in gamma-glutamyltransferase activity and three patients interrupted treatment because of central nervous system symptoms. Eight patients withdrew because of adverse events: rashes ($n = 3$), dizziness ($n = 2$), irritability and depression ($n = 1$), depression ($n = 1$), or hepatotoxicity ($n = 1$).

Comparative studies

In an open comparison of efavirenz and indinavir (plus two nucleoside analogues) in predominantly treatment-naive patients efavirenz-based triple therapy provided at least similar antiviral effects over 48 weeks (7). Furthermore, fewer patients discontinued efavirenz-based triple therapy than indinavir-based therapy because of adverse events. Adverse effects associated with efavirenz included a maculopapular rash and central nervous system disturbances (dizziness, vivid dreams, poor concentration, sleep disturbances), which generally occurred (but later resolved) within the first weeks of therapy.

Organs and Systems

Nervous system

In a randomized comparison of an efavirenz-containing regimen and a protease inhibitor-containing regimen, nervous system adverse effects were specifically sought (8). Patients were randomized to two NRTIs plus efavirenz ($n = 51$) or two NRTIs plus one or more protease inhibitors ($n = 49$). The patients who took efavirenz reported the following at week 4: dizziness (66%), abnormal dreaming (48%), light-headedness (37%), and difficulty in sleeping (35%). At week 24, dizziness (13%), abnormal dreaming (18%), light-headedness (13%), difficulty in sleeping (7%), and nervousness (13%) were significantly less common. Irritability, abnormal dreaming, and nervousness persisted at week 48 in 13%, 10%, and 8% respectively.

Psychological, psychiatric

Efavirenz has been associated with psychiatric problems, such as anxiety, depression, and confusion (9,10). In a retrospective study of 1897 patients, dementia and depression were significantly associated with efavirenz compared with other drugs; the respective odds ratios were 4.0 (95% CI = 1.2, 14) and 1.7 (1.0, 3.0) (11). However, those who were given efavirenz were perhaps more ill than those who were not, judging by CD4 counts and opportunistic infections.

Most clinicians tend to avoid efavirenz in patients with a psychiatric history. However, it is important to remember that efavirenz can precipitate sudden and severe psychiatric symptoms in patients with no such history. Three patients developed sudden irritability; excitability with anxiety; and insomnia, confusion, and amnesia (12).

The psychiatric adverse effects of efavirenz correlate with its plasma concentrations. In 130 HIV-infected patients, toxicity was three times more common in patients who had an efavirenz concentration over 4000 ng/ml (13).

Metabolism

In a randomized, double blind study of 327 patients, cholesterol and triglycerides were raised in patients taking

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efavirenz, although this did not reach statistical significance (4).

Liver

In a prospective study of the incidence of severe hepatotoxicity among 312 patients taking efavirenz, hepatitis C and hepatitis B viruses were detected in 7.7% of the patients (14). There was severe hepatotoxicity in 8.0%, but only 50% of the episodes were detected during the first 12 weeks of therapy. The risk was significantly greater among those with chronic viral hepatitis (69% of cases) and those taking concurrent protease inhibitors (82% of cases). However, 84% of patients with chronic hepatitis C or hepatitis B did not have severe hepatotoxicity.

Skin

Efavirenz has been associated with UV photosensitivity, which recurred after skin challenge with efavirenz powder (15).

Reproductive system

Gynecomastia and breast hypertrophy have been reported in at least three patients. All had had indinavir replaced by efavirenz. No other medications were changed, and gynecomastia was not present before substitution (16). The breast enlargement was generally asymmetrical and painful. Needle biopsy was consistent with gynecomastia. Six other reports have confirmed painful breast hypertrophy in patients taking efavirenz (17).

However, gynecomastia has also been reported in 15 patients taking a variety of antiretroviral drugs (18). The authors suggested that it was due to increased cytokine concentrations following immune restoration and this adverse effect may therefore not be unique to efavirenz among drugs used to treat HIV infection.

Immunologic

The incidence of allergic reactions to efavirenz is 10–34%. They usually cause an erythematous maculopapular rash, with or without fever, 1–3 weeks after the start of therapy. Desensitization has been reported (19).

- A 37-year-old HIV-positive white man was given efavirenz, amprenavir, stavudine, lamivudine, and didanosine after failure of a previous regimen. After 8 days he developed a generalized pruritic rash and all the drugs were withdrawn. Two weeks later he was given efavirenz, stavudine, didanosine, lamivudine, and lopinavir, but developed red itchy skin within a day. All the drugs were withdrawn. He was then successfully restarted on stavudine, didanosine, lamivudine, lopinavir, and amprenavir. Desensitization to efavirenz was undertaken, but on day 12 he again developed a rash on the trunk and limbs, which was treated with a topical steroid and diphenhydramine 45 minutes before each dose of efavirenz. The desensitization protocol was continued for another 4 days, and 16 months later he was taking full-dose efavirenz in combination with the other antiretroviral drugs.

Efavirenz can cause an allergic syndrome called the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms). It is a life-threatening reaction that typically includes a rash, fever, lymphadenopathy, hepatitis, interstitial nephritis, pneumonia, myocarditis, and hematological abnormalities, particularly eosinophilia and a mononucleosis-like atypical lymphocytosis. The DRESS syndrome has been described in an HIV-infected woman taking efavirenz (20).

- A 44-year-old HIV-1 infected woman from the Ivory Coast, who was taking stavudine, lamivudine, efavirenz, and pyrimethamine plus sulfadiazine for *Toxoplasma* encephalitis, developed a maculopapular rash on both arms. The sulfadiazine was withdrawn and clindamycin was added. Ten days later her condition had worsened. Her temperature was 40°C, pulse rate 137/minute, and respiratory rate 26/minute. She had a generalized maculopapular rash without mucosal involvement, moderate abdominal tenderness, hepatomegaly, jaundice, and bilateral crackles. Her white cell count was 16×10^9/l with 9% eosinophils and 51% lymphocytes. A chest X-ray showed moderate bilateral interstitial pneumonitis. All drugs were withdrawn and she was given intravenous methylprednisolone. The skin rash and all systemic manifestations resolved within 1 week and HIV treatment was restarted uneventfully with lamivudine, stavudine, and nelfinavir.

Although this syndrome has been described with sulfonamides (which the patient had taken), the fact that her condition worsened after withdrawal of sulfadiazine, and the characteristic timing of the syndrome (2–6 weeks after starting a drug), suggested efavirenz as the cause.

- In a 39-year-old man efavirenz caused a confluent maculopapular rash, and pulmonary interstitial infiltrates without lymphadenopathy (21). The symptoms resolved when efavirenz was withdrawn while other antiretroviral drugs were continued. The patient was rechallenged, and the rash and fever reappeared; however, recurrence of the pulmonary infiltrates was not addressed.

A leukocytoclastic vasculitis has been attributed to efavirenz (22).

- A 44-year-old man, having taken various antiretroviral drugs, started to take efavirenz; 5 days later he developed palpable purpura on both legs, with pruritus. His white cell count was 14.4×10^9/l and a skin biopsy showed a leukocytoclastic vasculitis. Efavirenz was withdrawn and he was given prednisolone for 3 days; the lesions disappeared, leaving only minimal hyperpigmentation.

Second-Generation Effects

Teratogenicity

- A boy, born at full term to a woman who had taken efavirenz, stavudine, and zidovudine before pregnancy and for the first 24 weeks, had a myelomeningocele (23). The baby was HIV-positive.

The authors suggested that the efavirenz had been responsible, based on previous studies in monkeys.

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Drug–Drug Interactions

Ciclosporin

Efavirenz causes increased requirements of ciclosporin by inducing CYP3A4.

- A 39-year-old man took ciclosporin 200 mg bd after a kidney transplant (24). The blood ciclosporin concentration was 307 ng/ml. The co-administration of prednisone caused the blood ciclosporin concentration to rise to 372 ng/ml, but it fell to 203 ng/ml when the dose was reduced to 175 mg bd. Efavirenz 600 mg/day, zidovudine 300 mg bd, and lamivudine 150 mg bd were added, and 7 days later the blood ciclosporin concentration fell to 80 ng/ml and later to 50 ng/ml.

HIV protease inhibitors

The effect of multiple-dose efavirenz 600 mg/day on the steady-state pharmacokinetics of the combination of indinavir (800 mg) + low-dose ritonavir (100 mg) bd, in which ritonavir is used to increase indinavir plasma concentrations, has been investigated in 14 healthy men (25). Efavirenz significantly reduced indinavir AUC (25%), C_{max} (17%), and C_{min} (50%). Ritonavir AUC, C_{max}, and C_{min} were reduced by 36%, 34%, and 39% respectively. The authors proposed that efavirenz had induced the activity of CYP3A and concluded that the dose of indinavir or ritonavir may need to be increased to maintain similar indinavir drug concentrations after the addition of efavirenz.

Indinavir

Increased dosage of indinavir is recommended if efavirenz is co-administered (25).

Methadone

Following a report of withdrawal symptoms in three patients taking methadone maintenance therapy, serum methadone concentrations were measured before and after starting efavirenz in one patient (26). Serum methadone concentrations were as follows: (*R*)-methadone (the active enantiomer) 168 ng/ml and 90 ng/ml before and after efavirenz. The corresponding (*S*)-methadone concentrations were 100 and 28 ng/ml. The dosage of methadone was increased from 100 to 180 mg/day before the patient's withdrawal symptoms resolved.

- Three patients taking methadone were given efavirenz-containing regimens and started to complain of opioid withdrawal symptoms 3–7 days later (27). In one case the plasma methadone concentration fell from about 170 ng/ml to about 50 ng/ml over 6 days.

Since methadone is partly metabolized by CYP3A4, the interaction of efavirenz with methadone has been investigated prospectively in 11 patients taking stable methadone maintenance therapy (28). Efavirenz reduced the steady-state methadone AUC by 50%. However, patients generally only needed a 22% increase in their methadone dose to eliminate the symptoms of methadone withdrawal, and the full basis of the interaction is not understood.

Rifamycins

Rifampicin induces the metabolism of efavirenz. In 24 patients (21 men, 3 women; mean age 37 years) with HIV infection and tuberculosis the C_{max}, C_{min}, and AUC of efavirenz interval fell by 24%, 25%, and 22% respectively in the presence of rifampicin (29).

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Eflornithine

General Information

Eflornithine is a specific irreversible inhibitor of ornithine decarboxylase, the enzyme involved in the first step of mammalian polyamine biosynthesis (1). Decarboxylation of ornithine is an obligatory and rate-limiting step in the biosynthesis of polyamines, such as putrescine, spermidine, and spermine. These low molecular weight polyamines play an essential role in the growth, differentiation, and replication of the cell by participating in nucleic acid and protein synthesis, and are needed in the process of decoding genetic messages. In vitro studies of different types of cell lines (including human malignant cells) exposed to eflornithine demonstrated inhibition of growth. Eflornithine added to human erythrocytes infected with *Plasmodium falciparum* reduced parasite growth and intracellular polyamine content. Polyamines play an important role in the cellular metabolism of trypanosomatids (SED-12, 708) (2,3). Eflornithine can arrest viral replication.

Eflornithine hydrochloride can be given intravenously and orally. Absorption after oral administration is adequate. After intravenous administration, 80% is excreted unchanged in the urine within 14 hours. It penetrates the nervous system, and cerebrospinal fluid concentrations are 10–45% of serum concentrations.

Eflornithine has been used in the chemotherapy and chemoprevention of some tumors, including glioblastoma and colorectal carcinoma in the presence of polyposis coli (4). It has been used in the treatment of malaria tropica, in AIDS, and in *Pneumocystis jiroveci* infections, with varied success. It has also been approved for use in *Trypanosoma gambiense* (SED-12, 708) (5,6).

The most important adverse effect of eflornithine is a natural consequence of its mode of action, myelosuppression, which is frequent and sometimes treatment-limiting. Gastrointestinal toxicity is also common, and is more marked with oral administration. Seizures, hearing loss, alterations in liver function tests, and rash have been described in the treatment of *P. jiroveci* infections in patients with AIDS (SED-13, 835). In 31 patients with AIDS and *P. jiroveci* pneumonia, intolerant of and/or unresponsive to co-trimoxazole or pentamidine, about 50% reacted favorably to eflornithine. The adverse effects were no different from those seen in patients without AIDS, but the frequency of adverse effects was higher. The most common effects in this group were myelosuppression, thrombocytopenia being the most serious, with hepatitis (3%) and hearing loss (9%) among the others (SEDA-17, 332).

Eflornithine in trypanosomiasis

Melarsoprol (an arsenical compound) is still the most effective compound against stage II (nervous system) disease in both East and West African trypanosomiasis. However, it is toxic and causes death in about 2–8% of subjects treated. Eflornithine is an alternative to melarsoprol for West African trypanosomiasis (both early and late). However, it is very expensive, and its usefulness in endemic areas may therefore be limited. The standard regimen is 100 mg/kg intravenously 6-hourly for 14 days.

There have been some anecdotal reports that a shorter 7-day course may be equally effective, with obvious cost-saving advantages.

There has been a multicenter, randomized, open comparison of treatment with eflornithine for 7 or 14 days ($n = 321$) (7). The subjects were divided into new cases and relapses. The 14-day course of eflornithine was superior to the 7-day course for the new cases, but there was no difference in the relapsing cases. However, the numbers of patients who relapsed were small ($n = 47$) and this may not have allowed the detection of a small difference between the groups. The most common adverse events associated with eflornithine were convulsions, altered consciousness, diarrhea, vomiting, nausea, abdominal pain, and secondary infections. Diarrhea and secondary infection were more common in subjects who took the 14-day course.

In 42 patients with late-stage *Trypanosoma brucei gambiense* trypanosomiasis, who relapsed after initial treatment with melarsoprol, a sequential combination of intravenous eflornithine (100 mg/kg every 6 hours for 4 days) followed by three daily injections of melarsoprol (3.6 mg/kg, up to 180 mg) was used (8). They were followed for 24 months. In one case, the administration of eflornithine had to be interrupted for 48 hours because of convulsions, but treatment was then resumed without recurrence. Other adverse effects during treatment were abdominal pain or vomiting ($n = 4$ each), diarrhea ($n = 1$), and loss of hearing ($n = 1$). Two patients died during treatment:

- A 37-year-old man died of an acute cholera-like syndrome, with severe diarrhea, vomiting, and dehydration, after the last dose of eflornithine but before receiving his first dose of melarsoprol.
- A 34-year-old man died of an unknown cause after having received all 16 doses of eflornithine as well as the first injection of melarsoprol.

Organs and Systems

Nervous system

The frequency of seizures in patients with trypanosomiasis taking eflornithine is about 7% (SEDA-16, 316) (9).

Sensory systems

Hearing loss is the dose-limiting toxic effect for eflornithine in patients taking over 2 g/m^2/day (10) (SEDA-11, 394). In one study, it was found in 48% of patients. In some cases the hearing loss was characterized audiographically as bilateral, sensorineural, primarily high frequency, with a median loss of 25–30 dB. All patients recovered within 1–3 months of withdrawal of therapy. There was no clear association between the total dose of eflornithine and the degree of hearing loss (11). Tinnitus has been reported in some patients taking eflornithine (12).

Hearing loss due to eflornithine is usually reversible, but irreversible hearing loss has also been described.

- A patient in a Barrett's esophagus chemoprevention trial developed a hearing deficit of 15 dB at frequencies of 250, 2000, and 3000 Hz in the right ear and a deficit of 20 dB or more at 4000–6000 Hz in the left ear after taking eflornithine 0.5 g/m^2/day for about 13 weeks (cumulative dose 45 g/m^2); clinical hearing was not affected, but the threshold shifts persisted 7 months after eflornithine was withdrawn (13).

In a placebo-controlled study in 123 patients with colorectal polyps and normal hearing at frequencies of 250–2000 Hz, eflornithine 0.075–0.4 g/m^2/day for 12 months had no effect on auditory pure-tone thresholds or distortion product otoacoustic emission (14). There was no hearing loss, in contrast to studies with higher dosages.

In 58 patients with metastatic malignant melanoma, 179 sequential audiograms were obtained from patients treated with eflornithine 2–12 g/m^2/day alone ($n = 16$) or in combination with interferon alfa-2b ($n = 42$) for 2–50 weeks (15). Total doses of 60–1390 g/m^2 correlated with clinical effects and pure-tone audiometric changes at multiple frequencies (500, 1000, 2000, 4000, and 8000 Hz). Patients with normal baseline audiography had more hearing loss than those with abnormal baseline audiography at the higher frequencies. Of the patients with normal prestudy hearing thresholds 10% or less developed a demonstrable hearing deficit at cumulative doses below 150 g/m^2. Conversely, up to 75% of the patients who received more than 250 g/m^2 developed hearing loss. Other factors that adversely affected hearing included age, male sex, and the concomitant use of interferon alfa-2b.

Hematologic

Myelosuppression, as evidenced by anemia, leukopenia, and thrombocytopenia, is common in patients taking eflornithine. The manufacturers quote respective incidence rates of 55, 37, and 14%. However, other reports have suggested that thrombocytopenia is the most frequent problem; it is dose-dependent and occurred in 90% of patients with cancer on a dose of 6–8 g/m^2 with eflornithine concentrations over 400 mmol/l (SED-12, 709) (16).

- A 32-year-old Haitian man with AIDS developed complications of *Isospora belli* enteritis (17). He was given intravenous eflornithine and developed severe thrombocytopenia, nausea, and vomiting, which recurred on rechallenge with low-dose oral eflornithine.

There is an impression that patients with AIDS have a higher incidence of adverse effects. The myelosuppression is reversible on withdrawal (SED-12, 708) (SEDA-16, 316).

Gastrointestinal

Nausea, vomiting, abdominal pain, and diarrhea, mild or severe, are seen with parenteral and oral administration, but more markedly after oral administration (SED-12, 708) (18).

Hair

Alopecia has been reported in 5–10% of patients with trypanosomiasis taking eflornithine (9).

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Second-Generation Effects

Teratogenicity

Animal studies have shown arrest of the growth of malignant cells and decrease in tumor size, but as one might expect, there was also an arrest of embryonic growth if eflornithine was given in the first days of pregnancy (SED-12, 708). On theoretical grounds, one would expect an effect on the development of the fast-growing embryo; whether or not this could lead to defects and/or deformities is not known.

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Emedastine

See also Antihistamines

General Information

Emedastine is a potent second-generation antihistamine with proven efficacy in allergic conjunctivitis (1).

Organs and Systems

Nervous system

The potential sedative effects of single and repeated doses of emedastine 2 mg and 4 mg bd on actual driving performance have been assessed in healthy volunteers (9 men and 10 women, aged 21–45 years) (2). The study was a four-period, double-blind, crossover design, and driving performance was measured in a standardized test at 3–4 hours after administration of the morning dose on days 1, 4, and 5. Emedastine significantly impaired driving in every test at both doses and the authors concluded that the drug could constitute a traffic hazard and that its users should be warned accordingly.

Drug–Drug Interactions

Ketoconazole

In a study of the interaction of emedastine difumarate 4 mg bd with ketoconazole 200 mg bd in 12 subjects there was a moderate but statistically significant interaction; however, there was no increase in the QT_c interval during concomitant therapy (3). The authors concluded that these findings are consistent with the multiple metabolic pathways that supplement the metabolism of emedastine by different enzymatic isoforms of CYP450, and that concomitant treatment with emedastine and ketoconazole in people with normal QT intervals can be undertaken without special precautions. However, it is difficult to determine the precise cardiac risk, if any, posed by the administration of emedastine eye-drops (4).

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Emepronium bromide

See also Anticholinergic drugs

General Information

Emepronium bromide is an anticholinergic drug. Doses of 200 mg tds (sometimes with a double dose in the evenings) are useful in relieving urinary frequency. It causes the expected milder anticholinergic adverse effects.

Organs and Systems

Gastrointestinal

Emepronium has repeatedly been shown to cause ulceration of the mouth and esophagus and widespread esophagitis (1–3). The buccal irritation is particularly marked if the tablets are retained in the mouth instead of being swallowed, and the problem as a whole is greater if the drug is not taken with sufficient fluid.

- Two women taking emepronium bromide developed extended ulcers of the esophageal mucosa. They had taken the tablets late in the evening with only a little fluid (4).

Drug Administration

Drug overdose

Central effects of emepronium are only serious in gross overdosage. In one case of attempted suicide with 100 tablets, there was severe confusion and derangement of breathing (due to neuromuscular paralysis) demanding mechanical ventilation (SED-12, 330).

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Emorfazone

General Information

Emorfazone is a pyridazinone NSAID that was developed in Japan. Sleepiness, dry mouth, rash, and various gastrointestinal disturbances are its most important adverse effects (1).

Reference

1. Anonymous. Emorfazone. Drugs Today 1985;21:63.

Enadoline

General Information

Enadoline is an opioid agonist at OP_2 (κ) receptors and has no effects attributable to OP_3 (μ) receptor actions, such as respiratory depression. However, enadoline does not offer any benefits over other currently available opioids (1).

Reference

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Enalapril

See also Angiotensin converting enzyme inhibitors

General Information

Enalapril is an ACE inhibitor used in the treatment of hypertension and heart failure and prophylactically in patients with asymptomatic left ventricular dysfunction.

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Organs and Systems

Cardiovascular

Of all studies of the effects of ACE inhibitors on mortality in acute myocardial infarction, only the CONSENSUS II trial did not show a positive effect. In this trial enalaprilat was infused within 24 hours after the onset of symptoms, followed by oral enalapril. The reasons for the negative result of CONSENSUS II remain unresolved, but hypotension linked to a poorer prognosis has been suggested as an explanation. In a small substudy of this large trial, 60 patients were investigated for residual ischemia before discharge, with exercise testing and Holter monitoring (1). Episodes of hypotension and predischarge ischemia were more common with enalapril than with placebo. The authors suggested that enalapril induced a proischemic effect in hypotension-prone patients, mediated through exacerbation of the hemodynamic response, since the initial blood pressure fall after myocardial infarction is related to residual ischemia and recurrent acute ischemic syndromes. This conclusion seems very speculative. The data were derived from a small substudy with multiple subanalyses and cannot support a cause-and-effect relation between the acute hemodynamic effect and the predischarge ischemic conditions. ACE inhibitors should still be used in acute myocardial infarction with cautious dose titration.

Neuromuscular function

Muscular weakness has been reported in a patient with mild renal impairment taking enalapril (2).

- A 78-year-old man, taking enalapril (10 mg/day), furosemide, and digoxin for cardiac failure due to ischemic heart disease, suddenly developed generalized muscle weakness. He had grade 3/5 weakness of all four limbs, his cranial nerves were intact, and there was no sensory impairment. His tendon reflexes were reduced and he had flexor plantar reflexes. The initial diagnosis was Guillain–Barré syndrome. Further investigation showed peaked T waves on his electrocardiogram, with a serum potassium of 9.4 mmol/l and a creatinine of 266 μmol/l. He was treated with glucose plus insulin, calcium gluconate, and sodium bicarbonate. Enalapril was withdrawn. His potassium concentration normalized.

Hyperkalemic muscle paralysis has been reported in renal insufficiency and trauma and in patients taking spironolactone and amiloride plus hydrochlorothiazide (co-amilozide). ACE inhibitors inhibit the release of aldosterone, reducing renal potassium loss, which can be enhanced by potassium-sparing diuretics or pre-existing renal insufficiency.

Endocrine

A single case of the syndrome of inappropriate secretion of antidiuretic hormone has been reported with enalapril (3).

Hematologic

Thrombocytopenia has been reported with enalapril in two elderly sisters (4). Both had the same HLA phenotype (B8DR3), which the authors postulated may reflect a genetic predisposition to this reaction. However, no further cases have been reported.

Enalapril-induced anemia has been reported in hemodialysis patients and in kidney transplant recipients. The anemia is usually normocytic, normochromic, and nonregenerative. Deficient bone-marrow erythropoiesis has occasionally been described. The anemia is reversible after withdrawal. Although the hypothesized mechanism of a reduction in erythropoietin blood concentrations by enalapril is controversial, in a prospective controlled study enalapril increased recombinant human erythropoietin requirements to maintain hemoglobin concentrations (5).

Enalapril-induced anemia has been reported in a child (6).

- A 7-year-old girl with segmental glomerulosclerosis and nephrotic syndrome failed to respond to prednisolone and cyclophosphamide, which were withdrawn. While her renal function was deteriorating she was given enalapril 2.5 mg bd. After 3 months, the enalapril was withdrawn because her hemoglobin fell from 12.7 to 6.2 g/dl. Ferritin, folate, and vitamin B_{12} were normal. Recovery was incomplete. Only 10 weeks after enalapril withdrawal her hemoglobin rose to 8.5 g/dl and remained unchanged thereafter.

The incomplete resolution of anemia in this case suggests that factors other than the speculated enalapril-related inhibition of erythropoietin may have contributed to the initial anemia (worsening renal function, frequent blood sampling, withdrawal of prednisolone).

An equivocal case of neutropenia has been ascribed to enalapril (7).

- A 52-year-old male renal transplant recipient on stable therapy (4.5 months) with ciclosporin, mycophenolate mofetil, and co-trimoxazole developed erythrocytosis and hypertension. His leukocyte count fell 19 days after he started to take enalapril. Enalapril was withdrawn, the dose of co-trimoxazole was halved, and the dose of mycophenolate was first reduced and then withdrawn on day 25. On day 28 the leukocyte and neutrophil counts were so low that granulocyte-stimulating factor had to be used. The leukocyte count normalized during continued treatment with ciclosporin and co-trimoxazole. CMV tests were negative.

The authors suggested a synergistic effect between enalapril and mycophenolate. As leukopenia is the commonest clinically significant adverse effect of mycophenolate, the evidence in this case is inadequate to support this hypothesis, particularly in the absence of information on mycophenolate blood concentrations.

Liver

Hepatitis has been attributed to enalapril.

- A 45-year-old man who had taken enalapril (dose not reported) for more than 2 years presented with hepatitis with negative viral serology (8). Biopsy showed necrosis and cholestasis. He recovered fully after drug withdrawal (timing not reported).
- A 46-year-old man had taken enalapril for hypertension for 3 years before he presented with jaundice and progressive liver failure (9). He was taking no other drugs and had a moderate daily consumption

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of alcohol. All known causes of acute liver failure were excluded by careful and extensive investigation. Analysis of liver biopsies showed a pathological pattern comparable to that observed in severe halothane hepatitis. Serological studies, including T cell stimulation with enalapril and a broad spectrum of tests for autoimmunity, were negative. The hepatitis persisted despite enalapril withdrawal and finally led to orthotopic liver transplantation and subsequently to death.

The mechanism of enalapril-induced liver injury in this case was obscure. The causal relation was unconvincing.

Skin

Adult Henoch-Schönlein purpura has been attributed to enalapril (10).

- A 41-year-old man with a history of hypertension and a recent stroke was admitted 10 days after starting to take enalapril (dose not reported). He complained of severe abdominal pain, myalgia, arthralgia, paresthesia, and Raynaud's phenomenon, and had a high erythrocyte sedimentation rate, but no leukocytosis or thrombocytopenia. He developed purpura-like cutaneous lesions with acute renal insufficiency, severe hematuria, and proteinuria. Liver tests became altered. There was a polyclonal rise in IgA concentrations. Skin biopsy suggested leukocytoclastic vasculitis, with deposition of IgA and complement. Other diagnostic procedures were negative. Enalapril was withdrawn and he was given glucocorticoids, after which he fully recovered (timing not reported).

The acantholytic potential of enalapril has been shown in vitro in skin cultures and in vivo acantholysis without pemphigus has been reported.

- A 66-year-old man, who had taken enalapril 10 mg/day for 1 year, had a basal cell carcinoma removed surgically (11). Histology showed suprabasal acantholytic clefts in the perilesional epidermis. Direct immunofluorescence did not show intracellular deposits of IgG, IgA, IgM, or C3. Indirect immunofluorescence showed serum anticellular antibodies (titer 1:80). He stopped taking enalapril, and 3 months later his anticellular antibody titer was 1:320. A further biopsy of apparently healthy skin on the back showed new foci of acantholysis. Another biopsy in the same location 2 months later showed no acantholytic changes. Direct immunofluorescence was negative and the anticellular antibody titer was 1:80. HLA typing showed pemphigus-predisposing antigens (DR14, DQ1), which has previously been reported as a predisposing factor for acantholytic changes in the epidermis exposed to enalapril.

As pemphigus vulgaris has been attributed to ACE inhibitors, it is not surprising that giving an ACE inhibitor to a patient with pemphigus could worsen the disease. Aggravation of pre-existing childhood pemphigus by enalapril has been reported (12).

- A 12-year-old boy with pemphigus vulgaris was treated with intravenous dexamethasone and prednisolone. He developed severe hypertension, which was unresponsive to atenolol, and he was given enalapril 2.5 mg bd. Although the blood pressure responded, the pemphigus deteriorated markedly over the next 2 weeks. Additional dexamethasone did not produce improvement. Enalapril was replaced by amlodipine, and the disease resolved over 3 weeks.

The evidence to date suggests that ACE inhibitors should be avoided in patients with pre-existing pemphigus.

Immunologic

Eosinophilic gastroenteritis after enalapril has been described (13). The authors briefly reviewed this rare condition, which is diagnosed on the basis of the presence of gastrointestinal symptoms, eosinophilic infiltration of the gastrointestinal tract, and the absence of parasitic or extra-intestinal disease. It has also been reported after clofazimine and naproxen.

- A 63-year-old hypertensive woman, who had a carcinoma of the distal esophagus resected 19 months earlier, developed chronic diarrhea. *Clostridium difficile* toxin was identified in her stools and the diarrhea resolved after treatment with metronidazole. Enalapril was added to her antihypertensive treatment, and 3 months later the diarrhea recurred. Stool examination was negative and there was no *Clostridium difficile* toxin. Her condition worsened and she lost 5 kg in weight. She had marked eosinophilia (2.4×10^9/l), and a small bowel biopsy showed mild chronic inflammation and edema, partial villous atrophy, and large clusters of eosinophils in the lamina propria with some focal infiltration of the epithelium. She stopped taking enalapril and her diarrhea promptly abated and the eosinophil count fell to 0.5×10^9/l at 3 weeks and 0.1×10^9/l at 2 months.

Body temperature

Fever has been attributed to enalapril (14).

- A 50-year-old man with heart failure and a valve prosthesis, taking digoxin, furosemide, and spironolactone, was given enalapril 5 mg/day. Two days later, after increasing the dose to 10 mg, he developed a fever with cough and clear sputum, with a normal chest X-ray. Enalapril was withdrawn and 24 hours later the fever resolved. It recurred immediately after rechallenge.

Drug Administration

Drug overdose

A single case of overdose of enalapril has been reported (15).

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Encainide

See also Antidysrhythmic drugs

General Information

Encainide is a class I antidysrhythmic drug. Reviews of its clinical pharmacology, clinical use, efficacy, and adverse effects have appeared (1–6).

Organs and Systems

Cardiovascular

In the wake of the preliminary and final reports of the Cardiac Arrhythmia Suppression Trial (CAST) (7,8), which showed that there was an increased risk of death among patients who took encainide and flecainide after myocardial infarction, there have been many publications in which the implications of these findings have been thoroughly discussed (9–13). The relative risk of death or cardiac arrest due to dysrhythmias in the treated patients was 2.6 and the relative risk due to all causes was 2.38. The risk of non-fatal cardiac adverse effects was no different in treated patients from that in those taking placebo and there was no difference between the groups in the use of other drugs.

Although there is a consensus that encainide and flecainide were associated with an increase in the rate of mortality in CAST, there are still some open questions. First, all the patients recruited to CAST had asymptomatic ventricular dysrhythmias after myocardial infarction, and it is not clear whether the results can be extrapolated to other patients. Secondly, the reasons for the increased mortality in the treated patients are not clear: ventricular dysrhythmias and worsening of left ventricular function are both possible. Thirdly, it is not clear whether the results of CAST in patients with asymptomatic ventricular dysrhythmias after myocardial infarction can also be applied to other Class I antidysrhythmic drugs.

Separate studies have confirmed the prodysrhythmic actions of encainide (14–17). The incidence of prodysrhythmias is much higher in patients being treated for ventricular dysrhythmias than in those being treated for supraventricular dysrhythmias (18).

Encainide has been reported to cause sinus node arrest in association with prolonged sinus node recovery time (19). It also raises the pacing threshold in patients with chronic implanted pacemakers (20), although this has not been reported to increase the failure rate of pacemakers.

Encainide has a negative inotropic effect on the heart and can cause hypotension (21) or worsen heart failure (22).

Nervous system

The most common non-cardiac effects of encainide are on the central nervous system, and include abnormal or blurred vision (11%), dizziness (7.3%), headaches (6.0%), nausea (4.3%), vertigo (2.3%), insomnia, and fatigue. The figures in parentheses are taken from a review of 349 patients with supraventricular dysrhythmias treated with encainide (14). These effects are common during long-term therapy, but may also occur transiently during intravenous administration and appear to be dose-related (23,24).

A case of encephalopathy has been attributed to encainide (25).

Sensory systems

There have been reports of a metallic taste in the mouth after intravenous administration of encainide (24).

Endocrine

Encainide can cause hyperglycemia (26), perhaps due to insulin resistance.

Gastrointestinal

Nausea can occur during long-term therapy with encainide, probably due to a central nervous effect (27).

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Skin

Skin rashes have been reported occasionally during long-term therapy with encainide (27).

Musculoskeletal

There have been reports of leg cramps after intravenous administration of encainide (24).

Susceptibility Factors

Genetic factors

Encainide is metabolized, at least partly, by oxidation to *O*-desmethylencainide, 3-methoxy-*O*-desmethylencainide, *N*-desmethylencainide, and *N*,*O*-didesmethylencainide. Of 112 healthy Caucasians 9 (8%) were defective in their ability to 4-hydroxylate debrisoquine (28). The cumulative frequency distribution of the 8-hour urinary recovery ratio of encainide/*O*-desmethylencainide indicated two distinct populations, an extensive metabolizer (EM) phenotype and a poor metabolizer (PM) phenotype. There was no 3-methoxy-*O*-desmethylencainide in the urine of the poor metabolizers. As *O*-desmethylencainide is a more potent antidysrhythmic drug than encainide and 3-methoxy-*O*-desmethylencainide is at least equipotent, these metabolites contribute significantly to the overall antidysrhythmic effect in extensive metabolizers. The low plasma concentrations of *O*-desmethylencainide and 3-methoxy-*O*-desmethylencainide in poor metabolizers would be expected to result in ineffective therapy when usual doses of encainide are given. However, in such individuals, chronic oral therapy results in accumulation of unmetabolized encainide to far higher concentrations than in extensive metabolizers, and as encainide itself has antidysrhythmic activity at these concentrations, this generally results in the desired response. It is possible that poor hydroxylators are at greater risk of adverse effects than extensive hydroxylators.

In 110 healthy subjects the changes in atrioventricular (PR) and intraventricular (QRS) conduction times produced by encainide were different in extensive and poor metabolizers and correlated with CYP2D6 activity, although the electrocardiographic response was never 100% specific and sensitive for the identification of either phenotype (29). Moreover, genotypic identification of heterozygous and homozygous extensive metabolizer subjects did not predict CYP2D6 activity, as determined by encainide metabolic ratios or encainide responses, as determined by intraventricular and atrioventricular changes.

Age

Children under the age of 6 months may be more liable to the prodysrhythmic effects of encainide than older children (30).

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Endothelin receptor antagonists

See also Individual agents

General Information

It is disappointing that mechanistically novel antihypertensive drugs have not emerged during the last decade or two. The only real novelty was the addition of angiotensin II receptor antagonists as a refinement of the approach introduced with ACE inhibitors. The expectations for direct renin antagonists have not been realized. Some of the cornerstone classes of antihypertensive drugs, such as the diuretics, beta-adrenoceptor antagonists, calcium channel blockers, and direct vasodilators, have been around for several decades. Advances have predominantly been made in the pharmacokinetic properties and pharmacodynamic specificities of compounds in existing antihypertensive drug classes.

With the emergence of knowledge about endothelial factors such as nitric oxide and endothelin, there was much expectation that endothelin antagonists would become useful in the management of hypertension. Endothelin was discovered in 1988 (1) and is the most potent vasoconstrictor known. In terms of pathophysiology, endothelin receptor antagonists could play a role in a variety of diseases associated with vasoconstriction, such as hypertension, renal disease, occlusive vascular disease, pulmonary hypertension, and congestive heart failure (2). Apart from vasoconstriction, endothelin is also involved in the structural changes associated with these diseases, and it is now recognized that there is a wider target in hypertension treatment than lowering blood pressure. Vascular and myocardial remodelling may be key issues in determining long-term outcome (3) and effects on myocardial fibrosis and vascular compliance may be as important as lowering blood pressure. ACE inhibitor treatment can produce regression of hypertensive myocardial fibrosis in animal models (4) and in hypertensive patients (5).

Trials of the effects of endothelin receptor antagonists in patients with heart failure, coronary artery disease, arterial hypertension, and pulmonary hypertension have been reviewed (6), as have their uses in treating cancers (7) and cerebral vasospasm (8), and their potential uses in atherosclerosis, re-stenosis, myocarditis, shock, and portal hypertension (9)

As far as hypertension is concerned, there is a substantial body of preclinical evidence of the potential efficacy of endothelin antagonists in hypertension, and this has been extensively reviewed (10). Circulating endothelin concentrations are not increased in hypertension, but it is postulated that there is an imbalance between the vasodilatory effects of nitric oxide and the vasoconstrictor effects of endothelin at a local vascular level, resulting in increased endothelin vasoconstrictor tone and endothelin-mediated end-organ damage (11,12).

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Enflurane

See also General anesthetics

General Information

Enflurane is a non-explosive halogenated volatile anesthetic that was first marketed in 1966. It was developed in the search for agents safer than halothane and methoxyflurane (1). However, the list of its halothane-like adverse effects has continued to grow.

Organs and Systems

Cardiovascular

Despite conflicting results, enflurane is generally considered to have little effect on the cardiovascular system. Cardiac output was mildly influenced in healthy men and the negative inotropic effects of enflurane (2) were more pronounced in patients with congestive heart failure (3). Myocardial damage was suggested to be an unlikely complication of enflurane anesthesia, even in patients with ischemic heart disease (4).

Cardiac dysrhythmias are generally considered to be less frequent, or at least less severe, with enflurane than with halothane (5,6). However, caution in the use of adrenaline is advisable, especially in patients with cardiac disease or hyperthyroidism. Isorhythmic atrioventricular dissociation was seen in 16 of 105 patients after the use of 1.0–1.5% enflurane (7).

Respiratory

Enflurane is usually not irritant to the respiratory tract, although bronchospasm has been reported (8). However, it is generally considered to be a bronchodilator. It causes respiratory depression at concentrations over 2%.

Nervous system

Cerebral irritability is a potential consequence of enflurane anesthesia, as evidenced by electroencephalographic recordings and by reported cases of convulsions (SED-11, 208) (9). Enflurane should be used with care (although it is probably not absolutely contraindicated) in patients with epileptiform tendencies, especially if they are deeply anesthetized and hyperventilated. There are reports of delayed convulsions after light general anesthesia not involving hyperventilation. A patient had a convulsion in a car after being discharged from a day-care anesthetic involving enflurane (9).

Motor neuron disease has been attributed to enflurane (10). The authors proposed that enflurane-induced release of glutamate may have caused changes in the spinal cord motor neurons. It is not clear what role alcohol abuse had in this case.

Neuromuscular function

Enflurane increased the sensitivity of the neuromuscular junction to d-tubocurarine in man (11).

Psychological, psychiatric

There was a reduced capacity for learning and decision-making in healthy volunteers after exposure to subanesthetic concentrations of enflurane (12,13).

Endocrine

The endocrine effects of enflurane anesthesia are minimal and clinically insignificant (14).

Metabolism

The effect of enflurane on heme metabolism has been tested in mice (15); the authors suggested that enflurane be added to the list of drugs that can precipitate acute attacks of porphyria.

Liver

One of the main advantages of enflurane over halothane is a reduced rate of liver damage, although such damage can occur (about one in 800 000 exposures) (16,17). With increasing use since 1980 there has been an increasing number of reports of enflurane-induced hepatitis (SED-11, 209), some in patients previously affected by halothane (18), and with some evidence that the risk may be higher in obese middle-aged women (19); some deaths have occurred. All the same, its hepatotoxic potential, although not entirely defined, is probably low, as evidenced by prospective studies of liver function during repeated enflurane anesthesia (20). Indeed, in May 1982 the FDA decided against incorporating a warning of hepatotoxicity on the drug's American labelling, and this policy has been maintained since.

Two patients with hepatic failure after enflurane anesthesia were reported from a hepatic transplant unit in France; both died while waiting for a liver transplant (21). In common with halothane, hepatic failure after enflurane is thought to be caused by the metabolite trifluoroacetic acid.

Urinary tract

Nephrotoxicity leading to renal insufficiency, particularly after prolonged anesthesia, is a potential consequence of general anesthesia with enflurane (22). Several cases of renal insufficiency have been described (SED-11, 209) (23,24), and the mechanism studied. On experimental

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grounds, it has been suspected that the inorganic fluoride ions to which enflurane is transformed may play a role. Despite evidence that enflurane can cause a significant reduction in maximum urinary osmolarity (tested using vasopressin administration) and in creatinine clearance in healthy volunteers (25), further investigations are warranted. Superimposition of nephrotoxic factors, for example drugs or underlying disease, should be avoided (1).

Musculoskeletal

Myoglobinuria, developing immediately after enflurane anesthesia, has been reported (26).

Second-Generation Effects

Teratogenicity

Experimental evidence is against a teratogenic role of enflurane (1).

Susceptibility Factors

Renal disease

It has been thought that patients with chronically impaired renal function might be at increased risk of nephrotoxicity due to enflurane, because of an increased fluoride load due to reduced excretion. However, this was not confirmed in 41 patients undergoing elective surgery with a stable increased preoperative serum creatinine concentration who were randomly allocated to receive sevoflurane ($n = 21$) or enflurane ($n = 20$) at a fresh gas inflow rate of 4 l/minute for maintenance of anesthesia (27). Peak serum inorganic fluoride concentrations were significantly higher after sevoflurane than after enflurane anesthesia. Laboratory measures of renal function remained stable throughout the postoperative period in both groups. No patient had permanent deterioration of pre-existing renal insufficiency and none required dialysis.

Drug–Drug Interactions

Amitriptyline

Amitriptyline may potentiate enflurane-induced cerebral irritability (19).

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Enoximone

See also Phosphodiesterase type III, selective inhibitors of

General Information

Enoximone is an inhibitor of phosphodiesterase type III, and has a positive inotropic effect. Its most common adverse effects are gastrointestinal and cardiac. The gastrointestinal effects include anorexia, nausea, vomiting, and diarrhea (1,2).

Other rarely reported adverse effects include thrombocytopenia, leukocytosis, increased appetite, increased serum activity of alanine transaminase, hyperglycemia, headache, lethargy, anxiety, dyspnea, and skin rashes (2–6).

Organs and Systems

Cardiovascular

The cardiac effects of enoximone include hypotension, transient atrial fibrillation, and bradycardia (3). Ventricular tachydysrhythmias have been reported in about 4% of patients (2) and myocardial ischemia can also occur (4,7).

Musculoskeletal

Enoximone has been reported to cause increased contraction in skeletal muscle in vitro in patients with a predisposition to malignant hyperthermia (8,9).

- Vastus lateralis muscle from a 48-year-old man with rhabdomyolysis had an increased in vitro response to increasing concentrations of enoximone above 0.6 mmol/l (10). He also had a heterozygous mutation in his ryanodine receptor gene, with substitution of arginine for glycine in position 2433, a mutation that is associated with malignant hyperthermia.

Phosphodiesterase inhibitors, such as enoximone, increase the release of calcium from the sarcoplasmic reticulum by activating ryanodine receptors, and the authors suggested that this may have been the mechanism whereby enoximone precipitated rhabdomyolysis in this case.

Death

Long-term treatment with inhibitors of phosphodiesterase type III is associated with increased mortality in congestive heart failure (SEDA-17, 217).

In 102 patients taking digoxin and diuretics the addition of enoximone did not confer any therapeutic advantage and there was a significantly higher dropout rate and a significantly higher mortality rate in those taking enoximone (11).

The use of a lower dose of enoximone in 105 patients with heart failure (New York Heart Association classes 2 or 3) has been studied over 12 weeks (12). Enoximone 25–50 mg tds improved exercise capacity and reduced dyspnea. There was no evidence of a dysrhythmic effect. The rates of adverse events were similar with enoximone and placebo, and there were fewer cases of dizziness, vertigo, or hypotension in those who took enoximone. There were two deaths in the 70 patients who took enoximone compared with four of the 35 who took placebo. However, this small short-term study does not rule out the possibility that even this small dose of enoximone can cause increased mortality during long-term administration or in patients with more severe cardiac failure.

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Enprofylline

General Information

Enprofylline (3-propylxanthine) is a xanthine derivative that has some actions in common with theophylline but has a negligible antagonistic effect at most adenosine receptor subtypes (1,2). Enprofylline is a more potent smooth muscle relaxant and antiasthmatic drug than theophylline but does not produce, for example diuresis, stimulant behavioral effects (restlessness and seizures) in the nervous system, gastric secretory effects, or free fatty acid release. Selectivity for the A_{2B} adenosine receptor subtype may underlie this lack of typical adverse effects associated with other theophylline-related drugs (3). Enprofylline has a short half-life (about 2 hours). The target plasma concentration is about 3 μg/ml. Its efficacy and tolerability have been briefly reported (4).

The most severe adverse effects of theophylline, namely seizures, are claimed to be absent even at high doses of enprofylline, although there are other disadvantages, such as cardiovascular effects, nausea, vomiting, and headache. Much more information is needed before claims of greater safety can be taken seriously.

The possibility of obtaining a steady-state plasma enprofylline concentration of 5 μg/ml by two constant rate infusions was examined in six asthmatic patients (5). The resulting adverse effects and bronchodilatation were compared with those obtained with theophylline at a steady-state concentration of 15 μg/ml. Headache, nausea, and vomiting became pronounced in two patients in whom the plasma enprofylline concentration was about 6 μg/ml. The authors concluded that by varying the infusion rate the plasma concentration of enprofylline can be controlled like that of theophylline, but they stressed the need for further studies of efficacy versus adverse effects.

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Enprostil

See also Prostaglandins

General Information

Enprostil is a synthetic analogue of PGE_2.

Organs and Systems

Gastrointestinal

Even in doses insufficient to control ulcer symptoms, enprostil has a higher incidence of adverse effects than the H_2-receptor antagonists. In a randomized, double-blind, endoscopically controlled study, 98 patients with gastric ulcers were treated with either enprostil 70 micrograms bd or ranitidine 150 mg bd (1). The healing rates at 4, 8, and 12 weeks were similar. After ulcer healing, half the patients were followed for 1 year without treatment and the others were given enprostil 70 micrograms/day. Diarrhea was a common adverse effect of enprostil, and seven patients withdrew because of diarrhea or abdominal pain.

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Entacapone

General Information

Entacapone is an inhibitor of catechol-*O*-methyltransferase, which catalyses a relatively minor pathway of dopamine metabolism. It therefore enhances the action of dopamine.

The safety of entacapone has been specifically addressed in a Finnish study in 326 patients (mean age 62 years, 217 men) taking levodopa plus a decarboxylase inhibitor (1). Two-thirds were randomized to take entacapone 200 mg/day and the remainder to take placebo. The withdrawal rate due to adverse events was 14% with entacapone compared to 11% with placebo. Dyskinesias were greatly increased in the former (29 versus 11%) and entacapone was also associated with increased incidences

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of diarrhea (9.2 versus 1.9%), dry mouth (6.0% versus 0), and discolored urine (6.9% versus 0). However, there was no evidence of liver toxicity with entacapone.

Placebo-controlled studies

In a placebo-controlled study in Germany and Austria, 301 patients with Parkinson's disease were randomized to receive placebo or entacapone 200 mg with each dose of levodopa, together with their other usual therapy (2). The mean age was 61 years and 40% of the entacapone group and 48% of the placebo group were men; the groups were also unequal in size (197 versus 104), for reasons that were not clearly defined. Entacapone reduced the Unified Parkinson's Disease Rating Scale score, increased "on" periods, and reduced "off" periods. In the patients who took entacapone there was more frequent dyskinesia (34 versus 26%), nausea (10 versus 4.8%), and diarrhea (8.1 versus 3.8%). All of these findings are consistent with enhanced dopaminergic activity. There was no evidence of hepatotoxicity in any of the patients.

Comparative studies

In 40 patients (mean age 64 years, 22 men) who took tolcapone for 3–7 months and were given entacapone in dosages titrated to 800–2000 mg/day after a transition period of 3–6 months with co-beneldopa, the improvements in "on" and "off" times were less impressive than they had been with tolcapone and there were more adverse effects (3). One patient had diarrhea and orthostatic hypertension with both drugs, but another six patients had increased dyskinesias and hallucinations and one developed myoclonus. There was no evidence of liver toxicity with either drug. The authors pointed out that entacapone, unlike tolcapone, not only increases the half-life of levodopa but also its peak concentration, causing significantly enhanced levodopa-related adverse effects. There is therefore a paradox: entacapone appears to be safer but overall causes more adverse effects.

Organs and Systems

Nervous system

Fatigue and light-headedness or dizziness have occurred relatively frequently during oral entacapone administration in small studies (up to 60% of patients) (4). Other less frequent central nervous system effects include confusion, anxiety, syncope (related to postural hypotension), and insomnia (5,6). Mood elevation has been observed occasionally (5). The inclusion of entacapone in levodopa therapy for Parkinson's disease increases the risk of dyskinesias, possibly through enhanced brain penetration of levodopa (4,5,7). This can be adjusted by reducing the dose of levodopa.

Gastrointestinal

Gastrointestinal adverse effects have been reported in up to 50% of patients taking oral entacapone, and include epigastric pain, abdominal pain, nausea, anorexia, and loose stools or diarrhea (4–6,8). These effects have generally been mild and not dose-limiting.

Liver

Whether entacapone is hepatotoxic is debatable.

- A 76-year-old Australian woman complained of nausea, anorexia, and malaise 2 weeks after starting to take entacapone 200 mg five times a day (9). A week later her bilirubin, alanine transaminase, alkaline phosphatase, and gamma-glutamyl transpeptidase were all raised (2–8 times higher than the upper limits of the reference ranges). Clotting was normal. Over the next 3 days her liver function tests deteriorated and the entacapone was withdrawn. All the laboratory data improved within 2 days, but not all were fully normal 4 weeks later. She refused a rechallenge.

The authors noted that two other patients in the Australian adverse reactions database also appeared to have had hepatotoxicity related to entacapone. In response, representatives of the manufacturers (Novartis) strongly contested the conclusion that any of the three reported cases demonstrated entacapone-induced hepatotoxicity, and concluded that two of the three patients had cholestasis, which is unlikely to be related to entacapone, while the third had no real evidence of hepatic dysfunction (10). These arguments were in turn rebutted by the original authors, and the possible hepatotoxicity of entacapone remains a matter of debate, although there can be no doubt that it is safer than tolcapone.

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Enteral nutrition

General Information

Enteral nutrition refers to any method of feeding that involves instillation of food into the gastrointestinal tract, such as normal feeding, feeding by nasogastric or nasoenteric tube, or feeding into a gastrostomy or enterostomy (for example a so-called PEG, a percutaneous endoscopic gastrostomy). Enteral nutrition should be tailored to the needs of the individual, but on average should provide about 30–40 kcal/kg/day.

Organs and Systems

Gastrointestinal

There is a risk of gastroesophageal reflux during nasogastric feeding, especially in mechanically ventilated and sedated patients (1).

- A 77-year-old man had a ruptured abdominal aortic aneurysm repaired and developed acute renal, respiratory, and heart failure. Six days postoperatively, enteral feeding was started with a standard formulation. This was well tolerated and the volume was increased to 2 l/day continuously. After 9 days, the nasogastric tube was accidentally dislodged. Reinsertion was attempted but failed owing to apparent obstruction at 25 cm. Until this, the patient had been nursed supine. Esophagoscopy showed impacted enteral feed obstructing the esophagus almost completely.

Gastroesophageal reflux during enteral nutrition is caused by a number of factors, including the presence of the nasogastric tube, the supine position, leakage from the tube at the teeth, and the administration of sucralfate. While the cause in this case was not entirely clear, it does show that mechanical obstruction of the esophagus due to reflux can occur without any obvious symptoms.

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Ephedra, ephedrine, and pseudoephedrine

General Information

Ephedra consists of a mixture of different members of the Ephedraceae family (*E. sinica*, *E. equisetina*, and *E. gerardiana*). Its actions are due to the presence of ephedrine and pseudoephedrine.

Ephedrine is a sympathomimetic drug prepared from members of the *Ephedra* family, such as *Ephedra vulgaris*, also called the sea grape. It is available as ordinary pharmaceutical formulations of ephedrine, but also in herbal formulations of *Ephedra*, including a Chinese herbal medicine called Ma huang, which has been used since ancient times as a stimulant and in the treatment of asthma, and in formulations combined with caffeine. It is used to treat asthma, nasal congestion, fever, obesity, and anhidrosis. It is also abused as a recreational drug. Of 140 reports of adverse events related to *Ephedra* supplements submitted to the FDA between June 1997 and March 1999, 31% were definitely or probably causally related to *Ephedra* (1). In 47% of the cases, there were cardiovascular symptoms and in 18% central nervous system effects; 10 patients died.

Pseudoephedrine is a stereoisomer of ephedrine, in which two of three chiral centers are different.

"Herbal ecstasy" is a term used for many different herbal formulations, none of which contains ecstasy. Some of the names for these herbs (which can be sold in stores) include "The Bomb," "Reds," and "Sublime." In New Zealand analysis of "The Bomb" showed substantial amounts of ephedrine and the Ministry of Health removed it from the market. Some symptoms associated with herbal ecstasy include headache, dizziness, palpitation, tachycardia, and raised blood pressure. Thus, in countries where the term "herbal ecstasy" is commonly used, it is important that those who see patients who have taken Herbal Ecstasy should not confuse it with ecstasy, as toxicity and medical management may be quite different (2).

Ephedrine is longer-acting than adrenaline and can exert any type of adrenergic effect, including metabolic changes and dysuria. It has a somewhat smaller effect on the cardiovascular system than adrenaline but a relatively larger effect on the central nervous system; even low doses can, in sensitive patients, cause tremor, insomnia, and anxiety, and such problems are much more marked if ephedrine is given together with caffeine, as it sometimes is for appetite control (SEDA-17, 161). In children, ephedrine sometimes paradoxically induces sedation. Psychosis has resulted from excessive self-medication (3).

Both ephedrine and pseudoephedrine remain worryingly popular (4) and are widely available without prescription. Based on increasing evidence of the risks of *Ephedra* self-medication, various national regulatory authorities are currently considering recalling *Ephedra* products from over-the-counter sales. Oral doses of ephedrine 25–30 mg are often prescribed, for example for orthostatic hypotension. Lower oral doses, present in some "cold remedies" in tablet form, are unlikely to be efficacious, although they are risky where the drug is

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contraindicated, for example in patients with cardiac disease. Ephedrine used in nasal sprays and drops can have systemic effects in the doses normally used. Such products are widely available over the counter in many countries. In Texas some 500 cases of adverse reactions were reported between 1993 and 1995 (SEDA-21, 153). Three of these cases have been highlighted because of their serious nature: one patient died from myocardial infarction, one had a series of generalized absence seizures, and a third had a fatal subarachnoid hemorrhage as the result of taking an unsuitable dose (SEDA-21, 153).

Organs and Systems

Cardiovascular

Cardiologists and pharmacologists from Boston have reviewed cases of possible cardiovascular toxicity associated with the use of Ma huang. Among over 900 cases of possible toxicity reported to the Food and Drug Administration, they identified 37 patients (23 women) in whom stroke ($n = 16$), myocardial infarction ($n = 10$), and sudden death ($n = 11$) appeared to be temporally related to consumption of Ma huang. The authors noted that in all but one of these cases the doses used were within the range recommended by the manufacturers. In the seven patients on whom autopsies were performed, coronary artery disease was found in three and cardiomyopathy in another three, with features suggesting sympathomimetic toxicity. The authors emphasized the toxicity of Ma huang in relatively young individuals—the mean age of the 37 patients was about 43 years—even though the relevant pathogenic mechanisms remain to be fully defined.

Hypertension

The cardiovascular effects, subjective effects, and abuse potential of single intranasal doses of ephedrine 5 and 10 mg have been compared with oral doses of (−)ephedrine 50 mg in 16 healthy Caucasian men with no drug/alcohol/nicotine abuse or dependence (5). Intranasal ephedrine caused an increase in blood pressure but associated orthostatic hypotension.

Pseudoephedrine is a component of some non-prescription basal decongestants given by mouth; even quite ordinary doses of such products (for example 120 mg) can cause a hypertensive reaction in sensitive subjects, such as those with a pheochromocytoma and those with at least a family history of hypertension (SEDA-17, 162).

- A 21-year-old man presented with hypertension (blood pressure 220/110 mmHg) and ventricular dysrhythmias after taking four capsules of herbal ecstasy (6). He was treated with lidocaine and sodium nitroprusside and his symptoms resolved within 9 hours.

Severe hypertension has been attributed to pseudoephedrine abuse (7).

- A 36-year-old man with hypertension taking no less than seven antihypertensive drugs had outpatient systolic pressures of over 190 mmHg. Investigations for primary causes of hypertension were negative and there was increasing suspicion of treatment noncompliance or factitious hypertension. Urine screening showed the presence of pseudoephedrine, which the patient could not explain. When he was given his normal antihypertensive drugs under close supervision his systolic blood pressure fell to 70 mmHg and his serum creatinine doubled. His blood pressure became normal when his medication was briefly suspended but he continued to deny any deliberate attempt to alter his blood pressure and discharged himself soon afterwards.

The authors concluded that this represented factitious hypertension due to pseudoephedrine, the first such case reported and a very unusual example of Munchausen's syndrome.

Cardiac dysrhythmias

Cardiac dysrhythmias have been attributed to ephedrine both in therapeutic doses (8) and when used as a drug of abuse (6).

- A 25-year-old woman became hypotensive after the administration of epidural anesthesia for an elective cesarean section. She was given intravenous ephedrine 9 mg, after which she complained of nausea. For an unexplained reason this was taken as an indication to give a further 9 mg of ephedrine. She immediately developed sinus tachycardia with atrial and multifocal ventricular extra beats, followed by short runs of ventricular tachycardia. She remained asymptomatic and recovered after about 5 minutes.

One must have some concerns about the high dose used here for a relatively modest level of hypotension with a systolic blood pressure of 100 mmHg.

- A 21-year-old Canadian man presented with severe headache, nausea and vomiting, hypertension (220/120 mmHg), and a sinus tachycardia of about 120/minute with frequent multifocal ventricular extra beats. He was treated with intravenous sodium nitroprusside and lidocaine and recovered fully within 24 hours.

The authors concluded that ephedrine was very largely responsible for the cardiovascular toxicity.

Myocardial ischemia

Myocardial infarction has been attributed to *Ephedra* (9).

- A previously healthy 19-year-old man took tablets containing a total of 24 mg of Ephedra alkaloids and 100 mg of caffeine, and 15 minutes later developed severe chest pain radiating down the left arm. An electrocardiogram showed an inferolateral myocardial infarct, confirmed by creatine kinase and troponin I measurements. He made a full recovery, and coronary angiography showed only minimal atherosclerotic disease of the left anterior descending artery.

The authors emphasized the dangers of *Ephedra*-containing over-the-counter formulations, even in fit young people.

Ephedrine is sometimes used to treat vasovagal episodes and has been reported to cause coronary artery spasm and myocardial infarction in these circumstances (10).

- Two apparently healthy women, aged 26 and 34 years, who were given spinal anesthesia for pelvic or hip surgery, both developed hypotension and bradycardia and were given intravenous ephedrine in divided doses, in

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one case a total of 20 mg and in the other 30 mg. In both cases this resulted in ventricular tachycardia and raised troponin I concentrations and creatine kinase activity, but Q waves did not follow. Coronary angiography showed normal arteries in both cases and the women recovered, apparently fully.

The authors rightly pointed out that atropine is a safer and more appropriate intervention in circumstances such as these.

Arteritis

Arteritis has been attributed to ephedrine (11).

- A 44-year-old French woman was given intravenous ephedrine during anesthesia and developed hypertension (systolic pressure 180 mmHg) with nausea, vomiting, and progressive drowsiness. She had a history of migraine, antiphospholipid antibodies, mitral valve prolapse, and atrial fibrillation treated with propranolol. Immediately after anesthesia she developed headache, vomiting, and drowsiness. CT scanning showed frontal and parietal hemorrhagic infarcts, and cerebral angiography showed multiple segments of constriction and dilatation consistent with arteritis. She was left with residual visual and memory deficits.

This is the first case of this kind associated with ephedrine, and it seems plausible that the patient's previous history indicated a genetic predisposition to vascular disease.

Others

A form of toxic shock syndrome on more than one occasion occurred in one patient who used pseudoephedrine (SEDA-18, 158).

Nervous system

In a consecutive stroke registry since 1988, 22 patients (10 men and 12 women) had strokes associated with over-the-counter sympathomimetic drugs (12). There was intracerebral hemorrhage in 17, subarachnoid hemorrhage in four, and ischemic stroke in one. Stroke was associated with the use of pseudoephedrine (60–300 mg) in four cases.

The largest manufacturer of *Ephedra*-containing supplements is Metabolife. The firm has repeatedly insisted that it was not aware of adverse events associated with its products, and claimed that they were "absolutely safe" (13). An investigation by the US Justice Department into the truth of these statements showed that between 1997 and 2002 the company had received over 13 000 reports of suspected adverse drug reactions; they included nearly 2000 reports of significant adverse reactions.

- A 33-year-old man had a stroke while taking a herbal remedy (Thermadrene) containing *Ephedra* alkaloids and guaraná for "boosting his energy" (14). He was immediately treated with alteplase and was referred for rehabilitation 9 days later. At follow-up 5 months later he still had a minor neurological deficit.

Psychological, psychiatric

Ma huang can cause psychiatric complications, which can last several weeks. These have been reviewed in the context of two cases of psychotic reactions (15).

- A 27-year-old US Marine presented with depressed affect, irritability, and poor concentration and eventually admitted 2 years self-medication with Ma huang to improve workout performance.
- A 27-year-old US Marine developed a frank psychosis with ideas of reference and some paranoid ideation. He had been taking two preparations containing Ma huang, although the duration of use was unclear.

After discontinuing the drug both made a full recovery. The authors emphasized the importance of recognizing possible abuse of such "natural" medications, widely perceived to be harmless despite warnings and attempted restrictions by regulatory authorities. Treatment is supportive while awaiting spontaneous recovery after drug withdrawal.

Pseudoephedrine is often used by scuba divers to avoid ear barotrauma. The psychometric and cardiac effects of pseudoephedrine have been evaluated at 1 atmosphere (100 kPa, sea level) and 3 atmospheres (30 kPa, 20 m) in a double-blind, placebo-controlled, crossover study in 30 active divers in a hyperbaric chamber (16). Pseudoephedrine did not cause significant alterations in psychometric performance at 3 atmospheres.

A young child suffered from visual hallucinations caused by high doses of pseudoephedrine (17).

Endocrine

One patient with Graves' disease who used pseudoephedrine developed a thyroid storm, suggesting that hyperthyroidism is a susceptibility factor (18).

Gastrointestinal

The vasoconstrictor action of pseudoephedrine can predispose susceptible patients to ischemic colitis, particularly in the watershed area of the splenic flexure. Perimenopausal women may be more susceptible (19). A group from Yale have described four patients, women aged 35–50 years, who developed ischemic colitis while taking pseudoephedrine (19). Three of them had taken the drug for about 1 week, the fourth for 6 months. In all cases there was ischemic colitis affecting predominantly the splenic flexure, and there was full recovery after drug withdrawal.

- A 33-year-old man took pseudoephedrine 240 mg/day for 5 days (20). His mesenteric vasculature was normal on subsequent magnetic resonance angiography and no other abnormalities were found, leading to the presumption that the drug had caused mesenteric vasoconstriction. He made a full recovery.
- A 51-year-old woman presented for the second time in 4 months with abdominal pain (21). On this as on the previous occasion, emergency laparotomy was needed and she was found to have patchy infarction of the terminal ileum and the ascending colon. It emerged that she had been taking pseudoephedrine for 2 years, because she found that it relieved her headaches. In fact she had often noticed abdominal pain and distension, with occasional bloody diarrhea, after taking

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pseudoephedrine. Before each of her two admissions she had been taking a remarkably high dose of 900 mg/day, and on many other occasions had taken as much as 600 mg/day. She made a good recovery and was said to have stopped taking pseudoephedrine.

The authors quoted seven other published cases of pseudoephedrine-related ischemic colitis, all occurring at much lower dosages, at most 240 mg/day.

Urinary tract

Seven patients (four men, three women, aged 21–52 years) taking large doses of over-the-counter formulations containing ephedrine and guaifenesin developed urinary stones (22). These largely contained guaifenesin metabolites, but presumably dependence on ephedrine was the reason for abuse of these formulations.

Skin

Non-pigmenting fixed drug eruptions proven by oral rechallenge have been reported with pseudoephedrine; in each of these cases the erythematous lesions spontaneously remitted without residual pigmentation (23–25).

- A 10-year-old boy given pseudoephedrine 60 mg/day developed a solitary eruption in the groin; rechallenge was positive (24).

Generalized skin reactions are even less frequent. A group of allergy specialists in Madrid have described two cases of generalized dermatitis with dissimilar histological findings in men aged 64 and 73 years (26). In one case there was severe eczema, in the other vacuolar interface dermatitis, which is rarer. Both patients had taken a proprietary formulation containing codeine and chlorphenamine as well as pseudoephedrine. Oral challenges with the former two drugs was negative in both cases, but was positive for pseudoephedrine in one patient; the other was not rechallenged, because of the severity of the original reaction.

- A hypersensitivity reaction was confirmed by patch testing in a 73-year-old woman who had taken a single (unspecified) dose of a compound formulation containing pseudoephedrine (27). This caused the memorably named baboon syndrome, a widespread symmetrical erythematous rash with papules and pustules.

Immunologic

Pseudoephedrine can cause hypersensitivity, as in three cases reported by allergy specialists from Spain (28).

- A 33-year-old man developed anaphylaxis on a second exposure to pseudoephedrine, having developed urticaria after a first exposure.
- A 24-year-old woman developed severe urticaria and fever, but no other systemic reaction, after a single dose of pseudoephedrine.
- A 67-year-old woman developed urticaria and angioedema of the eyelids after a single dose of pseudoephedrine.

In all three cases skin testing was performed; it was positive in the first two instances but not the third. The authors noted that such cases are reportedly uncommon and that cross-sensitivity is to be expected between pseudoephedrine and ephedrine.

Body temperature

Pseudoephedrine may have played a role in an episode of hyperthermia (29).

- A 21-year-old American military recruit, moderately obese, collapsed during a 3-mile run and was asystolic and hyperthermic (rectal temperature 42.2°C); he could not be resuscitated. Only 75 minutes earlier he had received vaccinations against typhoid and Japanese encephalitis and he was taking over-the-counter pseudoephedrine to promote weight loss.

The authors noted that this was only one of the factors predisposing to hyperthermia; one might also wonder whether it was wise to undertake such a run so soon after the vaccinations.

Death

Ephedra was implicated in the deaths of eight patients, and although it was pointed out that several had pre-existing conditions such as chest pain and hypertension (30), the authors justifiably responded that these were contraindications to the use of *Ephedra* in the first place, and they cast doubt on the adequacy of the warnings provided (31).

Susceptibility Factors

In patients with ischemic heart disease, ephedrine can cause myocardial infarction and potentially fatal dysrhythmias (31). Caution is needed in patients with any form of cardiac disease. At one time an attempt was made to use high doses of ephedrine for the early treatment of ventricular fibrillation, but its pharmacological effects militated against its use, since the immediate survival rate actually fell.

Thyrotoxic patients are unduly sensitive to the effects of ephedrine (SEDA-14, 179).

Drug Administration

Drug overdose

- In a suicide attempt, a 32-year-old woman took 60 tablets of a weight-loss supplement containing Ephedra (32). She was delivered to hospital comatose. Her symptoms resolved over the next 5 days without treatment. At follow-up 5 months later she was euthymic, had no suicidal ideation, and was not taking any psychotropic medications.

Drug–Drug Interactions

Amfebutamone

Acute coronary syndrome has been attributed to a combination of pseudoephedrine with amfebutamone (bupropion) (33).

- A 21-year-old man developed acute myocardial ischemia. Smoking was the only risk factor for coronary artery disease and he denied using cocaine. Angiography

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showed normal coronary arteries. He had recently started to take amfebutamone for smoking cessation and pseudoephedrine as a non-prescription influenza remedy.

The authors postulated that the combination of two sympathomimetics had caused acute coronary artery vasospasm. This is the first report linking amfebutamone to acute coronary syndrome, and one of a few cases associated with pseudoephedrine. It is also possible that erythromycin, which this patient was also taking, could have impaired the hepatic metabolism of amfebutamone.

Antihypertensive drugs

In patients taking antihypertensive drugs, self-medication with ephedrine-containing remedies can cause an increase in blood pressure (31).

Barbiturates

In intravenous solutions, ephedrine is physically incompatible with several barbiturates (34).

Cocaine

Chronic cocaine use sensitizes coronary arterial alpha-adrenoceptors up to agonists (SEDA-22, 154).

Dextromethorphan

Combinations of pseudoephedrine with dextromethorphan are often used in over-the-counter formulations. Although they are generally considered safe, two reports have emphasized the potential adverse effect of these cold and cough formulations (35,36).

- A 2-year-old child developed hyperirritability, psychosis, and ataxia after being overmedicated with a cough formulation containing pseudoephedrine and dextromethorphan. The child made an uneventful recovery after an observation period of 4 hours in the emergency department.
- Three adolescent girls developed acute psychoses associated with the use of similar over-the-counter formulations. They required several days of hospitalization, extensive invasive medical evaluation, and consultations with neurologists, infectious disease specialists, toxicologists, and psychiatrists. They were treated with risperidone.

It is not clear which was the primary causative drug in these cases or whether there was some degree of synergy or at least additive toxicity.

Entacapone

An interaction of ephedrine with entacapone, a specific, reversible, peripherally acting inhibitor of catechol-*O*-methyl transferase, has been reported (37).

- A 76-year-old woman with Parkinson's disease and closed-angle glaucoma was scheduled for eye surgery. She had severe choreoathetoid movements, and 3 weeks before surgery began to take entacapone 200 mg/day, in addition to her five daily doses of co-careldopa. General anesthesia was induced with intravenous propofol 80 mg and fentanyl 25 mg, and maintained with nitrous oxide–oxygen (2:1) and sevoflurane 1–1.5%. After 30 minutes her blood pressure fell from 145/85 to 85/35 mmHg. She was given an intravenous bolus of ephedrine 3 mg and her blood pressure immediately rose to 225/125 mmHg; it remained high despite an increase in the dose of sevoflurane, but was controlled by repeated doses of hydralazine 2 mg.

The effect of ephedrine, which is both a direct and indirect sympathomimetic, may have been enhanced by its not being metabolized by catechol-*O*-methyl transferase, because of the action of entacapone.

Halothane

Halothane and some other anesthetics sensitize patients to the risk of ephedrine-induced ventricular dysrhythmias and acute pulmonary edema, especially if hypoxia is present (31).

Hydrocortisone

In intravenous solutions, ephedrine is physically incompatible with hydrocortisone (34).

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors can dangerously potentiate the hypertensive effects of ephedrine (38).

Propofol

An interaction of propofol with ephedrine has been described (11).

- A 44-year-old woman was given ephedrine intravenously, to manage hypotension during spinal anesthesia. She developed intracranial hypertension and focal cerebral deficits related to multiple hemorrhagic cerebral infarcts. Angiography showed reversible beading, consistent with cerebral arteritis.

Owing to the risk of tachycardia, resulting in myocardial ischemia, the combination of propofol with ephedrine in elderly patients undergoing genitourinary surgery is not recommended (39). These reports should alert physicians to the potential hazards associated with the use of ephedrine during anesthesia.

SSRIs

- A 37-year-old New Zealand woman took a total of 480 mg of pseudoephedrine in various cold remedies over 4 days (40). She had also been taking fluoxetine 20 mg/day for seasonal affective disorder. She developed rapidly swinging mood changes, alternating between laughing and crying, and was sweating and shaking violently. Although her pulse rate was only 70/minute her blood pressure was 220/130 mmHg. She recovered within 4 hours and had no recurrence of her behavioral disturbance.

Although pseudoephedrine toxicity was a possible diagnosis, the authors concluded that serotonin syndrome was more likely, from an interaction of pseudoephedrine with fluoxetine. Patients should be warned about the hazards of taking selective serotonin re-uptake blockers and then self-medicating with ephedrine or pseudoephedrine.

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Tricyclic antidepressants

Tricyclic antidepressants inhibit the uptake of catecholamines, such as ephedrine, into sympathetic neurons and can enhance their cardiovascular effects (41).

- A 61-year-old woman taking amitriptyline 25 mg/day underwent oophorectomy for ovarian cancer under combined general and epidural lumbar anesthesia. After the administration of the local anesthetic she developed hypotension refractory to high doses of ephedrine and dopaminergic drugs. Control was achieved with noradrenaline 200 μg.

The authors suggested that even the small amounts of ephedrine present as additives in some local anesthetics can have a marked effect on the cardiovascular system.

Vaccines

Hyperthermia occurred shortly after immunization with typhoid and Japanese encephalitis vaccines in a service member using an over-the-counter formulation of pseudoephedrine (29).

- While exercising in mild weather the patient collapsed 75 minutes after vaccination. He presented with asystole, with a core temperature of 42.2°C, and there was no evidence of urticaria or angioedema.

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Eplerenone

See also Diuretics

General Information

Eplerenone is a potassium-sparing diuretic. It is similar to spironolactone as an aldosterone antagonist, but has less affinity for androgen and progesterone receptors and may therefore have fewer adverse effects (1).

Eplerenone is metabolized by CYP3A4 (2) and should not be given with inhibitors of CYP3A4 because of the risk of hyperkalemia (3).

Eplerenone has been compared with spironolactone in patients with heart failure (NYHA classes II–IV). In a dose-finding study, 321 patients maintained on ACE inhibitors and diuretics, with or without digoxin, were randomized to receive eplerenone 25–100 mg/day, spironolactone 25 mg/day, or placebo (4). After 12 weeks there was no improvement in heart failure in patients taking either eplerenone or spironolactone. Increases in plasma testosterone were significantly greater in men taking spironolactone than in those taking eplerenone. However, hyperkalemia was more frequent in patients taking eplerenone 100 mg/day (12%) than in those taking spironolactone 25 mg/day (8.7%). The potency of eplerenone relative to spironolactone remains to be established in patients with heart failure.

Organs and Systems

Electrolyte balance

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the addition of eplerenone 25–50 mg/day to optimal medical therapy in patients with an acute myocardial infarction complicated by left ventricular dysfunction and heart failure significantly reduced all-cause and cardiovascular mortality (5). Patients with a serum potassium concentration over 5.0 mmol/l at baseline were excluded. The incidence of hypokalemia was significantly lower with eplerenone. However, there was serious hyperkalemia (serum potassium 6.0 mmol/l or more) in 5.5% of those who took eplerenone compared with 3.9% of those who took placebo.

Reproductive system

Eplerenone has been reported to produce less gynecomastia than spironolactone (6,7). In patients with gynecomastia from spironolactone, eplerenone can be substituted and gynecomastia status reassessed.

Drug–Drug Interactions

ACE inhibitors

Co-administration of potassium-sparing diuretics with ACE inhibitors can cause severe hyperkalemia (SED-14, 674).

NSAIDs

The interaction between potassium-sparing diuretics and NSAIDs is well documented (SED-14, 674). The major complications are deterioration of renal function and hyperkalemia. The risk associated with the non-selective COX-2 inhibitors is unknown. However, three patients had hyperkalemia (8.5, 5.4, and 5.1 mmol/l) after developing acute renal insufficiency while taking these drugs (8).

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Epoprostenol

See also Prostaglandins

General Information

Epoprostenol is PGI_2 available for exogenous administration. It has become the preferred long-term treatment for patients with primary pulmonary hypertension who continue to have symptoms in spite of conventional therapy. However, tolerance, which always occurs, has made dosing uncertain. The effectiveness of epoprostenol given according to an aggressive dosing strategy for longer than 1 year has been investigated in these patients (1). The dose of epoprostenol was increased by 2.4 nanograms/kg/minute each month to the maximum tolerated dose. Adverse effects were common and included diarrhea, jaw pain, headaches, and flushing in all patients.

Organs and Systems

Respiratory

Pulmonary veno-occlusive disease is a rare form of pulmonary hypertension associated with fibrotic occlusion of the smaller pulmonary veins. Although vasodilator therapy is effective in many patients with primary pulmonary hypertension, the role of vasodilators in veno-occlusive disease is unclear, because of concerns about precipitating pulmonary edema. There have been reports of successful therapy with oral vasodilators or intravenous prostacyclin. In contrast, there has been a description of a patient who developed acute pulmonary edema and respiratory failure 15 minutes after the start of a low-dose prostacyclin infusion 2 nanograms/kg/minute, leading to death an hour later (2). This case has several important implications for the management of patients with pulmonary hypertension. Although previous reports suggested that prostacyclin may be safe in patients with pulmonary veno-occlusive disease, the experience reported here suggests that even in very low doses prostacyclin can produce acute decompensation. Thus, consideration must be given to the diagnosis of pulmonary veno-occlusive disease in all patients with suspected primary pulmonary hypertension.

Further cases of pulmonary edema have been reported during continuous intravenous epoprostenol in patients with severe pulmonary hypertension and pulmonary capillary hemangiomatosis, a rare condition characterized by proliferation of thin-walled microvessels in the alveolar walls (3). This report suggests that epoprostenol should not be used in such patients.

- A 66-year-old woman with scleroderma and severe pulmonary hypertension was given continuous intravenous epoprostenol 2 and then 4 nanograms/kg/minute (total duration 48 hours) (4). Two weeks later her dyspnea had improved, but her leg was swollen and her oxygen saturation had fallen. Her dosage of epoprostenol was increased to 5 nanograms/kg/minute. One month later she developed increasing dyspnea, a non-productive cough, severe edema of her legs, and severe hypoxemia. She had gained 5 kg in weight and there were new bibasal lung crackles. A chest X-ray showed bilateral air-space opacities and bilateral effusions. Her PaO_2 was 5.7 kPa, $PaCO_2$ 3.9 kPa, and the arterial pH 7.51. Pulmonary veno-occlusive disease was diagnosed and the infusion of epoprostenol was gradually tapered over the next 48 hours. She died 6 days later with right-sided heart failure. At autopsy, histological examination showed thickening of the alveolar septa by proliferation of dilated capillaries on both sides of the alveolar walls, consistent with pulmonary capillary hemangiomatosis.
- A 61-year-old woman developed pulmonary edema during treatment with epoprostenol for severe pulmonary hypertension associated with limited scleroderma (5). She received an infusion of epoprostenol 1 nanogram/kg/minute, and the dosage was increased by 1–2 nanograms/kg/minute every 15 minutes. At a dosage of 6 nanograms/kg/minute, her pulmonary vascular resistance had fallen by 60% and her cardiac output had increased by 55%. However, at this dosage, she became acutely dyspneic. Epoprostenol was withdrawn, she was treated with furosemide and high-flow oxygen, and her symptoms resolved. Because no other therapy was available, she agreed to restart epoprostenol therapy the next day, 1 nanogram/kg/minute, increasing by 1 nanogram/kg/minute every 24 hours to 3 nanograms/kg/minute at discharge. Over the next 6 months, the dosage of epoprostenol was gradually increased to 20 nanograms/kg/minute. She had a significant improvement in her exercise tolerance and there was no evidence of pulmonary edema. However, after about 7 months of marked clinical improvement, she developed right ventricular decompensation. Increased doses of epoprostenol were ineffective and she died. Autopsy showed severe obliterative and plexogenic pulmonary arteriopathy.

This is the first case in which epoprostenol has been successfully restarted. The authors commented that pulmonary edema during acute infusion of epoprostenol is considered a contraindication to its further use. They theorized that the pulmonary edema could have occurred secondary to the dramatic increase in pulmonary perfusion at 6 nanograms/kg/minute of epoprostenol and subsequent rapid shifts in vascular hydrostatic pressure. The slow increase in dosage during reinstitution may have averted the dramatic increase in pulmonary perfusion.

Hematologic

Patients with end-stage liver failure, portal hypertension, and associated pulmonary artery hypertension (portopulmonary hypertension) have a high mortality when undergoing liver transplantation. Successful transplantation in these patients may depend on efforts to reduce pulmonary artery pressure. To this end, some centers are using a continuous intravenous infusion of epoprostenol, which has been shown to improve symptoms, extend life span, and reduce pulmonary artery pressure in patients with primary pulmonary hypertension. There have been four cases in which treatment of portopulmonary hypertension with continuous intravenous epoprostenol was followed by the development of progressive splenomegaly, with worsening thrombocytopenia and leukopenia (6). This

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finding may limit the usefulness of epoprostenol in portopulmonary hypertension and influence the timing of transplantation in such patients.

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Eprazinone

General Information

Eprazinone hydrochloride is a cough suppressant that is also reported to have expectorant properties.

Drug Administration

Drug overdose

In a retrospective study of 199 cases of accidental or intentional acute poisoning with eprazinone, eprozinol, and zipeprol, collected at the Poison Control Center in Paris from 1975 to 1982, there were seven cases of seizures, all after ingestion of eight times the therapeutic dose. They resolved rapidly and without recurrence with symptomatic treatment (1).

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Eprosartan

See also Angiotensin II receptor antagonists

General Information

Eprosartan is a non-biphenyl, non-tetrazole competitive antagonist at angiotensin II type 1 (AT_1) receptors that is chemically distinct from other angiotensin II receptor antagonists (1). It causes dual blockade of AT_1 receptors both presynaptically and postsynaptically, reducing sympathetic nerve activity significantly more than other receptor antagonists.

Organs and Systems

Respiratory

In a multicenter controlled study in patients with hypertension and a history of ACE inhibitor-induced cough, eprosartan significantly reduced the risk of cough by 88% compared with enalapril (2).

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Eprozinol

General Information

Eprozinol hydrochloride inhibits bronchoconstriction and has been used in the treatment of asthma and bronchitis.

Drug Administration

Drug overdose

In a retrospective study of 199 cases of accidental or intentional acute poisoning with eprozinol, eprazinone, and zipeprol, collected at the Poison Control Center in Paris from 1975 to 1982, there were seven cases of seizures, all after ingestion of eight times the therapeutic dose. They resolved rapidly and without recurrence with symptomatic treatment (1).

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Ergot derivatives

General Information

Ergot derivatives include ergotamine tartrate (rINNM), dihydroergotamine (BAN, USAN), ergometrine (rINNM, also called ergonovine), and methylergotamine (rINNM). They are potent alpha$_1$-adrenoceptor and 5-HT receptor antagonists, and have been used to treat migraine (ergotamine, dihydroergotamine) and to stimulate uterine contraction (ergometrine, methylergotamine).

Ergotamine and dihydroergotamine

Ergotamine and dihydroergotamine have been used in preventing migraine attacks and dihydroergotamine in the treatment of hypotension (either orthostatic or caused by spinal or epidural anesthesia). When dihydroergotamine was given intravenously after coronary bypass surgery, despite increased filling pressure there was no rise in cardiac output, and despite increased cardiac work the bypass flow fell significantly. The significant decrease in regional myocardial vascular resistance found after the administration of dihydroergotamine may explain the absence of the expected increase in cardiac output and coronary bypass flow.

The combination of heparin with dihydroergotamine has been used in the prevention of thromboembolic complications. It was claimed that these two components act synergistically, allowing a lower dosage of heparin to be used. However, the lower risk of hemorrhagic complications is certainly not counterbalanced by a lowered risk of ergotism (SEDA-8, 147). Vasospastic reactions after giving heparin with dihydroergotamine seem to occur particularly in traumatized patients or when a limb is injured. Since the risk of vasospasm increases with treatment time, the Swedish Adverse Reactions Committee recommended that the duration of treatment with dihydroergotamine with heparin should not exceed 7 days (SEDA-15, 135).

With daily use of dihydroergotamine by injection, there is an ill-defined frequency of nausea, vomiting, abdominal pain, and diarrhea, but also a high incidence of muscle cramps and some cases of lethargy and peripheral edema (SEDA-17, 171).

An expert European group has re-evaluated the preclinical and clinical data on ergotamine as they relate to treatment of migraine and have tried to reach a consensus on how to use it prudently (1).

Ergometrine

Ergometrine is used in obstetrics, since its oxytocic effects are relatively more marked than its vascular effects. Nausea and vomiting can occur if it is given orally. Slight bradycardia is common, but tachycardia occurs in some patients, and there can be changes in intracardiac conduction and pacemaker function. Very rarely, hypertensive reactions and cardiac arrest have been described and there are two reports of myocardial infarction in healthy women who were smokers (SEDA-18, 160). A newborn infant inadvertently injected with ergometrine and oxytocin developed depression of respiration and convulsions (2).

The "ergonovine provocation test" has been used in the diagnosis of angina pectoris (by producing vasospasm during angiography) but it can cause myocardial infarction and even death (SED-12, 324) (3).

Co-dergocrine

Co-dergocrine mesylate (Hydergine) is a mixture of the methane sulfonates of the dihydrogenated derivatives of the three alkaloids of ergotoxin (dihydroergocornine, dihydroergocristine, and dihydroergocryptine). Dihydrogenation eliminates the vasoconstrictor effects of ergotoxin and enhances its alpha-adrenoceptor antagonist and 5-HT receptor antagonist properties. Co-dergocrine has other pharmacological effects, including inhibition of brain-specific phosphodiesterases, several of which are still poorly described.

Co-dergocrine is claimed to have some effect in brain ageing and has also been promoted as a "metabolic enhancer," mainly because it protects against metabolic alterations induced by hypothermia and ischemia in animals (4).

Many double-blind, controlled trials have been conducted with co-dergocrine in senile dementia, and almost all have reported improvements in scores on at least one psychomotor test scale. However, despite this evidence of short-term efficacy, many skeptical clinicians still consider it to be no better than placebo, and find support from a double-blind, placebo-controlled trial in which a group treated with the recommended dosage of 1 mg tds for 24 weeks did not perform better after treatment than did the placebo-treated group (5). The clinical value of co-dergocrine in patients with claudication and rest pain is poorly documented.

Although the recommended dosage has been tripled over the years (from 0.5 to 1.5 mg tds), significant unwanted effects are rare. Vomiting, blurred vision, skin rashes, nasal stuffiness, bad taste, postural hypotension, and vasospastic reactions are all uncommon (SED-12, 472). Diffuse fibrotic processes (for example retroperitoneal fibrosis), repeatedly reported with other ergot derivatives, such as methysergide and dihydroergotamine, have not been observed with co-dergocrine. In elderly people, co-dergocrine only occasionally causes diarrhea, nausea, gastric pain, orthostatic hypotension, and headache. In 40 children, nasal stuffiness and anorexia were most common adverse effects of co-dergocrine (6).

Organs and Systems

Cardiovascular

Ergot derivatives are powerful vasoconstrictors. The extremities become pale and cold, and arterial spasm in the arms and legs has been demonstrated; even the face can be affected. The condition can develop acutely even after brief use of the drug, and there is real risk of gangrene; if given early, intra-arterial infusion of prostaglandin E_1 can reverse the spasms. Protracted coronary spasm has

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also been reported in some cases (SEDA-14, 122). Renal arterial spasm has occurred after a dose of ergotamine of 10 mg in the form of suppositories given over 60 hours (SED-8, 308) (7), and bilateral papillitis with ischemia of the periaxial fibers has resulted from 2 weeks of maximum-dose treatment. High doses have also led on occasion to mesenteric vascular constriction, ischemic bowel disease, and partial necrosis of the tongue. Arterial stenosis can even result in aneurysm formation (8). The absence of symptoms does not mean that there is no adverse effect; in 30 patients who had taken ergotamine 1–5 mg/day for a year all had lowered systolic blood pressures in the foot.

Arterial spasm induced by ergotamine can be due to overdose, but some patients have an exaggerated response to a therapeutic dose. Interaction with other drugs, leading to potentiation, is a third mechanism. Four patients developed extreme limb ischemia after a therapeutic dose of ergotamine: one even took only a single dose of 1 mg. The symptoms responded to vasodilator therapy after withdrawal of ergotamine, but one needed a minor amputation. All patients were taking antiviral treatment for HIV infection, and ritonavir and indinavir may have potentiated the effect of ergotamine by inhibiting its metabolism (9–12).

Treatment of migraine can lead to subclinical ergotism for a prolonged period, and thence to occlusive peripheral vascular disease; peripheral systolic pressure (and liver function tests) should be monitored in patients taking regular ergotamine (SEDA-15, 135). Tolerance to these vasoconstrictive effects varies widely among individuals; such symptoms as cyanosis of the limbs, syncope, hypotension, and paresthesia have been seen in sensitive subjects after doses of up to 8 mg taken over as little as 10 days. The Swedish drug authorities have recommended that treatment should not be continued for more than 7 days (SEDA-13, 113).

- A 78-year-old woman developed gangrene in three fingertips on the right hand and two on the left after being given dihydroergotamine 10 mg/day as migraine prophylaxis (13). She had had Raynaud's syndrome for at least the previous 5 years and was thought to have a relatively mild form of systemic sclerosis.
- A 44-year-old woman developed claudication and rest pain after gross overuse of ergotamine 100 mg suppositories (up to 6 times a day) for chronic headaches over a period of several years (14). Angiography showed occlusion of both femoral arteries. Intra-arterial prostaglandin E (presumably E_1) followed by chemical sympathectomy normalized the circulation in both the legs.
- A 63-year-old Canadian woman who had been taking ergotamine (dosage unspecified) for migraine for 20 years developed acute ischemia of the right arm, with no palpable pulses below the axilla (15). Angiography showed multiple filling defects in upper limb arteries, partially reversible with intravenous phentolamine. She was given prazosin 2 mg/day and became pain-free after 5 days. Treatment was continued for 3 months and during this time attacks of migraine were treated with sumatriptan without adverse effects. Her pulses were entirely normal after 3 months, as was angiography.

Myocardial infarction has been reported.

- A 27-year-old woman with familial hypercholesterolemia already treated with lipid-lowering drugs developed acute chest pain after a prophylactic intramuscular injection of 0.5 mg ergometrine, given during the late stages of labor (16). Angiography showed three-vessel atherosclerotic disease and occlusion of the left anterior descending coronary artery. Angioplasty with stenting was successful and she made an excellent recovery.
- A 34-year-old woman had a myocardial infarction after being given ergonovine for an atonic uterus after cesarean section (17). Within minutes she became unresponsive, with bradycardia and then asystole followed by ventricular fibrillation during cardiopulmonary resuscitation. An electrocardiogram showed an acute anterior infarct and coronary angiography showed diffuse spasm of the circumflex and left anterior descending arteries, with subtotal occlusion of the latter. The spasm was reversed with intracoronary glyceryl trinitrate but she required ventilation for another 2 days and was eventually discharged 11 days after the infarct, with a borderline left ventricular ejection fraction of 45%.

The authors commented that the latter patient was of Asian origin and that such individuals are thought to have increased susceptibility to the vasoconstrictor effects of ergot derivatives.

The role of arterial spasm as a cause of angina after angioplasty has been studied in two men, aged 45 and 58 years, who had emergency angioplasties for acute coronary thrombosis (18). Although the primary procedures were successful in both cases, ischemic chest pain returned after 4 and 6 months respectively. Perhaps a little surprisingly, in both cases intravenous ergonovine (0.4 mg) was given during coronary angiography, causing severe arterial spasm, which resolved with intravenous isosorbide dinitrate. There was no evidence of restenosis. The authors noted that recurrence of angina does not necessarily imply restenosis, although it is not clear how many cardiologists will repeat this procedure with their own patients.

- A 48-year-old woman developed a cold pulseless right leg and no measurable blood pressure at the right ankle (19). She was a migraine sufferer and had been taking over-the-counter medications, some of which contained ergot derivatives, although the nature and quantity were not specified. Arteriography showed severe stenosis of the superficial femoral artery, with no identifiable tibial vessels. There was an initial improvement with intra-arterial glyceryl trinitrate infusion, and sustained normalization of the circulation in the leg after administration of sodium nitroprusside, nifedipine, prazosin, and heparin. She made a full recovery.

The authors reviewed the pharmacology of the ergot alkaloids and the acute and subclinical ischemic syndromes that they can produce. They pointed out that in some countries, notably in Latin America, ergot-containing formulations are freely available without a prescription.

Acute hypertensive encephalopathy has occurred in a patient given methylergotamine (SEDA-3, 121).

Diverticulum formation in the internal carotid artery occurred in a patient who had taken ergotamine for

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4 years (SEDA-10, 119). Rupture of a splenic artery aneurysm in a 46-year-old woman was ascribed to excessive ergotamine ingestion for migraine (20). The authors thought that significant vasospasm may have led to damage and weakening of the vessel wall and consequently to the development of a false aneurysm. It should be noted that splanchnic aneurysms are occasionally discovered in otherwise healthy people and carry a 5% risk of spontaneous rupture.

Long-term abuse of ergotamine can occasionally cause fibrosis of the cardiac valves (SEDA-18, 160).

Ear, nose, throat

During intranasal administration for migraine, nasal congestion, irritation, and sneezing can occur (21).

Nervous system

The cerebral vasculature can also be vulnerable to ergot-induced vasoconstriction.

- A 54-year-old woman with a 20-year history of migraine used a nasal ergotamine spray one evening during an episode of migraine (22). She used a second dose at 4 p.m. the next day since the migraine had persisted. The following morning she was given subcutaneous sumatriptan 6 mg. Some 30–45 minutes later she developed the symptoms of global amnesia, which resolved by the following morning. Magnetic resonance imaging showed a small infarct in the right thalamus.

It seems likely that the co-administration of two cerebral vasoconstrictors increased the likelihood of such an event.

- A 36-year-old woman developed a "cerebral angiopathy" within 36 hours after starting to take oral metergoline, an ergot derivative prescribed after delivery to suppress lactation (23). This angiopathy was apparently due to severe narrowing of small and medium cerebral arteries; its main features were sudden hypertension, seizures, and variable reversible neurological deficits.

Transient cortical blindness, with severe headache and hallucinations, has been associated with the intravenous injection of methylergometrine 0.2 mg in a postpartum patient reference.

The role of ergotamine and sumatriptan in drug-induced headache has been surveyed in over 2000 patients at a regional headache clinic (24). About 600 had taken ergot derivatives previously and a similar number had used sumatriptan, while nearly 250 had experience of both. Drug overuse was defined as the use of at least one dose of either drug on 18 or more days every month for at least 3 months. By these criteria the rates of ergotamine and sumatriptan overuse were estimated at 14 and 3.5% respectively. Drug-induced headache was much more common among ergotamine overusers than sumatriptan overusers (68 versus 32%).

Sensory systems

Bilateral ischemic optic neuropathy can develop secondary to acute ergotism after administration of ergotamine tartrate (25).

Psychological, psychiatric

Unlike the dopamine-mimetic ergolines, ergotamine is not usually regarded as a drug with major effects on the brain. However, this may not always be true.

- A 75-year-old woman in Arizona developed progressive confusion, auditory hallucinations, and aggressive behavior (26). Her systolic pressure was raised (194 mmHg). She had a history of migraine and many other problems, including hypertension. Her headaches had become more severe over the weeks before admission and she had been gradually increasing her intake of a formulation containing ergotamine 1 mg and caffeine 100 mg: just before the emergence of her psychiatric symptoms she was taking 14 tablets per week. After withdrawal of the ergotamine/caffeine, her mental state and blood pressure returned to normal, without antihypertensive medication, and remained so 12 months later.

Although there has been extensive discussion of the phenomenon of ergotism in medieval and early modern times, its features do not closely resemble this case, perhaps because of the co-administration of caffeine. However, regardless of that, there does seem to be a strong case for a drug effect here.

A syndrome resembling reversible dementia has been described in chronic ergotamine intoxication (SEDA-3, 121).

Gastrointestinal

Nausea and vomiting are common problems with effective doses of ergotamine. Rectal stenosis demanding treatment has several times been described after prolonged use or overuse (27). This pattern of use can also rarely cause reversible gastrointestinal ischemia, presenting as lower abdominal pain (SEDA-17, 146).

- A 50-year-old woman developed ischemic necrosis of the stomach wall after taking up to 5 mg/day of ergotamine tablets for 10 years because of daily headaches (28). The necrosis was seen on the greater curvature and was about 10 cm in diameter. She required laparotomy because of peritonitis and there was a 4 cm area of full-thickness necrosis within the ischemic area. She made a full recovery.
- A necrotic small intestine was resected in a 65-year-old man with ergotamine abuse (29). Histological examination showed hypertrophy of the smooth muscle of the mesenteric arteries resulting from chronic vasospasm. The patient developed postoperatively limb ischemia and tongue gangrene before he died.

Liver

Portal hypertension, presumably due to vasoconstriction, has been reported (SEDA-11, 131).

Skin

Anocutaneous ergotism (characterized by anal ulceration) has been observed in one case after excessive use of ergot suppositories (SEDA-10, 119).

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Serosae

Retroperitoneal fibrosis, as produced classically by methysergide, has been reported after the administration of ergotamine (SEDA-8, 147) and dihydroergotamine (SEDA-17, 170).

Other fibrotic reactions have been reported in patients taking ergot derivatives.

- A 67-year-old man in Germany with Parkinson's disease took co-careldopa and (somewhat unusually) alpha-dihydroergocryptine 45 mg/day, the latter in order to regulate fluctuations on motor function (30). After 2 years he developed a dry cough with dyspnea. Chest X-rays showed severe thickening of the pleura bilaterally with associated effusions. Biopsy confirmed fibrosis. The ergot drug was immediately replaced with pramipexole, eventually at a dose of 3 mg/day. Respiratory symptoms improved markedly within weeks, but there was little change radiologically.

Although this is the first description of such a reaction to this particular drug, it has been well documented with several other dopaminergic ergot derivatives.

Long-Term Effects

Drug dependence

If ergotamine tartrate is used chronically, which is in any case undesirable because of its vascular effects, a vicious cycle can arise, withdrawal headaches leading to the use of ever-increasing doses (SEDA-13, 113). Tolerance can develop to the point at which the doses being used exceed those that are normally regarded as safe. The only possible treatment is to withdraw the drug; the withdrawal symptoms tend to be poorly responsive to other drugs, but they usually abate within 72 hours, after which the patient can be treated with other antimigraine drugs. The best means of preventing ergotamine dependence is to limit the use of ergotamine tartrate to no more than 2 days per week and to ensure that the drug is not used unnecessarily for plain headaches, which have been labeled as migrainous.

Second-Generation Effects

Teratogenicity

Microcephaly occurred in a child whose mother had used ergotamine and caffeine (during the first trimester) and propranolol (during the second) for the relief of migraine (SEDA-13, 114). Although this suggests the possibility of teratogenicity, data in animals are not consistent. However, ergotamine should in any case not be used in pregnancy in view of its oxytocic effects (SEDA-8, 147), which can lead to fetal stress requiring cesarean section (31).

Lactation

Ergotamine does not affect the amount of milk secreted during lactation (32). It has been said that if ergotamine is used during lactation, the infant may have gastrointestinal upsets, cardiovascular instability, and even convulsions, but there is little documented evidence of this.

Susceptibility Factors

Hepatic disease

There are special risks in giving ergotamine in liver disease, since most of the drug is metabolized by the liver. Ergotamine also reduces liver blood flow by vasoconstriction and therefore reduces its own first-pass metabolism.

Other features of the patient

Women taking oral contraceptives and pregnant women are more susceptible to the vasospastic effects of the ergot alkaloids, as are patients in shock, with sepsis, and with Raynaud's disease or Buerger's disease. The risk of severe vascular reactions is increased in the presence of peripheral vascular disease or when sympathomimetic agents are given at the same time.

Drug Administration

Drug overdose

The signs of ergot poisoning initially include dizziness, frontal headache, depression, and leg and low back pain; more severe poisoning results in formication, severe cyanosis of the extremities, muscular twitching, tonic spasms, convulsions, delirium, and ultimately death (33).

Drug–Drug Interactions

Clarithromycin

Clarithromycin has been reported to potentiate the effects of ergotamine.

- A 41-year-old woman presented with pain and pallor in the leg and a sensation of coolness exacerbated by exercise (34). For many years she had been taking a formulation containing ergotamine 1 mg plus caffeine 100 mg, at a dose of one or two tablets daily, for both prophylaxis and treatment of migraine. For 7 days she had also taken clarithromycin (dose is not stated) for a chest infection. Her legs were cool and cyanosed, with no palpable popliteal or foot pulses and an ankle–brachial index of only 0.6 (normal >0.8).

The authors concluded that her symptoms had been precipitated by the introduction of clarithromycin, an inhibitor of CYP isozymes like the other macrolide antibiotics. However, she was also taking omeprazole, another inhibitor, which may have contributed to the problem. All drugs were withdrawn and nifedipine was given, with full recovery within a couple of days.

Ritonavir

Ritonavir has been reported to potentiate the effects of ergotamine.

- A 28-year-old woman was taking triple therapy for HIV infection, including the protease inhibitor ritonavir (35).

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She had also started to take a combined formulation containing ergotamine (0.6 mg/day), phenobarbital (40 mg/day), and belladonna extract (0.4 mg/day). Four days later she noted pain in both legs and all her extremities were cold, pale, and pulseless. She had diffuse arterial spasm in the aorta and all four limbs. Despite intensive vasodilator therapy, she developed bilateral gangrene of the toes, requiring transmetatarsal amputations.

- A 37-year-old woman with AIDS who had been taking ritonavir developed acute dysphasia and right-sided weakness having taken a total of 10 mg of ergotamine in suppository form for severe headaches that were presumed to be migraine (36). Transcranial Doppler and angiography showed multiple stenoses in vessels in the circle of Willis, and an MRI scan showed watershed infarcts in the right and left hemispheres. It was presumed that she had had ergotamine-induced vasospasm due to inhibition of ergotamine metabolism by ritonavir. She was treated with "hemodilution, hypertension and hypervolemia"; the cerebral flow velocities normalized over the next 18 days and the angiographic appearances by day 90. She was left with a slight right expressive dysphasia and weakness in the right leg.

Ritonavir is a very potent inhibitor of CYP3A4, which is responsible for the metabolism of ergotamine, and this interaction obviously led to toxic plasma concentrations of the alkaloid.

Sumatriptan

The combination of ergotamine with sumatriptan has been associated with vasospasm in the cerebral arteries (37).

- A 20-year-old woman developed a severe headache 24 hours after a spontaneous normal delivery. She was given sumatriptan 6 mg subcutaneously followed 24 hours later by three tablets of ergotamine. Shortly after this she had a secondarily generalized tonic-clonic seizure, starting in the left arm, and became hemiplegic. A CT scan showed cerebral edema and angiography showed multiple narrowings of the right vertebrobasilar and middle cerebral arteries. After several further seizures she gradually improved and was clinically normal after 10 days. An MRI angiogram was normal two days later.

The danger of combining two cerebral and coronary vasoconstrictors needs no emphasis.

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Ericaceae

See also Herbal medicines

General Information

The genera in the family of Ericaceae (Table 1) include heather, huckleberry, and rhododendron.

Arctostaphylos uva-ursi

Arctostaphylos uva-ursi (bearberry) contains a steroid, sitosterol, and triterpenoids, such as amyrin, betulinic acid, lupeol, oleanolic acid, taraxenol, ursolic acid, and uvaol. The main constituent is a glucoside called arbutin. Other constituents are methylarbutin, ericolin, ursone, gallic acid, and ellagic acid.

Its reputed antibacterial activity is ascribed to the urinary metabolite hydroquinone, which is excreted in the form of inactive conjugates and needs an alkaline urine to be liberated. As the urine of people who consume a Western non-vegetarian diet is usually acidic, it is sometimes suggested that one should alkalinize the urine of bearberry users with sodium bicarbonate. However, as the dosage recommended for this purpose is usually high, this carries well-known risks such as a high sodium load and interference with the renal clearance of certain other drugs.

Table 1 The genera of Ericaceae

Agarista (Florida hobblebush)
Andromeda (bog rosemary)
Arbutus (madrone)
Arctostaphylos (manzanita)
Befaria (befaria)
Calluna (heather)
Cassiope (mountain heather)
Chamaedaphne (leather leaf)
Comarostaphylis (summer holly)
Elliottia (elliottia)
Epigaea (trailing arbutus)
Erica (heath)
Gaultheria (snowberry)
Gaylussacia (huckleberry)
Gonocalyx (brittle leaf)
Harrimanella (harrimanella)
Kalmia (laurel)
Kalmiopsis (kalmiopsis)
Ledum (Labrador tea)
Leiophyllum (leiophyllum)
Leucothoe (dog hobble)
Loiseleuria (loiseleuria)
Lyonia (stagger bush)
Menziesia (menziesia)
Ornithostaphylos (ornithostaphylos)
Oxydendrum (swamp cranberry)
Phyllodoce (mountain heath)
Pieris (fetter bush)
Rhododendron (rhododendron)
Symphysia (symphysia)
Vaccinium (blueberry)
Xylococcus (mission manzanita)
Zenobia (honeycup)

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Adverse effects

The urine of patients taking bearberry can darken on standing.

Toxic reactions to bearberry have not been reported, except for an anomalous case of dyspnea, cyanosis, and skin reactions after the consumption of an aqueous decoction (1).

- A 56-year-old woman who had taken *uva ursi* for 3 years developed reduced visual acuity (2). She had a typical bull's-eye maculopathy bilaterally.

The authors suggested that the effect was due to impaired melanin synthesis.

Reports of carcinogenicity of hydroquinone after prolonged administration of high doses to rats or mice raise a question about the long-term safety of *A. uva-ursi* and other medicinal herbs that contain substantial amounts of arbutin (3).

Gaultheria procumbens

The volatile oil of *Gaultheria procumbens* (wintergreen) leaves consists largely of methyl salicylate (more than 95%).

Adverse effects

Salicylism has been attributed to the use of oil of wintergreen as part of an herbal skin cream for the treatment of psoriasis (4).

- A 40-year-old man became acutely unwell after receiving oil of wintergreen from an unregistered naturopath. Transcutaneous absorption of the methyl salicylate was enhanced in this case owing to the abnormal areas of skin that were covered and the use of an occlusive dressing. The patient developed tinnitus, vomiting, tachypnea, and the typical acid/base disturbance of salicylate toxicity. Decontamination of the skin followed by rehydration and establishment of good urine flow was successful.

Laryngeal edema has been attributed to oil of wintergreen (5).

Methyl salicylate in topical analgesic preparations can cause irritant or allergic contact dermatitis and anaphylactic reactions (6).

In a retrospective study 80 subjects who had taken aspirin tablets ($n = 42$) or topical oil of wintergreen ($n = 38$) were compared (7). The admission plasma salicylate concentrations were generally higher in those who had taken aspirin tablets, but the two highest readings (4.3 and 3.5 mmol/1) belonged to two of the subjects who had taken oil of wintergreen.

Oil of wintergreen in the form of candy flavoring was ingested by a 21-month-old boy who developed vomiting, lethargy, and hyperpnea but recovered rapidly with parenteral fluids and sodium bicarbonate (8).

Methylsalicylate is also an important constituent of the Red Flower Oil formulations that are popular herbal analgesics for topical application in Southeast Asia. Some users take small amounts of the oil orally to enhance its analgesic effects. There are many different brands, which provide variable amounts of declared or undeclared methylsalicylate (up to 0.78 g/ml of oil). A suicide attempt by deliberate ingestion of about 100 ml resulted in severe salicylate poisoning (9).

Ledum palustre

The essential oil of *Ledum palustre* (marsh Labrador tea), which contains flavones, monoterpenoids, and sesquiterpenoids, is a potent irritant of the gastrointestinal tract, kidneys, and urinary tract; other toxic effects include abortion.

Vaccinium macrocarpon

Vaccinium macrocarpon (cranberry, marsh apple) has been used to prevent and treat urinary tract infections, although it is not useful in established infections (10,11). It is supposed to act by preventing adhesion of bacteria to the bladder wall. It may also reduce the risk of formation of some types of urinary stone (12,13).

Adverse effects

Hematologic

Cranberry juice may contain small amounts of quinine, which can cause immune thrombocytopenia.

- After transurethral resection of his prostate, a 68-year-old man developed immune thrombocytopenic purpura (platelet count 1×10^9/l) (14). He had self-medicated with cranberry juice for 10 days before the operation and had also taken amlodipine and aspirin. He had oral petechiae, bleeding gums, hematuria, and bruises. He recovered within 3 days of being given human immunoglobulin and oral prednisolone, and 18 months later his platelet count was still normal.

Drug interactions

Cranberry juice has been reported to enhance the action of warfarin (15)

- After a chest infection a man in his 70s had a poor appetite for 2 weeks and ate next to nothing, taking only cranberry juice as well as his regular drugs (digoxin, phenytoin, and warfarin) (16). Six weeks later his international normalized ratio was over 50, having previously been stable. He died of gastrointestinal and pericardial haemorrhage. He had not taken any over the counter preparations or herbal medicines, and he had been taking his drugs correctly.

The Committee on Safety of Medicines has received several other reports through the yellow card-reporting scheme about a possible interaction between warfarin and cranberry juice.

In one case this effect was suggested to have been due to contamination with salicylic acid, which displaces warfarin from protein binding sites (17).

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Erythromycin

See also Macrolide antibiotics

General Information

For some decades erythromycin was the only macrolide antibiotic available, but with the development of new macrolides with remarkable pharmacokinetic and safety features (1), it has met fierce competition and has, at least in some health-care systems, lost its place as the most important macrolide.

Comparative studies

In a direct comparison of clarithromycin with erythromycin stearate, the rate of adverse events was 19% in 96 patients taking clarithromycin and 35% in 112 patients taking erythromycin (2). Most of the adverse events associated with clarithromycin affect the gastrointestinal tract (7%).

In a prospective, single-blind, randomized study of a 7-day course of clarithromycin (7.5 mg/kg bd) and a 14-day course of erythromycin (13.3 mg/kg tds) in 153 children with pertussis, the incidence of treatment-emergent drug-related adverse events was significantly higher with erythromycin than with clarithromycin (62 versus 45%) (3). Three subjects given erythromycin withdrew prematurely because of adverse events: one because of a rash; one with vomiting and diarrhea; and one with vomiting, abdominal pain, and rash.

In a double-blind, randomized, multicenter trial in 302 children, a 10-day course of erythromycin estolate (40 mg/kg/day in two doses) was as safe and effective as amoxicillin (50 mg/kg/day in two doses) in acute otitis media. Treatment-related adverse events occurred in 5.3% of patients given erythromycin and in 7.3% of patients given amoxicillin (4).

General adverse effects

Erythromycin is relatively well tolerated, with the exception of gastrointestinal adverse effects. Cholestasis resulting from the use of all forms of erythromycin is virtually the only serious effect. However, local irritation (affecting the gastrointestinal system, the muscles, or the veins, depending on the route of administration) is common. Erythromycin can increase serum theophylline concentrations and occasionally causes theophylline toxicity. Hypersensitivity reactions are rare, unless cholestasis is to be regarded as allergic. They probably have clinical effects in under 0.5% of treated patients, and consist mainly of maculopapular rashes, pruritus, urticaria, and angioedema; anaphylaxis and acute respiratory distress have also been reported. Fixed drug eruptions, urticaria, and Stevens–Johnson syndrome have also been reported.

Organs and Systems

Cardiovascular

Erythromycin has antidysrhythmic properties similar to those of Class IA antidysrhythmic drugs, and causes an increase in atrial and ventricular refractory periods. This is only likely to be a problem in patients with heart disease or in those who are receiving drugs that delay ventricular repolarization (5). High-doses intravenously have caused ventricular fibrillation and torsade de pointes (6). Each episode of dysrhythmia, QT interval prolongation, and myocardial dysfunction occurred 1–1.5 hours after erythromycin infusion and resolved after withdrawal.

In an FDA database analysis, 346 cases of cardiac dysrhythmias associated with erythromycin were identified. There was a preponderance of women, as there was among those with life-threatening ventricular dysrhythmias and deaths after intravenous erythromycin lactobionate. A sex difference in cardiac repolarization response to erythromycin is a potential contributing factor, since in an in vitro experiment on rabbit hearts, erythromycin caused significantly greater QT prolongation in female than in male hearts (7).

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In 35 women and 28 men erythromycin caused QT interval prolongation after the first few doses of erythromycin (8). Similarly, in a prospective, comparative study in 19 patients with uncomplicated community-acquired pneumonia, a single dose of intravenous erythromycin 500 mg increased the heart rate and prolonged the QT interval. These effects were seen after 15 minutes of infusion and disappeared 5 minutes after the infusion had been stopped (9).

Owing to prolongation of the QT interval, a newborn with congenital AV block developed ventricular extra beats and non-sustained ventricular tachycardia after intravenous erythromycin; the QT interval normalized after withdrawal (10).

- Intravenous erythromycin (1 g 6-hourly by intravenous infusion over 30 minutes) resulted in QT interval prolongation, ventricular fibrillation, and torsade de pointes in a 32-year-old woman (6).

Intravenous administration of erythromycin into peripheral veins relatively commonly causes thrombophlebitis, although the lactobionate form of erythromycin may be less irritating to veins than other parenteral forms (11,12). In a prospective study of 550 patients with 1386 peripheral venous catheters, the incidence of phlebitis was 19% with antibiotics and 8.8% without; erythromycin was associated with an increased risk (13).

Respiratory

Adverse effects involving the respiratory system were reported in 2% of patients taking erythromycin stearate (2).

A beneficial effect of erythromycin on sputum volume has been reported in a patient with severe airways obstruction due to bronchorrhea (14).

Nervous system

In patients without neuromuscular disease erythromycin caused subclinical loss of motor unit contractions, which improved with intravenous edrophonium or neostigmine (15).

Sensory systems

Ototoxicity, resulting in hearing loss, and usually reversible, has been reported in patients treated with erythromycin lactobionate 4 g/day or more or large oral doses of erythromycin estolate (16). Ototoxic reactions have also been seen after the use of esters of erythromycin, such as the ethylsuccinate, stearate, and propionate (17). High parenteral doses of erythromycin have resulted in transient perceptive deafness (18–21). Since renal and hepatic disease was a prominent feature in these patients, ototoxicity was thought to result from high blood concentrations (22). Recovery occurred within a few days after withdrawal. The phenomenon differs from the permanent type of ototoxicity caused by aminoglycosides. Erythromycin should not be given together with other potentially ototoxic drugs and hearing acuity should be monitored during erythromycin therapy, especially in the elderly. Acute psychotic reactions have been related to ototoxicity and high-dose erythromycin therapy (23).

Psychological, psychiatric

Erythromycin has been associated with complications such as confusion, paranoia, visual hallucinations, fear, lack of control, and nightmares. These suspected psychiatric adverse effects were seen within 12–48 hours of starting therapy with conventional doses. Such complications may even be under-reported (23–26).

Gastrointestinal

Erythromycin is a motilin receptor agonist (27–29). This mechanism may be at least partly responsible for the gastrointestinal adverse effects of macrolides.

Pylorospasm and hypertrophic pyloric stenosis is associated with early postnatal erythromycin exposure and has been observed in neonates after 1–2 days of oral erythromycin therapy (30). The prominent gastrokinetic properties of erythromycin have been postulated as the mechanism (31).

- Pyloric stenosis has also been reported in a boy born at 23 weeks gestation, weight 690 g, after treatment of the child with three doses of oral erythromycin 10 mg/kg/day (32).

The use of erythromycin in postexposure prophylaxis for pertussis in 200 infants was followed by an increased number of cases of infantile hypertrophic pyloric stenosis, and all seven cases had taken erythromycin prophylactically (33). A case review and cohort study supported these preliminary findings (34). In a retrospective study in 314 029 children, very early exposure to erythromycin (at 3–13 days of life) was associated with a nearly eightfold increased risk of pyloric stenosis (35). There was no increased risk in infants exposed to erythromycin after 13 days of life or in infants exposed to antibiotics other than erythromycin.

Intravenous erythromycin should be restricted to as few patients as possible. It can cause severe abdominal cramps, probably by a direct action on smooth muscle (36–38).

Liver

Erythromycin can cause two different types of liver damage (39,40). Administration of erythromycin as base or salt can be followed in 0–10% of cases by apparently benign increases in serum transaminases, which may or may not recur on rechallenge. In children, raised transaminases were noted at dosages of 40 mg/kg/day but not 20 mg/kg/day.

Cholestatic hepatitis, which is associated primarily with erythromycin estolate, can be caused by all forms of erythromycin, including the base, estolate, ethylsuccinate, propionate, and stearate (39,41). Although it was originally speculated that a hypersensitivity reaction to the estolate ester rather than to the erythromycin itself was responsible for this adverse reaction (42), erythromycin does inhibit bile flow (43). Most probably the differences in hepatotoxicity between the various erythromycin derivatives are of a quantitative rather than a qualitative nature (44,45), perhaps because of better intestinal absorption of the estolate. Potentially severe but rare cholestatic liver injury occurs in perhaps up to 2–4% of

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treated patients. Erythromycin-induced cholestasis is rare in children under the age of 12 years, but has occurred in infants at 6 weeks of age, in whom it can mimic acute cholecystitis, biliary atresia, or neonatal hepatitis (46).

- A young woman developed severe cholestasis and jaundice after taking erythromycin stearate (47). A second severe episode of jaundice and malaise occurred after treatment with erythromycin succinate 2 years later pointing to erythromycin itself as the culprit.

The syndrome generally starts 10–14 days after the start of therapy, but earlier after re-exposure, sometimes within 12–24 hours (48). At all ages it often begins with abdominal pain, nausea, vomiting, pyrexia, pruritus, and jaundice; fever, rash, leukocytosis, raised serum transaminases, and eosinophilia can also occur. However, it can be ushered in with severe acute upper abdominal pain or right subcostal tenderness, simulating an acute abdomen, or it can resemble obstructive jaundice. Serum bilirubin, alkaline phosphatase, and transaminases are raised. Histological examination typically shows intrahepatic cholestasis and periportal inflammatory infiltration, with lymphocytes, neutrophils, and disproportionate numbers of eosinophils (49). These histological findings could be interpreted as reflecting a hypersensitivity reaction, but this hypothesis has been rejected (43). If erythromycin is promptly withdrawn, the clinical signs often improve rapidly, although prolonged jaundice has been reported.

Urinary tract

Acute renal insufficiency has been observed in a patient with Henoch–Schönlein syndrome (50). Another case presented as interstitial nephritis with acute renal insufficiency (51).

Skin

Topical erythromycin in benzoylperoxide, marketed for acne treatment, must be compounded by a pharmacist and requires subsequent refrigeration, warranting the development of alternative formulations. In a double-blind, parallel-group, multicenter study in 327 patients, a single-use erythromycin in benzoylperoxide combination package was compared with the vehicle alone and the original, reconstituted formulation packaged in a jar. Dry skin was the most frequently reported skin-related adverse event; it occurred in 3.2% of patients who used the preformulated erythromycin in benzoylperoxide and 5.0% of those who used the reconstituted erythromycin in benzoylperoxide (52).

A fixed drug eruption due to erythromycin has been observed (53). In another case skin tests with erythromycin were positive for the immediate and or delayed types of hypersensitivity (54).

- A 27-year-old woman developed urticaria 30 minutes after taking a single dose of erythromycin (55). An identical episode had occurred three years before. Erythromycin-specific IgE was detected in her serum by radioimmunoassay.
- Stevens–Johnson syndrome developed in a 64-year-old man who took erythromycin stearate for non-specific upper respiratory tract symptoms (56). After four doses of 250 mg, he developed a fever and typical lesions in the mouth and conjunctivae and on the lips. He was treated with prednisolone and recovered rapidly.

Second-Generation Effects

Teratogenicity

In a retrospective study there was no evidence of an increased risk of pyloric stenosis among infants born to mothers exposed to erythromycin during pregnancy (57).

Drug–Drug Interactions

Antihistamines

The association of ventricular dysrhythmias with co-administration of erythromycin and terfenadine (58) is thought to be due to inhibition of CYP3A4 by erythromycin. This combination should be avoided.

Erythromycin increases concentrations of astemizole (59). This combination should be avoided.

A double-blind, crossover study of the potential interaction between erythromycin and loratadine in 24 healthy volunteers showed that the AUCs of loratadine and its metabolite descarboethoxyloratadine were increased 40% and 46% respectively by erythromycin, but with no discernible effect on the QT interval (60).

Combined desloratadine 7.5 mg/day plus erythromycin 500 mg qds in 24 healthy volunteers was well tolerated and had no clinically important electrocardiographic effects (61). Although co-administration of erythromycin slightly increased plasma concentrations of desloratadine, this change did not correlate with prolongation of the QT interval, and there was no toxicity.

Benzodiazepines

Erythromycin can increase concentrations of midazolam and triazolam by inhibition of CYP3A4, and dosage reductions of 50% have been proposed if concomitant therapy is unavoidable (59).

Buspirone

Co-administration of erythromycin with the anxiolytic drug buspirone increased the plasma concentration of buspirone (62).

Carbamazepine

Erythromycin can cause acute carbamazepine intoxication, probably by inhibiting its hepatic metabolism (63). Erythromycin may also directly inhibit the conversion of carbamazepine to its epoxide. In a controlled study of the effects of erythromycin on carbamazepine pharmacokinetics in healthy volunteers, the clearance of a single dose of carbamazepine was reduced by 19% during erythromycin treatment (64). In contrast, the single-dose pharmacokinetics of phenytoin were not affected by erythromycin (65,66). After withdrawal of the macrolide, carbamazepine concentrations quickly return to normal (67). If co-administration of erythromycin and carbamazepine cannot be avoided, a dosage reduction of

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carbamazepine of around 25% should be considered, with careful monitoring of serum concentrations (59).

Cilostazol

When erythromycin was given to 16 healthy non-smoking male volunteers taking cilostazol, the C_{max} and AUC of cilostazol increased significantly by 47 and 73% respectively, and the unbound clearance of the major metabolite of cilostazol, OPC-13015, fell by about 50% (68).

Cisapride

- QT interval prolongation and torsade de pointes occurred after co-administration of cisapride and erythromycin 500 mg qds for 1 week in a 47-year-old woman (69).

Digoxin

The interaction of erythromycin with digoxin (70,71) is probably due to inhibition of its presystemic metabolism by inhibition of the growth of *Eubacterium glenum*.

Disopyramide

Disopyramide altered protein binding of erythromycin and this resulted in increased plasma erythromycin concentrations in vitro (72). The interaction between erythromycin and disopyramide was potentially fatal in two cases (73).

Ergot alkaloids

The interaction of erythromycin with ergotamine or dihydroergotamine can cause ergotism, sometimes leading to gangrene, by inhibition of the metabolism of the ergopeptides (74).

Felbamate

Erythromycin (333 mg tds for 10 days) had no effect on the pharmacokinetics of felbamate (3.0 or 3.6 g/d) used as monotherapy in epilepsy (75).

Halofantrine

Erythromycin inhibited halofantrine metabolism in vitro, suggesting that increased cardiotoxicity might be clinically important (76).

Lidocaine

Erythromycin can increase the plasma concentration and toxicity of oral lidocaine, as shown in a crossover study in nine volunteers who took erythromycin orally (500 mg tds) for 4 days and 1 mg/kg of oral lidocaine on day 4 (77).

Oral anticoagulants

Erythromycin can interact with warfarin, resulting in a modest increase in blood concentrations and a rise in the prothrombin time of around 8% (78).

Erythromycin may potentiate acenocoumarol anticoagulant treatment, as reported in a 68-year-old man on stable anticoagulation with acenocoumarol 3 mg/day who took erythromycin ethylsuccinate 1.5 g/day (79).

Quinidine

Erythromycin reduced the total clearance of quinidine, reduced its partial clearance by 3-hydroxylation, and increased its maximal serum concentration in an open study in 30 healthy young volunteers (80).

Quinine

Erythromycin is a competitive in vitro inhibitor of quinine 3-hydroxylation and may therefore interact with quinine (81).

Selective serotonin re-uptake inhibitors (SSRIs)

- A 12-year-old boy developed the serotonin syndrome, which is normally associated with the interaction of two or more serotonergic agents, after the co-administration of erythromycin and sertraline.

This could have been due to erythromycin-induced inhibition of sertraline metabolism by CYP3A (82).

Statins

It has been proposed that the risk of myotoxicity increases when statins are prescribed concurrently with erythromycin (83). There are no data for any pharmacokinetic interaction with fluvastatin or pravastatin, but as in the case of simvastatin the major route of metabolism of these drugs is by CYP3A4 and there is potential for an adverse interaction.

Atorvastatin

When erythromycin was co-administered with atorvastatin, the mean C_{max} and AUC of atorvastatin increased by more than 30% (5,84).

Lovastatin

Rhabdomyolysis with or without renal impairment has been reported in patients taking both erythromycin and lovastatin (85). The exact mechanism is unknown, but lovastatin is extensively metabolized by CYP3A4 and its metabolism may therefore be inhibited by erythromycin. The manufacturers have advised that careful monitoring is required when these two drugs are given together.

Simvastatin

A case-control analysis of 7405 cases and 28 327 controls suggested that concomitant use of simvastatin and erythromycin is associated with an increased risk of cataract (86). Studies in dogs have shown that some statins are associated with cataract when given in excessive doses (87).

Theophylline and other xanthines

Erythromycin can increase the serum concentrations of theophylline by 20–25%. However, patients with an average serum concentration of theophylline under 15 μg/ml will probably only experience a small increase in their serum theophylline concentration during erythromycin therapy, whereas patients with steady-state concentrations above 15 μg/ml deserve careful monitoring and close observation for symptoms of theophylline toxicity during treatment with erythromycin (88,89).

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Tiagabine

Both tiagabine and erythromycin are metabolized by cytochrome P450. In an open, crossover study in 13 healthy volunteers, tiagabine (4 mg bd) and erythromycin (500 mg bd) were co-administered for 4 days (90). Maximum plasma concentration, AUC, and half-life of tiagabine were comparable when tiagabine was administered alone or in combination with erythromycin. The t_{max} was prolonged after administration with erythromycin in women; this effect may be due to a differential effect of erythromycin on gastric emptying. The interpretation of these findings is limited by the rather low doses of tiagabine used in the study and the short time of co-administration.

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Erythropoietin, epoetin alfa, epoetin beta, epoetin gamma, and darbepoetin

General Information

Erythropoietin is an endogenous glycosylated protein hormone that is produced mainly in the kidneys and stimulates the production of members of the erythroid series of blood cells. Epoetin is the name that has been given to recombinant forms, of which there are four: epoetin alfa, epoetin beta, epoetin omega, and darbepoetin alfa. Darbepoetin alfa is a supersialylated form of erythropoietin with a longer half-life.

Uses

Recombinant human erythropoietin (epoetin and darbepoetin) provides effective therapy with a very favorable risk–benefit ratio in hemodialysis patients with end-stage chronic renal insufficiency, and in patients with progressive renal insufficiency who are not yet being dialysed (1). It improves cognitive function and the quality of life of patients with chronic uremia (2–5) and is very effective in children with chronic renal graft rejection and anemia (6). It also offers new opportunities for treating anemia in non-uremic patients. In patients with chemotherapy-induced anemia, epoetin increases hemoglobin concentration, reduces transfusion requirements, and improves quality of life (7,8). The response rate to epoetin in patients with multiple myeloma and anemia, which is 55–85% (9), increases when GM-CSF or G-CSF is co-administered (10). Epoetin is also approved for indications such as anemia induced by zidovudine in HIV-infected patients, the prevention of anemia in surgical patients, and anemia of prematurity (10,11). Treatment with epoetin results in a substantial improvement in the rehabilitation and quality of life of patients with cancer, AIDS, and rheumatoid arthritis (12).

Anemia due to prematurity can also be treated with epoetin. However, there are still questions to be answered about its efficacy, dosage regimen, and route of administration (subcutaneously or intravenously) (13,14). A comparison of the efficacy of daily versus less frequent dosing schedules in preterm infants showed that dosage regimens that achieve lower peak serum concentrations over a more prolonged period of time may be more efficacious (14). Although growth retardation in children with renal insufficiency does not improve (15,16), well-being, energy, appetite, and cardiac function are enhanced, and by obviating the need for regular blood transfusions, iron overload, allo-immunization to cellular antigens, and transfusion-transmitted viral infections are avoided (17).

Patients with cancer often develop anemia, and several studies have shown that recombinant human epoetin is a useful alternative to blood transfusion in such patients (18). Response rates of up to about 80% have been reported in patients with cancer-related anemia, especially in patients treated with platinum-based chemotherapy (18). Whether epoetin will improve tumor control after radiotherapy is being investigated (19). Epoetin corrects low hemoglobin concentrations, resulting in a better quality of life and probably improving cure rates in cancer patients undergoing radiotherapy (19). It also relieves symptoms of fatigue in patients with cancer (20,21), increasing hemoglobin and reducing transfusion requirements (22). No acceleration of tumor growth by epoetin has been observed (23). Epoetin has also been used in combination with G-CSF and amifostine or G-CSF and IL-3 as adjunctive treatment for cytopenias complicating myelodysplastic syndrome (24,25). Although these combinations are well tolerated, they promote hemopoiesis only in a subgroup of these patients.

Epoetin combined with parenteral iron is effective and safe for moderate and severe iron deficiency anemia during pregnancy (26), and iron supplementation is often required (27). The use of epoetin in combination with intravenous iron makes collection of larger numbers of autologous erythrocyte units feasible. However, epoetin does not synergize with G-CSF for the mobilization of peripheral blood progenitor cells in healthy donors (28).

Epoetin has been used to reduce allogeneic transfusion needs by increasing the efficacy of autologous transfusion for elective surgery (29). The combination of autologous predonation and epoetin treatment reduces blood requirements during and after orthopedic and cardiac surgery (30). In elective open-heart surgery, 26 of 30 patients who received only iron preoperatively needed blood transfusions compared with one of 30 patients who received iron plus epoetin (30).

While epoetin is not of benefit after autologous bone marrow transplantation, in patients receiving allogeneic bone marrow transplantation epoetin accelerates erythroid engraftment, increases hemoglobin concentrations,

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reduces requirements for erythrocyte transfusions, and shortens the time to transfusion independence (31).

The main limiting factor in obtaining an optimal response to epoetin is the adequacy of the patient's iron stores (32,33); the response is abated in the presence of iron deficiency, occult blood loss, hemolysis, and other hematological diseases (34,35). Other causes of an inadequate response to epoetin include concurrent infection or inflammatory disease (1), aluminium toxicity, vitamin deficiencies, secondary hyperparathyroidism (36,37), and osteitis fibrosa (38,39).

Pharmacokinetics

Subcutaneous epoetin in patients undergoing hemodialysis can maintain the hematocrit at a desired target range using an average weekly dose lower than with intravenous administration (40). Intravenous administration leads to higher initial epoetin concentrations compared with subcutaneous administration. However, after intravenous administration the half-life is only 4–5 hours, compared with 19–22 hours after subcutaneous administration (41).

Observational studies

In a prospective trial in 3012 patients, the clinical benefits and adverse events profiles were similar with once-weekly epoetin compared with historical experience with thrice-weekly dosing (42).

In 194 patients a low dose of epoetin beta before elective surgery was well tolerated and reduced the need for transfusions (43).

Effective epoetin treatment has been reported in a transfusion-dependent beta-thalassemia major patient: there were no adverse effects (44).

In four patients with chronic diffuse gastrointestinal bleeding that was difficult to control, epoetin was successfully used as a hemostatic agent (45).

Placebo-controlled studies

In a double-blind, randomized, placebo-controlled, multicenter study in 80 critically ill patients, epoetin led to a 45% reduction in the number of erythrocyte units transfused. There were no epoetin-related adverse effects (46).

General adverse effects

Both epoetin alfa and beta and darbepoetin alfa are quite well tolerated (47). Common adverse effects are infection, hypertension, hypotension, shunt thrombosis, myalgia, nausea, headache, and chest pain (34,48). After the first few doses of epoetin, flu-like symptoms occur transiently, with an incidence of 5.4–18% (34,49). These can be avoided by injecting epoetin subcutaneously rather than intravenously (31,33,50,51). It has also been suggested that such symptoms can be avoided by dose escalation, starting with an ultra-low dose (49). Subcutaneous injection can cause local reactions, probably due to allergy (52).

Darbepoetin

Darbepoetin alfa is a long-acting form of erythropoietin, with additional sialic acid residues, and does not require such frequent administration as epoetin; its long half-life allows administration once every 1 or 2 weeks (53).

The safety profiles of epoetin and darbepoetin are similar. Adverse effects of darbepoetin include hypertension, injection site pain (generally mild and transient) in the case of subcutaneous administration, cardiovascular events, headache, vascular disorders (vascular access thrombosis), flu-like symptoms, and skin rashes (20,53,54). Adverse effects such as hypertension and thrombophlebitis are observed in uremic patients requiring dialysis but not in patients with hematological malignancies (55).

Organs and Systems

Cardiovascular

In a randomized study of 180 patients with anemia due to hormone-refractory prostate cancer, who were treated with epoetin beta 1000 IU or 5000 IU subcutaneously 3 times a week for 12 weeks, cardiovascular events were more frequent with the higher dosage. Four patients had deep vein thrombosis and two had myocardial infarctions; all were taking the higher dosage. However, only one of the patients with deep vein thrombosis had a high hemoglobin concentration (21).

Hypertension

Epoetin causes or aggravates hypertension in about 20–35% of dialysis patients (56–60). It can be accompanied by encephalopathy or seizures (61). In 44 children with chronic renal insufficiency treated with epoetin 150 U/kg/week, hypertension was mostly observed in patients on hemodialysis (66%) compared with peritoneal dialysis (33%) and predialysis patients (16%) (62).

Several factors contribute to the development of hypertension. One is the loss of the hypoxic vasodilatory response, leading to an increase in peripheral vascular resistance (63), but more important is the rise in blood viscosity, which increases with the hematocrit in both normotensive and hypertensive individuals (64). It is still being debated whether hypertension occurs only in patients with pre-existing hypertension or in normotensive patients as well, but about 30% of all patients require increased or de novo antihypertensive therapy as they respond to erythropoietin treatment (65).

Hypertension after epoetin has mostly been seen in uremic patients (66). However, in two of 44 cancer patients treated with epoetin during cisplatin-containing chemotherapy, epoetin was withdrawn owing to hypertension (diastolic pressure over 100 mmHg) (67).

Hypertensive encephalopathy can arise in connection with the sudden and extreme rises in blood pressure that occur in some patients given epoetin (52,68).

- A 14-year-old child developed hypertensive encephalopathy, a known rare adverse effect of erythropoietin, after 2 months (69).

During an open, uncontrolled study in 22 patients with end-stage renal disease treated with epoetin omega there was one case of hypertensive encephalopathy (70).

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Susceptibility factors

It is not clear why certain patients develop hypertension and hypertensive encephalopathy and others do not, but transfusion-dependent anemic patients with a low hematocrit (<20%) are particularly susceptible, as are those with previous hypertension and seizures. Careful control of blood pressure at the start of epoetin treatment and the use of low doses are therefore advised in patients at high risk.

If epoetin is given preoperatively without autologous predonation, there is an increased risk of hypertension, an increased risk of graft thrombosis and myocardial infarction in cardiac surgery, and an increased risk of venous thromboembolism in orthopedic patients (71).

Because of an increase in cardiac-related deaths, it has been recommended that in patients with congestive heart failure or ischemic heart disease the hematocrit should not be raised above 42% (3).

Mechanisms

One of the possible mechanisms of epoetin-induced hypertension is an imbalance of local endothelial factors, such as endothelium-derived relaxation factor and endothelin (61), a potent vasoactive peptide produced by endothelial cells (13), increased concentrations of which have been observed in adults with an increase in mean blood pressure of more than 10 mmHg. In contrast, in preterm infants receiving epoetin there were no acute effects of epoetin on endothelin-1 concentrations or mean blood pressure (13). When intravenous and subcutaneous epoetin were compared, only intravenous epoetin was accompanied by hypertension (57,61). Plasma concentrations of proendothelin-1 and endothelin-1 increased after infusion of epoetin only in patients with hypertension. In addition the molar ratio of endothelin-1 to proendothelin-1 was significantly higher in patients with hypertension than in patients without (61). The authors suggested that endothelin-1 converting enzyme may play a role in the pathogenesis of epoetin-induced hypertension (61). Studies in rats have confirmed that epoetin stimulates endothelin release and synthesis of vascular tissue (72). There is a relation between the dose of epoetin and postdialysis blood pressure, but not predialysis blood pressure (57). Risk factors for the development or worsening of hypertension are pre-existing hypertension, the presence of native kidney, a rapid increase in hematocrit, a low baseline hematocrit, high dosages of epoetin, and intravenous administration (57).

Epoetin has vascular effects that can cause an imbalance between vasoconstrictor-proproliferative-proatherogenic factors (angiotensin, endothelin, thromboxane) and vasodilator-antiproliferative-antiatherogenic factors (nitric oxide, prostacyclin). These changes may be related to the occurrence or aggravation of pre-existing hypertension in humans and can cause vascular hypertrophy and potentially accelerate the development of atherosclerosis (66).

Adrenomedullin, an endocrine peptide with vasodilatory and natriuretic actions, is increased in patients with hypertension and chronic renal insufficiency. In 54 patients with renal anemia, treated with epoetin 6000 IU once a week, there was a correlation between the progression of renal disease and circulating adrenomedullin; however, there was no relation between adrenomedullin and epoetin-induced hypertension (73).

The induction of hypertension by epoetin has been attributed to increased blood viscosity after a rapid increase in hematocrit and a loss of hypoxia-induced vasodilatation (59). Another pathogenic mechanism for the induction of hypertension by epoetin is enhanced endothelin production by endothelial cells (59).

In 10 normotensive hemodialysis patients with severe anemia treated with epoetin there was increased adrenergic activity (74).

Epoetin-induced hypertension may be associated with an angiotensinogen gene polymorphism; the incidence of hypertension was increased in patients carrying a homozygous T on position 235 of the angiotensinogen gene (75). The authors speculated that erythropoietin causes a rise in blood pressure via the T allele, which influences components of the renin–angiotensin system, thereby stimulating production of angiotensinogen, which leads to hypertension.

Management

Blood pressure should be monitored during treatment (18).

Erythropoietin-induced hypertension can easily be treated by initiating or increasing antihypertensive medication (76). For example, two of 26 pregnant women treated with epoetin for iron deficiency anemia had worsening of mild hypertension, which was managed effectively with methyldopa 250 mg tds (26).

Antiplatelet therapy reduces the incidence of epoetin-induced hypertension in predialysis patients (60).

Vascular disease

There is an increased incidence of peripheral vascular diseases in diabetic patients who receive peritoneal dialysis and epoetin (4). In these patients the time to a first vascular incident is shorter, the number of vascular events is increased, and more hospital days associated with vascular disease have been reported compared with patients receiving peritoneal dialysis without epoetin (4). Significant risk factors for the development of peripheral vascular disease are epoetin therapy, epoetin dose, and smoking (4). Peripheral vascular disease may be related to increased blood viscosity or other changes in blood rheology (4).

Thrombotic events related to epoetin include vascular access thrombosis, renal and temporal vein thrombosis, transient ischemic attacks, and myocardial infarction (66).

Vascular access thrombosis has been reported in up to 26% of patients treated with epoetin alfa (3,34,38). Most of the failures occurred in polytetrafluoroethylene grafts. There was no comparison with patients not treated with epoetin. It has been suggested that the increased risk of extracorporeal circuit clotting and the higher heparin requirements during hemodialysis may not be due to a hypercoagulable state, but rather to an increase in erythrocyte mass and consequently in whole blood viscosity (66).

- A patient with end-stage renal disease treated with epoetin-alfa developed a dural sinus thrombosis (5).

It was postulated that it was caused by polycythemia, because the hematocrit more than doubled in under 2 months, reaching 0.55 (5).

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Nervous system

Several neurological complications of epoetin, such as headache, seizures, visual hallucinations, transient myalgia, and hypertensive leukoencephalopathy, have been described (5,77).

Headache, probably due to intracranial hypertension, has been reported in 15% of patients with renal insufficiency treated with epoetin (23). Analysis of the safety of epoetin in cancer patients is often hampered by toxicity of the concomitant chemotherapy. In a prospective open study, three of 183 anemic cancer patients who did not receive chemotherapy complained of headache, possibly or probably related to epoetin (22). Complaints of dizziness and headache, possible due to epoetin, occurred in two of 44 cancer patients during cisplatin-containing chemotherapy (67).

Seizures have been reported in 2–17% of dialysis patients treated with epoetin (38,78). The mechanism is not known, but is most likely multifactorial, including increased peripheral vascular resistance, reversal of hypoxic vasodilatation, and a direct pressor effect of epoetin mediated by enhanced production of serum endothelin-1 (78). Seizures occur most often during the correction of anemia and are associated with a rapid increase in hemoglobin concentration and poor control of hypertension (38).

Reversible posterior leukoencephalopathy syndrome, in which imaging abnormalities are present in the parieto-occipital regions of the brain, is reversible after blood pressure control and withdrawal of epoetin (59,79). Monitoring of the blood pressure is indicated and the hematocrit should be increased slowly, with a target of not more than 30%. If hypertension and seizures are under control, epoetin therapy can be resumed (59).

Psychological, psychiatric

Visual hallucinations have been reported in patients receiving epoetin (59).

Endocrine

In two patients with non-insulin-dependent diabetes and uremia, glucose control deteriorated after the introduction of epoetin, requiring insulin therapy (80).

Hematologic

Iron deficiency is a common adverse effect (30%) in children with chronic renal insufficiency treated with epoetin, even with iron supplementation (62). In premature infants given enteral epoetin, there was a significant fall in ferritin concentrations despite iron supplementation (81), and there were increased numbers of hypochromic erythrocytes and soluble transferrin receptors (14). This implies that active erythropoiesis in premature infants causes increased iron requirements.

Erythrocytes

Worldwide, 112 cases of pure red cell aplasia have been reported after subcutaneous administration of epoetin alfa (especially Eprex) in patients with chronic renal insufficiency. In these patients, neutralizing anti-erythropoietin antibodies were detected (82–84); these antibodies cross-react with all other erythropoietin products. This adverse effect was probably restricted to patients with renal insufficiency because these patients had used subcutaneous erythropoietin for many years. The incidence was calculated as one in 10 000 patients after 1 year of use of erythropoietin.

In other reports from Canada and the UK, patients typically developed sudden worsening of anemia unresponsive to increasing doses of epoetin alfa or any other form of erythropoietin and became transfusion dependent (85). In patients who develop sudden lack of efficacy or worsening of anemia, typical causes of non-response (for example deficiencies of iron, folate, and vitamin B_{12}, infection or inflammation, blood loss, hemolysis, and aluminium intoxication) should be investigated. If pure red cell aplasia is suspected and no cause can be identified, erythropoietin antibodies should be sought.

The Australian Adverse Drug Reactions Advisory Committee has also received 12 reports of pure red cell aplasia associated with the use of epoetin alfa (Eprex) in patients with renal insufficiency (86). The patients were aged 28–76 years and the duration of epoetin alfa use, when known, was 4–13 months.

Janssen-Ortho Inc, in association with Health Canada, have issued a "Dear Health Professional" letter about the addition of a boxed section to the product monograph of epoetin-alfa (Eprex). The addition recommends that epoetin alfa should be administered intravenously rather than subcutaneously in patients with chronic renal insufficiency. This advice is based on the fact that most of the worldwide reports of pure red cell aplasia in patients treated with epoetin alfa have been associated with subcutaneous administration.

The suggested mechanism for these cases of pure red cell aplasia is an immune reaction that is probably induced by repeated, subcutaneous administration of a foreign protein, a biotechnologically processed erythropoietin. However, no antibodies toward darbepoetin alfa were detected in over 1534 patients treated for 2 years (87).

- A 70-year-old woman with a history of diabetes mellitus and renal insufficiency rapidly developed a severe anemia (with a hemoglobin concentration of 3.5 mmol/l). She had been treated with recombinant erythropoietin (4000 IU/week) for 6 months with an initial favorable response (hemoglobin concentration between 6.8 and 7.5 mmol/l) (82). Her bone marrow showed pure red cell aplasia with early termination of maturation. The dose of recombinant erythropoietin was increased to 8000 IU/week. She required 3 units of packed red cells per month.

This patient had developed antibodies against recombinant erythropoietin. After recombinant erythropoietin was withdrawn, the concentration of antibodies fell slightly. Because of persistent transfusion requirements, she received prednisone (1 mg/kg/day) for 6 months. At that time, antibodies against erythropoietin could not be detected anymore and the hemoglobin concentration was around 5.6 mmol/l.

Leukocytes

In neonates neutropenia has been described after treatment with high doses of epoetin. Neutrophil counts

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increased in these neonates after withdrawal of epoetin (88). Lymphopenia has been described (89), but the fall in lymphocyte count in patients with renal insufficiency is less significant. Pretreatment with imidazole-2-hydroxybenzoate, which inhibits the synthesis of prostaglandins, causes a less marked and delayed reduction of lymphocytes (89). However, neutropenia has not been noted in recent studies (14).

Thrombotic events have been reported in patients given epoetin (90,91), but there have been contradictory results on its effects on blood coagulation and fibrinolysis. There is currently no definitive evidence that epoetin further enhances hypercoagulability in uremic patients (66). In a prospective controlled study, epoetin for elective hip surgery did not activate coagulation and fibrinolysis (92). In 26 patients the effect of epoetin on hemostasis was minimal, with only a clinically insignificant fall in the total amount of protein S (93). In contrast to earlier studies, this study did not show changes in the number of platelets or platelet function. Regular epoetin treatment in 39 hemodialysis patients with anemia did not result in adversely high blood viscosity, and in an overview of data from 3000 patients there was no increase in shunt or fistula occlusion (94).

In a placebo-controlled study of severely anemic patients with low-grade non-Hodgkin's lymphoma, chronic lymphocytic leukemia, or multiple myeloma, a fatal case of pulmonary embolism was thought to have been related to treatment with epoetin beta (95). Thrombotic events, such as vascular access thrombosis, venous thrombosis, and pulmonary embolism, have occurred after treatment with epoetin or darbepoetin alfa (96). It is therefore recommended that a rapid rise in the hemoglobin concentration be avoided and that care should be taken that the hemoglobin concentration does not exceed 12.1 g/dl (7.5 mmol/l) (97).

In 173 renal patients with anemia, in which once-weekly administration of subcutaneous epoetin beta was compared with thrice-weekly administration, there were seven serious adverse events, possible related to epoetin beta (98). There were two cases of arteriovenous fistula thrombosis in the once-weekly group and three in the thrice-weekly group. A transient ischemic attack and a hypertensive crisis occurred in one patient in the once-weekly group.

Treatment of patients with sickle cell anemia has led to disastrous sickling crises (99), and there are at present no clinical data to support the use of erythropoietin in sickle cell disease (100).

Gastrointestinal

Of 183 anemic cancer patients who did not receive chemotherapy in a prospective open study, seven complained of nausea, possibly or probably related to epoetin (22).

Urinary tract

Because the erythrocyte volume increases under the influence of erythropoietin, the clearance achieved by the dialyser can fall, with a consequent increase in creatinine, potassium, and phosphate (101). However, earlier fears that the renal function of predialysis patients receiving epoetin might deteriorate prematurely have not been realized (65).

The use of darbepoetin alfa is associated with an increase in erythrocytes and a reduction in plasma volume, which can lead to reduced efficacy of dialysis (48).

Skin

Generalized skin rash and local swelling at the injection site have been reported after subcutaneous epoetin (8,20), as have urticaria and other skin rashes (48,102). Of 61 patients with malignancies of the oral cavity and oropharynx who were treated with epoetin before perioperative chemoradiation, one had a mild transient skin rash related to epoetin (103).

- Strawberry hemangiomas developed in a premature infant after 1 week of treatment with epoetin (104).

Strawberry hemangiomas are congenital vascular lesions characterized by endothelial hyperplasia during the proliferative phase. The development and proliferation of capillary endothelium requires the presence of angiogenic factors, such as vascular endothelial growth factor. Epoetin has a proliferative effect on endothelial cells and can induce angiogenesis (104,105).

- A rare case of generalized exfoliative dermatitis secondary to epoetin has been described (38). Epoetin was withdrawn and the lesions disappeared spontaneously after 20 days.

Hair

- At the start of treatment with epoetin alpha for anemia, a 60-year-old man with nephrotic syndrome developed reversible total alopecia (106).

Sexual function

- Veno-occlusive priapism occurred in a 25-year-old man with chronic renal insufficiency treated with epoetin. The episodes resolved after the epoetin dosage was reduced (107).

The exact mechanism of this adverse effect is not known. Several cases of priapism have been reported, and it has been hypothesized that androgen therapy probably contributes (107).

Immunologic

Occasionally low-titer antibodies have been reported in patients treated with epoetin (38,108). Neutralizing anti-erythropoietin antibodies have been found in patients with chronic renal insufficiency who develop pure red cell aplasia after subcutaneous administration of epoetin alfa (especially Eprex). This adverse effect was probably restricted to patients with renal insufficiency because they had used subcutaneous erythropoietin for many years. The incidence was calculated as one in 10 000 patients after 1 year of use of erythropoietin (82–84).

There is no evidence of antibody formation to darbepoetin alfa, probably in part owing to the fact that carbohydrate chains are rarely immunogenic (54,109,110). No antibodies to darbepoetin alfa were detected in over 1534 patients treated for 2 years (87).

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An allergic reaction led to early termination of epoetin treatment in one of 26 pregnant women treated with epoetin for iron deficiency anemia (26).

Anaphylaxis has been observed after the administration of epoetin that contained bovine gelatine as a stabilizer (2). Antibovine gelatine IgE antibodies were found. No anaphylactic reaction was observed after the administration of epoetin that contained human serum albumin as a stabilizer in the same patient.

Body temperature

Of 183 anemic cancer patients who did not receive chemotherapy in a prospective, open study, four had fever, possibly or probably related to the use of epoetin (22).

Long-Term Effects

Drug abuse

Epoetin has been abused by athletes, increasing the risk of hypertension and disseminated intravascular coagulopathy (10). In athletes epoetin causes increased blood viscosity, which will further increase during dehydration, leading to risks of myocardial infarction, cerebrovascular accident, or encephalopathy (10). Epoetin induces accelerated fibrinolysis, and so epoetin doping can be detected by analysis of fibrin degradation products in urine (10). In addition, hypochromic macrocytes are increased (10).

Susceptibility Factors

Age

The adverse effects of erythropoietin in neonates are minimal compared with adults. There were no hypertensive effects reported and no effect on development and growth measured at 18–22 months (111). In a multicenter, randomized, double-blind trial in 21 anemic HIV-infected children, who were concomitantly treated with antiretroviral drugs, epoetin was effective and safe (112).

In 30 preterm infants epoetin 300 μg/kg three times a week for 4 weeks reduced transfusion requirements without problems with tolerability (113).

High doses of epoetin in children undergoing long-term hemodialysis is associated with increased heparin requirements during hemodialysis, suggesting that careful monitoring of thrombotic events, especially in small children who need catheters for hemodialysis access, is warranted (114).

Drug Administration

Drug formulations

In the past, subcutaneous epoetin alfa resulted in more pain than epoetin beta, owing to citrate buffer in the product. Although the formulation of epoetin alfa has been changed to a phosphate buffer, discomfort after epoetin alfa is still greater than after epoetin beta (115,116).

Drug administration route

Epoetin can be administered in four ways: intravenously, subcutaneously, orally, and intraperitoneally (37). The subcutaneous route is preferred in patients undergoing dialysis, because subcutaneous epoetin provides better long-term utilization and maintains the same hematocrit with 20% lower dosages than intravenous administration. After intraperitoneal administration the absorption time is prolonged and only 5–10% of the dose is utilized (37). Local reactions occur at the site of injection when epoetin is given subcutaneously (117), and local pain has been reported after the administration of citrate- or phosphate-buffered epoetin (117,118).

After subcutaneous administration the systemic availability of epoetin is not complete (20%) and lower plasma concentrations are observed than after intravenous administration. However, the apparent half-life of epoetin is prolonged after subcutaneous injection, and this allows the use of lower doses to obtain an equivalent hemoglobin concentration (38). Subcutaneous injections are more effective when given thrice weekly rather than once weekly (38).

Patients with a skin-fold thickness of less than 20 mm at the injection site have a mean reduction in the maintenance dose of 36% when treatment is changed from two injections a week to daily injections (119). In patients with a thin layer of subcutaneous fat, the diffusion distance of epoetin to bloodstream is shorter than in patients with a thicker layer of subcutaneous fat. Therefore, the diffusion time in lean patients is shorter and the increase in plasma epoetin concentration is more pronounced but of shorter duration after each injection. More frequent injections of reduced amounts of epoetin creates an absorption curve whose area is more congruent with the area of the therapeutic plasma concentration.

Epoetin can also be given orally in premature infants, resulting in a significant increase in plasma epoetin concentration, increased peak reticulocyte counts, and reduced blood transfusion requirements (62,81).

In children undergoing peritoneal dialysis, epoetin is usually given intraperitoneally, resulting in similar systemic availability and dosages compared with subcutaneous administration. A follow-up study is required to determine if the risk of peritonitis is increased by intraperitoneal epoetin (120).

Drug–Drug Interactions

ACE inhibitors

During treatment of renal hypertension or heart failure with ACE inhibitors the response to epoetin therapy is reduced; this can be avoided by the use of angiotensin-II receptor antagonists instead (39).

Moxifloxacin

Possible synergy between erythropoietin and moxifloxacin was observed in a patient with myelodysplastic syndrome who did not respond to erythropoietin alone (121).

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Esmolol

See also Beta-adrenoceptor antagonists

General Information

Esmolol is a beta$_1$-selective adrenoceptor antagonist with an extremely short half-life (about 10 minutes), because of extensive metabolism by esterases in blood, liver, and other tissues.

Organs and Systems

Cardiovascular

Esmolol causes hypotension, sometimes symptomatic, in up to 44% of patients (1–3).

Drug Administration

Drug administration route

Irritation at the infusion site occurs in up to 9% of patients and depends on the duration of the infusion (4).

Drug–Drug Interactions

Digoxin

Esmolol increased digoxin concentrations by 10–20% in healthy volunteers (5).

Morphine

Co-administration of esmolol with morphine resulted in increased steady-state concentrations of esmolol (5).

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Esomeprazole

See also Proton pump inhibitors

General Information

Esomeprazole is the *S*-isomer of omeprazole. The pharmacology, pharmacokinetics, efficacy, and safety of esomeprazole have been reviewed (1). Esomeprazole produces acid control comparable to that of currently available proton pump inhibitors. It undergoes less hepatic metabolism than omeprazole, has an oral availability of 89% at a dose of 40 mg, and a half-life of 1.5 hours. Esomeprazole is well tolerated; its common adverse effects are diarrhea, headache, nausea, abdominal pain, respiratory infection, and sinusitis.

To assess symptom control, esomeprazole 20 mg on demand has been compared with placebo on demand (maximum of one dose a day) for 6 months in a multicenter, double-blind study in 342 endoscopy-negative patients with gastro-esophageal reflux disease (2). There was complete resolution of heartburn after 4 weeks of daily esomeprazole therapy. On-demand therapy with esomeprazole was significantly more effective than placebo in controlling symptoms. The frequencies of adverse effects and laboratory profiles were similar in the two groups when adjusted for the time spent in the study.

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To examine the pharmacokinetics and pharmacodynamics of esomeprazole, 12 healthy men took once-daily esomeprazole 5, 10, or 20 mg, or omeprazole 20 mg for 5 days in a crossover study (3). The pharmacokinetics of esomeprazole were time- and dose-dependent. There was greater acid inhibition with esomeprazole than with omeprazole.

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Estrogens

See also Individual agents

General Information

For a complete account of the adverse effects of estrogens, readers should consult the following monographs as well as this one:

- Diethylstilbestrol
- Hormonal contraceptives—emergency contraception
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens
- Hormone replacement therapy—estrogens + androgens
- Hormone replacement therapy—estrogens + progestogens.

The physiological secretion of endogenous estrogens rises and falls during the monthly cycle; it is much lower before the menarche and after the menopause than during the period of fertility. Any use of estrogens that deviates from this pattern is therefore unphysiological.

Types of estrogen

The primary estrogen in premenopausal women is 17-β-estradiol (E2), which is synthesized by developing ovarian follicles. Estradiol is oxidized to estrone (E1) and then to estriol (E3). Estrone is also produced in peripheral tissues by aromatization of androstenedione, an androgen precursor that is produced by both the ovaries and the adrenal glands; after the menopause, estrone produced in this way becomes the predominant estrogen. All of the estrogens are sulfated and glucuronidated before excretion.

Natural 17-β-estradiol undergoes first-pass metabolism when given by mouth, and other compounds have therefore been preferred for therapeutic purposes. For the estrogen component of the oral contraceptives, mestranol (ethinylestradiol-3-methyl ether) was originally used, but since it was suspected of adverse effects it was by 1969 largely replaced by unesterified ethinylestradiol. 17-α-estradiol has also been synthesized (or extracted from pomegranates) and studied, but it binds much more weakly than the 17-α congener to estrogen receptors. 17-β-estradiol in micronized form, to improve systemic availability, has also been used in various products, especially in Scandinavia.

For estrogen replacement therapy, the less potent estrogens, estrone and estriol, have been widely used, as well as the semi-synthetic compound epimestrol.

In North America, much publicity has for many years been devoted to the supposed merits of "equine estrogens," also known as "conjugated estrogens" (Premarin), described as comprising a natural product extracted from the urine of pregnant mares. However, since pregnant mares were an inadequate source of starting material, these preparations have for a long time apparently been based primarily on synthetic substances (estrone with some equilin), although in some products a small amount of natural material may be present. The Food and Drug Administration in the USA long took the view that sodium estrone sulfate and sodium equilin sulfate were the sole active ingredients of the original product, but this was challenged by the manufacturers, who adduced evidence that dehydroestrone sulfate, and perhaps other components, could play a role. Overall, however, the view seems to be that the effects of Premarin are similar to those of other weak estrogens, whether given singly or in combination.

For injectable formulations used in estrogenic hormone replacement therapy, various esters of beta-estradiol have been most widely used.

Estradiol (E2) (rINN)

As noted above, 17-β-estradiol has hardly been used by the oral route, except in micronized form. The micronized product is also available in the form of an intranasal spray for the treatment of menopausal symptoms; this can give rise to mild irritation, leading to sneezing (1).

Estriol (E3) (rINN) and estrone (E1) (rINN)

Estriol is a very weak estrogen, usually given in oral doses of 1–2 mg/day, which has effects similar to those of ethinylestradiol at about 1/100th of this dosage: that is the vulva and vagina respond, but there is little effect on the endometrium. Similar considerations apply to estrone and to conjugated equine estrogens; most of the activity in the latter is in fact due to the presence of sodium estrone, which appears to be added to most formulations, in view of the limited supply of genuine equine estrogens.

Epimestrol (rINN)

The adverse effects of epimestrol (3-methoxy-17-epiestriol), a very weak estrogen with some ovulation-inducing effects, are largely as one would expect. In one series, hot flushes, insomnia, anorexia, nausea, and vomiting were reported in 1.5%, headache in 3%, and uterine bleeding in 38% (2). Ovarian hyperstimulation is rare but not unknown. As is usual with such treatment, the incidence of the adverse effects reported varies greatly, no doubt

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reflecting differences in the motivation of the patients and the schemes of administration used.

Ethinylestradiol (rINN)
Ethinylestradiol is discussed under hormonal contraceptives.

Fosfestrol (rINN)
Fosfestrol is an unusual agent used in Japan for the treatment of prostatic carcinoma but not accepted by experts in Europe. Described as an estrogen, in European studies it had a high incidence of complications, including fluid retention (16%), myocardial infarction (10%), and thromboembolism (6.3%). A case of adrenocortical insufficiency has now been documented in Japan, involving a 59-year-old man who had taken the drug for 10 years (3).

Quinestrol (rINN)
Quinestrol is an ether of ethinylestradiol. It is stored in body fat and hence acts for weeks or months after a single oral dose; in the event of adverse reactions, this makes prompt termination of exposure impossible.

Non-steroidal estrogens
The non-steroidal estrogens diethylstilbestrol (rINN) and cyclofenine (rINN) are covered in separate monographs.

Uses

Estrogens are used principally for:

- relief of the symptoms of the menopause
- treatment of postmenopausal vaginal atrophy
- contraception, in combination with a progestogen
- hormone replacement therapy, alone or in combination with a progestogen, an androgen, or both.

Hormone replacement therapy should be distinguished from the short-term therapeutic use of estrogen (or hormonal combinations) around the time of the climacteric for the relief of acute (primarily vasomotor) symptoms; such treatment can generally be limited to some 6–12 months although if it is then withdrawn the symptoms may recur (4). Confusion between these two forms of treatment has led to a series of misunderstandings regarding the adverse effects of true hormone replacement therapy.

Oral contraception and hormone replacement therapy are dealt with specifically in separate monographs. Here the general adverse effects of estrogens for any indication are reviewed.

"Equine estrogens" (Premarin)

The controversy regarding the composition of Premarin and what are regarded as its generic equivalents has been outlined above. While still in use for hormone replacement therapy, these products have also been used as a means of reducing unwanted bleeding, for example in uremia (5,6), although their efficacy has been challenged. Estrogens have also been used in the treatment of bleeding in hereditary hemorrhagic telangiectasia (7,8).

General adverse effects

Salt and water retention due to estrogens can cause weight gain and a rise in blood pressure. Changes in liver function tests can occur and jaundice is sometimes seen. Mild gastrointestinal upsets are not unusual. Unwanted endocrine effects include uncomfortable stimulation of the breasts and endometrial bleeding. In men, estrogens produce gynecomastia. Hypersensitivity reactions are rare and include urticaria, edema, and bronchospasm.

Estrogens can be associated with endometrial carcinoma, liver tumors, and breast tumors; they can also promote the further growth of pre-existing estrogen-dependent tumors.

When conjugated estrogens are used to control bleeding they are generally given only in short courses and are therefore well tolerated. As recommendations for control of bleeding involve administration of Premarin on a limited number of occasions (no more than five or seven doses) the usual hormonal problems associated with estrogens will be avoided. Gross hepatic disease is regarded as a contraindication. Headache, flushing, and nausea have been observed after intravenous injections and slow injection is therefore recommended.

Men taking estrogens generally do so in the course of palliative treatment for malignancies (prostatic carcinoma), for which high doses have sometimes been used. Estrogen therapy in men with prostate cancer may be superior to castration in terms of efficacy, but orally administered estrogens are associated with adverse effects: gynecomastia, loss of sexual function, and unacceptable cardiovascular toxicity (9). Low-dose estrogens in combination with anti-androgens or antithrombotic agents may be better tolerated.

Estrogenic effects of non-estrogens

Over the last 50 years, it has been realized that environmental chemicals, such as pesticides and industrial chemicals, can have hormone-like effects in wildlife and humans (10). These chemicals may:

- mimic the effect of endogenous hormones
- antagonize the effect of endogenous hormones
- alter the synthesis and metabolism of endogenous hormones
- alter the synthesis and metabolism of hormone receptors.

There have been reports that aviation crop dusters handling DDT had reduced sperm counts and workers at a plant producing the insecticide kepone had reduced libido, became impotent, and had low sperm counts. Subsequently, animal experiments showed that these pesticides have estrogen-like activity. Man-made compounds used in the manufacture of plastics interfered with experiments on natural estrogens. Some detergents and antioxidants are not themselves estrogenic, but on degradation during sewage treatment can release estrogenic alkyl phenols, such as bisphenol-A, nonylphenol, and phenylphenols. Polycarbonate flasks release bisphenol-A, which can also contaminate the contents of canned food in which polycarbonate coatings are used; bisphenol-A is also used in dental sealants and composites and can leach from teeth into saliva. Polystyrene tubes can release

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nonylphenol. The surfactant nonoxynol is used as intravaginal spermicide and condom lubricant; in animals it is metabolized to free nonylphenol. Other xeno-estrogens include the plasticizers benzylbutylphthalate and dibutylphthalate, the antioxidant butylhydroxyanisole, the rubber additive *para*-phenylphenol, and the disinfectant *ortho*-phenylphenol.

Organs and Systems

Cardiovascular

Estrogens have both wanted and unwanted effects on the cardiovascular system, depending on the manner in which they are used. Hormone replacement therapy is used in the hope of reducing the risk of ischemic heart disease after the menopause. The reduction in risk may be as much as 50% and is attributed variously to vasodilatation mediated by the endothelial production of prostaglandin I_2 (prostacyclin), effects on coagulation factors and endothelial function, and improvements in serum lipids (increased concentrations of HDL cholesterol and reduced concentrations of LDL and total cholesterol) (11), but variable effects on triglycerides. However, estrogens (especially as used in contraception but also postmenopausally) can have a marked effect on clotting factors and renin substrate, increasing the risk of thromboembolism.

The Coronary Drug Project in men taking different doses of estrogens showed a dose-related increase in myocardial infarction and thromboembolic diseases (12).

Respiratory

Allergic bronchospasm occurs very rarely with estrogens (13), but has been reported several times in women with an existing allergic tendency or a history of asthma; some asthmatic women have worse symptoms during the luteal phase of the menstrual cycle. In affected cases, the link with estrogens can be demonstrated by rechallenge.

Nervous system

Various types of headache can occur; in patients with migraine, attacks can be precipitated, usually with prominent visual phenomena.

- In a woman with history of chorea in the distant past, a vaginal cream containing estrogens precipitated an attack.

In a randomized, double-blind, placebo-controlled arm of the Women's Health Initiative, 10 739 postmenopausal women, aged 50–79 years, with prior hysterectomies, were randomly assigned to receive either conjugated equine estrogen 0.625 mg/day or placebo. There was an increased risk of stroke (RR = 1.39; 95% CI = 1.10, 1.77).

Sensory systems

Retinal vein occlusion (14–17), retinal artery occlusion (18), and optic neuritis (19,20) have been described in women taking estrogens.

In older women, estrogens cause a slight rise in intraocular pressure (SED-12, 1031) (21).

Psychological, psychiatric

The effects of estrogens on mood tend to be positive, and improved performance in intellectual tests has been described (SEDA-20, 382) (22); this is in parallel with the known effects of endogenous estrogens. During the menopause some women become depressed and irritable, and the ability of estrogens to correct this has been delineated in various studies, including work with estradiol given transdermally (23). Some workers also claim increased vigilance, and have concluded that this is reflected in encephalographic changes. There is even some evidence of an improvement in mental balance and self-control when estrogens are given to demented and aggressive old people of both sexes (24). However, all of these effects of estrogens on mood or mental performance are only likely to last for as long as the treatment does, and the effects on mood may occur only at the start of treatment; altered mood can follow acute withdrawal.

Endocrine

In postmenopausal women taking long-term mestranol there was a fall in the serum concentration of unbound (free) thyroxine, but it was not associated with hypothyroidism; the serum concentration of thyroid-stimulating hormone was unchanged (25).

Metabolism

Conflicting data concerning the effects of oral contraceptives on carbohydrate metabolism have been presented; the effects are probably clinically insignificant. However, estrogen hormone replacement therapy with a sequential-type product containing mestranol and norethisterone caused significantly impaired glucose tolerance (26).

There is no doubt that with appropriate treatment regimens, altered lipid metabolism due to estrogens can improve (27). In women with familial hypertriglyceridemia or increased triglycerides from other causes, oral estrogens can increase triglyceride concentrations. However, transdermal estrogens can lower triglycerides and generally produce smaller changes in lipoproteins than oral therapy, although it may be that whatever differences are observed merely reflect differing degrees of absorption.

Porphyria can be precipitated by estrogens, and familial porphyria cutanea tarda can become manifest (28).

Metal metabolism

Estrogens increase serum copper concentrations (SED-12, 1030) (29).

Fluid balance

Retention of water and salt and consequent weight gain are common during estrogen therapy. Fluid retention can cause a feeling of abdominal pressure, sensations resembling the premenstrual syndrome, breast tenderness, bloating, and edema. These symptoms can largely be relieved by a mild diuretic, but it is only practicable to use this approach if the estrogen treatment is cyclical and

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the symptoms thus intermittent, since it is undesirable to give diuretics continuously to healthy women over a long period of time.

Hematologic

There is a risk of thrombosis with estrogens, discussed in detail in the monograph on Hormonal contraception. Both superficial and deep complications can occur in either sex. Effects on clotting factors and renin are involved: in one small study, men taking estrogens had increased concentrations of factor VII, factor VIII, and fibrinogen, pointing to a hypercoagulable state and platelet activation (30).

In hormone replacement therapy, the risk of deep vein thrombosis is increased by a factor of 2–4 (31–33). The absolute increase in the treated population as a whole is low, with about one case of venous thromboembolism in 5000 women-years of use of hormone replacement therapy. However, in the subgroup with pre-existing risk factors, such as obesity, varicose veins, smoking, and a prior history of venous thromboembolism or superficial thrombophlebitis, the increase in risk from hormone replacement therapy can be substantial; among these women are those with a genetic predisposition to thrombosis, generally due to some form of thrombophilia, such as deficiency of the coagulation inhibitors protein S, protein C, or antithrombin III. In any of these subjects thrombosis can occur early in hormone replacement therapy. However, this tendency to early occurrence of deep vein thrombosis also seems to be present in all those who take hormone replacement therapy.

The mechanisms of thrombotic complications are multiple. Fibrinolytic activity falls in postmenopausal women when a high dose (250 micrograms/day) of ethinylestradiol is given for 10 days in preparation for prolapse operation (34). On the other hand, long-term administration of mestranol 80 micrograms/day to postmenopausal women for 1 year or longer increased the concentrations of fibrinogen and l-trypsin inhibitor and reduced plasminogen (SED-12, 1030) (35). There is also evidence that even low doses of oral estrogens increase the amount of thrombin generated in vivo.

It has been suggested, on the basis of a case of multiple systemic arterial thrombi in a patient with a prosthetic heart valve, that if estrogens are needed in such individuals they should be combined with anticoagulants. One would be inclined to extend the warning: any woman with a pre-existing risk of thrombosis should be examined very carefully before deciding to give estrogens at all.

The hypercoagulability that can occur with conjugated estrogens has been reported to be less pronounced than with oral contraceptives, but it is not clear that it is less than that seen with other types of estrogen used in hormone replacement therapy (36). The hematological effects of different estrogens are additive; various reports have demonstrated this for ethinylestradiol and diethylstilbestrol (37), which would mean that nothing would be gained by using several estrogens in parallel at reduced doses.

Some work suggests that when estrogens are given parenterally or transdermally rather than orally, the unwanted effects on the clotting process are reduced (38). The most important pharmacokinetic difference is that first-pass metabolism in the liver is avoided in all forms of non-oral therapy, which in the case of estrogens includes percutaneous gels, implants into the abdominal wall or buttocks, transdermal patches, and vaginal tablets, rings, and creams. It may therefore be prudent to use transdermal estrogens or another form of parenteral therapy when seeking to prevent osteoporosis in women with a tendency to thrombosis or hypertension.

For reasons that are not clear, other facets of the blood system are also affected by estrogens. After 6-months treatment with low doses of conjugated estrogens, hemoglobin concentration and mean erythrocyte counts were significantly reduced (39); on the other hand, the hematocrit was significantly increased by high-dose estrogen + androgen at 6 months, while the mean white blood cell count was significantly increased by low-dose estrogen + androgen at 12 months (39).

Mesenteric venous thrombosis has been reported in men taking estrogen therapy for carcinoma of the prostate (SED-12, 1032) (40).

Gastrointestinal

Estrogens can cause dose-related nausea, which is not reduced by using enteric-coated tablets. It has been claimed that there is a significantly lower incidence of nausea with estrogen + androgen than with conjugated estrogens.

Intestinal ischemia has occasionally been attributed to conjugated estrogens (22,41).

There is some reason to distinguish this from the ischemia that can be caused by oral contraceptives, in that it is restricted to the colon, can have a chronic or remitting course, can present with non-specific abdominal and colonic symptoms, can be reversible despite continued use of estrogen, and does not require surgical treatment. The symptoms of intestinal ischemia resolve within days to weeks after withdrawal of the estrogen. However, oral contraceptives have also been reported to cause ischemic colitis.

- A 19-year-old woman developed abdominal cramps, nausea, vomiting, diarrhea, and rectal bleeding (42). She was taking no medications other than Norinyl-2 (norethindrone 2 mg and mestranol 1 mg), which she had taken for 6 months. Just before the onset of the symptoms she had taken dimenhydrinate 100 mg and two ExLax tablets (90 mg of phenolphthalein) for constipation. Colonic X-rays showed impaired mesenteric circulation and bowel ischemia. Her symptoms subsided within 96 hours of withdrawing the oral contraceptive and giving supportive therapy (including intravenous fluid infusion, nasogastric suction, analgesics, and antiemetics). Further radiology showed that the ischemia had resolved.

Estrogens can cause or aggravate constipation (43), but when it occurs it is more likely to be due to the calcium carbonate that many women take as a daily supplement in postmenopausal treatment.

Liver

Changes in liver function tests can occur during estrogen treatment (44). In one comparative study, ethinylestradiol had an unfavorable effect on liver protein synthesis (SED-12, 1030) (45).

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Cholestatic jaundice has often been reported with oral estrogens and is probably related to an effect on the permeability of the canalicular membrane (SEDA-20, 381). Cholestatic jaundice induced by a subcutaneous estrogen implant has also been reported in the absence of any other cause of liver disease (SEDA-20, 381). After removal of the implant the patient's symptoms resolved. The authors' explanation was that fragmentation of the implant had led to release of excessive amounts of estradiol.

The effects of estrogens on liver function differ with the type of estrogen used, problems being particularly associated with 17-substituted steroids. Significant reductions in transaminases, lactate dehydrogenase, and alkaline phosphatase have been found at 6 and 12 months with various forms of estrogen therapy. A reduction in mean bilirubin concentration has been described at 6 months with high-dose conjugated estrogens, and a significant increase in mean bilirubin concentration with low-dose estrogen + androgen at 12 months.

In some studies, women taking estradiol or conjugated estrogens for hormone replacement therapy had no cholestasis or hepatotoxicity, as assessed by rises in serum alkaline phosphatase, bilirubin, or transaminases, whereas these effects did occur with ethinylestradiol.

Pancreas

There is a small but significant risk of acute pancreatitis at 2–78 weeks after the start of hormone replacement therapy; the pain usually abates within 10 days of withdrawal (46).

Urinary tract

In the past, hypernephroma was thought to result from estrogen treatment. However, there is no clear evidence that this is so. There is evidence that older women with an intact uterus become more susceptible to urinary tract infections by taking estrogens (47). This is surprising, since some other studies, admittedly in selected patients, have shown a reduction in such infections when hormone replacement therapy is used. In another study, hormone replacement therapy improved urinary incontinence and nocturia after 6 months in postmenopausal women, without affecting bacteriuria (48).

Skin

Diffuse prickly erythema has been attributed to ethinylestradiol in various oral contraceptive formulations.

- A woman taking an oral contraceptive (Marvelon, ethinylestradiol 30 micrograms + desogestrel 150 micrograms) developed diffuse prickly erythema in an exposed site less than 20 minutes after sun exposure (49). Phototesting showed photosensitivity in the UVB and UVA ranges, but routine patch and photopatch tests with Marvelon were negative. All abnormal findings reversed 4 months after withdrawal of the oral contraceptive, but reappeared when she started using another oral contraceptive (Microgynon 30, ethinylestradiol 30 micrograms + levonorgestrel 150 micrograms). Phototesting was again abnormal. Her symptoms disappeared after withdrawal of the oral contraceptive. Porphyrin production was normal.

Although the estrogen and progestogen were not tested separately in this patient, the photosensitivity was most probably due to the estrogen, because the oral contraceptives that she used contained ethinylestradiol 30 micrograms with different progestogens, and photosensitivity has been described with estrogens (50).

- A 47-year-old postmenopausal woman developed eczematous lesions at the sites of application of an estradiol transdermal system and subsequently at the sites of application of an estradiol gel (51). She was therefore given oral estrogen instead, but this promptly elicited a systemic pruritic rash. The causal link was in all instances confirmed by patch-testing.

Estrogens can cause chloasma (52).

Papillomatous melanocytic nevi can be induced by estrogens (53), and melanocytic lesions can contain large numbers of estrogen and progestogen receptors (54).

When transdermal estrogens are used there can be problems with poor adhesion and skin irritation. The latter occurs more often in hot humid weather and can rarely proceed to edema, induration, a vesicular rash, residual pigmentation, itching, and erythema (55).

Three patients developed erythema nodosum during estrogen replacement therapy (56).

Topical estrogens can reduce skin aging (57), for example with reduced wrinkling and increased firmness in the dermis of perimenopausal women, although it is not clear that the effect is more marked than with oral treatment. Certainly, estrogens augment dermal water content by increasing hyaluronic acid and mucopolysaccharides, improving the structure of elastic fibers, and increase vascularization.

Sexual function

Libido, sexual activity (including masturbation), and orgasm increase in women taking the combination of an estrogen with an androgen, but it is not clear that estrogens alone have any such effect (58,59). Reduced libido and reduced sexual activity are to be expected in men treated with estrogens.

Reproductive system

All estrogens, even less potent ones, can cause endometrial hypertrophy and bleeding in a proportion of users after the menopause; in high doses the complication is common (60). With continuous estrogen therapy, the bleeding is irregular and unpredictable, whereas cyclical use of a combination with a progestogen is likely to produce something resembling normal menstruation, although it generally abates as treatment continues (60).

Estrogens can cause painful tingling and swelling of the breasts, sometimes requiring withdrawal of treatment. Frank gynecomastia can occur in men by exposure to estrogens in a factory environment and has even been described in an elderly man whose wife used an estrogen-containing vaginal lubricant (SEDA-6, 350).

In men, estrogens cause pigmentation of the areola followed by gynecomastia, both during oral treatment and local application (61). Estrogen-induced

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gynecomastia can be prevented in men with prostatic carcinoma by irradiating the breast region before starting therapy.

Immunologic

Estrogens can have adverse immunological effects, which could predispose to infections (62).

The immunological effects of two contraceptive combinations, namely Valette (dienogest 2.0 mg + ethinylestradiol 0.03 mg) and Lovelle (desogestrel 0.15 mg + ethinylestradiol 0.02 mg), have been examined during one treatment cycle (63). Lovelle significantly increased the numbers of lymphocytes, monocytes, and granulocytes. Valette reduced the CD4 lymphocyte count after 10 days and Lovelle did the opposite. Lovelle increased CD19 and CD23 cell counts after 21 days. Phagocytic activity was unaffected by either formulation. After 10 days both contraceptives reduced serum IgA, IgG, and IgM concentrations, which remained low at day 21 with Lovelle but returned to baseline with Valette. Secretory IgA was unaffected by either contraceptive. Neither treatment affected concentrations of interleukins, except for a significant difference between the treatment groups in interleukin-6 after 10 days, which resolved after 21 days. Concentrations of non-immunoglobulin serum components fluctuated; macroglobulin was increased by Valette. However, total protein and albumin concentrations were reduced more by Lovelle than Valette. Complement factors also fluctuated. There was no evidence of sustained immunosuppression with either Valette or Lovelle.

A severe anaphylactic reaction occurred in one patient who was given an intravenous formulation of conjugated estrogens (SED-12, 1033) (64). Some formulations of conjugated estrogens contain foreign (equine) material.

Long-Term Effects

Tumorigenicity

For the sake of simplicity the carcinogenic effects of estrogens in all formulations, including the combined oral contraceptives, are included here.

Knowledge of tumor induction by sex steroids is largely based on interpretation of epidemiological data, with careful exclusion of possible confounding elements. Hepatic tumors have given rise to most concerns, but some evidence also indicates an increased incidence of various other malignancies, including carcinomas of the breast, endometrium, and prostate (65).

The overall incidence of reproductive cancers attributable to oral contraceptive use has been estimated in a modeling analysis (66). The authors assumed a 50% reduction in ovarian and endometrial cancers associated with 5 years or more of tablet use, and used two alternative scenarios for breast and cervical cancer effects. If oral contraceptive use produces a 20% increase in breast cancer before age 50 and the same increase in cervical cancer, then for every 100 000 tablet users there would be 44 fewer reproductive cancers and these users would gain one more day free of cancer. If instead the increase in risk of early breast cancer and of cervical cancer is 50%, oral contraceptive users would have 11 fewer cancer-free days.

Liver tumors

In dealing with liver tumors, it is essential to consider all the various types of sex steroids in a single review since they seem to resemble one another closely in their long-term effects on this organ. The nomenclature used in the literature is unfortunately confusing: most reports differentiate between "hepatic adenoma" and "focal nodular hyperplasia," but the latter term is also sometimes used to cover the whole range. Other terms that have been used are "focal cirrhosis," "regenerative hyperplasia," "hamartoma," "mixed adenoma," and "benign hepatoma," while "peliosis" may constitute a precancerous state.

Androgens and anabolic steroids

There is no essential difference between androgens and so-called anabolic steroids. High doses of either, such as can be used in refractory anemias, have been associated with the induction of benign liver tumors and primary hepatocellular carcinoma. The fact that primary hepatoma, liver adenoma, and peliosis are uncommon conditions and that there is a considerable overlap between the patients concerned and the tiny fraction of the population taking high-dose androgens strongly suggests that the association of both events is more than coincidental (67). Some animal studies and in vitro studies have also pointed to a hepatic carcinogenic effect of anabolic steroids. No cases seem to have been described in sportsmen who have used high-dose androgens or in girls suffering from precocious puberty, but the former at least often use these drugs for relatively short periods; furthermore, such use is likely to be surreptitious and thus poorly documented. Most of the widely used compounds in this class, including methyltestosterone, have been reported to induce liver tumors. The apparent exceptions are the nortestosterone derivatives without 17-alpha substitution. Whether these drugs are indeed safer or whether they have merely been used less often in high doses is not known.

The incidence of liver tumors following the use of androgens and anabolic steroids still cannot be calculated. What is clear is that if these products are used in high doses or over long periods of time (and there is now much doubt about whether they are more than marginally effective in such conditions as osteoporosis and aplastic anemia), techniques such as CT scanning and ultrasonography should be used routinely to ensure early detection of liver lesions.

Oral contraceptives, estrogens, and benign liver tumors

The effects of oral contraceptives on the liver include not only benign liver tumors (focal nodular hyperplasia, hepatic adenoma, and hemangioma) (68) and hepatocellular carcinoma, but also peliosis hepatis (69), sinusoid dilatation (70), and such probably unrelated shorter-term complications as jaundice and gallstones.

However, the causal association between oral contraceptives and certain benign liver tumors has been well documented in humans, and the same association arises with conjugated estrogens (71), diethylstilbestrol, and

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probably antiestrogens. The evidence for the link is based on many case reports, reviewed in SEDA, and on some case-control studies, which first appeared in 1976 and 1981, pointing to a correlation (SED-14, 1450). The relative risk of benign liver tumors in users of conjugated estrogens or oral contraceptives compared with non-users may be about 40:1, although the figure is still low in absolute terms. Animal studies suggest in fact that estrogens, taken alone or in combination with progestogens, can increase the size of pre-existing liver tumors, but do not initiate tumor formation themselves; however, whether these formulations actually induce tumors or promote a latent tendency to tumor development is not of essential importance. Although there is some evidence that liver cell adenomas can regress after oral contraceptives are withdrawn (72), they do not always do so (73).

It is clear that any woman with "pill"-associated liver lesions should avoid all further use of hormonal contraceptives and related products.

Oral contraceptives and malignant liver cancer

Malignant cancer of the liver is still a very rare disease in young women, but case-control studies are possible. Evidence from both sides of the Atlantic suggested from 1987 onwards that there might be a significant relation between oral contraceptives and hepatocellular carcinoma (74–76). However, even the best of these studies had some limitations, for example incomplete data as regards a history of hepatitis or the extent of contraceptive use. One authoritative attempt to estimate the degree of risk was made by the World Health Organization in 1989, matching 122 newly diagnosed cases of primary liver cancer to 802 controls; the relative risk of liver cancer in women who had at any time used combined oral contraceptives was estimated at 0.71; there was no consistent link with months of use or time since first or last use (77). A major examination of the issue appeared in 1992, when it was concluded that the relative risk for sometime users of oral contraceptives was 1.6, rising to 2.0 in those who used the products for more than 10 years (78).

In a review of the earliest studies of hepatocellular carcinoma, it was concluded that oral contraceptives may not interact with other hepatic carcinogens, and that if they do not interact they may not measurably enhance the risk of liver cancer in parts of the world where hepatitis B virus is endemic and hepatocellular carcinoma is common (79). Others have since suggested a positive association between parity or gravidity and hepatocellular carcinoma, which needs to be further explored (80).

Conjugated estrogens

The same association with benign liver tumors arises with conjugated estrogens (71), diethylstilbestrol (q.v.), and probably antiestrogens. The evidence for the link is based on very numerous case reports from the field, reviewed in the Annuals in this series, but also on some case-control investigations. Studies of the latter type first appeared in 1976 and 1981, and both pointed to a correlation (SED-12, 1024). The relative risk of benign liver tumors in users of conjugated estrogens or oral contraceptives compared with non-users may be about 40:1, although the figure is still low in absolute terms.

Uterine tumors

The extent to which tumors of the reproductive tract are associated with hormonal treatment varies greatly with the type of tumor and the type of treatment involved.

Hormonal replacement therapy and endometrial carcinoma

In untreated women, the main risk factors for endometrial carcinoma are age, obesity, nulliparity, late menopause (and possibly early menarche), the Stein–Leventhal syndrome, exposure to exogenous estrogens, radiation, and certain systemic diseases, including diabetes mellitus, hypertension, hypothyroidism, and arthritis (SED-14, 1451) (81). Certain of these risk factors indicate that an altered endocrine state with increased estrogen stimulation is a predisposing cause, and one might thus in theory expect estrogen treatment (and notably hormonal replacement therapy) to increase the risk (SEDA-22, 466).

In women with an intact uterus, the risk of endometrial hyperplasia and cancer increases with increasing dose and duration of estrogen use. Adding a progestogen to estrogen-only therapy for at least 12 days a month greatly reduces this risk. However, it is not clear why the complication develops only in certain users. The risk of developing endometrial cancer during HRT seems to vary individually, perhaps because of genetic rather than exogenous factors. In women with endometrial cancer, women who reported ever taking HRT were more than twice as likely to develop endometrial cancer as women who had never taken it (OR = 2.24; 95% CI = 1.19, 4.23) and among these women the risk of endometrial cancer was higher for women homozygous for the CYP17 T-allele (OR = 4.10; 95% CI = 1.64, 10.3), but not for women with the C-allele. These preliminary findings suggest that CYP17 or other variants in estrogen biosynthesis or metabolism pathways may be markers of susceptibility to endometrial cancer among users of estrogen replacement therapy (82).

Two epidemiological studies published in 1975 first suggested that the use of estrogens during and after the menopause increased the risk of endometrial cancer, and in 1986 the authors of an authoritative review (83) endorsed these findings, concluding that there was an increase in risk among users, relative to non-users, of 4–9 times; the risk increased with both the strength of the medication and the duration of use. A 1990 review of data up to that time suggested that estrogen replacement therapy, continued for over 2 years without concurrent progesterone therapy, was associated with an approximately three-fold increase in the risk of both localized and extrauterine cancer; this risk increased with duration of use and persisted for over 6 years after withdrawal of therapy (84). These studies have been criticized from a methodological point of view, particularly since there is evidence of a detection bias that arises from the increased diagnostic attention received by women with uterine bleeding after estrogen exposure and perhaps also from a greater tendency of women to bleed from a pre-existing tumor when

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estrogens are given (85). It could be that the magnitude of the association between estrogens and endometrial cancer has been greatly overestimated for such reasons, and that the real odds ratio is less than estimated, but it seems unlikely that the risk can be disproved. There is, for example, some older evidence that even when the above-mentioned bias has largely been eliminated, there is still a correlation between the use of estrogens and endometrial carcinoma, the evidence being strongest for the first-generation oral contraceptive products, which contained large amounts of estrogen. One such study still found a six-fold risk among estrogen users compared with non-users (86); long-term users (over 5 years) had a 15-fold risk; there were excess risks for both diethylstilbestrol and conjugated estrogens. Another well-controlled study, from 1986, similarly found increased risks with conjugated estrogens, the greatest increases in risk being associated with a dosage of 0.625 mg/day or greater and duration of use of 10 years or more (87). Although according to this study the risk remained high even among women who had stopped using conjugated estrogens 5 or more years before, one cannot ignore an earlier finding, based on evidence from a large group practice, that a sharp downward trend in the incidence of endometrial cancer occurred in parallel with a substantial reduction in prescriptions for replacement estrogens (88).

Among the many papers that have since then incriminated estrogens, particularly the conjugated estrogens so widely used in North America, some have presented more subtle conclusions. One paper specifically incriminated estrone (89), but this is of course a major component of conjugated estrogens. A case-control study from Buffalo, New York, found that while patients with endometrial cancer and healthy controls had used similar amounts of menopausal estrogens, estrogen users had a significantly higher frequency of low-grade tumors and a correspondingly better survival rate (90). Menopausal estrogens became popular much later in Europe, and relatively little evidence has emerged to complement the US findings. In 1983, however, when Persson in Sweden completed a very large cohort study, he found that while among women treated with estrogens there was no significant increase in endometrial cancer compared with the control population, there was indeed a significantly increased incidence of premalignant lesions among women who had used estrogens alone for more than 3 years (91). A protracted case-control study in a Swiss population pointed in the same direction; the use of HRT for 5 years or more created a mean relative risk of 1.9, and use for 5 years or more a relative risk of 5.1 (CI 2.7, 9.8) (92). This, as well as evidence that progestogens have some protective effect on the endometrium (93), emphasizes the need for prospective studies in different subpopulations taking different types of replacement therapy.

Some helpful evidence comes from related fields. It should be borne in mind, for example, that the question of an increased risk of endometrial hyperplasia and endometrial cancer also arises in patients with estrogen-producing tumors of the ovaries, obesity, and polycystic ovarian syndrome (94) and in patients with breast cancer who are using tamoxifen (95).

During one 3-year study, under 1% of 596 women taking placebo or an estrogen + a progestogen had an abnormal endometrial biopsy. Of women taking an unopposed estrogen, 12% developed typical hyperplasia, 23% complex hyperplasia, and 28% simple hyperplasia. Use of HRT for 15 or more years resulted in a significantly higher relative risk of 1.3 for breast cancer, but was also associated with a significantly lower total mortality (96). The use of combined therapy was not associated with an increased risk of endometrial carcinoma, unless the progestogen was added for less than 10 days each month (97).

Detailed studies may also help to clarify further the risks and the possible interaction of estrogens with other susceptibility factors for endometrial tumors; there is, for example, an impression that the risk is greater in lean than in overweight women, although upper abdominal obesity is thought to reflect a higher risk. Patients who develop endometrial cancer often have an increase in estrogen production, reduced ovulation, and a lower sex hormone binding globulin concentration, resulting in high concentrations of free estrogen. As regards subjects of low susceptibility, the cancer threat may be less in women who have used oral contraceptives earlier.

One can also recognize some correlations between the subtype of tumor and the type of hormonal exposure. Unopposed hyperestrogenism is most likely to be associated with the endometrioid type of endometrial carcinoma, rather than with clear-cell, serous-papillary, and mucinous carcinomas.

Remarkably, the survival curves for women taking estrogens and developing adenocarcinomas are actually better than in women not taking estrogens and not developing adenocarcinomas. In 1822 women with angiographically documented severe coronary artery disease, the mortality among estrogen users was 4% compared with 35% among non-users, suggesting that the benefit of postmenopausal estrogen replacement therapy may be even greater in women with established coronary artery disease than it is in healthy women. A possible explanation is that estrogen replacement therapy in postmenopausal women reduces the risk of coronary heart disease by 5% or more.

Like a history of breast cancer, a history of cancer of the endometrium is commonly regarded as a reason to avoid HRT with estrogens. One study, though limited in duration, provided encouraging evidence that such treatment at least does not adversely affect the rate of recurrence or the survival time (98).

Of 249 women with surgical stage I, II, and III endometrial cancer treated between 1984 and 1998, 130 used estrogen replacement after their primary cancer treatments and half of these used progesterone in addition to estrogen. Among this cohort, 75 matched treatment-control pairs were identified. The hormone users were followed for a mean of 83 months and the non-hormone users for a mean of 69 months. There were two recurrences among the 75 HRT users compared with 11 recurrences in the 75 non-hormone users. Hormone users had a statistically significant longer disease-free interval than untreated women. Whether this is sufficient to conclude that the effect is actually positive is not clear, but no evidence of an increase in risk came to the fore.

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In view of the possibility that HRT can trigger malignancy in the endometrium itself, it is not surprising to find that it has also been reported to do so in endometriosis deposits elsewhere. An adenocarcinoma arose after many years of HRT in abdominal areas of endometriosis in a woman who had undergone hysterectomy and salpingo-oophorectomy 17 years before (99). It is of course known that some 1–2% of endometriosis deposits undergo malignant degeneration, and the link with HRT could therefore have been fortuitous.

The minimum dose of continuously administered norethindrone acetate needed to reduce significantly the incidence of endometrial hyperplasia associated with the use of 17-β-estradiol 1 mg/day has been investigated in a large, controlled, comparative study in 1146 women over 12 months (100). The results suggested that continuous norethindrone acetate at doses as low as 0.1 mg/day is fully effective, at least during the first year of treatment.

The evidence that concurrent use of progestogens reduces the risk of cancer induction needs to be further supplemented; if this beneficial effect of progestogens truly exists, one must still determine how they can best be used. They are widely used, but not consistently, and increase the risk of endometrial cancer both during and after treatment. Some workers have recommended that for partial protection of the endometrium, dosages of medroxyprogesterone acetate of 2.5 mg/day continuously or 5.0 mg/day given for 14 days per cycle are the minimum required to counteract the endometrial effects of continuous therapy with estrogens (101). The added medroxyprogesterone is claimed to have no effect on the efficacy of the estrogen in treating vasomotor symptoms or in preventing osteoporosis. Others have concluded that administration of continuous rather than cyclical estrogen + progestogen therapy is more likely to maintain the beneficial effects of the estrogen and yet protect against the increase in endometrial carcinoma that occurs with estrogen therapy alone (102). However, progestogens have a negative impact on circulating lipids (55); it is possible that this adverse effect is less when using natural progesterone, but this is hardly practicable. The risk of endometrial hyperplasia and endometrial cancer with estrogens given alone must therefore be balanced against this negative impact.

Thus, although our knowledge is still incomplete and needs to be extended, it is highly likely that estrogen replacement therapy given without progestogens considerably increases the risk of endometrial carcinoma. It seems likely that the use of concurrent progestogen treatment reduces the risk, but it is still uncertain how this supplementary treatment can best be administered.

The possibility that the risk of endometrial complications might have been incorrectly estimated and commonly underestimated has been examined with the hypothesis that the method of endometrial examination or sampling is crucial (103). Hysteroscopy was performed in 98 menopausal women with endometrial thickening, and the findings were matched with those of histopathology based on various means of tissue collection, including suction curettage, oriented-streak curettage, hysteroscopically targeted biopsies, or polypectomy and hysterectomy. There was an abnormal endometrium in 35 patients (65% in symptomatic and 22% in asymptomatic women) and there were six carcinomas, 18 polyps, and 11 cases of hyperplasia. Hysteroscopy had a sensitivity of 89% and a specificity of 98%. With blind sampling, tissue collection was too scant to make diagnosis possible in 29% of patients, while in 81% of patients in whom hysteroscopy showed cystic atrophy the pathologist failed to confirm this condition. Moreover, eight endometrial polyps (36%) detected by hysteroscopy were missed when samples were studied in the laboratory. Hysteroscopy with targeted sampling thus appears to be the most effective method for assessing the endometrial lining and detecting unwanted changes.

The endometrial effects of transdermal sequential combination therapy with estradiol and levonorgestrel in various doses has been examined over 1 year in 468 postmenopausal women, who each month used patches that released estradiol for 1 week followed later in the month by combined patches that released both estradiol and levonorgestrel, again for 1 week (104). The dose of estradiol was 50–100 micrograms/day and that of levonorgestrel 15–20 micrograms/day. Endometrial biopsies, obtained from 399 subjects, generally showed good tolerance for all the various combinations tested. However, there were two cases of endometrial hyperplasia at the highest doses, while the lowest dose was associated with less bleeding than the two higher doses and a somewhat different histological pattern.

Oral contraceptives and endometrial cancer

Suggestive case histories raised at an early phase the notion of a possible correlation of oral contraceptives with endometrial cancer. Among cases of endometrial cancer there seemed to be an excess of users of oral contraceptives, particularly of the early high-dose estrogen type. With the virtual demise of these early products, the situation seems to have reversed: a 1983 study from the Centers for Disease Control (CDC) in Atlanta showed that women who had used fixed combinations for oral contraception at some time in their lives had a relative risk of endometrial cancer of only 0.5 compared with never-users (105). The protective effect occurred only in women who had used oral contraception for at least 12 months, and lasted for at least 10 years after withdrawal. The WHO adopted the same view in 1988 in the light of multinational data (106). As in the case of hormonal replacement therapy, the protective effect seems to be due to the progestogen component.

Many studies have also shown a duration-related protective effect of combined oral contraceptives on endometrial cancer, the risk before age 60 being reduced by 38% after 2 years of use and up to a 70% reduction after 12 years (107). This beneficial effect continued for at least 15 years after the end of use. As with ovarian cancer, the CASH study results suggest that the lower-dose combined oral contraceptives have a protective effect similar to that of the higher-dose tablets (108).

Oral contraceptives, cervical neoplasms, and adenosis

A 1988 statistical analysis of data from the Royal College of General Practitioners study in Britain pointed clearly to an association between oral contraceptive use and cervical neoplasms (109); of 47 000 women followed

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since 1965, those who had at some time used oral contraceptives had a significantly higher incidence of cervical cancer than never-users after standardization of other variables, including a history of sexually transmitted disease. The incidence increased with duration of use, attaining four-fold control values after 10 years of use. Other studies (110,111) similarly showed an increased risk with increased duration of use but also with the use of formulations that contained a higher proportion of estrogen or in users with a history of genital infections or abnormal Papanicolaou smears. Benign cervical adenosis and adenomatous polyps have been seen in oral contraceptive users and were prominent in some early reports (SED-11, 857). They often (but not always) disappear when medication is stopped.

By the mid-1980s it was fair to conclude that: (a) oral contraceptive use did not appear to increase the subsequent incidence of abnormal cytology among women who had normal smears at the time they began to use the products; (b) extended oral contraceptive use (over 6 years) appeared to increase by several times the rate of conversion of pre-existing cervical dysplasia to carcinoma in situ. Generally speaking, subsequent data have tended to be compatible with those conclusions, for example pointing to an increased incidence of micro-invasive cervical carcinoma and again stressing the changes in cytology and the extent to which the effect differs with the strength and composition of the product. The average risk figures that emerge are generally in line with those found in a Norwegian study, in which, after correcting for other risk factors, relative rates were found of 1.5 for current users and 1.4 for past users as compared with never-users (112). Clearly, confounding factors, such as differences in sexual activity, age at first coitus, and the number of sexual partners, can confuse the issue and make interpretation more complex (113). In addition, any discussion of the issue must today take into account the current view of the human papilloma virus (HPV) as a sexually transmitted agent that is the main cause of cervical cancer (114), and the possible influence of Herpes simplex virus type 2, smoking, and other known or emergent risk factors.

The most authoritative view on cervical cancer at present is that expressed by the WHO in 1992: "Recent studies suggest that use of oral contraceptives for more than 5 years is associated with a modest increase in relative risk (ranging from 1.3 to 1.8). The extent to which this reflects a biological relationship is uncertain, particularly given the absence of reliable information on the role of possible infectious agents, such as the human papilloma viruses ⋯" (115). In the present state of knowledge, all women taking oral contraceptives over long periods should undergo regular routine screening by cervical cytology to ensure early detection of premalignant and malignant processes.

In 2002 the Chief Medical Officer of the UK Department of Health issued an urgent communication to all Health Professionals that oral contraceptives may contribute to the development of cervical cancer in women with high-risk type HPV, because of an association between an increased risk of cervical cancer and increasing duration of use of oral contraceptives (116). There was a three-fold increase in risk after 5–9 years of oral contraceptive use versus a four-fold increase after 10 or more years in women with HPV, which is sexually transmitted. There are more than 80 HPV, only a few of which are associated with an increased risk of cervical cancer. With the current evidence it is difficult to state what the main precipitating factors for cervical cancer are—the use of oral contraceptives, sexual activity, the type of HPV, or the duration of infection. While cervical screening is not perfect, 80–90% of cervical abnormalities can be detected and treated in women who attend regular screening programmes. The Chief Medical Officer therefore advised that all sexually active women, especially those taking long-term oral contraceptives, should be encouraged to have regular cervical smears.

Oral contraceptives and uterine fibroids

In a long-term, follow-up study in Scandinavia, the risk of fibroids fell consistently with increasing duration of oral contraceptive use (117). A decade earlier, the British Royal College of Physicians study had similarly suggested a protective effect, while an Oxford study had not, but once more the issue is confused by the change in composition of oral contraceptives over the years; more recent papers thus carry the most weight. On the other hand a causal relation between apoplectic leiomyomas and oral contraceptive usage was strongly suggested by Myles and Hart in the light of their study of five histologically distinctive uterine smooth muscle neoplasms with multifocal hemorrhages (118). They thought that effects of hormonal steroids on the blood vessels in pre-existing leiomyomas might be responsible for intimal hyperplasia with or without accompanying thrombi.

Ovarian tumors

Hormone replacement therapy

While the risk that hormone replacement therapy may cause endometrial tumors has been widely discussed, less attention has been given to the possibility that it could increase the risk of epithelial ovarian cancer. Since cancer of the ovary has some risk factors in common with endometrial cancer (notably low parity and obesity), this possible risk needs to be considered, especially in view of the fact that the endometrioid epithelial type of ovarian tumor is histologically so similar to adenocarcinoma of the endometrium.

The issue has been examined in a large Australian case-control study. A total of 793 eligible incident diagnoses of epithelial ovarian cancer in 1990–93 among women living in Queensland, New South Wales, and Victoria were identified. These were compared with 855 eligible female controls selected at random. Standard questionnaires were used to obtain histories. There were no clear associations between the use of hormone replacement therapy overall and the risk of ovarian cancer. However, unopposed estrogen replacement therapy was associated with a significant increase in the risk of endometrioid or clear-cell epithelial ovarian tumors. In addition, the risk associated with estrogen replacement therapy was much larger in women with an intact genital tract than in those with a history of either hysterectomy or tubal ligation. The authors therefore suggested that postmenopausal estrogen replacement may be a risk factor associated with endometrioid and clear-cell tumors in particular.

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The risk of ovarian cancer with various hormonal replacement regimens has been examined in a nationwide study in Sweden in relation to plain estrogen regimens as well as estrogen + sequentially added progestogens or continuously added progestogens (119). Between 1993 and 1995, the investigators enrolled 655 women with histologically verified ovarian cancers and 3899 randomly selected population controls, all aged 50–74. Data on the use of estrogen replacement therapy were collected by postal questionnaires. The risk of ovarian cancer was higher among ever-users than never-users as regards both plain estrogen supplementation (OR = 1.43, 95% CI = 1.02, 2.00) and estrogens with sequentially added progestogens (OR = 1.54, 95% CI = 1.15, 2.05); the increase in risk applied to the serous, mucinous, and endometrioid subtypes. For all cancer types combined, the greatest increases in risk were seen when hormone use exceeded 10 years. The odds ratios after ever use of low-potency estrogens were 1.18 (95% CI = 0.89, 1.55) for oral and 1.33 (95% CI = 1.03, 1.72) for vaginal use. There was no increase in risk among users of continuously added progestogens. In other words, the continuous addition of progestogens appeared to reduce or eliminate the risk.

Oral contraceptives

The results of two major British prospective studies of 1974 and 1976 (120,121) suggested that oral contraceptive treatment was unrelated to the development of benign ovarian tumors; these and other studies also suggested that follicular and lutein cysts are suppressed in women using oral contraceptives. With regard to ovarian cancer, somewhat later data suggested a reduced risk in oral contraceptive users; impressive case-control work from the USA in 1981 seemed to show this protective effect when oral contraceptives had been taken for 4 years or more, the risk of ovarian cancer then being decreased by a mean of some 40%; the effect was even greater when the contraceptives had been used for a longer period (122). Very similarly, in 1988, the results of a multi-country study backed by the WHO suggested that sometime users of combined oral contraceptives had a risk rate that was only 71% of that in non-users, while women who had used oral contraceptives for 5 or more years had about a 50% reduction in risk (106). It should be added, however, that not all reviewers find these trends significant.

A meta-analysis of epidemiological studies of ovarian cancer showed a summary estimated relative risk of 0.64 for ever-use of combined oral contraceptives, implying a 36% reduction in ovarian cancer risk (123). This protective effect increased with increasing duration of oral contraceptive use and continued for at least 10 years after discontinuation. Although most of the oral contraceptives reported in these studies were older, higher-dose formulations, the Cancer and Steroid Hormone (CASH) study included users of tablets containing ethinylestradiol 35 μg or less, and this subgroup of women had a reduced risk of ovarian cancer (108).

With conjugated estrogens, the risk of ovarian cancer was stated in 1977 to increase two- to three-fold (SED-12, 1026), but this conclusion was based primarily on findings in women who had also taken diethylstilbestrol, and it was therefore not generally accepted. A 1982 study in which there was an apparent slight increase in ovarian epithelial carcinoma among American women taking estrogens was similarly open to challenge (SEDA-7, 385) and the link cannot be regarded as having been established (124).

Breast neoplasms

Oral contraceptives

Shortly after the first oral contraceptives were introduced around 1959, the fact that some women noticed acute effects on the breast led to fears that the ultimate consequence might be induction of mammary disorders, particularly tumors; the same concerns were raised about estrogen replacement therapy (125). The debate on this issue has now continued for more than 30 years and it is characterized by contradictions, discrepancies in scientific findings, qualified statements, and controversies and a massive output of data and opinions. The present review will necessarily be confined to some of the highlights of the discussion, presented in Table 1, leading up to a summary of the present situation and the questions that still remain open.

It is clear from the studies reported in Table 1 (126–142) that there is no simple relation between treatment with hormonal oral contraceptives and the incidence of breast cancer. As in the case of other neoplasms, studies are confounded by the influence of many factors, including age, parity, age at first delivery, family history, pre-existent fibrocystic disease, geographical or environmental influences, the ages at which the menarche and menopause have occurred, and progressive changes in the spectrum of contraceptives in use. Information bias can easily mislead. The possible influence of the long latency likely to be involved in any effect has been heavily debated; breast tumors may have been present for many years by the time they become clinically detectable; many tumors induced by oral contraceptives may therefore so far have been missed, but conversely, oral contraceptives must often have been prescribed to women who unknowingly were already suffering from breast cancer. One must also bear in mind the apparently spontaneous increase in the incidence of breast cancer over the last 40 years. Finally, when cancers are found, there is little or nothing to distinguish them histologically from tumors that arise spontaneously (143).

Four meta-analyses have shown no increased risk of breast cancer in women who have ever taken an estrogen, compared with non-users. However, most studies suggest an increased risk of breast cancer among women who take estrogen for 5–10 years or longer. The summary relative risk estimate based on the findings of these studies is 1.32 (95% C1 = 1.16, 1.51) for women who reported long-term use compared with never-users. The increased risk of breast cancer may not persist after estrogen therapy is withdrawn, suggesting that estrogen acts as a promoter rather than a cause of breast cancer (144). In one publication from the Nurse's Health Study, the estimated risk of breast cancer associated with estrogen alone was 1.36 compared with 1.50 for estrogen + progestogen therapy (145). A later analysis from the same cohort showed that women who took unopposed estrogen had a 5% per year increased risk of breast cancer compared with 9% per year in women taking an estrogen + a progestogen. The

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Table 1 The possible association of oral contraceptives with breast neoplasms

Type of study	Findings	Source
Review of nine major studies of oral contraceptives	Reduced risk of breast cancer in eight studies; greater effect with higher doses; clinically significant with 2 years of use	(126)
Case-control study	Link between oral contraceptives and breast cancer, but only in those aged 30–34 years; coincidental?	(127)
Prospective epidemiological study	Link between oral contraceptives and breast cancer if used before first full-term pregnancy; high doses→higher risk	(128)
Case-control study	No link between oral contraceptives and breast cancer	(129)
Historical study of breast cancer cases	Four-fold increased risk with injectable estrogens	(130)
Case-control study	No link between oral contraceptives and breast cancer	(131)
Case-control study	Ever-users of oral contraceptives had 1.1 risk compared with never-users; higher doses produce a slightly higher risk; duration of use irrelevant; family history: higher risk; use after age 40: risk increased by 50%	(132)
Editorial	Greater risk if oral contraceptives used long-term in early life?	(133)
Case-control study	Ever-users of oral contraceptives had 0.9 (0.8, 1.2) risk compared with never-users; family history and use of oral contraceptives before first pregnancy irrelevant	(105)
Epidemiological study (extension of Pike, 1981)	Link between oral contraceptives and breast cancer if used before first full-term pregnancy: high doses→higher risk	(128)
Case-control study	Pike's results not confirmed; may be some protective effect of oral contraceptives?	(129)
Case-control study	No link with oral contraceptives	(134)
Case-control study	No link with oral contraceptives, except for a 30% increase if taken before first full pregnancy	(135)
Epidemiological study	No link with oral contraceptives, even in subpopulations	(136)
Epidemiological study	No link with oral contraceptives, even in subpopulations	(137)
Case-control study	Evidence of risk if duration and dosage considered	(138)
International case-control study	Risk doubled by use of oral contraceptives for 12 years; risk increased by duration of use; risk increased by use before first pregnancy; results may only be valid for Swedish women under 40; not seen in older or Norwegian women	(139)
Population-based case control study	No link with oral contraceptives	(137)
Narrative review	No risk	(140)
Systematic review	Greater risk with oral contraceptives in women with a history of fibroadenomas	(141)
Case-control study	Significantly more cases of breast cancer with depot medroxyprogesterone; no link with oral contraceptives	(142)
Population-based, case-control study	12-fold risk increase when young women use oral contraceptives for 12 years or more	(141)
Narrative review	Most studies have found no link with oral contraceptives; no reason for serious concern; possibly slightly higher frequency in industrialized countries	(106)
Narrative review	No increased risk from past use of oral contraceptives in women aged over 45 years; weak link in younger women with long-term use	(115)

most promising marker is the increase in breast density that occurs in 15–50% of women who take replacement estrogen (144).

There are some circumstances in which it is prudent to avoid using oral contraceptives, or in which frequent control of the state of the breasts is essential. These include (a) very long-term use before the first full pregnancy; (b) prolonged use of high-dose formulations; (c) uninterrupted use in women with a family history of breast cancer or with a personal history of fibroadenoma.

Finally, it is clear that the increase in the use of estrogen-containing contraceptives during the last 30 years cannot be held responsible for the current population-wide increase in breast cancer; as the International Committee for Research in Reproduction pointed out in 1989, the overwhelming proportion of the current rise in cases of breast cancer is among women who are too old to have taken oral contraceptives when they were younger. In addition, calculations suggest that even if an adverse effect among younger users of oral contraceptives were proved, it would still only account for a few percent of all breast cancers occurring in Western countries.

Patients with breast cancer who have discontinued estrogens less than 1 year before diagnosis have a significantly higher survival rate (146). Current users of estrogens at breast cancer diagnosis have a survival rate 5 years longer than non-users. However, they also have an increased incidence of breast cancer. This increased survival disappears when corrected for stage at diagnosis, when one can see that estrogen use relates most strongly to early-stage

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tumors. One might therefore expect that these tumors are less aggressive and that they result in an increased survival after diagnosis. The effect of hormone replacement therapy on breast cancer mortality may even be beneficial (147,148). Indicators of biological aggressiveness are the c-er 6 B2 oncoprotein, ploidy, tumor proliferation rate, and the presence of estrogen receptors (149).

Hormone replacement therapy

As far as hormone replacement therapy is concerned (Table 2) one must provisionally conclude, with the authors of a major Canadian study published in 1992, that long-term past use of estrogens is not related to risk, but that current estrogen use increases the risk of breast cancer to a modest degree, and that the addition of progestogens probably does not remove the increased risk resulting from the use of unopposed estrogen (150).

In the Iowa Women's Health Study of postmenopausal women for 11 years, during which 1520 specific breast cancers occurred in the at-risk cohort of 37 105 women, it was concluded that exposure to hormone replacement therapy was associated most strongly with an increased risk of invasive breast cancer with a favorable prognosis. There was a more modest increase in the risk of invasive ductal or lobular carcinoma of the breast (159).

Many clinicians continue to withhold estrogen-based replacement therapy from women who have a history of breast cancer because they fear impairing their prognosis; the evidence is not firm, but experts continue to urge caution in the absence of firm data either way (161). A well-designed study from Finland in 131 such women, two-thirds of whom used HRT, showed no increase in the breast cancer recurrence rate after an average of 2.5 years (162). However, the limited size of the study (and the fact that various different forms of HRT were used) make it difficult to exclude the risk on the basis of these data alone.

Because hyperplastic or fibrocystic changes in the breast may be pre-malignant, there has been a study of 42 women who at breast biopsy had atypical hyperplasia, 74 age-matched women with proliferative fibrocystic changes, and 74 with non-proliferative fibrocystic changes (163). The patients were aged 26–77 years, and had taken predominantly HRT (usually conjugated estrogen) but sometimes oral contraceptives. There was a strong association between exogenous hormone use and the presence of atypical hyperplasia. The authors considered that their results were in line with the theory that there is a continuum between hyperplasia and carcinoma and considered that exogenous hormone use may influence the transition from one to the other in a (still undefined) subset of women.

It is difficult to interpret a Japanese report of a woman aged 62 years who developed a benign fibrous tumor of the breast. The mass, which had been noted 1 year before, progressively enlarged. Bearing in mind that such fibrous tumors of the breast are almost always premenopausal, it may be significant that she had been taking estrogens irregularly for the previous 10 years but had taken them

Table 2 Some studies of the association between hormone replacement therapy and breast neoplasms

Type of study	Findings	Source
Prospective comparative study of users and non-users	Positive link between breast cancer and HRT, provided the menopause was natural	(88)
Cohort study following up long-term users of HRT	Slight increase in breast cancer, possibly accentuated by progestogens; possible methodological problems	(SED-12, 1027) (151)
	Risk increased with HRT by up to 30%	(152)
	Link between HRT and breast cancer uncertain, but Nurse's Health Study suggested a relative risk of 1.36; adding a progestogen reduces the risk	(153)
17 relevant studies of HRT reviewed	Risk increased by 20% with use for over 10 years and 50% with use for over 20 years	(154)
Review	At least 10 acceptable epidemiological papers point to a link between long-term HRT and breast cancer	(155)
Case-control study	No increase in risk among users of combined estrogen + progestogen HRT	(156)
Large case-control study	No increased risk of breast cancer with HRT	(157)
Case-control study	Increased risk among users of any type of HRT for more than 10 years; odds ratio 2.1	(158)
Iowa Women's Health Study	HRT associated most strongly with an increased risk of invasive breast cancer and modest increases in risk of invasive ductal or lobular carcinoma of the breast	(159)
Million Women Study	Current users of HRT more likely than never-users to develop breast cancer	(160)

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intensively during the last year. In addition, there was positive immunohistochemical nuclear staining for estrogen receptor antibodies in stromal cells (164).

By far the largest piece of evidence to emerge on the risk of breast cancer is that from the Million Women Study (160). In all, more than a million women aged 50–64 were recruited into this study between 1996 and 2001 and are being followed up with respect to cancer incidence and deaths. There were 9364 incident invasive breast cancers and 637 breast cancer deaths after an average of 2.6 and 4.1 years of follow-up respectively. Current users of HRT at recruitment were more likely than never-users to develop breast cancer (adjusted RR = 1.66; 95% CI = 1.58, 1.75) and die from it (1.22; 1.00, 1.48). Past users of hormone replacement therapy were not at an increased risk. The risk was significantly increased among current users of formulations containing estrogen only, estrogen + progestogen, and tibolone, but the risk was substantially greater for estrogen + progestogen than for other types of hormone replacement therapy. The risks were significantly increased separately for oral, transdermal, and implanted estrogen-only formulations. In current users of each type of hormone replacement therapy the risk of breast cancer increased with increasing total duration of use. Although the conclusions of this major study are roughly similar to those of the Women's Health Initiative, it has already been challenged on methodological and statistical grounds as presenting an unjustified threat to the continued use of HRT in women who need it (165).

When breast cancers occur in women taking estrogen replacement therapy they are sometimes claimed to be less aggressive than in other women. The effect of the duration or type of replacement therapy on the aggressiveness of such tumors has been studied in 1105 consecutive postmenopausal patients treated for operable breast cancer at the European Institute of Oncology (166). Tumors in women who had been exposed to estrogen replacement therapy were characterized by better stage distribution, a smaller diameter, and less extensive involvement of the axillary lymph nodes; histological grade III tumors were less common. The prognosis was generally better in women who took estrogen replacement therapy for more than 5 years. Tumors with estrogen-positive receptors were more common in the controls, but this tendency was reversed when the comparison was limited to those who had had particularly long exposure. Overall, these findings seem to confirm that prolonged use of estrogen replacement therapy does reduce the degree of aggressiveness of breast cancer, but they still have to be set against the evidence that the incidence of such cancers is increased.

A new approach to the study of the effects of hormone replacement therapy on the breast is to examine breast density, using mammography and the Wolfe classification. In a randomized study of 166 menopausal women, using this technique, there was increased breast density after 6 months of treatment; eight times more commonly in those who took estradiol and norethisterone acetate than in those who took tibolone (167). The significance of this increased density is not clear, but it should for the present be regarded as undesirable, perhaps representing the prodromal phase of more serious complications.

Malignant melanoma

Mortality and incidence rates of malignant melanoma and skin cancer have increased in most Western countries during the last 20 years, clearly for reasons unconnected with oral contraception. However, endocrinological factors can affect the melanocytes and the spread of malignant melanoma. Estrogen receptors have been noted in malignant melanoma cells, and estrogens are known to stimulate melanogenesis, an effect that is enhanced by simultaneous administration of progestogens. Oral contraceptives might therefore have an effect; the fact that chloasma has long been known to occur in some oral contraceptive users is perhaps relevant (168).

One large epidemiological study from California showed that women taking oral contraceptives, particularly long-term users, had a relatively high incidence of malignant melanoma (169). In Australia, there was a significant association with melanoma in women who had used oral contraceptives for at least 10 years before diagnosis (170). In a Canadian study, on the other hand, there was no association between the risk of superficially spreading melanoma or nodular melanoma and the use of either oral contraceptives or menopausal estrogens (SED-12, 1029) (171); however, it was suggested that there might be a risk in some subpopulations. One must be alert for confounding factors: for example, among oral contraceptive users there could be a relatively higher proportion of physically active and sporting women who are more susceptible than the average to expose themselves to sunlight. The results of a case control study in Philadelphia specifically on intraocular malignant melanoma showed that hormonal factors played only a limited role in the causation of this condition (SED-12, 1029) (172).

Pituitary tumors

A 1978 WHO report quoted an unpublished study by March in which pituitary adenomas were found in 26% of women with secondary amenorrhea following the use of oral contraceptives, yet in only 13% of cases who had not used these products (111). The difference was significant, but selection bias might have explained the results.

Second-Generation Effects

Fertility

In 1993, Sharpe and Skakkebaek published a theory that environmental and other forms of exposure of males to estrogens, particularly during fetal life, might explain the increasing incidence of reduced sperm counts and developmental disorders of the male genital system (173). Such exposure could be in part due, for example, to dietary changes in mothers: a low-fiber diet results in a great reabsorption of endogenous estrogens, and there is an increasing use in the diet of soya, which is a rich source of phytoestrogens. The topic goes beyond the scope of this volume, but it is not impossible that baseline exposure to estrogens in the diet or environment could increase the sensitivity of individuals to estrogens that are administered therapeutically or for purposes of contraception.

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Teratogenicity

The best-known second-generation effects of estrogens are the genital complications that result from the formerly widespread use in pregnancy of diethylstilbestrol (q.v.), mainly between 1940 and 1975. Although it is difficult to reconstruct medical histories dating back to this period, evidence continues to emerge. The evidence is covered in the monograph on Oral contraceptives.

Hormone replacement therapy is generally given at a time when pregnancy can be excluded, but in principle some of the risks discussed in connection with oral contraceptives would arise if a women taking hormone replacement therapy were to become pregnant. In 1980, an authoritative Scientific Group of the World Health Organization (WHO) surveyed the entire question of the effects of female sex hormones on fetal development and infant health (174), and after 25 years one can conclude that later reports in the literature have almost entirely supported its conclusions.

Congenital abnormalities

Records available in Finland have been used to seek correlations between hormonal treatment (with diethylstilbestrol, estrogens, or progestogens) and adverse effects, including cancers in the mother or infant. A retrospective cohort of 2052 hormone-drug exposed mothers, 2038 control mothers, and their 4130 infants was collected from maternity centers in Helsinki covering the period from 1954 to 1963 (175). Cancer cases were sought in national registers through record linkage. Exposures were examined by the type of the drug (estrogen + progestogen or progestogen only) and by timing (early in pregnancy or only late in pregnancy). There were no statistically significant differences between the groups with regard to maternal cancers, whether total or specified hormone-dependent cancers. However, the total number of malformations recorded, as well as genital malformations in male infants, was higher among exposed children. The number of cancers among the offspring was small, and none of the differences between groups was statistically significant. The authors suggested that their study supported the conclusion that estrogen or progestogen therapy during pregnancy causes malformations among children who were exposed in utero, but not the hypothesis that it causes cancer later in life in the mother; the power to study cancers in offspring was too low to draw firm conclusions. Non-existence of the risk, negative confounding, weak exposure, or a low study power may have explained the negative findings.

Susceptibility Factors

Age

Occasionally, children are exposed unknowingly to estrogens. Precocious puberty has been observed in young girls after contact with hair lotions and other products containing estrogenic compounds (SED-12, 1032) (176,177).

The short-term complications of estrogens are unpleasant rather than dangerous. A questionnaire survey among American pediatric endocrinologists has showed that these effects commonly included weight gain, nausea or vomiting, areolar or nipple pigmentation, headache, and irregular menses (178). However, there seems to have been no methodical follow-up to determine the long-term consequences.

The longer-term consequences have in recent years given rise to rather greater concern. The use of estrogens to arrest excessive growth in height in girls was first reported in 1956 (179). While the estrogen is given continuously, the addition of a progestogen given cyclically around the time of the menarche is customary in order to induce (or permit) menstrual periods and to prevent metropathia hemorrhagica. The estrogen produces a mean reduction in predicted height, provided the treatment is begun at a bone age of 12 years and before the menarche (180). The duration of treatment is from 8 months to 3 years.

There has been an anecdotal report of thrombosis in a girl taking estrogens in addition to older evidence that they can reduce antithrombin activity, which could indeed raise the risk of thrombotic complications (181).

It was long thought that there was no impairment of subsequent fertility or of the pituitary–ovarian axis in tall healthy girls treated with estrogens, but this is now uncertain. In a retrospective cohort study in Tasmania, using medical record reviews and interviews, women who had been treated with estrogen to suppress growth were significantly more likely to be infertile and were more than twice as likely to have ever taken fertility drugs than women who were not treated in this way (182).

Estrogen treatment of girls in whom growth in height tends to be excessive is progressively losing favor. In 2002, after reviewing the possible risks, which in its view could include miscarriage, endometriosis, and ovarian cysts as well as infertility, the USA Physicians' Committee for Responsible Medicine petitioned the FDA to issue appropriate warnings (178).

Sex

Following castration for cancer of the prostate, a high proportion of men have hot flushes, and estrogens can provide relief. In a study in 12 such men, estrogen in a low dose (0.05 mg) or high dose (0.10 mg) given as patches twice-weekly for 4 weeks provided considerable improvement (183). In this dosage, mild painless breast swelling or nipple tenderness was noted in two and five of the 12 men treated with the low- and high-dose patches respectively. Estradiol concentrations increased from 12 pg/ml to 16 and 27 pg/ml with the low-dose and high-dose patches respectively. There were no significant changes in serum testosterone or luteinizing hormone concentrations. This was a small study, and data on the tolerability of this topical treatment in a larger series would be welcome.

There is evidence for a role of estrogen in male bone metabolism, notably from studies in a man with a genetic defect in estrogen receptors and in men with aromatase deficiencies. Estrogen is likely to affect bone turnover in men throughout life, and it has been suggested that older men could have reduced bone resorption in response to estrogen therapy. In a study of this possibility, in 14 men with osteopenia of the femoral neck using micronized estradiol 1 mg/day for 9 weeks, that is a dose that is effective in postmenopausal women, estradiol and estrone concentrations increased significantly by more than 6-fold and 15-fold respectively (184). Concentrations of serum

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hormone binding globulin increased significantly by 17%, but concentrations of total and unbound testosterone fell significantly, by 27% and 34% respectively. Markers of bone resorption showed wide variations both at baseline and during treatment; they were too inconsistent to justify conclusions as to the potential usefulness of the treatment. However, the adverse effects of treatment were minimal, including (as might be expected) breast tenderness and reduced libido, which reversed after treatment.

Hepatic disease

Women with even mild liver disease can have an increased risk of the adverse effects of some estrogens on the liver (185,186). Furthermore, estrogens can potentiate and aggravate the organic complications of liver disease in other systems, for example increased cholesterol or lithogenesis (187,188).

Other features of the patient

Estrogens should be avoided in individuals with current thrombophlebitis or thromboembolism, estrogen-dependent tumors, abnormal genital bleeding without a diagnosis, and pregnancy. They are also contraindicated in apparently healthy women if they have an earlier history of jaundice in pregnancy, hepatic disease, thromboembolism, or porphyria.

Swedish workers have sought to develop a test system to define men who have a higher risk of cardiovascular complications when they take estrogens for cancer of the prostate (189). An investigational battery using exercise stress testing, evaluation of the peripheral circulation, blood volume estimation, chest X-ray, blood tests including hormonal status, lipoproteins, and antithrombin III, and history and physical examination taken by a cardiologist is claimed to make it possible to classify 84% of estrogen-treated patients as individuals with or without a particular risk of a cardiovascular complication and to identify an extremely high-risk subgroup.

Drug Administration

Drug administration route

Intranasal administration

Intranasal estradiol gives results comparable to transdermal estradiol, but substantially higher doses are needed. In 300 postmenopausal women, 17-β-estradiol 300 micrograms/day was as effective as two patches per week delivering 50 micrograms/day (190). Adverse events rates were similar but moderate, and severe mastalgia was significantly less frequent with intranasal estradiol (7.2%) than with the patch (15.5%); 66% of the patients chose to continue the intranasal therapy and 34% the transdermal therapy.

Subcutaneous implants

Implantable formulations of estrogens have been reviewed (191). Subcutaneous implants have as a rule durations of action of 4–12 months, depending on the dosage and formulation used; variations can be due to technical problems, such as disintegration or migration of an implant.

Transdermal patches

Typical patches of estradiol contain 50 micrograms, but there are important differences between the wanted and unwanted effects of the available products, because of the ways in which they are formulated. The wash-out period of estradiol after transdermal administration is about 6 weeks. Transdermal estrogens can also be supplemented periodically by an oral progestogen (192). New topical formulations of estrogens continue to be studied and marketed, although most studies have shown little difference between the various formulations available (193).

The reported incidence of adverse skin reactions to transdermal estradiol varies from 2% to over 25%, depending on the transdermal system, climatic conditions, and individual sensitivity. Of 78 women 29 reported one or more adverse events and eight discontinued prematurely (194). The main reasons for premature withdrawal included problems of adhesion, skin reactions, or undesirable systemic effects, such as headache, breast tenderness, weight gain, leg cramps, and unacceptable withdrawal bleeding.

Poor adhesion and skin irritation, with erythema and itching, are the principal drawbacks of transdermal therapy (195). Skin irritation can be overcome in some cases by changing the application site every day. In a direct comparison of transdermal patches, the duration, severity, and number of skin reactions depended on the individual formulation and excipients.

Allergic contact dermatitis from transdermal estrogen has been described in Korea, where the reaction was found to be due to 17-β-estradiol itself and not to an excipient (196). In some cases, allergic reactions and systemic contact dermatitis are clearly attributable to the patch material or to excipients. Even natural estradiol given in this way can occasionally cause hypersensitivity reactions, as determined by patch tests (197).

All the systemic effects of estrogens can occur with transdermal administration, subject to some modification as a result of the liver being bypassed (198).

Transdermal absorption of estrogen can lead to pseudoprecocious puberty in young girls, and to symptoms in young boys and adult men such as gynecomastia, loss of libido, impotence, and galactorrhea (199–201).

In a randomized, placebo-controlled, crossover study for 12 weeks, the estrogen matrix patch Estraderm MX, which unlike some other patches contains no alcohol, significantly relieved climacteric symptoms in both lower and higher strengths (50 and 100 micrograms of estradiol) (202). Local tolerability was good, but there was a slight increase in estrogen-related adverse effects (breast tenderness, leukorrhea) with the higher dose; there was a 4.8% overall incidence of endometrial hyperplasia in patients with an intact uterus. In women who have local reactions to alcohol, a patch of this type may be helpful.

Other work has confirmed the similar value of two patch formulations, Menorest and Climara; the latter has been reported to cause a much higher incidence of local reactions, but they are mild (203). The Fem 7 patch, which delivers estradiol 50 micrograms/day, was also well tolerated (204). Another effective and well-accepted variant on the patch theme is Demestril, which releases estradiol 25 or 37.5 micrograms/day depending on the formulation used (205). Differences in effect and tolerability between all these various estradiol patches are primarily a question

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of dosage and release rate, but it also seems that acceptance may be better when the drug is incorporated into the adhesive rather than being stored in a separate reservoir. The former type of patch shows better adhesion and is cosmetically more acceptable (206).

When low-dose patch therapy results in breakthrough bleeding it is supposedly more likely to occur in women with large, thin-walled, superficial endometrial vessels (82). If this finding is correct it might also apply to breakthrough bleeding with other forms of hormonal therapy.

Vaginal administration

Because weak estrogens, such as estriol and estrone (the main component of conjugated estrogens), are claimed to act primarily on the lower part of the genital tract, they have long been used topically for atrophic conditions of the vagina and vulva, and are reputed to have useful effects in doses that do not cause marked endometrial or systemic changes. However, everything may in fact be a question of dosage; it could well be that even a low dose of a potent estrogen would have a similarly selective effect. In 159 menopausal women with atrophic vaginitis who used either a conjugated equine estrogen vaginal cream (2 g/day containing conjugated estrogens 1.25 mg) or 17-β-estradiol pessaries 25 μg (one daily for 2 weeks), the two treatments provided equivalent relief of the symptoms of atrophic vaginitis, but at weeks 2, 12, and 24 there were increases in serum estradiol concentrations and suppression of follicle-stimulating hormone in significantly more patients who used the conjugated estrogen cream than in those who used the estradiol pessaries; the patients themselves rated the estradiol treatment more highly (207).

Another effective alternative to the use of weak estrogens is the administration of estradiol from an estradiol-releasing vaginal ring, which offers efficacy, safety, and tolerability with improved comfort and acceptability. The most frequent adverse events were vaginitis, breast tenderness, abdominal pain, pruritus, and vaginal discomfort (208). However, the incidence of these adverse events was similar to those of other estrogen vaginal delivery systems. In women with lower urinary tract symptoms after the menopause an estradiol-releasing vaginal ring was well tolerated and enjoyed better patient acceptance than local estriol (209).

With vaginal creams, used primarily in order to secure a marked local effect in arresting atrophy of the vulva and vagina, the degree of systemic effect can be variable, because of variations from day to day in vaginal vascularization and secretions (198).

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Etacrynic acid

See also Diuretics

General Information

Etacrynic acid (ethacrynic acid) is a loop diuretic with similar actions to furosemide and bumetanide. However, it has more adverse effects than the other loop diuretics and offers no clear advantages.

Organs and Systems

Sensory systems

Etacrynic acid is ototoxic after intravenous administration (1–3), an effect that is dose-related. It can sometimes be permanent (3,4). An association with nystagmus has also been reported (3,5). The risk has been estimated to

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be about seven per 1000 injections (6). The risk is increased in renal insufficiency and in patients who are also being given aminoglycoside antibiotics. Animal data suggest that etacrynic acid is more ototoxic than furosemide (7).

Metabolism

Like other diuretics etacrynic acid can impair glucose tolerance in patients with type 2 diabetes mellitus (8). Non-ketotic hyperglycemia has also been reported (9). However, hypoglycemia has also been reported in two patients with uremia (10).

There has been an anecdotal report of hyperuricemia and acute gout in a patient taking etacrynic acid (11).

Electrolyte balance

Etacrynic acid can cause excessive diuresis, natriuresis, and kaliuresis, leading respectively to dehydration and sodium and potassium depletion (12–17).

Mineral balance

Etacrynic acid can cause hypocalcemia and hypomagnesemia (18).

Hematologic

There have been anecdotal reports of agranulocytosis (12,19), hemolytic anemia (20), and thrombocytopenia (16,21).

Gastrointestinal

Nausea, abdominal pain (22), and diarrhea are relatively common with etacrynic acid (23,24), more so than with other loop diuretics. Data from the Boston Drug Surveillance Program showed that intravenous etacrynic acid was associated with an increased incidence of gastrointestinal bleeding (25,26). Overall 20% of the patients treated with etacrynic acid bled, compared with 5% of those who received furosemide. With intravenous etacrynic acid the risk of gastrointestinal hemorrhage was 26%, compared with 10% after oral administration. However, 12 of 28 patients who bled did so before etacrynic acid had been given (27), and it is not clear whether there is a true difference in risk with the different routes of administration.

Liver

Like other diuretics etacrynic acid can precipitate hepatic encephalopathy in the treatment of ascites in patients with hepatic cirrhosis (28). There has been an anecdotal report of focal hepatic necrosis in a patient taking etacrynic acid (29).

Pancreas

There has been an anecdotal report of necrotizing pancreatitis in a patient taking etacrynic acid (30).

Immunologic

Two patients developed a Henoch-Schönlein type of necrotic hemorrhagic rash of the legs and lower part of the body accompanied by histological evidence of vasculitis (31). In both cases the lesions appeared about 2–3 weeks after the start of treatment; in another case a hemorrhagic rash was accompanied by acute gastric and duodenal ulceration (32).

Drug Administration

Drug administration route

Intravenous administration of etacrynic acid causes burning at the site of injection (18).

Drug–Drug Interactions

Aminoglycoside antibiotics

Etacrynic acid potentiates aminoglycoside ototoxicity by facilitating the entry of the antibiotics from the systemic circulation into the endolymph (33). Animal evidence suggests that this effect may be potentiated by glutathione depletion (34). Conversely, neomycin can enhance the penetration of etacrynic acid into the inner ear (35).

Cardiac glycosides

Etacrynic acid potentiates the actions of cardiac glycosides if it causes potassium depletion.

- A patient developed digitalis intoxication and quinidine-induced cardiac dysrhythmias when hypokalemia occurred during etacrynic acid therapy (36).

In rats etacrynic acid inhibited the absorption of digitoxin from the small intestine (37), but an interaction of this sort has not been described in man.

Cefaloridine

Etacrynic potentiated the nephrotoxic effects of cefaloridine in mice, causing renal tubular necrosis (38).

Glucocorticoids

In a survey of the effects of etacrynic acid in 16 646 patients with gastrointestinal bleeding, the risk of major bleeding was increased in patients taking etacrynic acid (4.5% of 111 patients versus 0.2% of 10 637 patients taking no drugs). The risk was further increased in patients taking etacrynic acid plus glucocorticoids (9.1% of 22 patients) (25).

Glyceryl trinitrate

Etacrynic acid inhibited relaxation of large coronary microvessels in response to glyceryl trinitrate in pigs (39). The relevance of this to the clinical use of these drugs is not known.

Lithium

The loop diuretics increase the renal excretion of lithium after single-dose intravenous administration in both animals (40) and man (41). Furosemide has been used to treat lithium intoxication (42). The effect of etacrynic acid

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is larger than those of furosemide and bumetanide (41). However, long-term treatment with furosemide and bumetanide can cause lithium intoxication in some patients (43,44), perhaps by causing sodium depletion and a secondary increase in lithium reabsorption. An adverse interaction of lithium during long-term therapy with etacrynic acid is therefore theoretically likely.

Methotrexate

Etacrynic acid interacts with human serum albumin and modifies its binding properties (45). Since it binds to two binding sites on albumin, the benzodiazepine binding site and the warfarin binding site, it can displace drugs that bind at those sites (46). It competitively displaced 7-hydroxymethotrexate from its binding proteins in vitro (47). The clinical significance of this effect is not known.

Warfarin

Etacrynic acid interacts with human serum albumin and modifies its binding properties (45). Since it binds to two binding sites on albumin, the benzodiazepine binding site and the warfarin binding site, it can displace drugs that bind at those sites (46,48). This has been described for warfarin, whose anticoagulant effect it potentiated (49).

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Etamivan

General Information

Etamivan has actions similar to doxapram hydrochloride and has been used as a respiratory stimulant. However, it has a low therapeutic index and the incidence of adverse effects from intravenous etamivan is high. Laryngospasm, sneezing, and substernal chest pain have been among the reactions recorded after intravenous infusion.

Drug Administration

Drug overdose

If it is given too rapidly or in too high a dose; generalized convulsions sometimes occur (1). Epilepsy is a contraindication to etamivan.

Drug–Drug Interactions

Monoamine oxidase inhibitors

Concurrent use of monoamine oxidase inhibitors, which lower the seizure threshold, is a contraindication to etamivan.

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Etamsylate

General Information

Etamsylate (formerly also known as cyclonamine) is a synthetic water-soluble non-steroidal drug (diethylamine 2,5-dihydroxybenzenesulphonate), which was shown many years ago to increase platelet adhesion to glass beads. Subsequent clinical studies in animals reported dose-related reduced blood loss after experimental injury associated with etamsylate (1). In a small, randomized, double-blind trial, etamsylate reduced the prolongation of bleeding time and associated blood loss caused by aspirin (2). Treatment with etamsylate does not boost the platelet count or concentrations of coagulation factors (3). Etamsylate improves hemostasis by improving platelet adhesiveness and restoring capillary resistance through enhancement of the expression of P-selectin (4). It has also been suggested that it increases capillary vascular wall resistance (5).

Uses

Etamsylate is licensed for the prophylaxis and treatment of periventricular hemorrhage in neonates, in whom it is apparently effective (6,7). In a multicenter, double-blind, placebo-controlled trial in 330 infants, intraventricular and parenchymal hemorrhages developed in 30/162 infants in the treated group (etamsylate 12.5 mg/kg 6-hourly from within 1 hour of delivery for 4 days), compared with 50/168 in the control group (8). The incidence of intraventricular and parenchymal hemorrhage in survivors was 20/137 after etamsylate and 37/146 in the controls. No adverse effects were attributed to etamsylate. In a double-blind, prospective follow-up of this study, 268 of 276 survivors of the original study were seen at 3.5–4.2 years of age (9). There was no difference between the groups in neuromotor outcome (cerebral palsy) or in the general cognitive index of the McCarthy scales; fewer of the children who were given etamsylate had squints or required surgery for patent ductus arteriosus.

Etamsylate is more widely used to treat menorrhagia, including that associated with use of intrauterine contraceptive devices (10–12), although its efficacy has been challenged. A meta-analysis of drugs available in primary care showed that tranexamic acid was the most effective

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agent available for treatment of menorrhagia, while etamsylate was not associated with significant benefit (13). Guidelines published by the Royal College of Obstetricians and Gynaecologists in the UK stated that "at currently recommended doses, etamsylate is not an effective treatment for menorrhagia" (14). A significant proportion of women with primary menorrhagia turn out to have congenital disorders of coagulation, such as von Willebrand disease, and these cases do not respond to etamsylate (3).

No clinical benefit for patients without bleeding disorders undergoing surgical procedures has been established (15–17), although results in tonsillectomy have yielded conflicting results (18,19).

General adverse effects

Whatever the merits of etamsylate in reducing blood loss in various clinical conditions, it is at least clear that no serious adverse reactions have been attributed to it. A few patients experience nausea, but this is usually avoided by taking the drug after food. Minor adverse effects that have been reported include indigestion, headache, and vertigo (20). Toxicity studies in mice have also shown no adverse effects.

Organs and Systems

Cardiovascular

Modest but transient hypotension has occasionally been observed after intravenous injection, and elderly subjects appear to be more susceptible (21).

Hematologic

Marked leukopenia was reported in one retrospective study in children receiving etamsylate, but a causal link was not firmly established (1,22).

Skin

Skin rashes have occasionally been observed in patients taking etamsylate (23).

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Etanercept

General Information

Etanercept is a dimeric fusion protein consisting of two recombinant p75 tumor necrosis factor receptors fused with the Fc portion of human IgG1. It inhibits the binding of tumor necrosis factor alfa to its receptor and thereby neutralizes its biological activity. It has been used in the treatment of moderate to severe active rheumatoid arthritis, ankylosing spondylitis, psoriatic arthropathy, and juvenile rheumatoid arthritis in patients who have failed to respond to previous disease-modifying antirheumatic drugs. The clinical pharmacology and adverse effects of etanercept in patients with rheumatoid disorders have been reviewed (1).

Comparative studies

In a study of weekly oral methotrexate in two different doses (10 or 25 mg) or twice-weekly etanercept in 632 patients, etanercept produced fewer systemic adverse effects than methotrexate, but a higher incidence of injection site reactions (2). Despite theoretical concerns about the development of autoimmune reactions in patients taking etanercept, no evidence of clinical autoimmune disease emerged from this large trial.

General adverse effects

The therapeutic use and safety of etanercept have been reviewed (3). Mild-to-moderate injection site reactions were the most common adverse effects (42–49%), with a frequency 3.8 to 6 times greater than with placebo. Non-neutralizing antibodies to etanercept were rarely detected. Etanercept-treated patients more often developed new antinuclear antibodies or anti-double-stranded DNA antibodies, but no patient developed symptoms suggestive of an autoimmune disease during clinical trials.

Organs and Systems

Respiratory

The typical histological morphology of pulmonary rheumatoid nodules that developed during etanercept treatment has been reported (4,5). Pulmonary granulomas during etanercept treatment can be coincidental and difficult to distinguish from other pulmonary complications, such as relapse of tuberculosis. In two patients with rheumatoid arthritis who underwent lung biopsy for etanercept-associated pulmonary granulomas, there were non-caseating granulomas containing birefringent particulate in one (6) and caseating necrosis in the other (7). Infectious causes were ruled out. After etanercept withdrawal, the lesions resolved completely with steroid treatment in the first patient but persisted over 1 year despite antituberculosis treatment in the other.

Nervous system

Postmarketing warnings about etanercept that have been issued by regulatory agencies and the manufacturers relate to a possible increased risk of demyelinating disorders, such as multiple sclerosis, myelitis, and optic neuritis, in patients with pre-existing or a recent history of demyelinating disorders (SEDA-26, 399). This was in keeping with the results obtained in a placebo-controlled trial of lenercept, another recombinant tumor necrosis factor alfa receptor immunoglobulin fusion protein, in 168 patients with multiple sclerosis; compared with placebo, significantly more patients randomized to lenercept had exacerbation of multiple sclerosis, and exacerbation also occurred earlier (8).

Transverse myelitis of abrupt onset has also been reported (9).

- A 45-year-old woman with resistant rheumatoid arthritis was given etanercept 25 mg twice weekly. Nine days later she developed total acute sensory loss, with flaccid paraplegia, fecal incontinence, and urinary retention. MRI imaging and cerebrospinal fluid analysis were consistent with a diagnosis of transverse myelitis. She also had positive antinuclear and anticardiolipin antibodies. After etanercept withdrawal and treatment with dexamethasone and cyclophosphamide, her motor function improved with no change in sensory function.

Neurological events suggestive of demyelinating disorders in patients treated with tumor necrosis factor alfa antagonists and reported to the FDA's Adverse Events Reporting System have been reviewed (10). These included 17 cases temporarily associated with etanercept and two with infliximab, but complete information was lacking in a number of cases. One additional case with etanercept was more extensively detailed. The first symptoms occurred after a large range of delay after first drug administration (1 week to 15 months; mean 5 months) and mostly included paresthesia, optic neuritis, and confusion. MRI scans in 19 patients showed demyelination in various brain areas in 16. Although a causal relation was not proven, it is noteworthy that most patients improved after withdrawal and one patient had recurrent neurological symptoms after etanercept re-administration. The various hypothetical mechanisms by which tumor necrosis factor alfa antagonists might produce demyelinating events have been discussed elsewhere (11). Briefly, they cause increased peripheral T cell autoreactivity, and their inability to cross the blood–brain barrier may account for exacerbation of central demyelinating disorders.

Endocrine

- Transient hyperthyroidism occurred after 6 months of etanercept treatment in a 37-year-old woman with rheumatoid arthritis (12).

However, a direct causal relation with etanercept was debatable, because there was complete resolution with propranolol and despite continuation of etanercept.

Metabolism

Type 1 diabetes mellitus occurred after 5 months treatment with etanercept for juvenile rheumatoid arthritis in a 7-year-old girl (13). Antiglutamic acid decarboxylase antibodies were positive both before and during treatment, suggesting that etanercept may have prematurely triggered an underlying disease.

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Hematologic

Postmarketing warnings about etanercept that have been issued by regulatory agencies and the manufacturers relate to a possible risk of aplastic anemia and pancytopenia (10 reported cases, of which 5 ended in fatal sepsis) (8).

Etanercept has reportedly caused abrupt exacerbation of the macrophage activation syndrome (14).

- A 22-year-old woman with adult-onset Still's disease developed symptoms suggestive of the macrophage activation syndrome. After initial glucocorticoid treatment, she received two doses of etanercept, and within 6 days her white blood cell count fell from 6.4×10^9/l to 2.5×10^9/l and the neutrophil count from 0.8×10^9/l to 0.2×10^9/l. There was also thrombocytopenia and impaired coagulation and her liver enzymes were raised. A bone marrow aspirate showed delayed myelopoiesis. She received multiple transfusions, intravenous immunoglobulin, and granulocyte-macrophage colony-stimulating factor. The macrophage activation syndrome was diagnosed at that time and she was successfully treated with pulse methylprednisolone and ciclosporin. Epstein–Barr virus infection was subsequently confirmed.

Because soluble tumor necrosis factor alfa receptors are supposedly involved in the macrophage activation syndrome, the authors speculated that the administration of additional soluble receptors may have been the cause of a prolonged and exacerbated syndrome.

Urinary tract

Glomerulonephritis has been discussed as a possible consequence of etanercept treatment in two patients, with biopsy-proven mesangial deposits of IgA in one (15).

Skin

Injection site reactions are very common during the first month of treatment with etanercept. Histological findings in one patient showed a mild transient inflammatory response that did not suggest sensitization (16). The clinical and histological characteristics of these lesions have been analysed in a retrospective review of 103 etanercept-treated patients and in three other patients assessed prospectively (17). Of 103 patients, 21 had injection site reactions (erythema, pain, pruritus, or edema) within the first 2 months of treatment, and typically within 1–2 days after the last injection. In addition, eight patients developed recall reactions while continuing to take etanercept. Skin biopsies and immunohistological analysis of reaction sites in three patients showed an inflammatory infiltrate consistent with a T cell-mediated delayed hypersensitivity reaction.

There have been several descriptions of new cutaneous or pulmonary nodulosis in patients with rheumatoid arthritis treated with etanercept (4,18); concomitant cutaneous vasculitis was also reported in two patients (18). Although this may have been due to the natural history of rheumatoid arthritis or a lack of response to treatment, the short time to the occurrence of cutaneous nodulosis after the start of therapy in some patients implicated the etanercept.

Cutaneous vasculitis can also be the sole cutaneous manifestation of etanercept treatment (19). Purpuric lesions with histological features of leukocytoclastic vasculitis have been reported in a 58-year-old man (20) and a necrotizing vasculitis with eosinophils in a skin biopsy in a woman with rheumatoid arthritis (21). However, it is not known whether this resulted from the deposition of specific immune complexes.

- A 13-year-old girl developed a slowly reversible purpuric rash after 6 weeks of etanercept treatment, and the lesions recurred on re-administration (22). However, further administration of a gradually increasing dose of etanercept, with concomitant high-dose glucocorticoids, and antihistamines, was well tolerated, suggesting that tolerance can be obtained.

One patient who had separate episodes of vascular purpura during each of three sequences of treatment with etanercept, with leukocytoclastic vasculitis during the third episode, later developed similar cutaneous lesions after a third injection of infliximab (19).

Other types of skin reactions that have been described in isolated reports include urticaria-like eruptions with prurigo in two patients with juvenile arthritis (23) and discoid lupus erythematosus in a woman with rheumatoid arthritis (21). Erythema multiforme in three patients and a lichenoid eruption in one were attributed to infliximab; however, one patient had similar lesions after etanercept (24).

Musculoskeletal

Painless orbital myositis has been reported in a 42-year-old woman taking etanercept, but a causal relation was not established (25).

Immunologic

Although patients treated with etanercept commonly develop new antinuclear antibodies or anti-double-stranded DNA antibodies, there were no reports of cutaneous or systemic lupus erythematosus in early clinical trials. However, since then, at least eight cases have been reported, including five patients with a lupus-like syndrome, two with acute discoid lupus, and one with subacute cutaneous lupus erythematosus (26–29). All were women and they developed their first symptoms 6 weeks to 14 months after the first injection of etanercept. Antinuclear and/or anti-DNA antibodies were positive in most of them. Etanercept was withdrawn in all patients with features of systemic lupus erythematosus, and the symptoms resolved within 2–8 weeks. The skin lesions also improved with local glucocorticoids, despite continued etanercept treatment in two patients with discoid lupus or subacute cutaneous lupus erythematosus. This suggests that etanercept-induced autoantibodies are sometimes associated with clinical autoimmune disease.

Infection risk

In contrast to infliximab, etanercept is rarely associated with severe infectious complications. This has been attributed to different mechanisms of tumor necrosis factor alfa neutralization by the two drugs. Indeed, only nine cases of tuberculosis have previously been reported to the FDA from more than 100 000 patients treated worldwide (30). However, severe or uncommon infectious complications (severe viral pneumonia, fatal pneumococcal sepsis due to

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necrotizing fasciitis, osteoarticular tuberculosis) have been described in patients taking etanercept and long-term glucocorticoids (31–33).

Long-Term Effects

Tumorigenicity

There is great concern about the potential development of malignancy after blockade of tumor necrosis factor alfa, and it is biologically plausible. The FDA received reports of 26 cases of lymphoproliferative disorders in patients treated with etanercept ($n = 18$) or infliximab ($n = 8$) over 20 months (34). Although this reporting rate does not exceed the age-adjusted incidence of lymphomas in the USA, spontaneous reporting underestimates the true incidence. In addition, several findings were similar to those reported in patients taking immunosuppressive drugs after transplantation. For example, 81% of the reported cases were non-Hodgkin's lymphomas. Also, the median time to occurrence after the start of anti-TNF-alfa treatment was only 8 weeks. Finally, lymphoma regressed in two patients after withdrawal and without specific cytotoxic therapy. Although the actual incidence of neoplasia was low, additional long-term data that take into account concomitant or previous immunosuppressive treatment are needed before firm conclusions can be reached.

Susceptibility Factors

Age

In eight children with juvenile rheumatoid arthritis, who had failed to respond to disease-modifying anti-rheumatic drugs, high-dose etanercept was well tolerated (35). None withdrew because of etanercept-related adverse events. One child reported transient erythema at the injection site after the first injection. Three had mild transient upper respiratory tract infections. There were no laboratory abnormalities.

Interference with Diagnostic Tests

Troponin concentration

Non-neutralizing antibodies to etanercept have been identified in clinical trials. Although there was no correlation between these antibodies and the development of adverse effects (2), their presence was suggested as a likely explanation of false-positive rises in troponin concentrations in an assay that used mouse antihuman troponin (36).

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Ethacridine

See also Disinfectants and antiseptics

General Information

Ethacridine (6,9-diamino-2-ethoxyacridine) is widely used in the local treatment of inflammatory or ulcerative conditions of the skin, particularly crural eczema due to venous stasis. Many publications point to the high frequency of exacerbation involving local allergic reactions and also generalized eczematous reactions (SEDA-11, 474).

Ethacridine has also been given by slow extra-amniotic instillation of 150 ml of a 0.1% solution to induce abortion or delivery in patients with missed abortion or fetal death, and during the second and third trimester without or in combination with drip infusion of oxytocin or dinoprost (prostaglandin $F_{2\alpha}$) (SEDA-11, 474).

In 56 women (18–20 weeks gestation), treated at the Marie Stopes Clinic in Jodhpur, India, who underwent termination of pregnancy with 0.1% ethacridine lactate 150 ml injected into the intrauterine extra-amniotic space and in whom intravenous oxytocin was used to expedite the delivery of the abortus, ethacridine lactate induced successful abortion in 52 cases (1). Abortion failure occurred in the other four cases because of transverse lie of fetus ($n = 2$), cervical dystocia ($n = 1$), and uterine inertia ($n = 1$). In 41 women the abortion occurred at 12–24 hours after induction (mean 20 hours) which was shorter than that of previous reports (29.5–38 hours). There were complications in six cases: three women had cervical tears and three had incomplete expulsion. There was one case each of severe bleeding and vaginal laceration. There were no cases of sepsis. The authors concluded that ethacridine lactate performed better than other instillation abortion methods.

In a prospective, placebo-controlled study, tannin albuminate 500 mg plus ethacridine lactate 50 mg was given to 30 patients with Crohn's disease and chronic diarrhea for 5 days, followed by a 5-day break, and then a further 5 days treatment (2). Stool frequency was significantly reduced, albeit by only a small amount, with an improvement in the consistency of the stools.

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Ethambutol

See also Antituberculosis drugs

General Information

Ethambutol is tuberculostatic and acts against *Mycobacterium tuberculosis* and *Mycobacterium kansasii* as well as some strains of *Mycobacterium avium* complex. It has no effect on other bacteria. The sensitivities of non-tuberculous mycobacteria are variable. Ethambutol suppresses the growth of most isoniazid-resistant and streptomycin-resistant tubercle bacilli (1).

The adverse effects of ethambutol are mainly seen in patients taking very high doses, that is over 25 mg/kg/day. Dosages over 25 mg/kg/day should be administered for only about 2 weeks at the beginning of therapy. Treatment can then be continued with 15 mg/kg/day. If initial problems arise and ethambutol is essential, the daily dose should not exceed 10 mg/kg.

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About 80% of an oral dose of ethambutol is absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in 2–4 hours and the half-life is 3–4 hours. Within 24 hours, about 60% is excreted unchanged in the urine. In patients with renal insufficiency, the dose has to be altered (2). There is no indication for ethambutol monotherapy.

General adverse effects

Visual disturbances are the most common adverse effects and also the most important. These include diminished visual acuity, retrobulbar neuritis, retinal pigment displacement, and (rarely) hemorrhages. Gastrointestinal symptoms (abdominal pain or vomiting), and headache, dizziness, mental confusion, and hallucinations are all rarely seen. Adverse effects are more frequent in elderly patients and patients with alcoholism, diabetes, or renal insufficiency. Stevens–Johnson syndrome, toxic epidermal necrolysis (3), purpura-like vasculitis, acute thrombogenic purpura, joint pain, drug fever, tachycardia, and leukopenia have been attributed to allergy. As these reactions often arise during combined treatment with other tuberculostatic drugs, it is difficult or impossible to determine which drug is responsible. Tumor-inducing and teratogenic effects have not been described.

Organs and Systems

Nervous system

Peripheral neuropathy can precede or accompany ocular damage from ethambutol. These symptoms can serve as warning of impending eye damage (4). Loss of sensitivity, with numbness and tingling of the fingers, are relatively rare adverse effects (5). Electroneuromyography in ethambutol-induced neuropathy has confirmed that elderly patients are at increased risk (6). Sensory changes are more severe than motor dysfunction (5).

Sensory systems

Ocular disturbances due to ethambutol are dose-related. Dosages not over 25 mg/kg/day during the first 2 months of treatment and 15 mg/kg/day thereafter are generally accepted as adequate (7). At a dosage of 15 mg/kg/day, which should be regarded as a maximum for maintenance therapy, ocular toxicity developed in only 1.6% of patients (8). Advanced age (9), renal insufficiency, and diabetes can enhance ocular damage.

- The earliest onset of visual disturbance occurred in a 26-year-old man 3 days after beginning combined treatment including 15 mg/kg/day ethambutol, suggesting an idiosyncratic reaction (10).

Biochemical research has shown the importance of zinc metabolism in the retina (9). Zinc is found in high concentrations in the choroid, the retina, and especially the ganglion cells. Retinol dehydrogenase, a zinc-containing enzyme, interferes with the transformation of retinol (vitamin A_1), which is essential for color sensation and conal vision. Furthermore, zinc is involved in the biosynthesis of the specific transport of retinol from the liver to the effector cells. Ethambutol is a chelating agent and makes zinc unavailable for axoplasmic transport, provoking optic or retrobulbar neuritis (11). Patients with zinc blood concentrations below 0.7 μg/ml (reference range 0.9–1.0 μg/ml) before the use of ethambutol are at high risk of ocular disturbances (12).

The onset of visual loss can be sudden and dramatic, with color vision defects in the red–green or blue–yellow spectra, as well as variable field defects. In acute cases, disc edema is accompanied by splinter hemorrhages. Retrobulbar neuritis with ethambutol can be predominantly axial, presenting with reduced visual acuity and central scotoma, or periaxial, with peripheral field defects. In non-acute types the fundi and discs appear normal (13). Visual defects can be unilateral or bilateral.

Visual-evoked potential tests, such as flash electroretinography, flash and pattern visual-evoked responses, flicker fusion thresholds, and visual field perimetry, are reported to be the most reliable methods for early detection of ocular abnormalities (8,11,14). The routine use of visual-evoked potentials in the systematic follow-up of ethambutol-treated patients has been recommended (15).

Color vision and visual acuity should be examined before beginning ethambutol and every 2–4 weeks during treatment, using color tables and reading tests (SED-9, 525). Some recommend computerized perimetry of the central visual fields (SED-10, 581) (16,17). In patients with diabetes with retinopathy monthly monitoring of the fundi and visual acuity are mandatory. Early childhood, when visual examination is difficult or impossible, is a major indication for electroretinography. As a rule, ethambutol is not recommended for children under 5 years of age, because of the difficulty in reliably testing their visual acuity, unless the severity of tuberculosis makes the use of ethambutol necessary (15).

If ethambutol is not withdrawn when visual symptoms occur, optic atrophy or permanent blindness can occur. Patients therefore have to be instructed to interrupt treatment if they experience any visual abnormality. Hydroxocobalamin can accelerate recovery (18).

Metabolism

Blood urate concentrations can be increased because of reduced excretion of uric acid in patients taking ethambutol (19). This is probably enhanced by combined treatment with isoniazid and pyridoxine. Special attention should be paid when tuberculostatic drug combinations include pyrazinamide. However, severe untoward clinical effects are rare, except in patients with gout or renal insufficiency (2,20).

Hematologic

Acute thrombocytopenia, probably due to an immunological mechanism, has been described in a single patient (21).

Liver

Jaundice and non-icteric liver disturbances probably occur in under 0.1% of patients, as long as isoniazid and rifampicin are not given simultaneously (22).

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Second-Generation Effects

Pregnancy

Ethambutol in combination with isoniazid in pregnancy has been suspected of causing one case of gastrointestinal malformation, but other factors may have been implicated (SEDA-12, 256).

Teratogenicity

Fetal damage has not been attributed to ethambutol (23).

Fetotoxicity

Toxic effects in the newborn have not been attributed to ethambutol (24).

Lactation

No adverse effects during lactation have been attributed to ethambutol (24).

Susceptibility Factors

Renal disease

In patients with impaired glomerular filtration or any other renal dysfunction, ethambutol dosages have to be altered (25).

Drug–Drug Interactions

Antacids

In 13 patients with tuberculosis, aluminium hydroxide significantly lowered serum ethambutol concentrations during the first 4 hours after a dose; in healthy volunteers, both aluminium hydroxide and glycopyrrhonium, alone or in combination, reduced ethambutol absorption (26).

Isoniazid

The risk of optic neuropathy due to ethambutol may be increased when it is combined with isoniazid.

- A 40-year-old patient underwent unsuccessful cadaver kidney transplantation and was treated with ethambutol and isoniazid (27). Bilateral retrobulbar neuropathy with an unusual central bitemporal hemianopic scotoma developed and ethambutol was withdrawn, but there was only a small improvement. When isoniazid was also withdrawn, there was dramatic improvement in visual acuity.

In another patient taking isoniazid and ethambutol, optic neuropathy improved only when both drugs were withdrawn (28).

Isoniazid 300 mg/day orally for 7 days increased serum ethambutol concentrations at 4, 6, and 8 hours after a daily dose of 20 mg/kg; the cumulative percentage dose excreted was significantly reduced at 4, 6, and 24 hours (29). In another study from the same center, ethambutol 20 mg/kg did not alter the pharmacokinetics of a single dose of isoniazid 300 mg in 10 patients with tuberculosis (30).

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Ethanol

General Information

Ethanol (alcohol) is a drug of frequent abuse, and has long-term adverse effects that will not be discussed here. It is sometimes used therapeutically in the following ways:

- topically as an astringent.
- by direct instillation to embolize arteries.
- by direct injection into nerve ganglia or around nerve trunks to destroy them and relieve severe or chronic pain (for example trigeminal neuralgia); however, the results are generally only short-lasting.
- to swab the skin before venepuncture and other surgical procedures.
- as a rubefacient in some liniments.
- to harden the skin to prevent bedsores, and to harden the nipples before breastfeeding.
- to reduce sweating.
- in the treatment of acute methanol poisoning, since ethyl alcohol competes with methyl alcohol (methanol) for hepatic metabolism.

Alcohol is also widely used as a solvent in pharmaceutical preparations.

In 28 children from Argentina there was alcohol intoxication when ethyl alcohol was applied to the abdomen in alcohol-soaked cloths, as a home-remedy for disturbance of the gastrointestinal tract (1). The symptoms and signs included nervous system depression (100%), abdominal erythema (89%), alcoholic breath (86%), miosis (86%), hypoglycemia (54%), convulsions (18%), respiratory depression (18%), mydriasis (14%), acidosis (11%), and death (7%).

A danger of embolization of arteries is reflux of the instilled ethanol and the possibility of embolization of arteries other than the targeted ones. Infarction of the left testis secondary to transcatheter embolization of a malignant left renal tumor with ethanol has been reported (2). Colonic infarction following ethanol embolization of a renal tumor has been attributed to a reflux of ethanol from the renal artery into the aorta (3).

In combination therapy of unresectable hepatocellular carcinoma with transcatheter embolization and percutaneous injection of alcohol in 24 patients, 18 developed transient local pain and a burning sensation after the injection of alcohol, 16 had mild fever, and two had transient hypotension (4).

Organs and Systems

Cardiovascular

Alcohol is one of many drugs that cause or aggravate systemic hypertension. Acute alcohol exposure has an inconsistent effect on blood pressure, but cross-sectional population studies have shown a relation between chronic alcohol consumption and blood pressure, and the prevalence of hypertension up to three times higher in heavy drinkers (5). Although the mechanism of hypertension caused by chronic alcohol consumption is not known, it is suspected that it is partly related to repeated episodes of acute withdrawal, causing increased sympathoadrenomedullary activity, an increase in plasma renin activity, and increased ACTH secretion, which may be sufficient to have a mineralocorticoid effect (6).

Respiratory

In 36 patients with inoperable cancers of the esophagus who were treated by endoscopic injection of alcohol, complications included mediastinitis in one patient and tracheoesophageal fistulas in two (7).

Nervous system

Peripheral nerve block is created by injecting ethanol around the selected nerve. The effect of alcohol on nerve tissue has been examined in animal models and in postmortem specimens from patients who received neurolytic blocks (8,9). In general, alcohol causes destruction of nerve fibers, with subsequent Wallerian degeneration. The basal lamina around the Schwann cell usually remains intact. This leaves a tract available for axon regeneration without the formation of a neuroma. If the cell bodies are completely destroyed, regeneration will not occur. Contact of alcohol with unintended nerve roots underlies many of the more serious complications. Involvement of anterior rootlets sufficient to interrupt motor nerve function will result in muscle weakness or paralysis. Interruption of

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parasympathetic fibers in the anterior roots of the three middle sacral segments can result in bowel and bladder dysfunction and can cause urinary retention and anal sphincter paralysis.

In one study of 82 patients over a 20-year period who received repeated peripheral alcohol nerve blocks for trigeminal neuralgia, although moderate swelling and discomfort were invariable, significant complications occurred in only three of 413 nerve blocks (10):

- avascular necrosis, leading to a sequestrum, possibly due to repeated injections;
- necrosis of the lateral aspect of the nose, attributed to intravascular injection of alcohol;
- pallor and faintness after the injection followed by diplopia, which took 5 months to resolve.

Alcohol relatively commonly causes less serious complications, such as vomiting, headache, and paresthesia, which are but fortunately of limited duration, while loss of proprioception and profound numbness are disconcerting but almost always preferable to the pain that the alcohol injection has relieved (11).

Liver

Injection of ethanol into the liver to treat hepatocellular carcinoma commonly causes severe pain, fever, and hepatic dysfunction; there can also be pleural effusion, pneumothorax, ascites, vasovagal reaction, transient hypotension, myoglobinuria, and portal thrombosis. Fatal massive hepatic necrosis distant from the injection site has also been attributed to this treatment (SEDA-18, 377).

There have been three studies of the effects of percutaneous ethanol injections in the treatment of hepatocellular carcinoma, either alone (12,13) or in combination with transcatheter arterial embolization (14). The procedure was effective and safe and improved long-term survival. Adverse effects were generally mild and of short duration, and commonly included abdominal pain, fever, intoxication (especially among non-drinkers), transient rises in serum transaminases, and chemical thrombosis of the tributary branch of the portal vein. Hepatic infarction has been reported in two patients with hepatocellular carcinoma after percutaneous ethanol injection of the tumors (15). Both patients had previously been treated with transcatheter arterial infusion using a suspension of styrene maleic acid neocarzinostatin, and the liver damage may have occurred through a combination of arterial damage due to the neocarzinostatin and vasculitis caused by flow of the injected ethanol into a portal vein branch.

In an open trial, percutaneous ethanol injections into the liver improved prognosis compared with conservative treatment in 63 patients with cirrhosis and hepatocellular carcinoma who were not suitable for surgery or transcatheter arterial chemoembolization (16). Most of the patients had mild to moderate local pain during or immediately after injection and 29% developed fever.

Urinary tract

When 99% ethanol was instilled into renal cysts under ultrasound guidance in 25 cases, there were 12 complications after puncture, either related to the puncture itself or caused by the ethanol (17). They included flank pain, nausea, causalgia, and a feeling of drunkenness, which occurred immediately after instillation.

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Etherified starches

General Information

Etherified starches are synthetic colloids containing over 90% amylopectin, a waxy starch derived from maize, that has been variably etherified. There are two major forms, hetastarch and pentastarch (both BAN and USAN). They are produced synthetically by introducing hydroxyethyl groups into glucose units of starch molecules, followed by acid hydrolysis, which results in a product with a molecular weight of several thousands of daltons. In hetastarch 7 or 8 and in pentastarch 4 or 5 of the hydroxyl groups in each glucose molecule are etherified.

The etherified starches are used in solution as plasma substitutes. They are good alternatives to albumin, because they have an extended shelf-life, carry no risk of transmitting blood-borne diseases, and can be infused into patients who refuse blood products on religious grounds.

The elimination of etherified starches is complex and related to the size of the particles. The smaller molecules, with a molecular weight of less than 50 000 daltons, are excreted unchanged by glomerular filtration. The larger molecules are metabolized to smaller molecules and distributed to various body tissues, where they may undergo hydrolysis in the reticuloendothelial system or enzymatic degradation by amylases.

A detailed histological and immunohistochemical study of deposits of hetastarch in rat tissues has thrown some light on the relation between its adverse effects and its fate in the body (1). Thirteen days after a single intravenous injection the rats were sacrificed and their liver, spleen, lymph node, lung, kidney, and skin were studied. In all these organs anti-etherified starch antibody stained cells that were mainly regarded as mononuclear phagocytes (confirmed by the use of antimacrophage monoclonal antibody ED1). These findings suggested a degree of prolonged tissue storage of either etherified starch or of a degradation product that stains with the antibody, and this may account for persistent complications such as pruritus. However, in this histochemical study there was no mast cell degranulation or accumulation of inflammatory cells.

Nomenclature

Different types of etherified starch are designated by a number that indicates the molecular weight in kilodaltons followed by a number that indicates the degree of substitution of glucose units with hydroxyethyl groups. Thus, etherified starch with a molecular weight of 200 kDa and 62% substitution is designated 200/0.62.

Comparative studies

The efficacy and safety of hetastarch and albumin have been compared in 85 patients with postaneurysmal subarachnoid hemorrhage (2). Of 26 patients who developed clinical symptoms of vasospasm, 14 were treated with hetastarch, while the other 12 received albumin. In all patients who received hetastarch there was significant prolongation of the partial thromboplastin time after transfusion (pretransfusion mean 24 seconds, post-transfusion 33 seconds), while in patients treated with albumin the partial thromboplastin time was not significantly altered. The prolongation of the partial thromboplastin time resulted in increased occult blood loss in the hetastarch-treated patients, requiring blood transfusion in four patients. On the basis of hetastarch-associated coagulopathy and data that show that albumin may be the most effective agent for increasing cerebral blood flow and preventing infarction, the authors stopped using hetastarch in these patients and decided to recommend albumin exclusively.

Some authors have concluded that etherified starches and albumin do not differ with respect to efficacy and adverse effects on coagulation and renal function (3), but etherified starches clearly do have a distinct adverse reactions profile. Some of the problems that they cause, such as anaphylaxis, volume overload, cerebral hemorrhage, and acute renal insufficiency, are sufficient reason to avoid hetastarch when benefit is doubtful, such as ischemic brain infarction (4).

Placebo-controlled studies

Hypervolemic hemodilution with agents such as etherified starches or dextran increases cerebral blood flow and can therefore reduce ischemic tissue damage in the penumbra zones when given within the therapeutic time window. However, the clinical benefit of such therapy has yet to be proven. Since etherified starch is considered to be the safer choice, in particular the recently developed lower molecular weight form (etherified starch 130/0.4), an explorative, randomized, placebo-controlled, safety trial of etherified starch for hypervolemic hemodilution in patients with acute ischemic stroke has been undertaken (5). This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter study in 106 patients with acute ischemic stroke, who were recruited over 3 years. Treatment comprised high-dose hypervolemic hemodilution with either etherified starch 130/0.4 or placebo within 6 hours of the start of symptoms, with a randomization ratio of 2:1 in favor of etherified starch. There were no significant differences between the groups with regard to the incidence of specific adverse events (cardiovascular, bleeding complications, allergic reactions), assessed over days 1–30, or of deaths over days 1–8. The author, on behalf of the Hydroxyethyl Starch in Acute Stroke Study Group in Germany, noted that while the study was not designed to prove efficacy, the global tests of efficacy suggested a slight but insignificant trend toward better functional outcome with etherified starch.

General adverse effects

Transitory hyperamylasemia, chills, and mild increases in body temperature, pruritus, enlargement of the submandibular and parotid glands, and erythema multiforme can occur (6). The risk of anaphylactic reactions to hetastarch is very small (about 5 per million) (7).

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Organs and Systems

Cardiovascular

In a comprehensive comparison of the pharmacokinetics and pharmacodynamics of dextran and etherified starch (8), the effects of etherified starch on the cardiovascular system have been delineated. The mean arterial pressure, central venous pressure, wedge pressure, cardiac index, left ventricular stroke work index, and stroke output all rise, whereas the pulmonary vascular resistance falls. Oxygen availability to the tissues is improved. The effects of etherified starch on blood viscosity and erythrocyte aggregation, in particular, are more pronounced than with dextran.

Nervous system

The effect of hemodilution with colloids on somatosensory-evoked potentials in non-premedicated volunteers has been reported (9). In seven subjects, blood (20 ml/kg within 30 minutes) was removed and simultaneously replaced by gelatine 3% or etherified starches 6%. After 30 minutes, blood was retransfused. Median and posterior tibial nerve somatosensory-evoked potentials were recorded from the cortex, second cervical vertebra, Erb's point, and first lumbar vertebra. Hemodilution with gelatine or etherified starches or retransfusion did not affect somatosensory-evoked potentials, provided normovolemic conditions were maintained.

Acid–base balance

Two prospective, randomized studies of acid-base changes induced by etherified starches have been reported. In the first study (10), healthy volunteers were given 15 ml/kg of hetastarch 6% or albumin 5% intravenously over 30 minutes. Four weeks later they were given the other colloid. Arterial blood gases and electrolyte parameters were measured at baseline and at 30-minute intervals for 5 hours. There were statistically significant changes in bicarbonate, chloride ion, and albumin concentrations, base excess, and arterial carbon dioxide tension 30 minutes after infusion of hetastarch, but only the albumin concentration changed significantly in the albumin-treated group.

In the second study (11) there were acid–base changes caused by the same two colloids in patients undergoing acute normovolemic hemodilution during gynecological surgery. Two groups of 10 patients were randomly assigned to receive either albumin 5% or etherified starch 6%, containing chloride ion concentrations of 150 and 154 mmol/l respectively. The blood volume was well maintained in both groups. Acute normovolemic hemodilution caused slight metabolic acidosis with hyperchloremia. Plasma albumin concentrations fell after hemofiltration with etherified starches but increased after albumin. The authors concluded that acute normovolemic hemodilution with albumin or etherified starches led to some degree of metabolic acidosis, but not of clinical relevance.

Hematologic

After intravenous administration, hetastarch alters the rheological properties (12) of blood and increases the erythrocyte sedimentation rate (13).

Coagulation

Etherified starch can cause coagulation disorders. Administration of 10% hydroxyethyl starch 200/0.62 to 10 patients with cerebrovascular diseases over 10 days (a loading dose of 500 ml administered once over 45–60 minutes followed by 500 ml/day) had a markedly unfavorable effect on blood coagulation (14). There was a significant 43% increase in activated partial thromboplastin time. Factor VIII:C, von Willebrand ristocetin co-factor, and von Willebrand factor antigen fell during therapy below the limit required for hemostasis (30%), and in some patients below 10%. This was thought to be due to accumulation of large molecules that are difficult to break down and which unfavorably affect rheological and coagulation function.

The pathogenic mechanism that affects factor VIII/vWF complex has not been elucidated. There may be accelerated elimination after attachment of factor VIII/vWF complex to starch molecules. The significant fall in factor XI and factor XII shows that impairment of the intrinsic system of coagulation is not limited to factor VII/vWF complex (14). Even a small volume of 6% etherified starches (average molecular weight 450 kDa; 2.5 litres in 3 days) can cause a significant coagulation disorder (15).

In another study, administration for 24 hours of hetastarch (6%) or human serum albumin to 12 patients with septic shock caused moderate effects on hemostasis (prothrombin time, partial thromboplastin time, and quantitative platelet count). There was no increase in bleeding, and there were no statistically significant differences between these effects and those produced by human serum albumin (16); however, it should be noted that the number of subjects was so small as effectively to preclude a finding of significant difference between the groups studied. The authors' conclusion that hetastarch is a safe and effective volume expander in patients with sepsis and shock needs to be considered cautiously, particularly as the authors pointed out that there is an immediate fall in factor VIII coagulant to about half normal in patients receiving hetastarch. Furthermore, a patient with von Willebrand's disease had a markedly prolonged bleeding time and reduced platelet adhesiveness, although there was no overt bleeding.

- A man of 33 developed von Willebrand's disease shortly after he had been given 3 liters of hetastarch over 3 days after acute sensorineural hearing loss. He had a history of a prolonged activated partial thromboplastin time (APTT), although he had previously undergone bilateral hip arthroplasties with no evidence of abnormal bleeding. He had an episode of epistaxis and experienced weakness and pain in his leg. When hetastarch was withdrawn, it was noted that he had a raised APTT concentration, and reduced concentrations of factors XII and VIII:C. Over the next few months, the von Willebrand's syndrome was reversed, although his factor XII concentration remained reduced (17).

This case is typical of many others. In six patients with cerebral circulatory disturbances who received hemodilution therapy for 9–10 days with etherified starches (molecular weight 200 kDa and a high degree of substitution, 0.62), all the multimers of von Willebrand factor fell to the same extent. This corresponds to type 1 von

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Willebrand's syndrome (18). This potential hemorrhagic complication is treatable, since type 1 von Willebrand's syndrome can be controlled with the vasopressin derivative desmopressin.

A survey of formulations containing etherified starch, and particularly Elohes 6% (molecular weight about 200 kDa), carried out by the French Agency for Health Products identified eight cases of acquired von Willebrand disease (19). Three cases were fatal and in two cases there were hematomas with prolongation of the activated cephalin clotting time. All these effects were observed during the administration of Elohes for vasospasm secondary to meningeal hemorrhage due to rupture of a cerebral aneurysm in patients with no relevant previous history. Duration of treatment of more than 4 days appears to be a risk factor. Nine cases of hepatic overload were also reported, and could cause or aggravate portal hypertension. The Agency announced that the product information for products containing hetastarch would be revised, with a contraindication to the use of Elohes in patients with severe hepatic insufficiency, the stipulation of a maximum dose, a restriction on the duration of treatment, and instructions on the monitoring of hemostasis.

Of nine patients with hemostatic disorders, all treated with medium molecular weight etherified starch (Elohes), six developed type I von Willebrand's disease (20). Before the abnormalities in coagulation were discovered, the patients had received a mean dose of pentastarch of 121 ml/kg. The abnormalities resolved each time pentastarch was withdrawn. The authors hypothesized that accumulation of starch probably led to quantitative defects of complex factor VIII and von Willebrand factor by accelerated elimination from the circulation of complexes attached to starch molecules. Because Elohes is highly substituted, it is difficult to break down and is therefore eliminated more slowly. Accumulation of Elohes after repeated administration may explain why its adverse effects on coagulation resemble those of high molecular weight starch, while other medium molecular weight starches affect coagulation much less. The authors recommended that the dose of Elohes should be limited to 33 ml/kg/day and the cumulative dose to 80 ml/kg. Treatment should be given over no more than 3 days and Elohes is contraindicated in patients with coagulation disorders.

Etherified starch shortens the thrombin time by a fibrinoplastic effect. This accelerates the conversion of fibrinogen to fibrin, resulting in a less stable thrombus, which is more susceptible to lysis. The macromolecules in etherified starch induce an acquired von Willebrand's syndrome with reduced concentrations of all three main forms of factor VIII: factor VIII:C, von Willebrand factor, and von Willebrand factor antigen (vWFag).

Platelets

Plasma substitutes in general reduce the platelet count partly by a dilutional effect, even after a single dose. However, there are other mechanisms. In a study of the effects on platelet number and function of etherified starches, given for 10 days to 20 patients with cerebrovascular diseases, both medium- and low-molecular weight etherified starches caused a significant reduction in the number of platelets on the first day, in excess of a dilutional effect. During the course of treatment the platelet number increased, recovering its initial value. The number of large platelets fell disproportionately and significantly. Etherified starch did not affect spontaneous platelet aggregation. The fall in platelets was probably caused by colloid-osmotic shrinkage and increased degradation. There were no signs of impaired platelet function, as determined by spontaneous platelet aggregation (21). Patients suffering from thrombocytopenia or impaired platelet function should be carefully monitored when they are receiving large doses of etherified starches.

Macromolecules may coat the outer membrane of circulating platelets and cause a qualitative functional defect, thus prolonging bleeding time. Minor abnormalities of platelet aggregation have been observed after infusion of low volumes of etherified starches, and platelet defects probably contribute to the hemorrhagic state.

Etherified starch altered hemostasis in vitro in blood taken from patients undergoing abdominal surgery; the effect was more pronounced in patients with blood group O (22). The authors recommended that the intraoperative administration of etherified starches should be restricted in patients with blood group O undergoing surgical procedures with a high risk of bleeding.

Urinary tract

In a patient with normal renal function it is possible that the kidneys present a selective barrier to all but the smallest of starch molecules. The breakdown products are then eliminated by urinary excretion. Etherified starch can be associated with increasing serum creatinine concentrations (23). Associated clinical symptoms and signs include pain in the renal region and swelling of kidney parenchyma. In a study of 25 patients randomly allocated to control and treatment groups (the latter received 10% etherified starch 12 ml/kg) there were differences in renal tubular function in the latter. Those who received etherified starch had increased excretion of alpha$_1$-microglobulin, Tamm-Horsfall protein, and brush border enzyme acetyl-beta-glucosaminidase. There were no significant differences in glomerular function. The findings suggest a primary renal tubular lesion caused by etherified starch (23).

The risk of acute renal insufficiency associated with the use of etherified starch in volume replacement therapy has been critically reviewed (24). The author made the important point that not all etherified starch formulations are the same—they differ widely in physicochemical characteristics. Such differences have consequences for adverse events, including impaired renal function. Furthermore, all volume replacement therapies have potential hazards. The author therefore concluded that etherified starch, in particular products containing etherified starch with a low or medium molecular weight (for example 70, 130, or 200 kDa) and a low degree of substitution (0.4 or 0.5), can be considered for use in patients without pre-existing kidney dysfunction. It is recommended that all formulations of etherified starch, including the latest (molecular weight 130, degree of substitution 0.4), should be used only very cautiously in patients with some degree of renal impairment (plasma

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creatinine concentration greater than 365 μmol/l, 3 mg/l) and are probably best avoided for alternative regimens.

Osmotic nephrosis-like lesions have been reported in kidney transplant recipients, attributed to etherified starches that had been used in brainstem-dead patients before organ procurement (25). The incidence of these lesions was not influenced by cold ischemia time, the presence and length of delayed graft function, or the immunosuppressive regimen (including the use of ciclosporin). The lesions had no significant deleterious influence on the occurrence of delayed graft function or on serum creatinine at 3 and 6 months after transplantation. Osmotic nephrosis-like lesions can be long-lasting, since in three patients they were still present at 3 months after transplantation on routine renal biopsy. In patients without osmotic nephrosis-like lesions no kidney was lost, whereas among those with such lesions, seven of 31 were lost. Although there was no obvious short-term detrimental influence on renal function, these lesions might cloud the already difficult interpretation of renal transplant biopsies, especially for ciclosporin-induced nephrotoxicity. The authors recommended avoiding etherified starches in potential organ donors.

Two cases of osmotic nephrosis-like lesions have been reported in which similar changes have been noted, accompanied by evidence of renal insufficiency. The first case occurred after the administration of etherified starch during surgery (26).

- A 67-year-old woman with no history of nephritis was given etherified starch (500 ml) and Ringer's lactate (2.5 litres) for hypotension during surgery. Postoperatively she developed acute renal insufficiency (urine output below 600 ml/day) and her serum creatinine rose to 443 μmol/l, despite fluid challenge. Ultrasound showed no urinary obstruction, no thrombosis in the renal vessels, and normal kidneys. A renal biopsy showed major osmotic nephrosis-like lesions in the proximal tubules, but no lesions suggestive of acute tubular necrosis. Renal function returned to normal within 14 days after surgery.

The authors suggested that the renal insufficiency was due to the perioperative infusion of etherified starch, even though she received a much smaller dose (less than 10 ml/kg) than kidney donors usually receive. They further suggested that nephrotoxicity can occur within a few hours after even low-dose infusion of etherified starches.

- A 20-year-old man from Mali with polymyositis that had not responded to prednisolone, monthly infusions of immunoglobulin, and plasma exchanges with albumin and modified gelatin, was given ciclosporin, which led to marked improvement (27). When he developed hepatic cirrhosis the ciclosporin was withdrawn and glucocorticoids were reintroduced in association with plasma exchanges three times a week with 6% etherified starches and 4% albumin. After seven plasma exchanges (cumulative dose 320 g) his serum creatinine rose to 216 μmol/l without proteinuria or hematuria. Renal biopsy showed diffuse microvacuolization of the tubular epithelial cells (osmotic nephrosis-like lesions). Plasma exchange was restarted with 4% albumin alone, after which his renal function improved and the polymyositis stabilized.

The authors concluded that the most likely cause of renal insufficiency was etherified starch-induced tubulopathy and hypothesized that even low amounts of etherified starch as replacement fluid in plasma exchange can cause renal tubular lesions in patients predisposed for other reasons (such as drugs or renal hypoperfusion) to renal insufficiency. In this context, albumin should be combined with replacement fluids other than etherified starch.

The lesions of osmotic nephrosis involve the proximal and distal tubules. Severe changes in proximal tubules have been described in dogs after complete blood exchange with etherified starches. It is believed that smaller molecules (molecular weight under 50 kDa) are excreted unchanged by glomerular filtration, leading to a large amount of osmotically active small molecules in the ultrafiltrate. As a result of reduced glomerular filtration in these patients, a highly viscous ultrafiltrate, complicated by tubular stasis and osmotic nephrosis of tubular cells, may have been caused by reabsorption of etherified starches, resulting in acute renal insufficiency. In the two cases described in this report, and in the absence of either significant hypotension or oliguria, acute renal insufficiency due to purely prerenal (hypovolemic) causes was improbable (28).

Hetastarch can cause a discrepancy between urinary specific gravity and osmolality (29). High-molecular weight molecules present in the hetastarch solution produced a disproportionate rise in urine specific gravity compared with osmolality. In two patients, the combined effects of acute tubular necrosis secondary to hypotension and abnormal glomerular permeability were thought to have allowed high-molecular weight particles of hetastarch to be excreted in the urine. The hetastarch particles increased the urine specific gravity, but had a correspondingly smaller effect on osmolality. It was not thought that hetastarch itself was nephrotoxic. The authors concluded that in the setting of pre-existing renal disease, hetastarch may increase the urinary specific gravity without unduly affecting the ability of the kidney to concentrate urine. They recommended that urinary osmolality, rather than specific gravity, should be regarded as the preferred method of evaluating the urine after the administration of high-molecular weight colloid solutions.

Hemodilution therapy with etherified starch caused acute deterioration of an already existing nephropathy in two cases (29). The authors suggested, on theoretical grounds, that the deterioration in renal function was likely to have been the result of increased permeability caused by damage to the glomerular basement membrane. Etherified starch molecules are filtered above the physiological renal threshold, and this increases the viscosity of the urine. This can be counteracted by promoting diuresis. The authors managed to avoid precipitating renal insufficiency by ensuring a fluid intake of about 3 l/day. Without an adequate diuresis etherified starches accumulate in patients with renal dysfunction, with consequences that include further damage to the diseased kidneys.

Conclusions have differed as to whether use of etherified starch in brain-dead organ donors influences kidney graft function at 1, 3, and 6 months after transplantation (30–32). In one report (33), during the first 10 days after transplantation there was reduced kidney graft function

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with higher creatininemia or increased requirements for hemodialysis in recipients in those given etherified starch plus gelatin. Some other workers have not confirmed this finding (30,31), but it is not unique. In 69 other brain-dead patients followed up prospectively over a period of 18 months 33% of those who received etherified starch up to 33 ml/kg during the first 8 days after transplantation for colloid plasma volume expansion required extrarenal hemodialysis or hemodiafiltration, compared with 5% in a control gelatin-only group (33). Serum creatinine concentrations were significantly lower in the controls. The results suggested that etherified starch used as a plasma volume expander in brain-dead donors impairs renal function.

Skin

Severe pruritus after infusion of etherified starch is common and troublesome. In skin biopsies taken from 93 patients who had received etherified starches, half of whom had pruritus, immunoelectron microscopy was conducted using an antibody highly specific for etherified starches. After infusion of etherified starches, formation of intracytoplasmic storage vacuoles in the skin was demonstrated in all cases. Dose-related uptake of etherified starches was first detectable in macrophages and afterwards in endothelial and epithelial cells. There were vacuoles that reacted to etherified starches in the Schwann cells of unmyelinated as well as small myelinated nerve fibers, and in endoneural and perineural cells. Neural devacuolization paralleled the clinical improvement in itch (34). The authors of this study suggest that deposits of etherified starches in cutaneous nerves, as a consequence of a high cumulative dose, may account for the itching seen after infusion of etherified starch.

In 481 patients with diseases of the microcirculation of the cochleovestibular system, 149 of whom were treated with etherified starch, 43 (29%) complained of pruritus, compared with only 5.7% of another group of patients who were treated with dextran 40 (35). In more than 40% of the patients pruritus started in normal skin 1–3 weeks after therapy and lasted between 6 weeks and 6 months; the itching was resistant to therapy with antihistamines. Pruritus can be socially embarrassing, particularly when etherified starch has been given in high doses. The resistance of etherified starch-induced pruritus to standard therapy, including antihistamines, glucocorticoids, ultraviolet light, and other measures, has been described in a single case (36). This resistance to treatment is not unusual. Four patients with nausea or tinnitus who received intravenous etherified starch developed severe pruritus, especially on the trunk, without skin eruptions, 1–3 weeks after the start of treatment. The pruritus was refractory to treatment, and neither oral nor topical antihistamines were effective; only ultraviolet phototherapy or topical glucocorticoids gradually alleviated the pruritus after periods ranging from several weeks to 1 year (37).

In a retrospective study of 491 patients treated for various cochleovestibular disorders, 25 of 59 patients (42%) treated with etherified starch complained of pruritus, compared with four of 35 (11%) treated with dextran-40 (38).

Generalized itching occurred in 43 of 149 patients treated with etherified starch for acute or chronic microcirculatory disease causing neuro-otological disturbances (39).

In another retrospective study of 266 patients receiving etherified starch for otological indications 32% developed pruritus, which characteristically appeared as a pruritic crisis. In 55% of the patients the onset of symptoms was after the etherified starch had been withdrawn. The symptoms persisted on average for 8.8 weeks. Pruritus was generalized, but with a predilection for the trunk and genitalia. Coincidental atopic disease or higher age were not predisposing factors. The incidence of pruritus correlated well with the cumulative dosage and also depended on the type and molecular weight of the etherified starch given (6 or 10%, molecular weight 40 or 200 kDa). Light and electron microscopy showed deposits of etherified starch, especially within dermal macrophages and endothelial cells adjacent to nerve fibers (40). The authors suggested that a histamine-independent pathway is probably responsible for pruritus due to etherified starch. Antihistamines had no therapeutic effect on the patients reported.

After etherified starches treatment, vacuoles in the cells of various organs in humans occur, predominantly affecting the mononuclear phagocyte system (41). These vacuoles are indirect evidence for phagocytosis of etherified starch particles. In skin biopsies of patients who had received etherified starch and later suffered from itching, light and electron microscopy, immunohistochemistry, and immunoelectron microscopy using a polyclonal antihetastarch antiserum showed that storage of etherified starch was present in the skin of all patients. This was mainly in dermal macrophages, endothelial cells of blood and lymph vessels, some perineural cells and endoneural macrophages of larger nerve fascicles, some keratinocytes, and Langerhans cells. There were no morphological signs of histamine release from mast cells. The authors concluded that mediators other than histamine, released from hetastarch-affected cells, must be responsible for the itching.

In three patients with persistent pruritus after the administration of etherified starches during and after heart surgery, there was histopathological evidence of storage vacuoles containing etherified starch in the dermis (42). Etherified starch solutions are heterogeneous, containing molecules with a wide range of molecular weights. The smaller molecules (<50 kDa) are rapidly excreted by the kidneys, whereas larger molecules persist intravascularly until they are slowly hydrolysed or taken up by the mononuclear phagocyte system and other cells in various tissues. The mechanism by which storage of etherified starch causes pruritus is not adequately understood. It does not seem to be an allergic reaction mediated by the immune system, as there is usually little or no inflammatory cell infiltration, and the incidence of pruritus is dose-related. Whether macrophages, endothelial cells, keratinocytes, Langerhans cells, or other cells in which the starch molecules are deposited release mediators that induce itching, or whether there is a more direct effect on sensory nerve fibers, is uncertain. In this small series the number of mast cells was increased and mast cells were degranulated on electron microscopy. These features have not been seen in other studies. The

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resistance of the pruritus to treatment suggests that it is not simply mediated by histamine and indeed etherified starch does not release histamine (42).

- A 68-year-old woman developed marked and persistent periocular swelling after infusion of etherified starch for sudden hearing loss. In both the affected periocular skin and healthy skin there was lysosomal storage of etherified starches with a specific antibody in histiocytes, endothelial cells, basal keratinocytes, and small nerves. In the periocular skin there was more deposition of etherified starches, in addition to distinct xanthomatous changes and features of lymphedema. In addition, there was a 50% reduction in the pH-dependent activity of the lysosomal alpha-glucosidase in cultured fibroblasts.

This finding is consistent with a heterozygous glycogenosis type II (Pompe's disease) and is of potential pathogenic relevance for the intralysosomal accumulation of etherified starch. It is possible that alpha-glucosidase has a role in the elimination of tissue-stored etherified starch. Patients with reduced alpha-glucosidase activity may be at risk of unusual adverse effects after extraordinary and prolonged tissue storage of etherified starches, especially if it is infused in large quantities. There may be unusual lysosomal accumulation of etherified starches in endothelial cells and macrophages, which may in turn account for the higher risk of pruritus and other unusual adverse effects (43).

In a prospective, randomized, controlled, epidemiological comparison of 6% etherified starch solution (200/0.5) and lactated Ringer's solution, there were no more serious complications with the former than the latter. There was a greater than 10% incidence of pruritus in both groups (44).

In 26 patients who had received etherified starch (varying widely in both dose and duration), storage of etherified starch was dose-related, and fell in all organs over time; tissues deposits were greater in patients with pruritus (45). The authors concluded that tissue deposition is transitory and dose-related, but varies widely between subjects in both severity and duration. In a retrospective postal questionnaire in 100 consecutive intensive care patients who had previously received etherified starch, of 73 patients who replied, 34% had pruritus after discharge, of whom 44% had persistent pruritus that did not resolve with conventional treatments (46). There was a significant relation between the volume of etherified starch infused and the occurrence of pruritus.

In 120 patients who had received plasma substitutes (including 93 who had received etherified starch) skin biopsies showed lysosomal deposits in the histiocytes, some of them also in the cutaneous epithelium and endothelium (47). The extent of lysosomal storage correlated with the amount of etherified starch infused. Consecutive biopsies in some cases showed a slow reduction (over years) of etherified starch deposits in vacuoles. The authors suggested that pruritus after high cumulative doses of etherified starches was closely related to deposition of etherified starch in cutaneous nerves.

In a retrospective study of the dose-relatedness of pruritus caused by etherified starch, 50 consecutive patients were evaluated by questionnaire about 6 months after treatment; 37 returned the questionnaires, of whom 20 reported pruritus, lasting an average of 15 weeks (48). There was significantly more pruritus in patients who had received more than 5 liters of etherified starch compared with those who had received less than 5 liters. The pruritus had a delayed onset and occurred in acute bouts lasting 2–30 minutes. The authors concluded that hetastarch-induced pruritus is dose-related, and that in some cases it can be prolonged and severe.

Reproductive system

Ovarian hyperstimulation syndrome has been attributed to etherified starch (49).

- A 32-year-old Caucasian woman underwent IVF for primary tubal sterility and hyperandrogenemia as reflected by polycystic disease. Follicle formation was stimulated with FSH. The first stimulation cycle had to be discontinued because of threatened ovarian hyperstimulation syndrome. During the second attempt the dose of FSH was reduced to 100 IU/day for 10 days then 150 IU/day for 7 days, when follicles were observed. Ovulation was induced with a reduced dose of HCG (5000 IU). She was given crystalloids, 50 ml of serum albumin 20%, and 500 ml of medium molecular weight etherified starch 10% (HEAS, Fresenius). This was repeated on days 5–8 and 11–15, this time with high molecular weight etherified starch 6% (Plasmasteril, Fresenius), together with other fluids. After 4 days she developed massive ascites, abdominal pain, dyspnea, hemoconcentration, and a leukocytosis of 27×10^9/l. Her girth increased between days 7 and 12, and continuous abdominal paracentesis over 6 days was necessary. Her renal function was supported using diuretics and by a continuous infusion of dopamine. On day 17 she developed increased dyspnea and headache and a pleural effusion. Her anemia was severe (hemoglobin 7.8 g/dl) and nearly all the factors in the intrinsic coagulation cascade were greatly reduced. Disseminated intravascular coagulopathy and primary liver disease were excluded. The pleural effusion contained a high concentration of etherified starch (74% of the plasma concentration). She gradually improved and was discharged on day 36.

The authors concluded that the most likely cause of severe ovarian hyperstimulation syndrome was overinfusion of etherified starch.

Immunologic

Starch derivatives are relatively safer in terms of adverse reactions than other colloid plasma substitutes, but there is an incidence of anaphylactic reactions of 4–6 per million.

- An anaphylactic reaction has been attributed to etherified starches during re-infusion of autologous bone marrow in a man treated for malignant lymphoma (6). The re-infused material had been processed using etherified starches. The patient reported pruritus and carpal spasm. Edema and erythema of the hands were present, together with hypotension and tachycardia. A very small amount of etherified starches was present in the processed bone autograft.

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However, in this case other causes such as dimethylsulfoxide (DMSO) or plasma used while processing the autologous bone marrow for freezing could not be excluded.

- A 43-year-old male non-smoker, with a history of asthma, hypertension, and angina pectoris, was admitted to an intensive care unit for mechanical ventilation for acute severe asthma (50). He was given an inhaled bronchodilator, aminophylline, and prednisolone. His condition improved slowly but he became hypovolemic. Within 60 seconds of a fluid challenge with pentastarch 200 ml he had a severe anaphylactoid reaction.

Patients with allergy and atopy have an exaggerated response to chemical mediators released during adverse reactions. The incidence of allergy, atopy, and asthma in patients who have anaphylactic reactions is substantially greater than in non-reacting controls, which may have explained this incident. This sudden unanticipated severe reaction demanded immediate intervention, and its occurrence in a patient with pre-existing bronchospasm posed problems in maintaining ventilation and oxygenation.

Volume therapy with etherified starches in trauma patients results in a reduction in circulating adhesion molecules, an effect that is not observed with albumin infusion (51). Continuous infusion of pentoxifylline did not have a beneficial modulating action on circulating adhesion molecules. Adhesion molecules appear to play an important role in tissue damage secondary to the inflammatory process. Besides neutrophil- and endothelium-bound adhesion molecules, soluble forms have been detected in the circulating blood in trauma patients. They seem to be markers of endothelial damage, but they may also have other biological functions.

Of 1004 patients assessed at least 14 days after starch administration, using a highly sensitive enzyme-linked immunoadsorbent assay technique, one had a low titer (1:10) of etherified starch-reactive antibodies of the immunoglobulin M (IgM) class. Despite repeated infusions, no clinical reaction could be detected in this patient. The authors concluded that antibodies to etherified starches are extremely rare and that they do not necessarily cause anaphylaxis. This low antigenicity of etherified starches might explain their excellent tolerance, compared with other plasma expanders (52).

The reason for the considerable tolerability of etherified starch may be the raw material: etherified starch is synthesized from amylopectin by attaching hydroxyethyl groups. Amylopectin is very similar to glycogen, but whereas glycogen occurs in the cells of warm-blooded organisms, amylopectin is the lower-branched analogue in cells of plant origin. The human immune system is replete with this molecular structure. This may explain why the etherified starch-induced antibody was directed against the hydroxyethyl group and not against the starch molecule itself.

Second-Generation Effects

Pregnancy

Two healthy, full-term primigravidae with uneventful pregnancies and without a previous history of renal disease developed acute transient non-oliguric renal insufficiency after cesarean section under epidural anesthesia. During the procedure etherified starch 6% (70/0.5) was administered, 500 ml to one patient and 1000 ml to the other, for volume substitution after moderate blood loss (less than 800 ml). Acute non-oliguric renal insufficiency occurred on day 3 after cesarean section in the first patient and on day 2 in the second. Renal function recovered spontaneously.

Drug–Drug Interactions

Metamizole

- After plastic reconstruction with a neurovascular pedicular cutaneous sliding flap a healthy 46-year-old man developed acute renal insufficiency (53). He had received two 500 mg doses of the pyrazolone metamizole and two 500 ml infusions of 6% etherified starches.

A causative link between acute renal insufficiency and etherified starch in this case was tenuous, as it was with the metamizole. Simultaneous administration of the two is not advised.

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Ethionamide and protionamide

See also Antituberculosis drugs

General Information

Ethionamide is a synthetic derivative of thio-isonicotinamide. The initial oral dosage for adults is 250 mg/day, slowly increasing up to 15–20 mg/kg/day (maximum 1 g/day).

Protionamide is a pyridine derivative of ethionamide. The dosage is 250–300 mg/day.

Ethionamide and protionamide have often proved to be effective in non-tuberculous mycobacterial infections. Acute rheumatic symptoms and difficulty in the management of diabetes have been reported (1).

Organs and Systems

Nervous system

Mental depression, weakness, drowsiness, and hypotension are not rare in patients taking ethionamide or protionamide (1,2). Other neurological reactions include diplopia, olfactory disturbances, metallic taste, dizziness, paresthesia, headache, and tremor (3).

Psychological, psychiatric

Psychotic reactions have been described in patients taking ethionamide (4,5) and may be exacerbated by alcohol (6).

Endocrine

Goitrous hypothyroidism has rarely been described in patients taking ethionamide (7), with recovery after withdrawal (8). Ethionamide inhibits both the uptake of iodine and its incorporation into trichloroacetic acid-precipitable protein (9).

Metabolism

Thionamides lower the blood glucose concentration and also suppress appetite, which influences carbohydrate intake (10).

Gastrointestinal

Nausea, vomiting, and anorexia reflect gastric intolerance, and ethionamide is best taken with meals (1,2). Protionamide has better gastric tolerance, but patients with a history of stomach ulcer are susceptible to gastric problems (11).

Skin

Severe allergic skin reactions, alopecia, acne, and purpura can occur in patients taking ethionamide (1,12). Other adverse effects include acneiform eruptions, photodermatitis, and hair loss (13).

Sexual function

Gynecomastia, impotence, and menorrhagia have been observed in patients taking ethionamide (7,14).

Second-Generation Effects

Teratogenicity

Ethionamide is teratogenic (15,16), and neither ethionamide nor protionamide should be administered during the first trimester of pregnancy.

Susceptibility Factors

Hepatic disease

Since hepatitis occurs in about 5% of patients treated with ethionamide or protionamide, frequent monitoring of liver function is compulsory (17).

Drug–Drug Interactions

Rifamycins

When thionamides are used in combination with rifampicin, hepatotoxicity is more common and severe (18,19). There was a 13% incidence of hepatotoxicity in patients with multibacillary leprosy treated with dapsone, rifampicin, and protionamide 10 mg/kg/day, and a 17% incidence in 110 patients treated with dapsone, rifampicin, and protionamide 5 mg/kg/day; however, although the lower dose of protionamide did not reduce the incidence of hepatotoxicity, it did reduce its severity (20). Protionamide does not affect the pharmacokinetics of rifampicin (21).

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Ethosuximide

See also Antiepileptic drugs

General Information

The main adverse effects of ethosuximide include gastrointestinal disturbances, anorexia, dizziness, fatigue, drowsiness, headache, mood and behavioral disturbances, dyskinesias, and hiccups (1). Skin rashes (including Stevens–Johnson syndrome), systemic lupus erythematosus, scleroderma, nephrotic syndrome, blood dyscrasias, liver dysfunction, and autoimmune thyroiditis are rare.

Organs and Systems

Immunologic

Patients who develop antinuclear antibodies should be watched for the subsequent development of systemic lupus erythematosus (SEDA-19, 67) (SEDA-22, 83).

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Ethylene oxide

See also Disinfectants and antiseptics

General Information

Ethylene oxide is a gas that is used in the sterilization of equipment too large for other techniques, and for sterilizing rubber, plastic goods, and other materials that are damaged by heat and not adequately disinfected by other cold methods.

Ethylene oxide is highly toxic. If it is not eliminated after sterilization it can produce severe irritation and burns. In addition, it forms ethylene glycol with moisture and ethylene chlorhydrine with free chlorine atoms. Both products, also irritants, are absorbed by the sterilized object, from which they elute very slowly. The rate of elimination of ethylene oxide and its irritant reaction products depends on a variety of factors, such as the nature and thickness of the material, the duration and temperature of aeration, and the material used for wrapping the sterilized item. Ethylene oxide is also an alkylating agent, a directly acting mutagen and carcinogen.

Exposure

Exposure to ethylene oxide has been reported predominantly in workers in sterilization units, and should be kept as low as feasible. Health personnel working in close proximity to ethylene oxide should be given information about its dangers, and should be informed of the known and

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uncertain risks of exposure. Sterilizing equipment should be regularly checked, proper ventilation established, and alarm systems installed. These procedures must guarantee that the content of ethylene oxide is lower than 1 ppm, and that the content of halogenated ethylene hydrines is lower than 150 ppm on materials that have been sterilized by ethylene oxide at the time of use. The manufacturer of each device or instrument that should be sterilized by ethylene oxide must declare the conditions necessary for sterilization and decontamination (SEDA-11, 479).

Occupational exposure of sterilizing staff to ethylene oxide in hospitals, tissue banks, and research facilities can result during any of the following operations and conditions (1):

- changing pressurized ethylene oxide gas cylinders
- leaking valves, firings, and piping
- leaking sterilizer-door gaskets
- opening sterilizer doors at the end of a cycle
- improper ventilation at the sterilizer door
- improperly ventilated or unventilated air gap between the discharge line and the sewer drain
- removal of items from sterilizers and transfer of sterilized loads to aerators
- improper ventilation of aerators and aeration areas
- incomplete aeration items
- inadequate general room ventilation
- passing near sterilizers and aerators during operation.

In most studies, exposure appears to result mostly from peak emissions during such operations as opening the door of a sterilizer and unloading and transferring sterilized material. Although much smaller amounts are used in sterilizing medicinal instruments and supplies in hospitals and industrially, it is during these uses that the highest occupational exposures have been measured. On the other hand, proper engineering controls and work practices are reported to result in full-shift exposure of less than 0.1 ppm (0.18 mg/m^3) and short-term exposure of less than 2 ppm (3.6 mg/m^3) (1). Regular medical follow-up is advisable for sterilizing staff.

Monitoring exposure

Measurement of the concentration of ethylene oxide in workplace air is commonly used for exposure control. A standard of 1 ppm for workplace air is currently accepted as a threshold limit (SEDA-21, 254).

In 12 workers who were occupationally exposed to ethylene oxide during the sterilization of medical equipment, concentrations of 0.2–8.5 ppm were detected (2). This study also confirmed the relation between the ethylene oxide concentration in ambient air and the amount of *N*-2-hydroxyethylvaline in human globin, which has been used as a biological marker of carcinogenicity.

Disposition

Ethylene oxide is readily taken up by the lung. At steady state, 20–25% of inhaled ethylene oxide reaching the alveolar space is exhaled as unchanged compound and 75–80% is taken up by the body and metabolized. Aqueous ethylene oxide solutions can penetrate human skin.

Ethylene oxide is rapidly and uniformly distributed throughout the body. It is eliminated metabolically by hydrolysis and by conjugation with glutathione and glycol. The half-life has been estimated at 14 minutes to 3.3 hours (3–6). It is excreted mainly in the urine as thioethers; at higher doses, the proportion of thioethers is reduced, while the proportion of ethylene glycol increases.

Ethylene oxide alkylates nucleophilic groups in biological macromolecules. Hemoglobin adducts have been used to monitor tissue doses of ethylene oxide (7).

Local irritant effects

Some communications report irritating effects caused by liberation of residue of ethylene oxide and its reaction products in industrial materials, for example (SEDA-11, 479):

- tracheal stenosis by tracheotomy cannulae
- severe bronchospasm and asthmatic attacks after endotracheal anesthesia by endotracheal tubes
- anaphylaxis in a hemodialysis patient from plastic and rubber connecting tubes in an arteriovenous shunt
- postoperative inflammatory reactions to intraocular lenses
- allergic contact dermatitis
- hemolysis after exposure to plastic tubing sterilized with ethylene oxide.

Organs and Systems

Nervous system

In 12 men who were exposed to ethylene oxide after a sterilizer developed a leak, although the concentrations of ethylene oxide were not monitored, all four operators intermittently smelled the ethylene oxide gas, roughly indicating a concentration of more than 700 ppm (8). All four operators developed neurological disorders. One operator who had been working for only 3 weeks developed headache, nausea, vomiting, and lethargy, followed by major motor seizures. The other three had all been working for more than 2 years and had headache, limb numbness and weakness, increased fatigue, trouble with memory, and slurred speech. Three of them developed cataracts and one required bilateral cataract extractions. Four men, two of whom had not worked directly with the leaking sterilizer, had increased central corneal thickness with normal endothelial cell counts (SEDA-11, 479).

Other reports of neurological dysfunction related to acute and chronic exposure to ethylene oxide have appeared (9–15).

Sensory systems

Of 16 hospital sterilization operators who had been exposed to ethylene oxide and underwent medical and ocular examinations, 14 had lens opacities and 12 had abnormal contrast vision (an abnormality that is nonspecific to cataracts but which often supports the diagnosis) (16).

Hematologic

Epidemiological studies have associated ethylene oxide with hematological diseases (mainly anemia, leukopenia, and leukemia) (SEDA-24, 271). To determine whether occupational exposure to low concentrations of ethylene oxide can cause hematological abnormalities and whether

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blood monitoring could be used as health surveillance, a cross-sectional study was undertaken (17). Blood samples were collected from 47 hospital workers who were exposed to ethylene oxide during a mean period of 6.6 years. Ethylene oxide concentrations were in the range <0.01–0.06 ppm. The control group, individually matched by age, sex, and smoking habits, consisted of 88 workers from the administrative sector who had never been occupationally exposed to ethylene oxide. There were significant differences between the exposed and the control groups in the frequency of workers with low leukocyte counts. There was no significant difference in the absolute mean number of total leukocytes, but there was an increase in the mean number of monocytes and eosinophils and a reduction in the absolute mean number of lymphocytes in the exposed group compared with the controls. There was an increase in the percentage hematocrit and the mean absolute number of erythrocytes and a fall in the mean absolute number of platelets in the exposed group compared with the controls. The mean absolute numbers of eosinophils and erythrocytes were significantly higher, as was the hematocrit, and the mean absolute numbers of lymphocytes and platelets were significantly lower in the subgroups with a higher cumulative dose of exposure. There was a dose relation between cumulative exposure and the absolute mean number of eosinophils. The results of this study suggest that the total leukocyte count and the eosinophil count could be used to monitor for early detection of health problems in ethylene oxide workers.

Immunologic

Dialyser hypersensitivity syndrome (SEDA-11, 219) (SEDA-11, 479) presents as an acute anaphylactic reaction, the symptoms of which range from mild to life-threatening. The cause of the syndrome is unknown, but affected patients appear to have a high incidence of positive radioabsorbent tests to a conjugate of human serum albumin and ethylene oxide used to sterilize artificial kidneys. This conjugate may be the allergen responsible.

Immediate hypersensitivity reactions occurred in six of 600 donors who underwent automated platelet pheresis; skin-prick testing in four of them (but in none of 40 controls) was positive when an ethylene oxide human serum albumin reagent was used (18). Radioallergosorbent testing showed that serum from four of the six donors, but only one of 145 controls, contained IgE antibodies to ethylene oxide-albumin.

Long-Term Effects

Mutagenicity

There is overwhelming evidence that ethylene oxide produces genetic damage in a wide range of organisms and cells, including somatic cells of exposed humans (7,19). Ethylene oxide is a germ-cell mutagen in rodents. In male mice it induces chromosome breakage, leading to dominant lethal mutations and heritable translocations. Sensitive stages appear to be restricted to late spermatocytes and early spermatozoa.

In females, ethylene oxide also induces presumed, dominant, lethal mutations. When females are exposed shortly after mating or during the early pronuclear stage of the zygote, high frequencies of fetal anomalies are induced.

Ethylene oxide was ineffective in inducing morphological-specific locus mutations in spermatogonial stem cells; however, it produced dominant visible and electrophoresis-specific locus mutants in male mice, assumed to be derived from poststem cells.

The effectiveness of ethylene oxide in inducing chromosome breakage in germ cells of male mice is strongly influenced by varying degrees or rates of exposure. Since there was a dose-rate effect for ethylene oxide-induced, dominant, lethal mutations at high concentrations and over long exposure periods, considering the short burst exposure and low TWA exposure in humans, the question of whether significant dose-rate effects also exist at low exposures is unanswered.

Cytogenetic studies have been performed in the peripheral lymphocytes of humans exposed to ethylene oxide (SEDA-12, 574). Several studies in workers in hospital ethylene oxide sterilization units or plants have suggested that these workers have increased frequencies of chromosomal aberrations, including micronuclei and sister chromatid exchanges in peripheral lymphocytes.

The International Agency for Research on Cancer (IARC) Working Group reviewed the published studies of workers exposed to ethylene oxide in hospital and factory sterilization units and in ethylene manufacturing and processing plants (9). The studies consistently showed chromosomal damage in peripheral blood lymphocytes, including chromosomal aberrations in 11 of 14 studies, sister chromatid exchange in 20 of 23 studies, micronuclei in three of eight studies, and gene mutation in one study. In general, the degree of damage is correlated with the degree and duration of exposure. The induction of sister chromatid exchange appears to be more sensitive to exposure to ethylene oxide than is induction of either chromosomal aberrations or micronuclei. In one study, chromosomal aberrations were observed in the peripheral lymphocytes of workers 2 years after cessation of exposure to ethylene oxide, and sister chromatid exchanges 6 months after cessation of exposure. However, in one study, incidental exposure to high concentrations of ethylene oxide did not cause any measurable permanent mutational/cytogenetic damage in lymphocytes of exposed persons (20).

The effects of glutathione-*S*-transferase T1 and M1 genotypes on hemoglobin adducts in erythrocytes and sister chromatid exchange in lymphocytes have been examined in 58 hospital operators of sterilizers that used ethylene oxide and non-exposed workers (21). The results suggested that the glutathione-*S*-transferase T1 null genotype was associated with increased formation of ethylene oxide-hemoglobin adducts in relation to occupational exposure. This suggests that individuals with the glutathione-*S*-transferase T1 null genotype may be more susceptible to the genotoxic effects of ethylene oxide.

Tumorigenicity

Ethylene oxide is carcinogenic, assigned to Group 1 of the IARC (7). There is limited evidence of carcinogenicity in humans, but much evidence in experimental animals, and

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the IARC has classified ethylene oxide in category 1 ("carcinogenic in humans"), based primarily on evidence in animals and genotoxic considerations. The overall evaluation of the Working group of the IARC, updated in 1995, is based on the following supporting evidence.

Ethylene oxide is a directly acting alkylating agent that:

- induces a sensitive, persistent, dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone marrow cells of exposed workers;
- has been associated with malignancies of the lymphatic and hemopoietic systems in both humans and experimental animals;
- induces a dose-related increase in the frequency of hemoglobin adducts in exposed humans and a dose-related increase in the numbers of adducts in both DNA and hemoglobin in exposed rodents;
- induces gene mutations and heritable translocations in germ cells of exposed rodents;
- is a powerful mutagen and clastogen at all phylogenetic levels.

In 1979, three cases of hemopoietic cancer that had occurred between 1972 and 1977 were reported in workers at a Swedish factory where 50% ethylene oxide and 50% methyl formate had been used since 1968 to sterilize hospital equipment (22).

In epidemiological studies of exposure to ethylene oxide, the most frequently reported association has been with lymphatic and hemopoietic cancer. Two populations were studied: people using ethylene oxide as a sterilizing agent and chemical workers manufacturing or using ethylene oxide. Of studies of sterilization personnel, the largest and most informative is that conducted in the USA (23,24). Overall, mortality from lymphatic and hemopoietic cancers was only marginally raised, but there was a significant trend, especially for lymphatic leukemia and non-Hodgkin's lymphoma, in relation to estimated cumulative exposure. For exposure to 1 ppm (1.8 mg/m^3) over a working lifetime of 45 years, a ratio of 1.2 was estimated for lymphatic and hemopoietic cancers. The other studies of workers involved in sterilization in Sweden (25–27) and in the UK (28) each showed non-significant excesses of lymphatic and hemopoietic cancers. An assessment based on epidemiological data showed no increase in leukemia in those who had been exposed to ethylene oxide (29).

Because of the possibility of confounding occupational exposure in the studies of chemical workers exposed to ethylene oxide (20,25,26,28,30–38), less weight can be given to the positive findings. Nevertheless, they are compatible with a small but consistent excess of lymphatic and hemopoietic cancers found in studies of sterilization personnel. Some of the epidemiological studies have shown an additional risk of cancer of the stomach, which was significant only in one study from Sweden (25,26,30).

Second-Generation Effects

Teratogenicity

In animals, ethylene oxide has toxic effects on reproduction and is teratogenic, but the relevance of animal and epidemiological studies to occupational exposure of humans in the environment of sterilization units is unclear (SEDA-12, 576) (39).

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Ethylenediamine

General Information

Ethylenediamine is used to improve the solubility of theophylline in the formulation known as aminophylline (theophylline ethylenediamine). Aminophylline is converted to theophylline after oral and intravenous administration.

Ethylenediamine is also used as a stabilizer in creams and ointments.

Ethylenediamine tetra-acetic acid is a chelating agent that is used as an anticoagulant for collecting blood samples and for removing calcium from experimental fluids in laboratories.

Organs and Systems

Respiratory

Asthma has been reported after occupational exposure to ethylenediamine (1).

Skin

Cutaneous reactions have been reported with ethylenediamine (2).

Immunologic

Systemic contact dermatitis is a delayed hypersensitivity skin reaction that results from systemic exposure. Exanthematous systemic contact dermatitis from ethylenediamine has been reported with aminophylline. Disodium edetate (ethylenediamine tetra-acetic acid) has caused contact dermatitis after local application (SEDA-23, 242), and ethylenediamine cross-reacted in a patch test in a patient who had had contact dermatitis with hydroxyzine, an ethylenediamine derivative (SEDA-22, 178). Prior sensitization can occur to ethylenediamine in creams and ointments (SED-14, 485).

Originally described in 1984, baboon syndrome is a form of systemic contact dermatitis involving the buttocks and adjacent skin in a distribution reminiscent of the erythematous buttocks seen in baboons (3). Areas under the underwear, the inner thighs, and the axillae can also be affected. Most cases are caused by oral agents, suggesting that excretion of the antigen may be a factor. In one case systemic

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administration caused a reaction at a site that may have been previously exposed to topical ethylenediamine (2).

- A 64-year-old man developed a pruritic erythematous eruption in the perineal area a few hours after a stress test, during which he received dipyridamole and intravenous aminophylline. He had a morbilliform erythema of the perineal area under his underclothing anteriorly, with still more prominent erythema posteriorly. The measles-like rash lacked epidermal changes of exudation of scaling. A series of 20 standard patch tests were negative, except for a +++ response to ethylenediamine. On being questioned, he remembered using a topical medicament prescribed for his wife on this area in the distant past. He improved uneventfully with time and avoidance.

The authors proposed that the topical medicament had contained ethylenediamine.

- A 30-year-old woman developed a generalized urticarial reaction immediately after the intravenous administration of aminophylline (4). Skin intradermal testing was positive to ethylenediamine. Rechallenge was positive with intravenous aminophylline but negative with diprophylline, which does not contain ethylenediamine.

Most reports of aminophylline hypersensitivity reactions in the English language literature were delayed reactions. However, most of the Japanese cases were immediate reactions. Acetylation is the main metabolic pathway of ethylenediamine. Most Japanese are rapid or intermediate acetylators, while 50% of Caucasians are slow acetylators. This difference suggests an explanation for the different incidences of immediate and delayed reactions to ethylenediamine in Japanese and Caucasians.

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Etidocaine

See also Local anesthetics

General Information

Etidocaine is a highly lipid-soluble, long-acting aminoamide. It has a similar toxicity profile to that of bupivacaine and there is an increased risk of life-threatening cardiac events compared with lidocaine (1).

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Etifoxine

General Information

Etifoxine is a non-benzodiazepine drug, licensed in France for psychosomatic manifestations of anxiety.

Organs and Systems

Psychological, psychiatric

The psychomotor and amnesic effects of single oral doses of etifoxine (50 mg and 100 mg) and lorazepam (2 mg) were studied in 48 healthy subjects in a double-blind, placebo-controlled, randomized, parallel-group study (1). Its effects were assessed by a battery of subjective and objective tests that explored mood and vigilance, attention, psychomotor performance, and memory. Whereas vigilance, psychomotor performance, and free recall were significantly impaired by lorazepam, neither dose of etifoxine (50 mg and 100 mg) produced such effects. The results suggested that 50 mg and 100 mg single doses of etifoxine do not induce amnesia and sedation compared with lorazepam.

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Etodolac

See also Non-steroidal anti-inflammatory drugs

General Information

Etodolac, a pyranocarboxylic acid, was first marketed in the UK in 1986. By 1988, etodolac had been reported 27 times to the UK Committee on Safety of Medicines as being suspected of causing serious adverse reactions (1). In a French postmarketing safety study in 51 355 patients taking 200–600 mg/day, 10% of patients reported a total of 6236 adverse reactions and 9% dropped out because of adverse reactions, 21 of which were judged severe (2). In another four postmarketing surveillance studies in 8334 patients with rheumatic conditions who took 200–600 mg/day of etodolac for periods ranging from 4 weeks to 1 year, 23% reported adverse events and 9%

stopped taking the drug because of adverse reactions; gastrointestinal events were the most commonly reported (3).

Organs and Systems

Nervous system

Nervous system effects of etodolac include dizziness (4.4%), headache (6.0%), and tinnitus (2.6%).

Hematologic

One case of agranulocytosis, probably induced by etodolac, with the pattern common to the other NSAIDs, has been reported (4).

Gastrointestinal

Animal experiments, as well as endoscopic and ^{51}Cr blood loss studies in man, suggest that the gastric irritancy of etodolac is low (5,6), but such claims have to be regarded with the reservations expressed about all NSAIDs. Etodolac in short-term dosages of 200, 400, and 600 mg bd caused significantly less damage to both the gastric and the duodenal mucosa than aspirin 3.9 g/day (SEDA-12, 85). It had a less damaging effect on the stomach than naproxen in a short-term endoscopic study in rheumatoid arthritis (7). The most frequent adverse effects in 1379 patients in trials were gastrointestinal symptoms: 8.9% of patients had nausea, 5.8% epigastric pain, 5.7% heartburn, and 5.2% indigestion; 1.9% of patients had to be withdrawn because of these adverse effects.

Acute colitis demonstrated by endoscopy and rechallenge was reported in two patients taking etodolac for arthritis (8). Colonic strictures have been described in another report (SEDA-22, 115).

Skin

Skin rashes occur in 3% of patients who take etodolac (SEDA-12, 85).

Susceptibility Factors

Age

The safety profiles of etodolac in elderly and younger patients are similar (SEDA-19, 98).

Drug Administration

Drug formulations

The long-term treatment safety profile of a modified-release formulation of etodolac was similar to that of the standard formulation (SEDA-18, 104).

Drug dosage regimens

In 1986, the UK Drug Safety Research Unit at Southampton published a report on its prescription event monitoring study of etodolac (SEDA-13, 80). Etodolac was rated effective in only 56% of 9109 patients, and the Unit concluded that the average dosage used (400 mg/day) was too low to be effective. Consequently, the adverse reaction figures should be viewed with great caution. Indeed, at an adequate dosage they might actually be unfavorable, since in this study the rate of dyspepsia during the first month was 16 per 1000 compared with 3 per 1000 for piroxicam. After the first month, the rates were similar for etodolac and piroxicam. Few serious events were recorded: exfoliative dermatitis in one patient with psoriatic arthritis and 20 cases of hematemesis or melena.

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Etomidate

See also General anesthetics

General Information

Etomidate, a non-barbiturate anesthetic, is considered to be safe, especially in patients with hemodynamic instability. The most common complications of using etomidate are venous sequelae, pain on injection (1), and involuntary muscle movements (SED-11, 211) (2).

Organs and Systems

Cardiovascular

The cardiorespiratory tolerance of etomidate is usually excellent (3), but cardiovascular instability has been described after a bolus dose (4).

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Nervous system

In 104 patients, the frequency of pain on injection of etomidate was 32–53% and was severe in 5–20% of patients (5). The frequency of involuntary movements was 15–35%. The frequency of both pain and involuntary muscle movements was least when fentanyl 2.5 μg/kg was given before etomidate. There was no significant relation between pain and muscle movement. A medium-chain triglyceride and soya bean emulsion formulation has been used for anesthetic induction, in an attempt to reduce the unwanted adverse effects of pain on injection and thrombophlebitis (6).

Myoclonus has been noted, and can be dangerous in open eye surgery (7).

Etomidate produced activation of epileptiform activity, and electrographic seizures during craniotomy in epileptic patients (8). Generalized seizures were noted after etomidate induction in 20% of 30 patients without a history of epilepsy (9). Cerebral excitation can also occur after recovery from etomidate anesthesia, with potential respiratory disturbance (10,11). Caution should be exercised when giving etomidate to patients with a history of seizures (SEDA-18, 113).

When etomidate was given to 12 patients who had seizures of short duration during electroconvulsive therapy conducted previously under propofol anesthesia, mean seizure duration was significantly increased with etomidate anesthesia (12). However, there is no evidence that this observation is associated with an improved psychiatric outcome.

Endocrine

Adrenocortical function has been assessed in a randomized trial after intravenous etomidate in 30 patients who required rapid-sequence induction and tracheal intubation (13). The controls received midazolam. Etomidate caused adrenocortical dysfunction, which resolved after 12 hours.

Cortisol and aldosterone concentrations were reduced by etomidate in adults (14,15), but the clinical relevance was minimal after a single bolus (16). A reduction in cortisol was reported 2 hours after delivery in 40 infants whose mothers received etomidate for cesarean section. There were also nine cases of severe to moderate hypoglycemia in this study, but the changes in blood glucose concentration were not significantly different from those in controls (17).

Hematologic

Hemolysis has been reported after the administration of etomidate (18). It may be related to the use of propylene glycol as a solvent (19,20).

Platelet hyperaggregability after general anesthesia has been reported in patients undergoing vascular surgery. The effect of etomidate and thiopental on platelet function has now been examined in 46 patients undergoing infrainguinal vascular surgery (21). Etomidate caused significant platelet inhibitory effects, whereas the effects of thiopental were minor. This may affect the choice of anesthetic in patients with compromised hemostasis.

Immunologic

Transient erythema has been described, but histamine release does not occur (22).

Etomidate is the induction agent of choice in atopic patients, in whom etomidate, fentanyl, and vecuronium comprise the safest combination of drugs for general anesthesia. However, non-allergic anaphylactic (anaphylactoid) reactions have been observed, even with this combination (23,24), and it can even be life-threatening; one patient also had a myocardial infarction (24).

Drug Administration

Drug formulations

An oral transmucosal formulation of etomidate, which is absorbed over 15 minutes, has been studied in 10 healthy adults at four doses: 12.5, 25, 50, and 100 mg (25). Dose-related drowsiness and light sleep occurred 10–20 minutes after administration. Peak serum concentrations and clinical effects were noted at about 20 minutes, with no clinical effect noticeable by 60 minutes. There was no vomiting and only four patients had transient nausea. Two patients had brief episodes of involuntary tremor with the 100 mg dose. Of note was the increasingly unpleasant taste with increasing dose and the apparent reduction in absorption with higher doses.

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Euphorbiaceae

See also Herbal medicines

General Information

The genera in the family of Euphorbiaceae (Table 1) include various spurges, such as poinsettia and croton.

Breynia officinalis

Breynia officinalis (Chi R Yun) contains the saponin breynin, and terpenic and phenolic glycosides (1). Its Chinese name, Chi R Yun, means dizziness or vertigo for 7 days. It has been used to treat venereal diseases, contusions, heart failure, growth retardation, and

Table 1 The genera of Euphorbiaceae

Acalypha (copperleaf)
Adelia (wild lime)
Alchornea (alchornea)
Alchorneopsis (alchorneopsis)
Aleurites (aleurites)
Antidesma (china laurel)
Argythamnia (silverbush)
Bernardia (myrtle croton)
Bischofia (bishopwood)
Breynia (breynia)
Caperonia (false croton)
Chamaesyce (sandmat)
Chrozophora (chrozophora)
Claoxylon (claoxylon)
Cnidoscolusohl (cnidoscolus)
Codiaeum (codiaeum)
Croton (croton)
Dalechampia (dalechampia)
Ditta (ditta)
Drypetes (drypetes)
Euphorbia (spurge)
Flueggea (bushweed)
Gymnanthes (gymnanthes)
Hippomane (hippomane)
Hura (sandbox tree)
Hyeronima (hyeronima)
Jatropha (nettle spurge)
Leptopus (maidenbush)
Macaranga (macaranga)
Mallotus (mallotus)
Manihot (manihot)
Margaritaria (margaritaria)
Mercurialis (mercurialis)
Pedilanthus (pedilanthus)
Pera (pera)
Phyllanthus (leaf flower)
Reverchonia (reverchonia)
Ricinus (castor)
Sapium (milk tree)
Savia (savia)
Sebastiania (Sebastian bush)
Stillingia (toothleaf)
Tetracoccus (shrubby spurge)
Tragia (noseburn)
Triadica (tallow tree)
Vernicia (vernicia)

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conjunctivitis in combination with other traditional Chinese medicines.

Adverse effects

Taiwanese doctors have reported two cases of hepatocellular injury after oral administration of infusions of *B. officinalis* (2).

- One of the two patients had taken 1500 mg of the lower stem and root of *B. officinalis* boiled in water in a suicide attempt. She was admitted with vomiting and headache and later developed gastritis, hematuria, and liver damage. Symptomatic treatment resulted in full recovery.
- A 51-year-old woman consumed 20 pieces of the lower stem and root of *B. officinalis* to treat dermatitis. She developed nausea, vomiting, and dizziness, and had raised liver enzymes. Her liver function recovered 1 month after withdrawal of *B. officinalis*.

When *B. officinalis* was mistaken for a similar plant, *Securinega suffruticosa*, and was cooked in a soup used for muscle aches, lumbago, or as a tonic by 19 patients, 14 developed diarrhea, 10 had nausea and felt cold, nine had sensations of abdominal fullness, and seven vomited (3). Liver enzymes rose and the median times to median peak activities were 3 days for alanine transaminase, 2 days for aspartate transaminase, 5 days for alkaline phosphatase, and 12 days for gamma glutamyltranspeptidase. The liver damage was hepatocellular liver injury rather than cholestatic and marked jaundice did not develop.

Croton tiglium

The oil of *Croton tiglium* (croton) has a violent purgative action and contains tumor-promoting phorbol diesters and triesters.

Adverse effects

Croton oil has been used as a peeling agent in phenol as a carrier; its use in concentrations of 2% and over is almost always associated with depigmentation of the skin and delays in healing in areas other than the thick skin of the lower nose and around the mouth (4).

Croton is also the name given to *Codiaeum variegatum*, a highly decorative potted plant. Handling this plant over a period of 6 months produced contact eczema of the hands in a nursery gardener. Patch tests with croton leaves were positive (5).

Ricinus communis

Castor oil is the fixed oil obtained from the seeds of *Ricinus communis* (castor) by cold expression. The whole beans contain a variety of substances that are not expressed with the oil, including the toxin ricin (6,7).

Adverse effects

When taken by mouth, especially in large doses, castor oil can cause violent purgation with nausea, vomiting, colic, and a risk of miscarriage.

Transdermal exposure to ricin is not serious, since it is not well absorbed through the skin. Oral exposure, for example by ingestion of castor beans, can cause severe gastroenteritis, gastrointestinal hemorrhage, and death due to circulatory collapse. Parenteral injection of ricin is rapidly fatal, as is aerosol exposure; the lethal dose by these routes is 5–10 micrograms/kg (8).

Immunologic

Anaphylaxis has been attributed to consumption of whole castor beans (9).

- A 44-year-old woman chewed a castor bean seed and within minutes developed urticaria, drowsiness, Quincke's edema, and extreme hypotension. Her anaphylactic shock was treated with adrenaline, intravenous glucocorticoids, antihistamines, and intravenous fluids. She quickly recovered and a subsequent blood test demonstrated CAP-RAST to castor beans.

Fetotoxicity

In 498 women who had recently taken castor oil and possibly herbal substances called "sihlambezo" before artificial rupture of membranes, fetal passage of meconium was more common (10). However, in a study of 100 women castor oil had no effect on the rate of meconium-stained liquor (11).

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Everolimus

General Information

Everolimus is an immunosuppressive macrolide that also has synergistic actions with ciclosporin and interrupts the proliferative responses of vascular and bronchial smooth muscle cells. In a phase I trial, its safety profile and pharmacokinetics were assessed during a 4-week course of once-daily sequential ascending doses (0.75, 2.5, or 7.5 mg/day) in renal transplant recipients on a stable regimen of ciclosporin and prednisone (1). Pharmacokinetic data showed dose proportionality, a good correlation between trough and AUC concentrations, and moderate accumulation (2.5-fold). Absorption was within 2 hours, and the half-life was 16–19 hours. There was no evidence of a pharmacokinetic interaction of ciclosporin with everolimus. Virtually every patient in this study had at least one adverse event and 43% of patients treated with everolimus 7.5 mg/day had serious adverse events. In all everolimus groups there was an increased incidence of infectious episodes (*Herpes simplex*, upper respiratory infections, pharyngitis, pneumonia, and sinusitis). Similarly, adverse events involving the gastrointestinal system (diarrhea, nausea, and vomiting) were more common. Serum concentrations of triglycerides and total cholesterol increased significantly over time. Individuals treated with everolimus 7.5 mg/day had significant falls in white cell count (–2.6%) and platelet count (–51%); the nadir occurred on day 19 and the cell counts recovered spontaneously without withdrawal of the drug. Serum creatinine concentrations and blood pressure did not change.

Drug–Drug Interactions

Ciclosporin

Both everolimus and ciclosporin are extensively biotransformed by CYP3A and are substrates for P-glycoprotein. However, in a multicenter randomized double-blind study in 101 patients, 1 year after kidney transplantation, who were randomly assigned to receive everolimus 0.5, 1, and 2 mg bd plus ciclosporin and prednisone, the pharmacokinetics of ciclosporin were similar to published values in patients not taking everolimus (2).

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Eye-drops and ointments

General Information

Eye-drops and ointments are specialized pharmaceutical formulations intended to produce therapeutic concentrations of the active drug in ocular structures; a lower dose can be used than would be necessary to obtain the same effect by systemic administration. They can cause local adverse effects in the eye due either to the active ingredient or to excipients in the liquid or solid vehicle. The excipients included in modern ophthalmic medicines increase the viscosity of the drug, help to maintain it in solution or suspension, and are thought to stay longer on the exterior of the eye, leading to a longer contact time and possibly greater absorption of the drug than is the case with a simple aqueous solution (1).

Excipients

Methylcellulose is a vehicle used in eye-drops and contact lens solutions (SEDA-1, 369). It is non-irritant and has a good refractive index. A 1% solution is well retained in the conjunctival sac. Corneal cultures have been stimulated by methylcellulose, resulting in increased growth of cells (2); tear-film break-up time was increased four-fold with 2% methylcellulose. Hydroxypropyl methylcellulose is also used as artificial tears for people with dry eyes (3).

Petrolatum-mineral oil ointment is retained longer on the eye than other vehicles. The large molecules of the petrolatum-mineral oil-base ointment are not easily removed by blinking, and a component of the corneal tear film is a non-polar oil. Ointments are oil bases and non-polar, which is why they are readily absorbed by the pre-corneal and conjunctival tear films. To maintain drug contact with the eye, patching is recommended (1).

Polyvinyl alcohol, a synthetic long-chain alcohol, has been used as a component of various ophthalmic drug vehicles. For retaining clear vision and longer drug contact with the eye, polyvinyl alcohol is superior to saline. Polyvinyl alcohol has good drug compatibility and it acts as a wetting agent, lowering surface tension; at a concentration of 1.4% it does not interfere with corneal wound healing (1).

Systemic effects of ophthalmic medications

Of the drug that is administered in eye-drops, 80% diffuses into the general circulation and can have systemic effects, even when low concentrations are used (1). The lacrimal pump is the essential route of diffusion from eye-drops into the systemic circulation, through active cellular absorption in the lacrimal secretory pathways. The active ingredient avoids first-pass metabolism and reaches its site of action directly, resulting in increased systemic availability. All the same, this form of treatment is generally very well tolerated, when one bears in mind the immense volume of eye-drops prescribed by ophthalmologists each day.

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The systemic effects exerted by eye-drops are most pronounced in the case of agonists and antagonists in the autonomic nervous system. For example, beta-blockers in eye-drops can cause bronchospasm, heart failure, syncope, and psychiatric disorders (4–6), especially at high doses and with non-selective beta-blockers, although these adverse reactions are usually related to failure to observe prescribing precautions (1).

Alpha$_2$-adrenoceptor agonist eye-drops can cause hypotension (7).

Except in patients at special risk (children under the age of 30 months and the elderly) parasympathomimetic eye-drops cause few systemic adverse effects (SEDA-16, 543).

Cholinesterase inhibitors, which have curare-like properties, are contraindicated for 6 weeks before general anesthesia.

In the very young and the very old patients atropine eye-drops carry a risk of cardiovascular collapse and neuropsychiatric disturbances (SEDA-16, 543).

Systemic problems can also develop with antimicrobial eye-drops (8) and contact lens products (9,10).

Local adverse effects

Ophthalmic drugs can cause problems of local tolerance, but with variable frequency. They can cause pain on instillation, allergic reactions, delayed healing, punctate keratitis, and disturbances of lacrimal secretion and accommodation. These local problems may be responsible for poor patient adherence to therapy.

Contact dermatitis

Allergic contact dermatitis is the most common dermatological condition that affects the eyelids. Allergic contact dermatitis was found in a retrospective study in 151 (74%) of 203 patients with persistent or recurrent eyelid dermatitis with or without dermatitis elsewhere (11): 46 had protein-contact dermatitis, but only 14 had protein-contact dermatitis without concurrent allergic contact dermatitis; 23 patients had atopic eczema, of whom 16 also had allergic contact dermatitis, protein-contact dermatitis, or both. Other conditions included seborrheic dermatitis, psoriasis, dry eyes, and dermatomyositis or overlapping connective tissue disease. Important sources of contact sensitivity were topical ocular medications, including glucocorticoids, cosmetics, metals, dust mites, animal dander, and artificial nails; only five cases were caused by nail lacquer.

Susceptibility factors

Elderly people are particularly likely to make errors in the administration of ophthalmic medications, resulting in overdosage and adverse toxic effects or underdosage with inadequately controlled glaucoma (12). This may reflect impaired memory, mental confusion, impaired vision, hearing, and mobility, or a combination of these factors. It is wise to assess both adherence to therapy and administration technique to ensure the safe and effective use of ophthalmic formulations in these patients (SEDA-21, 487) (13).

Use of eye-drops

A few simple rules can reduce the incidence of adverse effects of eye-drops and improve adherence to therapy:

- respect the contraindications and precautions applicable to the drug (1);
- start with the lowest possible dose, especially in children and elderly people (12);
- never administer more than 30 µl of an eye-drop at any time, and give it only into the superolateral corner of the eye (13);
- close the medial canthus with the finger after instillation of the eye-drop to minimize systemic absorption (14).

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Ezetimibe

General Information

Ezetimibe is a selective potent inhibitor of the intestinal absorption of dietary and biliary cholesterol. A total of 432 patients were included in a pooled analysis of two phase-II studies, both lasting for 12 weeks; ezetimibe was well tolerated, with an adverse events profile similar to that of placebo (1). In 668 patients who took ezetimibe with simvastatin, the adverse effects were similar to those with simvastatin alone (2).

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Fabaceae

See also Herbal medicines

General Information

The genera in the family of Fabaceae (Table 1) (formerly Leguminosae) include broom, liquorice, senna, tamarind, and a variety of pulses, such as fava beans, lentil, peas, and vetches.

Cassia species

The leaves and fruits of *Cassia angustifolia* and *Cassia senna* (senna) contain laxative anthranoid derivatives. Mutagenicity testing of sennosides has produced negative results in several bacterial and mammalian systems, except for a weak effect in *Salmonella typhimurium* strain TA102 (1,2). No evidence of reproductive toxicity of sennosides has been found in rats and rabbits (3).

Senna is widely used in fairly low doses without serious problems; it has also been used in a very high dosage form to clear the colon before radiological examination. In this form it is generally well tolerated, but it should not be used if there is any predisposition to colonic rupture.

Adverse effects

The safety and efficacy of senna have been reviewed (4). Its rhein-anthrone-induced laxative effects occur through two distinct mechanisms, an increase in intestinal fluid transport, which causes accumulation of fluid intraluminally, and an increase in intestinal motility. Senna can cause mild abdominal complaints, such as cramps or pain. Other adverse effects are discoloration of the urine and hemorrhoidal congestion. Prolonged use and overdose can result in diarrhea, extreme loss of electrolytes, especially potassium, damage to the surface epithelium, and impairment of bowel function by damage to autonomic nerves. Abuse of senna has also been associated with melanosis coli, but resolution occurs 8–11 months after withdrawal. Tolerance and genotoxicity do not seem to be problems associated with senna, especially when used periodically in therapeutic doses.

Liver

Abuse of senna can cause hepatitis (5,6).

Skin

Occupational allergic contact dermatitis has been attributed to a species of *Cassia* (7,8), as has contact urticaria (9).

Musculoskeletal

Finger clubbing (hypertrophic osteoarthropathy) has been reported in patients who have abused senna (10–15).

Lactation

When a standardized preparation containing senna pods (providing 15 mg of sennosides per day) was given to breastfeeding mothers, the suckling infants were only exposed to a non-laxative amount of rhein, which

Table 1 The genera of Fabaceae

Abrus (abrus)
Acacia (acacia)
Adenanthera (bead tree)
Aeschynomene (joint vetch)
Afzelia (mahogany)
Albizia (albizia)
Alhagi (alhagi)
Alysicarpus (moneywort)
Amorpha (false indigo)
Amphicarpaea (hog peanut)
Anadenanthera (anadenanthera)
Andira (andira)
Anthyllis (kidney vetch)
Apios (groundnut)
Arachis (peanut)
Aspalathus (aspalathus)
Astragalus (milk vetch)

Baphia (baphia)
Baptisia (wild indigo)
Barbieria (barbieria)
Bauhinia (bauhinia)
Bituminaria (bituminaria)
Brongniartia (green twig)
Brya (coccuswood)
Butea (butea)

Caesalpinia (nicker)
Cajanus (cajanus)
Calliandra (stick pea)
Calopogonium (calopogonium)
Canavalia (jackbean)
Caragana (peashrub)
Carmichaelia (carmichaelia)
Cassia (cassia)
Centrosema (butterfly pea)
Ceratonia (ceratonia)
Cercis (redbud)
Chamaecystis (chamaecystis)
Chamaecrista (sensitive pea)
Chapmannia (chapmannia)
Christia (island pea)
Cicer (cicer)
Cladrastis (yellowwood)
Clianthus (glory pea)
Clitoria (pigeon wings)
Codariocalyx. (tick trefoil)
Cojoba (cojoba)
Cologania (cologania)
Colutea (colutea)
Copaifera (copaifera)
Coronilla (crown vetch)
Coursetia (baby bonnets)
Crotalaria (rattlebox)
Crudia (bedstraw)
Cullen (scurf pea)
Cyamopsis (cyamopsis)
Cynometra (cynometra)
Cytisus (broom)

Dalbergia (Indian rosewood)
Dalea (prairie clover)
Daniellia (daniellia)
Delonix (delonix)
Derris (derris)
Desmanthus (bundle flower)
Desmodium (tick trefoil)
Dialium (dialium)

Continued

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Table 1 Continued

Dichrostachys (dichrostachys)
Dioclea (dioclea)
Diphysa (diphysa)
Dipogon (dipogon)
Dipteryx (dipteryx)

Ebenopsis (Texas ebony)
Entada (callingcard vine)
Enterolobium (enterolobium)
Eriosema (sand pea)
Errazurizia (dunebroom)
Erythrina (erythrina)
Erythrophleum (sasswood)
Eysenhardtia (kidneywood)

Faidherbia (acacia)
Falcataria (peacock's plume)
Flemingia (flemingia)

Galactia (milk pea)
Galega (professor weed)
Genista (broom)
Genistidium (brush pea)
Gleditsia (locust)
Gliricidia (quickstick)
Glottidium (glottidium)
Glycine (soybean)
Glycyrrhiza (licorice)
Gymnocladus (coffee tree)

Haematoxylum (haematoxylum)
Halimodendron (halimodendron)
Havardia (havardia)
Hedysarum (sweet vetch)
Hippocrepis (hippocrepis)
Hoffmannseggia (rush pea)
Hoita (leather root)
Hymenaea (hymenaea)

Indigofera (indigo)
Inga (inga)
Inocarpus (chestnut)

Kanaloa (kanaloa)
Kummerowia (kummerowia)

Lablab (lablab)
Laburnum (golden chain tree)
Lathyrus (pea)
Lens (lentil)
Lespedeza (lespedeza)
Leucaena (lead tree)
Lonchocarpus (lance pod)
Lotononis (lotononis)
Lotus (trefoil)
Lupinus (lupin)
Lysiloma (falsetamarind)
Maackia (maackia)
Machaerium (machaerium)
Macroptilium (bush bean)
Macrotyloma (macrotyloma)
Marina (false prairie clover)
Medicago (alfalfa)
Melilotus (sweet clover)
Mimosa (sensitive plant)
Mucuna (mucuna)
Myrospermum (myrospermum)
Myroxylon (myroxylon)

Neonotonia (neonotonia)
Neorudolphia (neorudolphia)
Neptunia (puff)
Nissolia (yellowhood)

Olneya (olneya)
Onobrychis (sainfoin)
Ononis (restharrow)
Orbexilum (leather root)
Ormosia (ormosia)
Ornithopus (bird's foot)
Oxyrhynchus (oxyrhynchus)
Oxytropis (locoweed)

Pachyrhizus (pachyrhizus)
Paraserianthes (paraserianthes)
Parkinsonia (paloverde)
Parkia (parkia)
Parryella (parryella)
Pediomelum (Indian breadroot)
Peltophorum (peltophorum)
Pentaclethra (pentaclethra)
Pericopsis (peperomia)
Peteria (peteria)
Phaseolus (bean)
Physostigma (physostigma)
Pickeringia (chaparral pea)
Pictetia (pictetia)
Piscidia (piscidia)
Pisum (pea)
Pithecellobium (blackbead)
Poitea (wattapama)
Prosopis (mesquite)
Psophocarpus (psophocarpus)
Psoralidium (scurf pea)
Psorothamnus (dalea)
Pterocarpus (pterocarpus)
Pueraria (kudzu)

Retama (bridal broom)
Rhynchosia (snoutbean)
Robinia (locust)
Rupertia (rupertia)

Samanea (raintree)
Schizolobium (Brazilian firetree)
Schleinitzia (strand tangantangan)
Scorpiurus (scorpion's tail)
Senna (senna)
Serianthes (vaivai)
Sesbania (riverhemp)
Sophora (necklace pod)
Spartium (broom)
Sphaerophysa (sphaerophysa)
Sphenostylis (sphenostylis)
Sphinctospermum (sphinctospermum)
Stahlia (stahlia)
Strongylodon (strongylodon)
Strophostyles (fuzzy bean)
Stryphnodendron (stryphnodendron)
Stylosanthes (pencil flower)
Sutherlandia (sutherlandia)

Tamarindus (tamarind)
Taralea (taralea)
Tephrosia (hoarypea)
Teramnus (teramnus)
Tetragonolobus (tetragonolobus)
Thermopsis (golden banner)
Ticanto (gray nicker)
Trifolium (clover)
Trigonella (fenugreek)

Ulex (gorse)

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Vicia (vetch)
Vigna (cowpea)
Virgilia (virgilia)
Wisteria (wisteria)
Zapoteca (white stick pea)
Zornia (zornia)

remained a factor of 10^{-3} below the maternal intake of this active metabolite (16).

Tumorigenicity
A well-defined purified senna extract was not carcinogenic, when administered orally to rats in daily doses up to 25 mg/kg for 2 years (17).

Drug interactions
An unusual Antabuse-type reaction reported on one occasion seems to have been due to an interaction of metronidazole with the alcohol present in the high-dosage form X-Prep (SEDA-15, 398).

Crotalaria species

Most of the members of the *Crotalaria* (rattlebox) species contain pyrrolizidine alkaloids, such as crotaline and monocrotaline, and therefore have hepatotoxic potential (18). These alkaloids are covered in a separate monograph.

Adverse effects
Pyrrolizidine alkaloids cause obstruction of the hepatic venous system and can lead to hepatic necrosis. Clinical manifestations include abdominal pain, ascites, hepatomegaly, and raised serum transaminases. The prognosis is often poor, death rates of 20–30% being reported. In an outbreak of veno-occlusive disease in the Sarguja district of India, probably caused by consumption of cereals mixed with *Crotalaria* seeds, 28 of 67 patients died (19).

It is prudent to avoid exposing unborn or suckling children to herbal remedies containing pyrrolizidine alkaloids. Animal studies have shown that transplacental passage and transfer to breast milk are possible, and there is a human case on record of fatal neonatal liver injury, in which the mother had used a herbal cough tea containing pyrrolizidine alkaloids throughout her pregnancy.

Cyamopsis tetragonoloba

Guar gum, which is covered in a separate monograph, comes from the endosperm of the seeds of *Cyamopsis tetragonoloba* (cluster bean). It has a small hypolipidemic effect (20) and a small blood glucose-lowering effect (21).

Adverse effects
Guar gum causes abdominal pain, flatulence, diarrhea, and cramps (22). It has been repeatedly associated with esophageal obstruction (23).

Guar gum can cause occupational rhinitis and asthma. Of 162 employees at a carpet-manufacturing plant, in which guar gum is used to adhere the dye to the fiber, 37 (23%) had a history suggestive of occupational asthma and 59 (36%) of occupational rhinitis (24). Eight (5%) had immediate skin reactivity to guar gum. Eleven (8.3%) had serum IgE antibodies to guar gum.

Guar gum reduces the speed but not the extent of absorption of digoxin (25), nitrofurantoin (26), and paracetamol (27). It reduces both the speed and extent of absorption of phenoxymethylpenicillin (25).

Cytisus scoparius

Cytisus scoparius (Scotch broom) contains the toxic alkaloid sparteine and related quinolizidine alkaloids, such as isosparteine and cytisine. Sparteine has been used as a marker of drug metabolism by CYP2D6 (28) and is covered in a separate monograph.

Adverse effects
Inexpert self-medication with a broom tea has resulted in fatal poisoning with clinical symptoms of ileus, heart failure, and circulatory weakness.

It is prudent to avoid broom formulations during pregnancy, not only because sparteine has abortifacient potential but also because of evidence that the plant produced malformed lambs in feeding trials.

Dipteryx species

The seeds of *Dipteryx odorata* (Dutch tonka bean) and *Dipteryx oppositofolia* (English tonka bean) are said to yield 1–3% of the non-anticoagulant coumarin, which is covered in a separate monograph.

Genista tinctoria

Genista tinctoria (dyer's broom) contains 0.3–0.8% of toxic quinolizidine alkaloids, such as anagyrin, cytisine, and *N*-methylcytisine. The last two constituents have peripheral effects similar to those of nicotine, whereas their central activity may be different. Anagyrine is a suspected animal teratogen and cytisine has teratogenic activity in rabbits.

Glycyrrhiza glabra

Glycyrrhiza glabra (licorice) (29) contains a wide variety of chalcones, coumarins, flavonoids, and triterpenoids, some of which mimic the mineralocorticoid actions of aldosterone. The saponin glycoside glycyrrhizinic acid (glycyrrhetinic acid, carbenoxolone) (30) and deglycyrrhizinized licorice (Caved-S) (31) have both been used to treat gastric ulceration, but have been displaced by better drugs.

Licorice is used widely and is found in a variety of sources (32):

Licorice sticks, bricks, cakes, toffee, pipes, bars, balls, tubes, Catherine wheels, pastilles, and Licorice Allsorts
Torpedos
Blackcurrant
Pomfret (Pontefract) cakes
Servez vous

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Sorbits chewing gum
Stimorol chewing gum
Health products
Liquirizia naturale
Licorice-flavoured diet gum
Throat pearls
Licorice-flavored cough mixtures
Herbal cough mixtures
Antibron tablets
Licorice tea
All types of licorice root
Afghan, Chinese, Iranian, Russian, Turkish, and of unknown origin
Chewing tobacco
Alcoholic drinks
Belgian beers
Pastis brands
Anisettes (raki, ouzo, Pernod).

Adverse effects

Most individuals can consume 400 mg of glycyrrhizin daily without adverse effects, but some individuals develop adverse effects following regular daily intake of as little as 100 mg of glycyrrhizin (33).

Cardiovascular

In healthy volunteers who took licorice corresponding to glycyrrhizinic acid 75–540 mg/day for periods of 2–4 weeks, there was an average increase in systolic blood pressure of 3.1–14.4 mmHg (34). The increase in blood pressure was dose-related and the authors concluded that as little as 50 g/day of licorice for 2 weeks would have caused a significant rise in blood pressure.

Sensory systems

Five patients who had consumed large amounts (0.1–1 kg) of licorice subsequently had transient visual loss/aberrations (35). Glycyrrhizinic acid in licorice causes vasoconstriction in vascular smooth muscle and the authors therefore speculated that vasospasm of the retinal or occipital artery had caused the problems.

Electrolyte balance

The active ingredients of licorice inhibit the breakdown of mineralocorticoids by inhibiting 11-beta-hydroxysteroid dehydrogenase type 2, and its adverse effects relate mainly to mineralocorticoid excess, with sodium retention, potassium loss, and inhibition of the renin–angiotensin–aldosterone system (36).

In two cases prolonged intake of relatively small amounts of licorice resulted in hypertension, encephalopathy, and pseudohyperaldosteronism (37). Both patients were highly susceptible to the adverse effects of glycyrrhizinic acid because of 11-beta-hydroxysteroid dehydrogenase deficiency.

- A 44-year-old woman developed an irregular heart rhythm and repeated episodes of life-threatening torsade de pointes (38). Her serum potassium was 2.3 mmol/l. Treatment with an infusion of potassium and magnesium promptly restored normal rhythm. The cause of the problem was identified as the patient's habit of consuming large (but not more closely defined) quantities of licorice daily. One year after this episode she was still abstaining from licorice and showed no signs of cardiac disease.
- A 39-year-old woman had a potassium concentration of 2.9 mmol/l at a routine checkup (39). She denied taking any medications except a "cleansing tea" purchased from a health food company. The tea was analysed and found to contain significant amounts of licorice. Her potassium concentration normalized after withdrawal of the product and potassium supplementation.
- A 67-year-old Chinese man developed progressive muscular weakness (40). His medical history was unremarkable, but his urinary potassium excretion was high and he had hypokalemia and low plasma renin activity. He admitted taking a powdered Chinese herbal formulation for about 4 months, which was shown to contain large amounts of glycyrrhizinic acid (336 mg/day). He was treated with spironolactone, and 2 weeks later his potassium values had normalized.

Two patients who used licorice-flavored chewing gum developed severe hypokalemia (32).

- A 21-year-old woman who took licorice about 100 g/day developed a headache, hypertension (190/120 mmHg), and hypokalemia (2.6 mmol/l). She stopped eating licorice and instead used a chewing gum that also contained licorice (daily intake of glycyrrhizinic acid about 120 mg). Three weeks after she stopped using the gum her blood pressure was 110/80 mmHg and plasma potassium concentration 5.3 mmol/l.
- A 35-year-old woman developed pretibial edema and hypokalemia (2.2 mmol/1) after using a licorice-flavored chewing gum (about 50 mg of glycyrrhizinic acid per day). She stopped using the gum and improved within 2 weeks.

In six male volunteers who took glycyrrhizinic acid for 7 days, serum, urinary, and sweat electrolytes values were consistent with a mineralocorticoid-like effect (41). Plasma renin activity was suppressed, and plasma cortisol and aldosterone progressively fell during treatment. The authors proposed that glycyrrhizinic acid initially acts by increasing the effect of endogenous mineralocorticoids, and then when it or its metabolites accumulate it may also have a direct mineralocorticoid-like effect itself.

Lupinus species

Lupinus (lupin) seeds are commonly taken as an appetizer in Southern Europe and the Middle East. Lupin flour has been used as a source of energy and protein (42,43). An extract of *Lupus termis* has been used to treat chronic eczema (44).

Adverse effects

Anticholinergic effects of lupin poisoning have been reported (45).

- A 72-year-old Portuguese woman presented to an emergency department with classic anticholinergic

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signs: sudden onset of nausea and vomiting, blurred vision, generalized weakness, and tachycardia (46). She had taken a herbal product containing lupin seeds in the belief that it would cure her recently diagnosed diabetes mellitus.

Analysis of the product identified the preponderant compound as oxosparteine, which has powerful anticholinergic effects.

Medicago species

Medicago sativa (alfalfa) sprouts are commonly used as a source of protein.

Adverse effects

Skin

Dermatitis has been recorded after the ingestion of infusions made from alfalfa seeds. Dermatitis has also been reported in horse handlers exposed to the straw itch mite, *Pyemotes tritici*, contaminating alfalfa seeds (47).

Immunologic

Prolonged ingestion of alfalfa seeds or alfalfa tablets has been associated with the induction or exacerbation of a lupus-like syndrome in humans, perhaps because of the canavanine alfalfa contains (48,49).

Infection risk

Alfalfa seeds are readily infected and there have been numerous reports of infections arising from the consumption of alfalfa sprouts grown from contaminated seeds. The most common infections are with *Salmonella* species, including *Salmonella enterica* (50), *Salmonella havana* (51), *Salmonella kottbus* (52,53), *Salmonella mbandaka* (54), *Salmonella muenchen* (55), *Salmonella paratyphi* (56), *Salmonella stanley* (57), and other serotypes (58,59). Occasionally, other organisms occur, such as *Listeria* (60) and *Escherichia coli* (61,62).

Melilotus officinalis

Melilotus officinalis (sweet clover) contains coumarin, 3,4-dihydrocoumarin (melilotine), ortho-coumaric acid, ortho-hydroxycoumaric acid, and the ortho-glucoside of ortho-coumaric acid (melilotoside). Withering of the plant leads to enzymatic glycoside hydrolysis and the resulting ortho-coumaric acid is spontaneously transformed to coumarin; the dried herb therefore smells strongly of coumarin (see separate monograph). *M. officinalis* has been used to treat lymphedema and the edema of chronic venous insufficiency.

Myroxylon species

Balsam of Peru is derived from species of *Myroxylon* such as *Myroxylon balsamum* and *Myroxylon pereirae* and has been used in medicinal and cosmetic ointments for centuries. It contains about 25 different substances, including triterpenoids, and can cause allergic reactions. Its sensitizing constituents have been determined (63).

Adverse effects

Balsam of Peru is a topical photosensitizer (SEDA-19, 162) and can cause contact urticaria (64,65). A systemic contact dermatitis has been reported after oral administration (66). In one case an allergic contact dermatitis in a patient sensitive to balsam of Peru caused a primary eruption on the face with secondary purpuric vasculitis-like eruptions on both legs (67).

In 60 patients with positive patch-test reactions to a fragrance mix or *M. pereirae* resin (balsam of Peru) there were positive immediate contact reactions to *M. pereirae* resin in 57% and to the fragrance mix in 12% (68). In a control group ($n = 50$) of eczematous, patch test-negative patients there were positive immediate reactions to *M. pereirae* resin in 58% and to the fragrance mix in 12%. The authors commented that the absence of a significant difference between the fragrance-allergic group and the control group was in keeping with a non-immunological basis for the immediate contact reactions.

Pithecollobium jiringa

Pithecollobium jiringa (jering fruit) is valued in Malaysia and Indonesia as a delicacy and for its antidiabetic properties.

Adverse effects

Acute renal insufficiency is a rare complication of the use of jering. In one case there was dysuria, hematuria, vomiting, abdominal pain, and blue urine (69). In two other cases there was bilateral loin pain, fever, nausea, vomiting, oliguria, hematuria, and passage of sandy particles in the urine (70). Blood urea and serum creatinine were markedly raised. With conservative therapy, which included rehydration with isotonic saline and alkalinization of the urine with sodium bicarbonate, the acute renal insufficiency resolved.

Sophora falvescens

Sophora falvescens (Ku shen) contains a variety of matrine alkaloids, such as aloperine, cytosine, lehmannine, matrine, oxymartine, oxysophocarpine, sophocarpine, sophoramine, and sophoridine, the flavonoid kushenol, and the saponin sophoraflavoside. Ku shen is a Chinese herbal remedy made from the root of *S. falvescens*. And Qing luo yin, a Chinese herbal remedy for rheumatoid arthritis, is a combination of extracts of *Dioscorea hypoglauca*, *Phellodendron amurense*, *Sinomenium acutum*, and *S. flavescens*.

Adverse effects

A herbal record lists the following adverse effects of Ku shen: salivation, abnormal gait, dyspnea, tachycardia (71). In larger doses, nervous system stimulation with muscle spasm and seizures can occur. There have been three reports of adverse reactions such as nausea, vomiting, dizziness, bradycardia, palpitation, ataxia, pallor, sweating, seizures, and dysphasia.

Trifolium pratense

Trifolium pratense (red clover) contains flavones (isorhamnetin, pratensein), phenolic coumarins, phytoestrogens, and demethylpterocarpin. It has been used to treat menopausal symptoms, without good evidence of efficacy (72).

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Adverse effects

The coumarins in red clover may potentiate the effects of oral anticoagulants (73).

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Factor VII

See also Coagulation proteins

General Information

Factor VII is the most sensitive of the vitamin K-dependent clotting factors. The mode of action is tissue factor-dependent activation of factors Xa and IXa on the surfaces of activated platelets (1). Factor Xa leads to thrombin generation and hemostasis, by converting fibrinogen to fibrin. This process is limited to the site of injury, since exposure of tissue factor from the subendothelial matrix has a role in the action of recombinant factor VIIa, thereby reducing the risk of thromboembolic events (2).

Recombinant activated factor VII (factor VIIa) is indicated for patients with inhibitors of clotting factors VIII and IX (3–5). It has also been used to good effect preoperatively, in patients with severe thrombocytopenia, and in the treatment of life-threatening bleeding, including bleeding related to anticoagulant therapy or liver failure (3). The usefulness of recombinant factor VIIa for correcting the prothrombin time has been demonstrated in three neonates with liver failure undergoing liver biopsy and central venous catheter placement (6).

A disadvantage of recombinant factor VIIa is the need for frequent administration, because of its short half-life, about 2.7 hours with a clearance of 0.5 ml/kg/minute. The clearance is even faster in patients aged under 15 years. In one child the half-life was no more than 1 hour (7).

In general factor VII is well tolerated, with an incidence of non-serious adverse events of 3.6% (3). The most frequently reported adverse events are hypertension, skin reactions, fever, headache, epistaxis, reduced plasma fibrinogen, and prolonged prothrombin time (3,4).

Animal studies and case reports have suggested that recombinant factor VIIa should reduce the INR in patients taking oral anticoagulants and also has a hemostatic effect (8).

Organs and Systems

Cardiovascular

Thrombophlebitis at the infusion site is a common complication of continuous infusion of various clotting factor concentrates and has been noted after infusion of factor VIIa (9,10). Thrombophlebitis occurred in one of eight hemophiliacs with inhibitors who received continuous infusion of recombinant factor VIIa to allow elective surgery (11). In 25 hemophilia patients with inhibitors, who received recombinant factor VIIa for surgical procedures or spontaneous bleeding, there was one case of thrombophlebitis in 35 continuous infusion courses (12). In most instances, thrombophlebitis can be prevented by parallel infusion of saline or heparin.

- A 38-year-old patient with hemophilia A with factor VIII inhibitors was treated with recombinant factor VIIa for about 1 month and 18 days after the last infusion developed a distal deep venous thrombosis. An effect of the factor VIIa could not be ruled out, but long-term immobilization and severe infection could have contributed (13).

Angina pectoris and tachycardia have been reported after the use of recombinant factor VIIa (3). Among patients who had more than 2400 treatment episodes with recombinant factor VIIa, there were two cases of acute myocardial infarction (14). One of these patients had a history of cardiovascular disease and the other was very overweight and received massive transfusions, human factor VIII, activated prothrombin complex, and finally recombinant factor VIIa to treat severe intra-abdominal bleeding and shock.

Hematologic

Bleeding at sites other than the primary site (oozing at a central line insertion site, hemarthrosis, and epistaxis) has been reported during treatment with recombinant factor VIIa in four patients (7). The authors suggested that local fibrinolysis may have contributed to or actually caused bleeding from central line insertion sites. In three cases they found raised fibrin degradation products and in two cases a 15–35% fall in plasminogen activity.

No causality has been demonstrated between administration of recombinant factor VIIa and arterial thrombotic complications (15,16). However, venous thrombosis has been reported (17).

The risk of disseminated intravascular coagulation and other thrombotic events appears to be less with factor VII than with activated prothrombin complex products (1,18). However, disseminated intravascular coagulation after infusion of recombinant factor VIIa has been reported (19,20).

Urinary tract

In two patients with hemophilia with antibodies to both human and porcine factor VIII, continuous recombinant factor VIIa resulted in hematuria (21). In neither case was a cause of the hematuria found. The author suggested that mucosal bleeds, such as hematuria, are characterized by high fibrinolytic activity locally and may require higher peak concentrations of factor VII to generate sufficient thrombin to achieve and sustain hemostasis. The need for a full thrombin burst could relate to the role of thrombin in the activation of thrombin-activatable fibrinolysis inhibitor.

Immunologic

The development of antibodies against recombinant factor VIIa or hypersensitivity reactions to normal doses of recombinant factor VIIa have not so far been reported (7). No antibodies against recombinant factor VIIa were observed in a group of 222 hemophilia A and 16 hemophilia B patients with inhibitors treated with high doses of factor VIIa (14). However, antibodies to factor VII have been observed in a patient with factor VII deficiency who received 40 times the recommended dose of recombinant activated factor VIIa (3). Another case of low-titer and transient factor VII antibody formation has been reported in a patient with factor VII deficiency (10).

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Drug Administration

Drug administration route

Continuous infusion of recombinant factor VII appears to offer advantages over bolus dosing, with a reduction in the total dose of recombinant factor VIIa by 50–75% (7,22).

Drug–Drug Interactions

Heparin

Small doses of heparin are used for the prophylaxis of infusion-related thrombophlebitis (23). Low molecular weight heparin is added to recombinant factor VIIa to prevent a 50% loss of activity of factor VII within 4 hours of storage (9). In one case, however, there was co-precipitation of reconstituted factor VIIa and low molecular weight heparin in syringes (24). The authors therefore suggested that a parallel saline infusion be used instead of heparin to prevent thrombophlebitis.

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Factor VIII

See also Coagulation proteins

General Information

Lyophilized factor VIII has been used as substitution therapy in patients with hemophilia A. Most, but not all, recombinant factor VIII (recFVIII) is structurally and immunologically similar to plasma-derived factor VIII, and it has been well tolerated by patients in clinical trials. A major concern about recombinant factor VIII has been the occurrence inhibitors (1). However, there is evidence that there is no difference in the occurrence of inhibitors between recombinant factor VIII and plasma-derived factor VIII (2).

Highly purified animal coagulation factors, such as porcine factor VIII, continue to be used to good effect in

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patients with hemophilia with high-titer inhibitors. Adverse effects are relatively mild, consisting of fever and rare anaphylactoid reactions (3); platelet aggregation and progressive thrombocytopenia have also been observed (4).

Gene therapy

Trials of gene therapy in hemophilia A and B, to determine safety and efficacy, are under way (5). The hazards of current vectors include the development of inhibitors, as observed in substitution therapy, insertion mutagenesis (for example through disruption of a regulatory gene such as a tumor suppressor gene), and transmission of genes to germ cells (6). In the various phase I trials performed in patients with hemophilia such adverse events have not been observed (6). Other theoretical hazards are immunogenesis, hepatotoxicity, and carcinogenic effects. In particular, retroviral vectors have a considerable carcinogenic potential. Adenoviruses, which do not integrate into the genome and consequently have only a transient effect, are considered to be safer. Also adeno-associated viruses have a low pathogenic potential in humans, as do lentiviruses.

The death of a young patient who took part in a clinical gene therapy study, probably caused by an adverse reaction to the viral vector (7,8), has led to increased interest in the application of non-viral techniques for gene therapy. When factor VIII genes were introduced into autologous skin cells in culture by electroporation, and thereafter implanted in the omentum in six patients with hemophilia A, no adverse events were reported (9).

Organs and Systems

Cardiovascular

Thromboembolic complications developed in two of 81 patients with Von Willebrand disease treated with a high-purity factor VIII/Von Willebrand factor (VWF) concentrate (10). Four cases of venous thrombosis were reported in patients with Von Willebrand disease treated with an intermediate-purity factor VIII/VWF concentrate. Use of pure VWF concentrate without increased factor VIII:C is preferable (11).

Respiratory

In a retrospective study of 29 treatments with porcine factor VIII:C in 18 patients with hemophilia A with inhibitors, the initial bolus administration of porcine factor VIII:C before continuous infusion caused bronchospasm in one patient (12).

Nervous system

- A 71-year-old man with acquired hemophilia and high titers of antibodies to factor VIII developed a fatal thrombotic stroke while receiving porcine factor VIII (13).

Hematologic

Porcine factor VIII, used for the treatment of patients with inhibitors of factor VIII, can cause thrombocytopenia, which is dose-related and occurs during intensive treatment for severe bleeding or surgery (14,15).

During continuous infusion of porcine factor VIII:C in patients with hemophilia A with inhibitors there is a smaller fall in platelet count and fewer other adverse effects than during the period after the initial bolus administration, as was shown in a retrospective study of 29 treatments with porcine factor VIII:C of 18 patients with hemophilia A with inhibitors (13). The authors attributed these differences to the dose of factor VIII:C and the rate of administration.

Skin

Urticaria and periorbital edema after initial bolus administration of porcine factor VIII:C before continuous infusion have been observed in one of 18 patients with hemophilia with inhibitors receiving a total of 29 treatments with porcine factor VIII:C (13).

Immunologic

There has been some concern about the possible effects of factor VIII formulations on the immune system. In vitro experiments with coagulation factor concentrates have shown immunosuppressive effects (16,17), such as the impairment of Fc receptor-mediated phagocytosis and intracellular bacterial killing (18). Inhibition of IL-2 production, an impaired MLR, and impairment of PHA transformation have been demonstrated (19). A fall in the number of T4 lymphocytes has also been found. Whether these findings reflect functional impairment of the immune system is still unclear.

If the modulation of certain immune functions is in fact due to contaminating components in the preparations, one would expect the new generation of factor VIII preparations of very high purity to behave differently. Highly purified factor VIII with a specific activity of 100–150 U/mg protein is now available, as is factor VIII purified by immunoaffinity chromatography using mouse monoclonal antibodies.

In 58 previously treated patients with hemophilia treated with a recombinant factor VIII product for more than 5 years, there were neither allergic reactions to murine or hamster proteins nor any de novo formation of inhibitors of factor VIII (20).

Antibodies to factor VIII (factor VIII inhibitors)

Patients with bleeding disorders are at risk of developing antibodies against the coagulation protein that is absent, present in reduced amounts, or present in an inactive form in their blood. Such coagulation inhibitors make treatment very difficult. Gene deletions, truncations, and inversions of the factor VIII gene give rise to abnormal forms of the factor VIII protein, resulting in failure to induce tolerance against the normal form of factor VIII (21). Starting with factor VIII treatment at an early age is associated with an increased risk of developing inhibitors (22).

Frequency

Inhibitors of factor VIII are the most common and develop in 5–36% of patients with hemophilia A (23,24). Inhibitors of factor IX develop in 1–8% of patients with hemophilia B (24–26). Frequency varies with age (24). Patients with factor VIII inhibitors present clinically either as “high responders” who show a strong anamnestic response and a sharp rise in inhibitor concentrations

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after exposure to factor VIII, or "low responders", who show little or no anamnestic response (27).

Following the introduction of recombinant factor products, the incidence of antibody formation seemed to be higher than in patients using plasma products (28). However, after considering factors such as the number of exposure days, the severity of the disease, and the frequency of prospective monitoring, the prevalence and the incidence of antibody formation for both products were similar.

In two studies of previously untreated patients with severe hemophilia, who were given two different recombinant factor VIII products, the incidence of development of an inhibitor was comparable (about 30%) (29).

In 31 previously untreated and minimally treated children with severe hemophilia A, who received full-length recombinant factor VIII (formulated with sucrose) for home therapy and surgery, there was no difference in the incidence of inhibitor formation compared with other recombinant products or plasma-derived products (2).

Mechanism

Antibody formation in patients with mild and moderate hemophilia most likely results from the presence of structurally abnormal circulating factor VIII, so that administration of exogenous factor VIII leads to the development of antibodies by exposing the immune system to epitopes on factor VIII molecules not previously encountered (30). Data from the UK Haemophilia Centre Directors Organization have shown that 25% of patients who developed antibodies had mild or moderate hemophilia (30). It has been suggested that this high figure can be explained by improved data collection and by changes in clinical practice, namely the switch from lower purity to higher purity or recombinant products and the use of continuous infusion instead of repeated injections (30).

Novel molecular defects, Arg2163His and Phe2101Cys, were held responsible for inhibitor formation in two patients (31).

- Two patients (aged 60 and 73 years) with mild and moderate hemophilia respectively, without a family history of inhibitor formation, were exposed to factor VIII for more than 50 days. An inhibitor developed in both patients after an intermediate factor VIII product was replaced by a high-purity factor VIII product, which was given by continuous infusion during a surgical procedure.

Susceptibility factors

Six cases of factor VIII inhibitor development within the postoperative period have been described (32). Some patients have a greater tendency to develop inhibitors, such as patients with severe hemophilia who were sparingly treated, patients with moderate hemophilia and a family history of inhibitor development, patients who had transient inhibitors in the past, and patients with high-risk mutations in their factor VIII gene (32). It has been suggested that alteration of the immune system, by operative stress or the use of antibiotics, increases the risk of inhibitor development (32). Of 81 patients with Von Willebrand disease, who were treated with high-purity factor VIII/Von Willebrand factor concentrate, two had reduced in vivo recovery, suggesting antibody formation (10).

The formation of inhibitors of factor VIII is not restricted to patients with severe hemophilia. There have been two cases of high-titer factor VIII inhibitors in two children with mild hemophilia A; one occurred after only minimal exposure to factor VIII:C (33).

In 20 previously treated patients with severe or moderate hemophilia A treated with recombinant factor VIII formulated with sucrose, no inhibitors were found (34). The risk of forming inhibitors after treatment with B domain-deleted recombinant factor VIII was comparable to that seen with full-length recombinant products (35,36).

Management

Treatment options for patients with inhibitors are high dosages of clotting factor or recombinant factor VIIa for both hemophilia A and B or, in the case of hemophilia A, porcine factor VIII:C or activated prothrombin complex (37). Regular administration of intermediate or low-dose factor VIII concentrates leads to the rapid disappearance of factor VIII inhibitors in some high responders (27); this is thought to be due to the development of immune tolerance.

This may explain the effectiveness of treating patients with hemophilia who have inhibitors with high doses of factor VIII. Another approach involves the use of prothrombin complex concentrate to treat bleeding episodes in patients with factor VIII inhibitors (38); however, thromboembolic complications related to higher doses of prothrombin complex concentrate have been described, although these are relatively rare (39,40). Thrombotic events are extremely rare when highly purified factor IX is used. Activated prothrombin complex concentrate is also effective in patients with factor VIII inhibitors (41). Serious complications are rare, but disseminated intravascular coagulation has been reported (42).

If the inhibitor activity is under 10 Bethesda units/ml, patients can be treated with increased doses of factor VIII or IX concentrates (43). In addition, patients with hemophilia A with low or intermediate antibody titers can also be treated with porcine factor VIII (43). However, hemorrhagic episodes in patients with antibody activity over 10 Bethesda units/ml may result in life-threatening hemorrhage that cannot be treated by conventional therapy (26,43). Prevention or treatment of clinically significant bleeding episodes in these patients can be achieved by using so-called bypassing therapies, such as recombinant factor VIIa and activated prothrombin complex (23,26,43). Recombinant factor VIIa is both effective and safe in the treatment of inhibitors directed to either factor VIII or IX (44,45).

A less effective method of treating patients with inhibitors is to give them deamino-d-arginine vasopressin (DDAVP), which increases production of intrinsic factor VIII. This has a number of drawbacks, such as tachyphylaxis, flushing, headaches, myocardial ischemia, and fluid retention (46).

It has been recommended that non-hemophiliacs with autoantibodies be treated with porcine factor VIII products (14).

Inhibitor bypassing agents include prothrombin complex concentrates, activated prothrombin complex concentrates (such as FEIBA), porcine factor VIII, and recombinant factor VIIa. During 10 years usage of FEIBA (3.95×10^5 FEIBA units infused) a total of 16 thrombotic events were reported, corresponding to an incidence of 4.05 per 10^5

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infusions. In 13 of these 16 events, known risk factors, such as FEIBA overdose, obesity, and serum lipid abnormalities, were present (47). Antibody reactivity against factor VIIa, which was detected in patients with hemophilia with high-titer antibodies, was a response to treatment with blood products or bypassing agents or due to cross-reactivity. This reactivity might hamper the hemostatic effect (48).

The production process of porcine factor VIII does not incorporate virus-eliminating steps. However, each batch is extensively screened to confirm the absence of viruses. In a pharmacovigilance study of 81 hemophiliacs treated with porcine factor VIII, there were no cases of transmission of porcine viruses (porcine parvovirus, encephalomyocarditis virus, porcine respiratory, and reproductive syndrome virus) (49).

Body temperature

Febrile reactions occurred in two patients after the initial bolus administration of porcine factor VIII:C in a retrospective study of 29 treatments with porcine factor VIII:C in 18 patients with hemophilia A with inhibitors (13).

Drug Administration

Drug formulations

Recombinant factor VIII is stabilized with human serum albumin during purification and in the final product. Although albumin has an excellent safety record and no recombinant antihemophilic factors have been associated with virus transmission, there is still concern about the safety of products that contain human- or animal-derived components (50). A second-generation recombinant factor VIII product has been developed with a modified manufacturing process and a formulation in which the recombinant factor VIII is stabilized by sucrose instead of albumin (50).

Drug contamination

Plasma-derived factor VIII concentrates have been implicated in the transmission of the non-enveloped hepatitis A and parvovirus B19 (28). The virus-inactivating procedures now in use (chemical inactivation, wet-heat treatment, and nanofiltration) should provide coagulation factors without risk of transmitting HIV and with a very high safety for hepatitis virus. Nevertheless, recombinant factor VIII is considered a safer alternative.

Patients with hemophilia have various disturbances of immune function, resulting not only from infections with HIV and hepatitis, but also from chronic exposure to extraneous proteins in clotting factor concentrates (51). Protein contaminants, such as immunoglobulins, fibrinogen, and fibronectin, can depress immune function. It has been postulated that high-purity concentrates in HIV-positive hemophiliacs are associated with better maintenance of $CD4^+$ cells and other indicators of immune function compared with products of intermediate purity (51).

One of 81 patients with Von Willebrand disease treated with a high-purity factor VIII/Von Willebrand factor concentrate was infected with parvovirus B19 after infusion of a solvent/detergent-treated formulation. Parvovirus B19 is not lipid-enveloped and is resistant to treatment by solvent detergent (10).

Parvovirus B19 transmission occurred in a child who had received vapor heat-treated prothrombin complex concentrate (60°C for 10 hours and 80°C for 1 hour) and in another child who received dry-heated factor VIII concentrate (80°C for 72 hours). Both children had severe hemophilia A and were treated for factor VIII inhibitors (52).

Second-generation recombinant factor VIII products, which contain lower amounts of human albumin, and third-generation products, which are free of human proteins and thereby carry a lower risk of pathogen transmission, are on the market.

Drug administration route

Hemophiliacs are traditionally treated with bolus injections of factor VIII. This kind of administration is associated with peak and trough concentrations of these factors, with a risk of bleeding when the concentration of factor VIII falls below a critical concentration (53).

Several studies of continuous infusions of factor VIIa, factor VIII, and factor IX in hemophiliacs undergoing surgery have shown that this mode of administration is safe and effective when steady plasma concentrations of the clotting factors can be achieved (53–56). The total dosage of clotting factor concentrates is reduced, and so continuous infusions are cost-effective (53,56).

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Factor IX

See also Coagulation proteins

General Information

Factor IX is used as substitution therapy in patients with hemophilia B. Although the half-lives of recombinant and plasma factor IX products are comparable, the in vivo recovery of recombinant factor IX is 28% lower than a highly purified plasma-derived product. To treat hemorrhage the dosage of recombinant factor IX needs to be 20% higher than plasma-derived products to increase the circulating factor IX activity to 1% per IU of recombinant factor IX given (1).

General adverse effects

Mild adverse effects of factor IX include discomfort at the infusion site, fever, dizziness, allergic rhinitis, and lightheadedness (1).

Gene therapy

Trials of gene therapy in hemophilia A and B, to determine safety and efficacy, are under way (2). Three patients with hemophilia B were treated in a phase I trial with a recombinant adenovirus-associated vector expressing human blood-coagulation factor IX (3). There was no evidence of formation of inhibitory antibodies against factor IX. In a phase I trial with a recombinant adenovirus-associated vector expressing human blood-coagulation factor IX, there was no evidence of germ-line transmission of vector sequences (3).

The hazards of current vectors include insertion mutagenesis, immunogenesis, hepatotoxicity, and carcinogenic effects. In particular, retroviral vectors have a considerable carcinogenic potential. Adenoviruses, which do not integrate into the genome and consequently have only a transient effect, are considered to be safer. Also adeno-associated viruses have a low pathogenic potential in humans, as do lentiviruses.

Organs and Systems

Cardiovascular

Thrombophlebitis at the infusion site is a common complication of continuous infusion of various clotting factor concentrates. Continuous infusion of recombinant factor IX in six patients with hemophilia B undergoing surgery or suffering bleeding was complicated in two cases by thrombophlebitis (4). In most instances, thrombophlebitis can be prevented by parallel infusion of saline or heparin.

Respiratory

Shortness of breath was observed in a young patient with hemophilia B with inhibitors after a number of attempts to induce immune tolerance with a high dose of factor IX:C (5).

Urinary tract

During treatment with extremely high doses of factor IX concentrate, to induce immune tolerance, nephrotic syndrome has been described (6,7). Withdrawal or dosage reduction is of crucial importance for the resolution of nephrosis (6). Renal biopsy in one of these patients showed peripheral capillary wall thickening and deposits throughout the basement membrane (7). In addition minimal interstitial fibrosis and tubular atrophy were present. There were no deposits of factor IX in the glomeruli, which the authors attributed to absence of free factor IX epitope in the tissue (7).

In patients with hemophilia B with antibodies who undergo immune tolerance induction there is a risk of nephrotic syndrome (8).

Skin

A young patient with hemophilia B with inhibitors developed an urticarial rash after several attempts to induce immune tolerance with a high dose of factor IX:C (5). Recombinant factor IX gave rise to urticaria in patients with hemophilia B undergoing surgery (9).

Immunologic

Allergic and anaphylactic reactions due to factor IX inhibitor have been described (SEDA-21, 343) (6). Anaphylactic reactions occur particularly in patients with undetectable concentrations of factor IX, because of major disruptions in the factor IX gene (10). In patients with factor IX inhibitor, IgG1 subclass antibodies have been found, which may activate complement, resulting in allergic reactions (SEDA-21, 343) (10). However, it has also been suggested that allergic reactions to factor IX products are IgE-mediated.

- In two patients with severe factor IX deficiency and high concentrations of factor IX inhibitors who

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developed anaphylaxis to factor IX, RAST and skin test reactions to factor IX were positive (10). After desensitization, the circulating IgE antibodies to factor IX fell.

Treatment with high dosages of clotting factors to induce immune tolerance brings a risk of allergic reactions, as has been observed in a 4-year-old child with hemophilia B (5).

Antibodies to factor IX (factor IX inhibitors)

Patients with bleeding disorders are at risk of developing antibodies against the coagulation protein that is absent, present in reduced amounts, or present in an inactive form in their blood. Such coagulation inhibitors make treatment very difficult.

Inhibitors of factor VIII are the most common and develop in 5–15% of patients with hemophilia A. Inhibitors of factor IX develop in 1–4% of patients with hemophilia B (11,12). Patients with hemophilia B with complete gene deletions or derangement of the factor IX gene are particularly at risk of developing antibodies after the administration of factor IX concentrate (8). In patients with hemophilia B with antibodies, treatment with factor IX concentrate can result in an anaphylactic response.

Anaphylaxis in conjunction with inhibitor development has been described. Patients with hemophilia B with complete gene deletions have the greatest risk of anaphylaxis, with a minimum risk of 26%, whereas the risk in patients with null mutations was 2.4% and nearly zero for mis-sense mutations (13). Predisposing factors for the development of anaphylaxis, besides mutation type, are genetic predisposition and environmental experience, such as the type and frequency of factor IX product (13).

Drug Administration

Drug administration route

Hemophiliacs are traditionally treated with bolus injections of factor IX, which is associated with peak and trough concentrations of these factors, with a risk of bleeding when the concentration of factor IX falls below a critical concentration (14).

Several studies of continuous infusions of factor VIIa, factor VIII, and factor IX in hemophiliacs undergoing surgery have shown that this mode of administration is safe and effective when steady plasma concentrations of the clotting factors can be achieved (14–17). The total dosage of clotting factor concentrates is reduced, and so continuous infusions are cost effective (14,17).

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Famciclovir

General Information

Famciclovir is an oral prodrug of penciclovir, a selective antiviral drug with activity against *Varicella zoster* virus, *Herpes simplex* virus types 1 and 2, and Epstein–Barr virus, as well as human hepatitis B virus.

After oral administration, famciclovir is well absorbed (systemic availability 77%), with little intersubject variability, and is rapidly converted to penciclovir. This

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compares favorably with aciclovir, the absorption of which is slow and incomplete, with a highly variable systemic availability of only 10–20%.

Comparative studies

In a study of oral famciclovir versus oral aciclovir, designed to demonstrate equivalence of efficacy of the two drugs in the treatment of mucocutaneous *Herpes simplex* infection in HIV-infected individuals, there was no difference in the incidence or nature of adverse effects in the two groups (1). None of the withdrawals from the trial was considered by the investigator to be related to the study medication.

Placebo-controlled studies

In an integrated safety analysis of 1607 patients who had taken famciclovir for the treatment of *Herpes zoster* or genital herpes, famciclovir was extremely well tolerated with an adverse effect profile similar to placebo (2). Headache, nausea, and diarrhea were the most frequently reported adverse events in those taking both famciclovir and placebo.

In an experimental study of *Herpes simplex* labialis, adverse events (diarrhea and nausea) occurred with similar frequency with famciclovir and placebo (3). No laboratory abnormalities were consistently associated with famciclovir.

In a randomized, placebo-controlled study in 455 patients oral famciclovir (125 or 250 mg tds or 250 mg bd) used to suppress recurrent genital *Herpes simplex* infections, the toxicity profile of famciclovir was comparable to placebo (4). The only serious adverse effects reported as being possibly related to famciclovir were raised bilirubin concentration and lipase activity in one patient after 10 months of treatment with famciclovir 125 mg tds. However, these laboratory abnormalities resolved on therapy after 7 days and did not recur during the rest of the study.

Organs and Systems

Gastrointestinal

Adverse effects associated with famciclovir have been collected in over 6000 patients in two postmarketing surveillance studies (5). Only headache, abdominal symptoms, dizziness, vomiting, and diarrhea were associated with the drug. Two prospective trials have confirmed the low frequency of adverse effects, the more common ones being nausea, headache, vomiting, and diarrhea (6,7).

Sexual function

Prolonged administration of high dosages of famciclovir has been associated with reversible dose-dependent adverse effects on testicular function in rats and dogs. However, in a double-blind, placebo-controlled trial in which 34 men with recurrent genital herpes took famciclovir 250 mg bd for 18 weeks, there were no significant effects on sperm production or function (8).

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Famotidine

See also Histamine H_2 receptor antagonists

General Information

Famotidine is a histamine H_2 receptor antagonist. It does not affect drug metabolism and it has been claimed to be free of the antiandrogenic effect of cimetidine; however in one woman who accidentally took double doses of the drug for some months it did cause hyperprolactinemia and breast engorgement (SEDA-18, 372). In other ways it bears a very close resemblance to cimetidine; for example, headache and confusion with intravenous use are reported, as are thrombocytopenia and pancytopenia (SEDA-15, 395).

The effects of famotidine 20 mg bd and omeprazole 20 mg/day for 8 weeks have been compared in the treatment of reflux esophagitis in a randomized trial in 56 patients (1). Omeprazole was more effective in healing esophagitis and providing symptom relief. Adverse events, which were rare, were similar in the two groups, and consisted of nausea, palpitation, abdominal pain, and mild abnormalities of liver function tests.

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Organs and Systems

Nervous system

Histamine receptor antagonists can cause a variety of reactions involving the central nervous system. These are rare with famotidine.

- Five elderly patients (61–85-years-old) developed acute central nervous system reactions, consisting of confusion, agitation, hallucinations, and disorientation, 24 hours to a few days after starting to take famotidine 40 mg/day (2). These features resolved completely 24–48 hours after withdrawal. Rechallenge was not attempted.

Hematologic

Although it is hard to make a direct comparison between famotidine and cimetidine, since the former has been less extensively used, it is possible that the hematological problems occur more often with famotidine; there have been frequent well-documented reports of both thrombocytopenia and neutropenia, sometimes severe (SEDA-17, 417).

Liver

- Famotidine-induced cholestatic hepatitis has been reported in a previously healthy 13-year-old boy who had taken famotidine 40 mg/day for 30 days for epigastric pain (3). Other possible causes were excluded. He had a gradual and complete recovery 2 months after drug withdrawal.

Musculoskeletal

Rhabdomyolysis has been attributed to famotidine and might reflect its immunomodulating action (SEDA-17, 418).

Immunologic

Vasculitis occurred in a patient taking famotidine who had tolerated cimetidine well (4).

Body temperature

Hyperpyrexia has been attributed to famotidine, but the patient had pre-existing cerebral trauma as a facilitating factor (SEDA-16, 422).

Drug Administration

Drug overdose

After overdosage famotidine has a wide margin of safety; deliberate ingestion of very high doses did not appear to be associated with adverse sequelae (SEDA-21, 363) (5).

Drug–Drug Interactions

Omeprazole

Intragastric acid control by omeprazole 20 mg taken in the morning after variable dosing of over-the-counter famotidine 10 mg has been assessed in 12 healthy volunteers negative for *Helicobacter pylori* (6). Famotidine did not reduce the daytime efficacy of the next-morning dose of omeprazole.

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Fazadinium

See also Neuromuscular blocking drugs

General Information

Originally claimed, from animal experiments, to be of rapid onset, short duration, and free from important adverse effects, this non-depolarizing relaxant has been found to be less satisfactory in man. The usual doses are 0.5–0.75 mg/kg, although 1 mg/kg is sometimes advocated for fast intubation (within 1–2 minutes). The duration of action is similar in man to that of D-tubocurarine and pancuronium. Excretion is primarily in the urine (50–80%, mostly in the first 6 hours), although a biliary route has also been suggested. Metabolism occurs, probably to a minor extent, 1–3% being detected in the urine as inactive metabolites.

Organs and Systems

Cardiovascular

Cardiovascular effects account for the relative unpopularity of fazadinium. It has some ganglion-blocking activity (1) and blocks cardiac muscarinic receptors in the therapeutic dose range (2). Its vagolytic potency is about the same as that of gallamine. Fazadinium, like pancuronium, also blocks the reuptake of noradrenaline into sympathetic nerve endings. These actions explain its major cardiac adverse effect, namely significant tachycardia (3), which occurs even with small doses and is persistent.

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It is dose-related (4), the increase in heart rate varying between 30 and 100%, and is associated with a rise in cardiac output and falls in stroke volume and peripheral resistance. Hypertension or hypotension can occur (5,6). If fazadinium is used injudiciously, extreme and dangerous cardiovascular changes can ensue (7).

Immunologic

Histamine release from fazadinium is very uncommon, but hypotension associated with an urticarial rash and two cases of severe bronchospasm and cardiac arrest (in patients who had also received thiopental) have been reported (8) as probably being due to fazadinium.

Immunological investigations combined with positive intradermal tests have been used to confirm fazadinium as the causative agent in a severe reaction (9).

Second-Generation Effects

Fetotoxicity

Placental transfer occurs and, though there may be some fetal uptake, Apgar scores did not appear to be affected (10,11).

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Felbamate

See also Antiepileptic drugs

General Information

Felbamate is a broad-spectrum antiepileptic drug, whose use has been drastically curtailed owing to the risks of aplastic anemia and hepatotoxicity.

Benefit to harm balance

The Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society (1) has reviewed efficacy and safety data to establish recommendations for felbamate use in the light of the risk of aplastic anemia and liver toxicity (SEDA-22, 86). Felbamate was considered to have a favorable benefit to harm balance in patients with Lennox–Gastaut syndrome aged over 4 years who were unresponsive to primary anticonvulsants, in patients over 18 years of age with intractable partial seizures that have not responded to standard antiepileptic drugs in therapeutic concentrations, and in patients who are already taking felbamate and benefit from it for more than 18 months. There are conditions in which the benefit:harm balance is unclear, but for which use may be appropriate under certain circumstances, depending on the nature and severity of the seizure disorder; these include children with intractable partial epilepsy, patients with other generalized epilepsies unresponsive to primary agents, patients who have unacceptable sedative or cognitive effects with traditional antiepileptic drugs, and patients under 4 years with Lennox–Gastaut syndrome unresponsive to other antiepileptic drugs.

Assessment of its benefit to harm balance does not support the use of felbamate in new-onset epilepsy in children and adults, in patients who have significant prior hematological adverse events, in patients in whom follow-up and compliance will not allow careful monitoring, and in patients who are unable to discuss risk/benefits and for whom no parent or legal guardian is available to provide consent.

In patients taking felbamate, the benefit to harm balance should be constantly assessed. Patients should be educated about early signs of liver and bone-marrow toxicity, and about the manufacturers' recommendations. Laboratory monitoring has not been proven efficacious, but the manufacturer and the FDA suggest liver function and hematology testing at baseline and every 1–2 weeks for the first year. After that, the risk of aplastic anemia falls and the need for regular testing is less clear. A registry has been set up by the manufacturers to collect further safety data in patients started on the drug.

An open trial with 3-year follow up has been conducted in 36 patients with catastrophic childhood onset epilepsy (2). The overall responder rate (more than a 50% reduction in seizure frequency) fell with time: 69% at 3 months, 66% at 6 months, 47% at 1 year, and 41% at the end of the study. The most frequent adverse effects were anorexia, weight loss, urinary retention, somnolence, nervousness, and insomnia. Other reported adverse effects include skin reactions (including Stevens–Johnson syndrome), various blood dyscrasias, hepatotoxicity, and systemic lupus erythematosus (3).

Organs and Systems

Nervous system

Central nervous system adverse effects are common with felbamate, and consist mainly of insomnia, headache, impaired concentration, ataxia, dizziness, somnolence, behavioral disturbances, and mood changes. Movement disorders, psychosis, increased seizures, status epilepticus, and withdrawal seizures are less common (SEDA-19, 67) (SEDA-20, 61). The incidence of these effects is increased in the elderly, possibly owing to reduced drug clearance (4), whereas patients with mental retardation may be more prone to behavioral disorders (SEDA-19, 68).

Hematologic

Aplastic anemia affects 1 in 5000, or even 1 in 2000 patients (5), although a more recent estimate is 27–209 per million, compared with 2–2.5 per million in the general population (6). The underlying mechanism is unknown, although a deficiency in free radical scavenging activity may play a role (SEDA-22, 86).

Of 34 cases of aplastic anemia (mean age 41 years, mean time of felbamate exposure 154 days), 20 occurred in combination with other compounds implicated as a possible cause of aplastic anemia and 5 occurred concurrently with viral infections (7). Although 5 patients were taking felbamate monotherapy, 13 of the 34 suffered from autoimmune disease, and 1 was receiving cytostatic therapy. Past allergic or toxic reactions to other anticonvulsants were reported by 65% of the patients and blood dyscrasias by 45%, while 32% had serological evidence of a previous immune disorder. Eight of nine patients tested had experienced at least one episode of aplastic anemia associated with HLA antigens.

Felbamate is currently reserved for patients who are refractory to other drugs after careful consideration of the benefit:harm balance. In some countries the indication has been restricted to refractory Lennox–Gastaut syndrome. It is wise to avoid felbamate in patients with previous blood dyscrasias or autoimmune disorders, especially lupus erythematosus. Before they start to take it, patients should be informed about the potential risks and early symptoms of bone-marrow toxicity, such as bruisability, petechiae, fever of unknown origin, weakness, and fatigue. Hematology tests should be performed at baseline and during treatment, and dose escalation should be slow.

Because felbamate-induced aplastic anemia might be linked to the formation of atropaldehyde, a urine screening test has been developed that indirectly assesses the formation of this toxic metabolite (8). The risk of serious toxicity may also be related to HLA status, and HLA typing is being performed in patients entered in the manufacturer's felbamate registry. The potential value of these tests in reducing the risk of toxicity remains to be established.

Gastrointestinal

Felbamate is commonly associated with anorexia, nausea, and vomiting (9,10). Constipation and abdominal pain also occur. In 36 patients (12 men) aged 11–68 (mean 30) years in whom felbamate dosage was titrated gradually from 300 mg/day to a mean total daily maintenance dose of 1936 mg, the most frequent adverse events were: nausea, vomiting, anorexia, and weight loss (11).

Weight loss can occur. Of 65 patients with intractable seizures who received felbamate for a mean treatment time of 23 (range 6–116) weeks 49 lost weight (12). Among those over 15 years, there was a mean weight loss of 3.2 kg or 4.1% of body weight; 22 lost more than 4 kg, and 7 lost more than 8 kg. Among those aged 15 years or younger there was a non-significant mean weight loss of 0.20 kg or 1.8% of body weight.

However, in another study of 30 children aged 2–17 years with refractory partial seizures, felbamate up to a maximum of 45 mg/kg caused transient weight loss in 57%, maximal after 12 weeks and abating after 20 weeks (13). Anorexia and insomnia occurred in 20% and 16% of the patients respectively.

Liver

Of 23 reported cases of hepatic failure, only 10 (including 5 who died) were considered to be probably related to the drug (7,14). There have also been 20 cases of hepatitis in which no deaths occurred; in five of these a relation to felbamate was unlikely. Overall the incidence of fatal liver toxicity is estimated at 1 per 26 000–34 000. A careful history of past hepatic toxicity with other drugs should be taken and liver function tests are recommended before starting felbamate. Patients should have hepatic function monitored regularly and should be alerted to the signs and symptoms of hepatotoxicity.

Urinary tract

Urolithiasis has been associated with felbamate (15).

- A 15-year-old boy with Lennox–Gastaut syndrome taking felbamate(3000 mg/day), topiramate(200 mg/day), and lorazepam developed painful hematuria, bilateral urethral obstruction, and urinary retention. Kidney, bladder, and urethral stones were found. The stone material was identified as felbamate by chemical analysis. However, as the patient was also taking topiramate the association with felbamate was uncertain.

Susceptibility Factors

It is wise to avoid felbamate in patients with previous blood dyscrasias or autoimmune disorders, especially lupus erythematosus.

Drug–Drug Interactions

Carbamazepine-10,11-epoxide

Felbamate is a metabolic inhibitor and significantly increases blood concentrations of carbamazepine-10,11-epoxide (SEDA-19, 69) (SEDA-20, 61).

Clonazepam

Although felbamate increases the plasma concentrations of clonazepam only slightly, patients taking this

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combination are more vulnerable to central nervous system adverse effects (16).

Gestodene

Felbamate reduces the plasma concentrations of gestodene and may reduce its contraceptive efficacy (SEDA-20, 61).

Phenobarbital

Felbamate is a metabolic inhibitor and significantly increases blood concentrations of phenobarbital (SEDA-19, 69) (SEDA-20, 61).

Phenytoin

Felbamate is a metabolic inhibitor and significantly increases blood concentrations of phenytoin (SEDA-19, 69) (SEDA-20, 61).

The dose dependency and clinical relevance of the inhibition of phenytoin metabolism by felbamate has been examined in 10 patients (17). Phenytoin concentrations increased from 64 μmol/l at baseline to 84 and 107 μmol/l after felbamate 1200 and 1800 mg/day respectively. Owing to adverse effects, a reduction in phenytoin dosage was required in four patients after felbamate 1800 mg/day and in six patients after felbamate 2400 mg/day. Felbamate titration to doses of 3600 mg/day required overall phenytoin dosage reductions of 40% on average (range 20–72%), based on tolerability. Based on these findings, phenytoin dosage should be reduced by 20% when felbamate is added, and further dosage reductions are likely to be required when felbamate dosage is increased. Requirements for dosage reductions may be predicted by clinical signs of phenytoin intolerance, such as mental slowing, nausea, fatigue, and somnolence. The same study showed that in patients taking phenytoin co-medication serum felbamate concentrations are reduced by about 60% compared with those achieved in monotherapy.

Valproate

Felbamate is a metabolic inhibitor and significantly increases blood concentrations of valproic acid (SEDA-19, 69) (SEDA-20, 61).

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Felbinac

See also Non-steroidal anti-inflammatory drugs

General Information

Felbinac, an active metabolite of fenbufen, is used as a gel for topical treatment (1).

Organs and Systems

Skin

Felbinac can cause itching, rash, and eosinophilia (SEDA-16, 110).

Reference

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Felodipine

See also Calcium channel blockers

General Information

Felodipine is a dihydropyridine derivative with diuretic properties (1). Its diuretic properties are not unique but are shared by other dihydropyridines. Its vasodilator-related adverse effects include flushing, headache, and tachycardia (2,3). Reduced arterial oxygen saturation has been seen in patients given intravenous felodipine for pulmonary hypertension (4,5). Along with amlodipine, but unlike other calcium channel blockers, felodipine may be safer in severe chronic heart failure accompanied by angina or hypertension.

Organs and Systems

Skin

Different skin reactions have been reported with calcium antagonists, and in particular telangiectases in light-exposed areas of the skin with nifedipine and amlodipine (6).

- A 70-year-old woman took felodipine 10 mg/day and enalapril for about 1 year for hypertension. She developed telangiectatic lesions of both sides of the trunk. After excluding other causes, felodipine was withdrawn. After 2 months the lesions slightly abated, but never completely disappeared. The diagnosis was confirmed by histological evidence of enlarged capillaries parallel to the skin surface, in the absence of mast cells.
- Photodistributed telangiectases, made worse by solar radiation have been reported in a 67-year-old man taking felodipine 5 mg/day (7). Rosacea was also present. Felodipine was withdrawn and the telangiectases improved. Rechallenge was not performed.
- A 67-year-old man who had taken felodipine 5 mg/day for 4 years developed facial telangiectatic lesions that worsened with solar exposure for 9 months before felodipine was withdrawn; 2 months later the lesions had markedly diminished (7).

Drug–Drug Interactions

Erythromycin

The metabolism of felodipine is inhibited by erythromycin (SEDA-17, 239).

Grapefruit juice

In 12 elderly people (aged 70 years and over), grapefruit juice increased the AUC of felodipine three-fold and its peak concentration four-fold (8). Blood pressure was lower with grapefruit juice after a single dose of felodipine, but not at steady state. Heart rate was higher with grapefruit juice after both single and multiple doses. Elderly patients should avoid taking grapefruit juice during treatment with felodipine because of this marked and unpredictable interaction.

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Fenbendazole

General Information

The antiprotozoal activity of fenbendazole, a benzimidazole derivative, is similar to that of mebendazole; the target seems to be the microtubule protein beta-tubulin. Its adverse effects are comparable to those of mebendazole (1).

Reference

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Fenbufen

See also Non-steroidal anti-inflammatory drugs

General Information

The profile of fenbufen is similar to the profiles of other NSAIDs (1). The dropout rate due to adverse reactions was 12–22% in different studies.

Organs and Systems

Respiratory

Fenbufen can cause a pulmonary alveolitis with rash, dry cough, breathlessness, fever, hypoxia, sometimes eosinophilia, and bilateral alveolar shadowing or infiltrates, which regress after withdrawal (SEDA-12, 85) (SEDA-13, 80) (SEDA-15, 100).

Nervous system

Headache has been reported with fenbufen (2).

Severe encephalitis, with generalized erythema and maculopapular rash on the trunk, has been reported (SEDA-19, 98).

Hematologic

Hemolytic anemia, in some cases with signs of hypersensitivity, has been reported (SEDA-14, 94). Aplastic anemia has been described in two patients (SEDA-18, 104), but both recovered fully after withdrawal.

Liver

The incidence of hepatotoxicity with fenbufen varies greatly. Changes in liver function tests were recorded in 25% patients in an early study (SEDA-4, 68), but were not confirmed later (SEDA-5, 194) (SEDA-6, 96). Abnormalities in the liver function of patients with rheumatoid arthritis may be a non-specific reaction to inflammation; however, hepatotoxicity should be watched for in patients taking fenbufen.

Skin

About 5% of patients have itching, rashes, or erythema multiforme (3). Circulating immune complexes have been found (4). The UK's Committee on Safety of Medicines issued a warning about the high rate of cutaneous adverse reactions with fenbufen and noted that some are followed by severe illnesses (SEDA-13, 72) (SEDA-14, 94) (SEDA-15, 100). Toxic epidermal necrolysis, a life-threatening reaction, has also been reported (SEDA-6, 96) (SEDA-8, 106) and a 1981–85 review on its incidence in France identified fenbufen as the third most common NSAID, after isoxicam and oxyphenbutazone, as a causal factor (5). Another severe skin reaction with laboratory evidence of hepatotoxicity has been described (SEDA-22, 115).

Drug–Drug Interactions

Enoxacin

Many cases of epileptic seizures have been reported in Japan in patients taking a combination of fenbufen and enoxacin (SEDA-12, 85) (SEDA-15, 100).

Quinolones

Fenbufen can cause convulsions, which has mainly been described in patients taking quinolone antibiotics (SEDA-18, 104).

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Fenclofenac

See also Non-steroidal anti-inflammatory drugs

General Information

Fenclofenac was withdrawn in the UK after its license was not renewed because of its adverse drug reaction profile (1). Data from the UK's Committee on Safety of Medicines included records of seven deaths and 895 adverse effects in patients taking fenclofenac. Shortly afterwards it was withdrawn in all other countries in which it had been marketed.

Organs and Systems

Skin

Fenclofenac has the second highest incidence of complications and ranks first in the number and severity of skin reactions (2).

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Fenfluramines

See also Anorectic drugs

General Information

Although it resembles amfetamine structurally, the appetite suppressant fenfluramine does not produce central nervous system stimulation in therapeutic doses.

Dexfenfluramine, the dextrorotatory isomer, was previously widely marketed as an appetite suppressant in the management of obesity. It appears to be a pure serotonin receptor agonist without the dopaminergic and sympathetic activity of the racemic mixture.

Fenfluramine, dexfenfluramine, and phentermine have been used alone or in combination as an alternative to diet and surgery in the management of obesity. This therapy was halted in 1997 after reports of valvular lesions affecting almost one-third of patients treated with these drugs. The combination of fenfluramine and phentermine is called fen–phen.

General Adverse Effects

Dexfenfluramine

During both short-term and long-term therapy the adverse effects of dexfenfluramine seen with greater frequency than with placebo were tiredness, nausea, diarrhea, and dry mouth (1,2). Mydriasis, depression, withdrawal depression, insomnia, nervousness, headache, and increased urinary frequency have also been reported. So far, published clinical experience suggests that the greater selectivity of the dextrorotatory isomer leads to better tolerability. There has been only one long-term, that is longer than 6 months, trial on which to base this opinion (2). Since weight increase is common after withdrawal of treatment, long-term treatment is likely to be sought and given. Because studies on laboratory animals, including squirrel monkeys, suggest that there is a dose-dependent depletion of serotonin and metabolites along with a persistently reduced number of uptake sites, there has always been concern about a neurotoxic response with both isomers. However, it has also been pointed out that dexfenfluramine was used by more than 5 million patients for 6 years, and the parent compound by more than 20 million patients for 26 years, and yet it has not been associated with any serotonergic-mediated functional nervous system pathology in humans (SEDA-17, 1).

Fenfluramine

The main adverse effects of fenfluramine in two double-blind studies were sedation and drowsiness in addition to abdominal discomfort and dry mouth (3). Very rarely were these severe enough to justify withdrawal. At fairly high doses, the above-mentioned adverse effects became more severe and frequent. Drowsiness and gastrointestinal disturbances, consisting of colicky abdominal pain, were among the outstanding adverse effects in several other studies, most of them double blind; dizziness, light-headedness, and headaches were less frequent but occasionally quite marked (4). Shivering, teeth grinding, and alopecia have occasionally been reported as adverse effects of fenfluramine (4).

Phentermine

Phentermine is a central nervous system stimulant that can increase brain dopamine concentrations and has a structure similar to amfetamine.

Phentermine is indicated only for short-term treatment, and tolerance often develops. Its common adverse effects are dry mouth, insomnia, increased blood pressure, and constipation (5). It is the subject of a separate monograph (p. 2804).

Organs and Systems

Cardiovascular

Spontaneous rupture of a retroperitoneal aneurysm occurred in a 70-year-old woman who had been taking phentermine hydrochloride, 30 mg/day, for about 1 month (6). Other long-term medications included fluoxetine and amitriptyline, and she had no history of coronary artery disease, hypertension, diabetes, or complications of pregnancy. Although it is plausible that phentermine could have contributed to the ruptured aneurysm, other possibilities should be considered, particularly rupture of an anomalous retroperitoneal blood vessel.

Cardiomyopathy

Restrictive cardiomyopathy due to endocardial fibrosis occurred in a 35-year-old woman 5 months after she had started to take fenfluramine 10 mg tds and phentermine 15 mg/day (7). The endocardial findings strongly resembled the valvular lesions associated with the use of fenfluramine–phentermine. Endocardial and valvular fibrosis associated with anorectic drugs is strikingly similar to the plaque material found in patients with carcinoid syndrome and those exposed to methysergide, and all possibly arise from a common mechanism.

Valvulopathy

The fenfluramines and phentermine can cause valvular heart disease (8–10), and this has been reviewed (11). Fenfluramine was voluntarily withdrawn by the manufacturers on 15 September 1997, and the US Department of Health and Human Services issued interim recommendations for people previously exposed to fenfluramine or dexfenfluramine with cardiac valvulopathies (SEDA-22, 3).

The use of fenfluramine or dexfenfluramine alone or in combination with phentermine, in 2524 adult participants in the population-based Hypertension Genetic Epidemiology Network Study, was associated with aortic regurgitation independent of aortic dilatation or fibrocalcification (12). The association between the use of fenfluramine or dexfenfluramine (alone or with phentermine) and aortic regurgitation adjusted for potential confounders was analysed. Nineteen participants, all of whom had hypertension, were being treated with fenfluramine or dexfenfluramine (5 on these agents alone, 14 also with phentermine). Aortic regurgitation was present in 32% ($n = 6$) of those taking fenfluramine/dexfenfluramine versus 6% (162/2505) of the remaining subjects. In multivariate analyses, after adjusting for important confounders, in particular aortic root structure, treatment with fenfluramine or dexfenfluramine was associated with

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aortic regurgitation (OR, 5.2; 95% CI, 1.7–14) and fibrocalcification (OR, 5.2; 95% CI, 1.9–15).

The autopsy findings in the heart and lungs of a patient with pulmonary hypertension associated with fenfluramine and phentermine have been described (13).

- A 36-year-old woman with a body mass index of 47.5 kg/m^2, took fen–phen for 7 months and developed pulmonary hypertension. Her pulmonary arterial pressure was 56 mmHg and echocardiography showed right ventricular dilatation and hypokinesia. She had a cardiopulmonary arrest during right-heart catheterization and died 3 days later. At autopsy, there was right ventricular dilatation with a fibroproliferative tricuspid valve. The pulmonary arteries had fibroproliferative plaques which were more severe and prominent in the upper lobes than in the lower lobes.

More autopsy cases of patients with a history of fen–phen use are warranted to document the frequency of combined cardiac valvular disease and pulmonary hypertension.

Progressive pulmonary hypertension occurred in two patients who took fenfluramine for only 8 months (SEDA-6, 9). The symptoms abated on withdrawal but returned in one patient when rechallenged.

In 1996, in a case-control study, 95 patients from 35 centers in France, Belgium, the UK, and the Netherlands were compared with 355 age- and sex-matched controls (14). The use of anorexic drugs (mainly derivatives of fenfluramine) was associated with an increased risk of primary pulmonary hypertension. Association with recognized risk factors such as a family history of primary pulmonary hypertension, infection with HIV, or the use of intravenous drugs was also confirmed. The absolute risk for obese patients who took anorexic agents for more than 3 months was 30 times higher than in non-users.

Echocardiography with color Doppler in 22 patients aged 25–69 years (19 women and three men) who had taken fen–phen for more than 3 months showed that one patient with newly discovered aortic insufficiency was asymptomatic. Some were taking several other drugs, none of which is known to precipitate valvular heart disease. Echocardiography was normal in 12 cases and abnormal in 10 including significant aortic insufficiency and significant mitral regurgitation. Ten of the patients had significant aortic insufficiency and nine had at least mild mitral insufficiency. The author inferred that fenfluramine was the likely offending agent, because (a) while it is known to cause release of serotonin, phentermine does not; (b) carcinoid tumors, which secrete serotonin and ergotamine, a serotonergic drug, are known to cause valvular heart disease; *and* (c) none of the obese patients who took phentermine and fluoxetine for more than 2 years developed pulmonary hypertension (15) and the author found no valvular heart disease in this cohort either (16). The recommendation that phentermine should be combined with fluoxetine, sertraline, or fluvoxamine as safer alternatives (16) requires prospective studies.

It was suggested that in patients who met the FDA criteria for cardiac valvular abnormalities on echocardiography performed soon after the withdrawal of appetite suppressants, there was a possibility (ranging from as low as 5% to as high as 67%) that the abnormality was a naturally occurring phenomenon and not a consequence of drug use (17). However, various studies have supported earlier reports of an association between fenfluramine or its d-isomer and cardiac valvular regurgitation, although they have differed with regard to the strength and clinical significance of the association (17). Differences in design, including a lack of baseline cardiac evaluation in echocardiographic assessment (9,10,18), have precluded comparisons. Additional evidence linking the use of fenfluramine or dexfenfluramine to cardiac valvular regurgitation has reaffirmed the wisdom of the FDA's decision to withdraw them from the market.

Why was this type of valvulopathy not recognized sooner? Changes in medical practice seem to have played a role as long-term and widespread use of these drugs evolved in the 1990s. Furthermore, cardiac murmurs can be more difficult to detect in obese patients (19).

Prevalence

Although initially a prevalence of up to 30% was estimated, subsequent reports have suggested much lower rates. There are several reasons for this disparity including uncontrolled data and the limitations of echocardiography (20–22). The FDA surveys and the University of Minnesota study reported point prevalences and inherently overestimated the association of appetite suppressants with valvulopathy because a certain percentage of patients have pre-existing valvular lesions. The method of detection also plays a crucial role. Echocardiography is far more sensitive than clinical examination in detecting valvular regurgitation. The issue may also be confounded by lesion regression after withdrawal of therapy (23). Moreover, case-control studies are no substitute for objective evidence of the status of cardiac valves before drug exposure (8). Also the duration of exposure has varied widely in different reports.

Pulmonary hypertension and valvular heart disease associated with anorexigens have been described predominantly in women, which raises important questions about biological and psychological risk factors and ethical practice. Do women respond differently to these drugs because of genetic or physiological factors or are these drugs being prescribed almost exclusively for women? Was it realistic for the regulatory authorities to believe that these drugs would be used only to treat morbid obesity? Most important, what view of the benefit to harm balance of using anorexigenic drugs has allowed women and their physicians to justify the use of potentially lethal drugs to deal with concerns about body image and weight? These questions (24) are pertinent to the current scenario of appetite-suppressant drug-related concerns.

Studies in which baseline echocardiography was carried out before the drug was used showed that the risk of new or prospective valvular heart disease was much lower than implied by previous prevalence studies (8). In 46 patients who used fenfluramine or dexfenfluramine for 14 days or more, the primary outcome was new or worsening valvulopathy, defined as progression of either aortic regurgitation or mitral regurgitation by at least one degree of severity and disease that met FDA criteria. Two patients taking fen–phen developed valvular heart disease. One had mild aortic regurgitation that progressed to moderate regurgitation and the second developed new moderate aortic insufficiency. The authors argued that the referral bias in their study, which required an echocardiogram for inclusion, would have tended to result in a higher incidence of valvular disease.

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In an amended randomized double-blind placebo-controlled comparison of dexfenfluramine with an investigational modified-release formulation of dexfenfluramine, the study medication was discontinued and echocardiographic examinations were performed on 1072 overweight patients within a median of 1 month after withdrawal of treatment (18). These patients, 80% of whom were women, had been randomly assigned to receive dexfenfluramine (366 patients), modified-release dexfenfluramine (352 patients), or placebo (354 patients). The average duration of treatment was 71–72 days in each group. Echocardiograms were assessed blind. Pooling the fenfluramine groups, there was a higher prevalence of any degree of aortic regurgitation (17 versus 12%) and mitral regurgitation (61 versus 54%) with fenfluramine. Analyses carried out using the criteria set by the FDA showed that aortic regurgitation of mild or greater severity occurred in 5% of the patients taking dexfenfluramine, 5.4% of those in the two fenfluramine groups combined, and 3.6% of those in the placebo group. Moderate or severe mitral regurgitation occurred in 1.7 and 1.8% of those taking fenfluramine and 1.2% of those taking placebo. Aortic regurgitation of mild or greater severity, mitral regurgitation of moderate or greater severity, or both occurred in 6.5, 6.9, and 4.5% respectively.

This was an unusual study because patients enrolled for a different purpose were analysed mid-way through the study in response to withdrawal of fenfluramine. Exposure to fenfluramine in this study was relatively short (2–3 months) and the prevalences of mitral regurgitation and aortic regurgitation in this study were much lower than previously described (25).

Although the findings of this study may be reassuring for patients who have taken dexfenfluramine for 2–3 months, they should not preclude the appropriate investigation of a new murmur or new symptoms in any patient with a history of exposure to dexfenfluramine as specified in the American College of Cardiology Guidelines (26).

In 24 women who were evaluated an average of 12 months after starting to take fen–phen, echocardiography showed that all had unusual valvular morphology and regurgitation affecting valves on the right and left sides (27). Eight women also had newly documented pulmonary hypertension. Histopathological findings included plaque-like encasement of the leaflets and chordal structures with intact valve architecture. The histopathological features were like those seen in carcinoid or ergotamine-induced valve disease. As of the end of September 1997, the FDA had received 144 individual spontaneous reports (including the 24 cases reported earlier) involving fenfluramine or dexfenfluramine with or without phentermine in association with valvulopathy, 113 with complete information (28). Of these, 98% occurred in women of whom 2% used fenfluramine alone, 14% used dexfenfluramine alone, 79% used fenfluramine with phentermine, and 5% used a combination of all three; none had used phentermine alone. The median duration of drug use was 9 months (range 1–39 months). Cardiac valve replacement surgery was required in 24% and there was an 11% mortality.

Based on a prospective study carried out in 226 obese subjects (183 women and 43 men) with a mean body mass index of 40 kg/m^2, therapy with fen–phen was associated with low prevalence of significant valvular regurgitation (29). The authors suggested that valvular regurgitation in these subjects may have reflected age-related degenerative changes. However, several limitations of this study have been pointed out: (a) there was no control group and not all the subjects had echocardiography; (b) multiple readers interpreted the echocardiograms, rendering the comparison less accurate; (c) there was inherent inaccuracy in differentiating mild degrees of valvular regurgitation especially using qualitative scoring systems; (d) there was selection bias; and (e) neither direct inspection nor histopathological confirmation of valvular lesions was performed on any patient.

The risk of a subsequent clinical diagnosis of a valvular disorder of uncertain origin has been assessed in a population-based follow-up study using nested case-control analysis of 6532 subjects who took dexfenfluramine, 2371 who took fenfluramine, and 862 who took phentermine (10). The control group comprised 9281 obese subjects who did not take appetite suppressants matched with the treated subjects for age, sex, and weight. No subject had cardiovascular disease at the start of the follow-up for an average duration of 5 years. There were 11 cases of newly diagnosed idiopathic valvular disorders, five with dexfenfluramine and six with fenfluramine. There were six cases of aortic regurgitation, two of mitral regurgitation, and three of combined aortic and mitral regurgitation. There were no cases of idiopathic cardiac valve abnormalities among the controls or those who took phentermine. The 5-year cumulative incidence of idiopathic cardiac valve disorders was 0 per 10 000 among both those who had not taken appetite suppressants (95 CI = 0, 15) and those who took phentermine alone (CI = 0, 77), 7.1 per 10 000 among those who took either fenfluramine or dexfenfluramine for less than 4 months (CI = 3.6, 18), and 35 per 10 000 among those who took either of these medications for 4 months or more (CI = 16, 76). The authors concluded that the use of fenfluramine or dexfenfluramine, particularly when used for 4 months or longer, is associated with an increased risk of newly diagnosed cardiac valve disorders, particularly aortic regurgitation.

The above study was based on information derived from the General Practice Research Database in the UK. Subjects who had been given at least one prescription for dexfenfluramine, fenfluramine, or phentermine after 1 January 1988, and who were 70 years or younger at the time of their first prescription were included. Subjects were considered to have a new cardiac abnormality if they had no history, on the basis of clinical records, of cardiac valvular abnormalities and if there was evidence of a new valvular disorder on the basis of echocardiography or clinical examination after exposure to appetite suppressants. All the data had been recorded before the publication of recent reports of an association between appetite suppressants and cardiac valve disorders (25,27,30–32) or primary pulmonary hypertension (14). Hence, it was possible to exclude the possibility that enhanced awareness of possible serious adverse effects of appetite suppressants had led to closer surveillance of patients who were taking these drugs. Nevertheless, the study did not provide information on the frequency of idiopathic cardiac valve disorders that are asymptomatic or otherwise not clinically diagnosed.

Using the FDA case definition of appetite-suppressant related valvulopathy, the prevalence was 31% (60/191) in a selected group of Mayo Clinic patients at Rochester (33). The most common finding was mild aortic regurgitation. Of asymptomatic patients 28% had abnormal

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echocardiographic findings. This study emphasized the spectrum of diet- or drug-related cardiac disease and the potential for valvulopathy in asymptomatic patients.

In patients who had taken dexfenfluramine (n = 479) or fen–phen (n = 455) continuously for 30 days or more in the previous 14 months, there was an increase in the prevalence of aortic regurgitation compared with 539 control subjects (34). There was no increase in the prevalence of moderate or severe aortic regurgitation in treated patients, and no difference in the prevalence of mitral regurgitation between the untreated and treated groups, irrespective of duration of therapy. All evaluations were carried out using the FDA criteria. The authors were careful to point out that their study was not specifically designed or adequately powered to evaluate specific categories of anorexigen therapy duration.

Further evidence that the prevalence of significant valvular regurgitation is low in patients who take fen–phen has been reported (35). Transthoracic echocardiography was performed in 343 obese patients in a 3-year prospective study that began within 4 months from the withdrawal of fenfluramine and dexfenfluramine from the market. There were 281 women and 62 men, mean age 47 years, and mean body mass index 40 kg/m^2. Using the FDA's criteria, only 21 subjects (6.1%) had significant valvular lesions. Aortic regurgitation was detected in 18 subjects, mitral regurgitation in 3, and both aortic and mitral regurgitation in 1. Significant valvular disease did not correlate with age, sex, initial or final body mass index, drug dose, or the duration of therapy.

Mechanisms and risk factors

The determinants of valvulopathy in patients treated with dexfenfluramine have been investigated: age and blood pressure can also affect the prevalence of regurgitation (36,37), as can duration of exposure (36). Others have found no correlation between valvular disease associated with appetite suppressants and either dose or duration of drug exposure (29).

Cases of severe diffuse multivalvular disease associated with fen–phen have been described (38,39).

- A 52-year-old woman had a transesophageal echocardiogram 1 year before starting to take fen–phen, and had no significant valvular disease. She presented a year later with a new heart murmur and eventually required isolated aortic valve replacement. Pathological evaluation of the excised aortic valve was consistent with that described with fen–phen use.
- A 44-year-old woman who had previously taken appetite suppressants, developed valvular disease consistent with the effects of fen–phen. She had an identical twin who, despite having been treated with the same medication, remained symptom-free and without abnormal echocardiography. Both the patient and her sister took fen–phen for 2 years. However, the patient took a daily dose of fenfluramine of 60–120 mg (and often as much as 240 mg) and phentermine 90 mg (at times 180 mg), whereas her twin sister adhered to the daily amount prescribed (fenfluramine 60 mg and phentermine 24 mg).

The latter case suggests that dosage is important in the production of the valvular pathology. Mitral and tricuspid insufficiency developed in a 36-year-old woman who had taken fen–phen for 24 months (40). Transmission electron microscopy of the mitral and tricuspid valves showed many areas that appeared to contain intracellular, virus-like particles clustered in the cytoplasm, with a mean diameter of 32 nm. Whether this finding was incidental or related to the underlying pathology was uncertain.

There is further evidence, from an uncontrolled observational study in 85 patients, that the dose and duration of administration of fen–phen affects the risk of significant valvular disease (41). The authors suggested that it would be prudent to consider diagnostic echocardiography in patients who have used fen–phen either in a dosage of at least 60 mg/day or for at least 9 months. They also raised concerns that for patients with mild obesity, the prolonged use of larger cumulative amounts may lead to a higher risk of valve regurgitation.

There is further evidence of the relation between the duration of treatment with fen–phen and the prevalence of valvular abnormalities (42). In 1163 patients who had taken anorexigens within the previous 5 years and 672 control patients who had not, valvular abnormalities primarily involved those who had taken anorexigens for more than 6 months, and predominantly resulted in mild aortic regurgitation. The study had some noteworthy limitations: since fenfluramine has been withdrawn from use, a randomized trial was impossible; also the lack of baseline echocardiograms before treatment implies that one cannot be certain that the valvular regurgitation developed subsequent to drug treatment.

Diagnosis

It has been proposed that valvular disease can be attributable to appetite suppressants only if the following criteria are satisfied:

- the macroscopic and microscopic features are consistent with fenfluramine-related valvulopathy;
- clinical, echocardiographic, and intraoperative findings support the diagnosis;
- the history of drug exposure predates the development or exacerbation of valvular dysfunction (43).

It is obvious that these criteria can be applicable only in cases in which cardiac valves are explanted and are available for histopathological studies.

The prevalence and diagnostic value of cardiac murmurs for valvular regurgitation has been determined in 223 patients taking dexfenfluramine for 6.9 months and 189 matched controls. Experienced physicians, non-cardiologists, who were unaware of the echocardiographic findings, took a history and performed cardiac auscultation. Based on their findings the authors recommended that cardiac auscultation should be the screening method of choice for detecting valvular regurgitation in users of anorexigens (44). In this study, the absence of cardiac murmurs predicted the absence of clinically important valvular regurgitation in 93% of dexfenfluramine users. These results support the recommendation by the American Heart Association and American College of Cardiology (45) that asymptomatic users of anorexigens without a cardiac murmur do not warrant echocardiography. The data also suggest that in users of anorexigens with a 10% prevalence of valvular regurgitation and a 10–15% prevalence of cardiac

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murmurs, cardiac auscultation will prevent 85–90% of patients from undergoing unnecessary echocardiography. These implications may apply to all users of anorexigens because the prevalence of valvular regurgitation in recent large series is similar to that in this study (SEDA-24, 4). There are therefore large potential cost savings of cardiac auscultation, by preventing a large proportion of the more than 6 million Americans who are exposed to anorexigens from undergoing initial and follow-up echocardiography or from receiving empiric antibiotic prophylaxis for emergency procedures that preclude further cardiac evaluation.

Effects of withdrawal of therapy on valvulopathy

In a patient who was followed-up for 2 years after withdrawal, multivalvular regurgitation associated with fenfluramine and phentermine may have regressed (23).

- A 44-year-old woman with morbid obesity but no history of cardiac disease developed atypical chest pain. Myocardial infarction was ruled out, and an echocardiogram showed normal chamber sizes and mildly reduced global systolic function. However, moderate to moderately severe aortic regurgitation, mild mitral regurgitation, and moderate tricuspid regurgitation were present. The estimated pulmonary artery pressure was slightly raised. Her only medications were fenfluramine 60 mg/day and phentermine 30 mg/day, which she had taken for the previous 50 weeks, during which time she had lost 40 kg. These drugs were withdrawn and 6 months later an echocardiogram showed improved left ventricular function and a reduction in the severity of all her valvular lesions with no clinically significant change in the estimated pulmonary artery pressure. An echocardiogram obtained 2 years after the initial study showed only trace aortic and tricuspid regurgitation without mitral regurgitation.

In this case, serial echocardiography over 2 years documented regression of multivalvular regurgitation, first discovered while the patient was taking fenfluramine and phentermine. The authors argued that although she was also given lisinopril, the marked degree of improvement in all the valvular lesions after withdrawal of the appetite suppressants was unlikely to be attributable to this alone (46).

The small increase in prevalence of minor degrees of aortic regurgitation and mitral regurgitation in 941 patients treated with dexfenfluramine for 2–3 months was no longer present 3–5 months (median 137 days) after withdrawal (47). Echocardiograms were acquired using a standardized protocol and were assessed blindly.

In 50 patients with fenfluramine-associated valvular heart disease followed by serial echocardiography for 6–24 months after withdrawal of therapy (48), in most cases valvular heart disease either did not change or improved at least by one grade. Mitral and aortic regurgitation improved in some patients, and tricuspid and pulmonic regurgitation improved in most patients after withdrawal. When improvement did occur, regression of regurgitation often involved multiple valves on both the left and right sides of the heart, rather than affecting one valve in isolation. Although most of the patients stabilized or improved, a few had worsening of valvular regurgitation despite withdrawal.

Comparable results were also reported in a larger series in another study (49). Sequential echocardiographic evaluation 1 year after withdrawal of dexfenfluramine showed a significant reduction in aortic regurgitation. There were no significant changes in mitral regurgitation or any other valvular variables. Although these results can be applied only to the population studied (predominantly middle-aged, obese, white women who took dexfenfluramine for 2–3 months), the implications are considerable. Because valvular regurgitation remained stable or improved in most of the patients, surgical referral for patients with severe regurgitation may be delayed. Improvement in valvular regurgitation often occurred within months after drug withdrawal. Watchful waiting with serial echocardiography, prophylaxis against endocarditis, and medical therapy may be a reasonable management strategy in patients with severe regurgitation, minimal symptoms, and no evidence of left ventricular dysfunction (48).

However, reversibility may not occur in all cases (50).

- Cardiac allograft transplantation was carried out from a 35-year-old hypertensive donor with prolonged exposure to fenfluramine and phentermine. There was non-specific mitral valve thickening, with trivial mitral regurgitation and poor approximation of the mitral valve leaflets, due to reduced posterior leaflet mobility. There was no evidence of any other valvular lesion. Examination of the donor heart during cardiac implantation showed three discontinuous lesions along the left atrial surface of the mitral valve annulus and another firm nodular lesion of the annular endocardium. Transplantation of the heart was uneventful and intraoperative transesophageal echocardiography, performed after weaning from cardiopulmonary bypass, showed trivial mitral regurgitation with excellent allograft contractility. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day. Histological examination of the specimen showed a glistening appearance with proliferating myofibroblasts and associated fibrinous vegetations. There was no evidence of acute or chronic inflammation, and Gram staining did not show bacterial or fungal elements. A transthoracic echocardiogram 6 weeks after transplantation showed only trivial mitral regurgitation with improved mobility of the posterior leaflet. Hemodynamic data showed normal allograft function. However, after 6 months of follow-up, Doppler echocardiography showed worsening of mitral regurgitation to moderate severity, but no adverse effects of this hemodynamic load were noted and the patient remained stable.

Although conclusions based on single cases have limitations, they can often provide useful insights and act as catalysts for further studies. This report illustrates a few important features of cardiac valvulopathy associated with anorexigen use. There was no involvement of chordal apparatus and so the pathological changes within the valve leaflets and annulus represented the earliest site of an anorexigen-induced valvulopathy. This opportunity to observe a case of "early" valvulopathy visually and histopathologically offered insight into pathogenesis, and may have been helpful in staging the lesions temporally.

Of 120 patients who had follow-up echocardiography at least twice after stopping fen–phen, 99 met FDA criteria

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for valvulopathy (51). On second echocardiography, 57 of these 99 had no change in valvulopathy, 33 had improved, and 9 had deteriorated; nine patients no longer met FDA criteria for valvulopathy. The authors suggested that physicians must continue to be vigilant with patients who develop valvulopathy after taking fen–phen.

Obesity as a confounding factor in cardiac valvulopathy

It is not clear whether valvular insufficiency is related to the use of appetite suppressants or is simply a consequence of obesity. Obese patients who took dexfenfluramine alone, dexfenfluramine in combination with phentermine, or fenfluramine in combination with phentermine have been compared with a matched group of obese-control subjects who had not taken these medications (9). A total of 1.3% of the controls (3 of 233) and 23% of the patients (53 of 233) met the case definition for cardiac valve abnormalities (OR=23). The odds ratios for such cardiac valve abnormalities were 13 with dexfenfluramine alone, 25 with dexfenfluramine and phentermine, and 26 with fenfluramine and phentermine. This study showed that the prevalence of valvular insufficiency is significantly higher among obese patients who have taken appetite suppressants than among subjects matched for age, sex, and body mass index who did not take such drugs. Since a higher percentage of patients than controls had trace aortic valve insufficiency, the authors questioned whether the case definition threshold for cardiac valve abnormalities in association with appetite suppressants set by the FDA and Centers for Disease Control and Prevention is perhaps too high. In this study the factors that predisposed patients to valvular insufficiency were (a) age at the start of therapy, (b) use of dexfenfluramine, (c) combination of dexfenfluramine with phentermine, and (d) combination of fenfluramine with phentermine. Hence, neither the clinical significance nor the natural history of this type of valvular disease has been defined.

Other epidemiological studies have ruled out the possibility that obesity itself causes a high prevalence of cardiac valvular regurgitation (52–54).

Pulmonary hypertension

Pulmonary hypertension associated with fenfluramine was first reported in the early 1980s. A retrospective study further established the link (55). Subsequently a multicenter case-control study in 95 patients showed a high incidence of pulmonary hypertension in patients who had used fenfluramine or dexfenfluramine (14). Moreover, there was a strong suggestion of a dose–response effect, longer periods of use being associated with a progressive increase in the relative risk of pulmonary hypertension. In 1997, the first case of pulmonary hypertension in association with fen–phen was reported (56). Eight of the 24 patients with valvular disease had newly diagnosed pulmonary hypertension, although in most cases it was attributable to valvular abnormalities (57). It is not clear whether a combination of these agents poses a higher risk in predisposed individuals.

The results of a Belgian study in 35 patients with pulmonary hypertension and 85 matched controls have been published (58). The data were collected when there was no restriction on prescribing of appetite suppressants. Of the patients, 23 had previously taken appetite suppressants, mainly fenfluramines, compared with 5 controls. Moreover, the patients who had been exposed to appetite suppressants tended to be on an average more severely ill and to have a shorter median delay between the onset of symptoms and diagnosis.

Pulmonary artery pressure and cardiac valvular status were determined in a series of 156 mostly asymptomatic patients taking fenfluramine and phentermine (59). The anorexigen was withdrawn when abnormalities were noted. Pulmonary artery pressure was estimated and valvular examination was performed using Doppler echocardiography. There was borderline or mildly elevated pulmonary artery pressure in 21 patients and 31 patients had notable valvular abnormalities. It has therefore been established that asymptomatic patients may have significant echocardiographic abnormalities, representing early lesions.

- A 30-year-old woman who had taken dexfenfluramine for 7 months developed pulmonary hypertension and right heart failure during late pregnancy. She died of septicemia with multiorgan failure 4 days after a cesarean section (60).
- Pulmonary hypertension and multivalvular damage after prolonged use of fenfluramine with phentermine have been reported in a 70-year-old Israeli woman (61).
- Fatal pulmonary hypertension occurred in a 32-year-old man who had been taking phentermine in unknown doses for 4 months (62).

Incidence

The epidemiological association of pulmonary hypertension with aminorex and dexfenfluramine, both with respect to the strength of the association (estimate of relative risk) and its impact on public health, has been investigated (63). Control rates of exposure were used to estimate population exposure prevalences. The estimated odds ratio for the association between pulmonary hypertension and any exposure to aminorex was 98 and for dexfenfluramine 3.7. The strong association between aminorex and pulmonary hypertension projected a fivefold increase in the incidence of pulmonary hypertension, and thus a very noticeable epidemic. In contrast, the association with dexfenfluramine is expected to result in an incidence of only 20% and thus a repeat epidemic seems unlikely.

In a prospective surveillance study of 579 patients with pulmonary hypertension at 12 large referral centers in North America, 205 had primary pulmonary hypertension and 374 had secondary pulmonary hypertension (64). Among the drugs surveyed, only fenfluramine had a significant association with primary pulmonary hypertension compared with secondary pulmonary hypertension (adjusted odds ratio for use for more than 6 months = 7.5; 95% CI = 1.7, 32). The association was stronger with longer duration of use compared with shorter duration of use and was more pronounced in recent users than in remote users. An unexpectedly high (11%) number of patients with secondary pulmonary hypertension had used anorexigens. The high prevalence of anorexigen use in patients with secondary pulmonary hypertension also

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raised the possibility that these drugs precipitate pulmonary hypertension in patients with underlying conditions associated with secondary pulmonary hypertension.

The age-adjusted mortality rates from primary pulmonary hypertension in the years immediately preceding the use of fen–phen were not different from those reported during the years of widespread use among patients aged 20–54 years. This analysis failed to support the hypothesis that the widespread use of fen–phen in the years 1992–1997 increased the incidence of primary pulmonary hypertension. "If the use [of fen–phen] during these years created an epidemic of primary pulmonary hypertension, as some have declared, such an epidemic is not reflected in the mortality database maintained by CDC" (65).

Prognosis

Of 62 patients (61 women) exposed to fenfluramine compared with 125 sex-matched patients with primary pulmonary hypertension, 33 had used dexfenfluramine alone, 7 had used fenfluramine alone, and 5 had used both (66). In 17 cases fenfluramines were taken with amphetamines. Most of the patients (81%) had taken fenfluramines for at least 3 months. The interval between the start of therapy and the onset of dyspnea was 49 months (range 27 days to 23 years). The two groups differed significantly in terms of age and body mass index. Both groups had similar severe baseline hemodynamics, but the percentage of responders to an acute vasodilator was higher in patients with primary pulmonary hypertension. Hence, more patients with primary pulmonary hypertension were treated with oral vasodilators, and long-term epoprostenol infusion was more often used in fenfluramine users. Overall survival was similar in the two groups, with a 3-year survival rate of 50%.

Mechanism and pathophysiology

The mechanism of fenfluramine-associated pulmonary hypertension has been reviewed (SEDA-21, 3). Since only a minority of patients exposed to fenfluramines develop pulmonary hypertension, it has been postulated that a subset may be genetically susceptible. Whether there is a related genetic abnormality in the familial PPH gene located on chromosome 2q (67) or an abnormality of the angiotensin-converting enzyme gene (68) has yet to be explored.

Anorexigenic drugs accumulate in the lung and other tissues, especially in cellular organelles with an internal acid pH, such as lysosomes, where they bind to acidic enzymes. Lipid enzyme inhibition, lysosomal lipidosis, and associated myeloidosis are key events in the pathological cascade (69). Since several stimulants and other psychotropic drugs are cationic amphiphilic compounds that accumulate in the lung, brain, and other tissues, the variety of pathological mechanisms involved in the effects of this group of drugs should be kept in mind during long-term use (70,71).

The hypothesis that nitric oxide deficiency predisposes affected individuals to anorexigen-associated pulmonary hypertension has been tested in a prospective case-control comparison with two sex-matched sets of controls: patients with primary pulmonary hypertension ($n = 8$) and healthy volunteers ($n = 12$) (72). Lung production of nitric oxide and systemic plasma oxidation products of nitric oxide were measured at rest and during exercise, and were lower in patients with anorexigen-associated pulmonary hypertension than in patients with primary pulmonary hypertension. This deficiency may have resulted from increased oxidative inactivation of nitric oxide, as the concentrations of their oxidative products were raised in inverse proportion to nitric oxide. These findings, and earlier evidence from animal studies (73), have given support to the hypothesis incriminating nitric oxide as a determinant of individual susceptibility to anorexigen-associated pulmonary hypertension.

The pressure response to endothelin-1 in the canine circulation has been investigated in isolated perfused dog lung (74). Acute treatment of the isolated lobes with fenfluramine increased pulmonary arterial pressure. Chronic treatment with fenfluramine potentiated the pulmonary vasoconstrictor response to endothelin-1. Based on these findings, the authors proposed that the pulmonary vasculature becomes hyper-reactive to vasoactive substances, such as serotonin and endothelin-1, possibly leading to pulmonary hypertension.

Anorexigen-associated severe pulmonary hypertension is clinically and histopathologically indistinguishable from idiopathic or primary pulmonary hypertension. Analysis of clonality in microdissected endothelial cells of plexiform lesions in two patients with anorexigen-associated pulmonary hypertension showed a monoclonal expansion of pulmonary endothelial cells. Accelerated growth of pulmonary endothelial cells in response to anorexigens in patients with predisposition to primary pulmonary hypertension has been speculated (75).

Hypertension

In a few patients, hypertension was induced or aggravated by fenfluramine. The hypertension disappeared on withdrawal, but could not in all instances be reinduced by rechallenge (76).

Nervous system

The frequent occurrence of sedation, drowsiness, lightheadedness, and headaches has been referred to in the general section above.

Impaired powers of concentration during the first week, insomnia, apathy, tiredness, reduction in general memory, and a feeling of derealization, but not mood elevation, were noted in healthy people who took fenfluramine (SEDA-13, 3) (77).

Of special interest are studies on the effects of fenfluramine on sleep. After administration of 40 or 80 mg of fenfluramine, patients with chronic psychiatric disorders fell asleep normally, but a few hours later were troubled with a peculiar feeling of uneasiness that kept them awake for the rest of the night. The following night, however, they fell asleep more quickly, regardless of the medication. Moreover, one patient had nightmares after taking two tablets a day; when the dosage was reduced to a single tablet in the morning, the nightmares ceased (78). About half of a group of 50 obese women treated for 20 weeks with various doses, increasing gradually up to the maximum tolerated dose of

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160 mg/day and then reduced again, reported of increased dreaming (79). In other studies vivid and disturbing dreams were reported by patients who tools fenfluramine 20–60 mg/day (80,81).

A 43-year-old woman had tightening movements of the head and neck with tongue and throat muscle spasm after a single fenfluramine tablet (82).

With phentermine, adverse effects due to stimulation of the central nervous system are less than with dexamphetamine, although in one study withdrawal because of adverse effects was as high as 16 of 177 patients (9%); 2 of 13 healthy young volunteers withdrew because of unacceptable stimulation (83).

Insomnia is one of the most common adverse effects of phentermine. In a survey in Edinburgh, 20% of the subjects taking phentermine reported insomnia compared with 6% of those taking placebo (4).

Psychological, psychiatric

The effect of fenfluramine is usually not one of stimulation but of calmness or drowsiness. However, in predisposed subjects, it can precipitate psychotic illness. Several published cases illustrate this (84). It is wise to avoid fenfluramine in patients prone to endogenous depression or psychosis.

A schizophreniform-like psychotic disorder was attributed to phentermine in a young woman without a personal or family history of psychiatric disorders (85).

Metabolism

Fenfluramine tends to improve glucose tolerance and to cause small but significant reductions in fasting blood cholesterol and beta-lipoprotein concentrations. Although it has been suggested that metabolic effects may play a role in weight reduction, and that fenfluramine might even be used to reduce blood lipids, the metabolic effects observed are slight and of dubious clinical importance.

Hematologic

Hemolytic anemia has been attributed to fenfluramine (86).

- A 46-year-old woman took fenfluramine for 5 months without incident. Some time later she restarted therapy and after 2 months developed a hemoglobin concentration of 5.1 g/dl, a reticulocyte count of 8.6%, a white cell count of 17.1 $\times$ 10^9/l, and a positive direct Coombs' test, with IgG rhesus antibodies (anti-e and anti-nl). Fenfluramine was withdrawn and the Coombs' test became negative and the patient recovered after prednisolone infusion.

Two other cases are known of anemia in patients who received fenfluramine and propranolol (SED-9, 13).

A clotting disorder has been attributed to fen–phen (87).

- A 35-year-old woman developed calf-pain while taking fen–phen. It resolved when the medications were withdrawn, but her pain returned when fenfluramine was restarted. She had slight rises in aspartate transaminase and lactate dehydrogenase activities and a remarkably shortened prothrombin time. The clot was composed of very thin fibrin fibers. All laboratory abnormalities, including the abnormal fibrin structure, completely resolved when fen–phen was withdrawn.

Thin fibrin fibers are more resistant to lysis and can result from a variety of factors and increase the risk of thrombosis. Whether abnormal fibrin structure and an increased thrombotic tendency play a role in patients who develop fenfluramine-associated pulmonary hypertension and valvular heart disease is a question that deserves further investigation.

Gastrointestinal

Diarrhea, dry mouth, and nausea have been reported (88).

Urinary tract

Phentermine can cause allergic interstitial nephritis (89).

- A 47-year-old mildly obese woman began a weight-reduction program that included anorectic therapy with phentermine and phendimetrazine. She had normal renal function at the start of therapy. After 3 weeks of treatment she fell ill and discontinued treatment. She was subsequently found to have leukocyturia, a rash on her face and chest, and a rise in serum creatinine from 67 to 175 μmol/l (0.8–2.1 mg/dl). Renal biopsy confirmed the diagnosis of acute interstitial nephritis. She was treated with corticosteroids and her renal function returned to normal.

Sexual function

There have been occasional reports of erectile impotence that disappeared on withdrawal. Very high dose regimens of 240 mg/day seem to produce a fairly high incidence of loss of libido, especially in women (90).

Immunologic

Shortly after starting dexfenfluramine 30 mg/day, an 18-year-old woman died of sclerodermal renal crisis (91). Although there have been reports linking long-term fenfluramine use and the development of scleroderma (92,93), this is perhaps the first report implicating dexfenfluramine.

Long-Term Effects

Drug abuse

Fenfluramine has the potential to become a drug of abuse when used in high dosages. Of 438 drug-dependent subjects, 60 gave a history of fenfluramine abuse and experienced euphoria, depersonalization, and perceptual changes after taking up to 400 mg (SED-9, 13). In another report, three of the eight subjects taking fenfluramine 240 mg/day experienced psychedelic states (SED-9, 13). A 28-year-old woman became dependent on fenfluramine at an average dose of 240 mg/day (SEDA-1, 5).

Some cases of toxic psychosis have been reported with abuse doses of phentermine (94).

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Drug tolerance

While tolerance to the anorectic effects of fenfluramine appears to set in after 6–12 months, tolerance to its adverse effects is much more rapid in onset (90).

Drug withdrawal

Depression can occur but is more common during the first few days following sudden withdrawal (SED-9, 12). An explanation for the depression and irritability encountered after sudden withdrawal may be a rapid reduction in 5-hydroxytryptamine through which the central effect of fenfluramine is mediated.

Second-Generation Effects

Pregnancy

In a prospective cohort study of 98 women who had taken fen–phen at the recommended daily dose during the first trimester of pregnancy and 233 women who had not taken it, there was no evidence of an increased risk of spontaneous abortion or of major or minor anomalies in the offspring of women who took fen–phen (95). These findings are similar to those of a previous French Collaborative Study (96). However, the risk to the offspring of women who take fen–phen for more prolonged periods and at higher dosages during pregnancy is unknown.

Drug Administration

Drug contamination

There have been reports of herbal remedies adulterated with fenfluramine. There was public health concern in the UK after the referral of a 44-year-old woman with new-onset hypertension, palpitation, anxiety, and a body mass index of 19 kg/m^2. It became apparent that an alarming number of the local population had been attending a particular Chinese herbalist for weight loss remedies. Most had been taking multiple formulations and described "spectacular" results. Several reported considerable cardiovascular symptoms, but they were reassured that Chinese medicines are natural and can cause no harm. Analysis by gas chromatography showed a high concentration of fenfluramine in two of the products (sold as Qian Er and Ma Zin Dol, presumably mimicking the brand name Mazindol). Fenfluramine was also found in the patients' urine. Subsequently, a student nurse was admitted with severe fenfluramine toxicity which developed 2 hours after her first dose of a herbal slimming remedy (97). Following an investigation of this case the Medicines Control Agency published a report on traditional ethnic medicines and the current law (98). Stringent regulation of traditional medicines, at least to the standards of conventional practice, is urgently needed. The hazards associated with the use of dietary supplements containing ma huang, a herbal source of ephedrine, have also been reported (99).

Drug overdose

A systematic study of fenfluramine poisoning in 96 human subjects (38 in detail) has been reported (100). Convulsions and coma occurred in 75% of those who took more than 15 mg/kg. Increased muscle tone, hyper-reflexia, or clonus were common; one-third had hyperthermia, but less than 10% died of it; symptoms could last for days. Blood concentrations of 240–850 ng/ml were associated with tachycardia, mydriasis, and confusion. Deaths occurred beginning at 650 ng/ml. Early gastric lavage, activated charcoal, diazepam for seizures, chlorpromazine and cooling for malignant hyperthermia, and lidocaine and constant electrocardiographic monitoring for extra beats were recommended.

Drug–Drug Interactions

Fluoxetine

Following the withdrawal of the fenfluramines, alternative combinations have been explored as appetite suppressants. In an open study of a combination of phentermine + fluoxetine in 16 obese patients with binge-eating disorder, in the setting of cognitive behavioral therapy, there were significant reductions in weight, binge frequency, and psychological distress by the end of treatment; however, the patients regained most of the weight within 1 year (101). At follow-up at 18 months there was still a reduction in binge eating in patients who continued maintenance treatment. The results did not support the long-term value of adding phentermine/fluoxetine to cognitive behavioral therapy for binge-eating disorder. It is worth emphasizing that it is not known whether phentermine/fluoxetine is also associated with cardiac valvulopathy. Moreover, the recognition that phentermine is a monoamine oxidase inhibitor (102) raises further concerns about its safety.

Halothane

Following a report of death after an anesthetic in a 23-year-old woman who had been taking fenfluramine, a study was undertaken in rabbits to investigate the possibility of an interaction of fenfluramine with halothane. Electrocardiographic and phonocardiographic changes were recorded in rabbits given the combined treatment, and could not readily be reversed with beta-blockers and resuscitative drugs. It was recommended that fenfluramine be discontinued a week before anesthesia (SED-9, 13).

Monoamine oxidase inhibitors

Fenfluramine can cause acute confusion if it is given together with monoamine oxidase inhibitors (SED-9, 9).

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Fenoterol

See also Beta$_2$-adrenoceptor agonists

General Information

Fenoterol is a beta$_2$-adrenoceptor agonist with higher intrinsic activity than salbutamol; it produces a greater maximal effect and has greater systemic effects at higher than conventional doses. It is available as a multidose pressurized aerosol 100 and 200 micrograms/puff and as a nebulizer solution, respules, 4 ml containing 1.25 mg. A formulation for injection is available in some countries.

Like other beta$_2$-agonists fenoterol has been used in premature labor as well as in asthma.

The safety of fenoterol in severe asthma

Debate continues about the safety of fenoterol in the treatment of severe asthma. A sharp rise in asthma mortality in 1977 in New Zealand provoked debate about the safety of beta$_2$-adrenoceptor agonists, especially the short-acting compound fenoterol. This led to the withdrawal of fenoterol in New Zealand and amendment of the American Asthma Guidelines, suggesting caution in the regular use of beta$_2$-adrenoceptor agonists (1). Although there is evidence linking fenoterol to increased morbidity and mortality in asthma (2), the underlying mechanisms were not known. It was suggested that the increase in mortality might be linked to fatal cardiac dysrhythmias, developing under conditions of asthma-induced hypoxia and high doses of beta$_2$-adrenoceptor agonists (3).

In a report the manufacturers have discussed the epidemiological data linking the use of fenoterol to asthma mortality in New Zealand. They pointed out that asthma mortality started to fall in 1979 while fenoterol sales were still increasing. Sales of fenoterol in Austria, Belgium, and Germany were similar to those in New Zealand at the peak of the New Zealand asthma death epidemic, but asthma mortality in the other countries did not rise. The confounding problem that fenoterol was preferentially prescribed for the more severe cases of asthma was

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again mentioned. Researchers who adjust their data appropriately for asthma severity have concluded that the increased risk of death from asthma reported in patients using fenoterol is due to underlying severe disease in the patients using fenoterol. The proponents of the hypothesis have responded by pointing out that four case-control studies all showed a significantly higher death rate in patients taking fenoterol than in patients taking other $beta_2$ agonists. They have acknowledged that there is some evidence of selective prescribing of fenoterol in populations studied in New Zealand and Canada. However, they do not agree that the association between fenoterol and asthma deaths is due to confounding by asthma severity. A third group has concluded that the association between fenoterol and severe life-threatening asthma is explained by the preferential prescribing of fenoterol for patients with more severe disease. They have pointed out that doses of fenoterol (up to 3200 micrograms) or salbutamol (up to 1600 micrograms) failed to produce clinically relevant cardiac dysrhythmias in patients with acute severe asthma. This was despite the fact that the two-fold higher dose of fenoterol caused greater systemic $beta_2$ effects. They have concluded that although epidemiological evidence may implicate fenoterol as a cause of asthma deaths it can only generate a hypothesis. The hypothesis is not substantiated by data from carefully controlled pharmacodynamic and pharmacoepidemiological studies. They have supported the view that excessive use of $beta_2$ agonists, including fenoterol, in severe asthma is a marker of inadequate suppression of the underlying inflammatory process, indicating the need to introduce or optimize the dose of glucocorticoids.

It is interesting to reflect that a similar debate followed the rise in asthma deaths in the UK in the 1960s. Most physicians now accept that excessive use of beta-adrenoceptor agonists in worsening asthma indicates inadequate treatment rather than a toxic effect of the drugs.

Organs and Systems

Cardiovascular

The cardiovascular safety of high doses of inhaled fenoterol and salbutamol has been compared in acute severe asthma (SEDA-21, 183). It was concluded that in adequately oxygenated patients a total dose of 3.2 mg of fenoterol or 1.6 mg of salbutamol given over 60 minutes was safe in terms of cardiovascular effects in acute severe asthma.

Electrolyte balance

In one study, an intravenous infusion of fenoterol 0.5–2.0 micrograms/minute was given to 83 patients (aged 28–34 years) in premature labor (SEDA-22, 189). Pretreatment plasma potassium concentrations were normal (median 4.10 mmol/l; 25–75 percentiles 4.10–4.40 mmol/l). During the first 2 hours the serum potassium fell significantly to 2.88 mmol/l (2.80–3.00 mmol/l), but returned to normal during the first day and then remained in the reference range, despite continuous fenoterol administration. No potassium supplements were given. No clinical abnormalities, including cardiac dysrhythmias, due to hypokalemia were seen.

Liver

Liver damage has been attributed to fenoterol (SEDA-21, 183).

- A 27-year-old woman at 31 weeks of a second pregnancy was admitted in premature labor and treated with intravenous fenoterol 7.5 mg/day. Within 48 hours her liver enzymes were raised. Because the liver function tests became progressively worse and she had epigastric pain and severe nausea, the fenoterol was withdrawn after 9 days. The liver function tests quickly normalized and there appeared to be a clear relation between the administration of fenoterol and the occurrence of liver damage.

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Fenproporex hydrochloride

See also Anorectic drugs

General Information

Fenproporex, one of the lesser known anorectic drugs, is structurally related to amfetamine, to which it is rapidly metabolized after oral ingestion. Stimulatory effects, somnolence, and electroencephalographic abnormalities are reported to be the major undesired reactions (1).

Reference

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Fenspiride

General Information

Fenspiride is a bronchodilator and anti-inflammatory drug. Two in vitro studies have suggested possible mechanisms for these effects.

Functional studies in human isolated bronchi showed that fenspiride causes a shift to the left of concentration effect curves for relaxation induced by isoprenaline and

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sodium nitroprusside. Biochemical studies confirmed that phosphodiesterase type IV (cyclic AMP-specific) and phosphodiesterase type V (cyclic GMP-specific) are the main phosphodiesterase isoforms present in human bronchi. Fenspiride inhibited both isoforms. Fenspiride facilitates relaxation of human bronchial smooth muscle in vitro, and this effect may be due to inhibition of phosphodiesterases IV and V.

In a human lung epithelial cell line, in which histamine increased the intracellular calcium concentration and the formation of eicosanoids, this response was antagonized by the histamine H_1 receptor antagonist diphenhydramine but unaffected by the H_2 receptor antagonist cimetidine. Fenspiride inhibited H_1 receptor-induced calcium increase. Histamine also caused a biphasic increase in arachidonic acid release, which was inhibited by fenspiride. This study suggests a further mechanism that would promote anti-inflammatory and bronchodilator properties.

The findings in several thousand patients treated by 800 general practitioners have been reported (1). There were mild adverse effects in 10% of the patients, but they were not thought to be specific to the drug (gastrointestinal, neurovegetative).

Fenspiride has been used to treat 392 adults with acute respiratory tract infections, most of whom were considered to have a moderate symptom score that improved with 7 days of treatment with fenspiride. Adverse reactions were classified as mild and tolerance was excellent; only 20 of 392 patients discontinued the drug.

Reference

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Fentanyl

General Information

Fentanyl citrate is a synthetic opioid 1000 times more potent than pethidine. It has a relatively short duration of action, and its effects are rapidly reversed by opioid antagonists (1). It is useful (2) but has typical opioid adverse effects.

The analgesic effect of fentanyl 1.5 μg/kg has been compared with that of tramadol 1.5 mg/kg in 61 patients receiving standardized anesthetics for day-case arthroscopic knee surgery (3). Opioid adverse effects and analgesia were similar in the two groups.

The analgesic effects and adverse effects profiles of subcutaneous fentanyl and subcutaneous morphine have been compared in a double-blind, crossover, 6-day study in 23 patients with cancer pain (4). There were no significant differences in pain scores between the two drugs and no changes in the level of acute confusion (using the Saskatoon Delirium Checklist) or cognitive impairment (in tests of semantic fluency and trail-making tests). Fentanyl caused significantly less constipation. The patients in this study were highly stable and compliant, and the results cannot be generalized.

Organs and Systems

Cardiovascular

A hypertensive crisis occurred in a patient with a previously unknown pheochromocytoma (5).

Respiratory

Even small doses of fentanyl can cause respiratory depression. Delayed respiratory depression can be a particular problem in the elderly, in whom the half-life is approximately three times longer than in younger patients (6). Respiratory depression has been reversed with nalbuphine; doxapram could only antagonize this effect for 2–5 minutes (7). However, the need for prolonged treatment of respiratory depression with naloxone, because of pharmacokinetic variability and/or transdermal drug reservoir, has been emphasized by several authors (SEDA-16, 80) (SEDA-17, 80).

Fentanyl can evoke the pulmonary chemoreflex, as evidenced by 50% of patients in one study and 28% in another, who coughed after the administration of fentanyl through a central line (SEDA-16, 79) (8). The coughing caused by fentanyl is inhibited by terbutaline (SEDA-21, 88).

Cough has been attributed to fentanyl (9).

- A 7-year-old boy with trisomy 21 (Down syndrome) had explosive coughing, 30 seconds after fentanyl 50 μg (2 μg/kg) had been injected and flushed through an intravenous cannula. The cough was unproductive and persisted in spasmodic bursts for a further 2–3 minutes until anesthesia was induced with propofol 60 mg and atracurium 15 mg intravenously. The coughing immediately ceased. A petechial rash in the conjunctivae and periorbital regions was subsequently noted and disappeared by the end of the first postoperative day.

Nervous system

Movement disorders after withdrawal of continuous infusion, without the characteristic autonomic signs of opioid withdrawal, have been reported in children (SEDA-17, 80).

Fentanyl-induced seizures have been reported (10).

Life-threatening complications have included raised intracranial pressure and critically reducing cerebral perfusion (11).

- A 55-year-old man was given fentanyl 0.05 mg for treatment of left chest pain and immediately developed an acute confusional state and fluctuating tetraparesis (12). The symptoms abated 12 hours after withdrawal. A provocation test confirmed that fentanyl 0.1 mg was enough to cause myoclonic and dystonic reactions with increased agitation. Administration of intravenous naloxone 0.8 mg improved the condition.
- A 14-year-old girl developed a dystonic reaction to fentanyl 50 μg given as a general anesthesia for dental extraction; her abnormal movements stopped completely after 3 days (13).

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Fentanyl can displace bilirubin from albumin in neonates, with a risk of kernicterus; other drugs should be used (SEDA-17, 81).

Psychological, psychiatric

Mood alteration during patient-controlled epidural anesthesia with either morphine or fentanyl was compared in a randomized, double-blind study of 52 patients undergoing elective hip or knee joint arthroplasty under general anesthesia (14). Mood was assessed preoperatively and at 24, 48, and 72 hours, using the bipolar version of the Profile of Mood States. Pain intensity postoperatively did not vary with morphine or fentanyl and, as expected, both fentanyl and morphine users had significant somnolence, pruritus, and nausea compared with baseline. With morphine, the mean score for measures of composure/anxiety, elation/depression and clear-headedness/confusion increased, indicating a change toward the more positive pole, but there were negative changes for the fentanyl users' scores for five of the six components of the Profile of Mood States. The difference in test scores between morphine and fentanyl was significant at 48 hours of patient-controlled anesthesia and 24 hours after withdrawal. There was no correlation between mood scores and pain scores, and mood scores with fentanyl fell with increasing plasma concentrations. Previous investigations have shown transient positive feelings with intravenous fentanyl, followed by more negative feelings in the longer term. The authors suggested that the differences in mood between the two groups may have been explained by differences in the lipid solubility and pharmacokinetics of epidural morphine and fentanyl.

Urinary tract

There have been two cases of urinary retention leading to renal pelvocalyceal dilatation as a result of continuous infusion of fentanyl (3 μg/kg/hour) in premature neonates (15). In both cases the problem was resolved by inserting an indwelling catheter.

Skin

A rash has been attributed to fentanyl (16).

- A 70-year-old man with metastatic cancer of the colon was given transdermal fentanyl 50 mg for analgesia. After 10 days he developed an itchy pustular eruption on the trunk and limbs. The lesions subsided on withdrawal of fentanyl. When he restarted transdermal fentanyl 2 months later, the skin lesions reappeared and became more generalized. The pustules were scattered, sparse, and superficial, and included the tongue and buccal mucosa, but not the conjunctivae or genitalia. A history of eosinophilia suggested an immunoallergic origin.

Like other opioids, fentanyl can cause pruritus. Prophylactic intravenous ondansetron 8 mg with hyperbaric bupivacaine 7–10 mg and fentanyl 25 μg significantly reduced the incidence of intrathecal fentanyl-induced pruritus in 125 patients undergoing knee arthroscopy or urological surgery in a randomized, double-blind, placebo-controlled trial (17). The incidence of pruritus was 39% with ondansetron and 68% with placebo.

Musculoskeletal

There have been three reports and a prospective study of muscle rigidity after fentanyl administration in neonates (18,19).

- Two neonates had transient (0.5–2 minutes) chest wall rigidity after intravenous boluses of fentanyl 2 and 4 μg/kg. They were already compromised, one with a respiratory distress syndrome and one with a diaphragmatic hernia.
- A premature male infant of 28 weeks gestation was given an intravenous bolus of fentanyl 3 μg/kg before intubation and this was followed by isolated rigidity of the tongue lasting 20 seconds (18).

In a prospective case series study of 89 preterm and term infants who received fentanyl out of a total of 404 neonatal intensive care patients in one year, eight neonates (9%) had chest wall rigidity (19). The spectrum of neuromuscular activity extends from mild muscle rigidity through abnormal muscle movements (chewing) to tonic-clonic movements. In two cases there was laryngospasm with chest wall rigidity. In all cases low-dose fentanyl (3–6 μg/kg) had been given for analgesia or sedation.

Chest wall rigidity, sometimes lasting for more than 24 hours and causing hypoxia, can occur postoperatively; it can be attenuated with naloxone or neuromuscular blockers (SEDA-22, 98) (20).

Second-Generation Effects

Pregnancy

The efficacy of intrathecal fentanyl and sufentanil for labor analgesia has been studied in 75 nulliparous women in a two-part comparison (21). In the first phase, 20 subjects received varying doses of fentanyl; the ED_{50} of intrathecal fentanyl for 60 minutes of labor analgesia was 18 μg, with a potency ratio of intrathecal sufentanil to intrathecal fentanyl of 4.4. In the second phase, 55 subjects participated in a double-blind, randomized comparison of the efficacy and safety of either intrathecal fentanyl 36 μg or sufentanil 8 μg. Sufentanil gave 25 minutes longer analgesia than fentanyl. There were no significant differences in adverse effects between the two groups: 83% had pruritus and 27% of those given sufentanil and 10% of those given fentanyl had nausea.

In a randomized, double-blind, placebo-controlled study of whether patient-controlled epidural fentanyl could produce effective and safe postoperative analgesia following 25 μg of spinal fentanyl at cesarean section in 36 patients, the fentanyl group used a mean of 23 μg/hour of fentanyl compared with 27 μg/hour in the control group (22). There was pruritus in 15 patients given fentanyl compared with one control; 9 given fentanyl had mild or moderate drowsiness during the operation compared with 8 controls. Postoperative nausea, pruritus, and drowsiness did not differ between the two groups.

In a randomized, controlled trial, 52 patients in labor were randomly given either intrathecal fentanyl 25 μg with saline or fentanyl 25 μg with magnesium sulfate 50 mg as part of a combined spinal-epidural technique

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(21). The incidence of pruritus with fentanyl alone was 65%, significantly lower than with fentanyl plus magnesium sulfate (77%). However, fentanyl plus magnesium sulfate produced significantly better and longer-lasting pain control, potentially reducing postoperative opioid requirements.

Susceptibility Factors

Other features of the patient

When the concentration of α_1-acid glycoprotein is reduced, with reduced binding, highly protein-bound basic drugs, such as fentanyl, should be given with caution in order to avoid high unbound concentrations and unwanted effects (SEDA-17, 81).

Drug Administration

Drug formulations

- A woman suffered sedation, localized erythematous lesions on the hands, and reduced appetite with weight loss after removing transdermal fentanyl patches from her daughter's skin and replacing them without wearing protective gloves (23). She had severe headaches, night sweats, irritability, nausea, and insomnia. When she used gloves, her weight gradually increased and the sedation abated.
- A 57-year-old woman using transdermal fentanyl (75 μg/hour) developed a reduced respiratory rate and bilateral pinpoint pupils when an upper body warming blanket was used as a normal postoperative procedure (24). The resultant increase in skin temperature significantly enhanced skin perfusion, and increased the systemic absorption of fentanyl from the intracutaneous fentanyl depot, leading to symptoms of opioid overdose. She recovered after removal of the fentanyl patch and the intravenous administration of naloxone 60 μg.

Oral transmucosal fentanyl administration, avoiding first-pass metabolism, produces analgesia and sedation in both adults and children undergoing short painful outpatient procedures. The quality of analgesia is good, and the adverse effects are those typical of the opioids. However, an unusual reaction, with agitation and hyperactivity, progressing over a week to delirium, has been reported. Mild impairment of hepatic and renal function, with accumulation of norfentanyl, has been postulated as a possible mechanism (SEDA-20, 77).

Drug additives

Bupivacaine and/or adrenaline

The addition of bupivacaine and/or adrenaline to epidural fentanyl analgesia has also been studied in 100 women after elective cesarean section. All received fentanyl (3 μg/ml) by patient-controlled analgesia (PCA) for 48 hours and were randomly assigned double-blind to receive either bupivacaine 0.01%, ephedrine 0.5 μg/ml, both, or neither (25). Patients who received fentanyl alone made more attempts at PCA than the other groups, suggesting that this regimen was less effective and the higher dose of fentanyl used perhaps contributed to a higher incidence of nausea and urinary retention and to a higher frequency of severe pruritus. The authors suggested that with lower doses of fentanyl there was less rostral spread of the drug and lower concentrations at the brain stem, thus reducing adverse effects. Breast-fed neonates were neurologically assessed at 2 and 48 hours by a pediatrician and, despite the different fentanyl requirements of mothers, neurobehavioral scores were equally high in the different groups.

Bupivacaine

Effective postoperative pain relief can be obtained with a mixture of fentanyl and bupivacaine, which not only provides better analgesia than either drug alone, but also fewer adverse effects. There have been several studies of the efficacy of this mixture, using different doses and routes of administration, the addition of clonidine, and in comparison with morphine.

In a randomized, double-blind study in 56 patients, continuous infusion of fentanyl (1 μg/kg/hour or 0.5 μg/kg/hour) and bupivacaine 0.1 mg/kg/hour, with intravenous morphine PCA as rescue analgesia, produced better pain relief after knee ligament operations than epidural saline combined with intravenous morphine PCA (26). There was a non-significant increase in nausea in the fentanyl group.

In another randomized, double-blind study, 84 parturients requesting epidural analgesia were given either bupivacaine 20 ml only, followed by intravenous fentanyl 60 μg or bupivacaine 20 ml with fentanyl 60 μg followed by intravenous saline (27). The minimum local analgesia concentration (MLAC) of bupivacaine + intravenous fentanyl was 0.064% w/v and the MLAC of bupivacaine + epidural fentanyl was 0.034% w/v. The epidural fentanyl solution significantly increased the analgesic potency of bupivacaine by a factor of 1.88 compared with intravenous fentanyl. This was associated with increased pruritus with epidural fentanyl.

Women scheduled for cesarean section ($n = 32$) were given spinal bupivacaine 10 mg (0.5%) or spinal bupivacaine 5 mg (0.5%) plus fentanyl 25 μg (28). Those given fentanyl had adequate spinal anesthesia for cesarean section with fewer adverse effects (nausea and hypotension). This observation was reproduced by spinal anesthesia with bupivacaine 4 mg plus fentanyl 20 μg, which provided adequate spinal anesthesia for surgical repair of hip fracture in elderly patients, with fewer adverse effects than bupivacaine 10 mg (29).

Bupivacaine, clonidine

Different combinations of fentanyl, bupivacaine, and clonidine were investigated in a multicenter (6 sites) trial of 78 women undergoing elective cesarean section under "spinal block" (30). In some cases, this appeared to imply intrathecal administration, and in others combined intrathecal and epidural administration. Patients received hyperbaric bupivacaine alone, or with 75 μg of clonidine, or with 75 μg of clonidine and 12.5 μg of fentanyl. There were no reported hemodynamic differences between the groups, but sedation and pruritus were significantly more common in those who received fentanyl, occurring in 65% and 25% of

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subjects respectively. Apgar scores and umbilical artery blood pH were unaffected by the drug regimens.

Bupivacaine or ropivacaine

The addition of fentanyl 1 μg/ml to ropivacaine 7.5 mg/ml did not improve nerve blockade by axillary brachial plexus anesthesia in a double-blind, randomized study in 30 patients undergoing orthopedic procedures (31). In another double-blind, randomized study, 60 patients receiving axillary brachial plexus blockade were given 0.25% bupivacaine 40 mg, 0.25% bupivacaine 40 mg plus fentanyl 2.5 μg/ml, or 0.125% bupivacaine 40 mg plus fentanyl 2.5 μg/ml (32). The addition of fentanyl 2.5 μg/ml prolonged sensory and motor blockade without any improvement in the onset of anesthesia and no significant increase in adverse effects. These two studies have reaffirmed the current position of conflicting results in studies of the benefits of adding fentanyl to local anesthetics for peripheral nerve blockade.

Ropivacaine

In a randomized, placebo-controlled study, a mixture of ropivacaine 0.2% and fentanyl 2 μg/ml plus a background infusion of 5 ml/hour was given to 20 patients for postoperative patient-controlled epidural analgesia after gynecological surgery. Another 21 patients were given the same mixture without the background infusion. Both groups were monitored hourly for arterial blood pressure, heart rate, and respiratory rate, and pain, sedation, motor blockade, and sensory levels were monitored every 6 hours (33). There was no difference in pain scores or patient satisfaction scores between the two groups, but the patients who received the background infusion had a higher incidence of adverse effects (71 versus 30%). The authors suggested that there was no additional benefit in using a background infusion.

Fentanyl 2 μg/ml has been used in combination with ropivacaine 2 mg/ml to determine its impact on the quality of postoperative analgesia and the incidence of adverse effects after colonic surgery in 155 patients scheduled for elective colonic surgery in a multicenter, double-blind, randomized study (34). The incidences of hypotension and pruritus in those given fentanyl were significantly increased, although they had better analgesic control. They also had an increased incidence of serious adverse effects affecting the respiratory, cardiovascular, and genitourinary systems.

The ideal combination strength of ropivacaine with fentanyl for postoperative epidural analgesia has been investigated in two studies. In a double-blind, randomized study, 30 patients undergoing lower abdominal surgery received one of three solutions for PCA after a standardized combined epidural and general anesthetic: ropivacaine 0.2% plus fentanyl 4 μg, ropivacaine 0.1% plus fentanyl 2 μg, or ropivacaine 0.05% plus fentanyl 1 μg (35). All three solutions produced equivalent analgesia. Motor block secondary to the ropivacaine was significantly more frequent and intense with ropivacaine 0.2% plus fentanyl 4 μg. Pruritus, nausea, sedation, and hypotension occurred equally often in the three groups and were mild. It was therefore inferred that ropivacaine 0.2% plus fentanyl 4 μg is preferable for analgesia after lower abdominal surgery.

Sufentanil

There was no difference in analgesic efficacy or the incidence of adverse effects when fentanyl 100 μg was compared with sufentanil 20 μg in women in labor who requested epidural analgesia (36).

Bupivacaine or lidocaine

The addition of clonidine or fentanyl to local anesthetics for single shot caudal blocks has been studied in 64 children undergoing bilateral correction of vesicoureteral reflux randomized into four groups (37). The control group received a mixture of 0.25% bupivacaine with adrenaline plus 1% lidocaine; other groups received the same combination plus 1.5 μg/kg of clonidine, or the control combination plus 1 μg/kg of fentanyl, or the control combination plus 0.5 μg/kg of fentanyl plus 0.75 μg/kg of clonidine. The addition of either clonidine or fentanyl significantly prolonged anesthesia, and during recovery the groups receiving local anesthetics alone or with the addition of fentanyl alone had significantly increased heart rates. Two of the children who received extradural fentanyl had a transient reduction in oxygen of saturation to 92% in the first hour of recovery. One of these was from those who received fentanyl alone, while one had received fentanyl plus clonidine. Vomiting occurred only in children exposed to fentanyl (nine of 29 subjects). This is the first report of respiratory depression in children after the caudal administration of fentanyl or clonidine, this adverse effect having been previously described with extradural opioids and clonidine in adults.

Lidocaine

In 100 patients undergoing arthroscopic outpatient surgery minidose spinal lidocaine plus fentanyl (0.5% lidocaine 20 mg plus fentanyl 20 μg) has been compared with traditional spinal anesthesia (1% lidocaine 30 ml with titrated intravenous propofol infusion) (38). The study was randomized and prospective but unblinded. Whereas those given local anesthesia were more likely to have pain requiring analgesic medication before discharge (44 versus 20%), those given spinal anesthesia group were more likely to have nausea (8 versus 22%) or pruritus (8 versus 68%). Both techniques provided a high degree of patient satisfaction, with comparable efficacy both intraoperatively and postoperatively.

Drug dosage regimens

Fentanyl is widely used for obstetric analgesia and the dose–response relation for intrathecal fentanyl has been examined in a randomized study of 84 nulliparous full-term parturients in labor (39). They received intrathecal doses of fentanyl of 5–45 μg and visual analogue scales were used to measure analgesia and adverse effects. The mean duration of anesthesia increased in the dose range 5–25 μg of fentanyl and then reached a plateau. Adequate analgesia was obtained with all doses of fentanyl above 10 μg. Maternal systolic blood pressure was not significantly affected at any dose, although diastolic blood pressure fell significantly at 10–30 minutes after fentanyl. Nausea and vomiting were uncommon, but pruritus was common in all groups and was more severe with higher doses of fentanyl. Fetal heart rate did not change

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significantly with fentanyl at any dose, although the authors acknowledged that they did not undertake continuous fetal heart tracing. They concluded that there is no benefit in using doses of intrathecal fentanyl above 25 μg when fentanyl is used as the sole analgesic agent in labor.

Drug administration route

Opioids have traditionally been given intramuscularly and intravenously. Other methods of administration are oral, subcutaneous, rectal, intrathecal, and extradural. Novel routes include intranasal, inhalational, intra-articular, and transdermal.

Buccal

Oral transmucosal fentanyl citrate has two advantages: it is more acceptable as a flavored lozenge than an oral elixir or tablet would be, especially in children, and 25% goes directly into the systemic circulation without first-pass metabolism (SEDA-20, 77). Its main adverse effect is dose-dependent nausea and/or vomiting, which occurs in 25–50% of patients. In a double-blind, placebo-controlled comparison of oral transmucosal fentanyl citrate (10 μg/kg) and oral oxycodone (0.2 mg/kg) in outpatient wound care procedures in 22 children, there were similar outcomes and no adverse effects in either group (40).

Transdermal

Fentanyl can be used transdermally because of its high solubility in both fat and water, low molecular weight, high analgesic potency, and fewer adverse effects, especially gastrointestinal symptoms (41). It is easy to administer and can be given at 3-day intervals. Transdermal fentanyl has been extensively reviewed in patients with chronic cancer pain (22) and in a review in which the possibilities and techniques available for acute and/or chronic pain relief were considered (42).

Transdermal fentanyl has an adverse effects profile similar to that associated with parenteral administration (SEDA-20, 77). Local erythema and rash have been reported (43), as well as the usual opioid adverse effects. However, an unusual reaction, with progressive agitation to acute delirium, has occurred (SEDA-20, 79).

Local heating and cutaneous hyperthermia of the patch area can cause lethal problems of overdose, owing to increased release and absorption (SEDA-18, 80) (SEDA-19, 83).

Transdermal administration of fentanyl has been extensively reviewed (44). In systemic availability studies, 92% of the fentanyl dose delivered from the transdermal therapeutic system into the skin reached the systemic circulation as unchanged unmetabolized fentanyl (41). Morphine, codeine, and hydromorphone are not good candidates for transdermal administration. Pethidine has a high transdermal permeability but poor analgesic potency. Besides fentanyl, only sufentanil and buprenorphine would be suitable opioids for transdermal administration (45).

There are three techniques used for the transdermal administration of fentanyl. The transdermal therapeutic system (TTS) is a membrane-controlled system designed to release fentanyl at a constant rate for up to 3 days, and is useful in patients with chronic cancer pain (46). There are still limited and predominantly uncontrolled studies that show that TTS fentanyl is useful in chronic pain of neuropathic or somatic origin. An open randomized, crossover trial in 18 patients with painful chronic pancreatitis concluded that TTS fentanyl should not be the first-choice analgesic, because of a high incidence of skin adverse effects and low analgesic effects compared with morphine (47).

TTS fentanyl is not useful in acute or postoperative pain, because of the risk of respiratory depression due to the long delay and decay time, which do not allow adequate dose finding (44). Some patients have acute symptoms of morphine withdrawal, in spite of adequate pain control, when they are converted from morphine to transdermal fentanyl. The mechanism has not yet been determined (48,49).

Transdermal fentanyl was the cause of an opioid overdose when a 77-year-old man with a history of severe arthritis developed respiratory failure after starting epidural diamorphine–bupivacaine mixture for postoperative pain (50). The fentanyl patch was removed, the epidural infusion was stopped, and naloxone was given to counteract the excessive opioid effects.

Fentanyl transdermal delivery systems (FTDS) use an unsealed multilaminate system containing a solid matrix, in which fentanyl is embedded instead of the reservoir designed in the TTS. FTDS is not to be recommended for routine postoperative pain treatment, even though it has a faster onset of action (4–6 hours) after cases of fentanyl toxicity, especially respiratory depression. FTDS has not been investigated adequately in chronic pain and is not expected to be superior to the TTS technique.

Iontophoretic transdermal application of opioids is another technique that is currently being tested. The factors that affect the delivery of opioids like fentanyl and sufentanil by this technique include the physicochemical nature of the drug solution, the voltage used, and the duration and nature of the current used (51,52).

An electrotransport therapeutic system (ETS) for fentanyl has been developed. Preliminary studies show that ETS of fentanyl may be useful for the treatment of acute pain (53).

Transdermal fentanyl has been compared with modified-release oral formulations of morphine among 504 patients with advanced cancer in a multicenter, cross-sectional quality-of-life study using four widely validated scales plus original scales, generated and validated for this study (54). The authors used conversion rates "often reported in the literature" to calculate that the fentanyl group used significantly more opiate (200–300 mg of morphine-equivalent units/day) than the oral morphine users (195 mg/day). Despite this, transdermal fentanyl patients reported fewer and less bothersome adverse effects, although these were not separately identified; 50% reported never having any adverse effects compared with 36% of morphine users without adverse effects, although measures of pain intensity showed no significant difference between the two groups. Subgroup analysis by sex showed that the difference in adverse effects between the two modes of administration was significant only in men. However, it should be noted that the mean ages of

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the two treatment groups were significantly different, a fact that may qualify the reported results.

Transdermal fentanyl avoids the discomfort of injections and reduces fluctuations in drug concentrations. In an open study of transdermal fentanyl patches 50 μg for postoperative pain management in 15 thoracotomy patients, two patients had nausea and one had erythema over the site of application of the patch (55).

Transdermal fentanyl in chronic cancer pain control has been extensively reviewed (22). Data from non-blinded, randomized trials suggest that it is as effective as modified-release oral morphine and that the most common adverse effects include nausea, vomiting, and constipation. The most serious adverse effect reported was hypoventilation, which occurred in about 2% of patients. Skin reactions occurred in 1–3%. A number of non-comparative trials have described the use of transdermal fentanyl for periods of at least a year without serious adverse effects.

In a follow-up study of 78 patients with cancer who participated in a crossover, randomized study of transdermal fentanyl (mean final dose 100 μg/hour) and oral morphine for 4 weeks, the incidences of skin reactions and gastrointestinal symptoms were low (56). Other adverse effects reported were breakthrough pain, light-headedness, and diarrhea. In the original randomized study, which lasted 15 days, there was significantly less constipation with fentanyl than with morphine (57). These results suggest that many patients have stable analgesic requirements with transdermal fentanyl up to the time of death, with no need for additional medication.

In a questionnaire survey of 1005 patients, only 11 had chronic pain from non-malignant disease while taking transdermal fentanyl (58). Their physicians were asked to provide information about their reasons for switching to transdermal fentanyl and were then surveyed until withdrawal of fentanyl because of death, change in analgesic regimen, or serious adverse effects. Modified-release morphine (median dose 90 mg/day) was used in 72% of patients before switching to fentanyl. More than 20% of the cohort had received no continuous opioid medication before the start of transdermal therapy. Most of the patients were switched to fentanyl because of inadequate analgesia or opioid-induced gastrointestinal symptoms. The simplicity of administration and patients' wishes were also contributory factors. Transdermal fentanyl was discontinued primarily because patients died (46%); other reasons included inadequate pain relief (10%), pain relief with another analgesic regimen (10%), adverse effects (5%), rejection of transdermal therapy by the patient (6%), and other unspecified causes, such as pathological fractures and anemia (16%). There were opioid-related adverse effects in 26% of the patients. Serious neurotoxic effects, such as hallucinations (0.2%), withdrawal symptoms (0.1%), or convulsions (0.1%), were rare.

Under controlled conditions, transdermal fentanyl is a useful option for direct conversion from mild to strong opioids in cancer patients. In addition, 25 μg/hour daily incremental steps of transdermal fentanyl can be made by palliative care specialists, if it is required for cancer pain management (59).

Transdermal fentanyl for chronic non-cancer pain control has been studied in two open trials (60,61). In a multicenter, open, randomized study of 256 patients with a history of chronic non-cancer pain, 65% preferred transdermal fentanyl, whereas 28% preferred modified-release oral morphine. Subjective pain control and quality of life were significantly better in the patients who used transdermal fentanyl. Despite a preference for transdermal fentanyl, more patients withdrew because of adverse effects in the first fentanyl period (16%) than in the first morphine period (9%). The difference could have been related to patients' previous experience of morphine, with enhanced tolerance of its adverse effects.

In the second study, 35 patients with severe AIDS-related chronic pain were recruited in a prospective, open, before/after comparison of the analgesic efficacy and adverse effects profile of a stable dose of transdermal fentanyl (25–300 μg/hour) or oral morphine (less than 45 mg/day) for 15 consecutive days (61). Transdermal fentanyl alleviated chronic pain and those who were already dependent on an opioid needed less fentanyl for the same analgesic result.

The long-term use of transdermal fentanyl in patients with chronic non-cancer pain (back pain, leg pain, arthritic pain, trigeminal neuralgia, and intestinal cystitis), which is controversial, has been discussed (62). Transdermal fentanyl was effective and safe and improved quality of life and independent living. However, these case reports were collected by authors closely associated with the company that manufactures transdermal fentanyl patches; a degree of case selectivity and bias might have occurred.

In a prospective study, 64 patients with a recent history of at least one vertebral fracture caused by primary and secondary osteoporosis were recruited from six osteoporosis centers in Germany between December 1999 and April 2001 (63). Transdermal fentanyl 25 μg/hour was the recommended starting dose, with incremental steps of 25 μg/hour if there was insufficient analgesia. Treatment was stopped after less than 28 days in 15 patients (23%). In 10 of these, fentanyl was stopped because of nausea and/or vomiting and/or dizziness. In 49 patients, pain at rest (55% reduction) and on motion (47% reduction) abated significantly from baseline. The starting dose of 25 μg/hour of fentanyl was sufficient in most patients (70%).

The use of transdermal fentanyl in 113 patients with undertreated chronic cancer pain was studied in a non-randomized, uncontrolled, open study for 42 days (64). The mean dose of fentanyl increased from 25 μg/hour to 117 μg/hour between the start and end of the study. By day 3, six patients reported sleepiness and two reported dizziness; five reported nausea and two had vomiting, and by days 21–42 four of the 100 patients who completed the study had severe nausea and vomiting. Non-compliance was not related to the adverse effects of fentanyl, but to insufficient pain control (nine patients) and/or death (three patients).

Epidural

In view of the popularity of fentanyl as an epidural analgesic in labor, its site of action is of some

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interest, and this has been examined in a randomized study in 55 parturients who received 0.125% bupivacaine plus one of three treatments: epidural saline plus intravenous saline; epidural fentanyl (20 μg/hour) plus intravenous saline; epidural saline plus intravenous fentanyl (20 μg/hour) (65). Study treatments were continuously infused, while epidural bupivacaine was patient-controlled. There was a significant reduction (28%) in bupivacaine use with epidural but not intravenous fentanyl, but there was no significant difference in the incidence of adverse effects. This result suggested that the analgesic effects of epidural fentanyl in labor are due to a spinal mechanism, rather than to systemic absorption and a supraspinal effect. However, the authors acknowledged various limitations of their study and commented that they were able to use low doses of fentanyl because of the concomitant use of bupivacaine, which acts synergistically. It is possible that this synergy allows effective analgesia of the visceral afferents at a spinal level without the need for the higher doses that are required for analgesia with fentanyl alone. Higher doses of fentanyl may mask this spinal effect.

In a prospective study of 1030 mixed surgical patients receiving patient-controlled epidural analgesia with 0.05% bupivacaine and fentanyl 4 μg/ml, the incidence of adverse effects was broadly as expected (66): 17% had pruritus, 15% nausea, 13% sedation, 6.8% hypotension, 2% motor block, and 0.3% respiratory depression. Two patients required naloxone for respiratory depression and sedation. Analgesia was terminated electively in 82%, 12% of cases were terminated owing to a displaced catheter, and 3% of cases required anticoagulation, while infection, adverse effects, and inadequate analgesia each accounted for termination of epidural analgesia in 1% of cases. Risk factors for adverse effects were identified as: patient age under 58 years, weight under 73 kg, being female, high fentanyl consumption (over 9 ml/hour), and lumbar placement of the epidural catheter. There was a significant association between patient age and pruritus, and between female sex and nausea, hypotension, and sedation.

The relations between fentanyl and local anesthetics and their adverse effects profiles in epidural analgesia (67) further demonstrate the need for well-controlled, double-blind studies (68,69).

The use of a continuous epidural infusion of lidocaine 0.4% plus fentanyl 1 μg/ml in combination with intravenous metamizol 40 mg/kg provided significantly better analgesia than epidural morphine 20 μg/kg plus intravenous metamizol 40 mg/kg during the first 3 postoperative days in 30 children undergoing orthopedic surgery, without increasing the incidence of adverse effects; however, the difference in beneficial effect was small (70).

Prophylactic nalbuphine 4 mg and droperidol 0.625 mg with minidose lidocaine + fentanyl spinal anesthesia in a randomized, double-blinded, controlled study in 62 patients having outpatient knee arthroscopy provided significantly better analgesia and reduced nausea and pruritus than in another 62 patients who received only nalbuphine 4 mg with minidose lidocaine + fentanyl spinal anesthesia (71).

Intravenous patient-controlled analgesia

In a randomized, double-blind, multicenter trial, 150 postoperative patients who had undergone major surgery received demand doses of fentanyl 20, 40, or 60 μg delivered intravenously by PCA (72); higher doses of fentanyl were associated with improved analgesic effect. Adverse effects were reported in 70 patients; the most commonly reported were nausea and vomiting and most adverse effects were described as mild to moderate. Bradypnea occurred in 6% of patients who received fentanyl 60 μg, in one case sufficiently severe to warrant temporary withdrawal of treatment; respiratory depression and moderate hypoxia occurred in one patient on 40 μg and in one on 60 μg, again requiring withdrawal. Overall, mean respiratory rates in the 60 μg group were significantly lower than in the 20 μg group throughout the study, and at 6 hours after initiation compared with the 40 μg group. One patient developed acute confusion and aggression while receiving fentanyl 40 μg. The authors concluded that 40 μg of fentanyl is an appropriate dose for PCA, as this balances analgesic efficacy against the incidence of adverse effects.

Drug overdose

Accidental overdose can be caused by fentanyl patches.

- A 71-year-old woman was found unconscious, with reduced respiration and miotic pupils, having previously had nausea, dizziness, and drowsiness (73). She had inappropriately applied a fentanyl patch 100 μg/hour a day before the symptoms occurred. She recovered fully after treatment with intravenous naloxone 0.4 mg.
- A 24-year-old woman, with a history of polysubstance abuse and extensive psychiatric history, presented with acute opioid overdose caused by the intentional oral ingestion of a fentanyl patch (Duragesic) (74).

Drug–Drug Interactions

Bupivacaine

Bupivacaine is increasingly being used in combination with fentanyl for obstetric analgesia and has been reported to reduce the incidence of pruritus. In a prospective study, 65 parturients in labor were randomly assigned to receive intrathecal fentanyl (25 μg), intrathecal bupivacaine (2.5 mg), or both as part of epidural anesthesia (75). The group that received both drugs had more prolonged analgesia and significantly less pruritus than those who received fentanyl alone (36 versus 95%). However, the incidence of facial pruritus was not significantly different. The type of analgesia did not affect the outcome of labor, although one patient in the combined treatment group required ephedrine for reduced blood pressure. It was proposed that pruritus is the result of stimulation of mu receptors supraspinally and in the dorsal horn of the spinal cord, and that facial itching is associated with mu receptor activation in the medullary dorsal horn, affecting the trigeminal nerve. Local anesthetics may alter this adverse effect by local neuronal blockade or by direct modulation of mu-opioid receptors. Bupivacaine also promotes opioid binding to kappa-opioid receptors, which reduce pruritus. The failure to relieve facial pruritus suggests a direct effect of fentanyl in the brain stem.

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Cimetidine

The hepatic metabolism of fentanyl can be inhibited by cimetidine, leading to respiratory depression and sedation (76,77).

Droperidol

The addition of droperidol 2.5 mg to fentanyl 0.4 mg in 40 ml of 0.125% bupivacaine lowered the incidence of postoperative nausea and vomiting compared with a solution without droperidol or with butorphanol added instead in patients undergoing anorectal surgery in a prospective randomized, single-blind study (78).

Fentanyl plus droperidol (neuroleptanalgesia) was more effective than morphine in relieving anginal pain during unstable angina. However, the patients who received the neuroleptanalgesia also had longer hospital stays, because of significantly more cardiac instability and anginal episodes, and a higher total mortality (79).

Etodimate

Used as a pretreatment for anesthetic induction with etomidate, fentanyl 500 μg produced apnea in all patients, with a 67% incidence of nausea and a 47% incidence of postoperative vomiting (80).

Itraconazole

Oral itraconazole 200 mg did not alter the pharmacokinetics of intravenous fentanyl 3 μg/kg, despite being a strong inhibitor of CYP3A4 in vitro (81). In vitro research suggests that itraconazole should inhibit the elimination of fentanyl, as it has been shown to do to alfentanil. This difference can be accounted for by the higher hepatic extraction ratio of fentanyl (0.8–1.0) compared with alfentanil (0.3–0.5), so that even large changes in the activity of enzymes that metabolize fentanyl significantly affect its pharmacokinetics.

Midazolam

Several adverse effects have been reported with the combined use of fentanyl and midazolam, including chest wall rigidity, making ventilation with a bag and mask impossible (SEDA-16, 79).

In neonates, hypotension can occur (SEDA-16, 80), and respiratory arrest in a child and sudden cardiac arrest have been reported (SEDA-16, 80). However, in one study there were no cardiac electrophysiological effects of midazolam combined with fentanyl in subjects undergoing cardiac electrophysiological studies (SEDA-18, 80).

Monoamine oxidase inhibitors

There is a risk of hypertension, tachycardia, hyperpyrexia, and coma with the concurrent administration of opioids and monoamine oxidase inhibitors (SEDA-19, 83).

Prilocaine

The addition of fentanyl to the local anesthetic prilocaine does not seem to cause major analgesic benefits, but increases the incidence of adverse effects, particularly affecting the nervous system (82).

Propofol

The interaction between propofol and fentanyl has been studied in relation to suppressing the somatic or hemodynamic responses to three types of surgical event—skin incision, peritoneum incision, and abdominal retraction (83). Three of ninety-nine subjects were withdrawn from the study after bradycardia of under 50/minute occurred when intravenous fentanyl (dose not stated) was given to those already anesthetized with propofol. Propofol and fentanyl (concentration range 0.5–9 ng/ml maintained by computer-assisted continuous infusion for at least 30 minutes) had a predictable synergistic effect and caused a fall in systolic blood pressure. After stimulation, the different concentrations of fentanyl required to block somatic responses to surgery in 50% of subjects were 9.7 ng/ml, 15 ng/ml, and 28 ng/ml respectively for skin incision, peritoneum incision, and abdominal retraction. Concentrations required to give a 15% or less increase in post-incision systolic blood pressure were 5.3 ng/ml, 9.7 ng/ml, and 12 ng/ml respectively. At doses of less than 3 ng/ml of fentanyl the hemodynamic response to peritoneal incision or abdominal retraction was inadequate, even when sufficient propofol was present to suppress somatic responses. Somatic response suppression correlated with fentanyl for skin incision, fentanyl and propofol for peritoneal incision, and propofol for abdominal retraction. Prestimulation propofol reduced systolic blood pressure in a concentration-dependent fashion, while post-stimulation fentanyl significantly suppressed increases in systolic blood pressure. This difference in effect was attributed to propofol's mainly sedative and hypnotic effects, while fentanyl is primarily analgesic.

Ritonavir

Ritonavir is an inhibitor of HIV protease and a potent inhibitor of CYP3A4 and CYP2D6. The interaction between ritonavir and intravenous fentanyl has been investigated in 12 healthy volunteers in a double-blind, placebo-controlled, crossover study (84). The volunteers took ritonavir 600 mg on day 1, ritonavir 900 mg and intravenous fentanyl 5 μg/kg on day 2, and ritonavir 300 mg or placebo on day 3. Ritonavir reduced the clearance of fentanyl by 67% by inhibiting its metabolism. This could result in prolongation of fentanyl-induced respiratory depression in a patient with an already compromised cardiorespiratory system.

Ropivacaine

In a prospective, randomized, double-blind study, the analgesic effect and adverse effects profile of epidural ropivacaine (2 mg/ml) alone was compared with three different fentanyl/ropivacaine combinations (fentanyl 1, 2, and 4 μg/ml) for up to 72 hours of postoperative analgesia in 244 patients after major abdominal surgery, most commonly colorectal surgery (85). Hypotension was significantly more common with fentanyl 4 μg (52%) compared with the other three groups (31–34%) in the first 24 hours, but not later. Nausea was not significantly different among the groups, although there was more antiemetic drug use in patients given fentanyl 2 and 4 μg by day 3. Pruritus was significantly more common in patients who received fentanyl 4 μg throughout the whole 72 hours.

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Ropivacaine 2 μg/ml plus fentanyl 4 μg/ml provided the most effective pain relief over the 3 days.

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Fentiazac

See also Non-steroidal anti-inflammatory drugs

General Information

Fentiazac, a thiazoleacetic acid derivative, has the same adverse reactions profile as other NSAIDs. Adverse effects in as many as 56% of patients (5-56%), are even more frequent than with phenylbutazone (1).

In 40 patients with rheumatoid arthritis enrolled in a double-blind trial of fentiazac 400 mg/day or sulindac 200 mg/day for 3 months, adverse effects were reported in three patients taking fentiazac (rash, headache, epigastric pain) (2).

Organs and Systems

Nervous system

Adverse effects involving the central nervous system include headache, dizziness, mental confusion, sedation, giddiness, and blurred vision; dysesthesia and oral paresthesia have also been reported (3).

Gastrointestinal

Pyrosis, epigastric pain, nausea, constipation/diarrhea, and occult bleeding are the most frequent gastrointestinal effects of fentiazac (3). Rectal administration can cause both local and systemic adverse effects.

Liver

In one study, seven of 20 patients with rheumatoid arthritis had significant rises in aspartate transaminase and alkaline phosphatase activities (4). Reversible hepatotoxicity occurred in three of 33 patients who took fentiazac during long-term therapy (2).

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Feprazone

See also Non-steroidal anti-inflammatory drugs

General Information

Feprazone is an NSAID that is related to phenylbutazone. Feprazone was withdrawn in the UK because of its adverse effects, which resemble those of phenylbutazone. It was designated as a last-resort drug by the Japanese Committee on Safety of Drugs (SEDA-12, 83).

In an 8-week trial in 2693 patients with rheumatoid arthritis and osteoarthritis, 30% reported adverse effects and 11% failed to complete the study. However, two large short-term multicenter studies in general practices in 11 000 patients in Italy reported a very low percentage (1.2–9.8%) of adverse effects (1,2).

Gastrotoxicity, nephrotoxicity, edema, headache, tinnitus, and depression have been attributed to feprazone (3).

Organs and Systems

Hematologic

Thrombocytopenia and immune complex-mediated hemolytic anemia have been reported with feprazone (SEDA-7, 108).

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Skin

Skin reactions (including severe bullous dermatosis) have been attributed to feprazone (SEDA-9, 87). Contact dermatitis has been described with feprazone cream (SEDA-18, 101).

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Fexofenadine

See also Antihistamines

General Information

Fexofenadine is the active metabolite of terfenadine. It has antihistaminic but not dysrhythmogenic properties. It is not metabolized by the liver, but eliminated unchanged in the urine. It is efficacious and well tolerated in seasonal allergic rhinitis (1), with positive effects on nasal blockade (2), and in chronic idiopathic urticaria (1,3).

Organs and Systems

Cardiovascular

Fexofenadine is said to have little cardiotoxicity (4). In one study fexofenadine was well tolerated, and there were no statistically significant changes in PR interval, QT interval, QRS complex, or heart rate (5).

There has been a report of ventricular fibrillation during fexofenadine administration in a man with a pre-existing long QT interval (6). However, causality between fexofenadine and the cardiac effects was unclear.

The safety of fexofenadine in children aged 6–11 years with seasonal allergic rhinitis has been assessed in a large double-blind, randomized, placebo-controlled, parallel study (7). There were no statistically significant electrocardiographic effects, suggesting that fexofenadine is both efficacious and well tolerated in children with allergic disease.

Nervous system

The effects of fexofenadine (120, 180, and 240 mg) on performance and sleepiness have been studied in healthy volunteers. There were no changes at any time compared with placebo, and the authors suggested that fexofenadine may prove to be suitable for use by air personnel (8).

Psychological, psychiatric

Even in a high dose (360 mg bd versus the recommended dose of 60 mg bd) fexofenadine had no disruptive effects on psychomotor performance and cognitive function in healthy volunteers (9).

In one study fexofenadine did not alter driving and psychomotor performance when taken in the recommended dosage of 60 mg bd (10).

Skin

Eight episodes of a fixed drug eruption occurred in a 45-year-old man who was taking fexofenadine for seasonal allergies; after withdrawal of fexofenadine the rash did not recur (11).

Drug–Drug Interactions

Azithromycin

The effect of co-administration of azithromycin on plasma concentrations of fexofenadine 60 mg bd has been examined in a randomized third-party-blind, placebo-controlled, parallel-group study in 98 healthy volunteers (5). An initial loading dose of azithromycin (500 mg) was given on day 3, followed by 250 mg od for 4 days. Concomitant azithromycin caused increases in the C_{max} and AUC of fexofenadine (69 and 67% respectively). However, there were no statistically significant increases in the PR, QT, QT_c interval, QRS complex duration, or ventricular rate after administration of fexofenadine with or without azithromycin.

Grapefruit juice

In a non-blinded, randomized, single-dose, crossover study in 24 healthy adults, grapefruit juice reduced the rate of absorption and the systemic availability of oral fexofenadine by 30% (12). However, there were no clinically significant electrocardiographic changes after co-administration of grapefruit juice with fexofenadine compared with fexofenadine alone. The authors concluded that the systemic availability of drugs that do not undergo significant intestinal or hepatic metabolism, such as fexofenadine, may nevertheless be altered when they are given with agents that affect drug transport mechanisms.

St John's wort

St John's wort (*Hypericum perforatum*) is a popular and widely available herbal extract used as a remedy for anxiety, depression, and sleep disorders. Fexofenadine is transported by P glycoprotein in vitro (13) and there is evidence that St John's wort can alter P glycoprotein activity (14). The effects of St John's wort on the pharmacokinetics of fexofenadine have therefore been studied (15). Fexofenadine 60 mg was given orally twice—before a single dose of St John's wort 900 mg and again after 3 weeks treatment with 300 mg tds. A single dose of St John's wort significantly inhibited intestinal P glycoprotein activity and increased the maximum plasma concentration of fexofenadine by 45%. In contrast, long-term St John's wort caused a 35% reduction in the C_{max} of

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fexofenadine and increased its oral clearance. However, the authors concluded that these pharmacokinetic changes alone are unlikely to be clinically significant.

In addition to their effects on P glycoprotein, fruit juices and St John's wort can also inhibit organic anion transporting polypeptides (16). These findings suggest new models of intestinal drug absorption and mechanisms of drug interactions.

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Fibrates

General Information

Fibrates reduce plasma triglycerides by inhibiting their hepatic synthesis and increasing their catabolism. They reduce the synthesis of triglyceride–very low density lipoprotein (VLDL) by increasing the beta-oxidation of fatty acids in the liver. They increase triglyceride catabolism by inducing lipoprotein lipase gene transcription and reducing apoC-III gene transcription. Fibrates increase high-density lipoprotein (HDL) cholesterol by increasing apoA-I and apoA-II gene transcription. These effects are due to activation of peroxisome proliferator-activated receptors (PPAR) alpha and induction of the overexpression of genes containing a peroxisome proliferator response element (PPRE) in their promoter (1).

The fibrates include beclobrate, bezafibrate, biclofibrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, dulofibrate, etofibrate, fenirofibrate, fenofibrate, gemfibrozil, lifibrate, nicofibrate, picafibrate, pirifibrate, ponfibrate, ronifibrate, salafibrate, serfibrate, simfibrate, sitofibrate, tiafibrate, timofibrate, tocofibrate, urefibrate, and xantifibrate (all rINNs).

The adverse events of the fibrates are essentially the same with all members of the class and are generally mild or absent during short-term treatment. The observed frequency of adverse effects with a micronized formulation of fenofibrate is comparable to that associated with the usual formulation (SEDA-22, 490).

Organs and Systems

Nervous system

Nervous system adverse effects are rare, constituting 0.5% of all adverse effects (2). Gemfibrozil-induced headache has been reported (3) and occurred in one patient who had taken bezafibrate for 24 hours (4). Peripheral neuropathy has been observed with bezafibrate (SEDA-13, 1324) (5).

Metabolism

Of 70 patients with cutaneous T cell lymphomas, three who were taking gemfibrozil had to have it withdrawn because of increases in serum triglycerides (6).

- A 76-year-old woman with type 2 diabetes taking gemfibrozil for pronounced hypertriglyceridemia had recurrent episodes of hypoglycemia; her insulin requirements fell by 65% and her HbA_{1c} concentration fell from 9 to 6.5% over 5 months (7).

In patients taking fenofibrate and atorvastatin, increased concentrations of plasma homocysteine were attributed to an action of the fibrates themselves and not indirectly via their lipid-lowering effect (8). Concomitant administration of folic acid, at least in part, offset this adverse effect

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(9). The degree of rise in homocysteine differs among the various fibrates. It has been reported with fenofibrate and bezafibrate, and a study of fenofibrate and gemfibrozil substantiated a difference between the drugs (10). Because the concentration of plasma homocysteine depends on renal function, increased plasma homocysteine concentrations could result from renal function impairment caused by fenofibrate. In contrast, gemfibrozil does not affect renal function. This was tested in a crossover study in 22 patients who had hypertriglyceridemia, by giving them gemfibrozil 900 mg/day or fenofibrate 200 mg/day for 6 weeks (11). Lipids were altered similarly, but homocysteine, creatinine, and cystatin C were raised by fenofibrate but not by gemfibrozil. In another report, there was a 57% increase in homocysteine in 26 individuals who took ciprofibrate and a 17% reduction in homocysteine in 12 patients who took bezafibrate.

Fluid balance

Clofibrate has a mild antidiuretic effect (12), and animal studies suggest that this is due to release of antidiuretic hormone (ADH) (13). This effect has been used in the treatment of cranial diabetes insipidus (14).

Hematologic

Leukopenia has been reported with bezafibrate (15), clofibrate (16), and fenofibrate (17).

Gastrointestinal

Abdominal discomfort occurs in 5–10% of all patients taking fibrates. Epigastric fullness, nausea, meteorism, and mild diarrhea have been repeatedly described, and stomatitis has been incidentally mentioned. There are wide discrepancies in the figures given for such complications, ranging as they do from 2 (2) to 20%; the truth appears to be that during the first few days and weeks of treatment, mild discomfort of one sort or another is quite common, although some of it is due to a placebo effect; serious symptoms are most unusual. Bezafibrate is better tolerated than gemfibrozil (18). In a double-blind trial with fenofibrate, the incidence of gastrointestinal adverse effects was not different from that seen with placebo (19). Five of 1213 individuals taking beclobrate complained of diarrhea (20).

Liver

Assurance of good renal and hepatic function is mandatory before beginning treatment with the fibrates (21). Serum transaminase changes are regularly seen and hepatitis occurs (22). Several cases of hepatitis due to fenofibrate have been reviewed (23) and it has also been observed with etofibrate (24). One case of liver failure, probably due to beclobrate, has been reported (SEDA-13, 1324) (25). Liver biopsies showed a lymphoplasmocytic infiltrate in all of five cases of chronic hepatitis associated with fibrates (26).

Biliary tract

Fibrates produce bile that is supersaturated with cholesterol. Although gallstones are common with clofibrate, no excess frequency has been observed with fenofibrate (22). In the WHO study, 59 patients taking clofibrate had to be operated on for gallstones, compared with 24 and 25 respectively in the two placebo groups (27).

Pancreas

Pancreatitis has been attributed to bezafibrate.

- A 75-year-old white woman had fever and raised amylase on three consecutive occasions after taking a tablet of bezafibrate (28). After stopping taking the drug, she remained free of symptoms.

Urinary tract

Unexpected acute renal insufficiency occurred in four patients after uncomplicated cardiac surgery; each was taking a fibrate (29). Renal insufficiency occurred rapidly within 3 days of surgery and was associated with increased concentrations of skeletal muscle-derived creatine kinase. One patient developed myoglobinuria. Presumably, patients taking lipid-lowering drugs are at higher risk of acute renal insufficiency after cardiac surgery, because of rhabdomyolysis. This suggests that patients taking either statins or fibrates should discontinue them before cardiac surgery.

Fenofibrate was the probable cause of rises in serum creatinine concentrations in six patients in one clinic (30). The authors therefore recommended routine serum creatinine monitoring at baseline and at 1 month after starting fenofibrate.

Severe reversible renal insufficiency has been reported with fibrates (31).

Skin

Non-specific rashes have been reported in patients taking fibrates. With fenofibrate, rashes are reported significantly more often than with placebo (32), and occur in some 0.6% of patients (22). In a double-blind trial, the incidence of cutaneous adverse effects was 11% with fenofibrate and less than 1% with placebo; they included hives and urticaria (19). In another study, the difference was 6% (33).

- Chronic radiodermatitis after cardiac catheterization has been observed in a 62-year-old woman taking ciprofibrate. A second catheterization performed when she had stopped taking it did not provoke new lesions (34).

Photosensitivity due to fenofibrate (35) was confirmed by systemic photochallenge (36). Photodermatitis has been associated with cross-reactivity between ketoprofen and fenofibrate; this was thought to be due to chemical similarities between these two drugs (37).

Psoriasis was exacerbated by gemfibrozil in one case (38).

Stevens–Johnson syndrome has been associated with bezafibrate (39) and clofibrate (40).

Musculoskeletal

Rhabdomyolysis is a problem with several lipid-lowering drugs (SEDA-13, 1325) (SEDA-13, 1328) (SEDA-13, 1330) (SEDA-19, 409) (41–43), especially when they are used in combination (44). In individuals with pre-existing renal insufficiency, this can lead to an earlier need for

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chronic dialysis (45). Also, interactions between various hypolipidemic drugs and other drugs sometimes cause rhabdomyolysis (SEDA-18, 426).

Creatine kinase activity increased in five out of 1213 patients taking beclobrate (20). Myopathy during treatment has been reported with gemfibrozil (46) and ciprofibrate (47,48).

Hypothyroidism predisposes to rhabdomyolysis (49,50) and screening of thyroid function has been advocated before starting hypolipidemic drugs (SEDA-21, 458). This notion has been supported by observations in a 69-year-old man taking fenofibrate 200 mg daily (51). The muscular syndrome appears to be a special risk in patients with nephrotic syndrome (SEDA-13, 1325) (52).

- Two women, 55 and 57 years old, with renal insufficiency, had rhabdomyolysis after taking micronized fenofibrate in dosages a little higher than recommended (53). Both had mild hypothyroidism.

Reduced renal function in the elderly appears to be a risk factor for myopathy (SEDA-23, 472).

- A 73-year-old woman had an increase in serum creatinine concentration while she was taking long-acting bezafibrate and again when she was re-challenged by self-medication (54).
- Low-dose bezafibrate was associated with myositis in a patient with mild chronic renal insufficiency (serum creatinine 210 μmol/l) (55). She was a 58-year-old obese diabetic with isolated hypertriglyceridemia.

Sexual function

Erectile dysfunction has been reported in 12% of 339 men treated with fibrate derivatives or statins, compared with 5.6% of similar patients not taking these drugs (57). The mechanism is unknown and should be confirmed in randomized studies.

Gemfibrozil was suspected to have reduced libido in two cases (58,59), an effect that is well-known with clofibrate, and four cases of loss of libido and impotence involving gemfibrozil have previously been reported (SEDA-13, 1325) (60,61).

Immunologic

Vasculitis, Raynaud's phenomenon, and polyarthritis have been reported with gemfibrozil (62).

Allergic reactions have been reported with some fibrates.

- A 61-year-old woman with penicillin allergy suffered generalized urticaria, chest tightness, wheezing, nausea, vomiting, hypotension, and loss of consciousness (63). Two hours earlier, she had taken Eulitop Retard after lunch. She had intense positive responses to intradermal Eulitop Retard and its active component, bezafibrate; skin tests in control subjects were negative. Specific IgE tests (RAST) to Eulitop Retard were negative. The positive skin tests suggested that an IgE mechanism was responsible for this adverse reaction.
- A 69-year-old woman developed a major allergic reaction after taking fenofibrate 300 mg/day for 10 days (64). The clinical features included weakness, hyperthermia, and slight muscular pain. Biological abnormalities were mildly raised muscle enzymes and pancytopenia, which developed rapidly.

Long-Term Effects

Tumorigenicity

It has been suspected that low concentrations of serum cholesterol might be associated with an increased risk of cancer or overall mortality. All fibrates and statins cause cancer in rodents, but the relevance of this finding to man has been questioned (65). In an epidemiological study these risks were almost non-existent after adjusting for confounding factors.

Second-Generation Effects

Fetotoxicity

In pregnant mice given etofylline clofibrate and fenofibrate in doses of 12, 117, and 586 mg/kg orally from day 7 to day 16 of gestation, terminal maternal body weight was significantly reduced by all doses of etofylline clofibrate (66). The low and middle doses of etofylline clofibrate and fenofibrate had no adverse effects on embryofetal development, but the highest dose of etofylline clofibrate significantly reduced fetal weight at term. Postimplantation loss was significantly higher after the highest dose of fenofibrate. There were no teratogenic effects. The significance of these results to human pregnancy is unknown.

Drug–Drug Interactions

Bexarotene

Of 70 patients with cutaneous T cell lymphomas, three who were taking gemfibrozil had to have it withdrawn because of increases in serum concentrations of triglycerides and bexarotene, an RXR-selective retinoid "rexinoid", which is used for all stages of cutaneous T cell lymphoma (6).

Colchicine

Rhabdomyolysis due to the combination of colchicine with gemfibrozil has been reported in a 40-year-old man with amyloidosis and chronic liver disease (67).

Ibuprofen

Acute renal insufficiency occurred in one patient taking ciprofibrate 100 mg/day and ibuprofen 400 mg/day (68). Both drugs are highly protein-bound and contain propionic acid groups. Thus, ibuprofen may displace ciprofibrate.

Statins

The increased risk of myopathy observed during concomitant treatment with statins and fibrates may be partly pharmacokinetic in origin. In interactions between fibrates and statins there may be differences between

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the various fibrates (69). Eleven healthy volunteers took bezafibrate 400 mg/day, gemfibrozil 1200 mg/day, or placebo for 3 days. On day 3, each took a single dose of lovastatin 40 mg. Plasma concentrations of lovastatin, lovastatin acid, gemfibrozil, and bezafibrate were measured for up to 24 hours. Gemfibrozil markedly increased plasma concentrations of lovastatin acid, but bezafibrate did not. The risk of myopathy during concomitant therapy with lovastatin and a fibrate may be smaller with bezafibrate than with gemfibrozil.

In 80 patients with primary mixed hyperlipidemia, gemfibrozil used together with lovastatin resulted in 3% discontinuation because of myositis, but none attributable to rhabdomyolysis or myoglobinuria (70).

Sulfonylureas

Fibrates are highly bound to albumin and displace other similarly bound drugs. This can affect treatment with sulfonylureas. Hypoglycemia occurred in a diabetic patient taking glibenclamide plus gemfibrozil (71).

In 10 healthy volunteers, gemfibrozil 600 mg bd increased the mean total AUC of a single dose of glimepiride 0.5 mg by 23% (range 6–56%) (72). The mean half-life of glimepiride was prolonged from 2.1 to 2.3 hours. This effect may have been caused by inhibition of CYP2C9. However, there were no statistically significant effects on serum insulin or blood glucose variables.

Warfarin

Several interactions between warfarin and hypolipidemic drugs have been described (SEDA-21, 459), including clinically important potentiation of warfarin by bezafibrate (73) and gemfibrozil (74). Two patients developed a significantly increased anticoagulant effect of warfarin while taking fenofibrate (75).

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Fibrin glue

General Information

Fibrin glue is a topical tissue adhesive, a two-component system. One component contains highly concentrated fibrinogen, factor VIII, fibronectin, and traces of other plasma proteins. The other component contains thrombin, calcium chloride, and antifibrinolytic agents such as aprotinin. Mixing the two components promotes clotting. Fibrinogen is activated by thrombin in the presence of calcium, and the resultant clot aids hemostasis and tissue sealing and is completely absorbed during wound healing without foreign body reaction or extensive fibrosis. Fibrin glue thus imitates the final stages of coagulation (1) and is used for tissue sealing, hemostasis, and wound healing.

Because of its adverse effects, the original topical fibrin glue, which contained thrombin of bovine origin, has been withdrawn and replaced by a product (Quixil) whose components are all human in origin and not bovine or recombinant. Tranexamic acid is added in order to increase stabilization of the clot. The fibrinogen component is made from pooled plasma and is not highly purified; it therefore contains factor XIII, which also stabilizes the clot. Methods involving precipitation of fibrinogen by cryoprecipitation, polyethylene glycol, or ammonium sulfate have been described and evaluated.

All the components of fibrin glue are subjected to virucidal treatment (solvent/detergent treatment for fibrinogen and nanofiltration for thrombin).

Uses

The primary purpose of using fibrin glue is to reduce blood loss and hence the need for transfusion. It is sprayed on to a surgical field in aerosolized form with a double-barrelled syringe, using either compressed air or nitrogen. Its hemostatic and adhesive properties can be used in any surgical specialty, for example to control bleeding after organ injury (2). Its usefulness is particularly well documented in the fields of cardiovascular surgery (3,4), ENT surgery (5), neurosurgery (6), and thoracic surgery (7).

Fibrin glue has been widely used to treat anal fistulae. In a systematic review of 19 studies the reported success rates ranged from 0 to 100%, which may have been due to differences in patient selection (including fistula aetiology and type), treatment protocols, and follow-up duration (8).

The hemostatic efficacy of fibrin glue in a nasal spray has been studied in 24 patients with hereditary hemorrhagic telangiectasia and epistaxis (9). Fibrin glue produced immediate hemostasis and good healing of bleeding sites, no secondary bleeding, and no inflammation. Adverse events, including local swelling, pain, and slow healing of the bleeding site with atrophy of the nasal mucosa, were more frequent in those who were given foam nasal packing rather than fibrin glue spray.

Fibrin glue has also been used experimentally to deliver a high concentration of drug to a local site, as in the example of the use of losartan to prevent neointimal hyperplasia in pig saphenous artery (10).

Organs and Systems

Nervous system

The use of bovine fibrin glue in neurosurgery was associated with fatal neurotoxicity if the glue came into contact with the cerebrospinal fluid or dura (11,12); this has not been reported with fibrin glue of human origin.

Hematologic

In three patients who underwent cardiovascular surgery subsequent abnormalities in hemostasis, characterized by increased activated partial thromboplastin time, prothrombin time, and bovine thrombin time, and by a markedly reduced concentration of factor V, developed between the seventh and eighth postoperative days after exposure to fibrin glue containing bovine thrombin (13). It was suggested that the glue also contains small amounts of factor V and that this may have caused the abnormalities.

Immunologic

An anaphylactic reaction occurred after the use of bovine fibrin glue as a sealant after mastectomy, probably due to the presence of bovine aprotinin (14).

The use of preparations of fibrin glue containing bovine thrombin resulted in the development of antibovine thrombin antibodies. In a prospective study, 13 of 34 patients developed a thrombin inhibitor and reduced factor V activity (15,16). In another study a factor V inhibitor developed after cardiac surgery (17).

Severe hypotension has been reported after the use of bovine fibrin glue for hemostasis in hepatic injury (18). In one there was cardiac arrest and death. These effects may have been the result of an anaphylactic reaction to one or more components of the glue. Of the three ingredients used to prepare fibrin glue, cryoprecipitate and bovine thrombin are antigenic and potentially the most likely causes of anaphylaxis.

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Fish oils

General Information

Omega-3 fatty acids are long-chain polyunsaturated fatty acids. The parent fatty acid of this group is alpha-linolenic acid, an essential fatty acid that the body is unable to synthesize; alpha-linolenic acid can be converted in the body to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In animals and man, these acids reduce the production of several compounds that are involved in inflammation and thrombosis, such as eicosanoids (prostaglandins, thromboxanes, prostacyclin, and leukotrienes) and cytokines (interleukin II-1) (1). The extent of the conversion of alpha-linolenic acid to EPA and DHA is unclear. The conversion process appears to be inhibited by a high intake of linoleic acid, another essential fatty acid (2). In addition, alpha-linolenic acid is found in dark green vegetables and the oils of certain nuts and seeds, especially rape seeds and soya beans.

Oily fish and extracted fish oils contain high concentrations of EPA and DHA. Fish oils also contain vitamins A and D. Oil derived from cod, halibut, or shark liver, or from fish body, typically contains about 200 mg/ml of long-chain omega-3 fatty acids. In addition, cod liver oil provides 50 μg/ml of vitamin A and 2 μg/ml of vitamin D. Many fish oil supplements are artificially enriched with omega-3 fatty acids.

The safety of drugs containing EPA and DHA has been reviewed; the reported adverse effects were similar to those in control groups (3). Even 3–7 g/day for several months did not change liver enzyme activities, and there were no bleeding problems. Consumption of fish oils reduces the resistance of LDL to oxidative modification, and this is partly opposed by the addition of vitamin E (4). Belching or eructation with a fishy taste or smell, vomiting, flatulence, diarrhea, and constipation are relatively common.

Organs and Systems

Respiratory

Fish oils can cause exacerbation of asthma in aspirin-sensitive patients (5).

Cod liver oil supplements can cause lipoid pneumonia (6).

Metabolism

In high doses, fish oils can cause a rise in blood glucose concentration in patients with non-insulin-dependent diabetes mellitus (7).

Hematologic

Bleeding times can increase in patients taking fish oils (8), leading to more prolonged and frequent nose-bleeds (9). Fish oil supplements should be used with care in patients with hemophilia and anyone taking high doses of anticoagulants or aspirin.

Gastrointestinal

Of 39 patients with Crohn's disease, treated with an enteric-coated fish oil formulation, 4 were withdrawn because of diarrhea, the only reported adverse effect in this investigation (10).

In 814 patients randomly allocated to fish oils for 18 weeks for the reduction of re-stenosis after percutaneous transluminal coronary angioplasty, gastrointestinal adverse effects, most commonly bloating and burping, were reported in 37% of patients taking fish oils, versus 31% of those taking placebo (11).

Second-Generation Effects

Pregnancy

During early pregnancy, high doses of vitamin A (as found in halibut and shark liver oils) can lead to birth defects (12). Fish oil supplements rich in vitamin A should therefore be avoided by women in the first trimester and those who might become pregnant.

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Drug–Drug Interactions

Acetylsalicylic acid

In eight healthy men who took a total of 485 mg of aspirin over 3 days before beginning 2 weeks of fish oil supplementation (4.5 g of n-3 fatty acids/day), aspirin alone prolonged the bleeding time by 34% and fish oil alone prolonged it by only 9%; however, aspirin + fish oil prolonged the bleeding time by 78% (13). Although fish oil alone did not significantly raise aggregation thresholds for collagen, arachidonic acid, or platelet activating factor, it did reduce the extent of aggregation with collagen. When challenged by single or dual agonists, the combination of fish oil and aspirin did not make platelets less sensitive than aspirin alone.

However, in 18 healthy men randomly allocated to N-3 polyunsaturated fatty acids 10 g/day or placebo for 14 days, the addition of a single intravenous dose of acetylsalicylic acid 100 mg did not alter the small effect of polyunsaturated fatty acids on platelet aggregation (14).

In four subjects given a single oral dose of aspirin 37.5 mg before and after a natural stable fish oil daily for 1 week, serum thromboxane A_2 fell by 40% after aspirin alone, but by 62% after fish oil + aspirin, and leukotriene B_4 rose by 19% after aspirin and fell by 69% after fish oil + aspirin; serum prostacyclin fell equally in both cases (15).

In healthy subjects who took either fish oil or olive oil (control) daily for 3 weeks before exposure to aspirin or no aspirin, fish oil had no significant effect on mucosal prostaglandin E_2 or $F_{2\alpha}$ content or on the damaging effect of aspirin on the stomach, despite the fact that fish oil reduced serum triglyceride concentrations significantly (16).

Warfarin

In a placebo-controlled, randomized, double-blind study of the effect of fish oil supplements 3–6 g/day for 4 weeks on the International Normalized Ratio (INR) in 16 patients taking chronic warfarin therapy there was no statistically significant effect on anticoagulation (17).

However, fish oils can affect hemostasis, and there has been an anecdotal report of a possible interaction.

- A 67-year-old white woman who had been taking warfarin for 18 months doubled her dose of fish oil from 1000 to 2000 mg/day. The INR increased from 2.8 to 4.3 within 1 month and fell to 1.6 within 1 week of reduction of the dose of fish oil (18).

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5-HT$_3$ receptor antagonists

General Information

The 5-HT$_3$ antagonists, alosetron, granisetron, ondansetron, and tropisetron (all rINNs), are effective antiemetics used in treating cytotoxic-induced and postoperative vomiting.

There have been several reviews of the pharmacology and use of alosetron (1–5). In patients with irritable bowel syndrome, alosetron increases colonic transit time and colonic compliance. It produces significant improvement in abdominal pain, stool consistency, and frequency and

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urgency of defecation in non-constipated women with irritable bowel syndrome, but not in men. Constipation is the most common adverse effect. It occurs more commonly at higher doses and is more common in women, which is consistent with reported bowel function data.

Granisetron and tropisetron appear to have the same safety profile as ondansetron (6). Their adverse reactions include mild rises in transaminases (up to 17%), slight headache (8–42%), transient diarrhea (2–5%), which may be followed during longer-term therapy by constipation, dizziness (5%), and dry mouth (5–17%); the incidence of xerostomia is higher than with metoclopramide. Other reported adverse effects include anorexia, paresthesia, constipation or abdominal discomfort, changes in blood pressure, fever, facial edema, leg cramps, hot flushes, and enlargement of the spleen (7).

Observational studies

Granisetron

In 59 patients who were given intravenous granisetron 1 mg 30 minutes before treatment on days of chemotherapy, the most common adverse effects were headache, somnolence, and weakness (8).

In another open trial the combination of intravenous granisetron (1 mg) plus dexamethasone (10 mg) was effective and well tolerated for antiemetic control in 100 bone-marrow transplant patients receiving highly emetogenic chemotherapy with or without irradiation (9). Adverse effects were mild; headache, diarrhea, and constipation were the most frequent.

Tropisetron

The safety and efficacy of tropisetron in the prevention of chemotherapy-induced nausea and vomiting has been reviewed (10). Tropisetron monotherapy is effective for the control of acute, and to some extent delayed, nausea and vomiting in patients receiving emetogenic chemotherapy. Combining it with dexamethasone increases its efficacy.

The antiemetic efficacy of tropisetron has been confirmed in 22 children (median age 14 years) who received a total of 125 courses of highly emetogenic chemotherapy (11). The only reported adverse effects attributable to tropisetron were mild diarrhea during two treatment courses and dry mouth during three courses.

Comparative studies

Granisetron versus ondansetron

The efficacy and safety of oral granisetron (2 mg od) and oral ondansetron (8 mg tds for 3 days and bd on day 4) in the prophylaxis of nausea and vomiting have been studied in 34 patients receiving hyperfractionated total body irradiation in a randomized, double-blind trial (12). A historical group of 90 patients who received a similar irradiation regimen but no 5HT$_3$ receptor antagonists acted as a control group. Both drugs were safe and effective in preventing nausea and vomiting resulting from irradiation. The most frequent adverse effects were headache and diarrhea.

Oral granisetron (1 mg bd) plus intravenous dexamethasone (10 mg) have been compared with intravenous ondansetron (8 mg tds) plus dexamethasone (10 mg) for the control of nausea and vomiting in a randomized, open trial in 51 patients receiving emetogenic chemotherapy (13). The two combinations were equally effective, and the frequencies of adverse events (none serious) in the two groups were comparable. The most frequent were diarrhea with granisetron and constipation with ondansetron.

The efficacy of converting from intravenous ondansetron to oral granisetron in preventing chemotherapy-induced nausea and vomiting has been assessed in 608 patient interviews (14). There was no difference in the control of nausea and vomiting between the two treatments. Patient adherence to treatment increased from 48 to 78% after the use of oral granisetron. The costs of preventing acute chemotherapy-induced nausea and vomiting also fell, from US$107 to US$65 per treatment.

In a large double-blind study comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by chemotherapy in 1085 patients, the drugs were equally effective and gave rise to a similar frequency of adverse effects, commonly headache, weakness, and constipation (15). Dizziness and blurred vision were reported by significantly more of the patients who received ondansetron.

Granisetron and ondansetron were also effective in controlling nausea and vomiting related to emetogenic chemotherapy in a crossover study in 40 oriental patients (16). Adverse effects were similar to those reported in Western studies, constipation and headache being the commonest. In another placebo-controlled study of the efficacy and safety of granisetron (3 mg), droperidol (1.25 mg), and metoclopramide (10 mg) intravenously for the prevention of nausea and vomiting in 120 parturients undergoing cesarean section under spinal anesthesia, granisetron was the most effective antiemetic (17). The adverse events profiles of all three drugs were similar to that of placebo.

Granisetron versus ramosetron

Oral ramosetron 0.1 mg without water has been compared with oral granisetron 2 mg with water given 1 hour before infusion of chemotherapy in a multicenter, randomized, single-blind, crossover study in 73 patients with cancer (18). The two regimens had similar efficacy in the prevention of chemotherapy-induced anorexia, nausea, and vomiting. The incidence of adverse effects was similar in the two treatment groups. More patients given ramosetron (10%) complained of headache than those given granisetron (1.3%). The other important adverse effects were dry mouth, insomnia, heavy-headedness, and dizziness. In another multicenter, randomized, single-blind study in 194 patients receiving cisplatin chemotherapy for cancer, intravenous ramosetron 3 mg was as effective as intravenous granisetron 3 mg in preventing nausea and vomiting (19). Although the incidence of adverse effects was similar in the two groups, significantly more patients who received granisetron than ramosetron complained of dull headache.

Granisetron versus droperidol

In a randomized trial in 60 patients who underwent elective laparoscopic cholecystectomy the combination of intravenous granisetron 3 mg plus droperidol 1.25 mg

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was more effective in preventing postoperative nausea and vomiting than granisetron 3 mg alone (20). No significant adverse effects were reported in either group.

Granisetron versus droperidol and metoclopramide

The efficacy of intravenous granisetron 40 micrograms/kg, droperidol 20 micrograms/kg, and metoclopramide 0.2 mg/kg have been compared in the treatment of nausea and vomiting after laparoscopic cholecystectomy in a double-blind trial in 120 patients (21). The patients were observed for 24 hours after administration. Granisetron was significantly more effective than the other two drugs. All three drugs were equally well tolerated. The common adverse effects were headache and dizziness.

Ondansetron versus droperidol

Intravenous ondansetron (4 mg at induction of anesthesia and 0.13 mg with each 1 mg bolus of morphine) has been compared with intravenous droperidol (0.5 mg at induction and 0.05 mg with each bolus of morphine) in a double-blind trial in 142 patients (22). The two regimens had similar efficacy in the prevention of postoperative nausea and vomiting. The most important adverse effect was sedation; significantly more patients given droperidol (15%) had excessive sedation than patients given ondansetron (5%).

Ondansetron versus metoclopramide

The antiemetic effect of combined intravenous ondansetron 8 mg, oral dexamethasone 20 mg, and oral lorazepam 0.5 mg was significantly better than that of intravenous metoclopramide 10 mg, dexamethasone 20 mg, and oral lorazepam 0.5 mg in 30 patients receiving chemotherapy for ovarian cancer in a randomized trial (23). All the antiemetics were given 30 minutes before and 6 hours after chemotherapy. Significantly more patients given metoclopramide (40% versus 13%) complained of adverse effects. The most frequent adverse effects with both regimens were sedation and headache.

The antiemetic effects of intravenous metoclopramide 1 mg/kg tds and ondansetron 8 mg/kg tds, alone or in combination with dexamethasone or methylprednisolone, have been compared in an open study in 101 patients receiving several cycles of moderately emetogenic chemotherapy (24). The regimens had similar efficacy in controlling emesis during the first course of chemotherapy. However, ondansetron alone, ondansetron plus glucocorticoids, and metoclopramide plus glucocorticoids were more effective than metoclopramide alone during the next two cycles. All the antiemetic regimens were well tolerated and caused similar frequencies of adverse effects. The most common were headache, constipation, and diarrhea.

Ondansetron or tropisetron versus metoclopramide

In a randomized, double-blind trial in 179 patients undergoing thyroid or parathyroid surgery, premedication with oral tropisetron 5 mg was more effective in preventing postoperative nausea and vomiting in the initial postoperative period (0–2 hours) than either oral ondansetron 16 mg or oral metoclopramide 10 mg when given 1 hour before the operation (25). When the entire 24-hour postoperative period was considered, the incidence of vomiting was lower with ondansetron and tropisetron than with metoclopramide. The adverse effects profiles were similar in the three groups. Common adverse effects were headache, dizziness, pruritus, and visual disturbances.

Placebo-controlled studies

Alosetron

Alosetron (1 mg bd) was well tolerated and effective in alleviating abdominal pain, urgency, and stool frequency in a randomized, double-blind, placebo-controlled trial in 647 women with irritable bowel syndrome (26). Constipation occurred in 30% of patients taking alosetron and 3% of those taking placebo. Laboratory values, including liver function tests, were unchanged by alosetron.

The efficacy of alosetron in the treatment of irritable bowel syndrome has been evaluated in a double-blind, placebo controlled, dose-ranging study in 462 patients (27). In women, but not in men, alosetron 2 mg bd significantly increased the proportion of pain-free days and reduced the visual analogue scale score for diarrhea. Alosetron 0.5–2 mg bd led to significant hardening of stools and reduced stool frequency in the total population. The overall incidence of adverse effects was similar with alosetron and placebo. However, the incidence of constipation was significantly higher during treatment with alosetron 0.5 mg bd and 2 mg bd. There were no changes in laboratory values associated with alosetron.

In a randomized, double-blind, placebo-controlled, crossover trial, alosetron (2 mg bd) delayed left colonic transit in both patients with irritable bowel syndrome ($n = 13$) and healthy volunteers ($n = 12$) (28). In another double-blind, placebo-controlled trial in 25 non-constipated patients with irritable bowel syndrome, alosetron (1 and 4 mg bd) had no significant effect on gastrointestinal transit or rectal sensory and motor mechanisms (29).

Granisetron

Oral granisetron 2 mg has been studied in the prophylaxis of nausea and vomiting following fractionated upper abdominal radiotherapy in a double-blind, placebo-controlled trial in 160 patients (30). Granisetron was significantly more effective than placebo. The common adverse effects attributed to granisetron were diarrhea, weakness, and constipation.

In a crossover study in 90 patients receiving cisplatin-based chemotherapy, prednisolone 50 mg significantly improved the antiemetic effects of granisetron (3 mg intravenously) compared with placebo (31).

Tropisetron

In a randomized, double-blind, placebo-controlled study, intravenous tropisetron 2 mg and 5 mg was effective in preventing emesis in 60 patients who underwent general anesthesia (32). Both doses of tropisetron were equally effective. Adverse effects were not mentioned.

Organs and Systems

Cardiovascular

Hypertension or disturbances of cardiac rhythm can occur with 5HT$_3$ receptor antagonistsT3 antagnists HT, especially in elderly patients (SEDA-20, 316).

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Some patients have electrocardiographic changes, such as prolongation of the QT interval. In a double-blind, placebo-controlled, randomized study of the effects of dolasetron mesylate 0.6–5.0 mg/kg in 80 subjects, there were transient and asymptomatic electrocardiographic changes (small mean increases in PR interval and QRS complex duration versus baseline) in several subjects at 1–2 hours after infusion at doses of 3.0 mg/kg and over (33).

In one trial a patient who took ondansetron had syncope, presumably because of a change in blood pressure (SEDA-18, 370).

Nervous system

Ondansetron can cause extrapyramidal reactions (34). In two cases the reaction did not recur after a reduction in dosage or a change in the infusion time.

Hematologic

Thrombocytopenia has been observed in patients who were given 5 HT3 receptor antagonists, but was probably coincidental, since they were also given cytostatic drugs (35,36).

Gastrointestinal

Constipation is the commonest adverse effect of alosetron. In women with irritable bowel syndrome, alosetron 1 mg bd was more effective than placebo and mebeverine in relieving abdominal pain, discomfort, and diarrhea. The most frequent adverse effect was constipation (1–4). In 30 patients (15 men, 15 women) using scintigraphy to measure bowel transit, alosetron 1 mg bd for 6 weeks caused significantly delayed small bowel and colonic transit times (37). This effect was significantly greater in women. Alosetron 1 mg bd was significantly more effective than placebo in the treatment of diarrhea-predominant irritable bowel syndrome in a multicenter, double-blind, placebo-controlled study in 801 women (38). Constipation was the most frequently reported adverse effect. The tolerability and safety of alosetron 1 mg bd during long-term administration (48 weeks) has been studied in a multicenter, double-blind, placebo-controlled trial in 859 subjects (39). Alosetron was generally well tolerated. The frequencies of adverse events were similar in the two groups, with the exception of constipation, which occurred significantly more often in the treatment group (32% compared with 5%). In most cases (72%) constipation was mild to moderate. There were two deaths in subjects with pre-existing cardiovascular risk factors in the treatment group, but neither was attributed to alosetron. In a dose-ranging, randomized, placebo-controlled, multicenter trial in 320 patients with functional dyspepsia, alosetron 0.5 mg bd and 1 mg bd was better than placebo in symptom control (40). Women had significantly greater responses than men. Constipation was the most commonly reported adverse effect of alosetron (49% compared with 13% in the placebo group). In a randomized, double-blind, placebo-controlled trial in 626 women with diarrhea-predominant irritable bowel syndrome, alosetron 1 mg bd was significantly more effective than placebo in controlling symptoms (41). Constipation was the most common adverse effect of alosetron (25% compared with 5% in the placebo group).

Ischemic colitis has been attributed to alosetron (42).

- A 55-year-old man with irritable bowel syndrome who took alosetron 1 mg bd for 4 days developed symptoms of ischemic colitis, including rectal bleeding, and the diagnosis was confirmed macroscopically and histologically at colonoscopy. The symptoms suggestive of colitis abated on withdrawal of alosetron, but the symptoms of irritable bowel syndrome returned. Colonoscopy 2 weeks later showed a normal colon and biopsies showed normal colonic histology.

The combination of intravenous granisetron (40 micrograms/kg) and dexamethasone (8 mg) was more effective than granisetron alone for prophylaxis of postoperative nausea and vomiting after laparoscopic cholecystectomy in a randomized, double-blind trial in 120 patients (43). There was no difference in the incidence of adverse effects between the two groups. The most frequent were nausea, retching, and vomiting.

Drug Administration

Drug administration route

In a randomized, double-blind study, oral granisetron (1 mg) was more effective than intravenous granisetron (1 mg) in preventing emesis caused by high-dose chemotherapy in 51 patients who underwent peripheral blood progenitor cell or bone-marrow transplantation (44). There was no significant difference in adverse events. The more frequent were headache, diarrhea, extrapyramidal symptoms, and sedation.

Drug–Drug Interactions

Fluoxetine

In an open, non-randomized, crossover study in 12 healthy female and male volunteers alosetron 1 mg bd had no effect on the pharmacokinetics of fluoxetine 20 mg/day (45). Co-administration of the two drugs was well tolerated by all the subjects.

Zenoplatin

Data from a single trial suggest that ondansetron can enhance the nephrotoxicity of the cytostatic drug zenoplatin (SEDA-17, 415).

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Flavoxate

See also Anticholinergic drugs

General Information

Flavoxate is an anticholinergic drug that is used to treat bladder detrusor instability. It can cause all the adverse effects that would be expected from its anticholinergic action.

Organs and Systems

Skin

- An 83-year-old man developed a generalized pruritic erythematous reaction with a fever after taking flavoxate 200 mg tds for 6 months in combination with tamsulosin hydrochloride and allylestrenol for prostatic hyperplasia (1). Patch tests with these drugs showed a positive reaction on flavoxate 10% on day 3. Rechallenge with flavoxate caused generalized pruritic erythema with fever.

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Flecainide

See also Antidysrhythmic drugs

General Information

Flecainide is a class Ic antidysrhythmic drug. Its clinical pharmacology, clinical use, and adverse effects have been reviewed (1–3).

Comparative studies

In some patients treatment with a class I antidysrhythmic drug converts atrial fibrillation to atrial flutter. Of 187 patients with paroxysmal atrial fibrillation who were treated with flecainide or propafenone, 24 developed atrial flutter, which was typical in 20 cases (4). These patients underwent radiofrequency ablation, which failed in only one case. All the patients continued to take their preexisting drugs, and during a mean follow-up period of 11 months the incidence of atrial fibrillation was higher in patients who were taking combined therapy than in those taking monotherapy. The authors suggested that in patients with atrial fibrillation who developed typical atrial flutter due to class Ic antidysrhythmic drugs, combined catheter ablation and continued drug treatment is highly effective in reducing the occurrence and duration of atrial tachydysrhythmias. They did not report adverse effects.

In 33 patients with symptomatic and inducible supraventricular tachycardias single doses of placebo, flecainide 3 mg/kg, or diltiazem 120 mg plus propranolol 80 mg were used to terminate the dysrhythmia (5). Conversion to sinus rhythm was achieved within 2 hours in 17 patients with placebo, in 20 with flecainide, and in 31 with diltiazem plus propranolol. Time to conversion was shorter with diltiazem plus propranolol (32 minutes) than with flecainide (74 minutes) or placebo (77 minutes). Of those who were given flecainide, two had hypotension and one had sinus bradycardia.

Systematic reviews

A systematic review of 22 studies of the effects of flecainide used for at least 3 months in the treatment of supraventricular dysrhythmias suggested that flecainide is associated with a variety of adverse reactions, many of which are well tolerated, but carries a small risk of serious cardiac events (2%), which can lead to death (0.13%) (SEDA-21, 200).

In a meta-analysis of 122 prospective studies of the use of flecainide in 4811 patients with supraventricular

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Table 1 Numbers (%) of cardiac and non-cardiac adverse effects of flecainide in a meta-analysis of 4375 treatment courses compared with 1818 treatment courses in controls

System	Adverse effect	Flecainide	Controls
Cardiovascular	Angina pectoris	43 (1.0)	25 (1.3)
	Palpitation	17 (0.4)	6 (0.3)
	Hypotension	33 (0.8)	24 (1.3)*
	Syncope	5 (0.1)	3 (0.2)
	Heart failure/ dyspnea	40 (0.9)	13 (0.7)
	Sinus node dysfunction	52 (1.2)	22 (1.2)
	Bundle branch block	29 (0.7)	7 (0.4)
	Atrioventricular block	24 (0.5)	7 (0.4)
Nervous system	Total	412 (9.4)	65 (3.4)*
	Headache	88 (2.0)	53 (2.9)*
	Dizziness	148 (3.4)	45 (2.5)
	Vertigo	137 (3.1)	42 (2.3)
Sensory systems	Visual disturbances	175 (4.0)	16 (0.9)*
Gastrointestinal	Total	144 (3.3)	121 (6.7)*
	Diarrhea	29 (0.7)	50 (2.8)*
	Nausea	71 (1.6)	33 (1.8)

*Significantly different.

dysrhythmias, 21 were placebo-controlled and 37 were comparative studies with other antidysrhythmic drugs (6). The total exposure time was 2015 patient-years, with a mean oral flecainide dose of 216 mg/day. There were eight deaths (total mortality 0.17%, fatality rate per 100 patient-years 0.40; 95% CI = 0.17, 0.78), confirming the earlier finding. Three deaths were non-cardiac (cancer, suicide, urinary sepsis). Of the cardiac deaths, all but two occurred in patients with coronary heart disease. In controls, there was one death. There were prodysrhythmic events in 120 patients taking flecainide (2.7%) and 88 controls (4.8%), 58 (7.4%) of which occurred in patients taking placebo. Non-cardiac adverse effects are listed in Table 1. Thus, flecainide is safe in patients with supraventricular dysrhythmias with no cardiac damage, in contrast to patients with ventricular dysrhythmias after myocardial infarction.

Organs and Systems

Cardiovascular

In a review of 60 original articles detailing 1835 courses of intravenous and/or oral flecainide in both placebo-controlled and comparative studies as well as a large number of uncontrolled studies, unwanted cardiac events occurred in 8% of patients (7). The cardiac events were hypotension (1.3%), heart failure (0.4%), sinus node dysfunction (1.6%), bundle branch block (1.0%), atrial dysrhythmias (1.6%), and ventricular dysrhythmias (1.3%). However, in 8505 patients, 5507 of whom were administered flecainide for more than 4 weeks and most of whom took dosages of 100–300 mg/day, cardiac adverse effects occurred in only about 2% and non-cardiac effects in about 10% (8). The most common cardiac adverse effects were angina pectoris, dysrhythmias, worsening of heart failure, and hemodynamic changes. Of the long-term non-cardiac adverse effects the most common were nausea, vomiting, dizziness, bowel disturbances, headache, and visual disturbances.

Cardiac dysrhythmias

In the wake of the preliminary and final reports of the Cardiac Arrhythmia Suppression Trial (CAST) (9,10), which showed that there was an increased risk of death among patients who took encainide and flecainide after myocardial infarction, there have been many publications in which the implications of these findings have been thoroughly discussed (11–15). The relative risk of death or cardiac arrest due to dysrhythmias in the treated patients was 2.6 and the relative risk due to all causes was 2.4. The risk of non-fatal cardiac adverse effects was no different in treated patients from that in those taking placebo and there was no difference between the groups in the use of other drugs.

Although there is a consensus that encainide and flecainide were associated with an increase in the rate of mortality in CAST, there are still some open questions. First, all the patients recruited to CAST had asymptomatic ventricular dysrhythmias after myocardial infarction, and it is not clear whether the results can be extrapolated to other patients. Secondly, the reasons for the increased mortality in the treated patients are not clear: ventricular dysrhythmias and worsening of left ventricular function are both possible. Thirdly, it is not clear whether the results of CAST in patients with asymptomatic ventricular dysrhythmias after myocardial infarction can also be applied to other Class I antidysrhythmic drugs.

The prodysrhythmic effects of flecainide, by prolongation of the QT_c interval, have been widely discussed (SEDA-15, 175) (16–20). However, overall, cardiac dysrhythmias are less common with flecainide than with other antidysrhythmic drugs of Class I, and the dysrhythmogenic effects of flecainide in patients with supraventricular dysrhythmias may not be great (SEDA-22, 207). When dysrhythmias occur, prolongation of the QT interval is an important mechanism, but in a recent case it was suggested that tachycardia was due to re-entry within the His-Purkinje system (21). In another case flecainide reportedly caused a wide-complex tachycardia due to atypical atrial flutter with 1:1 conduction and aberrant QRS complexes (22). Although drugs of Class Ic, such as flecainide, can slow atrial and atrioventricular nodal conduction in patients with atrial fibrillation or atrial flutter, they do not alter the refractoriness of the atrioventricular node, and this allows 1:1 atrioventricular conduction as the atrial rate slows. This happens despite prolongation of the PR interval.

- Syncope occurred in a patient whose QRS complex duration was prolonged (23).
- In a 67-year-old woman taking flecainide 150 mg bd, widening of the QRS complex occurred during exercise; the effect did not occur at rest or with a dose of 50 mg bd (24).

Hypokalemia can increase the risk of torsade de pointes with flecainide, as with other antidysrhythmic drugs.

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- Torsade pointes has been attributed to mosapride (which is related to cisapride) and flecainide in a 68-year-old man with a plasma potassium concentration of 3.2 mmol/l and prolongation of the QT_c interval from 0.48 to 0.56 seconds (25). His plasma flecainide concentration was just above the target range at 1013 ng/ml, but the mosapride concentration was not reported.

The authors speculated that mosapride may have inhibited the metabolism of flecainide by CYP2D6.

In a retrospective analysis of 24 patients who developed atrial flutter while taking flecainide ($n = 12$) or propafenone ($n = 12$), the electrocardiogram was classified as typical atrial flutter in 13 cases, atypical atrial flutter in eight, or coarse atrial fibrillation in three (26). Counterclockwise atrial flutter was the predominant dysrhythmia. The acute results of ablation suggested that the flutter circuit was located in the right atrium and that the isthmus was involved in the re-entry mechanism. There was better long-term control of recurrent atrial fibrillation in patients with typical atrial flutter (85%) compared with atypical atrial flutter (50%). The authors suggested that patients who develop coarse drug-induced atrial fibrillation may not be candidates for ablation.

Cardioversion

In 24 patients with atrial fibrillation who underwent elective transvenous cardioversion for atrial fibrillation, flecainide reduced the energy requirements for further defibrillation after induction of atrial fibrillation by atrial pacing (27). There were no ventricular dysrhythmias, but transient bradycardia requiring ventricular pacing occurred in two patients. Two patients had transient asymptomatic hypotension after flecainide and one reported transient dizziness and some light-headedness.

Antidysrhythmic drugs increase the pacing threshold, but failure to capture is a rare consequence. It has, however, been reported twice with flecainide (28,29).

Electrocardiographic changes

ST segment elevation in leads II, III, and aVf, resembling an acute inferior myocardial infarction, have been reported with oral flecainide (30). Brugada syndrome is partial right bundle branch block with ST segment elevation in the right precordial leads of the electrocardiogram; it is due to an abnormality of sodium channels and occurs in 0.05–0.1% of the population; some cases are inherited (31). Flecainide can bring out Brugada-type changes on the electrocardiogram (32–34).

Hypotension

Flecainide has been reported to cause acute hypotension after intravenous administration (35).

Respiratory

Interstitial pneumonitis has only rarely been attributed to flecainide (SEDA-16, 181).

- Interstitial pneumonitis with acute respiratory failure was attributed to flecainide in a 59-year-old man with congenital heart disease related to the LEOPARD syndrome, in which there are multiple freckles (Lentigines), Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormalities of the genitalia, Retarded growth, and sensorineural Deafness (36). A CT scan showed diffuse interstitial injury characterized by thickening of the intralobular septa, with areas of ground-glass pattern. Flecainide was withdrawn and within 2 weeks the changes on CT scan had almost completely disappeared.
- A 75-year-old man, who had taken flecainide 100 mg/day for 22 months, developed fever, headache, and a dry cough (37). A CT scan of the lungs was normal and he responded to prednisone. His symptoms disappeared, but when prednisone was withdrawn they returned, with breathlessness, a dry cough, and weight loss. A chest X-ray showed bilateral patchy opacities and a CT scan subpleural ground-glass opacities and septal thickening. He had impaired lung function, including a reduced diffusion capacity. Biopsy showed diffuse interstitial thickening with lymphocytic and eosinophilic infiltrates. Flecainide was withdrawn and prednisone given, and he made a full recovery within 1 month.
- A 73-year-old man, who had taken flecainide 100 mg/day for 4 months, developed fever, weight loss, breathlessness, and a dry cough (37). A chest X-ray showed patchy infiltrates and a CT scan ground-glass opacities and subpleural septal thickening. He had normal lung function, apart from a reduced diffusion capacity. Flecainide was withdrawn and prednisone given, and he made a full recovery within a few months.

Nervous system

The most common non-cardiac adverse effects of flecainide are on the central nervous system and include dizziness, drowsiness, visual disturbances, headache, nausea, paresthesia, nervousness, and tremor. The incidence of these adverse effects has varied widely (38,39).

Other reported effects of flecainide include dysarthria and visual hallucinations (40), abnormal taste sensations, flushing, a glove-and-stocking type of peripheral neuropathy, and dystonia (SEDA-17, 223).

Sensory systems

Ocular adverse effects of flecainide have included corneal deposits in two patients, due to deposition of flecainide (41). In 38 patients taking flecainide 100–300 mg/day there were brown corneal epithelial deposits in 11 eyes, dryness in eight eyes, and slight blurring of vision on lateral gaze in four patients (42). Four patients had local symptoms, including tearing, itching, and burning. Color vision, contrast sensitivity, and visual fields were all unaffected.

Hematologic

Flecainide can cause neutropenia (43).

Liver

Flecainide can cause increases in the serum activities of transaminases (44). In one case cholestasis and jaundice occurred (45).

Urinary tract

Flecainide can cause acute urinary retention, perhaps due to a local anesthetic effect on the bladder mucosa (46).

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Skin

Flecainide reportedly caused a psoriasiform eruption (47).

Sexual function

Flecainide inhibits sperm motility in vitro (48), but this has not been reported to be of clinical relevance.

Flecainide can cause erectile impotence (49).

Second-Generation Effects

Pregnancy

Flecainide is occasionally used to treat fetal cardiac dysrhythmias by administration to the mother (50,51), although occasionally it can cause adverse effects in the child (SEDA-25, 184) and in the mother (52).

- At 30 weeks of gestation in a 41-year-old woman the fetus had hydrops, ascites, a pericardial effusion, and bilateral hydroceles. A supraventricular tachycardia with 1:1 conduction was treated by giving the mother oral flecainide 150 mg bd. However, during the next few weeks the mother developed evidence of hepatic cholestasis. The dosage of flecainide was reduced to 50 mg bd and the liver damage resolved. The child was born healthy but later required sotalol for a re-entry tachycardia.

Fetotoxicity

- A pregnant woman was given digoxin and flecainide at 29 weeks of gestation for fetal tachycardia and hydrops fetalis (53). The child was delivered spontaneously at 33 weeks and had mild respiratory distress. His electrocardiogram showed bifid P waves, a prolonged PR interval, deep wide Q waves, and raised ST segments. The QT interval was not prolonged. The serum digoxin concentration in the neonate was 1.2 mg/ml. The abnormalities resolved within 3 weeks of birth, despite continued digoxin therapy.

The authors attributed the electrocardiographic abnormalities to maternal use of flecainide.

Susceptibility Factors

Age

Reports of the use of flecainide in children suggest that the risk of adverse effects is low, although these studies have been very small (54–56).

Renal disease

Flecainide is cleared partly by dose-dependent hydroxylation and partly unchanged via the kidneys. Therefore, severe renal impairment and hepatic impairment both cause a reduction in its rate of clearance (57,58). Dosages should be reduced in these circumstances.

Hepatic disease

Flecainide is cleared partly by dose-dependent hydroxylation and partly unchanged via the kidneys. Therefore, severe renal impairment and hepatic impairment both cause a reduction in its rate of clearance (57,58). Dosages should be reduced in these circumstances.

Other features of the patient

Flecainide half-life is prolonged in poor hydroxylators (59) and poor metabolizers may be at an increased risk of adverse effects.

Drug Administration

Drug overdose

There have been a few reports of the effects of overdosage of flecainide (60–65). Various treatments have been used in these circumstances; none is specific.

- A 20-year-old woman took 3–4 g of flecainide and developed circulatory failure unresponsive to pacing, inotropic drugs, and sodium bicarbonate (66). She was then successfully treated with cardiopulmonary bypass for 30 hours. At peak, the plasma flecainide concentration was in excess of 4000 μg/ml, and although this fell during bypass to below 3.5 μg/ml, clinical recovery preceded this fall. Other complications included a coagulopathy with intravascular hemolysis, requiring the use of blood products, and renal insufficiency requiring hemodiafiltration.

The authors proposed that extracorporeal circulatory support had allowed increased perfusion of the liver and therefore more effective metabolism of the flecainide.

- Death has been reported in two patients who took flecainide (67). The postmortem femoral blood flecainide concentrations were 5.4 and 1.2 μg/ml (target range 0.2–1.0).
- Fatal flecainide overdose has been reported in a 65-year-old man who probably took 20 tablets of 100 mg each (68). However, no clinical details were available, because he was found dead. Flecainide was detected in his blood, gastric contents, and liver. *O*-dealkylated flecainide was found in his urine.

Of other fatal cases reviewed in the paper, in only one was there a slightly lower blood concentration of flecainide (7.3 compared with 7.7 mg/kg). The authors proposed that pre-existing cardiac damage could have predisposed this man to a dysrhythmic death.

Drug–Drug Interactions

Amiodarone

The combination of flecainide with amiodarone can result in reduced conduction, predisposing to bundle branch block and dysrhythmias (69,70).

Beta-adrenoceptor antagonists

The combination of flecainide with propranolol results in additive hypotensive and negative inotropic effects (71).

Lipophilic beta-adrenoceptor antagonists are metabolized to varying degrees by oxidation by liver microsomal cytochrome P450 (for example propranolol by CYP1A2 and CYP2D6 and metoprolol by CYP2D6). They can therefore reduce the clearance and increase the steady-state plasma concentrations of other drugs that undergo similar metabolism, potentiating their effects. Drugs that interact in this way include flecainide (72).

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Digoxin

Despite an early report that flecainide might alter the pharmacokinetics of digoxin, this action is minimal and probably of no clinical significance (72). The combination causes a significant increase in the PR interval; but the clinical significance of this is unclear, it may be important for patients with impaired sinus node function (73).

Quinidine

Flecainide is metabolized by CYP2D6, and is subject to polymorphic metabolism. In extensive metabolizers its clearance is reduced by quinine (74). Quinidine reduces the clearance of *R*-flecainide but not that of *S*-flecainide (75).

Verapamil

Although verapamil reduces the clearance of flecainide, this is probably not clinically important (76). However, there is also a pharmacodynamic interaction, since both drugs increase the PR interval and have additive effects on myocardial contractility and atrioventricular conduction (77).

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Floctafenine

See also Non-steroidal anti-inflammatory drugs

General Information

Floctafenine is a 4-aminoquinoline NSAID, closely related to antrafenine and glafenine, and its adverse effects profile is similar (1).

Organs and Systems

Urinary tract

Floctafenine has been detected in a urinary calculus (2).

Immunologic

Floctafenine has frequently been associated with anaphylactic reactions (3).

Drug Interactions

Cimetidine

Coma has been reported in a patient taking diuretics and cimetidine, who was given floctafenine (4).

Coumarin anticoagulants

Floctafenine may increase the action of coumarin anticoagulants (5).

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Flosulide

General Information

Flosulide is a COX-2 inhibitor.

Organs and Systems

Gastrointestinal

Flosulide caused less damage to the mucosa and was better tolerated than naproxen in a 2-week endoscopic study, but the clinical relevance of endoscopic studies of this sort is debatable (SEDA-14, 79).

Urinary tract

Clinical development of flosulide, a COX-2 selective inhibitor, has been discontinued because of nephrotoxicity (1). Measurement of renal prostaglandin synthesis did not predict the nephrotoxicity of flosulide in single-dose and short-term studies (2).

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Floxuridine

See also Cytostatic and immunosuppressant drugs

General Information

Floxuridine is a pyrimidine analogue that is used in regional arterial chemotherapy for primary and metastatic malignancies, delivered using an implantable pump.

Organs and Systems

Gastrointestinal

Nine patients who received hepatic arterial infusion chemotherapy developed gastritis heralded by epigastric pain and tenderness, nausea, vomiting, weakness, and anorexia (1). In 7 patients, 18 gastric ulcers were detected endoscopically. Mucosal damage developed despite prophylactic antiulcer therapy and healed only on withdrawal. In 17 biopsy specimens there were variously inflammatory changes, reactive glandular changes, and cell necrosis, even in patients without ulcers. In addition, there was floxuridine-induced glandular atypia in eight biopsy samples from six patients; the crowded glands

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were distorted and lined by large cells that included bizarre forms with pleomorphic nuclei.

- A patient who received regional intrahepatic chemotherapy from a continuous infusion pump for 31 months developed a gastroduodenal artery–duodenal fistula, and presented with signs and symptoms of upper gastrointestinal bleeding.

Six patients who had received an infusion of floxuridine, either via the hepatic artery or intravenously, developed severe diarrhea (2). In four, the entire ileum or its more distal part was markedly narrowed and in the other two there was thickening or effacement of the mucosal folds in the distal ileum. The symptoms resolved and the radiographic appearances improved after withdrawal.

Biliary tract

The principle of hepatic arterial infusion is based on the fact that hepatic tumors derive much of their blood supply from the hepatic artery, whereas the liver parenchyma receives its supply from the portal venous circulation.

- Acute and chronic cholecystitis has been reported after floxuridine hepatic artery infusion (3). Chemotherapy in this patient was associated with persistent epigastric pain with radiation to the back which was not accompanied by any fever or white blood cell elevation. Cholecystectomy showed a shrunken, thickened fibrotic gallbladder that was filled with thick, pasty, hemorrhagic material. There were no gallstones.

In 27 patients who received intrahepatic floxuridine, total dose 20–41 mg/kg extrahepatic biliary sclerosis was discovered by CT scan and ultrasound, followed by endoscopic retrograde cholangiopancreatography and/or percutaneous cholangiography in three cases (4). Radiological findings included complete obstruction of the common hepatic duct in one case, common hepatic duct stenosis in two cases, common bile duct obstruction in one case, and intrahepatic bile duct dilatation without identifiable obstruction in one case

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Fluconazole

See also Antifungal azoles

General Information

Fluconazole is an antifungal triazole that was derived from the older imidazoles. It has a lower molecular weight and is soluble in water. It can be administered orally and parenterally.

Pharmacokinetics

After oral administration, its systemic availability is about 90%; maximum plasma concentrations are seen in 1–2 hours, its half-life is about 30 hours and steady state is reached within 5–7 days. Fluconazole has low protein binding (about 12%), is hardly metabolized, and about 80% of it is excreted in the urine. Hemodialysis reduces plasma concentrations by about half in 3 hours (1–3). Tissue and body fluid penetration is good (2,4–9). The CSF concentration ratio is 0.5–0.9, the resultant concentrations being adequate for the treatment of cryptococcal meningitis (10–12). Penetration into the eye is good (13), and fluconazole has been used successfully in fungal endophthalmitis (14–17). In a patient in whom the concentrations of fluconazole in bile were studied, the concentrations after the first dose were about the same as in serum, but 10–12 hours after the dose, bile concentrations were higher than serum concentrations (18). Sputum concentrations are similar to plasma concentrations. Concentrations in vaginal secretions are slightly lower than in plasma, but persist for longer (19,20).

Like ketoconazole, fluconazole is a potent inhibitor of cytochrome P450, but with much higher specificity for fungal enzymes compared with human enzymes (21,22). Clinical interaction studies and some in vitro studies have suggested that azole antifungal drugs inhibit P glycoprotein. In a cell line in which human P glycoprotein was overexpressed, itraconazole and ketoconazole inhibited P glycoprotein function, with 50% inhibitory concentrations of about 2 and 6 μmol/l respectively; however, fluconazole had no effect (23).

Observational studies

The prophylactic use of oral fluconazole to prevent invasive *Candida* infections in 260 critically ill surgical patients has been investigated in a prospective, randomized, placebo-controlled trial in a single-center, tertiary-care surgical intensive care unit (24). The patients were randomly assigned to receive either oral fluconazole 400 mg/day or placebo. The risk of presumed and proven *Candida* infections in the patients who received fluconazole was significantly less than the risk in those who received placebo. After adjusting for several potentially confounding effects, fluconazole reduced the risk of presumed and proven fungal infection by 55%. There was no difference in death rate between fluconazole and placebo. The authors concluded that enteral fluconazole safely reduced the incidence of fungal infections in this high-risk population.

Comparative studies

Amphotericin

Fluconazole and amphotericin as empirical antifungal drugs in febrile neutropenic patients have been investigated in a prospective, randomized, multicenter study in 317 patients randomized to either fluconazole (400 mg qds) or amphotericin deoxycholate (0.5 mg/kg qds) (25). Adverse events (fever, chills, renal insufficiency, electrolyte disturbances, and respiratory distress) occurred significantly more often in patients who were given amphotericin (128/151 patients, 81%) than in those given fluconazole (20/158 patients, 13%). Eleven patients treated with amphotericin, but only one treated with fluconazole, were withdrawn because of an adverse event. Overall mortality and mortality from fungal infections were similar in both groups. There was a satisfactory response in 68% of the patients treated with fluconazole and 67% of those treated with amphotericin. Thus, fluconazole may be a safe and effective alternative to amphotericin for empirical therapy of febrile neutropenic patients; however, since fluconazole is ineffective against opportunistic molds, the possibility of an invasive infection by a filamentous fungus should be excluded before starting empirical therapy. Similarly, patients who take azoles for prophylaxis are not candidates for empirical therapy with fluconazole.

Conventional amphotericin deoxycholate (0.2 mg/kg qds) and fluconazole (400 mg qds) have been compared in a prospective, randomized study in 355 patients with allogeneic and autologous bone marrow transplantation (26). The drugs were given prophylactically from day –1 until engraftment. There was no difference in the occurrence of invasive fungal infections, but amphotericin was significantly more toxic than fluconazole, especially in related allogeneic transplantation, after which 19% of patients developed toxicity compared with none of those who received fluconazole.

Echinocandins

Caspofungin and fluconazole have been compared in adults with *Candida* esophagitis in a double-blind, randomized trial (27). Eligible patients had symptoms compatible with esophagitis, endoscopic mucosal plaques, and microscopic *Candida*. They were randomized to receive caspofungin (50 mg) or fluconazole (200 mg) intravenously once a day for 7–21 days. Most of them (154/177) had HIV infection, with a median CD4 count of 30×10^6/l. Favorable response rates were achieved in 66 of the 81 patients in the caspofungin arm and in 80 of the 94 patients in the fluconazole arm; symptoms had resolved in over 50% of the patients in both groups by the fifth day of treatment. Drug-related adverse effects were reported in 41% of patients given caspofungin and 32% of those given fluconazole; the most common events in both groups were phlebitis, headache, fever, nausea, diarrhea, abdominal pain, and rashes. Drug-related laboratory abnormalities developed in 29% of patients given caspofungin and in 34% of those given fluconazole. The most frequent laboratory abnormalities included reduced white blood cell count, hemoglobin concentration, and serum albumin concentration, and increased alkaline phosphatase and transaminases. No patient given caspofungin developed a serious drug-related adverse effect; therapy was withdrawn in only one patient (who was receiving fluconazole), because of an unspecified adverse effect.

Placebo-controlled studies

In a randomized, double-blind, placebo-controlled study in Saudi Arabia of oral fluconazole (200 mg/day for 6 weeks) in the treatment of cutaneous leishmaniasis, 106 patients were assigned to fluconazole and 103 to placebo (28). Follow-up data were available for 80 and 65 patients respectively. At the 3-month follow-up, healing of lesions was complete in 63 of the 80 patients who took fluconazole and 22 of the 65 patients who took placebo (relative risk of complete healing, 2.33; 95% CI = 1.63, 3.33). Adverse effects were mild and similar in the two groups.

General adverse effects

Fluconazole is generally well tolerated. The most common adverse effects are nausea and vomiting. Abnormal liver function tests and slight increases in hepatic enzymes have been reported, and there have been anecdotal reports of hepatitis and hepatic failure. Early studies have shown no changes in testosterone concentrations or in the adrenal response to ACTH. Rashes and a few cases of exfoliative skin disorder have been reported (SED-12, 681) and have been seen more frequently in patients with AIDS (29). Alopecia has been reported in a few cases with the use of high doses for prolonged periods of time (SEDA-18, 281). Rare instances of anaphylactoid reactions have been reported (SED-12, 681) (30). Rare instances of hypersensitivity reactions have occurred in other individuals (SEDA-16, 293) (SEDA-17, 320). Tumor-inducing effects have not been reported.

In a study using the UK General Practice Research Database to determine rates of drug-induced, rare, serious adverse effects on the liver, kidneys, skin, or blood, occurring within 45 days of completing a prescription or refill in 54 803 users of either fluconazole or itraconazole, three had illnesses for which a fluconazole-induced cause could not be ruled out; one with thrombocytopenia, one with neutropenia, and one with an abnormal liver function test just after receiving fluconazole (31). The rates were 2.8/100 000 prescriptions (95% CI = 0.8, 10) for serious, adverse blood events and 1.4/100 000 prescriptions (95% CI = 0.25, 8.2) for serious, adverse liver events. These results suggest that fluconazole does not commonly have serious adverse effects on the liver, kidneys, skin, or blood.

Organs and Systems

Cardiovascular

Prolongation of the QT interval is a class effect of the antifungal azoles and has occasionally been reported with fluconazole, with a risk of torsade de pointes.

- A 68-year-old woman with *Candida glabrata* isolated from a presacral abscess developed torsade de pointes after 8 days treatment with oral fluconazole 150 mg/day (32). She had no other risk factors for torsade de pointes, including coronary artery disease, cardiomyopathy, congestive heart failure, or electrolyte abnormalities. The dysrhythmia resolved when fluconazole was withdrawn, but she continued to have ventricular extra beats and non-sustained ventricular tachycardia for 6 days.

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- A 59-year-old woman with liver cirrhosis and *Candida* peritonitis developed long QT syndrome and torsade de pointes after intravenous therapy with 400–800 mg/day of fluconazole for 65 weeks, followed by intraperitoneal administration (150 mg/day) (33). One day after the second intraperitoneal administration, she developed palpitation, multifocal ventricular extra beats, and syncope. In contrast to a normal electrocardiogram on admission, electrocardiography showed polymorphic ventricular extra beats, T wave inversion, alternating T wave amplitude, and a prolonged QT_c interval of 606 ms. Torsade de pointes required cardiopulmonary resuscitation. The fluconazole plasma concentration was 216 μg/ml (usual target range at 400–800 mg/day: 18–28 μg/ml). Fluconazole was withdrawn and all conduction abnormalities reversed fully within 3 weeks.

These patients were not taking any concomitant drugs that prolong the QT interval, suggesting that fluconazole was to blame.

- A 25-year-old woman with worsening endocarditis had a prolonged QT interval at baseline and developed monomorphic ventricular dysrhythmias, which were managed successfully with pacing and antidysrhythmic therapy, including amiodarone (34). Several days later, she was given high-dose fluconazole (800 mg/day) for fungemia and after 3 days had episodes of torsade de pointes.

In this case torsade de pointes developed in the presence of known risk factors—hypokalemia, hypomagnesemia, female sex, baseline QT interval prolongation, and ventricular dysrhythmias.

Nervous system

Central nervous system abnormalities constitute the major dose-limiting adverse effects of fluconazole and are observed at dosages over 1200 mg/day (35).

Dizziness, headache, and seizures were seen in 2–5% of 232 patients with severe systemic fungal infections taking fluconazole (36). In the same group there were three cases each of delirium and dysesthesia (1.3%). A possible effect of the underlying illness has to be considered. In 14 patients treated with fluconazole for cryptococcal meningitis, dizziness was reported in 14% (SED-12, 681).

Two Japanese patients developed clonic convulsions while taking fluconazole 800 mg/day (37).

- A 66-year-old woman with complicated invasive *Candida tropicalis* infection but no renal impairment took fluconazole 800 mg/day. On the 21st day she developed clonic convulsions. The fluconazole trough concentration at the time of the event was 82 μg/ml.
- A 62-year-old man with deteriorating renal and hepatic function after coronary artery bypass surgery was given fluconazole 400 mg bd for a fungal sternal wound infection. On the 15th day he developed seizures. His trough plasma fluconazole concentration was 88 μg/ml. Nineteen days after dosage adjustment to 400 mg qds, he had another seizure. The trough fluconazole concentration was 103 μg/ml, probably because of deteriorating renal function.

In both cases, the seizures abated after dosage reduction. These case reports suggest an association between trough plasma fluconazole concentrations of 80 μg/ml and central nervous system toxicity; they re-emphasize the need for careful monitoring and dosage adjustment of fluconazole in patients with reduced renal function.

Endocrine

Preliminary studies concerning a possible effect on testosterone concentrations and the adrenal response to adrenocorticotropic hormone did not show any changes. However, determinations were performed after only 14 days of fluconazole administration.

- Two critically ill patients, a 77-year-old man with esophageal cancer and a 66-year-old woman with multiple organ failure, developed reversible adrenal insufficiency temporally related to the use of high-dose fluconazole (800 mg loading dose followed by 400 mg/day), as assessed by short stimulation tests with cosyntropin (ACTH) (38). Although anecdotal, these data suggest that the possibility that high-dose fluconazole can cause adrenal insufficiency in already compromised critically ill patients needs to be investigated further.
- A 63-year-old man received high-dose cyclophosphamide for peripheral blood stem-cell harvesting, having been taking fluconazole 200 mg/day (39). On day 3 he developed atrial fibrillation and his blood pressure fell to 78 mmHg. A rapid ACTH stimulation test showed a blunted adrenal response. He was suspected of having adrenal failure, and fluconazole was withdrawn. A rapid ACTH test was normal on day 14. To clarify the association between adrenal failure and fluconazole, he was rechallenged with fluconazole 400 mg/day from day 16 and a rapid ACTH test was performed on day 21; it showed a blunted adrenal response.

Mineral balance

Hypokalemia was observed in only a few patients taking fluconazole, which contrasts with experience with itraconazole (36,40). However, hyperkalemia was reported in one paper (SED-12, 681) (40).

Hematologic

Cytopenias occur but seem to be mild. Occasionally, more marked changes have been described, but these could have been connected with the underlying disease (SED-12, 681) (40,41). In a single placebo-controlled study of fluconazole prophylaxis using a relatively high dose of 400 mg/day, a post-hoc analysis suggested prolongation of granulocytopenia after intensive chemotherapy for hematological neoplasms in the fluconazole group. This may have been due to an interaction with the antineoplastic drug (42).

Leukopenia with eosinophilia has been attributed to fluconazole (43).

- A 75-year-old man with non-Hodgkin's lymphoma and cryptococcal meningoencephalitis developed neutropenia with eosinophilia associated with fluconazole. After 1 week of fluconazole 400 mg/day his total leukocyte count began to fall and his eosinophil count increased. Concurrent medications included levothyroxine, famotidine, and co-trimoxazole. The last two drugs were withdrawn and he was given G-CSF.

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However, his leukocyte count continued to fall and 4 days later reached a nadir of 700 × 10^6/l; the platelet count remained normal. The leukopenia and eosinophilia resolved promptly after withdrawal of fluconazole.

Since the leukopenia and eosinophilia did not resolve until fluconazole was withdrawn, an effect of the compound was plausible. This case and two other reported cases (44,45) emphasize the importance of recognizing fluconazole as a rare but potential cause of bone marrow suppression in patients in whom drug-induced agranulocytosis is suspected.

In one study in patients with AIDS taking prophylactic maintenance fluconazole for cryptococcal meningitis, there was a higher rate of hematological toxicity with fluconazole than with placebo, but this probably reflected the greater proportional and absolute amounts of zidovudine used in the fluconazole group; there was no serious hematotoxicity (SED-12, 682).

Gastrointestinal

Nausea and vomiting are mentioned in most reports of patients taking fluconazole, with an incidence of 10–15% (SED-12, 682) (36,40,41,46,47). Anorexia, mild abdominal pain, and diarrhea have been reported, but none was severe.

Liver

Raised liver enzyme activities have been reported in most studies. In some articles this effect was described as transient, in others as disappearing after withdrawal. The incidence varies from a few percent of cases to 35–45%, but occasionally the effect has been recorded in all cases treated. A temporal relation between these liver function changes and fluconazole treatment has been shown in many cases. Severe liver toxicity has not been reported (SED-12, 681) (21). While asymptomatic rises in transaminases were noted in some children with neoplastic disease who were treated concomitantly with fluconazole in a small study (48), there were no significant changes in a larger study in cancer patients treated with placebo or fluconazole 400 mg (42).

- A 45-year-old woman with protracted cryptococcal meningoencephalitis developed fulminant hepatic failure secondary to high fluconazole serum concentrations, possibly precipitated by renal dysfunction induced by concomitant amphotericin therapy or concomitant therapy with lisinopril, atenolol, or amlodipine (49). Four days after the withdrawal of fluconazole 400 mg/day the serum concentration of fluconazole was 40 μg/ml.

This case points to the potential risks of fluconazole therapy in the setting of renal insufficiency, in particular with higher dosages (400 mg/day and more).

Skin

Rashes of several types occur with fluconazole and are more frequent in immunocompromised patients.

The risk of serious skin disorders has been estimated in 61 858 users of oral antifungal drugs, aged 20–79 years, identified in the UK General Practice Research Database (50). They had received at least one prescription for oral fluconazole, griseofulvin, itraconazole, ketoconazole, or terbinafine. The background rate of serious cutaneous adverse reactions (corresponding to non-use of oral antifungal drugs) was 3.9 per 10 000 person-years (95% CI = 2.9, 5.2). Incidence rates for current use were 15 per 10 000 person-years (1.9, 56) for itraconazole, 11.1 (3.0, 29) for terbinafine, 10 (1.3, 38) for fluconazole, and 4.6 (0.1, 26) for griseofulvin. Cutaneous disorders associated with the use of oral antifungal drugs in this study were all mild.

Pruritus has also been reported (51). A few cases of Stevens–Johnson disease have been reported worldwide (SED-12, 682) (22,46,52), as well as a few instances of fixed-drug eruption (53). In cases of hypersensitivity, desensitization has reportedly been used with success (54).

Fixed drug eruption caused by systemic fluconazole has been reported (55).

- A 36-year-old woman with a history of atopy and recurrent *Candida* vaginitis developed a fixed drug eruption while taking fluconazole 150 mg/day. Local provocation with 10% fluconazole in petrolatum applied at the site of a previous site of fixed drug eruption reproduced the eruption clinically and histopathologically.

Nails

A patient developed a longitudinal band of pigmentation in the diseased nail after fluconazole therapy for onychomycosis at a dosage of 150 mg once a week for 4 weeks (56).

Second-Generation Effects

Teratogenicity

The teratogenic activity of triazole and two triazole derivatives, flusilazole (an agricultural triazole monoderivative fungicide) and fluconazole, has been studied in vitro (57). Rat embryos 9.5 days old (1–3 somites) were exposed in vitro to triazole 500–5000 μmol/l, flusilazole 3.125–250 μmol/l, or fluconazole 62.5–500 μmol/l and examined after 48 hours in culture. There were similar teratogenic effects (abnormalities at the branchial apparatus level and cell death at the level of the branchial mesenchyme) at 6.25 μmol/l and higher for flusilazole and 125 μmol/l and higher for fluconazole. In contrast, there was little effect at the highest concentrations of triazole, suggesting no teratogenic activity. These investigations have confirmed the embryotoxic potential of antifungal triazole derivatives, specifically on the branchial apparatus.

However, teratogenic effects have not been found in humans. The risk of malformations and other outcomes in children exposed to fluconazole in utero has been examined in 165 women who had taken fluconazole just before or during pregnancy, mostly in the form of a single dose of 150 mg to treat vaginal candidiasis (58). Birth outcomes (malformations, low birth weight, and preterm delivery) were compared with the outcomes among 13 327 women who did not receive any prescriptions during their pregnancies. The prevalence of malformation was 3.3% (four cases) among the 121 women who had used fluconazole in the first trimester, and 5.2% (697 cases) in offspring to controls (OR = 0.65; CI = 0.24, 1.77). The risks of preterm delivery (OR = 1.17; CI = 0.63, 2.17) and low birth weight (OR = 1.19; CI = 0.37, 3.79) were not significantly increased in association with fluconazole. Thus, the study showed no increased risk of congenital malformations, low birth weight, or preterm birth in offspring to women

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who had used single doses of fluconazole before conception or during pregnancy.

The potential ability of fluconazole to modulate phenytoin teratogenesis has been studied in Swiss mice (59). Pretreatment with a non-embryotoxic dosage of fluconazole (10 mg) potentiated phenytoin teratogenesis; combined treatment of fluconazole 50 mg with phenytoin resulted in a significant increase in embryo deaths. The mechanism of this teratological interaction remains to be established.

Lactation

Fluconazole is found in breast milk at concentrations comparable with those found in the blood after single or multiple doses (2); this may be of clinical relevance (60).

Susceptibility Factors

Age

In a group of children with fever, neutropenia, and neoplastic disease, there was an increase in renal fluconazole clearance (45). In infants and children, the volume of distribution of fluconazole is significantly higher and falls with age. With the exception of infants, who have a slower clearance rate, children clear the compound more rapidly (61). However, a second larger study reported slower elimination in children under 1 year of age, requiring dosage adjustments (62). Low birth-weight neonates have a particularly low clearance rate, which increases within weeks (63).

The use of fluconazole in 726 children under 1 year of age, reported in 78 publications, has been reviewed (64). They received a wide range of dosages for up to 162 days. Fluconazole was well tolerated and efficacious in the therapy of systemic candidiasis and candidemia in children under 1 year of age, including neonates and very low birth-weight infants. The daily dosage recommended by the manufacturers is 6 mg/kg, to be reduced in patients with impaired renal function in accordance with the guidelines given for adults.

The efficacy and safety of fluconazole in neonates with *Candida* fungemia has been evaluated in a multicenter prospective study (65). Fluconazole was safe and effective even in complicated cases, including infants of very low birth weights. Two of 50 neonates developed raised liver enzymes during fluconazole therapy and two others had raised serum creatinine concentrations. In none of them did these abnormalities necessitate discontinuation of antifungal therapy.

The safety profile of fluconazole has been assessed in 562 children (aged 0–17 years; 323 boys and 239 girls), enrolled into 12 clinical studies of prophylactic or therapeutic fluconazole in predominantly immunocompromised patients (66). Most of the children received multiple doses of fluconazole 1–12 mg/kg, given as oral suspension or intravenously. Overall, 58 children reported 80 treatment-related adverse effects. The most common adverse effects were associated with the gastrointestinal tract (7.7%), the skin (1.2%), or the liver and biliary system (0.5% or three patients). Overall, 18 patients discontinued treatment owing to adverse effects, mainly gastrointestinal. Dosage and age did not affect the incidence and pattern of adverse effects. Treatment-related laboratory abnormalities included transiently raised alanine transaminase (4.9%), aspartate transaminase (2.7%), and alkaline phosphatase (2.3%). Although 99% of patients were taking concomitant drugs, there were no clinical or laboratory interactions. The safety profile of fluconazole was compared with those of other antifungal agents, mostly oral polyenes, by using a subset of data from five controlled studies. Adverse effects were reported by more patients treated with fluconazole (45 of 382; 12%) than by patients treated with comparator agents (25 of 381; 6.6%); vomiting and diarrhea were the most common events in both groups. The incidence and type of treatment-related laboratory abnormalities were similar in the two groups. Fluconazole was well tolerated, mirroring the favorable safety profile seen in adults.

In 34 otherwise healthy infants with oral candidiasis randomized to either nystatin oral suspension qds for 10 days or fluconazole suspension 3 mg/kg in a single daily dose for 7 days, 6 of 19 were cured by nystatin and all of 15 by fluconazole (67). Fluconazole was tolerated without apparent adverse events.

Renal disease

If the creatinine clearance is below 40 ml/minute fluconazole doses should be adjusted (SED-12, 682) (7).

Drug–Drug Interactions

Alfentanil

In a randomized, double-blind, placebo-controlled, crossover study in nine subjects, fluconazole 400 mg reduced the clearance of alfentanil 20 micrograms/kg by 55% and increased alfentanil-induced subjective effects (68).

Amitriptyline

An interaction of fluconazole with amitriptyline has been reported (69).

- A 12-year-old boy with prostatic rhabdomyosarcoma had episodes of syncope periodically over 7 months while taking fluconazole for chemotherapy-induced mucositis. He had taken fluconazole in the past without problems but had also taken a stable dose of amitriptyline for neuropathic pain. On withdrawal of amitriptyline he had no further episodes. The effect was confirmed by readministration.

Concurrent administration of fluconazole probably causes increased exposure to amitriptyline. Three reports of adults have shown increased amitriptyline plasma concentrations with concurrent administration of fluconazole; in one patient, a 57-year-old woman, the QT interval was prolonged and torsade de pointes occurred (70).

Amphotericin

In vitro studies and experiments in animals have given conflicting results relating to potential antagonism between the effects of fluconazole and amphotericin on *Candida* species (71). However, large, randomized, double-blind comparisons of fluconazole with and without amphotericin for 5 days in non-neutropenic patients with

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candidemia showed no evidence of antagonism, but faster clearance of the organism from the blood and a trend toward an improved outcome in those who received the combination (72).

Antacids

Fluconazole absorption after oral administration is not influenced by gastric pH; thus there is no effect of antacids such as co-magaldrox (SED-12, 682) (73).

Antihistamines

The concurrent use of terfenadine with fluconazole can lead to dangerously high terfenadine concentrations, with resulting cardiotoxicity (74). It is suspected that the same may happen with astemizole (75).

Benzodiazepines

The interaction of fluconazole with bromazepam has been studied in 12 healthy men in a randomized, double-blind, four-way, crossover study (76). They received single oral or rectal doses of bromazepam (3 mg) after 4-day pretreatment with oral fluconazole (100 mg/day) or placebo. Fluconazole caused no significant changes in the pharmacokinetics and pharmacodynamics of oral or rectal bromazepam.

Fluconazole increased blood concentrations of midazolam (77) and triazolam (78).

The effects of fluconazole (400 mg loading dose followed by 200 mg/day) on the kinetics of midazolam have been studied in 10 mechanically ventilated adults receiving a stable infusion of midazolam (79). Concentrations of midazolam were increased up to four-fold after the start of fluconazole therapy; these changes were most marked in patients with renal insufficiency. During the study, the ratio of α-hydroxymidazolam to midazolam progressively fell. The authors concluded that in ICU patients receiving fluconazole, reduction of the dose of midazolam should be considered if the degree of sedation is increasing.

In a study of the pharmacokinetics and pharmacodynamics of oral midazolam 7.5–15 mg, switching from inhibition of metabolism by itraconazole 200 mg/day to induction of metabolism by rifampicin 600 mg/day caused an up to 400-fold change in the AUC of oral midazolam (80).

Calcium channel blockers

- Fluconazole enhanced the blood pressure-lowering effects of nifedipine by increasing its plasma concentrations in a 16-year-old patient with malignant pheochromocytoma taking chronic nifedipine for arterial hypertension who was given fluconazole for *Candida* septicemia (81).

Carbamazepime

Fluconazole can cause carbamazepine toxicity, presumably by inhibition of CYP3A4 (82).

- A 33-year-old man on stable therapy with carbamazepine (400 mg tds) for a seizure disorder became stuporose due to carbamazepine toxicity after taking fluconazole 150 mg/day for 3 days. Withdrawal of both drugs resulted in a fall in carbamazepine concentrations (maximum concentration 25 μg/ml) and return of the patient's baseline mental status. Carbamazepine was restarted and the patient had no further adverse events.
- Carbamazepine serum concentrations increased during concomitant fluconazole administration (400 mg/day) in a 38-year-old man (83).

Ciclosporin

Fluconazole can increase concentrations of ciclosporin by inhibiting CYP3A4. In some studies, minimal or no effects were recorded, but in others ciclosporin concentrations were increased by fluconazole. Differences in the dosage and duration of fluconazole treatment could have explained these discrepancies (SED-12, 682) (21,84–87). For example, there was no interaction at a fluconazole dosage of 100 mg/day, but high dosages of fluconazole (400 mg/day or more) increase blood ciclosporin and tacrolimus concentrations (88,89).

The interaction of ciclosporin with fluconazole has been retrospectively evaluated in 19 kidney and pancreas/kidney transplant recipients (90). Both intravenous and oral fluconazole altered the blood concentration of ciclosporin. Five subjects did not have a significant interaction and 15 did. No patient had nephrotoxicity or transplant rejection related to antifungal therapy.

The effects of higher dosages of fluconazole on ciclosporin immunosuppression have been investigated in six renal transplant patients in a prospective, unblinded, crossover study (91). Baseline renal function, ciclosporin AUC, C_{max}, C_{min}, t_{max}, and clearance were compared with those 2, 4, and 7 days after starting fluconazole orally in a dosage of 200 mg/day. From day 8 onwards the ciclosporin dose was reduced by 50% and the above parameters were repeated on day 14. The results are shown in Table 1. On repeated-measures ANOVA only the AUC and C_{max} on day 4 of fluconazole were significantly higher than on day 0. There were no significant changes in ciclosporin clearance and t_{max}. The authors concluded that changes in C_{min} may not be sensitive enough to detect the described interaction and suggested monitoring the AUC near day 4 of treatment to guide ciclosporin dosage adjustments in all patients taking concomitant flucona\zole.

Table 1 Changes in ciclosporin kinetics during co-administration of fluconazole

Parameter	Day 0	Day 4	Day 7	Day 14
AUC (hours.ng/ml)	2887	4750	4052	2330
C_{max} (ng/ml)	701	941	768	498
C_{min} (ng/ml)	207	274	293	174
Clearance (ml/minute/kg)	17	13	12	30
t_{max} (hours)	3.0	2.0	2.5	3.0

Cimetidine

Fluconazole absorption after oral administration is not influenced by gastric pH; thus there is no effect of cimetidine.

Clarithromycin

The effects of fluconazole and clarithromycin on the pharmacokinetics of rifabutin and 25-*O*-desacetylrifabutin

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have been studied in 10 HIV-infected patients who were given rifabutin 300 mg qds in addition to fluconazole 200 mg qds and clarithromycin 500 mg qds (92). There was a 76% increase in the plasma AUC of rifabutin when either fluconazole or clarithromycin was given alone and a 152% increase when both drugs were given together. The authors concluded that patients should be monitored for adverse effects of rifabutin when it is co-administered with fluconazole or clarithromycin.

Cyclophosphamide

Cyclophosphamide is a prodrug that is metabolized by CYP450 enzymes to produce alkylating species, which are cytotoxic, and the extent of cyclophosphamide metabolism correlates with both treatment efficacy and toxicity. In vitro studies in six human liver microsomes showed that the IC_{50} of fluconazole for reduction of 4-hydroxycyclophosphamide production was 9–80 μmol/l (93).

A retrospective study in 22 children with cancers addressed the potential interaction between fluconazole and cyclophosphamide. Children with an established profile of cyclophosphamide metabolism who were not receiving other drugs known to affect drug metabolism were selected; 9 were taking fluconazole and 13 were controls. The plasma clearance was significantly lower in patients taking concomitant fluconazole (2.4 versus 4.2 l/hour/m^2). It is unclear whether this interaction is associated with a reduction in the therapeutic efficacy of cyclophosphamide.

Doxorubicin

The effect of fluconazole on the plasma pharmacokinetics of doxorubicin has been investigated in a randomized, crossover study in non-human primates (94). Fluconazole (10 mg/kg/day) was given intravenously for 4 days before doxorubicin (2.0 mg/kg intravenously). Pretreatment with fluconazole had no effect on the pharmacokinetics of doxorubicin, and the incidence of severe neutropenia (absolute neutrophil count below 0.5×10^9/l) was higher with doxorubicin alone than with the combination of doxorubicin and fluconazole. Thus, fluconazole does not appear to contribute to the marrow-suppressive effects of doxorubicin.

Flucytosine

The concurrent use of fluconazole with flucytosine may have an additive effect (95). This combination could be useful in the treatment of cryptococcal meningitis (21).

HIV protease inhibitors

The pharmacokinetic interaction of fluconazole 400 mg od and indinavir 1000 mg tds has been evaluated in a placebo-controlled, crossover study for 8 days; there was no significant interaction (96).

The effect of fluconazole on the steady-state pharmacokinetics of ritonavir and saquinavir has been studied in patients infected with HIV-1 (97). They received the protease inhibitor (saquinavir 1200 mg tds, $n = 5$, or ritonavir 600 mg bd, $n = 3$) alone on day 1 and then with fluconazole 400 mg on day 2 and 200 mg on days 3–8. The median increase in saquinavir AUC was 50%, and the median increase in C_{max} was 56%. In contrast, fluconazole had no effect on the disposition of ritonavir.

Methadone

An interaction between fluconazole and methadone (a substrate of CYP3A4, CYP2C9, and CYP2C19) has been reported.

- While taking a stable dose of methadone, a 60-year-old man with advanced cancer developed respiratory depression 2 days after receiving intravenous fluconazole for refractory oral candidiasis (98). Intravenous naloxone reversed the respiratory depression.

In a randomized, double-blind, placebo-controlled study in 25 patients, fluconazole 200 mg/day increased methadone concentrations, but patients treated with fluconazole did not have signs or symptoms of significant narcotic overdose (99).

Omeprazole

Fluconazole absorption after oral administration is not influenced by gastric pH; thus there is no effect of omeprazole (100). Omeprazole is extensively metabolized in the liver by 5-hydroxylation and sulfoxidation reactions, catalysed predominantly by CYP2C19 and CYP3A4 respectively. Fluconazole is a potent competitive inhibitor of CYP2C19 and a weak inhibitor of CYP3A4. The effect of fluconazole on the pharmacokinetics of a single oral dose of omeprazole 20 mg has been evaluated after a single oral dose of fluconazole 100 mg and after 4 days of oral administration of 100 mg/day in 18 healthy male volunteers (101). Fluconazole increased the C_{max} and the mean AUC of omeprazole and prolonged its half-life (2.59 versus 0.85 hours).

Oral contraceptives

Fluconazole did not significantly alter the pharmacokinetics of ethinylestradiol or norgestrel, and this finding was interpreted by the investigators as suggesting that treatment with fluconazole in a user of oral contraceptives would not increase the risk of pregnancy (102). However, the study was carried out using a 50 mg dose of fluconazole, and experience with higher dosages has shown different results (SED-12, 682).

In another study, fluconazole reduced the systemic availability of ethinylestradiol in an oral contraceptive, but there was no information about the doses used (75).

In an open, crossover study in 10 young healthy subjects, fluconazole 150 mg increased the serum concentrations of ethinylestradiol 30–35 μg/day (103).

The potential pharmacokinetic interaction between fluconazole 300 mg once weekly and an oral contraceptive containing ethinylestradiol and norethindrone (Ortho Novum 7/7/7; Ortho-McNeil Pharmaceutical Inc, Raritan, NJ) has been studied in a placebo-controlled, double-blind, randomized, two-way, crossover study in 26 healthy women aged 18–36 years (104). During the first cycle they took the oral contraceptive only. During the second cycle they were assigned randomly to oral contraceptive + fluconazole or oral contraceptive + placebo. In the third cycle they

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were given the other treatment. Fluconazole caused small but statistically significant increases in the $AUC_{0–24}$ of both ethinylestradiol and norethindrone. There were no adverse events related to treatment in those given fluconazole.

It therefore appears that there is no threat of contraceptive failure because of concomitant fluconazole administration.

Phenytoin

Co-administration of fluconazole and phenytoin resulted in markedly higher phenytoin concentrations (SED-12, 682) (21,84,87,105).

Rifamycins

The combination of rifampicin with fluconazole has insignificant effects (SED-12, 682) (21,87,106).

Statins

The effects of fluconazole on plasma fluvastatin and pravastatin concentrations have been studied in two separate, randomized, double-blind, two-phase, crossover studies (107). Healthy volunteers were given oral fluconazole (400 mg on day 1 and 200 mg on days 2–4) or placebo. On day 4, they took a single oral dose of fluvastatin 40 mg or pravastatin 40 mg. Fluconazole increased the plasma AUC and the half-life of fluvastatin by 80% but had no significant effects on the pharmacokinetics of pravastatin. The mechanism of the prolonged elimination of fluvastatin was probably inhibition of CYP2C9. Pravastatin, in contrast, appears not to be susceptible to interactions with fluconazole and other CYP2C9 inhibitors.

The effect of fluconazole on the pharmacokinetics of rosuvastatin has been investigated in a randomized, double-blind, two-way, crossover, placebo-controlled study (108). Healthy male volunteers ($n = 14$) were given fluconazole 200 mg/day or matching placebo for 11 days; rosuvastatin 80 mg was co-administered on day 8. Plasma concentrations of rosuvastatin, *N*-desmethylrosuvastatin, and active and total HMG-CoA reductase inhibitors were measured up to 96 hours after the dose. Fluconazole increased the AUC and C_{max} of rosuvastatin by 14% and 9% respectively. Limited data available for the *N*-desmethylated metabolite showed that the C_{max} fell by about 25%. Fluconazole did not affect the proportion of circulating active or total HMG-CoA reductase inhibitors accounted for by circulating rosuvastatin. Thus, fluconazole produced only small changes in rosuvastatin kinetics, which were not considered to be of clinical relevance.

Sulfonylureas

The concurrent administration of fluconazole with tolbutamide resulted in increased tolbutamide concentrations (SED-12, 682) (71).

- A 56-year-old HIV-positive patient with diabetes mellitus taking gliclazide 160 mg/day developed severe hypoglycemia when treated with co-trimoxazole 480 mg/day and fluconazole 200 mg/day (109). The authors speculated that fluconazole might have inhibited gliclazide metabolism by inhibiting CYP2C9.

The effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride have been studied in a randomized, double-blind, crossover study in 12 healthy volunteers who took fluconazole 200 mg/day (400 mg on day 1), fluvoxamine 100 mg/day, or placebo once daily for 4 days (110). On day 4 they took a single oral dose of glimepiride 0.5 mg. Fluconazole increased the mean total AUC of glimepiride to 238% and the peak plasma concentration to 151% of control values, and the half-life of glimepiride was prolonged from 2.0 to 3.3 hours. This was probably due to inhibition of CYP2C9-mediated biotransformation of glimepiride by fluconazole. However, fluconazole did not cause statistically significant changes in the effects of glimepiride on blood glucose concentrations.

Tacrolimus

Since tacrolimus (FK506) is metabolized by intestinal and hepatic CYP3A4, drugs that inhibit CYP3A4 can reduce the metabolism of tacrolimus and increase tacrolimus blood concentrations (111). The effect of fluconazole on the blood concentrations of tacrolimus have been investigated in eight liver transplant patients in whom prophylactic fluconazole (200 mg/day) was withdrawn because of rises in hepatic transaminases ($n = 6$), renal dysfunction, or eosinophilia ($n = 1$ each) (112). Calculated tacrolimus concentrations fell by 13–81% (median 41%) between the fourth and ninth days after withdrawal of fluconazole. Tacrolimus blood concentrations should be carefully monitored and dosages increased as necessary after withdrawal of fluconazole.

The interaction of tacrolimus with fluconazole has been retrospectively evaluated in 19 kidney and pancreas/kidney transplant recipients (90). Both intravenous and oral fluconazole altered the blood concentration of tacrolimus. Five subjects did not have a significant interaction and 15 did. No patient had nephrotoxicity or transplant rejection related to antifungal therapy.

- A 17-year-old man with cystic fibrosis who took itraconazole after a lung-liver transplant had high trough concentrations of tacrolimus, despite the relatively low dosage (0.1–0.3 mg/kg/day) (113).
- A patient taking tacrolimus 0.085 mg/kg bd with itraconazole 200–400 mg/day developed ketoacidosis, neutropenia, and thrombocytopenia, requiring the withdrawal of both drugs (114).
- A 34-year-old renal transplant recipient taking a stable regimen of tacrolimus and methylprednisolone was given itraconazole 100 mg bd for a yeast infection of the urinary tract (115). Concomitant therapy with itraconazole led to a marked increase in tacrolimus trough concentrations on the second day of therapy (from 13 to 21 ng/ml) and an increase in serum creatinine concentrations, necessitating dosage reduction of tacrolimus by 50%.

When itraconazole was withdrawn the effect of itraconazole on the kinetics of tacrolimus took 12 days to reverse.

The inhibitory effect of itraconazole occurred quickly, while the time of disappearance was much longer, which is important for clinical management. Thus, during co-administration of itraconazole with tacrolimus, close

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monitoring of tacrolimus blood concentrations and careful dosage adjustments are essential to avoid toxicity.

Warfarin

Co-administration of fluconazole and warfarin has led in some cases to prolongation of the prothrombin time (21,87,106,116).

Zidovudine

Zidovudine glucuronidation in human hepatic microsomes in vitro was inhibited more by the combination of fluconazole with valproic acid than with other drugs, such as atovaquone and methadone (117).

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Flucytosine

General Information

Flucytosine is an antimetabolite of the fluoropyrimidine type. The principle of selectivity of flucytosine for the fungal cell is dual: it depends on an enzyme in order to penetrate the cell (fungal cytosine permease) and a fungal enzyme that deaminates flucytosine to the active antimetabolite 5-fluorouracil, which is metabolized to 5-fluorouridine. Replacement of 5-fluorouracil in RNA results in the disruption of protein synthesis in the fungus. Flucytosine has selective activity against pathogenic yeasts such as Candida, but only moderate activity against Aspergillus and chromoblastomycosis. There is synergy between flucytosine and amphotericin, and the combination is effective against meningeal cryptococcosis and pheohyphomycosis of the central nervous system, specifically disease caused by *Xylohypha bantiana* (1–3). Flucytosine can be given orally as well as parenterally. For most fungal infections it should not be given as a single agent, because of the development of secondary drug resistance (4), with the possible exception of urinary tract infection (5), in which secondary resistance does however also occur.

The mechanism of toxicity of flucytosine is not fully understood. Conversion of flucytosine to certain metabolites, in particular 5-fluorouracil, in the liver or by the intestinal microflora after oral administration has been proposed. Toxicity may also occur through impurities in the raw material and the formation of fluorouracil from flucytosine after sterilization and storage.

Pharmacokinetics

Flucytosine can be given orally, and peak serum concentrations occur within 1–2 hours in patients with normal renal function. The absorption of flucytosine can be delayed by food or antacids. Flucytosine is minimally bound to plasma proteins. It penetrates into the CSF, vitreous humor, peritoneal fluid, inflamed joints, and other fluid compartments. There are several methods for determining serum concentrations, particularly the creatinine iminohydrolase assay, which makes use of the spurious creatinine increase in serum, as measured by the Kodak Ektachem analyser, an apparatus widely available and providing a low cost method compared with HPLC (6). Flucytosine accumulates in patients with renal insufficiency, resulting in potentially toxic serum concentrations. About 90% of the dose is excreted unchanged in the urine. Dose adjustments in renal insufficiency can be made in proportion to the reduction in creatinine clearance (7). Metabolism occurs to a limited extent (8). There is evidence that some flucytosine (5-fluorocytosine) is converted into 5-fluorouracil by the intestinal flora (9,10); 5-fluorouracil may also be present as an impurity in the original formulation or after prolonged storage (11).

Observational studies

Experience with flucytosine monotherapy of cryptococcosis has been reviewed in 27 patients treated between 1968 and 1973 who were selected for this form of therapy on the basis of criteria associated with good prognosis (4). Flucytosine was given as primary therapy to 18 patients and as secondary therapy (following failure of amphotericin deoxycholate) to nine patients in dosages of 4–10 g/day in four divided doses for 8 weeks. Toxicity associated with flucytosine was uncommon and mild. Mild leukopenia (nadir 3–4 $\times 10^9$/l) developed in three patients, and mild thrombocytopenia (101×10^9/l) and worsening anemia occurred in one patient each. Therapy was stopped early or changed in two patients. In the first, therapy was stopped after 31 days because of a white cell count of 4.1×10^9/l; despite the shortened course of therapy, the patient achieved a long-term cure, and the leukopenia was ultimately believed to be secondary to sarcoidosis.

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There was bone marrow suppression in the second patient shortly after the withdrawal of flucytosine (because of failure to respond); later resumption of flucytosine during amphotericin therapy for this critically ill patient was associated with severe bone marrow suppression and death.

Comparative studies

Combination therapy with fluconazole (200 mg/day for 2 months) and flucytosine (150 mg/kg/day for the first 2 weeks; $n = 30$) has been compared with fluconazole monotherapy (200 mg/day for 2 months; $n = 28$) in a randomized open trial in Ugandan patients with AIDS-associated cryptococcal meningitis (12). Patients in both groups who survived for 2 months received maintenance therapy with fluconazole (200 mg three times per week for 4 months). There were no serious adverse events in any of the patients. The combination therapy prevented death within 2 weeks and significantly increased the survival rate at 6 months (32 versus 12%). However, the rate of positive cryptococcal antigen titers remained high at 2 months after treatment in both groups.

General adverse effects

The toxicity and drug interactions of flucytosine have been reviewed (13). Nausea, vomiting, and diarrhea are common. Enterocolitis is infrequent. Hepatic dysfunction, hepatitis, and even hepatic necrosis and blood disorders, including fatal aplastic anemia, can occur (14). Severe reactions mainly occurred at a time when the importance of high serum concentrations (in excess of 100 μg/ml) of flucytosine in causing these adverse effects was not recognized. The importance of parenteral versus intravenous administration in the development of enterocolitis is unclear. Patients have been described who suffered adverse effects, such as hepatotoxicity or eosinophilia, that were idiosyncratic and not related to flucytosine concentrations. Hypersensitivity reactions can occur. Neither teratogenic nor tumor-inducing effects have been recorded.

Organs and Systems

Cardiovascular

Life-threatening fluorouracil-like cardiotoxicity has been attributed to flucytosine (15).

- A 34-year-old woman took flucytosine, 500 mg 12 times a day for 2 days, for vaginal candidiasis. After the last dose she complained of chest pain, which persisted for a week and was associated with ST segment elevation during exercise. Coronary angiography showed normal coronary arteries. One month later she was rechallenged with 500 mg 12 times a day for 2 days. The day after completion of this regimen, she developed severe chest pain. Electrocardiography showed widespread ST segment elevation and echocardiography showed apicolateral septal hypokinesia with a left ventricular ejection fraction of less than 15%. Her flucytosine plasma concentration 48 hours after the last dose was not high, but the fluorouracil concentration was similar to that found during a 5-day continuous infusion of 5-fluorouracil. Her lymphocytes showed no abnormalities of intracellular flucytosine clearance, and cytosine deaminase, the enzyme that converts flucytosine to fluorouracil, was not detectable.

Similar cardiotoxicity has been reported with 5-fluorouracil. The reported events were generally consistent with a drug- or metabolite-induced increase in coronary vasomotor tone and spasm, leading to myocardial ischemia. The authors concluded that more attention should be given to the conversion of flucytosine to fluorouracil; however, it is not clear whether flucytosine should be contraindicated in patients with vasospastic or exertional angina.

Nervous system

Headaches, confusion, hallucinations, somnolence, and vertigo can occur. There have also been a few reports of peripheral neuropathy. However, it is difficult to establish the role of flucytosine in these adverse reactions (SED-12, 674). An acute cerebellopathy has been attributed to flucytosine (16).

Hematologic

Bone marrow suppression is a recognized toxic effect of flucytosine; anemia, leukopenia, and thrombocytopenia occur in about 5% of cases. The hematological effects are dose-related and occur after prolonged high blood concentrations of flucytosine (over 100 μg/ml). Hematotoxicity is seen more often in the presence of renal insufficiency and hence during the use of flucytosine in combination with amphotericin. If bone marrow reserve has already been depleted by underlying disease or by medications, the risk of hematotoxicity increases.

The relation between the toxicity and pharmacokinetics of flucytosine has been investigated in a retrospective study in 53 patients in an intensive care unit (17). Thrombocytopenia, as a marker of bone marrow depression, was associated with a reduced clearance of flucytosine; the lowest thrombocyte count was linearly related to the clearance of flucytosine. Patients with flucytosine concentrations over 100 μg/ml were at higher risk of thrombocytopenia and raised hepatic transaminases than those who did not exceed this threshold. In a second study, the authors corroborated their earlier findings and showed a significant relation between the lowest thrombocyte counts and thrombocyte counts predicted on the basis of the creatinine clearance in a new set of patients admitted to the intensive care unit (18).

In a pilot study in six patients receiving intravenous flucytosine, hematotoxicity was monitored by measuring platelet and leukocyte counts; flucytosine and 5-fluorouracil serum concentrations were measured using HPLC (19). The concentrations of 5-fluorouracil in the 34 available serum samples were below the limit of quantification (0.05 μg/ml), but flucytosine was detectable in all samples and the 5-fluorouracil metabolite, α-fluoro-β-alanine (FBAL), was detected at low concentrations in several samples. One patient developed thrombocytopenia (50×10^9/l) during therapy, and one developed leukopenia (2.6×10^9/l). The fact that 5-fluorouracil was not detected

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in the serum made it unlikely that the toxic effects of intravenous flucytosine resulted from exposure to 5-fluorouracil.

Patients with AIDS, treated for antifungal disease with flucytosine and amphotericin, are particularly susceptible to develop bone marrow depression (1,3). On the other hand, flucytosine can be safely administered to patients with cancer (6) or AIDS (12,20), if toxic concentrations are avoided and blood counts monitored.

Gastrointestinal

Nausea, vomiting, and diarrhea are the most common adverse effects of flucytosine.

Enterocolitis, usually sparing the rectosigmoid, has been described in some cases (21). This type of flucytosine toxicity may be associated with deamination of flucytosine to 5-fluorouracil in the gut (1). Potentially fatal ulcerative colitis has been suspected in a few patients; however, in most cases there were no diagnostic data to back up the diagnosis.

Liver

Abnormal liver function tests (above normal serum alkaline phosphatase and transaminases and, less often, raised serum bilirubin concentrations) have all been reported. Hepatic involvement is rarely serious (SED-12, 675) (22).

Liver cell necrosis, detected by means of liver biopsy, has been rarely described (SED-9, 477) (23).

The reason for antifungal treatment and the concurrent use of other medication may contribute to hepatotoxicity (SED-12, 675) (1,6).

Urinary tract

Crystalluria has been reported, with urinary gravel, consisting of a co-precipitate of flucytosine and uric acid (24).

Skin

Maculopapular and urticarial rashes severe enough to require drug withdrawal have been reported (SEDA-2, 242). The incidence is low.

Acquired photosensitivity has been described in two cases (25).

Immunologic

Anaphylaxis has been reported in a patient with AIDS (26).

Second-Generation Effects

Teratogenicity

Flucytosine is teratogenic in rats, and its close chemical relation to antimetabolites plus the fact that 5-fluorouracil is a metabolite make it inadvisable to administer flucytosine during pregnancy or to fertile women taking no contraceptive precautions.

Drug–Drug Interactions

Amphotericin

Amphotericin in combination with flucytosine results in an increased risk of hematological complications, because amphotericin often impairs renal function, causing retention of flucytosine (7). This combination also delays hematopoietic recovery after cytotoxic chemotherapy; it should not be used as empirical antifungal therapy in febrile patients with neutropenia (27).

Antifungal azoles

Flucytosine has been successfully used in combination with ketoconazole, fluconazole, and itraconazole. Flucytosine and ketoconazole were synergistic in about 40% of yeast isolates resistant to flucytosine alone. The synergistic action of flucytosine with the triazoles against *Candida* species was seen both in vitro and in vivo (3–6).

Cytarabine

The suggested interaction of cytarabine with flucytosine, in which there is competitive inhibition of antifungal activity, has not been confirmed (28).

Monitoring Therapy

Monitoring blood concentrations of flucytosine is essential, so that the dosage can be altered according to changing renal function and to avoid toxicity. Peak plasma concentrations should be 40–60 μg/ml after an oral dose, and under 100 μg/ml after intravenous infusion. To avoid fungal resistance, trough concentrations below 20 μg/ml are recommended (7).

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Fludarabine

See also Cytostatic and immunosuppressant drugs

General Information

Fludarabine phosphate is a purine nucleoside antitumor agent, which inhibits adenosine deaminase. It is mainly used to treat chronic lymphocytic leukemia. Dose-limiting myelotoxicity, nausea and vomiting, and raised liver enzymes were observed during early clinical studies. The most common adverse effect is myelosuppression (WHO grade 3 or 4), and other common adverse effects include infections and gastrointestinal disturbances, although these are usually of mild to moderate intensity (WHO grade 1 or 2) (1).

Organs and Systems

Respiratory

Fludarabine can cause interstitial pneumonitis (2,3).

- A 73-year-old woman developed fever and cough 2 weeks after completing a third cycle of fludarabine for chronic lymphocytic leukemia. A chest X-ray showed multiple pulmonary nodules and a biopsy showed a mononuclear interstitial infiltrate without evidence of malignant, infectious, granulomatous, or vascular causes. Her symptoms and pulmonary nodules resolved after treatment with glucocorticoids (4).

There has also been a report of an acute eosinophilic pneumonia associated with peripheral blood eosinophilia in a patient with follicular lymphoma (5).

Nervous system

Dose-intensified fludarabine causes severe central nervous system toxicity. In 70 patients with acute leukemia who received 95 courses of fludarabine 20–220 mg/m^2 for 5–7 days there was neurotoxicity in 36% of those who received doses over 96 mg/m^2/day, but in only 0.2% of those who received lower doses (6). The onset of neurological symptoms was at 21–60 days after the last course of fludarabine. Visual symptoms were the most common. There was progressive deterioration of mental state or encephalopathy leading to a vegetative state in 11 patients. Progressive demyelination in the central nervous system was the main factor causing the neurotoxic symptoms; this can occur as a result of viral complications during drug-related immunosuppression.

Hematologic

Fludarabine can cause or exacerbate autoimmune thrombocytopenia in chronic lymphocytic leukemia. Two patients with chronic lymphatic leukemia who developed thrombocytopenia while taking fludarabine were treated

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with high-dose glucocorticoids and initially responded with recovery of platelet counts (7). One developed recurrent thrombocytopenia on two occasions after re-exposure to fludarabine when his disease had become refractory to all other treatments. Of 45 patients with lymphoproliferative disorders treated with fludarabine over the previous 6 years, retrospectively reviewed, 2 had developed autoimmune thrombocytopenia and 3 had developed autoimmune hemolytic anemia.

In three patients with chronic lymphatic leukemia, fludarabine-associated thrombocytopenia responded to rituximab 375 mg/m^2/week for 4 weeks (8). Other similar cases have been reported (9). However, when rituximab was added to a regimen of fludarabine plus cyclophosphamide in patients with relapsed follicular lymphoma, there was unexpected severe hematological toxicity, with significant, prolonged thrombocytopenia WHO grade 3/4 in six of 17 patients (10). Older patients (mean age 65 versus 57 years) were significantly more likely to have this adverse effect, and no other clinical or hematological parameters differed between the patients with thrombocytopenia and those without.

Peripheral blood eosinophilia, in one case up to 7.9×10^9/l, has been attributed to fludarabine (11).

- A 58-year-old man who took fludarabine for 5 months developed a peripheral eosinophilia with a peak value of 1.7×10^9/l; thorough investigation for other causes of eosinophilia was negative (12).

A patient with a high-grade B cell non-Hodgkin's lymphoma treated with fludarabine developed a high-titer antibody to factor VIII while the lymphoma was in remission; the authors speculated that the occurrence of the inhibitor was an autoimmune adverse effect of fludarabine (13).

Gastrointestinal

Intestinal pseudo-obstruction has been attributed to fludarabine in a 66-year-old man with non-Hodgkin's lymphoma; it was successfully managed with a combination of parasympathomimetic drugs and mechanical decompression (14).

Immunologic

Treatment with fludarabine results in prolonged immunosuppression lasting over 6 months (15). Patients who are immunocompromised are at risk of infection with chemotherapy. Infection with JC virus, a human polyoma virus, occurred in two patients after fludarabine treatment of a low-grade lymphoma, which led to a progressive multifocal leukoencephalopathy (16). In one series of 27 patients who received fludarabine, serious infections developed in 24 (17).

Drug–Drug Interactions

Melphalan

Cardiotoxicity has rarely been reported with melphalan or fludarabine alone, but severe left ventricular failure developed in three of 21 patients treated with a combination of these two drugs (18).

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Flufenamic acid and meclofenamic acid

See also Non-steroidal anti-inflammatory drugs

General Information

Flufenamic acid and meclofenamic acid are anthranilic acid derivatives similar to mefenamic acid. The withdrawal rate because of adverse effects is 7–31% and is higher in long-term studies. Flufenamic acid and meclofenamic acid are not widely prescribed and so there is little evidence to show whether they have any advantages over other NSAIDs. Both have a high incidence of gastrointestinal adverse effects (30–60% of patients at recommended doses). Diarrhea affects 11–46% of patients (SEDA-4, 68) (SEDA-6, 99) (SEDA-7, 116) (SEDA-14, 95). Thrombocytopenia with positive rechallenge has been described (1). Rashes occur in under 10% of patients. Meclofenamic acid exacerbates psoriasis in psoriatic arthropathy (2).

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Flumazenil

General Information

Flumazenil is used as a benzodiazepine antagonist in the treatment of poisoning or the reversal of benzodiazepine effects in anesthesia (1,2) or in neonates (3). Guidelines for its use have been summarized (4). The problems in its use are those of dose adjustment, the risks of panic anxiety, seizures, or other signs of excessively rapid benzodiazepine withdrawal, and pharmacokinetic problems due to the short half-life of flumazenil (about 1 hour) compared with the longer half-lives of most benzodiazepines (5). Its use is also commonly associated with vomiting and headache, and rarely with psychosis or sudden cardiac death (SEDA-17, 46), especially in mixed overdoses. Flumazenil was not effective in reversing the amnesic effects of midazolam (6), but it may be useful in hepatic coma, regardless of cause (7). In patients with a history of seizures or chronic benzodiazepine dependence, or after mixed drug overdose, flumazenil can trigger convulsions, which are occasionally fatal. It is not generally helpful to measure benzodiazepine plasma concentrations, but they can assist in the diagnosis of overdose and thus guide the use of antagonists (8).

Midazolam can cause paradoxical reactions, including increased agitation and poor cooperation (9,10). Often other drugs are required to continue the procedure successfully. Reversal of these reactions by flumazenil has been reported. In 58 patients undergoing surgery under spinal or epidural anesthesia, flumazenil 0.1 mg over 10 seconds abolished the agitation without reversing sedation (total dose range 0.1–0.5 mg) (11). In 30 patients who had been given midazolam, flumazenil 0.15–0.5 mg resulted in cessation of the agitation without reversal of sedation (9). Adverse effects of flumazenil were not reported in these studies.

The usefulness and relative safety of midazolam in children have been reviewed (12). Myoclonic-like movements associated with midazolam in three full-term newborns were reversed by flumazenil (13). However, care must be taken when considering the use of flumazenil for reversal of midazolam-induced agitation, as no controlled trials have been published.

Organs and Systems

Nervous system

A case of opisthotonos after flumazenil has been reported (14).

- A healthy 17-year-old man received an interscalene brachial plexus block using mepivacaine 600 mg and bupivacaine 150 mg. He became disorientated and showed signs of local anesthetic toxicity, for which he was given midazolam 5 mg. Flumazenil 0.5 mg was given 23 minutes after the end of the procedure, causing opisthotonos.

Similar reports have appeared in the past in patients with seizure disorders. It is recommended that flumazenil not be used in patients predisposed to seizures.

Endocrine

The effects of flumazenil and midazolam on adrenocorticotrophic hormone and cortisol responses to a corticotrophin-releasing hormone challenge have been assessed in eight healthy men (15). Flumazenil significantly reduced adrenocorticotrophic responses compared with midazolam or placebo, but had no effects on cortisol secretion. The authors suggested that this agonist effect of flumazenil on the pituitary–adrenal axis might account for the anxiolytic activity of flumazenil, which has been observed during simulated stress.

Long-Term Effects

Drug withdrawal

Flumazenil can provoke acute withdrawal reactions and extreme anxiety (16). Its duration of action (less than 1 hour) is generally shorter than that of the original benzodiazepine, whose effects can therefore return while the patient is unobserved.

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Flunitrazepam

See also Benzodiazepines

General Information

Flunitrazepam has acquired a reputation for toxicity, abuse potential (1) and associated forensic problems (2), including being implicated in sexual assault ("date rape") (3). It has been withdrawn from general availability in various countries, including the USA, Australia, and New Zealand, and it is considered to be a narcotic in various European countries. It has a rapid onset of action but a long half-life. The earlier recommended hypnotic dose (1–2 mg) is excessive, and like some other benzodiazepines, such as triazolam, flunitrazepam is safer in a smaller dose (4). Like triazolam, it has been associated with nocturnal binge eating (5). Although its outpatient use in individuals who are susceptible to abuse is hazardous, intravenous flunitrazepam is useful for alcohol withdrawal delirium, but assisted ventilation should be available.

Long-Term Effects

Drug withdrawal

Withdrawal syndrome and delirium has been attributed to flunitrazepam (6).

- A 69-year-old man developed acute benzodiazepine withdrawal delirium following a short course of flunitrazepam after an acute exacerbation of chronic obstructive pulmonary disease. He was not an alcohol- or drug-abuser and he had not previously taken benzodiazepines. Six days after withdrawal of flunitrazepam he became agitated and confused, and had visual hallucinations, disorganized thinking, insomnia, increased psychomotor activity, disorientation in time and place, and memory impairment. Tachycardia and significant anxiety were also noted. He fulfilled the DSM IV criteria for withdrawal syndrome and delirium, and had spontaneous remission of symptoms within 48 hours.

The authors commented that physicians should be more aware of drug withdrawal syndromes, even after limited periods of administration of sedative drugs.

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Flunoxaprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Flunoxaprofen is an NSAID, an arylalkanoic acid derivative. Its adverse effects profile is similar to the profiles of other NSAIDs, including gastrointestinal disturbances (1).

Reference

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Fluoride salts and derivatives

General Information

Fluoride is the single most potent bone-forming agent currently available for therapeutic use (1). The active moiety is the fluoride ion itself, and its main pharmacological effect is on dental enamel and bone. Fluoride ions bind to calcium ions, stimulating trabecular bone formation. Different fluoride products have been used for the therapy of osteoporosis. The first was sodium fluoride (NaF), but that had several adverse effects, such as epigastric pain, gastric hemorrhage, leg pain, and so-called stress fractures (2).

In a study of the adverse effects of fluorinated drinking water (3), a few patients had non-specific ailments of varying duration, involving different systems. Severe headache, loss of strength, and abdominal cramps were noted, sometimes with polydipsia and polyuria. The symptoms disappeared promptly when fluorinated water was withdrawn, and reappeared immediately after rechallenge.

Therapeutic studies

There are currently no trial-based recommendations for the treatment of idiopathic osteoporosis in men. The effects of intermittent low-dose fluoride combined with continuous calcium supplementation on bone mass and future fracture events have been evaluated in 64 men with idiopathic osteoporosis (4). They were randomized to intermittent treatment with monofluorophosphate plus calcium or calcium supplementation alone for 3 years. Seven of the patients given fluoride had leg pain. In most cases the pain, which was generally confined to the ankle, disappeared during the fluoride-free month. In a few cases, the fluoride-free month had to be prolonged to 7 or 8 weeks before the symptoms subsided. During fluoride therapy, two patients had mild epigastric symptoms and one had diarrhea, but these appeared to be related to calcium; seven of the patients who were given calcium alone complained of epigastric discomfort and two had diarrhea. All the adverse events were mild to moderate and transient, and none led to discontinuation of treatment.

A 3-year, open study (5) has been performed with monofluorophosphate in 60 patients under 75 years old (average age 62 years, body weight 42–84 kg, height 148–174 cm) with established postmenopausal vertebral osteoporosis and a lumbar t-score lower than –2.5 BDM (measured by dual-energy X-ray absorptiometry) and at least one vertebral fracture diagnosed according to WHO criteria (6). The patients had taken hormone replacement therapy for an average of 2 years. Patients with inflammatory rheumatic diseases and those who were taking other medications that can modify bone metabolism, such as calcitonins, bisphosphonates, vitamin D, or anabolic agents, were excluded. There were adverse events in 19 patients, 10 of which were probably due to the monofluorophosphate or calcium components, three with gastrointestinal symptoms and seven with leg pain. The other nine adverse events were probably due to the hormone replacement therapy component: three with vaginal bleeding, four with breast tenderness, one with "heavy legs," and one with increased body weight. All the adverse events were of mild or moderate intensity and resolved spontaneously; none required withdrawal of treatment.

Organs and Systems

Nervous system

In a child, there were tetanic spasms and a convulsion more than 12 hours after fluoride ingestion, with a normal serum calcium. It is advisable that patients with intoxication should remain under surveillance for at least 24 hours, after the usual acute symptoms such as vomiting and diarrhea have settled (SEDA-10, 439).

Mouth and teeth

Fluoride poisoning can occur: after chronic ingestion of excessive amounts of fluoride, causing osteosclerosis and dental fluorosis (mottled enamel), due to accidental ingestion of fluoride mixtures during dental treatment (7,8), or after ingestion of insecticides or rodenticides containing fluoride salts.

Gastrointestinal

Fluoride can cause gastrointestinal damage (9). In 10 subjects, 3 g of a 0.42% fluoride gel caused mucosal petechiae and erosions in 7 cases; there were histopathological changes in nine cases, mostly affecting the surface epithelium (8). The authors advocated the use of a low concentration of fluoride gel instead of a 1.23% gel in small children, in order to avoid adverse gastric effects.

Skin

Fluoride in therapeutic doses can cause atopic dermatitis (9). Two patients who used fluoride gel preparations applied to the teeth developed papulonodular eruptions similar to halogenodermas (10).

Musculoskeletal

Although sodium fluoride can be used to treat osteoporosis, there is a risk of stress fractures (11–14). Fluoride has a dual effect on osteoblasts: it increases the rate of production of osteoblasts by a mitogenic effect on their precursors but also has a toxic effect on individual cells, causing impairment of mineralization and a reduced rate of apposition resembling osteomalacia (15). Fluoride increases axial bone density, but without matching changes in cortical bone. The effect on fracture rates of adding fluoride to the drinking water is not clear, but it probably only has a small impact. In two controlled studies the incidence of vertebral fractures fell, while in two other studies it increased.

Chronic ingestion of excessive amounts of fluoride can cause osteosclerosis (15). Severe dental fluorosis, hypersensitivity of teeth, and skeletal fluorosis have been reported in rural communities exposed over a long period of time to high concentrations of fluoride in the water (10 ppm) (16). There were deformities of the arms and legs with resultant genu valgum. There was osteosclerosis of the axial bones and osteoporosis in the

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appendicular bones. Serum calcium and inorganic phosphate were normal, but serum alkaline phosphatase was increased.

Perimalleolar pain with swelling (SED-12, 1243) and extremity pain after fluoride treatment in postmenopausal osteoporosis (17) have been reported.

Second-Generation Effects

Fertility

In a US study designed to determine whether fluoride affects human birth rate (18) the annual total fertility rate in women aged 10–49 years was calculated for 1970–88 in counties with water fluoride concentrations of at least 3 parts per million (ppm). For each region separately, the annual total fertility rate was tested by regression against the water fluoride content and sociodemographic co-variables. In most regions there was an association between increasing fluoride concentrations in drinking water and a falling total fertility rate. The study was based on population means rather than individual data, but there was no indication that the result was influenced by selection bias, inaccurate data, or inappropriate analytical methods. It does not necessarily follow that the effect of fluoride on fertility rate also applies to individual women, and that is a matter for further research.

Drug Administration

Drug overdose

Although 5–10 g of fluoride is considered to be the acute lethal dose, a fatality has been reported in a patient who took less than 50 mg, suggesting a wide variation in the lethal dose.

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Fluoroquinolones

See also Individual agents

General Information

Following the introduction of the first quinolone antibiotic (nalidixic acid, see separate monograph), structural modifications to the basic quinolone and naphthyridone nucleus and to the side-chains produced fluoroquinolones with improved coverage of bacterial pathogens, with high activity against Gram-negative species and a number of atypical pathogens, and good-to-moderate activity against Gram-positive species. However, despite their broad spectrum and clinical success, defects became evident, and compounds developed in recent years have targeted improvements in pharmacokinetic properties (improved systemic availability, once-daily dosing), greater activity against Gram-positive cocci and anerobes, activity against fluoroquinolone-resistant strains, and better coverage of non-fermenting Gram-negative species (1–4).

The following fluoroquinolones are covered in separate monographs: alatrofloxacin and trovafloxacin, ciprofloxacin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, sitafloxacin, sparfloxacin, and tosufloxacin (all rINNs).

Fluoroquinolones are administered by several routes (5). The duration of therapy can vary from a single dose to

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several weeks or months. Owing to their adverse effects (including severe anaphylaxis, QT interval prolongation, and potential cardiotoxicity), several fluoroquinolones have had to be withdrawn (for example temafloxacin and grepafloxacin) or strictly limited in their use (for example trovafloxacin) after marketing (6). A serious idiosyncratic reaction profile may be related to the immunologically reactive 1-difluorophenyl substituent that characterizes temafloxacin, trovafloxacin, and tosufloxacin (1).

Withdrawal of fluoroquinolones

Owing to adverse effects (including severe anaphylaxis, QT interval prolongation, and potential cardiotoxicity), several fluoroquinolones have had to be withdrawn (for example temafloxacin and grepafloxacin) or strictly limited in their uses (for example trovafloxacin) after marketing. A serious idiosyncratic reaction profile is possibly related to the immunologically reactive 1-difluorophenyl substituent that characterizes temafloxacin, tosufloxacin, and trovafloxacin (7).

The withdrawal of temafloxacin in 1992, only 6 months after its introduction, followed the observation of serious adverse events that were labeled the "temafloxacin syndrome" (8). Adverse effects, including hemolysis, renal dysfunction, coagulopathy, and hepatic dysfunction, were estimated to occur in one in 3500 patients. For comparison, incidence rates for these adverse events were about one in 17 000 patients treated with ciprofloxacin and one in 33 000 patients treated with ofloxacin.

In 1999 trovafloxacin was withdrawn after reports of lethal hepatic damage. Before this development, several studies had been published describing impressive clinical efficacy coupled with an almost flawless safety profile (9,10).

Grepafloxacin was withdrawn from the market in 1999 because of its adverse cardiovascular events, which included dysrhythmias (11).

Clinafloxacin has been withdrawn because of phototoxicity and hypoglycemia and sparfloxacin because of phototoxicity (12).

These experiences demonstrate the need to be vigilant about any untoward events associated with large-scale use of new fluoroquinolones.

Comparative studies

In a crossover, randomized study, 16 fasted volunteers (8 men, 8 women) took single oral doses of gemifloxacin 320 mg and ofloxacin 400 mg on two separate occasions, in order to assess urinary excretion (13). Urine concentrations of ofloxacin were higher than those of gemifloxacin. There were no adverse effects.

General adverse effects

In spite of widely publicized negative experiences, most fluoroquinolones are safe, and adverse events are, compared with other groups of antimicrobial agents, relatively rare (14). The rates of overall adverse events were similar in several comparisons of individual quinolones among themselves or with other antimicrobial agents. In one multicenter, double-blind, randomized study drug-related adverse events were reported by 8.9% of those taking levofloxacin and 8.2% of those taking ciprofloxacin for 7–10 days (15). A meta-analysis of data from 20 phase II and III studies in 4926 patients treated with moxifloxacin showed that adverse events led to withdrawal of treatment in 3.8% of patients (16). In a comparison of grepafloxacin and ciprofloxacin for exacerbations of chronic bronchitis withdrawal was precipitated by adverse events in 3% of 624 patients; there was no difference between ciprofloxacin and grepafloxacin (17). The most frequent causes of withdrawal were nausea, vomiting, dysgeusia, dizziness, and diarrhea. In smaller studies, adverse events are occasionally observed more often. In a prospective, double-blind comparison of ciprofloxacin, ofloxacin, and co-trimoxazole for short-course treatment of acute urinary tract infections, there were drug-related adverse events in 26% of patients treated with ciprofloxacin and 34% of patients treated with ofloxacin (18).

If analysis of the frequency of adverse events is based on prescription event monitoring (PEM), the rates of adverse events are usually substantially lower. In one study, over 11 000 patients taking each antibiotic were monitored (19). Among the fluoroquinolones, ciprofloxacin, norfloxacin, and ofloxacin were used. Adverse events resulted in withdrawal of norfloxacin or ofloxacin in under 1% of patients (19).

The main systems affected by adverse effects of the quinolones are the skin, liver, and nervous system. The best-known adverse effect is phototoxicity, the risk of which varies markedly among the quinolones; lomefloxacin and sparfloxacin carry a particularly high risk. The development of phototoxicity is based on an interaction between light and the drug. Neurotoxicity also occurs, with marked variation of incidence between the various compounds. Hypersensitivity reactions to quinolones are rare, and include anaphylactic shock and anaphylactoid reactions. Organ-specific reactions attributed to hypersensitivity involve the liver and kidneys. If hypersensitivity reactions occur, switching from one quinolone compound to another is probably not advisable, since there is cross-reactivity.

The risk of neoplastic disease is minimal, even during long-term use, but may be increased by exposure to UVA light.

Using electron spin resonance spectroscopy and spin trapping, ciprofloxacin has been shown to cause free radical production in a dose- and time-dependent manner; the authors suggested that this effect may contribute to drug-related adverse effects, including phototoxicity and cartilage defects (20).

The most common drug interactions include malabsorption interactions associated with multivalent cations and CYP450 interactions (21).

Pharmacoeconomics

The pharmacoeconomic impact of adverse effects of antimicrobial drugs is enormous. Antibacterial drug reactions account for about 25% of adverse drug reactions. The adverse effects profile of an antimicrobial agent can contribute significantly to its overall direct costs (monitoring costs, prolonged hospitalization due to complications or treatment failures) and indirect costs (quality of life, loss of productivity, time spent by families and patients receiving medical care). In one study an adverse event in a hospitalized patient was associated on average with an excess of 1.9 days in the length of stay, extra costs of $US2262 (1990–93 values), and an almost two-fold increase in the risk of death. In the outpatient setting, adverse drug

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reactions result in 2–6% of hospitalizations, and most of them were thought to be avoidable if appropriate interventions had been taken. In a review, economic aspects of antibacterial therapy with fluoroquinolones have been summarized and critically evaluated (22).

Organs and Systems

Cardiovascular

Some quinolones can prolong the QT interval, with a risk of cardiac dysrhythmias. In an in vitro study in isolated canine cardiac Purkinje fibers the rank order of potency in prolonging action potential duration was sparfloxacin > grepafloxacin = moxifloxacin > ciprofloxacin (23). In guinea-pig ventricular myocardium sparfloxacin prolonged the action potential duration by about 8% at 10 μmol/l and 41% at 100 μmol/l (24). Gatifloxacin, grepafloxacin, and moxifloxacin were less potent, but prolonged the action potential duration at 100 μmol/l by about 13%, 24%, and 25% respectively. In contrast, ciprofloxacin, gemifloxacin, levofloxacin, sitafloxacin, tosufloxacin, and trovafloxacin had little or no effect on the action potential at concentrations as high as 100 μmol/l.

Preclinical and clinical trial data and data from phase IV studies have shown that levofloxacin, moxifloxacin, and gatifloxacin cause prolongation of the QT interval, but that the potential for torsade de pointes is rare and is influenced by several independent variables (for example concurrent administration of class Ia and III antidysrhythmic agents) (25). There is a moderate increase in the QT interval associated with sparfloxacin, averaging 3%, and the few serious adverse cardiovascular events that have been reported during postmarketing surveillance all occurred in patients with underlying heart disease (26).

In patients taking quinolones (ciprofloxacin 11 477, enoxacin 2790, ofloxacin 11 033, and norfloxacin 11 110; mean ages 49–57 years) there was no evidence of drug-induced dysrhythmias associated with enoxacin within 42 days of drug administration (27). Of the other quinolones, atrial fibrillation was reported most often within 42 days of ciprofloxacin administration, with no change in event rate over that time. The crude rate of palpitation did not change significantly with ciprofloxacin, norfloxacin, or ofloxacin. Syncope and tachycardia were also reported with ciprofloxacin and ofloxacin. There was no evidence of drug-induced hepatic dysfunction within 42 days of drug administration with any of the quinolones used.

In a retrospective database analysis 25 cases of torsade de pointes associated with ciprofloxacin ($n = 2$), ofloxacin ($n = 2$), levofloxacin ($n = 13$), and gatifloxacin ($n = 8$) were identified in the USA (28). Ciprofloxacin was associated with a significantly lower rate of torsade de pointes (0.3 cases/10 million prescriptions) than levofloxacin (5.4/10 million) or gatifloxacin (27/10 million). When the analysis was limited to the first 16 months after initial approval of the drug, the rates for levofloxacin (16/10 million) and gatifloxacin (27/10 million) were similar.

Nervous system

The main central nervous system adverse effects of the fluoroquinolones include dizziness, convulsions, psychosis, and insomnia; levofloxacin, moxifloxacin, and ofloxacin are reportedly least likely to cause these effects, based on a study of European and international data from about 130 million prescriptions (29).

A review has suggested that fluoroquinolone-associated peripheral nervous system events are mild and short-term (30). Among 60 courses of quinolones in 45 patients (levofloxacin 33 courses, ciprofloxacin 11 courses, ofloxacin 6 courses, lomefloxacin 1 course, trovafloxacin 1 course; in eight cases the same antibiotic was prescribed twice) there were 36 severe events that typically involved multiple organ systems. The symptoms lasted more than 3 months in 71% of cases and more than 1 year in 58%. The onset of the adverse events in the 45 patients was usually rapid: 15 events began within 24 hours of the start of treatment, 26 within 72 hours, and 38 within 1 week.

Dizziness is not rare in patients taking fluoroquinolones, and was observed in 2.8% of patients taking moxifloxacin (16), in 8 and 9% of patients taking grepafloxacin 400 mg/day and 600 mg/day, and in 6% of patients taking ciprofloxacin (17). Prescription event monitoring found markedly lower rates of this adverse event during treatment with ciprofloxacin, norfloxacin, or ofloxacin (19).

Headache was recorded in 8% of patients taking ciprofloxacin and 9% taking ofloxacin during short-course treatment of urinary tract infections (18). Similar rates are reported for grepafloxacin (17).

In two patients with myasthenia gravis, ciprofloxacin and norfloxacin exacerbated the symptoms (31).

Encephalopathy with unconsciousness has been reported in a 48-year-old woman with Machado–Joseph disease after the administration of fleroxacin (200 mg/day) for 3 days (32). She recovered after withdrawal. The serum and cerebrospinal fluid concentrations of fleroxacin were within normal limits.

Seizures

Quinolone antibiotics vary in their ability to cause seizures. Trovafloxacin has the greatest potential and levofloxacin possibly the least. Ciprofloxacin can cause confusion and general seizures (33,34). Seizures also occurred in patients taking ofloxacin (35) and levofloxacin (34). However, this must be rare, since there have only been isolated case reports.

Among over 30 000 patients treated with ciprofloxacin, norfloxacin, or ofloxacin, no seizures were detected during prescription event monitoring (19). The risk of seizures during treatment with individual quinolones is currently unknown. Electrophysiological field potentials in animals are affected to varying degrees by different quinolones; the smallest effect was observed with ofloxacin, followed by ciprofloxacin and nalidixic acid, whereas there was an increasing excitatory effect with clinafloxacin, enoxacin, fleroxacin, lomefloxacin, moxifloxacin, and trovafloxacin (36). The pathophysiological basis for the triggering of seizures probably lies in the binding of fluoroquinolones to $GABA_A$ receptors in the brain, blocking the natural ligand GABA; this results in nervous system stimulation (37). Binding to this receptor is strongly influenced by the side chain in the 7-position; quinolones with bulky moieties, such as temafloxacin and sparfloxacin, bind less efficiently to GABA receptors.

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Sensory systems

Taste

Dysgeusia is reported with many quinolones. This was observed more often with higher doses of grepafloxacin (600 mg/day; 17%) than with lower doses (400 mg/day; 9%) (38). In another study there was a similar dose–response relation: 13% of patients taking 400 mg/day and 27% of those taking 600 mg/day (17).

In 135 unmedicated young volunteers, 13 elderly volunteers and 14 unmedicated HIV-infected patients, enoxacin applied to the tongue was described as metallic by young subjects, but bitter by elderly subjects; lefloxacin and ofloxacin were described as bitter (39).

Psychological, psychiatric

Isolated cases of depression (18) and psychosis have been described in temporal association with fluoroquinolones (40).

Hematologic

In over 33 000 patients treated with ciprofloxacin, norfloxacin, or ofloxacin, no case of hemolytic anemia was discovered by prescription event monitoring (19). However, ciprofloxacin has been associated with hemolysis in combination with a severe skin reaction in a young adult (41).

Leukopenia has been observed in 0.1–0.7% of patients given fluoroquinolones in Japan and eosinophilia was observed in 0.5–2.2% of these patients (42). Leukopenia was generally mild and reversible after dosage reduction or withdrawal (43,44).

Anemia, thrombocytopenia, and thrombocytosis have only rarely been reported (45–48).

Gastrointestinal

Adverse gastrointestinal events are not uncommon during treatment with fluoroquinolones. There may be some dose-dependency, since with grepafloxacin 600 mg/day the rates of the following adverse events were noticeably higher than with 400 mg/day: nausea (15 versus 11%), vomiting (6 versus 1%), and diarrhea (4 versus 3%) (38). In a randomized, double-blind comparison of prulifloxacin 600 mg/day and ciprofloxacin 500 mg bd in 235 patients with acute exacerbations of chronic bronchitis, the most common treatment-related adverse event was gastric pain of mild or moderate intensity, reported in 8.5% of the patients taking prulifloxacin and 6.8% of those taking ciprofloxacin (49).

Liver

Transient rises in serum transaminase and serum alkaline phosphatase activities have been observed with all fluoroquinolones. This occurred in 0.9–4.3% of patients in Japan. In the vast majority of the cases this alteration was self-limited and reversible without withdrawal of the drug (42).

Urinary tract

In a Medline search to investigate the incidence and features of fluoroquinolone nephrotoxicity only primarily case reports and temporally related events could be identified (50). Ciprofloxacin was associated with an increased risk of renal insufficiency, probably because it has been in use longer and more widely than the newer agents. Raised serum creatinine or blood urea nitrogen concentrations have been observed in 0.1–0.7% of patients (42).

Single cases of reversible, acute non-oliguric or oliguric renal insufficiency, probably due to tubulointerstitial nephritis, have been reported (51,52), as well as isolated cases of hematuria (53). The newer fluoroquinolones have only rarely been associated with nephrotoxicity, with an estimated incidence of 0.4–0.8%.

Rare cases of possibly drug-related crystalluria have been described in patients taking fluoroquinolones (54–56).

Skin

Skin rashes are relatively common with fluoroquinolones. A retrospective cohort study in patients in general practice in the Netherlands focused on the use of antibacterial agents and the occurrence of adverse cutaneous events covered 469 505 consultations with 87 475 patients, of whom 13 679 received prescriptions for antibiotics (57). After adjustment for age, sex, and co-medications, the incidence density ratio (incidence density per 1000 exposed days) for various groups of antibacterial agents was as follows: tetracyclines 1.0, macrolides 1.1, fluoroquinolones 2.8, penicillins 2.9, and cotrimoxazole 4.4 (57). No details of the types of skin reactions were given, and it is therefore possible that phototoxic events were included. Compared with other studies, the reported rate of antibiotic-associated adverse cutaneous events in this outpatient population was rather low.

Exposure to light causes photosensitivity reactions in patients taking quinolones and fluoroquinolones. In guinea-pigs the phototoxic potencies were: enoxacin, lomefloxacin > ofloxacin > nalidixic acid, tosufloxacin > norfloxacin, ciprofloxacin (58). Photosensitivity reactions to ofloxacin may be initiated by oxygen radicals and/or by ofloxacin radicals acting as haptens (59). In a mouse model pefloxacin and ciprofloxacin augmented the effect of ultraviolet A by increasing sunburn and apoptosis, depleting Langerhans cells, and suppressing local immune responses (60).

A combination of primary ear swelling analysis and cell counting of ear-draining lymph nodes after UV irradiation in mice was fast and highly predictive of the risks of photosensitization and photoirritancy of fluoroquinolones, depending on the route of exposure (oral or dermal) and may therefore be good tools for preclinical risk assessment in terms of discriminating photoreactions (61).

Tosufloxacin has been associated with a fixed drug eruption (62).

In a phase III, randomized, investigator-blinded comparison of the safety and efficacy of clinafloxacin with those of piperacillin/tazobactam in the treatment of adults with severe skin and soft-tissue infections, four of 84 patients randomized to clinafloxacin developed phototoxicity (63).

Photosensitivity

Photosensitivity is a common adverse effect of the fluoroquinolones. It results from an abnormal reaction of the skin to natural or artificial light sources, usually associated with the UVA part of the electromagnetic spectrum (315–400 nm), mediated by the absorption of light energy into fluoroquinolones, followed by degradation of the molecule and formation of cytotoxic photoproducts (64).

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The chemical structure at position 8 in the quinolone ring probably determines the phototoxic potential, since the introduction of a methoxy group at this position markedly reduces the phototoxicity of individual drugs (65).

The early fluoroquinolones, that is ciprofloxacin, norfloxacin, and ofloxacin, are mild photosensitizers (66–70). Clinically relevant photosensitivity was generally only observed when high dosages were used and the patient was exposed to large amounts of sunlight. The phototoxic potential of lomefloxacin, sparfloxacin, and fleroxacin is far greater than that of earlier compounds (71–76). However, even with fluoroquinolones that are reported to have a relatively high rate of phototoxicity, the incidence is low. In a Japanese study of 4276 patients, photosensitivity was found in 44 (1.03%) and was typically not severe (77). Patients with co-morbidity or those over 60 years were at higher risk. The risk may be further increased by a long duration of treatment.

The photosensitizing effect of grepafloxacin is relatively weak and similar to that of ciprofloxacin (38). In one study, one of 207 patients taking grepafloxacin 400 mg/day and six of 204 taking 600 mg/day developed phototoxicity (17). Moxifloxacin is not phototoxic (78). Data obtained in albino mice have suggested that the phototoxic potential of sitafloxacin is milder than that of lomefloxacin or sparfloxacin (79).

Musculoskeletal

Tendinopathy

Tendinopathy and partial or complete tendon rupture as adverse events of fluoroquinolones have been reported during or shortly after the use of fluoroquinolones (80–84). Pefloxacin and ofloxacin have been implicated, as has ciprofloxacin (85,86). In six patients taking fluoroquinolones risk factors included renal insufficiency, glucocorticoid therapy, secondary hyperparathyroidism, advanced age, and diabetes mellitus (87). Cases have also been reported among immunocompromised renal transplant recipients (88).

In 42 spontaneous reports of fluoroquinolone-associated tendon disorders, 32 patients had tendinitis, 24 bilaterally, and 10 had a tendon rupture; most affected the Achilles tendon (89). The median age was 68 years and there was a male predominance. In 16 cases ofloxacin was implicated, in 13 ciprofloxacin, in eight norfloxacin, and in five pefloxacin. The delay between the start of treatment and the appearance of the first symptoms was 1–510 (median 6) days. Most patients recovered within 2 months after withdrawal, but 26% had not yet recovered at follow-up.

In a retrospective analysis, quinolone arthropathy developed during the first 3 weeks, and depended on the patient's age and history (90). It resolved fully within 7 days to 3 months after drug withdrawal.

In a study of fibroblast metabolism in vitro, ciprofloxacin stimulated matrix-degrading protease activity and inhibited fibroblast metabolism; these effects may both contribute to the tendinopathy that is associated with fluoroquinolones (91).

Animal studies show that the propensity to induce tendon lesions varies among fluoroquinolones. Fleroxacin, pefloxacin, levofloxacin, and ofloxacin were the most toxic, while enoxacin, norfloxacin, and ciprofloxacin had little or no effect (92). The structure of the substituent at position 7 seems to be a determining factor. Quinolones with toxic effects in animals share a methylpiperadinyl substituent at the position 7 of the fluoroquinolone core structure, while this position is occupied by a piperadinyl substituent in ciprofloxacin, norfloxacin, and enoxacin (92). It is recommended that quinolones be discontinued at the first sign of tendon pain or inflammation and that the patient should not exercise until the diagnosis of tendonitis can be confidently excluded.

In rodents, pefloxacin (400 mg/kg for several days) caused oxidative damage to the type I collagen in the Achilles tendon; these alterations were identical to those observed in experimental tendinous ischemia and a reperfusion model (93). Oxidative damage was prevented by the co-administration of *N*-acetylcysteine (150 mg/kg).

Arthropathy

Arthropathy has been reported with various fluoroquinolones, particularly in children. In a Russian study in children with cystic fibrosis five were withdrawn (four taking ciprofloxacin and one taking pefloxacin) (94). Two had an arthropathy that was drug- and age-dependent. Quinolone-induced arthropathy was more common with pefloxacin and occurred only in children over 10 years old with a history of joint problems. The arthropathy fully recovered within 7 days to 3 months and there was no cartilage damage.

In Wistar rats treated with ciprofloxacin, there was poor healing of experimental fractures during the early stages of repair, suggesting that fluoroquinolones may compromise the clinical course of fracture healing (95).

Sexual function

In a large study vaginitis and vulvitis were detected by prescription event monitoring in a significantly higher proportion of women taking fluoroquinolones than women taking azithromycin or cefixime (19).

Immunologic

Fluoroquinolones have immunomodulatory effects, at least partly at the gene transcription level, demonstrated by inhibition of cytokine (IL-1α, TNF-α, IL-6, and IL-8) mRNA and cytokine (IL-1α and IL-1β) concentrations by grepafloxacin (1–30 mg/l) in vitro (96).

Anaphylactic shock associated with cinoxacin was reported in three patients by the Netherlands Center for Monitoring of Adverse Reactions to Drugs (97). Another 17 cases were reported to the WHO Collaborating Center for International Drug Monitoring. In some cases the reaction was observed immediately after the first dose of a repeat cycle of treatment. Anaphylactoid reactions to ciprofloxacin have been reported in patients with cystic fibrosis (98–100).

Organ-specific reactions attributed to hypersensitivity involve the liver and kidneys. In one instance centrilobular hepatic necrosis developed during treatment of a urinary tract infection with ciprofloxacin (101). Among 14 cases of drug-induced allergic nephritis, two were associated with quinolones (102). Isolated case reports of allergic nephropathy associated with norfloxacin and ciprofloxacin therapy suggest that this type of reaction is probably very rare (103), since the authors were able to find only 28 other reported cases. If hypersensitivity reactions occur, switching from one quinolone compound to

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another is probably not advisable, since oral provocation using different agents reproduced the initially observed hypersensitivity reaction (104). This clinical observation is supported by the results of in vitro lymphocyte transformation tests, which were positive with ofloxacin in two patients with allergy to ciprofloxacin (105).

Infection risk

Ciprofloxacin, norfloxacin, and ofloxacin increased gastrointestinal colonization by *Candida albicans* in 17 patients (106). Ciprofloxacin caused the largest increase, but the difference was not statistically significant.

In a retrospective cohort study of patients hospitalized in a Canadian teaching hospital during January 2003 to June 2004 there were 7421 episodes of care in 5619 patients, who were observed until they developed *Clostridium difficile*-associated diarrhea, or died, or for 60 days after discharge (107). Fluoroquinolones were the antibiotics that were most strongly associated with *Clostridium difficile*-associated diarrhea (adjusted hazard ratio = 3.44; 95% CI = 2.65, 4.47). Almost one-quarter of all in-patients received quinolones, for which the population-attributable fraction of *Clostridium difficile*-associated diarrhea was 36%. All three generations of cephalosporins, macrolides, clindamycin, and intravenous beta-lactam/beta-lactamase inhibitors were intermediate-risk antibiotics, with similar hazard ratios (1.56–1.89).

Long-Term Effects

Drug tolerance

To study the impact on the normal intestinal microflora, gatifloxacin was given to 18 healthy volunteers (400 mg/day orally). In the aerobic intestinal microflora *E. coli* strains were eliminated or strongly suppressed and the number of enterococci fell significantly, while the number of staphylococci increased. In the anerobic microflora the numbers of *Clostridia* and fusobacteria fell significantly. The microflora normalized 40 days after the gatifloxacin withdrawal. No selection or overgrowth of resistant bacterial strains or yeasts occurred (108).

Salmonella typhimurium DT104 is usually resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An outbreak of 25 culture-confirmed cases of multidrug-resistant *Salmonella typhimurium* DT104 has been identified in Denmark. The strain was resistant to the abovementioned antibiotics and nalidixic acid and had reduced susceptibility to fluoroquinolones. A swineherd was identified as the primary source (109). The DT104 strain was also found in cases of salmonellosis in Washington State, and soft cheese made with unpasteurized milk was identified as an important vehicle of its transmission (110).

From 8419 worldwide clinical isolates of *Streptococcus pneumoniae* associated with lower respiratory tract or blood infections obtained from 519 geographically distinct hospital laboratories during 1997–98, 69 had reduced susceptibility or resistance to fluoroquinolones. Only mutations in parC and gyrA (especially in combination), but not in gyrB or parE, contributed significantly to resistance. Efflux is probably crucial in reduced susceptibility for new hydrophilic fluoroquinolones (111).

In an in vitro study, ciprofloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, and sparfloxacin had similar good activity against *Haemophilus influenzae* and *Moraxella catarrhalis* (112). Against *S. pneumoniae* (irrespective of the strain's susceptibility to penicillin), grepafloxacin, levofloxacin, moxifloxacin, and sparfloxacin had better activity than ciprofloxacin and ofloxacin.

Clinafloxacin, moxifloxacin, sparfloxacin, and trovafloxacin were significantly more active in vitro than ciprofloxacin and levofloxacin against *Stenotrophomonas maltophilia*, a microorganism with inherent resistance to many antibiotics; new-generation quinolones may become very useful in the treatment of certain severe or life-threatening infectious conditions due to this bacterium (113).

In over 90 000 routine samples of *Escherichia coli* in five Dutch laboratories during 1989–98 resistance to norfloxacin increased from 1.3% to 5.8% (114). In addition, multiresistance, defined as resistance to norfloxacin and at least two other antibiotics (from a group consisting of amoxicillin, trimethoprim, and nitrofurantoin), increased from 0.5% to 4.0%.

Mutagenicity

In vitro lomefloxacin photochemically produced oxidative DNA damage, an effect known to be of mutagenic potential (115). This may be the basis of the photochemical mutagenicity and photochemical carcinogenicity of quinolones.

Tumorigenicity

Results of carcinogenicity studies have suggested that the risk of neoplastic disease is minimal, even during long-term use (116). However, the risk may be increased by exposure to UVA light. Skin tumors, only a minority of them malignant, developed in mice after treatment with various quinolones for up to 78 weeks and exposure to UV light. It therefore appears that fluoroquinolones have the potential to enhance the UVA-induced phototumorigenic effect (117).

Second-Generation Effects

Teratogenicity

Possible adverse outcomes were investigated in the newborns of 38 mothers who had received quinolones during pregnancy between 1989 and 1992. The majority (35 women) took norfloxacin or ciprofloxacin for urinary tract infections during the first trimester of pregnancy. There were no malformations in the quinolone group, whereas one child in the control group had a ventricular septal defect. There were no differences between the groups in the achievement of developmental milestones or in the musculoskeletal system (118). However, the authors of the study pointed out that the duration of follow-up may have been too short to draw firm conclusions regarding the safety of quinolones during pregnancy. In addition, the size of the study population was probably inadequate for statistically meaningful comparisons.

Treatment with fluoroquinolones during embryogenesis was not associated with an increased risk of major

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malformations in a multicenter, prospective, controlled trial in 400 women (119). There was a higher rate of therapeutic abortions in quinolone-exposed women. This may have been explained by the misperception of a major risk related to quinolones during pregnancy.

In pregnant rats fed with norfloxacin, there was DNA fragmentation in fetal tissues (14). Even though this effect was attributed to general toxicity rather than genotoxicity, quinolones should be avoided during pregnancy (120).

Lactation

Given the potential for untoward effects on the cartilage of breast-feeding infants, fluoroquinolones should be avoided by nursing mothers.

Susceptibility Factors

Genetic factors

The pharmacokinetics of fleroxacin (200 mg intravenously or 200 mg orally) have been studied in 19 Nigerian men. C_{max} and AUC were 3–4 fold lower than previously reported after identical doses, but systemic availability profile was as previously reported (121).

Age

Children

The use of fluoroquinolones in children is controversial. Fluoroquinolones have greatly facilitated the management of exacerbations of pulmonary infections in cystic fibrosis. Apart from this indication, they have rarely been used in children for other indications, such as urinary tract infection, prophylaxis in neutropenia, gastrointestinal infections, and nervous system infections (122). Thorough reviews of published experience suggest that fluoroquinolones can be used without increased risks of short-term or long-term adverse events. A study of adverse events within 45 days of receiving a prescription for ciprofloxacin was remarkable for the fact that among over 1700 children, no cases of newly diagnosed acute arthritis or other serious disturbances of liver or kidney function were recorded (123). One patient with hemolytic–uremic syndrome had an exacerbation that was possibly caused by ciprofloxacin.

Renal disease

Based on their predominant renal elimination, dosage adjustment is necessary in the presence of renal disease for ciprofloxacin, gatifloxacin, levofloxacin, and sitafloxacin (124).

Hepatic disease

The penetration of routinely used fluoroquinolones into ascitic fluid after intravenous administration has been studied in patients with uncompensated hepatic cirrhosis (125). Three patients received three doses of ciprofloxacin 200 mg, six received three doses of ciprofloxacin 300 mg, seven received three doses of pefloxacin 400 mg, and six received three doses of ofloxacin 400 mg. Pefloxacin and ofloxacin produced serum and ascitic fluid concentrations above the MICs of the common pathogens that cause spontaneous bacterial peritonitis, and the authors concluded that they could be given to cirrhotic patients in dosage regimens similar to those in patients with normal hepatic function.

Other features of the patient

Given the well-described risk of phototoxicity associated with fluoroquinolones, sunlight and direct exposure to the sun are risk factors. Patients therefore need to be instructed about protective measures.

In patients with leg ischemia fleroxacin diffused into both ischemic and non-ischemic tissues (bone, subcutaneous fat, muscle, and tendons) after a 400 mg intravenous dose (126). Since the maximum antibiotic concentrations were lower than the MICs of various relevant pathogens, the dose used for perioperative prophylaxis in these patients should be increased to 800 mg.

Drug–Drug Interactions

Antacids

Concurrent treatment with antacids reduces the oral absorption of many quinolones, such as ciprofloxacin and enoxacin (127), moxifloxacin (16), norfloxacin (128), ofloxacin (129), and sparfloxacin (130).

Caffeine

CYP1A2 participates in the metabolism of both enoxacin and caffeine, and inhibition of caffeine metabolism by enoxacin can cause adverse effects (131).

In 24 healthy volunteers, 12 men and 12 women, the women had significantly different caffeine pharmacokinetics in the presence of ciprofloxacin and fleroxacin compared with the men (132). There were also significant differences between the sexes in the pharmacokinetics of ciprofloxacin and fleroxacin in the presence of caffeine. The differences were in part due to different body weights.

Clinafloxacin 200 or 400 mg reduced the mean clearance of caffeine by 84% (133).

Cimetidine

Cimetidine reduces the metabolic clearance of both enoxacin and pefloxacin by about 20% (134,135).

Digoxin

The pharmacokinetics of digoxin were not altered by sparfloxacin (136).

Drugs that prolong the QT interval

In order to prevent any untoward effect on cardiac repolarization, agents that prolong the QT interval, such as terfenadine, astemizole, erythromycin, and agents with Class Ia and Class III antidysrhythmic activity, should not be used together with sparfloxacin (137).

Furosemide

The renal excretion of lomefloxacin and ofloxacin was reduced and plasma concentrations increased by furosemide, resulting in higher concentrations (138).

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Iron

All of the fluoroquinolones interact with polyvalent cations, and their systematic availability is reduced by 50% when they are co-administered with iron compounds; ciprofloxacin and moxifloxacin (16) are more affected than gemifloxacin or levofloxacin (139).

Ferrous salts reduce the systemic availability of fluoroquinolones (127), including sparfloxacin (140).

NSAIDs

Co-administration of fenbufen and fluoroquinolones has been associated with seizures (141). The structure at the 7-position greatly affects the risk of NSAID-potentiated nervous system effects. Fluoroquinolones with unsubstituted piperazinyl rings (ciprofloxacin, enoxacin, and norfloxacin) have a strong interaction with NSAIDs (142). The increased risk of seizures is not caused by increased serum concentrations of fluoroquinolones, since their pharmacokinetics are not altered by NSAIDs (143). The mechanism has been suggested to be facilitation by fenbufen of the fluoroquinolone-induced inhibition of $GABA_A$ receptor function in the hippocampus and frontal cortex (144).

Probenecid

Probenecid increases the serum concentrations of cinoxacin (145), enoxacin (146), and nalidixic acid (147) probably by inhibiting their renal tubular secretion.

Sucralfate

Sucralfate markedly reduces the systemic availability of fluoroquinolones (127,148,149).

Theophylline

Fluoroquinolones are potent inhibitors of hepatic cytochrome P450 isozymes (150). They inhibit theophylline metabolism, and accumulation of theophylline has led to seizures (151). Theophylline clearance is reduced by about 10% by norfloxacin, 30% by ciprofloxacin, and 70% by enoxacin (152–162). In a comparison of grepafloxacin (400 and 600 mg/day) and ciprofloxacin, increased theophylline concentrations associated with clinical symptoms were found with both doses of grepafloxacin but not in patients taking ciprofloxacin (17). The dosage of theophylline should be reduced when a quinolone is given.

No interaction has been reported with levofloxacin (139) or sparfloxacin (137,161).

Warfarin

The anticoagulant effect of warfarin was altered by ciprofloxacin (162) but not by sparfloxacin (149) or moxifloxacin (16).

Interference with Diagnostic Tests

Opioid immunoassays

The reactivity of 13 quinolones and fluoroquinolones (ciprofloxacin, clinafloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, pefloxacin, sparfloxacin, and trovafloxacin) with five commercial opiate immunoassays has been tested in vitro and in three healthy volunteers (163). In vitro, levofloxacin and ofloxacin (using Abbott AxSYM, CEDIA, EMIT II, and Roche OnLine assays), pefloxacin (using CEDIA, EMIT II, and Roche OnLine assays), enoxacin (using CEDIA and EMIT II assays), gatifloxacin (using EMIT II assay), and ciprofloxacin, lomefloxacin, moxifloxacin, and norfloxacin (using Roche OnLine assay) cross-reacted and cause a positive test result for opiates. Clinafloxacin, nalidixic acid, sparfloxacin, and trovafloxacin did not cross-react in any of the assays. A single dose of levofloxacin 500 mg caused a false-positive test result using the EMIT II assay within 2 hours for as long as 22 hours in all three volunteers. Ofloxacin (a single dose of 400 mg) produced a similar pattern. Detectable opiate activity in the urine was seen for more than 30 hours with both levofloxacin and ofloxacin.

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Fluorouracil

See also Cytostatic and immunosuppressant drugs

General Information

Fluorouracil is a fluorinated pyrimidine, which is converted intracellularly to the active form, fluorodeoxyuridine monophosphate, which inhibits thymidylate synthetase and hence reduces the production of thymidylic acid, the deoxyribonucleotide of thymine (5-methyluracil), a DNA pyrimidine base, blocking DNA synthesis. In addition, intracellular conversion to 5-fluorouridine monophosphate results in incorporation of the activated antimetabolite into RNA and consequent RNA dysfunction.

Fluorouracil is specific to the S phase of the cell cycle. It is primarily used intravenously to treat carcinoma of the breast and adenocarcinomas of the gastrointestinal tract (1). In addition, topical fluorouracil is used to treat actinic keratoses.

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General adverse effects

The dose-limiting toxic effects of fluorouracil vary with the dose and mode of administration.

- With five consecutive daily bolus injections of 450–600 mg/m^2, the dose-limiting effects are myelosuppression, mucositis, and diarrhea.
- With weekly injections of 450–600 mg/m^2, myelosuppression is dose-limiting.
- With continuous five-day infusion of 1000 mg/m^2/day, mucositis and diarrhea are dose-limiting.
- With protracted continuous infusion of 200–400 mg/m^2/day, mucositis and palmar–plantar erythrodysesthesia syndrome are the most common dose-limiting adverse effects (2).

Some very high-dose, short-exposure studies have been reported, including 14 g over 24 hours (3) and 2.6 g/m^2 weekly (4); in the latter study, neurotoxicity was dose-limiting; with 24-hour infusion of 2.6 g/m^2 weekly, palmar–plantar erythrodysesthesia syndrome is a major adverse effect.

Relation of toxicity to pharmacokinetics

The pharmacokinetics of fluorouracil have been determined in 19 patients receiving fluorouracil by protracted intravenous infusion of 190–600 mg/m^2/day (5). The steady-state fluorouracil plasma concentration and AUC were significantly lower in the nine patients who had WHO grade 2 toxicity or less compared with the nine patients who had greater than grade 2 toxicity. In contrast, there was no difference in fluorouracil plasma concentrations between the 10 responders and the nine patients who had no evidence of a clinical response. These investigations confirm previous observations that correlations can be drawn between fluorouracil pharmacokinetics and clinical toxicity (6). Furthermore, the data suggest that pharmacokinetic monitoring might permit identification of patients at increased risk of toxicity.

Organs and Systems

Cardiovascular

Fluorouracil can cause anginal chest pain, with non-specific ST–T electrocardiographic changes, during infusion (7). The outcome is favourable if the drug is withdrawn. Re-introduction of the drug has been associated with occasional fatal outcomes and is not recommended (8). The cardiotoxicity of 5-fluorouracil in 135 reported cases has been reviewed (9).

Presentation

More frequent use of fluorouracil by continuous infusion, increased awareness of the problems, and more sophisticated monitoring have increased the reported incidence. By 1990, more than 67 clinical cases had been described (10) and an incidence ranging up to 68% of silent ischemic electrocardiographic changes was identified in patients monitored by continuous 24-hour ambulatory electrocardiography during fluorouracil infusion (11). The clinical features include the following:

- Precordial pain (both non-specific and anginal) (10).
- Electrocardiographic ST–T wave changes (non-specific and ischemic) (10,11).
- Acute myocardial infarction (rare) (12,13).
- Atrial dysrhythmias (including atrial fibrillation) and less often, ventricular extra beats (including refractory ventricular tachycardia and fibrillation) (11–13).
- Ventricular dysfunction (usually global, less frequently segmental).
- Cardiac failure, pulmonary edema, and cardiogenic shock (with and without ischemic symptoms) (13–16).
- Sudden death, presumed to be caused by ventricular fibrillation (13,17,18).

In most patients with chest pain, with or without electrocardiographic changes, the creatinine kinase MB fraction remained normal (10,13,15).

Acute dilated cardiomyopathy with left ventricular dysfunction related temporally to fluorouracil and cisplatin infusion, with subsequent complete recovery, has been tentatively linked to fluorouracil (19). Other similar events have been reported (20,21). The association is more striking in patients who receive a continuous infusion of fluorouracil and in patients who receive concomitant cisplatin (22,23). For example, myocardial ischemia and infarction occur in about 10% of patients who receive fluorouracil by infusion and sudden death has occurred (24).

Five cases of paroxysmal atrial fibrillation and sinus bradycardia attributed to fluorouracil have been reported (25).

Acute pulmonary edema leading to lethal cardiogenic shock has been reported with fluorouracil. This occurred despite the fact that the patient had received eight infusions of leucovorin 100 mg/m^2 at weekly intervals (26).

Most often, cardiotoxicity develops during the second or later course of treatment, but some patients have problems during the first course (10). Those who develop cardiac toxicity and recover usually have symptoms again when re-challenged with another infusion (10,13).

Fluorouracil has also been associated with a number of vascular effects, particularly thromboembolic or circulatory in nature (27). Although Raynaud's phenomenon has been reported after cisplatin-based chemotherapy, the first case of digital ischemia and Raynaud's phenomenon has been reported with fluorouracil given in a De Gramond type schedule (28).

Mechanisms and pathophysiology

The mechanisms of fluorouracil cardiotoxicity are not known. Those that have been suggested include:

- direct uncoupling of electromechanical myocardial function at the level of ATP generation (20);
- an immunoallergic reaction following sensitization by a complex of fluorouracil and cardiac cells;
- vasospasm secondary either to fluorouracil or to released products;
- a direct toxic effect of the drug on the myocardium.

Most reports have attributed chest pain to vasospasm (29). Certainly, the ischemic-like pains and electrocardiographic findings, lack of changes in creatine kinase, and frequent responses to nitrates and at times to calcium antagonists in the setting of anatomically normal coronary angiography, plus reversible contractility defects suggest

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coronary vasospasm as a mechanism of fluorouracil cardiotoxicity. However, global dysfunction possibly due to stunned myocardium and the lack of universal response to coronary vasodilators leaves some questions about this hypothesis. Some investigators have postulated myocarditis or myocardiopathy (30–32). In 43 patients it did not interfere with the electrical properties of myocardial fibers (33).

Findings on autopsy and endomyocardial biopsy have shown diffuse, interstitial edema, intracytoplasmic vacuolization of myocytes, and no inflammatory infiltrate (34). Acute myocardial infarction has been demonstrated pathologically in some, but not all, patients with clinical infarction (10).

In patients with fluorouracil cardiotoxicity endothelin plasma concentrations were raised (35).

Susceptibility factors

With regard to susceptibility factors for cardiotoxicity with fluorouracil, there was no effect of age or sex on incidence (10). Symptoms have been reported in a 38-year-old man (16) and in several women in their forties (10,14) with no prior cardiac history. Cardiac findings have occurred when fluorouracil was given by infusion or bolus as a single agent or with cisplatin and other drugs (10,21). Although some felt that cardiac irradiation and pre-existing heart disease were susceptibility factors (11,36), others did not (10,37). Several investigators have documented normal coronary arteries in patients with severe symptoms (13,14).

Frequency

The cardiotoxicity of fluorouracil was first identified in 1975 (38). Of 140 patients treated with intravenous 5-fluorouracil, 4 developed ischemic chest pain within 18 hours of either the second or third dose. In three of these patients the pain recurred after subsequent doses. Predose electrocardiograms in two cases were normal. None of the four patients had a history of ischemic heart disease, although all had received left ventricular irradiation (39).

A 5% incidence of cardiotoxicity-complicating high-dose infusion of fluorouracil 1000 mg/m^2/day for 4 days has been reported and correlated with plasma fluorouracil concentrations in excess of 450 mg/ml (40).

In 910 patients toxicity was life-threatening in 0.55% (41). A combination of cisplatin, fluorouracil, and etoposide given for advanced non-small cell cancer of the lung caused only the expected amount of hematological toxicity, but was associated with a higher than expected incidence of cardiac, pulmonary, and cerebrovascular toxicity, including two myocardial infarctions, two cases of congestive heart failure, one pulmonary embolus, and one cerebrovascular accident in a study of 35 patients (42).

In 1083 patients there was cardiotoxicity in 1.1% of all patients and in 4.6% of patients with prior evidence of heart disease (36).

Management

Some investigators have reported success in preventing cardiotoxicity with calcium antagonists, such as nifedipine and diltiazem (29), while others had less success (15,43). Two patients with proven fluorouracil cardiotoxicity did not have cardiotoxicity when treated with the specific thymidylate synthase inhibitor raltitrexed 3 mg/m^2 every 3 weeks (44). The authors commented that fluorouracil cardiotoxicity is therefore not mediated via thymidylate synthase.

In most cases, fluorouracil-induced dysrhythmias were treatable and the ischemic-like symptoms and electrocardiographic changes disappeared if the infusion was discontinued or responded to nitrates, allowing the infusion to continue. The abnormalities of segmental and global ventricular function reverted to normal within days to weeks of withdrawal. In some patients intravenous inotropic and vasodilator support was needed during the initial period (14–16,19).

However, in one case, both oral nitrates and calcium antagonists failed to prevent chest pain associated with 5-fluorouracil (45).

- About 48 hours after starting her first course of 5-fluorouracil (1000 mg/m^2/day) a woman developed anginal chest pain and electrocardiographic changes that eventually normalized. She was readmitted for her second cycle whilst taking amlodipine 10 mg/day and isosorbide dinitrate 40 mg/day, and after 42 hours into the second cycle had the same chest pain and electrocardiographic changes. These were only controlled by withdrawal of the 5-fluorouracil and the intravenous administration of glyceryl trinitrate.

Respiratory

Pulmonary toxicity in the form of fibrosing alveolitis has been attributed to fluorouracil.

- A 55-year-old man with gastric adenocarcinoma received fluorouracil 1 g intravenously each week for 9 weeks and mitomycin 10 mg intravenously every 3 weeks (46). After 12 treatments he developed severe dyspnea.

Although mitomycin C was most likely the agent responsible for pulmonary toxicity in this patient, combined use with fluorouracil as a contributing factor cannot be ruled out. Necropsy confirmed that the patient had interstitial fibrosis (47).

Nervous system

Fluorouracil can cause neurotoxicity (48), with an incidence of 5–15% and with all schedules of administration in common use (49,50). The toxicity is acute in onset and cumulative dose-dependency has not been observed.

Acute cerebellar dysfunction, with gait ataxia, nystagmus, dysmetria, and dysarthria, is the most common form of neurotoxicity (48,49). A rare problem is optic neuropathy and impaired vision (51).

The acute cerebellar syndrome is considered to be associated with peak concentrations of fluorouracil (48,52). Continuous 5-day infusions appear not to cause neurological toxicity, even when the total dose is higher, although high-dose infusions can cause encephalopathy, with symptoms varying from lethargy to coma (53).

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Cerebral demyelination has been reported in a patient receiving fluorouracil and levamisole (54).

Two patients with some of the classic neurological complications of fluorouracil have been reported. One had a cerebellar syndrome in association with global motor weakness and bulbar palsy and the other a bilateral third cranial nerve palsy (55).

Peripheral neuropathy, possibly caused by fluorouracil, has been reported (56).

Five patients developed ischemic stroke within 2–5 days of finishing a 4-day course of fluorouracil plus low-dose cisplatin by continuous infusion (57). Whilst cisplatin has been implicated as having produced central ischemic events, most commonly in combination with vindesine and bleomycin, there has only been one other report involving fluorouracil. Although the causal link was not conclusive, the circumstantial evidence was strong.

The cause of neurotoxicity is not well understood. Acute neurological symptoms, including somnolence, cerebellar ataxia, and upper motor neuron signs, are primarily seen in patients receiving intracarotid infusions for head and neck tumors and also in patients receiving fluorouracil monotherapy in high doses. This syndrome has been reproduced in animals by a neurotoxic metabolite of fluorouracil, fluorocitrate, which has been believed to cause neurotoxicity (52,58). However, several patients have developed severe toxic symptoms due to deficiency of dihydropyrimidine dehydrogenase, the enzyme that is mainly responsible for metabolizing fluorouracil (59). This toxicity appears to be due to the parent compound and not metabolites. Patients with complete or partial deficiency of the enzyme are particularly subject to fluorouracil neurotoxicity.

The neurotoxicity is usually reversible by withdrawing fluorouracil. Since there is no cumulative effect, therapy can be resumed later if desired, usually with either a lower dose or a less frequent dosing schedule to prevent recurrence.

Sensory systems

Fluorouracil-containing regimens have been linked with several ocular adverse effects, including marked lacrimation, ocular pruritus, and a burning sensation in the eyes (60).

Striate melanokeratosis of the retina has been associated with 5-fluorouracil in reports from a number of centers; there has been no consistent explanation of the pathogenesis of this adverse effect (61–63).

Excessive lacrimation and other ocular disturbances have been reported secondary to intravenous fluorouracil (64–66). In a review of this subject, blurred vision, excessive lacrimation, excessive nasal discharge, and conjunctivitis were the most commonly reported ocular effects of fluorouracil (67). The symptoms, eye irritation and excessive tear production, can be aggravated by cold weather. The onset of symptoms varies from 15 minutes to 14 months after the start of treatment (64). The symptoms usually resolve 2–3 weeks after withdrawal of therapy, with or without the use of topical antibiotic-glucocorticoid combinations (64,67).

More severe toxic effects, including tear duct fibrosis and eversion of the lower eye lid, have been reported (64). Tear duct fibrosis develops in one of six patients with excessive lacrimation from fluorouracil (66). The eversion of the lower eyelid is reversible with conservative management (68) while the tear duct fibrosis may not be (69). Persistent lacrimation has been described in six patients receiving intravenous fluorouracil weekly for 6–10 months (69). Lacrimation persisted in five patients after the withdrawal of fluorouracil, suggesting an irreversible dacryostenosis. Lacrimal duct stenosis has also been reported (70). Bilateral cicatricial ectropion was also reported in a patient after topical administration of fluorouracil for the treatment of multiple facial actinic keratoses (71). If ectropion and tear duct stenosis progress, surgical correction may be required.

Three women developed lacrimal outflow obstruction while receiving fluorouracil, cyclophosphamide, and methotrexate for breast cancer (72). The authors commented on both the high incidence of excessive tearing in patients given fluorouracil, a probable precondition, and the rarity of permanent damage (12 patients reported worldwide), but counselled on the need for vigilance and early referral to an ophthalmologist. Others have suggested that the prevalence of tearing and canalicular fibrosis in patients receiving fluorouracil is related to total dose and duration of treatment, and that the risks become significant at 20–60 weeks of therapy and a total fluorouracil dose of 20–50 g (73).

- Ankyloblepharon (adherence of the eyelids resulting in narrowing of palpebral apertures) was reported in a 59-year-old man during fluorouracil therapy for metastatic adenocarcinoma of the stomach (74). It appeared that bilateral conjunctival ulcers, secondary to fluorouracil and ulcerative blepharitis, resulted in ankyloblepharon. Withdrawal of chemotherapy resulted in improvement and re-initiation of therapy resulted in recurrence of ocular lesions.

Transient, non-infectious, crystalline, intrastromal corneal deposits have been reported after subconjunctival administration of 5-fluorouracil (75). The deposits were treated with glucocorticoids and completely resolved in 4 days.

Psychological, psychiatric

Confusion and cerebral cognitive defects have been attributed to fluorouracil (49,76).

Metabolism

Patients with poorly controlled diabetes are at risk of greater or more severe fluorouracil toxicity, causing hyperglycemia, which has been fatal. This effect seems to be independent of previous diabetic control and or fluorouracil dosage schedules (77)

There have been attempts to unravel the mechanism of fluorouracil-induced hyperammonemia, lactic acidosis, and encephalopathy, a rare adverse effect associated with high-dose therapy. The cause is not known, although Krebs cycle metabolism is almost certainly involved (78,79).

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Hematologic

The hematological toxicity of fluorouracil is dose- and schedule-related (80). Leukocytes and platelets are affected, although the latter less so. Myelosuppression begins 4–7 days after the first dose, with recovery usually 14 days after the last dose (2). With continued treatment, anemia can develop in 3–4 months (81). Severe bone marrow depression causing death has been reported (82).

Leukopenia is the most common blood dyscrasia secondary to fluorouracil and usually occurs after every course. The lowest white cell counts are usually seen at 9–14 days after the first course of treatment, but can be delayed for up to 20 days (83,84). Leukopenia usually resolves after drug withdrawal. Leukopenia is often followed by megaloblastic anemia (85). Agranulocytosis has been reported during fluorouracil therapy (84).

Thrombocytopenia has occurred during fluorouracil therapy but is much less frequent than leukopenia (59).

The following summarizes the dose-relatedness of the hematological effects of fluorouracil (86,87):

- With a daily bolus of 12 mg/kg for 5 days, leukopenia (under 4×10^9/l) occurred in all of 70 patients; 31% had marked leukopenia (under 2×10^9/l).
- With a continuous infusion of 30 mg/kg/day for 5 days, the leukopenia was mild and occurred in only 12% of patients.
- A protracted continuous infusion of 300 mg/m^2/day caused one case of moderate leukopenia and four cases of mild/moderate thrombocytopenia.
- With a daily bolus of 500 mg/m^2 for 5 days there was a 38% incidence of leukopenia (with 20% below 2×10^9/l and an 8% incidence of thrombocytopenia (1% severe).

Gastrointestinal

The gastrointestinal toxicity of 5-fluorouracil is well documented and often dose-limiting. However, in a retrospective 10-year survey of gastrointestinal function in 19 patients who also had inflammatory bowel disease, although it did appear to increase the risk of exacerbation of diarrhea, it was not totally conclusive, as it was difficult to evaluate the contribution of other potentially causative factors, such as radiation (88).

Any site along the gastrointestinal tract can be affected, resulting in symptoms such as nausea and vomiting, stomatitis, dysphagia, retrosternal burning, abdominal pain, diarrhea, and proctitis.

Stomatitis is common and can be severe and life-threatening (84). Stomatitis may be preceded by a dry mouth and erythema of the mucosa followed by a white patchy membrane. In severe cases this is followed by ulceration and necrosis. Breakdown of the mucosa is very painful and can act as a focus for infection (2). Xerostomia at the start of therapy and a baseline neutrophil count of under 4×10^9/l are significantly associated with dose-limiting oral mucositis later in chemotherapy, according to the results of a logistic regression analysis of 63 patients (89). Mouth-cooling with oral ice chips for 30 minutes starting immediately before fluorouracil substantially reduced the severity of mucositis.

Nausea and vomiting are common but generally mild (84).

Gastric ulceration has been reported in patients receiving fluorouracil by intrahepatic infusion via percutaneous catheterization in doses of 20–30 mg/kg for 4 days followed by 15 mg/kg over 17 days. Symptoms were observed from 4 to 20 days after starting therapy (90). Gastrointestinal bleeding in three patients and death in one patient were also reported following intra-arterial fluorouracil (91).

Diarrhea is common, particularly in patients who receive a 5-day regimen. The diarrhea can be watery or bloody and life-threatening in severe cases. Repeated episodes of watery diarrhea (more than three movements per day) for several days should alert the oncologist to the potential dangers of dehydration and sepsis, which are potentially fatal adverse effects. Life-threatening diarrhea, with hematemesis, high intestinal obstruction, melena, septicemia, and shock, have been reported after total doses of 4–4.5 g of fluorouracil (92). Similarly, diarrhea followed by neutropenia and life-threatening or fatal sepsis occurred in two of 55 patients with advanced colorectal carcinoma in a pilot study of continuous infusion of fluorouracil (750 mg/m^2/day for 5 days) plus subcutaneous recombinant interferon alfa-2a (6–18 million units/day) (93). Severe diarrhea and mucosal ulceration of the colon with necrosis has also been reported (94).

- A 53-year-old man had a side-to-side ileo-descending colostomy for disseminated carcinoma. Fluorouracil was given in doses of 15 mg/kg for 4 days, then 7.5 mg/kg intravenously on days 6 and 8. He developed severe diarrhea and severe ulceration of the bypassed portion of the colon, resulting in necrosis, and death occurred as the result of bronchopneumonia. Autopsy showed ulcers from the ileocecal valve to the ileo-colostomy site. The mucosa of the stomach, small intestine, and colon distal to the colostomy were not involved.

In two cases the diarrhea and colitis associated with fluorouracil therapy were caused by toxigenic *Clostridium difficile*. Both patients responded to oral vancomycin (95).

Colitis has been reported as a rare complication of fluorouracil treatment. Two cases have been reported after intra-arterial chemotherapy (96). A further case has been reported, described by the authors as neutropenic enterocolitis, presenting as abdominal pain, diarrhea, and neutropenia (97). Proven pseudomembranous colitis followed 36 weekly doses of fluorouracil (700 mg) and folinic acid (150 mg); the authors believed that this was only the second reported case (98).

Liver

It has been suggested that handling cytostatic agents can insidiously cause hepatic damage and possibly irreversible fibrosis. Three case reports of hepatic injury in nurses after years of handling cytotoxic drugs (bleomycin, vincristine, cyclophosphamide, doxorubicin, dacarbazine, fluorouracil, and methotrexate) have been described (99). All had neurological symptoms associated with raised serum alanine transaminase and alkaline phosphatase

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activities. Liver biopsy showed portal hepatitis, with piecemeal necrosis in one and hepatic fibrosis and fat accumulation in the others.

- Diffuse hepatic necrosis has been described in a 29-year-old man receiving 500 mg/day fluorouracil for 4 days (route of administration unspecified) for adenocarcinoma (100). He developed nausea, vomiting, diarrhea, and massive and diffuse hepatic necrosis. The drug was withdrawn and he died 2 days later (6 days after starting medication).

However, the role of fluorouracil in inducing hepatic disease in this patient is unclear.

In a retrospective analysis of a study of *N*-phosphonoacetyl-L-aspartate (250 mg/m^2) followed by weekly boluses of fluorouracil (600–800 mg/m^2) in 44 patients with metastatic colorectal cancer, five of 17 patients with complete or partial responses to therapy developed transient ascites (with or without associated hypoalbuminemia) compared with one of 27 without such a response (101). Other significant findings in some of the responders included raised bilirubin concentrations and transaminase activities from metastasis. The authors cautioned that the adverse effects observed do not necessarily represent disease progression.

Biliary tract

Intrahepatic infusion of fluorouracil can cause biliary sclerosis (102), believed to result from perfusion of the blood supply to the gall bladder and upper bile duct with high local concentrations of the drug. The median time to onset of biliary sclerosis is three treatment cycles, and although fluorouracil may be restarted at a lower dose after normalization of serum hepatic enzyme activities, most patients become progressively less tolerant.

Of 57 consecutive patients treated with implanted hepatic arterial infusion pumps with a regimen of alternating floxuridine (0.1 mg/kg/day for 7 days) followed by a weekly pump bolus of 5-fluorouracil (15 mg/kg for 3 weeks), two developed biliary sclerosis and 12 had mild transient liver function abnormalities (103). The liver alone or in combination with another area was the site of first progression of disease in 40 patients.

Skin

Two types of skin rashes occur with fluorouracil. The more common form involves erythema of exposed skin areas. With continued fluorouracil therapy the skin becomes hyperpigmented, thin, and atrophic (82). Patients treated with fluorouracil also have an increased susceptibility to sunburn (104). Less commonly (about 1.5%), a severe seborrheic pruritic dermatitis occurs (82). These rashes are usually reversible on withdrawal of fluorouracil. Acute, painful, swollen, and self-limiting erythema of the hands and soles has been reported in association with protracted infusion of fluorouracil (105).

Fluorouracil commonly causes hyperpigmentation and multiple pigmented macules (106). Serpentine supravenous hyperpigmentation is a peculiar dermatological effect seen with continuous infusions of fluorouracil (82,107). Residual macular pigmentation can persist for 3 months after withdrawal. Hyperpigmentation occurs only in the tissues overlying the veins proximal to the infusion site in the limb used. The veins are not sclerosed and usually remain patent (108). This has also been reported in a 56-year-old black man after intravenous fluorouracil 750 mg/m^2/week over 24 weeks for stage-D prostatic carcinoma (109). The patient developed nasal mucosal friability, diffuse pigmentation of the face and hands, and markedly increased pigmentation of the skin immediately overlying the veins that had been used for multiple fluorouracil infusions. Many irregular dark streaks were noted, extending from the hand to the shoulder. These streaks were 1–1.5 cm wide and serpiginous in their course.

Fluorouracil, alone or in combination regimens, via continuous or intermittent infusions or bolus doses, has been associated with hand–foot syndrome or palmar–plantar erythrodysesthesia, a rare syndrome of unknown cause, characterized by varying degrees of painful, erythematous, swollen palms of the hand and soles of the feet (110). Tingling, tenderness, and desquamation can also occur. The pain can be so severe as to inhibit walking and hand grasping (110). The onset of the reaction has ranged from 3 days to 10 months (110,111). Severity appeared to be dose-related in one case (112). The condition gradually subsides over 5–7 days when the drug is withdrawn (112). However, it may recur on rechallenge (111). Pyridoxine 100–150 mg/day has been used to manage this syndrome, allowing continued treatment in a small number of patients (113,114). Topical 5-fluorouracil often causes skin irritation. However, allergic contact dermatitis is only infrequently reported, although it may be underdiagnosed.

- A 64-year-old man was treated with Efudix ointment (containing 5% fluorouracil) for actinic keratosis (115). Patch-testing with the constituents of the cream showed a doubtful reaction to fluorouracil 5% in petroleum jelly; however, intradermal injection of fluorouracil 10 mg/ml gave a positive reaction.

Topical fluorouracil has been associated with allergic contact dermatitis in patients with actinic keratosis and basal cell epitheliomas (116). Topical fluorouracil ointment (5%) was reported to exacerbate dermatitis when it was mistakenly given instead of fluocinonide ointment (117).

Telangiectasia and herpes labialis have been reported in four patients receiving topical 1% fluorouracil in propylene glycol applied three times a day for 7–28 days. Two patients developed herpes labialis 7–10 days after the start of therapy and two developed persistent telangiectasia at the application site (118).

- Bullous pemphigoid has been reported in an 84-year-old man after topical therapy with fluorouracil 1% solution daily over several days for actinic keratosis. All treated lesions became bullous, with the development of a few bullae on untreated areas of normal skin. Bullous lesions were pruritic and sore and some contained hemorrhagic fluid. There was a leukocytosis (11.7×10^9/l). The blister fluid contained predominantly eosinophils, and immunofluorescent studies of the serum and blister fluid showed anti-basement membrane antibody titers of 1:640 and 1:160 respectively. Fluorouracil was discontinued and the patient was treated with steroids and saline compresses, with abatement of symptoms (119).

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Fluorouracil not only augments the therapeutic effect of ionizing radiation on tumors, but also increases its mucocutaneous toxicity. The likelihood of severe toxicity within the radiation field is increased significantly and relates to the area irradiated (for example oral stomatitis, esophagitis, enteritis, and skin desquamation). The onset of these effects is within 7 days of the start of radiation.

Hair

Partial reversible alopecia is common after systemic fluorouracil therapy (84).

Nails

Diffuse blue superficial pigmentation, onycholysis, dystrophy, pain and thickening of the nail bed, transverse striations, paronychial inflammation, hyperpigmentation, and nail loss have all been reported with fluorouracil therapy (120–122). It has further been reported that the blue pigment may be scraped off (120).

Sexual function

Vaginitis (shedding of the vaginal epithelium) may be nearly as common as mucositis in women receiving systemic fluorouracil-based chemotherapy regimens (123).

Immunologic

- An anaphylactic reaction with shock after a 10th dose of fluorouracil 900 mg intravenously was reported in a 60-year-old man with colorectal adenocarcinoma (124). Two minutes after his 10th dose of fluorouracil, he became cyanotic and collapsed, with a rapid thready pulse of 120. His blood pressure was 30/0 mmHg. Adrenaline 1:1000, 1 ml, was given, with immediate and prompt signs of recovery. Within 25 minutes, his blood pressure, pulse, and skin color had returned to normal.

Second-Generation Effects

Pregnancy

Fluorouracil is contraindicated throughout pregnancy. The literature on pregnancy and cytotoxic drugs is necessarily limited, but it appears in general that risk of teratogenesis diminishes with the advancement of pregnancy. Therefore, most cytotoxic drugs are absolutely contraindicated in the first trimester, and when fluorouracil has been used in the first trimester it has been reported to cause multiple congenital abnormalities (125).

Administration of fluorouracil to pregnant rats on day 14 of gestation resulted in dose-dependent growth retardation and numerous malformations in near-term fetuses, including hind limb defects and cleft palate (126). After treatment, a number of rapid biochemical and cellular alterations were detectable in embryonic hind limbs and in craniofacial and other tissues, including inhibition of thymidylate synthetase and altered cell cycle progression. In order to assess the importance of these early events in fluorouracil-induced dysmorphogenesis, embryonic mid-facial tissues and hind limbs were dissected 3 or 6 hours after administration of fluorouracil to the dam and placed in explant culture. After 5 days in culture, craniofacial explants were evaluated morphologically for palatal closure, and growth was assessed by measuring total protein and DNA contents. Hind-limb explants were stained for cartilage using Alcian blue to evaluate development of digits. Craniofacial explants cultured at either 3 or 6 hours after exposure showed dose-dependent growth retardation and defects of palatal fusion at the end of the culture period. Deficits in protein and DNA content were similar to those in craniofacial tissues that continued to develop in utero after treatment, although morphological defects in cultured explants did not correlate well with the incidence of cleft palate in vivo. Dose-dependent deficits in metatarsal and phalanx development were observed in hind-limb explants dissected either 3 or 6 hours after maternal treatment.

Susceptibility Factors

Genetic factors

Anabolism of fluorouracil to pyrimidine nucleotide analogues is required for its cytotoxic effects and pyrimidine catabolism is important in the regulation of fluorouracil availability and its subsequent anabolism. Dihydropyrimidine dehydrogenase is the initial enzyme of pyrimidine catabolism, accounting for degradation of greater than 80% of a dose of fluorouracil. The importance of catabolism and particularly dihydropyrimidine dehydrogenase in fluorouracil chemotherapy has previously been demonstrated in studies with competitive inhibitors of dihydropyrimidine dehydrogenase and in patients with suspected or proven dihydropyrimidine dehydrogenase deficiency. Before 1991, only two cases of dihydropyrimidine dehydrogenase deficiency associated with fluorouracil toxicity in adults were reported, and in both cases it was the fluorouracil toxicity that focused attention on pyrimidine catabolism. In 1991 a third case of dihydropyrimidine dehydrogenase deficiency was reported (127), suggesting that it may be more frequent than initially thought. There was complete deficiency of dihydropyrimidine dehydrogenase in the affected patient, with evidence of partial deficiency in the patient's parents, daughter, brother, and the brother's children. This pattern of dihydropyrimidine dehydrogenase activity was consistent with the previous two reports, suggesting an autosomal recessive pattern of inheritance.

- A 35-year-old woman with breast carcinoma treated with doses of fluorouracil that were not unusually high. Chemotherapy with cyclophosphamide, fluorouracil, and methotrexate started 3 weeks after surgery. Following day 8 of the protocol, the patient had severe gastrointestinal adverse effects (nausea, prolonged vomiting, diarrhea, stomatitis), hematological toxicity (neutropenia), and fever. She also had mild neurological toxicity causing unsteadiness and difficulty in spelling simple words, which persisted for about 2 weeks.

The neurotoxicity of fluorouracil seems to be more prolonged and severe in patients with dihydropyrimidine dehydrogenase deficiency (128).

Only a few cases of dihydropyrimidine dehydrogenase deficiency have been identified: however, all cases exhibited remarkable toxicity. Enhanced toxicity occurring at normal doses is what usually sets these patients

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apart. The authors suggested that monitoring dihydropyrimidine dehydrogenase activity may be appropriate in the management of those who have severe toxicity from fluorouracil (127).

Additional studies are needed to characterize this genetic defect, in order to answer the following questions:

- What is the frequency of this gene defect in the general population?
- Does dihydropyrimidine dehydrogenase deficiency correlate with the occurrence of severe fluorouracil toxicity?
- Do individuals with partial dihydropyrimidine dehydrogenase deficiency (that is heterozygotes) have altered metabolism of fluorouracil?
- Is monitoring dihydropyrimidine dehydrogenase activity helpful in the management of patients experiencing severe toxicity to fluorouracil chemotherapy?

Age

Cancer is most common in older people, but little information is available with regard to the impact of age on the toxicity of chemotherapy. A study has been undertaken to determine if age is an independent risk factor for fluorouracil toxicity (129). Toxicity data from a prospective, randomized, multi-institution trial of fluorouracil-based treatment for advanced colorectal carcinoma were analysed. Toxicity for each organ system was graded. The results showed that advanced age was significantly associated with the occurrence of any severe toxicity (58 versus 36%), leukopenia (24 versus 10%), diarrhea (24 versus 14%), vomiting (15 versus 5%), severe toxicity in more than two organ systems (10 versus 3%), and treatment mortality (9 versus 2%). Age and sex were independent predictors of severe toxicity. Advanced age does not contraindicate the use of this type of chemotherapy, but monitoring for multiple organ toxicity and vigorous supportive care of those with toxicity are required.

Dosing decisions in older patients are difficult and must integrate assessments of organ function, co-morbidity, overall physical status, and goals of treatment, in an effort to ensure the best possible outcome for these patients.

Other features of the patient

Circadian variation in toxicity

If the rhythm in fluorouracil toxicity is linked to the asleep–awake circadian cycle across species, the least toxic time in man would correspond to 0400 hours. This hypothesis has been tested using a single-reservoir, programmable-in-time, external ambulatory pump (Chronopump, Autosyringe, Hooksett, USA) in 35 patients with metastatic colorectal cancer (130). Fluorouracil was infused for 5 days via an implanted venous access port, with peak drug delivery at 0400 hours and no infusion from 1800 to 2200 hours. Each course was repeated after a drug-free interval of 16 days. Intrapatient dose escalation was planned from 4 to 9 g/m^2/course (800–1800 mg/m^2/day for 5 days) if toxicity was less than grade 2 according to the World Health Organization (WHO). There was grade 2 or greater toxicity in under 5% of the courses, indicating adequate control of toxicity via dose escalation, and their incidence was dose-dependent. The median maximal tolerated dose was 7.5 mg/m^2/course in 30 patients assessed for this end point.

Cellular glutathione concentrations and fluorouracil toxicity

Little is known about whether components of the diet can modulate the efficacy of fluorouracil in patients with colon carcinoma. Glutathione, an important antioxidant and anticarcinogen, is present in many foods in varying amounts.

The effect of cellular glutathione concentration on the growth of human colon adenocarcinoma cells HT-29 and on the cytotoxic activity of fluorouracil in these cells has been studied (131). Glutathione and buthionine sulfoximine were used respectively to enhance or reduce the glutathione concentration in these cells. A 34% increase in cellular glutathione concentration had no effect on the growth of HT-29 cells, nor on the cytotoxic activity of fluorouracil. A 50% reduction in the cellular glutathione concentration enhanced fluorouracil cytotoxicity by 20–31%, depending on the fluorouracil concentration.

Drug Administration

Drug dosage regimens

Stomatitis and diarrhea are particularly frequent in patients who received a 5-day regimen. An alternative regimen using continuous intravenous infusion of fluorouracil at doses of 30 mg/kg/day for 5 days gives equivalent therapeutic results but a different pattern of toxicity (132). Gastrointestinal symptoms, such as stomatitis and diarrhea, are the principal dose-limiting toxic effects, but myelosuppression is less intense. When fluorouracil is given in combination with leucovorin in patients with metastatic colon cancer, there is enhanced gastrointestinal toxicity, irrespective of the fluorouracil schedule.

Drug administration route

Intravenous administration of fluorouracil 1 g has been compared with hepatic arterial infusion (133). When fluorouracil was administered over 2 hours, systemic drug exposure was 0.7 times lower and clearance 1.5 times higher with hepatic arterial infusion. When the duration of infusion was extended to 24 hours, systemic drug exposure was 0.4 times lower and the clearance was two- to three-fold higher with hepatic arterial infusion. For the 24-hour infusion, co-treatment with angiotensin II (given temporarily to increase tumor blood flow) and albumin microspheres, given to increase drug uptake by the liver via the hepatic artery produced an additional two-fold reduction in systemic fluorouracil exposure. Further evaluation is planned to determine if this will improve the therapeutic index of regionally administered fluorouracil.

Intraperitoneal administration of fluorouracil has been reported to produce a desirable regional advantage (134). The results of a phase I trial of intraperitoneal fluorouracil in escalating concentrations for 4 hours, along with a fixed dose of cisplatin 90 mg/m^2 every 28 days, has been used (135). There was dose-limiting neutropenia at a fluorouracil concentration of 20 mmol/l, although individual patients tolerated concentrations as high as 30 mmol/l.

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Other toxic effects included mild-to-moderate nausea and vomiting; diarrhea occurred less often. Peak plasma concentrations occurred 1 hour after instillation and there was a significant linear relation between the intraperitoneal fluorouracil dose and the peak plasma fluorouracil concentration. At every dose, the mean peak intraperitoneal fluorouracil concentration exceeded that in the plasma by two to three log units.

Drug overdose

Cases of deliberate overdosage are unknown, but excessive duration or dosage of therapy will produce life-threatening toxicity because of the hematological effects and other symptoms and signs that are qualitatively similar to the adverse effects. There is no specific antidote to fluorouracil toxicity; treatment consists of supportive care, including G-CSF and antidiarrheal agents.

Drug–Drug Interactions

Allopurinol

Concurrent administration of allopurinol with fluorouracil inhibits the intracellular formation of fluorouridine monophosphate from fluorouracil in normal tissues. In tumor cells that activate fluorouracil by alternative pathways, antitumor responses are still seen (2). Allopurinol increased the half-life of high-dose fluorouracil when it was given by intravenous bolus but not when it was given by 5-day continuous infusion (2).

Allopurinol ameliorates fluorouracil-induced granulocytopenia and possibly lessens the severity of mucositis (136). Allopurinol mouthwash (450 mg total in methylcellulose) given immediately and 1, 2, and 3 hours after fluorouracil reduced the incidence and severity of mucositis in six patients (137) and in another study of 42 patients there was significant reduction of oral toxicity and prolonged pain relief (138). In a randomized, double-blind, placebo-controlled trial, in 44 patients, allopurinol mouthwashes resolved stomatitis in nine of 22 treated patients, and diminished its intensity in 10 (139). However, in another randomized, double-blind, crossover study of allopurinol, mouthwash in 77 patients did not ameliorate fluorouracil-induced mucositis (140), nor did allopurinol reduce the toxicity of intravenously administered fluorouracil (141). Allopurinol is not currently recommended in the prophylaxis of fluorouracil-induced mucositis.

Cimetidine

Pre-treatment for 4 weeks with cimetidine 1 g/day increased the oral systemic availability of fluorouracil by 74%; the AUC was increased by 27% and total body clearance was reduced by 28% (142).

Dipyridamole

The pharmacokinetics of fluorouracil have been studied with escalating doses as a 72-hour intravenous infusion alone or in combination with a fixed dose of dipyridamole, a nucleoside transport inhibitor, and an enhancer of fluorouracil cytotoxicity (143). Stomatitis was dose-limiting at a fluorouracil dose of 2300 mg/m^2/day. For courses given with fluorouracil alone, the pharmacokinetics were linear for doses of 185–2300 mg/m^2/day; however, above this dose total body clearance fell significantly. Dipyridamole increased the total body clearance of fluorouracil, resulting in significantly lower mean steady-state fluorouracil plasma concentrations over the dose range studied. The clinical observation that dipyridamole did not appear to modulate fluorouracil-induced mucositis or leukopenia can be explained by lower exposure to fluorouracil. The basis for this pharmacokinetic interaction is not understood but it serves to underscore the importance of incorporating pharmacokinetic analysis in clinical trials involving new drug combinations.

Interferons

Initial studies have suggested that interferons may have synergistic activity with fluorouracil (144,145). Interferon alfa-2b has also been associated with an 80% increase in fluorouracil AUC (146).

Leucovorin

When combined with fluorouracil, leucovorin enhances the binding of the fluorouracil metabolite fluorouridine monophosphate to thymidylate synthetase. DNA-directed toxicity is increased, whilst RNA-directed toxicity is not affected (146). A qualitative alteration in toxicity is reported with increased gastrointestinal toxicity (2).

Methotrexate

There is sequence-dependent synergy between fluorouracil and methotrexate. Pretreatment with methotrexate enhances the formation of fluorouridine monophosphate and hence fluorouridine triphosphate and RNA-directed toxicity. In studies in which methotrexate has been given 1 hour before fluorouracil, response rates did not differ significantly. However, when it was given 4 hours or more before, there were significantly better response rates (147).

Metronidazole

Pretreatment with metronidazole increased the toxicity of fluorouracil given by daily bolus dose (148). The clinical significance of this is yet to be determined.

Pyridoxine

The dose and duration of protracted infusional fluorouracil is limited by mucositis, diarrhea, and/or palmar–plantar erythrodysesthesia. Typically, palmar–plantar dysesthesia begins several weeks to months after starting treatment. Although the dysesthesia abates within several weeks of discontinuing the infusion, it rapidly recurs when the infusion is resumed. Five patients who developed palmar–plantar dysesthesia during infusion of fluorouracil were treated with oral pyridoxine, 50 or 150 mg/day, once it reached moderate severity (149). The severity of the skin toxicity improved, with resolution of pain in four of the five patients, despite continued administration of fluorouracil. The ability of pyridoxine to modulate fluorouracil-induced cutaneous toxicity is currently undergoing evaluation in the randomized trial (150).

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Other Environmental Interactions

Ionizing radiation

Fluorouracil increases the activity and toxicity of ionizing radiation (2).

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Fluoxetine

See also Selective serotonin re-uptake inhibitors (SSRIs)

General Information

Fluoxetine is a selective serotonin re-uptake inhibitor (SSRI). The manufacturers of fluoxetine have published a review of the adverse effects that were noted in 1378 patients who took it for up to 2 years (1).

In a meta-analysis based on 9087 patients in 87 different randomized clinical trials fluoxetine was more effective than placebo from the first week of therapy (2). In bulimia nervosa, fluoxetine was as effective as other agents. It was as effective as clomipramine in the treatment of obsessive-compulsive disorder.

The major adverse effects of fluoxetine confirm its stimulant profile and its relative lack of anticholinergic actions. The most frequent adverse effects, which occurred in 10–25% of patients, were nausea (25%), nervousness, insomnia, headache, tremor, anxiety, drowsiness, dry mouth, sweating, and diarrhea (10%). Most of these adverse effects occurred early in treatment and seldom led to drug withdrawal.

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Organs and Systems

Cardiovascular

Fluoxetine appears not to have the cardiovascular effects associated with tricyclic compounds, but 10 patients did discontinue treatment because of tachycardia, palpitation, and dyspnea (3). Two older women each had a myocardial infarction and subsequently died, although these events may not have been drug-related.

In general, SSRIs are assumed to be safe in patients with cardiovascular disease, although there have been few systematic investigations in these patients. In a prospective study of 27 depressed patients with established cardiac disease, fluoxetine (up to 60 mg/day for 7 weeks) produced a statistically significant reduction in heart rate (6%) and an increase in supine systolic blood pressure (2%) (4). One patient had worsening of a pre-existing dysrhythmia and this persisted after fluoxetine withdrawal. These findings suggest that, relative to tricyclic antidepressants, fluoxetine may have a relatively benign profile in patients with cardiovascular disease. However, the authors cautioned that in view of the small number of patients studied, these findings cannot be widely generalized.

The effects of fluoxetine (20 mg/day for 12 weeks) on sitting and standing blood pressures have been reported (5). Fluoxetine modestly but significantly lowered sitting and standing systolic and diastolic blood pressures by about 2 mmHg. Patients with pre-existing cardiovascular disease showed no change. This study confirms that fluoxetine has little effect on blood pressure in physically healthy depressed patients and in those with moderate cardiovascular disease.

Fluoxetine-induced remission of Raynaud's phenomenon has been reported (SEDA-18, 20) (6).

Cardiac dysrhythmias

Fluoxetine has reportedly caused prolongation of the QT_c interval (7).

- A 52-year-old man had an abnormally prolonged QT_c interval of 560 ms, with broad-based T-waves. He had taken fluoxetine 40 mg/day over the previous 3 months, before which an electrocardiogram had shown a normal QT_c interval (380 ms). The fluoxetine was withdrawn, and 10 days later the QT_c interval was 380 ms. His only other medication was verapamil which he had taken for 3 years for hypertension.

Systematic studies of fluoxetine as monotherapy have not shown evidence of QT_c prolongation. It is possible in this case that fluoxetine interacted with verapamil to produce a conduction disorder.

An elderly man developed atrial fibrillation and bradycardia shortly after starting fluoxetine, and again on rechallenge (SEDA-16, 9). Dose-dependent bradycardia with dizziness and syncope has also been reported in a few patients taking fluoxetine (SEDA-16, 9) and in a presenile patient (8).

Nervous system

Several cases in which fluoxetine worsened parkinsonian disability have been described, and the problem of exacerbation of Parkinson's disease by fluoxetine has been reviewed (SEDA-18, 19).

Five patients taking fluoxetine developed akathisia, perhaps due to enhanced serotonergic inhibition of dopamine neurons (9). A causal link between fluoxetine-induced akathisia and suicidal behavior has been suggested (SEDA-17, 19) (SEDA-18, 19), and akathisia has also been associated with "indifference" (SEDA-18, 19).

One case of neuroleptic malignant syndrome has been described with fluoxetine (10).

One case of tics after long-term fluoxetine therapy has been described; the symptoms subsided several months after withdrawal (SEDA-18, 19).

One case of migraine associated with fluoxetine has been reported, with no further attacks when the drug was withdrawn (SEDA-18, 20).

Stuttering has been reported with fluoxetine (11).

Two patients who had been maintained successfully on fluoxetine (20 mg/day) for 6 and 10 years respectively began to have agitation, tension, and sleep disturbance (12). There had been no recent changes in medications or life events to explain these symptoms, which closely resembled the kind of adverse effects that can occur shortly after the start of SSRI treatment. Both patients improved after downward titration of the dose of fluoxetine. Blood concentrations of fluoxetine were not reported, so it is possible that for some reason (for example a change in diet or activity) plasma fluoxetine concentrations had recently increased in these subjects. However, the development of characteristic adverse effects after such a long trouble-free period suggests that patients taking maintenance medication need long-term follow-up, or at least ready access to specialist advice.

Seizures

Fluoxetine has been associated with seizures, both in therapeutic doses (3,13) and in overdose (3,14). It has also been shown to lengthen seizure duration during electroconvulsive therapy (SEDA-17, 20). Four patients had suspected seizures during studies (3) and one who took a 3000 mg overdose (3) had unequivocal convulsions but recovered.

Sensory systems

Tricyclic antidepressants can precipitate acute glaucoma through their anticholinergic effects. There are also reports that SSRIs can cause acute glaucoma, presumably by pupillary dilatation (see the monograph on Paroxetine).

In a placebo-controlled study in depressed patients a single dose of fluoxetine (20 mg) increased intraocular pressure by 4 mmHg (15). This increase is within the normal diurnal range, but could be of clinical consequence in individuals predisposed to glaucoma. However, post-marketing surveillance has not suggested an association between the use of fluoxetine and glaucoma (16).

Blurred vision has occasionally required withdrawal of fluoxetine (3).

Psychological, psychiatric

An analysis of severe adverse effects that caused drug withdrawal showed that psychotic reactions occurred in nine of 1378 patients; in four cases this appeared to

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be a stimulant psychosis and in three a conversion to mania (3).

Cognitive function can be impaired by fluoxetine; a negative effect on learning and memory has been described (SEDA-17, 20).

Reports of acute mania and manic-like behavior after treatment with fluoxetine or fluvoxamine have appeared (SEDA-13, 12) (SEDA-17, 20) (SEDA-18, 20), but there are not enough data to estimate the incidence.

Suicidal ideation has been described after 2–7 weeks of fluoxetine (17) and other case reports (SEDA-16, 9) (SEDA-17, 19). A causal link was initially questioned (SED-12, 57) (SEDA-15, 15) (SEDA-17, 19), and in one controlled trial there was no increase (SEDA-16, 9). Furthermore, a meta-analysis of controlled trials did not point to a greater risk of suicide attempts or suicidal ideation with fluoxetine than with tricyclic antidepressants (1).

In a meta-analysis based on 9087 patients in 87 different randomized clinical trials with fluoxetine there was no increased risk of suicide (2).

In an analysis of data from the National Institute of Mental Health Collaborative Depression Study in 643 patients with affective disorders who were followed up after fluoxetine was approved by the FDA in December 1987 for the treatment of depression, nearly 30% (n = 185) took fluoxetine at some point (18). There was an increased rate of suicide attempts before fluoxetine treatment in those who subsequently took fluoxetine. Relative to no treatment, fluoxetine and other antidepressants were associated with non-significant reductions in the likelihood of suicide attempts or completions. Severity of psychopathology was strongly associated with increased risk, and each suicide attempt after admission to the study was associated with a marginally significant increase in the risk of suicidal behavior. The authors concluded that the results did not support the speculation that fluoxetine increases the risk of suicide.

Endocrine

Fluoxetine causes weight loss, in contrast to tricyclic antidepressants (19). In one study there was a mean fall in weight of 3.88 pounds over 6 weeks compared with a gain of 4.6 pounds with amitriptyline (20).

Serotonin pathways are involved in the regulation of prolactin secretion. Amenorrhea, galactorrhea, and hyperprolactinemia have been reported in a patient taking SSRIs.

- A 71-year-old woman who had taken fluoxetine (dose unspecified) for a number of weeks noted unilateral galactorrhea and had a raised prolactin of 37 ng/ml (reference range 1.2–24 ng/ml) (21). She was also taking estrogen hormonal replacement therapy, benazapril, and occasional alprazolam. Withdrawal of the fluoxetine led to normalization of the prolactin concentration and resolution of the galactorrhea.

Estrogens also facilitate prolactin release, and so hormone replacement therapy may have played a part in this case.

Hematologic

Petechiae and prolongation of bleeding time have been reported in association with fluoxetine (SEDA-16, 10). In one case a 31-year-old woman taking fluoxetine developed bruising (22).

Aplastic anemia with fever, pleuritic chest pain, and pancytopenia developed in a 28-year-old woman (23) after 6 weeks of fluoxetine therapy. Bone-marrow examination confirmed acute marrow aplasia. She recovered 19 days after withdrawal. Neutropenia occurred rapidly after rechallenge. Another report described severe neutropenia during fluoxetine treatment (24).

Gastrointestinal

Gastrointestinal adverse effects are one of the major disadvantages of SSRIs (see General section). Two women developed stomatitis while taking fluoxetine; in one it recurred on rechallenge (25).

Liver

Chronic hepatitis associated with fluoxetine has been reported in a 35-year-old man (26).

In a post-marketing surveillance study there were some cases in which fluoxetine alone appeared to have precipitated hepatitis, which remitted when treatment was withdrawn (27). Fluoxetine can cause mild increases in liver enzymes, with a rate in clinical trials of about 0.5%. Rarely this can progress to hepatitis.

Skin

Rashes due to fluoxetine occur in a few percent of patients (28). Fluoxetine has been implicated in two cases of psoriasis (SEDA-17, 20). A woman taking fluoxetine monotherapy had painful burning, persistent erythema, and blisters on sun-exposed areas (SEDA-20, 8).

Hair

Reversible hair loss has been reported in patients taking fluoxetine (SEDA-16, 10) (SEDA-17, 20).

Sexual function

Fluoxetine can impair sexual function in both sexes, and particularly causes delayed orgasm or anorgasmia (SEDA-14, 14) (SEDA-17, 21) (SEDA-18, 21), in 5–10% of patients (29,30).

Fluoxetine has been implicated in one case of prolonged erection (SEDA-18, 21).

Yawning, clitoral engorgement, and spontaneous orgasm have been associated with fluoxetine (31).

Penile anesthesia has been reported in association with fluoxetine and sertraline (SEDA-17, 20).

Immunologic

Vasculitis has been attributed to fluoxetine (32,33).

- A patient who took fluoxetine for a manic-depressive disorder developed pulmonary inflammatory nodules with non-caseating giant cell granulomas, interstitial pneumonia, and non-necrotizing vasculitis, but remained asymptomatic (34). The diagnosis was made by open lung biopsy. The pulmonary nodules progressively resolved after withdrawal and the chest X-ray returned to normal in 9 months.

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Second-Generation Effects

Fetotoxicity

Fluoxetine can occasionally cause cardiac dysrhythmias in adults, and may have done so in a fetus, whose mother took fluoxetine during pregnancy.

A woman took fluoxetine (20–30 mg/day) from the 28th week of pregnancy (35). The fluoxetine was withdrawn during the 37th week, and at 38 weeks a male infant (2700 g) was born by spontaneous vaginal delivery. Both before and after delivery the baby was noted to have multiple atrial and ventricular extra beats. Echocardiography showed a normal heart and the baby was otherwise well. By discharge on day 5 the frequency of extra beats had fallen, and on follow-up 1 month later they were no longer present.

The long half-life of fluoxetine and its active metabolite, norfluoxetine, means that the active drug would have been present in the mother and baby for some weeks after withdrawal. However, as the authors pointed out, the baseline incidence of atrial extra beats in a fetus in utero is about 1–2%. It is therefore possible that treatment with fluoxetine in this case was coincidental.

Fluoxetine-related withdrawal effects have been reported in a neonate whose mother had taken fluoxetine during pregnancy (SEDA-18, 21).

Drug Administration

Drug overdose

Nine patients took overdoses of fluoxetine in amounts up to 3000 mg (37 times the recommended dose) (3). One, who also took several other drugs, including amitriptyline, died, but the other eight all recovered with relatively minor symptoms in most cases. Four patients had suspected seizures during studies (3) and one who took a 3000 mg overdose had unequivocal convulsions but recovered.

Overdosage of fluoxetine has been implicated in the development of seizures, but usually only when taken with other substances.

- A 15-year-old girl had a tonic-clonic seizure after overdosage of fluoxetine alone; she recovered uneventfully (36).

Drug–Drug Interactions

Beta-blockers

An interaction between metoprolol and fluoxetine with severe bradycardia has been described (SEDA-18, 23).

Carbamazepine

Fluoxetine can increase plasma concentrations of carbamazepine (SEDA-17, 21) (SEDA-18, 23).

Digoxin

Fluoxetine has been reported to increase serum digoxin concentrations (37).

- A 93-year-old woman with congestive cardiac failure, paroxysmal atrial fibrillation, and hypertension developed depression after the death of her daughter. For several months she had been taking captopril 25 mg bd, furosemide 40 mg/day, digoxin 0.125 mg/day, and ranitidine 150 mg bd. She was in sinus rhythm and her serum digoxin concentration was 1.0–1.4 nmol/l. She was treated with fluoxetine (10 mg/day), but a week later she developed anorexia. At that time the serum digoxin concentration was 4.2 nmol/l. Both digoxin and fluoxetine were withdrawn and the digoxin concentration returned to the target range within 5 days, with resolution of the anorexia. Digoxin was restarted and concentrations in the usual target range were achieved during the next 3 weeks (0.9–1.4 nmol/l). Because of persisting depressive symptoms, fluoxetine (10 mg/day) was given again, but the digoxin concentrations rose and after 4 days were 2.8 nmol/l. Both digoxin and fluoxetine were then withdrawn.

Because digoxin has a narrow therapeutic range, this interaction, if confirmed, may be of clinical significance. The mechanism is not clear, because digoxin is not a substrate for the cytochrome P450 enzymes that are inhibited by fluoxetine. The authors speculated that fluoxetine may reduce the renal clearance of digoxin; if so, it might do that by inhibiting the P-glycoprotein that is responsible for the active tubular secretion of digoxin.

Lithium

A report has been published of lithium toxicity induced by combined treatment with fluoxetine (38).

Monoamine oxidase inhibitors

The problem of the long half-life of fluoxetine, leading to interactions with monoamine oxidase inhibitors, even after withdrawal, has been discussed previously (SEDA-13, 12), and caused the manufacturer to circulate a warning to that effect.

Pseudopheochromocytoma, with hypertension, palpitation, and headache, has been reported in a patient taking fluoxetine and selegiline (SEDA-18, 23).

Phenytoin

Several case reports and one in vitro study have suggested that combined administration of fluoxetine with phenytoin can significantly increase phenytoin serum concentrations, leading to toxicity (19,39,40).

Risperidone

Combined treatment with atypical neuroleptic drugs and SSRIs is common and case reports have suggested that SSRIs can increase risperidone concentrations and increase the risk of extrapyramidal disorders (SEDA-23, 18).

- Severe parkinsonism with urinary retention occurred when fluoxetine 20 mg/day was added to risperidone 2 mg/day in a 46-year-old man with schizophrenia. Risperidone had been prescribed at this dose for 1 month without any adverse effects, and the authors considered that a pharmacokinetic interaction between fluoxetine and risperidone was the most likely mechanism (41).

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In a systematic open study in 11 hospitalized patients taking a steady dose of risperidone (4–6 mg/day), fluoxetine (20 mg/day) increased plasma concentrations of active antipsychotic medication (combined concentrations of risperidone and 9-hydroxyrisperidone) by 50% after treatment for 25 days (42). Despite this, the treatment was well tolerated and there were improvements in rating scales of psychosis and depressed mood. Whether this was due to the introduction of fluoxetine or the higher plasma concentrations of risperidone is not clear. Fluoxetine and norfluoxetine would require at least a further 2 weeks to reach steady state, so additional increases in risperidone concentrations might be anticipated over this time.

Triptans

Caution has been advocated when SSRIs such as fluoxetine are combined with the triptans that are used to treat acute episodes of migraine (SEDA-24, 16). There are case reports of symptoms suggestive of serotonin toxicity when fluoxetine has been combined with sumatriptan, perhaps because the SSRI can potentiate the 5-$HT_{1B/1D}$ agonist effects of the triptan (SEDA-22, 14).

The effect of fluoxetine 60 mg/day for 8 days on the pharmacokinetics of almotriptan has been studied in 14 healthy volunteers (43). Fluoxetine produced a significant increase in the peak concentration of almotriptan, but the AUC was not altered. These results suggest that CYP2D6 plays a minor role in the metabolism of almotriptan. The combined treatment was reported to be well tolerated, but this does not exclude the possibility of occasional cases of serotonin toxicity in some individuals.

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Flupentixol

See also Neuroleptic drugs

General Information

Flupentixol is a thioxanthene neuroleptic drug.

Organs and Systems

Nervous system

Autoamputation of the tongue in a patient who was taking flupentixol has been explained as being secondary to an acute, atypical, neuroleptic drug-induced orolingual dyskinesia (1).

- A 21-year-old man, who had been mentally retarded from birth, was given intramuscular flupentixol 50 mg/day and oral diazepam 7.5 mg/day for disruptive and inappropriate behavior, and 84 hours later began chewing his tongue repetitively, with resultant edema and bleeding from multiple lacerations. The biting abated within 2 hours after intravenous biperiden 5 mg and diazepam 5 mg; ampicillin, cloxacillin, and metronidazole were also given. One week after admission to hospital, he had an autoamputation of the distal one-third of his tongue.

Reference

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Fluphenazine

See also Neuroleptic drugs

General Information

Fluphenazine is a phenothiazine neuroleptic drug.

In a double-blind comparison of a group of stabilized outpatients taking a low dosage of fluphenazine enanthate (1.25–5 mg every 2 weeks) with a group taking a standard dosage (12.5–50 mg every 2 weeks), relapse rates were higher in the low-dose group (56%) than in the standard-dose group (7%) (1). However, patients in the low-dose group had a better outcome in terms of some measures of psychosocial adjustment and family satisfaction. Patients in the low-dose group had fewer signs of tardive dyskinesia, and relapses led less often to re-admission to hospital; they also responded more readily to treatment with temporary increases in medication than patients treated with standard doses.

In a comparison of a low dose of fluphenazine decanoate (5 mg) with a standard dose (25 mg) every 2 weeks, there was no significant difference in relapse at 1 year (2), nor was there a difference in survival at 1 year, but at 2 years, survival was significantly better with the 25 mg dose (64%) than with the 5 mg dose (31%) (3).

Organs and Systems

Gastrointestinal

Neuroleptic drugs, particularly phenothiazine derivatives, have been reported to cause colitis (SED-14, 150) (4) (SEDA-20, 43). The mechanism was thought to be an anticholinergic effect. Two other cases have been reported (5,6), one with positive rechallenge.

- A 41-year-old man developed acute abdominal pain with profuse diarrhea and fever (39°C) while receiving intramuscular fluphenazine decanoate 125 mg once every 3 weeks. During the previous 3 months he had also taken oral alimemazine 50 mg/day, levomepromazine 50 mg/day, and amitriptyline 100 mg/day. Colonoscopy showed necrotic ulcers in the mucosa of the sigmoid and descending colon. After three weeks of parenteral nutrition, there was a marked reduction in the colonic lesions and he recovered. Levomepromazine 50 mg/day and fluphenazine decanoate 100 mg/day were reintroduced. Two days later he complained again of abdominal pain, and tomodensitometry confirmed distension.

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Second-Generation Effects

Fetotoxicity

Severe rhinorrhea and respiratory distress occurred in a neonate exposed to fluphenazine hydrochloride prenatally (7).

Drug–Drug Interactions

Vitamin C

In one patient, ascorbic acid reduced serum fluphenazine concentrations, perhaps by liver enzyme induction or by reduced absorption (8).

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Flupirtine

General Information

Flupirtine is a non-opiate, centrally acting analgesic, with muscle relaxant properties. It causes predominantly nervous system adverse effects (visual, disorientation, confusion, tremor). About 26% of patients develop minor adverse reactions (1).

Reference

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Fluproquazone and proquazone

See also Non-steroidal anti-inflammatory drugs

General Information

Fluproquazone and proquazone, quinazoline derivatives, are analgesics of minor importance. Gastrointestinal adverse effects are the most frequent (SEDA-4, 69) (SEDA-5, 197) (SEDA-10, 88). Because fluproquazone caused hepatic injury in 14% of patients in clinical trials, evaluation was halted (1).

Reference

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Flurbiprofen

See also Non-steroidal anti-inflammatory drugs

General Information

In a short-term multicenter study of flurbiprofen only 6% of patients were withdrawn because of adverse effects (1). However, in a prolonged open study in 1200 patients, more than 50% reported adverse reactions and therapy had to be withdrawn in l9% (2).

Organs and Systems

Nervous system

Nervous system effects with flurbiprofen are less common than with indometacin (3). Flurbiprofen precipitates extrapyramidal reactions, albeit rarely (SEDA-15, 101), and a parkinsonian syndrome has been reported in a predisposed patient (SEDA-15, 101).

Gastrointestinal

Flurbiprofen causes more gastrointestinal adverse effects than naproxen or ibuprofen. In a series of controlled double-blind studies, adverse reactions occurred in 27–42% of patients and were most commonly gastrointestinal in origin (18–28%) (SEDA-12, 85).

Local tolerance of flurbiprofen suppositories is often satisfactory, but discomfort, irritation, tenesmus, and diarrhea have been observed (4).

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Urinary tract

Interstitial nephritis with the nephrotic syndrome and one case of renal papillary necrosis have been recorded (SEDA-12, 86) (SEDA-17, 110). Flurbiprofen can cause a membranous nephropathy (SEDA-21, 105).

Skin

There have been two reports of a dermatitis herpetiformis-like eruption in patients taking flurbiprofen (SEDA-18, 104).

Immunologic

Leukocytoclastic vasculitis caused by flurbiprofen has been observed in a patient with rheumatoid arthritis (SEDA-15, 101).

Susceptibility Factors

Age

Elderly patients seem to be particularly sensitive to and intolerant of flurbiprofen; one study reported adverse effects in 80% (SED-11, 183) (5).

Drug Administration

Drug administration route

Intramuscular flurbiprofen was effective and well tolerated in ureteric colic; local adverse effects were slight (SEDA-20, 93).

Drug–Drug Interactions

Acenocoumarol

Flurbiprofen potentiates the anticoagulant effect of acenocoumarol (SEDA-7, 112).

Furosemide

Flurbiprofen reduces the diuretic action of furosemide (6).

Quinolone antibiotics

The Japanese regulatory authority has suggested that the data sheet for flurbiprofen should include a warning that it can cause convulsions, which has mainly been described in patients taking quinolone antibiotics (SEDA-18, 104); quinolones should not be used concomitantly (SEDA-18, 104).

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Flurotyl

General Information

Flurotyl, a hexafluorinated ether, has been used as a therapeutic inhalational convulsant in psychiatry (SED-13, 11). Its intravenous use in a polyethylene glycol solution has been discontinued because of possible renal damage. In most Western and North American countries, flurotyl is not recommended because of variations in response and dosing difficulties.

Organs and Systems

Respiratory

Flurotyl is excreted via the lungs and there has been concern about the possibility of apnea, cardiac arrest, or vascular collapse; it has therefore been recommended that resuscitation facilities be available when it is used (1).

Nervous system

The main adverse effects of flurotyl are restlessness, confusion, dysphasia, headache, and dysmelia (SED-8, 5). Prolonged muscle twitching can occur, as can intermittent jerky movements of the limbs (SED-9, 2).

Psychological, psychiatric

Flurotyl caused toxic delirium in two of 135 patients with schizophrenia (SED-13, 12).

Drug–Drug Interactions

General

Flurotyl should not be used in combination with drugs that lower the seizure threshold, such as monoamine oxidase inhibitors and phenothiazines.

Reference

1. Council on Drugs. A convulsant agent for psychiatric use. Flurotyl (Indoklon) JAMA 1966;196(1):29–30.

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Flutamide

See also Cytostatic and immunosuppressant drugs

General Information

Flutamide is a non-steroidal antiandrogen that is used to treat prostatic cancer. Its most common adverse effects are liver damage and photosensitivity.

Organs and Systems

Respiratory

Flutamide has been associated with interstitial pneumonitis.

- An 88-year-old man with prostate cancer took flutamide 375 mg/day for 3 weeks and developed dyspnea and bilateral pulmonary interstitial infiltrates; glucocorticoid therapy and withdrawal of flutamide resulted in clinical improvement (1).

Metabolism

Flutamide has been implicated in cases of pseudoporphyria (2,3).

- A 75-year-old man with prostatic carcinoma took flutamide for 18 months and developed blisters on the back of the hands and fingers after exposure to the sun (4). The bullae were associated with skin fragility and atrophic scarring. Histopathology and direct immunofluorescence showed ultrastructural features similar to those described in porphyria cutanea tarda. However, porphyrin concentrations in the urine and blood were normal. Flutamide was withdrawn and the lesions healed, without relapse after 11 months.

Hematologic

Although it is the commonest of all antineoplastic adverse effects, there are sometimes peculiarities of hematological toxicity that make it worthy of comment (5).

Flutamide can cause methemoglobinemia (6–8) or sulfhemoglobinemia (5). The latter occurred in a 70-year-old man who had taken flutamide 150 mg tds for 1 month and developed cyanosis and anemia that was not responsive to methylthioninium chloride (methylene blue).

In 45 patients with prostatic cancer taking flutamide 250 mg tds, there was no evidence of methemoglobinemia (9). It is possible that anecdotal reports of this adverse effect are in patients with a particular susceptibility that was not represented in this study.

Gastrointestinal

Among 440 patients taking flutamide, gastrointestinal adverse effects (abdominal pain/distension, diarrhea, constipation, nausea/vomiting, and anorexia) occurred in about 22% (10).

Ischemic colitis has been attributed to flutamide (11).

Liver

Flutamide can cause liver damage, which can occasionally be fatal (12).

- A 74-year-old man developed life-threatening acute liver failure while taking flutamide (13). Other causes of acute liver failure were ruled out and there was no evidence of active prostate cancer or liver metastases.

The authors suggested that mitochondrial dysfunction is implicated in flutamide-associated liver damage.

Three patients with advanced prostate carcinoma who took flutamide 250 mg tds for 20–22 weeks developed signs of liver damage (jaundice, anorexia, nausea, dark urine) and changes in liver function tests (high transaminases and bilirubin), indicative of acute hepatitis; flutamide was withdrawn and there was spontaneous remission over the next 8 weeks (14).

In a retrospective study of 185 patients who had taken flutamide for 151 (range 4–443) days, 9 had liver damage (15). The most common features were weakness, anorexia, weight loss, nausea, vomiting, and jaundice. No patient had evidence of hypersensitivity. In two patients there was fulminant liver failure; one had a liver transplant and the other died. The authors suggested that liver function tests should be monitored during the first months of flutamide therapy and that the drug should be withdrawn if transaminases begin to rise.

Of 123 patients who had taken flutamide, 33 had liver disorders, mostly within 9 months (16). Three variables, body mass index, a past history of liver disorders, and raised transaminases were significantly related to the incidence of liver disorders. Smoking was related to a lower incidence.

Urinary tract

Flutamide rarely causes renal damage.

- A 54-year-old man with metastatic prostate cancer developed non-oliguric acute renal insufficiency while taking flutamide; after withdrawal his renal function returned to normal within 4 weeks (17). After rechallenge his blood urea nitrogen and serum creatinine rose again and recovered completely after withdrawal.

Skin

Flutamide can cause photosensitivity reactions (18–20) and can cause residual vitiligo (21,22). The spectrum of the effect is in the UVA range (23).

- A 68-year-old man had a photosensitive drug eruption while taking flutamide (24). The minimal erythema dose with ultraviolet A light was reduced to 2 J/cm^2 and recovered to over 16 J/cm^2 after withdrawal, without changing reactivity to ultraviolet B. The absorption spectrum of flutamide was not altered after ultraviolet A irradiation.

The authors thought that flutamide has low potency to act as a photohapten, and that a non-photohaptenic mechanism is responsible for this photosensitivity or that its active metabolite may act as a photosensitizer.

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Musculoskeletal

In 26 men who took androgen deprivation therapy for prostate cancer for 10 years there was reduced bone mineral density with increasing duration of androgen deprivation therapy across the whole 10-year period (25). The authors also noted that patients taking intermittent therapy had similar loss of bone mineral density at years 2 and 4, but less bone loss from year 6 onwards.

Susceptibility Factors

Renal disease

The pharmacokinetics of flutamide and its pharmacologically active metabolite, hydroxyflutamide, have been studied in 26 men with normal or reduced renal function, some of whom were undergoing hemodialysis; the pharmacokinetics were not altered by renal impairment or hemodialysis (26).

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Fluvastatin

See also HMG Co-A reductase inhibitors

General Information

It has been suggested that the pharmacokinetics of fluvastatin, including extensive biliary excretion and absence of circulating active metabolites, might be associated with a low incidence of systemic adverse effects compared with other statins. In over 1800 patients treated for an average of 61 weeks, fluvastatin was safe and tolerable (SEDA-19, 408). Pooled data from clinical trials have shown that gastrointestinal symptoms occurred in 14% of fluvastatin recipients compared with 9% taking placebo; other complaints occurred

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0.5–5% more often with fluvastatin, including insomnia, sinusitis, hypesthesia, tooth disorders, and urinary tract infections. Fluvastatin was withdrawn because of adverse events in 3.5% of 2585 patients taking monotherapy and in 3.2% of 842 patients taking placebo (1).

Organs and Systems

Liver

Hepatotoxicity has been reported with fluvastatin.

- Cholestatic hepatitis developed in a 71-year-old man with nephrotic syndrome (2). Hepatic function was normal after several months of fluvastatin 20 mg/day. Some weeks after the dose was increased to 40 mg/day, his gamma-glutamyl transpeptidase activity rose from normal to 1818 IU/l, with negative serology for viruses. After normalization, re-introduction of fluvastatin 20 mg/day was not tolerated, but he did tolerate simvastatin 20 mg/day.
- A 61-year-old woman developed symptoms of acute hepatitis 6 weeks after she began to take fluvastatin sodium 20 mg/day for hypercholesterolemia (3). Ultrasonography and liver biopsy confirmed the diagnosis of non-obstructive intrahepatic jaundice. Studies of viral markers and autoimmune factors excluded viral hepatitis and autoimmune hepatitis. There was a high serum concentration of a metabolite of fluvastatin, suggesting a possible anomaly of drug metabolism. All liver function tests normalized 8 weeks after the withdrawal of fluvastatin.

Pancreas

Acute pancreatitis has been attributed to fluvastatin (4).

- A 36-year-old man took fluvastatin 40 mg/day for 3 months and developed mild acute pancreatitis, which settled with medical treatment. Other causes were ruled out. Some months later, he started taking fluvastatin again and had a recurrence of pancreatitis within a few days.

According to the authors, statin-induced acute pancreatitis can occur on the first day of therapy or after several months. It is generally mild and runs a benign course; no deaths have been reported. Its frequency is unknown but it is probably rare.

Musculoskeletal

In a pooled analysis of a large population of patients with hypercholesterolemia taking fluvastatin 20 mg/day, 40 mg/day, and fluvastatin modified-release 80 mg/day, the frequency of significant rises in creatine kinase activity was low and not different from placebo (5). This applied to men and women both above and below the age of 65 years. There were no increases in the frequency of rises in creatine kinase activity with higher doses of fluvastatin.

Immunologic

- A 67-year-old woman had a fatal reaction 1 week after she started to take fluvastatin 20 mg/day. When the drug was withdrawn 10 weeks later, she had arthralgia, myalgia, an erythematous maculopapular rash, and breathlessness due to a widespread alveolitis (6).

Drug Administration

Drug formulations

Once-daily administration of modified-release formulation of fluvastatin 80–320 mg/day was generally safe and well tolerated in 40 patients with primary hypercholesterolemia over 13 days (7). However, fluvastatin 640 mg in this formulation was not well tolerated: six of seven patients had adverse events, including diarrhea, headache, and rises in serum transaminases. In addition, the pharmacokinetics of fluvastatin were non-linear at this dose, possibly because of saturation of first-pass metabolism, causing higher than expected serum drug concentrations.

Drug–Drug Interactions

Bezafibrate

Concomitant administration of fluvastatin and bezafibrate resulted in a 50% increase in the AUC of fluvastatin (SEDA-21, 460).

Ion-exchange resins

The systemic availability of fluvastatin is reduced by bile acid sequestrants (1).

Rifampicin

The systemic availability of fluvastatin is reduced by the hepatic enzyme inducer rifampicin (1).

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Fluvoxamine

See also Selective serotonin re-uptake inhibitors (SSRIs)

General Information

Fluvoxamine is a non-sedating antidepressant with fewer anticholinergic adverse effects than clomipramine or imipramine (1–3). Its major adverse effects, like those of other SSRIs, include nausea and vomiting. It has a half-life of 15 hours, and peak plasma concentrations occur at 1–8 hours after oral administration (4). It is metabolized (by oxidation, oxidative deamination, and hydrolysis) to nine metabolites, none of which is pharmacologically active (5). Studies of single versus multiple dosing have shown no significant differences (6,7). Usual doses are in the range of 150–300 mg/day, and once-a-day dosing is possible.

Fluvoxamine appears to have no specific effects on laboratory tests (4,8,9); although some have reported a significant fall in platelet count and an increase in serum creatinine, most of the values remained well within the reference ranges (10).

Organs and Systems

Cardiovascular

A slight, clinically unimportant reduction in heart rate has been reported with fluvoxamine (11,12). There has been one report of supraventricular tachycardia in a woman with no previous cardiovascular disease, but the association with fluvoxamine was unclear since there was no rechallenge (SEDA-16, 9).

Nervous system

In a yearlong study of 31 patients there was agitation, which required withdrawal in two patients early in treatment, dry mouth, tremor, and insomnia (13). Increased agitation and insomnia may require the addition of a sedative or hypnotic.

Acute dystonia has been described in association with fluvoxamine (SEDA-18, 20).

Seizures have been reported in a predisposed subject given fluvoxamine (SEDA-17, 20).

Treatment with serotonin-potentiating drugs in usual therapeutic doses can sometimes produce the serotonin syndrome. There are also case reports of this reaction with single doses of SSRIs (see also the monograph on Sertraline) (14).

- An 11-year-old boy was brought to the emergency room about 2 hours after taking a single tablet of fluvoxamine (50 mg) prescribed for treatment of attention-deficit disorder. He was also taking benzatropine and perphenazine (dosages not stated). On arrival, he was agitated and unresponsive, with bilateral ankle clonus, muscle rigidity, fasciculations, and profuse sweating. His temperature rose to 39.7°C. He was paralysed, intubated, and ventilated, after which his condition improved. Two days after admission, he had fully recovered.

The dopamine receptor antagonist properties of perphenazine may have played a part in producing the syndrome in this case.

SSRIs can cause insomnia and daytime somnolence; however, the symptoms seem to reflect a sleep–wake cycle disorder. It is conceivable that disruptions in the normal pattern of melatonin secretion, particularly a delay in the normal early morning fall in plasma concentrations, could be involved in the pathophysiology of these symptoms. The fact that these sleep disorders were seen only with fluvoxamine would also support a role of melatonin (see the section on Endocrine in this monograph).

Psychological, psychiatric

Reports of acute mania and manic-like behavior after treatment with fluoxetine or fluvoxamine have appeared (SEDA-13, 12) (SEDA-17, 20) (SEDA-18, 20), but there are not enough data to estimate the incidence.

Endocrine

Fluvoxamine causes increased plasma melatonin concentrations. In an in vitro preparation, melatonin was metabolized to 6-hydroxymelatonin by CYP1A2, which was inhibited by fluvoxamine at concentrations similar to those found in the plasma during therapy (15). This effect was not shared by other SSRIs or by tricyclic antidepressants, which do not have prominent effects on melatonin secretion. Whether increased concentrations of melatonin and loss of its normal circadian rhythm might cause symptoms is unclear. However, melatonin is believed to play a role in the regulation of circadian rhythms, including entrainment of the sleep–wake cycle. There have been 10 cases of circadian rhythm sleep disorder associated with fluvoxamine (16). All the patients had delayed sleep-phase syndrome, which is characterized by delayed-sleep onset and late awakening. The delay in falling asleep and waking up in the morning was 2.5–4 hours. In nine of the cases withdrawal of fluvoxamine or a reduced dosage led to resolution of the sleep disorder. When the patients were given alternative serotonin potentiating agents, such as clomipramine or fluoxetine, the sleep disorder did not recur.

Serotonin pathways are involved in the regulation of prolactin secretion. Amenorrhea, galactorrhea, and hyperprolactinemia have been reported in a patient who was already taking an antipsychotic drug after starting treatment with fluvoxamine (SEDA-17, 20).

Three cases of fluvoxamine-induced polydipsia, attributed to the syndrome of inappropriate ADH secretion (SIADH), have been reported (SEDA-18, 20).

Hematologic

Fluvoxamine-associated bleeding has been described (17–19).

Skin

A case of toxic epidermal necrolysis after fluvoxamine has been described; although the patient was taking other drugs, the authors concluded that the skin reaction was probably due to fluvoxamine (SEDA-18, 20).

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Hair

Hair loss has been associated with fluvoxamine (20).

Long-Term Effects

Drug withdrawal

Withdrawal symptoms have been reported with fluvoxamine (SEDA-17, 20) (SEDA-18, 21).

Second-Generation Effects

Lactation

In two cases, treatment of breast-feeding mothers with fluvoxamine (300 mg/day) was associated with undetectable concentrations of fluvoxamine (below 2.5 ng/ml) in the plasma of both infants (21). These results are encouraging, but further data will be needed before it can be concluded that fluvoxamine has an advantage over other SSRIs in this respect.

Drug Administrations

Drug overdose

There have been four cases of overdosage with fluvoxamine in amounts ranging from 600 to 2500 mg (22).

Drug–Drug Interactions

Buspirone

In 10 healthy volunteers, fluvoxamine (100 mg/day for 5 days) significantly increased the peak concentrations of the anxiolytic drug buspirone. Concentrations of the active metabolite, 1-(2-pyrimidinyl)-piperazine, were reduced (23). These effects were probably mediated through inhibition of CYP3A4 by fluvoxamine.

Clozapine

In a prospective study fluvoxamine, in a low dosage of 50 mg/day, produced a threefold increase in plasma clozapine concentrations (n = 16) (24).

Other reports have confirmed that fluvoxamine increases plasma concentrations of clozapine and its metabolites (25,26) (SEDA-21, 12). The mechanism is probably inhibition of CYP1A2.

Methadone

Fluvoxamine increases methadone concentrations in patients taking methadone maintenance treatment for the management of opioid dependence (SEDA-19, 11). The addition of sertraline (200 mg/day) produced a modest (16%) increase in methadone concentrations in 31 depressed opioid-dependent subjects after 6 but not 12 weeks of combined treatment (27). The increase in methadone concentrations was more modest than that reported with fluvoxamine, presumably because sertraline is a less potent inhibitor of CYP1A2 and CYP3A4, both of which are involved in methadone metabolism.

Olanzapine

The atypical antipsychotic drug olanzapine is also metabolized by CYP1A2.

- A 21-year-old woman with schizophrenia and depression, who had been taking fluvoxamine (150 mg/day) and olanzapine (15 mg/day) for several months, developed an extrapyramidal movement disorder, including rigidity and tremor (28). The plasma fluvoxamine concentration was 70 ng/ml (usual target range is 20–500 ng/ml), while that of olanzapine was 120 ng/ml (usual target range is 9–25 ng/ml). The dosage of olanzapine was reduced to 5 mg/day and the plasma olanzapine concentration fell to 38 ng/ml, with resolution of the tremor and rigidity. When fluvoxamine was replaced with paroxetine (20 mg/day) the olanzapine concentration fell further to 22 ng/ml.

Of the SSRIs, fluvoxamine is the most potent inhibitor of CYP1A2 and is therefore likely to increase plasma olanzapine concentrations. The extrapyramidal effects in this case were presumably due to excessive blockade of dopamine D_2 receptors by raised olanzapine concentrations.

Phenytoin

Fluvoxamine inhibits CYP2C9 and CYP2C19, the enzymes responsible for the metabolism of phenytoin.

- A 45-year-old woman taking phenytoin 300 mg/day had a plasma phenytoin concentration of 66 μmol/l (29). When she became depressed fluvoxamine 50 mg/day was added. A month later her depressive symptoms had improved, but she was ataxic and the plasma phenytoin concentration was 196 μmol/l. The fluvoxamine was withdrawn and the phenytoin dose reduced to 150 mg/day. Her plasma phenytoin concentration fell to 99 μmol/l, with resolution of the ataxia.

In vitro studies suggest that fluvoxamine is the most potent SSRI in terms of its ability to inhibit phenytoin metabolism. Inhibition of CYP2C19 or CYP2C9 could be responsible, although fluvoxamine is a relatively weak in vitro inhibitor of CYP2C9. However, in 14 healthy volunteers fluvoxamine (150–300 mg/day for 5 days) significantly reduced the clearance of tolbutamide (30). This suggests that fluvoxamine should be used with caution when it is co-administered with drugs such as tolbutamide, phenytoin, and warfarin, which are substrates for CYP2C9.

Thioridazine

Fluvoxamine inhibits CYP1A2, and a low dosage (50 mg/day) produced a 225% increase in plasma thioridazine concentrations in 10 patients with schizophrenia (31). This was not reflected in an increased incidence of clinical adverse events; however, thioridazine prolongs the QT_c interval, which was not measured.

Tolbutamide

In 14 healthy volunteers fluvoxamine (150–300 mg/day for 5 days) significantly reduced the clearance of tolbutamide (30). This suggests that fluvoxamine should be used

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with caution when it is co-administered with drugs that are substrates for CYP2C9, such as tolbutamide, phenytoin, and warfarin.

Tricyclic antidepressants

Fluvoxamine is a potent inhibitor of cytochrome CYP1A2, which may lead to interactions with several tricyclic antidepressants and theophylline (32).

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Folic acid, folinic acid, and calcium folinate

See also Vitamins

General Information

Folic acid (pteroylglutamic acid) is a vitamin of the B group, whose Average Dietary Requirement in adults has been set at 140 micrograms/day, with a Population Reference Intake of 200 micrograms/day. Red cell folate concentrations above 150 ng/ml indicate sufficiency (1). However, higher doses are used for specific purposes, including in pregnancy, apparently without ill effects. Neural tube defects can be prevented in offspring by periconceptual ingestion of

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400 micrograms/day (2). One aspect of folate metabolism concerns the recycling of the putatively atherogenic amino acid, homocysteine (3). For reasons that are not clear, homocysteine accumulates in the blood of dialysis patients, and this accumulation is inversely related to folate status. Because of the association of folate with a risk factor for atherosclerosis—it is the major cause of morbidity and mortality in dialysis patients—folate supplementation has been widely recommended as a strategy to reduce homocysteine concentrations, and a daily dose of 800 micrograms has been proposed as part of a mass strategy to reduce the risk of heart attacks and strokes by over 80% (4).

Folinic acid is a reduced form of folic acid. The adverse effects of antifolate drugs that are tetrahydrofolate reductase inhibitors, such as methotrexate, cannot be prevented by giving folic acid, since antifolate drugs inhibit the conversion of folic acid to folinic acid. Folinic acid is therefore given instead, as calcium folinate (leucovorin). However, in patients who take antifolate drugs intermittently (for example methotrexate once a week in psoriasis or rheumatoid arthritis) folic acid taken on another day is adequate.

Recommendations that women who plan to become or have just become pregnant should take daily oral folic acid supplements in order to prevent neural tube defects were issued by health authorities in several European countries from 1991 onwards (5). The recommendations generally follow the lead of the US Public Health authorities which recommended a supplementation dose of 400 micrograms/day (6). This is what a woman would consume if she followed the US Dietary Guidelines and Dietary Pyramid (7). The etiology of neural tube defects is not entirely clear; the condition may have several different causes, only some of which may be responsive to folate (8,9). Rates of neural tube defects vary considerably between countries; in the USA rates of neural tube defects isolated from other birth anomalies fell over the period 1968–89 (10). The justification for a recommendation for general high-dose supplementation or food fortification is still under discussion (11). The debate elicited by this recommendation has spurred interest in possible adverse effects, and a thorough review published in 1998 (12) identified the following potential safety issues of folic acid supplementation in addition to those mentioned above: folate neurotoxicity, reduced zinc absorption, association with malignant neoplasms, hypersensitivity reactions, and increased susceptibility to malaria. However, the data are weak and consist predominantly of case series and individual reports. Furthermore, it is likely that even if such adverse effects did occur, the benefit to harm balance would still be highly favorable.

The main argument against an increase in folic acid supply to the population as a whole is the possible masking of vitamin B_{12} deficiency by normalization of the blood count (see the section *Does folic acid mask vitamin B_{12} deficiency?* in this monograph). However, while certain animal findings and some case reports have actually suggested worsening of the neurological effects of vitamin B_{12} deficiency when patients are treated with folic acid, these do not prove a causal relation (see the section *Does folic acid enhance the neurological symptoms of vitamin B_{12} deficiency?* in this monograph). Nevertheless, because the available data do not exclude such an effect, in the US-Canadian "Dietary Reference Intakes" in adults the upper limit has been set at 1000 micrograms/day folic acid in supplements or enriched food preparations and in children (1–18 years of age) the upper limit has been set at 300–800 micrograms. At doses of 5 mg/day in more than 100 patients there was progression of neurological complications, but there have only been eight case reports of the effect of lower doses of folic acid. Because there is no NOAEL (no observed adverse effect level), a LOAEL (lowest observed adverse effect level) of 5 mg/day had to be used for the upper limit. In contrast, in 1996 the FDA fixed an upper limit of 1000 micrograms/day folic acid (natural and synthetic preparations) (6,13). It was also argued that in children of vegetarians natural folate had masked vitamin B_{12} deficiency. These previous values have now been re-evaluated by the FDA. Dietary supplementation with both folic acid and vitamin B_{12} offers a solution to this problem. No risks of increasing the supply of vitamin B_{12} are expected, but the dosage that would correct vitamin B_{12} deficiency remains to be defined (6,12).

General adverse effects

Negative effects resulting from dietary intake of high concentrations of folic acid have only rarely been documented in some older case reports and uncontrolled intervention studies. Some of these negative effects were not confirmed in subsequent randomized, controlled intervention studies (14).

In humans the toxicity of folic acid is low, even after long-term use (12,15,16). Only in one trial in 14 volunteers (six women, eight men, aged 22–57 years) were there adverse effects, such as gastrointestinal disturbances, insomnia, irritability, or depressive states (17). As a possible cause the authors suggested a high folic acid concentration in the cerebrospinal fluid (5–10 times higher than that in serum). However, these findings were not confirmed in subsequent trials with high-dose folic acid supplementation.

Does folic acid mask vitamin B_{12} deficiency?

Vitamin B_{12} deficiency most frequently is seen in people over 60 years of age (11). Deficiency of vitamin B_{12} in younger adults is rare, but can occur as a result of reduced absorption of vitamin B_{12}, for example in pernicious anemia, atrophic gastritis type B, long-term use of blockers of acid secretion, or short bowel syndrome after resection of the terminal ileum (18,19). Vitamin B_{12} deficiency in children usually depends on inborn defects of vitamin B_{12} metabolism or on insufficient support during pregnancy and breastfeeding.

Vitamin B_{12} deficiency can present as hematological, gastrointestinal, and neurological disturbances. The anemia of B_{12} deficiency is actually due to functional deficiency of folic acid, and results from accumulation of folic acid derivatives in the form of 5-methyltetrahydrofolate, which prevents regeneration of tetrahydrofolic acid and consequently, by interfering with the synthesis of purines and DNA, reduces cell proliferation. Therefore, giving folic acid to patients with vitamin B_{12} deficiency can abolish the hematological effects but will not affect the neurological symptoms. Normalization of

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the blood count requires high doses of folic acid in the absence of B_{12} replacement therapy. Treatment with folic acid 0.3–1 mg/day normalizes the blood count in 50% of patients with B_{12} deficiency, while at doses over 5 mg/day the hematological changes are normalized in most patients (20). However, the hematological effects can recur, even after treatment with high doses of folic acid (5–500 mg/day), if the vitamin B_{12} deficiency is not treated.

Concerning possible masking of vitamin B_{12} deficiency by folic acid, blood counts in 11–33% of the patients with neurological symptoms of vitamin B_{12} deficiency are in the reference range. That means that in patients with severe funicular myelosis, a vitamin B_{12} deficiency psychosis, changes in the blood count may not occur, while on the other hand in patients with severe pernicious anemia neurological symptoms are not inevitably present.

Organs and Systems

Nervous system

Does folic acid enhance the neurological symptoms of vitamin B_{12} deficiency?

The results of some animal experiments and case reports have suggested that high doses of folic acid can enhance or worsen the neurological effects of vitamin B_{12} deficiency. Thus, in animals with vitamin B_{12} deficiency being treated with folic acid, neurotoxicity developed more rapidly than in the untreated controls (21–23). Some unproven hypotheses about how folic acid could enhance the neurological symptoms of vitamin B_{12} deficiency have been discussed, for example redistribution of B_{12} from the nervous system into the bone marrow, accompanied by a fall in serum concentration and reticulocytosis (20). There have also been some reports that in patients with vitamin B_{12} deficiency neurological complications occurred for the first time or increased in severity when folic acid was given, the severity and onset of the complications correlating with the dose of folic acid.

Whether folic acid is responsible for these observations or whether the neuropathy depends on progressive vitamin B_{12} deficiency and simply coincides with the administration of high doses of folic acid cannot be determined from these reports. In patients who were treated beforehand with liver extracts the neurological changes were weaker and occurred later than in patients who were treated with folic acid exclusively. This suggests that progressive reduction in cobalamin pools is as important for the development of the neurological complications as the supply of folic acid. Furthermore, rapid worsening of neurological changes in patients with cobalamin deficiency has also been seen in patients who have not received folic acid.

Because there have been no double-blind, placebo-controlled intervention studies of the effect of folic acid, the question of whether folic acid in patients with vitamin B_{12} deficiency aggravates the neurological complications cannot be answered definitively. From the data at hand we cannot exclude the possibility that folic acid may exacerbate the effects of vitamin B_{12} deficiency. For that reason an upper limit of 1 mg/day folic acid (in supplements or a vitamin-enriched diet) has been set in the "Dietary Reference Intakes" (15).

Folic acid and seizures

In patients with a history of seizures, worsening of the seizures and an increase in their frequency have been reported in relation to folic acid (24).

- A 26-year-old woman with a family history of spinal amyotrophy and multiple sclerosis sought prepregnancy counselling and was given folic acid 800 micrograms/day to prevent neural tube defects. At 2 years of age, 6 months after a chickenpox infection, she had had recurrent fits and language regression, successfully treated with ethosuximide. At 12 years of age she developed seizures nearly every month, characterized by sensations of fear, loss of contact, fixed eyes, motor automatism, and postictal aphasia. This had responded to carbamazepine. After starting to take folic acid she had a generalized tonic-clonic seizure for the first time and a significant increase in seizure frequency.

There has been some discussion as to whether an adverse effect of folic acid on seizures represents a direct epileptogenic effect or results from interference with the effects of anticonvulsants. Initially, it was supposed that folic acid provokes seizures, and the first report of an epileptic patient with megaloblastic anemia in whom folate therapy resulted in an exacerbation of seizures was published in 1960. Although several subsequent controlled studies failed to show any adverse effect on seizure frequency linked to folic acid supplementation, case reports and uncontrolled studies have documented worsening seizure frequency in some patients given folic acid, but the susceptibility factors at play have not been identified.

Antiepileptic drugs reduce serum folate concentrations. Conversely, the use of folic acid can reduce the effects of antiepileptic drugs such as phenytoin and can reduce their serum concentrations (25,26).

Besides its effect on antiepileptic drugs, folic acid in animal experiments was neurotoxic and epileptogenic (27). However, when the neurotoxicity of folic acid was investigated in two groups of patients—the newborns of mothers who had taken folic acid during pregnancy and patients with parkinsonian syndromes—neurotoxicity was not found in either group (12).

Metal metabolism

The authors of the "Dietary Reference Intakes" (15) have concluded that reports of the effect of folic acid supplementation on the intestinal absorption of zinc are controversial, but that the recent literature shows that folic acid supplementation has either no effect or an extremely weak effect on zinc supply.

Hematologic

High doses of folic acid and vitamin B_{12} increase the reticulocyte count. Use of either of these vitamins can therefore mask a deficiency of the other (SEDA 17, 440). If anemia due to deficiency of either of these nutrients is suspected, serum concentrations of both vitamin B_{12} and folic acid should be assessed (28).

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Immunologic

There have been some reports of hypersensitivity after oral, parenteral, and intradermal administration of folic acid, and a case has recently been reported with folinic acid (29).

- An 80-year-old woman had a colonic resection for Duke's C stage adenocarcinoma and was then given fluorouracil 400 mg/m^2/day and folinic acid 200 mg/m^2/day for 5 days every 4 weeks. She later developed metastases and a second course of chemotherapy included irinotecan (180 mg/m^2), fluorouracil 400 mg/m^2, followed by a continuous infusion of 2400 mg/m^2 over 2 days, folinic acid 200 mg/m^2, ondansetron, and atropine. During the first course of chemotherapy she developed urticaria following the administration of ondansetron and folinic acid. The ondansetron was withdrawn and replaced by metoclopramide and prednisone. During the next course, just after the administration of folinic acid, metoclopramide, and prednisone, she had more urticaria and profound hypotension and required intravenous adrenaline. Folinic acid was withdrawn and subsequent courses were uneventful.

Using a published method (30) the reaction in this case was considered to be very probably due to folinic acid.

IgE-antibodies to folic acid have been demonstrated in a woman with anaphylactic reactions to two multivitamin formulations containing folic acid (31).

Long-Term Effects

Tumorigenicity

In a large US cohort study folic acid was associated with an increased risk of cancer in general and of cancers of the oropharynx and hypopharynx (32). However, the authors pointed to the possibility that the observed association could have depended on confounding by alcohol and smoking.

Second-Generation Effects

Pregnancy

High doses of folic acid (commonly 4–5 mg) have been used in pregnancy to prevent neural tube defects, without apparent ill effects (33). In a non-randomized, Swedish study in 2569 women the number of twin births in those who took folic acid supplements during early pregnancy was increased (34). In those who took folic acid the rate of twin births was 2.8% compared with 1.5% overall. However, in the large, randomized, multicenter MRC study with high doses of folic acid (4 mg/day) there was no increase in the frequency of twin births (33). Because of the higher rate of complications in twin pregnancies and twin births, the authors suggested that folic acid prophylaxis in countries with low frequencies of spina bifida might be harmful rather than useful. Similar results have also been seen in other studies (35,36).

Drug–Drug Interactions

Anticonvulsant drugs

An interaction of anticonvulsant drugs with the metabolism of folate has been described (SEDA-13, 348) (see also the section on *Nervous system* in this monograph).

Folic acid can alter the metabolism of phenytoin. In one case folic acid 5 mg/day reduced the serum phenytoin concentration to below the target range, and a breakthrough seizure occurred (25). The Km of phenytoin metabolism was significantly reduced, suggesting competitive inhibition of metabolism. In another series folic acid reduced the serum concentrations of phenytoin (37). Furthermore, the administration of folic acid to treat folate deficiency can reduce the beneficial effects of anticonvulsants (38). Rare but serious cases in which this epileptogenic effect of folic acid has been very pronounced have been reported (39). However, folic acid is well tolerated by many other patients with epilepsy who require folic acid.

Fluorouracil

Reduced folates are co-factors for the 5-fluorodeoxyuridine monophosphate-thymidilate synthetase reaction. Leucovorin (calcium folinate) therefore potentiates the toxicity of 5-fluorouracil, and fatal adverse effects have been reported in patients over 65 years of age receiving high-dose treatment with leucovorin simultaneously with fluorouracil. This has led some groups to recommend that initial dose levels of fluorouracil should be lowered by 20% and that therapy be stopped temporarily at the first sign of distal gastrointestinal adverse effects (SEDA-15, 414).

Methotrexate

Methotrexate is an antagonist of folic acid and is used for treating neoplastic diseases and non-neoplastic diseases such as rheumatoid arthritis and psoriasis. As methotrexate reduces the activity of dihydrofolate reductase, supplementation with folic acid and especially with folinic acid could reduce the beneficial effects of methotrexate. This assumption has been supported by the results of an intervention study (40). Patients with rheumatoid arthritis treated with methotrexate (15 g/week) had an increase in symptoms. An open intervention trial of folinic acid 45 mg/week also showed an increase in arthritis symptoms (41). However, other trials showed no effects of this sort, and administration of folic acid or folinic acid is important in preventing methotrexate-induced blood dyscrasias.

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Follitropin

General Information

The first gonadotropins available for clinical use were extracted from the urine of postmenopausal women. Human menopausal gonadotropin (hMG) is in limited supply and contains other proteins, which may be allergenic, as well as luteinizing hormone. Purified preparations of follicle-stimulating hormone (FSH; urofollitropin and highly purified urofollitropin) are also extracted from

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human urine. Recombinant FSH (follitropin-alfa) prepared from a Chinese hamster ovarian cell line is likely to replace other gonadotropins because of its purity and ease of patient self-administration.

Follitropin treatment for infertility has been reviewed in detail (1,2). Multiple pregnancy occurs in 20% of patients, 80% being twin pregnancies. There is no documented increase in congenital abnormalities in children conceived after ovulation induction with follitropin.

Organs and Systems

Nervous system

- A 32-year-old woman who was not obese developed benign intracranial hypertension in association with ovarian hyperstimulation syndrome after ovulation induction using goserelin, follitropin, and human chorionic gonadotropin (hCG) (3). The syndrome did not recur during a second pregnancy in which follitropin and hCG were not used

Reproductive system

Ovarian hyperstimulation syndrome (OHSS) is characterized by massive ovarian enlargement and fluid shift from the intravascular space to the peritoneal, pleural, and pericardial cavities. Rates of up to 20% for all grades and 1–2% for severe OHSS have been documented and do not differ between preparations of follitropin. Women with polycystic ovarian syndrome are at higher risk of this complication. In rare cases women have died of pulmonary embolism, disseminated intravascular coagulation, or adult respiratory distress syndrome. If the patient is pregnant, OHSS is more severe and prolonged (1). Generally, it resolves within 7 days if the patient is not pregnant or in 10–20 days if she is. The underlying cause of this adverse effect is not known.

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Fomivirsen

General Information

Fomivirsen (ISIS 2922) is an antisense oligonucleotide that specifically inhibits replication of human cytomegalovirus. It has been developed for intravitreal administration to treat cytomegalovirus retinitis in patients with AIDS.

Organs and Systems

Sensory systems

The most common adverse effects of fomivirsen reported in clinical trials have been increased intraocular pressure and mild to moderate uveitis (1,2). These events were generally transient or reversible with topical glucocorticoids.

In 150 patients who were given intravitreous fomivirsen 165 micrograms/injection (35 eyes, 30 patients) or two different regimens of 330 micrograms/injection (142 eyes, 110 patients), anterior chamber inflammation and increased intraocular pressure were dose-related and schedule-dependent: 165 micrograms/injection, 4.1 events/patient-year; 330 micrograms/injection, 6.6 events/patient-year (less intense regimen) and 8.4 events/patient-year (more intense regimen) (3). A large number of other ocular adverse events may not have been related to the drug.

In 309 eyes of 238 patients there were two cases of bull's-eye maculopathy, which resolved after withdrawal (4).

Retinal pigment epithelial changes have been noted at doses of fomivirsen that overlap with those used to treat CMV retinitis (2). In one case there was nyctalopia and reduced visual acuity (20/50 OD) in conjunction with mid-peripheral epithelial pigmentation and cotton-wool spots around the perifoveal capillary network (5).

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Fondaparinux

General Information

Fondaparinux is a synthetic pentasaccharide that mimics the site of heparin that binds to antithrombin III and inhibits factor Xa activity, which in turn inhibits thrombin generation. It does not release tissue factor pathway inhibitor. It is nearly completely absorbed after subcutaneous

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administration, has a rapid onset of action and a long half-life (14–20 hours), and is excreted by the kidneys. Its pharmacology, clinical pharmacology, and uses have been reviewed (1–16).

Fondaparinux has been approved in some countries for the prophylaxis of venous thrombosis after orthopedic surgery in a fixed dose of 2.5 mg/day without monitoring. A structural analogue, idraparinux sodium, has additional methyl groups, a long half-life, and once-weekly administration. Both drugs are being developed as antithrombotic drugs for venous and arterial thrombosis, acute coronary syndrome, and stroke, and as adjuncts to thrombolytic therapy.

There is currently no specific antidote for fondaparinux: it is not neutralized by protamine sulfate. Fondaparinux shows no cross-reactivity with antibodies associated with heparin-induced thrombocytopenia.

Comparative studies

There have been two double-blind, randomized comparisons of fondaparinux 2.5 mg/day or enoxaparin 40 mg/day after hip fracture surgery (17), or elective major knee surgery (18). Fondaparinux reduced the risk of thromboembolism by 56% in the first study ($n = 1250$) and by 55% in the second ($n = 724$). There were no significant differences between the two groups in the first study in the incidence of death or clinically important bleeding. In the second study, major bleeding occurred more often with fondaparinux, but there were no significant differences between the two groups in the incidence of bleeding leading to death or reoperation, or occurring in a critical organ.

In a double-blind, randomized study of 2309 consecutive patients undergoing elective hip replacement, postoperative subcutaneous fondaparinux 2.5 mg/day was compared with preoperative enoxaparin 40 mg/day (19). By day 11, venous thromboembolism had occurred in 85 (9%) of 919 patients assigned to enoxaparin and in 37 (4%) of 908 patients assigned to fondaparinux, a relative risk reduction of 56% (95% CI = 33, 73). In a similar comparison of postoperative fondaparinux 2.5 mg/day and enoxaparin 30 mg bd in 2275 consecutive patients undergoing elective hip replacement, by day 11 venous thromboembolism had occurred in 48 (6%) of 787 patients assigned to fondaparinux and in 66 (8%) of 797 patients assigned to enoxaparin, a relative risk reduction of 26% (95% CI = 11, 53) (20).

In a meta-analysis of these studies, bleeding was slightly, but not significantly, more frequent with fondaparinux than with enoxaparin (21,22).

Drug–Drug Interactions

Aspirin

In healthy volunteers, steady-state fondaparinux did not alter the pharmacodynamic effects of a single dose of aspirin 975 mg (23). Aspirin did not alter the pharmacokinetics of fondaparinux.

Digoxin

In a randomized, crossover study in 24 healthy volunteers, the pharmacokinetics of fondaparinux sodium 10 mg/day subcutaneously for 7 days were unaffected by digoxin 0.25 mg/day orally for 7 days (24).

Piroxicam

In healthy volunteers, steady-state fondaparinux did not alter the pharmacodynamic effects of a single dose of piroxicam 20 mg (23). Piroxicam did not alter the pharmacokinetics of fondaparinux.

Warfarin

There was no pharmacodynamic interaction of subcutaneous fondaparinux 4 mg with warfarin in 12 healthy men (25).

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Formaldehyde

See also Disinfectants and antiseptics

General Information

Aldehydes such as formaldehyde, glyoxal, and glutaral (glutaraldehyde) are used as solutions and vapours for disinfection and sterilization. They are irritating and sensitizing and cause contact dermatitis in health-care workers (SEDA-21, 254).

Formulations

Formaldehyde is released by numerous agents, such as paraformaldehyde, dichlorophene, Dowicil 75 and Dowicil 200 (*cis*-1-(3-chloroalkyl)-3,5,7-triaza-l-azonia-adamantane chloride), bronopol, Biocide DS 52–49 (1,2-benzoisothiazoline-3-one plus a formaldehyde releaser), and Bakzid (cyclic aminoacetal). Formalin is an alternative name for an aqueous solution of formaldehyde, but the latter name is preferred, since formalin is also used as a brand name in some countries.

Free formaldehyde is used in cosmetics, especially in hair shampoos, and in many disinfectants and antiseptics. The solid paraformaldehyde is used as a source of formaldehyde vapor for the disinfection of rooms. Noxythiolin, polynoxylin, hexamidine, and taurolidine act by slow release of formaldehyde. Formaldehyde solution contains 34–38% of formaldehyde methanol as a stabilizing agent to delay polymerization of the formaldehyde. Formaldehyde gel contains 0.75% of formaldehyde and is used to treat warts.

Formaldehyde cannot be applied safely to the skin or the mucous membranes in the concentration necessary to rapidly kill microbes, and formaldehyde solutions have to be diluted before use to a 2–8% solution to disinfect inanimate objects and to a 1–2% solution for disinfection by scrubbing. For fumigation of air a concentration of 1–2% is used.

General adverse effects

Discussion about the toxicity, mutagenicity, and potential carcinogenicity of formaldehyde relates more to occupational and environmental exposure, caused by its release from urea formaldehyde resins used for wood products and from foams for cavity-wall insulation, than its use in disinfection and sterilization (SEDA-11, 476) (SEDA-12, 569). However, the concentrations of formaldehyde that are found in the air after scrubbing with formaldehyde-containing disinfectants can be several hundred percentage higher than the maximum safe workplace concentration, even when scrubbing is carried out properly (1). Very high concentrations have also been found in pathologists' workrooms. In the pathology departments of two Italian hospitals the highest values of 2.6 and 6.0 ppm were measured in the dissection laboratories; in the histology and cytology laboratories, concentrations were less than 1 ppm, except when technicians handled formaldehyde solutions (2).

Primary irritant effects of formaldehyde

The minimum amount of formaldehyde that can be detected by odor varies considerably between individuals and ranges from 0.1 to 1.0 ppm (0.12–1.2 mg/m^3), close to the concentration at which minimal irritant effects are felt in the eyes and in the pulmonary airways (3). Thus, the fundamental toxicity of formaldehyde lies in primary irritation to the eyes, nose, and throat when the subject is exposed to concentrations in the range of 1–5 ppm. Concentrations above 2–5 ppm cause irritation of the pharynx, lungs, and eyes, and some erythema of vaporized areas of the skin, such as the face and neck. Acute exposure to concentrations of formaldehyde of the order of three times the maximum threshold of detection of the

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odor will most likely produce severe acute pulmonary edema after only a few minutes.

Acute toxicity after local administration of formaldehyde-containing solutions

Dilute solutions of 1–10% formalin have been instilled into the bladder to treat inoperable profusely bleeding tumors or intractable hemorrhagic cystitis. Anuria was a severe complication. This was due either to edematous obstruction of the ureter or to tubular or papillary necrosis, probably caused by systemic absorption. Bladder perforation with intraperitoneal spillage, peritonitis, and finally death was described in an elderly patient with a carcinoma of the uterine cervix (SEDA-11, 476).

In 1983, Godec and Gleich reviewed all published results of treatment of intractable hematuria with formalin. Dilutions of 1–10% formalin (containing 0.37–3.7% formaldehyde) were used; the most commonly used concentration of formalin was 10%. The authors concluded that formalin was probably the most effective tool for controlling massive hematuria, but also probably the most dangerous. The review covered 23 articles and 118 patients; in 104 cases, treatment was successful. However, in only 10 reports had the treatment been used without serious adverse effects; the other 13 articles listed four deaths and many serious local and systemic complications. The complication rate increased when the formalin concentration was higher, but the contact time and the volume instilled did not influence the occurrence of adverse effects. The most frequent local complications were reflux and hydronephrosis. Fibrosis of the bladder with reduced capacity was the usual clinical outcome. A systemic effect was tubular necrosis with anuria, with two deaths. Another complication was ureteric obstruction, which was not related to ureteric fibrosis or bladder wall fibrosis obstructing the intramural ureter; in two cases the obstruction appeared to be due to retroperitoneal fibrosis (SEDA-11, 476) (4).

In 1989, Donahue and Frank (SEDA-12, 569) (SEDA-14, 205) (5) published a systematic review of 235 cases of intravesical hemorrhagic cystitis treated with intravesical instillations of diluted formalin in concentrations of 1, 5, or 10%. Complete response rates were 71, 78, and 83% respectively. The average duration of a complete response was 3–4 months; the recurrence rate fell gradually with the use of higher concentrations. Complications were divided into two groups: "minor complications" included all mild or transient problems not requiring surgical intervention (fever, tachycardia, transient or minor rises in blood urea nitrogen or creatinine, mild hydronephrosis, grades I and II uricourethral reflux, increased urinary frequency, urgency, incontinence, suprapubic pain, or a reduction in bladder capacity not requiring urinary diversion); "major complications" were those that required surgical intervention, resulting in loss of renal function or causing damage to the supravesical urinary tracts (stricture formation), including anuria, acute tubular necrosis, papillary necrosis, ureteric or retroperitoneal fibrosis, uterovesical or uteropelvic junction obstruction, severe hydronephrosis, grades III or IV vesicoureteric reflux, any vesical fistula, or a reduction in bladder capacity requiring urinary diversion. Major complications occurred in all treatment groups, including those treated with 1% formalin. The higher rate observed with 10% formalin was not significantly different from the rates associated with the use of 1 or 5% formalin. The mortality rates were 2.2% in all the formalin groups, but the rates were not significantly different. Formalin 10% resulted in a higher and favorable response rate, a lower recurrence rate, equal numbers of major complications and mortality rate, and a three-fold higher rate of minor complications than 5% formalin in patients with hemorrhagic cystitis due to radiotherapy for bladder tumors. In contrast, formalin 5% was more effective than formalin 10% in treating patients with intractable hematuria due to unresectable bladder tumors or cyclophosphamide-induced cystitis.

The use of 2 or 4% formaldehyde as a scolecidal agent for injection into hydatid cysts and for peritoneal lavage was followed by shock in seven cases and resulted in death in three. All three patients who died had undergone a peritoneal lavage with 2–8 liters of 2 or 4% formaldehyde (SEDA-11, 476).

Immunogenicity

Formaldehyde is one of the most frequent contact allergens. If the responses in some individuals to acute exposure to formaldehyde are immunogenically mediated, they are of serious clinical significance. These individuals should not be exposed to any concentration of the agent. However, the intensity and nature of the immunogenic response can so resemble a primary irritant effect that a different diagnosis is not possible.

Mutagenicity and carcinogenicity

Formaldehyde is mutagenic in vitro and although there is conflicting evidence about its carcinogenicity, this should be taken seriously.

Organs and Systems

Respiratory

Formaldehyde-induced bronchial asthma occurred in a laboratory technician and in a neurologist preparing brain specimens for a student demonstration (6).

In a renal dialysis unit, five of 28 members of the staff had respiratory symptoms associated with formaldehyde, and in two cases, attacks of wheezing could be provoked by exposure to formaldehyde. One nurse was particularly affected, the asthmatic wheeze persisting for 8 days after exposure (7).

Of 230 people who had been exposed to formaldehyde and had asthma-like respiratory symptoms with a bronchial provocation test, 12 were considered to be caused by specific sensitization to formaldehyde, 11 were triggered by a concentration of 2.5 mg/m^3, and one by 1.2 mg/m^3 (SEDA-11, 477) (8). The authors concluded that formaldehyde-induced asthma, although apparently rare, is under-reported.

Biliary tract

Three cases of secondary sclerosing cholangitis developed during the early postoperative phase of surgical treatment of hydatid liver cysts in which formaldehyde was used; one

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patient died within 3 months and the remaining two underwent liver transplantation following biliary sclerosis. Another group also reported three cases of sclerosing cholangitis. Both groups of authors concluded that because of the risk of complication and the unproven efficacy of intracystic injection of a scolecidal solution in preventing dissemination of the parasite, this technique should be abandoned in the surgical treatment of hydatid disease of the liver. However, in 560 patients, there were no cases of sclerosing cholangitis when the concentration was not more than 2% and the solution was injected only into cysts that contained clear fluid content (SEDA-11, 476) (9).

Skin

Formaldehyde-releasing preservatives, such as quaternium-15, diazolidinyl urea, and imidazolidinyl urea, are widely used in cosmetics and topical medications and are well-known contact sensitizers. In spite of positive patch test reactions to these preservatives in a number of patients, only some of these patients will react when they use the corresponding commercial formulations. This is because the concentrations of preservatives in the commercial products are often below the threshold necessary to produce a clinical reaction. This finding confirms the importance of using commercial formulations of topical agents in estimating the clinical relevance of patch test results (10).

The formaldehyde concentration in patch-testing, which has been lowered to 1% in the standard series in recent years, has been studied in a comparison of concentrations of 1% and 2% in 3734 consecutively patch-tested patients (11). Since there was no significant difference between 1 and 2% formaldehyde with respect to the frequency of positive patch test reactions, while there were more irritant reactions with 2%, a 1% patch test concentration can still be recommended.

Allergic dermatitis has been demonstrated from direct skin contact and from exposure to gaseous formaldehyde in the air. Various forms of reaction occur, from simple erythema to maculopapular lesions, hyperesthesia, and angioedema. Five patients developed an allergic contact dermatitis to plaster casts, caused by free formaldehyde released by a melamine–formaldehyde resin incorporated in the plaster.

Urticaria with acute Quincke's edema was reported following the use of a formaldehyde-containing dental paste (SEDA-11, 477) (12).

The first published case of photosensitivity to formaldehyde was reported in 1982 in a man who developed pruritus, burning, and redness of the skin within minutes of exposure to sunlight; photopatch tests showed specific photosensitivity to formaldehyde (13).

Immunologic

Aldehydes are irritating and sensitizing and cause contact dermatitis in health-care workers (SEDA-21, 254). The incidence of allergy to aldehydes has been examined in 280 health-care workers with skin lesions (14). Allergy was diagnosed in 64 (23%). Most (86%) were sensitive to only one aldehyde. Formaldehyde caused allergy slightly more often (14%) than glutaraldehyde (12%). Only five (1.9%) were sensitive to glyoxal. This hierarchy of sensitivity was also confirmed in animal testing.

Immediate-type allergy to formaldehyde mediated by ice occurred during the use of a formaldehyde reconditioned dialyser in a 20-year-old woman without a personal or familiar history of atopy.

A specific cold agglutinin cross-reacting with anti-N was detected in the sera of 68 (21%) of 325 hemodialysis patients; each had used a dialyser that had been sterilized with formaldehyde. The results of transfusion experiments suggested in vivo hemolytic activity of this antibody. The authors postulated that such in vivo exposure to formaldehyde might make the MN-receptor on erythrocytes immunogenic, thus inducing the formation of the anti-N-like antibody.

The commonly used Clinitest reaction for residual formaldehyde in reused dialysers fails to detect concentrations below 50 ppm (15). The use of Schiff reagent in ratios of 1:1 to 3:1, which can detect formaldehyde at concentrations of 3.6–5.0 ppm, has therefore been recommended (SEDA-12, 571) (16). It can also be used in combination with a glucose-containing dialysate.

Long-Term Effects

Mutagenicity

Formaldehyde is mutagenic in many laboratory test systems, for example fruit flies (Drosophila), grasshoppers, flowering plants, fungi, bacteria, and cultured human bronchial fibroblasts.

Formaldehyde may be genotoxic by a dual mechanism: direct damage to DNA and inhibition of repair of mutagenic and carcinogenic DNA lesions by other chemical and physical carcinogens.

Marked chromosomal abnormalities and chromosomal breaks were found in metaphases in direct bone marrow preparations from 40 patients undergoing maintenance hemodialysis (SEDA-11, 477) (17). During the period of these cytogenetic studies, the dialysers were reused after sterilization with formaldehyde, and each patient may have received residual amounts of as much as 127 (sd 51) mg of formaldehyde during each dialysis.

Tumorigenicity

There is evidence of possible carcinogenicity of formaldehyde from two inhalation studies on rats and mice (SEDA-10, 423) (SEDA-11, 477) (SEDA-12, 571) (13).

In man, a number of epidemiological studies using different designs have been conducted (17) on the health risks of non-medical exposure to formaldehyde and also in health-care professionals (18–23), with contradictory results. Cancers in excess in more than one study were: Hodgkin's disease (24,25), leukemia (18,19,22,23,26), cancers of the buccal cavity and pharynx (particular the nasopharynx) (18,19,25,27,28), lung (18,24,27,29–31), nose (32–36), prostate (19,24,26), bladder (19,23,26), brain (20), colon (18–20,25,27), skin (18,25), and kidney (27).

There was no association between formaldehyde exposure and lung cancer in a case-referral study among Danish physicians working in departments of pathology, forensic medicine, and anatomy (21).

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Mortality from prostatic cancer was increased among embalmers (19) and industrial workers (24,26), but the excess was statistically significant only among embalmers (19). A slight excess of mortality from bladder cancer (19,22,26), a significant excess of colon cancers (18,19,27), and a significant excess mortality from skin cancer (18,25) were noted among British pathologists (22), embalmers (18,19), and industrial workers (25–27).

Excess mortality from leukemia and cancer of the brain was generally not seen among industrial workers, which suggests that the increased rates of these cancers among professionals (anatomists (20), pathologists (22), embalmers (18,19), and undertakers (23)) is due to factors other than just formaldehyde.

It is of course possible that the studies that have provided positive evidence of a link between formaldehyde and cancer related to more intensive exposure; for example, reports on the risk associated with chronic exposure to low concentrations of formaldehyde suggest that formaldehyde cannot be a potent carcinogen; if it were, the high degree of environmental exposure would result in much clearer evidence of risk. However, any compound that produces cancer in experimental animals or mutagenicity in several test systems should be considered as a potential cancer risk to human subjects, even though humans and animals may differ in their susceptibility to formaldehyde. The contradictory evidence from human studies should therefore be taken seriously and efforts should be made to reduce exposure.

The need to re-evaluate the rationale underlying the use of formaldehyde, formocresol, and paraformaldehyde in dentistry has been stressed, since the clinical use and delivery of these products are considered to be arbitrary and unscientific (37).

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Formoterol

See also Beta$_2$-adrenoceptor agonists

General Information

Formoterol is a long-acting selective beta$_2$-adrenoceptor agonist that is more potent than salmeterol (1) and has a similar duration of action (12 hours) but a rapid onset of effect similar to that of salbutamol. It is available as a multidose, pressurized aerosol and as a dry powder inhaler, delivering 0.006 or 0.012 mg per dose. The usual dose is 0.012 mg bd.

The pharmacokinetics and pharmacodynamics of a single oral dose of formoterol 168 μg have been studied in eight healthy men. Plasma concentrations reached a maximum of 94 pg/ml 70 minutes after administration. The biological effects peaked later, at 4 hours. Plasma potassium fell from 3.98 mmol/l to 2.33 mmol/l. There was a fall in blood eosinophil count from 277 $\times$ 10^6/l to 47 $\times$ 10^6/l (2).

In a postmarketing surveillance study of the long-acting beta$_2$-adrenoceptor agonist formoterol in the UK using the technique of prescription event monitoring, exposure and outcome data in 5777 patients aged 3–96 years were collected (3). The most commonly reported events, excluding those related to respiratory disease, were headache, tremor, palpitation, cramp, and nausea and vomiting, events known to be associated with beta$_2$-adrenoceptor agonists (4). However, the frequencies of nausea and vomiting (1.3%) and pruritus (0.5%) differed from the frequencies reported in the premarketing trials.

Therapeutic studies

Observational studies

The cardiovascular and metabolic responses to increasing doses of formoterol 12, 24, 48, and 96 μg administered from a dry powder inhaler have been assessed in a randomized, double-blind, crossover study in 20 patients with mild to moderate asthma. There was no difference in the maximum effects of formoterol 12 micrograms and placebo. The 24 micrograms dose significantly reduced plasma potassium (average fall 0.2 mmol/l) and increased blood glucose (average rise 1.8 mmol/l). After formoterol 96 micrograms the rise in heart rate was 9/minute greater than after placebo, systolic blood pressure rose by an average of 4 mmHg, and diastolic pressure fell by an average of 3 mmHg. Plasma potassium fell by an average of 0.5 mmol/l and blood glucose rose by an average of 2.6 mmol/l. The effects on extrapulmonary parameters would only be of clinical significance at the highest dose of formoterol studied (5).

A 3-month, open, uncontrolled, multicenter trial has been carried out in 1380 patients with moderate to severe persistent asthma taking inhaled corticosteroids (6). Formoterol was given via a single-dose, breath-activated device (Foradil). There were significant increases in peak flow and a three-fold reduction in the need for rescue treatment with short acting beta$_2$-adrenoceptor agonists. By the end of the study, 72% of the patients were taking formoterol 12 micrograms bd and 29% were taking 24 micrograms bd. Physician evaluation indicated that tolerability was very good or good in 93% of the patients. There were only minor drug-related adverse events similar to those produced by other beta$_2$-agonists.

Placebo-controlled studies

In a double-blind, crossover study 12 healthy subjects were randomized to receive either inhaled placebo or inhaled budesonide 1.2 mg bd for 7 days, with a minimum 7-day washout period between the two treatments (7). They used formoterol 24 micrograms bd during both treatment periods. A dose-response curve for systemic beta$_2$-adrenoceptor responses to inhaled salbutamol (0.8–3.2 mg) was carried out before and after 7 days of each treatment. The pretreatment value of plasma cortisol averaged 407 nmol/l and fell to 22 nmol/l after 7 days of budesonide; placebo had no effect. There was a significant reduction in the peak heart rate response to salbutamol when formoterol was given with placebo. This was partially reversed when formoterol was combined with budesonide. The peak rise in heart rate with salbutamol after formoterol and placebo was 24/minute and increased to 35/minute when formoterol was given with budesonide. The peak fall in potassium with salbutamol after formoterol and placebo was 0.48 mmol/l and did not change significantly when formoterol was combined with budesonide (0.36 mmol/l).

In multiple dose studies with formoterol (Oxis, Turbuhaler, Astra) 6, 12, and 24 micrograms bd, terbutaline 0.5 mg qds, or placebo in a total of 1199 patients, at least one adverse event was reported by 65% of the patients in each treatment group (8). Adverse events related to the respiratory system were reported by 37% of the patients and were attributed to underlying disease. Tremor was reported by 2% of patients taking formoterol 6 micrograms bd, by 4% with 12 micrograms bd, and by 12% with 24 micrograms bd. Tremor was reported by 5% of patients taking terbutaline 0.5 mg qds. No patient reported tremor with placebo.

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In 397 adults with mild to moderate asthma randomly allocated to one of three treatments for 12 weeks (formoterol 6 micrograms bd, terbutaline 0.5 mg qds, and placebo), formoterol was significantly more effective than either terbutaline or placebo in reducing asthma symptoms (9). It also resulted in significantly higher evening peak flow readings and less use of rescue medication. The bronchodilator response to the study drugs and an additional 1.25 mg of terbutaline was similar before and at the end of the 12 weeks. This suggested that there was no loss of beta-adrenoceptor mediated bronchodilatation in any of the treatment groups. No patient in any group reported a clinically relevant adverse effect.

Of 31 patients with asthma and a mean FEV_1 of 1.97 litres in a double-blind, randomized, placebo-controlled, crossover study of single inhaled doses of placebo or formoterol, 6, 12, 24, or 48 micrograms on five separate days, most had at least a 50% increase in specific airway conductance within 1–4 minutes (10). The maximum increase in FEV_1 was dose-dependent, rising by 12% (6 micrograms), 18% (12 micrograms), 19% (24 micrograms), and 26% (48 micrograms). At 12 hours after the administration of 6, 12, 24, and 48 micrograms of formoterol, the mean increases in FEV_1 were still 7, 15, 18, and 27%, respectively, above the value seen with placebo. The most frequently reported adverse effect was headache, which occurred with all treatments, including placebo. After inhalation of formoterol 48 micrograms, three patients had mild tremor lasting for less than 1 hour. One patient had the same effect for 3 hours after placebo.

Comparative studies

Formoterol has been compared with various other $beta_2$-adrenoceptor agonists.

Fenoterol and salbutamol

Formoterol 24 micrograms, fenoterol 0.4 mg, and salbutamol 0.4 mg all caused an increase in heart rate and plasma glucose, and a fall in diastolic blood pressure and plasma potassium (1). Fenoterol had a greater maximum effect on heart rate than either salbutamol or formoterol. Formoterol and fenoterol caused a similar maximum reduction in plasma potassium greater than that seen with salbutamol.

Salmeterol

The relative efficacy of the long-acting $beta_2$-adrenoceptor agonists formoterol and salmeterol has been studied in a randomized, double-blind, crossover trial in 15 patients with asthma taking regular corticosteroids and salbutamol (11). The patients had methacholine challenges performed after varying single doses of formoterol (12, 60, and 120 micrograms) and salmeterol (50, 250, and 500 micrograms). The maximal protective effect of salmeterol against methacholine challenge was reached at 250 micrograms, whereas formoterol showed a dose-response relation, with maximum protection at the highest dose. This confirmed the authors' hypothesis that salmeterol is a partial agonist at beta-adrenoceptors compared with formoterol. The higher affinity of formoterol for beta-adrenoceptors also produced more adverse effects. There was a significant fall in serum potassium concentration after 60 micrograms of formoterol but not after 250 micrograms of salmeterol. The serum potassium concentration was also significantly lower with the highest dose of formoterol compared with the highest dose of salmeterol (minimum concentration 3.1 mmol/l). The highest dose of formoterol also resulted in more tremor than the highest dose of salmeterol. The increases in heart rate and QT interval were similar with the two drugs. It should be noted that the doses used in this study were higher than recommended. It is unclear whether the partial agonist activity of salmeterol is clinically important, but this seems unlikely.

Terbutaline

In 12 stable asthmatic patients who took high doses of formoterol or terbutaline, terbutaline had significantly greater systemic effects than formoterol, as indicated by pulse, blood pressure, and heart rate. Baseline serum potassium concentrations were all within the reference range (3.7–5.3 mmol/l). There was no significant difference between the mean potassium-lowering effects of formoterol 72 micrograms and terbutaline 6 mg. Mean maximal systolic blood pressure rose from 150 to 155 mmHg with formoterol 72 micrograms and from 139 to 153 mmHg with terbutaline 6 mg. The difference between treatment groups, 5 mmHg, was statistically significant. Diastolic blood pressure fell significantly with both formoterol (from 86 to 70 mmHg) and terbutaline (from 85 to 66 mmHg). Heart rate rose from 61/minute to 79/minute on day 3 in patients taking formoterol 72 micrograms/day compared with a rise from 63/minute to 86/minute with terbutaline 6 mg; this difference was statistically significant.

Formoterol 120 micrograms had significantly smaller effects than terbutaline 10 mg/day on serum potassium concentrations, pulse, and heart rate. During treatment with formoterol 120 micrograms/day, potassium concentrations were under 3.7 mmol/l in 10 patients on day 1, six patients on day 2, and five patients on day 3. With terbutaline 10 mg the corresponding numbers were 12, 10, and 9. However, the effect of terbutaline 10 mg was significantly greater than formoterol 120 micrograms over the three treatment days. Formoterol 120 micrograms/day caused a rise in baseline systolic blood pressure from 134 to 145 mmHg; terbutaline 10 mg produced a rise from 131 to 141 mmHg. The difference between the groups, 0.6 mmHg, was not statistically significant. With formoterol 120 micrograms/day the heart rate rose from 65/minute to 78/minute, and with terbutaline 10 mg/day it rose from 63/minute to 86/minute. The difference in mean heart rate rise of 8/minute was statistically significant. A patient taking formoterol 72 micrograms/day developed atrial fibrillation on day 1. Minor adverse events occurred in seven patients taking formoterol 72 micrograms/day and six patients taking terbutaline 6 mg/day. Eight patients reported adverse events when taking formoterol 120 micrograms/day, as did 10 patients taking terbutaline 10 mg/day. Minor adverse effects included headache, muscle cramps, fatigue, and tremor with all four treatments. Tremor was reported in two of 12 patients taking terbutaline 6 mg and in five of 15 patients taking terbutaline 10 mg. The corresponding numbers for formoterol were none with formoterol 72 micrograms and one of 15 with formoterol 120 micrograms (12).

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High-dose formoterol (Oxis Turbuhaler) and terbutaline (Bricanyl Turbuhaler) have been compared in a randomized, double-blind trial in 48 patients with obstructive airways disease (mean FEV_1 0.98 liter or 33% predicted) (13). Patients with acute bronchoconstriction received either a cumulative dose of 90 micrograms inhaled formoterol or 10 mg inhaled terbutaline (corresponding to 20 puffs each) within the first 3 hours of admission. Treatment included intravenous prednisolone 40 mg after 1.5 hours and oxygen during the first 3 hours. FEV_1 improved similarly in both treatment groups, serum potassium concentration fell in both groups but to the same extent, and the mean 12-hour pulse rate was significantly higher with terbutaline. The authors concluded that formoterol is at least as safe and equally well tolerated as terbutaline.

Organs and Systems

Cardiovascular

The cardiac effects of formoterol and salmeterol have been studied in 12 patients with COPD, hypoxemia (PaO_2 below 60 mmHg), and cardiac disease. Holter monitoring showed that the heart rate was higher after formoterol 24 micrograms than after either formoterol 12 micrograms or salmeterol 50 micrograms. Supraventricular or ventricular extra beats occurred more often after formoterol 24 micrograms. Formoterol 24 micrograms caused a significant reduction in the plasma potassium concentration for 9 hours after administration. The authors suggested that in patients with COPD, hypoxemia, and pre-existing cardiac dysrhythmias, long-acting $beta_2$-adrenoceptor agonists can cause adverse cardiac effects. However, the recommended single dose of salmeterol or formoterol allows a higher safety margin than inhaled formoterol 24 micrograms (14).

The non-pulmonary effects of formoterol have been carefully studied in an uncontrolled observational trial in 10 patients with asthma who were already taking regular inhaled budesonide (400 micrograms bd) (15). A 24-hour Holter recording was taken at baseline, and after a 2-week treatment period with formoterol 12 micrograms bd, there were no significant changes in blood pressure, heart rate, cardiac morphology, or the circadian rhythm of autonomic regulation as assessed by measurements taken from the Holter monitor after the treatment period.

Respiratory

The effect of formoterol 18 micrograms on histamine-induced plasma exudation into sputum has been investigated in 16 healthy subjects in a double-blind, placebo-controlled, crossover study. Plasma exudation into the airways was produced by inhalation of histamine. Sputum was induced by inhalation of hypertonic (4.5%) saline. Induced sputum was obtained at baseline and then at 30 minutes and 8 hours after histamine inhalation. Sputum concentrations of $alpha_2$-macroglobulin were measured as a marker of microvascular-epithelial exudation of bulk plasma. Histamine-induced plasma exudation 30 minutes after placebo was considerably greater than at baseline. The median difference was 11 μg/ml (95% CI = 0.9, 90) expressed as $alpha_2$-macroglobulin. The effect of histamine was reduced by 5.1 μg/ml (CI = 0.9, 62) 30 minutes after formoterol compared with placebo. At 8 hours, histamine exudation was much less and was no longer inhibited by formoterol (16).

Nervous system

The non-pulmonary effects of formoterol have been carefully studied in an uncontrolled observational trial in 10 patients with asthma who were already taking regular inhaled budesonide (400 micrograms bd) (15) There was a significant increase in upper limb tremor with formoterol and this was assessed as discomfort by one patient. This was considered due to stimulation of $beta_2$-adrenoceptors in skeletal muscle.

Long-Term Effects

Drug tolerance

Several studies have shown that regular use of formoterol results in the development of tolerance to its bronchoprotective effects, even with treatment periods as short as 1 week. The significance of this tolerance is unclear, but it is potentially important clinically.

A randomized, double-blind, placebo-controlled, crossover trial was designed to see whether formoterol given once daily was associated with less subsensitivity. Ten asthmatics using inhaled steroids were given inhaled formoterol dry powder 24 micrograms od or bd or identical placebo for 1 week. Bronchoprotection was estimated by measuring the PC_{20} for adenosine monophosphate (AMP) 12 hours after the first and last doses of each treatment. The PC_{20} is the concentration of AMP that causes a 20% fall in the FEV_1 and is directly proportional to the degree of bronchoprotection. With placebo, the PC_{20} values for AMP at the start and end of one week were 71 μg/ml and 75 μg/ml. There was a significant loss of bronchoprotection after 1 week of treatment with twice-daily formoterol. The PC_{20} for AMP at the start was 475 μg/ml, indicating significant bronchoprotection by formoterol compared with placebo. After 1 week the PC_{20} had fallen to 127 μg/ml, a near four-fold loss of the bronchoprotective effect of formoterol. When formoterol was given daily for a week the PC_{20} values were 367 μg/ml and 127 μg/ml, a three-fold loss of bronchoprotection. There was no significant difference in the effects of formoterol given once or twice a day (17).

A randomized, parallel-group, double-blind study in 67 patients with stable asthma requiring inhaled glucocorticoids used the PC_{20} for inhaled methacholine as a measure of bronchoprotection. The patients were treated for 2 weeks with formoterol 12 micrograms od, 6 micrograms bd, or 24 micrograms bd, terbutaline 500 micrograms qds, or placebo. Each of the four active treatments caused a significant fall in the PC_{20} for metacholine, and there was no significant difference between them. In contrast to the reduced bronchoprotective effect the bronchodilator effect of formoterol was maintained over the 2-week treatment period (18).

The effect of a bolus of inhaled budesonide on formoterol-induced subsensitivity in airway beta-adrenoceptors has been studied in a randomized, double-blind, crossover study in 10 asthmatic patients taking regular inhaled

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glucocorticoids (19). Challenge testing with AMP was performed at baseline and after one week of regular formoterol (24 micrograms bd). Before the second challenge the patients were given either a dose of inhaled budesonide (1600 micrograms) or placebo via a dry powder inhaler. After one week of formoterol, the PC_{20} for the second challenge fell significantly (by a factor of 3.9). However, when the second challenge was performed after a bolus of budesonide, there was no fall in the PC_{20}, suggesting protection against formoterol-induced tolerance. Lymphocyte beta-adrenoceptor density fell with regular formoterol, but not after a bolus of budesonide. These results have implications for the treatment of acute severe asthma in patients taking regular long-acting $beta_2$-adrenoceptor agonists. It may be appropriate to give a bolus dose of inhaled glucocorticoids to these patients early in an acute asthma attack, particularly if they are poorly responsive to initial therapy with short-acting bronchodilators.

Susceptibility Factors

Age

The use of long-acting beta-adrenoceptor agonists in the management of asthma in children has been comprehensively reviewed (20). In children, as in adults, regular long-acting beta-adrenoceptor agonists can produce bronchodilator subsensitivity to short-acting beta-agonists and tolerance to the bronchoprotective effects of long-acting beta-agonists against challenges with exercise and methacholine. The clinical significance of these findings is unclear. Formoterol and salmeterol have similar adverse effects profiles, similar to that of salbutamol. The most common medication-related adverse effects are cardiovascular, such as increased heart rate and palpitation, or tremor and headache. Small changes in serum potassium and glucose can also be seen, but all changes are minor. The exact role of long-acting beta-adrenoceptor agonists in childhood asthma remains to be defined.

Drug Administration

Drug formulations

Formoterol 12 and 24 micrograms, delivered from either a multidose pressurized aerosol or a dry powder inhaler, did not affect heart rate. However, at doses of 48 and 96 micrograms the heart rate rose significantly after the dry powder formulation. Tremor was significantly higher after the 48 micrograms dose of dry powder compared with the multidose pressurized aerosol. The two formulations were equipotent in producing bronchodilatation (SEDA-21, 184).

Drug–Drug Interactions

Salbutamol

The interaction of formoterol and salmeterol with salbutamol has been studied in a randomized, double-blind, crossover study in 16 asthmatic patients (21). The patients were taking regular inhaled corticosteroids and were responsive to methacholine challenge, with a PD_{20} (that is the dose of methacholine that produced a fall in FEV_1 of 20%) of less than 500 μg. The patients had methacholine challenges performed 12 hours after a single dose of formoterol 12 micrograms, salmeterol 50 micrograms, placebo, and either a low dose (400 micrograms) or a high dose (1600 micrograms) of salbutamol. With placebo, challenge after high-dose salbutamol resulted in a higher PD_{20} than after low-dose salbutamol (as expected). However, after both formoterol and salmeterol, the higher dose of salbutamol did not give as great an increase in PD_{20} over the lower dose of salbutamol. This suggests that prior treatment with formoterol and salmeterol can antagonize the protective effect of salbutamol against bronchoconstriction. This effect may be important in patients with acute asthma.

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Foscarnet

General Information

Foscarnet (trisodium phosphonoformate hexahydrate) is a pyrophosphate analogue that interacts with the enzymatic action of polymerases and inhibits the cleavage of pyrophosphate from the nucleoside triphosphate. Because of this mechanism, the antiviral activity of the drug is broad. Foscarnet is a non-competitive inhibitor of herpesvirus DNA polymerase, hepatitis B virus DNA polymerase, and reverse transcriptases (1). Intravenous foscarnet has been used for the treatment of mucocutaneous disease due to acyclovir-resistant *Herpes simplex* (2) and for the treatment of severe CMV infection (3,4). Foscarnet has been shown to be as effective as ganciclovir in the treatment of gastrointestinal CMV and CMV retinitis in patients with AIDS (5). The two drugs differ, however, in their respective toxicity profile, and in a comparison in CMV retinitis, ganciclovir was better tolerated (6). Treatment-limiting adverse effects are renal toxicity, hypocalcemia, and mucosal ulceration.

Organs and Systems

Electrolyte balance

Significant electrolyte abnormalities have been attributed to foscarnet in a bone marrow transplant recipient on parenteral nutrition (7).

- A 39-year-old man with acute myelogenous leukemia developed a fever after allogeneic bone marrow transplantation and was given prophylactic ganciclovir and antibiotics. Parenteral nutrition was started when severe mucositis and diarrhea limited oral nutrition. On the 18th day after transplantation CMV DNA was detected in his blood and he was given foscarnet. His requirements for potassium, calcium, magnesium, and phosphorus increased dramatically, while his sodium requirements fell. Electrolyte depletion occurred within 24 hours and was accompanied by deteriorating renal function (serum creatinine 106–220, reference range 60–125 μmol/l). On withdrawal of foscarnet, the serum creatinine fell within 24 hours and the electrolyte concentrations returned to normal.

Mineral balance

The second most common adverse effect of foscarnet is symptomatic hypocalcemia, which may be responsible for the cardiac dysrhythmias and seizures that occur after acute overdose or excessively rapid infusion of foscarnet. Foscarnet stimulates the release of parathyroid hormone, which raised concerns about long-term administration (8). However, in a study of seven patients receiving a 14-day foscarnet induction regimen, there were no changes in calcium or phosphate metabolism (9).

Recognizing that foscarnet is a potent chelator of divalent cations, and that acute ionized hypocalcemia and hypomagnesemia are common adverse effects, a trial of intravenous magnesium sulfate has been conducted for foscarnet-induced hypocalcemia and hypomagnesemia in 12 AIDS patients with CMV infection (10). Increasing doses of magnesium sulfate reduced or eliminated foscarnet-induced ionized hypomagnesemia but had no discernible effect on ionized hypocalcemia, despite significant increases in serum parathyroid hormone concentrations. On this basis, intravenous supplementation for patients with normal serum magnesium concentrations was not recommended during treatment with foscarnet.

Urinary tract

Alterations in creatinine clearance or acute renal insufficiency occur in 10–20% of patients with AIDS receiving intravenous foscarnet (11), due to acute tubular damage. Severe renal insufficiency can be prevented in most cases by careful hydration before and during therapy (12). To minimize the residual incidence of nephrotoxicity, the dose of foscarnet should be frequently recalculated, based on the estimated creatinine clearance.

Patients who have undergone renal transplantation and then require treatment for cytomegalovirus infection are at special risk of renal damage due to foscarnet.

- One renal transplant recipient developed the nephrotic syndrome, with microscopic hematuria and non-oliguric acute renal insufficiency within 15 days after starting foscarnet therapy for cytomegalovirus infection (13). A kidney biopsy showed crystals in all glomeruli and in the proximal tubules. The crystals consisted of several forms of foscarnet salts. Renal function and proteinuria nevertheless improved progressively, and a second transplant biopsy 8 months after the first one showed

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fibrotic organization of half of the glomeruli and of the interstitial tissues, and a reduction in the amount of crystals.

The renal damage caused by foscarnet can itself alter the drug's kinetics; the dosage needs to be substantially reduced when renal complications occur, and appropriate guidelines have been developed (14).

Skin

Painful oral, penile, and vulvar ulceration can occur during foscarnet therapy (15), most probably due to local accumulation of the drug (SEDA-17, 338). Penile ulcers have been reported to be the reason for discontinuation of foscarnet therapy in up to 10% of patients (16).

Eosinophilic folliculitis is a common skin manifestation associated with HIV infection, but not commonly associated with medications.

- A 38-year-old patient with AIDS was given intravenous foscarnet 400 mg tds and no other medications (17). On the second day, a pruritic, erythematous, maculopapular, urticarial rash was noted on the limbs and trunk. The infusion was stopped and the reaction disappeared. On restarting the infusion, the reaction recurred but did not clear after withdrawal. Histology showed a pattern consistent with eosinophilic folliculitis. After UVB phototherapy for 2 months the folliculitis resolved.

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Fosfomycin

General Information

Fosfomycin is a broad-spectrum antibiotic used to treat uncomplicated lower urinary tract infections. It penetrates interstitial space fluids of soft tissues well and reaches concentrations sufficient to substantially inhibit the growth of relevant bacteria at the target site (1).

Fosfomycin has relatively low toxicity. Its penetration into tissues, including bones and joints, and into the cerebrospinal fluid is good. When given orally (2–3 g/day), it can produce gastrointestinal distress; when injected intramuscularly, it can cause local pain. Fosfomycin is recommended in daily doses of 4–16 g intravenously for the treatment of severe infections resistant to other commonly used antibiotics. Fosfomycin diffuses moderately well into bone tissue (2).

During systemic administration, rises in the activities of serum transaminases and lactate dehydrogenase, skin reactions, eosinophilia, and altered vision have been noted (3).

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Comparative studies

In a multicenter trial in 749 ambulatory women aged at least 12 years with an acute uncomplicated urinary tract infection, a single dose of fosfomycin tromethamine 3 g had an equivalent bacteriological and clinical cure rate as a 7-day course of nitrofurantoin (4). Adverse events were reported by 5.3% of fosfomycin-treated patients (versus 5.6%). The most common adverse effects were diarrhea (2.4%), vaginitis (1.8%), and nausea (0.8%), and 1.9% of fosfomycin-treated patients were withdrawn owing to adverse events (versus 4.3%).

Organs and Systems

Nervous system

Fosfomycin concentrations in brain interstitium were measured in two patients after the intravenous administration of 4 g (5). Brain C_{max} values were above MIC for relevant pathogens, such as *Streptococcus pneumoniae* and *Neisseria meningitidis*. Variability in brain penetration might be explained by the degree to which the integrity of the blood–brain barrier is disrupted by the underlying disease.

Hematologic

The effects of fosfomycin on several indices of neutrophil function have been studied in vitro (6). Phagocytosis was unaffected but there was enhanced bactericidal ability, increased intracellular calcium concentrations, raised extracellular reactive oxygen intermediate production, and reduced chemotaxis; fosfomycin did not affect intracellular oxygen intermediate production or chemokinesis.

Liver

Fosfomycin-induced recurrent liver toxicity occurred in a patient with cystic fibrosis (7).

Urinary tract

In Japanese children the use of fosfomycin within the first two days for treatment of illness caused by *Escherichia coli* O157 reduced the risk of subsequent hemolytic–uremic syndrome (8). However, treatment with oral fluoroquinolones may be preferable (9).

In rats, co-administration of fosfomycin significantly reduced the nephrotoxicity of vancomycin (10).

Immunologic

The immunomodulatory effect of fosfomycin may in part be explained by an effect on cytokine production, as shown in mice in vivo (11).

Infection risk

Bacterial biofilms develop on a number of living and inert surfaces within the urinary tract, producing chronic intractable urinary tract infections. Combination therapy with fosfomycin and a fluoroquinolone (or a fluoroquinolone and a macrolide) may be the most effective regimen available at present. Nevertheless, management of the local urinary condition and removal of the local underlying disease are the most effective approaches for treating urinary biofilm infection (12).

Long-Term Effects

Drug tolerance

There is a serious reduction in the susceptibility of strains of *E. coli* to amoxicillin (due to R-TEM enzymes), to co-trimoxazole, and to trimethoprim. However, fosfomycin trometamol remains highly active against urinary *Enterobacteriaceae*, and over 90% of *E. coli* are susceptible (13). Fosfomycin is as active as fluoroquinolones or better for treating intestinal infections caused by *Salmonella* species, pathogenic *E. coli*, *Campylobacter* species, and *Shigella* species (14).

Drug–Drug Interactions

Cisplatin

Fosfomycin is both otoprotective and nephroprotective against cisplatin-induced toxicity, without inhibiting the tumoricidal activity of cisplatin (15). Mice treated with cisplatin and fosfomycin also survived longer than animals treated with cisplatin alone, probably owing to lessening of immediate cisplatin systemic toxicity (16).

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Fosinopril

See also Angiotensin converting enzyme inhibitors

General Information

Fosinopril is a phosphorus-containing ester prodrug of the ACE inhibitor fosinoprilat. Its clinical pharmacology, clinical use, and safety profile have been reviewed (1).

Organs and Systems

Respiratory

Claims that cough is less often observed with fosinopril than with other ACE inhibitors are primarily based on a single open unconvincing study (2).

Liver

Hepatic injury has been described from time to time with ACE inhibitors. Severe, prolonged cholestatic jaundice has been reported with fosinopril (3). The evidence of a link to fosinopril was convincing.

- A 61-year-old man developed weakness, severe jaundice, pruritus, and weight loss over 2 weeks. He had started to take metoprolol, fosinopril, and diazepam for hypertension 5 weeks before. He had raised hepatic transaminases and bilirubin. A liver biopsy showed cholestasis in a normal cellular architecture. A lymphocyte transformation assay showed reactivity to fosinopril but not diazepam or metoprolol. Bilirubin concentrations took 4 months to normalize and pruritus persisted for 6 months.

Skin

There is a recognized association between the use of ACE inhibitors and the development of pemphigus vulgaris, for example with enalapril (SEDA-26, 235). A case of worsening of pemphigus vulgaris with fosinopril, and a subsequent in vitro mechanistic study, has been published (4).

- A 64-year-old woman with insulin-dependent diabetes mellitus and pemphigus vulgaris controlled by deflazacort 12 mg/day was given fosinopril 10 mg/day for hypertension. Within 1 month her skin lesions worsened and an indirect immunofluorescence test became positive. Fosinopril was withdrawn and her skin lesions improved without modification of her steroid regimen; 10 months later the immunofluorescence test was negative.

Following this, normal human skin slices (obtained after informed consent from mammoplasty patients) were incubated with increasing concentrations of either fosinopril or captopril for 2–24 hours. Sera from patients with pemphigus vulgaris, containing antidesmoglein-3 antibodies (anti-Dsg3) were tested on the skin samples incubated with fosinopril and captopril, as well as control skin samples incubated with 0.9% saline. Indirect immunofluorescence testing showed that captopril at a concentration of 1.7×10^{-9} mmol/l blocked the binding of anti-Dsg3 to the keratinocyte surface, probably because captopril blocked adhesion molecules. In contrast, fosinopril only had this effect at a concentration of 1.7×10^{-2} mmol/l, a concentration much higher than would occur in vivo. The authors proposed that captopril produces acantholysis by blocking adhesion molecules, but that fosinopril does not have this effect, and that another mechanism must have been involved in the case that they reported.

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Fosmidomycin

General Information

Fosmidomycin is an antimicrobial drug that acts by inhibiting 1-deoxy-D-xylulose 5-phosphate reductoisomerase, a key enzyme of the non-mevalonate pathway of isoprenoid biosynthesis. It inhibits the synthesis of isoprenoids by *Plasmodium falciparum* and suppresses the growth of multidrug-resistant strains in vitro.

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In an open, uncontrolled study, fosmidomycin was administered for 3–5 days (1.2 g every 8 hours) to 27 adults with malaria, of whom 16 reported possibly drug-related adverse events (1). The most frequent adverse events were headache, weakness, myalgia, abdominal pain, and loose stools. There were two cases of raised alanine transaminase activity.

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Fragrances

General Information

The fragrance mix, introduced in 1977 by Larsen (1), is used to detect sensitivity to fragrances in, for example, cosmetics and household products (SEDA-20, 149) (2). The mix contains eight widely used fragrance compounds. Additional indicators of fragrance allergy are balsam of Peru and colophony.

Organs and Systems

Immunologic

Contact sensitivity to fragrance mix is not infrequent and reflects the ubiquitous presence of these substances (3). The frequency of positive patch tests to the fragrance mix has increased over recent years. However, the mix has been estimated to miss 15% of relevant contact allergies (4). In a study of 1855 consecutive patients, patch tests with additional fragrance allergens has shown that lyral (2.7% positive reactions), citral (1.1%), and farnesol P (0.5%) are valuable additions when patch-testing to detect a fragrance allergy. Several other compounds that were tested at the same time were positive less often (5). A similar study in 1606 consecutively tested patients showed that ylang-ylang oil I (2.6% positive patch tests), ylang-ylang oil II (2.5%), lemongrass oil (1.6%), narcissus absolute (1.3%), jasmine absolute (1.2%), and sandalwood oil (0.9%) are the most important ingredients (6). In this series, limonene was positive in 0.6% of cases, but in another series of 2273 consecutive patients it was positive in 2.8%, of whom 57% did not react to the fragrance mix (7).

These and other compounds were patch-tested in another series of fragrance-sensitive patients (8). Of the 218 subjects tested, 76% were positive to the fragrance mix. Ten fragrances were not detected by the fragrance mix: benzenepropanol; beta, beta, 3-methylhexylsalicylate; dl-citronellol; synthetic ylang-ylang oil; benzyl mixture (containing benzyl alcohol, benzyl salicylate, and benzyl acetate); cyclohexylacetate; eugenyl methyl ether; isoeugenyl methyl ether; 3-phenyl-1-propanol; and 3,7-dimethyl-7-methoxyoctan-2-ol. In earlier studies by this group, significant additional reactions were found to sandela, geranium oil bourbon, spearmint oil, galaxolide (1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran), omega-6-hexadecenlactone, and tripal (dimethyltetrahydrobenzaldehyde) (9,10).

Patients with chronic venous insufficiency and venous leg ulcers are at risk of sensitization to topical medications. The frequency of sensitization in these patients is up to 67% (11). In a study using an expanded European standard series and 20 different wound dressings for patch-testing in 36 patients with chronic venous insufficiency, sensitization to fragrance mix was found in three cases (12).

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Fructose and sorbitol

General Information

Attention has been drawn to the use of fructose-based and sorbitol-based solutions for parenteral administration in Germany and German-speaking countries, where they are available for routine fluid replacement and intravenous feeding, and are widely prescribed, even after minor surgical procedures (1). Their main advantage is claimed to be the avoidance of a blood glucose raising effect, particularly in severely ill patients with glucose intolerance. In such cases it may be possible to avoid insulin therapy, since the first steps in the metabolism of these carbohydrates are insulin-dependent.

Organs and Systems

Metabolism

Infusions of fructose or sorbitol can cause lactic acidosis (2,3), particularly in combination with ethanol.

- In one patient, blood lactate concentration was monitored frequently over 5 days during intravenous feeding with a sorbitol-ethanol-amino acid mixture. During the first five infusions, blood lactate rose only moderately, but with the final infusion, lactate rose to 11 mmol/l and the patient had a severe metabolic acidosis. In retrospect the patient had had worsening renal and hepatic function tests during the preceding 24 hours. On ending the infusions, the blood lactate concentration fell rapidly.

The problems that can result from the administration in total parenteral fluid infusions of D-fructose or sorbitol have been reviewed (4). Either of these can cause life-threatening hypoglycemia, unless glucose is administered concurrently, in patients who have underlying hereditary fructose intolerance. Unless there is a clear clinical history of the condition, it may not be readily identified. In some countries, fructose and D-glucitol (sorbitol) have been eliminated from the pharmacopoeia for this reason.

Acid–base balance

The combination of fructose with sorbitol (which is converted to fructose by sorbitol dehydrogenase) causes lactic acidosis and hyperuricemia (reflecting purine nucleotide breakdown in the liver). The assimilation of fructose (as the free monosaccharide or derived from the oxidation of sorbitol or hydrolysis of sucrose) differs from that of sucrose. Fructose is phosphorylated rapidly in the intestine and liver by the catalytic action of ketohexose kinase (fructokinase) at the 1-carbon position. Cleavage of fructose-1-phosphate by aldolase B ensures its metabolic incorporation into the pathways of glycolysis and gluconeogenesis. Inherited deficiency of aldolase B occurs in hereditary fructose intolerance, an autosomal recessive condition (5). After ingestion of fructose and related sugars in this disorder, high concentrations of fructose-1-phosphate accumulate in the liver, intestine, and proximal renal tubules, and a profound metabolic disturbance occurs. Metabolic acidosis, hypophosphatemia, hypoglycemia, and hyperuricemia result, and functional impairment and pathological injury occur in these tissues with continued administration (6).

Severe lactic acidosis, with serum lactate concentrations of 8.7, 8.6, and 7.9 ml developed in three patients with hyperosmolar syndromes (7). Each had received rehydration treatment with 5% fructose in water (fructose dosage was 0.5 g/kg/hour). After correction of the electrolyte disturbances, continued infusion of fructose in the same dosage increased the plasma lactate concentration in two of the patients to 4.9 and 4.0 mmol/l, indicating near normalization of hepatic lactate utilization. In addition to peripheral insulin resistance and reduced muscular glucose utilization, the hyperosmolar state was also associated with reduced tolerance to fructose. It follows that in rehydration therapy for hyperosmolar syndromes infusion solutions containing fructose should not be used. This "functional fructose intolerance" is thought to be due to impaired gluconeogenesis. In order to administer 50 g of fructose, infusion rates up to 1000 ml/hour are necessary to achieve a positive fluid balance and to match the osmotic diuresis that is produced. Failure to maintain proper balance can cause serious metabolic complications, such as hyperlactemia, lactic acidosis, and circulatory shock.

Hereditary fructose intolerance affects one in 21 000 persons, and there have been more than 12 severe complications caused by these solutions, several lethal. Since a prior history of fructose intolerance is often not obtained, it has been argued that the use of fructose- and sorbitol-containing infusion fluids must be regarded as offering doubtful advantage but carrying definite lethal risk, and that their use should be discontinued. A modified intravenous fructose tolerance test should at least be carried out before infusions of fructose or sorbitol are given (8).

Liver

Four children aged 2.5–14 years were given infusions of fructose, sorbitol, and xylitol after sustaining head trauma ($n = 3$) or after attempting suicide with carbromal ($n = 1$). After transitory polyuria, renal insufficiency of varying severity set in 3–6 days after the start of treatment. Serum osmolality fell to 265–274 mosmol/kg, the hematocrit to 0.25–0.31, and hyponatremia developed. Serum creatinine rose to a maximum of 256–930 μmol/l. Liver damage developed in parallel with renal insufficiency. Two of the children died of acute liver atrophy. The other patients were given symptomatic treatment with balanced equalization of the hyponatremia, administration of furosemide, and carbohydrate substitution. They were discharged after 4 and 8 weeks respectively, with normal renal and hepatic function. Dialysis was not required. The hepatic and renal abnormalities were attributed to the large amounts of fructose, sorbitol, and xylitol that had been administered, to totals of 7.1–23.0 g/kg on the first day (9).

Susceptibility Factors

Genetic factors

Hereditary fructose intolerance is an autosomal recessive disorder with reduced activity of aldolase B in the liver, kidney, and small intestine. Ingestion of only a few grams

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of fructose, sorbitol, or sucrose causes abdominal pain and vomiting (SEDA-13, 479). Affected individuals develop an aversion to sugary foods and drinks, and in severe cases exposure during infancy may result in progressive liver damage and death. Exclusion of fructose from the diet allows them to develop and grow normally.

- A 16-year-old girl died after an uncomplicated appendicectomy (10). She had undiagnosed hereditary fructose intolerance and had been given sorbitol and fructose postoperatively.

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Fumaric acid esters

General Information

Fumaric acid esters are used to treat a variety of skin disorders, including psoriasis (1), cutaneous sarcoidosis (2), necrobiosis lipoidica diabeticorum (3), and disseminated granuloma annulare (4).

In 39 patients with psoriasis (12 women, 27 men) in a randomized, double-blind, placebo-controlled study, three different treatments were used: (a) tablets containing a combination of topical dimethylfumarate plus different salts of monoethylfumarate, (b) octylhydrogen fumarate tablets, and (c) placebo (5). Five patients dropped out because of adverse effects or aggravation of the skin lesions. The patients who used the combination of monoethylfumarate plus dimethylfumarate had a significantly better therapeutic response than those who took placebo or octylhydrogen fumarate. Adverse effects of the fumarate-containing tablets were flushing, diarrhea, a reversible rise in transaminases, lymphocytopenia, and eosinophilia. One patient developed impaired renal function, which normalized after withdrawal.

In 83 patients with severe psoriasis vulgaris, the fumaric acid ester formulations Fumaderm initial and Fumaderm caused adverse effects in 62%, mainly flushing and gastrointestinal complaints, which decreased in frequency during the course of the study (6).

Of 101 patients with severe psoriasis vulgaris, 70 completed the treatment period of 4 months (7). Discontinuation was due to adverse events in 7, lack of efficacy in 2, and other reasons, such as non-attendance, in 22. There was a slight overall reduction in lymphocyte count, which was more than 50% below baseline in 10 patients. During weeks 4 and 8, mean eosinophil counts were above the reference range, but by the end of the therapy the eosinophil counts had returned to normal. None of the patients had changes in renal function. Adverse events were reported in 69%, consisting mainly of gastrointestinal complaints (56%) and flushing (31%). In five patients gastrointestinal complaints and in two patients flushing led to withdrawal from the study.

In 66 patients with severe psoriasis who took fumaric acid esters for up to 14 years, there were adverse events in 73%, usually mild and mainly consisting of flushing (55%), diarrhea (42%), nausea (14%), tiredness (14%), and stomach complaints (12%) (8). There was a relative lymphocytopenia in 76%, resulting in permanent withdrawal in four patients. There were transient eosinophilia in 14%, and moderate liver enzyme rises were observed in 25%.

The effect of systemically and/or topically administered ethyl fumarate on psoriasis was studied in six patients. Two patients who had been treated with locally applied ointments, consisting of 3 or 5% ethyl fumarate in petrolatum, developed symptoms of renal toxicity (9).

Organs and Systems

Skin

Topical monoethyl fumarate caused contact dermatitis in a patient with atopic eczema and a generalized, partly pustulous, exanthema in a patient with psoriasis (10). The authors suggested that the mechanism was non-immunological contact urticaria.

In 12 healthy volunteers, topical monoethyl fumarate caused spontaneous persistent erythema and systemic administration caused flushing (11). In patients with

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urticaria pigmentosa the effect was significantly greater in the diseased skin than in the healthy skin, suggesting that monoethyl fumarate causes mast cell degranulation.

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Furaltadone

General Information

Furaltadone, 5-morpholinomethyl-3-(5-nitrofurfurylidenamino)oxazolidin-2-one), is a crystalline antibiotic powder, which is added to animal feeds.

Organs and Systems

Immunologic

Furaltadone can provoke contact allergic reactions (1). A case of contact allergy to the antibiotic in eardrops, with positive patch tests, has been reported (2).

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Furazolidone

General Information

Furazolidone is used in the treatment of giardiasis. Its adverse effects are usually mild and transient: abdominal discomfort, nausea, and vomiting. The urine may be dark-colored (SEDA-11, 597). Metabolites of furazolidone inhibit monoamine oxidase (1) and there is therefore the potential for interactions with foods containing tyramine (2) and with opioid analgesics; hyperpyrexia has been reported in rabbits that were given furazolidone and pethidine (3).

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Furosemide

See also Diuretics

General Information

Furosemide is the classic member of the group of so-called high-ceiling or loop diuretics, which can achieve a much greater peak diuresis than the thiazides. It is widely and frequently used both orally and parenterally over a wider dosage range than the thiazide diuretics, because its concentration-effect curve is steeper and because it is effective in patients with moderate renal insufficiency (creatinine clearance 5–25 ml/minute), in

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whom the thiazide diuretics and most related compounds are ineffective.

Furosemide is quickly and almost completely excreted by kidney unmetabolized. The usual oral dose is 20–120 mg, but much larger doses (for example 1000 mg) have been used in renal insufficiency. It is very effective after intravenous injection, and doses of 500 mg and more can be used in emergencies (renal insufficiency, pulmonary edema). The majority of adverse effects occur with the use of high doses, 95% of the reactions being dose dependent (1).

General adverse effects

Disturbances of fluid and electrolyte balance, such as hyponatremia, hypokalemia, and dehydration with circulatory disturbances (such as dizziness, postural hypotension, and syncope), have been reported. Rarely gastrointestinal symptoms are problems with high dosages and in the elderly. Pancreatitis and jaundice seem to occur more often than with the thiazide diuretics, but deterioration of glucose tolerance seems to be less common. At serum concentrations over 50 μg/ml, tinnitus, vertigo, and deafness, sometimes permanent, have been reported. Hematological disorders, particularly thrombocytopenia, and serious skin disorders occur occasionally, as do hypersensitivity reactions. Neither tumor-inducing effects nor second-generation effects have been documented.

Organs and Systems

Cardiovascular

Because furosemide, apart from its diuretic effect, has transient but pronounced vasodilator properties (changes in both venous capacitance and peripheral arteriolar resistance have been described in anephric patients), it can cause postural hypotension and syncope, particularly if given together with other blood pressure-lowering drugs (SED-8, 458) (SED-9, 349) (SED-9, 350). Ischemic complications have been reported in elderly patients. Reactions due to extracellular volume depletion accounted for 9% of all adverse effects observed in 535 patients treated with furosemide (1). Neuroendocrine activation and resultant increased peripheral resistance (afterload) after furosemide reduce cardiac output and stroke volume and increase cardiac work, with the possibility of worsening myocardial and tissue ischemia. Since many patients with heart failure have underlying myocardial ischemia or infarction, initial symptomatic benefit from furosemide can be followed by detrimental effects on myocardial perfusion, with extension or completion of myocardial necrosis.

When it is used in cardiac failure, furosemide acts in two ways: besides its diuretic effect it produces an immediate fall in left ventricular filling pressure, which is independent of and precedes diuresis. If furosemide is given intravenously in stable chronic heart failure (which it normally is not), this can be an unwanted effect, causing deterioration (SEDA-11, 199), particularly in patients with pure right ventricular failure.

Nervous system

Visual disturbances and drowsiness have been described, but it is not clear whether these were caused by reduced cerebral perfusion or by a direct effect of the drug itself.

Sensory systems

At high doses, and especially if serum concentrations are over 50 μg/ml, furosemide can cause ototoxic reactions, such as tinnitus, vertigo, and even deafness, sometimes permanent (SED-9, 351). Subclinical, audiometrically determined, high-tone deafness has been reported to occur in 6.4% of furosemide-treated patients (2). It is generally considered advisable to use another diuretic in patients whose hearing is already impaired, and to avoid using furosemide along with other ototoxic drugs, such as the aminoglycosides.

Sensorineural hearing loss occurs in a small proportion of very premature babies who are given furosemide. Various causative mechanisms have been suggested, including bilirubin, drugs, infection, and/or hypoxic brainstem injury. In a case-control study of 15 children and 30 controls born before 33 weeks of gestation, renal insufficiency and/or aminoglycoside use in conjunction with furosemide was associated with sensorineural hearing loss (3).

Endocrine

Furosemide rarely causes the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (although it has been found useful in treating some patients with SIADH who cannot tolerate water restriction (4)). In furosemide-induced cases (SEDA-7, 246), serum ADH concentrations were raised, total body sodium was normal, total body potassium greatly reduced, and intracellular water raised at the expense of extracellular fluid volume. However, such cases are rare, and no new cases have been published since this complication was reported in SEDA-7.

Nutrition

Patients with congestive heart failure taking high doses of furosemide can develop thiamine deficiency, which is improved by thiamine supplementation. There is whole-blood thiamine phosphate deficiency, but no reduction in the storage form of thiamine, thiamine diphosphate. These observations suggest that thiamine supplementation may not be necessary in elderly patients taking furosemide for congestive heart failure (5).

Hematologic

Agranulocytosis, thrombocytopenia, and hemolytic anemia have been reported occasionally (SED-8, 484) (SED-9, 350) (SEDA-1, 180). The commonest complication is thrombocytopenia (6), although it is often mild and asymptomatic (7).

Gastrointestinal

With normal doses, nausea, vomiting, and diarrhea are very uncommon, accounting for less than 1% of all

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adverse reactions (SED-9, 350). The incidence rises with higher doses and in the presence of uremia.

Liver

Although furosemide is very hepatotoxic in experimental animals, only a few cases of jaundice have been reported (SED-8, 484) (SED-8, 485), and no fully documented cases have so far been published. However, in patients with cirrhosis furosemide readily precipitates hepatic encephalopathy (SED-8, 485), even when low doses are used (1).

Biliary tract

Biliary colic has been attributed to furosemide (SED-11, 427).

Pancreas

Increases in serum isoamylase (SEDA-6, 213) and pancreatitis have been reported in patients taking furosemide.

Urinary tract

Excessive diuresis and dehydration often cause a transient reduction in glomerular filtration rate and a rise in serum urea (about 8% of all adverse reactions) (SED-8, 350). The sudden diuresis can cause loin pain, particularly in elderly patients, and acute urinary retention and overflow incontinence in elderly men with prostatic hyperplasia.

Although it is often described in children, medullary nephrocalcinosis with furosemide has been rarely described in adults.

- A 40-year-old woman who had taken furosemide (40–160 mg/day) for 15 years developed medullary nephrocalcinosis (8).

Chronic tubulointerstitial nephritis has been reported with furosemide.

- A 25-year-old woman developed biopsy-proven chronic tubulointerstitial nephritis with accompanying distal renal tubular acidosis in association with furosemide abuse (up to 1.2 g/day for several months) (9).

Four children with the nephrotic syndrome developed transient hypercalciuria and intraluminal calcification in renal histopathological specimens without radiological evidence of renal calcification. These children were resistant to corticosteroids and were receiving furosemide plus albumin for the management of edema (10). This result stresses the pervasive effect of furosemide, and probably all loop diuretics, in increasing urinary calcium excretion, with resultant nephrocalcinosis. Whenever possible, steps should be taken to limit the hypercalciuric effect of loop diuretics. Such maneuvers could include limiting the sodium content of the diet and/or combining the loop diuretic with a thiazide diuretic.

Skin

Rashes seem to be just as common with furosemide (SED-8, 484) as with other oral diuretics, but severe skin reactions (exfoliative dermatitis, erythema multiforme, acquired epidermolysis bullosa), which are rare with other diuretics, have been occasionally reported with high doses of furosemide in renal insufficiency (SED-12, 503) (SEDA-18, 234).

Cases of furosemide-induced lupus-like syndrome (11), bullous pemphigoid (12,13), and lichenoid drug eruptions (14) have been reported.

A review of furosemide-induced skin reactions included a description of a unique case of an 88-year-old man who developed an eruption that clinically and histologically simulated Sweet's syndrome (acute febrile neutrophilic vasculitis) after 6 weeks (15). Atypical features and rapid resolution suggested a drug eruption rather than true Sweet's syndrome. However, a similar mechanism may have been implicated a hypersensitivity reaction involving immune complexes.

Linear IgA bullous dermatosis associated with the administration of furosemide has been reported (16).

- An 86-year-old woman, with a history of stable schizophrenia, chronic obstructive pulmonary disease, ischemic cardiomyopathy, and type 2 diabetes, was admitted with cardiac insufficiency, which was treated by introduction of enalapril. A chest infection was treated with co-amoxiclav with gradual alleviation of symptoms over 10 days. At this point, furosemide was begun, because of persistent signs of heart failure. After 3 days, erythema and bullae were noted on her palms and soles, and later on the trunk, extremities, hard palate, and buccal mucosa. Biopsy showed the characteristic features of linear IgA bullous dermatosis, with linear deposition of IgA along the basement membrane. Co-amoxiclav and furosemide were withdrawn; no new lesions were noted thereafter.

Furosemide has previously been related to other bullous dermatoses, particularly bullous pemphigoid (SED-14, 671). In this case only a temporal relation was demonstrated, as rechallenge was judged to be unethical. The other putative offending drug, co-amoxiclav, was regarded as unlikely to be causative, because it had been given many times before without noticeable skin lesions.

Furosemide has been associated with disseminated superficial porokeratosis, a heritable disorder of cornification (17).

A man developed acute generalized exanthematous pustulosis while taking furosemide (18). A positive lymphocyte transformation test suggested an immunological mechanism.

Immunologic

It has long been thought that loop and thiazide diuretics pose a theoretical risk of cross-sensitivity in patients with sulfonamide allergy because of their common structures. However, the available literature does not provide sufficient numbers of well-documented cases to support this impression (19). It seems that careful administration of diuretics is permissible in patients with documented sulfonamide allergy, but as always such a drug challenge should not be attempted without careful follow-up. A furosemide rechallenge protocol, based on a method that has been used to rechallenge with a sulfa-containing antimicrobial agent, safely allowed the long-term reinstitution of loop diuretic therapy with furosemide (20).

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Body temperature

Several cases of furosemide-associated fever have been reported (SEDA-20, 204) (SEDA-21, 229) (SEDA-22, 238). These had certain features in common: (1) the affected infants were in their first year of life; (2) there was congestive heart failure as a result of congenital abnormalities or cardiomyopathy; (3) the temperature was raised to 38.5–40°C and there was a resemblance to septic fever; (4) concomitant treatment with digoxin; (5) negative physical examination and investigations for a source of infection; (6) withdrawal of furosemide was followed by disappearance of fever within 1–2 days. In some cases, the use of furosemide in lower dosages or on alternate days avoided fever. The mechanism of this adverse effect is unclear, but it appears to be dose-related. Consideration of furosemide as a cause of fever in such patients may save unnecessary laboratory studies and lead to early resolution.

Long-Term Effects

Drug withdrawal

The more intensive diuretic treatment is the greater the risk from sudden withdrawal. In one series of 38 patients, taking 20–40 mg furosemide or equivalent, generally for heart failure, withdrawal was attempted when all had been free of heart failure or hypertension for at least 3 months; it was followed by clinical or radiological relapse in 29% and one of the patients died (21). In another five patients, withdrawal in three led to severe symptoms necessitating admission to hospital (SEDA-10, 192) (SEDA-10, 193). The best advice is to withdraw intensive diuretic treatment only with the utmost caution and not to attempt withdrawal at all if there is any radiological evidence of heart failure. In patients with congestive heart failure, independent predictors of the need for continued diuretic were furosemide dosage greater than 40 mg/day, a left ventricular ejection fraction less than 0.27, and hypertension (22).

The effects of furosemide withdrawal on postprandial blood pressure have been assessed in 20 elderly patients (mean age 73 years) with heart failure and preserved left ventricular systolic function (ejection fraction 61%) (23). In 13 who were able to discontinue furosemide (mean dose 32 mg/day), maximum systolic blood pressure fell significantly from 25 mmHg to 11 mmHg and diastolic blood pressure from 18 to 9 mmHg over 3 months. In the continuation group (mean furosemide dose 21 mg/day), there was no change in the postprandial fall.

However, there are sometimes opportunities for withdrawal of furosemide (SEDA-22, 237). If diuretics are withdrawn suddenly in patients with a normal sodium intake, there will be rebound retention of sodium and water, because compensatory mechanisms that maintain sodium balance in the face of diuretics continue to act for several days after the diuresis has worn off. There are two methods of mitigating rebound retention of sodium and water: gradual reduction of the dosage or institution of a low sodium diet so that only a small amount of sodium can be retained when the diuretic is withdrawn. Rebound retention of sodium and water, with consequent edema, may convince the doctor that continued diuretic therapy is necessary, and the patient is then committed to life-time exposure. Even in patients with heart failure, reduced intake of salt may remove the need for diuretics or allow the use of lower dosages.

Second-Generation Effects

Pregnancy

Although furosemide has embryotoxic properties in some animal species, it has been widely used in pregnant women without any adverse effects. Nevertheless, it should be used with great caution, since hypovolemia can lead to reduced uterine and placental blood flow. Careful monitoring of fetal heart action is necessary. Furosemide passes the placenta and increases fetal urine production. It can also increase acid concentrations in maternal serum, fetal serum, and amniotic fluid, thus masking a useful index for the development of pre-eclampsia (24). Its use in pregnant women should therefore be restricted to the treatment of cardiac failure.

Lactation

Furosemide passes into the breast milk in a concentration 80% of that in serum at pH 7.0, but the total amount of drug ingested is probably too low to affect the neonate (25).

Susceptibility Factors

Age

In premature infants furosemide can cause persistent patent ductus arteriosus (SEDA-9, 208). The use of furosemide in this age group needs to be re-evaluated (SEDA-14, 182) (SEDA-15, 217).

Renal disease

High doses of furosemide in uremia are potentially ototoxic (26).

Hepatic disease

Although high-dose furosemide can be very useful in incipient acute renal insufficiency, it should be used with extreme caution in patients with severe hepatic insufficiency (SEDA-14, 183) and not at all in hepatic coma.

Drug–Drug Interactions

ACE inhibitors

Acute renal insufficiency with severe hyponatremia has been attributed to vigorous diuretic treatment (metolazone, furosemide, spironolactone) with an ACE inhibitor (27). Because ACE inhibition impairs renal protection against reduced perfusion, the combination of an ACE inhibitor with high-dose furosemide causes a reduction in glomerular filtration rate linearly related to the change in blood pressure.

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In congestive heart failure, single conventional doses of captopril (25–75 mg) attenuated the natriuretic response to furosemide, while a low dose (1 mg) significantly enhanced furosemide-induced natriuresis (SEDA-17, 268) (SEDA-18, 236). The mechanism of this interaction is uncertain, but captopril did not affect delivery of furosemide to its site of action (28). In the long-term, intensive treatment with captopril enhanced the natriuretic response to furosemide (SEDA-17, 268).

Allopurinol

Interstitial nephritis with granulomatous hepatitis has been attributed to an interaction of furosemide with allopurinol (29). As in previous reports (SEDA-11, 198) the evidence for this interaction is not convincing. The role of allopurinol in causing the illness is credible, but the role of furosemide is doubtful.

Aminoglycoside antibiotics

Furosemide increases the ototoxic risks of aminoglycoside antibiotics (30,31) by reducing their clearance by about 35% (32); permanent deafness has resulted from the use of this combination.

- A 60-year-old woman developed moderately severe sensorineural hearing loss bilaterally after receiving five doses of gentamicin and one of furosemide 20 mg (33).

The cumulative dose and duration of aminoglycoside therapy are more important than serum concentrations in the development of gentamicin ototoxicity, except when interacting medications such as furosemide are co-administered.

Aspirin

Furosemide inhibits the absorption of aspirin (34), and aspirin 75 mg/day and 300 mg/day inhibits the venodilator effect of furosemide (35). These data raise the issue of whether aspirin should be routinely used in patients with congestive heart failure using furosemide.

Cephaloridine

The nephrotoxic effects of cefaloridine are potentiated by concurrent administration of furosemide (36,37), perhaps by a direct interaction and probably also because furosemide lowers the clearance of the antibiotic (38). Such combinations are better avoided.

Digoxin

It is advisable to monitor serum potassium concentrations closely if furosemide is combined with any cardiac glycoside.

Lithium

Furosemide can cause lithium toxicity by inhibiting the renal tubular excretion of lithium ions (39).

Mannitol

The combination of furosemide with mannitol can rapidly cause acute renal insufficiency (40) and potentiate the effect of curare (41).

NSAIDs

Furosemide inhibits the absorption of indometacin (42), while the diuretic and hypotensive effects of most diuretics are blunted by indometacin and probably also other NSAIDs (43). Intravenous furosemide is commonly given to patients with acute heart failure to relieve pulmonary congestion. Symptomatic relief occurs before the onset of diuresis, and the beneficial effect is believed to result from a venodilator action of furosemide, which precedes its diuretic effect. This venodilator response is inhibited by indometacin, suggesting that it occurs through local prostaglandin release.

Furosemide inhibits the absorption of meloxicam (44), an NSAID that is relatively selective for COX-2, sparing the physiologically important isoform that mediates vasodilator prostaglandins, which maintain renal function.

Phenytoin

The diuretic response to furosemide is reduced by approximately 50% during concurrent administration of phenytoin (45), probably through reduction of furosemide absorption (46).

Potassium-wasting drugs

The hypokalemic effects of furosemide can be potentiated by drugs such as licorice (47) and carbenoxolone (48).

Theophylline

Furosemide increases steady-state theophylline concentrations (SED-11, 428) (SED-14, 673).

A randomized, controlled study has shown an enhanced diuretic response to furosemide in infants taking theophylline during extracorporeal membrane oxygenation (49). The underlying mechanism was uncertain, but may have been an increase in glomerular filtration rate.

Thiazide diuretics

The use of thiazide and loop diuretics in combination to treat resistant hypertension often causes severe deterioration in renal function (50,51). It is not clear whether this is the result of excess diuresis or excessive blood pressure reduction.

Vancomycin

Ten preterm infants receiving regular theophylline for apnea of prematurity, who subsequently received vancomycin and furosemide, have been studied (52). When vancomycin was introduced in the infants who were established on furosemide and theophylline, there was a consistent failure to achieve therapeutic concentrations. Starting furosemide in infants who were already receiving vancomycin resulted in falls in serum vancomycin to subtherapeutic concentrations in all but one case. Serum concentrations fell by a mean of 24% (range 12–43%), in the 24 hours after the start of furosemide treatment. Two of the 10 infants had persistence

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of coagulase-negative staphylococcal sepsis while vancomycin concentrations were suboptimal. While the mechanism of this interaction is uncertain, the changes in serum vancomycin concentration may indicate acute changes in glomerular filtration rate. Preterm infants receiving theophylline and furosemide need shorter vancomycin dosage intervals to avoid therapeutic failure.

Warfarin

In patients taking warfarin, furosemide, like other diuretics, reduces the prothrombin time without changing the plasma warfarin concentration (SEDA-22, 238). The reduced anticoagulant effect is probably secondary to diuretic-induced volume depletion, mediating increases in clotting factors. Any effect is likely to be short-lived.

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Fusidic acid

General Information

Fusidic acid is the best-known representative of a group of antibiotics with steroid structures, which are eliminated primarily by biliary excretion as microbiologically inactive metabolites. The antibacterial action of fusidic acid is bacteriostatic, although it can be bactericidal at higher concentrations. It exerts its antibacterial effect by inhibiting protein synthesis, but the exact mechanism by which this inhibition occurs has not yet been elucidated. It has a narrow antibiotic spectrum, with a bacteriostatic or slow bactericidal effect mainly directed at both coagulase-negative staphylococci and *Staphylococcus aureus* (1). Fusidic acid may also have a role as a clinically useful suppressor of immunoinflammatory processes (2).

Fusidic acid is adequately absorbed from the gastrointestinal tract, but has also been used topically. It has the important property of good tissue penetration, including entry into bones and joints, but does not reach the cerebrospinal fluid. Elimination of fusidic acid is primarily by non-renal mechanisms, and a proportion is metabolized to several breakdown products detectable in bile. Systemic clearance is increased by hypoalbuminemia, reduced by severe cholestasis, and is unchanged in renal insufficiency (3).

General adverse effects

The most common adverse effects of fusidic acid are minor and are related to the gastrointestinal tract (discomfort, diarrhea). Rare adverse events include granulocytopenia, thrombocytopenia, venous spasm, and skin reactions (4). Fusidic acid has detergent properties and can cause hemolysis when injected intravenously or can induce tissue damage when given intramuscularly. However, its systemic toxicity is relatively low.

Bacterial resistance has been an obstacle to the widespread use of fusidic acid; it develops in a single step in vitro and has also been observed in patients, particularly during prolonged administration (5).

Organs and Systems

Gastrointestinal

Oral fusidic acid can cause *Klebsiella oxytoca*-associated colitis (6).

Liver

Fusidic acid is chemically very similar to bile acids and hence competes with them for elimination and metabolism. A patient with a past history of alcohol-induced cirrhosis developed cholestatic jaundice after taking oral fusidic acid for 2 days (7).

Urinary tract

Severe hypocalcemia and acute renal insufficiency developed in two diabetic patients who took oral fusidic acid 500 mg tds (8).

Skin

Acanthosis nigricans has been associated with fusidic acid (9).

Sensitization to sodium fusidate is rare, and most often found in patients with stasis dermatitis or atopic dermatitis.

- Allergic contact dermatitis has been reported in a 26-year-old Korean woman after treatment of an abrasion

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on the left knee with fusidic acid ointment and povidone iodine (Betadine) (10). The diagnosis was confirmed by a strongly positive patch test for sodium fusidate.

Immunologic

Fusidic acid may have an immunomodulatory effect that seems to be partly mediated by suppression of cytokine production. The effect on several diseases has been investigated, but it remains to be characterized more in detail whether there is any therapeutic usefulness (4).

Positive patch tests occurred in three of 1119 patients who had used topical fusidic acid (11). In the second part of this study, all cases of positive patch tests to fusidic acid over the previous 20 years were reviewed; the average frequency was 1.62 patch-tested patients per year (1.45%) of those who were patch-tested.

Long-Term Effects

Drug tolerance

Mechanisms of resistance to fusidic acid include alterations in elongation factor G (whose inhibition at the ribosome level mediates the effect of fusidic acid), altered drug permeability, binding by chloramphenicol acetyltransferase type 1, and enhanced efflux (12).

Most studies show low levels of resistance in staphylococci, with a slightly higher rate in methicillin-resistant *S. aureus* (MRSA) (12). This has been confirmed in recent studies. Only 1 of 106 isolates of methicillin-resistant *S. aureus* was also resistant to fusidic acid (13). Only very little resistance to fusidic acid has been reported from Wales (14). However, clonal spread of fusidic acid-resistant methicillin-resistant *S. aureus* has been documented in Norway (15). A resistance rate of about 50% has been found in coagulase-negative staphylococci isolated in eight Swedish intensive care units between 1995 and 1997 (16). A high rate of resistance to fusidic acid was also found in bacteria that were cultured from blood after dental treatment (17).

Pathogenic nocardia may inactivate fusidic acid (18). In an in vitro study, salicylate and related compounds increased the MIC in strains of *S. aureus* both resistant and susceptible to fusidic acid (19).

In a prospective randomized trial, oral fusidic acid alone (500 mg tds for 7 days) failed to eradicate methicillin-resistant *S. aureus* colonization but resulted in the emergence of fusidic acid-resistant strains (20).

In an in vitro susceptibility study of 170 clinical isolates of *Mycobacterium tuberculosis* to fusidic acid, 19 isolates were resistant to at least one first-line antituberculosis drug (21). In all, 1.8% of the isolates were resistant to fusidic acid. Fusidic acid can be a potential supplementary drug for the treatment of infections due to multidrug-resistant strains of *M. tuberculosis*.

Susceptibility Factors

Other features of the patient

The half-life of fusidic acid was shortened in ten patients with severe burns treated with 500 mg tds intravenously (22). This effect may be explained by translesional extrahepatic clearance and an increase in hepatic clearance.

Drug–Drug Interactions

HIV protease inhibitors

In a 32-year-old man infected with HIV plasma concentrations of ritonavir, saquinavir, and fusidic acid were significantly raised when these drugs were administered in combination, possibly from mutual inhibition of metabolism (23).

Phenazone

Activation of the CYP450 enzyme system, demonstrated by an increase in the metabolism of phenazone (antipyrine), has been found in 30 HIV-positive drug abusers (24). This activating effect was demonstrated after 28 but not after 14 days of treatment with fusidic acid 500 mg/day, suggesting time dependency.

Statins

Acute rhabdomyolysis has been attributed to an interaction of fusidic acid with simvastatin (25).

- A 66-year-old kidney transplant recipient developed a gangrenous lesion on the left foot infected with *S. aureus* and *Escherichia coli*. He was given ciprofloxacin and clindamycin for 6 weeks and then fusidic acid 1500 mg/day for 2 weeks. He became ill, with myalgia and no active movement of his legs, and rhabdomyolysis was established by laboratory tests. He had also taken atorvastatin 10 mg/day and he slowly recovered after withdrawal of both atorvastatin and fusidic acid.

The authors identified only one previous report of a patient with rhabdomyolysis who had taken simvastatin and fusidic acid.

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Gabapentin

See also Antiepileptic drugs

General Information

Gabapentin is used as adjunctive treatment for partial seizures and may be useful in some non-epileptic disorders, such as neuropathic pain. It has a favorable tolerability profile and is devoid of significant interactions with other anticonvulsants (1).

The use of gabapentin has been reviewed (2). Its adverse effects are limited to neuropsychological disorders, namely dizzy spells, drowsiness, fatigue, and headache. The risk of interactions is also limited.

The efficacy of gabapentin in dosages up to 3600 mg/day as adjunctive therapy has been studied in 2016 patients with partial seizures (3). The four most commonly reported adverse events were somnolence (15%), dizziness (10%), weakness (5.8%), and headache (4.5%).

In an uncontrolled trial using dosages up to 6000 mg/day in 50 patients with refractory partial epilepsy, tiredness, dizziness, headache, and diplopia were the most common adverse effects (4). At dosages above 3600 mg/day three patients developed flatulence and diarrhea and two had myoclonic jerks. At least in some patients, gabapentin gastrointestinal absorption did not become saturated within the explored dosage range.

The effectiveness of gabapentin has been studied in 22 patients with bipolar disorder who had an incomplete response to other mood stabilizers (5). Somnolence was common (six patients); adverse events that occurred in two patients each included irritability, memory impairment, headache, and tremor. One patient dropped out because of a mild rash.

In 237 children aged 3–12 years with refractory partial seizures gabapentin 24–70 mg/kg/day was used as add-on therapy over 6 months (6). There was a more than 50% reduction in partial seizures in 34% of the children. Somnolence was the most common adverse event related to gabapentin. Emotional lability and hostility were related to gabapentin in 3.4 and 3.0% of the patients respectively.

In a non-interventional observational cohort study, using the technique of prescription-event monitoring, patients taking gabapentin were identified from dispensed National Health Service prescriptions (7). Outcome data were obtained from questionnaires sent to the doctor 6 months after the initial gabapentin prescription. The cohort included 3100 patients, of whom 136 (4%) were children. The median duration of treatment was 8.1 months. The most frequently reported adverse events during the first month of treatment were neurological: drowsiness/sedation (6.7% of patients), headache/migraine (3.6%), malaise/lassitude (3.5%), dizziness (2.4%), and nausea/vomiting (2.6%). These events were also the commonest reasons for withdrawal of gabapentin and were reported as suspected adverse drug reactions. There were no congenital anomalies in the 11 babies born to women who used gabapentin during the first trimester of pregnancy. The crude mortality rate was five times that in the general population but similar to that in other published studies in patients with epilepsy. Thus, this report does not disclose new unrecognized adverse effects of gabapentin.

Comparative studies

Gabapentin and lamotrigine have been compared in an open, parallel-group, add-on, randomized study in 109 patients with uncontrolled partial epilepsy and learning disabilities (8). The two drugs were similarly efficacious, with similar incidences of adverse events and serious adverse events. Neither lamotrigine nor gabapentin exacerbated any of the challenging behaviors observed in these patients. The most common adverse effect of gabapentin was somnolence, which was mostly reported during the initial titration phase.

In a double-blind comparison of gabapentin and lamotrigine in 309 patients with new-onset partial or generalized seizures, the target doses were gabapentin 1800 mg/day and lamotrigine 150 mg/day (9). Severe adverse events were reported in 11% of patients taking gabapentin and 9.3% of patients taking lamotrigine. Two patients had serious adverse events thought to be related to the study drug; one took an overdose of gabapentin and the other had convulsions with lamotrigine. The most frequent treatment-related adverse events in both treatment groups were dizziness, weakness, and headache; 11% of patients taking gabapentin and 15% of those taking lamotrigine withdrew because of adverse events. There was an increase of over 7% in body weight from baseline in 14% of the patients taking gabapentin and 6.6% of those taking lamotrigine. There were benign skin rashes in 4.4% of those taking gabapentin and 11% of those taking lamotrigine.

Organs and Systems

Ear, nose, throat

Rhinitis is uncommon with gabapentin (10).

Nervous system

Drowsiness, dizziness, fatigue, or ataxia are seen in 10–20% of patients who use gabapentin (SEDA-19, 70) (SEDA-20, 62) (10). Of 240 adults followed for about 1 year, only 4% discontinued treatment because of adverse events (SEDA-19, 70). Adverse effects reported by more than 10% of patients were nystagmus, somnolence, diplopia, tremor, ataxia, and dizziness.

Gabapentin occasionally exacerbates absence and myoclonic seizures and causes de novo myoclonus (SEDA-21, 71). Myoclonus has been studied in 104 patients taking gabapentin for epilepsy (11). There were 13 cases of mild myoclonus, which did not significantly interfere with daily activities. All the patients had refractory epilepsy and were taking other antiepileptic drugs. Six had a severe chronic static encephalopathy; five had no medical diagnosis other than seizures. Ten developed multifocal myoclonus and three developed focal myoclonus, contralateral to their epileptic focus. Two had an

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exacerbation of pre-existing myoclonus. Withdrawal led to rapid resolution.

Choreoathetosis, dyskinesias, dystonic or myoclonic movement disorders (including oculogyric crises), and stuttering have been reported rarely (SEDA-21, 71) (SEDA-22, 87).

- Sensory neuropathy occurred in a 58-year-old man who had been given up to 2400 mg/day for over 5 months for the treatment of head pain (12). A mild pruritic rash had been present since starting treatment. Neuropathic symptoms included a burning sensation in the legs and hips. After withdrawal, reduced perception of tactile and noxious stimuli and neurogenic bladder dysfunction (with an associated syncopal episode) were recorded. The neuropathy improved over several months.

Gabapentin is used often to treat neuropathic pain, and its role in causing the sensory neuropathy in this patient was uncertain.

Gabapentin-induced myoclonus may be more common than initially thought. In a retrospective survey, 13 of 104 consecutive patients developed myoclonus at gabapentin dosages of 800–3200 mg/day (11). Six of the patients had severe chronic static encephalopathy. Three had focal myoclonus, contralateral to the epileptic focus, and two had exacerbation of pre-existent myoclonus. In all cases the myoclonus was mild and did not interfere with daily activities. The fact that in three patients the electroencephalogram did not show epileptiform discharges suggests that, at least in some cases, the myoclonus is non-epileptic in nature.

In a comparison of twice- and thrice-daily gabapentin, 29 stable responders were selected and followed for 3 months (13). The mean number of seizures per month was 4.2 at baseline, 1.0 during the thrice-daily and 0.9 during the twice-daily period. Adverse effects were reported by 11 patients during the thrice-daily period and by five patients during the twice-daily period; sedation and vertigo were the most frequent.

The efficacy and safety of gabapentin in relieving the symptoms of panic disorder have been studied in 103 patients in a randomized, placebo-controlled, double-blind study for 8 weeks (14). Adverse events included somnolence, headache, and dizziness. One patient had a serious adverse event, a car accident, while taking gabapentin.

Of 12 patients with moderate to severe dementia and severe behavioral disorders given gabapentin (200–1200 mg/day) for 8 weeks, 5 had adverse events such as gait instability, emotional instability, and sedation; two patients discontinued treatment prematurely because of severe adverse effects (15).

The role of gabapentin in patients with neuropathic pain has been evaluated in a systematic review (16). The most common adverse events were dizziness and somnolence, which occurred in about 25% of patients; ataxia occurred in about 8%. Adverse effects were dose-related.

- A 68-year-old man with essential tremor who was taking propranolol 80 mg/day had several daily episodes of paroxysmal dystonic movements in both hands 2 days after the addition of gabapentin 900 mg/day (17). The dose of propranolol was reduced to 40 mg/day and the dystonic movements resolved. The authors suggested that there had been a synergistic effect between propranolol and gabapentin.
- A 60-year-old woman with post-herpetic neuralgia developed asterixis after having taken gabapentin for 4 days (18). The authors proposed that the mechanism was GABAergic.

Two cases of gabapentin-related dyskinesia have been reported (19). The patients were 60 and 41 years old and took gabapentin 900–1200 mg/day for generalized anxiety. Generalized dyskinetic movements and facial tics appeared after 3 days and disappeared after 2 days of withdrawal.

Psychological, psychiatric

Gabapentin has rarely been implicated in psychiatric reactions. Two cases, one of mania (20) and one of catatonia (21), have been reported.

- A 35-year-old woman with epilepsy without a history of psychiatric disorders developed elevated mood after being stabilized on gabapentin monotherapy (3200 mg/day). After 5 months she developed a manic episode, which remitted when gabapentin was withdrawn.
- Catatonia was reported in a 48-year-old woman with bipolar disorder within 48 hours of withdrawal of gabapentin, 500 mg/day. The condition lasted for several days and disappeared after treatment with a benzodiazepine.

In the first case the presentation was strongly suggestive for a causative role of the drug. In the second it was speculated that the condition might have been provoked by altered GABAergic transmission after gabapentin withdrawal.

Two women, aged 37 and 38 years, took gabapentin and after a few days developed behavioral changes associated with euphoria (22). In one case the symptoms were transient and in the other they resolved after withdrawal. The behavioral changes were not related to seizure activity.

In a double-blind, crossover comparison of the cognitive effects of carbamazepine (mean dose 731 mg/day) and gabapentin (2400 mg/day), each given for 5 weeks, in 35 healthy volunteers performance on gabapentin was better than on carbamazepine for 8 of 31 variables (visual serial addition test, choice reaction times at initiation and total, memory paragraph I and delayed recall, Stroop Word and Interference, Vigor measure), whereas carbamazepine was better than gabapentin on none (23). Although these data suggest that gabapentin produces fewer cognitive effects than carbamazepine, the applicability of the findings to long-term therapy in epileptic patients is uncertain.

Behavioral disturbances, including aggressiveness, irritability, hyperactivity, and/or dysphoric changes, occur in up to 22% of patients. Children and patients with mental retardation or a history of similar disorders may be at special risk (SEDA-20, 61). In a recent study, hyperactivity, irritability, and agitation occurred in 15 of 32 mostly

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mentally retarded children, and required drug withdrawal in four (24).

The cognitive effects of carbamazepine and gabapentin have been compared in a double-blind, crossover, randomized study in 34 healthy elderly adults, of whom 19 subjects withdrew (15 while taking carbamazepine, probably due to excessively rapid dosage titration) (25). The primary outcome measures were standardized neuropsychological and mood state tests, yielding 17 variables. Each subject had cognitive testing at baseline (pre-drug), the end of the first drug phase, the end of the second drug phase, and 4 weeks after completion of the second drug phase. Adverse events were frequently reported with both antiepileptic drugs, although they were more common with carbamazepine. There were significant differences between carbamazepine and gabapentin for only 1 of 11 cognitive variables, with better attention/vigilance for gabapentin, although the effect was modest. Both carbamazepine and gabapentin can cause mild cognitive deficits in elderly subjects, and gabapentin has a slightly better profile.

Gabapentin has been associated with hostility, especially in children. Two cases of aggression in adults taking gabapentin for bipolar disorder have been reported (26). Neither patient had a history of aggression. In one the symptoms appeared after 3 days of treatment (1200 mg/day), and in the other after 48 hours (600 mg/day). In the second case, aggression was associated with auditory hallucinations. It is hard to associate new antiepileptic drugs with psychiatric adverse effects in patients with severe psychiatric disorders, and rechallenge with the offending drug should ideally have been tried before postulating a causal relation.

Endocrine

A 28-year-old woman with bipolar depression developed clinical and biochemical evidence of hyperthyroidism, ascribed to thyroiditis, while taking gabapentin (4800 mg/day) in a clinical trial (27). The condition cleared after withdrawal, and subsequent exposure to a lower dose of gabapentin (1500 mg/day) was uneventful.

Whether gabapentin was responsible for the thyroiditis is doubtful.

Metabolism

Weight gain occurs in up to about one-third of patients and may be more frequent at high dosages (SEDA-20, 61) (SEDA-22, 87). Of 44 patients given mean dosages of 3520 mg/day for at least 12 months, 10 gained more than 10% and 15 gained between 5 and 10% of their initial weight (28). The weight gain started after 2–3 months and tended to stabilize after 6–9 months.

Hematologic

In one case of reversible granulocytopenia attributed to gabapentin, cause and effect was dubious (SEDA-22, 88).

Gastrointestinal

Nausea and vomiting are uncommon with gabapentin (10).

Liver

Hepatotoxicity is exceedingly rare. The role of gabapentin in one patient with markedly raised liver enzymes after 12 weeks of treatment was unclear (SEDA-22, 88).

Gabapentin-induced cholestasis has been reported (29).

- A 50-year-old man was given gabapentin for diabetic neuropathic pain. He had also taken metformin, amitriptyline, dihydrocodeine (30 mg as required), and ramipril for over 12 months. After taking the gabapentin for 2 weeks, he developed clinical and biochemical evidence of cholestasis. Liver function tests were: bilirubin 199 μmol/l, aspartate transaminase 104 U/l, alkaline phosphatase 210 U/l, and gamma-glutamyltransferase 839 U/l. He had negative hepatitis A, B, and C serology and negative antinuclear antibody and anti-smooth muscle antibody. A blood count, renal profile, and liver ultrasound scan were also normal. A liver biopsy showed normal liver architecture with evidence of patchy steatosis, cholestasis, and some foci of chronic inflammation, thought to be consistent with a drug-induced etiology. Gabapentin was withdrawn and his symptoms and liver function tests improved gradually over 7–12 weeks.

The authors attributed the cholestasis to gabapentin because of the temporal relation. However, they failed to mention whether they withdrew other concomitant medications that could also have caused liver damage, a more likely explanation. Moreover, the number of dihydrocodeine tablets the patient took before admission was not stated.

Urinary tract

Urinary incontinence occurs rarely (SEDA-22, 88). Of 119 adults with partial seizures, 5 (4%) developed urinary incontinence which resolved after gabapentin withdrawal (30). Four of the five patients had signs of spasticity, suggesting that this may be a predisposing factor.

- A 27-year-old man with bipolar disorder had an increased serum creatinine concentration (up to 1.7 mg/dl, 150 μmol/l) after taking gabapentin 2000 mg/day for several weeks, the change being reversible after drug withdrawal (31).

The possibility of renal dysfunction as a rare adverse effect should be considered. The patient had a history of allergic reactions to lithium, carbamazepine, clozapine, haloperidol, and lamotrigine.

A renal transplant recipient with a long-term stable functioning allograft developed reversible acute renal dysfunction after beginning gabapentin therapy for chronic pain in diabetic neuropathy (32). The authors suggested that this was due to renal afferent vasoconstriction.

Patients on chronic hemodialysis are at risk of gabapentin toxicity. A patient undergoing hemodialysis and

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taking gabapentin 400 mg/day developed a very high serum concentration (56 μg/ml) and clinical toxicity manifested by stupor (33). A subsequent pharmacokinetic analysis suggested that in patients undergoing chronic hemodialysis, gabapentin should be started at 300 mg/day and post-hemodialysis dosing should be reduced to 100 mg/day, at least in some patients.

Skin

Skin rashes are rare with gabapentin.

There has been one case of diffuse alopecia reversible after drug withdrawal (SEDA-22, 88).

- A 32-year-old woman with HIV infection and cerebral toxoplasmosis developed histologically confirmed Stevens–Johnson syndrome after taking gabapentin (300–900 mg/day) for 3 days (34). Although other drugs were given, the condition resolved after withdrawal of gabapentin alone.

Whether the underlying condition played a role is open to speculation.

- In a 26-year-old woman who had severe Stevens–Johnson syndrome induced by phenytoin and later by carbamazepine, gabapentin resulted in an erythematous pruriginous skin eruption limited to the legs without mucosal involvement (35).

Although gabapentin has a lower allergenic potential than most other anticonvulsants, patients with a history of severe drug-induced idiosyncratic reactions may be at higher risk of gabapentin-induced skin reactions.

Sexual function

Anorgasmia has been quoted in the Physicians Desk Reference as an infrequent adverse effect.

- Anorgasmia was reported by a 52-year-old man while he was taking gabapentin, 900–1500 mg/day, for the treatment of neuropathic pain (36). The condition lasted for over 2 months and remitted when gabapentin was replaced with mexiletine.
- A 25-year-old man taking gabapentin 900 mg/day reported anorgasmia during sexual intercourse (37). He was given valproate instead and his symptom resolved within 12 days.
- Gabapentin-induced anorgasmia and reduced libido have been reported in two women (38). Both were taking relatively low doses of gabapentin (900–1800 mg). In one case the symptoms disappeared with dosage reduction but in the other gabapentin had to be withdrawn.

Immunologic

- A hypersensitivity syndrome secondary to gabapentin has been described in a 72-year-old patient after 9 days (39). The symptoms (altered mental status, fever, diffuse macular rash, and an enlarged spleen) resolved after withdrawal.

However, the concomitant use of levofloxacin made the association of gabapentin with the hypersensitivity syndrome unclear.

Body temperature

Gabapentin may be effective in the treatment of hot flushes (hot flashes), and by the same token has been reported to have increased the frequency of hypothermic episodes in a 38-year-old man with hypothalamic dysfunction (40).

Long-Term Effects

Drug withdrawal

Three cases of withdrawal symptoms after abrupt withdrawal of high-dose gabapentin have been reported in adults with psychiatric conditions (41). The patients were restless and anxious, with sweating and tachycardia. The symptoms improved after gabapentin was reintroduced.

Drug Administration

Drug dosage regimens

Two different regimens of add-on gabapentin have been compared in a double-blind, randomized trial (42). In 574 patients randomized to either slow initiation (300 mg on day 1, 600 mg on day 2, then 900 mg/day) or rapid initiation (900 mg/day immediately after the placebo lead-in), the four most common adverse events, which occurred equally in the two groups, were somnolence, dizziness, ataxia, and fatigue. The frequency of adverse events in a subgroup of elderly patients was similar to that in younger adults.

Drug overdose

- A 30-year-old woman with renal insufficiency on hemodialysis three times a week suffered no significant toxicity after ingesting 600 mg tds of gabapentin for 3 weeks, a large dose in view of her impaired kidney function (43). The blood gabapentin concentration was 496 μmol/l.

These data suggest that gabapentin poses no major risk in overdose, partly because large doses are poorly absorbed.

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Gadolinium

General Information

Gadolinium chelates for MRI (SEDA 18, 446) (SEDA-20, 419) (SEDA-21, 475) (SEDA-22, 503) are inert, non-metabolized, small molecules, with essentially the same pharmacokinetic properties as the iodinated contrast agents. They are rapidly distributed in the extracellular fluid spaces, both intravascular and extravascular, although they do not cross the normal blood–brain barrier, and are almost entirely excreted by glomerular filtration, with no significant active tubular excretion or re-absorption. Hepatic excretion occurs in patients with

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severely impaired renal function, and trace amounts are normally excreted in the saliva, sweat, and tears (SEDA-21, 475).

Gadolinium-based contrast agents of intermediate size act like blood-pool contrast agents during the first pass (1). However, because they diffuse into the interstitium, they later act like extracellular agents. Examples are P760 (gadolinium tetra-azacyclododecanetetra-acetic acid, Gd-DOTA) and Gadomer-17 (gadolinium diethylenetriaminepenta-acetic acid, Gd-DTPA). Intermediate-sized agents are used for the following purposes:

- the detection of small, slow-flowing, tortuous vessels;
- the detection of increased capillary permeability in sufficiently injured tissues;
- improved and prolonged demonstration of zones of myocardial ischemia;
- estimating myocardial blood flow;
- tumor characterization.

The classical macromolecular blood-pool contrast agents are based on gadolinium DTPA or gadobenate dimeglumine, which are linked to albumin, dextran, or polylysine (1). Albumin-based agents are not considered optimal for clinical development, as it is difficult to obtain highly consistent synthetic products. There are also problems with cardiovascular toxicity and retention of gadolinium in bones and liver. Dextran-based agents appear to be safer, and an agent called CMD-A2-gadobenate dimeglumine (CMD = carboxymethyldextran) has a favorable toxicity profile.

Gadolinium chelates include ionic high-osmolar agents, such as gadolinium pentetate dimeglumine (Gd-DTPA) and low osmolar non-ionic agents, such as gadodiamide. They generally have similar MR relaxivities, pharmacokinetics, and biodistribution, behaving as non-specific extracellular fluid space agents analogues to iodinated contrast media. The similar safety and efficacy of ionic and non-ionic gadolinium-based extracellular contrast agents suggests that the choice of contrast medium will in future be determined by economic rather than clinical considerations (2).

The use of gadolinium-based contrast agents as an alternative to iodinated contrast agents has been reported in a patient with a history of allergy to the latter (3).

- A 77-year-old woman had a gadolinium-enhanced MRI scan followed by gadolinium-enhanced spiral CT pulmonary angiography for suspected pulmonary embolism. Gadodiamide 0.4 mmol/kg (60 ml) was injected intravenously at a rate of 2 ml/second. There were no adverse reactions.

Note on brand names

The various gadolinium salts are often known by their brand names, because their chemical names are complex. The following is a key to various brand names:

- AngioMARK: gadofosveset
- Dotarem, Guerbet SA: gadolinium tetra-azacyclododecanetetra-acetic acid (Gd-DOTA)
- Gadovist: gadobutrol (Gd-BT-DO3A)
- Magnevist: gadopentetate dimeglumine; the di-*N*-methylglucamine salt of gadopentetate (gadolinium diethylenetriamine penta-acetic acid, Gd-DTPA)
- MultiHance: gadobenate dimeglumine (Gd-BOPTA)
- Omniscan: gadodiamide
- OptiMARK: gadoversetamide (Gd-DTPA-BMEA).
- Primovist (Eovist): gadoxetic acid
- ProHance: gadoteridol.

Comparative studies

In a multicenter, randomized, double-blind comparison of the safety, tolerability, and efficacy of gadoversetamide (a non-ionic gadolinium chelate) and gadolinium DTPA in 99 patients during contrast-enhanced hepatic imaging, both agents were well tolerated and there were no serious or unexpected adverse events (2). A total of 154 adverse events were recorded in 82 patients, of which 33 (21%) were thought to be related to either agent. Headache and taste disturbances were the most common adverse effects; they occurred in about equal frequency in the two groups. There were no clinically relevant changes in electrocardiography or any laboratory parameter in either group.

The efficacy and the safety of gadoversetamide and gadopentetate dimeglumine have been compared in a multicenter, randomized, double-blind, parallel-group study in patients with suspected central nervous system pathology who required MRI examination (4). They were randomized to receive 0.1 mmol/kg of either gadoversetamide ($n = 262$, aged 1–80 years, mean volume of contrast medium injected 15 ml) or gadopentetate dimeglumine ($n = 133$, aged 20–73 years, mean volume of contrast medium injected 16 ml). There were no significant differences in adverse effects or diagnostic efficacy between the two groups. Of those given gadoversetamide, 71 patients (27%) had adverse events, severe in only 5 (1.9%). Of those given gadopentetate dimeglumine, 31 patients (23%) had adverse events, severe in only 5 (3.8%). The adverse effects included headache, chest pain, taste disturbance, and leg cramps.

In controlled studies, gadobenate dimeglumine has been compared with gadolinium chelates in 222 patients and with placebo in 189 patients (5). There were no serious events and no differences in the incidence of adverse effects between the groups. Adverse effects included vomiting, dizziness, and rashes. Similarly, there were no differences between children and adults or between subjects with renal or liver insufficiency. The authors concluded that gadobenate dimeglumine is safe, with a very low incidence of serious events, and that it compares favorably with other MR contrast agents, such as gadolinium DTPA.

Gadobenate dimeglumine, in cumulative doses of 0.15 and 0.2 mmol/kg, has been compared with gadodiamide 0.3 mmol/kg in 205 patients (aged 20–88 years) with suspected central nervous system lesions (6). Gadobenate dimeglumine was well tolerated and the safety profile was similar to that observed with gadodiamide. In the three groups, adverse effects occurred in 28, 23, and 32% respectively. The most common adverse events of gadobenate dimeglumine were headache (16%), dizziness (4.6%), and taste disturbances (4.6%); the most common adverse events of gadodiamide were headache (7.2%),

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nausea (5.8%), and taste disturbances (5.8%). All adverse events were classified as mild to moderate. There were no significant changes in vital signs, hematology, or serum chemistry in any group. There were no significant differences in the diagnostic quality of the examination.

General adverse effects

The reported rate of adverse reactions of gadolinium chelates at a dose of 0.1 mmol/kg is 2.4%. Most of these reactions tend to be mild and do not require treatment (SEDA-15, 505). Serious reactions are extremely rare. However, several severe anaphylactoid reactions and angioedema have been reported (SED-12, 1187) (SEDA-16, 537) (SEDA-17, 538) (SEDA-18, 446) (7). The incidence of adverse effects is slightly higher in patients with a history of asthma or allergy (3.7%). For patients with a history of a previous reaction to an MRI or iodinated X-ray contrast agent, the reported adverse reaction rates were 21 and 6% respectively (SEDA-20, 419). Adverse effects at a dose of 0.3 mmol/kg included urticaria, vomiting, diarrhea, flushing, paresthesia, and headache, which have previously been reported with standard doses. The most common adverse effects were nausea and a metallic taste. In a study of 79 patients given 0.3 mmol/kg no adverse effects were recorded (SEDA-22, 503).

There is no significant difference in the incidence of adverse effects between ionic and non-ionic gadolinium chelates (SEDA-21, 483).

Gadobenate dimeglumine (Gd-BOPTA)

Gadobenate dimeglumine is a novel paramagnetic contrast agent that combines the properties of a conventional extracellular contrast agent with those of a liver-specific contrast agent. It has potential for both hepatic and non-hepatic targeted imaging. Unlike standard gadolinium chelates, which are excreted by the kidneys, 3–5% of gadobenate dimeglumine is taken up by functioning hepatocytes and is excreted unchanged in the bile. It also has an inherently higher T1 relaxivity than conventional gadolinium chelates, and so causes very marked enhancement of the liver parenchyma on T1 images, which persists for up to 2 hours. Liver tumors generally do not contain functioning hepatocytes and therefore do not take up gadobenate dimeglumine; they therefore appear as unenhanced hypointense lesions.

In 74 patients over the age of 18 years with possible metastatic brain disease, a total cumulative dose of 0.2 mmol/kg of gadobenate dimeglumine injected intravenously over 20 minutes was safe and enhanced the assessment of brain secondaries (8).

The safety and efficacy of gadobenate dimeglumine in phase 1, 2, and 3 studies have been reviewed in 732 patients, of whom 168 received 0.05 mmol/kg and 564 received 0.1 mmol/kg (9). The overall incidence of adverse events was 14% with the lower dose and 9.9% with the higher dose. The vast majority of events were mild, transient, and self-limiting. There were no sex-, age-, or dose-related differences and no clinically important effects on vital signs or laboratory parameters. The most common adverse events were hypertension (1.37%), nausea (1.09%), tachycardia (0.96%), and albuminuria (0.75%). The authors concluded that gadobenate dimeglumine is safe and efficacious as a contrast agent for use in hepatic MRI.

The safety of gadobenate dimeglumine has been confirmed in phase 2 and phase 3 studies in Japan (10,11). The overall adverse reaction rate was 3.5–5% and all the reactions were mild or moderate. There were no differences in the rates of adverse reactions with different dosage regimens (0.05–2.0 mmol/kg).

A safety evaluation of gadobenate dimeglumine in patients with renal impairment has also been reported (12). In a placebo-controlled, double-blind study there were no changes in laboratory parameters or vital signs and no clinically important adverse events.

The safety of gadobenate dimeglumine has been evaluated in 2367 adults aged 18-88 years and 173 children. The overall incidence of adverse events was 20%. Events related to the contrast agent were reported in 15% of the adults. Most of the adverse events were mild and transient and resolved spontaneously. Headache, injection site reactions, nausea, taste disturbance, and vasodilatation were the most common, with frequencies of 1.0–2.6%. Serious adverse events potentially related to the contrast agent were reported in 0.2%. These events included laryngospasm, which developed 10 minutes after the contrast injection in a 51-year-old woman, severe vomiting in a 5-year-old child, and pulmonary edema in a 65-year-old patient.

Gadobenate dimeglumine (intravenous bolus injection of 0.05 mmol/kg) was well tolerated by 103 patients (mean age 56 years) with acute myocardial infarction (13). Minor adverse effects in 27 patients included injection site reactions (13%), paresthesia (6.8%), dry mouth (6.8%), taste disturbance (2.9%), and headache (1.9%). The authors concluded that the use of a bolus dose of gadobenate dimeglumine 0.05 mmol/kg up to 6 days after acute myocardial infarction is safe.

The safety of intravenous gadobenate dimeglumine 0.025, 0.05, 0.1, and 0.2 mmol/kg in MR angiography has been assessed in 94 patients (mean age 58 years). Diagnostic accuracy was optimal at a dose of 0.1 mmol/kg (14). All the doses were well tolerated and there were no significant changes in safety parameters. Six patients reported mild adverse effects related to the contrast agent, including urticaria ($n = 2$), nausea ($n = 2$), and mild increases in liver enzymes (gamma-glutamyl transpeptidase, alanine transaminase, and aspartate transaminase) ($n = 2$). All the adverse events resolved spontaneously.

Similar observations were made in another study using similar doses of gadobenate dimeglumine for MR angiography (15). There were no important adverse effects, and the authors concluded that gadobenate dimeglumine is safe for MR angiography and that the optimal diagnostic dose is 0.1 mmol/kg.

Gadobutrol

Gadobutrol 1.0 is an extracellular neutral gadolinium chelate belonging to the class of macrocyclic neutral gadolinium complexes. It has the lowest osmolality of gadolinium-based contrast agents (1.60 osmol/kg). In preclinical evaluation there was good tolerance up to a dose of 0.5 mmol/kg, and this has been confirmed in phase I

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clinical studies. In a phase II study, 89 patients with suspected cerebrovascular insufficiency received Gadovist 1.0 in doses of 0.1 ($n = 11$), 0.2 ($n = 21$), 0.3 ($n = 21$), 0.4 ($n = 21$), or 0.5 ($n = 15$) mmol/kg (16). There were no significant changes in vital signs or any serious adverse reactions. Two patients had nausea and dry mouth. A dose of 0.3 mmol/kg was diagnostically adequate.

Gadodiamide

Adverse events associated with the non-ionic, gadolinium-based contrast agent gadodiamide have been reported in 1–2% of patients. Most of the commonly reported adverse events have been headache, dizziness, or nausea and vomiting.

The safety and effectiveness of gadodiamide-enhanced magnetic resonance angiography (MRA) with single and triple doses in the assessment of abdominal arterial stenosis has been investigated in 105 patients, of whom 53 (aged 45–83 years) received 0.1 mmol/kg and 52 (aged 38–85 years) received 0.3 mmol/kg (17). There were no serious adverse events. Six patients in the single-dose group felt a sensation of heat or warmth in the abdomen, lumbar spine, upper legs, hips, or groin; five of these events were mild and one was moderate; one patient felt a mild cold sensation at the injection site. Six patients in the triple-dose group felt a warm discomfort in the abdomen, pelvis, or buttocks (two mild and four moderate); four other patients felt a cold sensation at the injection site or in the arm (three mild and one moderate). The authors concluded that gadodiamide-enhanced MRA performed with single and triple doses is safe and effective in assessing major abdominal arterial stenosis. Triple-dose MRA was better at evaluating image quality and the degree of arterial stenosis.

The safety of gadodiamide-enhanced MRI in staging suspected or recurrent soft tissue tumors of the head and neck has been investigated in 48 patients (aged 37–86) (18). There was only one adverse event, moderate thirst. The authors concluded that the use of gadodiamide for MRI contrast-enhanced examination of the head and neck is safe and provides more diagnostic information than unenhanced images.

Gadofosveset

Gadofosveset (MS-325) is a gadolinium-based small molecular weight chelate, which binds strongly and reversibly to human serum albumin after injection (19). Because of albumin binding it has a long half-life and increased relaxivity ($RI = 48\ mM^{-1}sec^{-1}$ at 0.47 T and 37°C, which is 10 times higher than gadolinium DTPA). These properties are particularly useful for contrast-enhanced, three-dimensional MRA. Furthermore, MS-325 can be given as a bolus, allowing dynamic arterial imaging. Prolonged blood-pool retention also allows steady-state imaging. There are promising results from early studies of carotid and coronary arteries. No serious adverse effects have been reported after the injection of gadofosveset, although transient nausea and paresthesia were reported in two of seven volunteers (1).

The safety and diagnostic efficacy of gadofosveset in MRA of the carotid arteries has been investigated in 26 patients aged 42–81 years with suspected carotid artery stenosis. It was given intravenously to 4, 9, and 13 patients in single doses of 0.01, 0.03, or 0.05 mmol/kg respectively. There were no serious or severe adverse events. Two patients who received 0.05 mmol/kg had five adverse events within 3 hours after the injection (nausea, cramps, metallic taste, and pruritus), which were rated as mild. There were no significant changes in serum chemistry. High-quality MRA scans were obtained in all the patients.

Gadopentetate dimeglumine

Gadopentetate dimeglumine (1 ml mixed with 4 ml of 5% saline) has been used in myelocisternography in four patients (aged 28–62 years) to demonstrate the exact site of cerebrospinal fluid (CSF) leakage in patients with CSF rhinorrhea (20). All tolerated the examination without adverse effects or complications.

Gadoversetamide

The safety of intravenous gadoversetamide, 0.1, 0.3, and 0.5 mmol/kg, has been confirmed in a study of its pharmacokinetics, safety, and tolerability in 163 patients with nervous system or liver pathology and varying degrees of renal function (21). All the adverse events that were thought to be related to gadoversetamide were mild or moderate, and there was no difference between doses. There were no changes in laboratory parameters. Gadoversetamide was well tolerated, even in patients with prolonged elimination due to renal impairment.

The safety of gadoversetamide at doses of 0.1–0.7 mmol/kg has been evaluated in 18 clinical studies (22). Adverse events related to the contrast agent were reported in 31% of injections. There were no serious adverse events.

Gadoxetic acid

Gadoxetic acid (gadolinium ethoxybenzyl diethylenetriaminepenta-acetic acid) was developed as a tissue-specific contrast agent for the liver and biliary system to be used in MRI and is a derivative of gadolinium DTPA with higher lipophilicity. It is taken up into hepatocytes and undergoes biliary excretion. Intravenous gadoxetic acid disodium has been used to assess liver enhancement and detect lesions in CT scanning of 15 patients with known liver metastases. The contrast agent was administered as an intravenous infusion over 20 or 30 minutes in doses of 0.2, 0.35, and 0.5 mmol/kg. There were three mild adverse reactions and one moderate reaction. Two patients reported a burning sensation at the site of infusion or retrosternally, which resolved when the flow rate of the infusion was reduced. Two other patients reported right upper quadrant pain, which began 4 hours after the infusion; this resolved spontaneously after a few hours. There were also minor reversible alterations in liver enzymes in some patients. Overall patient tolerance was acceptable and the images showed good or excellent liver enhancement, liver to tumor attenuation difference, and tumor visualization in the majority of cases with doses of 0.35 and 0.5 mmol/kg (SEDA-22, 504).

Uses of gadolinium other than in MRI scanning

Gadolinium can sufficiently attenuate X-rays to be visualized with digital subtraction angiography, although the

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quality of image is consistently inferior to that produced by iodinated agents. Of 13 patients who underwent transplant angiography with 16–20 ml of either gadopentetate dimeglumine (0.5 mmol/ml) or gadolinium (0.5 mmol/ml), there was no significant deterioration in renal function in 11 patients (23). In the other two there were significant increases that were not considered to be due to either gadolinium or the administration of CO_2. These findings are consistent with previous studies (SEDA 22, 504) showing that gadolinium compounds are not nephrotoxic.

Organs and Systems

Pancreas

Acute pancreatitis has been attributed to gadodiamide.

- A 58-year-old man was given intravenous gadodiamide (non-ionic gadolinium chelate) 16 ml (0.2 mmol/kg) for hepatic MRI and immediately after the injection developed fatigue, nausea, vomiting, sweating, and later intense upper abdominal pain (24). His serum amylase was 4262 IU/l and abdominal MRI showed a diffusely enlarged pancreas, confirming the diagnosis of acute pancreatitis. A full history and biliary tract ultrasound excluded other causes. The attack was mild and the clinical course uneventful.
- A 68-year-old woman with long-standing peripheral vascular disease and chronic renal insufficiency (serum creatinine 334 μmol/l) underwent peripheral angiography with gadodiamide (dose not stated) and 6 hours later developed nausea, epigastric pain, and two episodes of vomiting, with further epigastric pain 5 hours later (25). Her serum amylase and lipase activities were 246 and 1314 U/l respectively (reference ranges 0–140 and 0–200 U/l). The next morning they were 684 and 1646 U/l respectively. Ultrasound scan of the liver and gallbladder was normal. She subsequently developed acute renal insufficiency, electrolyte imbalance, and pulmonary edema. Urine microscopy showed muddy brown casts consistent with acute tubular necrosis. Her pancreatitis resolved without any further complications.

The authors of the second case highlighted the fact that there is no recommended maximum safe dose of gadolinium, nor a minimum creatinine clearance below which gadolinium should not be used.

Urinary tract

Intravenous gadoterate meglumine 35 ml has been used as a contrast agent for arm venography using digital fluorography in 45 patients with end-stage renal insufficiency (age 26–88 years, serum creatinine 262–1360 μmol/l) before the creation of an arteriovenous fistula (26). The mean serum creatinine did not change significantly. There were no significant adverse effects. Only one patient developed vomiting. A good diagnostic examination was obtained in all cases.

The use of gadolinium-DTPA as a suitable contrast agent in patients with renal insufficiency undergoing vascular intervention with standard X-ray screening has been reported (SEDA-22, 504). During angiography two patients received gadolinium DTPA 50–60 ml without alterations in serum creatinine or any other adverse effect.

- A 55-year-old woman with polycystic kidney disease and chronic renal impairment (serum creatinine concentration 181 μmol/l) received gadodiamide (Omniscan) for cerebral angiography; there were no adverse effects and the serum creatinine was unchanged. (27)

The authors concluded that gadodiamide is a safe alternative to iodinated contrast media in patients with renal impairment.

However, the use of large volumes of gadolinium-based contrast agents can cause deterioration in renal function, and the safety of these agents in relation to the kidney when a large volume is used is not known (27).

The use of gadolinium-DTPA has been described in 28 patients (22 men, 6 women, mean age 51 years) for angiography (28). The mean dose of gadolinium was 35 (range 20–60) ml. All the patients had renal impairment (serum creatinine over 133 μmol/l). Gadolinium was well tolerated, but 17 patients noted a mild heat sensation and one complained of transient pain during the injection. Only one patient, who received 40 ml, developed worse renal function, with an increase in serum creatinine from 360 to 450 μmol/l. Although the gadolinium was well tolerated in this group of patients, gadolinium-based contrast agents should be used with extreme care, particularly in patients with renal impairment, as they can be nephrotoxic in large doses.

A prospective, randomized, double-blind, placebo-controlled trial has also confirmed the safety of gadolinium infusion in 32 patients with renal impairment in dosages typically used during MRI examination (29). Nine patients had moderate renal impairment (mean age 57 years, creatinine clearance 30–60 ml/minute) and 11 had severe renal impairment (mean age 63 years, creatinine clearance 10–29 ml/minute). They were given an intravenous bolus of gadobenate dimeglumine 0.2 mmol/kg. A comparable control group received an injection of isotonic saline. There was no significant deterioration in renal function in any group during the following 7 days.

- A 67-year-old woman with chronic renal insufficiency secondary to interstitial nephritis had rapid deterioration over several months, with a rise in serum creatinine from 150 to 290 μmol/l (30). Renal artery stenosis was suspected. She had anaphylaxis during spiral CT angiography with an iodinated contrast medium (details not given), which showed right renal artery stenosis. After further deterioration in renal function (serum creatinine 480 μmol/l) she underwent renal arteriography with 30 ml of a gadolinium-based contrast agent (0.3 mmol/kg) injected into the abdominal aorta just above the renal arteries. Her renal function was monitored for 15 days after the procedure, and there was no further rise in serum creatinine.
- A 64-year-old obese man with a history of radiocontrast-induced nephropathy had an MRI scan, which confirmed the presence of an aortic aneurysm from just below the renal arteries to the aortic bifurcation (31). Percutaneous stenting of the aortic aneurysm

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Table 1 European Society of Urogenital Radiology (ESUR) position statement on the use of gadolinium-based contrast media for radiographic examinations (34)

Legal position	Gadolinium-based contrast media are not approved for X-ray examinations
Reported uses of gadolinium-based contrast media for X-ray examinations	Significant renal impairment Prior severe generalized adverse reaction to iodinated contrast media Imminent thyroid treatment with radioactive iodine
ESUR position	The use of gadolinium-based contrast media for radiographic examinations is not recommended to avoid nephrotoxicity in patients with renal impairment, since they are more nephrotoxic than iodinated contrast media in equivalent X-ray attenuating doses The use of gadolinium-based contrast media in approved intravenous doses of up to 0.3 mmol/kg will not give diagnostic radiographic information in most cases

was carried out with 0.5 mol/l gadoteridol solution 90 ml (0.375 mmol/kg) instead of an iodinated contrast agent. There was no further deterioration in renal function.

The authors of the second report erroneously concluded that gadolinium-containing contrast agents are not nephrotoxic, and they recommended their use in patients in whom conventional iodinated contrast agents are contraindicated. However, gadolinium-based contrast agents have more nephrotoxic potential than iodinated contrast agents in equimolar concentrations. Their use in patients with renal impairment should be carried out with care and the dosage should not exceed 0.3 mmol/kg.

This case underlines the fact that there is still misunderstanding about the nephrotoxic potential of gadolinium-based contrast agents. They should not replace iodinated contrast agents in patients with renal insufficiency. The recommended doses of up to 0.3 mmol/kg will not give satisfactory radiographic diagnostic information in most cases.

Susceptibility Factors

Renal disease

The use of gadolinium-based contrast media for radiographic examination as an alternative to iodinated contrast media in patients with impaired renal function has been erroneously endorsed by several authors. For example, in a German study gadopentetate dimeglumine (average dose 0.34 mmol/kg) was used in 29 patients (mean age 61 years) with renal impairment (mean baseline serum creatinine 318 μmol/l) as an alternative to an iodinated contrast agent for angiographic procedures (32). Only one patient developed contrast medium-induced renal damage, defined as an increase in serum creatinine by more than 88 μmol/l within 72 hours of injection of the contrast agent. The authors suggested that gadopentetate dimeglumine is a safe alternative to iodinated contrast agents for radiographic examinations in patients with renal impairment.

In another study, gadodiamide was used as an alternative for angiographic procedures in patients with contraindications to iodinated contrast media; 17 patients (mean age 74 years) received a mean volume of 136 ml of gadodiamide (range 60–200 ml) (33). The contraindications to iodinated contrast injection were renal impairment (12 patients, serum creatinine 200–500 μmol/l), a history of iodinated contrast reaction ($n = 3$), and hyperthyroidism ($n = 4$). Several of the patients had renal artery stenosis, and renal function improved after successful angioplasty. There were no cases of nephrotoxicity. The authors concluded that patients with contraindications to iodinated contrast injection can safely receive gadolinium-based contrast media for radiographic examinations.

The authors of these reports have erroneously suggested that gadolinium-based contrast media are less nephrotoxic than iodinated contrast media. However, at equimolar concentrations gadolinium-based contrast media are more nephrotoxic than iodinated contrast media, and at equivalent X-ray attenuation gadolinium-based contrast media are actually more nephrotoxic. The Contrast Media Safety Committee of the European Society of Urogenital Radiology has recently produced a report on the use of gadolinium-based contrast media for radiographic examinations, and its position is summarized in Table 1.

The safety and dialysability of gadobutrol 0.1 or 0.3 mmol/kg have been investigated in 11 patients (median age 42 years) with end-stage renal insufficiency who required hemodialysis (35). The patients were monitored for 120 hours. There were no important changes in hematology, clinical chemistry, or vital signs. Hemodialysis was effective in removing the gadolinium contrast agent from the body, and by the third session, 98% of the injected dose had been eliminated.

Hepatic disease

The safety of gadobenate dimeglumine has been evaluated in 16 subjects with liver impairment, 11 of whom (mean age 48 years) received gadobenate dimeglumine (0.1 mmol/kg) intravenously and five of whom (mean age 42 years) received placebo (36). There were no important adverse effects and no significant changes in laboratory parameters. The pharmacokinetics of the contrast agent were not different from those with normal liver function.

Drug Administration

Drug administration route

The safety of intrathecal gadopentetate dimeglumine has been investigated in 95 patients (aged 1 month to 78 years) (37). The contrast agent was injected into the

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subarachnoid space via a lumbar puncture needle; 3–5 ml of cerebral spinal fluid were withdrawn and mixed with 0.5, 0.7, 0.8, or 1 ml of gadopentetate dimeglumine. There were no significant behavioral changes, neurological changes, or seizure activity, but 19 patients had headache after lumbar puncture, 6 had nausea, and 2 had vomiting. All the adverse effects resolved within the first 24 hours with bed rest.

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Gallamine triethiodide

See also Neuromuscular blocking drugs

General Information

Gallamine is a non-depolarizing muscle relaxant. For intubation about 2 mg/kg (some authors say 3–4 mg/kg) are necessary, and the duration of effect is then similar to the usual intubating doses of D-tubocurarine or pancuronium. A dose of 1–1.5 mg/kg is usually sufficient to produce apnea and adequate abdominal relaxation. Such doses are said to be short-acting (20 minutes) but can provide clinical relaxation (75% or more depression of twitch height) for some 30–40 minutes. Individual variation is considerable, and complete spontaneous reversal of blockade is relatively slow.

Organs and Systems

Cardiovascular

Tachycardia invariably accompanies the use of gallamine. It is seen after doses as low as 20 mg and reaches a maximum at around 100 mg in adults (1). It is often extreme, rates above 120 per minute being not uncommon. The increase in heart rate outlasts the neuromuscular blocking effect (1). Usual clinical doses also result in a slight increase in mean arterial pressure, a slight fall in systemic vascular resistance, and a marked rise in cardiac index (2,3). These cardiovascular effects are principally accounted for by the strong vagolytic action of gallamine, the cardiac muscarinic receptors being almost as sensitive to its blocking action as the acetylcholine receptors of the neuromuscular junction (4). Blockade of noradrenaline reuptake and an increased release of noradrenaline from cardiac adrenergic nerve endings (5,6) may contribute, although an inotropic effect in man is disputed (7). Ganglion-blocking activity is slight and is not seen in the usual dose range. The possible mechanisms have been reviewed (8–10). Gallamine should therefore not be used when tachycardia has to be avoided.

Immunologic

Histamine release may be associated with the use of gallamine more often than was previously believed, according to several studies involving large numbers of patients (11–14). There have been several reports of reactions involving skin flushing, bronchospasm, or cardiovascular collapse possibly due to gallamine, including anaphylactoid reactions to small precurarizing doses (15,16).

Second-Generation Effects

Fetotoxicity

Placental transfer has been variously reported, usually only small amounts being detected in the umbilical blood, with no clinically obvious effects on the newborn (17).

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Susceptibility Factors

Renal disease

Gallamine does not undergo biotransformation and depends entirely on glomerular filtration for its excretion (17). In renal insufficiency the neuromuscular blockade that it causes is considerably prolonged and gallamine is contraindicated.

Drug–Drug Interactions

Azathioprine

Azathioprine reduces sensitivity to gallamine in experimental animals, possibly as a result of phosphodiesterase inhibition, increasing transmitter release (SEDA-4, 87) (18), (SEDA-13, 104).

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Gallium

General Information

Gallium is a metallic element (symbol Ga; atomic no. 31) that has been used in the form of a radiopharmaceutical (^{67}Ga as the citrate) in diagnostic imaging of cancers, inflammation, and infection (1–3). The mechanisms of the therapeutic activity of gallium have been reviewed (4).

Gallium nitrate is being increasingly used as a therapeutic agent in certain malignancies (5), since it has been shown to be concentrated in various neoplasms in both animals and man and to have antitumor activity (6), and the anticancer activity of new compounds, such as gallium maltolate, doxorubicin gallium transferrin conjugate, and trisquinolinolato gallium, is being explored (7).

Abnormal uptake of ^{67}Ga is reported as an adverse effect in diagnostic procedures, as in three cases:

- A 72-year-old man with acute lymphocytic leukemia who had normal ^{67}Ga uptake in all tissues except the liver (8).
- A 26-year-old pregnant woman with a mediastinal lymphoma that did not accumulate ^{67}Ga (9).
- A 49-year-old man with fever and increased ^{67}Ga uptake in the lungs but no other evidence of infection or cancer (10).

Gallium nitrate has been used as an alternative to bisphosphonates in hypercalcemia of malignancy (11), in which it is effective but associated with a higher frequency of renal toxicity (10%) and of nausea and vomiting (14%) than the bisphosphonates. The pathophysiology and treatment of hypercalcemia of malignancy has been reviewed and the role of gallium nitrate considered (12,13).

An early Phase I evaluation and subsequent reports presented similar pictures, with predominant renal and hematological adverse effects (14,15), but as a rule gallium has been used alongside other cytostatics and it is not possible to determine which of these has produced any particular effect. Other adverse effects observed have been nausea and/or vomiting, maculopapular skin rash, a metallic taste, and diarrhea (16).

Gallium alloys are still considered to be useful alternatives to amalgams in dental medicine, in spite of their tendency to corrosion, their controversial biocompatibility, and lack of knowledge about gallium's environmental impact (17).

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Organs and Systems

Sensory systems

- A patient developed bilateral visual loss after systemic administration of gallium nitrate (SEDA-22, 244) (18). The condition worsened after oral corticosteroid therapy and partial recovery of optic nerve function in both eyes was present only after 12 months of oral ferrous sulfate administration.

Ototoxicity has been reported in a few patients taking gallium nitrate (19).

Hematologic

Hematological toxicity of gallium nitrate has been noted, for example granulocytopenia and anemia (19).

Mouth and teeth

Gallium is used in dental prostheses and is a source of increased sensitivity to postoperative dental pain (20). In a pilot study of a direct-placement gallium alloy (Galloy) in nine patients, 30 dental restorations were inserted and assessed over 3 years (21). The initial 18-month results were encouraging, but at 21 months there was one fractured tooth and within another year two molars had the cracked-tooth syndrome (incomplete tooth fracture). The fractured teeth were restored with amalgam. Tarnish and a rough surface were noted on many of the gallium restorations. These results suggest that Galloy, used with either of two sealing resins, is not a suitable dental restorative material.

Urinary tract

An early Phase I clinical evaluation indicated dose-related nephrotoxicity and this has led to much caution in dosage (19). At least one death from kidney failure has been reported. Maintaining adequate diuresis with 5% dextrose/saline may reduce the risk of nephrotoxicity.

In a comparative study of gallium nitrate and etidronate in acute control of cancer-related hypercalcemia, a significantly higher proportion of the patients treated with gallium nitrate developed asymptomatic hypophosphatemia (22).

Reproductive system

Gallium used in semiconductors has been found in animal studies to adversely affect male sperm count and to raise the proportion of abnormal sperm (SEDA-21, 235).

Immunologic

- A 40-year-old woman had multiple bone injuries, severe sepsis, and coma after a car accident; a retroperitoneal hematoma caused by lumbar fractures was drained, but she continued to be pyrexial (23). She had prominent accumulation of ^{67}Ga, which had been used for bone scanning, in her multiple recent fractures and an area of accumulation in the soft tissue related to a fractured vertebra. Post-traumatic paravertebral calcifications had accumulated ^{67}Ga and simulated the presence of an infected hematoma.

Susceptibility Factors

Renal disease

Because it is nephrotoxic, gallium nitrate should be avoided in renal dysfunction and in patients taking nephrotoxic drugs. Renal dysfunction also alters the kinetics of gallium (SED-12, 519).

Drug–Drug Interactions

Aminoglycosides

Concomitant treatment with aminoglycoside antibiotics in two cases resulted in acute renal insufficiency (24).

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Gammahydroxybutyrate

General Information

Sodium gammahydroxybutyrate (GHB or sodium oxybate) is an endogenous compound, a precursor of GABA, which increases the release of dopamine and acetylcholine in the brain. It was first synthesized in 1960 as a potential anesthetic, and was popular in the late 1980s and early 1990s as a dietary supplement (as a replacement for L-tryptophan after it had been recalled from the market), an aid to sleep, and a bodybuilding agent. It was subsequently used in the treatment of narcolepsy. However, it has also been used as a party drug, since it causes alcohol-like effects and aroused sexuality. In large doses it can cause disorientation, nausea and vomiting, and muscle spasms. It is also known as BDO, Blue Nitro, Enliven, GBH, Liquid ecstasy, Midnight Blue, RenewTrient, Reviarent, Serenity, and SomatoPro. An analogue, gammavalerolactone (GVL), is a precursor and has also been used recreationally, but it is very expensive.

In 1990 the FDA limited the availability of gammahydroxybutyrate, and in March 2000, the Drug Enforcement Agency made it a Schedule I drug. In 2001 the Expert Advisory Committee on Drugs (EACD) in New Zealand advised the New Zealand Medicines and Medical Devices Safety Authority to schedule gammahydroxybutyrate under the Misuse of Drugs Act 1975 (1). In June 2003 gammahydroxybutyrate was categorized as a Class C drug in the UK.

Ingestion of 0.5–3 teaspoons of sodium gammahydroxybutyrate can produce vomiting, drowsiness, hypotonia, and/or vertigo; loss of consciousness, irregular respiration, tremors, or myoclonus can follow. Seizure-like activity, bradycardia, hypotension, and/or respiratory arrest have also been reported. The severity and duration of symptoms depend on the dose and on the presence of other nervous system depressants, such as alcohol.

In a double-blind, randomized, placebo-controlled, crossover study in 24 patients with narcolepsy, gammahydroxybutyrate 60 mg/kg in a single night-dose for 4 weeks reduced the daily number of hypnagogic hallucinations, daytime sleep attacks, and the severity of subjective daytime sleepiness, and tended to reduce the number of daily attacks of cataplexy (2). It reduced the percentage of wakefulness during REM sleep and the number of awakenings out of REM sleep, and tended to increase slow wave sleep. Adverse events were few and mild.

Organs and Systems

Nervous system

In a double-blind, double-dummy comparison of clomethiazole and gammahydroxybutyrate in ameliorating the symptoms of alcohol withdrawal, alcohol-dependent patients were randomized to receive either clomethiazole 1000 mg or gammahydroxybutyrate 50 mg/kg (3). There was no difference between the treatments in ratings of alcohol withdrawal symptoms or requests for additional medications. After tapering the active medication, there was no increase in withdrawal symptoms, suggesting that physical tolerance did not develop to either clomethiazole or gammahydroxybutyrate during the 5-day treatment period. The most frequently reported adverse effect of gammahydroxybutyrate was transient vertigo, particularly after the evening double dose.

Drug Administration

Drug overdose

Some who have taken gammahydroxybutyrate without knowing what it was have subsequently awakened in hospital having been deeply comatose for a few hours, without after-effects (4).

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Ganciclovir

General Information

Ganciclovir (dihydroxypropoxymethylguanine) is a nucleoside analogue with antiviral activity in vitro against herpesviruses. Intracellular phosphorylation of ganciclovir to its triphosphate derivative, which acts as a competitive inhibitor of deoxyguanosine triphosphate, leads to the inhibition of viral DNA synthesis. Because its toxicity profile is more favorable than those of foscarnet and cidofovir, it should be considered first-line treatment of life-threatening or sight-threatening cytomegalovirus (CMV) infections in immunocompromised patients. Ganciclovir is administered by infusion or by intravitreal injection (1). Oral ganciclovir as maintenance therapy for CMV retinitis in patients with AIDS has been reviewed (2). Oral ganciclovir has also been the subject of a pilot study in hepatitis B infection (3).

Observational studies

In 261 patients with CMV retinitis given oral ganciclovir 3–6 g/day or intravenous ganciclovir 5 mg/kg/day the most common adverse effects were on the gastrointestinal tract (nausea in 29–43%, vomiting in 17–23%, diarrhea in 33–52%, and flatulence in 2–18%) (4). There were rashes in 9–32%, a low neutrophil count (below 0.5×10^9/l) in 12–16%, a low hemoglobin concentration (below 8 g/dl) in 8–15%, a low platelet count (below 25×10^9/l) in 0–3%, and a raised serum creatinine in 17–27%.

General adverse effects

The proportion of patients in whom ganciclovir therapy is subsequently interrupted or withdrawn because of adverse effects is estimated at 32% (1).

Fever, rash, and abnormal liver function values are each reported to occur in about 2% of ganciclovir recipients (1). Other infrequently reported adverse effects, which may or may not be associated with ganciclovir, include chills, edema, malaise, vomiting, anorexia, diarrhea, dyspnea, reduced blood glucose, alopecia, impaired renal function, inflammation, pain, or phlebitis at the infusion site (1). These effects may also be due to the underlying illness in such patients.

Organs and Systems

Nervous system

Adverse effects of ganciclovir involving the central nervous system occur in about 5% of patients and include confusion, seizures, abnormal thinking, psychosis, hallucinations, nightmares, anxiety, tremor, dysesthesia, ataxia, coma, headache, and somnolence (1,5,6).

- A clear case of encephalopathy has been described in a patient who had received a bone marrow transplant; the problem resolved on withdrawal (7).

Sensory systems

Adverse effects reported in patients receiving intravitreal ganciclovir include foreign body sensation, conjunctival hemorrhage, mild conjunctival scarring, scleral induration, bacterial endophthalmitis, and retinal detachment (1).

For HIV-infected patients who have failed the intravenous CMV treatment options, intravitreal injections may be the last line. In one case only mild iris atrophy was noted, despite high-dose intravitreal ganciclovir (3 mg twice weekly) and high-dose intravitreal foscarnet (2.4 mg twice weekly) (8).

Endophthalmitis with scleral damage has been associated with a ganciclovir implant (9).

- A 39-year-old woman complained of increasing pain and complete loss of vision in the left eye 1 month after insertion of a ganciclovir implant. The eye was enucleated and pathological examination showed a vitreous abscess; the implant suture tab was intrasclerally located.

The authors concluded that intraocular infection had resulted from a foreign body (the surgical implant) in the scleral gap.

Metabolism

Six infants with cholestasis (aged 3–16 weeks) and signs of CMV infection were given intravenous ganciclovir for 3–7 weeks (10). One patient with septo-optic dysplasia and hypothyroidism had episodes of symptomatic hypoglycemia during treatment, which was withdrawn.

Hematologic

The adverse hematological effects of ganciclovir are generally rapidly reversible after withdrawal (1).

Pure red cell aplasia has been reported in one bone marrow transplant recipient (11) and hemolysis has been observed in two other patients (5).

Neutropenia is the most frequent adverse effect of ganciclovir. It usually occurs before a total dose of 200 mg/kg has been given. Other hematological adverse effects include thrombocytopenia, anemia, and lymphopenia. Since ganciclovir maintenance treatment is often necessary, concomitant use of G-CSF is often required in patients with AIDS with ganciclovir-associated neutropenia (12).

In a study of oral ganciclovir in 36 severely immunocompromised HIV-positive children with CMV disease, toxicity was minimal and manageable and similar to that in adults in controlled trials of the oral formulation (13). About 20% of the children withdrew, mainly as a result of intolerance of the large volume of oral suspension or numerous capsules. As in adults, neutropenia was the main toxic effect and it was successfully treated with G-CSF.

Of 40 patients who had achieved engraftment after allogeneic hemopoietic stem cell transplantation, 23 of whom had high-risk features, including transplant from an HLA-mismatched or unrelated donor, or associated acute graft-versus-host disease, 19 had pre-emptive therapy with ganciclovir in an initial dose of 5 mg/kg/day (4). There were no significant adverse effects attributed

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to ganciclovir, except low total leukocyte counts (below 0.5×10^9/l) in three patients, lasting 3, 4, and 14 days, while they were treated with granulocyte colony-stimulating factor.

Second-Generation Effects

Fertility

Animal data suggest that ganciclovir can inhibit spermatogenesis and fertility (14), but in one study there was no significant change in serum gonadotropin hormone concentrations in 32 men during ganciclovir therapy (15).

Drug Administration

Drug administration route

Treatment options for CMV retinitis include the intravitreal insertion of ganciclovir implants. This method of drug delivery has the attraction of avoiding systemic drug toxicity, but the inherent danger of introducing bacterial infection has been highlighted (16).

- A 42-year-old man with AIDS and a history of CMV retinitis developed pain in his right eye and reduced visual acuity 10 days after receiving a ganciclovir intraocular implant into that eye. A therapeutic vitrectomy was performed and a vitreal tap produced frank pus and white fluffy debris. Cultures grew oxacillin-resistant *Staphylococcus aureus* sensitive only to vancomycin, rifampicin, and co-trimoxazole. The ganciclovir implants were removed and he was given a 4-week course of vancomycin and rifampicin. The bacterial endophthalmitis left him blind in his right eye.

Drug–Drug Interactions

Trimethoprim

The interaction kinetics and safety profile of oral ganciclovir when co-administered with trimethoprim have been investigated in HIV- and CMV-seropositive patients (17). Trimethoprim significantly reduced the renal clearance of ganciclovir and prolonged its half-life, although the changes are unlikely to be clinically important. Ganciclovir did not alter trimethoprim pharmacokinetics, with the exception of a 13% increase in C_{min}. Ganciclovir was well tolerated when given alone or in this combination.

Zidovudine

Zidovudine and ganciclovir have overlapping toxicity profiles with respect to adverse hematological effects. Severe life-threatening hematological toxicity has been reported in 82% of patients treated with a combination of zidovudine and ganciclovir (18). The combination of ganciclovir with didanosine was much better tolerated (19).

Food–Drug Interactions

A well-controlled investigation using high doses of oral ganciclovir in HIV- and CMV-seropositive subjects has shown that food markedly increases the systemic availability of ganciclovir. For example, there is a doubling of blood concentrations and AUC if the drug is given within 30 minutes after a meal rather than on an empty stomach (20). Whatever dosage instructions are given, it seems clear that the relation to meal times should be explained, for example with a firm recommendation to take the drug consistently with food.

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Garenoxacin

See also Fluoroquinolones

General Information

Garenoxacin is an orally and parenterally available 6-des-fluorinated quinolone, which has a high degree of in vitro activity against a broad range of bacterial pathogens (1).

Organs and Systems

Musculoskeletal

In dogs garenoxacin concentrations in plasma and joint tissue were higher than those of ciprofloxacin and norfloxacin (2). However, the articular toxicity of garenoxacin was much less than that of the other two quinolones.

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Gatifloxacin

See also Fluoroquinolones

General Information

Gatifloxacin is an 8-methoxyfluoroquinolone with enhanced activity against Gram-positive, atypical agents, and some anerobes, and broad-spectrum activity against Gram-negative bacteria (1–4). It is bactericidal and produces a post-antibiotic effect in Gram-positive and Gram-negative bacteria. Gatifloxacin is well absorbed from the gastrointestinal tract (oral availability almost 100%), and concomitant administration of a continental breakfast, 1050 kcal, had no effect on its availability (5). The standard dose is 400 mg od and both oral and intravenous formulations are available (6,7).

Since gatifloxacin has a high oral systemic availability (96%), oral and intravenous formulations are bioequivalent and interchangeable (8). It has a large volume of distribution (about 1.8 l/kg), low protein binding (about 20%), broad tissue distribution, and is primarily excreted unchanged in the urine (over 80%) (7). After daily repeated administration, there was predictable modest accumulation; steady state concentrations were reached after the third dose (9).

The in vitro antibacterial spectrum of gatifloxacin has been tested against a variety of clinically important microorganisms (10). It is two to four times more potent than ciprofloxacin and ofloxacin against staphylococci, streptococci, pneumococci, and enterococci. However, it is two times less potent than ciprofloxacin, but the same as or two times more potent than ofloxacin against *Enterobacteriaceae*. Gatifloxacin and ofloxacin have similar antipseudomonal activity, while ciprofloxacin is two to eight times more potent. Gatifloxacin is highly potent against *Hemophilus influenzae*, *Legionella* species, and *Helicobacter pylori*, and also has activity against *Bacteroides fragilis* and *Clostridium difficile*. Like other quinolones, it has poor activity against *Mycobacterium avium* intracellulare, but is 8–16 times more potent against *Mycobacterium tuberculosis*.

Intravenous gatifloxacin can cause dose-related local reactions (8).

Gatifloxacin does not interact with drugs metabolized by the CYP450 enzyme family, as assessed in 14 healthy adult men using midazolam as a probe (11).

Organs and Systems

Cardiovascular

Although early studies suggested that gatifloxacin has little effect on the QT interval of the electrocardiogram (7,12), clinical trial data and data from phase IV studies

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have shown that it prolongs the QT interval (13). Four cases of gatifloxacin-associated cardiac toxicity have been reported in patients with known risk factors for this adverse event (14).

Nervous system

In patients taking gatifloxacin there have been reports of myoclonus and generalized seizures (15) and ataxia and generalized seizures (16).

Metabolism

Gatifloxacin was well tolerated in patients with non-insulin-dependent diabetes mellitus maintained with diet and exercise (17). It had no significant effect on glucose homeostasis, beta cell function, or long-term fasting serum glucose concentrations, but it caused a brief increase in serum insulin concentrations.

Gastrointestinal

Diarrhea and nausea were the most common adverse events in several clinical studies of gatifloxacin (4,18–20).

Liver

Gatifloxacin can cause hepatitis (21,22).

- A 44-year-old woman developed acute hepatitis while taking gatifloxacin for chronic sinusitis (23). After 5 days she developed nausea, lethargy, and abdominal pain, all of which progressed over the next few days. Liver function tests were abnormal, and the bilirubin peaked at 161 μmol/l. A percutaneous liver biopsy showed acute hepatitis with eosinophilic infiltrates, consistent with drug-induced hepatitis.

Susceptibility Factors

Age

Gatifloxacin can be administered without dose modification in the elderly (24).

Sex

Gatifloxacin can be administered without dose modification in women (24).

Hepatic disease

Gatifloxacin can be administered without dose modification in patients with hepatic impairment (25).

Drug–Drug Interactions

Oral hypoglycemic drugs

Four cases of severe persistent hypoglycemia due to gatifloxacin 400 mg/day have been reported in adults with diabetes mellitus who were taking oral hypoglycemic agents (repaglinide, glibenclamide, glimepiride) (26,27).

Oxycodone

Oral oxycodone and gatifloxacin can be co-administered without a significant reduction in systemic availability (28).

Warfarin

Enhanced hypoprothrombinemia has been reported when gatifloxacin was given with warfarin (29).

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Gemcitabine

See also Cytostatic and immunosuppressant drugs

General Information

Gemcitabine is an S-phase-specific pyrimidine nucleoside analogue of deoxycytidine (2′,2′-difluorodeoxycytidine) that is structurally similar to cytosine arabinoside. It has been used to treat metastatic urothelial carcinoma of the bladder, pancreatic cancer, and some other solid tumors.

General adverse effects

In a retrospective study of the adverse effects of gemcitabine 1000 mg/m^2 on days 1 and 8 in patients with non-small cell lung cancers, the adverse effects of gemcitabine involved the gastrointestinal system (nausea, vomiting, and diarrhea) and the hemopoietic system (leukopenia, neutropenia, thrombocytopenia, and anemia), but only in the last (8th–11th) cycles (1). There was grade 4 vomiting in three patients, grade 4 thrombocytopenia in two, and grade 3 leukopenia in three. Other adverse effects were mild. None of the patients died during chemotherapy.

Organs and Systems

Cardiovascular

In a retrospective chart review of patients with gemcitabine-associated thrombotic microangiopathy diagnosed between January 1997 and February 2002, the cumulative incidence was 0.31% (8 cases among 2586 patients), higher than previously reported (0.015%) (2). The median age was 53 years, the median time to development was 8 (range 3–18) months, and the cumulative dose was 9–56 g/m^2. New or exacerbated hypertension was a prominent feature in seven of nine patients and preceded the diagnosis by 0.5–10 weeks. Treatment included withdrawal of gemcitabine, antihypertensive therapy, plasma exchange, and dialysis. Six patients survived and three died of disease progression; none died as a direct result of thrombotic microangiopathy, but two developed renal insufficiency requiring dialysis, and one developed chronic renal insufficiency.

Gemcitabine can occasionally cause systemic capillary leak syndrome (3,4).

Respiratory

Gemcitabine can cause pulmonary toxicity. The clinical presentation is subacute and often non-specific. Chest X-ray usually shows reticulonodular interstitial infiltrates (5).

- A 75-year-old man with non-small cell lung cancer developed acute respiratory distress syndrome after intravenous gemcitabine monotherapy (6). The total dose of gemcitabine was 1500 mg, and the latent period was 3 days. Chest X-rays and a high resolution CT scan showed bilateral ground-glass opacity. He died on the fourteenth postchemotherapeutic day in respiratory failure. Postmortem examination of the lung showed mixed exudative and fibrotic stages of diffuse alveolar damage.

In one study, the incidence was as high as 15%, even with low-dose gemcitabine 600 mg/m^2 on days 1, 8, and 15 and docetaxel 60 mg/m^2 on day 1; all resolved after withdrawal of treatment and administration of glucocorticoids (7).

In a retrospective review pulmonary toxicity was defined as dyspnea, interstitial pneumonitis, lung disorder, lung edema, lung fibrosis, pneumonia, respiratory disorder, and respiratory distress syndrome (8). Based on 4448 patients, the incidences of dyspnea and other

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serious pulmonary toxicity were 0.45 and 0.27% respectively. Based on an estimated 217 400 patients treated with commercial gemcitabine worldwide, the crude incidences of dyspnea and other serious pulmonary toxicity were 0.02 and 0.06% respectively.

In a retrospective study of 312 patients treated with gemcitabine over 5 years, 18 developed episodes of acute dyspnea; 6 were attributed to the drug; 4 had a notifiable industrial disease secondary to asbestos exposure (OR = 85, 95% CI = 13, 546); and 5 were active smokers (5).

Liver

- Fatal cholestatic liver failure occurred in a 45-year-old woman with metastatic breast cancer who was given gemcitabine and carboplatin and pre-existing liver damage. After four courses of gemcitabine + carboplatin she developed severe decompensated cholestatic hepatitis (9). Liver biopsy showed marked cholestasis and hepatocellular injury consistent with drug-induced hepatotoxicity.

Urinary tract

Hemolytic–uremic syndrome has occasionally been attributed to gemcitabine (10–12). The manufacturers reviewed their database of 78 800 patient exposures, which confirmed that gemcitabine causes hemolytic–uremic syndrome with a crude overall incidence rate of 0.015% (13).

Skin

Erythema multiforme has been attributed to gemcitabine (14). Toxic epidermal necrolysis has been reported in an elderly man receiving gemcitabine for a transitional cell carcinoma of the bladder (15).

- Scleroderma-like changes of the legs occurred after treatment with gemcitabine in a patient with metastatic carcinoma of the bladder (16). There was initial inflammatory edema and subsequent scleroderma-like changes after 2 cycles of gemcitabine. Cutaneous biopsies showed diffuse sclerosis without involvement of the fascia or muscle. Withdrawal of gemcitabine resulted in resolution of the edema, softening of the skin, and partial reversibility of the fibrotic process.

Patients occasionally develop erysipeloid skin reactions, often, although not always, associated with previous radiotherapy or lymphedema (17).

A cutaneous reaction mimicking acute lipodermatosclerosis has been attributed to gemcitabine (18).

Immunologic

Two patients developed necrotizing enterocolitis after a first cycle of chemotherapy for epithelial ovarian/peritoneal cancer; both were due to vasculitis (19).

- In a 56-year-old man with a transitional cell carcinoma of the bladder gemcitabine plus cisplatin caused extensive necrotizing vasculitis with muscle damage after the second course of therapy (20). Chemotherapy was withdrawn immediately but the symptoms of severe myalgia and swelling persisted, and he needed additional treatment, consisting of cyclophosphamide and prednisolone.

Other cases of vasculitis have been reported (21).

- A 70-year-old woman with a bladder cancer was given gemcitabine 1700 mg on days 1 and 8 and 3–4 days later developed paresthesia of the fingers, Raynaud's phenomenon, an intermittent fever, digital necrosis, and fingertip gangrene (22). Angiography showed occlusion of the digital arteries of the second, third, and fourth fingers. Skin biopsy showed hyperkeratosis, acanthosis, and papillomatosis, with endothelioangiitis and nonspecific arterial inflammation.

Radiation recall consists of inflammatory reactions triggered by cytotoxic drugs in previously irradiated areas; most are skin reactions. Gemcitabine has been implicated in several cases. The authors of a literature review discovered 12 cases of radiation recall caused by gemcitabine and reported a case of myositis in the rectus abdominis muscle of a patient with pancreatic adenocarcinoma as an effect of radiation recall (23). Most of the cases had inflammation of internal organs or tissues and 30% had dermatitis or mucositis. This is different from the effect of other agents that commonly cause radiation recall (anthracyclines and taxanes), with which 63% are skin reactions. Compared with anthracyclines and taxanes, the interval from the completion of radiation therapy to the start of chemotherapy is less with gemcitabine (median time 56 days, compared with 218 days for the taxanes and 646 days for doxorubicin).

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Gemeprost

See also Prostaglandins

General Information

Gemeprost is an analogue of PGE_2. Vaginal gemeprost is effective in inducing first and second trimester abortion and in cervical priming before vacuum aspiration. Pyrexia, vomiting, and diarrhea were experienced in 20% of patients (1).

In a double-blind, randomized, controlled trial, 896 healthy women requesting a medical abortion (57–63 days gestation, mean age 25 years) were randomized to a single oral dose of mifepristone 200 or 600 mg, both followed in 48 hours by gemeprost 1 mg vaginally (2). The complete abortion rates were similar with the lower and higher doses of mifepristone (92 versus 92%). The incidences of adverse effects were similar, with the exception of nausea at 1 week, which was less frequent in the low-dose group (3.6 versus 7.6%).

Organs and Systems

Cardiovascular

Two women developed myocardial ischemia during treatment with gemeprost for termination of pregnancy (3).

- A 29-year-old woman, a smoker with a history of renal insufficiency, obesity, hypertension, hypercholesterolemia, and cardiac dysrhythmias, underwent termination of pregnancy at 10 weeks with a pessary of gemeprost 1 mg and 5 hours later dilatation and evacuation, followed by tubal ligation. After surgery, her blood pressure became unmeasurable, her heart rate dropped to 40/minute, and she developed ventricular fibrillation. She was given streptokinase and intravenous heparin for suspected pulmonary embolism; her blood pressure rose and was maintained with adrenaline and noradrenaline. Angiography showed an 80% stenosis of her right coronary artery and complete occlusion of the anterior interventricular branch. Blood flow was re-established by coronary angioplasty.
- A 32-year-old woman, a smoker, had an evacuation after the death of her fetus at 18 weeks. Two pessaries of gemeprost 1 mg were inserted 7.25 hours apart, and about 90 minutes later she became unconscious, apneic, and cyanotic, and had dilated pupils and no detectable blood pressure or pulse. She was given 100% oxygen, intravenous adrenaline and dobutamine, and a crystalloid infusion. Her systolic pressure rose to 100 mmHg. Coronary angiography showed left and circumflex coronary artery spasm.

The author commented that the myocardial ischemia experienced by both of these patients was thought to be due to prostaglandin-induced coronary spasm. It would be prudent to monitor every woman treated with gemeprost during the course of an abortion.

Skin

Toxic epidermal necrolysis has been attributed to mifepristone/gemeprost (4).

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Gemifloxacin

See also Fluoroquinolones

General Information

Gemifloxacin is a fluoroquinolone that has enhanced affinity for topoisomerase. Compared with other fluoroquinolones, gemifloxacin was the most potent against penicillin-intermediate and penicillin-resistant pneumococci, methicillin-susceptible and methicillin-resistant *Staphylococcus epidermidis* isolates, and coagulase-negative staphylococci (1,2). It has excellent activity against *Haemophilus influenzae* and *Moraxella catarrhalis* and is unaffected by beta-lactamases. It is generally twofold less active than ciprofloxacin against most *Enterobacteriaceae* (3). Atypical respiratory pathogens (*Legionella*, *Mycoplasma*, and *Chlamydia* species) and *Neisseria gonorrheae* are highly susceptible (4).

The pharmacokinetics of oral gemifloxacin have been characterized in healthy male volunteers (5). About 20–30% of the dose was excreted unchanged in the urine. The renal clearance was 160 ml/minute on average after single and multiple doses, which was slightly greater than the accepted glomerular filtration rate. There were no adverse effects.

Observational studies

In phase II trials oral gemifloxacin 320 mg/day produced bacteriological responses in 94% of patients with acute exacerbations of chronic bronchitis (6–8) and in 95% of patients with uncomplicated urinary tract infections. Adverse events included nausea, abdominal pain, headache, and a mild rash in both patients and healthy volunteers.

After a single dose of 20–800 mg of gemifloxacin, there were no significant changes in clinical chemistry, hematology, or urinalysis, vital signs, or 12-lead electrocardiograms in healthy men, irrespective of dose (9).

Gemifloxacin 320 mg od and trovafloxacin 200 mg od have been compared in 571 patients with community-acquired pneumonia in a multicenter, double-blind, parallel-group, randomized study (10). Gemifloxacin was slightly more effective (88%) than trovafloxacin (81%). Gemifloxacin was well tolerated and the incidence of transient liver function abnormalities was very low.

The effect of oral gemifloxacin 320 mg for 7 days on the human intestinal microflora has been investigated in 10 healthy subjects (11). The numbers of enterobacteria, enterococci, and streptococci were reduced. No other aerobic microorganisms were affected. The numbers of anerobic cocci and lactobacilli were reduced. The microflora normalized 49 days after withdrawal. There was no selection or overgrowth of resistant bacterial strains or yeasts.

Organs and Systems

Hematologic

Gemifloxacin reached intracellular concentrations in human polymorphonuclear leukocytes eight times higher than extracellular concentrations. Uptake was rapid, reversible, and non-saturable and was affected by environmental temperature, cell viability, and membrane stimuli (12).

Gastrointestinal

In a randomized, double-blind, multicenter comparison of a 5-day course of gemifloxacin 320 mg/day with a standard 7-day regimen of clarithromycin 500 mg bd in 712 patients with acute exacerbations of chronic bronchitis, the most frequently reported gemifloxacin-related adverse events were diarrhea (5.1%) and nausea (4.3%) (13).

Liver

Gemifloxacin was generally well tolerated in a pharmacokinetic study, although one subject was withdrawn after 6 days at 640 mg because of mild, transient rises in alanine transaminase and aspartate transaminase not associated with signs or symptoms (5).

Skin

Gemifloxacin has a low potential for mild phototoxicity (14).

Drug–Drug Interactions

Iron

In an open, randomized, single-dose, five-way crossover study of the effects of ferrous sulfate on the systemic availability of gemifloxacin, there were no changes when gemifloxacin was given at least 2 hours before or at least 3 hours after ferrous sulfate (9).

Sucralfate

In an open, randomized, single-dose, five-way crossover study of the effects of sucralfate on the systemic availability of gemifloxacin, there were no changes when gemifloxacin was given at least 2 hours before sucralfate (9).

Food–Drug Interactions

Food had a minor and clinically insignificant effect on the systemic availability of gemifloxacin (320 and 640 mg) (15).

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Gemtuzumab ozogamicin

See also Monoclonal antibodies

General Information

Gemtuzumab ozogamicin (Mylotarg) consists of a humanized anti-CD33 monoclonal antibody conjugated to the cytotoxic enediyne antibiotic calicheamicin. It has been used to treat a subset of patients with acute myeloid leukemia in association with topotecan + cytarabine. Its most common adverse effects are myelosuppression, increased hepatic enzyme activity, infections, fever and chills, bleeding, nausea and vomiting, and dyspnea.

Infusion-related adverse effects of gemtuzumab ozogamicin can be treated with a brief course of an intravenous glucocorticoid. Of 143 patients with refractory myeloid leukemia treated with gemtuzumab ozogamicin, 110 received paracetamol 650 mg orally with diphenhydramine 50 mg intravenously and 33 received the same premeditations plus methylprednisolone sodium succinate 50 mg intravenously before the infusion and repeated 1 hour later (1). There were grade 2 or worse infusion-related adverse events in 32 (29%) of the former, but in only one of the latter (3%).

Organs and Systems

Liver

Hepatotoxicity, with raised bilirubin and liver enzymes, is common with gemtuzumab (30–50%) and is mostly reversible. A more severe complication, hepatic veno-occlusive disease, a syndrome consisting of hyperbilirubinemia, painful hepatomegaly, and fluid retention or ascites, is less common and is mostly seen in patients previously undergoing bone marrow transplantation (4–5%). It occurs most commonly after high-dose chemotherapy and hemopoietic stem cell transplantation. Patients with severe veno-occlusive disease die from progressive multiorgan failure. Close monitoring of patients receiving gemtuzumab is necessary, even if they have not had previous bone marrow transplantation (2).

In 119 patients (92 with acute myeloid leukemia, 25 with advanced myelodysplastic syndrome, and two with chronic myeloid leukemia), who did not receive concomitant stem cell transplantation, 14 developed veno-occlusive disease (3). Five of these 14 patients had not received prior antileukemic therapy, and in two cases gemtuzumab ozogamicin was used as single-agent chemotherapy.

Of eight patients who were given an infusion of gemtuzumab 9 months after hemopoietic stem cell transplantation, seven had normal serum bilirubin concentrations, and all eight had transaminase and alkaline phosphatase activities that were less than 1.5 times the upper limit of the reference range (4). Six had no evidence of hepatotoxicity. One developed abdominal pain, ascites, and mildly raised transaminases. A CT scan showed no evidence of hepatic disease. This patient did not meet the criteria of veno-occlusive disease. Patient 8 did meet the criteria of veno-occlusive disease 3 days after infusion

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with gemtuzumab. She developed multi-organ failure and died.

Of 17 patients who were given gemtuzumab, three developed grade 3 hyperbilirubinemia, and five developed grade 3–4 hepatic transaminitis after a median of 13 days, including one who developed veno-occlusive disease (4). This patient had abrupt onset of weight gain, associated with ascites, abdominal distension, acute hepatic failure, and right upper quadrant pain, and died. As a possible mechanism gemtuzumab may selectively target CD33-expressing cells in hepatic sinusoids, activate stellated cells, damage sinusoidal endothelial cells, and cause sinusoidal vasoconstriction or ischemic hepatocyte necrosis. Liver histology showed sinusoidal injury with extensive sinusoidal fibrosis, centrilobular congestion, and hepatocyte necrosis (5).

Immunologic

There has been one report of an anaphylactic reaction in a patient receiving gemtuzumab (6).

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Genaconazole

See also Antifungal azoles

General Information

Genaconazole is an *N*-substituted triazole with a wide antifungal spectrum. Its absorption is slow, with peak concentrations 2–4 hours after a single dose and mean peak concentrations markedly higher after 16 days of administration. The mean elimination half-life is about 90–100 hours (1). It has high tissue penetration, including the CNS, and good broad-spectrum antifungal activity. However, it causes hepatocellular carcinoma in animals and the manufacturers stopped developing it because of concerns about toxicity.

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General anesthetics

See also Individual agents

General Information

The inhalational and injectable agents that are covered in separate monographs are listed in the table below.

Inhalational	Injectable
Halogenated	*Barbiturates*
Chloroform	Methohexital
Desflurane	Thiamylal
Enflurane	Thiopental
Halothane	*Others*
Isoflurane	Alfadolone/alfaxolone
Methoxyflurane	Etomidate
Sevoflurane	Ketamine
Trichloroethylene	Propanidid
Others	Propofol
Anesthetic ether	
Cyclopropane	
Nitrous oxide	
Xenon	

The inhalational agents in common use share similar adverse effects, albeit with differing incidences. Initial hopes that new agents will be less problematic generally fade as their use increases and familiarity with their adverse effects grows. Although some untoward reactions related to inhalational anesthetics are unpredictable, it is important for the anesthetist/anesthesiologist to determine which patients are primarily at risk, so that safer use of anesthetic agents and better supervision of surgical patients can be achieved.

Anesthetic combinations

The importance of multiple anesthetics should not be overlooked. For example, patients in whom halothane anesthesia is given twice, at an interval of less than 6 weeks, are at major risk of developing jaundice. Some anesthetists avoid any second exposure to this agent. However, there are several reasons why single agents are often insufficient in anesthesia: different problems require separate treatments; the severity of the adverse effects of individual drugs can sometimes be reduced by

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the use of combinations; and repeated administration of a single agent can lead to cumulative effects. Drug interactions in anesthesia are therefore potentially common and have been reviewed, both systematically (1) and as uncritical listings (2,3). Many of the interactions are beneficial, the concurrent use of two or more different agents improving the quality of anesthesia. Several reviews of this have appeared (4–6). Disadvantages of combinations include unpredictability of synergistic actions or toxicity, mutual alterations in pharmacokinetics, increased likelihood of errors in drug administration, and difficulties in planning drug therapy when adverse effects occur and are not attributable to a particular drug.

Dental anesthesia

Adverse effects of dental anesthesia represent a special problem, about which reliable data are hard to obtain. Several studies of the safety of dental anesthesia have been performed in the USA (SEDA-18, 113); unfortunately, all have weaknesses. More informative is an American survey in which 47 oral and maxillofacial surgeons were approached directly, and all responded (7). Among the 74 871 patients to whom they had given general anesthesia, there were 250 cases of laryngospasm, 51 of phlebitis, 30 of dysrhythmias sufficiently severe to require therapy, 17 of hypotension requiring drug therapy, and 13 of bronchospasm. A few patients had allergic reactions requiring drug therapy ($n = 4$), convulsions ($n = 4$), hypertension ($n = 2$), myocardial infarction ($n = 2$), or vomiting with aspiration ($n = 2$); in one case an injection was inadvertently given into an artery.

Sedation for endoscopy

Gastrointestinal endoscopy is one of the most commonly performed invasive procedures in clinical practice (for example about 500 000 procedures per annum in Australasia). Propofol is a short-acting intravenous anesthetic with a rapid onset of action and a short half-life, making it eminently suitable for day procedures. However, the use of propofol by non-anesthetists has been controversial because of the perceived risks of its low therapeutic ratio.

The incidence of adverse events related to an endoscopy sedation regimen that included propofol (in addition to midazolam and fentanyl), delivered by specially trained general practitioners, has been examined in a prospective audit (8); 28 472 procedures were performed over 5 years. There were 185 sedation-related adverse events, 107 with airway or ventilation problems; 123 interventions were necessary to maintain ventilation. No patients required tracheal intubation and there were no deaths. The authors concluded that appropriately trained general practitioners encountered a low incidence of adverse events and could safely use propofol for sedation during endoscopy. It should be noted that all the general practitioners had some experience in anesthesia or intensive care and were individually trained by the Director of Anesthesia.

Sedation for surgery under regional anesthesia

Sedation during prolonged surgical procedures under regional anesthesia can be quite challenging. The $beta_2$ adrenoceptor agonist dexmedetomidine has potent sedative and analgesic-sparing properties. In therapeutic doses it does not cause respiratory depression, making it attractive for infusion sedation. However, it causes reduced sympathetic outflow, which might cause untoward hemodynamic upset during intraoperative sedation. Dexmedetomidine has been compared with propofol in a prospective randomized trial in 40 patients (9). Dexmedetomidine provided slightly slower onset and offset of sedation, higher intraoperative blood pressure, and better postoperative analgesia.

Remifentanil is a highly selective OP_3 (μ) opioid receptor agonist with an extremely short onset and offset of action, allowing rapid and accurate titration of infusion rate to drug effect with rapid down-titration in case of respiratory adverse effects. This makes it attractive for sedation. The efficacy and adverse effects profiles of remifentanil and propofol have been compared in a randomized, single-blind trial in 125 patients undergoing surgery with regional anesthesia (10). In those given remifentanil, nausea and vomiting were more frequent (27 versus 2%) and there was significantly more respiratory depression (46 versus 19%).

Sedation in intensive care

It has been proposed that a combination of propofol and midazolam may have advantages over either drug alone, reducing adverse effects while preserving the potential benefits ("co-sedation"). Propofol combined with a constant low dose of midazolam (1.0 mg/hour) has been compared with propofol alone for postoperative sedation in a randomized, placebo-controlled, double-blind trial in 60 patients undergoing coronary artery surgery under high-dose fentanyl anesthesia (11). Target sedation was achieved more readily with co-sedation (91 versus 79%) but at the expense of prolonged weaning from mechanical ventilation (432 versus 319 minutes). However, it is not clear whether this slightly prolonged time on the ventilator affected length of stay in the ICU.

It remains a source of much concern that those working in operating theaters spend their time in such a polluted environment, in spite of attempts to introduce scavenging of waste anesthetic gases (12). This is not without its effects. There is, for example, a relation between asthma and occupational exposure to various respiratory hazards, including anesthetic gases (13).

Comparative studies

Halothane versus propofol

A randomized prospective trial in 60 children undergoing outpatient anesthesia showed a 30% shorter time from discontinuation of anesthesia to eye opening and return to full wakefulness in patients receiving propofol alone compared with halothane + nitrous oxide anesthesia (14). Propofol was associated with a 17% incidence of emesis compared with 58 and 53% for halothane + nitrous oxide and propofol + nitrous oxide anesthesia respectively.

Isoflurane + nitrous oxide versus propofol

The risk of postoperative nausea and vomiting has been studied in a randomized, controlled trial of total intravenous anesthesia with propofol versus inhalational

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anesthesia with isoflurane and nitrous oxide in 2010 patients (15). It was accompanied by an economic analysis. Propofol total intravenous anesthesia reduced the absolute risk of postoperative nausea and vomiting up to 72 hours postoperatively from 61 to 46%, in inpatients (NNT = 6) and from 46 to 28% in outpatients (NNT = 5). Both anesthetic techniques were otherwise similar. Anesthesia drug costs were more than three times higher for propofol total intravenous anesthesia (as propofol is substantially more expensive than isoflurane + nitrous oxide). However, the patients preferred propofol.

Isoflurane versus sevoflurane

A study of single vital-capacity breath inhalational induction using either isoflurane or sevoflurane combined with 67% nitrous oxide in 67 adults showed that isoflurane was unsuitable for this technique (16). There was an 87% incidence of induction complications with isoflurane, including involuntary movements, cough, laryngospasm, and failure of induction.

In 75 patients of ASA grades 1 or 2, recovery from anesthesia after maintenance with isoflurane + nitrous oxide was significantly slower than with sevoflurane + nitrous oxide (17).

Isoflurane and sevoflurane have been compared in a randomized study in 180 patients undergoing knee arthroscopy (18). In those given sevoflurane there were significantly more respiratory and cardiovascular complications and increased nausea and vomiting.

In a comparison of sevoflurane and isoflurane anesthesia in 2008 patients there was a 3–4 minute reduction in time to recovery end-points with sevoflurane (19). These differences became larger in anesthetics lasting over 3 hours and were trivial in cases less than 1 hour. Patients aged over 65 years had a 5-minute increase in recovery times after receiving isoflurane. There was no significant difference in the incidence of nausea or vomiting between isoflurane, sevoflurane, and propofol.

Propofol versus sevoflurane

Sevoflurane is pleasant to breathe and has a rapid onset and offset of action. It is challenging the tradition of intravenous anesthetic induction in adult patients. In a meta-analysis of 12 studies in 1102 adult patients, intravenous bolus doses of sevoflurane 7–8% and propofol for anesthetic induction were compared (20). Anesthesia maintenance included nitrous oxide 50–70% and either propofol infusion or sevoflurane inhalation, and spontaneous ventilation via a laryngeal mask. Patients in the sevoflurane group were significantly more likely to have postoperative nausea and vomiting (odds ratios 4.2 and 3.2). There were non-significant trends toward greater patient dissatisfaction and a longer induction time in the sevoflurane group, and more frequent apnea in the propofol group. There were no significant complications in either group. Both agents are suitable for anesthetic induction, but propofol retains a small advantage in having better recovery characteristics.

Single-agent induction and maintenance of anesthesia has been compared in a randomized study of 44 patients undergoing elective spinal surgery (21). Patients received either propofol 4–6 μg/ml via a target-controlled infusion or sevoflurane 8% for induction, and sevoflurane 3.5% + 67% nitrous oxide for maintenance plus alfentanil as required. Patients in the propofol group required a significantly larger dose of opiate during the procedure (2.2 mg versus 0.3 mg). Two patients who received propofol complained of pain on injection. There was no significant breath-holding or laryngospasm in either group. Heart rate was significantly lower in the sevoflurane group compared with propofol both before and after incision. The numbers of adjustments to the patient's depth of anesthesia were similar in both groups. The authors concluded that either technique was suitable for spinal surgery. The inclusion of nitrous oxide in the sevoflurane group accounted for the differences in opioid requirements.

The effects of hypercapnia on cerebral autoregulation during sevoflurane or propofol anesthesia have been studied in a randomized, crossover study in eight healthy patients (22). Hypercapnia began to inhibit cerebral autoregulation, as measured by transcranial Doppler at a mean value of 56 mmHg P_aCO_2 with sevoflurane 1.0–1.1% and at 61 mmHg P_aCO_2 with propofol 140 μg/kg/minute. Patients also received remifentanil for analgesia, a drug with no known effects on cerebral autoregulation. The study is important, because one advantage of both propofol anesthesia and sevoflurane anesthesia is the lack of inhibition of cerebral autoregulation at standard doses. Clearly, careful control of ventilation is required for this to be true.

The effects of isoflurane, sevoflurane, and propofol on jugular venous oxygen saturation (S_jO_2) in patients undergoing coronary artery bypass surgery have been studied (23). S_jO_2 values were significantly lower in the propofol group 1 hour after bypass, suggesting an imbalance of oxygen supply and demand with propofol. Because anesthetic agents also reduce the cerebral metabolic rate, the implications of this finding are uncertain. However, low S_jO_2 values have previously been associated with postoperative neuropsychiatric dysfunction after cardiopulmonary bypass.

Vital capacity inhalational induction of anesthesia with sevoflurane has been compared with intravenous induction using propofol in 56 adults undergoing ambulatory anesthesia (24). The patients were randomized to either sevoflurane 8% + nitrous oxide 75% mixture at 8 l/minute ($n = 32$), or propofol 2 mg/kg bolus ($n = 24$), without any premedication. Induction time was significantly shorter with sevoflurane (average 51 seconds) than propofol (average 81 seconds). Adverse effects were different in the two groups: sevoflurane caused cough and hiccups, while propofol caused a fall in blood pressure and reduced movements. The overall incidence of adverse effects was similar. Postoperatively, there was mild nausea in 78% of the patients who received sevoflurane compared with 50% for propofol. However, no antiemetics were needed and discharge times were not delayed.

The characteristics of sevoflurane anesthesia have been compared with those of target-controlled infusion of propofol in 61 day-case adults undergoing surgery (25). All received nitrous oxide 50% and fentanyl 1 μg/kg. After insertion of a laryngeal mask airway the propofol target concentration was reduced from 8 to 4 μg/ml and the

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inspired concentration of sevoflurane was reduced from 8 to 3% and subsequently titrated to clinical effects. Mean times to loss of consciousness and laryngeal mask airway insertion were significantly longer after sevoflurane (73 and 146 seconds respectively) than with propofol (50 and 116 seconds respectively). Sevoflurane was associated with a lower incidence of intraoperative movements (10 versus 55%), necessitating less adjustment to the dose. The incidence of movement in the propofol group was comparable to other studies. Emergence was faster after sevoflurane (5.3 versus 7.1 minutes) but sevoflurane was associated with more postoperative nausea (30 versus 17%) and vomiting (3 versus 0%), resulting in delayed discharge times (258 versus 193 minutes) and a higher total cost. The finding of significantly earlier discharge times after propofol anesthesia was unusual.

Propofol + alfentanil + nitrous oxide anesthesia has been compared with sevoflurane + nitrous oxide anesthesia in 44 patients undergoing dilatation and evacuation of the uterus (26). There was significantly less intraoperative uterine bleeding, as estimated by the gynecologist, with propofol. Above-average bleeding occurred in 5% of the patients with propofol anesthesia and 27% of patients with sevoflurane. This result was not surprising, given that sevoflurane reduces uterine tone, while propofol has no effect.

In a prospective randomized study of 120 day-surgery patients, desflurane and sevoflurane were associated with shorter times to awakening, extubation, and orientation than propofol infusion (27). Average times to awakening at the end of anesthesia were 5, 5, and 8 minutes respectively. There were no significant differences in time-to-home readiness or actual discharge times. A review of 436 patients undergoing either sevoflurane or propofol-based anesthesia showed no difference in similar recovery end-points (19).

There has been a prospective randomized comparison of 185 patients who received propofol 6–8 mg/kg/hour and sevoflurane 1.5% for maintenance of anesthesia (28). The patients were ventilated via a laryngeal mask and no muscle relaxants were given. Both agents were suitable for this technique. Emergence was significantly faster after sevoflurane but associated with more excitatory phenomena and tachycardia.

Sevoflurane versus thiopental

Sevoflurane 8% plus nitrous oxide 66% has been compared with thiopental 4 mg/kg for induction of anesthesia in brief outpatient procedures (29). Sevoflurane was safer, more efficacious, and better accepted by 78 unpremedicated adults with laryngeal cancer undergoing direct laryngoscopy for staging and biopsy. All received suxamethonium 50 mg on loss of the eyelash reflex and the surgeon then performed the laryngoscopy. Hemodynamic stability was greater and immediate recovery was faster after sevoflurane (9.7 versus 11.4 minutes). The incidence of dysrhythmias was also higher with thiopental (19 versus 12 patients). The dysrhythmias were predominantly ventricular extra beats with sevoflurane and ventricular bigemini with thiopental. The high incidence of dysrhythmias was partly due to the lack of opioid medication as part of the anesthetic.

Organs and Systems

Cardiovascular

Volatile anesthetic agents depress cardiac output, especially in the elderly. A study of 80 patients aged over 60 years compared the effects of halothane and isoflurane with and without nitrous oxide 50% (104). Doses were carefully adjusted to be equipotent in all four groups. Isoflurane caused a 30% reduction in systolic and diastolic arterial pressures compared with a 17% reduction with halothane. The reductions in cardiac index were similar with the two agents, about 17%. The addition of nitrous oxide attenuated the reductions in arterial pressure. In the case of the combination of isoflurane with nitrous oxide, there was a small increase in cardiac index and a small reduction in the halothane/nitrous oxide group. Systemic vascular resistance was reduced by a greater extent with isoflurane compared with halothane and little altered by the addition of nitrous oxide. The result suggests that nitrous oxide supplementation may be advantageous in the elderly, but interpretation is limited by the fact that it does not include the effects of surgery on these important cardiac parameters.

The long QT syndrome is associated with potentially fatal ventricular dysrhythmias under anesthesia. The effect of halothane and isoflurane on the QT interval was studied in 51 healthy children (31). Isoflurane 2.3–3.0% increased the average QT interval from 425 to 475 milliseconds at the time of induction. Halothane reduced the average QT interval from 428 to 407 milliseconds. The result suggested that halothane may be the more desirable agent in children with a prolonged QT interval.

The frequencies of cardiac dysrhythmias during halothane and sevoflurane inhalation have been compared in 150 children aged 3–15 years undergoing outpatient general anesthesia for dental extraction (32). They were randomized into three groups and received either halothane or sevoflurane in 66% nitrous oxide whilst breathing spontaneously. One group received 0.75% increments of halothane every two to three breaths to a maximum of 3.0% for induction, and then 1.5% for maintenance of anesthesia. One group received sevoflurane in 2% increments to a maximum of 8% and then a maintenance dose of 4%. The final group received 8% sevoflurane for induction and then a maintenance dose of 4%. The children who received halothane had a 48% incidence of dysrhythmias, significantly higher than the 16% incidence in the sevoflurane group and 8% in the incremental sevoflurane group. The halothane-associated dysrhythmias mainly occurred during dental extraction or emergence from anesthesia, and were usually ventricular. Six children in the halothane group had ventricular tachycardia. The longest run of ventricular tachycardia lasted 5.5 seconds, and one child had 13 separate episodes. Sevoflurane-associated dysrhythmias were mainly single supraventricular extra beats, and did not differ between the two administration methods. Although there was insufficient evidence to suggest that transient dysrhythmias associated with halothane in dental anesthesia can lead to cardiac arrest, sustained ectopic ventricular activity, including ventricular tachycardia, even if self-limiting, results in reduced cardiac output and cannot be ignored. These results imply that sevoflurane may be the preferable agent in this setting.

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The hemodynamic responses to induction and maintenance of anesthesia with halothane have been compared with those of sevoflurane in 68 unpremedicated children aged 1–3 years undergoing adenoidectomy (30). The children received either sevoflurane 8% or halothane 5% + nitrous oxide 66% for induction of anesthesia and tracheal intubation, without neuromuscular blocking drugs. Anesthesia was maintained by adjusting the inspired concentration of the volatile anesthetic to maintain arterial blood pressure within 20% of baseline values, and the electrocardiogram was continuously recorded. The incidence of cardiac dysrhythmias was 23% with halothane and 6% with sevoflurane. Most of the dysrhythmias were short-lasting/self-limiting supraventricular extra beats or ventricular extra beats. Although the overall incidence of dysrhythmias was low in both groups, the result again shows that sevoflurane causes fewer dysrhythmias in children and may be the preferable agent.

QT dispersion, defined as the difference between QT_{max} and QT_{min} in the 12-lead electrocardiogram, is a measure of regional variation in ventricular repolarization (33). It is greater in patients with dysrhythmias. The effects of halothane and isoflurane on QT dispersion have been studied in 46 adult patients undergoing general anesthesia. QT dispersion was increased in both groups both with and without correction for heart rate. The increase was significantly greater with halothane than with isoflurane. The clinical significance of this finding is not known. In isolation, QT dispersion reflects an abnormality in ventricular repolarization and correlates with dysrhythmic events. Although there were no overt dysrhythmias in this study, the effect suggests a reason for the variable results of past studies of the QT interval: most studies showed prolongation of the QT interval, but some showed no change, or shortening. Larger studies are needed to elaborate on the possible clinical importance of this phenomenon, but it may be a significant cause of dysrhythmias with volatile anesthetics.

Respiratory

The incidence of perioperative respiratory complications has been studied prospectively in 602 children aged 1 month to 12 years undergoing elective surgery using a halothane-based anesthetic (34). Exposure to environmental smoke was assessed using the history of exposure to cigarette smoke and measurement of urinary cotinine concentrations, and the respiratory complications of laryngospasm, bronchospasm, stridor, breath holding, coughing, and excessive mucus production were recorded. The incidence of respiratory concentrations in patients with a urinary cotinine concentration over 40 ng/ml was 42%, dropping to 24% in patients with a urinary cotinine concentration less than 10 ng/ml. Female sex and lower socioeconomic status of the mother increased the incidence of respiratory complications. The study showed the importance of factors other than the anesthetic drugs and techniques used in determining complications precipitated by anesthesia.

The respiratory effects of sevoflurane and halothane have been investigated in 30 infants aged 6–24 months (35). Respiratory depression was greater in the sevoflurane group, with a mean minute ventilation of 4.5 compared with 5.4 l/minute/m^2 and respiratory rate was lower at 38 compared with 47 breaths/minute. There was a lower incidence of thoracoabdominal asynchrony with sevoflurane, but no difference in respiratory drive, as evidenced by the flow pressure generated during 100 milliseconds of occlusion of the airway.

The effects of desflurane and sevoflurane on bronchial smooth muscle reactivity have been compared in a randomized study of 40 patients (36). Anesthesia was induced with thiopental, followed by muscle relaxation and ventilation. Airway pressures were recorded during administration of desflurane or sevoflurane at one minimal alveolar concentration (MAC). Airway resistance increased by 5% in the desflurane group and fell by 15% in the sevoflurane group. The increase in airways resistance was greater in smokers and with desflurane, but did not differ with sevoflurane. The result was a surprise, given that desflurane stimulates the sympathetic nervous system. Thiopental also increased airways resistance by 10%. The result is important, because induction of anesthesia can cause bronchospasm and desflurane can exacerbate this.

Nervous system

The effects of sevoflurane and isoflurane anesthesia on interictal spike activity have been studied in 12 patients with refractory epilepsy (37). The patients were undergoing insertion of subdural electrodes and were also given fentanyl during surgery. Electroencephalogram spike frequency increased significantly in all patients during 1.5 MAC sevoflurane anesthesia compared with awake recordings; hypocapnia did not change this increased spike activity. The electrocorticographic interictal spike frequency was also significantly higher in all patients during 1.5 MAC sevoflurane anesthesia and in eight of 10 patients during 1.5 MAC isoflurane anesthesia, compared with 0.3 MAC isoflurane anesthesia. In susceptible individuals, both sevoflurane and isoflurane can provoke interictal spike activity. This effect is only well described for enflurane, but it is a dose-dependent feature of most volatile agents.

Convulsions during anesthesia are of concern because with the use of muscle relaxants they may go unrecognized. The epileptogenic properties of isoflurane and sevoflurane have been compared under a range of different ventilatory conditions in 24 ASA I or II mentally handicapped patients undergoing dental operations (38). Half had a history of epilepsy and half did not. Each patient was ventilated with 100% oxygen (end-tidal carbon dioxide = 40 mmHg; A), then 50% oxygen 50% nitrous oxide (end-tidal carbon dioxide = 40 mmHg; B), and then 100% oxygen (end-tidal carbon dioxide = 20 mmHg; C). With each different mode of ventilation, isoflurane was given at 1 MAC then at 1.5 and 2.0 MAC. The process was repeated 3 months later with sevoflurane. The electroencephalogram was concurrently recorded. The spike and wave index increased significantly from 2.0% during 1.0 MAC sevoflurane to 6.1% during 2.0 MAC in group A in those with epilepsy, while no spike activity was seen in those without epilepsy. Only a few spikes were observed in the isoflurane group in A, with none in B or C. Supplementation with nitrous oxide

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or hyperventilation suppressed the occurrence of spikes. The authors concluded that sevoflurane has stronger epileptogenic properties than isoflurane, but that this can be counteracted by nitrous oxide or hyperventilation.

There has been an impressive French study of the risks of occupational exposure of hospital personnel to anesthetics among the staff of 18 Paris hospitals (excluding doctors) over 12 years (39). Among 557 staff who had been exposed to anesthetics and 566 workers who had been less exposed, neuropsychological and neurological symptoms (tiredness, nausea, headaches, memory impairment, reduced reaction time, tingling, numbness, cramps) were reported some three times more commonly by workers in theaters that had been less often scavenged than by controls; no difference was found between workers from well-scavenging theaters and controls. Neuropsychological symptoms were reported in several earlier papers (40).

Neuromuscular function

Both desflurane and sevoflurane significantly increase the neuromuscular blocking effects of rocuronium compared with isoflurane or propofol (41,42). The effective doses of rocuronium for 50% depression of single twitch height were 95, 120, 130, and 150 μg/kg for desflurane, sevoflurane, isoflurane, and propofol respectively. There were no differences in recovery profiles between the four drugs using equieffective doses. Desflurane, sevoflurane, and to a lesser extent isoflurane, also potentiated the neuromuscular blocking effect of cisatracurium by 30% compared with propofol (43,44).

Hematologic

Hemostasis can be impaired by both surgery and general anesthetics (45). Fentanyl, halothane, and enflurane enhance fibrinolytic activity significantly (46). In addition, there was a raised plasma beta-thromboglobulin concentration (a good indicator of platelet activation) in 61 patients after the use of nitrous oxide, oxygen, and halothane compared with controls (47).

In an in vitro study of the inhibitory effects of thiopental, midazolam, and ketamine on human neutrophil function, thiopental and midazolam inhibited chemotaxis, phagocytosis, and reactive oxygen species production at clinically relevant concentrations (48). Ketamine only impaired chemotaxis. These results may be relevant in guiding anesthetic drug therapy in septic patients.

Gastrointestinal

In a prospective study of 556 adults using isoflurane-, halothane-, or enflurane-based anesthesia for ear, nose, throat, and eye procedures, the incidences of emesis in the various groups over the ensuing 24 hours were 36, 41, and 46% respectively (49). Other drugs given during anesthesia included midazolam, thiopental, morphine, and nitrous oxide. Antiemetic requirements were also less with isoflurane: 12% of patients required an antiemetic compared with 23% with halothane and enflurane. There were no differences in the overall incidences of headache or analgesic requirements in the three groups.

In another prospective study of nausea and vomiting in 50 patients undergoing arthroscopy, sevoflurane was compared with desflurane (50). Other drugs given during anesthesia included propofol and alfentanil. There was no difference in the incidence of nausea, 8 and 16% respectively, and no vomiting in either group. The desflurane group had a significantly higher incidence of sore throat (32 versus 8%). These studies have confirmed that the newer volatile anesthetics isoflurane, sevoflurane, and desflurane cause less nausea and vomiting than halothane or enflurane.

Because population measures of anesthetic dosages do not consider the individual's anesthetic needs, anesthetists often err on the side of relative overdosage during balanced anesthesia, in order to prevent the devastating consequences of unintentional awareness during surgery. This excessive depth of anesthesia contributes to delayed recovery and more adverse effects, which is particularly important in ambulatory surgery. Monitoring of the bispectral index-processed electroencephalogram has enabled anesthetists to monitor the depth of anesthesia and has brought greater precision to the administration of intravenous and inhaled anesthetics and opioids. The hypothesis that titration of the maintenance dose of sevoflurane during outpatient gynecological surgery using bispectral index monitoring reduces postoperative vomiting and improves recovery has been tested in a randomized, controlled study in 22 patients (51). The monitored patients had significantly less vomiting than the controls (16 versus 40%).

Several small clinical trials have suggested that total intravenous anesthesia with propofol reduces the incidence of postoperative nausea and vomiting and results in shorter emergence times. However, a systematic review (52) and a meta-analysis (53) have shown that most studies were small, did not have follow-up for more than 6 hours postoperatively, and were sponsored by industry. The results were difficult to combine, owing to heterogeneous definitions of postoperative nausea and vomiting.

A simplified risk score for predicting postoperative nausea and vomiting in adult patients undergoing general anesthesia has been developed. In a study of 520 adults from Finland and 2202 patients from Germany who had received anesthesia that included benzodiazepine premedication, thiopental, fentanyl or alfentanil, isoflurane, enflurane or sevoflurane, and non-steroidal or opioid drugs for postoperative analgesia no antiemetic prophylaxis was given (54). The final derived score consisted of four predictors: female sex, a history of motion sickness or postoperative nausea and vomiting, non-smoking, and the use of postoperative opioids. The incidence of postoperative nausea and vomiting was 10% when there were no risk factors, 21% (one risk factor), 39% (two risk factors), 61% (three risk factors), and 79% (four risk factors). Only one of the four risk factors related to the drugs used.

Postoperative nausea and vomiting in children has been reviewed in detail, including multimodal strategies for management and prevention (55).

Urinary tract

Methoxyflurane, enflurane, isoflurane, and sevoflurane all release inorganic fluoride ions as a result of hepatic metabolism. Fluoride is nephrotoxic.

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Renal function and fluoride ion release after anesthesia using not more than 2.4% sevoflurane or 1.9% isoflurane have been studied in 50 patients of ASA grades 1–3 undergoing operations lasting at least 1 hour (56). Serum fluoride ion concentrations were significantly increased in both groups, peaking at 28 μmol/l after sevoflurane and 5 μmol/l after isoflurane, both at 1 hour. Of more concern, three of the patients in the sevoflurane group had peak fluoride ion concentrations above 50 μmol/l; two of them had increases in serum blood urea nitrogen and creatinine at 24 hours after surgery. The half-life of fluoride ion was 22 hours.

Nephrotoxicity has been found with methoxyflurane when serum fluoride ion concentrations exceeded 50 μmol/l (SEDA-20, 106). Although this safety threshold has been applied to other volatile anesthetics as well, renal toxicity has not been reported for the other three anesthetics, even though the threshold can be exceeded during prolonged anesthesia.

Volatile agents do not cause nephrotoxicity in adults with normal renal function (57). However, using sensitive urinary markers, both sevoflurane and isoflurane caused mild transient glomerular and tubular functional impairment in 13 patients aged 70 years or over undergoing gastrectomy. The patients received epidural analgesia combined with inhalation anesthesia using 5 l/minute fresh gas flow. The mean dose of sevoflurane was 5.1 MAC-hours and of isoflurane 3.7 MAC-hours. The mean urinary albumin excretion increased from 65 to 148 mg/g creatinine in the sevoflurane group and from 44 to 197 mg/g creatinine in the isoflurane group, and returned to preoperative values on the first postoperative day. The mean urinary β_1 and β_2 microglobulin concentrations also increased markedly in both groups, from 9.3 and 0.8 mg/g to 31 and 6.2 mg/g with sevoflurane and from 7.4 and 0.7 mg/g to 44 and 11 mg/g with isoflurane. These values had returned to normal by day 7 postoperatively. The mean urinary *N*-acetyl-β-D-glucosaminidase concentration also increased significantly. These changes suggest transient renal tubular injury in both groups. There has not been any agreement on how these results should be interpreted, and larger studies are warranted.

Musculoskeletal

A spectrum of muscle reactions to all inhalational agents has been described. Masseteric muscle spasm can occur as an isolated phenomenon or can progress either to rhabdomyolysis with renal insufficiency or to malignant hyperpyrexia (58–61).

Generalized muscle rigidity and hypercapnia, followed by raised creatine kinase activity, have been reported in a child undergoing general anesthesia (62).

- A 2-year-old girl with a past history of asthma, developmental delay, short neck, and lumbar lordosis, but no known genetic defect or syndrome underwent anesthesia with midazolam and paracetamol premedication, halothane and nitrous oxide induction, and isoflurane plus nitrous oxide for maintenance of anesthesia. Difficulty with mouth opening was noted and endotracheal intubation was difficult. Limb rigidity developed rapidly. Thiopental and cisatracurium were given and the muscle rigidity abated over the next 10 minutes. The procedure was continued with a propofol infusion. No treatment for malignant hyperpyrexia was undertaken and no other markers for malignant hyperpyrexia were observed. She made a normal recovery from anesthesia. Creatine kinase activities were raised at 2370 U/l intraoperatively and 18 046 U/l at 20 hours postoperatively.

The case is interesting in that although episodes of masseter spasm, rigidity, rhabdomyolysis, and malignant hyperpyrexia are well known after the use of halothane and suxamethonium, they have only rarely been reported when suxamethonium was not used.

Immunologic

The issue of hypersensitivity reactions during general anesthesia is a matter of concern. However, despite considerable work on the subject, there is divergence in interpretation (63). In patients with no pre-anesthetic immunological anomaly, general anesthesia is unlikely to affect immune status significantly (64).

Widespread erythema and edema, the most dangerous form of which affects the glottis, occur in some cases of hypersensitivity. Hypotension is also seen, together with compensatory tachycardia. Bronchospasm is a common respiratory finding (65).

There were significant immunological changes in the peripheral blood film of personnel working in unscavenged operating theaters in Croatia (66). Some of the effects persisted beyond a 4-week period away from that environment.

In a review of 23 444 anesthetics given during 12 months, one patient in 630 had generalized erythema and edema and one in 1230 had erythema and hypotension (67). One patient died of shock. Female patients aged 15–25 with a history of allergy, subjects with excessive anxiety, and those who had previously undergone general anesthesia had a statistically significant higher risk of developing non-allergic anaphylactic reactions. The incidence of allergic anaphylactic reactions (with IgE antibodies) is said to be one in 4500–20 000 general anesthetics per year (68). However, the diagnosis is often missed (69).

The patient's history is hardly helpful; neither the presence nor the absence of a previous reaction gives guidance as to the likelihood of its occurring on future exposure. The mechanisms underlying such reactions may or may not involve histamine release, but the distinction between allergic anaphylactic and non-allergic anaphylactic (anaphylactoid) reactions is often unclear, for lack of definitive and easily available investigations. Furthermore, because anesthetic drugs are often given rapidly and in combination, it can be impossible to decide which was responsible for the reaction. Intradermal injection of a test dose is of limited predictive value (70); false-positive and false-negative results are often obtained, particularly with opiates, tubocurarine, and atracurium. What is more, the test is dose-dependent and can itself precipitate a hypersensitivity reaction (71). It has been suggested that leukocyte histamine release on exposure to drugs can be used in combination with paper radioallergosorbent testing for IgE antibodies, to detect the precise cause of any anaphylactic reaction: these techniques point

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to neuromuscular blocking drugs as being most commonly implicated in anaphylaxis (70).

In a French study, 1585 patients underwent diagnostic investigations after anaphylactic shock during anesthesia; 813 of them had a reaction of immunological origin. The drugs involved were muscle relaxants (70%), latex (13%), anesthetic drugs (5.6%), opioids (1.7%), colloids (4.7%), and antibiotics (2.6%) (72). Among the 45 patients in whom anesthetics were involved, the agents implicated were thiopental ($n = 18$), propofol ($n = 10$), ketamine ($n = 1$), midazolam ($n = 7$), diazepam ($n = 5$), and flunitrazepam ($n = 4$). These data did not differ from those reported in a UK study (73). In both studies there was a high proportion of cases in which muscular relaxants were used alongside anesthetics, resulting in a two-fold risk of hypersensitivity.

Body temperature

Malignant hyperthermia

Malignant hyperpyrexia is a life-threatening condition that involves sustained muscle contraction, muscle damage, and the production of vast quantities of metabolic heat, carbon dioxide, and potassium. Although it is a rare complication of general anesthesia, it remains a topic of considerable interest (74).

The incidence is difficult to determine, but it is currently estimated at one in every 10 000–20 000 anesthetics.

Diagnosis

Generalized muscle rigidity (found in 70% of the patients involved) and a progressive rise in body temperature (sometimes beyond 43°C) are the main clinical features, often associated with tachycardia, hypoxia, metabolic acidosis, cardiac dysrhythmias and, less often, disseminated intravascular coagulation, cerebral edema, and acute renal insufficiency. Diagnosis relies on the clinical signs, that is muscle rigidity and hyperpyrexia, and on raised serum activities of skeletal and cardiac muscle enzymes, for example aldolase and creatine kinase.

Genetic markers for malignant hyperpyrexia may soon make identification of risk groups simpler than the currently used muscle biopsy technique (75).

Susceptibility factors and prophylaxis

Although malignant hyperthermia is usually associated with the muscle relaxant suxamethonium, all inhalational anesthetics have been implicated and will be unsafe if risk factors for this condition are present, for example a family history or one of the congenital muscle disorders (76). This must be considered in patients at risk, as there are readily acceptable alternatives, such as propofol (77) and midazolam (78).

Malignant hyperthermia is probably due to the inability of certain individuals to control calcium concentrations in the muscle fiber and may involve a generalized alteration in cellular or subcellular membrane permeability, as suggested from research on pigs. This anomaly is genetically determined, but pre-anesthetic evaluation of susceptibility to malignant hyperthermia is a matter of controversy: measurement of blood creatine kinase, ATP muscle depletion, or myophosphorylase A, histological examination of muscle fibers, and in vitro exposure to caffeine or halothane have all been proposed. However, if susceptible patients require general anesthesia, despite the risk, prophylactic use of intravenous dantrolene 2.4 mg/kg during induction of anesthesia has been recommended (79).

Treatment and prognosis

Around 1970, mortality was as high as 70%, but it is now less than 10%. This reduction in mortality has been due to the use of dantrolene, the only specific treatment available, and also to an increased understanding of the condition (74).

Treatment is by withdrawal of the anesthetic, hyperventilation with 100% oxygen, cooling, and dantrolene. Doses of dantrolene of 2.5–5 mg/kg are usually recommended, given as early as possible to ensure rapid and complete resolution of the hyperthermic response (80).

Death

Correct estimates of the incidence of anesthetic deaths are difficult to obtain, since many deaths are multifactorial. Mortality due to anesthetic drugs is one in 10 000–20 000 (81). The adverse effects of anesthetics have been reviewed (82). Dose-related reactions are common and carry a low mortality, while non-dose-related reactions are less common and carry a high mortality.

A national prospective survey of complications related to anesthesia was carried out in France from 1978 to 1982 (83,84). In 198 103 anesthetic procedures, only 63 deaths were recorded, of which only 15 were definitely attributed to anesthesia (85). The Confidential Enquiry into Perioperative Deaths, conducted a decade ago in three British Health Regions (86) and covering a total of 555 248 patients, showed that the incidence of death within 30 days of surgery and anesthesia was 0.73% (4034 cases). Only about 14 of these deaths were considered to be partly or totally attributable to the anesthesia, and indeed in most cases other factors were also involved, including the surgery itself, the presurgical condition, and intercurrent illnesses. In a review of 25 deaths during anesthesia in 1982–86, only six were considered to be drug-related; of these, two were due to overdose and two more were the result of adverse effects of non-anesthetic agents (87).

Finally, except for certain specific effects that have a clear relation to a particular agent (for example liver damage after halothane), it is difficult to designate one anesthetic as being more risky than another. It has been authoritatively concluded that "the current level of research effort cannot distinguish mortality and serious morbidity between the most common anesthetic agents, and the clear differences in hemodynamic patterns among these anesthetic agents have an unknown, perhaps non-existent, relationship with mortality and serious morbidity" (88).

Long-Term Effects

Mutagenicity

Genetic damage was demonstrated in 10 non-smoking veterinary surgeons exposed to isoflurane and nitrous oxide compared with 10 non-smoking, non-exposed

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veterinary physicians acting as controls (89). The surgeons were monitored for 1 week in a working environment comparable to that of pediatric anesthesia, with the use of uncuffed endotracheal tubes and open-circuit breathing systems during operations on small animals. The overall calculated 8-hour time-weighted average exposure of cases was 5.3 ppm for isoflurane and 13 ppm for nitrous oxide. The European exposure limits are 10 ppm and 100 ppm respectively, and the corresponding values recommended by USA-NIOSH are 2 ppm and 25 ppm respectively. These values therefore violated the USA-NIOSH limit for isoflurane. The mean frequency of sister chromatid exchanges in peripheral blood lymphocytes was significantly higher in exposed workers than in controls (10 versus 7.4) and the proportion of micronuclei was also significantly higher in exposed workers (8.7 versus 6.8 per 500 binucleated cells). These measures reflect the mutagenicity of isoflurane and nitrous oxide. The findings are comparable to smoking 11–20 cigarettes a day. However, this study did not distinguish between the potential genotoxic effects of isoflurane and nitrous oxide; nor did it show a dose-dependency of genotoxicity, owing to the small sample size.

Second-Generation Effects

Fertility

Nitrous oxide may be the most serious of anesthetic pollutants; female dental assistants exposed to large amounts of nitrous oxide (5 hours or more of exposure per week) are significantly less fertile than women who are not exposed or who are exposed to lower amounts (90).

Pregnancy

The pharmacology and adverse effects of anesthetic drugs used for cesarean section have been reviewed (91).

Teratogenicity

In an epidemiological study, anesthetists had significantly greater exposure and perhaps more adverse effects than other operating-room personnel (92). Among women, exposure certainly causes an increased risk of spontaneous abortions in the first trimester, although teratogenicity is less clear-cut (93).

Susceptibility Factors

Underlying disease

Underlying disease is probably one of the most complex risk factors. Although general anesthesia is potentially more hazardous in patients with underlying disease in general (94) or specifically suffering from intracardiac conduction disturbances (95), severe hypertension (96), hypothyroidism (97), or cancer (98), it is extremely difficult to provide clear-cut recommendations, because the relative severity of disease in a given patient and the patient's response to the pathological process needs to be taken into account: while, for instance, thiopental may precipitate cardiovascular collapse, both pre-existing cardiac status and the dose of the drug are relevant.

Critically ill patients

Drug metabolism is reduced in critically ill patients. When the serum from five critically ill patients was incubated with microsomes prepared from three different human livers, the activity of CYP3A4, assessed by metabolism of midazolam to 1-hydroxymidazolam, was significantly inhibited compared with serum from healthy volunteers (99). The authors pointed out that many other drugs are also metabolized by this enzyme, including alfentanil, ciclosporin, cortisol, erythromycin, lidocaine, and nifedipine. This observation accounts for past reports of very slow metabolism of midazolam in seriously ill patients, resulting in high blood concentrations and delayed awakening.

Pre-anesthetic drug therapy

The consequences of pre-anesthetic drug therapy as a risk factor are obviously closely related to those of the underlying disease. The problem has attracted considerable attention in recent years and has been extensively reviewed (100). Interactions of drugs with anesthesia are dealt with here primarily in monographs on the drugs concerned. Although many pharmacological interactions with general anesthesia are firmly established, others remain ill-explained or unpredictable. Individual factors are likely to play a major role. Moreover, pre-anesthetic drug withdrawal in itself can be more dangerous than continuation of therapy, as exemplified by the case of the antihypertensive drug clonidine (101) or beta-blockers (102).

Driving

The hazard of driving shortly after general anesthesia is still difficult to evaluate. Although abstention from driving has been recommended for 48 hours after general anesthesia (103), it is still difficult to draw clear-cut conclusions from the available data. The matter is also referred to under individual anesthetic drugs.

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Gentamicin

See also Aminoglycoside antibiotics

General Information

Gentamicin is well established for the treatment of several bacterial infections, especially those caused by Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Klebsiella* species, and *Serratia marcescens*. In adults, it is usually given in daily doses of 240–360 mg.

Observational studies

In 17 patients with suspected postoperative endophthalmitis treated with 0.2 mg vancomycin and 0.05 mg gentamicin intravitreally, there were adequate intravitreal vancomycin and gentamicin concentrations for over a week; there were no adverse effects (1).

Intratympanic gentamicin therapy has gained some popularity in the treatment of vertigo associated with Menière's disease, as it offers some advantages over traditional surgical treatment. In a 2-year follow-up of 15 patients with Menière's disease, gentamicin solution 0.5 ml (20 mg/ml) injected intratympanically once a week minimized the risk of hearing loss in the treated ear, allowing complete control of vertigo in eight patients after two doses and in 14 patients after four doses (2).

In an open, randomized, controlled trial, once-daily and thrice-daily gentamicin were compared in 173 children aged 1 month to 12 years; there was no nephrotoxicity or ototoxicity (3). Daily doses of gentamicin in both groups were 7.5 mg/kg (under 5 years old), 6.0 mg/kg (5–10 years old), and 4.5 mg/kg (over 10 years old).

Organs and Systems

Respiratory

Acute respiratory failure with near-fatal bronchoconstriction has been reported in an adult with bronchiectasis and chronic *P. aeruginosa* airways colonization immediately after the first inhalation of a commercially available gentamicin solution (4).

Nervous system

Intraventricular gentamicin can cause aseptic meningitis (5).

Sensory systems

The frequency of aminoglycoside-associated hearing loss is 2–45%. Since gentamicin-induced ototoxicity in most cases only involves vestibular function, the symptoms are easily overlooked in severely ill patients who are unable to sit. If diagnosed early, the vestibular damage is usually reversible. In some cases, severe long-term disability has been described (6). Six patients presented with unilateral vestibulotoxicity after systemic gentamicin therapy (7). All had ataxia and oscillopsia, but none had a history of vertigo. The authors suggested that a subacute course of vestibulotoxicity with time for compensation or asymmetrical recovery of vestibular function after bilateral

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vestibular loss could have explained the lack of vertigo in these patients.

The risk of ototoxicity from gentamicin in children is probably less than in adults. In many studies of serious neonatal infections treated with gentamicin there have been very few cases that have provided unequivocal evidence of gentamicin-induced ototoxicity. Gentamicin can be an excellent drug in neonatal sepsis, and its potential toxicity should not preclude its use when it is needed.

Gentamicin ear-drops can cause serious adverse effects (for example vertigo, imbalance, ataxia, oscillating vision, hearing loss, and tinnitus) when they are used by patients with perforated tympanic membranes or tympanostomy tubes (8).

The symptom complex known as visual vestibular mismatch can be caused by peripheral vestibular disease. In a retrospective study of 28 patients with Menière's disease, 17 had visual vestibular mismatch; gentamicin therapy increased the number of positive answers (9).

In a retrospective analysis of 85 patients treated with intratympanic gentamicin, using a fixed-dose regimen of 26.7 mg/ml tds on 4 consecutive days, hearing loss occurred in 26% of individuals (10).

The characteristics of ototoxicity of topical gentamicin have been studied retrospectively in 16 patients (11). All used ear-drops for more than 7 days before the development of symptoms, and all had some degree of vestibulotoxicity, but only one had a worsening of cochlear reserve. Even if the tympanic membrane is intact, one should hesitate to use gentamicin in ear-drops or in other topical forms for the treatment of otitis media.

In patients with acute bacterial conjunctivitis there were adverse drug reactions in 4 of 103 treated with gentamicin (12). The adverse effects included redness, itching, and burning, and none was serious.

In two animal studies methylcobalamin or dimethylsulfoxide inhibited the ototoxic adverse effects of gentamicin (13,14).

Psychological, psychiatric

There are several case reports of acute toxic psychoses due to gentamicin (15).

Mineral balance

Gentamicin-induced magnesium depletion is most likely to occur in older patients when large doses are used over long periods of time (16). Under these circumstances, serum concentrations and urinary electrolyte losses should be monitored.

Liver

Increases in alkaline phosphatase after gentamicin have been described (17).

Urinary tract

A full course of gentamicin therapy causes nephrotoxicity in 1–55% of patients. Two types of gentamicin-induced nephrotoxicity are recognized: (1) a gradual reduction in creatinine clearance, occurring after about 2 weeks, in about 5–10% of patients receiving the drug in full doses, the reduction being rapidly reversible in most cases as soon as gentamicin is withdrawn; (2) acute renal insufficiency due to tubular necrosis, usually associated with oliguria lasting 10–12 days, followed by a diuretic phase; this type of nephrotoxicity occurs far less often than the first type.

The following order of relative nephrotoxicity has been found in many animal experiments: neomycin > gentamicin > tobramycin > amikacin > netilmicin (18,19). However, in humans, conclusive data regarding the relative toxicity of the various aminoglycosides are still lacking. An analysis of 24 controlled trials showed the following average rates for nephrotoxicity: gentamicin 11%; tobramycin 11.5%; amikacin 8.5%; and netilmicin 2.8% (20). In contrast to this survey, direct comparison in similar patient groups showed no significant differences between the various agents in most trials (21–27). In fact, the relative advantage of lower nephrotoxicity rates observed with netilmicin in some studies may be limited to administration of low doses. One prospective trial showed a significant advantage of tobramycin over gentamicin (28). However, these findings could subsequently not be confirmed (29). The risk of gentamicin nephrotoxicity is increased in biliary obstruction (SEDA-20, 235).

In a few cases, gentamicin nephrotoxicity was associated with a Fanconi syndrome, with raised serum enzymes activities in the urine. Among these, muramidase seemed to be especially useful in checking for proximal tubular dysfunction (30).

Gentamicin is of considerable value in the management of sepsis in immunosuppressed patients and renal transplant recipients. Although it has been suggested that gentamicin should be avoided in such patients because of potential renal toxicity in the allograft (31,32), experienced physicians have felt that gentamicin may be given, provided the dosage schedule is adapted to the degree of allograft function and that blood concentrations are monitored.

After a full course of gentamicin 1–55% of patients have nephrotoxicity. The increased serum creatinine concentration peaks on day 6 of therapy and is reversible in most cases within 30 days. Nephrotoxicity appears to be more common among patients with pre-existing renal impairment, longer treatment duration (over 7 days), repeated courses of aminoglycosides, and after the coadministration of other nephrotoxic drugs (for example amphotericin, cisplatin, daunorubicin, furosemide, and vancomycin). Animal studies have suggested that hydrocortisone, angiotensin converting enzyme inhibitors, and hypercalcemia can also increase aminoglycoside nephrotoxicity, whereas acetazolamide, bicarbonate, ceftriaxone, lithium, magnesium, melatonin, piperacillin, polyaspartic acid, pyridoxal-5′-phosphate, and a high protein diet may be protective (33,34).

In 87 patients with intertrochanteric hip fractures, preoperative antibiotic prophylaxis (gentamicin 240 mg and dicloxacillin 2 g) had no significant effect on wound infections; however, there were 16 reversible cases of nephrotoxicity and 1 irreversible case among patients who received antibiotic prophylaxis, compared with only 4 cases of reversible kidney damage among 76 patients who did not receive antibiotics (35).

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- Acute renal insufficiency occurred in an 83-year-old woman after two-stage revision of an infected knee prosthesis with gentamicin-impregnated beads and block spacers (36). The combined use of beads and a cement block spacer, both gentamicin impregnated, may have caused this severe complication.
- A 43-year-old black woman with a 13-year history of lupus developed severe acute tubular necrosis secondary to gentamicin (37).

Since serum creatinine does not accurately reflect renal function in patients with spinal cord injury, dosage regimens of gentamicin should be individualized, based on age, sex, weight, height, the level of spinal cord injury, and renal function (38).

In animals melatonin (39,40) or l-carnitine (41) protected the kidneys against oxidative damage and the nephrotoxic effect of gentamicin.

Nephrocalcinosis occurred in 16 of 101 babies born at less than 32 weeks gestation (42). Multivariate analysis showed that the strongest predictors of nephrocalcinosis were duration of ventilation, toxic gentamicin/vancomycin concentrations, low fluid intake, and male sex.

Skin

Erythema multiforme developed in a 4-year-old girl after treatment with topical aural gentamicin sulfate (0.3%) plus hydrocortisone acetate (1%) prescribed for otorrhea (43).

Immunologic

Allergic contact dermatitis due to gentamicin is rare in patients with eyelid dermatitis, but it can occur.

- A 55-year-old housewife developed pruritic, erythematous, scaly plaques on the eyelids, spreading in a few days periorbitally after treatment with gentamicin eye-drops (Colircusi Gentamicina) (44). A positive patch test reaction to kanamycin, to which the patient had not been previously exposed, suggested cross-reactivity.

Second-Generation Effects

Teratogenicity

During pregnancy the aminoglycosides cross the placenta and they might theoretically be expected to cause otological and perhaps nephrological damage to the fetus. However, no proven cases of intrauterine damage by gentamicin have been recorded.

Susceptibility Factors

Age

In premature neonates, gentamicin clearance depends on gestational age, with a cut-off at 30 weeks: younger neonates have lower gentamicin clearance, a slightly higher volume of distribution, and a longer half-life compared with the older neonates (45). Loading doses of 3.7 and 3.5 mg/kg followed by maintenance doses of 2.8 mg/kg/day and 2.6 mg/kg/18 hours have been recommended for younger and older neonates respectively.

Drug Administration

Drug contamination

Several patients developed severe shaking chills, often accompanied by fever, tachycardia, and/or a significant reduction in systolic blood pressure within 3 hours of receiving intravenous once-daily dosing regimens of gentamicin produced by Fujisawa USA, Inc (Deerfield, Illinois). Investigations showed that gentamicin formulations that contain concentrations of endotoxin that are within the USP standards may deliver amounts of endotoxin that are above the threshold for pyrogenic reactions with once-daily dosing (46).

Of 155 patients (38% men, mean age 41 years) with pyrogenic reactions due to gentamicin, 81% received once-daily dosing (70% in a dose of 5–7 mg/kg) and 10% received a conventional dose (3 mg/kg in three divided doses (47)). Reactions typically occurred within 3 hours after infusion (98%) and lasted for less than 3 hours (96%). Patients reported chills, shaking, or shivering (75%), rigors (23%), fever (68%), tachycardia (17%), hypertension or hypotension (17%), and respiratory symptoms (47%). More serious reactions also occurred, including cyanosis (4%), oxygen saturation below 80% (7%), and pulmonary edema (one patient); 8% had severe reactions leading to hospitalization (with intubation, resuscitation, or admission to the intensive care unit in five cases), but none died. An FDA investigation showed that 10% of gentamicin lots tested had raised endotoxin concentrations, and an additional 4% of the lots would have exposed a patient to concentrations above the acceptable threshold with once-daily dosing. The two products implicated in these clusters involved the same supplier of bulk gentamicin; inadequacies in manufacturing practices had led to an increase in overall impurities (48,49).

Drug dosage regimens

Once-daily regimens are appealing for cost saving and may have a therapeutic advantage and reduced toxicity. A prolonged distribution time has been noted with high-dose gentamicin (7 mg/kg). Higher doses are used for extended-interval aminoglycoside therapy. In 12 healthy volunteers receiving extended-interval high-dose gentamicin, sampling within 90 minutes after the start of the infusion provided information that led to overestimation of peak serum concentration/minimum inhibitory concentration and inaccurate pharmacokinetic calculations (50).

Although once-daily dosing appears to be effective in limited studies in children, its role in Gram-positive coccal endocarditis, in individuals with neutropenia or cystic fibrosis, and in individuals with altered volumes of distribution remains uncertain (51).

In 18 patients receiving empirical therapy for CAPD-related peritonitis, once-daily intraperitoneal gentamicin (0.6 mg/kg) had less therapeutic benefit and peak serum gentamicin concentrations were lower than the suggested value of 4 μg/ml, whereas trough serum gentamicin

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concentrations were higher than the minimum toxic concentration; dialysate gentamicin concentrations were higher than therapeutic concentrations for only 4.75 hours of each day (52).

In 45 neonates (53) and 123 older children (54) gentamicin 4–5 mg/kg once a day produced peak concentrations associated with greater efficacy and trough concentrations associated with less toxicity than 2.0–2.5 mg/kg bd.

In febrile neutropenic episodes after intensive chemotherapy, once-daily gentamicin (7 mg/kg/day) in combination with azlocillin was more effective than a multiple-daily dosing regimen, but the incidence of toxicity was low overall and was slightly but not significantly higher in the once-daily group (55).

For external otitis, therapeutic local antibiotic concentrations can be achieved by giving gentamicin ear-drops twice daily; more frequent administration is not needed (56).

Drug administration route

Oral administration of gentamicin in low dosages to reduce the intestinal flora is rarely practiced, although it is probably as effective as neomycin. In the presence of intestinal mucosal inflammation more than 10% of the dose can be absorbed.

Endotracheal administration of gentamicin can be used in patients with a tracheotomy. This route of administration does not produce toxic plasma concentrations, but in patients with renal insufficiency the absorption of a certain amount via the respiratory tract should be taken into account.

Topical application of gentamicin to large areas of burns has caused ototoxic effects, ranging from mild to severe loss of hearing, with decrease of vestibular function (57). Positional vertigo occurred in one patient (58). In another case a woman complained of tinnitus each time she treated her paronychia with gentamicin cream (59).

Intrathecal gentamicin can cause neurotoxic lesions (60).

Increased penetration of gentamicin through a thin sclera can lead to toxic concentrations of the drug in a localized area adjacent to the site of injection, as has been shown in rabbits (61). These toxic effects are also influenced by the degree of pigmentation and acute inflammation. In a case of accidental injection of gentamicin 20 mg into the vitreous in a 70-year-old man during vitrectomy, no toxic signs occurred after the operation (62).

There is uncertainty about the risk of ototoxicity after the topical administration of aminoglycosides into the ear when the indication was appropriate (63,64). Nine cases of iatrogenic topical vestibulotoxicity have been reported (65). All had used ear-drops containing gentamicin sulfate and betamethasone sodium phosphate for prolonged periods. Toxicity was primarily vestibular rather than cochlear. Although compensation occurred in unilateral cases, the disability in bilateral cases was typically severe and often resulted in litigation.

Drug overdose

Although aminoglycoside antibiotics are dialysable, peritoneal dialysis may not remove them from the blood after overdosage. However, hemodialysis is effective (66).

Drug–Drug Interactions

Beta-lactam antibiotics

Gentamicin and other aminoglycosides have increased activity when they are combined with beta-lactams, resulting in increased bacterial aminoglycoside uptake (33). The proposed mechanism of synergism is damage to the cell membrane by the beta-lactam, followed by improved diffusion of gentamicin across the outer bacterial membrane. A second type of synergism, pharmacodynamic synergism, occurs when high serum concentrations of aminoglycosides cause efficient bacterial killing, resulting in reduced bacterial concentrations, which are more effectively eliminated by beta-lactams, as they work more efficiently against lower bacterial concentrations. The action of gentamicin is inhibited by some antimicrobials, which are bacteriostatic rather than bactericidal; for example antagonism occurs with macrolides, tetracycline and doxycycline, and chloramphenicol. The clinical significance of this antagonism is unknown.

There are many reports of acute renal insufficiency from combined treatment with gentamicin and one of the cephalosporins (67–69). The potential nephrotoxic effect of this combination seems to be related mainly to the nephrotoxic effect of gentamicin.

Methylthioninium chloride

Gentamicin is synergistic with methylthioninium chloride (methylene blue) in vitro against *P. aeruginosa* (70).

Metronidazole

In guinea-pigs, metronidazole augmented gentamicin-induced ototoxicity, determined by the measurement of compound action potentials (71).

NSAIDs

Aminoglycosides used in combination with non-steroidal anti-inflammatory drugs can be associated with renal insufficiency.

- An adolescent with cystic fibrosis developed renal insufficiency and severe vestibular toxicity after treatment with gentamicin and standard-dose ibuprofen (72). A low intravascular volume was a possible contributing factor.

Monitoring Therapy

During multiple-daily dosing regimens peak serum concentrations of gentamicin over 5–7 μg/ml are associated with improved survival in patients with septicemia and pneumonia caused by Gram-negative bacteria (73,74). On the other hand, excessive peak concentrations (over 10–12 μg/ml) and trough concentrations (over 2 μg/ml) of gentamicin increase the risk of ototoxicity and nephrotoxicity (75).

Salivary sampling is of potential interest in monitoring drug therapy, especially in children. Although there was no correlation between serum gentamicin concentrations and salivary concentrations when gentamicin was given

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two or three times daily in children with uncomplicated infections, there was a good correlation after once-daily dosing (76).

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Gentianaceae

See also Herbal medicines

General Information

The genera in the family of Gentianaceae (Table 1) include centaury and various types of gentian.

Gentiana species

Gentiana (gentian) root is mutagenic in bacteria, which is due to the xanthone derivatives, gentisin and isogentisin. In experimental animals *Gentiana olivieri* is

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Table 1 The genera of Gentianaceae

Bartonia (screwstem)
Centaurium (centaury)
Cicendia (cicendia)
Enicostema (whitehead)
Eustoma (prairie gentian)
Frasera (green gentian)
Gentiana (gentian)
Gentianella (dwarf gentian)
Gentianopsis (fringed gentian)
Halenia (spurred gentian)
Lisianthius (lisianthius)
Lomatogonium (lomatogonium)
Obolaria (obolaria)
Sabatia (rose gentian)
Schultesia (wingcup)
Swertia (felwort)
Voyria (ghostplant)

hypoglycemic, an effect that has been attributed to isoorientin, which is present in several species of *Gentiana* (1) and which also has antinociceptive and anti-inflammatory effects in animals (2). Some species of *Gentiana* inhibit monoamine oxidase (3) and acetylcholinesterase (4) in vitro.

Gentian violet is a purple dye that is obtained from coal tar; it is so called because its color resembles that of the flower and it has nothing to do with *Gentiana* species.

Swertia species

Swertia species (felwort) are mutagenic in bacteria, because of the several xanthone derivatives that it contains. The clinical relevance of this remains to be established. They also have hypoglycemic effects in animals (5).

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Germanium

General Information

Germanium is a metallic element (symbol Ge; atomic no. 32) that is found as the sulfide in the mineral argyrodite.

In several countries, organic or inorganic germanium has acquired a remarkable reputation in self-medication as a widely useful prophylactic and therapeutic agent, but with little scientific evidence to support it. Some germanium compounds, particularly spirogermanium, do have certain immunoregulatory activities, but germanium itself does not seem to play a role in this. There has been some attempt to use germanium in cancer chemotherapy. The unsupervised use of germanium-containing "health products" is of particular concern. Finally, there may be non-medicinal exposure, for example from some semiconductors.

Renal and other organ failure has been caused by germanium intoxication.

Organs and Systems

Nervous system

Nephropathy and neuropathy have been attributed to germanium toxicity (1).

- A 53-year-old man developed severe general weakness, anorexia, and weight loss (16 kg in 3 months). Over the preceding 17 months he had taken a total of 400 g of lysine germanium oxide in powder form. After 15 months he developed a tingling sensation in the palms and soles and weakness of the limbs, especially the legs. Neurological examination showed grade IV motor strength and negative deep tendon reflexes in the legs. Laboratory tests showed impaired renal function and anemia. Urinary concentration of beta$_2$-microglobulin was raised. The blood germanium concentration was 63 ng/ml and the urine concentration 2190 ng/l (normal less than 5 ng/ml). Renal sonography showed no morphological abnormalities. Nerve conduction studies and needle electromyography suggested a sensorimotor polyneuropathy, predominantly involving sensory nerves. Renal biopsy showed tubulointerstitial nephritis. Abstinence from germanium and conservative management of the chronic renal insufficiency resulted in slight improvement of the weakness and renal function.

Urinary tract

Occupational exposure to inorganic germanium compounds can cause slightly impaired renal function (2). However, severe nephrotoxic reactions have been described, and it has become clear that these can occur both with inorganic and organic germanium compounds (SEDA-21, 235).

A 58-year-old man developed nausea, vomiting, anorexia, and weight loss (3). He had taken germanium lactate citrate, illegally purchased in a pharmacy, recommended as a natural antioxidant, anticancer, and immunostimulatory remedy. He took a total dose of 426 g orally over

6 months and developed renal insufficiency and proteinuria, implying tubular damage. His serum TSH, fasting glucose, glycosylated haemoglobin, and C-peptide were increased. Abdominal ultrasound showed normal kidneys. Cardiac ultrasound showed a pericardial effusion. An electrocardiogram showed a sinus tachycardia. Nerve conduction studies and electromyography showed pathological spontaneous muscular activity and myotonic discharge. The neural conduction velocity was normal in the median nerve and delayed in the peroneal nerve. He received intravenous nutrition, insulin, and electrolytes. The pericardial effusion regressed but the sinus tachycardia continued. The renal dysfunction and the polyneuropathy persisted.

- A middle-aged woman who had taken germanium lactate-citrate for at least a year (with an estimated cumulative dose of 32.1 g of germanium) developed renal insufficiency with a creatinine clearance of 10 ml/minute, raised creatine kinase activity, and moderately raised liver enzymes. Biopsy showed highly vacuolated cytoplasm in the epithelial cells of the distal renal tubules and microvesicular and macrovesicular steatosis of centrilobular hepatocytes. After withdrawal of the germanium the laboratory values normalized but moderately severe renal impairment persisted (SEDA-16, 231).
- A 63-year-old man developed membranous glomerulonephritis after having taken 10–12 tablets of a germanium-containing ginseng formulation about 10 days before (4). He responded to diuretic treatment and was discharged in improved condition. However, on the day after discharge he restarted his intake of the formulation; over the next 14 days, his weight increased by 12 kg and he developed worsening edema and hypertension, despite an increase in the dosage of furosemide to 240 mg bd. He was re-admitted and given intravenous furosemide (240 mg every 8 hours). The nutritional supplements were withheld and after 48 hours diuresis took effect.

While other causes may have contributed in part to this man's poor response to furosemide, the facts strongly suggest that germanium played an important role in producing a diuretic-refractory renal dysfunction in this case.

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Ginkgoaceae

See also Herbal medicines

General Information

The family of Ginkgoaceae contains the single genus, *Ginkgo*, and a single species, *Ginkgo biloba*.

Ginkgo biloba

Ginkgo biloba (maidenhair tree, silver apricot) contains ginkgolides, which inhibit platelet-activating factor, reducing aggregability; this may contribute to bleeding disorders in patients taking *G. biloba*. *Ginkgo* has small beneficial effects in patients with intermittent claudication (1) and dementias (1,2).

Extracts from the leaves of *G. biloba* are marketed in some countries for the treatment of cerebral dysfunction and of intermittent claudication. In a review it was concluded that seven out of eight controlled trials of good quality showed positive effects of *G. biloba* compared with placebo on the following symptoms: memory difficulties, dizziness, tinnitus, headache, and emotional instability with anxiety (3). For intermittent claudication, the evidence for efficacy was judged unconvincing.

No serious adverse effects have been noted in any trial. However, *G. biloba* has been associated with gastrointestinal complaints, headache, and allergic skin reactions (SED-13, 538). Bleeding has been associated with chronic *G. biloba* ingestion because of its adverse effects on platelet aggregability, since the ginkgolide constituents of *G. biloba* inhibit platelet-activating factor.

Adverse effects

Ginkgo biloba has been associated with gastrointestinal complaints, headache, antiplatelet effects, and allergic skin reactions.

Nervous system

Ginkgo biloba can precipitate seizures in patients with well-controlled epilepsy (4).

- A 78-year-old man and an 84-year-old woman with previously well-controlled epilepsy presented with recurrent seizures (4). There were no obvious reasons for these events, and the investigator suspected self-medication with *G. biloba* extracts. Both patients had started taking *G. biloba* within 2 weeks of the start of the seizures. The herbal remedy was withdrawn and both patients remained seizure-free several months later. No other change of medication was made.

The author postulated that 4-0-methylpyridoxine, a constituent of *G. biloba* and a known neurotoxin, had caused the seizures.

Hematologic

Ginkgo biloba has well-documented antiplatelet effects, and bleeding complications can occur, including strokes.

- A 59-year-old man developed bleeding complications after liver transplantation while taking *G. biloba* supplements (5). Postoperatively, he developed large hematomas in the subphrenic space and near the porta hepatis. They were drained and his hematocrit fell to 21%. Three weeks later he complained of blurring in the right eye, and a vitreous hemorrhage was diagnosed. He then admitted to taking an unknown amount of *G. biloba*, which was withdrawn. Subsequently, no further bleeding episodes occurred.
- A 78-year-old man developed progressive right-sided muscular weakness after a fall (6). A CT scan showed a subdural hematoma. He had taken 150 mg of *G. biloba* extract.
- A 56-year-old man had a stroke without apparent risk factors (7). A CT scan confirmed a right parietal hematoma. He had not taken any medications, except for a *G. biloba* extract (3 × 40 mg/day) which he had started 18 months before.
- A 34-year-old woman had a laparoscopic cholecystectomy and started bleeding into the surgical wound postoperatively (8). This led to a fall in hemoglobin from 16.5 to 12.4 g/dl. She was given blood transfusions and recovered uneventfully.
- Hyphema led to temporarily impaired vision in a man who had taken *G. biloba* for 2 weeks; no other cause was found; the lesion regressed after withdrawal and did not recur (9).
- A spontaneous cerebellar bleed occurred in a man who had taken *G. biloba* (10).

In each case the authors believed that self-medication with *G. biloba* had caused the bleeding through its effect on platelets. In some cases another factor that implicated the extract was the absence of recurrence after withdrawal, although this is a weak argument.

Spontaneous bilateral subdural hematomas and increased bleeding time have been associated with chronic ingestion of *G. biloba* (120 mg/day for 2 years) (11).

Skin

- A 40-year-old Afro-American woman developed an exfoliative rash and blistering and swelling of the tongue (12). A diagnosis of Stevens–Johnson syndrome was made. She had not taken any medications other than two doses of a formulation that contained *G. biloba*. Her condition responded to treatment with prednisolone, clotrimazole, and famotidine. *G. biloba* was withdrawn and no further events occurred. However, 5 months later she still had tenderness in the soles of the feet, peeling of the nails, and discoloration of the skin.

Formulations

Subarachnoid hemorrhage associated with *G. biloba* (13) stimulated a vigorous discussion on the differences between the usual extract sold over the counter and a ginkgolide mixture, and their respective (absence of) effects on platelet-aggregating factor and bleeding time (14,15). The dispute points to confusion that can arise when formulations of similar origin but with variable composition are available.

Drug overdose

Acute poisoning with *G. biloba* seeds is occasionally seen in East Asian countries.

- A 36-year-old woman, without any past or family history of epilepsy, developed frequent vomiting and generalized convulsions about 4 hours after taking about 70–80 ginkgo nuts, seeds of *G. biloba*, in an attempt to improve her health (16).
- A 2-year-old girl was admitted with vomiting, diarrhea, and irritability a few hours after eating a large quantity of *G. biloba* seeds and then developed an afebrile generalized clonic seizure (17). Her serum concentration of 4-methoxypyridoxine, the putative toxic agent in the seed, was extremely high at 360 ng/ml.

Administration of pyridoxal phosphate, a competitive antagonist of 4-methoxypyridoxine, which inhibits the formation of gamma-aminobutyric acid (GABA), prevented further seizures in this case.

Drug interactions

Because of its antiplatelet activity *G. biloba* can interact with anticoagulants.

- A 78-year-old woman who had taken warfarin for 5 years, took *G. biloba* for 2 months, when she developed signs of a stroke, diagnosed as intracerebral hemorrhage (13).

Even though it is impossible to establish causality in this case, it is conceivable that the stroke was the result of over-anticoagulation induced by the herbal medication (11).

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Glafenine

See also Non-steroidal anti-inflammatory drugs

General Information

Glafenine, an anthranilic acid derivative, has been withdrawn in much of the world (1). Until 1991 it was sold in about 70 countries (although never marketed or accepted in others), despite a long history of severe reactions (particularly anaphylaxis, fatal hepatotoxicity, and nephrotoxicity, even with normal doses). As late as 1989 the EC Committee on Proprietary Medicinal Products (CPMP) astonishingly recommended keeping glafenine on the market but controlling its distribution and monitoring adverse effects more closely (2). Firm restrictions or prohibitions nevertheless preceded or followed this recommendation in several European countries, and the CPMP finally condemned glafenine early in 1992. See also floctafenine.

Organs and Systems

Cardiovascular

A rise in blood pressure coupled with renal adverse effects has been reported. Coronary artery spasm leading to myocardial infarction was described as part of an allergic reaction with Quincke's edema (SED-11, 190) (3).

Hematologic

Acute hemolytic anemia, probably as part of an allergic reaction (SED-9, 154) (4,5), leukopenia through an unknown mechanism, and thrombocytopenic purpura with hemorrhage have been documented (6).

Liver

Liver injury has repeatedly been described in patients taking glafenine (SEDA-4, 69) (SEDA-5, 106), with fatal hepatotoxicity as part of a general toxic reaction in several cases (7). Glafenine-associated hepatic injury is characterized by a high prevalence of jaundice, a high death rate, and a predominantly hepatocellular histological pattern of liver lesions, varying from spotty panlobular, centrilobular, and submassive necrosis (acute pattern) to fibrosis and cirrhosis (chronic pattern) (8).

Biliary tract

Gallstones containing glafenic acid have been reported in a patient taking long-term therapy (SEDA-14, 95).

Urinary tract

Many nephrotoxic features have been observed in preclinical and clinical studies of glafenine in therapeutic doses and more especially in overdosage (SEDA-4, 69). Acute oliguria, anuria, increased blood urea and creatinine, proteinuria, and raised blood pressure have been repeatedly reported. Glafenine stones have been documented in five patients (9).

Musculoskeletal

Symptoms of rhabdomyolysis, associated with other disorders, occurred in two patients a few hours after glafenine (10).

Immunologic

Although rash has sometimes occurred (11), hypersensitivity reactions have been much more serious. Many acute anaphylactic reactions have been observed (SEDA-4, 69) (SEDA-6, 98) (12,13), with shock in more than 50% of cases; it was recorded in 24 of 1517 reports on the drug collected by the Pharmacovigilance Unit in Lyons, France (11). Occasional isolated fever, confirmed by rechallenge (14), is probably also of hypersensitive origin. Interstitial nephritis, hepatitis, and pulmonary hypersensitivity have been reported.

Drug–Drug Interactions

Methotrexate

An interaction of glafenine with methotrexate has been described in a patient with rheumatoid arthritis (SEDA-14, 95).

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Glaucine

General Information

Glaucine is a non-narcotic antitussive agent. The D-isomer of glaucine is an alkaloid from *Glaucium flavum Crantz*, a species of Papaveraceae. It is better tolerated in doses claimed to be equieffective with codeine. Glaucine (30 mg capsules 3 times daily for 28 days) caused mild constipation in five patients (1).

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Glucagon

General Information

Glucagon, which is produced in the alpha cells of the islets of Langerhans, is used in diabetes mellitus type 1 to stimulate glucose output from the liver during hypoglycemia (1 mg subcutaneously, repeated once or twice) when glucose cannot be given intravenously. In some countries it is often used by personnel, such as family members, who are not medically qualified, as the first action when the patient cannot take sugar orally. The antihypoglycemic effect of an intramuscular injection is longer lasting and more potent than that of intravenous glucagon (1). It is sometimes given by infusion to treat chronic hypoglycemia. However, when there is insulin reserve in the pancreas, glucagon induces hypoglycemia by stimulating insulin release (2).

Glucagon has also been used to stimulate insulin and C-peptide secretion, to see whether the islets still produce insulin, as a stimulatory test during pheochromocytoma, hyperinsulinism, and Zollinger–Ellison syndrome, or as an additive in upper gastrointestinal X-ray investigations (0.5–1 mg). It has been used in myocardial infarction, although its inotropic effects may present a risk. It has also been used to treat overdoses with beta-blockers (3) and calcium channel blockers (4), although its efficacy in such cases has only been demonstrated in animals (5) and to treat overdose with tricyclic antidepressants (6,7).

During long-term administration glucagon can cause the same effects as a glucagonoma: hyperglycemia, necrolytic migratory erythema, weight loss, anemia, angular cheilitis, and venous thrombosis (8).

Organs and Systems

Cardiovascular

Glucagon has been reported to have caused myocardial ischemia (9).

Metabolism

When there is insulin reserve in the pancreas, glucagon can cause hypoglycemia by stimulating insulin secretion.

Electrolyte balance

Hyponatremia can occur during long-term administration of glucagon (10).

Hematologic

Thrombocytopenia can occur during long-term administration of glucagon (10).

Gastrointestinal

Glucagon can cause nausea, vomiting, and diarrhea (11).

Skin

Chronic administration of glucagon can cause an eczema-like maculopapular scaly rash, which can progress to necrolytic migratory erythema, as in glucagonoma (8,12,13). Erythema multiforme has also been reported (14).

Glucagon, used to treat persistent hyperinsulinemic hypoglycemia of infancy, caused erythema necrolyticum migrans in two neonates (15).

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- In the first child, a monozygotic twin girl, delivered at 30 weeks, diazoxide, chlorothiazide, and nifedipine did not alter glucose requirements, but octreotide halved the need, and intravenous glucagon lowered it further. However, the child then developed a maculopapular rash on the face and trunk. After 4 weeks the lesions worsened, increased in size, and became superficially necrosed with thick-caked scales. The rash also involved the limbs and mucous membranes, making feeding almost impossible. When glucagon was withdrawn the skin lesions resolved from the center within 2 days and disappeared without scarring in 10 days.
- The second child, who was delivered at term, had a blood glucose of 0.8 mmol/l 6 hours after birth and suffered a seizure that was treated with subcutaneous glucagon, octreotide, and other drugs. It was impossible to give sufficient feeding, and notwithstanding subcutaneous glucagon 11 micrograms/kg/hour and octreotide 4.3 micrograms/kg/hour, she had a generalized seizure when the blood glucose was 1.4 mmol/l. At 6 months, subtotal pancreatectomy was performed. During glucagon therapy she had seborrheic skin with silvery scales and on the thoracic skin an area of pale lichenification with mild hyperkeratosis. Within 2 weeks after surgery (and withdrawal of glucagon) the skin became totally normal.

Susceptibility Factors

Age

Hypoglycemia often occurs in premature children and can usually be treated by intravenous glucose. For intractable hypoglycemia an infusion of glucagon can be used. However, it can cause thrombocytopenia and hyponatremia with convulsions (10).

- A female triplet was born at 35 weeks by cesarean section after a normal pregnancy, during which her mother had had normal glucose tolerance. At 2 hours the baby's serum glucose was 1.0 mmol/l. Intravenous glucose was not effective. At 36 hours, dexamethasone was added, but 24 hours later her blood glucose was below 2.0 mmol/l. Dexamethasone was withdrawn and glucagon 1 mg/day was added to the infusion. After 4 hours the blood glucose became stable at 4.0 mmol/l. Her serum sodium fell from 138 to 116 mmol/l at about 120 hours, her potassium rose to 7.6 mmol/l, and her platelet count fell to 13×10^9/l. The glucagon infusion was stopped and within 24 hours her sodium and platelets normalized.

Glucagon infusion in premature babies is risky; more information is necessary.

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Glucagon-like peptide-1

General Information

Glucagon-like peptide-1 is an intestinal hormone that increases insulin secretion and biosynthesis, has a trophic effect on beta cells, suppresses glucagon secretion, delays gastric emptying, increases satiety, and reduces food intake (1). Its effects are glucose-dependent and it should not cause hypoglycemia. However, in healthy subjects hypoglycemia can occur after high doses or after fasting.

Although it is a candidate for the treatment of type 2 diabetes, it has to be injected and is extremely rapidly degraded by dipeptidyl peptidase IV. Analogues that are resistant to degradation and inhibitors of the degrading enzyme are being investigated.

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In a randomized, crossover study with glucagon-like peptide-1, metformin, or the combination, there were no differences between the monotherapies (2). The combination had additive effects in lowering blood glucose and tended to reduce appetite.

In a crossover study, 20 patients with type 2 diabetes were treated for 6 weeks with glucagon-like peptide-1 or saline added to continuous subcutaneous insulin infusion; glucagon-like peptide-1 reduced appetite and caused nausea and reduced well-being (3).

In healthy volunteers, a fatty acid derivative of glucagon-like peptide-1, NN2211, which binds to albumin and has a half-life of about 12 hours, caused more dizziness, headache, nausea, and vomiting than placebo (4,5).

Organs and Systems

Metabolism

In a double-blind, randomized, crossover study in 10 healthy subjects, subcutaneous glucagon-like peptide-1 after a 16-hour fast caused a near five-fold rise in plasma insulin concentration and circulating plasma glucose concentrations fell below the reference range in all subjects (6). One subject had symptoms of hypoglycemia. A rise in pulse rate correlated with the fall in plasma glucose concentration and there was an increase in blood pressure.

In eight patients with type 2 diabetes and seven matched non-diabetics, subcutaneous glucagon-like peptide-1 and intravenous glucose caused reactive hypoglycemia in five controls but not in the patients (7). Glucagon was suppressed.

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Glucametacin

General Information

Glucametacin is a glucosamide derivative of indometacin, with no advantages over indometacin and the same pattern of adverse effects, the most common of which are nausea and heartburn (1).

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Glues

General Information

Hair bonds and hair extensions are being increasingly used both as cosmetic hair alterations and in localized or diffuse alopecia. The commercial glues used to affix the exogenous hair are gelatinous liquids that contain pigments, antioxidants, and natural latex.

Organs and Systems

Immunologic

Two patients developed severe type I allergic reactions to a hair bond.

- A 37-year-old atopic patient had generalized pruritus, diffuse urticaria, angioedema, rhinoconjunctivitis, and tachycardia within minutes of having glued a hair bond to her scalp. Skin tests with the glue (diluted 1:10 000 in saline) were positive, as was an IgE RAST on latex proteins (1).
- A 40-year-old woman noted palmar irritation, followed by generalized pruritus, a feeling of faintness, facial edema, and difficulty in breathing. A latex skin prick test was positive (2).

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Glutaral

See also Disinfectants and antiseptics

General Information

Aldehydes such as glutaral, formaldehyde, and glyoxal are used as solutions and vapors for disinfection and sterilization.

The safety and biocidal efficacy of glutaral has led to its endorsement by the CDC and WHO as a substitute for formaldehyde in high-level disinfection and cold sterilization (1,2). Glutaral is used in a 2% aqueous solution buffered to a pH of about 8 for sterilization of endoscopic and dental equipment and for other equipment that cannot be sterilized by heat.

Occupational safety considerations for glutaral largely relate to its volatility, and stringent precautions in handling are especially needed in tropical climates (3). The lack of precautionary details for glutaral fumes, especially in warm climates is inadequate. Manufacturers should provide details of possible adverse effects that could arise from glutaral vapor, and of the precautions that should be taken to keep the air concentration below the recommended limit. The odor threshold for glutaral vapor is about 0.04 ppm, the irritation threshold about 0.3 ppm, and the recommended Ceiling Threshold Limit Value 0.2 ppm. It should not be exceeded at any time during the working day (4–6). It is likely that glutaral vapor will be smelt before reaching overexposure concentration, but there is an urgent need to develop affordable and effective methods of containing glutaral fumes.

Of 169 nurses working in 17 hospitals, especially in endoscope units, 68% had symptoms, 38% two or more. The major complaints were eye irritation in 49%, skin discoloration or irritation in 41%, and cough or shortness of breath in 34% (7). Complaints were not related to habits, atopic status, or duration of exposure. In two hospitals, the time-weighted average concentrations were estimated. The 10-minute time-weighted average was below the UK occupational exposure standard of 0.2 ppm. In a similar survey of 150 staff in two Middlesex hospitals who were exposed to glutaral, the rate of complaints was in the same range (8).

Organs and Systems

Cardiovascular

Nine of 184 implantations of glutaral-preserved mitral valves became incompetent (9). This incidence of dehiscence substantially exceeded that previously noted with synthetic valves, and the authors suggested that incomplete removal of glutaral from the prosthesis might have contributed to failure of healing. Collagen ultrastructure investigations of glutaral-treated porcine aortic valve tissue showed that the long-term mechanical durability of treated aortic valves can be substantially increased if careful consideration is given to the pressure at which initial fixation of glutaral is carried out.

Respiratory

Nurses working in endoscopy units complained of respiratory symptoms on exposure to glutaral (10). The provocation test was positive in two of these patients.

Sensory systems

The eye is particularly sensitive to glutaral. The threshold for conjunctival irritation is 0.2–0.5% and for corneal injury 0.5–1.0%. At 2%, eye injury is moderate, whereas at 5% and above it is severe (6,11). In one case, acute eye injury was caused by a leakage of retained glutaral in an anesthesia mask (SEDA-13, 648).

Gastrointestinal

Residues of glutaral in endoscopes can cause significant mucosal injury resulting in acute colitis within 12–48 hours. Symptoms include hematochezia, fever, and tenesmus. Histological findings in biopsy specimens are similar to those of ischemic colitis, with crypt dilatation followed by epithelial cell dropout and subsequent acute inflammation. It cannot be diagnosed by histological analysis alone (12,13). Distinct from the type of colitis that is caused by hydrogen peroxide, the detrimental effects of glutaral are not immediately recognizable during the endoscopic examination. It does not cause raised white mucosal plaques (“pseudolipomatosis”) (13).

Colitis was observed during endoscopy of the lower gastrointestinal tract in 21 patients (14). Some patients developed rectal bleeding, tenesmus, and increased frequency of stools, lasting 12 days.

The histological findings in 12 patients with suspected glutaral-induced hemorrhagic colitis were similar to those in rats after colonic instillation of the sterilizing solution (15).

Skin

Solutions of glutaral can cause skin irritation. With sustained contact under occlusion or on sensitive skin, the threshold for producing irritation is 0.2–0.5% (6). However, concentrations up to 5% may not be irritant if applied only briefly to non-occluded skin. The site of skin contact, the length of contact time, and whether the area is occluded are factors that determine the likelihood and severity of irritation.

A few people develop allergic contact dermatitis to glutaral (SEDA-11, 478) (SEDA-12, 572) (6,16).

Immunologic

Aldehydes are irritating and sensitizing and cause contact dermatitis in health-care workers (SEDA-21, 254). The incidence of allergy to aldehydes has been examined in 280 health-care workers with skin lesions (17). Allergy was diagnosed in 64 (23%). Most (86%) were sensitive to only one aldehyde. Formaldehyde caused allergy slightly more often (14%) than glutaral (12%). Only 5 (1.9%) were sensitive to glyoxal. This

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hierarchy of sensitivity was also confirmed in animal testing.

Anaphylaxis occurred in a woman after the fourth intramuscular injection of a glutaral-containing pollen formulation (SEDA-11, 478) (18).

Drug Administration

Drug overdose

The symptoms of overexposure to glutaral vapor include watery and/or burning eyes, nose and throat irritation, and some respiratory discomfort. Glutaral also causes asthma-like symptoms in a few hypersensitive individuals. However, in none of these cases was there evidence that an immune-mediated process was present; these cases probably represent bronchial hyper-reactivity rather than respiratory sensitization (6).

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Glycerol

General Information

Glycerol is a colorless syrupy liquid that is used medically as a laxative given orally, as an enema, or in the form of suppositories. Oral hypertonic glycerol has been used as a test for reversibility of the symptoms of Menière's disease (1); however, it causes headache, nausea, and vomiting and is of poor sensitivity and specificity.

Intravenous glycerol has been given to reduce cerebral edema and hence reduce intracranial pressure.

Iodinated glycerol is used as a mucolytic agent in respiratory disorders. Organically bound iodine is changed to unbound iodide after absorption. Iodide inhibits the binding of iodine to the tyrosine residue of the thyroglobulin molecule, inhibiting the synthesis of thyroxine and triiodothyronine. In patients with iodide-induced goiter, there is increased iodine transport, further reducing thyroid hormone synthesis and causing thyroid hyperplasia (2).

Glycerol has been injected into nerve ganglia to destroy them. In 139 patients, 260 consecutive retrogasserian glycerol rhizotomies for trigeminal neuralgia were retrospectively analysed for technical surgical difficulties and immediate and early complications (3). There were technical obstacles in 47%. In 21 cases, the surgical procedure had to be interrupted because of vasovagal reactions, cardiac arrest, or difficulty in finding the trigeminal cistern. There were either transient or persistent complications in 67%, in most cases mild sensory defects. Other complications included labial herpes (3.8%), anesthesia dolorosa (0.8%), moderately or severely impaired sensation (19%), dysesthesia (23%), chemical meningitis (1.5%), and infectious meningitis (1.5%). In five patients hearing was affected, including deterioration of pre-existing tinnitus in one case. Although the frequency of surgical difficulties was high, success was hampered only in a few procedures.

Organs and Systems

Nervous system

In 122 patients with trigeminal neuralgia who underwent percutaneous retrogasserian glycerol injection (4), complications associated with the treatment were

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significant: 63% had marked hyperesthesia of the face and 29% unpleasant dysesthesias, including two cases of anesthesia dolorosa. Sensory disturbances were most frequent in patients who had previously undergone an alcohol block procedure. Because of the high rates of recurrence and sensory disturbances, the authors preferred microvascular decompression for the management of trigeminal neuralgia. In a study of glycerol injection in trigeminal neuralgia, paresthesia and dysesthesia were reported (5).

Rotatory vertigo with vertical nystagmus has been attributed to glycerol (6).

Sensory systems

Temporary loss of hearing has been reported after the oral administration of hypertonic glycerol in the diagnosis of Menière's disease (7).

Endocrine

Reversible hypothyroidism has been reported in nursing-home residents without a history of thyroid disease, who had been taking iodinated glycerol as an expectorant (8). Hypothyroidism has been reported after long-term treatment with iodinated glycerol (9).

Metabolism

Glycerol can increase plasma insulin concentrations and thereby worsen diabetes; it can particularly cause hyperosmolar non-ketotic hyperglycemia in patients with type 2 diabetes (10,11).

Fluid balance

Large oral doses of glycerol can cause severe derangements of water balance, which can be dangerous in patients in poor physical condition.

Hematologic

Intravascular hemolysis occurred during intravenous glycerol therapy in patients with acute stroke (12).

Gastrointestinal

Oral glycerol can cause nausea and vomiting (SEDA-20, 440) and less commonly diarrhea. Rectal administration can cause mucosal erosion.

Skin

Moisturizing creams have beneficial effects in the treatment of dry, scaly skin, but they can cause adverse skin reactions. In a double-blind, randomized study, 197 patients with atopic dermatitis, none of whom had known allergy to ingredients in the test creams, were randomized to one of three creams: 20% glycerol (55 women and 13 men, mean age 35 years), 4% urea plus 4% sodium chloride (47 women and 16 men, mean age 32 years), and vehicle (49 women and 17 men, mean age 34 years); they were asked to apply the cream at least once daily for 30 days (13). After 2 weeks the patients were asked to score the degree of smarting sensation (a sharp, local, superficial effect), stinging, itching, and dryness/irritation on a five-point scale (0–4). They were also asked to note skin dryness at the beginning of the study and after 1 month on a visual analogue scale. A dermatologist assessed dry skin at the start and after 30 days using the product of the sum of severity scores and area affected in four body regions (14). Adverse skin reactions such as smarting were significantly less common among patients who used the 20% glycerol cream (10%) compared with the urea + saline cream (24%). There were no differences in other skin reactions, such as stinging, itching, and dryness/irritation.

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Glycine

General Information

Glycine is an amino acid that is often used during transurethral prostatectomy for bladder irrigation, sometimes continuously for 24 hours after surgery.

Transurethral resection syndrome

Systemic absorption of the fluid used for bladder irrigation during transurethral resection of the prostate can cause a variety of disturbances of the circulatory and nervous systems, which are often referred to as the transurethral resection syndrome. The lack of a consistent definition and varying degrees of awareness of mild forms of this complication probably explain the different figures given for the incidence of the syndrome in prospective studies, varying from 2 to 10% of all transurethral resections performed. Many urologists claim they have not encountered the transurethral resection syndrome for many years (1–3). However, the incidence and severity of symptoms of the transurethral resection syndrome on absorption of increasing volumes of glycine solution have been described (4).

The signs and symptoms of the transurethral resection syndrome were evaluated and recorded during and after 273 transurethral prostatic resections performed at two hospitals between 1984 and 1993. Glycine solution was used as the irrigant and ethanol served as a tracer for fluid absorption. The incidence and severity of symptoms that could possibly be related to the syndrome increased progressively as more glycine solution was absorbed. Patients who absorbed up to 300 ml of glycine solution had an average of 1.3 such symptoms. This number increased to 2.3 when 1000–2000 ml were absorbed, 3.1 when 2000–3000 ml were absorbed, and 5.8 for volumes greater than 3000 ml. Nausea and vomiting occurred significantly more often when 1000–2000 ml were absorbed compared with no absorption. Confusion and arterial hypotension were other prominent signs of fluid absorption, whereas hypertension was not. The severity of symptoms was markedly aggravated when more than 3000 ml were absorbed. Extravasation resulted in higher risks of bradycardia, hypotension, and failed spontaneous diuresis postoperatively than absorption by the intravascular route.

Nausea after glycine irrigation can be partly explained by toxic effects of glycine and its secondary metabolites in addition to the effects of water intoxication and hyponatremia (5).

The fact that glycine can act as an inhibitory neurotransmitter may explain why absorption of glycine-containing irrigating fluid from the pelvic cavity or directly into the blood during transurethral prostate resection has been linked to loss of sight and vivid postoperative hallucinations (6). Ammonia production due to accumulation of glycine in tissues, and the mentioned neuroinhibitory effects of glycine should be considered risk factors when deciding on glycine as an irrigating fluid (7).

Rapid and massive fluid absorption due to leakage of fluid into the peritoneal cavity has also been reported during percutaneous nephrolithotomy (8).

It has been recommended that glycine irrigation should be confined to the time of operation, and an adequate diuresis should be ensured postoperatively (9).

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Glycols

General Information

Glycols are aliphatic dihydric alcohols. Primary and secondary glycols are thick liquids, and tertiary glycols (pinacones) are crystalline solids. The principal glycols to which people are or have been exposed, either occupationally or in medicinal products, are:

- Diethylene glycol $HO.CH_2.CH_2.O.CH_2.CH_2.OH$
- Ethylene glycol $HO.CH_2.CH_2.OH$
- Ethyl glycol (ethylene glycol monoethyl ether) $C_2H_5.O.CH_2.CH_2.OH$
- Methyl glycol (ethylene glycol monomethyl ether) $CH_3.O.CH_2.CH_2.OH$
- Polyethylene glycol $HO.CH_2.(CH_2.O.CH_2)_nCH_2OH$
- Propylene glycol $CH_3CH(OH)CH_2OH$.

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Diethylene glycol

Diethylene glycol is important in the history of adverse drug reactions.

The first major drug catastrophe in the 20th-century history of the public control of drugs occurred in 1937 in the USA and involved diethylene glycol. A pharmacist introduced a drug, Elixir Sulfanilamide, that consisted of sulfanilamide dissolved in diethylene glycol. It had been tested for flavor, appearance, and fragrance, but not for safety. After taking the drug, over 100 patients died in severe pain; many were children, who were given Elixir Sulfanilamide for sore throats and coughs. Public outrage created support for proposed legislation to reinforce the public control of drugs that was pending in the US Congress (1). And so, the US 1938 Food, Drug, and Cosmetic Act came into being, and is still the country's legal foundation for the public control of drugs and devices intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals. It has been a model for similar legislation in many other countries.

The 1938 Food, Drug, and Cosmetic Act prohibited traffic in new drugs, unless they were safe for use under the conditions of use prescribed on their labels. The Act also explicitly required the labelling of drug products with adequate directions for use.

The burden of proof of harm of new drugs was laid on the Federal Food and Drug Agency (FDA). Companies that wanted to manufacture and sell new drugs in interstate commerce had to investigate their safety and report to the FDA. Unless the FDA, within a specified period of time, found that the safety of a drug had not been established, the company could proceed with its marketing. The FDA was also authorized to remove from the market any drug it could prove to be unsafe (2).

The US Supreme Court also established in 1941, in a legal case over drug adulteration, that responsible individuals in a company can be held personally accountable for the quality of the products manufactured by the company, and that distributors of pharmaceuticals are responsible for the quality of their products, even if they are manufactured elsewhere (3).

After the World War II, the pharmaceuticals market changed radically, as many companies started industrial production of drugs that had previously been manufactured in pharmacies. Announcements of new industrially produced drugs were hailed as part of technological advancement, as significant a sign of progress as the launching of satellites and putting a man on the moon. However, public safeguards against the risks of drugs remained unchanged in most countries. Thus, control of the effects of drugs largely lay in the hands of the manufacturers, even though the responsibility for taking precautions rested with pharmacists and doctors.

Diethylene glycol has been reported to cause acidosis and renal insufficiency (SEDA-19, 446).

Ethylene glycol, ethylene glycol monoethyl ether, and ethylene monomethyl ether

Ethylene glycol is a colorless, sweet-tasting liquid that is used as an anti-freeze, in the manufacture of polyester fibers and films, as a heat-transfer fluid, in aircraft and runway de-icing mixtures, to provide freeze-thaw stabilization to latex coatings, to improve the flexibility and drying time of paints, as a dehydrating agent in natural gas, in motor oil additives, as an additive in inks, pesticides, wood stains, and adhesives, and as a solvent and suspending medium for ammonium perborate, the conductor in most electrolytic capacitors. The monoethyl ether of ethylene glycol, 2-ethoxyethanol or ethyl glycol, has been used as an excipient in some drug formulations, in the semiconductor industry, in duplicating fluids, epoxy resins, lacquers, paints, printing inks, varnish removers, and wood stains. The monomethyl ether of ethylene glycol, 2-methoxyethanol or methyl glycol, is used as a jet fuel de-icer and as a solvent for cellulose acetate, dyes, enamels, nail polishes, resins, varnishes, and wood stains.

In one study, occupational exposure to ethylene glycol was not associated with adverse effects (4). However, other adverse effects of occupational exposure have been noted, including anemia, subfertility, and renal stones.

Ethylene glycol is sometimes used in suicide attempts. It is not itself toxic, but is converted to toxic metabolites. Conversion to glycoaldehyde by alcohol dehydrogenase is the rate-limiting step, and further metabolism yields glycolate, glyoxylate, and oxalate.

Polyethylene glycol

Polyethylene glycol is a high molecular weight inert molecule that is commonly combined with electrolytes (potassium chloride, sodium bicarbonate, sodium chloride, and sodium sulfate) in colonic lavage systems. Owing to the osmotic properties of these solutions, there is little absorption or secretion of electrolytes or water, although small amounts of polyethylene glycol and sulfates have been detected in the urine of healthy patients and higher concentrations in the urine of patients with inflammatory bowel disease (5). Common adverse effects of solutions containing polyethylene glycol and electrolytes include nausea, abdominal fullness, and bloating in up to 50% of patients. These solutions are contraindicated in patients with gastric outlet obstruction or gastroparesis, gastrointestinal obstruction or perforation, ileus, or toxic colitis (6).

Polyethylene glycol (PEG) is also used to convert certain compounds of relatively high molecular weights to more soluble products, known as pegylated derivatives. Such compounds include pegylated interferons and interleukins. The safety and activity of outpatient-based continuous intravenous interleukin-2 (IL-2) or a modified-release pegylated IL-2 have been studied in 115 HIV-positive patients with CD4 cell counts of 200–500 $\times$ 10^6/l randomized to antiretroviral therapy plus cyclical continuous intravenous IL-2 ($n = 27$), subcutaneous pegylated IL-2 ($n = 58$), or no IL-2 ($n = 30$) (7). The termination rates due to adverse events were 4% with continuous intravenous IL-2 and 7% with pegylated IL-2. The frequency and severity of grade 3 and 4 adverse events were similar in both IL-2 groups, with the exception of local erythema and induration associated with subcutaneous injections of pegylated IL-2. Fever, fatigue,

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stomatitis, erythema, gastrointestinal symptoms, and mood alterations constituted the majority of clinically significant toxic effects. Most of the adverse events resolved by 8–15 days of each cycle. There were several unusual adverse effects of IL-2 that were not dose-related. These included worsening of pre-existing diarrhea, cardiomyopathy in a patient with a history of heroin abuse, and attempted suicide in a patient with a psychiatric history.

In 68 patients randomly assigned to receive either sulfate-free polyethylene glycol electrolyte lavage or sodium picosulfate plus magnesium sulfate, the day before colonoscopy, bowel cleansing was significantly better with picosulfate plus magnesium sulfate (8). Adverse effects were more common with polyethylene glycol electrolyte lavage, especially nausea, vomiting, and palpitation, and four patients did not complete treatment owing to adverse effects.

Propylene glycol

Propylene glycol is widely used as a solvent in topical glucocorticoids, other medicines (including diazepam, etomidate, and lorazepam), foodstuffs, cosmetics, household detergents, paints, and brake fluids.

Organs and Systems

Respiratory

Polyethylene glycol has reportedly caused fulminant pulmonary edema (9).

Nervous system

Polyethylene glycol has reportedly caused seizures (SEDA-20, 440).

Metabolism

Lactic acidosis and convulsions have been associated with the use of propylene glycol (SEDA-15, 537) and polyethylene glycol, the latter after the administration of a high dose of lorazepam (10).

Hematologic

Propylene glycol causes acute hemolysis with raised lactate dehydrogenase activity, and raised bilirubin and plasma hemoglobin concentrations after use of a stock solution during intravenous administration of glyceryl trinitrate (11).

In 53 impregnation workers from two factories making copper-clad laminate with ethylene glycol monomethyl ether as a solvent and 121 lamination workers with indirect exposure, hemoglobin, packed cell volume, and erythrocyte count in the exposed workers were significantly lower than in the controls, and the frequency of anemia was significantly higher (26 versus 3.2%); there was no difference in spermatogenesis (12).

Pancreas

Severe acute pancreatitis has been reported in a 75-year-old woman who had been given polyethylene glycol 4 litre rectally (13).

Urinary tract

In silkscreen printers exposed to glycol ethers, the excretion of calcium increased according to the urinary alkoxyacetic acid load. The excretion of ammonia and chloride was higher among exposed workers than among controls. The tendency to form urinary stones was 2.4 times higher among silkscreen printers than among office workers (14).

However, in 33 aviation workers exposed to de-icing fluid containing ethylene glycol there was no evidence of acute or chronic kidney damage that could be attributed to working in the presence of ethylene glycol (15).

Polyethylene glycol has been associated with raised creatinine concentrations in eight patients who were given a continuous intravenous infusion of lorazepam (range 2–28 mg/hour) (16).

- A 57-year-old man with a history of alcohol abuse developed acute respiratory failure and was given lorazepam up to 18 mg/hour during alcohol withdrawal (17). On day 43 (cumulative intravenous lorazepam dose 4089 mg, containing about 220 ml of polyethylene glycol 400), he developed oliguric acute tubular necrosis with proteinuria and granular casts.

The authors attributed the renal damage to polyethylene glycol, perhaps enhanced by concurrent administration of vancomycin.

Skin

Contact dermatitis has been reported after exposure to glue containing 25% 2-hydroxyethyl methacrylate and 0.4% ethylene glycol dimethacrylate (18).

Propylene glycol has also been reported to cause contact dermatitis (19–24).

Reproductive system

In one study, occupational exposure to ethylene glycol was associated with delayed fertility in women (25).

In 1150 pregnancies, 561 in female employees of semiconductor manufacturers and 589 in the wives of male employees the former had increased risks of spontaneous abortion (RR = 2.8; 95%CI = 1.4, 5.6) and subfertility (OR = 4.6; 95%CI = 1.6, 13); both of these risks had a dose-response relation with potential exposure to ethylene glycol (26).

Immunologic

Polyethylene glycol has reportedly caused anaphylaxis (SEDA-20, 440).

Propylene glycol can be used in allergic individuals, although propylene glycol itself can cause allergic skin reactions. The incidence of propylene glycol allergy among patients with eczema is thought to be greater than 2% (27). Used in dermatological formulations, propylene glycol can occasionally perpetuate eczema in hypersensitive patients (28).

Drug Administration

Drug formulations

In 1995, a topical solution of erythromycin (Erythromycine Balleul) was withdrawn from the market because of its high

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content of ethylene glycol monoethyl ether, which is easily absorbed via the skin, is teratogenic in animals, and alters spermatogenesis.

Drug overdose

Ethylene glycol poisoning can cause acidosis, central nervous system depression, pulmonary edema, acute oliguric renal failure with crystalluria, liver damage due to calcium oxalate deposition, nausea, abdominal pain, and cramping, acute colonic ischemia (29), and papilledema and abducens nerve palsy (30).

- Hemorrhage in the globus pallidus occurred in a 50-year-old Afro-Caribbean alcoholic man after ethylene glycol poisoning; there was evidence of lactic acidosis and the ethylene glycol concentration was 6.06 mmol/l (31).
- A 36-year-old long-distance truck driver took 200 ml of ethylene glycol in a suicide attempt (32). He vomited, lost consciousness, and had miosis and external ophthalmoplegia. There was a severe metabolic acidosis with a wide anion gap and many crystals in the urinary sediment. Acute oliguric renal failure required continuous hemodialysis for 6 days. A CT scan of the brain showed low-density areas in the bilateral basal ganglia, midbrain, and pons. A renal biopsy showed tubular oxalate deposits. He gradually recovered within 36 days.

Treatment of ethylene glycol toxicity is with ethanol, which inhibits alcohol dehydrogenase, fomepizole, which also inhibits alcohol dehydrogenase, and bicarbonate to treat acidosis (33). In some cases hemodialysis has been used (34,35).

Propylene glycol has been reported to cause lactic acidosis after overdose (36).

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Glycopyrronium

General Information

Glycopyrronium is a quaternary ammonium compound with anticholinergic properties (1).

In 22 patients with Frey syndrome (localized facial gustatory sweating and flushing) treated with topical glycopyrrolate 0.5–2% in a solution, cream or roll-on lotion, 1012 applications were recorded (SEDA-8, 160). There were seven adverse events: blurred vision (one), minor eye infections (two), itchy or dry eyes (one), and dry mouth (three). In the control group blurred vision and dry mouth were also recorded as adverse events.

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Gold and gold salts

General Information

Gold is a heavy yellow-colored element (symbol Au; atomic no. 79). Its symbol derives from the Latin word aurum. It is usually found as the metallic element but can occur as salts such gold telluride (sylvanite).

Metallic gold is used in dentistry, and gold salts still form one of the mainstays of treatment for rheumatoid arthritis. The radioactive isotope ^{198}Au is used therapeutically in the treatment of certain malignancies. In Japan, chrysotherapy has a reputation for efficacy in bronchial asthma. The antitumor activity of novel gold compounds is being pursued (1). The molecular mechanisms of action of gold have been reviewed (2).

Gold salts

Sodium aurothiomalate is water-soluble and is given intramuscularly as an aqueous solution. Aurothioglucose is water-soluble and is given intramuscularly in either an aqueous solution or an oily suspension. Sodium aurothiopropanol sulfonate, aurotioprol, and aurothiosulfate have similar actions and uses to those of sodium aurothiomalate. They are given by intramuscular injection.

Auranofin

Auranofin is a triethylphosphine gold derivative for oral administration. It is in some respects strikingly different from the rest. Some 25% of an oral dose is absorbed through the intestinal wall and blood concentrations are some 15–25% of those reached with parenteral therapy. Auranofin is bound to cellular elements of the blood, is excreted mainly in the feces, and exhibits less tissue retention and total body gold accumulation than parenteral forms. It is more effective in acute inflammatory models and is a potent inhibitor of lysosomal enzyme release, antibody-dependent cellular toxicity, and superoxide production. Auranofin also affects humoral and cellular immune reactions. However, some have found auranofin to be rather less effective than parenteral gold. Auranofin is used in doses of 2–9 mg/day (generally 6 mg/day), which is less than the dose originally recommended.

In view of all this it is not surprising that auranofin has a distinct profile of therapeutic and adverse effects, the differences being so great that one actually suspects differences in the mechanism of action between oral and parenteral forms. Like the latter, however, auranofin shows no clear correlation between whole blood gold concentrations and either efficacy or adverse effects.

Use in rheumatoid arthritis

In rheumatoid arthritis the most commonly used gold salts are sodium aurothiomalate and aurothioglucose (3). There is some reason to believe that adverse effects are less frequent with the suspensions (of aurothioglucose or aurothiosulfate) than with the more rapidly absorbed solution (of sodium gold thiomalate) (SEDA-16, 233) (4).

Whereas gold was previously regarded as one of the most toxic drugs in the pharmacopeia, many authors now share the view that its adverse effects can to an important extent be contained by individually adapted dosage regimens and careful monitoring. However, it is not strictly possible to predict the nature or timing of the complications that an individual may experience, and it has to be borne in mind that some reactions are immunological (SEDA-21, 236). The prevalence of adverse gold reactions seems to be similar in patients given 25 or 50 mg of gold weekly (SED-12, 520) (5). Some studies have suggested that the frequency of mucocutaneous and renal adverse reactions may be higher in the initial

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months of treatment. In one series of patients receiving gold sodium thiomalate, a plateau in the cumulative incidence of withdrawals due to rash was reached only after 40 months (45% of all patients), while withdrawals due to proteinuria reached a plateau after 18 months (l5%) (6). Hematological complications can occur at any stage.

It is widely considered that the patients who are most likely to develop adverse reactions to gold salts are those who react most favorably. In the past, many rheumatologists intensified treatment with high doses of gold salts until a skin eruption occurred, only then seeking to reduce to a maintenance dosage.

After withdrawal due to adverse reactions, treatment with gold compounds can be cautiously reintroduced without the previous adverse effects necessarily reappearing. However, clearly one will not take this course if life-threatening reactions have occurred. It should always be borne in mind that many adverse reactions allegedly due to chrysotherapy may have other causes, particularly in the case of skin reactions. Most patients have been or are using other drugs at the same time. The concomitant use of penicillamine can be particularly confusing, since its pattern of adverse effects closely resembles that produced by gold.

Use in dentistry

Dental gold alloys continue to be used and remain a source of contact hypersensitivity (7), including contact stomatitis and skin eruptions at sites not usually associated with dentistry. Contact dermatitis to metallic gold, for example in jewellery, has also repeatedly been observed (SED-8, 510) (SEDA-22, 245). A gold surgical clip has also caused an apparently allergic reaction, characterized by sterile abscess formation (8). However, such reactions are rare and may in part be due to other metals contained in the alloy.

General adverse effects

Intravenous gold salts

Adverse effects of gold salts occur in about one-third of systemically treated patients, the incidence varying from 25 to 40%. The dropout rate due to adverse reactions has been assessed as 22–26% (9). Children are considered to show the same pattern of adverse reactions as adults.

Cutaneous lesions are the most frequent adverse effects of gold salts, followed by involvement of the mucous membranes and kidneys. Pruritus and a wide range of skin reactions can occur. In the gastrointestinal system inflammation can occur at all levels, from the buccal cavity to the colon. Glossitis, cheilitis, and stomatitis are less common than dermatitis. Enterocolitis is a rare but very serious complication. Mild proteinuria is often seen in patients receiving chrysotherapy, while severe nephrotic syndrome is much less common. Blood dyscrasias of any type can occur either during therapy or after withdrawal. Leukopenia and thrombocytopenia are the most common hematological complications, although both are clearly less common than the mucocutaneous and renal adverse effects. Unusual reactions include pulmonary infiltration, intrahepatic cholestasis, and peripheral neuropathy. By and large, undesirable effects are transient and mild, but occasional deaths continue to be reported, usually because of hematological complications.

Apart from the "nitritoid" cardiovascular reaction, which is unique to sodium aurothiomalate, and possible differences between slowly and rapidly absorbed gold salts in the relative frequency of adverse effects, the general pattern of adverse reactions is similar for all parenteral gold salts.

Although most adverse effects of gold have traditionally been characterized as toxic, various factors show that some of the complications due to chrysotherapy are, at least in part, manifestations of hypersensitivity. Eosinophilia, raised IgE concentrations, immune complexes, and a positive reaction to gold in the lymphocyte transformation test have been observed in association with many adverse reactions to chrysotherapy and point to immunological mechanisms (10). With aurothiomalate both pemphigus and erythroderma have been described (SEDA-22, 246). It may be that gold facilitates the development of autoimmunity in patients with rheumatoid arthritis. Gold-induced membranous glomerulonephritis is believed to be an immune complex (type III) reaction, although the role of gold in the development of proteinuria has not yet been clarified. Gold-induced antibody deficiency may be more common than is usually recognized. In 22 patients with rheumatoid arthritis subnormal serum immunoglobulin concentrations developed as a consequence of gold treatment (11). There were mild deficiencies of single immunoglobulin isotypes or severe deficiencies affecting two or three isotypes. There may be transient exacerbation of rheumatoid symptoms before a therapeutic response to gold occurs. In one series of 43 patients with rheumatoid arthritis serious exacerbation of the disease occurred in 17% (12). Tumor-inducing effects have not been observed.

Auranofin

Auranofin is well tolerated by most patients; its adverse effects resemble those of parenteral gold salts, but the pattern differs, with gastrointestinal reactions predominating. Adverse reactions to auranofin are also generally less severe. Where serious adverse effects have been attributed to auranofin, cause and effect has usually remained in doubt. Adverse effects on the lower gastrointestinal tract are the most common; early studies showed a change in bowel habit in some 40% of cases, but this does not often amount to frank diarrhea (13). The same authors noted proteinuria (4%) and hematological reactions (2%). Mucocutaneous reactions (pruritus, conjunctivitis, stomatitis) often occur but are rarely severe and are less problematic than with sodium aurothiomalate. Most adverse effects occur during the first few months; age, sex, and duration of disease do not influence the risk of developing an adverse effect. The adverse effect-related withdrawal rates for injectable gold, auranofin, and placebo were 40, 14, and 6% respectively. Rashes occur in some 20% of cases but rarely require withdrawal. Tumor-inducing effects have not been observed.

Metallic gold

Dental gold alloys can cause contact hypersensitivity (7). Contact dermatitis to metallic gold, for example in jewellery, has also repeatedly been observed (SED-8, 510) (SEDA-22, 245). A gold surgical clip has also caused

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an apparently allergic reaction, characterized by sterile abscess formation (8). However, such reactions are rare and may in part be due to other metals contained in the alloy.

Organs and Systems

Cardiovascular

Acute vasodilatory (nitritoid) reactions occur in a minority of patients receiving parenteral gold, especially sodium aurothiomalate (SEDA-22, 245). A few minutes after injection the patient experiences weakness, flushing, hypotension, tachycardia, palpitation, sweating, and sometimes syncope (14). Very rarely myocardial infarction and stroke follow (14,15). The mechanism is unknown, but it has been suggested that the vehicle might be responsible, and that aurothioglucose might therefore be preferable to sodium aurothiomalate in elderly patients or in those with a history of cardiovascular disease.

Respiratory

Gold-induced lung toxicity is an infrequent adverse effect in patients with rheumatoid arthritis and psoriatic arthritis. There are three types: interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia, and bronchiolitis obliterans; the first is the most frequent. There have been two reports of gold-induced lung toxicity in psoriatic arthritis (16).

- A 54-year-old woman with psoriatic polyarthritis was treated with aurothiomalate 50 mg/week. When the cumulative dose reached 250 mg she developed weakness, dyspnea, fever, nausea, vomiting and erythematous skin lesions. Chest X-ray and CT scan showed diffuse interstitial pneumonitis. Gold was withdrawn and she was given prednisone 60 mg/day. She recovered in 6 months.
- A 62-year old woman with psoriatic arthritis was given aurothiomalate 50 mg/week. After a cumulative dose of 135 mg she developed an itchy rash, dyspnea, and fever. Chest X-ray and CT scan suggested pneumonitis and she was given prednisone 40 mg/day. She recovered in 6 months.

More than 60 cases of "gold lung" have been reported and there must be many more unpublished cases. Beginning as a rule some weeks or months after starting treatment, the patient develops dyspnea on exertion, weakness, a dry cough, and malaise. Chest X-rays show bilateral pulmonary infiltrates of varying extent, but cases have been described in which the radiography is entirely normal (17). If chrysotherapy is continued, pulmonary insufficiency can follow. In fact two types of process need to be distinguished; fibrosing alveolitis and obliterative bronchiolitis occur and can co-exist (18); some patients develop proliferative and immunoallergic changes, perhaps even mimicking malignant processes. In treating rheumatism, it can be difficult to distinguish "gold lung" from rheumatoid lung disease (SEDA-21, 236).

Bronchoalveolar lavage in "gold lung" tends to show an increase in the total cell count and predominance of the percentage of lymphocytes with an inverse helper/suppressor ratio. The prognosis is generally good; if gold is immediately withdrawn, the pulmonary lesions as a rule subside, although incomplete regression or even persistence of dyspnea and impaired lung function have been described, despite glucocorticoid therapy (19).

The pulmonary toxicity of gold salts uncommonly causes life-threatening respiratory failure. Patients who suffer from this do not usually need mechanical ventilation, and the toxicity can be difficult to diagnose when it occurs in patients with an illness with pulmonary involvement. However, severe respiratory failure requiring mechanical ventilation has been attributed to gold salt toxicity in a patient with rheumatoid arthritis (20). Glucocorticoid therapy was life-saving and induced complete resolution of the lung damage.

Pneumonitis associated with gold has been reported in a woman with rheumatoid arthritis.

- A 77-year-old woman with rheumatoid arthritis was given sodium aurothiomalate 50 mg intramuscularly weekly, following a test dose of 10 mg (21). Her rheumatoid arthritis responded well, but after a cumulative dose of 560 mg she became progressively short of breath on exertion and generally felt unwell. She had bilateral basal inspiratory crackles and widespread ill-defined shadowing on the chest X-ray, predominantly in the middle and lower zones of both lungs. A high-resolution CT scan showed ground glass opacities, particularly in the upper zones, and thickening of the peribronchovascular interstitium and interlobular septa in the middle and lower zones. Pulmonary function tests showed a restrictive lung defect. The gold injections were discontinued and she responded well to methylprednisolone. A CT scan 10 months later showed almost complete resolution, with some heterogeneity of lung density posteriorly in the lower lobes.

Interstitial pneumonia has been described in an adult who had taken auranofin for only 6 days; glucocorticoids were required (SEDA-17, 276).

Nervous system

Gold can damage nervous tissue. Peripheral neuropathy due to gold is possibly not as rare as was previously assumed and can co-exist with a neuroencephalopathy or other symptoms, such as dizziness and nausea (22). Nervous damage can take other forms: peripheral pain, general malaise, psychiatric disorders, and insomnia can be the first uncharacteristic symptoms and can easily be overlooked as adverse effects. Acute polyneuropathy of the Guillain-Barré type (SED-12, 521) (23), myokymia (Morvan-type fibrillating chorea) (SEDA-6, 216) (24), and gold encephalopathy (25) are rare neurological complications of chrysotherapy that have, however, all been well documented from different sources (24).

- A woman in whom gold had been withdrawn because of a rash developed a severe parkinsonian tremor of the hands a week later (22).

An axonal polyneuropathy has been attributed to gold (26).

- A 63-year-old man with a 4-month history of rheumatoid arthritis developed progressive malaise, anorexia,

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and weight loss, and had a 2-day history of diarrhea, fever, and chills. He had epigastric and periumbilical pain radiating to the back, associated with nausea, abdominal distension, and jaundice. He was taking prednisone 5 mg bd and diclofenac sodium 100 mg bd. He had recently started weekly gold injections (total dose of gold 150 mg). He received two test doses before starting induction therapy, with no adverse effects. Both gold and diclofenac sodium were withdrawn and 2 weeks later he complained of symmetrical distal paresthesia in a glove and stocking distribution. There was no weakness, parallel reflexes were diminished, and the ankle reflexes were both absent. Nerve conduction studies showed a reduction in sensory nerve action potential amplitude in the sural and median nerves, with normal motor conduction. There was a slightly increased threshold for warm and cold sensations in the foot, with normal results in the hand. A liver needle biopsy showed preserved liver architecture with marked cholestasis mainly in the central and mid zones. A positive lymphocyte transformation test to gold suggested a cell-mediated hypersensitivity reaction.

Intrathecal colloidal gold has been used as an adjunct in the treatment of childhood neoplasms, including medulloblastoma and leukemia. Long-term follow-up of patients treated with intrathecal colloidal gold has been described and the high incidence of delayed cerebrovascular complications and their management has been emphasized (27).

Between 1967 and 1970, 14 children with a posterior fossa medulloblastoma underwent treatment consisting of surgical resection, external beam radiotherapy, and intrathecal colloidal gold. All had persistent or recurrent disease and six died within 2 years of treatment. The eight surviving patients developed significant neurovascular complications 5–20 years after treatment. Three patients died as a result of aneurysmal subarachnoid hemorrhage and five developed cerebral ischemic symptoms from a severe vasculopathy that resembled moyamoya disease. Although therapy with colloidal gold results in long-term survival in a number of cases of childhood medulloblastoma, this study suggests that its severe cerebrovascular adverse effects fail to justify its use. The authors recommended routine screening of any long-term survivors after colloidal gold therapy, to exclude the presence of an intracranial aneurysm and to document the possibility of moyamoya disease.

Sensory systems

Chryseosis corneae (deposition of gold crystals in the cornea) occurs rarely in patients treated with a cumulative dose of up to 500 mg of gold, but they occur in nearly all patients who have received 1500 mg or more (28). Deposition of gold as such has no clinical consequences. Gold can occasionally cause a keratitis or keratoconjunctivitis, but these are usually associated with skin involvement and are not a consequence of gold deposits in the cornea.

Gold keratopathy has been reported in a woman with rheumatoid arthritis (29).

- A-60-year-old woman with rheumatoid arthritis who was taking prednisone, azathioprine, sulindac, plaquenil, and receiving intramuscular injections of gold sodium thiomalate (50 mg once weekly) developed intense, bilateral ocular irritation and photophobia. She had received a total of 7.4 g of gold over the past 3 years. Her conjunctivae were mildly injected, with bilateral perilimbal chemosis. The peripheral corneae showed 360° stromal edema. Mid-stromal vessels were seen entering the edematous stroma from the limbus. She was given topical prednisolone acetate hourly for rheumatoid marginal keratitis. Over the next 2 months her symptoms gradually resolved, but granular, golden-brown, pigmented deposits appeared in the corneal stroma in the same peripheral ring-like distribution as the resolved stromal keratitis. Gold was discontinued. Over the next 6 months, the stromal deposits partially cleared. She then had a milder episode of photophobia and irritation, with stromal edema in the same distribution. This was controlled by topical prednisolone. One year later, she continued to use topical prednisolone once a day and was asymptomatic, with no stromal inflammation, but persistent fine golden granules.

Conjunctivitis has occurred in some 10% of patients treated with auranofin, either early or late in treatment, and has led to withdrawal in about in 1% (30).

Metabolism

In one case, diabetes was destabilized after 3 weeks of auranofin treatment (31).

Hematologic

Because of the hematological effects of gold salts, full blood counts should be monitored regularly at least during the first 2 years of treatment (32).

Pure red cell aplasia occurred in a patient with cholestatic jaundice taking sodium aurothiomalate (SEDA-17, 275). Anemia has been reported occasionally with auranofin (0.1%) either as a direct effect or secondary to hematuria.

Eosinophilia in the peripheral blood is the most frequent hematological effect of parenteral gold salts, affecting up to 40% of patients. It is no longer believed that it is a reliable advance marker of more serious reactions of any type (33). Among the latter are severe blood dyscrasias, which sometimes appear unexpectedly, despite regular blood counts.

Auranofin has been associated with eosinophilia (range of incidence in various reports 0.1–13%). In a retrospective study of 82 patients with rheumatoid arthritis there was eosinophilia in 21% taking sodium aurothiomalate and 13% taking auranofin (33). However, early eosinophilia is not a reliable indicator of potential toxicity.

Leukopenia is rare, sometimes very mild, and not always related to gold (SED-12, 522). Granulocytopenia can evolve slowly or suddenly, and its course can be transient or prolonged. Some workers have found gold-associated granulocytopenias to be brief and self-limiting; indeed, if other marrow elements are unimpaired, full recovery can occur even from severe agranulocytosis. Full-fledged aplastic anemia and pancytopenia are the most serious and feared conditions, and although they are today uncommon,

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deaths continue to occur (SEDA-13, 192), particularly because of superimposed infections or hemorrhage. Auranofin has been associated with leukopenia (0.1%), lymphopenia, and neutropenia (SEDA-10, 207).

Leukopenia with liver damage has been reported (34).

- A 62-year-old woman with rheumatoid arthritis developed swelling and pain of both knees. Aurothiomalate was given in a test dose of 12.5 mg, followed the next day by a dose of 25 mg, and then 50 mg twice weekly (total cumulative dose 137.5 mg). She had a leukocyte count of 2.2×10^9/l, a normochromic anemia, and a normal platelet count. Her liver enzyme activities were raised. Aurothiomalate was withdrawn and about 6 weeks later her liver function tests returned to normal and her white cell count rose to 6.9×10^9/l.

Thrombocytopenia occurs in 0.7–3% of cases and can be severe (35). It presents with petechiae, hematuria, oral mucosal bleeding, and other hemorrhagic phenomena. Some cases are due to immune reactions, others to a direct toxic effect of gold on the megakaryocytes, and it is important to distinguish the two types. For an immunologically mediated thrombocytopenia, high-dose steroid therapy should be used if necessary, followed or accompanied by immunosuppressive drugs, infusions of fresh frozen plasma or high-dose immunoglobulin, and even splenectomy. Toxic thrombocytopenia probably demands gold chelator therapy. There is no correlation between the appearance of thrombocytopenia and effects on the skin or kidney (36). Thrombocytopenia is known with auranofin but rare (0.5%). Three patients developed serious thrombocytopenia after taking auranofin for 3 months (35). Auranofin was withdrawn and two of the patients were given oral glucocorticoids; platelet counts normalized within 8 weeks.

It has been postulated that early treatment with very high doses of intravenous *N*-acetylcysteine and the use of immunomodulatory drugs, such as antithymocyte globulin and ciclosporin, can improve the recovery of hematological parameters, even in the case of pancytopenia (37). One case of gold-induced aplastic anemia, unresponsive to various treatments, recovered after therapy with antithymocyte globulin (SED-12, 522).

Lymphadenopathy is a rare complication of gold injections (SEDA-12, 188). In one case lymphadenopathy in association with a patient with rheumatoid arthritis; biopsy of the lymph nodes showed crystalline material containing gold (SEDA-16, 234).

- A 34-year-old woman was given intramuscular sodium aurothiomalate for rheumatoid arthritis after little response to anti-inflammatory drugs (38). After the sixth injection she developed enlarged neck and axillary lymph nodes. Biopsy showed subtotal infarction of a reactive node, confirmed by histochemical, immunohistochemical, and molecular techniques. Gold was withdrawn and the lymphadenopathy gradually resolved over the next 2 months. She continued to suffer from rheumatoid arthritis with no evidence of malignant lymphoma after 3 years.

This case provides strong evidence that gold salts can cause malignant lymphoma.

Although there is no direct evidence of potentiation of hematological toxicity, the concomitant use of drugs that are known to carry a risk of blood dyscrasias is unwise. Simultaneous use of glucocorticoids in small doses is not thought to detract from the beneficial effects of gold and can delay the onset of adverse reactions (39)

Mouth and teeth

Stomatitis, sometimes preceded by a metallic taste, is a frequent complication of gold. It can take the form of superficial buccal erosions, which produce mild symptoms but tend to run a protracted course (40).

There has been one unusual report of obstructive sialadenitis caused by local compression of the excretory ducts of the parotid glands due to deposits of gold in the intraparotid lymphoid tissues; there was swelling of both parotid glands on eating (41).

Gastrointestinal

Fulminant enterocolitis or panenteritis are rare manifestations of gold intolerance; more than 30 cases have been published since 1945 (42) and one-third of them have been fatal. The presenting symptoms are diarrhea, rectal bleeding, and vomiting. Bowel dilatation can develop. The course of the disease is occasionally complicated by overwhelming infection. The X-ray picture sometimes simulates regional or ischemic enteritis. Pathological findings include intense mucosal edema, ulceration, hemorrhage, and infiltration of lymphocytes and plasma cells. No treatment is known. However, there is a milder eosinophilic type of enterocolitis due to gold, which, it has been suggested, responds to treatment with cromoglicate. Two cases of ischemic colitis have also been described, presenting as abdominal pain and rectal bleeding (SEDA-21, 236) (43).

The most common adverse effects of auranofin are gastrointestinal. About half of all users have loose stools at some time during treatment; this effect can be transient, can occur at any time, and is rarely severe. No infective cause or signs of malabsorption has been found in any case and neither was gold absorption adversely affected. In a long-term study, diarrhea was mainly observed in the first 6 months of therapy with auranofin 6 mg/day; in 8% of the cases this was a reason for withdrawal (44). There is experimental evidence in animals of a direct effect of auranofin on ion and water absorption from the intestine with inhibition of enterocyte Na^+/K^+-ATPase activity (SED-12, 525).

Stomatitis occurs in about 10% of patients taking auranofin, generally early in treatment, demanding withdrawal in up to 1% (45) (SEDA-9, 217).

Two patients developed fulminant colitis with toxic megacolon during treatment with auranofin (46,47). Both recovered completely within 4–6 weeks with supportive treatment, including high doses of prednisone.

Liver

Liver injury is an extremely rare complication of gold therapy (SEDA-14, 189) (48). The underlying mechanisms are probably complex and certainly variable. Overdosage can cause centrilobular necrosis and bile

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stasis. With normal doses intrahepatic cholestasis with an absence of necrosis is more likely, although there can be both bile duct damage and canalicular damage (49); an immunological mechanism for this disorder has been suggested. Several cases of a severe form of idiosyncratic hepatic necrosis soon after starting chrysotherapy have been described (11,50). However, most hepatic lesions as a rule resolve rapidly after withdrawal of chrysotherapy, and mild or moderate liver injury of any type is not necessarily a contraindication to gold treatment.

- A 62-year-old man with rheumatoid factor positive rheumatoid arthritis developed painless icterus, nausea and vomiting, and discolored stools (51). He had previously been given methotrexate without effect, and was instead given aurothioglucose 50 mg/week (cumulative dose 160 mg). He reported sweating, fatigue, and myalgia shortly after each gold injection. The liver was tender but not enlarged, and there were no signs of splenomegaly. Liver function tests showed a cholestatic pattern and predominantly conjugated hyperbilirubinemia. All potentially hepatotoxic drugs (aurothioglucose, naproxen, and aspirin) were withdrawn and his dose of prednisone was increased to 15 mg/day. His liver function tests normalized 4 weeks later.

Mild and transient abnormalities in serum transaminase and alkaline phosphatase activities have been reported during therapy with auranofin (0.4%). This is noteworthy, since almost all patients were taking acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, which also can cause increases in transaminases. There has been a report of two cases of toxic hepatosis in patients taking auranofin (52).

Urinary tract

Mild proteinuria develops in 2–3% of patients receiving chrysotherapy; it is usually benign and reversible within a few weeks after discontinuation of therapy (53). No deterioration in creatinine clearance has been found at periodic follow-up. It is not always necessary to stop gold treatment if a patient develops proteinuria, provided there is no marked loss of renal function and proteinuria is not in the nephrotic range. Gold therapy can be continued under close monitoring for at least 10 months without causing permanent renal damage (54).

Proteinuria has been observed in many trials of auranofin, but in contrast to cases associated with parenteral gold it has only rarely progressed to nephrotic syndrome. Of 1283 auranofin-treated patients, 38 had a raised urinary protein concentration, but only in nine it was heavy, and in most patients who continued treatment the proteinuria did not persist beyond the first 12 months of treatment; seven of eight who were rechallenged, after auranofin had been withdrawn and the protein had cleared, were able to continue treatment without relapse. Biopsy showed membranous glomerulonephritis, suggesting an underlying immunopathological mechanism (55).

Microhematuria has long been considered a manifestation of nephrotoxicity from chrysotherapy, but one multicenter study showed no higher an incidence than in patients receiving placebo (SED-12, 522). Hematuria associated with auranofin has been reported in a few patients, generally after at least 2–3 months of treatment (56).

Serious nephrotoxicity is uncommon, but nephrotic syndrome can develop in about 0.3% of patients, generally among those who have experienced mild proteinuria earlier in treatment. Very exceptionally, acute renal insufficiency can occur; peritoneal dialysis has been reported to promote recovery.

The histological findings in cases of gold nephropathy range from essentially normal glomeruli to a focal increase in mesangium, glomerular basement membrane thickening or splitting, membranous glomerulonephritis (57,58), periglomerular fibrosis with proliferation of Bowman's capsule, and even hyalinization of glomeruli. Chronic interstitial nephritis can also occur (59). Fortunately, many cases of renal complications run a benign course if gold is withdrawn (58).

Gold nephropathy is often considered to be an immunological disorder, and IgG and C3 are usually present in fine granular immune complex deposits along the capillary walls of the glomeruli. Oddly, however, X-ray microanalysis fails to detect gold as a component of the deposited immune complexes, throwing doubt on the concept that gold itself acts as an antigen or a hapten. Gold might however alter the proximal tubular cells in such a way that tubular autoantigens are released, resulting in the development of antigen–antibody complexes; these would then become attached to the glomerular basement membrane, inducing membranous glomerulopathy and proteinuria. That gold does damage the tubular cells is well known, although there appears to be no correlation with dosage and duration of therapy. Gold-containing, electron-dense, filamentous, cytoplasmic inclusions have been found in proximal tubular cells. The urinary excretion of beta-glucosaminidase, leucine aminopeptidase, $beta_2$-microglobulin, and other tubular proteins has often been found to be increased in patients treated with gold compounds (SEDA-15, 229). Tubular dysfunction can persist for up to 2 years after the end of chrysotherapy.

Skin

Skin reactions are the most frequent of all adverse effects of gold; they develop in about 25% of patients, sometimes in association with other forms of gold intolerance. Up to 30% of patients taking auranofin develop mucocutaneous adverse effects and 18–24% develop a rash or pruritus, meriting withdrawal in some 4% of cases (SEDA-10, 208).

Skin reactions to gold salts can be toxic or immunological, and patch-testing is often positive (51). No increase in gold concentration in the skin has been found, nor is there any correlation with blood concentrations of gold. Skin biopsies show that both macrophages and Langerhans cells are actively involved in the pathogenesis of gold dermatitis (61).

Pruritus is the commonest and earliest manifestation of such reactions and can precede an eruption by some weeks. Lesions are of every conceivable type, ranging from transient, non-specific, localized, or generalized dermatitis (eczema) and erythematous, maculopapular rash to lichen planus-like eruptions, discoid eczema, pityriasis rosacea, erythema multiforme, erythema nodosum,

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scaling eruptions, urticaria, photosensitivity, hyperkeratosis, seborrheic dermatitis, toxic epidermal necrolysis, and granuloma annulare. Exacerbation of pre-existing psoriasis has been reported (62). Patients receiving aurothioglucose have sometimes developed a dermatitis closely resembling contact dermatitis (SED-12, 523). More than one of these effects can occur in the same patient.

Gold can also cause pemphigus (63).

- A 53-year-old woman with rheumatoid arthritis who had reacted to D-penicillamine treatment by developing myasthenia gravis was given gold instead and 12 months later developed pemphigus vulgaris (60).

Not every gold-induced skin disorder is necessarily wholly disfiguring; in one curious case, the patient was seen to "glitter" with tiny specks of a gold-coloured (and gold-containing) material covering the skin of the neck, upper arms, and back (64).

Chrysiasis, a gray, blue, or purple pigmentation on light-exposed skin areas, is a complication that tends to be permanent (SEDA-20, 210). In one series of 40 patients receiving sodium aurothiomalate it appeared in 31 (65).

Inadvertent gold administration has reportedly caused an allergic skin rash (66).

- A 31-year-old woman developed a rash, similar to the rash she had experienced after wearing gold jewellery. The evening before she had taken about 90–120 ml of Goldschlager liquor, a cinnamon schnapps that can contain as much as 8–17 mg of gold in 750 ml. The rash was isolated to her neck, upper chest, and hands and was erythematous and pruritic with no borders or margins. Her rash resolved over 2 weeks without desquamation.

In patients with a history of localized hypersensitivity to metallic gold, allergic skin reactions can develop in the sensitized region after gold injections (SEDA-13, 193).

Worldwide experience with auranofin points to a 2% incidence of alopecia, but this included older experience at high doses; at current doses, alopecia is rather less common (30).

If skin reactions are not serious, withdrawal of gold is not essential, and some physicians deliberately increase the dosage to the point where some skin reaction occurs, as a means of securing the best possible therapeutic effect. Once troublesome reactions have appeared they can often be relieved simply by reducing the dosage or the frequency of administration. More troublesome reactions will demand withdrawal of gold, and in that case most skin lesions will begin to subside within a few days or a week, and disappear within several weeks more; it may then be possible to resume gold at a reduced dosage (67). On the other hand, some gold-induced skin lesions can run a protracted course, in certain cases necessitating topical or systemic glucocorticoid treatment. A patchy brown discoloration can persist after the disorders have resolved. When gold has been withdrawn it can often be restarted later without recurrence of the lesion.

Nails

Gold rarely causes yellow thickening of the nails and onycholysis, followed by irreversible nail dystrophy (SED-9, 373).

- A 34-year-old woman with severe rheumatoid arthritis developed yellow thickening of all 20 nails 2 years after starting gold therapy (68). She had received 50 mg of gold salts intramuscularly at intervals of 2–4 weeks after an initial course of weekly injections (total cumulative dose 90 mg/kg) over 4 years. There was associated thickening of the nail plate, increased transverse curvature, and mild subungual hyperkeratosis. There was onycholysis of both thumbnails and the right little fingernail. There was no associated chrysiasis. Gold was withdrawn. The yellow discoloration began to grow out and fingernail growth increased in the next 3 months. Six months later there was further improvement, although light yellow discoloration of all nails persisted and there was markedly increased longitudinal growth. Both thumbnails showed transverse depressions of the nail plate (Beau's lines) where the change in growth rate had presumably occurred.

Immunologic

Several patients with selective IgA deficiency and even a panhypogammaglobulinemia during intramuscular gold treatment have been described (SEDA-14, 190) (SEDA-15, 230) (SEDA-21, 237).

Polyarteritis (69) and systemic lupus erythematosus (70) have been reported after the administration of gold compounds.

- After taking sodium aurothiomalate for 10 months (cumulative dose 550 mg) a 12-year-old girl with severe exudative polyarthritis developed pericarditis, high titers of antinuclear antibodies, and antibodies to native double-stranded DNA (70). After withdrawal her symptoms rapidly disappeared and did not recur after a follow-up period of 5 years. The titers of autoantibodies fell to normal within 1 year.

In one series of some 5500 patients with juvenile rheumatoid arthritis, 105 were found to have developed secondary amyloidosis; 37 of the latter had been receiving sodium aurothiomalate. In 12 of these children the time between withdrawal of gold (because of adverse effects) and the finding of amyloid A was less than six months (SEDA-21, 237).

- A 63-year-old woman with rheumatoid arthritis was given intramuscular gold sodium thiomalate and began to have nausea, vomiting, anorexia, and watery diarrhea (71). A year later the watery diarrhea became more frequent (more than 10 times within a day) and she developed proteinuria. Biopsies from the stomach, duodenum, and kidney showed systemic amyloidosis. This was a rare case of secondary systemic amyloidosis associated with rheumatoid arthritis. It is not clear from the report what the role of gold was in this case.

Infection risk

An increased incidence of *Herpes zoster* was found in a series of patients receiving sodium aurothiomalate; the mechanism is unknown, but herpesvirus infection can also occur in association with some other heavy metals, for example in environmental poisoning.

The incidence of *H. zoster* infection in auranofin-treated patients was slightly higher (0.9%) than in patients

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with rheumatoid arthritis not receiving gold therapy (0.4%), but less frequent than in patients given parenteral gold compounds (3.1%).

Body temperature

There may be transient exacerbation of rheumatoid symptoms before a therapeutic response to gold occurs. In one series of 43 patients with rheumatoid arthritis serious exacerbation of the disease occurred in 17% (12).

Second-Generation Effects

Teratogenicity

In 1980, alarm was caused by a report of a seriously malformed child born to a mother who had been treated with sodium aurothiomalate during pregnancy (72), particularly since a partially congruent pattern of neural abnormalities had earlier been described in rats and rabbits, and given the fact that gold crosses the placenta. On the other hand, a Danish team in 1983 studied eight children born after exposure to gold in utero from weeks 2–9 or longer; no abnormalities were found, and the children appeared to develop normally during a follow-up period averaging 8.6 years (73). In view of the lack of further incriminating evidence some physicians today adopt the view that chrysotherapy can be continued in selected pregnant women whose rheumatoid arthritis is of such severity as to warrant treatment.

Lactation

Breastfeeding is not recommended since gold salts are excreted in the milk (SEDA-12, 188) (SEDA-13, 193).

Susceptibility Factors

Genetic factors

There is good evidence that patients with rheumatoid arthritis who carry the DR3 antigen run a greater risk of proteinuria (74), mucocutaneous reactions (75), and hematological actions (76) to parenteral gold compounds as well as to penicillamine, although such patients also tend to react rather better than others to aurothioglucose (77). The same applies to the B8, DR3 haplotype (81). The prevalence of the HLA antigens DR2 and DR7 is lower among rheumatoid arthritis patients with toxic reactions than among patients without toxic reactions or among controls (79). Because of conflicting results and the low relative risk, HLA typing has not been of much practical help as a guide to forecasting the risk of therapy.

Patients with rheumatoid arthritis and poor sulfoxidation state are six times more susceptible than others to the adverse effects of sodium aurothiomalate (80). This parallels an earlier similar finding with penicillamine, which has the same sulfhydryl group in its structure.

Age

Several studies have shown that in juvenile chronic arthritis auranofin gives rise to fewer adverse reactions than in adults, but the therapeutic effect is dubious and variable (SEDA-17, 277).

Elderly patients were once thought to be more likely than younger individuals to develop severe reactions (81) but this seems not to be so (82).

Other features of the patient

There are various contraindications to gold therapy (83): active hepatic disease, impaired renal function, colitis, patients with a history of hematological disorders, and patients who have recently had radiotherapy (because of the depressant action of radiotherapy on hemopoietic tissue).

Drug Administration

Drug overdose

- Severe overdosage of sodium aurothiopropanol sulfonate (1.1 g daily for 13 days) caused jaundice and skin eruptions. Liver biopsies showed modest centrilobular necrosis and significant bile stasis. Serum hepatic enzyme activities were increased. The patient was treated with dimercaprol and recovered after 2 months, although alkaline phosphatase and gamma-glutamyltransferase activities remained high for 6 months.

It seems advisable in cases of acute gold intoxication to adopt a conservative strategy. Should severe complications occur, supportive therapy can be given in combination with such treatments as chelation, glucocorticoids, or gamma-globulin.

Drug–Drug Interactions

Glucocorticoids

In a placebo-controlled study auranofin reduced the doses of glucocorticoids needed in asthma (84). This is perhaps a parallel effect rather than an interaction since, as noted above, gold itself may have an effect in asthma.

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Gonadorelin

General Information

The effects of gonadorelin depend on the duration of use. Gonadotropin release is stimulated in the short term, but is later suppressed owing to down-regulation of hypophyseal receptors. Its therapeutic indications have been summarized (SEDA-13, 1311) (1). Long-acting and depot formulations have the same adverse effects as shorter-acting analogues. The available gonadorelin analogues include buserelin, goserelin, leprorelin, nafarelin, and triptorelin (all rINNs).

Gonadorelin and its analogues cause an initial surge in follicle-stimulating hormone (FSH), luteinizing hormone (LH), and gonadal steroids. Receptor down-regulation and gonadotropin suppression occur after prolonged administration. Thus, both the clinical and adverse effects depend on the duration of administration. Biological activity and adverse effects also vary between gonadorelin agonists.

Comparative studies

In 67 premenopausal Japanese women randomized to 4-weekly, low-dose buserelin 1.8 mg or leuprorelin 1.88 mg, women given leuprorelin had a more rapid clinical response and a higher rate of hot flushes (2).

Adverse effects and quality of life have been compared in 431 men with prostate cancer treated with a gonadorelin agonist or orchidectomy (3). Of the men who reported normal sexual function before treatment, 51% had reduced libido and 69% became impotent. Of those given gonadorelin, 57% had hot flushes. Breast swelling was more common in those given gonadorelin (25% compared with 10% after orchidectomy).

Of 547 men randomized to leuprorelin plus flutamide for 3 or 8 months, those treated for 8 months had a higher overall rate of adverse events, and 87% had hot flushes, compared with 72% of those who were treated for 3 months (4).

Organs and Systems

Cardiovascular

Gonadorelin inhibits nitric oxide-mediated arterial relaxation, which disappears within 3 months after stopping treatment. This effect was abolished with "add-back" hormone replacement in a prospective, randomized study of 50 women treated for 6 months (5).

Respiratory

- A 75-year-old man developed a high fever and cough immediately after an injection of leuprorelin acetate 3.75 mg and 8 days after starting flutamide 375 mg/day (6). He died of respiratory failure after a month, and interstitial pneumonitis was confirmed postmortem.

There have been two other reports of pneumonitis associated with gonadorelin agonists.

Ear, nose, throat

Local irritation or rhinitis occurs uncommonly when gonadorelin agonists are taken intranasally.

- A 34-year-old woman had to stop using nafarelin nasal spray after 14 days because of exacerbation of maxillary sinusitis (7).

Nervous system

Pituitary apoplexy (hemorrhagic infarction presenting with sudden severe headache, often followed by pituitary hormone deficiency) has been reported after intravenous gonadorelin testing to investigate a pituitary macroadenoma and in several patients with gonadotropin-secreting pituitary macroadenomas who were given gonadorelin to treat prostate cancer (8). It may be advisable to assess gonadotropin status prior to therapy in such patients.

- A 43-year-old woman with a pituitary macroadenoma, who took quinagolide 37.5 micrograms/day for 33 months, developed a severe headache, nausea and vomiting, and photophobia 30 minutes after diagnostic testing with gonadorelin 50 micrograms intravenously (9). Although a CT scan at the time showed no evidence of hemorrhage, an MRI scan 18 months later showed a partial empty sella.
- A 67-year-old man with prostate cancer and an unsuspected pituitary macroadenoma developed a severe frontal headache, nausea and vomiting, and blindness within 12 hours of insertion of a goserelin implant (10).

Two further cases have been reported, in which gonadorelin was administered either alone (11) or with insulin (12). The mechanism of pituitary apoplexy in these cases is unclear. Gonadorelin may have a direct effect on vascular tone or may increase tumor metabolic activity.

There has been one previous report of seizure exacerbation during leuprorelin treatment, in a girl with pre-existing brain damage (13), and a case of de novo seizures has also been reported (14).

- A 13-year-old girl, who had previously had surgery and radiotherapy for a medulloblastoma, developed atypical absence seizures for the first time after 3 months of therapy with leuprorelin. The seizures stopped 1 month after treatment was withdrawn and did not recur until 30 months later. The seizures were not related to estradiol concentrations or the menstrual cycle.

Neuromuscular function

Prolonged administration of gonadorelin is commonly associated with reduced muscle bulk and voluntary muscle function. In a prospective, uncontrolled study of 62 men with prostate cancer, treatment with cyproterone acetate and goserelin caused an increase in fatigue scores and increased muscle fatiguability on objective testing within 6 weeks, in 66% of subjects (15). Fatigue was unrelated to psychological complaints or to self-reported functional ability.

Sensory systems

Blurred vision, sometimes associated with headache and dizziness, is common soon after the commencement of

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treatment and usually resolves within 2–3 weeks. It has recurred in some patients after rechallenge (16).

Psychological, psychiatric

Depressed mood and emotional lability occur in up to 75% of gonadorelin recipients, and there are rare reports of more severe mood disturbances (17). Defects of verbal memory have been described and may be reversed by "add-back" estrogen treatment (17) and sertraline (18).

- A 32-year-old woman had psychotic symptoms of persecutory delusions, agitation, and auditory hallucinations a few days after her second injection of triptorelin (19). Her symptoms recurred after a pregnancy, suggesting that they were due to the rapid fall in estrogen in both instances.

During a 6-month, randomized trial, men randomized to gonadorelin agonists had reduced attention and memory test scores, compared with men who were not given gonadorelin agonists but were closely monitored, in whom there was no change (20).

Endocrine

Symptoms of hypoestrogenism, including hot flushes, vaginal dryness, reduced libido, and mood changes, occur in almost all women on long-term gonadorelin. Men also experience hypogonadal symptoms with prolonged gonadorelin administration, including hot flushes and reduced libido, although this is a therapeutic effect rather than an adverse effect. Gynecomastia occasionally occurs in men.

"Add-back" estrogen replacement reduces the frequency and severity of these symptoms without apparently compromising the effectiveness of gonadorelin in women with endometriosis (18,21). In a randomized, multicenter, double-blind comparison of intranasal nafarelin twice daily and depot leuprolide acetate monthly for 6 months in 192 young women with endometriosis, nafarelin caused fewer hypoestrogenic symptoms, although the difference between the two groups was statistically significant only after 3 months of therapy (22).

"Draw-back" therapy, in which the dosage of nafarelin was reduced after 4 weeks, had similar efficacy, but a smaller degree of bone loss and fewer vasomotor adverse effects compared with full-dose therapy, in a randomized study in 15 premenopausal women (23).

- A 47-year-old woman developed symptoms of thyrotoxicosis (palpitation, tremor, tachycardia, and goiter) due to Graves' disease, after using goserelin acetate for 13 months (24).
- A 45-year-old woman developed transient thyroiditis associated with antithyroid antibodies in taking leuprorelin (25).

The second patient had other risk factors for autoimmune thyroid disease, and the association was probably coincidental, but the episode may have been precipitated by low estrogen concentrations, as is hypothesized in postpartum thyroiditis.

Metabolism

In 20 premenopausal women treated with triptorelin for 8 weeks, the mean LDL concentration rose from 2.7 to 3.9 mmol/l and HDL fell from 1.6 to 1.5 mmol/l (26). Although the change in HDL was not clinically relevant in isolation, the increases in LDL and LDL:HDL ratio were significant, suggesting an increased risk of atherogenesis. "Add-back" conjugated equine estrogen did not reverse these changes over 24 weeks.

- A woman with type 2 diabetes had worse glycemic control while receiving buserelin (27). Her blood glucose returned to its previous concentration after withdrawal.

Hematologic

Leuprolide acetate has been reported to cause normochromic normocytic anemia in patients with benign prostatic hyperplasia (28). The anemia is usually transient, and the hemoglobin returns to baseline 6 months after stopping androgen suppression. There is a single case report of more serious red cell aplasia in a patient receiving gonadorelin, with resolution after treatment was withdrawn (29).

Skin

Injection site reactions are common with gonadorelin receptor agonists. In 119 women randomized to subcutaneous triptorelin a local reaction (redness, pain, or bruising) was present after 1 hour in 24% and persisted for 24 hours in 9.5% (30). In another study in 105 women randomized to leuprorelin acetate, moderate local reactions occurred in 24% and severe reactions in 1% (31).

- A 48-year-old woman developed an itchy skin eruption and spotted dark brown pigmentation 3 weeks after starting nasal buserelin 900 micrograms/day. The lesions resolved when buserelin was withdrawn, and recurred with rechallenge; some persisted for up to 2 years (32).
- A 78-year-old man treated with subcutaneous leuprorelin acetate had repeated local reactions, with erythema, induration, abscesses, and an ulcer on one hip (33).

Altered skin pigmentation has been previously reported in pregnancy and after sex hormone administration, so the initial surge in gonadotropins after gonadorelin treatment was a probable cause for the first patient's presentation. In the second case the lactic acid/glycolic acid vehicle may have caused the reaction rather than leuprorelin.

Musculoskeletal

Osteoporosis, trabecular bone being most affected, has been regularly observed in both sexes with chronic gonadorelin agonist treatment (34), and the duration of therapy for prostate cancer is inversely related to bone mineral density (35,36). Intravenous pamidronate may prevent bone loss in these patients (37,38).

- A 44-year-old woman with no previous history of widespread pain, depression, or anxiety developed a diffuse pain syndrome consistent with fibromyalgia after leuprorelin treatment. Her symptoms increased in severity with three successive monthly injections, and persisted for several months (39).

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In 47 children treated with depot leuprolide acetate for precocious puberty for 2 years, bone mineral density decreased significantly and markers of bone turnover increased significantly during treatment but were normal for age 2 years after treatment was withdrawn (40).

Since women have a lower initial bone mass than men their fracture risk is higher. Osteoporosis is reversible in premenopausal patients after gonadorelin withdrawal (41). However, the treatment period should be limited to 6 months.

Cross-sectional (42) and longitudinal (43) studies of men with prostate cancer have shown a significant relation between the duration of gonadorelin treatment and bone loss.

Estrogens, etidronate, and parathyroid hormone have been used with partial success to prevent gonadorelin-induced bone loss. In a prospective study of 49 women treated with goserelin and randomized to estradiol plus norethisterone or placebo, bone loss persisted 6 years after stopping therapy, and the hormone replacement therapy had only a minor protective effect (44).

- An 87-year-old man developed progressive proximal limb weakness 1 year after starting leuprolide therapy for prostate cancer (45). Electromyography showed a moderately severe non-inflammatory myopathy without evidence of fiber necrosis or associated biochemical changes. Within 6 months after stopping leuprolide he was able to resume his usual activities.

Three men developed rheumatoid arthritis 1–9 months after starting antiandrogen therapy with either cyproterone acetate or leuprolide acetate (46).

Reproductive system

Ovarian hyperstimulation syndrome (OHSS) affects up to 33% of women undergoing ovulation induction with gonadorelin receptor agonists and gonadotropins given in combination (47), or with gonadotropins alone (48). Gonadotropins are usually withheld if the diagnosis is made before conception (47,49).

OHSS is characterized by cystic ovarian enlargement, increased capillary permeability, and third space fluid accumulation (that is in an extracellular compartment that is not in equilibrium with either the extracellular or intracellular fluid, for example the bowel lumen, subcutaneous tissues, retroperitoneal space, or peritoneal cavity). Risk factors include a previous history of OHSS, age under 30 years (probably because more follicles are available), and polycystic ovary syndrome. Non-pregnant patients usually recover within 14 days with supportive treatment. The severe form (with ascites or pleural effusion and hemoconcentration) occurs in 1–10% of patients (49,50). In critical cases, hypoxemia, renal insufficiency, thromboembolism, and rarely death can occur (51).

- A 29-year-old woman with polycystic ovary syndrome had her first in vitro fertilization cycle of leuprorelin acetate, FSH, and human chorionic gonadotropin (hCG) (52). Within 2 days she complained of abdominal distension, shortness of breath, and abdominal pain. Over the next few days she developed massive ovarian enlargement, ascites, hyponatremia, respiratory failure, and renal insufficiency. This was further complicated by duodenal perforation, probably due to severe physical stress.
- Ovarian hyperstimulation syndrome occurred in a woman with polycystic ovarian syndrome, 3 weeks after an intramuscular injection of leuprorelin acetate for endometriosis (53). She was later given further courses of the drug without this complication.
- A 35-year-old obese woman with a previously undiagnosed pituitary gonadotroph adenoma developed multiple ovarian cysts and abdominal distension after 1 month of leuprolide therapy (54).
- A 32-year-old woman who was not obese developed benign intracranial hypertension in association with ovarian hyperstimulation syndrome after ovulation induction using goserelin, FSH, and hCG (55). The syndrome did not recur during a second pregnancy in which FSH and hCG were not used.

It is unclear which of the hormonal agents used was responsible for this complication in the last case.

Gonadorelin receptor antagonists have been reported to lower the risk of OHSS significantly. A meta-analysis showed that cetrorelix but not ganirelix reduced the incidence of OHSS by 75%, both overall and the severe form (56).

Thromboembolism is a serious complication of OHSS (57–60).

- A previously healthy 34-year-old woman who underwent ovulation induction with leuprorelin acetate and FSH developed abdominal ascites due to OHSS, followed by acute aphasia and right hemiparesis (61). The stroke was caused by a large intracardiac thrombus.

A review identified 54 other reports of thromboembolic disease associated with ovulation induction; 60% were in upper limb veins and two-thirds of the patients had OHSS (62). The mechanism for the increased risk of thrombosis in these patients has not been determined, but hemoconcentration or a hypercoagulable state associated with high estrogen concentrations could be responsible.

Immunologic

Altered immune function has been reported in several cases associated with gonadorelin agonist therapy. This is possibly related to the initial surge in sex steroids that occurs with these agents, but there is no evidence that this is the mechanism. Cardiac allograft rejection occurred in three men within months of starting gonadorelin therapy for prostate cancer. One died of heart failure, but the other two recovered cardiac function after the gonadorelin agonist was withdrawn (63).

Systemic lupus erythematosus can be exacerbated in the initial gonadotropin-stimulating phase of gonadorelin therapy: in one case this was fatal (64).

Long-Term Effects

Tumorigenicity

Tumor flare occurs in up to 30% of treated patients after the first 4–7 days of gonadorelin therapy, due to an initial surge in gonadotropin concentrations (65). For this reason

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antiandrogen treatment is often given before gonadorelin in men with prostate cancer. However, despite tumor flare there was no difference in survival in a prospective, multicenter comparison of gonadorelin and surgical oophorectomy in 136 patients (66).

Second-Generation Effects

Teratogenicity

Pregnancies have occurred both after low-dose gonadorelin agonist therapy for ovulation induction and after higher-dose therapy for endometriosis or other indications: these have been reviewed in the context of a report of a 36-year-old woman who stopped monthly goserelin injections at 16 weeks of gestation and delivered a healthy girl. Congenital abnormalities have been reported in a few cases, including one child with trisomy 13, one with trisomy 18, and an intrauterine death due to thrombosis; however most pregnancies have had normal outcomes (67).

Drug Administration

Drug formulations

There is no difference in the adverse effects profiles of long-acting or depot formulations compared with shorter-acting analogues used continuously.

Drug-Drug Interactions

Oral contraceptives

There were mild increases in serum triglyceride and cholesterol concentrations in 13 hirsute women treated with triptorelin and a triphasic oral contraceptive, in a randomized comparison of triptorelin with flutamide + cyproterone acetate (68). Altered lipid profiles have not been described before in patients receiving gonadorelin agonists and oral contraceptives.

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Gonadorelin antagonists

General Information

The gonadorelin antagonists include abarelix, cetrorelix, degarelix, detirelix, ganirelix, iturelix, prazarelix, ramorelix, and teverelix (all rINNs).

Gonadorelin agonists suppress the release of gonadotropin after an initial surge: pituitary suppression takes up to 2 weeks to develop. Competitive antagonists at gonadorelin receptors cause immediate inhibition of gonadotropin secretion without down-regulating the receptor. This class of agents would therefore be preferable to gonadorelin agonists when a rapid clinical effect is desired, for example in controlled ovarian stimulation.

Early gonadorelin antagonists were of low potency and tended to cause histamine release (1). However, ganirelix and cetrorelix are better tolerated (1,2). They do not share the lipophilic and histamine-releasing properties of earlier generation gonadorelin antagonists and neither do they lead to depot formation. There appears to be a narrow therapeutic margin in ovarian stimulation protocols. Ganirelix concentrations correlate with body weight, and it has been suggested that the dose should be adjusted to weight to maximize pregnancy rates (3). The adverse effects of ganirelix are usually mild and include minor injection site reactions, mild nausea, and malaise (1).

Organs and Systems

Endocrine

In a small, controlled study of 10 healthy men, cetrorelix increased concentrations of insulin, leptin, and apolipoprotein A-I compared with placebo (4). The clinical significance of these findings has yet to be determined.

Skin

Local injection reactions are common and probably dose-related. In an open study of cetrorelix in its lowest effective dose of 0.25 mg/day, 3 of 346 women described local reactions (5). In another study of 154 women, 115 of whom were randomized to one 3 mg dose of cetrorelix, 25% had transitory redness or itching at the injection site (2). In a multicenter European study of 463 women randomized to ganirelix and 238 to buserelin, 17% of those given ganirelix had moderate skin redness, bruising, pain, or itching 1 hour after subcutaneous injection; this had mostly disappeared after 4 hours (6).

Five of 168 men with prostate cancer treated with abarelix had urticaria and pruritus, which resolved without treatment (7).

Reproductive system

Ovarian hyperstimulation syndrome is far less common with gonadorelin receptor antagonists than agonists in induction of ovulation (2,5). Hot flushes are rare, in contrast to gonadorelin receptor agonists: in a prospective, uncontrolled study of 346 women given cetrorelix, there was only one case of hot flushes (5).

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Gonadotropins

General Information

Human chorionic gonadotropin (HCG, hCG), extracted from the urine of pregnant women, has mainly luteinizing hormone (LH) activity. Human menopausal gonadotropin (HMG, hMG) contains both follicle-stimulating hormone (FSH) and luteinizing hormone in about equal amounts. Where materials of natural origin are used, the relative amounts of follicle-stimulating hormone and luteinizing hormone in pituitary gonadotropin extracts vary with the extraction procedure used. However, in recent years, both pure recombinant versions of human FSH and human LH (rhFSH, rhLH) have become available and have increasingly replaced the natural products.

Luteinizing hormone-releasing hormone (LHRH) is used in the treatment of infertility (1). It induces pulsatile release of gonadotropin, and excessive stimulation can result. However, if used over a period of time, the receptors cease to respond and there can be a fall in the concentrations of luteinizing hormone and follicle-stimulating hormone and a fall in sex steroid concentrations to the castrato range.

Treatment schedules for induction of ovulation have been described in a number of papers, but individual sensitivity of the ovaries varies greatly. Complications are generally considered more likely when the dose is excessive compared with individual needs; their incidence varies greatly from clinic to clinic, apparently because of differences in formulations and the dosage schedule used. Problems include superovulation, multiple pregnancy, and the hyperstimulation syndrome, which consists of rapid ovarian enlargement with intraperitoneal effusion (2). Ascites and hydrothorax are occasionally seen, probably due to an increase in vascular permeability at high estrogen concentrations (3). Vascular accidents have been reported, namely thrombophlebitis (4) and obstruction of the basilar artery (SED-12, 1033) (5). Gonadotropins have also been stated, although with much less certainty, to cause cardiomyopathy and behavioral and intellectual disturbances (SED-12, 1033) (6,7).

Observational studies

The European Metrodin HP Study Group has assessed the efficacy and safety of a highly purified urinary FSH in combination with human chorionic gonadotropin in inducing spermatogenesis in 28 men with primary complete isolated hypogonadotrophic hypogonadism, of whom 25 achieved spermatogenesis (8). Mean testicular volume increased by about 7 ml during treatment. Adverse events considered to be related to human chorionic gonadotropin were acne ($n = 3$), weight gain ($n = 2$), and gynecomastia ($n = 1$). Acne can be attributed to increased testosterone. Gynecomastia is an adverse effect of human chorionic gonadotropin treatment (9), and it may be caused by raised serum estradiol concentrations.

In 71 women undergoing in vitro fertilization and embryo transfer using recombinant human follicle-stimulating hormone in doses sufficient to attain a pregnancy rate of 24% (10), the main adverse effect was mild pain at the site of injection (less than 20% of patients) but there were two cases of ovarian hyperstimulation syndrome. In less than 10% of patients, redness, swelling, or bruising was seen and one patient developed headache.

The efficacy of recombinant human luteinizing hormone (rhLH) for supporting follicular development induced by recombinant human follicle-stimulating hormone (rhFSH) has been investigated in hypogonadotropic hypogonadal women (11). A total of 42 adverse events were reported in 14 of the 53 cycles in this study. Of these, 32 adverse events occurred in 11 of the 42 cycles treated with rhLH, and 10 occurred in three of the 11 cycles not treated with rhLH. The most frequent adverse events were pelvic and abdominal pain, headache, breast pain, nausea, ovarian enlargement, and somnolence. These adverse events are similar to those reported during therapy with follicle-stimulating hormone alone (11).

Comparative studies

When recombinant and urinary versions of follicle-stimulating hormone were compared under double-blind conditions in an in vitro fertilization program in a randomized, multicenter study (12), the former was more potent. There were no clinically relevant differences in safety between the two products and no cases of ovarian hyperstimulation syndrome.

The efficacy and safety of recombinant human follicle-stimulating hormone (r-hFSH) has been compared with that of highly purified urinary follicle-stimulating hormone (u-hFSH HP) in women undergoing ovarian stimulation for in vitro fertilization, including intracytoplasmic sperm injection, in a prospective, randomized study in 278 patients, who were treated with gonadotropin-releasing hormone and then received one of the two formulations in doses of 150 IU/day subcutaneously for

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the first 6 days; on day 7 the dose was adjusted, if necessary, according to the ovarian response (13). Human chorionic gonadotropin (10 000 IU subcutaneously) was administered once there was more than one follicle 18 mm in diameter and two others of 16 mm or larger. Rr-hFSH was more effective than u-hFSH HP in inducing multiple follicular development. There were seven cases (5.0%) of ovarian hyperstimulation syndrome in those given r-hFSH and three (2.2%) in those given u-hFSH HP; this difference was not significant.

General adverse effects

The short- and long-term effects of ovulation induction have been reported (8). In the short term, clomiphene and gonadotropins cause ovarian hyperstimulation syndrome (ovarian enlargement, bloating, and nausea) and multiple pregnancies; gonadotropins also cause ectopic pregnancy. In the long term, clomiphene may cause an increased risk of ovarian cancer.

Recombinant human chorionic gonadotropin

Recombinant human luteinizing hormone has now very largely replaced the product prepared from the urine of pregnant women (uhCG). In an open, randomized trial in 297 ovulatory infertile women in 20 US infertility centers, recombinant hCG 250 micrograms and 500 micrograms was compared with urinary hCG 10 000 U USP in assisted reproduction (14). The women were treated for a single cycle with one or the other. The mean numbers of oocytes retrieved per treatment group were equivalent (13–14). Although the numbers of fertilized oocytes on day 1 after oocyte retrieval and of cleaved embryos on the day of embryo transfer were significantly higher with 500 micrograms of recombinant hCG than with 250 micrograms, the incidence of the anticipated adverse events also tended to be higher.

More exact data on the adverse effects and relative safety of the recombinant and urinary formulations have been provided in a similar investigation in 259 women (15). In terms of safety, rhCG was well tolerated at a dose of up to 30 000 IU. Moderate ovarian hyperstimulation syndrome was reported in 12% of patients who received uhCG and 12% of those who received two injections of rhCG. There were no moderate or severe complications in patients who received a single dose of rhCG up to 30 000 IU. The results seem to show that a single dose of rhCG is effective in inducing final follicular maturation and early luteinization in in vitro fertilization and embryo transfer patients and is comparable with uhCG 5000 IU. The dose of rhCG that gave the highest efficacy to safety ratio was 15 000–30 000 IU.

The recombinant and urinary forms of human chorionic gonadotropin have also been compared in an international multicenter study, with similar findings (16), but it was notable that significantly more patients who were given uhCG reported local reactions (particularly inflammation and pain), presumably because of the presence of biological impurities.

Organs and Systems

Hematologic

Resistance of activated protein C and deep calf vein thrombosis has been reported during controlled ovarian stimulation for in vitro fertilization (17). The thrombosis occurred on the eighth day of human menopausal gonadotropin use and before human chorionic gonadotropin was given.

Reproductive system

There is a risk of ovarian hyperstimulation when an ovulation-inducing drug is followed by rapid ovarian enlargement with peritoneal effusion. The incidence of these complications varies with the product and dosage schedule used; in experienced hands, the frequency of complications may be no more than about 4%.

- In an unusual case reported in detail from Saudi Arabia, a 28-year-old woman receiving gonadotropins developed acute respiratory distress, abdominal pain, and severe hyponatremia associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (18). A multiple pregnancy nevertheless resulted and three fetuses went to term successfully.

While it is possible that the gonadotropins themselves induced SIADH, it seems more likely that it was a secondary complication of ovarian hyperstimulation.

The dangers of ovarian hyperstimulation with gonadotropins should not be underestimated. Quite apart from the risks of abdominal complications and even myocardial infarction, it can cause marked changes in liver function tests (19). It has been suggested that ultrasonographic monitoring is a means of detecting impending ovarian hyperstimulation, so that treatment can be suspended in good time (20).

- A 33-year-old woman developed severe symptomatic ovarian hyperstimulation after being given 10 000 IU of urinary human chorionic gonadotropin for empty follicle syndrome (21).

Although it has generally been thought that ovarian hyperstimulation would not occur when treating cases of empty follicle syndrome, this suggests that even when dealing with such patients, particularly if there is any reason to think that they are at risk of ovarian hyperstimulation, it is wise to take the usual precautions, using a much lower dose of human chorionic gonadotropin and adding progesterone for luteal support.

Just how dangerous and even life-threatening such hyperstimulation can be is illustrated by a recent case (22).

- A 28-year-old woman who had undergone attempted hormonal induction of ovulation presented some days later with ascites, oliguria, and vomiting. Over 2 weeks she developed severe hypoalbuminemia, due to a combination of intractable vomiting, intravenous rehydration, paracentesis, hypercatabolism, and proteinuria, with gross edema and progressively worsening liver function. Her serum albumin dropped to 9 g/l with liver function abnormalities: aspartate transaminase

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462 IU/l, alkaline phosphatase 706 IU/l, bilirubin 26 μmol/l, prothrombin time 19 seconds. Paracentesis and total parenteral nutrition coincided with rapid clinical improvement.

Other presenting signs of ovarian hyperstimulation include ascites, hydrothorax, thrombophlebitis, and, as in one recently reported case, acute dyspnea (23).

"Prolonged coasting" may offer possibilities as a means of preventing ovarian hyperstimulation syndrome where excessive doses of gonadotropins have been given (SEDA-20, 389); it involves temporarily withholding the gonadotropins and giving only a gonadotropin-releasing hormone agonist until the plasma estradiol concentration has fallen sufficiently; however, experience to date shows that it is not foolproof and that spontaneous abortions can result where pregnancies have already started.

In vitro maturation of immature oocytes represents a potential alternative for fertility treatment in patients who are likely to suffer hyperstimulation. In two patients considered to be at risk of hyperstimulation, because of polycystic ovaries, priming with hCG 10 000 IU (specified only as the IVF-C brand) was followed by removal of the oocytes 36 hours later (24). Oocytes considered to be mature at the time of collection were inseminated using in vitro fertilization or intracytoplasmic sperm injection (ICSI), and the resulting embryos were cultured to the blastocyst stage. Transfer of these blastocysts resulted in pregnancy in both patients. Immature oocytes were matured in a culture medium containing 30% human follicular fluid, recombinant follicle-stimulating hormone 1 IU/ml, hCG 10 IU/ml, and recombinant epidermal growth factor (rhEGF) 10 ng/ml. ICSI was then carried out. Two and five expanded blastocysts were obtained after 5 days of culture and were cryopreserved. The findings suggested that one can avoid the risk of ovarian hyperstimulation when using hCG in women with polycystic ovaries and that (at least when using mature oocytes) pregnancy can be established.

Immunologic

Gonadotropins of natural origin contain various allergens, which can give rise to hypersensitivity reactions. This was a serious problem with the "PMS" gonadotropin formulations formerly made from the serum of pregnant mares but now apparently obsolete; it was also described in the past with an FSH formulation of porcine origin. However hypersensitivity reactions can also occur to extracts of human material.

- A generalized allergic reaction to human menopausal gonadotropin (Pergonal) has been described during controlled ovarian hyperstimulation (25). In this case a desensitization protocol allowed the patient to complete her treatment cycle without further problems. Subsequently recombinant follicle stimulating hormone was used successfully and uneventfully.

On occasion, there have even been such reactions to highly purified human products, notably FSH; they can be managed by changing the treatment to intramuscular recombinant follicle stimulating hormone (26).

Long-Term Effects

Tumorigenicity

In a prospective study of 1200 infertile women in Israel, including a subgroup of women who developed breast cancer, there was no statistical association with the use of fertility-inducing drugs (27).

A subfertile man treated with human menopausal gonadotropin + human chorionic gonadotropin (hMG + hCG) developed a malignant teratoma of the testis; however, in view of his history a cause-and-effect relation was dubious (28).

Malignant melanoma

Concern that the drug treatment of female infertility might predispose the user to malignant melanoma was first engendered by a US study published in 1995 (29). Among women who had used clomiphene citrate for infertility the incidence of melanoma was higher (RR = 1.8; 95% CI = 0.8, 3.5) than among American women in general. However, in a case-cohort study of nearly 4000 infertile women there was a similar increase in the incidence of melanoma among those who had been treated with human chorionic gonadotropin compared with the rest; there was no association with the use of clomiphene.

Quite apart from the inherent discrepancy in these findings, several pieces of evidence have confused the debate. In the first place, the cohort of melanoma cases was small—barely a handful. In the second place, some earlier papers had suggested that infertility in women might of itself have an association with melanoma. The same impression came from various studies, in which the incidences of cancers in infertile women were examined (30–32). If that were true, it could affect the initial findings in either direction: a high spontaneous incidence might mask a real drug effect, or it might provide a predisposition to melanoma, which the drugs might then more readily trigger.

In the meantime, data from Australia have shown no greater incidence of melanoma among women who had used fertility drugs and undergone in vitro fertilization than in the country's general female population (33). Since then there has been one more significant paper, again from Australia, using data from a specialized fertility clinic in Queensland, relating to all women who attended the center over a decade (34). Whenever possible, the women were traced and their subsequent history noted. Originally intended as a retrospective case-cohort study using a subcohort, the approach had to be amended because no cases of melanoma were found in the subcohort. The work therefore proceeded as a matched case-control study; all the data were taken and set against publicly available figures on melanoma in Queensland. After some necessary exclusions, 3186 women were included; care was taken to minimize recall bias. Fourteen women developed melanoma after fertility treatment, eight cases being invasive. The expected incidence in the general population would have been 15.8 cases in the same period. The incidence actually observed was therefore only 0.89 of that anticipated (95% CI = 0.54, 1.48).

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The numbers of women who had used clomiphene or human menopausal gonadotropin were too small to make more differentiated calculations, but the incidence of melanoma seemed to correspond to that in the general population.

On current evidence, there seems no reason to discourage fertility-promoting drug treatments because of any risk of melanoma; they may even reduce it to some extent. However, this does not alter the fact that the data are deficient in various ways. Quite apart from the small numbers of melanoma cases that have been recorded, all the work to date has been performed in relatively sunny parts of the world; it is not known what would happen in other climates. Within countries, there are sharp differences in melanoma figures; in the USA, where about 32 000 new cases of skin melanoma were projected for 1994 (35), the highest melanoma rates occur among light-skinned populations in areas of intense sunlight, for example Arizona; the same applies to Queensland, Australia. In the USA as a whole there is a melanoma incidence among whites of 12.4 per 100 000 (36), while mortality rates vary inversely with latitude (37). Furthermore, in whites there has been a recent increase in the incidence of melanoma, during the precise period that this type of treatment has become popular, but probably for entirely different reasons, which may be associated with lifestyles and holiday habits; the reported incidence in whites rose by no less than 102% from 1973 to 1991 (37). Finally, as the Australian authors themselves stressed, the fact that the Queensland clinic was a private institution specializing in IVF/GIFT therapy means that women with endocrine- or ovulation-associated infertility may not so readily have been referred to it.

All this makes it very difficult to find a baseline incidence for melanoma with which cases treated for infertility can be compared. It is to be hoped that data of this type will continue to arrive from other centers, so that a definitive judgement will become possible.

Ovarian cancer

The hypothesis that the use of fertility drugs, including human gonadotropins and clomiphene, which increase the endogenous secretion of gonadotropins, might increase the risk of ovarian cancer appears to have come first clearly into the open in 1996 (38). However one can distil similar suggestions from other work from 1992 onwards (39–41), and anecdotal reports of an association have accumulated. The hypothesis has emerged that the increased number of ovulations (or the high concentrations of estrogen and gonadotropin) induced by drugs given to treat infertility could promote the development of ovarian cancers.

Ovarian cancer is much less common in married women, and during the last 30 years a direct inverse association has been found between the number of pregnancies and the duration of use of oral contraception on the one hand and the occurrence of ovarian cancer on the other. In 1971 a Lancet reviewer suggested that incessant ovulation might be a causal factor for the development of cancer of the ovary, in that the repeated rupture of follicles involved a cycle of damage to the surface epithelium, alternating with repair involving mitogenic activity and thereby in turn a risk of mutations (42). On the other hand, as has been pointed out, no correlation has been found between the risk of ovarian cancer and the age at menarche and menopause, that is the length of the fertile period, which might be anticipated if the so-called "ovulation hypothesis" is correct.

An alternative suggestion has been that gonadotropins, by enhancing the transformation of ovarian epithelial cells, also increase the risk of malignant transformation in this tissue. This idea is compatible with the inverse relations between ovarian cancer and pregnancy or oral contraception, since the latter processes suppress the secretion of gonadotropins.

Both the hypothesis of ovarian injury and that of gonadotropic influence seem to provide tempting explanations for any relation that there may be between infertility treatment and ovarian cancer, since such treatment both induces further ovarian "injury" by ovulation (sometimes multiple) and increases circulating gonadotropin concentrations. However, the existence of a possible mechanism does not prove that there actually is an association.

The stumbling block in either proving or disproving a link between the drugs and the cancers is the fact that infertility itself proves to be a risk factor for ovarian cancer. Women who fail to become pregnant have a higher risk of ovarian malignancy than other women, irrespective of whether they are taking drugs or not. A study from Denmark in 1997 showed that among infertile women the overall risk of ovarian cancer was not influenced by the use (or otherwise) of treatment with antifertility drugs (43). There is also American work that shows that among infertile women with a high risk of ovarian cancer circulating gonadotropin concentrations are low, which is what one would expect in such a group, but which does not tally well with the theory of gonadotropic causation (44).

Given current evidence, and with anecdotal reports that add nothing to the discussion of a possible cause-and-effect relation, one can discern considerable polarization in the discussion. It is not irrelevant, nor is it uncharitable, to point out that whereas fully independent academic workers have been most vocal in expressing concern, the papers that seek to dismiss an association between the drugs and the cancers have tended to emerge from groups that acknowledge support from pharmaceutical companies that produce the drugs used in this field. That is natural, and it results in the sort of argument and counter-argument that may do something to promote the emergence of the truth. However, it is currently unhelpful to the physician who is treating women for infertility and who is anxious to know what to tell the concerned patient, as well as finding some way of reducing whatever risks treatment may carry. However, bearing in mind the fact that the use of high doses of fertility drugs certainly brings with it other risks (for example that of sometimes dangerous overstimulation), this could be a reason for applying some of the more restrained available dosage schemes, and for avoiding persisting with this inherently abrasive treatment when it has failed to produce results on two or more occasions.

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Drug Administration

Drug formulations

The composition of different formulations of hCG is not entirely consistent, and could account for some discrepancies in clinical studies, as well as introducing risks. For example, previously, formulations of hCG have been shown to be toxic to Kaposi's sarcoma (KS) cells. However, clinical studies using commercial hCG formulations in the human sarcoma are highly contradictory (45). The apparent discrepancies between different studies may be because both pro- and anti-KS components are present in varying proportions in different hCG formulations. As certain hCG formulations may not only lack the ability to control Kaposi's sarcoma, but also contain contaminant KS growth factor(s), the authors suggested caution when using crude hCG for the treatment of Kaposi's sarcoma.

These findings point to the need to reconsider the international standards applicable to the standardization, formulation, and marketing of hCG products, whether of natural or recombinant origin.

Drug dosage regimens

The incidence of ovarian hyperstimulation is highly dependent on the therapeutic regimen. In one study (46) the following methods were compared:

- a conventional human menopausal gonadotropin + human chorionic gonadotropin (hMG + hCG) program;
- the hMG step-down method, in which the daily dose of hMG was reduced from 150 IU to 75 IU when the follicle diameter reached 11–13 mm;
- the sequential hMG + gonadotropin-releasing hormone (GnRH) method, in which hMG injection was switched to pulsatile GnRH administration (20 micrograms/120 minutes subcutaneously) when the follicle diameter reached 11–13 mm;
- a new, modified hMG + GnRH method, in which pulsatile GnRH was injected together with hMG; daily hMG was stopped and the GnRH dosage was changed from 10 to 20 micrograms when the follicle diameter reached 11–13 mm.

Initially, the established methods were used randomly to treat 34 cycles in 20 women; subsequently, five patients who failed to conceive after treatment with sequential hMG + GnRH were then treated by the new method. More than eight growing follicles and multiple pregnancies were observed during treatment by the conventional method. The incidence of ovarian hyperstimulation syndrome was 26% with the conventional method, 20% with the step-down method, and 0% with the sequential hMG + GnRH method; however, the rate of ovulation was only 50% with the sequential hMG + GnRH method. By contrast, with the new method fewer than three growing follicles occurred in 82% of patients, there was a 100% rate of ovulation, and there were no multiple pregnancies or ovarian hyperstimulation syndrome. Moreover, the new method induced pregnancy in three out of five patients. The authors considered their modified method suitable for the treatment of severe hypogonadotrophic amenorrhea. In view of the risks attached to ovarian hyperstimulation, this type of program certainly merits further evaluation.

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Granulocyte colony-stimulating factor (G-CSF)

See also Myeloid colony stimulating factors

General Information

Granulocyte colony-stimulating factor (G-CSF) primarily increases the production and function of neutrophils by stimulating the proliferation of committed myeloid precursors, rather than pluripotential stem cells (1).

Recombinant human forms of G-CSF that have been developed include filgrastim (rINN), lenograstim (rINN), nartograstim (rINN), and pegfilgrastim (rINN) and peg-nartograstim (rINN), which are pegylated derivatives of filgrastim and nartograstim.

Besides common therapeutic indications, G-CSF has also been used in severe chronic neutropenic diseases (congenital, cyclic, idiopathic), aplastic anemia, and neonatal neutropenia. G-CSF is sometimes used in healthy volunteers to mobilize blood progenitor cells or granulocytes before infusion into neutropenic patients.

Observational studies

In all clinical studies carried out to date, G-CSF has been well tolerated, whether given subcutaneously or intravenously. At the recommended doses (5–10 micrograms/kg), generalized musculoskeletal and transient bone pains, headache, and mild rash are the commonest adverse effects (2). No additional adverse effects or delayed consequences have been so far reported in neonates treated at birth for presumed bacterial sepsis (SEDA-20, 337). An increase in the size of the spleen has been reported (3,4). Transient rises in alkaline phosphatase, lactate dehydrogenase, and uric acid are considered to be normal physiological consequences of the rise in the neutrophil count (5). Long-term G-CSF administration in patients with severe congenital neutropenia has also been considered to be relatively safe, with discontinuation or temporary withdrawal in only seven of 44 patients (6).

Two reviews have examined the available data on the effects of hemopoietic growth factors on the duration of neutropenia and mortality in drug-induced agranulocytosis, which mostly consists of isolated case reports or small series of patients (7,8). The authors reached contrasting opinions, suggesting that hemopoietic growth factors might or might not be of interest in patients with severe drug-induced agranulocytosis. Adverse effects were noted in 13 of 118 case reports (7). Although most of them were benign, pulmonary toxicity or acute respiratory distress syndrome have been noted in a few patients.

Comparative studies

Few studies have directly compared the safety of the various available colony-stimulating factors. The frequency and severity of adverse effects associated with the prophylactic use of filgrastim (a bacterial cell-derived G-CSF) or sargramostim (a yeast cell-derived GM-CSF) have been assessed in a retrospective review of the medical records of 490 cancer patients from 10 centers (9). Sargramostim-treated patients had significantly more frequent non-infectious fever, fatigue, diarrhea, injection site reactions, edema, and dermatological adverse effects, whereas skeletal pain was more frequent with filgrastim. In addition, switching to the alternative treatment was more frequent in the sargramostim group (18% of patients) than in the filgrastim group (none of the patients). The authors tried to minimize selection bias, but the strength of the results was limited by the retrospective nature of the study.

The effects and the safety of a 5-day regimen of G-CSF ($n = 9$) or GM-CSF ($n = 8$) have been compared (10). Most patients complained of flu-like symptoms in both groups (six and seven respectively), but rash at the injection site was observed only in four patients treated with GM-CSF. In the G-CSF group, there was a fall in platelet count (below 150×10^9/l) in five patients, raised serum lactic dehydrogenase activity, and raised uric acid concentrations; three patients required transient treatment with allopurinol.

Use in healthy volunteers

The G-CSF is sometimes used in healthy volunteers to mobilize blood progenitor cells or granulocytes before infusion into neutropenic patients (11).

The safety of filgrastim in healthy donors has been evaluated in a large prospective multicenter study (12). The interim results, obtained from the first 150 enrolled donors aged 18–64 years who received either 10 or 16 micrograms/kg/day, have shown that 99 patients had at least one adverse effect graded as mild (grade I) in 35% of cases, moderate (grade II) in 62%, and severe (grade III) in 3%. Bone pain and headaches were the most common acute adverse events, and all the patients completely recovered after withdrawal of filgrastim. There were no apparent differences in the proportion, the severity, or the type of adverse effects according to the administered regimen.

That the use of G-CSF in healthy donors of peripheral blood progenitor cells is reasonably safe has been confirmed in an analysis of adverse effects in 737 evaluable patients included in three independent databases from Spain, the USA, and Japan (13–15). In one study, the overall incidence of adverse effects was 67%. The most common adverse effects were bone pain (71–90%), headache (17–54%), fatigue (6–33%), insomnia (up to 14%), nausea/vomiting (3–13%), and low-grade fever (6%). Although most adverse effects were rated as moderate, about two-thirds of the patients required analgesics for bone pain or headache. Other adverse events, such as non-cardiac chest pain, paresthesia, itching, or minor injection site reactions, were rare. Very few patients discontinued G-CSF because of clinical toxicity. Doses higher than 8.8 micrograms/kg/day, patients younger than 35 years of age, and female sex were significant risk factors for bone pain, headache, and nausea/vomiting respectively (15).

Moderate thrombocytopenia was common after apheresis; there was more severe but asymptomatic and promptly reversible thrombocytopenia (below 50×10^{12}/l) in up to 3.9% of patients (14,15). However, the respective contributions of apheresis and G-CSF in

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thrombocytopenia are difficult to assess. There was also a fall in the absolute neutrophil count to less than 1×10^9/l in 3% of patients 9–16 days after G-CSF withdrawal (15). Serum alkaline phosphatase and lactate dehydrogenase activities were increased about two-fold compared with pre-treatment, a finding that was explicable by G-CSF-induced neutrophilia (14,15). Symptoms of hypercoagulability have also been found in healthy donors.

However, more severe or unexpected consequences, including spontaneous splenic rupture, anaphylactoid reactions, deep necrotizing folliculitis, a psoriasiform eruption, acute gouty arthritis, iritis or episcleritis, and unexpectedly prolonged thrombocytopenia have been mentioned (SEDA-20, 337) (SEDA-21, 378) (SEDA-22, 407).

Among 90 healthy donors given 10 and 16 micrograms/kg/day of filgrastim for stem cell mobilization, severe adverse effects were mostly found in patients who had been given the higher dose (16), but one obese patient (body weight 170 kg) who received 10 micrograms/kg/day had a non-traumatic spleen rupture that resolved spontaneously.

Sufficient data on the potential long-term effects of G-CSF in healthy volunteers are still lacking. In one study, 101 healthy donors who had received filgrastim for a median of 6 days were questioned after a median of 43 (range 34–74) months to assess their current health; 70 donors also had a complete blood count (17). No unusual disease was detected and the blood counts were within the reference range. In 20 donors followed for 6–12 months after peripheral blood progenitor cell collection, there were no particular symptoms or hematological abnormalities (15).

The possible carcinogenic effects of G-CSF have also been discussed. There is as yet no indication of an increased risk of cancer, and no cases of acute or chronic leukemia were detected in a telephone interview study performed after a median of 39 months after peripheral blood progenitor cell donation in 281 donors (18).

Organs and Systems

Cardiovascular

Cardiovascular events have seldom been described in patients given colony-stimulating factors. However, possible excesses of cardiovascular events and unexpected deaths have been suggested (SED-13, 1115) (19), although the actual risk was not fully evaluated. In three isolated reports, acute arterial thrombosis or angina pectoris were deemed to have resulted from hypercoagulability with extreme leukocytosis and G-CSF-induced abnormalities in platelet aggregation (SEDA-20, 337) (SEDA-21, 377) (20). Increased platelet aggregation has also been found in healthy volunteers (21). Although the relevance of these findings is unclear, caution is warranted in patients predisposed to thromboembolic events.

- A 46-year-old donor denied pre-existing cardiac symptoms, but smoking and a family history of coronary artery disease were noted as possible risk factors (22). The pre-treatment electrocardiogram was normal. Six hours after the second and the third doses of G-CSF 10 micrograms/kg before peripheral blood progenitor cell collection, he developed symptoms and signs of cardiac ischemia, including palpitation, chest discomfort, trigeminy, and T wave inversion. However, troponin was unchanged. Cardiac catheterization showed severe coronary artery occlusion and he underwent percutaneous transluminal coronary angioplasty. He finally admitted mild exertional chest discomfort 2 weeks before the first dose of G-CSF.

Although not described during clinical trials, typical capillary leak syndrome has been anecdotally observed after G-CSF administration, illustrating the possible consequences of accelerated release of activated granulocytes (SEDA-22, 407) (23).

Microthrombotic necrotizing panniculitis has been reported (24).

- A 49-year-old woman received subcutaneous filgrastim 300 micrograms/day into the upper thighs for neutropenia prophylaxis after treatment of relapsing Hodgkin's disease with mitoguazone, etoposide, vinorelbine, and ifosfamide. After 3 days she suddenly developed fever, painful livedo, deeply infiltrated edema on the legs and thighs, and inflamed livedoid erythema on both soles. Deep biopsy specimens showed small vessel thrombosis with subcutaneous necrosis and hemorrhage. She recovered over the next 4 weeks after filgrastim withdrawal and prednisone treatment.

Although a causal relation was difficult to ascertain in the context of malignancy and cytotoxic chemotherapy, the short time to occurrence after G-CSF favored a causative role.

Respiratory

Pulmonary toxicity in patients receiving chemotherapy

Whether G-CSF can cause pulmonary toxicity or enhance chemotherapy-induced pulmonary toxicity is a matter of continuing debate (SED-13, 1115) (SEDA-21, 377). Some studies have suggested an increased risk of pulmonary complications in patients with hematological malignancies treated with various chemotherapeutic regimens who received G-CSF. In a review of 20 cases of interstitial pneumonia (including three that were fatal) observed during or within 10 days of G-CSF treatment, the chemotherapy regimen consisted of cyclophosphamide (95%), bleomycin (55%), methotrexate (25%), and etoposide (20%); most patients had non-Hodgkin's lymphoma (25). In another report, acute febrile interstitial pneumonitis occurred in five patients with non-Hodgkin's lymphoma who were receiving prophylactic G-CSF ($n = 3$) or GM-CSF ($n = 2$) within less than 48 hours after the second to fourth cycles of chemotherapy (doxorubicin, cyclophosphamide, bleomycin, methotrexate, plus methylprednisolone) (26). Lymphocytic alveolitis was confirmed in four of these patients, and all three patients tested had an increased number of CD8+ T cells. Even though all the patients received high-dose methylprednisolone, two died as a result of diffuse and extensive interstitial pulmonary fibrosis, identified at postmortem.

Several epidemiological studies have more accurately focused on this potential problem, but the results are

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conflicting. Unfortunately, most of them were retrospective and involved historical controls. Interstitial pneumonia was identified in eight of 40 patients treated with antineoplastic drugs (mostly methotrexate and bleomycin) plus G-CSF, while no such cases were found before the use of G-CSF among 35 historical controls (27). Severe pulmonary toxicity was observed in four of 12 patients treated with BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, plus prednisone) plus G-CSF compared with one of 24 historical controls who did not receive G-CSF (28). Of 52 patients treated with CHOP (cyclophosphamide, doxorubicin, vincristine, plus prednisolone), pulmonary symptoms were found in six who received G-CSF compared with none of 49 patients treated before the availability of G-CSF (29). This last study also raised the possibility that the intensified schedule of CHOP administration (every 2 weeks instead of every 3 weeks) allowed in patients undergoing G-CSF is a possible explanation for increased pulmonary toxicity. In contrast, other investigators failed to confirm that G-CSF increases the pulmonary toxicity of antineoplastic drugs, at least bleomycin (SEDA-21, 377). This was particularly exemplified by French authors who were unable to find an increased incidence of pulmonary complications in an analysis of two randomized controlled trials in 278 patients who received a bleomycin-containing regimen plus G-CSF or placebo (30).

Other predisposing factors have been suggested in five of 310 patients who developed acute adult respiratory distress syndrome (ARDS) after receiving G-CSF after allogeneic bone marrow transplantation or conventional chemotherapy (31). All had also been exposed to drugs or procedures with significant pulmonary toxicity. Respiratory symptoms developed suddenly, in conjunction with rapid recovery of the white blood cell count. Retrospective investigations showed that all five patients had the HLA-B51 or HLA-B52 antigens. In addition, plasma concentrations of tumor necrosis factor alfa and interleukin-8 were high at the onset of the ARDS. These effects did not occur in 45 patients who did not develop ARDS. The authors suggested that the risk of G-CSF-induced ARDS increases when the white blood cell count rises rapidly in patients who have the following conditions: HLA-B51 or HLA-B52 antigens, treatment with drugs with pulmonary toxicity, and a concomitant infection before recovery from granulocytopenia.

Whatever the truth of the matter, G-CSF should be regarded as a possible cause of pulmonary complications. The abrupt increase in the number of activated neutrophils after G-CSF may account for exacerbation of latent chemotherapy-induced pulmonary damage. Endothelial damage subsequent to increased neutrophil activity (that is, enhanced superoxide release and increased adhesion molecule expression and adherence) or the release of cytokines (IL-1, IL-6, TNF) has been advanced as possible mechanisms. In addition, transient slight hypoxia was found in G-CSF users, although no relation with specific cytotoxic drug treatment or previous radiotherapy was identified (32). A sudden increase in neutrophil count, a rise in LDH and C reactive protein, and the occurrence of dyspnea or fever in G-CSF-treated patients were proposed as possible early signs of the subsequent development of interstitial pneumonia.

Pulmonary toxicity in patients not receiving chemotherapy

The G-CSF can cause severe pulmonary toxicity in patients who are not receiving concomitant chemotherapy. For example, several reports have suggested that G-CSF administration for drug-induced agranulocytosis can play a role in the development or worsening of the adult respiratory distress syndrome (ARDS) (33).

- Fatal non-cardiac pulmonary edema has been reported in a 59-year-old man with renal amyloidosis who received G-CSF for 3 days for stem cell mobilization (34).

The authors extensively reviewed the available experimental and clinical data on the pulmonary toxicity of growth factors.

Another case suggested that G-CSF alone can cause severe pulmonary toxicity (35).

- A 72-year-old man with a normal chest X-ray was unnecessarily treated with G-CSF (5 micrograms/kg/day) for very moderate cytopenia. Five days later, he complained of dyspnea and fatigue, but without fever. His chest X-ray showed diffuse bilateral alveolar opacities and he had a low oxygen saturation. Blood cultures were negative, and infectious pneumonitis (with *Mycobacterium tuberculosis*, *Pneumocystis jiroveci*, *Herpes simplex*, and cytomegalovirus) was ruled out. Despite glucocorticoid and antibiotic treatment, he required mechanical ventilation and died 12 days after the onset of symptoms.

Nervous system

There is no clear evidence of specific central nervous system adverse effects due to G-CSF. In one patient, neurological symptoms, such as blurred vision, weakness, and headache, were attributed to G-CSF-induced extreme hyperleukocytosis with subsequent hyperviscosity (SEDA-21, 377). Encephalopathy, cortical blindness and seizures have also been mentioned in single case report (SEDA-21, 377).

Sensory systems

Severe retinal hemorrhage with a slowly reversible loss of visual acuity, and massive vitreous hemorrhage recurring after further G-CSF treatment and resulting in irreversible loss of vision in the affected eye have each been reported in single patients (SEDA-21, 378) (SEDA-22, 408). Concomitant hyperleukocytosis was suggested as a possible cause in the first patient, whereas G-CSF-induced reactivation of primary ocular inflammation (probably infectious in origin) was advanced as an explanation in the second case.

- A 61-year-old healthy donor developed marginal keratitis with associated mild uveitis after being given injections of filgrastim and sargramostim for 3 days (36). Topical prednisolone and withdrawal of sargramostim produced improvement within 24 hours, while filgrastim injections were continued.

Iritis and episcleritis have also been mentioned in healthy donors of blood progenitor cells.

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Endocrine

Several studies have suggested that single or short-term administration of G-CSF did not produce significant changes in the serum concentrations of cortisol, growth hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, or thyrotropin (SEDA-20, 337) (SEDA-21, 378).

Thyroid function and thyroid antibodies were not modified in 20 breast cancer patients (37), and only one case of hypothyroidism with increased thyroid antibodies has been reported (SEDA-20, 337). G-CSF had no effect on thyroid function in 33 patients with cancer, even in patients with pre-existing antibodies (38). Subclinical and spontaneously reversible hyperthyroidism occurred in eight patients without thyroid antibodies and with normal thyroid function before treatment, but this was felt to be related to stressful procedures.

Metabolism

Reductions in serum cholesterol concentrations have been sometimes noted in patients receiving G-CSF (2).

Hematologic

Erythrocytes

In a healthy woman, G-CSF was suggested to have transiently reactivated an alloantibody to an erythrocyte antigen (anti-Jka antibody) (39). This antibody was apparently passively transferred to the transplant recipient, who developed a high-titer of anti-Jka antibody during the first month after transplantation. This report raised the possibility that transplant recipients may develop hemolytic reactions to G-CSF subsequent to erythrocyte transfusion.

Leukocytes

The transient and moderate rises in leukocyte alkaline phosphatase and uric acid serum concentrations that are often observed after G-CSF treatment are considered to arise from an increased neutrophil count (SEDA-17, 396). Similarly, serum lactate dehydrogenase and alkaline phosphatase activities are often increased, and this should be interpreted as the consequence of enzyme release after growth factor-induced leukocyte recovery (SED-13, 1115).

Eosinophilia can occur in patients receiving long-term G-CSF for congenital neutropenia (6). Patients with congenital neutropenia or Felty's syndrome may also be susceptible to anemia and/or thrombocytopenia (6,40).

Platelets and clotting factors

There have been isolated reports of arterial thrombosis in patients or donors treated with G-CSF. In one study, there was more frequent and significantly more severe thrombocytopenia in patients who received G-CSF until 2 days before chemotherapy compared with controls, who had post-chemotherapy G-CSF only (41). This suggests that administration of G-CSF before chemotherapy can increase the bone marrow toxicity of the latter, a potentially relevant finding in patients undergoing intensification of chemotherapy with shortening treatment intervals. Isolated cases of thrombocytopenia have been reported in HIV-infected patients (SEDA-20, 337), and a reduced platelet count, sometimes associated with coagulation abnormalities, was retrospectively identified in nine of 28 patients who received prolonged G-CSF with antiretroviral drugs (42). Emperipolesis of neutrophils within megakaryocytes, an unusual feature of thrombocytopenia, was also reported in one patient receiving high-dose G-CSF (43).

Although abnormalities in platelet aggregation have been described in healthy volunteers (21), coagulation disorders are not typical features in patients who receive G-CSF. Only one HIV-infected patient treated with zidovudine and increasing G-CSF doses had a disseminated intravascular coagulopathy (42).

Hemostatic changes due to G-CSF have been investigated in 22 healthy donors (44). The patients received G-CSF 5 micrograms/kg bd for 5 days and underwent a series of laboratory tests before and 96 hours after G-CSF administration, that is, immediately before leukapheresis. The results suggested possible hypercoagulability, including significant increases in Von Willebrand factor and factor VIII and evidence of thrombin generation. The clinical relevance of these findings and of the previously reported effects of G-CSF on platelet aggregation (SED-14, 1270) is unknown.

Treatment with G-CSF in 26 healthy donors for 5–7 days produced transient changes in endothelial cell and clotting activation markers (45). Although these abnormalities may indicate a risk of thrombotic complications, their clinical relevance to healthy donors is unknown.

- A 53-year-old man with aplastic anemia had clinically asymptomatic and reversible hypercoagulability after the transfusion of granulocytes obtained from G-CSF-stimulated donors (46).

The authors stressed the recurrence of the disorder after each of the three granulocyte transfusions that the patient had received and suggested that adverse effects might occur after transfusion performed with G-CSF-mobilized granulocytes, even though the patient has not been given G-CSF.

The differential effects of G-CSF and GM-CSF on several coagulation parameters have been compared in 34 patients who received the colony-stimulating factors after bone marrow transplantation (47). The data suggested activation of the coagulation system in patients treated with GM-CSF, which resulted in a tendency to more frequent veno-occlusive disease of the liver and a significantly higher incidence of hemorrhage.

Hemopoietic tissues

Asymptomatic but significant increases in spleen volume (up to 150%) concomitant with neutrophilia have been reported in about 25% of patients treated with G-CSF for severe chronic neutropenia (6,48).

Of 13 patients with glycogen storage disease type 1b and neutropenia or neutrophil dysfunction treated with G-CSF, all developed splenomegaly, usually after 3 months of treatment (49). Hypersplenism, as defined by moderate thrombocytopenia on at least two consecutive blood counts, was found in five patients, but none required specific interventions. In one carefully

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documented case, splenomegaly with extramedullary hemopoiesis was deemed to result from the mobilization of early hemopoietic progenitors from the marrow to the spleen (50). Experimental data suggested that reseeding of hemopoietic cells from the bone marrow may account for this phenomenon (51).

Splenic rupture has been reported in patients with cancer and in healthy donors, and should be anticipated by regular assessment of splenic size during prolonged treatment.

- Spontaneous splenic rupture, with histological evidence of massive extramedullary myelopoiesis after splenectomy, has been reported in a 33-year-old healthy donor who received G-CSF for 6 days (52).
- Life-threatening splenic rupture occurred in a 22-year-old woman with acute myeloid leukemia (53). The rupture was diagnosed in the presence of abdominal pain and signs of hypovolemic shock, 10 days after she started G-CSF treatment to support peripheral blood stem cell transplantation. Histology after splenectomy showed only small clusters of myeloblasts and no specific cause for the rupture. In particular, she was still pancytopenic at the time of splenic rupture.

One patient also had rapid and generalized lymph node enlargement and lymphopenia with recurrence of lymphadenopathy after a further course of G-CSF (54).

Liver

Clinical trials did not suggest G-CSF-induced hepatotoxicity, and very few cases of liver abnormalities have been reported (SED-13, 1116) (SEDA-19, 343). Although it may have been coincidental, the chronological features were in keeping with drug-induced hepatotoxicity in at least two patients, since increases in serum liver enzymes or acute hepatitis associated with pancreatitis recurred after renewed administration of G-CSF. One additional case of fatal fulminant hepatitis could have been due to alcohol abuse and the use of several concomitant drugs.

Urinary tract

No evidence of nephrotoxicity emerged from clinical trials, but a transient increase in serum creatinine concentration has been described (SEDA-20, 337).

- A 4-year-old girl was given filgrastim (30 micrograms/kg/day) for severe congenital neutropenia diagnosed at birth (55). Two months later she developed microscopic hematuria and recurrent episodes of macroscopic hematuria and proteinuria. Renal ultrasonography was normal and no obvious cause was found, but filgrastim was continued. Microscopic hematuria and multiple episodes of macroscopic hematuria with mild proteinuria persisted for 4 years. At this stage, she had an acute episode of macroscopic hematuria with more severe proteinuria and an increase in serum creatinine concentration (202 μmol/l). There were features of membranoproliferative glomerulonephritis type I on renal biopsy. Her renal function improved after filgrastim withdrawal and again deteriorated after reintroduction, with a persistent increase in serum creatinine concentration. Hematuria and proteinuria partially responded to glucocorticoids. Filgrastim was finally replaced by lenograstim when she was 13 years old, and this resulted in reduced proteinuria and improved renal function.

Although the girl also had hepatitis C virus infection during the course of her disease, renal dysfunction preceded this. The persistence of hematuria and proteinuria after the disappearance of hepatitis C virus RNA also argued against a role of hepatitis C infection.

Isolated and reversible hematuria was noted in several patients receiving long-term treatment for congenital neutropenia (6).

Although suggested in one report, G-CSF does not appear to increase the risk of renal allograft rejection (SEDA-20, 337).

Skin

A wide range of cutaneous reactions have been reported in patients receiving G-CSF. Most skin disorders were minor with a skin rash or itching in about 8% of patients (56).

Injection-site reactions

Localized cutaneous lesions were sometimes noted after subcutaneous injection and mimicked those described with GM-CSF. Injection-site subcutaneous nodules infiltrated by leukemic cells have been found in patients treated for acute leukemia (SEDA-19, 343), but in two other patients, inflammatory macrophages were misinterpreted as malignant cells (SEDA-20, 337).

The G-CSF can cause a lichenoid reaction at injection sites (57).

- A 40-year-old woman with metastatic breast cancer received cyclic subcutaneous G-CSF for chemotherapy-induced neutropenia. After 5 months she had a pruritic rash at injection sites. She did not change the injection sites and the lesions recurred after each injection. Biopsy showed a lichenoid reaction and the lesions healed with residual pigmentation after topical steroid application and G-CSF discontinuation. GM-CSF was well tolerated.
- Erythema exsudativum multiforme developed in a 40-year-old healthy donor 3 days after lenograstim was started for peripheral blood stem cell mobilization (58). The lesions were on the hips, apart from the site of lenograstim injection, and resolved 1 week after withdrawal.

Neutrophilic dermatitis

The possible role of G-CSF in inducing or exacerbating neutrophilic dermatitis (Sweet's syndrome) is in keeping with its stimulant effects on the production and functions of neutrophils. Although the ability of G-CSF to induce Sweet's syndrome (acute febrile neutrophilic dermatosis) is disputed, because the underlying malignant disease is a possible confounding factor, several reports of biopsy-proven Sweet's syndrome have been convincing; they have shown variously a close temporal relation between G-CSF treatment and the variations in neutrophil count or the recurrence of the lesions after G-CSF re-administration; one report concerned two patients with chronic neutropenia (SED-13, 1116) (SEDA-20, 338) (SEDA-21,

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378). Localized Sweet's syndrome can also occur (SEDA-20, 338). The spectrum of forms of G-CSF-induced neutrophilic dermatitis is wide. In two children with painful erythematous lesions attributed to G-CSF, histology showed microscopic, sterile, neutrophilic abscesses in one and neutrophilic panniculitis in the other (59). Other forms of neutrophilic dermatitis mentioned in G-CSF-treated patients have included isolated cases of bullous pyoderma gangrenosum and neutrophilic eccrine hidradenitis (SEDA-21, 378) (SEDA-22, 408) (60). Sweet's syndrome has also been described in a case of hairy cell leukemia (61).

Other skin complications

Disseminated vesiculopustular lesions, generalized and indurated erythematous papules or plaques, severe exacerbation of acne, and lenograstim-induced erythema nodosum, with recurrence on filgrastim administration, were mentioned in isolated patients (SED-13, 1116) (SEDA-20, 337). Finally, several reports convincingly involved G-CSF in exacerbations of chronic psoriasis or psoriatic arthritis, suggesting that activated neutrophils play an important role in the occurrence and propagation of skin inflammation (SEDA-21, 378) (62).

Musculoskeletal

Transient bone and musculoskeletal pain preceding myeloid recovery by 2–3 days are the commonest adverse effects of G-CSF, and occur in up to 25% of patients. Bone pain usually disappears despite continued treatment, but severe, narcotic-resistant, generalized bone pain was attributed to bone marrow necrosis in one patient (63).

The G-CSF-induced exacerbation of pseudogout occurred in two patients (SEDA-20, 337) (SEDA-22, 408).

- A 69-year-old man with a non-small-cell lung cancer treated with paclitaxel and nedaplatin developed polyarthralgia and myalgia with rising fever after receiving G-CSF for 5 days (64). Similar symptoms recurred after the second cycle of chemotherapy and on retreatment with G-CSF. Synovial biopsy showed acute synovitis with a foreign body-type giant cell reaction.

Worsening of rheumatoid symptoms has been reported in patients receiving G-CSF, particularly in patients with neutropenia due to Felty's syndrome (SEDA-19, 344) (SEDA-20, 338). Although concern about the short-term safety of G-CSF has been raised in these patients, other investigators feel that G-CSF can be used for a prolonged period in most patients without a flare-up of rheumatoid symptoms (SEDA-22, 408). Similar conclusions were reached in patients with underlying rheumatoid arthritis (SEDA-21, 378). The mechanisms of rheumatological flare-up are unclear. G-CSF-induced localized neutrophil activation or G-CSF-mediated increases in local neutrophil responses to TNF-alfa have both been suggested as underlying processes.

Several investigators have diagnosed bone mineral loss, with features of osteopenia/osteoporosis on radiography, quantitative computed tomography, or absorptiometry, in patients receiving long-term G-CSF for severe congenital neutropenia (6,65). In one child there was significant improvement in bone mineral density with pamidronate (66). In another child, who had osteoporotic vertebral collapse, extensive investigations showed reduced bone mineral content, reduced concentrations of osteocalcin, and features of osteoporosis on bone biopsy (SEDA-19, 344). The role of G-CSF was unclear, because bone mineral loss is a possible complication of the underlying disease. Indeed, improvement or stabilization during G-CSF treatment was noted in several patients (6). Furthermore, there was no apparent effect on height, head circumference, or weight in patients under 18 years of age (6). In another study, there was bone mineral loss with features of osteopenia/osteoporosis in 15 of 30 patients treated with G-CSF for a mean of 5.8 years for severe chronic neutropenia (65). However, six of nine patients investigated before G-CSF treatment had evidence of osteopenia/osteoporosis.

These reports and the findings of G-CSF-induced mobilization of osteoclastic progenitors in healthy volunteers (67) support a possible role of G-CSF in bone changes.

Immunologic

Leukocytoclastic vasculitis is a well-described and confirmed adverse effect of G-CSF, as documented in several reports, with recurrence after renewed administration of G-CSF (SEDA-19, 343). Most cases were confined to the skin, and renal insufficiency with hematuria and proteinuria was noted in only very few patients. Based on 18 cases reported in the literature or to the manufacturers, vasculitis was thought to have occurred in 6% of patients with chronic benign neutropenia, but in only six of about 200 000 patients with malignant disease (68). Vasculitis usually developed when the neutrophil count rose above 800×10^6/l, suggesting that an increase in neutrophil count may play a role in necrotic vasculitis. Against this background, the occurrence of vasculitis is not considered as treatment-limiting and does not preclude further G-CSF administration if the absolute neutrophil count is lower than 1000×10^6/l.

Antibodies to rG-CSF have not so far been reported, even in patients on long-term treatment.

Exacerbation of lupus-like symptoms, with seizures, psychosis, and vasculitis, has been noted during three of 12 treatment courses in neutropenic patients with severe systemic lupus erythematosus (69).

Type I reactions

Although IgE-specific antibodies have not been yet detected, filgrastim is undoubtedly associated with type I allergic reactions. This has been illustrated in well-documented reports of anaphylactic reactions, urticaria, and angioedema, with positive intradermal tests in several patients (SEDA-20, 338) (70,71). However, anaphylaxis to G-CSF is supposedly rare and the manufacturer is aware of only two cases of anaphylactoid reactions among 20 000 patients treated with filgrastim (72). One report has suggested possible cross-reactivity between filgrastim and other products derived from *Escherichia coli* (73). Although one patient who developed an anaphylactic-like reaction, with dyspnea, hypotension, and a pruritic erythematous skin rash, within minutes of G-CSF

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injection, later tolerated GM-CSF uneventfully (74), possible cross-reactivity between G-CSF and GM-CSF has been reported in at least one patient (75).

Long-Term Effects

Tumorigenicity

G-CSF-induced leukemia and myelodysplasia in patients with aplastic anemia or congenital neutropenia

Concerns have arisen over the prolonged use of G-CSF in patients with aplastic anemia, congenital neutropenia, or similar disorders and a possible increased or accelerated risk of myelodysplasia or acute leukemia (SED-14, 1274). Several investigators have noted reversible increases in circulating blasts during G-CSF treatment, and isolated reports have indicated a shortened delay in the occurrence of myelodysplasia and/or acute myeloid leukemia in this setting (SED-13, 1117) (SEDA-20, 338) (76). An abnormal karyotype (mostly monosomy 7) was sometimes found, and in vitro proliferation of myeloblasts by G-CSF was obtained in several patients. In addition, the potential role of point mutations on the G-CSF receptor has been also discussed as regards four of 28 patients with congenital neutropenia, two of whom developed acute myeloid leukemia (77). Myelodysplastic syndrome with monosomy 7 was also associated with G-CSF in another patient, with a reduction in the number of monosomy 7 positive cells after G-CSF withdrawal and a further increase after readministration (78).

This has been analysed in a number of epidemiological studies, most of which involved historical controls. The underlying predisposition of patients with aplastic anemia to develop myeloid malignancy has usually confounded attempts to determine whether growth factors are contributing factors.

In a retrospective study of 72 adults with aplastic anemia, of whom 18 received G-CSF and 23 received ciclosporin, five developed myelodysplastic syndrome (79). Four of them had received G-CSF + ciclosporin and all four had monosomy 7. The hematological disease was diagnosed within 16–31 months after the diagnosis of aplastic anemia and 12–20 months after the start of G-CSF treatment. Two died from acute leukemia. The incidence of myelodysplastic syndrome in this subgroup of patients was therefore 8.3% after 2 years and 39% after 3 years, whereas no case was observed over a 20-year period in patients not receiving this combined treatment. Univariate analysis showed that G-CSF + ciclosporin and G-CSF alone for more than 1 year were the most significant risk factors for the short-term development of monosomy 7 myelodysplastic syndrome.

In a prospective, multicenter, cohort study of 113 patients with aplastic anemia under 18 years of age, 12 developed myelodysplastic syndrome after a median of 37 months after the diagnosis of aplastic anemia and four others developed other cytogenetic clonal changes, of which the most common abnormality was monosomy 7 (80). From a multivariate analysis, G-CSF treatment duration and non-response to immunosuppressive therapy at 6 months were statistically significant risk factors for the development of myelodysplastic syndrome. The risk increased in proportion to the duration of G-CSF treatment, and the relative risks of the myelodysplastic syndrome were respectively 4.4 and 8.7 times higher in patients who received G-CSF for more than 120 and 180 days, compared with those who received it for less.

In contrast, a number of other studies did not confirm that the G-CSF increases the risk of myelodysplasia or acute leukemia, but the authors did not rule out a possible leukemogenic effect. In a study of patients with severe aplastic anemia the frequencies of cytogenetic abnormalities and myelodysplasia or leukemia were similar in 87 patients treated with G-CSF in addition to immunosuppressive treatment compared with 57 patients who did not receive G-CSF (81). Although the authors stated that a leukemogenic effect of G-CSF was unlikely, they mentioned that the median interval of appearance of cytogenetic abnormalities was shorter in the G-CSF group.

In another study the data from an international register of patients with severe chronic neutropenia were analysed (82). Of 352 patients treated with G-CSF for congenital neutropenia and followed for a mean of 6 years (maximum 11 years), 31 developed myelodysplasia or leukemia, whereas there were no cases in 344 patients with idiopathic or cyclic neutropenia. Associated cytogenetic clonal changes consisted of partial or complete loss of chromosome seven in 18 patients and abnormalities in chromosome 21 in nine. Isolated cytogenetic abnormalities were also found in nine other patients. None of the patients had abnormal marrow cytogenetic changes before G-CSF therapy. A more complete analysis failed to identify any correlation between G-CSF dose and treatment duration in patients who developed myelodysplasia or leukemia compared with those who were not affected. Although this argues against a role of G-CSF in the conversion of congenital neutropenia to myelodysplasia or leukemia, the authors recognized that a direct leukemogenic role of G-CSF could not be completely ruled out.

After a median follow-up of 43 months in 123 children treated with G-CSF, there was no difference in the incidence of secondary myelodysplasia or acute myeloid leukemia, in patients with aplastic anemia who survived longer than 2 years compared with the expected rate calculated before the use of G-CSF (83). Similarly, there was no evidence of an increased risk of myelodysplasia or acute myeloid leukemia in 54 patients treated with G-CSF for 4–6 years for severe congenital neutropenia (6).

Finally, in a randomized study in 102 patients of the safety and efficacy of lenograstim (5 micrograms/kg/day for 14 weeks) combined with standard immunosuppressants, there were no differences between the groups in survival, hematological response, or the occurrence of secondary leukemia (one case of myelodysplastic syndrome in each group) at a median follow-up of 5 years (84).

The role of G-CSF in leukemic transformation therefore remains unproven, primarily because these patients might be otherwise predisposed or have a previous history of immunosuppressive therapy. Although the clinical benefits of G-CSF probably outweigh any hazard of leukemogenesis, the possibility of an increased risk of myelodysplastic syndrome or acute myeloid leukemia under the influence of G-CSF should be borne in mind.

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Careful monitoring of morphological bone marrow changes and cytogenetic studies are therefore recommended, and large randomized trials with long-term follow-up are still awaited to clarify these findings.

Stimulation of tumors or leukemic cells in patients with cancer

Because growth factor receptors are found on several tumor cell lines, there has been great concern that G-CSF may stimulate tumor progression (SED-13, 1117) (SEDA-20, 338) (SEDA-21, 378), with some anecdotal evidence of a temporal relation between G-CSF administration and the development or acceleration of malignancies, such as gastric cancer or Hodgkin's diseaseodgkin's disease (SED-13, 1117) (85–87). However, early clinical data and the results of several randomized controlled trials in patients with various malignancies provided no evidence for increased relapse rates (88,89).

With the demonstration of growth factor receptors on leukemic cells, the question has also been raised of whether there could be stimulation of leukemic cell growth with promotion of malignancies, or acceleration in the progression of myelodysplastic syndromes to acute myeloid leukemias. Although there has been some reluctance to use G-CSF in acute myeloid leukemia, no clear evidence of disease acceleration or recurrence was found in several trials (SED-13, 1117) (SEDA-21, 379). Based on an analysis of available in vitro data and published clinical trials, the risk of significant stimulation of leukemia or leukemic clone with an increased incidence of leukemia regrowth is currently estimated to be very low (90). Although clinical benefits are still debated in this setting, growth factors are considered to be safe in reducing the duration of neutropenia in patients with acute myeloid leukemia.

Although G-CSF is not believed to stimulate malignant lymphoid cells, G-CSF receptors have been found in patients with T cell leukemia, and this was associated with a significant increase in T cell leukemia cells in several patients (SEDA-21, 379). Other uncommon consequences of G-CSF have included blast mobilization with a phenotype change from common acute lymphoblastic leukemia to biphenotypic leukemia in one patient (87).

The risk of secondary cancer has been assessed in 412 children treated with etoposide and anthracyclines for acute lymphoblastic leukemia, 99 of whom also received G-CSF and 58 of whom received cranial irradiation (91). Overall, 20 children developed myeloid leukemia and myelodysplastic syndrome at a median of 2.3 years after treatment. The 6-year cumulative incidence of these secondary cancers was 11% among patients who received G-CSF, close to that observed in those who received cranial irradiation (12%), but significantly higher than in those who received neither irradiation nor G-CSF (2.7%).

Acceleration of myelodysplastic syndrome

A reversible increase in circulating blasts has been noted during G-CSF treatment in several patients with myelodysplastic syndrome, and other reports have documented a reversible secondary myelodysplastic syndrome or accelerated progression of a previous myelodysplastic syndrome (SEDA-21, 379) (89). In other instances, pseudoleukemia features or transient leukoerythroblastosis were evidenced on bone marrow biopsy (SEDA-19, 344) (SEDA-20, 338). Although there was no increased incidence of acute myeloblastic leukemia in G-CSF-treated patients with myelodysplastic syndrome, it has been considered that patients whose bone marrow contains more than 20% of blast cells should be regarded as being at higher risk of leukemic transformation (89).

Myeloma

The safety of growth factors in patients with myeloma is also of concern, as they can stimulate the proliferation of myeloma cells through IL-6 expression. Only isolated case reports, including accounts of the mobilization of clonal myeloma cells into the peripheral circulation, rapid progression of a multiple myeloma, or the new onset of a monoclonal gammopathy, directly or indirectly support the view that caution should be exercised in patients with multiple myeloma (SED-13, 1118) (92).

Susceptibility Factors

Renal disease

A hemodialysis patient developed refractory pleural effusion with prolonged leukopenia and thrombocytopenia, and another developed sudden cyanotic dyspnea with subsequent death after G-CSF administration for drug-induced neutropenia (93). The authors suggested that hemodialysis patients receiving G-CSF may have an increased risk of adverse effects.

Drug Administration

Drug formulations

Pegfilgrastim was developed by adding a polyethylene glycol molecule to the *N*-terminus of filgrastim. In a phase III study in 301 patients with advanced breast cancer who underwent myelosuppressive chemotherapy a single injection of pegfilgrastim had similar efficacy and safety profile to repeated injections of filgrastim (94).

Drug–Drug Interactions

Theophylline

A 30% increase in theophylline clearance occurred after the administration of G-CSF or GM-CSF (SEDA-20, 338).

Vincristine

In one study there was a synergistic effect of GM-CSF or G-CSF and cumulative doses of vincristine in causing severe atypical neuropathy (SEDA-20, 339).

Interference with Diagnostic Tests

Blood glucose analysis

Artifactual hypoglycemia occurred in patients taking G-CSF when blood glucose was analysed on the Ektachem 700 analyser (SEDA-20, 339).

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Hepatitis B surface antigen

A single dose of G-CSF in a healthy donor produced a false positive test for hepatitis B surface antigen using an enzyme immunoassay (95).

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Granulocyte–macrophage colony-stimulating factor (GM-CSF)

See also Myeloid colony stimulating factors

General Information

Granulocyte–macrophage colony-stimulating factor (GM-CSF) primarily increases the production and activity of neutrophils, and stimulates the proliferation of monocytes and eosinophils.

Recombinant human forms of GM-CSF that are in use include molgramostim and sargramostim. Based on a retrospective review and historical comparison, the safety of molgramostim has been thought to be less than that of sargramostim (1). However, there were no significant differences in the adverse effects profiles and severity of adverse effects with GM-CSF and G-CSF in 181 patients with cancers randomized to receive sargramostim (a yeast cell-derived GM-CSF) or filgrastim (a bacterial cell-derived G-CSF) for chemotherapy-induced myelosuppression (2).

Uses

The potential clinical applications of GM-CSF have been lengthily reviewed (3). It is used:

- to reduce chemotherapy-induced myelosuppression in patients with metastatic sarcoma, breast cancer, or melanoma.
- to facilitate the harvesting of peripheral blood stem cells for autologous bone marrow transplantation.
- in cyclic neutropenia.
- to aid recovery after high doses of ionizing radiation, and less successfully, for severe aplastic anemia.

GM-CSF has also been approved for the alleviation of neutropenia following myeloablative treatment with autologous bone marrow transplantation and ganciclovir-induced neutropenia in patients with AIDS (4).

General adverse effects

The adverse effects of GM-CSF are dose-related and have usually been tolerable. At the doses usually recommended, systemic adverse effects develop in 25–30% of patients, but they are rarely treatment-limiting (5). Doses over 250 micrograms/m^2 and the intravenous route are associated with more frequent adverse effects.

Bone pain and flu-like symptoms, with fever, myalgia, chills, and headache, are the most frequent adverse effects (5–7). These reactions occur in 40–60% of all treated patients (8) and are probably due to the activation of secondary cytokines (such as TNF-alfa and IL-1) (9). Other frequently reported adverse effects include erythematous eruptions at the injection site, thrombophlebitis, nausea, facial flushing, dyspnea, and gastrointestinal disorders with anorexia and weight loss. Severe fatigue and weakness are rare.

The first dose of GM-CSF can be followed within 3 hours by flushing, hypotension, tachycardia, dyspnea, musculoskeletal pain, and nausea and vomiting (6). At very high doses (generally over 16 micrograms/kg/day), erythroderma, weight gain, and edema with pleuropericardial effusions and ascites have been reported (10). Renal symptoms have also been described (11,12), as have various biochemical abnormalities, possibly due to secondary hyperaldosteronism (13–15).

Fever was observed in up to 50% of patients at doses over 3 micrograms/kg. The fact that the fever peaks at a constant time after GM-CSF injection, the lack of clinical and biological signs of infection, and a prompt response to paracetamol have been proposed as criteria to recognize GM-CSF-induced iatrogenic fever (16), but this concept is still disputed (17).

Organs and Systems

Cardiovascular

Mild local phlebitis sometimes occurs at intravenous sites of administration of GM-CSF. Central venous catheter site thrombosis, inferior vena cava thrombosis, and possible pulmonary embolism have sometimes been observed (5,18). Although chemotherapy for breast cancer is associated with a higher risk of developing vascular thrombosis, iliac artery thrombosis was attributed to GM-CSF in two patients (19).

Raynaud's phenomenon has been reported, but confounding factors including the use of high-dose antineoplastic drugs are possible (5).

A rapidly reversible first-dose syndrome (dyspnea, hypoxia, tachycardia, and hypotension) can occur within the first hour after the first continuous infusion in 15–30% of patients (5). A dose-limiting vascular leak syndrome was consistently described in patients receiving GM-CSF 30 micrograms/kg/day or more, but lower doses were also reported to induce a clinically relevant capillary leak syndrome (SEDA-22, 408) (20,21). Continuation of GM-CSF treatment at the same dose or lower and careful management was possible in some patients. Endothelial cell damage with an increase in the transcapillary escape rate of albumin and the possible role of IL-1 and TNF production by GM-CSF-activated monocytes were

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suggested as possible mechanisms. This was consistent with the observation of marked hypoalbuminemia in some instances associated with edema and ascites after GM-CSF in four of nine patients treated for myelodysplastic syndrome or aplastic anemia (22).

Respiratory

It has been suggested that, as in the case of G-CSF, GM-CSF can increase the pulmonary toxicity of bleomycin and facilitate the development of the adult respiratory distress syndrome (ARDS), but evidence is still very sparse (SED-13, 1112) (SEDA-19, 342).

Acute febrile interstitial pneumonitis occurred within less than 48 hours after the second to fourth cycles of chemotherapy (doxorubicin, cyclophosphamide, bleomycin, methotrexate, plus methylprednisolone) in five patients with non-Hodgkin's lymphoma who were receiving prophylactic G-CSF ($n = 3$) or GM-CSF ($n = 2$) (23). Lymphocytic alveolitis was confirmed in four of these patients and all three patients tested had an increased number of CD8+ T cells. Even though all the patients received high-dose methylprednisolone, two died as a result of diffuse and extensive interstitial pulmonary fibrosis, demonstrated at postmortem. Although both G-CSF and GM-CSF can cause acute pneumonitis in patients with cancers, it is still unknown to what extent hemopoietic growth factors are involved in this complication.

In one patient, interstitial pulmonary edema with pulmonary failure was supposedly a first-dose reaction (24). Reversible eosinophilic pneumonia has also been reported (SEDA-19, 342).

One patient had acute bronchospasm after a subcutaneous injection of GM-CSF around a lower limb ulcer (25).

Nervous system

Very few neurological adverse effects have been associated with GM-CSF.

- Mania occurred in a 41-year-old woman taking GM-CSF who had previously tolerated G-CSF (SEDA-20, 339).
- A 49-year-old woman with chronic hepatitis C received filgrastim (G-CSF) for interferon-alfa-induced leukopenia (26). Filgrastim was withdrawn after 3 months, because of leg cramps and back pain. She later received sargramostim (GM-CSF) 500 micrograms twice weekly and she noticed gait unsteadiness and headaches within 2 weeks. During the next 3 months, she developed progressive confusion, forgetfulness, and lethargy, and both interferon alfa and sargramostim were withdrawn. She rapidly deteriorated and died from central hypoventilation 6 days later. Autopsy showed atypical, perivascular, lymphoid infiltrates in the white matter, basal ganglia, hypothalamus, brain stem, cerebellum, and spinal cord. Serum hepatitis C virus DNA sequences were not detected.

This case of fulminant perivascular lymphocytic proliferation suggests that some of the effects of GM-CSF on white blood cell proliferation can sometimes produce unexpected adverse effects.

Endocrine

Three patients with positive thyroid antibodies before GM-CSF treatment developed hypothyroidism or biphasic thyroiditis (27,28), whereas no similar thyroid dysfunction has been observed in patients without pre-existing thyroid antibodies (27). Based on these reports, GM-CSF has been thought to exacerbate underlying autoimmune thyroiditis.

Metabolism

Serum cholesterol concentrations have reportedly fallen in patients given GM-CSF (29).

Electrolyte balance

Severe symptomatic hypokalemia was thought to have resulted from increased intracellular potassium uptake linked to massive leukocytosis after GM-CSF (15).

Hematologic

Acute exacerbation of autoimmune thrombocytopenia (30) or hemolytic anemia has been linked to macrophage activation (31), and it has been suggested that patients with previous autoimmune blood disorders are at increased risk of hematological toxicity from GM-CSF.

A transient, moderate, and reversible rise in leukocyte alkaline phosphatase, lactate dehydrogenase (LDH) and serum uric acid concentrations is usually observed in cancer patients receiving supportive treatment with GM-CSF or G-CSF. Serum LDH increased from 37 to 85% and there was a linear relation between increased leukocyte production and the rise in serum LDH (32). Increases in serum LDH activity should therefore not be interpreted as indicative of disease progression, unless LDH activity remains high after growth factor withdrawal.

Erythrocytes

A typical vaso-occlusive crisis with increased hemolysis was noted within minutes after intracutaneous injection of GM-CSF in a patient with stable sickle cell disease (SEDA-19, 342). Topical GM-CSF was later uneventful.

Leukocytes

Dose-related and sometimes marked eosinophilia has been noted after GM-CSF (33). Although usually not associated with symptoms, excessive eosinophilia with fatal necrotizing pneumonia and Loeffler's endocarditis has been described (34).

Clotting factors

A marked reduction in vitamin K-dependent coagulation factors, which was prevented by vitamin K administration, has been described in patients with acute myeloid leukemia who were given GM-CSF (SEDA-19, 342).

The differential effects of G-CSF and GM-CSF on several coagulation parameters have been compared in 34 patients who received the colony-stimulating factors after bone marrow transplantation (35). The data suggested activation of the coagulation system in patients treated with GM-CSF, which resulted in a tendency to more frequent veno-occlusive disease of the liver and a significantly higher incidence of hemorrhage.

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Hemopoietic tissues

Although GM-CSF acts primarily on neutrophils, stimulating effects on the myeloid lineage and other cells or cytokines of the immune system can be associated with deleterious consequences, as illustrated in several case reports. Splenomegaly with histologically documented splenic extramedullary hemopoiesis of all three lineages and histiocytic bone marrow proliferation have been described (36–38). More severe outcomes have been described, such as reactive hemophagic histiocytosis resulting in fatal pancytopenia in two bone marrow transplant patients (39). Extensive and persistent bone marrow histiocytosis was considered the likely cause of delayed bone marrow engraftment and subsequent death in both patients. These effects may have been the consequences of GM-CSF-induced proliferation and activation of the monocyte/macrophage system.

Liver

A moderate increase in serum transaminase activities sometimes occurs in patients receiving GM-CSF. More severe hepatotoxicity has been briefly reported in patients who received GM-CSF after autologous bone marrow transplantation (SEDA-19, 342). Hyperbilirubinemia was also found in 8% of bone marrow transplant patients and considered as possible ground for molgramostim withdrawal (1).

Urinary tract

There was no evidence of nephrotoxicity secondary to GM-CSF during clinical trials, but the possible occurrence of transient renal insufficiency has been discussed (1).

Skin

Cutaneous reactions to GM-CSF occur in about 50% of patients and have been reviewed (40); there is concern that autoimmune skin diseases, psoriasis, and other dermatoses might be exacerbated.

GM-CSF often causes erythema and itching at subcutaneous injection sites, with a particularly high incidence of relapsing macular pruritic infiltrates at sites of injection in patients with inflammatory breast cancer (SEDA-20, 339). Based on a retrospective review, molgramostim-induced rash was the most common treatment-limiting adverse event in bone marrow transplant patients, but further administration of sargramostim may be well tolerated (1).

Cutaneous reactions in 57 cancer patients given GM-CSF have been described in detail. They included localized immediate angioedema (8%), generalized cutaneous reactions (21%), or both (16%) (41). Generalized reactions consisted mostly of maculopapular, exfoliative, and urticarial eruptions, which resolved after topical treatment, dosage reduction, or treatment withdrawal. There was usually hyperkeratosis, mild spongiosis, lymphocytic exocytosis, and perivascular infiltration by lymphocytes, neutrophils, and eosinophils. Eosinophil activation was supposedly involved in the pathogenesis of these lesions, as was also suggested in the report of atopic dermatitis-like eruptions in two patients (42) or the acute revelation of an underlying epidermolysis bullosa acquisita in a previously asymptomatic patient (43).

As with G-CSF, GM-CSF-induced activation of neutrophils can play a critical role in the occurrence of neutrophilic dermatoses and other skin disorders. Other reports have described acute exacerbation of previous pyoderma gangrenosum (44) and subcorneal pustular dermatosis around injection sites (SEDA-19, 342).

Additional isolated reports suggesting an immunological response or inappropriate cytokine secretion subsequent to GM-CSF administration include accounts of erythema multiforme (SEDA-19, 342) and acutely generalized exacerbation of pre-existing psoriasis (45). The latter report is in keeping with the finding that GM-CSF is sometimes raised in patients with psoriasis.

Musculoskeletal

Transient bone pain is common with GM-CSF. Prompt reactivation or worsening of rheumatoid symptoms has been observed in several patients with Felty's syndrome and in one seropositive rheumatoid arthritic patient (SED-13, 1113) (46,47). GM-CSF-induced acute IL-6 release and an increase in acute phase proteins were thought to be involved.

Immunologic

Hypersensitivity reactions

Although anaphylactic reactions without any documented immune-mediated mechanism have been reported in about 8% of patients with testicular cancer given GM-CSF (48), GM-CSF has only otherwise rarely been associated with allergic reactions. Of two patients who had possible immune-mediated reactions (SEDA-19, 342) one had an immediate recurrent local reaction followed by systemic hypersensitivity reaction after sargramostim, and the other had a maculopapular pruritic eruption after molgramostim. Cross-reaction between the two recombinant forms of GM-CSF was suggested by the results of skin prick tests in one patient, but both patients thereafter tolerated filgrastim uneventfully.

However, cross-sensitivity and possible desensitization have been documented.

- A 42-year-old woman with defective immunological function had generalized pruritus, flushing, shortness of breath, and general discomfort within 30 minutes of her 16th intravenous injection of molgramostim (49). Her symptoms resolved with adrenaline, hydrocortisone, and promethazine. Despite the prophylactic use of glucocorticoids and antihistamines, she developed a similar reaction after molgramostim readministration and 4 hours after the fourth injection of filgrastim. Positive skin prick tests to molgramostim and filgrastim suggested IgE-mediated hypersensitivity. An acute desensitization protocol starting with molgramostim 0.0008 micrograms increasing to 320 micrograms was successful, and molgramostim was later continued uneventfully.

Vasculitis

GM-CSF can cause or exacerbate cutaneous leukocytoclastic vasculitis with possible renal or pulmonary involvement (SED-13, 1113). This adverse effect was substantiated by the prompt recurrence of vasculitis

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after drug re-administration in several patients or the report of relapsing necrotizing vasculitis at all GM-CSF injection sites.

Antibodies to GM-CSF

Formation of antibodies to recombinant GM-CSF has been detected in 31% of patients treated with sargramostim and in 95% of patients treated with molgramostim derived from *Escherichia coli* (50,51). Although the clinical relevance of this is uncertain, a significant modification of exogenous GM-CSF pharmacokinetics, a reduction in the rise in leukocyte count, and a reduction in the frequency of GM-CSF-associated adverse effects have been suggested as possible consequences. Use of the subcutaneous route and repeated administration were deemed to increase the likelihood of antibody occurrence (51). However, the fact that most patients receiving growth factors are already likely to be immunocompromised as a result of intensive chemotherapy might also account for discrepancies between the widespread use of growth factors and the paucity of reports on antibodies against growth factors. In fact only one of eight potentially immunocompromised patients had anti-GM-CSF antibody titers and they were very low (51). Antibodies to GM-CSF have not been found after prolonged use in patients with AIDS (52).

Death

There were more frequent adverse effects and an increased death rate due to pulmonary complications, sepsis, or arterial thrombosis in lung cancer patients treated with chemotherapy plus radiotherapy and GM-CSF (SEDA-20, 339).

Long-Term Effects

Tumorigenicity

Previous fears that GM-CSF might give rise to progression of pre-leukemic conditions have not been substantiated (53).

The possibility that growth factors can stimulate the growth of malignant and leukemic cells, or accelerate the progression of myelodysplastic syndrome to acute myeloid leukemia has been discussed in the monograph on G-CSF section. At the moment, there is no indication from clinical trials that GM-CSF actually increases the risk of tumor growth or the relapse rate in patients with various malignancies (29,54–56). Isolated reports have referred to delayed occurrence of B cell non-Hodgkin's lymphoma after GM-CSF treatment for aplastic anemia and de novo occurrence of diffuse oligoclonal plasmocytosis after both GM-CSF and G-CSF for high-grade glioma (SEDA-19, 342).

Although reversible increases in circulating blasts during GM-CSF treatment are sometimes noted and have raised concern on the possible accelerated occurrence of acute leukemia, the progression of myelodysplastic syndromes to acute myeloid leukemia has been only anecdotally reported (SEDA-19, 342) (57). There was no evidence of significant leukemic cell proliferation in patients with acute myeloid leukemia, and no increased risk of graft failure, leukemogenesis, relapse, or death after a median follow-up of 36 months in 128 patients who underwent autologous bone marrow transplantation for lymphoid malignancies (29,58). Finally, one report has suggested that a GM-CSF-induced abrupt rise in peripheral blasts may have caused diffuse infiltration and proliferation of leukemic blast cells in the spleen, and subsequent fatal hemorrhagic spleen rupture (59).

Susceptibility Factors

Age

In a large, randomized, placebo-controlled trial in 264 very low birth weight neonates, treatment with GM-CSF for 28 days was not associated with specific toxic effects, but the incidence of nosocomial infections was not reduced (60).

Other features of the patient

Bone marrow transplantation

Because the production of cytokines (for example IL-1 or TNF-alfa) involved in the stimulation of cells responsible for graft-versus-host disease can be enhanced by hemopoietic growth factors, the use of growth factors after allogeneic transplantation is theoretically risky. However, in reviews of trials of G-CSF or GM-CSF in allogeneic bone marrow transplantation there were no increases in late engraftment failures, relapse rates, or exacerbation of graft-versus-host disease (54,61).

HIV infection

The safety and activity of subcutaneous GM-CSF (300 micrograms/day for 1 week and 150 micrograms twice weekly for 11 weeks) has been compared with no treatment in 244 leukopenic HIV-infected patients (62). Adverse effects were reported in most of the patients treated with GM-CSF and consisted of flu-like symptoms (98%), bone pain (42%), and injection site reactions (85%). There was a two-fold increase in serum transaminase and alkaline phosphatase activities in 5.7% of patients. There was a moderate, but not significant, increase in HIV p24 antigen concentration. The few relevant clinical trials have provided no convincing evidence that GM-CSF enhances HIV replication or accelerates HIV-associated diseases (for example infections or neoplasms) in patients with AIDS (63). Only one patient with AIDS and ultrasonographic confirmation of enhanced Kaposi's sarcoma lesions temporally related to GM-CSF used for interferon- and zidovudine-related severe neutropenia has been reported (SEDA-19, 343).

Drug–Drug Interactions

Theophylline

A 30% increase in theophylline clearance occurred after the administration of G-CSF or GM-CSF (SEDA-20, 338).

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Vincristine

In one study there was a synergistic effect of GM-CSF or G-CSF and cumulative doses of vincristine in causing severe atypical neuropathy (SEDA-20, 339).

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Grepafloxacin

See also Fluoroquinolones

General Information

Grepafloxacin is a synthetic fluoroquinolone antibiotic with extensive tissue distribution and strong antibacterial activity in vivo (1,2). However, it was withdrawn in 1999 because of its adverse cardiovascular effects, which included dysrhythmias (3–5).

Observational studies

In phase II and III trials of grepafloxacin in a total of more than 3000 patients, the most common adverse events with grepafloxacin 400 or 600 mg were gastrointestinal, such as nausea, vomiting, and diarrhea. Significantly more patients reported a mild unpleasant metallic taste with grepafloxacin than with ciprofloxacin, but under 1% of patients withdrew because of this. Headache occurred significantly more often with ciprofloxacin than grepafloxacin. In a study of more than 9000 patients, only 2.3% reported adverse events (nausea 0.8%; gastrointestinal symptoms 0.4%; dizziness 0.3%; photosensitization 0.04%). Rarely, an unpleasant taste has been reported as an adverse event in spontaneous reports (6).

Organs and Systems

Nervous system

Headache was recorded in patients taking grepafloxacin, at rates similar to those reported with ciprofloxacin and ofloxacin (8–9%), during short-course treatment of urinary tract infections (7).

Gastrointestinal

With grepafloxacin 600 mg/day the rates of the following adverse events were noticeably higher than with 400 mg/day: nausea (15 versus 11%), vomiting (6 versus 1%), and diarrhea (4 versus 3%) (8).

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Griseofulvin

General Information

Griseofulvin was originally isolated in 1939 as a natural product of *Penicillium griseofulvum* (1). It interferes with fungal microtubule formation, disrupting the cell's mitotic spindle formation and arresting the metaphase of cell division. Griseofulvin is a fungistatic compound and is active against *Trichophyton*, *Microsporon*, and *Epidermophyton* species (2). With the development of newer safer azoles and the introduction of terbinafine, all of which are easy to administer, the indications for griseofulvin have dwindled (3).

Pharmacokinetics

Griseofulvin is commercially available for oral administration as griseofulvin microsize (4 μm particle size) and griseofulvin ultramicrosize (1 μm particle size). The oral availability of the micronized formulation is variable, 25–70%; ultramicronized griseofulvin, in contrast, is almost completely absorbed (4–6). Peak plasma concentrations occur about 4 hours after dosing. Griseofulvin distributes to keratin precursor cells and is concentrated in skin, hair, nails, liver, adipose tissue, and skeletal muscle. In skin, a concentration gradient is established over time, with the highest concentrations in the outermost stratum corneum (7,8). However, within 48–72 hours after withdrawal, plasma concentrations of griseofulvin are markedly reduced and it is no longer detectable in the stratum corneum (4–6). The half-life of griseofulvin is 9–21 hours (9). It is oxidatively demethylated and conjugated with glucuronic acid, primarily in the liver; its major metabolite, 6-desmethylgriseofulvin, is microbiologically inactive (10). Within 5 days, about one-third of a single dose of micronized griseofulvin is excreted in the feces, and 50% in the urine, predominantly as glucuronidated 6-desmethylgriseofulvin (10,11). The slow penetration rate of griseofulvin into tissues may explain difficulties and delays in eradication of infection in nails (SED-12, 676) (12).

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General adverse effects

The more common adverse effects of griseofulvin include headache and a variety of gastrointestinal symptoms. Griseofulvin can cause photosensitivity and exacerbate lupus and porphyria. Cases of erythema multiforme-like reactions, toxic epidermal necrolysis, and a reaction resembling serum sickness have been reported. Proteinuria, nephrosis, hepatotoxicity, leukopenia, menstrual irregularities, estrogen-like effects, and reversible impairment of hearing have been reported rarely (4–6,13). Griseofulvin is teratogenic in animals and has mutagenic and carcinogenic potential, but the significance of these observations for humans is unclear (13).

Organs and Systems

Nervous system

Headache is the most common adverse effect of griseofulvin (14). It occurs in about 50% of patients and can be severe. Drowsiness, dizziness, fatigue, confusion, depression, irritability, and insomnia have also been observed (14). Impaired co-ordination and unsteadiness while walking have been reported in some cases when there was confusion (15). Peripheral neuritis has been attributed to griseofulvin, but with little proof of a causal relation (16).

Sensory systems

Eyes

Blurring of vision has been reported with griseofulvin (17).

Taste

Griseofulvin can cause dysgeusia; both taste and smell disturbances may occur more frequently than has been realized (SED-12, 676)(18).

Psychological, psychiatric

The psychiatric effects of griseofulvin can be very disturbing and are aggravated by alcohol (SED-12, 676) (14).

Endocrine

An estrogen-type effect has been reported in children, affecting the genitals and the breasts (SED-11, 567)(19).

Griseofulvin interferes with porphyrin metabolism. In man, transient increases in erythrocyte protoporphyrin concentrations have been demonstrated, and the production and excretion of porphyrins is increased. Acute intermittent porphyria is an absolute contraindication to griseofulvin. In patients with other forms of porphyria it should also be avoided, in view of the many alternatives (20–25).

Hematologic

There is no evidence that griseofulvin can cause serious blood disorders. However, leukopenia, neutropenia, and monocytosis have been reported (14,26).

Gastrointestinal

Anorexia, a feeling of bloating, mild nausea, and mild diarrhea are common (17). Vomiting, abdominal cramps, and more severe diarrhea are rare. Black, furry tongue, glossodynia, angular stomatitis, and taste disturbances have been described (18).

Liver

While there have been anecdotal reports of hepatitis (14) and cholestasis (27), a causal relation has never been shown.

Skin

Dermatological adverse effects are not uncommon with griseofulvin and are of considerable variety. The following have been described: urticaria (28,29), photosensitivity eruptions (30), erythema multiforme (31), morbilliform rashes (32), serum sickness-like reactions (33), fixed drug eruption (29,34,35), Stevens–Johnson syndrome (36), vasculitis (37), toxic epidermal necrolysis (38,39), and lupus erythematosus (40,41).

- A 40-year-old woman had a burning sensation and erythema of the lips, buccal mucosa, palate, and vulva, which recurred within 4 hours of oral rechallenge with griseofulvin 125 mg (42).

The risk of serious skin disorders has been estimated in 61 858 users, aged 20–79 years, of oral antifungal drugs identified in the UK General Practice Research Database (43). They had received at least one prescription for oral fluconazole, griseofulvin, itraconazole, ketoconazole, or terbinafine. The background rate of serious cutaneous adverse reactions (corresponding to non-use of oral antifungal drugs) was 3.9 per 10 000 person-years (95% CI = 2.9, 5.2). Incidence rates for current use were 15 per 10 000 person-years (1.9, 56) for itraconazole, 11.1 (3.0, 29) for terbinafine, 10 (1.3, 38) for fluconazole, and 4.6 (0.1, 26) for griseofulvin. Cutaneous disorders associated with the use of oral antifungal drugs in this study were all mild.

Immunologic

The triggering of a lupus-like syndrome by griseofulvin, by way of an allergic reaction, has been described, but is rare (44).

Second-Generation Effects

Pregnancy

Embryotoxicity and mutagenicity have been shown in animal experiments with high doses of griseofulvin. Although for this reason most handbooks and drug formularies warn against the use of griseofulvin during pregnancy, there are no reports of any adverse effects on the human fetus, despite the fact that griseofulvin has been on the market since the early 1960s and has been used extensively and, no doubt, during many pregnancies (SED-12, 676) (19,45–47).

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Susceptibility Factors

Patients with porphyria are at risk; acute intermittent porphyria is an absolute contraindication to griseofulvin.

Exposure to intense natural or artificial sunlight should be avoided during treatment with griseofulvin.

Patients with pre-existing systemic lupus erythematosus may be more susceptible to the development of skin manifestations from griseofulvin (48).

Drug–Drug Interactions

Alcohol

The effects of alcohol are potentiated by griseofulvin, and the use of alcohol increases the risk and severity of psychiatric disturbances.

Ciclosporin

Ciclosporin blood concentrations halved in a patient who took griseofulvin 500 mg/day, despite an increase in ciclosporin dose by 70% (49). When griseofulvin was withdrawn, the ciclosporin concentration rose. This interaction is attributable to induction of cytochrome P450 by griseofulvin.

Coumarin anticoagulants

Griseofulvin is a potent inducer of cytochrome P450 and has a significant effect on P450 expression in hepatocytes (SEDA-12, 236). It therefore increases the rate of metabolism of coumarin anticoagulants (50). However, both increases and decreases in prothrombin time have been reported (SED-12, 676) (18).

Oral contraceptives

The combination of griseofulvin with oral contraceptives can lead to oligomenorrhea, amenorrhea, and breakthrough bleeding; unintended pregnancies have been reported (51). In a case of oligomenorrhea after treatment with griseofulvin, the use of a higher estrogen oral contraceptive restored regularity of the menstrual cycle (SEDA-12, 237) (51). The fact that griseofulvin has an estrogen-like effect in children suggests that it may affect the rate of estrogen metabolism (SED-12, 676) (52).

Phenobarbital

The concomitant use of phenobarbital reduces griseofulvin concentrations, an effect that has been attributed to induction of liver enzymes by phenobarbital (53).

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Guanethidine

General Information

Guanethidine, an adrenergic neuron blocking drug, which was once used to treat hypertension, is obsolete for oral use and this indication. However, it has been used as eye-drops in cases of glaucoma, chemical sympathectomy, ptosis, and eyelid retraction (SEDA-1, 366). The reduction in intraocular pressure is small. In general, tissues treated topically with guanethidine become sensitized to sympathomimetic acting drugs. This is useful in glaucoma, for which adrenaline can be administered in low dosage in combination with guanethidine. After instillation of guanethidine-containing eye-drops, conjunctival hyperemia, ocular pain, and stinging have been described (1,2).

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Guar gum

General Information

Guar gum is a low-viscosity water-soluble dietary fiber that has been used to treat diabetes because it slows the absorption of glucose from the gut. However, adverse effects such as regurgitation, obstipation, abdominal cramps, diarrhea, and itching are common (1). Partially hydrolysed guar gum has been added to enteral formulas and food products as a source of dietary fiber; it can reduce laxative use, diarrhea in septic patients receiving total enteral nutrition, and symptoms of irritable bowel syndrome (2).

In a systematic review of 11 trials of the use of guar gum to treat obesity, the most common adverse events were abdominal pain, flatulence, diarrhea, and cramps; 11 patients (3%) dropped out owing to adverse events (3).

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Organs and Systems

Gastrointestinal

Of 26 reports of suspected adverse reactions to a diet formulation containing guar gum (Cal-Ban 3000), there were 18 cases of esophageal obstruction and seven of small bowel obstruction (4). There were pre-existing esophageal or gastric disorders in 50% of those with esophageal obstruction, including peptic stricture, pyrosis, hiatus hernia, esophagitis, gastric stapling, Schatzki ring, and muscular dystrophy. Fourteen patients with esophageal obstruction were treated successfully by endoscopy, although the tenacious gel-like material was often difficult to remove. One patient who developed a pulmonary embolism after surgical repair of an intraoperative esophageal tear died.

Immunologic

Guar gum can cause occupational rhinitis (5) and asthma (6). Of 162 employees at a carpet-manufacturing plant where guar gum was used to adhere dye to the fiber, 37 (23%) had a history suggestive of occupational asthma and 59 (36%) occupational rhinitis (7). Eight (5%) had immediate skin reactivity to guar gum and 11 (8.3%) had serum IgE antibodies to guar gum.

An employee of a pet food plant developed a severe cough, rhinitis, and conjunctivitis, and skin tests confirmed guar allergy. The symptoms resulted in obstructive sleep apnea which resolved after absence from work and recurred after rechallenge with guar gum dust (8).

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Gum resins

General Information

Gum resins comprise a diverse variety of substances, including asafoetida (*Ferula*), colophony, frankincense (*Boswellia*), and myrrh (*Commiphora*).

Colophony

Colophony, a natural unmodified gum resin from *Pinus* species (terebinth), used in cosmetics such as mascara, lipsticks, creams, and hair removal products, is a known contact allergen. Modifications have been made to colophonium, resulting in a variety of ester gums.

Frankincense

Preparations from the gum resin of *Boswellia serrata* have been used as traditional remedies in Ayurvedic medicine in India for inflammatory diseases (1). The gum contains substances that have anti-inflammatory properties; they are pentacyclic triterpenes related to boswellic acid, which inhibit leukotriene biosynthesis in neutrophilic granulocytes by inhibiting 5-lipoxygenase. Certain boswellic acids also inhibit elastase in leukocytes, inhibit proliferation, induce apoptosis, and inhibit topoisomerases in cancer cell lines.

Use in asthma

In a double-blind, placebo-controlled study in 40 patients aged 18–75 years with bronchial asthma who were given *Boswellia serrata* 300 mg tds for 6 weeks, 28 had improved dyspnea, a reduced number of attacks, increases in FEV_1, FVC, and peak flow, and reduced eosinophil counts and ESR (2). Of 40 patients, aged 14–58 years, given lactose 300 mg tds for 6 weeks, only 11 improved.

Use in colitis

In patients with ulcerative colitis, *Boswellia serrata* 350 mg tds for 6 weeks produced improvements in stool properties, histopathology of rectal biopsies, hemoglobin, serum iron, calcium, phosphorus, proteins, and total leukocyte and eosinophil counts, with remission in 82% of patients (3). The corresponding figure with sulfasalazine 1 g tds was 75%.

In 30 patients aged 18–48 years with chronic colitis, characterized by vague lower abdominal pain, rectal bleeding, diarrhea, and palpable tender descending and sigmoid colons, *Boswellia serrata* (900 mg/day for 6 weeks) produced remission in 14 of 20 patients, and sulfasalazine (3 g/day for 6 weeks) in 4 of 10 patients (4). There were few adverse effects.

Myrrh

Myrrh is an oleo gum resin obtained from the stem of *Commiphora molmol*, a tree that grows in north-east Africa and the Arabian Peninsula. In mice, myrrh showed no mutagenic effects and was a potent cytotoxic drug against solid tumor cells (5). The antitumor potential of *C. molmol* was comparable to that of cyclophosphamide. Studies in hamsters suggested an antischistosomal activity of myrrh (6).

Use in schistosomiasis

The efficacy and adverse effects of myrrh and the most effective dosage schedule have been studied in 204 (169 men and 35 women) patients with schistosomiasis, aged 12–68, years and 20 healthy non-infected age- and sex-matched volunteers (6). The patients were divided into two groups: 86 patients with schistosomal colitis and 118 with hepatosplenic schistosomiasis, the latter being further divided into two subgroups: 77 patients with compensated disease and 41 with decompensated disease. All but 12 had received one or more courses of praziquantel. The dosage of myrrh was 10 mg/kg/day for 3 days on an empty stomach 1 hour before breakfast. A second course of 10 mg/kg/day for 6 days was given to patients who still had living ova in rectal or colonic biopsy specimens. The response rate to a single course of myrrh was 92% in 187 patients. The cure rates were 91%, 94%, and 90% in patients with schistosomal colitis, compensated hepatosplenic schistosomiasis and decompensated hepatosplenic schistosomiasis respectively. The cure rate was less in patients who had previously taken praziquantel and in patients with impaired liver function. *Schistosoma hematobium* infection was the most responsive ($n = 4$, cure rate 100%), followed by mixed infections ($n = 29$, cure rate 93%). Those infected with *Schistosoma mansoni* had the lowest cure rate ($n = 171$, cure rate 91%). There was no impairment of liver function after treatment with myrrh. In contrast, liver function tests significantly improved in patients with impaired liver function. There were no significant effects of myrrh on the electrocardiogram. Adverse effects of myrrh were reported in 24 of the 204 patients. Giddiness, somnolence, and mild fatigue were the most common (2.5%), and all other adverse effects were minor and less frequent. None of the healthy volunteers reported any adverse effects, nor were there any significant changes in liver or kidney function. A second course of myrrh resulted in a cure in 13 of the 17 patients who did not respond to a single course.

Use in fascioliasis

The efficacy of myrrh has been studied in seven patients aged 10–41 years (five men, two women) with fascioliasis and 10 age- and sex-matched healthy volunteers (7). Myrrh was given orally in the morning on an empty stomach in a dosage of 12 mg/kg/day for 6 days. All the patients were passing *Fasciola* eggs in their stools (mean 36 eggs per gram of stool). The symptoms and signs of fascioliasis resolved during treatment with myrrh, and *Fasciola* eggs could not be demonstrated in the stools 3 weeks and 3 months after treatment. Anti-fasciola antibody titers became negative in six of the seven patients. There were no adverse effects.

Organs and Systems

Immunologic

In a retrospective study, 1270 patients with leg ulcers were tested for contact allergy with colophonium and the modified ester gum: 31 patients were positive to colophonium alone, 41 to the ester gum alone, and 33 to both colophonium and the ester gum (8). The authors recommended that the patch test tray for patients with leg ulcers should include both colophonium and the ester gum resin.

Two other patients with cheilitis due to contact allergy to a lipstick reacted positively to glyceryl hydrogenated rosinate, an ester gum, and the main component of the rosinate, glyceryl abietate (both patchtested at 20% in petrolatum) (9).

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Gusperimus

General Information

Gusperimus is a guanidine derivative with antitumor and immunosuppressive properties. Its mechanism of action is not well understood and may involve blockade of the maturation of B and T lymphocytes and monocytes, with inhibition of both cell-mediated and antibody-mediated immunity. In preliminary clinical trials in transplant patients, adverse effects at low doses included mild-to-moderate leukopenia, facial and perioral numbness, anorexia, gastrointestinal disturbances, facial flushing,

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and weakness (1–3). Bone marrow suppression has been observed at high doses.

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Haemophilus influenzae type b (Hib) vaccine

See also Vaccines

General Information

Haemophilus influenzae causes several infectious diseases in man, the most serious being meningitis. Most cases of *Haemophilus influenzae* infection are due to type b of the organism (Hib). Two types of Hib vaccines have been developed: Hib capsular polysaccharide (PRP) vaccines are first-generation Hib vaccines, while Hib conjugate vaccines are second-generation vaccines. The capsular polysaccharide vaccines do not protect infants and children under 18 months, whereas Hib conjugate vaccines have greater immunogenicity and induce a high rate of protection in children under 18 months. The latter have therefore completely replaced the first-generation polysaccharide vaccines.

Comparisons of adverse reactions to different vaccines are difficult, because vaccines are virtually always administered together with other vaccines. However, the general experience is that adverse reactions to Hib vaccine are mild. Most reactions develop when the vaccine is given simultaneously with DTP vaccine. There have been no deaths or permanent sequelae attributable to Hib immunization.

Four different types of conjugated vaccines are commercially available:

1. PRP-D Hib vaccine (a mutant polypeptide of diphtheria toxin covalently linked to PRP), for example ProHIBit (produced by Connaught Laboratories, Philadelphia).
2. HbOC vaccine (Hib oligosaccharides linked to the non-toxic diphtheria toxin variant CRM197), for example HibTITER (produced by Lederle-Praxis Biologicals, Pearl River, NY).
3. PRP-OMC (PRP conjugated to outer membrane protein of Neisseria meningitidis group B), for example PedvaxHIB (produced by Merck Sharp & Dohme Research Laboratories).
4. PRP-T Hib vaccine (tetanus toxoid linked to PRP), for example ActHIB or OmniHIB (produced by Pasteur Merieux, Lyon, France) and PRP-T (produced by Pasteur Mérieux Connaught and Glaxo SmithKline).

PRP-D-Hib has been almost completely replaced by different conjugated Hib vaccines (1–3). The four types of conjugated Hib vaccines have been reviewed (SED-12, 803) (SEDA-16, 377) (SEDA-17, 367) (SEDA-18, 330). More than 100 million doses of conjugated vaccines have now been administered worldwide, and no reports of deaths, anaphylaxis, or residual neurological damage have been causally connected with them.

In a study of the tolerability and immunogenicity of Hib vaccines, 30 volunteers aged 69–84 years were immunized with either Pedvax-Hib (a conjugate of Hib polysaccharide and an outer membrane protein complex of *Neisseria meningitidis*-PRP-OMP) or Hib TITER (a conjugate of Hib oligosaccharide and a non-toxic mutant diphtheria toxin, CRM 197-HbOC) (4). The volunteers received a pediatric dose. Before immunization, 40% of the volunteers had serum anti-PRP antibody concentrations below 1.0 μg/ml. Four weeks after immunization, all the volunteers had concentrations over 1.0 μg/ml, which is generally considered to be protective. Adverse effects of immunization were mild, except in one volunteer given HbOC, who developed extensive erythema and swelling at the injection site.

Different vaccines and immunization strategies have been evaluated in Denmark, Finland, Iceland, Norway, and Sweden (5). Few places outside Scandinavia have collected data on Hib immunization programs for so long (more than a decade has elapsed since universal Hib immunization was initiated in Scandinavia) and with similar accuracy. Phase 3 studies with PRP-D-Hib vaccine were done in Finland in the late 1980s, and PRP-D-Hib vaccine has been the only vaccine used in Iceland. HbOC vaccine was first compared with PRP-D-Hib vaccine in Finland and then reintroduced to the primary health-care system as the only Hib vaccine used. Finally, PRP-T-Hib vaccine was first temporarily used in Finland, and then as almost the only vaccine in Denmark, Norway, and Sweden. Besides the different conjugate vaccines, the immunization programs have differed in other aspects, such as immunization schedule and administration of vaccines (separate versus simultaneous administration with other vaccines, such as DT, DTP, DTaP, IPV, or MMR).

Experience with PRP-D derives from Finland and Iceland. In Finland, 14.1 adverse reactions per 100 000 doses were reported in all, consisting respectively of 5.3, 6.3, 4.4, and 2.9 per 100 000 doses of local reactions, fever, rash, and irritability. These rates probably underestimate the true rate. In Iceland, adverse effects have not been monitored, but no serious events have been reported. For PRP-CRM, there were 17.8 per 100 000 doses in all, of which 7.7 per 100 000 doses were due to local reactions, 8.9 to fever, and 8.3 to rash. PRP-T currently enjoys the largest use in Scandinavia, being the routine choice in three countries. Of 115 reactions reported in Denmark, none was of serious concern; most were local reactions, fever, or rash. In Norway, the incidence of systemic reactions was 1 in 550 doses; fever and other symptoms and signs similar to those after DTP vaccination were the most common complaints. However, two findings were characteristic of Norway, where local reactions were reported with an overall frequency of 1/1500 doses:

- immediate mild allergic reactions were more common than if DTP or IPV was given alone; their incidence was 1 in 35 000 doses of PRP-T;
- large swellings at the vaccination site, with edema and sometimes bluish or other discoloration of the legs, were reported in 18 children, suggesting an incidence of about 1 in 30 000 doses; this reaction developed within hours after vaccination and subsided within 24 hours; all the vaccinees recovered spontaneously without treatment or sequelae.

About 1.5 million doses of PRP-T have been used in Sweden. Similar concerns about adverse reactions have been raised as in Norway, and further elucidation has recently begun. In Finland (where PRP-T was used in

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1990–93), there were 15.9 reports per 100 000 doses; 6.2 per 100 000 doses were local reactions, 5.9 fever, 2.8 rash, and 2.4 irritability (5).

Notwithstanding the different approaches taken in the various Scandinavian countries, the results are similar: before vaccination against invasive Hib diseases, first introduced in Finland in 1986, the incidence of cases in the five Scandinavian countries was 49 per 100 000 per year in 0- to 4-year olds and 3.5 per 100 000 overall. During the next decade, Hib conjugates given to young children had about 95% effectiveness, regardless of which conjugate was used, whether two or three primary doses were used, and at no matter what age in early infancy the first vaccination was given. Invasive diseases due to Hib have thus been nearly eliminated.

On the request of the French Drug Agency, the Regional Pharmacovigilance Center of Tours has analysed the adverse events that occurred in 1986–90 with the use of three different tetravalent DTwP-IPV vaccines produced by French vaccine manufacturers (6). The most frequent adverse events were local reactions (43% of the 631 events reported). Serious adverse events represented 25% of all reported events, including 23 reports of persistent crying, 12 febrile seizures, 14 apyretic seizures, and 3 reports of shock-like events.

Immunological interference, particularly to the Hib response, has been assessed in 135 infants at 2, 4, 6, and 18 months of age in studies of two different types of administration of DTaP and Hib vaccines: combined administration of the two vaccines mixed in the same syringe and simultaneous administration of separate injections at different sites (7). The vaccines were well tolerated and there were no differences in the rates of local and systemic reactions. Immune responses were also comparable between the two groups.

In 57 volunteers, 32 of whom had recently undergone splenectomy, who received Hib conjugate vaccine, antibodies to Hib were measured at 2, 6, 12, 24, and 36 months after immunization (8). All tolerated the vaccine well and reached protective antibody titers. The authors concluded that the vaccine is safe and protective in patients with thalassemia.

Combinations of vaccines

Since immunization against diphtheria, tetanus, and pertussis is recommended at the same age as immunization against *Haemophilus influenzae*, children must usually receive two intramuscular injections at separate sites during the same visit. Combined vaccines, for example DTP/Hib vaccines, requiring one injection, could be preferable and are commercially available. Results of clinical trials comparing the safety and efficacy of combined and simultaneously administrated vaccines (Hib, DTP, MMR, IPV) have been presented (SEDA-17, 369) (SEDA-18, 330). In general, the rates of local and systemic reactions and antibody responses did not differ significantly between the groups. The immunogenicity and safety of a diphtheria–tetanus–pertussis–Hib combination vaccine (tetanus-conjugated Hib vaccine) have been compared with those of the same combination obtained by the reconstitution of lyophilized Hib vaccine with liquid DTP vaccine in 262 healthy infants randomized to receive injections at 2, 4, and 6 months of age, a subgroup of 134 of whom received a booster dose at 12 months (9). Systemic and local reactions were generally mild and did not differ significantly between the two groups. With regard to Hib antibodies, the combination vaccine was at least as immunogenic as the lyophilized formulation.

Four-, five- and six-component combination vaccines based on DTaP or DTwP vaccine, and including other antigens such as hepatitis B or Hib or IPV, will play an important role in future worldwide immunization programs. The first hexavalent combination vaccines (DTaP-IPV-HB-Hib) were licensed in Germany; two hexavalent vaccines are available, manufactured by SmithKline Beecham and Aventis Pasteur.

The Hexavalent Study Group has compared the immunogenicity and safety of a new liquid hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and Hib (DTP + IPV + HB + Hib vaccine, manufactured by Aventis Pasteur MSD, Lyon, France) with two reference vaccines, the pentavalent DTP + IPV + Hib vaccine and the monovalent hepatitis B vaccine, administrated separately at the same visit (10). Infants were randomized to receive either the hexavalent vaccine ($n = 423$) or (administered at different local sites) the pentavalent and the HB vaccine ($n = 425$) at 2, 4, and 6 months of age. The hexavalent vaccine was well tolerated (for details, see the monograph on Pertussis vaccines). At least one local reaction was reported in 20% of injections with hexavalent vaccine compared with 16% after the receipt of pentavalent vaccine or 3.8% after the receipt of hepatitis B vaccine. These reactions were generally mild and transient. At least one systemic reaction was reported in 46% of injections with hexavalent vaccine, whereas the respective rate for the recipients of pentavalent and HB vaccine was 42%. No vaccine-related serious adverse event occurred during the study. The hexavalent vaccine provided immune responses adequate for protection against the six diseases.

Regimens using different conjugated vaccines for primary series

Currently most advisory bodies for immunization practice recommend that the same Hib conjugate vaccine used to initiate a priming series should be continued for the entire series. However, interest in using different vaccines for sequential doses (mixed regimens) has been long-standing. Two- or three-dose mixed regimens of Hib conjugate vaccines have been compared in two randomized trials in 140 and 181 infants (11). In both trials, a group of infants received PRP-meningococcal protein conjugate vaccine (OMP, outer membrane protein) at 2 months of age, followed by either the same or another conjugate vaccine, oligosaccharide CRM197 Hib vaccine (HbOC, Hib oligosaccharides linked to the non-toxic diphtheria toxin variant CRM197) or PRP-tetanus toxoid Hib vaccine, either once (at 4 months of age) or twice (at 4 and 6 months of age). All the mixed regimens provided a mean anti-PRP antibody concentration that did not differ substantially compared with currently recommended regimens of proven or inferred efficacy. Recipients of a second dose of OMP vaccine had higher rates of swelling, erythema, and induration compared with the other recipients.

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Organs and Systems

Nervous system

The neurological complications of conjugated Hib vaccines have been reviewed (12). A single convulsion occurred 12 hours after immunization in a 3-month-old child and a hyporesponsive episode occurred in another 3-month-old child.

Guillain–Barré syndrome has been reported after immunization with several different vaccines, including Hib conjugate vaccine (13,14). One patient had also received DTP and oral poliomyelitis vaccine.

Metabolism

The incidence of diabetes mellitus has been studied in Finnish children born between October 1983 and September 1985 compared with children born between October 1985 and 1987 (1). Of the children born in 1985–87, 50% received Hib vaccine (diphtheria conjugated PRP-D-Hib vaccine) at 3, 4, and 6 months as a primary course and a booster dose at 14–18 months; the other 50% received one dose of the same vaccine at the age of 24 months. Taking into account the documented increase in diabetes in Finnish children, the small difference between the incidence rate of diabetes in children born during the period 1985–87 and immunized at 18 months and the incidence rate of children born in 1983–85 and not immunized against Hib disease was expected, with a slightly higher non-significant incidence in immunized children. In children over 4 years of age primed during the first year of life the incidence rate of diabetes was also slightly but non-significantly higher than in children immunized at 18 months of age. The authors concluded that early PRP-D-Hib immunization does not increase the risk of diabetes during the first 10 years of life.

This study has been criticized on the grounds that the authors did not present data comparing the incidence rates of children born in 1985–87 and primed during the first year of life with children born in 1983–85 and not immunized (15). The critics presented significant differences in the incidence rate of diabetes between the two groups of children and concluded that immunization had increased the risk of diabetes. However, the relative risk of diabetes during the first 10 years of life in the immunized children born in 1985–87 was 1.19 compared with the non-immunized children born in 1983–85.

In another Finnish study, about 116 000 children born in Finland between 1 October 1985 and 31 August 1987 were randomized to receive four doses of Hib vaccine (PPR-D, Connaught) starting at 3 months of life or one dose starting after 24 months of life (16). A control cohort included all 128 500 children born in Finland in the 24 months before the study. The difference in cumulative incidence between those who received four doses of the vaccine and those who received none was 54 cases of diabetes per 100 000 at 7 years (relative risk = 1.26). Most of the extra cases of diabetes occurred in statistically significant clusters starting about 38 months after immunization and lasting about 6–8 months. The authors concluded that exposure to Hib immunization is associated with an increased risk of type 1 diabetes mellitus.

In 1997, US researchers suggested that immunization at 28 days after birth can cause type 1 diabetes mellitus in susceptible individuals. In May 1998, several institutions, including the National Institute of Allergy and Infectious Diseases, the Centers for Disease Control, the World Health Organization, and the UK's Department of Health, sponsored a workshop to assess the evidence of a possible link. Immunologists, diabetologists, epidemiologists, policymakers, and observers debated the available evidence and concluded that a causal link between immunization and type 1 diabetes is not supported. The results of a large, randomized, controlled trial of immunization against Hib carried out in Finland in 1985–87 (5) were also reanalysed and showed no association between the incidence of diabetes mellitus and the addition of another antigen to the schedule, irrespective of timing. Data reanalysis was made possible by prospective linking of individual information on exposure (in this case infant immunization or the administration of placebo) with the Finnish diabetes register (17).

Susceptibility Factors

Other features of the patient

Of 23 patients with Hodgkin's disease and splenectomy immunized with Hib conjugate vaccine, most responded, although the antibody response was significantly lower than in healthy people (18). There were adverse effects in three of the vaccinees: in one case nausea, vertigo, and weakness occurred 2–4 days after administration of the vaccine, myalgias occurred in another case, and fever and myalgias (after primary immunization, with milder symptoms after the booster) in a third.

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Hair dyes

General Information

Hair dyes (for example henna, paraphenylenediamine, and paratoluenediamine) have been reviewed (1). They have moderate to low acute toxicity. Poisoning is rare and occurs only after oral ingestion. Contact sensitization usually occurs from unprotected professional exposure, but the prevalence has stabilized or fallen over the years. In vitro genotoxicity tests of hair dye ingredients have often been positive, but the relation to in vivo carcinogenicity is not clear and there is no in vivo evidence of genotoxicity. Despite the results of various studies that have suggested an association between the use of hair dyes and bladder cancer, a number of studies, including prospective investigations in large populations and systematic reviews, have shown no convincing associations with bladder cancer and other cancers. The results of direct toxicity studies and epidemiological studies suggest that hair dyes and their ingredients do not cause adverse reproductive effects.

Organs and Systems

Immunologic

Allergic reactions to constituents of hair dyes are not uncommon and are generally due to delayed hypersensitivity. Immediate hypersensitivity reactions have been described, but they are rare and seldom life-threatening.

Contact allergy to the paraphenylene group of hair dyes is well established (2). To test for cross-reactivity between these oxidative dyes and the new generation of hair dyes, 40 hairdressers allergic to paraphenylenediamine were selected; none reacted to any of the four acid dyes, two FD&C dyes, or four D&C dyes, suggesting that these newer hair dyes are safe alternatives to the paraphenylene-based hair dyes (3).

There is a risk of sensitization from paraphenylenediamine when it is applied to the skin in combination with henna (4–6). This can result in contact allergic reactions as well as persistent contact leukoderma, as illustrated in five patients with paint-on henna tattoos (7). All were positive on patch-testing with paraphenylenediamine. One developed erythema multiforme 4 weeks after the last application and the authors found no other causes of erythema multiforme.

The use of the combination of henna and paraphenylenediamine in 20 cases over 2 years in Khartoum (Sudan) resulted in severe toxicity (SEDA-9, 142). The initial symptoms were those of angioedema, with massive edema of the face, lips, glottis, pharynx, neck, and bronchi. These occurred within hours of the application of the dye-mix to the skin. In some the symptoms progressed on the second day to anuria and acute renal insufficiency, with death on the third day. Dialysis helped some patients, but others died from renal tubular necrosis.

The oxidation product of paratoluenediamine has been identified as a rare cause of a life-threatening immediate hypersensitivity reaction (8).

- A 45-year-old woman developed extensive urticarial lesions 30 minutes after the application of a hair dye, starting on the scalp and face, followed by abdominal cramps, watery diarrhea, vomiting, dysphonia, and loss of consciousness. A prick test with a 1/128 dilution of the hair dye showed a positive reaction, but individual dye constituents did not. Prick testing with the oxidation products of the individual dye constituents showed a strongly positive reaction to oxidized paratoluenediamine, which was weaker after addition of an antioxidant to the mixture.

Ten healthy controls had negative prick tests with the oxidized paratoluenediamine.

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Long-Term Effects

Tumorigenicity

In a review of cohort and case-control studies of occupational exposure to hair dyes among hairdressers, barbers, and beauticians, the relative risk of bladder cancer was 1.4 from cohort studies, and somewhat over 1.0 from case-control studies; however, there were confounding factors, particularly since allowance for smoking was lacking or inadequate in most studies (9). In five case-control studies of personal use of hair dyes, there was no evidence of an increased risk of bladder cancer. In nine cohort studies the relative risk of lymphoid neoplasms overall was 1.2 (1.5 for non-Hodgkin's lymphomas and 1.1 for multiple myeloma). Of five case-control studies, three reported some association with lymphoid neoplasms, but the estimates of relative risk were only moderately above 1.0 and there was insufficient allowance for potential confounding factors, including social class and greying hair, which could correlate with both hair dye use and lymphoid neoplasms. No other neoplasms, including those of breast, skin, and lung were related to the use of hair dyes. In another study there was an increased risk of Hodgkin's disease among women who reported the use of hair coloring products before 1980 (OR = 1.3; CI = 1, 1.8) (10).

Drug Administration

Drug overdose

In one case deliberate ingestion of paraphenylenediamine with suicidal intent caused severe oropharyngeal edema, rhabdomyolysis, and cardiac death after 4 hours despite full supportive treatment (11).

Myocarditis has been attributed to paraphenylenediamine poisoning (12).

- An 18-year-old woman developed asphyxia and rhabdomyolysis after taking paraphenylenediamine 5 g. An electrocardiogram showed ventricular extra beats and inverted T waves. The serum CK activity was 28 020 μkat/l. Transthoracic echocardiography showed left and right ventricular hypokinesis and a left ventricular apical thrombus. Anticoagulation treatment with heparin was initiated. A follow-up echocardiogram performed on the 15th day showed normalization of ventricular function and disappearance of the thrombus.

In two patients acute oliguric renal insufficiency due to acute tubular necrosis followed paraphenylenediamine intoxication; there was associated vomiting, angioedema, cyanosis, and intravascular hemolysis (13). One patient recovered and the other died with septicemia. In four other cases acute renal insufficiency was due to rhabdomyolysis.

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Halofantrine

General Information

Halofantrine is a phenanthrene-methanol derivative of an aminoalcohol, active against multidrug-resistant *Plasmodium falciparum* malaria. Halofantrine was known during World War II but was little used at that time. It is slowly and incompletely absorbed with peak concentrations 3.5–6 hours after dosing. Its absorption in its original formulation was unpredictable (SEDA-13, 820).

Dose-finding studies with halofantrine showed treatment failures with a single dose but cures with two doses, one of 1000 mg and one of 500 mg. A regimen of 500 mg at 6-hourly intervals was also effective. Three doses of 500 mg at 6-hourly intervals were also used in

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a French study and treatment resulted in cure in semi-immune subjects. The dosage was insufficient in non-immune Caucasian patients.

Halofantrine is not indicated for prophylactic use. However, of 480 army personnel who took two doses of 1500 mg each on the third and the tenth days after they had returned to a non-malarial area, only one had *P. falciparum* malaria during the next 5 months (SEDA-13, 820) (1). There were no adverse effects, except for one case of morbilliform rash possibly due to the halofantrine.

General adverse effects

Adverse effects with the dosages originally recommended have in general been mild, no more than nausea, diarrhea, headache, and pruritus (SEDA-13, 820) (2–4). Pruritus occurred markedly less often with halofantrine than with chloroquine (SEDA-16, 306). A comparison between high-dose chloroquine (35 mg/kg total in three daily doses) and halofantrine in the standard dose (total 25 mg/kg given at 6-hour intervals) in patients 4–14 years old showed a fairly similar frequency of adverse effects. Itching was a common adverse effect of chloroquine (4).

Organs and Systems

Cardiovascular

In 1993, the sudden cardiac death of a 37-year-old woman after her ninth dose of halofantrine was reported. A subsequent prospective study showed that halofantrine was associated with a dose-related lengthening of the QT interval by more than 25% (SEDA-17, 328). Mefloquine did not cause such changes, but the combination of mefloquine with halofantrine had a more pronounced effect on the electrocardiogram. However, in the region where this investigation was carried out (on the Thai–Burmese border area) thiamine deficiency is common, and patients in this area have longer baseline QT intervals than are usually reported (SEDA-17, 328). Two patients, mother and son, both with congenital prolongation of the QT interval, suffered sustained episodes of torsade de pointes after a total dose of 1000 mg of halofantrine, and there have been other reports of dysrhythmias, including death in a patient who took mefloquine and halofantrine (SEDA-20, 260) (SEDA-21, 295). Dysrhythmias due to halofantrine may respond to propranolol (5).

African children who received halofantrine (three doses of 8 mg/kg 6-hourly) for uncomplicated *P. falciparum* malaria had increases in both the PR interval and the QT_c interval; out of 42 children in the study, two children developed first-degree heart block and one child second-degree heart block; the QT_c interval either increased by more than 125% of baseline value or by more than 0.44 seconds (an effect that persisted for at least 48 hours) (6).

There have been recent reports in the French medical press of cases of significant QT_c prolongation in children returning to France, and caution in its use has been urged (7). A small trial in non-immune adults in the Netherlands and France also showed increased QT_c dispersion with halofantrine but not artemether + lumefantrine (8).

- Death due to a dysrhythmia was reported in a woman who had taken halofantrine for malaria (9). She had a normal electrocardiogram before treatment and no family history of heart disease.

Prolongation of the QT interval occurred in 10 of 25 children treated with halofantrine (24 mg/kg oral suspension in three divided doses) for acute falciparum malaria (10).

Electrocardiographic monitoring is recommended for children and adults taking halofantrine.

Gastrointestinal

Gastrointestinal adverse effects are more common with halofantrine than with other antimalarial drugs (11).

Immunologic

Anaphylactic shock has been attributed to halofantrine (12).

Long-Term Effects

Drug tolerance

Early laboratory studies suggested cross-resistance of halofantrine with mefloquine. In rats, parasites that are resistant to mefloquine, quinine, chloroquine, and amodiaquine are also markedly resistant to halofantrine (13).

Susceptibility Factors

Pre-existing cardiac conduction abnormalities, including those induced by other drugs, are a definite risk. Due consideration should be given not only to the half-life of such drugs, but also to the tissue concentrations and total clearances of the agents involved.

Drug Administration

Drug formulations

Halofantrine is available in a micronized form. Early information suggested that this improved absorption, but two later studies provided conflicting evidence: there was a wide range of serum concentrations of halofantrine and its main metabolite *N*-desbutylhalofantrine after the administration of half of the standard dose (2) or the usual dose of 500 mg given three times with 6-hour intervals (3). In general, concentrations were similar to those obtained with the older formulation. Taking the drug with food is thought to increase absorption.

Food–Drug Interactions

Grapefruit juice

Since halofantrine is metabolized to *N*-debutyl-halofantrine by CYP3A4, grapefruit juice increases its systemic availability (14). Twelve healthy men and women took halofantrine 500 mg with water, orange juice, or grapefruit juice (250 ml/day for 3 days and once 12 hours before halofantrine) in a crossover study. Compared with water, grapefruit juice significantly increased halofantrine AUC

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and C_{max} 2.8-fold and 3.2-fold respectively; there was no significant change in half-life. Maximum QT_c interval prolongation increased significantly from 17 ms when halofantrine was taken with water to 31 ms when it was taken with grapefruit juice. Grapefruit juice should be avoided by patients taking halofantrine.

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Halogenated quinolines

General Information

The halogenated quinolines include clioquinol (iodochlorohydroxyquinoline), diiodohydroxyquinoline, broxyquinoline, and chlorquinaldol (all rINNs). Once regarded as a prophylactic and remedy for simple diarrhea, some of them remain in limited use for special purposes, notably for the treatment of amebiasis when no alternative is available.

A major epidemic of subacute myelo-optic neuropathy (SMON) in Japan during 1956–70 was identified as being due to clioquinol, which led to the withdrawal of halogenated quinolines in Japan itself and subsequently elsewhere. There is every reason to believe that the adverse effects seen with clioquinol can occur with the other hydroxyquinolines, but some of them are still sold freely in various parts of the world (1).

Organs and Systems

Nervous system

DoTS classification (BMJ 2003;327:1222–5)
- Adverse reaction: subacute myelo-optic neuropathy
- Dose-relation: collateral effect
- Time-course: intermediate
- Susceptibility factors: genetic (?Japanese more susceptible)

There was a major epidemic of subacute myelo-optic neuropathy (SMON) in Japan during 1956–70. In 1970 a clinical observation led to case-control and cohort studies, which identified clioquinol as the culprit. A few cases were also reported elsewhere in the world, in Australia (2), Denmark (3), the Netherlands (4), Sweden (5–7), Switzerland (8), the UK (9–11), and the USA (12); some cases involved halogenated quinolines other than clioquinol. Prolonged use of diiodohydroxyquinoline in high doses has been associated with loss of vision and optic atrophy (SED-11, 594) (13). Halogenated quinolines were withdrawn in Japan and the epidemic abated (14).

The main abdominal symptoms of SMON are diarrhea and abdominal pain, sometimes accompanied by nausea, vomiting, constipation, a bloated feeling in the abdomen, and meteorism. The neurological symptoms are acute or subacute in nature; sensory disturbances are characteristic and spread gradually from the feet up to the navel. Some 20–40% of cases have visual disturbances ranging from blurred vision to atrophy of the optic nerve and blindness. There is a wide range of mental symptoms.

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The clearest proof of the cause-and-effect relation in Japan was the finding of clioquinol chelates in the green furring of the tongue and the greenish urine. There has been no clear explanation for the much higher incidence of cases in Japan than elsewhere, but several hypotheses have been suggested (15).

The risk is related to dose and duration of therapy (16):

- at a dose of 750 mg/day for less than 4 weeks there is little risk
- at a dose of 750–1500 mg/day for less than 2 weeks the risk is about 1%
- at a dose of 750–1500 mg/day for more than 2 weeks the risk is about 35%
- a dose of 1800 mg/day can cause symptoms within 5 days
- higher doses can cause symptoms within 24 hours.

The events in Japan, where the total of documented cases was some 10 000 (17), have been fully documented in earlier volumes from 1968 onwards (see for example SEDA-4, 253). Little further evidence has since accumulated, despite a major international conference at Kyoto, Japan, in April 1979 to examine the evidence. Since the withdrawal of such drugs in Japan descriptions of large numbers of new cases have ceased. The effect should now be largely of historical interest, but the condition continues to be reported very sporadically (SEDA-10, 326).

Endocrine

Diiodohydroxyquinoline can slightly enlarge the thyroid gland (18).

Hematologic

Thrombocytopenia has (unconvincingly) been ascribed to topical clioquinol (19).

Drug Administration

Drug administration route

Up to 40% of topically applied clioquinol can be absorbed percutaneously in man (20). Formulations that contain clioquinol are often used to treat diaper rash; in a child of 10 kg treated with 1 g of clioquinol 3% tds, the amount of drug applied would be 9 mg/kg/day. However, it is possible that in infants with diaper rashes the actual absorption of the drug would be over 40%, since absorption through inflamed skin occurs more readily than through intact skin, and infant skin is more permeable than adult skin (21).

In dogs treated with 5 g of a topical clioquinol 3% formulation twice daily over 28 days (about 17 mg/kg/day) there was significant toxicity (loss of weight, lethargy, paralysis, hepatotoxicity) (22).

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Haloperidol

See also Neuroleptic drugs

General Information

Haloperidol is a butyrophenone neuroleptic drug. The enzymes involved in its biotransformation include oxidative cytochrome P450 isozymes, carbonyl reductase, and

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uridine diphosphoglucose glucuronosyltransferase (1). It is mainly cleared by glucuronidation.

There has been a randomized, placebo-controlled comparison of haloperidol (mean dose 1.8 mg/day), trazodone (200 mg/day), and behavior management techniques in 149 patients with Alzheimer's disease (2). Although 34% of the subjects improved relative to baseline, there were no significant differences in outcomes among the four arms; there were significantly fewer cases of bradykinesia and parkinsonian gait in those given behavioral therapy. These results suggest that other treatments for agitation in dementia need to be considered and evaluated; likewise, they are consistent with the results of a meta-analysis (3) and a clinical trial (4).

Haloperidol 2–3 mg/day and 0.50–0.75 mg/day have been compared in 71 outpatients with Alzheimer's disease (5). After 12 weeks, there was a favorable therapeutic effect of haloperidol 2–3 mg/day, although 25% of the patients developed moderate to severe extrapyramidal signs.

A thorough review of the pharmacokinetics of haloperidol, with special emphasis on interactions, has been published (1).

Organs and Systems

Cardiovascular

Intravenous haloperidol is often prescribed to treat agitation, and torsade de pointes has on occasions occurred (SEDA-20, 36). In a cross-sectional cohort study QT_c intervals were measured before the intravenous administration of haloperidol plus flunitrazepam, and continuous electrocardiographic monitoring was performed for at least 8 hours after ($n = 34$) (6); patients who received only flunitrazepam served as controls. The mean QT_c interval after 8 hours in those who were given haloperidol was longer than in those who were given flunitrazepam alone; four patients given haloperidol had a QT_c interval of more than 500 ms after 8 hours. However, none developed ventricular tachydysrhythmias.

In a case-control study, haloperidol-induced QT_c prolongation was associated with torsade de pointes (7). The odds ratio of developing torsade de pointes in a patient with QT_c prolongation to over 550 ms compared with those with QT_c intervals shorter than 550 ms was 33 (95% CI = 6, 195). The sample consisted of all critically ill adult patients in medical, cardiac, and surgical intensive care units at a tertiary hospital who received intravenous haloperidol and had no metabolic, pharmacological, or neurological risk factors known to cause torsade de pointes, or if the dysrhythmia developed more than 24 hours after intravenous haloperidol. Of 223 patients who fulfilled the inclusion criteria, eight developed torsade de pointes. A group of 41 patients, randomly selected from the 215 without torsade de pointes, served as controls. The length of hospital stay after the development of haloperidol-associated torsade de pointes was significantly longer than that after the maximum dose of intravenous haloperidol in the control group. The overall incidence of torsade de pointes was 3.6% and 11% in patients who received intravenous haloperidol 35 mg or more over 24 hours.

Several cases of torsade de pointes have been reported with intravenous haloperidol used with low-dose oral haloperidol (8).

The effects of haloperidol dose and plasma concentration and CYP2D6 activity on the QT_c interval have been studied in 27 Caucasian patients taking oral haloperidol (aged 23–77 years, dosages 1.5–30 mg/day) (9). Three patients had a QT_c interval longer than 456 ms, which can be considered as the cut-off value for a risk of cardiac dysrhythmias. There was no correlation between QT_c interval and haloperidol dosage or plasma concentrations or CYP2D6 activity.

Asystolic cardiac arrest has been reported after intravenous haloperidol (10).

In one case, the use of carbamazepine and haloperidol led to prolongation of the QT_c interval and cardiac complications (11).

- A 75-year-old man developed ventricular fibrillation and cardiac arrest after intravenous haloperidol (12). His past history included coronary bypass surgery and coronary angioplasty. As he continued to have severe chest pain, emergency angioplasty was performed. On day 3 he received haloperidol by infusion 2 mg/hour, with 2 mg increments every 10 minutes (up to 20 mg in 6 hours) as needed for relief of agitation. Before haloperidol, his QT_c interval was normal; after haloperidol it increased to 570 ms. The next day he developed ventricular fibrillation. Subsequent electrocardiograms showed prolonged QT_c intervals of 579 and 615 ms, and haloperidol was withdrawn; the QT_c returned to normal.
- A 76-year-old man developed torsade de pointes while taking tiapride 300 mg/day; the QT_c interval 1 day after starting treatment was 600 ms; the dysrhythmia resolved when tiapride was withdrawn (13).
- A 39-year-old man died suddenly 1 hour after taking a single oral dose of haloperidol 5 mg (14). He had myasthenia, alcoholic hepatitis, and electrolyte abnormalities due to inadequate nutritional state. His electrocardiogram showed prolongation of the QT_c interval (460 ms). Autopsy showed a cardiomyopathy but no explanation for sudden death.

However, malignant dysrhythmias can occur without changes in the QT interval (SEDA-24, 54).

- A 64-year-old woman underwent coronary artery bypass surgery and was given intravenous haloperidol for agitation and to avoid postoperative delirium; she developed torsade de pointes (15).
- Asystolic cardiac arrest occurred in a 49-year-old woman after she had received haloperidol 10 mg intramuscularly for 2 days; no previous QT_c prolongation had been observed (16).

Respiratory

A single case of fatal pulmonary edema was reported in 1982 in association with haloperidol (17).

Nervous system

Three cases of radial nerve palsy were reported in demented elderly patients confined to wheelchairs who were treated with haloperidol. The combination of

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extrapyramidal and sedative adverse effects, added to wheelchair confinement, may have resulted in pressure on the upper arm with subsequent neuropathy (18).

Extrapyramidal effects

- A 28-year-old woman simultaneously developed four types of tardive extrapyramidal symptoms (dystonia, dyskinesia, choreoathetotic movements, and myoclonus) while taking haloperidol; the symptoms were subsequently relieved by the use of low-dose risperidone (3 mg/day) (19).

Akathisia

A nocturnal eating/drinking syndrome secondary to neuroleptic drug-induced restless legs syndrome has been attributed to low-dose haloperidol in a 51-year-old schizophrenic woman (20).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been reported with haloperidol (21).

- A 21-year-old Turkish man with succinic semialdehyde dehydrogenase deficiency and mental retardation developed neuroleptic malignant syndrome after a single dose of haloperidol 10 mg for anxiety and agitation, having never received a neuroleptic drug before.

Several reports have suggested a higher incidence and severity of extrapyramidal symptoms during haloperidol treatment in congenitally poor metabolizers of substrates of CYP2D6 and a patient with a poor metabolizer polymorphism of the CYP2D6 gene developed neuroleptic malignant syndrome after receiving haloperidol (22). All frequent polymorphisms of CYP2D6 were therefore investigated in the second patient, who was a carrier of the wild-type genotype CYP2D6 *1/ *1, which is common in subjects of Caucasian origin. The authors concluded that a genetic defect of haloperidol metabolism via CYP2D6 was unlikely as a reason for the neuroleptic malignant syndrome in this case.

Endocrine

The relation of prolactin concentrations and certain adverse events has been explored in large randomized, double-blind studies. In 813 women and 1912 men, haloperidol produced dose-related increases in plasma prolactin concentrations in men and women, but they were not correlated with adverse events such as amenorrhea, galactorrhea, or reduced libido in women or with erectile dysfunction, ejaculatory dysfunction, gynecomastia, or reduced libido in men (23).

No further rise in plasma prolactin concentration was observed with dosages of haloperidol over 100 mg/day, which was explained as being related to saturation of the pituitary dopamine receptors by a modest amount of haloperidol (24).

The time-course of the prolactin increase has been examined in 17 subjects whose prolactin concentrations rose during the first 6–9 days of treatment with haloperidol (25). The increase was followed by a plateau that persisted, with minor fluctuations, throughout the 18 days of observation. Patients whose prolactin concentrations increased above 77 ng/ml ($n = 2$) had hypothyroidism, and it is known that TRH (thyrotropin) stimulates the release of prolactin (26).

The effects of haloperidol and quetiapine on serum prolactin concentrations have been compared in 35 patients with schizophrenia during a drug-free period for at least 2 weeks in a randomized study (27). There was no significant difference in prolactin concentration between the groups at the start of the study; control prolactin concentrations were significantly lower with quetiapine than with haloperidol. Two patients taking haloperidol had galactorrhea related to hyperprolactinemia.

Metabolism

Glucose metabolism has been studied in 10 patients taking haloperidol; none had impaired glucose tolerance and only one had a glycemic peak delay (28).

Liver

Occasional reports of cholestatic jaundice with haloperidol have been published (29,30).

Urinary tract

Retroperitoneal fibrosis has been attributed to haloperidol; since this condition affects the kidney, it should be differentiated from other causes of obstructive uropathy (31).

Skin

Haloperidol has been reported to have caused skin rashes.

- A 41-year-old man who had been taking weekly methotrexate 15 mg for 10 months for psoriasis started to take haloperidol 1.5 mg bd for a psychotic illness, and 2 weeks later developed sudden redness and swelling of the face and hands accompanied by redness and watering of both eyes (32). He had diffuse erythema, edema, scaling, and erosions over his face, the anterior aspect of the neck, and the backs of both hands. A skin biopsy showed parakeratosis, acanthosis, spongiosis, focal epidermal cell degeneration, and dermal edema, accompanied by a moderate lymphomononuclear infiltrate, consistent with subacute dermatitis. A diagnosis of pellagra-like photosensitivity dermatitis, caused by combined deficiency of niacin, riboflavin, and other water-soluble vitamins, probably precipitated by haloperidol, was therefore considered. Haloperidol was withdrawn, vitamins were administered, and the condition resolved in the next 5 days.
- A 55-year-old man who had been treated for a manic-depressive disorder for about 5 years developed toxic epidermal necrolysis after being given carbamazepine and haloperidol (33).

Sexual function

Sexual dysfunction can occur with neuroleptic drugs (SED-14, 149) (SEDA-22, 54) (34,35).

- A 49-year-old man with bipolar disorder had erectile dysfunction shortly after starting to take haloperidol 50 mg/day and lithium 1500 mg/day (36). Before this he had had normal sexual function. After 2 months, the dosage of haloperidol was reduced to 20 mg/day, but the sexual dysfunction persisted and did not

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improve with sildenafil. He was then switched to olanzapine 10 mg/day and lithium 1200 mg/day and 1 week later his sexual dysfunction had disappeared.

Second-Generation Effects

Pregnancy

Although studies have failed to identify an increased rate of malformations with haloperidol, isolated cases have been reported (SED-14, 152) (37) (SEDA-22, 54) (38,39).

Teratogenicity

Several instances of limb reduction after the use of haloperidol during pregnancy suggest that it would be prudent not to use this drug during the first trimester, the period of limb development (37). There is also reason to argue that prenatally administered drugs of this class influence the offspring after the drug has been eliminated, and can produce behavioral teratogenicity; since neurotransmitter systems continue to develop long after birth, such drugs might influence behavior in an adverse way over a very long time (40).

Fetotoxicity

A neonate had severe hypothermia after antenatal exposure to haloperidol (41). He weighed 3710 g at birth and did not need resuscitation; his axillary temperature was 35°C and he had severe generalized hypotonia. His temperature rose to 36.5°C after 6 hours of rewarming with an overhead radiant heater.

Drug Administration

Drug additives

General allergic reactions have also been reported following injections of parabens-containing formulations of lidocaine and hydrocortisone and after oral use of barium sulfate contrast suspension, haloperidol syrup, and an antitussive syrup, all of which contained parabens (42).

Drug–Drug Interactions

General

Based on published data in humans, concomitant medications were classified as potential inhibitors (cimetidine, fluoxetine, levopromazine, paroxetine, and thioridazine) or inducers of haloperidol metabolism (carbamazepine, phenobarbital, and phenytoin).

Alcohol

Haloperidol increased blood alcohol concentrations (43).

Anticoagulants

Haloperidol has been reported to lower anticoagulant effectiveness through enzyme induction (44).

Buspirone

Buspirone increases haloperidol concentrations in some patients (SEDA-21, 39).

Carbamazepine

Haloperidol inhibits the metabolism of carbamazepine. In Japanese patients with schizophrenia, serum concentrations of carbamazepine were about 40% lower in the absence of haloperidol (45).

Chlorpromazine

- A 40-year-old man with schizophrenia developed a raised plasma concentration of haloperidol in combination with chlorpromazine and during overlap treatment with clozapine (46). Like haloperidol, chlorpromazine is a competitive inhibitor of CYP2D6; however, clozapine appears to be largely metabolized by CYP1A2.

Itraconazole

Adverse effects can result from increased plasma concentrations of haloperidol during itraconazole treatment. This has been observed in 13 schizophrenic patients treated with haloperidol 12 or 24 mg/day who took itraconazole 200 mg/day for 7 days (47). Plasma concentrations of haloperidol were significantly increased and neurological adverse effects were more common. Itraconazole is a potent inhibitor of CYP3A4.

Lithium

Persistent dysarthria with apraxia has been reported with a combination of lithium carbonate and haloperidol (48).

Lorazepam

Several cases of torsade de pointes have been reported with intravenous haloperidol used with lorazepam to treat delirium (SEDA-18, 30) (SEDA-18, 47). Acid mucopolysaccharide deposition may be associated with neuroleptic drug treatment as a possible mechanism contributing to rare cardiovascular adverse events (49).

Methyldopa

Dementia occurred when methyldopa was combined with haloperidol (50).

Nefazodone

Hepatic enzyme inhibition by nefazodone can significantly raise concentrations and toxicity of haloperidol (1).

Valproate

An interaction between valproate and haloperidol has been reported (51).

- A 30-year-old man with bipolar affective disorder was given intravenous sodium valproate 20 mg/kg/day without any major problem. Later, he was given oral haloperidol 10 mg bd for persistent aggressive behavior and manic symptoms. The next day he developed a sense of imbalance and started swaying. He was drowsy and had cerebellar ataxia. Haloperidol was withdrawn and

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within 1 day his ataxia had disappeared completely in spite of continuing valproate.

Food–Drug Interactions

Grapefruit inhibits CYP3A4, but in one study there was no interaction with haloperidol (52).

Smoking

The extent to which smoking, the genotype for CYP2D6, and the concomitant use of enzyme inducers or inhibitors can explain variations in steady-state plasma concentrations of haloperidol has been evaluated in 92 patients (53). Smokers were treated with higher doses of haloperidol than non-smokers, supporting the view that smokers require larger doses of neuroleptic drugs than non-smokers to achieve therapeutic effects. Poor metabolizers had higher concentrations of haloperidol metabolites, but not of haloperidol, than extensive metabolizers. Altogether, the patients took about 150 different drugs; compared with the rest of the group, there was a tendency for patients taking inducers to be treated with slightly higher doses of haloperidol on average and to have lower dose-normalized plasma concentrations of haloperidol, although the differences were not significant.

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Halothane

See also General anesthetics

General Information

Halothane is a non-inflammable hydrocarbon that induces anesthesia, with little tendency to excitement. Contrary to earlier assumptions, halothane is metabolized, the consequences of which are discussed below (1,2).

Organs and Systems

Cardiovascular

Halothane, isoflurane, and sevoflurane are potent coronary vasodilators, able to produce some degree of coronary steal in ischemic regions. Despite this, halothane may preferentially dilate large coronary arteries and/or interfere with platelet aggregation. If these experimental effects are confirmed, halothane may be the anesthetic of choice in the non-failing ischemic heart (3).

Halothane has a mild depressive effect on cardiac performance (4). In human ventricular myocardium, halothane interacted with L-type calcium channels by interfering with the dihydropyridine binding site; this may, at least in part, explain its negative inotropic effect (5).

Halothane depressed cardiovascular function significantly more than isoflurane in younger adults, but the falls in systolic and diastolic blood pressures in elderly patients were significantly greater with isoflurane (6).

Cardiac dysrhythmias

Halothane produces bradycardia, but dysrhythmias, most often ventricular in origin, also occur during maintenance of anesthesia. They were noted in 53% of 679 patients (7). Concomitant administration of catecholamines increases the risk of dysrhythmias.

Bundle branch block and aberrant conduction were noted in children during halothane anesthesia (8).

In a double-blind, randomized, controlled study of 77 children undergoing halothane anesthesia for adenoidectomy, the effects of atropine 0.02 mg/kg, glycopyrrolate 0.04 mg/kg, and physiological saline were compared (9). There was no difference in the incidence of ventricular dysrhythmias. Atropine prevented bradycardia but was associated with sinus tachycardia in most patients. The bradycardias that occurred in the groups that received glycopyrrolate or placebo were short-lived and resolved spontaneously.

Pulsus alternans in association with hypercapnia occurred in a study of 120 patients who breathed spontaneously during halothane anesthesia (10). End-tidal

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carbon dioxide concentration was allowed to rise freely until pulsus alternans or other cardiac dysrhythmias occurred. Ten of the patients developed pulsus alternans, which was promptly relieved on institution of positive pressure ventilation and the return of end-tidal carbon dioxide concentration to normal. The mechanism and the significance of this phenomenon are not well understood.

Respiratory

Halothane is not irritant to the respiratory tract. Respiratory depression is a consequence only of high concentrations of halothane. A certain degree of bronchodilatation is observed, and may explain the fact that a beneficial effect of halothane was described in a 17-year-old woman with acute severe asthma who did not respond to conventional treatment (11).

Preterm infants can become apneic during the immediate postoperative period, even if the ventilatory response to CO_2 is not depressed after halothane anesthesia (12). In a prospective study in 167 preterm infants after inguinal herniorrhaphy with halothane/nitrous oxide anesthesia, only one had an episode of apnea up to 2 days postoperatively; however, the authors recommended careful monitoring until complete recovery from anesthesia has occurred (13).

Nervous system

In contrast to enflurane, cerebral irritability is very rare with halothane (14).

Halothane can cause an increase in intracranial pressure (15), as can other inhalational anesthetics, which can constitute a particular risk if the pressure is already raised before anesthesia. In neonates, the intracranial pressure may fall (16).

A child who underwent induction of anesthesia with halothane developed hiccups associated with pulmonary edema (17).

- An 8-year-old girl with a history of seizures and cerebral ischemic strokes secondary to moyamoya disease underwent anesthetic induction with halothane and 70% nitrous oxide. She had had three previous uneventful anesthetics. Hiccups started within seconds of induction of anesthesia and did not cease until 20 minutes later, when she was paralysed, intubated, and ventilated. During the next 20 minutes a period of hemodynamic instability ensued, with increasing oxygen requirements. The procedure was stopped and pulmonary edema was confirmed on chest X-ray. The child was transferred to the intensive care unit and ventilated overnight. Further recovery was uneventful.

Hiccups during anesthesia are often thought to be benign. Negative pressure pulmonary edema is usually associated with an obstructed airway, as occurs with laryngospasm, or other causes of upper airway obstruction, but was presumably the cause in this child.

The effect of increasing and decreasing concentrations of halothane on the cerebral circulation in 11 young children (aged 4 months to 3.5 years) undergoing minor urological surgery under general relaxant and caudal anesthesia has been studied (18). Cerebral blood flow velocity was measured in the middle cerebral artery using transcranial Doppler ultrasound. There was significantly increased cerebral blood flow velocity when the dose was increased from 0.5 to 1.0 minimum alveolar concentration (MAC) and from 0.5 to 1.5 MAC, but not when it was increased from 1.0 to 1.5 MAC. When the halothane concentration was reduced from 1.5 to 1.0 MAC, cerebral blood flow velocity fell significantly, whereas there was no effect when the concentration was reduced from 1.0 to 0.5 MAC. These results suggest that there is cerebrovascular hysteresis in response to increasing and decreasing concentrations of halothane.

Psychological, psychiatric

Slight depression of mood, lasting up to 30 days, along with a non-specific slowing of the electroencephalogram for 1–2 weeks, was observed after halothane. In 16 healthy young men, halothane anesthesia had negative effects on postoperative mood and intellectual function, the changes being greatest 2 days after anesthesia, with restoration of function after 8 days (19). In seven subjects, serial electroencephalography, serum bromide determinations, and psychological tests before and after halothane anesthesia showed that there was significant psychological impairment 2 days after anesthesia (20).

The effect of a single preoperative dose of the opioid oxycodone on emergence behavior has been studied in a randomized trial in 130 children (21). Oxycodone prophylaxis, compared with no premedication, significantly reduced the incidence of post-halothane agitation.

Mineral balance

Halothane can cause an increase in circulating concentrations of bromide and fluoride (20), which can be associated with impaired urine-concentrating ability in response to antidiuretic hormone (22).

Hematologic

Halothane produced inhibition of in vitro platelet aggregation and an increase in bleeding time (23).

Gastrointestinal

Postoperative nausea and vomiting can occur after halothane anesthesia (24). In one series, postoperative vomiting occurred in 13 of 29 patients who had received halothane for induction, but when dyxirazine was added during anesthesia the incidence of postoperative vomiting was significantly reduced (three of 29 patients) (25).

Liver

The greatest disadvantage of halothane is its ability to cause liver damage (26).

Incidence

The death rate due to halothane-induced liver damage was estimated in 1993 at one in 35 000 anesthetics (27), three times greater than the one in 110 000 incidence reported in 1976 (28). Both immune function and the metabolism of halothane play important roles in the pathophysiology of liver damage (29). Human hepatic microsomal carboxylesterase is a target antigen in halothane hepatitis, protein disulfide isomerase is an important factor in the mechanism of liver impairment, and an associated immune response

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may be involved (SEDA-18, 116). So-called halothane-induced liver antigens are novel antigens found in the livers of some individuals who have been exposed to halothane, but not in the livers of unexposed individuals (30).

A retrospective review of the case-notes of 44 patients with drug-induced hepatotoxicity diagnosed in 1978–96 found only one case attributable to halothane (31). Antibiotics, non-steroidal anti-inflammatory drugs, and psychotropic drugs accounted for 73% of the cases.

Mechanisms

The mechanisms by which halothane causes hepatic toxicity have been reviewed (32). Oxidative metabolism of halothane to trifluoroacetate occurs in the liver, probably via CYP2E1. In rats, trifluoroacetylated CYP2E1 has been identified after exposure to halothane, as has antibody formation to this antigen (33). Covalent binding of halothane (34), after its activation to the trifluoroacetyl halide, to proteins in human liver microsomes has also been shown (35). It has been suggested that some genetic factor determines the risk of developing halothane hepatitis (36). A report of halothane hepatitis in three pairs of closely related women (37) raised the possibility of a pharmacogenetic defect in these patients, with increased production of hepatotoxic metabolites.

Most recorded cases of liver disorders occurred after either repeated exposure (38) or prolonged exposure (39) to halothane. In one case, hepatitis developed 3 weeks after a single halothane anesthetic in a 37-year-old renal transplant recipient who had previously been exposed to isoflurane (40); this report suggests that previous exposure to isoflurane may predispose to subsequent halothane toxicity.

Halothane also reduces liver blood flow during anesthesia, and this could increase the release of potentially hepatotoxic halothane metabolites. The role of reduced halothane metabolites and inorganic fluoride, which may covalently link to liver macromolecules, has been stressed; in keeping with this hypothesis is the observation of halothane hepatitis in patients who simultaneously take enzyme-inducing agents, for example barbiturates (41) or rifampicin (42).

It is therefore tempting to suggest that patients with one or several predisposing factors, for example a pharmacogenetic trait, hepatic hypoxia, or enzyme induction, are likely to produce large amounts of hepatotoxic halothane metabolites that covalently bind to liver macromolecules, rendering them immunogenic. The finding that repeated administration increases the risk of halothane jaundice (43,44) supports this hypothesis.

Presentation

Two patterns of liver damage associated with halothane have been observed (45). One pattern is a mild derangement of liver enzymes, which occurs in about one in four anesthetics. The other pattern is rare but is associated with severe hepatitis, often resulting in fulminant liver failure. This severe form occurs more often in middle-aged, obese women, usually after multiple anesthetics, and is known as halothane hepatitis. It is defined as unexplained severe liver damage occurring within 28 days of halothane exposure in a person with a previously normal liver, and it occurs in 1:35 000 halothane exposures. With repeated exposure to halothane within 1 month, the frequency of acute liver failure increases to 1:3700. The overall incidence of halothane hepatitis is falling, owing to reduced use of halothane. Survival after liver transplantation in patients with fulminant hepatic failure is lower than that after liver transplantation for other reasons.

A case of halothane hepatitis has been reported in a child (46).

- A 6-year-old boy sustained pelvic injuries and a femoral fracture. The first anesthetic he received consisted of thiopental, suxamethonium, isoflurane, and nitrous oxide. He also received two units of blood. He subsequently underwent four halothane anesthetics over 6 weeks for dilatation of a urethral stricture. Two days after the last anesthetic he was noted to be jaundiced. He had a negative viral screen but was positive for antitrifluoroacetyl IgG antibodies. He developed fulminant hepatic failure with grade 2 hepatic encephalopathy and underwent an auxiliary liver transplantation 24 days after his last exposure to halothane. He died of septicemia 18 days later. Both at autopsy and on a previous hepatobiliary scan he was noted to have had extensive native liver regeneration.

Halothane hepatitis in children is rare, and occurs in 1:82 000 to 1:200 000 exposures. Children as young as 11 months are not exempt from the risk, contrary to what was once thought and there is a growing number of reports of halothane hepatitis in children (47). It has been noted that sevoflurane is not metabolized to trifluoroacetic acid and may prove to be a better alternative for repeated anesthesia in children (48).

A retrospective review of the case-notes of 44 patients with drug-induced hepatotoxicity diagnosed in 1978–96 found only one case attributable to halothane (31). Antibiotics, non-steroidal anti-inflammatory drugs, and psychotropic drugs accounted for 73% of the cases.

Urinary tract

Renal blood flow, glomerular filtration rate, and urinary volume are sometimes mildly and reversibly reduced. In contrast, repeated massive polyuria has been reported in a 46-year-old man after two anesthetics with halothane (49). Acute renal insufficiency has been described (50) but is rare.

Skin

A young nurse complained of a skin rash with edema of the eyelids after repeated professional exposure to halothane (51).

Immunologic

Halothane can suppress host defence mechanisms; the clinical consequences are unclear (SED-11, 210) (SEDA-3, 101) (SEDA-4, 77) (SEDA-5, 121) (SEDA-11, 109).

Body temperature

Halothane reduces body temperature and can cause shivering, although active thermoregulation does not occur

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until the core temperature is reduced by 2.5°C (52). The shivering can be attenuated by flumazenil, despite a lower core temperature (53).

Halothane in association with suxamethonium is the most frequent cause of malignant hyperthermia attributed to general anesthesia (54). Standard in vitro caffeine-halothane contracture testing was performed on 32 patients with a past history of malignant hyperthermia diagnosed on clinical grounds; they were compared with a matched control group of 120 subjects who were considered clinically to be at low risk of malignant hyperthermia (55). The sensitivity of the test was 97% and the specificity 78%.

Second-Generation Effects

Pregnancy

Halothane strongly reduces uterine contractility during labor (56).

Fetotoxicity

Halothane can be used as an anesthetic by maternal inhalation for fetal surgery and improves surgical exposure by relaxing the uterus. However, the effects of halothane on fetal cardiovascular homeostasis have been evaluated, and the authors concluded that halothane had a significant negative effect on the fetal heart and peripheral vasculature; it was therefore considered a poor anesthetic for this purpose (57).

Lactation

Halothane is readily excreted into breast milk (58).

Drug Administration

Drug administration route

In a randomized, double-blind, placebo-controlled comparison of intranasal and intramuscular atropine in 80 children, the intranasal route was equally effective at preventing halothane-induced bradycardia (59).

Drug overdose

Suicide attempts with halothane have sometimes succeeded, but in patients who recovered there was no residual damage. A 4-year-old boy was accidentally given halothane intravenously; he recovered fully within a few hours (60). Accidental intravenous injection and illicit inhalation have both caused pulmonary edema (61).

Drug–Drug Interactions

Disulfiram

Disulfiram is an inhibitor of CYP2E1. In 20 patients undergoing halothane-based maintenance of anesthesia at an end-tidal concentration of 1% for an average of 3 hours, disulfiram 500 mg taken the night before substantially attenuated trifluoroacetate production, as judged by its urinary excretion (62). It was suggested that a single dose of disulfiram may provide effective prophylaxis against halothane hepatitis.

Non-depolarizing muscle relaxants

Halothane potentiates the effects of non-depolarizing muscular relaxants (SED-11, 210) (63).

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Helicobacter pylori eradication regimens

General Information

Drugs and regimens for *Helicobacter pylori* eradication have been reviewed (1,2). The major factor in choosing an antibiotic regimen is the pattern of antibiotic resistance in the community. Generally two antimicrobial drugs plus bismuth or ranitidine or a proton pump inhibitor such as omeprazole are required to achieve a cure rate of over 90% and avoid the resistance that occurs when clarithromycin or metronidazole is the single antimicrobial used. In regions where metronidazole and clarithromycin resistance is common initial quadruple therapy with bismuth, metronidazole, tetracycline, and a proton pump inhibitor is recommended. In general, higher doses and longer duration of therapy are associated with better outcomes. Although therapy for 1 week has become accepted in first-line regimens, therapy for 2 weeks is better when treating nitroimidazole-resistant or clarithromycin-susceptible strains.

Adverse effects of these regimens are related to the individual drugs used.

Comparative studies

The MACH-2 study has assessed the role of omeprazole in triple therapy in 539 patients with duodenal ulcers associated with *H. pylori* (3). The addition of omeprazole resulted in significantly higher eradication rates (over 90%) than antibiotics alone (amoxicillin plus clarithromycin about 25%; clarithromycin plus metronidazole 70%), and reduced the impact of primary resistance to metronidazole. About one-third of the patients who took amoxicillin reported diarrhea/loose stools. The frequency of taste disturbance was dose-dependent with clarithromycin. Increased liver enzymes were more commonly reported in those taking metronidazole. The addition of omeprazole did not increase the frequency of reported adverse effects.

The DU-MACH study assessed the efficacy of two omeprazole-based triple therapies (omeprazole, amoxicillin, clarithromycin versus omeprazole, metronidazole, clarithromycin) given for 1 week to 149 patients for eradicating *H. pylori*, healing duodenal ulcers, and preventing ulcer relapse over 6 months after treatment (4). Both regimens achieved high eradication rates (about 90%) and were well tolerated. Adverse effects were similar in the two groups, and included diarrhea, taste disturbance, headache, nausea, and dyspepsia.

Ranitidine 300 mg bd and omeprazole 20 mg bd have been compared as components of triple therapies (combining them with either amoxicillin plus clarithromycin or amoxicillin plus metronidazole) in 320 patients with *H. pylori* (5). Omeprazole and ranitidine combined with two antibiotics for 1 week were equally effective in eradicating *H. pylori*. This result questions the role of profound acid suppression in eradication. There was no difference in the reported adverse effects, which included nausea, vomiting, diarrhea, metallic taste, skin rashes, and headache.

In a similar study in 221 patients with peptic ulcer disease associated with *H. pylori*, rabeprazole has been compared with omeprazole and lansoprazole (combining them with amoxicillin plus clarithromycin for 1 week) (6). Rabeprazole was as effective as omeprazole and lansoprazole in eradicating *H. pylori* (84–88% each). There were no differences in reported adverse events. Common adverse effects were soft stools, glossitis, taste disturbances, and skin rashes.

Dual therapy (omeprazole plus clarithromycin) for 2 weeks has been compared with triple therapy (omeprazole plus amoxicillin and clarithromycin) for 1 week in the eradication of *H. pylori* in 145 patients with duodenal ulcers (7). Triple therapy was significantly more effective in eradicating *H. pylori* (71 versus 48%). There were no significant differences in compliance or adverse effects. The most frequent adverse effects were metallic taste and nausea in the dual-therapy group and metallic taste, mild abdominal pain, and diarrhea in the triple-therapy group.

Quadruple therapy (omeprazole, amoxicillin, roxithromycin, and metronidazole for 1 week) has been studied in an open trial in 169 patients with *H. pylori* (8). This regimen achieved an eradication rate of 92%. It was also beneficial in patients infected with pretreatment resistant strains to the antibiotics, in which cases the eradication rates achieved (over 90%) were similar to eradication rates in patients infected with sensitive strains. Compliance was good and there was only one serious adverse effect, anaphylaxis, probably due to amoxicillin. Frequent adverse effects were abdominal distension (10%), glossitis (9%), and diarrhea (8%).

Sucralfate 1 g tds in combination with amoxicillin 500 mg tds and clarithromycin 400 mg bd for 2 weeks was as effective as a combination of lansoprazole 30 mg bd plus amoxicillin 500 mg tds and clarithromycin 400 mg bd for 2 weeks for *H. pylori* eradication in a randomized, multicenter trial in 150 patients (9). There was no significant difference in adverse effects between the two groups. Diarrhea, abdominal pain, glossitis, and taste disturbance were the adverse effects commonly reported.

In an open trial, 7-day triple therapy with omeprazole 30 mg bd, amoxicillin 500 mg tds, and clarithromycin 400 mg bd was safe and effective in eradicating *H. pylori* in 12 of 13 patients undergoing hemodialysis (10). There were adverse effects in two patients (compared with three of 27 patients not undergoing hemodialysis) and treatment had to be discontinued in one, owing to severe nausea and vomiting.

Placebo-controlled studies

The effect of eradicating *H. pylori* in 20 patients with chronic idiopathic urticaria has been assessed in a

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randomized, placebo-controlled trial (11). After 7 days of treatment with omeprazole 20 mg bd, amoxicillin 500 mg bd, and clarithromycin 500 mg bd *H. pylori* was eradicated in nine of 10 patients (compared with three of 10 in the placebo group) and there was a significant improvement in urticaria in four of these nine (compared with one of the seven in whom *H. pylori* was not eradicated). No serious adverse effects were reported in either treatment group.

In a randomized, controlled trial in 120 patients supplementation with inactivated *Lactobacillus acidophilus* tds significantly improved the efficacy of a standard 7-day regimen with rabeprazole 20 mg bd, clarithromycin 250 mg tds, and amoxicillin 500 mg tds (12). There was no significant difference in adverse effects between the two groups. Those reported were abdominal pain, nausea, and diarrhea.

In a randomized, placebo-controlled trial in 60 healthy, asymptomatic subjects who screened positive for *H. pylori*, supplementation with *Lactobacillus* GG twice daily for 14 days significantly reduced the adverse effects (diarrhea, nausea, taste disturbance) and improved the overall tolerability of a standard 7-day eradication regimen consisting of rabeprazole 20 mg bd, clarithromycin 500 mg bd, and tinidazole 500 mg bd (13).

Organs and Systems

Gastrointestinal

Pseudomembranous colitis has been reported in an 86-year-old woman with non-ulcer dyspepsia a few days after she had taken triple eradication therapy (omeprazole 20 mg bd, metronidazole 400 mg tds, and clarithromycin 500 mg bd); she recovered after treatment with oral vancomycin (14).

Susceptibility Factors

Age

The efficacy of triple therapy with bismuth plus amoxicillin and metronidazole has been assessed in an open trial in 26 children with duodenal ulcers associated with *H. pylori* (15). *Helicobacter pylori* was eradicated in 25 children and the ulcer was healed in 24. During a mean follow-up of nearly 2 years, the annual ulcer relapse rate was 9% (compared with 56% in historical controls, in whom the infection was not eradicated). Adverse events were reported by 13% of the children, and included diarrhea, dizziness, nausea, and vomiting.

Triple therapy with bismuth plus amoxicillin and metronidazole for 2 weeks has been compared with dual therapy with omeprazole plus amoxicillin for 2 weeks in 126 patients over the age of 60 years, who were *H. pylori* positive and had functional dyspepsia (16). Eradication rates were similar in the two groups 2 months after the end of therapy (66% with triple therapy and 64% with dual therapy), and there was a significant reduction in dyspeptic symptoms in patients in whom *H. pylori* was eradicated compared with those in whom infection persisted. Adverse effects were reported by 15% of patients who took triple therapy (nausea and metallic taste) compared with 4% of those who took dual therapy (nausea and headache). In all cases no adverse effect was severe enough to interrupt therapy.

Drug Administration

Drug dosage regimens

The effect of adding adherence-enhancing measures to triple therapy with omeprazole plus amoxicillin and metronidazole for 10 days has been studied in 119 Australian patients with *H. pylori* infection (17). The adherence-enhancing measures were:

- the provision of the medication in a dose-dispensing unit;
- the use of a medication chart;
- the provision of an information sheet about the treatment;
- a reminder by telephone 2 days after the start of therapy.

Ten days of triple therapy was effective for *H. pylori* eradication (85–90%) and patient adherence was excellent in both groups (97%). Attempts to improve adherence had no impact on outcome and adverse effects were common and were significantly associated with treatment failure and poor adherence to therapy in both groups. There were no significant differences in the adverse effects profiles. Female sex predicted more adverse effects. Two patients reported severe adverse effects, 19 reported moderate adverse effects, and 75 reported mild adverse effects. Common adverse effects included anorexia and nausea (35%), vomiting (7%), constipation (16%), diarrhea/flatulence (37%), abdominal pain/cramps (27%), a metallic taste (44%), headache/dizziness (48%), rash/itch (3%), lethargy/confusion (9%), and insomnia/agitation (4%). The authors attributed the unusually high prevalence of adverse effects to comprehensive reporting.

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Hemin and heme arginate

General Information

Hemin (hematin), an exogenous source of heme, is used to treat acute intermittent porphyria and other hepatic porphyrias. It is generally well tolerated in the recommended doses, although thrombophlebitis, coagulation defects, circulatory collapse, and occasional renal insufficiency have been reported (1).

Thrombophlebitis is seen in up to 10% of patients, and this effect, as well as effects on coagulation (prolongation of the prothrombin and thromboplastin times, increased fibrin degradation products, and thrombocytopenia), may be caused by degradation products of hemin (2). There is evidence that slower infusion rates reduce the risk of adverse effects (3).

Heme arginate is more stable than hemin, but it is still not established whether its adverse effects (thrombophlebitis, anaphylaxis, and psychosis) (4) are fewer and whether its therapeutic effect is better than that of hemin (5).

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Hemostatic compounds, miscellaneous

General Information

A number of compounds that have, or supposedly have, hemostatic activity are reviewed here. Some of them are obsolete and are included largely for historical interest. Others, such as fibrin glue, are still in use.

Aminaphtone

Experiments in the 1970s with aminaphtone (2-hydroxy-3-methyl-1,4-naphthohydroquinone-2-*p*-aminobenzoate) suggested that it could significantly shorten the bleeding time in both normal and heparinized rabbits and mice (1). Subsequent clinical experiments showed no adverse effects and toxicological studies in animals showed no evidence of

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acute or long-term toxicity, even at quite high doses (1). No adverse effects were noted when patients who had initially been involved in an efficacy study of limited duration were treated with aminaphtone for a further year (2). No data are available on the absorption or metabolism of aminaphtone in humans. It has been claimed that aminaphtone may improve symptoms related to chronic venous insufficiency as well as lymphatic stasis (3).

Carbazochrome and carbazochrome salicylate

Adrenochrome, an oxidation product of adrenaline, is stabilized by binding to monosemicarbazone (adrenochrome monosemicarbazide). Its solubility is greatly enhanced by combination with sodium salicylate. The product, carbazochrome salicylate, can be given either by intramuscular injection or orally. The solution for intramuscular injection is hypertonic, and patients usually experience a brief stinging pain at the site of injection. Experiments in animals have shown a significant reduction in normal bleeding time when adrenochrome monosemicarbazide is given (4). This has been attributed to a direct effect on capillaries, as increased capillary resistance has been observed in experimental animals. Despite documentation of a transient reduction in bleeding time in humans in early experiments in the 1940s, subsequent double-blind controlled trials did not identify a useful reduction in blood loss after surgery (5–8). Despite the similarity to adrenaline, it is remarkably non-toxic and administration is not associated with the general systemic effects of sympathomimetic drugs (such as tachycardia, anxiety, or hypertension).

Fibrin glue

Fibrin glue is a topical biological adhesive, the effect of which imitates the final stages of coagulation. It contains two separate components, fibrinogen plus factor XIII, and thrombin plus calcium chloride. It is covered in a separate monograph.

5-Hydroxytryptamine creatinine sulfate

Platelets contain serotonin (5-hydroxytryptamine), which they take up from the plasma and store in dense granules. The serotonin is released when platelets are activated. Although serotonin was originally believed to play a vital part in platelet aggregation, it is now known that it does not, although it can contribute to local vasoconstriction. Treatment with reserpine induces depletion of serotonin in platelets, but this is not associated with any bleeding tendency (9). Nevertheless, belief in the importance of serotonin in hemostasis stimulated the search for analogues that might prove to be useful hemostatic agents, and 2-(5-hydroxy-3-indolyl) ethylamine creatinine sulfate was proposed as a hemostatic agent. However, subsequent clinical studies offered no evidence of benefit. Vertigo and tachycardia were reported in some patients who received the drug by rapid intravenous injection (10).

Naftazone

Naftazone (beta-naphthoquinone semicarbazone) is prepared by diazotization of sulfonic acid with beta-naphthol, and its properties are similar to those of adrenochrome. Naftazone significantly reduces the normal bleeding time as well as blood loss in rabbits and dogs. In many ways, this drug resembles adrenochrome, but it may in addition have certain effects at the cellular level. A double-blind, controlled study in patients undergoing prostatectomy reported significantly lower blood loss and transfusion requirements in the subjects receiving naftazone (11). No significant adverse effects were reported, but 4% of patients complained of transient and moderate nausea and gastric pain in a multicenter study of the efficacy and tolerance of naftazone in which two dosage regimens were compared (12).

Pectin

Pectin is a carbohydrate found in fruits, and is particularly rich in the rind of citrus fruits and in apples. It is a gelling agent and contributes to the solidification of jams. A formulation of pectin called Sangostop® was introduced as a hemostatic agent in 1935, and it was claimed that it could reduce bleeding in a variety of conditions. The active component consisted of colloidal polygalacturonic acid esters from apple pectin. It was given in a variety of ways: locally, orally, by subcutaneous or intravenous injection, or per rectum. The solution for local and oral use contained 5% pectin (3% for the preparation for intravenous administration). Several published reports from the 1930s claimed that pectin had a hemostatic effect, but these were based purely on subjective clinical judgement. Randomized controlled trials, with quantification of blood loss, have never been carried out.

It is clear that pectin, which has been given to a large number of patients in the past, rarely has adverse effects (13), although the toxicological investigations which would now be required by regulatory authorities have not been conducted. The largest study involved the use of Sangostop® in more than 400 patients undergoing surgery (14). Pectin was subsequently shown to have antifibrinolytic activity in vitro (15), which could explain its hemostatic effect. There has been one report of anaphylaxis in a patient given Sangostop® intravenously (16).

Sulfonaphtine

A number of claims were made in the 1950s that sodium 4-amino-1-naphthalene-1-sulphonate (sulfonaphtine glucoside, naphthionine glucoside) had hemostatic properties of clinical value. It was subjected to clinical evaluation because it is related to Congo Red dye, for which similar claims had been made in 1933. Thrombophlebitis was a common problem after intravenous administration of Congo Red, and so clinical trials with that dye were abandoned while other congeners were sought. Sulfonaphtine has been reported to enhance blood coagulation and to reduce the whole blood clotting time and bleeding time (17,18). However, no randomized, double-blinded clinical trials have been conducted. No adverse effects of sulfonaphtine, including thrombophlebitis, have been reported. It is no longer available commercially.

Thrombin and thromboplastin

Numerous tissue extracts, prepared from a variety of animal tissues, have been claimed to be effective

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hemostatic agents. Examples of tissue extracts that are no longer available include thrombin extracts (such as Thrombinar and Thrombostat) and thromboplastin extracts (such as Clauden, Fibraccel, and Tachostyptan). Others include Coagulen, Clauden, Coazimol, Manetol, Thrombocytine, and Frénovex.

Thrombin is prepared from bovine plasma by reacting thrombin with thromboplastin in the presence of calcium. Thromboplastin is prepared as a micellar suspension of at least six phospholipids extracted from porcine brain and mixed in fixed proportions. It is stable at +4°C for several years (19).

Thromboplastin accelerates in-vitro coagulation, but only at certain concentrations and has been given intravenously by injection or infusion. Infusion shortens the bleeding time and normalizes both thrombin generation and prothrombin consumption in vitro for up to 3 hours in a small group of uremic patients (20). It has been used to treat postoperative hemorrhage in the oral cavity (21) and biliary tract (22). There were no adverse effects involving circulatory or cardiac function in healthy human subjects after intravenous injection of 10 ml, but rapid injection can reduce the blood pressure (23).

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Heparins

General Information

Heparins are mucopolysaccharides whose molecules are of varying lengths. Unfractionated (standard) heparin contains molecules of average molecular weight of 12 000–15 000 Da. Low molecular weight heparins contain molecules whose average molecular weight is below 5000 Da. Each formulation of a low molecular weight

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heparin contains a different range of sizes of molecules, but they have in common more activity against factor X than thrombin compared with standard heparin, a longer duration of action, and a lower risk of thrombocytopenia. They can be given subcutaneously once a day without the monitoring of activated partial thromboplastin time that is necessary for standard heparin. Low molecular weight heparins include bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, reviparin, and tinzaparin.

Non-anticoagulant uses

A therapeutic role for heparin has been proposed in inflammatory bowel disease, particularly in ulcerative colitis (1). This beneficial response may result from mechanisms other than anticoagulation, including the restoration of high-affinity receptor binding by anti-ulcerogenic growth factors, such as basic fibroblast growth factor, that normally rely on the presence of heparian sulfate proteoglycans (2).

General adverse effects

The major adverse effect of heparin is bleeding. Thrombocytopenia occurs in some 5% of patients receiving standard heparin but is uncommon in those receiving low molecular weight heparins; bleeding as a result is rare. Long-term use can lead to osteoporosis. General vasospastic reactions have been reported and, exceptionally, skin necrosis can occur. Allergic reactions to heparin are well-known but rare. Tumor-inducing effects have not been described and the possibility of an anti-tumor effect has been raised.

Organs and Systems

Cardiovascular

Bolus administration of heparin causes vasodilatation and a fall in arterial blood pressure of 5–10 mmHg (3). Some convincing data have been reported concerning the role in these reactions of chlorbutol which has been used as a bactericidal and fungicidal ingredient in some heparin formulations (4).

Cardiogenic shock can occur in parallel with disseminated intravascular coagulation (5). In these circumstances heparin is thought to act as a hapten in a heparin–protein interaction that stimulates antibody production and an antigen–antibody reaction associated with release of platelet and vasoactive compounds.

General vasospastic reactions have been described in patients receiving heparin, exceptionally complicated by skin necrosis (6). Vasospastic reactions are probably part of the syndrome of thrombohemorrhagic complications considered above.

Nervous system

Effects of heparin on the nervous system, other than those due to bleeding, have not been reported.

Endocrine

Heparin-induced hypoaldosteronism is well documented, both in patients treated with standard heparin, even at low doses, and in patients treated with low molecular weight heparin (7,8). The most important mechanism of aldosterone inhibition appears to be a reduction in both the number and affinity of angiotensin II receptors in the zona glomerulosa (7). A direct effect of heparin on aldosterone synthesis, with inhibition of conversion of corticosterone to 18-hydroxycorticosterone, has also been suggested. This effect is believed to be responsible for the hyperkalemia that can occur in heparin-treated patients with impaired renal function and particularly in patients on chronic hemodialysis (9), or with diabetes mellitus, or who are taking other potentially hyperkalemic drugs.

Metabolism

Heparin has a strong clearing action on postprandial lipidemia by activating lipoprotein lipase. This has been thought to be associated with an increase in free fatty acid-induced dysrhythmias and death in patients with myocardial infarction.

- Substantial hypertriglyceridemia occurred in a pregnant woman who received long-term subcutaneous heparin treatment (10).

However, the risk of hyperlipidemia seems to have been exaggerated, since the extent of lipolysis is usually small (11).

Electrolyte balance

Hyperkalemia is an occasional complication of heparin therapy. It has been attributed to hypoaldosteronism, and fludrocortisone has been used to treat it (12). It has been suggested that marked hyperkalemia is only likely to occur in the presence of other factors that alter potassium balance (13).

Low molecular weight heparin is less likely to cause hyperkalemia than standard heparin. In 28 men, mean age 70 years, given low molecular weight heparin (40 mg subcutaneously every 12 hours) for deep venous thrombosis prophylaxis after an operation, the serum potassium concentration did not change significantly after 4 days of therapy (4.25 mmol/l before therapy and 4.35 mmol/l) (14).

However, in 85 patients enoxaparin therapy was associated with an increase in mean potassium concentration from 4.26 mmol/l at baseline to 4.43 mmol/l on the third day; potassium concentrations exceeded 5.0 mmol/l in 9% (15). There was no life-threatening or symptomatic hyperkalemia. Neither plasma renin activity nor aldosterone concentrations changed significantly and there was no correlation between the increase in potassium concentrations and the presence of diabetes mellitus or treatment with angiotensin converting enzymes inhibitors, angiotensin receptor blockers, beta-blockers, or potassium-wasting diuretics.

Hematologic

Hemorrhage

The major adverse effect of heparin is bleeding, and it can occur with low molecular weight heparins as well as with standard heparin (16).

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DoTS classification (BMJ 2003;327:1222–5)
Dose-relation: toxic effect
Time-course: early
Susceptibility factors: treatment with antiplatelet drugs, sex, age, renal function

Frequency
An authoritative review of the relevant literature was published in 1993 and is still valid (17). Its authors concluded that the use of heparin in therapeutic dosages (over 15 000 IU/day) is typically marked by an average daily frequency of fatal, major, and major and minor bleeding episodes of 0.05, 0.8, and 2.0% respectively; these frequencies are about twice those expected without heparin therapy. In 2656 medical patients studied by the Boston Collaborative Drug Surveillance Program, the crude risk of bleeding from heparin (route unspecified) was 9% but varied with dose: 4.9% for doses below 50 IU/kg per dose, 8.1% for doses of 50–99 IU/kg per dose, and 17% for doses of 100 IU/kg per dose or more (18). The 7-day cumulative risk for any kind of bleeding was 9.1%. Melena, hematomas, and macrohematuria were the most frequent manifestations; intracranial bleeding and pulmonary bleeding were rare.

Presentation
In the Boston Collaborative Drug Surveillance Program study mentioned above (18), the localization of bleeding, expressed in percentages and broadly classified as major/minor, was as follows:

- gastrointestinal hemorrhage 49/11
- vaginal hemorrhage 11/8 (1/3 postpartum)
- bleeding from wounds and accidental soft-tissue trauma 11/28
- retroperitoneal bleeding 6/0
- genitourinary bleeding other than vaginal 6/35
- intracranial hemorrhage 5/0
- epistaxis 4/10
- other forms of blood loss 8/8.

An FDA Health Advisory warning was issued in December 1997 after 30 cases of spinal hematoma had been reported in patients undergoing spinal or epidural anesthesia while receiving low molecular weight heparin perioperatively. In the European literature, the risk of spinal hematoma in patients receiving low molecular weight heparin was not considered clinically significant. In Europe, low molecular weight heparin is given once a day and at a smaller total daily dose; this enables the placement (and removal) of needles and catheters during periods of reduced low molecular weight heparin activity. Identification of further risk factors is difficult, owing to the rarity of spinal hematoma. However, several possible risk factors have been suggested: about 75% of the patients were elderly women, in 22 patients an epidural catheter was used, and in 17 patients the first dose of low molecular weight heparin was administered while the catheter was indwelling; 12 patients received antiplatelet drugs and/or warfarin in addition to low molecular weight heparin (19). The authors formulated recommendations for minimizing the risk of spinal hematoma, including using the smallest effective dose of low molecular weight heparin perioperatively, delaying heparin therapy as long as possible postoperatively, and removing catheters when anticoagulant activity is low. Furthermore, they warned against combining low molecular weight heparin with antiplatelet drugs or oral anticoagulants.

Relation to dose
Subgroup analyses of randomized trials and prospective cohort studies point to an association, as one would expect, between the incidence of bleeding and the anticoagulant response as measured by a test of blood coagulation, for example the activated partial thromboplastin time (APTT). For instance, there were five major bleeding episodes in 10 patients whose APTT was prolonged to more than twice the upper limit of their therapeutic range but only one episode in 40 patients whose APTT remained in the therapeutic range (relative risk 20) (20). Furthermore, there is an increased rate of major bleeding with intermittent intravenous use compared with continuous intravenous heparin infusion. No differences in major bleeding are generally detected between continuous intravenous and subcutaneous heparin (21).

Time-course
In the Boston Collaborative Drug Surveillance Program study mentioned above, the peak incidence of bleeding was on the third day after the start of heparin therapy, which suggests a relatively safe initial 48-hour period in systemic heparinization (18). However, bleeding can be expected at any time during therapy, if the dosage becomes excessive or if susceptibility factors, such as trauma, intervene.

Susceptibility factors
In the Boston Collaborative Drug Surveillance Program study mentioned above, bleeding correlated with aspirin treatment, with sex, and probably with age and renal function (18). A meta-analysis of randomized trials reported that those aged over 70 are associated with the risk of major bleeding (22). Recent surgery or trauma also increase the risk.

Low molecular weight heparin
Because of its reduced activity on overall clotting, low molecular weight heparin is expected to cause less bleeding than standard heparin. However, several meta-analyses of randomized comparisons of low molecular weight heparin with standard heparin in the prevention of postoperative deep venous thrombosis showed no difference in the incidence of major bleeding (23,24). For low molecular weight heparin, the rates of major bleeding ranged from 0 to 3% and fatal bleeding from 0 to 0.8% (21). A later meta-analysis of randomized comparisons in the initial curative treatment of deep venous thrombosis showed a 35% reduction in major bleeding in patients treated with low molecular weight heparin, but this result was not significant (25).

Thrombocytopenia
Thrombocytopenia (100×10^9/l or lower) occurs in about 3–7% of patients, independent of the mode of administration or the dose and type of heparin (26,27). The incidence varies largely among published series, but the overall average may be some 5% (28). There was a higher incidence in some older studies (29), but this may have

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been due to the presence of impurities in the heparin then available, and some of the studies clearly included cases of thrombocytopenia not attributable to heparin. Even the current incidence is to some extent uncertain, because of differences in methods of diagnosis and in the definitions used (30,31). Low molecular weight heparin is significantly less likely to cause thrombocytopenia than unfractionated heparin (27).

Two types of heparin-induced thrombocytopenia have been defined. Type I (mild) occurs within the first few days of heparin administration, while type II (severe), which is less common, is generally seen after a week or more of treatment and is often complicated by the recurrence of thromboembolic events.

A third variety, so-called "delayed-onset heparin-induced thrombocytopenia" has also been described in several reports. In 12 patients, recruited from secondary and tertiary care hospitals, thrombocytopenia and associated thrombosis occurred at a mean of 9.2 (range 5–19) days after the withdrawal of heparin; nine received additional heparin, with further falls in platelet counts (32). In a retrospective case series, 14 patients, seen over a 3-year period, developed thromboembolic complications a median of 14 days after treatment with heparin (33). The emboli were venous ($n = 10$), or arterial ($n = 2$), or both ($n = 2$); of the 12 patients with venous embolism, 7 had pulmonary embolism. Platelet counts were mildly reduced in all but two patients at the time of the second presentation. On readmission, 11 patients received therapeutic heparin, which worsened their clinical condition and further reduced the platelet count.

- A 44-year-old woman developed delayed-onset thrombocytopenia and cerebral thrombosis 7 days after a single dose of standard heparin 5000 units (34).

Type I heparin-induced thrombocytopenia

DoTS classification (BMJ 2003;327:1222–5)
Dose-relation: toxic effect
Time-course: early
Susceptibility factors: not known

Type I heparin-induced thrombocytopenia is common and is characterized by a mild transient thrombocytopenia (with platelet counts that usually do not fall below 50×10^9/l); the thrombocytopenia occurs on the first few days of heparin administration (usually 1–5 days) and requires careful monitoring but not usually withdrawal of heparin. Type I thrombocytopenia is generally harmless and very probably results from direct heparin-induced platelet aggregation. Thrombocytopenia is most common when large doses of heparin are used, or in some particular circumstances, such as after thrombolytic therapy (35) or in the early orthopedic postoperative period (36); it can abate in spite of continued therapy. Type I thrombocytopenia is a non-immune reaction, probably due to a direct activating effect of heparin on platelets.

Type II heparin-induced thrombocytopenia

DoTS classification (BMJ 2003;327:1222–5)
Dose-relation: hypersusceptibility effect
Time-course: delayed
Susceptibility factors: previous heparin therapy, co-administration of antiplatelet drugs or oral anticoagulants

Type II heparin-induced thrombocytopenia is less common than Type I but is often associated with severe thrombocytopenia. It is generally accepted that heparin-induced thrombocytopenia refers to platelet counts of less than 150×10^9/l or a reduction in platelet count of 30–50% to a previous count. In some cases, platelet counts that have fallen to 50% from a high normal previous count would remain apparently normal but should be considered as potentially heparin-induced thrombocytopenia.

Mechanism

Type II thrombocytopenia is probably an immune-mediated phenomenon, a fact that has been the subject of much specific investigation (27,37–42). It has been proposed that the diagnosis should depend on two criteria: the association of one or more clinical events and laboratory evidence of a heparin-dependent immunoglobulin (36).

Diagnosis

Laboratory diagnosis of heparin-induced thrombocytopenia can be made either using functional tests (demonstration of platelet activation of normal donor platelets in vitro by the patient's serum in the presence of heparin) or by screening for antibodies (27,43). The duration of the antibody response can vary from weeks to months up to 1 year. The two types of tests are complementary; both should be used when the reported results of either are inconsistent with the clinical problem.

Susceptibility factors

The risk of thrombocytopenia is increased in patients with a history of previous heparin therapy (44). Thrombocytopenia and/or thromboembolic complications can occur sooner in patients with a history of previous exposure to heparin, suggesting an anamnestic response (28,43).

The results of some prospective studies, including mainly transient benign thrombocytopenia (type I heparin-induced thrombocytopenia), have suggested that thrombocytopenia is more common in patients who have received the bovine lung type of heparin than in those who have received the porcine intestinal mucosa type (45–47). Type II thrombocytopenia is certainly more common in patients treated with standard heparin than in those treated with low molecular weight heparin (36), but there is usually cross-reactivity between standard heparin and low molecular weight heparin.

Heparin-coated catheters can sustain the thrombocytopenia in patients with heparin-associated antiplatelet antibodies (48,49) and therefore have to be removed from such patients.

Presentation

Heparin-induced thrombocytopenia usually occurs with a delayed onset (a week or more) and is often complicated by paradoxical recurrence of thromboembolic events, leading to life-threatening complications. The general term "heparin-induced thrombocytopenia" is as a rule used to designate this phenomenon.

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Thrombosis can occur before the onset of overt thrombocytopenia (36). In some cases dramatic thrombotic events occur in association with antibodies without significant fall in platelet count (43). Thrombotic complications include new or recurrent arterial thromboembolism, often localized in the distal aorta and legs or presenting as myocardial infarction and hemiplegia (50), but also in the brachial artery (51), often requiring surgical treatment. In older reports there was a higher incidence of arterial than of venous thrombosis, but later reports documented that venous thrombosis is four times more common than arterial thrombosis (52). Heparin-induced thrombocytopenia can be associated with deep venous thrombosis and pulmonary embolism, but unusual forms of thrombosis, such as adrenal hemorrhagic infarction due to adrenal vein thrombosis, a complication that must be considered in patients who develop abdominal pain or unexplained hypotension during heparin therapy, are not uncommon.

Venous limb gangrene due to heparin-induced thrombocytopenia is characterized by distal tissue losses, with extensive venous thrombosis involving large veins and small venules (53). This reaction seems to be related to acquired deficiency of protein C induced by concomitant oral anticoagulants.

Patients with heparin-induced thrombocytopenia have a reported mortality of 25–30% and amputation rates of up to 25% (54). The development of the syndrome is not related to the dose of heparin in the therapeutic range (that is it is a hypersusceptibility reaction). This has been confirmed by the fact that thrombocytopenia with thromboembolic complications sometimes occurs after the limited exposure that is involved in "flushing" with heparin and saline to maintain the patency of venous catheters (55).

Management

In view of the severity of the Type II syndrome, it has been recommended that heparin therapy be monitored by twice-weekly platelet counts (56).

Heparin-induced thrombocytopenia demands immediate withdrawal of heparin (43), after which platelet counts usually return to normal within 2–3 days, that is much faster than after early-onset thrombocytopenia. Rechallenge with heparin leads to an abrupt fall in the number of platelets and to reappearance of the clinical signs and symptoms, sometimes leading to sudden death (57).

From the therapeutic point of view, prophylaxis of thrombosis must be continued after withdrawal of heparin, since even when there is no evidence of thrombosis in association with heparin-induced thrombocytopenia, thrombosis can follow after some days (52). Because of cross-reactivity, low molecular weight heparin should not be used when heparin has been withdrawn because of heparin-induced thrombocytopenia; nor should warfarin be used, because of the risk of venous gangrene, at least until the thrombocytopenia has resolved. Patients with life-threatening or limb-threatening thrombosis can be treated with thrombolytic drugs. Current views are that two antithrombotic drugs should be used, for example danaparoid plus lepirudin (58).

Eosinophilia

Eosinophilia has rarely been attributed to heparin, with positive rechallenge (52,59).

Liver

Minor increases in serum transaminases without evidence of liver dysfunction are common in patients receiving standard heparin or low molecular weight heparin given therapeutically or prophylactically (60,61). This rise is more pronounced for alanine transaminase than for aspartate transaminase and occurs after 5–10 days of heparin treatment (61). The source of heparin has no relation to the development of raised transaminases. After withdrawal of heparin and sometimes even in spite of continued treatment (60,61), the transaminases return to normal (62,63). The mechanism of these increases has not been elucidated. A concomitant increase in gamma-glutamyl transpeptidase activity has been described in some patients (64).

In one study of patients receiving heparin, the isoenzyme pattern of lactate dehydrogenase was studied; all had rises in the hepatic form of the enzyme, suggesting hepatocellular damage as the most likely source (60).

Heparin-associated hepatotoxicity has not been reported.

Skin

Erythematous nodules or infiltrated and sometimes eczema-like plaques at the site of injection are common adverse effects of subcutaneous standard heparin 3–21 days after starting heparin treatment. They are probably delayed-type hypersensitivity reactions and are also seen with low molecular weight heparin (65–69). There can be cross-reactivity between standard heparin and low molecular weight heparin (69).

Erythromelalgia has been described with enoxaparin (70).

In cases of local reactions, skin tests should not be performed, since they are rarely helpful in detecting potential cross-reactivity between low molecular weight heparin and heparin (65,71).

Two renal transplant recipients developed calcinosis cutis (tender erythematous subcutaneous nodules with induration, ulceration, and necrosis), confirmed by bone scan and biopsies, at the site of subcutaneous administration of nadroparin (72). Both had secondary hyperparathyroidism and a raised calcium-phosphate product at the time of administration. The authors suggested that the high concentration of calcium in nadroparin (220 mmol/l) had been an important factor, since in the same patients subcutaneous injections of nicomorphine or dalteparin did not cause subcutaneous nodules. Three more cases were found after retrospective examination of all 51 adult patients who underwent a renal transplantation in the same hospital during 7 months, and there were no other cases of calcinosis cutis at the injection sites of low molecular weight heparins after nadroparin was replaced by dalteparin.

Skin necrosis

Heparin-induced skin necrosis was first described in 1973 (73) and was later observed in patients with the

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thrombohemorrhagic syndrome (74,75). The skin pathology develops 6–9 days after the start of subcutaneous heparin treatment and usually develops at the site of subcutaneous injection. However, it can also occur at sites distant from the site of injection (76) or after intravenous therapy (77). Vasculitis is likely to be present, perhaps with fever (78). There is an increased risk of thrombocytopenia and thrombotic complications in patients who have had previous heparin-associated skin necrosis episodes (79).

Various physiopathological mechanisms have been suggested (80), particularly heparin-induced thrombocytopenia, vasculitis caused by a type III hypersensitivity reaction, local trauma at the site of injection, and poor vascularization of adipose tissue resulting in reduced absorption of heparin, as seen in diabetic lipodystrophy. This form of skin necrosis must be distinguished from vasospastic skin necrosis and from skin necrosis induced by cholesterol embolization. Ergotism will be a differential diagnosis in patients who are receiving prophylaxis with the combination of low dose heparin and dihydroergotamine (81). In evaluating any necrotic skin reaction, one must always consider its infectious origin (particularly *Escherichia coli* or *Pseudomonas*) related to unsterile injections (82).

Several patients with heparin-induced skin necrosis were positive for HIT-IgG using the platelet ^{14}C-serotonin release assay, even though they did not develop thrombocytopenia (83). Skin necrosis has been particularly reported in patients receiving standard heparin but also occasionally with low molecular weight heparins, such as dalteparin (84) or enoxaparin (79).

The clinical and histological pictures of heparin-induced skin necrosis are similar to those found in so-called "coumarin necrosis." Laboratory examinations show inflammatory changes, with anemia, leukocytosis, eosinophilia, a raised erythrocyte sedimentation rate, and a positive capillary fragility test. The vasculitis can lead to organ involvement, such as glomerulonephritis (85).

Heparin-induced skin necrosis can be associated with high morbidity and occasional mortality. Heparin should be withdrawn when it occurs. The risk of recurrence if heparin is given again later is not known (86).

Musculoskeletal

Heparin-associated osteoporosis is observed with both standard heparin and low molecular weight heparin, although it is far less pronounced with the latter. The incidence of heparin-associated osteoporosis is not known, but it is probably less than 5% with standard heparin. The highest estimates are derived from studies of pregnant patients and should be interpreted cautiously, since pregnancy, even in the absence of heparin therapy, is sometimes itself associated with osteoporosis. Overall, it appears that osteoporosis can occur in patients given heparin for longer than 10 weeks and usually for a minimum of 4 months. The effect is rarely complicated by fractures. It has been suggested that during long-term heparin therapy, calcium supplements be given (87).

The processes involved are bone resorption and inhibition of bone deposition. Standard heparin may affect both phenomena, whereas low molecular weight heparin seems to affect only the rate of bone formation. Heparin-associated osteoporosis has been attributed to enhancement of collagenolysis or to enzyme inhibition by heparin. Other authors have stressed the resemblance to hyperparathyroid osteopathy. Further possibilities include deficiency of vitamin D analogues (88) and ascorbic acid deprivation at the site of osteoblast activity. Heparin-induced osteolysis may explain the metastatic calcification that can occur in patients with end-stage renal insufficiency treated by hemodialysis, which is sometimes associated with calcified subcutaneous nodules (89).

Sexual function

Heparin has been associated with priapism (90). The frequency and severity of iatrogenic priapism as a result of heparin therapy seems to be greater than with any other type of medical treatment (91). However, it is uncertain whether it is heparin or the underlying thrombotic condition that causes the complication.

Immunologic

A wide range of allergic reactions have been described in patients receiving heparin, including urticaria, conjunctivitis, rhinitis, asthma, cyanosis, tachypnea, a feeling of oppression, fever, chills, angioedema, and anaphylactic shock.

- A patient with end-stage renal disease developed recurrent anaphylaxis after receiving heparin during hemodialysis (92). There were raised concentrations of total and mature tryptase at 1 hour, but although the latter returned to normal by 24 hours the former did not. Prick tests were negative with heparin, enoxaparin, and danaparoid, but intradermal skin tests were positive with heparin and enoxaparin. Danaparoid was used as an anticoagulant during dialysis for the next 3 years without any adverse effects.

In some cases of allergy to a heparin formulation, the precipitating agent will prove to be a preservative, such as chlorocresol (93) or chlorbutol (94), rather than heparin itself.

Second-Generation Effects

Pregnancy

The maternal rate of bleeding complications during heparin treatment is about 2%. This is consistent with the reported rates of bleeding associated with heparin therapy in non-pregnant women, and in warfarin therapy when used for the treatment of venous thrombosis (95). Subcutaneous heparin given just before labor can also cause a persistent anticoagulant effect at the time of delivery; the mechanism of this prolonged effect is unclear (96).

Another pregnancy-associated hazard of long-term heparin administration is maternal osteoporosis, as clearly illustrated by several reports of pregnant women who developed severe osteoporosis after having received heparin, in some cases complicated by multiple vertebral fractures (97,98). Long-term heparin therapy during pregnancy results in changes in calcium homeostasis, which may be dose-related in the therapeutic range of doses (99). The incidence of osteoporotic fractures was 2.2% (four

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patients) in 184 women receiving long-term subcutaneous prophylaxis with twice-daily heparin during pregnancy (100). In another study, the incidence of osteopenia in 70 pregnant women on long-term heparin was 17%; there was also a regression in the degree of osteopenia postpartum (101). It is difficult to distinguish between the mean bone loss that occurs in normal pregnancy and the additive effect on bone demineralization that results from heparin therapy; further prospective studies on bone demineralization during pregnancy are needed to clarify this point.

Fetotoxicity

An adverse fetal outcome occurs in about one-third of pregnancies after either oral anticoagulant or heparin treatment (102). However, the high rate of adverse fetal outcomes associated with heparin during pregnancy is in part a reflection of the severity of pre-existing maternal diseases (103). Moreover, some studies have suggested that unfractioned heparin is relatively safe for the fetus and is the anticoagulant therapy of choice during pregnancy, whereas oral anticoagulants may not be, particularly during the first trimester (95,104). Heparin does not cross the placenta, and therefore does not have the potential to cause fetal bleeding or teratogenicity (105). Low molecular weight heparins and heparinoids similarly do not cross the placenta (106,107).

Lactation

Heparin is not secreted into breast milk and can be given safely to nursing mothers (108).

Drug–Drug Interactions

Benzodiazepines

In healthy non-fasting subjects, 100–1000 IU of heparin given intravenously caused a rapid increase in the unbound fractions of diazepam, chlordiazepoxide, and oxazepam (109,110), but no change in the case of lorazepam (109). The clinical implications of this finding are not known.

Digitoxin

Reduced plasma protein binding of digitoxin has been reported after the administration of heparin (111). In 10 hemodialysed patients taking maintenance digitoxin therapy, there was reduced binding in vitro because of heparin-induced lipolysis, and not as a consequence of in vivo binding of digitoxin to plasma proteins.

Dobutamine hydrochloride

Dobutamine hydrochloride and heparin should not be mixed or infused through the same intravenous line, as this causes precipitation (112).

Glyceryl trinitrate

Resistance to heparin has been observed in patients in coronary care units receiving intravenous glyceryl trinitrate. Although this has been imputed to propylene glycol in glyceryl trinitrate formulations (113), resistance has also been described with propylene glycol-free formulations. The underlying mechanism might be a qualitative abnormality of antithrombin III induced by glyceryl trinitrate (114). It has also been reported that heparin concentrations can be markedly reduced by glyceryl trinitrate (115).

Interference with Diagnostic Tests

Acid phosphatase activity

Concentrations of heparin as low as 1 IU/ml give 80% inhibition of acid phosphatase activity in leukocytes (116).

Aminoglycosides

Heparin can interfere with the determination of aminoglycosides by enzyme-multiplied immunoassays, resulting in lower values than with the use of other assays (117,118). In the case of gentamicin, the lower values may be due to direct binding of gentamicin to heparin, as well as a more complex interaction involving heparin, gentamicin, and proteins (117). Blood samples for the determination of aminoglycosides by enzyme immunoassays should not be collected in heparinized tubes or from indwelling lines (118).

Arterial blood gases

Heparin can affect the analysis of arterial blood gases (119). Addition of excess heparin and acid mucopolysaccharide to the syringe can alter the Henderson–Hasselbalch equation, simulating metabolic acidosis. It is advisable to coat the syringe with heparin and remove all excess heparin before blood sampling.

Calcium

Pseudo-hypocalcemia can occur in hemodialysis patients, particularly in those who have chylomicronemia before administration of heparin (120). This spurious hypocalcemia is thought to result from lipolytic activity in vitro, sufficient to produce calcium soaps of fatty acid. This can be detected and eliminated by the analysis of blood samples immediately after venepuncture. During hemodialysis, there is a significant fall in plasma ionized calcium after intravenous administration of heparin (an average reduction of 0.03 mmol/l after 10 000 IU) (121).

Chromogenic lysate assay for endotoxin

Heparin has a dose-related inhibitory effect on the chromogenic lysate assay for endotoxin (122). There was a 90% reduction in detectable endotoxin at concentrations of heparin as low as 30 U/ml.

Ciclosporin

Measured ciclosporin concentrations differ according to the use of heparin or EDTA as anticoagulant (123).

Propranolol

Interference by heparin with the measurement of propranolol when the blood is collected from a heparinized cannula is well documented (124). There is no in vivo interaction, since the beta-blockade is unchanged (125).

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Thyroid function tests

Artefactual increases of as much as 50% in total thyroxine, estimated by a competitive protein-binding assay, and of as much as 30% in triiodothyronine resin uptake are probably due to rapid and continuing lipolytic hydrolysis of triglycerides after blood has been drawn (126). Thyroid function tests should therefore always be performed on blood samples taken before (or a sufficient time after) heparin treatment (127). An increase in serum-free thyroxine concentrations has also been reported after low molecular weight heparin, by up to 171% in specimens taken 2–6 hours after injection. When specimens were obtained 10 hours after injection, the effects were smaller, but with concentrations still up to 40% above normal the results can still cause errors of interpretation (128).

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Hepatitis vaccines

See also Vaccines

General Information

Hepatitis A

The successful propagation of hepatitis A virus in cell culture made the development of hepatitis A vaccines a realistic possibility. Various experimental hepatitis A vaccines have been tested in clinical trials. In December 1991, the first hepatitis A vaccine was licensed in Western European countries. Currently, two different hepatitis vaccines (prepared using different inactivation process) as well as vaccines for children (containing 720 enzyme-linked immunosorbent assay units per dose) and adults (containing 1440 units per dose) are commercially available and further products are under development. The results of safety and immunogenicity testing of hepatitis A vaccines developed by SmithKline-Beecham and by Merck Research Laboratories have been reviewed (SEDA-16, 384) (SEDA-17, 373) (SEDA-18, 333) (SEDA-21, 331). These vaccines were highly immunogenic. There were mild transient reactions at injection sites, but systemic reactions were minor and uncommon.

In a paper dealing mainly with indications for the use of hepatitis vaccine, the data on the hepatitis A vaccines most widely used, HAVRIX (manufactured by Glaxo SmithKline) and VAQTA (manufactured by Merck), have been summarized (1). The data are based on prelicensure clinical trials and worldwide follow-up reports. No serious adverse effects have been attributed to hepatitis A vaccines. In children who received HAVRIX, soreness (15%) and induration (4%) at the injection site, feeding problems (8%), and headaches (4%) have been the most frequently observed adverse effects. In children who received VAQTA, the most common adverse effects were pain (19%), tenderness (17%), and warmth (9%) at the injection site. The reported frequencies were similar to the frequencies reported with hepatitis B vaccines.

Hepatitis B

Two types of hepatitis B vaccine are commercially available: plasma-derived hepatitis B vaccine and yeast recombinant hepatitis B virus vaccine. The two vaccines are equally immunogenic, protective, and safe. However, in most countries the recombinant vaccine is considered the vaccine of choice.

Plasma-derived hepatitis B virus vaccine

Plasma-derived hepatitis B virus vaccine is prepared from the plasma of chronic HBsAg carriers, and consists of purified, inactivated 20-nm HBsAg particles adsorbed on to an aluminium adjuvant. The use of a vaccine produced with plasma derived from infected individuals represented a major departure from conventional approaches, and safety testing has therefore been designed to cover all possibilities of risk and to ensure freedom from transmission of residual HBV and other blood-borne agents. Various clinical trials (SEDA-10, 289) (SEDA-11, 289) have confirmed the safety of plasma-derived hepatitis B virus vaccines produced by different manufacturers. Fears that plasma-derived vaccine may transmit AIDS can be considered unfounded.

Subsequent to the identification of HIV and the growing knowledge of its relatively easy inactivation with procedures such as heat or triple-step chemical inactivation, the complete safety and suitability of plasma-derived vaccines that meet WHO requirements has now been generally accepted and their safety demonstrated (SEDA-12, 279). This type of hepatitis B vaccine is generally well tolerated. The most common adverse effect has been local soreness at the injection site. Less common local reactions include erythema, swelling, and induration; all usually subside within 48 hours. Transient low-grade fever has occurred occasionally; but malaise, fatigue, vomiting, dizziness, myalgia, and arthralgia have been infrequent. Individual reports of more severe suspected adverse effects (erythema multiforme, hepatitis-like changes in liver function, hypersensitivity, lichen planus, menstrual abnormality, myasthenia gravis, neurological disorders including transverse myelitis and Guillain–Barré syndrome, reactive arthritis, Takayasu's arteritis, urticaria, uveitis) are very rare and are no more than could be

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expected by chance (SED-12, 804) (SEDA-16, 384) (SEDA-17, 373) (SEDA-18, 334). In one reported case with neurological symptoms, a preceding viral illness was the likely cause and in the patient with hepatitis-like symptoms mentioned above, the possibility of other causes was not excluded. In a case with urticaria, patch tests revealed a hypersensitivity to thiomersal, the preservative in the vaccine.

By 1988 it was possible to summarize the adverse effects reported after the distribution of over 1.8 million doses of plasma-derived hepatitis B vaccine (Table 1) (2). From 1982 onwards, the Centers for Disease Control, the Food and Drug Administration, and the manufacturers, Merck Sharp & Dohme, had supported a special surveillance system to monitor spontaneous reports of reactions to plasma-derived hepatitis vaccine. During the first 3 years, about 850 000 persons were immunized. In all, 41 reports were received for one of the following neurological adverse events: convulsion ($n = 5$), Bell's palsy ($n = 10$), Guillain–Barré syndrome ($n = 9$), lumbar radiculopathy ($n = 5$), brachial plexus neuropathy ($n = 3$), optic neuritis ($n = 5$), and transverse myelitis ($n = 4$). Half of these events occurred after the first vaccine dose. However, no conclusive causal association could be made between any neurological adverse event and the vaccine (3).

Yeast-derived recombinant hepatitis B vaccine

The yeast-derived recombinant vaccines first licensed in 1986 represented the first vaccine of any kind manufactured by recombinant technology. The vaccines are prepared using antigen produced by recombinant technology in yeast (*Saccharomyces cerevisiae*). The recombinant vaccine produced by Merck, Sharp & Dohme was as immunogenic and protective against hepatitis B as plasma-derived vaccine (4). Clinical reactions in this series were mild and transient. About 17% of all recipients had pain, soreness, and tenderness at the injection site. A smaller proportion reported headache, weakness, nausea, or malaise. Between February 1984 and August 1986, 33 investigators in 19 countries carried out clinical trials with the yeast-derived recombinant hepatitis B vaccine produced by SmithKline Biologicals. Among other risk groups, neonates, patients with thalassemia and sickle cell anemia, and hemodialysis patients have been vaccinated. All the results point to the safety and acceptability of a yeast-derived vaccine. The incidence of reported reactions varied widely in different studies depending on the scrupulousness with which minor signs were reported. No serious, severe, or anaphylactic reactions occurred. The incidence of local and systemic reactions reported in each study tended to decrease after successive doses, suggesting that immunization did not induce hypersensitivity (SEDA-12, 280).

Reports of studies of the efficacy and safety of recombinant hepatitis vaccines have been published (SED-12, 805) (SEDA-14, 282) (SEDA-15, 351) (SEDA-16, 385) (SEDA-17, 373) (SEDA-18, 334). Table 1 shows the adverse effects reported after the distribution of 205 000 doses of recombinant vaccine.

Third-generation hepatitis B vaccines

Between 5 and 15% of healthy immunocompetent individuals do not seroconvert after receipt of the currently licensed hepatitis B vaccines containing only the major surface protein HbsAg without pre-S epitopes. In a study of a hepatitis B vaccine containing pre-S1, pre-S2, and antigenic components of both viral subtypes adw and ayw, all three antigenic components were produced in a continuous mammalian cell line, after transfection of the cells with recombinant hepatitis B surface antigen DNA (5). The vaccine was manufactured as an aluminium hydroxide adjuvant formulation. The new vaccine (5, 10, 20, or 50 μg) was given to 68 individuals with HBs antibody titers below 10 IU/l. Seroconversion rates in the four groups were 60, 76, 64, and 80%. There were local or systemic reactions in 15%. No dose-related incidence was seen.

Surveillance of hepatitis B adverse events in the USA and Australia

Adverse events after hepatitis B vaccine reported between 1 January 1991 and 31 May 1995 to the US Vaccine Adverse Events Reporting System have been reviewed (6). The patients included 58 neonates and 192 infants who were immunized with hepatitis B

Table 1 Adverse effects after immunization with recombinant and plasma-derived hepatitis B vaccine

Adverse effect	Recombinant vaccine[a]		Plasma-derived vaccine[b]	
	Number of adverse effects	Rate per dose	Number of adverse effects	Rate per dose
Pruritus	2	1:103 000	38	1:48 000
Urticaria	2	1:103 000	23	1:79 000
Exanthems	6	1:103 000	58	1:30 000
Angioedema	–	–	8	1:228 000
Facial edema	1	1:205 000	10	1:182 000
Eczema	–	–	2	1:912 000
Nodule formation	–	–	3	1:608 000
Erythema nodosum	1	1:205 000	1	1:1 823 000
Total	12	1:17 000	99	1:18 000

[a] Over 200 000 doses distributed (August 1986–April 1987).
[b] Over 1.8 million doses distributed (July 1982–December 1987).

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vaccine alone and 1469 infants who had received hepatitis B vaccine in combination with DTP vaccine. The serious adverse events reported in neonates and infants included fever, agitation, and apnea. The events reported for infants who received hepatitis B vaccine and DTP vaccine simultaneously were compared with the events reported for infants who received either DTP vaccine or hepatitis B vaccine alone. The reports filed for the infants who received DTP vaccine alone or in combination with hepatitis B vaccine differed from the reports filed for infants who received hepatitis B vaccine alone, suggesting that these events may have been associated with the DTP vaccine. The reviewers concluded that no unexpected adverse events had occurred in neonates and infants given hepatitis B vaccine, despite the administration of at least 12 million doses.

Between 1988 and 1996, the Australian Drug Evaluation Committee received some 600 reports of suspected adverse events after hepatitis B immunization. There were no serious events, and the overwhelming majority were well-known mild-to-moderate local or systemic reactions (7). Musculoskeletal symptoms, such as arthralgia, arthritis, and myalgia, were mentioned in 106 reports.

General adverse effects

The reports of major adverse reactions that have been published since the introduction of recombinant hepatitis B vaccine have been reviewed (8). In the clinical trials with hepatitis B vaccine, the most frequent adverse effects were soreness at the injection site, sometimes accompanied by erythema (3–29%), fatigue (15%), headache (9%), and a temperature increase higher than 37.7°C. The postmarketing surveillance literature (4.5 million doses) showed an overall rate of one adverse effect per 15 500 doses. Of these, local reactions were reported at a rate of 1 in 85 000 doses. Systemic reactions included nausea, rash, headache, fever, malaise, fatigue, flu-like symptoms, diarrhea, urticaria, paresthesia, and somnolence, all of which resolved, generally within 24–48 hours of vaccine administration. Reactions were less frequent with subsequent doses. Major adverse effects have been published as case reports: anaphylaxis; urticaria, erythema nodosum, lichen planus; arthritis, Reiter's syndrome; pulmonary and cutaneous vasculitis; systemic lupus erythematosus; glomerulonephritis; Evan's syndrome, thrombocytopenic purpura; acute posterior multifocal placoid pigment epitheliopathy; Guillain–Barré syndrome, transverse myelitis, multiple sclerosis, acute cerebellar ataxia; chronic fatigue syndrome. Table 2 summarizes the reports. Discussing the cause of the reported major adverse effects and a possible causal relation with vaccine administration, the authors considered that apart from anaphylaxis and urticaria, most of the reactions described were not allergic in nature and that the symptoms were those of immune-complex disease due to autoimmune mechanisms. Because of the extreme rarity of such serious adverse events, coincidence seems the

Table 2 Summary of important adverse effects after recombinant hepatitis B vaccination

Adverse effect	Sex	Age (years)	Number	Time after immunization	Duration of symptoms
Nervous system					
Cerebellar ataxia	F	25	2	10 days	4 months
Demyelination	F	26	3	6 weeks	3 weeks
Demyelination	F	28	2	6 weeks	3 months
Multiple sclerosis	F	43	1	7–10 weeks	4 weeks
Transverse myelitis	M	40	1	2 weeks	6 weeks
Hematologic					
Evans' syndrome	M	33	2	2 days	2 months
Thrombocytopenic purpura	F	15	3	4 weeks	4 months
Thrombocytopenic purpura	F	21	2	3 weeks	2 months+
Skin					
Erythema nodosum	F	43	1	4 days	Several weeks
Lichen planus	F	19	2	2 months	Not reported
Lichen planus	M	50	2	1 month	3 months
Acute posterior multifocal placoid pigment epitheliopathy	M	31	4	3 days	9 months
Urticaria	F	24	1	30 minutes	30 minutes
Musculoskeletal					
Polyarthritis + erythema nodosum	M	31	1	1 day	6 weeks
Polyarthritis	F	41	1	2 weeks	7 months
Reiter's syndrome	M	29	2	4 weeks	4 months
Rheumatoid arthritis	F	49	1	24 hours	Not reported
Immunologic					
Pulmonary and cutaneous vasculitis	F	45	1	2 days	1 week
Systemic lupus erythematosus	F	43	1	2 weeks	Not reported
Median		31		14 days	8 weeks
Average		32		19 days	11 weeks

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simplest explanation, but an immune-complex mediated pathogenesis should not be excluded, given the close temporal relation between immunization and the onset of disease. Apart from immune-complex mechanisms, there may be reactions to other components of the vaccine, such as thiomersal, aluminium, or small quantities of yeast proteins.

Hexavalent immunization, including hepatitis B

The Hexavalent Study Group has compared the immunogenicity and safety of a new liquid hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and *Haemophilus influenzae* type b (DTP + IPV + HB + Hib vaccine, manufactured by Aventis Pasteur MSD, Lyon, France) with two reference vaccines, the pentavalent DTP + IPV + Hib vaccine and the monovalent hepatitis B vaccine, administrated separately at the same visit (9). Infants were randomized to receive either the hexavalent vaccine ($n = 423$) or (administered at different local sites) the pentavalent and the HB vaccine ($n = 425$) at 2, 4, and 6 months of age. The hexavalent vaccine was well tolerated (for details, see the monograph Pertussis vaccines). At least one local reaction was reported in 20% of injections with hexavalent vaccine compared with 16% after the receipt of pentavalent vaccine or 3.8% after the receipt of hepatitis B vaccine. These reactions were generally mild and transient. At least one systemic reaction was reported in 46% of injections with hexavalent vaccine, whereas the respective rate for the recipients of pentavalent and HB vaccine was 42%. No vaccine-related serious adverse event occurred during the study. The hexavalent vaccine provided immune responses adequate for protection against the six diseases.

Hepatitis E

Hepatitis E is an important cause of morbidity and mortality in young adults in developing countries, and is particularly dangerous in pregnant women. Through recombinant technology a hepatitis E vaccine has been developed; in its first clinical trials the vaccine was found to be safe and immunogenic (10).

Organs and Systems

Nervous system

Hepatitis A

Probable posthepatitis A immunization encephalopathy has been reported (11).

Hepatitis B

Neuralgic amyotrophy (12), febrile convulsions (13), and Guillain–Barré syndrome (14) have been attributed to hepatitis B vaccine. Fatal inflammatory polyradiculoneuropathy has been reported in temporal relation to hepatitis B administration (15).

Demyelination

Two patients developed neurological symptoms and signs of central nervous system demyelination 6 weeks after administration of recombinant hepatitis B vaccine (16). One was a known case of pre-existent multiple sclerosis but the other had no history of neurological diseases. Both had HLA haplotype DR2 and B7, which are associated with multiple sclerosis. A causal link between immunization and demyelination cannot be established from these two case reports, but the time interval would fit a proposed immunological mechanism. In addition, the Centers for Disease Control (CDC) in Atlanta, Georgia, received reports on four cases of "chronic demyelinating disease." Several other reports describe related conditions or other forms of neurological disorder.

- Acute myelitis occurred in a 56-year-old man 3 weeks after hepatitis B immunization (17).
- Optic neuritis has been attributed to hepatitis B vaccine (18).
- Transverse myelitis developed 3 weeks after the first dose of hepatitis B vaccine in an 11-year-old girl (19).

Guillain–Barré syndrome occurred in a 7-year-old girl after the administration of recombinant hepatitis vaccine (20). The author noted that several other such incidents had been reported after the use of recombinant vaccines, two involving optic neuritis and one Guillain–Barré syndrome.

Multiple sclerosis

Eight cases of nervous system diseases suspected to be either recurrent disseminated encephalitis or multiple sclerosis after hepatitis B immunization have been reported (21). Symptoms started in four cases at 4–14 days after vaccination, and in the other four cases 42–70 days after vaccination. There was a family history of multiple sclerosis in two patients, one of whom had had symptoms compatible with optic neuritis before immunization. In a third patient, there was a history of an episode compatible with Lhermitte's sign. The authors concluded that the risk of demyelinating diseases is unknown. They recommended avoiding hepatitis B immunization in individuals with a personal or familial history of symptoms suggestive of an inflammatory or demyelinating disease.

- A 45-year-old woman with a history of epilepsy developed a lumbosacral acute demyelinating polyneuropathy 1 month after her second hepatitis B immunization (22). She had an uncommon syndrome that combined demyelinating and axonal features confined to the lumbosacral roots whose relation to Guillain–Barré syndrome was unclear. Viral or bacterial causes of the disease could not be found.

The authors concluded that a relation between immunization and disease could not be excluded.

- A 44-year-old female health worker developed bilateral optic neuritis 7 days after immunization against poliomyelitis (OPV) and hepatitis B (23). All hematological, biochemical, bacterial, and virological investigations were normal, and there was no evidence of demyelination on MRI scanning.

Although the current hepatitis B vaccine seems to be one of the safest ever produced, concerns are still sometimes expressed (SEDA-22, 346) (24), particularly since 1996 when a French neurologist announced that he had seen

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several cases of multiple sclerosis or demyelinating disease in women who had received hepatitis B vaccine. This report was taken up by the media and anti-immunization groups, resulting in further inquiry. In 1998 the French Health Authorities invited leading experts in the fields of immunization and possible adverse effects to meet in Paris and discuss scientific studies carried out in France on the possible relation between hepatitis B vaccine and multiple sclerosis. The conclusion of the meeting was that there was no evidence of a causal link between multiple sclerosis and hepatitis B vaccine. Nevertheless, the Minister of Health decided to stop hepatitis B immunization of schoolchildren aged 11–12 years, but to continue immunizing infants and adults at high risk. The rationale for this decision was the limited opportunity for the full discussion needed to attain informed consent during immunization sessions carried out in schools. It was recommended that immunization of school children and adolescents would in future be performed by general practitioners, who have a better opportunity to discuss the benefits and risks of immunization on an individual basis and to obtain informed consent.

The impact of this decision, or any other to curtail an immunization program, should not be underestimated. It raises concerns not only about the safety of the hepatitis B vaccine, but also about the safety of vaccines in general. In view of this, the WHO took strong action, and its Global Program on Immunization issued a statement in 1997 (after the French media had taken up the issue) that there was no evidence that hepatitis B vaccine causes multiple sclerosis (25). This conclusion was based on the following considerations:

- A comparison of the geographical incidence and prevalence of hepatitis B with that of multiple sclerosis, which shows large differences: Scandinavia and Northern Europe have the highest rates of multiple sclerosis and the lowest rates of hepatitis B infection, whereas in Africa and in Asia there are very low rates of multiple sclerosis and the highest rates of hepatitis B infection. If the virus does not cause multiple sclerosis, it is unlikely that the vaccine can do so.
- None of the postmarketing surveillance studies from the different vaccine manufacturers in North America showed any evidence of an increased risk of multiple sclerosis.
- Reanalysis by the WHO of the French data showed that the notification rate of demyelinating diseases following the administration of the hepatitis B vaccine was 0.6 cases/100 000 vaccinees, which is a lower rate than the expected incidence in the same population (estimated in France to be 1–3 cases/100 000 vaccinees).

The data and analyses were examined once more at a scientific conference organized by the Viral Hepatitis Prevention Board in collaboration with WHO, assisted by experts from many disciplines. Their final conclusion, published in a press release, was that the available scientific data did not demonstrate a causal association between hepatitis B vaccine and central nervous system diseases, including multiple sclerosis (26). It was pointed out moreover that since 1981 more than a billion doses of hepatitis B vaccine had been used worldwide, with an outstanding record of safety and efficacy. The WHO also warned of the consequences of stopping any immunization program on the basis of unfounded concerns, as had happened with pertussis vaccine in the UK, leading to major epidemics of natural pertussis in that country.

The National Multiple Sclerosis Society in the USA made a statement referring to anecdotal reports suggesting that immunization against hepatitis B may increase the risk of multiple sclerosis (27). They noted that:

- such reports had not been confirmed by any statistically significant scientific studies to date;
- because of the potential for public concern about this issue, further studies of the possibility of association of hepatitis B vaccine and demyelinating disease, including multiple sclerosis, were already under way in the USA and Europe;
- hepatitis B infection could result in serious, sometimes fatal, disease and immunization was effective in its prevention.

The official French position on hepatitis B immunization, expressed in January 1999, was that children should be vaccinated against hepatitis B, that adolescents should receive a dose of hepatitis B vaccine if they have not been vaccinated earlier, that adults at risk should be similarly vaccinated, and that the obligation is maintained for health professionals to be vaccinated against hepatitis B. The steps taken in 1998 had sought only to ensure that informed consent could be attained before children were vaccinated.

All available data that may throw light on the hypothesis that hepatitis B vaccine is causally linked to multiple sclerosis have been carefully reviewed (28). The authors concluded that the most plausible explanation for the observed temporal association between immunization and multiple sclerosis is coincidence.

A statement from the Viral Hepatitis Prevention Board (8 June 2000), working closely together with the WHO, is worth repeating: the data available to date do not show a causal association between hepatitis B immunization and central nervous system demyelinating disease, including multiple sclerosis. No evidence presented indicates a need to change public health policies with respect to hepatitis B immunization. Therefore, based on demonstrated important benefits (including prevention of liver cirrhosis and primary liver cancer) and a purely hypothetical risk, the Viral Hepatitis Prevention Board supports the recommendation of the WHO that all countries should have universal infant and/or adolescent immunization programs and should continue to immunize adults at increased risk of hepatitis B infection as appropriate (29).

However, the French Ministry of Health has already compensated 14 patients on the basis of a link between hepatitis B vaccine and neurological effects (multiple sclerosis, retrobulbar neuritis) or rheumatological symptoms. According to a press release from the French Ministry of Health, the decision was taken in the interest of the patients, and despite the fact that even the experts from the Agence française de securité sanitaire des produits, who were charged with regularly re-evaluating the safety profile of hepatitis B vaccine, have not yet been able to conclude whether there is an actual association between the vaccine and the development of

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multiple sclerosis or autoimmune disorders. It also stated that the decision in no way challenges the benefit:harm evaluation of hepatitis B vaccine and recommendations with respect to national immunization policies (30).

In the USA, following public discussions on the safety of hepatitis B vaccine, health officials, testifying in 1999 before the Government Reform Subcommittee on Criminal Justice, Drug Policy, and Human Resources, said that use of the vaccine has been monitored for 15 years, that it has not been proven to be the cause of deaths, and is only rarely linked to serious adverse effects (31).

Further studies have confirmed that there is no scientific evidence of a causal link between hepatitis B vaccine and multiple sclerosis (32–35). A European-wide study should be particularly mentioned. In 643 patients in various European countries during 1993–97, 15% of whom received various immunizations within 1 year before relapse, there was no increase in the risk in immunized patients compared with patients who did not receive any vaccine (36).

The results of a hospital-based case-control study in 121 patients with a first episode of central nervous demyelination occurring within 180 days after either hepatitis B vaccine or other vaccines have been reported (37). The results were compared with age- and sex-matched controls seen during the same period. No conclusion regarding a causal relation between hepatitis B vaccine and a first MS episode could be drawn, but the authors were not able to exclude such an association with certainty.

In summary the international consensus is that hepatitis B vaccine is still among the safest and most powerful vaccines in immunization programs and that it should be used worldwide.

Leukoencephalitis

Two episodes of leukoencephalitis occurred in a previously healthy patient after a second dose of HB vaccine and rechallenge with a third dose (38).

- A 39-year-old woman developed a complete right homonymous hemianopia and severe dyslexia 4 weeks after receiving a second dose of HB vaccine. Brain MRI showed a large lesion that occupied most of the left occipital lobe and extended into the splenium of the corpus callosum. Histological examination with immunoperoxidase staining, although not pathognomonic, was consistent with demyelinating disease. She underwent surgery and 1 week later there was marked improvement in her condition. Three months later (4.5 months after the second dose), she received a third dose of HB vaccine and 11 days later developed a left hemiparesis and acute progressive deterioration in vision. Brain MRI showed a new large lesion in the right parieto-occipital region, with the characteristics associated with the previous lesion. In comparison with previous findings, there was significant improvement in the left occipital lobe, in which there remained a proencephalic cyst. She was treated with dexamethasone and markedly improved. At 1 year and 2.5 years after the first episode she had residual dyslexia and a complete right homonymous hemianopia. An MRI scan showed almost complete resolution of the previous findings, with the exception of the proencephalic cyst.

The authors considered that acute leukoencephalitis is a rare but possible complication of HB vaccine.

Sensory systems

Eyes

Three days after recombinant hepatitis B booster immunization, a 31-year-old man developed acute posterior multifocal placoid pigment epitheliopathy (visual loss) and eosinophilia (39,40).

Papillitis (41) and retinal vein occlusion (42) have been attributed to hepatitis B vaccine.

Optic neuritis has been attributed to immunization with hepatitis A and B (43).

- A 21-year-old woman developed acute irreversible loss of vision to 0.05 and a nasal visual field defect in the left eye 2 weeks after immunization with hepatitis A and B and yellow fever vaccine. An MRI scan showed hyperintense thickening of the optic nerve, and a diagnosis of optic neuritis was made. Vision acuity did not recover but the scotoma disappeared within 6 weeks.

Ears

Two cases of hearing loss have been reported in patients given hepatitis B immunization (39). Acute tinnitus with permanent audiovestibular damage has been reported in temporal relation to hepatitis B administration (44).

Hematologic

There have been reports of individual cases of thrombocytopenia purpura (45) and pancytopenia (46) in temporal relation with hepatitis B vaccination.

- A healthy 7-year-old girl developed thrombocytopenic purpura after hepatitis B immunization, three doses of vaccine every month followed by a booster (47).

Pancytopenia has been reported in temporal relation to hepatitis B administration (48).

Mouth

Oral lichenoid lesions have been reported in temporal relation to hepatitis B administration (49).

Urinary tract

Acute glomerulonephritis (50) and minimal-change nephrotic syndrome (51) have been attributed to hepatitis B vaccine.

Skin

Erythema multiforme (52) and pityriasis rosea (53) have been reported after hepatitis B vaccination.

Alopecia (54), anetoderma (a disorder characterized by loss of dermal substance clinically and loss of elastic substance histologically) (55), lichen planus (56), urticaria (57), and white dot syndrome (58) have been attributed to hepatitis B vaccine.

Four cases of urticaria and one case of angioedema have been reported after hepatitis B immunization (59). The results emphasize that urticaria can be due to

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sensitization to the hepatitis Bs antigen itself, hyperimmunization, or a non-allergic reaction.

The first case of erythermalgia (paroxysmal attacks of bilateral pain in the extremities, with an acute increase in local heat in the affected parts, the production and aggravation of the distress by heat, relieved by cold) probably caused by hepatitis B vaccine has been reported (60).

- A 17-year-old boy developed the symptoms of erythermalgia two days after a third dose of hepatitis B vaccine. He was severely ill and recovered only 2 months after treatment with immunoglobulin and hypnotherapy. During hospitalization it was learned that he had had transient moderate pain of both feet for 3 nights after the second dose of vaccine.

The disease that followed the third dose of hepatitis B vaccine therefore met the criteria for positive rechallenge.

Musculoskeletal

In 31 cases of suspected chronic fatigue syndrome associated with hepatitis B immunization, no causal relation was determined (61).

Juvenile chronic polyarthropathy (62) and reactive arthritis (63) have been attributed to hepatitis B vaccine. Erythema nodosum and polyarthritis occurred the day after Engerix-B vaccine administration (64). The authors referred to reports of three other cases of polyarthritis in the literature.

Immunologic

Hepatitis A

Vasculitis suspected to be caused by the first dose of hepatitis A vaccine has been reported (SEDA-21, 331).

Hepatitis B

Polyarteritis nodosa (53), Sjögren's syndrome (65), lymphocytic vasculitis (66), vasculitis (67), and systemic lupus erythematosus (68) have been attributed to hepatitis B vaccine.

- After hepatitis B immunization, three doses of vaccine every month followed by a booster, a healthy 24-year-old woman lost weight and developed migratory arthralgia (47). Acute disseminated lupus erythematosus was diagnosed.

The authors discussed the possibility that immunization could have introduced an antigen that may have provoked an autoimmune reaction in genetically predisposed family members.

Churg–Strauss vasculitis (allergic angiitis and granulomatosis) has been attributed to hepatitis B immunization (69).

- A 20-year-old woman developed chronic rhinitis 1 month after the last dose of hepatitis B, followed about 1 year later by severe asthma, nasal polyposis, and petechial purpura in her fingernail beds and on her feet. A skin biopsy from the left leg showed infiltrates consistent with leukocytoclastic vasculitis.

The interval between immunization and the development of the vasculitis made it very difficult to establish a causal relation in this case.

Large artery vasculitis (two cases) (70) and polyarteritis nodosa (71) have been reported in temporal relation to hepatitis B administration.

A case of arthritis (72) and three cases of vasculitis (73) have been described 7–20 days after immunization with hepatitis B. A causal relation in such very rare cases is unclear, and probably they do not occur more than could be expected by chance.

Second-Generation Effects

Teratogenicity

In the children of 10 women who had received hepatitis B vaccine during the first trimester of pregnancy there were no congenital abnormalities; at 2–12 months the infants were physically and developmentally normal for their ages (74).

Drug Administration

Drug additives

To increase immunogenicity, the hepatitis A vaccines commercially available are coupled to adjuvant aluminium phosphate or aluminium hydroxide. However, alum precipitates provoke inflammatory responses at the injection site. Immunostimulating reconstituted influenza virosomes have therefore been used as an alternative adjuvant. In 1994, a hepatitis A vaccine using the new adjuvant was licensed in Switzerland, and it was later approved for use in other countries: the vaccine was well tolerated and highly immunogenic (SEDA-20, 290) (SEDA-22, 344). Nine people with a history of ocular sensitivity were immunized with hepatitis B, without untoward reactions. However, this result in such a small series should not be overestimated (75). There have been reports of three cases of inflammatory nodular reactions after hepatitis B immunization; aluminium allergy was confirmed (76–78).

Four cases of reactions to thiomersal in hepatitis B vaccines (both plasma-derived and recombinant) have been reported from two centers (79,80). Although thiomersal is present in these vaccines at a concentration of only 1:20 000, it can cause severe cutaneous reactions of the delayed hypersensitivity type, and sometimes the reactions can be very long lasting.

To interpret strictly the package insert for hepatitis B vaccines would preclude its administration to persons with a history of ocular sensitivity to thiomersal.

Drug dosage regimens

Revaccination is sometimes necessary because only 50–70% of immunocompromised persons, especially dialysis patients, develop antibodies, and the anti-HBs titers in these cases are low. In revaccinated non-responders to primary hepatitis immunization using either 20 μg of plasma-derived vaccine or 10 μg of recombinant vaccine, depending on the vaccine used for previous doses, the revaccinations were well tolerated (81,82). Only 6.6% of the vaccinees reported slight irritation at the injection site, tenderness, minimal pain, or swelling lasting for a few hours up to 2 days.

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Drug administration route

Aiming at cost reduction of hepatitis B immunization programs, the administration of low doses (2 micrograms) of vaccine given intradermally had by 1987 been evaluated in clinical trials in health-care workers (83) and children (84). The resulting seroconversion rates were 96 and over 90%, respectively. A minimum of local side effects occurred. In a comparison of antibody responses and adverse effects after intradermal or subcutaneous administration of 2 micrograms of a plasma-derived hepatitis B vaccine and intramuscular administration of 20 μg, the intradermal and intramuscular routes gave the highest seroconversion rates (100 and 96%, respectively) and the highest mean titers of anti-HBs (85). The aluminium adjuvant in the vaccine was assumed to cause a substantial number of local reactions (37% discoloration, 17% itching, and 13% nodule formation) after intradermal administration; other routes of administration showed adverse effects only rarely. Correct intradermal deposition of the vaccine is crucial.

Drug–Drug Interactions

Other vaccines

When recombinant hepatitis B vaccine was given together with DTP vaccine and oral poliomyelitis vaccine, there was no evidence of increased reactogenicity after simultaneous administration compared with hepatitis B vaccine alone (86).

In 40 children born to HBsAg-positive mothers who had received second and third doses of hepatitis B vaccine simultaneously with DTP vaccine and inactivated poliomyelitis vaccine, immunogenicity and reactogenicity were comparable with non-simultaneous administration of the different vaccines (87).

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Herbal medicines

See also Individual plant genera

General Information

In principle, herbal medicines have the potential to elicit the same types of adverse reactions as synthetic drugs; the body has no way of distinguishing between "natural" and man-made compounds. Herbal medicines consist of whole extracts of plant parts (for example roots, leaves) and contain numerous potentially active molecules. Synergy is normally assumed to play a part in the medicinal effects of plant extracts, and medical herbalists have always claimed that whole plant extracts have superior effects over single isolated constituents. Similarly, it is also claimed that combinations of herbs have synergistic effects. There is in vitro and/or in vivo evidence to support the occurrence of synergism between constituents in certain herbal extracts (1,2); however, clinical evidence is lacking, and it is in any case uncertain how far the principle extends. Synergy is also taken to mean an attenuation of undesirable effects, another key tenet of herbalism being that the toxicity of plant extracts is less than that of a single isolated constituent. However, theoretically, plant constituents could also interact to render a herbal preparation more toxic than a single chemical constituent. Virtually no evidence is available to substantiate either hypothesis. It is also important to determine whether herbal treatments that have been shown to be as effective as conventional drugs have a better safety profile. Contrary to the belief of most herbalists, long-standing experience is by no means a reliable yardstick when it comes to judging the risk of adverse reactions (3).

Herbal medicine continues to be a growth area. In the UK, retail sales of complementary medicines (licensed herbal medicines, homoeopathic remedies, essential oils used in aromatherapy) were estimated to be £72 million in 1996, an increase of 36% in real terms since 1991 (4). This, however, is likely to be a gross underestimate as popular products sold as food supplements, including *Ginkgo biloba* and garlic, were not included. According to a detailed analysis of the herbal medicines market in Germany and France, total sales of herbal products in those countries in 1997 were US$1.8 billion and US$1.1 billion respectively (5). In 1994, annual retail sales of botanical medicines in the USA were estimated to be around US$1.6 billion; in 1998, the figure was closer to US$4 billion (6).

Some of the most useful data on trends in the use of herbal medicines come from two surveys of US adults carried out in 1991 and 1997/98, which involved over 1500 and over 2000 individuals respectively (7,8). The use of at least one form of complementary therapy in the 12 months preceding the survey increased significantly from 34% in 1990 to 42% in 1997. Herbal medicine was one of the therapies showing the most increase over this time period: there was a statistically significant increase in self-medication with herbal medicine from 2.5% of the sample in 1990 to 13% in 1997 (8). Disclosure rates to physicians of complementary medicine use were below 40% in both surveys (8). Furthermore, 18% of prescription medicine users took

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prescription medicines concurrently with herbal remedies and/or high-dose vitamins. These aspects of user behaviour clearly have implications for safety.

A hospital-based study from Oman has suggested that 15% of all cases of self-poisoning seen in this setting are with traditional medicines (9). A case series from Thailand has suggested that in patients with oral squamous cell carcinoma the use of herbal medicines before the first consultation with a healthcare professional increases the risk of an advanced stage almost six-fold (10) and survey data from the USA have suggested that herb–drug interactions may be a significant problem in a sizeable proportion of patients (11).

Several herbal medicines pose serious problems for surgical patients, for example through an increased bleeding tendency (12,13). Vulnerable populations also include children (14), and too few safety data are available to recommend herbal medicines during pregnancy or lactation (15). Several investigators have pointed out the potential of herbal medicines to harm certain organs, for example the liver (16) or the skin (17). Laxatives are often based on herbal extracts, and the risks of herbal laxatives have been emphasized (18). Many authors have reviewed the risks of herbal medicines in general terms (19,20).

The reasons for the popularity of herbal medicine are many and diverse. It appears that complementary medicine is not usually used because of an outright rejection of conventional medicine, but more because users desire to control their own health (5) and because they find complementary medicine to be more congruent with their own values, beliefs, and philosophical orientations toward health and life (21). Also, users may consult different practitioners for different reasons (5). An important reason for the increase in use is that consumers (often motivated by the lay press) consider complementary medicine to be "natural" and assume it is "safe". However, this notion is dangerously misleading; adverse effects have been associated with the use of complementary therapies (22). Furthermore, complementary therapies may not only be directly harmful (for example adverse effects of a herbal formulation), but like other medical treatments have the potential to be indirectly harmful (for example through being applied incompetently, by delaying appropriate effective treatment, or by causing needless expense) (23).

Incidence of adverse effects

Most of the data on adverse effects associated with herbal medicines is anecdotal, and assessment and classification of causality is often not possible. Likewise, there have been few attempts to determine systematically the incidence of adverse effects of non-orthodox therapies.

Of 1701 patients admitted to two general wards of a Hong Kong hospital, 3 (0.2%) had adverse reactions to Chinese herbal drugs; two of the three were serious (24). In a retrospective study of all 2695 patients admitted to a Taiwan department of medicine during 10 months 4% were admitted because of drug-related problems, and herbal remedies ranked third amongst the categories of medicines responsible (25). In an active surveillance adverse drug reaction reporting program conducted in a family medicine ward of the National Taiwan University Hospital, Chinese crude drugs were responsible for five hospital admissions (22% of the total) or 12% of all adverse reactions observed in the study (26). This is a part of the world where the herbal tradition is particularly strong; the figures do not apply elsewhere.

The incidence of contact sensitization associated with topical formulations containing plant extracts was significant when evaluated in 1032 consecutive or randomly selected patients visiting patch test clinics in The Netherlands (27).

In a 5-year toxicological study of traditional remedies and food supplements carried out by the Medical Toxicology Unit at Guy's and St. Thomas' Hospital, London, 1297 symptomatic enquiries by medical professionals were evaluated (28). Of these, an association was considered to have been confirmed, probable, or possible in 12, 35, and 738 cases respectively. Ten of the confirmed cases were related to Chinese or Indian herbal remedies. As a result of these findings, in October 1996 the UK Committee on Safety of Medicines extended its yellow card scheme for adverse drug reaction reporting to include unlicensed herbal remedies, which are marketed mostly as food supplements in the UK (the scheme had always applied to licensed herbal medicines) (29,30). This was an important milestone in herbal pharmacovigilance.

A report from the Uppsala Monitoring Centre of the WHO has summarized all suspected adverse reactions to herbal medicaments reported from 55 countries worldwide over 20 years (31). A total of 8985 case reports were on record. Most originated from Germany (20%), followed by France (17%), the USA (17%), and the UK (12%). Allergic reactions were the most frequent serious adverse events and there were 21 deaths. The authors pointed out that adverse reactions to herbal medicaments constitute only about 0.5% of all adverse reactions on record.

General adverse effects

Several reviews have focused on herbal medicines and have covered:

- the toxicity of medicinal plants (32–34);
- the safety of herbal products in general (35–46);
- adverse effects in specific countries, for example the USA (47) and Malaysia (48);
- adverse effects on specific organs (49), such as the cardiovascular system (50), the liver (51,52), and the skin (53,54);
- the safety of herbal medicines in vulnerable populations: elderly patients (55), pregnant women (56), and surgical patients (57,58);
- carcinogenicity (59);
- the adverse effects of herbal antidepressants (60);
- the adverse effects of Chinese herbal medicaments (61,62);
- the adverse effects of Ayurvedic medicines (63);
- herb–drug interactions (64–75);
- pharmacovigilance of herbal medicines (76).

Direct effects associated with herbal medicines can occur in several ways:

- hypersusceptibility reactions
- collateral reactions
- toxic reactions
- drug interactions
- contamination

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- false authentication
- lack of quality control.

Some of these effects relate to product quality. While there are some data on certain of these aspects, information on other aspects is almost entirely lacking. For example, there are isolated case reports of interactions between conventional medicines and complementary (usually herbal) remedies (23,77,78), although further information is largely theoretical (79).

Even a perfectly safe remedy (mainstream or unorthodox) can become unsafe when used incompetently. Medical competence can be defined as doing everything in the best interest of the patient according to the best available evidence. There are numerous circumstances, both in orthodox and complementary medicine, when competence is jeopardized:

- missed diagnosis
- misdiagnosis
- disregarding contraindications
- preventing/delaying more effective treatments (for example misinformation about effective therapies; loss of herd immunity through a negative attitude toward immunization)
- clinical deterioration not diagnosed
- adverse reaction not diagnosed
- discontinuation of prescribed drugs
- self-medication.

The attitude of consumers toward herbal medicines can also constitute a risk. When 515 users of herbal remedies were interviewed about their behavior vis a vis adverse effects of herbal versus synthetic over-the-counter drugs, a clear difference emerged. While 26% would consult their doctor for a serious adverse effect of a synthetic medication, only 0.8% would do the same in relation to herbal remedies (80).

The only way to minimize incompetence is by proper education and training, combined with responsible regulatory control. While training and control are self-evident features of mainstream medicine they are often not fully incorporated in complementary medicine. Thus the issue of indirect health risk is particularly pertinent to complementary medicine. Whenever complementary practitioners take full responsibility for a patient, this should be matched with full medical competence; if on the other hand, competence is not demonstrably complete, the practitioner in question should not assume full responsibility (81).

Asian herbalism

Most reports of adverse effects associated with herbal remedies relate to Chinese herbal medicines (82). This is an issue of growing concern, particularly because in many Western countries the popularity of Chinese herbalism is increasing. This is happening in the almost complete absence of governmental control (83) or of systematic research into the potential hazards of Chinese herbal formulations (84).

There have been several reports of adverse effects associated with Asian herbal formulations (85–105). Most of the serious adverse effects of Chinese herbal remedies are associated with formulations containing aconitine, anticholinergic compounds, aristolochic acid, or podophyllin, contaminating substances (106). Problems with Chinese herbal formulations are intensified because of nomenclature, since common, botanical, and Chinese names exist side by side, making confusion likely.

In a German hospital specializing in Chinese herbalism of 145 patients who had been treated within 1 year 53% reported having had at least one adverse effect attributable to Chinese herbal medicines (107). Nausea, vomiting, and diarrhea were the most common complaints. It should be noted that causality in these cases can only be suspected and not proven. In the same institution about 1% of 1507 consecutive patients treated with Chinese herbal mixtures had clinically relevant rises in liver enzymes (108,109). *Glycyrrhiza* radix and *Atractylodis macrocephalae* rhizome were most consistently associated with such problems. In most of these cases there were no associated clinical signs and the abnormalities tended to normalize without specific therapy and in spite of continued treatment with the Chinese herbal mixtures.

When 1100 Australian practitioners of traditional Chinese medicine were asked to complete questionnaires about the adverse effects of Chinese herbal mixtures, they reported 860 adverse events, including 19 deaths (110). It was calculated that each practitioner had encountered an average of 1.4 adverse events during each year of full-time practice.

A physician prospectively monitored all 1265 patients taking traditional Chinese medicines at his clinic during 33 months (111). Liver enzymes were measured before the start of therapy and 3 and 10 weeks later. Alanine transaminase activity was raised in 107 patients (8.5%) who initially had normal values. Of these patients, about 25% reported symptoms such as abdominal discomfort, looseness of bowels, loss of appetite, or fatigue.

A retrospective analysis of all adverse events related to herbal medicines and dietary supplements reported to the California Poison Control System has given data on the risks of the adverse effects of herbal medicines (112). Between January 1997 and June 1998, 918 calls relating to such supplements were received. Exposures resulting in adverse reactions occurred most often at recommended doses. There were 233 adverse events, of which 29% occurred in children. The products most frequently implicated were zinc (38%), *Echinacea* (8%), witch hazel (6%), and chromium picolinate (6%). Most of the adverse events were not severe and required no treatment; hospitalization was required in only three cases.

Quality control and purity of herbal products

Quality control for herbal medicaments that are sold as dietary supplements in most countries is poor (113,114). Thus, considerable variations in the contents of active ingredients have been reported, with lot-to-lot variations of up to 1000% (115). In most countries, the sale and supply of herbal remedies is to a large extent uncontrolled and unregulated; most herbal remedies are sold as unlicensed food supplements and their safety, efficacy, and quality have therefore not been assessed by licensing authorities. Adulteration and contamination of herbal remedies with other plant material and conventional drugs have been documented (25,116) (Table 1).

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Table 1 Potential adulterants that should be taken into account in the quality control of herbal medicines

Type of adulterant	Examples
Allopathic drugs	Analgesic and anti-inflammatory agents (for example aminophenazone, indometacin, phenylbutazone), benzodiazepines, glucocorticoids, sulfonylureas, thiazide diuretics, thyroid hormones
Botanicals	*Atropa belladonna*, *Digitalis* species, *Colchicum*, *Rauwolfia serpentina*, pyrrolizidine-containing plants (see separate monograph on pyrrolizidines)
Fumigation agents	Ethylene oxide, methyl bromide, phosphine
Heavy metals	Arsenic, cadmium, lead, mercury
Micro-organisms	*Escherichia coli* (certain strains), *Pseudomonas aeruginosa*, *Salmonella*, *Shigella*, *Staphylococcus aureus*
Microbial toxins	Aflatoxins, bacterial endotoxins
Pesticides	Carbamate insecticides and herbicides, chlorinated pesticides (for example aldrin, dieldrin, heptachlor, DDT, DDE, HCB, HCH isomers), dithiocarbamate fungicides, organic phosphates, triazine herbicides
Radionuclides	^{134}Cs, ^{137}Cs, ^{103}Ru, ^{131}I, ^{90}Sr

The authors of a survey of German importers of Chinese herbs concluded that "only rarely" had herbal drugs to be returned because of contamination (117). The authors also stated that "a 100% check for all possible contaminants is not possible." However, there have been many reports of adulteration and contamination relate to Chinese herbal remedies (118). Instances include adulteration/contamination with conventional drugs (119,120), heavy metals (121–127), and other substances (128,129).

When 27 samples of commercially available camomile formulations were tested in Brazil, it was found that all of them contained adulterants and only 50% had the essential oils needed to produce anti-inflammatory activity (130).

Concerns about the quality and safety of herbal remedies are justified, and there have been repeated calls for greater control and regulation (28,131,132).

Adulteration with allopathic drugs

Barbiturates

Phenobarbital has been reported as a contaminant in a Chinese patent medicine (133).

- A 10-year-old boy developed respiratory depression and became comatose after taking the Chinese patent medicine "Diankexing" for 6 months. His urine phenobarbital concentration was 95 μg/ml (target range 20–40 μg/ml). The remedy was withdrawn and he was successfully treated with activated charcoal.

Benzodiazepines

The Botanical Lab in the USA has manufactured the herbal medicines PC-SPES and SPES (134). These two products are marketed as "herbal dietary supplements" for "prostate health" and for "strengthening the immune system" respectively. They are sold through the internet, by mail order, by phone order, and through various distributors and health care professionals. An analytical report from the California Department of Health in 2002 showed that samples of PC-SPES and SPES have been contaminated with alprazolam and warfarin. The Canadian Medicines Regulatory Authority also reported similar contaminations. In view of these reports Health Canada, the Irish Medicines Board, and the State Health Director of California all warned consumers to stop using these two products immediately and to consult their healthcare practitioners. Botanic Lab also informed consumers of these laboratory findings and issued a product recall of all lots of PC-SPES, pending further reports from additional testing of PC-SPES in both commercial and academic laboratories.

In 2001 the California State Health Director warned consumers to stop using the herbal product Anso Comfort capsules immediately, because the product contains the undeclared prescription drug chlordiazepoxide. Chlordiazepoxide is a benzodiazepine that is used for anxiety and as a sedative and can be dangerous if not taken under medical supervision (135). Anso Comfort capsules, available by mail or telephone order from the distributor in 60-capsule bottles, were clear with dark green powder inside. The label was yellow with green English printing and a picture of a plant. An investigation by the California Department of Health Services Food and Drug Branch and Food and Drug Laboratory showed that the product contained chlordiazepoxide. The ingredients for the product were imported from China and the capsules were manufactured in California. Advertising for the product claimed that the capsules were useful for the treatment of a wide variety of illnesses, including high blood pressure and high cholesterol, in addition to claims that it was a natural herbal dietary supplement. The advertising also claimed that the product contained only Chinese herbal ingredients and that consumers could reduce or stop their need for prescribed medicines. No clear medical evidence supported any of these claims. The distributor, NuMeridian (formerly known as Top Line Project), voluntarily recalled the product nationwide.

A San Francisco woman with a history of diabetes and high blood pressure was hospitalized in January 2001 with life-threatening hypoglycemia after she consumed Anso Comfort capsules. This may have been due to an interaction of chlordiazepoxide with other unspecified medications that she was taking.

Glucocorticoids

Wau Wa cream is marketed in several countries as a herbal cream for eczema. After repeatedly observing surprising therapeutic successes, UK doctors analysed three samples of this cream given to them by three patients (136). The samples contained 0.013% clobetasol propionate, a powerful glucocorticoid that does not occur naturally.

Betamethasone, 0.1–0.3 mg per capsule, has been detected in Cheng Kum and Shen Loon, two herbal medicines that are popular for their benefits in joint pain, skin

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problems, colds, menopausal symptoms, and dysmenorrhea (137). Over-exposure to betamethasone can result in typical signs of glucocorticoid excess, such as moon face, hypertension, easy bruising, purple abdominal striae, truncal obesity, and hirsutism. The recommended daily adult dose of Cheng Kum is 1–3 capsules per day, and there have been reports of glucocorticoid-induced adverse effects in patients taking Cheng Kum and Shen Loon, even in the absence of other exogenous corticosteroid consumption.

- Two patients, a 29-year-old woman and a 10-year-old girl, developed Cushingoid features after taking Shen Loon for 4 and 5 months respectively (138). Their morning plasma cortisol concentrations were increased and adrenal suppression was confirmed by a short Synacthen test. Both recovered after withdrawal of the remedy and treatment with prednisone.

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) has notified that the further importation of these herbal products into New Zealand will be stopped at Customs. However, because of the risk of adrenal suppression from glucocorticoid, consumers have been sent a letter advising them against abruptly discontinuing these products. They should continue with the treatment and see their general practitioner as soon as possible for instructions on how they can be safely weaned off the product. Medsafe has issued a letter to doctors advising them to determine whether patients taking Cheng Kum or Shen Loon are at risk of adrenal suppression by estimating the potential total dose of glucocorticoid (from Cheng Kum or Shen Loon plus any exogenous steroids) and the duration of use, by examining the patient for signs of glucocorticoid excess, and by ascertaining if other risk factors for adrenal suppression are present (such as Addison's disease and AIDS).

Hypoglycemic drugs

Herbal medicines, particularly Chinese ones, are sometimes contaminated with conventional synthetic drugs (139). In 2000 the California Department of Health Services Food and Drug Branch issued a warning to consumers that they should immediately stop using five herbal products because they contained two prescription drugs that were not listed as ingredients and that are unsafe without monitoring by a physician (140). The products were Diabetes Hypoglucose Capsules, Pearl Hypoglycemic Capsules, Tongyi Tang Diabetes Angel Pearl Hypoglycemic Capsules, Tongyi Tang Diabetes Angel Hypoglycemic Capsules, and Zhen Qi Capsules. The products were available by mail order and could be purchased by telephone or via the Internet. Their manufacturers claimed that they contained only natural Chinese herbal ingredients. However, after a diabetic patient in Northern California had had several episodes of hypoglycemia after taking Diabetes Hypoglucose Capsules, an investigation by the Department showed that they contain the antidiabetic drugs glibenclamide (glyburide) and phenformin.

Penicillamine

Penicillamine unexpectedly caused myasthenia gravis when present as an unrecognized additive in Chinese herbs (141).

Various

A systematic review included 18 case reports, two case series, and four analytical studies showing adulteration with various allopathic drugs (142). The adulterants included phenazone (aminopyrine), clobetasol propionate and other glucocorticoids, diazepam, diclofenac, glibenclamide, hydrochlorothiazide, indometacin, mefenamic acid, methylsalicylate, phenacetin, phenylbutazone, and phenytoin.

In 2002 the Medicines Safety Authority of the Ministry of Health in New Zealand (Medsafe) ordered the withdrawal of several traditional Chinese medicines sold as herbal remedies, since they contained scheduled medicines and toxic substances (143). The products included the following allopathic drugs:

- Wei Ge Wang tablets, which contained sildenafil
- Sang Ju Gan Mao Pian tablets, which contained diclofenac and chlorphenamine
- Yen Qiao Jie Du Pian capsules, which contained chlorphenamine, diclofenac, and paracetamol
- Xiaoke Wan pills, which contained glibenclamide
- Shuen Feng cream, which contained ketoconazole
- Dezhong Rhinitis drops, which contained ephedrine hydrochloride.

The New Zealand Director General of Health issued a Public Statement asking people to stop taking these products and to seek medical advice. Medsafe asked all importers and distributors of traditional Chinese medicines to cease all distribution and sale of these products, to withdraw them from retail outlets, and to ensure that other products they sell do not contain scheduled medicines.

Adulteration with botanicals

Two cases have been reported of contamination of plantain (a plant of the genus *Plantago*) by *Digitalis lanata* (144). Both patients suffered from serious overdose of cardiac glycosides with toxic serum digoxin concentrations as a result.

Adulteration with heavy metals

In 2002 the Medicines Safety Authority of the Ministry of Health in New Zealand (Medsafe) ordered the withdrawal of several traditional Chinese medicines sold as herbal remedies, since they contained scheduled medicines and toxic substances (143). The products included Niu Huang Jie Du Pian tablets, which contain 4% arsenic.

In Taipei, 319 children aged 1–7 years were screened for increased blood lead concentrations (145). The consumption of Chinese herbal medicines was significantly correlated with blood lead concentrations. In 2803 subjects from Taipei a history of herbal drug taking proved to be a major risk factor for increased blood lead concentrations (146).

- A 56-year-old woman developed the signs and symptoms of lead poisoning after taking an Indian herbal medicine for many years (147). Her blood and urine lead concentrations were 1530 ng/ml and 4785 μg/day. She also had raised liver enzymes. After withdrawal of the remedy and treatment with penicillamine, she made a full recovery.
- Czech doctors reported the case of a 26-year-old woman who had taken an Ayurvedic remedy (Astrum FE Femikalp) for sterility (148). It contained lead 113 mg/kg. Her blood lead concentration was raised and

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normalized 1 month after withdrawal of the remedy. Lead poisoning was also confirmed by hair analysis.

Of 260 Asian patent medicines available in California, 7% contained undeclared pharmaceuticals. When 251 samples were tested for heavy metals, 24 products contained at least 10 parts per million of lead, 36 contained arsenic, and 35 contained mercury (149).

Three Singapore patients with chronic arsenic poisoning with characteristic skin changes had taken Chinese herbal remedies for many years to treat their asthma; two had cancers likely to be due to arsenic (150).

Cases of adulteration with the heavy metals mercury (151) and lead (152) have been reported.

- A 5-year-old Chinese boy developed motor and vocal tics. His parents had given him a Chinese herbal spray to treat mouth ulcers. The spray contained mercury 878 ppm. Mercury poisoning was confirmed by the blood mercury concentration (183 nmol/l, normal value for adults under 50 nmol/l).
- A 5-year-old boy of Indian origin with encephalopathy, seizures, and developmental delay developed persistent anemia. The more obvious causes were ruled out and his blood lead concentration was high (860 ng/ml). He was treated with chelation therapy and his blood lead concentration fell. For the previous 4 years his parents had given him "Tibetan Herbal Vitamins," produced in India, which contained large amounts of lead. The investigators calculated that over that time he had ingested around 63 g of lead.

A total of 54 samples of Asian remedies, purchased in Vietnam, Hong Kong, Florida, New York, and New Jersey, were analysed for heavy metal adulteration (153). They contained concentrations of arsenic, lead, and mercury that ranged from merely exceeding published guidelines (74%) to toxic (49%).

Ayurvedic medicines have also been reportedly adulterated and contaminated (154). For example, they have repeatedly been associated with arsenic poisoning, including hyperpigmentation and hyperkeratosis (155). Of 70 unique Ayurvedic products manufactured in India or Pakistan and sold in Boston, mostly for gastrointestinal disorders, 14 contained lead, mercury, and/or arsenic, in concentrations up to about 100 mg/g (156).

Adulteration with inorganic chemicals

There is a practice among urbanized South African blacks to replace traditional herbal ingredients of purgative enemas with sodium or potassium dichromate. This switch can result in serious toxicity, characterized by acute renal insufficiency, gastrointestinal hemorrhage, and hepatocellular dysfunction (157,158).

Contamination with micro-organisms

When 62 samples of medicinal plant material and 11 samples of herbal tea were examined in Croatia, fungal contamination was found to be abundant (159). *Aspergillus flavus*, a known producer of aflatoxins was present in 11 and one sample respectively. Mycotoxins were found in seven of the samples analysed.

Kombucha "mushroom" is a symbiotic yeast/bacteria aggregate surrounded by a permeable membrane. An outbreak of skin lesions affecting 20 patients from a village near Tehran has been reported (160). The lesions were painless and had a central black necrotic area, marginal erythema, and severe peripheral edema. These clinical signs led to the suspicion of anthrax infection. It turned out that all patients had applied Kombucha mushroom locally as a painkiller. The skin lesions had developed 5–7 days after the application of the material. Cultures from the skin lesions confirmed the presence of *Bacillus anthracis*. Cultures of the Kombucha mushrooms were inconclusive, owing to multiple bacterial contamination and overgrowth, but it was shown that anthrax would grow on uncontaminated material. The patients all recovered with antibiotic therapy.

Contamination with pesticides

Some herbal medicaments are contaminated with pesticides (161).

Drug overdose

In a retrospective study of 2764 poisoning cases admitted to eight urban hospitals in Zimbabwe between 1998 and 1999, 7% of all cases and 13% of all deaths were related to traditional medicines (162). The authors noted that these figures were markedly lower than those from a similar survey 10 years earlier.

Susceptibility factors

Owing to extensive modifications of drug formulations and chemical extracts from an expanding range of natural products, herbal formulations may contain ingredients that are particularly harmful to individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Extra vigilance is therefore required when herbal medicinal formulations, including topical applications, are used by patients with G6PD deficiency and even their carers (163).

Thallophytes

Liver damage has been attributed to *Spirulina*, a type of blue–green algae.

- A 52-year-old Japanese man was admitted with signs and symptoms consistent with toxic liver damage (164). His medical history relevant to liver disease was unremarkable; in particular, his liver enzymes had been normal. It turned out that 5 weeks before admission he had started taking a remedy containing *Spirulina*. A lymphocyte stimulation test for *Spirulina* was positive and infectious hepatitis was excluded. Liver biopsy was consistent with toxic liver injury. After withdrawal of *Spirulina* all his liver enzymes quickly returned to normal.

Proprietary herbal mixtures

Numerous herbal mixtures are promoted worldwide, for example through the Internet. In many cases their herbal ingredients are not disclosed.

Copaltra

Copaltra is a herbal tea sold in France as an adjuvant therapy for diabetes. It contains *Coutarea latiflora* (50 g) and *Centaurium erythreae* (50 g).

- A 49-year-old black woman was admitted with jaundice and raised liver enzymes 4 months after starting to take

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Copaltra (165). She also took fenofibrate, polyunsaturated fatty acids, metformin, benfluorex, and veralipride. Liver biopsy confirmed the diagnosis of acute, severe, cytolytic hepatitis, most likely drug-induced. She made a full recovery after withdrawal of Copaltra.

The authors mentioned that five similar cases of Copaltra-induced hepatitis have been reported to the French authorities.

Essiac

Essiac is a Canadian herbal mixture promoted as a cancer cure. It has been reported to have caused fever (166).

- A 46-year-old woman with a squamous cell carcinoma of the cervix developed neutropenic fever during radiation therapy, 10 days after taking Essiac. The fever resolved after antibiotic therapy, but it delayed her radiation therapy for 9 days and required 4 days of hospitalization.

The authors felt that Essiac had caused this problem, but causality was uncertain, not least because she also took four other herbal medicaments.

Herbalife

Herbalife is a complex herbal formula that is promoted for weight loss. Acute mania has been attributed to it (167).

- A 39-year-old man developed classic symptoms of mania within 4–72 hours of taking Herbalife. He continued to take it and after several days became psychotic, paranoid, and out of control, culminating in a high-speed car chase with the police. Bipolar disorder was diagnosed and treated, including withdrawal of the Herbalife, and he remained free of symptoms 3 months later.

The author thought it likely that the herbal mixture had caused the psychotic illness in a man who had no previous history of mental disturbance.

Iberogast

Iberogast contains extracts of bitter candy tuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, lemon balm leaves, angelica root, celandine, and milk thistle fruit, and has been used to treat dyspepsia (168). In a systematic review, adverse events were rare and similar to those found with placebo (169).

Isabgol

Isabgol is an Italian herbal mixture that is promoted for constipation.

- Syncytial giant cell hepatitis occurred in a 26-year-old woman who used Isabgol (170). Autoimmune disease and viral infections were excluded.

The authors felt that the causative role of the Isabgol was supported by the spontaneous and dramatic clinical, biochemical, and histological improvement that followed the withdrawal of Isabgol without any further therapy.

Jai Wey Guo Sao

- A 36-year-old woman was admitted to hospital because of general malaise (171). She had lost 5 kg within 6 months. She was found to have interstitial renal fibrosis and irreversible renal insufficiency. She had taken a Chinese herbal mixture Jai wey guo sao to treat irregular menses. The formulation contained *Angelica sinensis* root, *Rhemanniae* root and rhizome, *Ligustici* rhizome, *Paeoniae lactiflore* root, ginseng root, *Eucommiae* cortex, and honey.

The causative agent in this case could not be identified beyond doubt.

Kampo medicines

All admission records of patients suspected of having liver problems related to Kampo medicines between 1979 and 1999 in a Japanese Department of Oriental Medicine were reviewed (172). There were 30 cases that were suspected of being caused by Kampo medicines. On closer examination, nine seemed to be definitely unrelated, six were probably unrelated, nine were possibly related, and six were definitely or probably related to Kampo medicines. There were no deaths on record.

Sho-saiko-to is a so-called kampo medicine, a mixture of herbs, including Chinese date, ginger root, and licorice root. It is reportedly contraindicated in patients taking interferons, patients with liver cirrhosis or hepatoma, and patients with chronic hepatitis and a platelet count of 100×10^9/l (http://www.kamponews.com). Sho-saiko-to has repeatedly been implicated in interstitial or eosinophilic pneumonias.

- A 45-year-old woman developed a high fever, a non-productive cough, and severe dyspnea (173). Her chest X-ray showed bilateral alveolar infiltrates. Treatment with antibiotics was not successful and her condition deteriorated. She was finally put on mechanical ventilation and subsequently improved dramatically. It turned out that she had previously taken sho-saiko-to for liver dysfunction of unknown cause.

Based on a positive lymphocyte stimulation test, the authors were confident that this herbal remedy had caused pulmonary edema.

Corneal opacities causing photophobia have been attributed to a Kampo medicine (174).

- A 30-year-old Japanese woman developed bilateral photophobia. There were dust-like opacities in both corneae. She had a superficial keratectomy, and electron microscopy identified the opacities as lipid-like particles. She had intermittently taken a Kampo medicine composed of 18 different herbal ingredients. Her photophobia coincided with episodes of taking this medicine. The remedy was withdrawn and her symptoms subsequently subsided. She then abstained from the Kampo medicine without recurrence.

Severe liver damage has been attributed to a Kampo medicine (175).

- A 50-year-old Japanese woman with a 20-year history of asthma was taking steroids and bronchodilators when she started self-medicating with a Kampo mixture called Saiko-Keishi-Kankyo-To. Two months later, she developed acute severe liver damage. The Kampo mixture was withdrawn and she promptly recovered.

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The authors attributed the liver damage to one ingredient of the mixture, *Trichosanthes* radix, a Chinese medicament that is prepared from the root of *Trichosanthes kirilowii maxim* (Tian-hua-fen).

Lipokinetix
The slimming aid "LipoKinetix" contains norephedrine hydrochloride, sodium usinate, 3,5-diiodothyronine, yohimbine hydrochloride, and caffeine. Seven patients all had the signs and symptoms of acute toxic hepatitis after taking this dietary supplement (176). Three patients had taken no other concomitant medications. All recovered spontaneously after "LipoKinetix" was withdrawn.

Rio Hair Naturalizer System
Rio Hair Naturalizer System is a complex mixture of metallic salts and botanical extracts promoted to straighten curled hair. The product has been popular with African Americans in the USA. A survey of 464 individuals who had complained to the FDA about this remedy showed that 95% had experienced hair breakage and hair loss (177). Three-quarters of those who had hair loss had lost 40% or more; regrowth took 8 months on average.

Ting kung teng
Cholinergic poisoning has been attributed to a Chinese herbal mixture, Ting kung teng.

- A 73-year-old man developed a cholinergic syndrome, with dizziness, sweating, chills, lacrimation, salivation, rhinorrhea, nausea, and vomiting after taking the Chinese patent medicine Ting kung teng for arthritis (178). The herbal mixture contained tropane alkaloids with cholinergic activity. After withdrawal of the remedy he made a swift and complete recovery.

Tsumura
Tsumura, a Japanese herbal mixture has been associated with hepatotoxicity (179).

- A 49-year-old Japanese woman had taken oral Tsumura for about 6 weeks to treat internal hemorrhoids when she felt unwell. Her liver enzymes were raised and a diagnosis of drug-induced hepatic damage caused by *Angelica radix* and *Bupleuri* radix contained in the mixture was made. The liver function tests normalized 4 months after withdrawal.

Monographs on herbal products

Each of the monographs on herbal products in this encyclopedia has the following structure:

- Family: each monograph is organized under a family of plants (for example Liliaceae).
- Genera: the various genera that are included under the family name are tabulated (for example the family Liliaceae contains 94 genera); the major source of information on families and genera is the Plants National Database (http://plants.usda.gov/index.html).
- Species: in each monograph some species are dealt with separately. For example, in the monograph on Liliaceae, four species are included under their Latin names and major common names—*Sassafras albidum* (sassafras), *Allium sativum* (garlic), *Colchicum autumnale* (autumn crocus), and *Ruscus aculeatus* (butcher's broom).

Each monograph includes the following information in varying amounts:

- Alternative common names; the major sources of this information are *A Modern Herbal* by Mrs M Grieve (1931; http://www.botanical.com/botanical/mgmh/mgmh.html) and *The Desktop Guide to Complementary and Alternative Medicine: an Evidence-Based Approach* by E Ernst, MH Pittler, C Stevenson, and A White (Mosby, 2001).
- Active ingredients; the major source of this information is the *Dictionary of Plants Containing Secondary Metabolites* by John S Glasby (Taylor & Francis, 1991).
- Uses, including traditional and modern uses.
- Adverse effects.

The families of plants and their species that are the subjects of monographs are listed in Table 2 by alphabetical order of family. The same data are listed in Table 3 by alphabetical order of species. Other monographs cover the Basidiomycetes (*Lentinus edodes*, shiitake) and algae. Table 4 gives the Latin equivalents of the common names. To locate a plant by its common name, convert the common name into the Latin name using Table 4 and then find out to which family it belongs by consulting Table 3.

Table 2 Families of plants and their species that are the subjects of monographs in this encyclopedia (by alphabetical order of family)

Family (common name)	Species (common name)
Acoraceae (calamus)	*Acorus calamus* (calamus root)
Aloeaceae (aloe)	*Aloe capensis* (aloe)
	Aloe vera (aloe)
Amaranthaceae (amaranth)	*Pfaffia paniculata* (Brazilian ginseng)
Anacardiaceae (sumac)	*Rhus species* (sumac)
Apiaceae (carrot)	*Ammi majus* (bishop's weed)
	Ammi visnaga (toothpick weed)
	Angelica sinensis (dong quai)
	Conium maculatum (hemlock)
	Coriandrum sativum (coriander)
	Ferula assa-foetida (asafetida)
Apocynaceae (dogbane)	*Rauwolfia serpentina* (snakeroot)
Araliaceae (ginseng)	*Eleutherococcus senticosus* (Siberian ginseng)
	Panax ginseng (Asian ginseng)
Arecaceae (palm)	*Areca catechu* (areca, betel)
	Serenoa repens (saw palmetto)
Aristolochiaceae (birthwort)	*Aristolochia* species (Dutchman's pipe)
	Asarum heterotropoides (Xu xin)
Asclepiadaceae (milkweed)	*Asclepias tuberosa* (pleurisy root)
	Xysmalobium undulatum (xysmalobium)

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Family (common name)	Species (common name)
Asteraceae (aster)	*Achillea millefolium* (yarrow)
	Anthemis species *and Matricaria recutita* (chamomile)
	Arnica montana (arnica)
	Artemisia absinthium (wormwood)
	Artemisea annua (Qinghaosu)
	Artemisia cina (wormseed)
	Artemisia vulgaris (common wormwood)
	Calendula officinalis (marigold)
	Callilepis laureola (impila, ox-eye daisy)
	Chrysanthemum vulgaris (common tansy)
	Cynara scolymus (artichoke)
	Echinacea species (coneflower)
	Eupatorium species (thoroughwort)
	Inula helenium (elecampane)
	Petasites species (butterbur)
	Senecio species (ragwort)
	Silybum marianum (milk thistle)
	Tanacetum parthenium (feverfew)
	Tussilago farfara (coltsfoot)
Berberidaceae (barberry)	*Berberis vulgaris* (European barberry)
	Caulophyllum thalictroides (blue cohosh)
	Dysosma pleianthum (bajiaolian)
	Mahonia species (barberry)
Boraginaceae (borage)	*Cynoglossum officinale* (hound's tongue)
	Symphytum officinale (black wort)
	Heliotropium species (heliotrope)
Brassicaceae (mustard)	*Armoracia rusticana* (horseradish)
	Brassica nigra (black mustard)
	Raphanus sativus var. niger (black radish)
	Sinapis species (mustard)
Campanulaceae (bellflower)	*Lobelia inflata* (Indian tobacco)
Cannabaceae	*Humulus lupulus* (hop)
Capparaceae (caper)	*Capparis spinosa* (caper plant)
Celastraceae (bittersweet)	*Catha edulis* (khat, qat)
	Euonymus europaeus (spindle tree)
	Tripterygium wilfordii (Lei gong teng)
Chenopodiaceae (goosefoot)	*Chenopodium ambrosioides* (American wormseed)
Clusiaceae (mangosteen)	*Hypericum perforatum* (St John's wort)
Convolvulaceae (morning glory)	*Convolvulus scammonia* (Mexican scammony)
	Ipomoea purga (jalap)
Coriariaceae	*Coriaria arborea* (tutu)
Cucurbitaceae (cucumber)	*Bryonia alba* (white bryony)
	Citrullus colocynthis (colocynth)
	Ecballium elaterium (squirting cucumber)
	Momordica charantia (karela fruit, bitter melon)
	Sechium edule (chayote)
Cupressaceae (cypress)	*Juniperus communis* (juniper)
Cycadaceae (cycad)	*Cycas circinalis* (false sago palm)
Droseraceae (sundew)	*Dionaea muscipula* (Venus flytrap)
Dryopteraceae (wood fern)	*Dryopteris filix-mas* (male fern)
Ericaceae (heath)	*Arctostaphylos uva-ursi* (bearberry)
	Gaultheria procumbens (wintergreen)
	Ledum palustre (marsh Labrador tea)
	Vaccinium macrocarpon (cranberry)
Euphorbiaceae (spurge)	*Breynia officinalis* (Chi R Yun)
	Croton tiglium (croton)
	Ricinus communis (castor oil plant)
Fabaceae (pea)	*Cassia* species (senna)
	Crotalaria species (rattlebox)
	Cyamopsis tetragonoloba (cluster bean)
	Cytisus scoparius (Scotch broom)
	Dipteryx species (tonka beans)
	Genista tinctoria (dyer's broom)
	Glycyrrhiza glabra (liquorice)
	Lupinus species (lupin)
	Medicago sativa (alfalfa)
	Melilotus officinalis (sweet clover)
	Myroxylon species (balsam of Peru)
	Pithecollobium jiringa (jering fruit)
	Sophora falvescens (Ku shen)
	Trifolium pratense (red clover)
Gentianaceae (gentian)	*Gentiana* species (gentian)
	Swertia species (felwort)
Ginkgoaceae	*Ginkgo biloba* (maidenhair)
Hippocastanaceae (horse chestnut)	*Aesculus hippocastanum* (horse chestnut)
	Illicium species (star anise)
Illiciaceae (star anise)	*Crocus sativus* (Indian saffron)
Iridaceae (iris)	*Juglans regia* (English walnut)
Juglandaceae (walnut)	*Krameria* species (ratany)
Krameriaceae (Krameria)	*Hedeoma pulegoides* (pennyroyal)
Lamiaceae (mint)	*Lavandula angustifolia* (lavender)
	Mentha piperita (peppermint)
	Mentha pulegium (pennyroyal)
	Salvia miltiorrhiza (danshen)
	Salvia officinalis (sage)
	Scutellaria species (skullcap)
	Teucrium species (germander)
Lauraceae (laurel)	*Cinnamonum camphora* (camphor tree)
	Laurus nobilis (laurel)
	Sassafras albidum (sassafras)
Liliaceae (lily)	*Allium sativum* (garlic)
	Colchicum autumnale (autumn crocus)
	Ruscus aculeatus (butcher's broom)
	Veratrum species (hellebore)
Loganiaceae (Logania)	*Strychnos nux-vomica* (nux vomica)
Lycopodiaceae (club moss)	*Lycopodium serratum* (clubmoss)
Malvaceae (mallow)	*Gossypium* species (cotton)
	Psoralea corylifolia (bakuchi)
Meliaceae (mahogany)	*Azadirachta indica* (bead tree)
Menispermaceae (moonseed)	*Stephania* species (Jin bu huan)
Myristicaceae (nutmeg)	*Myristica fragrans* (nutmeg)
Myrtaceae (myrtle)	*Eucalyptus* species (eucalyptus)
	Melaleuca alternifolia (tea tree)
Onagraceae (evening primrose)	*Oenothera biennis* (evening primrose)
	Chelidonium majus (celandine)

Continued

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Table 2 Continued

Family (common name)	Species (common name)
Papaveraceae (poppy)	*Papaver somniferum* (opium poppy)
	Passiflora incarnata (passion flower)
Passifloraceae (passion flower)	*Harpagophytum procumbens* (devil's claw)
Pedaliaceae (sesame)	*Phytolacca americana* (pokeweed)
Phytolaccaceae (pokeweed)	*Piper methysticum* (kava kava)
Piperaceae (pepper)	*Plantago* species (plantain)
Plantaginaceae (plantain)	*Anthoxanthum odoratum* (sweet vernal grass)
Poaceae (grass)	*Polygonum* (knotweed)
Polygonaceae (buckwheat)	*Rheum palmatum* (rhubarb)
	Aconitum napellus (monkshood)
Ranunculaceae (buttercup)	*Cimicifuga racemosa* (black cohosh)
	Delphinium species (delphinium)
	Hydrastis canadensis (golden seal)
	Pulsatilla species (pasque flower)
	Ranunculus damascenus (buttercup)
	Rhamnus purshianus (cascara sagrada)
Rhamnaceae (buckthorn)	*Ziziphus jujuba* (dazao)
	Crataegus species (hawthorn)
Rosaceae (rose)	*Prunus* species (plum)
	Zingiber officinale (ginger)
	Asperula odorata (sweet woodruff)
Rubiaceae (madder)	*Cephaelis ipecacuanha* (ipecac)
	Hintonia latiflora (copalchi bark)
	Morinda citrifolia (noni)
	Rubia tinctorum (madder)
	Uncaria tomentosa (cat's claw)
	Agathosma betulina (buchu)
Rutaceae (rue)	*Citrus auranticum* (bergamot)
	Citrus paradisi (grapefruit)
	Dictamnus dasycarpus (densefruit pittany)
	Pilocarpus species (pilocarpus)
	Ruta graveolens (rue)
	Salix species (willow)
Salicaceae (willow)	*Blighia sapida* (akee)
Sapindaceae (soapberry)	*Paullinia cupana* (guaraná)
	Selaginella doederleinii (spike moss)
Selaginellaceae (spike moss)	*Anisodus tanguticus* (Zangqie)
Solanaceae (potato)	*Capsicum annum* (chili pepper)
	Datura candida (angel's trumpet)
	Datura stramonium (Jimson weed)
	Datura suaveolens (angel's trumpet)
	Lycium barbarum (Chinese wolfberry)
	Mandragora species (mandrake)
	Nicotiana tabacum (tobacco)
	Scopolia species (scopola)
	Sterculia species (sterculia)
Sterculiaceae (cacao)	*Taxus* species (yew)
Taxaceae (yew)	*Camellia sinensis* (green tea)
Theaceae (tea)	*Urtica dioica* (stinging nettle)
Urticaceae (nettle)	*Valeriana* (valerian)
Valerianaceae (valerian)	*Vitex agnus-castus* (chaste tree)
Verbenaceae (verbena)	*Phoradendron flavescens* (American mistletoe)
Viscaceae (Christmas mistletoe)	*Viscum album* (mistletoe)

Table 3 Families of plants and their genera or species that are the subjects of monographs in this encyclopedia (by alphabetical order of genus or species)

Genus or species (common name)	Family (common name)
Achillea millefolium (yarrow)	Asteraceae (aster)
Aconitum napellus (monkshood)	Ranunculaceae (buttercup)
Acorus calamus (calamus root)	Acoraceae (calamus)
Aesculus hippocastanum (horse chestnut)	Hippocastanaceae (horse chestnut)
Agathosma betulina (buchu)	Rutaceae (rue)
Allium sativum (garlic)	Liliaceae (lily)
Aloe capensis (aloe)	Aloeaceae (aloe)
Aloe vera (aloe)	Aloeaceae (aloe)
Ammi majus (bishop's weed)	Apiaceae (carrot)
Ammi visnaga (toothpick weed)	Apiaceae (carrot)
Angelica sinensis (dong quai)	Apiaceae (carrot)
Anisodus tanguticus (zangqie),	Solanaceae (potato)
Anthemis species (chamomile)	Asteraceae (aster)
Anthoxanthum odoratum (sweet vernal grass)	Poaceae (grass)
Arctostaphylos uva-ursi (bearberry)	Ericaceae (heath)
Areca catechu (areca, betel)	Arecaceae (palm)
Aristolochia species (Dutchman's pipe)	Aristolochiaceae (birthwort)
Armoracia rusticana (horseradish)	Brassicaceae (mustard)
Arnica montana (arnica)	Asteraceae (aster)
Artemisea annua (qinghaosu)	Asteraceae (aster)
Artemisia absinthium (wormwood)	Asteraceae (aster)
Artemisia cina (wormseed)	Asteraceae (aster)
Artemisia vulgaris (common wormwood)	Asteraceae (aster)
Asarum heterotropoides (xu xin)	Aristolochiaceae (birthwort)
Asclepias tuberosa (pleurisy root)	Asclepiadaceae (milkweed)
Asperula odorata (sweet woodruff)	Rubiaceae (madder)
Azadirachta indica (bead tree)	Meliaceae (mahogany)
Berberis vulgaris (European barberry)	Berberidaceae (barberry)
Blighia sapida (akee)	Sapindaceae (soapberry)
Brassica nigra (black mustard)	Brassicaceae (mustard)
Breynia officinalis (chi r yun)	Euphorbiaceae (spurge)
Bryonia alba (white bryony)	Cucurbitaceae (cucumber)
Calendula officinalis (marigold)	Asteraceae (aster)
Callilepis laureola (impila, ox-eye daisy)	Asteraceae (aster)
Camellia sinensis (green tea)	Theaceae (tea)
Capparis spinosa (caper plant)	Capparaceae (caper)
Capsicum annum (chili pepper)	Solanaceae (potato)
Cassia species (senna)	Fabaceae (pea)
Catha edulis (khat, qat)	Celastraceae (bittersweet)
Caulophyllum thalictroides (blue cohosh)	Berberidaceae (barberry)
Cephaelis ipecacuanha (ipecac)	Rubiaceae (madder)
Chelidonium majus (celandine)	Papaveraceae (poppy)
Chenopodium ambrosioides (American wormseed)	Chenopodiaceae (goosefoot)
Chrysanthemum vulgaris (common tansy)	Asteraceae (aster)
Cimicifuga racemosa (black cohosh)	Ranunculaceae (buttercup)

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Genus or species (common name)	Family (common name)
Cinnamonum camphora (camphor tree)	Lauraceae (laurel)
Citrullus colocynthis (colocynth)	Cucurbitaceae (cucumber)
Citrus auranticum (bergamot)	Rutaceae (rue)
Citrus paradisi (grapefruit)	Rutaceae (rue)
Colchicum autumnale (autumn crocus)	Liliaceae (lily)
Conium maculatum (hemlock)	Apiaceae (carrot)
Convolvulus scammonia (Mexican scammony)	Convolvulaceae (morning glory)
Coriandrum sativum (coriander)	Apiaceae (carrot)
Coriaria arborea (tutu)	Coriariaceae
Crataegus species (hawthorn)	Rosaceae (rose)
Crocus sativus (Indian saffron)	Iridaceae (iris)
Crotalaria species (rattlebox)	Fabaceae (pea)
Croton tiglium (croton)	Euphorbiaceae (spurge)
Cyamopsis tetragonoloba (cluster bean)	Fabaceae (pea)
Cycas circinalis (false sago palm)	Cycadaceae (cycad)
Cynara scolymus (artichoke)	Asteraceae (aster)
Cynoglossum officinale (hound's tongue)	Boraginaceae (borage)
Cytisus scoparius (Scotch broom)	Fabaceae (pea)
Datura candida (angel's trumpet)	Solanaceae (potato)
Datura stramonium (Jimson weed)	Solanaceae (potato)
Datura suaveolens (angel's trumpet)	Solanaceae (potato)
Delphinium species (delphinium)	Ranunculaceae (buttercup)
Dictamnus dasycarpus (densefruit pittany)	Rutaceae (rue)
Dionaea muscipula (Venus flytrap)	Droseraceae (sundew)
Dipteryx species (tonka beans)	Fabaceae (pea)
Dryopteris filix-mas (male fern)	Dryopteraceae (wood fern)
Dysosma pleianthum (bajiaolian)	Berberidaceae (barberry)
Ecballium elaterium (squirting cucumber)	Cucurbitaceae (cucumber)
Echinacea species (coneflower)	Asteraceae (aster)
Eleutherococcus senticosus (Siberian ginseng)	Araliaceae
Eucalyptus species (eucalyptus)	Myrtaceae (myrtle)
Euonymus europaeus (spindle tree)	Celastraceae (bittersweet)
Eupatorium species (thoroughwort)	Asteraceae (aster)
Ferula assa-foetida (asafetida)	Apiaceae (carrot)
Gaultheria procumbens (wintergreen)	Ericaceae (heath)
Genista tinctoria (dyer's broom)	Fabaceae (pea)
Gentiana species (gentian)	Gentianaceae (gentian)
Ginkgo biloba (maidenhair)	Ginkgoaceae
Glycyrrhiza glabra (liquorice)	Fabaceae (pea)
Gossypium (cotton)	Malvaceae (mallow)
Harpagophytum procumbens (devil's claw)	Pedaliaceae (sesame)
Hedeoma pulegoides (pennyroyal)	Lamiaceae (mint)
Heliotropium species (heliotrope)	Boraginaceae (borage)
Hintonia latiflora (copalchi bark)	Rubiaceae (madder)
Humulus lupulus (hop)	Cannabaceae
Hydrastis canadensis (golden seal)	Ranunculaceae (buttercup)
Hypericum perforatum (St John's wort)	Clusiaceae (mangosteen)
Illicium species (star anise)	Illiciaceae (star anise)
Inula helenium (elecampane)	Asteraceae (aster)
Ipomoea purga (jalap)	Convolvulaceae (morning glory)
Juglans regia (English walnut)	Juglandaceae (walnut)
Juniperus communis (juniper)	Cupressaceae (cypress)
Krameria species (ratany)	Krameriaceae (Krameria)
Laurus nobilis (laurel)	Lauraceae (laurel)
Lavandula angustifolia (lavender)	Lamiaceae
Ledum palustre (marsh Labrador tea)	Ericaceae (heath)
Lobelia inflata (Indian tobacco)	Campanulaceae (bellflower)
Lupinus species (lupin)	Fabaceae (pea)
Lycium barbarum (Chinese wolfberry)	Solanaceae (potato)
Lycopodium serratum (clubmoss)	Lycopodiaceae (club moss)
Mahonia species (barberry)	Berberidaceae (barberry)
Mandragora species (mandrake)	Solanaceae (potato)
Matricaria recutita (chamomile)	Asteraceae (aster)
Medicago sativa (alfalfa)	Fabaceae (pea)
Melaleuca alternifolia (tea tree)	Myrtaceae (myrtle)
Melilotus officinalis (sweet clover)	Fabaceae (pea)
Mentha piperita (peppermint)	Lamiaceae
Mentha pulegium (pennyroyal)	Lamiaceae (mint)
Momordica charantia (karela fruit, bitter melon)	Cucurbitaceae (cucumber)
Morinda citrifolia (noni)	Rubiaceae (madder)
Myristica fragrans (nutmeg)	Myristicaceae (nutmeg)
Myroxylon species (balsam of Peru)	Fabaceae (pea)
Nicotiana tabacum (tobacco)	Solanaceae (potato)
Oenothera biennis (evening primrose)	Onagraceae (evening primrose)
Panax ginseng (Asian ginseng)	Araliaceae (ginseng)
Papaver somniferum (opium poppy)	Papaveraceae (poppy)
Passiflora incarnata (passion flower)	Passifloraceae (passion flower)
Paullinia cupana (guaraná)	Sapindaceae (soapberry)
Petasites species (butterbur)	Asteraceae (aster)
Pfaffia paniculata (Brazilian ginseng)	Amaranthaceae (amaranth)
Phoradendron flavescens (American mistletoe)	Viscaceae (Christmas mistletoe)
Phytolacca americana (pokeweed)	Phytolaccaceae (pokeweed)
Pilocarpus species (pilocarpus)	Rutaceae (rue)
Piper methysticum (kava kava)	Piperaceae (pepper)
Pithecollobium jiringa (jering fruit)	Fabaceae (pea)
Plantago species (plantain)	Plantaginaceae (plantain)
Polygonum (knotweed)	Polygonaceae (buckwheat)
Prunus species (plum)	Rosaceae (rose)
Psoralea corylifolia (bakuchi)	Malvaceae (mallow)
Pulsatilla species (pasque flower)	Ranunculaceae (buttercup)
Ranunculus damascenus (buttercup)	Ranunculaceae (buttercup)
Raphanus sativus var. niger (black radish)	Brassicaceae (mustard)
Rauwolfia serpentina (snakeroot)	Apocynaceae (dogbane)
Rhamnus purshianus (cascara sagrada)	Rhamnaceae (buckthorn)

Continued

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Table 3 Continued

Genus or species (common name)	Family (common name)
Rheum palmatum (rhubarb)	Polygonaceae (buckwheat)
Rhus species (sumac)	Anacardiaceae (sumac)
Ricinus communis (castor oil plant)	Euphorbiaceae (spurge)
Rubia tinctorum (madder)	Rubiaceae (madder)
Ruscus aculeatus (butcher's broom)	Liliaceae (lily)
Ruta graveolens (rue)	Rutaceae (rue)
Salix species (willow)	Salicaceae (willow)
Salvia miltiorrhiza (danshen)	Lamiaceae (mint)
Salvia officinalis (sage)	Lamiaceae (mint)
Sassafras albidum (sassafras)	Lauraceae (laurel)
Scopolia species (scopola)	Solanaceae (potato)
Scutellaria species (skullcap)	Lamiaceae (mint)
Sechium edule (chayote)	Cucurbitaceae (cucumber)
Selaginella doederleinii (spike moss)	Selaginellaceae (spike moss)
Senecio species (ragwort)	Asteraceae (aster)
Serenoa repens (saw palmetto)	Arecaceae (palm)
Silybum marianum (milk thistle)	Asteraceae (aster)
Sinapis species (mustard)	Brassicaceae (mustard)
Sophora falvescens (ku shen)	Fabaceae (pea)
Stephania species (jin bu huan)	Menispermaceae (moonseed)
Sterculia species (sterculia)	Sterculiaceae (cacao)
Strychnos nux-vomica (nux vomica)	Loganiaceae (Logania)
Swertia species (felwort)	Gentianaceae (gentian)
Symphytum officinale (black wort)	Boraginaceae (borage)
Tanacetum parthenium (feverfew)	Asteraceae (aster)
Taxus species (yew)	Taxaceae (yew)
Teucrium species (germander)	Lamiaceae (mint)
Trifolium pratense (red clover)	Fabaceae
Tripterygium wilfordii (lei gong teng)	Celastraceae (bittersweet)
Tussilago farfara (coltsfoot)	Asteraceae (aster)
Uncaria tomentosa (cat's claw)	Rubiaceae (madder)
Urtica dioica (stinging nettle)	Urticaceae (nettle)
Vaccinium macrocarpon (cranberry)	Ericaceae (heath)
Valeriana (valerian)	Valerianaceae (valerian)
Veratrum species (hellebore)	Liliaceae (lily)
Viscum album (mistletoe)	Viscaceae (Christmas mistletoe)
Vitex agnus-castus (chaste tree)	Verbenaceae (verbena)
Xysmalobium undulatum (xysmalobium)	Asclepiadaceae (milkweed)
Zingiber officinale (ginger)	Rosaceae
Ziziphus jujuba (dazao)	Rhamnaceae (buckthorn)

Table 4 Conversion of common names of plants to Latin names

Common name	Latin name (genus or species)
Akee	*Blighia sapida*
Alfalfa	*Medicago sativa*
Aloe	*Aloe capensis*
Aloe	*Aloe vera*
American mistletoe	*Phoradendron flavescens*
American wormseed	*Chenopodium ambrosioides*
Angel's trumpet	*Datura candida*
Angel's trumpet	*Datura suaveolens*
Areca, betel	*Areca catechu*
Arnica	*Arnica montana*
Artichoke	*Cynara scolymus*
Asafetida	*Ferula assa-foetida*
Asian ginseng	*Panax ginseng*
Autumn crocus	*Colchicum autumnale*
Bajiaolian	*Dysosma pleianthum*
Bakuchi	*Psoralea corylifolia*
Balsam of Peru	*Myroxylon* species
Barberry	*Mahonia* species
Bead tree	*Azadirachta indica*
Bearberry	*Arctostaphylos uva-ursi*
Bergamot	*Citrus auranticum*
Bishop's weed	*Ammi majus*
Black cohosh	*Cimicifuga racemosa*
Black mustard	*Brassica nigra*
Black radish	*Raphanus sativus* var. niger
Black wort	*Symphytum officinale*
Blue cohosh	*Caulophyllum thalictroides*
Brazilian ginseng	*Pfaffia paniculata*
Buchu	*Agathosma betulina*
Butcher's broom	*Ruscus aculeatus*
Butterbur	*Petasites* species
Buttercup	*Ranunculus damascenus*
Calamus root	*Acorus calamus*
Camphor tree	*Cinnamonum camphora*
Caper plant	*Capparis spinosa*
Cascara sagrada	*Rhamnus purshianus*
Castor oil plant	*Ricinus communis*
Cat's claw	*Uncaria tomentosa*
Celandine	*Chelidonium majus*
Chamomile	*Anthemis* species
Chamomile	*Matricaria recutita*
Chaste tree	*Vitex agnus-castus*
Chayote	*Sechium edule*
Chi r yun	*Breynia officinalis*
Chili pepper	*Capsicum annum*
Chinese wolfberry	*Lycium barbarum*
Clubmoss	*Lycopodium serratum*
Cluster bean	*Cyamopsis tetragonoloba*
Colocynth	*Citrullus colocynthis*
Coltsfoot	*Tussilago farfara*
Common tansy	*Chrysanthemum vulgaris*
Common wormwood	*Artemisia vulgaris*
Coneflower	*Echinacea* species
Copalchi bark	*Hintonia latiflora*
Coriander	*Coriandrum sativum*
Cotton	*Gossypium* species
Cranberry	*Vaccinium macrocarpon*
Croton	*Croton tiglium*
Danshen	*Salvia miltiorrhiza*
Dazao	*Ziziphus jujuba*
Delphinium	*Delphinium* species
Densefruit pittany	*Dictamnus dasycarpus*
Devil's claw	*Harpagophytum procumbens*
Dong quai	*Angelica sinensis*
Dutchman's pipe	*Aristolochia* species
Dyer's broom	*Genista tinctoria*
Elecampane	*Inula helenium*
English walnut	*Juglans regia*
Eucalyptus	*Eucalyptus* species
European barberry	*Berberis vulgaris*
Evening primrose	*Oenothera biennis*
False sago palm	*Cycas circinalis*
Felwort	*Swertia* species
Feverfew	*Tanacetum parthenium*
Garlic	*Allium sativum*

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Common name	Latin name (genus or species)
Gentian	*Gentiana* species
Germander	*Teucrium* species
Ginger	*Zingiber officinale*
Golden seal	*Hydrastis canadensis*
Grapefruit	*Citrus paradisi*
Green tea	*Camellia sinensis*
Guaraná	*Paullinia cupana*
Guar gum	*Cyamopsis tetragonoloba*
Hawthorn	*Crataegus* species
Heliotrope	*Heliotropium* species
Hellebore	*Veratrum* species
Hemlock	*Conium maculatum*
Hop	*Humulus lupulus*
Horse chestnut	*Aesculus hippocastanum*
Horseradish	*Armoracia rusticana*
Hound's tongue	*Cynoglossum officinale*
Impila, ox-eye daisy	*Callilepis laureola*
Indian saffron	*Crocus sativus*
Indian tobacco	*Lobelia inflata*
Ipecac	*Cephaelis ipecacuanha*
Jalap	*Ipomoea purga*
Jering fruit	*Pithecollobium jiringa*
Jimson weed	*Datura stramonium*
Jin bu huan	*Stephania* species
Juniper	*Juniperus communis*
Karela fruit, bitter melon	*Momordica charantia*
Kava kava	*Piper methysticum*
Khat, qat	*Catha edulis*
Knotweed	*Polygonum*
Ku shen	*Sophora falvescens*
Laurel	*Laurus nobilis*
Lavender	*Lavandula angustifolia*
Lei gong teng	*Tripterygium wilfordii*
Liquorice	*Glycyrrhiza glabra*
Lupin	*Lupinus* species
Madder	*Rubia tinctorum*
Maidenhair	*Ginkgo biloba*
Male fern	*Dryopteris filix-mas*
Mandrake	*Mandragora* species
Marigold	*Calendula officinalis*
Marsh Labrador tea	*Ledum palustre*
Mexican scammony	*Convolvulus scammonia*
Milk thistle	*Silybum marianum*
Mistletoe	*Viscum album*
Monkshood	*Aconitum napellus*
Mustard	*Sinapis* species
Noni	*Morinda citrifolia*
Nutmeg	*Myristica fragrans*
Nux vomica	*Strychnos nux-vomica*
Opium poppy	*Papaver somniferum*
Pasque flower	*Pulsatilla* species
Passion flower	*Passiflora incarnata*
Pennyroyal	*Hedeoma pulegoides*
Pennyroyal	*Mentha pulegium*
Peppermint	*Mentha piperita*
Pilocarpus	*Pilocarpus* species
Plantain	*Plantago* species
Pleurisy root	*Asclepias tuberosa*
Plum	*Prunus* species
Pokeweed	*Phytolacca americana*
Qinghaosu	*Artemisea annua*
Ragwort	*Senecio* species
Ratany	*Krameria* species
Rattlebox	*Crotalaria* species
Red clover	*Trifolium pratense*
Rhubarb	*Rheum palmatum*
Rue	*Ruta graveolens*
Sage	*Salvia officinalis*
Sassafras	*Sassafras albidum*
Saw palmetto	*Serenoa repens*
Scopola	*Scopolia* species
Scotch broom	*Cytisus scoparius*
Senna	*Cassia* species
Siberian ginseng	*Eleutherococcus senticosus*
Skullcap	*Scutellaria* species
Snakeroot	*Rauwolfia serpentina*
Spike moss	*Selaginella doederleinii*
Spindle tree	*Euonymus europaeus*
Squirting cucumber	*Ecballium elaterium*
St John's wort	*Hypericum perforatum*
Star anise	*Illicium* species
Sterculia	*Sterculia* species
Stinging nettle	*Urtica dioica*
Sumac	*Rhus* species
Sweet clover	*Melilotus officinalis*
Sweet vernal grass	*Anthoxanthum odoratum*
Sweet woodruff	*Asperula odorata*
Tea tree	*Melaleuca alternifolia*
Thoroughwort	*Eupatorium* species
Tobacco	*Nicotiana tabacum*
Tonka beans	*Dipteryx* species
Toothpick weed	*Ammi visnaga*
Tutu	*Coriaria arborea*
Valerian	*Valeriana*
Venus flytrap	*Dionaea muscipula*
White bryony	*Bryonia alba*
Willow	*Salix* species
Wintergreen	*Gaultheria procumbens*
Wormseed	*Artemisia cina*
Wormwood	*Artemisia absinthium*
Xu xin	*Asarum heterotropoides*
Xysmalobium	*Xysmalobium undulatum*
Yarrow	*Achillea millefolium*
Yew	*Taxus* species
Zang qie	*Anisodus tanguticus*

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Hexacarbacholine

General Information

Hexacarbacholine is obsolete. Accounts of its adverse effects will be found in earlier volumes in this series (SED-10, 213) (SEDA-6, 131).

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Hexachloroparaxylene

General Information

Hexachloroparaxylene has been used in China and Russia as an antihelminthic drug, principally to treat the liver fluke infections (clonorchiasis due to *Clonorchis sinensis*, schistosomiasis due to *Schistosoma japonicum*, and opisthorchiasis due to *Opisthorchiidae* (1,2). However, other treatments are preferred. It is also used very extensively in the veterinary field in Russia.

Hexachloroparaxylene causes gastrointestinal reactions, cardiac dysrhythmias (perhaps in over 50% of cases), and nephrotoxicity. Hemolysis can occur both early and late, and death can occur from the hemolytic–uremic syndrome (SEDA-4, 219). Late-onset hemolysis after treatment is associated with beta-thalassemia, while early-onset hemolysis is associated with hemoglobin H disease.

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Hexachlorophene

See also Disinfectants and antiseptics

General Information

Hexachlorophene has been extensively used as an ingredient of innumerable kinds of consumer goods and medical formulations. Since 1961, when it was reported that daily bathing of newborn infants with a 3% hexachlorophene suspension prevented colonization of the skin by coagulase-positive staphylococci, hexachlorophene has been widely used in hospital nurseries.

However, hexachlorophene readily penetrates excoriated or otherwise damaged skin and absorption through intact skin has also been described. The most dramatic complication reported was due to accidental use in talcum powder in neonates, with neurological and other features and many deaths (1). Since then there has been reticence to use hexachlorophene in young infants at all, and certainly the customary 3% emulsion is too strong (2).

As a result of investigations of the toxicity of hexachlorophene in animals and reports of accidental intoxication in France, the FDA in 1972 banned all nonprescription uses of this drug, restricting hexachlorophene to prescription use only, as a surgical scrub and hand-wash product for health-care personnel. Hexachlorophene was excluded from cosmetics, except as a preservative in concentrations not exceeding 0.1%. Other countries followed suit. An extensive critical review of hexachlorophene is given by Delcour-Firquet (3).

Organs and Systems

Respiratory

- Occupational asthma occurred in a pediatric nurse who had worked with hexachlorophene for 15 years (4). The initial symptom was rhinitis but at the time of diagnosis she was also suffering from attacks of asthma.

Nervous system

Neurotoxicity has been observed after dermal application of hexachlorophene to large areas of burned or otherwise excoriated skin, after accidental application of extremely high concentrations on intact skin, and after ingestion. If hexachlorophene is applied in high concentrations or at frequent intervals to the intact skin, excoriation will result, increasing the risk of systemic effects.

In animals, there is a clear relation between dosage, blood concentrations, duration of treatment, and morphological and functional disturbances of the nervous system. In the lower dose range, there is unequivocal histological evidence of neurotoxicity, but without symptoms of neurotoxicity (SEDA-9, 397) (SEDA-11, 486).

Five Chinese patients aged 14–39 years were treated for *Conorchiasis sinensis* infection with oral hexachlorophene 20 mg/kg for 5–6 days (5). They developed nausea, vomiting, diarrhea, abdominal pain, general muscle weakness, and soreness in the eyeballs and legs. Of eight children treated similarly, one became comatose on the fourth day, with temporary loss of light reflex, alternating dilatation and contraction of the pupils, and positive cerebrospinal tract signs (6). The fundus showed papillary edema. Recovery followed symptomatic treatment.

In experimental animals, hexachlorophene can cause cerebral edema (7), and occasional cases have also been reported in humans (8). It affects exclusively the white matter of the brain and spinal cord and produces a spongiform encephalopathy, transforming the white matter into an extensive network of cystic spaces lined by fragments of myelin. Electron microscopy shows intramyelinic edema, with splitting and separation of the myelin lamellae. Nerve damage due to hexachlorophene appears to be reversible, although it takes many weeks for all the holes in the white matter to disappear. However, extensive edema occurring within a rigid structure such as the spinal canal can result in infarction of nervous tissue. In one study of all premature infants who weighed under 1400 g at birth and who survived at least 4 days, there was a significant association between repeated whole-body bathing in 3% hexachlorophene soap (undiluted pHisoHex) and a vacuolar encephalopathy of the brainstem reticular formation (9).

Sensory systems

Optic atrophy has been described after oral or topical use of hexachlorophene (10).

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Second-Generation Effects

Teratogenicity

Teratogenicity has been reported (11), but was not confirmed in an expert review (12). In a 1977 study of Swedish medical personnel it was suggested that repeated handwashing with hexachlorophene-containing detergents during the first trimester of pregnancy could be associated with a greatly increased incidence of both major and minor birth defects in the offspring (11). This publication was the subject of extensive discussion, but it had several serious methodological deficiencies, and the hypothesis that hexachlorophene was teratogenic has never been further examined or confirmed. One reason why it was initially taken seriously was the fact that hexachlorophene crosses the placenta and accumulates in fetal neural tissue in mice and rats; the administration of toxic doses in these species is associated with birth defects, including cleft palate, hydrocephalus, anophthalmia, and microphthalmia in rats.

Topical exposure of male neonatal rats to a commercial hexachlorophene formulation produced significantly reduced fertility, resulting in inability to ejaculate. It was possibly caused by dioxin, an "androgenic" contaminant of hexachlorophene, responsible for permanent disruption of the integrated ejaculatory reflex. However, in subneurotoxic concentrations, hexachlorophene did not seem to cause significant impairment of spermatogenesis in rats or dogs.

Lactation

Hexachlorophene is secreted into breast milk (13).

Susceptibility Factors

Age

The blood concentrations of hexachlorophene, determined during newborn skin care with hexachlorophene bathing, cover a range that varies between studies (14–17) but are similar to the concentrations associated with neurotoxicity in monkeys (18), rats (19), and mice (SEDA-9, 397). In interpreting hexachlorophene plasma concentrations, it must be remembered that most of the hexachlorophene is probably distributed very rapidly into lipophilic tissues and that low plasma concentrations may correspond to high tissue concentrations.

A critical review of the available data on the risk of hexachlorophene bathing or other kinds of hexachlorophene use in neonatal skin care has suggested that there is ample evidence of the toxic potential of this disinfectant. It is absolutely contraindicated in infants with a low birth weight (under 2000 g), excoriated areas of the skin, and raised serum bilirubin. The use of a dusting powder with a maximal concentration of 0.3–0.5% seems to be connected with a lower risk of toxicity, but there was marked absorption of hexachlorophene after the application of 0.33% hexachlorophene dusting powder (20) and further information is needed about the pharmacokinetics of hexachlorophene in neonates.

The view that a small degree of edematous change in the central nervous system caused by hexachlorophene use in neonates should be reversible and is very probably without influence on the further development of the child cannot be accepted, because these changes are certainly the first signs of central nervous system toxicity.

- In a neonate treated with a 3% hexachlorophene lotion which had not been rinsed off, the skin became excoriated 4 days later and there was muscular twitching, which progressed to convulsions (21). Four days after withdrawal of hexachlorophene, the convulsions disappeared; recovery was complete.

In assessing the use of hexachlorophene in the nursery, one also has to consider the fact that infections with highly infective strains of staphylococci, producing serious life-threatening diseases, do not appear to be prevented or aborted by hexachlorophene bathing, and the problem that reduced staphylococcal colonization of infants by hexachlorophene may lead to an increased number of infections with Gram-negative bacteria.

Other features of the patient

Owing to the high absorption rate of hexachlorophene through damaged skin and the risk of fatal intoxication, the use of hexachlorophene in the treatment of burns or on otherwise excoriated skin is strongly contraindicated.

- A 10-year-old boy who had sustained 25% first-degree and second-degree burns and was treated with frequent daily applications of a 3% hexachlorophene emulsion (diluted and undiluted) developed a fatal encephalopathy (7).

In six of eight burned children, including four with a history of convulsive seizures after hexachlorophene use, serum concentrations of hexachlorophene were 4–74 ng/ml (approximately equivalent to blood concentrations of 2–37 ng/ml) (22).

In 1972, six deaths related to the use of hexachlorophene in patients with burns were reported to the FDA (23).

In four children, two of whom were being treated with 3% hexachlorophene baths for burns and two for severe congenital ichthyosis, the interval between exposure and symptoms ranged from 6 hours to 10 days (24). All showed severe vacuolation of the white matter in different areas of the cerebrum and cerebellum.

Drug Administration

Drug administration route

Hexachlorophene in vaginal lubricants is variably absorbed from the vaginal mucosa, and hexachlorophene can be identified in maternal and cord serum in an appreciable number of women in whom vaginal examinations during labor were carried out with a hexachlorophene-containing antiseptic lubricant (25). Because of the potential for neonatal hexachlorophene toxicity, the use of alternative lubricants for pelvic examinations is recommended.

Drug overdose

In France, in 1972, 6% hexachlorophene was accidentally included in certain batches of a baby talcum powder. French law prohibited publication of the detailed report

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on the consequences of this contamination, until litigation was concluded. In 1977, a detailed report of 18 children involved in this accidental poisoning appeared (26) and in 1982 a report described 204 children (SEDA-10, 433) (1). Follow-up investigations of 14 surviving children have also appeared (26). There were no obvious cerebral sequelae, but follow-up was not long enough to exclude the possibility of more subtle damage, which may be manifest by learning difficulties or behavior disorders.

In four cases of accidental ingestion of hexachlorophene in human subjects, anorexia, nausea, vomiting, abdominal cramps, and diarrhea occurred (27). No neurological symptoms were reported.

- Bilateral atrophy of the optic nerve occurred in a 31-year-old woman who had ingested 10–15 ml of a 3% hexachlorophene emulsion orally each day for 10–11 months. She had also applied large amounts of hexachlorophene solution to her face every day as self-treatment for pimples. She was depressed during this period, noted no headache, diplopia, or dizziness, but may have had intermittent numbness of the left foot.
- Acute bilateral optic nerve necrosis occurred in a 7-year-old boy who accidentally received 3% hexachlorophene emulsion (about 12 g) over 52 hours. After the last dose he complained of intermittent blindness. Peritoneal dialysis was ineffective, and he died 98 hours after the last dose.

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Hexanetriol

General Information

1,2,6-hexanetriol is used as a humectant, solvent, and viscosity-controlling agent in medicaments and cosmetics.

Organs and Systems

Immunologic

- A 35-year-old woman had a 3-week history of pruritic erythema, edema, and linear vesiculation of the upper arms where she had applied fluocinonide cream (1). Patch tests with the cream were positive, but the active ingredient fluocinonide (0.05% in petrolatum) was negative, while 1,2,6-hexanetriol 5% showed strong positive reactions on days 3 and 7.

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Hexetidine

See also Disinfectants and antiseptics

General Information

Hexetidine has been used as an oral cavity antiseptic. At the concentration normally used (1 mg/ml), it is effective in vitro against Gram-positive bacteria and *Candida albicans*, but insufficiently active against most Gram-negative bacteria. However, the duration of the reduction in germ count is not longer than 1 hour. When applied to mucosae it also appears to have a mild local anesthetic property. Very little critical work on hexetidine has been published (SEDA-11, 482).

Organs and Systems

Sensory systems

Of 61 patients in whom hexetidine was used as a buccal and pharyngeal antiseptic, a minority, generally those who had just undergone tonsillectomy, complained of a burning sensation and a salty taste (1).

Skin

Allergic contact dermatitis has been reported (SEDA-11, 482) (2).

Drug Administration

Drug administration route

It is not clear whether the use of hexetidine as a spray, of which some will certainly be inhaled, affects its clinical tolerance. Adverse effects were not recorded in 81 patients treated in this way, but the report was not sufficiently detailed for a full assessment (3).

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Hippocastanaceae

See also Herbal medicines

General Information

The family of Hippocastanaceae contains the single genus *Aesculus* (buckeye, horse chestnut).

Aesculus species

Aescin is a complex mixture of triterpene saponins prepared from the seeds of the horse chestnut, *Aesculus hippocastanum*. It consists of a water-soluble fraction (alpha-aescin) and a water-insoluble fraction (beta-aescin).

Adverse effects

A systematic review of randomized trials of extracts of horse chestnut in chronic venous insufficiency showed that adverse effects are usually mild, for example pruritus, nausea, headache, dizziness, and gastrointestinal symptoms (1).

Urinary tract

Beta-aescin has been repeatedly associated with acute renal insufficiency when given intravenously in massive doses. Whether such effects can also occur after oral administration is unclear, as animal studies have shown poor absorption of beta-aescin from the gastrointestinal tract. (SEDA-3, 181) (SEDA-9, 190).

Skin

Contact dermatitis has been ascribed to aescin (2), as has contact urticaria (3).

Drug interactions

Beta-aescin can precipitate renal insufficiency when combined with aminoglycoside antibiotics (SEDA-3, 181) (SEDA-9, 190).

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Histamine H_2 receptor antagonists

See also Individual agents

General Information

The histamine H_2 receptor antagonists are selective antagonists at histamine receptors in the stomach, reducing gastric acid secretion.

The overall safety record of the currently marketed agents, particularly cimetidine and ranitidine, which have had extensive worldwide use, is excellent, and in practice safety issues seldom affect drug choice (1), except perhaps when it is necessary to avoid interactions with phenytoin, theophylline, or warfarin. Surveillance studies, which have been going on for a quarter of a century (including 10-year studies in many patients, mainly involving cimetidine and ranitidine), have failed to detect any serious adverse effects other than those recognized by 1980, or any adverse effect on mortality (2).

The H_2 receptor antagonists do not prevent gastroduodenal ulceration by non-steroidal anti-inflammatory drugs, but they do prevent stress-induced ulceration and bleeding. In intensive care units there is evidence of a beneficial effect, but in patients with hematemesis and melena there is little evidence that H_2 receptor antagonists reduce rates of transfusion, surgical intervention, or mortality (SEDA-19, 326).

Observational studies

The use, efficacy, and adverse effects of non-prescription H_2 receptor antagonists and alginate-containing formulations obtained from community pharmacies have been evaluated in 767 customers with dyspepsia (3). Most obtained some or complete symptom relief (75%) and were completely satisfied with the product (78%). H_2 receptor antagonists were more likely to produce complete relief of symptoms than alginate-containing formulations. Only 3% reported adverse effects: diarrhea, constipation, bloating, and flatulence from alginate formulations, and dry mouth, altered bowel habit, diarrhea, and constipation from H_2 receptor antagonists.

Changes in healthcare utilization resulting from a formulary switch from nizatidine to cimetidine have been studied in 704 patients (4). There was no evidence of increased healthcare utilization during the 6 months after the formulary switch, which led to considerable pharmaceutical savings. During this period only four (0.004%) adverse drug reactions associated with cimetidine were reported; urticaria, nausea and vomiting, leg cramps, and impotence.

Comparative studies

Several treatments are available for promoting the healing of gastric and duodenal ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs). They include histamine receptor antagonists, proton pump inhibitors, and prostaglandin analogues. Two large randomized, double-blind, multicenter trials in a total of 1456 patients have compared the efficacy of ranitidine 150 mg bd with omeprazole 20 or 40 mg/day (ASTRONAUT study) (5) and omeprazole 20 or 40 mg/day with misoprostol 200 micrograms qds (OMNIUM study) (6) in the treatment of NSAID-induced ulcers. The proportions of the patients with treatment success at 8 weeks were 77% with both doses of omeprazole, 63% with ranitidine, and 71% with misoprostol. The most frequent adverse effects were diarrhea in 11% and abdominal pain in 8% of patients taking misoprostol. Both these adverse effects were 2–4 times more frequent with misoprostol than with omeprazole. Withdrawal from the study owing to adverse effects was also more frequent in the misoprostol arm of the OMNIUM study.

Placebo-controlled studies

The effects of ranitidine 75 mg, famotidine 10 mg, and placebo, given 1 hour after a standard lunch, on intragastric acidity have been compared in 24 healthy volunteers (7). Low-dose ranitidine and famotidine reduced acidity significantly more than placebo during the daytime and nighttime. The effect of ranitidine was significantly greater than famotidine during the first 2.5 hours after dosing.

Organs and Systems

Cardiovascular

Rapid intravenous administration of ranitidine, cimetidine, or famotidine can precipitate cardiovascular complications, notably bradycardia, hypotension, and dysrhythmias (SEDA-20, 317).

Hematologic

H_2 receptor antagonists cause a significant reduction in the absorption of vitamin B_{12} from food. This is thought to be due to impaired release of the vitamin from food protein, which requires gastric acid and pepsin as the initial step in the absorption process. This can be sufficient to cause vitamin deficiency and anemia, notably in patients who have low body stores of vitamin B_{12} and are taking an H_2 receptor antagonist over a long period (8).

- Vitamin B_{12} deficiency has been reported in a 78-year-old non-vegetarian white woman with gastro-esophageal reflux who had taken H_2 receptor antagonists and omeprazole for 4.5 years (9).

Pancreas

The risk of acute pancreatitis associated with the use of acid-suppressing drugs has been assessed in a retrospective cohort study with a nested case-control design within the General Practice Research Database in the UK (10). The study included 180 178 people aged 20–74 years who had received at least one prescription for cimetidine, famotidine, nizatidine, ranitidine, lansoprazole, or omeprazole from January 1992 to September 1997, and who did not have major risk factors for pancreatic diseases. There were no cases of pancreatitis among users of famotidine, lansoprazole, or nizatidine. The relative risk compared with non-use, corrected for age, sex, calendar year, and use of medication known to be associated with pancreatitis was 1.3 (95% CI = 0.4, 4.1) for ranitidine, 2.1 (0.6,7.2) for cimetidine, and 1.1 (0.3,4.6) for omeprazole. The results do not support an association between acute pancreatitis and acid-suppressing drugs.

Musculoskeletal

In 33 patients taking cimetidine, ranitidine, or famotidine for more than 2 years there was little effect on the degree of bone mineral density (11).

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Immunologic

Early studies suggested an increased risk of nosocomial pneumonia associated with H_2 receptor antagonists in critically ill patients. To investigate this further, two randomized studies have been performed. One compared ranitidine (0.25 mg/kg/hour intravenously) with sucralfate (1 g every 6 hours via nasogastric tube) for prophylaxis against stress-induced gastritis in 96 severely injured patients (12). Ranitidine was associated with a 1.5 times increased risk of developing any infection compared with sucralfate. Furthermore, of the 49 patients who received ranitidine, 14 developed 26 separate episodes of pneumonia, while of the 47 patients who received sucralfate, 10 developed 14 episodes of pneumonia. The other study, placebo-controlled, compared intravenous ranitidine (50 mg tds) and pirenzepine (10 mg tds) in 158 patients who were being mechanically ventilated; the pneumonia rates were similar in the three groups (13).

In another study of stress ulcer prophylaxis, 53 critically ill patients were randomized to receive sucralfate 1 g 6-hourly, cimetidine 300 mg 8-hourly, or cimetidine 900 mg/day by continuous intravenous infusion (14). Although bacterial colonization was increasingly likely in patients with a persistent alkaline gastric environment, gastric luminal pH and the degree of bacterial colonization of the stomach were similar in the three groups.

Long-Term Effects

Tumorigenicity

Tumor-inducing effects have been much discussed ever since the introduction of the H_2 receptor antagonists but their existence has not been clearly established. The discussion was seeded by:

- findings of intestinal metaplasia of the gastric epithelium in rats used for chronic toxicity studies, though only at extraordinarily high doses, followed by the appearance of intramucosal carcinomas in the pyloric region after 11 months of study;
- reports of patients taking cimetidine in whom gastric carcinoma was diagnosed; however, the drug has been widely (and sometimes without careful prior diagnosis) used in patients with a range of gastric disorders, and some of these are believed to have had early carcinomas at the time when cimetidine was started (15);
- the fact that cimetidine can undergo nitrosylation to form a mutagen;
- the structural resemblance of cimetidine to tiotidine, which can cause gastric carcinoma in animals.

In a retrospective case-control assessment of medical records of 56 patients who died of cardio-esophageal adenocarcinoma and 56 age- and sex-matched controls who died of myocardial infarction, subjects who died of cardio-esophageal adenocarcinoma were more likely to have consumed H_2 receptor antagonists (RR = 7.5; 95% CI = 1.3,42) (16).

However, there is still no valid reason for considering the H_2 receptor antagonists to be tumorigenic, and when studies have detected some excess incidence of gastric cancer in long-term users of H_2 receptor antagonists this was attributable to selection bias (17). The fact that drugs of this type have now been released for self-medication in many countries seems very likely to lead to an increase in the incidence of cases in which an H_2 receptor antagonist is used without prior exclusion of premalignant or malignant change, thus confusing the situation further.

Second-Generation Effects

Teratogenicity

In 178 women who took H_2 receptor antagonists during the first 3 months of pregnancy and 178 pregnant controls there was no evidence of teratogenicity (SEDA-21, 362).

Susceptibility Factors

Renal disease

In patients with renal insufficiency the elimination of H_2 receptor antagonists is subject to significant and clinically relevant alterations (18). Doses should be reduced, and ranitidine bismuth citrate should be avoided altogether in severe renal insufficiency.

Dialysis has no major effect on dosage schedules, because only negligible amounts of H_2 receptor antagonists are removed by this route (SEDA-19, 326).

Drug–Drug Interactions

Alcohol

A meta-analysis of 24 studies showed that cimetidine and ranitidine, but not famotidine or nizatidine, caused small increases in blood alcohol concentrations (19). The mechanism is unclear, but one possibility is inhibition of gastric alcohol dehydrogenase. However, relative to accepted legal definitions of intoxication the effect of any histamine receptor antagonist on blood alcohol concentrations is unlikely to be clinically significant.

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HMG coenzyme-A reductase inhibitors

See also Individual agents

General Information

Statins inhibit HMG-CoA reductase and reduce cellular cholesterol synthesis (1). Lower intracellular cholesterol concentrations cause over-expression of the LDL receptor in the plasma membrane of hepatocytes. This overexpression increases the clearance of circulating LDL, reducing plasma concentrations of LDL cholesterol.

The statins include atorvastatin, bervastatin, cerivastatin, crilvastatin, dalvastatin, fluvastatin, glenvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, and tenivastatin (all rINNs). Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin are covered in separate monographs.

The adverse effects of the statins are mostly limited to slight increases in liver and muscle enzymes in the blood. Hypersensitivity reactions are very rare. There is no evidence of tumor-inducing effects. Second-generation effects are suspected, and statins should not be used during pregnancy.

Organs and Systems

Nervous system

Ratings on a depression scale rose in four out of six men given cholesterol-lowering drugs, in two of them to a degree that met the criteria for mild clinical depression (2).

Statins interfere with the production of isoprene which is somehow connected with sleep, but there have been neither changes in sleep EEG measures relevant to insomnia nor changes in the quality of sleep (SEDA-13, 1327) (3). However, there has been a report of sleep disturbances (4).

- Three months after starting to take metoprolol 100 mg bd and simvastatin 10 mg/day, a 55-year-old man reported restless nights and nightmares, which he had not previously experienced. The dose of metoprolol was reduced to 50 mg bd, with no observable benefit. Simvastatin was withdrawn 2 weeks later and pravastatin 20 mg/day was prescribed, with substantial improvement in the quality of sleep; however, some unpleasant nightmares still occurred. Four weeks later, metoprolol was also withdrawn and atenolol 100 mg/day was prescribed. Thereafter, the quality of sleep was significantly improved, and 6 months later the patient did not report any nightmares. Sleep disturbances recurred after a later attempt to reintroduce simvastatin in place of pravastatin. The same effect occurred when, during treatment with pravastatin, substitution of atenolol with metoprolol was attempted.

In this case, the statins may have interacted with metoprolol, and it may have been relevant that metoprolol is more lipid-soluble than atenolol.

Peripheral neuropathy occurs with statins, and perhaps with all cholesterol-lowering drugs, and may be related to reduced production of ubiquinone, as suggested in a review (5). Moreover, it appears that once a statin produces a neuropathy, rechallenge with any other statin is likely to cause a recurrence. This is reported to occur 1–3 weeks after rechallenge, whereas the resolution takes 4–6 weeks after withdrawal (5).

In a series of seven cases of neuropathy, all were axonal peripheral neuropathies and both thick and thin nerve fibers were affected (6). No cause of peripheral neuropathy other than statin treatment could be identified. In this

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series at least four of the cases were irreversible, probably due to long exposure to statins (4–7 years versus 1–2 years in previous reports). Besides an effect on ubiquinone, interference with cholesterol synthesis may alter nerve membrane function, since cholesterol is a ubiquitous component of human cell membranes. Neuropathy has not been observed in extensive long-term trials of lipid-lowering drugs. It could be due to patient selection, a low frequency of the adverse effect, or lack of attention to symptoms of peripheral neuropathy. The observed association may also not be causal.

In a case-control study of 166 cases of idiopathic polyneuropathy, of which 35 had a definite diagnosis, the odds ratio for neuropathy was 14 for statin users compared with non-users (7).

With the current level of information, it is prudent to consider withdrawal of statins in patients with symptoms compatible with polyneuropathy.

Sensory systems

One should be alert to the possibility of color blindness due to statins (8), although the risk is uncertain.

Owing to the high cholesterol content of the human lens, ocular changes have been looked for during trials with statins. It has been concluded that cataract does not occur. Although the degree of lens opacities increases during treatment, the incidence does not differ from that seen in an untreated control population (9). With fenofibrate serving as control, lovastatin or simvastatin did not reduce visual acuity during treatment for 2 years (SEDA-13, 1328) (10). According to a review, there is no danger during long-term treatment and there should be no requirement for regular ophthalmological examination (11).

Psychological, psychiatric

Animal and cross-sectional studies have suggested that serum lipid concentrations can cause altered cognitive function, mood, and behavior (11).

Metabolism

Although the statins seem to be similar in their ability to lower LDL, there are also dissimilarities. For instance, simvastatin increases HDL cholesterol with increasing doses, whereas atorvastatin does not (12). The clinical significance of this is unknown.

Hematologic

Hematological adverse effects can occur during treatment with both simvastatin and atorvastatin, according to a brief review (13). They include thrombotic thrombocytopenic purpura and severe thrombocytopenic purpura.

Liver

HMG CoA reductase inhibitors can be associated with small rises in alanine transaminase activity, but have not been definitely associated with severe morbidity involving altered hepatic function. All cases of acute liver failure related to the use of lovastatin have been reviewed, and probably the frequency is similar to the background rate. This suggests that periodic monitoring of alanine transaminase in these patients would be burdensome and expensive (14).

The term "transaminitis" has been coined to describe a rise in the activities of serum transaminases without clinical symptoms. One author has suggested that in such cases one should switch from one statin to another, thereby preventing unnecessary withdrawal of statin treatment in dyslipidemic patients at high cardiovascular risk (15).

A return to normal or only slightly increased values of transaminases is often seen after a short period. The overall probability of having an increase in transaminase activity more than three times the top of the reference range is 0.7% (16). The probability may be increased in patients with pre-existing minor hepatic changes, as has been seen in one patient with systemic lupus erythematosus (17). There seems to be no difference between the various drugs in this respect (11), but when simvastatin and atorvastatin, each at a dose of 80 mg/day, were compared in 826 hypercholesterolemic patients there were fewer drug-related gastrointestinal symptoms and clinically significant transaminase rises with simvastatin (18). Frank hepatitis is rare. A cholestatic picture has also been reported (19). The mechanisms of these reactions are not known.

In one series, the frequency of liver toxicity was similar in patients taking pravastatin or simvastatin (20), while in another study there was a difference 6 months after the start of the study when the simvastatin group showed increases in liver enzymes (SEDA-13, 1327) (21).

In a comparison of atorvastatin with pravastatin, of 224 patients taking atorvastatin, two had clinically significant increases in alanine transaminase activity (22). They recovered during the next 4 months, one after withdrawal of atorvastatin and the other after a dosage reduction. Withdrawals due to adverse effects were similar in the two groups. One patient developed hepatitis while taking atorvastatin, but was able to tolerate simvastatin (23). The authors concluded that this adverse effect was not a class effect. Eosinophils in a liver-biopsy specimen pointed to an immunological mechanism.

Pancreas

Pancreatitis has been observed during treatment with simvastatin (q.v.).

- A 77-year-old woman taking rosuvastatin developed acute pancreatitis, which resolved on withdrawal (24). No other cause for the pancreatitis was found. She had had a similar episode 1 year before precipitated by atorvastatin, which resolved on withdrawal.

The authors suggested that pancreatitis may be a class effect of the statins.

Skin

Adverse effects of statins on the skin are rare, although statins can affect cutaneous lipid content. A series of skin reactions have been described in patients using statins (25).

Musculoskeletal

Rhabdomyolysis is a problem with several lipid-lowering drugs (SEDA-13, 1325) (SEDA-13, 1328) (SEDA-13,

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1330) (SEDA-19, 409), especially when they are used in combination (26). In individuals with pre-existing renal insufficiency this can lead to an earlier need for chronic dialysis (27). Interactions between various hypolipidemic drugs and other drugs also sometimes cause rhabdomyolysis (SEDA-18, 426). For instance, itraconazole markedly increases plasma concentrations of lovastatin, and in one subject plasma creatine kinase was increased 10-fold within 24 hours of administration of this combination (28).

In four patients with muscle symptoms while taking statins, creatine kinase activity was normal, but they were subsequently able to distinguish from their symptoms whether they were taking drug or placebo; muscle biopsies showed evidence of mitochondrial dysfunction (29).

Hypothyroidism predisposes to rhabdomyolysis and screening thyroid function has been advocated before starting hypolipidemic drugs (SEDA-21, 458).

Myopathic symptoms, predominantly stiffness and tenderness of proximal limb muscles and difficulty in rising from a low chair, can develop within a month of starting therapy and most cases develop within 3 months. Most patients recover after withdrawal. Sometimes a glucocorticoid is needed to reverse the myopathy. In one patient, histological investigation of muscle biopsies suggested that the myopathy was due, at least in part, to an inflammatory reaction (30). The serum coenzyme Q concentration is reduced by about 30% during statin treatment, because the enzyme is carried by LDL particles, although the concentrations during long-term treatment are equal to those in healthy controls (SEDA-13, 1328) (31,32). Ubiquinone (coenzyme-Q) is part of the oxidative respiratory pathway generating ATP, and deficiency could impede the function of myocytes, leading to an increase in serum creatine kinase and even cell destruction, with release of myoglobin, which in its turn can block kidney tubules and thereby produce anuria.

- Simvastatin 5 mg/day caused rhabdomyolysis in a 61-year-old man who was not taking concomitant interacting drugs (33).
- An elderly lady with chronic renal insufficiency developed rhabdomyolysis during simvastatin therapy (34). Her symptoms of muscle pain, fatigue, myoglobulinuria, oliguria, and pulmonary edema occurred 48 hours after the first dose of simvastatin. Simvastatin was immediately withdrawn, and she was dialysed for 1 week.

Myopathy, defined as muscle symptoms with a rise in creatine kinase greater than 10 times the upper limit of the reference range, was found in one study in only one patient who was taking 40 mg od and in four patients taking 80 mg/day, out of a total of 8245 patients. The number of patients with rhabdomyolysis was, according to postmarketing reporting from the first million individuals taking lovastatin, 24 in all. Seventeen of those had taken other medications that are known to increase the risk (35). There is some evidence that patients with other concomitant illnesses may be at greater risk of myopathy than would be anticipated from experience in controlled trials.

Diplopia may be an early sign of generalized drug-induced muscle dysfunction. Altogether, 71 cases of diplopia, possibly related to various HMG-CoA inhibitors, have been collected from adverse drug reactions-reporting databases. The information was mostly too scanty to judge a causal relation, but improvement occurred in 33 on withdrawal, and two patients had positive rechallenge data (36).

- A 67-year-old woman had ocular myasthenia while taking various statins and also bezafibrate (37). Atorvastatin had the smallest effect.

The authors suggested that this was a variant of a generalized myopathy and was due to a low co-enzyme Q10 concentration.

Exercise-induced muscle pain, without myopathy and a rise in creatine kinase activity, can probably be caused by statins. This has been described in seven patients with heterozygous familial hypercholesterolemia and consisted of pain during exercise and cramps in the following hours (38).

Symptomatic rises in creatine kinase activity to over 10 times the upper end of the reference range occurred in 0, 1, and 0.9% of patients taking placebo, cerivastatin 0.4 mg, or cerivastatin 0.8 mg respectively (39), and rhabdomyolysis has been described in patients taking cerivastatin (40,41). However, in a review of the pharmacological properties and therapeutic efficacy of cerivastatin in hypercholesterolemia, it was stated that cerivastatin only infrequently causes rhabdomyolysis when given alone (42).

Four cases of tendinopathy have been reported in three men and one woman taking statins (43). The diagnoses were extensor tenosynovitis in the hands, tenosynovitis of the tibialis anterior tendon, and Achilles tendinopathy. Two patients were taking simvastatin and two atorvastatin. The tendinopathy developed 1–2 months after the start of treatment. The outcome was consistently favorable within 1–2 months after drug withdrawal.

Sexual function

Erectile dysfunction has been reported in 12% of 339 men treated with fibrate derivatives or statins, compared with 5.6% of similar patients not taking these drugs (44). The mechanism is unknown and should be confirmed in randomized studies. A class effect has been suggested by the case of a 57-year-old man who had impotence after taking lovastatin for 2 weeks and also when he later tried pravastatin (45).

Immunologic

Lupus-like symptoms have been reported in patients taking statins (46).

Long-Term Effects

Tumorigenicity

It has been suspected that low concentrations of serum cholesterol might be associated with an increased risk of cancer or overall mortality. All fibrates and statins cause cancer in rodents, but the relevance of this finding to man has been questioned (47). In an epidemiological study these risks were almost non-existent after adjusting for confounding factors. However, in the CARE study, breast cancer occurred in one patient in the control group and 12 in the pravastatin group (48). The incidence of cancers,

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both during clinical studies and up to 9 years after, has been reassuring (49).

Drug–Drug Interactions

General

Many statins are metabolized by CYP3A4, and this and other mechanisms of drug interactions involving statins have been reviewed (50). Other drugs metabolized by CYP3A4 can greatly increase statin concentrations in the body and precipitate rhabdomyolysis. Although the statins are similar in their ability to lower cholesterol concentrations, there are dissimilarities in their interactions with other drugs.

With the exception of fluvastatin and pravastatin, the statins are metabolized by CYP3A4. Selective inhibition of CYP3A4 or of P-glycoprotein (50) in the small intestine probably increases the systemic availability of CYP3A4 substrates. Some drugs that are metabolized by this enzyme, such as the macrolide antibiotics and the antidepressant nefazodone, can greatly enhance the concentrations of statins in the body and thereby precipitate rhabdomyolysis. However, other drugs that are metabolized by CYP3A4, such as cimetidine, have not been reported to have this effect.

Antifungal azoles

The antifungal azoles inhibit CYP isozymes and can therefore interact with some statins.

Fluconazole

In a randomized, double-blind, crossover study in 12 healthy volunteers, fluconazole increased the plasma concentrations of fluvastatin and prolonged its elimination; the mechanism was probably inhibition of the CYP2C9-mediated metabolism of fluvastatin (51). Care should be taken if fluconazole or other potent inhibitors of CYP2C9 are given to patients using fluvastatin.

Itraconazole

The effects of itraconazole, a potent inhibitor of CYP3A4, on the pharmacokinetics of atorvastatin, cerivastatin, and pravastatin have been evaluated in an open, randomized, crossover study in 18 healthy subjects who took single doses of atorvastatin 20 mg, cerivastatin 0.8 mg, or pravastatin 40 mg, with and without itraconazole 200 mg (52). Itraconazole markedly raised atorvastatin plasma concentrations (2.5-fold) and produced modest rises in the plasma concentrations of cerivastatin (1.3-fold) and pravastatin (1.5-fold). These results suggest that in patients taking itraconazole, cerivastatin or pravastatin may be preferable to atorvastatin.

Physicians should check for lipid-lowering drugs before treating elderly individuals with itraconazole (53). Susceptibility to this interaction varies from statin to statin, in that simvastatin is more affected than pravastatin (54). Concomitant use of simvastatin with itraconazole should be avoided, and the same holds true for atorvastatin (55). In another study, the blood concentration of fluvastatin was not significantly increased, whereas that of lovastatin was (56).

Ketoconazole

Ketoconazole can also cause rhabdomyolysis when taken with both lovastatin and simvastatin (57).

Chlorzoxazone

- A 73-year-old woman had rhabdomyolysis, cholestatic hepatitis, and mild renal insufficiency 14 days after she started to take the centrally acting muscle relaxant chlorzoxazone while also taking simvastatin (58). Withdrawal of the causal medication and conservative therapy with volume substitution and forced diuresis was followed by almost complete resolution of the symptoms.

The authors believed that either the two drugs had interacted by metabolism through the same hepatic enzyme, or that chlorzoxazone had caused cholestasis which then increased the blood concentration of simvastatin.

Ciclosporin

Most drug interactions associated with rhabdomyolysis occur when ciclosporin is combined with simvastatin or lovastatin. It has been suggested that if a statin is to be combined with ciclosporin, pravastatin or fluvastatin should be chosen instead (59).

Coumarin anticoagulants

Interactions of statins with warfarin, resulting in an increased bleeding tendency, have been reported (35), including interactions of anticoagulants with both lovastatin (35) and fluvastatin (60).

Three patients taking fluvastatin 20 mg/day had raised international normalized ratios (INRs), with a risk of bleeding (61).

- A 67-year-old man receiving a stable maintenance dosage of warfarin experienced an increased INR without bleeding when his atorvastatin therapy was switched to fluvastatin. His warfarin dosage was reduced and his INR stabilized. The fluvastatin was switched back to atorvastatin, and the warfarin dosage was increased to maintain the patient's goal INR (62).

In 46 adults taking warfarin, a change from pravastatin to simvastatin caused a significant increase in INR from 2.42 to 2.74 without an overall change in the dose of warfarin; there were no unusual episodes of bleeding (63).

In three patients taking stable warfarin dosages with INRs in the target range, the INRs increased when fluvastatin was added (60). Although none had a bleeding episode, they did require a reduction in their weekly warfarin dosage to achieve an appropriate degree of anticoagulation.

In contrast, in 12 patients chronically maintained on warfarin, atorvastatin 80 mg/day for 2 weeks had no important effect on mean prothrombin time (63).

In 21 healthy men, cerivastatin 300 micrograms did not alter the pharmacokinetics of *R*- and *S*-warfarin, or the pharmacodynamics of a single oral dose of warfarin 25 mg (64).

In a patient given the anticoagulant acenocoumarol, the INR increased from the target range (2–3.5) to 9.0, 3 weeks after starting simvastatin 20 mg/day. It is

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conceivable either that the two drugs competed for hepatic metabolism or that the oral anticoagulant was displaced from plasma albumin by simvastatin (65). The former mechanism is supported by the observation that pravastatin, which is only bound 50% to albumin, interacted with the anticoagulant fluindione and raised the INR (66).

Diltiazem

Diltiazem interacts with lovastatin but not with pravastatin (67). In 10 healthy volunteers given lovastatin orally with or without intravenous diltiazem in a randomized, two-way, crossover design, the interaction of diltiazem with lovastatin was primarily a first-pass effect, due to inhibition of CYP3A4 (68). Thus, drug interactions with diltiazem may become evident when a patient is switched from intravenous to oral dosing.

Fibrates

In a retrospective series, 4 (5%) out of 80 subjects taking lovastatin and gemfibrozil developed a myopathy. Based on this and on reports to US Food and Drug Administration the combined use of the two drugs is discouraged, especially in patients with compromised renal and/or hepatic function. Elderly women may be at special risk (69,70).

Some investigators have concluded that rare drug-induced reversible hepatotoxicity calls for close monitoring of liver enzymes in long-term treatment with statin-fibrate combinations (71).

Combination therapy with fluvastatin and bezafibrate 400 mg/day in 71 patients with persistent hypertriglyceridemia resulted in no significant increase in creatine kinase activity or in the frequency of myalgia (72).

- In contrast, although in vitro studies have not shown any evidence of pharmacokinetic interactions between cerivastatin and gemfibrozil (42), there was myalgia and a marked increase in creatine kinase in a 74-year-old woman with normal renal function who took gemfibrozil 1200 mg/day 3 weeks after she started to take cerivastatin 0.3 mg/day (41).

Since then several other cases have been described:

- a 64-year-old woman (73)
- a 63-year-old man with diabetes mellitus (74)
- a 75-year-old man (75)
- a 68-year-old man (76).

The last patient fared well on a combination of gemfibrozil and cerivastatin until he received influenza vaccination. Rhabdomyolysis has been reported with various viruses, including influenza A and B and inactivation of the virus does not totally prevent this.

Gemfibrozil also increased plasma concentrations of simvastatin and its active form, simvastatin acid, in a randomized, double-blind, crossover study in 10 healthy volunteers given gemfibrozil or placebo orally for 3 days before a single dose of simvastatin (77). This suggests that the increased risk of myopathy in combination treatment is at least partly pharmacokinetic in origin. Because gemfibrozil does not inhibit CYP3A4 in vitro, the mechanism of the pharmacokinetic interaction is probably inhibition of non-CYP3A4-mediated metabolism of simvastatin acid.

Grapefruit juice

Grapefruit juice inhibits CYP3A4, and serum concentrations of atorvastatin, but not of pravastatin, increased after administration of double-strength grapefruit juice 200 ml tds for 2 days (78).

When 10 healthy volunteers took simvastatin 24 hours after a large amount of grapefruit juice in a non-randomized, crossover study, the effect on the AUC of simvastatin was only about 10% of the effect observed when grapefruit juice and simvastatin were taken together (79). The interaction potential of even large amounts of grapefruit juice with CYP3A4 substrates dissipates within 3–7 days after ingestion of the last dose.

HIV protease inhibitors

Healthy volunteers were given protease inhibitors and statins, and the authors concluded that simvastatin should be avoided and that atorvastatin could be used with caution in people taking ritonavir and saquinavir (80). Dosage adjustment of pravastatin may be necessary with co-administration of ritonavir and saquinavir. Pravastatin does not alter the pharmacokinetics of nelfinavir, and thus appears to be safe for co-administration.

Macrolides

The macrolide antibiotic erythromycin together with statins enhances the risk of rhabdomyolysis (SED-13, 1328) (81), as do clarithromycin and azithromycin (82).

Nefazodone

The antidepressant nefazodone increases the risk of rhabdomyolysis from statins (83).

Red yeast rice

Rhabdomyolysis in a stable renal transplant recipient was attributed to the presence of red yeast rice (*Monascus purpureus*) in a herbal mixture (84). The condition resolved when he stopped taking the product. Rice fermented with red yeast contains several types of mevinic acids, including monacolin-K, which is identical to lovastatin. The authors postulated that the interaction of ciclosporin with these compounds through cytochrome P450 had resulted in the adverse effect. Transplant recipients must be cautioned against using herbal products to lower their lipid concentrations, in order to prevent such complications.

St John's wort

St John's wort induces CYP3A4 and reduces blood concentrations of CYP3A4 substrates. In one study, St John's wort reduced plasma concentrations of simvastatin but not pravastatin (85).

Troglitazone

When troglitazone was added in four men with diabetes using insulin and taking atorvastatin, serum LDL cholesterol and triglycerides increased by 23 and 21%

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respectively (86). This suggests a drug interaction, but further studies are warranted to substantiate this.

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Hormonal contraceptives—emergency contraception

See also Estrogens

General Information

For a complete account of the adverse effects of estrogens, readers should consult the following monographs as well as this one:

- Diethylstilbestrol
- Estrogens
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens
- Hormone replacement therapy—estrogens + androgens
- Hormone replacement therapy—estrogens + progestogens

A review of the English language literature has shown that in the USA, the source of most of the evidence, the two most commonly used forms of emergency contraception are the Yuzpe regimen (high-dose ethinylestradiol + high-dose levonorgestrel) and "Plan B" (high-dose levonorgestrel alone) (1). Although both methods sometimes stop ovulation, they may also act by reducing the probability of implantation, through an effect on the endometrium (the "post-fertilization effect"). The available evidence for the latter mechanism is moderately strong. If this is the manner in which development of a zygote is prevented one would anticipate a certain proportion of failures, with the possibility of second-generation injury. This finding also has potential implications in such areas as informed consent, emergency department protocols, and conscience clauses, since it is more in the character of abortion than true contraception, making the term "emergency contraception" or "post-coital contraception" a slight misnomer.

Estrogens

Various estrogens and estrogen + progestogen combinations have been used in post-coital contraception. Courses of high-dose oral diethylstilbestrol, ethinylestradiol, conjugated estrogens, or combinations of estrogen and progestogen for 4–6 days are all effective. Estrogens are postovulatory rather than post-coital contraceptives, and so it is necessary to know the exact time of unprotected intercourse in relation to a woman's menstrual cycle (2). Depending on the frequency and timing of intercourse, a 5-day course of post-coital estrogen, introduced within 72 hours, gives a pregnancy rate of 0.03–0.3%.

Diethylstilbestrol has been widely used as a post-coital contraceptive. However, it is no longer in use in many countries for this purpose, because of the possible adverse effect on the development of a surviving fetus (see separate monograph).

Ethinylestradiol has been used in the past as a post-coital contraceptive, with a daily dose of 5 mg/day for 5 days. This method has a high incidence of adverse reactions, nausea, vomiting, and breast tenderness being the most frequent (3); the first menstrual cycle after treatment is likely to be abnormal.

Progestogens

Clinical trials of desogestrel implants showed that they were effective, but with bleeding irregularities and ovarian cysts as the primary adverse effects (4).

The "morning after" method of suppressing pregnancy is usually less well tolerated than normal hormonal contraception, and variants on the dosage schedule continue to be studied in an attempt to improve tolerability without undermining the reliability of the method.

Two regimens for emergency contraception started within 72 hours of unprotected coitus have been studied: (a) the progestogen levonorgestrel in two separate doses each of 0.75 mg; (b) the Yuzpe regimen of combined oral contraceptives—ethinylestradiol 100 micrograms + levonorgestrel 0.5 mg repeated 12 hours later (5). The relative risk of pregnancy for levonorgestrel compared with the Yuzpe regimen was 0.36 (95% C1 = 0.18, 0.70). Nausea and vomiting were significantly less frequent with the levonorgestrel regimen. Adverse effects of both regimens were nausea, vomiting, dizziness, fatigue, headache, breast tenderness, and low abdominal pain. However, all of these adverse effects were less frequent with levonorgestrel.

Estrogen + progestogen combinations

In recent years it has become common to use a combination of estrogen and progestogen for post-coital contraception. For example, a tablet containing ethinylestradiol 100 micrograms and levonorgestrel

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0.5 mg (or norgestrel 1 mg) taken twice with an interval of 12 hours has been used (6). This treatment must begin within 72 hours of unprotected intercourse. The approach seems to be as effective as ethinylestradiol alone, while producing somewhat less nausea and vomiting (7). Apart from this the adverse effects most commonly experienced are as with estrogen alone. Overall failure rates are about 2–3%, with perhaps twice this failure rate when taken at mid-cycle. However, bearing in mind the rate of pregnancy after unprotected intercourse, the protective effect is not impressive; the chance of pregnancy is probably only halved.

It is probably impossible to define an ideal dose for this purpose. Essentially the aim is to provide a sufficient hormonal jolt to derange nidation and the development of the zygote, and this might be attained in various ways; the most acceptable dosage schemes will be those that are best tolerated. Because oral contraceptives are generally more readily available than specially formulated products, they have sometimes been used for this purpose in deliberate overdose. Even low-dose oral contraceptives, if taken in sufficient quantities, will prove effective post-coital contraception (8); progestogen-only tablets are also effective in a single dose, for example levonorgestrel 0.6 mg taken within 12 hours, but irregular bleeding, nausea, and dizziness are common adverse effects (SEDA-16, 466).

The FDA has approved a marketing application for the Prevent Emergency Contraceptive Kit (Gynetics), which contains tablets for post-coital emergency contraception, packaged with a urinary pregnancy test. The application is based on a regimen that consists of two tablets containing ethinylestradiol and levonorgestrel to be taken within 72 hours of unprotected intercourse and two tablets to be taken 12 hours later. This regimen is about 75% effective in preventing pregnancy. The most common adverse effects are nausea, vomiting, menstrual irregularities, breast tenderness, headache, abdominal pain and cramps, and dizziness (9).

Androgens

The synthetic androgen danazol has also been evaluated for post-coital use, but with inconsistent results (8); doses of twice 400 mg or twice 600 mg seem to be reliable while a single dose of 600 mg seems to be insufficient. A 10% incidence of vomiting, headache, and breast tenderness has been reported and a lower incidence (1–2%) of vomiting (10).

Antiprogesterones

The antiprogesterone mifepristone, almost exclusively used as an abortifacient, has also been tried as a post-coital contraceptive (11). In one randomized comparative trial, a single dose of mifepristone 600 mg was at least as effective as the usual hormonal method (12). Women who took mifepristone had lower rates of adverse effects, particularly nausea and vomiting, but their next menstrual period was more likely to be delayed. In another randomized trial, both methods were equally effective (SEDA-16, 466). The use of an estrogen + a progestogen had a higher total incidence of adverse effects, but mifepristone was associated with the greatest cycle disruption. If mifepristone was given in the follicular phase, 52% of women had a delay of 4 days or more in the onset of their next menstrual period (indicating that ovulation had been inhibited); when it was given in the luteal phase, 84% of women menstruated on time.

Physical methods

A non-hormonal approach to emergency contraception is insertion of an intrauterine contraceptive device up to 7 days after ovulation in a cycle during which unprotected intercourse has occurred (13).

Comparison of methods

The combined estradiol + levonorgestrel (Yuzpe regimen), the levonorgestrel-only regimen, and post-coital copper intrauterine devices have been compared by the Clinical Practice Gynaecology and Social and Sexual Issues Committees of the Society of Obstetricians and Gynaecologists of Canada. Sponsor: The Society of Obstetricians and Gynaecologists of Canada (13) and the following recommendations made:

1. Women who have had unprotected intercourse and want to prevent pregnancy should be offered hormonal emergency contraception up to 5 days after intercourse.
2. A copper IUCD can be used up to 7 days after intercourse in women who have no contraindications.
3. Women should be advised that the levonorgestrel regimen is more effective and causes fewer adverse effects than the Yuzpe regimen.
4. Either one double dose of the levonorgestrel regimen (1.5 mg) or the regular two-dose levonorgestrel regimen (0.75 mg each dose) can be used, as they have similar efficacy with no difference in adverse effects.
5. Hormonal emergency contraception should be started as soon as possible after unprotected sexual intercourse.
6. Women of reproductive age should be provided with a prescription for hormonal emergency contraception in advance of need.
7. The woman should be evaluated for pregnancy if menses have not begun within 21 days after emergency contraception.
8. A pelvic examination is not indicated for the provision of hormonal emergency contraception.

Second-Generation Effects

Pregnancy

In pregnancies that occur after failure of progestogen-only emergency oral contraception, the possibility of ectopic pregnancy should be considered, according to a Prescriber Update article recently posted on the New Zealand Medsafe website (14). This may occur by the same mechanism by which pregnancies in women using daily progestogen-only oral contraceptives are more likely to be ectopic than pregnancies in users of other contraceptive methods. The Centre for

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Adverse Reaction Monitoring has received three reports of ectopic pregnancies after the use of progestogen-only emergency oral contraceptives, and prescribers are reminded to advise women about the possibility of ectopic pregnancy after failure of progestogen-only emergency oral contraceptives. Women should seek prompt medical attention if, after using a progestogen-only emergency oral contraceptive, amenorrhea or any other symptoms suggestive of pregnancy occur.

Susceptibility Factors

Post-coital contraception should not be used when there are absolute contraindications to estrogen; these include pregnancy, unstable angina, transient ischemic attacks, liver disease, undiagnosed genital bleeding, or a history of thromboembolism. Some absolute contraindications to long-term use, such as breast cancer and arterial disease, are not contraindications to short-term use (15).

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Hormonal contraceptives—intracervical and intravaginal

See also Progestogens

General Information

The intracervical and intravaginal methods of contraception have not come into regular use, and experience with them has therefore been limited.

For a complete account of the adverse effects of progestogens, readers should consult the following monographs as well as this one:

- Hormonal contraceptives—progestogen implants
- Hormonal contraceptives—progestogen injections
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens + progestogens
- Medroxyprogesterone
- Progestogens.

Intracervical contraceptives

When an intracervical device releasing levonorgestrel 20 mg/day was studied in 198 women over 2 years of use, a total of seven pregnancies occurred (1). All began during the first year and six occurred after the unnoticed expulsion of the device. One pregnancy occurred in an epileptic woman taking carbamazepine, while the intracervical device remained in place. In three cases the device was removed because of infection, in all three instances during the first year of use; in one case *Neisseria gonorrhoeae* was found and in another *Chlamydia trachomatis*. During the study, mean body weight increased, but remarkably there was a statistically significant reduction in the mean diastolic and systolic blood pressures after 1 and 2 years of use compared with the pre-insertion values.

Intravaginal contraceptives

As early as 1978, the vaginal administration of steroids for contraceptive purposes was attempted, at that time using vaginal rings containing medroxyprogesterone acetate or both norgestrel and estradiol. It was later found that complete inhibition of ovulation could as a rule be attained by the daily intravaginal application of a product containing norethisterone 1 mg and mestranol 50 micrograms (2).

Progestogen-only vaginal rings

Vaginal administration of steroid-containing polymer rings has been studied for at least 25 years as a means of

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contraception, without gaining wide acceptance. In a large multicenter WHO trial with a levonorgestrel ring, releasing 20 micrograms/day, the 1-year pregnancy rate was 4.5% (3). The main reason for discontinuation was menstrual disturbances (17%), followed by frequent expulsion of the ring and vaginal symptoms.

The finding of erythematous lesions in the vagina in some women has led to the development of a more flexible device. The Population Council has also developed a vaginal ring containing Nestorone progestin (16-methylene-17α-acetoxy-19-norpregn-4-ene-3,20-dione) for 6 months of continuous use (4). Ovulation inhibition was achieved in over 97% of the segments studied, with rings releasing 50, 75, or 100 micrograms/day. No pregnancies occurred in women who used the low-dose ring, while one pregnancy each occurred with the intermediate-dose and high-dose rings, for 6-month cumulative pregnancy rates of 0.0, 1.9, and 2.1% respectively; it is not clear why the reported pregnancy rates were higher with the higher doses. However, bleeding irregularities were common, and this form of contraception still demands further development work.

A low-dose levonorgestrel vaginal ring has also been studied. Women using vaginal rings releasing levonorgestrel 20 mg/day had more bleeding or spotting days than women using other hormonal contraceptives, with menstrual patterns similar to those of progestogen-only tablet users (5). Irregular and infrequent bleeding was also recorded by some women. Analysis of menstrual calendar data from WHO phase III clinical trials showed that the percentage of women who experience bleeding patterns defined as "acceptable" increases steadily from 39% in the first 3 months to 56% during months 10–12 (6). Frequent and irregular bleeding were the most common problems. In another study in 108 women there were four pregnancies during 1 year of investigation, with a discontinuation rate of 71%. Menstrual disturbances were the main adverse effects and also the most common reason for discontinuation, occurring in 45% of cycles during the first month (7).

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Hormonal contraceptives—male

General Information

The notion that an oral contraceptive closely similar to that used in women might be developed for men has been discussed for about 45 years, but the concept has not yet found wide acceptance. Delays in putting the concept into practice have related variously to difficulties in finding an effective combination, complaints of reduced libido or potency, and the long delay between the start of treatment and the attainment of azoospermia.

Of the many possible formulations tested all have proved to have unacceptable facets, generally including a very slow onset of action, uncertain reliability, and undesirable effects on biochemistry, body weight, or sexual function. However, some progress has been made with the combination of oral desogestrel and intramuscular testosterone.

In a study of the effects of various combinations of desogestrel and testosterone, including a sequential pattern, the optimal dosage to induce azoospermia seemed to be desogestrel 300 micrograms/day by mouth and testosterone enantate 50 mg weekly by intramuscular injection (1). Among 24 subjects, there were no withdrawals clearly related to the treatment. During weeks 1–3, adverse effects were reduced sex drive ($n = 4$), tiredness ($n = 1$), and a sensation of depression ($n = 1$); during weeks 4–24 they included mild acne ($n = 10$), increased sexual interest ($n = 3$), emotional lability ($n = 2$), tiredness ($n = 2$), night sweats ($n = 1$), and headache ($n = 1$). However, laboratory studies showed that desogestrel had clear effects on lipid metabolism in dosages of 150 micrograms/day or more, with reductions in HDL cholesterol, apolipoprotein, A1 lipoprotein, sex hormone binding globulin, and to some extent total cholesterol and LDL cholesterol. If this approach can be developed to provide a more convenient dosage scheme, these biochemical changes will be among those that need to be followed carefully.

A combination of oral desogestrel 150 or 300 micrograms + intramuscular testosterone 50 or 100 mg has been tested in 24 young men and compared with historical data from studies on a combination of oral levonorgestrel + intramuscular testosterone (2). All the doses tested achieved azoospermia. All the groups tended to gain weight compared with their baseline, but the weight gain was greatest (and statistically significant) in men who received the higher dose of testosterone. Adverse effects were acceptably low; acne occurred in occasional cases, but no one developed gynecomastia.

In a similar study limited to 8 weeks, the various formulations rapidly suppressed LH and FSH to a similar extent, irrespective of dosage, while testosterone concentrations fell slightly during treatment, with evidence of a linear dose-response relation (3). There were minor changes in plasma concentrations of inhibin B, but in seminal fluid it was suppressed, becoming undetectable in all the men who took desogestrel 300 micrograms/day. There were no significant changes in

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lipoproteins, fibrinogen, or sexual behavior during treatment, and only minor falls in hematocrit and hemoglobin concentration.

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Hormonal contraceptives—oral

General Information

For a complete account of the adverse effects of estrogens, readers should consult the following monographs as well as this one:

- Diethylstilbestrol
- Estrogens
- Hormonal contraceptives—emergency contraception
- Hormone replacement therapy—estrogens
- Hormone replacement therapy—estrogens + androgens
- Hormone replacement therapy—estrogens + progestogens.

For a complete account of the adverse effects of progestogens, readers should consult the following monographs as well as this one:

- Hormonal contraceptives—implants
- Hormonal contraceptives—progestogen injections
- Hormonal contraceptives—intracervical and intravaginal
- Hormone replacement therapy—estrogens + progestogens
- Medroxyprogesterone
- Progestogens.

Hormonal contraception relies on the actions of estrogens and progestogens, of which oral contraceptives contain a mixture. The adverse effects of the separate components are discussed in other monographs.

The commonly available combinations of oral contraceptives include (estrogen first):

- ethinylestradiol + desogestrel
- ethinylestradiol + levonorgestrel
- ethinylestradiol + norethisterone
- ethinylestradiol + norgestimate
- mestranol + norethisterone.

Other forms of administration include:

- implantation
- intracervical administration
- intramuscular injection
- intravaginal administration
- transdermal administration.

These forms of contraception are covered in other monographs.

Efficacy

Hormonal contraceptives based on combinations of estrogen + progestogen, administered cyclically each month, are among the most effective forms of contraception. During typical use, only some 3% of women using combined oral contraceptives become pregnant in the first year of use, despite the failures of compliance that inevitably occur (1). The pregnancy rate for progestogen-only oral contraceptives is somewhat higher, about 5% (2). Compared with the original high-dose combination products, the lower dosages now in current use offer a smaller margin for error if tablets are missed; the efficacy of progestogen-only contraceptives is even more dependent on correct use. The accidental pregnancy rates for injectable and implanted hormonal contraceptives are lower than for the oral products, primarily because they do not depend on the daily taking of a tablet. The 1-year pregnancy rate for depot medroxyprogesterone acetate (injectable) is 0.3% and for levonorgestrel implants 0.09%.

Mechanisms of action

Estrogen and progestogen together inhibit gonadotropin secretion and thus prevent ovulation. Estrogen also stabilizes the endometrium and potentiates the action of the progestogen. In addition, the progestogen has contraceptive effects on the cervical mucus (thickening the mucus to make it hostile to sperm penetration), the endometrium (interfering with implantation), and the fallopian tubes (altering ovum transport). The original fixed-dose combinations have given way to formulations that contain lower doses, as well as to variants on the principle. The estrogen dosage, originally 150 micrograms or more, today normally lies in the range of 30–35 micrograms ethinylestradiol; even lower doses have been investigated, but these result in an unsatisfactory bleeding pattern and have little effect on ovulation. Doses of progestogens have fallen from the 5 mg (or even 10 mg) originally in use in 1960 to 1 mg or less today. To calculate the dose of progestogen that offers the highest benefit-to-harm balance is not easy, particularly since the relative potency of any progestogen can be expressed in various ways (for example in terms of its effect on the human endometrium, its androgenic or corticosteroid potency, or its ability to inhibit ovulation); these do not run parallel to one another and it is not at all clear which of these activities are relevant to the various long-term safety issues.

Progestogen-only products do not have inhibition of ovulation as their main effect; up to half of all cycles are ovulatory, and the contraceptive potential relates largely to changes in the consistency of the cervical mucus and the creation of a hostile environment for the sperm, as

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well as changes in tubal motility and ovum transport; after a period of treatment, endometrial atrophy occurs, rendering nidation unlikely.

Unusual combinations

Ethinylestradiol + chlormadinone acetate
In 19 650 women who had received six cycles of treatment with chlormadinone acetate 2 mg and ethinylestradiol 30 micrograms, cycle control was good, with beneficial reductions in intracyclic bleeding, severe withdrawal bleeding, dysmenorrhea, and amenorrhea (3). At baseline, 70% of the women had androgen-related skin disorders. After six cycles of chlormadinone acetate 2 mg + ethinylestradiol 30 micrograms, these disorders were improved in 87% of patients, including 29% who had complete resolution. The incidence of greasy or very greasy hair fell from 47 to 17%. There were two cases of venous thromboembolism. Breast pain (3.6%) and migraine or headache (2.6%) were the most frequently reported adverse events, but these symptoms disappeared in most women (85 and 80%) who had had them before treatment.

Ethinylestradiol + drospirenone
The effects of a monophasic oral contraceptive containing drospirenone 3 mg and ethinylestradiol 30 micrograms on pre-existing premenstrual symptoms has been studied in 326 women during 13 menstrual cycles (4). There were beneficial effects on water retention and appetite. Concentration was not significantly affected, and assessments of undesired hair changes and feelings of well-being did not change appreciably. There were no adverse effects of note.

Cyproterone acetate + a progestogen
There has been a single report of autoimmune hepatitis with the combination of cyproterone acetate and a progestogen (5). Similar events have been described very occasionally with other oral contraceptives and with diethylstilbestrol; they are not unique to cyproterone.

General adverse effects

The incidence of common adverse reactions to oral contraceptives varies with population and product. Many users have some mild reactions during the initial months of treatment, which disappear entirely as use continues; a small proportion of users withdraw at an early phase, because of individual intolerance, and turn to other methods of contraception. Relatively common adverse effects of combined oral contraceptives include intermenstrual bleeding, nausea or vomiting, breast tenderness, and headaches, although reactions are highly individual and problems can often be overcome by changing to a formulation with a greater or lesser content of active substances. Some women develop mild fever. Occasionally, oral contraceptive users report depression (or more usually a vague sensation of malaise), reduced libido, acne, or weight gain. Women taking combined oral contraceptives are also at greater risk of *Chlamydia* infection and of modest impairments of glucose and lipid metabolism. The most serious complications attributable to oral contraceptives are cardiovascular diseases, but these are extremely rare and are even less common now, with lower-dose formulations, than in earlier decades; these much discussed risks are reviewed separately above. Hypersensitivity reactions have been observed, but only very rarely.

Tumor-inducing effects are discussed in the monograph on estrogens. The risks of epithelial ovarian and endometrial cancer are reduced by combined oral contraceptives. Effects on other cancers are slight.

Overall benefit-to-harm balance of combined oral contraceptives

A comprehensive analysis by The Alan Guttmacher Institute in the USA in 1991 evaluated the health risks of various contraceptive methods, as well as the health risks of a normal female reproductive life without contraceptives (6). Because combined oral contraceptives are highly effective, they prevent pregnancy-related deaths, particularly those associated with ectopic pregnancy. This factor more than offsets the small increased risk of cardiovascular disease related to current use, resulting in averted deaths at all ages (ranging from 3.9 per 100 000 current users at ages 15–19 up to 19 per 100 000 at ages 40–44 in the USA). They also prevent future deaths from ovarian and endometrial cancers (from 23 per 100 000 at ages 15–19 to 10 per 100 000 at ages 40–44). Current oral contraceptive use also prevents 1614 hospitalizations per 100 000 users annually. Most of these avoided hospital admissions are because of prevention of the complications of pregnancy, but they also include a reduced rate of hospitalization due to ovarian cysts, benign breast disease, upper genital tract infection, urinary tract infection, and invasive cancers of the ovary and endometrium. The conditions for which hospitalization rates may be slightly increased among combined oral contraceptive users include: myocardial infarction; stroke; venous thrombosis and embolism; invasive cancers of the breast, cervix, and liver; cervical intraepithelial neoplasia; and gallbladder disease.

Data from the classic Nurses' Health Study, followed up in 1994, reflected no difference in all-cause mortality between women who had ever used oral contraceptives and those who had never used them (7). There was also no increase in mortality associated with duration of use and no relation with time since first use or time since last use. Similarly, in the OFPA (Oxford) study, the overall 20-year mortality risk for oral contraceptive users compared with women using diaphragms or IUCDs was 0.9, suggesting no effect (8). Although the number of deaths from each cause was small, the pattern is consistent with the risks found in other studies. Oral contraceptive users had somewhat higher death rates from ischemic heart disease and cervical cancer, but lower rates of ovarian cancer mortality. Breast cancer mortality was similar for oral contraceptive users and non-users.

In developing countries, wherever there is a high maternal mortality rate, the risk of oral contraception is low in comparison (9). For all women in developing countries below the age of 40, oral contraceptive use is substantially safer than no method at all or traditional methods, about as safe as IUCDs, but not as safe as

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sterilization or as traditional methods backed by legal abortion performed by trained physicians.

Some of the risks have only become evaluable with much longer experience, for example those relating to the development of malignancies (covered in the monograph on estrogens). Data on these matters, too, seem reassuring; any cancer-promoting effect in one direction is at least counterbalanced by the reduction of risk in another.

Any consideration of major issues relating to the balance of benefit and harm, such as cancer or mortality rates, should be supplemented by a consideration of less prominent ones, for example, a reduction in disorders of the menstrual cycle (such as dysmenorrhea, menorrhagia, and the premenstrual syndrome) and the reduced risks of iron deficiency anemia, functional ovarian cysts, uterine fibroids, benign breast disease, pelvic inflammatory disease, and ectopic pregnancy (10,11).

Finally, since much of the work relates to high-dose products, it is important to stress that more recent work and reviews have confirmed the even greater relative safety of lower-dose products, although one must now express concern that the third-generation products may have increased certain risks once more. All the same, the broad picture of the safety of oral contraception is reassuring. Even at an earlier stage, such authoritative workers as Vessey and Doll (12) emphasized that the medical and social benefits of using oral contraceptives considerably outweighed the risks, while emphasizing the need to contain such risks as there are, that is by careful patient selection and supervision and by the use of oral contraceptives with the lowest possible dosages.

Progestogen-only oral contraceptives

Progestogen-only oral contraceptives are taken continuously and not cyclically. They not only lack the estrogen component of combined oral contraceptives but also have a lower dose of progestogen than even the current low-dose combined oral contraceptives. Progestogen-only contraceptives are therefore indicated for women who desire oral contraception but who have contraindications to or poor experience with the estrogen in combined oral contraceptives, who are breastfeeding, who are older (especially smokers), or who simply wish to keep their exogenous hormone doses to a minimum (11). The drawbacks of progestogen-only contraceptives are that menstrual irregularity is common and that careful compliance is necessary in order to achieve high efficacy.

The pharmacokinetics of progestogens in progestogen-only contraceptives are somewhat different from those in combined oral contraceptives, because of the interaction of estrogen and progestogen in the combination products. One of the major differences is that, as noted above, the plasma concentrations of progestogen rise over time in users of combined oral contraceptives; this does not happen in women taking progestogen-only contraceptives. The change is due in part to estrogen stimulation of serum hormone-binding globulin (SHBG) production, increased binding of progestogen to SHBG, and reduced progestogen clearance with combined oral contraceptives. In contrast, progestogen-only contraceptives cause reduced SHBG concentrations and modest falls in progestogen concentrations over time.

Organs and Systems

Cardiovascular

The cardiovascular complications of oral contraceptives include venous thrombosis and thromboembolism, arterial damage, and hypertension.

Venous thromboembolism

A central issue almost from the beginning of the oral contraceptive era has been the undoubted ability of these products to increase the risk of thromboembolic and allied complications. It was the dominant reason for the progressive reduction in hormonal content of these products during their first 20 years; it led at one point to a precipitate and poorly motivated replacement of mestranol by ethinylestradiol as the estrogenic component; and rightly or wrongly it has played a central role in the recent debate concerning modified products based on newer progestogens.

History

The fact that some women could develop thromboembolic complications as a result of taking oral contraceptives first emerged in 1961, although at that time the evidence was anecdotal and poorly quantified. The first reasonably quantified investigation conducted on a sufficient scale to merit conclusions was published in 1967 by the UK Medical Research Council (13). This and other large studies conducted during the early years (and considered in older volumes in this series) concluded that women using oral contraceptives ran a greater risk than non-users of developing deep venous thrombosis, pulmonary embolism, cerebral thrombosis, myocardial infarction, and retinal thrombosis. Later papers and case reports described deep venous thrombosis, portal venous thrombosis, and pulmonary embolism (14–16). The Boston Collaborative Drug Surveillance Program follow-up study of more than 65 000 healthy women in 1980–82 found a positive association between current oral contraceptive use and venous thromboembolism (rate ratio 2.8); there was also a positive association between current oral contraceptive use and stroke or myocardial infarction (17). A UK study using data from 1978, by which time lower-dose products were increasing in use, pointed to an approximate doubling of the risk of thromboembolism compared with controls (SEDA-7, 387). The early 1980s were nevertheless marked by a series of critical papers that sought to question the entire concept of there being a link.

Much of the work on both sides of the argument was less than watertight. Some studies failed to consider the confounding effects of other risk factors (notably smoking) or the likelihood of detection bias (particularly for venous thromboembolism, which is much more common in young women than myocardial infarction or stroke). The results of some studies were also confounded by uncertainties in the history of drug exposure. A landmark

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paper to resolve the issue concluded that the link with venous thromboembolism in subjects without predisposition had been consistently observed in case-control and cohort studies (18). However, the evidence regarding myocardial infarction, various types of stroke, and cardiovascular mortality was less consistent. By 1990, an international Consensus Development Meeting reached agreement on the following statement regarding the relation between oral contraceptive use and cardiovascular disease (19):

> The majority of epidemiological studies strongly suggest an association between current oral contraceptive use and certain cardiovascular deaths. Although the relative risk is increased, the absolute risk is small. Because the risk of myocardial infarction is apparent in current users, disappears on cessation of use, and is not associated with duration of use, there is no epidemiologic support for the hypothesis that risk of cardiovascular diseases is of atherogenic origin .... Whether particular formulations or progestogens have qualitative advantages or disadvantages merits further study. Estrogens and progestogens interact at many levels, and in epidemiologic studies of users of combined oral contraceptives it is difficult to assign a risk to either component separately. Moreover, it is physiologically unsound to do so .... Alterations in plasma lipid, carbohydrate, and hemostasis variables are of major importance for the development of cardiovascular diseases, and their concentrations can be influenced by sex steroids, including artificial steroids contained in oral contraceptives. The pharmacodynamic responses ... are dependent on not only the type and dosage of sex steroids, but also on intra- and interindividual variability in pharmacokinetics.

Frequency

It has been confirmed that the incidence and mortality rates of thrombotic diseases among young women are low (20). However, the risk is increased by oral contraceptives and there is variation in the degree of risk, depending on the accompanying progestogen. The spontaneous incidence of venous thromboembolism in healthy nonpregnant women (not taking any oral contraceptive) is about five cases per 100 000 women per year of use. The incidence in users of third-generation formulations is about 15 per 100 000 women per year. The incidence in users of third-generation formulations is about 25 per 100 000 women per year: this excess incidence has not been satisfactorily explained by bias or confounding. The risks of venous thromboembolism increase with age and is likely to be increased in women with other known factors for venous thromboembolism, such as obesity. The risk in pregnancy has been estimated at 60 cases per 100 000 pregnancies.

The Medicines Commission of the UK has reviewed all currently available relevant data and has confirmed that the incidence of venous thromboembolism is about 25 per 100 000 women per year of use (21). The incidence of venous thrombembolism in users of second-generation combined oral contraceptives is about 15 per 100 000 women per year of use. This indicates a small excess risk of about 100 000 women-years for women using third-generation combined oral contraceptives containing desogestrel or gestodene, which has not been satisfactorily explained by bias or confounding. However, the absolute risk of venous thromboembolism in women taking combined oral contraceptives containing desogestrel or gestodene is very small and is much less than the risk of venous thromboembolism in pregnancy.

The incidence of venous thromboembolic disease in about 540 000 women born between 1941 and 1981 and taking oral contraceptives was 4.1–4.2 cases per 10 000 woman-years (22).

In another study, the figures ranged from 1895 events per 100 000 women-years when norgestimate was used to 3969 per 100 000 women-years when desogestrel was used (23). Although the authors did not find the difference statistically significant, it runs parallel to findings from other work regarding a higher risk when third-generation progestogens are used.

In women aged 15–29 years who used oral contraceptives containing third-generation progestogens, venous thromboembolism was twice as common as arterial complications. In women aged 30–44 years of age the number of arterial complications exceeded the number of venous complications by about 50%. However, in women under 30 years, deaths from arterial complications were 3.5 times more common than deaths from venous complications and in women aged 30–44 years 8.5 times more common. Women over 30 years of age who take oral contraceptives containing third-generation progestogens may have a lower risk of thrombotic morbidity, disability, and mortality than users of second-generation progestogens. However, a weighted analysis such as this does not result in any consistent recommendation of a particular progestogen type.

Nevertheless, some groups continue to produce data from their own systems that fail to confirm this. Some of these studies, including unpublished data circulated to experts for purposes of special pleading, have used selected material, and one can only consider them flawed. On the other hand, Jick et al. may be entirely right in their finding that, insofar as the special risk of idiopathic cerebral hemorrhage is concerned, no material difference in risk has been demonstrated between products of the second generation and those of the third generation (24).

And in another study it was found that users of oral contraceptives with second-generation progestogens have 30% greater increased risk of thrombotic diseases, a 260% greater increased risk of thrombotic deaths, and a 220% greater increased risk of post-thrombotic disability than users of oral contraceptives with third-generation progestogens (20).

Effects of dosage and formulation

As noted above, the early recognition of thromboembolic complications had repercussions for the formulation of the oral contraceptives; the progestogen and estrogen contents were both progressively reduced, and in 1969/70 mestranol was replaced by ethinylestradiol, on the grounds that the dose could thereby be halved (although it is not at all certain that this reduced the estrogenic

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contribution to thromboembolic events). By the late 1980s, when a major cohort study based in Oxford examined the problem (8), products containing estrogen 50 micrograms accounted for about 70% of the woman-years of tablet use, most of the remainder being accounted for by lower doses.

By the mid-1990s it was reasonably well proven that progressive dose reduction had reduced the risk of thrombotic complications (25). Epidemiological studies showed that users of low-dose combined products had small, and often statistically non-significant, rises in the risks of myocardial infarction (SEDA-16, 465) (26,27), thrombotic stroke (28–30), venous thromboembolism (31), and subarachnoid hemorrhage (28,30,32). Several of these studies compared the risks presented by different doses and found somewhat higher rates for products containing more than 50 micrograms of estrogen but somewhat lower rates among women currently using the lower-dose formulations (26,28,29,33).

A group in The Netherlands has stressed the fact that even though the risk of venous thrombosis is small in absolute terms, oral contraceptives form the major cause of thrombotic disease in young women. The risk is higher during the first year of use (up to one per 1000 per year), among women with a prothrombotic predisposition, and with third-generation progestogens (34).

Presentation

The commonest presentation is deep venous thrombosis in the leg, which can lead to pulmonary embolism. Fatal pulmonary embolism has even been reported after intravenous injections of conjugated estrogens (35). Despite the improvement noted with reduced doses, incidental case reports of severe cardiovascular events during the use of low-dose products have continued to appear. They include incidents of cerebral venous thrombosis and subarachnoid hemorrhage, fatal central angiitis, sinus thrombosis, and cerebral ischemia. In one series of 22 cases of cerebral infarction involving either arteries or veins, all the oral contraceptives that had been used contained a low dose of ethinylestradiol (36). Thromboembolism in other veins, such as the hepatic vein, that is Budd–Chiari syndrome, has occasionally been reported (37); the first 10 such cases were reported as long ago as 1972 and the increasing number since then has at times raised some concern (SEDA-6, 344) (SEDA-7, 386). A case of renal vein thrombosis has also occurred (38). Incidental reports continue to appear of thrombotic incidents in relatively unusual forms, including a further case of mesenteric thrombosis leading to intestinal necrosis (39) and a report of fatal pulmonary embolism following intravenous injections of conjugated estrogens (35).

The incidence of hepatic veno-occlusive disease in 249 consecutive women treated with norethisterone who underwent allogenic hemopoietic stem cell transplantation was 27% compared with 3% in women without this treatment (40). One-year survival rates were 17% and 73% in patients with ($n = 24$) or without veno-occlusive disease ($n = 225$) respectively. Because of this adverse effect, norethisterone should not be used in patients undergoing bone-marrow transplantation. Heparin prophylaxis does not affect the risk of death from veno-occlusive disease.

Susceptibility factors

By 1980 it was considered clear that the risk of thromboembolic events was further increased under particular conditions. It was higher in smokers, in older women, and in the obese, and appropriate warnings were issued. The fact that these warnings to a large extent eliminated the high-risk individuals who had formed part of the early population of oral contraceptive users means that data from the early period cannot be used to provide a valid historical comparison with later findings (41,42).

Thrombotic diathesis

Early epidemiological data on the recurrence of thrombosis (43) indicated something of an inherited predisposition, and others found a low content of fibrinolytic activators in the vessel wall of women who 6–12 months earlier had experienced a thrombotic complication while using oral contraceptives (44); high doses of estrogen affected the concentrations of such activators (45). However, such lesions are apparently not exclusive to users of oral contraceptives (SEDA-8, 360) and examination of the vessel wall is not of predictive value in determining risk.

The risk of venous thrombosis among carriers of the factor V Leiden mutation is increased eight-fold overall and 30-fold among carriers who take an oral contraceptive (46,47). This mutation results in resistance to activated protein C and thereby potentiates the prothrombotic effect of oral contraceptives. Early work suggested a greater risk after major surgery (48,49). However, epidemiological studies of postoperative venous thromboembolism are limited and disputed (50). There is no documented excess risk of postoperative thrombosis associated with low-dose combined oral contraceptives among women without other risk factors (51). If it is correct that some effects on coagulation persist for several weeks, it is wise to withdraw these products a month before surgery (50). From a practical point of view, any decision regarding possible discontinuation of combined oral contraceptives before surgery should take into consideration the need for alternative and adequate contraception during the interim. If the woman chooses to stop taking combined oral contraceptives, progestogen-only formulations (as well as barrier methods) are deemed suitable (50). A recommended alternative to discontinuation of a combined oral contraceptive is heparin in low doses (51).

Age

The increase in risk with age is clear (6), although the underlying risk of cardiovascular disease also rises as age progresses. The US Food and Drug Administration has concluded that the benefits may outweigh the risks in healthy non-smoking women over age 40, and it has in most countries been common for over two decades to advise reticence in the use of oral contraceptives after the age of 35.

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Obesity

Obesity has repeatedly been shown to play a role, and its relevance to particular types of complication has been demonstrated. The Oxford Family Planning Association's 1987 data showed that the risk of myocardial infarction or angina increased significantly with weight (52).

Smoking

Smoking has been very clearly incriminated as a susceptibility factor for thromboembolism and arterial thrombosis in women taking the oral contraceptive, and its apparently synergistic role has been well defined and quantified (53,54). The 1989 case-control analysis of the RCGP cohort study estimated the relative risk of myocardial infarct during current oral contraceptive use at only 0.9 for non-smokers, but at 3.5 for women smoking under 15 cigarettes per day, and as much as 21 for users of more than 15 cigarettes per day (55). Smoking increases not only the risk of myocardial infarction among oral contraceptive uses (27), but also the risk of angina pectoris (52), thrombotic stroke (28,29), and subarachnoid hemorrhage, and it can double or treble mortality (56–58). There has also been further confirmation that the effect is dose-related, light smokers having twice the risk of coronary heart disease and heavier smokers having up to four times the risk, compared with non-smokers; cessation of smoking is accompanied by a reduction in risk of coronary heart disease to the level prevalent among non-smokers within 3–5 years (54).

Smoking contributes to effects on the procoagulation process in young women (59). The effects of oral contraceptives on the coagulation system are much greater in smokers than non-smokers (44). Oral contraceptive users who were smokers generally have significantly lower fibrinolytic activity than non-smokers (60), but not consistently (61).

Others

Women of blood group O have less of a risk of thromboembolism (15). The risk of thromboembolic complications may be greater where there is a history of diabetes, hypertension, and pre-eclamptic toxemia. In some studies there has been an association with type II hyperlipoproteinemia, hypercholesterolemia, and atheroma (62–66). Hypertension may be an additional risk factor when considered in relation to oral contraceptive use.

Mechanisms

Study of the mechanisms that might underlie the link between oral contraceptives and thromboembolic events is of importance in developing safer formulations, but also in identifying, if possible, individuals at particular risk who should be advised to change to alternative contraceptive methods.

The 1990 international consensus statement cited above noted that: "Oral contraceptives induce alterations in hemostasis variables. There are changes in the concentrations of a large number of specific plasma components of the coagulation and fibrinolytic systems, although usually within the normal range .... It is conceivable that these effects are estrogen-mediated because they have not been demonstrated in progestogen-only preparations. There is a dose-dependent relationship in the case of estrogen, although in combination tablets, the progestogens might exert a modifying effect .... Further attention should be given to changes in factor VIIc and fibrinogen induced by oral contraceptives and also to the association between carbohydrate metabolism and fibrinolysis."

Quantification of coagulation factors is notoriously difficult, because of the interrelations among the various components of the coagulation cascade, the broad range of normal values, and considerable inter-laboratory variability (51). This variability is illustrated by a WHO study of users of combined oral contraceptives, conducted on several continents, which showed statistically significant differences among clinical centers in prothrombin time, fibrin plate lysis, plasminogen, and activated partial thromboplastin time (SEDA-16, 464). Effects also vary between different populations, users of different doses, users of different products, and tests performed at different periods of the medication cycle (61,67).

The term "hypercoagulability" has been used to describe a supposed pre-thrombotic state, identifiable by certain changes in the hemostatic system, but to date there is no broad-spectrum laboratory test for assessing the risk of thrombosis in a given individual, although coagulation changes in vitro have sometimes been regarded as proof of a thrombotic state. Deviations in laboratory data from patients with thromboses have often been interpreted as demonstrating the cause of the thrombosis, whereas they may simply be a consequence.

Despite the variations that are found, the overall conclusion is that oral contraceptives cause an increase in coagulation factors I (fibrinogen), II, VII, IX, X, and XII, and a reduction in antithrombin III concentrations, which would be expected to predispose to venous thromboembolism, especially if not counterbalanced by an increase either in fibrinolytic activity or of other inhibitory proteins of the coagulation, such as protein C (68).

There is also fairly strong evidence that immunological mechanisms play a role in thrombotic episodes associated with oral contraceptives, especially when they occur in the absence of risk factors for vascular disease (69), although this has been contested (70). In one series of reports on cerebral infarction, circulating immune complexes and/or specific antihormone antibodies were found in 15 of 20 patients (36). In a large series of women with venous or arterial thrombosis, anti-ethinylestradiol antibodies were absent in non-users but present in 72% of users; they were also present in 33% of healthy oral contraceptive users without thrombosis (SEDA-16, 465). In half of the cases there were both anti-ethinylestradiol antibodies and a history of smoking were found jointly in half of the cases.

There is a significant rise in fibrinogen concentrations during the early months of oral contraceptive use, and concentrations return to baseline after withdrawal (71). Prolonged use of oral contraception also seems to lower concentrations of antiaggregatory prostacyclin (72).

Some work that was considered to show severe acquired plasma resistance to activated protein C among users of third-generation (as opposed to second-generation)

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products has been re-examined by a French group (73). In their view the technical measures used to demonstrate the effect of activated protein C introduced a bias of interpretation and hence false results; they have further argued that such a test cannot demonstrate the presence of a raised thromboembolic risk in asymptomatic women taking these contraceptives, since it is non-specific and subject to changes in the plasma concentrations of many coagulation factors that are themselves increased or decreased by estrogens and progestogens. They point, for example, to protein S (74), changes in which account for the differential effect of oral contraceptives on Rosing's assay (75), but which are in their view irrelevant to issues of thromboembolic risk with oral contraceptives; the androgenic potential of the progestogen may further counteract the effect of estrogens in the test. More generally, in such a complex situation in which there is a "modification of the modification," there is no hemostasis-related test that provides a risk indicator for thrombosis. This argument is sound, but it naturally remains theoretical; the question of thromboembolism with the third-generation products must, as pointed out above, be resolved on the basis of epidemiological data, and certainly those data now strongly point to an increased risk.

Relative roles of estrogens and progestogens

The risk of thrombosis is closely associated with the estrogen component (76) for both arterial and venous events and with the progestogen for arterial events; however, if a particular progestogen is metabolized to estrogen or raises estrogen concentrations, it will make a contribution to venous complications. Estrogen alone has after all been incriminated as a cause of thromboembolism when given to men (77); the risk of puerperal thromboembolism after estrogen inhibition of lactation has been shown in several studies (78); non-contraceptive estrogens clearly increase the risk of acute myocardial infarction in women under 46 years of age (79). Changes in coagulation factors appear to be related to the estrogen dose (44,45,80,81). Progestogen-only formulations do not have any significant effect on the coagulation system.

Third-generation oral contraceptives and thromboembolism

There are now reasons to doubt whether the third-generation oral contraceptives are indeed safer than their predecessors in respect to thromboembolism and substantial grounds for believing that they present greater risks.

The first reason is theoretical. The demonstrated effects of the new substances and combinations on lipids and carbohydrates do not have any major relevance to the thromboembolic process. The latter is linked primarily to changes in the hemostatic system and blood coagulation, involving platelet aggregation, coagulation factors, fibrinogen concentrations, and blood viscosity.

The second reason is kinetic. It is true that the dose of estrogen (probably the main instrument in inducing thromboembolism) has been kept to a minimum, but the new progestogen gestodene tends to accumulate in the system with continued use, and the concentrations of ethinylestradiol increase simultaneously; this increase is due to the ability of gestodene to inhibit cytochrome P450 and therefore to inhibit the breakdown of estrogen, as well as its own metabolism (82). Similar findings emerged with desogestrel, although they were somewhat less marked (83).

The third reason is hematological. The third-generation contraceptives have greater adverse effects on the clotting system than those of the second generation. In particular, women using the third-generation products have a greater resistance to activated protein C (84), a shift that is associated with a higher risk of thrombosis.

The fourth reason is epidemiological. During the period 1987–88, when the third-generation products were relatively new, anecdotal reports of thromboembolic events appeared, including at least one death, and partly for this reason a series of large controlled studies were set up. The findings of three such studies (British, European, and global) became available to the drug control authorities late in 1995 and were subsequently published. The UK Committee on Safety of Medicines, considering all three, concluded that the risk of venous thromboembolic events in these third-generation oral contraceptives was about double that in users of the previous generation of products using the older progestogens (30 as opposed to 15 per 100 000 woman-years, the risk in healthy women being only five per 100 000). Despite the different populations studied, the individual studies produced broadly consistent results. The global study on four continents found a relative risk of 2.6 when comparing the desogestrel/gestodene products with the older variety, while the European study found a relative risk of 1.5–1.6. Various later papers pointed in the same direction. In Denmark, there was an increase in hospital admissions for primary venous thromboembolism in young women coinciding with the introduction of the third-generation products (85). Papers from The Netherlands have confirmed the main trend (86,87).

Authoritative reviews and editorials have further confirmed the correctness of the above findings. There has been some criticism of the individual studies on various points of detail, but it is difficult to see that this in any way undermines what is now very consistent evidence that the third-generation oral contraceptives increase the risk of thromboembolic events to a substantially greater degree than previous products. Some work that has been advanced as pointing to the safety of third-generation products (88) proves to relate primarily to the second-generation combinations, with only a few late entrants using the more recent oral contraceptives, and other work was performed on a very small scale.

As a rule, the study of adverse reactions must relate to current and emergent issues. However, now and again it can be instructive to look back into recent history. When a drug problem has been fairly clearly defined, and particularly when it has for a time been the subject of debate and even frank controversy, one can learn something from the processes involved. How did the facts become known? Why did the controversy emerge? And could the risk have been detected and eliminated earlier?

Since their appearance in the late 1950s, oral contraceptives have gone through several stages of development. What are now in retrospect referred to as

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first-generation oral contraceptives were high-dose combinations of progestogens (more particularly norethynodrel, norethisterone, and lynestrenol in doses of 2.5 mg or more) and the estrogen mestranol 75 micrograms. A decade later a second generation emerged, with substantially lower doses, commonly half of those used earlier and some new progestogens, notably the more potent levonorgestrel. Finally, in the early 1980s some manufacturers introduced so-called third-generation products, a particular characteristic of which was the use of entirely new, very potent progestogens, among them desogestrel and gestodene. Clinical studies of contraceptives that contained gestodene and desogestrel suggested that they are very similar to one another, although differences in dosage and potency could account for reports that products that contain gestodene provide better cycle control (89).

Almost from the earlier years, the risk of thromboembolic complications among users of "the pill" was recognized, and by the mid-1960s it was well documented (90,91). Progressive reductions in dosage, in particular that of the estrogenic component, during the period that first- and second-generation products held sway were widely regarded as having reduced this risk to manageable proportions, although it was not eliminated. The relative risk with first-generation products was highly variable (2–11), but the best work in the UK and the USA fairly consistently reached an estimate of 4–6 (92–94). With the second-generation products the relative risk of thromboembolic complications was again variously estimated, but a large cohort study published in 1991 set it at 1.5 with products containing the lowest doses of estrogen, and 1.7 with products containing intermediate doses of estrogen (33).

The fact that both prescribers and users of medicines are likely to anticipate that new drugs will be in some way better than those that have gone before means that both groups are in principle receptive to potentially spurious claims and suggestions. By the time the third-generation oral contraceptives were marketed, this type of contraception had been around for a quarter of a century; the risk of thromboembolism, the most widely publicized problem in the field, seemed by that time to have receded with progressive reductions in dosage. There was every reason to hope that it would recede further with the newest generation of products. That expectation was further nurtured by the even lower doses latterly attainable. It also seems to have been fostered by some of the suggestive promotion that appeared, although that in fact related as a rule merely to an improved lipid spectrum, which in turn raised the theoretical possibility, also discussed but not documented by some clinical investigators (95), that arterial and cardiac risks might be less.

What in fact happened was that by 1989 alarm bells began to ring in Germany, where the regulatory authorities were alerted to the submission of an unusually high number of spontaneous reports of thromboembolic complications thought to be associated with the new products. Cases continued to accumulate, long-term studies already begun were completed, and in 1995 Britain's Committee on Safety of Medicines made a public statement to the effect that the risk of thromboembolic complications among hitherto healthy users of third-generation products was approximately twice than that seen with second-generation products (SEDA-19, xix). The studies in question, including work by the World Health Organization and others (SED-14, 1410), were subsequently published and confirmed that conclusion, as did later work (96). It was further reinforced by others (97), who worked on a smaller scale but provided well-documented evidence that while a factor V Leiden mutation or a biased family history could increase the risk in individual cases, they did not explain the higher thrombosis risk seen with a product based on desogestrel than with contraceptives that incorporated levonorgestrel, norethisterone, or lynestrenol.

Currently one must ask why the particular risk of the third-generation contraceptives was identified so late. These third-generation products had been in development since the late 1970s and the first had been marketed in 1981–82, some 14 years before the Committee on Safety of Medicines issued its statement. Could society not have done better and thereby reduced the risks to which women were exposed? There are two principal answers, both of them at least partly in the affirmative.

The first is that products of this type could well have been entered at an earlier date into large studies of oral contraception and their effects. A series of university centers around the world, as well as bodies such as Britain's Royal College of Physicians and Royal College of General Practitioners, have throughout the oral contraceptive era either sponsored or participated in prolonged cohort and case-control studies of these products. Experience with data on thromboembolism suggests that significant data are likely to be obtainable in a cohort study of manageable size within some 5–7 years. The use of third-generation products may have been small in the early years, but they were aggressively promoted in major oral contraceptive markets to ensure rapid growth, in all probability sufficient to provide adequate recruitment. One would hesitate to argue that such studies should be a universal condition of the marketing of drugs, but when the products concerned have immense social significance and considerable potential for good and harm, as the oral contraceptives do, and when the compounds involved are entirely new, there is at least a sound medical reason for such work in every case. That work was performed with successive forms of the earlier oral contraceptive products, in which dosages were progressively reduced, and there was particular reason to set it in motion on the introduction of products that contained new chemical components with some significant structural and pharmacological differences from the older progestogens. A straightforward statistical calculation shows that an early cohort study involving some 30 000–50 000 women taking a third-generation product could within 2 years have shown the degree of increase in the thrombotic risk, which was actually not elicited until much later.

The second answer with respect to the earlier acquisition of risk data must come from the laboratory. Not from animal studies, which in this field are of very restricted value, but from biochemical and particularly hematological work. When during the 1990s various groups began to examine in detail the effects of the third-generation contraceptives on processes related to the clotting system, they identified a series of properties that could very well explain an increased incidence of thrombosis.

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The first of these was an increase in circulating concentrations of factor VII produced by the desogestrel plus estrogen combination, which was some 20–30% higher than that seen with a second-generation product based on levonorgestrel (98). The methods used to carry out this work were available before 1988 (99), and it is not at all clear from the published material whether there was a failure to compare the two generations in this respect at an early date, or whether such work was performed and either overlooked or misinterpreted.

A second finding related to the effects of activated protein C on thrombin generation in low-platelet plasma via the intrinsic or extrinsic clotting pathways. Using a method developed on the basis of work first published in 1997 (100), a Dutch group in Maastricht found that all types of combined oral contraceptives induced acquired resistance to activated protein C. With the third-generation contraceptives, however, the effect was significantly more marked than with those of the second generation: in other words, these drugs significantly reduced the ability of activated protein C to down-regulate the formation of thrombin (84). However, this work only became feasible in the late 1990s.

A third underlying mechanism seems to involve a reduction in concentrations of free protein S, again more pronounced with third-generation products. When protein S falls, the antifibrinolytic effect of the so-called thrombin-activated fibrinolysis inhibitor is increased; in other words, fibrinolysis is impeded, with an increased risk of clotting problems (101). Again, however, these are recent methods, which were not available when the third-generation products were launched.

The laboratory findings therefore suggest that a greater thrombosis-inducing effect of the third-generation oral contraceptives can be explained and even anticipated on the basis of known mechanisms. Not all the relevant methods were available in the early years, but that relating to factor VII most certainly was. It is unfortunate, to say the least, that such work was either not performed or not properly interpreted.

All in all, had a combination of hematological methods and field studies been initiated sufficiently soon, the increased risk of thromboembolism with the third-generation oral contraceptives could have been detected some years earlier, sufficient for society to take decisions on the benefit-to-harm balance of these drugs before so much needless injury was incurred.

The third-generation oral contraceptives: a judicial assessment

It was extraordinary to find a major epidemiological dispute regarding drug safety being handled by the High Court in England in late July 2002, when the Court handed down its decision regarding thromboembolic events induced by the third-generation oral contraceptives (102). Essentially, a group of women who claimed to have been injured as a consequence of having using this latest version of "the pill," based on two new progestogens, had sought to reclaim extensive damages from the manufacturers, since in their view the product did not possess the degree of safety which, in the words of European law, the user was legitimately entitled to expect. Since the safety achieved with the widely used products of the second generation was so widely regarded as acceptable, the Court had to decide whether the newer products had significantly failed to meet that standard. Faced with a long procession of expert epidemiological witnesses from both sides, and with some flat contradictions, the judge was obliged to rule on their arguments.

However, that it was an English court in which the issue came to be debated was not surprising, for it was in England that the Committee on Safety of Medicines had written to prescribers in 1995 stating that three unpublished studies on the safety of combined oral contraceptives in relation to venous thromboembolism had indicated about "a two-fold increase in the risk of such conditions" compared with the preceding generation of products. This issue of a "two-fold increase" became crucial to the case. "For reasons of causation," as the Judge put it, the claimants had accepted the burden of proving that the increase in risk was not less than two-fold.

In fact, the English authorities, having rejected a vigorous defence of these products by the manufacturers, were by 1999 speaking more precisely of an increase in risk, as compared with the earlier products "of about 1.7–1.8 after adjustment," which was "not fully explained by bias or confounding"; appropriate label warnings were therefore imposed. These new warnings, summarized, said that an increased risk associated with combined oral contraceptives generally was well established, but was smaller than that associated with pregnancy (60 cases per 100 000 pregnancies). In healthy non-pregnant women who were not taking any combined contraceptive it was about five cases per 100 000 woman-years; in those taking the second-generation products it was about 15; and for third-generation products it was about 25. By September 2001, the European Union's Committee on Proprietary Pharmaceutical Products had formed its own view, and here too it was concluded that the "best estimate of the magnitude of the increased risk is in the range of 1.5–2.0."

In Court to support the claimants, Professor Alexander Walker assessed the relative risk of the third-generation products at 2.2, Dame Margaret Thorogood at 2.1, and Professor Klim McPherson at about 1.9. The experts for the defendants took the view that the relative risk was well below two, and could well be zero. As Mr Justice Mackay noted, having listened to these experts: " . . . the debate between them has been unyielding, at times almost rancorous in tone, and with a few honourable exceptions . . . devoid of willingness to countenance that there may be two sides to the question. So, science has failed to give women clear advice spoken with one voice."

There was also fundamental disagreement on confidence intervals when calculating relative risks in such matters: "The Defendants say that to establish causation in the individual, and therefore a relative risk which is greater than two, there must be seen not just a point estimate but also a lower confidence interval which is greater than two in order for the result to be significantly different from two."

The Court was faced with "a series of studies with different point estimates and largely overlapping confidence intervals. Time after time experts have had their attention drawn to point estimates from studies that appear, to the layman's eye, to be very different. Almost invariably they have dismissed those apparent differences

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by reference to the overlapping confidence intervals, saying that the figures are statistically compatible and there is no significant difference." Confronted with such material, the Court chose to set aside as inexact and theoretical much of the statistical rhetoric. Having done that, the Judge felt himself in a position to emerge "from that forest into broader more open country where the simpler concept of the balance of probabilities rules." Constructing his judgement in that way, Mr Justice Mackay advanced in the course of 100 pages to the conclusion that the claimants had failed to demonstrate a doubling of the risk. In his view, "the most likely figure to represent the relative risk is around 1.7."

This extraordinary and wise judgement merits most careful reading by anyone anxious to understand the safety issues surrounding oral contraceptives. First, because of the insight that it demonstrates into the manner—not always edifying—in which evidence in this vital matter has been adduced, interpreted, and argued over in the course of more than a decade. Secondly, because it arrives, through a process of tight reasoning, at what is for the moment the most reliable conclusion we have. It seems beyond all possible doubt that the third generation of oral contraceptives is primarily characterized by an increased risk of thromboembolic complications. Whether that risk is great enough to warrant financial compensation is a matter for lawyers to decide. But given the lack of any tangible benefit to the user, the risk is clearly significant in human terms, and it is hard to see that there is any valid reason at all for continuing to use these products.

Arterial complications

Arterial disease and acute arterial disorders and their links to oral contraception have long been a matter of concern, partly because of actual reported instances of apparent complications, but largely because of the metabolic changes caused by the oral contraceptives. In particular, it has been thought that the effects of these products in raising blood pressure, affecting clotting, or changing the circulating concentrations of blood lipids and carbohydrates could result in cardiac and arterial risks, including an earlier onset of atherosclerosis and the occurrence of myocardial infarction and stroke. Basilar artery occlusion secondary to thrombosis (103), cerebral infarction (104,105), retinal vascular complications (106), and encephalopathy with renovascular hypertension (107) and acute myocardial infarction (108,109) have all been reported. There have been over 40 reports of intestinal ischemia and infarction in oral contraceptive users, with a high mortality rate (39,110).

The initial question must be whether the clinical data point to the emergence of complications of this type. The 1990 International Consensus Meeting found an increase in acute cardiovascular accidents during use of oral contraceptives, but not persisting after they had been discontinued. There is also a great deal of anecdotal evidence, although in view of the massive scale on which oral contraceptives have been used over 40 years, coincidence alone would lead to the accumulation of many reports of adverse events. Other evidence suggesting an increase in arterial thrombotic events has been noted incidentally in the discussion of venous events above. There is also evidence that the chance of unexpected cardiovascular death is lower in oral contraceptive users who have been taking a product based on one of the new progestogens in particular. In over 300 000 women there was a cardiovascular death rate of 4.3 per 100 000 women-years among users of combined oral contraceptives containing levonorgestrel, 1.5 per 100 000 among users of those based on desogestrel, and 4.8 per 100 000 among users of oral contraceptives containing gestodene (111). The relative risk estimates compared with levonorgestrel were 0.4 (95% CI = 0.1, 2.1) and 1.4 (0.5, 4.5) for desogestrel and gestodene respectively. However, it should be added that this is precisely one of the studies that concluded that the new progestogens substantially increased the incidence of venous thromboembolism.

However, a fatal flaw of most such studies was their failure to provide an adequate analysis of co-existent risk factors other than oral contraception. In fact, there is not a great deal of evidence of appreciable risks of this type among oral contraceptive users, unless other risk factors are present. The 1989 case-control analysis of the Royal College of General Practitioners cohort study showed that current oral contraception increased the risk of acute myocardial infarction, but only among smokers. The large cohort study from the Oxford Family Planning Association (OFPA) similarly found no significantly increased risk of myocardial infarction or angina pectoris among either current or former use of oral contraceptives, but a strong dose-related effect of current smoking. In an analogous manner, many studies have shown that the risk of coronary heart disease in oral contraceptive users or other women increases directly with body weight (52,54) and with age (6), but not clearly with oral contraceptive use alone. Nor does one find any published evidence that the risk of late arterial disease, notably atherosclerosis, is higher among users of oral contraceptives, despite the fact that with some 40 years of experience one would expect any such trend to have become evident by the end of the 20th century.

Alongside this clinical material one is faced with the biochemical evidence of changes in the oral contraceptive user. However, various findings make it impossible to draw clear pathogenetic conclusions from these biochemical data. As far as lipids are concerned, there is no doubt that oral contraceptives as a group increase low-density lipoprotein and reduce high-density lipoprotein and cholesterol; this shift is usually regarded as inducing a propensity to atherosclerosis, but here its significance is not so simple to assess. HDL cholesterol, for example, can be divided into subfractions, of which HDL2 seems to be more responsive to estrogens and progestogens; the concentration of HDL2 has been thought to correlate better with a reduced risk of cardiovascular disease than does total HDL cholesterol (112). The picture is further complicated by the fact that when estrogens are used in postmenopausal women they can raise HDL, a change that might be considered to have a favorable effect (113–115). What is more, the effects of these products on lipids change with time, rendering short-term studies useless as a basis for risk assessment. It could be that the older oral contraceptives raise the risk in the short term, as suggested above, but actually lower it in the long term.

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It is by no means impossible that the overall effect of oral contraceptives on the arterial system is exercised through a complex of different mechanisms. In this respect it is worth recalling the "insulin resistance syndrome" or "metabolic syndrome," which comprises a set of metabolic risk factors for cardiovascular disease (specifically coronary heart disease and arterial disease) (116). These interrelated risk factors include hyperinsulinemia and impaired glucose tolerance, hypertriglyceridemia, reduced high-density lipoprotein (HDL) concentrations, and hypertension, with insulin resistance as a potential underlying factor. Hormonal contraceptives can variously affect these metabolic conditions, and the effect depends in part on steroid type and dose. Lower doses and newer formulations do not change HDL concentrations or increase blood pressure, but insulin resistance and hypertriglyceridemia still occur. These latter changes are caused primarily by the estrogen component of combined oral contraceptives, but the progestogen component can also modify these effects. The formulations with the least unfavorable metabolic effects are those that contain norethindrone or that are based on the newer progestogens, such as desogestrel, gestodene, or norgestimate. However, as noted elsewhere, it has yet to be determined whether the metabolic changes confer any clinical benefit.

Finally, it is fair to set the possible adverse effects of these hormonal products, and particularly of estrogen, against the fact that estrogen also has certain favorable effects on the arterial wall. It has been suggested that estrogen has a calcium channel blocking effect that relaxes the vessel walls, thus increasing blood flow (117). Others have documented in monkeys the fact that estrogens dilate the coronary arteries, an effect unrelated to plasma lipid concentrations, blood pressure, or heart rate (SED-13, 1217) (118). They have also found evidence in their animal studies that estrogen + progestogen administration to hypercholesterolemic animals reduces both their HDL cholesterol concentrations and their arterial lesions.

Frequency

West German data over the period 1955–80 showed no community-wide increase in the incidence of ischemic heart disease, cerebral vascular embolism, or pulmonary embolism, despite the rapid growth in oral contraceptive use (and the prevalence of high-dose products) during much of that period (119). The Oxford Family Planning Association's 1989 paper on its cohort study, which had followed up more than 17 000 women for an average of nearly 16 years, found no significant overall effect of oral contraceptive use on mortality, with a relative risk of 0.9 (8). Mortality from diseases of the circulatory system had slightly increased; the relative risk of death from ischemic heart disease in current or past oral contraceptive users was 3.3 (95% CI = 0.9–17.9), while data on fatal cerebrovascular disease were too few to be interpreted.

Similarly, a massive Finnish mortality study, covering 1 585 000 women-years of oral contraceptive use and two million women-years of copper-bearing intrauterine device use, showed no increase in relative risk among oral contraceptive users for myocardial infarction or cerebral hemorrhage deaths; however, there might have been an increased risk of death from pulmonary embolism among users of oral contraceptives (42).

An analysis of the cardiovascular mortality risk associated with low-dose oral contraceptives (under 50 micrograms of ethinylestradiol) in the USA showed that among non-smokers and light smokers the mortality among current oral contraceptive users was likely to be lower than the mortality due to pregnancy (25). Only among heavier smokers over 30 years old did the risk of oral contraceptive use exceed the risk of pregnancy. The researchers noted that in countries with higher maternal mortality rates than the USA, even older women who are both heavy smokers and oral contraceptive users would have a lower mortality risk than that associated with pregnancy.

A 5-year case-control study involving all Danish hospitals has once more quantified the thromboembolic risks associated with oral contraceptives as a whole; the risk with third-generation products was some 30% higher than with second-generation products (RR = 1.3; CI = 1.0, 1.8) (120). However, data on cerebral thrombosis from the same study showed that with third-generation products the mean risk was some 40% lower than with second-generation products (RR = 0.6; CI = 0.4, 0.9) (121).

Susceptibility factors

The effect of smoking has been investigated on a large scale in Denmark, where the incidence of smoking among women is much higher than in many other countries (122). Evidence has emerged that the combination of smoking with oral contraceptive use may have a synergistic effect on the risks of acute myocardial infarction and cerebral thromboembolism (but not of venous thromboembolism), particularly among users of high doses (50 micrograms). The authors therefore suggested that the very low-dose products, which in Denmark contain 20 micrograms of ethinylestradiol, should be preferred in smokers. While this conclusion is clear and defensible, the situation is somewhat complicated by the fact that in Denmark the only products that contain this low dose of estrogen are those in which it is combined with either desogestrel or gestodene, that is third-generation progestogens. It could well be that the safest combined oral contraceptives for smokers will prove to be those in which the 20 micrograms dose of estrogen is combined with a more traditional progestogen.

For current or potential users of oral contraceptives the question arises whether it is not wise to examine the individual's possible predisposition to thromboembolism (thrombophilia) before deciding for or against this form of birth control. It has been suggested that in teenage users who might prove to be carriers of the Factor V Leiden mutation, routine screening would not be economically justified (123). It was instead the author's view that clinicians can use thoughtful screening questions to identify potentially high-risk patients for thrombophilia and consider testing for inherited risk factors case by case.

Estrogens versus progestogens

As far as the estrogens are concerned, the original estrogen, mestranol, was abruptly replaced by ethinylestradiol in most or all products after a wide-scale panic relating to the thrombosis issue in 1969. The motive lay entirely in

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the fact that the ethinylestradiol was about twice as potent, so that the dose could be halved. Whether this in fact led to any reduction in cardiovascular thromboembolic risk was never specifically examined. The choice of estrogen might still be relevant to the extent that (physiological) 17-β-estradiol in microcrystalline form later became available for oral use and in theory might prove safer in some respects than semisynthetic estrogens, since it seems to have less effect on the fibrinolytic system.

The question of the progestogens has come acutely to the fore as a result of the debate regarding the third-generation progestogens gestodene and desogestrel. At the time of marketing, no specific claim appears to have been made that they would present a lesser degree of risk of thromboembolism. However, emphasis was placed on experimental findings that might indicate a better cardiovascular prognosis. The older oral contraceptives produce an increase in low density lipoprotein and a reduction in high density lipoprotein and cholesterol; those changes may have some relevance to the occurrence of arterial disease. By avoiding them, and having the lowest possible estrogen content, the new combinations were expected to be safer, although this had in no sense been proven. However, the manner in which this information was presented could have introduced a degree of confusion in the minds of prescribers and users, and the belief appears to have arisen that these third-generation oral contraceptives might prove less likely than their predecessors to cause thromboembolic disorders. That this is not so in relation to venous thromboembolism is discussed above. The theoretical argument that the risk of atherosclerosis and its associated complications might in the long run be less is so far entirely unproven, and with the fall in use of these products following these unfavorable findings (124), it seems uncertain whether the data necessary to examine that hypothesis will ever be accumulated.

Persistence of risk after discontinuation

Most, but not all, studies have concluded that the effect of oral contraception on the risk of cardiovascular disorders disappears after withdrawal (6,41,54,125–127). The Nurses' Health Study found no differences in either incidence of or mortality from various cardiovascular diseases between never-users and past-users, regardless of the duration of use, or the time since last use (7). The nested case-control analysis of the RCGP study showed that, although stroke risk was higher among current oral contraceptive users regardless of smoking status, former users had an increased risk only if they were current smokers. Such conclusions are supported most strongly by a 1990 meta-analysis of published studies on the relation between past use of oral contraceptives and myocardial infarction, which produced an adjusted relative risk estimate of 1.01, suggesting no association (128). Thus, there does not appear to be a long-term mechanism at work, such as atherosclerosis, but rather an effect confined to current use, such as thrombosis (41,54). However, there have been only a few studies of stroke in relation to previous oral contraceptive use, and those studies have produced inconsistent results; thus, meta-analysis of stroke data is precluded.

With some of the newer drugs, the effects may (as seems to be the case with the older drugs) persist for a number of weeks and justify the withdrawal of these products some time before surgery or other risks. A study of changes in hemostasis after withdrawal of the newer combined oral contraceptives (ethinylestradiol 30 micrograms plus either desogestrel or gestodene) (41) showed that several weeks elapsed before plasma concentrations of fibrinogen, factor X, and antithrombin III returned to baseline.

It should be noted that a few studies have produced deviant conclusions, for reasons that are not clear. Some found that the risk of fatal myocardial infarction was similar for current and past users (26), whereas others actually reported a lower risk of cerebral thromboembolic attack in former users compared with never users (29).

In summary, the final chapter in the story of oral contraceptives and arterial lesions has not yet been written. However, in the light of long experience there is currently reason for optimism. There is no reasonable evidence that oral contraceptives, whatever their biochemical effects, actually do increase the risk of atherosclerosis; as to the occurrence of acute arterial events, these are explained largely or entirely by the presence of risk factors other than oral contraception.

Hypertension

The association between combined oral contraceptives and hypertension, noted and confirmed as early as 1961, has been explored in a multicenter clinical trial carried out by the WHO (129,130) and on a lesser scale in many other reports, yet the facts remain surprisingly puzzling. It has become clear that the use of oral contraceptives in any dose can cause a mean increase in blood pressure, the effect being much more marked in some individuals than others. With the current range of oral contraceptives a substantial proportion of users show some increase in blood pressure compared with their pre-treatment condition (131), but the rise is rarely of clinical significance. Clinical hypertension seems unlikely to occur in more than 1–5% of women (132). The incidence may have been higher with the older high-dose products, but that is not entirely clear. The figures have to be set against the incidence of hypertension in a population of otherwise healthy women of fertile age, which is about 2%. The rise in blood pressure can appear at any time during treatment and persists for at least as long as the drug is taken, sometimes for several months longer, but even then it generally returns to normal. In order to detect women who react poorly, blood pressure measurements should be an integral part of the follow-up care of all women taking oral contraceptives. Considerable research has shown no overall increase in blood pressure or in the prevalence of hypertension associated with use of progestogen-only contraceptives; nor does the available information point to any increase in other cardiovascular disorders.

It is not clear why many women remain normotensive while others have a rise in blood pressure. No confirmation has been obtained of early beliefs that hypertension during oral contraception was more likely to occur in black American women, or in women with a history of hypertension during pregnancy (56,133). However, there is clinical evidence that this can occur and that the women involved

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may have a defect in dopaminergic transmission affecting blood pressure and prolactin secretion (134); pre-existent abnormalities of platelet function and fibrinolysis have also been linked with this complication (SEDA-6, 348).

Published studies, in which various doses have been used, show that there is no clear relation between blood pressure and estrogen intake. The progestogens seem to be involved, but here too most specific studies fail to detect a dose–response relation (131). However, some do: in a 1977 analysis of data from the large prospective study by the Royal College of General Practitioners (RCGP), with oral contraceptives containing ethinylestradiol 50 micrograms and norethisterone acetate 1, 3, or 4 mg, the risk of hypertension increased with increasing progestogen dose (135).

The rise in blood pressure might reflect water retention caused by the mineralocorticoid effect of progestogens, but that is probably not the complete explanation. These drugs have an effect on the renin-angiotensin system, but there actually seems to be some fall in responsiveness to plasma renin activity. Other possible pathophysiological mechanisms discussed so far include insufficient adaptation to increased production of angiotensin and aldosterone, an increase in cardiac output, and changes in the metabolism of catecholamines. The estrogenic component of oral contraceptives has been stated to be the more important factor in producing abnormalities in the renin system, but the progestogen may also play a role. Some workers have found higher estrogen concentrations in oral contraceptive users who develop hypertension (136).

As might be expected, the few women with severe hypertension during oral contraceptive use, whether or not they were hypertensive before that time, run a somewhat greater risk of acute secondary complications due to hypertension, such as subarachnoid hemorrhage. If the hypertension is severe and persistent one might anticipate long-term effects on the cardiovascular system and kidneys. Nested case-control studies using data from the RCGP study showed that hypertension was an independent risk factor for both stroke (28) and myocardial infarction (55); after controlling for other variables, including oral contraceptive use, the odds ratios (or estimated relative risks) associated with hypertension were 2.8 for stroke and 2.4 for myocardial infarction. In that study, oral contraceptive use did not further increase the risk associated with either hypertension or a history of toxemia of pregnancy. Nevertheless, hypertensive women who take oral contraceptives should be monitored carefully.

Respiratory

Oral contraception is not considered to be relevant to the induction or aggravation of respiratory disorders, although the fact that a very few women have allergic reactions to these formulations could in theory be relevant to the occurrence of asthma.

Nervous system

Headache has long been reported as a reaction to oral contraceptives, just as it occurs unpredictably with many other forms of drug treatment; it is probable that women who are susceptible to headaches at certain phases of the menstrual cycle are more likely to react to oral contraceptives in this way. However, it does not seem to be in any sense consistent; in a placebo-controlled trial conducted as long ago as 1971, when doses of estrogens were high, headache was not found to be associated with use of combined oral contraceptives containing mestranol either 50 or 100 mg (137). In many other studies of the adverse effects of oral contraceptives, it is not possible to ascertain whether the prevalence of specific complaints, such as headache, is actually increased, because there is no appropriate comparison group.

Because migraine headaches are of vascular origin and are sometimes linked to the menstrual cycle, it is pertinent to consider whether hormonal contraception is appropriate in women suffering from this condition (138). No association of migraine headache with stroke has been demonstrated. However, some women with migraine have an increase in the severity and frequency of headache when they take combined oral contraceptives, just as some other migraine sufferers describe a relation to the menstrual cycle. As a precaution, women who have migraine headaches with focal neurological symptoms should not take combined oral contraceptives.

Despite initial concern (SEDA-6, 349), combined oral contraceptives do not appear to worsen seizure control in most women with epilepsy, although seizure frequency should be carefully monitored. The primary consideration in selecting a contraceptive method for an epileptic woman is the need for dependability, but antiepileptic drugs that are enzyme inducers reduce the effectiveness of hormonal contraceptives. Women who wish to take combined oral contraceptives, but for whom enzyme-inducing drugs provide the best seizure control, should be given combined oral contraceptives with a relatively high dose of estrogen (for example ethinylestradiol 50 micrograms). Fewer seizures occur during the luteal phase (low estrogen) of the menstrual cycle, suggesting that estrogens (or oral contraceptives) may be epileptogenic.

Reversible electroencephalographic changes, probably due to progestogenic effects (139), have been observed in 25–60% of oral contraceptive users.

There are various reports of chorea (140,141), hemichorea (142), and paraballism (143). In one case, chorea was the first sign of lupus erythematosus (144).

Acute abdominal symptoms in users of hormonal contraceptives suggest embolism or infarction at some site, but there can be unusual explanations.

- Right-sided lower abdominal pain occurred in a 15-year-old girl, and had been present throughout the 3 months that she had used the product but it had now become so severe as to demand emergency care. The problem was traced to cutaneous nerve entrapment in the abdominal wall (145).

It is not clear how this could have resulted from the treatment, but it might have entailed fluid redistribution in or around an old appendicectomy scar. It may be noted that nerve entrapment is recognized as a possible adverse effect of oral contraceptives in the carpal tunnel syndrome.

Results from the Oxford Family Planning Association Study showed no relation between oral contraceptive use and the incidence of multiple sclerosis (146). Conversely, multiple sclerosis is no longer considered to be a contraindication to hormonal contraceptive use.

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Sensory systems

Eyes

It is still difficult to judge whether there is a correlation between ocular pathology and the use of oral contraceptives, with the exception of thromboembolic incidents that affect the retinal circulation. Oral contraceptives have several times been reported to reduce the tolerability to contact lenses, but in any case this abates in some people as the years pass. However, pregnancy itself may result in loss of contact lens tolerance both for scleral and corneal lenses, lenses often having to be refitted after pregnancy; a similar effect of oral contraceptives is thus not entirely unlikely (147), even though other workers have failed to detect any such change (148). Similar doubts relate to the induction of macular hole with retinal detachment, but in one study 20 of 24 women with this complication were using oral contraceptives (SEDA-6, 348). Finally, there is one case report of retinal migraine linked to the end of oral contraceptive treatment cycles (149).

Ears

Aggravation of existing otosclerosis has been observed several times; in one series of five cases, withdrawal of the medication stabilized four cases while the fifth improved (150). There is no reason to expect a reduction in hearing except in cases of otosclerosis; indeed, in a study of several thousand American women, hearing was generally found to be better among current oral contraceptive users than in never-users, and was intermediate in past users (151). A long-term study of chronic oral contraceptive users, which included otological, audiological, and vestibular examinations, found no impairment of the function of the healthy internal ear (152).

Psychological, psychiatric

Psychiatric symptoms have been described in women taking oral contraceptives in isolated case reports (153,154), probably reflecting non-specific effects in susceptible individuals. As to psychological effects, many physicians have found that certain women react to oral contraceptives by becoming morose or unhappy (155), but this does not necessarily mean that they meet the clinical criteria of true depression, the incidence of which has not been found to be increased (156). Several possible biological mechanisms for mood changes have been suggested; however, when nervousness and depression among combined oral contraceptive users are carefully evaluated over time, the pattern is so inconsistent that it is difficult to study. If one looks for anything like consistent depression one is unlikely to find it (137).

Many women who change to an oral contraceptive after unsatisfactory experience with other forms of contraception find greater sexual satisfaction (156) because of relief from worry about pregnancy.

Endocrine

Both long-term and short-term progestational therapy can suppress pituitary ACTH production to some extent, as studied with the metyrapone test. Medroxyprogesterone and chlormadinone suppress the reaction to metyrapone almost completely. Recovery was rapid after withdrawal of therapy. However, no conclusion was drawn as to the relative effect of the ethinylestradiol that was also given. The cortisol secretion rate is depressed in women taking norethindrone and mestranol, and the suggestion has been made that the gluconeogenic effect of glucocorticoids is markedly potentiated in subjects taking estrogens or estrogen-like substances. Adrenal cortical insufficiency has been related to the use of ethinylestradiol and dimethisterone taken during 1 year. The ascorbic acid content of the anterior pituitary is reduced in the presence of estrogen-induced adenohypophyseal hypertrophy.

Fasting growth hormone concentrations are higher in women using a contraceptive agent than in controls (157).

Oral contraceptives can cause an increase in total thyroxine (158) and a fall in the percentage of free thyroxine (159). The uptake of radioactive iodine in the thyroid is usually normal; total uptake of radioactive iodine may be reduced (159). The effect of progestogens on thyroxine-binding globulin may possibly counteract the estrogenic action. The net result will be a rise in protein-bound iodine and a fall in resin triiodothyronine uptake (160). It has been suggested that oral contraceptives may actually have some protective effect against thyroid disease.

Metabolism

Lipid metabolism

The 1990 report of the International Consensus Development Meeting stated the following regarding the effects of oral contraceptives on carbohydrate and lipid metabolism (19): "All currently used oral contraceptives can cause deterioration in glucose tolerance accompanied by hyperinsulinemia. There is no evidence that the use of combined oral contraceptives is accompanied by overt symptoms of diabetes .... The progestogen component is mainly responsible for the effects of oral contraceptives on carbohydrate metabolism, but the estrogen component may modulate the influence. The magnitude of the impact on glucose metabolism depends on the type of progestogen and also on the doses of a given steroid."

As has become clear since that time, these effects do not run parallel for all oral contraceptives; the third-generation products, which contain either desogestrel or gestodene, have rather different effects, the significance of which is unclear.

Lipid changes seen with the most widely used combined oral contraceptives comprise an increase in low density lipoprotein and reductions in high density lipoprotein and cholesterol. The third-generation products have these effects to a much smaller extent, leading to claims that they would be less likely to have long-term adverse cardiovascular effects related to atherosclerosis. However, such a claim reflects an all too readily adopted belief that the lipid changes produced by the more traditional combined oral contraceptives are in this respect capable of causing this type of (primarily arterial) cardiovascular disease. This is of itself far from certain.

Changes in lipid metabolism among users of progestogen-only contraceptives are minimal. Some studies have shown very small falls in HDL and HDL2 cholesterol, but no effect on other parameters of lipid

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metabolism. The androgenicity of progestogens parallels their effect on lipoprotein metabolism, but dosage must also be taken into account. For example, although levonorgestrel is more androgenic than norethindrone, its progestational potency is also greater, and levonorgestrel is therefore given in a lower dose for contraceptive purposes; the net result is that there is no clinical difference in lipid effects, as has been shown conclusively (161).

Adolescents with polycystic ovary syndrome are regarded as candidates for long-term combined hormonal treatment using a product of the oral contraceptive type, and there has been some concern about possible unfavorable late metabolic effects, notably on lipids. The risks with two combined products, one based on cyproterone acetate 2 mg and the other on desogestrel 0.15 mg, both with an estrogen, have been estimated in 24 women (95). After 12 months the hirsutism score was improved, but while triglycerides and HDL cholesterol were significantly increased by cyproterone, the only relevant effect of the desogestrel combination was a raised concentration of apolipoprotein A1. The authors concluded that the desogestrel combination was therefore to be preferred in such patients.

Carbohydrate metabolism

Carbohydrate metabolism was known at an early date to be affected by combined oral contraceptives. A mild to moderate degree of insulin resistance was found in some investigations (162,163). However, the considerably impaired glucose tolerance described in some users in the 1960s was directly dose-dependent. Although findings since then have not been entirely consistent (164), it is clear that the low-dose products introduced after the first decade of use had much less marked effects (165), as did the third-generation products based on newer progestogens. The clinical significance of these effects is limited. Even for the second-generation products, no difference was found across the board between ever users and never users in the incidence of diabetes mellitus. Prospective studies in England in 1979 and 1989 (166,167) showed no increased risk of diabetes in oral contraceptive users compared with controls or ex-users. These are, however, population-wide findings, and in some high-risk individuals, the effects on carbohydrate metabolism can be undesirable, with a significant deterioration in glucose tolerance (168); patients with serious or brittle diabetes should therefore not use these forms of contraception (169). It may also be wise to advise other contraceptive methods in women with a history of gestational diabetes, who might possibly be sensitive to these effects of the oral products (170). However, because of the increased risk of pregnancy complications in diabetic women, a highly effective contraceptive method such as the combined oral contraceptive is usually desirable, and it has been reasonably well demonstrated that there is no reason to avoid this type of formulation completely in a woman with stable and well-controlled diabetes. A clinical study of young women with insulin-dependent diabetes mellitus showed no significant differences between women using various combined oral contraceptives (containing up to 50 micrograms of ethinylestradiol) and non-users in hemoglobin A_{1c} concentrations, albumin excretion rates, and diabetic retinopathy (171). Possible very long-term consequences of changes in carbohydrate (and lipid) metabolism are considered further in this record and in connection with the cardiovascular system.

Most studies of carbohydrate metabolism have shown little effect of progestogen-only contraceptives, but there is a suggestion of slight deterioration in glucose tolerance and raised plasma insulin concentrations. Women with diabetes mellitus can generally take progestogen-only contraceptives without a change in insulin requirements.

Body weight

Body weight tends to increase in some women without a clear explanation, although it could be attributable in some individuals to improved appetite, water retention, or conceivably the anabolic effect of an androgenic progestogen. The increase is usually less than 2 kg and occurs during the first 6 months of use. Studies that record weight change over time have generally found similar fluctuations in oral contraceptive users and non-users (137). Cyclic weight gain purely due to fluid retention can also occur.

Nutrition

Alterations in plasma vitamin concentrations have been observed in oral contraceptive users, and attributed to reduced absorption and changes in plasma protein-binding capacity (172).

Vitamin A

While most vitamin concentrations in the blood fall (168), vitamin A concentrations increase, although carotene concentrations fall. Curiously, an isolated report of hypercarotenemia has been published (173).

Vitamin B_6

Alterations in vitamin B_6 metabolism have been discussed, particularly in connection with the suspicion that an oral contraceptive might cause depression. An additional daily intake of pyridoxine has long been suggested as a means of correcting the complex changes observed during use of oral contraceptives (174,175); there are no firm data proving that such medication has any useful effect in most women, but the approach may be tried empirically when mood changes are a problem (176).

Vitamin B_{12}

Vitamin B_{12} deficiency has been seen in healthy oral contraceptive users in whom serum vitamin B_{12} binding proteins were not altered.

Folate

Both sequential and non-sequential types of oral contraceptives impair the absorption of polyglutamic folate but not that of monoglutamic folate; the change can result in megaloblastic anemia in predisposed subjects, for example those with celiac disease or having a deficient diet (177).

Vitamin C

Some studies have suggested that ascorbic acid concentrations are lower in the leukocytes and platelets of oral contraceptive users (178); however, this has not been confirmed (179).

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Vitamin D

Studies of the effects of oral contraceptives on serum concentrations of vitamin D derivatives have given variable results.

Wintertime concentrations of 25-hydroxycolecalciferol were measured in 66 young women aged 20–40 years who did and did not use oral contraceptives (180). The initial mean 25-hydroxycolecalciferol concentration in the 26 users was 41% higher than in the 40 non-users before adjustment for age and vitamin D intake (83 versus 59 nmol/l), and 39% higher after adjustment. In five women who stopped taking oral contraceptives during the year after the initial measurement the 25-hydroxycolecalciferol concentrations fell by an average of 26 nmol/l, whereas the concentrations in women whose use or non-use of oral contraceptives was constant did not change. The effect on 25-hydroxycolecalciferol concentrations was not related to the dosage of ethinylestradiol, the type of oral contraceptive, or the duration of use.

However, in another study there was no difference in the concentrations of 25-hydroxycolecalciferol between controls and women who took oral contraceptives containing ethinylestradiol 30–50 micrograms for more than 1 year (181).

The time of year and the point during the menstrual cycle during which vitamin D derivatives are measured may be important. In seven women there was a two-fold rise in the serum concentration of 1,25-dihydroxycolecalciferol on day 15 of the menstrual cycle compared with days 1 and 8, without a detectable change in the serum calcium concentration (182). This increase did not occur in five women taking oral contraceptives, and there was a small but significant fall in the serum calcium concentration.

Mineral balance

Users of oral contraceptives excrete significantly less calcium than non-users (183) and estrogen treatment prevents bone loss in postmenopausal women (184); it is thus likely that the diminished urinary calcium excretion observed in women using oral contraceptives results from suppression of bone resorption by exogenous estrogens. Long-term use of oral contraceptives may therefore affect skeletal bone stores and prevent the development of osteoporosis. In line with these findings is an investigation showing an increase in radio-opacities in the mandibles of women using oral contraceptives (185).

Metal metabolism

Sex hormones can cause changes in metal metabolism, including both increased and reduced plasma zinc concentrations and raised serum copper; however, serum magnesium is not affected (186). The clinical importance of these effects is not known.

Hematologic

Iron status is improved in most oral contraceptive users because of reduced menstrual blood loss; an important benefit of oral contraceptive use is therefore a reduction in the prevalence of iron deficiency anemia (187). Much of the relevant research has been with higher dosages than are currently used. However, a study of a low-dose combined oral contraceptive (ethinylestradiol 30 micrograms plus desogestrel 0.15 mg) documented significantly lower menstrual blood loss than at baseline (188). Most women had normal values of hemoglobin, hematocrit, erythrocyte index, and serum ferritin both before and during oral contraceptive administration, with no significant changes. However, two women who had menorrhagia (defined as menstrual blood loss greater than 80 ml) and low serum ferritin before oral contraceptive use experienced improvement in both of these parameters while taking oral contraceptives. The cyclic variation in serum iron during the menstrual cycle has also been found to be less pronounced during the use of anovulatory agents (189).

The binding capacity of serum proteins is altered by oral contraceptives (190) and leads to alterations in the serum concentrations of various substances, including thyroxine, cortisol, and serum iron (191), and in serum iron binding capacity, which are all increased.

Erythrocyte enzymopathies have rarely been observed during pregnancy and oral contraceptive treatment (192) and in these cases a cause and effect relation seems likely.

Hemostatic variables have been reviewed in women taking oral contraceptives containing desogestrel and gestodene in comparison with oral contraceptives containing levonorgestrel (193). The database of 17 comparative studies was homogeneous. There were no differential effects for coagulation and fibrinolysis parameters, except for factor VII, which was consistently increased by 20% among users of third-generation oral contraceptives than among users of second-generation oral contraceptives. Factor VII is not a risk marker for venous thrombotic disease.

Data from the Leiden Thrombophilia Study have been used to construct a case-control study, based on contraceptive users who had experienced a first episode of objectively proven deep vein thrombosis (97). Patients and controls were considered thrombophilic when they had protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden mutation, or a prothrombin 20210 A mutation. Among healthy women, the risk of developing deep vein thrombosis was trebled in the first 6 months and doubled in the first year of contraceptive use. Among women with thrombophilia, the risk of deep vein thrombosis was increased 19-fold during the first 6 months and 11-fold (95% CI = 2.1, 57) in the first year of use. Venous thrombosis during the first period of oral contraceptive use might actually point to the presence of an inherited clotting defect.

Coagulation factors in users of progestogen-only contraceptives have not been studied extensively using current laboratory methods, but there appears to be little effect. Perhaps the most informative study is a randomized clinical trial of two progestogen-only contraceptives (norethindrone 0.35 mg and levonorgestrel 0.03 mg) (161), which showed a reduction in several coagulation factors among women who switched from a combined oral contraceptive, but no change among women who had not previously been using a hormonal contraceptive. Thus progestogen-only contraceptives appear to be particularly suitable for women who desire oral contraception but who are at increased risk of thrombosis, including older women who are smokers.

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Mouth and teeth

Gingivitis, of varying degrees of severity, is sometimes associated with oral contraceptive use, apparently because the steroids alter the microbial flora in the mouth (194). A case of gingival hyperplasia is described under "Reproductive system".

Even a low-dose oral contraceptive combination has an effect on the composition of saliva (195); although large individual variations were noted, protein, sialic acid, hexosamine, fucose, hydrogen ion concentration, and total electrolyte concentration fell, while the secretion rates increased. The sodium and hydrogen ion concentrations increased in parotid gland secretion and sodium in submandibular gland secretion. To what extent these changes might affect the dental status of the patient is unknown.

Oral pyogenic granulomata have been reported both in pregnant patients and in patients using oral contraceptives (196).

Progestogens, alone or together with estrogen, cause an increase in the width and tortuosity of peripheral blood vessels in the oral mucosa, which become more susceptible to local irritants and show increased permeability (197).

Gastrointestinal

Mild gastrointestinal complaints, such as nausea, vomiting and vague abdominal pain, were seen in 10–30% of patients in earlier studies when high-dose products were in use. A placebo-controlled clinical trial in 1971 documented a higher prevalence of nausea and vomiting among combined oral contraceptive users than among women taking either a placebo or a progestogen-only oral contraceptive; the prevalence was also higher for the combined oral contraceptive containing mestranol 100 micrograms than for the combination product containing mestranol 50 micrograms (137). Such effects are much less common with the low doses used today. Nausea, if it occurs, is associated with the estrogen component of combined oral contraceptives; its frequency and severity generally decline over time.

The relation between oral contraceptive use and inflammatory bowel disease was analysed in two case-control studies published in the 1990s (198,199). Both found a significantly increased risk among current users compared with never users for Crohn's disease, but only the former study detected an increased risk of ulcerative colitis; a dose–response effect was suggested for Crohn's disease. When the data were stratified by smoking status in the latter study, the increased risk was found only among current smokers.

Reversible ischemic colitis, an unusual condition in young people, has been described in 17 young women, with evidence for an association with oral contraceptives (200). Ischemic colitis occurs uncommonly in younger people. The median duration of illness was 2.1 days (range 1–4 days). All recovered with supportive care. Ten women (59%) were using low-dose estrogenic oral contraceptive agents, compared with the 1988 US average of 19% oral contraceptive users among women aged 15–44 years. The odds ratio showed a greater than 6-fold relative risk for the occurrence of ischemic colitis among oral contraceptive users.

Diarrhea, probably coincidental, is bound to occur on occasion in the very large population of oral contraceptive users; when it does so, the efficacy of the product is likely to be diminished and additional contraceptive methods may need to be used.

Liver

During the early years of oral contraception, with high-dose products in use, jaundice and other hepatic complications were a source of concern; with current products this is no longer the case. Most women experience no adverse effects on liver function, but occasional hepatic changes can occur, including intrahepatic cholestasis, cholelithiasis, vascular complications, and even tumors, which are discussed in the record on estrogens. It has been argued (37) that women with a history of liver disease whose liver function tests have returned to normal can take oral contraceptives with careful monitoring. However, it is widely considered that oral contraception should be avoided in women with a history of cholestatic jaundice of pregnancy; past or current benign or malignant hepatic tumors; active hepatitis; or familial defects of biliary excretion.

The most common change is a short-term rise in serum transaminases (201), which often abates if treatment is continued. An increase in serum alkaline phosphatase is usual, while serum transaminases can be normal to markedly increased (202). Long-term use leads to changes in hepatic ultrastructure, with involvement of the mitochondria, which develop crystalline inclusions. Furthermore, hypertrophy of the smooth endoplasmic reticulum and changes in the biliary canaliculi have been shown (203,204). These changes are not usually accompanied by any clinical symptoms. The Budd–Chiari syndrome can occur in connection with thromboembolism.

Benign liver tumors (hepatocellular adenoma and focal nodular hyperplasia) are extremely rare conditions that appear to be related to oral contraceptive use (205).

Jaundice as a result of oral contraceptive treatment has been repeatedly described. Whereas in the Swedish population figures between 1:100 and 1:4000 were published when the early high-dose formulations were still in use (206), the overall incidence was estimated in 1979 at about 1:10 000 (9), and the current incidence is certainly further reduced. When such hepatic symptoms occur, they usually do so within the first month of medication (207), and jaundice may be accompanied by anorexia, malaise, and pruritus. Very few cases arise after the third month of medication and those reported are regarded by some as unlikely to be due to oral contraceptives. Microscopic examination of the liver shows intrahepatic cholestasis. When medication is stopped, symptoms usually disappear rapidly and the reaction does not seem to leave any sequelae (208). Genetic components seem to be important for the development of the reaction; women who have experienced jaundice or severe pruritus in late pregnancy seem to be especially susceptible to jaundice or gallbladder disease when using oral contraceptives (209). Discussion of mechanisms has related mostly to estrogens (210), but cases have been described in individuals taking progestogens only (206); the explanation might be the conversion of the latter to estrogens in vivo (211). The cause of cholestasis is unknown, but animal data suggest that there is inhibition of bile flow and of the biliary excretion of bilirubin and bile salts.

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Peliosis hepatis has been described in association with contraceptive-induced hepatic tumors and has sometimes developed in isolation, perhaps as a herald of more serious changes to follow, for example cirrhosis and portal hypertension; one such case ultimately required an orthotopic liver transplant (212).

Sinusoidal dilatation in the liver has been reported rarely.

- A 23-year-old woman developed an acute painful syndrome with cytolysis after 7 years of oral contraceptive use; she recovered promptly after oral contraceptive withdrawal (213).

Hepatic adenomatosis, which seems to have been reported only some 38 times, is a condition with a female preponderance; in earlier work it was noted that in 46% of the female patients oral contraception had been used. This means, however, that in the other 54% it had not, and it should be borne in mind that the condition can also occur in men.

- A 35-year-old woman, who had been fitted with Norplant 2 years before and had used oral contraceptives for some 20 years before that, developed epigastric and right upper quadrant abdominal pain (214). A liver mass was found and at surgery proved to consist of multiple adenomata; part of the liver had to be resected.

What is of potential concern is that in this case, as in a very few previously described, there was also evidence of hepatocellular dysplasia, which could be a pre-malignant condition. However, with widespread use of Norplant, some reported adverse events, such as this, may be purely coincidental.

Results in 1977 from the Boston Collaborative Drug Surveillance Program suggested that oral contraceptive users are more often diagnosed as having acute hepatitis than are non-users (215). There was no similar finding in the similarly early study by the UK Royal College of General Practitioners (135).

Biliary tract

The Boston Collaborative Drug Surveillance Program found in 1973 that of a large series of 212 patients with gallbladder disease 31% were using oral contraceptives, compared with only 20% of controls (216). In another study, the risk of gallbladder surgery was twice as high in oral contraceptive users as in non-users (217). A decade later, after dosages had fallen, a 1982 study from the UK Royal College of General Practitioners showed that there was no overall increased risk of gallbladder disease in the long term and that the previously demonstrated short-term increase in risk is due to acceleration of the onset of gallbladder disease in women already susceptible to it (135). The risk may also be age-related, the relative risk of gallstone disease being higher in young women using oral contraceptives than in older users (218–220).

- A 21-year-old woman developed increasing jaundice, with severe pruritus and weight loss, after a bout of dyspepsia (221). She had been taking contraceptives for 4 years (cyproterone acetate 2 mg, ethinylestradiol 0.035 mg). Laboratory tests at first suggested cholestatic hepatitis, but ultrasonography showed biliary sludge in the gallbladder and dilatation of the common bile duct and the smaller biliary passages. There was a space-occupying lesion near the papilla: it was not fixed and had no vascular supply. At endoscopic retrograde cholangiopancreatography the lesion was removed. It consisted of jelly-like viscous streaky bile without calculi. Within a few days the jaundice disappeared, the pruritus ceased, and liver function returned to normal.

A meta-analysis in 1993 of the relation between combined oral contraceptives and gallbladder disease yielded a small increased risk for women who had ever used oral contraceptives (pooled estimated RR = 1.38) (222). There was a dose-related effect in the therapeutic range of doses, suggesting that, although the risk is less with lower-dose combined oral contraceptives, there may still be a weak relation. The increased risk appears to be concentrated in the early years of oral contraceptive use, suggesting that oral contraceptives accelerate the development of the disease. On the other hand, the 1994 findings in the Nurses' Health Study II showed no substantial increase in risk associated with ever use of oral contraceptives, but relative risks of 1.6 for long-term use and for current use, after adjusting for body mass index and several other confounding variables (218). A 1994 report from the Oxford FPA study similarly suggested no relation with ever use of oral contraceptives (223).

The finding that oral contraceptive use causes an increase in the cholesterol concentration in bile and a shift in the chenodeoxycholic/cholic acid ratio suggests a biochemical basis for the increase in gallbladder disease among oral contraceptive users (224,225). Effects on gallstone formation may well be due to the estrogen content, for example since exogenous estrogens seem to increase the risk of gallbladder disease in men (226), while in women they can increase the cholesterol saturation of bile and hence the lithogenic index (227).

Pancreas

Acute pancreatitis has been reported as a very unusual complication of oral contraceptive treatment (228), as have increases in serum amylase (229).

Urinary tract

Over the years a few reports have suggested a higher incidence of urinary infections in users of oral contraceptives, but this probably reflected differing or altered patterns of sexual behavior.

Hemolytic–uremic syndrome seen in one very long-term user may have been due to antisteroid hormone antibodies (230).

Skin

Various types of skin reactions can occur during oral contraceptive treatment, but bearing in mind the vast number of women who take oral contraceptives, major skin reactions due to oral contraceptive treatment seem to be rare. The incidence, even including all minor complications, has been estimated at 5% (231), but field experience suggests that that is a generous figure. The figure

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includes chloasma, seborrhea, hirsutism, pruritus, herpes gestationis, porphyria cutanea tarda, and allergic reactions such as urticaria.

Low-dose combined oral contraceptive use generally results in improvement of acne, although occasionally a user has worsening of acne owing to the androgenic potency of the progestin used. Use of a less androgenic progestogen, for example norgestimate (232) or desogestrel or the antiandrogen cyproterone acetate (233,234), can have a favorable effect in patients with pre-existing acne, reducing the severity of the condition; an oral contraceptive in which cyproterone acetate replaces the progestogen has proved helpful in women with pre-existing acne.

The efficacy and adverse effects of oral cyproterone acetate 2 mg in combination with ethinylestradiol 35 micrograms in facial acne tarda have been studied in 890 women aged 15–50 years, of whom 96 withdrew prematurely from the study (235). Of these 96 women, only 30 withdrew because of adverse events: menstrual problems ($n = 11$), headache ($n = 10$), increased body weight ($n = 3$), and thrombophlebitis ($n = 1$). Five women withdrew because of poor efficacy. In all, 260 patients had adverse events during treatment. The incidence fell as the study progressed. Of those events that first occurred during treatment, the most frequently cited were breast tension (12%), headache (8.9%), nausea (5.8%), nervousness (4.0%), and dizziness (2.6%). There were no serious adverse events. There were no clinical significant changes in body weight or blood pressure.

There is a possible association of oral contraceptives with erythema nodosum, which has been linked to the use of either estrogens or progestogens or a combination of the two; however, probably neither hormone directly causes the condition but merely creates a fertile background for its generation by other antigens.

Pre-existing condyloma acuminata have been stated to increase during oral contraception, with regression after withdrawal (236).

Increased pigmentation of areas exposed to sunlight, as well as photosensitivity, has been incidentally observed in some users, and is probably analogous to the pigment changes that can occur in pregnancy.

In one case, pityriasis lichenoides disappeared after withdrawal of oral contraceptives (237).

Sweet's syndrome (acute febrile neutrophilic dermatosis) has been attributed to an oral contraceptive (238). However, bearing in mind that the syndrome has a variable presentation and is thought to represent a form of hypersensitivity reaction, it is not at all clear that there was a true cause-and-effect relation.

Hair

Contraceptives induce a condition of pseudopregnancy, and alopecia during treatment and after withdrawal has been seen. Of five women who developed diffuse alopecia while taking oral contraceptives, three had male pattern baldness while they were taking the treatment; two began to lose their hair after having stopped taking treatment, and these resembled postpartum baldness (239). One woman did not regain her hair 20 months after having stopped taking the oral contraceptive. However, the incidence of alopecia among users of oral contraceptives is very low, and the association may be coincidental, since there are also case reports of improvement in the quality of the hair (240).

Musculoskeletal

Although some studies have shown that combined oral contraceptives increase bone mineral density, the available evidence suggests that any beneficial effect is rather small (241), and is presumably related to the dosage of estrogen. The effects may depend in part on the age of women being studied, as normally bone mass density continues to increase until it peaks in women in their 20s and 30s, and then remains constant until the premenopausal period, when it begins to fall. For example, a study of young women (aged 19–22 years) showed that those taking very low-dose combined oral contraceptives (with as little as 20 micrograms of ethinylestradiol) had no change in bone density over 5 years, whereas non-users had a significant increase (242).

There were some early reports of localized mandibular osteitis in women using oral contraceptives subsequent to surgery of the mandibular molar teeth (SEDA-2, 316). It has been suggested that changes in the hemostasis could be the cause.

It appears that oral contraceptive use reduces the prevalence of severe disabling rheumatoid arthritis. Although studies of this have produced discrepant results, a meta-analysis of studies that met specific methodological criteria produced an overall adjusted pooled odds ratio of 0.73 (243). The authors suggested that oral contraceptives do not actually prevent rheumatoid arthritis, but modify the disease process to prevent progression to severe disease. Pregnancy has similar effects. It is unclear whether it is the estrogen or the progestogen component of oral contraceptives that is responsible.

Sexual function

Occasionally, women report reduced libido, which may have a hormonal basis. One study showed that users of oral contraceptives had no rise in female-initiated sexual activity at the time when ovulation should have occurred, whereas non-users did show such an increase in sexual activity (244).

Reproductive system

Tumor-inducing effects of hormonal contraceptives are dealt with in the record on estrogens.

Breasts

Breast tenderness or pain can occur in some women (245,246), especially with estrogen-dominant formulations, although it is notable that other women with a history of breast discomfort experience improvement when they begin to take oral contraceptives.

- A woman with Wilson's disease treated with penicillamine developed severe hirsutism (247). After treatment with oral contraceptives, her breasts enlarged rapidly, and she had cyclic mastodynia. Around the same time she also developed gingival hyperplasia.

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Benign breast disease (including fibroadenoma and cystic change) is less common among users of combined oral contraceptive than in the general population (205).

Ovaries

Women currently taking oral contraceptives are less likely than non-users to have functional ovarian cysts. This protective effect appears to be more modest with lower dose monophasic formulations than with those containing 35 micrograms or more of estrogen (248,249). Functional ovarian cysts (or persistent ovarian follicles) occur more often in users of progestogen-only contraceptives than in combined oral contraceptive users or in women using no hormonal contraceptive method. Follicular development is delayed and the follicle continues to grow for a period of time, but these enlarged follicles usually regress spontaneously and are not of clinical significance.

Uterus

Effects on menstrual function depend on the dose used and the sensitivity of the individual user; they may be welcome or unwelcome (188,250). Menses generally become more regular and predictable, and dysmenorrhea is less common and less severe. The number of days of blood loss in each menstrual period is often reduced, as is the amount of menstrual flow; thus women who previously had iron deficiency anemia associated with menorrhagia have increased iron stores. A comparison of women who kept menstrual diary records as part of WHO trials has confirmed that users of combined oral contraceptives in adequate dosages have more regular menstrual cycles than do users of other hormonal methods (251). None of the combined oral contraceptive users in these studies had amenorrhea (defined as the absence of bleeding throughout a 90-day reference period), although shorter periods of amenorrhea have occasionally been reported in other studies, particularly with very low-dosage formulations and with longer-term use.

Intermenstrual bleeding (breakthrough bleeding or spotting) often occurs, especially during the first few cycles of treatment, and is often the reason that women choose to stop taking an oral contraceptive. When using products based on newer progestogens it seems that better control may be offered by formulations that contain gestodene compared with desogestrel and by levonorgestrel compared with norethindrone (252), but the absence of standardized methods makes such conclusions tentative. Research on triphasic formulations is too sparse to allow firm conclusions on this point. One study confirmed the long-standing experience that intermenstrual bleeding rates vary inversely with both estrogen and progestogen dose (253). However, one finds no evidence that breakthrough bleeding is an indication of reduced contraceptive efficacy, despite speculation regarding a possible relation.

Dysmenorrhea is less common and less severe among women who use oral contraceptives of any type, provided that ovulation is inhibited; this emerges both from experience and from prospective studies; the effect seems to be maintained as long as the oral contraceptive is continued. There seem to be no significant differences in this respect between monophasic products with low or high progestogen doses, those with high progestogen doses, or triphasic products (250).

Since post-treatment amenorrhea of more than 6 months duration was first suggested as an adverse reaction in around 1965, much work has been devoted to delineating the risk and prognosis of menstrual changes after the withdrawal of hormonal contraception. It is now recognized that post-treatment amenorrhea occurs in 0.7–0.8% of women, but this is no different from the background rate of spontaneous secondary amenorrhea. No cause and effect relation between oral contraceptive use and subsequent amenorrhea has been documented.

Menstrual irregularities are common among women taking progestogen-only contraceptives and are often the reason a user chooses to discontinue the method (254,255). Users of progestogen-only contraceptives are more likely than users of other hormonal contraceptive methods to have frequent bleeding (251). Infrequent bleeding, amenorrhea, and irregular bleeding among progestogen-only contraceptive users are more likely than among combined oral contraceptive users, but less prominent than among women using levonorgestrel-releasing vaginal rings or DMPA.

There has been concern at various times that prolonged oral contraception might cause permanent changes in the genital system. When high-dose products were in use, various studies showed condensation of the superficial cortical layers of the ovary (SEDA-8, 863). Severe atrophy of the endometrium after a period of oral contraception has been described (256), but the report usually quoted is one that dates from a period when high doses were in use, and the incidence is not known, since the endometrium is not usually examined. Certainly, the endometrium will go into a resting phase in women who have amenorrhea, but there is no reason to believe that it will become permanently unresponsive.

Epidemiological studies of the relation between oral contraceptive use and pelvic endometriosis have variously shown an increased risk, a reduced risk, and no effect (257). For example, an Italian study showed an increased risk among ever users of oral contraceptives, but this increase occurred only among former users, not current users (258). Furthermore, the authors noted that a similar pattern had been shown in several large cohort studies (OFPA, RCGP, and Walnut Creek). There was no association in the Italian study with recency, latency, or duration of use, suggesting that any relation to oral contraceptive use is not a true biological relation but instead the result of selection and other biases.

Pelvic inflammatory disease, often resulting in infertility, ectopic pregnancy, or chronic pelvic pain, is a well-known pathological state that actually occurs at a somewhat lower incidence in oral contraceptive users and also tends to be less severe in these women compared with non-users (259–261). The biological mechanism for this protective effect may be the changes in cervical mucus or reduced menstrual bleeding (and thus reduced retrograde menstrual blood in the uterus). On the other hand, the relevant reviews have concluded that combined oral contraceptives provide no protection against lower reproductive tract infection (particularly cervical infections with *Chlamydia* or gonococcus) and may even have an adverse effect. This possible increased risk appears to be the result of an increase in the area of cervical ectropion associated with the estrogen in combined oral contraceptives.

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Candidiasis of the vagina in oral contraceptive users without evidence of diabetes mellitus has often been reported.

Immunologic

There is a sex difference in immune responsiveness, but little attention has been paid to the possible role played by sex hormones in its regulation. This lack of insight has led to the question of whether the use of oral contraceptives might affect the immune response, for better or for worse. An authoritative review of the immunological effects of estrogens and progestogens has concluded that, although understanding of any effect is incomplete, it is not likely that the low doses used in oral contraceptives would have negative effects on the immune system (262).

If that is the case, there must be another explanation for periodic reports that suggest an increased risk of systemic infections in oral contraceptive users. In a 1974 study by the British Royal College of General Practitioners oral contraceptive users had a higher than average incidence of certain infectious diseases (135).

Support for the concept that oral contraceptives might increase the risk of infection has been presented in other studies, and workers in the tropics have remarked that pregnant women appear to be unduly sensitive to malarial infestation (WHO, unpublished data).

The antibody response to tetanus toxoid in women is considerably lower in oral contraceptive users than in controls (263).

A depressed lymphocyte response to phytohemagglutinin has been observed in a series of women taking oral contraceptives (264); the reduction in phytohemagglutinin response reflects impaired T cell function, and this finding is of interest in view of the fact that a deficiency of T cell function is important in certain autoimmune diseases. Another consequence of prolonged impairment of T cell function would be an increased susceptibility to infectious diseases.

There have been several studies of the effect of sex hormones on serum immunoglobulin titers. In a study of the effect of four different oral contraceptives on the serum concentration of IgA, IgG, and IgM, the concentrations of all three immunoglobulins fell during the first course of treatment and returned to normal during subsequent cycles (265). There was some evidence that the steroid-induced reduction in immunoglobulins was predominantly caused by the estrogenic component. Subsequently, a study was conducted in which plasma from women currently taking combined oral contraceptives, past users of such products, women who had never used them, and non-users with a history of venous thrombosis was examined for the presence of immunoglobulin G (IgG) that showed specific binding of ethinylestradiol (266). There was no increase in "specific" IgG and no evidence of ethinylestradiol binding in oral contraceptive users compared with non-users. This study therefore provided no support for the hypothesis that a significant percentage of oral contraceptive users develop a specific IgG with high binding affinity for ethinylestradiol, which might be causally linked to the development of thrombotic phenomena in oral contraceptive users.

Numerous case reports have suggested that combined oral contraceptives can cause systemic lupus erythematosus (144,267). However, systematic examination of this issue in a 1994 case-control study showed no association (268).

Aggravation of bronchial asthma, eczema, rashes, angioedema, and vasomotor rhinitis have been incidentally observed, and cold urticaria has been reported in women taking oral contraceptives (269). It is not known whether in any particular individual the hypersensitivity reaction is due to the hormones themselves or to other ingredients in the tablet. Nasal provocation tests with suspensions of contraceptive steroids in patients with allergic rhinitis or pollinosis who had been taking these products showed a positive response in one-third of cases; the same patients also reacted to topical estrogens (270). Life-threatening anaphylaxis with a positive rechallenge test occurred in a young woman using oral contraceptives, but this must be extraordinarily rare (271).

The immunological effects of two contraceptive combinations, namely Valette (ethinylestradiol 0.03 mg + dienogest 2.0 mg) and Lovelle (ethinylestradiol 0.02 mg + desogestrel 0.15 mg), have been examined during one treatment cycle (272). The latter significantly increased the numbers of lymphocytes, monocytes, and granulocytes. Valette reduced the CD4 lymphocyte count after 10 days and Lovelle did the opposite. Lovelle increased CD19 and CD23 cell counts after 21 days. Phagocytic activity was unaffected by either treatment. After 10 days, both contraceptives reduced the serum concentrations of IgA, IgG, and IgM, which remained low at day 21 with Lovelle but returned to baseline with Valette. Secretory IgA was unaffected by either contraceptive. Neither treatment affected concentrations of interleukins, except for a significant difference between the treatment groups in interleukin-6 after 10 days, which resolved after 21 days. Concentrations of non-immunoglobulin serum components fluctuated; macroglobulin was increased by Valette. However, total protein and albumin concentrations were reduced more by Lovelle than Valette. Complement factors also fluctuated. There was no evidence of sustained immunosuppression with either Valette or Lovelle.

Infection risk

Data on the risk of infection with HIV (human immunodeficiency virus) with combined oral contraceptives are sparse; some studies suggest an adverse effect and others show no association (259,273).

Body temperature

Body temperature tends to rise slightly in some users of oral contraceptives (274,275) Progesterone has a mild thermogenic effect, reflected in changes in body temperature during the normal menstrual cycle. Mild pyrexia in users of oral contraceptives may reflect this, but the patient should always be examined to exclude infection.

Long-Term Effects

Drug abuse

Children under 6 years who have accidentally ingested oral contraceptives have experienced nausea and

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vomiting for 10–15 hours after ingestion (SEDA-1, 306). Occasionally, apathy, drowsiness, and slight increases in transaminase activities have been reported.

Drug withdrawal

Although it was originally believed that women who stopped taking oral contraceptives, particularly after a long period of use, were more likely to have amenorrhea, careful analysis has shown that that is not the case. The likelihood of conception is reduced during the first 1–2 months after discontinuation, but cumulative conception rates after several months are not affected.

Tumorigenicity

The carcinogenic effects of oral contraceptives are covered in the monograph on estrogens.

Second-Generation Effects

Fertility

The return of fertility after a period of oral contraception has been differently assessed at different times. Although there can be a delay of 1–2 months in the return of fertility after withdrawal of a combined oral contraceptive, within a few months conception rates are similar to those of women who stop using non-hormonal contraception (41,276,277). In 48 patients classified as having amenorrhea after oral contraceptive use the subsequent conception rate was no lower than in a control group not with amenorrhea (278). There appears to be a shorter delay with low-dose than high-dose products (279). Delay in the return of ovulation has on occasion led to the erroneous conclusion that the first pregnancy after oral contraceptive use might be unduly prolonged (SEDA-6, 351).

There does not appear to be any clinically significant delay in return of fertility after discontinuation of progestogen-only contraceptives. Although there have been no large studies, data from several small studies suggest no effect. Furthermore, because progestogen-only contraceptives prevent ovulation in only about half of cycles, and because the pregnancy prevention effects fall rapidly if a tablet is taken late, the normal reproductive physiology presumably returns quickly after tablet discontinuation.

Pregnancy

The likelihood of ectopic pregnancy in women taking oral contraceptives has to be set against the normal incidence in the population, taking care to use the same denominator; one can express it as the proportion of women who experience such an event, or as the proportion of pregnancies that occur and prove to be ectopic (280). The proportion of pregnancies that implant at an extrauterine site is 0.005 for both combined oral contraceptive users and women using no contraception, but, because oral contraceptive users are much less likely to conceive, their rate of ectopic pregnancy is much lower (0.005 per 1000 woman years, compared with 2.6 per 1000 woman years for women using no contraception). The incidence of ectopic pregnancies is also somewhat lower for combined oral contraceptives than for other contraceptive methods. In the past there was some concern about a possible increased risk of ectopic gestation after withdrawal of oral contraceptives (281), but this is no longer considered to be an issue.

Up to 10% of pregnancies among users of progestogen-only contraceptives implant outside the uterus; this is not greatly different to the ectopic pregnancy rate in unprotected women, but it is much higher than among users of adequate combined oral contraception (280). The reasons may relate to changes in tubal motility and delay in ovum transport.

Teratogenicity

Oral contraceptives are neither teratogenic nor mutagenic, and there is little concern about the risk of congenital anomalies if an oral contraceptive is accidentally taken during an early unrecognized pregnancy. The American College of Obstetrics and Gynecology concluded in 1993 that there was no causal link (282). Reviews have come to the same conclusion (283,284), as has a meta-analysis completed in 1995 (285). In theory the androgenicity of a progestogen could result in virilization, but it is most unlikely to be taken sufficiently late or in sufficiently high doses to have this effect.

Gene toxicity

The fear that oral contraceptives might prove to induce chromosomal abnormalities was expressed when they were relatively new, but has largely been laid to rest. When aborted fetuses from women who used oral contraceptives were compared with those from non-users, there was no difference in the frequency of abnormal karyotypes or in sex ratio between the two groups. Certainly, data have been presented showing a slightly raised frequency of minor chromosomal changes in children whose mothers had been exposed to oral contraceptives before pregnancy, but from a genetic point of view, these scattered findings are not alarming.

Sex of the offspring

There was early minor evidence that the use of oral contraceptives might result in a predominance of female births (286). However, later evidence has been indecisive (287,288). If there is any effect at all it must be extremely small.

Congenital anomalies

A number of early American studies appeared to show that children exposed in utero to oral contraceptives ran a slightly increased risk of being born with certain types of birth defects; in particular a syndrome was described comprising multiple malformations involving the vertebrae, anus, cardiac structures, trachea, esophagus, renal structures and limbs (abbreviated to VACTERL) (289). The entire VACTERL syndrome was in fact seldom or never encountered; clusters of defects falling within this group were seen, but the associations were very variable. Furthermore, virilization of the female fetus and some of the other elements in the VACTERL group have been described after exposure to certain progestogens, hormonal

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pregnancy tests, or (rarely) to oral contraceptives taken in error in early pregnancy.

In a 1983 retrospective study of 155 children with congenital limb reductions 18 mothers (12%) were found to have taken oral contraceptives inadvertently during early pregnancy compared with only one mother in a control group, a relative risk of 24; adjustment for smoking hardly altered the figure (289). However, other work has suggested that smoking carries a higher risk of malformations than the use of oral contraceptives (SED-12, 1022) (290).

The results of such studies have led some reviewers to conclude that oral contraceptives are slightly teratogenic, but caution is needed. The conclusion of the 1980 WHO report cited above that such an effect is slight or absent probably remains valid for all widely used oral contraceptives; naturally, newer products might have other effects.

Congenital malformations may occur after the use of hormonal (estrogen + progestogen) pregnancy tests, now obsolete, since these high doses of a hormonal combination represented aggressive interference with any early pregnancy. A 1967 report suggested some association with meningomyelocele or hydrocephalus, and later retrospective studies provided some evidence of cardiac defects or limb reduction anomalies. Such studies always raise methodological doubts, but it is not unthinkable that these tests were harmful, since they sometimes induced bleeding even in early pregnancy; they could thus impair embryonic nutrition.

Lactation

The effects of combined oral contraceptives on lactation have been examined carefully (291,292), since estrogens are well-known inhibitors of ovulation in large doses. Even products containing 30 micrograms of ethinylestradiol reduce the volume of milk (293); the composition of the milk is also slightly altered, but again one has the impression that the effect is not important, except in a very poorly nourished population. Both progestogens and estrogens are excreted in the milk, their proportions correlating with those in plasma, but the absolute concentrations are lower. The plasma/milk ratio varies from compound to compound, probably owing to variations in the degree of protein binding and (for progestogens) also to the variable amount of fat in the milk. The amount of steroid transferred in 600 ml of milk is estimated at 0.1% or less of the daily dose taken. Although newborn infants might be relatively sensitive to these hormonal substances, because of the immaturity of their detoxification systems, no adverse effects have been found when they were looked for systematically; nevertheless, isolated cases of gynecomastia have been noted in babies when their mothers were taking oral contraceptives during lactation.

In an 8-year follow-up of Swedish children whose mothers used combined oral contraceptives while breastfeeding, there were no negative effects on health, growth, or development (294). It should be realized that the hormonal content of natural human milk and cows' milk is not negligible. If hormonal contraception is to be used during lactation, it would be sensible to prefer low-dose progestogens rather than combinations with estrogens; they are not the most effective contraceptives, but probably sufficient to supplement the contraceptive effect of lactation itself and they are unlikely to inhibit lactation.

There is much evidence that progestogen-only contraceptives (including tablets, injectables, and implants) have no adverse effects on milk production (295); they reach the milk in negligible amounts and have no adverse effects on the breast-fed infant (296).

Susceptibility Factors

There are no hard and fast rules about prescribing oral contraceptives in women at risk of complications; the degree of risk resulting from a particular factor has to be considered from case to case.

Absolute contraindications

Combined oral contraceptives should not be used by women with the following absolute contraindications:

1. thrombophlebitis or venous thromboembolic disorders (current or past)
2. cerebrovascular disease (current or past)
3. coronary artery or ischemic heart disease (current or past)
4. breast cancer (current or past)
5. endometrial cancer or other estrogen-dependent neoplasia (current or past)
6. hepatic adenoma or carcinoma (current or past)
7. impaired liver function (current)
8. less than 2 weeks postpartum
9. breastfeeding and less than 6 weeks postpartum
10. known or suspected pregnancy
11. use of enzyme-inducing drugs, specifically the antimicrobial drugs rifampicin and griseofulvin and many anticonvulsants.

Relative contraindications

Combined oral contraceptives should be used only with caution and careful monitoring by women with the following relative contraindications:

1. aged over 35 years and/or obese and/or currently smoking 15 or more cigarettes per day; when all three factors are present this can be regarded as an absolute contraindication
2. migraine, particularly with focal neurological symptoms
3. hypertension (current, controlled)
4. diabetes, particularly with retinopathy, neuropathy, or vascular disease
5. familial hyperlipidemia or current treatment for hyperlipidemia
6. gallbladder disease (current)
7. cholestatic jaundice of pregnancy or with prior oral contraceptive use
8. unexplained abnormal vaginal bleeding
9. breastfeeding, particularly if less than 6 months postpartum
10. major surgery, with prolonged immobility.

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Although sickle cell disease is sometimes listed as a contraindication to oral contraceptive use, it has been suggested that this may not be justified (297). Women with sickle cell disease need highly effective contraception, because pregnancy is associated with increased morbidity and mortality to both mother and fetus, as well as the increased likelihood that the infant will have sickle cell disease. Theoretically, combined oral contraceptives should be given with caution, because of the increased risk of thrombosis associated with both sickle cell disease and combined oral contraceptives, but the limited available evidence indicates no change in hematological parameters among women using hormonal contraceptives. Progestogen-only formulations may be preferred, not only to avoid the potential risk of thrombosis but also because studies suggest that sickle cell crises may be inhibited.

The Oxford Family Planning Association's continuing study has shown convincingly that death from all causes is more than doubled in oral contraceptive users who smoke 15 or more cigarettes daily (298).

Drug Administration

Drug formulations

Low-dose oral contraceptives based on the older progestogens are relatively well tolerated in the short term, better so than the products that preceded them and those that came later. Two placebo-controlled studies with the combination of levonorgestrel 100 micrograms and ethinylestradiol in 704 patients over six cycles showed no differences in unwanted effects compared with placebo; in particular there was no evidence of weight gain (299).

Drug dosage regimens

Different schemes of administration have been studied and compared with one another without identifying any pattern of use that is ideal for all women. Various sequential programs of use, intended to mimic more closely the physiological changes in hormone secretion during the normal cycle rather than using a fixed combination throughout, have given better cycle control in some women, but others react better to the traditional pattern, in which the same combination is used throughout the 20-day period of use. The normophasic formulations use a popular sequential scheme; in these products the seven first tablets contain only estrogen and the next 14 tablets both estrogen and progestogen, giving an endometrium of a more normal secretory phase type; this in turn leads to more pronounced withdrawal bleeding. A further development of this principle, the triphasic type of product, involves administering a three-step regimen, in which the change from estrogenic to progestogenic dominance is more gradual; it appears to be helpful in avoiding excessive intermenstrual bleeding when this has been a problem, and it is apparently less likely than monophasic products to cause an unwanted reduction in HDL cholesterol (300). However, there is evidence that triphasic formulations based on norgestrel could carry the same increased risk of thromboembolic disorders as that seen with the third-generation oral contraceptives, because of a higher resistance to activated protein C than with the corresponding monophasic products (301).

In the "estrophasic" form of administration, ethinylestradiol 20 micrograms is given on days 1–5 of the cycle, 30 micrograms on days 6–12, and 35 micrograms on days 13–21. Norethisterone acetate 1 mg is also given throughout this period. The literature to date has not shown that this regimen, although claimed to be more "physiological" in its composition, is in fact better tolerated than a comparable combination in which ethinylestradiol is given in a dose of 30 micrograms throughout (302). However, the reduction in what may at some phases of the cycle be an unnecessarily high estrogen dose, that is more than is needed to maintain cycle control, is a healthy step, and it may be useful to have a further alternative product for women who do not find any existing formulation fully satisfactory.

There is continued interest in natural 17-β-estradiol in a form suitable for oral use, in view of the likelihood that it will produce fewer adverse effects than the synthetic estrogens used in most oral contraceptives. The particular problem has been to secure adequate cycle control with 17-β-estradiol, which is rapidly metabolized to estrone in the intestinal wall and liver; the degradation process is actually accelerated by progestogens. One approach under development in Germany involves combining this estrogen with dienogest, a progestogen that is reported to have no antiestrogenic activity (303). Preliminary work suggests that this can be successful, but one must be cautious in assuming that the end-product will be safer in all respects. There is evidence of a lesser effect of the natural estrogen on fibrinolysis, liver function, and lipid metabolism, but one must bear in mind that the true incidence of thromboembolic and other complications of the existing oral contraceptives is only now emerging after many years of worldwide use.

Drug–Drug Interactions

General

Two categories of drug interactions have been reported with oral contraceptives (304).

Interactions in which other drugs influence the effects of contraceptive steroids

The best known interactions are those in which another drug impairs the effect of the contraceptive steroids, leading to breakthrough bleeding and even pregnancy; such interactions are due primarily (but not exclusively) to enzyme induction, resulting in accelerated breakdown of the contraceptive steroids (305). This is a greater problem today than it was when higher-dose contraceptives with a larger reserve of contraceptive potency were in use. Many reported interactions of this type are single cases, and in some such instances it is likely that contraceptive failure was in fact due to poor adherence to therapy, diarrhea, or vomiting, rather than a direct interaction (306). However, with at least the enzyme-inducing anticonvulsants and rifampicin there are well-established major interactions.

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In a few cases the activity of oral contraceptives is enhanced by other drugs; this is less likely to cause problems, but if the effect is very marked or prolonged one might suffer the consequences of hyperestrogenicity (306).

Interactions in which oral contraceptives interfere with the metabolism of other drugs

Studies in animals and in vitro studies in human liver microsomes have shown that oral contraceptives can inhibit the metabolism of other drugs that undergo various forms of oxidative metabolism. In contrast, oral contraceptives seem to induce glucuronidation. For example, oral contraceptives reduce the clearance of aminophenazone (aminopyrine) (307), phenazone (antipyrine) (308,309), and pethidine (310). It has been suggested that the estrogenic component of oral contraceptives is necessary for inhibition of drug oxidation, since women taking progestogens alone had a normal clearance of phenazone, whereas those taking a combination tablet had impaired elimination of phenazone (311). However, such interactions are rarely of clinical significance.

Alcohol

Women taking oral contraceptives have a significant fall in the absolute elimination rate of ethanol (105 mg/kg/hour) compared with controls (121 mg/kg/hour). The percentage elimination rate of ethanol is also significantly reduced in women taking oral contraceptives (0.015% per hour) compared with control subjects (0.019% per hour). These results are consistent during the three phases of the menstrual cycle and when body leanness is taken into consideration (312).

Antacids

Antacids apparently do not affect the systemic availability of oral contraceptives, but since magnesium-containing antacids can cause diarrhea, they might reduce absorption of contraceptive steroids.

Anticoagulants

Oral contraceptives have been reported to reduce the effect of anticoagulants, probably because oral contraceptives have an antagonistic effect on certain clotting factors, although they potentiate the action of acenocoumarol (SEDA-5, 371).

One study showed a significant increase in the clearance of phenprocoumon, owing to accelerated glucuronidation. As phenprocoumon is metabolized by hydroxylation as well as by direct glucuronidation, the increased clearance may mean that induction of the latter process over-rides inhibition of the former (313).

Antiepileptic drugs

Enzyme inducers

Failure of contraceptive therapy and breakthrough bleeding have been noted repeatedly in patients concurrently taking various enzyme-inducing anticonvulsant drugs (305,314). These include phenytoin, primidone, ethosuximide, phenobarbital, and carbamazepine. The specific isozyme responsible for metabolic 2-hydroxylation of ethinylestradiol is CYP3A4, which is induced by anticonvulsants (304). However, in addition to enzyme induction, the anticonvulsants can increase the binding of sex hormone- binding globulin. Since sex steroids bind with high affinity to sex hormone-binding globulin and since phenobarbital increases sex hormone-binding globulin capacity, unbound active steroid concentrations will tend to fall during treatment with phenobarbital (315). In addition, in animals, phenobarbital increases steroid metabolism in both the gut wall and liver (316).

The newer anticonvulsants have not been studied as intensively as the older drugs, but felbamate, oxcarbazepine, and topiramate have enzyme-inducing activity and reduce plasma steroid concentrations (317).

Non-enzyme inducers

Valproic acid, which is not an enzyme inducer, has no detectable effect on the pharmacokinetics of progestogens and estrogens (318).

The newer anticonvulsants have not been studied as intensively as the older drugs as regards the possibility of interference with the effects of oral contraceptives. The available data suggest that women taking oral contraceptives can also take gabapentin, lamotrigine, tiagabine, and vigabatrin without significant pharmacokinetic interactions; the effect of zonisamide is uncertain (313).

Management

The use of an alternative contraceptive method has long been advised in women taking antiepileptic drugs, unless they can be treated with the traditional high-dose oral products, for example containing 80–100 micrograms of estradiol (314); for effective protection they may also need a shortened tablet-free interval. A fair test is to see whether a woman taking oral contraceptives and anticonvulsants has adequate cycle control; if not, for example if there is mid-cycle spotting, this is a sign of interference and an alternative method will certainly be advisable.

Ascorbic acid

Ascorbic acid (vitamin C) is extensively sulfated in the gastrointestinal mucosa and competes with ethinylestradiol, which is also extensively sulfated. Plasma ethinylestradiol concentrations are increased by ascorbic acid in women, both after a single dose of ethinylestradiol and during long-term oral contraceptive use, but the results are not consistent. On one occasion it was claimed that this effectively transformed a low-dose oral contraceptive into a high-dose formulation (319). It seems very dubious whether ascorbic acid in fact interferes significantly with the effects of oral contraceptives.

Benzodiazepines

Oral contraceptives alter the metabolism of some benzodiazepines that undergo oxidation (chlordiazepoxide, alprazolam, diazepam) or nitroreduction (nitrazepam) (320). Oral contraceptives inhibit enzyme activity and reduce the clearances of these drugs. There is nevertheless no evidence that these interactions are of clinical importance. For other benzodiazepines that undergo oxidative metabolism, such as bromazepam and clotiazepam, no change has ever been found in oral contraceptive users.

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Some other benzodiazepines are metabolized by glucuronic acid conjugation. Of these, the clearance of temazepam was increased when oral contraceptives were administered concomitantly, but the clearance of lorazepam and oxazepam was not (321). Again, it is unlikely that these are interactions of clinical importance.

Beta-blockers

Oral contraceptives increase the AUC and plasma concentrations of metoprolol, oxprenolol, and propranolol, but statistical significance is reached only with metoprolol. The changes are consistent with inhibition of hydroxylating enzymes, but are unlikely to be of clinical relevance (322).

Broad-spectrum antibiotics

There are sporadic, but well documented, reports of women using oral contraceptive steroids who became pregnant while taking a variety of antibiotics (323). However, there is much interindividual variation, which may explain the fact that some studies have shown no interference between oral contraceptives and antibiotics. Current suspicion focuses primarily on the broad-spectrum antibiotics (324), including ampicillin and the tetracyclines. The purported mechanism is apparently not enzyme induction but interference with the enterohepatic circulation of ethinylestradiol. Ethinylestradiol can be conjugated with both sulfate and glucuronic acid; sulfation occurs primarily in the small intestinal mucosa, while glucuronidation occurs mainly in the liver. These conjugates are excreted in the bile and then reach the colon, where they may be hydrolysed by gut bacteria to liberate unchanged ethinylestradiol, which can be reabsorbed (304). Broad-spectrum antibiotics may suppress this bacterial effect, resulting in reduced plasma hormone concentrations. The antibiotics doxycycline (325) and tetracycline (246) have been shown to have no effect on serum concentrations of exogenous estrogens and progestogens in women taking combined oral contraceptives containing ethinylestradiol 35 micrograms; however, in one of these studies endogenous progesterone was also assessed and there was no mid-cycle rise suggestive of ovulation.

Ciclosporin

Several case reports have suggested that the elimination of ciclosporin can be impaired by oral contraceptives, resulting in increased plasma ciclosporin concentrations. Ciclosporin undergoes hydroxylation and *N*-demethylation, in which cytochrome P450 is involved, so competitive enzyme inhibition probably explains the interaction. Dosages of ciclosporin should be reviewed carefully (326).

Clofibric acid

Oral contraceptives increase the plasma clearance of clofibric acid, which is mainly metabolized by glucuronidation (327,328).

Fluconazole

The effect of fluconazole 150 mg on circulating ethinylestradiol concentrations has been studied on day 6 of one of two cycles in women taking oral contraceptives (329). The serum concentrations of ethinylestradiol (C_{max} and AUC) were significantly increased by fluconazole, but t_{max} was not affected. These findings suggest that there is a potential for a clinically significant interaction between fluconazole and ethinylestradiol, by inhibition of estrogen metabolism.

Since oral contraceptive users sometimes need to be treated for vaginal candidiasis, the question arises which of the available treatments can be used without risk of impairing contraception. In a crossover placebo-controlled study, fluconazole 300 mg weekly for two cycles has been studied in 21 healthy women using Ortho-Novum 7/7/7 as a contraceptive (330). Fluconazole in this dose, which is twice that ordinarily recommended, produced small but statistically significant increases in the $AUC_{0–24}$ for both ethinylestradiol (mean 24% increase) and norethindrone (mean 13%). The C_{max} of ethinylestradiol was slightly, but just significantly, higher with fluconazole than placebo. The C_{max} for norethindrone was not different between the two groups. There were no adverse events related to fluconazole. These changes are such that one should not anticipate any increased risk of contraceptive failure when fluconazole is given simultaneously.

Glucocorticoids

In standard reference works, oral contraceptives are commonly listed as increasing the circulating concentrations of glucocorticoids (80), but variable effects have been reported with different glucocorticoids.

In oral contraceptive users there is a 30–50% reduction in the clearance of prednisolone and a prolonged half-life (331). These alterations result from changes in both protein binding, which is increased, presumably owing to increased concentrations of glucocorticoid-binding globulin, and unbound drug clearance, which is reduced, presumably owing to inhibition of metabolism. It has therefore been suggested that lower doses of prednisolone should be used in oral contraceptive users.

In 40 healthy women oral contraceptives had a greater effect on prednisolone than on budesonide (44). In oral contraceptive users, the average plasma concentration of simultaneously administered prednisolone was 131% higher than in a control group, whereas the average plasma concentration of budesonide was only 22% higher. Mean plasma cortisol concentrations were suppressed by 90% and 82% with prednisolone and by 22% and 28% with budesonide in oral contraceptive users and controls, respectively. Ethinylestradiol plasma concentrations were not affected by either glucocorticoid. The authors concluded that the oral contraceptive made no difference to the plasma concentrations of budesonide or cortisol suppression after the administration of budesonide capsules. These findings suggest that oral budesonide can be used in the usual doses without problems in women using oral contraceptives.

Griseofulvin

Griseofulvin modifies hepatic enzyme activity in mice, and although there is no good evidence of a major enzyme-inducing effect in humans, several case reports of pregnancies in women taking both oral contraceptives and griseofulvin suggest an interaction; the authorities in

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several countries have warned that the contraceptive effect may be diminished (332).

Methylxanthines

The clearances of both theophylline and caffeine are reduced in oral contraceptive users and half-lives are increased, probably because of inhibition of hepatic metabolism by cytochrome P450 (333). Caution in dosage is advisable.

Neuroleptic drugs

A single case of neuroleptic malignant syndrome has been described in a woman taking haloperidol and thioridazine, 12 hours after she started to take an oral contraceptive. The authors suggested that this could have been a pharmacodynamic interaction involving dopaminergic neurotransmission (334).

A kinetic study in which ziprasidone (40 mg/day) or placebo were co-administered with a second-generation oral contraceptive has provided evidence that ziprasidone is unlikely to interfere with oral contraception (335).

Opioid analgesics

Increased glucuronidation may explain the fact that oral contraceptives enhance morphine clearance (336).

Paracetamol

Paracetamol might have a similar effect to ascorbic acid, that is competition with ethinylestradiol for sulfation capacity in the gut. Paracetamol significantly reduced the AUC of ethinylestradiol sulfate but had no effect on plasma levonorgestrel concentrations

In six healthy women, a single dose of paracetamol 1 g significantly increased the AUC of ethinylestradiol by 22% and reduced the AUC of ethinylestradiol sulfate (337). Plasma concentrations of levonorgestrel were unaltered. This interaction could be of clinical significance in women taking oral contraceptives who take paracetamol regularly or suddenly stop taking it, but it is doubtful whether it has any practical repercussions.

The clearance of paracetamol was 22% greater in men than women, entirely because of increased glucuronidation, there being no sex-related differences in the sulfation or oxidative metabolism of paracetamol (338). Paracetamol clearance in women using oral contraceptive steroids was 49% greater than in the control women. Glucuronidation and oxidative metabolism were both induced in contraceptive users (by 78% and 36% respectively) but sulfation was not altered. Although sex-related differences in paracetamol metabolism are unlikely to be of clinical importance, induction of paracetamol metabolism by oral contraceptive steroids may have clinical and toxicological consequences.

Rifamycins

Increased intermenstrual or breakthrough bleeding and pregnancy have been reported in women taking rifampicin in conjunction with contraceptive steroids (339). There is evidence that rifampicin increases the rate of metabolism of both the estrogenic and progestogenic components of oral contraceptives through hepatic microsomal enzyme induction (340) involving the same CYP isozyme as that induced by anticonvulsants, CYP3A. A four-fold increase in the rate of steroid metabolism has been shown; it is therefore unwise for women taking rifampicin to rely on steroid contraception and an alternative method should be used.

Roxithromycin

Roxithromycin does not interfere with the pharmacokinetics of oral contraceptives (341).

Salicylates

In a small study, the degree of erythrocyte aggregation during oral contraception was, at least in the short term, partly reversed by treatment with acetylsalicylic acid 100 mg/day (342).

Salicylic acid clearance is higher in users of oral contraceptives, owing to increases in the glycine and glucuronic acid conjugation pathways. In eight men, eight women, and eight women taking oral contraceptive steroids, the clearance of salicylic acid after an oral dose of aspirin 900 mg was 61% higher in the men than in the control women, largely because of increased activity of the glycine conjugation pathway (salicyluric acid formation) (343). Salicylic acid clearance was 41% higher in contraceptive users than in the control women, because of increases in both the glycine and glucuronic acid conjugation pathways. These data confirm the importance of hormonal factors in the regulation of drug conjugation reactions and suggest that sex-related differences in the disposition of salicylic acid and aspirin may be of clinical importance.

Tricyclic antidepressants

Oral contraceptives reduce the clearance of imipramine, probably by reducing hepatic oxidation, and thus increase its half-life. Hydroxylation of amitriptyline is inhibited by contraceptive steroids. The clinical significance is uncertain, but there is at least anecdotal evidence of an increase in antidepressant adverse effects (344). Caution should be exercised when tricyclic antidepressants are used long term in women taking oral contraceptives.

Troleandomycin

There have been several reports of hepatic cholestasis in women taking both troleandomycin and oral contraceptives (345). Oxidation of troleandomycin by CYP3A4 produces a derivative (probably a nitrosylated derivative) that binds tightly to the enzyme and thereby causes inactivation. This inhibition is highly selective for CYP3A4, and hepatic accumulation of ethinylestradiol is possible.

Smoking

The polycyclic hydrocarbons in cigarette smoke are potent inducers of certain cytochrome P450 isozymes. There is a marked increase in the 2-hydroxylation of natural estradiol in smokers, but not of ethinylestradiol, suggesting that the two estrogens are metabolized by different P450 enzymes. There is thus probably no pharmacokinetic interaction between smoking and oral

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contraceptives, but women taking oral contraception should be encouraged to avoid heavy smoking because of the risks to the cardiovascular system.

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Hormonal contraceptives—progestogen implants

See also Progestogens

General Information

Hormonal formulations for implantation contain progestogens, including the following:

- levonorgestrel
- etonogestrel
- desogestrel
- megestrol
- norethisterone.

For a complete account of the adverse effects of progestogens, readers are urged to consult the following monographs as well as this one:

- Hormonal contraceptives—progestogen injections
- Hormonal contraceptives—intracervical and intravaginal
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens + progestogens
- Medroxyprogesterone
- Progestogens.

Levonorgestrel

Subdermal implanted silastic rods containing levonorgestrel (Norplant) have been widely studied and used with the support of the Population Council, but have fallen out of favor in a number of industrialized countries, because of complications. Six rods are inserted subdermally into the arm using a special device; each contains 35 mg of levonorgestrel, which is released into the circulation over 5 years. The total amount of levonorgestrel released daily during the first 500 days averages about 60 micrograms, falling to a plateau of 30 micrograms/day for the remainder of the 5-year period during which the product remains effective. It then has to be removed and replaced. The contraceptive effect of the implant does not seem to be caused primarily by ovulation inhibition, since after about the first year of use the hormone concentrations are too low to have this effect (1,2).

A product similar in approach to Norplant is the biodegradable subdermal capsular implant Capronor, which releases levonorgestrel over 12–18 months. Doses of 12 and 21.6 mg in capsules of differing size have been compared (3). Ovulation occurred in all cycles at the lower dose and in a quarter of cycles at the higher dose, so it is likely that the contraceptive

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effect results essentially from other progestogen-induced changes. Several users had local swelling or itching of the skin at the capsule insertion site, relieved by topical glucocorticoids.

The effectiveness, adverse events, and acceptability of the FDA-approved variant of levonorgestrel capsule implants in the USA over 5 years and the determinants of these outcomes have been studied (4). There were three pregnancies, yielding a 5-year cumulative rate of 1.3 per 100 users, an average annual rate of three per 1000 women. Ectopic pregnancy occurred at a rate of 0.6 per 1000 woman-years. There were no pregnancies in women who weighed less than 79 kg. Medical conditions that most often led to removal of the implant were prolonged or irregular menstrual bleeding, followed by headache, weight gain, and mood changes. Weight gain averaged 1 kg/year.

Etonogestrel

Implanon, which became available in 1999, is a subdermal implant that contains 68 mg of etonogestrel, the active metabolite of desogestrel. The product and field experience is therefore still limited. During the first 2 years after implantation, there is no ovulation; ovulation occurs occasionally in the third year, and it is recommended that the implant be removed after this time. As with Norplant, the principal problem is the occurrence of irregular bleeding (5), which leads some 25–30% of users to ask that the implant be removed. After some time, amenorrhea occurs in some 20% of users. There was a clinically significant increase in bodyweight in 20% of women carrying the implant (6). There may also be some local irritation from the implant, and minor scarring at the implantation site (7,8). In clinical trials the implant had no effect on coagulation measures, hemostasis, fat metabolism, or hepatic function, but according to the approved product information sheet the possibility of a slight increase in insulin resistance cannot be excluded.

Desogestrel

In clinical trials, implants containing desogestrel were effective, but with bleeding irregularities and ovarian cysts as the primary adverse effects (9).

Megestrol

Implants filled with megestrol acetate gave an unexpectedly high incidence of tubal pregnancies, while the absolute number of ectopic pregnancies was clearly greater than that expected for the general population (10). This finding reflects the same type of effect as has been described from time to time with oral progestogen-only products.

Norethisterone

A biodegradable delivery system using subcutaneous implants of fused pellets made from norethisterone and pure cholesterol has been tested (11).

General adverse effects

Generally speaking, the systemic effects of progestogen implants are very similar to those of low-dose oral progestogen-only contraception, except for variations due to the progressive change in the amount of hormone released. Many studies using various metabolic measures have shown no significant pattern of deviation from normal values (12,13), either during use of the implant or after removal (14).

Acceptability

As in the case of injectable depot contraceptives (SED-14, 1433) subdermal contraceptive implants are more likely to be used in developing countries, in order to overcome social and compliance problems, and that this can in principle involve risks to which underprivileged populations may be especially subject. All the same, acceptance is strikingly good (15). In a survey of data from eight developing countries, information was available on 7977 women starting Norplant, of whom 6625 used intrauterine devices and 1419 had been sterilized; most of the participants were followed for 5 years. All of the methods produced satisfactory degrees of contraception and, with a few exceptions, no characteristic morbidity was detected among Norplant users compared with the other groups. The two principal exceptions concerned gallbladder disease, which was 50% more common in women who used Norplant, and hypertension and borderline hypertension, the incidence of which was markedly raised in current implant users (RR = 1.81; 95% CI = 1.12, 2.92). Other unexpected findings were increased rates of respiratory disease and reduced risks of inflammatory disease of the genital tract in users of Norplant compared with sterilized women and those who used an intrauterine device (16).

In Burkina Faso, experience in 1660 women over 4 years has been critically reviewed (17). There were 247 withdrawals before the fourth year, for various reasons, including cycle disorders (60 withdrawals), unspecified medical reasons ($n = 53$), personal objections ($n = 47$), weight gain ($n = 14$), and contraceptive failure ($n = 2$). Menstrual disorders, including amenorrhea, spotting, and hypermenorrhea, occurred in 51% of the cases. The investigators stressed the need for a good information and sensitization campaign to reduce the number of implant withdrawals before the fourth year of use, since the product often seems to be withdrawn for insufficient reasons.

A study in Senegal produced similar findings over 5 years; the method was safe and effective, but dissatisfaction with cycle control was again a prominent reason for requesting removal of the implant (18).

A Thai study in 88 asymptomatic, young, HIV-1-positive women immediately after delivery has similarly confirmed the good acceptability of Norplant in a developing country, despite the high incidence of irregular bleeding and some instances of headache and hair loss (19).

In 10 718 women in China, Norplant was reliable and no serious or fatal effects were reported (20). When pregnancies did occur, only 3.1 per 100 were ectopic, which is higher than for the general population in Beijing but much lower than in US studies of Norplant (presumably

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because of lower rates of pelvic inflammatory disease in China). The 5-year continuation rate was 72 per 100 acceptors. Hemoglobin concentrations increased during the first year of use and remained high, presumably because of a reduction in menstrual blood loss. Although early findings suggested a reduction in platelet counts, follow-up work showed that in this population these were already low on admission to the study. Insertion-related complications necessitated removal in only 21 users.

In a study in Greece the method was well accepted by adolescents, although the study was small (13 subjects) (21). No significant problems arose during the 24-month follow-up period.

On the other hand, Norplant has been criticized in some Western countries, primarily because of adverse effects at the implantation site. An overview of adverse events reported to the FDA over 3 years, during which more than 700 000 implants were estimated to be in place, cited reports of 24 women hospitalized for infections at the insertion site and 14 who were either hospitalized or disabled because of difficulties associated with capsule removal (22). Fourteen women (two per 100 000) were reportedly hospitalized because of strokes. Three women developed thrombotic thrombocytopenic purpura and six developed thrombocytopenia. Finally, 39 Norplant users developed pseudotumor cerebri (benign intracranial hypertension), an incidence of 5.5 per 100 000; this condition is associated with obesity or recent weight gain, conditions that were present in most of the women for whom data were given. Although the rates of stroke and pseudotumor cerebri were slightly less than the expected rates in the general population of women of reproductive age, one has to take into account the well-known underreporting of adverse events to agencies such as the FDA; the figures could therefore mean that Norplant users are actually at increased risk.

Reviewing the overall scene in Britain, Hannaford has pointed to the considerable difference in acceptance rates for Norplant in the industrialized world and developing countries and has stressed the fact that the adverse reaction incidence is, according to the best evidence, low (23).

Rapid rejection of implantable progestogen-based contraceptives by some users, because of discomfort and local complications (for example because of breakage or migration of the device, or less than expert placement and removal), has attracted much attention in past reviews.

Organs and Systems

Cardiovascular

Norplant does not alter the blood pressure (24).

Nervous system

Headache is fairly common in women using progestogen implants (25).

Psychological, psychiatric

Two cases of major depression and panic disorder, developing soon after insertion of Norplant and resolving after removal, have been reported, but a causal association was not proven (26).

Five women using the Norplant system developed major depression, two of whom also developed obsessive-compulsive disorder and one of whom also developed agoraphobia (27). They had no prior psychiatric history but developed major depression within 1–3 months after insertion of Norplant. The depression worsened over time and in all cases resolved within 1–2 months after removal of Norplant. There was no recurrence of depression after 7–8 months in four cases available for follow-up. In addition to major depression, obsessive-compulsive disorder developed in two women and symptoms of agoraphobia developed in one woman during Norplant treatment, which resolved after removal.

Metabolism

Norplant does not alter body weight (28).

Hematologic

Research on blood coagulation has produced inconsistent results, usually showing little effect, as one would expect from a progestogen-based method without an estrogen component (29).

During 1 year of observation of 23 healthy fertile African women, beginning at the time that a Norplant device was inserted, the mean packed cell volume rose slightly but significantly from 40.5 to 42.2, but the mean total leukocyte, neutrophil, and lymphocyte counts all fell significantly, as did the mean platelet count (30). In four patients, the platelet counts were only 50–80 $\times$ 10^9/l. The rise in packed cell volume might, according to the authors, help to counter anemia in people in developing countries. However, the fall in the platelet count is hard to explain.

Skin

Some women who use progestogen implants develop acne, because of the androgenic activity of levonorgestrel. Three women developed severe acne vulgaris within several weeks to a few months after either insertion of a levonorgestrel IUCD (two women, 27 and 33 years of age) or subcutaneous implantation of etonogestrel (a 26-year-old woman) (31).

Reproductive system

The most frequent adverse effect of progestogen implants is irregular menstrual bleeding (32), which in some countries has reduced the acceptability of the treatment (33). It is common during the first year of use but tends to become much less marked thereafter (12,28,34). In one study, the incidence of menstrual irregularity in Norplant users was 73% compared with only 5% in a comparable population using oral contraceptives (35). There is also a fairly high incidence of breakthrough bleeding or amenorrhea (36). The cause of the irregular bleeding is not fully understood, but there is evidence that an increase in endometrial vascular fragility might precipitate vessel breakdown and hence breakthrough bleeding (37).

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It is not clear why some women are more susceptible to this complication than others. In a Thai study in a large number of Norplant users irregular bleeding was characterized by low estradiol concentrations, absence of luteal activity, and a thin hyperechoic pattern in the endometrium (38). The possible role of cellular apoptosis in the endometrial response to Norplant has been investigated using immunohistochemistry, but with negative results (39). However, among Norplant users the superficial endometrial blood vessels are more fragile than in controls and even more fragile than in untreated women with dysfunctional uterine bleeding (40).

An unusual approach to dealing with this irregular bleeding has been to give an antiprogestogen simultaneously. In 50 Chinese women with implants, mifepristone 50 mg once every 4 weeks has been compared with placebo (41). In all the women, regardless of treatment, the frequency of bleeding fell significantly over 1 year of observation, as it commonly does. However, women who took mifepristone had significantly shorter episodes of bleeding during treatment than during the 90 days before treatment started; the duration of bleeding episodes fell more gradually in the controls. Women who used mifepristone were more likely to find the treatment acceptable than the women who used placebo. Despite concerns that antiprogestogenic effects may jeopardize contraception, there were no pregnancies. In the view of the investigators, this approach may offer a useful strategy to relieve unwanted adverse effects of implants until bleeding patterns improve spontaneously with time.

A second unusual approach to the bleeding problem has been to give vitamin E. There is evidence that there is a poor angiogenic response in the endometrium of users of Norplant, and it has been hypothesized that this might be caused by an imbalance of pro-oxidant and antioxidant processes. A placebo-controlled study has suggested that vitamin E (200 mg/day for 10 days monthly) significantly reduces the number of monthly bleeding days (42). However, there was also some reduction in bleeding days with placebo, and this approach would need further study before the results could be accepted as clinically useful.

Amenorrhea is uncommon in women with progestogen implants, but the monthly blood loss is usually reduced rather than increased (43). Menstrual irregularity does not appear to be correlated with body mass index.

The appearance of enlarged ovarian follicles is a recognized complication of Norplant, but the reported incidence varies, probably because different methods are used to recognize them. Serial ultrasonography produces much higher figures than clinical methods and has led to exaggerated concern; the enlarged follicles are transient and do not require intervention (44).

Breast discharge has been reported in some women with progestogen implants (45).

Infection risk

Insertion-related complications include infection, hematoma formation, local irritation, scar formation, early implant expulsions, and allergic reactions to the dressing. A pooled analysis of insertion site complications in multicountry studies showed that 0.8% of women develop infection after insertion of Norplant, generally within the first week, but sometimes several months later (46). Implant expulsion occurred at some stage in 0.4% of users, often because of infection but sometimes because of poor placement. Two-thirds of expulsions were reported more than 2 months after insertion. The rates of such complications vary widely between practices and between countries.

Second-Generation Effects

Fertility

As with other progestogen-based contraceptive methods, the return of fertility after withdrawal is rapid: serum levonorgestrel concentrations are undetectable within a week after implant removal, and normal cycles usually resume during the first month.

Teratogenicity

Because the pregnancy rate among users of Norplant is quite low, the rate of ectopic pregnancy is also very low. There is no evidence that infants conceived during Norplant use are at higher risk of birth defects.

Lactation

One particular advantage of progestogen-only contraception is its suitability for use during breastfeeding, since there are no estrogens to impede lactation. The infant's intake of steroids is low and appears to be acceptable; its daily intake of steroids (estimated from concentrations in maternal milk during the first month of use) has been estimated to be 90–100 nanograms of levonorgestrel (Norplant), 75–120 nanograms of etonogestrel (Implanon), and 50 and 110 nanograms of nestorone (Nestorone and Elcometrine implants respectively) (47). However, it is still considered advisable to defer the implantation of these devices until 6 weeks after delivery, in view of the theoretical possibility of an adverse influence on the neonate.

Drug Administration

Drug formulations

The practical problems associated with Norplant have related to its physical form rather than its pharmacological profile. Practitioners specially trained in the insertion and removal of the device usually handle it without major problems, but without this special instruction it can be difficult to ensure that the rods are properly placed and that they are removed without scarring or other complications. Even given appropriate handling, the rods can cause problems as a result of migration or breakage in situ.

An implant can usually be removed in under a quarter of an hour under local anesthesia, but removal can be more difficult if the clinician is inexperienced, if the rods were not positioned properly at insertion, or if fibrous tissue has grown around them.

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If removal is not expertly handled in problematic cases, considerable scarring can result, and some users have proceeded to litigation as a consequence of such complications. Complications in the removal of Norplant capsules have been evaluated in 3416 cases from 11 countries (48). Complications were reported in 4.5% of removals, usually attributable to implants being broken during removal (1.7%) or being embedded below the subdermal plane (1.2%). Logistic regression analysis showed that the most important risk factors for complicated removals were complications at insertion and an infection at the implant site (before or at the time or removal). For women without complications, the mean removal time was 12 minutes, but for those with complications the mean increased to 30 minutes. These results illustrate the necessity of proper insertion technique, under aseptic conditions. Capsules become surrounded by a fibrous sheath within 3 months after implantation; beyond a few months, there is no difference in complication rate by duration of use.

Modified Norplant

A modified system, Norplant-2, requires only two instead of six rods. In 140 women using the Norplant-2 contraceptive subdermal implant system there were no accidental pregnancies over 3 years (49). Adverse effects that caused withdrawal from the study were acne, headache, and pain at the implant site. The termination rate for these medical reasons in year 3 of the study was 4.6%. The other main reason for termination was prolonged menstrual flow; the 3-year cumulative termination rate for menstrual irregularities was 3.8%.

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Hormonal contraceptives—progestogen injections

See also Progestogens

General Information

For a complete account of the adverse effects of progestogens, readers should consult the following monographs as well as this one:

- Hormonal contraceptives—intracervical and intravaginal
- Hormonal contraceptives—oral
- Hormonal contraceptives—progesterone implants
- Hormone replacement therapy—estrogens + progestogens
- Medroxyprogesterone
- Progestogens.

Injectable hormonal contraceptives, which are normally composed of long-acting esters of progestogens, have obvious practical advantages over oral products when user compliance is poor, for example in illiterate or mentally subnormal women or in some populations in developing countries. However, the fact that they are used in this type of patient has led to some social protest against their use, as if they were intended to undermine free will or provide cheap but unpleasant contraception for the underprivileged. This may in turn explain some unbalanced criticism of these products in terms of efficacy and safety. Their sometimes incomplete cycle control is indeed a practical disadvantage, but not a risk, and the fact that they contain no estrogen actually means that they are safer in those respects when risks of hormonal contraception are due mainly to estrogenic effects, particularly thromboembolic complications. All in all, the injectable hormonal contraceptives provide effective, reversible, and relatively safe contraception, which can well be used not only in the populations named above but also, for example, in some women who smoke or when an estrogen is contraindicated (1,2).

General adverse effects

The degree to which women tolerate the adverse effects of long-acting injectable contraceptives seems to vary from one population to another, and it can be important to examine the frequency and severity of complaints in different environments. Particularly in developed countries, these products are often stated to cause mood changes, weight gain, and demineralization, but in developing countries they are very widely used. A worldwide review has surveyed the incidence of these conditions in users and has compared some of the figures with those found with an implantable product (Norplant; see the monograph on Hormonal contraceptives–progestogen injections) (3). Perhaps surprisingly, a consensus seems to be emerging that depot medroxyprogesterone acetate implants do not in fact result in an increase in the incidence of depression or in the severity of pre-existing depression, even after 1 or 2 years, nor do they cause significant weight gain. Similarly, Norplant did not cause depression.

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Subgroups of users of depot medroxyprogesterone acetate may have reduced spinal bone density, but this seems to be reversible after withdrawal, even after several years of drug exposure (4). Bone mineral density in one cross-sectional study was lower among users of depot medroxyprogesterone acetate, but withdrawal was followed by complete recovery of normal bone density (4). A current study in the USA is expected to provide further data on this matter in women who have used medroxyprogesterone acetate for as long as 10 years.

Norethisterone enantate

The adverse effects of norethisterone enantate when used as a 2-monthly injectable contraceptive have been compared in various populations with those of depot medroxyprogesterone acetate and were found to be closely similar (5,6).

The largest single trial conducted with norethisterone enantate, covering some 9000 women-months of use, provided a fair picture of its adverse effects. Menstrual irregularity (prolonged bleeding, spotting, or amenorrhea) was the main complaint. Other adverse effects were periodic abdominal bloating and tender breasts, both of which were thought to be due to water retention and were relieved by diuretics. There was no associated weight gain. More than 50 of the women had pre-existing hypertension, and in these users the injections did not significantly affect blood pressure, which generally remained below 140/90 mmHg. Blood clotting was also not affected. High density lipoprotein cholesterol concentrations in the women treated were significantly lower than in the controls. The results of glucose tolerance tests did not differ significantly (7).

Three studies carried out in Bangladesh (8), Pakistan (9), and China (10) showed similar adverse reactions patterns. In the Bangladeshi study, nine of 254 women had a rise in both systolic and diastolic blood pressures, but five had a reduction of the same magnitude. In the Chinese women there were no significant changes in blood pressure. However, five Chinese women developed abnormal liver function tests and three of these women had liver enlargement after treatment for more than 2 years.

Other compounds and combinations

Other progestogen-only injectables have been tested, but those examined so far appear to have similar properties to the formulations that are already available.

Combined estrogen + progestogen injectables have been the subject of much experimentation. Administered monthly, they were developed in order to provide more dependable patterns of vaginal bleeding. Many formulations have been evaluated, and two of these have undergone phase III clinical trials by the WHO: one contains medroxyprogesterone acetate 25 mg with estradiol cipionate 5 mg and the other norethisterone enantate 50 mg plus estradiol valerate 5 mg. Analysis of daily menstrual diary record cards for women using these methods, compared with several other contraceptive methods and no method, showed that bleeding patterns for women receiving monthly injections were more regular, but not entirely normal (11). Although the median experience was similar to that of women not using contraception, the range of menstrual patterns was much wider. The outcome in this respect was found to be acceptable in only 70% of cycles during the first year of use, but later this figure rose to 85–90%. Under 10% of women discontinued use during the first year because of bleeding irregularities or amenorrhea, a rate that is presumably related in part to thorough counselling.

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Hormonal replacement therapy—estrogens + androgens

See also Estrogens *and* Androgens

General Information

For a complete account of the adverse effects of estrogens, readers should consult the following monographs as well as this one:

- Diethylstilbestrol
- Estrogens
- Hormonal contraceptives—emergency contraception
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens
- Hormone replacement therapy—estrogens + progestogens.

An estrogen + an androgen

This variant on the theme of estrogen replacement therapy has been propagated from various centers for different reasons (1,2).

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The theoretical starting point is the observation that (particularly after oophorectomy) there are deficiencies of both testosterone and androstenedione (3) and from the observation that estrogens alone do not relieve all menopausal symptoms. While there may well be justification for androgen replacement after oophorectomy, it is not clear that most of the claims made for use of this approach following a natural menopause are sufficiently well founded to justify the risks involved.

Adding an androgen to estrogen replacement therapy in the menopause has been thought to provide supplementary benefit with respect to climacteric symptoms, fatigue, and impaired libido, as well as favorably affecting muscle mass, skin quality, and bone density. It is also stated that androgens improve relief of vasomotor symptoms and relieve depression and anxiety when they occur after the menopause in this group of patients. Some workers have concluded that in women who respond to conjugated estrogens with a rise in blood pressure (not a common response by any means), this effect could be avoided by the addition of an androgen. Yet others have asserted that when the hematocrit falls during estrogen therapy, the effect can be prevented by an androgen.

The main reason for caution with the use of androgens is the susceptibility of menopausal women to their virilizing effects, which can sometimes prove irreversible. Deepening of the voice, hirsutism, and acne can occur in many patients at an early stage of treatment and can prove distressing. There may be enlargement of the clitoris, although not consistently.

However, there are other reasons for caution. Statements with respect to the effect of estrogen + androgen combinations on blood lipids are, for example, contradictory, depending on the combinations used. If androgens are to be used, the effect on lipoproteins should at all events be monitored (1).

It is doubtful whether one can avoid unwanted androgenic effects by cautious dosing. For example, the published data seem to show that a desired effect on libido is only likely to occur at androgen doses sufficient to produce serum testosterone concentrations in the virilizing range (over 2 ng/ml), and that even after withdrawal of such doses virilizing concentrations of testosterone are maintained for many months.

Finally, androgens actually appear in some respects to counter the desired effects of estrogens in this patient group. Doppler flowmetry has been used to study the cardiovascular effects of adding an androgen to an estrogen in an open, randomized study in 40 patients over 8 months, all of whom were using transdermal estradiol (50 micrograms/day) and cyclic medroxyprogesterone acetate (10 mg/day) (4). Half of the subjects then received additional testosterone undecanoate (40 mg/day). The investigators concluded that while the androgen improved sexual desire and satisfaction and had no effect on endometrial thickness, it did in part counteract the beneficial effects of the estrogens on cerebral vascular activity and lipids. The most notable change was a significant increase in the pulsatility index of the middle cerebral artery. The androgen also resulted in a 10% reduction in HDL cholesterol concentration within 8 months. The authors therefore urged caution in using androgens, at least in the manner used in this study.

There are naturally some groups that have worked together with manufacturers to profile the supposed advantages of particular estrogen + androgen regimens, especially when these are available in the form of fixed combination formulations.

The adverse effects of estrogen + androgen therapy include mild hirsutism and acne (5). One group of workers, who examined the use of "Estratest" (an esterified combination of estrogen and methyltestosterone), concluded that in their experience under 5% of women developed acne or facial hirsutism, a frequency similar to that experienced when using conjugated estrogens 0.625 mg/day. Women had significantly less nausea with the estrogen + androgen treatment than with conjugated estrogen therapy. Cancers, cardiovascular disease, thromboembolism, and liver disease were stated to be rare among users of the combination. The only adverse events exceeding 4% of total reports were alopecia, acne, weight gain, and hirsutism (6). However, much higher rates of complications with such combinations have been reported from other centres (1).

The evident disadvantage of a fixed combination is that it renders it impossible to carry out any fine adjustment of dosages, such as might be called for in the light of the clinical response and adverse effects in a given individual.

All in all, it seems very doubtful whether any of the supposed benefits of androgen therapy justify the risks involved, except possibly as a transitional measure in those recently oophorectomized women who have acute symptoms of sudden androgen withdrawal.

An estrogen + an androgen + a progestogen

Another variant on hormone replacement therapy involves using all three types of sex steroid in parallel, starting from the argument that during the fertile period all three are synthesized by the ovary (7). A "natural" version of this therapy uses estradiol, testosterone (with or without dehydroepiandrosterone), and progesterone in an appropriate pharmaceutical form (for example micronized), so that absorption is attained without the need for 17-substitution. This approach naturally avoids some of the undesirable effects of the synthetic steroids, and has been stated to improve menopausal depression and anxiety. However, the adverse effects of all three types of component can be experienced.

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Hormone replacement therapy—estrogens

See also Estrogens

General Information

For a complete account of the adverse effects of estrogens, readers should consult the following monographs as well as this one:

- Diethylstilbestrol
- Estrogens
- Hormonal contraceptives—emergency contraception
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens + androgens
- Hormone replacement therapy—estrogens + progestogens.

Estrogen replacement therapy was until recently widely recommended for the prevention of osteoporosis in middle-aged and older women (1). Long-term estrogen therapy also reduces the incidence of ischemic heart disease in such women (2). However, it has always been difficult to know in which women such prophylactic use is likely to be needed, and this dilemma is compounded by the prospect of adverse reactions, which can include any of the acute effects listed in the estrogen monograph, but also in some cases long-term effects such as tumors.

The multiplicity of hormone replacement therapy regimens in use (involving one or two drugs, continuous or intermittent treatment, and various forms of administration) makes it difficult to express any general conclusion about the benefit-to-harm balance, and there has been a thoughtful review of the obstacles to assessing these matters objectively and scientifically, including questions of both ethics and trial design (3). Even the ultimate effect of hormone replacement therapy on the incidence of ischemic heart disease remains subject to dispute (4), and incidental reports of cardiac complications, sometimes in women with entirely healthy coronary vessels, continue to cause concern (5). For such reasons, much work has been devoted to determining the lowest effective dose of estrogen needed to achieve particular results.

An extraordinarily thorough review of all significant controlled studies of estrogen replacement therapy has been published by the Cochrane Collaboration (6). The participants totalled 2511 and the trials lasted 0.25–3 years. The primary purpose was to confirm efficacy, but data on adverse effects were also collected. Withdrawal because of adverse events, commonly breast tenderness, edema, joint pains, and psychological symptoms, was not significantly higher with HRT than placebo (OR = 1.38; 95% CI = 0.87, 2.21). Breast tenderness and withdrawal bleeding were the only significant problems in terms of frequency. The studies did not justify the conclusion that there are serious adverse effects, such as thrombosis and malignancies.

Carefully assessed data like these illustrate the delicacy of the balance in the debate regarding the benefit-to-harm balance of long-term HRT; extreme statements have been made in both directions, and clearly most are not justified. A reasoned critical review, stressing how inadequate many of the data still are on both efficacy and safety issues, has been published (7).

Observational studies

A Japanese study of the use of estriol 2 mg/day for 12 months in 68 postmenopausal women with climacteric symptoms showed a significant effect in relieving hot flushes, night sweats, and insomnia (8,9). There were significant falls in serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) concentrations, but no effect on lipids, bone demineralization, or blood pressure. There was slight vaginal bleeding in 14% of women treated during a natural menopause, but histological and ultrasound evaluation showed no changes in the endometrium or breasts. It is evident, however, that higher doses might be needed when treating women of other races with a higher body weight. Other workers have found that when given with a progestogen over long periods, estriol 2.0 mg/day seems much less likely to cause undesirable lipid changes than are equine conjugated estrogens, which can cause increased HDL cholesterol and triglyceride concentrations (10).

Comparative studies

In a randomized, multicenter study in Denmark 376 perimenopausal women with climacteric symptoms were randomly allocated to oral sequential combined treatment with regimens based on estrogen plus either desogestrel or medroxyprogesterone acetate (11). Both treatments effectively alleviated menopausal complaints within 6 months and gave good cycle control. Bleeding pattern and mood disturbances were more favorably affected by desogestrel, but overall the differences in adverse effects (irregular bleeding and a slight tendency to hypotension) were not large. It should be noted, however, that with cyclic combined hormone replacement therapy treatment, the bleeding pattern alone does not seem to be a reliable means of distinguishing cases in which the endometrium is atrophic or inactive from those in which it is proliferative or hyperplastic (12).

Organs and Systems

Cardiovascular

One of the most serious aspects of the thromboembolic complications now widely acknowledged as being associated with HRT is that their emergence coincides with the development of the conclusion that the role of HRT in reducing the risk of coronary heart disease is at best unproven. A form of treatment that was originally viewed

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as potentially beneficial to the cardiovascular system is at present on balance perhaps harmful (13).

A US group examined potential risk factors for venous thromboembolic events in women assigned to HRT in the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, a 3-year double-blind study in 875 postmenopausal women designed to assess the effects of HRT on heart disease risk factors (HDL cholesterol, fibrinogen, blood pressure, and insulin) (14). Women with a history of estrogen-associated venous thromboembolic events were excluded. Ten women, all assigned to HRT, had a venous thromboembolic event during the study. Only baseline fibrinogen varied significantly between those who had a venous thromboembolic event while assigned to HRT event (mean 2.49 g/l) and those who did not have an event (mean 2.81 g/l). Adjusting for covariates did not affect this finding. As the authors remarked, the lower fibrinogen concentrations among women who subsequently reported venous thromboembolic events may be a marker for a specific, but as yet undefined, coagulopathy that is magnified in the presence of exogenous hormones. However, larger studies are needed to confirm this hypothesis.

Since much of the evidence of thromboembolic complications with HRT relates to the use of conjugated equine estrogens, the degree of risk when natural 17-beta-estradiol was used instead has been examined in Norway in a population-based case-control study involving consecutive women, aged 44–70 years, discharged from a University Hospital between 1990 and 1996 with a diagnosis of deep venous thrombosis or pulmonary embolism (15). Women with cancer-associated thrombosis were excluded. Random controls were used. The material comprised 176 cases and 352 controls, that is two controls for each case. All the women who received HRT had been given estradiol. The frequency of HRT use was 28% (50/176) in cases and 26% (93/352) in controls. The estimated matched crude odds ratio was 1.13 (CI = 0.71, 1.78), which shows no significant association of overall use of estradiol-based HRT and thromboembolism. However, when the duration of exposure to HRT was taken into account by stratification, there was an increased risk of thromboembolism during the first year of use, with a crude odds ratio of 3.54 (CI = 1.54, 5.2). This effect was reduced by extended use to a crude odds ratio of 0.66 (CI = 0.39, 1.10) after the first year of use. The authors concluded that the use of estradiol for HRT was associated with a three-fold increase in the risk of venous thromboembolism, but that this increased risk was restricted to the first year of use. One is bound to wonder whether this shift in risk was genuine or reflects only the limitations of the study.

Among the less common forms of thromboembolism that have been reported is occlusion of the retinal vein, familiar with the oral contraceptives but unusual with HRT (16).

Ear, nose, throat

Visual hallucinations have been associated with estrogen in a patient with Charles Bonnet syndrome (17).

- An 84-year-old woman with poor visual acuity secondary to bilateral, non-exudative, age-related macular degeneration had non-threatening visual hallucinations 2 weeks after starting oral estrogen for osteoporosis. The estrogen was withdrawn and the hallucinations subsided. She was given estrogen twice more and each time the hallucinations recurred.

In this patient estrogen may have promoted release phenomena and triggered the hallucinatory episodes.

Nervous system

Over the years there have been reports that headache or classical migraine is either alleviated or exacerbated by HRT. This has been studied in 50 menopausal women with headaches who were randomized to either transdermal estradiol 50 micrograms for 7 days a month or oral conjugated estrogens 0.625 mg/day for 28 days, both regimens being supplemented with medroxyprogesterone acetate 10 mg/day during the latter half of each month (18). In patients with episodic tension headache there was no significant change in headache pattern. However, in women with migraine without aura the frequency and duration of the attacks increased significantly during HRT in the subgroup using the oral formulation; the transdermal formulation had no effect on the migraine pattern.

Sensory systems

The possibility that estrogen replacement therapy might cause dryness of the eyes has been reviewed in the light of data from the large Women's Health Study in the USA (19), and this work has been further reviewed (20). Questionnaires were sent to 25 665 participants. For every 3-year increase in the duration of replacement therapy there was a 15% increase in the incidence of dry eye syndrome. The risk was greater in women who used estrogen alone than in those who used combined estrogen + progestogen regimens. The evidence was not statistically strong, but it suggests that there is some correlation and that users and prescribers should be aware of it.

Metabolism

Lipids

Changes in lipids have been observed with both HRT and oral contraceptives and have sometimes been promoted as potentially advantageous, but it is not clear how significant such changes are, at least in biochemical terms. A review and pooled analysis of 248 prospective studies available up to the year 2000 has provided data on this issue in postmenopausal women (21). All estrogen-only regimens raised HDL cholesterol and lowered LDL and total cholesterol. Oral estrogens raised triglycerides. Transdermal 17-beta-estradiol lowered triglycerides.

Weight

Weight gain is widely believed to be a common consequence of HRT, and the desire to avoid obesity is a major reason why some women decline treatment. However, the potential effects of HRT need to be distinguished from effects that could be due to changing lifestyle or ageing. The effects of short-term hormone replacement and age on alterations in weight, body composition, and energy balance have therefore been studied in a prospective

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study in 18 healthy women aged 45–55 years and in 15 aged 70–80 years, with measurements at baseline, repeated after 1 month of transdermal estrogen (Estraderm 50 micrograms/day), and again after a further month of transdermal estrogen with vaginal progesterone (100 mg bd) added for the final 7 days (22). In neither age group did estrogen treatment correlate with anthropometric changes. Resting energy expenditure and activity were positively correlated with fat-free mass, while energy intake was not. Resting energy expenditure, energy intake, and activity were lower in older women when adjusted for fat-free mass. Changes in weight during treatment were not statistically significant. In addition, there was no difference between the groups in body mass index, fat mass, fat-free mass, total body water, or waist-to-hip ratio. This work has confirmed the reduction in energy expenditure that occurs with ageing, and it suggests that there is no effect of HRT on resting energy expenditure or body weight.

Hematologic

There has been a randomized, placebo-controlled study in 25 postmenopausal women to investigate the mechanisms that could underlie the induction of thrombosis by unopposed estrogens (23). Fasting and fat-load-stimulated plasma concentrations of clotting factor VII were measured after 8 weeks of oral 17-beta-estradiol (2 mg/day). Estradiol increased the mean fasting and postprandial plasma concentrations of total factor VII by 17 and 21% respectively, but did not affect the fasting and/or postprandial plasma concentrations of active factor VII. These findings argue against the idea that raised concentrations of total factor VII underlie the increased risk of arterial thromboembolism in these women.

It has been firmly concluded, in the light of prior evidence, that HRT increases the risk of venous thrombosis, this risk not being outweighed by any demonstrable benefit in terms of arterial cardiovascular disease (24). This conclusion is now being increasingly accepted, and the effects of postmenopausal HRT on blood coagulation have been intensively studied and documented over the years. However, the effects in older women, who have the highest risk of thromboembolism, are not well defined, and a US group has studied the association between HRT and concentrations of natural anticoagulant proteins in this subpopulation in a cross-sectional study in women of 65 years or older participating in the Cardiovascular Health Study (25). Protein C antigen and antithrombin were measured in HRT users (230 taking an unopposed estrogen and 60 taking an estrogen with a progestogen) and a comparison group of 196 non-users. Estrogen use was associated with significantly higher protein C concentrations (4.80 versus 4.30 micrograms/ml); the results were similar with estrogen/progestogen. In both user groups, antithrombin was significantly lower than in non-users (109% for each treatment group versus 115% in non-users). Adjustment for factors related to prescription of HRT and to anticoagulant protein concentrations had little impact on the results. For antithrombin, the association with HRT was larger for thinner Caucasian women and black women. The authors concluded that venous thrombosis from HRT may be partly mediated by alterations in antithrombin, but not by protein C concentrations.

Although the thrombogenic potential of oral estrogen in postmenopausal women is well documented, it has been argued that direct studies of the effect of estrogen replacement on hemostasis are largely lacking and not well known (26). A review of a series of randomized trials has shown that the treatment has no significant effect on concentrations of fibrinogen and factor VII. Plasma concentrations of antithrombin and protein S fell with oral estrogen but not with transdermal estrogen. No form of replacement affected protein C concentrations, but there was activation of coagulation in the presence of oral estrogen, as reflected by a rise in the concentration of prothrombin fragment 1 + 2. As far as fibrinolysis is concerned, oral estrogen reduces plasma PAI-1 and tPA, leading to an increase in fibrinolytic potential. The absence of an effect of transdermal estrogen on coagulation and fibrinolysis suggests that the route of estrogen administration is important, but it has not to date been convincingly shown that transdermal estrogen in equieffective doses is less thrombogenic than the oral form.

Urinary tract

Since microalbuminuria can be regarded as being associated with renal and cardiovascular disease, evidence that the incidence of microalbuminuria is higher during treatment with oral contraceptives or hormone replacement therapy deserves to be taken seriously. A Dutch group has performed a case-control study of baseline and dispensing data relating to 4301 women participating in a study on the prevention of renal and vascular disease; the main outcome measure was microalbuminuria (30–300 mg/day) (27). After adjusting for age, hypertension, diabetes, obesity, hyperlipidemia, and smoking, the odds ratio for microalbuminuria was 1.90 (CI = 1.23, 2.93) for premenopausal oral contraceptive users and 2.05 (1.12, 3.77) for postmenopausal hormone replacement therapy users. The point estimate increased dose-dependently, albeit insignificantly, according to the estrogen content of the oral contraceptives (30–50 micrograms) and was greater in oral contraceptives with a second-generation progestogen (OR = 2.04) than those using a third-generation progestogen (OR = 1.39; CI = 0.63, 3.06). In the case of HRT, the odds ratio increased with the duration of HRT, that in women who had used the product for more than 5 years being double that in others.

Skin

- A 54-year-old woman developed melasma, macular hyperpigmentation associated with increased estrogen states, in atypical sites after starting to take HRT; on withdrawal it began to fade (28).

Musculoskeletal

Despite the evidence that estrogens can be of value in countering osteoporosis, some studies have suggested that women who use them are more likely to have back pain than those who do not; the possible causal link has remained unclear, and continues so despite recent confirmation of the phenomenon. Baseline information on

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estrogen replacement therapy, functional status, back pain and function, and other variables has been obtained in 7209 elderly white American women (mean age 71 years) enrolled in a study of osteoporotic fractures; X-rays were also taken at baseline and an average of 3.7 years later (29). A total of 1039 women were using estrogen replacement therapy at baseline, 2016 reported former use, and 4154 had never used estrogen replacement therapy. Compared with never-users, a significantly higher percentage of current estrogen users reported clinical back pain (53 versus 43%) and back impairment (12 versus 9.2%) at baseline and at the follow-up visit (pain 51 versus 41; impairment 16 versus 12%). This occurred despite a higher prevalence of vertebral fractures in never-users of estrogen at the baseline visit. The increased likelihood of back pain and impairment of function in current and former estrogen users remained in evidence, despite statistical adjustment for possibly interfering factors. The relative risks for impaired back function in former and current users at follow-up were 1.1 (0.9, 1.3) and 1.6 (1.3, 2.0) respectively (30).

Reproductive system

Breasts

Two doses of transdermal estrogen, 50 and 100 micrograms/day, have been compared with placebo in preventing bone loss in postmenopausal women over 24 months (31). Bone mineral density in the lumbar spine was only marginally better with the higher dose; the slightly better effect was largely offset by a higher incidence of breast pain, reported by 8% of women on placebo, by 6% of those who took 50 micrograms/day, and by 17% of women who took 100 micrograms/day.

Uterus

It has long been recognized that periodic or irregular uterine bleeding will occur in some women using HRT. While it is simple to dismiss this merely as a reactivation of endometrial proliferation and shedding, some workers have sought to examine the precise mechanism of this unwanted complication, particularly because it might prove to be the harbinger of more serious events involving the endometrium. From recent work in the UK it has been concluded that estrogen treatment appears to alter the endometrial expression of matrix metalloprotease 9 (MMP-9) and the tissue inhibitor of metalloproteases (TIMP-1) as well as the local balance between these molecules (32). This alteration may promote breakdown of the endometrial extracellular matrix and blood vessels and hence bleeding.

There could be fairly simple ways of screening for endometrial disorders in women using HRT. A study in 93 such women has confirmed the earlier finding that if a Papanicolaou smear is taken from the vagina the presence of endometrial cells in the smear gives some (non-specific) indication that there are endometrial changes, which may range from hyperplasia or polyps to endometrial carcinoma (33).

Immunologic

Two healthy young women took estrogen supplements for some 3 years and then developed classic Sjögren's syndrome (34). The syndrome was most severe in the woman who had taken the higher dose. These cases seem to have confirmed earlier reports that estrogens can play a role in the pathogenesis of Sjögren's syndrome in susceptible patients.

Long-Term Effects

Drug dependence

While the effects of estrogen treatment on mental function and mood are generally assessed as positive, work in Britain has raised the possibility of some form of psychological dependence. The starting point was the finding in various studies that a proportion of women in whom hormone replacement therapy was terminated had a return of psychological symptoms, such as low mood and tiredness, despite the fact that their circulating estrogen concentrations were high. A questionnaire-based study was therefore carried out in 600 women, mean age 46 years; in most of them, HRT with implants had been undertaken after hysterectomy, and the mean duration of use was 5 years. Among those with high circulating estradiol concentrations (more than 500 pmol/l) 40% reported a need to use top-up doses of HRT to cope with daily activities, 78% spoke of low mood and tiredness (apparently when estrogen concentrations were falling), 80% experienced a "buzz" (which was undefined) 1–2 weeks after receiving a new implant, and 75% claimed that life without an implant would be "terrible." These effects, interpreted as evidence of dependence, were almost absent in women with lower circulating estrogen concentrations. The authors were of the opinion that circulating concentrations of some 300 pmol/l, which are sufficient to maintain bone mass, should be the therapeutic aim, and that there will then be much less of a dependence problem than when higher concentrations are attained (35,36).

Mutagenicity

A finding that needs further study is that when estrogens are used for the treatment of osteoporosis they may have some genotoxic potential, as evidenced by their ability to cause an increased frequency of sister chromatid exchange (37).

Tumorigenicity

The associations between hormone replacement therapy and breast, endometrial, and ovarian cancers are discussed in the monograph on estrogens.

Susceptibility Factors

Age

When a young woman undergoes a surgical menopause it is clear that estrogen replacement treatment, if given at all, is likely to be needed for many years, and in the present state of knowledge this is probably justifiable, provided that the effects are monitored. The dilemma that the physician faces in such cases has been discussed in the light of a patient in whom gross obesity compounded the possible risk of thrombosis; the patient was

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nevertheless treated with an implant and remained well for 4 years (38).

Renal disease

Estrogen replacement therapy may have untoward effects in patients with renal disease, including an increased risk of thrombosis of dialysis access and potentially worsening of coronary artery disease, probably because the excretion of estrogens is impaired (39).

Drug Administration

Drug dosage regimens

The amount of estrogen taken during estrogen replacement is usually about one quarter of that found in oral contraceptives, and is intended to be sufficient to restore physiological amounts of endogenous estrogens. During the physiological cycle, menstrual discomfort of all types is at its mildest (and usually absent) during the mid-follicular phase when plasma estradiol concentrations are 60–150 pg/ml (40). In replacement therapy some workers seek to titrate the dose of estrogen individually in order to maintain this level, hoping thereby not only to avoid adverse effects associated with hyper- or hypo-estrogenicity but also to optimize the therapeutic effect. Strictly speaking this individualized treatment is called for because of the variability of estrogen clearance, but in normal women plasma levels are rarely measured, an approximate adaptation of dosage being undertaken purely on the basis of subjective reactions.

There is no benefit and sometimes a disadvantage to giving estrogen alone for only 25 days a month; in particular, estrogen withdrawal symptoms such as decreased well being, headaches, and hot flushes can occur each time the treatment is interrupted.

It is widely recommended that estrogen replacement therapy, if it is to be used at all, should be initiated at the time of menopause or within 3 years of it, since it is at this time that bone loss can be most severe. Many physicians go on to argue that once it has been started hormonal replacement therapy should continue for at least 20 years and perhaps indefinitely, in view of evidence that withdrawal may be followed by accelerated bone loss, at least comparable to that observed after the menopause. Later use of estrogen, once bone has already been lost, does not result in appreciable recovery of bone, although further loss can still be prevented. Large comparative studies have suggested that a series of alternative regimens for hormone replacement therapy should be available, so that for each individual woman the most appropriate form of treatment can be chosen; no one regimen is ideal for all, and finding the best approach for a given patient may be a matter of trial and error (41).

For the acute treatment of climacteric vasomotor symptoms it seems clear that micronized 17-beta-estradiol in a dose as low as 0.25 mg can be sufficient; however, a starting dose of 1 mg is advisable, with subsequent adjustments as necessary. At a dose of 2 mg the proportion of women who withdraw from treatment with the active product because of adverse effects was twice that seen with placebo (42). To provide longer-term protection against early postmenopausal bone loss, treatment with estradiol in a dose of 1 mg/day, balanced by a progestogen, is adequate (43). Most workers believe that the estrogen is best counterbalanced by a progestogen when used in the long term, but here there is still some disagreement about the doses needed.

Drug administration route

If it is indeed true that transdermal estrogens have certain advantages over oral estrogens in terms of safety, this needs to be better documented than hitherto; as in so many instances, the evidence is confusing, because of the multiplicity of products and doses. In 35 postmenopausal women who had been amenorrheic for at least 1 year, two consecutive 2-month courses of transdermal estrogen (estradiol patches 25 micrograms and 50 micrograms) were randomly followed by a 2-month course of treatment with either an estradiol patch 100 micrograms/day or an estradiol patch 50 micrograms/day combined with either progesterone 300 mg/day or medroxyprogesterone acetate 5 mg/day during the last 14 days (44). Neither transdermal estradiol alone nor transdermal estradiol plus progestogen altered the lipoprotein profile, LDL resistance to oxidation, or LDL particle size. However, all treatments similarly reduced myeloperoxidase protein concentrations.

In a case-control study 155 postmenopausal women who had had venous thromboembolism were compared with 381 matched controls (45). In all, 32 cases and 27 controls were current users of oral replacement therapy, whereas 30 cases and 93 controls were current users of transdermal products. After adjustment for potential confounding variables, the estimated risk ratio for venous thromboembolism in current users of the oral products compared with the transdermal users was 4.0 (1.9–8.3). This is strong evidence that the transdermal route was considerably safer. However, the conclusions of different studies continue to conflict with one another, no doubt in part because of variations in the formulations and patterns of use of the products.

Drug–Drug Interactions

Dexamfetamine

Preclinical studies (as well as anecdotal clinical reports in the course of the years) seem to show that estrogens, through their effects on the central nervous system, can affect behavioral responses to psychoactive drugs. In an unusual crossover study, the subjective and physiological effects of oral dexamfetamine 10 mg have been assessed after pretreatment with estradiol (46). One group of healthy young women used estradiol patches (Estraderm TTS, total dose 0.8 mg), which raised plasma estradiol concentrations to about 750 pg/ml, and a control group used placebo patches. Most of the subjective and physiological effects of dexamfetamine were not affected by acute estradiol treatment, but the estrogen did increase the magnitude of the effect of dexamfetamine on subjective ratings of "pleasant stimulation" and reduced ratings of "want more." Estradiol also produced some subjective effects

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when used alone, raising ratings of "feel drug," "energy and intellectual efficiency," and "pleasant stimulation."

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Hormone replacement therapy—estrogens + progestogens

See also Estrogens *and* Progestogens

General Information

For a complete account of the adverse effects of estrogens, readers should consult the following monographs as well as this one:

- Diethylstilbestrol
- Estrogens
- Hormonal contraceptives—emergency contraception
- Hormonal contraceptives—oral
- Hormone replacement therapy—estrogens
- Hormone replacement therapy—estrogens + androgens.

For a complete account of the adverse effects of progestogens, readers should consult the following monographs as well as this one:

- Hormonal contraceptives—intracervical and intravaginal
- Hormonal contraceptives—oral
- Hormonal contraceptives—progestogen implants
- Hormonal contraceptives—progestogen injections
- Medroxyprogesterone
- Progestogens.

Two alternatives to long-term estrogen therapy have been proposed, because of the fear of certain risks (particularly malignancy) that might result in postmenopausal women:

- combined estrogen + progestogen regimens with a monthly interruption to allow for withdrawal bleeding
- long-term therapy with estrogens alone periodically interrupted by a cycle of combined treatment.

In those few countries in which hysterectomy is still endemic it has been argued that in the residual minority of women with an intact uterus combination therapy should be the normal form of HRT. Therapeutic benefits have also been claimed from using the combination. Unfortunately, some of the publications that have made claims for the therapeutic advantages of adding progestogens to estrogens in HRT have not provided exact comparative data, and the beneficial effects which are described are not clearly different from those claimed for estrogen alone.

The dispute about the benefit to harm balance of the various competing forms of HRT for use in the climacteric or postmenopausally is becoming increasingly intense, with a sharp division of opinion between protagonists and critics of the individual patterns of treatment. The view was often defended by earlier workers that, at least for certain classes of users, some form of combined estrogen + progestogen treatment is likely to be more appropriate and perhaps more physiological than estrogen replacement alone. Many variants have been used and none is likely to be ideal for all subjects. Some have argued that in the climacteric there are sound reasons for using estrogen with intermittent progestogen and that it is much underused, despite the fact that uterine bleeding and other adverse progestogenic effects are, with some combined formulations (but not all), major reasons for patient noncompliance and early withdrawal (1).

Observational studies

In 104 women with established postmenopausal osteoporosis, continuous estrogen + progestogen therapy resulted in increases in bone mineral density of the femoral neck and a fall in systolic blood pressure; the most common adverse effects were mastalgia (44%) and vaginal bleeding (29%) (2).

The combined use of estradiol and dydrogesterone reduce both diastolic and systolic blood pressures in postmenopausal women in whom the diastolic pressure had been raised (3). Evidence is also advanced from various quarters that adding a progestogen to adequate dosages of an estrogen promotes new bone formation, restores bone that has been lost and reduces the risk of carcinoma of the breast.

When 16 diabetic and hypertensive postmenopausal women aged 47–57 years were treated cyclically with estradiol plus norgestrel, existing proteinuria and even creatinine clearance often improved (4). The effects were unrelated to conventional risk factors for vascular complications, such as raised blood pressure, plasma glucose, or serum cholesterol.

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General adverse effects

Of 206 postmenopausal women who took the oral combination of estradiol valerate plus norethisterone (5) eight withdrew because of bleeding during year 1; during years 2 and 3 there were no withdrawals because of bleeding. By the end of year 3, 133 patients had completed the study. There were serious adverse effects in 24, but there was no definite relation to therapy. The numbers of adverse events reported each year by the patients who completed the study are shown in Table 1. The authors concluded that this combination was effective in the majority of patients and was well tolerated.

Distinguishing adverse effects due to estrogens or progestogens

When patients have adverse effects during combined hormone replacement therapy it is necessary to determine whether the progestogen or the estrogen is causing the problem. If heavy bleeding or breast tenderness is the primary complaint, the estrogen component is probably the problem and therefore the dose should be reduced. If the patient complains of irritability, depression, water retention, or headaches, the problems are probably due to the progestogen component and the latter should in that case be changed or the dose adjusted; since several different progestogens are in use (particularly norethindrone, norethindrone acetate, medroxyprogesterone acetate, and micronized progesterone) there is a degree of choice.

Benefit to harm balance

With increasing concern over the long-term safety of hormone replacement therapy, the benefit to harm balance has to be continually reassessed, and conclusions as to its prophylactic or therapeutic value need to be adjusted as experience accumulates. Not all the promises held out for the benefits of this therapy have been confirmed. For example, while estrogens prevent peripheral bone loss they do not prevent vertebral fractures (6) and in a 2-year placebo-controlled, crossover study in 34 healthy postmenopausal women, treatment with transdermal estrogen alone (Menorest 50 micrograms/day) did not improve lipid profiles or any indices of arterial function (7).

Table 1 The numbers of adverse events in 3 successive years in patients taking estradiol valerate + norethisterone (5)

Adverse event	Year 1 ($n = 164$)	Year 2 ($n = 144$)	Year 3 ($n = 133$)
Cardiovascular			
Hypertension	5	3	—
Palpitation	4	4	3
Phlebitis	3	—	—
Respiratory			
Breathlessness	3	0	1
Metabolism			
Weight gain	10	5	2
Gastrointestinal			
Abdominal pain	2	2	—
Musculoskeletal			
Fractures	7	1	1
Joint/bone pain	6	3	6
Reproductive system			
Menopausal symptoms	4	1	5
Breast tenderness	63	4	3
Breast lumps	2	4	2
Bleeding/spotting	91	60	24
Abnormal smear	—	2	—
Ovarian cysts	1	1	4
Other adverse events	105	53	34
Total	306	143	85

It is remarkable that, despite decades of accumulated observational evidence, the balance of benefits and harms for hormone use in healthy postmenopausal women remains uncertain (8). Quite apart from the constantly changing spectrum of the available data, one explanation for the confusion is the relatively high proportion of poor-quality clinical work, particularly studies that are designed to promote particular commercialized forms of treatment from among the many alternatives available.

A study that cannot be faulted on that score is the Women's Health Initiative, a randomized, controlled, primary prevention trial (planned to last for 8.5 years), in which 16 608 postmenopausal women aged 50–79 years with an intact uterus at baseline were recruited at 40 US clinical centers over the period 1993–98 (9). In one part of this study, 8506 participants received conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day; 8102 were given placebo. The primary desired outcome was reduction of coronary heart disease (non-fatal myocardial infarction and death), with invasive breast cancer as the primary anticipated adverse outcome. After a mean of 5.2 years, the data and safety monitoring board recommended stopping the trial of estrogen plus progestogen versus placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported harms exceeding benefits. The estimated hazard ratios (and 95% confidence intervals) were:

- coronary disease 1.29 (1.02, 1.63; $n = 286$)
- breast cancer 1.26 (1.00, 1.59; $n = 290$)
- stroke 1.41 (1.07, 1.85; $n = 212$)
- pulmonary embolism 2.13 (1.39, 3.25; $n = 101$)
- colorectal cancer 0.63 (0.43, 0.92; $n = 112$)
- endometrial cancer 0.83 (0.47, 1.47; $n = 47$)
- hip fracture 0.66 (0.45, 0.98; $n = 106$)
- death due to other causes 0.92 (0.74, 1.14; $n = 331$).

What the above amounts to is that the absolute excess risks per 10 000 woman-years attributable to the use of an estrogen plus a progestogen were seven more coronary heart disease events, eight more strokes, eight more pulmonary embolisms, and eight more invasive breast cancers, while the risk reductions per 10 000 woman-years were six fewer colorectal cancers and five fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10 000 woman-years. The overall harms in this study thus clearly exceeded the benefits. All-cause mortality was not affected.

Other published studies, many of which are of limited scope, do not run closely parallel to the above findings

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from the Women's Health Initiative, and the data on cardiovascular effects remain particularly confusing. However, Beral and colleagues have pointed out optimistically that "substantial new data should soon be available from randomized trials of estrogen-alone hormonal replacement therapy versus placebo," although they added that "few additional trial data on combined hormone replacement therapy are expected for about a decade" (10). They also pointed out that existing randomized trials are too small to provide reliable evidence on some basic matters, including the relative risks of the various compounds in use.

Organs and Systems

Cardiovascular

Despite biologically plausible mechanisms whereby estrogens might be expected to confer cardioprotection in postmenopausal women, as well as observational data suggesting cardiovascular benefit, the literature continues to provide contradictory outcomes on this. Electrocardiographic work has suggested that not only the estrogen but also the progestogen component of HRT can have some impact on the electrophysiological properties of the heart (11), the clinical significance of which, if any, is not understood. The picture is further confused by evidence that a particular regimen may initially increase the risk, yet confer long-term benefit, as in the Heart and Estrogen/progestin Replacement Study (HERS), while in other well-planned work, such as the recent Estrogen Replacement and Atherosclerosis trial (ERA), there was no benefit (12).

There has been a randomized trial in 270 postmenopausal women to evaluate the effects on cardiovascular risk markers of two continuous combined estrogen + progestogen replacement products (17-beta-estradiol 1 mg with or without norethindrone acetate 0.25 or 0.5 mg) compared with unopposed estrogen or placebo (13). LDL cholesterol was reduced to a similar extent in all those who took the active treatment (10–14% from baseline). Compared with unopposed 17-beta-estradiol, 17-beta-estradiol plus norethindrone acetate 0.5 mg enhanced the reductions in total cholesterol and apolipoprotein B concentrations. The combination of 17-beta-estradiol plus norethindrone blunted or reversed the increases in concentrations of high-density lipoprotein cholesterol, apolipoprotein A-I, and triglycerides produced by 17-beta-estradiol alone. The effects of 17-beta-estradiol plus norethindrone on hemostatic variables were similar to those of 17-beta-estradiol alone, except for factor VII activity, which was significantly reduced by 17-beta-estradiol plus norethindrone acetate 0.25 and 0.5 mg. The combination of 17-beta-estradiol plus norethindrone blunted reductions in C peptide and insulin concentrations produced by unopposed 17-beta-estradiol, but did not affect them compared with placebo. The authors concluded that 17-beta-estradiol plus norethindrone produced favorable changes in most cardiovascular risk markers and had a profile distinct from that of unopposed estrogen.

The findings of the randomized HERS suggested that in women with clinically recognized heart disease, HRT might be associated with early harm but late benefit in terms of coronary events. The findings of that study seem in the meantime to have been confirmed by some further US work. In one study the histories and subsequent course of 981 postmenopausal women who had survived a first myocardial infarct and had thereafter used estrogen or estrogen + progestogen were examined (14). Relative to the risk in a parallel group of women not currently using hormones there was a suggestion of increased risk during the first 60 days after starting hormone therapy (RR = 2.16; CI = 0.94, 4.95) but of reduced risk with current hormone use for longer than 1 year (RR = 0.76), although the confidence intervals were wide.

However, in a second study, data on 1857 women from the Coumadin Aspirin Reinfarction Study were used to assess the incidence of cardiac deaths or unstable angina as related to the use of HRT. Of the population studied, 524 (28%) had used HRT at some point and 111 of the latter (21%) had started HRT after suffering a myocardial infarct ("new users"). Women who began HRT after their first myocardial infarct had a significantly higher subsequent incidence of unstable angina than women who had never used hormones (39 versus 20%); however, these new hormone users suffered death or recurrence of myocardial infarct at a much lower rate than never-users (4 versus 15%). These differences are striking. Prior/current users had no excess risk of the composite end-point after adjustment. Users of estrogen plus progestogen had a lower incidence of death, infarct, or unstable angina during follow-up than users of estrogen only (RR = 0.56) (15). As Grady and Hulley have commented in an editorial, current data seem to make it clear that "postmenopausal hormone therapy should not be used for the purpose of preventing coronary disease unless future data from well-designed randomized trials document such benefit" (16).

The thrombotic complications of combined HRT in a potentially high-risk group have been assessed in a randomized, multicenter study in the USA in 2763 women, average age 67 years (17). All had some degree of pre-existing coronary heart disease but no previous venous thromboembolism, and none had undergone hysterectomy. They took either conjugated equine estrogens 0.625 mg + medroxyprogesterone acetate 2.5 mg or a placebo. During an average 4.1 years of follow-up, 34 women in the hormone therapy group and 13 in the placebo group had venous thromboembolism (relative risk = 2.7, excess risk = 3.9 per 1000 woman-years). The mean risk for venous thromboembolism was increased among women who had leg fractures (RR = 18) or cancer (RR = 4) and it was also raised several-fold for 3 months after in-patient surgery or non-surgical hospitalization. The risk was approximately halved by the use of aspirin or statins.

Metabolism

Hyperlipidemic postmenopausal women taking combined sequential estrogen + progestogen replacement therapy have large fluctuations in lipid and lipoprotein

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concentrations. These fluctuations depend on the hormonal phase, that is estrogen alone or combined with progestogen. Progestogens blunt or even overwhelm the estrogenic effects on lipoproteins (18).

Progestogen has also been claimed to produce more favorable concentrations of HDL cholesterol (19), but this is a questionable conclusion; most work seems to show that whereas estrogen alone increases HDL concentrations (for example by some 7%), combined treatment weakens this favorable effect and actually can reduce HDL concentrations by some 16%.

Changes in lipids have been observed with both HRT and oral contraceptives and have sometimes been promoted as potentially advantageous, but it is not clear how significant such changes are, at least in biochemical terms. A review and pooled analysis of 248 prospective studies available up to the year 2000 has provided data on this issue in postmenopausal women (20). All estrogen-only regimens raised HDL cholesterol and lowered LDL and total cholesterol. Oral estrogens raised triglycerides. Transdermal 17-beta-estradiol lowered triglycerides. Progestogens had little effect on estrogen-induced reductions in LDL and total cholesterol. Estrogen-induced increases in HDL and triglycerides were opposed according to the type of progestogen in the following order (from least to greatest effect): dydrogesterone and medrogestone, progesterone, cyproterone acetate, medroxyprogesterone acetate, transdermal norethindrone acetate, norgestrel, and oral norethindrone acetate. Tibolone reduced HDL cholesterol and triglyceride concentrations. Raloxifene reduced LDL cholesterol concentrations. In 41 studies of 20 different formulations, HRT generally lowered lipoprotein (a). Thus, the route of estrogen administration and the type of progestogen used determine the effects of HRT on lipid and lipoprotein concentrations.

In another study an estrogen + progestogen combination produced no adverse effects on serum lipids or lipoproteins (21), but this again may depend very much on the exact combination and duration of treatment.

Whatever the truth, the question arises whether the modifications in lipid effects resulting from the addition of progestogen will not interfere with the favorable impact of estrogen on coronary artery disease; there has been some earlier evidence that the combined therapy is rather less effective than plain estrogen in preventing cardiac disorders (SEDA-16, 459).

Female sex hormones can also have effects on lipids when they are given transdermally, and this has been studied retrospectively in 159 women who used transdermal or oral replacement therapy (22). All used either transdermal estradiol 0.05 mg twice weekly or oral conjugated estrogen 0.625 mg/day, each combined with oral medroxyprogesterone acetate 2.5 mg/day. The mean increases in HDL cholesterol in the first year and second year averaged 10 and 31% with oral treatment, the corresponding figures for transdermal therapy being 14 and 34%. With oral therapy the mean reductions in total cholesterol in the first and second years were 2.9 and 15%, and with transdermal treatment 5.6 and 5.7%. With oral treatment, the mean falls in LDL cholesterol in the first and second years were 6.2 and 18% and with transdermal treatment 7.9 and 16% respectively. Transdermal treatment reduced triglyceride concentrations by 34%, whereas oral estrogen treatment increased them by 19% at the end of 2 years. Both treatments changed serum lipids favorably. Nevertheless, triglycerides were increased by oral estrogen but reduced by transdermal treatment at 2 years.

It has been hypothetically suggested that the use of HRT could slow the progression of atherosclerosis by an effect on lipids. In a 1-year study of 321 women with increased thickness of the carotid intima media who were using either various forms of HRT or none at all, there was no slowing in the progression of subclinical atherosclerosis and no unfavorable effect on the process (23). HRT significantly reduced LDL cholesterol, fibrinogen, and FSH.

Reproductive system

Adding a progestogen to estrogen therapy means that regular withdrawal bleeding occurs, probably in some 97% of users up to the age of 60 years. This could explain why such combinations, although increasingly advocated, have not been used on a wider scale; few women relish the prospect of regular "menstrual" bleeding persisting for many years after the menopause, and it might introduce new and unforeseen risks, particularly to the aging uterus. However, on theoretical and practical grounds, such combinations have been developed and used for relatively short periods of treatment during the climacteric itself to regularize bleeding and to relieve menopausal symptoms. The pattern of short-term adverse effects of these products is very similar to that of the combined oral contraceptives.

Some cases have underlined the need to use an estrogen in combination with a progestogen, rather than unopposed estrogen, when treating women who have undergone radical surgery (removal of both the ovaries and uterus) for endometriosis. If unopposed estrogen replacement is given, any residual area of endometriosis will rapidly expand (24).

Continuous administration of an estrogen + progestogen combination is effective in achieving amenorrhea with prolonged use (75% at 6 months). An adverse effect of such a regimen is a high incidence of unpredictable break-through bleeding, particularly during the initial months of treatment (25).

Mammary tension and mastodynia are adverse effects related to the action of estrogens (26). In postmenopausal women estrogen + progestogen replacement therapy can be associated with an increase in mammographic density and with the onset or worsening of mastodynia. Tibolone, a steroid with estrogenic, progestogenic, and some androgenic activity, does not seem to affect breasts of normal structure and can be considered a first-rate replacement therapy in women whose breasts are rather dense or who have benign mastopathy (26).

Various companies and investigational groups continue to examine the relative efficacy and safety of different forms of combined postmenopausal treatment. In a randomized, placebo-controlled trial 579 women were treated for 26 cycles with sequential combinations of 17-beta-estradiol 1 mg plus dydrogesterone 5 or 10 mg or 17-beta-estradiol 2 mg with dydrogesterone 10 or 20 mg (27). The effects of these treatments in the 442 women who underwent biopsy were considered satisfactory in terms of

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cycle control and endometrial response, but the 1 mg dose of 17-beta-estradiol was associated with more intermittent uterine bleeding than the 2 mg dose. Higher doses of dydrogesterone were associated with a higher incidence of cyclical bleeds and a later time of onset.

Long-Term Effects

Tumorigenicity

Breast cancer

The complexity of the relation between hormonal replacement therapy and breast cancer has been stressed in previous volumes (SED-14, 1454) (SEDA-22, 465), and much depends on the type of replacement therapy given and the class of tumor studied. This latter point has been underscored by a US study that provided evidence that the use of combined hormonal replacement therapy increases the risk of lobular, but not ductal, breast carcinoma in middle-aged women (28).

An American cohort study designed to determine whether increases in risk associated with an estrogen + progestogen regimen are greater than those associated with estrogen alone has been carried out based on follow-up data for 1980–1995 from the National Breast Cancer Detection Demonstration Project (29). From 46 355 postmenopausal women, mean age at the start of follow-up was 58 years, 2082 cases of breast cancer were identified. Increases in risk with estrogen only and estrogen + progestogen were restricted to use within the previous 4 years, the relative risks being 1.2 and 1.4 respectively. The relative risk increased by 0.01 with each year of estrogen use and by 0.08 with each year of estrogen + progestogen use. Among women with a BMI of 24.4 kg/m^2 or less, the mean increases in relative risk were 0.03 and 0.12 with each year of estrogen use and estrogen + progestogen use respectively. These associations were evident for the majority of invasive tumors with ductal histology and regardless of the extent of invasive disease. The risk in heavier women did not increase with the use of estrogen only or estrogen + progestogen. These data suggest that estrogen + progestogen increases the risk of breast cancer beyond that associated with estrogen alone.

Endometrial cancer

Because sequential combined hormone replacement therapy with estrogen + progestogen for 10–24 days per month can increase the risk of endometrial cancer in the long run, attention has been devoted to the possibility of giving the two types of hormone continuously. In one retrospective case-control study in the USA it was concluded that the risk of endometrial cancer among users of continuous combined treatment, relative to women who had never used hormone replacement therapy, was 0.6 (95% CI = 0.3, 1.3); the risk relative to women who used intermittent combined therapy was 0.4 (CI = 0.2, 1.1) (30). The authors' conclusions were cautious, since most continuous combined hormonal therapy had been fairly short-term (under 72 months), but the figures suggested that women taking continuous combined hormone replacement therapy for several years were not at an increased risk of endometrial cancer compared with women who had never taken hormone replacement therapy and might in fact be at reduced risk of endometrial cancer.

In the meantime, others have concluded that the risk of endometrial cancer is present, but is less with combined therapy than with unopposed estrogen. However, the picture is not simple; the contradictions could be explained by the fact that risks appear to vary both by usage patterns and by patient characteristics, such as body weight and a history of diabetes (31).

Susceptibility Factors

Genetic factors

In a population-based, case-control study in 232 postmenopausal women who had had a non-fatal myocardial infarct during the previous 3 years, a stratified random sample of 723 postmenopausal women without a history of infarction acted as controls (32). Among hypertensive women, the presence of the prothrombin 20210 G→A variant was a significant risk factor for infarct (OR = 4.32; 95% CI = 1.52, 12) and in this group there was also a significant interaction between the use of HRT and the presence of the prothrombin variant in increasing the risk of infarction. Compared with non-users of HRT with the wild-type genotype, women who were current users and who had the prothrombin variant ($n = 8$) had a nearly 11-fold increase in the risk of a non-fatal myocardial infarct. The interaction was absent among non-hypertensive women. No interaction with HRT was found for factor V Leiden in either hypertensive or non-hypertensive women. These findings suggest that screening for the prothrombin variant may allow a better assessment of the risks and benefits associated with HRT in individual postmenopausal women.

Other features of the patient

While the extent of vaginal bleeding when using estrogens plus progestogens varies somewhat with the exact formulation and dose, another determining factor is the pretreatment state of the endometrium: a thick endometrium at the start of treatment results in significantly more bleeding days than a thin endometrium (33). This might be a helpful predictor of the extent to which a particular woman will find this type of HRT acceptable.

Drug Administration

Drug formulations

The impact of a new formulation of low-dose micronized medroxyprogesterone plus 17-beta-estradiol on lipid profiles in menopausal women has been studied for 12 months. Total cholesterol concentrations fell 8.4%, low-density lipoprotein cholesterol fell 18%, and high-density lipoprotein cholesterol increased 6.9%; total triglycerides increased 12%. The most frequently reported adverse events were menorrhagia, breast tenderness, cervical polyps or cysts, bloating, fatigue or lethargy,

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influenza or a flu-like syndrome, back pain, headaches, irritability, and depression (34).

Drug dosage regimens

In 438 postmenopausal women, randomly assigned to either constant 17-beta-estradiol (1 mg/day) plus inter mittent norgestimate 90 micrograms (3 days off, 3 days on) or a fixed combination of 17-beta-estradiol (2 mg/day) with norethisterone acetate (1 mg), the two regimens had similar bleeding profiles and provided comparable relief from vasomotor symptoms (1). However, breast discomfort and edema were experienced by twice as many subjects who used the fixed combination. The intermittent regimen was notably free of endometrial hyperplasia.

Drug administration route

In an open, non-comparative study, the efficacy of a low dose transdermal estrogen (Oesclim 25 transdermal patches, releasing 17-beta-estradiol 25 micrograms/day) was tested in 60 women with postmenopausal symptoms over 8 weeks (35). The dosage could be doubled if required and sequential treatment with an oral progestogen was also given for 12 days or more each month in all non-hysterectomized women. Of the 60 patients, 53 reacted satisfactorily to the basic dose and all the various treatments were said to be well tolerated. One could cite a dozen similar papers from the recent past in which the findings were so amorphous that they have not made a serious contribution to the evolution of knowledge.

In two multicenter, double-blind, randomized, controlled trials of three once-a-week transdermal systems delivering continuous combined 17-beta-estradiol + levonorgestrel (estrogen 45 micrograms/day + progestogen 15, 30, or 40 micrograms/day) to treat vasomotor symptoms and prevent estrogen-induced endometrial hyperplasia in 1138 women, all were highly effective (36). Reactions at the site of application, vaginal hemorrhage, and breast pain were the most common adverse events, and the proportion of women with amenorrhea increased over time in all the treatment groups.

Drug–Drug Interactions

Statins

With growing interest in the use of statins in women, the question naturally arises whether hormonal replacement could have any effect on their efficacy or safety. Data from the HERS (conducted in women with cardiac disorders) seem to have shown that there is no interaction (37). Estrogen replacement itself resulted in a significant increase in the early risk of primary events in women who did not use statins but not in statin users. Adjustment for statin use after randomization showed no adverse effect of estrogen on the efficacy of statins, in terms of either cardiovascular events or mortality.

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Human immunodeficiency virus (HIV) vaccine

See also Vaccines

General Information

The difficult problems connected with clinical trials that have not been approved by independent authorities were highlighted in 1991 when Zagury published the first reports of immunization of humans using *Vaccinia* vaccine expressing HIV glycoprotein gp-160 (1,2). The first HIV vaccine approved for clinical trial status (1989) by the US Food and Drug Administration (FDA) was a recombinant gp-160 vaccine produced in a baculovirus-insect cell expression system by MicroGeneSys (3). Since then, various clinical trials using different HIV vaccines have been carried out. However, all HIV vaccines are still experimental. An overview of the current status of HIV vaccine development, with emphasis on efficacy and safety, has been provided by the AIDS Division of the National Institute of Allergy and Infectious Diseases (4).

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Human papilloma virus (HPV) vaccine

See also Vaccines

General Information

Cervical cancer is the second most common cause of cancer deaths in women worldwide and the number one cause in the developing world. It is almost invariably associated with HPV infection. HPV type 16 is found in about 50% of cervical cancers. About 70% of cervical cancers are associated with HPV types 16, 18, and 8 other HPV types. Types 18, 31, and 45 account for 25% of HVP-positive tumors. HPV types 6 and 11 can cause genital warts. The development of a safe and effective HPV vaccine could prevent pre-malignant and malignant disease associated with HPV infection. Various HPV vaccines are under development or are undergoing clinical trials. Among others, GlaxoSmithKline (bivalent HPV types 16 and 18) and Merck (HPV types 6, 11, 16, 18) are both conducting expanded phase III trials and the researchers say the results so far have been promising. Merck plans to apply for approval to the US Food and Drug Administration in late 2005.

Clinical studies with a recombinant vaccine (using *Vaccinia* virus expressing HPV 16, 18, E6, and E7 proteins) in patients with preinvasive and invasive cancer have been reviewed (1).

Observational studies

There has been a trial of a papilloma (HPV-16) virus-like particle vaccine in 72 healthy volunteers, aged 18–27 years (2). The vaccine was well tolerated and highly immunogenic.

Placebo-controlled studies

In a double-blind study in 2392 young women (aged 16–23 years) randomly assigned to either three doses of placebo or HPV-16 vaccine at day 0, month 2, and month 6, the vaccine reduced the incidence of both HPV-16 infection (3.8 per 100 woman-years at risk in the placebo group versus 0 per 100 woman-years at risk in the vaccine group) and HPV-16-related cervical intraepithelial neoplasia (all nine cases of neoplasia occurred among the placebo recipients) (3).

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Hyaluronic acid

General Information

Hyaluronic acid is a naturally occurring polysaccharide that is widely distributed in body tissues and intracellular fluids, including the aqueous and vitreous humour, synovial fluid, and in the ground substance that surrounds cells (1). It is a high-molecular weight substance originally developed for use as a vitreous replacement. Although 98% of the product consists of water, it is very viscoelastic.

Uses

Hyaluronic acid is considered to have low inflammatory and antigenic potential, and has been used in various intraocular procedures. In addition to filtration bleb formation, it has been used to protect the corneal endothelium during intraocular lens implantation and keratoplasty, to reform the anterior chamber, to push back a bulging vitreous face, and in retinal detachment surgery as a vitreous replacement.

Hyaluronate sodium is also combined with sodium chondroitin sulfate (in Viscoat) as a corneal transplant preservation medium. Sodium chondroitin sulfate and other viscoelastic substances protect the corneal endothelium during intraocular surgery.

Hyaluronic acid is used topically to promote wound healing. A film containing hyaluronate sodium and carmellose is used to prevent surgical adhesion. Hyaluronic acid is increasingly being used in cosmetic dermatology to treat wrinkles in patients who are sensitive to bovine collagen.

Intra-articular injections of hyaluronic acid formulations of different molecular weights have been used in patients with osteoarthritis and can provide short-term benefit (2).

General adverse effects

The major adverse effect associated with the use of viscoelastic substances, such as hyaluronate sodium, is a transient rise in intraocular pressure in the immediate postoperative period, attributed to its viscoelastic nature, resulting in coating and plugging of the trabecular meshwork. For this reason, it is advisable to dilute hyaluronate sodium at the end of the surgical procedure with a balanced salt solution. Chondroitin sulfate is relatively less likely to precipitate such extreme rises in intraocular pressure because it is cleared rapidly from the trabecular meshwork. However, with any technique or chemical used in surgery there is always the potential for an unexpected adverse effect, and the risks of Viscoat include subepithelial calcium deposition and keratopathy (3).

After intra-articular injection, sodium hyaluronate can cause hemarthrosis, increased joint effusion volume, and possibly phlebitis. Other adverse effects are joint pain,

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septic arthritis, acute pseudogout, and anaphylaxis (4,5). Adverse events of this route of administration reportedly occur in about 2–4% of patients (6).

Organs and Systems

Skin

- An exudative granulomatous reaction started 2 days after the injection of hyaluronic acid (Hylaform) (dose not stated) for perioral wrinkles (7). The eczematous papular skin changes disappeared completely within 6 weeks, and could be provoked by intracutaneous testing with Hylaform (dose not stated). Histological examination showed a foreign body granuloma.

Immunologic

Immediate and delayed hypersensitivity reactions have been reported with hyaluronic acid (8).

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Hycanthone

General Information

Hycanthone is a derivative of lucanthone, but has less gastrointestinal and nervous system toxicity. It is effective against both *Schistosoma hematobium* and *Schistosoma mansoni* and is given as a single intramuscular injection in doses of 1.0–2.5 mg/kg (1,2). However, it has largely been superseded in the treatment of schistosomiasis by more recent, less toxic compounds. The most common adverse reactions to hycanthone, which occur in up to half of all patients treated with higher-dose regimens, is nausea and vomiting (3), often associated with abdominal colic and diarrhea. There can be muscle pain, and electrocardiographic changes can occur (4).

Organs and Systems

Liver

Hepatotoxicity occurs with hycanthone; serum transaminases are often raised and less commonly there is overt jaundice (5,6). Hepatitis was the major complication with hycanthone in the treatment of schistosomiasis, sometimes associated with pancreatitis (7,8). Hycanthone has also been evaluated as a potential antitumor agent, being used as a radiosensitizer; here too, hepatitis was a dose-limiting effect, occurring in some patients with doses of 100 mg/m2 per day (3). The lowest dosage that caused hepatitis was 70 mg/m2/day. In several cases the hepatotoxicity proved fatal (SED-11, 597) (7–9).

Long-Term Effects

Mutagenicity

Experimentally, hycanthone has been reported to be mutagenic in *Salmonella typhimurium* and *Escherichia coli*, but no human data are available (10,11).

Tumorigenicity

Experimentally, hycanthone has been reported to be carcinogenic in mice (12,13), but no human data are available.

Second-Generation Effects

Teratogenicity

Experimentally, hycanthone has been reported to be teratogenic (14,15), although no human data are available.

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Hydralazine

General Information

Hydralazine is a direct vasodilator that acts on vascular smooth muscle to produce systemic vasodilatation. As a result there is baroreceptor-mediated activation of the sympathetic nervous system and the renin–angiotensin system.

Vasodilators (as monotherapy) are associated acutely with flushing, headache, dizziness, reflex tachycardia, and palpitation. Chronic treatment can be complicated by fluid retention.

Organs and Systems

Cardiovascular

Aggravation of angina, presumably as a result of reflex tachycardia, has been reported with hydralazine.

- Pericarditis has been attributed to hydralazine in a 75-year-old man who developed a full-blown hydralazine-induced autoimmune syndrome (1).

The authors referred to a similar previously published case of late pericarditis after hydralazine treatment.

Nervous system

Peripheral neuropathy has been described in association with deficiency of pyridoxine (vitamin B6) in slow acetylators (2).

Metabolism

Salt and water retention mediated by secondary hyperaldosteronism can complicate hydralazine treatment, leading to weight gain and peripheral edema, loss of blood pressure control, and rarely cardiac failure (SED-8, 474).

Gastrointestinal

Anorexia, nausea, and vomiting can complicate hydralazine treatment, particularly initially (SED-8, 474).

Liver

Acute hepatitis (usually with negative antinuclear antibodies) has been attributed to hydralazine (3–7).

Skin

- A 44-year-old man taking hydralazine (dose not stated) developed a pruritic rash, attributed to a drug-induced lichenoid eruption, based on biopsy findings (8). The hydralazine was withdrawn and the rash resolved in a few weeks.

Immunologic

The lupus-like syndrome (SED-9, 318) with hydralazine occurs particularly in slow acetylators (and only rarely in fast acetylators) and in patients with the HLA-DR4 antigen. Blood dyscrasias and necrotizing vasculitis are additional features.

Current knowledge about the possible mechanisms of drug-induced lupus-like syndrome has been reviewed (9). Three mechanisms seem most plausible. One involves a change, possibly caused by a reactive metabolite, in the way that antigens are processed and presented to T cells, leading to the presentation of cryptic antigens. Another possibility is that a reactive metabolite binds to the class II major histocompatibility antigen and induces an autoimmune reaction analogous to a graft-versus-host reaction. A third possibility is that hydralazine inhibits DNA methylation, leading to an increase in DNA transcription and a generalized activation of the immune system.

A variety of vasculitic diseases, including Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome, and crescentic glomerulonephritis, are associated with antineutrophil cytoplasmic antibodies (ANCA) or leukocytoclastic vasculitis. In drug-induced ANCA-positive vasculitis, antimyeloperoxidase antibodies are most often found; they produce a perinuclear pattern of staining by indirect immunofluorescence (pANCA), but antiproteinase 3 (anti-PR3) antibodies can also occur (cANCA).

The possible drug causes of ANCA-positive vasculitis with high titers of antimyeloperoxidase antibodies in 30 new patients have been reviewed (10). The findings illustrate that this type of vasculitis is a predominantly drug-induced disorder. Only 12 of the 30 cases were not related to a drug. The most frequently implicated drug was hydralazine (10 cases); the remainder involved propylthiouracil (3 cases), penicillamine (2 cases), allopurinol (2 cases), and sulfasalazine.

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Second-Generation Effects

Fetotoxicity

Thrombocytopenia has been reported in infants whose mothers were taking hydralazine with no evidence of the lupus-like syndrome (11).

The administration of hydralazine 25 mg bd at 34 weeks to a hypertensive pregnant woman was associated, within 1 week, with atrial extra beats in the fetus. These subsided when hydralazine was withdrawn, and the rest of the pregnancy and delivery was uneventful (12).

- A 29-year-old woman, 26 weeks pregnant, was treated with hydralazine for toxemia of pregnancy. She developed arthralgia and dyspnea and was subsequently found to be antinuclear antibody-positive. Following an induced labor, a low-birth-weight infant was born but died aged 36 hours. At autopsy the neonate was found to have a pericardial effusion and tamponade (13).

Although hydralazine was implicated as the cause of a maternal and neonatal lupus-like syndrome, the toxemia and low birth weight of the child make interpretation of the case difficult.

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Hydrazine

General Information

Hydrazine sulfate is sometimes promoted as an alternative cancer cure.

Organs and Systems

Liver

Hydrazine has been reported to cause liver damage (1).

- A 55-year-old man with maxillary sinus cancer declined conventional therapy and opted to treat his condition with hydrazine sulfate obtained via the Internet. He had followed the recommended regimen for 4 months when he developed fulminant hepatorenal failure, hepatic encephalopathy, and profound coagulopathy. He died of severe gastrointestinal hemorrhage.

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Hydrocodone

See also Opioid analgesics

General Information

Hydrocodone is a semisynthetic narcotic analgesic and a cough suppressant, similar to codeine. It is metabolized to the *O*- and *N*-demethylated products, hydromorphone and norhydrocodone (1).

Drug Administration

Drug administration route

Five patients who abused prescribed opioids intranasally have been described (2). All took hydrocodone bitartrate plus cocaine ($n = 2$), codeine phosphate ($n = 2$), oxycodone hydrochloride ($n = 2$), or methadone hydrochloride ($n = 1$). The symptoms included nasal obstruction and congestion, foul smelling nasal crusting and discharge, headaches and nasal pain, and in one case dysphagia with odynophagia. Physical findings included a perforated septum, soft palate erosion, and a mucopurulent exudate. All except one patient had positive fungal cultures and two had invasive rhinitis. Not only can intranasal opioids cause septal perforation, commonly associated with intranasal cocaine, but it is also possible that intranasal abuse of opioids, especially hydrocodone, can cause localized immunosuppression, supporting the growth of fungal organisms.

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Hydromorphone

See also Opioid analgesics

General Information

Intolerable adverse effects or inadequate analgesia occur in 10–15% of patients with chronic pain given continuous intrathecal morphine. Hydromorphone is a semisynthetic derivative of morphine used extensively in the management of cancer pain. It is more soluble than morphine, has a slightly shorter duration of action, and is about five times more potent when given systemically.

In a retrospective review of 37 patients with chronic non-malignant pain (mostly from failed lumbosacral spine surgery) treated with intrathecal hydromorphone there was an analgesic response in six of the 16 patients who were switched from morphine to hydromorphone because of poor pain relief (1). Opioid-related adverse effects, such as nausea, vomiting, pruritus, and sedation, were also reduced by hydromorphone in the 21 patients who were switched to hydromorphone because of morphine-related adverse effects, especially 1 month after use. These results should be treated cautiously, because of the limitations of a retrospective study that lacks strict inclusion criteria, with obvious population bias and under-reporting, and without standardized procedures for rotation to hydromorphone.

Three randomized, double-blind comparisons of morphine and hydromorphone have been reported. Modified-release hydromorphone hydrochloride 4 mg bd was compared with modified-release morphine sulfate 30 mg bd in 89 patients with cancer pain (2). In all, 88 adverse effects were thought to be directly related to the study medication. Other adverse events were related to the disease process, the re-emergence of pain, or not specified.

In a comparison of hydromorphone and morphine delivered by continuous subcutaneous infusion in 74 patients with severe cancer pain, the number of adverse effects was small and comparable in both groups (3).

When epidural morphine (Duramorph 10 micrograms/kg/hour) was compared with epidural fentanyl (1 microgram/kg/hour) and epidural hydromorphone (1 microgram/kg/hour) in 90 children undergoing orthopedic procedures, hydromorphone was considered to be safe and efficacious (4). The combined incidences of pruritus, nausea, and vomiting were 25, 20, and 10% respectively and for pruritus alone 35, 15, and 8% respectively.

Organs and Systems

Sensory systems

In a retrospective review in a specialized otological center, 12 patients were identified with rapidly progressive hearing loss and a concurrent history of hydrocodone overuse with paracetamol (5). These patients were helped by cochlear implantation.

Drug Administration

Drug administration route

The use of intrathecal hydromorphone in the management of chronic non-malignant pain has been described (1).

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Hydroxycarbamide

See also Cytostatic and immunosuppressant drugs

General Information

Hydroxycarbamide (hydroxyurea) is used to treat a variety of cancers, myeloproliferative disorders, and sickle cell disease, and has been studied in patients with HIV infection (1). It inhibits ribonucleotide reductase and increases concentrations of iron nitrosyl hemoglobin, nitrite, and nitrate, suggesting in vivo metabolism of hydroxycarbamide to nitric oxide (2).

Organs and Systems

Hematologic

Concern about the toxicity of hydroxycarbamide, expressed in a report from the AIDS Clinical Trials Group (ACTG 5025 report), has led to a retrospective study of the antiviral activity, immunological effects, and

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tolerability of hydroxycarbamide in combination with didanosine (3). Hematological adverse events were the most frequent and involved 37 of the 65 patients. Neutropenia was the commonest adverse event (26 patients) and it was occasionally accompanied by anemia or thrombocytopenia. However, these effects normalized spontaneously, despite continued therapy.

Of 16 children receiving hydroxycarbamide in combination with nucleoside analogues, 4 developed neutropenia (below 1.5×10^9/l) by weeks 2 or 4 (4). Hydroxycarbamide was temporarily withdrawn and then reintroduced without further ill effects after the neutrophil count had returned to normal.

Mouth and teeth

In a retrospective study of the antiviral activity, immunological effects, and tolerability of hydroxycarbamide in combination with didanosine, mouth ulceration was recorded in eight of the 65 patients and this led to discontinuation in one patient (3).

Pancreas

In a retrospective study of the antiviral activity, immunological effects, and tolerability of hydroxycarbamide in combination with didanosine, there was increased serum amylase activity in 15 of the 65 patients; although asymptomatic, it occasioned withdrawal of therapy in four patients (3).

Skin

The incidence of skin lesions in patients taking hydroxycarbamide is 10–35%. They usually occur after several years of maintenance therapy. However, one patient developed lichen planus-like dermatitis on his hands after just 15 days of treatment (5).

Hydroxycarbamide can cause hyperpigmentation of the nails and palmar creases and leg ulcers (6,7). Leg ulcers occurred in 41 patients taking hydroxycarbamide (8). They had a mean age of 67 years and mean therapy duration of 5 years, and none had any underlying vascular disease. There were megaloblastic erythrocytes trapped in the capillary beds, causing local tissue anoxia, and the authors postulated that the megaloblastic erythrocytes had resulted from hydroxycarbamide and that the ulcers were due to consequent impaired circulation and cutaneous atrophy; they also commented that there was no major vascular disease that could have accounted for the leg ulcers. The degeneration of lichen planus-like skin lesions into full-blown ulcers has been described in 14 patients who developed extremely painful leg ulcers, most commonly on the malleoli. The patients had been taking hydroxycarbamide for an average of 6 years and nine had multiple ulcers (9).

Acral erythema, dermatomyositis-like changes on the backs of the hands, squamous cell neoplasms on sun-exposed sites, and ulcers on the legs, genitalia, and oral mucosae have also been reported (10).

Immunologic

Hydroxycarbamide has been associated with Behçet's syndrome (11).

Body temperature

- A 64-year-old woman with essential thrombocythemia developed a fever after 3 weeks of treatment with hydroxycarbamide 1000 mg/day; the fever subsided on withdrawal and recurred on rechallenge (12).

Drug–Drug Interactions

Busulfan

During long-term follow-up of patients treated with busulfan and hydroxycarbamide for essential thrombocythemia, seven patients (13%) taking hydroxycarbamide developed secondary acute leukemia, myelodysplasia, or solid tumors, compared with only one of the control group; none of the 20 patients who had never been treated with chemotherapy developed secondary malignancies compared with three of the 77 given hydroxycarbamide only and five of the 15 given busulfan plus hydroxycarbamide. This suggests that the combination of busulfan plus hydroxycarbamide causes a significantly increased risk of secondary malignancies (13).

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Hydroxyzine

See also Antihistamines

General Information

Hydroxyzine is a first-generation antihistamine, a piperazine derivative, with antimuscarinic and sedative properties.

Organs and Systems

Skin

Two cases of drug allergy have been reported in a 37-year-old woman and a 66-year-old man, who received hydroxyzine for premedication before anesthesia (1,2). In these patients immediate skin tests with the implicated drug were positive.

Second-Generation Effects

Fetotoxicity

Hydroxyzine used in a fairly high dose (600 mg/day) in pregnancy has been reported to produce a neonatal withdrawal syndrome after delivery; this was characterized primarily by hyperactivity and irritability (SEDA-2, 151).

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Hyoscine

See also Anticholinergic drugs

General Information

Hyoscine is an anticholinergic drug, a stereoisomer of atropine. It is available in different salts, hyoscine hydrobromide and hyoscine butylbromide.

When given parenterally hyoscine butylbromide is effective but very short-acting; when given by mouth it is virtually inactive, even in doses up to 1 g, since it is hardly absorbed.

Hyoscine hydrobromide is used primarily in motion sickness; doses of 0.6 mg appear to be effective, particularly in combination with drugs having a mild central stimulant effect such as ephedrine.

Organs and Systems

Nervous system

Despite being a stereoisomer of atropine, hyoscine tends to have central depressant effects in conditions where atropine might be expected to cause excitation; however, excitation can occur (1). Hyoscine hydrobromide produces somnolence and dryness of the mouth in a high proportion of patients, and when ephedrine is not given the somnolence is likely to be present in the majority; some individuals also have headache, giddiness, and blurred vision.

Transdermal hyoscine is used by some anesthetists to minimize postoperative nausea and vomiting. The safety and efficacy of this form of treatment has been reviewed in an analysis of data from 23 trials involving 979 patients treated with hyoscine and 984 with placebo (2). The authors concluded that of 100 patients who are treated with hyoscine, 17 will escape postoperative nausea and vomiting that would otherwise have occurred; however, 18 will have visual disturbances, 8 will complain of dry mouth, 2 of dizziness, and 1 will become agitated. Although these are not necessarily prohibitive problems, they certainly do need to be considered when choosing a drug for this indication.

Psychological, psychiatric

In one study hyoscine premedication had detrimental effects on memory and on motor tasks compared with placebo, while atropine did not (3), although the difference is unlikely to be absolute. In view of certain of these effects, hyoscine hydrobromide is not a suitable antiemetic for those likely to drive vehicles before the effect has worn off, for example air passengers.

Immunologic

An isolated case of angioedema has been described during the use of hyoscine butylbromide (SEDA-8, 148).

Second-Generation Effects

Pregnancy

Two Japanese primigravidae, aged 25 and 28 years, developed the HELLP syndrome, a severe variant of pre-eclampsia in which there is Hemolysis, Elevated Liver enzymes, and a Low Platelet count (4). They were given parenteral hyoscine butylbromide for abdominal pain and had seizures 60–90 minutes later. One died from intracerebral hemorrhage some days later and the other survived after a cesarean section soon afterward. The authors speculated that anticholinergic drugs may enhance sympathetic nervous system activity, and in particular vasoconstriction, and should be avoided in pre-eclampsia. It is not clear how widespread their use is

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in other countries in managing abdominal pain in these circumstances.

Drug Administration

Drug administration route

A transdermal delivery system has been developed for prevention of motion sickness and vomiting, using an adhesive patch for postauricular application; the drug is released at a uniform rate for 72 hours. The adverse effects of this formulation are qualitatively typical of those reported for the oral and parenteral formulations of hyoscine and its congeners, although comparative studies suggest that the incidence is reduced with transdermal administration. Nevertheless, adverse effects involving the central nervous system, vision, bladder, and skin have been described, as have withdrawal symptoms after the patch is removed.

Dry mouth occurs in about 67% of subjects and drowsiness in about 16%. Transient effects on ocular accommodation, including blurred vision and mydriasis, have also been observed, in some cases possibly due to finger-to-eye contamination. Adverse effects on the central nervous system, including toxic psychosis (5) and hallucinations, have been reported only occasionally, as have other adverse reactions, such as dry, itchy eyes, difficulty in urinating, rashes, and erythema (6).

Attention has been drawn to potentially confusing clinical signs that can occur if a patch is applied for its antiemetic effect before general anesthesia; in one case the patient developed a right fixed pupil and became uncooperative; intravenous physostigmine had to be administered (SEDA-22, 157).

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Ibopamine

General Information

Ibopamine is an orally active dopamine derivative that has been studied in patients with congestive heart failure (1). In theory, most, if not all, of the reported adverse effects can be considered to result from the drug's known pharmacological actions. Its gastrointestinal effects can be interpreted as being dopaminergic in nature, the occasional dizziness, flushing, and tremor as beta$_2$-adrenoceptor agonist effects, the tachycardia as an effect of beta$_1$-adrenoceptor stimulation or a reflex response to beta$_2$-adrenoceptor agonism. A reversible leukopenia has been described, but the relation to the drug was uncertain (2).

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Ibritumomab

See also Monoclonal antibodies

General Information

Ibritumomab is a murine IgG$_1$ anti-CD20 antibody, the parent of the engineered chimeric antibody rituximab, a monoclonal antibody with mouse variable and human constant regions. It induces apoptosis and has antiproliferative effects. Ibritumomab tiuxetan (Zevalin) is composed of the monoclonal antibody ibritumomab, the linking chelator tiuxetan, and the radioisotope ^{90}yttrium (1).

General adverse effects

A wide range of adverse effects of ibritumomab has been reported. Most were hematological, thrombocytopenia being the most common, followed by a low hemoglobin and leukopenia. The most common non-hematological events were related to infusion and were similar to those reported with rituximab; they included weakness (54%), nausea (35%), chills (15%), and fever (21%) (2,3). Infectious complications during treatment with ibritumomab are rare, pneumonia being the most common. There is no obvious hepatotoxicity.

Organs and Systems

Immunologic

There has been one report of an anti-antibody response to ibritumomab (2).

Long-Term Effects

Tumorigenicity

Acute myelogenous leukemia has been attributed to ibritumomab (4).

- An 80-year-old woman with a small B cell extranodal lymphoma was initially given chlorambucil for 10 months, with complete remission for 2 years. When she developed recurrent lymph node swelling she was given ibritumomab tiuxetan, with near-complete remission. When she developed progressive disease 14 months later, she received cyclophosphamide, vincristine, and prednisone for one cycle. She had persistent pancytopenia, and a bone marrow biopsy showed extensive infiltration by acute myelogenous leukemia.

This seems to be the first case of drug-related acute myelogenous leukemia. Fluorescent in-situ hybridization studies on the bone marrow showed a signal consistent with rearrangement of the mixed myeloid leukemia (MLL) gene on chromosome 11. This abnormality was not present before treatment.

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Ibuprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Like other NSAIDs, ibuprofen is a potent inhibitor of prostaglandin synthesis, and many or all of its therapeutic and toxic effects are linked to this characteristic. The general impression is that it is less potent and thus less toxic than indometacin in usual doses, but it has often been used in the past in relatively low doses. In a comparative, double-blind, crossover study of ibuprofen, naproxen, fenoprofen, and

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tolmetin in patients with rheumatoid arthritis, ibuprofen in equieffective doses was the best tolerated; however, patients and physicians preferred naproxen (1).

There are few data on the long-term safety of NSAIDs in the treatment of juvenile rheumatoid arthritis. In a study of the adverse reactions of patients treated with long-term ibuprofen, gastrotoxicity was directly correlated with dosage and 5% withdrew early because they had gastrointestinal bleeding, vomiting, severe rash, hearing loss, and abnormalities of liver function tests (SEDA-16, 110).

High dosages of ibuprofen for 4 years were used in 41 patients with cystic fibrosis to slow progression of lung disease and only two adverse effects (conjunctivitis and epistaxis) were drug-related (SEDA-20, 93).

General adverse reactions

Gastrointestinal adverse effects are the most frequent. They occur in up to 30% of patients and range from abdominal discomfort to serious bleeding or activation of peptic ulcer. Nervous system effects, with headache and dizziness, are very common. Severe renal impairment has not been noted. Blood dyscrasias can occur when high dosage treatment is prolonged. There is no significant general hepatotoxicity, but both the liver and the central nervous system (meningitis) can be affected as part of a hypersensitivity reaction.

Hypersensitivity reactions are uncommon, but they can be severe. Aseptic meningitis, hypotension, fever, conjunctivitis, arthralgias, and leukopenia were reported in a woman with systemic lupus erythematosus (2). Other similar patients have experienced fever with rashes, abdominal pain, headache, nausea and vomiting, signs of liver damage, and meningitis. This type of reaction seems to occur especially (but not exclusively) in patients with connective tissue diseases (SEDA-5, 105) (SEDA-10, 84) and it can be difficult to differentiate between a hypersensitivity reaction and a flare-up of the disease. Ibuprofen can provoke bronchospasm and anaphylaxis in asthmatics (SEDA-22, 116).

Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Apart from the consequences of salt and water retention, ibuprofen does not affect myocardial or vascular function. Congestive heart failure has rarely been reported (3).

In a small comparison of ibuprofen and indometacin in preterm infants with patent ductus arteriosus there was no apparent difference in the rate of patent ductus arteriosus closure; ibuprofen did not impair cerebral hemodynamics or oxygenation, while indometacin impaired cerebral oxygen delivery (4).

Respiratory

Ibuprofen rarely provokes attacks of asthma in predisposed individuals. There is probably cross-sensitivity with aspirin; a death was reported after an asthmatic patient with no history of aspirin sensitivity took two ibuprofen tablets (SEDA-12, 86).

Pulmonary infiltrates with eosinophilia have been described with ibuprofen (SEDA-18, 104).

Two episodes of acute pulmonary edema and progressive pulmonary infiltrates without eosinophilia have been reported in a man with HIV infection after ibuprofen (SEDA-18, 104).

Nervous system

Headache, vertigo, tinnitus, and insomnia are the most frequent nervous system effects, but are rarely severe. Depression and other psychotic reactions have been reported. Some nervous system reactions (meningism and meningitis, lethargy, and irritability) are thought to result from hypersensitivity (SEDA-9, 91) (SEDA-18, 104) (5). This has been confirmed by a report of aseptic meningitis with increased intrathecal IgG synthesis and evidence of immune complexes in the cerebrospinal fluid (SEDA-16, 110).

Analgesic-induced headache, not uncommon in adults, has also been described in children. One report (6) described 12 children, aged 6–16 years, who gave a history of headaches on at least 4 days a week, for 3 months to 10 years. Eleven of the children had been taking paracetamol, six in combination with codeine, and one was taking ibuprofen alone. They were taking at least one dose of an analgesic for each headache and eight were taking analgesics every day. The headaches presented with increasing frequency and were related to overuse of analgesics, a typical finding in analgesic-induced headache. The analgesics were withdrawn; in six children the headaches resolved completely, another five children experienced a reduced frequency of headaches, and one resumed analgesic abuse.

The second report (7) was a retrospective study of patients seen in a pediatric headache clinic. During 8 months 98 patients were seen for headache; 46 of them suffered from daily or near daily headache and 30 were consuming analgesics daily. Follow-up information was available in 25. The average number of doses of analgesics per week they consumed was 26. The most commonly used medications were paracetamol and ibuprofen. In addition, a minority were taking combinations that contained aspirin, codeine, caffeine, propoxyphene, or butalbital, or other NSAIDs. Abrupt withdrawal of all analgesics concomitant with the use of amitriptyline 10 mg/day (in 22 patients) prompted a significant reduction in the frequency and severity of headache.

Sensory systems

Ocular reactions described to date are reversible and not severe. They include blurred vision, changes in color perception, and toxic amblyopia (8).

Ibuprofen significantly correlated with high-altitude retinal hemorrhages (SEDA-17, 110).

Vortex keratopathy has been described in a woman taking oral ibuprofen (SEDA-21, 105).

Metabolism

An increase in serum concentrations of uric acid has been described with ibuprofen (9).

Hematologic

Ibuprofen prolongs bleeding time, although less than aspirin (10). There are reports that a daily dose of less than 1 g does not affect the bleeding time (11).

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Blood dyscrasias, ranging from thrombocytopenia and granulocytopenia to agranulocytosis and fatal pancytopenia, have been reported. (SED-9, 150). Reversible pure white cell aplasia with bone marrow plasmacytosis and complement-dependent IgG antibody has been observed in one patient (12).

Fatal autoimmune hemolytic anemia has been attributed to ibuprofen in a patient who was taking other drugs (13). Reversible hemolytic anemia has been described during ibuprofen treatment, but tartrazine, the orange dye in the coating of the brand used (Motrin 400), may have been responsible (14).

Gastrointestinal blood loss due to ibuprofen can cause iron deficiency anemia.

Gastrointestinal

When ibuprofen was first introduced, its gastrointestinal tolerance was regarded as better than with other NSAIDs, especially aspirin and indometacin. However, with the use of higher doses, which were probably equipotent with the usual doses of older agents, there seemed to be no significant differences. As with other NSAIDs there is a close correlation between efficacy and adverse effects. Gastrointestinal adverse effects include a variety of symptoms, such as irritation, nausea, anorexia, vomiting, dyspepsia, heartburn, abdominal discomfort, bleeding, hematemesis, and activation of peptic ulcer; 10–30% of patients taking prescription doses (for example for rheumatic conditions) develop these adverse effects (SED-9, 150) (15). It is not possible to give a reliable estimate of the frequency when the drug is used as a self-medication analgesic in lower doses, since exact information on the complications of self-medication is rarely available and there is always likely to be a proportion of misuse (for example ingestion of higher or lower doses than recommended).

Bleeding from a Meckel's diverticulum has been described with oral ibuprofen (SEDA-17, 110).

Irritation of the rectal mucosa after ibuprofen suppositories has also been reported (16). Ulcerative proctitis has been reported in a patient with systemic lupus erythematosus (SEDA-14, 94).

Liver

Ibuprofen is not directly hepatotoxic, but the liver can be damaged as part of a generalized hypersensitivity reaction. Toxic hepatitis with Stevens–Johnson syndrome has been described (17).

Ibuprofen has been rarely thought responsible for liver damage. A recent report has described three patients, 33–44 years old, with chronic hepatitis C infection who developed more than five-fold increases in serum liver transaminases after taking ibuprofen for musculoskeletal pain. In all three there were no associated symptoms of hepatitis, and serum transaminases normalized after ibuprofen was withdrawn (18).

Biliary tract

The vanishing bile duct syndrome has been associated with the use of ibuprofen in an atopic man, but the causal relation was not certain (19).

Urinary tract

Ibuprofen can cause renal impairment, ranging from an insignificant reduction to an acute fall in creatinine clearance associated with a general hypersensitivity reaction, especially in patients with systemic lupus erythematosus or acute tubular necrosis (20). The nephrotic syndrome without renal insufficiency and acute interstitial nephritis without the nephrotic syndrome have been described after self-administration of over-the-counter ibuprofen (SEDA-12, 86).

Irreversible renal insufficiency due to acute cortical necrosis triggered by severe renal hypoperfusion has been reported (SEDA-12, 86). A pharmacokinetic study showed that conversion of inactive *R*-ibuprofen to active *S*-ibuprofen was greater in patients with renal impairment than in healthy controls; this may aggravate renal insufficiency (21).

Acute deterioration in renal function can occur also in other at-risk patients, such as those with renal transplants (22,23).

Skin

Skin rashes usually occur during general hypersensitivity. Urticarial, purpuric, and erythematous changes with pruritus have been reported (15). Bullous pemphigoid has been described after 6 months of treatment and was observed in two other patients on ibuprofen (SEDA-14, 94). Photosensitization has been attributed to ibuprofen (SEDA-17, 110). The association between ibuprofen and dermatological superinfection in children with recent *Varicella* infection has not been demonstrated in a retrospective cohort study (SEDA-22, 116).

Ibuprofen exacerbates psoriasis (SEDA-12, 86) (SEDA-7, 108) (SEDA-8, 102).

Hair

Alopecia has been described in black women; normal hair growth returned after therapy was stopped (SED-11, 183) (24).

Immunologic

Anaphylaxis after ibuprofen was reported in a patient with asthma who was also taking zafirlukast, a leukotriene receptor antagonist (SEDA-22, 116).

Susceptibility Factors

Age

The controversy over the use of ibuprofen as an antipyretic or analgesic is still open and the question of whether it is safer than paracetamol in children has not been answered (SEDA-16, 110) (SEDA-17, 110) (SEDA-19, 96).

Other features of the patient

In patients with a history of peptic ulcer or systemic lupus erythematosus the benefit-to-harm balance must be evaluated before prescribing ibuprofen. The first group is in danger of ulcer exacerbation and the second of a severe generalized hypersensitivity reaction.

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Drug Administration

Drug formulations

Modified-release formulations seem to cause the same adverse effects as conventionally formulated ibuprofen (25), and four-times-daily treatment is better tolerated than twice-daily (SEDA-12, 86).

Ibuprofen lysine is more rapidly absorbed than ibuprofen free acid, but the comparative tolerability of the two formulations is not known (SEDA-20, 93).

Drug overdose

In spite of the large number of prescriptions and over-the-counter sales, acute intoxication is rare. Symptoms are usually limited to nausea and vomiting, but more severe cases of coma, acidosis, mild hypothermia, renal insufficiency, and acute papillary necrosis have been described (SEDA-12, 86) (SEDA-22, 116). Treatment is supportive (SEDA-9, 81).

Drug–Drug Interactions

Aminoglycoside antibiotics

High-dose ibuprofen can slow the progression of lung disease in patients with cystic fibrosis and is usually well tolerated (SEDA-20, 93). However, transient renal insufficiency developed in four children with cystic fibrosis who were taking maintenance ibuprofen when an intravenous aminoglycoside was added to their regimen to treat an exacerbation of lung disease (26). Ibuprofen should probably be stopped during intravenous aminoglycoside therapy.

Antihypertensive agents

Ibuprofen interacts with antihypertensive agents, reducing their efficacy (27).

Aspirin

Patients with arthritis and vascular disease sometimes take both low-dose aspirin and other NSAIDs. However, concomitant treatment with ibuprofen can limit the cardioprotective effects of aspirin, according to the results of a study of the effects of ibuprofen, diclofenac, coxibs, and paracetamol on the antiplatelet activity of aspirin (28). The following combinations of drugs were used: aspirin (81 mg every morning) 2 hours before ibuprofen (400 mg every morning) or in the reverse order; aspirin 2 hours before rofecoxib (25 mg every morning or in the reverse order); enteric-coated aspirin 2 hours before ibuprofen (400 mg tds); and enteric-coated aspirin 2 hours before modified-release diclofenac (75 mg bd). Inhibition of the formation of serum thromboxane B2 (an index of COX-1 activity in platelets) and platelet aggregation by aspirin was blocked when a single daily dose of ibuprofen was given before aspirin, as well as when multiple daily doses of ibuprofen were given. Diclofenac, paracetamol, and rofecoxib did not affect the pharmacodynamics of aspirin. These results suggest that ibuprofen, but not diclofenac, paracetamol, or rofecoxib, antagonizes the irreversible inhibition of platelet COX-1 by aspirin and can therefore limit the cardioprotective effects of aspirin.

This hypothesis has now been supported in a study of over 7000 patients who were discharged after a first admission for cardiovascular disease between 1989 and 1997 and who took low-dose aspirin and survived for at least 1 month (29). The adjusted hazard ratios for all-cause mortality (HR = 1.93; 95% CI = 1.30, 287) and for cardiovascular mortality (HR = 1.73; CI = 1.05, 2.84) were significantly raised in patients who took ibuprofen (mean dose 1210 mg/day) in addition to the aspirin. There was no increase in hazard in patients who combined aspirin with diclofenac, which is consistent with the in vitro data. However, this study had many limitations (30), and further epidemiological studies are needed to address this potentially important interaction. In the meantime, when patients taking low-dose aspirin for cardioprotection also require long-term treatment with an NSAID, diclofenac would be preferable to ibuprofen.

Lithium

Ibuprofen can increase the serum lithium concentration (SEDA-13, 81).

Methotrexate

Ibuprofen can potentiate methotrexate-induced renal toxicity (31).

Pancreatic enzymes

An interaction between ibuprofen and pancreatic enzymes causing serious gastrointestinal damage has been described in animals (SEDA-21, 105).

Phenytoin

Ibuprofen inhibits the metabolism of phenytoin (32).

Sulfonylureas

Ibuprofen (150 mg, 3 doses) for arthralgias was associated with hypoglycemia in a 72-year-old man who was taking glibenclamide 2.5 mg/day for type 2 diabetes mellitus; after the last dose he lost consciousness, and his blood glucose concentration was under 2.2 mmol/l (33).

Tacrolimus

Acute renal insufficiency has been described in concomitant treatment with tacrolimus in two liver transplant recipients (SEDA-18, 104).

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Ibuproxam

See also Non-steroidal anti-inflammatory drugs

General Information

Ibuproxam is an NSAID that causes similar adverse effects to other NSAIDs.

Organs and Systems

Gastrointestinal

Gastrointestinal adverse effects have been reported with ibuproxam, including nausea, vomiting, occult gastrointestinal blood loss, and rectal pain (1).

Skin

Skin rashes have been reported with ibuproxam (1).

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Idoxuridine

General Information

Idoxuridine, which is active against *Herpes simplex* and *Varicella zoster*, has only been used in topical antiherpetic solutions. Idoxuridine has been used to treat superficial keratitis, but with poor results in deep stromal diseases because of poor solubility. However, idoxuridine is unstable and cannot eliminate the virus from the eye. Drug allergy and toxicity occur in 5–8% of patients.

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Drug Administration

Drug administration route

Idoxuridine eye-drops are locally toxic, especially in patients with dry eyes, because of increased concentrations (or reduced tear secretion), and is topically sensitizing. Lacrimal punctum stenosis, lacrimation, follicular conjunctivitis, narrowing of meibomian gland orifices, inhibition of keratocyte mitosis and corneal stromal repair, and reductions in the strength of healing corneal wounds and the rate of epithelial regeneration are observed (1). After prolonged administration many changes in the conjunctival and corneal epithelium can occur, such as conjunctival cicatrization, punctate keratitis, subepithelial and intra-epithelial edema, and corneal opacities. Idoxuridine can also induce the emergence of resistant virus strains (2).

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Ifosfamide

See also Cytostatic and immunosuppressant drugs

General Information

Ifosfamide is an alkylating agent belonging to the group of oxazaphosphorines. It is used to treat a variety of solid tumors in children, including rhabdomyosarcoma, soft tissue sarcomas, Wilms' tumor, bone sarcomas, and neuroblastoma, and leukemias and lymphomas in adults. It is also sometimes used in combination with other drugs, such as doxorubicin or cisplatin and etoposide.

Organs and Systems

Cardiovascular

Atrial fibrillation has been attributed to ifosfamide after a dose of only 1800 mg/m^2, with mesna, in a regimen for metastatic breast cancer (1).

Nervous system

Convulsions, severe facial spasms, and trismus occurred 7 hours after an infusion of ifosfamide in a dose of 7 g/m^2, having not occurred at a dose of 5 g/m^2, during a phase II study in patients with solid tumors (2).

Severe encephalopathy has been noted in children treated with ifosfamide (1.8 g/m^2) alone. There were no susceptibility factors, such as impaired renal function or lowered albumin. Electroencephalographic abnormalities and seizures were reversible, despite prolonged coma (3).

In an evaluation of ifosfamide in 57 children with malignant solid tumors, all received 1.6 g/m^2/day for 5 days followed by mesna 400 mg/m^2 at 0.25, 4, and 6 hours after ifosfamide (4). Neurological toxicity occurred in 13 patients. The usual symptoms were somnolence and general weakness followed by confusion, tremors, ataxia, aphasia, urinary incontinence, and cranial nerve paralysis. The symptoms of neurotoxicity disappeared spontaneously within 72 hours of completion of the 5-day course. Some patients had recurrent neurotoxicity on rechallenge. In an analysis of the incidence and features of electroencephalographic changes associated with Ifosfamide/mesna therapy there was no significant association between the electroencephalographic record before and during treatment; electroencephalographic changes developed 12–24 hours before clinical toxicity. Discriminant analysis identified low serum albumin, high serum creatinine concentrations, and pelvic involvement by the underlying malignant disease as susceptibility factors for severe encephalopathy (5).

In 12 of 52 patients treated with ifosfamide there was neurocortical toxicity greater than grade 2 (6). They were successfully treated with intravenous methylthioninium chloride (methylene blue) 50 mg 3-hourly, which was also prophylactic in three patients.

Vitamin B_1 (thiamine) has also been suggested to be beneficial in treating ifosfamide-associated neurotoxicity (7).

Urinary tract

It has been thought that the metabolism of ifosfamide to chloroacetaldehyde is the mechanism whereby ifosfamide causes renal damage. However, this was not confirmed in a study of repeated doses of 6–9 g/m^2 in 15 children, in whom there was no correlation between the pharmacokinetics of ifosfamide or its metabolites and either acute renal toxicity or chronic renal toxicity at either 1 or 6 months after treatment (8). However, there were changes in the metabolism of ifosfamide with time, particularly a reduction in dechloroethylation, which correlated with the risk of chronic nephrotoxicity.

Children and adolescents given cumulative doses of 32–112 g/m^2 had only transient disturbances in renal function (9). In five children with renal tubular Fanconi syndrome caused by ifosfamide, all went on to develop rickets in the face of declining renal function. None had had pre-existing tubular damage and the syndrome developed at cumulative doses of ifosfamide of 39–99 g/m^2. There were low serum bicarbonate and phosphate concentrations, and supplementation of these resulted in bone healing but not renal recovery (10).

The susceptibility factors associated with chronic ifosfamide nephrotoxicity up to 28 months after treatment have been studied in 23 children. The authors concluded that cumulative doses of 100 g/m^2 or higher should be avoided in children with cancers (11).

Like cyclophosphamide, ifosfamide causes a hemorrhagic cystitis in a high proportion of patients, with an occasionally fatal outcome. The damage to urinary bladder epithelium is caused by acrolein, a metabolite that is excreted in the urine. In bone marrow transplant recipients, prior administration of busulfan, which itself causes hemorrhagic cystitis, can increase this risk of oxazaphosphorines (12). Mesna (sodium

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mercaptoethanesulfonate) is used to prevent this adverse effect. It is excreted by the kidney, and it binds and detoxifies acrolein in the urine; mesna also prevents the breakdown of acrolein precursors.

The phosphate disturbance that leads to Fanconi syndrome is well documented with ifosfamide. Of 43 children who received ifosfamide 3.5 g/m^2/day for 5 days for metastatic osteosarcoma, three developed the syndrome (13).

Second-Generation Effects

Fetotoxicity

The effects of second-trimester or third-trimester exposure to ifosfamide are poorly documented, although normal children have been described (14). In a 17-year-old pregnant woman with Ewing's sarcoma doxorubicin and ifosfamide during the 25th to 30th weeks of gestation did not affect the child, which was delivered at 32 weeks (15).

Drug Administration

Drug dosage regimens

There is a higher incidence of ifosfamide encephalopathy associated with the oral form compared with the intravenous form of ifosfamide; this has been attributed to metabolic differences between the two (16).

Drug–Drug Interactions

Cisplatin

Ifosfamide is associated with a peripheral neuropathy when it is given in combination with cisplatin (17). These symptoms improved within a few days after treatment with haloperidol.

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Illiciaceae

See also Herbal medicines

General Information

The family of Illiciaceae contains a single genus, *Illicium*, the star anise species.

Illicium species

Illicium anisatum contains sesquiterpenoids, such as anisatin, anisotin, neoanisatin, and pseudoanisatin. *Illicium religiosum* (Japanese star anise) contains shikimic acid, anisatin and neoanisatin. *Illicium verum* (Chinese star anise) contains the monoterpenoid transanethole. Chinese star anise has been used to treat infant colic, but can be confused with Japanese star anise, which contains the neurotoxin anisatin.

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Safrole is a mutagenic and animal carcinogenic monoterpenoid. It is the major component of oil of sassafras, and lesser quantities occur in essential oils from cinnamon, mace, nutmeg, and star anise. Some of its known or possible metabolites have mutagenic activity in bacteria and it has weak hepatocarcinogenic effects in rodents. Experiments in mice have suggested the possibility of transplacental and lactational carcinogenesis.

Adverse effects

When Japanese star anise was mixed into a commercially sold herbal tea, perhaps inadvertently consumption of the tea was associated with adverse events in 63 Dutch consumers (1). Their symptoms occurred 2–4 hours after they drank the tea and included general malaise, nausea, and vomiting. In 22 cases hospitalization was required, and 16 had generalized tonic-clonic seizures. All made a full recovery after withdrawal of the herbal tea. Anisatin is a non-competitive GABA receptor antagonist, which causes nervous system hyperactivity, and the authors believed that this mechanism explained the high rate of seizures in these patients.

- A 1-month-old girl developed status epilepticus after being given a large amount of star anis for colic (2).
- Two infants whose parents gave them star anise herbal tea developed tremors or spasms, hypertonia, hyperexcitability with crying, nystagmus, and vomiting (3). The Chinese star anise tea had been contaminated with Japanese star anise.

From February to September 2001, a matched case-control study was performed in infants aged under 3 months admitted to the pediatric emergency departments of two hospitals in Madrid (4). There were 23 cases, whose symptoms and signs were irritability, abnormal movements, vomiting, and nystagmus. The odds ratio for anise consumption was 18.0 (CI = 2.03, 631). Laboratory analyses showed contamination of *I. verum* by *I. anisatum*.

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Iloprost

See also Prostaglandins

General Information

Iloprost is an analogue of prostacyclin (PGI_2), the pharmacodynamic properties of which it mimics, namely inhibition of platelet aggregation, vasodilatation, and cytoprotection (as yet ill-defined). Iloprost has greater chemical stability than prostacyclin, which facilitates its clinical use (1).

Iloprost is mainly used in patients with chronic critical leg ischemia due to atherosclerosis or Buerger's disease. Episodic digital ischemia in patients with systemic sclerosis or related disorders is another use. The most frequently observed adverse effects, facial flushing and headache, are caused by profound vasodilatation.

Most clinical experience with iloprost has been gained in patients with critical leg ischemia. An intermittent intravenous infusion of up to 2 nanograms/kg/minute for 2–4 weeks reduced rest pain and improved ulcer healing in roughly half of the patients with critical leg ischemia, including diabetics. Compared with placebo, the improvement obtained with iloprost was significant in most but not all individual clinical trials. In addition, a meta-analysis showed a 15% reduction in major amputation rate compared with placebo (2).

Observational studies

The use of iloprost has been proposed in patients with systemic sclerosis, a disease that is often characterized by pulmonary hypertension and Raynaud's phenomenon. Three patients with systemic sclerosis who were treated with iloprost developed acute thrombotic events (3). In one case, intestinal infarction occurred 1 day after infusion of iloprost. In another patient the left kidney was not perfused 22 days after the last infusion of iloprost because of thrombosis of the left renal artery. The last patient, 9 months after the start of treatment with iloprost, and 5 days after the last infusion, had an anterolateral myocardial infarction. The authors commented that their observations did not allow them to conclude that there is a direct relation between infusion of iloprost and thrombotic events. However, they said that this possibility should be considered, and they suggested that risk factors for thromboembolism should be carefully evaluated in each patient with systemic sclerosis who is receiving iloprost.

Inhalation of aerosolized iloprost is being tested in patients with severe primary or secondary pulmonary hypertension refractory to conventional therapy. The aim is to produce predominantly pulmonary vasodilatation without significant systemic effects. In an uncontrolled series of 19 patients, the most common adverse effects of inhaled iloprost were coughing, nausea, edema, and thoracic pain (4). In most patients, these effects were transient and rarely required a change in therapy.

Placebo-controlled studies

A multicenter, randomized, parallel-group comparison of two different doses of oral iloprost and placebo has been

conducted, to identify the optimal dose of oral iloprost on the basis of efficacy and tolerability in patients with Raynaud's phenomenon secondary to systemic sclerosis (5). A total of 103 patients were given total daily doses of iloprost of 100 micrograms ($n = 33$) or 200 micrograms ($n = 35$) or placebo ($n = 35$) for 6 weeks. The mean percentage reductions in the frequency, total daily duration, and severity of attacks of Raynaud's phenomenon were greater in the iloprost groups at the end of treatment and at the end of follow-up. Adverse effects were reported by 80% of patients taking placebo, 85% taking oral iloprost 100 micrograms/day, and 97% taking oral iloprost 100 micrograms/day. There were significant differences in the frequency of five types of adverse events. Headache, flushing, nausea, and trismus were all more common with increasing iloprost dose, while flu-like illnesses were most commonly reported in the placebo group. Treatment was prematurely discontinued in 9, 30, and 51% respectively, and discontinuation was precipitated by adverse events in 6, 27, and 51%.

Comparative studies

In a randomized, controlled study of cyclic iloprost or nifedipine in 46 patients with systemic sclerosis, the predictable adverse effects of iloprost (headache, nausea and vomiting, and diarrhea) were common but quickly resolved after the end of the infusion (6). They rarely required a temporary dose reduction. Hypotension occurred less often than with nifedipine.

General adverse effects

The adverse effects of iloprost occur within or above the usual dosage range and are predictable from its pharmacological effects. Minor vascular reactions during infusion (characterized by facial flushing and headache) are so common as to make double-blind trials impossible. Gastrointestinal effects become more prevalent at higher dosages, and include nausea, vomiting, abdominal cramps, and diarrhea. Less common adverse effects include restlessness, sweating, local erythema along the infusion line, wheals, fatigue, and muscle pain. Clinically significant hypotension is rare with the doses tested. The untoward effects resolve rapidly after the infusion is discontinued.

Therapy with iloprost is usually started with a dosage of 0.5 nanogram/kg/minute and increased in increments until either minor vascular reactions occur or a dosage of 2 nanograms/kg/minute has been reached. The optimal total dose remains to be established.

Organs and Systems

Cardiovascular

Myocardial ischemia is unusual during infusion of iloprost. It mainly occurs in patients with pre-existing coronary disease, when it is ascribed to a steal phenomenon detrimental to the subendocardial tissue. As a rule it is transient and exceptionally proceeds to infarction. However, such an event has now been reported in a patient with systemic sclerosis (7).

- A 57-year-old man with a 1-year history of systemic sclerosis and ischemia of several digits received a first infusion of iloprost using the recommended stepwise increasing dosage scheme; he developed sudden chest pain, with inferior ST segment elevation. Emergency coronary angiography showed an occlusion of the circumflex coronary artery, for which a stent was inserted. At angiography 3 years earlier his coronary arteries had been normal. He died 5 months later from cardiogenic pulmonary edema.

Musculoskeletal

Four women with CREST syndrome or systemic sclerosis had pain and eventually contracture of the masseter muscles during infusion of iloprost for severe attacks of Raynaud's phenomenon (8). The adverse effect was quickly reversed by reducing the infusion rate. There were no electrocardiographic or cardiac enzyme changes. The mechanism of this effect is obscure.

Drug Administration

Drug administration route

An oral formulation has been investigated in patients with Raynaud's phenomenon secondary to systemic sclerosis and in patients with severe ischemia due to Buerger's disease or to atherosclerosis. The first reports were not particularly encouraging in terms of efficacy. Tolerance is acceptable: 6% of patients discontinued iloprost compared with 2% with placebo (9,10).

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Imidapril

See also Angiotensin converting enzyme inhibitors

General Information

Imidapril is a long-acting, non-sulfhydryl ACE inhibitor that has been used in patients with hypertension, congestive heart failure, acute myocardial infarction, and diabetic nephropathy. It is a prodrug, rapidly converted in the liver to its active metabolite imidaprilat, which has a half-life of about 15 hours. Imidapril and its metabolites are mainly excreted in the urine.

Organs and Systems

Respiratory

The incidences of cough with imidapril and enalapril have been compared in a poorly designed open study in 489 hypertensive patients (1). The authors claimed a significantly smaller incidence of cough with imidapril. However, because of important methodological flaws, this result cannot be trusted.

Mineral balance

Hyperkalemia is a well-known adverse effect of ACE inhibitors and can sometimes be severe (2).

- An 85-year-old woman with diabetes mellitus and a prior myocardial infarction, who was taking ioxoprofen and imidapril, lost consciousness owing to marked bradycardia caused by hyperkalemia (7.4 mmol/l). An electrocardiogram showed T wave changes compatible with hyperkalemia. After right ventricular pacing she promptly recovered consciousness. She was given glucose and insulin and her plasma potassium fell to 4.1 mmol/l within 3 hours. Simultaneously her heart rate became normal.

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Imipraminoxide

See also Tricyclic antidepressants

General Information

Imipraminoxide is an imipramine metabolite. In a comparison with the parent drug, efficacy was identical; adverse effects were of the same type but possibly less frequent (1).

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Imiquimod

General Information

Imiquimod is an immune response enhancer that induces production of interferon and several other cytokines. It is used, in formulations containing 5%, to treat external genital and perianal warts/condylomata acuminata in adults (1). As imiquimod-treated warts regress, serum concentrations of interferon-alfa, interferon-beta, interferon-gamma, and tumor necrosis factor rise (2). Trials of imiquimod have failed to identify any particular systemic or laboratory abnormalities.

In one study, there was no deleterious effect on disease progression in HIV-infected patients, and the incidence of local adverse events with imiquimod (5% three times a week) for the treatment of anogenital warts was lower than has previously been reported in healthy individuals (3). In an uncontrolled trial of topical imiquimod 5% for the treatment of common warts and molluscum contagiosum in otherwise healthy patients, fever, healing with scarring, and healing with hyperpigmentation were each reported by one participant (4).

Organs and Systems

Skin

In randomized, double-blind studies, the most common adverse effects were inflammatory reactions at the injection site (mostly erythema and itching), which usually occurred after 2–5 weeks of treatment (5–7). These local reactions included erythema, erosions, excoriation, flaking, edema, scabbing, and induration, and were rarely severe enough to warrant withdrawal. Mild to moderate irritation has to be expected in up to 70% of patients if a 5% imiquimod cream is applied three times per week (6).

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Immunoglobulins

General Information

Immunoglobulin preparations are concentrated protein solutions derived from the pooled plasma of adults or animals. They contain specific antibodies in proportion to the infectious and immunization experience of the population from whose plasma they are prepared (1). Large numbers of donors (at least 1000 donors per lot of final product) are used, in order to ensure inclusion of a broad spectrum of antibodies. Intravenous immunoglobulin is also derived from the pooled plasma of adults, but the alcohol-fractionation procedure is modified to a product suitable for intravenous use. The use of intravenous immunoglobulins in selected immunodeficiency and autoimmune diseases has been reviewed (2).

Specific immunoglobulins, termed "hyperimmune globulins," are derived from human donors known to have high titers of the desired antibody. Specific immunoglobulin preparations for use in infectious disease prevention include hepatitis B, rabies, tetanus, *Varicella zoster*, vaccinia, and cytomegalovirus immunoglobulin.

Specific immunoglobulins of animal origin still currently in use in some countries include antirabies immunoglobulin, diphtheria antitoxin, botulinum antitoxin, antivenins, antilymphocyte globulin, and antithymocyte globulin. Horse antisera against diphtheria (and subsequently against tetanus as well) were produced and used in therapy from about the beginning of the 20th century. Antidiphtheria and antitetanus immunoglobulins are now produced almost exclusively as fractions of plasma of human origin. There are, however, a few cases in which xenogeneic antisera are still used, despite their many and often serious adverse effects.

Uses

Preparations of human immunoglobulins given by intramuscular/subcutaneous administration are mainly given to prevent or treat specific diseases, such as rhesus disease (anti-D) or certain viral infections, for example measles, hepatitis A, hepatitis B, rabies, and cytomegalovirus. Polyclonal antilymphocyte preparations (for example antilymphocyte globulin and antithymocyte globulin) have been developed because of evidence that T cells are primarily responsible for rejection of transplants. Indications for treatment with, for example, horse antilymphocyte globulin and/or antithymocyte globulin are very much the same as the indications for the mouse monoclonal anti-CD3 (muromonab), namely acute rejection of transplants, and aplastic anemia (3,4).

Preparations for intravenous administration are mainly used in patients with general immune deficiency states (primary or secondary) or diseases like idiopathic thrombocytopenic purpura (ITP) and autoimmune diseases (5,6). Neurological disorders (for example Guillain–Barré syndrome and chronic demyelinating polyneuropathy) have been treated with intravenous immunoglobulin (7–9).

The efficacy and safety of intravenous immunoglobulin have been reported in primary and secondary immunodeficiency, as well as in some immune disorders such as idiopathic thrombocytopenic purpura, Kawasaki disease, and Guillain–Barré syndrome (10–15). Intravenous immunoglobulin is also used empirically in a variety of several autoimmune diseases (16). Higher dosages of intravenous immunoglobulin are used for autoimmune indications (400–2000 mg/kg) than in immunodeficiency diseases (100–400 mg/kg). Minor adverse effects, such as headache, myalgia, chest discomfort, and fever, occur in 10% of patients (17). The efficacy of intravenous immunoglobulin has been reported in patients with membranous and membranoproliferative lupus nephritis (16). High-dose intravenous immunoglobulin has also been beneficial in myasthenia gravis, multiple sclerosis, and multifocal motor neuropathy (18,19) and in patients with pemphigus vulgaris and bullous pemphigoid unresponsive to conventional immunosuppressive drugs (20,21).

Intravenous immunoglobulin administered to allogeneic bone marrow transplant recipients modifies graft-versus-host disease and prevents interstitial pneumonia and infections (14).

The use of intravenous immunoglobulins in selected immunodeficiency and autoimmune diseases has been reviewed (2).

Mechanisms of action

The effect of immunoglobulin therapy is either protection against microorganisms (antibody substitution, passive immunization), or immunomodulation, or both. The mechanism of the response in non-infectious diseases is

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still not clear, but in idiopathic thrombocytopenic purpura an early fall in platelet-associated IgG and IgM may be a primary event, due to interference with antibody binding by platelets (22). Several other mechanisms of action of intravenous immunoglobulin in autoimmune diseases have been suggested, such as enhanced suppressor activity, Fc receptor blockade on neutrophils and macrophages (23), inhibition of complement activation and modulation of anti-idiotype responses (24), cytokine modification, neutralization of superantigens, and regulation of T cells and the idiotypic network (16,25). The suppression of polyclonal immunoglobulin biosynthesis induced by high-dose immunoglobulin infusions has also been suggested as a possible mechanism (26).

General adverse effects

Specific immunoglobulins

When administering different lots of the same product of equine rabies immunoglobulin, significant differences in adverse reactions, reflecting differences in production or purification processes and protein content, have been observed (27). It has been concluded in the past that the incidence of reactions to antirabies immunoglobulin is particularly high, but any of these immunoglobulins can cause severe reactions. The WHO has recommended that animal immunoglobulins should be used only after tests to rule out hypersensitivity.

A review of the discovery of antitoxins, the development of antibody formulations, and possible adverse effects has appeared (28).

Intramuscular immunoglobulin

Allerglobuline is a human gammaglobulin formulation, given intramuscularly, that has been reported to have a protective effect against type I allergic diseases and chronic infections of the upper respiratory tract in both adults and children. In 64 patients given allerglobuline, pain and inflammation at the injection site were the most common adverse effects (29). Fever, drowsiness, headache, nausea, back pain, and conjunctivitis occurred in only few patients. One patient had a rash and myalgia after the third injection; when the rash occurred again after the fourth injection, the patient was withdrawn.

Intravenous immunoglobulin

Adverse effects of intravenous immunoglobulin are generally mild and self-limiting (25). Although more common during the first two infusions, reactions appear to be primarily related to the speed of infusion. When infusions are given over a 1–3-hour period, the incidence of reactions is less than 5% and they occur during the transfusion; when infusions are given rapidly, the reactions may appear soon after completing the infusion. In about 10% of cases they occur 30–60 minutes after the start of the infusion.

Reactions include flushing, myalgia, headache, fever, chills and shaking, low backache, nausea and vomiting, diarrhea, chest tightness and shortness of breath, wheezing, changes in blood pressure, tachycardia, and rashes (30,31). Most of the adverse effects are related to the rate of administration and can be attenuated by slowing the rate of the infusion (32) or by prior administration of hydrocortisone and/or an antihistamine. When infusions are given over a 1–3-hour period, the incidence of reactions is less than 5% and they occur during the transfusion; when infusions are given rapidly the reactions may appear soon after completing the infusion. The current high dosage of 0.8–1.0 g/kg intravenous immunoglobulin for 1–2 days (instead of the original dosage regimen of 0.4 g/kg for 5 days) for patients with idiopathic thrombocytopenic purpura is probably associated with an increased risk of adverse effects (33).

The rate of adverse effects associated with intravenous immunoglobulin varies among different studies, which has been attributed to factors such as the indication, the dosage, the infusion rate, and the patient's age (12). In one study, headache and chills were related to a higher dosage.

Of 37 patients with primary hypogammaglobulinemia who received 1235 immunoglobulin infusions, 10 had adverse reactions during 34 infusions (2.8% of all infusions), but only five reactions were moderately severe. The reactions are related to the rate of administration (34); a rate of 5 mg/kg/minute was well tolerated.

Of 56 patients with autoimmune diseases who received high dosages of intravenous immunoglobulin, 20 had at least one adverse effect after one or more courses of treatment (12). The most frequently reported adverse effects were low-grade fever, headache, and chills. The authors concluded that the occurrence of adverse effects with intravenous immunoglobulin was not related to the clinical response to treatment. However, patients who developed adverse effects during the first course of treatment were more at risk of adverse effects during subsequent courses.

Patients with thrombocytopenia generally tolerate intravenous immunoglobulin well (35). In 16 young patients aged 9 months to 22 years with immune-mediated hemocytopenias (13 with childhood immune thrombocytopenic purpura), who received a total of 210 infusions, minimal adverse effects (transient headaches) were experienced during only four infusions, and later infusions were problem-free in three of the four patients (36).

The most frequent adverse effects of intravenous immunoglobulin (Sandoz) for the treatment of various disorders (affecting 1–3% of patients in all) were headache, nausea, vomiting, and fever. Some other mild symptoms have an incidence below 1%, including abdominal pain, diarrhea, fatigue, malaise, dizziness, myalgia, and chest tightness.

Allerglobuline is an intravenous human gammaglobulin formulation that has been reported to have a protective effect against type I allergic diseases and chronic infections of the upper respiratory tract in both adults and children. In 64 patients given allerglobuline, pain and inflammation at the injection site were the most common adverse effects (29). Fever, drowsiness, headache, nausea, back pain, and conjunctivitis occurred in only few patients. One patient had a rash and myalgia after the third injection; when the rash occurred again after the fourth injection, the patient was withdrawn.

Polyclonal antilymphocyte immunoglobulins

Short-term toxicity from polyclonal antilymphocyte immunoglobulins has been particularly marked in

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patients treated with combined antilymphocyte/antithymocyte globulin preparations from immunized horses (37). Immediate adverse effects include leukopenia and thrombocytopenia, fever, arthralgia, rash, urticaria, hepatotoxicity, hyperglycemia, hypertension, and diarrhea (38). A later adverse effect is serum sickness. Many of the effects may be due to an increase in tumor necrosis factor (39).

The longer-term effects of immunosuppression, and in particular the residual hematological and immunological abnormalities in patients with aplastic anemia treated with antilymphocyte globulin, have been documented: there is toxicity to hemopoietic cells, eventually leading to clonal marrow diseases years after treatment (37). Paroxysmal nocturnal hemoglobinuria, refractory sideroblastic anemia, chronic myelomonocytic leukemia, or acute leukemia can develop 4–10 years after treatment (40).

Organs and Systems

Cardiovascular

Intravenous immunoglobulin expands the plasma volume and increases blood viscosity, which can lead to volume overload in patients with cardiac insufficiency (41). Stroke, thromboembolic events, and myocardial infarction have been reported after high-dose treatment with intravenous immunoglobulin, which increases plasma viscosity (41–43).

Thrombosis in elderly patients with an increased risk of thrombosis, such as those with hypertension or previous episodes of infarction, has been described (44). A few cases of thrombosis subsequent to intravenous immunoglobulin have been reported, including myocardial infarction in five patients, stroke in four cases, and spinal cord ischemia in one (45). It has been postulated that these events are induced by platelet activation and increased plasma viscosity (12).

Several cases of thrombosis have been reported after administration of intravenous immunoglobulin (31).

- A 75-year-old man with idiopathic thrombocytopenia purpura who was treated with intravenous immunoglobulin developed recurrent myocardial ischemia (46).
- A 54-year-old woman with idiopathic thrombocytopenic purpura received intravenous immunoglobulin 1 g/kg/day for 2 days and had an ischemic stroke with hemiparesis; 3 days later she had a deep vein thrombosis (47).
- A 33-year-old woman with Evans' syndrome received intravenous immunoglobulin 400 mg/kg/day and developed a deep vein thrombosis after 1 week (47). She was treated with warfarin, and 6 months later received an additional course of intravenous immunoglobulin for recurrent hemolytic anemia; 1 day later she died of pulmonary thromboembolism.
- A 70-year-old woman with polycythemia rubra vera and Guillain–Barré syndrome, but no known risk factors for thrombosis, had a cerebral infarction 10 days after receiving intravenous immunoglobulin; the authors wondered whether there was a relation to the polycythemia vera (48).

In a randomized, controlled study in 56 patients with untreated autoimmune thrombocytopenic purpura, who were treated with intravenous immunoglobulin 0.7 g/kg/day for 3 days, one had a deep vein thrombosis complicated by pulmonary embolism (49). One of 10 children with toxic epidermal necrolysis, for which they were given intravenous immunoglobulin 0.5 g/kg/day, developed a deep vein thrombosis requiring heparin (50). Of the 10 children, this child was the only one who received intravenous immunoglobulin for 7 days instead of the standard 4-day course.

- Transient hypertension occurred in a patient with dermatomyositis during therapy with intravenous immunoglobulin (51). In the past, his diastolic blood pressure had been 104–106 mm Hg, but he was normotensive with antihypertensive drug medication.

Several mechanisms for this transient hypertension were postulated, for example stimulation of the vascular endothelium to secrete endothelin to inhibit nitric oxide synthesis.

It has been recommended that patients with cardiac diseases should be monitored during intravenous immunoglobulin therapy, because hypertension and cardiac failure have occurred, presumably as a result of fluid overload or electrolyte shifts (52).

Respiratory

- A 35-year-old woman with idiopathic thrombocytopenic purpura treated with high dosages of intravenous immunoglobulin developed a recurrent lymphocytic pleural effusion (53).
- In a patient with Guillain–Barré syndrome, and a history of ischemic heart disease, intravenous immunoglobulin 400 mg/kg for 5 consecutive days caused severe bronchospasm and hypercapnia after a dose of 12.5 g had been given (15). The complaints disappeared after withdrawal of the intravenous immunoglobulin.

Nervous system

Headache occurred in 25% of all patients who received an infusion of intravenous immunoglobulin, probably related to larger volumes and fluid shifts, protein loads, and infusion rates (54). Intravenous immunoglobulin caused severe headache in 56% of patients without a history of migraine (55). The pathogenesis of this headache is unknown.

Severe headache has also been reported in children with idiopathic thrombocytopenic purpura using intravenous immunoglobulins (33). In a randomized, controlled study of patients with myasthenia gravis, two of six patients who received intravenous immunoglobulin developed severe headache after the initial dose of 2 g/kg (56).

In 14 patients with primary immunodeficiency disease, progressive neurodegeneration occurred and a possible relation to immunoglobulin therapy could not be ruled out (57).

Aseptic meningitis

Aseptic meningitis is characterized by headache, photophobia, nausea, vomiting, and meningism, and is confirmed by cerebrospinal fluid pleocytosis with 10–90%

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polymorphonuclear cells, increased concentrations of several proteins, and negative cultures (SEDA-22, 344) (54,58,59). It has been described in 1–15% of patients receiving high dosages of intravenous immunoglobulin (60,61) and especially in subjects with a history of migraine (25,43,60). However, aseptic meningitis has also been reported after a low dose of intravenous immunoglobulin.

- A 50-year-old man developed aseptic meningitis after a low dose of intravenous immunoglobulin (3.5 g) (60). A few weeks after the first infusion, he received a second infusion and again developed symptoms of aseptic meningitis.

The authors thought it unlikely that aseptic meningitis had been caused by an allergic reaction. They proposed that the mechanism of aseptic meningitis involved the entry of immunoglobulin molecules into the cerebrospinal fluid, causing an inflammatory reaction.

It has also been suggested that release of histamine, serotonin, and prostaglandins affects the meningeal microvasculature (31).

- Two children with idiopathic thrombocytopenic purpura developed aseptic meningitis after receiving intravenous immunoglobulin 1 g/kg/day, with unusual large numbers of leukocytes in the cerebrospinal fluid (62).

To prevent aseptic meningitis, it has been advised that intravenous immunoglobulin should be infused at a slow rate and that diluted immunoglobulin solutions should be used (58). Aseptic meningitis can be prevented by the administration of propranolol (41,58). In addition, prehydration and an antihistamine have been helpful in some patients (41,58).

Possible mechanisms of aseptic meningitis include hypersensitivity reactions, stabilizing products, cytokines, cerebrovascular sensitivity, and direct meningeal irritation. It has been suggested that it is caused by aggregated immunoglobulin, antibody–antigen complex formation with subsequent complement activation, or stabilizing carbohydrates used during manufacture (30,59).

Cerebrovascular disease

Stroke and ischemic encephalopathy, probably caused by cerebral vasospasm after intravenous immunoglobulin, have been reported as possible complications of intravenous immunoglobulin (63).

- Hemiplegia occurred on the third day of intravenous immunoglobulin therapy in a 58-year-old man with graft-versus-host disease after transfusion of non-leukocyte-depleted erythrocytes (64). The hemiplegia resolved one day after withdrawal of intravenous immunoglobulin.
- Hemiplegia occurred in a child given intravenous immunoglobulin for idiopathic thrombocytopenic purpura (65).

The authors of both reports suggested that the hemiplegia had been caused either by transient hyperviscosity or by vasospasm.

Cerebral vasospasm, cerebral vasculitis, and serum hyperviscosity have been implicated in the pathogenesis of cerebral infarction after intravenous immunoglobulin (66).

Metabolism

Blood glucose should be monitored in patients with diabetes mellitus who receive glucose-containing intravenous immunoglobulin (41).

Hematologic

It has been recommended that the blood count be monitored during intravenous immunoglobulin therapy if there is evidence of mild leukopenia, neutropenia, or thrombocytopenia before the first infusion (18).

Erythrocytes

Severe acute hemolysis due to acquisition of red cell alloantibodies from donor serum has been reported (67–69). In other cases, the suggested mechanism of hemolytic anemia after high dosages of intravenous immunoglobulin was the presence of anti-A and/or anti-B antibodies in the plasma product (70).

Various immunoglobulin products contain IgG of molecular weight of a dimer or greater (over 300 kDa), which in the presence of serum can mimic immune complexes and bind to erythrocytes via CR1 (71). Especially in young adults, the immune complex-like moieties in intravenous immunoglobulin bind to erythrocytes and serve as opsonins in the mediation of erythrocyte sequestration, resulting in significant drops in hematocrit and hemoglobin concentrations (71). It has been suggested that the presence of immune complex-like moieties bound to erythrocyte CR1 after intravenous immunoglobulin treatment is correlated with in vivo hemolysis.

- Severe hemolytic anemia after high doses of intravenous immunoglobulin occurred in a 23-year-old woman with polymyositis (72).

This adverse reaction was probably due to the presence of allohemagglutinins A and B and high molecular weight IgG complexes in the formulation. Specifications in pharmacopeial monographs and product licenses require that intravenous immunoglobulin be free of significant titers of anti-A anti-B antibodies (SEDA-24, 385).

Leukocytes

High-dose immunoglobulin has been reported to cause neutropenia (31,73,74), disseminated intravascular coagulation and serum sickness (75). Neutropenia after intravenous immunoglobulin is frequent and seems to be transient and self-limiting (76). Neutropenia is not dose-related in the therapeutic range of doses.

It has been suggested that transient neutropenia can be induced by the presence of antineutrophil antibodies present in intravenous immunoglobulin. However, the possibility that immunoglobulin-mediated neutrophil agglutination causes pseudoleukopenia has also been raised (74). Increased leukocyte aggregation in the circulating pool of peripheral blood, induced by intravenous immunoglobulin, is particularly observed in people with hyperfibrinogenemia (74). It has been suggested that leukopenia detected by electronic counting is not necessarily associated with a real reduction in the absolute number of white blood cells in the peripheral blood, but is artefactual (74).

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Platelets

In elderly patients, thrombotic events have been described in up to 10% in patients aged over 60, some of them fatal. Thrombotic events may be related to a rapid rise in numbers of circulating platelets (44,77).

Several cases of intravenous immunoglobulin-related thrombosis have been reported (78,79). It can be either venous or arterial (80). It has been suggested that thrombosis can be caused by platelet activation and increased plasma viscosity (79). In patients with vascular risk factors, such as old age, hypertension, and a history of stroke or coronary artery disease, complications, such as myocardial infarction, pulmonary embolism, stroke, and acute spinal cord events, have been described (80). Intravenous immunoglobulin enhances platelet aggregation and the release of adenosine triphosphate in human platelets in vitro. In addition, there is a dose-related increase in plasma viscosity with increasing plasma immunoglobulin concentration (79,80).

Liver

Although transient rises in liver enzymes have been documented, they are not considered to be serious (68).

Fatal hepatic veno-occlusive disease, characterized by hyperbilirubinemia, hepatomegaly, ascites, and weight gain, has been associated with intravenous immunoglobulin administered prophylactically to prevent transplant-related infections (79). To avoid such thrombotic complications, intravenous immunoglobulin should be infused at a slower rate in patients at risk, and high dosages (400–1000 mg/kg) should not be infused.

Urinary tract

Renal insufficiency after high dosages of intravenous immunoglobulin has been observed, mostly in patients with pre-existing renal disease (81). Acute renal insufficiency occurred within 7 days after the administration of intravenous immunoglobulin, with a peak at 5 days. About 40% of patients needed dialysis and 15% died despite treatment (all with severe underlying diseases); the mean time to recovery in survivors was about 10 days (82).

The US FDA has issued recommendations on safety precautions that physicians should take to reduce the potential risk of acute renal insufficiency, which appears to be uncommonly associated with infusion of intravenous immunoglobulin products (83,84). Since 1981, the FDA has received over 114 reports of renal dysfunction and/or acute renal insufficiency in patients given immunoglobulin, and a total of 17 deaths have been reported (32). As the problems have been associated with the use of specific immunoglobulin products, the FDA advises, that "physicians should carefully weigh the potential benefits of administering sucrose-containing intravenous immunoglobulin products against the risks of causing renal damage." Other cases of acute renal insufficiency have been described after the intravenous infusion of immunoglobulin (SEDA-22, 345) (73).

The pathophysiology of acute renal insufficiency due to immunoglobulins is probably related to hyperosmolar renal damage, due to sucrose present in 50 ml intravenous formulations (13,43,85–87). Acute renal insufficiency has also been attributed to sucrose in a kidney allograft recipient treated with intravenous immunoglobulin (88). The high solute load in the kidney can cause osmotic damage (32,82). The histopathology of renal tissue shows osmotic tubular injury, tubular vacuolization, and tubulointerstitial infiltrates (89,82). Cytological findings in the urine included the presence of macrophage-like tubular epithelial cells with multivacuolated cytoplasm (90). Formulations of intravenous immunoglobulin with sucrose as a stabilizer should not be used in patients with renal disease (31,81,91).

In a retrospective study of a heterogeneous group of 119 patients receiving intravenous immunoglobulin, two developed irreversible renal insufficiency and six had a rise in serum creatinine. These patients had received high dosages of two different formulations of intravenous immunoglobulin, one containing sucrose 1.76 g per gram of intravenous immunoglobulin; the other 0.5 g per gram. There was no relation between the amount of sucrose in the intravenous immunoglobulin and the development of renal insufficiency (82).

Studies in rats have suggested that after pinocytosis by renal tubular cells, sucrose is incorporated into phagolysosomes (32). The intracellular accumulation of sucrose leads to vacuole formation and cellular swelling. On withdrawal, renal insufficiency resolves in most cases. However, sometimes hemodialysis is necessary (69,89).

Risk factors for this adverse effect are pre-existing renal disease, age over 65 years, dehydration, diabetes mellitus, hypertension, and a high infusion rate (SEDA-22, 345) (10,13,32,43,86,92). To minimize the risk of renal insufficiency, it has been suggested that immunoglobulin should be diluted with hypotonic fluid, that the infusion rate should be reduced, and that dosing intervals should be increased (89). Patients should be adequately hydrated and potent diuretics should be avoided (10).

In most cases the acute renal insufficiency is reversible and recovery occurs after 7–15 days (10).

It has been suggested that kidney function should be monitored during intravenous immunoglobulin therapy if it is abnormal before the first infusion (18). In addition, these patients should be adequately hydrated during treatment with intravenous immunoglobulin (52).

Skin

Skin reactions to intravenous immunoglobulin are rare (52,93–95). Other reported reactions include urticaria, maculopapular rashes, petechiae, eczema, and erythema multiforme (31,96).

Pompholyx has been observed 5–7 days from the last day of therapy in three of 23 neurological patients treated with intravenous immunoglobulin (17,97). Pompholyx occurs on the palms of the hands and is characterized by small papules, subdermal vesicles, desquamation, and crusting.

Cutaneous vasculitis has been attributed to intravenous immunoglobulin (96)

- In a patient with type II mixed cryoglobulinemia, intravenous immunoglobulin caused severe cutaneous vasculitis accompanied by an increased cryocrit (98).

A simple method of mixing the patient's serum in vitro with intravenous immunoglobulin could probably predict this.

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Hair

There have been a few cases of alopecia after the concomitant administration of intravenous immunoglobulin and steroid (49,99–102).

Immunologic

The administration of equine or other immunoglobulins is associated with a considerable risk of adverse effects and can produce virtually any type of early or late hypersensitivity reaction, ranging from asthma and urticaria to serum sickness and fatal anaphylaxis (103–106). Encephalitis (107), myocarditis (108), nephritis (109), and uveitis (110) can all be manifestations of such reactions. In one case, leukocytoclastic vasculitis was attributed to human immunoglobulin (96).

Of systemic reactions to immunoglobulins, those of an inflammatory nature are thought to be due to the presence of small complexes or microaggregates, probably leading to activation of the complement system. The symptoms are usually mild and influenza-like, and generally respond to slowing down or temporary interruption of the infusion. They include headache, hypotension, sweating, chills, fever, nausea, and vasomotor reactions. The frequency of such adverse reactions has fallen, probably because of the improved quality of the preparations. In 1978, the frequency of adverse reactions was as high as 55% in those receiving intravenous preparations containing 10–13% polymeric immunoglobulin, whereas by 2000, intravenous immunoglobulin preparations caused adverse reactions in only 3–4% (5). The more severe reactions may also be complement-mediated and may be due to a spontaneous activation of the complement system by the immunoglobulin preparation concerned; immunoglobulin aggregates may again be involved. The symptoms may be similar to those of inflammatory reactions, though they can be more severe. Such serious effects, including rare reactions of an anaphylactic type, may occur in as few as one in 6000 cases (111).

IgA deficiency is one of the more commonly encountered genetic disorders, and homozygotic deficiency is present in 0.3–0.03% of Caucasian populations. Such individuals may develop anti-IgA antibodies and have serum-sickness-like symptoms after the first administration of immunoglobulins, sometimes experiencing more severe reactions after repeated injections (112–114). A mild reaction due to sensitization to genetic IgA variants can also occur. Selective IgA deficiency is a contraindication to intravenous immunoglobulin, because of the risk of anaphylactic shock in patients with IgA deficiency and IgE or IgG antibodies against IgA, which react with IgA in intravenous immunoglobulin (13,17,30,31,41,52,61,94).

Some reports suggest that anaphylaxis due to intravenous immunoglobulin infusion occurs most often in patients with primary hypogammaglobulinemia (115,116). However, anaphylactic reactions have been seen in two atopic patients with idiopathic thrombocytopenic purpura, and the authors warned that children with atopic disease should not receive intravenous immunoglobulin (117).

In recipients of left ventricular assist devices awaiting cardiac transplantation treated with intravenous immunoglobulin, clinical manifestations of immune complex disease occurred during four of 27 (15%) monthly courses (118). The immune complex disease was characterized by fever, arthralgia, and maculopapular rashes.

Intravascular hemolysis is a rare adverse effect of immunoglobulins, due to the presence of anti-blood group antibodies (119–123).

Body temperature

Intravenous immunoglobulin can cause malaise and fever in patients with infections, probably through a temporarily increased titer of antibodies against different pathogenic microorganisms (124).

Multiorgan failure

Multiorgan failure has been described after intravenous infusion of immunoglobulin (125).

- A 3-year-old mentally retarded girl was given intravenous sulfonated immunoglobulin for prophylaxis of measles. After infusion of about 100 mg, she became cyanotic, confused, and tachycardic. Despite hydrocortisone she developed hypotensive shock. Multiorgan failure developed, with symptoms of disseminated intravascular coagulation, acute renal insufficiency, hepatic dysfunction, respiratory distress syndrome, and rhabdomyolysis. After plasma exchange and continuous hemofiltration she recovered without sequelae. The drug-induced lymphocyte stimulation test using gammaglobulin was negative. In addition, serum concentrations of IgA and IgG were normal. However, concentrations of cytokines, such as interleukin-6, TNF-α, and soluble interleukin-2 receptor, were very high. Complement C3, C4, and CH50 were reduced, but C3a was raised.

The authors suggested that an unknown mechanism associated with intravenous immunoglobulin infusion had caused non-specific activation of complement systems accompanied by fulminant hypercytokinemia.

Second-Generation Effects

Teratogenicity

Intravenous immunoglobulin is indicated for idiopathic thrombocytopenic purpura in pregnancy. No fetal abnormalities have been reported (101).

Susceptibility Factors

Because of reports of severe adverse effects, the presence of rheumatoid factor in patients with B cell neoplasia may constitute a contraindication to intravenous immunoglobulin (83).

Autoimmune disease

The risk of reactions to antilymphocyte globulin is increased in patients with autoimmune disease (126). Fever and chills, sometimes with extreme hyperpyrexia, nausea and vomiting, urticaria, and reduced platelet and granulocyte counts were reported after the administration of horse antithymocyte globulin.

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Infusion of intravenous immunoglobulin 0.14 g/kg in 17 patients with autoimmune diseases, in whom circulating immunoglobulins had been depleted, was associated with a high incidence of serious adverse effects (94). Treatment was terminated in four patients because of adverse effects, including urticaria, severe hypotension, arthralgia, and chest discomfort.

In two reviews of intravenous immunoglobulin in systemic lupus erythematosus, there was worsening proteinuria and/or a rise in serum creatinine (127,128), whereas others treating similar patients did not detect deterioration (117,129).

Transplant recipients

The adverse effects of rabbit antithymocyte globulin in transplant recipients were pain and erythema at the injection site and in one instance polyarthritis with urticaria (130). Four cases in which malignant lymphoma developed in renal transplant recipients treated with antithymocyte globulin of animal origin have been reported (131).

Drug Administration

Drug contamination

Specifications in pharmacopeial monographs and product licences require intravenous immunoglobulin products to be free from significant amounts of anti-A and anti-B antibodies (132). It has been advised that a specification be adopted that will prevent the use of batches of intravenous immunoglobulin with abnormally high anti-D titers (over 1:64) (132).

Coagulation factors

Activated factor XIa has been demonstrated in samples of reconstituted intravenous immunoglobulin from eight different manufacturers (11). The degree of factor XIa contamination in intravenous immunoglobulin correlated with the manufacturer, suggesting that the purification process can affect residual factor XI concentration. Factor XIa can activate factor IX to factor IXa, and it can be hypothesized that there is a direct correlation between the presence of factor XI in intravenous immunoglobulin products and an increased risk of thrombotic complications.

Transmission of infection

The transmission of viral infections by immunoglobulins has occasionally been suspected. However, intravenous immunoglobulin preparations are considered relatively safe, and there are no reports of transmission of HIV or hepatitis B (44,101). This is probably because of the high degree of viral inactivation of the cold ethanol fractionation and the screening of every donation for several viruses, such as HIV and hepatitis B and C (85). Of 56 patients with autoimmune diseases who received 167 infusions of intravenous immunoglobulin, none developed antibodies to human immunodeficiency virus and hepatitis C virus or hepatitis B surface antigen (12).

In 1994, several cases of hepatitis C were reported, all traceable to a specific product (Gammagard®) (133). However, since the introduction of additional viral inactivation steps, such as solvent detergent, intravenous immunoglobulin is not considered to pose an infectious risk (69,101,134).

There has been some concern about possible transmission of hepatitis G. However, hepatitis G is an enveloped flavivirus with homology to hepatitis C and is probably also inactivated by the current procedures (58).

Although transmission of Creutzfeldt–Jakob disease through blood components and plasma products has never been documented, the FDA has suggested that there is a theoretical possibility that blood products may carry the responsible agent (135).

Transmission of hepatitis B and HIV after infusion of intravenous immunoglobulin has never been reported.

Life-threatening fulminant hepatitis due to transmission of human parvovirus B19 by intravenous immunoglobulin has been reported (136). The manufacturing process of this intravenous immunoglobulin product includes pasteurization (60°C for 10 hours), treatment with polyethylene glycol, ethanol fractionation, and nanofiltration. Removal of the small, non-lipid-enveloped parvovirus B19, which is highly resistant to different virus-reducing and inactivating steps, requires 15 nm nanofiltration.

A novel DNA virus, TT virus, has been implicated as a cause of post-transfusion hepatitis. A high prevalence of TT virus infection has been found in patients who received blood or blood components, such as factor VIII and IX concentrates. However, the PCR for TT virus DNA was negative in all 17 patients with immunodeficiency, who were treated prophylactically with intravenous immunoglobulin, as well as in 15 tested immunoglobulin formulations (137).

Drug administration route

Intramuscular, subcutaneous

Adverse effects associated with intramuscular or subcutaneous administration of immunoglobulin are extremely rare, and are usually related to IgA deficiency in the patient or to additives in the preparation (for example preservatives). Adverse effects associated with intravenous immunoglobulin are more frequently seen and may be either local or systemic (138,139). Local reactions are essentially attributable to the technique used and are not specific to the intravenous immunoglobulin.

Intravenous

Intravenous immunoglobulin is approved for the following indications: primary immune deficiencies, immune-mediated thrombocytopenia, Kawasaki disease, bone marrow transplantation, chronic B cell lymphocytic leukemia, and pediatric HIV infection (135). In addition, intravenous immunoglobulin is a promising immunomodulatory therapy for several neurological diseases, such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy (41). Intravenous immunoglobulin has also been used in the treatment of several other antibody-mediated diseases, such as dermatomyositis, autoimmune neutropenia, pemphigus vulgaris, and pemphigus foliaceus (140–142).

Mild adverse effects of intravenous immunoglobulin, such as headache, chills, nausea, backache, and flushing, occur at a rate of 5–10% (101,135). Most of these

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reactions are self-limiting and associated with over-rapid infusion (41). In patients with adverse reactions to intravenous immunoglobulin there was a significant rise in plasma IL-6 and thromboxane B_2 (143).

Drug–Drug Interactions

Contrast media

Acute renal insufficiency after intravenous immunoglobulin therapy has been reported in association with the injection of iodinated radiocontrast agents (144). Contrast media and intravenous immunoglobulin formulations containing maltose or sucrose both have toxic effects on renal cells.

Interference with Diagnostic Tests

Serum sodium measurement

Pseudohyponatremia, a laboratory artefact due to hyperproteinemia, has been observed during intravenous immunoglobulin treatment (145).

- In a 38-year-old man with end-stage renal insufficiency and thrombocytopenia secondary to systemic lupus erythematosus, pseudohyponatremia occurred after treatment with intravenous immunoglobulin 1 g/kg for 2 days (146).

This phenomenon is explained by the fact that intravenous immunoglobulin increases the non-aqueous phase of the plasma, resulting in a relative loss of plasma water volume. Sodium is virtually restricted to serum water, so each volume of plasma measured will contain less sodium and be interpreted as hyponatremia. Using a direct ion-selective electrode avoids this problem.

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Immunotherapy

General Information

Desensitization is used in the treatment of IgE-mediated disease. Increasing doses of an allergen are injected subcutaneously over a varying time span. The aim of the treatment is to decrease sensitivity to the allergen and prevent the clinical symptoms caused by exposure to the allergen. Following immunotherapy, there can be an initial rise in specific serum IgE to the allergen, followed by a fall in specific IgE and a rise in specific IgG (blocking antibody). Immunotherapy also leads to reduced mediator release from mast cells in vitro, altered lymphocyte subsets, and down-regulation of cytokine secretion (interleukins 2, 4, and 5) by T cells (1).

It has been estimated that 60 million patients receive this treatment annually (2). Bearing in mind that about 40% of the population have atopy and that about half of these develop clinical disease ranging from rhinitis to life-threatening asthma, the scope for an effective and safe programme of desensitization is very large. However, there is no consensus on which extracts should be used, how often therapy should be given, and how long it should be continued if there is clinical improvement.

Efficacy

As far as the efficacy of immunotherapeutic desensitization is concerned, the merits of the treatment must be judged on the basis of:

1. Relief of symptoms and signs—a reduction in the response of a target organ to the specific allergen. In pollen rhinoconjunctivitis, a reduced response to the instillation of pollen into the conjunctival sac would be relevant. A reduction in the skin reaction to the specific allergen, especially a reduction in the late phase skin response (IgE-mediated), may be demonstrated. In asthma, a reduction in the specific bronchial response to inhaled allergen with an associated reduction in non-specific reactivity (measured by histamine or methacholine provocation) would indicate a response to treatment.
2. A reduction in or elimination of drug treatment.

Risks of desensitization

The risks of desensitization have to be set against the chance of benefits. The dominant risk is that of an allergic reaction. Subcutaneous injection of allergenic extracts can lead variously to:

- a transient wheal and flare at the injection site
- a localized delayed subcutaneous swelling with itching
- a systemic reaction in which urticaria, asthma, and hypotension may occur, the reaction not being severe enough to be classified as anaphylaxis
- anaphylaxis.

Large local reactions should be managed by a temporary reduction in the dose of the allergen, the use of antihistamines if needed, and ice applied to the injection site. Systemic reactions may resolve spontaneously or after one injection of adrenaline.

Anaphylaxis can be fatal and requires immediate treatment and measures to prevent recurrence. The Committee on Safety of Medicines, in a report cited below, recommended that allergenic products should only be given when facilities for full cardiopulmonary resuscitation are immediately available and that patients should be kept under medical observation for at least 2 hours after receiving an injection (3).

There is at present no evidence of any undesirable long-term adverse effect of repeated courses of allergenic

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extracts, although non-allergic individuals may develop hypersensitivity, particularly when they receive extracts that contain aluminium. An isolated case of extensive subcutaneous inflammation and fibrosis with overlying skin changes was seen in a patient after 5 months of maintenance therapy (SEDA-17, 207).

The extent and timing of the risk has been delineated in some individual studies. In 419 patients treated with extracts of grass pollen or house dust mite adsorbed on to aluminium hydroxide, local reactions occurred in 10.5% and systemic reactions in 4.8% (4). In a survey of 27 806 injections there were 143 (0.51%) systemic reactions, of which 83% were mild and 17% (that is five reactions) needed treatment with adrenaline (5).

In a 10-year review (1981–91) of the reactions caused by subcutaneous immunotherapy, when 192 505 injections were given to 2206 outpatients, there were 115 systemic reactions, with no deaths. The most frequent reaction (67% of the total) was asthma with urticaria, while asthma alone occurred in 22%. Systemic reactions were much more frequent in asthmatic patients, although one-third of patients with reactions had never previously suffered from asthma. Most systemic reactions occurred during maintenance therapy. Almost always a reaction occurred within 30 minutes of the injection and was promptly controlled by routine therapy (SEDA-21, 189).

Improved formulations

It has been suggested that tyrosine-absorbed formulations with relatively short half-lives may be more dangerous in terms of immediate anaphylaxis. The alumpyridine formulation Allpyral has a long half-life, and in the UK over 4 million injections have been given with no deaths reported. Most allergen extracts are today in fact alum-precipitated, thus slowing absorption of the allergen, providing sustained immune stimulation and reducing the risk of serious anaphylaxis. Further modifications of standard allergens have been tried. Interaction between formaldehyde and allergen extract causes changes in the net charge of the allergen proteins and their tertiary structure. This reduces allergenicity/IgE-binding activity but retains immunogenicity, allowing more "allergoid" than untreated allergen to be injected before anaphylactic symptoms occur. At the higher doses tolerated a higher specific IgG concentration results. The adsorption of the allergoid on to aluminium hydroxide results in a depot formulation.

Enzyme-potentiated allergen is formed when low doses of allergen are mixed with beta-glucuronidase. It has been claimed that this formulation of allergen results in minimal or no adverse effects (6).

An alternative to injection treatment is oral immunotherapy. Gastric protein degradation prevents the use of orally administered peptide immunotherapy, but an oral delivery system using enteric-protected antigen protopolysaccharide microspheres has been developed. These formulations have been assessed in clinical trials, but to date the patient numbers have been too small to allow any useful conclusions about efficacy or the risk of adverse effects (SEDA-21, 189) (SEDA-21, 190) (SEDA-22, 196).

Benefit to harm balance

The benefit to harm balance in desensitization treatment was examined in a meta-analysis published in 1995, covering 20 randomized, placebo-controlled, double-blind trials of allergen immunotherapy for asthma. Systemic reactions occurred in a mean of 32% (20–44%) of patients, but anaphylaxis was reported on only four occasions. It was concluded that immunotherapy was a treatment option in highly selected patients with extrinsic allergic asthma where a clinically relevant and unavoidable allergen is identified (7).

The US Food and Drug Administration appointed a panel of experts to review desensitization therapy in 1974. The panel concluded that extracts used in accordance with generally accepted principles are associated with a minimal and acceptable risk of immediate reaction.

The Committee on Safety of Medicines reviewed the UK experience with desensitization in 1986, weighing efficacy against risk. They considered the evidence for efficacy and found it convincing for ragweed pollen, bee and wasp venom, and some antibiotics, but thought the evidence for grass pollen and house-dust mite less convincing. The Committee warned of the dangers of anaphylaxis and bronchospasm and noted that 26 patients had died since 1957, 5 in the preceding 18 months. With different products the risk of death varied from one in 8000 to one in 321 750 with no deaths recorded with some formulations. Anaphylaxis and bronchospasm had been reported with all formulations, the incidence varying from one in 300 to one in 14 998 (3).

The Committee on Allergen Standardization of the American Academy of Allergy and Immunology investigated 46 fatalities that occurred during immunotherapy or skin testing. They noted that the nature and severity of the initial symptoms did not appear to predict the fatal outcome or indicate the cause of death (SEDA-13, 136). In the 5 years from 1985 to 1989, 17 deaths due to allergen immunotherapy were reported, of which 16 were in patients with asthma. None occurred with skin testing. Unstable asthma or accidental overdoses were major contributory factors. The annual fatality rate in the USA from administration of allergenic extracts is low, at one fatality per 2 million doses (8).

Risk management

Some circumstances of special risk can be identified and avoided (9). The frequency of systemic reaction varies from less than 1% in patients receiving conventional immunotherapy to more than 36% in patients receiving rush immunotherapy. Common risk factors for a fatal or systemic reaction include a history of asthma, increasing allergen dose, high allergen sensitivity, a previous systemic reaction and injection during the active allergen season.

The Canadian Society of Allergy and Clinical Immunology have published guidelines for the use of allergen immunotherapy and these are similar to those developed by the American Academy of Allergy, Asthma, and Immunology. They recommend therapy with specific, standardized allergenic materials, administered in high-dose schedules, to patients with allergy to

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insect stings or allergic rhinoconjunctivitis, and in some patients with asthma. The latter should be correctly diagnosed by a meticulous history, confirmed by positive skin tests and be insufficiently controlled by allergen avoidance and appropriate drug treatment (10).

The Thoracic Society of Australia and New Zealand and the Australasian Society of Immunology and Allergy have published guidelines for the use of specific allergen immunotherapy in the treatment of asthma patients (2). These should be read by practitioners who are considering immunotherapy for patients, especially those with asthma, who have a higher risk of a serious systemic reaction.

Specific allergens

Dermatophagoides farinae

The incidence of adverse systemic reactions during immunotherapy for perennial allergic rhinitis using standardized extracts of *Dermatophagoides farinae* has been estimated in 386 patients who received 22 722 injections. The incidence of systemic reactions was 6.22% per patient and 0.12% per injection. Systemic reactions began 3–30 minutes after an injection (average 11 minutes). Asthma, atopic dermatitis, and a high concentration of IgE (but not specific IgE) in serum were identified as important risk factors for severe systemic reactions. Systemic reactions occurred in 12 of 18 patients who had an IgE concentration over 100 U/ml and asthma and/or atopic dermatitis. In patients who had none of these risk factors the incidence of systemic reaction was 1.64% per patient. The authors estimated that the rate of systemic reactions could be reduced by 75% if patients with identified risk factors were strictly excluded from immunotherapy for allergic rhinitis (11).

Insect venoms

The efficacy of desensitization using subcutaneous maintenance venom immunotherapy is well established and is usually considered in patients with severe systemic allergic reactions to both yellow jacket and bee venom (grade III or IV according to Mueller).

Among 160 patients who were mostly allergic to bee venom and who were assessed for systemic allergic reactions to sting challenges while increasing the intervals of maintenance venom immunotherapy from 4–6 weeks to 3 months there were no serious adverse events (12). Two of 44 patients, who were deliberately stung during the 3-monthly maintenance therapy, had a mild systemic reaction. After withdrawal of venom immunotherapy, 22 patients allergic to bee venom were sting-challenged; one had a mild systemic reaction. In conclusion, the conventional 4–6 week maintenance interval can be safely extended to 3 months in most patients without any adverse events.

In 36 patients with a history of systemic reactions (grade III or IV according to Mueller) after exposure to a wasp sting, who were given immunotherapy with aluminium hydroxide-adsorbed wasp venom extract in an open retrospective study, a maintenance monthly depot of 50 000 SQU (50 micrograms) of venom was used (13). After the first year, the dose was injected every other month. Desensitization therapy was well tolerated. There were few mild local adverse events. Thirteen patients were exposed to stings during maintenance immunotherapy and four after withdrawal at the end of the 5-year treatment period. Field stings only provoked local skin reactions.

Near-fatal anaphylaxis, a rare complication of immunotherapy, has been reported (14).

- A 55-year-old man was stung by a *Polistes* wasp and had an anaphylactic reaction. Intradermal skin tests with wasp venoms were negative. Intradermal honeybee venom 1.0 microgram/ml and *Polistes* wasp venom 0.1 microgram/ml produced induration and erythema. Venom immunotherapy was given using the protocol of the Bayer Corporation: monthly maintenance injections of Bayer honeybee venom and *Polistes* wasp venom, 100 micrograms of each for 13 months without incident. Because of a national shortage of *Polistes* wasp venom manufactured by Bayer, *Polistes* wasp venom manufactured by ALK was substituted. Within minutes of receiving injections of 100 micrograms of Bayer honeybee venom and ALK *Polistes* wasp venom (both from new vials) he became light-headed and developed syncope. He recovered consciousness but remained hypotensive (74/0 mmHg). In a serum sample 2 hours after the start of the reaction serum tryptase was raised at 38 micrograms/ml (reference range 5.6–14 micrograms/ml) and IgE anti-honeybee venom and IgE anti-*Polistes* wasp venom concentrations were 3 and 10 ng/ml respectively.

The authors performed RAST inhibition to measure the relative potencies of the different venom extracts using the patient's serum as a source of IgE anti-venom. Although they initially suspected the new source of *Polistes* wasp venom, the relative potency tests showed greater variation in the honeybee venom. The IgG concentrations were consistent with this finding. This report emphasizes the care that must be taken with the preparation of each injection, especially when using a new batch of antigen.

Serum sickness has been described as a result of immunotherapy for wasp venom hypersensitivity. The illness was severe and treatment with glucocorticoids and seven plasma exchanges was required to induce a remission. There were two further relapses requiring the same treatment before recovery (SEDA-22, 197).

A follow-up of patients for 5 years after stopping venom immunotherapy has been reported. The authors concluded that the residual risk of a systemic reaction to a sting was 5–10% in adults. No severe or life-threatening reactions occurred with 270 challenge stings in 74 patients after 1–5 years without venom immunotherapy. The authors have extended these observations to 5–10 years and attempted to identify patients at greater risk of a reaction. Patients were surveyed for 3 consecutive years to determine the frequency of systemic reactions to field stings and the course of venom sensitivity. The patients included the original 74 (group 1) and 51 other patients followed after stopping venom immunotherapy (group 2). Eleven of the 74 patients in group 1 had field stings again after 3–7 years without venom immunotherapy. One systemic reaction (dyspnea) was reported. Of the 51 patients in group 2, 15 were stung, of whom 4 (26%) had systemic reactions, including respiratory symptoms necessitating the use of adrenaline. Six of the 13 patients (groups 1 and 2) with a systemic reaction to a sting after stopping

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venom immunotherapy had had a systemic reaction during venom immunotherapy (to an injection or a sting). Only six of 76 patients who had no reaction during venom immunotherapy had a systemic reaction when stung after cessation of venom immunotherapy. Other risk factors were persistent strongly positive skin test sensitivity and the severity of the pretreatment reaction (15).

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Indanediones

General Information

Indanediones have the same anti-vitamin K action as the coumarins. However they are generally more toxic than the coumarins, and can cause allergic reactions capable of involving many organs and sometimes resulting in death (1). These reactions are mainly observed with phenindione and are very rare with other indanediones, such as fluindione.

In an MRC trial (2), a 2.25% incidence of reactions necessitated withdrawal of phenindione.

Organs and Systems

Cardiovascular

As with the coumarins, the main complication of the indanediones is bleeding. The incidence of hemorrhage varies, depending on the age of the patient, the intensity of treatment, and the indication for using an anticoagulant. Hematuria, bruising, and gastrointestinal bleeding are the commonest signs. The most common site of fatal hemorrhage is intracranial (3).

Hematologic

Agranulocytosis can occur during the first month of treatment with phenindione (4). Anemia, thrombocytopenia (5), and leukemoid reactions (6) have also been described.

Liver

Hepatitis can rarely occur during indanedione treatment, most often with phenindione, although occasionally with fluindione (7,8). The mechanism is probably allergic. Resistance to treatment may be associated with the appearance of this reaction (8).

Urinary tract

Phenindione can cause renal insufficiency and the nephrotic syndrome, usually preceded by fever and skin reactions. In such cases, renal biopsy shows interstitial edema with infiltration by eosinophils and plasma cells. Tubular necrosis has also been observed(9).

Skin

Skin reactions are the commonest manifestations of allergic reactions. They generally occur during the first month of treatment and include erythematous, scarlatiniform, papular, and urticarial rashes, sometimes accompanied by fever. Severe exfoliative dermatitis has been reported (10,11).

Skin necrosis can occur during therapy with phenindione (12), as it does with the coumarin congeners.

Second-Generation Effects

Lactation

Massive neonatal scrotal hematoma occurred while the breast-feeding mother was taking phenindione (13).

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Indapamide

See also Diuretics

General Information

Indapamide is a thiazide-like diuretic. Although it was introduced as a specific antihypertensive drug without appreciable diuretic action, the effects of indapamide are no different from those of bendroflumethiazide.

Organs and Systems

Sensory systems

Transient myopia associated with diffuse choroidal thickening has been described in a 38-year-old white man who had taken indapamide for hypertension; it resolved after withdrawal (1).

Metabolism

The metabolic effects of indapamide appear to be as common as those of thiazides (SEDA-14, 185) (SEDA-15, 216). The metabolic effects of hydrochlorothiazide 25 mg/day and indapamide 2.5 mg/day for 6 months have been compared in a randomized, double-blind study in 44 patients with mild to moderate hypertension (2). There was little difference between the effects of the drugs on a wide range of lipid parameters, glucose, and potassium. The purported metabolic differences with indapamide are unlikely to be of sufficient magnitude to warrant its preferential use in hyperlipidemia.

Electrolyte balance

Cases of severe indapamide-induced hypokalemia have been reported (SED-11, 424) (SEDA-15, 213).

Liver

Severe acute hepatitis associated with indapamide has been reported (3). Serum bilirubin and liver enzymes were greatly raised. All normalized over 6 months after withdrawal of indapamide.

Urinary tract

Interstitial nephritis leading to acute renal insufficiency has been reported with indapamide (4).

Skin

Hypersensitivity to indapamide can provoke serious adverse skin reactions (SEDA-17, 260) (SEDA-18, 234).

One patient had several episodes of fixed drug eruption during treatment with indapamide (5). The diagnosis was confirmed by positive controlled oral challenge.

Pemphigus foliaceus has been described in relation to indapamide (6).

Drug–Drug Interactions

Sulfamethoxazole

The possibility of cross-reactivity with other sulfonamide derivatives was investigated by controlled oral challenge tests with sulfamethoxazole, sulfadiazine, and furosemide. The test with sulfamethoxazole was positive.

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Indinavir

See also Protease inhibitors

General Information

Indinavir is an HIV protease inhibitor.

Organs and Systems

Cardiovascular

A hypertensive crisis caused a secondary reversible posterior leukoencephalopathy in a patient taking indinavir-containing antiretroviral therapy (1).

- A 40-year-old man, who had taken stavudine 30 mg bd, lamivudine 150 mg bd, and indinavir 800 mg qds, developed an occipital headache, nausea, and vomiting. His blood pressure was 220/140 mmHg and he had bilateral papilledema. His blood pressure was controlled and his symptoms disappeared. An MRI scan of the brain showed lesions in the periventricular white matter; the nuclei semiovale and occipital asta were most severely affected. Indinavir was withdrawn and replaced by nelfinavir; his blood pressure returned to normal and the MRI white matter lesions disappeared.

In a retrospective analysis of 198 normotensive patients in a protease inhibitor comparison study, 30% of those who took indinavir developed stage I or worse hypertension, compared with none of the patients who took nelfinavir, ritonavir, or saquinavir (2).

Respiratory

Shock and respiratory failure have been attributed to indinavir (3).

- A 36-year-old HIV-positive man had started to take zidovudine and zalcitabine 9 months earlier together with co-trimoxazole as primary prophylaxis against *Pneumocystis jiroveci*, but switched to indinavir, stavudine, and lamivudine. Two hours after the first dose of indinavir he developed a high fever, generalized myalgia, and malaise and started to vomit. After the second dose he developed shock and cyanosis. A chest X-ray was compatible with adult respiratory distress syndrome. All cultures were negative for bacterial, viral, mycobacterial, and fungal pathogens. He recovered in 6 days and antiretroviral treatment without indinavir was reintroduced without recurrent problems.

The authors suggested that the severe shock and respiratory distress syndrome had been due to an idiosyncratic reaction to indinavir.

Nervous system

There has been a report of painful neuropathy in two patients who took ritonavir and indinavir respectively (4).

Paraparesis due to epidural lipomatosis has been attributed to indinavir (5).

- A 35-year-old man, who had taken indinavir 2400 mg/day, lamivudine 300 mg/day, and stavudine 80 mg/day for 10 months, developed a slowly progressive paraparesis, with sensory disturbances in the legs. An MRI scan was consistent with epidural lipomatosis. On withdrawal of indinavir, the symptoms gradually resolved.

Although indinavir can cause abnormal fat accumulation, this is thought to have been the first report of epidural lipomatosis.

Metabolism

Protease inhibitors are associated with hyperglycemia and possible diabetes mellitus. In a prospective study in 12 patients indinavir caused hyperglycemia and reduced insulin sensitivity (6).

Hematologic

Indinavir has been associated with severe hemolytic anemia (7).

- A 32-year-old Caucasian, who was taking lamivudine, stavudine, and indinavir for HIV infection, presented with pallor following a period of fatigue and headache (8). His hemoglobin was 8.2 g/dl and there were no clinical findings to suggest bleeding. The reticulocyte count was 3.5% and a direct Coombs' test was negative. A diagnosis of hemolytic anemia secondary to indinavir was made, the indinavir was stopped, and he was transfused with concentrated erythrocytes. The other antiretroviral drugs were continued, saquinavir was added, and a normal hemoglobin concentration was maintained.

Indinavir has been associated with thrombocytopenia (9).

Liver

Indinavir has been compared with abacavir in a randomized equivalence trial in 562 patients who were also taking lamivudine and zidovudine (10). The only significant difference in adverse effects was that there was hyperbilirubinemia in 8% of those taking indinavir and 2% of those taking abacavir. It has been postulated that indinavir-induced hyperbilirubinemia is due to inhibition of bilirubin UDP glucuronyl transferase activity, since it is more common in individuals with Gilbert's syndrome (11).

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Urinary tract

Indinavir causes nephrolithiasis as a result of precipitation of indinavir crystals in the urinary tract (12,13). It is dose-related and can be prevented by adequate hydration. In 615 patients (18 864 person-years of follow-up) who did not have risk factors for nephrolithiasis, the incidence was 8.6 episodes per 1000 person-years (14).

Several reports have suggested that patients using indinavir may also develop a syndrome consisting of back or flank pain, accompanied by crystalluria, renal function abnormalities, and evidence of tubulointerstitial nephritis on renal biopsy, but without obvious renal calculus formation (15–17).

In a French analysis of 22 510 urinary calculi performed by infrared spectroscopy, drug-induced urolithiasis was divided into two categories: first, stones with drugs physically embedded ($n = 238$; 1.0%), notably indinavir monohydrate ($n = 126$; 53%), followed by triamterene ($n = 43$; 18%), sulfonamides ($n = 29$; 12%), and amorphous silica ($n = 24$; 10%); secondly, metabolic nephrolithiasis induced by drugs ($n = 140$; 0.6%), involving mainly calcium + vitamin D supplementation ($n = 56$; 40%) and carbonic anhydrase inhibitors ($n = 33$; 24%) (18). Drug-induced stones are responsible for about 1.6% of all calculi in France. Physical analysis and a thorough drug history are important elements in the diagnosis.

The incidence of urolithiasis with indinavir has been estimated at 9% (19) but, according to some, may be as high as 20%. Indinavir calculi are often radiolucent and may be missed on CT scan rather than by using a contrast medium (which is itself not without risk) (20,21). It may therefore be that in some cases in which other renal complications with indinavir have been described there was in fact undetected renal stone formation. Any patient taking indinavir who develops renal colic should be suspected of having renal stones (22).

In two cases long-term use of indinavir appeared to have been responsible for renal atrophy (23), and again one wonders whether crystals may have been present but radiologically invisible.

Reversible renal insufficiency (which again could have been due to crystalluria) has been reported with indinavir (24).

- A 38-year-old man developed renal insufficiency while taking indinavir. His serum creatinine increased over a period of about 1 year, but urinalysis was persistently normal. A renal biopsy showed marked tubular crystal deposition. The indinavir was withdrawn, and after 2 months his serum creatinine returned to normal.

Since the basic problem in many such cases is probably crystalluria, it should be possible to treat it with rehydration, perhaps supplemented by brief interruption of therapy; this has been the conclusion of a study in which the unwanted renal effects of indinavir were prominent (25). Of 74 individuals infected with HIV-1 and taking indinavir 2.4 g/day orally, 15 had indinavir-related urological adverse effects (19 episodes), most commonly dull flank pain and dysuria. Microhematuria occurred in 16 of the 19 episodes. Four patients had urinary tract distension on ultrasonography as a possible indirect sign of urolithiasis and one passed a stone. In 4 patients treatment had to be stopped permanently, but in the other 11 it was continued. Some patients required dosage reduction and/or interruption of treatment: only conservative therapeutic measures were required, consisting of rehydration (fluid intake of at least 1.5 l/day) and analgesics.

Of 23 indinavir-treated patients with persistent pyuria, four had interstitial nephritis, seven had urothelial inflammation, 10 had both interstitial nephritis and urothelial inflammation, and two had non-specific urinary tract inflammation (26). In all, 21 patients had multinucleated histiocytes identified by cytological testing of urine specimens. Urine abnormalities resolved in all 20 patients who stopped taking indinavir, and pyuria persisted in the other 3. Six patients had raised serum creatinine concentrations, which returned to baseline when indinavir was withdrawn.

Skin

HIV-positive/AIDS patients using indinavir develop rashes early in treatment, a finding that is familiar with various other drugs used in this condition. This problem has been quantified in a study using data from postmarketing surveillance (27). Of 110 HIV/AIDS patients with a rash, 67% reported that it had occurred within 2 weeks of the start of indinavir therapy. The rash was initially localized in all cases, but in the majority it went on to spread to other body areas, involving all parts of the body in no less than 44%. It was usually pruritic but not accompanied by fever. Relief was often obtained by use of topical antihistamines or oral or topical glucocorticoids. More than half the patients decided to continue therapy despite the rash.

However, cutaneous toxicity can have a major influence on adherence to treatment and can impact adversely on the quality of life. Of 84 patients taking indinavir plus two nucleoside reverse transcriptase inhibitors for 20 months, 48 developed cheilitis, 34 had skin dryness and pruritus, 10 developed asteatotic dermatitis on the trunk, arms, and thighs, and 10 complained of scalp defluvium (28). Severe alopecia was observed in one patient, while six reported that their body hair had become fairer and thinner and shed considerably. Multiple pyogenic granulomas were observed in the toenails of five patients and softening of the nail plate was noted in five. The temporal relation between starting indinavir and the onset of these effects was striking and regression occurred on withdrawal.

Suggested mechanisms for these adverse effects include:

- retinoid-like effects due to homologies of the amino acid sequences of the HIV-1 protease and cytoplasmic retinoic-acid binding protein type 1 (CRABP-1)
- inhibition of CYP3A by indinavir, resulting in reduced oxidation of retinoic acid and hence augmentation of its biological effects.

Hair

Alopecia has been attributed to indinavir in 10 men (29). Of 337 patients who were given indinavir as part of

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combination antiretroviral therapy with nucleoside analogues, five (1.5%) developed severe alopecia a median of 50 days after starting indinavir. Three had diffuse shedding of hair involving the entire scalp, and two were initially aware of circumscribed circular areas of alopecia resulting in complete severe hair loss. Although indinavir was discontinued in all five cases, there was no regrowth a median of 30 days later (30).

Nails

Paronychia associated with indinavir has been reported (31,32). In 288 patients in a retrospective cohort study, paronychia was associated with indinavir, with a hazard ratio of 4.7 (33).

Musculoskeletal

Increased bone mineral density has been documented in patients taking indinavir (34) although in another study protease inhibitor-containing regimens caused accelerated loss of bone density (35).

- Widespread osteosclerosis, accompanied by increased serum concentrations of osteocalcin and C telopeptide, developed in a 56-year-old man who took indinavir 800 mg tds for 27 months (36).

This patient had been taking vitamin A 1 mg/day for 20 years and the authors proposed that the indinavir had also had a vitamin A-like effect.

Frozen shoulder has been attributed to indinavir (SEDA-24, 347) (37). In one case it was associated with Dupuytren's contracture and in one case each with arthralgias and tendinitis (38). An adhesive capsulitis seems to be present.

The results of a questionnaire survey of 878 people with HIV infection treated with antiretroviral drugs confirmed the risk of arthralgias in patients taking indinavir. The authors suggested that crystal deposition in joints, analogous to the crystalluria with nephrolithiasis that indinavir and other protease inhibitors can cause, might be responsible.

Susceptibility Factors

Sex

The pharmacokinetics of indinavir in 220 women and 94 men have been compared; there was no difference (39).

Drug–Drug Interactions

Cannabinoids

The effects of smoked marijuana (3.95% tetrahydrocannabinol; up to three cigarettes per day) and oral dronabinol (2.5 mg tds) on the pharmacokinetics of indinavir 800 mg 8-hourly ($n = 28$) have been evaluated in a randomized, placebo-controlled study in HIV-infected patients (40). On day 14, marijuana reduced the 8-hour AUC of indinavir by 15%, the C_{max} by 14%, and the C_{min} by 34%. However, only the change in C_{max} was significant. Dronabinol had no effects.

Carbamazepine

Failure of combination therapy including indinavir has been attributed to an interaction of indinavir with carbamazepine (41).

- A 48-year-old HIV-positive man taking indinavir, zidovudine, and lamivudine developed *Herpes zoster* infection, which was treated with famciclovir. Postherpetic neuralgia was treated with carbamazepine, and his plasma indinavir concentration fell substantially. The carbamazepine was withdrawn after 2.5 months and 2 weeks later HIV-RNA was detectable in his plasma (6×10^3/ml). His circulating virus was resistant to lamivudine. With a further increase in viral load, his therapy was changed to nevirapine, didanosine, and stavudine.

This treatment failure, and possibly the resistance to lamivudine, was attributed to induction of drug metabolism by carbamazepine.

Didanosine

The absorption of indinavir was not affected by co-administration of didanosine in an encapsulated enteric bead formulation in 24 patients (42).

Levothyroxine

Inhibition of glucuronyl transferase activity by indinavir has been blamed for an interaction of indinavir with levothyroxine, causing hyperthyroidism (43).

- A 36-year-old woman, who had taken levothyroxine for several years, took stavudine, lamivudine, and indinavir for 1 month and developed nervousness, palpitation, restlessness, weakness, and weight loss. She had an undetectable serum TSH concentration and raised unbound serum T4 and T3. The dose of levothyroxine was reduced to one-third and then to one-sixth of the previous dose, and the thyroid function tests returned to normal.

Phenylpropanolamine

In one case the use of phenylpropanolamine with triple drug therapy for HIV prophylaxis led to a hypertensive crisis (44). As the patient had previously tolerated phenylpropanolamine well, one must suspect that one or more of the anti-HIV drugs (probably indinavir) had interfered with the metabolic breakdown of the phenylpropanolamine.

Ritonavir

Using ritonavir as a booster may allow indinavir to be given twice daily and with food. In a cohort survey of 100 patients the combination of indinavir plus ritonavir (400 mg/400 mg or 800 mg/100 mg bd) was a safe and effective option to reduce the tablet burden and improve adherence (45).

Sildenafil

There is good evidence that indinavir can substantially increase plasma concentrations of sildenafil (46). Since HIV infection commonly leads to erectile dysfunction,

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the drugs may well be used together and it will then be prudent to use a lower dose of sildenafil.

Silybum marianum (milk thistle)

The pharmacokinetics of indinavir 800 mg 8-hourly have been studied in the presence and absence of milk thistle 175 mg (containing silymarin 153 mg) tds for 3 weeks in an open study in 10 healthy volunteers; milk thistle had no significant effect except a small reduction in $C_{min.ss}$ (47).

Venlafaxine

Venlafaxine 50 mg 8-hourly reduced the AUC of a single dose of indinavir 800 mg by 28% in nine healthy subjects (48).

Diagnosis of Adverse Drug Reactions

The adverse effects of indinavir have been retrospectively evaluated and correlated with indinavir trough concentration in 63 patients taking indinavir + ritonavir 800/100 mg bd (49). The median indinavir trough concentration of 1446 ng/ml was associated with 60% of measured toxicity. Of 49 patients with an indinavir trough concentration over 500 ng/ml, 46 had at least one dosage adjustment; the main reason for dosage adjustment was toxicity ($n = 43$). The common adverse effects affected the skin (vitamin A-like reactions; $n = 39$), kidneys (renal colic, nephrolithiasis, renal insufficiency; $n = 35$), gastrointestinal tract (nausea, vomiting, and diarrhea; $n = 32$), and liver ($n = 14$). After dosage adjustment, the median indinavir trough concentration was 459 ng/ml, which was associated with 8% of toxicity. Trough concentrations over 500 ng/ml correlated with increased toxicity. The authors concluded that indinavir trough concentrations below 500 ng/ml are safe, and that an optimal concentration range for indinavir trough concentration could be 150–500 ng/ml in patients taking twice daily indinavir + ritonavir.

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Indometacin

See also Non-steroidal anti-inflammatory drugs

General Information

Indometacin is the best-known and most thoroughly tested indoleacetic acid derivative. It is one of the most effective NSAIDs, and most of its toxic and therapeutic effects appear to be due to marked inhibition of prostaglandin synthesis. Because of its potency, its clinical efficacy is comparable, if not superior, to any other NSAID, but for precisely the same reason its adverse effects on the gastrointestinal tract and the nervous system inevitably limit its use. However, patients who tolerate it reasonably well are naturally not anxious to exchange it for any newer drugs with fewer problems but less potency. A meta-analysis of patients' preference in 37 crossover comparisons of indometacin with newer NSAIDs did not provide evidence of a trend to replace indometacin with newer NSAIDs (1).

Tropesin is the tropic acid ester of indometacin, and its adverse effects profile is similar to that of indometacin (SEDA-17, 113).

General adverse reactions

Adverse effects, in up to 60% of patients, are closely related to indometacin's strong anti-inflammatory potency. Gastric irritation, including ulcers, bleeding, and perforation, predominates. Nervous system complications are related to cerebral edema. Headache is common. Hematological effects are infrequently reported. Nephrotoxicity is exacerbated by pre-existing renal impairment. Ocular toxicity can follow long-term use.

Cross-reactivity with aspirin has been reported (2). The hazards of administering topical indometacin to asthmatic patients should be widely known (3).

Tumor-induced effects have not been demonstrated.

Organs and Systems

Cardiovascular

Clinical experience and reports have provided little evidence that indometacin precipitates angina or myocardial infarction. However, an individual angina-provoking

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effect has been documented (4), and there are grounds for believing that it can happen.

Intravenous administration of indometacin increases blood pressure, coronary vascular resistance, and myocardial oxygen demands, decreasing coronary flow. A controlled short-term study showed that indometacin increased blood pressure in patients with mild untreated essential hypertension (SEDA-17, 108). In view of the increasing use of parenteral administration, the acute hemodynamic effects of indometacin may now occur more often, especially in the elderly (5). The mechanism is poorly understood, but apparently a direct action is exerted on the resistance vessels in various regions. This is probably independent of indometacin's action on prostaglandin formation. The clinical relevance is largely unknown, but other NSAIDs should probably be prescribed for patients with occlusive vascular diseases affecting the cerebral and/or coronary vessels.

Other systemic cardiovascular adverse effects are due to salt and fluid retention and also to a reduction in the vasodilator action of circulating prostaglandins E_2 and I_2 (6).

Unlike other NSAIDs, indometacin acts as a cerebral vasoconstrictor. It reduces cerebral flow by up to 35% and the response to hypercapnia disappears (SEDA-10, 79). It also reduces blood flow in the splanchnic vascular bed, by increasing local vascular resistance, but does not impair circulation in the forearm and leg muscles.

Respiratory

Inhibition of prostaglandin synthesis explains indometacin's ability to provoke or aggravate asthma in hypersensitive patients (7). Indometacin in ophthalmic solution reportedly caused such deterioration in asthmatic patients as to require mechanical ventilation (3,8). Cross-sensitivity between indometacin and aspirin has been observed.

Nervous system

Adverse reactions to indometacin involving the central nervous system are frequent and come second in importance only to gastrointestinal effects. They are attributed to salt and water retention. Up to 60% of patients experience headache (often migraine-like), frontal throbbing, and vertigo. Vomiting, tinnitus, ataxia, tremor, dizziness, and insomnia follow. Somnolence, confusion, hallucinations (especially in the elderly), and psychotic symptoms have been described. Coma, clonic seizures, and myoclonic spasms (SEDA-18, 101) can develop. Muscle weakness and paresthesia, that is, peripheral neuropathy, may develop in elderly patients, but recede after withdrawal (9,10).

Indometacin is used for non-invasive closure of symptomatic ductus arteriosus in the preterm infant. Intravenous administration causes an instant reduction in cerebral blood flow, increasing cerebral vascular resistance. The clinical significance for the nervous system of these hemodynamic changes is unknown (11,12), but they seem to be linked to the effects seen in the central nervous system. Advantage has been taken of this effect for reducing intracranial hypertension in patients with severe head injury (SEDA-15, 99).

Indometacin is also used in preterm infants as prophylaxis against intraventricular hemorrhage. In a prospective, randomised, placebo-controlled trial in 431 preterm neonates, low-dose indometacin prevented intraventricular hemorrhage without adverse cognitive or motor outcomes at 36 months (13).

Low-dose indometacin (0.1 mg/kg), begun in the first 24 hours of life and given every 24 hours for 6 doses, was not associated with adverse neurodevelopmental outcome at 36 months corrected age (14).

Sensory systems

Prolonged therapy can cause a number of adverse reactions in the eyes. Trivial effects are ocular discomfort, conjunctival pain, and increased ocular tension, but mydriasis, photophobia, blurred vision, diplopia, amblyopia, and loss of vision can occur. The most serious complications are retinopathy with reduced retinal sensitivity, and corneal and retinal pigmentation. They are reversible, but improvement is slow. A report on indometacin retinopathy has added more doubt than certainty to the question of the frequency and severity of retinal toxicity (SEDA-14, 93). Patients taking prolonged therapy should have regular ophthalmic examinations.

Metabolism

Indometacin reduces the area under the corticotropin (ACTH) plasma concentration–time curve after insulin in normal men, possibly because of the role of prostaglandins in the control of ACTH secretion (15).

One report has described low plasma ascorbic acid concentrations during indometacin treatment, and a case of hyperglycemia has been reported (16).

Electrolyte balance

Hyperkalemia has been reported in patients with preexisting renal disease treated with indometacin (SEDA-4, 65) (SEDA-5, 90) (SEDA-6, 93) and in a patient with Bartter's syndrome receiving concomitant oral potassium chloride (SEDA-11, 92) (17). Indometacin caused a high serum potassium concentration in a young athlete (SEDA-14, 93).

Mineral balance

During indometacin therapy, urinary excretion of zinc and calcium can increase significantly (18). The clinical relevance is not known.

Fluid balance

Salt and fluid retention is an adverse effect of indometacin, although it is less important than with the pyrazolone derivatives. Indometacin can antagonize antihypertensive agents, including beta-adrenoceptor antagonists (19,20). The effect on blood pressure in normotensive patients has not been adequately studied.

Severe water intoxication caused by inappropriate ADH secretion has been described in an elderly woman taking indometacin (SEDA-17, 108).

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Hematologic

Anemia caused by repetitive gastrointestinal bleeding is a relatively frequent, although indirect, hematological adverse effect.

Blood dyscrasias, sometimes fatal aplastic anemia (21), isolated granulocytopenia, and agranulocytosis have been reported (22). The International Agranulocytosis and Aplastic Anemia study showed that indometacin was significantly associated with agranulocytosis and aplastic anemia (23).

Since indometacin is an inhibitor of platelet aggregation, impairment of thrombocyte function is frequent, but thrombocytopenia is rare. Severe clotting defects due to inhibition of platelet aggregation in premature infants have been described (24). Postoperative bleeding is significantly more frequent in indometacin-treated patients. Indometacin should probably not be used postoperatively in patients at increased risk of bleeding (SEDA-8, 103).

Gastrointestinal

Gastrotoxicity is the main adverse effect of indometacin, and symptoms range from abdominal discomfort to ulcer penetration and perforation (25). The phenomenon of gastric mucosal adaptation has been evoked to explain the relatively low incidence of severe adverse effects, compared with the acute gastric damage that occurs in short-term studies. In healthy volunteers, indometacin produced acute gastroduodenal damage in all cases, but resolved in almost all, despite continuing administration. The author hypothesized that the severity of mucosal damage depends on the reduction in mucosal blood flow (SEDA-16, 108) (SEDA-17, 108).

Small bowel ulceration with thickening of the bowel wall and stricture formation in the terminal ileum and the ileocecal junction occurred in a patient with rheumatoid arthritis taking long-term indometacin (SEDA-12, 84). This is one reason why prolonged courses of indometacin should be avoided whenever possible, especially in elderly women.

Osmosin, a formulation that contains potassium bicarbonate and releases indometacin osmotically, was withdrawn because of reports of intestinal irritation, bleeding, perforation, and even death. These adverse effects were most probably caused by the very high local concentrations of indometacin and potassium in the lower part of the gastrointestinal tract produced by the tablet, which shifted the adverse reactions from the stomach to the intestine (SEDA-8, 103) (26).

Like other NSAIDs, a diaphragm-like right-sided colonic stricture has been described in a woman taking indometacin suppositories (27). Perforation of colonic diverticula has been described (28).

The use of indometacin suppositories can be associated with rectal irritation, mucosal inflammation, or necrosis with bleeding (29). The local effect on the gastric mucosa is less important than the systemic one, and suppositories do not cause fewer gastric lesions than oral formulations (30).

Liver

Despite reversible changes in liver enzyme tests (31) and a fatal case of acute hepatocellular necrosis, which may have been related to indometacin, the drug is rarely hepatotoxic (32). Indometacin-associated cholestatic liver injury has been described. The reaction was not severe and recovery was rapid and uneventful (33).

Urinary tract

Indometacin nephrotoxicity is rare in patients with normal renal function, but indometacin can aggravate preexisting renal impairment, as has been observed in patients with glomerulonephritis, nephrotic syndrome, systemic lupus erythematosus, and cirrhosis complicated by ascites (SED-8, 219) (SEDA-4, 65) (SEDA-7, 108) (SEDA-11, 85). Severe but reversible loss of renal function in patients with systemic lupus erythematosus in the absence of active renal disease suggests that mesangial contraction in the glomerulus could significantly reduce the capillary surface area available for filtration and hence reduce the glomerular filtration rate (34,35). There is a significant reduction in the glomerular filtration rate and a concomitant drop in renal excretion of sodium and water in patients with compensated cirrhosis without ascites treated with indometacin (SEDA-18, 101).

Probable indometacin-induced renal papillary necrosis has been described in two patients with chronic juvenile arthritis (SEDA-8, 103).

Reversible acute renal insufficiency with eosinophilia has been described (36).

The harmful effect of indometacin on renal function has been used therapeutically to induce medical nephrectomy (SEDA-7, 108).

Skin

Reactions to indometacin range from urticaria and pruritus to fixed rashes, purpura, and maculopapular and morbilliform eruptions. Toxic epidermal necrolysis has also been described (37). The frequency of skin reactions is lower than with pyrazolone derivatives. There is cross-sensitivity with aspirin.

Whether indometacin exacerbates psoriasis is not certain, but one report (38) suggests that it can.

Indometacin can exacerbate dermatitis herpetiformis (SEDA-10, 81).

Musculoskeletal

Progressive destruction of large weight-bearing hip joints was first observed during long-term indometacin therapy more than 25 years ago (SEDA-11, 87) (39). In one comparison of the effects of azapropazone and indometacin, the osteoarthritic process in the hip progressed more quickly in patients treated with indometacin, no doubt a further indication of its powerful inhibitory effect on prostaglandin synthesis (40). The mechanisms responsible for the harmful effect of NSAIDs on osteoarthritic joints have been reviewed (SEDA-11, 87).

Sexual function

Inhibition of prostaglandin synthesis can cause impotence. A healthy man became impotent while taking short-term indometacin 150 mg/day (SEDA-5, 101).

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Immunologic

Masking of infection and abnormal immune reactions have been reported (41). It is not clear whether this has any clinical significance.

Second-Generation Effects

Fertility

Ovulation was inhibited by indometacin at high doses in the preovulatory period (SEDA-16, 109).

Pregnancy

The use of indometacin in late pregnancy has been much debated. Because of its ability to inhibit prostaglandin synthesis it can be used to arrest premature labor for a short time, although there is no evidence that it reduces the incidence of premature delivery. The hazards of using it as a tocolytic agent seem to outweigh any theoretical advantage, since there are many reports of serious adverse neonatal effects after the treatment of preterm labor with indometacin. They include premature closure of the ductus arteriosus, pulmonary hypertension with persistent fetal circulation, fetal anuria, severe oligohydramnios, necrotizing enterocolitis, perinatal death, and severe respiratory distress syndrome resulting in oxygen dependence for several days (SED-11, 179) (42–44) (SEDA-5, 101) (SEDA-6, 93) (SEDA-7, 108) (SEDA-8, 102) (SEDA-9, 88) (SEDA-12, 84) (SEDA-15, 99) (SEDA-16, 109) (SEDA-17, 108). The risks might be linked to the duration of use, but one study provided evidence that short-term indometacin can cause closure of the ductus arteriosus, even if several weeks elapse between treatment and delivery (45).

The risks involved in longer-term use are multiple, as several studies have shown. The use of indometacin and ibuprofen for more than 72 hours in 67 women in preterm labor was significantly associated with more oligohydramnios than either ritodrine or magnesium sulfate. Oligohydramnios developed in 70% of 37 women treated with indometacin, in 27% treated with ibuprofen, and in 2 controls (46).

Pregnant women taking beta-blockers for hypertension in pregnancy should not be given indometacin, as it can raise the blood pressure (47).

Teratogenicity

Indometacin in pregnancy is probably safe, provided its use is limited to the first 32 weeks of gestation. However, a possible teratogenic effect has been ascribed to it (48).

Cerebral ischemia has been described in premature twins following maternal use of indometacin (49).

The incidence and type of cerebral lesions were studied by ultrasound in 159 preterm infants: 76 fetuses were exposed to indometacin used as a tocolytic agent; in the other 83 pregnancies, tocolysis was either not started or limited to fenoterol. The incidence of periventricular leukomalacia was increased in infants exposed to any tocolytic agent; cystic lesions occurred more often in those exposed to indometacin (50).

Oligohydramnios and renal dysgenesis developed in one identical twin exposed to early prolonged high-dose indometacin. As indometacin causes oligohydramnios and renal dysgenesis in fetal monkeys, it may also have caused the abnormalities in this patient (51).

Antenatal indometacin therapy has been extensively reviewed (SEDA-18, 102). Data from a retrospective cohort study of 57 premature infants, born between the 24th and 30th weeks of gestation, whose mothers had been treated unsuccessfully with indometacin for preterm labor, confirmed several fetal and neonatal complications (52). However, the overall results provided inconclusive or contradictory data on the benefit to harm balance of indometacin as a tocolytic agent or as treatment for hydramnios (SEDA-18, 102).

Fetotoxicity

The possible association of indometacin tocolysis with neonatal necrotizing enterocolitis has been the subject of a case-control study (53). All cases of proven necrotizing enterocolitis were ascertained and four controls for each case were randomly identified. During 18 months there were 24 cases of necrotizing enterocolitis. Indometacin as a single tocolytic agent was not associated with necrotizing enterocolitis (OR = 1.0, 95% CI = 0.2, 4.8).

Lactation

The effects of indometacin during lactation are unclear. Convulsions in a breast-fed infant were linked to indometacin in the milk (54).

Susceptibility Factors

Age

Children

Pharmacokinetic factors (slow metabolism) may underlie the marked effect of indometacin on platelet aggregation in premature infants and small children. The use of indometacin in children with patent ductus arteriosus can be followed by a severe general reaction. Nephrotoxicity, abdominal distension, hemorrhagic enteritis, and necrotizing enterocolitis have been observed (SEDA-10, 81) (24,55). No retrospective study has shown that indometacin-treated infants have a higher incidence of retrolental hyperplasia or visual problems (56). Reopening of the ductus after indometacin-induced occlusion has been described (SEDA-18, 101), but the risks of using intravenous indometacin are few and it is more efficacious and safer than ligation.

Elderly people

Elderly patients are susceptible to the adverse effects of NSAIDs on the nervous system. A psychotic reaction has been described in one elderly man taking indometacin (57) and behavioral changes in another (58).

Gastrotoxicity is more frequent in this age group. Of 125 516 residents of US nursing homes during 1992–1996, patients who received at least one prescription for aspirin (n = 19 101) or NSAIDs (n = 9777) were identified (59). NSAID exposure increased the overall gastrointestinal-event-related hospitalization rate. The rates were highest in those taking sulindac, naproxen, or indometacin.

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Other features of the patient

Patients with asthma or allergic rhinitis may be hypersensitive to indometacin and can develop severe general allergic reactions, especially if they are allergic to aspirin.

Indometacin should probably not be used postoperatively in patients with an increased risk of bleeding (SEDA-8, 103), because of its anti-platelet activity.

In athletes in training for a marathon, the use of indometacin may be dangerous, since it can provoke hyperkalemia and there is a risk of serious dysrhythmias (SEDA-14, 93).

Drug Administration

Drug formulations

Indometacin in eye-drop form can cause burning sensations, pruritus, local congestion and irritation, corneal epithelial changes, and edema of the eyelids (60).

Osmosin (Indosmos)

Osmosin (Indosmos) was an osmotic pump version of indometacin, which after a brief career, was withdrawn from the market in the summer of 1982. Indometacin, as a potent NSAID, found itself at the beginning of the 1980s facing heavy competition from a series of newer drugs that were about to be introduced; all were under patent, whereas some of the indometacin patents were about to expire, which could lead to a substantial fall in prices; some of the newer drugs (notably benoxaprofen, itself soon withdrawn, and piroxicam) were suitable for use as a single daily oral dose, which provided at least a marketing advantage; several were claimed, rightly or wrongly, to be relatively well-tolerated by the stomach. One possible answer to these problems seemed to be offered by developing an osmotic pump form of indometacin; in this form, the drug could be released relatively slowly, perhaps prolonging its duration of action and improving its gastric tolerability.

In fact, the question as to whether this form of indometacin really had these advantages has never been satisfactorily settled. The literature (61–64) does not appear to have shown a reduction in gastric adverse effects, at least not if one assesses the papers in question with the critical eye that must be brought to bear on claims of this type. On the other hand, it is clear that if a drug that has a potentially irritant action on the gastrointestinal tract is put into a modified-releasing form, tolerability problems may be displaced from the stomach to the lower parts of the gastrointestinal tract.

In the course of 1982, serious suspicions arose that this was indeed happening. In August, the UK's Committee on Safety of Medicines (CSM) stated that it had received 200 reports of adverse reactions to the product, which was considered a relatively high reporting level for a new drug, though more than 400 000 prescriptions had been issued over the previous 7 months. Many of the reports were of effects traditionally associated with indometacin (such as headache and gastrointestinal problems) and these did not seem to be less frequent with the new system. Two of the reports were of intestinal perforation distal to the duodenum, an unusual site for damage by NSAIDs. The CSM remarked that the release characteristics of the system might expose certain areas of the bowel to higher concentrations of indometacin than usual. It was also noted that the formulation contained potassium bicarbonate, a known bowel irritant (26).

It subsequently became clear that a fair number of cases of intestinal irritation, bleeding, perforation, and probably even death were attributable to the new formulation, leading to the product's withdrawal in countries where it had already been introduced.

The proposed mechanism of small bowel damage due to Osmosin is that the tablets adhered to the intestinal wall (or became lodged in diverticula), resulting in much higher local concentrations of indometacin and potassium than usual.

Indometacin-farnesil

Limited early experiences with indometacin-farnesil, a lipid-soluble indometacin derivative esterified with farnesol, suggested an adverse-effects profile similar to the indometacin, even though the compound was synthesized to reduce gastrotoxicity (SEDA-17, 109).

Drug administration route

Intravenous administration (in the treatment of ureteric colic) is effective and well tolerated. However, in 90% of patients who receive slow (5 minutes) intravenous injection, hypertension, nausea, vertigo, vomiting, and peptic ulcer symptoms have been documented (65). Intravenous administration should be avoided in patients with heart failure.

Intramuscular indometacin causes few adverse effects at the site of injection (redness, pain, induration) (SEDA-8, 102) and seems to have better systemic tolerability than intravenous indometacin: 26% of 388 patients treated with indometacin 100 mg/day developed an adverse effect (gastrointestinal or nervous system-related) and 4.6% interrupted treatment (66).

Drug–Drug Interactions

ACE inhibitors

Although lisinopril in association with indometacin reduced proteinuria in a small group of patients with nephritic syndrome, the combination also caused impairment of renal function and hyperkalemia in many patients (SEDA-16, 109).

Anti-platelet drugs

Indometacin potentiates the effect of anti-platelet drugs and anticoagulants (67).

Aspirin

Indometacin reduces the absorption of aspirin (68).

Beta-blockers

Attenuation of the hypotensive effect of propranolol and thiazide diuretics by indometacin was shown several years ago in a double-blind, placebo-controlled study of patients with essential hypertension (SEDA-6, 94).

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Two women with pre-eclampsia treated with pindolol and propranolol became extremely hypertensive when indometacin was added for premature contractions (47). Pregnant women taking beta-blockers for hypertension in pregnancy should not be given indometacin, as it can raise the blood pressure (47).

Cyclophosphamide

Synergy between indometacin and cyclophosphamide has been advanced as the cause of a life-threatening acute water intoxication and severe hyponatremia observed in a patient with multiple myeloma and normal renal function (SEDA-15, 99).

Dipyridamole

Marked water retention has been observed during acute administration of dipyridamole in combination with indometacin (SEDA-13, 79).

Diuretics

Indometacin reduces the effect of diuretics (69). Combination of indometacin with Moduretic (co-amilozide; amiloride + hydrochlorothiazide) results in hyperkalemia (70).

Metformin

Renal insufficiency and severe metabolic acidosis developed in a patient with diabetes mellitus taking metformin after recent treatment with indometacin (SEDA-22, 118).

Muronomab

The interaction of indometacin with the immunosuppressive agent muromonab, a monoclonal antibody to CD3, is characterized by an increased risk of encephalopathic or psychotic features (71).

Probenecid

Probenecid inhibits the tubular secretion of indometacin (SEDA-4, 66).

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Indoprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Indoprofen is one of several NSAIDs that have been withdrawn because of adverse effects. The UK Licensing Authority suspended the product licence on grounds of safety in 1983, and in 1984 the Italian manufacturers decided to withdraw it from the world market. The UK decision was taken because there was a high rate of adverse drug reactions in a voluntary postmarketing surveillance study and the spontaneous adverse reaction reporting system had noted 217 serious adverse effects, mainly gastrointestinal bleeding and perforation. According to the manufacturers, the adverse effects profile in the UK did not emerge in other countries (1). A survey of adverse reactions in 6764 patients, mostly treated for 1 month or less, showed that life-threatening events were rare. A postmarketing surveillance study in 3823 osteoarthritic patients showed that serious adverse reactions were even less frequent (2).

Organs and Systems

Hematologic

The fact that indoprofen prolongs bleeding time and reduces platelet aggregation could result in indirect interactions with anticoagulants (3).

Gastrointestinal

When the UK Licensing Authority suspended the product licence the spontaneous adverse reaction reporting system had received 217 reports of serious adverse effects, mainly gastrointestinal bleeding and perforation.

Death

There were 46 deaths associated with indoprofen in three countries (UK 34, Italy 7, Germany 5), but only 11 were judged to be probably or possibly drug-related. Nine of these deaths were caused by gastrointestinal reactions.

Long-Term Effects

Tumorigenicity

The manufacturers' ultimate reason for worldwide withdrawal was the finding of carcinogenicity in long-term animal studies. To what extent the clinical events actually played a role in their decision is not clear.

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Indoramin

See also Alpha-adrenoceptor antagonists

General Information

Indoramin is a postsynaptic selective alpha$_1$-adrenoceptor antagonist that is chemically distinct from the quinazolines. Unlike some other alpha-blockers, indoramin lowers blood pressure without a resulting reflex tachycardia or postural hypotension (1). However, it has largely been supplanted by more modern drugs, such as doxazosin, prazosin, and terazosin.

Organs and Systems

Nervous system

Indoramin penetrates the nervous system significantly and is reported to have a relatively high incidence of adverse effects, including sedation, dizziness, depression, headache, palpitation, dry mouth, and constipation (2). In a comparison with prazosin, prazosin produced a lower incidence of sedation, which is the most common adverse effect of indoramin, usually transient, in about 19% of cases (1). Other adverse effects that have sometimes led to withdrawal of indoramin have been dry mouth, dizziness, and failure of ejaculation. These adverse effects can be reduced by starting therapy with small doses and titrating gradually.

Drug–Drug Interactions

Alcohol

The sedative effect of indoramin is enhanced by alcohol (3).

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Infliximab

See also Monoclonal antibodies

General Information

Infliximab, a monoclonal chimeric human/murine antibody directed against tumor necrosis alfa, has been used in the treatment of severe active Crohn's disease (1,2), rheumatoid arthritis (3), and ankylosing spondylitis (4). From the available data submitted for Crohn's disease to the US and European regulatory agencies, the most significant acute adverse reactions were infusion reactions, defined as symptoms within 2 hours after intravenous infusion. The symptoms consisted of fever, chills, urticaria, dyspnea, chest pain, or hypotension, and occurred in 16% of infliximab-treated patients versus 6–7% of placebo-treated patients. Several adverse effects, such as upper respiratory tract infections, headaches, rash, or cough, were more common than with placebo, but severe adverse effects were only slightly more frequent (3.6 versus 2.6%). Clinical trials also showed an increase in the prevalence of antinuclear antibodies or the development of double-stranded DNA antibodies (9% of patients). Although there were clinical features suggestive of the lupus-like syndrome in only very few patients, this issue needs to be further investigated. Also of great concern is the report in several patients of lymphoma (5) or severe opportunistic infections (6). Patients taking concomitant immunosuppressive drugs should be carefully observed for such complications.

Organs and Systems

Cardiovascular

The preliminary results of a phase II trial in patients with moderate to severe congestive heart failure showed a higher incidence of worsening congestive heart failure and death in patients treated with infliximab compared with placebo (7). This led to warnings from regulatory agencies and to the limited use of infliximab in patients with congestive heart failure.

Death due to worsening of cardiac insufficiency in patients with congestive heart failure has been reported (SEDA-26, 401).

Respiratory

Allergic granulomatosis of the lung has been described after a second infusion of infliximab in one of 35 patients with active ankylosing spondylitis (8). The clinical and radiological symptoms resolved 8 weeks after withdrawal, but no other details were given.

- A 32-year-old man with Crohn's disease developed an eosinophilic pleural effusion soon after a second infusion of infliximab (9). He recovered within 8 weeks, but the effusion recurred after infliximab re-treatment 1 year later.

Nervous system

Features of aseptic meningitis have been reported after multiple infliximab injections (10).

- A 53-year-old man with severe rheumatoid arthritis and mixed type III cryoglobulinemia received his first four injections of infliximab uneventfully, but 4 hours after the fifth injection had severe muscle pain in the lower limbs, which required morphine and abated within 3 days. Similar symptoms were observed after the sixth injection. There were no signs of meningitis, the cerebrospinal fluid contained lymphocytes and increased concentrations of protein and IgG. Cultures were negative and MRI scans of the brain and the spine were normal. The CSF was normal 1 month later.

The authors speculated that the most likely explanation for these observations was linked to the lack of transfer of high-molecular weight soluble receptors and IgG across the blood–brain barrier, implying that control of brain tumor necrosis factor alfa cannot be obtained with monoclonal antibodies. They thought that neurological complications in diseases other than multiple sclerosis might be related to control of tumor necrosis factor alfa in the periphery, resulting in an enhanced contribution of brain-derived tumor necrosis factor alfa or other cytokines, such as interleukin-1.

Neurological events suggestive of demyelinating disorders in patients treated with tumor necrosis factor alfa antagonists and reported to the FDA's Adverse Events Reporting System have been reviewed (11). These included 17 cases temporarily associated with etanercept and two with infliximab, but complete information was lacking in a number of cases. The various hypothetical mechanisms by which tumor necrosis factor alfa antagonists might produce demyelinating events have been discussed (12). Briefly, they cause an increase in peripheral T cell autoreactivity, and their inability to cross the blood–brain barrier may account for exacerbation of central demyelinating disorders.

Sensory systems

Optic neuropathy has been described in patients with rheumatoid arthritis taking infliximab. In three patients aged 54–62 years, blurred vision or visual field loss in one or both eyes occurred after the third dose (13).

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Ophthalmic examination showed anterior optic neuropathy in all three patients and MRI scanning ruled out demyelinating optic neuritis. In one patient an additional infusion of infliximab produced similar symptoms in the previously unaffected eye; vision failed to improve despite infliximab withdrawal and steroid treatment.

- Retrobulbar optic neuritis was diagnosed after the ninth dose of infliximab in a 55-year-old woman (14). MRI scanning showed demyelination of the left optic nerve and the visual field defect improved after treatment with prednisone.

Hematologic

The possible role of infliximab in the development of hypercoagulability disorders has been discussed in the context of a case of arterial thrombosis (15).

- A 72-year-old woman with refractory sarcoidosis developed venous thrombosis at a catheter site and extensive multiple thromboses in small arteries in her legs after receiving a third dose of infliximab for severe enteropathy. Anticardiolipin antibodies were detected, but antinuclear and anti-double-stranded DNA antibodies were negative.

Although infliximab has been associated with autoantibody production, it is not known whether it contributed to hypercoagulability in this patient.

Liver

Acute hepatitis with infliximab has been described (16).

- A 44-year-old woman, who had used oral contraceptives for many years and had taken mesalazine, mercaptopurine, and prednisone for Crohn's disease for 7 years, developed clinical and biological signs of acute mixed hepatitis 19 days after a single dose of infliximab 5 mg/kg. There were no symptoms suggestive of hypersensitivity and liver histology showed cholestasis without inflammation or eosinophilia. Other causes, such as a recent viral infection (hepatitis A, B, C, cytomegalovirus, *Herpes simplex*) or gallstones, were ruled out. Among various autoantibodies, only antinuclear antibody titers were slightly raised. Complete normalization was observed 2 months later.

Although the patient took other potentially hepatotoxic drugs, the time-course suggested that infliximab was the cause.

Skin

Skin reactions, including erythema multiforme in three patients and a lichenoid eruption in one, were attributed to infliximab (17). One patient had similar lesions after etanercept. Patch tests with infliximab in three patients were negative, but produced a flare-up of lesions in one patient and recurrence of malaise and nausea in another patient, suggesting that infliximab is well absorbed percutaneously.

- A 72-year-old man developed bullous skin lesions the day after receiving his fourth dose of infliximab for rheumatoid arthritis (18). Human antichimeric antibodies were positive, as were antinuclear antibodies, and he completely recovered after treatment with prednisone.

In three patients with severe Crohn's disease who required digestive surgery, infliximab before or immediately after surgery was discussed as an additional possible cause of postoperative poor wound healing with serious complications (19).

Patients with congestive heart failure has been reported (SEDA-26, 401).

Immunologic

Antibodies to infliximab

Treatment with infliximab can be associated with the formation of human antichimeric antibodies. Such antibodies were rarely detected in patients with rheumatoid arthritis who were also taking methotrexate, and low titers were detected in about 13% of patients with Crohn's disease. Their clinical relevance is unclear, although their presence has sometimes been associated with an increased risk of infusion reactions, the occurrence of serum sickness-like reactions after delayed re-treatment, and a shorter duration of response.

In a randomized, placebo-controlled trial in 573 patients with Crohn's disease, who responded to an initial infusion of infliximab and were then given repeated infusions, antibodies to infliximab were found in 14%; there was a trend toward a lower incidence of antibodies in patients taking concurrent glucocorticoids and immunosuppressive drugs (20). The incidence of infusion reactions was also higher in patients positive for antibodies to infliximab compared with patients without antibodies (16 versus 8%) and lower in patients who were taking both glucocorticoids and immunosuppressants compared with patients who were receiving neither (8 versus 32%).

The clinical significance of antibodies to infliximab has also been explored in 125 patients with Crohn's disease who were given infliximab, of whom 61% had antibodies after the fifth infusion; however, there was no further increase in incidence after subsequent treatment (21). The presence of antibodies was associated with a 2.4-fold increase in the risk of infusion reactions, lower serum infliximab concentrations, and a shorter duration of clinical response, compared with patients with no infliximab antibodies. Patients who received concomitant immunosuppressive therapy had a lower incidence of infliximab antibodies, higher infliximab serum concentrations, and a longer duration of clinical response. Pretreatment with glucocorticoids may reduce the risk of antibody formation, but it is not known whether a pretreatment test for human antichimeric antibodies has a predictive value for adverse reactions (22). However, there were technical issues relating to the antibody assay and definition of clinically relevant antibody titers in this study.

Autoantibodies and autoimmunity

Infliximab may increase the risk of autoimmunity, but the presence of antibodies did not predict the risk of lupus-like syndrome. In trials, the incidence of infliximab-induced anti-double-stranded DNA antibodies ranged from 5 to 34% of patients, depending on the assay method

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used and the duration of exposure (20–24). However, these abnormalities were rarely associated with clinical manifestations. In two large randomized trials in more than 900 infliximab-treated patients, only three developed a lupus-like syndrome, with no evidence of systemic organ involvement (20–24). However, since then, several reports have detailed infliximab-induced, lupus-like syndrome in patients with Crohn's colitis or rheumatoid arthritis, with improvement on withdrawal of infliximab (25,26).

Of 40 patients who had received multiple doses of an investigational liquid formulation of infliximab 2–4 years before, 10 had a severe delayed hypersensitivity reaction within 3–12 days after the first or the second re-infusion (27). This reaction mostly included myalgia, rash, fever, polyarthralgia, and pruritus. Although the six patients tested were negative for antibodies to infliximab before re-infusion, these antibodies were consistently raised after the reaction.

Infliximab binds to tumor necrosis factor alfa on cell surfaces and produces apoptotic cell death, releasing the nucleosomal autoantigens that induce autoantibody formation (28).

- A 69-year-old woman with a 5-year history of rheumatoid arthritis developed drug-induced lupus after receiving infliximab for 23 weeks. She had initially been given methotrexate and prednisone for 4 years. Then, because of lack of efficacy, infliximab was introduced. After three infusions of infliximab and only partial remission the dose was increased to 5 mg/kg, with success. However, before the sixth infusion she developed fever, polyarthralgia, myalgia, and general malaise. Serology excluded viral infection. Autoantibody assessment was positive, confirming the diagnosis of drug-induced lupus.

Hypersensitivity reactions

Both acute and delayed hypersensitivity reactions to infliximab have been reported in clinical trials (SEDA-24, 439).

Immediate infusion reactions to infliximab are usually defined by any significant adverse effect that occurs during or within 1–2 hours after the infusion. The symptoms mostly consist of flushing, rash, shortness of breath, wheeze, hotness, chest pain, vomiting, and abdominal pain.

Delayed reactions are defined by the occurrence of arthralgia and joint stiffness (that is a serum sickness-like reaction) in the days after infliximab administration; they have mostly been observed in patients with Crohn's disease who have received episodic treatment. In one patient the complication was associated with acute respiratory distress syndrome, which only became evident 10 days after re-treatment (22).

Incidence

Immediate hypersensitivity reactions to infliximab occur in 6–19% of adults.

In a retrospective evaluation of 165 patients (479 infliximab infusions) with Crohn's disease, the overall incidence of infusion reactions was 6.1% (29 episodes) (29). Acute infusion reactions within 24 hours of infusion were the most frequent (26 episodes) and delayed infusion reactions from 1 to 14 days after treatment were noted in three instances only. Prophylaxis with diphenhydramine and paracetamol and the use of a test dose of infliximab allowed additional infusions without consequences in patients with mild or moderate previous acute infusion reactions. Three of the four patients who had acute severe reactions received the same prophylaxis plus corticosteroids before re-treatment: one had a similar severe acute reaction, while the other two had no recurrences. This study also suggested that acute infusion reactions are probably not IgE-mediated, as tryptase and IgE serum concentrations were not raised.

Of 86 patients with Crohn's disease receiving infliximab 14% of patients experienced severe systemic reactions, with a significant difference between adults (21%) and children (3%), the reason for which was unclear (30).

There were severe infusion reactions, defined by any significant change in vital signs or the development of chest pain, wheeze, dyspnea, vomiting, abdominal pain, or rash, in 16 of 100 patients with refractory Crohn's disease (31). Half of them occurred during the first infusion, and the rate of infusion reactions was similar in patients taking concurrent immunosuppressants or glucocorticoids compared with those who were not. One patient had anaphylactic shock, five had significant hypotension, six had acute pulmonary symptoms, two had pruritus, flushing, or rash, and one had vomiting. The final patient, who had a previous history of chronic pancreatitis, had acute pancreatitis within 1 hour of treatment.

Immediate hypersensitivity reactions

Acute hypersensitivity reactions can mimic an anaphylactic reaction, but specific IgE antibodies have not so far been identified. A dose-escalation protocol has been proposed to desensitize patients who have had acute systemic reactions (32), but this has not always been successful (33). Although most reported anaphylactic reactions to infliximab have been mild, severe reactions can occur.

- A 36-year-old man with Crohn's disease became refractory to standard anti-inflammatory treatment (glucocorticoids, mercaptopurine, methotrexate, ciclosporin, tacrolimus) (33). Remission over 8 months was achieved with a single infusion of infliximab. With the onset of relapse he was given another infusion of infliximab and had an anaphylactic-like reaction within 1 minute.
- A 35-year-old woman with known hypersensitivity to mesalazine had severe symptoms, namely chest pain, dyspnea, productive cough, skin rash, and hypotension, during a third infusion of infliximab, and died 6 hours later from refractory hypotension and respiratory failure (34). Specific IgE or human antichimeric antibodies were not checked.
- A 33-year-old man with a 3-year history of Crohn's disease had previously received a well-tolerated single infusion of infliximab. When, 14 months later, he received a second infusion for exacerbation of the disease he had no immediate adverse effects, but complained of myalgia, arthralgia, nausea, and vomiting 7 days later and received diphenhydramine. After 3 days he had dyspnea, fever, and chills. An open lung biopsy showed features of eosinophilic pneumonia and no

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infections or other obvious causes were found. He subsequently worsened and required intubation and mechanical ventilation for 13 days. He was given glucocorticoids and quadruple antituberculosis drug therapy and recovered completely within 2 months. Human antichimeric antibodies were raised (13 times normal).
- A 73-year-old woman had three separate episodes of vascular purpura (with leukocytoclastic vasculitis during the third episode) during each sequence of treatment with etanercept; she later developed similar cutaneous lesions after a third injection of infliximab (35).

Delayed hypersensitivity reactions

Delayed hypersensitivity reactions were mostly observed in patients with Crohn's disease who received episodic treatment. In one patient, this complication was associated with acute respiratory distress syndrome, which became evident only 10 days after retreatment (22).

Susceptibility factors

Susceptibility factors for the development of severe systemic reactions after infliximab retreatment have been analysed in 52 adults and 34 children with Crohn's disease (30). Acute severe systemic reactions were defined by symptoms of anaphylactic reactions that required pharmacological treatment, and delayed severe systemic reactions were defined by the occurrence of arthralgia and joint stiffness (that is serum sickness-like symptoms) requiring glucocorticoids in the days after infliximab retreatment. According to these definitions, severe systemic reactions developed in 14% of patients (four acute and eight delayed) during retreatment. They were significantly more frequent in adults than in children (21 versus 3%), and delayed systemic reactions were observed exclusively in adults. These reactions mostly occurred during the second infusion of infliximab, and particularly when retreatment was distant from the first infusion, that is beyond a 20-week interval. This suggested a higher potential for delayed hypersensitivity reactions when repeated doses are given within a longer time interval, and led the authors to recommend multiple early infusions if future infliximab retreatment is anticipated.

In a retrospective review of 361 infliximab infusions in 57 children with inflammatory bowel disease there were 35 episodes of infusion reactions (36). Female sex, previous episodes of infusion reactions, and the use of immunosuppressive therapy for less than 4 months were significant predictors of subsequent infusion reactions.

Infection risk

Infliximab can increase the susceptibility of patients to severe infections, and in particular opportunistic infections (SEDA-26, 402). In patients who received repeated infusions of infliximab, infections requiring antimicrobial treatment occurred in about 30% of patients and severe infections in 4% (20).

Bacterial infections

Blockade of tumor necrosis factor alfa impairs resistance to infections with intracellular pathogens such as mycobacteria, *Pneumocystis jiroveci*, *Listeria monocytogenes*, and *Legionella pneumophila* (37,38). Severe streptococcal and staphylococcal infections have also been observed. Case reports with very severe or fatal outcomes have usually been reported in patients taking concomitant immunosuppressants and have included:

- necrotizing fasciitis due to streptococcal infection (39)
- septicemia due to *Staphylococcus aureus* (40)
- *Listeria monocytogenes* infection (41)
- disseminated tuberculosis (42)
- listeriosis (37).

The safety and efficacy of infliximab have been assessed in 40 patients with severe active spondylarthropathy in a double-blind, randomized, placebo-controlled trial (43). One 65-year-old patient improved but 3 weeks after the third infusion developed a systemic illness. He had enlarged mediastinal lymph nodes and nodular lesion of the liver and spleen. Biopsy of the mediastinal lymph nodes showed tuberculosis, which was confirmed by culture. He was treated and recovered slowly.

Reactivation of latent tuberculosis is a major concern with infliximab (SEDA-26, 402), and accounts for about one-third of infections in these patients. According to data from the manufacturers, 130 cases of active tuberculosis were notified up to October 2001. Many of the cases were disseminated or extrapulmonary tuberculosis, and several patients died. Several case reports have provided detailed information in at least seven other patients, including three who developed miliary tuberculosis and one who developed *Mycobacterium tuberculosis* enteritis (44–48). A detailed analysis of 70 cases of tuberculosis reported to the FDA has been published (49). Two-thirds of the cases were noted after three or fewer infusions and 57% of the patients had extrapulmonary disease. There were 64 cases from countries with a low incidence of tuberculosis. From these reports and the number of patients treated with infliximab, the estimated rate of tuberculosis in patients with rheumatoid arthritis treated with infliximab was four times higher than the background rate. Patients with evidence of active infection should not receive infliximab until the infection is under control; all should be screened for tuberculosis before starting infliximab (50). From these and other data it has been estimated that the risk of tuberculosis in the first year of infliximab treatment is 0.035 in US citizens and 0.2% in non-US citizens. Further investigations, such as a chest X-ray and a Mantoux test, and prophylactic treatment with isoniazid, will show whether the incidence can be reduced in patients taking anti-TNF treatment (51).

In a multicenter trial in 70 patients with ankylosing spondylitis given infliximab, treatment had to be withdrawn in three patients because of systemic tuberculosis, allergic granulomatosis of the lung, or mild leukopenia; after withdrawal all three recovered (8). However, the allergic granulomatosis of the lung was probably due to a hypersensitivity reaction.

- An 11-year-old boy with Crohn's disease received infliximab and 3 days later developed fever, signs of cardiac failure, and *S. aureus* sepsis (52). At surgery an intramyocardial para-aortic abscess with destruction of the aortic valve was found, suggesting chronic infection, possibly activated by the use of infliximab.

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Crohn's disease can lead to vasculitic changes of the aorta, which may have favored the development of the intramyocardial abscess in this case. The size of the abscess suggested persistence for several weeks.

Severe necrotizing fasciitis has been reported in a patient who was given infliximab (39).

- A 54-year-old man with rheumatoid arthritis for 12 years was given infliximab, with remission. He then developed a painful, confluent, erythematous, pustular rash over his trunk and limbs. Skin biopsy showed an acute pustular dermatitis. Five hours later he collapsed with a tachycardia (140/minute) and a blood pressure of 120/70 mmHg. He was apyrexial. His left leg was very tense, painful, and swollen, and he had a disseminated intravascular coagulopathy. There was marked necrosis of his adductor compartment and fascia of his left thigh and necrotic muscles were debrided. Blood cultures and skin swabs grew group A hemolytic streptococci. He then became unstable and died, despite efforts at resuscitation.

Viral infections

Infliximab can compromise antiviral defence mechanisms. There have been detailed reports of cytomegalovirus retinitis (53) and life-threatening disseminated cytomegalovirus infection (54). Most of these patients were taking concomitant immunosuppressants at the time of diagnosis.

- A 67-year-old woman with a 5-year history of rheumatoid arthritis, who had taken prednisone and methotrexate, was given infliximab (55). Her rheumatoid arthritis improved, but she developed multiple bilateral lesions of molluscum contagiosum on the upper and lower eyelids, despite normal CD4 and CD8 counts. She had had similar lesions during a previous course of infliximab. Excision biopsy confirmed the diagnosis.

Protozoal infections

There has been a detailed report of *P. jiroveci* pneumonia (56).

Fungal infections

In a review of 10 cases of histoplasmosis in patients treated with infliximab ($n = 9$) or etanercept ($n = 1$) the infection occurred within 1 week to 6 months after the first dose (57). Of these 10 patients, nine required treatment in an intensive care unit and one died. All lived in regions in which histoplasmosis was endemic. It was not possible to determine which patients had new infections or reactivation of previous infections.

In 41 patients with rheumatic disease who received a total of 300 infusions of infliximab over 9 months there were severe adverse effects in 15%, one of which was a case of histoplasmosis (58).

- A 28-year-old woman with unresponsive rheumatic disease developed histoplasmosis after a second infusion of infliximab. She had pet birds, and the authors thought that she had had reactivation of an infection rather than a new infection.

There have been other reports of histoplasmosis (59), invasive pulmonary aspergillosis (60), and extensive pulmonary coccidioidomycosis (61).

Death

- A 64-year-old man without heart failure was found dead 18 hours after a single infusion of infliximab for rheumatoid arthritis (62). No obvious cause was found at autopsy, except that the patient was known to have had frequent intervention by a pacemaker that had been implanted for several years.

Long-Term Effects

Tumorigenicity

There is great concern about the potential development of malignancy after blockade of tumor necrosis factor alfa, and it is biologically plausible. However, it is unclear whether this is a drug-related or a disease-related phenomenon.

There have been several cases of lymphoproliferative disease (B cell non-Hodgkin's lymphoma and nodular sclerosing Hodgkin's disease) in the 9 months after infliximab infusion in patients with Crohn's disease (63). The FDA received reports of 26 cases of lymphoproliferative disorders in patients treated with etanercept ($n = 18$) or infliximab ($n = 8$) over 20 months (64). Although this reporting rate does not exceed the age-adjusted incidence of lymphomas in the USA, spontaneous reporting underestimates the true incidence. In addition, several findings were similar to those reported in patients taking immunosuppressive drugs after transplantation. For example, 81% of the reported cases were non-Hodgkin's lymphomas. Also, the median time to occurrence after the start of anti-TNF-alfa treatment was only 8 weeks. Finally, lymphoma regressed in two patients after withdrawal and without specific cytotoxic therapy. Although the actual incidence of neoplasia was low, additional long-term data that take into account concomitant or previous immunosuppressive treatment are needed before firm conclusions can be reached.

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Influenza vaccine

See also Vaccines

General Information

Influenza vaccine viruses are propagated in embryonated chicken eggs. The virus-containing extra-embryonic fluid is harvested, purified, and inactivated with formalin. Inactivated flu vaccine is produced either as whole virus vaccine or ether-disrupted split or subunit preparations. However, many other new or modified influenza vaccines are already available or are expected to appear in the near future, for example vaccines containing new adjuvants, live attenuated vaccines, and vaccines administered by alternative routes.

Comparisons of reactogenicity (and immunogenicity) of different vaccine types have been provided (SEDA-8, 299) (SEDA-10, 290) (SEDA-11, 290) (SEDA-12, 282) (SEDA-13, 286) (SEDA-14, 284) (SEDA-15, 351) (SEDA-16, 386) (SEDA-17, 375) (SEDA-18, 335) (1). In most of these trials the investigators found little difference in reactogenicity between the various vaccines.

The safety and immunogenicity of an inactivated subunit influenza vaccine containing MF59 (oil-in-water emulsion, squalene, and Tween 80 and sorbitan trioleate as stabilizers) as an adjuvant has been described in two studies of 92 and 211 elderly persons (65 years of age and over) (2,3). Investigations were carried out during three consecutive influenza seasons. Compared with a commercial non-adjuvant subunit vaccine containing the same influenza strains recommended by the World Health Organization, geometric mean titers and seroconversion rates were higher after the use of the newly developed vaccine. The adjuvant vaccine caused more local reactions than the conventional vaccine. However, the reactions were mild and limited to the first 2–3 days after immunization. Systemic reactions were not significantly different, except for mild transient malaise. Considering the better immunogenicity of the adjuvant vaccine, the authors recommended it particularly for elderly people, who are at greatest risk of developing severe influenza disease. The vaccine manufactured by Chiron Behring has been already licensed for persons of 65 years of age and over in Italy and Germany.

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The results of several clinical trials with a liposomal influenza vaccine have been reviewed (4). This trivalent liposomal influenza vaccine consists of purified influenza hemagglutinin inserted into a membrane of phosphatidylcholine and phosphatidyl-ethanolamine; it contains 15 micrograms of hemagglutinin per viral strain per dose. The trials included two randomized studies (in 126 healthy nursing home residents aged 63–102 years and 72 elderly individuals aged 60–98 years) and four double-blind studies (in a total of 831 elderly persons aged 67–71 years and younger adults aged 28–38 years); further studies included 24 children and adults with cystic fibrosis and 49 children at high risk of influenza. In all of these studies, the liposomal vaccine was compared with commercially available whole and subunit influenza virus vaccines. In general, seroconversion rates were significantly higher with the liposomal vaccine than with the commercially available vaccines. Local adverse reactions, such as pain at the injection site (up to 62% of children and up to 11% of adults), local induration and swelling (33% of all vaccine recipients), or redness (5% of adults and 20% of children) were transient and usually mild. One child with cystic fibrosis and two elderly persons had severe pain. Between 68 and 100% of children with cystic fibrosis reported at least one systemic reaction (fatigue, cough, coryza, headache) after the liposomal vaccine compared with 23–50% after the commercially available subunit vaccine. Fatigue (up to 19%), malaise (up to 14%), headache (up to 10%), and cough (up to 8%) were the most common systemic reactions reported by young adults and elderly people. There were single cases of severe fatigue, cough, and diarrhea in children with cystic fibrosis, young adults, and elderly people. Liposomal influenza vaccine did not induce a mean anti-phospholipid antibody response in the elderly volunteers.

In a randomized, double-blind study, trivalent, live, attenuated, cold-adapted intranasal influenza vaccine (FluMist) has been compared with intranasal placebo plus a trivalent injected inactivated influenza vaccine (5). The 200 patients were aged 65 years and over and had chronic cardiovascular or pulmonary conditions or diabetes mellitus. During the 7 days after immunization, sore throat was reported on at least one day by significantly more of the FluMist recipients (15 versus 2%). The increased frequency of sore throat may have been attributable to direct or indirect effects of vaccine virus replication. No other symptom was associated with FluMist. These findings were consistent with evaluations of other live, attenuated, cold-adapted influenza vaccine formulations in older adults. However, further studies of the safety of FluMist are warranted.

The immunogenicity and safety of inactivated intranasal influenza vaccine have been reviewed (6). The author concluded that the vaccine is highly immunogenic and well tolerated by most vaccinees, in terms of both local nasal symptoms and possible vaccine-mediated systemic symptoms. The symptoms were primarily mild, occasionally moderate, and in a few cases more severe; in most cases they lasted for only 1–2 days.

In 1997, an avian influenza A/Hongkong/97 (H5N1) virus emerged as a pandemic threat. A non-pathogenic variant influenza A/duck/Singapore/97 (H5N3) was identified as a leading vaccine candidate, but the non-adjuvanted antibody response was poor; however, the addition of the adjuvant MF59 (oil-in-water suspension) boosted the antibody responses to protective levels. In 65 volunteers who received either the non-adjuvanted or the adjuvanted vaccine, both vaccines were well tolerated and did not differ significantly. There was pain at the injection site of varying intensity in nine of the 32 volunteers who received the adjuvanted vaccine, and in none of the volunteers who received the non-adjuvanted vaccine (7).

General adverse effects

Local adverse reactions after flu immunization are few and infrequent. Slight to moderate tenderness, erythema, and induration at the injection site lasting 1–2 days occur in 15–30% of recipients. Fever, malaise, myalgia, and other symptoms of toxicity are rare (about 2%) and most often affect persons with no prior exposure to the flu antigens in the vaccine, for example young children. These reactions usually begin 6–12 hours after immunization and can last 1 or 2 days. They have been attributed to the vaccine, although the virus is inactivated. On the other hand, cases of respiratory diseases among vaccinees are coincidental. Although current flu vaccines are highly purified, they can cause hypersensitivity reactions such as hives or angioedema, perhaps due to residual egg protein (8,9). Notwithstanding the fact that the egg protein content is small, asthma or anaphylactic reactions with vascular purpura and encephalopathy can occur in those who are sensitive to the material (10,11).

Incidence

A nationwide surveillance system covering illness after flu immunization in the USA in 1976–77 among over 48 million persons immunized in 1976 with A/New Jersey/76 influenza vaccine (swine flu vaccine) resulted in a total of 4733 reports of illness, including reports of 223 deaths (12). Since most of the deaths occurred within 48 hours of immunization, the figures for deaths per 100 000 vaccinees (by diagnosis) were compared with the expected death rate (by the same diagnosis) per 100 000 population for a 2-day period. In general, the crude expected death rate was much higher than the death rate among vaccinees. Other than Guillain–Barré syndrome and rare cases of anaphylaxis, no serious illnesses seemed to be causally associated with flu immunization. However, widespread under-reporting of illness and death in the passive phase of this surveillance system impaired the validity of the study. Allergic skin reactions were reported at a rate of 0.3 per 100000 vaccinees and severe anaphylaxis at a rate of 0.024 per 100000. There was a cluster of four cases of encephalitis within 1 week of vaccine administration in one state. There were three deaths from cardiovascular disease in chronically ill persons over 70 years of age immunized in one clinic. It was not possible to establish a causative link between immunization and death. Persons immunized in the clinic died at rate of 5 per 100000 per day, in contrast to the expected rate of 17 per 100000 per day for people aged 65 years and older in the respective state.

Case reports of complications temporarily connected with the administration of flu vaccine have been

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published. They include reports of acute disseminated encephalitis (13), acute thrombocytopenic purpura (14), acute transverse myelitis (15), aseptic meningitis (16), bullous pemphigoid (SEDA-21, 334), encephalopathy (17), erythromelalgia (18), optic neuritis (19) with reversible blindness (SEDA-4, 226) (SEDA-21, 334), optic atrophy (SEDA-6, 287), pericarditis (SEDA-7, 324), polymyalgia rheumatica (20), microscopic polyangiitis involving the skin and joints (21), acute symmetrical polyarthropathy with orbital myositis and posterior scleritis (22), systemic vasculitis (23), a trigeminal neuralgia-like symptoms (24), and vascular purpura with histological features of cutaneous necrotizing vasculitis (25).

The current status of adjuvanted influenza vaccines has been reviewed (26). The authors concluded that the vaccine produces a higher titer of antibodies than non-adjuvanted or virosomal vaccines. Local reactions occur more often, but are mild and transient. The results of a trial with two doses of an intranasally administered inactivated virosome-formulated influenza vaccine containing *Escherichia coli* heat-labile toxin as a mucosal adjuvant in 106 volunteers aged 33–63 years have been reported (27). About 50% of vaccinees had local adverse reactions (44% after the first dose and 54% after the second dose) or systemic adverse reactions (48 and 46%) after administration of the vaccine. Rhinorrhea, sneezing, and headache were the most common reactions; they were mild and transient and resolved within 24–48 hours. No febrile reactions were associated with immunization. Between 77 and 92% of vaccinees developed protective hemagglutination inhibition antibody titers against the two influenzae A strains of the vaccine, whereas protective antibody titers against the B strain of the vaccine were achieved in only 49–58%.

Organs and Systems

Cardiovascular

Influenza infection has been a significant problem in cardiac transplant patients; immunization of such patients could therefore be beneficial. However, its use has been limited by concern that stimulation of the immune system might in principle cause an increased risk of cardiac rejection. In the renal transplant experience, influenza infection itself can trigger an immunological response to cause graft rejection, as well as predisposing to other infections. Another concern is whether an immunosuppressed cardiac transplant recipient could seroconvert sufficiently. In a case-control study in 18 cardiac transplant recipients and 18 control patients 6 months or more beyond transplant surgery, there were no differences in the incidence of cardiac rejection or immune responses (28).

There have been reports of pericarditis (29,30) in temporal relation to influenza vaccine.

Respiratory

Of 109 children with asthma aged 6 months to 18 years immunized with trivalent subvirion influenza vaccine, 59 vaccinees had no asthma symptoms on the day of immunization, but 50 had an exacerbation requiring prednisone (31). Antibody responses were not different in the two groups. Adverse effects, including local swelling at the injection site, fever, rash, and headache, were not different in the two groups.

Nervous system

Adverse effects of flu immunization on the nervous system range from polyneuropathy to meningoencephalitis and Guillain–Barré syndrome (32).

Examination of new cases of multiple sclerosis among the 45 million swine flu vaccine recipients indicated no excess over the expected frequencies. Inactivated swine flu vaccine did not influence the onset or exacerbation of the disease (33).

Guillain–Barré syndrome

Guillain–Barré syndrome was observed during the 1976/7 mass immunization campaign in the USA. The vaccine then used was A/New Jersey/76 (H1N1) flu vaccine (swine influenza). The overall incidence of cases of Guillain–Barré syndrome attributed to the use of vaccine at that time was 4.9–5.9 per million vaccinees (34). Various authors tried to settle the question of a cause and effect relation. Detailed reports have been published (SEDA-10, 289) (SEDA-11, 290) and the resulting litigation has been reviewed (35). In an analysis of computerized summaries of 1300 cases, immunized cases with extensive paresis or paralysis occurred in a characteristic epidemiological pattern, suggesting a causal relation between immunization and Guillain–Barré syndrome (34). Cases with limited motor involvement showed no such pattern. Unlike the 1976 swine flu vaccine, vaccines used subsequently have not been associated with an increased frequency of Guillain–Barré syndrome. It has been calculated that the risk of polyneuropathy following immunization is one in 200 000, compared with a population incidence of spontaneous Guillain–Barré syndrome of one in 1 000 000 (36).

The original Centers for Disease Control study of the relation between A/New Jersey/876 (swine flu) vaccine and Guillain–Barré syndrome showed a statistically significant association and suggested a causal association between the two events. In an evaluation of the medical records of all previously reported adult patients with Guillain–Barré syndrome in Michigan and Minnesota from 1 October 1976 to 31 January 1977, the relative risk during the 6 weeks after flu immunization in adults was 7.10 (excess cases attributed to the vaccine: 8.6 per million vaccinees in Michigan and 9.7 per million vaccinees in Minnesota), comparable to the relative risk of 7.60 found in the original study (37). There was no increase in the relative risk of Guillain–Barré syndrome beyond 6 weeks after immunization.

A retrospective study (1980–88) conducted to determine if the US Army's mass influenza immunization program was associated with an increased incidence of Guillain–Barré syndrome found no temporally related increase (38).

The number of reports of influenza vaccine-associated Guillain–Barré syndrome to the US Vaccine Adverse Event Reporting System increased from 37 in 1992–93 to 74 in 1993–94, raising concerns about a possible increase in vaccine-associated risk. Detailed data analyses

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showed that the relative risk of Guillain–Barré syndrome associated with influenza immunization, adjusted for age, sex, and vaccine season, was 2.0 for the 1992–93 season and 1.5 for the 1993–94 season. For the two seasons combined, the adjusted relative risk of 1.7 suggested that there was slightly more than one additional case of Guillain–Barré syndrome per million vaccinees. An accompanying editorial also referred to the occurrence of Guillain–Barré syndrome during the swine flu immunization campaign in 1976. The authors considered the results of this study as epidemiological evidence that immunization against strains of influenza other than swine flu may increase the risk of Guillain–Barré syndrome, albeit minimally (39).

Sensory systems

Four patients with corneal transplants developed ocular manifestations (bilateral graft rejection in two cases, uveitis, and epithelial and stromal herpetic kerato-uveitis) at 3 days to 6 weeks after the receipt of inactivated influenza vaccine (40). Whereas case reports of ocular manifestations after influenza immunization are known, this is perhaps the first report of vaccine-related herpetic recurrence. The authors advised caution when influenza immunization is considered for patients who have had a corneal transplant.

Urinary tract

There has been a report of minimal-change nephrotic syndrome (41) in temporal relation to influenza vaccine.

Skin

Influenza vaccine is one of at least 30 drugs believed to cause bullous pemphigoid or cicatricial pemphigoid (42).

- A 90-year-old woman developed a generalized bullous eruption resembling bullous pemphigoid 12 hours after influenza immunization (43).

Influenza vaccine can also cause pemphigus (44).

Musculoskeletal

There has been a report of rhabdomyolysis (45) in temporal relation to influenza vaccine.

Immunologic

Changes in the lymphocyte population similar to those observed during virus infections occurred within the first 2 weeks after immunization (46). There were no reports describing more severe courses of infectious diseases during this period.

The question of whether egg allergy is a justified contraindication to influenza immunization has been studied in 80 individuals with egg allergy and 124 control subjects, who received influenza vaccine containing ovalbumin/ovomucoid 0.02, 0.1, or 1.2 μg/ml (47). The individuals with egg allergy received the vaccine in two doses 30 minutes apart; the first dose was one-tenth and the second dose nine-tenths of the recommended dose. The patients with egg allergy, even those with significant allergic reactions after egg ingestion, safely received influenza vaccine in this two-dose protocol with vaccine containing no more than 1.2 μg/ml of egg protein.

There have been reports of individual cases of giant cell arteritis (48) and polymyalgia rheumatica (49,50) in temporal relation to influenza vaccine.

- A 70-year-old man, previously healthy, developed giant cell arteritis 5 days after influenza immunization (51).

The authors mentioned another case reported in 1976.

Drug Administration

Drug dosage regimens

Current recommendations for the use of influenza vaccine in adults are based on a single injection. This may not be valid in case of a new pandemic caused by an antigenic shift of the influenza virus. Currently, the only group for whom a second dose is recommended comprises children who have never been immunized. However, when two-dose regimens in adults have been studied, the second dose of vaccine has not been associated with higher rates of reactions than the first. People who have a stronger local reaction after a first injection are more likely to have another such reaction after a second injection (31).

Drug administration route

The intranasal administration of influenza vaccines has been reviewed (52). Trivalent cold-adapted intranasal influenza vaccine was used to immunize 1602 healthy children aged 15–71 months in a randomized, double-blind, placebo-controlled trial (53). One year later 1358 were reimmunized. The vaccine provided efficacy of 92% during 2 years against virologically confirmed influenza. Transient, minor symptoms of respiratory illness (rhinorrhea, nasal congestion, low-grade fever) were reported more often in vaccinees than in controls; no significant differences were noted after dose 1 and dose 2.

Drug–Drug Interactions

Anticoagulants

In a prospective study of the effect of flu immunization on the prothrombin time in eight patients taking long-term anticoagulant treatment the prothrombin time was prolonged by 40%. In healthy subjects there was no significant effect on warfarin metabolism (SEDA-10, 289).

- An 81-year-old patient who had been well controlled by anticoagulants for 12 years had an episode of gastrointestinal bleeding associated with influenza immunization (54).

However, others did not confirm this effect (55), and the lack of a clinical interaction with warfarin has also been confirmed by a report of the US Immunization Practices Advisory Committee (9).

Anticonvulsants

In a study of serum concentrations of the anticonvulsants phenytoin, phenobarbital, and carbamazepine, before and after mentally retarded patients received flu vaccine, the

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authors concluded that serum concentrations of these drugs may increase as a result of flu immunization and that dosage adjustments may be necessary (56).

Benzodiazepines

The metabolism of lorazepam and chlordiazepoxide was not altered by flu immunization (57).

Theophylline

After influenza immunization there was a reduction in blood theophylline concentrations in patients and healthy volunteers (58). The authors concluded that flu vaccine may influence the pharmacokinetics of several drugs, and a second group found that theophylline oxidation was significantly reduced at 1 day, but not at 7 days, after immunization (57). However, others did not confirm these effects (55,59). The lack of a clinical interaction with theophylline has also been confirmed by a report of the US Immunization Practices Advisory Committee (9).

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Inhaler propellants

General Information

Pulmonary delivery of drugs is the administration route of choice in respiratory diseases such as chronic obstructive pulmonary disease and asthma. Different devices are available, including metered-dose inhalers, dry powder inhalers, and nebulizers, and nearly 80% of asthmatic patients worldwide use metered dose inhalers (1). Chlorofluorocarbons have been used as an aerosol propellant in metered-dose inhalers; however, they deplete the ozone layer and are being replaced by more environment-friendly propellants, even though the contribution of aerosols of this type to the total global burden of chlorofluorocarbons is less than 0.5%. The first chlorofluorocarbon-free metered-dose inhaler for asthma treatment was approved by the FDA in 1996 (2) and the European Union has set 2005 as a target date for the withdrawal of all chlorofluorocarbon-based inhalers (1). In the USA, prescriptions for chlorofluorocarbon-free medications rose from 16.4 million in 1996 to 33.8 million in 2000 (2). Most of the chlorofluorocarbon-free medications were steroids for nasal use (27.2 million). However, chlorofluorocarbon-containing medications still represented two-thirds of all prescriptions and increased from 63.0 to 67.6 million dispensed (2).

Specific propellants

Freons (chlorofluorocarbons)

The multidose pressurized aerosols using chlorofluorocarbon propellants have been widely used.

In animal experiments, plasma concentrations of Freon 11 and Freon 12 of 20–35 μg/ml sensitized the heart to adrenaline and exercise. Severely ill asthmatic subjects (mean oxygen tension = 55 mmHg, range 50–80) were studied following therapeutic doses of a beta$_2$-adrenoceptor agonist pressurized aerosol. Plasma concentrations of

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Freon 11 up to 4.53 μg/ml and of Freon 12 up to 4.73 μg/ml were measured after two inhalations. It was concluded that a toxic concentration could only be reached if the aerosol was taken on every breath for over 12 consecutive breaths (3).

Other excipients

The effects of other constituents present in multidose pressurized aerosols have been investigated in 11 850 asthmatic patients. Three aerosols were compared. Two placebo multidose pressurized aerosols contained the same chlorofluorocarbons but different dispersing chemicals, oleic acid (MDI-OA) and lecithin NF (MDI-L). Another contained salmeterol xinafoate (0.025 mg) plus lecithin NF (MDI-S). Peak expiratory flow rate was measured before and 5 minutes after inhalation. A 20% fall in peak expiratory flow rate was defined as clinically significant bronchoconstriction. A total of 180 (1.5%) patients developed bronchoconstriction, 43 in the MDI-S group, 67 in the MDI-L group, and 70 in the MDI-OA group. Bronchoconstriction was significantly less with the salmeterol aerosol. It was suggested that one of the inert constituents is the likely irritant causing occasional acute bronchoconstriction. The risk of this effect increased with age and decreasing pretreatment peak expiratory flow rate (4).

Preservatives

Inhalation of distilled water will cause bronchoconstriction in 60% of infants with a history of wheeze (SEDA-17, 212). If nebulizer solutions are hypotonic or hypertonic or contain preservatives (such as benzalkonium chloride, edetic acid, sulfites and metabisulfite) they can cause paradoxical bronchoconstriction. It has been recommended that all nebulizer solutions should be isotonic and free of preservatives (SEDA-13, 132). Unit dose vials are available in which the drug solution is isotonic and preservative-free. However, multidose formulations are still available and are widely used, as the cost per dose is less.

Benzalkonium chloride at concentrations greater than 0.005 mg/ml causes histamine release from mast cells in vitro. At a concentration of 0.03 mg/ml an excess of 90% of the histamine content is released (5). This is in the range of the minimum concentration of benzalkonium chloride recommended as a disinfectant (0.025 mg/ml). Inhalation of benzalkonium chloride nebulizer solution causes concentration-related falls in FEV_1 in patients with asthma (6). Benzalkonium chloride 0.3 mg also causes a temporary increase in airway reactivity to histamine. This amount of benzalkonium chloride is similar to that in a 2.5 mg dose from a multidose vial of salbutamol (7). Ipratropium containing benzalkonium chloride 0.25 mg/ml causes bronchoconstriction in a proportion of patients with asthma. Bronchodilatation is seen when 2 ml (0.5 mg) of preservative-free ipratropium bromide solution is inhaled (8). Benzalkonium chloride 0.1 mg/ml does not alter the bronchodilator effect of salbutamol. The difference between salbutamol and ipratropium may be the lower concentration of benzalkonium chloride in the salbutamol solution (0.1 versus 0.25 mg/ml) and the greater potency and more rapid onset of the bronchodilator response to salbutamol (9). Individual case reports suggest that multiple doses of nebulized salbutamol (containing benzalkonium chloride) can cause serious deterioration in severe asthma. This can be reversed by changing to a benzalkonium chloride-free formulation (10).

EDTA (edetate) is also used as a preservative in nebulizer preparations and produces a concentration-related bronchoconstriction (11).

Hydrofluoroalkanes

The search for ozone-friendly propellants has concentrated on two hydrofluoroalkanes with physicochemical properties similar to the chlorofluorocarbons: hydrofluoroalkane 134a and hydrofluoroalkane 227 (1). A new generation of chlorofluorocarbon-free metered dose inhalers has been designed by the pharmaceutical industry to be equivalent to the currently marketed chlorofluorocarbon-containing inhalers in terms of efficacy, safety, and dose delivery. This goal was achieved by using the Modulite technology, by dissolving the drug in the propellant with the aid of a glycerol-like co-solvent (12).

$Beta_2$-adrenoceptor agonists

The therapeutic effects of salbutamol and salmeterol were unaffected by hydrofluoroalkane 134a, and there were no clinically significant differences in safety parameters (13,14). The safety of the hydrofluoroalkane 134a salbutamol sulfate inhaler, Airomir, has been evaluated in a postmarketing surveillance study (15). A non-randomized study has been performed in 6614 patients with obstructive airways disease taking metered doses of salbutamol delivered by inhalers using either hydrofluoroalkane or chlorofluorocarbon as the propellant. There were no significant differences between the groups in the rate of hospital admissions for the condition for which salbutamol was prescribed, in visits to accident and emergency departments, or in unscheduled home visits. There were adverse events in 25% of patients in both groups. The most common adverse events were infection, bronchospasm, and upper respiratory tract infection. Adverse events attributed to the medication occurred in 3.1% of the patients who used the hydrofluoroalkane propellant and 0.7% of those who used the chlorofluorocarbon. This difference was significant (OR = 4.34; 95% CI = 2.22, 8.52). In contrast, serious adverse events occurred more often with the chlorofluorocarbon (3.7%) than with the hydrofluoroalkane (2.7%), but this difference was not significant.

More patients using the hydrofluoroalkane (18%) withdrew from the study than patients using the chlorofluorocarbon (4.8%). Most of the withdrawals in both groups were unrelated to safety (9 and 3.2% respectively). The reasons for withdrawal included intercurrent illness, loss to follow-up, and inadvertent prescription errors. More patients using the hydrofluoroalkane withdrew because of an adverse event or because of the taste of the inhaler, 3.8 versus 0.9% and 3.1 versus 0.2% respectively. The authors concluded that the data supported the evidence already obtained in clinical trials that reformulation of salbutamol in a hydrofluoroalkane propellant does not result in changes in safety compared with a chlorofluorocarbon formulation.

Hydrofluoroalkane 134a and chlorofluorocarbon have been compared in two randomized, double-blind, placebo-controlled studies with salbutamol. Salbutamol 180 μg in

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hydrofluoroalkane 134a given 30 minutes before an exercise challenge was as safe and effective as 180 μg in chlorofluorocarbon in 24 patients with documented exercise-induced bronchospasm (16). In 63 patients with mild to moderate asthma salbutamol in hydrofluoroalkane 134a or chlorofluorocarbon were of comparable efficacy without any difference in the incidence of adverse events (17).

Glucocorticoids

Beclomethasone dipropionate and budesonide Modulite formulations have been compared with equivalent chlorofluorocarbon products in small groups of healthy volunteers and asthmatic patients (18): there was no significant difference in morning serum cortisol or urinary cortisol excretion, suggesting that the systemic availability of the inhaled corticosteroids with different propellants is similar. Moreover, plasma profiles of beclomethasone dipropionate and B17MP were similar after inhalation of beclomethasone dipropionate Modulite and beclomethasone dipropionate-chlorofluorocarbon, suggesting that pulmonary delivery to the lung is comparable with the two propellants (18).

There have been three randomized, double-blind studies in adult asthmatics of the efficacy and safety of a beclomethasone dipropionate-hydrofluoroalkane 134a formulation, equivalent in dose per actuation to the currently marketed beclomethasone dipropionate chlorofluorocarbon products (19–21). Daily doses of beclomethasone dipropionate hydrofluoroalkane 134a 1000 μg over 12 weeks given by metered-dose inhaler (19) or a spacer jet device (20) were equivalent in terms of safety and efficacy compared with beclomethasone dipropionate chlorofluorocarbon 1000 μg. The same was true for doses of 400 μg (21).

In another study, different doses of flunisolide hydrofluoroalkane were tested in 21 healthy adult volunteers for 4.5 days (170, 340, and 680 μg); there was a dose-related response after both single- and multiple-dose administration (22). There was no accumulation of flunisolide with repeated dosing, suggesting that the systemic availability of flunisolide hydrofluoroalkane is low. A randomized, double-blind, placebo-controlled study with daily doses of 80 and 160 μg over 12 weeks in 353 asthmatic children gave similar results (23).

These results suggest that the transition from chlorofluorocarbon-containing to chlorofluorocarbon-free metered-dose inhalers is possible without concerns about safety and efficacy.

Infection risk

Certain problems are peculiar to the use of wet nebulization inhalation devices. There is a risk of contamination of the airways with bacterial flora, which increases when treatment is given in a hospital (SEDA-2, 154). In one series of 41 patients in an intensive care unit who were being ventilated and were receiving nebulized salbutamol, all developed respiratory tract infections due to *Burkholderia* (*Pseudomonas*). The same organism (confirmed by molecular fingerprinting) was isolated from nebulizers and a multiple-dose bottle of salbutamol used for several of the patients. Appropriate infection control measures resolved the problem (SEDA-20, 185).

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Inosine pranobex

General Information

Inosine pranobex is a synthetic product, also known as isoprinosine or inosine dimepranol acedobene, with antiviral properties that are assumed to be related to its effect on T cell-mediated immunity rather than to direct antiviral activity. It has been tried in a wide range of viral diseases and also in rheumatoid arthritis (1), multiple sclerosis (2), and alopecia (3). However, clinical trials have mostly shown only modest therapeutic benefit or none at all (1,4), and no specific adverse effects, except for an increase in serum uric acid concentrations (5), reflecting the metabolic pathways of purines (6).

Organs and Systems

Immunologic

Anecdotal reports have attributed aggravation of polymyositis (7) and generalized *Herpes zoster* virus infection to inosine pranobex (8).

Drug–Drug Interactions

Zidovudine

Inosine pranobex increased zidovudine plasma concentrations and half-life (9).

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Insulin

General Information

Insulin is used for substitution therapy in patients with an absolute or relative deficiency of insulin. Most of the insulins now prescribed are either human or highly purified insulins of animal origin or synthetic insulins closely related to human insulin. The use of insulin of lesser purity is declining, but it is still used in considerable quantities in Eastern and Central Europe and in less developed countries. In some countries, both highly purified insulins of Western origin in concentrations of 100 U/ml, and locally produced less pure insulins in concentrations of 20, 40, or 80 U/ml are available at the same time, creating confusion. Patients have to realize that the syringe used for injection has to be concordant with the specific strength of insulin for which it has been made. The manner and the site of administration, the variation in duration of action of the various insulin formulations, the grade of purification, and differences in concentration cause specific problems.

The effects of insulin are modified by various factors. The speed and extent of absorption of insulin depends, for example, on the site of injection (1), the depth of the subcutaneous injection, skin temperature (2), the presence of lipodystrophy, and variation in the extent of inactivation of injected insulin. The disposal of insulin depends on many factors. Exercise and hard work lower the blood glucose and thereby increase the effect of

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insulin. Infections and obesity reduce its effect. The timing of food intake and the composition of meals are also related to the action of insulin. A thin layer of fat, as sometimes occurs in the upper arm or in the thighs of thin men, can result in intramuscular injection, leading to faster absorption of long-acting insulins. This can reduce the absorption time by half (3). The major factors that affect the fate of injected insulin (and thereby also its risks) are listed in Table 1 (4).

Insulin has a half-life of only a few minutes when injected intravenously. It is therefore prepared in different formulations for subcutaneous injection, with different half-lives of absorption, giving different durations of action. The main formulations, with their approximate durations of action are given in Table 2.

An alternative method of altering the duration of action of insulin is to use analogues in which there are amino acid substitutions. Analogues are listed in Table 3. Insulin aspart, insulin detemir, insulin glargine, and insulin lispro are all covered in separate monographs.

General adverse effects

The major adverse effect of insulin is hypoglycemia, which is specifically dangerous when the patient's awareness of hypoglycemia is reduced or when long-acting formulations are used. Allergic reactions, although less common with newer formulations, regularly occur (5).

Table 1 The major factors that affect the fate of injected insulin

Variable	Clinical relevance
Insulin formulation	Ultra-short-acting insulin (half-life 0.5–2 hours) Regular insulin (half-life 2–4 hours) Intermediate-acting insulin (half-life 16–20 hours) Prolonged-acting insulin (half-life 36 hours and over) Intraindividual variation in absorption up to 50% Interindividual variation from day-to-day up to 25%
Insulin species	Of minimal importance
Injection technique	Contributes to variance
Injected region	Absorption faster from abdominal region than from femoral and gluteal regions; exercising the injected limb speeds up absorption (applies especially to regular insulin)
Subcutaneous blood flow	A major determinant of absorption rate and clinically significant for regular insulin (influenced by smoking, ambient temperature, exercise, and local massage)
Subcutaneous degradation of insulin	Usually of no clinical significance; in rare cases after insulin need exceeds 120 IU/day it might explain brittleness
Insulin antibodies	Increase unpredictably the circulating fraction of insulin and prolong its half-life; a rare cause of insulin resistance

Table 2 Formulations of human insulin (all rINNs) and their durations of action

Type of insulin	Onset of action (hours)	Maximum action (hours)	Duration of action (hours)
Ultra-short-acting			
Insulin aspart, insulin lispro	0.05–2	0.5–1.5	4
Short-acting			
Neutral insulin injection	0.3–0.5	1–3	5–8
Intermediate-acting			
Insulin zinc suspension (amorphous) (semilente)	1–2	6–10	12–16
Isophane insulin (Neutral Protamine Hagedorn, NPH)	1–2	4–6	11–20
Globin zinc insulin suspension	1–2	6–10	10–18
Compound insulin zinc suspension (lente)	2–4	3–12	14–24
Long-acting			
Protamine zinc insulin injection	4–6	16–24	24–36
Insulin zinc suspension (crystalline) (ultralente)	4–6	16–24	24–36
Insulin glargine, insulin detemir	0.5–1	1–24	22–28
Combined formulations			
Diphasic insulin injection	0.7–1	3–18	12–24

Rare complications are lipoatrophy or hypertrophy and insulin edema. Insulin has to be given by injection, with pumps or specific devices for intensive therapy, which all generate specific problems. Other ways of administrating insulin are still experimental.

Additives introduced as preservatives or to change the duration of action of insulin can also cause adverse effects.

Table 3 Insulin analogs

Analogue	Comments
Insulin aspart	Rapid-acting, short-acting; the proline at site 28 of the B chain is replaced by aspartate (B28Asp)
Insulin defalan	Prepared from insulin by removal of the terminal phenylalanine
Insulin detemir	Long-acting; the threonine is deleted at B30 and the lysine at B28 is acylated with a miristoyl side-chain (B29Lys (ϵ-tetradecanoyl)desB30)
Insulin glargine	Long-acting; the asparagine at A21 is replaced by glycine and two arginines are added to the C terminus of the B chain (A21Gly,B31Arg,B32Arg)
Insulin glulisine	Rapid-acting, short-acting; the asparagine at B3 is replaced by lysine and the lysine at B29 is replaced by glutamic acid (B3Lys,B29Glu)
Insulin lispro	Rapid-acting, short-acting (2–4 hours); the lysine at site 29 and the proline at site 28 of the B chain are interchanged (B28Lys,B29Pro)

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Organs and Systems

Nervous system

Cerebral edema has been described during therapy of diabetic ketoacidosis with a large volume of fluid, resulting in rapid changes in plasma osmolality, mostly in young patients (SEDA-26, 462). However, in 10 adults with ketoacidosis, no signs of cerebral edema (supported by CT scans) were found (6).

Susceptibility factors for cerebral edema during ketoacidosis in children have been investigated in 61 cases of cerebral edema during 6977 hospital admissions (7). They were matched with two types of controls for each case: three children with ketoacidosis randomly selected and three children matched for age (within 2 years), onset of diabetes, blood pH, and serum glucose at entry. The results suggested that high initial serum urea concentrations and a low $PaCO_2$ are associated with an increased probability of cerebral edema. Children with these abnormalities should be monitored for signs of neurological deterioration, and hyperosmolar therapy should be immediately available. Treatment with bicarbonate was associated with an increased risk and should be avoided. In an accompanying editorial it was stated that high doses of insulin, hypotonic fluids, and bicarbonate are often seen as culprits, but it is also possible that it is an idiosyncratic response to diabetic ketoacidosis; there is no proof of either theory (8).

Metabolism

Hypoglycemia

The most frequent complication of insulin therapy is inadvertent hypoglycemia (9–11). Over 5% of deaths in diabetes can be attributed to hypoglycemia. The frequency increases with rigorous maintenance of normoglycemia (12,13). In the Diabetes Control and Complications Trial (DCCT) (14) the frequency of serious hypoglycemia was more than three times increased in the intensively treated group, and the frequency of the attacks was related to the concentration of HbA_{1c} (15). The UK Prospective Diabetes Study in patients with type 2 diabetes also showed an increased risk of hypoglycemia with more intensive treatment (16).

Attacks of hypoglycemia are often preceded by less marked attacks, which are unnoticed or not reported to the family or physician. Attacks can be caused by reduced resistance to insulin or switch to a type of insulin with a different duration of action. The reasons for hypoglycemia can be inaccurate or excessive insulin injections, heavy physical exercise, or omission of meals. The action of highly purified insulins and some new analogues, even when in long-acting form, is somewhat faster and shorter compared with less pure formulations. Errors in injection techniques, such as superficial subcutaneous injections, forming nodules or causing bleeding, can introduce variation in the absorption of insulin, resulting in an increase in the mean administered dose and in inadvertent hypoglycemia. Twice-daily isophane insulin for 6 months has been compared with once-daily ultralente insulin in 60 patients (17). Isophane was associated with fewer attacks of hypoglycemia, lower HbA_{1c}, lower evening glucose concentrations, and greater patient satisfaction.

The Somogyi effect, unnoticed hypoglycemia during sleep, causes a rebound increase in morning blood glucose with accompanying glycosuria. When, in response to this, the evening dose of long-acting insulin is increased, the risk of nocturnal hypoglycemia also increases, creating a vicious cycle. Blood glucose monitoring late at night helps to establish the diagnosis. Of 39 poorly controlled patients with insulin-treated diabetes aged 9–66 years, 22 had recurrent nocturnal hypoglycaemia, the best clinical clue to which was intermittent symptoms, however mild and infrequent they appeared to be (18).

Hypoglycemia can also be induced by concomitant diseases, for example renal disease, hepatic disease (cirrhosis), hypopituitarism, hypoadrenocorticalism, hypoglucagonism, hypothyroidism, malnutrition, anorexia nervosa, pregnancy, termination of pregnancy, recovery from infections, operations, or stress.

Frequency

In a review of 102 consecutive drug-induced, hospital-related cases of coma, 23 were caused by insulin only, 14 by insulin + glibenclamide, and 3 by insulin + metformin (19). The likelihood of readmission for hypoglycemia after a previous admission was 2.9 times greater.

Of 546 Spanish diabetic children and teenagers, 14% had one period of hypoglycemia and 21% had more than one episode (20). The highest incidence was in the morning, possibly related to the frugal Spanish breakfast and abundant food intake in the evening.

Hypoglycemia was retrospectively monitored in 1055 patients who had had type 2 diabetes for more than 2 months, and who visited the clinic at least twice in 6 months (21). They all received aggressive treatment to reach near-normal blood glucose concentrations. Symptoms of hypoglycemia were mentioned by 12% of those treated with diet alone, 16% of those using oral agents, and 30% of those using any form of insulin. In only five patients, all using insulin, was there severe hypoglycemia. A low HbA_{1c} concentration at follow-up, symptoms of hypoglycemia at the initial visit, and younger age were independently associated with an increased incidence of symptoms.

During 12 months, 244 episodes of severe hypoglycemia in 166 patients were recorded in a district with a population of 367 051 people (8655 with diabetes); there were 69 (7.1%) episodes in people with type 1 diabetes, 66 (7.3%) in people with type 2 diabetes using insulin, and 23 (0.8%) in those taking a sulfonylurea. Age, duration of diabetes, and lower social class were risk factors. The total cost of emergency treatment was estimated to be no more than $92 078 per year (22). In a German study in a comparable group of 200 000 people, there were 92 cases in those with type 1 diabetes and 146 cases in those with type 2 diabetes during 3 years (23). The estimated costs were lower: $88 676 per year for type 2 diabetes and $16 258 for type 1 diabetes.

In 28 children aged 3.1–8.3 years using twice- or thrice-daily insulin, blood glucose was measured with a subcutaneous continuous glucose monitoring system on 3 consecutive days and nights (24). Hypoglycemia was defined as a blood glucose concentration below 3.3 mmol/l for longer than 15 minutes. The prevalence

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of hypoglycemia was 10% and it was more common at night than during the day (19 versus 4.4%). Hypoglycemia at night had a longer duration (median 3.3 hours) and was asymptomatic in 91% of the episodes. The highest prevalence occurred at between 04.00 and 07.30. On a thrice-daily insulin injection regimen, nightly hypoglycemia was less frequent, but the frequency was higher on the following morning. With increasing age there was less hypoglycemia.

Mechanisms

The concentrations of the counter-regulatory hormones adrenaline and glucagon were higher before treatment of coma in insulin-treated persons admitted to hospital for hypoglycemia than in the fasting state. However, concentrations of adrenaline, glucagon, cortisol, and growth hormone are lower during a hypoglycemic episode in a diabetic than when these hormones are measured during induced hypoglycemia in non-diabetics (25). There was an inverse correlation between glucose and adrenaline in hypoglycemia, but no direct relation between the other hormones and blood glucose concentrations. The addition of intramuscular glucagon during intravenous glucose therapy did not result in different glucose concentrations at any time (25). In type 2 diabetes counter-regulatory hormones are reduced compared with controls, but the patients release the hormones at higher blood glucose concentrations than type 1 diabetics, and the glucagon response is not blunted (26,27).

- Low responses of counter-regulatory hormones during induced hypoglycemia in a 27-year-old woman with poorly controlled diabetes (HbA_{1c} 11%), with frequent hypoglycemic instances of which she was not aware, improved dramatically after 3 months of good regulation (28); only growth hormone showed no reaction.

Hypoglycemia increased beta-adrenoceptor sensitivity in healthy subjects but reduced it in type 1 diabetes (29).

In 20 insulin-treated diabetic patients with episodes of severe hypoglycemia in 1982–84, re-evaluated in 1992–94, emergency visits were reduced from 1.05/year to 0.42/year between 1984 and 1994 (30). There were no cases of fatal hypoglycemia. There was no association with HbA_{1c}. Multiple daily insulin doses reduced the frequency of hypoglycemia to one-third. In 1984, unawareness was a predisposing factor and most of the patients had deficient counter-regulation (adrenaline). Most patients had a long history of insulin injections (mean 29 years). In 1994, six patients were partly and eight patients totally retested and compared with 10 matched control patients with type 1 diabetes. When hypoglycemia was induced by insulin the patients with frequent hypoglycemia reached values under 3.0 mmol much faster, and in six patients the test had to be stopped before the normal duration of 3 hours for hypoglycemia; this never happened in the control patients. Counter-regulation was deficient in both 1984 and 1994, indicating that reduced counter-regulation can be permanent and does not only depend on specific circumstances.

In 86 intensively treated patients with type 1 diabetes aged 7–18 years, the incidence of severe hypoglycemia correlated with the serum activity of acetylcholine esterase. Patients with acetylcholine esterase activity at the median or above reported 3.0 events/year and those with acetylcholine esterase activity below the median reported 0.5 events/year, suggesting that a genetic factor may play a role in the emergence of severe hypoglycemia (31).

Presentation

Symptoms of hypoglycemia have to be expected when the blood glucose concentration is below 2.6 mmol/l. The effects of hypoglycemia vary from patient to patient and can vary in the same patient. The symptoms and signs are of two types: adrenergic effects, due to release of catecholamines, and neuroglycopenic effects, due to the effects of hypoglycemia on the nervous system.

- *Adrenergic effects* Hunger, restlessness, profuse sweating, palor, tachycardia, and palpitation.
- *Neuroglycopenic effects* Headache, confusion, drowsiness, fatigue, difficulties in finding words, frequent yawning, anxiety, blurred vision, diplopia, and numbness of the nose, lip, and fingers.

Some patients do not experience the noradrenergic symptoms of hypoglycemia. They are taken by surprise, may lose consciousness and have hypoglycemic blood glucose concentrations without any preceding symptoms. After frequent episodes of hypoglycemia, there is altered awareness of hypoglycemia (18,32,33). It is difficult to substantiate altered awareness. Neuroendocrine responses and symptoms of hypoglycemia, but not cognitive dysfunction, are shifted to lower plasma glucose concentrations after recent hypoglycemia (34). Repeated episodes of hypoglycemia reduce the awareness of symptoms of hypoglycemia. This is accompanied by a lower blood glucose concentration, to elicit the response of counter-regulatory hormones (35). Beta-blockers also suppress the adrenergic symptoms, apart from sweating, which is mediated by sympathetic cholinergic transmission. Training increases awareness (36). Intensively treated patients may have reduced preservation of higher brain functions (37). Some groups, mainly in the UK, have suggested that transfer from animal to human insulin increases unawareness (SEDA-15, 452) (38), but this was not substantiated in other studies (39–41).

Every patient treated with insulin (or with hypoglycemic agents) who develops a neurological or psychiatric disorder has to be considered to be hypoglycemic until proven otherwise.

A rapid fall in blood glucose in a diabetic patient can cause symptoms of hypoglycemia, even when blood glucose concentrations are still normal or above normal. Experience with pumps has shown that many patients continue to feel hypoglycemic for a long time after normoglycemia has been restored. After an attack of hypoglycemia, patients often felt less well for a period of up to 48 hours. Headache, tiredness, and lack of initiative may disappear only gradually. These symptoms in the morning may indicate unnoticed hypoglycemic periods during sleep. Wet pyjamas or sheets may also indicate unnoticed hypoglycemia. During anesthesia, profuse sweating may indicate hypoglycemia.

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A rise in C reactive protein has been observed during spontaneous attacks of hypoglycemia in diabetics and after experimental hypoglycemia in healthy controls (42).

Cardiovascular effects of hypoglycemia

The cardiovascular effects of hypoglycemia include angina pectoris, dysrhythmias, electrocardiographic changes, and coronary thrombosis. Raised concentrations of catecholamines and reduced concentrations of potassium contribute to cardiac damage during hypoglycemia.

Respiratory effects of hypoglycemia

- A 19-year-old woman with diabetes developed hypoglycemia with pulmonary edema (43). This has previously been seen as a complication of insulin shock therapy for psychiatric illnesses.

Nervous system effects of hypoglycemia

When hypoglycemia does not resolve spontaneously or is not terminated, cerebral dysfunction becomes manifest as confusion or reduced consciousness. Lethargy and depression or obstructive behavior develop and are accompanied by loss of consciousness, snoring, deep respiration, and facial paralysis. Neurological involvement can appear as cramps, paralysis, hemiplegia, or paraplegia. Epileptic seizures can accompany attacks of hypoglycemia. In deep coma the pupils are dilated, but they may react to light. Coma can develop very rapidly.

In a teaching hospital in Edinburgh, 56 admissions of 51 patients for hypoglycemia were registered during 12 months; 41 patients had diabetes mellitus and 33 were using insulin (44). There was a high incidence of neurological effects. Psychiatric illness or alcoholism was common. Four patients died but only one as a direct consequence of hypoglycemia. A further six patients died within 15 months, not related to hypoglycemia.

In 37 drivers with type 1 diabetes, fewer corrective actions were taken when the blood glucose was below 2.8 mmol/l (45). This was related to increased neuroglycopenic symptoms and increased electroencephalographic theta-wave activity. The authors suggested that diabetics should not begin to drive when the blood glucose concentration is in the 4.0–4.5 mmol/l range. In two editorials, the possibility of further restricting driving licenses in people with diabetes has been discussed (46,47). However, there is no evidence of higher accident rates in drivers with diabetes.

A retrospective questionnaire was sent to 195 consecutive patients addressing questions of severe hypoglycemia, coma, awareness of hypoglycemia, and fear of hypoglycemia (48). The mean duration of diabetes was 20 years and 82% had received intensive therapy. Coma was reported in 19% and severe hypoglycemia in 41%. Coma was independently related to neuropathy, beta-blockers, and alcohol.

In reaction to a report of pulmonary edema and hypoglycemia (SEDA-24, 488) it has been noted that in many cases, one or more seizures precede pulmonary edema (acute respiratory distress syndrome), suggesting a neurogenic mechanism (49).

In 304 insulin-treated patients, 8.2% of those with type 1 diabetes and 2.2% of those with type 2 diabetes had blood glucose concentrations below 4 mmol/l on arrival in the clinic (50). None had complained of symptoms of hypoglycemia or had taken glucose, but when questioned, 59% had autonomic symptoms and 12% had neuroglycopenic symptoms; 29% were asymptomatic.

Autonomic failure can occur as a result of hypoglycemia, since antecedent hypoglycemia causes both defective glucose counter-regulation and lack of awareness of hypoglycemia. The role of the brain in lack of awareness of hypoglycemia and the question of whether the brain is the primary site for sensing hypoglycemia has been discussed (51). In older people, markedly fewer autonomic symptoms are reported and there is greater slowing of psychomotor performance. In young children, hypoglycemia can lead to more mood and behavioral disturbances than in adults, although they also occur in the latter. It may be that the cortical responses to recurrent hypoglycemia are less plastic and reversible than the hypothalamic and glucose-sensing functions (52).

Psychological and psychiatric effects of hypoglycemia

Using evidence from auditory-evoked brain potentials and hypoglycemic clamps, it has been argued that antecedent hypoglycemia not only reduces awareness, but also that several aspects of cognitive function are attenuated during subsequent hypoglycemia 18–24 hours later (53). However, there were no effects of repeated hypoglycemia on cognitive function in patients included in the DCCT, a large American study that included more than 1400 patients, which showed that normalization of blood glucose prevents or delays the development of secondary (microvascular) complications in type 1 diabetes (54).

Nevertheless, long periods of hypoglycemia can cause permanent brain damage. There is concern that frequent attacks of hypoglycemia impair brain function but there are few hard data.

Hypoglycemic coma due to insulin with extensive mental changes has been reported, including a review of six comparable cases in patients aged 37–56 years, whose coma lasted from 36 hours to 31 days (55).

- A 37-year-old man could not be wakened in the morning. He had injected insulin without eating. His blood glucose was 1.5 mmol/l and he did not improve with intravenous glucose 16 g. In hospital he remained unconscious with a blood glucose of 12.2 mmol/l. There was no alcohol in the blood, his pH was 7.35, and he had a normal anion gap (18 mmol/l). His serum creatinine concentration was 288 μmol/l and his creatine kinase activity was high, suggesting rhabdomyolysis. A brain CT scan was normal and repeated electroencephalography showed slow waves with reduced voltages but no focal changes or irritation. He gradually recovered and was discharged after 6 days. Because of the dissociation between physical and mental improvement he was checked after 6 months and still had antegrade memory loss and problems with memory, complaining that he needed reminders on paper, and had less vitality and reduced emotionality.

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Of the six reviewed patients, two died in coma; the other four had neuropsychological problems that did not improve after 6 months and up to 2 years. They had comparable electroencephalographic changes. During coma there was hypokalemia and hypocalcemia combined with increased lipolysis; this may have accounted for the permanent cerebral changes.

Of 20 patients with severe hypoglycemic coma and 20 with no or light coma, those with hypoglycemia had chronic depression and anxiety and performed persistently more poorly in several cognitive tests (56).

In 42 patients with at least two episodes of severe hypoglycemia in the previous 2 years and 51 patients with no episodes, low blood glucose, hypoglycemia-impaired ability to do mental subtractions, and awareness of neuroglycopenia and hypoglycemia predicted future severe attacks of hypoglycemia (57). In another study, blood glucose awareness training increased adrenaline responses to hypoglycemia (58). However, in a reanalysis of data from the Diabetes Control and Complications Study, a large study relating the development of secondary complications to less strict control of blood glucose (14), there was no effect of repeated hypoglycemia (54).

The effect of hypoglycemia on cognitive function has been investigated in 142 children aged 6–15 years with type 1 diabetes intensively treated for 18 months; 58 had 111 periods of treatment. There were no effects on cognitive functions (59). In 29 prepubertal children, with diabetes for at least 12 months and using twice-daily mixed insulin, observed for two nights, asymptomatic hypoglycemia occurred in 13 children on the first night and in 11 children on the second night; cognitive performance was not altered, but mood was reduced (60).

In healthy volunteers hypoglycemia caused significant deterioration in short-term attention, whereas sustained attention and intelligence scores did not deteriorate (61).

Sensory effects of hypoglycemia

Temporary blindness after severe coma (62,63) and retinal damage by gazing in the sun during hypoglycemia (64) have been reported.

Differential diagnosis

When a patient does not react rapidly to sufficient therapy, other diagnoses have to be considered during suspected attacks of hypoglycemia.

Alcohol can confuse the diagnosis of hypoglycemia (SEDA-5, 386). Alcohol inhibits gluconeogenesis. It makes the patient more susceptible to hypoglycemia and can even cause hypoglycemia in healthy individuals. The symptoms of alcohol abuse and hypoglycemia are almost identical. If hypoglycemia is predominant, glucose administration will help. In attacks of hypoglycemia, the symptoms disappear rapidly after glucose intake.

Vascular episodes in older diabetics can mimic attacks of hypoglycemia. True epilepsy or strokes can cause comparable symptoms or accompany hypoglycemia.

Differentiation of hypoglycemia from hyperglycemic coma is usually not difficult. The development of hyperglycemic coma takes a longer time and the blood glucose concentration is high. However, urine testing may show positive glycosuria, if urine produced before the hypoglycemic period is still in the bladder. Even ketonuria may be present if a patient has been fasting for a long period.

Timing

The emergence of attacks of hypoglycemia depends on the times and amounts of food eaten and the duration of action of the insulin used (see Table 2). When only one type of insulin is used, the symptoms of hypoglycemia mostly occur at the end of the period of maximal insulin activity. Modern insulin therapy involves using a combination of long-acting and short-acting insulins. Long-acting insulins are given once or twice a day in combination with and/or in addition to short-acting insulins, which are given 2–4 times a day. Hypoglycemia can then develop at times when the combined effects are most prominent. Hypoglycemia in the mid-morning can be a consequence of the action of the long-acting insulin of the previous day and the short-acting insulin given earlier in the same morning. Hypoglycemia during the night or in the early morning can be caused by too much long-acting insulin or by short-acting insulin late at night without sufficient food. Repeated symptoms of hypoglycemia at the same time of the day indicate that the timing of the insulin injection or the relative proportions of long-acting and short-acting insulins have to be changed. If the interval between insulin injection and the subsequent meal is very short, the effective insulin concentration in the blood will still be low when glucose is absorbed from the gut. This will cause very high postprandial glucose concentrations. An increase in the dose of insulin will then cause hypoglycemia at a later time. It is therefore advisable to try first to increase the interval between the injection and start of the meal. New synthetic insulins, like lispro insulin, give a more rapid increase and fall of insulin concentrations than regular insulin; in that case, postprandial hypoglycemia can occur 1–3 hours after the injection (65).

Susceptibility factors

Hypoglycemia is an important problem in children (66–68). Children do not always establish the connection between the symptoms of threatening hypoglycemia and the danger involved. Overdosage of insulin is relatively common (SEDA-7, 406).

Older patients are particularly susceptible to hypoglycemia (69). Factors such as cerebral blood flow, blood PO_2 and PCO_2, permeability of the blood–brain barrier, and the presence of underlying neurological defects influence the hypoglycemic effects.

Hypoglycemic periods are often seen in "brittle diabetics," many of whom are overtreated with insulin. Changes in the insulin regimen (reduced use of long-acting insulin, frequent small injections of short-acting insulin) or the use of continuous infusion pumps can often lead to better results, but not everyone with brittle diabetes responds in that way (SEDA-7, 405). Apparently brittle diabetes may in fact be due to factitious hypoglycemia, the hypoglycemic periods of which are caused by surreptitious self-injection of insulin, Munchausen syndrome by proxy (SEDA-18, 413), or manipulation of the prescribed doses. In factitious hypoglycemia, low blood

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glucose concentrations are accompanied by high insulin concentrations but low concentrations of C peptide (70). Suicide attempts with insulin may be less uncommon than is often thought. A Medline search between 1966 and 1999 identified 46 papers containing 69 cases of factitious hypoglycemia; 46 were women, 52 were not diabetic, 29 had no close links with diabetes in their environment (71). In 47 the hypoglycemia was induced by insulin. Two patients died and one had severe impairment of intellectual function and short-term memory. In 32 cases unnecessary surgical procedures were performed.

Impaired hypoglycemic awareness was associated with an increased rate of severe hypoglycemia in 130 children and adolescents (aged 3–17 years) (72). One-third of the severe episodes developed without warning symptoms. Impaired awareness, young age, and recent attacks of hypoglycemia were independent susceptibility factors.

The authors of a systematic review of whether there is a difference in the frequency and awareness of hypoglycemia induced by human or animal insulins identified 52 randomized, controlled trials; 37 were double-blind (73). They found no support for the supposition that human insulin per se affects the frequency, severity, or symptoms of hypoglycemia. In a few studies, mainly of less rigorous design, there was an effect when people were transferred from animal to human insulin, indicating increased frequency or reduced awareness of hypoglycemia.

A questionnaire about the prevalence of severe hypoglycemia in relation to susceptibility factors was answered by 387 patients in 1984 and by 641 patients in 1998; 178 patients answered both questionnaires (74). The following changed significantly from 1984 to 1998: multiple injection therapy increased from 71 to 98%, daily self-monitoring from 17 to 48%, episodes of nocturnal hypoglycemia from 76 to 83%, and lack of awareness from 40 to 55%; HbA_{1c} fell from 7.6 to 7.4%.

Awareness of hypoglycemia

Avoidance of hypoglycemia for 3 months can improve hypoglycemic awareness for a period of over 3 years (75). In contrast, supervised induction of brief hypoglycemia twice weekly reduced clinical awareness of hypoglycemia by 33% and reduced the important adrenaline response, so reducing the behavioral and physiological defences against hypoglycemia (76).

Management

Patients have to be instructed to have a rapidly absorbed form of carbohydrate (for example dextrose tablets) available at all times and to use it when the first symptoms of hypoglycemia are felt. Often they fail to do so (77). If patients are used to self-monitoring, it is advisable that they monitor blood glucose first, although they should be told that a rapid drop in blood glucose concentration without reaching hypoglycemic values can cause a hypoglycemic reaction. Hypoglycemic reactions are sometimes difficult to discriminate from other feelings of malaise. Carbohydrate will always give rapid relief if the diagnosis is hypoglycemia and it is always safe to try taking it.

The conscious patient should take oral glucose at once. The treatment of choice in hypoglycemic coma is immediate intravenous injection of 20–50 g of dextrose. The patient may try to resist the injection, and help with the immobilization of the arm may therefore be needed. Injection of concentrated glucose solution outside a blood vessel leads to inflammatory and necrotic reactions. If intravenous injection of glucose is impossible, 1 mg of glucagon can be injected subcutaneously. However, in patients with residual insulin secretion (type 2 diabetes) glucagon may elicit extra insulin secretion and perpetuate hypoglycemia (78). The Epipen (a pen filled with a solution of adrenaline) is not a good substitute for the glucagon pen (in which glucagon must be dissolved before it can be used) in the treatment of hypoglycemia (79).

When the patient has taken high doses of long-acting insulin, hypoglycemia may relapse after a single dose of glucose has provided temporary relief, and monitoring should continue for a longer period. After hypoglycemic reactions elicited by long-acting insulins or oral hypoglycemic drugs the patient should be observed for possible recurrence during the next few days (80). The longer the duration of coma, the poorer the prognosis. Persistent posthypoglycemic coma can be due to cerebral edema. Fever can accompany this severe form of coma, which requires treatment with intravenous mannitol and glucocorticoids. Severe coma can last for several days and require intensive management. Encephalopathy with neurological symptoms can be the consequence.

Infusion of too much glucose over an extended period in the treatment of hypoglycemia is dangerous (81). Glucose utilization in the postabsorptive state is 2 mg/kg/minute and can increase, if insulin concentrations are high, to 6 mg/kg/minute (about 600 g/day in a 70 kg individual). It is better to infuse glucose in concentrations of 10 or 20% rather than 40%.

The opinion of experts about when and how to treat asymptomatic hypoglycemia in children varies greatly (82). Hypoglycemia in children is often undetected. Using a subcutaneous continuous glucose monitoring system (83) or the non-invasive Glucowatch biographer (84), hypoglycemic periods were more frequent and prolonged than when only fingerprick testing was available. For treating hypoglycemia in children, small doses of glucagon are suggested. The contents of a 1 mg/ml ampoule can be drawn into a 1 ml U100 syringe. For children under 2 years, 20 micrograms should be given initially; 10 micrograms is added for every year, up to 150 micrograms at age 15. When the effect is insufficient, the dose can be repeated once or twice (85).

Fat metabolism

- A 14-year-old adolescent girl, who had only used regular insulin developed lipoatrophy (86). Histology showed lipoblastoma-like cells, a possible sign of dedifferentiation. Skin tests showed no signs of allergy. The concentrations of immunoglobulins and TNF-alfa were normal.

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Body weight

The DCCT Research Group has reported that patients in the intensive treatment group had substantial excess weight gain (87). In the first 9 months a group of patients who received intensive treatment gained 3.3 kg, compared with 1.2 kg in the control group; the percentage of people who gained more than 5 kg/m^2 was consistently higher with intensive therapy. This weight gain was related to both lean body mass and fat.

Fluid balance

Insulin edema is a rare complication, more often seen in the earlier years of insulin therapy (SEDA-11, 364). It is mostly seen when dysregulated patients with progressive weight loss are treated with relatively high amounts of insulin. Reduced sodium excretion (88), sodium reabsorption, and water retention by a possible direct action of insulin on the kidney may be involved (89). The role of aldosterone or of inhibition of the renin–angiotensin–aldosterone system in insulin edema is unclear. Insulin edema is a specific adverse effect, but it can aggravate pulmonary edema, congestive heart failure, and hypertension. Treatment consists of reduction of the insulin dose, after which the edema resolves within 3–4 days.

Insulin edema has been described in children with newly discovered diabetes (90).

- A 13-year-old girl with diabetes was given insulin 2 U/kg/day. She developed generalized edema and gained 20 kg over 2 weeks. With less insulin, furosemide, and later ephedrine the edema disappeared within 1 month.
- A 14-year-old girl with diabetes was given insulin up to 1.5 U/kg/day and gradually developed edema and gained 8.5 kg over 9 days. With furosemide, the edema gradually disappeared in 1 month.

Both of these children received rather high doses of insulin and they lacked the extreme acidosis that often occurs in young people when diabetes first appears.

Liver

Hepatic damage by regular human insulin has been reported (91).

- A 45-year-old man, who drank alcohol 60 g/day until diabetes was diagnosed, had mild liver function test abnormalities 6 months earlier, but only the gamma-glutamyl transpeptidase was raised (167 IU/l). When insulin was given, the transaminases also increased. Liver function normalized after withdrawal of insulin. Reinstitution of insulin and a switch to another human insulin formulation again increased the liver enzymes. He was managed with glibenclamide and liver biopsy was not performed. Lymphocyte stimulation tests gave negative results to all insulin formulations. All hepatitis-related virus markers were negative.

As the changes in this case were seen with different types of insulin, it is improbable that additions to the formulation were responsible. It is possible that the use of alcohol made the liver more sensitive to the damaging effects of exogenous insulin.

Skin

Hypertrophy of the subcutaneous tissues after insulin injections leads to delayed and variable insulin absorption. Of 282 children (160 boys and 122 girls, median age 12 years) prospectively evaluated for 3 months, 29% had mild skin hypertrophy and 18% had massive hypertrophy (92). The latter had higher HbA_{1c} concentrations and longer durations of diabetes and required more daily injections. There was no relation to the length of the needles used.

Amyloid-like deposition in the skin has been reported in a patient using porcine insulin (93).

- A 34-year-old man with a 17-year history of type 1 diabetes developed a 7 cm firm mass, distinct from adjacent areas of lipohypertrophy, and numerous smaller lesions of the same consistency. The lump consisted of acellular waxy material that appeared to be amyloid, formed by insulin. He had used porcine insulin for a long time.

This complication has been described before (SEDA-14, 373).

Musculoskeletal

A specific complication of the use of large amounts of insulin during hyperosmolar diabetic coma is rhabdomyolysis (94). Low intramuscular phosphate and potassium concentrations, often masked by relatively high blood glucose concentrations, may be important contributory factors.

Immunologic

Insulin allergy is quite common (SEDA-7, 403) (95–97). Allergy has been reported to human insulin and protamine (98) and to human insulin (99,100).

- A 41-year-old woman became allergic to all types of insulin (beef, pork, human, lente, etc.). She had used insulin for the first time during pregnancy and was intermittently treated unsatisfactorily with oral agents. She used lispro insulin for more than 6 months without an allergic reaction.
- A 54-year-old woman with gestational diabetes was later found to be allergic to chromium, pollen, dust, penicillin, acarbose, and metformin (101). She was treated with diet and glibenclamide, but later required insulin. With Humulin N insulin she developed a wheal of 15 mm immediately after the injection, which resolved in a few hours. However, a painful itchy induration appeared 2–3 hours after the injection and lasted a few days. She had an immediate reaction to isophane insulin, with induration, but insulin lispro was well-tolerated.
- A 5-year-old child with diabetes, Pierre Robin syndrome, cleft palate, allergic rhinitis, recurrent sinusitis, and obstructive sleep apnea, who had previously had skin rashes after penicillin, sulfonamides, and clindamycin, was given soluble and isophane human insulins (102). Three years later she developed local reactions, 2–5 cm areas, 30–120 minutes after injection. Skin-prick tests were negative for the diluent, isophane, and soluble insulin, but intradermal testing was positive with

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both insulins. Cetirizine and dexamethasone added to the insulin gave temporary relief. She was then given insulin lispro by pump. After about 8 months, she started to develop local reactions again but with cetirizine and the pump her reactions were manageable.

- A 6-year-old boy developed recurrent generalized urticaria 1 year after he started to use human Mixtard insulin (103). The rash started 10 minutes after injections in the arms, thighs, and buttocks, at sites where earlier injections had been given, and disappeared within 12 hours. When he was changed to insulin lispro he had three urticarial reactions in the first 2 weeks and then sporadically. The reactions were treated with chlorphenamine for 2 years.

Presentation

Although serious systemic reactions are rare, local reactions at the site of injection are not infrequent. They appear as reddening, swelling, heat, burning, and itching, with or without frankly painful sensations. They can set in immediately or after some hours. The lesion can extend gradually and persist for variable periods. Some immediate reactions are related to IgE (or IgE/IgG) concentrations (104), but a direct relation between allergic reactions and a specific IgG fraction cannot be established (105).

- A 45-year-old woman who had used insulin for 4 years had a biphasic hypersensitivity reaction to human insulin (or another component of the injection fluid) (106). Within 20 minutes after the injection a swelling developed and in a later phase papular lesions with lichenoid features and post-inflammatory hyperpigmentation emerged. Histologically, there was neutrophilic infiltration with erythrocyte extravasation and eosinophilic amorphous material, surrounded by neutrophilic infiltrate. Saline injection did not elicit an effect. IgE anti-insulin antibodies were not found. There was no Arthus reaction (type IV allergy).

Other reactions are of the tuberculin granulomatous type or of the local vasculitis Arthus type. The local reactions can be accompanied, preceded, or followed by a generalized reaction, such as urticaria, nausea, vomiting, diarrhea, angioedema, wheezing, or anaphylactic shock. The last of these is rare, but sometimes fatal.

Insulin can induce local, painful lumps at injection sites. Sclerosing granulomata are occasionally seen (107) perhaps due to zinc (108). Such reactions are most commonly a consequence of an incorrect injection technique, generally the use of too short a needle or too superficial an injection. General edema (SEDA-11, 364) or abscesses (SEDA-7, 406) generated by insulin injections are extremely rare.

Lipodystrophy, lipoatrophy, or lipohypertrophy can be a consequence of chronic local insulin reactions that can be elicited by less pure as well as by highly purified preparations (109), but such reactions can also develop at sites distant to the injection.

Leukocytoclastic vasculitis has been attributed to human insulin.

- A 48-year-old woman with type 1 diabetes developed tender induration within 2–6 hours and persisting for 1–3 days after injection of both isophane and regular insulins (110). This was followed by intense itching and redness, but no wheal-and-flare reaction. Switching to semisynthetic insulin and other insulin analogues or continuous subcutaneous insulin infusion had no effect. After 3 years the condition became incapacitating. Humalog 5–6 times a day, including an injection at 0300 hours was the best tolerated regimen. Intradermal tests showed allergy to human, porcine, and bovine insulins, but no reaction to protamine or other additives. Skin biopsies showed a leukocytoclastic vasculitis. Prednisolone 10 mg/day plus azathioprine 50 mg/day, later replaced by methotrexate 7–15 mg/week, produced complete resolution within 8 weeks.

Pathogenesis

Allergic reactions to insulin were originally thought to be caused by impurities present in the formulation. However, after the introduction of monocomponent insulins and human synthetic insulins, these reactions continued to be seen, even in patients without a history of treatment with other insulins (111). Switching from animal to human insulin can paradoxically cause allergic reactions, which subside when treatment with animal insulin is re-introduced (112). In patients who have never used other types of insulin, allergic reactions can be seen when human insulin is used and anti-insulin antibodies can be demonstrated (113). Antibodies against human insulin have also been found in sera collected from patients before human insulin was available (114). However, insulin antibodies can be found during or before the emergence of type 1 diabetes. Circulating insulin-binding antibodies can increase insulin resistance (115) and extend insulin action by slowing release. The titers of antibodies fall when purified insulins or human insulin are used, but they can be demonstrated even when modern insulins of high purity have been used exclusively. Anti-receptor antibodies are seldom seen.

In India, insulin antibodies have been investigated in 25 patients with type 1 diabetes, 19 patients with so-called malnutrition-related diabetes, and eight patients with fibrocalculous pancreatopathy, who used bovine insulin because it was cheaper (116). Antibodies appeared within 3 months of treatment. The development of antibodies was not related to the type of diabetes. There was a fall in antibody titer with increased duration of treatment. There was no correlation between daily insulin requirement and antibody titers.

Allergic reactions can also be elicited by excipients in insulin formulations, such as Surfen (aminoquinuride) (117), zinc (118), and protamine (119,120). Remnants of fluids used for cleansing the skin can be co-injected in micro-amounts and elicit allergic reactions (121). Allergy to latex in vial tops or syringes can become manifest during insulin treatment (122). In excised (infected) lumps, amyloid fibrils, proteins containing intact insulin, were demonstrable (123). Plastic syringes can release silicone particles, which can diminish the effect of insulin (124) or themselves induce granulomatous reactions (125).

It has been suggested that increased concentrations of corticotropin-releasing hormone, which has an immunomodulatory effect and causes vasodilatation and mast cell

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degranulation, could play a role in urticaria that develops during hypoglycemic periods in type 1 diabetes (SEDA-13, 381). Adrenal hyperandrogenemia is found in many diseases with hypersensitivity (126).

Susceptibility factors

Intermittent insulin administration seems to favor the development of allergic reactions to insulin (SEDA-6, 369).

Continuous intraperitoneal infusion of insulin causes increased insulin immunogenicity, but it is not known if this is accompanied by an increased frequency of autoimmune diseases. Antibodies against insulin, thyroglobulin, thyroperoxidase, gastric parietal cells, smooth muscle, mitochondria, liver and kidney microsomes, endomysium, and gliadin, and antinuclear antibodies were determined before and yearly after transfer to continuous intraperitoneal infusion of insulin in 28 patients; 19 remained negative for all investigated antibodies and in the other 9 the anti-insulin titer increased but other antibody titers remained constant or fluctuated (127). The authors concluded that during continuous intraperitoneal infusion of insulin in type 1 diabetes the frequency of other autoimmune diseases like hyperthyroidism was not increased. However, this conclusion was criticized, as the small numbers did not allow a positive or negative conclusion (128).

Treatment

In 95% of cases the local reactions disappear spontaneously. A switch to less immunogenic, highly purified insulin, or insulin lispro (129), is necessary if the reactions persist. For local allergic reactions, antihistamines or the addition of hydrocortisone 2 mg along with the insulin are seldom needed. Hydrocortisone suppresses local allergic reactions. For generalized reactions, skin testing is often necessary to establish allergic desensitization. One should start with low intradermal doses and, if necessary, add hydrocortisone.

For therapy of local lumps, extravasation, etc., one should first seek to improve the injection technique. Substitution with highly purified insulin is recommended. Injection with purified insulin into the affected area may speed up resorption of the lumps. Lipodystrophy or lipoatrophy improve after switching to highly purified human or insulin lispro. Lipohypertrophy, on the other hand, often fails to respond to changes in the insulin regimen (130). Varying the injection site may help, but differences in absorption rate then have to be taken into account.

Insulin resistance is said to be present when more than 200 U/day have to be injected; it is generally due to insulin antibodies. In general, antibody titers fall when highly purified insulins are used, but they sometimes persist after the switch. Some diseases, such as infections, endocrine hyperfunctional states (acromegaly, Cushing's syndrome, thyrotoxicosis), leukemia, or stress, can contribute to insulin resistance. Recombinant IGF-I (insulin-like growth factor I), which has a structure comparable to insulin, may help to overcome insulin resistance (131); adverse effects are burning at the injection site, hypoglycemia, fluid retention, facial edema, increased heart rate, arthralgia, myalgia, parotid gland tenderness, and dyspnea.

Continuous subcutaneous insulin infusion with fast-acting insulin has been used in two cases.

- A 43-year-old man with type 1 diabetes developed local pruritus, redness, and swelling 4–5 times a week, 15–20 minutes after an injection, subsiding within 1–2 hours (132). Later he had a generalized urticarial reaction 5 minutes after an injection. Insulin lispro did not help. When checked for allergens, he was positive for all types of insulin and negative for additives. With oral mizolastine the local reactions abated for a week, but then reappeared with every injection. Generalized urticaria recurred later. With continuous subcutaneous insulin infusion the local reactions immediately disappeared and metabolic control was improved.
- A 79-year-old man used mixed insulin for 2 months and developed swelling at injection sites, lasting 48 hours (133). The lesions persisted despite switching to various types of insulin. He was allergic to insulin, as shown by a raised eosinophil count, a markedly increased IgE concentration, and antibodies to human, bovine, and porcine insulins in the RAST test. He was not allergic to needles or additives. With subcutaneous bolus doses of insulin lispro and Humulin he developed induration and wheal-and-flare reactions. When hydrocortisone 10 mg was added to each injection, the allergic reactions disappeared, but they recurred after 2 months. With continuous subcutaneous insulin infusion there were no allergic responses for 3 months. His raised IgE concentrations fell.

Long-Term Effects

Drug tolerance

Insulin resistance has been reported with continuous subcutaneous infusion.

- Diabetes mellitus in a 36-year-old man with acute pancreatitis could not be controlled with continuous subcutaneous insulin infusion, even with doses up to 1800 U/day, because of insulin resistance (134). Intravenous insulin by pump had to be stopped because of a catheter infection. The continuous subcutaneous infusion of freeze-dried insulin and the addition of aprotinin, a protease inhibitor, soluble dexamethasone or prednisolone, and intravenous immunoglobulin was ineffective. An implantable pump for intraperitoneal delivery established good regulation at a dosage of 30 U/day.
- A 23-year-old diabetic woman had severe subcutaneous insulin resistance for 11 years (135). Continuous subcutaneous insulin infusion with regular or insulin lispro did not prevent periods of fluctuating responses to insulin. The addition of heparin to insulin lispro in the pump improved serum insulin concentrations and metabolic control. The addition of heparin to regular insulin gave no improvement.

Heparin may improve the transport of insulin lispro but not of regular insulin.

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Second-Generation Effects

Pregnancy

In a longitudinal cohort survey of 278 pregnant women with type 1 diabetes, the frequency of severe hypoglycemia increased two to three times compared with the last 4 months before pregnancy (25%, including 9% with hypoglycemic coma, before pregnancy and 41%, including 19% with coma, during pregnancy) (136). A history of severe hypoglycemia before pregnancy, a longer duration of diabetes, an HbA_{1c} concentration of 6.5% or less, and a daily insulin dose of over 0.1 U/kg were indicators of increased risk.

Continuous subcutaneous insulin infusion in pregnancy has been studied retrospectively in a nested case-control study (137). Those who used the pump had higher fasting blood glucose concentrations at the start, came sooner to the pregnancy clinic, used more insulin, put on more weight, and were more likely to have the baby admitted to the special baby care unit. Birth weights and neonatal hypoglycemia were similar.

- A 37-year-old nurse with type 1 diabetes was adequately treated with lispro and isophane insulin during her first pregnancy (138). In her second pregnancy, 3 years later, she had frequent episodes of hypoglycemia with the same regimen, for which she sometimes needed an injection of glucagon during the night. When the isophane in the evening was changed to glargine she had no more serious episodes of hypoglycemia.

Teratogenicity

In animals, teratogenicity of insulin during pregnancy has been observed (SEDA-8, 908) (139). No proof has been given that this also holds good in humans. A statistical significant relation found between insulin use for or during pregnancy and musculoskeletal anomalies (140) may also be caused by increased blood glucose or other to diabetes related factors.

Susceptibility Factors

Age

In 3805 children and adolescents with type 1 diabetes in 21 pediatric centers in 17 countries, feedback was given on the overall mean HbA_{1c} concentration in all the centers (141). After 3 years insulin therapy was more intensive, but glycemic control improved in only three centers. The relative risk of severe hypoglycemia was lowest in the center with the best glycemic control.

Drug Administration

Drug formulations

The formulation of insulin differs in various countries. A strength of 100 U/ml (U100) is increasingly used in many countries, but in other countries strengths of 20, 40, or 80 U/ml (U20, U40, and U80) are still in use. The increased frequency of travelling and tourism has increased the importance of the problem. In some countries in various parts of the world, both U40 insulin of variable purity and highly purified U100 insulin are available at the same time. U100 insulin used in U40 syringes causes severe unexpected hypoglycemia and the reverse induces apparent insulin resistance (SEDA-6, 367).

Drug contamination

A skin reaction to latex in rubber associated with an insulin formulation has been reported (142).

- In a 35-year-old woman, pruritic, erythematous, urticated plaques occurred at insulin injection sites, and persisted for 48 hours, after the use of a prefilled cartridge pen containing Humulin (Lilly) and Human Monotard (Novo Nordisk) aspirated from a punctured vial, but not when the insulin was taken directly from the vial. She had positive skin-prick tests to latex solutions. Both the cartridge bungs and the vial bungs contain butyl rubber with added natural rubber latex. Switching to latex-free vials alleviated the problem.

Drug administration route

The American Diabetes Association has published revised guidelines on insulin administration, including storage of insulin, use and reuse of needles, alternatives to syringes, injection techniques, and patient management related to dosing of insulin, self-monitoring, and hypoglycemia (143).

Developments in the administration of insulin through the skin, the mouth, the nose, and the lung have been reviewed (144). Methods of absorption other than subcutaneous, such as nasal insulin, buccal insulin, rectal insulin, and insulin in enteric-coated capsules, are still experimental. A problem in nasal administration is still how to get a daily reproducible dose (145). The frequency of hypoglycemia is comparable to the frequency with subcutaneous insulin (146). Nasal irritation, sometimes with congestion, and dyspnea (147) can occur. Pulmonary insulin, delivered by aerosol inhalation, is another experimental method. No lung obstruction was reported, but the uptake varied considerably (148).

Insulin syringes

Disposable syringes can release silicon particles into the insulin vials, reducing the effectiveness of insulin (149). This can happen when insulin is injected back into the vial, during correction for the desired dose, and is specifically seen when low doses are used for long periods. Flocculation of insulin, found before the expiry date, may be related to this problem (SEDA-12, 360).

Insulin pens

Insulin pens are being increasingly used for intensive insulin therapy. For low doses, pens are more accurate than syringes (150). In 48 children and adolescents pen devices were more accurate than syringes when under 5 U of insulin had to be injected; for higher doses pens and syringes were comparable (151).

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Long-acting isophane insulin in pens can be insufficiently resuspended before an injection, resulting in a great variation in the dose of insulin per injection; in one study isophane content ranged from 5 to 214% (151). Only 10% of 109 patients tipped and rolled the pen more than 10 times. There was no relation between inadequate suspension and the number of attacks of hypoglycemia. It was mechanically proven that 20 cycles are necessary for good suspension. After education, suspension errors were less common in 80% of the patients. They had fewer attacks of hypoglycemia, but HbA_{1c} did not change.

A warning has been given that over 0.3 μl of blood (and viruses) can reflux in insulin cartridges in pen-like injectors. Reflux was measured using a rubber tube containing a dye solution. A questionnaire study in 193 patients using cartridges showed that 20 patients sometimes noted a reddish cartridge and that two patients shared their cartridges with other patients (152).

After injecting insulin, the pen has to be kept in place for some time. Many pens leak from the tip of the needle when the pen is removed from the injection site 7 seconds after the injection is finished. In one study only the Novopen 1.5 ml and Novolet 1.5 ml showed no leakage; eight of twenty 3 ml BD pens and Novo pens, 16 of 20 Novolets 3 ml and 19 of 20 Saline pens 3 ml (Lilly) leaked 4.0, 4.7, 5.9, and 9.2 mg respectively (153). It is necessary to keep the needle in place for 10–30 seconds after injection. Measured by ultrasonography, 86% of injections with needles of 12.7 mm and 38% of injections with needles of 8 mm in diabetic children with a BMI below the 60 percentile were intramuscular instead of subcutaneous (154). The injection changed from intramuscular to subcutaneous in half of the injections in the arm and in two-thirds of injections in the thigh when 8 mm needles were used. Nowadays, 6 mm needles are available in many countries.

In general, intensive therapy produces lower blood glucose concentrations and HbA_{1c} concentrations. This may result in worsening of proliferative retinopathy (155), or weight gain M14.42.9]. Pens can develop inaccuracies in rare instances, which may be unnoticed by the patient (156). Clogging of the system is often the cause. The result is diabetic coma or ketoacidosis, but this is not more frequent than with other systems. When needles are not regularly renewed, infections may emerge.

Insulin pumps

The usefulness of devices for constant subcutaneous, intravenous, or intraperitoneal insulin administration is well established. To establish feedback systems reliable, constantly functioning insulin sensors are essential, but they have been in a developmental phase for more than 25 years, and no long-acting glucose sensors for non-experimental use are yet available (157). Experience with pumps in large groups of patients has been reported (158–160). When starting intensive therapy, temporary worsening of secondary complications, mostly retinopathy, but sometimes nephropathy, has been reported (SEDA-14, 374). Weight gain is also a complication. The major candidates for insulin pump therapy include patients with type 1 diabetes, pregnant women, some types of brittle diabetics, patients wanting to become pregnant, and children.

Most pumps deliver insulin subcutaneously. Implantable pumps delivering insulin intraperitoneally with remote control devices are increasingly used (161,162). Pumps provide signals to alert users to malfunction, but leakage of connections often does not activate the alarm. Since the patient has no natural reserve of insulin, breakdown of the pump, leakage, or intercurrent infection without adjustment of the dose rapidly leads to ketoacidosis. The sudden release of insulin from a "runaway" pump is an exceptional event. Hypoglycemic deaths, infections (for example with *Mycobacterium fortuitum*) (163), local allergic reactions and infections, thrombosis in intravenous systems, allergy to nickel in needles (164), skin infections (165), needle breakage (SEDA-13, 382), problems with bad batteries, breakdown of the pump, leakage in delivery systems, or wrong insertion of the needle have all been described (SEDA-7, 405) (166). Pumps with sealed reservoirs (waterproof) can expel more insulin when used at high altitudes (skiing, mountaineering, pressurized cabins in airplanes) inducing serious hypoglycemia (SEDA-16, 486) (167); adapters that allow pressure equilibrium obviate this. Pumps that deliver insulin intravenously are almost obsolete, since they can cause thrombosis, vasculitis, and septicemia.

Efficacy

Continuous subcutaneous insulin infusion has been reviewed (168,169). Probably more than 100 000 patients in the USA are using it. Some studies have shown no difference in mean glucose concentration or HbA_{1c} compared with intensive treatment, but most have shown a slight difference favoring continuous subcutaneous infusion. With fast-acting analogues the postprandial glucose peaks are lower. In one study, when insulin delivery was intentionally interrupted, the increase in glucose concentrations or the development of ketonuria was later with regular insulin, but in another study there was no difference in the development of hyperglycemia or beta-hydroxybutyric acid between fast-acting analogues and regular insulin. Patients preferred to continue treatment with pumps.

Insulin delivery by a pump may be superior to glargine insulin. Continuous subcutaneous insulin infusion was compared with intensive therapy with insulin glargine plus insulin lispro in 19 patients (170). The patients who received insulin glargine were exposed to glucose concentrations under 3.9 mmol/l overnight for three times as long as those who used continuous subcutaneous insulin infusion.

In a meta-analysis of the metabolic and psychosocial impact of pumps, 52 studies were found; 22 were published before 1987 and 13 after 1993, the year in which the results of the DCCT were published (171). The authors stated that therefore conclusions about efficacy are not definitive. All pump malfunctions were reported before 1988. All types of changes were reported when the frequency and severity of hypoglycemia were compared with prepump times. Infection and skin irritation were expressed in different ways in the various studies. The risk of diabetic ketoacidosis fell after 1993. Most users preferred to continue pump treatment, mainly because of more flexibility, greater freedom, and improved glycemic control.

When continuous subcutaneous insulin infusion and sulfonylureas were compared in nine normolipidemic

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patients with type 2 diabetes, HbA_{1c} was not different but triglycerides and small LDL particles were reduced by the continuous infusion (172).

Continuous subcutaneous insulin infusion treatment is feasible in obese patients (BMI over 30 kg/m^2) with type 2 diabetes and severe insulin resistance, as has been shown in a study in 10 patients over 40 weeks (173). HbA_{1c} improved from 12 to 9.6% and weight was reduced by 2.5 kg. There were no adverse effects.

Use in children

In a randomized, crossover study in 10 children aged 7–10 years who used subcutaneous insulin pumps only in the evening and at nighttime, fasting, and 0300 hours, concentrations of blood glucose and fructosamine were improved (174). There was a better quality of life and a reduced fear of hypoglycemia. Children of this age may not be capable of handling a pump during the day.

In 95 patients aged 4–18 years with a median follow-up of 28 months, continuous subcutaneous insulin infusion produced no change in medical complications (diabetic ketoacidosis, visit to the emergency department), but there was a reduction in the number of episodes of hypoglycemia (175). HbA_{1c} was significantly lower than pre-pump values, but gradually increased in the first year and then remained stable.

In 118 children aged 1.5–18 years treated with continuous subcutaneous insulin infusion, HbA_{1c} in preschool children fell from 7.1 to 6.5%, in school children from 7.8 to 7.3%, and in adolescents from 8.1 to 7.4% (176). Daily insulin consumption did not increase and the frequency of severe episodes of hypoglycemia fell.

General adverse effects

Continuous intraperitoneal insulin infusion with implantable pumps has been assessed in 34 patients with poorly controlled diabetes (177). In two patients, the pump was explanted: in one patient with Werner's syndrome (no subcutaneous fat) the pump was explanted because of infection in the pocket, and one pump was explanted because the patient had local complaints and psychological problems. One patient refused to be included. Patients were followed for 58 months. HbA_{1c} fell from 10.0 to 9.0% in the first year and remained there. Median days in hospital fell from 45 to 13 after 1 year. The quality of life was relatively low and many had psychiatric problems. Although long-term glycemic control improved and lengths of hospital stay were reduced, normal glucose control and normal quality of life could not be achieved.

Local adverse effects

Implantable insulin infusion pumps have been reviewed (178,179), as has the use of pumps in children (180). In 31 centers, 914 pumps were implanted, representing 2121 patient-years. Some commonly reported pump complications were (178):

- hematoma or seroma, usually resolved by needle aspiration;
- pump migration, the frequency lessening with experience; surgical intervention is necessary;
- rare pump pocket infections; the causes were difficult to determine, but in two patients, coagulase-negative staphylococci were found, suggesting contamination with skin flora during refill;
- progressive thinning of the skin, 1–30 months after implantation in 2 per 100 patient-years; pain and skin erosion often followed; the cause is unclear; only a correlation with physical activity could be found.

Catheter malfunction was the most frequent event (obstruction, total occlusion, and peritoneal adhesions: 13, 10, and 3.1 events per 100 patient-years respectively). Flushing sometimes prevented occlusion. Better tip design had a big effect. Adhesion formation decreased with daily injections of heparin. The frequency of ketoacidosis was comparable to that reported with continuous subcutaneous insulin infusion and was usually related to catheter obstruction. It diminished during the review period. Episodes of severe hypoglycemia were fewer than during intensive subcutaneous therapy.

The tendency of insulin molecules to aggregate in concentrated solutions sometimes requires specific insulin or insulin lispro for pumps. There is a difference of opinion about whether insulin absorption kinetics change (improve) during placement of the catheter (SEDA-16, 488) (SEDA-18, 412). Changing the injection site and renewing the infusion system every 2–4 days is important in preventing clogging, local allergy, and infection at the insertion site.

In implanted pumps, catheters for continuous intraperitoneal insulin infusion can be obstructed by deposits of fibrin on the catheter tip. They mostly reappear after the plug is blown out, necessitating replacement (181). Hematoma, skin erosions, infections (182), pain, pump migration, and pocket complications are not rare (SEDA-20, 397) (183). Erosion of the cecum, mimicking appendicitis, is reported (184). During the start of pump therapy, some patients feel as if they are constantly hypoglycemic, even though low blood glucose concentrations cannot be objectified.

There was no macrophage activation in 10 patients with obstructed ($n = 3$) or non-obstructed ($n = 7$) catheters in implantable pumps (185).

When insulin delivery stops during continuous subcutaneous insulin infusion, ketoacidosis can develop rapidly, but it can be easily corrected if ketoacidosis has developed recently, although exceptions occur (186).

- A 32-year-old woman with well-regulated diabetes, using about 35 U/day of insulin by continuous subcutaneous infusion, tried a sauna for the first time when her blood glucose was 7 mmol/l. She stayed for about 45 minutes and the temperature reached 70°C for 10 minutes. The blood glucose concentration rose to 11 and 17 mmol/l, despite a bolus of insulin 6 units. She felt sick and vomited during the night; the next morning her blood glucose was 21 mmol/l and she had ketonuria, abdominal cramps, and extreme fatigue. Insulin 25 units by pump produced no improvement, but after opening a new vial, the situation improved; within 6 hours she was normoglycemic, and her ketonuria disappeared within 16 hours.

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It is not clear in this case whether insulin had formed aggregates and fibrils due to the high temperature or if the action of counter-regulatory hormones induced by hyperthermia was increased, or both.

Problems with insulin delivery in implanted pumps are difficult to correct. A change in Hoechst 21 pH-neutral semisynthetic insulin 400 U/ml in accordance with regulations of the European Pharmacopoeia (SEDA-20, 397) resulted in more frequent clogging when this insulin was used in the Minimed 2001 implantable pump (MIP 2001). From October 1995 to October 1996, 17 pumps were implanted (187). The refilling period was reduced from 90 to 30–45 days and the reservoirs were washed with insulin-free buffer before each refill. Backflow was seen in 13 pumps after a mean period of 7.2 months. Modification of the manufacturing process produced 21PH ETP insulin (human semisynthetic insulin, Genapol-stabilized) 400 U/ml, Hoechst, with improved stability since July 1997. All pumps were specifically cleaned before the new insulin was used for refill. The refill period was increased from 38 to 78 days. In 16 pumps, only one backflow was seen after 14 months. The incidence of catheter blockage did not change. The better stability of this insulin for implantable pumps has been confirmed in a study in which 88 pumps were refilled every 45 days and 108 pumps every 90 days (188).

Pump failure

Almost all pumps are programmable and pump failure is rare (2 per 100 patient-years) (178).

Risk of hypoglycemia

Continuous subcutaneous insulin infusion in 75 youths aged 12–20 years has been compared with multiple daily injections over 12 months (189). HbA_{1c} was lower, and the number of attacks of hypoglycemia in the pump group was 50% less. Ketoacidosis seldom occurred: once during intensive therapy and twice during pump therapy. Weight increased more during pump treatment. Coping with diabetes was less difficult with pump therapy.

In 103 patients who used continuous subcutaneous insulin infusion for 2 years, the incidence of severe hypoglycemia fell from 0.70 cases/patient/year before treatment to 0.06 cases/patient/year during treatment, and HbA_{1c} improved from 7.7 to 7.2% (190). The incidence of abscesses was 0.1 cases/patient/year and of ketoacidosis 0.01 cases/patient/year. The patients with HbA_{1c} concentrations above 8.5% had a higher incidence of serious hypoglycemia and abscesses. Quality of life assessments showed great improvements. The reasons for continuous subcutaneous insulin infusion were optimization of metabolic control, greater flexibility, or prevention of severe hypoglycemia.

In 138 patients treated with continuous subcutaneous insulin infusion for 7 years, there was a fall in the incidence of episodes of serious hypoglycemia (from 0.31 to 0.09 cases/patient/year) and ketoacidosis (from 0.41 to 0.11 cases/patient/year); the number of infections was unchanged (0.2 infections/patient/year) (191).

When continuous subcutaneous insulin infusion was instituted in patients with long-standing poor glycemic control during a crossover study in 79 patients for 32 weeks, 17 dropped out after the first crossover, making it impossible to use the second arm. HbA_{1c} and quality of life both improved. There were more episodes of mild hypoglycemia with continuous subcutaneous insulin infusion (192). The authors of an editorial concluded that continuous subcutaneous insulin infusion can anticipate changes in insulin need, which is important for diabetics with a variable lifestyle or an exaggerated dawn phenomenon (193). For a large group the increase in cost and the hassle of continuous subcutaneous insulin infusion do not offset that, and multiple daily injections with glargine as basal insulin (see below) can be equally effective.

Continuous subcutaneous insulin infusion was found to be feasible in 56 children and adolescents (aged 7–23 years) (194). HbA_{1c} improved in 36 and deteriorated in 6. The rate of severe attacks of hypoglycemia fell, but not significantly. Hypoglycemia and seizure frequency were less overall in the group, with better HbA_{1c} concentrations. One patient had a catheter infection and was treated with local antibiotics and a new infusion system at another site.

Suitable types of insulin

Short-acting neutral buffered insulin by pump is sometimes ineffective. Treatment with non-buffered insulin can make things worse, but short-acting acidified insulin can improve HbA_{1c}. This type of insulin is well tolerated for over 3 years. The acid insulin may contain more monomers than neutral insulin, which may act less rapidly, as it contains more polymers (195).

Insulin lispro is sometimes less beneficial in continuous subcutaneous insulin infusion (196).

- A 58-year-old man with diabetes and unawareness of hypoglycemia had 53 emergency hospital admissions in 2 years before he started regular continuous subcutaneous insulin infusion. His attacks of hypoglycemia were reduced to one every 2–3 weeks. His mean blood glucose was 7.0 mmol/l. When insulin lispro was introduced in the pump he had an attack every 2–3 days for 68 days and hospital admission was required seven times. The mean blood glucose was 6.3 mmol/l. After he used soluble insulin instead of insulin lispro, the number of attacks of hypoglycemia fell substantially. The mean blood glucose was 6.4 mmol/l.

It may be that the more rapid diffusion and absorption of insulin lispro in diabetics who achieve tight metabolic control and have hypoglycemia unawareness destabilizes glycemic control.

Continuous subcutaneous insulin infusion with insulin lispro has been reported to give variable control (197).

- A 12-year-old boy with type 1 diabetes had problems with insulin lispro in his pump. After multiple daily injections, he started continuous subcutaneous insulin infusion with insulin lispro and could freely adjust his eating schedule; he had fewer episodes of hypoglycemia and his HbA_{1c} was 5.4%. Later, he developed a pattern of variable responsiveness to insulin, starting with increased responsiveness on the day on which he changed his subcutaneous needle, followed by reduced sensitivity and hyperglycemia on the third day. The infusion site was changed and Velosulin was added to insulin lispro, making it possible for him to use his injection site for 3 days

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consistently; the HbA_{1c} was 7.2%. After 2.5 years he started using insulin aspart. It then became possible to change the infusion site every 4–5 days, when the cartridge was empty. The HbA_{1c} fell to 6.2%.

Continuous subcutaneous insulin infusion has been compared with short-acting insulins plus glargine or isophane as long-acting insulins for 1 year in 32 patients with poor control (198). Four of them had serious attacks of hypoglycemia. There were no differences in HbA_{1c} or other metabolic parameters (including lipids). In those treated with continuous subcutaneous insulin infusion, the reduction in the amount of insulin required was larger.

Hoechst 21 pH-neutral insulin in intraperitoneal pumps increases the production of antibodies to insulin, in contrast to the same insulin in subcutaneous pumps (199). It is not clear whether the intraperitoneal route or modification of insulin during storage in the implanted reservoir causes greater antigenicity. When a newly designed side-port catheter on the Minimed pump was used in 40 patients for 450 days per patient, there was one catheter encapsulation, one clogging, and six cases of catheter/pump related underdelivery (200). This was comparable to the position before 1994, when the formula of the Hoechst 21 pH-neutral insulin was changed for the first time.

Other devices

Other devices, such as long-term subcutaneous catheters (201,202), which have to be renewed every 4 days (203), or intraperitoneal catheters (204) for pumps, pose the same types of problems as subcutaneous catheters for pumps, except that the catheters are indwelling for longer periods. The jet-stream injector, introduced as an alternative for people who are afraid of injections, has given problems with delayed pain and bleeding. The advantages of these methods are questionable.

Oral administration

Metabolism of insulin and the lack of a specific carrier to transport insulin through the gut made the oral route impossible (144).

Inhaled insulin

In the lungs, insulin has to be absorbed from the alveoli (144). Enhancers to give the particles the right size and constituency to reach the alveoli improve systemic availability (205). The relative potency of inhaled insulin is about 10%, which means that a 10-fold increase in dose is necessary. The effects of inhaled insulin are comparable to those of injected regular or fast-acting insulins or even faster. However, it is difficult to get a good action profile. The anatomy of the pharynx affects the transport of the particles. In smokers, the permeability of the lung epithelium is much greater and absorption from the alveoli is faster and higher than in non-smokers; during actual smoking, uptake is reduced. In the short term the excipients in the sprays have no adverse effects. More participants in a study of inhaled human insulin were satisfied with inhaled insulin than they were with subcutaneous insulin (206).

Ten severely hyperglycemic patients with type 2 diabetes taking oral agents were treated at random with two injections of isophane daily or with lyophilized nasal insulin before each meal, with an added injection of subcutaneous isophane when necessary (207). The periods were separated by 2 months. Nasal insulin produced control of diabetes comparable to isophane, except in three patients. Adverse effects included transient pruritus, sneezing and rhinorrhea, and chronic nasal crusts. One patient was withdrawn because of cough and dizziness after each nasal dose.

Inhaled insulin has been studied in 72 patients in an open, parallel-group, randomized trial for 12 weeks; 35 used inhaled insulin (152). The inhaled insulin was given three times before meals with isophane insulin at bedtime. Controls used their regular insulin two or three times a day with a long-acting insulin at bedtime. HbA_{1c} did not differ between the groups and there was no difference in the frequency or severity of attacks of hypoglycemia. Pulmonary function tests were stable and showed no differences between the groups. There were no serious or major adverse effects.

The dose of inhaled insulin is about 10 times higher than the subcutaneous dose that produces the same hypoglycemic effect. In an open, randomized, crossover study subcutaneous insulin was compared with a 10 times higher dose of inhaled insulin in 15 non-smoking patients with type 2 diabetes (208). The peak action of inhaled insulin was earlier. Apart from that, the effects were similar. There were no differences in FEV_1 at baseline or at 4 or 8 hours after treatment. Absorption of inhaled insulin is significantly higher in smokers (209). In non-diabetics, absorption is reduced in asthma (210). Inhaled insulin may increase the titer of insulin antibodies (211).

Nasal administration

Insulin is rapidly absorbed after nasal administration, but even with absorption enhancers its systemic availability is low and its metabolic effect very short (144).

Gelified nasal insulin has been compared with twice daily isophane insulin and three times daily subcutaneous regular insulin in 16 patients with type 1 diabetes (207). Three patients had to withdraw because of nasal burning and one because of persistent sinusitis. One patient had purulent sinusitis after 6 months. The efficacy of gelified insulin was comparable to that of regular insulin.

Transdermal administration

Application to the skin, a highly efficient general barrier, did not result in sufficient and reproducible absorption (144).

Drug overdose

- Insulin overdose has been reported in patients without diabetes (212) and in a 25-year-old man with Munchausen's syndrome (213).
- Suicide by insulin has been reported in a 68-year-old, non-diabetic physician who had also taken metoprolol and alcohol. The blood metoprolol concentration was 0.4 microgram/ml (usual target range 0.035–0.5 microgram/ml) and alcohol 122 mg/dl (27 mmol/l). C-peptide could not be detected, serum insulin was 1849 μU/ml (normal fasting concentration below 16 μU/ml) (214).

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Hypokalemia, hypophosphatemia, and hypomagnesemia can occur after insulin overdose (215).

- A 47-year-old man with type 2 diabetes attempted suicide by taking a bottle of wine, triazolam 2 mg, zoplicone 75 mg, and subcutaneous insulin (soluble 300 U and isophane 1800 U). His blood glucose was 1.5 mmol/l, potassium 2.4 mmol/l, phosphate 0.74 mmol/l, and magnesium 1.06 mmol/l. After 80 ml of 50% glucose and gastric lavage he needed a glucose infusion 6.6 mg/kg/minute for 24 hours to keep his blood glucose at 5.5–11.1 mmol/l. There was no brain damage on neurological examination or CT scan.

Acute liver damage has been attributed to insulin overdose followed by excessive glucose administration (79).

- In a suicide attempt, a 48-year-old woman took clomipramine 225 mg, diazepam 50 mg, oxazepam 150 mg, flurazepam 120 mg, and aspirin 10 g and injected insulin subcutaneously (1000 U short-acting and 1000 U long-acting). Her blood glucose was undetectable. She was intubated and given 40% glucose 20 ml and an infusion of 20% glucose (total 100 g over 2 hours). She continued to receive intravenous glucose 40% with potassium chloride for 36 hours (total 4430 g) in spite of high glucose concentrations. Her aspartate and alanine transaminase activities rose to 420 and 610 U/l respectively, the total bilirubin to 147 μmol/l (mainly unconjugated), the alkaline phosphatase to 178 U/l, and the serum lactate to 6.8 mmol/l. An ultrasound scan of the liver was normal. When the glucose infusion was stopped, everything normalized rapidly.

Acute steatosis of the liver may have explained this presentation. In insulin overdose, the combination of greatly increased hepatic production of triglycerides from glucose and reduced production of apolipoprotein B 100 results in an insufficient increase in the transport of triglycerides in VLDL particles from liver to muscle and adipose tissue and contributes to the steatosis.

Drug–Drug Interactions

ACE inhibitors

Whether ACE inhibitors aggravate or generate hypoglycemia is debated (216). In a case-control study of 404 cases and 1375 controls, the risk of hypoglycemia was 5.5 times greater (95% CI = 4.0, 7.6) in insulin versus sulfonylurea users and was not influenced by use of ACE inhibitors overall (217). However, the use of enalapril was associated with an increased risk of hypoglycemia (OR = 2.4; 95% CI = 1.1, 5.3).

Beta-blockers

Beta-blockers have various effects on glucose metabolism, but these are usually too small to be of clinical significance (217,218). However, beta-blockers can block the adrenergic symptoms of hypoglycemia.

- A 68-year-old woman with diabetes and hypertension using 42 units of isophane insulin and propranolol 20 mg qds died with a blood glucose concentration below 1.4 mmol/l without any symptoms of hypoglycemia (219).

Clozapine

Severe insulin resistance with ketoacidosis (pH 6.9) has been reported with clozapine (220). After withdrawal, insulin requirements fell. Reinstitution of clozapine induced an identical increase in insulin need.

Glucocorticoids

Glucocorticoids are counter-regulatory and can cause increased insulin requirements. Conversely, reducing the dose of a glucocorticoid, without changing the dosage of insulin, can cause hypoglycemia.

Maprotiline

- Maprotiline, a tetracyclic antidepressant, repeatedly induced hypoglycemia in a 39-year-old woman with type 1 diabetes, even when the insulin dosage was reduced from 20 U/day to 4–10 U/day. Maprotiline seems to prolong the half-life of insulin. A glucagon stimulation test showed a maximum C-peptide concentration of only 0.22 nmol/l (221).

Olanzapine

Olanzapine has been reported to have precipitated diabetes (222).

- A 31-year-old man with a treatment-refractory psychiatric disorder without prior diabetes was given olanzapine 10 mg/day. After 3 months he developed hyperglycemia and an acidosis (pH 7.11). After treatment he needed at least 64 U/day of insulin, but 15 days after stopping olanzapine his insulin requirements fell and 15 days later insulin was withdrawn.

Interference with Diagnostic Tests

Blood glucose measurement

Three diabetic patients on chronic ambulatory peritoneal dialysis (CAPD) had symptoms of hypoglycemia when glucose readings on strips were higher than 4 mmol/l (223). Venous testing showed glucose concentrations as low as 1.8 mmol/l. Large amounts of glucose are used in CAPD, which not only affects the regulation of diabetes but can also affect the peritoneal wall. Since 1999, icodextrin has been used in dialysis fluids. Icodextrin is glucose-free and reduces the need for insulin. However, it is also absorbed systematically and can be metabolized to maltose and maltotriose. Paper systems that use either glucose oxidase or glucose dehydrogenase overestimate glucose readings when icodextrin is used, and patients and their carers are not able to measure low blood glucose concentrations. Another factor is that during end-stage renal insufficiency, insulin catabolism is reduced. This contributes to the problems when CAPD is changed to automated (overnight) peritoneal dialysis, in which daytime hypoglycemia can be prevented by reducing the amount of insulin used during the day.

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Monitoring Therapy

Frequent self-control by pricking the fingertips can cause anemia (224) or pyoderma gangrenosum and fingertip ulceration (225).

Problems with the use of blood glucose measurement systems are reported from time to time. For example, it is easy to read glucose meters wrongly (SEDA-25, 508). Hypoglycemia was missed when a patient inadvertently switched the glucose meter from mmol/l to mg/dl and read 266 mg/dl as 26.6 mmol/l and 158 mg/dl as 15.8 mmol/l (226).

- An 89-year-old man wrongly read the glucose concentrations in his home glucose meter (227). The meter read 561 mg/dl and 591 mg/dl but testing in the clinic 2 hours later showed concentrations of 175 mg/dl and 188 mg/dl. He had read the digital display upside down: 591 instead of 165 and 561 instead of 195.

Patients should be instructed about the correct orientation of digital meters.

In Raynaud's phenomenon, blood glucose concentrations measured by finger prick are often lower than the real values (50). The arm reacts more slowly to rapid changes in glucose concentrations. When glucose is monitored in the arm, changes in glucose concentrations are later seen than when monitored by finger prick (228). Rubbing the arm reduces the differences (229).

The development of glucose sensor systems has been reviewed (230). An automated device for sampling in the arm (231) and a microdialysis-based glucose sensor system (232) have been developed.

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Insulin aspart

See also Insulin

General Information

Insulin aspart is a rapid-acting synthetic insulin in which proline is replaced by aspartate at position 28 in the B chain. Insulin aspart has been reviewed (1). Its adverse effects do not differ from those of soluble human insulin and it has a similar effect on the blood glucose concentration (2).

A new development is the binding of two 9-fluorenylmethoxy-carbonyl moieties to two amino acids in the structure of aspart insulin, phenylalanine and lysine (3). This compound has no biological activity but gradually releases its groups and keeps diabetic animals in a good metabolic state over 2–3 days. Experiments in humans have not yet been reported.

Aspart insulin and biphasic insulin aspart (30% soluble rapid-acting insulin and 70% protamine-bound aspart insulin) have been reviewed (4).

Comparative studies

In a double-blind, crossover study of insulin aspart or soluble human insulin before meals and protamine zinc insulin before bedtime, 90 of 104 patients with type 1 diabetes completed the trial (5). Insulin aspart improved postprandial control by reducing hyperglycemic and hypoglycemic variations, but night-time control was inferior. There were 547 hypoglycemic episodes in the aspart period compared with 615 in the regular insulin period (no significant difference). However, there were only 20 major hypoglycemic events in 16 patients using aspart versus 44 events in 24 patients using human insulin. One patient was withdrawn with fatigue and anorexia during aspart. Convulsions during hypoglycemia occurred once in each group.

Insulin aspart had an increased maximal effect compared with regular insulin in euglycemic clamps in nondiabetics (6).

In an open comparison of insulin aspart and regular human insulin for 6 months in 882 patients with type 1 diabetes and extended to 714 patients for another 6 months, postprandial glucose concentrations were lower with insulin aspart (7). HbA_{1c} was slightly but significantly lower (7.78 versus 7.93%). There were no differences in hypoglycemic periods or adverse events.

Insulin aspart has been compared with regular insulin in 1065 patients for 26 weeks (8). HbA_{1c} improved significantly with aspart. The number of major attacks of hypoglycemia fell in the aspart group from 11 to 8%; there were no other differences.

Insulin aspart has been compared with buffered regular insulin by continuous subcutaneous infusion (9). There was some crystal formation with both formulations, but less with insulin aspart. Patients who used aspart required a slightly higher basal dose of insulin but had fewer unexplained attacks of hypoglycemia.

Frequent addition of isophane to a regimen of insulin aspart is unnecessary, as has been shown in a multicenter, multinational, randomized, open study in 368 patients

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followed for 64 weeks (10). Frequent addition of isophane up to four times daily to insulin aspart did not improve HbA_{1c} or change the number of episodes of hypoglycemia compared with regular insulin combined with isophane. Only postprandial blood glucose concentrations were reduced.

When insulin lispro and insulin aspart were compared in a single-blind, randomized, crossover study in 14 patients with type 1 diabetes, insulin lispro had a faster onset of action but a shorter duration (11). However, in another study the pharmacokinetic and the pharmacodynamic profiles of insulin aspart compared with human insulin were the same in 24 healthy Japanese as in non-Japanese (12). Insulin aspart and insulin lispro were equally effective in another 24 patients with type 1 diabetes (13).

Combination with long-acting insulin

In a multinational study for 6 months in 448 patients with type 1 diabetes, two-thirds were given the long-acting insulin detemir and one-third received isophane, both in addition to premeal rapid-acting insulin aspart (14). HbA_{1c} concentrations were comparable, but in the detemir group the risk of hypoglycemia was 22% less and the risk of nocturnal hypoglycemia was 34% lower. There were two cases of severe hypoglycemia with detemir and one with isophane. Three patients who used detemir developed reactions at the injection site (pain, myalgia, redness, or lipodystrophy) compared with one who used isophane (itching). One potentially allergic reaction was possibly related to detemir.

The new, short-acting insulins can be bound to protamine, allowing the preparation of mixed formulations. In an open, randomized, single-dose, three-way, crossover trial biphasic insulin aspart 30 (30% aspart plus 70% protaminated aspart, BIAsp 30), biphasic insulin lispro 25 (25% lispro plus 75% protaminated lispro, Mix 25), and biphasic human insulin 30 (30% regular plus 70% isophane insulin, BHI 30) were compared in 45 patients (15). Biphasic insulin aspart improved postprandial control better. There were 23 episodes of hypoglycemia with BIAsp 30, 19 with Mix 25, and 11 with BHI 30; two episodes with BIAsp 30, five with Mix 25, and two with BHI 30 required third-party intervention.

When 30% insulin aspart plus 70% protamine aspart was compared with the same mixture of regular plus isophane insulins, both injected twice-daily for 12 weeks, in 294 patients with type 1 and type 2 diabetes, control was better with the aspart mixture (16). There were fewer episodes of major hypoglycemia (20 versus 42) but the same number of minor episodes (362) with aspart.

Placebo-controlled studies

In a double-blind, crossover study with insulin aspart and human insulin in type 1 diabetes, human insulin was given 30 minutes before a meal with placebo immediately before the meal, or placebo was given 30 minutes before the meal with aspart insulin or human insulin immediately before the meal (17). On average, insulin aspart was absorbed twice as fast as human insulin. Postprandial glucose control improved on aspart. There were no episodes of serious hypoglycemia.

Organs and Systems

Immunologic

When short-acting insulins are given to patients who are allergic to regular insulin the allergic reactions can disappear. Although the short-acting insulins often have the same immunogenic epitopes, rapid dissociation of the fast-acting insulins into monomers can reduce their antigenic effects. Insulin lispro is known to be beneficial, and this has also been reported for aspart insulin (18).

- A 45-year-old man with type 2 diabetes treated with glibenclamide and metformin received combined chemotherapy for non-Hodgkin's lymphoma and was given premixed insulin. He developed local wheal-and-flare reactions immediately after the injections. Skin prick tests were positive for various types of insulin but weakly positive for lispro and negative for insulin aspart. He tolerated aspart insulin without any allergic reactions.

A few patients treated with insulin aspart developed antibodies, which cross-reacted with antibodies against human insulin and fell after 3 months (19). In lipodystrophy with lipoatrophic diabetes high insulin resistance is often found, for which leptin deficiency is one contributory factor.

Allergic reactions have been described with insulin aspart.

- A 53-year-old woman had type 2 diabetes that was not well controlled with diet and oral hypoglycemic drugs (20). She took intermediate-acting insulins, and after 2 months noticed redness and itching at injection sites. When she used insulin aspart and insulin lispro successively, the local reactions continued. She had a high serum concentration of total IgE (748 IU/ml; reference range below 400) and insulin-specific IgE (20 IU/ml; reference range below 0.34), positive insulin antibodies, and positive prick tests for insulin lispro, insulin aspart, human insulin, porcine insulin, and protamine. With intensive nutrition therapy and oral drugs her HbA_{1c} fell to 5.5%.
- A 29-year-old woman with raised insulin concentrations during therapy had lipodystrophy and high insulin antibody titers with high binding capacity and high affinity (21).

Insulin antibodies are rarely found in patients with lipodystrophy.

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Insulin detemir

See also Insulin

General Information

Insulin detemir is a long-acting insulin analogue that lacks threonine at the B30 position and is acylated with a 14-carbon myristoyl fatty acid side-chain at the epsilon-amino group of the lysine in the B28 position. This stimulates binding to albumin and increases the half-life, extending its duration of action.

Comparative studies

In healthy volunteers, there was a dose-related increase in blood insulin concentrations after the administration of insulin detemir (1). However, there was no clear dose-response metabolic effect and individual variability was high.

Insulin detemir has been compared with protamine zinc insulin in 59 patients with type 1 diabetes (2). All used insulin detemir for 6 weeks and protamine zinc insulin for 6 weeks in a randomized order. About 2.35 times higher doses of detemir were necessary than protamine zinc insulin. Fasting blood glucose concentrations were lower at the end of the detemir period and there were fewer attacks of hypoglycemia.

In a 6-month, multinational, open, parallel-group comparison of insulin detemir and protamine zinc insulin in 448 patients with type 1 diabetes, the two treatments produced comparable HbA_{1c} concentrations and fasting plasma glucose concentrations with less within-subject variation in fasting blood glucose with insulin detemir (3). The risk of hypoglycemia was 22% lower with insulin detemir and 34% lower for nocturnal hypoglycemia.

Combination with short-acting insulin

In a multinational study for 6 months in 448 patients with type 1 diabetes, two-thirds were given insulin detemir and one-third received isophane, both in addition to premeal rapid-acting insulin aspart (3). HbA_{1c} concentrations were comparable, but in the detemir group the risk of hypoglycemia was 22% less and the risk of nocturnal hypoglycemia was 34% lower. There were two cases of severe hypoglycemia with detemir and one with isophane. Three patients who used detemir developed reactions at the injection site (pain, myalgia, redness, or

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lipodystrophy) compared with one who used isophane (itching). One potentially allergic reaction was possibly related to detemir.

Organs and Systems

Immunologic

An unspecified allergic reaction to insulin detemir has been reported (3).

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Insulin glargine

See also Insulin

General Information

Insulin glargine is a new long-acting human insulin analogue, in which phenylalanine is removed from site 30 of the C terminal of the B chain and two arginine molecules replace it, adding two positive charges; asparagine on site 21 of the A chain is replaced by the more stable glycine to avoid deamination. Older long-acting insulins, such as protamine zinc insulin and insulin zinc suspension (crystalline) (ultralente), had a maximal hypoglycemic effect after about 20 hours (in the middle of the night), and the glucose-lowering action then abated gradually. The newer analogues have a more constant profile of action (1–3).

The binding of insulin analogues to insulin and IGF-I receptors and their metabolic and mitogenic properties have been evaluated in vitro (4). In general the metabolic potencies correlated with insulin receptor binding and the mitogenic properties correlated with IGF-I receptor binding. The rapid-acting analogues resembled insulin, except that the binding of insulin lispro to the IGF-I receptor was slightly increased. Insulin glargine had a 6- to 8-fold greater affinity for IGF-I and mitogenic potency than human insulin (suggesting greater growth-stimulating potential). In insulin detemir the balance between the metabolic and mitogenic potency was not changed, but receptor affinity was reduced, which may explain its lower efficacy on a molar base in humans.

Insulin glargine has been reviewed (5,6). The general conclusion was that it is an effective long-acting insulin with no pronounced peaks of action. Patients using insulin glargine have a reduced risk of hypoglycemia. Insulin glargine, which is metabolically active for at least 24 hours, could have an overlapping effect after a second injection. However, there was no evidence of accumulation when insulin glargine, mean dose 24 U/day, was used in combination with insulin lispro for 11 days (7). In reaction to comments, and discussing whether fluctuations in insulin concentrations still occur during the administration of insulin glargine, the authors agreed that the dose should be constant for at least 2 days before a change is made. It is also not clear whether higher doses of insulin glargine could accumulate because of slower inactivation (8).

Comparative studies

The absorption of insulin glargine was delayed compared with protamine zinc insulin in a study using radioactive tracers (9).

In single-dose, double-blind, euglycemic clamp studies, insulin glargine had a smoother metabolic effect with a peakless profile of action starting at 2–4 hours and continuing over 24 hours than protamine zinc insulin, whose peak occurred at 4 hours and whose activity subsequently fell (10).

In a randomized, parallel-group study, there were fewer episodes of nocturnal and serious hypoglycemia when insulin glargine was compared with once- or twice-daily protamine zinc insulin (11,12). Other adverse reactions and reactions at the injection sites were identical.

Insulin glargine did not cause a peak in blood insulin concentration, compared with protamine zinc insulin and crystalline insulin zinc suspension (ultralente); the effect lasted 24 hours, almost comparable to continuous subcutaneous infusion of a short-acting insulin (13).

In general, one daily injection of insulin glargine gives more constant insulin concentrations and fewer nightly attacks of hypoglycemia than protamine zinc insulin. Treatment satisfaction was constantly better with insulin glargine in 517 patients (14). There was a consistent mean reduction in the perceived frequency of attacks of hypoglycemia. Other adverse effects were not mentioned.

- A 60-year-old man with type 2 diabetes received radiation therapy for a carcinoma of the esophagus and needed continuous enteric tube feeding (15). One daily injection of glargine controlled his diabetes well: his HbA_{1c} concentration was 6.1% and he had no episodes of hypoglycemia for almost 4 months. This made continuous infusion of a short-acting insulin unnecessary.

However, control can be inadequate with a once-daily injection.

- A 53-year-old man with type 1 diabetes needed tube feeding after a stroke and received glargine insulin once daily (16). He had marked hyperglycemia after 22 hours and when the dose was divided into two equal doses every 12 hours, the hyperglycemia was reduced.

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Insulin glargine and protamine zinc insulin have been compared in 349 children and adolescents in a multicenter, open, randomized study (17). Besides the usual thrice-daily regimen of regular insulin they took either insulin glargine at bedtime or protamine zinc insulin at bedtime or twice daily. HbA_{1c} did not differ. The target for fasting blood glucose was 4.4–8.8 mmol/l, and 5% more patients who used insulin glargine reached the target (44% compared with 39% of the patients who used protamine zinc insulin). Symptomatic hypoglycemia was similar with the two treatments.

Six children were treated with insulin glargine and six with protamine zinc insulin as the long-acting insulin component (18). After 3 months, unbound insulin concentrations were lower during the night with insulin glargine. There were three cases of hypoglycemia with protamine zinc insulin and one with insulin glargine.

Combination with short-acting insulin

Insulin glargine plus a short-acting insulin has been compared with isophane insulin for 4 weeks in a double-blind study in 256 patients with type 1 diabetes (19). The patients were all taking once- or twice-daily isophane insulin and continued to do so or switched to insulin glargine with added zinc 30 or 80 micrograms/ml at bedtime. The patients who used insulin glargine had more attacks of hypoglycemia at the start of the study than those who used isophane insulin, but this tended to equalize during the 4 weeks. Fasting plasma glucose was lower in those who used insulin glargine. HbA_{1c} concentrations were not reported.

The combinations insulin lispro + insulin glargine and regular + isophane have been compared in a randomized, crossover study for 32 weeks in 25 patients (20). HbA_{1c} was not different, but the total insulin dose was lower with insulin lispro + insulin glargine and there were fewer episodes of nocturnal hypoglycemia.

Organs and Systems

Metabolism

In 619 patients with type 1 diabetes treated with protamine zinc insulin and insulin lispro, randomized to once-daily insulin glargine or to once-daily or twice-daily protamine zinc insulin for 16 weeks in an open study, there was no difference in the frequency of hypoglycemic episodes, severe hypoglycemia, or HbA_{1c} (21). Fasting plasma glucose concentrations were lower with insulin glargine.

In 518 patients with type 2 diabetes using protamine zinc insulin, with or without short-acting insulin, randomized to insulin glargine or protamine zinc insulin, there was less nocturnal hypoglycemia with insulin glargine (22). HbA_{1c} and mild symptomatic hypoglycemia was the same in both groups.

In 426 patients with type 2 diabetes poorly controlled with oral therapy, randomized to protamine zinc insulin or insulin glargine, glucose concentrations after dinner were lower with insulin glargine and there were significantly fewer attacks of hypoglycemia (23). HbA_{1c} was 8.2 and 8.1% with insulin glargine and protamine zinc insulin respectively.

Immunologic

Insulin glargine solved a problem in a man with type 1 diabetes after pork, beef, and human insulins had elicited allergic reactions (24). Antihistamines ameliorated the reactions but did not resolve them. Insulin glargine elicited no reactions, even when regular insulin was given. This case suggests that the A chain, which is modified in insulin glargine, is part of the allergic epitope. Tolerance to insulin glargine appeared to suppress allergy to regular insulin.

Drug Administration

Drug formulations

In contrast to most medium- and long-acting formulations, insulin glargine is a clear solution. In two cases, patients gave themselves rapid-acting insulin instead of glargine.

- A 25-year-old woman and a 52-year-old woman injected lispro instead of insulin glargine (25). The first realized her mistake and managed to prevent severe hypoglycemia by eating continuously, despite a fall in blood glucose to 3.7 mmol/l. The other had a blood glucose of 3.1 mmol/l and recovered after intravenous dextrose.

Four other mistakes have been reported (26,27). The authors advised the use of pens for injection of short-acting insulins, as all the mistakes were made by patients who used vials and syringes to administer both types of insulin.

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Insulin lispro

See also Insulin

General Information

Insulin lispro induces more rapid and constant release of insulin from the injection site, since it consists of monomeric insulin. The change of one or more amino acids in the insulin molecule prevents insulin from forming dimers or hexamers. More rapid absorption, rapid availability, and rapid inactivation make the action better than that of endogenously secreted insulin. When the interval between meals is long, the premeal blood glucose concentration increases rapidly.

After the administration of insulin lispro it is not necessary to delay a meal until sufficient insulin is absorbed. Insulin lispro can be given immediately before or during a meal and can be used when rapid action is important, as in outpatient treatment of ketonuria (1) or in continuous subcutaneous insulin infusion (2). Insulin lispro can be successful in patients with subcutaneous insulin resistance (3).

Observational studies

During Ramadan, insulin lispro reduced the number of attacks of hypoglycemia and reduced postprandial blood glucose (4). It also reduced post-snack raised blood glucose concentrations when sugar-rich snacks were used (5).

Combination with long-acting insulin

The combinations insulin lispro + insulin glargine and regular + NPH have been compared in a randomized, crossover study for 32 weeks in 25 patients (6). HbA_{1c} was not different, but the total insulin dose was lower with insulin lispro + insulin glargine and there were fewer episodes of nocturnal hypoglycemia.

The new short-acting insulins can be bound to protamine, allowing the preparation of mixed formulations. In a randomized, open, crossover study for 24 weeks, a 50% mixture of insulin lispro and protamine lispro injected immediately before each meal plus NPH in the evening gave a comparable profile to regular insulin injected 30 minutes before each meal plus NPH in the evening (7). There were no differences in HbA_{1c} or

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episodes of hypoglycemia. When Mix25TM (25% insulin lispro plus 75% protamine lispro) was compared with 30/70 human insulin in an open, randomized, crossover study during Ramadan, the daily average blood glucose concentration was better with the insulin lispro combination. The number of hypoglycemic episodes was the same with the two formulations (8).

In an open, randomized, single-dose, three-way, crossover trial, biphasic insulin aspart 30 (30% aspart plus 70% protaminated aspart, BIAsp 30), biphasic insulin lispro 25 (25% lispro plus 75% protaminated lispro, Mix 25), and biphasic human insulin 30 (30% regular plus 70% NPH insulin, BHI 30) were compared in 45 patients (9). Biphasic insulin aspart improved postprandial control better. There were 23 episodes of hypoglycemia with BIAsp 30, 19 with Mix 25, and 11 with BHI 30; two episodes with BIAsp 30, five with Mix 25, and two with BHI 30 required third-party intervention.

Comparative studies

In an open, randomized, crossover study, 113 patients with at least 6 months of continuous subcutaneous insulin infusion before the study were treated with regular insulin or insulin lispro (2). Postprandial blood glucose was lower and HbA_{1c} fell more with insulin lispro. There were no differences in catheter obstruction, hypoglycemic episodes, or other adverse effects. Satisfaction with treatment was better with insulin lispro.

There were no differences between human protamine zinc insulin and human ultralente insulin when either was added once or twice daily to insulin lispro (10).

When either insulin lispro or regular insulin was given during the evening meal in a randomized, double-blind study in insulin-using adolescents, insulin lispro reduced the number of hypoglycemic episodes at night but redistribution of evening carbohydrate might be necessary to reduce postprandial hypoglycemia (11).

Premeal hyperglycemia is common. The short action of insulin lispro can then be extended by the addition of protamine zinc insulin. In a 3-month study in addition to a once-daily injection of protamine zinc insulin, at each meal insulin lispro or insulin lispro + protamine zinc insulin was injected; the postprandial blood glucose concentration was lower, but the post-absorptive glucose concentration was higher in the insulin lispro-only group; there was no difference in HbA_{1c}. The addition of protamine zinc insulin (30% at breakfast, 40% at lunch, and 10% at dinner) improved post-absorptive glucose and HbA_{1c} (12).

Insulin Mix 25 (25% insulin lispro and 75% neutral protamine zinc insulin) reduced the glucose response to a standardized breakfast meal better than premixed 30% regular + 70% protamine zinc insulin when 22 patients with type 2 diabetes were studied three times in a double-blind fashion (13). Protamine zinc insulin mixed with insulin lispro has the same action profile of insulin lispro, with the continuing action of the long-acting component (14). The same mixture given three or four times daily provides acceptable control (15), but gives no possibility of adjusting the short-acting insulin regularly. Protamine zinc insulin must be mixed with insulin lispro in the syringe immediately before the meal (16). The mixture is not stable for longer as there is partial exchange of the rapid-acting analogue and the protamine-bound human insulin. Instant mixing is no solution when pens are used.

The use of insulin lispro instead of regular insulin reduced the frequency of nocturnal attacks of hypoglycemia but did not change HbA_{1c} (17). This was confirmed by the UK Prospective Diabetes Study (18), which also found a fall in postprandial glucose with an increase in fasting and preprandial glucose.

In an open, crossover, randomized study in 33 patients with type 1 diabetes who used regular or insulin lispro, the latter was associated with a lower incidence of severe hypoglycemia, mostly due to reduced nocturnal hypoglycemia; HbA_{1c} was not different (19).

A crossover comparison of regular insulin + protamine zinc insulin at bedtime with insulin lispro + multiple protamine zinc insulin showed no effect on overall hypoglycemia but there was less frequent severe hypoglycemia with the second treatment (20). The reduction in HbA_{1c} was small and not significant. Insulin doses were the same. Patients preferred the second treatment.

In an open, randomized, multicenter study, 33 women with type 1 diabetes for at least 2 years were randomized to preprandial lispro or regular insulin in week 15 of their pregnancy; both groups used NPH insulin as well (21). HbA_{1c} concentrations fell at the same rate. One patient in the regular group had one episode of severe hypoglycemia and one had three episodes. Biochemical hypoglycemia (under 3.0 mmol/l) was significantly more frequent in the lispro group (5.5 versus 3.9%). Retinopathy progressed during pregnancy in three of the 16 who used lispro and six of the 17 who used regular insulin; retinal aneurysms were seen at the beginning of the study in 10/16 and 5/17 patients respectively. There were no differences in the neonates.

When insulin lispro and insulin aspart were compared in a single-blind, randomized crossover study in 14 patients with type 1 diabetes, insulin lispro had a faster onset of action but a shorter duration (22). However, in another study, the pharmacokinetic and pharmacodynamic profiles of insulin aspart compared with human insulin in 24 healthy Japanese were the same as those in non-Japanese subjects (23).

Insulin aspart, insulin lispro, and buffered regular insulin in continuous subcutaneous insulin infusion have been compared in an open, randomized, parallel-group study in 146 patients (24). HbA_{1c}, hypoglycemic episodes, and blockages of pumps or infusion sets did not differ.

Insulin lispro and insulin aspart were equally effective in 24 patients with type 1 diabetes (25).

Insulin lispro and repaglinide were given to seven patients with diabetes related to cystic fibrosis (26). They had normal fasting blood glucose and insulin concentrations, but postprandial glucose concentrations were substantially raised. Insulin lispro had a larger and more sustained effect in lowering postprandial glucose than repaglinide. However, the doses of insulin lispro (0.1 U/kg) and repaglinide (1 mg) may not have been comparable.

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Organs and Systems

Metabolism

Hypoglycemic events in 24 controlled trials of rapid-acting insulin analogues have been analysed (27). In 22 trials, insulin lispro was used, 19 studies were open and unblinded, and five were double-blind. In five of 22 studies there was a significant reduction in mild hypoglycemia, but there were no changes in the frequency of severe hypoglycemia in 10 of 12 studies that reported these events; there was a fall in nocturnal hypoglycemia in 6 studies, but in 18 studies there was no fall. The author stated that rapid-acting insulins are only appropriate in intensive therapy, which involves well-educated and well-motivated patients.

Lipoatrophy is rare with human recombinant insulin. Two cases of lipoatrophy induced by insulin lispro during continuous subcutaneous insulin infusion have been reported (28).

- An 8-year-old girl was switched to continuous subcutaneous insulin infusion using insulin lispro for better regulation after 4 years of diabetes. After 12 months she developed lipoatrophy of the abdominal wall, which progressed during the next months. When she changed to neutral buffered regular human insulin, no further lipoatrophy developed, but the existing atrophy did not improve either.
- A 51-year-old woman started to use continuous subcutaneous insulin and after 2 years the insulin was changed to insulin lispro. She developed lipoatrophy in the abdomen and buttocks 1 year later and there was an increase in the time before the bolus started to peak. Buffered regular human insulin stopped progression of the lipoatrophy.

Skin

Insulin lispro can cause lipoatrophy, but it was less extensive in a case in which it had occurred with regular insulin, perhaps because of the greater solubility of insulin lispro.

- Several combinations of regular and NPH insulin reduced the risk of hypoglycemia and optimized blood glucose in a 29-year-old woman who had had type 1 diabetes for 6 years (29). Continuous subcutaneous insulin infusion with regular insulin reduced the risk of hypoglycemia, but after 7 months she developed lipoatrophy. Changing the site of the cannula did not help. She was given insulin lispro instead and after 11 months a new, less extensive area of lipoatrophy emerged, which did not disappear.

Immunologic

The long-term antigenicity of insulin lispro and cross-reactivity with human insulin antibodies over 4 years has been investigated in 1221 patients with both type 1 and type 2 diabetes, either insulin-naïve or with prior insulin treatment, in a multicenter combination of controlled and non-controlled open studies (30). Like recombinant human insulin, insulin lispro elicited a low immunogenic response. The reversal of amino acids in B28 and B29 is in a relatively non-immunogenic area. Moreover, antigenicity often correlates with residence of insulin in subcutaneous tissues, and insulin lispro has a short residence time. The patients did not develop increased dosage requirements. Intermittent treatment did not increase specific or cross-reactive responses. The antibody responses were slightly higher in type 1 than in type 2 diabetes. In lipodystrophy with lipoatrophic diabetes, high insulin resistance is often found, for which leptin deficiency is one contributory factor.

Second-Generation Effects

Pregnancy

Rapid improvement of regulation by insulin lispro during pregnancy causes proliferative diabetic retinopathy more often. In 14 patients treated with insulin lispro to improve control before or at the beginning of pregnancy, six of the 10 patients with normal optic fundi remained negative. However, three patients developed bilateral progressive retinopathy with marked vision impairment, in two cases with vitreous hemorrhage; one patient with a negative examination 6 months before pregnancy, but with minimal lesions 18 months earlier, developed progressive retinopathy with vitreous hemorrhages in spite of multiple coagulations (31). The authors advised care when starting insulin lispro in patients with a history of retinal lesions and to look for those at risk by performing fluorescein angiography, which distinguishes incipient changes better.

In a comparison of premeal regular insulin and premeal insulin lispro in gestational diabetes there were fewer attacks of hypoglycemia, but fasting glucose, postprandial glucose, and HbA_{1c} were similar in the two groups (32). There were no fetal or neonatal abnormalities.

Susceptibility Factors

Age

The newer insulins are not registered for use in children in many countries. A report of the use of postprandial insulin lispro versus preprandial regular insulin in an open, crossover, randomized study in 24 prepubertal children showed no large differences (33). Fasting blood glucose was higher with insulin lispro. The number of hypoglycemic episodes was almost the same with both insulins. There was one case of severe hypoglycemia.

Renal disease

The pharmacodynamic and pharmacokinetic properties of regular soluble insulin and insulin lispro have been investigated in 12 patients with and without nephropathy in a double-blind, crossover study with euglycemic glucose clamping (34). Insulin clearance was reduced by 30–40% in patients with nephropathy, but in both groups the time to reach the maximal effect was shorter with insulin lispro. The overall metabolic effect of regular soluble insulin, but not of insulin lispro, was lower in nephropathy, in which a 50% higher dose of regular insulin may be necessary.

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Drug Administration

Drug administration route

Insulin lispro by repeated injection has been compared with insulin lispro by continuous subcutaneous infusion in 41 patients who were C-peptide negative (35). HbA_{1c}, mean blood glucose concentrations, and mean insulin doses were significantly lower during continuous subcutaneous infusion; the frequency of attacks of hypoglycemia was the same.

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Insulin-like growth factor (IGF-I)

General Information

Insulin growth factor (IGF) and the IGF-I receptor are structurally comparable to insulin and the insulin receptor. Recombinant human IGF-I has 54% identity to proinsulin. Insulin and IGF-I can bind to both receptors, but insulin can only transfer 1% of the IGF message on the IGF receptor and IGF-I only 1% of the insulin message on the insulin receptor.

Recombinant human IGF-I is used as an adjunct to insulin therapy in patients with large daily variations in insulin effect. It is sometimes given in insulin resistance syndromes caused by changes in the insulin receptor or in type B insulin resistance syndrome caused by antibodies to the insulin receptor.

In 14 adolescents, the addition of IGF-I to diabetic treatment for 12 weeks did not change leptin concentrations (1).

IGF-I was given as co-therapy with insulin in 223 patients for 12 weeks twice-daily (2). The doses of IGF-I were 40/40, 80/40, or 80/60 micrograms/kg. Patients who received co-therapy were able to reduce their daily doses of insulin. The number of episodes of hypoglycemia was the same, but glucose regulation was tighter during IGF-I co-therapy. The fall in HbA_{1c} concentration was greater with co-therapy (–1.2%) than with intensive therapy only (–0.7%). The dosage regimen of 40/40 micrograms/kg was well tolerated. Higher doses had no greater effect but were associated with edema, jaw pain, headache, palpitation, tachycardia, syncope, or early worsening of retinopathy.

Organs and Systems

Sensory systems

Of 199 patients, 16 developed significant worsening of retinopathy, including neovascularization, over 12 weeks; 12 of the 16 had optic disc swelling, which necessitated laser therapy in three of them (3). This was mostly seen in patients using a high dose of IGF-I, but a long-term effect of low-dose IGF-I could not be excluded either.

Immunologic

IGF-I can cause allergic reactions (4).

- A 75-year-old man with glucose intolerance, severe hyperinsulinemia, and extreme insulin resistance with anti-insulin receptor antibodies had immunosuppressive therapy and plasmapheresis to remove the antibodies, without lasting success. Treatment with hrIGF-I, 0.4 mg/kg/day, reduced HbA_{1c} from 13.8% to 8.0%. After 5 months he developed a generalized skin eruption 20 minutes after the injection. When IGF-I was withdrawn the HbA_{1c} rose again. After careful desensitization with hrIGF-I, 0.1 mg three times a week, IGF-I was continued, with good effect on HbA_{1c}.

Long-Term Effects

Tumorigenicity

A non-Hodgkin's lymphoma developed in the right femur of a 58-year-old man who had used IGF-I 40 micrograms bd (5) in a study of the effect of adding IGF to insulin therapy (SEDA-23, 457).

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Interferon alfa

See also Interferons

General Information

Interferon alfa is used as purified natural leukocyte or lymphoblastoid human interferon, or as a recombinant DNA preparation. Work to assign the most frequently observed amino acids at each position has led to a so-called consensus interferon alfa (1). Relatively low doses (3–10 MU three times a week) are now being used in most indications, except in AIDS-related Kaposi's sarcoma (up to 30 MU/day). Although the half-life is only 4–5 hours, its biological effects persist for 2–3 days.

Observational studies

Considerable efforts have been made to improve the efficacy of interferon alfa in patients with chronic hepatitis C. Currently used regimens, including long-term interferon alfa alone or in combination with ribavirin, produce a sustained response rate of 40–50%. Other possibly effective strategies include a longer duration of treatment, higher fixed doses, and high-dose induction (2). A longer duration of treatment has been evaluated in patients with chronic hepatitis B. In 118 patients, treatment for 32 rather than 16 weeks enhanced the virological response to hepatitis B without increasing the severity of adverse effects, except for hair loss, which was more frequent during prolonged therapy (3).

A wide range of persistent symptoms has been reported during interferon alfa treatment for chronic hepatitis C. An analysis of 222 patients from the USA and France, enrolled in a multicenter trial, suggested that pretreatment symptoms were an important predictor of moderate or severe (defined as debilitating) adverse effects during treatment with interferon alfa (4). Compared with baseline, the incidences of moderate and severe fatigue, myalgia, arthralgia, headache, dry eyes, and dry mouth increased significantly after 6 months. In each case, the development of these debilitating adverse effects was associated with the presence of that symptom at baseline. They were more often reported in patients who received interferon alfa daily than three times weekly, and in US than French patients, suggesting possible differences in cultural attitudes toward illness. There was also increased use of antidepressants during the 6-month survey.

Low daily doses of interferon alfa have been used with small doses of cytarabine in the treatment of early chronic myelogenous leukemia (5). With doses sufficient to obtain a good cytogenetic response (for example 3.7 MU/m^2/day plus cytarabine 7.5 mg/day) toxicity was considered acceptable. There was significant fatigue in 43% of cases, significant neurological changes in 27%, weight loss in 19%, and oral ulcers in 4%.

Comparative studies

Interferon alfa, in combination with ribavirin, is currently first-line therapy for patients with chronic hepatitis C and compensated liver disease, and its use has been extensively reviewed (6). A meta-analysis of trials in patients who were previously non-responsive to interferon alfa alone showed that treatment withdrawal for an adverse event was more frequent in patients who received combination therapy (8.8%) compared with interferon alfa monotherapy (4%) (7). However, treatment withdrawal is more frequent in practice. In a retrospective analysis of 441 consecutive patients treated with interferon alfa and ribavirin, 25% of patients discontinued treatment because of adverse effects (8). The study identified female sex, a dose of interferon alfa above 15 MU/week, and naive patients as independent susceptibility factors for premature withdrawal.

Comparisons of different forms of interferon alfa

In a randomized comparison of recombinant interferon alfa-2b and interferon alfa n-3 (9 MU/week for 1 year) in 168 naive patients with chronic hepatitis C, there was no significant difference in clinical outcomes and the incidence or type of adverse effects between the groups (9). There was a non-significant trend toward more severe leukopenia and a higher incidence of severe thyroid disorders in patients who received recombinant interferon alfa-2b.

Pegylated interferon alfa-2a is a modified form of interferon alfa; it produces higher serum concentrations and has greater efficacy. In 1530 patients with chronic hepatitis C, pegylated interferon alfa-2b had a similar profile of adverse effects to unmodified interferon alfa-2b, but with more frequent dose-limiting neutropenia (10). Two other studies have shown that peginterferon alfa-2a once weekly is more effective than unmodified interferon alfa-2a three times weekly in patients with chronic hepatitis C (11,12). The frequency and severity of adverse effects with the two treatments were very similar and were consistent with the known adverse effects of interferon alfa. In one study, a neutrophil count below 0.5×10^9/l was more frequent with peginterferon alfa than with unmodified interferon alfa (12/265 versus 4/261), but none of these patients required treatment withdrawal or had serious infections in relation to neutropenia (12). In the other study, the proportion of patients who required dosage modification because of thrombocytopenia was also higher with peginterferon alfa (18 versus 6%), but no patients had clinically significant bleeding disorders (11). Taken together, these studies suggest that pegylated interferon alfa may produce more frequent or more severe hemotoxic effects than unmodified interferon alfa.

In 1530 patients with chronic hepatitis C, pegylated interferon alfa-2b had a similar profile of adverse effects to unmodified interferon alfa-2b, but with more frequent dose-limiting neutropenia (10). No particular adverse effect has emerged since the use of this new formulation.

General adverse effects

The adverse effects of interferon alfa have mostly been reported after systemic administration, as intranasal use was not associated with more frequent adverse effects than placebo (13). Almost all patients treated with interferon alfa have experienced adverse effects, most of which are mild to moderate in intensity and easily manageable without withdrawal of treatment (14). The incidence and profile of adverse effects reported with the available types

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of interferon alfa are very similar (SEDA-21, 369) (SEDA-22, 399), but they differ with the dose, schedule of administration, and the disease. At least 4–5% of patients with chronic hepatitis C had to discontinue treatment because of adverse effects, and dosage reduction was required in 9–22% of those receiving 9–15 MU/week (15). In a large retrospective evaluation of 11 241 patients with chronic viral hepatitis, the incidence of fatal or life-threatening adverse effects related to interferon alfa was one in 1000; events included irreversible liver failure, severe bone marrow depression, and attempted suicide (16). Overall, severe adverse effects were observed in 1% of patients, and comprised mostly thyroid disorders, neuropsychiatric manifestations, and cutaneous adverse effects. In other studies in patients with chronic hepatitis, the incidence of major adverse effects was 25% in 659 patients (17); in Japan, dosage reduction or withdrawal was necessary in 31% of 987 patients receiving relatively high dosages of interferon alfa (18–70 MU weekly) (18). The safety of interferon alfa in children appears to be similar to that in adults (19). The pathogenesis of most adverse effects observed with interferon alfa is poorly understood, but two main mechanisms are commonly postulated, namely a direct toxic effect or an indirect immune-mediated effect.

During the first days of treatment, virtually all patients have a flu-like syndrome with fever, chills, tachycardia, malaise, headache, arthralgias and myalgias, but tachyphylaxis usually develops after 1–2 weeks of treatment (20). Late febrile reactions are rarely noted (21). Although the severity increases with the dose, the flu-like syndrome is rarely treatment-limiting and it can be partly prevented by the prophylactic administration of paracetamol (acetaminophen). The acute release of fever-promoting factors, for example the eicosanoids, IL-1, and TNF alfa, secondary to interferon alfa is the suggested mechanism.

Although the adverse effects profiles of the currently available formulations of interferon alfa are very similar, patients who have adverse effects with one formulation can be successfully re-treated with another type of interferon alfa. This has been shown in 22 patients in whom lymphoblastoid interferon alfa was withdrawn because of severe adverse effects (leukopenia, thrombocytopenia, thyroid disorders, and psychiatric disturbances) and were successfully re-treated with similar dosages of leukocyte interferon alfa (22). Only one of these patients had severe leukopenia again.

Organs and Systems

Cardiovascular

Hypotension or hypertension, benign sinus or supraventricular tachycardia, and rarely distal cyanosis, have been reported within the first days of treatment in 5–15% of patients receiving high-dose interferon alfa (20). These adverse effects are usually benign, except in high-risk patients with a previous history of dysrhythmias, coronary disease, or cardiac dysfunction.

Cardiac complications

Severe or life-threatening cardiotoxicity is infrequent and mostly reported in the form of a subacute complication in patients with cancer, and in those with pre-existing heart disease or receiving high-dose interferon alfa. Atrioventricular block, life-threatening ventricular dysrhythmias, pericarditis, dilated cardiomyopathy, cardiogenic shock, asymptomatic or symptomatic myocardial ischemia or even infarction, and sudden death have been observed (SED-13, 1091) (SEDA-20, 326) (SEDA-22, 369) (23). The combination of high-dose interleukin-2 (IL-2) with interferon alfa enhanced cardiovascular complications, namely cardiac ischemia and ventricular dysfunction (24).

Cardiomyopathy has been attributed to interferon alfa in an infant (25).

- A 3-month-old boy was given interferon alfa (2.5–5.5 MU/m^2) for chronic myelogenous leukemia. After 7.5 months he developed progressive respiratory distress, with anorexia, irritability, and nocturnal sweating. A chest X-ray showed cardiomegaly, an echocardiogram showed a markedly dilated left ventricle, and an electrocardiogram showed left ventricular hypertrophy with abnormal repolarization. Viral cultures and serology for cytomegalovirus, parvovirus B19, and enterovirus were negative. Infectious diseases and metabolic disturbances were excluded. Interferon alfa was withdrawn and digoxin, furosemide, and an angiotensin-converting enzyme inhibitor were given. One year later, he was asymptomatic without further cardiac treatment.

Similar, but anecdotal reports were also described in patients without evidence of previous cardiac disease and receiving low-dose interferon alfa (SEDA-20, 326). In chronic viral hepatitis, only seven of 11 241 patients had severe cardiac adverse effects (16). The exact risk of such cardiovascular adverse effects is unknown. In patients with chronic viral hepatitis, cardiovascular test results were not modified when patients were re-examined after at least 6 months of treatment, even where there was an earlier cardiac history (26), but there was a potentially critical reversible reduction in left ventricular ejection of more than 10% in another prospective study (27).

Myocardial dysfunction can completely reverse after withdrawal of interferon alfa and does not exclude further treatment with lower doses (28).

- A 47-year-old man with renal cancer and no previous history of cardiovascular disease developed gradually worsening exertional dyspnea after he had received interferon alfa in a total dose of 990 MU over 5 years. Echocardiography and a myocardial CT scan confirmed a dilated cardiomyopathy, with left ventricle dilatation and diffuse heterogeneous perfusion at rest. He improved after interferon alfa withdrawal and treatment with furosemide, quinapril, and digoxin. Myocardial scintigraphy confirmed normal perfusion. He restarted low-dose interferon alfa (6 MU/week) 1 year later and had no recurrence of congestive heart failure after a 1-year follow-up period.

Patients with pre-existing cardiac disease are more likely to develop cardiovascular toxicity while receiving interferon alfa, but these complications are rare. Among 89 patients with chronic hepatitis C, 12-lead electrocardiography monthly during a 12-month treatment period and follow-up for 6-months showed only minimal and non-specific abnormalities in five patients (two had right

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bundle branch block, one left anterior hemiblock, and two unifocal ventricular extra beats) (29). None of these disorders required treatment withdrawal, and complete noninvasive cardiovascular assessment was normal. Overall, the role of interferon alfa was uncertain and the 5.6% incidence of electrocardiographic abnormalities was suggested to be similar to that expected in the general population. Nevertheless, severe cardiac dysrhythmias are still possible in isolated cases, as illustrated by the development of third-degree atrioventricular block, reversible on withdrawal, in a 57-year-old man with lower limb arteritis but no other cardiovascular disorder (30).

Peripheral vascular complications

Raynaud's phenomenon

Raynaud's phenomenon can occur, particularly in patients with chronic myelogenous leukemia (SEDA-20, 326) (31), and severe cases were complicated by digital necrosis (SEDA-20, 326) (SEDA-21, 369).

In 24 cases of Raynaud's syndrome, interferon alfa was the causative agent in 14, interferon beta in 3, and interferon gamma in 5 (32). There was no consistent delay in onset and the duration of treatment before the occurrence of symptoms ranged from 2 weeks to more than 4 years. The most severe cases were complicated by digital artery occlusion and necrosis requiring amputation. Few patients had other ischemic symptoms, such as myocardial, ophthalmic, central nervous system, or muscular manifestations. Severe Raynaud's phenomenon was also reported in a 5-year-old girl with hepatitis C (33).

Cryoglobulinemia

Although most patients with mild-to-moderate clinical manifestations of hepatitis C virus-associated mixed cryoglobulinemia improved during treatment with interferon alfa, acute worsening of ischemic lesions has been reported in three patients who had prominent cryoglobulinemia-related ischemic manifestations (34). All three had acute progression of pre-existing peripheral ischemia or leg ulcers within the first month of treatment, and transmetatarsal or right toe amputations were required in two. The lesions healed after interferon alfa withdrawal. It was therefore suggested that the antiangiogenic activity of interferon alfa may also impair revascularization and healing of ischemic lesions in patients with initially severe ischemic manifestations.

Venous thrombosis

Whereas clinically insignificant coagulation abnormalities have been documented in patients receiving high-dose continuous interferon alfa (35), isolated cases of venous thrombosis have been observed (SEDA-20, 329) (36). Interferon alfa can also induce the production of antiphospholipid antibodies (SEDA-20, 329) (SEDA-21, 371). In one study, antiphospholipid antibodies were found in five of 12 patients with melanoma treated with interferon alfa alone or with interferon alfa plus interleukin-2; deep venous thrombosis occurred in four patients with antiphospholipid antibodies (37). Although the underlying neoplasia undoubtedly played a role in the further development of venous thrombosis, the causative role of interferon alfa was suggested by the absence of antiphospholipid antibodies and venous thrombosis in eight patients treated with interleukin-2 alone.

Other vascular complications

Other anecdotal reports included acrocyanosis and peripheral arterial occlusion (SED-13, 1095) (SEDA-22, 400). Although the causal relation is unclear, interferon alfa was considered as a possible cause in the triggering of acute cerebrovascular hemorrhage or ischemic neurological symptoms in few patients (SEDA-21, 370) (SEDA-22, 400). The pathogenic mechanisms of these vascular effects are still unclear; vasculitis, hypercoagulability, vasospasm, a paradoxical anginal effect of interferon alfa, or an underlying cardiovascular disease have all been suggested as underlying processes.

Respiratory

The respiratory adverse effects of interferon alfa include interstitial pneumonitis (38), which is rare. Since the first description of interstitial pneumonitis associated with interferon alfa in Japanese patients who also used the popular "Sho-saiko-t" herbal formulation, similar cases have been described in Western patients, suggesting that interferon alfa can be the sole cause in some patients (SED-13, 1091) (SEDA-20, 326) (SEDA-21, 370) (39,40).

Interferon alfa was also suspected to be involved in one case of biopsy-proven bronchiolitis obliterans-organizing pneumonia (41). Clinical symptoms of pneumonitis appeared 3–12 weeks after the onset of interferon alfa therapy, and after withdrawal of treatment they usually completely resolved, either spontaneously or after a short course of glucocorticoid treatment. Immune-mediated pulmonary toxicity involving the activation of T cells was considered as a likely mechanism. The uncommon features of bronchiolitis obliterans-organizing pneumonia have been reported in three other patients who received interferon alfa together with ribavirin or cytosine arabinoside (42,43).

In four patients with hematological malignancies who developed symptoms suggestive of pneumonitis (that is a dry cough and dyspnea) after 1 week to 38 months of interferon alfa treatment, there was a marked reduction in carbon monoxide diffusion capacity in all cases, whereas there were pathological findings in ordinary chest X-rays in only two (44). What the authors called ultracardiography and high-resolution CT scanning were suggested to have higher sensitivity in evaluating pulmonary symptoms. In three patients, complete reversal was obtained after interferon alfa withdrawal, either spontaneously or after corticosteroid treatment, although one patient required long-term glucocorticoid treatment.

In a retrospective review of 70 patients with hepatitis C enrolled in four clinical trials, there were four cases of significant pulmonary toxicity (two of bronchiolitis obliterans and two of interstitial pneumonitis) (45). Three recovered completely, but one still required glucocorticoids for exertional dyspnea that persisted 17 months after interferon alfa withdrawal. The authors suggested that there was an increased risk with high-dose interferon, because three of these patients received high doses (5 MU/day) or pegylated interferon alfa. In contrast, they were unaware of any significant pulmonary

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toxicity in any of their approximately 500 patients with hepatitis C.

Interferon alfa can cause exacerbation of asthma (SED-14, 1248).

- Acute exacerbation of asthma has been reported in two men aged 27 and 57 years with a previous history of mild asthma (46). They developed progressive aggravation of asthma within 8–10 weeks of treatment for chronic hepatitis C, and finally required emergency treatment with systemic glucocorticoids and inhaled beta$_2$ adrenoceptor agonists. Severe asthma recurred 2–3 weeks after interferon alfa rechallenge in both patients.

Although these cases are anecdotal, they strongly suggest that interferon alfa should be regarded as a possible cause of asthma exacerbation in predisposed patients.

- Sustained and isolated dry cough has been attributed to interferon alfa in a 49-year-old woman (47). The symptoms disappeared after withdrawal, recurred on readministration, and again resolved after withdrawal. No other cause was found after thorough investigation.

Pleural effusion has been attributed to interferon alfa (48).

- A 54-year-old man received interferon alfa-2a, 9 MU/day, for chronic hepatitis C. He developed an asymptomatic right pleural effusion after 14 days. Although his serum titer of antinuclear antibodies was slightly increased, a more complete screening for autoimmune disease was negative. An infectious origin was also ruled out. The pleural effusion spontaneously disappeared after interferon alfa withdrawal and did not recur.

Although the mechanism of this adverse effect was purely speculative, it was suggested that interferon alfa might have induced a reaction similar to the immunopathological mechanism involved in serositis associated with systemic lupus erythematosus.

Pulmonary artery hypertension has been attributed to interferon alfa (49).

- A 23-year-old man taking hydroxycarbamide 1.5 g/day and interferon alfa-2b (less than 10 MU/day) for chronic lymphocytic leukemia had progressive dyspnea and a non-productive cough after about 5 months. The electrocardiogram showed right-axis deviation, incomplete right bundle-branch block, and right ventricular hypertrophy. The estimated pulmonary artery pressure by echocardiography was 80 mmHg and there were signs of right heart failure. Respiratory function tests showed a restrictive defect, and the chest X-ray showed pulmonary congestion without infiltrates. The patient's clinical status and respiratory function tests improved rapidly after withdrawal of interferon alfa while hydroxycarbamide was continued, and a mean pulmonary artery pressure of 34 mmHg was measured by right heart catheterization 1 month later. At 6 months, the systolic pulmonary artery pressure estimated by echocardiography had fallen to 35 mmHg and the electrocardiogram returned to normal after 1 year.

The authors mentioned that intravenous interferon alfa in sheep had caused an increase in pulmonary artery pressure.

Nervous system

Peripheral neuropathy

Dose-related distal paresthesia occurred in as many as 7% of patients (20), but new onset or worsening of neuropathy has rarely been attributed to interferon alfa. A sensorimotor polyneuropathy was the most frequent presentation (50). The symptoms usually developed after 2–28 weeks of treatment. Such reports were mostly described in patients who received high cumulative doses of interferon alfa, but induction or exacerbation of peripheral sensorimotor axonal neuropathy, particularly in patients with chronic hepatitis C and mixed cryoglobulinemia, was also observed after long-term or low-dose treatment (SED-13, 1092) (SEDA-20, 327) (SEDA-21, 370) (51). Nerve biopsy showed necrotizing vasculitis or axonal degeneration. Most patients stabilized or improved slowly over several months after interferon alfa withdrawal and/or treatment with corticosteroids. Several patients also required plasmapheresis or cyclophosphamide. Although several authors have suggested an autoimmune process, the underlying pathogenic mechanism is unclear.

Other rare forms of neuropathy (SED-13, 1092) include mononeuropathy multiplex (52), acute axonal polyneuropathy (53), anterior ischemic optic neuropathy (54), trigeminal sensory neuropathy (55), bilateral neuralgic amyotrophy (56), brachial plexopathy (57), and symptoms suggestive of leukoencephalopathy (58).

Cranial nerve palsies

There have been reports of interferon alfa-induced cranial nerve palsies, including Bell's palsy.

Two patients, one of whom also received ribavirin, had facial nerve palsy after 5 and 8 months of interferon alfa therapy (59). The palsy resolved completely in one patient after withdrawal and the administration of prednisolone; however, in the other case, the palsy resolved without drug withdrawal, suggesting coincidence.

Two other cases of Bell's palsy, which reversed after interferon alfa withdrawal, have been reported (60). Although the delay in onset (7.5 and 8 weeks) suggested that interferon alfa might be the cause, one patient had no recurrence after rechallenge. A coincidental adverse event cannot therefore be completely ruled out.

Demyelination

Various forms of interferon alfa-induced neuropathy have been reported (SED-14, 1249), but chronic inflammatory demyelinating polyneuropathy has seldom been described (61,62).

- In two patients with chronic hepatitis C or malignant melanoma, paresthesia and tiredness occurred after 6 weeks and 9 months of treatment respectively. Despite withdrawal of interferon alfa, the neurological symptoms worsened initially and a diagnosis of chronic inflammatory demyelinating polyneuropathy was finally confirmed several weeks later. One patient improved after an extended course of plasma exchange and the other required immunoglobulins and prednisolone. Mild to moderate neurological abnormalities persisted at follow-up in both patients.

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Multiple sclerosis has been attributed to interferon alfa (63).

- A 29-year-old woman received interferon alfa-2b (6–10 MU/day) for chronic myeloid leukemia, and about 3 years later developed headaches, back pain, progressive visual disturbance, and a sensory deficit in the legs. MRI scans of the brain and spinal cord suggested a first episode of multiple sclerosis. In addition, the myelin basic protein concentration was slightly raised, and perimetry showed bilateral optic neuritis. Most of her neurological symptoms, except central vision impairment, improved after interferon alfa withdrawal and treatment with high-dose methylprednisolone. As a major partial cytogenetic response had been obtained with interferon, she was given natural interferon alfa (3 MU/day) 2 months later. After 2 days of treatment, she complained of transient but severe pain in the back and the legs, and developed acute paraplegia and loss of micturition desire. Again, interferon was withdrawn and she was given high-dose methylprednisolone. There was no further neurological deterioration at follow-up.

This account is reminiscent of the various autoimmune diseases that can be unmasked or exacerbated by interferon alfa.

Extrapyramidal effects

Extrapyramidal effects have been occasionally reported as a manifestation of persistent neurotoxicity induced by interferon alfa. This issue has been addressed in a report of severe refractory akathisia (64).

- A 28-year-old man received interferon alfa (5 MU/day for 28 days) for chronic hepatitis B. At the end of treatment he developed a slight parkinsonian gait, and 8 days later had a fever with vomiting, insomnia, restlessness, and raised serum creatine kinase activity (4946 IU/l). He had severe akathisia with psychomotor excitement and parkinsonism. Despite treatment with clonazepam, thioridazine, propranolol, trihexyphenidyl, and bromocriptine, his condition progressively worsened. He was finally given intravenous levodopa for 8 days and recovered dramatically within the next few days.

This report, together with previous experimental data, suggests that levodopa might be useful in alleviating some of the manifestations of persistent interferon alfa-induced neurotoxicity.

In two other patients, akathisia occurred shortly after they had started to take interferon alfa; one improved after the frequency of injections was reduced (65). Unfortunately, this report did not provide sufficient convincing evidence for a causal relation; the development of akathisia may have been coincidental.

Chorea is a very rare manifestation of interferon alfa neurotoxicity (SEDA-20, 327).

- A 68-year-old woman developed progressive personality changes and 2 months later permanent choreic movements of the four limbs (66). She had taken interferon alfa-2b (3 MU/day) and hydroxyurea 50 mg/kg/day for chronic myeloid leukemia for 2 years and had no history of psychiatric disorders. Neuropsychological testing showed frontal subcortical dysfunction. There were no abnormalities in the Huntington disease gene. She progressively worsened over the next 6 months. The electroencephalogram was disorganized, with diffuse slow waves, and she was bedridden. Interferon alfa was withdrawn. The chorea ceased 1 month later and she completely recovered cognitive function. Electroencephalography was normal 6 and 12 months later.

The authors attributed these events to antidopaminergic effects of interferon alfa.

Seizures

Although generalized tonic-clonic seizures have occasionally been described during trials of high doses of interferon alfa, they have also been reported after the use of intermediate or even low doses (67–69). There was a 1.3% incidence of generalized seizures in a retrospective study of 311 patients treated with low doses for chronic viral hepatitis (70). In another study, tonic-clonic seizures were identified in 4% of children treated for chronic hepatitis B (71). As seizures occurred only in children under 5 years of age with fever or potential perinatal nervous system injury, immaturity of the nervous system was suggested to be an additional factor for interferon alfa-induced neurotoxicity in children.

- In three patients, seizures occurred after a cumulative dose of 266–900 MU (72,73). Two were retreated with a lower dose and remained free of seizures, so that the strength of the causal relation was debatable (72). However, a dose-related effect was still possible.
- Another patient with a history of bipolar mood disorder experienced had his first four episodes of seizures with a prolonged delirious state 1 week after withdrawal of interferon alfa (73).

Reversible photosensitive seizures have also been reported (74).

- A 62-year-old man without a personal or family history of epilepsy received interferon alfa (3 MU three times a week) for 2 years for multiple myeloma. He had frequent episodes of myoclonic jerks in the face, especially when the sun was shining while driving his car. He also had one generalized seizure. Electroencephalography showed a paroxysmal response to intermittent photic stimulation and magnetic resonance imaging was normal. The seizures disappeared and his electroencephalogram normalized after interferon alfa withdrawal.

In this case, the possible role of interferon alfa was suspected only late during treatment, indicating that patients should be regularly questioned about neurological symptoms, because more severe complications might have occurred.

In a prospective study of the effect of interferon alfa (56 MU/day for 4 weeks then 27 MU/week for 20 weeks) in 56 patients with chronic hepatitis C, there was diffuse electroencephalographic slowing at 2 and 4 weeks of treatment, suggesting mild encephalopathy (75). These changes completely reversed after withdrawal. However, the dosage used in this Japanese study was relatively high compared with the dosages currently used in Western countries. In addition, the clinical relevance of these electroencephalographic changes was not investigated.

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Neuromuscular function

A number of reports have confirmed that interferon alfa can induce or unmask underlying silent myasthenia gravis (SED-13, 1097) (SEDA-20, 327) (SEDA-21, 370). The diagnostic criteria for myasthenia gravis were clearly fulfilled in these reports, and an autoimmune reaction was the most likely mechanism, as each patient had positive serum anti-acetylcholine receptor antibodies and required permanent anticholinesterase drugs long after interferon alfa withdrawal. Myasthenia gravis developed in two patients treated with interferon alfa-2b for chronic hepatitis C, one of whom also took ribavirin (76,77). Both had an increase in acetylcholine receptor antibody titers and required permanent pyridostigmine and immunosuppressant treatment. These findings suggest that interferon alfa does not cause myasthenia gravis but unmasks it.

Sensory systems

Eyes

Ophthalmic disorders can occur during interferon alfa treatment (78–84) and some of the literature has been reviewed (85). Retinopathy consisting of cotton-wool spots and/or superficial retinal hemorrhages has been reported with a variable incidence (18–86%), and the available data suggest that the increased incidence can be influenced by an initial high dose of interferon alfa. Whereas diabetes mellitus and systemic hypertension have been identified as possible susceptibility factors, the incidence of retinopathy was not significantly increased in 19 patients with chronic renal insufficiency, compared with 17 patients without chronic renal insufficiency (86). However, it was felt that renal insufficiency may be associated with the most severe cases, that is those requiring dosage reductions.

In one study, in which prospective ophthalmic examinations were made before and at regular 2-week intervals after the beginning and end of treatment, 28 of 81 patients who received a uniform total dose of natural interferon alfa (478 MU) for chronic hepatitis C developed the typical findings of interferon-induced asymptomatic retinopathy (cotton-wool spots and/or retinal hemorrhages) (84). In contrast, there were no lesions in the 25 patients with chronic hepatitis C who did not receive interferon alfa or in the 20 with diabetes mellitus and/or hypertension but without chronic hepatitis C. Most of the cases were observed within 4 months of treatment, and the lesions always abated after withdrawal or even despite continuation, suggesting that treatment can be continued unless patients develop symptoms. Indeed, most patients with retinopathy associated with interferon alfa remained asymptomatic.

The pathogenesis of retinopathy associated with interferon alfa is unclear. In 45 patients with chronic hepatitis C (25 treated with interferon) there was an association between retinal hemorrhages caused by interferon alfa (six patients) and a concomitant significant increase in plasma-activated complement (C5a), compared with baseline C5a serum concentrations (87). However, the signification and contribution of raised C5a concentrations in the pathogenesis of ocular complications needs to be clarified, although it has been suggested that retinal hemorrhage could be predicted on the basis of raised C5a concentrations (88).

Although most patients with interferon alfa retinopathy remain asymptomatic, ocular complications, such as reduced vision or complete visual loss due to occlusive vasculitis, central retinal artery occlusion, or anterior ischemic optic neuropathy, continue to be reported in a very few patients (SED-13, 1096) (82,85,89–93). However, subclinical but eventually long-lasting or even irreversible abnormally long visual evoked responses have been identified in 24% of patients (SEDA-22, 403). Regular ophthalmological monitoring to detect retinal changes, even though the patient is still asymptomatic, is therefore strongly recommended in patients receiving interferon alfa.

Other isolated reports of ophthalmic abnormalities refer to optic neuritis with blurring of vision, cortical blindness with fatal encephalopathy, mononeural abducent nerve paralysis, and complete but reversible bilateral oculomotor nerve paralysis (SED-13, 1096) (94–97).

- A 60-year-old smoker was treated with interferon alfa (100 MU/week for 2 months and 9 MU/week for 15 weeks) for cutaneous melanoma. Ocular examination was normal before treatment, but he developed acute loss of peripheral vision in his left eye after 23 weeks. Examination was consistent with anterior ischemic optic neuropathy, and there was optic disc edema, a pupillary defect, and circular visual field constriction in the left eye. There was renal artery constriction in both eyes. Despite treatment with aspirin, high-dose dexamethasone, heparin, and finally withdrawal of interferon alfa, loss of visual function progressed and affected both eyes. Ciclosporin was started, but he was considered to have irreversible loss of visual function.

This report shows that interferon alfa can be a potent precipitator of extremely severe ocular disorders and also argues for careful ocular surveillance in patients receiving adjuvant interferon alfa for high-risk resected melanoma.

Of 57 patients treated with interferon for renal cell carcinoma, two developed multiple retinal exudates associated with visual disturbance; both had taken vinblastine concurrently. The precise role of interferon in this reaction is unknown (98).

Ears

In 49 patients, there was reversible otological impairment with tinnitus, mild-to-moderate hearing loss or both in respectively 8, 16, and 20% of patients after interferon alfa or interferon beta administration (SEDA-19, 336). These disorders tended to occur more frequently in patients on high cumulative doses, but led to withdrawal of treatment in only two patients. Complete but reversible hearing loss, and acute unilateral vestibular dysfunction with spontaneous vertigo and nystagmus have each been reported in one patient receiving interferon alfa (SEDA-21, 372).

Sudden hearing loss has been reported (SEDA-21, 372) and in one case of promptly reversible hearing loss on interferon alfa withdrawal, the presence of anti-endothelial cell antibodies was suggested to have played a role in the development of autoimmune microvascular damage (99).

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Smell

Patients treated with interferon alfa sometimes complain of transient taste or smell alterations, but anosmia has been reported (SEDA-22, 403) (100).

- A 37-year-old man received interferon alfa for chronic hepatitis C. After 2 weeks he complained of smelling difficulties and subsequently developed complete anosmia. There were no other neurological symptoms and complete neurological examination was normal. Anosmia still persisted 13 months after drug withdrawal.
- In both patients, the persistence of anosmia late after interferon alfa was resumed indicates that a causal relation to treatment is purely speculative.

Psychological, psychiatric

Neuropsychiatric complications of interferon alfa were recognized in the early 1980s and represent one of the most disturbing adverse effects of interferon alfa (SED-13, 1091) (SEDA-20, 327) (SEDA-22, 400). Reviews have provided comprehensive analysis of the large amount of experimental and clinical data that have accumulated since 1979 (101,102).

DoTS classification (BMJ 2003; 327:1222–5)
Dose-relation: collateral effect
Time-course: intermediate or delayed
Susceptibility factors: pre-existing psychiatric disorders, organic brain injury, or addictive behavior

Presentation

Within a large spectrum of symptoms, complications are classified as acute, subacute, or chronic.

Acute neuropsychological disturbances are usually associated with the flu-like syndrome and include headache, fatigue, and weakness, drowsiness, somnolence, subtle impairment of memory or concentration, and lack of initiative (20). This pattern of cognitive impairment is similar to changes observed during influenza and has also been described in healthy patients who have received a single dose of interferon alfa (103). More severe acute manifestations (for example, marked somnolence or lethargy, frank encephalopathy with visual hallucinations, dementia or delirium, and sometimes coma) have been almost exclusively described in patients receiving more than 20–50 MU (20); vertigo, cramps, apraxia, tremor and dizziness were also reported.

The subacute or chronic neuropsychiatric effects of long-term therapy are usually non-specific, with cognitive impairment (for example visuospatial disorientation, attentional deficits, memory disturbances, slurred speech, difficulties in reading and writing), changes in emotion, mood, and behavior (for example psychomotor slowing, hypersomnia, loss of interest, affective disorders, irritability, agitation, delirium, paranoia, aggressiveness, and murderous impulses). Post-traumatic stress symptoms have also been reported (SEDA-22, 400). As a result, severe psychic distress can be observed during long-lasting treatment or in patients who are otherwise not severely affected (20,104). The most severe psychiatric complications of interferon alfa include rare cases of homicidal ideation, suicidal ideation, and attempted suicide (105).

The clinical features of mania have been described in four patients with malignant melanoma, with a detailed review of nine other published cases (106). Although seven suffered from depression during treatment, the onset of mania or hypomania was often associated with interferon alfa dosage fluctuation (withdrawal or dose reduction) or introduction of an antidepressant for interferon alfa-induced depression. In these patients, the risk of mood fluctuations persisted for several months after interferon alfa withdrawal, and low-dose gabapentin was considered useful in treating manic disorders and in preventing mood fluctuations. Interferon alfa was suggested as a possible cause of persistent manic-depressive illness for more than 4 years in a 40-year-old man (107). Although the manic episodes may have been coincidental, the negative history and the age of onset are in keeping with a possible role of interferon alfa treatment.

The clinical features, management, and prognosis of psychiatric symptoms in patients with chronic hepatitis C have been reviewed using data from 943 patients treated with interferon alfa (85%) or interferon beta (15%) for 24 weeks (108). Interferon-induced psychiatric symptoms were identified in 40 patients (4.2%) of those referred for psychiatric examination. They were classified in three groups according to the clinical profile: 13 cases of generalized anxiety disorder (group A), 21 cases of mood disorders with depressive features (group B), and six cases of other psychiatric disorders, including psychotic disorders with delusions/hallucinations ($n = 4$), mood disorders with manic features ($n = 1$), and delirium ($n = 1$) (group C). The time to onset of the symptoms differed significantly between the three groups: 2 weeks in group A, 5 weeks in group B, and 11 weeks in group C. Women were more often affected than men. There was no difference in the incidence or nature of the disorder according to the type of interferon used. Whereas most patients who required psychotropic drugs were able to complete treatment, 10 had to discontinue interferon treatment because of severe psychiatric symptoms, 5 from group B and five from group C. Twelve patients still required psychiatric treatment for more than 6 months after interferon withdrawal. In addition, residual symptoms (anxiety, insomnia, and mild hypothymia) were still present at the end of the survey in seven patients. Delayed recovery was mostly observed in patients in group C and in patients treated with interferon beta. Although several patients with a previous history of psychiatric disorders are sometimes successfully treated with interferon alfa, severe decompensation with persistent psychosis should be regarded as a major possible complication (109).

The neuropsychological adverse effects of long-term treatment have been assessed in 14 patients with myeloproliferative disorders using a battery of psychometric and electroneurological tests before and after 3, 6, 9, and 12 months of treatment (median dose 25 MU/week) (110). In contrast to several previous studies, there was no significant impairment of neurological function, and attention and short-term memory improved during treatment. Despite the small number of patients, these results suggest that prolonged interferon alfa treatment did not cause severe cognitive dysfunction, at least in patients with cancer.

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Diagnosis

Electroencephalographic (EEG) findings show reversible cerebral changes with slowing of dominant alpha wave activity, and occasional appearance of one and two activity in the frontal lobes, suggesting a direct effect on fronto-subcortical functions. Marked electroencephalographic abnormalities are sometimes observed in asymptomatic patients. The pattern of changes is identical whatever the dose, but the severity of symptoms is dose- and schedule-related. Most patients improve or recover after dosage reduction or withdrawal, and protracted toxicity, with impaired memory, deficits in motor coordination, persistent frontal lobe executive functions, Parkinson-like tremor, and mild dementia, have been occasionally reported (111).

In a study of 67 patients with chronic viral hepatitis, the self-administered Minnesota Multiphasic Personality Inventory (MMPI), which determines the patient's psychological profile, significantly correlated with the clinical evaluation and was a sensitive and reliable tool for identifying patients at risk of depressive symptoms before the start of interferon alfa therapy (112). It was also successfully used to monitor patients during treatment.

Frequency

The most typical psychiatric symptoms reported by patients taking interferon alfa are depressive symptoms, at rates of 10–40% in most studies (113–116). In four clinical studies in a total of 210 patients with chronic hepatitis C, the rate of major depressive disorders during interferon alfa treatment was 23–41% (117–120).

Suicidal ideation or suicidal attempts have been reported in 1.3–1.4% of patients during interferon alfa treatment for chronic viral hepatitis or even within the 6 months after withdrawal (121,122), but the excess risk related to interferon alfa is not known.

Time-course

Subacute or chronic neuropsychiatric manifestations are more typically identified after several weeks of treatment and are among the most frequent treatment-limiting adverse effects (104,115,123–125). The onset can be insidious in patients treated with low doses, or subacute in those who receive high doses. Most patients develop severe depressive symptoms within the first 3 months of treatment (117–120).

Although psychiatric manifestations usually appear during interferon alfa therapy, delayed reactions can occur.

- A 37-year-old man without a previous psychiatric history developed major depression with severe psychotic features within days after the discontinuation of a 1-year course of interferon alfa-2b (126).

In 10 patients with melanoma and no previous psychiatric disorders, depression scores measured on the Montgomery-Asberg Depression Rating Scale were significantly increased after 4 weeks of high-dose interferon alfa (127). Patients whose scores were higher before treatment developed the worst symptoms of depression during treatment. This positive correlation provides striking evidence that baseline and regular assessment of mood and cognitive functions are necessary to detect disorders as early as possible.

Mechanisms

Although very few studies have specifically investigated the role of the underlying disease, the findings of significant neuropsychiatric deterioration during interferon alfa treatment compared with placebo or no treatment in chronic hepatitis C, chronic myelogenous leukemia, or amyotrophic lateral disease strongly suggested a causal role of interferon alfa (128–130).

The mechanism by which the systemic administration of interferon alfa produces neurotoxicity is unclear, and might result from a complex of direct and indirect effects involving the brain vasculature, neuroendocrine system, neurotransmitters and the secondary cytokine cascade with cytokines which exert effects on the nervous system, for example interleukin-1, interleukin-2, or tumor necrosis factor alfa (131). Whether a clinical effect is directly mediated through the action of a given cytokine or results from a secondary pathway through the induction of other cytokines or second messengers is difficult to determine.

A study in 18 patients treated with interferon alfa for chronic hepatitis C has given insights into the possible pathophysiological mechanism of depression (132). Depression rating scales, plasma tryptophan concentrations, and serum kynurenine and serotonin concentrations were measured at baseline and after 2, 4, 16, and 24 weeks of treatment with interferon alfa 3–6 MU 3–6 times weekly. During treatment, tryptophan and serotonin concentrations fell significantly, while kynurenine concentrations rose significantly. Depression rating scales also rose from baseline after the first month of treatment, with continued increases thereafter. In addition, there was a relation between increased scores of depression and changes in serum kynurenine and serotonin concentrations. These changes suggested a predominant role of the serotonergic system in the pathophysiological mechanisms of interferon alfa-associated depression. Accordingly, 35 of 42 patients included in three open trials of antidepressant treatment responded to a selective serotonin reuptake inhibitor drug, such as citalopram or paroxetine, and were able to complete interferon treatment (119,133,134).

Susceptibility factors

Various possible susceptibility factors have been analysed in several studies (118–120,135). Sex, the dose or type of interferon alfa (natural or recombinant), a prior personal history of psychiatric disease, substance abuse, the extent of education, the duration and severity of the underlying chronic hepatitis, and scores of depression before interferon alfa treatment were not significantly different between patients with and without interferon alfa-induced depression. Advanced age was suggested to be a risk factor in only one study (120). Although a worsening of psychiatric symptoms was noted during treatment in 11 patients receiving psychiatric treatment before starting interferon, only one was unable to complete the expected 6-month course of interferon alfa and ribavirin therapy (118).

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Of 91 patients treated with interferon alfa-2b and low-dose cytarabine for chronic myelogenous leukemia, 22 developed severe neuropsychiatric toxicity (136). Their symptoms consisted mostly of severe depression or psychotic behavior, which resolved on withdrawal in all patients. The time to toxicity ranged from as early as 2 weeks to as long as 184 weeks after the start of treatment. Five of six patients had recurrent or worse symptoms after re-administration of both drugs. Several baseline factors were analysed, but only a pretreatment history of neurological or psychiatric disorders was considered to be a reliable risk factor. Severe neuropsychiatric toxicity developed during treatment in 63% of patients with previous neuropsychiatric disorders compared with 10% in patients without. It is unlikely that the combination of interferon alfa-2b with low-dose cytarabine potentiated the neuropsychiatric adverse effects of interferon alfa in this study. Indeed, previous experience with this combination, but after exclusion of patients with a psychiatric history, was not associated with such a high incidence of neuropsychiatric toxicity or any significant difference in toxicity between interferon alfa alone and interferon alfa plus low-dose cytarabine.

Patients receiving high doses of interferon alfa or long-term treatment are more likely to develop pronounced symptoms (123). A previous history of psychiatric disorders, organic brain injury, or addictive behavior are among potential susceptibility factors, but worsening of an underlying psychiatric disease is not the rule, provided that strict psychiatric surveillance and continuation of psychotropic drugs are maintained (137). Other putative susceptibility factors include the intraventricular administration of interferon alfa, previous or concomitant cranial irradiation, asymptomatic brain metastases, and pre-existing intracerebral ateriosclerosis (SED-13, 1092) (115,138–142). Despite early findings, co-infection with HIV has not been confirmed to be a susceptibility factor (SEDA-20, 327).

The occurrence of psychiatric disorders has been prospectively investigated in 63 patients who received a 6-month course of interferon alfa (9 MU/week) for hepatitis C (143). All were assessed at baseline with the Structured Clinical Interview for DSM-III-R (SCID) and monitored monthly with the Hopkins Symptoms Checklist (SCL-90). Most had a history of alcohol or polysubstance dependence, and 12 had a lifetime diagnosis of major depression. There were no significant changes in the SCL-90 scores during the 6-month period of survey in the 49 patients who completed the study, even in those who had a lifetime history of major depression. At 6 months, there was probable minor depression in eight patients and major depression in one; none had attempted suicide.

In a prospective study, 50 patients with chronic hepatitis B or C who received 18–30 MU/week of natural or recombinant interferon alfa were followed for 12 months (144). The SCID before starting interferon alfa identified 16 patients with a current psychiatric diagnosis and eight with a previous psychiatric disorder; 26 patients free of any psychiatric history constituted the control group. Psychiatric manifestations during treatment occurred in 11 patients (five from the control group), major depression in five, depressive disorders in three, severe dysphoria in two, and generalized anxiety disorder in one. Most of them were successfully treated with psychological support and drug therapy. Overall, 20 patients interrupted interferon alfa (10 in each group), including three for psychiatric adverse effects, but patients with a pre-existing or recent psychiatric diagnosis were no more likely to withdraw from treatment than the controls.

Of 33 patients with chronic hepatitis C treated with interferon alfa, 9 MU/week for 3–12 months, prospectively evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS) before and after 12 weeks of treatment, eight developed depressive symptoms, of whom four had major depression without a previous psychiatric history (145). All four recovered after treatment with antidepressants. This study confirmed that a high baseline MADRS is significantly associated with the occurrence of depressive symptoms.

These studies have confirmed that previous psychiatric disorders are not necessarily a contraindication to a potentially effective treatment. However, patients with depressive symptoms immediately before treatment are still regarded at risk of severe psychiatric deterioration with treatment (113).

Management

The management of the psychiatric complications of interferon alfa has not been carefully investigated, but multiple approaches are theoretically possible. Various pharmacological and non-pharmacological interventions have been discussed (146), and prompt intervention should be carefully considered in every patient who develops significant neuropsychiatric adverse effects while receiving interferon alfa. Depending on the clinical manifestations, proposed treatment options include antidepressants, psychostimulants, or antipsychotic drugs.

Based on a possible reduction in central dopaminergic activity mediated by the binding of interferon alfa to opioid receptors, naltrexone has been proposed as a means of improving cognitive dysfunction (123).

Selective serotonin re-uptake inhibitors have been advocated as the drugs of choice to allow completion of interferon alfa treatment (113), but that was based on very limited experience and the unproven assumption that SSRIs are safe in patients with underlying liver disease. The preliminary results of a double-blind, placebo-controlled study showed that 2 weeks of pretreatment with paroxetine significantly reduced the occurrence of major depression in 16 patients on high-dose interferon alfa for malignant melanoma (147). In a placebo-controlled trial, the preventive effects of paroxetine (mean maximal dose of 31 mg) were studied in 40 patients with high-risk malignant melanoma and interferon alfa-induced depression (148). Treatment started 2 weeks before adjuvant high-dose interferon alfa. Paroxetine significantly reduced the incidence of major depression (45% in the placebo group and 11% in the paroxetine group) and the rate of interferon alfa withdrawal (35 versus 5%). Although the number of patients was small and the duration of the survey short (12 weeks), this suggests that paroxetine effectively prevents the risk of depressive disorders in patients eligible for high-dose interferon alfa. However, these results are

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limited, because patients with melanoma who receive adjuvant high-dose interferon alfa are particularly likely to develop depression. The safety of prophylaxis with paroxetine also requires additional data, because three patients taking paroxetine developed retinal hemorrhages, including one with irreversible loss of vision.

- In contrast to this study, a 31-year-old woman with major depressive disorder, which responded to paroxetine and trazodone, had progressive recurrence of mood disorders after the introduction of interferon alfa for essential thrombocythemia (149).

This suggests that interferon alfa can also reverse the response to antidepressants.

Endocrine

Pituitary

Interferon alfa can stimulate the hypothalamic–pituitary–adrenal axis, with a marked increase in cortisol and adrenocorticotrophic hormone secretion after acute administration (SED-13, 1093). No further stimulation was observed after several weeks of treatment, pointing to possible down-regulation of the ACTH secretory system. As a result, long-term treatment with interferon alfa is not thought to influence pituitary hormones significantly, and the concentration of several hormones, for example calcitonin, LH, FSH, prolactin, growth hormone, ACTH, cortisol, testosterone, and estradiol, were not modified by prolonged interferon alfa treatment (150,151). No clinical endocrinopathies attributable to such disorders in the regulation of these hormones have yet been reported.

Although the rate of growth was significantly lower than predicted in 35% of children receiving long-term treatment for recurrent respiratory papillomatosis (152), only one case of growth retardation has been reported in other settings (SEDA-19, 335). A significant reduction in weight and nutritional status was observed during treatment with interferon alfa for 6 months for chronic viral hepatitis in children aged 4–16 years, but this was transient and not associated with growth impairment (153).

Reversible hypopituitarism with antibodies to pituitary GH3 cells and exacerbation of Sheehan's syndrome have been reported (SED-13, 1093) (SEDA-21, 371).

A syndrome resembling inappropriate antidiuretic hormone secretion has been described in a few patients receiving high-dose interferon alfa (SED-13, 1093) (154).

Thyroid

Since the original 1988 report of hypothyroidism in patients with breast cancer receiving leukocyte-derived interferon alfa (155), numerous investigators have provided clear clinical and biological data on thyroid disorders induced by different forms of interferon in patients with various diseases (21,156–159). Two of these reports also mentioned associated adverse effects that developed concomitantly, namely myelosuppression and severe proximal myopathy (Hoffmann's syndrome).

Presentation and outcomes

The spectrum of interferon alfa-induced thyroid disorders ranges from asymptomatic appearance or increase in antithyroid autoantibody titers to moderate or severe clinical features of hypothyroidism, hyperthyroidism, and acute biphasic thyroiditis. Antithyroid hormone antibodies have also been found in one patient, and this could have been the cause of erroneously raised thyroid hormone concentrations (160).

The clinical, biochemical, and thyroid imaging characteristics of thyrotoxicosis resulting from interferon alfa treatment have been retrospectively analysed from data on 10 of 321 patients with chronic hepatitis (75 with chronic hepatitis B and 246 with chronic hepatitis C) who developed biochemical thyrotoxicosis (161). Seven patients had symptomatic disorders, but none had ocular symptoms or a palpable goiter. Six had features of Graves' disease that required interferon alfa withdrawal in four and prolonged treatment with antithyroid drugs in all six. Three presented with transient thyrotoxicosis that subsequently progressed to hypothyroidism and required interferon withdrawal in one and thyroxine treatment in all three.

Although much work on thyroid autoimmunity associated with interferon alfa has accumulated, little is known about the very long-term outcome of this disorder. In 114 patients with chronic hepatitis C and no previous thyroid disease who were treated with interferon alfa-2a for 12 months, data on thyroid status were retrospectively obtained at the end of treatment, 6 months after withdrawal, and after a median of 6.2 years (162). Among 36 patients who had thyroid autoantibodies at the end of treatment, the authors identified three groups according to the long-term outcome: 16 had persistent thyroiditis, 10 had remitting/relapsing thyroiditis (that is antibodies became negative after 6 months of therapy and were again positive thereafter), and 10 had transient thyroiditis. Therefore, 72% of these patients had chronic thyroid autoimmunity at the end of follow-up and 12 developed subclinical hypothyroidism. In contrast, only one of 78 patients negative for thyroid autoantibodies developed thyroid autoantibodies. Although none of the patients had clinical thyroid dysfunction, this study suggests that long-term surveillance of thyroid disorders is useful in patients who have high autoantibody titers at the end of treatment with interferon alfa.

Although thyroid disorders in patients treated with interferon alfa generally follows a benign course after interferon alfa withdrawal or specific treatment, severe long-lasting ophthalmopathy resulting from Graves' disease has been described in a 49-year-old woman (163).

Time-course

Clinical symptoms usually occur after 2–6 months of treatment and occasionally after interferon alfa withdrawal.

- A middle-aged woman developed subacute thyroiditis by the sixth month of treatment with interferon alfa (164). She also had the classic symptoms of hyperthyroidism, although it is clear that these could easily have been mistaken for adverse effects of interferon alfa itself, for example weakness, weight loss, and palpitation.

After 6 months of treatment, 12% of patients with chronic hepatitis C had thyroid disorders, compared with 3% of patients with chronic hepatitis B. This study also suggested a possible relation between low free triiodothyronine serum concentrations before treatment and the

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subsequent occurrence of thyroid dysfunction. After a follow-up of 6 months after the end of interferon alfa treatment, 60% of affected patients with chronic hepatitis C still had persistent thyroid dysfunction; all had been positive for thyroid peroxidase antibodies before treatment. Long-term surveillance is therefore needed in these patients.

Frequency

In a prospective study, the overall incidence of biochemical thyroid disorders was 12% in 254 patients with chronic hepatitis C randomized to receive ribavirin plus high-dose interferon alfa (6 MU/day for 4 weeks then 9 MU/week for 22 weeks) or conventional treatment (9 MU/week for 26 weeks) (165). There was no difference in the incidence or the time to occurrence of thyroid disorders between the groups. Of the 30 affected patients, 11 (37%) had positive thyroid peroxidase autoantibodies (compared with 1% of patients without thyroid dysfunction), nine developed symptomatic thyroid dysfunction, and only three had to discontinue treatment. There was no correlation between the viral response and the occurrence of thyroid disorders, and only female sex and Asian origin were independent predictors of thyroid disorders.

Data on the incidence of thyroid disorders in interferon alfa-treated patients vary, largely because the follow-up duration, the nature of the study (prospective or retrospective), biological monitoring, diagnostic criteria, and the underlying disease differ from study to study (156). The incidence of clinical or subclinical thyroid abnormalities is generally 5–12% in large prospective studies in patients with chronic hepatitis C treated for 6–12 months, but it reached 34% in one study (21,166). The incidence was far lower in patients with chronic hepatitis B, at 1–3%. A wider range in incidence was found in patients with cancer, with no clinical thyroid disorders in 54 patients treated during a mean of 16 months for hematological malignancies (167), whereas in many other studies there was a 10–45% incidence (156). Even more impressive was the escalating incidence of thyroid disorders in patients with cancer receiving both interferon alfa and interleukin-2 (qv).

Mechanisms

Possible mechanisms need to be clarified. Since thyroid autoantibodies are detected in most patients who develop thyroid disorders, the induction or exacerbation of preexisting latent thyroid autoimmunity is the most attractive hypothesis. This is in accordance with the relatively frequent occurrence of other autoantibodies or clinical autoimmune disorders in patients who develop thyroid disorders (168). However, 20–30% of patients who develop thyroid diseases have no thyroid antibodies, and it is thus not yet proven that autoimmunity is the universal or primary mechanism. In fact, there were subtle and reversible defects in the intrathyroidal organification of iodine in 22% of antithyroid antibody-negative patients treated with interferon alfa (169). In addition, the acute systemic administration of interferon alfa in volunteers or chronic hepatitis patients reduces TSH concentrations (SED-13, 1093) (170), and in vitro studies have suggested that interferon alfa directly inhibits thyrocyte function (SED-13, 1093) (171). Finally, the thyroid autoantibody pattern in patients who developed thyroid dysfunction during cytokine treatment was not different from that of patients without thyroid dysfunction, but differed significantly from that of patients suffering from various forms of spontaneous autoimmune thyroid disease (172).

Susceptibility factors

In addition to the underlying disease, there are many potential susceptibility factors (21,173). There is as yet no definitive evidence that age, sex, dose, and duration of treatment play an important role in the development of thyroid disorders. However, patients with previous thyroid abnormalities are predisposed to develop more severe thyroid disease (SEDA-20, 328). The incidence of thyroid disease was not different between natural and recombinant interferon alfa. Although this should be taken into account, a previous familial or personal history of thyroid disease was generally not considered a major risk factor. Finally, only pre-treatment positivity or the development of thyroid antibodies during treatment seem to be strongly associated with the occurrence of thyroid dysfunction.

In 175 patients with hepatitis B or C virus infections, women with chronic hepatitis C and patients with previously high titers of antithyroid autoantibodies were more likely to develop thyroid disorders (174).

The immunological predisposition to thyroid disorders has been studied in 17 of 439 Japanese patients who had symptomatic autoimmune thyroid disorders during interferon alfa treatment (175). There was a significantly higher incidence of the human leukocyte antigen (HLA)-A2 haplotype compared with the general Japanese population (88 versus 41%), suggesting that HLA-A2 is a possible additional risk factor for the development of interferon alfa-induced autoimmune thyroid disease.

Among other potential predisposing factors, treatment with iodine for 2 months in 21 patients with chronic hepatitis C receiving interferon alfa did not increase the likelihood of thyroid abnormalities compared with eight patients who received iodine alone, but abnormal thyroid tests were more frequent compared with 27 patients who received interferon alfa alone (176). This suggests that excess iodine had no synergistic effects on the occurrence of thyroid dysfunction induced by interferon alfa.

The occurrence of thyroid dysfunction in 72 patients treated with interferon alfa plus ribavirin (1.0–1.2 g/day) has been compared with that of 75 age- and sex-matched patients treated with interferon alfa alone for chronic hepatitis C (177). Of the former, 42 patients, and of the latter, 40 patients had received previous treatment with interferon alfa alone. There was no difference in the rate of thyroid autoimmunity (antithyroglobulin, antithyroid peroxidase, and thyroid-stimulating hormone receptor antibodies) between the two groups, but the patients who received interferon alfa plus ribavirin developed subclinical or overt hypothyroidism more often (15 versus 4%). Similarly, the incidence of hypothyroidism increased to 19% in patients who underwent a second treatment with interferon alfa plus ribavirin compared with 4.8% after the first treatment with interferon alfa alone, while the incidence remained essentially the same in patients who had two consecutive treatments with interferon alfa alone

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(4.7 and 7.1% respectively). Furthermore, there was no higher incidence of thyroid autoimmunity or clinical disorders after a second course of interferon alfa whether alone or combined with ribavirin in patients who had no thyroid autoantibodies at the end of a first course of interferon alfa alone, suggesting that these patients are relatively protected against the development of thyroid autoimmunity.

Management

The management of clinical thyroid dysfunction depends on the expected benefit of interferon alfa. Assay of thyroid antibodies before treatment, and regular assessment of TSH concentrations in treated patients, even after interferon alfa withdrawal, are useful as a means of predicting and detecting the risk of thyroid disorders. Complete recovery of normal thyroid function is usually observed after thyroxine replacement but sometimes requires interferon alfa withdrawal. Sustained hypothyroidism requiring long-term substitution treatment has occasionally been observed (SED-13, 1092) (178), and is more likely in patients with initially severe hypothyroidism and raised thyroid antibody titers (179). By contrast, hyperthyroidism generally requires the prompt withdrawal of interferon alfa, and severe forms may require radical radioiodine therapy. Although not enough data are available on the long-term consequences of interferon alfa-induced thyroid dysfunction, the recurrence of thyroid abnormalities after the administration of pharmacological doses of iodine should be borne in mind (180).

Parathyroid

Exacerbation of secondary hyperparathyroidism occurred in a 20-year-old renal transplant patient who also developed psoriasis during interferon alfa treatment (181). Both disorders resolved after withdrawal.

Adrenal

Of 62 initially autoantibody-negative patients treated with interferon alfa for chronic hepatitis C for a mean of 8 months, three developed antibodies to 21b-hydroxylase, a sensitive assay of adrenocortical autoimmunity (182). However, there were no cases of Addison's disease or subclinical adrenal insufficiency. This study suggested that the adrenal cortex is another potential target organ of autoimmune effects of interferon alfa, along with thyroid and pancreatic islet cells.

Metabolism

Diabetes mellitus

The development or worsening of insulin-dependent diabetes mellitus is limited to isolated case reports in patients treated with interferon alfa or interferon alfa plus interleukin-2 (SEDA-20, 328) (SEDA-21, 371). In chronic hepatitis, diabetes mellitus was noted in only 10 of 11 241 treated patients (16). Although a relation between chronic hepatitis C and the occurrence of glucose metabolism disorders is possible (183), reports of diabetes mellitus in patients treated with interferon alfa were probably more than coincidental. Indeed, there have been reports of prompt amelioration or complete recovery after interferon alfa withdrawal (SED-13, 1092) (184–186) and of successive episodes of diabetes after each course of interferon alfa (SEDA-21, 371).

- In three middle-aged patients, diabetes was diagnosed after 3–7 months of treatment with interferon alfa-2b and ribavirin, and two presented with severe ketoacidosis (187,188). There was a family history of diabetes in one patient and two had high titers of glutamic acid decarboxylase antibodies before treatment. One patient never had diabetes-related serum autoantibodies before or after interferon alfa therapy. All three required permanent insulin treatment despite withdrawal of interferon alfa.
- Insulin-dependent diabetes mellitus has been reported after 2 weeks to 6 months of treatment with interferon alfa in four patients with chronic hepatitis C (189). All discontinued interferon alfa, and one woman who restarted treatment had a subsequent increase in insulin requirements.

A 75 g oral glucose tolerance test was performed before and after 3 months of interferon alfa treatment in 32 patients with chronic hepatitis C, of whom 15 also had an intravenous glucose test (190). Baseline evaluation showed that five patients had mild diabetes mellitus, three had impaired glucose tolerance, and 24 were normal. After 3 months of treatment, two patients with diabetes mellitus shifted to impaired glucose tolerance, and all patients with impaired glucose tolerance had normal glucose tolerance. Only three initially normal patients developed impaired glucose tolerance and none had newly diagnosed diabetes mellitus. From these results, and in contrast to previous reports (SED-14, 1250), it appears that interferon alfa did not have any adverse effects on insulin sensitivity and glucose tolerance after 3 months of treatment.

Interferon alfa may produce more severe changes than interferon beta (191).

- A 39-year-old man with diabetes, stabilized with insulin 22 U/day for 13 years, received interferon beta (6 MU/day) for chronic hepatitis C. His diabetes progressively worsened, necessitating insulin 50 U/day. After 4 weeks, interferon beta was replaced by interferon alfa (10 MU/day). Shortly afterwards he developed severe diabetic ketoacidosis and shock, which reversed after hemodynamic support and continuous hemodiafiltration.

Mechanisms

Autoimmunity was suggested as a likely mechanism, with HLA-DR4 haplotype and/or islet cell antibody (ICA) positivity at the time of diagnosis in several patients. Because the induction of ICA antibodies in patients treated with interferon alfa has never been otherwise demonstrated (21), the triggering, rather than the induction, of a latent autoimmune phenomenon in patients with a genetic susceptibility is probable (192).

More direct interference with glucose metabolism cannot be excluded. Interferon alfa can reduce the sensitivity of peripheral tissues or liver to insulin and accelerate the destruction of stimulated pancreatic beta-cells (193,194); this could be a possible mechanism in patients not exhibiting islet cell antibodies. This is also

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in keeping with rare instances of induction or exacerbation of type II non-insulin dependent diabetes mellitus (SEDA-19, 335).

Insulin antibodies were also found in six of 58 patients treated for chronic viral hepatitis (195) and that was associated with signs of insulin allergy in one patient (SEDA-19, 335).

Susceptibility factors

Patients with obesity and a family or previous history of glucose intolerance should be considered more predisposed to interferon alfa-induced diabetes, but the association is not consistently found (SEDA-20, 328).

Dyslipidemia

Interferon alfa often affects lipid metabolism and produces a reversible reduction in cholesterol and, more consistently, increases in triglyceride concentrations (SEDA-20, 328) (SEDA-21, 371). Meticulous blood lipid investigation showed a significant rise in serum triglyceride and lipoprotein(a) concentrations and reductions in total cholesterol, HDL cholesterol, LDL cholesterol, and apoprotein A1.

Marked hypertriglyceridemia (10–20 μg/ml), which abates when treatment is withdrawn, has sometimes been observed (SED-13, 1093) (196,197). Inhibitory effects of interferon alfa on lipoprotein lipase and triglyceride lipase or increased hepatic lipogenesis have been suggested (198,199). Diet and lipid-lowering drugs have been proposed as means of maintaining acceptable triglyceride concentrations during long-term interferon alfa therapy. Although the possibility of pancreatic or cardiovascular complications should be borne in mind, no secondary clinical consequences of interferon alfa-induced blood lipid disorders have been so far reported.

In a prospective study of lipid changes in 36 patients with chronic hepatitis C treated with interferon alfa for 6 months, the most prominent findings included increases in triglycerides, VLDL cholesterol, and apolipoprotein B, and falls in HLD cholesterol and apolipoprotein A1 (200). Three patients also developed chylomicronemia and two of those had severe hypertriglyceridemia. All three patients had triglycerides over 2 μg/ml before treatment, suggesting that patients with abnormal serum triglyceride concentrations at baseline are more likely to develop marked hypertriglyceridemia.

Porphyria

- A severe acute flare of porphyria cutanea tarda has been reported in a 61-year-old man after 4 months of treatment with interferon alfa-2b plus ribavirin for chronic hepatitis C (201). No further relapse was observed after chloroquine treatment, despite continuation of the antiviral drugs.

This patient had previously had episodes of small blisters that spontaneously resolved, and hereditary porphyria cutanea tarda was demonstrated by chromatographic and mutation analysis.

Hematologic

Hematological toxicity due to interferon alfa commonly includes dose-related leukopenia, neutropenia, and thrombocytopenia, whereas anemia is rare and usually moderate (202).

Reductions in platelet count and leukocyte count were usually in the range of 30–50% compared with baseline, but severe and reversible thrombocytopenia ($<49 \times 10^9$/l) or neutropenia ($<0.9 \times 10^9$/l) were noted in 10 and 20% of patients (203). However, life-threatening neutropenia or thrombocytopenia were reported in only six of 11 241 patients with chronic viral hepatitis (16), and reports of Coombs'-negative hemolytic anemia or complete agranulocytosis are sparse (SED-13, 1094) (SEDA-20, 329).

In a retrospective study of 158 patients with chronic viral hepatitis treated for 6–12 months, lymphoblastoid interferon alfa produced the largest fall in leukocyte and platelet counts (−38 and −32% versus baseline values), recombinant interferon alfa was associated with intermediate toxicity (−32 and −26%), and leukocyte interferon alfa produced the smallest reduction (−27 and −22%) (204). The lowest mean values were observed after an average of 4–5 months. However, the clinical relevance of these differences is probably minimal, because the overall reduction in leukocyte and platelet numbers was small, and no patients developed clinical symptoms of cytopenia.

Mechanisms

Interferon alfa has direct myelosuppressive effects and can also cause hematological disorders by immune blood cell destruction, as suggested by reports of immune-mediated thrombocytopenia, immune hemolytic anemia (205,206), or a positive direct Coombs' test, with or without hemolysis (207–209).

The kinetics of the hemotoxic effects of interferon alfa have been studied in 76 patients with chronic hepatitis C (210). There were significant falls in white blood cell count and platelet count within 12 hours after the first injection, and a second fall in platelet count after 2 weeks, but not further thereafter. This rapid time-course suggests that liver or spleen sequestration of blood cells, rather than direct bone marrow suppression or immune-mediated hematological toxicity, is the most likely explanation for this acute hemotoxic effect, which does not preclude continuation of treatment.

Susceptibility factors

Susceptibility factors for severe hematological toxicity include cirrhosis and hypersplenism.

Prior interferon alfa treatment lasting for more than 6 months and withdrawn for 2–3 months was also one of the most significant factors to explain a reduced yield of peripheral blood stem cells in 88 previously autografted patients with myeloma undergoing G-CSF stimulation for future autotransplantation (211). As suggested by this study, the myelosuppressive effects of interferon alfa may be prolonged to such an extent that a minimum delay of more than 2–3 months after interferon alfa withdrawal should be considered before harvesting bone marrow cells.

Pancytopenia or aplasia, sometimes fatal, have been reported only in patients who had received previous

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chemotherapy, as has severe and even fatal erythrocytosis in patients with hairy cell leukemia (SED-13, 1094) (212–216).

Anemia

Isolated anemia is not a common feature of the hemotoxic effects of interferon alfa, and pure red cell aplasia has been reported in two patients with chronic leukemia for several months (217,218). Both patients improved progressively after replacement of interferon alfa by hydroxyurea. However, one required erythrocyte transfusions for 14 months.

- Pernicious anemia with a low vitamin B_{12} concentration and positive intrinsic factor antibodies has been reported in a 54-year-old woman who was receiving interferon alfa as a maintenance treatment for relapsing chronic hepatitis C (219).

Rapid exacerbation (1–21 days) or delayed (3–38 months) de novo appearance of immune hemolytic anemia has been reported after initiation of interferon alfa treatment in nine patients with lymphoproliferative disorders (220). However, this rare event was identified in only 1% of 581 patients receiving interferon alfa alone or as part of a chemotherapeutic regimen for chronic myelogenous leukemia (221). A mechanism close to that observed with alpha-methyldopa has been thought to be involved (208). The direct antiglobulin test was positive in 32% of 28 chronic myeloid leukemia patients after a median of 1 year of treatment with interferon alfa (222).

Interferon alfa can also induce multiple antibody formation to transfused blood cell antigens, with subsequent massive hemolysis (223).

- A 33-year-old man developed a delayed hemolytic reaction 7 days after red cell transfusion (224). Additional investigations showed the presence of an anti-M antibody, the production of which was supposedly caused by chemoimmunotherapy (interferon alfa, interleukin-2, and 5-fluorouracil) which was begun 24 hours after transfusion.

Leukopenia

The dose of interferon alfa is usually halved when the neutrophil count falls below 0.75×10^9/l or the drug is permanently withdrawn when it falls below 0.5×10^9/l. However, this issue has recently been challenged by a retrospective analysis of 11 patients with compensated cirrhosis, four of whom had severe neutropenia (that is 0.4 to 0.67×10^9/l) during the first 2 months of treatment (225). They remained asymptomatic and the neutropenia spontaneously reversed despite continued treatment.

In one study in 119 patients treated with interferon alfa and ribavirin for chronic hepatitis C, in whom neutropenia was not considered as a cause for exclusion or dosage modification, the neutrophil count fell by an average of 34% (31–74%) (226). During the course of treatment, 32 patients had at least one neutrophil count below 1×10^9/l, 11 had a neutrophil count below 0.75×10^9/l, and 2 had a neutrophil count below 0.5×10^9/l; however, none of these patients required dosage modification because of neutropenia. None of the 22 patients who developed documented or suspected bacterial infections during or immediately after treatment withdrawal had concomitant neutropenia. The three black patients with constitutional neutropenia (pretreatment neutrophil counts below 1.5×10^9/l) had only minimal changes in their neutrophil counts during treatment and no infection, suggesting that these patients can be safely treated.

Thrombocytopenia

Although inhibition of stem-cell proliferation is the most likely mechanism of hematological toxicity, increased platelet hepatic uptake has been suggested to account for thrombocytopenia (227). Raised serum thrombopoietin concentrations were found in patients with interferon alfa-induced thrombocytopenia (228). However, there is evidence that serum thrombopoietin concentrations in patients who have had thrombocytopenia during interferon alfa treatment for chronic viral hepatitis C either do not increase (in patients with compensated cirrhosis) or increase only moderately and less than expected (in non-cirrhotic patients) (229). The authors proposed that interferon alfa impairs liver production of thrombopoietin, raising the possibility of testing thrombopoietin administration in patients with severe thrombocytopenia before or during treatment with interferon alfa (230).

- In a 45-year-old man treated with pegylated interferon alfa-2b for relapsing chronic hepatitis C, thrombocytopenia recovered over 2 months, despite initial treatment with glucocorticoids and immunoglobulin (231).

Interferon alfa-induced immune-mediated thrombocytopenia shares many features with idiopathic thrombocytopenic purpuras and may be therefore coincidental (SED-13, 1094) (SEDA-20, 328) (SEDA-21, 371), but recurrence of thrombocytopenia on interferon alfa readministration strongly supports a causal role of interferon alfa (232). Cross reaction with interferon beta was not found in an isolated report (SEDA-20, 329). Even though severe and even fatal worsening of idiopathic thrombocytopenic purpura has been observed after administration of interferon alfa (SED-13, 1094) (SEDA-20, 328), interferon alfa was not considered harmful in patients with chronic hepatitis C who were previously positive for platelet-associated immunoglobulin G (233).

Thrombotic thrombocytopenic purpura is a possible complication of interferon alfa in patients with chronic myelogenous leukemia, and can develop even after a successful prolonged (2–3 years) treatment (234). Complete recovery is expected after prompt medical management with plasma exchange and glucocorticoids.

Platelet aggregation

The effects of interferon alfa-2b on platelet aggregation have been studied in 29 patients with melanoma who received a low-dose regimen (9 MU/week in five patients) or a high-dose regimen (100 MU/m^2/week intravenously for 4 weeks, then 30 MU/m^2/week subcutaneously for 48 weeks in 24 patients) (235). Compared with pretreatment values and healthy controls, there was significant inhibition of platelet aggregation in the high-dose group, while the effects were minimal in the low-dose group. In the high-dose group, the inhibition was more prominent during the subcutaneous maintenance dose and was still

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detectable 8 weeks after interferon alfa withdrawal in 60% of the tested samples. An increased risk of bleeding should therefore be anticipated in patients who receive high-dose interferon alfa.

Clotting factors

Clotting disorders due to interferon alfa have rarely been reported.

- Asymptomatic prolongation of the activated partial thromboplastin time associated with lupus anticoagulant and a reduction in the coagulation activity of factors IX, XI, and XII occurred after 10 weeks of interferon alfa-2b and ribavirin in a 60-year-old woman with chronic hepatitis C (236). There were no arguments in favor of an antiphospholipid syndrome, and all the abnormalities normalized after withdrawal.

Interferon alfa was suspected of having induced the development of anti-factor VIII autoantibodies in one patient with hemophilia who survived and one without hemophilia who subsequently died from acute hemorrhage (SED-13, 1094) (237,238).

- There was significant bleeding with hematomas in association with an inhibitor of factor VIII in a 58-year-old man who took interferon alfa for 1 year for chronic myelogenous leukemia (239). The factor VIII inhibitor, which was markedly raised, disappeared within 6 weeks of interferon alfa withdrawal and prednisone treatment.

By contrast, in a small uncontrolled study, there was no increase in antifactor VIII antibodies in patients with hemophilia A treated with interferon alfa (240).

Gastrointestinal

Mild and transient gastrointestinal disorders, namely nausea, vomiting, diarrhea or anorexia, were observed in 30–40% of patients, and their severity is typically dose-related (20). Dryness or inflammation of the oropharynx, and moderate stomatitis were sometimes noted, but severe painful oral ulcers recurring after interferon alfa re-administration have been reported (241). More severe forms of digestive disease have been described in isolated case histories with microscopic colitis and the occurrence or the exacerbation of ulcerative colitis (SED-13, 1094) (SEDA-21, 372).

Celiac disease

Celiac disease was observed after 2–3 months of interferon alfa treatment in two patients with chronic hepatitis C aged 34 and 38 years (242). Both had total villous atrophy on distal duodenal biopsy, were positive for antiendomysial antibodies, and responded to a gluten-free diet. Three other cases were reported after 1–5 months of treatment for chronic hepatitis C (37,243). The diagnosis was confirmed in all three patients, based on the presence of total villous atrophy on distal duodenal biopsy, positivity of antiendomysial antibodies, and recovery with a gluten-free diet. Pretreatment antiendomysial antibodies were positive in the two patients tested. As suggested in one patient, interferon alfa can be safely continued providing that a gluten-free diet is strictly respected.

Enteritis

Eosinophilic enteritis has been attributed to interferon alfa (244).

- A 23-year-old man with no previous history of digestive disorders took interferon alfa for chronic hepatitis C. After 2 weeks of treatment, he had severe abdominal pain and diarrhea. The absolute eosinophil count was 7.5×10^9/l, with 40% eosinophils on bone marrow aspiration and a markedly high IgE concentration. Radiological examination showed diffuse jejunal and ileal wall thickening and gross ascites with numerous eosinophils. Complete resolution was obtained after interferon alfa withdrawal and prednisolone treatment. There was no recurrence after prednisolone was withdrawn.
- A 23-year-old man with no previous history of digestive disorders took interferon alfa for chronic hepatitis C. After 2 weeks of treatment, he had severe abdominal pain and diarrhea. The absolute eosinophil count was 7.5×10^9/l, with 40% eosinophils on bone marrow aspiration and a markedly high IgE concentration. Radiological examination showed diffuse jejunal and ileal wall thickening and gross ascites with numerous eosinophils. Complete resolution was obtained after interferon alfa withdrawal and prednisolone treatment. There was no recurrence after prednisolone was withdrawn.

Colitis

Microscopic colitis and new or worsened ulcerative colitis have been attributed to interferon alfa (SED-13, 1094) (SEDA-21, 372). Ischemic colitis has been reported in two of 280 patients treated for chronic hepatitis C (245).

Liver

Asymptomatic and reversible rises in serum transaminases have been reported in 25–30% of patients receiving high-dose interferon alfa (20). Although direct hepatotoxicity has been suspected in isolated and unexplained cases of severe liver failure (SED-13, 1094), most data favored exacerbation of chronic viral hepatitis or latent autoimmuine hepatitis.

Exacerbation of chronic viral hepatitis

In the treatment of chronic hepatitis B, HBe seroconversion was sometimes preceded by transient and moderate worsening of serum transaminases, but severe exacerbation of chronic hepatitis B infection and fatal liver failure can occur. Such fatalities were reported in under 0.5% of patients with hepatitis B (246). Patients with active cirrhosis or a previous history of decompensated cirrhosis are particularly susceptible to these complications (247).

Acute exacerbation of hepatitis is an extremely rare complication of chronic hepatitis C treatment. An exaggerated immune response to hepatitis virus was supposedly the cause of acute icteric hepatitis in two patients (SEDA-21, 372) (248).

- A 43-year-old man had a moderate rise in hepatic transaminase activities after 4 weeks of interferon alfa treatment. His liver tests normalized after withdrawal, but the aspartate transaminase activity increased dramatically shortly after treatment was restarted. His

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condition rapidly deteriorated, with a diagnosis of hepatorenal failure, and he finally required liver transplantation. Histological examination of the liver showed advanced micronodular cirrhosis, a feature not found on pretreatment liver biopsy.

In another study, only four of 11 241 patients treated with interferon alfa died of fulminant liver failure (16).

Autoimmune hepatitis

More disturbing are reports of interferon alfa-induced acute exacerbation of latent autoimmune hepatitis (SED-13, 1094) (249–256). Further analysis showed that these patients were initially misdiagnosed as having hepatitis C, and autoimmune hepatitis reversible by glucocorticoid treatment was later proven to be the correct diagnosis. It was later found that latent chronic autoimmune hepatitis can be present in patients with unequivocal serological evidence of chronic hepatitis C (249,257). The co-existence of serological markers of autoimmune hepatitis and confirmed hepatitis C before treatment with interferon alfa in the same patient is very disturbing, because the distinction cannot readily be made on the basis of biological and histological data. As glucocorticoids can increase the extent of viremia, and since in addition interferon alfa can acutely exacerbate latent autoimmune liver disease, this has raised the question of how to deal with these patients. In those without serological markers of autoimmune liver disease, only close monitoring of liver function to detect any sudden increase in alanine transaminase activity is helpful, because the systematic detection of autoantibodies proves unable to predict the risk of overt autoimmune hepatitis (257). In those with both hepatitis C virus and autoantibodies, there is as yet no consensus on the therapeutic management. Glucocorticoids may actually increase the extent of viremia, while interferon alfa may exacerbate autoimmune hepatitis. As a result, controversies have emerged, with several investigators advocating glucocorticoids as first line treatment and providing a safe option in patients with high antibody titers, whereas others have found interferon alfa to be more appropriate (SED-13, 1094) (SEDA-20, 329) (SEDA-21, 372).

De novo induction rather than exacerbation of autoimmune hepatitis is still possible, as indicated by anecdotal reports in patients with cancer or chronic viral hepatitis (SED-13, 1094) (SEDA-22, 402). Such a very rare event is in keeping with the usual absence of autoantibody specific for autoimmune liver disease after interferon alfa treatment.

Positive serological markers of autoimmune hepatitis before treatment in patients with concomitant chronic hepatitis C are sometimes associated with further exacerbation of an underlying autoimmune liver disease during interferon alfa treatment. Of three patients with raised antimitochondrial antibodies (over 1:160), only the two patients with M2 (with or without M4 or M8) subtypes had biochemical exacerbation of cholestasis and an unfavorable response to interferon alfa (255). Although very few patients were investigated, determination of antibodies against submitochondrial particles may help to identify patients who are likely to have no benefit and even exacerbation of liver disease with interferon alfa.

In 25 children with chronic hepatitis C, pretreatment positivity for liver/kidney microsomal type 1 (LKM-1) antibodies was associated with more frequent treatment-limiting increases in serum alanine transaminase activity (256). Withdrawal of interferon alfa-2b because of hypertransaminasemia was required in three of four LKM-1 positive children compared with two of the 21 LKM-1 negative children. Although none developed features of autoimmune hepatitis, careful surveillance of hepatic function is recommended in LKM-1-positive patients.

Other complications

Interferon alfa-associated macrovesicular steatosis has been reported (258).

- A 50-year-old woman without a history of liver disease, dyslipidemia, diabetes, obesity, or alcoholism started taking interferon alfa (7.5 MU/day) for chronic myelogenous leukemia together with allopurinol and hydroxyurea for 2 weeks. Her liver tests were normal before treatment but transaminase activities were greatly increased after 2 weeks. Serological tests for hepatitis B and C and HIV were negative, as was screening for serum antitissue antibodies. Liver biopsy showed severe macrovesicular steatosis (80% of hepatocytes) without steatohepatitis. Liver tests completely normalized on interferon alfa withdrawal. A few weeks after interferon alfa was restarted in a lower dose (3–5 MU/day), she again had a rise in liver enzymes, and a second liver biopsy showed unchanged findings. Liver tests remained stable despite treatment continuation.

Other adverse liver effects reported with interferon alfa include primary biliary cirrhosis (SEDA-20, 329) and granulomatous hepatitis (SEDA-20, 329) (SEDA-21, 372) (259).

Pancreas

Asymptomatic rises in pancreatic enzymes and reversible acute pancreatitis have been reported in isolated patients, with no mention of hypertriglyceridemia (SEDA-19, 336).

- A 54-year-old man developed abdominal pain from the beginning of interferon alfa treatment (260). Two weeks later his serum amylase and lipase peaked at about three times the upper limit of normal. Careful radiological investigations ruled out pancreatic calcification and biliary or pancreatic lithiasis and showed only pancreatic enlargement. Complete improvement occurred after treatment withdrawal. As in the very few previous cases, there was no hypertriglyceridemia in this patient.

A definite case of pancreatitis proven by positive rechallenge was also briefly cited in a review of drug-associated pancreatitis spontaneously reported to the Dutch adverse drug reactions system (261).

Two cases of interferon alfa-induced acute pancreatitis in patients with chronic hepatitis C were particularly convincing, because other causes were carefully ruled out and clinical symptoms or biological abnormalities recurred after rechallenge in both patients (262). Although one patient also took ribavirin, recurrence was observed

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after re-administration of interferon alfa alone. Lipid disorders were not found in these patients, confirming that interferon alfa-induced pancreatitis is not due to hypertriglyceridemia.

Urinary tract

Mild and usually asymptomatic proteinuria, leukocyturia, microscopic hematuria, or moderate increases in serum creatinine were observed in 15–25% of patients (20). There was moderate deterioration of glomerular and tubular renal function in most interferon alfa-treated patients assessed prospectively with a number of renal function markers (263).

In patients receiving high-dose interferon alfa, severe proteinuria and nephrotic syndrome have sometimes been noted (264).

- A 57-year-old woman developed severe nephrotic syndrome after 3 months of interferon alfa re-treatment, and renal biopsy showed minimal change nephrotic syndrome with T cell-predominant interstitial nephritis (265). Proteinuria persisted despite interferon alfa withdrawal and resolved only after glucocorticoid treatment.
- A 55-year-old woman was treated with interferon alfa and ribavirin for 1 year and developed asymptomatic nephrotic syndrome with focal segmental glomerulosclerosis on renal biopsy (266). Proteinuria slowly improved over the next 21 months.

Interferon alfa-induced acute renal insufficiency is rare and has mostly been reported in patients with underlying renal disease, in those receiving high dosages, or in those with varied malignancies (SED-13; 1095) (SEDA-20, 329) (SEDA-21, 372) (267,268). Very few cases have been described in patients with chronic hepatitis (SEDA-21, 372) (SEDA-22, 402). It has also been reported after intravesical administration (SEDA-21, 372). When available, pathological findings have pointed variously to nephrotic syndrome with minimal-change nephropathy and acute tubulointerstitial nephritis, nephrotic syndrome with severe glomerular changes, membranoproliferative glomerulonephritis, extracapillary glomerulonephritis with crescents, focal segmental glomerulosclerosis, and acute tubular necrosis. Renal dysfunction usually resolves after withdrawal of interferon alfa, but irreversible alteration or incomplete resolution of renal function have occasionally been noted.

A review of 15 other available reports of renal insufficiency and proteinuria in patients with chronic myeloid leukemia or other malignancies confirmed that the histological spectrum of renal lesions associated with interferon alfa is varied, and includes membranous glomerulonephritis, minimal change glomerulonephritis, acute interstitial nephritis, hemolytic–uremic syndrome, and thrombotic microangiopathy. Renal complications were reversible in nine patients; three patients had persistent proteinuria, and four had persistent renal dysfunction, of whom three required chronic hemodialysis. Two-thirds of the patients developed renal complications within 1 month of treatment with interferon alfa, and one-third had received a relatively low dosage of interferon alfa (9–15 MU/week).

The mechanism of interferon alfa nephrotoxicity is probably multifactorial and may involve a direct nephrotoxic effect with a possible additive effect of concomitant NSAID therapy, a T cell-mediated immune effect, immune-complex renal disease, or an autoimmune etiology (SED-13, 1095) (269–274).

Acute renal insufficiency has also occurred as a consequence of interferon alfa-induced hemolytic–uremic syndrome, thrombotic thrombocytopenic purpura, or renal thrombotic microangiopathy (SED-13, 1095) (234,275–278). The diagnosis was made after 7 months to 10 years of treatment (median 50 months) with weekly doses of 15–70 MU. This rare but extremely severe complication has almost exclusively been reported in patients treated for chronic myelogenous leukemia, so that the respective roles of interferon alfa and the underlying hematological malignancy are undetermined. However, at least one case has been reported in a patient with hepatitis C (SEDA-22, 402). From a total of 15 cases, renal prognosis was poor, with early deaths in four patients, chronic hemodialysis in eight, and chronic renal insufficiency in three.

To determine the characteristics of thrombotic microangiopathy associated with interferon alfa, data from eight patients were carefully examined (279). All had chronic myeloid leukemia and had received high-dose interferon alfa (mean 39 MU/week) for a long time (mean 32 months) before diagnosis. Severe arterial hypertension was the most common sign before diagnosis. Five patients had distal ischemic lesions that required amputation in one, and all had typical lesions of renal thrombotic microangiopathy involving both glomeruli and small arterioles. After interferon alfa withdrawal, two recovered normal renal function, three had persistent renal insufficiency, one relapsed 17 months after treatment withdrawal, and two required chronic dialysis. One patient had already had reversible renal insufficiency during a previous course of interferon alfa. From a review of 21 other previously published similar cases, the authors confirmed that interferon alfa-induced thrombotic microangiopathy mostly occurred in patients with chronic myeloid leukemia, whereas only two cases were reported in patients with chronic hepatitis C and one in a patient with hairy cell leukemia. The delayed occurrence of renal toxicity was also suggested to be highly predictive of histological thrombotic microangiopathy.

Possible deleterious effects of interferon alfa on renal graft function are repeatedly reported (280).

- A 43-year-old man with stable renal graft function, taking ciclosporin, methylprednisolone, and azathioprine, developed chronic myelogenous leukemia and received interferon alfa (3 MU/day). Seven weeks later, he became tired and had increased proteinuria and a raised serum creatinine concentration (574 μmol/l). Interferon alfa was withdrawn and he received high-dose methylprednisolone for suspected acute graft rejection. This was unsuccessful and a first renal biopsy showed widespread interstitial edema that could not be correctly interpreted. Hemodialysis was restarted, and he finally developed a catheter infection and died from sepsis. Histology of the explanted renal graft showed severe, predominantly acute, vascular rejection.

The rapid occurrence of renal dysfunction after interferon alfa in this case suggested a causal relation.

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Skin

A wide range of skin lesions has been reported, and most include skin dryness, rash, diffuse erythema, or urticaria, occurring in 5–12% of patients (20,281). However, severe dermatological complications are rare. In a prospective survey of 120 patients treated during 6–18 months for chronic viral hepatitis, only three developed lichen planus and one relapsing aphthous stomatitis (282).

Injection site reactions

Subcutaneous interferon alfa sometimes causes local erythema and skin induration, which can be prevented by regularly changing the site of injection. Isolated reports have described more severe local reactions, with inflammatory painful nodules, purpuric papules and vasculitis, local ulceration, and injection site necrosis (SED-13; 1095) (SEDA-20, 330) (SEDA-21, 372) (SEDA-22, 402). Despite previous findings, even patients receiving low-dose interferon alfa can have severe injection site reactions. A localized intradermal bullous eruption, which recurred following each interferon alfa injection, was also reported (283).

Severe injection site reactions have been extensively detailed in six patients who had local cutaneous necrosis or indurated erythema after 1–10 months of treatment with low-dose interferon alfa (284). Four patients had concomitant risk factors known to reduce microcirculation, that is beta-blockers, dihydroergotamine, and cigarette smoking. The lesions healed after medical treatment in five patients, but one required surgical excision. The ulcers healed slowly and full recovery occurred only after a mean of 16 weeks after drug withdrawal. The lesions did not recur after interferon alfa re-administration at the other injection sites.

As with interferon alfa, pegylated interferon alfa has been associated with injection site skin necrosis (285). Severe local reactions after subcutaneous injections mostly consist of ulceration and skin necrosis, but a variety of reactions have been described. Prominent suppuration and granulomatous dermatitis at the injection sites of interferon alfa have been reported in two patients (286). Three patients who had severe rashes while receiving pegylated interferon alfa-2a or 2b had positive intracutaneous tests to both pegylated forms of interferon alfa but not to standard interferon alfa-2a or 2b (287). One of these patients subsequently tolerated standard interferon alfa. Cutaneous ulcers have also been reported in patients treated with peginterferon alfa-2b (288,289). In the latter case, the lesions healed under local therapy and the same dose of interferon was maintained.

Lichen planus

The new occurrence or exacerbation of lichen planus is a well-known complication of interferon alfa, but this has been a source of a considerable debate (SED-13, 1095) (SEDA-20, 330) (SEDA-22, 402). Indeed, most patients have received interferon alfa for chronic hepatitis C, an underlying disease that is controversially thought to be associated with a spontaneously higher incidence of lichen planus (290). In addition, complete reversibility of previous lichen planus was sometimes observed in patients treated with interferon alfa (SEDA-20, 330). Whatever the truth of the matter, the recurrence of lesions after interferon alfa re-administration or reports of lichen planus in patients with cancer (291–293) argues strongly for a direct causal link with interferon alfa. Local treatment and PUVA were sometimes sufficient to alleviate symptoms, but withdrawal of interferon alfa was required in the most severe cases (SED-13, 1095).

Pemphigus and pemphigoid

Bullous pemphigus and pemphigoid with circulating pemphigus-like autoantibodies, pemphigus foliaceus with anti-intercellular IgG antibodies, and paraneoplastic pemphigus due to interferon alfa have rarely been reported (SED-13, 1095), as has extensive oral pemphigus (294).

- A 28-year-old woman developed oral ulcers after a 5-month course of interferon alfa-2a for chronic hepatitis C. She had multiple erosions on both lips, the tongue, the floor of the mouth, the soft palate, the pharyngeal walls, and the laryngeal mucosa, but there were no skin or genital lesions. Raised double-stranded DNA antibody titers were found. Histology showed pemphigus vulgaris, and complete resolution was obtained by withdrawal of interferon alfa and immunosuppressive and local treatment.

This case was thought to have been due to the immunomodulatory effects of interferon alfa.

Psoriasis

The first reports of psoriasis in cancer patients treated with high-dose interferon alfa were followed by a controversial debate (295,296). However, numerous cases have confirmed that interferon alfa can either induce typical psoriasis or worsen pre-existing psoriasis (SED-13, 1095) (297), an observation that is compatible with interferon alfa-induced imbalance toward an increased Th1 response. This was particularly exemplified by the reversibility of the lesions after withdrawal of treatment and the prompt recurrence of symptoms after interferon alfa re-administration. Exacerbation of psoriasis usually occurred within the first month, whereas a minimum of 2–3 months of treatment was required in patients without a past history of psoriasis (297). Psoriatic lesions at the sites of injection were suggested to be potential indicators for further generalization of psoriasis. In more severe cases, there was concomitant development of monoarticular or polyarticular joint symptoms (SED-13, 1095) (SEDA-21, 372). Pustular psoriasis with balanitis and erosive monoarthritis, suggesting incomplete Reiter's syndrome, was also reported in one patient with HLA-B27 (298).

Vitiligo

Vitiligo has sometimes been reported in patients with malignant melanoma, for example in 17–25% of patients receiving interferon alfa alone (SEDA-21, 372). There have also been a few reports of vitiligo in patients with chronic hepatitis C (SEDA-20, 330), and one patient had both scleroderma and vitiligo (SEDA-19, 336).

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Other complications

A spectrum of cutaneous lesions has been described distant from sites of interferon alfa injection. The clinical and histological characteristics of inflammatory skin lesions that occurred away from injection sites have been investigated in 20 patients treated with interferon alfa-2a or 2b plus ribavirin for chronic hepatitis C (299). Cutaneous lesions developed between 2 weeks and 4 months and consisted of pruritic papular erythematous eruptions with occasional vesicles. These eczema-like skin lesions predominated on the distal limbs, the head, and the neck. Photosensitivity was also noted in four patients and mucous lesions in two. Skin biopsy mostly showed non-specific mononuclear infiltrates. The skin lesions were promptly reversible in 10 patients who required treatment withdrawal, while others improved after symptomatic treatment. Two of the three patients who again received the same or another type of interferon alfa had recurrence of their lesions. Skin tests performed in six patients were negative, including the two patients who relapsed after rechallenge with interferon alfa, and were therefore considered unhelpful.

- Radiation recall dermatitis developed in a 29-year-old woman after high-dose intravenous interferon alfa-2b was given 5 days after the completion of radiotherapy for malignant melanoma (300).

The authors suggested that interferon alfa can trigger an inflammatory reaction in patients whose inflammatory response threshold has been lowered by irradiation.

- A 46-year-old woman developed transient facial erythema with telangiectasia after each injection of interferon alfa, resolving within 1–2 days, and completely disappearing after definitive withdrawal of treatment 7 months later (301).
- Two patients treated with pegylated interferon alfa-2b and ribavirin developed cutaneous thrombotic microangiopathy (302).
- A 54-year-old woman had small bullous lesions mainly on the backs of her hands and feet after 6 months of treatment with pegylated interferon alfa-2b plus ribavirin for chronic hepatitis C. The lesions lasted 48 hours and healed rapidly after rupture of the bullae.
- A 62-year-old woman developed generalized pruritus and excoriated lesions after 5 months of treatment with pegylated interferon alfa-2b plus ribavirin. The lesions were maximal on the backs of her hands and feet after 8 months of treatment, but there were no bullae.

Skin biopsies in the last two patients showed microthrombi of the dermal capillaries and a necrotic epidermis. Immunofluorescence showed only fibrinogen. Some bullous lesions were still present 1 month after withdrawal in the first patient, while the second patient responded to local corticosteroids and a reduced dose of pegylated interferon alfa, but continued to have episodes of severe pruritus.

Other dermatological complications have in most instances been reported as single case histories, so that any causal relation with interferon alfa awaits confirmation. These reports have included worsening of lichen myxedematosus, injection site pyoderma gangrenosum, a polymorphous light eruption (SEDA-22, 372), and a fatal case of histiocytic cytophagic panniculitis (SEDA-20, 330).

- Meyerson's phenomenon, multiple focal and transient eczematous eruptions around melanocytic nevi, has been reported in a 24-year-old man when the dosage of interferon alfa for Behçet's disease was doubled (303).
- Bullous lesions with specific infiltrates of mycosis fungoides have been reported in a 67-year-old woman who took interferon alfa for 2 months for mycosis fungoides (304).

Although in the second case the syndrome could not be definitely attributed to interferon alfa, the authors noted that bullous mycosis fungoides is an extremely rare variant of this disease and withdrawal of interferon alfa led to healing of the blisters without further recurrence.

Hair

Moderate and reversible alopecia secondary to telogen effluvium is common (7–30%), and sometimes recedes despite continued treatment (305). Alopecia areata has very occasionally been described (306).

- Injection-site alopecia has been reported in three patients, affecting the thighs in two patients and the abdomen in one (307). A reversible focal telogen effluvium secondary to high local concentrations of interferon alfa was the most likely cause, indicating that rotating injection sites are needed to prevent this adverse effect.
- Alopecia areata after 7 months of interferon alfa, slowly reversible on withdrawal, has also been reported in a 36-year-old woman (308).

In two patients with previously natural curly hairs, the combination of interferon alfa plus ribavirin was suggested to have triggered a rapid change in hair texture, with diffuse straightening hairs, eyelashes, and eyebrow hypertrichosis (309). In one patient, a causal role of treatment was supported by the spontaneous recovery of hair abnormalities after withdrawal and the recurrence of similar abnormalities on rechallenge.

Excessive growth of eyelashes and nail damage due *to Tinea unguium* have been occasionally reported in patients receiving interferon alfa (SED-13, 1095) (SEDA-21, 372). Hypertrichosis of the eyelashes (trichomegaly) developed in two of 36 patients with chronic viral hepatitis who were examined for ocular complications during treatment with high-dose interferon alfa (18–30 MU/week) (86). These two patients had received the highest dose of interferon alfa.

Musculoskeletal

Arthralgia, myalgias, and muscle weakness are typically observed during the early influenza-like reaction (20). Direct muscle toxicity of interferon alfa can result in acute rhabdomyolysis, in some cases fatal after the dose of interferon alfa was increased (SEDA-19, 330) (SEDA-21, 372).

- A 26-year-old man with a malignant melanoma had two episodes of acute severe rhabdomyolysis after each exposure to a chemotherapy regimen containing interferon alfa and dacarbazine (310). As a few cases of

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rhabdomyolysis have been previously reported after interferon alfa alone (SEDA-19, 336) (SEDA-20, 330) (SEDA-22, 403), interferon alfa was suggested as the most likely cause.

- Acute rhabdomyolysis occurred in a 34-year-old woman with a melanoma treated with interferon alfa 20 MU/m^2/day (311). There was no recurrence on retreatment with a lower dose (down to 6.6 MU/m^2/day), suggesting that this was a dose-related complication.
- A 34-year-old man with scleromyxedema had flu-like symptoms and muscle pain after the first injection of interferon alfa 6 MU (312). After three additional injections at 2-day intervals, his muscle symptoms worsened and were associated with mild quadriparesis, reduced deep tendon reflexes, dark urine, confusion, and agitation. Biological findings were consistent with acute rhabdomyolysis, and electromyography showed rare denervation potentials. His symptoms resolved and the laboratory findings normalized within 15 days.

Delayed muscular adverse effects have been occasionally reported including the clinical exacerbation of a latent myopathy (SEDA-19, 336), delayed and severe myopathic changes (313), myositis, polymyositis, and a Lambert–Eaton-like syndrome (SEDA-19, 336) (SEDA-20, 330) (SEDA-22, 403).

- Three patients developed unilateral or bilateral avascular necrosis of the femoral head after 3–54 months of treatment with interferon alfa for chronic myelogenous leukemia (314). One required bilateral hip replacement and two significantly improved after interferon alfa withdrawal. One patient received further interferon alfa without exacerbation.

Although there were risk factors for avascular necrosis in two of the patients (a short course of methylprednisolone and moderate alcohol consumption), the authors did not consider them to be significant. They identified seven other reported cases of avascular necrosis in patients with chronic myeloid leukemia, including two patients who were taking interferon alfa at the time of the complication. One patient with pre-existing avascular necrosis had an acute exacerbation within 1 month of interferon alfa and required hip replacement. Although any causal relation with treatment remains purely speculative, the authors argued that the known antiangiogenic effects of interferon alfa could have predisposed patients to avascular necrosis.

Sexual function

Sexual complaints attributed to interferon alfa, namely decreased libido, impotence, or erectile failure, are usually concomitant to other neuropsychiatric symptoms, and cases of reversible impotence are anecdotal (315). The mechanisms accounting for these adverse effects are unclear, and changes in sex hormone concentrations have not been consistently reported. In one study in healthy women, interferon alfa produced falls in serum progesterone and estradiol concentrations (316), but neither impairment of libido nor impairment of fertility has apparently been reported in women. No evidence of gonadal toxicity or sexual dysfunction was found in 43 men with hairy cell leukemia who received interferon alfa for 2–12 months compared with 33 patients who received no systemic therapy (317). Finally, sexual complaints reported during interferon alfa treatment of chronic hepatitis C were presumably related to fatigue, anxiety, or psychological disorders rather than to endocrinological changes (SEDA-21, 373).

Immunologic

Hypersensitivity reactions

No IgE-mediated immediate-type allergic reactions to interferon alfa have ever been conclusively documented. A recurrent non-IgE-mediated anaphylactic reaction, possibly due to mast cell degranulation, has been described in a patient with mastocytosis (318).

- A 64-year-old man with no history of allergy had progressive fatigue, loss of appetite, and facial edema after 6 months of interferon alfa-2b treatment for chronic hepatitis C (319). Angioedema was diagnosed and it resolved after withdrawal of interferon alfa and a short course of prednisolone. Serum immunoglobulin E and plasma bradykinin concentrations were raised, but the C1 esterase inhibitor and serum complement concentrations were normal.
- A 47-year-old man, who had previously received a 2-month course of interferon alfacon-1 for chronic hepatitis C, started interferon alfa-2b 8 months later (320). He developed mild generalized pruritus the day after the second injection, and dyspnea with diffuse urticaria within a few hours after the third injection. Skin tests were not performed, and IgG but not IgE antibodies to interferon alfa were found.

These cases do not formally show a causal relation with interferon alfa, and at best they suggest that an IgE-mediated reaction is probably not the cause of hypersensitivity reactions to interferon alfa. In the first case, the mechanism may have been similar to that observed with angiotensin-converting enzyme inhibitors.

Cases of contact dermatitis have suggested that interferon alfa-2c can cause cell-mediated delayed hypersensitivity (321,322).

Interferon alfa antibodies

Both binding and neutralizing antibodies to interferon alfa can be detected in interferon alfa-treated patients, and the incidence or clinical significance of these antibodies is the subject of continuous controversy, which has been addressed in a number of studies or general reviews (SED-13, 1096) (SEDA-20, 330) (SEDA-21, 373) (156,323–325).

In various studies, the incidence of antibody formation has ranged from zero to more than 50% of patients. However, any comparison between studies is difficult, because the underlying treated disease, the type of interferon used, the route of administration, the dosage regimen, the schedule of treatment, and the method of assay have differed from one investigation to another. Antibodies to interferon alfa have been reported to be more frequent in patients receiving long-term, instead of short-term, treatment, in patients receiving subcutaneous rather than intravenous interferon alfa, and in patients receiving low rather than high doses (156). Complete disappearance of interferon

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alfa antibodies was usually observed after withdrawal. Interferon alfa formulations also differ in antigenicity. Using the same anti-interferon alfa antibody assay, a higher frequency of antibodies to recombinant interferon alfa-2a has repeatedly been reported compared with other recombinant or natural interferon alfa formulations in patients treated by the same route and with the same treatment schedule. In 296 patients with chronic hepatitis, binding and neutralizing antibodies were found in 45 and 20% respectively of patients receiving recombinant interferon alfa-2a compared with 15 and 6.9% of those receiving recombinant interferon alfa-2b, and 9.4 and 1.2% of those receiving interferon alfa-n1 (326,327). There were similar differences in the immunogenic potential of the two recombinant interferon alfa formulations in 159 patients with chronic myelogenous leukemia (328). Overall, the incidence of binding antibodies is in the range of 20–50% for recombinant interferon alfa-2a, 6–10% for recombinant interferon alfa-2b, and 1–6% for interferon alfa-n1 (324).

The clinical significance of binding antibodies appears to be limited to a possible change in interferon alfa pharmacokinetics. By contrast, neutralizing antibodies, which are usually detected within 2–4 months of treatment, can theoretically reduce the clinical response to interferon alfa and cause interpatient variability in response to treatment, but this is still debated (323–325). Although several studies have failed to detect any loss of therapeutic response, response failure or the reversal of an initial clinical response, simultaneously with (or soon after) the appearance of neutralizing antibodies, have been reported. In large-scale studies, the clinical response to recombinant interferon alfa was significantly less in patients with neutralizing antibodies, and it has therefore been suggested that the appearance of neutralizing antibodies provides the prime explanation for those instances in which there is a relapse or a breakthrough of the disease before the completion of treatment (329–335). In addition, in patients who cease to respond therapeutically after recombinant interferon alfa antibody formation, a change to natural interferon alfa has proved successful in restoring the response in some cases (335–338). This has led to the suggestion that the formation of neutralizing antibodies represents a specific immune response to the recombinant preparations, and that natural interferon alfa can overcome the neutralizing activity of antibodies to recombinant interferon alfa. On the other hand, neutralizing antibodies were not associated with immune complex-associated diseases or hypersensitivity reactions, and exerted no influence on interferon alfa-associated adverse effects. They can even be accompanied by improvement in the flu-like syndrome.

Autoantibodies

Collectively, several antibodies (mostly antinuclear, antithyroid, parietal cell, liver/kidney microsome, and smooth muscle antibodies, and rheumatoid factor) can be detected before interferon alfa treatment in about one-third of patients. Increased titers or the occurrence of various autoantibodies were observed in 4–30% of previously autoantibody-negative patients (21,156). These autoantibodies do not affect the response to interferon alfa treatment (339–341). Although it was initially felt that interferon alfa might facilitate the development of autoimmune disease in patients previously positive for non-organ-specific autoantibodies, the evidence is still limited and the clinical consequences of such autoantibodies are unclear. Except for thyroiditis, large studies in patients with chronic viral hepatitis C receiving interferon alfa did not show a significant increase in overt autoimmune diseases, despite the pre-existence or further positivity of several autoantibodies (SED-13, 1096) (SEDA-20, 330) (SEDA-21, 373) (SEDA-22, 405). However, in 83 patients with chronic hepatitis C there were one or more pre-existing autoantibodies (mostly low-titer antinuclear antibodies) in 35 patients (group I), of whom seven had clinical evidence of immune-mediated disorders, whereas five of 48 patients without pre-existing autoantibodies (group II) had similar disorders (342). After 12–48 weeks of treatment with interferon alfa in 44 patients, there were new immune-mediated disorders in six of the 20 patients in group I (thyroid disorders in three, arthropathy in two, and psoriasis in one), but none in the 24 patients in group II. Patients who are positive for autoantibodies before interferon alfa may therefore be much more likely to develop autoimmune diseases, particularly thyroid disorders, during interferon alfa treatment.

As a result, there is no clear consensus about the management of patients previously positive for non-organ specific autoantibodies, but it is usually considered that low autoantibody titers or the absence of concomitant symptoms suggestive of autoimmune disease is not a contraindication to treatment.

Autoimmune disorders

The possibility of autoimmune disorders during interferon alfa treatment has been addressed by many authors. The spectrum of interferon alfa-induced immune diseases includes organ-specific and systemic autoimmune diseases, such as thyroiditis, diabetes, hematological disorders, systemic lupus erythematosus, rheumatoid arthritis, dermatological disease, and myasthenia gravis (156). Several have been discussed in appropriate sections elsewhere in this monograph. The exact role of interferon alfa is usually difficult to ascertain, because the underlying disease, that is chronic hepatitis C, can also be associated with immune-mediated disease.

Two studies have provided insights into the incidence and risk factors of the immune-mediated complications of interferon alfa in patients with chronic myeloid leukemia. In the first study, 13 of 46 patients had autoimmune manifestations consisting of a combination of autoimmune thyroiditis in four, a direct antiglobulin test without hemolysis in eight, cryoagglutinins in one, Raynaud's phenomenon in two, and chronic autoimmune hepatitis in one (343). Overall, six patients had clinically symptomatic manifestations after a median of 15 months of treatment. In the second study, there were autoimmune diseases in seven of 76 patients after a median of 19 months of treatment, including hypothyroidism in one, immune-mediated hemolysis in two, systemic lupus erythematosus in two, Raynaud's phenomenon in one, and mixed connective tissue disease in one (344). In

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both studies there was a strong association with female sex and it was confirmed that patients who developed clinical autoimmune complications had had relatively long exposures to interferon alfa.

The management of patients with chronic hepatitis C and associated features of autoimmune disease carries the risk of exacerbating the underlying disease. Different treatment strategies, including interferon alfa alone or combined with ribavirin or glucocorticoids, or no treatment, have been discussed (345).

Behçet's disease

Characteristic features of Behçet's disease or isolated positive skin tests were found in one study of patients with chronic myelogenous leukemia treated with interferon alfa (346). No other reports confirmed these findings.

Dermatomyositis

Occasional reports have suggested that interferon alfa can cause dermatomyositis (347).

- A 57-year-old woman received adjuvant high-dose interferon alfa 16 months after removal of a malignant melanoma. About 6 weeks later, she developed hand swelling, fatigue, myalgia, arthralgia, and weakness. Interferon alfa was withdrawn. She had multiple joint involvement, and radiological imaging showed bilateral interstitial pulmonary infiltrates. Anti-Jo antibodies were positive but other autoantibodies were negative. She also had violet eyelid discoloration with edema, tenderness in various muscle groups, and reduced strength in the shoulders. The muscle biopsy showed scattered necrotic fibers and basophilic regenerative fibers. She gradually recovered with methotrexate and corticosteroids, and the titer of anti-Jo antibodies fell dramatically.

Polyarteritis nodosa

Severe polyarteritis nodosa-like systemic vasculitis has been reported (SEDA-20, 330) and cutaneous polyarteritis nodosa has been attributed to interferon alfa (348).

- A 50-year-old woman was given interferon alfa for chronic hepatitis C and primary biliary cirrhosis, and within 2 months became febrile and developed a diffuse nodular erythematous rash. The skin biopsy showed typical features of necrotizing angiitis, and cutaneous periarteritis nodosa was diagnosed. Full recovery was obtained after interferon alfa withdrawal and prednisolone treatment.

According to the authors, it is not known whether this complication was directly due to interferon alfa, represented the triggering of latent periarteritis nodosa in a patient with primary biliary cirrhosis, or whether it was a coincidental adverse event.

Polymyositis

- Polymyositis has very rarely been associated with interferon alfa, but has been reported together with autoimmune thyroiditis in a 48-year-old woman after treatment for 5 months for malignant melanoma (349).

There have been two reports of polymyositis in association with interferon alfa treatment for hematological malignancies (123,350). In both cases, clinical and/or electrophysiological recovery occurred after drug withdrawal, spontaneously or after a short course of glucocorticoids.

Sarcoidosis

The early impression that interferon alfa, alone or in combination with ribavirin, could reactivate or cause new subcutaneous sarcoid nodules and pulmonary or generalized sarcoidosis, has been confirmed by several reports, with prompt recovery after interferon alfa withdrawal (SED-13, 1097) (SEDA-20, 330) (SEDA-22, 404). The incidence may have been underestimated; in one series, 3 patients out of 60 who received interferon alfa alone or combined with ribavirin developed pulmonary sarcoidosis (351). In a review of 27 cases, the time to onset was 15 days to 30 months, and there were dermatological signs in 50% (352). Five patients had also taken ribavirin, but an enhanced T cell immune reaction from the combination of interferon alfa plus ribavirin is speculative. However. the association of cutaneous or systemic sarcoidosis with interferon alfa, alone or in association with ribavirin, has been exemplified by various reports (353,354), including one patient whose sarcoidosis resolved with prednisone despite continued interferon alfa treatment (355).

- A 60-year-old woman receiving interferon alfa developed cutaneous sarcoid foreign body granulomas at the sites of a previously childhood skin injury (356).

This suggests that interferon alfa may facilitate the development of cutaneous sarcoid granuloma from particulate foreign matter.

De novo sarcoidosis has been reported in six patients (357–361) and reactivation of pre-existing disease in one (362). One of these patients had chronic hepatitis B, suggesting that interferon alfa treatment rather than the underlying disease was the most probable triggering factor. Remission was observed in all patients after withdrawal, either spontaneously or after glucocorticoid treatment.

Sjögren's syndrome

One report of Sjögren's syndrome in a patient taking interferon alfa should be regarded with caution (SEDA-20, 330).

Systemic lupus erythematosus and rheumatoid arthritis

The possible role of interferon alfa in the development of rheumatoid arthritis or systemic lupus erythematosus has been described in isolated cases (363,364), and confirmed cases of systemic lupus erythematosus have very occasionally been reported (SED-13, 1096) (SEDA-20, 330). In most of these cases, the predominance of young patients and female sex, the presence of renal or skin involvement, the findings of positive antibodies to double-stranded DNA, and the rapid onset after the start of treatment, as well as persistence of symptoms after interferon alfa withdrawal, are more in keeping with unmasking by interferon alfa of idiopathic lupus rather than with a new drug-induced illness. The reactivation or appearance of inflammatory rheumatological disorders consistent with rheumatoid arthritis or lupus-like polyarthritis were

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also consistently reported (SEDA-20, 330) (365,366). In a review of 37 published cases of interferon alfa-induced arthritis, symmetrical polyarthritis was the most common feature, and antinuclear antibodies or rheumatoid factor were found in 72 and 34%, respectively (367). Although spontaneous improvement was sometimes observed after withdrawal of interferon alfa, more severe cases required anti-inflammatory, antimalarial, or immunosuppressive drugs. In five of eight patients rechallenged with interferon alfa, there was recurrence of arthritis.

There was an unexpectedly high incidence of rheumatoid and lupus-like symptoms (27 of 137 patients), namely arthralgia, arthritis, myalgia, and Raynaud's phenomenon, in patients with myeloproliferative disorders taking interferon alfa alone or combined with interferon gamma (365). However, only a minority of affected patients fulfilled the diagnostic criteria for systemic lupus erythematosus. By contrast, systemic autoimmune diseases appeared to be genuine but very rare complications of interferon alfa in chronic hepatitis C, with only one case of lupus-like syndrome and two cases of polyarthritis in a survey of 677 patients (18).

Other reports included seronegative polyarthritis, acute seronegative monoarthritis of the hip, and seropositive monoarthritis of the metatarsophalangeal of the right foot (SED-13, 1097).

Systemic lupus erythematosus has been reported in two patients given interferon alfa for chronic hepatitis C (363,368). However, it is not known whether this complication was coincidental or treatment-related.

Systemic sclerosis

Systemic sclerosis has been attributed to interferon alfa-2a (369).

- A 52-year-old woman received interferon alfa-2a for chronic myeloid leukemia and after about 2 years developed fever, dyspnea, and limb edema. The erythrocyte sedimentation rate was 50 mm/hour and pulmonary imaging showed pulmonary vascular congestion. She improved after interferon alfa withdrawal and administration of diuretics, but similar symptoms recurred 3 months later. She also had progressive thickening of the skin on the hands and wrists. There was diffuse parenchymal and interstitial fibrosis of the lungs, absence of peristalsis on esophagogastroduodenoscopy, renal impairment, and positive antisclero-70 antibodies. Capillaroscopy showed typical features of scleroderma. Based on these findings, a diagnosis of systemic sclerosis was suggested and she slowly improved over the next months with cyclophosphamide, prednisone, iloprost, and hydroxyurea.

This patient had the HLA-DR11 haplotype, which is associated with systemic sclerosis, and this suggests that interferon alfa may have triggered the autoimmune phenomenon.

Vasculitis with cryoglobulinemia

Interferon alfa can sometimes aggravate hepatitis C-related cryoglobulinemia.

- A fatal exacerbation of hepatitis C-related cryoglobulinemia, preceded by rapid deterioration of neurological status, massive upper gastrointestinal bleeding, and diffuse hemorrhagic gastritis with vasculitic changes on gastroscopy, has been reported within the first 3 weeks of interferon alfa treatment in a 51-year-old woman (370).

However, cryoglobulin-associated vasculitis is a recognized manifestation of hepatitis C infection. Reports of vasculitis in interferon alfa-treated patients should therefore be interpreted with caution (SED-13, 1095) (371). In addition, several isolated reports suggested that exacerbation of cryoglobulinemia might also be the result of interferon alfa treatment (SEDA-19, 337).

Interferon alfa and transplantation

A possibly deleterious effect of pre- or post-transplant interferon alfa therapy in transplant recipients has been emphasized by several studies and case reports. These point to a higher incidence or greater severity of graft-versus-host reactions in patients who have received an allogeneic bone marrow transplant (SED-13, 1097) (372,373), significant deterioration of renal function or an increased risk of glucocorticoid-resistant rejection in renal transplant patients (SED-13, 1097) (374), and a possibly increased risk of acute or chronic rejection in liver transplant patients (375,376). These findings are still the subject of debate, as the available data consist mainly of retrospective or poorly controlled studies with a limited number of patients (377,378). In addition, several other investigators have failed to identify any deleterious influence of interferon alfa treatment in transplant recipients (SEDA-21, 373) (SEDA-22, 403). This issue warrants further large scale, prospective, controlled studies.

Immunosuppressive effects

Isolated reports of *Candida* esophagitis or *Pneumocystis jiroveci* (*Pneumocystis carinii*) infections in immunocompetent patients and the possible decrease in CD4+ T cells with or without opportunistic infections in several HIV-infected patients (SED-13, 1097) (379) suggest that unexpected immunosuppressive effects of interferon alfa can occur. An autoimmune destruction of CD4 cells in patients with a particular HLA haplotype has been proposed as a possible mechanism (380). One patient also had an acute and fatal acute precipitation of infection with *Entamoeba histolytica* (SEDA-22, 403). However, the available evidence is still very limited and no firm conclusion can be drawn on a possible association between interferon alfa treatment and a fall in CD4 cell count or an immunosuppressive effect.

Two patients aged 38 and 54 years with hemodialysis-dependent end-stage renal insufficiency developed severe bacterial infections, osteomyelitis, and prostatitis, within 3 months of interferon alfa-2b treatment for hepatitis C virus infection (381).

Possible exacerbation of latent parasitic infection by interferon alfa has been reported (SEDA-22, 403).

- Two patients receiving interferon alfa plus ribavirin for chronic hepatitis C developed symptomatic strongyloidiasis within 2–3 weeks of treatment (382).

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Because both drugs have immunomodulatory effects, it was not determined which one was the more likely cause.

Graft-versus-host disease

There are still uncertainties about the possible relation between interferon alfa and an increased incidence or severity of acute graft-versus-host disease after bone marrow transplantation. Late-onset, severe, atypical chronic graft-versus-host disease has been attributed to interferon alfa (383).

- A 44-year-old woman received interferon alfa 6 MU/day for relapse of chronic myeloid leukemia 7 years after successful bone marrow transplantation. About 2 years later, interferon alfa was withdrawn because of diffuse erythematous skin lesions with discoid lupus erythematosus on skin biopsy and severe dysphagia with esophagitis and pseudomembranes at endoscopy. Fever, bilateral pulmonary infiltrates, and respiratory distress syndrome subsequently developed, and she required mechanical ventilation. An open lung biopsy showed features of chronic pulmonary graft-versus-host disease. All her symptoms completely resolved with ciclosporin and corticosteroids. An infectious cause was ruled out.

In this case, the clinical presentation was compatible with typical chronic graft-versus-host disease. Whether interferon alfa induced or aggravated chronic graft-versus-host disease in this patient was an open question.

Death

There is a debate as to whether previous interferon alfa adversely affects the outcome of bone marrow transplantation in chronic myelogenous leukemia.

In a retrospective study of 153 patients who underwent bone-marrow transplantation for chronic myelogenous leukemia, pretransplant interferon alfa treatment for more than 12 months was associated with a significant increase in transplant-related mortality during the first 2 years when compared with patients who received pretransplant interferon alfa for less than 12 months (28 of 46 patients versus nine of 38) (384). This adverse outcome was also more frequent in patients who discontinued treatment less than 3 months before transplantation.

Of eight studies, five showed no harmful effect and three suggested an increased risk of post-transplant complications or mortality (SEDA-22, 403) (SEDA-23, 395).

The outcome of bone marrow transplantation in 152 patients (86 on interferon alfa, 66 on chemotherapy) included in two consecutive randomized trials, has been analysed prospectively (385). Whereas the duration of interferon alfa treatment did not influence the outcome of transplantation, there was a significant reduction in survival: the 5-year survival was 45% in the 50 patients who were still receiving interferon alfa within 3 months before bone marrow transplantation and 71% in the 36 patients who were not. According to the authors, interferon alfa should not be prescribed in patients who are likely candidates for early bone marrow transplantation.

Long-Term Effects

Tumorigenicity

Compared with untreated patients and patients treated with busulfan or hydroxyurea, interferon alfa produced a significantly higher frequency of clonal aberrant cytogenetic abnormalities and chronic clonal evolution in patients with chronic myeloid leukemia (386). However, the possible role of interferon alfa in the secondary occurrence of hematological malignancies is purely speculative. Only isolated cases of myeloproliferative syndrome, leukemia, or lymphoma have been attributed to interferon alfa (SED-13, 1098) (SEDA-20, 331) (SEDA-21, 373). There was no increased incidence of second cancers in patients treated for hairy cell leukemia (SEDA-20, 331).

Second-Generation Effects

Teratogenicity

In experimental models there has been no evidence of mutagenic or teratogenic effects of interferon alfa, and placental transfer is unlikely or very low (387). Immediately after delivery, interferon alfa concentrations in the breast milk or in the sera of two newborns were very low compared with maternal serum concentrations (388). Uncomplicated and successful pregnancies have been detailed in several patients treated for hematological malignancies or chronic hepatitis C, with interferon alfa exposure during the first trimester or even the whole of pregnancy (SED-13, 1098) (SEDA-20, 331) (389–392). In only three cases have premature delivery or moderate intrauterine growth retardation been observed, and any direct causal relation to interferon alfa treatment is doubtful. One report mentioned transient and moderate thrombocytopenia in a neonate born to a woman who had received interferon alfa throughout pregnancy (391).

Although no long-term follow-up is as yet available, clinical examination performed up to 2–3 years after delivery in at least seven babies has proved normal. Despite these reassuring data, the safety of interferon alfa during pregnancy still awaits further documentation, and it is advisable to delay therapy of non-life-threatening disease in pregnant women, especially during the first trimester.

Susceptibility Factors

Age

There is little information on the use of interferon alfa in children with chronic hepatitis C. In a review of 19 studies published between 1990 and 2000, there were data on only 366 treated children (105 untreated) and they suggested a higher rate of sustained response than in adults (393). Besides flu-like symptoms, reversible weight loss, neutropenia, and alopecia were the most commonly reported adverse events, but adverse events were not systematically recorded in these studies.

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Although the anti-angiogenic effects of interferon alfa have been successfully used to treat severe hemangiomas in infants, the possibility of spastic diplegia is a matter of concern (SEDA-22, 404). Spastic diplegia developed in five of 26 infants during treatment, with possibly significant functional sequelae (394), and in one of 53 infants treated for a median of 51 weeks (395). Persistent, severe, spastic diplegia occurred after 1 year of treatment in a 5-month-old boy (396). Because the immature central nervous system of infants may be more susceptible to interferon alfa toxicity, it has been stressed that this treatment should be reserved for infants with life-threatening hemangiomas (397). That interferon alfa can play a role in the occurrence of this acute neurological complication has been further substantiated by the finding of abnormally high interferon serum concentrations in 45% of neonates with spontaneous cerebral palsy compared with control children (398).

Renal disease

High daily dosage or serum concentrations of interferon alfa may be associated with more frequent and more severe adverse effects during the treatment of chronic hepatitis C in hemodialysis patients. In one study, three of 10 hemodialysis patients had severe neurological adverse effects (generalized seizures or posterior leukoencephalopathy) (399). In another study, three of six patients receiving daily injections had to discontinue treatment because of depression, loss of consciousness, and persistent high-grade fever, while no serious adverse effects were reported in three other patients who received interferon alfa three times a week (400). In both studies, there were significant changes in interferon alfa pharmacokinetics (higher C_{max}, AUC, and half-life) in hemodialysis patients compared with patients with normal renal function, consistent with altered clearance of interferon alfa.

Drug Administration

Drug formulations

The FDA has expanded the indications for a combination product to include patients with chronic hepatitis C who have not been treated with interferon alfa. This product, Rebetron Combination Therapy (Schering), contains recombinant interferon alfa-2b for injection (Intron A) plus ribavirin (Rebetol) in capsules, and was previously only approved for patients who had relapsed after treatment with interferon alone (401). Serious adverse effects, such as depression, suicidal ideation, and suicide, have occurred with this regimen and patients should be closely monitored.

Drug administration route

The use of intraspinal interferon alfa (1 MU three times a week for 4 weeks) in 22 patients with neoplastic meningitis was associated with frequent adverse effects that mostly manifested as chronic fatigue syndrome in 91% of patients (severe in 45%) and arachnoiditis in 73% (severe in 9%) (402). Interferon alfa-induced immune dysregulation in an immunologically predisposed patient was suggested to account for this complication.

Drug–Drug Interactions

Alcohol

Even moderate but continuing alcohol consumption needs to be taken seriously in patients receiving interferon alfa, and exacerbation of previous acute alcohol hepatitis has been reported in two patients with chronic hepatitis C, despite reduced alcohol consumption (403). Liver transaminases subsequently normalized after withdrawal of interferon alfa in both patients.

Angiotensin-converting enzyme inhibitors

An increased risk of severe and early but reversible neutropenia has been found in patients taking angiotensin-converting enzyme inhibitors (enalapril and captopril) with interferon alfa (404).

Carmustine

Owing to its antineoplastic properties, interferon alfa is sometimes used with cytostatic drugs. In 275 patients randomized to receive radiation and carmustine either alone or with interferon alfa for high-grade glioma, there was no significant improvement in the overall survival and time to disease progression in those given interferon alfa, but a higher incidence of adverse effects, namely fever, chills, myalgia, lethargy, headache, and seizures (405).

13-Cisretinoic acid

The combination of interferon alfa with 13-*cis*-retinoic acid may have potentiated the occurrence of fatal radiation pneumonitis (SEDA-21, 374).

Clozapine

Agranulocytosis was observed when interferon alfa was given to a patient taking long-term clozapine (SEDA-22, 404), but this is a known risk of the latter.

Coumarin anticoagulants

There have been two reports of increased prothrombin time in patients taking warfarin or acenocoumarol (SEDA-19, 337) (SEDA-22, 374).

Cyclophosphamide

Depending on the timing of exposure, interferon alfa may adversely affect the pharmacokinetic and hematological effects of cyclophosphamide. In 10 patients with multiple myeloma, interferon alfa given 2 hours before cyclophosphamide infusion significantly reduced cyclophosphamide clearance and produced less exposure to its metabolite 4-hydroxycyclophosphamide compared with interferon administration 24 hours after cyclophosphamide (406). This resulted in a significantly greater fall in white blood cell count in patients who received interferon alfa after cyclophosphamide.

Erythropoietin

Reduced efficacy of human erythropoietin, requiring increased erythropoietin dosages, has been clearly documented in several patients receiving interferon alfa

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(407–409), an effect that is probably mediated by interferon alfa-induced suppression of erythropoiesis.

5-Fluorouracil

One would expect drugs with myelosuppressive effects to exacerbate the hematological toxicity of interferon alfa. However, even though interferon alfa is increasingly used with other cytotoxic drugs, no specific and unexpected adverse effects have been reported, except for the combination of interferon alfa with 5-fluorouracil, which produced increased serum concentrations of fluorouracil and a significantly higher incidence of severe adverse effects, namely gastrointestinal and myelosuppressive adverse effects (410,411).

Melphalan

Interferon-induced fever has been thought to increase the cytotoxicity of melphalan (412).

Oral hypoglycemic drugs

There has been one report of hypoglycemia in a patient treated with metformin and chlorpropamide (SEDA-21, 374).

Paroxetine

It has been suggested that concomitant treatment with paroxetine may be a susceptibility factor for retinal damage by interferon alfa (82).

Phenazone (antipyrine)

Interferon alfa inhibits several hepatic microsomal cytochrome P_{450} enzymes in vitro and in vivo (SED-13, 1099) (20,413). However, repeated injections of interferon alfa produced conflicting results, with no change in salivary phenazone clearance (SED-13, 1099) (414).

Ribavirin

The combination of interferon alfa with ribavirin is one of the most promising treatments for chronic hepatitis C. However, two patients developed rapid and particularly severe anemia within 4 and 6 weeks of combined treatment (415). One patient required erythrocyte transfusions, and both recovered after withdrawal. The combination of pure red cell aplasia due to interferon alfa and hemolytic anemia due to ribavirin was suggested to have accounted for this possible interaction.

There was an increased incidence of adverse skin effects, mostly eczema, malar erythema, and lichenoid eruptions, in 33 patients who received combination of interferon alfa with ribavirin compared with 35 patients treated with interferon alfa alone (416).

Thalidomide

In 13 patients with metastatic renal cell carcinoma, the combination of interferon alfa-2a (27 MU/week) and thalidomide produced severe neurological toxicity in four patients, an incidence that was considered to be far greater than would be expected with either drug alone (417).

Theophylline

Interferon alfa inhibits several hepatic microsomal cytochrome P_{450} enzymes in vitro and in vivo (20) and reduces theophylline clearance (SED-13, 1099) (418–420).

Zidovudine

Synergistic hemotoxicity has sometimes resulted from the combination of interferon alfa with zidovudine in AIDS-associated Kaposi's sarcoma, but this regimen is considered to be relatively safe (421,422).

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Interferon beta

See also Interferons

General Information

Interferon beta is used in the form of natural fibroblast or recombinant preparations (interferon beta-1a and interferon beta-1b) and exerts antiviral and antiproliferative properties similar to those of interferon alfa. Although its efficacy has been debated (1), interferon beta has been approved for the treatment of relapsing–remitting multiple sclerosis, and more recently for secondary progressive multiple sclerosis.

The general toxicity of interferon beta is very similar to that of interferon alfa (2), with no apparent differences between the two recombinant preparations with any route of injection (SEDA-20, 332) (3–6). In multiple sclerosis, fatigue and a transient flu-like syndrome responsive to paracetamol or the combination of paracetamol plus prednisone have been observed in about 60% of patients during the first weeks of treatment, and tachyphylaxis usually developed after several doses (7). Patients with chronic progressive disease are more likely to discontinue treatment because of adverse effects (8).

Clinically relevant adverse effects associated with interferon beta and their management have been lengthily reviewed (9). Interferon beta-1a and beta-1b, the two recombinant available forms of interferon beta, have not been directly compared. From the results of a randomized, crossover study in 12 healthy volunteers, a single injection of interferon beta-1a 6 MU (Rebif) was suggested to produce less frequent and less severe fever than interferon beta-1b 8 MU (Betaseron), but identical pharmacodynamic effects (10).

A flu-like illness is the most common adverse effect of interferon beta. In an open, randomized study of the effects of paracetamol 1 g or ibuprofen 400 mg before and 6 hours after interferon beta injection on interferon beta-induced flu-like symptoms in 104 patients, the two drugs were equally effective (11).

Organs and Systems

Cardiovascular

Cardiovascular adverse effects of interferon beta include isolated reports of severe Raynaud's phenomenon (SEDA-22, 374) and acute myocarditis (SEDA-21, 374).

Fatal capillary leak syndrome has been reported (12).

- A 27-year-old woman had an 8-month history of relapsing–remitting neurological symptoms and a monoclonal gammopathy. She started to take interferon beta-1b for multiple sclerosis, but had marked somnolence 30 hours after a single injection. She rapidly became unresponsiveness, and hemodynamic tests showed low central venous and pulmonary capillary wedge pressures with generalized peripheral edema, ascites, and bilateral pleural effusions. She died within 80 hours after injection from multiple organ failure. At postmortem she was found to have C1 esterase inhibitor deficiency.

In the light of the possible effects of interferon beta on cytokine release and complement activation, a cytokine-mediated reaction was discussed as the cause of the capillary leak syndrome in this case.

Respiratory

Bronchiolitis obliterans with organizing pneumonia has been reported in a patient taking interferon beta (13).

- A 49-year-old man had a progressive unproductive cough and right hemithoracic pain after 3 months of interferon beta-1a 30 micrograms/week for multiple sclerosis. A CT scan showed a right basal pulmonary infiltrate and transbronchial biopsies showed features consistent with bronchiolitis obliterans with organizing pneumonia. The lesions resolved fully on interferon beta-1a withdrawal and prednisone treatment.

Nervous system

Although direct toxic effects of natural interferon beta on the nervous system have been regarded as a possible risk of intraventricular and/or intratumoral injection (14), interferon beta is considered to be markedly less neurotoxic than interferon alfa (15).

Although headache was not specifically identified as an adverse effect of interferon beta in pivotal trials, the frequency, duration, and intensity of headache increased during the first 6 months of treatment in 65 patients (16). There was a 35% probability of aggravated headaches in patients with pre-existing headaches.

The possible deleterious effects of interferon beta-1b on increased spasticity have been examined in 19 patients with primary progressive multiple sclerosis, 19 untreated matched patients, and 10 patients treated with interferon beta-1b for relapsing–remitting multiple sclerosis (17). Patients with primary progressive multiple sclerosis had frequent (68%) and clinically relevant increased spasticity (seven required oral baclofen), usually after about 2 months of treatment, whereas only two (11%) of the untreated patients and none of the patients with relapsing–remitting multiple sclerosis had similar disabling spasticity. Seven patients had to discontinue treatment after 6 months because of spasticity, and symptoms improved over several months after withdrawal. The authors suggested that this possible adverse effect should be taken into account in clinical trials because it could mask the positive clinical effects of interferon beta-1b.

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Neurosarcoidosis has been reported in a patient with chronic hepatitis C who was treated with interferon beta.

- A 56-year-old woman developed numbness and difficulty in swallowing and in closing her left eye several weeks after starting interferon beta for chronic hepatitis C (18). She had facial paresthesia, a left facial nerve palsy, dysphagia, and signs of radiculopathy on the left side. Serum angiotensin-converting enzyme activity was raised. She had bilateral hilar lymphadenopathy without interstitial changes and increased radiogallium uptake in hilar lymph nodes and the parotid glands. Although the cerebrospinal fluid was normal, a diagnosis of neurosarcoidosis was considered, and she recovered completely after interferon beta withdrawal and glucocorticoid therapy.

Moderate exacerbation of multiple sclerosis sometimes occurs in the first 3 months of interferon beta treatment.

- A 21-year-old man had an acute and very severe clinical relapse, with multiple disseminated demyelinating lesions and axonal injury on MRI and cerebral biopsy, after the third injection of interferon beta-1a (19).

Whether this case was due to interferon beta or resulted from spontaneous exacerbation was open to question.

Sensory systems

Retinal complications of interferon alfa in chronic viral hepatitis patients are well known, but few cases have been described with interferon beta.

- Bilateral retinopathy with similar features to those observed with interferon alfa has been reported in a 40-year-old woman treated with interferon beta-1b for multiple sclerosis (20).

In 49 patients, there was reversible otological impairment with tinnitus, mild-to-moderate hearing loss, or both in respectively 8, 16, and 20% of patients after administration of interferon alfa or interferon beta (SEDA-19, 336). These disorders tended to occur more frequently in patients on high cumulative doses, but led to withdrawal of treatment in only two patients.

Psychological, psychiatric

There have been reports of depression, suicidal ideation, and attempted suicide in patients receiving interferon beta (2,8,21). The lifetime risk of depression in patients with multiple sclerosis is high, and there has been a lively debate about whether interferon beta causes or exacerbates depression in such patients. Impressions of a possibly raised incidence of depression among patients treated with interferon beta for multiple sclerosis should be interpreted in the light of the spontaneous tendency to depressive disorders and suicidal ideation, which is encountered even in patients with untreated multiple sclerosis. Moreover, no raised incidence of these complications has been recorded in some studies (4,5). A critical review of the methodological limitations in studies that assessed mood disorders in patients on disease-modifying drugs for multiple sclerosis may help explain the widely divergent results from one study to another (22). Some results have argued against a specific role of interferon beta in the risk of depressive disorders.

A multicenter comparison of 44 and 22 micrograms of interferon beta-1a and placebo in 365 patients showed no significant differences in depression scores between the groups over a 3-year period of follow-up (23). In 106 patients with relapsing–remitting multiple sclerosis, depression status was evaluated before and after 12 months of interferon beta-1a treatment (24). According to the Beck Depression Inventory II scale, most of the patients had minimum (53%) or mild (32%) depression at baseline, and depression scores were not significantly increased after 1 year of treatment. There were no cases of suicidal ideation. In another study of 42 patients treated with interferon beta-1b, major depression at baseline was found in 21% of patients and was associated with a past history of psychiatric illness in most cases (25). Major depression was not considered as an exclusion criterion for interferon beta treatment when patients were on antidepressant therapy. There was a three-fold reduction in the prevalence of depression over the 1-year course of interferon treatment, suggesting a possible beneficial effect of treatment on mood. Finally, a single subcutaneous injection of interferon beta-1b did not alter cognitive performance and mood states in eight healthy volunteers (26).

The emotional state of 90 patients with relapsing–remitting multiple sclerosis has been carefully assessed with a battery of psychological tests at baseline and after 1 and 2 years of treatment with interferon beta-1b (27). In contrast to what was expected, and despite the lack of controls, there was significant improvement in emotional state, as shown by significant reductions in scores of anxiety and depression over time. In addition, there was no effect of low-dose oral glucocorticoids in a subgroup of 46 patients.

Depression has been quantified by telephone interview in 56 patients with relapsing multiple sclerosis 2 weeks before treatment, at the start of treatment, and after 8 weeks of treatment (28). Patients with a high depressive score 2 weeks before treatment significantly improved on starting treatment and returned to baseline within 8 weeks, whereas the depression score in non-depressed patients remained essentially unchanged. The investigators therefore suggested that patients' expectations had temporarily resulted in improvement of depression, and that increased depression during treatment is more likely to reflect pretreatment depression.

The clinical features, management, and prognosis of psychiatric symptoms in patients with chronic hepatitis C have been reviewed using data from 943 patients treated with interferon alfa (85%) or interferon beta (15%) for 24 weeks (29). Interferon-induced psychiatric symptoms were identified in 40 patients (4.2%) of those referred for psychiatric examination. They were classified in three groups according to the clinical profile: 13 cases of generalized anxiety disorder (group A), 21 cases of mood disorders with depressive features (group B), and six cases of other psychiatric disorders, including psychotic disorders with delusions/hallucinations ($n = 4$), mood disorders with manic features ($n = 1$), and delirium ($n = 1$) (group C). The time to onset of the symptoms differed significantly between the three groups: 2 weeks in group A, 5 weeks in group B, and 11 weeks in group C.

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Women were more often affected than men. There was no difference in the incidence or nature of the disorder according to the type of interferon used. Whereas most patients who required psychotropic drugs were able to complete treatment, 10 had to discontinue interferon treatment because of severe psychiatric symptoms, five from group B and five from group C. Twelve patients still required psychiatric treatment for more than 6 months after interferon withdrawal. In addition, residual symptoms (anxiety, insomnia, and mild hypothymia) were still present at the end of the survey in seven patients. Delayed recovery was mostly observed in patients in group C and in patients treated with interferon beta.

One debatable case of visual pseudo-hallucinations occurred only, but not reproducibly, within 30–60 minutes after interferon beta-1a injection in a 37-year-old woman with disseminated encephalomyelitis (30).

Endocrine

While no evidence of thyroid dysfunction or antithyroid antibodies was found in 20 patients receiving interferon beta during 24 weeks for hematological malignancies (31), antithyroid antibodies were detected in 29% of patients with multiple sclerosis after a prospective follow-up performed at 6, 12, and 18 months of treatment (32). Biological thyroid abnormalities without antithyroid antibodies have also been found (SEDA-20, 332). Overall, thyroid disorders with antithyroid antibodies were reported in only three patients on long-term interferon beta treatment for multiple sclerosis (32,33).

Thyroid disorders before and during the first 9 months of interferon beta-1b treatment have been systematically investigated in eight patients with relapsing–remitting multiple sclerosis (34). Before treatment, one patient had positive thyroperoxidase antibodies and one was taking thyroxine for multinodular goiter. After 3 months three other patients developed sustained positive titers of thyroperoxidase antibodies, of whom one developed hypothyroidism after 9 months. These results are in accordance with a previous similar study and isolated case reports (SEDA-21, 374) (SEDA-22, 405), and suggest that interferon beta, like interferon alfa, can cause thyroid autoimmunity.

As suggested in a more comprehensive long-term follow-up study, interferon beta-induced thyroid dysfunction is often transient or has limited clinical consequences (35). Of 31 patients with multiple sclerosis regularly assessed for 30–42 months for thyroid function, 13 developed thyroid disorders during treatment with interferon beta-1b. None withdrew because of thyroid disorders. Of the eight patients with no previous thyroid disorders, one had a persistent but isolated increase in antithyroglobulin titer, six developed transient signs of hypothyroidism or hyperthyroidism during the first year of therapy, and only one had overt hypothyroidism after 12 months of treatment and required thyroxine replacement. Of the five patients with baseline signs of Hashimoto's thyroiditis, one had a transiently positive antithyroglobulin titer, one developed transient hyperthyroidism, and the three patients who had previously had or who newly developed subclinical hypothyroidism remained stable throughout the study. Overall, thyroid disorders occurred only during the first 12 months of treatment and no additional cases were detected after the first year of therapy. In the authors' opinion, pre-existing or new thyroiditis is not a contraindication to continuing interferon beta-1b treatment. Two patients took thyroxine replacement and continued to receive interferon beta-1b (36).

Metabolism

Severe hypertriglyceridemia, a well-known adverse effect of interferon beta, has been reported and fully investigated in a 39-year-old man receiving interferon beta for chronic hepatitis C (37).

Hematologic

Moderate reductions in white blood cell count (that is lymphopenia, leukopenia, and granulocytopenia) have been observed with recombinant interferon beta, and marked eosinophilia recorded in an atopic patient (SEDA-21, 374).

- A 42-year-old woman developed aplastic anemia after using interferon beta-1a for 1 year (38). There was hematological improvement after withdrawal and immunosuppressive therapy.

Reversible autoimmune hemolytic anemia (SEDA-20, 332) has also been reported.

Liver

Adverse hepatic effects of interferon beta were usually limited to a dose-dependent increase in transaminases, but transient autoimmune hepatitis has been described in one patient (39).

It has been suspected that interferon beta can accelerate hepatocellular carcinoma (40).

- A 62-year-old man with severe chronic hepatitis and positive serum anti-HCV, HBs, and HBc antibodies underwent unsuccessful treatment with interferon alfa for 3 months and then received interferon beta for 6 months with a partial response. During treatment, his alfa-fetoprotein (normal before treatment) progressively increased to seven-fold the upper limit of the reference range. There was also a slight increase in interleukin-6 serum concentration. A hepatocellular carcinoma was diagnosed 9 months later.

Liver carcinoma is an unexpected consequence of interferon beta in patients with chronic hepatitis C. However, the authors cited other published Japanese reports of hepatocellular carcinoma during or after interferon treatment. It is worth noting that interferon beta, but not interferon alfa, significantly increased serum interleukin-6 concentrations in patients with chronic hepatitis C (41), and that interleukin-6 has been suggested to promote the growth of hepatocellular carcinoma.

Fulminant liver failure has been attributed to interferon beta-1a (42), but it was subsequently confirmed that this case was confounded by concomitant exposure to nefazodone, which is hepatotoxic (43).

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Urinary tract

Reversible hemolytic–uremic syndrome has been reported (SEDA-22, 405).

- Two women aged 24 and 44 years, whose primary diagnosis was relapsing multiple sclerosis, developed renal impairment and a thrombotic thrombocytopenic purpura-like syndrome within 2–4 weeks after starting interferon beta-1a (44). Thrombocytopenia and renal function normalized in the first patient, whereas the second patient had thrombotic angiopathy on renal biopsy and required dialysis while awaiting renal transplantation.

As interferon alfa has also been suggested to produce hemolytic–uremic syndrome with thrombotic thrombocytopenic purpura, it is tempting to speculate that either interferons or other cytokines may play a role in this syndrome.

Proteinuria, nephrotic syndrome, and various forms of renal lesions can be caused or exacerbated by interferon alfa (SED-14, 1252).

- Proteinuria with minimal–change nephrotic syndrome on renal biopsy has been attributed to interferon beta in a 64-year-old man with malignant melanoma (45). Although the proteinuria abated after withdrawal, the potential role of previous chemotherapy cannot be excluded.
- Nephrotic syndrome with segmental glomerulosclerosis has been reported in a 32-year-old woman with multiple sclerosis receiving interferon beta (46).

The clinicopathological features of proteinuria have been investigated in 23 patients with chronic hepatitis C who had new or worsened proteinuria during interferon treatment (interferon alfa 6–10 MU/day in three patients and interferon beta 6 MU/day in 20 patients (47)). Renal function and urinary findings were normal before treatment in 21 subjects. Proteinuria appeared after a mean of 12 (range 5–30) days after the start of treatment, and the mean value was 2.1 g/day. There was low selective proteinuria in 78% of the patients. Renal histopathology in 11 patients showed IgA glomerulonephritis in five, mesangial proliferative glomerulonephritis in four, membranoproliferative glomerulonephritis in one, and nephrosclerosis in one. There was only trace deposition of hepatitis C virus core antigen in three of nine patients, suggesting that hepatitis C was not the primary cause of these glomerulopathies.

Skin

Injection-site reactions are common after subcutaneous injection of interferon beta-1b, and are more frequent than with any other available interferons. In a multicenter placebo-controlled trial, 65% of patients receiving interferon beta-1b had reactions at the injection site compared with 6% in the placebo group (2). In contrast, only 5% of those who received interferon beta-1a had injection site reactions (3). The clinical features of injection site reactions to interferon beta-1b mostly consist of benign inflammatory reactions, but they can sometimes be more severe, with sclerotic dermal plaques, painful erythematous nodules, and deep cutaneous ulcers with skin necrosis (SEDA-21, 374) (48). Late severe reactions have included a case of squamous cell carcinoma at the injection site (SEDA-21, 375) and a case of panniculitis (49).

Since interferon beta-1b became available, 1443 instances of injection site reactions, 212 cases of injection site necrosis, and 10 cases of non-injection site necrosis were notified to the US Food and Drug Administration, and antibiotic therapy or surgery was required in 20–30% of patients (50). Severe necrotizing cutaneous lesions have also been attributed to subcutaneous interferon beta-1a (51).

In contrast to previous claims, even low-dose interferon beta-1b can produce severe local reactions and cutaneous necrosis, with no recurrence after interferon alfa injection and expected better tolerance to interferon beta-1a (52–55). The mechanisms of interferon beta-induced local skin reaction might involve a local vascular inflammatory process or platelet-dependent thrombosis, but positive intracutaneous tests to interferon beta have also been found (56).

There have been other isolated reports of skin lesions.

- Intravascular papillary endothelial hyperplasia with multiple lesions on both hands has been attributed to interferon beta-1b in a 50-year-old man with multiple sclerosis (57).
- Granulomatous dermatitis with disseminated pruritic papules and histological features resembling those of sarcoid granulomas has been described in a 57-year-old man who received interferon beta-1b (58). The first lesions were observed after 2 months of treatment, persisted for 2 years, and slowly improved after interferon beta withdrawal and treatment with hydroxychloroquine PUVA.
- Erythromelalgia has been attributed to interferon beta-1a in a 38-year-old woman (59). Complete recovery was obtained only after interferon withdrawal.
- In one patient, there was cutaneous mucinosis on skin biopsy, and skin lesions persisted for several months before healing spontaneously (60).

Other reports include exacerbation of quiescent psoriasis or induction of psoriatic lesions at the injection sites (SED-13, 1099) (SEDA-20, 332), and the development or exacerbation of lichen planus (SEDA-21, 375).

Musculoskeletal

Rhabdomyolysis associated with interferon beta has been reported (61).

- A 39-year-old man developed acute generalized myalgia and weakness in all four limbs 3 months after starting interferon beta-1a (22 micrograms three times a week) for relapsing–remitting multiple sclerosis. Serum creatine kinase activity peaked at about 95 times the upper limit of the reference range. Infectious and metabolic causes were ruled out and there was no argument in favor of an underlying metabolic muscle disorder. He recovered fully after interferon beta withdrawal and supportive treatment.

Although rhabdomyolysis has not been previously attributed to interferon beta, this case is in keeping with those described with interferon alfa.

- A 39-year-old man developed monoarthritis in his right elbow after receiving interferon beta for 16 days for chronic hepatitis C (62).

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Although the arthritis resolved after withdrawal, this report casts doubt on the causal relation, as there was no recurrence on re-administration.

Reproductive system

Mild to moderate menstrual disorders were twice as frequent in patients receiving interferon beta compared with placebo (17 versus 8%). Severe persistent vaginal bleeding has been reported in a 19-year-old woman (SEDA-21, 375).

Immunologic

Hypersensitivity reactions

Hypersensitivity reactions to interferon beta are rare, with only two cases of immediate-type reactions (SEDA-20, 332) (63), and one case of urticaria associated with exacerbation of asthma (64).

- A 21-year-old woman had a severe anaphylactic-like reaction with laryngospasm and undetectable blood pressure within 10 minutes after interferon beta-1a injection (63). It is still uncertain that anaphylaxis was definitely attributable to interferon, because rechallenge and skin tests were not performed in this patient, who had tolerated the treatment for the 6 previous months.
- Urticaria developed after 9 months of treatment with interferon beta-1b in a 32-year-old woman with a previous history of penicillin allergy (64). She also had an exacerbation of asthma shortly after starting treatment. A positive intradermal test to interferon beta-1b, but not to interferon beta-1a or the diluents, suggested a specific IgE allergic reaction.

Another isolated case history has suggested that interferon beta-1b might have favored the development of a non-IgE-mediated anaphylactic reaction to previously well-tolerated injections of methylprednisolone (65).

Autoimmune disorders

In contrast to interferon alfa, the autoimmune consequences of interferon beta treatment have been poorly evaluated. Interferon beta does not appear to be associated with the appearance or increased titres of several auto-antibodies, and no clinical features of autoimmune disease were observed in patients receiving a 6-month course of interferon beta-1a or interferon beta-1b (66,67).

Subcutaneous lupus erythematosus reversible on withdrawal of treatment (SEDA-22, 405) and myasthenia gravis (SEDA-21, 375) have been described, but each only in a single patient receiving interferon beta.

The possible involvement of interferon beta in the occurrence of sarcoidosis has been noted in two patients (68,69).

Interferon beta antibodies

In multiple sclerosis, neutralizing antibodies to recombinant interferon beta occurred in 12–38% of patients treated for 2–3 years (3–5,70). There were no adverse consequences in patients who developed antibodies to interferon beta-1a (4), but there was reduced therapeutic efficacy in terms of clinical relapse rate or magnetic resonance imaging in several patients who had neutralizing antibodies to interferon beta-1b (SEDA-20, 332) (5,71).

The systemic availability of interferon beta-1b, measured by a myxovirus protein A assay, was completely inhibited in patients with neutralizing antibodies (72). The presence of increased titers of serum-binding antibodies increased the likelihood of neutralizing antibodies. From an in vitro study of nine patients who developed neutralizing antibodies against the available formulations of recombinant interferon beta (three on interferon beta-1a and six on interferon beta-1b), it appears that these antibodies systematically cross-react in both binding and biological assays (73). Although the sample size was small and lacked clinical confirmation, these results suggest that clinical benefit will not be obtained by switching to an alternative formulation when the absence of response or relapse during treatment is due to neutralizing antibodies.

The clinical significance of these antibodies is uncertain (74) and it has been proposed that decisions to discontinue treatment should be based on individual clinical responses and unequivocal demonstration of neutralizing antibodies with a reliable assay (70).

One study has shown that antibodies can spontaneously disappear in patients receiving long-term treatment. Of 24 of 51 patients who initially developed neutralizing antibodies, generally during the first year of treatment, only five still had antibodies after a mean treatment duration of 102 months (75). The mean time to antibody disappearance was 20 months.

A randomized study has been conducted in 161 patients to evaluate whether a monthly intravenous pulse of methylprednisolone reduces the frequency of neutralizing antibodies to interferon beta-1b (76). The patients who received both interferon beta and methylprednisolone had a 55% relative reduction in the development of neutralizing antibody and were significantly more likely to remain negative for neutralizing antibodies after 6 months of treatment compared with those who received interferon beta alone. The overall frequency of adverse effects and the number of withdrawals were similar between the groups, but headaches, fatigue, and myalgia were less frequent in the combination therapy group. A limitation of this study was that there was no difference in clinical outcome between the two groups.

Finally, possible differences in the immunogenic potential of recombinant and natural interferon beta preparations were found in a small study (77).

Second-Generation Effects

Teratogenicity

Data on outcomes in pregnancy after treatment with interferon beta-1a in patients with multiple sclerosis have been obtained from clinical trials (78). Of 29 pregnancies that occurred during or shortly after treatment withdrawal, 13 resulted in normal outcomes, two in premature births, one in fetal death, six in induced abortions, and seven in spontaneous abortions.

- A child whose mother had received interferon beta until 2.5 months before pregnancy had a right incomplete double renal pelvis and ureter (79). Although the authors discussed the possible role of interferon

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therapy, the timing of exposure was obviously not suggestive of a causal relation.

Although the data are still very limited, it is advisable to reassure exposed patients and to withdraw interferon beta up to the time of delivery.

Drug Administration

Drug dosage regimens

In 188 patients with relapsing–remitting multiple sclerosis assigned to receive interferon beta-1a 30 micrograms intramuscularly once a week or interferon beta-1b 44 micrograms subcutaneously three times a week, only injection site reactions and neutralizing antibodies to interferon beta were significantly more frequent in the interferon beta-1b group (80). These differences were probably related to the subcutaneous route of administration of interferon beta-1b. In contrast, there were significant differences in favor of interferon beta-1b for clinical outcomes after 2 years of treatment.

In a comparison of two regimens of interferon beta-1a (44 micrograms Rebif subcutaneously three times a week versus 30 micrograms Avonex intramuscularly once a week) in 677 patients with relapsing–remitting multiple sclerosis, Rebif was more effective on primary clinical outcomes (patients remaining relapse-free at 24 weeks), but produced significantly more frequent injection site reactions (88 versus 28%), asymptomatic and mild liver enzyme abnormalities (18 versus 9%), mild white cell abnormalities (11 versus 5%), and neutralizing antibodies to interferon beta (25 versus 2%) (81). However, the severity of adverse events and withdrawal due to an adverse event were similar in both groups.

Drug–Drug Interactions

Theophylline

Interferon beta reduced theophylline clearance by 29% in seven patients (SED-13, 1099).

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Interferon gamma

See also Interferons

General Information

Recombinant interferon gamma (interferon gamma-1b) is currently only approved as an adjunct to antibacterial therapy in chronic granulomatous disease (1), but its immunoregulatory potential has been investigated in other diseases. Clinical experience with interferon gamma is therefore limited and the most relevant information on long-term safety has been obtained from the ICGDSCG trial (2). In this study, adverse effects that were significantly more frequent with interferon gamma-1b (1.5 micrograms/kg or 50 micrograms/m^2) than with placebo included mild fever and flu-like symptoms, headache, and moderate injection site reactions. There were no adverse consequences on growth and development in children followed for a mean of 2.5 years (3,4). Several other adverse effects have been reported to the manufacturers, but causal evaluation is lacking (1).

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Interferon gamma has been investigated in 27 patients with systemic sclerosis randomized to receive interferon gamma for 12 months. Most of them complained of symptoms consistent with a flu-like syndrome, namely headache (85%), fever (81%), and arthralgia and myalgia (70%) (5). There were adverse events (one or more per patient) leading to treatment withdrawal in four cases, including arthralgia, cardiac pain, atrioventricular block, reversible loss of hearing, and impotence; however, a causal relation with interferon gamma was not documented.

Organs and Systems

Cardiovascular

Heart rate, ventricular or supraventricular extra beats, and asymptomatic cardiac events were not significantly different during treatment compared with baseline in 20 patients receiving interferon gamma (6). Interferon gamma rarely produced cardiovascular adverse effects. Hypotension, dysrhythmias, and possible coronary spasm were sometimes observed, mostly in patients receiving high doses or with previous cardiovascular disorders (SEDA-20, 333) (SEDA-22, 405) (7,8).

Exacerbation of Raynaud's syndrome occurred in five of 20 patients with systemic sclerosis treated with interferon gamma (SEDA-20, 333).

Respiratory

Of 10 patients treated with interferon gamma-1b 200 micrograms three times a week for advanced idiopathic pulmonary fibrosis, four developed irreversible acute respiratory failure (9). All four patients had increasing dyspnea, fever, and rapidly progressive hypoxemia, and had new alveolar opacities on lung imaging. The symptoms occurred shortly after interferon gamma had been started in three patients, and after 35 injections in the fourth. Three patients died from refractory hypoxemia and the fourth underwent lung transplantation, but died a few weeks later. Pathological examination in two patients showed diffuse alveolar damage with pre-existing interstitial pneumonitis. Interferon gamma was suspected, as no other cause of abrupt pulmonary deterioration was found. Although the number of patients was small, the authors noted that before interferon beta pulmonary function tended to be worse in the four patients who developed acute respiratory failure than in the other six.

Psychological, psychiatric

Neuropsychiatric disturbances have not been consistently found in patients receiving interferon gamma, despite electroencephalographic monitoring and psychometric tests (10). However, careful examination led to the impression that interferon gamma can cause neurophysiological changes similar to those of interferon alfa (11), and data from the manufacturers also point to rare cases of nervous system adverse effects in patients treated with high-dose interferon gamma (1).

Endocrine

Interferon gamma can increase serum cortisol concentrations (12).

Metabolism

Reversible dose-dependent hypertriglyceridemia has been attributed to interferon gamma (13).

Hyperglycemia, reversible on interferon gamma withdrawal and a short course of insulin, has been reported in one patient (SEDA-22, 406).

Hematologic

Interferon gamma was supposedly the cause of asymptomatic non-immune hemolytic anemia in one patient receiving both interleukin-2 and interferon gamma (14).

Only minimal effects of interferon gamma on white blood cell counts have been observed (15).

Auto-immune thrombocytopenia occurred in a patient receiving interferon gamma (SEDA-22, 406).

Gastrointestinal

A convincing case of severe aphthous stomatitis has been reported in a patient receiving interferon gamma (SEDA-20, 333).

Urinary tract

Dose-related asymptomatic proteinuria was sometimes observed, and severe proteinuria with nephrotic syndrome has been reported once after low-dose interferon gamma (SED-13, 1100). Acute renal insufficiency is extremely rare (SEDA-20, 333) (16).

Skin

Induction of psoriatic lesions at the injection site has been observed in 10 of 42 patients treated with interferon gamma for psoriatic arthritis, while the joint symptoms were improved (17).

Single or multiple lesions of erythema nodosum leprosum occurred in 60% of patients given intradermal interferon gamma for lepromatous leprosy, and severe systemic symptoms required thalidomide treatment in two patients (18).

Severe erythroderma was observed in five of 10 patients after interferon gamma was added to ciclosporin for autologous bone marrow transplantation (19).

Immunologic

An anaphylactoid reaction and severe bronchospasm have been reported once after the first injection of interferon gamma (10).

Although interferon gamma is mainly used for its immunoregulatory properties, the possibility of clinical immune adverse consequences has been addressed in a limited number of prospective studies. In two studies involving patients with chronic hepatitis B treated for 4–6 months, most developed a new autoantibody (20,21), but none developed clinical evidence of autoimmune disease. However, other reports suggested that interferon gamma can either improve or aggravate immune or inflammatory conditions. Although no change in antinuclear antibodies

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was reported in a trial of 54 patients with rheumatoid arthritis (22), increased or new antinuclear antibodies were observed in three of six patients with rheumatoid arthritis who received interferon gamma for 2–8 months, and two patients had clinical exacerbations of the disease (23). Isolated cases of systemic lupus erythematosus have been reported in patients receiving interferon gamma for rheumatoid arthritis (24,25). Rheumatoid or lupus-like symptoms associated with raised antinuclear antibodies titers were also noted in 17% of patients receiving interferon alfa and interferon gamma for myeloproliferative disorders, and in only 8.3% of patients treated with interferon alfa alone (26). Interferon gamma was also involved in the induction or reactivation of seronegative arthritis in patients with cutaneous psoriasis (27) and the unexpected exacerbation of multiple sclerosis in 39% of patients (28). Finally, neutralizing antibodies have exceptionally been found (SEDA-20, 333).

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Interferons

See also Individual agents

General Information

The interferons, first described in 1957, include at least five natural human glycoproteins (alfa, beta, gamma, omega, and tau). Only the first three types are currently used, and they differ both structurally and antigenically. Interferon alfa is produced by macrophages, B cells, and null lymphocytes, interferon beta by fibroblasts, epithelial cells, and macrophages, and interferon gamma from T lymphocytes and macrophages after antigenic or mitogenic stimulation. The interferons share 30–40% of sequence homology and have antiviral and antiproliferative actions. Interferon gamma, produced by activated T cells and natural killer cells, is recognized by a different receptor and acts primarily as an immunoregulatory cytokine.

Uses

The uses of interferons are listed in Table 1.

Two authoritative reviews have outlined the therapeutic potential of interferons (1,2). A wide range of viral diseases or cancers are other candidates for interferon therapy (3–5).

Mechanisms of action

On binding to surface receptors, interferon alfa results in activation of cytoplasmic enzymes affecting messenger RNA translation and protein synthesis (6). The antiviral state takes hours to develop but can persist for days. Besides broad antiviral activity, interferons are of major importance in regulating immunological functions.

General adverse effects

The adverse effects of interferon are multifarious and the natural products seem to be less toxic than the pure synthetic compounds. Influenza-like symptoms with fever, chills, fatigue, myalgia, arthralgia, nausea, and lethargy, starting within 1 week after the start of treatment and lasting 1–7 days, seem to be very common (7,8). Adverse effects also include neurotoxicity (paresthesia, polyneuropathy), hepatic toxicity, renal toxicity, and an increase in eyelash growth (9–13). Neutralizing antibodies can lead to resistance in patients with hairy cell leukemia and chronic myeloid leukemia (14,15). The route of administration influences the provocation of an antibody response, and recombinant interferon beta is more likely to be immunogenic when given subcutaneously or intramuscularly than when given intravenously (16). Raynaud's phenomenon has been described after treatment with interferon alfa (17), and exacerbation of multiple sclerosis has been observed after treatment with interferon gamma.

The most common adverse effects reported in two large multicenter studies were fever (60%), leukopenia (43%), increased serum aspartate transaminase activity (30%), anorexia (30%), thrombocytopenia (25%), fatigue (21%), nausea, and vomiting (17%) (18,19). Compared with subcutaneous administration, intravenous interferon alfa is associated with similar adverse effects of greater severity and frequency (20,21).

Table 1 Names of different types of interferons and their indications

Generic name and trade name	Indications
Interferon alfa	Malignant diseases: hairy cell leukemia, chronic myelogenous leukemia, cutaneous T cell lymphoma, follicular lymphoma, multiple myeloma, Kaposi's sarcoma, diffuse melanoma, renal cell carcinoma, carcinoid tumors Viral diseases: condylomata acuminata, chronic active hepatitis B and C
Human natural leukocyte interferon alfa (IFN alfa-n3; Alferon)	
Lymphoblastoid interferon alfa (IFN alfa-n1; Welferon)	
Recombinant interferon alfa-2a (rIFN alfa-2a; Roferon)	
Recombinant interferon alfa-2b (rIFN alfa-2b; Intron A)	
Recombinant interferon alfa-2c (rIFN alfa,2c; Berofor)	
Interferon beta	Multiple sclerosis
Natural fibroblast (Fiblaferon)	
Recombinant interferon beta (rIFN beta; Avonex)	
Recombinant interferon beta-1b (rIFN beta-1b; Betaseron)	
Interferon gamma	Chronic granulomatous disease
Recombinant interferon gamma-1b (rIFN gamma-1b; Actimmune)	

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Interleukin-1

General Information

Interleukin-1-alfa and interleukin-1-beta are produced by two distinct genes with only 25% homology, but they act through the same receptor and share similar in vitro biological properties. Interleukin-1 on its own has modest antitumor activity and limited hemopoietic effects. It also acts synergistically with other colony-stimulating factors (for example GM-CSF, G-CSF, interleukin-3, or interleukin-6) to promote colony formation and stimulate hemopoietic recovery in patients undergoing autologous bone marrow transplantation or receiving cytotoxic anticancer treatment (1).

General adverse effects

Both forms of interleukin-1 have been investigated in humans, and they produce a wide and very similar spectrum of adverse effects (SED-13, 1101) (2). Whatever the dose, fever and chills are universal but only occasionally treatment-limiting. Tachyphylaxis can develop during prolonged administration. Other frequent but moderate adverse effects include transient fatigue, myalgia, arthralgia, dose-dependent headache, nausea, vomiting, diarrhea, and abdominal pain. Injection site reactions included local phlebitis, while subcutaneous injection of interleukin-1-beta can cause local pain and erythema. Interleukin-1-alfa can cause transient and moderate increases in bilirubin, aspartate transaminase, and serum creatinine concentrations.

Organs and Systems

Cardiovascular

The most significant adverse effect of both forms of interleukin-1 is dose-limiting hypotension resulting from a capillary leak phenomenon with clinical features of septic shock (2). Although mild weight gain, dyspnea, and pulmonary infiltrates can occur, severe capillary leak syndrome is usually not observed. Shortness of breath requiring oxygen and benign supraventricular dysrhythmias were sometimes noted. The maximum tolerated dose of interleukin-1 with pressors is therefore 0.3 micrograms/kg/day. The most probable mechanism underlying these complications is an interleukin-1-induced increase in nitric oxide production by vascular smooth muscle.

Nervous system

A few patients given interleukin-1 complain of somnolence, agitation, delusional ideation, photophobia or

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subjective blurred vision, but at high doses some patients experienced a greater degree of central nervous system toxicity, with complaints of confusion, severe somnolence and seizures (3).

Endocrine

Various endocrinological effects have been observed, but without clinically apparent endocrinopathies (SEDA-20, 333).

Metabolism

Interleukin-1-beta has been associated with transient hypoglycemia (4).

Mouth and teeth

Interleukin-1-alfa can cause mucositis and xerostomia (3) and can increase the severity of chemotherapy-induced oral mucositis and erythema (5).

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Interleukin-3

General Information

Interleukin-3 is produced by activated T lymphocytes and stimulates the proliferation and differentiation of the granulocyte, macrophage, eosinophil, basophil, erythroid, megakaryocyte, and mast cell lineages (1).

Observational studies

Subcutaneous recombinant interleukin-3 has been investigated in patients with chemotherapy-induced myelotoxicity, in the setting of autologous bone marrow transplantation or peripheral stem cell harvesting, or in patients with myelodysplastic syndrome, aplastic anemia, and Diamond–Blackfan anemia (1,2). Interleukin-3 given alone has limited clinical effects, but an enhanced hemopoietic response has been obtained with a genetically engineered GM-CSF/interleukin-3 fusion protein, PIXY321 (SEDA-21, 376) (3).

The specific toxicity of subcutaneous recombinant human interleukin-3 derived from *Escherichia coli* has been addressed in a 4-day study performed in healthy volunteers (4). All had mild-to-moderate dose-independent symptoms; flu-like symptoms, including fever, chills, headache, conjunctival congestion, myalgia, and diffuse aching, were the most frequent. Minor erythematous reactions at the injection site were also consistently described, and one patient had histological features of an allergic vasculitis resembling that reported with GM-CSF (SEDA-20, 335). Mild-to-severe skin rashes or urticaria were also sometimes observed, and there were bullae with hemorrhagic necrosis of the skin in one patient (5). In preliminary clinical trials, malaise, eye pain, nasal congestion, weakness or lethargy, tachycardia, and gastrointestinal disorders occurred in under 16% of patients (6). None of these effects was clearly related to dose, and withdrawal of treatment was not required. A similar safety profile was reported in patients who subsequently developed tachyphylaxis, and the adverse effect profile of yeast or interleukin-3 derived from *E. coli* did not appear to be different (6). Overall, the rate of withdrawal of treatment because of adverse effects was 17–50% in patients receiving 10 micrograms/kg/day. Constitutional symptoms, generalized skin reactions, and facial edema were the most frequent dose-limiting adverse events. In autologous bone marrow transplantation, the maximum tolerated dose was only 2 micrograms/kg/day. Interleukin-3-associated fever is supposedly the result of a dose-dependent increase in interleukin-6 and acute phase protein production.

Adverse effects related to interleukin-3 were observed in a comparison of G-CSF alone, GM-CSF alone, and sequential interleukin-3 and GM-CSF in 48 patients with cancer (16 in each group) receiving high-dose cyclophosphamide (7). In particular, fever above 38.5°C, skin rash, and headaches were more frequent during interleukin-3 administration. As a result, 90% of patients receiving interleukin-3 required pharmacological treatment for adverse effects.

Placebo-controlled studies

The potential hemopoietic benefits of postchemotherapy interleukin-3 are limited. In a phase III trial in 185 ovarian cancer patients treated with carboplatin and cyclophosphamide, premature withdrawal was significantly more frequent in patients randomized to received recombinant interleukin-3 (5 micrograms/kg from day 3 to day 12) than in the placebo group (8). The most frequent adverse effects were allergic reactions (50 versus 23%), which required interleukin-3 withdrawal in 21 patients compared with one in the placebo group, and headache (46 versus 19%). In this setting, interleukin-3 stimulated hemopoiesis, but did not reduce platelet transfusions or increase adherence to the chemotherapeutic regimen.

The benefit of interleukin-3 in promoting hemopoietic reconstitution after autologous bone marrow

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transplantation has been investigated in 198 patients with malignant lymphoma who received either interleukin-3 (10 micrograms/kg for 4 weeks, 130 patients) or placebo (68 patients) (9). There was no significant advantage of interleukin-3 over placebo in regard to the number of platelet transfusions before engraftment, the time to platelet engraftment, or the incidence of hemorrhagic complications. This confirms that interleukin-3 alone has limited clinical effects. In contrast, significantly more patients who received interleukin-3 had to discontinue treatment because of adverse events (26 versus 7%). Adverse events that were significantly more frequent with interleukin-3 than with placebo included mucositis (69 versus 44%), headache (38 versus 13%), and rash (25 versus 12%). It is not yet known whether the initial route of administration (continuous intravenous infusion for 7 days followed by subcutaneous administration for 21 days) might account for these findings.

General adverse effects

Constitutional symptoms, generalized skin reactions, and facial edema are the most frequent. Although they are not easily attributable to interleukin-3, other significant adverse events noted during treatment have included exacerbation of arthralgia in a seronegative patient (5) and transient thrombocytopenia in patients with myelodysplastic syndrome or aplastic anemia (10). Signs of meningism with neck rigidity were sometimes found (10).

As with G-CSF and GM-CSF, the presence of interleukin-3 receptors on leukemia cells suggests a theoretical risk of disease aggravation. However, accelerated tumor growth has not been noted in patients with non-hemopoietic tumors or newly diagnosed non-Hodgkin's lymphoma (6). Overall, some types of disease progression were observed in 11 of 86 patients with myelodysplastic syndrome, but no clear relation between interleukin-3 and disease acceleration can be assessed at the moment.

PIXY321

The clinical and hematological effects of PIXY321, a genetically engineered GM-CSF/interleukin-3 fusion protein, have been evaluated in 71 women with breast cancer (11). In addition to chemotherapy (four cycles of fluorouracil, doxorubicin, and cyclophosphamide), the patients received either PIXY321 or placebo from days 3–15. Although the incidence and/or duration of chemotherapy-induced severe neutropenia was significantly reduced by PIXY321, there were more frequent systemic adverse effects (fever, chills, abdominal pain, arthralgia, and injection-site reactions) and more severe thrombocytopenia during cycles 3 and 4. Based on these results and the lack of a demonstrable advantage of PIXY321 over GM-CSF (12), the development of PIXY321 as an adjuvant treatment in cancer was halted. In one study only insomnia and rash were more common in patients treated with subcutaneous PIXY321 compared with intravenous GM-CSF alone after autologous bone marrow transplantation (13).

Organs and Systems

Cardiovascular

Hypotension, exacerbation or new onset of atrial fibrillation, and dyspnea were infrequently observed in clinical trials (6). Although weight gain and peripheral edema can develop, only one fatal case, compatible with a capillary vascular leak syndrome, has been reported (SEDA-20, 335).

Thrombophlebitis was recorded in 45% of patients treated for advanced ovarian cancer who also received intravenous interleukin-3 (14), and deep venous thromboses were reported in children treated with maintenance interleukin-3 for Diamond–Blackfan anemia (15). In addition, one smoking breast-cancer patient developed severe hypotension and cerebellar and superior mesenteric thrombosis after subcutaneous interleukin-3 administration (SEDA-19, 340). Collectively, these case reports suggest that interleukin-3 may contribute to the development of thrombosis, but a possible increased risk of thrombosis with interleukin-3 remains to be demonstrated.

Hematologic

Interleukin-3 caused a transient rise in circulating atypical B lymphocytes, with enlargement of the spleen and lymph nodes in two patients with large-cell lymphoma and the development of a clonally-related transient plasmocytosis in one patient with relapsing follicular non-Hodgkin's lymphoma (SED-13, 1109) (10,16).

There has been one case of bone marrow histiocytosis in a patient treated with interleukin-3 for refractory aplastic anemia (SED-13, 1109).

Immunologic

An anaphylactoid reaction to recombinant human interleukin-3 (rHuinterleukin-3) has been described (17).

- A 66-year-old man with radiation-induced aplastic anemia and myelodysplastic features failed to respond to multiple therapeutic regimens. A trial of recombinant human interleukin-3 was begun, but he had transient shortness of breath and hypotension after the first subcutaneous injection. On the next day, 2 hours after the second dose, he had restlessness, dyspnea, spasticity, wheezing, cyanosis, hyperthermia, tachycardia, and hypotension (70/50 mmHg). Full recovery was obtained with fluids, adrenaline, promethazine, and glucocorticoids.

Histamine release from circulating basophils was the suggested mechanism.

Drug–Drug Interactions

Angiotensin-converting enzyme (ACE) inhibitors

Severe hypotension within hours after interleukin-3 injection has been observed in three of 26 patients treated with angiotensin-converting enzyme inhibitors (SEDA-19, 340). Indirect synergy between ACE and interleukin-3 on nitric oxide production was suggested to be involved.

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Carboplatin

In patients with ovarian cancer, the combination of interleukin-3 with high-dose carboplatin was poorly tolerated; severe fever, malaise, protracted nausea, vomiting, severe hypotension, and nephrotoxicity required withdrawal of interleukin-3 in 60% of patients when interleukin-3 was given only 24 hours after high-dose carboplatin (18).

GM-CSF

Combined sequential administration of interleukin-3 plus GM-CSF in patients treated for myelodysplastic syndrome suggested unacceptable toxicity (19).

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Interleukin-4

General Information

Interleukin-4 is a pleiotropic cytokine, mostly produced by activated T cells, which acts on the proliferation and differentiation of B and T lymphocytes and enhances the function of natural killer cells, eosinophils, and mast cells (1). It is being investigated for potential antitumoral and hemopoietic actions.

General adverse effects

Moderate fever with flu-like symptoms, arthralgias, fatigue, anorexia, nausea, vomiting, headache, and transient hypotension were frequent at all doses and by all routes of administration, but were more severe and prolonged at high doses (2). Periorbital, facial, and peripheral edema were also noted. Frequent discomfort caused by severe and resistant nasal congestion, supposedly due to edema and vascular engorgement from histamine stimulation,

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was sometimes dose-limiting. Mild asymptomatic increases in liver enzymes and minimal changes in serum creatinine concentrations can occur. No significant effects on serum hormone (ACTH, cortisol, thyrotropin, thyroxine, prolactin) or lipid concentrations have been noted (SEDA-20, 336). Other adverse events, as yet not clearly related to interleukin-4, included reversible Coomb's-positive hemolytic anemia, transient partial blindness, photophobia, and visual hallucinations. At the moment, only one report has suggested that long-term interleukin-4 may have stimulated the development of multiple myeloma (SEDA-21, 376).

Of 49 patients with advanced renal cell carcinoma treated with subcutaneous interleukin-4 (4 micrograms/kg/day for 28 days followed by a 7-day rest), nine had 13 episodes of grade 4 toxicity (3). Severe unexpected toxic effects included three cases of Bell's palsy and one episode of severe hypoglycemia in a previously well-controlled patient with diabetes mellitus.

Organs and Systems

Cardiovascular

The vascular leak syndrome was observed at a dose of 15 micrograms/kg by bolus or continuous intravenous administration, but a moderate capillary leak syndrome was also noted at lower subcutaneous doses (4).

Cardiac toxicity, consistent with myocardial infarction, was observed in three of seven patients with metastatic cancer receiving intravenous bolus interleukin-4 to a daily total of 800 micrograms/m^2 (5). A unique pattern of myocarditis with predominant polymorphonuclear, eosinophil, and mast cell infiltration was the possible cause of death in one case and suggested an allergic inflammatory myocardial process.

Endocrine

Permanent hypothyroidism associated with vitiligo was reported in a woman treated with interleukin-4 for metastatic malignant melanoma (SEDA-20, 336).

Hematologic

Unexpected severe neutropenia has been found in 33% of patients with AIDS-related Kaposi's sarcoma given interleukin-4 (SEDA-21, 376).

Isolated coagulation abnormalities with minor prolongation of prothrombin time were consistently observed, in patients given interleukin-4, particularly those with pre-existing liver disease (2).

Gastrointestinal

Significant gastrointestinal toxicity was described in patients who received interleukin-4 alone or in combination with interleukin-2 for advanced malignancy (6).

Antral or prepyloric ulcers and erosive gastritis were identified after 12 of 84 courses of interleukin-4 in 72 patients, of whom three suffered from life-threatening bleeding. There were no treatment-related deaths and no clear correlation with the dose of interleukin-4. A possible protective effect of interleukin-2 on the gastrointestinal mucosa was suggested. Although all but one of these patients also took indometacin, there was no recurrence of symptoms in several patients who developed ulcers during interleukin-4 treatment and further received interleukin-2 and indometacin. The ability of interleukin-4 to affect prostaglandin E_2 synthesis strongly suggests that interleukin-4 alone can contribute to the development of digestive mucosal injury.

Skin

Rare dermatological adverse effects have been noticed and consisted of a papular eruption. One patient had a pruritic papulovesicular eruption, which recurred after interleukin-4 re-administration and was compatible with transient acantholytic dermatosis (7).

Vitiligo associated with permanent hypothyroidism was reported in a woman treated with interleukin-4 for metastatic malignant melanoma (SEDA-20, 336).

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Interleukin-6

General Information

Interleukin-6 is produced by T cells, monocytes, fibroblasts, endothelial cells, and keratinocytes, and regulates pleiotropic biological functions. Recombinant interleukin-6 is being evaluated for thrombopoietic and antitumoral properties (1).

General adverse effects

During clinical trials, intravenous and subcutaneous interleukin-6 produced universal moderate fever and flu-like symptoms (2). Mild nausea, weight loss, and taste

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disorders sometimes occurred, and central nervous system symptoms (somnolence, restlessness, confusion, hallucinations) were dose-limiting in patients with advanced malignant cancer (SEDA-21, 376), but no clear dose-related effects have been demonstrated. Moderate injection site reactions usually followed subcutaneous interleukin-6 administration, and a diffuse maculopapular erythema occurred in one patient. In contrast to several other cytokines, interleukin-6 has not been associated with signs of vascular leak syndrome or hypotension. Neutralizing antibodies to interleukin-6 were rarely evidenced (SEDA-20, 336).

Whereas no major signs of toxicity appeared at doses up to 20 micrograms/kg/day in patients with malignant disease, the maximum tolerated dose of interleukin-6 was 5 micrograms/kg/day in patients with myelodysplasia or thrombocytopenia, and only 1 microgram/kg/day in autologous bone marrow transplant patients who developed hyperbilirubinemia and severe maculopapular rash with microvesicular steatosis as treatment-limiting adverse effects (2). Combination of interleukin-6 with G-CSF or GM-CSF was not associated with significant synergism or new forms of toxicity.

Biochemical effects of interleukin-6 included asymptomatic increases in liver function tests, transient proteinuria, and increased serum creatinine concentrations. Reductions in serum albumin and cholesterol concentrations, and increases in blood glucose concentrations were dose-related (SEDA-21, 376) (2).

Organs and Systems

Sensory systems

One isolated report documented reduced visual acuity and bilateral uveitis in a patient receiving a 2-week regimen of interleukin-3 and interleukin-6 for secondary myelodysplastic syndrome (SEDA-19, 341).

Endocrine

Interleukin-6 reduced serum thyrotropin and thyroid hormone concentrations and increased LH concentrations (SEDA-20, 336).

Hematologic

Dose-dependent and reversible normochromic normocytic anemia was consistently noted within several days after starting interleukin-6, and required blood transfusion at the highest dose (3). Hemodilution was considered as the primary mechanism.

Skin

Diffuse maculopapular erythema with histological features consisting of epidermal spongiosis and interstitial mixed inflammatory cell infiltrate was reported in one patient, and a causal role was suggested by the recurrence of symptoms after interleukin-6 re-administration (SEDA-19, 341).

Long-Term Effects

Tumorigenicity

The possibility of interleukin-6 might accelerate tumor growth was suggested by findings in two patients with solid tumors (SEDA-19, 341).

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Interleukin-10

General Information

Interleukin-10 is a potent anti-inflammatory and immunosuppressive cytokine with beneficial effects expected in a wide range of diseases (1). In healthy volunteers, its adverse effect profile mostly consisted of flu-like symptoms at the highest dose (SEDA-20, 336). First-degree atrioventricular block was noted in a few patients. Due to immunomodulating properties, potential adverse immunological effects, namely an increased risk of infections, autoimmune disorders, or B cell lymphoproliferative disorders, can be anticipated.

Organs and Systems

Hematologic

The mechanisms of mild thrombocytopenia after multiple doses of interleukin-10 have been extensively explored in 12 healthy volunteers, of whom four received placebo and eight received subcutaneous interleukin-10 (8 micrograms/kg/day for 10 days) (2). Compared with placebo, there was a 40% fall in platelet count during interleukin-10 treatment and prompt normalization after interleukin-10 withdrawal. There were also moderate changes in hemoglobin concentration. Bone marrow function, platelet production, and serum thrombopoietin concentrations suggested that a reduction in bone marrow platelet production was the primary cause.

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10-induced thrombocytopenia in normal healthy adult volunteers: evidence for decreased platelet production. Br J Haematol 2000;111(1):104–11.

Interleukin-12

General Information

Interleukin-12, an immunomodulatory cytokine, has potential effects in several cancer and infectious diseases. Although interleukin-12 was considered to be reasonably safe in early clinical trials, severe and sometimes fatal multiple organ adverse effects have been described in subsequent studies (SEDA-20, 336). This unexpected profile of toxicity was later shown to result from schedule-dependent toxicity, which occurred only in patients with cancer who received multiple high doses without an initial single dose of interleukin-12 (1). This severe toxicity has since been avoided.

Organs and Systems

Hematologic

Single cases of agranulocytosis and Coombs' negative hemolytic anemia have been attributed to twice-weekly interleukin-12 in 28 patients with renal cell cancer or melanoma (2). The patients responded only to cyclophosphamide and/or glucocorticoids, and the causative role of interleukin-12 was therefore inconclusive.

Immunologic

Interleukin-12 has been involved in the pathogenesis of several autoimmune disorders.

- A 53-year-old woman with previously mild and stable rheumatoid disease had an exacerbation of severe rheumatoid arthritis after each course of interleukin-12 for cervical carcinoma (3).

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Iodinated contrast media

General Information

The radio-opacity of X-ray contrast media depends on the fact that they contain substances that have high atomic numbers, which absorb X-rays. Bismuth, now largely obsolete, has an atomic number of 83, barium 56. Since the soluble salts of barium are poisonous, the insoluble salt, barium sulfate, is used as a suspension. Soluble contrast media are based on iodine, which has an atomic number of 53. This means that in principle they can have the various adverse effects of other iodine-containing compounds.

Iodinated water-soluble contrast agents are of four types:

- High-osmolar ionic monomers (for example amidotrizoate (diatrizoate) iodamide, iotalamate, ioxitalamate, metrizoate)
- Low-osmolar ionic dimers (for example ioxaglate)
- Low-osmolar non-ionic monomers (for example iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioversol)
- Iso-osmolar non-ionic dimer (for example iodixonal, iotrolan).

These are mainly used intravascularly, but can also be injected into body cavities, including the bile ducts and pancreatic ducts, which can be outlined during endoscopic retrograde cholangiopancreatography (ERCP), particularly the low-osmolar contrast agents. The high-osmolar water-soluble contrast agent Gastrografin (sodium amidotrizoate and meglumine amidotrizoate in a ratio of 10:66) is suitable only for oral or rectal administration. Oil-based iodinated contrast agents, such as Lipiodol, are also available and can be used to outline the ducts of the salivary glands and the lacrimal ducts. Currently, the low-osmolar contrast agents are routinely used for these applications.

The high-osmolar ionic monomers, which are sodium and meglumine salts of tri-iodinated benzoic acid, have been available since the 1950s. They are very hyperosmolar, having 5–8 times the osmolality of the blood. The hyperosmolality greatly increases the hemodynamic and toxic effects of these agents. In the 1970s, low-osmolar contrast media became available. This was achieved through converting tri-iodinated benzoic acid into a non-ionic molecule by replacing the COOH radical with an amide ($CONH_2$). This molecule in solution will not dissociate, allowing the availability of three atoms of iodine with only one active particle (a ratio of 3:1). Another development was the introduction of the monoacid dimer, in which two tri-iodinated benzoic rings are linked with a bridge and the COOH of one ring is converted into an amide. This gives the same iodine:particle ratio of 3:1 in solution, since there are six iodine atoms and two active particles in one molecule. The osmolality of the ionic dimeric contrast media is almost the same as that of the non-ionic monomeric agents and is about twice that of blood at iodine concentration of 300 mg/ml. In the late 1980s the non-ionic dimeric contrast media were synthesized by attaching two non-ionic, tri-iodinated benzoic rings. These dimers give iodine:particle ratio of 6:1, since

there are six iodine atoms and only one active particle in the molecule. The osmolality of the non-ionic dimers (iotrolan and iodixanol) at an iodine concentration of 300 mg/ml is equal to that of the blood. Iodixanol is the only non-ionic dimer currently in intravascular use (SEDA-21, 475) (SEDA-22, 502) (1–4).

Uses

For many types of investigation, contrast media have to be given intravascularly. Intravascular iodine-based contrast media are used for angiography and computed tomography, but since they are excreted mainly by the kidney, they are also used for excretory urography. Although the low-osmolar contrast media are safer than the high-osmolar contrast media, their use has not been universal because of high costs. However, the prices of low-osmolar contrast media are dropping, and in many countries high-osmolar ionic contrast media are no longer used intravascularly (SEDA-18, 441) (SEDA-22, 499). The media now used to outline cavities are mainly water-soluble and are preferred to water-insoluble or oily contrast agents.

- Cholecystography requires a contrast medium that is excreted primarily by the liver; iodipamide and ioglycamide have been long preferred, but the newer iodoxamate and iotroxate are more efficiently excreted by this route. However, cholecystography has become obsolete, with the availability of high quality real-time ultrasound scanning.
- In the gastrointestinal tract the insoluble barium sulfate is still most commonly used, but water-soluble iodinated media can be used in special circumstances.
- For retrograde urography, many different water-soluble iodinated media can be used, provided they are diluted sufficiently.
- For arthrography, ductography, and sinography, many different water-soluble iodinated media can be used, provided they are diluted sufficiently.
- For lymphography and ductography, iodinated oil is used. Iodinated water-soluble non-ionic dimeric media have also been used.
- Hysterosalpingography is now performed at most centers with low-osmolar water-soluble media.
- Bronchography was performed in the past with an aqueous or oily suspension, but these formulations have been withdrawn; the water-soluble non-ionic dimer iotrolan has been successfully used for fiberoptic bronchography.
- Myelography represents a special challenge, because of the sensitivity of nervous tissues to direct toxic effects; for this purpose the ionic media (which are neurotoxic) and the oily medium iophendylate have been superseded by non-ionic media, including the iso-osmolar non-ionic dimers (iotrolan and iodixanol), which are isotonic with cerebrospinal fluid and well tolerated by nervous tissues. However, myelography is rarely used in modern diagnostic imaging departments and has been widely replaced by magnetic resonance imaging (MRI).

Comparative studies

The authors of a large review of the comparative tolerability of contrast media used for coronary intervention recommended the use of ionic or non-ionic dimers over non-ionic low-osmolar monomeric agents, because of the antithrombotic advantage of the dimers (5). However, the recommendation to use ionic low-osmolar contrast media in preference to non-ionic contrast media is not widely endorsed, since the latter are less toxic than ionic media. In another study, there was no difference in the incidence of contrast media reactions between the non-ionic monomeric contrast agents iopamidol and iopromide, and both agents were well tolerated following left ventricle and coronary angiography (6). The authors concluded that both agents are perfectly acceptable for cardiac angiography.

Iodixanol 320 ($n = 307$) has been compared with the low-osmolar ionic dimer ioxaglate 320 ($n = 311$) in patients undergoing percutaneous coronary intervention (7). The two groups were well matched for basic demographic data and comparable in relation to cardiovascular state and other medical conditions. Fifteen patients (4.9%) in the iodixanol group and 27 patients (8.7%) in the ioxaglate group had reactions within 24 hours of the procedure; they were likely to have been due to the contrast medium, and included nausea, vomiting, flushing, facial edema, urticaria, and wheezing. There was no significant difference in the outcome of the procedure between the two groups. The authors suggested that in view of the higher incidence of adverse effects with ioxaglate, its automatic selection for percutaneous coronary intervention should be reviewed.

General adverse effects

The main types of collateral adverse effects of contrast media are listed in Table 1.

Low-osmolar contrast media are better tolerated than high-osmolar ionic media in cardiac and coronary angiography. However, it has been suggested that ionic contrast media may be advantageous during percutaneous transluminal coronary angioplasty, as they have some anticoagulant effect, which non-ionic media do not (SEDA-22, 501). The effects of the iso-osmolar non-ionic dimer iodixanol (iodine 320 mg/ml) and the low-osmolar ionic dimer ioxaglate (iodine 320 mg/ml) have been compared in 1411

Table 1 Adverse effects of soluble contrast media

Minor effects	Intermediate effects	Severe effects
Nausea, retching, and slight vomiting	Faintness	Collapse
Feeling of heat	Severe vomiting	Loss of consciousness
Limited urticaria	Extensive urticaria	Bronchospasm
Mild pallor or sweating	Edema of face or glottis	Edema of the glottis
Itchy rashes	Bronchospasm	Pulmonary edema
Arm pain	Dyspnea	Cardiac arrest
	Rigors	Myocardial infarction syndrome
	Chest pain	Cardiac dysrhythmias
	Abdominal pain	
	Headache	
	Tetany	

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patients, mean age 62 years, undergoing percutaneous transluminal coronary angioplasty in a multicenter, randomized, double-blind study (8). The groups were comparable in relation to the prevalence of cardiac and other medical conditions, including diabetes, obesity, and smoking habits. All the patients received heparin and all but four received an antiplatelet agent (100 mg or more of aspirin and/or ticlopidine). There was no significant difference between the two groups—the incidence of major adverse cardiac events was 4.7% (192 patients) after iodixanol and 3.9% (197 patients) after ioxaglate. However, hypersensitivity reactions and adverse drug reactions were significantly less common with iodixanol ($n = 5$) than with ioxaglate ($n = 18$). The reactions to iodixanol were mainly rashes and urticaria-like reactions. The reactions to ioxaglate were anaphylaxis ($n = 1$), urticaria ($n = 12$), coughing and throat tightness ($n = 12$), and in one patient rigors, fever, vomiting, and flushing.

The diagnostic accuracy of bronchography with iotrolan is similar to that reported with Dionosil (9). No serious complications or significant change in spirometry measurements and oxygen saturation are observed with bronchography using iotrolan. The main adverse effects are nausea and vomiting. Pyrexia, pulmonary infection, and urticaria-like reactions are rare (9,10).

Serious delayed reactions have been reported from Germany and Japan in 26 cases; the features included shock, hypotension, angioedema, and dyspnea (11).

Time-course

Most reactions occur within 5–10 minutes of injection, but they can be delayed for up to 7 days; it is advisable for patients to be under close observation for about 20 minutes after injection. In 449 fatal reactions to ionic media, deaths occurred in all age groups, but the incidence peaked in the age group of 50–70 years; 80% of the reactions began in the first 5 minutes after injection, and the other 20% began at 5–15 minutes after injection (12). Late but mild reactions can also occur, notably those that are due to "iodism" (SEDA-11, 411).

Delayed reactions to both ionic and non-ionic media have an incidence of 0.4–18%. Most reactions are not serious or life threatening; they include a flu-like illness, parotitis, nausea and vomiting, abdominal pain, headache, and allergy-like reactions with skin manifestations. The incidence of delayed skin reactions to iso-osmolar non-ionic dimers is twice as high as the incidence of delayed skin reactions to low-osmolar non-ionic monomers, and twice as high in Japan and USA as in Europe. The pathophysiology of these delayed reactions is unknown. In response to reports of delayed skin reactions to the non-ionic dimer iotrolan, particularly in Japan, the manufacturer (Schering, Berlin) decided to withdraw it from the market as an intravascular agent (SEDA-21, 482).

The incidence of delayed adverse reactions has been investigated in 2001 patients who underwent cardiac angiography with either iopamidol 340 (a non-ionic monomer; $n = 738$, ages 22–88 years, mean dose 1.79 ml/kg), ioxaglate 320 (an ionic dimer; $n = 644$, ages 28–86 years, mean dose 1.8 ml/kg) or iodixanol 320 (a non-ionic dimer; $n = 619$, ages 26–85 years, mean dose 1.74 ml/kg) (13). The authors considered reactions that occurred within 24 hours as early reactions and those that occurred after 24 hours but within 1 week of the cardiac catheterization as late reactions. The incidences of early reactions were 22% with ioxaglate, 8.8% with iopamidol, and 7.6% with iodixanol. The commonest early reactions were urticaria and nausea and vomiting, the respective incidences being 6.8 and 4.0% with ioxaglate, 0.8 and 1.0% with iopamidol, and 0.5 and 1.1% with iodixanol. A few patients developed sudden hypotension, 0.5% with iopamidol, 1.4% with ioxaglate, and 0.3% with iodixanol. Cardiac arrest occurred in two patients with iopamidol, three with ioxaglate, and one with iodixanol. The frequencies of delayed skin reactions, which were generally benign, were 12% with iodixanol, 4.3% with ioxaglate, and 4.2% with iopamidol. The authors concluded that selection of a contrast agent for diagnostic cardiac catheterization should take account of adverse effects. Iodixanol was the best-tolerated agent in the early phase of the study, but it was associated with a higher incidence of delayed skin reactions. The authors did not consider that the skin reactions represented a contraindication to iodixanol, although patients should be advised of this particular adverse effect. Furthermore, no contrast agent was free from these effects. Ioxaglate was the least well-tolerated agent in the early phase, with a much greater chance of causing nausea/vomiting and allergic reactions.

Incidence

In various earlier surveys of conventional ionic contrast media, the incidence of minor reactions was one in 13–30 cases, the incidence of intermediate reactions one in 57–130 cases, and the incidence of severe reactions one in 1000–4000 cases. The figures for the non-ionic media are much more favorable. In 1990, the Japanese Committee on the Safety of Contrast Media surveyed 169 284 patients who had received ionic media and 168 363 who had received non-ionic contrast media (14). In patients with a previous history of reactions to contrast media, the incidence of severe reactions was 0.73% with ionic media and only 0.18% with non-ionic media. Among patients with asthma, severe and very severe reactions occurred in 1.88% with ionic media and 0.23% with non-ionic media. In a Canadian survey of 1992, the overall incidence of adverse effects to contrast media was 3.9% for ionic media and only 0.9% for non-ionic media, despite the fact that the proportion of patients with heart disease as a pre-existing susceptibility factor was much higher in the non-ionic group (SEDA-22, 500).

In a study from France the incidence of adverse drug reactions after 1480 injections of low-osmolar iodinated contrast media was 0.34%; the frequency was higher in patients with a history of allergy (1.5%) (15). In a similar study of the prevalence of adverse drug reactions amongst in-patients in a North Indian referral hospital over 3 years, 317 adverse reactions were reported (0.3%) (16). Skin reactions (123 cases, 39%) and gastrointestinal disturbances (90 cases, 28%) made up a large proportion of the reported adverse reactions. Of all the adverse reactions, 15% (48 cases) were due to iodinated contrast media (details of the types of contrast media used were not provided in the report) and the common reactions were nausea/vomiting (24 cases, 7.5%) and rashes

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(16 cases, 5%); however, there was serious life-threatening anaphylaxis in three cases (0.9%).

The incidence of adverse reactions has been investigated in Taiwan in 28 364 patients after intravenous injection of contrast agents during intravenous urography and CT scanning (17). There were adverse reactions in 495 patients (1.75%), including 467 patients (2.03%) of 20 260 examined with ionic contrast agents and 28 (0.34%) of 8076 patients examined with non-ionic contrast agents. The authors concluded that the risk of adverse reactions to non-ionic contrast agents is significantly lower than with ionic agents. Skin rashes, such as urticaria, were the most common adverse effects, followed by nausea and vomiting. Shock requiring cardiopulmonary resuscitation was rare and occurred in only six patients (0.02%); there were no deaths in this series.

Adverse reactions to intravascular iodinated agents are usually classified as minor, intermediate, or severe life-threatening. All types of reactions to low-osmolar contrast media are five times less common than reactions to high-osmolar contrast agents (SEDA-22, 489) (SEDA-23, 494) (SEDA-24, 519), and very severe adverse reactions to contrast media are rare, with a frequency of about 0.04% with high-osmolar agents and 0.004% with low-osmolar agents. However, there are no important differences in the safety profiles of the different low-osmolar non-ionic monomers (18).

In one US study of cardiac angiography, the incidence of adverse events was 32% with diatrizoate and 10% with iohexol; it should be noted however that the diatrizoate used in that study (Renografin 76^{TM}) causes calcium binding, which may have increased the rate of cardiac complications (19). The non-ionic agent iodixanol 320, which is virtually iso-osmolar, has been tested in cardiac angiography against iohexol and seemed to be better tolerated (20).

The safety of the non-ionic contrast agents has also been emphasized in a review from Germany, in which the authors documented a reduced risk of adverse drug reactions with non-ionic contrast agents during interventional cardiology (21). According to reports to the FDA, the incidence of lethal complications was 3.9% with ionic monomers, 6.39% with the ionic dimer ioxaglate, and 2.07% with non-ionic monomers. The authors also stated that non-ionic contrast agents do not have thrombogenic potential, a previous concern; currently, most authors would support this view (SEDA-22, 501) (SEDA-23, 497).

There was no difference in the incidence of adverse effects between iotrolan 320 and iohexol 350 in cardiac angiography for ischemic heart disease in 120 patients (22). There were no serious adverse events. One patient developed mild urticaria after iotrolan. Five patients in each group had mild unspecified delayed reactions.

An analysis of adverse reactions associated with drugs in Poland (1997–98) has shown that 11.5% of these reactions were due to radiographic contrast media. People aged 36–65 were the largest group to have adverse drug reactions (23).

According to a survey conducted by the Royal Australian College of Radiologists in 1986, the incidence of severe reactions with high-osmolar ionic contrast media was 0.36% in high-risk patients (patients with a strong history of allergy or bronchial asthma or a history of reactions to contrast media) and 0.09% in low-risk patients (24). The incidence of these reactions with low-osmolar non-ionic media was 0.03% in high-risk patients, and 0% in low-risk patients.

In another survey, the incidence of contrast media reactions after intravenous administration was evaluated over 14 years (25). The incidence of all reactions to contrast media was 6–8% with high-osmolar contrast media and only 0.2% with low-osmolar non-ionic agents. Most of the reactions (over 90%) were allergic-like, and severe reactions were rare (0.05%). One death was reported after the use of a low-osmolar agent. These data are compatible with previous reports, which showed that low-osmolar contrast media have a much better safety profile than high-osmolar media and that there is no significant difference in the incidence of acute adverse reactions between non-ionic dimeric and monomeric contrast media.

In another study there was no significant difference in the incidence of adverse effects associated with the use of the non-ionic dimer iodixanol or the non-ionic monomer iopromide in femoral angiography (26).

Delayed reactions

There are conflicting data on the risk of delayed reactions, comparing non-ionic monomers and iso-osmolar non-ionic dimers (iotrolan, iodixanol). European studies (27) have shown no significant difference (0.62% iotrolan, 0.82% non-ionic monomers), but studies from Japan and the USA have suggested that delayed reactions are 2–5 times more common with iotrolan.

The incidence of delayed adverse reactions to various non-ionic monomers in Japanese patients undergoing contrast-enhanced CT has been compared with the incidence in control patients who did not receive contrast. Delayed reactions occurred in 12% of patients who received contrast compared with 10% in the control group. The authors concluded that the frequency of delayed reactions that can be attributed to contrast media is 2.1%. The most common reactions were itching and limited urticaria (28). This report highlights the difficulty of verifying that adverse events that occur many hours after contrast administration are directly caused by the contrast agent.

The incidence of delayed reactions has been assessed in 403 Italian patients who received intravenous iopamidol during CT or urographic examination (29). A total of 50 patients (12%) developed delayed reactions. Allergy, previous exposure to a contrast agent, and being female were associated with a significantly higher incidence of delayed reactions. The most frequently reported delayed reactions were nausea and vomiting, drowsiness, rash, itching, and headache. All reported reactions were mild and resolved spontaneously.

In a questionnaire study of 11 121 Japanese patients, 216 (1.4%) developed immediate adverse reactions and 1058 (9.5%) reported having had delayed reactions after intravenous contrast administration during various CT examinations (30). Delayed reactions were reported by 18 patients (13%) of the 136 patients with immediate reactions who answered the questionnaire. All the patients, with the exception of 360 who received the non-ionic dimer iotrolan, were given non-ionic

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monomeric contrast media. The dose was 60–200 ml. Delayed reactions were more frequent in patients with a history of allergy, past adverse reactions to contrast media or with a serum creatinine concentration over 180 μmol/l. Delayed reactions were also more frequent in women and in patients who had not previously received contrast media. There was no significant relation between the occurrence of immediate adverse reactions and the development of delayed reactions. The commonest delayed reactions were itching and skin reactions, which developed in 5.5% and 3.0% of the patients respectively. Skin reactions were observed twice as often in patients who were given iotrolan compared with those who were given monomeric agents. In the iotrolan group, 7.3% of the patients developed a skin reaction, 9.9% reported itching, and 60% of the reactions were severe or moderate. A quarter of the delayed reactions occurred within 6 hours after the examination and more than half occurred within 24 hours. Most of the reactions occurred within the first 3 days.

The incidence of delayed adverse reactions has been investigated in 2001 patients who underwent cardiac angiography with either iopamidol 340 ($n = 738$, aged 22–88 years, mean dose 1.79 ml/kg), ioxaglate 320 ($n = 644$, aged 28–86 years, mean dose 1.8 ml/kg) or iodixanol 320 ($n = 619$, aged 26–85 years, mean dose 1.74 ml/kg) (13). The authors considered reactions that occurred within 24 hours as early reactions and those that occurred after 24 hours but within 1 week as late reactions. The incidences of early reactions were 22% with ioxaglate, 8.8% with iopamidol, and 7.6% with iodixanol. The commonest early reactions were urticaria and nausea and vomiting, the respective incidences being 6.8 and 4.0% with ioxaglate, 0.8 and 1.0% with iopamidol, and 0.5 and 1.1% with iodixanol. A few patients developed sudden hypotension, 0.5% with iopamidol, 1.4% with ioxaglate, and 0.3% with iodixanol. Cardiac arrest occurred in two patients with iopamidol, three with ioxaglate, and one with iodixanol. The frequencies of delayed skin reactions, which were generally benign, were 12% with iodixanol, 4.3% with ioxaglate, and 4.2% with iopamidol. The authors concluded that selection of a contrast agent for diagnostic cardiac catheterization should take account of adverse effects. Iodixanol was the best-tolerated agent in the early phase of the study, but it was associated with a higher incidence of delayed skin reactions. The authors did not consider that the skin reactions represented a contraindication to iodixanol, although patients should be advised of this particular adverse effect. Furthermore, no contrast agent was free from these effects. Ioxaglate was the least well-tolerated agent in the early phase, with a much greater chance of causing nausea/vomiting and allergic reactions.

The Federal Institute of Drugs and Medical Devices in Germany has surveyed a total of 1135 adverse drug reactions (acute and late) associated with iotrolan 280 and 1354 reports associated with iodixanol at various iodine concentrations (31). There were late adverse reactions (observed later than 1 hour after injection) in 757 cases (67%) associated with iotrolan 280, and in 525 cases (39%) associated with iodixanol. Late reactions were observed mainly in the first 24 hours, with occasional reports at 24–72 hours after injection. Rarely, delayed contrast reactions have been reported more than 72 hours after injection, although they are difficult to substantiate. This study emphasizes the importance of extending the surveillance period for at least 72 hours after contrast administration. Most delayed reactions in this study were non-serious allergic-like reactions, with symptoms including itching, urticaria, erythema, edema, and bronchospasm. In a very few cases there were serious or life-threatening reactions, including Quincke's edema and hypotension.

The incidence of late adverse reactions to the iso-osmolar agent iodixanol has also been investigated in a retrospective comparison with the non-ionic monomer iohexol. Reactions after 3075 injections were reviewed. Patients were sent a written questionnaire to find out about the incidence of any acute or delayed reactions. Those who developed reactions were interviewed by telephone and specific second questionnaires were administered. The incidence of adverse reactions was low (2% for late adverse reactions and 2.3% for acute reactions). There was no significant difference in the incidence of acute or delayed adverse reactions to iohexol and iodixanol and there were no serious reactions (32).

Delayed reactions are generally benign, but not always. In a Japanese study, the incidence of delayed reactions was investigated in 6764 patients who received the low-osmolar non-ionic contrast medium iohexol intravenously (33). Delayed reactions (rash, pruritus, nausea, vomiting, fever, headache, and others) occurred in 192 patients (2.8%). There were no severe delayed reactions. A history of allergy and hay fever were risk factors for delayed adverse reactions.

Delayed adverse reactions to ioxaglate have been documented after coronary angiography with ioxaglate (34).

- A 63-year-old housewife had an acute myocardial infarction. Diagnostic coronary angiography was performed with ioxaglate and repeated 1 week later. On the morning after, she had intense shivering and generalized malaise, a temperature of 39.2°C, and hypotension. Several hours later she developed a non-pruritic maculopapular rash, starting on the face and extending within the next 48 hours to cover the entire body but sparing the mucous membranes. She had a mild eosinophilia (600×10^6/l) with a raised erythrocyte sedimentation rate (52 mm at 1 hour). Her IgE concentration was raised at 1593 kU/l. Blood cultures were negative. The initial clinical impression was that she had sepsis and she was therefore given vancomycin, netilmicin, and cefotaxime (dosages not stated). She improved rapidly and the fever and the rash resolved completely. She was discharged taking atenolol 100 mg/day and lysine acetylsalicylate 250 mg/day, but 3 days later she returned with a temperature of 39.8°C and recurrence of the skin rash. She had a marked eosinophilia (1.4×10^9/l) and raised liver enzymes, lactate dehydrogenase, and aldolase, but creatine kinase activity was in the reference range. She had a significantly raised concentration of circulating immune complexes. Atenolol and lysine acetylsalicylate were withdrawn and she was given acenocoumarol 2 mg/day and amlodipine 5 mg/day. The inflammatory syndrome rapidly disappeared and the enzymes and eosinophil count returned to normal. She had immunological investigations 2 months later. The total IgE was still raised. The leukocyte count and C-reactive protein concentration were within

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the reference ranges. The serum antinuclear antibody titer was 1/256 and the antimitochondrial antibody titer was 1/128. Tests for antinative DNA, antihistone, and anti-smooth muscle antibodies were negative. Skin prick tests, intradermal tests, and patch tests with lysine acetylsalicylate, atenolol, heparins, vancomycin, netilmicin, cefotaxime, and the contrast agents ioxaglate, sodium ioxitalamate, iopamidol, and iohexol were negative at 15 minutes, but at 48 hours indurated erythematous papules were observed with ioxaglate, ioxitalamate, and iopamidol. A biopsy from the ioxaglate skin reaction showed discrete spongiosis of the epidermis associated with slight lymphocytic exocytosis. The basal layer contained numerous apoptotic keratinocytes. The superficial dermis was edematous and there was a perivascular inflammatory infiltrate composed mainly of T lymphocytes. There were no mast cells or eosinophils. Immunohistological examination showed no staining with anti IgE, IgG, IgM, C1q, C3, or C4. During follow-up she was completely normal at up to 1 year, with a normal eosinophil count and an IgE concentration of 440 kU/l.

This report documents a rare clinical reaction to ioxaglate, with a combination of a maculopapular rash, fever, hepatic and muscle involvement, eosinophilia, and a very high serum IgE concentration. The intradermal tests confirmed a delayed hypersensitivity reaction to ioxaglate. Histological examination of a skin biopsy identified the predominantly T lymphocyte nature of the infiltrate. A contributing role of the beta-blocker atenolol to the seriousness of the clinical syndrome must also be considered.

Mechanisms and susceptibility factors

The mechanisms underlying idiosyncratic adverse reactions are far from clear. Although many resemble allergic or anaphylactic events, the evidence does not suggest that they are as a whole induced immunologically, though some certainly are, and there is no doubt that in some cases contrast media act as antigens. Lalli believes that all contrast media reactions are explicable on a neurological basis; this hypothesis is not generally accepted, but most would agree that anxiety can be an important predisposing factor, for example to cardiac dysrhythmias. It has been suggested that contrast media act as histamine liberators, and there is evidence from animal experiments that this is the case, the methylglucamine media being more potent in this respect than the corresponding sodium salts (though ioxaglate may apparently also elicit histaminoid reactions (35); the antihistamine diphenhydramine has been recommended both for preventing and treating reactions (see below) and may have some efficacy. A further theory is that bradykinin is an essential mediator in systemic contrast media reactions (36). There is also older experimental evidence that contrast media can activate serum complement by the "alternative pathway," and it is postulated that this may be one of the factors in systemic adverse reactions, possibly by liberation of anaphylatoxin and with a risk of disseminated intravascular coagulation.

Adverse reactions to contrast agents have been linked to an in vivo interaction with enzymes involved in cholinergic activity. However, experimental results on this topic are conflicting. In a study of the in vivo effects of the non-ionic monomer iohexol and the high-osmolar ionic monomer diatrizoate on human plasma acetylcholinesterase and butyrylcholinesterase, both contrast agents significantly inhibited the enzymes (37). The effect was more pronounced with iohexol, which has a lower incidence of adverse effects than diatrizoate. The significance of this observation is not certain, but activation of these enzymes is not likely to be important in mediating the adverse effects of contrast agents. Other enzymes that are inhibited by iodinated contrast agents include hexokinase, glucose-6-phosphate dehydrogenase, and alcohol dehydrogenase (38).

More minor adverse reactions to the second-generation non-ionic water-soluble contrast media, such as headache, nausea, and vomiting, are more frequent in women than in men, particularly in women aged 26–50 years. Early ambulation increases the incidence of headaches. In one study, there was a higher incidence of delayed headaches after iopamidol in comparison with iohexol. Long-distance travel also appeared to increase the incidence of headaches after myelography (SEDA-15, 503). Dizziness was more frequent in patients over the age of 50 years. In a meta-analysis of 25 published studies, the incidence of symptoms after myelography was significantly higher when needles larger than 22G were used.

The risks (expressed as risk ratios) of adverse effects of contrast media after intravenous injection related to some susceptibility factors are listed in Table 2.

Prevention and management

Intravenous pre-testing is unreliable in determining susceptibility; in one survey of 33 400 patients, most of the reactions were not predicted by pretesting, although a positive pre-test did indicate an increased risk of a reaction (39). The value of the lymphoblast transformation test is very limited, although it certainly provides interesting evidence that contrast media can sometimes act as antigens (SEDA-16, 531) (40).

The value of prophylactic use of glucocorticoids to reduce the risk of contrast reactions is contentious. The Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) considered this issue and produced guidelines on how to reduce the risk of generalized reactions to intravascular use of contrast media (Table 3) (41).

In high-risk patients, and more particularly those with a history of poor tolerance of contrast media, measures will

Table 2 Risk ratios for adverse effects of contrast media after intravenous injection related to susceptibility factors

History	Minor reactions	Intermediate reactions	Severe reactions	Death
Allergy (all types)	1.6	2.6	3.9	
Hay fever	1.7	1.8	2.3	
Urticaria	1.5	4.8	2.0	
Asthma	1.2	2.7	5.1	
Heart disease	1.1	0.9	4.5	8.5
Previous reaction to a contrast medium	6.9	8.7	11	
Previous reaction to other drugs	1.8	2.0	3.2	

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Table 3 European Society of Urogenital Radiology (ESUR) Guidelines on prevention of generalized contrast medium reactions in adults

A. Susceptibility factors for reactions
Previous generalized reaction to a contrast medium, either moderate (for example urticaria, bronchospasm, moderate hypotension) or severe (for example convulsions, severe bronchospasm, pulmonary edema, cardiovascular collapse)
Asthma
Allergy requiring medical treatment
B. To reduce the risk of generalized contrast medium reactions
Use non-ionic agents
C. Premedication is recommended in high-risk patients (defined in A)
When ionic agents are used
When non-ionic agents are used, opinion is divided about the value of premedication
D. Recommended premedication
Glucocorticoids
Prednisolone 30 mg orally or methylprednisolone 32 mg orally 12 and 2 hours before contrast medium
Glucocorticoids are not effective if given less than 6 hours before contrast medium
Histamine H_1 and H_2 receptor antagonists may be used in addition to corticosteroids, but opinion is divided
E. Remember for all patients
Have a trolley with resuscitation drugs in the examination room
Observe patients for 20–30 minutes after contrast medium injection
F. Extravascular administration
When absorption or leakage into the circulation is possible, take the same precautions as for intravascular administration

be necessary to contain risks of hypersensitivity reactions. Apart from using non-ionic and low-osmolar media, and diluting media for certain purposes, one can consider prophylactic premedication. Glucocorticoid premedication alone has often been advocated, particularly in patients with asthma; although it has been condemned as unnecessary with the current generation of contrast media (SEDA-18, 442) (SEDA-19, 426) it seems to be well founded in experience, reducing both the frequency and severity of reactions, but it certainly does not eliminate risk (42). A double regimen based on prednisolone and the antihistamine diphenhydramine has been advocated in various centers (SEDA-16, 531) (SEDA-18, 442) (43,44). To be effective, glucocorticoids should be given sufficiently far in advance; in some cases, an intravenous injection of dexamethasone given immediately before an infusion of contrast media failed to prevent an anaphylactic reaction (45).

H_1 and H_2 receptor antagonists, aminocaproic acid, or hyposensitization have all been proposed as means of reducing risk prophylactically. Aminocaproic acid was formerly used prophylactically in France, but was associated with a risk of massive intravascular coagulation (46).

In severe reactions, intravenous glucocorticoids are usually given on an empirical basis, with oxygen as required. Non-cardiogenic hypotensive shock usually responds best to fluid replacement, but vasopressors are occasionally required. Adrenaline is primarily indicated for bronchospasm and other allergic-type reactions, but caution is required to avoid cardiac dysrhythmias. Intravenous antihistamines are useful in angioedema, but can aggravate hypotensive reactions. Chemotoxic convulsions require intravenous diazepam and oxygenation.

Systemic adverse effects of enteral contrast agents

Oral radiographic contrast media can intravasate during gastrointestinal examination. Septicemia has been reported (47).

- A 46-year-old patient developed ischemic necrosis of the small bowel complicating mesenteric volvulus. Small bowel resection was carried out and ileal and jejunal stomas were established. Six weeks after the operation Gastrografin was given through the jejunal stoma. A mesenteric vein filled with Gastrografin and this was followed by rapid washout of the intravascular contrast medium. The examination was stopped immediately and 60 minutes later the patient developed chills and a high fever. Hemodynamic instability required the use of vasoactive drugs and infusion of isotonic solutions. Blood cultures grew *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter* species. Treatment included imipenem and after 48 hours the patient was stable and the vasoactive agents were stopped. Endoscopy through the jejunal stoma showed multiple stenoses, which required surgical treatment, and the jejunum in the area of intravasation was resected.

Gram-negative septicemia possibly related to oral Gastrografin has also been reported in a premature neonate with necrotizing enterocolitis (48).

- A baby born after 26 weeks of gestation received oral Gastrografin (0.5 ml 8 hourly) for gut stimulation. Three days after the last dose of Gastrografin there was sudden clinical deterioration leading to shock. Blood cultures grew *Enterobacter*. Progressive deterioration continued to occur, with multisystem failure, leading to death. Autopsy was not performed.

The authors suggested that the high osmolality of Gastrografin may have aggravated the pre-existing mucosal injury in the gastrointestinal tract, leading to complete loss of mucosal integrity and an increase in gut permeability to micro-organisms and toxins. Oral Gastrografin and other hyperosmolar contrast media should not be used in patients, particularly neonates, with compromised bowel integrity, since the high osmolarity may aggravate the bowel injury. Low-osmolar contrast media should always be used in such patients.

Disseminated intravascular coagulation and severe hypotension have been documented after intravenous administration of Gastrografin, which is suitable only for oral or rectal administration (47).

Cost to benefit ratio

At a time when reductions in the costs of medical care are critical, decisions about which classes of contrast media to use are not determined purely on clinical grounds, but by a consideration of the cost to benefit ratio. Concern about

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financial implications has been the major factor in preventing a universal conversion to non-ionic contrast agents, which are better tolerated but more expensive than high-osmolar ionic agents. In the USA, the Health Care Finance Administration (HCFA) has recommended that the use of the expensive non-ionic contrast media should be restricted only to patients with severe cardiac disease, a history of asthma, severe allergy, severe debility, sickle cell disease, or a previous severe adverse reaction to contrast media.

The results of a study in 1324 patients who underwent diagnostic arteriography have supported the selective use of non-ionic contrast agents following the HCFA guidelines. A cost saving of $41 per patient was possible without an increase in the incidence of complications (49).

Organs and Systems

Cardiovascular

Most severe reactions to contrast media are associated with cardiovascular manifestations, causing hypotensive shock and in some cases ventricular fibrillation and cardiac arrest; these events are reversible in most cases in which prompt treatment is given. In a case of hypotensive collapse reported in 1977, and followed by a small number of others, there was disseminated intravascular coagulation (50). In milder cases there is only hypotension, which can be transient and symptomless; in some cases there is bradycardia (due apparently to vagal overactivity) rather than tachycardia.

In more than 90 000 cardiac angiographies performed in US hospitals during 1991, the overall rate of complications with low-osmolar contrast media was 1.5%, including idiosyncratic reactions in 0.25%, vascular complications in 0.44%, neurological complications in 0.05%, dysrhythmias in 0.31%, and myocardial infarction in 0.06%; the death rate was 0.11%. In percutaneous coronary angioplasty major complications, generally of the same type, occurred in 5% of cases (51). In one large series of digital subtraction angiography examinations using iopamidol, the overall incidence of reactions was 2.5%; some occurred with a delay of 1 hour or more (52).

The safety of iodixanol 320 and iohexol 350 has been investigated in Swedish patients undergoing cardiac angiography for suspected coronary artery disease (53). Of 1020 patients, 502 aged 25–83 years received iohexol (median dose 105 ml, range 20–440) and 518 aged 18–85 years received iodixanol (median dose 115 ml, range 30–400). There were 134 patients with unstable angina in the iohexol group and 167 in the iodixanol group. Cardiac adverse events (angina pectoris, dysrhythmias, and dyspnea) within 24 hours of the examination were reported by 9% of the patients who received iohexol and 7% of patients who received iodixanol. There were two cases of ventricular fibrillation, both after iohexol. Cardiac adverse events in patients aged 65 years or more occurred in 11% with iohexol and 7% with iodixanol. The proportions of patients with unstable angina and cardiac adverse events were 18% with iohexol and 12% with iodixanol. The authors concluded that iodixanol could be advantageous in old patients and in those with unstable angina.

Iodixanol (a non-ionic dimer, 320 mg of iodine per ml) and ioxaglate 320 (a low-osmolar ionic dimer, 320 mg of iodine per ml) have been compared in a randomized study in 110 consecutive patients referred for coronary angiography and ventriculography (54). The incidence of adverse reactions was significantly higher with ioxaglate (28 versus 3%) but there was no difference in angiographic quality between the two agents. The increase in left ventricular end-diastolic pressure was significantly less with iodixanol than with ioxaglate. The QT interval was significantly prolonged by both agents, but the changes were less marked after iodixanol. The authors concluded that iodixanol and ioxaglate are of comparable diagnostic efficacy in coronary angiography and ventriculography but that iodixanol is better tolerated and has less marked hemodynamic and electrophysiological effects.

The hemodynamic effect of direct intra-arterial injection of contrast agents on capillary perfusion in man has been investigated (55). This was achieved through continuous recording of perfusion in the nail-fold capillaries of the right hand before and after a bolus injection of 20 ml of iodixanol 270 (a non-ionic dimer) or iopentol 150 (a non-ionic monomer) into the right axillary artery. The high-viscosity contrast agent iodixanol (5.8 mPa.s) caused a significant reduction in erythrocyte velocity, while iopentol, which has a much lower viscosity (1.7 mPa.s), had no effect. The authors concluded that high-viscosity contrast media can cause reduced organ perfusion. This effect could be significant in patients with atherosclerotic disease, as it might lead to reduced perfusion of the myocardium during coronary angiography.

Effects on blood pressure

Rapid peripheral intravenous injection of concentrated ionic contrast media produces a brief rise in systemic arterial pressure followed by a prolonged fall; the diastolic pressure decreases more than the systolic pressure and the heart slows; the pulse contour changes, and the venous pressure rises; the arterial hypotension is more marked if injection is rapid. The electrocardiogram can show flattening, splitting, or T-wave inversion; tachycardia is probably compensatory, as are the concomitant increases in venous pressure and pulmonary arterial pressure. Hypotension associated with a vasovagal reaction probably explained four deaths from acute coronary insufficiency (two each with iodoalphionic acid and iopanoic acid) in patients with ischemic heart disease.

- A 44-year-old man had a CT scan of the head with intravenous contrast enhancement (35 ml of ioversol 350) (56). He developed severe back pain 90 minutes later and then became acutely unwell, with nausea, vomiting, chills, tremor, and faintness. He rapidly became shocked (systolic blood pressure 80 mmHg, pulse 140/minute) and had a petechial rash over the trunk and upper limbs. He was given intravenous fluids (polygeline 2 liters and crystalloid 2 liters and adrenaline. Blood cultures were negative, and echocardiography, CT scan of the chest and abdomen, and abdominal ultrasound were normal. He continued to deteriorate, developed acute renal insufficiency with disseminated intravascular coagulation, and was given dopamine, aggressive fluid resuscitation, and antibiotics

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(gentamicin, ceftriaxone, and erythromycin). His general condition gradually improved and he recovered fully.

The authors attributed these events to a severe delayed reaction to the contrast medium, manifesting as prolonged hypotension.

Injection of contrast media into the right side of the heart or pulmonary artery can be followed by transient pulmonary hypertension but systemic hypotension. The pulmonary hypertension is partially due to an increase in the pulmonary vascular resistance from capillary blockage by the altered erythrocytes, which have a reduced elasticity due to the effect of a hypertonic contrast medium. Reduced cardiac output accompanied by cardiac slowing and diminished force of contraction seem to explain the initial systemic hypotension; persistence of hypotension thereafter is probably due to the vasodilator effect of the contrast medium on the systemic vessels. Pulmonary angiography is particularly dangerous when the right ventricular end-diastolic pressure exceeds 20 mmHg. Iohexol appears to be a safer medium for pulmonary angiography (SEDA-14, 423).

Injection into the left ventricle or the proximal aorta is likely to produce more marked effects. Cardiac rate, stroke volume, and cardiac output increase. There is a rise in right and left atrial pressures and left ventricular end-diastolic pressure. The pulmonary arterial pressure is also increased. The blood volume expands and peripheral blood flow increases and then decreases as systemic resistance falls. The hematocrit falls and venous pressure gradually rises. As the systemic arterial pressure falls, the heart rate increases. These responses are largely due to the injection of strongly hypertonic solutions, which promote a rapid expansion of the plasma volume; water shifts from the extravascular fluid spaces to the blood and moves out of the erythrocytes, which shrink and become crenated. Blood viscosity rises, but plasma viscosity does not increase significantly. The erythrocytes give up potassium to the plasma and this might contribute to the observed reduction in peripheral vascular resistance.

In two cases of severe hypotensive collapse with generalized itching after left ventricular angiography with 76% sodium methylglucamine diatrizoate, the hypotension failed to respond to vasoconstrictors, and measurements of right atrial and right ventricular pressures showed marked reduction in filling pressures. Rapid intravenous infusion of isotonic saline caused prompt improvement in the blood pressure. A similar case of hypotension with a beneficial response to plasma expanders occurred in a case of prolonged shock after intravenous urography. Severe and prolonged hypotensive collapse has also been seen after antegrade pyelography through a nephrostomy tube under general anesthesia, but the patient in question had a previous history of an acute reaction (SEDA-18, 445). In two cases, injection of diatrizoate during arteriography under general anesthesia caused severe hypotensive collapse (SEDA-7, 452).

Acetrizoate has a more marked effect in this respect than an equiosmolar solution of diatrizoate. Methylglucamine salts appear to be relatively less vasoactive in the peripheral vessels. All these changes are considerably less marked with low-osmolar media such as ioxaglate, iopamidol, or iohexol, but not necessarily absent. Abdominal aortography with iohexol has been found to produce both a decrease in the systemic blood pressure and an increase in the plasma concentration of atrial natriuretic peptide; this may be due to increased intravascular volume (SEDA-16, 533).

Intra-arterial injection of conventional ionic contrast media results in vasodilatation. This is due mainly to hypertonicity of the medium, but toxicity is also a factor. The vasodilatation may in addition be partly due to an anti-cholinesterase action, since it is partially blocked by atropine. In clinical practice, aortography and peripheral arteriography are usually associated with a slight fall in blood pressure, tachycardia and discomfort in the limbs, such as heat or pain.

During cerebral angiography with either ionic or non-ionic agents, hypotension, bradycardia, and even transient asystole can occur, though there can also be reflex tachycardia (57), which can result in hypertension. These changes are more marked during vertebral angiography when the posterior cerebral arteries have been filled, suggesting that they are due to involvement of centers in the hypothalamus or brain stem. Visual disturbances can also occur, due to involvement of the occipital cortex (58). The reflex cardiovascular changes may be more serious in patients with coronary artery disease and can give rise to left ventricular failure. Both electrocardiographic and electroencephalographic changes are less common when methylglucamine salts are used. Premedication with atropine reduces the incidence of the cardiovascular changes, but not that of focal electroencephalographic effects. Their incidence has also been reduced by use of very small doses of contrast agents and by premedication with hypertonic mannitol in patients with raised intracranial pressure. One patient with metrizamide encephalopathy developed severe hypertension (SEDA-11, 415) (SED-12, 1182).

Electrocardiographic effects

In a comparison of the effects of iodixanol and ioxaglate during coronary angiography, 22 patients received ioxaglate for the first injection into the left coronary artery and iodixanol for the next injections, and 20 patients received the media in the reverse order (59). Those who received ioxaglate first received a mean of 102 ml of contrast medium and the iodixanol group 104 ml. The first three injections into the left coronary artery were subjected to electrocardiographic analysis. Deviation from baseline was greater in those who received ioxaglate first. The most pronounced effects of ioxaglate were on the ST segment and T wave: the T wave change vector magnitude increased 11-fold from baseline after ioxaglate and 5-fold after iodixanol; the increase in ST change vector magnitude was 4-fold with ioxaglate and 3-fold with iodixanol. The authors concluded that iodixanol caused less pronounced electrocardiographic changes than ioxaglate. These findings are in accord with experimental evidence that iodixanol is well tolerated by the myocardium.

Certain contrast media, notably the high-osmolar products based on sodium methylglucamine, Renografin-76 and MD-76, have calcium-binding properties and cause

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more hemodynamic changes and a higher risk of ventricular fibrillation than the calcium-enriched media Angiovist and Hypaque-76 (60). In nine patients undergoing coronary arteriography, plasma measurements from the coronary sinus, there was a significant reduction in ionized calcium concentrations immediately after injection of Renografin 76 (sodium methylglucamine diatrizoate) into the coronary arteries. The effect was most marked and lasted longer in patients with vascular disease. The reduction in ionized calcium was attributed to the chelating agents (disodium EDTA and sodium citrate) present in some contrast media. This may have been a factor in causing electromechanical dissociation in cardiac muscle (SEDA-11, 412). The hypocalcemic effect of ionic contrast media can potentiate the effect of a calcium blocker such as verapamil (SEDA-8, 429) (SEDA-9, 410).

Non-ionic media cause fewer electrocardiographic changes than ionic media (SEDA-10, 424) (SEDA-11, 412). Non-ionic contrast media are almost sodium-free; they have little tendency to cause ventricular fibrillation or to depress cardiac contraction, and this small risk might (if in vitro animal studies are dependable) be further reduced by the addition of a very small amount of sodium (61). Following studies in dogs in which methylglucamine salts of diatrizoate or iotalamate produced only temporary T wave changes while sodium salts produced more marked changes with a fall in blood pressure and increase in coronary flow, the US manufacturers of a product containing sodium methylglucamine diatrizoate removed virtually all of its sodium content, but without announcing the change (62). Radiologists using the altered contrast medium noticed an unexpected increase in the incidence of ventricular fibrillation after coronary arteriography. Subsequent animal experiments confirmed that the new medium caused this effect, apparently by prolonging the time of depolarization. The addition of small quantities of sodium to the medium lessened this prolongation of the depolarization phase.

Prinzmetal angina with electrocardiographic changes has been seen 10 minutes after a dose of iodipamide (SEDA-2, 373). In another case an anaphylactoid reaction after left ventriculography was associated with electrocardiographic changes apparently due to coronary artery spasm (63).

In a comparison of the effects of ioxaglate (a low-osmolar ionic dimer) with iopamidol (a non-ionic monomer), iopamidol caused fewer electrocardiographic changes and a reduction in ventricular excitability compared with ioxaglate (64).

The electrocardiographic effects of different types of non-ionic low-osmolar contrast media have been investigated in 41 patients undergoing left ventricular angiography (65). There was transient prolongation of the QT interval in all of the patients. The effect did not cause important cardiac events and was less than 60 ms in most cases. The authors concluded that this effect was too brief to present any significant risk.

Left ventricular failure

Of 65 patients being investigated for intermittent claudication under general anesthesia, five developed pulmonary edema after retrograde aortic injection of sodium iotalamate (Conray 325 or 420). Three of the five had a history of myocardial disease and another had received 200 ml of Conray 420.

Although it is now widely acknowledged that low-osmolar non-ionic contrast media are better tolerated than high-osmolar ionic media, the choice of contrast agent does not affect the early results of percutaneous transluminal coronary angioplasty (66). However, the authors acknowledged that high-osmolar ionic agents carry higher risks of acute left ventricular failure. They retrospectively reviewed 401 patients who underwent percutaneous transluminal coronary angioplasty, 220 of whom received high-osmolar ionic media and 181 of whom received non-ionic contrast media. Acute left ventricular failure occurred more often in the high-osmolar group (1.4 versus 0%). There were no differences in the incidences of acute myocardial infarction (3.3% in each group) or urgent surgical intervention (0.5% with the high-osmolar agents and 0.6% with the low-osmolar non-ionic media). There were two cases of mild and transient central nervous system complications (loss of orientation and transient hemiparesis) with the high-osmolar contrast media. The authors concluded that in the majority of cases, the type of contrast medium used does not influence the early results of percutaneous transluminal coronary angioplasty in relation to its efficacy, the degree of revascularization, and residual narrowing. However, they acknowledged that the use of high-osmolar ionic media increases the risk of acute left ventricular failure after angioplasty. They attributed the finding that non-ionic contrast media increased the risk of abrupt vessel closure (4.5 versus 1.5%) to intravascular clotting. The suggestion that non-ionic agents are procoagulant is contentious, and there is no conclusive evidence to support this view (SEDA-22, 501).

Myocardial infarction

In spite of the safety of the non-ionic contrast media cardiac arrest can complicate the infusion of these agents.

- A 47-year-old man with chest pain and a myeloproliferative disorder had a CT scan of the abdomen with contrast enhancement (the type of contrast medium was not stated) (67). He had no significant past medical history or history of allergy. During a later CT scan of the abdomen infusion of 60 ml of the non-ionic monomer iohexol (iodine 300 mg/ml) caused a sudden cardiac arrest. Resuscitation was ineffective and post-mortem examination showed intramural acute and old organizing infarctions in the entire left ventricular wall.

Although the authors suggested that this event was an adverse effect of the contrast medium, it is possible that the cardiac arrest in this patient was secondary to an acute coronary event independent of the contrast agent.

Respiratory

Transitory changes in lung function can occur after bronchography due to retention of the contrast medium in the bronchi; normal diffusing capacity may not return for 3 days and it is better to avoid thoracic surgery during this period. When bronchography with propyliodone

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preparations is performed during fiberoptic bronchoscopy, there may be marked arterial oxygen desaturation (SEDA-15, 504).

Some contrast medium inevitably reaches the lungs after injection, and tracer studies in the early 1960s showed that some degree of pulmonary oil embolism occurred in every patient (68). Pulmonary function studies have shown abnormalities, in particular a reduction in pulmonary diffusing capacity and pulmonary capillary blood volume, even in the absence of clinical signs or symptoms (69). Most cases are symptomless, although there can be mild pyrexia, while X-rays show stippling or an arborization pattern. If hypotension, cyanosis, dyspnea, and pleuritic pain occur, infarction should be suspected. The risk that blockage of lung capillaries by oil will endanger the patient is naturally greater if pulmonary function is already compromised, for example by neoplastic or fibrotic disease, or by radiotherapy.

In some patients, this phase of mechanical obstruction is followed after some days or 3–4 weeks by a chemical reaction, presumably as the oil breaks down to irritant fatty acids, which cause exudation and hemorrhage. Interference with the production of lung surfactant can also occur and a marked intravascular cellular reaction has been described (70). The chemical irritative phase is marked by fever, cough with sputum (often blood) and a variable degree of respiratory distress; there may even be tachycardia and hypotension.

Non-cardiogenic pulmonary edema has been seen several times after contrast media in patients with a prior history of myocardial infarct (SEDA-16, 531); it can also be a component of anaphylactic shock. Non-cardiogenic pulmonary edema has been reported as a complication of intravenous injection of iomeprol (71).

- A 68-year-old man with chronic obstructive pulmonary disease underwent CT examination of the abdomen with intravenous infusion of iomeprol for suspected hepatocellular carcinoma and 2 hours later developed severe dyspnea. A chest X-ray showed bilateral diffuse shadowing of the lungs and the heart shadow was not enlarged. A diagnosis of non-cardiogenic pulmonary edema was made and he improved with glucocorticoids.

Contrast media can cause severe bronchospasm, particularly in patients with asthma (72). Subclinical bronchospasm can occur after bolus injections of ionic contrast medium; the incidence is lower with non-ionic media (SEDA-8, 427).

Life-threatening adult respiratory distress syndrome after intravascular radiographic contrast injection is rare. It has been successfully managed by extracorporeal membrane oxygenation (73).

- A 62-year-old man developed adult respiratory distress syndrome 5 minutes after receiving a low-osmolar ionic contrast medium (140 ml of ioxaglate 200) during coronary angiography. His respiratory rate was 35/minute, blood pressure 60/40 mmHg, pulse rate 125/minute, PaO_2 49 mmHg, main pulmonary artery pressure 21 mmHg, central venous pressure 9 mmHg, and pulmonary capillary pressure 10 mmHg. A chest X-ray showed pulmonary edema. Laboratory investigations, electrocardiography, echocardiography, and coronary angiography were normal. In view of life-threatening hypoxia, extracorporeal membrane oxygenation was given for 50 hours, and 2 weeks later he was discharged without pulmonary symptoms.

In one case adult respiratory distress syndrome was accompanied by disseminated intravascular coagulation (SEDA-16, 531).

- Respiratory arrest occurred after aspiration of water-soluble contrast material in a 12-year-old girl who had been injured in a traffic accident. Gastrografin diluted with tap water (540 ml) was given into the stomach via a nasogastric tube as part of CT-enhanced contrast examination of the abdomen. She also received 150 ml of non-ionic contrast media (iopamidol, iodine 300 mg/ml) intravenously, which was followed by vomiting attacks. She became irritable and had an acute fall in oxygen saturation and progressive respiratory distress, which required endotracheal intubation. The CT scan that was performed after she became stable showed contrast material in the lungs.

The authors concluded that aspiration of contrast material can be life-threatening and that administration of oral contrast media after trauma can increase the risk of aspiration of gastric contents (74).

Accidental inhalation of hypertonic contrast media during oral administration can cause fatal non-cardiogenic pulmonary edema (75).

In pediatric bronchography, segmental collapse occurs in half the cases, but is particularly common with the aqueous media. Collapse also seems to be more common when halothane and oxygen are used as the anesthetic agents (SEDA-15, 504); this has been attributed to the rapid absorption of the anesthetic gases combined with the partial bronchial block caused by the contrast medium.

Pulmonary fibrosis and microlithiasis has been reported as a late complication of lymphography with iodized oil, but a causative relation was uncertain (SEDA-12, 397).

Nervous system

Animal experiments with the ionic media have shown that these damage the blood–brain barrier, thereby creating a degree of risk to brain tissue when they are used in cerebral angiography, although they have often been used safely. Other evidence suggests that sodium increases the neurotoxicity of the contrast medium, possibly by increasing its diffusibility into the brain. Methylglucamine, on the other hand, reduces neurotoxicity. The addition of a small quantity of calcium also appears to reduce toxicity, at least when added to sodium. There are only marginal differences in neurotoxicity as measured in animal experiments between the diatrizoate, iotalamate, and metrizoate anions. Calcium methylglucamine metrizoate probably has the lowest neurotoxicity of the ionic media, followed closely by methylglucamine iotalamate. In clinical use, however, the calcium-containing formulations appear to cause a greater degree of discomfort because they cause a sensation of heat.

Although the non-ionic media produced less injury to the blood–brain barrier in animals, clinical studies have not generally shown them to be better tolerated when

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used for cerebral angiography, and it has been argued that these expensive media should now only be used where the blood–brain barrier is thought to be defective (76).

Transient neurological changes after myelography include asterixis, aphasia, and reversible visual defects. In one patient, asterixis and head bobbing were still present 3 months after myelography with metrizamide (SEDA-7, 453). An isolated case of persistent cervical myelopathy has also been reported after lumbar myelography with metrizamide.

A variety of other neurological complications have also been recorded. These include Guillain–Barré syndrome, auditory or visual disturbances, motor aphasia, sixth nerve palsy (SEDA-8, 431), mania, organic brain syndrome (SEDA-10, 425), confusional changes, and absence status. Absence status responds rapidly to intravenous diazepam (SEDA-14, 415).

Death has occurred following deterioration of neurological status. There has been a higher incidence of such complications in diabetics (SEDA-11, 415). Aspiration of 20–25 ml of cerebrospinal fluid after metrizamide myelography appears to reduce the incidence of neurological adverse effects (77).

All ionic contrast media are neurotoxic and they should not be injected into the subarachnoid space or intrathecally, and stern warnings against such use have been issued, for example by the American FDA (SEDA-18, 445). When they have accidentally been used, deaths have resulted (SEDA-18, 445) (78). Accidental misuse of diatrizoate for myelography, with fatal consequences, has been a serious problem (SEDA-22, 500). Lavage of the subarachnoid space with saline in such cases has been effective in reducing toxicity (SEDA-15, 504).

Accidental injection of diatrizoate into the subarachnoid space has occurred as a result of misplacement of the needle in arteriography, in discography, from inadvertent use in myelography, or during injection of a myelocele. Severe convulsions with extensor spasms occur and can result in death, particularly if the agent comes into contact with the brain; the onset of convulsions can be rapid, but they can also be delayed for several hours. Two patients developed renal insufficiency as an additional complication (SEDA-8, 1046).

The earliest water-soluble medium used for lumbar myelography or radiculography, sodium methiodal, had an irritant effect and required spinal anesthesia, which sometimes caused hypotension. Methylglucamine iotalamate was less irritant, while methylglucamine iocarmate had still lower neurotoxicity. However, even these two media could cause convulsions or muscle spasms if the contrast agent came into contact with the conus medullaris. For this reason the patient was postured with the head raised for several hours after the examination to prevent the contrast medium passing above the L-l vertebral level. Diazepam might also be given prophylactically. When convulsions did occur they could be severe, even resulting in fractures or dislocation of a hip. A convulsive pattern without actual convulsions has also been seen on the electroencephalogram in some patients.

Metrizamide was the first non-ionic contrast medium and became widely used for myelography and ventriculography. It was much less neurotoxic than iocarmate, although electroencephalographic changes lasting up to 3 days were found in some 16% of cases in early studies. Today, metrizamide is no longer used and has been succeeded by new generations of non-ionic monomers (iopamidol, iohexol) and dimers (iotrolan, iodixanol) which are well tolerated with low neurotoxicity (SEDA-22, 501). The need for intrathecal injection of contrast media in the developed world has dramatically fallen with the wide availability of MRI.

Visual evoked responses 20 hours after myelography can be delayed, with a correlation with the severity of headache after myelography; the delay in visual-evoked response is less marked with iopamidol than with metrizamide. It has been suggested that this technique may be useful in the assessment of myelographic contrast media toxicity (79).

In 439 myelographic procedures with metrizamide the most frequent adverse effect was headache, which could be differentiated into early-onset headache (related to hydrodynamic modifications in the spinal fluid following lumbar puncture) and late-onset headache (reflecting a specific metrizamide effect) (80). The frequency of late-onset headache was at least 27%, but altogether 46% of the patients had headache at one time or another. In this series, meningeal irritation was seen in 5%, sometimes in a severe form, mimicking a septic complication. There was spinal irritation in two cases and epileptic fits in one. An acute psychotic organic syndrome was common after cervical myelography with high doses of metrizamide. There was a severe anaphylactic reaction in one patient. The results of this study have generally been confirmed by others; seizures are clearly very rare with these non-ionic media, though they have occurred, even with iohexol (81), as have involuntary movements and facial twitching (82) and nystagmus (83). Meningeal irritation and paraplegia have both been seen with iohexol (SEDA-16, 536) and a case of aseptic meningitis with iotrolan (SEDA-16, 536).

In comparative trials, iopamidol and iohexol produced fewer adverse effects than metrizamide and they do not so far appear to have given rise to the psychosyndrome, but slight electroencephalographic changes can occur even with the newer media. Seizures and clonic jerks have been reported when relatively large doses of iopamidol have been used in myelography (SEDA-7, 455) (SEDA-13, 436).

Four cases of cauda equina syndrome have been described with methylglucamine iocarmate used for radiculography, although in two cases faulty technique was perhaps contributory.

Loss of consciousness can occur if there is hypotensive collapse; rarely there can be prolonged coma.

Convulsions, seen as part of an idiosyncratic reaction, tend to occur in patients with an existing tendency to epilepsy, or to occur as consequences of hypotensive collapse, cardiac arrest, or overdose.

Intraventricular metrizamide can cause perivascular mononuclear infiltration in the walls of the ventricles. This histological appearance may be mistaken for encephalitis if previous exposure to metrizamide is not considered (SEDA-7, 454).

A few cases of severe purulent meningeal reactions to iopamidol have been briefly described (84). In one exceptional report, a hemorrhagic meningeal reaction and

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thrombosis of the superior longitudinal sinus followed sacroradiculography with iopamidol (85). A case of transitory abducent nerve palsy has been reported after myelography with iopamidol (SED-12, 1183) (86).

Electroencephalographic changes

In 292 patients undergoing examinations with metrizamide, electroencephalography showed minor non-specific changes in 13% 24 hours after the injection. In 4% there were more marked abnormalities, such as spikes, spikes and waves, or paroxysms of bilateral synchronous high voltage rhythmic delta waves, apparently due to a direct toxic action of metrizamide on the cerebral cortex. They occurred shortly after the injection, and in the patients involved, a large amount of the contrast medium had flowed intracranially. Diazepam did not appear to have any significant effect on the electroencephalographic changes (SEDA-15, 504).

In a series of 308 cerebral angiograms in which metrizamide and meglumine metrizoate were compared on a randomized, double-blind basis, metrizamide caused a lower incidence of electroencephalographic changes, but the incidence of clinical complications showed no significant difference in the two groups, suggesting that the problems were mainly caused by other factors, such as thromboembolism; thromboembolism has indeed been suspected after cerebral angiography, even with iohexol (SEDA-13, 435).

Acute encephalopathy

Acute encephalopathy has been reported after intrathecal administration of non-ionic media (87).

- Six hours after 10 ml of iohexol (Omnipaque, iodine 240 mg/ml) had been injected into the left lateral ventricle during an operation on the thalamus of a 63-year-old man with Parkinson's disease, his level of alertness deteriorated and he became disorientated and confused. A CT scan of the head showed the surgical lesion and artefacts due to contrast medium, but no other abnormalities. After 24 hours, he became more alert, with coherent speech, but there was still mild disorientation. These symptoms resolved within the next 2 days.

According to the authors, this was the first case of encephalopathy after iohexol ventriculography, with the onset of symptoms several hours earlier than in myelography cases, probably owing to direct administration into the ventricular system. Awareness of this complication can be helpful in patient management after procedures in which iohexol is given intrathecally.

Transient contrast encephalopathy has been reported after carotid artery stenting (88).

- An 82-year-old right-handed man was given 50 ml of the ionic low-osmolar contrast agent ioxaglate 320 for carotid angiography. The next day his right internal carotid artery was stented and a total of 180 ml of ioxaglate was used. Aspirin, ticlopidine, and heparin 5000 units were given during the procedure. While he was still on the table he developed rapidly worsening confusion and a left hemiparesis. A CT scan without contrast 4 hours later showed marked cortical enhancement and cerebral edema in the distribution of the right anterior and middle cerebral arteries. He rapidly improved and had complete neurological recovery after 48 hours; 1 month later he was asymptomatic.

The cerebral contrast enhancement on the CT scan suggested disruption of the blood–brain barrier. This could have been due to the large volume of contrast medium used during the stenting procedure. This complication must be differentiated from massive cerebral infarction and hyperperfusion syndrome: the rapid radiological resolution and clinical recovery excluded cerebral infarction; hyperperfusion syndrome would have involved the carotid distribution exclusively, rather than both the ipsilateral carotid and posterior circulations. The authors recommended close follow-up of patients after such procedures. The safety of subsequent cerebral angiography in a patient with a history of such a reaction has not been studied extensively, and extreme caution must be exercised should the need for repeat angiography arise later.

Adhesive arachnoiditis

Methylglucamine iocarmate and methylglucamine iotalamate have both caused persistent arachnoiditis, leading to obliteration of nerve roots and constriction of the dural sac; operative treatment after myelography increases the risk of arachnoiditis, which is dose-dependent and varies with the contrast medium used (89,90).

Aseptic meningitis

Aseptic meningitis has been reported after iohexol myelography (91).

- A 74-year-old woman underwent lumbar myelography with iohexol (12 ml, iodine 240 mg/ml) for low back pain, having had iohexol myelography 2 years before with no complications, and 18 hours later developed headache, pyrexia (39°C), shivering, sweating, neck stiffness, nausea, and mild confusion. She had a leukocytosis (16.4×10^9/l) and a high C-reactive protein (145 micrograms/ml). There were leukocytes in the cerebral spinal fluid (11.5×10^9/l, 98% polymorphonuclear leukocytes), with protein 6.6 g/l and glucose 3 mmol/l, but a Gram stain was negative and no microorganisms were grown. She recovered spontaneously.

The authors suggested that this was a meningeal reaction to iohexol, since the interval between the injection of iohexol and the onset of symptoms was short, the symptoms resolved quickly, and there was no evidence of infection.

In the Netherlands, around 1979 there were several reports of aseptic meningitis after the use of metrizamide (SED-12, 1183) (92), and the complication has been reported since with iopamidol (93). Streptococcal meningitis has also been reported (94).

Convulsions

Up to 1979 it was estimated that some 360 000 cases of myelographies had been performed with metrizamide and that there had been 40 cases of epileptic attacks after its use (95); although they tended to relate to investigations in the upper part of the spine, three related to cases of lumbar myelography; a further case was later described. In some of these instances the use of other drugs may

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have played a role, including chlorpromazine, antihypertensive drugs, diphenhydramine, and pethidine (SED-12, 1182). The role of chlorpromazine in facilitating metrizamide-induced convulsions has been confirmed in animal studies; it was formerly recommended that phenothiazines should be withdrawn at least 48 hours before intrathecal use of metrizamide. Some, but by no means all, of the patients experiencing convulsions with metrizamide have a history of epilepsy.

- A 69-year-old man with idiopathic nasal bleeding underwent contrast-enhanced CT examination of the head with an intravenous non-ionic low-osmolar contrast medium (96). Convulsions and tremor developed 1 hour after the examination and lasted for 50 minutes.

There was an increased risk of seizures in patients with a previous history of seizures and in association with antineoplastic therapy (97). Patients with thrombotic thrombocytopenic purpura also appear to be at greater risk of seizures during contrast examination. Fatal status epilepticus can occur during CT (98). The non-ionic agent iopamidol appears to be less likely to cause seizures (76).

Cortical blindness

Cortical blindness after exposure to contrast agents has been reported to be as high as 1–4% in patients undergoing vertebral angiography, even with modern non-ionic low-osmolality contrast agents. It has been thought to be due to breakdown of the blood–brain barrier of the occipital cortex with subsequent direct neurotoxicity of the contrast medium. Repeated exposure to contrast agents did not cause recurrent episodes of cortical blindness. The outcome seems to be favorable, with return of vision within 24–48 hours and probably no increased risk on re-exposure. Occasionally cortical blindness can be caused by other procedures, for example coronary angiography (99).

- During coronary angiography, a 55-year-old man was given 280 ml of non-ionic contrast media iomeprol (iodine 350 mg/ml). Ten minutes later he became progressively confused and developed complete loss of vision. A CT scan of the head showed pronounced intracerebral enhancement of contrast media in the posterior third of the brain without evident relation to a vascular territory and a straight border towards normal brain tissue. Angiography of the right vertebral artery showed normal patency of the vertebrobasilar and venous systems, excluding thromboembolic events in the posterior cerebral circulation. Another CT scan of the head 1 day later showed clearing of the contrast medium. The neurological deficit resolved more slowly, but there was normal vision and minimal amnestic deficit after 5 days.

These findings were compatible with leakage of contrast medium through the blood–brain barrier, direct or indirect neurotoxicity of the contrast media being the most likely explanation for the neurological symptoms.

- A 64-year-old man developed transient cortical blindness after right subclavian, aortic, and femoral arteriography for ischemic pain in his left leg (100). Iopromide 250 ml (iodine 300 mg/ml) was used. The patient was hemodynamically stable throughout the procedure, at the end of which he had blurred vision and a slight headache. He could see shapes and colors but could not focus. There were no field defects. His pupillary reflexes and eye movements were normal. His vision improved 3 hours later and fully recovered after 48 hours.
- A 29-year-old man had a subarachnoid hemorrhage due to an arteriovenous malformation, which was embolized (101). During the procedure he suddenly lost consciousness, regained it 15 minutes later, but complained of total blindness. Cerebral angiography showed no arteriovenous malformation and no abnormality in the vertebrobasilar system. A CT scan of the head showed considerable contrast enhancement of the occipital lobes and 2 hours later the contrast had cleared. An MRI scan 12 hours later showed no evidence of infarction in the occipital lobes. Two days later his sight gradually returned and 7 days later he had completely recovered.

The authors of the second report thought that these adverse effects were probably due to the low-osmolar non-ionic contrast agent. Disruption of the blood–brain barrier is a factor in the pathophysiology of this complication.

- After difficult cardiac angiography in the supine position, an elderly man with arteriosclerosis developed transient cortical blindness (102). On CT scan there was contrast enhancement of the occipital lobes.

The best explanation of this observation is that a large amount of contrast medium entered the vertebral artery and passed upwards, passing a defective blood–brain barrier. Similar complications have been described in other patients, sometimes with amnesia, after cardiac catheterization and angiography (SEDA-18, 444).

- A 63-year-old woman with a left-sided spastic hemiparesis underwent cardiac and coronary angiography with a large volume (300 ml) of the non-ionic contrast medium iomeprole (iodine 350 mg/ml) (103). After the procedure her hemiparesis dramatically worsened, prompting emergency CT scanning of the head, which showed a marked hyperdensity in the right cerebral hemisphere. She recovered from this acute event, and follow-up CT of the brain showed complete resolution of the hyperdensity.

The right hemisphere was more affected in this case, because the contrast medium injected into the left ventricle or ascending aorta during angiography is likely to reach the right brachiocephalic artery first. The hyperdensity of the affected cerebral hemisphere seen on CT scanning was due to leakage of the iodinated contrast medium into the extracellular space, because of an increase in the permeability of the blood–brain barrier.

Paraplegia

Paraplegia can occur after angiography (104). In one series of five patients, four had tetraplegia (three being due to parathyroid arteriography and one after angiography of the posterior fossa), and in the fifth, paraplegia followed attempted renal angiography. When these

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neurological complications occur after angiography, the iodine content of the cerebrospinal fluid is raised.

There are various explanations, backed by animal studies, for this complication. When there is obstruction to the normal outflow of blood from the aorta, there is an increased risk that the contrast agent will be diverted into the spinal circulation. This effect can be aided by a gravitational factor if the examination is performed with the patient in the supine position.

The risk may not be the same for all contrast agents; the relation between the compound used and the neurotoxic effects is discussed below in connection with cerebral angiography.

Stroke

Cerebral effects can complicate thoracic aortography when excessive doses of concentrated agent are injected, particularly if the catheter is sited so that the major dose of contrast agent is directed into the cerebral circulation. In one case, 10 ml of sodium iotalamate 70% was injected into the carotid artery, being mistaken for methylglucamine iotalamate 60%; this was followed by an immediate convulsion, with loss of consciousness for 2 minutes. The patient at first appeared to have recovered completely, but hemiparesis followed and persisted for some 24 hours. Such changes are presumably due to cerebral edema after transient damage to the blood–brain barrier.

Cerebral oil embolism has been described in nine patients in one series of 3500 lymphograms (105) and in eight patients in another series of 16 501 investigations (106). All nine patients in the former series developed neurological signs, usually within 48 hours, reaching a peak in 4–7 days; the symptoms included motor dysfunction, paraplegia, and deep coma lasting for some weeks; three of the nine died. The electroencephalographic findings in these patients pointed to diffuse brain emboli. Evidence of retinal fat embolism can be useful in confirming the diagnosis and computed tomography can show collections of ethiodol in the brain. In the early phase after radiotherapy to the lungs, the vasculature is damaged, so that contrast agent is less effectively retained in the lungs. If lymphography is performed at this stage, there is an increased risk of cerebral embolism.

Sensory systems

Hearing impairment has been attributed to contrast agents.

- A 37-year-old man with recurrent attacks of low back pain underwent drip intravenous pyelography to exclude the possibility of stones of the urinary tract (8). Iohexol 300 was used, but the total volume was not documented. He had had drip intravenous pyelography for suspected urinary calculi 5 years before. A few hours after the procedure he suddenly had bilateral hearing loss and tinnitus in the right ear. He complained of dizziness and nausea but had no rotatory vertigo or skin rash. A pure-tone audiogram 2 days later showed complete right-sided and partial left-sided deafness. CT and MRI scans showed no abnormalities in the inner ear, internal auditory canal, or posterior fossa. He was given intravenous high-dose hydrocortisone sodium succinate, 10% dextran, and batroxobin, but there was no improvement in hearing. The dizziness and tinnitus in the right ear persisted, as did the deafness, for a further 2 months.

Hearing disturbances attributable to contrast agents are extremely rare. The hearing loss in this patient developed more than 1 hour after the injection of iohexol, without any evidence of other causes. The authors suggested that the hearing disturbance might have been attributable to cochlear impairment caused by a delayed allergic reaction or chemical toxicity of the contrast medium.

Psychological, psychiatric

To reduce the incidence of generalized reactions to contrast media in high-risk patients some authors have advocated the prophylactic administration of glucocorticoids (prednisolone 30 mg orally or methylprednisolone 32 mg orally, 12 and 2 hours before contrast injections). In one case an acute psychosis complicated glucocorticoid premedication to reduce the risk of contrast reactions (107).

- A 13-year-old girl with bipolar disorder and a history of adverse reactions to contrast media was given methylprednisolone (32 mg/day) and ranitidine (300 mg/day) before a CT scan of the head with intravenous contrast enhancement. One day after, she developed psychiatric symptoms, which were more severe than her initial symptoms, including extreme agitation and mental confusion. All medications were withdrawn and her symptoms resolved within 2 weeks.

The authors suggested that the recurrence of the manic symptoms could have been due to premedication with prednisolone. Exacerbation of manic symptoms after the use of glucocorticoids has been documented before, but never in a case of short-term premedication before contrast-enhanced radiographic examination. This report shows that even a short-term course of glucocorticoids can have significant adverse effects in patients with a history of mood disorders.

In 2500 cases of cervical myelography with metrizamide, there were transient mental reactions in 25, including 13 cases of confusion or disorientation, four of depression, two of hallucinations, two of psychosis, and one each of anxiety, drowsiness, dysphasia, and nightmares (108).

Of 18 German patients undergoing lumbar myelography with metrizamide, six had an organic psychosis, characterized by impaired memory and depression, but it was demonstrable only by psychometric tests and disappeared within 5 days (109). In four of the 18 patients there was hyporeflexia or areflexia and in three there were electroencephalographic changes; there was no correlation between these various types of effect.

Visual hallucinations are very rare adverse effects of contrast media, with isolated reports after vertebral angiography or myelography. The mechanism of this adverse reaction could be similar to that reported in transient cortical blindness after infusion of contrast agents. However, other possibilities include a toxic effect of contrast media on the optic nerve, transient impairment of cerebral blood flow, which could be mediated through the release of the potent vasoconstrictor endothelin, or the formation of microclots. Two cases of

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visual hallucinations after coronary angiography have been reported (110).

- A 70-year-old woman with a history of mastectomy developed syncope which lasted a few seconds. She had taken tamoxifen 10 mg bd for 10 years and had no history of allergic reactions. Doppler ultrasound showed aortic stenosis and coronary angiography was performed using 150 ml of iopromide (a non-ionic contrast medium, iodine 370 mg/ml). She had visual hallucinations (spiders on the wall, moving curtains) 30 minutes after the injection of iopromide. The symptoms resolved 72 hours later without any specific treatment. Neurological and psychiatric examinations were normal, as were brain MRI and Doppler ultrasound of the carotid and vertebral arteries.
- A 64-year-old man with a history of ischemic heart disease underwent coronary angiography with 150 ml of iopromide (iodine 370 mg/ml). One hour later he had visual hallucinations (moving objects, pictures of familiar persons), which resolved about 40 hours later without any treatment. He had taken the following drugs for a year: nifedipine 10 mg tds, metoprolol 50 mg bd, and aspirin 325 mg/day. His serum creatinine concentration was in the reference range and there was no history of allergies or previous exposure to contrast media.

Myelography with either iopamidol or metrizamide can cause transitory deterioration in memory as determined by psychological tests, but the effect is less with iopamidol (111).

Many of the psychiatric complications of cerebral angiography may be due to arterial trauma rather than to the toxic effect of the contrast agent. If the investigation is undertaken under general anesthesia, the use of a volatile anesthetic can in itself cause an increase in intracranial pressure and thereby constitute an aggravating factor (112). Focal electroencephalographic changes can occur on the side of the injection, and if these are prolonged they can be followed by evidence of neurological involvement. Transient global amnesia and confusional states have been reported after cerebral angiography, even with non-ionic media (SEDA-9, 410) (113).

Endocrine

Contrast agents contain very large amounts of iodine, though it is in a bound form. Liberation of iodine (114) from these agents can produce some inhibition of thyroid function in healthy subjects for up to 3 months, but can also increase hormonal synthesis in a thyroid adenoma, and cases of frank thyrotoxicosis have been attributed to these agents, the effect starting within a few days (115). Hypothyroidism has also been reported, particularly in neonates. Contrast medium-induced hyperthyroidism is rare and usually occurs in patients with autonomous thyroid function. Treatment is exclusively symptomatic. Prophylaxis with sodium perchlorate should be considered in cardiac patients with a goiter and a subnormal concentration of thyroid stimulating hormone (TSH) (SEDA-21, 478) (116). In premature babies and neonates thyroid complications can develop after intravascular administration of iodinated contrast media and great caution should be exercised during radiological examinations in infants (SEDA-20, 420).

Thyroid metabolism has been prospectively investigated in 102 patients undergoing diagnostic coronary angiography (117). Thyroid function tests (T3, rT3, T4, free T4, and TSH) and urinary iodine excretion were measured before and 3 weeks after diagnostic intra-arterial administration of iodinated contrast agents. Only euthyroid patients were included, in order to determine whether the administration of non-ionic iodine-containing contrast agents causes significant thyroid function changes in euthyroid patients and whether thyroid morphology is a prognostic factor for the risk of hyperthyroidism. Serum concentrations of thyroid autoantibodies (TPO-Ab, Tg-Ab, TSH-receptor-Ab) were measured. Thyroid ultrasound showed that 37 patients had normal thyroid glands. The gland was of normal size but nodular in 16 patients, there was a diffuse goiter in 15 patients, and a nodular goiter in 34 patients. In 25 patients Tg-Ab was positive and in 13 patients TPO-Ab was positive; TSH-receptor-Ab was not detected in any patient. T3 concentrations did not change significantly after the administration of iodine. T4 and free T4 concentrations underwent significantly different changes in the four groups. The amount of iodine given did not affect the changes in the serum concentrations of TSH, T3, T4, free T4, or rT3. Raised concentrations of urinary iodine correlated with the amount of contrast medium given. There were no cases of hyperthyroidism. The study showed that thyroid function was significantly altered after coronary angiography, independent of antibody status and the amount of contrast agent given, but dependent on thyroid morphology.

The effects of iopromide on thyroid function have been investigated in 20 pre-term infants with very low birth weights and 26 matched premature infants who did not receive contrast medium (118). The dose of iopromide (iodine 300 mg/ml) was 0.3–1.0 ml. Iopromide did not affect the concentrations of free thyroxine and thyroid stimulating hormone. This was attributed to the small amount of free iodide that iopromide contains (0.6 microgram/ml) compared with other contrast media, in which the free iodide concentration ranges from 1.8 micrograms/ml (iohexol) to 4 micrograms/ml (ioxaglate). Furthermore, hypothyroidism has previously been described after the injection of less than 1 ml of ioxaglate 320 in 13 premature infants of less than 34 weeks gestational age and in other children after the injection of iopamidol. The authors concluded that iopromide may be superior to other contrast media in protecting infants of very low birth weight from thyroid dysfunction. It is advisable to monitor thyroid function when contrast media are given to such infants.

- A 54-year-old man developed Graves' disease and hypoadrenalism secondary to adrenocorticotropin deficiency soon after a cranial CT scan with an iodine-containing contrast agent (119).

It was presumed that the iodine load (about 30 g) had precipitated thyrotoxicosis in this patient, who had antibodies to the thyrotropin receptor, which in turn precipitated collapse due to adrenal insufficiency.

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In three women (aged 63, 72, and 75 years) with subclinical goiters, hyperthyroidism developed after the intravenous administration of iodinated contrast medium (120). There was a marked rise in the concentration of free T4. The hyperthyroidism improved spontaneously in all three.

In 51 sick neonates given two different non-ionic, iodine-containing contrast agents, metrizamide and iohexol, urinary iodine excretion was increased on day 5 after iodine exposure (121). In 17 term neonates given Amipaque, the median TSH concentration was normal after 5 days and 2 weeks, and there was only one case of transient hypothyrotropinemia; median concentrations of T3 and T4 were in the lower reference ranges. However, in 15 neonates given Omnipaque the median TSH was raised and T3 and T4 concentrations were very low. There was hypothyroidism in six of the eight preterm and one of the seven term neonates.

- Mild hypothyroidism with a goiter developed in a 15-year-old boy 6 weeks after lymphangiography with Lipiodol ultrafluid; the goiter disappeared after 3 months treatment with levothyroxine (SEDA-7, 454).

Metabolism

Iopanoic acid is as potent a uricosuric agent as probenecid and this effect might explain some renal complications; aspirin reduces the uricosuric effect but can also impair X-ray visualization because of competition at plasma protein-binding sites. Fluctuations of serum urate after oral cholecystography can interfere with diagnostic tests and even precipitate an attack of gout (122).

Electrolyte balance

Iodinated contrast media can cause increased release of potassium from blood cells and vascular endothelial cells, as has been investigated in vitro using blood, collected from 52 patients, mixed with iodinated contrast media for 30 minutes (123). The following contrast media were used: iopamidol (iodine 370 mg/ml), ioxaglate (iodine 320 mg/ml) and diatrizoate (iodine 370 mg/ml). Potassium release increased after exposure to the contrast media and the high-osmolar diatrizoate caused the greatest release, followed by iopamidol and then ioxaglate. The osmolality of contrast media may play an important role in the mechanism responsible for the release of potassium from blood cells. Chemotoxicity may also play a role. There are no data to suggest that the release of potassium is due to hemolysis, and it is most likely due to increased membrane permeability.

Mineral balance

Contrast agents can lower serum calcium and magnesium concentrations (124), which may be relevant to the occasional occurrence of tetany (SEDA-7, 452).

Hematologic

A single case of severe but reversible hypoplastic anemia has been attributed to sodium diatrizoate (125). Ionic contrast media have a disaggregating effect on erythrocytes, and hyperosmolar agents reduce their elasticity (SEDA-22, 501). When blood is diluted with 90% sodium diatrizoate in vitro, there is initially a reduction in erythrocyte diameter, due to the hypertonic environment, but as more contrast medium is added, the erythrocytes increase in diameter because of damage to the cell wall; this tallies with the fact that cases of hemolysis and hemoglobinuria have been reported with amidotrizoate (126).

Iodinated water-soluble contrast agents have traditionally been contraindicated in patients with sickle cell disease, because of possible shrinkage of erythrocytes secondary to the high osmolality of these agents, which can lead to impaired blood flow through the microcirculation and can precipitate or exacerbate a sickle cell crisis. The hematological and rheological effects in vitro of four contrast agents of different osmolalities (iodixanol 290 mmol/kg, ioxaglate 600 mmol/kg, iohexol 844 mmol/kg, and diatrizoate 1940 mmol/kg) have been compared (127). Blood was tested from 10 healthy and 10 sickle cell donors at drug concentrations of 0, 1, 10, and 30% w/v in an attempt to approximate the circulating concentrations of contrast medium that might occur during bolus injection. There were significant hematological effects in the blood of both the healthy and sickle cell donors: there was a concentration-related reduction in hematocrit and MCV and an increase in MCHC, all of which varied directly with the osmolality of the contrast medium (amidotrizoate > iohexol > ioxaglate > iodixanol). Only with amidotrizoate at concentrations of 10–30% was there marked echinocytosis. There was no significant increase in the number of irreversibly sickled cells in donors with hemoglobin S. The filterability of erythrocyte suspensions through capillary-sized pores was impaired in both healthy and sickle cell samples in direct proportion to the osmolality of the contrast medium. Filterability effects were greater with sickle cells than healthy erythrocytes. Iodixanol, which is iso-osmolar with blood, had little effect on erythrocyte volume and had no significant effect on the filterability of healthy or sickle cells. These results suggest that microcirculatory impairment after infusion of contrast agents can occur in sickle cell disease because of the unusual rheological sensitivity of HbSS erythrocytes and may be avoided by using low-osmolar or iso-osmolar contrast agents.

Acute thrombocytopenic purpura has been reported in three patients given contrast agents (SEDA-11, 413). Severe thrombocytopenia has rarely been reported after iopanoic acid (128), iocetamic acid (129), and sodium iopodate; in the last case there was evidence that the patient had developed platelet antibodies of the type associated with other drug-induced thrombocytopenias (130).

- Thrombocytopenia occurred 24 hours after 100 ml of iopamidol was given intravenously during cranial CT scanning to investigate a 9-month history of headache (131). The patient reported purpuric lesions on her legs, abdomen, and gingival bleeding within 24 hours of the scan, and examination of the peripheral blood at 48 hours confirmed severe thrombocytopenia. A bone marrow smear showed a prominent increase in megakaryocytes and dysmegakaryopoiesis. The bleeding time was longer than 15 minutes. Other laboratory values were within normal limits. Within 10 days, all the lesions disappeared spontaneously and the platelet count improved gradually and returned to normal within 2 months.

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The pathogenesis of this complication is not understood but is most likely an immunological response to the contrast agent.

Clotting time is longer shortly after administration of ionic contrast agents (132). Non-ionic contrast agents do not have a similar anticoagulant action. In contrast, if blood is allowed to mix with a non-ionic medium in a syringe or catheter, thrombus formation can occur and this could be a cause of thromboembolism (SEDA-15, 502) (133). The non-ionic agents are not so much thrombogenic as less anticoagulant than their ionic predecessors (SEDA-19, 429). The risk of thromboembolism with ionic agents has been described in some contested studies as being 4–10 times higher (SEDA-17, 537) (SEDA-18, 444) (134). The non-ionic agents produce profound degranulation of platelets in vitro, but this is unrelated to thrombin generation (135). However, some prefer to heparinize when giving the non-ionic media. This issue is contentious, and although non-ionic agents are viewed as being less anticoagulant than ionic agents, they are not considered to be procoagulant (SEDA-22, 501). Adherence to a high standard of angiographic technique, with regular flushing of the catheter with isotonic saline is crucial to avoid thromboembolic complications during angiography.

The effects of contrast agents on leukocytes, platelets, and endothelium have been investigated in 19 subjects (mean age 63 years) undergoing angiography with the non-ionic contrast medium iohexol 350 (median volume 40–160 ml) for leg ischemia (136). Blood was obtained from the external iliac vein before and at several intervals after the injection of the contrast agent into the ipsilateral femoral artery. Markers of endothelial cell injury (von Willebrand factor), platelet activation (soluble P selectin), and leukocyte activation (neutrophil elastase and soluble L selectin) were measured in citrated plasma. Soluble intracellular adhesion molecule-1 and thromboxane B_2, which are non-specific markers of inflammation, were also measured. Compared with the sample before angiography, concentrations of soluble L selectin and soluble intracellular adhesion molecule-1 were reduced immediately after passage of the last bolus of contrast medium; 15 minutes later the concentrations returned to normal, but the concentration of von Willebrand factor had increased. After 30 minutes, only thromboxane B_2 concentrations were increased. On the next day both von Willebrand factor and soluble P selectin were increased. These data point to both early and late effects of contrast agents on markers of endothelial, platelet, and leukocyte function. The authors suggested that these adverse changes may increase the risk of coagulopathy and thrombosis after contrast examination and increase the risk of re-stenosis after angioplasty.

The hematological effects of ioxaglate (a low-osmolar ionic dimer) 105 (range 95–114) ml ($n = 15$) and iopromide (a low-osmolar non-ionic monomer) 102 (range 90–108) ml ($n = 16$) have been investigated in patients undergoing abdominal and femoral angiography (137). The aim was to investigate in vivo whether non-ionic contrast media are less anticoagulant or more prothrombotic than ionic agents. Activation of coagulation and platelets were found in almost 50% of patients before any contrast medium was given. Both iopromide and ioxaglate caused further increases in thrombin-antithrombin complex, prothrombin fragments $1 + 2$, and beta-thromboglobulin; the degree of activation was similar with both agents. In contrast to the findings in in vitro studies, there were no significant differences between the effects of the non-ionic agent iopromide and the ionic agent ioxaglate. The results supported the notion that the catheterization procedure per se may represent a source of hemostatic activation and that ionic contrast agents have insufficient anticoagulant effect to prevent clotting activation being induced by the procedure. The study also yielded no support for the concept that non-ionic contrast media are less anticoagulant or more prothrombotic than ionic agents.

However, it has been suggested that anticoagulant effects are high with ionic media and low with non-ionic media (138). The authors also suggested that there is no direct activation of platelets with low-osmolar ionic and non-ionic dimeric contrast agents but a high degree of activation with non-ionic monomeric contrast media. They concluded that although the interaction between contrast media and coagulation has been widely studied in vitro and in vivo, this issue is contentious and further studies are required for better understanding.

Within a few hours after lymphography, the lymph nodes show dilatation of the marginal and intermediate sinuses and a giant-cell reaction, with diffuse reticulocytosis and sinus histiocytosis. Diffuse plasmacytosis and an increase in the eosinophil count can also occur. The response is maximal after 10–14 days, but the changes in the lymph nodes may not be eliminated for as long as 15 months (SED-12, 1184) (139).

The thrombotic complications after angioplasty have been investigated in patients with unstable angina (140). There was no significant difference in the incidence of thrombotic complications between patients who received the low-osmolar ionic dimer ioxaglate ($n = 103$) and those who received the non-ionic agent iopamidol ($n = 102$), although there was a non-significant trend towards more thrombus formation in the non-ionic group (21 of 129 patients) compared with the ionic group (15 of 141 patients). The two groups were well matched with respect to age, sex, class of unstable angina, and susceptibility factors. There was no significant difference between the two groups with respect to clinical outcome in the first 24 hours after percutaneous coronary angioplasty.

- Disseminated intravascular coagulation has been described in a 63-year-old man who received 50 ml of the non-ionic monomer iobitridol (iodine 300 mg/ml) for arteriography (141).

Mouth and teeth

Swelling of the parotid glands has been recognized as an occasional effect of contrast agents for very many years (142). It occurs particularly when there is renal insufficiency; the swelling usually occurs 2–4 days after the procedure and can last for several days, but evanescent salivary gland enlargement can also occur within a few minutes of injection and last for a number of hours. In one case the complication was associated with paralysis of the facial nerve, which largely subsided over the next 9 weeks.

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Gastrointestinal

Nausea and vomiting can occur in reaction to contrast agents. Diarrhea is less common but has been repeatedly reported, sometimes with angioedema of the bowel (143).

Infarction of the bowel was formerly a very occasional complication of abdominal aortography and was due to injection of contrast medium into the mesenteric arteries. Most of these cases were due to the older media, such as acetrizoate; however, small bowel injury has occurred after injection of a concentrated bolus of sodium iotalamate (144). Ileus has been reported after mesenteric angiography in a patient with renal insufficiency (SED-12, 1177) (145).

Intra-arterial injection of lipiodol (iodized oil) has been used to enhance the accuracy of computed tomography in hepatic tumors. This can cause transient bowel ischemia with nausea, vomiting and diarrhea.

The use of Gastrografin for pre-operative mechanical bowel preparation has been investigated in 58 patients (aged 45–80 years) listed for elective colorectal operations (146). One group (30 patients, mean age 67 years) was given oral Gastrografin 200 ml and 3 liters of water for 2 days before the operation. The rest (28 patients, mean age 65 years) were given Ringer's solution 5–20 liters, warmed to body temperature, through a nasogastric tube; preparation was considered complete when the patient excreted clear fluid. All were given metronidazole and cefuroxime as antibiotic prophylaxis during the perioperative period. There were no significant adverse effects in the Gastrografin group, apart from nausea in six patients. In the Ringer's solution group there was nausea in 15 patients and vomiting in eight. A clean colon was found at operation in 93% of patients in both groups. The authors concluded that Gastrografin is well tolerated and can be used successfully for mechanical bowel preparation before elective colorectal surgery.

The rectal administration of Gastrografin 400–1000 ml in patients with suspected diverticular disease before CT examination of the abdomen has been investigated in 308 patients (aged 19–97 years) (147). None of the CT scans showed extravasated contrast material in the peritoneal cavity as a sign of bowel perforation. No patient had sudden clinical deterioration after the examination. All tolerated the contrast medium well and there were no allergic reactions. High-quality diagnostic examinations were obtained in all patients.

Contrast agents caused release of vasoactive intestinal polypeptide in a patient with a vipoma of the pancreas and hepatic secondaries (SEDA-11, 411) (148).

The high-osmolar agents amidotrizoate and iotalamate were formerly recommended for oral use in preference to barium where there was a risk of perforation, but the osmotic effect of such material can lead to diarrhea and fluid loss, which can be dangerous in weak patients. Amidotrizoate, despite its cathartic action, can occasionally cause ileus when given postoperatively (149); it can also be precipitated as a solid mass in the stomach when gastric acidity is high, but also in an achlorhydric gastric stump following partial gastrectomy if there is stomal obstruction. On one occasion, when diatrizoate was used to fill the gastric balloon of a Sengstaken–Blakemore tube, hydrogen ions from the gastric content apparently penetrated the balloon, precipitated the contrast medium, and thus prevented the balloon's removal.

Low-osmolar media such as iohexol are now preferred for oral use; they can still cause some diarrhea, for example in 18 out of 40 cases in one series (SEDA-16, 529). Absorption can be increased if there is mucosal damage in the bowel, such as in Crohn's disease, resulting in delayed excretion but not apparently involving risk (SEDA-18, 441).

Amidotrizoate enemas are still sometimes used to treat meconium ileus or constipation, and it is important to give intravenous fluids so as to avoid dehydration. Hypomagnesemia can also occur (150). Osmotic effects lower in the gastrointestinal tract have even led to distention and cecal perforation (151). Stasis of amidotrizoate in dilated loops of bowel can cause inflammatory changes or necrosis (152,153).

Liver

Sulfobromphthalein retention is increased by sodium iopodate or iopanoic acid, probably by competition in the hepatic excretory pathway. The mechanism is not clear. Serum bilirubin concentration can rise, and there can be a slight increase in serum enzymes, persisting for a few days.

There have been several reports of hepatotoxicity of iodipamide, variously characterized by epigastric pain, nausea and vomiting, jaundice, pyrexia, and tenderness over the liver, with abnormal liver function tests. Biopsy has shown centrilobular necrosis (154). The incidence of abnormal liver function tests may be as high as 18% after a dose of 40 ml, and the quantity given should be as small as possible. Prior administration of glucocorticoids or sulfonylureas impairs hepatic excretion of ioglycamide. Both iodoxamate and iotroxate can affect liver function tests; in a small series of cases, the degree of intrahepatic cholestasis appeared to be relatively more marked after iodoxamate than after iotroxate (SED-12, 1168) (155).

- A 19-year-old woman without previous hepatic impairment developed abdominal pain and an acute rise in liver enzymes after an injection of iopromide (156). During intravenous infusion of iopromide she developed vomiting and hypotension, which resolved within a few hours. Repeat laboratory tests showed a rise in serum transaminases, which peaked on the second day and then rapidly fell. There was a slight prolongation of the prothrombin time and a moderate increase in total serum bilirubin. Serum gamma-glutamyl transpeptidase activity was normal. Ultrasonography of the liver and biliary tree was normal and serological markers for viral hepatitis were negative. Two weeks later, liver function tests were all in the normal range.

An acute rise in liver enzymes after intravascular iopromide is uncommon and has been previously reported only in some patients with concomitant hepatic impairment. In this case, the temporal association (rapid clinical onset and raised serum transaminases after the injection of iopromide) suggested that iopromide may have played a role in the occurrence of the hepatitis-like picture.

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Biliary tract

Embolization of the cystic artery can cause acute acalculous cholecystitis (SEDA-15, 505).

Water-soluble contrast media are used to examine the pancreas and bile ducts during ERCP. Contrast media can affect the examination of bile for microlithiasis (157). Bile contaminated with contrast media during ERCP had pseudo-microlithiasis, mimicking calcium bilirubinate granules. This effect was observed with both the high-osmolar contrast medium sodium amidotrizoate and the low-osmolar medium iohexol. The authors concluded that bile collected during ERCP to be examined for microlithiasis should be collected without contamination by contrast agents. If this is not possible, pathologists should be aware that contrast media can cause pseudo-microlithiasis. Awareness of this effect may prevent unnecessary cholecystectomy.

Pancreas

Contrast agents can cause transitory enlargement of the pancreas (SEDA-11, 411). Oral and intravenous cholangiography have very rarely been reported to precipitate acute pancreatitis (158).

An experimental study has suggested that intravenous injection of contrast media can cause increased mortality associated with severe pancreatitis (SEDA-19, 425). There was little difference between ionic and non-ionic agents. The authors argue that contrast-enhanced CT should be avoided in patients with severe pancreatitis as it can exacerbate it.

Acute pancreatitis is a well-recognized complication of ERCP, and contrast media have been incriminated in its pathogenesis. It has been suggested that the use of low-osmolar non-ionic contrast media may minimize the risk. However, this has not been proven conclusively.

The iso-osmolar non-ionic dimer iotrolan and the low-osmolar ionic monomer iopromide (osmolarity about twice that of the blood) have been compared in 40 patients who underwent ERCP (159). They were randomized to receive either iopromide (iodine 300 mg/ml, 770 mosmol/kg, mean dose 15 ml) or iotrolan (iodine 300 mg/ml, 320 mosmol/kg, mean dose 12 ml). Pancreatitis after ERCP occurred in two patients given iopromide and in five given iotrolan. There were no significant differences between the groups in the time-course of changes in serum pancreatic enzyme activities, changes in acute-phase proteins, or the incidence of abdominal pain.

Experimental data suggest that high-osmolar ionic contrast media are more likely to cause chemical irritation of the pancreas, precipitating pancreatitis (159). However, clinical trials have not shown a clear advantage in using non-ionic media in ERCP. For example, in the above-mentioned study, iotrolan did not offer an advantage compared with iopromide (159). The authors suggested that overfilling of the pancreatic duct with contrast medium could be an important factor in the pathogenesis of ERCP-induced pancreatitis and that careful technique is important to avoid this complication.

Urinary tract

The kidney is the main route of elimination of water-soluble contrast agents. Ideally, the agents should be filtered without causing functional or structural changes in the kidney. Unfortunately, this is far from attainable and these agents cause altered renal function and structural changes in the renal tubules. These effects are usually of no clinical significance in patients with normal kidneys. However, in the presence of renal impairment, further significant deterioration in renal function can occur and can lead to significant morbidity and even mortality in some cases (4). Clinical experience has shown that non-ionic low-osmolar contrast media are less nephrotoxic than high-osmolar agents, particularly in patients with pre-existing renal impairment (SEDA-19, 428). However, renal tolerance of the different commercial formulations of non-ionic agents seems to be comparable.

Contrast medium-induced renal damage is associated with impaired renal function (an increase in serum creatinine by more than 25% or 44 μmol/l) within 3 days after the intravascular administration of a contrast medium in the absence of an alternative cause.

Presentation

A slight transitory increase in serum creatinine commonly occurs after the administration of contrast agents, and dysuria can occur. Acute renal insufficiency is uncommon with the agents currently in use, but some 100 fatalities were reported with bunamiodyl sodium. The mechanism is not clear; diffuse acute tubular necrosis, sometimes with crystals of calcium salts, has been found at biopsy or autopsy (160). A reduction in creatinine clearance within the reference range is common. The possibility that these agents might simply block the renal tubules has been advanced, but they are only present in the urine in small amounts in their non-conjugated, that is relatively insoluble, form. An effect on uric acid excretion might be involved. In any event, sufficient fluid should be given to ensure an adequate flow of urine.

The term "contrast nephrotoxicity" implies that impairment in renal function (an increase in serum creatinine by more than 25% or 44 μmol/l) has occurred within 3 days after the intravascular administration of contrast agents and the absence of an alternative cause (161). The increase in serum creatinine, which reflects a reduction in glomerular filtration rate, often peaks within 3–4 days after the administration of contrast agents. Mild proteinuria and oliguria can also occur. However, most patients with contrast nephrotoxicity tend to be non-oliguric, except those with pre-existing advanced chronic renal insufficiency. Heavy proteinuria is an unusual feature of contrast medium nephrotoxicity (162). Urinary enzymes are often increased after the administration of contrast agents. However, no relation has been established between a reduced glomerular filtration rate, a raised serum creatinine (the characteristic features of contrast nephrotoxicity), and the presence of enzymuria after the administration of contrast agents. It is therefore argued that the detection of urinary enzymes is of little importance to the clinical assessment and management of contrast medium nephrotoxicity (163). A persistent nephrogram on plain radiography or CT of the abdomen for 24–48 hours after the injection of a contrast agent has also been described as a feature of contrast nephrotoxicity

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(162,164). This sign is now considered to be non-specific and can be observed in a number of cases without nephrotoxicity (165). However, the presence of this sign may discourage the administration of further doses of contrast agents (161). Fortunately, most episodes of contrast medium nephrotoxicity are self-limiting and resolve within 1–2 weeks. Permanent renal damage is rare and occurs only in a very few instances. However, contrast medium nephrotoxicity can increase the risk of severe non-renal complications and prolong hospital stay (4,161).

Contrast nephrotoxicity can be confused with the syndrome of atheroembolism that can occur after angiography. This condition is not caused by contrast agents, but results from trauma to atherosclerotic blood vessels, precipitating cholesterol microemboli. The clinical picture is characterized by acute renal insufficiency associated with distal digital infarction and skin mottling. Renal histology shows the pathognomonic microvascular cholesterol emboli (4).

Incidence

There are wide variations in the reported incidence of contrast nephrotoxicity because of differences in patient selection, the type of radiological procedure, and the definition of renal impairment. Contrast nephrotoxicity is relatively uncommon in people with normal renal function, in whom it is 0–10%. Pre-existing renal impairment increases the frequency, with a reported incidence of 12–27% in several prospective controlled studies. In some studies the incidence was as high as 50%, in spite of the use of low-osmolar contrast agents and adequate hydration. Dialysis may be required in some of these patients (SEDA-22, 502).

The causes of acute renal insufficiency have been surveyed in elderly patients (over 60 years) admitted to a hospital in India over 12 months (166). Of 4176 patients 59 (1.4%) developed acute renal insufficiency during hospitalization. Contrast medium injection was the culprit in 10 patients.

The incidence of contrast-induced renal damage has been investigated in 100 consecutive trauma patients (mean age 37 years) who underwent angiographic embolization (mean dose of contrast agent "non-ionic low osmolar" 248 ml) for bleeding in the abdomen or pelvis (167). None had diabetes or renal impairment before the injury (mean baseline serum creatinine 88 μmol/l). The serum creatinine increased by more than 25% of baseline in five patients, and returned to baseline within 5 days.

Comparative studies

The renal effects of iodixanol 40–100 ml and iohexol 42–102 ml have been compared in 116 patients undergoing renal and/or peripheral angiography (168). The two groups had the same baseline renal function and prevalence of diabetes. The serum creatinine rose by more than 10% in 15% of the patients given iodixanol and in 31% of the patients given iohexol and by more than 25% in 3.7% of the patients given iodixanol and in 10% of the patients given iohexol during the week after angiography. There was a correlation between the dose of contrast medium and the change in serum creatinine in both groups. These results suggest that iodixanol may be slightly less nephrotoxic than iohexol. However, previous reports have failed to show a significant difference between the non-ionic dimers and non-ionic monomers in relation to renal tolerance. The authors suggested that factors other than contrast media may have contributed to the rise in serum creatinine in some of their patients.

The renal effects of low-osmolar contrast agents (iopromide, ioversole, and ioxaglate) have been evaluated in 45 patients who underwent cardiac angiography (169). Iopromide (iodine 370 mg/ml, mean dose 1.9 g/kg) was used in 15 patients (mean age 62 years, mean serum creatinine 107 μmol/l, mean creatinine clearance 67 ml/minute), ioversole (iodine 320 mg/ml, mean dose 1.8 g/kg) in 15 patients (mean age 62 years, mean serum creatinine 103 μmol/l, mean creatinine clearance 71 ml/minute), and ioxaglate (iodine 320 mg/ml, mean dose 1.8 g/kg) in 15 patients (mean age 63 years, mean serum creatinine 100 μmol/l, mean creatinine clearance 71 ml/minute). All were normally hydrated and none had been examined with contrast agents in the months before the study or had been treated with nephrotoxic drugs. There were minor increases in serum creatinine 24 hours after ioversole (from 103 to 107 μmol/l) and ioxaglate (from 100 to 106 μmol/l) and at 48 hours after iopromide (from 107 to 115 μmol/l). Plasma concentrations of $beta_2$-microglobulin increased only with ioxaglate (from 1.9 to 2.0 micrograms/ml at 24 hours). There was a reduction in creatinine clearance from 71 to 55 ml/minute only with ioxaglate 6 hours after the administration, but it returned to baseline 24 hours later. There were no significant variations in creatinine clearance at 48 hours after angiography. There were increases in the activities of different tubular enzymes in the urine after angiography with all the contrast agents, but the changes were larger after ioxaglate. The tubular effects were maximum at 6–24 hours and returned to baseline within 72 hours after angiography. In summary, all three low-osmolar contrast agents caused reversible tubular damage, indicated by increased enzymuria, which was higher after ioxaglate. In addition, ioxaglate slightly impaired glomerular function. None of the observed changes in renal function were clinically relevant and they were not statistically significant. In summary, none of the three low-osmolar contrast agents caused significant changes in renal function. However, the authors suggested that ioxaglate is probably more nephrotoxic than non-ionic monomeric agents, and that other physicochemical properties beside osmolality play a role in nephrotoxicity due to contrast agents.

Placebo-controlled studies

The clinical and biological tolerance of iobitridol (Xenetix, a non-ionic medium, osmolality 915 mosmol/kg at an iodine concentration of 350 mg/ml) has been assessed in a placebo-controlled study in 21 patients with chronic renal insufficiency (glomerular filtration rate less than 60 ml/minute) (170). Serum creatinine and creatinine clearance remained stable 24 and 48 hours after the procedure. No patient had a nephrotoxic reaction or acute oliguria. Only one patient given iobitridol had an increase in serum creatinine of more than 15% from baseline; the serum creatinine normalized within 4 days of contrast administration. One patient given placebo had

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a similar increase in serum creatinine, which recovered within 48 hours. The author suggested that the use of non-ionic media such as iobitridol should result in a substantial reduction in the incidence of contrast nephropathy.

Susceptibility factors

There are several susceptibility factors for the development of contrast agent-induced renal damage, including pre-existing renal insufficiency, particularly if it is secondary to diabetes mellitus, dehydration, multiple repeat exposure to contrast media within a short period of time (72 hours), congestive heart failure, or concurrent administration of nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs (171).

- A 45-year-old man with aggressive hypertension underwent abdominal aortography to assess the possibility of renal artery stenosis (172). His baseline renal function was reduced and the serum creatinine was 210 μmol/l. He received 1000 ml of saline solution intravenously as prophylaxis against contrast nephropathy. An unidentified high-osmolar contrast medium was injected into the abdominal aorta above the level of the renal arteries. There were atherosclerotic changes in the abdominal aorta and a discrete stenosis of left renal artery. Oliguria developed 24 hours later and the serum creatinine rose to 350 μmol/l. He was given isotonic saline (2 l/day) with 100 mg of furosemide. After 2 days the serum creatinine concentration fell to 190 μmol/l and his daily urine volume increased to 1.6 l/day.

The risk of contrast-induced acute renal insufficiency is particularly high in patients with diabetic nephropathy. Diabetes mellitus per se without renal impairment is not a susceptibility factor. The degree of renal insufficiency before the administration of contrast agents largely determines the severity of the nephrotoxicity. Old age (over 60 years), dehydration, and congestive cardiac failure are also risk factors. Multiple myeloma has been considered in the past as a risk factor for contrast nephrotoxicity. However, if dehydration is avoided, low-osmolar contrast agents rarely cause acute renal insufficiency in patients with myeloma. The concurrent use of nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides, potentiates the nephrotoxic effects of contrast media. The importance of hypertension, hyperuricemia, or proteinuria per se as susceptibility factors for contrast nephrotoxicity is not clear (161,162). Large doses of contrast agents and multiple injections within 72 hours increase the risk of contrast nephrotoxicity. However, it has been reported that the intravenous administration of high doses of low-osmolality non-ionic iodinated contrast agent is safe in patients who have no pre-existing renal dysfunction or other underlying risk factors, even if doses as high as 800 ml are used (SEDA-21, 479). The route of administration is also important, and contrast agents are less nephrotoxic when administered intravenously than when given intra-arterially into the renal arteries or the aorta proximal to the origin of the renal blood vessels. The acute intrarenal concentration of contrast agent is much higher after intra-arterial injection than after intravenous administration. The type of contrast agent is also an important predisposing factor for contrast nephrotoxicity. High-osmolar contrast media are more nephrotoxic than low-osmolar contrast media, particularly in patients with pre-existing renal impairment. Whether the non-ionic dimers, which are iso-osmolar and highly hydrophilic, are less nephrotoxic is not yet clear. Clinical experience has so far shown no difference in the renal tolerance of non-ionic monomers and the iso-osmolar dimers (161).

The pharmacokinetics and safety of the low-osmolar non-ionic contrast agent iomeprole have been investigated in healthy volunteers and patients with various degrees of renal impairment (173). Six patients had normal renal function (glomerular filtration rate over 100 ml/minute, aged 22–58 years), six had mild renal impairment (glomerular filtration rate 51–75 ml/minute, aged 36–74 years), six had moderate renal insufficiency (glomerular filtration rate 26–50 ml/minute, aged 58–79 years), and four had severe renal impairment (glomerular filtration rate below 25 ml/minute; aged 34–73 years). Eight patients (aged 24–62 years) with end-stage renal disease who were receiving chronic hemodialysis were also studied. All received a single intravenous 50 ml bolus injection of iomeprole (iodine 400 mg/ml) and dialysis was performed about 2 hours later. The half-life of iomeprol increased progressively with increasing renal impairment. The half-life was 2 hours in patients with normal renal function, 4–6 hours in those with mild renal impairment, and 16–48 hours in those with severe renal impairment. Fecal excretion over 120 hours ranged from 1.6% of the total dose in healthy subjects to 7.2% in those with severe renal impairment. Thus, the pharmacokinetics of iomeprole are similar to those of other water-soluble contrast agents.

Hepatic cirrhosis is not a susceptibility factor, according to the results of a study in 72 patients with hepatic cirrhosis and 72 controls, who received 100–150 ml of low-osmolar contrast media intravenously for abdominal or chest CT scans (174). Serum creatinine was measured before and 48–72 hours after the administration of the contrast agent. The incidence of contrast nephrotoxicity was comparable in the two groups (two patients in the cirrhosis group and one control).

The type and dose of contrast media are important factors in the development of contrast nephrotoxicity. In patients with pre-existing renal impairment, low-osmolar non-ionic contrast agents are less nephrotoxic than high-osmolar agents and the iso-osmolar non-ionic dimers are less nephrotoxic than the low-osmolar non-ionic monomers. In 129 diabetic patients (mean age 71 years) with renal impairment (baseline serum creatinine 133–309 μmol/l) requiring angiographic examinations, the iso-osmolar dimer iodixanol ($n = 64$) was significantly less nephrotoxic than the low-osmolar non-ionic monomer iohexol ($n = 65$) (175). The incidence of contrast nephrotoxicity was 3% in the iodixanol group and 26% in the iohexol group. The authors concluded that iodixanol has low nephrotoxicity and should be the contrast agent of choice in patients at high risk of this complication.

Pathophysiology

The pathophysiology of contrast nephrotoxicity involves a reduction in renal perfusion caused by a direct effect of

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contrast agents on the kidney and toxic effects on the tubular cells. The mechanisms responsible for the reduction in renal perfusion involve tubular and vascular events. The endogenous vasoactive peptide endothelin seems to play an important role in mediating the nephrotoxic effects (SEDA-20, 421) (161).

Renal damage can occur in infants who receive large doses of ionic contrast agents during cardioangiography. Fatal cases after doses of more than 3 ml/kg had renal medullary necrosis or severe proximal tubular vacuolation. In other infants, such doses have produced microscopic hematuria. Renal necrosis has occurred in infants after intravenous administration of sodium diatrizoate 1–3 ml/kg, but these children were in very poor general condition. In high-risk adults, cardioangiography can similarly cause contrast nephropathy (SEDA-15, 501).

In abdominal aortography, the contrast agent reaching the renal parenchyma is relatively undiluted, so that factors of concentration and volume are more important, particularly if a bolus of high concentration is accidentally injected directly into the renal artery. In the early days of abdominal aortography, renal damage was a significant hazard, mainly because the agents then in use were relatively toxic, but at high doses or high concentrations the agents now used can also cause renal damage. In 400 patients undergoing angiography with high doses of an ionic contrast agent, the overall incidence of acute renal dysfunction was 11%, but in patients with pre-existing renal disease the incidence was 42%. Injections close to the renal arteries are more likely to cause renal damage than a similar dose of contrast agent injected intravenously for digital vascular imaging (SEDA-9, 408). In a patient with renal artery stenosis an intra-aortic injection of 30 ml of 50% methylglucamine diatrizoate at the level of the renal arteries resulted in oliguria with pyrexia within a few hours, and the urine output only gradually recovered over about 2 months (176). Diabetes was a predisposing factor in another case (SED-12, 1177) (177). In two other cases, renal insufficiency was followed by nephrogenic diabetes insipidus and nephrotic syndrome (SED-8, 1042) (178).

Contrast media, particularly high-osmolar agents, can cause a significant natriuresis and diuresis. In 42 patients who underwent cardiac angiography, the fractional excretion of sodium, the urinary excretion of the renal natriuretic peptide urodilatin, and the plasma concentration of atrial natriuretic peptide were measured before and after intravascular diatrizoate (an ionic high-osmolar contrast agent) 55 ml, or the non-ionic agent iopamidol 200 ml (179). None of the patients had diabetic nephropathy or multiple myeloma. Diuretics, angiotensin converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs were withheld for at least 12 hours before the examination, and 11 patients received a mean of 600 ml of isotonic saline intravenously before and during angiography, because of mild chronic renal insufficiency. The other 31 received no volume expansion. Both groups received a similar volume of radiocontrast agent. After angiography the plasma concentration of atrial natriuretic peptide and the urinary excretion of urodilatin both increased. Urinary urodilatin excretion correlated with an increase in the fractional excretion of sodium. There was no correlation between the serum concentration of atrial natriuretic peptide and urinary sodium excretion. This study suggests that the intravascular administration of contrast agents causes a natriuresis associated with the urinary excretion of urodilatin. This is consistent with the hypothesis that urodilatin may contribute to sodium excretion after radiocontrast administration in a paracrine manner.

Transient proteinuria is common after aortography and selective nephroangiography, because of an increase in glomerular permeability. Ioxaglate, iopamidol, and iohexol cause only negligible proteinuria (SEDA-8, 428) (SEDA-11, 413).

Enzymuria has been reported after the intravascular administration of high-osmolar or low-osmolar contrast media (180). The study suggested that the brush-border enzyme gamma-glutamyl transpeptidase is a better marker for tubular toxicity due to contrast media than alanine aminopeptidase. However, no relation has been established between a reduction in glomerular filtration rate, a rise in serum creatinine (the characteristic features of contrast nephrotoxicity), and the presence of enzymuria. It has been argued that the detection of urinary enzymes is of little importance to the clinical assessment and management of contrast medium nephrotoxicity (161).

In patients who have received iodinated contrast media, urinary beta$_2$-microglobulin, albumin, epidermal growth factor, and gamma-glutamyl transpeptidase, *N*-acetyl-beta-D-glucosaminidase, and serum angiotensin-converting enzyme (ACE) activities are sensitive markers for the early detection of subclinical contrast medium-induced nephrotoxicity (181). At 24 hours after injection of contrast agents in 16 patients (aged 18–62 years, nine men), serum ACE and urinary beta$_2$-microglobulin, albumin, and enzymes were significantly raised. At 48 hours, serum creatinine concentrations increased significantly and urinary excretion of albumin remained significantly increased, but urinary enzyme excretion began to recover. Urinary excretion of epidermal growth factor was significantly reduced, due to tubular injury; healthy tubular cells release this factor into the urine and it is not filtered at the glomeruli. The observation that urinary albumin excretion continued to increase after the urinary enzymes started to recover suggests that the albuminuria induced by contrast media is probably due to glomerular and not tubular dysfunction. The mechanism of the rise in serum ACE activity is not known, but it may be due to damage to the vascular endothelial cells of glomeruli, ACE release from the brush borders of the epithelial cells of the proximal tubules, or an increase in vascular permeability and leakage of the enzyme into the blood.

Acute reduction in renal perfusion is considered important in the pathophysiology of contrast agent-induced nephrotoxicity. Color-coded duplex sonography has been used in assessing intrarenal vascular resistance in 10 patients (mean age 51 years) after intravenous injection of 100 ml of the low-osmolar contrast medium iopamidol (iodine 300 mg/ml) (182). The resistive index was measured at 1-minute intervals over 10 minutes after injection in each patient. There was a statistically significant rise in resistive index at 2, 3, 4, and 5 minutes after injection, mean values 0.74, 0.75, 0.72, and 0.75

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respectively. The resistive index then fell progressively to baseline values (mean 0.70) within 10 minutes. The authors concluded that color-coded duplex sonography is a simple method for checking changes in renal flow resistance after intravascular contrast agents. They suggested that arterial Doppler flow measurement is ideal for investigating the pathophysiological mechanism of contrast agent-induced nephrotoxicity.

Prevention

Prevention of contrast nephropathy rests largely on the exclusion of high-risk cases, such as very ill patients with diabetic renal insufficiency, severe cardiovascular disease with reduced renal blood flow, jaundice, pre-existing uremia, and multiple myeloma. When the investigation is nevertheless needed in these conditions, the lowest possible dose of a low-osmolar non-ionic contrast medium should be used in patients at high risk of this complication. High-osmolar contrast media and large doses should be avoided. In addition, intravenous hydration with saline (1 ml/kg /hour for 4–6 hours before contrast injection to be continued for 12 hours afterwards) should be given. The concomitant use of other potentially nephrotoxic agents should be avoided. Finally, since the small amounts of contrast agent that remain in the body after a radiographic examination can potentiate renal damage resulting from subsequent events, there should be a delay of at least 12 hours after the examination before undertaking any surgery that could adversely effect the kidney, for example, procedures requiring temporary renal clamping or percutaneous balloon dilatation of the renal artery. A similar delay is advised between cerebral angiography and renal harvesting for transplantation. If renal glomerular filtration is reduced by 50% or more, a delay of 24 hours or more may be advisable after aortofemoral angiography (SEDA-15, 502).

Saline

Whether half-strength or isotonic saline should be used has been investigated in 809 patients who received half-strength saline and 811 patients who received isotonic saline (183). The two groups were matched in relation to baseline characteristics, and the mean serum creatinine before contrast injection was 80 μmol/l. All underwent coronary angioplasty using the low-osmolar non-ionic contrast medium iopromide (mean volume 234 ml). The incidence of contrast nephrotoxicity in those who received isotonic saline was 0.7% and in those who received half-isotonic saline it was 2%. The authors concluded that isotonic saline is superior to half-strength solution in reducing the incidence of contrast media nephrotoxicity.

Hemodialysis

Although hemodialysis is effective in removing contrast media from the body, its ability to prevent contrast nephrotoxicity has been disappointing. Hemodialysis after contrast administration in patients with pre-existing renal impairment does not prevent contrast nephropathy (SEDA-22, 502) because of the very rapid onset of renal damage (SEDA-21, 481) (SEDA-22, 501), since the effect of contrast media on the kidney after intravascular administration is almost instant and hemodialysis is usually offered at best 30–60 minutes after the procedure, which is too late to prevent the effects of contrast media on the kidney.

In patients with pre-existing renal impairment, hemodialysis did not influence the incidence or outcome of contrast-induced nephropathy, in spite of eliminating contrast agents effectively from the circulation. The same group has now confirmed their previous observation in a bigger study in 30 patients with pre-existing renal impairment (184). Hemodialysis did not influence the incidence or outcome of contrast-induced nephropathy, in spite of effective elimination of contrast medium from the circulation. The failure of hemodialysis to protect against the development of contrast nephropathy is due to the very rapid onset of renal injury after the administration of contrast medium.

The use of hemodialysis immediately after intravascular administration of contrast agents to prevent the development of nephrotoxicity in patients with renal impairment has been investigated in 15 patients with a mean serum creatinine of 234 μmol/l before contrast injection (185). The patients were randomized to receive either conservative treatment or hemodialysis for 2–3 hours, starting as early as possible (mean 106 minutes) after administration of the contrast agent. The increase in serum creatinine on days 2 and 3 after contrast injection was higher in the dialysed group. The incidence of nephrotoxicity, defined as an increase in serum creatinine by more than 44 μmol/l within 48 hours after administration of the contrast agent, was significantly higher in the dialysed group (43 versus 13%). The authors concluded that hemodialysis performed within 2 hours after contrast injection did not prevent the development of nephrotoxicity in patients with reduced renal function; indeed, it seems to have made things worse.

The use of prophylactic hemodialysis, in most cases starting more than 20 minutes after injection of a contrast agent, has been investigated in 113 patients with renal insufficiency (serum creatinine concentration over 200 μmol/l) (186). Hemodialysis did not reduce the incidence of contrast nephrotoxicity. This failure could have been related to the rapid onset of renal injury after the administration of the contrast agent.

The Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) has produced useful guidelines on dialysis and the intravascular use of contrast media (Table 4) and has reviewed the literature on this subject (187). In addition, they have produced guidelines on the prevention of contrast medium-induced renal damage (Table 5) following a consensus of experts in this field and of members and fellows of the society (188).

Acetylcysteine

The antioxidant *N*-acetylcysteine has also been recommended to reduce the risk of contrast nephrotoxicity. *N*-acetylcysteine 600 mg bd for 2 days, starting the day before the examination, in addition to hydration, reduced the incidence of contrast nephrotoxicity in 41 patients (189). The incidence of contrast nephrotoxicity was 2%

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Table 4 European Society of Urogenital Radiology (ESUR) simple guidelines on dialysis and contrast media administration (188)

Patients on dialysis	Recommendations
Hemodialysis (all contrast media can be removed by hemodialysis)	Avoid osmotic and fluid overload Correlation of the time of contrast media injection with the hemodialysis session is unnecessary Extra hemodialysis session for removal of contrast media is unnecessary
Continuous ambulatory peritoneal dialysis (CAPD) (all contrast media can be removed by peritoneal dialysis)	X-ray examinations To protect residual renal function, refer to ESUR guidelines to avoid contrast medium-induced renal damage Hydration should be considered only after careful evaluation of fluid balance state of the patient Hemodialysis is unnecessary MRI scans To protect residual renal function, use doses under 0.3 mmol/kg of gadolinium-based contrast agents
Patients with severely reduced renal function	Refer to ESUR guidelines to avoid contrast medium-induced renal damage (hydration, use small doses of low-osmolar contrast media) Hemodialysis is unnecessary In MRI avoid doses over 0.3 mmol/kg of gadolinium-based contrast agents

Table 5 European Society of Urogenital Radiology (ESUR) simple guidelines to avoid Contrast Medium Nephrotoxicity (227)

Definition	Contrast medium nephrotoxicity is a condition in which an impairment in renal function (an increase in serum creatinine by more than 25% or 44 μmol/l) occurs within 3 days after the intravascular administration of a contrast medium in the absence of an alternative cause
Susceptibility factors	Raised serum creatinine concentration, particularly secondary to diabetic nephropathy Dehydration Congestive heart failure Age over 70 years Concurrent administration of nephrotoxic drugs, for example NSAIDs
In patients with susceptibility factors	*Do* Make sure that the patient is well-hydrated; give at least 100 ml/hour orally (for example soft drinks) or intravenously (isotonic saline) depending on the clinical situation, starting from 4 hours before to 24 hours after contrast administration; in hot climates increase the fluid volume Use low-osmolar or iso-osmolar contrast media Stop administration of nephrotoxic drugs for at least 24 hours Consider alternative imaging techniques that do not require the administration of iodinated contrast media *Do not* Give high-osmolar contrast media Administer large doses of contrast media Administer mannitol or diuretics, particularly loop-diuretics Perform multiple studies with contrast media within a short space of time

in patients who received acetylcysteine (baseline serum creatinine 220 μmol/l) following intravenous injection of 75 ml of low-osmolar non-ionic contrast media, and 21% in controls (baseline serum creatinine 211 μmol/l). However, the dose of contrast medium used was rather small and the patients did not have advanced renal impairment before contrast injection.

A study from Germany has shown that the antioxidant acetylcysteine plus intravenous saline 0.45% prevented the reduction in renal function induced by contrast agents (190). The authors prospectively studied 83 patients with chronic renal impairment (creatinine clearance under 50 ml/minute). The patients took oral acetylcysteine 600 mg bd for 1 day before and 1 day after the contrast medium. Saline 0.45% was given intravenously at a rate of 1 ml/kg/hour for 12 hours before and 12 hours after 75 ml of iopromide (iodine 300 mg/ml) intravenously. All the patients were encouraged to drink if they were thirsty. A matched control group received placebo and saline. The mean serum creatinine in the control group (42 patients, mean age 65 years) rose from a mean of 212–226 μmol/l 48 hours after contrast injection. In those given acetylcysteine (41 patients, mean age 66 years) the serum creatinine was 220 μmol/l before contrast injection and 186 μmol/l 48 hours after. One patient given acetylcysteine and nine controls developed contrast-induced nephrotoxicity. This suggests that the prophylactic oral administration of the antioxidant acetylcysteine in patients who are adequately hydrated with saline prevents contrast-induced nephrotoxicity in patients with chronic renal insufficiency. The main limitation of this study was the relatively small dose of intravenous contrast medium used (75 ml). It is important to determine whether acetylcysteine plus saline would still offer the same protection if higher doses of contrast media were used or if the agent was given intra-arterially.

Calcium channel blockers

In addition to using a small dose of low-osmolar non-ionic contrast medium and offering hydration, some authors have recommended the use of calcium channel blockers in patients at high risk of contrast nephrotoxicity. However, the effectiveness of this class of drugs in preventing contrast nephrotoxicity has not been consistently

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proven, particularly in patients with pre-existing advanced renal disease (191). Furthermore, some studies have suggested that the prophylactic administration of renal vasodilators, such as dopamine or calcium channel blockers, could have a deleterious effect, particularly in patients with diabetic nephropathy (SEDA-18, 444) (161). There is no conclusive evidence that these drugs are effective, particularly in patients with diabetic nephropathy who are at high risk of this complication (SEDA-19, 428).

Dopamine receptor agonists

In a study from the USA, dopamine was effective in preventing further deterioration in renal function in patients with a raised serum creatinine undergoing angiography for lower limb ischemia (192). Dopamine (2.5 mg/kg) was given to 28 patients beginning 1 hour before injection of contrast medium (Omnipaque 300, mean volume about 140 ml) and continuing for a total of 12 hours. Patients in the control group received an equal volume of isotonic saline. Serum creatinine was measured daily for 4 days after arteriography. Dopamine reduced the incidence of contrast nephrotoxicity (defined as an increase in the baseline serum creatinine concentration over 44 μmol/l) from 44 to 18%. Previous studies have not shown any protective effect of dopamine against contrast-induced nephropathy, in spite of marked increase in renal blood flow shown in a study of patients undergoing cardiac catheterization (161).

A report from Italy has suggested that intravenous saline 0.4% before and after administration of the contrast medium, an infusion of dopamine 3 micrograms/kg/minute for 24 hours after the contrast medium, intravenous furosemide 80 mg 30 minutes before the contrast medium, or intravenous mannitol (20%) 250 ml 1 hour before and 1 hour after the contrast medium each prevented the reduction in renal function caused by the non-ionic agents iobitridol, ioversol, or iodixanol (193). However, the protocol of the study was not described, and previous studies have shown that dopamine, furosemide, and mannitol do not offer good protection against contrast media-induced nephrotoxicity. On the other hand, volume expansion with intravenous saline has been found to offer some protection (190).

Fenoldopam, a selective dopamine D_1 receptor agonist, has also been advocated to reduce the risk of contrast nephrotoxicity. It is a renal vasodilator and increases glomerular infiltration rate. The authors of a review of studies that used fenoldopam to prevent contrast nephrotoxicity concluded that it offers good protection (194). In another study, the incidence of contrast nephrotoxicity was 4.7% in patients who received intravenous fenoldopam 0.1 micrograms/kg/minute starting 15–20 minutes before contrast injection and continued for 6 hours after and 19% in controls (195). However, fenoldopam has not been consistent in offering good protection against contrast nephrotoxicity, it has to be given by intravenous infusion, and it requires careful monitoring of blood pressure and dosage adjustment if hypotension develops.

Endothelin receptor antagonists

Although endothelin is considered to be an important mediator of the renal effects of contrast media, a report from the USA has shown that prophylactic administration of a non-selective endothelin receptor antagonist not only did not protect against contrast nephrotoxicity but exacerbated it (196). In this study, 158 patients with chronic renal insufficiency (mean serum creatinine 242 μmol/l) undergoing cardiac angiography were randomized to receive either the non-selective endothelin antagonist SB290670 (mean age 65 years, 51 men, 26 women) or placebo (mean age 67 years, 59 men, 22 women). The mean doses of contrast medium were 104 ml in the SB290670 group and 122 ml in the placebo group. Only low-osmolar radiographic contrast media were used. The dose of SB290670 was 100 micrograms/kg over 10 minutes followed by an infusion of 1 microgram/kg/minute starting 30–150 minutes before administration of contrast medium and continuing for 12 hours after. All the patients received intravenous hydration with saline 0.45% (1 ml/kg/hour) beginning 2–12 hours before contrast medium and continuing for at least 12 hours after. The mean increase in serum creatinine 48 hours after angiography was higher with SB290670 than placebo (64 versus 34 μmol/l). The incidence of radiocontrast nephrotoxicity was significantly higher with SB290670 than placebo (56 versus 29%). The authors concluded that a non-selective endothelin receptor antagonist may increase the incidence of contrast media nephrotoxicity and they questioned the role of endothelin in mediating the renal effects of contrast media. However, there were flaws in the design of this study. First, the endothelin receptor antagonist was administered only for a maximum of 12 hours after contrast examination—a longer period (2–3 days) should have been considered, since the reduction in renal function after contrast examination peaks at 48–78 hours, and in previous studies a single dose of nitrendipine 20 mg did not prevent contrast nephrotoxicity, whereas 20 mg/day for 3 days offered good protection. Secondly, a non-selective endothelin receptor antagonist is probably not suitable for the prevention of contrast nephrotoxicity. Blocking endothelin B receptors does not offer an advantage, since these receptors mediate renal vasodilatation and they also act as clearance receptors for endothelin. B receptor blockade could have caused the raised plasma endothelin concentrations that were observed in the treated group and may explain why the non-selective endothelin antagonist exacerbated contrast medium nephropathy. A selective endothelin A receptor antagonist should be studied before a role for this class of drugs in preventing contrast nephrotoxicity is excluded.

Theophylline

Theophylline, a non-selective adenosine receptor antagonist, has also been recommended, since adenosine has been suggested to be an important mediator of contrast-induced nephrotoxicity. Patients undergoing coronary angiography with the high-osmolar contrast medium diatrizoate (iodine 370 mg/ml) were randomized to receive either theophylline (200 mg bd orally 24 hours before and for 48 hours after coronary angiography, $n = 35$, mean age 54 years, mean dose of contrast medium 78 ml) or placebo ($n = 35$, mean age 52 years, mean dose of contrast medium 80 ml) (197). The glomerular filtration rate

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at 48 hours was reduced by 36% (from a mean of 85 ml/minute to a mean of 67 ml/minute) in the placebo group and by 9% in the theophylline group. Contrast nephrotoxicity, defined as a fall in glomerular filtration rate by 25% or more from baseline at 48 hours developed in 11 patients in the control group and only in one patient in the theophylline group. The authors concluded that nephrotoxicity induced by high-osmolar contrast media can be reduced by prophylactic administration of theophylline.

The protective effect of theophylline against contrast media nephrotoxicity has also been shown in another study (198). Intravenous theophylline 100 mg 30 minutes before intravascular administration of 100 ml of low-osmolar contrast medium offered good protection against contrast nephrotoxicity in patients with chronic renal insufficiency (mean serum creatinine 183 μmol/l). The incidence of contrast nephrotoxicity was 4% in the theophylline group and 16% in the placebo group (base line serum creatinine 110 μmol/l). The authors concluded that theophylline offers good protection against contrast nephrotoxicity in patients with pre-existing renal impairment. However, the dose of contrast medium was relatively small (100 ml) and the pre-existing renal impairment was not advanced. The consistency of theophylline in offering good protection against contrast nephrotoxicity has not been confirmed at higher doses of contrast media and in patients with more advanced renal disease.

Comparative studies

The protective effects of intravenous hydration alone (0.45% isotonic saline, 1 ml/kg/hour for 12 hours before and 12 hours after contrast administration), fenoldopam (0.1 microgram/kg/minute for 4 hours before and 4 hours after the procedure), and acetylcysteine (600 mg bd 24 for hours before and 24 hours after the procedure) have been compared in preventing contrast nephrotoxicity after intravascular administration of low-osmolar non-ionic contrast medium (199). The incidence of nephrotoxicity was 15% in the hydration group, 16% in the fenoldopam group, and 18% in the acetylcysteine group. All the groups were comparable and baseline creatinine clearance was about 60 ml/minute in all the patients who received a similar dose of the contrast medium (1.5 ml/kg). The authors concluded that fenoldopam and acetylcysteine do not offer extra protection against contrast nephrotoxicity over hydration alone.

Skin

The incidence of skin reactions to drugs has been analysed from spontaneous reports in Italy (200). Antibiotics most commonly caused skin reactions, followed by NSAIDs, analgesics, and radiocontrast agents, which were responsible for 2.7% of the reactions (71 cases); these included nine cases of exanthemas and 36 cases of urticaria.

Fixed drug eruption caused by non-ionic contrast media is rare (SEDA-22, 502), but has been attributed to the non-ionic contrast medium iomeprol (Iomerone, Bracco) (201).

- A 67-year-old Japanese woman developed multiple pea-sized erythematous plaques on the trunk and extremities 4 days after receiving 100 ml of iomeprol intravenously for a CT scan. She was treated with oral betamethasone 1.5 mg/day and glutathione 300 mg/day for 3 days. She then used topical betamethasone valerate ointment for a month until the erythematous plaques completely disappeared, leaving pigmentation. Six months later she was erroneously given 100 ml of iomeprol intravenously during a CT scan and the next morning developed erythematous plaques mixed with vesicles at the same sites as before. Biopsy showed histological changes compatible with a fixed drug eruption. In addition, both patch testing and intradermal testing were positive to iomeprol.

This report shows that non-ionic contrast media can cause multiple fixed eruptions and that repeated administration of the causative agent can be associated with a more severe eruption.

Rarely typical iododerma, sometimes with other skin and systemic complications, can occur (202) and causes a papulopustular eruption. Vegetating iododerma, in which pustules and vesicles coalesce to form large vegetating masses that later ulcerate, is very rare and its pathogenesis is unclear. A cell-mediated immune reaction, an inflammatory mechanism, and an idiosyncratic reaction in patients with other underlying diseases have been suggested. Iododerma occurs more often in patients with renal insufficiency, because of impaired clearance of contrast media. Oral or topical glucocorticoids have been of some benefit in treating this condition. Vegetating iododerma with a fatal outcome has been reported (203).

- A 65-year-old woman with a history of allergy to penicillin and abnormal renal function had cardiac angiography and a week later became breathless and slightly febrile and developed pustulovesicular lesions on the face, elbows, and legs. The lesions on the face coalesced into vegetating masses. Cultures from the skin lesions did not yield bacteria, fungi, or mycobacteria. Histological examination of the vegetating mass showed an inflammatory exophytic lesion with an ulcerated surface and an inflammatory infiltrate consisting mainly of neutrophils and eosinophils in the dermis. The lesions responded to 1:1000 copper sulfate solution. However, she continued to deteriorate despite hemodialysis and died 6 days later.

In this patient, renal insufficiency contributed to the development of iododerma and her death was due to poor cardiorespiratory function.

Delayed skin rashes have been noted in 5% of patients undergoing urography. Allergic-like skin reactions to intravascular contrast media can develop 24–96 hours after administration (204).

- A 73-year-old woman underwent CT scanning with contrast enhancement (250 ml of intravenous iopentol, a non-ionic contrast medium, iodine 300 mg/ml) for staging a malignant melanoma. Four days later she developed progressive pruritus beginning on the back and neck. On the sixth day she had a disseminated pruriginous papular partially confluent exanthema involving the trunk, neck, and proximal extremities. The eruption became generalized while she was receiving local corticosteroids and oral clemastine. Remission

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of the eruption was achieved with intravenous prednisolone 64 mg and dimethindene maleate 12 mg. Patch and intracutaneous tests to iopentol, but not to other contrast media, evoked a red indurated skin reaction after 48 and 72 hours. Histology and immunocytochemistry of the skin test site to iopentol showed an infiltrate consisting mainly of CD45RO+ and CD4+ lymphocytes together with eosinophils.

This reaction shared the features of a delayed hypersensitivity reaction (exanthematous rash, positive patch test) and of a late phase reaction (CD4+ lymphocytic infiltrate together with eosinophils). The authors emphasized the importance of skin testing in the diagnosis of delayed skin reactions to contrast media.

Other cases of delayed skin reactions have been reported.

- A 64-year-old woman with a history of an exanthematous skin eruption to an antibiotic and allopurinol had had a previous adverse reaction after angiography with radiographic contrast media. Her symptoms had included shivering and a generalized pruritic exanthema. Then, 30 minutes after intravenous angiography with iopromide (a non-ionic contrast medium), she developed shivering and dyspnea immediately followed by loss of consciousness; 3 hours later a generalized pruritic maculopapular rash developed.
- A 63-year-old woman with glomerulonephritis underwent angiography. She had a history of an immediate adverse reaction to lidocaine and of dyspnea, wheeze, and paresthesia of the fingers to repeated infusion of contrast media. Several hours after the last procedure she developed a generalized pruriginous maculopapular rash.
- A 60-year-old man underwent coronary angiography with iopamidol 200 ml. One day later he developed infiltrated erythema of the face with a generalized maculopapular rash. The skin symptoms receded within 1 week after treatment with a corticosteroid ointment. Coronary angiography with iopamidol was repeated 3 years later and again within 1 day a maculopapular rash developed and regressed within a few days with intravenous dimethindene and prednisolone-21-hydrogen succinate.
- A 54-year-old woman and a 68-year-old man developed rashes 24 hours after intravascular injection of iohexol (a non-ionic monomer) (205). The woman developed widespread pruritic erythema and eyelid edema. The man developed a maculopapular rash involving the trunk and legs. Both patients were treated with antihistamines, which resulted in complete recovery within 1 week. The man had slight desquamation of the affected area after his rash resolved. Patch tests were positive to iohexol in both patients. The man also had a positive patch test to iodixanol and the woman was positive to the non-ionic monomer ioversol.

Intracutaneous and patch tests were performed in the first two patients (206) with a series of ionic and non-ionic contrast media in concentrations of 1% according to international guidelines. In the first patient there were late positive intracutaneous and patch tests after 24–48 hours only to some of the tested contrast agents. In the second patient intracutaneous and patch tests showed late reactions to nearly the same contrast media. More than 20 patients with only immediate anaphylactoid reactions to contrast media gave negative results to these tests. The authors concluded that positive skin tests suggest an immunological basis for late reactions to contrast media. In the third case (207) patch and prick skin tests were performed using several iodinated contrast media. Intravenous provocation tests were also performed with several water-soluble contrast media using 5 ml in each case at strengths of 1:1000, 1:100, 1:10, and undiluted. Positive skin tests were observed with iopamidol, and the intravenous provocation test caused infiltrated erythema of the face and generalized maculopapular rashes. Skin biopsies showed heavy lymphohistiocytic infiltration at the site of positive skin tests. The authors concluded that the rashes represented delayed allergy to iopamidol.

Delayed skin reactions after contrast media have the features of true delayed hypersensitivity reactions, including positive skin tests (SEDA-24, 523). A generalized macular rash 24 hours after injection of ioversol with positive skin tests has been reported (208).

- A 61-year-old man received ioversol during a CT examination and 1 day later developed a generalized macular rash, which lasted for 2 weeks. Prick, intradermal, and patch tests with different types of non-ionic contrast media showed a delayed hypersensitivity reaction to ioversol, which lasted for 7 days.

Urticarial or erythematous rashes can occur and persist for a few days. Rarely acute vasculitis, Stevens–Johnson syndrome, and bullous lichen planus have been reported (SEDA-11, 411) (SEDA-14, 422).

- A 33-year-old man had three contrast-enhanced CT scans with iohexol over about 2 weeks, and developed a disseminated erythematous skin rash. Because drug allergy was suspected, all drugs were withdrawn (209). Because of a persistent fever a fourth CT scan was performed with iohexol, and 2 hours later he developed malaise, pruritic erythema, hypotension, and cutaneous bullae affecting 50% of his body surface and his oral mucosa. He was treated for toxic epidermal necrolysis and his skin healed without scarring or altered pigmentation. Skin patch tests, prick tests, intradermal tests, and intravenous and oral single-blind challenges with the antibiotics he had received were negative. However, a patch test with iohexol (iodine 300 mg/ml) was positive at 48 hours: erythema and multiple small flaking blisters appeared in the patch area. Identical patch tests in healthy controls were negative.

Other rarities reported sporadically (but all in more than one case) include the Koebner phenomenon (210), fixed drug eruptions (for example with iotalamate (211)), and delayed reactions of various types. Reports of severe drug eruptions have become more frequent since the introduction of the non-ionic contrast media, but this may simply be due to the fact that in recent years there has been greater awareness of such reactions (SEDA-16, 538) (SEDA-19, 427) (SEDA-22, 502).

Iocetamic acid seems more likely than other agents to cause skin reactions. Persistent urticaria has been seen in cases where iophendylate was used in myelography and the residue remained in situ (SED-12, 1180) (SEDA-16, 536).

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Exacerbation of a lupus-like illness after injection of iodinated contrast agents has been reported (SEDA-9, 411) (SEDA-19, 427). All iodinated contrast agents should be used with caution in patients with systemic lupus erythematosus and perhaps in other types of vasculitis.

Reticulated purpura has been reported after the use of diatrizoate meglumine, a high-osmolar water-soluble contrast agent, for hysterosalpingography (212).

- Within 48 hours of a hysterosalpingogram using diatrizoate meglumine, a 34-year-old woman developed a burning sensation in her left leg, 4 days later developed tenderness and redness on the left posterior thigh and calf, and 4 days after that mottling of the skin of the thigh. Two weeks later she had marked tenderness and purpuric macules in a reticulated pattern on both legs. A skin biopsy showed changes suggestive of erythema multiforme. There was no evidence of vasculitis. The skin lesions persisted unchanged for about 1 week, after which they resolved without treatment.

This clinical picture of reticulated purpura with the formulation of a few bullae has not been previously reported after injection of contrast agents. The histological changes supported the diagnosis of a drug reaction. Although some of the histological findings are seen in erythema multiforme the patient's clinical presentation did not support that diagnosis.

The skin can be involved in allergic reactions after lymphography. Dermatitis has also been described some days after lymphography and apparently due to extravasation of the iodized oil into the tissues (SED-12, 1184) (213). Since lymphography requires an incision, wound infections can occur and rarely lymphangitis.

In 17 of 53 cases with obstructive lymphedema there was an increase in limb volume after lymphangiography with Lipiodol ultrafluid (iodinated poppy seed oil), and 10 cases had features resembling lymphangitis. In one patient there was an allergic reaction, with rapid development of edema and an increase in limb volume by 2 liters. Whereas contrast medium virtually disappears from normal lymphatics within 8 hours, in cases of obstructive lymphedema Lipiodol remains in the lymphatics for several days and it appears to cause a low grade chemical inflammation with obliteration of the lymphatics (SEDA-7, 454).

- A woman with an inoperable carcinoma of the cervix developed reticulohistiocytosis with arthritis and skin papules after lymphography with Lipiodol ultrafluid (214). Two later examinations with diatrizoate caused exacerbation of the disease within 24 hours. The condition receded spontaneously after 12 months, and subsequent examinations with metrizamide and iodamide were symptom-free.

Lymphatic obstruction is also an important factor in the etiology of oil embolism during lymphography causing shunting via distal lymphovenous communications.

Musculoskeletal

A transitory myopathy has been reported after iopamidol (215).

Immunologic

French workers investigating the causes of severe reactions to iodinated contrast agents suggested that any patient who has had a severe anaphylactoid or anaphylactic reaction after the injection of a contrast agent should undergo immunological assessment (216). The diagnosis of drug anaphylaxis is usually based on the history, proof of mediator release, and the presence of drug-specific IgE antibodies or positive skin tests. In five patients with severe anaphylactoid reactions after the intravascular injection of an iodinated contrast agent, the clinical symptoms, biology, and skin tests were consistent with anaphylaxis. The authors also reported that no premedication has proved effective in preventing subsequent allergic reactions to contrast agents.

In one study iodinated contrast agents were among the top 10 drugs responsible for anaphylaxis (161 cases due to contrast media out of 1338 reports of anaphylaxis) (217). Dextran was the most common cause of anaphylaxis (418 cases). The overall death rate was significantly higher in men than in women and increased with age. The report also suggested that since the introduction of low molecular weight dextran 1 the incidence of severe anaphylaxis to dextran has fallen markedly and that radiographic contrast agents may now be the most common agents causing anaphylaxis. Most of the anaphylactic reactions and all the fatal cases were due to ionic agents.

Patients allergic to additives, such as parabens in sodium iopodate, can react to them, for example with rash (218).

Hypersensitivity reactions seem to be less common after arteriography than after urography, perhaps because the agent does not pass directly through the lungs, although the data are limited. There were mild allergic reactions in six of 167 patients who underwent arteriography with iodamide (SED-12, 1175) (219). Two severe delayed generalized cutaneous reactions with blistering occurred after lumbar aortography with iopamidol and iohexol (SED-12, 1175) (220).

Three cases of mild allergic-like reactions to oral water-soluble iodinated contrast media during CT examinations of the abdomen have been documented (221). Two patients received Gastrografin and the third received the same agents under the brand name Gastroview. The main reaction was a skin rash that resolved within 2 days. The author advised that clinicians and radiologists should be aware of the potential for adverse reactions to oral iodinated contrast agents. In another case, a severe systemic allergic reaction occurred in a patient who was given oral iohexol (222). In a patient with known allergy to iodinated contrast media it would be prudent to consider barium suspension in preference to an iodinated agent to outline the bowel.

Allergic or even anaphylactic reactions can occur after lymphography, either to the contrast agent or to the dye; in hypersensitive patients, prior use of glucocorticoids and antihistamines may fail to prevent a severe reaction (223).

Non-IgE-mediated anaphylactic (anaphylactoid) reactions

A life-threatening anaphylactoid reaction occurred in a child after intravenous administration of a non-ionic contrast medium (ioversol) (224).

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- A 3-year-old girl was investigated for hypertension and a renal arteriogram was performed. Her blood pressure before the study was 125/60 mmHg. She received 30 ml of ioversol (iodine 320 mg/ml). Within 30 seconds she developed tachycardia (200/minute) and hypotension (60/20 mmHg). She developed diffuse urticaria over her entire body and there was wheezing on auscultation. Cardiopulmonary resuscitation was begun and she received a saline infusion and adrenaline 1:1000 subcutaneously, 0.01 ml/kg, intravenous diphenhydramine 1 mg/kg, and intravenous hydrocortisone 5 mg/kg. She responded rapidly. Surprisingly, the authors thought that the contrast medium had not caused this response, and the patient was subsequently given a second injection of ioversol 320 in a dose of 1 ml/kg. Within 60 seconds she again became tachycardic and hypotensive and urticaria reappeared over the whole body with wheezing. Similar treatment was offered and she responded rapidly.

The authors claimed that this was the first case report of anaphylactoid shock after the administration of ioversol in a child.

A fatal anaphylactoid reaction to an intravenous non-ionic contrast medium occurred during a CT scan (225). The authors highlighted the value of measuring serum tryptase in the diagnosis of anaphylactoid reactions.

- An 81-year-old man underwent CT scanning of the head with intravenous contrast enhancement (100 ml of the non-ionic contrast medium iopamidol). After the injection he complained of sweating and nausea and had a cardiorespiratory arrest. Immediate resuscitation and intravenous dexamethasone and adrenaline were not successful. Mast cell tryptase activity in a sample taken 4 hours after death was high. At autopsy, the coronary and pulmonary arteries were patent. The right heart chambers were moderately enlarged. The lungs were hyperemic and edematous and there was obstructive edema of the larynx.

This patient had all the features of anaphylactoid reactions, which include pulmonary and laryngeal edema and a massive rise in serum tryptase. The half-life of tryptase is about 2 hours. Moderately raised post-mortem tryptase activity in the absence of anaphylaxis has been described. Therefore, only very high serum tryptase activity, as seen in this case, should be regarded as specific for fatal anaphylactoid reactions.

Graft-versus-host disease

Three cases of cutaneous graft-versus-host disease triggered by contrast agents have been reported (226).

- A 49-year-old man with acute myeloid leukemia underwent allogeneic bone marrow transplantation from his brother. Pre-existing pulmonary aspergillosis was treated with intravenous amphotericin. ACT scan of the chest and abdomen 120 ml of the non-ionic dimer iodixanol was performed and 6 hours after the injection he developed generalized erythema with a pruritic painful skin rash. Skin biopsies showed changes typical of chronic graft-versus-host disease. He received prednisolone 50 mg orally and the rash resolved within a few weeks.
- A 30-year-old woman with acute myeloid leukemia received an allogeneic bone marrow transplant from her brother. A CT scan of the abdomen was performed a few weeks after transplantation using 150 ml of iodixanol. Two days later she developed acute cutaneous graft-versus-host disease, which was treated with intravenous methylprednisolone 1 g/day for 4 days. Four months later, another CT was performed with 150 ml of iodixanol and 2 hours later she developed a generalized maculopapular rash over the whole body, which was diagnosed as grade-2 graft-versus-host disease. Intravenous methylprednisolone 1 g and clemastine 2 mg did not control the rash, which worsened. She was given daclizumab 50 mg/day for 2 days, prednisolone 100 mg/day, and mycophenolate mofetil 2 g/day. The rash resolved completely within 10 weeks.
- A 38-year-old man with acute myeloid leukemia underwent allogeneic bone marrow transplantation from his brother. He received iopromide 120 ml during CT scanning of the chest 15 months after the transplantation and 6 hours later developed generalized erythroderma, which was treated with oral prednisolone 50 mg. The lesion persisted and cholestatic jaundice developed. Graft-versus-host disease of the skin and liver was diagnosed. The patient still required immunosuppressive therapy and prednisolone 18 months after the event.

The authors suggested that the skin manifestations had been due to graft-versus-host disease triggered by the contrast medium and not a type-IV immunological reaction. Skin biopsy in one of the patients showed typical features of graft-versus-host disease. In addition, the reactions in these patients lasted for longer than one would expect in simple delayed reactions with skin manifestations, which usually resolve within 7–10 days.

Prevention

Prophylactic use of immunosuppression has been described to prevent delayed hypersensitivity reactions to contrast media (227).

- A 19-year-old man developed delayed hypersensitivity skin reactions to iopamidol (a low-osmolar contrast medium) after cerebral angiography for an arteriovenous malformation. Three months later he required embolization of the malformation. He was given prophylactic betamethasone (4 mg/day) for 2 days before the procedure in which iopamidol was used again. Three days after the embolization he developed a generalized maculopapular rash with severe itching. The rash resolved completely after intramuscular chlorphenamine 10 mg bd for 10 days and oral prednisone 25 mg bd. Skin tests confirmed a delayed hypersensitivity reaction to iopamidol and other types of contrast media. One month later he required further embolization and underwent immunosuppression with oral ciclosporin 100 mg bd and intramuscular methylprednisolone 40 mg/day for 1 week before and 2 weeks after the embolization. The contrast medium iobitridol, which gave negative results in skin tests, was used. The patient tolerated the procedure and did not develop further reactions.

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Infection risk

Malarial relapse followed administration of iodipamide in two cases (228).

Body temperature

Several patients have developed hyperthermia after receiving metrizamide (SEDA-10, 425). A fatal case of malignant hyperthermia occurred after 100 ml of diatrizoate (229).

Death

There has been a review of 449 fatal reactions to ionic media (12). Deaths occurred in all age groups, but the incidence peaked in the 50–70 year age group; in this older group, cardiovascular collapse, cardiac arrest, and pulmonary edema were the most common features, but pulmonary edema appeared to be the commonest autopsy finding in all age groups (230). Of 53 deaths due to urography or computed tomography; 35 were of cardiac origin and eight were attributed to pulmonary edema. The presenting features in eight cases were nausea and vomiting, while seven patients developed shock or hypotension.

A fatal reaction has been reported in a case of Waldenström's IgM paraproteinemia (231). Ioglycamide produced fatal gel precipitation of the plasma in a case of Waldenström's IgM monoclonal paraproteinemia (232).

Long-Term Effects

Mutagenicity

An increased frequency of chromosomal aberrations and sister chromatid exchanges has been found in lymphocytes up to 1 week after intravenous urography; diatrizoate produced more changes than ioxaglate (SEDA-19, 430) (233). Earlier it was reported that the incidence of chromosomal aberrations in the lymphocytes of seven infants who underwent angiocardiography was higher than expected. Whether this means that contrast media produce significant cytogenetic damage is not at all clear.

Tumorigenicity

Some have suggested that the passage of contrast agents through malignant lymph nodes may facilitate metastases; one relevant case relates to Hodgkin's disease (234) and another to melanoma (235). There is also some animal evidence of this. However, it has generally been considered that lymphography is unlikely to be a significant factor in malignant dissemination and that its diagnostic value in planning treatment far outweighs any theoretical risk. Computed tomography and magnetic resonance imaging have now largely replaced lymphography for the demonstration of malignant lymph nodes.

Second-Generation Effects

Fetotoxicity

The main adverse effect of iodine-containing contrast agents after amniofetography is transient hypothyroidism, which has often been reported (236–246).

Iophenoxic acid, now obsolete, passes the placental barrier and can alter thyroid function in mothers and fetuses (247). In one case, a child was born with congenital hypothyroidism 5 years after the mother had undergone cholecystography (248); in a similar case the mother had been given iophenoxic acid 8 years before pregnancy (SED-12, 1167) (249).

Lactation

Contrast agents are excreted into breast milk, and they should not be used in breastfeeding women (SEDA-6, 404).

Susceptibility Factors

Genetic factors

Racial differences could be a factor in the high incidence of delayed skin reactions to contrast media in Japan, as 43% of Japanese are deficient in acetaldehyde dehydrogenase. This deficiency results in the accumulation of acetaldehyde, which potentiates the ability of contrast agents (especially dimers), to bridge proteins, which is a probable causative factor in many of their adverse effects (11).

In 1798 Indian patients the prevalence of adverse reactions to high-osmolar ionic iodinated contrast media was 21% (mild 19%, moderate 1.3%, and severe 0.3%) and there was only one death. The incidence of adverse effects was significantly higher in patients with risk factors, such as a history of previous contrast reactions (46%), bronchial asthma (69%), and diabetes mellitus (60%), compared with patients with no risk factors (21%). The authors tried to throw some light on the relation between race and incidence of contrast reactions. They showed that the incidence of mild reactions in the Indian patients (19%) was significantly higher than reported in white patients (5–15%) but that there was no difference in the incidence of moderate or severe reactions between the two populations (250).

The incidence of contrast reactions amongst patients of Indian origin in the UK was significantly higher than in the endogenous white population, with an eight-fold increase in severe reactions (251). There was also a significant increase in the incidence of reactions amongst patients of Mediterranean origin, but to a lesser degree.

There is no clear explanation for racial differences in the incidences of contrast agent reactions.

Age

Neonates are particularly sensitive to the effects of iodine, and transient hypothyroidism has often been reported, particularly in pre-term infants (237,252,253). The low glomerular filtration rate in infants can also result in delayed excretion of contrast agents.

The efficacy and safety of iodixanol has been documented in children. Iodixanol was well tolerated without any important adverse events in 25 children under 4-years-old undergoing excretory urography (254).

The use of low-osmolar contrast media in gastrointestinal imaging has been investigated in children under 16 years. One group received the iso-osmolar dimer

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iodixanol (74 patients, mean age 5.8 years, range 0–15, mean volume of contrast medium 87 ml) and the other group received the low-osmolar non-ionic monomer iohexol (78 patients, mean age 6.4 years, range 0–15, mean volume of contrast medium 93 ml) (255). There was a lower frequency of adverse events with iodixanol than with iohexol. Diarrhea developed in 16% of the patients given iodixanol and in 36% of those given iohexol.

The safety of the iso-osmolar dimer iotrolan in imaging the upper gastrointestinal tract has been investigated in neonates and young children (81 patients, age range 2 days to 14 years), 21 of whom were under 1 month old (256). The dose of contrast medium was 15–30 ml. There were no significant adverse effects and the authors concluded that iotrolan is a safe contrast agent for imaging the gastrointestinal tract in children.

Renal disease

In patients receiving hemodialysis, the mean plasma iomeprole concentration fell by 36% at 2 hours after administration when hemodialysis was started. The mean half-life on dialysis was 4.4 hours. The effective fall in plasma iomeprole concentration after a single dialysis was about 70%. The mean fraction of the dose recovered in the dialysate was 58%. The mean dialysis clearance was 81 ml/minute. The extraction efficiency of the dialyser was about 40%. The only adverse effect was infection of an arteriovenous fistula in a patient with end-stage renal disease, which was unrelated to the contrast agent. There were also mild to moderate adverse effects, but all resolved without sequelae. The most common adverse effects were headaches and sensations of warmth. Others were paresthesia, abdominal pain, taste disturbance, and nausea. None of the events was considered to be clinically important. There were no clinically important changes in vital signs, physical examination, electrocardiography, or clinical laboratory evaluations. The authors concluded that iomeprole is safe and well tolerated and can be almost completely eliminated both in patients with renal impairment and in patients receiving dialysis.

Hepatic disease

The risk of renal insufficiency after contrast agents is greater in the presence of hepatic insufficiency, apparently because in such cases both blood concentrations and renal excretion of the contrast medium are greater (SEDA-10, 422).

Other features of the patient

A high incidence of histamine release and anaphylactoid reactions to contrast media has been reported in patients with malignant tumors (257). Patients with malignant tumors were randomized into two groups. One group ($n = 66$) received non-ionic low-osmolar contrast media (iopamidol) and the other ($n = 64$) received high-osmolar ionic contrast media (ioxitalamate). An average of 100 ml of contrast medium (range 60–140 ml) was given before CT scanning in both groups. The incidence of reactions (tachycardia, bradycardia, hypertension and hypotension, a fall in oxygen saturation, nausea, vomiting, headache, and skin reactions) was similarly high in both groups (58% with iopamidol and 42% with ioxitalamate). The increases in plasma histamine concentrations were also similar: median 0.43 (range 0–13) ng/ml with iopamidol and 0.15 (0–12) ng/ml with ioxitalamate. The authors concluded that patients with malignancies are at risk of histamine-associated contrast reactions and suggested that antihistamine prophylaxis with histamine H_1 and H_2 receptor antagonists should be considered in these patients. However, there is no conclusive evidence that antihistamines offer effective prophylaxis against reactions to contrast media.

Routine electrocardiographic monitoring during intravenous urography shows that there are significant abnormalities in patients with heart disease and that the incidence of these abnormalities appears to be related to the dose of contrast agent and the speed of injection (258). Patients with a history of angina can develop ischemic electrocardiographic changes with or without chest pain after the injection of a contrast agent into the superior vena cava; one such patient developed ventricular fibrillation (259).

In patients with myasthenia gravis, crises may be precipitated by contrast agents (260). An acute myasthenic crisis with apnea was induced by contrast CT with diatrizoate in two patients with myasthenia gravis and this was followed by prolonged aggravation of the myasthenia (261). This has also occurred with iopamidol (SEDA-12, 396).

Patients with pre-existent thyrotoxicosis present a problem, since the condition may be aggravated by contrast agents, even to the point of precipitating a thyroid storm (262).

Patients with a history of previous reactions to contrast media have a 35–40% chance of reacting again if re-examined.

In patients with sickle-cell disease, a high local concentration of contrast medium in the blood during arteriography can cause sickling, with resulting thrombosis. One patient with sickle cell disease developed severe intravascular hemolysis, thrombocytopenia, leukocytosis, and pulmonary infiltrates after left ventriculography and coronary angiography with meglumine diatrizoate (263). In vitro studies suggest that the non-ionic agent iopamidol causes significantly less sickling than conventional ionic contrast agents, and iopamidol would therefore be preferable for arteriography in patients with this disorder (SEDA-7, 453).

There appears to be an increased risk of seizures due to vasospasm if cerebral angiography is performed during or shortly after an attack of migraine (SEDA-11, 412).

Drug Administration

Drug formulations

BR21 is a sterile pyrogen-free suspension containing iomeprol, both free in solution and entrapped in liposomal vesicles. The suspension ideally contains iodine 320 mg/ml with an osmolality of 560 mosmol/kg. The liposomes are 0.4 μm unilamellar vesicles in which the membrane is made of phospholipid. The total lipid concentration of the suspension is about 20 mg/ml. About

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40 mg/ml of iodine are trapped within the liposomal vesicles and there is 280 mg/ml in the external phase. BR21 is taken up by the reticuloendothelial system and can enhance normal liver tissue, whereas neoplastic lesions, which lack reticuloendothelial cells, are not enhanced.

The safety and pharmacokinetics of intravenous BR21 have been evaluated in 30 healthy adult men in a phase I, single-blind, placebo-controlled, ascending-dose study (264). Four volunteers each received a single intravenous dose of BR21 (0.5, 1.0, 1.5, 2.0, or 2.5 ml/kg), and for each dose of BR21 two volunteers received saline 0.9%. All adverse events (headache, metallic taste, nausea, back pain, dizziness, tremors, sweating) were minor or mild and resolved rapidly without treatment. There was no difference in the incidence of adverse events from dose to dose of BR21 or between BR21 and saline. There were no significant changes in vital signs, electrocardiography, or laboratory findings.

A formulation of liposome-encapsulated iodixanol has been evaluated as part of a phase 1 assessment of diagnostic efficacy and safety (265). The formulation is a ready-to-use suspension of multilamellar liposomes with a mean size of 340 nm. The main constituents of the liposome wall are phosphatidylcholine and phosphatidylserine. The concentration of iodine in the formulation is 200 mg/ml (encapsulated iodine 80 mg/ml). The encapsulated iodine-to-lipid ratio is 1.5. This new formulation was injected in doses of 10, 30, 70, and 100 mg of encapsulated iodine per kg in 5, 8, 8, and 8 healthy volunteers (mean age 30 years). Saline was given to two volunteers in each dose group, in a volume matching that of iodixanol at the 70 mg dose. The intravenous injection was carried out using a power injector at a rate of 2 ml/second. There were dose-dependent changes in leukocyte count. During the first 2 hours the leukocyte count fell and then rose. At 10 and 30 mg doses the changes were small and in most of the volunteers did not exceed the reference range. At higher doses there was a prominent increase in neutrophils with rod-shaped nuclei, suggesting increased release from the bone marrow. C-reactive protein also rose dose-dependently, suggesting a cytokine-mediated reaction. Leukocyte count and C-reactive protein normalized spontaneously after 24 hours. The volunteers had subjective adverse events at doses of 70 and 100 mg; these included chills (88%), back pain (25%), flu-like symptoms (13%), and nausea and vomiting (38%); they started within 1 hour and recovered spontaneously within 3 hours. No adverse events were interpreted as severe, but they were judged to be too pronounced to be clinically acceptable. Research is needed to find a formulation that causes fewer adverse events without compromising diagnostic quality.

Another hepatocyte-specific contrast formulation, dysprosium ethoxybenzyltris(carboxylatomethyl)triazaundecanedioic acid diethylenetriaminepenta-acetic acid (Dy-EOB-DTPA), has been used for liver CT imaging (266). It contains calcium-EOB-DTPA (0.5 mg/ml), trometamol (1.2 mg/ml), and hydrochloric acid (final pH 7.4). It has been described as a stable metal chelate with high tolerability in vitro and in animal studies, in which a long-lasting increase in CT density of about 30 Hounsfield units has been reported. A total of 40 healthy male volunteers (mean age 33 years) received intravenous infusions of Dy-EOB-DTPA, 0.05, 0.1, 0.25, 0.375, or 0.5 mmol/kg over 10 minutes ($n = 6$ in each group), or placebo ($n = 2$ in each group). There were adverse effects in four of the 10 patients who were given placebo and 22 of the 30 who were given Dy-EOB-DTPA. The most common adverse events were nausea (25%), headache (18%), paresthesia (15%), loss of appetite, allergic reactions, back pain, and injection site hemorrhage (7.5%). The adverse effects were generally mild or moderate, but there was a slight increase in intensity at the higher doses. There were gastrointestinal adverse events in all six of the volunteers who received 0.5 mmol/kg. Nausea was the longest lasting and in one case it was severe. The results of laboratory tests did not exceed the reference ranges. Vital signs, hemodynamic parameters, and electrocardiography were not affected by the contrast agent. Over 50% of the adverse events were considered to be unrelated to the drug. The authors concluded that this liver-specific contrast formulation has a good safety profile.

Drug contamination

Contrast media used for arteriography contain a variety of microscopic particles. When glass ampoules are opened, they contain a larger number of particles than rubber-capped vials because of the vacuum effect on glass particles during the opening of the ampoule (267). This can theoretically cause microembolism. Angiographic catheters and guide wires also contain a very large number of particles derived from the manufacturing process, and the release of these particles is increased some sixfold after the insertion of the guide-wire into the catheter (SED-12, 1179) (268). Vials should be opened by removing the cap and not by puncture of the membrane, since the needle usually pushes large rubber particles into the solution. Ideally, contrast media should be filtered before injection, but this will often not be practicable.

In the case of glass ampoules, if the ampoule is allowed to stand for 30–60 seconds after opening, most of the larger particles will have sedimented to the bottom of the ampoule. These can then be avoided by leaving the lower 2–3 mm of contrast medium in the ampoule.

Drug administration route

Oral and rectal

The high-osmolar contrast agents diatrizoate and iotalamate were formerly recommended for oral use in preference to barium when there was a risk of perforation, but the osmotic effect of such material can lead to diarrhea and fluid loss, which may be dangerous in weak patients. Diatrizoate, which has a cathartic action, can occasionally cause ileus when given postoperatively (149); it can also be precipitated as a solid mass in the stomach when gastric acidity is high, but also in an achlorhydric gastric stump after partial gastrectomy if stomal obstruction is present. On one occasion when diatrizoate was used to fill the gastric balloon of a Sengstaken–Blakemore tube, hydrogen ions from the gastric content apparently penetrated into the balloon, precipitating the contrast medium and preventing the balloon's removal. Accidental inhalation of hypertonic contrast media during oral administration can cause fatal pulmonary edema (75).

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Low-osmolar agents such as iohexol are preferred for oral use; however, they can still cause some diarrhea, for example in 18 out of 40 cases in one series (SEDA-16, 529). Absorption can be increased if there is mucosal damage in the bowel, such as in Crohn's disease, resulting in delayed excretion but not apparently involving risk (SEDA-18, 441).

Diatrizoate enemas are still sometimes used to treat meconium ileus or constipation and it is important to give intravenous fluids so as to avoid dehydration. Hypomagnesemia can also occur (150). Osmotic effects lower in the gastrointestinal tract have even led to distention and cecal perforation (151). Stasis of diatrizoate in dilated loops of bowel can cause inflammatory changes or necrosis (152,153).

Severe systemic reactions to enterally administered water-soluble contrast media are rare but they do occur, for example with oral iohexol (222).

Intra-arterial injection

Local vascular complications associated with angiography include intramural injection of contrast medium (leading to dissection of the arterial wall), arterial thrombosis, phlebitis, venous thrombosis, embolic phenomena, and damage to atheromatous plaques in the aorta leading to cholesterol embolism (SEDA-14, 423) (269). Injection of contrast material into an intervertebral disc during angiography can cause lumbar pain associated with disc necrosis. Acute pancreatitis has been reported after aortography with sodium acetrizoate 70% w/v accidentally injected into the celiac axis. A report from 1958 described a fatal case of bilateral adrenal necrosis following lumbar aortography (SED-12, 1178) (270). Aortography in patients with pheochromocytoma can produce hemorrhage into and around the adrenal tumor; in one case adrenal insufficiency followed bilateral adrenal venography (271).

Cerebral angiography

The risk of neurological complications after cerebral angiography is 0.55–3.2% but increases to 10% in patients with symptomatic carotid stenosis; the incidence of clinically silent cerebral embolism is unknown. Diffusion-weighted magnetic resonance imaging before and after cerebral angiography has been carried out to assess the prevalence of embolic events in 100 consecutive angiographies in 91 patients (272). The patients underwent neurological assessment before, immediately after, and 1 day after angiography. There were 42 bright lesions in 23 patients after 23 procedures in a pattern consistent with embolic events. There were no new neurological deficits after any angiographic procedure. The frequency of lesions correlated significantly with a history of atherosclerotic arterial disease, the complexity of the angiographic procedure, and the amount of contrast medium used. The authors concluded that after diagnostic and interventional cerebral angiography embolic events are more frequent than the neurological complication rate. The incidence of embolism is closely related to the vascular risk profile.

Intravenous injection

Subcutaneous extravasation of contrast media during rapid intravascular injection can cause local irritation and inflammatory responses. The severity of these effects depends on the volume and osmolality of the extravasated contrast medium. High-osmolality contrast media can cause skin ulceration and necrosis. Subcutaneous hyaluronidase, aspiration of fluid, elevation of the limb, and topical application of cold compresses are some of the measures used to treat this complication.

The frequency of extravasation of ionic and non-ionic contrast media during rapid bolus injection in 5106 CT contrast-enhanced scans was 0.9% (31 patients had extravasation of ionic media and 17 patients had extravasation of non-ionic media) (273). There was no correlation between the injection rate and the frequency of extravasation. None of the patients who had extravasation had permanent damage.

With highly concentrated sodium-containing media, such as sodium iotalamate 420, severe arm pain and late thrombosis can occur (274). In a comparison of the sodium and methylglucamine salts of diatrizoate, even with lower concentrations, the incidence of arm pain was higher with the sodium salt. Extravasation of ionic contrast medium in the soft tissues can cause a chemical cellulitis, leading to skin necrosis, particularly if the circulation is compromised (SEDA-10, 424); tissue damage is less severe with the non-ionic media. The risk of extravasation is greatest with the rapid injection of large doses needed in computed tomography. In rare cases, this has resulted in gangrene, particularly in venography. Arterial insufficiency probably results in slower removal of the agent and hence more prolonged exposure to it.

As in many other areas, the non-ionic media are less noxious in this respect; this has been shown in animal studies (SEDA-16, 530) and in a number of clinical cases in which extravasation of large volumes of iopamidol responded to palliative measures and had no lasting ill-effects (275). Among the ionic media, the methylglucamine media seem to have more local toxicity than their sodium equivalents.

Extravasation of ionic and non-ionic contrast media after rapid bolus infusion has been studied in 5106 CT studies in adults (276). The mean infusion rate was 2.8 ml/second and extravasation occurred in 48 patients (0.9%). Injection rate did not correlate with the frequency or amount of extravasation. Average age and use of ionic versus non-ionic contrast medium were identical in patients with and without extravasation. There was no sex difference. There was extravasation of ionic contrast medium in 31 patients, nine of whom had extravasation of at least 50 ml. There was extravasation of non-ionic contrast medium in 17 patients, of whom seven had extravasation of at least 50 ml. Hyaluronidase infiltration was often used to treat more extensive extravasation in 10 patients each with extravasation of ionic or non-ionic media. No patient required surgical intervention and none had severe or long-term effects.

The adverse effects of contrast agents during computed tomography (CT) are broadly similar to those during excretion urography, but the incidence of serious reactions and deaths may be higher, because reactions are harder to treat when the patient is in a scanner (SEDA-7, 451). Renal insufficiency can occur in patients with diabetes and pre-existing renal disease or as a result of multiple examinations. In *Herpes simplex* encephalitis,

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there can be prolonged retention of contrast medium in the brain. In patients with spinal tumors, stimulus-sensitive extensor spasms can occur in the trunk and limbs (SEDA-7, 453).

For computed tomography, large volumes of contrast medium have to be injected under pressure and this can lead to problems such as subclinical air embolism (SEDA-14, 422) and extravasation. In one series of 20 950 CT scans using non-ionic media, there was extravasation of 3–100 ml in 28 cases; the degree of extravasation depended on the pressure applied. When extravasation occurs, the extent of tissue damage depends primarily on the osmolarity of the contrast medium, but it is clear that of the ionic agents, the methylglucamine salts cause more damage than the sodium salts do (277).

Phlebography sometimes causes superficial thrombophlebitis in the injected vein. Of 61 previously healthy patients who had undergone phlebography, four had clear evidence of subsequent deep vein thrombosis and in two of these there were signs of non-fatal pulmonary embolism. The incidence of thrombosis may indeed have been higher, because there was abnormal fibrinogen uptake in 20 individuals, although the result could have been non-specific (278). The risk of thrombophlebitis is significantly less when low-osmolar media are used (SEDA-9, 410) (SEDA-11, 414).

Necrosis of the skin can follow peripheral venography (279); in these cases there had been some extravenous injection, and impaired circulation probably resulted in slower removal of the agent and hence more prolonged exposure to it. Gangrene of the toes has also occurred.

Polyarthropathy, in a severe and acute form, has been described as a rare complication of venography in patients with end-stage renal insufficiency (SEDA-18, 445).

Fat embolism is a rare complication of intra-osseous phlebography (280,281).

Orbital venography has been largely superseded by computed tomography and magnetic resonance imaging. This technique has usually been safe, but there have been reports of hemorrhage in a lymphangioma of the orbit and of transitory retinal artery spasm or retinal hemorrhage, the last two involving subjects with diabetes (SED-12, 1179) (282).

Priapism due to venous thrombosis has been reported after penile cavernosography with ioxaglate and diluted iotalamate (283). Contrast agents can cause endothelial damage in the corpus cavernosum. Prior injection of 1000–2000 units of heparin into the corpus cavernosum and the use of diluted non-ionic media have therefore been advocated for this procedure (284).

Subcutaneous or intramuscular injection

In the past, when intravascular injection proved difficult, contrast media were sometimes given by the subcutaneous or intramuscular routes. On occasion, severe sloughing of tissue resulted. Addition of hyaluronidase in order to alleviate this problem only aggravated it, and dilution with water, saline, or procaine solution also proved useless. If, in exceptional circumstances, these routes have to be used, the medium should be injected in small quantities at multiple sites.

Intra-articular injection

Minor reversible edematous changes have been noted in the synovial membrane after arthrography, and a chemical synovitis can occur (SEDA-10, 425).

Amniofetography

Ultrasound has superseded amniofetography, a procedure in which contrast media are injected into the amniotic sac during pregnancy to delineate fetal abnormalities. Diatrizoate, iotalamate, and, earlier, iodized oil were used. There is a theoretical risk of premature labor. Accidental injection of contrast medium into the fetal subcutaneous tissues could cause sloughing of the skin or subcutaneous necrosis. Cases of thyroid hyperplasia or hypothyroidism were also commonly described.

Arthrography

After injection of a contrast agent into a joint, the synovium becomes edematous and hemorrhagic within 2 hours. At 24 hours, there is tissue eosinophilia and vascular congestion. Eosinophilia of the synovial fluid can also occur. The complications reported in a survey of 126 000 examinations (285) are shown in Table 6.

Bronchography

Computed tomography of the lungs has reduced the requirement for bronchography, but it is still of value in selected cases. Iotrolan is most commonly used and is well tolerated. Adverse effects resulted from earlier products used in the field.

Hytrast (a mixture of iopydol and iopydone in aqueous suspension with carboxymethylcellulose) was generally withdrawn because it gave rise to a foreign body reaction. Iodized oil was formerly popular, but iodism was not uncommon and sometimes even fatal; sulfanilamide was added to one particular formulation of iodized oil to increase its viscosity and on occasion produced methemoglobinemia and cyanosis. Late granulomatous reactions in the lungs, followed by long-term fibrosis were also described with iodized oil, as were early allergic granulomatous reactions and other types of allergic reaction, such as pneumonitis and urticaria.

About one-third of patients undergoing bronchography have some type of reaction. The most common symptoms

Table 6 Complications of arthrography in 126 000 examinations

Complication	Number
Death	0
Severe reactions	
Hypotension	4
Vasomotor collapse and laryngeal edema	1
Air embolism	1
Vagal reactions	83
Subsequent seizures	6
Apnea	1
Urticaria	61
Cellulitis	1
Sepsis	3
Massive effusion	1
Severe pain	5
Sterile chemical synovitis	150

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are headache, nausea and vomiting, fever, iodism, and dyspnea. Less frequent reactions include wheezing, diarrhea, dizziness, cyanosis, chest pain, and pneumonia. Aqueous propyliodone produces more reactions than the oily form, but as a rule the product that produces most reactions also produces the best visualization. Symptoms are also related to the volume of agent used and the degree of alveolarization.

In a survey of 100 000 bronchograms published in 1967, 18 deaths were attributed to the technique. However, half of the deaths were due to the local anesthetic, generally used in excessive amounts. Fatalities tended to occur in children, patients with limited respiratory reserves, or subjects with severe hypersensitivity reactions (SED-12, 1185) (286).

If the cricothyroid route is used for bronchography, contrast medium may be accidentally injected into the soft tissues of the neck; propyliodone has under these conditions produced an inflammatory reaction leading to dysphagia, pain on movement of the neck, and mediastinal spread, rarely with electrocardiographic changes suggesting pericarditis. Oral glucocorticoids with antibiotic cover usually produce dramatic relief of symptoms.

Heating lowers the viscosity of propyliodone and should be avoided. Death from progressive acute respiratory failure resulted from bilateral bronchography under general anesthesia using propyliodone which had been heated in an autoclave.

Cholecystography and cholangiography

Ultrasonography is now the primary imaging technique for the assessment of the gall bladder and bile ducts, and oral cholecystography is obsolete. Contrast agents that have been used for oral cholecystography are weak iodinated organic acids that are absorbed and then largely conjugated with glucuronic acid. The most widely used agents have been iopanoic acid and sodium or calcium iopodate; tyropanoate and iocetamic acid have also been used. Bunamiodyl sodium, which was nephrotoxic, has been withdrawn.

The use of intravenous cholangiography has fallen dramatically in recent years, largely because of the advent of new and safer techniques for imaging the biliary tree, including high-quality ultrasound. However, with the introduction of laparoscopic cholecystectomy, the technique is occasionally used to assess bile duct anatomy before surgery (SEDA-19, 426). Intravenous cholangiography with meglumine iotroxate was reported to be acceptably safe. Contrary to popular opinion, reactions are apparently no more frequent with modern agents for intravenous cholangiography than with angiographic agents (SEDA-20, 416).

In a national survey in Britain in 1970, when drugs were generally given for this purpose in a single injected dose, intermediate reactions to iodipamide occurred once in every 700 cases, severe reactions once in every 1600, and deaths once in every 5000 (SED-12, 1168) (72). The introduction of infusion cholangiography (in which the contrast medium is given over 15–30 minutes) reduced the incidence of minor reactions, allowing the liver to excrete the contrast medium more efficiently, so that doses as low as 3–5 ml of ioglycamide or 10 ml of 50% iodipamide can be used. According to a 1975 report from France, serious reactions nevertheless occurred once in every 310 infusion cholangiographies (SEDA-10, 422) (287).

Pyrexial reactions occurred in 5.3% of cases after postoperative cholangiography through a T-tube; in two patients there was endotoxic shock (SEDA-5, 420).

A fatal reaction occurred when diatrizoate was used for operative cholangiography and contrast medium entered the bloodstream (288).

Using a fine needle, with sodium diatrizoate as the contrast medium, percutaneous hepatic cholangiography is a relatively safe technique for use in cases of obstructive jaundice in which the high serum bilirubin precludes oral or intravenous techniques. The complications of bile peritonitis and internal hemorrhage are best avoided by decompression of dilated ducts. Bile blood fistula can lead to fatal endotoxic shock due to bacteria escaping from the obstructed biliary tract (289). The rapid appearance of a pyelographic shadow can be a useful diagnostic sign, calling for immediate antibiotic therapy. However, it is now usual to give a broad-spectrum antibiotic immediately before the examination. Acute renal insufficiency has been reported after transhepatic cholangiography (SEDA-10, 423).

Cholangiopancreatography

Although a severe contrast medium reaction with shock has been observed, this was the only contrast medium reaction in a series of 2000 cases of ERCP reported in 1977 (290). In some other reports, there were milder degrees of allergic reactions (291). In a series of 10 000 cases reported in the USA in 1976 (292), the most serious adverse effects were cholangitic sepsis (0.8%, fatal in 0.08%) and pancreatic sepsis (0.3%, fatal in 0.06%), but there was a 1% incidence of injection pancreatitis and other cases of drug interactions (diazepam, spasmolytic agents), instrumental injury, and aspiration pneumonia. Pancreatitis can result from over-filling of the pancreatic duct. To minimize the risk of pancreatitis after ERCP the examination should be performed with care. High-pressure injection of the contrast medium should be avoided to reduce the risk of overfilling and extraductile extravasation. In addition, low-osmolar non-ionic contrast agents should be used (SEDA-19, 425) (SEDA-20, 417). Significant quantities of contrast agent can be absorbed after ERCP. Transient asymptomatic hyperamylasemia can occur (SEDA-14, 422), and in one series there was a 15% incidence of mild renal dysfunction (293).

Discography

Subdural empyema with residual quadriparesis has been reported as a rare complication of discography (294).

Hysterosalpingography

Water-soluble agents are generally preferred for hysterosalpingography, agents such as diatrizoate or iotalamate being most commonly selected. It has sometimes been suggested that low-osmolar contrast media should be preferred; however, a double-blind comparison of the low-osmolar medium ioxaglate (Hexabrix 320) with methylglucamine diatrizoate (Conray 280) in 100 patients showed no difference in the incidence of early or late adverse effects between the two agents (295).

There is no justification for using specialized formulations based on the more toxic molecules acetrizoate or

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iodipamide; these cause more severe pain and can also cause hypotension and shock.

Iodized oil, at one time widely used, caused less pain but was suspected of causing adhesions and there was certainly some risk of oil embolism after intravasation, for example retinal embolism with visual impairment lasting for some months and several cases of pulmonary oil embolism (SEDA-16, 537). Skin testing with iodized oil on occasion resulted in both local and generalized reactions. Like later agents, lipiodol could also cause salpingitis.

The main remaining disadvantage of the currently used water-soluble media is their tendency to cause lower abdominal pain, which can be severe, during or shortly after the injection; it can last for 24 hours or longer. These adverse effects are likely to be less severe with low-osmolar non-ionic media. Vaginal bleeding can occur and the following menstrual period can be deranged. With all contrast media there is a possibility of hypersensitivity reactions, and dextran as an additive has on occasion produced anaphylactic symptoms (SEDA-15, 505). Salpingitis can occur with any contrast agent.

Lymphography

Lymphography is rarely required with the availability of modern CT and MRI scanners. However, intradermal injection of 2–4 ml (iodine 300 mg/ml) of iso-osmolar non-ionic dimers (iotrolan and iodixanol) at a rate of 0.1 ml/minute can be used to assess the lymphatics in limbs with lymphedema. The procedure is safe with no serious adverse effects, but idiosyncratic and allergic like reactions can occur.

Iodized oils are usually used as contrast media for lymphography and can cause iodism. Reactions can also occur to the dye "patent blue violet," which is injected subcutaneously before lymphography to enable the lymphatics to be visualized; it colors the skin and urine blue. The incidence of serious reactions to lymphography in 32 000 cases is shown in Table 7.

Myelography and ventriculography

Myelography and ventriculography are techniques that, irrespective of the agent used, have some unpleasant effects, including headache, nausea, and dizziness, which are frequent problems and are possibly more frequent in women, in people with multiple sclerosis, and in investigations at the higher levels of the central nervous system. Nevertheless, the nature and incidence of the adverse reactions depend on the contrast agent used, oily agents, the ionic water-soluble agents, and the non-ionic water-soluble agents. Today, MRI has substantially replaced these unpleasant invasive procedures (SEDA-19, 430).

The incidences of adverse effects in 4568 cases of lumbar myelography and 1232 cases of cervical myelography are shown in Table 8 and Table 9.

Oily media

Oily media are no longer used for myelography or other imaging techniques of the nervous system. Iofendylate was formerly widely used for myelography and to some extent for ventriculography. In the USA, where myelography was generally performed with large volumes of contrast agents, it was the custom to aspirate the iofendylate at the end of the investigation, whereas in some other countries smaller volumes were used under the assumption that these would be gradually absorbed. In patients with multiple sclerosis, myelography with iofendylate can cause particularly severe reactions.

Aseptic meningitis can occur 3–67 days after myelography, and in one case it was associated with evidence of cerebral vasospasm and infarction. An unusual ophthalmic complication in another patient followed the passage

Table 7 Frequency of serious complications in 32 000 episodes of lymphography

Event	Number	Frequency
Hypertensive crisis	6	0.0002
Pulmonary infarction	81	0.0025
Pulmonary edema	10	0.0003
Pneumonia	13	0.0004
Prolonged fever	24	0.0008
Hypersensitivity reactions		
Oily contrast medium	40	0.0012
Vital blue dye	57	0.0017
Cerebral disorders	9	0.0003
Death	18	0.0006

Table 8 Frequency of adverse effects after lumbar myelography (SEDA-4, 335)

Adverse effect	Frequency (%)
Headache	32
Nausea	11
Vomiting	7
Dizziness	7
Increased pain	7
Hypotension	<1
Micturition disturbance	1.1
Muscle fibrillation	0.35
Fever	0.26
Allergic reactions	0.13
Neck stiffness	0.11
Meningism	0.09
Numbness, paresthesia	0.07
Vasovagal attack	0.07

Table 9 Frequency of adverse effects after cervical myelography, other than tonic-clonic seizures (SEDA-4, 335)

Adverse effect	Frequency (%)
Headache	37
Nausea	20
Vomiting	14
Pain	7
Dizziness	5
Mental changes	2
Numbness, paresthesia	0.65
Micturition disturbance	0.65
Weakness in limbs	0.49
Myoclonus	0.32
Neck stiffness	0.16
Allergic reactions	0.16
Hematemesis	0.08
Eye flickering	0.08

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of iofendylate into the region of the clivus and along the course of the optic nerve during cervical myelography; the patient had transient pain and flashes of light in the eye, followed by periorbital pain for 2 days. A month later, severe visual impairment with renewed pain occurred; the condition responded to systemic glucocorticoids (296).

Venous intravasation occurs rarely during lumbar myelography; pulmonary oil embolization has resulted and has also been described after ventriculography with iofendylate in a hydrocephalic child with a ventriculovenous shunt. In that case the symptoms were mild, but the agent can obstruct the valve and in any patient the medium should therefore be removed at the completion of the procedure.

Arachnoiditis is a recognized and much-discussed problem, which has given rise to group litigation. Extensive adhesions due to iofendylate have been described, leading to neurological complications and death; there are two cases on record with clinical changes resembling Sudeck's atrophy. Animal experiments have shown that the ability of iofendylate to cause arachnoiditis is especially pronounced if it is mixed with blood; it should therefore be avoided if there is the possibility that bleeding has occurred into the cerebrospinal fluid.

It is common to see evidence of iofendylate residues for many years after myelography. The residue problem extends to the skull and it is common to find symptomless deposits of iofendylate there after myelography; however, in several patients residues in the skull have apparently caused convulsions (SEDA-14, 424). They can also be associated with persistent headache (SEDA-8, 430) and perhaps with the development of vestibular disturbances many years later (SEDA-17, 538).

In two cases, ventriculography with iofendylate resulted in adhesions with obstruction to the outflow of cerebrospinal fluid (in one case at the level of the third ventricle, in the other at the level of the fourth) producing obstructive hydrocephalus (SED-12, 1180) (297).

An iofendylate cyst causing a thoracic radiculopathy has been reported (298).

- A 45-year-old woman had severe root pain at T10, which had gradually become more intense over the preceding 4 years. She had undergone spinal myelography about 30 years before. Clinical examination was normal. A plain X-ray of the thoracic spine showed a radio-opaque abnormality at the level of T10, which axial CT showed was in the vertebral canal, compressing the left posterolateral margin of the theca. At thoracic laminectomy, a well-circumscribed subarachnoid extramedullary cyst was identified, from which a small volume of oily material was removed. The cyst collapsed and its posterior wall was excised. Histology confirmed a benign arachnoid cyst. Within 24 hours the thoracic root pain had gone.

Recurrent febrile nodular non-suppurative panniculitis (Weber–Christian syndrome) has been described 1 month after myelography with iofendylate; the causal link was uncertain (299).

Persistent symptoms can be caused by residues of iofendylate after myelography; allergy with urticaria and anaphylactic episodes recurring for 17 years was described in one patient who was hypersensitive to iofendylate; after removal of most of the residue, the symptoms improved (300). In one unusual case of anaphylactic collapse, marked bilateral parotid enlargement was the presenting sign (SEDA-18, 442).

When metrizamide was used to outline the basal cisterns in association with computed tomography of the skull, headache occurred in about 50% of patients and vomiting in 26–56%, depending on the dose used; the symptoms occurred 2–6 hours after injection and cleared within 12 hours. Convulsions have occurred with this procedure (301).

Tolerance of non-ionic contrast media in myelography has been well documented (SEDA-22, 500). A report from India has documented the safety and diagnostic efficacy of the non-ionic monomer iohexol 7–10 ml (iodine 300 mg/ml) injected into the subarachnoid space in 25 patients (302). Only three patients developed minor adverse effects—headache and paresthesia in the legs.

Sialography

In randomized comparison of Lipiodol ultrafluid (ethiodized oil) with melumine diatrizoate 290 for sialography in 60 patients, pain and swelling of the parotid gland was more frequent after Lipiodol UF (303).

Extravasation of oil-based contrast agents used for sialography and dacryocystography can cause lipogranuloma formation (304).

- A four-year-old boy with epiphora had a left dacryocystogram with the iodinized oil-based contrast agent Lipiodol under general anesthesia. During injection, a false passage was inadvertently formed, with extravasation of the contrast agent from the lacrimal duct into the surrounding tissues. This was confirmed radiographically. He developed swelling and erythema, which gradually resolved over 6 months.

Iso-osmolar non-ionic dimers, such as iotrolan or iodixanol, are the safest contrast agents for such a procedure. Extravasation of these agents causes minimal tissue reaction.

Urography

The use of intravenous urography has been in decline for some years with the advent of high-quality real-time ultrasonography (SEDA-20, 417).

For retrograde and anterograde urography, only iodinated water-soluble contrast media should be used. The high-osmolar contrast agents, diatrizoate or iotalamate, are generally used in these procedures. Barium sulfate has been used for cystography in the past, but is inadvisable; if ureteric reflux occurs, the barium can become inspissated in the calyceal system of the kidney; in view of experimental findings, this might be expected to cause granulomatous reactions with fibrosis.

Retrograde urography is often followed by irritation and edema of the urethral and bladder mucosa. In animals this effect was maximal at 48 hours and persisted for at least 1 week. Factors that reduced the inflammatory response in the bladder were dilution of the medium and the use of smaller volumes instilled at lower pressure. In clinical use, diatrizoate has seemed to be less irritant than acetrizoate (305).

Retrograde pyelography can rarely cause deterioration of renal function, with acute renal insufficiency, particularly if there has been marked pyelorenal back flow; exceptionally, the complication can be fatal (306).

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Retrograde pyelography with potassium bromide has caused renal insufficiency (SEDA-11, 413).

Small amounts of contrast agents can be absorbed after retrograde urography, mainly via the calyces. In one case, 12.5% of the contrast medium was absorbed (307). A severe generalized reaction has been reported after cystography with diatrizoate (SED-12, 1174) (308), and another in a patient with ureteric reflux given meglumine iotalamate; in the latter, there was circulatory collapse but it responded to simple change in posture and adrenaline was not required (SEDA-18, 445). Miliary dissemination of tubercle bacilli from an infected urinary system after retrograde pyelography with pyelovenous back flow is very rare. An anaphylactoid reaction to contrast medium injected into a ureter via a percutaneous nephrostomy has been reported (SEDA-19, 430).

Bladder rupture is a risk of cystourethrography. In two children with myelomeningoceles and ventriculoperitoneal shunts, bladder rupture had particularly serious consequences. The diatrizoate that was used passed into the peritoneal cavity and then via the shunt into the cerebral ventricles and subarachnoid space, causing tonic convulsions (SEDA-17, 538).

Autonomic dysreflexia (facial flushing, sweating, nasal congestion, headache and paroxysmal hypertension) can occur in quadriplegic patients in response to bladder distention during cystography (SEDA-19, 430).

Drug overdose

Fatal cases of accidental overdosage have been reported in infants; the complications leading to death were either pulmonary edema or convulsions. The latter can be due to hyperosmolarity (leading to hypertonic dehydration) or to the chemical toxicity of the contrast agent.

- In a fatal case, a massive overdose of 340 ml Renigrafin 76 was injected into a 7-year-old child with coarctation of the aorta, and computed tomography showed the presence of contrast agent in the brain (98).

A patient who was given 30 g of iopanoic acid, instead of 3 g, had severe nausea with vomiting and diarrhea but no more serious effects (SED-12, 1167) (309).

Drug–Drug Interactions

Antihistamines

Contrast media should not be mixed with antihistamines in a syringe, since precipitation can result (SED-8, 1034) (310).

Beta-blockers

Field experience, backed by a case-control study of 1991, strongly suggests that patients taking beta-blockers have a risk ratio of adverse reactions to contrast media of 2.7. Hypotension is the main effect, sometimes dangerously so, even with non-ionic media (SEDA-11, 411) (SEDA-17, 536) (311).

Cardiac glycosides

Diatrizoate and strophanthin K may have a synergistic toxic effect (312).

Heparin

Ionic contrast media cause temporary prolongation of clotting time in patients treated with heparin; this effect may last for 6 hours and may interfere with laboratory assays (132). Non-ionic media do not have this anticoagulant effect, and if blood is allowed to mix with a non-ionic medium in the syringe or catheter, thrombus formation can occur, which could be a potential cause of thromboembolism (SEDA-15, 502).

In contrast, in 664 patients undergoing percutaneous coronary intervention with insertion of a sirolimus-eluting stent, the addition of heparin was associated with significantly higher incidences of hematomas (8.5 versus 3.8%) and overall vascular complications (5.3 versus 0.01%), including pseudoaneurysm (2.6 versus 0.0%); more patients required surgical repair (1.8 versus 0.3%) and there was a trend toward a higher rate of blood transfusion (6.6 versus 2.6%) (313). The authors concluded that routine addition of low-dose heparin to contrast agents during percutaneous coronary intervention is associated with higher rates of bleeding and vascular complications.

Hydralazine

Hydralazine seems to increase the risk of acute cutaneous vasculitis in patients given iopamidol (314).

Interleukin-2

Prior interleukin-2 therapy can induce atypical contrast medium hypersensitivity in the form of toxic recall reactions of various types (SEDA-17, 537), and these cannot be prevented by glucocorticoid premedication (315).

Metformin

The use of contrast media in patients taking metformin should be carried out cautiously. Contrast-induced nephropathy can lead to retention of metformin and lactic acidosis. However, there is no conclusive evidence that intravascular contrast agents precipitate metformin-induced lactic acidosis in patients with normal serum creatinine concentrations (under 130 μmol/l). This complication was almost always observed in non-insulin dependent diabetic patients with abnormal renal function before injection of contrast media (4,316).

Lactic acidosis can occur after the use of intravascular iodinated contrast agents in patients taking metformin. Metformin is excreted by the kidneys, and renal insufficiency can lead to its retention, which can cause fatal lactic acidosis. The manufacturers have recommended that metformin should be withdrawn for 48 hours before and 48 hours after the administration of intravascular contrast media, which can cause renal damage, and treatment should not be restarted until normal renal function is confirmed. Reviews of reported cases of lactic acidosis after contrast administration have shown that there was pre-existing renal impairment in all cases. A retrospective evaluation of patients taking metformin who underwent

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contrast angiography has also confirmed this observation (317). Of 33 patients, 29 had a normal serum creatinine before the angiographic procedure and none had a rise after angiography. Four had an abnormal serum creatinine before angiography; all four had a significant deterioration in renal function and died, two from unrelated causes and two from acute renal insufficiency and acidosis. The authors concluded that administration of contrast media is hazardous in diabetic patients with pre-existing renal impairment and that patients with normal renal function taking metformin are not at risk of lactic acidosis. They recommended that serum creatinine should be measured in all patients before angiography. In patients taking metformin with a normal serum creatinine, intravascular contrast is not contraindicated.

NSAIDs

Non-steroidal anti-inflammatory drugs may increase the risk of contrast nephropathy (SEDA-15, 502).

Papaverine

Ioxaglate has been reported to be precipitated by papaverine, which has been used in penile cavernosography (SEDA-11, 413), but some cases may have been due to an interaction between heparin and papaverine, perhaps not involving the contrast medium (SEDA-18, 444); in one case, the use of iopamidol 370 immediately after an injection of papaverine was followed by extensive intra-arterial thrombosis (SEDA-17, 537).

Pethidine

When pethidine is given with iodipamide, a myocardial infarction-like syndrome can occur due to spasm of the sphincter of Oddi (SED-8, 1026) (318).

Protamine

Protamine sulfate has a pH of 3–4 and causes precipitation of diatrizoic acid; if injected into a catheter containing diatrizoate in heparinized patients, it could cause a precipitate which in theory might result in an embolus.

Uricosuric drugs

Drugs that increase uric acid excretion may precipitate contrast nephropathy (SEDA-7, 452).

Interference with Diagnostic Tests

Urinalysis

Urinalysis after intravenous urography can give misleading results. Increased specific gravity, false positive tests for protein (with the sulfosalicylic acid and nitric acid ring methods, but not the bromophenyl dye test), and the presence of needle-like crystals have been reported. Pseudo-albuminuria can occur with a false-positive sulfosalicylic acid test (319).

Black copper reduction test

A positive result in the black copper reduction test, suggesting alcaptonuria, can follow the use of diatrizoate, iotalamate or iodipamide (320).

Urinary catecholamines

Methylglucamine-based contrast media interfere with the estimation of urinary catecholamines in patients with pheochromocytoma (SEDA-10, 423).

Para-aminohippuric acid

Diatrizoate can interfere with *para*-aminohippuric acid extraction studies (SEDA-15, 502) (321).

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Iodine-containing medicaments

General Information

Iodine is a non-metallic halogen element (symbol I; atomic no 53) which exists as a near-black solid but readily sublimates, giving a purple-colored vapor. It is found in nature both free (for example in large amounts in seaweeds such as kelp and in low concentrations in seawater) and in minerals such as iodyrite (silver iodide) and Chile saltpetre (sodium iodide).

Iodine-containing medicaments

Iodine must be present in the normal diet to prevent iodine-deficiency goiter or cretinism, and iodine deficiency-related disorders are still a worldwide (although preventable) group of diseases that affect about 150 million people in at least 40 countries. The WHO sponsored a program to control these disorders by the year 2000 (1,2), and since 1990 there has been a remarkable progress in prevention of iodine deficiency disorders. However, by the year 2000 one-third of the population affected by iodine deficiency disorders still did not have access to iodized salt (3).

Scepticism about the introduction of population-wide programs to prevent iodine-deficiency disorders is occasionally encountered in regions of mild iodine deficiency, especially in Europe (4). The main arguments against introduction of iodized salt are a temporary rise in the incidence of hyperthyroidism (5), a possible increase in the incidence of Graves' disease, and the fact that the remission rates with antithyroid drug therapy will fall (6). The value of preventing mild iodine deficiency has been supported by a longitudinal study from Switzerland, in which 109 000 people in a defined catchment area were studied before and for 9 years after correction of mild iodine deficiency (7). The incidence of toxic nodular goiter increased in the first year by 27%, but thereafter there was a steady fall in the incidence of both toxic nodular goiter (–73%) and Graves' disease (–33%). The range of optimal iodine intake is fairly narrow. Mild and moderate iodine excess are probably associated with higher frequency of hypothyroidism (8).

Some drugs contain iodine in amounts that considerably exceed the optimum daily intake of inorganic iodine. Such drugs include:

- most radiographic contrast media
- amiodarone and benziodarone
- iodoquinoline
- iodine-containing antiseptics (for example povidone-iodine).

Radioactive iodine

Different forms of radioiodine have been used at different times, including ^{123}I, ^{125}I, and ^{131}I. Radioactive iodine is used to scan the thyroid gland and in the treatment of thyrotoxicosis. See in the monograph on Radioactive iodine.

Potassium iodide and potassium iodate

Potassium iodide is the inorganic iodide most commonly used in high dosage for acute thyrotoxicosis. Indeed, large amounts of iodine cause reduced organification of iodine and a temporary block of thyroid hormone secretion (Wolff–Chaikoff effect) and therefore result in a more rapid thyrostatic effect than synthesis inhibitors. Potassium iodine is also used for preoperative treatment of goiter, especially to reduce preoperative bleeding. It can be used in combination with thyrostatic drugs but should never be prescribed in combination with potassium perchlorate, since each abolishes the other's effects. The thyrostatic effects of iodide are evident even at a dose of 6 mg/day, but doses between 50 and 100 mg/day are usually recommended. In some cases of intolerance to higher doses, perchlorate can be used, for example for preoperative treatment.

Potassium iodide has been widely used in asthma and chronic bronchitis as an expectorant. There is considerable controversy about its efficacy. It should not be used in adolescent patients because of its potential to aggravate and induce acne and its effect on the thyroid gland. In view of its doubtful efficacy and definite toxicity, it would be preferable if physicians stopped prescribing it as an expectorant.

Potassium iodide and potassium iodate are commonly added to table salt to prevent iodine deficiency and associated thyroid disease.

Iodine in protecting the thyroid against radioiodine

Accidents with nuclear reactors or nuclear bombs can expose large numbers of people to several decay products of uranium, and iodine isotopes are among the most abundant compounds released in such reactions. It is therefore logical to use salts of stable isotopes of iodine to prevent the accumulation of radioiodine in a person or population at risk of such exposure. The accidents in Windscale (UK), Three Mile Island (USA), and

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particularly Chernobyl (Ukraine) drew attention to such problems. The major question is therefore whether the potential adverse effects of stable iodine when given indiscriminately to large groups of people would outweigh the risk of radioiodine exposure. Stable iodine needs to be rapidly available when disasters occur, since, in order to be effective, it has to be given in sufficient amounts (100 mg) within a short time before or after (–12 to +3 hours) radioiodine exposure. Potassium iodate (KIO_3) is more stable than potassium iodide (KI), since the latter readily evaporates during prolonged storage. However, the dose recommended for radioprotection of 100 mg of iodine daily over several days (138 mg iodate per day) are close to retinotoxic doses of iodate reported in cases of accidental intoxication. In these doses iodate cannot be recommended. As an additive to salt for correcting iodine deficiency, much smaller doses of iodate are used (up to 1.7 mg/day), and in these doses iodate is probably safe (9).

The main adverse effects of stable iodine are shown in Table 1.

Iodine should be given to the general population if the risk of radioiodine exposure is sufficient (over 15–100 rem), but people with increased susceptibility to the adverse effects of iodine (previous thyroid disease or known serious allergies) should be excluded (10–15). In elderly people the benefit of stable iodine probably does not outweigh its potential adverse effects, while in pregnant women and infants the benefit to harm balance is not established; rapid evacuation of such people from fallout zones should be given the highest priority (SEDA-11, 358).

Tincture of iodine

Tincture of iodine (aqueous iodine oral solution, Lugol's solution) is a solution of iodine 5% plus potassium iodide 10% in water, which is used to reduce the vascularity of the thyroid gland in thyrotoxicosis before surgery.

Iodinated glycerol

Iodinated glycerol is used as a mucolytic agent in respiratory disorders, but its efficacy is controversial. Organically bound iodine is changed to unbound iodide after absorption.

Table 1 Adverse effects of iodine given for protection against radioiodine

Adverse effect	Susceptible individuals
Iodine-induced goiter	
Iodine-induced hypothyroidism	Fetus and neonate
Iodine-induced hyperthyroidism	People living in iodine-deficient areas; people with a history of hyperthyroidism
Sialadenitis and taste disturbances	
Nausea and abdominal pain	
Skin rashes	
Edema (including face and glottis)	
Allergic-like reactions (iodine fever, eosinophilia, serum sickness-like symptoms, vasculitis)	People with hypocomplementemic vasculitis

Iodoform

Iodoform is a lemon-yellow-colored crystalline organic salt of iodine (CHI_3), analogous to chloroform, with a saffron-like odor, used as an antiseptic.

Iodophors

Iodophors are labile complexes of elemental iodine with macromolecular carriers that both increase the solubility and provide sustained release of iodine. Povidone-iodine is a water-soluble iodophor that is used as an antiseptic and is said to be free of the undesirable effects of iodine tincture. However, iodine can be absorbed from it through burned areas (16), vaginal mucosa (17), oral mucosa (18), and in children even with normal skin (19). Povidone-iodine is discussed in a separate monograph under the title Polyvinylpyrrolidone.

Radiocontrast media

Many radiocontrast media contain iodine. These include iodixonal, iohexol, iomeprole, iopamidole, iopanoic acid, iopitridole, iopromide, iothalamate, iotrolan, ioversol, and ioxaglate. They are covered in a separate monograph.

General adverse effects

It has been estimated that in 1994 some 1.5 billion people in 118 countries were at risk of iodine deficiency, this being regarded as the world's most significant cause of preventable brain damage and mental retardation. Fortification of all salt for animal and human consumption has been chosen as the preferred method for the prevention of iodine deficiency disorders, and this approach is proving effective in reducing the incidence of such disorders. However, iodine supplementation is not without risks, which have been discussed (20) and which include allergic reactions and iodine-induced hyperthyroidism. It has been clearly shown that the benefits of iodine deficiency outweigh the risks on a population basis, but it is nevertheless evident that introduction of iodine supplementation is associated with clinical problems in individual subjects.

Because of its adverse effects, it is logical to omit iodine from all pharmaceutical formulations whenever possible, and at least clearly label its presence when it is necessary. The adverse effects of iodine include goiter and hypothyroidism (19,21), hyperthyroidism (SEDA-18, 176), neutropenia (22), metabolic acidosis (23), and generalized iododerma (16).

The term "iodism" covers a group of adverse effects that include irritation of the skin, the mucous membranes, and the conjunctiva. Allergic reactions are rare and mainly cause rashes, pruritus, fever, eosinophilia, and allergic vasculitis (24–27). Leukocytosis, swelling of the salivary glands, iodine coryza, and gastric upsets have also been reported. Headache can accompany the other reactions. In rare cases, jaundice, bleeding from the mucous membranes, and bronchospasm can occur. Inflammatory states may be aggravated by these adverse reactions.

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Effects of iodine on thyroid function

Iodine excess can induce hyperthyroidism or hypothyroidism (SEDA-12, 355) (SEDA-13, 378). Pharmacological amounts of iodine induce only a temporary inhibition of thyroid hormone secretion, since even during continuous administration of iodine normal thyroid function reappears ("escape from inhibition"), at least in most healthy subjects. For some unknown reasons, thyroid function can remain suppressed, resulting in hypothyroidism, secondary hypersecretion of TSH, and development of goiter (28). Patients with autoimmune thyroiditis or partial thyroid resection and very young infants (or fetuses) are especially susceptible to iodine-induced hypothyroidism. That therapeutic doses of iodine could induce hyperthyroidism was already known in the nineteenth century shortly after its introduction for the prevention and treatment of iodine deficiency (5,29). Thereafter, similar observations were made in several other parts of the world when iodine supplementation was introduced in iodine-deficient areas. Such iodine-induced hyperthyroidism (the "Jod-Basedow" phenomenon) can also occur in patients with other thyroid diseases (especially multinodular goiter), even when the diet was sufficient in iodine before the excess intake of iodine. This can even be found in patients with apparently normal thyroid glands. The Jod-Basedow phenomenon is usually associated with a slight goiter, high concentrations of both free levothyroxine (T4) and triiodothyronine (T3) and a very low uptake of radioactive iodine. The disease disappears spontaneously weeks or months after interruption of the excess iodine (30–32). Such a disorder should be differentiated from the temporary increase in T4 and reciprocal fall in T3 that can occur 1–2 weeks after the administration of iodine or iodine-containing drugs and that is not associated with symptoms of thyroid dysfunction (33).

Organs and Systems

Cardiovascular

Cardiac dysrhythmias have been seen after accidental ingestion of a large amount of potassium iodide solution (34). In one case administration of iodide was associated with pulmonary edema and iododerma (SEDA-7, 190).

Endocrine

It has been estimated that in 1990 iodine deficiency affected almost one-third of the world's population and represented the greatest single cause of preventable brain damage and mental retardation. Fortification of all salt for animal and human consumption has been chosen as the preferred method for the prevention of iodine deficiency disorders, and this approach is effective in reducing the incidence of such disorders. However, iodine supplementation is not without risk, particularly iodine-induced hyperthyroidism and thyroiditis. The issue of benefit versus harm has been reviewed and the view, previously expressed, that the benefits of correcting iodine deficiency far outweigh risk of iodine supplementation has been reiterated (35). Complications of iodine administration are not confined to those taking dietary supplements to correct deficiency, but can also occur in those given iodine-containing contrast media and with the use of iodine-containing antiseptic solutions.

Shortly after the administration of iodine-containing drugs, there is a self-limited increase in serum thyroxine (T4), which sometimes exceeds the reference range, and a reciprocal fall in serum triiodothyronine (T3). This usually resolves spontaneously, but can persist during further treatment (so-called isolated hyperthyroxinemia). In some patients, true hyperthyroidism (increases in both T4 and T3 with clinical symptoms) occurs, for example in about 5% of patients taking long-term amiodarone, whereas evolution to iodine-induced hypothyroidism is less frequent (36–38). On the other hand, the frequency of iodine-induced hyperthyroidism can comprise about half of all cases of hyperthyroidism, at least in elderly patients taking several drugs (SEDA-7, 399).

The use of iodine has been held responsible for the increasing frequency of relapse of Graves' disease in the USA. Treatment of more severe cases of iodine-induced hyperthyroidism can be difficult, as thyroid synthesis inhibitors are not immediately active and ^{131}I cannot be used because of low thyroid uptake. The carefully supervised combination of perchlorate and methimazole is effective (39), but surgery has also occasionally been advocated.

A summary of the occurrence and epidemiology of iodine-induced hyperthyroidism has been published (40), based on the authors' experience in Tasmania, Zaire, Zimbabwe, and Brazil. Another review has more specifically examined the cardiac features of iodine-induced hyperthyroidism and has emphasized the importance of awareness, monitoring, and treatment of such hyperthyroidism in areas in which iodine supplementation has been recently introduced (41).

The complexity of the interaction between iodine intake and autoimmune thyroid disease has been highlighted by reports of evidence that iodide (compared with thyroxine) induces thyroid autoimmunity in patients with endemic (iodine deficient) goiter (42), while in those with pre-existing thyroid autoimmunity, evidenced by the presence of antithyroid (thyroid peroxidase) antibodies, administration of iodine in an area of mild iodine deficiency led to subclinical or overt hypothyroidism (43).

More importantly, in a study from Italy the use of iodine-containing disinfectants was responsible for transient neonatal hypothyroidism in more than 50% of cases identified (another common cause being transfer of maternal antibodies) (44). These findings led the authors to conclude that pregnant women should be advised of the adverse effects of using iodine-containing products and that their use should be generally discouraged.

Because of reports of severe hyperthyroidism after the introduction of iodized salt in two severely iodine-deficient African counties (Zimbabwe and the Democratic Republic of the Congo), a multicenter study has been conducted in seven countries in the region to evaluate whether the occurrence of iodine-induced hyperthyroidism after the introduction of iodized salt was a generalized phenomenon or corresponded to specific local circumstances in the two affected countries (45). Iodine deficiency had been successfully eliminated in all of the areas investigated and the prevalence of goiter had fallen markedly. However, it was clear that some areas were now exposed to iodine excess as a result of poor

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monitoring of the quality of iodized salt and of the iodine intake of the population. In these areas, iodine-induced hyperthyroidism occurred only when iodized salt had been recently introduced.

This complication of iodine administration is not confined to those receiving dietary supplements. Two of 788 unselected patients from a relatively iodine-deficient area of Germany who underwent coronary artery angiography with an iodine-containing radiographic contrast agent developed hyperthyroidism within 12 weeks (despite the absence of the typical risk factors of advanced age, preceding nodular goiter, or a low serum TSH) (46). While this represents a relatively low incidence, this series highlights the importance of recognizing the role of iodine-containing drugs in inducing hyperthyroidism, even in developed countries.

Iodinated glycerol

After the administration of iodinated glycerol organically bound iodine is changed to unbound iodide, causing thyrotoxicosis, hypothyroidism, or goiter in some patients (47). Reversible hypothyroidism has been reported in nursing-home residents, without a history of thyroid disease, who had been taking iodinated glycerol as an expectorant (48). Hypothyroidism has been reported after long-term treatment with iodinated glycerol (49).

Iodophors

Extensive iodine absorption from povidone-iodine can cause transient hypothyroidism or in patients with latent hypothyroidism the risk of destabilization and thyrotoxic crisis (SEDA-20, 226) (SEDA-22, 263). Especially at risk are patients with an autonomous adenoma, localized diffuse autonomy of the thyroid gland, nodular goiter, latent hyperthyroidism of autoimmune origin, or endemic iodine deficiency (50).

Hyperthyroidism from povidone-iodine is rarer than hypothyroidism (SEDA-20, 226), but a history of long-term use of iodine-containing medications should be considered when investigating the cause of hyperthyroidism.

- A 48-year-old woman developed palpitation and insomnia (51). The clinical history, physical examination, and laboratory tests supported hyperthyroidism. Since July 1994 she had been combating constipation by improper use of an iodine-containing antiseptic cream for external use only. She had inserted povidone-iodine into her rectum by means of a cannula. The iodine-containing cream was withdrawn and she was given a beta-blocker. The palpitation resolved within 2 weeks and her plasma thyroid hormone concentrations normalized within 1 month.

Hyperthyroidism in this patient was probably triggered by improper long-term use of an over-the-counter iodine-containing cream.

Potassium iodide

Iodine-induced hypothyroidism has been described as the result of prolonged intake of potassium iodide and iodinated glycerol as mucolytics (52).

Patients with an underlying disorder of the thyroid gland may be more predisposed to this complication.

The case of a severe iodine-induced thyrotoxicosis in a patient who had been using iodine-containing eye-drops for more than 10 years has been reported (53).

Mouth and teeth

Occasionally, after a high dose of iodine, sudden swelling of the parotid and submandibular glands develops (54).

- Acute sialadenitis ("iodide mumps") has been described in a 70-year-old man who underwent femoral artery angiography with an iodine-containing contrast agent; he gave a history of a similar episode 24 hours after a previous angiogram (55).

This effect is thought to be a hypersensitivity reaction due to formation of a complex between iodide and plasma proteins.

Urinary tract

Iodinated radiographic contrast media can cause acute renal insufficiency, perhaps as a result of reduced renal blood flow, an intrarenal osmotic effect, or direct tubular toxicity (56). Diuretics, calcium channel blockers, adenosine receptor antagonists, acetylcysteine, low-dose dopamine, the dopamine D_1 receptor agonist fenoldopam, endothelin receptor antagonists, and captopril have all been used to prevent contrast nephropathy.

Skin

A complication of the use of alcoholic iodine solution has been described in three women undergoing cesarean section, who developed painful, superficial, inflammatory reactions on their buttocks after skin preparation for surgery with 10% iodine in alcohol (57). These lesions were believed to have been caused by pooling of the solution underneath the patients, topical skin damage being exacerbated by heat and occlusive drapes.

Induction and aggravation of acne is a typical reaction to iodide (58).

Iododerma, which is thought to be an allergic reaction, starts with an acneiform lesion, localized in the area of the sebaceous glands, which spreads to form verrucous granulomatous lesions (59,60). After discontinuation of iodide, the skin clears over a few weeks. In addition to this typical picture of iodide sensitivity, iodide can cause urticaria and erythema and even hemorrhagic rashes. In order to verify the etiology of the skin conditions in certain cases, sensitivity testing may be required, but is not without risk.

Immunologic

Allergy to iodides can occur (61,62).

Of 126 participants in a study of the metabolism of radiolabelled proteins, four repeatedly developed urticaria and other symptoms after potassium iodide administration (63). Two of them were challenged with oral potassium iodide and developed urticaria, angioedema, polymyalgia, conjunctivitis, and coryza. Ten control patients were also challenged without adverse effects.

- Delayed hypersensitivity to potassium iodide occurred in a 66-year-old man who was given a cough syrup, Elixifilin, which contained potassium iodide (130 mg/15 ml), as well

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as theophylline and alcohol. Dyspnea, angioedema, itching, and erythema of the face and neck developed a few hours after the second dose. His symptoms disappeared 24 hours after treatment with parenteral glucocorticoids. Five hours after Elixifilin or iodide challenge, he developed edema of the face and neck, itching of the pharynx and eyes, and a sensation of heat (64).

Second-Generation Effects

Pregnancy

Iodine readily crosses the placenta, and the fetal concentration usually exceeds the maternal concentration. The placenta does not seem to have a regulating transfer mechanism, implying that excess maternal intake of iodine will also expose the fetus to iodine intoxication. This usually results in hypothyroidism and development of goiter. Such goiters may become very large and even create obstetrical problems during delivery or mechanical compression during early postnatal life (SEDA-4, 295) (SEDA-5, 328). In neonates iodine excess is a well-known cause of transient hypothyroidism. Iodine-containing antiseptics should therefore be avoided in both the delivery room and the neonatal ward. A similar warning against the use of iodine or iodine-containing drugs applies during lactation since iodine is actively secreted in milk.

Fetotoxicity

Large quantities of iodine reduce the organic binding of iodine (the Wolff–Chaikoff effect). Thus, the regular use of iodide during pregnancy can cause development of a goiter in the fetus. The size of the goiter in the child can be large enough to cause difficulty during delivery. Treatment of vaginitis with iodine-containing solutions in pregnant women can lead to goiter and hypothyroidism in the infant (17).

Neonatal goiter caused by the use of potassium iodine as an expectorant during pregnancy has been reported (65). The neonate, a girl, had acute hypothyroidism, with myxedema and respiratory distress. She was given levothyroxine for 6 months, with complete normalization of thyroid function.

Severe transient postnatal hypothyroidism has been reported in infants whose mothers have received high doses of iodine during pregnancy or multiple local applications of povidone-iodine during pregnancy and for delivery (SED-14, 472). Transient neonatal hypothyroidism during breastfeeding after postnatal maternal topical iodine treatment has also been reported (66).

- A baby girl was born prematurely at 29 weeks. Her weight, length, and head circumference were appropriate to her gestational age. Parenteral feeding was stopped at 20 days, and breastfeeding was gradually increased. TSH screening for congenital hypothyroidism on day 5 was negative (below 1 μU/ml; reference range 0.45–10.0), but a second screening on day 23 was high at 23 μU/ml. There were no signs of hypothyroidism and no palpable goiter. A confirmatory laboratory test on day 29 showed a high serum TSH concentration (288 μU/ml) and reduced concentrations of free thyroxine (2.8 ng/l; reference range 19–23) and free tri-iodothyronine (1.52 pg/ml; reference range 2.2–5.4). The mother had developed an abscess of the abdominal wall 1 week after cesarean section and had been treated with intravenous antibiotics and iodine tampons, 60 cm^2 daily to the abscess wound, containing about 10.5 mg of iodine. Maternal thyroid function was normal (TSH 1.59 μU/ml and free thyroxine 12 ng/l). Thyroid antibodies to thyroglobulin, TSH receptors, and thyroperoxidase were negative. Iodine concentrations in the maternal milk and infant urine were extremely high: 4410 (reference range 29–490) micrograms/l and 3932 (reference range below 185) micrograms/l respectively. Treatment with levothyroxine (25 micrograms/day) was started on day 32, breastfeeding was discontinued, and disinfection with iodine was stopped. Thyroid function normalized after 6 days, levothyroxine was withdrawn, and breastfeeding was restarted. Thyroid function remained normal over a follow-up period of 4 months.

Skin disinfection with iodine also caused goiter and hypothyroidism in five of 30 newborns under intensive care (67). Antiseptics containing iodine should be avoided not only during pregnancy and delivery but also after the delivery during breastfeeding.

Drug Administration

Drug overdose

- A patient who deliberately took potassium iodide solution 50 ml and a small dose of mefenamic acid (six capsules) as part of a suicide attempt developed acute renal insufficiency necessitating hemodialysis (68). Normal renal function returned after 10 days of hemodialysis.

The authors postulated that iodide toxicity had resulted in hemolysis and hemoglobinuria, which, together with acute interstitial nephritis secondary to inhibition of prostaglandin synthesis from mefenamic acid ingestion, had resulted in acute renal insufficiency. The mechanism of hemolysis resulting from toxic doses of iodine is not clear, although it may reflect inhibition of various red cell enzymes.

Interference with Diagnostic Tests

Thyroid function tests

Estimation of protein-bound iodine and tracer studies for the estimation of thyroid function are interfered with by the use of iodine-containing compounds (69).

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Iodopropynylbutylcarbamate

General Information

Initially used as a preservative in wood paints and metalworking fluids, iodopropynylbutylcarbamate is being increasingly used in cosmetics (1).

Organs and Systems

Immunologic

Four contact allergic reactions were reported in a series of 3168 consecutively patch-tested patients (2). In another study there were 16 positive reactions (0.3%) in 4883 consecutive patients (3).

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Ion exchange resins

General Information

The ion exchange resins colestyramine (rINN) and colestipol (rINN) are not absorbed, and their main adverse effects are therefore on the gastrointestinal tract. They can also interfere with the absorption of other drugs or fat-soluble vitamins.

Organs and Systems

Metabolism

The ion exchange resins tend to increase serum triglyceride concentrations, especially in patients with hypertriglyceridemia (1).

Nutrition

Serum total carotenoid and vitamin A concentrations fell by 30% in patients taking colestipol 30 g/day (2).

Acid–base balance

Colestyramine has been reported to have caused a hyperchloremic metabolic acidosis.

- A 70-year-old woman with a 2-year history of primary biliary cirrhosis confirmed by histological and immunological criteria took colestyramine sachets twice daily for 2 months and developed lethargy, confusion, and drowsiness (3). She had signs of chronic liver disease, portal hypertension, and hepatic encephalopathy. Laboratory investigations confirmed a metabolic acidosis (pH 7.15) and hyperchloremia. Multiple cultures failed to reveal sepsis, and a urinary pH of 4.85 together with tests of renal acidification excluded renal tubular acidosis. No other cause was found and she responded

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to 600 mmol of sodium bicarbonate intravenously over 36 hours.

Hematologic

Inhibition of vitamin K absorption can cause vitamin K deficiency, leading to hypoprothrombinemia and hence to bleeding (4).

Gastrointestinal

Patients taking colestyramine often have constipation, abdominal discomfort, and heartburn, but dietary fiber, such as psyllium, can reduce the symptoms (5,6). Other effects are flatulence, nausea, and fecal impaction; a mild laxative may be needed, particularly in the elderly. Many other patients complain of anorexia and occasionally there is diarrhea. Doses of colestyramine higher than the 10–16 g normally used can cause steatorrhea (7).

A small child died when impacted resin obstructed the colon (SEDA-8, 935) (8).

The most common adverse effect of colestipol is constipation (30%). In the first months of therapy nausea and bloating can also occur. There is disappointingly poor adherence to therapy in young patients (9). The encapsulated form of the drug is better tolerated (10).

Liver

- A 65-year-old man with type IIa dyslipidemia who took flavored colestipol granules 2 scoops/day for 3 months developed asymptomatic hepatotoxicity (11). Several of his liver enzymes were raised to 10 times the upper limit of the reference range. One week after withdrawal of colestipol, his serum transaminases fell dramatically and 3 weeks later all his liver function tests were normal.

Rechallenge was not attempted, but other potential causes of hepatocellular injury were ruled out.

Musculoskeletal

A degree of osteoporosis or osteomalacia can occur because of reduced vitamin D absorption (12).

Drug–Drug Interactions

General

Ion-exchange resins do not have systemic adverse effects, but they can affect the absorption of other drugs from the gut, particularly if they undergo enterohepatic or enteroenteric recirculation, since they will adsorb them in the gut and prevent their reabsorption.

There is reason to anticipate problems if the resin is given along with acidic drugs and some other drugs that have a narrow safety margin, such as oral anticoagulants (coumarins), cardiac glycosides, and thyroid hormones (thyroxine, triiodothyronine). Interference with the absorption of other acidic drugs, including the barbiturates, naproxen, phenylbutazone and its congeners, and the thiazide diuretics, can almost certainly occur, but is of little or no clinical importance, since the doses of these drugs can easily be adjusted as time goes by, to allow for any reduction in absorption, or alternative drugs can be used. Interference with anticoagulants and cardiac glycosides presents the most serious problems, because they have a low therapeutic index. It has often been said that problems can be avoided provided the drugs are not given simultaneously; however, this is not true when the drug in question undergoes enterohepatic circulation, as is the case with digitoxin and phenprocoumon, as a result of which these substances are present in the gastrointestinal tract for a long time and can be exposed to an ion exchange resin at any time. The interval principle for other drugs is useful, but the interval should be at least 1 hour and in the case of thyroxine 4–5 hours, in which case the drug should be given before the resin.

Cardiac glycosides

Colestyramine and colestipol bind digoxin and digitoxin and can affect their absorption. When the ion exchange resins and digoxin are co-administered the absorption of digoxin is reduced (13). However, even when they are not administered together, the resins can bind cardiac glycosides that have re-entered the gut after absorption by virtue of enterohepatic recycling and enteral secretion, increasing their rate of elimination. This action has been used to treat digoxin toxicity (14–16), digitoxin toxicity (17), and toxicity from derivatives of digoxin (18).

Coumarin anticoagulants

The interaction of colestyramine with coumarins is due to the enterohepatic recirculation of coumarins, which is interrupted by colestyramine.

Phenprocoumon undergoes enterohepatic recycling, and its elimination can be enhanced by ion exchange resins, sometimes with fatal consequences (19).

Warfarin also undergoes enterohepatic recycling, and its elimination can be enhanced by ion exchange resins (20); this has been used to treat warfarin toxicity (21).

Folic acid

Malabsorption of folic acid has been reported in patients taking colestyramine (SEDA-13, 1326) (22).

In children taking colestipol supplementary folic acid may need to be provided (23).

Valproic acid

The systemic availability of valproic acid is reduced by colestyramine unless they are given 3 hours apart (24).

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Ipecacuanha, emetine, and dehydroemetine

General Information

Ipecacuanha is an extract of the root of *Psychotria ipecacuanha*, also known as *Cephaelis ipecacuanha*, a member of the Rubiaceae. It contains the emetic alkaloids cephaeline and emetine. It has often been used as a home remedy for various purposes, and not only as an emetic. It is a traditional ingredient of some expectorants, since expectoration often accompanies vomiting. Misuse of ipecacuanha by patients with anorexia nervosa and bulimia has resulted in severe myopathy, lethargy, erythema, dysphagia, cardiotoxicity, and even death. Use in infancy generally seems safe.

Emetine, once the drug of choice for the treatment of amebiasis, despite marked cardiotoxicity, has largely been replaced by metronidazole and related compounds for this indication. Large doses of emetine can damage the heart, liver, kidneys, intestinal tract, and skeletal muscle. Allergic reactions and tumor-inducing effects have not been described. Dehydroemetine is a little less toxic but also less effective than emetine; its adverse effects are similar (SED-11, 594).

Gastrointestinal decontamination in acute toxic ingestion has been reviewed (1).

- Although ipecac generally seems to have a good safety profile, it can be associated with protracted vomiting. Other reported adverse effects include drowsiness, agitation, abdominal cramps, diarrhea, aspiration pneumonia, cerebral hemorrhage, pneumoperitoneum, and pneumomediastinum. Its use is not currently recommended (2).

Gastric lavage can be useful in some patients who have taken life-threatening doses of highly toxic substances. However, toxin absorption can be enhanced by gastric lavage. Reported adverse effects mainly include laryngospasm, hypoxemia, aspiration pneumonia, bradycardia, electrocardiographic ST segment elevation, and rarely mechanical injury to the gastrointestinal tract.

- Activated charcoal has gained popularity as a first choice for gut decontamination, based on its efficacy and relative lack of adverse effects. Poor patient acceptance is a disadvantage. Frequent vomiting can rarely become a problem.
- Saline laxatives (magnesium citrate, magnesium sulfate, sodium sulfate, and disodium phosphate) or saccharide laxatives (sorbitol, mannitol, lactulose) are also used in poisoned patients. Common adverse effects are abdominal cramps, excessive diarrhea, and abdominal distension. Dehydration and electrolyte imbalance in children, and hypermagnesemia and magnesium toxicity (with magnesium-based cathartics) have also been reported.
- Whole bowel irrigation to wash the entire gastrointestinal tract rapidly and mechanically is similar to the methods used by gastroenterologists to prepare patients for colonic investigation or bowel surgery. It is safe, even in children, pregnant women, and patients with cardiac or respiratory failure. Polyethylene glycol isotonic electrolyte solution is commonly used. Complications are

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usually minor and include nausea, vomiting, abdominal distension and cramps, and anal irritation.

Organs and Systems

Cardiovascular

Cardiotoxicity is the most serious and dangerous adverse effect of emetine. The clinical signs are tachycardia, dysrhythmias, and hypotension. Deaths have been described. Electrocardiographic abnormalities occur in 60–70% of cases; increased T wave amplitude, prolongation of the PR interval, ST segment depression, and T wave changes are all common. It seems possible that emetine influences the cell permeability of sodium and calcium ions, and this could be the basis of its effect on cardiac automaticity and contractility and on the electrocardiogram (SED-11, 594). The symptoms of emetine toxicity suggest that an effect on intracellular magnesium concentrations could be another possible explanation, but there are no data to support this hypothesis (SED-11, 594).

Respiratory

Asthma can occasionally be induced by ipecacuanha; when the compound was more widely used in medicine this was a familiar problem for those compounding medicines (3).

Gastrointestinal

Nausea and vomiting are frequent, perhaps in as many as one-third of all cases. In about half the cases, diarrhea is induced or existing diarrhea aggravated. Melena can occur, but this seems unlikely to be drug-induced (SED-11, 594).

Skin

Dermatitis has been attributed to emetine (4), as has cellulitis at the site of injection (5).

Musculoskeletal

Complaints of weakness, tenderness, and stiffness of skeletal muscles, especially in the neck and shoulder, are common. Following emetine aversion therapy for alcohol abuse, muscle weakness and pathological changes in muscle biopsy specimens have been described (SED-11, 594).

A reversible myopathy secondary to abuse of ipecacuanha by individuals with eating disorders has been noted (SED-12, 945) (SEDA-17, 421); the active alkaloid may have been responsible.

Long-Term Effects

Drug abuse

Munchausen's syndrome by proxy involving syrup of ipecacuanha has been reported in an 18-month-old child who was brought by his mother with persistent vomiting for 4 weeks with generalized myopathy and pneumonia (6). Its over-the-counter availability, low cost, and effective emetic properties give this drug a high appeal for such abuse.

Drug Administration

Drug overdose

There is some suggestion of cardiac impairment with overdosage, presumably also myopathic. Forced emesis can lead to esophageal damage or even complete rupture; pneumomediastinum and pneumoperitoneum have therefore sometimes complicated induced emesis (SEDA-10, 326). A bizarre case of neonatal vomiting, irritability, and hypothermia was attributed to the mother having added ipecacuanha surreptitiously to her baby's feed; at any age, however, emetine in excess can be very irritant to the gastrointestinal tract, resulting, for example, in bloody diarrhea.

Drug–Drug Interactions

Activated charcoal

Activated charcoal, sometimes used to treat self-poisoning, binds the active ingredients of ipecacuanha and inactivates them, at least partly (7). The administration of ipecacuanha also delays the administration of charcoal (8). They should not be co-administered.

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Ipratropium bromide

See also Anticholinergic drugs

General Information

Ipratropium hydrobromide is a quaternary amine, the semisynthetic isopropyl derivative of atropine, which has low lipid solubility and is poorly absorbed. It has anticholinergic properties and is used to treat asthma.

The metered dose of ipratropium is some 20 micrograms. Its limited availability accounts for its relative bronchial selectivity when ipratropium is given in low doses by the aerosol

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route. In healthy volunteers, 120–280 micrograms given by intravenous injection reduced salivary secretion and increased heart rate. Inhaled doses, up to a total of 1.2 mg, had no significant effect on heart rate, although some patients reported dryness of the mouth (1). Only if substantial overdosage occurs (for example 1 mg by inhalation) do traces of generalized atropine-like effects begin to appear.

Ipratropium has established a place in the therapy of asthma as an alternative to $beta_2$-adrenoceptor agonist aerosols for patients who fail to respond adequately to these agents. Ipratropium may be more effective than $beta_2$-adrenoceptor agonists for patients with non-atopic asthma and chronic bronchitis. It has been reported to augment the effects of $beta_2$-adrenoceptor agonists when given by nebulized inhalation in acute asthma (2).

Therapeutic doses from an aerosol are free of systemic adverse effects because of the very low blood concentration after inhalation. Transient dryness of the mouth and scratching in the trachea can occur in up to 25% of patients receiving wet nebulizer treatment with the drug.

Therapeutic studies

There is continuing discussion about the role of inhaled antimuscarinic drugs combined with $beta_2$-adrenoceptor agonists in the treatment of acute asthma (3). Five trials involving 453 patients examined the efficacy of using a single dose (250 micrograms) of ipratropium bromide with a $beta_2$ agonist. There were no reductions in hospital admission rates when pooling the two trials that reported this outcome (RR = 0.93; CI = 0.65–1.32). In three trials in which pulmonary function was the major outcome measure, there was a significantly greater improvement in lung function at 60 minutes and 120 minutes after a single inhalation of a combination of an antimuscarinic drug and a $beta_2$ agonist. The addition of a single dose of an antimuscarinic drug was not associated with increased vomiting or tremor, but there was an apparent reduction in nausea (RR = 0.55; CI = 0.33–0.91). Five trials involving 366 children examined the effects of multiple treatments with combined ipratropium and a $beta_2$ agonist. Pooling of four trials using hospital admission as an outcome measure showed a 30% reduction (RR = 0.72; CI = 0.53–0.99). The authors cautioned that the total number and size of studies were small and that their conclusions could be modified by results of larger trials (3).

Comparative studies

Perennial rhinitis is common in both adults and children and is usually treated with intranasal corticosteroids, intranasal ipratropium bromide, antihistamines, intranasal cromones, and decongestants. Treatment-related adverse effects are common and monotherapy is often inadequate. There are few published studies of the comparative efficacy of rhinitis treatments.

Budesonide

Ipratropium bromide (42 micrograms per nostril bd) has been compared with budesonide (84 micrograms per nostril bd) for 6 months in a randomized, double-blind trial in 146 children with perennial rhinitis (4). Both treatments resulted in significant improvements in rhinorrhea, sneezing, and congestion (as rated by both patients and physicians) and improved quality of life. Budesonide achieved better control of sneezing than ipratropium throughout the study period and better control of congestion than ipratropium in the later part of the study. Of 36 patients who did not complete the study, largely for administrative reasons, six using ipratropium withdrew owing to lack of efficacy. There were no reports of systemic anticholinergic adverse effects. The commonest nasal adverse events in both groups were nasal congestion (23% with ipratropium and 18% with budesonide) and rhinitis (13% with ipratropium and 7% with budesonide). Of nasal adverse events considered to be related to treatment, epistaxis and nasal irritation were more common with budesonide (10 and 4% respectively) than with ipratropium (8 and 0%). Sneezing occurred in 5% of those using ipratropium and in none of those using budesonide, probably reflecting the better efficacy of budesonide for control of sneezing. Overall both drugs were well tolerated.

Ipratropium (42 micrograms per nostril tds), budesonide (84 micrograms per nostril bd), and ipratropium plus budesonide for 2 weeks have been studied in a randomized, double-blind, placebo-controlled trial in 533 patients with perennial rhinitis (5). As monotherapy, both ipratropium and budesonide produced significant reductions in rhinorrhea compared with placebo, and budesonide was more effective than ipratropium in reducing congestion and sneezing. Non-nasal adverse events occurred equally in all three groups. The incidences of epistaxis, nasal congestion, and nasal irritation were similar in all three groups (1–5%) but there was a greater incidence of nasal dryness (3 versus less than 1%) and blood-tinged mucus (4 versus 2%) with ipratropium. Combination therapy with ipratropium and budesonide reduced the severity and duration of rhinorrhea in 74 and 66% of patients compared with 57 and 50% for ipratropium, 64 and 54% for budesonide, and 47 and 38% for placebo. There were no other advantages for combination therapy over budesonide. Nasal adverse events occurred in all groups, including placebo, but patients who had two weeks of budesonide in the monotherapy arm of the study followed by combination therapy had more epistaxis (5%) and more nasal dryness (5%) than patients who had ipratropium before combination treatment. The authors concluded that combination therapy is superior to monotherapy, with no increase in adverse effects. However, the effect of combination therapy over monotherapy in this study is quite small and does not appear to have reached statistical significance. Nevertheless, most adverse effects seem to have been related to budesonide rather than to ipratropium. The addition of ipratropium in a patient already taking budesonide seems to be safe and may increase efficacy.

Salmeterol

A double-blind, double-dummy, parallel-group study in 144 patients with severe COPD (FEV_1 41% of predicted) has been conducted over 12 weeks to determine whether the combination of salmeterol 50 micrograms bd plus ipratropium 40 micrograms bd was better than salmeterol alone (6). At the beginning of treatment salmeterol

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increased FEV_1 (at peak 7% of predicted) for over 12 hours. Salmeterol plus ipratropium produced a greater bronchodilator response (at peak 11% of predicted) than salmeterol alone during the first 6 hours after inhalation. There were significant improvements in daytime symptom scores and peak flows with both salmeterol and salmeterol plus ipratropium compared with placebo. Adverse events were similar in the treatment groups; headache (six patients with salmeterol plus ipratropium, four with salmeterol, and 11 with placebo) and cough were the most common drug-related adverse events. Over the 12 weeks, 35 patients had an exacerbation of COPD, 36% with placebo, 23% with salmeterol, and 13% with salmeterol plus ipratropium.

Organs and Systems

Respiratory

In some patients with atopic asthma, bronchoconstriction can follow the use of ipratropium (SEDA-9, 127).

There has been concern that ipratropium and other antimuscarinics may cause drying and inspissation of sputum with resulting sputum retention. In vitro studies show no effect on ciliary activity. In healthy subjects and patients with chronic bronchitis, inhaled ipratropium did not affect the rate of tracheobronchial clearance of a previously inhaled radioactive carrier aerosol. In studies using therapeutic doses for 2–14 days sputum volume and viscosity did not change (1).

Sensory systems

Pupillary dilatation has several times been reported, possibly because the spray enters the eye; it is risky in cases of glaucoma (7).

Blurred vision can occur in patients given ipratropium by inhaler (8).

- A 68-year-old man's visual acuity dramatically improved (20/100 to 20/40) after he discontinued ipratropium bromide, which he had been taking in a dose of two puffs every 6 hours for chronic obstructive pulmonary disease.

Angle-closure glaucoma precipitated by ipratropium has been reported following both nebulizer and pressurized aerosol treatment (9,10); however, a specific study showed that in asthmatic children with no pre-existing ocular abnormalities, the risk of an ocular adverse effect from nebulized ipratropium is extremely small (11). A Turkish group studied the acute effects of inhaled ipratropium bromide, given both by metered dose inhaler and nebulizer, in 21 men (mean age 61 years) with a smoking history of 47 pack-years and FEV_1 values less than 50% of predicted at baseline (12). They did not have glaucoma. The doses of ipratropium bromide were 40 micrograms by inhaler and 250 micrograms by nebulizer. Intraocular pressure was measured at baseline and 120 minutes after drug administration. There was no increase in pressure with either dose, but this does not exclude the possibility that there may be a more pronounced effect in patients who have glaucoma, nor that chronic administration may have a greater effect.

A bad taste in the mouth has been reported by 20–30% of patients.

Psychological, psychiatric

Ipratropium produces no significant impairment of cognitive or psychomotor function in elderly patients with chronic airway obstruction (SEDA-21, 187).

Gastrointestinal

One case of paralytic ileus has been reported (SEDA-15, 137).

Urinary tract

In elderly men, who may have prostatic hyperplasia, ipratropium should be used with caution since it can cause urinary retention (SEDA-14, 122) (13).

Drug Administration

Drug administration route

The removal of chlorofluorocarbons from industrial and household products underlies the 1987 "Montreal Protocol on Substances that Deplete the Ozone Layer". A reformulation of ipratropium bromide using an alternative, non-chlorofluorocarbon propellant, hydrofluoroalkane, 134a (1,1,1,2-tetrafluoroethane), has been compared with the marketed, chlorofluorocarbon-containing ipratropium bromide aerosol in a randomized, double-blind, placebo-controlled trial in 507 patients with moderate to severe obstructive airways disease (14). The patients were treated with hydrofluoroalkane/ipratropium bromide 42 micrograms, hydrofluoroalkane/ipratropium bromide 84 micrograms, hydrofluoroalkane/placebo, chlorofluorocarbon/ipratropium bromide 42 micrograms, or chlorofluorocarbon/placebo. The incidences of adverse clinical and laboratory events and significant cardiographic effects were not different across the groups.

A nasal spray (isotonic aqueous ipratropium pump) has been used in allergic and non-allergic rhinitis as well as the common cold. The spray caused no systemic adverse effects and only minor infrequent episodes of nasal dryness and epistaxis, which did not interfere with treatment (15,16).

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Iprindole

See also Monoamine oxidase inhibitors

General Information

Iprindole is a 6,5,8 tricyclic compound, whose first two rings form an indole nucleus (SED-7, 27). It is of some theoretical interest, in that it is weak in its action on the amine pump mechanism. Adverse effects are reported as being similar to those of other tricyclic antidepressants (1,2).

Organs and Systems

Liver

The major adverse effect of serious concern has been jaundice. A review of 21 cases of liver damage during iprindole treatment showed that the onset was at 4–21 days after starting treatment (3). Recovery was rapid after withdrawal. Liver biopsy showed predominantly cholestasis. This complication seems to be similar to that seen after chlorpromazine. In one instance (4), jaundice was accompanied by a marked eosinophilia of 30% and laboratory signs suggesting some hepatocellular damage as well. Jaundice promptly recurred when the drug was re-administered. All the features of this case suggested an allergic reaction.

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Irbesartan

See also Angiotensin II receptor antagonists

General Information

Irbesartan is a potent selective angiotensin II type 1 (AT_1) receptor antagonist. Its pharmacology is the same as that of other angiotensin II receptor antagonists (1). In the registration studies and other controlled trials adverse effects were not dose-related and not different from placebo.

An updated review of the pharmacology and therapeutic use of irbesartan in cardiovascular disorders has been published, including a brief section on drug tolerability, which referred to an unpublished postmarketing surveillance study in which 14% of the patients (1232 of 9009) had mostly mild adverse events (2). No further details were given on the nature of the adverse events.

Organs and Systems

Liver

Cholestasis with irbesartan has been reported (3).

- A 62-year-old woman developed deep icterus and hepatomegaly 1 month after starting to take irbesartan 300 mg/day. She had been hypertensive for 15 years and had no history of liver disease or risk factors for liver disease. Her bilirubin was 403 µmol/l, alkaline phosphatase 3193 IU/l, and aspartate transaminase 177

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IU/l. Serology and autoimmune screens were negative, as were liver ultrasonography and computerized tomography. Cholangiopancreatography was normal. Irbesartan was replaced by amlodipine and metoprolol, and 2 months later she remained jaundiced (bilirubin 324 μmol/l). Liver biopsy showed portal tract expansion, minimal inflammation, ectatic ductules, and cholestatic rosettes. Within 16 weeks she fully recovered and continued to be anicteric more than 1 year later.

The temporal profile in this case and the lack of an alternative cause for liver dysfunction suggested a drug reaction.

Urinary tract

Renal insufficiency has been attributed to irbesartan.

- A 77-year-old woman took captopril 25 mg tds and furosemide 40 mg/day for decompensated heart failure (4). Irbesartan 75 mg/day then replaced captopril, and 3 days later she developed renal insufficiency. Irbesartan was withdrawn and her renal function normalized within 5 days. It was not stated whether her blood pressure also changed.
- A 78-year-old Caucasian man with insulin-treated type II diabetes, hypertension, and stable mild renal insufficiency took captopril 25 mg/day and torasemide 150 mg/day (5). His general physician substituted irbesartan 150 mg/day for the captopril. The basal average serum creatinine rose from 220 to 294 μmol/l 10 days after beginning irbesartan, and to 752 μmol/l 3 weeks later, at which stage he was admitted with acute renal insufficiency, oliguria, and edema with a 6 kg weight gain. Two days after withdrawal of irbesartan his creatinine reached a maximum of 907 μmol/l and then fell progressively to 570 μmol/l and never returned to basal values. The patient was started on chronic hemodialysis. Renal Doppler and MRI scans showed no renal artery stenosis, but there were signs of chronic renal ischemia, which may have contributed to the adverse drug reaction.

It is possible in the second case that irbesartan 150 mg/day produced abrupt and more pronounced inhibition of the renin–angiotensin system than the basal stable small dose of captopril 25 mg/day.

A further convincing case of ACE inhibitor-related renal insufficiency has been described with irbesartan and losartan (6).

- A 67-year-old woman with congestive heart failure developed oliguric renal insufficiency 2 days after the introduction of irbesartan. She rapidly recovered after withdrawal, and was then given losartan. The condition recurred shortly afterwards and subsided when losartan was stopped.

Drug–Drug Interactions

Simvastatin acid

A small well-designed study in 14 healthy subjects showed no significant effect of irbesartan on the single-dose pharmacokinetics of total simvastatin acid (7).

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Iridaceae

See also Herbal medicines

General Information

The genera in the family of Iridaceae (Table 1) include *Crocus*, *Freesia*, and some types of lilies.

Table 1 The genera of Iridaceae

Acidanthera (acidanthera)
Alophia (alophia)
Aristea (aristea)
Belamcanda (belamcanda)
Calydorea (violet lily)
Chasmanthe (African cornflag)
Crocosmia (crocosmia)
Crocus (crocus)
Dietes (dietes)
Eleutherine (eleutherine)
Freesia (freesia)
Gladiolus (gladiolus)
Herbertia (herbertia)
Homeria (Cape tulip)
Iris (iris)
Ixia (African cornlily)
Libertia (libertia)
Nemastylis (pleatleaf)
Neomarica (neomarica)
Olsynium (grass widow)
Romulea (romulea)
Schizostylis (Kaffir lily)
Sisyrinchium (blue-eyed grass)
Sparaxis (wandflower)
Tigridia (peacock flower)
Trimezia (trimezia)
Watsonia (bugle-lily)

Crocus sativus

The stamens of *Crocus sativus* (Indian saffron) have been used primarily as a coloring and flavoring agent. Its potential use as an anticancer agent has been reviewed (1,2). No risks have been documented for daily doses up to 1.5 g, but 5 g is toxic, 10 g is abortive, and 20 g is lethal.

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Iron oxide

General Information

Ultrasmall superparamagnetic particles of iron oxide (USPIOs) of median diameter no less than 50 nm have been studied as blood-pool agents and are given intravenously to enhance liver imaging in patients with cirrhosis and to visualize lymph nodes. They consist of non-stoichiometric microcrystalline iron oxide cores, which are coated with dextrans (in ferumoxides) or siloxanes (in ferumoxsils). The most common form of iron oxide used is magnetite, which is a mixture of Fe_2O_3 and FeO; a mixture of Fe_2O_3 and Fe_3O_4 can be used instead.

After injection, the particles accumulate in the reticuloendothelial system. Liver tumors have few or no reticuloendothelial cells and so there is a contrast between normal liver and tumor.

These contrast agents are well tolerated, with no serious adverse effects. The reported adverse effects include low back pain, vomiting and diarrhea, urticaria, flushing, dizziness, and muscle spasm (SEDA-20, 419). The incidence of adverse effects is higher with these particulate iron oxide agents than with gadolinium chelates. However, that is not a great cause for concern, since few of the reactions are severe and all are self-limiting.

Ferristene

The USPIO contrast agent ferristene (Abdoscan, Amersham) is effective and safe in delineating the gastrointestinal tract after oral ingestion. Different rectal formulations of ferristene with different viscosities and iron concentrations have been evaluated in a phase II clinical study, in which ferristene enemas (200–500 ml) and intravenous gadodiamide (0.1 mmol/kg) were used in the evaluation and staging of rectal cancer in 113 patients (1). Five patients had 10 adverse events, including rectal pain, diarrhea, edema, a phobic reaction, nausea, and a skin rash; all recovered without further therapy. The high-viscosity formulation (70 g of granules/l) was better than the low-viscosity formulation in tumor staging, but the iron concentration (30 or 59 micrograms/ml) of the contrast agent was less important.

Ferucarbotran

Ferucarbotran (carboxydextran coated iron oxide nanoparticles, SHU 555 C, Resovist, Schering AG) is a contrast agent that consists of iron oxide microparticles coated with carboxydextran. After intravenous injection it is sequestered by the reticuloendothelial system, mostly in the liver and spleen. MRI iron oxide causes loss of signal intensity, especially on T1 and T2 weighted images, and the contrast between the lesions and the surrounding tissues is increased owing to loss of signal in the healthy tissues.

Feruglose

Feruglose (NC100150, Clariscan, Nycomed, Oslo, Norway) has been given to 18 healthy men in doses of 2, 3, and 4 mg/kg (2). There were no significant adverse effects during or after the scans. However, NC100150 interferes with iron metabolism, since iron is incorporated into the body after biodegradation. NC100150 shows promise for myocardial perfusion analysis. Studies in animals have also suggested a role for NC100150 in the detection and localization of intra-abdominal bleeding (3).

Ferumoxtran

Ferumoxtran-10 (Combidex, Advanced Magnetics, Cambridge, MA) is an ultrasmall superparamagnetic iron oxide agent. It targets the reticuloendothelial system but also functions as a blood-pool agent. In a phase 2 study in 104 patients with focal liver or spleen pathology who underwent MRI with ferumoxtran-10 (0.8, 1.1, and 1.7 mg of iron per kg), 15% reported a total of 33 adverse events, most commonly dyspnea (3.8%), chest pain (2.9%), and rashes (2.9%) (4). There were no serious adverse events during the 48-hour observation period and no changes in vital signs, physical examination, or laboratory parameters. The authors concluded that ferumoxtran-10 is safe and well tolerated.

SHU 555 A

The diagnostic efficacy and safety of SHU 555 A has been investigated in 19 patients aged 43–89 years who had been referred for investigation of hepatocellular carcinoma (eight patients), liver metastases (four patients), liver hemangioma (four patients), cholangiocarcinoma (two patients), and focal nodular hyperplasia (one patient) (5). The dose of iron was 6.0–11.7 μmol/kg. Patients under 60 kg received 0.9 ml as a bolus intravenous injection and patients over 60 kg received 1.4 ml. None of the 19 patients reported any pain or discomfort at the injection site. One had a diffuse erythematous rash associated with a feeling of pressure in the thorax, which lasted for 30 minutes. There was a significant increase in systolic blood pressure (from 137 to 141 mmHg) 5 minutes after injection; it returned to normal within 4 hours. There was a statistically significant fall in diastolic blood pressure from 75 to 70 mmHg at 4 hours after the injection. These changes were not considered to be of clinical importance. There were also minimal changes in the

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results of blood tests, which were not of clinical importance. High-quality diagnostic information was provided by the MRI examination.

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Iron salts

General Information

Iron is a metallic element (symbol Fe; atomic no. 26). The symbol is derived from the Latin word for iron, ferrum.

Iron is found widespread in nature in ores such as almandine hercynite (iron aluminate); scorodite (iron arsenate); pyrites (iron disulfide); laterite (iron hydroxide); columbite (iron niobate); chromite, hematite, ilmenite, limonite, magnetite, mugearite, stilpnosiderite, and umber (iron oxides); lazulite (iron phosphate); babingtonite, crocidolite, cummingtonite, epidote, eudialyte, fayalite, gadolinite, glauconite, hornblende, hypersthene, olivine, pennine, piedmontite, and riebeckite (iron silicates); coquimbite, inkstone, and jarosite (iron sulfates); ankerite, arsenopyrites, bornite, chalcopyrite, pentlandite, and pyrrhotite (iron sulfides); marcasite (iron sulfite); and wolframite (iron tungstate).

The body has no physiological route for the excretion of excess iron, and iron overload is a constant risk of therapy. Long-term use of iron by any route in large amounts can lead to hemosiderosis, simulating hemochromatosis; the danger is greatest when the mucosal barrier is bypassed by parenteral injection. Even the safety of iron-fortified food is uncertain (SEDA-4, 171). As with other metals there is environmental exposure to iron in many forms. The use of iron cooking utensils is often considered a useful source of supplementary iron in the diet. Various iron oxides and hydroxides are used as pigments in cosmetics.

The molecular basis of iron overload and toxicity has been reviewed (1,2). Much attention has been paid to mechanisms of hemochromatosis (3,4). There have been reviews of the comparative tolerance and safety of iron salts (5) and their use in specific conditions, such as renal insufficiency (6).

In elderly people, iron deficiency is usually a sign of bleeding, and it is wiser to track down and correct the cause of the blood loss (for example gastric malignancy) than to prescribe iron, which can merely mask the problem and delay diagnosis.

In the following sections, adverse reactions are considered in connection with the types of iron therapy with which they have most commonly been associated, but any adverse effect of iron can in principle occur with any formulation or as a result of mixed medical and non-medical exposure.

Oral iron

New oral formulations with improved intestinal iron absorption are being marketed and their efficacy and toxicity are being studied (7).

Despite the use of recombinant erythropoietin, anemia remains a significant problem for patients with end-stage renal disease (8). Because oral iron formulations are relatively ineffective and poorly tolerated, intravenous iron dextran has been widely used, despite the risk of adverse effects.

Parenteral iron

Like oral iron, parenteral iron is used too widely. When iron is truly needed, oral administration is generally preferable (9). Intractable gastrointestinal intolerance to oral formulations, hyperemesis in pregnancy, very severe blood loss, and possibly ulcerative colitis are some of the few valid indications for parenteral iron. A low iron-binding capacity (for example due to prior saturating iron therapy or malnutrition), folic acid deficiency, and an allergic constitution predispose the patient to adverse reactions to parenteral iron. Iron injections have been reported to provoke hemolytic anemia in cases of paroxysmal nocturnal hemoglobinuria.

Most parenteral iron is administered intramuscularly, but intravenous injections have enjoyed a wave of popularity for no very good medical reason; it seems particularly likely to precipitate acute allergic or anaphylactic reactions in sensitive individuals, sometimes involving cardiac dysrhythmias, hypotension, circulatory collapse, and pulmonary edema.

The adverse effects of iron formulations have resulted in trials to optimize dose regimens. A large database of clinical variance reports from Fresenius Medical Care North America (FMCNA) has been analysed to determine the incidence of suspected adverse drug reactions of iron dextran and the associated patient characteristics, dialysis practice patterns, and outcomes (8). A case-cohort design was used, comparing individuals who had suspected adverse drug reactions with the overall population. Out of 841 252 intravenous iron dextran administrations over 6 months, there were 165 reported suspected adverse drug

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reactions, corresponding to an overall rate of about 20 per 100 000 doses. Hospital evaluation was required in 43 patients (26%), 18 (11%) required hospitalization, and one (0.6%) died. Dyspnea (43%), nausea (34%), vomiting (23%), flushing (27%), pruritus (25%), hypotension (23%), and neurological symptoms (23%) were the most common adverse reactions. Serious adverse reactions to intravenous iron dextran are rare and difficult to predict; the risk appears to depend on the specific formulation of intravenous iron dextran.

In a retrospective analysis of the incidence of adverse effects associated with 250 mg of ferric gluconate infused over 1–4 hours in 40 patients with severe chronic renal insufficiency, who received 79 treatments, four treatments in two patients were associated with adverse effects, including diarrhea, vomiting, low back pain, hypotension, and a burning sensation in the feet. The duration of the infusion did not influence the adverse effects profile.

Intramuscular iron

Iron compounds for intramuscular administration are iron sorbitol–citric acid complex (iron sorbitex), iron dextran, iron glycerin–citric acid complex, and iron polyisomaltose. The work on these formulations is largely old and has been reviewed in previous volumes in this series.

Intramuscular iron injections are often painful, can produce topical discoloration of the skin, and some local inflammation with lymphadenopathy. Rarely, more severe local reactions follow (SEDA-6, 224), such as transient lipomyodystrophy. An unpleasant metallic taste in the mouth is common and can persist for some hours or days. Some patients develop general symptoms, such as headache, flushing, sweating, nausea, vomiting, dizziness, generalized aches and pains, malaise, arthralgia, palpitation, and pericardial or abdominal pain. Although very rare, a severe anaphylactic reaction to intramuscular iron dextran can occur.

The safety and efficacy of iron dextran have been evaluated in patients on home renal replacement therapies, without any adverse effects (10).

Intravenous iron

Iron dextran is now the most commonly used iron compound for intravenous use, and most reported adverse reactions to intravenous iron relate to this formulation.

Local reactions to intravenous iron dextran include transient pain (in some 4% of cases) and phlebitis. The risk of the latter may be reduced by using saline instead of 5% dextrose as diluent. Nevertheless, deep vein thrombosis has been observed in a few patients infused with a dilution of iron dextran in normal saline (SED-8, 514).

Systemic reactions to iron dextran given intravenously are more common than those to intramuscular iron; they include non-immunological and immunological, immediate and delayed reactions. Flushing, a sensation of warmth, and a metallic taste are often associated with excessively rapid injection, but usually subside within less than a minute after slowing or stopping the injection. In about 1% of cases, including patients with no known prior exposure to dextran, life-threatening anaphylactoid reactions occur rapidly, with hypotension, cardiovascular shock, syncope, cyanosis, bronchospasm, respiratory arrest, urticaria, and angioedema; deaths have ensued. Milder allergic reactions comprise mild and transient hypotension, malaise, itching, and urticaria. Desensitization under an umbrella of glucocorticoids, antihistamines, and ephedrine has been carried out successfully (11).

Delayed systemic reactions to intravenous iron dextran appear to be more common, the reported incidence ranging from 5 to 15%. They start within 4–48 hours of injection and can last for 3–7 days. Characteristic symptoms are fever, arthralgia, myalgia, headache, and lymphadenopathy, singly or in combination, and a classic serum sickness has been seen (SEDA-16, 26). Chills may also occur and individual patients may experience dizziness, tinnitus, paresthesia, a feeling of stiffness in the arms and neck, pruritus, urticarial or other cutaneous eruptions, pallor, nausea, vomiting, and nasal irritation. There may be hepatosplenomegaly. These delayed reactions are more frequent in children and, for some reason, in patients of Chinese origin. They tend to be more severe in patients with low body weight given higher doses, and in patients with rheumatoid arthritis or other types of inflammatory disease.

Large doses of intravenous iron dextran and iron saccharate have been compared in a retrospective study of 379 patients who had attended peritoneal dialysis clinics in the past 5 years (12). Of these, 62 were selected to receive intravenous iron based on ferrokinetic markers of iron deficiency, non-adherence to oral iron, ineffectiveness of oral iron, or increased erythropoietin requirements. Intravenous iron was given as two injections of 500 mg each 1 week apart in 61 patients, 33 of whom received iron dextran, 23 iron saccharate, and five both iron dextran and iron saccharate. One patient developed anaphylaxis to a test dose of iron dextran and was excluded from further therapy. Blood samples were collected before and 3 and 6 months after iron infusions. Five of the 34 patients who received iron dextran developed minor adverse effects and one had an anaphylactic reaction to the test dose. Of the 23 patients who received iron saccharate, one had an anaphylactic reaction and two had transient chest pain, which subsided without therapy. There were more adverse effects with iron dextran (7.4% of injections) compared with iron saccharate (4.3% of injections), but this difference was not statistically significant. The number of episodes of peritonitis also increased during the 6 months after intravenous iron infusion, especially with iron dextran, compared with the number of episodes during the 6 months before iron infusions, although the difference was not statistically significant.

Other iron compounds for intravenous use

Saccharated iron oxide is strongly alkaline and hypertonic; if injected outside the vein it can cause marked local reactions. Significant serum hypophosphatemia has on occasion been observed during treatment, accompanied by reduced renal tubular reabsorption of phosphate. The mechanism of these changes, which were reversible after stopping the iron injections, has not been clarified (13).

Topical iron

Iron chloride is sometimes used topically as a hemostyptic after minor surgery. It can result in persistent brown staining at the site of application. Use of Monsel's solution (ferric subsulfate), another hemostyptic agent, can cause

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fibrovascular proliferation accompanied by strongly pigmented macrophages after an interval of up to 3–5 weeks; the condition may be mistaken for malignant melanoma.

Organs and Systems

Cardiovascular

Intramuscular iron

The major hazard of the intramuscular use of iron sorbitex consists of severe systemic reactions with cardiac involvement, which may be fatal; they occur in up to 1% of cases, they start 10–30 minutes after injection and a patient who has received an injection must be monitored for an hour. Nausea, chest pain, profuse sweating, cardiac dysrhythmias, and loss of consciousness can occur. Cardiac complications include complete atrioventricular block, ventricular tachycardia, and ventricular fibrillation.

Intravenous iron

Non-transferrin-bound iron, which increases after intravenous ferric saccharate, has been suggested to act as a catalytic agent in oxygen radical formation in vitro, and may therefore contribute to endothelial impairment in vivo (14). The effect of ferric saccharate infusion 10 mg has been investigated in 20 healthy volunteers. Ferric saccharate caused a greater than four-fold increase in non-transferrin-bound iron and transient significant reduction in flow-mediated dilatation 10 minutes after infusion of ferric saccharate. The generation of superoxide in whole blood increased significantly 10 and 240 minutes after infusion of ferric saccharate by 70 and 53% respectively. Thus, infusion of iron leads to increased oxygen radical stress and acute endothelial dysfunction.

Respiratory

Spontaneously regressing bronchial necrosis with granuloma formation has been associated with the aspiration of a tablet of ferrous sulfate in a single case (15).

Acute respiratory distress syndrome has been attributed to iron (16).

- A 3.5-year-old girl was admitted after accidental ingestion of 50–60 tablets of ferrous sulfate 200 mg. She was unresponsive and her serum iron concentration was 138 μmol/l. She required resuscitation and ventilation and an intravenous infusion of deferoxamine was started at a rate of 15 mg/kg/hour, reducing to 5 mg/kg/hour 20 hours later, when the iron concentration was 27 μmol/l. At that time, her liver function deteriorated, with raised alanine transaminase activity (57 IU/l), raised bilirubin (56 μmol/l), and a coagulopathy with an INR of 2.7. She was given an infusion of *N*-acetylcysteine 12.5 mg/kg/hour and her hepatic function stabilized. After about 40 hours she had acute respiratory deterioration with tachypnea and hypoxemia. A chest X-ray showed widespread bilateral infiltrates. A diagnosis of acute respiratory distress syndrome was made.

Aspiration of iron tablets can produce an acute reaction in the airways since they are highly irritative; immediate removal bronchoscopy is necessary to avoid permanent damage (SEDA-16, 236). Lung damage has been reported in a man who had inhaled an oral iron formulation containing 350 mg of elemental iron (17).

- A 75-year-old man developed chest discomfort and hemoptysis. A chest X-ray showed left lower lobe collapse and fiberoptic bronchoscopy showed that the left endobronchial mucosa was friable, edematous, and golden-yellow, with interspersed erythematous ulcerated areas with marked contact bleeding. There was heavy deposition of yellow–brown pigment on the basement membrane of the superficial bronchial epithelium, on the basement membrane of the bronchial glands, and on fibrillar material in the stroma. Pigment deposition was greatest in the necrotic fragments of mucosa, but was also seen in viable mucosa. This material stained strongly for ferric ion with Perls' stain. Iron was withdrawn and the left lower lobe collapse improved.

Metabolism

In erythropoietic protoporphyria, iron can cause a relapse of symptoms (18). An involvement of iron overload in the pathogenesis of some cases of porphyria cutanea tarda has been suggested (19).

Hematologic

Latent folic acid deficiency can become manifest during iron therapy due to additional demand for the vitamin secondary to increased erythropoietic activity (20).

Intramuscular iron

Thrombocytopenia has been attributed to intramuscular iron (21).

- A 30-year-old woman had a hemoglobin concentration of 3.1 g/dl, a mean cell volume of 77 fl, a reticulocyte count of 2.13%, a platelet count of 426 $\times$ 10^9/l, a serum iron concentration of 5 ng/ml, a transferrin saturation of 1%, and a ferritin concentration of 8 ng/ml. She was intolerant of oral iron and was given intramuscular iron dextran, 100 mg/day for 8 days, when she developed asymptomatic thrombocytopenia (platelet count 20 $\times$ 10^9/l). Iron dextran was withdrawn and she took oral ferrous fumarate 200 mg/day plus ascorbic acid 120 mg/day. Within 2 days her platelet count improved.

Mouth and teeth

Most liquid ferrous products stain dental enamel, but this is usually reversible (22).

Gastrointestinal

Severe gastrointestinal necrosis and strictures after iron overdose are well described. However, mucosal injury in patients taking therapeutic iron has received only scant recognition, despite its widespread use. In 36 upper gastrointestinal tract biopsies from 33 patients (24 gastric, nine esophageal, one gastro-esophageal junctional, and two duodenal) there was characteristic brown crystalline iron material (23). Most of the biopsies (32 of 36) contained luminal crystalline iron adjacent to the surface epithelium or admixed with luminal fibrinoinflammatory exudate. In 30 biopsies there was crystalline iron deposition in the lamina propria, either covered by an intact

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epithelium, subjacent to small superficial erosions, or admixed with granulation tissue. Three biopsies showed iron-containing thrombi in mucosal blood vessels. Erosive or ulcerative mucosal injury was present in 30 of 36 biopsies. The amount of iron accumulation in cases with mucosal injury was greater than in the cases without mucosal injury. About half of the patients (17 of 33) also had underlying infectious, mechanical, toxic, or systemic medical conditions that could have initiated or exacerbated tissue injury. Crystalline iron deposition was found in 0.9% of upper gastrointestinal endoscopic examinations (12 of 1300), and iron medication-associated erosive mucosal injury was present in 0.7% (nine of 1300). These results suggest that crystalline iron deposition in the upper gastrointestinal tract is not uncommon. It can cause or exacerbate a distinctive histological pattern of erosive mucosal injury, especially in patients with associated upper gastrointestinal disorders.

Oral iron

Though iron clearly does have the ability to irritate the mucous membranes, its widespread reputation for poor gastric tolerance is undeserved, generally reflecting its having been given in excess. Of patients taking up to 200 mg/day of elemental iron, only a few highly susceptible individuals will develop gastrointestinal adverse effects, and constipation is then the most usual feature. Higher doses can give rise to gastric discomfort, nausea, vomiting, or to either constipation or diarrhea. In sensitive individuals with complications in the upper gastrointestinal tract, histopathologically distinctive lesions are found in mucosal biopsies of the stomach and esophagus (24); there can be heavy iron accumulation within ulcer granulation tissue, in the connective tissue and blood vessels of the mucosal lamina propria, and within glandular and squamous epithelia. The appearance is similar to that seen after overdosage.

Oral iron can color the feces black, which can be mistaken for melena. Fewer gastrointestinal adverse effects occur if the iron dose is gradually increased to the desired level or if iron is taken with food, but since insoluble iron complexes may be formed with food it has been recommended that iron salts be taken between meals. Despite many claims for the better gastric tolerance of expensive iron formulations, it is still not entirely proven that they are any better tolerated than plain ferrous sulfate if the latter is properly dosed. Iron supplementation via a gastric delivery system did not produce any gastrointestinal adverse reactions while efficacy was similar to that of a ferrous sulfate elixir (25). Carbonyl iron has also been studied, although mainly as a means of reducing acute toxicity if such a product is accidentally taken by children (SEDA-16, 235). Iron protein succinylate is another iron derivative for oral use, providing protein-bound iron (26); it is more slowly absorbed than divalent iron, which probably explains the claimed improvement in gastrointestinal tolerability; again it is not at all clear that tolerance is truly improved as related to the amount of iron actually absorbed.

True gastrointestinal risks occur if a solid dosage form becomes lodged in the pharynx, esophagus, or intestinal diverticula; severe erosion can follow (SEDA-6, 224) (SEDA-20, 211). An accumulation of ferrous sulfate tablets with a non-soluble matrix has been the source of ileus in a case of Crohn's disease (SEDA-16, 236). This sort of risk is greatest with modified-release formulations and absent with liquid iron formulations; the latter should therefore be preferred in cases of delayed gastric emptying, pyloric stenosis, or diverticula of the alimentary tract.

Gut pigmentation has been attributed to an iron salt (27).

- An 80-year-old Japanese woman presented with epigastric discomfort and nausea. She had a history of hypertension, rheumatoid arthritis, iron deficiency anemia, chronic renal insufficiency, and had taken oral ferrous sulfite for 19 months. Endoscopic examination of the duodenum showed marked pigmentation of the duodenal mucosa. Histological examination showed that the pigment had histochemical features compatible with hemosiderin and was located mainly within macrophage lysosomes in the lamina propria. Ferrous sulfite was withdrawn and the pigmentation disappeared within 7 months.

Liver

There is much evidence that normal or even mildly increased amounts of iron in the liver can be damaging, particularly when combined with other hepatotoxic factors, such as alcohol, porphyrogenic drugs, or chronic viral hepatitis (28).

Oral iron

Chronic liver disease has been attributed to oral iron.

- A healthy 5-year-old girl, who had taken large doses of oral ferrous sulfate 300 mg five times a day (300 mg of elemental iron/day) for 5 years, developed severe hemosiderosis (29). Liver biopsy showed preserved lobular architecture, but the portal tracts were expanded by fibrosis and there was mild septal fibrosis. There was siderosis of the hepatic parenchymal cells and hemosiderin deposition in the Kupffer cells. She had no underlying hematological disease and her iron absorption was normal. HLA phenotypes and DNA analysis for the most common mutations associated with hemochromatosis excluded homozygous and heterozygous hereditary hemochromatosis. She was successfully treated by phlebotomy. Iron studies 10 years later were normal.
- A 22-year-old woman with adult-onset Still's disease and massive hyperferritinemia became progressively more anemic, with a fall in hemoglobin to 8.2 g/dl, and was given oral ferrous fumarate 300 g bd (30). She developed acute florid hepatitis with an intraparenchymatous histiocytic infiltration, which settled on withdrawal of the iron.

In the latter case iron may have exacerbated the macrophage hyperactivity that is presumed to be present in adult-onset Still's disease. Oral iron may be inadvisable in the acute phase of this disease.

Skin

Reversible skin eruptions have been described in occasional patients taking oral iron. One case presented with a generalized exanthematous pustular eruption following the use of ferrous fumarate (31), another with erythema

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and lichenification on sun-exposed areas after taking sodium ferrous citrate (32). Both these cases developed 2 weeks after starting treatment; it was suggested that in the latter case iron itself or the transferrin iron complex (diferric transferrin) might have acted as a photosensitizer.

Musculoskeletal

Parenteral iron

Intramuscular iron

The possible sarcoma-inducing potential of intramuscular iron was fully discussed 15 years ago (SED-9, 375) (33) and no new information on the topic has come to light. The conclusion at that time was that the evidance linking intramuscular iron to sarcomatous change was scanty.

Intravenous iron

Saccharated ferric oxide, an intravenous formulation of iron that is used when oral iron is not effective in anemia, can cause osteomalacia during long-term use. The underlying mechanism of nephropathy leading to bone toxicity has recently been reviewed (34).

Oral iron

Although total dose infusions of iron (see the section on Intravenous iron under Immunologic) can cause rheumatoid arthritis to flare up, this has not been demonstrated with oral iron. However, a patient who has reacted in this way to an infusion can subsequently relapse if given oral iron.

Immunologic

Iron enhances the pathogenicity of micro-organisms, adversely affects the function of macrophages and lymphocytes, and enhances fibrogenic pathways, all of which may enhance hepatic injury due to iron itself or to iron alongside other factors.

Oral iron

Skin reactions to oral iron are extremely rare.

- A 40-year-old woman with iron deficiency anemia due to menstrual blood loss took oral iron for 3 months without any adverse effects (35). Nine months later she became anemic again and 2 hours after an oral dose of ferrous sulfate 525 g (105 mg of elemental iron) she developed generalized pruritus and an erythematous maculopapular rash. This recurred 1 week later, when she took ferrous protein succinilate 800 g (40 g of iron). Desensitization with oral iron was carried out. Skin prick tests and patch tests with iron formulations were negative. Two single-blind, placebo-controlled oral challenges were performed and she began to have similar cutaneous symptoms. A slow desensitization protocol, using increasing doses, was tolerated without adverse effects. Chronic oral iron therapy once a day for 9 months sustained the desensitized state and the anemia disappeared.

Parenteral iron

Intravenous iron

Patients with a history of allergy may be at risk of developing undesired immunological reactions, for example attacks of asthma, after parenteral iron dextran; however, the incidence of such reactions seems to be low, and the risk probably also exists with other iron compounds as well. A test infusion is not recommended as it may or may not detect susceptibility to immediate reactions and can itself elicit violent reactions.

There was at one time impressive but limited case evidence that systemic reactions to iron dextran might be more frequent in patients with rheumatic or other inflammatory diseases; no further evidence has been published. There might be confusion with the ability of intravenous iron to induce a flare-up of an existing rheumatic condition (see the section on Oral iron under Musculoskeletal).

Single dose infusions of iron dextran appear to have increased the occurrence of malaria in endemic regions. There was an increased mortality after oral or parenteral iron therapy in children with severe malnutrition (kwashiorkor), perhaps due to overwhelming infections (36). Reactivation of quiescent infections of various other types has been observed in African nomads following ferrous sulfate therapy (SEDA-4, 171). Iron dextran has similarly been associated with a flaring up of latent tuberculosis in children.

Persistent hypogammaglobulinemia has been described in a patient receiving gold; a year after drug withdrawal the gamma-globulin concentrations were still unchanged (37).

An insulin autoimmune syndrome, marked by presence of insulin antibodies and small granulomas in the skin, has been documented in Japanese cases, many of whom had also received penicillamine (38,39).

Intramuscular iron

Iron dextran administration is associated with a high incidence of adverse reactions, including anaphylaxis and death (5). Although it is the dextran rather than the iron that is believed to be the cause of these reactions, which raises the question of whether patients who are sensitive to iron dextran can safely be given another form of parenteral iron, namely sodium ferric gluconate in sucrose. In a double-blind, controlled trial sodium ferric gluconate in sucrose or placebo was given to 144 iron dextran-sensitive patients for comparison with 2194 patients who had been tolerant to iron dextran. Serum tryptase concentrations were also measured. Of 144 patients who were sensitive to iron dextran and who were exposed to sodium ferric gluconate in sucrose, three were intolerant; all had suspected allergic reactions, including one with a serious reaction. One dextran-sensitive patient had a suspected allergic reaction after placebo. In contrast, among the 2194 iron dextran-tolerant patients, reactions to sodium ferric gluconate in sucrose were significantly less common, with intolerance in seven patients, including five who had suspected allergic events, but none who had serious events. Two iron-dextran tolerant patients had allergic-like reactions to placebo. Two of the three suspected allergic events in the iron dextran-sensitive group were confirmed as mast cell-dependent, by a 100% increase in serum tryptase, while there were no confirmed allergic events in the iron dextran-tolerant group. Long-term exposure to sodium ferric gluconate in sucrose in iron dextran-sensitive patients resulted in intolerance in only one additional patient and no serious adverse events.

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Patients with a history of iron dextran sensitivity had about seven-fold higher rates of reaction to both placebo and sodium ferric gluconate in sucrose compared with iron dextran-tolerant patients. However, logistic regression analysis, performed to account for the higher reaction rate to placebo, suggested that this increased reactivity was neither drug-specific nor immunologically mediated, but represented host idiosyncrasy. These results support the conclusions that reactions to sodium ferric gluconate in sucrose can be attributed to pseudoallergy, and that it is not a true allergen.

Iron dextran was particularly likely to cause hypersensitivity reactions when it was used in 537 dialysis patients (40), the most common adverse reactions were itching, dyspnea, wheezing, chest pain, nausea, hypotension, angioedema, dyspepsia, diarrhea, flushing, headache, cardiac arrest, and myalgia. Most of the reactions were mild, but of a subseries of 27 patients exhibiting adverse effects, three patients had to be hospitalized including the individual who had suffered cardiac arrest.

After intramuscular iron dextran, symmetrical allergic purpura of the lower limbs due to hypersensitivity vasculitis has been observed in a child (41).

Infection Risk

In a 10-year consecutive series of 263 allogeneic bone marrow transplant recipients, there were five cases of invasive mucormycosis (42). Only one infection occurred within the first 100 days after transplantation, while the rest complicated the late post-transplant course (median day of diagnosis, 343). Sites of infection were considered "non-classical" and included pulmonary, cutaneous, and gastric. There were no cases of fungal dissemination. Mucormycosis was the primary cause of death in three of the five patients. Corticosteroid-treated graft-versus-host disease, either acute or chronic, or severe neutropenia were present in all cases. However, compared with a matched control population, the most striking finding was severe iron overload in each patient. The mean serum ferritin concentration, transferrin saturation, and the number of transfused units of red cells in the study group were all significantly higher than in the control group. There was a striking association between the occurrence of mucormycosis in dialysis patients and the use of deferoxamine for the treatment of iron and/or aluminium overload. From experimental work and observational data, it appears that iron overload, either transfusional or due to dyserythropoiesis, may be an important risk factor in the development of mucormycosis in this transplantation patient population.

Long-Term Effects

Tumorigenicity

The risk of colorectal cancer due to iron has been specifically examined in a prospective investigation in more than 14 000 patients (43). Iron appears to confer an increased risk of colorectal cancer, and the localization of risk may be attributable to the mode of epithelial exposure. It seems that luminal exposure to oral iron increases the risk proximally, whereas an increased serum iron concentration increases the risk distally.

Genetic hemochromatosis constitutes a high risk factor for the development of hepatocellular carcinoma. It is widely accepted that venesection prevents the evolution of cirrhosis in hemochromatosis and indirectly protects against the development of hepatocellular carcinoma. However, three cases did not conform to the "siderosis-cirrhosis-carcinoma" sequence, and prompt and adequate iron depletion did not protect against the development of cancer (44).

- A 39-year-old army officer had bouts of palpitation and dizziness. There were no risk factors for chronic liver disease apart from a family history of hemochromatosis. His cardiovascular and nervous systems were normal but there was 5 cm hepatomegaly. Percutaneous liver biopsy showed grade 4 siderosis in parenchymal and non-parenchymal liver cells and a mild inflammatory infiltrate with minimal portal fibrosis. He had 45 liters of blood venesected over the next 18 months and a repeat biopsy 3 years later showed a non-cirrhotic liver with no stainable iron. He developed a non-resectable primary hepatocellular clear cell carcinoma 17 years after the initial diagnosis.
- The other two cases were male siblings. One presented with atypical chest pain and had 3 cm hepatomegaly. Liver biopsy showed parenchymal grade 4 siderosis with normal architecture. He had 170 liters of blood venesected over the next 27 years, but then his iron indices indicated reaccumulation. Ultrasound showed a hyperechoic lesion in the liver due to a moderately differentiated hepatocellular carcinoma. His elder sibling, who had grade 4 siderosis and normal hepatic architecture, also developed a well-differentiated hepatocellular carcinoma.

Second-Generation Effects

Pregnancy

The case once made against use of iron dextran in pregnancy because of a supposed risk of possible uterine cramps (SED-9, 377) or a greater risk of systemic reactions (SED-8, 513) has not been substantiated. However, in one case a pregnant woman had anaphylactic shock as a reaction to intravenous iron, and this resulted in fetal cerebral damage (SEDA-22, 246).

Susceptibility Factors

Age

Age is a possible risk factor regarding adverse reactions to total-dose infusions of iron dextran (45).

Renal disease

Iron deficiency is a common and important cause of poor response to erythropoietin in patients with severe chronic renal insufficiency, in whom oral iron supplements fail to correct iron deficiency (6). Ferric gluconate has a low adverse effects profile, but the recommended dose of 62.5–125 mg per treatment is not practical for patients

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who are not on hemodialysis. In a retrospective analysis of the incidence of adverse effects associated with 250 mg of ferric gluconate infused over 1–4 hours in 40 patients with severe chronic renal insufficiency, who received 79 treatments, four treatments in two patients were associated with adverse effects, including diarrhea, vomiting, low back pain, hypotension, and a burning sensation in the feet. The duration of the infusion did not influence the adverse effects profile.

Other features of the patient

Iron toxicity can be expected if the amount of free iron released into the plasma exceeds the plasma iron-binding capacity. This is more likely to occur when using iron sorbitol–citric acid complex (iron sorbitex), since the iron is less firmly bound than with iron dextran. Several conditions associated with low iron-binding capacity, such as malnutrition (kwashiorkor, malnutrition syndrome) and previous or simultaneous oral iron therapy appear to predispose to the development of these toxic reactions. In addition, folic acid deficiency has been reported to be a predisposing factor (SED-9, 516), the likely mechanism being altered iron utilization secondary to folic acid deficiency, which results in an increased saturation of iron-binding capacity.

Drug Administration

Drug administration route

Oral iron

Although modified-release formulations seem to be better tolerated, this is almost certainly a reflection of their less complete absorption. Iron is best absorbed in the duodenum, and most of the iron in modified-release tablets is released only when the tablets reach the lower parts of the gastrointestinal tract (46).

Parenteral iron

Total dose infusion of iron

With total dose infusion, the amount of iron that is required is delivered in a single infusion rather than by intermittent therapy. Although iron concentrations can rise to very high values, for example 100 000 micrograms/ml (45), there are unlikely to be signs of iron intoxication (SED-8, 513).

However, toxic reactions to intravenous iron occur when ionized iron exceeds plasma binding capacity. With iron dextran, the iron moiety is so firmly bound to dextran that ionized iron does not exceed plasma iron-binding capacity even when total plasma iron concentrations are extremely high. However, there are adverse effects, which were at first underestimated; whenever possible other routes or methods of iron dextran administration should be preferred.

Immediate reactions occurred in nine of 40 adults, variously in the form of anaphylaxis, chills, malaise, hypertension, gastrointestinal reactions, epistaxis, or chest pain. Monitoring for these early reactions is always necessary, but elderly patients require particular attention since they are more likely to react in this way.

Symmetric allergic purpura following the intravenous infusion of iron dextran has exceptionally been noted. In children, transient hepatosplenomegaly has been described as a common finding.

An adverse effect on rheumatic disorders of intravenous iron is well documented (SEDA-12, 190), with exacerbation of joint symptoms, perhaps by promoting lipid peroxidation (47). Of 11 patients with rheumatoid arthritis who received a total dose infusion of iron for anemia, nine experienced an exacerbation of the synovitis, and the two other patients had an anaphylactic reaction. The exacerbations occurred 24–48 hours after completion of the iron dextran infusion and settled in all patients within 11 days. One of these patients had synovial flares when challenged with oral ferrous sulfate. In a single reported case, total dose iron infusion was followed by prolonged polyarthritis, mainly of the large joints, in a patient with no previous evidence of rheumatoid arthritis or ankylosing spondylitis (48). Despite prolonged glucocorticoid therapy, clinical resolution of the problem took 6 months. It may also be relevant that when an iron infusion was given to 20 dialysis patients several of them developed muscular aches, an influenza-like condition or joint pain (SEDA-17, 278).

Organ calcification has very rarely been described after use of iron dextran in uremic patients (SED-8, 515).

Iron overload due to transfusions

Symptoms and signs of iron overload in transfusion-dependent anemias occur after a total transfusion burden of about 100–150 units of blood (49).

Drug overdose

The toxicokinetics and toxicodynamics of iron poisoning have been reviewed (50).

Oral iron

Acute poisoning of children who have taken iron tablets found in the medicine cabinet or elsewhere in the home has repeatedly been reported. The tablets, often attractively coloured and sugar-coated, are readily assumed to be confectionery.

The number of young children who have accidentally swallowed iron has more than doubled since 1986, since when more than 110 000 children under 6 years who accidentally swallowed iron tablets were reported to poison control centers. Many of the children were hospitalized and at least 33 died. The children who died had swallowed as few as five to as many as 98 tablets. In some cases, toddlers found tablets within their reach in uncapped or loosely capped containers. In other cases a young child managed to open a container. In 1995 the number of cases of unintended ingestion of iron by children was estimated at some 22 000 in the USA alone (51). Acute toxicity is associated with free radical formation. Emetics, gastric lavage, and even surgery may be called for to remove the excess.

Much more common is chronic poisoning due to excessive intake over a long period, with deposition of iron within cells. Iron has a toxic effect in almost all organs, especially the liver, heart, and endocrine glands. Histological evidence of iron-mediated tissue damage

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can be obtained before the clinical picture becomes evident. Combined management with ascorbic acid and deferoxamine can yield high rates of deferoxamine-induced urinary iron excretion without obvious adverse effects on the heart.

The FDA has proposed regulations requiring warning labels on iron formulations, such as tablets and capsules, and requiring unit dose packaging for products containing 30 mg or more of iron in each dosage unit (52). The proposed regulations apply to both dietary supplements and drugs containing iron, but not to iron-fortified foods, such as enriched flour. This proposal is based on findings that iron-containing drugs and supplements are the leading cause of accidental poisonings in children. In 1988–92, about 17% of childhood deaths reported to poison control centers in the USA were blamed on iron poisoning: in 1984–87 the incidence was only 5%.

The Consumer Product Safety Commission, which regulates child-resistant packaging for household substances, requires such packaging for any oral iron product that contains 250 mg or more iron per container. In addition, the FDA's proposed regulations would require manufacturers to wrap iron tablets and capsules containing more than 30 mg per dosage unit in individual units, such as in blister packs.

Drug–Drug Interactions

Antacids

Iron absorption is reduced by antacids (for example magnesium trisilicate and carbonate) (53).

Colestyramine

Iron absorption is reduced by colestyramine (54).

Penicillamine

Concomitant ingestion of iron reduces the copper-excretory effect of penicillamine (SED-12, 527) and penicillamine reduces iron absorption (55).

Tetracyclines

Concomitant oral administration of tetracyclines and iron grossly reduces the absorption of both, because complexes are formed (56,57); there should be an interval of 2–3 hours between the use of the two.

Interference with Diagnostic Tests

Urine

Urine can turn dark in color in the first 24 hours after parenteral iron injection. The reddish-brown color, which has been observed after the intramuscular injection of iron sorbitol–citric acid complex (SED-8, 515), is due to urinary excretion of part of the iron compound. It has to be distinguished from the black discoloration that may develop if urine of patients who have received iron-sorbitex is allowed to stand, assumed to be due to production of iron sulfide by bacterial growth. Phenomena of this kind are unlikely to occur after the use of iron dextran, which is not normally filtered by the renal glomerulus.

Blood grouping

If blood grouping is to be performed, samples should be taken before the intravenous iron dextran injection, since it interferes with the reaction.

Plasma discoloration

Single-dose infusion of iron dextran can cause plasma discoloration, which may be misinterpreted as a sign of severe hemolysis.

Calcium and phosphorus

In one case iron dextran administration falsely reduced total serum calcium concentration and increased the phosphorus concentration (58).

^{99}Tc-diphosphonate

The distribution of ^{99}Tc-diphosphonate in bone was reportedly altered by circulating iron dextran complex in an elderly woman patient undergoing scintigraphy (59).

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Isepamycin

See also Aminoglycoside antibiotics

General Information

Isepamicin is similar to amikacin but has better activity against strains that produce type I 6′-acetyltransferase. It can cause nephrotoxicity, vestibular toxicity, and ototoxicity. However, it is one of the less toxic of the aminoglycosides (1). The antibacterial spectrum of isepamicin includes *Enterobacteriaceae* and staphylococci; anaerobes, *Neisseriae*, and streptococci are resistant (1). Isepamicin was as effective and safe as amikacin in the treatment of acute pyelonephritis in children and might prove an advantageous alternative in areas with a high incidence of resistance to other aminoglycosides (2).

Isepamicin is given intravenously or intramuscularly in a dosage of 15 mg/kg/day or 7.5 mg/kg bd. It is not bound to plasma proteins, it distributes in extracellular fluids, and it enters some cells (outer hair cells, kidney cortex) by an active transport mechanism (1); the transference of isepamicin to the bone marrow is excellent (3). Isepamicin is not metabolized and is renally excreted with a half-life of 2–3 hours in adults with normal renal function. Its clearance is reduced in neonates, and a dose of 7.5 mg/kg/day is recommended in children younger than 16 days. Its clearance is also reduced in elderly people, but no dosage adjustment is required. In patients with chronic renal impairment, isepamicin clearance is proportional to creatinine clearance.

The bone tissue penetration of isepamicin has been studied in an open, non-comparative study, and the results compared with microbiologic data to estimate the clinical efficacy of isepamicin in bone infections (4). In 12 subjects of similar age, body weight, height, and creatinine clearance, who were undergoing elective total hip replacement, a single parenteral dose of isepamicin 15 mg/kg achieved concentrations in both cancellous and cortical bone tissue greater than the minimum concentrations required to inhibit the growth of 90% of strains of most of the susceptible pathogens commonly involved in bone infections.

Organs and Systems

Sensory systems

Hereditary deafness is a heterogeneous group of disorders, with different patterns of inheritance and due to a multitude of different genes (5,6). The first molecular defect described was the A1555G sequence change in the mitochondrial 12S ribosomal RNA gene. Two cases of hearing loss after short-term exposure to isepamicin sulfate, an aminoglycoside with milder adverse effects than other aminoglycosides, have also been described in patients with the A1555G mutation (7).

Urinary tract

Fleroxacin had a protective effect on isepamicin-induced nephrotoxicity in rats (8).

Drug Administration

Drug dosage regimens

In a randomized, multicenter study 236 patients were randomly assigned to isepamicin in a calculated dose or a loading dose of 25 mg/kg (9). The calculated dose was estimated using a specific population model with a Bayesian method, including information about age, weight, height, sex, and serum creatinine. The Bayesian method was significantly more accurate and performed particularly well in ventilated patients and severely ill patients, compared with a loading dose of 25 mg/kg, in obtaining a first isepamicin peak concentration of 80 micrograms/ml in patients in an intensive care unit.

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Isoetarine

General Information

Isoetarine is a beta-adrenoceptor agonist bronchodilator given orally in a modified-release formulation (SED-13, 363) (SEDA-21, 184). It is slightly more $beta_2$-selective than isoprenaline but has a beta-blocking metabolite.

When isoetarine was compared with salbutamol in the treatment of acute severe asthma in adults who received hourly nebulized isoetarine 5 mg or salbutamol 2.5 mg the two drugs were equally effective in relieving bronchoconstriction (SEDA-21, 184). However, adverse effects occurred in 36% of patients who used isoetarine and 4% of those who used salbutamol. The adverse effects included dizziness, nervousness, and bouts of palpitation, tremor, headache, and worsening shortness of breath.

Organs and Systems

Respiratory

In several patients, administration of isoetarine resulted in a pink coloration of the sputum, due to the presence of a reddish metabolite; in such cases, hemoptysis may be wrongly suspected (1).

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Isoflurane

See also General anesthetics

General Information

Isoflurane is a potent inhalation anesthetic. An isomer of enflurane, it has many of the same adverse effects. It is hardly metabolized (about 0.2%), which has encouraged its prolonged use as a sedative agent or bronchodilator in patients with acute severe asthma. However, it may not be as inert in all patients.

Organs and Systems

Cardiovascular

Although atrial dysrhythmias have been reported in 3.9% of patients and ventricular dysrhythmias in 2.5% (1), the dysrhythmogenicity of isoflurane is less pronounced than that of halothane (2). Indeed, the incidence of dysrhythmias due to catecholamines in cardiovascular anesthesia and during oral surgery is reduced by using isoflurane rather than the other agents.

The most controversial adverse effect of isoflurane is its potential to cause coronary steal in patients with critical stenosis in the coronary circulation. Most recent work suggests that the risk of myocardial ischemia is not increased, as long as the hemodynamics, especially heart rate, are well controlled (3). However, there are still isolated reports, suggesting that the issue is not settled. In some cases isoflurane has caused a specific coronary steal even with good hemodynamic control (4).

Respiratory

Marked respiratory depression has been documented in children (5) and coughing associated with nausea and vomiting occurs in about 10% of subjects (1).

Like halothane, isoflurane is useful in cases of life-threatening acute severe asthma refractory to drug therapy.

- An 11-year-old girl with acute asthma, severe CO_2 narcosis, and ventricular fibrillation induced by hypoxemia was successfully treated with isoflurane in oxygen for 14 hours. Her recovery may have been due to bronchodilatation and the treatment that was possible because of the low dysrhythmogenic effect of isoflurane (6).

Nervous system

Seizures are uncommon with isoflurane, but reports continue to appear.

The neuromuscular blocking effects of vecuronium bromide can be enhanced by inhalation anesthetics.

- Symptoms suggestive of severe sensorimotor neuropathy developed in a 40-year-old woman 15 days after admission for a severe exacerbation of asthma (7). During this time she was given isoflurane 0.5–3% in oxygen, vecuronium bromide 4–6 mg/hour, and fentanyl 100 micrograms/hour. The neuropathy resolved spontaneously over the next 3 months.

In this case, isoflurane may have been the trigger.

- A fine tremor occurred when isoflurane was used in the management of a 3-year-old boy with pneumonia and underlying congenital myasthenia gravis (8).

Liver

Hepatic damage related to isoflurane anesthesia has very occasionally been described (9,10), including one report of hepatic necrosis and death (11). Hepatitis or hepatocellular injury has been described with all current volatile anesthetics. Among these, halothane-associated hepatitis has been best characterized and is probably caused by an immune reaction induced by hepatocyte proteins that have been covalently trifluoroacetylated by the trifluoroacetyl metabolite of halothane. The reactive acyl-halide metabolite of trifluoroacetic acid can trifluoroacetylate liver proteins, resulting in immune-mediated hepatic necrosis (12). However, isoflurane biotransformation to trifluoroacetate is less than 0.2%, compared with 15–20% for halothane.

In an interesting case report, clinical, histochemical, and immunohistochemical evidence supporting the role of trifluoroacetyl-modified proteins has been presented in a patient with hepatitis associated with isoflurane (13).

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The role of CYP2E1 as the predominant route of metabolism of isoflurane to trifluoroacetic acid and inorganic fluoride ions has been confirmed using the enzyme inhibitor disulfiram as a metabolic probe in 22 adults randomized to either disulfiram 500 mg the evening before surgery or placebo. Anesthesia with 1.5% isoflurane lasted for an average of 8 hours. Postoperative plasma concentrations were increased and urinary excretion of trifluoroacetic acid was inhibited by 80–90% in the disulfiram group. Whether the use of disulfiram would reduce the incidence of hepatitis is unknown. Patients with increased activity of CYP2E1 or CYP2A6 appear to be at higher risk of isoflurane hepatotoxicity.

Acute hepatotoxicity has been reported with isoflurane (14). The authors hypothesized that induction of cytochrome P-450 by phenytoin had caused enhanced transformation of isoflurane to trifluoroacetic acid. They suggested that caution should be taken in the use of halogenated anesthetics in patients taking drugs that induce cytochrome P-450 isozymes.

- An obese 35-year-old diabetic woman developed isoflurane-induced hepatotoxicity (15). She had had four previous halothane anesthetics, the last two of which were associated with jaundice. She made a full recovery and during a subsequent anesthetic received an infusion of propofol. Unfortunately, trifluoroacetic acid antibody titers were not performed. Liver function does not appear to have been severely affected: peak alanine transaminase activity was 1410 IU/l.

Fatal hepatotoxicity associated with isoflurane has been reported (16).

- A 76-year-old woman with previous exposure to isoflurane 3 years earlier underwent an above-knee amputation for a liposarcoma using isoflurane anesthesia. On day 3 postoperatively she became febrile and confused. Bacterial cultures later showed *Staphylococcus aureus* in the sputum and *Escherichia coli* in the urine. Associated hypotension for 2 hours resolved with inotropic support and here renal function remained normal. On day 6 she became jaundiced and developed further hypotension. Despite intensive care treatment she died on day 7. An autopsy showed centrilobular necrosis consistent with drug-induced hepatitis. All liver serology was negative.

The clinical details in this case were similar to those seen in halothane hepatitis. The authors concluded that although there was no direct evidence that isoflurane was the causative agent, it was likely to have caused this type of hepatitis. Unfortunately, trifluoroacetic acid antibodies titers were not measured, because this test, if positive, would have confirmed the diagnosis.

Urinary tract

High concentrations of fluorine ions, potentially damaging to the kidney, can be found after prolonged use (17).

Four patients with renal dysfunction in an intensive care unit received isoflurane inhalation for sedation for 8–26 days. The concentrations of isoflurane used were 20–50% of the minimum alveolar concentration. Only small increases in fluoride ion concentration, the highest being 25 μmol/l, were recorded, well below the 50 μmol/l threshold associated with adverse effects on renal function (18).

Immunologic

Anaphylaxis has been reported in a patient who received isoflurane (19).

Body temperature

Malignant hyperthermia is a possible complication of isoflurane anesthesia (20).

Shivering after an anesthetic develops in as many as a half of patients recovering from isoflurane anesthesia. Most postoperative shivering appears to be thermoregulatory, although volatile anesthetics can themselves facilitate muscular activity. In 60 adult patients the incidence of postoperative shivering was 40% in a control group, 7% after physostigmine 0.04 mg/kg, zero after meperidine 0.5 mg/kg, and zero after clonidine 1.5 micrograms/kg (21). The centrally acting adrenoceptor agonist phenylpropylamine methylphenidate, the 5-hydroxytryptamine antagonist ketanserin, magnesium sulfate, doxapram, and hypercapnia also reduce the incidence of postoperative shivering.

Drug–Drug Interactions

Alfentanil and esmolol

The effects of alfentanil and esmolol on isoflurane requirements for anesthesia have been studied in a randomized trial in 100 patients (22). Alfentanil infusion to a targeted effect site concentration of 50 ng/ml, but not esmolol, reduced the minimum alveolar concentration of isoflurane required to suppress movement to surgical pain by 25%. The combination of esmolol and alfentanil caused a 74% reduction in isoflurane requirements. This study is interesting, because the beta-blocker esmolol had a profound effect on the isoflurane-sparing effects of alfentanil, while having little effect on its own.

Clonidine

In a randomized, double-blind, controlled trial in 61 patients, oral clonidine 5 micrograms/kg was given 90 minutes before surgery to reduce the concentration of isoflurane at which patients wake at the end of surgery by 8% (23). There was a 6–7 minute delay in waking in the clonidine group compared with the control group. Clonidine 2.5 micrograms/kg had no significant effect.

Rocuronium

The infusion requirements of rocuronium necessary to maintain twitch depression were reduced by 40% during anesthesia involving isoflurane (24). In another study in 60 patients undergoing maintenance anesthesia, isoflurane plus nitrous oxide anesthesia reduced the dosage requirement of rocuronium by 35–40% (25).

Suxamethonium

Isoflurane in nitrous oxide inhibited suxamethonium-induced muscle fasciculation in children (26).

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Isometheptene

General Information

Isometheptene, used in the treatment of migraine, is an indirect sympathomimetic with a tyramine-like action and is also an agonist at alpha-adrenoceptors.

In one case an autonomic dysreflexic syndrome developed after the use of an isometheptene combination to treat migraine (1). In other respects its adverse reactions are similar to those of adrenaline and ephedrine.

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Isoniazid

See also Antituberculosis drugs

General Information

Isoniazid is the hydrazide of isonicotinic acid. It is a first-line drug for therapy and prophylaxis of tuberculosis. It is bactericidal for rapidly dividing mycobacteria, but bacteriostatic for "resting bacilli". Among non-tuberculous mycobacteria, only a few strains, such as *Mycobacterium kansasii*, are susceptible. As a rule, sensitivity should always be tested in vitro, since the minimum inhibitory concentration varies greatly.

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Isoniazid diffuses rapidly into body fluids and cells, including cerebrospinal fluid. It is as effective against bacteria growing within cells as it is against bacteria in culture media. There is no cross-resistance between isoniazid and other antituberculosis drugs.

The daily dose of isoniazid is 5 mg/kg, with a maximum of 300 mg/day in adults with normal liver and kidney function. In children, 8–10 mg/kg/day is an appropriate dosage, with a maximum daily dose of 300 mg, since the metabolism of isoniazid in children is rapid. Untoward effects of isoniazid as a single antituberculosis drug can be evaluated in preventive tuberculosis therapy, since curative regimens usually consist of multiple drugs.

Pharmacokinetics

After oral administration, isoniazid reaches a peak plasma concentration of 3–5 micrograms/ml within 1–2 hours. It equilibrates into all body fluids and tissues and 75–95% is excreted in the urine within 24 hours. The most important urinary metabolites are products of acetylation (acetylisoniazid) and hydrolysis (isonicotinic acid). Isonicotinyl glycine, isonicotinyl hydrazones, and *N*-methylisoniazid appear in only small amounts. The rate of acetylation of isoniazid significantly alters its plasma concentrations and half-life. The mean half-life of isoniazid in rapid acetylators is about 70 minutes and in slow acetylators 3 hours.

General adverse reactions

In a survey of more than 2000 patients treated with isoniazid, the most frequent adverse effects were rash (2%), fever (1.2%), jaundice (0.6%), and peripheral neuropathy (0.2%). Seizures can also occur. Isoniazid prolongs the half-life of rifampicin and other drugs metabolized by the liver. Morbilliform, maculopapular, purpuric, and urticarial rashes, with or without fever, are considered to be of allergic origin. Hematological adverse effects consist of agranulocytosis, thrombocytopenia, pure red cell aplasia, and eosinophilia (SEDA-9, 268). Dyspnea, with thoracic pain, cough, fever, and eosinophilia, as well as micronodular densities in the chest X-ray, may also be due to an immunological process (1). Vasculitis associated with antinuclear antibodies has been observed, as well as arthritic symptoms (2). Liver injury (mainly hepatocellular) has been considered another form of hypersensitivity reaction, but usually occurs during combined antituberculosis treatment with rifampicin in combination with anticonvulsants or halothane, or in association with alcoholism. Some are of the opinion that the main factor that induces liver damage is the fast acetylator phenotype (3), while others have found no correlation (4). No increase in cancer deaths was observed in a series of 338 women treated with isoniazid for pulmonary tuberculosis (5). Isoniazid is a potent inhibitor of hepatic enzymes and interferes with the metabolism of many drugs (SEDA-8, 287) (SEDA-11, 271).

Organs and Systems

Respiratory

Symptoms suggestive of bronchial obstruction occur only very rarely during isoniazid treatment (1).

Nervous system

Untoward neurological effects (peripheral neuropathy and focal seizures) occur in 2% of patients if pyridoxine is not given and in 12–20% taking higher doses of isoniazid (10–15 mg/kg) (6).

Peripheral neuropathy due to isoniazid results from inhibition of the formation of the co-enzyme form of vitamin B6, pyridoxine. Numbness or tingling of the extremities in the "glove and stocking" distribution can occur early during treatment with isoniazid when pyridoxine is not given. Neuropathy was noted by several authors in up to 20% of malnourished patients and fast acetylators taking isoniazid in doses over 5–6 mg/kg. Only 2% of patients taking 5 mg/kg of isoniazid plus pyridoxine developed neuropathy. Symptoms generally consist of hyperesthesia, reduced vibration and position sense, and exaggerated or reduced tendon reflexes, but ataxia, muscle weakness, and even paralysis can develop (7). Shoulder–arm syndrome has also been described.

Neurohistology shows disappearance of synaptic vesicles, mitochondrial swelling or condensation, and fragmentation of axon endings. Alterations in the lumbar and sacral spinal ganglia and the spinal cord have also been reported (8).

The addition of pyridoxine to usual doses of isoniazid of 5 mg/kg/day in adults and 8–10 mg/kg/day in children markedly reduces neurotoxicity (9). Adherence to therapy is improved by prescribing combined tablets containing 20 mg of pyridoxine per 100 mg of isoniazid. In otherwise healthy people, prescription of pyridoxine is not mandatory. However, it should be routinely given to malnourished patients and those predisposed to neuropathy (for example pregnant women, elderly people, and people with diabetes, alcoholism, or uremia) (7).

Pellagra-associated encephalopathy has been suspected as an adverse effect of isoniazid administration in several patients with tuberculosis. Deficiency of niacin (nicotinic acid) is characterized by dermatitis, diarrhea, and dementia. Other symptoms can occur, such as seizures, hallucinations, spasticity, and glossitis. Pellagra induced by isoniazid is promoted by malnutrition or a vegetarian diet with low intake of the nicotinamide precursors tryptophan and nicotinic acid. Specific supplementation is essential (10).

Sensory systems

Optic neuritis and atrophy have occurred in patients taking isoniazid (11).

Psychological, psychiatric

Isoniazid can cause neuropsychiatric syndromes, including euphoria, transient impairment of memory, separation of ideas and reality, loss of self-control, psychoses (9), and obsessive-compulsive neurosis (12). Isoniazid should be used with caution in patients with pre-existing psychoses, as it can cause relapse of paranoid schizophrenia (13). Patients on chronic dialysis appear to be vulnerable to neurological adverse drug reactions, because of abnormal metabolism of uremic toxins. It is therefore recommended that a higher than usual dose of pyridoxine be given to patients on dialysis taking isoniazid (14,15).

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Endocrine

Cushing's syndrome, gynecomastia, amenorrhea, and precocious puberty have been regarded as reflecting the enzyme-inhibitory activity of isoniazid, with resulting derangement of hormone metabolism in the liver.

Metabolism

Isoniazid can cause transient hyperglycemia in overdose (16).

In five volunteers taking isoniazid 15 mg/kg/day over a period of 6 weeks, serum cholesterol concentrations were reduced (SEDA-9, 268).

Hematologic

Agranulocytosis, thrombocytopenia, hemolytic anemia, sideroblastic anemia (17), pure red cell aplasia (18), methemoglobinemia, and eosinophilia can occur exceptionally during isoniazid treatment (SEDA-9, 268) (19). An acquired coagulation factor XIII inhibitor developed in a patient taking isoniazid and resulted in a bleeding disorder (20).

Gastrointestinal

No severe gastrointestinal adverse effects of isoniazid have been observed; symptoms are limited to such as epigastric distress, gastric burning, and dry mouth. Of 814 patients with pulmonary tuberculosis treated for 9 months with isoniazid and rifampicin, 18 had minor symptoms of gastrointestinal intolerance (21). Nausea can occur, particularly if the drug is taken before breakfast or in combination with other antituberculosis drugs; 5.5% of 912 patients taking a fixed tablet combination of isoniazid, protionamide, and diaphenyl sulfone plus rifampicin had sensations of fullness, nausea, or vomiting (22).

Liver

Abnormal liver function is the most commonly described adverse effect of isoniazid (23). It may be related to acetylator phenotype.

Hepatotoxicity caused considerable alarm after an episode in Washington DC, when 19 of 2231 government employees given isoniazid prophylaxis developed clinical signs of liver disease within 6 months; 13 were severely jaundiced and 2 died (23).

In a series of 13 838 individuals treated prophylactically, 114 developed overt hepatic disease (SED-9, 574) (24). There were 13 deaths, submassive necrosis in 9 cases, and massive necrosis in 4. The 20 other patients from whom hepatic tissue was available included 16 with moderately severe acute hepatocellular injury (four with a mixed hepatocellular-cholestatic pattern), and four with chronic hepatic damage (one with cirrhosis). The effects of liver disease before the onset of jaundice included vague digestive and "viral" disease-like complaints, some with and some without gastrointestinal symptoms. Jaundice was the presenting complaint in 10%, fever and rash were reported in under 4%, and there was a modest eosinophilia in about 10%. Liver damage was recognized during the first month of administration in 15% and during the second month in a further 31%. The other 54% had taken isoniazid for 2–11 months. Although liver damage in these patients may have been related to isoniazid, some probably had viral hepatitis.

In a study of isoniazid prophylactic therapy in Seattle, USA, only 11 patients of 11 141 had hepatotoxic reactions (25). The rate was 0.1% of those starting and 0.15% of those completing the course of therapy. The duration of therapy was not stated, but 10 of the 11 episodes occurred within 3 months of starting.

The mechanism responsible for hepatotoxicity is not known. A metabolite of isoniazid, acetylhydrazine, causes hepatic damage and may play a role. Alcoholic hepatitis is an aggravating factor. The sensitivity of chronic carriers of hepatitis B virus is controversial (26). In an investigation in which the urinary metabolic profile of isoniazid was assayed in patients who developed isoniazid-related liver damage, it was impossible to predict which patients would be susceptible. It was also impossible to show that rifampicin plays a significant role in inducing liver damage when added to isoniazid (27,28). Nevertheless, it is conceivable that enzyme induction by rifampicin alters the metabolism of isoniazid. Further risk factors are alcoholism, malnutrition, diabetes, previous liver damage, renal insufficiency, and drug abuse. Age is certainly another risk factor: hepatic damage seems to be rare in patients under the age of 20; the incidence of liver toxicity is 0.3% between the ages of 20 and 34, and increases with age to 1.2% between 34 and 49 and 2.3% over the age of 50 (9). Even in prophylaxis with isoniazid monotherapy, adverse effects are more frequent in patients aged over 35 years (29).

Liver damage usually appears 1–2 months after the start of therapy. In children, raised liver enzymes are common during the first few months of treatment, but withdrawal is seldom necessary. A careful watch should be kept for early symptoms of isoniazid-induced hepatitis, such as malaise, fatigue, nausea, and epigastric distress. The dangers of continuing isoniazid after the onset of symptoms of toxicity have been highlighted (30). The earliest symptoms of isoniazid toxicity should be clearly described to the patient, particularly to hepatitis B carriers, who may be more susceptible to hepatotoxicity (26).

It is advisable to measure the liver enzymes aspartate transaminase and alanine transaminase before treatment and monthly thereafter, for as long as isoniazid administration lasts. Isoniazid should be withdrawn if the transaminases increase to over five times normal (9).

Pancreas

Acute pancreatitis has been attributed to isoniazid (31,32).

- A 42-year-old Asian man developed clinical, biochemical, and imaging features of acute pancreatitis 11 days after starting to take rifampicin, isoniazid, and pyrazinamide for spinal tuberculosis (33). He had no history of excessive alcohol or other drug therapy. He improved after withdrawal of all drugs, but the pancreatitis recurred on reintroduction of isoniazid and resolved after withdrawal.

Causality here was difficult to establish. Pancreatitis has rarely been seen in patients who have taken an overdose

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of isoniazid. Rifampicin, also used in this case, is more likely to cause pancreatitis in usual doses.

Urinary tract

Isoniazid can rarely cause renal damage (34).

Urinary retention is a rare complication of isoniazid overdose (35).

Skin

Morbilliform, maculopapular, or urticarial rashes have been observed in up to 2% of patients (9). In one study, acneiform eruptions developed in only 11 cases (1.4%), including 0.5% of patients taking isoniazid, 1.5% of patients taking rifampicin, and 0.6% of patients taking ethambutol (36).

Acquired cutis laxa has been mentioned in a single child taking isoniazid, but it was probably coincidental (37).

Erythema nodosum and purpura have been described in patients taking isoniazid (38).

Pellagra has been reported in a patient taking isoniazid, despite concomitant pyridoxine prophylaxis (39).

- A 52-year-old man developed pellagra with a classical photosensitive distribution after taking isoniazid for 14 months; the first 6 months being treatment for possible tuberculous meningitis, the rest to provide antituberculosis protection while glucocorticoids were given for possible neurosarcoidosis. He was said to take alcohol only occasionally and took pyridoxine throughout the entire period of treatment. He improved rapidly on withdrawal of isoniazid and supplementation with nicotinamide.

The authors noted that isoniazid-induced pellagra was first described in 1956, shortly after the introduction of isoniazid for the treatment of tuberculosis, but that subsequent reports have been very uncommon.

Isoniazid has also been reported to cause subepidermal blistering (40).

- A 63-year-old man developed bullous lesions on the trunk and limbs and a six-fold rise in liver enzymes 15 days after treatment for tuberculosis. His skin recovered and his liver enzymes returned to normal within 2 weeks of withdrawal of all treatment, but the abnormalities recurred when treatment was resumed. At this point a skin biopsy showed subepidermal blistering. Once again withdrawal of treatment led to improvement, and when treatment was resumed without isoniazid the improvement continued.

Desensitization to isoniazid has been attempted in some patients with drug fever or rashes. A procedure of rush desensitization over a few days or a week can be used, starting with 1 mg orally and increasing the dosage every second day (41) or even every few hours.

Musculoskeletal

Arthritic symptoms, with back pain, bilateral proximal interphalangeal joint involvement, arthralgia of the knees, elbows, and wrists, and the so-called "shoulder–arm" syndrome with cervicobrachial neuralgia can occur (9).

Rhabdomyolysis occurred in subjects with isoniazid poisoning in a retrospective analysis of 270 patients seen over a 5-year period at the Phillipine General Hospital in Manilla (42). Skeletal muscle creatine kinase activity was raised in 31 of the 52 evaluable subjects who had taken more than 2.4 g/day of isoniazid. Creatine kinase activity peaked on days 5–6 and fell thereafter. Two patients developed acute renal insufficiency and required dialysis. Seizures occurred in all patients, and their duration, but not their frequency, correlated with raised creatine kinase activity. However, it is likely that factors other than seizures contribute to rhabdomyolysis in patients with isoniazid poisoning.

Immunologic

The expansion or new development of tuberculous lesions during ultimately successful therapy has been termed a "paradoxical response." It is most often reported in relation to intracranial tuberculomata, but is probably most common in tuberculous lymphadenopathy. It is also described in tuberculous pleurisy and in parenchymal lung disease. In most cases, the problem eventually settles, but sometimes glucocorticoid therapy is used empirically.

A lupus-like syndrome or vasculitis, with arthritis, rheumatic pain, fever, pleurisy, and leukopenia, has been reported in patients taking isoniazid (38,43). Tests for antinuclear antibodies are useful to distinguish idiopathic systemic lupus erythematosus and drug-induced lupus-like syndromes. However, many patients taking isoniazid have antinuclear antibodies, usually without signs or symptoms of systemic lupus erythematosus. Isoniazid can also exacerbate pre-existing systemic lupus erythematosus (38,43). Long-term glucocorticoid treatment may be necessary if symptoms persist after withdrawal of isoniazid.

- Two Japanese patients developed pleural effusions while taking antituberculosis therapy and were believed to have isoniazid-induced lupus-like syndrome (44). This diagnosis was based on the presence of antinuclear antibody in the effusate, and in one patient, a positive lymphocyte stimulation test using isoniazid; in the other patient it was negative. Both had moderately strongly positive serum antinuclear antibodies (1:160). In the first patient, the effusion disappeared 2 weeks after withdrawal of isoniazid; in the other treatment was continued but the effusion nevertheless resolved in 10 weeks.

It is worth checking for evidence of lupus-like syndrome in patients with paradoxical responses to antituberculosis therapy but it remains to be seen how many cases would be explained by it.

Long-Term Effects

Mutagenicity

Isoniazid is not mutagenic (SEDA-6, 276), but patients taking combined isoniazid and rifampicin therapy for 3–10 months developed an increased rate of chromosomal aberrations in peripheral blood lymphocytes (SEDA-9, 276). However, this effect is not known to have clinical consequences.

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Second-Generation Effects

Fertility

Isoniazid has no effect on fertility (SEDA-6, 276).

Pregnancy

Isoniazid is the safest antituberculosis drug for use during pregnancy (45,46). During pregnancy, isoniazid with ethambutol is considered to be the preferred combination (45).

Teratogenicity

Isoniazid diffuses into blastocytes, but no teratogenic effects have been reported (46).

Lactation

Isoniazid is the safest antituberculosis drug for use during lactation (45,46). However, as isoniazid passes into breast milk, a watch must be kept for adverse effects in the infant when a nursing mother is taking isoniazid (47). However, the serum concentrations that occur in children have no therapeutic effect and cannot be considered as a form of preventive chemotherapy in infants of mothers with active tuberculosis.

Susceptibility Factors

Genetic factors

People are divided genetically into rapid and slow acetylators of isoniazid, depending on the amount of *N*-acetyltransferase they have. The rate of acetylation of isoniazid depends on race, but is not influenced by sex or by age after childhood. In Eskimos and Japanese, fast acetylators predominate. Slow acetylation is the predominant phenotype in most Scandinavians, Jews, and North African Caucasians (9). Slow acetylators are homozygous for an autosomal recessive gene, while fast acetylators are homozygous or heterozygous for a dominant gene. In the case of isoniazid (which has a low hepatic extraction ratio) the rate of acetylation significantly alters its plasma concentrations and half-life. The mean half-life of isoniazid in rapid acetylators is about 70 minutes and in slow acetylators 3 hours. Despite this, there is probably no difference in the effectiveness of isoniazid in the two phenotypes. The relation between isoniazid toxicity and acetylator status continues to be discussed (3,4,6).

Drug Administration

Drug overdose

Acute poisoning with isoniazid in children (48) and adults (13,26,35) causes recurrent seizures, profound metabolic acidosis, coma, and even death. In adults, toxicity can occur with the acute ingestion of as little as 1.5 g of isoniazid. Doses larger than 30 mg/kg often produce seizures and 80–150 mg/kg or more can be rapidly fatal. The first signs and symptoms of isoniazid toxicity usually appear 0.5–2.0 hours after ingestion, by which time peak absorption occurs (49), and include nausea, vomiting, slurred speech, dizziness, tachycardia, and urinary retention, followed by stupor, coma, and recurrent tonic-clonic seizures. The seizures are often refractory to antiepileptic therapy. However, pyridoxine, 20–1500 mg per gram of isoniazid ingested, usually eliminates seizure activity and helps to correct the metabolic acidosis (50).

Drug–Drug Interactions

Antacids

Absorption of isoniazid can be inhibited by aluminium-containing antacids (51).

Barbiturates

Barbiturates which induce liver drug-metabolizing enzymes increase the rate of metabolism of isoniazid, rifampicin, or combined antituberculosis treatment, since they may result in accelerated breakdown of these drugs (52).

Benzodiazepines

In healthy volunteers, the half-life of triazolam was prolonged from 2.5 to 3.3 hours when it was given with isoniazid (SEDA-9, 267). However, isoniazid did not affect the pharmacokinetics of oxazepam.

Beta-adrenoceptor antagonists

Lipophilic beta-adrenoceptor antagonists are metabolized to varying degrees by oxidation by liver microsomal cytochrome P450 (for example propranolol by CYP1A2 and CYP2D6 and metoprolol by CYP2D6). They can therefore reduce the clearance and increase the steady-state plasma concentrations of other drugs that undergo similar metabolism, potentiating their effects. Drugs that interact in this way include isoniazid (53).

Carbamazepine

Patients taking carbamazepine can develop signs of carbamazepine intoxication; serum concentrations of carbamazepine are increased by isoniazid, probably through enzyme inhibition (54).

Disulfiram

In seven patients taking isoniazid 0.6–1.0 g/day for at least 1 month, disulfiram 0.5 g/day caused dizziness, disorientation, staggering, insomnia, irritability, listlessness, lethargy, and in one case hypomania (55). This interaction may have been due to inhibition of isoniazid metabolism by disulfiram or to a complex interaction with dopamine metabolism.

Ethosuximide

In one case, isoniazid increased blood concentrations of the antiepileptic drug ethosuximide and caused hiccups, anorexia, nausea, vomiting, insomnia, and an acute psychosis (SEDA-9, 267) (56). This may have been due to inhibition of ethosuximide metabolism by isoniazid.

Monoamine oxidase inhibitors

Isoniazid inhibits monoamine oxidase, and hence reduces tyramine metabolism; this effect is enhanced by co-administration of other monoamine oxidase inhibitors (57).

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Phenazone

Isoniazid significantly reduces the hepatic clearance of phenazone (antipyrine) by about 40% (SEDA-9, 267).

Phenytoin

Isoniazid inhibits the parahydroxylation of phenytoin. Symptoms of phenytoin intoxication, such as dizziness, incoordination, or excessive sedation, can occur, particularly in patients who are slow acetylators (SEDA-11, 271). Dosages of phenytoin should be adjusted according to plasma concentrations (58).

Stavudine

A five-fold increase in the risk of distal sensory neuropathy has been reported in patients taking stavudine plus isoniazid (55 versus 11%) compared with patients taking stavudine without isoniazid (59). In nine of 12 patients, the neuropathy resolved on changing antiretroviral drugs. Peripheral neuropathy is a distressing complication during treatment with stavudine and the risk is considerably increased with co-administration of isoniazid. This combination of drugs should be avoided, if possible, in patients with tuberculosis and AIDS.

Food–Drug Interactions

Tyramine-containing foods

Adverse reactions during treatment with isoniazid have been noted after ingestion of several kinds of cheese (60,61). Flushing, palpitation, tachycardia, and increased blood pressure have been observed 0.5–2 hours after cheese. The symptoms generally disappear within 2–4 hours. Interference by isoniazid with monoamine oxidase, and hence with tyramine metabolism, has been incriminated.

Histamine-containing foods

Headache, palpitation, erythema, redness of the eyes, itching, diarrhea, and wheezing can occur with isoniazid after skipjack fish (*Thunnidae*) (60,62), probably because of the high histamine content of this fish.

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Isoprenaline

See also Adrenoceptor agonists

General Information

As a non-selective beta-adrenergic receptor stimulant, isoprenaline produces a wide range of adrenergic effects. Those that involve the heart present the most marked problems in practice. Doses of up to 10 micrograms/minute are used to improve the peripheral circulation in shock. In respiratory disease, isoprenaline in sublingual tablets (up to 10 mg) and inhalers were used in the past, but have been supplanted by selective $beta_2$-adrenoceptor agonists. Isoprenaline inhalers sometimes provided more than the 20 micrograms needed for a maximum effect on the bronchi, resulting in adverse effects. Oral isoprenaline was also used to treat some forms of heart block, but is now obsolete.

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Organs and Systems

Cardiovascular

Tachycardia, dysrhythmias, palpitation, flushing, and attacks of angina pectoris were disadvantages of isoprenaline when it was used in respiratory disease. Users tended to raise the dose (hence increasing the degree of cardiac toxicity), possibly because a metabolite (3-alpha-methylisoprenaline), which may act as a weak beta-blocker, accumulates and makes the original doses ineffective. Isoprenaline produces electrocardiographic changes compatible with myocardial infarction or can lead to ventricular fibrillation or even cardiac muscle necrosis if infusions are not given with the utmost caution (SED-12, 312) (1,2). Exceptionally, the tachycardia produced by an infusion of isoprenaline can be overshadowed by a reflex bradycardia, even while the drug is being given (SEDA-17, 163).

Respiratory

In relaxing bronchial smooth muscle, isoprenaline can impair the ventilation:perfusion ratio and aggravate hypoxemia even as it reduces airway resistance; thus, the patient may feel better but be worse off. In addition, paradoxical bronchospasm can occur, a response of this type having been found in 30% of patients in one series.

Nervous system

Headache, tremor, apprehension, dizziness, and faintness are common problems with isoprenaline.

Gastrointestinal

Quite apart from the fact that systemic adverse reactions appear to be more common when isoprenaline is given in the form of sublingual tablets, these commonly cause mouth ulcers. Their long-term use has also been reported on one occasion to have caused tooth destruction (SED-8, 305), but this was probably coincidental.

Second-Generation Effects

Teratogenicity

Isoprenaline has often been given in pregnancy, and animal studies do not suggest that it is teratogenic.

Susceptibility Factors

Isoprenaline is better avoided whenever stimulation of the heart or the central nervous system is undesirable, for example in patients with angina pectoris or thyroid disease. There is no reliable information on the risks in liver or renal disease.

Drug–Drug Interactions

Theophylline

The toxicity of isoprenaline in animals is increased if it is given with theophylline (3). There is no evidence of this in humans, although an interaction does occur at the cellular level (4).

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Isopropamide iodide

General Information

A 5–10 mg oral dose of the anticholinergic drug isopropamide iodide produces typical anticholinergic adverse effects. In patients with Zollinger–Ellison syndrome the combination of cimetidine plus isopropamide 20–40 mg/day was generally more effective in suppressing acid secretion than cimetidine alone (1).

Organs and Systems

Urinary tract

The presence of isopropamide iodide in some over-the-counter cold remedies, for example alongside antihistamines, should be borne in mind as a hidden cause of urinary retention.

Immunologic

Isopropamide iodide can cause allergic reactions in patients who are sensitive to iodine.

Interference with Diagnostic Tests

Thyroid function

By virtue of its iodine content, isopropamide iodide can interfere with thyroid function tests.

Reference

1. McCarthy DM, Hyman PE. Effect of isopropamide on response to oral cimetidine in patients with Zollinger–Ellison syndrome. Dig Dis Sci 1982;27(4):353–9.

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Isopropanolamine

General Information

Isopropanolamine is used in cosmetics, hair perms, hair sprays, and in tanning lotions as a buffering agent.

Organs and Systems

Immunologic

- Contact dermatitis to a gel containing biphenylacetic acid, a non-steroidal anti-inflammatory agent, carbomer, and isopropanolamine has been reported (1). Patch tests showed a positive reaction to isopropanolamine (1% aqueous) on day 4. Patch-testing of 22 patients as controls showed one case of slight irritation.

Reference

1. Cooper SM, Shaw S. Contact allergy to isopropanolamine in Traxam gel. Contact Dermatitis 1999;41(4):233–4.

Isoxepac

General Information

Evidence about the properties of the NSAID isoxepac is minimal; only increases in gastrointestinal blood loss over pretreatment levels have been described (1).

Reference

1. Mitchell H, Barraclough D, Muirden KD. Blood-loss studies for new non-steroidal anti-inflammatory drugs. Med J Aust 1982;1(8):328.

Isoxicam

See also Non-steroidal anti-inflammatory drugs

General Information

The oxicam NSAID isoxicam has a shorter half-life (30 hours) than piroxicam. However, there are large variations in half-life, clearance, and mean steady-state plasma concentrations. Except for edema, the incidence of adverse effects is unrelated to age (1).

Organs and Systems

Gastrointestinal

The main adverse effects of isoxicam are gastrointestinal (pain, dyspepsia, nausea, vomiting, stomatitis, constipation, and occasionally peptic ulcer), which occur in up to 80% of patients.

Skin

Serious skin reactions (Stevens–Johnson syndrome and Lyell's syndrome) caused temporary withdrawal of isoxicam in several countries, even though an analysis of 1800 patients with rheumatoid arthritis or degenerative joint disease failed to confirm an increased risk (2).

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Isoxsuprine

See also Adrenoceptor agonists

General Information

Isoxsuprine is a beta$_2$-adrenoceptor agonist that also has antagonist action at alpha-adrenoceptors. It has been variously presented as a beta-agonist, a specific vasorelaxant, a uterine relaxant, and an agent that reduces blood viscosity. In high dosages it also inhibits platelet aggregation. There is slim evidence that isoxsuprine improves cognitive function and mental performance in a limited number of patients, but the practical benefit is minor. There is no convincing proof of its efficacy in patients with claudication. It has been widely used in horses for treating navicular syndrome and laminitis, with little evidence of efficacy (1).

Since its efficacy has been doubted with respect to both its vascular and its obstetric use, one must suspect that underdosage of the drug is the best explanation for the low reported incidence of adverse reactions, which are generally of the type regarded as anecdotal (nausea, vomiting, palpitation, dizziness, weakness). Minor facial flushing and tremor are common. As patients tend to increase the dosage gradually, diarrhea, vomiting, headache, vertigo, and rash can occur (SEDA-3, 177) (SEDA-7, 228). The important adverse reactions of isoxsuprine are tachycardia and orthostatic hypotension, but they occur only at high dosages.

Second-Generation Effects

Fetotoxicity

The beta-adrenoceptor agonist effect is sufficient to cause fetal tachycardia when isoxsuprine is given intravenously in late pregnancy, although one large survey suggested that it may be better tolerated by the mother (as regards cardiac and stimulant effects) than salbutamol (SED-12, 313). The fact that maternal blood

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pressure can fall may reflect a direct relaxant effect on the blood vessels.

Reference

1. Erkert RS, Macallister CG. Isoxsuprine hydrochloride in the horse: a review. J Vet Pharmacol Ther 2002;25(2):81–7.

Isradipine

See also Calcium channel blockers

General Information

Isradipine is a dihydropyridine calcium channel blocker.

The MIDAS study (1) was a randomized trial of isradipine versus hydrochlorothiazide over 3 years in 883 patients, designed primarily to assess the effect on the rate of progression of medial intimal thickness in carotid arteries. The control of diastolic blood pressure was equivalent in both groups, but mean systolic blood pressure was 3.5 mmHg higher in isradipine group at 6 months, a significant difference that persisted throughout the study. This might explain the higher incidence of vascular events with isradipine, although there was no difference in the rate of progression of medial intimal thickness between the groups.

Drug–Drug Interactions

Ethanol

Studies in rodents and primates have suggested that calcium channel blockers, including darodipine, nifedipine, and verapamil, can attenuate the behavioral effects of ethanol. Isradipine seems to be the most effective. However, the results of published reports in man on the effects of calcium antagonists on the acute subject-rated, performance-impairing, and cardiovascular effects of ethanol have suggested that the behavioral effects of ethanol are not attenuated by verapamil, nifedipine, or nimodipine. The same conclusions have been reached from a study in nine healthy volunteers (2). Combined ethanol and isradipine produced increases in heart rate and reductions in blood pressure that were not observed with either drug alone. Isradipine significantly reduced peak breath alcohol concentrations, but it did not significantly alter the subject-rated performance-impairing effects of ethanol.

Phenytoin

An interaction of isradipine with phenytoin has been reported (3).

- A 21-year-old white man, who was taking phenytoin and carbamazepine for seizures, developed severe lethargy, ataxia, and weakness after isradipine was prescribed for blood pressure control. The interaction was verified 2 months later, when he was rechallenged with the same dose of isradipine, 2.5 mg bd, and developed the same symptoms. Phenytoin plasma concentrations were at the upper limit of the usual target range (maximum assayed 100 μmol/l) and did not fall when the dose of phenytoin was reduced while he was taking isradipine.

Both pharmacokinetic and pharmacodynamic mechanisms can explain these observations. Isradipine inhibits CYP450 isoforms that are responsible for the metabolism of phenytoin, and both isradipine and phenytoin can bind to calcium channels in the brain and thereby affect neurological function.

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Itraconazole

See also Antifungal azoles

General Information

Itraconazole is a triazole antifungal drug. It is used orally to treat oropharyngeal and vulvovaginal candidiasis, pityriasis versicolor, dermatophytoses unresponsive to topical treatment, and systemic infections, including aspergillosis, blastomycosis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis. It is also used to prevent fungal infections in immunocompromised patients.

Pharmacokinetics

The systemic availability of itraconazole and the bioequivalence of single 200 mg doses of itraconazole solution and two capsule formulations have been evaluated in a crossover study in 30 male volunteers (1). Itraconazole and hydroxyitraconazole were 30–37% more available from the solution and were greater than from either capsule formulation. However, the values of C_{max}, t_{max}, and half-lives were comparable. There were no differences in safety and tolerance. The normal t_{max} of itraconazole is 1.5–4 hours and serum concentrations are dose-related. Steady-state concentrations are reached after about 10–14 days and are high in comparison with those attained after single doses. With single daily dose treatment the half-life is 20–30 hours. Itraconazole is highly protein bound. The tissue concentrations in lung, kidney, liver, bone, spleen, and muscle are 2–3 times higher than the corresponding

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serum concentrations. Concentrations in omentum and adipose tissue are particularly high, and higher concentrations are also found in various parts of the genital tract. Itraconazole is markedly keratinophilic; after withdrawal it will take 1–2 weeks before concentrations in the skin start to fall. Itraconazole concentrations in urine, saliva, eye fluids, and cerebrospinal fluid are low. Penetration of itraconazole into ocular tissues is low compared with those of ketoconazole and fluconazole (2,3). Itraconazole is degraded in the liver and excreted via the bile and to some extent in the urine. Its metabolism is not altered by renal dysfunction (4–6).

Observational studies

The pharmacokinetics, safety, and antifungal efficacy of intravenous itraconazole (400 mg for 2 days then 200 mg for 12 days), followed by 12 weeks of oral capsules (400 mg/day) have been investigated in 31 immunocompromised patients with invasive pulmonary aspergillosis (7). All received intravenous itraconazole and 26 then took oral itraconazole for a median of 79 days. Potentially therapeutic trough plasma itraconazole concentrations of 0.5 microgram/ml or more were achieved in 64% of the patients by day 2 and were generally maintained after switching to oral therapy. There was a complete or partial response in 15 patients. There were adverse events during intravenous therapy in 28 patients, and 13 had adverse events that were possibly related to the drug. The main events (at least 10% incidence) were fever, diarrhea, increased blood urea nitrogen, and nausea. Two of these 13 patients had intravenous therapy withdrawn. There were no consistent clinically relevant changes in laboratory parameters. During oral therapy, nine patients had similar adverse events that were possibly related to itraconazole. Treatment was withdrawn in seven patients because of adverse events during this phase. There were no deaths related to itraconazole.

The pharmacokinetics and safety of intravenous itraconazole for 7 days (200 mg bd for 2 days, then 200 mg od for 5 days), followed by itraconazole oral solution 200 mg od or bd for 14 days, have been assessed in 17 patients with hematological malignancies requiring antifungal prophylaxis (8). The mean trough plasma concentration at the end of the intravenous period was 0.54 microgram/ml. This concentration was not maintained during once-daily oral treatment but increased further during twice-daily treatment, with a trough itraconazole concentration of 1.12 micrograms/ml at the end of oral treatment. All patients had some adverse events, mainly gastrointestinal. The two patients who were withdrawn from the study during intravenous treatment both reported fever; one also had pneumonitis and died from pneumonia 2 weeks after withdrawal, but this was unrelated to the drug. Patients were withdrawn during oral treatment because of fever ($n = 3$), pneumonitis ($n = 2$), colitis ($n = 1$), and abdominal pain and diarrhea ($n = 1$). Biochemical and hematological abnormalities were frequent, but there were no consistent changes.

The efficacy and safety of intermittent itraconazole therapy have been investigated in 635 patients with onychomycosis (9). Intermittent itraconazole (400 mg/day for 1 week per month for 2 months) was effective and safe. Most adverse events were minor and occurred infrequently; there were no major changes in liver function tests.

Two dosages of itraconazole have been compared in the treatment of tinea corporis or tinea cruris in a multicenter, randomized, double-blind, parallel-group study, which showed that itraconazole 200 mg for 1 week (54 patients) is similarly effective, equally well tolerated, and at least as safe as the established regimen of itraconazole 100 mg for 2 weeks (60 patients) (10). In a similar study in tinea pedis or tinea manum, itraconazole 400 mg once a week (66 patients) and itraconazole 100 mg once every 4 weeks (69 patients) were both effective; the two schedules were equally well tolerated and safe (11).

Comparative studies

Amphotericin

Data on the safety of itraconazole have been collected in an open, randomized, multicenter study in 277 adults with cancer and neutropenia (12). Itraconazole oral solution (100 mg bd, $n = 144$) was compared with a combination of amphotericin capsules and nystatin oral suspension ($n = 133$). Adverse events were reported in about 45% of patients in each group. The most frequent were vomiting (14 versus 12 patients), diarrhea (12 versus 9), nausea (5 versus 12), and rash (2 versus 13 patients). There were no differences in liver function test abnormalities. Treatment had to be withdrawn because of adverse events (including death) in 34 patients who took itraconazole and 33 of those who took amphotericin plus nystatin; there were 17 deaths in each group and death was recorded as adverse event in 13 and 9 patients, respectively.

Itraconazole (400 mg intravenously for 2 days, 200 mg intravenously for up to 12 days, then 400 mg/day orally) and intravenous amphotericin deoxycholate (0.7–1.0 mg/kg) have been compared in 384 granulocytopenic patients with persistent fever in a randomized, multicenter trial (13). The median duration of therapy was 8.5 days. The incidence of drug-related adverse events (5 versus 54%) and the rate of withdrawal due to toxicity (19 versus 38%) were significantly lower with itraconazole. The most frequent reasons for withdrawal in patients taking itraconazole were nausea and vomiting (5%), rash (3%), and abnormal liver function tests (3%). Significantly fewer of the patients who received itraconazole had nephrotoxicity (5 versus 24%); however, more had hyperbilirubinemia (10 versus 5%). There was no difference in gastrointestinal adverse events between the two groups.

Itraconazole elixir 2.5 mg/kg bd ($n = 281$) has been compared with amphotericin capsules 500 mg qds ($n = 276$) for the prophylaxis of systemic and superficial fungal infections in a double-blind, randomized, placebo-controlled, multicenter trial for 1–59 days (14). While itraconazole significantly reduced the frequency of superficial fungal infections, it was not superior in reducing invasive fungal infections or in improving mortality. Adverse events were reported in 222 patients taking itraconazole (79%) and in 205 patients taking amphotericin (74%). The commonest adverse events were gastrointestinal, followed by rash and hypokalemia, with no

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differences between the two regimens. In both groups, 5% of the adverse events were considered to be definitely drug-related. Comparable numbers of patients in the two groups permanently stopped treatment because of adverse events (including death), 75 (27%) in the itraconazole group and 78 (28%) in the amphotericin group. Nausea (9 and 11%) and vomiting (8 and 7%) were the most frequently reported adverse events that led to withdrawal. Biochemical changes were comparable in the two groups.

Other antifungal azoles

The safety of continuous itraconazole (50–200 mg/day for up to 3 months) in the treatment of onychomycosis and dermatomycosis has been reviewed, using published and unpublished data from clinical trials (15). The overall incidence of adverse events in patients who took continuous itraconazole (21%) differed little from that in patients who took either topical miconazole or oral placebo (18%). The most frequently reported adverse events were gastrointestinal disorders (6.7%), headache (4.2%), and skin disorders (2.7%). No data were given on the incidence of serious adverse events attributed to itraconazole. Among laboratory abnormalities, clinically significant rises in liver function tests occurred in 3.4% of 527 patients treated with itraconazole (2.6% in patients treated with 50–200 mg/day for dermatomycosis versus 6.6% in patients treated with 200 mg/day for 3 months for onychomycosis).

Oral fluconazole 400 mg qds and oral itraconazole 200 mg bd have been compared in a randomized, double blind, placebo-controlled trial in 198 patients with progressive non-meningeal coccidioidomycosis (16). Overall, 57% and 72% of patients responded to 12 months of therapy with fluconazole and itraconazole, respectively. Relapse rates after withdrawal did not differ significantly. Both drugs were well tolerated. Serious adverse events occurred in eight of 97 fluconazole-treated patients and six of 101 itraconazole-treated patients. They included raised liver enzymes, gastrointestinal disturbances, hypokalemia, and skin rash. Alopecia was reported in 15 of 97 patients taking fluconazole and in only four of 101 patients taking itraconazole. Similarly, dry lips were reported in 11 of 97 patients taking fluconazole and in none of 101 patients taking itraconazole. Both adverse events have previously been reported with fluconazole.

In a double-blind comparison in oropharyngeal candidiasis in 244 patients with AIDS, itraconazole oral solution and fluconazole capsules (each 100 mg/day for 14 days) were equally efficacious; there were no significant differences in adverse effects (17).

Itraconazole oral solution and fluconazole tablets have been compared in oropharyngeal candidiasis in HIV/AIDS patients in a prospective randomized, blind, multicenter trial (18). Both regimens of itraconazole oral solution (100 mg bd for 7 days or 100 mg od for 14 days) were equivalent to fluconazole (100 mg od for 14 days). Itraconazole oral solution was well tolerated.

Oral itraconazole solution has been compared with intravenous/oral fluconazole for the prevention of fungal infections in a randomized, controlled trial in adult liver transplant recipients, who were randomized to receive either oral itraconazole solution (200 mg bd) or intravenous/oral fluconazole (400 mg/day) (19). Prophylaxis was started immediately before transplant surgery and continued for 10 weeks after transplantation. Proven fungal infection developed in nine of 97 patients given itraconazole and in four of 91 patients given fluconazole. Mortality from fungal infection was very low and occurred in only one of the 188 patients. Except for more frequent gastrointestinal adverse effects (nausea, vomiting, diarrhea) with itraconazole, both drugs were well tolerated and neither was associated with hepatotoxicity. Mean trough plasma concentrations of itraconazole were over 250 ng/ml throughout the study and were not affected by H_2 histamine receptor antagonists or antacids.

Terbinafine

Itraconazole (28 patients) and terbinafine (27 patients) have been compared in a double-blind, randomized study in tinea capitis (20). The cure rates at week 12 were 86% and 78% respectively. Adverse events were mild and did not warrant discontinuation of therapy.

Placebo-controlled studies

In a double blind, randomized, placebo-controlled, multicenter trial in plantar or moccasin-type tinea pedis in 72 patients, itraconazole 200 mg bd was significantly more effective than placebo; its safety and tolerability were comparable with placebo (21).

General adverse effects

Most of the reported adverse effects of itraconazole are transient. Gastrointestinal reactions, mild dyspepsia, pyrosis, nausea, vomiting, diarrhea, and epigastric pain are not uncommon. In many of the published reports mention is made of increases in serum liver enzyme activities and hypertriglyceridemia, and symptomatic liver toxicity has been reported. Itraconazole does not induce drug-metabolizing enzymes and is a weaker inhibitor of microsomal enzymes than ketoconazole (4,22). In rats given doses of up to 160 mg/kg, there was no induction or inhibition of the metabolism of xenobiotics (SEDA-16, 285). Hypokalemia has often been reported, without an explanation of the mechanism. The use of higher doses (400 or even 600 mg/day) causes an increased incidence of adverse effects; among those documented at these dosages are severe hypokalemia, reversible adrenal insufficiency, and (in one published case) arrhythmias, the latter being connected with an interaction with terfenadine (SEDA-16, 295) (SEDA-18, 198). Skin rashes and pruritus have been reported. Tumor-inducing effects have not been described.

In patients taking itraconazole capsules for prolonged periods the common adverse effects were nausea and vomiting (in under 10%), hypertriglyceridemia (9%), hypokalemia (6%), raised transaminases (5%), rashes and/or pruritus (2%), headache or dizziness (under 2%), and foot edema (1%) (23).

In a study using the UK General Practice Research Database to determine rates of rare, serious drug-induced, adverse effects on the liver, kidneys, skin, or blood, occurring within 45 days of completing a prescription or refill in 54 803 users of either fluconazole or

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itraconazole, one patient had an abnormal liver function test while taking itraconazole in whom a drug-induced etiology could not be ruled out, a rate of 3.2 per 100 000 prescriptions (95% CI = 0.6, 18) for serious adverse liver effects (24). Thus, itraconazole does not commonly have serious adverse effects on the liver, kidneys, skin, or blood.

Organs and Systems

Cardiovascular

Ventricular fibrillation has been attributed to itraconazole-induced hypokalemia (25).

- Pleural and subsequent pericardial effusion developed in a woman treated with itraconazole 200 mg bd for a localized pulmonary infection with *Aspergillus fumigatus* (SEDA-18, 282). After more than 9 weeks of treatment she developed a pericardial effusion, which necessitated drainage. Itraconazole was withdrawn. Six weeks later, and 2 weeks after the resumption of itraconazole, she developed signs of pulmonary edema and cardiac enlargement. These signs disappeared rapidly on discontinuation of itraconazole.

Studies in dogs and healthy human volunteers have suggested that itraconazole has a negative inotropic effect; the mechanism is unknown. A systematic analysis of data from the FDA's Adverse Event Reporting System (AERS) identified 58 cases suggestive of congestive heart failure in patients taking itraconazole (26). A simultaneous search did not identify any cases of congestive heart failure in patients taking fluconazole and ketoconazole, ruling out the possibility of a class effect. In consequence, the labeling of itraconazole has been revised. Itraconazole is now contraindicated for the treatment of onychomycosis in patients with evidence of ventricular dysfunction. For systemic fungal infections, the risks and benefits of itraconazole should be reassessed if signs or symptoms of congestive heart failure develop.

Nervous system

Headache due to itraconazole has been mentioned in some reports (27). Dizziness is an uncommon complaint, as are mood disturbances.

Psychological, psychiatric

Visual hallucinations with confusion have been reported in a 75-year-old woman, occurring on three separate occasions, each time about 2 hours after a 200 mg dose of itraconazole. Her symptoms abated spontaneously over about 8 hours (28).

Electrolyte balance

Hypokalemia, occurring either in isolation or with hypertension, has been reported regularly in a small fraction of patients (23). Marked ankle edema with weight gain was seen in a patient taking itraconazole 400 mg/day, in whom there was no explanation other than the use of the drug; after withdrawal of the itraconazole the symptoms disappeared. Hypokalemia and edema have also been observed in a number of patients taking high-dose therapy (600 mg/day) (SED-12, 680) (29) (SEDA-16, 295) (SEDA-17, 321) (4,25,29,30), associated with mildly depressed aldosterone concentrations (SED-12, 680) (SEDA-16, 295).

Gastrointestinal

Dyspepsia, pyrosis, nausea, vomiting, mild epigastric discomfort, and diarrhea can occur in patients taking itraconazole (31). These gastrointestinal complaints are generally mild, but they seem to be the most frequent adverse effects during treatment. The total incidence of adverse effects was 3–5% in patients treated for superficial mycosis and 8% in 99 patients treated for deep mycosis (SED-12, 680) (32). An incidence closer to 15% was reported in a multicenter trial (SEDA-17, 321).

In 50 women with acute vaginal candidiasis, adverse effects were reported in 17 (35%), nausea in seven, headache in six, dizziness in three, and bloating in three, while aspartate transaminase activity was raised in one (33).

Of 1108 patients with HIV treated for mucosal candidiasis, 239 reported gastrointestinal symptoms (34).

Pseudomembranous colitis has been reported in association with exposure to itraconazole (35).

- A 54-year-old man developed new abdominal pain and non-bloody diarrhea 1 month after exposure to a 7-day course of oral itraconazole 200 mg/day. He was taking stable chronic sertraline, valproic acid, and perphenazine, and had not taken antimicrobial drugs for 6 months. Flexible sigmoidoscopy after clinical progression showed pseudomembranes, and subsequent evaluation excluded other causes of diarrhea. Although *Clostridium difficile* culture and toxin assay were eventually negative, possibly because of delayed stool sampling, he responded to a 10-day course of anti-anaerobic drug therapy and was discharged with completely resolved symptoms.

The authors proposed that itraconazole had disrupted the resident fungal flora of the colon.

Liver

In most clinical reports, there were some cases of raised liver enzyme activities; the changes were transient or disappeared after withdrawal of itraconazole (36). More serious hepatotoxicity was not reported.

- Focal nodular hyperplasia of the liver has been reported in a 38-year-old woman who had taken itraconazole 200 mg/day for 4 months for a fungal infection of the fingernails (37). She had taken no other drugs in the year during which focal nodular hyperplasia developed.
- Of three patients, two women aged 62 and 57 and a man aged 75 years, who developed symptomatic hepatic injury 5–6 weeks after starting to take itraconazole, two had the biochemical pattern of cholestatic liver damage (38).

All itraconazole clinical trials sponsored by Janssen Research Foundation for the treatment of onychomycosis, in which there was an assessment of laboratory safety, have been analysed (39). There were no significant differences in the number of code 4 abnormalities (baseline

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value is in the reference range and at least two values, or the last testing in the observation period, exceed twice the upper limit of the reference range) in liver function tests (alanine transaminase, aspartate transaminase, alkaline phosphatase, and total bilirubin). The incidence of all the code 4 abnormalities was under 2%. Itraconazole pulse therapy for onychomycosis appears to be safe, especially from the perspective of potential liver damage. In the itraconazole package insert, liver function tests are recommended in patients receiving continuous itraconazole for over 1 month. There is no such monitoring requirement for the pulse regimen, unless the patient has a history of underlying hepatic disease, the liver function tests are abnormal at baseline, or signs or symptoms suggestive of liver dysfunction develop at any time.

Skin

Different types of rash, including a case of acneiform rash, have been reported in patients taking itraconazole. In one case there were bloody bullae (SED-12, 680) (40–43).

- A 29-year-old man developed an infiltrative maculopapular eruption after 1 week of itraconazole 100 mg bd for tinea corporis (44). Itraconazole was withdrawn, and the lesions disappeared within 7 days. Scratch tests, patch tests, scratch-patch tests, and drug induced lymphocyte stimulation tests for itraconazole were negative; however, rechallenge with systemic itraconazole induced a maculopapular eruption on the face, hands, and the dorsa of the feet. Empty itraconazole capsules had no cutaneous effects, suggesting an allergic reaction to a metabolite of the compound.

Photosensitivity has been attributed to itraconazole (200 mg qds for 5 days), with reduced minimal erythema dose for both UVB (0.12 J/cm^2) and UVA (20.1 J/cm^2), negative photopatch testing, and a positive photochallenge (45). The authors proposed a photoallergic mechanism because earlier exposure to itraconazole had been uneventful. However, details about sun exposure during the first exposure and about the intensity of sun exposure during the oral photochallenge procedure were not given. The eruption responded to oral steroids, which is more typical of photoallergic than phototoxic reactions.

The risk of serious skin disorders has been estimated in 61 858 users of oral antifungal drugs, aged 20–79 years, identified in the UK General Practice Research Database (46). They had received at least one prescription for oral fluconazole, griseofulvin, itraconazole, ketoconazole, or terbinafine. The background rate of serious cutaneous adverse reactions (corresponding to non-use of oral antifungal drugs) was 3.9 per 10 000 person-years (95% CI = 2.9, 5.2). Incidence rates for current use were 15 per 10 000 person-years (1.9, 56) for itraconazole, 11.1 (3.0, 29) for terbinafine, 10 (1.3, 38) for fluconazole, and 4.6 (0.1, 26) for griseofulvin. Cutaneous disorders associated with the use of oral antifungal drugs in this study were all mild.

Sexual function

There are inconsistent reports about the effects of itraconazole on sex steroids. Concentrations of testosterone, corticosterone, and progesterone were unchanged in rats and in six dogs in whom possible endocrine effects were studied (SED-12, 680). On the other hand, the administration of itraconazole to seven male volunteers for 2 weeks did not produce detectable changes in plasma testosterone or cortisol concentrations. There was a slightly reduced cortisol response to ACTH stimulation 2 weeks after the start of high-dose itraconazole therapy (600 mg/day) in one of eight patients with severe mycosis (29).

Erectile impotence, with normal steroid concentrations, has been reported, as has a reduction in libido (SEDA-17, 321) (47).

Immunologic

Itraconazole 200 mg bd for 2 weeks caused a serum sickness-like reaction in a 53-year-old woman with Menière's disease (48).

Second-Generation Effects

Teratogenicity

Since embryotoxicity and teratogenicity have been found in rats, albeit after the administration of high doses, itraconazole should be avoided during pregnancy (SED-12, 681) (49).

Susceptibility Factors

Age

The safety, tolerability, and pharmacokinetics of itraconazole and its active metabolite hydroxyitraconazole after administration of itraconazole solution in hydroxypropyl-β-cyclodextrin have been investigated in a multicenter study in 26 infants and children aged 6 months to 12 years with mucosal candidiasis or at risk of invasive fungal disease (50). There was a trend to lower minimum plasma concentrations in children aged 6 months to 2 years. The systemic absorption of the solubilizer hydroxypropyl-β-cyclodextrin was less than 1%. Given at 5 mg/kg/day, this formulation provided potentially therapeutic concentrations in plasma, somewhat lower than those attained in adults, and it was well tolerated and safe.

Itraconazole 100 mg/day has been studied in 24 children with *Trichophyton tonsurans* tinea capitis (51). Itraconazole was well tolerated, but 15 children required re-treatment due to persistent infection.

The safety, pharmacokinetics, and pharmacodynamics of an oral suspension of cyclodextrin itraconazole (2.5 mg /kg od or bd for 15 days) have been investigated in an open, sequential, dose-escalation study in 26 children and adolescents, 5–18 years old, infected with HIV (mean CD4 count 128 $\times$ 10^6/l) with oropharyngeal candidiasis (52). Apart from mild to moderate gastrointestinal disturbances in three patients, cyclodextrin itraconazole was well tolerated. Two patients withdrew prematurely because of adverse events. The oropharyngeal candidiasis score fell significantly from a mean of 7.46 at baseline to 2.8 at the end of therapy, demonstrating antifungal efficacy in this setting. Based on these results, a dosage of 2.5 mg/kg bd was recommended for the treatment of oropharyngeal candidiasis in children aged 5 years and over.

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The safety and efficacy of oral cyclodextrin itraconazole (5 mg/kg/day) as antifungal prophylaxis has been assessed in an open trial in 103 neutropenic children (median age 5 years; range 0–15 years) (53). Prophylaxis was started at least 7 days before the onset of neutropenia and continued until neutrophil recovery. Of the 103 patients, only 47 completed the course of prophylaxis; 27 withdrew because of poor compliance, 19 because of adverse events, and 10 for other reasons. Serious adverse events (other than death) occurred in 21 patients, including convulsions ($n = 7$), suspected drug interactions ($n = 6$), abdominal pain ($n = 4$), and constipation ($n = 4$). The most common adverse events considered definitely or possibly related to itraconazole were vomiting ($n = 12$), abnormal liver function ($n = 5$), and abdominal pain ($n = 3$). Tolerability of the study medication at end-point was rated as good (55%), moderate (11%), poor (17%), or unacceptable (17%). There were no unexpected problems of safety or tolerability.

Other features of the patient

Adverse effects due to drug–drug interactions are not expected in diabetic patients using insulin and oral hypoglycemic drugs that are not metabolized by CYP3A4 (for example tolbutamide, gliclazide, glibenclamide, glipizide, and metformin). The pharmacokinetic and safety data from clinical trials and postmarketing surveillance have been reviewed to assess the safety of itraconazole in diabetic patients with onychomycosis or dermatomycosis (54). Postmarketing surveillance, including all adverse event reports in patients taking itraconazole concomitantly with insulin or an oral hypoglycemic drug, revealed 15 reports suggestive of hyperglycemia and nine reports suggestive of hypoglycemia. In most patients there was no change in antidiabetic effect. From clinical trials in 189 diabetic patients taking itraconazole for various infections, one itraconazole-related adverse event was recorded; this was a case of aggravated diabetes in a renal transplant patient who was also taking ciclosporin.

Drug Administration

Drug formulations

Itraconazole is poorly soluble in water and highly lipophilic. It is available as capsules, as oral and parenteral solutions that both contain hydroxypropyl-β-cyclodextrin as a solubilizer.

Absorption of itraconazole from capsules depends on a low gastric pH and is reduced by fasting and improved by the presence of food and acidic beverages; it is unpredictable in patients with hypochlorhydria. The t_{max} occurs at 1.5–2 hours. When polyethylene glycol is used as a solvent, the absorption is not as good. Inadequate plasma concentrations are often found in patients receiving cytotoxic drug therapy, which predisposes them to mucositis, poor food intake, and vomiting. The absorption of oral itraconazole seems to be reduced in patients with AIDS (2,3).

Systemic absorption of the cyclodextrin carrier after oral administration is negligible. After intravenous administration the cyclodextrin is not metabolized and is almost completely eliminated by glomerular filtration within 24 hours. Although the cyclodextrin enhances the systemic availability of itraconazole, it can have gastrointestinal adverse effects when used in escalating dosages exceeding 400 mg/day.

A dose-ranging study of itraconazole in antifungal prophylaxis in 123 neutropenic patients with hematological malignancies has been reported (55). The dosing regimens included itraconazole capsules 400, 600, or 800 mg/day and itraconazole cyclodextrin solution 400 and 800 mg/day (with an additional loading with 800 mg of the capsule formulation for 7 days). Ten of twenty-eight patients taking 800 mg/day as a solution withdrew after 1–6 days with severe nausea and vomiting in temporal relation to ingestion of the drug. All the patients who discontinued the solution continued medication with itraconazole capsules in the same dosage without gastrointestinal adverse effects.

Drug–Drug Interactions

Amphotericin

The in vitro effects of the combination of amphotericin with itraconazole was tested using six strains of *A. fumigatus*, and an antagonistic effect was found after pretreatment for all strains in vitro and for one strain in a mouse model of aspergillosis (56).

The effect of the combination of itraconazole with amphotericin on liver enzyme activities has been studied retrospectively in 20 patients with hematological malignancies or chronic lung disease complicated by fungal infection or colonization (57). They took itraconazole 200–600 mg/day for a median of 143 (range 44–455) days. Nine had no abnormal liver function tests, including periods of high concentrations of itraconazole (over 5000 ng/ml) and its active hydroxylated metabolite; only one had received concomitant amphotericin. All of the 11 patients with liver function abnormalities had received concomitant amphotericin. For each patient, liver function abnormalities were greatest during the time of concomitant therapy with both antifungal drugs. Although liver enzyme abnormalities are uncommon with amphotericin (58), and although this retrospective analysis was subject to several flaws and potential biases, it nevertheless suggests that hepatotoxicity should be carefully monitored if itraconazole and amphotericin are co-administered.

Antihistamines

It seems likely that combining itraconazole with astemizole (59) and terfenadine (60,61) will lead to increased effects of these antihistamines (62).

Barbiturates

Barbiturates lower itraconazole concentrations (SED-12, 681) (4,22).

Benzodiazepines

The effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of estazolam has been studied in a double-blind, randomized, crossover study in

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10 healthy male volunteers, who took oral itraconazole 100 mg/day or placebo for 7 days and on day 4 a single oral dose of estazolam 4 mg (63). Blood samplings and evaluation of psychomotor function by the Digit Symbol Substitution Test, Visual Analogue Scale, and Stanford Sleepiness Scale were conducted up to 72 hours after estazolam. There was no significant difference between the placebo and itraconazole phases in peak plasma concentration, clearance, and half-life. Similarly, psychomotor function was unaffected. These findings suggest that CYP3A4 is not involved to a major extent in the metabolism of estazolam.

In a study of the effects of itraconazole 200 mg/day and rifampicin 600 mg/day on the pharmacokinetics and pharmacodynamics of oral midazolam 7.5–15 mg during and 4 days after the end of the treatment, switching from inhibition to induction of metabolism caused an up to 400-fold change in the AUC of oral midazolam (64).

Bupivacaine

The interaction of itraconazole 200 mg orally od for 4 days with a single intravenous dose of racemic bupivacaine (0.3 mg /kg given over 60 minutes) has been examined in a placebo-controlled crossover study in 10 healthy volunteers (65). Itraconazole reduced the clearance of *R*-bupivacaine by 21% and that of *S*-bupivacaine by 25%, but had no other significant effects on the pharmacokinetics of the enantiomers. Reduction of bupivacaine clearance by itraconazole is likely to increase steady-state concentrations of bupivacaine enantiomers by 20–25%, and this should be taken into account in the concomitant use of itraconazole and bupivacaine.

Buspirone

The interaction of itraconazole with the active 1-(2-pyrimidinyl)-piperazine metabolite of buspirone has been studied after a single oral dose of buspirone 10 mg (66). Itraconazole reduced the mean AUC of the metabolite by 50% and the C_{max} by 57%, whereas the mean AUC and C_{max} of the parent drug were increased 14.5-fold and 10.5-fold respectively. Thus, itraconazole caused relatively minor changes in the plasma concentrations of the active piperazine metabolite of buspirone, although it had major effects on the concentrations of buspirone after a single oral dose.

Busulfan

Reduced elimination and increased toxicity of busulfan co-administered with itraconazole has been postulated (67).

Carbamazepine

Low and sometimes very low serum concentrations of itraconazole have been seen during concurrent therapy of itraconazole with carbamazepine (68).

Ciclosporin

The combination of itraconazole with ciclosporin leads to a marked increase in blood ciclosporin concentrations, and this can result in a rise in serum creatinine, clearly pointing to renal damage as a result of the high ciclosporin concentrations (SED-12, 681) (69,70–72). However, an interaction has not been demonstrated in all cases (73).

Two cases of rhabdomyolysis caused by itraconazole in heart transplant recipients taking long-term ciclosporin and simvastatin have been reported (74,75). To avoid severe myopathy, ciclosporin concentrations should be monitored frequently and statins should be withdrawn or the dosage should be reduced, as long as azoles need to be prescribed in transplant recipients. Patients need to be educated about signs and symptoms that require immediate physician intervention.

Citrate-phosphate buffer

The citrate-phosphate buffer used to facilitate the absorption of dideoxyinosine (didanosine), prescribed for the treatment of AIDS, may interfere with the absorption of itraconazole (76).

Clarithromycin

A report of three HIV-negative patients has suggested that concomitant therapy with itraconazole and clarithromycin can lead to increased clarithromycin exposure, with an increased metabolic ratio, possibly related to itraconazole's effect on CYP3A4 (77). Nevertheless, in none of the three reported individuals were there adverse effects from this presumed interaction.

Clozapine

Itraconazole 200 mg had no significant effect on serum concentrations of clozapine 200–550 mg/day or desmethylclozapine in 7 schizophrenic patients (78).

Digoxin

Itraconazole inhibits the elimination of digoxin, eventually leading to toxicity (4,79–82) (SEDA-18, 198).

Itraconazole increases the digoxin $AUC_{0–72}$ by about 50%, and reduces its renal clearance by about 20% (83). Apart from inhibition of the renal secretion of digoxin, which is probably mediated by inhibition of P glycoprotein, a study in guinea pigs also showed significantly reduced biliary excretion of digoxin by itraconazole, suggesting that the interaction between itraconazole and digoxin may not only be due to a reduction in renal clearance, but also to a reduction in the metabolic clearance of digoxin by itraconazole (84).

The importance of this interaction has been emphasized by a report of two renal transplant patients who had digoxin toxicity when they took itraconazole concurrently (85).

Famotidine

Famotidine 40 mg/kg/day reduced the peak and trough concentrations of itraconazole 200 mg/kg/day by about 35% in 18 patients undergoing chemotherapy for hematological malignancies (86).

Fentanyl

Fentanyl is a substrate of CYP3A4, CYP2C9, and CYP2C19. However, in one study, the pharmacokinetics

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and pharmacodynamics of fentanyl 3 micrograms/kg were similar after itraconazole 200 mg and placebo in 10 healthy volunteers (87).

- An interaction of itraconazole with fentanyl has been reported in a 67-year-old man with cancer on a stable dose of transdermal fentanyl 50 micrograms/hour (88). He took itraconazole 200 mg bd for oropharyngeal candidiasis, and 24 hours later developed signs of opioid toxicity, which was reversed by withdrawal of fentanyl and replacement with short-acting opioids.

This may be an interaction to which only some individuals are susceptible.

Flucytosine

The activity of itraconazole against black fungi can be augmented by combining it with flucytosine; the combination has prevented the development of flucytosine resistance (89).

Glucocorticoids

Itraconazole can inhibit the metabolic clearance of glucocorticoids by interfering with CYP3A4 and can directly inhibit steroidogenesis, thereby causing serious adverse effects. The effects on different glucocorticoids differ.

Budesonide

Two patients with cystic fibrosis developed profound adrenal failure and impairment of inhaled steroid clearance, resulting in paradoxical Cushing's syndrome, after long-term treatment with itraconazole and inhaled budenoside (90,91). Pituitary–adrenal axis and gonadal function was then assessed in 37 patients treated with itraconazole with or without budesonide (92). An adrenocorticotropic hormone (ACTH) test (tetracosactide 250 micrograms) was performed in 25 patients with cystic fibrosis taking itraconazole and budesonide and in 12 patients taking itraconazole alone (6 with cystic fibrosis and 6 with chronic granulomatous disease). Mineralocorticoid and gonadal steroid function were evaluated by measurements of plasma renin activity and follicle-stimulating hormone, luteinizing hormone, progesterone, estradiol, testosterone, and serum inhibin A and B concentrations. ACTH tests performed as part of a pretransplantation program in a further 30 patients with cystic fibrosis were used as controls. Eleven of the twenty-five patients who took both itraconazole and budesonide had adrenal insufficiency. None of the patients taking itraconazole alone and none of the control patients with cystic fibrosis had an abnormal ACTH test. Mineralocorticoid or gonadal insufficiency was not observed in any patient. Only one patient with an initial pathological ACTH test subsequently normalized; the other 10 patients improved but had not achieved normal adrenal function 2–10 months after itraconazole had been withdrawn.

The effects of itraconazole on the pharmacokinetics and cortisol-suppressing activity of budesonide by inhalation were further investigated in a randomized, double-blind, two-phase, crossover study in 10 healthy subjects who took oral itraconazole 200 mg/day or placebo for 5 days (93). On day 5, 1 hour after the last dose of itraconazole or placebo, they took budesonide 1000 micrograms by inhalation. Plasma budesonide and cortisol concentrations were measured up to 23 hours. Itraconazole increased the mean total AUC of inhaled budesonide 4.2-fold (range 1.7–9.8) and the peak plasma concentration 1.6-fold compared with placebo. The mean half-life of budesonide was prolonged from 1.6 to 6.2 hours. The suppression of cortisol production after inhalation of budesonide was significantly increased by itraconazole compared with placebo, with a 43% reduction in the AUC of plasma cortisol from 0.5 to 10 hours and a 12% reduction in the cortisol concentration measured 23 hours after budesonide, at 8 a.m. Thus, itraconazole markedly increased the systemic exposure to inhaled budesonide. This interaction resulted in enhanced systemic effects of budesonide, as shown by suppression of cortisol production.

Dexamethasone

Itraconazole markedly increases both systemic exposure to dexamethasone and its effects. This interaction has been investigated in a randomized, double-blind, placebo-controlled, crossover study (94). Eight healthy volunteers took either oral itraconazole 200 mg od or placebo for 4 days. On day 4, each subject was given oral dexamethasone 4.5 mg or intravenous dexamethasone sodium phosphate 5.0 mg. Itraconazole reduced the systemic clearance of intravenous dexamethasone by 68%, and increased its AUC and prolonged its half-life more than three-fold; the AUC of oral dexamethasone was increased nearly four-fold and its half-life nearly three-fold. Morning plasma cortisol concentrations at 47 and 71 hours after dexamethasone were significantly lower after itraconazole than placebo.

Methylprednisolone

The interaction of itraconazole with oral methylprednisolone has been examined in a randomized, double-blind, crossover study in 10 healthy volunteers taking either oral itraconazole 200 mg/day or placebo for 4 days (95). On day 4 each subject took methylprednisolone 16 mg. Itraconazole increased the total AUC of methylprednisolone 3.9-fold compared with placebo, the peak plasma methylprednisolone concentration 1.9-fold, and the half-life 2.4-fold. This effect was probably through inhibition of CYP3A4.

Similar effects were found in a study of the effects of itraconazole on the kinetics of intravenous methylprednisolone in a double-blind, randomized, crossover study in nine healthy volunteers (96). Itraconazole (200 mg for 4 days) increased the AUC of methylprednisolone (16 mg on day 4) 2.6-fold, and the $AUC_{12–24}$ 12-fold. The systemic clearance of methylprednisolone was reduced to 40% by itraconazole and the half-life was increased from 2.1 to 4.8 hours. The mean morning plasma cortisol concentration was only 9% of that during the placebo phase. Thus, concomitant itraconazole greatly increased exposure to methylprednisolone during the night-time and led to enhanced adrenal suppression.

The effects of oral itraconazole (400 mg on the first day, then 200 mg/day for 3 days) on the pharmacokinetics of a single oral dose of methylprednisolone 48 mg have

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been studied in 14 healthy men in a two-period, crossover study (97). Plasma cortisol concentrations were determined as a pharmacodynamic index. Itraconazole significantly increased the mean AUC of methylprednisolone from 2773 to 7011 hours.ng/ml and the half-life from 3.2 to 5.5 hours. Cortisol concentrations at 24 hours were significantly lower after the administration of methylprednisolone with itraconazole than after methylprednisolone alone (24 versus 109 ng/ml).

Prednisolone

The effects of oral itraconazole (400 mg on the first day then 200 mg/day for 3 days) on the pharmacokinetics of a single oral dose of prednisolone 60 mg or methylprednisolone 48 mg have been studied in 14 healthy men in a two-period, crossover study (97). Plasma cortisol concentrations were determined as a pharmacodynamic index. The disposition of prednisolone was unchanged.

The effects of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone have been investigated in a double-blind, randomized, crossover study (98). Ten healthy subjects took either oral itraconazole 200 mg od or placebo for 4 days. On day 4 they took oral prednisolone 20 mg. Itraconazole increased the plasma AUC of prednisolone by 24% and its half-life by 29% compared with placebo. The peak plasma concentration and time to the peak of prednisolone were not affected. Itraconazole reduced the mean morning plasma cortisol concentration, measured 23 hours after prednisolone, by 27%.

The minor interaction of itraconazole with oral prednisolone is probably of limited clinical significance. The susceptibility of prednisolone to interact with CYP3A4 inhibitors is considerably smaller than that of methylprednisolone, and itraconazole and probably also other inhibitors of CYP3A4 can be used concomitantly with prednisolone without marked interaction.

Grapefruit juice

The effect of grapefruit juice on the systemic availability of itraconazole capsules has been investigated in a randomized, two-way, crossover design in 11 healthy volunteers (99). Grapefruit juice reduced the mean itraconazole $AUC_{0–48}$ by 43% and the mean hydroxyitraconazole $AUC_{0–72}$ by 47%. Grapefruit juice also significantly delayed the mean itraconazole t_{max} from 4 to 5.5 hours. The mechanisms for the impaired absorption of itraconazole in the presence of grapefruit juice remain to be elucidated; however, grapefruit juice is acidic and an inhibitor of CYP3A4.

Unexpectedly, in another study, grapefruit juice did not affect the pharmacokinetics of itraconazole in 22 healthy men while orange juice reduced the C_{max}, t_{max}, and AUC (100).

Haloperidol

The effects of itraconazole 200 mg/day for 7 days on the steady-state plasma concentrations of haloperidol and its reduced metabolite have been investigated in schizophrenic patients receiving haloperidol 12 or 24 mg/day (101). Itraconazole significantly increased trough plasma concentrations of both haloperidol and reduced haloperidol (17 versus 13 ng/ml and 6.1 versus 4.9 ng/ml respectively). There was no change in clinical symptoms, but neurological adverse effects of haloperidol were significantly increased during itraconazole co-administration. Similar findings in a similar study were reported for bromperidol and its reduced metabolite, although there were no differences in clinical symptoms or neurological adverse effects during concomitant itraconazole therapy (102).

Omeprazole

In 11 healthy volunteers, omeprazole 40 mg reduced the systemic availability of itraconazole 200 mg; these two drugs should therefore not be used together (103).

Oral contraceptives

Itraconazole can delay withdrawal bleeding in women using oral contraceptives (104). An analysis using data from a spontaneous adverse drug reaction reporting system in the Netherlands and logistic regression analysis showed an odds ratio of 85 (CI = 32, 230) for delayed withdrawal bleeding in women who used both drugs concomitantly compared with woman who used neither oral contraceptives nor itraconazole. Nine of the ten reports of delayed withdrawal bleeding concerned oral contraceptives containing desogestrel. In an open, crossover study in 10 young healthy subjects, fluconazole 150 mg increased the serum concentrations of ethinylestradiol at a close of 30–35 micrograms/day (105).

Phenytoin

Low and sometimes very low serum concentrations of itraconazole have been seen during concurrent therapy of itraconazole with phenytoin (68). At the same time, phenytoin concentrations may themselves be lowered when it is used with itraconazole (68).

Quinidine

In vitro studies have suggested that the oxidation of quinidine to 3-hydroxyquinidine is a specific marker reaction for CYP3A4 activity. In six healthy young men the pharmacokinetics of a single oral dose of quinidine 200 mg were studied before and during daily administration of itraconazole 100 mg (106). Itraconazole reduced quinidine total clearance, partial clearance by 3-hydroxylation, and partial clearance by *N*-oxidation by 61, 84, and 73% respectively.

Rifamycins

Rifampicin 600 mg/day for 14 days had a very strong inducing effect on the metabolism of a single dose of itraconazole 200 mg, indicating that these two drugs should not be used concomitantly (107).

Ropivacaine

The effects of clarithromycin (250 mg bd) and itraconazole (200 mg od) for 4 days on the pharmacokinetics of ropivacaine (given intravenously as a single dose of 0.6 mg/kg on day 4) have been studied in a double-blind, three-way, crossover study in eight healthy volunteers (108). There were no significant changes in the

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pharmacokinetics of ropivacaine after clarithromycin or itraconazole. Although clarithromycin and itraconazole inhibited formation of the (*S*)-2′,6′-pipelodoxylidide metabolite of ropivacaine, there were no significant changes in the pharmacokinetics of ropivacaine itself.

Saquinavir

The HIV protease inhibitor saquinavir has limited and variable oral systemic availability and ritonavir, an inhibitor of CYP450 and P glycoprotein, is widely used to increase its systemic exposure. A small pilot study in three HIV-infected patients has suggested that oral itraconazole can have similar effects on the oral availability of saquinavir (109). Concomitant use of itraconazole 200 mg/day with a combination of saquinavir and two nucleoside reverse transcriptase inhibitors led to a 2.5- to 6.9-fold increase in the AUC of saquinavir, a 2.0- to 5.4-fold increase in peak plasma concentrations, and a 1.6- to 17-fold increase in trough plasma concentrations. The effect of itraconazole on saquinavir was comparable to that of ritonavir.

Selegiline

The effects of itraconazole (200 mg/day for 4 days) on the pharmacokinetics of selegiline (10 mg on day 4) have been investigated in a randomized, placebo-controlled, crossover study (110). Itraconazole did not alter the pharmacokinetics of selegiline and its primary metabolites, desmethylselegiline and 1-metamfetamine. In human liver microsomes, itraconazole did not inhibit the formation of either metabolite. These findings suggest that selegiline is not susceptible to interactions with CYP3A4 inhibitors.

Statins

Itraconazole increases the risk of skeletal muscle toxicity of some statins by increasing their serum concentrations, but not all statins are equally affected. Concomitant use of atorvastatin, lovastatin, and simvastatin with itraconazole should be avoided or the doses should be reduced; fluvastatin and pravastatin have much less potential than other statins for clinically significant interactions with itraconazole and other CYP3A4 inhibitors; the effects of cerivastatin are intermediate.

In a randomized, open, three-way, crossover study, 18 healthy subjects took single doses of cerivastatin 0.8 mg, atorvastatin 20 mg, or pravastatin 40 mg without or with itraconazole 200 mg (111). Concomitant cerivastatin + itraconazole and pravastatin + itraconazole produced small increases in AUC, C_{max}, and half-life (up to 51%, 25%, and 23% respectively). However, itraconazole markedly increased atorvastatin AUC (150%), C_{max} (38%), and half-life (30%). Thus, itraconazole markedly increases systemic exposure to atorvastatin, but results in only modest increases in the plasma concentrations of cerivastatin and pravastatin.

Atorvastatin

Itraconazole increases serum concentrations of atorvastatin by inhibiting CYP3A4. In a randomized, double-blind, crossover study in 10 healthy volunteers, itraconazole 200 mg increased the AUC and half-life of atorvastatin 40 mg about three-fold, with a change in C_{max} (112). The AUC of atorvastatin lactone was increased about 4-fold, and the C_{max} and half-life were increased more than 2-fold. Itraconazole significantly reduced the C_{max} and AUC of 2-hydroxyatorvastatin acid and 2-hydroxyatorvastatin lactone and increased the half-life of 2-hydroxyatorvastatin lactone. The concomitant use of itraconazole and other potent inhibitors of CYP3A4 with atorvastatin should therefore be avoided, or the dose of atorvastatin should be reduced accordingly.

Cerivastatin

Cerivastatin uses a secondary CYP2C8-mediated metabolic pathway, which is unaffected by itraconazole (113). The effects of itraconazole on the pharmacokinetics of cerivastatin and its major metabolites have been investigated in a randomized, double-blind, crossover study (114). Inhibition of the CYP3A4-mediated M-1 pathway led to raised serum concentrations of cerivastatin, cerivastatin lactone, and metabolite M-23, resulting in increased concentrations of active HMG-CoA reductase inhibitors. However, the effect was modest.

Fluvastatin

The effects of itraconazole 100 mg on the pharmacokinetics of fluvastatin 40 mg have been studied in a randomized, placebo-controlled, crossover study in 10 healthy volunteers (115). Itraconazole had no significant effect on the C_{max} or total AUC of fluvastatin, but slightly prolonged its half-life.

Lovastatin

The effects of itraconazole 100 mg on the pharmacokinetics of lovastatin 40 mg have been studied in a randomized, placebo-controlled, crossover study in 10 healthy volunteers (115). Itraconazole, even in this low dosage, greatly increased plasma concentrations of lovastatin and its active metabolite, lovastatin acid, and increased the C_{max} of lovastatin about 15-fold and the total AUC by more than 15-fold; similarly, the C_{max} and total AUC of lovastatin acid were increased about 12-fold and 15-fold respectively.

Pravastatin

The effects of itraconazole 200 mg on the pharmacokinetics of pravastatin have been studied in a randomized, double-blind, crossover study in 10 healthy volunteers (116). Itraconazole slightly increased the AUC and C_{max} of pravastatin, but the changes were not statistically significant; the half-life was not altered.

Simvastatin

The effects of itraconazole 200 mg on the pharmacokinetics of simvastatin have been studied in a randomized, double-blind, crossover study in 10 healthy volunteers (116). Itraconazole increased the C_{max} and AUC of simvastatin and simvastatin acid at least 10-fold. The C_{max} and AUC of total simvastatin acid (naive simvastatin acid plus that derived by hydrolysis of the lactone) were

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increased 17-fold and 19-fold respectively, and the half-life was increased by 25%.

In two cases, rhabdomyolysis was caused by itraconazole in heart transplant recipients taking long-term ciclosporin and simvastatin (74,75). To avoid severe myopathy, ciclosporin concentrations should be monitored frequently and statins should be withdrawn or the dosage should be reduced, as long as azoles need to be prescribed in transplant recipients. Patients need to be educated about signs and symptoms that require immediate physician intervention.

Tacrolimus

Tacrolimus concentrations and toxicity are affected by itraconazole (117).

- In a 17-year-old man with cystic fibrosis who received a hepato-pulmonary transplant, there was an interaction of itraconazole 600 mg bd with tacrolimus (118). High trough concentrations of tacrolimus were noted, despite the relatively low dosage (0.1–0.3 mg/kg/day).
- Another patient experienced an interaction of tacrolimus 0.085 mg /kg bd with itraconazole 200–400 mg per day, with resulting ketoacidosis, neutropenia, and thrombocytopenia, requiring the withdrawal of both drugs (119).
- A 30-year-old man with a renal transplant had a more than two-fold increase in blood tacrolimus concentrations after starting to take itraconazole 200 mg/day, accompanied by a reduced glomerular filtration rate and biopsy-proven tacrolimus-associated tubulopathy (120).

Because of the narrow therapeutic index of tacrolimus, blood concentrations should be monitored particularly carefully when itraconazole is co-administered, and the dosage of tacrolimus may have to be altered (121).

The interaction of itraconazole (100 mg bd) with tacrolimus has been studied in 28 heart or lung transplant recipients (122). Tacrolimus blood concentrations were monitored on alternate days for up to 21 days after the start of itraconazole therapy ($n = 18$) or withdrawal ($n = 10$). The dose of tacrolimus was adjusted with the aim of keeping the 12-hour trough blood concentration at 7–12 micrograms/ml. The mean dose of tacrolimus during itraconazole therapy fell significantly from 8.4 to 2.9 mg/day. There was no significant change in serum creatinine or liver function tests. In patients in whom itraconazole was withdrawn, the mean dose of tacrolimus required increased significantly from 4.7 to 8.8 mg/day. Thus, substantial changes in the dose of tacrolimus were required both when itraconazole was begun and when it was withdrawn, and it was difficult to maintain tacrolimus blood concentrations within the target range during the first 2 weeks. However, major toxicity or rejection did not occur. Co-administration of itraconazole may reduce the cost of post-transplant immunosuppression. This interaction is probably due to inhibition of CYP3A4 by itraconazole.

Vinca alkaloids

Enhanced and potentially life-threatening neurotoxicity of vinca alkaloids through concomitant therapy with itraconazole has been the subject of several compelling reports (123–126). Enhancement of vincristine neurotoxicity results in polyneuropathy and paralytic ileus (80,127,128). The interaction is reversible, and readministration of vinca alkaloids may be safe after a prolonged washout (123). The mechanism has not been formally elucidated, but may be either competition for oxidative metabolism, leading to increased systemic exposure (129), or inhibition of the transmembrane P glycoprotein efflux pump (130), leading to increased intracellular concentrations of vinca alkaloids (130). The concomitant use of itraconazole and vinca alkaloids is therefore contraindicated.

Two adults with acute lymphoblastic leukemia developed unusually severe neurotoxicity caused by vincristine, which was probably the result of an interaction with itraconazole suspension (127).

Warfarin

Itraconazole can alter warfarin concentrations.

- Following the addition of itraconazole to a treatment regimen comprising warfarin, ranitidine, and terfenadine, cardiac dysrhythmias developed in a 62-year-old man. The signs and symptoms included prolongation of the QT interval and ventricular fibrillation (SEDA-18, 198).

This particular regimen apparently resulted in a second interaction, since unexpectedly very high concentrations of terfenadine were found (SEDA-18, 283). The phenomenon has been described by others, with a marked rise in terfenadine serum concentrations, and increased toxicity of the drug during concurrent ingestion of itraconazole. The mechanism is not known, but it is likely to be related to inhibition of CYP3A4 (62).

Zolpidem

Zolpidem is mainly transformed by CYP3A4. However, itraconazole 200 mg did not alter the pharmacokinetics and pharmacodynamics of zolpidem 10 mg in 10 healthy volunteers (131). Therefore, zolpidem may be used in normal or nearly normal doses together with itraconazole.

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Ivermectin

General Information

Ivermectin, a dihydroavermectin B1, is an effective microfilaricide used in the treatment of strongyloides, scabies, and all types of filariasis except *Dipalonema (Mansonella) perstans* infections.

Over a number of years, ivermectin has shown excellent results in the treatment of onchocerciasis, both in controlled studies and in the field, including use in the WHO-sponsored program of treatment. This experience has provided a thorough picture of its adverse effects. The effective dosage is of the order of 50–200 micrograms/kg. After a single oral dose, skin microfilariae remain at low levels for up to 9 months.

As antihelminthic drugs go, ivermectin can be considered a reasonably safe drug, and it is generally better tolerated than diethylcarbamazine. Clinical experience has often shown relatively little toxicity, although mild adverse effects, presumably due to the killing of the microfilariae, involve at least one-third of patients; some work has suggested that neutrophil activation may play a role in the development of these reactions (1). It has also been well tolerated in combinations, for example when given with albendazole in order to kill adult worms (which cannot be achieved with ivermectin alone) or with diethylcarbamazine for bancroftian filariasis (SEDA-20, 281).

The principal reservation from the start was that ivermectin has a long half-life and that some late effects might occur in certain individuals. During the early phases it was recommended that in areas where the drug had been widely used the health workers involved should continue to observe patients for a time, in case problems did arise, but no late complications have in fact been documented.

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Mode of action

The mode of action of ivermectin has been reviewed (2). It has tentatively been identified as agonism at GABA receptors, with inhibition of ion channels that control specific nerve cell connections. The functioning of chloride channels should thus be altered in most organisms, leading to paralysis and death of parasites. Several sites of action have been proposed:

- a postsynaptic agonist site either on the receptor or in its immediate neighborhood;
- a presynaptic site of activation of GABA release;
- potentiation of GABA binding to its receptor.

Another mechanism of action involves the binding of ivermectin to P glycoprotein.

Observational studies

Among the published studies some have specifically sought to define the pattern of adverse effects. In one such study (3), although a single dose of the drug was combined in some patients with diethylcarbamazine, the adverse effect pattern was similar to that when ivermectin was used alone (SEDA-18, 312). There now seem to be some circumstances in which a single low dose of ivermectin is sufficient to have a prolonged effect, for example in loaiasis a dose of 150 micrograms/kg resulted in a very much reduced level of microfilaria as much as a year later, and seemed to eliminate the infestation entirely in more than half the users (4,5). If further work confirms the validity of this approach, the adverse reactions problem may be lessened, since at these doses the few reactions experienced were limited to the skin and joints, although some calabar-like swellings were also noted.

Brugia malayi

In an open study from India 21 asymptomatic microfilaria carriers (with counts of 109–6934/ml of blood) were treated with a single oral dose of ivermectin 400 micrograms/kg and a single oral dose of diethylcarbamazine 6 mg/kg for infection with *Brugia malayi* (6). Twelve hours after treatment microfilaria counts fell by 96–100% in all patients and 12 patients had become afilaremic. All had an adverse reaction, lasting up to 48 hours after treatment: fever ($n = 20$), myalgia ($n = 19$), headache ($n = 17$), lethargy ($n = 15$), chills ($n = 13$), sweating ($n = 11$), anorexia ($n = 11$), sore throat and pharyngeal congestion ($n = 10$), arthralgia ($n = 6$), giddiness ($n = 4$), nausea and vomiting ($n = 3$), abdominal pain ($n = 2$), and cough ($n = 1$). Postural hypotension, lasting 1 day, was noted in two individuals. Transient dilated and painfully inflamed lymphatic channels, which stood out in cords, were seen in two individuals. Most adverse effects were mild and self-limiting.

Loa loa

The use of ivermectin and its adverse effects in patients infected with *Loa loa* have been reviewed (7). It was concluded that ivermectin in a single dose of 150–300 micrograms/kg is effective in reducing microfilaria counts by over 90% with suppressed counts to 25% of pretreatment values after 1 year. An even more sustained effect can be reached by more frequent dosing. There is also some evidence that ivermectin in higher doses (400 micrograms/kg twice yearly) can affect the adult *Loa loa*. Tolerance to ivermectin is generally excellent, but serious adverse effects, especially encephalopathy, can occur, principally in more heavily infected individuals.

Onchocerciasis

The impact of 5 years of annual community treatment with ivermectin on the prevalence of onchocerciasis and onchocerciasis-associated morbidity in the village of Gami (Central African Republic) has been assessed (8). Pruritus, onchocercal nodules, and impaired vision were all significantly reduced by annual treatment with ivermectin.

In a study of the effect of ivermectin on adult *Onchocerca* worms (9) the following regimens were compared:

- 150 micrograms/kg yearly (reference group; $n = 166$)
- 400 micrograms/kg then 800 micrograms/kg yearly ($n = 172$)
- 150 micrograms/kg 3-monthly ($n = 161$)
- 400 micrograms/kg then 800 micrograms/kg 3-monthly ($n = 158$)

After 3 years of treatment more female worms had died in those who were treated every 3 months than in the reference group; female worms were also less fertile. There was no difference between the two groups of patients who were treated yearly. There were no serious adverse events, even at high doses. However, subjective complaints of visual disturbances, such as blurred vision, ocular pain, or dyschromatopsia, were more frequent in those who were given 800 micrograms/kg than in those who were given 150 micrograms/kg; the effects lasted less than 1 week. Detailed ocular examination showed no differences between patients from the reference group and the three other groups.

Sarcoptes scabiei

In an uncontrolled open study 101 patients with scabies were treated with a single oral dose of ivermectin 200 micrograms/kg and then followed at 3 days and at 2 and 4 weeks (10). Two weeks after the start of treatment 89 patients were completely free of scabies, while another three had only mild lesions and pruritus with negative skin scrapings. The other nine patients had persistent pruritus and new lesions and were treated with a second dose, with a complete cure in all cases after 4 weeks. Twelve patients reported minor adverse effects, consisting of drowsiness ($n = 4$), arthralgia and bone aches ($n = 2$), dyspnea ($n = 3$), headache ($n = 1$), nausea ($n = 1$), and blurred vision ($n = 1$). The adverse effects were mostly reported at the first follow-up and were easily tolerated. Ivermectin appears to be a safe and effective treatment for scabies in a dose of 200 micrograms/kg, although a second dose is necessary for complete cure in a few patients.

- An 11-year-old girl developed severe crusted Norwegian scabies (11). Gamma-benzene hexachloride lotion and topical keratolytics had no significant

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effect. She was given a single oral dose of ivermectin 6 mg/kg with dramatic effect. The pruritus subsided in 4 hours and the lesions started to clear 2 days later. A second dose of 6 mg was given after 3 weeks when no skin lesions were found anymore. The only adverse effect was some edema of the skin after the first dose, which did not occur after the second dose, suggesting that the reaction was more related to the intensity of the infection then to the effect of the drug itself.

Outbreaks of scabies in elderly people require special management for disease control. Owing to the frequent failure of repeated non-synchronized therapeutic efforts with conventional external antiscabie treatments, special eradication programs are required. The management of outbreaks of scabies with allethrin, permethrin, and ivermectin has been evaluated (12). Healthy infested people ($n = 240$) were treated once simultaneously with an external scabicide, such as allethrin or permethrin; this was effective in 99%. Those with crusted scabies ($n = 12$) were hospitalized and treated with systemic ivermectin or ivermectin plus permethrin; seven patients received ivermectin twice after an interval of 8 days and one received permethrin three times. Unfortunately, no details of adverse effects were given.

Strongyloidiasis

The efficacy and adverse effects of ivermectin 200 micrograms/kg, repeated 2 weeks later, have been studied in 50 patients with chronic strongyloidiasis, aged 30–79 years (13). The eradication rate was 96% at 2 weeks after the first dose and 98% after the second dose. There was no recurrence after follow-up of 4 months. One patient had nausea and vomiting 3 hours after the first dose and again after the second dose, but they were transient and required no therapy. In four patients there were mild laboratory abnormalities (slight increases in liver function tests in two, microscopic hematuria in one, and mild leukopenia and lymphocytosis in one). Of the 50 patients 12 were positive for human T lymphotropic virus type-I.

Wuchereria bancrofti

Early-stage elephantiasis caused by bancroftian filariasis in a 27-year-old traveller was treated with a single-dose oral combination of ivermectin 24 mg plus albendazole 400 mg, followed by albendazole 800 mg for 21 days (14). To avoid a severe Mazzotti-like reaction, he was given oral glucocorticoids and antihistamines for 3 days. He had a transient rash, pruritus, and mild hypotension on the days after the initial treatment, but otherwise remained well and the swelling subsided. Within 1 month he was free of symptoms. At the last follow-up examination, 3 years after treatment, there was no clinical or laboratory evidence of relapse. The authors thought that this type of treatment should be evaluated on a wider scale, given the minimal adverse events and apparent therapeutic efficacy.

The efficacy of annual mass chemotherapy with a combination of diethylcarbamazine and ivermectin on bancroftian filariasis in rural southern India has been studied, as has the supplementary role of controlling the vector mosquito *Culex quinquefasciatus* (15). Nine villages, topographically and ecologically similar but reasonably isolated from each other, were selected and split into three comparable groups of three villages each. Group A received chemotherapy with diethylcarbamazine at about 6 mg/kg and ivermectin at 400 micrograms/kg. Group B received chemotherapy and vector control. The most important vector-breeding sites were soakage pits, which were treated with expanded polystyrene beads. Minor vector-breeding sources, such as domestic or irrigation wells, were treated by adding larvae-eating Talapia fish or a commercial insecticide based on *Bacillus sphaericus*. Group C received no intervention. After the first round of treatment, combination chemotherapy alone caused a 60% drop in the annual filarial transmission potential, whereas the combined strategy reduced the transmission potential by 96%. After two rounds of treatment, the reduction in transmission potential was similar with the two strategies (about 91–96% reduction), whereas the prevalence of microfilaremia was reduced by 88–92%. Adverse events after combination therapy were reported in 20% of those who had taken diethylcarbamazine and ivermectin for the first time. The patients with adverse events had increased microfilarial counts. The most common adverse effects were headache (72% of adverse events), giddiness (67%), fever, and weakness. The incidence of adverse events among those taking combination therapy for a second time was relatively low (5.5%). The adverse events were also less severe in the second round than in the first. When antifilarial treatment was withdrawn in the third and final year of the study, transmission was resumed in the absence of vector control, whereas no infective female mosquitoes were detected in villages with vector control. Vector control, although obviously not cost-effective in the short term, could therefore play an important supplementary role in an integrated program, by preventing re-establishment of transmission after chemotherapy has been completed.

Comparative studies

Sarcoptes scabiei

In a randomized trial a single oral dose of ivermectin (200 micrograms/kg) has been compared with 1% gamma-benzene hexachloride lotion for topical application overnight in 200 patients with scabies (16). The patients were assessed after 48 hours, 2 weeks, and 4 weeks. After 4 weeks, 83% showed marked improvement with ivermectin, compared with 44% of those treated with gamma-benzene hexachloride. There were no adverse events reported with gamma-benzene hexachloride. Headache was reported only once with ivermectin.

In 80 children aged 6 months to 14 years a single dose of ivermectin 200 micrograms/kg was compared with topical benzyl benzoate for the treatment of pediatric scabies in a randomized, controlled trial (17). Ivermectin cured 24 of 43 patients and topical benzyl benzoate cured 19 of 37 patients at 3 weeks after treatment. There were no serious adverse effects with either treatment, although benzyl benzoate was more likely to produce local skin reactions. These results are in line with those of another study, in which 18 children aged 14 months to 17 years with either scabies ($n = 11$) or cutaneous larva migrans ($n = 7$) were

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treated with a single dose of ivermectin 150–200 micrograms/kg (18). A single oral dose cured 15 patients, and three patients with crusted scabies required a second dose. None had significant adverse reactions.

Wuchereria bancrofti

In a study in which doses of 200 or 400 micrograms were used, with or without diethylcarbamazine, for *Wuchereria bancrofti* infection, there was a higher than average incidence of reactions (and a higher incidence with ivermectin than with diethylcarbamazine), but this perhaps reflected an unusually high success rate or the severity of the original infection (19). For similar reasons, repeated courses of treatment tend to show a falling incidence of adverse effects. Normally, such general symptoms as fever, weakness, anorexia, malaise, and chills occur in a substantial minority of patients on a first course, while at least one-third have muscle and/or joint pains. Vertigo, dyspnea, diarrhea and abdominal disturbances affect a few patients. The severity of adverse effects is not related to serum concentrations of the drug (20), which again reflects the fact that they are largely a consequence of the parasitic breakdown, rather than toxic effects of ivermectin.

Placebo-controlled studies

Emesis, ataxia, and mydriasis are cardinal signs of ivermectin toxicity. The safety, tolerability, and pharmacokinetics of escalating high-dose ivermectin have been studied in 68 healthy subjects in a randomized, double-blind, placebo-controlled study (21) in the following doses:

- 30 mg fasted ($n = 15$)
- 60 mg fasted ($n = 12$)
- 90 mg fasted ($n = 12$)
- 120 mg fasted ($n = 12$)
- 30 mg fed ($n = 11$)

Ivermectin was generally well tolerated. Quantitative pupillometry ruled out any mydriatic effect of ivermectin. There was no nervous system toxicity associated with oral ivermectin at any of the doses. There were no serious clinical or laboratory adverse events. Three of the fifty-one subjects who took ivermectin fasted reported minor adverse gastrointestinal events: fecal abnormality ($n = 1$), nausea ($n = 1$), and vomiting ($n = 1$); six reported minor neurological adverse events: headache ($n = 4$), anxiety ($n = 1$), and dizziness ($n = 1$). There were no adverse events in the subjects who took ivermectin 120 mg. The absorption of ivermectin was about 2.5 times higher when it was given after a high-fat meal.

Sarcoptes scabiei

In a randomized, double-blind comparison of the efficacy of oral ivermectin and topical gamma-benzene hexachloride 53 patients were randomly allocated to either a single oral dose of ivermectin 150–200 micrograms/kg and a placebo topical solution, or a single dose of gamma-benzene hexachloride topical solution 1% and placebo tablets (22). Patients who did not fulfil the criteria for clinical cure within 15 days, defined as the absence of both pruritus and clinical lesions or a reduction in signs and symptoms to a mild degree, repeated the initial treatment. Of the 53 patients 43 completed the study (19 of those treated with ivermectin and 24 of those treated with gamma-benzene hexachloride). After 15 days 74% of the patients treated with ivermectin and 54% of the patients treated with gamma-benzene hexachloride were considered to be cured. At 29 days both treatments were equally effective, with cure rates of 95% and 96% respectively. Adverse effects were mild and transient in both groups. One of the patients treated with ivermectin had hypotension, one had abdominal pain, one had vomiting, and one complained of headache. There were no abnormalities on routine laboratory testing.

Wuchereria bancrofti

In a double-blind, placebo-controlled study in Ghana single doses of ivermectin 150–200 micrograms/kg and albendazole 400 mg, either separately or in combination, were given to 1425 individuals for *Wuchereria bancrofti* infection (23). Of these, 340 were microfilariae-positive before treatment. Ivermectin and ivermectin plus albendazole both produced statistically significant reductions in mean microfilaria counts at follow-up; the effect of ivermectin was longer lasting. Albendazole produced a non-significant reduction. Adverse reactions were few and mostly mild, and there were no severe reactions.

General adverse effects

Acute symptoms, often flu-like or affecting the skin, are related almost entirely to the release of toxic products and allergens from the killed filariae, and can affect two-thirds of patients; in conditions in which this type of reaction does not occur one may suspect that the drug is ineffective. The mechanism of the effects also explains why they tend to occur early and sometimes briefly, that is immediately after the microfilariae die. For similar reasons, these effects are most severe in patients with a high microfilaria count (24).

Despite the sometimes transient and apparently tolerable nature of the skin effects, they can persist in patients requiring long-term treatment, for example for onchocerciasis, and under these conditions they are sufficient to impair compliance with treatment (SEDA-21, 317).

The effects of age, sex, dosing round, time of day, and distance from the nurse monitor on adverse event reporting during mass ivermectin administration in Achi in South-East Nigeria have been examined (25). There was a significant increase in adverse reporting with age, but not sex. Fewer adverse effects were reported after starting at night than after starting by day. There was no significant effect of distances up to 1 km on adverse events reporting. Both compliance and adverse reporting were less after the second dosing round than after the first. These variables should be included in the standardization of adverse events reporting.

Onchocerciasis

Although adverse reactions after ivermectin in onchocerciasis are usually less severe than after diethylcarbamazine, they still affect a significant number of patients with onchocerciasis after the first dose. With subsequent treatments, these reactions become less frequent and

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severe. The so-called Mazzotti reaction, which is often seen after treatment of *Onchocerca volvulus* with diethylcarbamazine or ivermectin, is characterized by fever, tachycardia, hypotension, adenitis, pruritus, arthralgia, a papular or urticarial rash, and lymphedema. It is ascribed to an inflammatory host response to microfilarial killing and tends to be more severe in those who have greater numbers of parasites. The roles of chemoattractants, such as eotaxin, RANTES, and MCP-3, in the recruitment of eosinophils to the site of parasite killing has been studied in 13 patients with onchocerciasis and two control subjects before and after ivermectin (26). There were adverse reactions in eight patients, but none were severe. The reactions were fever (54%), pruritus (62%), rash (46%), and lymphedema (46%). There was no significant postural hypotension. There was endothelial expression of both RANTES and eotaxin after ivermectin, suggesting that these chemoattractants have an important role in eosinophil recruitment into the skin during killing or degeneration of parasites after ivermectin.

A role for the release of *Wolbachia* bacterial endosymbionts has been suggested in the pathogenesis of the Mazzotti reaction (SEDA-26, 345). There was a good correlation between *Wolbachia* DNA, serum TNF-alfa, and the antibacterial peptides calprotectin and calgranulin after treatment with ivermectin or diethylcarbamazine, supporting a role for *Wolbachia* products in mediating these inflammatory responses (27).

There has been an epidemiological survey of the endemicity of human onchocerciasis and the effects of subsequent mass distribution of ivermectin in villages of the Nzerem-Ikpem community in Nigeria (28). Of 1126 people studied, 527 were positive for skin microfilariae, 329 had a leopard skin (characterized by focal skin depigmentation), 385 had nodules, and 167 had onchodermatitis. There were adverse effects in 362 patients (19%): pruritus in 13%, limb swelling in 8.5%, facial swelling in 2%, weakness in 4.8%, nausea and vomiting in 3.4%, headache in 5.8%, diarrhea in 3.4%, and rheumatism in 3.5%. There were no severe reactions.

Organs and Systems

Cardiovascular

Supine and postural tachycardia with postural hypotension can occur; in one large study, such effects were found in three of 40 patients (SEDA-14, 262) (SEDA-22, 327). In another there was hypotension in 13 of 69 cases (SEDA-20, 280), but in some series these effects have not been observed at all (SEDA-17, 356). A massive community study in Ghana noted hypotension in only 37 of nearly 15 000 patients treated (29). Transient electrocardiographic changes are sometimes seen.

Respiratory

In the treatment of *Wuchereria bancrofti* filariasis in 23 patients with single doses up to 200 micrograms/kg respiratory capacity was evaluated; there was a transient but significant fall in vital capacity some 24–30 hours after administration, apparently due to bronchodilatation (30). Frank dyspnea occurred in 2% of cases in the study cited above (3). In other studies, a few patients have developed a transient cough and in others pneumonitic patches have been seen in the chest X-ray (SEDA-18, 313).

Nervous system

Headache and vertigo are very common and even usual as part of the flu-like reaction to ivermectin.

A puzzling reaction was recorded in a small hospitalized Canadian population of elderly subjects treated for scabies with a single dose of ivermectin (150–200 micrograms/kg). Within 6 months, 15 of the 47 patients had died. All those who died had developed a sudden change in behavior, with lethargy, anorexia, and listlessness before death (31). The effect may have been an artefact with some extraneous cause, and it is notable that other groups using this treatment for scabies have not recorded similar reactions.

Loa loa encephalopathy

When treating *Loa loa* infections on a large scale with ivermectin, the encephalopathy that was a much-feared complication with diethylcarbamazine again seems to occur, especially with heavily infected or older individuals (32). For this reason, mass use of ivermectin in areas of endemic *Loa loa* infection is no longer recommended (33).

Ivermectin appears to promote the passage of *Loa loa* microfilaria into the cerebrospinal fluid, with a maximum after 3–5 days, followed by an intense allergic reaction to the dying microfilaria. The Mectizan Expert Committee defined a definite case of *Loa loa* encephalopathy related to ivermectin as having to satisfy two criteria:

1. encephalopathy in which there is microscopic evidence of vasculopathy in the brain associated with *Loa loa* microfilaria;
2. the onset of symptoms of disturbed nervous system function within 5 days after treatment with ivermectin, progressing to coma without remission.

A probable case of *Loa loa* encephalopathy was defined as having to satisfy four criteria:

1. coma in a previously healthy individual;
2. the onset of nervous system signs within 5 days of treatment with ivermectin progressing to coma;
3. an initial microfilaremia of over 10 000/ml, or 1000/ml in a blood sample taken within 2 months of treatment;
4. the presence of *Loa loa* microfilaria in the CSF.

Clinically common features of this condition are impaired consciousness appearing 3–4 days after treatment and lasting for 2–3 days.

There is no consensus on the proper management of ivermectin-associated *Loa loa* encephalopathy, and it is uncertain if co-administration of glucocorticoids is of any use. In several patients with more severe reactions, conjunctival hemorrhages were seen.

A systematic examination of the conjunctivae in 1682 patients complaining of any adverse reactions showed that these hemorrhages were closely correlated with the pretreatment microfilaria counts. This sign can be found 2 days after treatment and may thus single out patients susceptible to encephalopathy and needing closer follow-up. Although the incidence of such cases is very low (in

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the order of 1 in 10 000 treated patients), this serious adverse effect makes mass treatment of *Loa loa* infection problematic, and also mass treatment of onchocerciasis in areas in which *Loa loa* is endemic. To illustrate this point three probable cases of *Loa loa* encephalopathy after ivermectin treatment for onchocerciasis have been described (34). All three were young men treated with ivermectin 150 micrograms/kg in a mass-treatment campaign in onchocerciasis.

- A 26-year-old previously healthy man developed nervous system symptoms in the form of an inability to stand or eat and stiffness of the neck by the third day. On the fourth day he had difficulty swallowing and speaking. On the fifth day he could not speak and was incontinent of urine. He was given dexamethasone, diazepam, furosemide, and atropine. On the sixth day he became comatose. On the ninth day he developed a high fever, and was given penicillin and tube-feeding. His condition gradually worsened and he died on the 21st day. Serum microfilaria counts on day 13 after treatment were still high (3600/ml), and live *Loa loa* (10/ml) were found in the CSF.
- A 32-year-old man with alcoholism had a very high pretreatment serum microfilaria count (50 000/ml). After starting ivermectin he took to his bed and would not speak. On the third day he developed a fever, possibly attributed to malaria and treated with chloroquine. On the fourth day he was unable to stand, and alternately restless or somnolent; his CSF contained live *Loa loa* microfilaria. He became more incoherent and fidgety and had a marked grasp reflex. Later in the day he developed spastic hypertonia. On the fifth day he became incontinent and still would not speak. Over the following days he gradually improved and 4 months later had no neurological abnormalities, although his relatives found that his behavior had changed and that he was much calmer then in the past. An electroencephalogram on day 15 showed periodic diffuse discharges of large amplitude during hyperventilation and on day 146 an asymmetric tracing with focal activity in the right parieto-occipital area, which worsened during hyperventilation. On day 233 the electroencephalogram was normal.
- An 18-year-old previously healthy man was given ivermectin. On the second day he was unable to work and stayed at home. On the third day he was found unconscious in bed, incontinent of urine and feces. On the fourth day he did not move and had absent pain sensation. There was hypertonia in the arms with marked cogwheeling. On the fifth and sixth days there was a swinging horizontal movement of the eyeballs, but otherwise he appeared to improve. On the seventh day he could stay seated in bed with help and spoke several sentences. He could perform slow voluntary movements and his muscle strength and sensation returned to normal, although the cogwheel phenomenon still persisted. He gradually returned to normal over the following weeks. After 5 months the neurological examination was normal but he still complained of headaches and episodic amnesia. His pretreatment serum microfilaria counts were high (152 940/ml) and the CSF collected on the fourth day contained live *Loa loa* microfilaria. An electroencephalogram on the 19th day was slow with spontaneous, diffuse, paroxysmal, monomorphic theta activity, lasting 2–3 seconds. An electroencephalogram on the 105th day showed improvement, but focal abnormalities persisted in the left occipital region. On the 159th day all previously recorded abnormalities had disappeared.

Sensory systems

Careful ophthalmological examination shows a striking increase in the number of microfilariae in the anterior chamber of the eye in a significant minority of patients, and a new inflammatory infiltrate can appear during treatment in already damaged areas of the retina (SEDA-15, 334). However, no permanent ocular sequelae have been documented. Most of the other ophthalmic symptoms, including edema and local inflammation, are those of the primary infection.

Conjunctival hemorrhages have been recorded in patients living in areas in which loiasis is endemic. Although ivermectin is usually well tolerated, these patients had serious adverse reactions after taking ivermectin, including an encephalopathy similar to that seen after treatment with diethylcarbamazine. In retrospect, these cases all had high *Loa loa* microfilaremia and *Loa loa* microfilariae in the cerebrospinal fluid. The authors suggested that ivermectin might have provoked the passage of *Loa loa* microfilariae into the cerebrospinal fluid. In a subsequent study of 1682 patients with loiasis treated with ivermectin 150 micrograms/kg, conjunctival hemorrhages were found in 41, nine of whom had previously received a microfilaricidal drug (35). The initial mean *Loa loa* microfilaremia was 14 900 microfilariae/ml (range 0–182 400; median 37 500), compared with 14.5 microfilariae/ml (range 0–97 600; median 0) in those without conjunctival hemorrhage. In addition, male sex and *Dipalonema perstans* microfilaremia were associated with conjunctival hemorrhages. There was a close relation between conjunctival hemorrhages and retinal lesions. Based on observations in three patients who all developed coma after ivermectin the authors suggested that retinal lesions may reflect what occurs in the cerebral circulation in patients with high *Loa loa* microfilaremia and neurological problems after ivermectin.

Hematologic

When 28 Sudanese patients were treated with a single dose of ivermectin for onchocerciasis they developed a prolonged prothrombin time, which continued to lengthen significantly during the next 4 weeks; there were no changes in other clotting parameters (36). After a month, two of them developed hematomas, which continued to enlarge for the next 3–4 days. Both of these patients had received ivermectin 150 micrograms/kg. One was given a transfusion; the swellings in both cases resolved within a week. For a time it was considered that the prothrombin changes observed in some such cases were a potential problem; more recent work suggests that the prolongation of prothrombin ratio is in fact hardly more than with placebo, and that in fact ivermectin merely has a mild effect on vitamin K metabolism and

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little effect on coagulation (37). However, lymphadenitis has been noted in a few patients. In one Guatemalan study of biannual treatment of the population to eradicate *Onchocerca volvulus* infection, upper limb edema was noted in nearly 20% of cases receiving the treatment for the first time (38).

Gastrointestinal

In the late stages of *Strongyloides* hyperinfection, ileus can develop and hamper the absorption of oral medication (39).

- A 39-year-old Afro-Caribbean man with stage IVB T cell lymphoma due to HTLV-1 infection had invasive Strongyloides hyperinfection that did not respond to oral ivermectin plus albendazole because of concurrent ileus. He was treated with two 6 mg doses of a veterinary formulation of ivermectin subcutaneously. There were no adverse effects, apart from pain at the injection site.

Urinary tract

Proteinuria is unusual but has been described; it was detected 14 days after a single dose and disappeared during follow-up (SEDA-18, 313).

Observations that proteinuria and hematuria may occur in patients with filariasis bancrofti and loiasis, which may exacerbate after treatment with diethylcarbamazine or ivermectin, led to the study of kidney function in patients with onchocerciasis before and after treatment with ivermectin (40). The occurrence of renal abnormalities was studied in a population-based study in a meso-endemic village (40% microfilaria carriers), in a group of patients with a generalized or hyper-reactive form of onchocerciasis, and in 46 patients treated with ivermectin in a single oral dose of 150 micrograms/kg. All individuals in all three study groups were examined clinically and had skin snips, serological testing for onchocerciasis, and nodulectomy (when relevant). Tests for malaria, schistosomiasis, intestinal nematodes, and hepatitis B, and serum glucose, creatinine, IgE, and electrophoresis were also performed. The urine was tested for erythrocytes, leukocytes, protein, nitrites, pH, glucose, ketone bodies, urobilinogen, and creatinine. All the patients underwent renal ultrasound examination. There was no difference in renal function and renal ultrasound between patients with and without onchocerciasis. A raised urinary protein concentration (over 70 mg/g of creatinine) was common and occurred in 47% of the patients with onchocerciasis and 63% of the patients without onchocerciasis. In the 46 patients treated for onchocerciasis with a single dose of 150 micrograms/kg there was a slight but statistically significant increase in total urine protein after 2 and 5 days, especially in 16 patients with high pretreatment skin microfilaria counts. The abnormalities were minor and insignificant. Neither onchocerciasis itself nor treatment with ivermectin was associated with abnormalities of renal function.

Skin

A degree of pruritus, soreness, or burning sensation is common with ivermectin, and rashes or skin edema can occur, while pre-existing conditions of this type can be aggravated (SEDA-17, 355) (SEDA-22, 327). The skin over hematomas can be discolored. Swelling of the limbs and face, like the dermatological symptoms, is probably a reaction to breakdown products of the helminth (SEDA-20, 280).

Patients with severe skin involvement ("sowda") as a facet of their onchocerciasis can experience transient aggravation of the condition, but the course is favorable, and they are less likely to have the same problem if it is later necessary to repeat treatment (SEDA-20, 281).

Rashes and swelling of the lymph nodes seem to be more common in patients with AIDS who take ivermectin (41).

Musculoskeletal

Joint or bone pains are common but usually mild; in one study myalgia occurred in 33% of cases and arthralgia in 33% (3).

Reproductive system

Orchitis or epididymitis with scrotal tenderness occurs in a few patients as a manifestation of the acute reaction as the parasite succumbs (SEDA-17, 356) (SEDA-22, 327).

Second-Generation Effects

Teratogenicity

There is no evidence of second-generation injury from ivermectin, but it is prudent to avoid it in pregnant women.

Lactation

Only a small amount of ivermectin is excreted in the breast milk (42) and it has been suggested that it is unnecessary to exclude lactating mothers from mass chemotherapy with ivermectin.

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IX 207-887

General Information

IX 207-887 (10-methoxy-4*H*-benzo-(4,5)-cyclohepta-(1,2–6)-thiophene-4 ylidene acetic acid) is a slow-acting drug for use in rheumatoid arthritis. Its mechanism of action involves inhibition of the release of interleukin-1. Adverse effects have occurred in 22% of cases, most commonly skin reactions, but also hepatitis and gastrointestinal disorders (1).

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Japanese encephalitis vaccine

See also Vaccines

General Information

During the last half century, Japanese encephalitis has been recognized as an important arboviral disease in man in Japan, China, Korea, Thailand, India, Nepal, Sri Lanka, and Vietnam. In 1954, Japanese encephalitis vaccine of the mouse brain type for human use was licensed in Japan. However, there was strong criticism of mouse brain vaccine, which has continued for many years. Therefore, in 1965, the Nippon Institute of Biological Products and the Biken Foundation implemented more advanced purification procedures, such as alcohol precipitation and ultracentrifugation.

Three types of Japanese encephalitis vaccine are currently produced:

1. mouse brain-derived inactivated vaccine, commercially available;
2. cell culture-derived inactivated vaccine;
3. cell culture-derived attenuated vaccine, produced and used exclusively in China.

The Chinese cell culture-derived inactivated vaccine is produced in primary hamster kidney cells; a highly purified Vero cell culture-derived inactivated vaccine is under clinical development in France. A Chinese live-attenuated vaccine is also produced in primary hamster kidney cells. The efficacy of one dose is 80%, and the efficacy of two doses, given 1 year apart, is 97.5%; this vaccine was evaluated in a randomized trial in 26 239 children, half of whom received the vaccine and half served as controls, and its adverse effects have been reviewed (SEDA-22, 350).

In 1965, a special surveillance team was formed by the Japanese Ministry of Health and Welfare to investigate adverse events following the administration of Japanese encephalitis vaccine. No severe adverse event was reported among 21 396 vaccinees of whom 18 401 were adolescents and children under 18 years of age. Some mild reactions (fever, malaise, abdominal symptoms) were noted in 1.2% of the vaccinees. Using a countrywide hospital network, the surveillance team studied any severe neurological disease occurring within 1 month after receipt of the vaccine. During 1957–66, 26 cases (nine cases of meningitis, ten cases of convulsions, five cases of polyneuropathy, and two cases of demyelinization) were analysed. No evidence was provided showing a causative relation between these clinical syndromes and Japanese encephalitis immunization. The incidence of neurological disease was considered minor compared with the millions of doses distributed annually in Japan (1).

Since 1989, urticaria and/or angioedema of the extremities, face, and oropharynx, and respiratory distress have been reported from Europe, North America, and Australia as a new pattern of adverse effects. Collapse due to hypotension has required hospitalization in several cases, and erythema multiforme and erythema nodosum have also occurred; the reported rates of such adverse effects varied markedly in different countries (respective ranges 0.7–12 per 10 000 and 50–104 per 10 000). The vaccine constituents responsible for the adverse effects have not yet been identified.

Japanese encephalitis vaccine has been reviewed (2). A supplementary volume of the journal Vaccine has dealt with results presented at a WHO meeting held in Bangkok, Thailand, in 1998 (3–6). Comprehensive data were provided on the epidemiological and virological situation in southeast Asia and Australia, control measures, vaccine production capacities, and different vaccines against Japanese encephalitis. Adverse events after the use of inactivated mouse brain vaccine (the only vaccine that is currently licensed for international use) have been reviewed in detail (3).

Organs and Systems

Nervous system

Postmarketing surveillance data of adverse events after Japanese encephalitis immunization in Japan and the USA have been compared (7). The rates of total reported adverse events were 2.8 per 100 000 doses in Japan and 15.0 per 100 000 doses in the USA. In Japan, 17 neurological disorders were reported from April 1996 to October 1998 (0.2 per 100 000 doses), whereas in the USA there were no serious neurological adverse events temporally associated with Japanese encephalitis vaccine from January 1993 to June 1999. Rates for systemic hypersensitivity reactions were 0.8 and 6.3 per 100 000 doses in Japan and the USA respectively.

Acute disseminated encephalomyelitis after Japanese encephalitis immunization has been reported from Japan.

- A 6-year-old girl and a 5-year-old boy had drowsiness, paresthesia, and gait disturbance 14 and 17 days respectively after immunization with Japanese encephalitis vaccine. Treatment with prednisolone improved the clinical findings (8,9).

Another report included seven cases of acute disseminated encephalomyelitis after administration of Japanese encephalitis vaccine between 1968 and 1990 (10). Three other cases of neurological complications after the use of Japanese encephalitis vaccine have been reported in Denmark. In two cases the clinical picture was consistent with acute demyelinating encephalomyelitis (SEDA-21, 334).

The rate of neurological complications seen in Japan in 1965–73 was of the order of 1 per 2.3 million vaccinees, and in Denmark the rate was 3 per 175 000 immunized individuals (one of them with a predisposition to multiple sclerosis) (11).

Two deaths from acute anaphylaxis and four cases of acute encephalopathy or acute disseminated encephalomyelitis (two fatal), temporally related to Japanese encephalitis immunization, have been reported from the Republic of Korea (3). The live-attenuated vaccine developed and used in China had 98% efficacy in a two-dose schedule. Concern that a live vaccine derived from an encephalitogenic virus might lead to vaccine-associated encephalitis could not be addressed satisfactorily, even

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in a study of 26 000 children. During efficacy studies in different geographic areas of China and in different years, the observations were combinable: the average encephalitis risk after live-attenuated Japanese encephalitis vaccine was 1.59 per 100 000 vaccinees.

Immunologic

Hypersensitivity reactions (generalized urticaria or angioedema) after the use of Japanese encephalitis vaccine have been reported from some countries (see Table 1); the vaccine constituents responsible for these events have not been identified (12). There has been a detailed report of the adverse effects, mainly allergic mucocutaneous reactions, of Biken vaccine in Danish travellers and US Marine Corps personnel (SEDA-22, 351).

The Advisory Committee on Immunization Practices (ACIP) has recommended that vaccinees should be observed for 30 minutes after immunization and that medications to treat anaphylaxis should be available (12) [http://www.cdc.gov/mmwr/PDF/rr/rr4201.pdf]. A personal history of allergic disorders should be considered when weighing the risks and benefits of the vaccine for an individual. Japanese encephalitis vaccine should not be given to persons who had a previous adverse reaction after receiving Japanese encephalitis vaccine or a previous hypersensitivity reaction to other vaccines of neural origin.

In Japan, children who had immediate-type allergic reactions to Japanese encephalitis vaccine had antigelatin IgE in their sera. However, the immunological mechanism of non-immediate-type allergic reactions that consist of cutaneous signs developing several hours or more after Japanese encephalitis immunization is not yet clear. Serum samples taken from 28 children who had non-immediate-type allergic skin reactions have been compared with serum samples taken from 10 children who had immediate-type reactions (13). All the children who had had immediate-type reactions had antigelatin IgE and IgG. Of 28 children who had had non-immediate-type reactions, one had antigelatin IgE and nine had antigelatin IgG. These results suggest that some children who develop non-immediate-type allergic reactions have also been sensitized to gelatin.

Table 1 Allergic reactions after Japanese encephalitis immunization

Country	Estimated number of vaccines	Number of reactions	Estimated rate per 100 000 vaccines
Denmark	42 000	21	50
Sweden	15 000	1	7
UK	1950	1	51
Australia			
Nationwide	3400	4	118
Fairfield Hospital	601	3	499
Canada			
University of Calgary	96	1	1042
USA			
Travellers	1328	2	151
Army	526	1	190
Army and dependents (Okinawa)	35 253	220	624
Total	100 154	254	254

Susceptibility Factors

An association between reactions to Japanese encephalitis vaccine and a history of urticaria or allergic rhinitis has been identified (14).

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Josamycin

See also Macrolide antibiotics

General Information

In a randomized open study, 325 children aged 2–15 years with acute tonsillitis and a positive test for *Streptococcus pyogenes* antigen were treated with josamycin 25 mg/kg bd for 5 days, or penicillin 50 000–100 000 IU/day for 10 days; in five patients taking josamycin treatment was withdrawn because of gastrointestinal adverse events (nausea/vomiting) (1).

Organs and Systems

Liver

Cholestatic hepatitis has been attributed to josamycin (2).

Biliary tract

In female rats josamycin caused bile duct proliferation at a high dose of 1460 mg/kg (3).

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Juglandaceae

See also Herbal medicines

General Information

The family of Juglandaceae contains three genera:

1. *Carya* (hickory)
2. *Juglans* (walnut)
3. *Pterocarya* (pterocarya).

Juglans regia

The fresh fruit-shell of *Juglans regia* (English walnut) contains the naphthoquinone constituent juglone, which is mutagenic and possibly carcinogenic. The juglone content of dried shells has not yet been studied adequately.

In a placebo-controlled study in 60 Persian hyperlipidemic subjects, walnut oil encapsulated in 500 mg capsules reduced plasma triglyceride concentrations by 19–33% of baseline (1).

Adverse effects

Hyperpigmentation and contact dermatitis have been attributed to *J. regia* (2) as has dermatitis bullosa (3).

A brown orange pigmentation occurred in a patient who used the bark of *J. regia* for cleaning teeth (4).

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Kanamycin

See also Aminoglycoside antibiotics

General Information

Kanamycin can be used for short-term treatment of severe infections caused by susceptible strains (for example *Escherichia coli*, *Proteus* species, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Mima-Herellea*) that are resistant to other less ototoxic aminoglycosides. It is not indicated for long-term therapy, for example in tuberculosis.

Organs and Systems

Neuromuscular function

Like the other aminoglycosides, kanamycin has neuromuscular blocking properties, particularly if given directly into the peritoneum (1). However, it seems to be less dangerous in this respect than neomycin or streptomycin.

Sensory systems

Kanamycin causes mainly cochlear damage (2). After prolonged administration (for example 1 g for periods of 30–180 days) the frequency of this adverse reaction is higher than 40%. Vestibular toxicity occurs in less than 10% of cases treated with usual doses and is generally reversible soon after withdrawal.

Gastrointestinal

Presurgical bowel preparation with oral kanamycin is seldom practiced and can be followed by an intestinal malabsorption syndrome (3). Only negligible amounts of kanamycin are absorbed through an intact intestinal mucosa, but increased systemic availability and potential toxicity can result from the presence of ulcerated or denuded areas.

Urinary tract

Kanamycin causes very little nephrotoxicity after short courses of treatment with daily doses of less than 15 mg/kg; if total doses of 30 g or more are given, the incidence of renal damage can be 50% or higher (1).

Immunologic

Sensitization (rash, drug fever) after parenteral administration of kanamycin is less frequent than with streptomycin. Anaphylaxis has only rarely been described. Cross-allergy with the other aminoglycosides is frequent (4).

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Kaolin

General Information

Kaolin, commonly given together with pectin in the treatment of diarrhea, is generally regarded as safe.

The absorbent properties of kaolin could result in the binding of other drugs that are given at about the same time. For example, kaolin adsorbs mefenamic acid and flufenamic acid, phenylbutazone, indometacin, and methiazinic acid (1). One should not therefore be surprised if it reduces the effect of any non-steroidal anti-inflammatory agent, requiring an increase in dosage by 50–100% to maintain efficacy. The reduction of lincomycin absorption is quite drastic, perhaps amounting to 90% of the dose given (2).

Organs and Systems

Respiratory

Industrial exposure to kaolin can cause lung damage. In more than 2000 kaolin workers from east central Georgia the presence of ventilatory impairment was related to the presence of complicated pneumoconiosis, employment in clay calcining, and cigarette smoking (3). In those who worked with calcined clay, there was an increased prevalence of abnormal FEV_1, but not FVC, compared to both wet and dry processors, which could not be explained by either cigarette smoking or the presence of pneumoconiosis. However, the magnitude of abnormality in the calcined clay workers was unlikely to lead to disabling impairment. Of those who had been exposed for more than 3 years, 90 had simple pneumoconiosis and 18 had complicated pneumoconiosis, adjusted prevalences of 3.2 and 0.63% respectively. Dry processing was associated with a greater risk of pneumoconiosis than wet processing.

In one case, multiple pulmonary kaolin granulomata developed secondary to the use of a liquid kaolin suspension for pleural poudrage to treat recurrent spontaneous pneumothoraces, presumably because the kaolin entered the lung through pleuro-alveolar or pleuro-bronchial openings (4).

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Kebuzone

See also Non-steroidal anti-inflammatory drugs

General Information

Kebuzone is an NSAID that is related to phenylbutazone. Allergic reactions, gastrotoxicity, nephrotoxicity, local reactions with necrosis (1), and liver damage have been reported (SED-11, 176) (2). The Japanese authorities have asked that the package insert should indicate that this drug must be used only as a last resort when other anti-inflammatory agents and uricosuric drugs are ineffective (SEDA-12, 83).

Organs and Systems

Liver

In 20 cases of kebuzone-induced liver damage, biopsy showed hepatocellular damage with or without cholestasis, reactive hepatitis, or cholangiolitis (3). There was hepatitis with central lobular necrosis in one case. In five patients, a lymphocyte proliferation test was positive.

Skin

Nicolau syndrome (embolia cutis medicamentosa) is a very rare complication of intramuscular injections, in which there is extensive necrosis of the injected skin area, perhaps due to accidental intra-arterial and/or para-arterial injection; it usually occurs in children (4). Nicolau syndrome has been reported in three patients who had received intramuscular injections of kebuzone (5).

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Ketamine

See also General anesthetics

General Information

Ketamine is a short-acting anesthetic that is widely used by emergency physicians (1) and can be given intravenously, intramuscularly, orally, and even nasally (2). Multiple ketamine anesthetics may be safe (3).

Subanesthetic low-dose ketamine is being used increasingly often for acute pain therapy, day-case surgery, and chronic pain management. Ketamine is now available in chiral (*S*+ and *R*–) forms as well as the standard racemic form. *S*-ketamine has twice the analgesic potency of racemic ketamine and four times that of *R*-ketamine. Thus, low dose *S*-ketamine may avoid adverse effects while providing high-quality analgesia.

The pharmacology of ketamine, including its adverse effects, has been reviewed (4), as has the use and adverse effects of *S*-ketamine in the intensive care unit (5).

Ketamine relaxes smooth muscles in the airways and may therefore be a useful induction agent in children with asthma (6). If endotracheal intubation is required, lidocaine 1–2 mg/kg intravenously before intubation has been recommended, although the use of a laryngeal mask airway may be more appropriate. When used in combination with midazolam by infusion, ketamine provides analgesia and prevents and relieves bronchospasm (7).

The addition of ketamine to bupivacaine for spinal anesthesia has been studied in 60 patients undergoing spinal anesthesia for insertion of intracavitary brachytherapy implants for cervical carcinoma (8). They were randomly assigned to receive either bupivacaine 10 mg or bupivacaine 7.5 mg plus ketamine 25 mg. Motor recovery was significantly quicker in the ketamine group. Blood pressure was significantly lower in the bupivacaine group 5 minutes after administration, and perioperative intravenous fluid requirements were significantly higher. Patients given ketamine reported more sedation and dizziness, both intraoperatively and postoperatively. There were no nightmares or dissociative features. Overall satisfaction was better with bupivacaine. The study was abandoned after 30 patients, because of the high rate of adverse effects with ketamine. Although ketamine had local anesthetic-sparing properties, its adverse effects made it unsuitable for intrathecal administration.

When added to standard doses of morphine and a non- steroidal analgesic, *S*-ketamine 0.5 mg/kg had no additional benefit in a randomized, double-blind study in 30 patients undergoing anterior cruciate ligament repair (9).

Organs and Systems

Cardiovascular

Tachycardia and hypertension are common after anesthetic induction with ketamine, although the hypertension can be limited by the addition of diazepam (10). Nodal dysrhythmias can also occur (11). Because of possible

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reduced cardiac and pulmonary performance, ketamine should be avoided in critically ill patients (12). Pulmonary vasoconstriction and increased ventricular preload secondary to ketamine can be deleterious (13).

The effects of intramuscular premedication with either clonidine 2 micrograms/kg or midazolam 70 micrograms/kg on perioperative responses to ketamine anesthesia have been assessed in a placebo-controlled study in 30 patients (14). Clonidine significantly reduced intraoperative oxygen consumption, mean arterial pressure, and heart rate compared with midazolam and placebo. Thus, clonidine was as effective as midazolam, the standard drug used for this purpose, in reducing the undesirable sympathetic stimulation of ketamine.

Oral clonidine, 2.5 or 5.0 micrograms/kg, 90 minutes before ketamine 2 mg/kg has been compared with placebo in 39 patients (15). In those given clonidine 2.5 micrograms/kg, heart rate responses were reduced compared with placebo (maximum heart rate 97 versus 76 beats/minute). In those given clonidine 5 micrograms/kg, heart rate responses were less (maximum heart rate 97 versus 77 beats/minute) and mean arterial pressure was lower (121 versus 141 mmHg), and there were fewer nightmares and less drooling.

Respiratory

Apnea occurred after the intramuscular injection of ketamine 4 mg/kg to sedate a healthy 4-year-old boy (16). This case illustrates the need for adequate monitoring and preparation for emergency airway management when using ketamine for sedation.

Nervous system

Ketamine causes a significant rise in cerebrospinal fluid pressure, increased electroencephalographic activity, and possibly epileptiform discharges (17).

Delayed acute intracranial hypertension has been described after ketamine anesthesia (18).

Oral ketamine is an effective analgesic in patients with chronic pain. In 21 patients with central and peripheral chronic neuropathic pain treated with oral ketamine, the starting dose was ketamine 100 mg/day, titrated upward by 40 mg/day increments every 2 days until a satisfactory effect was achieved, or until adverse effects became limiting (19). Nine patients discontinued ketamine because of intolerable adverse effects, including psychotomimetic symptoms, such as "elevator" effect or dissociative feelings, somnolence or insomnia, and sensory changes such as taste disturbance and somatic sensations.

In a study of 21 outpatients with refractory neuropathic pain treated with oral ketamine, 17 reported adverse events (20). The most common were light-headedness, dizziness, tiredness, headache, a nervous floating feeling, and bad dreams. The adverse effects were sufficiently important to prevent ten patients from continuing with the trial.

Neurotoxicity due to focal lymphocytic vasculitis has been reported close to the catheter injection site in a patient who received intrathecal ketamine infusion for chronic cancer pain (21).

- A 72-year-old woman with abdominal pain due to peritoneal malignant mesothelioma was given patient-controlled analgesia with morphine and then a thoracic epidural infusion of bupivacaine 0.125% and morphine 0.04 mg/ml at a rate of 6–12 ml/hour, with minor success. A thoracic intrathecal catheter was inserted for infusion of bupivacaine 0.25% plus morphine 0.12 mg/ml at a rate of up to 3.5 ml/hour. The morphine concentration was increased to 0.3 mg/ml and then clonidine 3 micrograms/ml was added. Satisfactory pain relief was finally achieved by adding ketamine 1 mg/ml, containing benzethonium chloride as a preservative. The mean daily intrathecal dose of ketamine was 67 mg. After 7 days she had an acute psychotic reaction and the ketamine was withdrawn. There were no neurological deficits. She died 10 days later. There was focal lymphocytic vasculitis in the spinal medullary tissue, in the nerves, and in the leptomeninges of the thoracolumbar spinal cord.

This neurotoxicity could have been due to the preservative benzethonium chloride or the ketamine. However, several other agents, including bupivacaine, morphine, and clonidine, were also given intrathecally, so causality was not proven, even though the other agents have not been associated with this problem.

There have been several attempts to understand the pathophysiology of schizophrenia using subanesthetic doses of ketamine to probe glutaminergic function in healthy and schizophrenic volunteers; no long-term adverse consequences were attributable to ketamine (22).

Psychological, psychiatric

In a randomized, double-blind, crossover study of cognitive impairment in 24 volunteers who received *S*-ketamine 0.25 mg/kg, racemic ketamine 0.5 mg/kg, or *R*-ketamine 1.0 mg/kg, the ketamine isomers caused less tiredness and cognitive impairment than equianalgesic doses of racemic ketamine (23). In addition, *S*-ketamine caused less reduction in concentration capacity and primary memory.

A placebo-controlled study of low-dose ketamine infusion in ten volunteers showed formal thought disorder and impairments in working and semantic memory (24). The degree of thought disorder correlated with the impairment in working memory.

Psychotomimetic effects

The psychotomimetic effects of ketamine, apart from encouraging illicit use, can lead to distressing psychic disturbances, particularly in children (13); there can be nightmares, delirium, and hallucinations (25). Oral ketamine is an effective analgesic in patients with chronic pain. In 21 patients with central and peripheral chronic neuropathic pain treated with oral ketamine, the starting dose was ketamine 100 mg/day, titrated upward by 40 mg/day increments every 2 days until a satisfactory effect was achieved, or until adverse effects became limiting (19). Nine patients discontinued ketamine because of intolerable adverse effects, including psychotomimetic symptoms, such as "elevator" effect or dissociative feelings, somnolence or insomnia, and sensory changes such as taste disturbance and somatic sensations.

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The pharmacological effects of the *R*- and *S*-enantiomers of ketamine have been compared in 11 subjects who received *R*-ketamine 0.5 mg and then *S*-ketamine 0.15 mg, separated by 1 week (26). Before and after each drug administration they were subjected to a painful stimulus using a nerve stimulator applied to the right central incisor tooth. Pain suppression was equal with the two drugs. The subjects reported more unpleasant psychotomimetic effects with *S*-ketamine and more pleasant effects with *R*-ketamine. Seven of eleven subjects preferred *R*-ketamine, while none preferred *S*-ketamine. These results suggest that the neuropsychiatric effect of ketamine may be predominantly due to the *S*-enantiomer, and that *R*-ketamine may be a better alternative. This study is in direct distinction to earlier work suggesting that *R*-ketamine is responsible for most of the undesirable neuropsychiatric side effects of ketamine.

A placebo-controlled study in 10 healthy young men showed a linear relation between ketamine plasma concentrations of 50–200 ng/ml and the severity of psychotomimetic effects (27). The psychedelic effects were also similar to those observed in a previous study of dimethyltryptamine, an illicit LSD-25 type of drug, and were a function of plasma concentration rather than simply an emergence phenomenon. Clinically useful analgesia was obtained at plasma concentrations of 100–200 ng/ml. At plasma concentrations of 200 ng/ml, all subjects had lateral nystagmus. When ketamine is given in large doses, patients rapidly become unresponsive, and so the effects described in this study are usually only observed during the recovery phase.

There have been several attempts to understand the pathophysiology of schizophrenia using subanesthetic doses of ketamine to probe glutaminergic function in healthy and schizophrenic volunteers; no long-term adverse consequences were attributable to ketamine (22).

Prevention

There have been several attempts to attenuate the unpleasant psychological adverse effects that occur after sedation with ketamine.

Prior use of benzodiazepines or opiates limits the psychotomimetic effects of ketamine. There has been a double-blind, placebo-controlled study of the role of lorazepam in reducing these effects after subanesthetic doses of ketamine in 23 volunteers who received lorazepam 2 mg or placebo, 2 hours before either a bolus dose of ketamine 0.26 mg/kg followed by an infusion of 0.65 mg/kg/hour or a placebo infusion (28). The ability of lorazepam to block the undesirable effects of ketamine was limited to just some effects. It reduced the ketamine-associated emotional distress and perceptual alterations, but exacerbated the sedative, attention-impairing, and amnesic effects of ketamine. However, it failed to reduce many of the cognitive and behavioral effects of ketamine. There were no pharmacokinetic interactions between subanesthetic doses of ketamine and lorazepam.

The effect of intravenous midazolam 0.05 mg/kg on emergence phenomena after ketamine 1.5 mg/kg intravenously for painful procedures has been assessed in a randomized, double-blind, placebo-controlled study in 104 children (29). Midazolam was given 2 minutes after the ketamine. There was no significant difference between the two groups in levels of agitation. The overall rate of agitation was low, but probably high enough to detect any significant differences between the groups.

The neuropsychiatric effects of ketamine were modulated by lamotrigine, a glutamate release inhibitor, in 16 healthy volunteers (30). Lamotrigine 300 mg was given 2 hours before ketamine 0.26 and 0.65 mg/kg on two separate days. There were fewer ketamine-induced perceptual abnormalities, fewer schizophreniform symptoms, and less learning and memory impairments. Mood-elevating effects were increased with lamotrigine. The authors commented that the results were experimental and that further studies are needed to confirm the potential benefits in a larger group of patients.

The hypothesis that the unpleasant emergence phenomena that often accompany the use of ketamine, including odd behavior, vacant stare, and abnormal affect, would be reduced by the use of a selected recorded tape played during the perioperative period has been tested in 28 adults (31). The incidence of dreams was higher when the recorded tape was connected. This report emphasizes the current recommendations that a quiet room with minimal stimuli is best for reducing emergence phenomena after ketamine sedation.

Endocrine

In a double-blind, randomized, placebo-controlled crossover comparison of the effects of ketamine and memantine in 15 male volunteers, ketamine increased serum prolactin and cortisol concentrations, whereas memantine and placebo did not (32).

Liver

Serum enzyme activities (alkaline phosphatase, aspartate transaminase, alanine transaminase, and gamma-glutamyl transpeptidase) were raised in 14 of 34 patients anesthetized with ketamine; the significance of this is unknown (33).

Long-Term Effects

Drug abuse

Media reports suggest that in some countries the non-medical (illicit) use of ketamine has greatly increased (34).

Drug Administration

Drug administration route

The addition of ketamine to bupivacaine for spinal anesthesia has been studied in 60 patients undergoing spinal anesthesia for insertion of intracavitary brachytherapy implants for cervical carcinoma (8). They were randomly assigned to receive either bupivacaine 10 mg or bupivacaine 7.5 mg plus ketamine 25 mg. Motor recovery was significantly quicker in the ketamine group. Blood pressure was significantly lower in the bupivacaine group 5 minutes after administration, and perioperative

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intravenous fluid requirements were significantly higher. Patients given ketamine reported more sedation and dizziness, both intraoperatively and postoperatively. There were no nightmares or dissociative features. Overall satisfaction was better with bupivacaine. The study was abandoned after 30 patients, because of the high rate of adverse effects with ketamine. Although ketamine had local anesthetic-sparing properties, its adverse effects made it unsuitable for intrathecal administration.

Drug–Drug Interactions

Alfentanil

The interaction of ketamine with the respiratory depressant effect of alfentanil has been studied in eight healthy men, who received alfentanil as a continuous computer-controlled infusion aiming at a plasma concentration of 50 ng/ml and either an infusion of racemic ketamine increasing step-wise through 50, 100, and 200 ng/ml or placebo (35). Alfentanil caused hypoventilation by reducing respiratory rate, and this was antagonized by ketamine in a concentration-dependent manner. This combination may be effective in overcoming the adverse effects of either agent individually.

Haloperidol

The interaction of the dopamine antagonist haloperidol 5 mg orally with subanesthetic doses of ketamine has been studied in a placebo-controlled study in 20 healthy volunteers over 4 days (36). Haloperidol pretreatment reduced impairment of executive cognitive functions produced by ketamine and reduced the anxiogenic effects of ketamine. However, it failed to block the ability of ketamine to produce psychosis, perceptual changes, negative symptoms, or euphoria, and it increased the sedative and prolactin responses to ketamine. These results imply that ketamine may impair executive cognitive functions via dopamine receptor activation in the frontal cortex, but that the psychoactive effects of ketamine are not mediated via dopamine receptors, but rather via NMDA receptor antagonism.

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Ketanserin

General Information

Ketanserin is a selective 5-HT_2 receptor antagonist with antihypertensive action. Because it antagonizes the vasoconstriction and platelet aggregation induced by 5-HT and increases erythrocyte deformability, its potential usefulness in peripheral vascular disease has been extensively investigated, although never convincingly demonstrated. It has been reported to be beneficial in pre-eclampsia (1).

Most of the adverse effects attributable to ketanserin seem, not surprisingly, to be on the central nervous system. They include drowsiness, fatigue, headache, sleep disturbances, and dry mouth. Other complaints include dizziness, light-headedness, lack of concentration, and dyspepsia. A gradual increase in dosage is therefore recommended. These adverse effects occur in about 10% of patients and lead to withdrawal of the drug in 3–4% (SEDA-17, 243).

Organs and Systems

Cardiovascular

Dose-related prolongation of the QT interval on the electrocardiogram occurs in roughly one-third of patients taking ketanserin (2). Several cases of ventricular dysrhythmias with QT prolongation, leading to syncope, have been reported (SED-11, 392) (SED-12, 473), but the exact incidence of significant ventricular dysrhythmias on the basis of QT prolongation during ketanserin therapy is unknown.

Drug–Drug Interactions

Ecstasy

In 14 healthy subjects, ketanserin attenuated the perceptual changes, emotional excitation, and acute adverse responses induced by ecstasy, but had little effect on positive mood, well-being, extroversion, and short-term sequelae (3). Body temperature was lower with ecstasy plus ketanserin than with ecstasy alone.

Potassium-wasting diuretics

Prolongation of the QT interval by ketanserin is more pronounced when it used in combination with potassium-wasting diuretics (4). This combination must therefore be avoided.

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Ketobemidone

General Information

Ketobemidone is an opioid receptor agonist, with pharmacokinetics and potency similar to morphine. Combined with the antispasmodic drug, *N*,*N*-dimethyl-3,3-diphenyl-1-methylallylamine chloride, ketobemidone is often used in Scandinavia.

In a study of postoperative pain relief, ketobemidone equalled morphine and pethidine with respect to efficacy of analgesia and adverse effects, such as shivering, nausea, and vomiting (SEDA-16, 81).

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Organs and Systems

Respiratory

Early cough in 40 of 121 patients given ketobemidone for postoperative analgesia has been reported. Four of the patients found it severe and distressing. The lower frequency of cough in patients previously exposed to ketobemidone in the premedication may reflect tachyphylaxis (SEDA-17, 81).

Ketoconazole

See also Antifungal azoles

General Information

Ketoconazole was the first azole available for oral administration. However, it has been supplanted by newer azoles with fewer adverse effects and more reliable absorption from the gastrointestinal tract. Even after years of use, new adverse effects (often related to high doses and/or newer indications) continue to be reported.

Ketoconazole is water-soluble at a pH of below 3. Its oral absorption is influenced by the acidity of the stomach contents, and the concomitant administration of histamine H_2 receptor antagonists, proton pump inhibitors, antacids, or food affects its absorption. A high carbohydrate meal ingested with ketoconazole reduces total drug absorption, while a high lipid meal increases it. Erratic absorption is particularly apparent in patients with AIDS. Peak serum concentrations are seen within 2–3 hours. The half-life is about 8 hours. CSF penetration is less than 10% (1). Ketoconazole is extensively metabolized in the liver and excreted in the bile in an inactive form; less than 1% of the active drug is excreted in the urine. Clearance is not significantly altered by renal dialysis (1).

In man, higher doses of ketoconazole affect cortisol/cortisone and androgen/testosterone substrates. This finding has led to the use of ketoconazole in Cushing's disease and prostate cancer, but the phenomenon is also responsible for some of the adverse effects, especially those associated with higher doses and prolonged use (SED-12, 677). The potency of ketoconazole in inhibiting P450 isozymes (such as CYP3A4) is a cause of interactions with several other drugs.

Use in non-infective conditions

The efficacy of ketoconazole 400 mg qds in the early treatment of acute lung injury and acute respiratory distress syndrome has been investigated in a randomized, double-blind, placebo-controlled trial in 234 patients (2). Ketoconazole was safe but had no effects on mortality, lung function, or the duration of mechanical ventilation.

Because of its potent inhibitory effects on adrenal steroidogenesis by interference with cytochrome CYP450, ketoconazole controls hypercortisolism when surgery is contraindicated or unsuccessful. The effects of oral ketoconazole 200–1200 mg qds for 65–83 months in three patients who had residual or recurrent Cushing's disease after surgical treatment have been reported (3). The dosage of ketoconazole was adjusted according to the clinical response and 24-hour urinary excretion of free cortisol. All three patients had good clinical and biochemical responses to therapy with ketoconazole and had no adverse effects.

General adverse effects

Gastrointestinal complaints, including anorexia, nausea, gastralgia, and constipation are the most frequent adverse effects of ketoconazole. Hepatotoxicity, varying in degree from mild disturbances of liver function tests to hepatitis and rare cases of fulminating hepatic necrosis, has been reported. Some cases have been reported in the first weeks of treatment, but duration of treatment is of importance and in prolonged courses of treatment, monitoring is advisable. With the use of high doses, especially for longer periods of time, the effects of interference with hormonal balance should be watched for. Adrenal insufficiency has been reported even with low-dose treatment. Pruritus and skin reactions have been reported, but do not in general cause major problems. Hypersensitivity reactions are rare. Tumor-inducing effects have not been reported.

Organs and Systems

Respiratory

Patients undergoing esophagectomy are at increased risk of acute lung injury, perhaps related to increased concentrations of thromboxane in the postpulmonary circulation. In 38 consecutive patients undergoing esophagectomy, perioperative ketoconazole, which inhibits thromboxane synthesis, reduced the incidence of acute lung injury (4).

Nervous system

Headache, dizziness, nervousness, and somnolence have been reported (SED-11, 573). The incidences are low. Encephalopathy can occur as a result of severe liver damage.

Sensory systems

Eyes

Papilledema has been reported in one patient taking ketoconazole. The condition cleared on withdrawal of ketoconazole and recurred on resumption 2 months later (SEDA-18, 284).

Psychological, psychiatric

In one patient taking a high dosage for prostate cancer, weakness was associated with mental disturbances, notably confabulation and disorientation in time and space (SEDA-13, 233).

Endocrine

Gynecomastia was occasionally observed in men when ketoconazole first became available. Ketoconazole has a marked effect on steroid concentrations, including a change in the testosterone/estradiol ratio, and this is most likely to be the basis of the gynecomastia. A lowering of testosterone serum concentrations and

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a reduced response of testosterone concentrations to human gonadotropin have been shown (SED-11, 573) (5). Various studies have shown suppression of testosterone, androstenedione, and dehydroepiandrosterone, with reciprocal increases in gonadotrophins.

Reductions in serum and urinary cortisol concentrations have been reported in patients taking ketoconazole and signs of hypoadrenalism have been seen during high-dose treatment. However, it is not clear whether the asthenia syndrome described in the past (severe muscle weakness, most pronounced in the legs, fatigue, apathy, and anorexia) is related to hypoadrenalism. In some cases, hypoadrenalism has been described shortly after the start of low-dose treatment. Substitution therapy may be required, since simple withdrawal of ketoconazole may not redress hormonal balance quickly enough.

Various studies have shown that ketoconazole interferes with 17- and 20-hydroxylases and inhibits mitochondrial 11-α-hydroxylase and cytochrome P450-dependent steroid hydroxylase enzymes (SED-12, 677) (6) (SEDA-12, 228) (SEDA-14, 234).

Because of its effects on the pituitary/adrenal system, ketoconazole has been used in the long-term control of hypercortisolism of either pituitary or adrenal origin (SED-12, 677). In seven patients with Cushing's disease and one with an adrenal adenoma, ketoconazole 600–800 mg/day for 3–13 months produced rapid persistent clinical improvement (7). Plasma dehydroepiandrosterone sulfate concentrations and urinary 17-ketosteroid and cortisol excretion fell soon after the start of treatment, and remained normal or nearly so throughout treatment. Urinary tetrahydro-11-deoxycortisol excretion rose significantly. Plasma cortisol concentrations fell. Plasma ACTH concentrations did not change and individual plasma ACTH and cortisol increments in response to CRH were comparable before and during treatment. The cortisol response to insulin-induced hypoglycemia improved in one patient and was restored to normal in another. The patients recovered normal adrenal suppressibility in response to a low dose of dexamethasone during ketoconazole treatment.

The effect of ketoconazole appears to be mediated by inhibition of adrenal 11-β-hydroxylase and 17,20-lyase, and in some unknown way it prevents the expected rise in ACTH secretion in patients with Cushing's disease (SEDA-12, 228) (SEDA-17, 323). It may, however, cause such a rapid reduction in serum cortisol concentrations that a crisis is precipitated, and patients' adrenal function should be carefully monitored. While ketoconazole (400–800 mg/day) may be a good alternative to other adrenal steroid inhibitors, patients should be observed for signs of hepatotoxicity. Acute adrenal crisis occasionally occurs (8).

Because ketoconazole has antiandrogenic properties, it is particularly suitable for women, in whom it has few effects on menstruation and does not cause hirsutism. In men, however, long-term inhibition of androgen production can be disruptive, especially if it leads to gynecomastia and hypogonadism. Combination with aminoglutethimide and metyrapone has been advocated in order to avoid these effects (SEDA-17, 323).

Ketoconazole (400 mg/day) has been used for the treatment of hirsutism and acne in women, but adverse effects, such as headache, nausea, loss of scalp hair, hepatitis, and biochemical changes, were impressive (9–11).

Hematologic

Fatal aplastic anemia has been reported during ketoconazole therapy (12).

Gastrointestinal

Nausea, mild gastrointestinal symptoms, and vomiting can occur in patients taking ketoconazole; diarrhea has been reported, but the incidence is low (SED-12, 678). The incidence of gastrointestinal complaints is higher with the use of daily doses above 800 mg (13).

Liver

Mild and often transient rises in serum liver enzyme activities are not uncommon in patients taking ketoconazole; the incidence is reported to be about 10–15% (SEDA-12, 229). This figure is higher than originally thought (SED-11, 573) (14), the newer figures probably representing a greater awareness of the risk rather than a true increase; it is possible, however, that the use of higher doses plays a role (SED-12, 678).

The incidence of symptomatic hepatic injury associated with ketoconazole is estimated to be about one in 10 000 treated cases (SEDA-18, 284). Biochemically, the pattern was hepatocellular in 54%, cholestatic in 16%, and mixed cholestatic-hepatocellular in 30%. Histology (14 cases) showed a predominantly hepatocellular pattern in 57%, with extensive centrilobular necrosis and mild to moderate bridging (14,15). Lethal cases of toxic hepatitis and a case necessitating transplantation have been reported (14,16,17).

- A girl developed fatal liver failure while taking ketoconazole for Cushing's syndrome (18). The authors proposed using metyrapone when temporary control of hypercortisolism is required in childhood and adolescence.

A cohort study of the risk of acute liver injury among users of oral antifungal drugs has been performed in the general population of the General Practice Research Database in the UK (19). The cohort included 69 830 patients, free from liver and systemic diseases, who had received at least one prescription for oral griseofulvin, fluconazole, itraconazole, ketoconazole, or terbinafine between 1991 and 1996. Five cases of acute liver injury occurred during the use of oral antifungal drugs. Two of the patients were taking ketoconazole, another two itraconazole, and one terbinafine. The incidence rates of acute liver injury were 134 (CI = 37, 488) per 100 000 person-months for ketoconazole, 10 (CI = 2.9, 38) for itraconazole, and 2.5 (CI = 0.4, 14) for terbinafine. One case was associated with past use of fluconazole. Ketoconazole was the antifungal drug that was associated with the highest relative risk, 228 (CI = 34, 933) compared with the risk among non-users, followed by itraconazole and terbinafine, with relative risks of 18 (CI = 2.6, 73) and 4.2 (CI = 0.2, 25) respectively.

Skin

The risk of serious skin disorders has been estimated in 61 858 users, aged 20–79 years, of oral antifungal drugs identified in the UK General Practice Research Database

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(20). They had received at least one prescription for oral fluconazole, griseofulvin, itraconazole, ketoconazole, or terbinafine. The background rate of serious cutaneous adverse reactions (corresponding to non-use of oral antifungal drugs) was 3.9 per 10 000 person-years (95% CI = 2.9, 5.2). Incidence rates for current use were 15 per 10 000 person-years (1.9, 56) for itraconazole, 11.1 (3.0, 29) for terbinafine, 10 (1.3, 38) for fluconazole, and 4.6 (0.1, 26) for griseofulvin. Cutaneous disorders associated with the use of oral antifungal drugs in this study were all mild.

Pruritus and occasional rashes can occur in patients taking ketoconazole (21). Rare cases of a fixed drug eruption have been reported (SED-12, 678) (22) (SEDA-17, 323).

Musculoskeletal

- Muscle weakness and diffuse myalgia were reported in a 17-year-old man with multiple endocrine neoplasia syndrome type 1 taking ketoconazole for oral candidiasis. The electromyogram showed a distinct myopathic pattern. Withdrawal of the ketoconazole was followed by rapid improvement (SEDA-17, 323).

In rats, high doses (80 mg/kg) caused syndactyly in one experiment (SED-11, 574). There are insufficient data to determine whether there might be a harmful effect in humans.

Second-Generation Effects

Lactation

Ketoconazole can be found in the milk of lactating dogs receiving ketoconazole; there are insufficient data to decide whether harm might ensue to the breast-fed child.

Susceptibility Factors

Age

Because ketoconazole interferes with steroid synthesis and vitamin D metabolism, ketoconazole should not be used in children. It is not approved for use in children and there is no pediatric dosage range based on pharmacokinetic information in this population.

Sex

Liver complications may be more common in elderly people, in women, or in subjects in whom liver function is already compromised for other reasons.

Other features of the patient

Ketoconazole interferes with steroidogenesis, and those who are critically ill (23) or HIV-positive (24) are particularly susceptible to adrenal insufficiency from the use of ketoconazole.

Drug–Drug Interactions

Aciclovir

Ketoconazole seems to have a synergistic antiviral effect when it is taken with aciclovir (25).

Alcohol

A disulfiram-type reaction of ketoconazole with alcohol has been reported (SEDA-12, 231).

Amphotericin

Combination of ketoconazole with amphotericin reportedly leads to antagonism, particularly if ketoconazole therapy precedes amphotericin (26).

Antacids

Co-administration of antacids reduces the absorption of ketoconazole (13).

Antihistamines

Ketoconazole can increase the concentrations of astemizole and terfenadine by inhibition of CYP3A4. High concentrations of terfenadine can cause cardiac toxicity. Increased plasma concentrations of unmetabolized terfenadine prolong the QT interval and carry the risk of torsade de pointes and other fatal ventricular arrhythmias (13).

Ebastine (10 and 20 mg/day) had no clinically important effect on QT_c interval in adults, including elderly people, children, and patients with hepatic or renal impairment, and co-administration with ketoconazole or erythromycin did not lead to significant changes in the QT_c interval (27,28).

The pharmacokinetic and pharmacodynamic interactions of emedastine difumarate and ketoconazole have been investigated in 12 healthy volunteers (29). Emedastine difumarate 4 mg was given orally for 10 consecutive days, and on days 6–10 ketoconazole 200 mg bd was co-administered. Emedastine steady-state pharmacokinetics were slightly altered by ketoconazole: the AUC rose by about 33% and total clearance fell by about 30%, with no change in the half-life, suggesting that the volume of distribution also changed; this pattern could have arisen from protein binding displacement. However, there was no change in the QT_c interval after 5 days of co-treatment. The authors concluded that concomitant treatment with emedastine and ketoconazole in subjects with normal QT intervals could therefore be undertaken without special precautions.

When single doses of erythromycin (333 mg) or ketoconazole (200 mg) were given to healthy men who used levocabastine, two sprays per nostril (0.05 mg/spray) bd for 6 days, there were no changes in the pharmacokinetics of levocabastine or in the QT_c interval (30).

Ketoconazole affects plasma concentrations of loratadine, a non-sedating antihistamine, but appears to be devoid of any electrocardiographic effects (31). In a randomized, single-blind, multiple-dose, three-way, crossover study, concomitant administration of loratadine 10 mg qds and ketoconazole 200 mg bd resulted in significantly increased mean loratadine plasma

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concentration by 307% and desloratadine plasma concentrations by 73%; ketoconazole plasma concentrations were unaffected by loratadine. Despite increased concentrations of loratadine and its metabolite, there were no statistically significant differences in the electrocardiographic QT_c interval.

Benzodiazepines

In a double-blind, crossover kinetic and dynamic study of the interaction of ketoconazole with alprazolam and triazolam, two CYP3A4 substrate drugs with different kinetic profiles, impaired clearance by ketoconazole had more profound clinical consequences for triazolam than for alprazolam (32). By the same mechanism ketoconazole also inhibits the metabolism of midazolam (33).

Calcium channel blockers

The effects of ketoconazole 200 mg on the pharmacokinetics of nisoldipine 5 mg have been investigated in a randomized, cross-over trial (34). Pretreatment with and concomitant administration of ketoconazole resulted in 24-fold and 11-fold increases in the AUC and C_{max} of nisoldipine, respectively. The ketoconazole-induced increase in plasma concentrations of the metabolite M9 was of similar magnitude. Thus, ketoconazole and other potent inhibitors of CYP3A should not be used concomitantly with nisoldipine.

In an intestinal perfusion study of the effect of ketoconazole 40 μg/ml on the jejunal permeability and first-pass metabolism of (*R*)- and (*S*)-verapamil 120 μg/ml in six healthy volunteers, ketoconazole did not alter the jejunal permeability of the isomers, suggesting that it had no effect on the P-glycoprotein mediated efflux. However, the rate of absorption increased, suggesting inhibition by ketoconazole of the gut wall metabolism of (*R/S*)-verapamil by CYP3A4 (35).

Carbamazepine

Serum concentrations of ketoconazole are reduced by concomitant use of drugs that induce hepatic microsomal enzymes, such as carbamazepine. There may at the same time be a change in serum carbamazepine concentration (13,25).

Ciclosporin

The fact that ketoconazole inhibits cytochrome P450 accounts for some of its interactions. Ketoconazole increases ciclosporin concentrations, enhancing the risk of renal impairment, as shown by a fall in creatinine clearance (SED-12, 678) (6,13,25,36).

The effect of ketoconazole in ciclosporin-treated kidney transplant recipients has been the subject of a prospective randomized study (37). In 51 ketoconazole-treated patients and 49 controls there was a similar frequency of acute rejection episodes. However, in the control group, rejection episodes were more recurrent, with a poorer response to treatment. Acute ciclosporin nephrotoxicity was more common in the ketoconazole group, but this was encountered more at induction and rapidly reversed on further reduction of the dose of ciclosporin. Chronic graft dysfunction was significantly less in the ketoconazole group during the first year, but by the end of the study the difference was not statistically significant. Hepatotoxicity was similar in the two groups. Serum concentrations of cholesterol, low-density lipoprotein, and triglycerides were lower in the ketoconazole group. The authors concluded that long-term low-dose ketoconazole in ciclosporin-treated kidney transplant recipients is safe and cost-saving.

Citalopram

The effect of ketoconazole on the pharmacokinetics of citalopram has been studied in a double-blind, three-way, crossover trial in 18 men and women (38). The subjects received three treatments with a 14-day washout period: a single dose of ketoconazole 200 mg plus placebo, a single dose of citalopram 40 mg plus placebo, and a single dose of ketoconazole 200 mg plus a single dose of citalopram 40 mg. There were no changes in the pharmacokinetics of citalopram after co-administration of ketoconazole, suggesting that ketoconazole and other CYP3A4 inhibitors can be safely co-administered with citalopram.

Clozapine

The interaction of ketoconazole (400 mg/day for 7 days) with clozapine has been evaluated in five patients with schizophrenia given a single dose of clozapine 50 mg at the end of ketoconazole therapy (39). Ketoconazole did not significantly change the disposition of clozapine or its metabolism to its principal metabolites, desmethylclozapine and clozapine-*N*-oxide.

Donepezil

Donepezil 5 mg produced no change in plasma concentrations of ketoconazole 200 mg (40).

Erythromycin

If erythromycin and ketoconazole, both CYP3A4 inhibitors, are taken in combination, there will be an even more dramatic effect on the metabolism of other drugs, such as terfenadine and astemizole, midazolam and triazolam, and ciclosporin.

Halofantrine

Halofantrine, a highly lipophilic antimalarial drug with poor and erratic absorption, is metabolized to its equipotent metabolite desbutylhalofantrine and this is inhibited by oral ketoconazole (41).

Histamine H_2 receptor antagonists

Co-administration of histamine H_2 receptor antagonists reduces the absorption of ketoconazole (13).

HIV protease inhibitors

The effects of co-administration of ketoconazole 400 mg and amprenavir 1200 mg, which is mostly metabolized by CYP3A4, have been studied in an open, randomized, balanced, single-dose, three-period, crossover study in 12 healthy men (42). Co-administration of the two drugs increased the amprenavir AUC by 31% and reduced its C_{max} by 16%. Amprenavir increased the AUC of

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ketoconazole by 44% and increased its half-life and C_{max} by 23% and 16% respectively. Thus, co-administration of amprenavir and ketoconazole result in statistically significant increases in the AUCs of both agents, but the clinical significance of these changes remains to be investigated.

The pharmacokinetic interaction of fluconazole 400 mg od and indinavir 1000 mg tds has been evaluated in a placebo-controlled, crossover study for 8 days; there was no significant interaction (43).

The effect of ketoconazole (200 and 400 mg qds) on plasma and cerebrospinal fluid concentrations of ritonavir (400 mg bd) and saquinavir (400 mg bd) have been investigated in a two-period, two-group, longitudinal pharmacokinetic study in 12 HIV-infected patients (44). Ketoconazole significantly increased the AUC and trough concentrations of ritonavir and prolonged its half-life (by 29%, 62%, and 31% respectively). It produced similar changes (37%, 94%, and 38% respectively) in the kinetics of saquinavir. Ketoconazole significantly increased the ritonavir CSF concentration at 4–5 hours after the dose by 178% (from 2.4 to 6.6 ng/ml), with no change in the paired unbound plasma concentration (26 ng/ml). The changes were not related to ketoconazole dose or plasma exposure. The corresponding changes in saquinavir CSF concentrations were not significant. The authors concluded that ketoconazole inhibited the systemic clearance of ritonavir and, because of the disproportionate increase in CSF concentrations compared with the increase in plasma concentrations, that there was greater inhibition of drug efflux from the CSF.

A study in seven HIV-infected men who took saquinavir 600 mg tds in addition to two other antiretroviral drugs and concomitant ketoconazole (200 mg qds for 7 days, followed by 400 mg qds for another 7 days) showed no significant differences in peak and trough concentrations of saquinavir after the addition of ketoconazole (45). There was substantial inter-subject variability in the study, and the authors concluded that saquinavir concentrations may be unpredictable in individual patients and that drug monitoring may be required for optimizing saquinavir treatment.

Ifosfamide

The effect of ketoconazole on the CYP-mediated metabolism of ifosfamide to 4-hydroxyifosfamide and the ultimate cytotoxic ifosforamide mustard, and its deactivation to 2- and 3-dechloroethylifosfamide has been studied in a randomized, crossover study in 16 patients, who received intravenous ifosfamide 3 g/m^2/day, either alone or in combination with ketoconazole 200 mg bd 1 day before treatment and during 3 days of concomitant administration (46). Ketoconazole did not affect the fraction metabolized or exposure to the dechloroethylated metabolites and thus did not alter the pharmacokinetics of ifosfamide or its metabolism.

Isoniazid

Combined administration of ketoconazole with isoniazid can lead to increased concentrations of the latter, and there are possibly also alterations in ketoconazole concentrations (SED-12, 678) (25).

Methylprednisolone

The effect of ketoconazole on steroid metabolism is reflected in other interactions. Ketoconazole increases the total amount of methylprednisolone in the body (SED-12, 678) (47).

Oral contraceptives

The reported reduction in the effect of oral contraceptives (SEDA-12, 231) concurs with the effect of ketoconazole on steroid metabolism; the effect seems to be mild and may be mainly of importance during the use of formulations with low estrogen content (SED-12, 678) (48).

Phenazone

Ketoconazole reduces the clearance of phenazone (antipyrine) (SED-11, 574) (49).

Phenytoin

Serum concentrations of ketoconazole are reduced by concomitant use of drugs that induce hepatic microsomal enzymes, such as phenytoin. There may at the same time be a change in serum phenytoin concentration (SED-12, 678) (13,25,50).

Proton pump inhibitors

Co-administration of proton pump blockers reduces the absorption of ketoconazole (13).

Reboxetine

Reboxetine is metabolized by CYP3A4. In 11 healthy volunteers, ketoconazole increased the AUC of reboxetine by about 50% and increased its half-life (51). The adverse effects profile of reboxetine was not altered by ketoconazole.

Rifamycins

Serum concentrations of ketoconazole are reduced by concomitant use of drugs that induce hepatic microsomal enzymes, such as rifampicin. There may at the same time be a change in rifampicin serum concentration (SED-12, 678) (13,25,36).

Ropivacaine

Ketoconazole 400 mg caused a minor reduction in the clearance of ropivacaine, which is mostly metabolized by CYP1A2 (52).

Statins

In two cases, rhabdomyolysis occurred after co-administration of simvastatin 20 mg/day and ketoconazole (53).

Theophylline

The combination of ketoconazole with theophylline was reported to have reduced theophylline concentrations, suggesting increased metabolism of theophylline (SEDA-13, 234). This is surprising, since one would have expected ketoconazole to have inhibited the metabolism of theophylline, if at all. However, in 10 healthy, non-smoking men aged 18–40 years

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aminophylline 6 mg/kg intravenously before and after they had taken oral ketoconazole 200 mg/day for 7 days caused no change in the half-life or clearance of theophylline (54), so there is probably no important interaction between these two drugs.

Tolterodine

Tolterodine is eliminated by two different oxidative metabolic pathways: hydroxylation, catalysed by CYP2D6, and *D*-alkylation, catalysed by CYP3A. The pharmacokinetics and safety of tolterodine and its metabolites in the absence and presence of ketoconazole have been investigated in healthy volunteers with deficient CYP2D6 activity (poor metabolizers) (55). Clearance of tolterodine fell by 60% during co-administration of ketoconazole, resulting in a 2.1-fold increase in AUC. Thus, caution is needed when ketoconazole and other potent inhibitors of CYP3A are used concomitantly with tolterodine.

Tretinoin

A potential interaction of ketoconazole with tretinoin (all-trans retinoic acid), resulting in slowed metabolism, is probably not of importance (56).

Warfarin

Potentiation of the effects of warfarin has been reported in one case (SED-12, 678) (57), but absence of interference with anticoagulants was also claimed.

Ziprasidone

Ziprasidone is oxidatively metabolized by CYP3A4, but it does not inhibit CYP3A4 or other isoenzymes at clinically relevant concentrations. The effect of ketoconazole 400 mg qds for 6 days on the single-dose pharmacokinetics of ziprasidone 40 mg has been evaluated in an open, placebo-controlled, crossover study in healthy volunteers (58). Ketoconazole caused a modest increase in the mean AUC (33%) and the mean C_{max} (34%) of ziprasidone. This effect was not considered clinically relevant and suggests that other inhibitors of CYP3A4 are unlikely to affect the pharmacokinetics of ziprasidone significantly. Most of the reported adverse events were mild. The adverse events that were most commonly reported in subjects who took the drugs concomitantly were dizziness, weakness, and somnolence. There were no treatment-related laboratory abnormalities or abnormal vital signs during the study and at the 6-day follow-up evaluation.

Zolpidem

Zolpidem is metabolized by CYP3A. Ketoconazole 200 mg bd impaired the clearance of zolpidem 5 mg and enhanced its benzodiazepine-like pharmacodynamic effects. In contrast, itraconazole 100 mg bd and fluconazole 100 mg bd had small effects on zolpidem kinetics and dynamics (59).

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Ketolides

General Information

The ketolides cethromycin (ABT-773) and telithromycin are semisynthetic derivatives of 14-membered-ring macrolide antibiotics, members of the macrolide-lincosamide-streptogramin-B, MLS(B), class of antimicrobials, but they differ from macrolides by having a 3-keto group instead of an L-cladinose group on the erythronolide A ring (1–3). In a study of the efficacy of the ketolides HMR 3004 (previously RU 004) and telithromycin (HMR 3647, previously 66 647) against beta-lactamase-producing *Haemophilus influenzae*, the in vitro activity of both ketolides against 30 clinical isolates was comparable to that of azithromycin and superior to clarithromycin and erythromycin A. Furthermore, HMR 3004 and HMR 3647 were both active in a murine model of experimental pneumonia, as assessed by pulmonary clearance of beta-lactamase producing *H. influenzae* (4).

Telithromycin has a good spectrum of activity against respiratory pathogens, including penicillin-resistant and erythromycin-resistant pneumococci, intracellular bacteria, and atypical bacteria. It has an absolute oral availability of 57% in young and elderly subjects (5), and the rate and extent of absorption is unaffected by food (6). It penetrates rapidly into bronchopulmonary, tonsillar, sinus, and middle ear tissues/fluids, achieves high concentrations at sites of infection, and concentrates within polymorphonuclear neutrophils. In a dosage of 800 mg/day it is well tolerated across all patient populations, and adverse events, most commonly diarrhea, nausea, dizziness, and vomiting, are generally mild to moderate in intensity and seldom lead to treatment withdrawal (7–9).

Organs and Systems

Cardiovascular

Telithromycin causes prolongation of the QT interval, especially in elderly patients with predisposing conditions (2).

Long-Term Effects

Drug tolerance

In subjects receiving oral telithromycin (800 mg/day for 10 days), high drug concentrations were detected in the saliva indicating a good therapeutic profile for throat infections. Quantitative ecological disturbances in the normal microflora during administration of telithromycin were moderate, and no overgrowth of yeasts or *Clostridium difficile* occurred. However, resistant bacterial strains emerged (10).

The in vitro activity of cethromycin was very similar to that of telithromycin, with an MIC_{90} of 0.5 mg/l or less for all bacteria examined, except methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *H. influenzae*, and *Bacteroides* species. However, the antichlamydial activity of cethromycin was greater than that of telithromycin (11).

Drug–Drug Interactions

Cytokines

Cytokines modify phagocyte activity and may interfere with the immunomodulating properties of antibacterial agents. In an in vitro study, TNF-α and GM-CSF reduced the inhibitory effect of telithromycin on oxidant production by polymorphonuclear neutrophils, suggesting an effect of telithromycin downstream of the priming effect of cytokines. In addition, TNF-α and GM-CSF moderately impaired the uptake of telithromycin by polymorphonuclear neutrophils; the inhibitory effect of these two cytokines seemed to be related to the activation of the p38 mitogen-activated protein kinase (12).

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Ketoprofen

See also Non-steroidal anti-inflammatory drugs

General Information

The spectrum of adverse effects of ketoprofen is similar to that of ibuprofen.

Ketoprofen was originally approved for over-the-counter sales in the USA by the FDA, but in the same year, in Italy, the Ministry of Health transferred two ketoprofen-containing products from non-prescription to prescription status (SEDA-20, 93). The reasons for this difference are not clear.

Organs and Systems

Respiratory

A fatal asthmatic reaction has been described (1), and severe bronchospasm with respiratory and cardiac arrest has been reported in a young man with a history of mild asthma after he took ketoprofen (2). Topical application can provoke asthma in predisposed subjects (3).

Even topical formulations of NSAIDs should be avoided in patients with a history of analgesic-induced asthma (4).

- A 74-year-old woman with a history of sinusitis, nasal polyps, and analgesic-induced asthma had a sudden life-threatening attack of asthma 2 hours after the application of a 2% ketoprofen adhesive tape. Asthma had not previously occurred when she had used a 0.3% ketoprofen adhesive patch.

Nervous system

Retention of salt and water, sometimes with reversible pseudotumor cerebri, can occur with ketoprofen (5).

Gastrointestinal

The overall frequency of adverse reactions was 15–50% in different trials; gastrotoxicity predominated, at a frequency of 6.5–42% (6–8), even after rectal administration. In some epidemiological studies, ketoprofen in prescription doses was more gastrotoxic than other NSAIDs (SEDA-18, 99).

There are very few data on the gastrointestinal toxicity of over-the-counter doses of ketoprofen. In an endoscopic short-term study in healthy subjects ketoprofen was associated with significant gastrointestinal toxicity (9). Another endoscopic study showed that the *R*-enantiomer of ketoprofen has less gastrointestinal toxicity than the racemic mixture or the *S*-enantiomer while retaining good analgesic activity (SEDA-22, 116).

Local symptoms, including rectal bleeding, can accompany treatment with ketoprofen suppositories (8.3% of patients) (6).

Liver

Hepatotoxicity has rarely been reported with ketoprofen (SEDA-17, 110).

Urinary tract

Like many other NSAIDs, ketoprofen can cause acute interstitial nephritis (10). Renal insufficiency and the nephrotic syndrome due to membranous glomerulonephritis (an unusual cause of NSAID-induced nephrotic syndrome) have been described in an elderly patient taking long-term ketoprofen (SEDA-12, 86).

As topical NSAIDs can be absorbed via the skin, they cannot be considered safe in high-risk patients, in whom all NSAIDs are contraindicated.

- A 62-year-old woman developed acute renal insufficiency after using topical ketoprofen for 5 days (11). She had several predisposing factors to NSAID-induced acute renal insufficiency, such as advanced age, chronic renal impairment due to polycystic kidney disease, and treatment with an ACE inhibitor and furosemide.

Ketoprofen use has been followed by red discoloration of urine (SEDA-16, 110).

Skin

Topical ketoprofen can cause contact dermatitis and photodermatitis, like other NSAIDs (SEDA-18, 104) (SEDA-22, 116). Data from Sweden have confirmed the photosensitizing potential of topical gel formulations of ketoprofen and have included a number of reports of contact dermatitis (12). In some cases ketoprofen can be responsible for very prolonged photosensitivity after only a single application (13).

Toxic epidermal necrolysis has been described with ketoprofen (SEDA-21, 105).

Drug Administration

Drug administration route

Studies on a modified-release formulation of ketoprofen showed a similar pattern of adverse effects to the usual formulations (SEDA-12, 86).

An injectable form of ketoprofen has acceptable tolerability (6,7), but about 4.5% of patients have local reactions.

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Drug overdose

A 64-year-old woman had auditory and visual hallucinations, persecutory delusions, and slurred speech after she took an overdose of ketoprofen; her psychiatric symptoms resolved within 48 hours (14).

Drug–Drug Interactions

Aspirin

Concurrent administration of aspirin reduces ketoprofen protein binding and increases its clearance. Salicylate also reduces the metabolic conversion of ketoprofen to its conjugates and their renal elimination, and enhances its conversion to non-conjugated metabolites (15).

Co-triamterzide

Irreversible renal insufficiency has been reported in an elderly patient who took ketoprofen in combination with co-triamterzide (triamterene + hydrochlorothiazide) (16). The interaction with triamterene is well documented (SEDA-12, 80) and co-administration with ketoprofen has proved dangerous.

Warfarin

Although data from healthy subjects indicate no interaction of ketoprofen with warfarin, severe gastrointestinal bleeding and a prolonged prothrombin time have been attributed to this combination (SEDA-13, 81).

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Ketorolac

See also Non-steroidal anti-inflammatory drugs

General Information

Ketorolac is, like several other NSAIDs, promoted as a non-narcotic analgesic. This is merely a marketing ploy, which does not reflect any special characteristics, except that it is one of many NSAIDs that can be given parenterally. A pyrrolizine carboxylic acid derivative, it is structurally and pharmacologically related to tolmetin, zomepirac, and indometacin. The trometamol salt of ketorolac enhances its solubility and allows parenteral administration; single intramuscular injections are better tolerated than morphine.

Opinions on the safety of ketorolac in EC drug regulatory authorities are conflicting (SEDA-18, 104) (1). However, the risk of adverse effects is higher when ketorolac is used in higher doses, in elderly subjects, and for more than 5 days (SEDA-21, 105).

Other information on the benefit-to-harm balance of parenteral ketorolac tromethamine as a postoperative analgesic has been provided by three studies (SEDA-21, 105). The overall risk of gastrointestinal and operative site bleeding and acute renal insufficiency associated with parenteral ketorolac and a parenteral opiate were relatively small.

The most commonly reported symptoms are somnolence, headache, dizziness, nausea, dyspepsia, and abdominal pain. Edema, hyperkalemia, diarrhea, sweating, self-limiting wheezing, and itching have also been reported occasionally (SEDA-12, 86) (SEDA-16, 110) (SEDA-17, 111).

There are contrasting data on the benefit-to-harm balance of parenteral ketorolac as an analgesic (SEDA-21, 105). This prompted regulatory review of ketorolac in many countries, leading to revision of labelling, dosage recommendations, and prescribing practices. The use of ketorolac should be limited in dosage and duration; in elderly patients it should probably not be used at all. It is important for prescribers to understand that increasing the dosage of ketorolac beyond the label recommendations (60–120 mg/day for a maximum of 2–5 days) will not provide better efficacy, but will increase the risk of serious adverse reactions (2).

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Organs and Systems

Sensory systems

Reversible hearing loss with tinnitus and headache were described in a woman with a predisposition to ototoxicity in end-stage renal disease (SEDA-21, 106).

Hematologic

Ketorolac prolongs bleeding time reversibly. The clinical significance of the effect of ketorolac on hemostasis in perioperative use is still imperfectly understood. Serious bleeding, either at the operative site or in the gastrointestinal tract after perioperative administration of ketorolac, has been documented in several reports (SEDA-18, 105) and in controlled studies (SEDA-20, 93). Concomitant use of anticoagulants increases the risk of bleeding (SEDA-18, 105).

Gastrointestinal

Gastric lesions (endoscopically demonstrated erosions, ulcers, and giant duodenal or gastric ulcers) have been described in healthy volunteers (SEDA-14, 94) and patients (SEDA-18, 105) treated with parenteral ketorolac (SEDA-14, 94); gastric damage is dose-related (SEDA-17, 112). A case-control study on hospitalization for upper gastrointestinal tract bleeding and/or perforation provided further evidence of the unfavorable benefit-to-harm balance of ketorolac compared with other NSAIDs. Ketorolac was five times more gastrotoxic than all other NSAIDs. The relative risk with intramuscular ketorolac was higher than with oral ketorolac (SEDA-22, 117).

Further evidence of the unfavorable benefit-to-harm balance of ketorolac compared with other NSAIDs has been provided by another case-control study on first-time hospitalization for gastroduodenal ulcer (documented by endoscopy, radiology, surgery, or autopsy), with or without bleeding or perforation. Of all the NSAIDs used in outpatients the highest rate ratio for lesions of any degree of severity was seen with piroxicam (4.6; 95% CI = 1.4, 8.3); ketorolac ranked second highest (3.4; 95% CI = 1.4, 8.3). For patients who suffered hemorrhage or perforation, the highest rate ratio observed was for ketorolac (5.9; 95% CI = 2.1, 16) (3).

Colonic ulceration with massive bleeding has been reported in a woman who received ketorolac intramuscularly (SEDA-21, 106).

Urinary tract

There have been several reports of impaired renal function in patients taking ketorolac (SEDA-17, 112) (SEDA-18, 105) (SEDA-22, 117). The severity varies from slight to severe forms of renal insufficiency, which may even occur after a single dose of 30 mg. Because recent major surgery is considered a risk factor for renal insufficiency, particularly in elderly patients, the use of ketorolac, or other NSAIDs, for postoperative pain management is warranted only in carefully selected patients. Furthermore, a case report confirmed that oral ketorolac can cause acute renal insufficiency in young subjects without any predisposing factors (SEDA-21, 106).

Immunologic

Anaphylaxis and anaphylactoid reactions have been reported (SEDA-17, 112).

Second-Generation Effects

Pregnancy

As ketorolac crosses the placental barrier, it should not be used in pregnant women. When it is given to mothers during labor, it significantly inhibits platelet aggregation in the neonate (SEDA-14, 94).

Susceptibility Factors

Other features of the patient

Children undergoing tonsillectomy had a significant increase in the risk of major postoperative hemorrhage without beneficial effects, compared with opioid analgesics (SEDA-21, 106).

Several reports have documented the high risk of ketorolac in patients with a history of asthma, nasal polyposis, and sensitivity to aspirin or any other NSAID (SEDA-18, 105). Exacerbation of chronic asthma has been reported after the use of ketorolac eye-drops (SEDA-21, 106).

Drug–Drug Interactions

Lithium

Reports of lithium neurotoxicity resulting from an interaction with ketorolac have been published (SEDA-22, 117) (4).

In a pharmacokinetic study in healthy volunteers ketorolac increased the concentration of lithium in both serum and erythrocytes, which may reflect concentration of the drug in the nervous system more accurately. Ketorolac can therefore increase the risk of adverse reactions of lithium (5), as do many other NSAIDs.

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Ketotifen

See also Antihistamines

General Information

Ketotifen was originally developed as a drug that would inhibit the release of vasoactive substances from mast cells, as an oral alternative to cromoglicate, but its actions in asthma are probably attributable to its antihistaminic effect (SED-13, 423) (SEDA-22, 194), which occurs within minutes after administration and lasts for up to 12 hours. It also stabilizes mast cells, preventing histamine release, inhibits eosinophil accumulation in the lungs of animals exposed to platelet-activating factor, and reverses beta-adrenoceptor tachyphylaxis (1). It is classified as an antiallergic drug and is used as a prophylactic medicine.

Some trials have suggested that ketotifen has similar efficacy to cromoglicate in asthma (2) and also a small steroid-sparing effect (3). It is more effective than placebo in the treatment of atopic dermatitis (4). The normal therapeutic dose is 1–2 mg/day.

Conjunctival injection, headache, and rhinitis are common. Allergic reactions, stinging, discharge, eye pain, and photophobia occurred in less than 5% of patients. The most common adverse effects noted in long-term clinical trials are sedation and weight gain (SEDA-7, 1).

In young children (with an average age 16 months) effective doses of ketotifen produced adverse effects similar to those seen in adults, including dry mouth (28%) and sometimes increased appetite (5). In a series of 257 older children, increased weight was reported in 17, sedation in 13, and nausea in 3 (6). An evaluation of postmarketing surveillance of ketotifen in the UK showed, however, that the percentage of adverse effects reported in children was rather lower than in adults, sedation occurring in only 6% at the beginning of treatment. The corresponding figure in adults was 14.2% (7).

Organs and Systems

Nervous system

There is considerable controversy about the frequency and severity of sedation. Although it is commonly reported when ketotifen is started (23% in one study), its incidence falls during the first 2 months to about 6%. Only 2–3% of patients discontinue therapy for this reason (8). In a study involving 1791 patients, with allergic paroxysmal asthma, somnolence occurred in 13%. This effect started early in treatment and wore off in more than one-third of the patients (2).

Ketotifen produced seizures in a 5-year-old epileptic boy with allergic rhinitis. This was not specific to ketotifen but the result of H_1 receptor blockade. Administration of D-chlorphenamine increased the number of epileptic discharges seen on the electroencephalograph. It is recommended that centrally acting H_1 receptor antagonists should be avoided in epileptic patients, especially children (9).

Two cases of seizures in children induced by ketotifen have been reported (10).

- A 3-month-old boy was given ketotifen (0.1 mg/kg/day) for atopic dermatitis and after 8 days developed tonic spasms of a mixed flexor extensor type, consisting of flexion of the neck and arms with extension of the legs more than 10 times a day. Each seizure lasted for 5–15 minutes. An electroencephalogram showed a hypsarrhythmic trace. Ketotifen was withdrawn and the seizures were successfully controlled with ACTH and valproic acid. An MRI scan was normal.
- A 3-month-old boy was given ketotifen, 0.1 mg/kg/day, for asthmatic bronchitis. After 10 days his facial movements altered and 1 month after ketotifen was started tonic spasms began. His seizures consisted of a sudden contraction, usually bilateral and symmetrical involving the muscles of the neck, trunk, and limbs. An electroencephalogram showed a hypsarrhythmic trace. He was treated with ACTH and clonazepam without benefit. Ketotifen was withdrawn and ACTH and clonazepam were replaced with valproic acid. This resulted in seizure control, after which the electroencephalogram showed no abnormal discharges. Blood tests and an MRI scan were normal.

There is evidence that the central histaminergic neurons play an important role in inhibiting convulsions in the immature brain, where the GABA system is less effective than in the adult brain. Histamine acts via an H_1 receptor and other H_1 receptor antagonists can cause seizures. The authors proposed that ketotifen induces infantile spasms by antagonizing H_1 receptors.

Urinary tract

A single case of drug-induced cystitis has been reported. The patient had never taken tranilast, and the symptoms resolved on stopping ketotifen and recurred when the drug was restarted. Aseptic pyuria was found and cystoscopy revealed significant reddening over the urinary bladder (11).

Drug Administration

Drug overdose

Eight cases of overdose have been reported in which the patients took doses ranging from 10 to 120 mg (12). The plasma concentrations were considerably higher than those after therapeutic doses. The symptoms of overdose were drowsiness, confusion, coma, dyspnea, bradycardia and tachycardia, hyperexcitability, convulsions, and nystagmus. Six patients were treated with gastric lavage and after supportive treatment all eight patients made a full recovery within 12 hours of admission.

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Krameriaceae

See also Herbal medicines

General Information

The family of Krameriaceae contains the single genus *Krameria* (ratany). Contact dermatitis has been reported in a patient using an extract of *Krameria triandra* (1).

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Labetalol

See also Beta-adrenoceptor antagonists

General Information

Labetalol is a non-selective alpha- and beta-adrenoceptor antagonist; these actions reside in four different enantiomers.

Labetalol is less likely to increase airways resistance in patients with bronchial asthma or to reduce peripheral blood flow. However, it can produce postural hypotension (SEDA-3, 166–7), and paresthesia of the scalp (1,2) and perioral numbness (3) have been described.

Organs and Systems

Cardiovascular

Labetalol is generally used effectively as an antihypertensive drug without reports of high vascular resistance, even in patients with pheochromocytoma. However, a case of pheochromocytoma with increased systemic vascular resistance and reduced cardiac index has been described (4).

- A 36-year-old man with a pheochromocytoma underwent adrenalectomy. After induction of anesthesia he was given intravenous labetalol 30 mg, and after intubation his blood pressure rose from 147/85 to 247/150 mmHg, his systemic vascular resistance index rose from 1958 to 3458 dyn·sec^{-1} m^2 cm^5, and his cardiac index fell to 3.6 l min^{-1} m^2. During tumor resection, he was given sodium nitroprusside to reduce his blood pressure. After tumor resection, his blood pressure fell to 77/52 mmHg and his systemic vascular resistance index to 1635 dyn·sec^{-1} m^2 cm^5. His blood pressure was effectively controlled with dobutamine.

This case affords a reminder that intravenous labetalol can increase the systemic vascular resistance and cause a hypertensive crisis. In these cases, labetalol should be replaced with a pure alpha-blocker or another vasodilator, to prevent the possibility of cardiovascular complications.

Neonatal cardiac arrest was precipitated in one case by labetalol (5).

Electrolyte balance

Three cases of severe hyperkalemia have been reported in renal transplant recipients taking labetalol for acute hypertension (6) and life-threatening hyperkalemia has been reported after intravenous labetalol (7).

- A 28-year-old man with severe hypertension and end-stage renal disease was given two intravenous doses of labetalol 20 mg 1 hour apart for malignant hypertension. The serum potassium concentration before treatment was 6.2 mmol/l, but 8 hours after labetalol it rose to 9.9 mmol/l and he developed left bundle branch block, ventricular tachycardia, and hypotension. He was given intravenous calcium gluconate, sodium bicarbonate, and lidocaine and reverted to sinus rhythm. The potassium concentration after 2 hours was 8.0 mmol/l. After hemodialysis the potassium concentration fell to 6.1 mmol/l.

In a retrospective chart review in 103 transplanted patients from January to November 1994, hypertension requiring perioperative treatment was observed in 51 cases (8). Treatment for hyperkalemia was necessary in 13 of the 38 patients who were treated with labetalol, compared with 11 of the 65 who were treated with another antihypertensive treatment.

Patients with end-stage renal disease on dialysis can have an enhanced hyperkalemic response to labetalol, which is partly attributable to electrochemical disturbances in the cells, characterized by an increase in intracellular sodium and chloride and a fall in intracellular potassium.

Liver

Eleven cases of hepatotoxicity have been reported with labetalol (9). Acute hepatitis has been described in an East-Asian man (10).

- A 50-year-old man with chronic hepatitis B infection, a hemiparesis due to a hemorrhage in the left basal ganglia, and a high systolic blood pressure was given intermittent intravenous labetalol followed by oral therapy (200 mg bd). After 1 week, his aspartate transaminase, alanine transaminase, and bilirubin started to rise. Ultrasonography of the liver and gallbladder was normal. Labetalol was withdrawn, and all the liver function tests normalized within a few days.

Prior hepatitis B infection may have predisposed this patient to labetalol-induced liver toxicity.

Musculoskeletal

Two children developed a proximal myopathy and rhabdomyolysis, which resolved on withdrawal of labetalol (11).

Immunologic

Antinuclear and antimitochondrial antibodies develop not uncommonly during long-term administration of labetalol (12).

Second-Generation Effects

Fetotoxicity

Labetalol has a high transplacental transfer rate.

- A single intravenous dose of labetalol 30 mg given to a woman with severe pregnancy-related hypertension 20 minutes before cesarean section was associated with significant neonatal beta-adrenoceptor blockade (hypoglycemia, bradycardia, and hypotension), and there were high labetalol concentrations in the umbilical cord blood (150–180 ng/ml) (13).
- An infant was born dead to a woman given intravenous labetalol 50 mg, which lowered her blood pressure from 170/110 to 115/85 mmHg before surgery (14).

Oral labetalol is well tolerated in pre-eclampsia, but if intravenous treatment is necessary, a small dose (5–10 mg) should be used initially and titrated up as necessary.

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Lamiaceae

See also Herbal medicines

General Information

The genera in the family of Lamiaceae (Table 1) include basil, catnip, germander, lavender, mints, origanum, rosemary, sage, skullcap, and thyme.

Hedeoma pulegoides and *Mentha pulegium*

The volatile oil of pennyroyal (prepared from *Hedeoma pulegoides* or *Mentha pulegium*) is a folk medicine used as an abortifacient. The doses that are required for this effect can cause serious symptoms, including vomiting, seizures, hallucinations, renal damage, hepatotoxicity and shock; deaths have also occurred (1,2).

Adverse effects

The hepatotoxicity of pulegone, the principal constituent of pennyroyal oil, has been demonstrated in animal studies and reported in humans (3).

Two cases of serious or fatal toxicity have been described in two infants who had been treated with herbal tea containing pennyroyal oil (4). One infant developed fulminant liver failure with cerebral edema and necrosis; the other infant developed hepatic dysfunction and a severe epileptic encephalopathy.

Lavandula angustifolia

The volatile oil of *Lavandula angustifolia* (lavender) contains linrayl acetate and linalool, and lavender also contains coumarins. It has been used in aromatherapy to treat insomnia and headaches, and may have small beneficial effects (5).

Adverse effects

Patch tests with lavender oil from 1990 to 1998 in Japan were positive in 3.7% of cases (6). In five of 11 positive cases in 1997 and eight of 15 positive cases in 1998, the patients had used dried lavender flowers in pillows, drawers, cabinets, or rooms.

- A 53-year-old patient with relapsing eczema had contact allergy to various essential oils used in aromatherapy (7). Sensitization was due to previous exposure to lavender, jasmine, and rosewood. Laurel, eucalyptus, and pomerance also produced positive tests, without previous exposure.

Contact dermatitis has been attributed to a lavender oil pillow (8), and to lavender in an analgesic gel (9).

Mentha piperita

The oil of *Mentha piperita* (peppermint) contains cineol, limonene, menthofuran, menthol, and menthone. It has been used as a carminative and antispasmodic for esophageal spasm and irritable bowel syndrome (10).

Adverse effects

Contact dermatitis has been attributed to menthol in peppermint (11).

Salvia species

In China, the root of *Salvia miltiorrhiza* (danshen) has been used traditionally for the treatment of coronary diseases.

The leaf of *Salvia officinalis* (sage) contains 1.0–2.5% of essential oil, consisting of 35–60% of thujone.

Adverse effects

A patient taking warfarin and who had taken a decoction of *S. miltiorrhiza* presented with a prolonged bleeding time and melena (12) and other cases have been reported (13). Pharmacodynamic and pharmacokinetic studies in rats have shown that danshen increases the absorption rate constant, AUC, C_{max}, and half-lives of both *R*- and *S*-warfarin, and reduces their clearances and apparent volumes of distribution (14,15).

Thujone can cause toxicity when the herb is taken in overdose (more than 15 g per dose) or for a prolonged period. Pregnancy is listed as a contraindication to the use of the essential oil or alcoholic extracts of *S. officinalis*.

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Table 1 The genera of Lamiaceae

Acanthomintha (thorn-mint)
Acinos (acinos)
Agastach (giant hyssop)
Ajuga (bugle)
Ballota (horehound)
Blephilia (pagoda-plant)
Brazoria (brazos-mint)
Calamintha (calamint)
Cedronella (cedronella)
Chaiturus (lion's tail)
Clinopodium (clinopodium)
Coleus (coleus)
Collinsonia (horsebalm)
Conradina (false rosemary)
Cunila (cunila)
Dicerandra (balm)
Dracocephalum (dragonhead)
Elsholtzia (elsholtzia)
Erythrochlamys (erythrochlamys)
Galeopsis (hemp nettle)
Glechoma (glechoma)
Haplostachys (haplostachys)
Hedeoma (false pennyroyal)
Hyptis (bushmint)
Hyssopus (hyssop)
Isanthus (fluxweed)
Lallemantia (lallemantia)
Lamiastrum (lamiastrum)
Lamium (dead nettle)
Lavandula (lavender)
Leonotis (lion's ear)
Leonurus (motherwort)
Lepechinia (pitchersage)
Leucas (leucas)
Lycopus (waterhorehound)
Macbridea (macridea)
Marrubium (horehound)
Marsypianthes (marsypianthes)
Meehania (meehania)
Melissa (balm)
Mentha (mint)
Moluccella (moluccella)
Monarda (beebalm)
Monardella (monardella)
Mosla (mosla)
Nepeta (catnip)
Ocimum (basil)
Origanum (origanum)
Orthosiphon (orthosiphon)
Perilla (perilla)
Perovskia (perovskia)
Phlomis (Jerusalem sage)
Phyllostegia (phyllostegia)
Physostegia (lion's heart)
Piloblephis (piloblephis)
Plectranthus (plectranthus)
Pogogyne (mesamint)
Pogostemon (pogostemon)
Poliomintha (rosemary mint)
Prunella (self heal)
Pycnanthemum (mountain mint)
Rhododon (sand mint)
Rosmarinus (rosemary)
Salazaria (bladder sage)
Salvia (sage)
Satureja (savory)
Scutellaria (skullcap)
Sideritis (ironwort)
Solenostemon (solenostemon)
Stachys (hedge nettle)
Stachydeoma (mock pennyroyal)
Stenogyne (stenogyne)
Synandra (synandra)
Teucrium (germander)
Thymus (thyme)
Trichostema (bluecurls)
Warnockia (brazos mint)

Scutellaria species

The *Scutellaria* species (skullcap) include over 40 members, which contain a variety of flavonoids and terpenoids, the latter including scutellariosides and smithiandienol. Some also contain pyrrolizidine alkaloids (see separate monograph), which have repeatedly been implicated in veno-occlusive disease of the liver.

Adverse effects

Although Western skullcap formulations are supposed to come from *Scutellaria lateriflora*, it is unclear whether it is responsible for the liver damage that has been associated with skullcap. In the UK, the American germander (*Teucrium canadense*) has been widely used to replace *S. lateriflora* in commercial skullcap materials and products. In one UK case of skullcap-associated hepatotoxicity, the material was found to come from *T. canadense*. This raises the possibility that other cases of skullcap toxicity may also have involved *Teucrium* rather than *Scutellaria* (16).

Respiratory

- A 53-year-old Japanese man, who had taken skullcap intermittently for hemorrhoids, developed recurrent interstitial pneumonitis (17). Re-challenge, after he had stopped taking the herbal remedy and had become symptom free, resulted in a high fever and signs and symptoms of interstitial pneumonitis. Transbronchial lung biopsy showed lymphocytic alveolitis with eosinophilic infiltration. The symptoms subsided again after withdrawal.

Liver

Skullcap has repeatedly been associated with hepatotoxicity, and veno-occlusive disease has been reported (18).

- A 28-year-old man presented with jaundice after taking six tablets of skullcap (together with zinc and pau d'arco) daily for the previous 6 months to help his multiple sclerosis. His liver enzymes were raised and hepatitis A, B, and C serologies were negative. He developed progressive liver failure and received a transplant but died shortly after. His explanted liver showed fibrous stenosis and obliteration of most of the terminal venules with extensive perivenular fibrosis, indicative of veno-occlusive disease.

Teucrium species

Teucrium species (germander) contain a variety of iridoids, monoterpenoids, diterpenoids, and sesquiterpenoids.

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Adverse effects

The hepatotoxicity of germander has been well documented. An animal study suggests that the hepatotoxicity resides in one or more reactive metabolites of its furanoditerpenoids (19).

In France, many cases of hepatitis have been associated with the normal use of *Teucrium chamaedrys* (wall germander). The frequency of this adverse effect has been estimated at one case in about 4000 months of treatment (20). Two cases of hepatitis in women who had been taking germander daily for 6 months have been reported from Canada (21). Although most cases are not serious, deaths have been reported (22), and progression to liver cirrhosis has also been described (23).

Seven patients developed hepatitis after taking *T. chamaedrys* and had no other cause of liver damage (24). The hepatitis was characterized by jaundice and a marked increase in serum transaminases 3–18 weeks after taking germander. Liver biopsies in three patients showed hepatic necrosis. After withdrawal of germander the jaundice disappeared within 8 weeks and recovery was complete in 1.5–6 months. In three cases, germander was followed by prompt recurrence of hepatitis.

- A 62-year-old man had taken a tea made from *T. capitatum* for 4 months when he developed anorexia, nausea, and malaise (25). He also noted dark urine and jaundice. He was admitted to hospital with acute icteric hepatitis. A liver biopsy showed bridging necrosis, inflammatory infiltration, and bile emboli. After withdrawal of the herbal tea he made a full recovery within 3 months.

Several other cases have been reported (26–30).

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Lamivudine

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Lamivudine (3TC) is a nucleoside analogue reverse transcriptase inhibitor that has been widely used against HIV infection which also has antiviral effects against hepatitis B (1).

Observational studies

In a 24-week phase I/II study, 89 children aged 3 months to 17 years (median 7.3 years) were treated with lamivudine for 24 weeks in dosages of 1–20 mg/kg/day (2). Dosages over 20 mg/kg/day were not tested because of reported neutropenia in adults at this dosage (3). Lamivudine was generally well tolerated in these children. Ten children were withdrawn because of presumed adverse effects: three because of increased serum transaminase activities, three because of neutropenia, and two because of hyperactivity. One child became ataxic shortly after the start of therapy, and one developed pancreatitis during hospitalization for acute cryptosporidiosis. All of these events resolved with supportive care on withdrawal of lamivudine, except one case of hepatitis, which persisted up to 10 months after withdrawal. Treatment was discontinued temporarily in other patients because of pancreatitis ($n = 2$), rashes ($n = 2$), neutropenia ($n = 1$), anemia ($n = 1$), and increased serum transaminase activities ($n = 1$). On resolution of the presumed adverse reaction, the drug was reintroduced in all of these cases without further problems. There were no significant hematological or biochemical changes. Neither the incidence nor the severity of the observed adverse events was dose-related. The assignment of causality to lamivudine of most of the adverse events was complicated by intercurrent conditions and concomitant medications.

In a study of the efficacy of lamivudine (25, 100, or 300 mg/day for 12 weeks) in the treatment of chronic hepatitis B virus infections, lamivudine was similarly well tolerated in 32 patients (4). Only minor non-specific non-dose-related adverse reactions were observed. In addition, there were mild asymptomatic increases in serum activities of amylase, lipase, and creatine kinase, which in most cases resolved despite continued therapy.

Comparative studies

The safety and efficacy of lamivudine (300–600 mg/day) in combination with zidovudine (600 mg/day) in the treatment of antiretroviral-naive and zidovudine-experienced HIV-infected persons has been compared with zidovudine monotherapy in two placebo-controlled studies of 129 and 223 patients (5,6). There were no significant differences in the incidence or severity of adverse effects between patients taking zidovudine alone or in combination with lamivudine. In both studies gastrointestinal symptoms, notably nausea, were the most commonly observed adverse reactions, occurring in 5–11% of zidovudine-experienced patients and 23–29% of antiretroviral drug-naive individuals. Although one antiretroviral drug-naive patient taking combined therapy had an asymptomatic rise in pancreatic amylase activity, acute pancreatitis was not observed in either study. Grade 1 peripheral neuropathy was reported in one zidovudine-experienced patient taking low-dosage lamivudine (150 mg bd) and zidovudine.

Organs and Systems

Hematologic

A case report has provided strong evidence that lamivudine can on rare occasions cause severe anemia; the mechanism is unclear (7).

Gastrointestinal

In a 1-year trial of lamivudine in 10 children with vertically acquired chronic hepatitis B, lamivudine made serum hepatitis B viral DNA undetectable in all the patients within 24 weeks (8). Serum alanine transaminase activity returned to the reference range within 36 weeks. Although nausea and vomiting were reported in one child, it was not necessary to withhold treatment.

Liver

Lamivudine is used orally to treat chronic hepatitis B in adults and children (9). It increases the rate of loss of hepatitis B e antigen and seroconversion in compensated chronic carriers, with improvement of histology at a similar rate to interferon alfa. However, the tyrosine-methionine-aspartate-aspartate (YMDD) mutation prevents efficacy and can cause flares of hepatitis. The indications for treatment must therefore be established with care and only by those who have expert knowledge of the disease, the drug, and the YMDD mutation.

Nails

Paronychia has been reported in 12 HIV-infected patients who had taken lamivudine only for 3 months before the onset of symptoms (10). Microbiological investigations for fungi or bacteria were negative. All were treated with topical antiseptics; surgical procedures were performed in four. Five patients healed without recurrence,

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while the paronychia recurred in six. There was no mention of withdrawal of lamivudine. The causative role of lamivudine in the development of paronychia in these patients remains obscure.

Long-Term Effects

Drug tolerance

The incidence of viral resistance to lamivudine increases with the duration of therapy in patients with chronic hepatitis B (11). However, the effect of viral resistance on hepatic synthetic function has not been well defined. In 38 patients (26 with cirrhosis) in an open study there was an initial antiviral response in all patients (hepatitis B virus DNA became undetectable by a hybridization assay), and nine of 22 (41%) hepatitis B e antigen-positive patients underwent hepatitis B e antigen seroconversion. In 29 patients with undetectable serum hepatitis B viral DNA at the end of the study, the mean serum albumin concentration rose from 40 to 43 g/l, corresponding to a yearly increase of 1.85 g/l; this was largely attributable to an increase in the cirrhotic patients. Resistance to lamivudine developed in nine patients. Suppression of viral replication by lamivudine improves hepatic synthetic function in chronic hepatitis B patients, but emergence of drug resistance is associated with a rapid fall in serum albumin.

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Lamotrigine

See also Antiepileptic drugs

General Information

Lamotrigine is widely used in the management of partial and generalized seizures. It has a favorable tolerability profile, even though neurological adverse effects and hypersensitivity reactions are sometimes troublesome. Its pharmacology, clinical pharmacology, adverse effects, and interactions have been reviewed (1). Its adverse events are primarily neurological, gastrointestinal, and dermatological and are typically mild or moderate and transient, with the exception of a potentially serious rash. Maculopapular or erythematous skin rashes occur in about 12% of children and are the most common reason for withdrawal. More severe forms of rash, including Stevens–Johnson syndrome, occur occasionally, with a three-fold higher incidence in children (about 1%) than adults (about 0.3).

Observational studies

Among 11 316 patients in a postmarketing surveillance study that included 3994 patients followed for 6 months or longer, the main events leading to drug withdrawal were rash ($n = 210$), drowsiness ($n = 74$), nausea ($n = 66$), dizziness ($n = 63$), headache ($n = 61$), vomiting ($n = 33$), ataxia ($n = 32$), malaise ($n = 29$), and aggression ($n = 26$). Rare serious adverse events included Stevens–Johnson syndrome in 12 cases, neutropenia in 4, thrombocytopenia in 3, and disseminated intravascular coagulation in 2. Leukopenia, a meningitic reaction, acute renal insufficiency, hepatotoxicity, and a lupus-like reaction occurred in one patient each (2).

In an open study, there were adverse events (details not given) in two of 30 patients with serum lamotrigine concentrations between 16 and 39 μmol/l, and in 5 of 11 patients with serum concentrations between 39 and 86 μmol/l (3). This is one of the few studies to have provided preliminary evidence for a relation between serum lamotrigine concentrations and the risk of adverse effects.

The efficacy of lamotrigine as monotherapy has been studied retrospectively in 83 children (mean age 8.7 years) with focal epilepsy ($n = 43$), generalized epilepsy ($n = 32$), or not classified ($n = 8$) (4). The median follow-up period was

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8 months (mean = 8.5). Rash was the most common adverse effect, in five patients; two patients discontinued treatment. There were no cases of Stevens–Johnson syndrome.

Lamotrigine has been used as maintenance monotherapy for rapid-cycling bipolar disorder in 324 patients (open label) and 182 patients (double-blind) with rapid-cycling bipolar disorder (5). In all, 265 patients reported adverse events during the open phase. The most common adverse events (over 10%) were headache, infection, influenza, nausea, abnormal dreams, dizziness, and rash. During the double-blind phase 122 patients reported adverse events, equally with lamotrigine and placebo.

In 44 patients with profound mental retardation a retrospective assessment of adjunctive lamotrigine (272 mg/day) showed a significant reduction in seizure frequency from 10.1 to 5.8 seizures per month (6). There were no treatment-related changes in laboratory parameters, vital signs, or body weight, and no serious rashes. In three of five patients there was worsened self-injurious behavior, requiring drug withdrawal.

Lamotrigine has been studied in 32 children with epilepsy refractory for at least 1 year to other antiepileptic drugs (7). Adverse effects were uncommon, and there were no skin rashes.

The efficacy and safety of lamotrigine have been prospectively evaluated in 41 children and young adults (aged 3–25 years) with drug-resistant partial epilepsies (8). Lamotrigine withdrawal was mainly due to lack of efficacy (46%); only two patients developed a transient skin rash, which did not require withdrawal.

The adverse effects of lamotrigine have been surveyed retrospectively in 2701 patients in five tertiary referral epilepsy centers in the UK; 1326 were excluded because lamotrigine and/or comparators had been begun outside the study centers (9). The most common adverse events were rash (10%), dizziness, ataxia, and diplopia. There were four cases of life-threatening adverse events: one case each of hepatic insufficiency, acute exacerbation of ulcerative colitis, disseminated intravascular coagulation, and renal insufficiency caused by rhabdomyolysis and myoglobinuria. The mortality rate was 1.7 per 100 patient-years and the standard mortality ratio was 10.4, similar to other antiepileptic drugs (gabapentin and vigabatrin). No deaths were directly attributable to lamotrigine.

In an open randomized study in 417 patients over 2 years old who took lamotrigine or carbamazepine monotherapy for new-onset epilepsy there was similar efficacy (65% were free of seizures with lamotrigine and 73% with carbamazepine) (10). Although the patients taking lamotrigine tended to have fewer adverse events than those taking carbamazepine (52 versus 60%), the difference was not significant. Somnolence was the only adverse event reported at an incidence of over 5% and it was more frequent in patients taking carbamazepine (11 versus 4% with lamotrigine).

Comparative studies

In a 48-week, double-blind, monotherapy trial of 260 patients with newly diagnosed epilepsy, the proportion withdrawn because of adverse events was 11% in the lamotrigine group (9% with rash) and 21% in the carbamazepine group (13% with rash). Somnolence was more frequent with carbamazepine (22 versus 12%), but the incidence of other common complaints (headache, weakness, rash, nausea, dizziness) did not differ between groups (11). Although it was concluded that lamotrigine is tolerated better than carbamazepine, in this and other trials a design that involved twice-daily dosing may have placed carbamazepine at a disadvantage in the comparison.

In a multicenter, double-blind comparison of lamotrigine and phenytoin (titrated over 6 weeks from starting dosages of 100 and 200 mg/day respectively) in 181 patients with newly diagnosed epilepsy there were comparable seizure freedom rates and comparable trial discontinuation rates with the two drugs (12). Skin rashes leading to withdrawal occurred in 12% of patients assigned to lamotrigine and in 5% of those assigned to phenytoin, but the risk associated with lamotrigine might have been overestimated, owing to an excessively high starting dose. Central nervous system adverse effects were more common with phenytoin, the difference being statistically significant for weakness (29 versus 16%), somnolence (28 versus 7%), and ataxia (12 versus 0%).

A review of the manufacturer's safety database from the adult clinical trial program has been published (13). In placebo-controlled add-on trials involving a total of 1555 patients, the most common adverse events were dizziness (35 versus 15% on placebo), headache (26 versus 21%), diplopia (25 versus 6%), ataxia (20 versus 6%), nausea (19 versus 9%), blurred vision (14 versus 4%), rhinitis (11 versus 8%), somnolence (10 versus 7%), rashes (10 versus 5%), and vomiting (10 versus 5%). Dizziness and rashes led to withdrawal most commonly, each in 2% of patients. Dizziness, diplopia, nausea, blurred vision, and headache occurred more commonly in patients co-medicated with carbamazepine than in those co-medicated with other drugs. In randomized comparative monotherapy studies, somnolence, weakness, dizziness, and ataxia occurred less often with lamotrigine than with carbamazepine or phenytoin, whereas insomnia was slightly more frequent with lamotrigine. Withdrawals due to adverse events were fewer with lamotrigine than with the other drugs. Rash associated with lamotrigine typically occurred within the first 8 weeks. Exceeding the currently recommended slow dosage escalation guidelines and co-administration of valproate are risk factors for rashes. In adults, the incidence of Stevens–Johnson syndrome was approximately 1:1000, but higher rates (1 in 50 to 1 in 300) have been reported in children (SEDA-22, 89).

In a multicenter, double-blind, monotherapy trial in 150 elderly patients with newly diagnosed epilepsy (mean age 77 years) lamotrigine (median dosage 100 mg/day) was better tolerated than carbamazepine (400 mg/day) (14). The drop-out rate for adverse events was 18% with lamotrigine compared with 42% with carbamazepine. Patients taking lamotrigine had a lower incidence of skin rashes (3 versus 19%), somnolence (12 versus 29%), and dizziness (10 versus 17%). Lamotrigine may be a better choice for initial treatment in elderly people, although the toxicity of carbamazepine might have been overestimated by giving a non-modified-release formulation twice daily. Seizure control was comparable with the two drugs, but statistical power was insufficient to demonstrate equal efficacy.

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In 126 patients with carbamazepine-resistant or valproate-resistant epilepsy given lamotrigine, 50% during add-on therapy and 53% during lamotrigine monotherapy had at least 50% reduction in total seizures (15). There were adverse events in 49 patients, including respiratory tract infections ($n = 11$), dizziness ($n = 8$), headache ($n = 7$), diplopia ($n = 5$), tremor ($n = 5$), somnolence ($n = 4$), insomnia ($n = 4$), nausea ($n = 4$), and weakness ($n = 3$). Treatment was discontinued in nine patients because of adverse events, in five cases because of rash.

Cognitive adverse effects of lamotrigine and valproate have been compared in a double-blind, randomized, placebo-controlled study in 30 healthy volunteers who took lamotrigine 50 mg, valproic acid 900 mg, or placebo for 12 days (16). Lamotrigine had a relatively good cognitive profile but no different from that of valproic acid at the doses tested. Lamotrigine was associated with a selective general psychostimulant effect. As this study was performed in healthy volunteers taking a low dose, and conducted over a very short time, its conclusions are not generalizable to patients with epilepsy taking long-term treatment.

In a double-blind comparison of gabapentin and lamotrigine in 309 patients with new-onset partial or generalized seizures, the target doses were gabapentin 1800 mg/day and lamotrigine 150 mg/day (17). Severe adverse events were reported in 11% of patients taking gabapentin and 9.3% of patients taking lamotrigine. Two patients had serious adverse events thought to be related to the study drug; one took an overdose of gabapentin and the other had convulsions with lamotrigine. The most frequent treatment-related adverse events in both treatment groups were dizziness, weakness, and headache; 11% of patients taking gabapentin and 15% of those taking lamotrigine withdrew because of adverse events. There was an increase of over 7% in body weight from baseline in 14% of the patients taking gabapentin and 6.6% of those taking lamotrigine. There were benign skin rashes in 4.4% of those taking gabapentin and 11% of those taking lamotrigine.

Placebo-controlled studies

Lamotrigine has been used as maintenance monotherapy for rapid-cycling bipolar disorder in 324 patients (open label) and 182 patients (double-blind) with rapid-cycling bipolar disorder (5). In all, 265 patients reported adverse events during the open phase. The most common adverse events (over 10%) were headache, infection, influenza, nausea, abnormal dreams, dizziness, and rash. During the double-blind phase 122 patients reported adverse events, equally with lamotrigine and placebo.

The analgesic efficacy of lamotrigine in painful HIV-associated distal sensory polyneuropathy has been studied, given anecdotal reports of its efficacy, in a randomized, double-blind, placebo-controlled study (18). Of 42 subjects, 13 did not complete the 14-week study. Of those who took lamotrigine five dropped out because of rashes and one because of a gastrointestinal infection. The rashes were mild or moderate morbilliform rashes and resolved after withdrawal.

Organs and Systems

Nervous system

The most common adverse effects of lamotrigine include dizziness, weakness, headache, diplopia, ataxia, blurred vision, and somnolence (SEDA-18, 65) (SEDA-20, 63) (19). These effects resemble those seen with carbamazepine and can result from an adverse pharmacodynamic interaction. Tolerability is better when lamotrigine is given as monotherapy or with drugs other than carbamazepine; however, tremor develops in some patients taking valproate in combinations (SEDA-18, 66). During monotherapy, serum lamotrigine concentrations associated with intolerable adverse effects (mostly headache, dizziness, and ataxia) were 0.4–18.5 μg/ml and overlapped widely with those tolerated in other patients (20).

Irritability and aggressive behavior occur occasionally, and mentally retarded patients are possibly at greater risk (SEDA-22, 88). Rare central nervous system effects include insomnia, psychosis (SEDA-20, 63), downbeat nystagmus (SEDA-22, 89), movement disorders (SEDA-21, 72), and a Tourette-like syndrome. Lamotrigine can increase seizure frequency and severity in children with severe myoclonic epilepsy (SEDA-21, 72).

- A 47-year-old man developed a rash, fever, and rigors after taking lamotrigine (50 mg/day at maintenance) for 1 month (21). The reaction subsided after withdrawal, but 3 days later he complained of left shoulder pain and numbness in the left arm. The pain worsened over the next 3 weeks and then subsided. Thereafter, he developed weakness of the left arm with muscle wasting and signs of denervation in the biceps, infraspinatus, and supraspinatus. The condition was diagnosed as neuralgic amyotrophy. Almost complete recovery occurred over 8 months.

It is possible that the initial hypersensitivity reaction in this case determined focal neuronal involvement at the brachial plexus.

Worsening seizures

In a multicenter study, lamotrigine aggravated seizures in children with severe myoclonic epilepsy (22). Of 21 patients with severe myoclonic epilepsy given lamotrigine in dosages of 2.5–12.5 mg/kg/day, seizures were worsened in 17. The frequency of convulsive seizures increased by more than 50% in eight of 20 patients and myoclonic seizures worsened in six of 18. Of five patients who improved in at least one seizure type, four had concomitant worsening of more incapacitating seizures. The drug was withdrawn in 19 patients, with consequent improvement in 18. These findings suggest that lamotrigine is inappropriate in severe myoclonic epilepsy.

Paradoxical seizure aggravation may occur in other types of epilepsy.

- In a 5-year-old girl with benign rolandic epilepsy, the addition of lamotrigine (0.5–5 mg/kg/day) to valproate resulted in a temporary reduction in seizure frequency (23). However, her school performance deteriorated insidiously, with poor memory and concentration, clumsiness, stuttering, and emotional lability. After 4 months she developed new daily brief absence-like episodes,

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with staring, dropping of the head and jaw, and flickering of the eyelids, without loss of consciousness. Ictal electroencephalography showed anterior-predominant 3 Hz sharp slow wave complexes. Withdrawal of lamotrigine resulted in rapid improvement of cognitive function and gradual remission of the new attacks.

- A 9-year-old girl with Lennox–Gastaut syndrome, who had initially had an improvement in seizure frequency, insidiously developed myoclonic status epilepticus after the lamotrigine dosage was increased from 15 to 20 mg/kg (24). Withdrawal of lamotrigine resulted in rapid disappearance of status.
- Two patients (age unspecified) with severe epileptic encephalopathy who had improved on lamotrigine in combination with valproate developed continuous myoclonic jerks after 2–3 years; these were ascribed to high serum concentrations of lamotrigine (65 and 69 μmol/l) (25).

In the last report, the causative role of the drug is difficult to assess, because no mention was made of whether myoclonus regressed after reducing the dosage.

Sleep disorders

Insomnia is a recognized adverse effect of lamotrigine. Among 109 patients treated with lamotrigine in an adult tertiary referral center, 7 had insomnia of sufficient severity to require a change of therapy (26). The symptom occurred shortly after the start of treatment, was dose-dependent, and resolved after withdrawal or dosage reduction. Unlike previous reports, in which insomnia occurred in patients with impaired cognition, no predisposing factor could be identified.

In another report, two boys aged 6 and 8 years developed severe difficulties in falling asleep and fragmented sleep (in one case associated with scary dreams) after being stabilized on lamotrigine, 8 mg/kg (27). These disturbances improved when the dosage was reduced.

Tics

Tics are a rare adverse effect of lamotrigine.

- Three boys and two girls (mean age 7 years) developed simple motor tics (associated with verbal tics in two cases) within 10 months of starting lamotrigine (maintenance dosage 4–18 mg/kg) (28). When lamotrigine was withdrawn, the tics resolved within 3 months in three cases (with recurrence after rechallenge in one child) and improved in one. In the fifth child, improvement occurred despite continuation of treatment. Two of the affected patients had acquired epileptic aphasia syndrome, one had expressive and receptive language dysfunction, one had a static encephalopathy, and one had no mental or neurological impairment.

These data suggest that children with severe language dysfunction may be at increased risk of developing lamotrigine-induced tics.

- A 51-year-old man developed blepharospasm 4 months after starting lamotrigine, while taking a maintenance dosage of 500 mg/day (29). The condition cleared 4 weeks after withdrawal.
- Lamotrigine (250–324 mg/day) caused Tourette syndrome in three children aged 7, 8, and 12 years; in the 12-year-old boy, the syndrome was accompanied by behavioral abnormalities suggestive of obsessive-compulsive disorder (30). All the symptoms disappeared when the dosage was reduced to 175–225 mg/day and recurred on rechallenge with higher dosages.
- Two young men (aged 18 and 22 years) with epilepsy had disabling myoclonic jerks after taking lamotrigine after 2–3 years of therapy when their plasma lamotrigine concentrations rose to about 70 μmol/l (31).
- A retrospective survey yielded five cases of tics in three men and two women aged 2.5–12 years) within the first 10 months of therapy (4–17 mg/kg/day) (32). Four had simple motor tics and one had mostly vocal tics (gasping sounds) with normal laryngoscopic evaluation. In three cases the tics resolved completely within 1 month of drug withdrawal and recurred in two after reintroduction. A fourth had gradual improvement over 4 months after withdrawal; in the fifth, simple motor tics improved spontaneously with a reduction in dose.

Psychological, psychiatric

The cognitive and behavioral effects of lamotrigine 150 mg/day have been compared with those of carbamazepine 696 mg/day in 25 healthy adults in a double-blind, crossover, randomized study with two 10-week treatment periods (33). Lamotrigine had significantly fewer cognitive and behavioral adverse effects than carbamazepine, and 48% of the variables favored lamotrigine. The differences encompassed cognitive speed, memory, graphomotor coding, neurotoxic symptoms, mood, sedation, perception of cognitive performance, and other quality-of-life perceptions. The cognitive and behavioral changes favored lamotrigine over carbamazepine, but the magnitude of the observed effects was modest, although it could be relevant in some patients.

Endocrine

In two children with cranial diabetes insipidus, desmopressin requirements fell while they were taking lamotrigine (34). Lamotrigine may act at voltage-sensitive sodium channels and reduce calcium conductance. Both of these mechanisms of action are shared by carbamazepine, which can cause hyponatremia secondary to inappropriate secretion of antidiuretic hormone.

Metabolism

In a prospective evaluation of the effect of lamotrigine 3.5–14.2 mg/kg on growth in 103 children and adolescents aged 1.6–16 years with epilepsy treated with lamotrigine monotherapy for 6–71 months, the children had normal growth, although the study had several methodological shortcomings (35).

Hematologic

Aplastic anemia occurred in one patient who had recovered 7 years earlier from bone-marrow aplasia ascribed to carbamazepine (SEDA-20, 63). Severe pure red cell aplasia in a patient with heterozygous beta-thalassemia reversed rapidly after lamotrigine withdrawal; however,

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lamotrigine did not affect hematology parameters in another patient with the same condition (SEDA-20, 64). In two other cases of anemia associated with increased platelet counts the role of lamotrigine could not be ascertained (SEDA-22, 89).

There have been a few reports of leukopenia or neutropenia, and one case of septic shock secondary to leukopenia possibly due to lamotrigine (SEDA-20, 64).

- An 11-year-old girl with congenital left renal agenesis, epilepsy from cortical dysgenesis, and chronic hepatitis B and C, developed a skin rash and agranulocytosis (white cell count 3.1×10^9/l, lymphocytes 92%, and monocytes 8%) 15–20 days after starting to take lamotrigine (36). She recovered rapidly after drug withdrawal.

An inappropriately high starting dose (50 mg/day) may have contributed to this reaction.

Lamotrigine has been associated with agranulocytosis (37).

- A 59-year-old woman, with seizures after resection of a low-grade glioma, chemotherapy, and radiotherapy 2 years before, took lamotrigine 300 mg/day for 9 weeks and developed an agranulocytosis. The lamotrigine serum concentration was 2.2 μg/ml (usual target range 1–15 μg/ml). A bone marrow biopsy showed a hypocellular marrow with reduced myelopoiesis, a shift to the left, and normal cytogenetics. Over the next few days she developed a fever but no infection. She recovered after 10 days, having been given granulocyte-colony-stimulating factor and prophylactic antibiotics for 7 days.
- A 29-year-old woman with Blackfan–Diamond anemia developed an erythroblastopenic crisis after taking phenytoin on two separate occasions and then again after taking lamotrigine (38). The proposed mechanism was inhibition of dihydrofolate reductase, and the crisis responded to treatment with folinic acid. Lamotrigine was then continued without ill effect.
- Reversible agranulocytosis developed in a 30-year-old woman who had taken lamotrigine 100 mg/day for 6 weeks and valproate 250 mg/day for 2 weeks (39). Her white cell count fell from 6.7×10^9/l at 4 weeks to 2.6×10^9/l at 6 weeks and the absolute neutrophil count was 580×10^6/l. The white cell count recovered after withdrawal of lamotrigine; the valproate was continued.

Liver

Liver toxicity from lamotrigine is extremely rare. Acute hepatic necrosis occurred in the context of a hypersensitivity reaction that also involved the skin (SEDA-20, 64).

Four children developed reversible lamotrigine-associated hepatotoxicity (40). One had pre-existing encephalitis and the other three had multiple medical and neurological problems, fever and infections, were taking many other drugs, and had very frequent seizures; two had epilepsia partialis continua. The information given was insufficient to assess the role of lamotrigine in the pathogenesis of the hepatic dysfunction.

Reversible hepatotoxicity occurred in three children taking lamotrigine (41). In one there was severe hepatic failure. The liver abnormalities resolved after withdrawal.

Pancreas

Pancreatitis was reported in a 26-year-old man who had taken lamotrigine for 5 months, but cause and effect was dubious (SEDA-19, 61).

Skin

The rates of lamotrigine-related rash have been analysed from 12 multicenter studies of bipolar depression in 1955 patients taking open-label lamotrigine, 1198 taking lamotrigine in controlled studies, and 1056 taking placebo (42). In controlled studies, the rates of benign rash were 8.3% for lamotrigine and 6.4% for placebo. There were no serious rashes. In the open studies 13% ($n = 257$) had rashes with lamotrigine and one was reported as a mild form of Stevens–Johnson syndrome that did not require hospitalization. Thus, the risk of severe allergic rashes with lamotrigine is low, provided that there is a low initial dose and slow upward titration.

A rash, usually urticarial or maculopapular, is the most common event leading to early withdrawal of lamotrigine. In add-on trials, rashes occurred in up to 15% of patients and led to withdrawal in 2%. Six patients who developed a rash with lamotrigine later had similar rashes after exposure to structurally unrelated anticonvulsants, such as phenytoin and barbiturates (SEDA-22, 89). In 12 patients with probable Alzheimer's disease and seizures and 16 with other neurological disorders, lamotrigine caused three cases of mild rashes (43).

Published and unpublished cases of Stevens–Johnson syndrome ($n = 43$) and toxic epidermal necrolysis ($n = 14$) associated with lamotrigine have been reviewed (44). The patients with Stevens–Johnson syndrome were younger than those with toxic epidermal necrolysis (21 versus 31 years); the median time to onset for both reactions was 17 days; the median dosage at onset (50 mg for Stevens–Johnson syndrome, 87.5 mg for toxic epidermal necrolysis) did not differ significantly. Valproate comedication was present in 74% and 64% of patients with Stevens–Johnson syndrome and toxic epidermal necrolysis respectively. In three patients, toxic epidermal necrolysis occurred in the context of the anticonvulsant hypersensitivity syndrome.

An expert panel has reviewed published and unpublished data on the incidence and risk factors for lamotrigine-induced rash (45). An allergic skin rash occurs in about 10% of patients, usually in the first 8 weeks. In clinical trials, the incidence of rashes leading to hospitalization, including those associated with hypersensitivity syndrome, was about 1:300 in adults (one third as Stevens–Johnson syndrome) and 1:100 in children (50% as Stevens–Johnson syndrome). The risk increased with excessively rapid dosage titration and in patients comedicated with valproate. Up to March 1997, the manufacturer had received a total of 150 postmarketing reports of possible cases of Stevens–Johnson syndrome or toxic epidermal necrolysis, and 46 of these were in children aged 12 years or under. Of the 46 children, three were reported as having toxic epidermal necrolysis, 40 as

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Stevens–Johnson syndrome, and 3 as suggestive of Stevens–Johnson syndrome; two deaths were reported. Rashes associated with one or more symptoms of hypersensitivity reactions occurred in 19 children. Of 29 patients with Stevens–Johnson syndrome, toxic epidermal necrolysis, or hypersensitivity reactions, for whom precise details were available, 83% were taking lamotrigine with concomitant valproate and 85% were taking lamotrigine dosages higher than recommended.

- A 33-year-old woman, who had taken valproate for 3 years, developed Stevens–Johnson syndrome soon after starting to take lamotrigine 150 mg/day (46). Lamotrigine was withdrawn and prednisolone given; the signs and symptoms progressively resolved over 10 days.

Although serious skin rashes have been reported with traditional anticonvulsants, the risk of Stevens–Johnson syndrome and toxic epidermal necrolysis with these drugs appears to be lower than with lamotrigine. Data from the Saskatchewan Health Plan suggest that the risk of serious rashes is in the order of 0.9:1000 (1.4:1000 in children) for phenytoin, 0.6:1000 (1.4:1000 in children) for carbamazepine, and 0:1000 for valproate, but Stevens–Johnson syndrome constituted only a small minority of these cases (47).

The panel agreed on the following conclusions

(1) most skin rashes from lamotrigine are benign and resolve on withdrawal;
(2) serious skin rashes occur almost entirely during the first 8 weeks and increased vigilance is recommended during this period;
(3) death from skin rashes is extremely rare (under 10 known cases);
(4) a mild rash can progress to a severe rash or to systemic involvement; fever, lymphadenopathy, facial edema, vomiting, or raised liver enzymes may indicate a hypersensitivity reaction and can precede the appearance of a rash;
(5) the following features suggest the development of a serious rash: mucous membrane lesions, blistering or peeling, facial edema, lymphadenopathy, raised liver enzymes, and leukopenia or thrombocytopenia;
(6) the risk of a rash, and possibly also serious rashes, is increased with excessive initial dosages or too fast rates of titration, combination with valproic acid (particularly in the absence of enzyme-inducing drugs), and possibly a history of skin or allergic reactions to another anticonvulsant; physicians should follow dosing instructions carefully, and be aware that dosing varies according to whether lamotrigine is added to valproate, an enzyme-inducing antiepileptic drug (such as phenytoin), or both, or is used as monotherapy;
(7) potential risks and benefits should be discussed with the patient, who should be informed about symptoms suggestive of hypersensitivity;
(8) if a rash appears, the patient should be seen by a physician within 24 hours and, if necessary, a specialist opinion should be sought; suspected cases of Stevens–Johnson syndrome and toxic epidermal necrolysis should be hospitalized for specialist care;
(9) blood chemistry and hematology may be useful to detect systemic involvement;
(10) if no alternative explanation exists, the rash should be presumed to be due to lamotrigine and the drug should be withdrawn; in patients with a rash nontypical of drug-induced rashes, lamotrigine can be continued cautiously under close monitoring if its use is deemed essential.

Fast dose escalation rate and co-administration of valproate are the most important risk factors for skin reactions. Patients should be warned to report immediately any sign of hypersensitivity, such as rash, fever, or lymphadenopathy. In selected patients who have experienced a mild rash, rechallenge with lower initial doses and slower escalation can be attempted under close supervision (48), but this should be done only when the drug is absolutely necessary, owing to the risk of serious reactions. For adults taking valproate (with or without other anticonvulsants), the dose escalation rate currently recommended by the manufacturer is 25 mg on alternate days during weeks 1 and 2, followed by 25 mg daily during weeks 3 and 4, with further increments by 25–50 mg every 1–2 weeks up to the usual maintenance dose of 100–200 mg/day (Europe) or 100–400 mg/day (USA) (49). For adults taking enzyme inducers without valproate, the escalation rate is 50 mg/day during weeks 1 and 2 followed by 50 mg bd during weeks 3 and 4, with further increments by 100 mg daily every 1–2 weeks up to the usual maintenance dose of 200–400 mg/day (Europe) or 300–500 mg/day (USA). For children aged 2–12 years, starting dosages are 0.15 mg/kg/day in the presence of valproate and 0.3 mg/kg bd in the presence of enzyme inducers without valproate (50).

Data on skin reactions from the German registry have confirmed that the risk of serious rashes is reduced by slower dose escalation (51). In 1993 there were five cases of Stevens–Johnson syndrome or toxic epidermal necrolysis, all in patients who were also taking valproate, among 1270 new patients taking lamotrigine, that is one per 254 recipients. After the recommended starting dose with valproate was reduced by a factor of four, the rates of Stevens–Johnson syndrome or toxic epidermal necrolysis fell to two of 15 500 recipients in 1994 and two of 34 700 recipients in 1995. However, this apparent change in incidence could have been explained in part by additional factors, such as greater risk awareness and consequent more cautious use of the drug, prompter withdrawal at first appearance of a rash and possibly changes in ascertainment rates.

Safe reintroduction of lamotrigine proved possible in seven young people (aged 5–19 years) who had previously had a mild rash associated with a first course (52). The lamotrigine was withdrawn immediately when the rash was identified and was subsequently reintroduced after 47–236 days using a slow escalation regimen, starting with 0.1 mg/day. Lamotrigine was successfully reintroduced without recurrence of persistent rash and without any adverse effects in all seven cases.

Hair, nails, sweat glands

Hair loss and hirsutism have been reported rarely with lamotrigine (SEDA-18, 66) (SEDA-19, 71).

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Sexual function

- A 37-year-old schizoaffective woman taking lamotrigine monotherapy developed loss of libido and an unpleasant feeling when her erogenous zones were touched when the dosage of lamotrigine was increased from 200 to 400 mg/day (53). Surprisingly, no attempt was made to determine whether the condition could be reversed by lowering the dosage.

The authors speculated that this effect could have been related to inhibition of serotonin reuptake by lamotrigine.

Immunologic

A phenytoin-like hypersensitivity syndrome with skin rash, leukocytosis, and laboratory evidence of liver and kidney dysfunction has been attributed to lamotrigine (SEDA-22, 89).

Twenty-six lamotrigine-associated reactions consistent with the features of the anticonvulsant hypersensitivity syndrome have been reviewed, including nine previously published (54). The patients were aged 3.5–74 (mean 28) years and 14 were female. Valproate was used as comedication in 60%. Fever was present in all patients, a skin rash in 77% (with Stevens–Johnson syndrome or toxic epidermal necrolysis in five cases), hematological abnormalities in 69% (including eosinophilia in 19%), liver abnormalities in 65%, renal involvement in 23%, disseminated intravascular coagulation in 15%, and musculoskeletal disorders in 8%. Multiorgan involvement was present in 46%. One patient died. Overall, the characteristics of the syndrome were comparable to that induced by aromatic anticonvulsants, except for a somewhat higher incidence of severe skin rashes and a lower frequency of eosinophilia and lymphadenopathy.

- A 35-year-old man with Lennox–Gastaut syndrome developed tender cervical lymphadenopathy 14 weeks after lamotrigine was introduced, when the dosage was increased to 200 mg/day (55). Frozen section examination of a biopsy specimen 10 weeks later suggested lymphoma, but further histopathological investigations documented lymphoid hyperplasia consistent with a diagnosis of pseudolymphoma, which resolved 1 month after withdrawal.

This seems to have been the first report of pseudolymphoma associated with lamotrigine.

Systemic hypersensitivity reactions to lamotrigine can be severe.

- A 27-year-old woman developed disseminated intravascular coagulation, fever, rash, and hepatic dysfunction 11 days after starting lamotrigine (56). The drug dosage was not stated.
- A 17-year-old girl with a history of bipolar disorder developed fever, lymphadenopathy, skin rash, diarrhea, and acute renal insufficiency requiring dialysis after taking lamotrigine for 4 weeks (57). Renal biopsy showed acute interstitial nephritis with focal granulomas; colonic biopsy showed colitis and ileitis with non-necrotizing epithelioid granulomas.
- Severe hypersensitivity affecting the skin, lymph nodes, and liver has been reported with lamotrigine in a 36-year-old man, who had taken high doses of sodium valproate and lamotrigine for about a month (58). Skin tests were negative with both drugs, but lymphocyte stimulation tests were twice positive with lamotrigine. Later re-exposure to sodium valproate was tolerated.

Drug-induced lupus-like syndrome has been associated with lamotrigine (59).

- A 57-year-old woman, who had taken lamotrigine 2 mg/kg/day for about 2 years developed arthralgia affecting the small joints of the hands, wrists, and knees, an erythematous skin rash, myalgia, and Raynaud's phenomenon. Serum antinuclear antibodies were positive (1:320, speckled pattern), as was anti-Ro/SSA. Rheumatoid factor and anticardiolipin antibodies were negative and serum complement was normal. Lamotrigine was withdrawn and the symptoms and abnormal tests gradually normalized.

Multiorgan failure

Multiorgan failure and disseminated intravascular coagulation have been described occasionally with lamotrigine. Although these were originally considered to be secondary to seizure activity and not to lamotrigine itself (SEDA-13, 154), in at least three recent cases the drug was probably implicated (SEDA-20, 64) (60). In two affected children the presentation included fever, rash, hepatic and renal dysfunction, hypoalbuminemia, intravascular coagulation, and changes in alertness.

Death

Sudden unexplained death in epileptic patients taking lamotrigine has been considered to be related to the underlying disease and not to its treatment (SEDA-21, 72).

Long-Term Effects

Drug withdrawal

Psychomotor inhibition after rapid withdrawal of lamotrigine has been reported (61).

- A 26-year-old man with refractory generalized seizures had taken lamotrigine since the age of 22. At age 26, during presurgical evaluation with video-electroencephalography, lamotrigine was withdrawn and valproic acid 1200 mg/day and levetiracetam 1000 mg/day were continued. After 5 days he became anhedonic and had hyperhidrosis of the hands. He claimed that he had the impression that he was floating or that he was drunk. He had visual hallucinations, with stars in both visual fields, but no diplopia. He had a tremor and a slight tachycardia. Biological and toxicological results were unremarkable. An electroencephalogram ruled out status epilepticus.

The interpretation of this case is confounded by the use of levetiracetam at the onset of the symptoms. In addition, his symptoms appeared just after an admission for video-electroencephalography, during which he suffered at least one generalized tonic-clonic seizure. Thus, his symptoms could have been a mild form of postictal psychosis.

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Second-Generation Effects

Pregnancy

Plasma lamotrigine concentrations in one woman fell during pregnancy and increased about six-fold after delivery; such changes could affect the clinical outcome (62).

Changes in lamotrigine clearance before, during, and after pregnancy were retrospectively analysed in 12 pregnancies (63). There was a significant (over 65%) increase in apparent clearance between preconception and the second and third trimesters. In 11 pregnancies higher doses of lamotrigine were required to maintain therapeutic concentrations. In the postpartum period, apparent clearance returned to the preconception baseline, and lamotrigine doses had to be reduced.

Teratogenicity

There were birth defects in eight of 123 offspring exposed to lamotrigine polypharmacy during the first trimester of pregnancy (95% CI = 3, 13%) and in none of 40 exposed to monotherapy (CI = 0, 11%) (64). The wide confidence intervals indicate that sample size was not sufficiently large to determine whether lamotrigine has a lower teratogenic risk than other anticonvulsants.

The results of a prospective study on the outcomes in pregnant women exposed to lamotrigine have been published (65). The report included 168 outcomes in women exposed to lamotrigine monotherapy and 166 after pregnancies exposed to lamotrigine polytherapy during the first trimester. Three of 168 neonates (1.8%) exposed to lamotrigine monotherapy had major birth defects (95% CI = 0.5, 5.5%). There were five major birth defects in 50 neonates (10%) after lamotrigine polytherapy with valproic acid during the first trimester (95% CI = 3.7, 23%). The proportion of major defects on exposure to lamotrigine polytherapy without valproate during the first trimester was 5 of 116 (4.3%) (95% CI = 1.6, 10%). There were no specific patterns of major birth defects in any subgroup or within the register as a whole. Thus, it appears that lamotrigine-exposed women have a relatively low frequency of major birth defects and that the combination of lamotrigine and valproic acid could potentially be especially detrimental in this respect. However, the wide confidence intervals preclude a firm conclusion. Moreover, there were several methodological limitations to this study, such as lack of standardization in outcome ascertainment and other potential sources of bias.

Fetotoxicity

The outcomes of pregnancy in 53 women exposed to lamotrigine included 4 spontaneous abortions, 13 induced abortions (none because of a prenatally detected defect), 34 newborns without birth defects, and 2 newborns with unspecified defects (66). No information on co-medication was given, and more data are required for risk assessment.

Lactation

The breast milk to plasma lamotrigine concentration ratio is about 0.6, and in breast-fed infants serum drug concentrations reach about 30% of maternal concentrations. Although no toxicity has been reported in these infants, close observation is warranted (SEDA-22, 88) (62).

Susceptibility Factors

Age

In adults, the incidence of Stevens–Johnson syndrome was approximately 1:1000, but higher rates (1 in 50 to 1 in 300) have been reported in children (SEDA-22, 89).

The effects of lamotrigine in children have been reviewed (67). Its efficacy has been demonstrated in 13 studies in 1096 children with a variety of seizure types. Generally, lamotrigine treatment in these trials was at higher initial doses and faster dose escalations than are currently recommended. Most adverse events associated with lamotrigine were mild to moderate and did not result in withdrawal. In placebo-controlled, add-on trials 85% of those who took lamotrigine had an adverse event compared with 83% of those who took placebo. Lamotrigine was associated with an increased risk of adverse events in the nervous system (dizziness, tremor, ataxia, and diplopia), gastrointestinal tract (nausea), and urinary tract (infection). Skin rash was reported more often with lamotrigine than placebo and more often by children than by adults.

Other features of the patient

Exceeding the currently recommended slow dosage escalation guidelines and co-administration of valproate are risk factors for rashes.

Drug Administration

Drug overdose

The effects of overdosage of lamotrigine include sedation, ataxia, diplopia, nausea, vomiting, hypertonia, nystagmus, and prolongation of the QRS complex (SEDA-18, 66). Cardiac rhythm should be monitored. Multiple oral dosing with activated charcoal enhances lamotrigine elimination, but its value in overdose is unknown.

The manifestations of acute lamotrigine overdose can mimic the anticonvulsant hypersensitivity syndrome (68).

- A 49-year-old man with bipolar disorder inadvertently took four daily doses of lamotrigine 2700 mg each. He developed a low-grade fever, a skin rash, and periorbital edema. He had a leukocytosis, raised liver enzymes, and acute renal insufficiency. He recovered fully after lamotrigine withdrawal and steroid therapy.

Postmortem blood and tissue concentrations of lamotrigine have been reported in a case of suicide attributed to "mixed drug toxicity" with carbamazepine, lamotrigine, paroxetine, and thioridazine (69). The blood lamotrigine concentration was 155 μmol/l. Two other individuals with high postmortem blood lamotrigine concentrations, who did not die of an overdose, were also taking valproate.

Severe encephalopathy due to lamotrigine overdose has been reported (70).

- A 55-year-old woman taking lamotrigine and valproate for partial epilepsy took an overdose of lamotrigine and

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became stuporose. A CT scan was unremarkable and the cerebrospinal fluid was normal. Electroencephalography showed generalized slowing without epileptiform activity. The serum valproate concentration was 65 μg/ml and the lamotrigine concentration 32 μg/ml. A toxicology screen was negative. Lamotrigine was withheld and she remained unresponsive for 3 days, when she awoke disoriented. On day 5 she was alert and fully oriented (serum lamotrigine 15 μg/ml).

Drug–Drug Interactions

Carbamazepine

The effects of other antiepileptic drugs on the pharmacokinetics of lamotrigine have been studied in 62 patients with epilepsy (71). Carbamazepine, phenytoin, and phenobarbital, all enzyme inducers, increased the oral clearance of lamotrigine, individually by 58% and in combination by nearly 200%.

The time-course of de-induction following the step-wise withdrawal of carbamazepine in patients treated concomitantly with lamotrigine has been analysed (72). This study was part of an active-control, monotherapy trial. Patients taking carbamazepine were given lamotrigine to attain a target dose of 500 mg/day, while carbamazepine was withdrawn in weekly 20% decrements. After withdrawal, lamotrigine was continued as monotherapy for a further 12 weeks. Of 156 patients, 76 were assigned to lamotrigine, 43 of them completed the withdrawal to monotherapy, and 28 of these 43 successfully completed the study. In a subset analysis of completers, lamotrigine concentration increased by 62% in those who had taken carbamazepine. These differences were significantly different and occurred when carbamazepine plasma concentrations were very low or undetectable.

Cimetidine

The effect of cimetidine on the pharmacokinetics of lamotrigine has been studied in 10 healthy men (73). Cimetidine had no effect on the pharmacokinetics of lamotrigine.

Ketamine

Because some of the cognitive effects of ketamine may be mediated through increased glutamate release, lamotrigine, which inhibits glutamate release, has been used to reduce the neuropsychiatric effects of ketamine in 16 healthy subjects (74). Lamotrigine significantly reduced ketamine-induced perceptual abnormalities and increased its immediate mood-elevating effects.

Lithium

The effect of lamotrigine on steady-state lithium pharmacokinetics has been studied in 20 healthy adult men (75). Lamotrigine did not significantly change the pharmacokinetics of lithium.

Methsuximide

The interaction of methsuximide with lamotrigine has been studied in 16 patients aged 9–19 years with a variety of seizure types and syndromes (76). The mean lamotrigine serum concentration before starting or after stopping methsuximide was 54 μmol/l and the mean concentration while taking methsuximide was 25 μmol/l. Methsuximide lowered the serum lamotrigine concentration in every case, with a mean fall of 53% (range 36–72%). In some patients this led to a deterioration in seizure control when methsuximide was added or an improvement in seizure control after methsuximide was withdrawn. The mechanism is thought to be induction of metabolism.

Oral contraceptives

Plasma concentrations of lamotrigine were reduced in seven women taking an oral contraceptive (mean reduction 49%, range 41–64%), probably through induction of glucuronide conjugating enzymes (77).

Phenobarbital

The effects of other antiepileptic drugs on the pharmacokinetics of lamotrigine have been studied in 62 patients with epilepsy (71). Carbamazepine, phenytoin, and phenobarbital, all enzyme inducers, increased the oral clearance of lamotrigine, individually by 58% and in combination by nearly 200%.

Phenytoin

The effects of other antiepileptic drugs on the pharmacokinetics of lamotrigine have been studied in 62 patients with epilepsy (71). Carbamazepine, phenytoin, and phenobarbital, all enzyme inducers, increased the total oral clearance of lamotrigine, individually by 58% and in combination by nearly 200%.

Choreoathetosis is a rare adverse effect of some anticonvulsants, but has especially been associated with phenytoin. In a retrospective survey, three of 39 adults and one of 38 children developed choreoathetosis acutely when lamotrigine was added to phenytoin or vice versa (78). The effect was reversible by withdrawing one of the drugs. It was calculated that the risk of choreoathetosis is increased more than 50-fold when these drugs are combined, possibly owing to a pharmacodynamic interaction.

The time-course of de-induction following the step-wise withdrawal of phenytoin in patients treated concomitantly with lamotrigine has been analysed (72). This study was part of an active-control, monotherapy trial. Patients taking phenytoin were given lamotrigine to attain a target dose of 500 mg/day, while phenytoin was withdrawn in weekly 20% decrements. After withdrawal, lamotrigine was continued as monotherapy for a further 12 weeks. Of 156 patients, 76 were assigned to lamotrigine, 43 of them completed the withdrawal to monotherapy, and 28 of these 43 successfully completed the study. In a subset analysis of completers, lamotrigine concentration increased by 160% in patients who had previously taken phenytoin. These differences were significantly different and occurred when phenytoin plasma concentrations were very low or undetectable.

Rifampicin

The effects of rifampicin on the pharmacokinetics of lamotrigine have been studied in 10 healthy men (73).

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Rifampicin induced the glucuronidation of lamotrigine, increasing total clearance about two-fold.

Valproate

Effects of valproate on lamotrigine

Co-administration of valproate is one of the most important risk factors for skin reactions to lamotrigine; valproate co-medication was present in 74 and 64% of patients with Stevens–Johnson syndrome and toxic epidermal necrolysis respectively (44).

Valproate reduced the oral clearance of lamotrigine by about 70%, but the effect was not related to the concentration of valproate (hence the rather misleading title of the paper, that is there was an effect but it did not appear to be concentration-related) (71). There was no effect on lamotrigine clearance when a single enzyme inducer was combined with valproate, but combinations of enzyme inducers had almost the same effect in the presence or absence of valproate. Consistent with this result, it has also been shown that the effect of valproate on the clearance of lamotrigine is independent of valproate dose and steady-state concentration in 28 patients with intractable epilepsy (79). However, in contrast to these findings, there were good relations between the dose of valproate 200–1000 mg/day and the increase in lamotrigine AUC and the prolongation of half-life in eight patients with epilepsy (80).

Twenty-six lamotrigine-associated reactions consistent with the features of the anticonvulsant hypersensitivity syndrome have been reviewed, including nine previously published (54). The patients were aged 3.5–74 years (mean 28) and 14 were female. Valproate was used as co-medication in 60%.

Effects of lamotrigine on valproate

In a study of 400 serum concentrations from 372 patients taking lamotrigine and valproic acid, lamotrigine was associated with a slight reduction in valproate serum concentrations (81). However, the size of the effect was probably of no clinical significance.

Effects of the combination of lamotrigine with valproate

The tolerability of lamotrigine added to valproate has been assessed in 108 mostly adult patients (82). The median starting dose was 21 mg/day and upward titrations were usually made at 2-week intervals; although these were more cautious than in earlier studies, in many patients the initial dose or titration rate still exceeded those currently recommended by the manufacturer. Adverse events led to withdrawal in 14 patients, including seven of 14 who had a rash. Other adverse events included fatigue (12%), gastrointestinal symptoms (9%), dizziness, headache, and insomnia (3% each). Serious events were hallucinations (two patients), increased liver enzymes (two patients), irritability, and leukopenia (one patient each). These results suggest that, with cautious dosage escalation, lamotrigine can be added to valproate with acceptable safety. In this study, the incidence of rash was not higher than that seen among 310 patients in whom lamotrigine was added to other drug regimens not including valproate (13 versus 14%).

In an open prospective trial, patients with partial seizures who had not responded to lamotrigine or valproate given separately responded well to the combination; this was not due to an effect of valproate on serum lamotrigine concentrations, because after adjusting dosages based on clinical response the serum concentrations of both drugs were lower during combination therapy (83). Hand tremor developed in all 13 patients who took the combination, compared with three of 20 who took valproate without lamotrigine and none of 17 who took lamotrigine without valproate. These findings confirm that valproate plus lamotrigine is a valuable combination in patients unresponsive to either drug alone, partly because of a pharmacodynamic interaction. Patients co-medicated with valproate should be treated with a lower starting dose of lamotrigine and with slower dosage escalation to minimize the risk of a skin rash. Maintenance lamotrigine dosage requirements are also reduced by valproate co-medication. Although tremor is common, it can be maintained within acceptable limits by adjusting the dosage of either drug.

Diagnosis of Adverse Drug Reactions

The usual target range for plasma lamotrigine concentrations is 4–16 μmol/l (1–4 μg/ml).

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Lansoprazole

See also Proton pump inhibitors

General Information

Lansoprazole is a proton pump inhibitor. Its safety profile has been reviewed based on premarketing clinical studies, and has to be regarded with the reservations appropriate to this type of material. In 4749 patients the most frequent adverse effects were headache (4.7%), diarrhea (3.2%), abdominal pain (2.2%), pharyngitis (1.8%), and nausea (1.4%); some patients had upper respiratory complaints or suffered anxiety or depression, or myalgia (1). The adverse reaction profile appears to be closely similar to that of omeprazole.

Lansoprazole 15 and 30 mg/day were more effective than placebo, but not misoprostol 200 micrograms qds, for the prevention of NSAID-induced gastric ulcers in a multicenter, double-blind, placebo-controlled trial in 537 patients without *Helicobacter pylori* infection who were long-term users of NSAIDs (2). However, adverse effects were significantly more frequent (31% versus less than 20%) and treatment adherence significantly less (71% versus more than 90%) in patients taking misoprostol. The most commonly reported adverse effects in all groups were diarrhea, abdominal pain, and nausea.

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Drug–Drug Interactions

Roxithromycin

The effect of lansoprazole on roxithromycin concentrations in plasma and gastric tissue have been investigated in 12 healthy volunteers who took lansoprazole 30 mg bd with or without roxithromycin 300 mg bd over 6 days (3). The medications were well tolerated, with only mild adverse events. The more frequent adverse events were nausea, bloating, and diarrhea. Lansoprazole and roxithromycin did not alter the systemic availability of each other. However, lansoprazole increased the local concentration of the antibiotic in the stomach.

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Latanoprost

See also Prostaglandins

General Information

Latanoprost is an analogue of $PGF_{2\alpha}$, used to treat glaucoma. The use of latanoprost and unoprostone in the treatment of open-angle glaucoma and ocular hypertension has been reviewed (1). More data on safety are needed to calculate its benefit-to-harm balance.

Latanoprost caused reduced intraocular pressure by 20–40% in adults with open-angle glaucoma or ocular hypertension, but its efficacy and safety in children have not been widely reported. Most children reported so far gained little benefit on intraocular pressure from latanoprost, but older children and those with juvenile-onset open-angle glaucoma do gain a significant ocular hypotensive effect. Systemic and ocular adverse effects in children using latanoprost are infrequent (2).

Organs and Systems

Cardiovascular

Two patients in their seventies developed hypertension during treatment with topical latanoprost (dosage not stated) for open-angle glaucoma; both were also taking tocopherol (vitamin E) supplements. Neither had a previous history of hypertension (3). The authors commented that it is likely that systemic absorption of topical latanoprost could cause hypertension. Self-medication with vitamin E has been reported to aggravate or precipitate hypertension.

Respiratory

Latanoprost rarely causes systemic effects. However, it aggravated respiratory symptoms in a patient with chronic bronchitis and emphysema, with improvement after latanoprost was withdrawn (4).

Nervous system

Three cases of headache after latanoprost have been described (5).

- A 65-year-old man with primary open-angle glaucoma intolerant of dipivefrin and beta-blockers used latanoprost in both eyes at bedtime. He had no prior history of migraine, but he began to have headaches, the frequency and severity of which increased until they were occurring daily. The pain was not relieved by over-the-counter or narcotic analgesics, and he was virtually incapacitated. Latanoprost was discontinued and he had almost immediate relief, with only one migraine during the following week, and he was headache-free for the next 10 months. He then agreed to rechallenge. After the second night of latanoprost therapy his headache recurred, and therapy was withdrawn 2 days later when he had incapacitating pain. Headache did not recur within 4 months of follow-up.
- A 65-year-old man with primary open-angle glaucoma, using levobunolol hydrochloride 0.5%, was given a nighttime dose of latanoprost. The next morning he awoke with a severe bifrontal throbbing headache, photophobia, and slight blurring of vision. The headache intensified, and 4 days later a CT scan was normal. On the sixth day he stopped using latanoprost. His headache disappeared within 24 hours and did not recur during follow-up for 1 year.
- A 54-year-old woman with primary open-angle glaucoma, using betaxolol hydrochloride 0.5%, had mild progression of visual field loss in her left eye. Latanoprost was added nightly to her left eye. A few hours after the first dose she was awakened by a severe unilateral pounding headache extending from the left eye and brow to the left cranium. There were no associated neurological symptoms. The headache resolved spontaneously the next day, but recurred on three nights after instillation of latanoprost. On the fourth night the headache did not occur. She continued to use latanoprost, and the headache did not return.

Sensory systems

Corneal damage

Four patients treated with latanoprost developed dendritiform epitheliopathy, a sign of corneal toxicity; the lesions reversed in 1–4 weeks after latanoprost withdrawal (6).

Three cases of *Herpes simplex* keratitis developed during latanoprost therapy (7).

- One patient, with a history of *H. simplex* keratitis, had recurrence with latanoprost (4 months); the infection resolved on withdrawal but recurred on rechallenge.

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- The second patient, with a history of *H. simplex* keratitis, had bilateral recurrence with latanoprost (1 month); antiviral therapy did not eradicate the infection until latanoprost was withdrawn.
- The third patient developed the infection after 1 month; the keratitis cleared on withdrawal of latanoprost and antiviral therapy; reinstitution of latanoprost with prophylactic antiviral medication (valaciclovir) kept the cornea clear, but as soon as the antiviral drug was discontinued, *H. simplex* virus keratitis reappeared.

Although the mechanism is unclear, it is known that inhibitors of prostaglandin synthesis reduce recurrence of epithelial *H. simplex* infections and prostaglandins may stimulate their occurrence.

Iris pigmentation

Latanoprost can produce darkening of the iris in 10–25% of patients treated for 0.5–2 years. The incidence of iris pigmentation differs between eyes with differently colored irises: green–brown, yellow–brown, and blue–brown eyes, in that order, have the highest incidences, whereas eyes with uniformly blue, grey, or green irises are much less affected, even after 2 years of treatment. About 60% of eyes with an initial green–brown iris will have increased pigmentation within 1 year. The corresponding figure for initially blue–brown eyes is about 20%. All patients who have developed increased pigmentation of the iris have been withdrawn from studies, and during follow-up for up to almost 3 years the change in iris pigmentation has been stable without signs of reversibility or further increase. Nevi and freckles have not changed color or size. Apart from the change in color the iris looks normal and pigmentation dispersion has not been observed. No cell proliferation is involved and the change in color is due to melanogenesis. It has been concluded that the change in iris pigmentation is unlikely to cause any long-term consequence besides the cosmetic one. The possibility of late loss of pigment and induction of a pigmentary glaucoma also seems unlikely; melanocytes in the iris are continent and do not release melanin (8). In an observational cohort study of 43 patients, 30 had a definite acquired iris anisochromia (9).

The time of onset of the changes in iris pigmentation can be as early as 3 months. The earliest reported change in iris color occurred in a 78-year-old woman, whose iris color changed from blue–green to brown–green within 4 weeks (10). The pigmentation is irreversible. In a 50-year-old man with peripheral iris darkening after latanoprost treatment, the darkening did not change appreciably for several years after withdrawal (11).

The fine structure of an iridectomy specimen from a 65-year-old woman treated with latanoprost has been reported (12). She received latanoprost for 13.5 months and the drug was withdrawn because of iris color change. She underwent cataract surgery 16 months after stopping the drug and a sector iridectomy was obtained. The authors found some melanocytes with atypical features, including nuclear chromatin margination, prominent nucleoli, and invagination of the nucleoli. These characteristics are also seen in precancerous lesions, in the normal ageing iris, and in patients with glaucoma.

The mechanism of iris pigmentation due to latanoprost is unknown. In an in vitro experiment using uveal melanocytes, the addition of latanoprost increased melanin content, melanin production, and tyrosinase activity (13). Alpha-methyl-para-tyrosine, an inhibitor of tyrosinase (the enzyme that transforms tyrosine to levodopa), completely prevented the latanoprost-induced stimulation of melanogenesis.

Of 17 patients requiring filtering surgery for primary open-angle glaucoma randomized to receive latanoprost ($n = 8$) or alternative medications ($n = 9$) for 3 months before surgery, all had peripheral iridectomy specimens, and there were color changes in one case (14). No morphological changes or cellular proliferation were found in any specimen.

Iris cyst associated with latanoprost has been described in a 76-year-old woman (15). Latanoprost was given for 5 weeks, and during a re-examination a large iris cyst was observed in her right eye. The cyst disappeared 3 weeks after latanoprost withdrawal.

Uveitis

In four patients with complicated open-angle glaucoma, in whom anterior uveitis appeared to be associated with latanoprost, the uveitis was unilateral and occurred only in the eye receiving latanoprost in three patients. In one patient, latanoprost was used in both eyes, and the uveitis was bilateral (16). Four of five eyes had a history of prior inflammation and/or prior incisional surgery. All patients were rechallenged. The uveitis improved after withdrawal and recurred after rechallenge in all eyes. The authors concluded that topical prostaglandin analogues may be relatively contraindicated in patients with a history of uveitis or prior ocular surgery. There may also be a risk in eyes that have not had previous uveitis or incisional surgery.

Optic disc and macular edema

A case of bilateral optic disc edema has been described (17).

- A 64-year-old woman was included in a randomized, double-blind trial of drugs used in the treatment of ocular hypertension. After 3 months, examination of the optic nerve showed bilateral edema. She had been using latanoprost 0.0005% eye-drops at night to both eyes. Latanoprost was withdrawn and the disc edema resolved at 1 week.

Cystoid macular edema developed in two patients treated with topical latanoprost for glaucoma (18). Latanoprost was withdrawn, and the cystoid macular edema was treated with topical corticosteroids and ketorolac, with improvement in visual acuity. The macular edema resolved in both cases.

Cystoid macular edema has been reported in four other patients shortly after they started to use latanoprost (19) and other reports have appeared (20–24). A possible explanation is enhanced disruption of the blood–aqueous barrier induced by latanoprost (23).

A review of the published literature (28 eyes in 25 patients) has shown that in all cases there were other associated risk factors, so that a definitive conclusion about a causal relation cannot be reached (25). Nevertheless, latanoprost should be used with caution in patients with risk factors for cystoid macular edema and special surveillance is necessary.

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Skin

Hyperpigmentation of the eyelids can occur during latanoprost therapy.

- A 62-year old Korean woman treated with latanoprost for 4 months developed eyelid pigmentation in both upper and lower eyelids of both eyes (26). There was no increase in iris pigmentation. The eyelid pigmentation gradually diminished after withdrawal, but minimal brownish coloration remained along the lower eyelid folds in both eyes at 4 months.
- A 75-year-old woman with open-angle glaucoma who had used latanoprost for 15 months reported that the skin around her eyes was much darker than on the rest of her face (27). The darkening had occurred gradually. Latanoprost was withdrawn; 1 month later there was a discernible lightening of the periocular skin and 2 months after withdrawal the skin was significantly lighter.

Hair

Eyelashes

Latanoprost causes growth of lashes and ancillary hairs around the eyelids, with greater thickness and length of lashes, additional rows of lashes, and conversion of vellus to terminal hairs in canthal areas and regions adjacent to lashes. As well as increased growth, there is also increased pigmentation. Vellus hairs on the lower eyelids also undergo increased growth and pigmentation. Latanoprost caused changes in eyelashes in 26% of 194 patients over 12 months; the changes included increased length, thickness, density, and color (14).

Latanoprost therapy for 2–17 days can cause changes comparable to chronic therapy. The increased number and length of visible lashes are consistent with the ability of latanoprost to induce and prolong anagen growth in telogen (resting) follicles while producing hypertrophic changes in the involved follicles. Laboratory studies suggest that the initiation and completion of the effects of latanoprost on hair growth occur very early in the anagen phase and that the likely target is the dermal papilla.

Latanoprost can even reverse alopecia of the eyelashes (28).

- A 53-year-old woman, with glaucoma and loss of the eyelashes secondary to alopecia following an allergic response to ibuprofen was given latanoprost (29). After 3 weeks her eyelashes were noticeable and 2 months later full growth had occurred.
- Quantitative analysis of eyelash lengthening in 17 patients treated with latanoprost showed a significant increase in eyelash length in the treated eyes (30).

Increased pigmentation of the eyelashes has been reported in a patient treated with latanoprost (31).

Sweat glands

Heavy sweating occurred in a 6-year-old boy with aniridia and glaucoma during treatment with latanoprost eye-drops (32). Other combinations of drugs for glaucoma had been ineffective in reducing the intraocular pressure. He was given latanoprost eye-drops (dose not stated) at night in combination with a beta-blocker during the day. However, at night he had very heavy sweating. His pyjamas had to be changed regularly about 1–2 hours after he went to sleep. When latanoprost was withdrawn, the heavy sweating resolved. When it was restarted, the heavy sweating recurred.

The author commented that systemic absorption occurred for the most part through the mucous membranes of the nose and throat, since the sweating was less severe when the boy's lacrymal points were compressed for 10 minutes after the administration of latanoprost.

Infection risk

Two cases of *H. simplex* virus dermatitis of the periocular skin have been reported in patients using latanoprost (33). Cases of *H. simplex* keratitis are mentioned above, under sensory systems.

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Latex

General Information

Latex is present in many medical devices, including surgical and examination gloves, catheters, intubation tubes, anesthesia masks, and dental fillers. Reported allergic reactions range from contact urticaria to anaphylaxis (1). There has been a marked worldwide increase during recent years in the rate of reactions to latex. These reactions are due to either or both:

1. The formulation chemicals (vulcanizers, stabilizers, preservatives). These cause mainly local delayed hypersensitivity reactions. However, some of these chemicals are also carcinogenic, and may have more serious and not immediately apparent consequences.
2. Proteins in the latex. These can cause generalized systemic allergic reactions, including anaphylaxis, which can be severe and life-threatening.

Latex condoms degrade over time. Such degradation has a significant effect on the product's ability to provide a barrier to sexually transmitted agents, including human immunodeficiency virus (HIV). The FDA has issued a final regulation requiring that the labelling of latex condoms shall contain an expiry date based on physical and mechanical testing performed after exposing the product to varying conditions that age latex, both on the outside packaging and on the individual packaging (2). The agency has also stipulated that if a latex condom contains spermicide and if the expiry date based upon spermicidal stability testing is different from the expiry date based on latex integrity testing, the product shall bear only the earlier expiry date.

Organs and Systems

Urinary tract

Urethritis has been described in patients with urinary catheters containing latex (3). In 100 men, the incidence of urethritis with latex catheters was 22% compared with 2% in patients managed with silicone catheters. In all cases, symptoms developed within 12 hours of use and urine specimens were sterile.

Immunologic

Severe anaphylactic reactions have been reported in response to dental work (latex dental dams), barium enemas (latex enema devices), and numerous surgical procedures involving mainly latex gloves and catheters. The two major contributing factors appear to be a hereditary disposition and occupational exposure. The latter has increased rapidly owing to progress in medical technology, the associated increase in the use of medical devices, and increased awareness among health-care professionals of the need to wear protective gloves during various procedures. This increased exposure has meant that a growing number of people have become sensitized to latex proteins; in one study, 6–7% of surgical personnel and 18–40% of patients with spina bifida were sensitive to latex (4). Particularly high-risk circumstances appear to be direct contact of a latex device or air-borne particles from a latex device (for example corn starch carrying latex proteins) with mucous membranes or with tissues exposed as a result of surgical procedures.

FDA investigations, which eventually identified natural latex/natural rubber (NLNR) allergy as an emerging public health concern, were started in response to voluntary reports submitted by physicians, nurses, and technologists (5). The first reports described deaths that

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occurred during barium enema procedures, before the administration of barium. Over the past decade, the FDA has received more than 1700 reports of severe allergic reactions, including 16 deaths, related to medical devices containing latex. The deaths all occurred in 1989 among children with spina bifida and were caused by a reaction to the latex cuffs used on the tip of barium enema catheters.

In Australia, regulatory changes have been proposed for the labeling and safety requirements of latex-containing devices that directly or indirectly come into contact with body tissues (6). Most latex-containing devices are in this category, and include tubes, catheters, empty containers, syringes, medical gloves, and devices such as condoms and diaphragms. The FDA is requiring all medical devices containing latex to be labeled as such and to carry a caution that latex can cause allergic reactions (7). The FDA has also urged manufacturers of latex containing medical devices to set the protein levels in their products as low as possible. The FDA also requires that "hypoallergenic" claims should not be attached to medical devices, because they incorrectly imply that the devices may be safely used by people who are sensitive to latex.

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Lauraceae

See also Herbal medicines

General Information

The genera in the family of Lauraceae (Table 1) include cinnamon and sassafras.

Cinnamonum camphora

Camphor is a white crystalline substance, obtained from the tree *Cinnamonum camphora* (camphor tree), but the name has also been given to various volatile substances found in different aromatic plants.

Camphor has been used as a substance of abuse for many centuries, both by ingestion and by inhalation. Today it is found in many non-prescription vaporized or topical "cold cures," topical musculoskeletal anesthetic rubs, "cold sore" formulations, sunscreens, and mothballs. It has also been used to procure an abortion (1).

Adverse effects

The acute effects of ingesting camphor were described by Louis Lewin in "Phantastica" (1924):

> After ingestion of 1.2 grains [72 g] the following symptoms occur: an agreeable warmth of the skin, general nervous excitation, a desire to move, tickling of the skin, and a peculiar feeling of ecstasy similar to drunkenness. One addict said that "he saw his destiny full of great possibilities clearly and distinctly before his eyes." This state continued for one and a half hours. After ingestion of 2.4 grains there was an urgent desire to move. All movements were generally facilitated, and when walking the limbs were lifted far more than necessary. Intellectual thought was impossible. There was a flood of ideas, chasing each other with great rapidity, without any one being analysed. The individual lost perception of his identity. After vomiting, awareness returned, although distraction, forgetfulness and vacancy of mind persisted. On awaking the state of intoxication seemed to have been extraordinarily long and full of events of which the subject did not remember any. After 3 hours he was able to pull himself together and return to full consciousness, but the effect on the brain was so potent that unconsciousness and convulsions again occurred within an hour and lasted for half an hour, after which the subject gradually regained his full mental faculties and normal muscle function.

Lewin also described the effects of chronic abuse:

> Loss of the sense of location and brief gaps in memory usually succeed gastric irritation and convulsions when camphor is taken habitually. The lost memories finally reappear, but in a very strange fashion, so that, according to the statement of an addict, all affairs, events, and things that he had forgotten seemed new, as if he had had no previous knowledge of them. Even after he recognized all the members

Table 1 The genera of Lauraceae

Aniba (aniba)
Beilschmiedia (beilschmiedia)
Cassytha (cassytha)
Cinnamomum (cinnamon)
Cryptocarya (cryptocarya)
Endiandra
Eusideroxylon (ironwood)
Laurus (laurel)
Licaria (licaria)
Lindera (spicebush)
Litsea (litsea)
Nectandra (sweetwood)
Ocotea (sweetwood)
Persea (bay)
Sassafras (sassafras)
Umbellularia (California laurel)

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of his family, the objects in his room seemed unfamiliar, as if they had just been given to him. In Slovakia convulsive states similar to epilepsy are so common in consumers of camphor that all cases of similar fits are directly attributed to it.

Nervous system
Convulsions can occur after transdermal absorption of camphor (2).

- A 20-month-old girl developed status epilepticus after ingesting camphor and required ventilation. She was treated with intravenous diazepam and phenobarbital and nasogastric-activated charcoal and made a complete neurological recovery (3).

Liver
Hepatotoxicity occurred in a 2-month-old baby after a camphor-containing cold remedy was applied to the skin; liver function tests returned to normal after the remedy was withdrawn (4).

Chronic ingestion of camphor can mimic Reye's syndrome (5).

Skin
Contact dermatitis has been reported from the use of camphor in ear-drops (6). Photo-distributed skin eruptions have been reported after use of a sunscreen containing camphor (7).

Drug overdose
In children exposure to as little as 500 mg of camphor can be fatal (8). More commonly, a dose of 750–1000 mg is associated with seizures and death. Products that contain 10% camphor contain 500 mg in 5 ml.

After taking an unknown amount of a 10% camphor spirit (maximum dose 200 ml), a 54-year-old woman became comatose, having developed tonic-clonic seizures and respiratory failure (9). After gastric lavage, hemoperfusion was performed with amberlite XAD4 but did not alter either the pharmacokinetics of camphor or the course of the intoxication.

Laurus nobilis

Laurus nobilis (laurel) has well-known analgesic, diaphoretic, antipyretic, and diuretic effects (10), and is widely used in rheumatic, pyrexial, and infective disorders (11), as well as in the perfume and soap industries (10).

Adverse effects
Laurel oil obtained from the berries of *L. nobilis* is a potent skin sensitizer, owing to the presence of allergenic sesquiterpene lactones, and is usually seen in aromatherapists or their clients (12–14).

- A 55-year-old woman developed erythema and edema over her knees (12). She had applied laurel oil, obtained from a herbalist, to her knees to relieve joint pain 15 days earlier. After 3 days, the erythema and edema had begun to appear. She had erythema, edema, and papules over her patellae, and eczema around the eye. She was treated with an oral antihistamine and a topical glucocorticoid. Two days later, the lesions worsened and systemic glucocorticoid therapy was needed. The lesions started to heal, leaving slight postinflammatory hyperpigmentation. Patch-testing was performed with a European standard series and commercial laurel oil 1 month later. There was a +++ reaction to the oil only, and no reaction to either fragrance mix or *Myroxylon pereirae* resin in the standard series. The same formulation of laurel oil was negative on patch-testing in 15 control subjects.

Sassafras albidum

Sassafras albidum (sassafras) root contains 1–2% of volatile oil, which in turn consists largely of safrole, a weakly hepatocarcinogenic agent in laboratory animals. Some metabolites of safrole have mutagenic activity in bacteria and weak hepatocarcinogenic effects in rodents. The carcinogenic effect is primarily mediated by the formation of 1′-hydroxysafrole, followed by sulfonation to an unstable sulfate that reacts to form DNA adducts; these metabolites are formed by CYP2C9 and CYP2E1, the latter contributing three-fold more to the metabolic clearance than the former (15).

In one case sassafras tea caused sweating (16).

In Germany, the health authorities have proposed the withdrawal of sassafras-containing medicines, including homeopathic products up to D3, from the market (17). Of particular concern is the uncontrolled availability of sassafras oil because of its use in aromatherapy. Internal use of sassafras oil in recommended doses up to 12 drops/day can lead to a daily intake up to 0.2 g of safrole (18).

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Lauromacrogols

General Information

Lauromacrogols are mixtures of monolauryl esters of macrogols. They have the following general formula: $C_{12}H_{25}(OCH_2CH_2)_nOH$. Each is named after the number n in its formula. For example, in lauromacrogol 400 (polidocanol), $n = 400$. They have been used as surfactants, spermicides, solvents, and non-ionic emulsifiers.

Lauromacrogol 9 has been used as a sclerosant and local anesthetic.

Lauromacrogol 400 (polidocanol) has been used as a solvent and non-ionic emulsifier that contains 95% hydroxypolyethoxydodecane and 5% ethyl alcohol. In medicaments it has been used as a topical anesthetic, an antipruritic, and a sclerosant.

Organs and Systems

Immunologic

Contact allergic reactions to lauromacrogol 400 have been reported (1). Patch-testing can yield irritant reactions. In a retrospective study of 8739 patients tested with a topical drug patch test series, 3186 patients were tested with 0.5% lauromacrogol 400 in water (2). There was slight irritation in 0.88%, weakly positive reactions in 0.97%, and strongly positive reactions in 0.25%. In 6202 patients tested with a 3% solution of lauromacrogol 400 in petrolatum, there was slight skin irritation in 0.48%, weakly positive reactions in 1.77%, and strongly positive reactions in 0.34%. Among the 649 patients tested with both formulations, concurrence was moderate.

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Laxatives

General Information

Laxatives can be classified according to their several mechanisms of action:

- bulk-forming laxatives, such as bran, methylcellulose, *Plantago* extracts (ispaghula and psyllium), and sterculia;
- stimulant laxatives, such as the anthraquinones (senna and dantron), bisacodyl, docusate sodium (also a fecal softener), and sodium picosulfate; cascara, castor oil, oxyphenisatin, and phenolphthalein are obsolete stimulant laxatives;
- fecal softeners, such as arachis oil and the obsolete liquid paraffin;
- osmotic laxatives, such as lactulose, lactitol, the polyethylene glycols, magnesium salts, sodium citrate, and phosphates.

General adverse effects of laxatives

If laxatives of any type are heavily used, not necessarily to the point of abuse, diarrhea will be common, as well as a tendency to nausea and fluid and electrolyte imbalance. The possibility of laxative-induced colonic injury, with damage to the autonomic nervous innervation of the large intestine, has been much discussed and was probably a problem with the violent cathartics formerly used (podophyllin, aloes, and cascara), but is not on record with the laxatives normally used today. Chronic abuse of laxatives, such as senna, can cause changes in colonic structure and function.

Habitual, usually secretive, abuse of laxatives is much more common in women than in men and there is overlap with the anorectic/bulimic syndrome. Abuse of irritant agents such as senna and cascara have been the commonest varieties (SED-10, 704), but many proprietary laxatives have been abused. Abuse can lead to a condition characterized by chronic diarrhea, hypokalemia, and fluid depletion. The features also include hypomagnesemia, hypocalcemia, and hypoalbuminemia, with thirst, lassitude, weight loss, edema, and occasionally osteomalacic bone pain and clubbing. In one small series of cases of laxative abusers, pseudo-Bartter's syndrome was induced; the complications included confusion, convulsions, muscle weakness (with or without paralysis or rhabdomyolysis), and

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bone changes; hypokalemia and hypophosphatemia were common, and when the laxatives were withdrawn some patients suffered prolonged edema (1).

Bulk-forming laxatives

The bulking agents include vegetable fiber products (such as bran), paraffin and methylcellulose (which absorbs water into the intestinal tract), agar (which expands to form a gel), and psyllium seeds or other mucilaginous plant products. Bulking agents are largely free of adverse effects, but any non-absorbable agent can aggravate symptoms associated with pre-existent intestinal stricture. Abdominal bloating due to bacterial fermentation of unabsorbed carbohydrate is a common sequel to excessive intake. The sugar content of some bulk laxatives can be sufficient to impair diabetic control; the vegetable matter in other preparations can cause bezoars and is potentially allergenic.

Plantago species (psyllium and ispaghula)

Plantago seeds are widely used as bulk laxatives under the names of "psyllium" (from *Plantago psyllium* or *Plantago indica*) and "ispaghula" (from *Plantago ovata*).

Psyllium husk combined with microencapsulated paraffin has been compared with standard psyllium for the treatment of constipation in a randomized, double-blind study (2). There was a significant increase in the weekly number of defecations with the combined formulation, which was well tolerated; no adverse effects were reported.

The efficacy, speed of action, and acceptability of ispaghula husk, lactulose, and other laxatives in the treatment of simple constipation in 394 patients have been studied by 65 general practitioners (3). Ispaghula was used by 224 patients and other laxatives by 170. After 4 weeks of treatment ispaghula husk was assessed by the GPs to be superior to the other laxatives. In patients' assessment, ispaghula users had a higher proportion of normal stools and less soiling than patients using other laxatives. Diarrhea and abdominal pain and gripes and were less common with ispaghula. Distension, flatulence, indigestion, and nausea were equally frequent in the two groups.

Esophageal obstruction by a bezoar after ingestion of psyllium has been reported (4).

- A 69-year-old man with Parkinson's disease developed severe dysphagia after taking granules of the bulk laxative Perdiem (82% psyllium and 18% senna formulated as granules). Disimpaction of the bezoar was performed via a rigid endoscope under general anaesthesia.

Occupational exposure to *Plantago* species has resulted in sensitization, with symptoms ranging from rhinitis and lacrimation to more severe respiratory compromise. This problem arises in a more serious form among the personnel of pharmaceutical factories processing psyllium (SEDA-16, 426), and eosinophilia has also been recorded. The allergen appears to reside in the endosperm or embryonic seed components and not in the husk, which is the laxative component; in principle, therefore, it should be feasible to supply a non-antigenic form of purified psyllium husk (SEDA-17, 423).

Ingestion of psyllium has been associated with rare cases of generalized urticarial rash and anaphylactic shock (5,6). The possibility that the intestinal absorption of lithium and other drugs may be inhibited by psyllium should also be considered (7).

Sterculia

The family of *Sterculia* plants yield a fiber that has bulk laxative effects.

Esophageal obstruction after ingestion of sterculia has been reported (8).

- A 91-year-old man presented with complete esophageal obstruction after taking a tablespoonful of sterculia granules (Normacol) without water. There was no predisposing esophageal disease. The severity of obstruction was such that endoscopic clearance was not possible, and the patient required gastrotomy and manual disimpaction of the lower esophagus.

Stimulant laxatives

All of the anthraquinones can cause cramping and abdominal discomfort. Chronic use can be associated with melanosis coli. The urine can be colored red. The possibility of colonic injury has been discussed (see General adverse effects of laxatives in this monograph). Hepatitis, confirmed by rechallenge, has been reported, possibly due to re-absorption of rhein anthron produced in the intestine (SEDA-16, 425).

The Food and Drug Administration (FDA) has ruled that the stimulant laxatives aloe (including aloe extract and aloe flower extract) and cascara sagrada (including casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, and cascara sagrada fluid extract) in over-the-counter formulations are not safe and effective or are misbranded (9).

Anthranoid derivatives occur in various laxative herbs (such as aloe, *Cascara sagrada*, medicinal rhubarb, and senna) in the form of free anthraquinones, anthrones, dianthrones, and/or O- and C-glycosides derived from these substances. They produce harmless discoloration of the urine. Depending on intrinsic activity and dose, they can also produce abdominal discomfort and cramps, nausea, violent purgation, and dehydration. However, they are all mutagenic and carcinogenic and should not be used in the long term.

In an epidemiological study, chronic abusers of anthranoid laxatives (identified by the detection of pseudomelanosis coli) had an increased relative risk of 3.04 (95% CI = 1.18, 4.90) for colorectal cancer (10).

Anatomical changes in the colon have been reported in patients taking chronic stimulant laxatives, defined as laxative ingestion more than three times a week for a year or more (11). Loss of haustra, which suggests neuronal injury, or damage to colonic longitudinal musculature, was seen in eight of 29 patients who used a variety of diphenylmethane and anthranoid laxatives but in none of the 26 patients who were not using these drugs. In 18 consecutive patients who were chronic users of stimulant laxatives, there was loss of haustra in 15 who took bisacodyl, phenolphthalein, senna, or casanthranol.

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Aloe species

Aloe species contain laxative anthranoid derivatives, the main active ingredient being isobarbaloin. Large doses are claimed to cause nephritis and use during pregnancy is discouraged, since intestinal irritation might lead to pelvic congestion. Aloe is thought to aggravate hemorrhoids.

- Melanosis coli occurred in a 39-year-old liver transplant patient who took an over-the-counter product containing aloe, rheum, and frangula (12). The typical brownish pigmentation of the colonic mucosa developed over 10 months. The medication was withdrawn and follow-up colonoscopy 1 year later showed normal-looking mucosa. However, a sessile polypoid lesion was found in the transverse colon. Histology showed tubulovillous adenoma with extensive low-grade dysplasia.

Bisacodyl (rINN)

Bisacodyl increases peristalsis by a direct effect on the small intestine. Its only specific adverse effect is abdominal cramping, which a minority of patients find troublesome. As with other laxatives, however, heavy or chronic use can derange the system in various ways, for example hypokalemia with rhabdomyolysis (SEDA-16, 425).

Bisacodyl tablets plus an unrestricted diet and a phosphate enema has been compared with Picolax (sodium picosulfate + magnesium citrate) plus clear fluids in a randomized, single-blind trial in bowel preparation for colonoscopy in 66 children aged 18 months to 16 years (13). Bowel cleansing was significantly better with Picolax. Compliance with both regimens was excellent. Bisacodyl produced significantly more abdominal pain. Some children given Picolax reported vomiting ($n = 3$) and were distressed because of lack of solid food ($n = 6$). The other adverse effects included abdominal discomfort and fecal incontinence.

Bisacodyl suppositories can make the rectal mucosa appear inflamed (14), and this can be mistaken for idiopathic proctitis. However, the effect is transient.

Cascara sagrada

Cascara sagrada has been reported to cause liver damage (15).

- A 48-year-old man developed cholestatic hepatitis and hypertension shortly after he started to use the herbal laxative *Cascara sagrada*, which contains an anthracene glycoside. He took 1 capsule (425 mg of aged *C. sagrada* bark) tds for 3 days and subsequently developed right upper quadrant pain, nausea, abdominal bloating, anorexia, and jaundice. The *Cascara* was withdrawn, but his symptoms persisted and his liver function tests were abnormal. One week later, he developed ascites and jaundice and underwent liver biopsy, which showed moderately severe portal inflammation, intracanalicular bile stasis, portal bridging fibrosis, and mild steatosis. He gradually improved without specific treatment, and 3 months later his ascites and jaundice had resolved.

Dantron (rINN)

Dantron is a synthetic analogue of the anthraquinones. All are bacterial mutagens, and dantron, in addition to being genotoxic as assessed by DNA repair testing, induces intestinal tumors in animals (SED-11, 788) (16). Emodin, aloe-emodin, and dantron probably act by inhibiting the catalytic activity of topoisomerase (17).

Therefore, the anthraquinones should no longer be used, except to treat constipation in patients with terminal cancer (18). For this purpose, dantron is available as co-danthramer (BAN; dantron + poloxamer 188) and co-danthrusate (BAN; dantron + docusate sodium).

Oxyphenisatine (rINN)

Oxyphenisatine, once a very widely used laxative, was withdrawn before 1980 in most countries because of chronic persistent/active hepatitis; a full account will be found in volumes in this series from 1971.

Phenolphthalein (rINN)

Phenolphthalein was once widely used as a laxative for self-treatment, often camouflaged in chocolate and thus liable to abuse or accidental use; it is now obsolete. Skin rashes of various types are repeatedly reported, sometimes with pruritus. Pigmentation defects have been described. The most serious albeit rare adverse effect on the skin to have been reliably documented is toxic epidermal necrolysis. A fixed drug eruption with bullous erythema multiforme is associated with auto-sensitization, and direct intracellular immunofluorescence is found (19). A hypothesis that phenolphthalein might increase the risk of development of adenomatous colorectal polyps has not been confirmed (20).

The Federal Institute for Drugs and Medical Devices in Germany has recommended that marketing authorizations for phenolphthalein products be revoked, in view of its potential toxic effects (21), including genotoxicity and carcinogenicity (22). Further to the actions taken in the USA and France to withdraw laxative products containing phenolphthalein, the following measures have been taken (23).

Canada After reviewing the benefits and risks associated with the use of phenolphthalein-containing laxatives, Health Canada concluded that there is a risk that phenolphthalein may cause cancer in humans; therefore authority to sell and distribute these products has been revoked.
European Union At a Pharmacovigilance Working Party meeting in September 1997, it was indicated that national competent authorities were either considering immediate suspension of phenolphthalein or were discussing with the relevant marketing authorization holders voluntary withdrawal down to the wholesale level. If voluntary action was not agreed by marketing authorization holders, the national competent authorities concerned would consider suspension of the products.
Japan Manufacturers voluntarily withdrew products containing phenolphthalein.

Rheum palmatum (medicinal rhubarb)

Rhubarb contains the anthranoids, sennosides and rhein. In a study of patients taking regular doses of rhubarb-containing Kampo medicines (extracts or decoctions) and patients taking excess doses, there was tolerance to initial stimulant pain in the abdomen during excess use (24). The authors proposed that the absence of tenderness on pressure over the umbilical region could predict increasing or excess use of rhubarb.

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In 14 616 patients who used various Kampo medicines, some of which contained rhubarb, there was no association between the use of rhubarb and the development of gastric carcinoma (25).

Senna

The leaves and fruits of *Cassia angustifolia* and *Cassia senna* contain sennosides, which are laxative anthranoid derivatives. Mutagenicity testing of sennosides has produced negative results in several bacterial and mammalian systems, except for a weak effect in *Salmonella typhimurium* strain TA102 (26,27). There was no evidence of reproductive toxicity of sennosides in rats and rabbits (28). When a standardized formulation containing senna pods (providing 15 mg of sennosides per day) was given to breastfeeding mothers, the suckling infants were only exposed to a non-laxative amount of rhein, which remained a factor of 1000 below the maternal intake of this active metabolite (29). A well-defined purified senna extract was not carcinogenic when given orally to rats in daily doses up to 25 mg/kg for 2 years (30).

Senna is widely used in fairly low doses without serious problems; it is also used in a very high dosage form (X-Prep) to clear the colon before radiological examination. In this form it is generally well tolerated, but it should not be used if there is any predisposition to colonic rupture.

The safety and efficacy of senna have been reviewed (31). Its rhein-anthrone-induced laxative effects occur through two distinct mechanisms, an increase in intestinal fluid transport, which causes accumulation of fluid intraluminally, and an increase in intestinal motility. Senna can cause mild abdominal complaints, such as cramps or pain. Other adverse effects are discoloration of the urine and hemorrhoidal congestion. Prolonged use and overdose can result in diarrhea, extreme loss of electrolytes, especially potassium, damage to the surface epithelium, and impairment of bowel function by damage to autonomic nerves. Abuse of senna has also been associated with melanosis coli, but resolution occurs 8–11 months after withdrawal. Tolerance and genotoxicity do not seem to be problems associated with senna, especially when used periodically in therapeutic doses.

Exceptional complications of senna abuse include hepatitis as well as finger clubbing and hypertrophic osteopathy.

An unusual disulfiram-type reaction reported on one occasion seems to have been due to an interaction of metronidazole with the alcohol present in X-Prep (SEDA-15, 398).

Sodium picosulfate (rINN)

Oral sodium picosulfate and oral sodium phosphate have been compared for bowel preparation before elective colorectal surgery and colonoscopy in randomized studies in 256 patients (32). Oral sodium phosphate was superior to sodium picosulfate on surgical assessment of bowel preparation, fecal residue in the resected specimen, and endoscopic score. However, there was no significant difference with regard to abdominal pain, nausea, vomiting, embarrassment, fear, and fatigue between the two groups.

Oral sodium picosulfate plus magnesium citrate (Picolax) has been compared with a self-administered phosphate enema for bowel preparation before flexible sigmoidoscopy in a randomized, single-blind trial in 1142 subjects (33). A single self-administered phosphate enema about 1 hour before leaving home was a more acceptable and effective method of preparing the distal bowel than oral Picolax. Although more patients felt unwell after taking the enema (15%) than after taking Picolax (7%), over 80% in both groups felt normal. More of the itemized adverse effects were rated as moderate or severe in the Picolax group, including wind, incontinence, and sleep disturbance. Anal soreness was reported more frequently in the enema group. The other reported adverse effects were abdominal pain/cramps, nausea/vomiting, and faintness/dizziness.

Two cases of generalized urticarial skin reactions occurred after a first dose of sodium picosulfate (34). This may have represented an interaction with aminosalicylate derivatives, which were being administered at the same time, or a simple adverse effect to one of the agents.

A dubious case of status epilepticus attributed to picosulfate has been published (SEDA-16, 425).

Fecal softeners

Liquid paraffin

It has been recommended for many years that the use of liquid paraffin should be discontinued because of its propensity to cause malabsorption of fat-soluble vitamins, to leak and soil the perineal skin, and to cause lipid pneumonia if aspirated; at the very least it should be avoided in young children (35).

Osmotic laxatives

The osmotic laxatives include inorganic salts and the synthetic disaccharide, lactulose, as well as magnesium salts and sodium phosphate. Osmotic agents are largely free of adverse effects, apart from flatulence, cramps, and abdominal discomfort.

Lactulose (rINN) and lactitol (rINN)

Lactulose is a non-absorbable disaccharide that is hydrolysed in the large bowel by intestinal bacteria, yielding monosaccharides that act as osmotic agents; it is also metabolized to hydrogen and carbon dioxide.

In a double-blind, placebo-controlled study in 10 healthy volunteers, lactulose powder 10 g/day for 26–33 days was an effective food-grade prebiotic (36). Fecal bifidobacteria increased significantly during lactulose intake, with a concomitant decrease in *Clostridia*.

The most common adverse effects of lactulose are flatulence, cramps, and abdominal discomfort. Non-toxic megacolon has been seen in some elderly patients and, as with other laxatives, there is always a possibility of dependence (SEDA-11, 374).

- Two women aged 88 and 82 taking lactulose for constipation, developed life-threatening dilatation of the bowel (16). Both underwent surgery. One had cancer of the bowel and an uneventful postoperative recovery. No mechanical abnormalities were found in the second patient but she died in respiratory insufficiency after aspiration.

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Low-dose polyethylene glycol electrolyte solution and lactulose have been compared in chronic constipation in a randomized multicenter study in 115 patients with chronic constipation (37). After 4 weeks the patients who took polyethylene glycol had a higher number of stools, a lower median daily score for straining at stool, and greater overall improvement than patients who took lactulose. Except that significantly fewer patients who took polyethylene glycol reported flatus, other adverse effects were similar in the two groups and included liquid stools, abdominal pain, bloating, and rumbling.

- Pneumatosis intestinalis and pneumoperitoneum have been reported in a 57-year-old cirrhotic man with colonic inertia who had been taking oral lactulose 30 ml tds (38). Because of constipation the dose of lactulose had been gradually increased to 60 ml qds together with lactulose enemas. Both conditions resolved 3 days after oral lactulose was withdrawn.

Lactitol is another disaccharide, similar to lactulose. It has been claimed to be more palatable and to have fewer adverse effects (SEDA-18, 374), but it has not been used as widely as lactulose.

The effects of lactulose and lactitol in daily doses of 18–36 g for 6 months have been evaluated in a prospective, open study in 31 cirrhotic patients with chronic encephalopathy (38). Mean daily stool frequency (2.5 versus 1.7) and the frequency of reported adverse effects (59 versus 14%) were significantly higher with lactulose. Common adverse effects were nausea, intestinal discomfort, flatulence, and diarrhea.

There has been a systematic review of 30 randomized comparisons in hepatic encephalopathy of lactulose or lactitol with no intervention, placebo, or antibiotics and comparisons of lactulose with lactitol (39). Compared with placebo or no intervention, non-absorbable disaccharides had no statistically significant effect on mortality, but appeared to reduce the risk of no improvement of hepatic encephalopathy. However, this result might have reflected bias, owing to the poor quality of the majority of the studies.

Phosphates

Oral sodium phosphate 90 ml mixed with 300 ml of clear liquid has been compared with 2 liters of polyethylene glycol solution in a colonoscopist-blinded, randomized trial in 100 patients undergoing colonoscopy as a day-care procedure (40). Sodium phosphate was well tolerated and safe and provided bowel cleansing similar to polyethylene glycol. Five patients who received polyethylene glycol and four who received sodium phosphate reported nausea, and eight patients who received polyethylene glycol and one who received sodium phosphate complained of abdominal fullness.

The standard regimen of sodium phosphate used for bowel cleansing before colonoscopy is 40 tablets (60 g). In a randomized, multicenter, endoscopist-blinded trial in 98 patients undergoing colonoscopy, two smaller doses of sodium phosphate, 28 tablets (42 g) and 32 tablets (48 g), were effective (quality of colon cleansing excellent or good in over 80%) and well tolerated (41). The incidences of adverse effects were similar in the two groups. The reported adverse effects were nausea, vomiting, dizziness, and headache.

Tonic-clonic seizures have been reported in four adults who took oral sodium phosphate as Visicol (InKline Pharmaceutical; total 40 tablets) for bowel cleansing before colonoscopy (42). None of the patients had a history of seizures or electrolyte abnormalities. In all cases the seizures were associated with electrolyte abnormalities, mainly hyponatremia, after administration of Visicol.

Aphthous ulcers in the rectal mucosa have been reported in association with the use of Fleet-phospho-soda enema in preparation for colonoscopy in a 54-year-old woman (43).

Bowel cleansing solutions

Colonic ulceration has been attributed to the use of hydrogen peroxide in an enema (44).

- A 13-year-old girl was given 10% hydrogen peroxide as an enema for constipation. She developed severe rectal bleeding, and colonoscopy showed mucosal ulceration up to the splenic flexure. Histology confirmed ulceration due to traumatic burns. She improved gradually on conservative treatment, and 2 months later a repeat colonoscopy was normal.

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Lead

General Information

Lead is a heavy soft bluish-gray metal (symbol Pb; atomic no. 82) that is widespread as different salts in minerals such as chromite (oxide), crocoisite (chromate), Jamesonite and zinkenite (sulfides), mimetite (arsenate and chloride), pyromorphite (phosphate and chloride), and vanadinite (vanadate and chloride).

Lead has no place in internal medical treatment, although lead acetate has retained a very small place as an astringent. Its toxic effects are known primarily from environmental and occupational exposure and occasionally

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from the use of alternative remedies or cosmetics. For example, lead sulfide in eye-drops originating in India has caused lead poisoning, and lead has been found in some supposed aphrodisiacs from India. Children with circulating lead concentrations in excess of 600 ng/ml have impaired intellectual performance and electrocardiographic changes, and at any age excessive intake can cause encephalopathy, neuropathies, anemia, anorexia, colic, and renal damage. Lead poisoning from occupational and environmental sources continues to be reported. The biological chemistry of lead has been reviewed (1).

No significant effects have been attributed to lead as a contaminant in infant formulas or total parenteral nutrition. In an investigation of the protective effect of calcium supplements against lead absorption, 103 infants aged 3.5–6.0 months were randomly assigned to receive an infant formula (iron-fortified, containing 465 micrograms/ml of calcium and 317 micrograms/ml of phosphate) or the same formula with added calcium glycerophosphate (1800 micrograms/ml of calcium and 1390 micrograms/ml of phosphate) for 9 months (2). There was no significant difference between the groups in the mean ratio of urinary calcium to creatinine, serum calcium, or serum phosphorus, nor any change in iron status. At month 4, the median increase was 0.07 μmol/l in the control group and 0.04 μmol/l in the supplemented group. This significant effect was attenuated during the latter half of the trial, with overall increases in blood lead of 0.12 μmol/l in controls and 0.10 μmol/l in the supplemented group. Supplementation did not have a measurable effect on urinary calcium excretion, calcium homeostasis, or iron status. The significant effect on blood lead concentration was expected, although it was not sustained during the whole study, and so no prevention could be concluded.

Herbal remedies

Raised blood lead concentrations in an adult have been attributed to an Asian remedy for menstrual cramps ("Koo Sar Pills") (3).

- A Cambodian woman, her husband, and their two children were screened at a free lead-screening event sponsored by a nursing school community health promotion. The husband and children had normal blood lead concentrations, but the woman had a concentration of 440 ng/ml. She reported no symptoms associated with lead poisoning (for example, muscle pains or weakness, headaches, or loss of appetite). Samples of any medicines, teas, or cosmetics that she had used that might have been the source of the lead were analysed. Lead was found only in bottles of red tablets, at concentrations of 3.5 ppm from one bottle and 1.2 ppm in a second bottle. For 3–4 years she had taken six of these tablets a day on 7 days of each month to treat menstrual cramps. She stopped taking them, and her blood lead concentrations fell from 280 to 12 ng/ml over 6 months. Further laboratory analysis of other bottles showed lead in amounts of 12.5 ppm in tablets from a third bottle and 4.5 ppm in tablets from a fourth bottle. The tablets were traced to a San Francisco-based Hong Kong company who sold them in packages with the brand name listed on the outside of the package as "Koo So Pills" and on the package insert as "Koo Sar Pills." The package literature was written in Chinese. Lead was not among the 11 listed ingredients. The insert stated "These medical pills are good for general debility." The directions for dosage were one pill taken with warm water twice a day (not six per day). The lead content in samples purchased at different shops in San Francisco was 2.7 ppm (0.9 micrograms/tablet) and 4.3 ppm (1.4 micrograms/tablet).

No other cases of lead poisoning have been reported in association with Koo Sar tablets, and it is thought that the varying lead concentrations in the different tablets resulted from varying amounts of lead present during the manufacture of the red dye.

- A 23-year-old Asian butcher developed diffuse abdominal pain, vomiting, and diarrhea, followed by constipation (4). He had a sinus tachycardia and generalized abdominal tenderness without peritonism. His serum bilirubin concentration and alanine transaminase activity were raised, but alkaline phosphatase activity, albumin concentration, and prothrombin time were normal. He had a blood lead concentration of 767 ng/ml and a raised zinc protoporphyrin concentration, diagnostic of lead poisoning. He had taken an herbal medicine, purchased in India, for vague ailments. He stopped taking it, and 3 months later was asymptomatic, with normal liver function tests and marked falls in blood lead (387 ng/ml) and zinc protoporphyrin.

Lead toxicity has been reported in a child who was exposed to lead in a Tibetan herbal remedy (5).

- A 5-year-old Indian boy had static encephalopathy, seizures, and developmental delay from neonatal asphyxia and was referred to a hematologist for persistent anemia (hemoglobin 9.2 g/dl) without basophilic stippling, refractory to iron therapy. He was alert and active but nonverbal, able to stand with support but not able to walk, and had no focal neurological defects. Skeletal and abdominal X-rays showed no lead lines and no gastric lead particles. He had normal iron stores and normal hemoglobin electrophoresis. The blood lead concentration was 860 ng/ml. He was given EDTA and dimercaprol (BAL), and his lead concentration fell to 256 ng/ml. His mother had been giving him a Tibetan herbal vitamin, in the form of tablets, three times a day for the previous 5 years. A traditional medicine healer had told her that the tablets were pure medicinal herbs and plants prepared according to ancient Tibetan pharmacological traditions. They were said to be free from harmful or toxic substances and would actually promote brain growth and improve his mental capabilities. The tablets were produced in India and each was individually wrapped. They were analysed for lead, arsenic, cadmium, and mercury, and it was estimated that he had ingested about 63 g of lead over 4 years. Seven months later his blood lead concentration was 760 ng/ml and he was given EDTA and BAL. On day 2 he had a tonic-clonic seizure lasting 1 minute and his urinary lead concentration was 2310 ng/ml. On discharge his blood lead concentration was 413 ng/ml. During the next 4 years he had a further six chelation treatments with succimer when

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his lead concentration was over 450 ng/ml. After 4 years his lead concentration was 245 ng/ml.

Topical lead

A 64-year-old woman had treated extensive ulcers of both legs with daily dressings of diachylon ointment, containing 15% lead oxide, for more than a year. She then developed general weakness, loss of weight, anemia, hypotension, and neuropathy. Lead concentrations in the blood were increased three-fold and urinary lead concentrations ten-fold, and a diagnosis of percutaneous lead intoxication was made. Treatment with dimercaptopropane sulfonic acid resulted in considerable reduction of the lead deposits, and the symptoms of poisoning subsided (6).

Second-Generation Effects

Fetotoxicity

Intrauterine lead intoxication has been reported.

- A 24-year-old pregnant woman, who had recently emigrated from India, had periodically over the course of 9 years taken tablets prescribed by an Ayurvedic doctor for a gastrointestinal complaint. The tablets had a high lead content. She presented at 30 weeks gestation with abdominal pain and progressive confusion, culminating in seizures (7). Her erythrocytes showed typical basophilic stippling and her blood lead concentration was 5.2 (reference range 0.06–0.6) μmol/l. She was given intramuscular dimercaprol and intravenous calcium disodium edetate and 36 hours later had an antepartum hemorrhage; labor was induced and she gave birth by vaginal delivery to a 1.6 kg girl, who was flaccid and areflexic and did not move in response to noxious stimuli, but had spontaneous ocular movements. She had bilateral diaphragmatic palsy. The cord blood lead concentration was 7.6 μmol/l, the erythrocyte porphyrin concentration was 20 (reference range 0.4–1.7) μmol/l, and radiography of the long bones showed increased bone density adjacent to the metaphyses. The infant was given chelation dimercaprol (4 mg/kg every 4 hours) and intravenous calcium disodium edetate 50 mg/kg. The blood lead concentration initially rose to 12 μmol/l and then fell rapidly over the next few days. A high urinary lead concentration on day 4 (52 μmol/l) showed that lead was being excreted. Facial, bulbar, proximal limb, and diaphragmatic muscle activity improved.

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Lefetamine

General Information

Lefetamine is an opioid receptor partial agonist, which combines the actions of amphetamines with opioid-like effects. It was a drug of abuse in Japan in the 1950s and later also in Italy (1). In 10 opiate addicts, lefetamine relieved acute opiate withdrawal symptoms and did not precipitate withdrawal symptoms in stable addicts (2).

During ordinary use sedation, tiredness, gastrointestinal disturbances, headache, sweating, and flushing have been observed with lefetamine (3).

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Leflunomide

General Information

The prodrug leflunomide (*N*-(4′-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide) is an isoxazole derivative. Its main metabolite is the active compound, A77 1726 (1).

Mechanism of action

A77 1726 inhibits dihydro-rate dehydrogenase, the rate-limiting enzyme in pyrimidine synthesis. It inhibits the proliferation of T and B cells, and probably acts via the production and action of interleukin-2. Besides its immunomodulatory action, A77 1726 also has an anti-inflammatory action by inhibition of nuclear factor kappa B (NFκB), tumor necrosis factor alfa (TNF-α),

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and interleukin 1 beta (IL-1β), and increased production of transforming growth factor beta-1 (TGF-β1) (2–5).

Pharmacokinetics

After oral administration, leflunomide undergoes rapid metabolism in the gut wall, plasma, and liver to A77 1726 (M1), peak plasma concentrations of which are reached after 6–12 hours. A77 1726 is highly (99%) bound to plasma proteins. Its pharmacokinetics are not affected by food, and dosage requirements are not influenced by age or sex. Enterohepatic recirculation and biliary recycling contribute to the long half-life of 2 weeks. About 90% of a single dose of leflunomide is eliminated, 43% in the urine, primarily as leflunomide glucuronides and an oxalinic acid derivative of A77 1726, and 48% in the feces, primarily as A77 1726. Impaired renal function can result in increased plasma concentrations of A77 1726. Elimination of A77 1726 can be dramatically increased by using colestyramine or activated charcoal (6,7).

Indications and clinical efficacy

Leflunomide has anti-inflammatory, immunosuppressive, and virustatic effects. Its efficacy has been demonstrated in patients with rheumatoid arthritis and psoriatic arthritis and other conditions in randomized, double-blind, placebo-controlled trials and other studies (8–32), and it was approved for treatment of adult rheumatoid arthritis in August 1998 (Table 1) (33). In three large phase III trials (US301, $n = 482$; MN301, $n = 358$; MN302, $n = 999$), leflunomide was as effective and well tolerated as methotrexate and sulfasalazine and superior to placebo (34). These data were confirmed by a meta-analysis (35,36). Leflunomide is therefore indicated for patients with rheumatoid arthritis who have failed first-line disease modifying anti-rheumatic drug therapy on the basis of efficacy, safety, and costs (36). It is effective as monotherapy and in combination with methotrexate or infliximab (6).

Clinical experience with leflunomide in patients with other autoimmune diseases is limited. Extended indications for the use of leflunomide include treatment of Crohn's disease in patients who are intolerant of standard immunomodulator therapy (31), chronic sarcoidosis (32), maintenance therapy of complete or partial remission in Wegener's granulomatosis (30), and mild to moderate systemic lupus erythematosus (29) (Table 1).

Leflunomide has been used as an immunosuppressive agent in kidney and liver transplant recipients to spare calcineurin inhibitors and glucocorticoids and to slow progression of chronic kidney graft dysfunction (28,37) (Table 1).

In animals, leflunomide had excellent antiviral activity against cytomegalovirus (CMV). It is currently indicated as second-line therapy for CMV disease after solid organ transplantation and in recipients intolerant of ganciclovir (38). Leflunomide also reduces HIV replication by about 75% at concentrations that can be obtained with conventional dosing (39).

General adverse drug reactions

The safety profile of leflunomide has been said to be excellent, with no myelosuppressive or nephrotoxic adverse effects (40,41). Its major adverse effects are gastrointestinal symptoms (diarrhea and nausea), abnormal liver function tests, skin rashes and pruritus, allergic reactions, alopecia, infections, weight loss, and hypertension (35,42–45). Minor adverse effects are musculoskeletal disorders. Rare adverse effects include sepsis, pancytopenia, interstitial lung disease, hypertriglyceridemia, vasculitis, aseptic meningitis, reversible neuropathy, and serious skin reactions (35,46–49).

In 3325 patients who took leflunomide, the rate of drug withdrawal was 42% within 33 months after approval by the US Food and Drugs Administration, and was more likely in patients who received a loading dose. The most common causes of discontinuation were inefficacy (30%), gastrointestinal symptoms (29%), non-adherence to therapy or loss to follow-up (14%), and raised liver enzymes (5%) (50).

However, the rate of adverse effects associated with leflunomide was significantly lower than with methotrexate and other disease-modifying antirheumatic drugs (DMARDs) in an analysis of 40 594 patients with rheumatoid arthritis (8,51). The incidences of adverse events per 1000 patient-years were as follows:

- no DMARDs: 383
- methotrexate: 145
- leflunomide monotherapy: 94
- methotrexate + other DMARDs: 70
- leflunomide + other DMARDs: 59
- leflunomide + methotrexate: 43
- other DMARDs: 143.

Leflunomide monotherapy also had the lowest rate of hepatic events in the DMARD monotherapy groups.

Further developments

Synthetic malononitrilamides (MNA) have been derived from A77 1726. FK778 is the most promising derivative, because of its much shorter half-life. It also blocks replication of herpesvirus in vitro and in vivo. It has therefore been used as part of an immunosuppressive regimen and as an antiviral agent after solid organ transplantation (52). FK778 is under investigation in a phase II trial after kidney transplantation (53).

Organs and Systems

Cardiovascular

The incidence of hypertension in patients with rheumatoid arthritis taking leflunomide 25 mg/day was 11% in a phase II trial (54). During phase III trials, there was new-onset hypertension in 2.1–3.7% (9,10). Increased sympathetic drive has been implicated in its pathogenesis, because leflunomide-induced hypertension is accompanied by an increased heart rate (55). However, this hypothesis remains to be tested.

Pulmonary hypertension has been described in association with leflunomide (56).

Respiratory

Respiratory symptoms in the MN301, US301, and MN302 trials in patients with rheumatoid arthritis included respiratory infections (21–27%), bronchitis (5–8%), increased cough (4–5%), rhinitis (2–5%), pharyngitis (2–3%), pneumonia (2–3%), and sinusitis (1–5%) (9,10,12).

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Table 1 Summary of the efficacy of leflunomide in controlled trials

Disease	Type of study; duration	Intervention	Outcome	References
Rheumatoid arthritis	Double-blind, randomized, controlled trial; 24 weeks	Leflunomide 50–100 mg/day for 1 day, then 5–25 mg/day ($n = 300$) versus placebo ($n = 102$)	Leflunomide 10 and 25 mg/day was significantly more effective than placebo	(8)
Rheumatoid arthritis	Double-blind, randomized, controlled trial; 12 months	Leflunomide 100 mg/day for 3 days, thereafter 20 mg/day ($n = 182$) versus methotrexate 7.5–15 mg/week ($n = 180$) versus placebo ($n = 118$)	American College of Rheumatology response and success rates were: leflunomide 52% and 41%, methotrexate 46% and 35%, and placebo 26% and 19%	(9)
Rheumatoid arthritis	Double-blind, randomized, controlled trial; 24 weeks	Leflunomide 100 mg/day for 3 days, then 20 mg/day ($n = 133$) versus sulfasalazine 2 g/day ($n = 133$) versus placebo ($n = 92$)	American College of Rheumatology 20 response rates were: leflunomide 55%, sulfasalazine 56%, and placebo 29%	(10,11)
Rheumatoid arthritis	Double-blind, randomized, controlled trial; 52 weeks	Leflunomide 100 mg/day for 3 days, then 20 mg/day ($n = 501$) versus methotrexate 7.5–15 mg/day ($n = 498$)	Both drugs effective, although methotrexate resulted in significantly greater improvement in tender and swollen joint counts compared with leflunomide	(12)
Rheumatoid arthritis	Double–blind, randomized, controlled trial; 6 months	Leflunomide 100 mg/day for 3 days, then 20 mg/day ($n = 133$) versus sulfasalazine 0.5–2 g/day ($n = 133$), versus placebo ($n = 92$)	Leflunomide slowed disease progression as early as 6 months, and there was continued retardation of radiographic progression at 2 years	(13)
Rheumatoid arthritis	Follow-up study; 2 years	Leflunomide ($n = 98$) versus methotrexate ($n = 101$)	American College of Rheumatology 20, 50, and 70 response rates for leflunomide versus methotrexate were 79 versus 67%, 56 versus 43%, and 26 versus 20%	(14)
Rheumatoid arthritis	Follow-up study; 2 years	Leflunomide 20 mg/day versus sulfasalazine 2 g/day	American College of Rheumatology 20 response rates were 82% leflunomide versus 60% sulfasalazine after 24 months	(15)
Rheumatoid arthritis	Follow-up study; 5 years	Leflunomide 10–20 mg/day (phase III) continued ($n = 214$)	American College of Rheumatology 20, 50, and 70 response rates after 1 year were maintained for up to 5 years	(16)
Rheumatoid arthritis	Single-center experience; 32 weeks	Leflunomide 100 mg/day for 3 days, then 20 mg/day plus infliximab 3 mg/kg at 2, 4, 8, 16, and 24 weeks ($n = 20$)	11/20 withdrawn (four infliximab infusion reactions, one Stevens–Johnson syndrome); the other patients achieved American College of Rheumatology 20 and 70 response rates in >80% and 46%	(17)
Rheumatoid arthritis	Double-blind randomized controlled trial; 24 weeks	Leflunomide 100 mg/day for 2 days, then 10 mg/day ($n = 130$) versus placebo ($n = 133$), both with methotrexate 10–25 mg/day	American College of Rheumatology 20 rates at 24 weeks: leflunomide + methotrexate 46% versus placebo + methotrexate 20%; similar drug withdrawal and adverse events rates	(18)
Rheumatoid arthritis	Multicenter experience; 24 weeks	Leflunomide 100 mg/day for 3 days, then 20 mg/day ($n = 969$)	191 withdrawn (107 adverse events, 26 lack of efficacy, 58 other reasons); 24% good and 45% moderate responses on the disease activity score, and 61%, 34%, and 9.6% achieved American College of Rheumatology 20, 50, and 70 response rates	(19)
Rheumatoid arthritis	Single-center experience; 3 months	Leflunomide 100 mg/day for 3 days, then 20 mg/day plus infliximab 3 mg/kg at 0, 6, and every 8 weeks ($n = 17$)	20 adverse effects in 13 patients; 8 discontinued	(20)
Rheumatoid arthritis	Single-center experience; 24 weeks,	Leflunomide 100 mg/day for 3 days, then 100 mg/week ($n = 50$)	American College of Rheumatology 20, 50, and 70 response rates at 24 weeks were 74%, 64%, and 28% (five withdrawn, six lost to follow-up)	(21)

Continued

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Table 1 Continued

Disease	Type of study; duration	Intervention	Outcome	References
Rheumatoid arthritis	Single-center experience; 6 months	Leflunomide 100 mg/day for 3 days, then 20 mg/day ($n = 378$)	American College of Rheumatology 20, 50, and 70 response rates at 6 months were 48%, 25%, and 12%	(22)
Rheumatoid arthritis	Extension of double-blind, randomized, controlled trial; 48 weeks	Leflunomide + methotrexate continued ($n = 96$) and placebo + methotrexate switched to leflunomide 10 mg/day + methotrexate ($n = 96$)	American College of Rheumatology 20 response rate was 59% at 24 weeks and 55% at 48 weeks in patients maintained on leflunomide + methotrexate, and patients switched from placebo to leflunomide + methotrexate increased their American College of Rheumatology 20 response rates from 25% at 24 weeks to 57% at 48 weeks	(23)
Rheumatoid arthritis	Double-blind, randomized, controlled trial; 24 weeks	Leflunomide 10 mg/day and 100 mg on day 3 ($n = 202$) versus 20 mg/day and 100 mg on days 1–3 ($n = 200$)	American College of Rheumatology (20 response rates: leflunomide 10 mg 50% and 20 mg 57%; adverse events: leflunomide 10 mg 15% and 20 mg 12%	(24)
Rheumatoid arthritis	Multicenter experience; 11–911 days	Leflunomide 100 mg/day for 3 days, then 20 mg/day ($n = 136$)	76% clinical response after 12 months, but 76/136 (56%) leflunomide withdrawn (29% adverse drug reactions and 13% lack of efficacy)	(25)
Psoriatic arthropathy, psoriasis	Double-blind, randomized, controlled trial; 24 weeks	Leflunomide 100 mg/day for 3 days, then 20 mg/day ($n = 95$) versus placebo ($n = 91$)	Leflunomide 59% and placebo 30% were responders at 24 weeks according to the psoriatic arthritis response criteria	(26)
Psoriasis	Phase II study; 12 weeks	Leflunomide 20 mg/day ($n = 8$)	6/8 clinical effectiveness (psoriasis area and severity index score 20 at baseline versus 13 at 12 weeks)	(27)
Liver and kidney transplant recipients	Single-center experience	Leflunomide dosage adjusted to a trough concentration of 100 μg/ml ($n = 53$)	Immunosuppressive potency in liver and kidney transplant recipients, allowing dosage reduction of calcineurin inhibitors and glucocorticoids, but anemia might be dose-limiting after kidney transplantation	(28)
Systemic lupus erythematosus	Single-center experience, double-blind, randomized, controlled trial; 24 weeks	Leflunomide 100 mg/day for 3 days, then 100 mg/day ($n = 6$) versus placebo ($n = 6$)	Disease activity fell significantly in both groups after 6 months, and the reduction in SLE disease activity index from baseline to 24 weeks was significantly greater with leflunomide than with placebo	(29)
Wegener's granulomatosis	Phase II study; 52 weeks	Leflunomide 20–40 mg/day ($n = 20$)	Maintenance of complete or partial remission after cyclophosphamide + glucocorticoid therapy resulted in one major and eight minor relapses	(30)
Crohn's disease	Single-center experience; 3 years	Leflunomide 20 mg/day ($n = 12$)	8/12 clinical responses; seven continued maintenance therapy and one relapsed after follow-up of 6–78 weeks	(31)
Chronic sarcoidosis	Single-center experience; 1 year	Leflunomide 100 mg/day for 3 days, then 10–20 mg/day ($n = 32$; 17 leflunomide and 15 leflunomide + methotrexate)	Complete or partial responses in 13/17 leflunomide and in 12/15 leflunomide + methotrexate	(32)

In Japan, acute interstitial pneumonia due to leflunomide has been mentioned as a serious and severe adverse effect, with an incidence of 1.1% and a fatal outcome in 0.36% (57–59).

- A 49-year-old man with rheumatoid arthritis taking methotrexate developed a skin eruption and a severe non-productive cough after taking leflunomide for 17 days (58). He died of respiratory failure 128 days after the diagnosis of acute interstitial pneumonia.
- A 54-year-old woman with rheumatoid arthritis developed an interstitial pneumonia 2 weeks after the end of a 6-week course of treatment with leflunomide (60).

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The onset of the pneumonia was preceded by raised serum liver enzymes and hypertension. The acute respiratory failure improved with prednisolone and colestyramine.

However, clinical trials and subsequent observational studies outside Japan have not suggested that leflunomide causes an excess of pulmonary adverse effects (61).

Nervous system

Leflunomide can cause a peripheral reversible neuropathy (49,62–65). This neuropathy is usually axonal in nature, affecting multiple sensory or motor nerves of distal extremities. The mean time of onset of peripheral neuropathy was 6 months after the start of leflunomide therapy, with a range of 3 days to 3 years. Neurological improvement was more likely after drug withdrawal within 30 days after the onset of the symptoms of neuropathy compared with continuous administration (63).

Peripheral neuropathy attributed to leflunomide was observed in two patients (49).

- A 76-year-old man, with an 18-month history of seropositive rheumatoid arthritis, chronic emphysema, and pulmonary fibrosis, developed polymyalgia and was treated with glucocorticoids and azathioprine. Azathioprine was withdrawn after a rise in aspartate transaminase. He was then given leflunomide 100 mg over 3 days followed by 10 mg/day as a maintenance dosage. After 2 weeks, he developed a sensory neuropathy with a stocking distribution up to the malleoli and leflunomide was withdrawn 4 weeks later. During this time he had also been taking prednisolone, tramadol, disodium etidronate, indoramin, and celecoxib, none of which is known to cause neuropathy. Glucose, vitamin B12, serum folate, thyroid function, serum proteins, Bence–Jones protein electrophoresis, cryoglobulins, anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, the Venereal Disease Research Laboratory test, and hepatitis B and C serology were all normal or negative. Nerve conduction was consistent with motor sensory axonal peripheral neuropathy of the lower limbs. On review 3 months after withdrawal of leflunomide, there was clear subjective and objective improvement of the neuropathy, confirmed by repeat nerve conduction studies.
- A 69-year-old woman with a 10-year history of seropositive erosive rheumatoid arthritis, previously treated with gold salts followed by methotrexate, started to take leflunomide and 3 months later reported numbness in the fingertips and feet bilaterally, with a glove-and-stocking sensory neuropathy involving all fingertips and extending to the mid-shins. Leflunomide was withdrawn. Other medications included prednisolone, lansoprazole, simvastatin, losartan, and amiodarone, which she had been taking for a long time without adverse effects. Screening tests for neuropathy, as in the previous case, were normal or negative. There was no cord or nerve root compression on magnetic resonance imaging of the cervical spine. Nerve conduction studies confirmed a sensory motor peripheral neuropathy. She reported marked improvement in her symptoms 3 months after withdrawal of treatment, and this was confirmed on clinical examination and repeat nerve conduction studies.

One case of leflunomide-induced aseptic meningitis has been reported (48).

Metabolism

Life-threatening hypertriglyceridemia has been described during treatment with leflunomide (46).

Hematologic

Pancytopenia, thrombocytopenia, and anemia can occur during leflunomide treatment (21,66–68). The risk of pancytopenia is increased when it is used in combination with methotrexate and in elderly patients. Its course can be fatal and the time of onset ranges from 11 days to 4 years (66). Anemia has been reported in renal transplant recipients (28).

Leflunomide-associated thrombocytosis and leukocytosis resolved after colestyramine washout and withdrawal of leflunomide (69).

Mouth and teeth

In the MN301, US301, and MN302 trials, mouth ulceration occurred in 3–5% (9,10,12).

Gastrointestinal

In the MN301, US301, and MN302 trials, gastrointestinal symptoms consisted of diarrhea (22–27%), nausea (13%), dyspepsia (6–10%), abdominal pain (6–8%), mouth ulceration (3–5%), vomiting (3–5%), anorexia (3%), and gastroenteritis (1–3%) (9,10,12). Diarrhea and nausea are more common in patients who receive a loading dose, but the onset of action can be delayed without the loading dose (36). Gastrointestinal symptoms occur mainly during the first 6 months after initiation of leflunomide. The severity of symptoms was mild. If there is severe diarrhea and/or weight loss, withdrawal of leflunomide and endoscopic examination is advised, since ulcerative and microscopic colitis have been detected under such circumstances (70). The pathophysiology of leflunomide-associated diarrhea and weight loss is unclear. Weight loss of 9–24 kg was observed in five of 70 patients who took leflunomide, despite normal concentrations of thyroid-stimulating hormone and no other gastrointestinal complaints (44).

Liver

Leflunomide can cause abnormal liver function tests, but the risk of serious and non-serious hepatic adverse events is not higher than with methotrexate (71). In the MN301, US301, and MN302 trials, there were abnormal liver enzymes in 6–10% (9,10,12). The co-administration of methotrexate is a risk factor (18,72–74). According to the National Cancer Institute Common Toxicity Criteria, 8.9% of patients developed grade 2 or 3 hepatotoxicity within the first year, mainly within 6 months and in combination with methotrexate, after the start of leflunomide therapy based on liver enzyme determinations (72). The use of folate was also associated with less

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frequent changes in liver function tests (9,10,12). Nevertheless, leflunomide can cause severe liver injury (75–78), estimated at a rate of one in 200 users (79). Leflunomide is therefore not recommended in patients with significant liver impairment or evidence of infection with hepatitis B or C virus (80).

A CYP2C9 polymorphism has been implicated in the pathogenesis of leflunomide hepatotoxicity (77).

- A 67-year-old woman with rheumatoid arthritis developed diarrhea and raised liver enzymes after taking leflunomide for 15 days. Histologically, the liver showed acute hepatitis. She was homozygous for the CYP2C9*3 allele. The liver damage subsided within a few weeks.

Urinary tract

Interstitial nephritis occurred in one case of chronic overdose of leflunomide (81).

Skin

Adverse effects of leflunomide on the skin in patients with rheumatoid arthritis include alopecia (9–17%), rash (11–12%), pruritus (5–6%), dry skin (3%), and eczema (1–3%) (9,10,12). Single cases of an erythema multiforme-like drug eruption (82), exfoliative dermatitis (83), a lichenoid drug reaction (84), and skin ulceration (85) have been reported.

Immunologic

In the treatment of rheumatoid arthritis leflunomide can cause a vasculitis, and acute necrotizing vasculitis is rare but serious (47,86).

Long-Term Effects

Mutagenicity

A minor metabolite of leflunomide, 4-Trifluoromethylaniline, was mutagenic in vitro (87).

Tumorigenicity

Male mice had an increased incidence of lymphoma at an oral leflunomide dose of 15 mg/kg, and female mice had a dose-related increased incidence of bronchoalveolar adenomas and carcinomas beginning at 1.5 mg/kg (87).

Second-Generation Effects

Fertility

Leflunomide did not affect fertility in rats (87).

Teratogenicity

In oral embryocytotoxicity and teratogenicity studies in rats and rabbits, leflunomide was embryocytotoxic (growth retardation, embryolethality) and teratogenic (malformations of the head, rump, vertebral column, ribs, and limbs) (87). Not only is leflunomide teratogenic and fetotoxic in animals, but its active metabolite is detectable in plasma up to 2 years after withdrawal. Therefore, the fetus could have in utero exposure to leflunomide up to 2 years after the end of treatment. Leflunomide has been classified as pregnancy category X by the Food and Drug Administration (87,88). However, experience in a very small group of pregnant women who took leflunomide and continued their pregnancy to term gave no indication of an increase in teratogenesis (89). Nevertheless, the majority of 30 pregnant women were elected to interrupt their pregnancies, except three patients (87). At present, withdrawal of leflunomide is mandatory before pregnancy, and colestyramine treatment is advised to wash out leflunomide (80,87,90,91). Both men and women who want to have a child should discontinue leflunomide and take colestyramine to wash it out. Leflunomide has not been studied in children, possibly because of its cytotoxic nature. In particular, its teratogenic potential may be a concern when treating adolescent girls (92).

Lactation

Breastfeeding by nursing mothers is not recommended, because it is unknown if leflunomide is excreted in human milk (80,87).

Drug Administration

Drug dosage regimens

Leflunomide is taken orally. In most regimens it is begun with a loading dose of 100 mg/day over 3 days followed by a maintenance dosage of 10–20 mg/day. Leflunomide 100 mg/week had similar effectiveness and less toxicity in open trials compared with daily dosing (21,93).

Drug–Drug Interactions

Infliximab

The administration of infliximab after or simultaneously with leflunomide seems to be safe and effective in patients with rheumatoid arthritis (20,94,95).

Rifampicin

Multiple doses of rifampicin increase leflunomide concentrations (96).

Warfarin

A case of probable interaction of leflunomide with warfarin has been reported (97).

- A 49-year-old man with resistant rheumatoid arthritis took leflunomide 100 mg/day for 3 days. His international normalized ratio (INR) had been stable for 1 year while he was taking warfarin, and 2 days before starting treatment with leflunomide it was 3.4. After he took the second dose of leflunomide, he developed gross hematuria. His INR had risen to 11, and warfarin was withdrawn. The hematuria resolved spontaneously several hours later, but his INR remained raised for the next 2 days, even though he had stopped taking warfarin. He was given intravenous vitamin K 1 mg on the third day, and 12 hours later the INR fell to 1.9.

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Subsequently he began taking warfarin again, but at a lower dose of 1 mg/day, which was sufficient to maintain his INR within the target range.

A77 1726 inhibits CYP2C9 and might increase the systemic availability of CYP2C9 substrates, such as warfarin and phenytoin (97,98).

Management of Adverse Drug Reactions

Usually, overdosage and adverse events can be managed by dosage reduction, the addition of colestyramine, and symptomatic therapy (36). However, in one study in patients with rheumatoid arthritis, leflunomide 10 mg/day compared with 20 mg/day was associated with less efficacy and more adverse events leading to treatment withdrawal (24). Colestyramine 3 × 8 g/day for 11 days is recommended to wash out leflunomide, if A77 1726 plasma concentrations do not fall to 0.02 mg/l or less, additional colestyramine is advised. Without this washout procedure, it can take up to 2 years to reach A77 1726 plasma concentrations of 0.02 mg/l. Oral activated charcoal 50 g every 6 hours for 24 hours also reduced plasma A77 1726 concentrations (80).

Plasma A77 1726 concentrations can be measured by high-performance liquid chromatography (99,100). Monitoring of platelets, white blood cells, hemoglobin, and alanine transaminase activity is advised at baseline, monthly for 6 months, and every 6–8 weeks thereafter. Leflunomide should be withdrawn if pulmonary symptoms such as cough and dyspnea start or worsen (80).

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Lentinan

General Information

Lentinan is an immunomodulating glucan that is extracted from the mushroom *Lentinus edodes*. It has been used in small numbers of patients with gastric cancers (1–3) and malignant effusions (4). It has also been used in HIV-positive patients (5) and to ameliorate impairment of natural killer cell activity after cardiopulmonary bypass (6).

General adverse effects

The incidence of adverse effects due to lentinan, particularly those requiring withdrawal, is low (5). Of 98 patients with HIV infection, treatment had to be withdrawn in four because of adverse effects; other adverse effects included one case each of an anaphylactoid reaction, back pain, leg pain, depression, rigors, fever, chills, granulocytopenia, and raised liver enzymes (5).

Organs and Systems

Hematologic

Leukopenia occurred in one of 19 patients with unresectable or recurrent gastric cancers when they were given lentinan 2 mg/kg intravenously together with TS-1 (tegafur + gimestat + otastat potassium in a molar ratio of 10:4:10) 80 mg/m^2/day (7).

Skin

Skin rashes have been noted in 4% of patients treated with lentinan (8).

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Lercanidipine

See also Calcium channel blockers

General Information

Lercanidipine is a third-generation dihydropyridine for once-daily dosing in hypertension. It has similar antihypertensive efficacy and tolerability to other calcium channel blockers (1).

Reference

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Lesopitron

General Information

Lesopitron is a non-benzodiazepine anxiolytic drug. Its structure is similar to that of buspirone, and it is an agonist at central serotonin (5-HT$_{1A}$) receptors.

A 6-week, double-blind, randomized, parallel, phase II, single-center, outpatient study has been performed to study the efficacy and safety of lesopitron 40–80 mg/day compared with lorazepam 2–4 mg/day and placebo in 161

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patients with generalized anxiety disorder (1). The most common adverse events associated with lesopitron were somnolence, headache, and dyspepsia, compared with headache, somnolence, and insomnia with lorazepam. Patients treated with placebo mainly experienced headache, somnolence, and pharyngitis.

Reference

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Letosteine

General Information

Letosteine is taken orally to loosen bronchial secretions and facilitate expectoration (SEDA-5, 170) (SEDA-7, 191) (1).

Organs and Systems

Gastrointestinal

Two of 37 patients experienced gastralgia and vomiting, severe enough to stop therapy (SEDA-7, 191). In another series of 40 patients, five had gastralgia and nausea, requiring withdrawal of therapy in three.

Reference

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Leukotriene receptor antagonists

General Information

The leukotriene receptor antagonists are antagonists of cysteinyl leukotrienes at $CysLT_1$ receptors and include zafirlukast, montelukast, and pranlukast.

Therapeutic studies

Placebo-controlled studies

The efficacy and tolerability of montelukast, in combination with a selective histamine H_1 receptor antagonist (loratadine), has been investigated in a randomized, double-blind, crossover study for 2 weeks in 125 asthmatic subjects (mean FEV_1 67% predicted), who took montelukast 10 mg plus loratadine 20 mg or placebo od for 2 weeks (1). The subjects were symptomatic, in that their mean baseline daily use of $beta_2$-adrenoceptor agonists was 5.1 inhaled metered doses. During the study, the percentage increase in FEV_1 from baseline was significantly greater with montelukast plus loratadine than with montelukast alone (14 versus 9.7%). The most common adverse events during the trial were headache and upper respiratory tract infection (each in about 10% of subjects). There were no significant differences in the frequencies of adverse experiences between montelukast plus loratadine and montelukast alone. Ten patients withdrew because of an adverse event; six had exacerbation of asthma requiring steroid administration (three in each of the two arms of the study). One patient taking montelukast plus loratadine and four taking montelukast alone had transient self-limiting laboratory abnormalities.

The acute effects of intravenous and oral montelukast on airway function have been compared in a randomized, double-blind, crossover study in 51 asthmatic patients (mean FEV_1 63.8% predicted) (2). The intravenous dose (7 mg) was known to produce a comparable AUC to that obtained with an oral dose of 10 mg. FEV_1 was measured at 0.25, 0.5, 1, and 2 hours and then at regular intervals up to 24 hours after dosing. After intravenous and oral montelukast, the FEV_1 $AUC_{0–24}$ was significantly greater than after placebo (mean increases 21, 16, and 7.8% for intravenous, oral, and placebo respectively). The mean percentage change in FEV_1 for intravenous montelukast was greater than for oral montelukast in the first hour (18 versus 13%). The most frequently reported adverse events included headaches, which occurred in three patients taking placebo, four taking oral montelukast, and one taking intravenous montelukast. Influenza was reported in two patients taking placebo. It was noteworthy that there were no local adverse events at the intravenous site of the montelukast administration. This study has raised the possibility that a bolus dose of intravenous montelukast may have a role in the management of acute exacerbations of asthma.

Organs and Systems

Respiratory

Leukotriene receptor antagonists and Churg–Strauss syndrome

Churg–Strauss syndrome is a rare form of allergic granulomatous vasculitis, first described in 1951, characterized by the histological findings of eosinophilic tissue infiltration, extravascular eosinophil granulomas, and necrotizing vasculitis. It develops in patients with a history of upper airway disease (especially allergic rhinitis and sinusitis) and asthma. There are different definitions of the syndrome, and it is important to know which definition is being used when the results of different incidence studies are being compared. Clinically the syndrome has been defined (3) as a combination of asthma, peripheral eosinophilia (over 1.5×10^9/l), and a systemic vasculitis involving two or more extrapulmonary organs. Recognized clinical risk factors include moderate to severe asthma, chronic sinusitis, and a recent reduction in systemic corticosteroid therapy (4). An important feature is the phasic developmental pattern of the disease, and corticosteroid therapy suppresses some manifestations of the syndrome, leading to incomplete disease. Churg and colleagues labeled these cases "formes frustes" of Churg–Strauss syndrome (5). Careful monitoring must be ensured when tapering corticosteroids in steroid-dependent patients to avoid development of incomplete disease.

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Presentation

Of 22 asthmatic patients taking leukotriene receptor antagonists who developed Churg–Strauss syndrome, 13 had used zafirlukast, eight montelukast, and one pranlukast (6). All had used inhaled or oral glucocorticoids. The onset of the syndrome was at 2 days to 10 months after starting treatment with the leukotriene receptor antagonist; the interval between the last dose of oral steroids and the recognized onset of Churg–Strauss syndrome ranged from 3 days to 8 months. In several patients the signs and symptoms of Churg–Strauss syndrome became manifest after the start of leukotriene receptor antagonist treatment and tapering of inhaled/oral steroids (13 of 23 patients).

Eight patients with steroid-dependent asthma, who had been able to either discontinue or reduce their oral glucocorticoid requirement subsequent to starting treatment with zafirlukast, developed Churg–Strauss syndrome (7).

- Two 50-year-old men, both using inhaled glucocorticoids, presented with Churg–Strauss syndrome after taking montelukast for 4–5 months, not related to steroid tapering (8). One had a history of asthma and recurrent sinusitis for 5 years with intermittent short-course oral glucocorticoids and continued inhaled steroids, whereas the other had had asthma for 1 year treated with only inhaled glucocorticoids.
- Two women (aged 60 and 62 years) with allergic rhinitis and asthma, one using inhaled glucocorticoids and the other oral glucocorticoids, developed Churg–Strauss syndrome after taking montelukast (9). In the woman using oral steroids, dosage reduction preceded the onset of the syndrome; in the woman using inhaled steroids there was no dosage reduction. The authors also presented the case of a 54-year-old man with a history of Churg–Strauss syndrome who relapsed after taking montelukast.
- A 50-year-old man with a history of severe asthma and tapering of prednisone took montelukast and developed an erythematous rash and mononeuritis multiplex; skin biopsy confirmed the diagnosis of Churg–Strauss syndrome (10).
- A 54-year-old man with no history of glucocorticoid therapy presented with systemic symptoms and a purpuric rash after taking zafirlukast; the diagnosis was Churg–Strauss syndrome (11).
- An 18-year-old woman with childhood asthma, using inhaled glucocorticoids and zafirlukast, developed Churg–Strauss syndrome 10 days after starting to use rokitamycin (12).

Other case reports of interest include pulmonary eosinophilia in association with montelukast (13) and the clinical exacerbation of ulcerative colitis in a patient with steroid-dependent asthma after the introduction of zafirlukast (14). Drug-induced lupus syndrome has been reported in a child with an onset 10 days after beginning treatment with zafirlukast. The child had not been taking oral glucocorticoids (15).

Mechanism

It was originally postulated that the patients had a primary eosinophilic disorder, which was unmasked by the reduction (or withdrawal) of glucocorticoids, which was possible because the addition of zafirlukast had controlled their asthma. A subsequent report of two patients, who were not taking systemic glucocorticoids and developed Churg–Strauss syndrome in association with zafirlukast, raised some doubts about the hypothesis (16). However, there must be uncertainty about implicating zafirlukast in one of these cases, as there appeared to be a delay of 2 months from the withdrawal of zafirlukast to the onset of symptoms, which were subsequently attributed to Churg–Strauss syndrome.

- A 52-year-old woman developed Churg–Strauss syndrome some 12 weeks after beginning treatment with pranlukast and 8 weeks after discontinuing low-dose oral prednisolone (5 mg on alternate days) (17).
- Churg–Strauss syndrome has been reported with montelukast in a patient who had not taken oral glucocorticoids. Symptoms developed within 2 days of beginning treatment with montelukast (18).

The hypothesis of unmasking of Churg–Strauss syndrome (meaning either unmasking of a previously contained pathological condition or the clinical declaration of a "forme fruste") after reduction of glucocorticoid dosage (4,19) is supported by the fact that Churg–Strauss syndrome has also been reported in asthmatic patients who taper their doses of glucocorticoid after the introduction of other antiasthmatic drugs (4). It seems unlikely that leukotriene receptor antagonists themselves provoke Churg–Strauss syndrome, since none of the established mechanisms of adverse drug reactions provides a plausible explanation for the association (4).

There remains the unlikely possibility that in some cases there is direct allergy to the drugs, manifesting as a granulomatous angiitis. In any event, clinicians should be aware of this possibility, although it is rare, and discontinue the drugs in cases of suspicion and undertake appropriate investigations.

Incidence

There are sufficient cases of Churg–Strauss syndrome to estimate its incidence as probably less than one per 20 000 patients. Whilst this may be more than the estimated incidence of this syndrome in the general population, this apparent increase in incidence does not of itself implicate the drugs as being causal. For example, there may be increased detection related to the increased vigilance associated with the introduction of this new class of drugs. If the antileukotriene drugs are implicated in some way in the development of Churg–Strauss syndrome, the precise mechanism is uncertain. Unmasking pre-existing Churg–Strauss syndrome by permitting glucocorticoid withdrawal is one possibility. Another possibility is that the drugs elicit an allergic response that manifests itself as a granulomatous angiitis, a phenomenon that has been reported rarely with other drugs.

The incidence of Churg–Strauss syndrome among asthmatic patients has been calculated in a cohort study of 36 230 patients with asthma (20). The incidence rates of definite Churg–Strauss syndrome were 0–67 cases per million per year, depending on the definition used. The small number of cases did not allow subgroup analysis. The occurrence of Churg–Strauss syndrome during leukotriene receptor antagonist therapy could therefore be coincidental, because the rate of 64 cases per million patients per

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year in association with leukotriene receptor antagonists is comparable to the estimated rate of 18–74 cases per million patients per year in the asthma population observed before the introduction of these drugs (4,6,19). Large epidemiological studies, including data on glucocorticoid-naive patients using leukotriene receptor antagonists, are needed to address this question further.

Liver

Asymptomatic increases in serum liver enzymes, to two or three times the upper limit of the reference ranges, were reported in 1.5% of over 4000 patients in the premarketing clinical trials of zafirlukast, but no severe hepatotoxicity was reported. With more extensive use of zafirlukast, some case reports of severe liver injury appeared. Three patients developed severe liver injury after taking zafirlukast 20 mg bd for several months (21). The evidence that zafirlukast was the probable cause of the hepatic injury was based on the rigorous exclusion of other causes of acute hepatitis, liver biopsies with histological characteristics consistent with toxic injury, the presence of hypersensitivity suggestive of a drug reaction in one patient, and inadvertent rechallenge in one patient. In one case a liver transplant was required. The authors stated that the mechanism of the drug-induced hepatotoxicity was not known but they speculated that it may be of immunological origin or, alternatively, that metabolism by CYP2C9 may create toxic metabolites. Whatever the mechanism, hepatotoxicity with zafirlukast is rare. The Acute Liver Failure Study Group, a consortium of 20 academic medical institutions in the USA cooperating in the prospective collection of data on acute liver failure, has not identified any other cases of acute liver injury associated with zafirlukast.

Urinary tract

Glomerulonephritis has been attributed to montelukast (22).

- A 46-year-old woman developed a severe systemic inflammatory reaction characterized by eosinophilia and necrotizing glomerulonephritis. About 4 months after montelukast was added to her existing treatment with budesonide, formoterol, and terbutaline for asthma. At the time of her initial presentation she was treated with azithromycin and amoxicillin, but these drugs were discounted as possible causes as her illness had already begun before she was treated with them. Once the diagnosis was made, montelukast was withdrawn and she improved with glucocorticoids over the next 4 months.

From the limited detail of this brief case report, it is by no means certain that montelukast was the cause of the systemic illness.

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Levamisole

General Information

Levamisole is the levorotatory isomer of tetramisole. Originally used only as an antihelminthic drug, it acts by paralysing the musculature of susceptible nematodes so that they are expelled by peristalsis. It is rapidly metabolized and excreted, with a half-life of about 4 hours.

Use in infective conditions

Treatment of ascariasis with a single oral dose of levamisole 2.5 mg/kg is effective, with evidence of toxicity in under 1% of patients.

Levamisole has been used experimentally in leprosy, particularly in combination with dapsone. This combination was used in a documented series of Indian patients, some currently lepromatous and others in the course of a leprosy reaction (1). When using doses sufficient to provide as good an effect as that obtained with clofazimine + dapsone in a comparison group, adverse effects were limited to gastrointestinal intolerance (which was usually mild), affecting only five of the 30 patients treated; an incidental case developed pyrexia.

Use in non-infective conditions

Levamisole has immunostimulatory activity by modulating the cell-mediated immune response and restoring T cell functions. It has therefore been used extensively and for extended periods of time in various rheumatic and other chronic diseases, in aphthous ulceration, nephrotic syndrome, warts, and malignancies, such as cancers of the head and neck and, in combination with 5-fluorouracil, colorectal cancer (SEDA-20, 348). Under these conditions, its adverse effects are more frequent and rather different because of the differing dosage scheme and presumably also the greater sensitivity of the individual, quite apart from the fact that it is often used in combination, for example with 5-fluorouracil; some 5% of patients fail to complete the course of treatment because of adverse effects. Most of the material in this record is necessarily derived from experience with long-term treatment; where possible a distinction will be drawn between adverse effects occurring under these conditions and those experienced during the acute treatment of tropical disorders.

Observational studies

Aphthous stomatitis

Levamisole has been used in the treatment of recurrent aphthous stomatitis (2) and its value reviewed (3). In four of seven placebo-controlled studies there was a reduction in the frequency and duration of aphthous ulcers during levamisole treatment. Efficacy did not differ whether levamisole was given routinely or started at the first sign of ulcers. In most patients levamisole was well tolerated. Of 128 patients who took levamisole, two withdrew as result of adverse effects (nausea and flu-like symptoms). The most frequent adverse effects were dysgeusia (21%) and nausea (16%). The other adverse effects occurred in less than 10% of the patients and included dysosmia, headaches, diarrhea, flu-like symptoms, and rash, but not all may have been due to levamisole. Levamisole rarely results in objective clinical improvement, and the associated adverse effects discourage its use.

Cancers

In 63 patients with stage III and stage IV squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx, and larynx, with no distant metastases, randomized to either adjuvant oral chemotherapy with futraful, uracil, and levamisole ($n = 29$) or no treatment ($n = 34$), oral chemotherapy showed a trend of better control of distant tumor recurrence (4). However, there was no statistically significant improvement in overall long-term survival. Of the 29 patients who received adjuvant oral chemotherapy, 17 finished the 1-year course without withdrawing. In nine patients futraful, uracil, and levamisole was withdrawn because of local, regional, or distant metastases. Three patients withdrew after 4 months because of vomiting and mucositis. One developed a mild gastric upset and completed the course. There were no major hematological or nephrotoxic adverse effects.

Candidiasis

In two patients with thymoma associated with myasthenia gravis, who both had recurrent oral candidiasis after thymectomy, radiotherapy, and chemotherapy levamisole was added as adjunctive therapy in combination with oral nystatin (5). Oral candidiasis responded favorably and substantial relief was obtained, with a concurrent increase in T cells and CD4/CD8 ratio, suggesting restoration of T cell immunity. Adverse effects were not mentioned.

Glomerulonephritis

In an extensive review of the treatment of minimal lesion glomerulonephritis the use of levamisole was briefly mentioned (6). The author concluded that levamisole has a beneficial effect in this disorder, although no new studies have appeared in recent years and well-controlled studies are scarce. Levamisole appears to be well tolerated in this condition. The adverse effects were neutropenia, rash, and raised liver transaminases.

Nephrotic syndrome

In 11 children with nephrotic syndrome, of whom five were glucocorticoid-sensitive, six glucocorticoid-resistant, and all resistant to other immunosuppressive drugs, levamisole 2.5 mg/kg was given every 48 hours for up to 18 months (7). Two patients were also given ciclosporin. All the patients in the steroid-sensitive group but none in the steroid-resistant group reacted favorably to levamisole, with disappearance of protein from the urine. There

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were serious adverse effects in two patients: one developed a transient leukopenia 2 months after the start of treatment and another developed a severe exacerbation of pre-existing psoriasis, although that may have been due to the withdrawal of cyclophosphamide.

Levamisole 2 mg/kg on alternate days was given to 25 glucocorticoid-dependent children with frequent relapses of idiopathic nephrotic syndrome (8). The steroid was tapered, and continued for 3–14 months. During treatment with levamisole the relapse frequency was reduced by 40%. Two patients developed mild transient leukopenia, which disappeared 2 weeks after withdrawal. One had a slight rash that disappeared while treatment was continued and one complained of epigastric pain, which led to drug withdrawal.

In a detailed review of the management of nephrotic syndrome in childhood, levamisole was advocated as a weak but effective glucocorticoid-sparing agent (9). In a prospective study in 20 children (aged 3–15 years; 16 boys, 4 girls) with steroid-dependent minimal-change nephrotic syndrome, there were no significant adverse effects during adjunctive therapy with levamisole, which led to successful withdrawal of glucocorticoids after 2 months in 11 children (10).

Pediculosis capitis

In 28 patients with pediculosis capitis (aged 7–12 years) levamisole was given in a dose of 3.5 mg/kg for 10 days; there were no adverse reactions (11).

Rheumatoid arthritis

The possible benefits of levamisole in rheumatoid arthritis are generally outweighed by its adverse effects (SEDA-11, 277) (12).

Comparative studies

Colorectal cancer

The efficacy of levamisole has been studied in several studies of patients with colorectal carcinoma (13–15). In a phase III trial 5-fluorouracil alone, 5-fluorouracil with levamisole, and 5-fluorouracil with hepatic irradiation have been compared in patients with residual, non-measurable, intra-abdominal metastases after resection of colorectal carcinoma (13). The adverse effects were as expected, and there were no differences between any of the treatments. The main adverse effects were hematological and gastrointestinal. However, analysis of life-threatening adverse effects showed some slight differences: there were fewer than expected in the 5-fluorouracil alone group, and more than expected in the 5-fluorouracil plus hepatic irradiation group. There was no treatment advantage for any of the combinations over 5-fluorouracil alone.

Levamisole combined with 5-fluorouracil in the adjuvant treatment of resected colon cancer has been studied in a prospective, randomized trial in which 891 patients were randomized to receive either intensive fluorouracil and leucovorin combined with levamisole, or a standard regimen of fluorouracil plus levamisole (16). The patients were then again randomized to receive either 6 or 12 months of treatment. Standard fluorouracil plus levamisole was not as effective as fluorouracil, levamisole, and leucovorin, and treatment for 12 months was not superior to treatment for 6 months. Unfortunately, there was no treatment arm with fluorouracil and leucovorin only, which is now widely considered to be the treatment of choice. Serious grade 3–4 adverse effects were more frequent in the three-drug treatment groups, and consisted of diarrhea (13 versus 3 patients in the 6-month groups, 17 versus 7 in the 12-month groups) and stomatitis (10 versus 3 in the 6-month groups, 11 versus 6 in the 12-month groups). Leukopenia occurred more frequently in the standard treatment groups (10 versus 18, one of whom died, in the 6-month groups, and 13 patients, one of whom died, versus 14, one of whom died). There were four treatment-associated deaths.

In another study combined intravenous and intraperitoneal fluorouracil plus leucovorin was compared with standard treatment with fluorouracil and levamisole in 241 patients with resected stage 3 or high-risk stage 2 colon cancers (17). In the combined treatment group there was an increased disease-free interval, an estimated 43% reduction in death rate, and a reduction in local tumor recurrence. Adverse effects were relatively uncommon and were generally judged to be mild to moderate; they were slightly more common in those treated with fluorouracil and levamisole, and consisted of nausea and vomiting (18 versus 14%), diarrhea (16 versus 10%), mucositis (17 versus 12%), granulocytopenia (29 versus 23%), and thrombocytopenia (5 versus 3%). Four cases of unspecified nervous system toxicity were noted in those given fluorouracil plus levamisole. There was abdominal pain during or shortly after intraperitoneal drug administration in 19% of patients. Overall 53% of the patients given fluorouracil plus levamisole and 56% of those given fluorouracil plus leucovorin had mild to moderate adverse effects. Severe reactions, requiring a 20% dosage reduction of fluorouracil, were more common in the fluorouracil plus levamisole arm (13 versus 3%). There were no deaths. Unfortunately, in this study no patients were treated with fluorouracil and leucovorin intravenously only.

It is likely that most of these reported adverse effects, although perhaps enhanced by levamisole, except for the nervous system toxicity noted in a few individuals, were caused by fluorouracil. This has been further emphasized by a dose-finding study to determine the maximum tolerated dose of levamisole in the treatment of colon cancer in 38 patients with advanced non-resectable colon cancer, treated with fluorouracil 450 mg/m^2 by rapid intravenous infusion for 5 days (18). Levamisole was given orally three times daily for 5 days every 5 weeks until disease progression. The main dose-limiting toxic effects were nausea and vomiting and an unpleasant metallic taste. The dose used was about five times the total amount of levamisole given in the standard fluorouracil plus levamisole regimen. Levamisole enhanced the gastrointestinal toxicity of fluorouracil, with anorexia, nausea, vomiting, and occasional diarrhea, but did not enhance the bone-marrow suppression associated with fluorouracil. Increasing the dose of levamisole to 150 mg/m^2 tds for 5 days resulted in significant nervous system toxicity, with confusion, vertigo, and severe vomiting. None of the patients treated with this dosage were able to complete the course.

Fluorouracil plus leucovorin has been compared with fluorouracil plus levamisole and combined fluorouracil

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plus leucovorin and levamisole in 2151 patients with Dukes B and C colon cancers (19). The regimens were as follows:

- fluorouracil plus leucovorin: six 8-week cycles of leucovorin 500 mg/m^2 as a 2-hour infusion repeated weekly for six doses and fluorouracil 500 mg/m^2, given as an intravenous bolus 1 hour after the start of the leucovorin infusion, also weekly for six doses; the cycle was repeated after a rest period of 2 weeks;
- fluorouracil plus levamisole: fluorouracil 350 mg/m^2 as an intravenous bolus daily for five consecutive days, then once weekly starting on day 29 and levamisole orally tds for 3 days and repeated every 14 days;
- fluorouracil plus leucovorin plus levamisole: the same fluorouracil plus leucovorin treatment as described above, with the addition of levamisole in the dose used in the fluorouracil plus levamisole group.

There was a small prolongation of the disease-free interval and overall survival in favor of fluorouracil plus leucovorin, although of borderline statistical significance. Information on toxicity was obtained in 98% of the patients. Eighteen died while on chemotherapy, four in the fluorouracil plus leucovorin group, three in the fluorouracil plus levamisole group, and 11 in the fluorouracil plus leucovorin and levamisole group. Grade 3–4 toxicity was reported equally in the three groups: fluorouracil plus leucovorin 35%, fluorouracil plus leucovorin and levamisole 36%, and fluorouracil plus levamisole 28%. They consisted mainly of adverse effects attributed to fluorouracil, such as diarrhea, vomiting, and stomatitis. Hematological toxicity was minimal (less than 2% in grades 3–4) and not significantly different across the groups. Neurotoxicity was rare. Ataxia was the most frequent neurological disorder, in 2% of the patients who received fluorouracil plus levamisole and in 1% of the patients in the other two groups combined.

QUASAR was a study of the effects of a higher dose of leucovorin or the addition of levamisole to 5-fluorouracil and leucovorin on survival in 4927 patients with colorectal cancer with no evidence of residual disease after resection (14). High-dose leucovorin was not associated with a survival or recurrence benefit compared with low-dose leucovorin. The addition of levamisole had no apparent survival benefit compared with placebo, with slightly more deaths in patients assigned to levamisole than placebo. Tumor recurrences were also higher in those who took levamisole. Dermatological adverse effects were significantly more frequent in those who took levamisole compared with placebo.

In 680 patients with curatively resected stage III colon cancer, adjuvant treatment with 5-fluorouracil plus leucovorin was significantly more effective than 5-fluorouracil plus levamisole in reducing tumor relapse and improving survival (15). There were fewer adverse effects in those given 5-fluorouracil plus levamisole compared with 5-fluorouracil plus leucovorin (820 versus 1190); the difference was mainly due to gastrointestinal toxicity. Only a few patients developed grade 3 or grade 4 adverse effects. There were no treatment-related deaths in either group.

The Gastrointestinal Intergroup has studied postoperative adjuvant chemotherapy and radiation therapy in 1659 patients with T3/4 and lymph-node-positive rectal cancer after potentially curative surgery to try to improve chemotherapy and to determine the risk of systemic and local failure (20). There was no advantage to regimens containing leucovorin or levamisole over bolus 5-fluorouracil alone in the adjuvant treatment of rectal cancer when combined with irradiation. Local and distant recurrence rates were still high, especially in T3 and T4 lymph node positive patients, even with full adjuvant chemoradiation therapy.

Nephrotic syndrome

In a retrospective analysis in 51 children with glucocorticoid-dependent nephrotic syndrome, the ability of levamisole to reduce the relapse rate and to spare prednisone therapy was compared with that of cyclophosphamide (21). Apart from one patient who had a spontaneously resolving skin rash with levamisole and three patients who had transient neutropenia with cyclophosphamide, there were no other clinically significant adverse effects.

Warts

In 44 patients with multiple recalcitrant warts randomized to either oral cimetidine 30 mg/kg/day in three doses for 12 weeks, or 30 mg/kg/day for 12 weeks plus levamisole 2.5 mg/kg for 2 days per week, cimetidine plus levamisole produced significant improvement (22). Adverse effects of levamisole were infrequent, except for a metallic taste in one patient and nausea in two. In one patient the nausea was severe enough to necessitate withdrawal. There were no significant changes in leukocyte count or differential counts.

Placebo-controlled studies

Colorectal cancer

Fluorouracil (370 mg/m^2) plus high-dose (175 mg) or low-dose (25 mg) folinic acid and either active or placebo levamisole has been evaluated in 4927 patients with colorectal cancer (23). Levamisole produced a significant excess of adverse dermatological events. Serious unexpected adverse events were rare. The authors concluded that the inclusion of levamisole in chemotherapy regimens for colorectal cancer does not delay recurrence or improve survival.

Organs and Systems

Cardiovascular

Hypotension has been attributed to levamisole (24).

Nervous system

Several reports point to a condition that can best be described as multifocal inflammatory leukoencephalopathy, occurring in about four cases in every thousand, during treatment with levamisole either alone (25) or in combination with 5-fluorouracil (SEDA-21, 321) (26,27). It presents with confusion, ataxia, dysarthria, diplopia, focal neurological signs, and seizures, and has been extensively discussed and reviewed (28).

One large literature survey (29) concluded that 6% of patients taking long-term levamisole, mostly for

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malignancies, experienced "sensory stimulation," for example in the form of "hyperalert states" or insomnia, although depression is less commonly on record. Diplopia and tremor have been observed, whilst a number of children treated for juvenile rheumatoid arthritis or nephrotic syndrome have developed generalized convulsions and coma, with EEG abnormalities suggestive of encephalitis (SED-12, 771) (30); the condition recovers spontaneously, but for a time anticonvulsants may be needed.

- A 65-year-old man developed impaired cognition and a disturbed gait 6 months after the removal of a Dukes C colon cancer with adjuvant chemotherapy with fluorouracil and levamisole. Three months later he developed arthralgias in the hands, elbows, and knees, followed 1 month later by intermittent monocular diplopia, an ataxic gait, and deteriorating cognitive function. An MRI scan of the brain showed multiple small round and oval hyperintense lesions in the periventricular white matter, without surrounding edema or mass effect. Most of the lesions showed ring enhancement after intravenous gadolinium. The cerebrospinal fluid protein content was raised, but cytology was normal. A stereotactic biopsy of one of the lesions showed marked cellularity of the white matter, with mononuclear cells in both the parenchyma and perivascular areas, and severe demyelination of the white matter with relative preservation of the axons. Most of the parenchymal cells were macrophages, containing myelin debris. All the findings were consistent with a diagnosis of multifocal inflammatory leukoencephalopathy after treatment with levamisole. The adjuvant therapy was discontinued and he was treated with methylprednisolone 1 g/day intravenously for 3 days, followed by dexamethasone 4 mg qds orally. Within weeks he started to improve, with resolution of the ataxia and improved cognitive function. However, there was residual mild left hemiparesis and he remained moderately unsteady on his feet. The glucocorticoids were slowly tapered and an MRI scan several weeks later still showed multiple patchy areas of bright signal, corresponding to the previous demyelination, but without enhancement. A further MRI scan after 1 year showed complete resolution. His neurological condition and performance had further improved, but there was residual impairment of short-term memory.

The authors suggested that this syndrome may be more common than supposed, and that it is likely that levamisole is the main causal factor, since the same symptoms have been described after treatment with high-dose levamisole alone, but that the effect may be enhanced by the co-administration of fluorouracil, which potentiates the immunostimulatory action of levamisole. Although there is no conclusive evidence of the value of glucocorticoids in this syndrome, an adequate course of glucocorticoids is advised, comparable to the treatment of multiple sclerosis.

- A 57-year-old man had a Dukes C colon cancer removed and was given adjuvant chemotherapy with fluorouracil and levamisole at 4-week intervals (31). Four months later he developed insomnia, diplopia, and a reduced level of consciousness. He was disoriented in time and place, but there were no focal neurological defects. The cerebrospinal fluid protein concentration was slightly raised. A provisional diagnosis of fluorouracil/levamisole-induced neural toxicity was made and he was treated with dexamethasone 4 mg qds. There was an improvement in orientation after 3 days of treatment, but he remained mentally dull. After 28 days of therapy the corticosteroids were tapered. An MRI scan showed multiple focal hyperintensities, with involvement of both deep and subcortical white matter. The lesions were not associated with a mass effect and were mildly enhanced by gadolinium. At 30 months follow-up the patient was well without evidence of relapse. An MRI scan at 24 months showed small, residual, hyperintense lesions, which were not further enhanced by gadolinium, consistent with gliotic scars.
- A 3-year-old girl who took levamisole 100 mg bd for 3 days for anorexia suddenly developed hyperkinesia, paresthesia, fidgetiness, an unstable gait, and frequent falling (32). An MRI scan of the brain did not show any demyelinating changes. She recovered fully within 48 hours without any specific intervention.

The authors suggested that levamisole overdose had contributed to the profound encephalitis-like effects.

Fatal viral encephalitis due to enterovirus type 71 has been reported during use of levamisole (33).

Psychological, psychiatric

Anxiety and depression have been associated with levamisole (34).

Psychosis has also been reported (35).

- A 28-year-old man, without a psychiatric history, developed a paranoid psychosis. He had been taking levamisole twice a week in an unspecified dose for 2 years for a stage 4 melanoma and metastatic lymph nodes in the axilla. Physical examination, a CT scan, an electroencephalogram, and standard laboratory tests were all normal. He was treated with perphenazine, with partial success, but after tapering of the dose his symptoms reappeared. It was thought likely that the psychosis had been caused by levamisole, which was discontinued. Three weeks later he had recovered completely. Levamisole was not reintroduced.

Hematologic

Agranulocytosis has often been reported during long-term treatment with levamisole. Most cases are reversible and transient, but deaths have occurred. In 3900 patients on whom data were available to the manufacturers, there were 88 cases of agranulocytosis and 43 of leukopenia; such dyscrasias occurred in 4% of patients with rheumatoid arthritis and 2% of oncological cases (29). In other published material the incidence has sometimes been higher; such differences do not appear to be related to the dose or duration of therapy. Agranulocytosis is more prevalent in rheumatoid patients with an HLA-B27 genotype (SEDA-7, 317). Children are also susceptible, and fatal outcomes because of hematological disorders have been described in cases of juvenile rheumatoid arthritis treated intermittently with levamisole. Other

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deaths have occurred in adults concurrently taking glucocorticoids for several years.

Agranulocytosis can be asymptomatic and, since it occurs unpredictably, regular monitoring of the leukocyte count is advisable, especially in patients concurrently receiving combination chemotherapy. Whilst the mechanism is not clear, granulocyte-agglutinating antibodies have been found, suggesting that levamisole acts as a hapten on the leukocyte membrane.

Thrombocytopenia has been reported in a woman with rheumatoid arthritis; it recurred after rechallenge (36).

Gastrointestinal

Nausea, vomiting, and diarrhea are very common in patients taking levamisole, and are sometimes accompanied by abdominal pain or constipation, although when such symptoms occur it is not always clear that they are due to the drug rather than to its interaction with the disease.

Exacerbation of peptic ulceration has been described, and mouth ulcers and abnormalities of taste sensation can be troublesome in patients taking long-term therapy.

Liver

Neither animal nor most human studies point to hepatotoxicity, but in a series of 11 patients with pyoderma treated with levamisole two had increases in aspartate transaminase activity. Liver toxicity has also been reported in a child with nephrosis (37).

Urinary tract

There has been one published case of uremia (38) and one of a reversible nephropathy in a patient with rheumatoid arthritis (39).

Skin

Type I allergic reactions have caused pruritic rashes and urticaria.

Ischemic necrosis of the skin, reversible on withdrawal, has been documented (40).

Single cases of erythema multiforme and erythema nodosum have been observed (SEDA-7, 317).

Two patients developed lichenoid skin eruptions, which subsided when the drug was stopped, although one of these was left with severe scarring, alopecia of the scalp, and widespread atrophic and hyperpigmented skin lesions.

A healed varicose ulcer has been observed to break down after treatment (41).

Necrotizing vasculitis

Cutaneous necrotizing vasculitis with histological changes resembling a type III hypersensitivity reaction has been described in patients taking levamisole (42,43). In a well-documented case, a widespread vasculitic rash, chiefly affecting the limbs, appeared in a woman with rheumatoid arthritis treated for 2 months. In these cases, serum complement was normal and there were no circulating immune complexes, although a histamine skin wheal test produced a vasculitis at a clinically non-affected site. Both cases were reversible.

- Leukocytoclastic vasculitis has been attributed to levamisole in a 7-year-old boy with glucocorticoid-dependent nephrotic syndrome (44).

The authors estimated that about 0.5% of patients treated with levamisole develop cutaneous vasculitis with circulating autoantibodies.

Five of 160 children with nephrotic syndrome developed distinctive vascular purpura (45). They had taken levamisole for a mean of 24 months when they developed purpuric erythematous macules, which evolved to ecchymotic and necrotic purpura. The lesions were mostly on the external ear. Biopsies obtained from the ear lesions in four patients showed vasculopathic reaction patterns, ranging from leukocytoclastic and thrombotic vasculitis to vascular occlusive disease without true vasculitis. There were anticardiolipin, antinuclear, and/or antineutrophil cytoplasmic antibodies in four patients. The lesions resolved within 2–3 weeks after levamisole withdrawal, whereas anticardiolipin and antineutrophil cytoplasmic antibodies disappeared after 2–14 months only. A direct effect of levamisole on the endothelial cells or levamisole-induced or unmasked latent immunological abnormalities was suspected.

Musculoskeletal

Arthritis has occurred in patients with Crohn's disease or Behçet's disease treated with levamisole (46,47), although it is well known that this can occur with either disease irrespective of drug treatment.

Muscle pain can be severe when levamisole is given with 5-fluorouracil for colonic cancer (48), or there can be a painless rise in creatine kinase activity (49).

Immunologic

Allergic reactions often reflect the effects of the drug or of parasitic breakdown products. They include pruritic skin eruptions, arthritic pain and swelling, muscular pain and swelling, especially in patients already suffering from rheumatoid arthritis, Sjögren's syndrome (50), or psoriatic arthropathy. Skin reactions of various types can occur and type III reactions have been noted. Influenza-like symptoms might be an unusual form of type I allergy or a consequence of restoration of cellular immunity.

Disseminated autoimmune disease has been described during treatment with levamisole for nephrotic syndrome (51).

- An 8-year-old boy had a 5-year history of steroid-dependent nephrotic syndrome. After half a year of glucocorticoid treatment he was given levamisole 2.5 mg/kg on alternate days for 1 year, with complete suppression of the proteinuria. The proteinuria reappeared after withdrawal of levamisole, and glucocorticoids and levamisole were reintroduced as before. Two years later, while still taking levamisole, he developed hepatosplenomegaly, a low-grade fever, and a Coombs' negative hemolytic anemia. The anticardiolipin IgM titer was high, p-ANCA antibodies were positive, C3 was moderately low and antinuclear anti-DNA antibodies were negative. Levamisole was withdrawn. Two weeks later the clinical parameters had normalized and 4 weeks later the liver enlargement

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had disappeared. Although p-ANCA antibodies persisted at 1 month the anticardiolipin IgM titer had returned to normal. After 6 months there still was splenomegaly but no other symptoms, and proteinuria was absent.

The same group of authors have also described a distinctive vasculitis with circulating antibodies in children with nephrotic syndrome associated with long-term levamisole, presenting with purpura of the ears (45).

- Four boys and one girl (mean age 10 years) had had nephrotic syndrome for 2–8 years and had taken levamisole orally in doses of 1.7–2.5 mg/kg/day for 16–44 months (mean 24 months). All had a sudden onset of rapidly enlarging purpuric and erythematous macules progressing to the formation of necrotic areas, purpuric plaques, and hemorrhagic bullae. The pinnae were involved in all five. In three there were also lesions on the cheek or lower limbs. One had fever and another complained of arthralgia. Routine laboratory tests were all normal. Antibodies to extractable nuclear antigen, cryoglobulin, rheumatoid factor, Coombs' test, circulating immune complexes, and complement and components were all negative or normal. However, antiphospholipid antibodies and/or anticardiolipin IgG and IgM were positive in three patients, p-ANCA was positive in three, and c-ANCA in one. Antinuclear antibodies were positive in two patients and anti-double stranded DNA antibodies were positive in one. Biopsies of the skin lesions in four patients showed vasculitis, ranging from a leukocytoclastic and thrombotic vasculitis to vascular occlusive disease without true vasculitis. Two patients had a hypersensitivity vasculitis in the superficial and deep dermis, with neutrophilic infiltration of the vessel walls and fibrinoid necrosis. Features of panniculitis with occlusion of deep and superficial blood vessels by fibrin-platelet thrombi were found in one patient. The lesions completely resolved in all patients within 2–3 weeks after the withdrawal of levamisole. The serum autoantibodies had disappeared in all cases after 2–14 months.

Although leucocytoclastic immune-complex vasculitis induced by levamisole is well known, this specific presentation with involvement of the ears has not been described before.

Second-Generation Effects

Teratogenicity

Animal studies do not point to a teratogenic effect, but there are insufficient human data to assess the safety of levamisole in pregnancy, and the WHO recommends delaying treatment until after pregnancy when possible.

Susceptibility Factors

Age

The adverse effects that occur after monotherapy with levamisole in children with nephrotic syndrome include taste disturbance (dysgeusia), arthralgia, myalgia, anxiety, sleep disturbances, depression, neutropenia, diarrhea, nausea, and vomiting.

Hepatic disease

Levamisole is mostly metabolized to *para*-hydroxylevamisole (52). It should not be used in severe hepatic disease, nor should it be combined with hepatotoxic antihelminthic drugs or other drugs presenting risks to the liver.

Other features of the patient

Both Sjögren's syndrome (50) and psoriatic arthropathy (53) are conditions in which levamisole is probably better avoided because of the risk of hypersensitivity reactions.

In the treatment of the hyperimmunoglobulin E recurrent infection syndrome (Job's syndrome), infectious complications are more serious when levamisole is given, even where there is normal chemotactic responsiveness (54).

The risk of severe adverse reactions is greater in lymphatic filariasis (55).

Drug Administration

Drug overdose

Acute overdose of levamisole has been described (56).

- A 43-year-old man treated himself with a levamisole enema of 10 g (33 times the therapeutic dose) for a gastrointestinal worm infestation. Soon after he developed malaise, tachycardia, nausea, vertigo, and profuse diarrhea. He lost consciousness and developed generalized seizures and a respiratory arrest. He was intubated, ventilated, and treated with clonazepam. His condition improved after 4 hours. He remained somnolent for 6 hours, and was nauseated and vomited for 24 hours. There was hypokalemia after the diarrhea, raised creatine kinase activity, and a leukocytosis. An electrocardiogram showed ST depression. By the fourth day all his symptoms had subsided.

The symptoms in this case were attributed to the cholinergic effect that levamisole has at this high dose.

Drug–Drug Interactions

Salicylates

Levamisole increases serum concentrations of salicylates, but the effect does not appear to have any clinical consequences (57).

Warfarin

Levamisole and 5-fluorouracil interact with warfarin to produce bleeding (58). The mechanism of this effect is unclear, but the reports are sufficiently clear to point to the need for careful monitoring when this drug combination is used.

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Levetiracetam

See also Antiepileptic drugs

General Information

Levetiracetam is a piracetam derivative used in the treatment of refractory partial seizures. In trials it has shown an excellent tolerability profile. The main dose-related adverse effects are sedation, fatigue, and headache. Other possible adverse effects include dizziness, unsteadiness, diplopia, nausea, infection, memory impairment, and disturbances of mood and behavior, although in controlled trials the incidence of most of these was no greater than with placebo (1).

The pharmacology, clinical pharmacology, uses, and adverse reactions and interactions of levetiracetam have been reviewed (2–6).

The safety profile of levetiracetam has been reviewed (7). The authors assessed the integrated summary of safety reports submitted for regulatory review in order to obtain information about abnormal laboratory test values and adverse events collected during the overall levetiracetam development program. The analysis included 3347 patients exposed to levetiracetam in clinical trials for epilepsy, cognition, and anxiety disorders. Safety data from all the studies showed a similar pattern of adverse effects, predominantly somnolence, weakness, and dizziness, which occurred most often during the first month of treatment. Laboratory tests that changed significantly in placebo-controlled trials nevertheless stayed in the reference ranges. The incidences of any types of allergic reactions were similar between levetiracetam and placebo (0.3% and 0.2%). Cases of common cold and upper respiratory infection were significantly more frequent with levetiracetam than placebo (13 versus 7.5%), but were not preceded by low neutrophil counts that might have suggested impaired immunological status. There was worsening of seizures (an increase of over 25%) in 14% of patients taking levetiracetam and 26% of patients taking placebo. There were nine sudden, unexplained deaths; the overall mortality rates and standardized mortality rates were higher in the placebo group (1.8% levetiracetam versus 2.5% placebo). Behavioral problems occurred in 5.2–14% of those taking

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levetiracetam and in 4.1–6.0% of those taking placebo. There were higher incidences of adverse effects, particularly behavioral effects, among patients with epilepsy than in elderly patients with cognitive disorders or in patients with anxiety disorders.

Observational studies

The efficacy and tolerability of levetiracetam 1–4 g/day as add-on treatment for refractory epilepsy have been studied in 29 patients with refractory epilepsy (8). The most common adverse events were somnolence and weakness, the frequency and severity of which increased with increasing doses.

The efficacy and tolerability of levetiracetam 1–2 g/day as add-on therapy have been studied in 324 patients with refractory partial seizures (9). Levetiracetam did not affect the plasma concentrations of other antiepileptic drugs or alter vital signs or laboratory measurements. The most commonly reported adverse effects in patients taking levetiracetam were weakness, headache, and somnolence.

The long-term retention rate, efficacy, and safety of levetiracetam have been evaluated in all patients with epilepsy exposed to the drug during its developmental program ($n = 1422$) (10). The retention rate was 60% after 1 year and 32% after 5 years. Seizures were reduced by over 50% in 39% of the patients, and 13% became seizure free for at least 6 months. The commonest treatment-emergent adverse events requiring withdrawal were convulsions (3.4%), somnolence (2.0%), weakness (0.6%), depression (0.6%), dizziness (0.5%), and headache (0.5%). There was no evidence of idiosyncratic adverse effects or any serious hematological or biochemical abnormalities during exposure to levetiracetam. Eight patients died suddenly and unexpectedly, about one death per 300 patient-years, which is within the expected range in patients with refractory epilepsy.

Placebo-controlled studies

In a pooled analysis of safety data from double-blind, placebo-controlled add-on trials of levetiracetam (1–3 g/day) in adults with refractory partial seizures, adverse events occurring in at least 3% of patients and with at least 3% higher incidence in the active treatment group were tiredness (14 versus 10%), somnolence (15 versus 10%), dizziness (9 versus 4%), and common cold or upper respiratory tract infections (13 versus 7%) (11). The proportions of patients requiring withdrawal of treatment or dosage reduction owing to adverse events were 15% with levetiracetam and 12% with placebo. The efficacy and tolerability of levetiracetam monotherapy in refractory partial seizures have been studied in a double-blind, placebo-controlled study in 286 patients (12). Adverse events that were more common with levetiracetam and that occurred in more than 5% of cases included weakness, infection, and somnolence. Of 181 patients who took levetiracetam, 36 completed the study compared with only 10 of 105 who took placebo. The tolerability and efficacy of levetiracetam, 2 or 4 g/day, as add-on therapy have been studied in 119 patients with refractory epilepsy (13). Somnolence was the most common reason for withdrawal and occurred more often with levetiracetam than placebo, as did weakness. Somnolence was more common with the higher dose, which was not more effective than the lower dose. Nausea, dizziness, and urinary tract infections were also more common with the higher dose. The efficacy and safety of levetiracetam 1 and 3 g/day as adjunctive therapy for refractory partial seizures have been studied in a double-blind, randomized, placebo-controlled trial in 294 patients with uncontrolled partial seizures (14). Treatment-associated adverse events that occurred in at least 10% of patients and had incidences higher than placebo were weakness, dizziness, a flu-like syndrome, headache, infection, rhinitis, and somnolence. These effects were mostly mild to moderate.

Organs and Systems

Psychological, psychiatric

Psychiatric adverse events, most often hostility and irritability, have been reported in children taking levetiracetam. Four cases of acute psychosis have also been reported (15).

- A 5-year-old girl with refractory epilepsy treated with a ketogenic diet was given levetiracetam 250 mg bd (25 mg/kg/day). She had a history of mild mental retardation and was receiving special education. Two weeks later she started to have visual hallucinations, became agitated, bit relatives, and could not sleep. Levetiracetam was withdrawn and her symptoms resolved within 24 hours and did not recur.

Susceptibility Factors

Age

The safety of levetiracetam has been assessed in 24 children with uncontrolled partial-onset seizures in an open study (16). The most commonly reported adverse events were headache (33%), infection (33%), anorexia (25%), and somnolence (25%). The adverse events profile of levetiracetam was similar to that seen in adults. Owing to a dispensing error, one patient received an accidental overdose of 71 mg/kg/day, rather than 40 mg/kg/day, during the last 4 weeks of the evaluable phase of the study. No ill effects were reported or observed on examination or laboratory testing, and the patient completed the trial.

Drug Administration

Drug overdose

Overdosage of levetiracetam can cause respiratory depression (17).

- A 38-year-old woman took 60 tablets of levetiracetam 500 mg. She vomited 4 hours later, and 2 hours after that was obtunded with respiratory depression. Her levetiracetam serum concentration was 400 μg/ml at 6 hours, 72 μg/ml at 18 hours, and 60 μg/ml at 20.5 hours (target serum concentration 10–37 μg/ml). The half-life was 5.1 hours, similar to the usually reported half-life. She was extubated the next day and recovered without sequelae.

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Drug–Drug Interactions

Carbamazepine

Four patients with refractory epilepsy taking carbamazepine were given added levetiracetam and developed central nervous system effects (ataxia, diplopia, nystagmus) suggestive of carbamazepine toxicity (18). Reduction in the dose of carbamazepine resolved the symptoms in three cases. Carbamazepine and carbamazepine-epoxide blood concentrations were not altered during levetiracetam co-medication. Thus, a pharmacodynamic interaction between carbamazepine and levetiracetam is likely.

Digoxin

Two placebo-controlled studies in healthy subjects have shown no interaction of levetiracetam with digoxin (19).

Oral contraceptives

In a double-blind, crossover study 18 healthy women taking an oral contraceptive containing ethinylestradiol 30 μg plus levonorgestrel 150 μg took levetiracetam 500 mg/day or placebo (20). The plasma concentration–time curves and pharmacokinetics of ethinylestradiol and levonorgestrel were not altered.

Warfarin

Two placebo-controlled studies in healthy subjects have shown no interactions of levetiracetam with warfarin (21).

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Levobupivacaine

See also Local anesthetics

General Information

Levobupivacaine is the levorotatory isomer, *S*(−)-bupivacaine, of bupivacaine, an amide local anesthetic.

In a comparison of the clinical efficacy of epidural *S*(−)-bupivacaine with standard racemic *RS*-bupivacaine in 88 patients *S*(−)-bupivacaine was clinically indistinguishable from *RS*-bupivacaine in the three groups studied (0.75% or 0.5% *S*(−)-bupivacaine and 0.5% *RS*-bupivacaine). Hypotension was distributed evenly across the groups and five patients complained of minor neurological abnormalities (hypesthesia and paresthesia), which resolved quickly after the operation (1).

Organs and Systems

Cardiovascular

Levobupivacaine is less cardiotoxic than racemic bupivacaine (2). In seven sheep, racemic bupivacaine caused

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mild cardiac depression, which was superseded by central nervous system toxicity and then proceeded to severe ventricular dysrhythmias, which were fatal in three sheep, at doses of 125, 150, and 200 mg (3). Levobupivacaine was consistently less toxic than bupivacaine, and higher doses were needed to produce adverse effects. Convulsions were less severe and of shorter duration, and although levobupivacaine produced QRS prolongation and ventricular dysrhythmias, there were no deaths.

Several animal studies have shown that levobupivacaine on an equivalent dose basis is safer than bupivacaine; 32–57% more levobupivacaine is required to cause death (4). In sheep, the mean lethal dose of levobupivacaine was 78% higher than that of bupivacaine; the author suggested that there may be a similar trend in humans and concluded that levobupivacaine should be used in preference to bupivacaine, based on safety data alone.

Nervous system

Tonic-clonic seizures have been attributed to levobupivacaine.

- A 60-year-old 70 kg woman with a fractured radius had an axillary brachial plexus block for postoperative analgesia after uneventful general anesthesia (5). A 50 mm insulated regional block needle attached to a nerve stimulator was used to locate the brachial plexus, and after negative aspiration, levobupivacaine 125 mg was injected with intermittent aspiration. Within 30 seconds the patient had a generalized tonic-clonic seizure which lasted about 30 seconds and self-terminated. She remained cardiovascularly stable and made an uneventful recovery.

The authors proposed that some or all of the local anesthetic had been inadvertently injected intravascularly, despite negative aspiration tests. There were no cardiovascular complications, underlining the proposed greater cardiovascular safety of levobupivacaine over bupivacaine. The authors accepted that if the patient had been awake during the procedure, earlier detection of neurological symptoms might have been possible.

Hematologic

The effects of the low molecular weight heparin enoxaparin in combination with levobupivacaine on coagulation have been studied in vitro (6). Whole blood from 10 patients treated with enoxaparin was mixed with levobupivacaine to concentrations of 2.5 μg/ml and 2.5 mg/ml, followed by thromboelastography. Levobupivacaine produced a dose-dependent reduction in clotting. The clinical implications of these findings are yet to be acknowledged; larger, in vivo studies are required.

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Levocabastine

See also Antihistamines

General Information

Levocabastine is a second-generation antihistamine (SEDA-17, 201) (SEDA-18, 183) (SEDA-19, 174) (SEDA-20, 163) (SEDA-21, 176).

Since levocabastine is applied locally in the eye or nose, local reactions are most often seen. Most frequent is ocular irritation followed by nasal irritation. Sedation does not seem to be common and no cardiac effects have been registered.

Drug–Drug Interactions

Erythromycin

Single doses of erythromycin 333 mg or ketoconazole 200 mg were given to healthy men who used levocabastine, two sprays per nostril (0.05 mg/spray) bd for 6 days (1). There were no changes in the pharmacokinetics of levocabastine or in the QT_c interval.

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Levocetirizine

See also Antihistamines

General Information

Levocetirizine is the *R*-enantiomer of cetirizine dihydrochloride and, like cetirizine, undergoes minimal hepatic metabolism (1). Levocetirizine has twice the affinity for H_1 receptors as cetirizine (1). It is efficacious and well tolerated in patients with seasonal allergic rhinitis (2).

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Organs and Systems

Nervous system

Two comprehensive studies have suggested that levocetirizine causes little sedation (3,4). The effect of levocetirizine 5 mg/day on actual driving performance by 48 healthy volunteers has been compared with the effect of the first-generation antihistamine diphenhydramine 50 mg/day in a double-blind, placebo-controlled, randomized study (5). Treatments were administered on days 1, 2, 3, and 4, 90 minutes before the start of a standardized driving test on day 1 and day 4. In contrast to diphenhydramine, driving performance was not significantly affected by levocetirizine.

Psychological, psychiatric

The effects of levocetirizine on cognitive function have been assessed in two comprehensive well-controlled studies. The first analysed the effects of single and multiple doses of levocetirizine on measures of nervous system activity, using integrated measures of cognitive and psychometric performance. In a three-way crossover design, 19 healthy men took either levocetirizine 5 mg, diphenhydramine 50 mg (positive control), or placebo once daily on 5 consecutive days. Critical flicker fusion tests were performed on days 1 and 5 at baseline and up to 24 hours after drug administration. The primary outcome was that, in contrast to diphenhydramine, levocetirizine did not have any deleterious effect on any cognitive or psychometric function compared with placebo (3).

In a double-blind, crossover study levocetirizine 5 mg once daily for 4 days was compared with cetirizine 10 mg, loratadine 10 mg, promethazine 30 mg, and placebo in terms of nervous system inhibitory effects in 20 healthy volunteers (4). With the exception of promethazine none of the drugs had disruptive or sedative effects on objective measurements in a comprehensive battery of psychomotor and cognitive tests. These studies suggest that levocetirizine has minimal sedative effects in healthy individuals when given in its recommended dose.

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Levodopa and dopa decarboxylase inhibitors

General Information

Nigrostriatal dopamine is depleted in patients with Parkinson's disease, but it cannot be used to treat the disease since it is poorly absorbed from the gastrointestinal tract and is metabolized extensively in the periphery, hardly penetrating the central nervous system. Levodopa, a precursor that is decarboxylated to dopamine, but is much more lipid soluble, was developed to overcome this problem. It was originally given alone, but because of the extent to which it was decarboxylated outside the central nervous system, large doses had to be given, and gastrointestinal intolerance was a problem. By combining levodopa with a decarboxylase inhibitor (carbidopa or benserazide) tolerance is improved and the dose can be reduced. The combination of levodopa + carbidopa is also called co-careldopa and the combination of levodopa + benserazide is also called co-beneldopa.

General adverse effects

When levodopa is given alone, severe gastrointestinal upsets are very common during the first year of treatment; they are much less common when a decarboxylase inhibitor is also given. Postural hypertension is not uncommon. Dyskinesias occur in some patients only after starting therapy. Some mental changes are seen in a high proportion of cases. Psychological dependence occurs in a small subset of patients (1). Effects on the liver, renal function, and hematological parameters are usually slight. Individual prescribers and clinics tend to develop their own approaches to obtaining the best balance between effects and adverse reactions; a "drug holiday" (for example 2 days/week) has long been recommended by some workers to reduce the incidence of adverse effects (2), but others have described a neuroleptic malignant syndrome when the administration of the drug was temporarily discontinued (SEDA-17, 147) (3). Allergic type reactions do not seem to occur, but carbidopa has been reported to produce a fixed drug eruption. Cases of malignant melanoma (on one occasion within a congenital nevus) have been described in patients taking levodopa; the causal link has not been established, but patients should be monitored for skin changes (4).

Organs and Systems

Cardiovascular

Postural hypotension has been estimated to occur in some 15% of patients who take plain levodopa during the first year of treatment, and in 10% of patients who take

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co-careldopa; it is doubtful whether the difference is significant. On the other hand, some patients become hypertensive; they may be individuals who absorb or metabolize the drug at an abnormal rate. Levodopa can cause ventricular dysrhythmias in patients with pre-existing cardiac disorders. Transient flushing of the skin is common; palpitation is unusual.

Respiratory

An isolated case of respiratory dysrhythmia has been reported (5); it was dose-related and impeded adequate treatment, but was ultimately suppressed with tiapride.

Two men with Parkinson's disease, aged 66 and 78 years, developed abnormal respiration (tachypnea and irregularity in the depth of breathing) when levodopa was either introduced at a dose of 300 mg/day in the first case or increased from 300 to 600 mg/day in the other (6). The authors cited a number of earlier similar reports.

Nervous system

Ever since the introduction of levodopa as the mainstay of antiparkinsonian therapy, there has been concern that it may be toxic, causing long-term damage to dopamine neurons. Three reviews have addressed this question in the light of experimental and clinical evidence over the last 30 years. One reviewer concluded that there is no evidence for irreversible levodopa-induced damage in man, only for reversible adverse effects associated with neuronal dysfunction but not neuronal death (7). Others reached broadly the same conclusion, although they noted that there is in vitro evidence of damage associated with oxidative metabolism of levodopa (8). They also described potential toxicity from levodopa in animals in which the nigrostriatal pathway is already damaged by other means. A third reviewer has pointed out that levodopa therapy is an entirely non-physiological means of dopamine replacement, arguing that the intermittent nature of the dopaminergic stimulus provided by most therapies, particularly levodopa, predisposes to motor complications (9). He suggested that more continuous activation of dopamine receptors could minimize or eliminate these problems.

Asterixis, a jerky relaxation of tonically contracted postural muscles, was observed in some patients with structural lesions of the brain or metabolic encephalopathy who were taking levodopa, but not in patients with Parkinson's disease (10).

For most patients fluctuations are variations in the severity of motor manifestations of Parkinson's disease. However, other types of fluctuations can also occur, many of which are of non-motor in nature: these include sensory fluctuations (pain and paresthesia), akathisia or restless legs, autonomic fluctuations (dyspnea, tachycardia, pallor, blood pressure changes, dysphagia, penile erection, urinary frequency) or cognitive effects, such as hallucinations, depression, hypomania, or hypersexuality.

An unusual symptom of Parkinson's disease is apraxia of eyelid opening, a particular aspect of the difficulty in initiating movements (11).

- A 76-year-old woman with atypical Parkinsonism had a poor motor response to levodopa and developed apraxia. An increase in dosage (to levodopa 300 mg/day with benserazide 75 mg/day and selegiline 200 mg/day) caused worsening of the apraxia. Drug withdrawal caused no motor deterioration, but the apraxia disappeared. Challenge with subcutaneous apomorphine reinitiated the symptom, strongly supporting its dopaminergic origin in this patient.

The authors cited the therapeutic use of botulinum toxin in a similar case, but this was ineffective in their patient.

A less well defined adverse effect of levodopa is sedation. This has been studied in 22 volunteers given levodopa 200 mg with benserazide 50 mg or triazolam 0.125 mg or placebo in a randomized crossover design (12). Both active drugs caused drowsiness, more particularly triazolam. During a further 11 days of treatment with levodopa 600 mg/day sedation persisted. Two points are worth noting. First, triazolam was presumably chosen because of its short half-life, but it is a somewhat risky choice, given its known psychiatric adverse effects. Secondly, the very rapid increase in levodopa dosage, from 200 to 600 mg/day, would be unrealistic in a clinical context, when dosage titration would be much more gradual. It is therefore hard to assess the practical relevance of this study.

The advantages and disadvantages of levodopa have been summarized, with particular focus on adverse effects and their management (13). The author concluded that there is no convincing evidence for neurotoxicity of levodopa in humans.

Neurologists from New York and Yugoslavia have noted the variable time to the development of motor complications after starting levodopa (14). Of 40 patients (21 men, mean age 67 years), 17 were at Hoehn and Yahr stage I at the start of levodopa therapy, 13 at stage II, and 10 at stage III. The median times to the development of motor fluctuations were respectively 64, 55, and 14 months in the three groups and the times to onset of dyskinesias were similar. This reinforces the clinical experience of neurologists in general.

Dyskinesias

Dyskinesias occurring during long-term use of levodopa have been classified in various ways. One system presents them as falling broadly into three groups:

- "On" dyskinesias—These coincide with periods of clinical response to the drug; they include chorea, myoclonus, and dystonic movements. They are enhanced by dopamine receptor agonists and reduced by dopamine receptor antagonists.
- "Off" dyskinesias—These coincide with periods of poor response and comprise mainly dystonic postures, affecting in particular the feet; they are inhibited by both dopamine receptor agonists and antagonists.
- "Dysphasic dyskinesias"—These occur at the beginning and end of "on" periods. They involve repetitive stereotyped movements of the lower limbs, and they too react well to both dopamine receptor agonists and antagonists.

There is reason to believe that dyskinesias during prolonged levodopa treatment result from an interaction between the levodopa and the underlying condition rather than from one or the other. In many cases of severe Parkinson's disease one can speak of a "peak dose dyskinesia," which is only problematic when the patient is

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taking a relatively high dose, which tends to be most marked on the most severely diseased side, and which responds to dosage reduction (15).

The long-term consequences of levodopa therapy have been considered in a review by predominantly Canadian authors, but whose senior author was Oleh Hornykiewicz, the doyen of the dopamine concept of Parkinson's disease (16). Their conclusions were not at all unexpected. Levodopa was given to 42 patients (30 men, mean disease duration of 16 years, mean follow-up about 9 years). There were adverse effects in over 70%: dyskinesias in 62%, on–off effects in about 17%, and end-of-dose wearing-off in about 7% (the last perhaps surprisingly low). Dyskinesia was not only the most common but also the earliest adverse effect. It should be noted that the mean levodopa dosage in this population was rather low, only 500 mg/day.

An interesting case report has drawn attention to the fact that severe response fluctuations can occur soon after the start of treatment in patients with severe disease (17).

- Two men aged 76 and 72 years presented with advanced symptoms of Parkinson's disease and were treated with levodopa. Disabling dyskinesia occurred within days of reaching maintenance dosages of levodopa (1–1.5 g/day with benserazide).

Clearly, the disease status of the patients was the determinant for this adverse reaction, not the duration of levodopa therapy.

In 17 parkinsonian patients three tests of proprioception were carried out 1 hour after the administration of levodopa or a dopamine receptor agonist (18). Although data were not provided for individual patients, there was an overall 11–31% deterioration in the mean scores in all three of the tests. There was no difference between patients with and without dyskinesias, but the authors suggested that abnormal proprioception may be a factor in drug-induced dyskinesia.

There is some evidence that the atypical neuroleptic drug clozapine can alleviate levodopa-induced dyskinesia while itself providing additional relief in Parkinson's disease (SEDA-18, 159); clozapine may also relieve levodopa-induced psychosis (SEDA-17, 166).

"Start hesitation" (paradoxical akinesia) is the name given to sudden episodes during which the patient feels a sensation of extreme heaviness of the feet and finds himself unable to start walking; the legs tremble and the patient falls forward; the condition can improve if the levodopa dosage is reduced.

The "on–off effect" seen after prolonged therapy in some patients is characterized by sudden swings between severe parkinsonian symptoms (with freedom from adverse effects) and normal mobility (but with marked adverse drug effects). It is likely that unexplained variations in dopamine concentrations in the central nervous system are responsible; the condition has been seen less often since combinations with decarboxylase inhibitors came into general use.

Hiccups, an unusual form of dyskinesia, have been attributed to levodopa (19).

- An 80-year-old man with Parkinson's disease and dementia developed worsening bradykinesia, and the dose of co-careldopa was increased from 12.5/50 mg bd to 25/100 mg bd. Two days later, he developed hiccups, which lasted for 1 week and which ceased when the dosage was reduced to the previous level. Ocular dyskinesias have been described in a 60-year-old Spanish man who showed intermittent upward and leftward deviations of gaze associated with peak concentrations of levodopa, in doses of up to 800 mg/day plus benserazide (20).

It should be noted that the patient was and apparently still is taking pramipexole and amantadine in addition to levodopa.

Sleep disorders

Daytime sleepiness and nocturnal wakefulness can both occur in relation to dopaminergic drug therapy, but sleep attacks are rare (21). Many factors beside drug treatment can lead to sleep disorders in parkinsonian patients, including the disease process itself and episodes of sleep apnea; some are skeptical about the existence of sleep attacks as a phenomenon distinct from increased general drowsiness (22), although others disagree. Neurologists from King's College London have concluded that all dopaminergic drugs are capable of causing sleepiness and that in a minority of patients it may take the form of a narcolepsy-like phenotype, possibly amenable to improvement by selegiline or modafinil; they have recommended that affected individuals should not drive (23). Although it was their view that this is a class effect of dopamine agonists, they nevertheless suggested that switching from one agonist to another may sometimes be helpful.

Some remarkable case reports have previously been published (SEDA-25, 169) and reports continue to appear, supplemented by prospective studies and other analyses. For instance, 11 studies involving ropinirole or pramipexole in a total of 2066 patients have been reviewed (24). Four of these (two each with ropinirole and pramipexole) were placebo-controlled. The pooled relative risk of somnolence was 4.98 compared with placebo: there was a non-significant trend for greater somnolence with ropinirole, but the confidence intervals were much wider than with pramipexole. In the other studies levodopa alone was compared with levodopa plus the newer drugs; the relative risk was 2.06 compared with levodopa alone. It must be borne in mind that somnolence and sleep attacks may be separate phenomena, although this is controversial.

The whole field of sleep disorders in Parkinson's disease has been reviewed in a consecutive series of 320 patients from Houston, with analysable data from 303 (sex distribution unknown) (25). The mean age was 67 years and the mean duration of the disease was 9.1 years. All the patients completed the Epworth Sleepiness Scale and answered specific questions about falling asleep while driving and about the restless legs syndrome. The mean sleepiness score was 11.1, values greater than 10 being regarded as abnormal. As one would expect, just over half the patients had scores at that level. Higher scores correlated with longer duration and greater severity of the disease, with male sex, and with the use of dopamine receptor agonists. There was no apparent difference in

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this regard between the three most commonly prescribed drugs in these patients (pergolide, ropinirole, and pramipexole, the last being the most frequent). Among those currently driving, 23% reported falling asleep in the car and nearly 20% had features of the restless legs syndrome. This study has therefore reinforced the view that sleep disorders are common in Parkinson's disease, especially in its advanced stages, and are exacerbated by dopamine agonists as a class. However, one can draw no conclusions about individual drugs from this review.

The effects of pramipexole, cabergoline, and levodopa on daytime sleepiness have been assessed in three groups of patients with Parkinson's disease (26). The first group was 19 patients taking pramipexole (mean age 60 years, mean dosage 4.5 mg/day, 8 as monotherapy, the remainder with levodopa); the second group was 22 patients taking cabergoline (mean age 63 years, mean dosage 4.1 mg/day, 10 as monotherapy); the third group was 14 patients taking levodopa (mean age 69 years, mean dosage 789 mg/day) as monotherapy. The scores on the Epworth Sleepiness Scale were virtually identical (8.0, 8.1, 8.1). Scores of greater than 16, indicating excessive daytime sleepiness, were also evenly distributed across the three groups, and were attributed to only four individuals; there were no reports of sleep attacks.

These results have been supported by a study in 160 patients with Parkinson's disease (mean age 66 years) divided into four equal groups and taking levodopa alone, levodopa with bromocriptine, levodopa with ropinirole, or levodopa with pramipexole (27). They were compared with 40 healthy younger controls (mean age 58 years). All the subjects were evaluated using the Epworth Sleepiness Scales. All the drug regimens were associated with increased sleepiness compared with the controls but there were no distinct sleep attacks. The authors noted that all the drug regimens produced similar levels of sedation, although the data appeared to show a trend toward greater somnolence with ropinirole and more particularly pramipexole.

However, these are not uncontested findings. In a study that was described as prospective, but was strictly speaking not, 236 patients (106 men, 130 women, mean age 67 years) were questioned (28). All but one was in Hoehn–Yahr stages II–IV. Sleep attacks were reported by 72 patients, of whom 70% were considered to have autonomic dysfunction. The authors concluded that the highest risk was attributable to ropinirole (OR = 7.35), followed by bromocriptine (5.78) and lisuride (5.68); for comparison, the figure for levodopa was 0.61. No patients took pramipexole. Again, it is uncertain whether sleep attacks can truly be distinguished from "ordinary" sleepiness, but the results emphasize the sedative potential of dopamine receptor agonists.

On the other hand, these results have been disputed in another report, with authors in common with the previous report. They presented four case studies, three men and one woman, aged 49–87 years, who had had Parkinson's disease for 8–17 years; the longest duration was in the youngest patient (29). All four were taking levodopa (300–1500 mg/day) plus a decarboxylase inhibitor. All four reported sudden irresistible sleep episodes, even during conversations: two also complained of sleepiness distinct from these attacks. Two of the patients also had definite autonomic disturbances. The authors concluded that sleep attacks do occur and may be associated with levodopa as well as with dopamine receptor agonists.

The sedative potential of levodopa has been examined in 16 healthy volunteers (mean age 25 years, eight men), although of course this represents a very different neuropsychological context from Parkinson's disease (30). They were given levodopa 200 mg or a placebo as a single dose, with domperidone to minimize peripheral adverse effects, followed by the active drug or control in a crossover design. Sedation was assessed using a visual analogue scale and reaction time by the response to a light stimulus. There was no overall change in reaction time, but this concealed considerable interindividual variation. Four subjects complained of nausea and one of excitation after levodopa and all had slower reaction times without complaining of sedation. However, seven subjects reported a greater level of sedation with levodopa than placebo, and this correlated ($r = 0.7$) with their reaction times. In other words, levodopa can cause sedation in normal young people but does not necessarily do so, at least after a single dose. The extent to which these results can be extrapolated to elderly parkinsonian patients is debatable.

In a Canadian survey of 638 parkinsonian patients who were fully independent and with no evidence of dementia, just over half (327) had excessive daytime sleepiness, as assessed by the Epworth Sleepiness Scale and the Inappropriate Sleep Composite Score (31). Only 16 patients had fallen asleep while driving and of these 3 had no warning; all had high scores on the scales mentioned. Unfortunately, the structure of the survey did not allow conclusions regarding drug therapy, although all the patients were taking levodopa (80%), or a dopamine receptor agonist, or both.

In another survey, from Texas, Epworth scores were studied in 368 patients with Parkinson's disease and 243 with other neurological disorders, mostly other movement disorders, including other causes of parkinsonian syndromes (32). The former had scores 25% higher; however, it should be noted that matching for age and other parameters was not clearly described. Using a multivariate model the authors calculated that levodopa dosage, the use of dopamine receptor agonists, and the severity of the disease accounted for only a minor extent (about 9%) of the variation in scores in the parkinsonian group. Even so, they concluded that progression of the disease, the dosage of levodopa, and the use of dopamine receptor agonists are contributory factors in increased daytime somnolence.

Several smaller-scale studies and case reports have also been published. An Italian group have reported polysomnographic studies in a 44-year-old woman with a 5-year history of idiopathic Parkinson's disease (33). She was taking modified-release levodopa, to which pergolide 3 mg/day was added, titrating up from a lower dose. After taking this dosage for 5 days she developed irresistible sleep attacks up to 5 times a day with no warning or obvious triggers. Polysomnography showed that these episodes closely resembled narcolepsy. The episodes ceased after pergolide withdrawal.

Six German patients (aged 36–68 years, disease duration 7–12 years, four men) were studied after reporting

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sleep attacks following the addition of pramipexole or ropinirole to a levodopa-based treatment regimen (34). Five had abnormal results in the multiple sleep latency test, and three of these also had increased errors in a test of driving vigilance. The authors concluded that patients should be assessed individually in terms of their safety to drive. They also suggested that sleep attacks are at the extreme end of the spectrum of daytime sleepiness, although it is not clear that such a conclusion can be reached so unequivocally from such a small study.

A French group has tested the effects of ropinirole 3 mg on sleep latency in 20 healthy men (mean age 24 years) compared with placebo (35). The time to sleep onset was significantly quicker in the ropinirole-treated subjects (2.6 versus 4.8 minutes), but sleep attacks did not occur. Clearly this is a very different group of individuals from the usually much older group with Parkinson's disease, so again definite conclusions are elusive.

Overall, the current evidence suggests that sedation is a class effect of all dopaminergic drugs, including levodopa. It may be more severe with the newer synthetic agents pramipexole and ropinirole, but this cannot yet be stated with certainty. The existence of discrete sleep attacks also remains controversial, although on balance one would conclude that they can occur.

Psychological, psychiatric

Toxic psychoses and toxic delirium can occur, particularly in individuals with a history of postencephalitic parkinsonism or psychiatric disease (36). Nearly half of all patients with Parkinson's disease are demented or have significant cognitive impairment (37). These patients are particularly susceptible to delirium induced by levodopa and other antiparkinsonian drugs. The author recommended dosage reduction or elimination of drugs that may be responsible, starting with anticholinergic drugs but leaving levodopa unchanged if possible. He also recommended the use of the atypical neuroleptic drugs clozapine or olanzapine in severely disturbed patients in whom drug withdrawal is not feasible.

Much more common are such symptoms as confusion (13% of cases), depression (9% of cases, often requiring antidepressant drugs), and sleep disturbances (20% of cases). Vivid hallucinations are common. Psychotic symptoms appear to be more common when enzyme inhibitors are used or anticholinergic drugs given. Panic attacks seem to occur in some 20% of cases during the "off" phases of an "off/on" cycle (38).

Libido has been found to increase, at least for some time, in a proportion of patients (39); whilst perhaps in part reflecting the improved mobility and sense of well-being, a causative relation with prolactin inhibition by levodopa has been suggested.

There may be subtle neuropsychiatric adverse effects of dopaminergic medication. The syndrome of hedonistic homeostatic dysregulation, generally associated with substance abuse, has been described in 15 patients with Parkinson's disease (40). Four patients were described in detail. The authors noted that 12 of the 15 patients were men (three of the four described in the paper) and had early onset of Parkinson's disease: those described were aged only 36–42 years. Characteristically, these patients were taking large and increasing doses of levodopa (or other dopamine agonists, including apomorphine) despite worsening dyskinesias; they had impaired social functioning, including absence from work, belligerent behavior, and hypersexuality; they had a hypomanic or bipolar affect; they underwent a withdrawal reaction on reducing levodopa dosage, with depression, dysphoria, and anxiety; and they had a disorder with the above features lasting at least 6 months. All of the four patients described in detail had taken apomorphine at some time (75–170 mg/day) and tended to use higher than prescribed doses by intermittent injection. All were also taking levodopa (maximum dose 1875–5500 mg/day). The authors noted that the long-term management of this condition can be very difficult. They suggested management of acute psychosis with atypical neuroleptic drugs, such as olanzapine or risperidone, the use of antidepressants if needed, and careful supervision of patient self-medication. They conceded that this may be extremely difficult.

In a prospective study of 89 patients with Parkinson's disease, of whom 60 were free of hallucinations at entry, though most of these had disturbed sleep patterns, after 4 years 50% of the original non-hallucinators were experiencing hallucinations, while only 14% of those with hallucinations at entry were no longer affected by them (41). Those classified as having severe hallucinations increased from 10% at entry to 35% after 4 years. The development or worsening of hallucinations was not associated with levodopa dosage but was strongly correlated with the use of dopamine receptor agonists in combination with levodopa: some 59% of patients with hallucinations were taking agonists as against 33% of non-hallucinators.

It is a pharmacological truism that exogenous dopamine is not a central dopamine receptor agonist, because it cannot cross the blood–brain barrier. However, the possibility that it might, and could thus contribute to the development of delirium, has been examined (42). Of over 21 000 inpatients in Stanford University Hospital, 1164 were given intravenous dopamine. Although the authors conceded that the methods that they used to assess the presence of delirium were imprecise, they nevertheless calculated that intravenous administration of dopamine nearly triples the likelihood of the need for subsequent antipsychotic medication. This raises at least the possibility that in some pathological states significant amounts of exogenous dopamine can enter the brain. A prospective study is needed to clarify this. Meanwhile the authors have proposed that it might be useful to give dopamine receptor antagonists to patients who are about to receive dopamine infusions. However, most clinicians would probably be reluctant to do this on the existing evidence.

Endocrine

Occasional increases in protein-bound iodine have occurred (43).

Levodopa usually increases plasma growth hormone concentrations (44).

Disruption of diurnal cortisol rhythm has been detected and could explain some of the sleep disturbances and psychic adverse effects that levodopa can have (SEDA-8, 143).

Levodopa can stimulate glucagon secretion (45).

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Metabolism

Carbohydrate tolerance is slightly impaired by levodopa.

Electrolyte balance

There is a tendency to potassium loss and hypokalemia. Some patients are particularly susceptible to this adverse effect. In three patients with hypokalemia and five without, levodopa caused increased excretion of potassium, and sometimes also of sodium, in the hypokalemic but not in the normokalemic patients; this effect was prevented by the administration of a peripheral dopa decarboxylase inhibitor (46).

Hyponatremia has been reported in one published case, and the patient had earlier the same reaction with amantadine (SEDA-18, 159).

Hematologic

Very occasionally there are falls in white blood cell count, hemoglobin, and hematocrit. The Coombs' test can be positive and there is an isolated report of hemolytic anemia and another of thrombocytopenia with a positive antinuclear antibody test (SED-12, 315). An otherwise unexplainable acute severe non-hemolytic anemia in an elderly man taking levodopa with benserazide has also been observed (SEDA-12, 124).

Gastrointestinal

Despite the fact that gastrointestinal tolerance can be improved by cautious dosing, very gradual dosage increases, and the use of antiemetics, anorexia, nausea, and vomiting have been estimated to occur in 36–83% of patients taking levodopa alone, and some 10% of patients never succeed in tolerating the dose that was optimally effective for them (47). Gastrointestinal tolerance is substantially better with the combined products; provided the combination is taken during meals, digestive disturbances are usually mild and transitory, and only a few patients require antiemetics.

Liver

Liver function tests are as a rule unchanged, but isolated changes in aspartate transaminase, alanine transaminase, bilirubin, and lactate dehydrogenase have been recorded.

Urinary tract

Blood urea concentration occasionally rises. One report suggested darkening of the urine, but this seems to have been coincidental.

Urinary retention has been described in a case of hypertonic bladder, but the association may have been fortuitous (48).

There have been several reports of a diuretic effect of levodopa; although it is seldom recognized, the effect is probably fairly consistent and not limited, as was at one time suggested, to obese subjects (49). It is presumably mediated through renal dopamine receptors.

Skin

Pemphigus erythematosus has been reported after 18 months of treatment with co-careldopa (50).

Darkening of the sweat has been described (43).

Darkening of the white hair of a patient who was taking levodopa in combination with bromocriptine for Parkinson's disease has been reported (SEDA-15, 133).

There is some evidence suggesting a link between levodopa and the development of melanoma (SEDA-17, 167), but a prior history of melanoma should not be regarded as a contraindication to levodopa treatment.

Hair

Treatment with levodopa has very rarely been associated with reversible alopecia (51).

Musculoskeletal

There seems to be no doubt that patients who take levodopa are more likely to have a fracture (1). The most likely explanation is simply that they are more mobile and thus more likely to fall than before treatment was begun, but it should be borne in mind that benserazide caused skeletal changes in rats in the original toxicity studies.

"Black cartilage" (intense black pigmentation confined to the costal cartilage) has been found at necropsy in a man who had taken co-careldopa for 13 years (SED-12, 316).

The uric acid concentration can increase and in some cases frank gout occurs, occasionally within a few days of starting treatment (52).

Sexual function

Libido can increase, at least for some time, in a proportion of patients (39); while this perhaps in part reflects improved mobility and sense of well-being, a causative relation with prolactin inhibition by levodopa has been suggested.

Long-Term Effects

Drug withdrawal

A serious relapse of Parkinson's disease can occur after withdrawal. The most dangerous potential consequence is a syndrome identical to the neuroleptic malignant syndrome, with hyperthermia, semistupor, rigidity, and tremor, after withdrawal of levodopa (53,54).

Second-Generation Effects

Teratogenicity

Parkinson's disease is very rare in pregnancy, but has been described (55).

- A 36-year-old woman with a 4-year history of Parkinson's disease, who had been taking pergolide 3 mg/day and levodopa 200 mg/day continued to take it during pregnancy. The end-of-dose wearing-off effect completely disappeared, and reappeared at their previous intensity after delivery. There were no adverse effects in the mother. The baby was healthy at birth and remained so at the time of the report, at the age of 13 months.

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Susceptibility Factors

Genetic factors

Drug-induced hallucinations are a more familiar aspect of the treatment of Parkinson's disease. Susceptibility to these shows great interindividual variation and it is hardly surprising that researchers are seeking genetic bases for these. Polymorphisms of dopamine receptor genes seem obvious candidates, and this has been studied by a group in Sheffield (56). They found an association between late-onset hallucinations and a polymorphism close to the D_2 receptor. However, the effect is not overwhelming: the abnormal allele of the Taq IA polymorphism was found in 82% of those who hallucinated and 59% of those who did not. This is statistically significant but, as often in this type of study, the biological and clinical relevance is far from certain.

Other features of the patient

Because of the cardiovascular effects of levodopa, patients with cardiac disorders are at risk.

Levodopa should not be used in patients with a history of mental illness, hemolytic anemia, or any serious organic disease.

Neurologists from Madrid have studied 168 consecutive patients treated for at least 6 months with levodopa (57). About 10% of the patients per year developed dyskinesias over 7 years. Younger age (under 50 years) at the onset of the disease and high initial levodopa dosages (more than 600 mg/day) were the most important susceptibility factors identified.

Drug Administration

Drug formulations

When four patients from Argentina experienced deterioration of their Parkinson's disease it was discovered that their medication contained not 250 mg levodopa plus benserazide, as labeled, but only 60 mg of levodopa alone (58).

Drug–Drug Interactions

Monoamine oxidase inhibitors

The combination of a monoamine oxidase inhibitor with levodopa causes hypertension, sometimes with very high pressures (59,60).

Neuroleptic drugs

Neuroleptic drugs can aggravate parkinsonism; if an antiemetic is required, a non-phenothiazine should therefore be chosen.

Papaverine

Papaverine can reduce the effects of levodopa (61,62).

Propranolol

Propranolol may improve the effect of levodopa on tremor (63).

Pyridoxine

Pyridoxine interferes with the desired nervous system effect of levodopa (64,65), since it is a co-decarboxylase, which facilitates the transformation of levodopa to dopa outside the central nervous system.

Interference with Diagnostic Tests

Urinary glucose

Treatment with levodopa results in false-positive tests for urinary glucose (66).

Urinary ketone bodies

Treatment with levodopa results in false-positive tests for urinary ketone bodies (67).

Diagnosis of Adverse Drug Reactions

A group from the National Hospital for Neurology in London has described the use of continuous subcutaneous apomorphine infusions in 19 patients with Parkinson's disease with severe unpredictable motor fluctuations while taking levodopa (68). The objective was to replace levodopa during waking hours with apomorphine monotherapy. During apomorphine treatment ranging from 9 months to nearly 8 years, there was a 65% reduction in dyskinesia severity and an 85% reduction in frequency and duration, with a 70% reduction in the "off" time. Nearly half the patients stopped taking levodopa altogether.

A less radical and much less expensive approach to the management of motor fluctuations has been described in 14 patients with advanced Parkinson's disease and levodopa-induced motor disorders (69). Amantadine (mean dose 350 mg/day) reduced the severity and duration of dyskinesias by 33–75%, depending on the parameter measured. The rationale was that amantadine blocked *N*-methyl-D-aspartate receptors.

Unilateral stereotactic pallidotomy has been described in 42 patients, with dramatic improvement in dyskinesias at 3 months after surgery: the number of patients with moderate to severe dyskinesias was reduced from 36 to 5, although it is not clear whether there was any change in other aspects of the disease (70).

A novel pharmacological approach has been described by a group in Israel, who have used the glutamate receptor antagonist riluzole in six patients with severe Parkinson's disease and dyskinesias (71). At a dose of up to 50 mg/day riluzole significantly reduced dyskinesias, did not worsen parkinsonian symptoms, and was well tolerated.

As regards susceptibility factors for the development of levodopa-induced dyskinesias, neurologists from Madrid have studied 168 consecutive patients treated for at least 6 months with levodopa (57). About 10% of the patients per year developed dyskinesias over 7 years. Younger age (under 50 years) at the onset of the disease and high initial levodopa dosages (more than 600 mg/day) were the most important susceptibility factors identified.

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The efficacy of clozapine has been described in 60 patients with levodopa-induced neuropsychiatric syndromes (32 assigned to the active drug and 28 to placebo) (72). The mean age was 72 years, the mean duration of disease was 12 years (Hoehn and Yahr stage 3.2), and the mean levodopa dosage was 774 mg/day. At a dose of up to 50 mg/day, clozapine significantly improved psychotic features, with minimal effects on parkinsonian symptoms. Clozapine caused somnolence but was otherwise well tolerated.

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Levofloxacin

See also Fluoroquinolones

General Information

Levofloxacin, the levorotatory (*S*)-enantiomer of the racemate ofloxacin, is an oral and parenteral fluoroquinolone that has bactericidal activity against a wide spectrum of Gram-negative and Gram-positive bacilli (including *Streptococcus pneumoniae*), as well as atypical respiratory pathogens.

In patients with meningitis, levofloxacin penetration in cerebrospinal fluid and the liquor-to-plasma ratio was assessed at 2 hours after dosing in five patients with spontaneous acute bacterial meningitis. Cerebrospinal fluid levofloxacin concentration at 2 hours after dosing was 2.0 μg/ml, and the liquor-to-plasma ratio at 2 hours after dosing was 0.35 (1).

Observational studies

In 10 patients who took levofloxacin 500 mg/day and rifampicin 600 mg/day for 2–6 months, there were no adverse reactions in 46% of patients, occasional digestive symptoms in 40%, and mild diarrhea in 13%; these patients also took unspecified anti-inflammatory drugs (2). There was sleeplessness in 6% but neither tendinitis nor changes in liver function.

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In a prospective, multicenter open trial, 313 patients with clinical signs and symptoms of bacterial infections of the respiratory tract, skin, or urinary tract were treated with levofloxacin (3). Of these, 134 patients had a pathogen recovered from the primary infection site and had an MIC of the pathogen to levofloxacin determined. Levofloxacin generated clinical and microbiological response rates of about 95%. These response rates included pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus*. In a logistic regression analysis, the clinical outcome was predicted by the ratio of peak plasma concentration to MIC and site of infection. Microbiological eradication was predicted by the peak concentration/MIC ratio. Both clinical and microbiological outcomes were most likely to be favorable if the peak concentration/MIC ratio was at least 12.

Of 17 individuals with suspected latent multidrug-resistant tuberculosis treated with pyrazinamide and levofloxacin, 11 developed musculoskeletal adverse effects related to therapy, 5 had nervous system effects, and 15 had raised liver enzymes, uric acid, or creatinine kinase (4).

Comparative studies

In comparative trials involving commonly used regimens, levofloxacin had equivalent if not greater activity in the treatment of community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis, acute pyelonephritis, and complicated urinary tract infection (5).

General adverse effects

The adverse effects rates of levofloxacin are 1.3% for nausea, 0.1% for anxiety, 0.3% for insomnia, and 0.1% for headache. No levofloxacin-related adverse events were reported at a rate higher than 1.3%, and most were less common. High-dose levofloxacin (750 mg) was also well tolerated. Surveillance data reported low adverse event rates: nausea 0.8%, rash 0.5%, abdominal pain 0.4%, and diarrhea, dizziness, and vomiting 0.3%. The adverse drug reactions rate for levofloxacin is still one of the lowest of any fluoroquinolone, at 2% compared with 2–10% for other fluoroquinolones (6–9).

Organs and Systems

Cardiovascular

Preclinical and clinical trial data and data from phase IV studies have suggested that levofloxacin causes prolongation of the QT interval (10). There were cardiovascular problems in 1 in 15 million prescriptions compared with 1–3% of patients taking sparfloxacin, who had QT_c prolongation to over 500 ms. Polymorphous ventricular tachycardia with a normal QT interval has been associated with oral levofloxacin in the absence of other causes (6,9,11,12).

Among 23 patients who took levofloxacin 500 mg/day there was prolongation of the QT_c interval by more than 30 ms in four patients and 60 ms in two patients (13). There was absolute QT interval prolongation to over 500 ms in four patients, one of whom developed torsade de pointes.

Phlebitis can occur during parenteral administration of levofloxacin. High concentrations of levofloxacin (5 mg/ml) significantly reduced intracellular ATP content in cultured endothelial cells and reduced ADP, GTP, and GDP concentrations (14). These in vitro data suggest that high doses of levofloxacin are not compatible with maintenance of endothelial cell function and may explain the occurrence of phlebitis. Commercial formulations should be diluted and given into large veins.

Respiratory

Eosinophilic pneumonia complicated by bronchial asthma has been attributed to levofloxacin (15).

- A 76-year-old woman took levofloxacin for a productive cough with non-segmental infiltration in both lung fields. She developed eosinophilia in both the peripheral blood (24%) and the sputum (10%), airflow limitation, hypoxemia, and increased airway responsiveness to methacholine. Bronchoalveolar lavage fluid showed increased total cells and a 55% increase in eosinophils, and the CD4/CD8 ratio was reduced to 0.8. Histological features included increased infiltration of eosinophils in the alveolar and interstitial compartments and goblet cell metaplasia. Levofloxacin was withdrawn, and her symptoms improved without steroid therapy. A leukocyte migration test for levofloxacin was weakly positive.

Nervous system

Levofloxacin can cause seizures (16). In one study convulsions occurred in two per million prescriptions (9,17).

- A 75-year-old white woman was given oral levofloxacin (500 mg on day 1 followed by 250 mg/day) for ischemic toes (16). After three doses she had a seizure. One month later, she was challenged with ciprofloxacin 400 mg intravenously every 12 hours and again had a seizure.
- A 74-year-old white woman was given oral levofloxacin 500 mg/day for bacterial pneumonia and had a seizure after five doses (16).

Sensory systems

Taste disturbance occurred in less than three per million prescriptions of levofloxacin (9).

Gastrointestinal

Of 48 patients taking pyrazinamide 30 mg/kg/day plus levofloxacin 500 mg/day for 1 year, 27 discontinued therapy within 4 months owing to adverse events. Gastrointestinal intolerance was the major adverse event that resulted in early withdrawal (18).

Levofloxacin can cause pseudomembranous colitis due to *Clostridium difficile* (19).

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Liver

In a study based on European and international data from about 130 million prescriptions, the adverse effects profile of levofloxacin was compared with that of other fluoroquinolones; there was a low rate of hepatic abnormalities (1/650 000) (6). However, two cases of severe acute liver toxicity were reported in patients who had received intravenous levofloxacin (20,21).

Pancreas

Two case reports have suggested that levofloxacin can cause pancreatitis (22).

Urinary tract

Two reports have suggested that levofloxacin can cause tubulointerstitial nephritis (23). A case of nephrotoxicity and purpura associated with levofloxacin has also been reported; allergic interstitial nephritis or vasculitis was believed to be the underlying pathologic process (24).

- A 73-year-old white man took levofloxacin for a lower urinary tract infection for 3 days and developed palpable purpura and erythematous skin lesions over the lower limbs and trunk, with a markedly reduced urine output. Serum creatinine was 560 μmol/l (6.4 mg/dl). Levofloxacin was withdrawn, and prednisone, furosemide, and intravenous fluids were given. The patient recovered fully over the next 4 weeks.

Skin

In a double-blind, randomized study in 30 healthy adults oral levofloxacin (500 mg/day for 5 days) had a low photosensitizing potential (25), as it did in preclinical animal studies and postmarketing surveillance (26). In preclinical studies levofloxacin was 20 times less phototoxic than sparfloxacin. Phototoxicity occurs in only 1 in 1.8 million cases.

Levofloxacin can cause a rash similar to the ampicillin rash in patients with infectious mononucleosis (27).

- A 78-year-old woman developed a rash with blistering 2 days after completing a course of levofloxacin (28). The rash progressed to toxic epidermal necrolysis in 7 days. She was treated with intravenous fluids and wound dressings. Her condition improved and she was discharged after 22 days.

Musculoskeletal

Tendinopathy has been reported with levofloxacin. Four cases of Achilles tendinitis have been reported in patients taking levofloxacin (29). Two were on chronic dialysis, one was a kidney transplant recipient, and one had chronic vasculitis. In all four cases, tendinitis had an acute onset with bilateral involvement and was incapacitating. In three cases the onset was early during levofloxacin treatment and in one case it began 10 days after the end of treatment. All the patients recovered completely after 3–8 weeks.

Old age, renal dysfunction, and concomitant corticosteroid therapy are predisposing risk factors (30,31). Tendon rupture occurred in less than four per million prescriptions (9).

Immunologic

Anaphylactic and anaphylactoid reactions are rare adverse events after the administration of fluoroquinolones (about 0.46–1.2 per 100 000 patients).

- On two occasions a 49-year-old asthmatic woman who took levofloxacin for a chest infection developed worse respiratory distress, requiring intubation (32). The second reaction was accompanied by a marked skin reaction.

An in vitro study in rat peritoneal mast cells showed that levofloxacin-mediated release of histamine may be closely linked to activation of pertussis toxin-sensitive G proteins (33).

Susceptibility Factors

The pharmacokinetics of intravenous levofloxacin have been studied in intensive care unit patients during continuous venovenous hemofiltration or hemodiafiltration (34,35). Levofloxacin clearance was substantially increased during both types of continuous renal replacement therapy. Levofloxacin 250 mg/day maintained effective plasma drug concentrations in these patients.

Drug–Drug Interactions

Chinese medicines

Chinese medicines did not influence the systemic availability or renal excretion of levofloxacin (36).

Efavirenz

Levofloxacin pharmacokinetics in HIV-positive patients were not altered by steady-state treatment with efavirenz (37).

HIV protease inhibitors

Levofloxacin pharmacokinetics in HIV-positive patients were not altered by steady-state treatment with nelfinavir (37).

Lithium

Co-administration with levofloxacin can cause severe lithium toxicity; the authors did not discuss the mechanism (38).

Theophylline

Theophylline clearance was reduced by levofloxacin plus clarithromycin in a 59-year-old Japanese man, who had stimulation, insomnia, and tachycardia due to theophylline toxicity (39).

The mechanism was probably inhibition of theophylline metabolism by CYP1A2 and CYP3A4.

Warfarin

Enhanced hypoprothrombinemia has been reported when levofloxacin was given with warfarin (40–42).

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Levosalbutamol

See also Beta$_2$-adrenoceptor agonists and salbutamol

General Information

Levosalbutamol is the (*R*)-enantiomer of the beta$_2$-adrenoceptor agonist salbutamol. It has been suggested to have a better therapeutic index than racemic salbutamol. As levosalbutamol has a much higher receptor affinity than the (*S*)-enantiomer, the therapeutic effects of racemic salbutamol are assumed to be mediated by levosalbutamol. However, toxicity of levosalbutamol is unrelated to beta$_2$-receptor binding, and so the (*S*)-enantiomer may significantly contribute to the toxicity of racemic salbutamol.

The issue of enantioselective efficacy and safety of salbutamol has been reviewed (1). Interest in "chiral switch," that is the replacement of the racemic formulation by the pharmacologically active (*R*)-enantiomer levosalbutamol, may be hampered by enantiomeric interconversion in vivo and marked interindividual variation in salbutamol pharmacokinetics and pharmacodynamics, owing to complex interactions between genetic and environmental effects. The authors concluded that the advantage of levosalbutamol over the racemic formulation appears to be small with respect to efficacy and controversial with respect to safety. Two large crossover studies with multiple inhaled doses of (*S*)-salbutamol in asthmatic patients showed no evidence of adverse effects on FEV_1 (2,3).

The effects of two doses of inhaled levosalbutamol (0.63 and 1.25 mg) and racemic salbutamol (1.25 and 2.50 mg) on FEV_1 have been studied in a randomized, double-blind trial in 362 asthmatic patients over 4 weeks (4). The average peak FEV_1 for levosalbutamol was significantly greater than that for racemic salbutamol after the first dose but not at week 4. The possible superior bronchodilatation achieved with lower doses of levosalbutamol may be more cost-effective (5).

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Lidocaine

See also Local anesthetics

General Information

Lidocaine is the most widely used aminoamide local anesthetic agent, with a low toxic potential; its effects are mostly typical for this class of drug. It can be given by injection or topically and is also combined with prilocaine in Emla for topical administration. It is also used as an antidysrhythmic drug and has occasionally been used in other conditions, such as multiple sclerosis, chronic daily headache, migraine and cluster headaches, and neuropathic pain, such as postherpetic neuralgia.

Local anesthetic gels and creams used liberally on traumatized epithelium can be rapidly absorbed, resulting in systemic effects, such as convulsions, particularly if excessive quantities are used. This has been highlighted in the case of a 40-year-old woman who developed seizures after lidocaine gel 40 ml was injected into the ureter during an attempt to remove a stone (1). Site of administration is also important, as local conditions, particularly vascularity, affect the rate of absorption. Adverse effects of lidocaine when it is used as a local anesthetic can also occur after inadvertent intravascular injection.

The incidence of adverse effects to lidocaine in antidysrhythmic dosages is low. In one series of 750 patients given lidocaine intravenously for cardiac dysrhythmias, adverse reactions occurred in only 47 (6.3%) and were thought to have been life-threatening in 12 (1.6%) (2). However, the risk of adverse effects is dose-related and increases at intravenous infusion rates of around 3 mg/minute (3). Most of the adverse effects are on the cardiovascular and central nervous systems. Nervous system toxicity is directly related to blood concentrations, with symptoms that include light-headedness, headache, dizziness, tremor, confusion, tinnitus, dysarthria, paresthesia, alterations in the level of consciousness from drowsiness to coma, respiratory depression, and convulsions. Cardiovascular effects, including dysrhythmias and very rarely worsening of cardiac function, only occur at very high blood concentrations. The intravenous dose of lidocaine required to produce cardiovascular collapse is seven times that which causes seizures. Risks of serious systemic effects do not increase with age. Deaths have occurred with voluntary intoxication, primarily because of the cardiac effects.

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The active metabolites of lidocaine, glycinexylidide and monoethylglycinexylidide, are toxic and intravenous infusion should not continue for more than 24–48 hours.

Hypersensitivity reactions are rare, and not all reports are clear, but cases do occur and are usually mild (SED-12, 255) (4). Some patients are highly sensitive to lidocaine, yet insensitive to other aminoamide local anesthetics (5), and the reverse has also been found (SEDA-14, 109). True anaphylaxis with rechallenge has been documented (6). A few cases of contact dermatitis have been reported.

Even topical administration of lidocaine continues to generate reports with tragic outcomes, as absorption from mucosal surfaces is underestimated.

- A patient due to have a bronchoscopy was given an overdose of lidocaine to anesthetize the airway by an inexperienced health worker. He was then left unobserved and subsequently developed convulsions and cardiopulmonary arrest (7). He survived with severe cerebral damage.

His lidocaine concentration was 24 μg/ml about 1 hour after initial administration (a blood concentration over 6 μg/ml is considered to be toxic).

Drug studies

Lidocaine has been used to treat some of the symptoms of multiple sclerosis in 30 patients with painful tonic seizures, attacks of neuralgia, paroxysmal itching, and Lhermitte's sign (8). Lidocaine was given by intravenous infusion for 5.5 hours in a maintenance dose of 2.0–2.8 mg/kg/hour after a loading dose, and the mean steady-state concentration was 2.4 μg/ml. Lidocaine almost completely abolished the paroxysmal symptoms and markedly alleviated the persistent symptoms of multiple sclerosis. Adverse effects were not specifically mentioned, but in one case, when the plasma concentration of lidocaine rose above 3.5 μg/ml, weakness of the left leg became marked and was associated with an extensor plantar response; this disappeared when the lidocaine was replaced by saline single-blind, but subsequently the positive symptoms recurred.

Intravenous lidocaine has been used to treat severe chronic daily headache in 19 patients (three men, median age 37 years) (9). There were adverse effects during four infusions of lidocaine: hyperkalemia (6.4 mmol/l), which did not resolve after withdrawal of lidocaine; transient hypotension (75/50 mmHg), which was attributed to concomitant droperidol; an unspecified abnormality of cardiac rhythm and on another occasion a transient bradycardia; and chest pain with a normal electrocardiogram, fever, and intractable nausea. The study was neither randomized nor placebo-controlled, and in no case was the adverse event strongly associated with the administration of lidocaine.

In a double-blind, placebo-controlled study of the use of intravenous lidocaine for neuropathic pain, 16 patients were given 5 ml/kg intravenously over 30 minutes (10). Lidocaine was better than placebo in relieving pain. The major adverse effect was light-headedness, which occurred in seven patients given lidocaine and none given saline. Other adverse effects included somnolence, nausea and vomiting, dysarthria or garbled speech, blurred vision, and malaise. In two patients the rate of infusion had to be reduced because of adverse effects.

Organs and Systems

Cardiovascular

Lidocaine can cause dysrhythmias and hypotension. The dysrhythmias that have been reported include sinus bradycardia, supraventricular tachycardia (11), and rarely torsade de pointes (12). There have also been rare reports of cardiac arrest (2) and worsening heart failure (13). Lidocaine can also cause an increased risk of asystole after repeated attempts at defibrillation (14). Lidocaine may increase mortality after acute myocardial infarction, and it should be used only in patients with specific so-called warning dysrhythmias (that is frequent or multifocal ventricular extra beats, or salvos) (15).

Sinus bradycardia has been seen after a bolus injection of 50 mg, atrioventricular block after a dose of 800 mg given over 12 hours, and left bundle branch block after a mere subconjunctival injection of 2% lidocaine.

- High-grade atrioventricular block has been reported in a 14-day-old infant who was given lidocaine 2 mg/kg intravenously (SED-12, 255) (16).

A death due to ventricular fibrillation after 50 mg and another due to sinus arrest after 100 mg have been reported (SED-12, 255) (17). Two cases of ventricular fibrillation and cardiopulmonary arrest occurred after local infiltration of lidocaine for cardiac catheterization (SEDA-21, 136).

Lidocaine does not usually cause conduction disturbances, but two cases have been reported in the presence of hyperkalemia (18).

- A 57-year-old man with a wide-complex tachycardia was given lidocaine 100 mg intravenously and immediately became asystolic. Resuscitation was unsuccessful.
- A 31-year-old woman had a cardiac arrest and was resuscitated to a wide-complex tachycardia, which was treated with intravenous lidocaine 100 mg. She immediately became asystolic but responded to calcium chloride.

In both cases there was severe hyperkalemia, and the authors suggested that hyperkalemia-induced resting membrane depolarization had increased the number of inactivated sodium channels, thus increasing the binding of lidocaine and potentiating its effects.

The degree of hypotension occurring after epidural anesthesia with alkalinized lidocaine (with adrenaline) was greater than with a standard commercial solution (SED-12, 255) (19).

In 23 patients there was a significant dose-dependent reduction in blood pressure following submucosal infiltration of lidocaine plus adrenaline compared with saline plus adrenaline for orthognathic surgery (20). The study was randomized but small; larger studies are needed to confirm effects that could easily have been due to multifactorial causes in patients undergoing general anesthesia.

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Respiratory

Topical anesthesia of the airways is commonly used to facilitate endoscopy and sometimes manipulation of the airways. This can result in an increase in airway flow resistance, possibly due to laryngeal dysfunction (21). Lidocaine spray 10%, used for upper airways anesthesia for fiberoptic intubation in a grossly obese patient, caused acute airway obstruction. The patient went on to have a percutaneous tracheotomy, and it was postulated that the local anesthetic had abolished laryngeal receptors responsible for airway maintenance, or that laryngospasm and reduced muscle tone due to the lidocaine might have been the cause (SEDA-22, 140).

Life-threatening bronchospasm can occur after either spinal or topical use of lidocaine. In one series of patients being treated with lidocaine spray 40 mg for persistent cough, there was an increase of airway resistance (SED-12, 255) (22).

Ear, nose, throat

Local anesthesia to the larynx, for example with 4% lidocaine, is generally safe. Laryngeal edema has been reported in a few cases and could be due to the propellant rather than to lidocaine itself (23).

Intranasal 4% lidocaine has been used for migraine and cluster headaches with success and few serious adverse effects: a bitter taste was common and some patients complained of nasal burning and oropharyngeal numbness (SEDA-20, 127).

Lidocaine gel is not recommended for lubrication of laryngeal masks. It confers no benefits and increases the incidence of adverse effects such as intraoperative hiccups, postoperative hoarseness, nausea, vomiting, and tongue paresthesia (24).

Nervous system

Nervous system toxicity is most often seen with rapid intravenous infusion (3,25,26). The effects include headache, dizziness, tremor, confusion, tinnitus, dysarthria, paresthesia, respiratory depression, altered level of consciousness (from drowsiness to coma), and convulsions.

Two cases have illustrated the effects of lidocaine in precipitating partial seizures in patients with a previous history of epilepsy (27).

- A 36-year-old woman developed chest pain and ventricular tachycardia. She had a 14-year history of right-sided focal motor seizures controlled with phenytoin. After receiving intravenous lidocaine 100 mg to treat the dysrhythmias, she developed a typical seizure involving the right side of her face and arm. She was given a loading dose of phenytoin and the seizure abated. However, the ventricular tachycardia persisted and was treated with additional lidocaine 50 mg followed by an infusion of 3.3 mg/minute; 6 hours later she had a generalized seizure with a venous blood lidocaine concentration of 21 μg/ml. The infusion was stopped and the seizure was treated with intravenous diazepam 10 mg.
- A 41-year-old woman with a long-standing history of focal and secondarily generalized seizures controlled with carbamazepine underwent cerebral arteriography, during which she was inadvertently given lidocaine 20 mg via an intra-arterial catheter in the right internal carotid artery; within 20 seconds she had a focal seizure.

These two patients had their typical partial seizures triggered by high doses of lidocaine. In both cases the serum concentrations of their usual anticonvulsants were initially low. The first patient received a loading dose of phenytoin after the partial seizure, was then given a second bolus of lidocaine and an infusion, and then had a second seizure, which was generalized. There was no evidence that this second seizure evolved from the left seizure focus. The authors concluded that lidocaine can activate seizure foci in patients with a history of partial seizures and that this may be more likely if the serum concentrations of anticonvulsants are low. However, therapeutic concentrations of antiepileptic drugs may not prevent generalized seizures that result from the widespread lowering of seizure threshold caused by high concentrations of lidocaine.

A tonic-clonic seizure occurred after the application of 400 mg of lidocaine jelly to traumatized ureteric mucosa (SEDA-22, 142).

- A 54-year-old woman who was given lidocaine, 200 mg intravenously, for ventricular fibrillation during cardiopulmonary bypass, had a tonic-clonic seizure (28). The seizure occurred immediately after the administration of lidocaine and was relieved by the intravenous administration of thiopental and midazolam. Her ventricular fibrillation responded to procainamide 1 g intravenously over 10 minutes.

The pharmacokinetics of lidocaine are altered by cardiopulmonary bypass, because of hemodilution, changed protein binding, the exclusion of the lungs as an organ for first-pass elimination, altered acid-base balance, and sometimes drug interactions. In particular, reduced protein binding may have contributed in this case to the risk of seizure, but plasma lidocaine concentrations were not measured.

- A 30-year-old woman received two 5 g applications of 40% lidocaine cream with occlusion by plastic wrap during and after laser therapy to areas of her skin (29). She developed dizziness and headache postoperatively, followed 45 minutes later by light-headedness, increasing dizziness, and confusion. The dressings were removed. The lidocaine concentration was 2.7 μg/ml 7 hours later.

It is recommended that repeat applications of lidocaine, especially in high-concentration formulations, be avoided and the area of application limited.

- A 16-year-old woman had had an adverse reaction after administration of an unknown local anesthetic agent for a dental procedure. Patch testing had elicited similar symptoms with lidocaine only, and 20 minutes after subcutaneous lidocaine 0.05 mg she developed perioral paresthesia, nausea, vomiting, vertigo, dizziness, mild agitation, drowsiness, and euphoria. Hemodynamic parameters remained stable but her symptoms were thought to be part of a genuine non-allergic, neuropsychiatric reaction, as the patch testing was double-blind and placebo-controlled (30).

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Transient and permanent nerve damage can occur after regional anesthesia, particularly neuraxial anesthesia. The mechanism of this nerve damage is unclear. Some studies have shown an indirect effect. However, in crayfish giant axon, lidocaine had a dose- and time-dependent effect on isolated nerve function in vitro (31). At high concentrations lidocaine caused irreversible conduction block and total loss of resting membrane potential. These results in an isolated nerve suggest a direct neurotoxic effect of lidocaine.

Sensory systems

Tinnitus and visual disturbances are early components of a systemic toxic reaction to lidocaine.

Eyes

A potentially beneficial effect of lidocaine has been studied in a randomized, double-blind, placebo-controlled study of the effects of preinstillation of lidocaine on tropicamide-induced mydriasis (32). Pupillary diameter was significantly increased by the instillation of lidocaine before tropicamide. It was thought that lidocaine can enhance intraocular penetration and hence potentiate the effect of tropicamide.

Double vision and difficulty in focusing have been attributed to lidocaine applied to the tongue (33).

- A 22-year-old man developed double vision and difficulty in focusing after using 2% viscous lidocaine for a painful tongue ulcer. He used viscous 2% lidocaine 10 ml hourly and developed symptoms when the daily dose exceeded 240 ml (4800 mg of lidocaine hydrochloride) after 10 days of use. At that time his serum lidocaine concentration was 6.7 μg/ml. His symptoms persisted when the serum concentration of lidocaine fell to below toxic concentrations, implying that metabolites of lidocaine had contributed.

Temporary blindness, an unusual feature of lidocaine toxicity, has been reported in an otherwise healthy young woman (34).

- A 21-year-old 50 kg woman, previously fit, was to have an open reduction and fixation of a fractured proximal phalanx with intravenous regional anesthesia. As a result of misreading the vial label, 30 ml (600 mg) of 2% lidocaine was injected, and this inadvertent error was immediately recognized. The decision was made to continue with the procedure, which was uneventful, with a tourniquet time of 45 minutes. At this point the patient complained of severe tourniquet pain, and without the anesthesiologist's knowledge the cuff was deflated. Immediately she developed a tachycardia, complained of visual disturbances, and became unconscious. She had a seizure, which lasted 30 seconds and resolved with midazolam. She became more alert, but complained of reduced vision. Neurological examination was normal, apart from temporary blindness; this fully resolved within 10 minutes. There were no long-term neurological or visual sequelae.

The authors suggested that the visual symptoms could have occurred as a result of occipital lobe seizure activity or subcortical stimulation, due to the acute high cerebral concentration of lidocaine. The speed of spontaneous resolution was consistent with the pharmacokinetics of lidocaine.

Pupillary mydriasis occurred in a neonate who was given intravenous lidocaine 3 mg/kg/hour as an anticonvulsant (35).

Taste

Taste disturbance has been reported with lidocaine (36).

- A 73-year-old woman was given a Nadbath Rehman block behind the left pinna to provide motor blockade of cranial nerve VII, before retrobulbar block for cataract surgery. Several minutes later she complained of a metallic taste in her mouth. After surgery she had altered taste sensation on the anterior left side of the tongue, with recovery a day later.

The author postulated this to be due to block of the chorda tympani, which runs with cranial nerve VII close to the site of the Nadbath Rehman block.

Metabolism

High systemic doses of lidocaine can cause transient hypoglycemia (SED-12, 255) (37).

Electrolyte balance

There has been one report of hypokalemia (2.2 mmol/l), probably due to potassium channel blockade, after administration of high-dose intravenous lidocaine (8 mg/l) for raised intracranial pressure (SEDA-21, 136).

Hematologic

Severe thrombocytopenic purpura with a lidocaine-mediated antiplatelet IgM antibody has been reported (SED-12, 255) (38).

Three cases of lidocaine-induced methemoglobinemia have been reported in patients undergoing topical anesthesia of the airway and oropharynx (39).

- A 26-year-old woman undergoing bronchoscopy received lidocaine jelly 2% to each nostril, lidocaine solution 2% sprayed on the throat, and 10 ml of lidocaine solution 2% into the trachea. She was also given intravenous diazepam 5 mg and pethidine 75 mg and intramuscular atropine 0.6 mg. She developed dyspnea and cyanosis after the procedure and despite 100% oxygen, her SpO_2 was 85%. Her methemoglobin concentration was 14%.
- A 61-year-old woman was given 15 ml of lidocaine solution 2% and lidocaine spray 4% for topical anesthesia of the throat and oropharynx before upper gastrointestinal endoscopy. She was also sedated with intravenous midazolam 2 mg and pethidine 75 mg. She became cyanosed and desaturated (SpO_2 78%) immediately after the procedure. Her SpO_2 did not recover, despite 100% oxygen. Her methemoglobin concentration was 37%.
- In preparation for transesophageal echocardiogram, a 73-year-old woman was given 15 ml of lidocaine solution 2% and lidocaine spray 4% to anesthetize the oropharynx, plus intravenous midazolam 1 mg and pethidine 12.5 mg. She very rapidly became cyanosed, but remained

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asymptomatic. Her SpO_2 was 85% on oxygen 2 l/minute and her methemoglobin concentration was 25%.

Liver

Liver damage due to lidocaine has rarely been reported. However, severe liver damage has been reported shortly after the withdrawal of mexiletine 300 mg/day and the introduction of lidocaine 1000 mg/day, although lidocaine in the same dose had been used during the previous week (40). The lidocaine was withdrawn and the liver enzymes normalized after treatment with prednisolone.

Skin

Topical 5% lidocaine to 33 patients with postherpetic neuralgia in a crossover trial provided significantly more pain relief than a vehicle patch placebo (41). There was no difference in reported adverse effects: skin redness or rash was reported by 9 in the lidocaine patch phase and 11 in the placebo phase. One patient stopped using the placebo patch owing to red irritated skin, which resolved after the application of lidocaine patches.

Treatment of 27 HIV-infected patients with distal sensory polyneuropathy (the most common neurological disorder associated with HIV) with 5% lidocaine gel resulted in effective analgesia in 75% of patients; three had dry skin and one had blisters (42).

In a phase IV trial, 66% patients with postherpetic neuralgia gained relief from a 5% lidocaine patch applied to the most painful area of the body (43). The lidocaine patch was well tolerated, a rash being the most common adverse effect, in 14% of patients.

Several cases of contact dermatitis have been reported with lidocaine. Generalized exfoliative dermatitis has also been noted once. Local inflammation and necrosis, possibly due to mechanical pressure, are both complications at the injection site.

- A 60-year-old woman was given infiltration anesthesia with lidocaine hydrochloride for removal of a melanoma (44). She developed an itchy dermatitis over the area 36 hours later. Conventional patch testing was negative at 48 and 72 hours to lidocaine and mepivacaine (both amides), as was intracutaneous testing with lidocaine 2%, mepivacaine 2%, and bupivacaine 0.5%. However, intradermal testing at 1/100 dilutions was positive, with itching and erythema at 48 hours with lidocaine and mepivacaine, suggesting delayed hypersensitivity to these drugs, but not with bupivacaine.

It has previously been reported that lidocaine and mepivacaine have a high degree of cross-reactivity not seen with bupivacaine.

Sexual function

Two cases of impotence after anesthesia for elective circumcision in adults have been described (SED-12, 256) (45), but it is very doubtful whether this was a pharmacological and not merely a psychological effect.

Immunologic

There have been 62 reports of allergic contact dermatitis to lidocaine worldwide between 1972 and 1996; 49 were in Australia and several showed cross-reactivity with other amide local anesthetics, such as bupivacaine, mepivacaine, and prilocaine (46).

Body temperature

There is no reliable evidence to support reports of malignant hyperthermia due to local anesthetic agents. In 307 dental patients susceptible to malignant hyperthermia who received local anesthesia, only one had ever developed symptoms suggestive of malignant hyperthermia, after mepivacaine and on another occasion lidocaine (47). Both reactions resolved without specific therapy. There has been one case report of cyanosis, muscle rigidity, tachycardia, tachypnea, a temperature of 41.5°C, and loss of consciousness in a patient who received epidural lidocaine and bupivacaine (48). However, perioperative stress may itself be a potential trigger of malignant hyperthermia.

Death

In New York City, five of 50 000 deaths over a 5-year period were associated with tumescent liposuction; all had received lidocaine in doses of 10–40 mg/kg in association with general anesthesia and/or intravenous sedation and analgesia (49). Three patients died as a result of severe acute intraoperative hypotension and bradycardia with no identified cause, one died of fluid overload, and another died of pulmonary embolism. The authors speculated that lidocaine toxicity or lidocaine-related drug interactions could have contributed to some of the deaths, but other causes could not be ruled out.

In California, six cases of cardiac arrest or severe hypoxemia associated with outpatient liposuction resulted in four deaths over a 3.5-year period, all in women aged 38–62 years; one had a cardiac arrest after sedation and the administration of local anesthetic but before liposuction was started, four had respiratory difficulties and cardiac arrest after liposuction, and one had respiratory difficulties during liposuction (50). Whether the cause of morbidity and mortality in any of these cases was related to local anesthetic toxicity was not mentioned.

A weak solution of lidocaine has sometimes been injected into excess fat before liposuction, so that the procedure can be carried out without general anesthesia. The technique is generally regarded as safe (51). However, deaths are increasingly reported, associated with local anesthetic toxicity or drug interactions (49).

A 19-year-old healthy volunteer undergoing bronchoscopy was given about 1200 mg of lidocaine to anesthetize the airway and was sent home after the procedure, despite complaining of chest pain. Shortly afterwards she had a tonic-clonic seizure and cardiopulmonary arrest and died 2 days later. The research protocol had failed to specify an upper dose limit for lidocaine (52).

Second-Generation Effects

Fetotoxicity

Because of rapid transfer across the placenta and the prolonged half-life of lidocaine in neonates, lidocaine can cause fetal acidosis (SEDA-8, 127). Fetal bradycardia

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is usually observed only in those fetuses with pre-existing heart rate deceleration. Despite massive intoxication at birth, one child had normal behavioral development at 7 months of age (SED-12, 256) (53).

Lactation

Low concentrations of lidocaine and its metabolite monoethylglycinexylidide (MEGX) have been found in breast milk after a dental procedure, but no risk seems to be involved (54).

Susceptibility Factors

Age

Children

Two reports have illustrated the need for particular care when using local anesthetics in neonates and small children. A 2-year-old child died from the combined effects of chloral hydrate, lidocaine, and nitrous oxide for a dental procedure (55). The doses used were not clarified, but in postmortem blood the plasma concentration of lidocaine was 12 μg/ml. The level and adequacy of perioperative monitoring was also not clear.

A neonate who needed a tracheostomy 10 days after a tracheoesophageal fistula repair was given intravenous lidocaine, 1 mg/kg followed 15–20 minutes later by 0.7 mg/kg. Immediately after, tonic-clonic seizures developed. The child recovered, with no observable ill effects at 6 months.

The authors pointed out that the dose of lidocaine used was well within recommended dosage limits. However, they stressed that a more appropriate dosing schedule should be worked out for neonates.

Lidocaine pharmacokinetics tend to follow a single compartment model in neonates, with an increased half-life, and substantially reduced protein binding, leading to a much larger volume of distribution than in adults, but an increased proportion of unbound drug (56).

Elderly people

In the elderly, some local anesthetics (including lidocaine and bupivacaine) have longer durations of action (57).

Sex

That sex differences can affect lidocaine pharmacokinetics is suggested by a report of higher blood concentrations in men than in women after administration of the same dose (SED-12, 256) (58).

Hepatic disease

In patients with heart and liver disease, the dosage requirement of lidocaine is reduced; the half-life of lidocaine is substantially longer in patients with liver disease (59).

Other features of the patient

The adverse effects of lidocaine are dose-related, and are more common in people of light weight and in patients with acute myocardial infarction or congestive cardiac failure. There is also an increased risk of central nervous system effects during cardiopulmonary bypass (60). In cardiac failure, shock, and postoperatively, there are reductions in both the metabolism and the apparent volume of distribution of lidocaine; dosages should be altered accordingly (61).

Drug Administration

Drug additives

The addition of dextran to a lidocaine + adrenaline solution used for infiltration reduced the absorption of both (62).

Alkalinization of local anesthetic solutions should theoretically lead to a faster onset of effect and prolonged anesthesia. However, raising the pH of the solution can cause the local anesthetic to precipitate out of solution, and one study with 2% lidocaine has shown no difference in quality or onset of anesthesia (SEDA-20, 129).

Adrenaline 1:100 000, added to lidocaine 2%, has caused full-thickness skin necrosis when used for ambulatory phlebectomy for varicose veins (SEDA-21, 136).

Drug administration route

Creams and gels

Cutaneous absorption of lidocaine is negligible through normal skin after short-term application. However, when applied to erosive lesions over large body areas, significant absorption may occur. When the drug is applied to mucous membranes, blood levels simulate those resulting from intravenous injection. Local anesthetic creams and gels used liberally on traumatized epithelium can be rapidly absorbed, resulting in systemic effects, such as convulsions, particularly if excessive quantities are used. This has been highlighted in the case of a 40-year-old woman who developed seizures after lidocaine gel 40 ml was injected into the ureter during an attempt to remove a stone (1).

Topical administration of lidocaine to the nasal mucosa occasionally causes severe methemoglobinemia in patients who have the heterozygous form of NADH methemoglobin reductase deficiency (63).

Subcutaneously in liposuction

Some have suggested that lidocaine is unnecessary and potentially toxic in liposuction, and that it provides no postoperative pain relief (64). Others think that lidocaine toxicity is not a major cause of death during liposuction, stating that all reported deaths after liposuction have been associated with general anesthesia or sedation, including the five in New York, and that doses of lidocaine higher than those used in these cases (10–40 mg/kg) are routinely used in tumescent liposuction, no deaths having been reported (50,65). It is possible that adrenaline, high pressure injection, removal of lidocaine by liposuction, and the development of tolerance all contribute to delay in absorption and lack of toxic symptoms at higher than expected plasma concentrations (66).

Patches

Lidocaine is available as a topical analgesic in an adhesive patch formulation for the pain of postherpetic neuralgia.

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The pharmacokinetics and safety of the 5% lidocaine patches have been studied in 20 healthy volunteers, who applied four patches to the skin either every 24 hours or every 12 hours for 3 days (67). Mean steady-state plasma concentrations were 186 and 225 ng/ml respectively, well below those required for an antidysrhythmic effect (1500 ng/ml) or a risk of toxicity (5000 ng/ml). The patches were well tolerated, with no major cutaneous adverse effects. This is in line with data from postmarketing surveillance studies, which have shown that since the availability of lidocaine patches in 1999, no adverse cardiac or other serious adverse events have been reported (68).

The pharmacokinetics of lidocaine in patches have been investigated in two studies. In 20 healthy volunteers, 5% lidocaine patches were applied for 18 hours/day on 3 consecutive days (69). The mean peak concentrations on days 1, 2, and 3 were 145, 153, and 154 ng/ml respectively; the median values of t_{max} were 18.0, 16.5, and 16.5 hours; and the mean trough concentrations were 83, 86, and 77 ng/ml. The patches were well tolerated; local skin reactions were generally minimal and self-limiting. In 20 healthy volunteers, 4 lidocaine patches were applied every 12 or 24 hours on 3 consecutive days (67). The mean maximum-plasma lidocaine concentrations at steady state were 225 and 186 ng/ml respectively. There was no loss of sensation at the site of application. No patient had edema and most cases of erythema were very slight. No systemic adverse events were judged to be related to the patches.

Drug overdose

Inadvertent intravenous injection of lidocaine 1 g resulted in asystole, apnea, and tonic-clonic seizures, with full recovery after 6 hours of intensive resuscitation (SED-12, 256) (70).

Fatal accidental overdose has been reported in a child (71).

- An 18-month-old infant died after swallowing an unknown amount of 2% viscous lidocaine. He rapidly became unwell at home, with convulsions, followed by an asystolic cardiorespiratory arrest. He was intubated and resuscitated by paramedics, but continued to have seizures. He was given anticonvulsants and cardiorespiratory resuscitation was unsuccessful. Toxicological tests identified high concentrations of lidocaine and its metabolites.

Owing to the rare but serious poisonings reported to date, 2% viscous lidocaine should not be prescribed for children under 6 years of age.

An unusual case of homicide using an overdose of intravenous lidocaine has been described (72).

- A 32-year-old man, who had been in hospital for several months because of acute intermittent porphyria and chronic pancreatitis, had a seizure and an asystolic cardiac arrest. Resuscitation was unsuccessful. There was a suspicion of patient mistreatment by one of the attending nurses, and toxicological analyses showed high blood concentrations of lidocaine, diazepam, phenytoin, and promethazine. Diazepam and phenytoin had been administered during resuscitation but lidocaine had not.

The cause of death was given as a ventricular dysrhythmia caused by a lidocaine overdose (total dose about 1500 mg); a nurse was later arrested and tried for murder.

Drug–Drug Interactions

Argatroban

The thrombin inhibitor argatroban had no effect on the pharmacokinetics of intravenous lidocaine 1.5 mg/kg for 10 minutes followed by 2 mg/kg/hour for 16 hours in 12 healthy volunteers; the argatroban was given as an intravenous infusion of 2 μg/kg/minute for 16 hours (73).

Beta-adrenoceptor antagonists

The combination of lidocaine with beta-adrenoceptor antagonists is associated with a slightly increased risk of some minor non-cardiac adverse events (dizziness, numbness, somnolence, confusion, slurred speech, and nausea and vomiting) (74). The combination is not associated with an increased risk of dysrhythmias.

Some beta-blockers reduce hepatic blood flow and inhibit microsomal enzymes, reducing the clearance of lidocaine; there is a clinically significant increase in the plasma concentration of lidocaine during concomitant propranolol therapy (75).

Cimetidine

Cimetidine inhibits the metabolism of lidocaine (76,77) and reduces protein binding, increasing toxicity.

Erythromycin

The effects of erythromycin, an inhibitor of CYP3A4, on the pharmacokinetics of lidocaine have been studied in nine healthy volunteers. Steady-state oral erythromycin had no effect on the plasma concentration versus time curve of lidocaine after intravenous administration, but erythromycin increased the plasma concentrations of the major metabolite of lidocaine, MEGX (78). It is not clear what the interpretation of these results is, particularly since the authors did not study enough subjects to detect what might have been small but significant changes in various disposition parameters of lidocaine and did not report unbound concentrations of lidocaine or its metabolites. However, whatever the pharmacokinetic explanation, the clinical relevance is that one would expect that erythromycin would potentiate the toxic effects of lidocaine that are mediated by MEGX.

Itraconazole

The effects of itraconazole, an inhibitor of CYP3A4, on the pharmacokinetics of lidocaine have been studied in nine healthy volunteers. Steady-state oral itraconazole had no effect on the plasma concentration versus time curve of lidocaine after intravenous administration nor on the plasma concentrations of the major metabolite of lidocaine, MEGX (78).

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Mexiletine

An interaction of lidocaine with mexiletine, which resulted in toxic concentrations of lidocaine, has been reported (79).

- An 80-year-old man with a dilated cardiomyopathy was given a lidocaine infusion started at 90 mg/hour for a ventricular tachycardia. He was already taking mexiletine 400 mg/day, and the plasma concentration was within the usual target range; however, the dose was reduced to 200 mg/day to avoid possible adverse effects. Intermittent ventricular tachycardia persisted, and so the lidocaine infusion was increased to 120 mg/day, but adverse effects (involuntary movements, muscle rigidity) were observed. The lidocaine infusion was stopped and within 20 minutes the adverse effects abated; the lidocaine concentration was 6.84 μg/ml. The ventricular tachycardia persisted, lidocaine was restarted at a lower rate, and the oral dose of mexiletine was increased to 450 mg/day. This resulted in an unexpectedly high concentration of lidocaine and the lidocaine concentration was significantly higher while the mexiletine dose was high.

Further studies suggested that mexiletine had displaced lidocaine from tissue binding sites. The authors suggested that this finding has implications for loading doses and acute effects of lidocaine in the concurrent therapy of lidocaine and mexiletine and highlighted the importance of close monitoring of lidocaine concentrations in this setting.

Opioid analgesics

A synergistic interaction of intrathecal fentanyl 100 μg and morphine 0.5 mg, given before induction, with systemically administered lidocaine 200 mg 4 hours later for ventricular tachycardia, resulted in potentiation of opioid effects in a 74-year-old man with major heart disease after coronary artery bypass grafting; during the 5 minutes after lidocaine he had a respiratory arrest with loss of consciousness and miotic pupils, all reversed by naloxone (80). The proposed mechanism was thought to be a reduction in calcium ion concentrations in opioid-sensitive CNS sites.

Propafenone

The CNS toxicity of lidocaine was increased in 11 healthy volunteers who simultaneously received propafenone, which reduced the metabolism of lidocaine (81).

Propofol

Propofol dose-dependently reduced the threshold for lidocaine-induced convulsions in rats (82). Higher doses of propofol completely abolished convulsions. However, there was no difference in the dose of lidocaine that caused cardiac arrest and death, when it was given with three different propofol infusions and placebo.

Ranitidine

Ranitidine inhibits the clearance of lidocaine (77).

Suxamethonium

Procaine and cocaine are esters that are hydrolysed by plasma cholinesterase and may therefore competitively enhance the action of suxamethonium (83). Chloroprocaine may have a similar action. Lidocaine also interacts, although the mechanism is not clear unless very high doses are used (84).

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Lidoflazine

See also Calcium channel blockers

General Information

Lidoflazine is a calcium channel blocker (1). The use of lidoflazine in patients with microvascular angina has been associated with malignant ventricular dysrhythmias (SEDA-16, 199).

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Liliaceae

See also Herbal medicines

General Information

The genera in the family of Liliaceae (Table 1) include various types of lily, amarylis, asphodel, crocus, daffodil, fritillary, hyacinth, onions (including garlic), snowdrop, and tulip.

Food allergy to spices accounts for 2% of all cases of food allergies but 6.4% of cases in adults. Prick tests to native spices in 589 patients with food allergies showed frequent sensitization to the Liliaceae garlic, onion, and chive (4.6% of prick tests in children, 7.7% of prick tests in adults) (1).

Allium sativum

Allium sativum (garlic, camphor of the poor, da suan, poor man's treacle, rustic treacle, stinking rose) contains a variety of amino acids and steroids, including ajoene, alliin, allicin, glutamyl-*S*-allylcysteine, and glutamyl-*S*-(2-carboxy-1-propyl)-cysteinglycine. Traditionally it has been used as an antiseptic, diaphoretic, diuretic, expectorant, and stimulant and in the treatment of asthma, hoarseness, cough, difficulty in breathing, chronic bronchitis, leprosy, tubercular consumption, whooping-cough, worms, epilepsy, rheumatism, dropsy, and hysteria. In modern times it has been used as a hypolipidemic (2), although its effect is small (3).

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Table 1 The genera of Liliaceae

Aletris (colicroot)
Allium (onion)
Alstroemeria (lily of the Incas)
Amaryllis (amaryllis)
Amianthium (amianthium)
Androstephium (funnel lily)
Asparagus (asparagus)
Asphodelus (asphodel)
Astelia (pineapple grass)
Bloomeria (golden star)
Brodiaea (brodiaea)
Calochortus (mariposa lily)
Camassia (camas)
Chamaelirium (chamaelirium)
Chionodoxa (chionodoxa)
Chlorogalum (soap plant)
Chlorophytum (chlorophytum)
Clintonia (blue bead)
Colchicum (crocus)
Convallaria (lily of the valley)
Cooperia (rain lily)
Cordyline (cordyline)
Crinum (swamp lily)
Curculigo (curculigo)
Dasylirion (sotol)
Dianella (dianella)
Dichelostemma (snake lily)
Disporum (fairy bells)
Echeandia (echeandia)
Eremocrinum (eremocrinum)
Erythronium (fawn lily)
Eucharis (Amazon lily)
Fritillaria (fritillary)
Gagea (gagea)
Galanthus (snowdrop)
Gloriosa (flame lily)
Habranthus (copper lily)
Harperocallis (harperocallis)
Hastingsia (rush lily)
Helonias (helonias)
Hemerocallis (day lily)
Hesperocallis (desert lily)
Hippeastrum (hippeastrum)
Hosta (plantain lily)
Hyacinthoides (hyacinthoides)
Hyacinthus (hyacinth)
Hymenocallis (spider lily)
Hypoxis (star grass)
Kniphofia (red hot poker)
Leucocrinum (star lily)
Leucojum (snowflake)
Lilium (lily)
Liriope (lily turf)
Lloydia (alp lily)
Lophiola (lophiola)
Lycoris (lycoris)
Maianthemum (may flower)
Medeola (Indian cucumber)
Melanthium (bunch flower)
Merendera
Milla (milla)
Muilla (muilla)
Muscari (grape hyacinth)
Narcissus (daffodil)
Narthecium (asphodel)
Nolina (bear grass)
Nothoscordum (false garlic)
Odontostomum (Hartweg's doll's-lily)
Ophiopogon (ophiopogon)
Ornithogalum (star of Bethlehem)
Ornithoglossum
Pleea (pleea)
Pleomele (hala pepe)
Polygonatum (Solomon's seal)
Ruscus (broom)
Schoenocaulon (feathershank)
Schoenolirion (sunnybell)
Scilla (scilla)
Scoliopus (fetid adder's tongue)
Stenanthium (featherbells)
Sternbergia (winter daffodil)
Streptopus (twisted stalk)
Tofieldia (tofieldia)
Tricyrtis (tricyrtis)
Trillium (trillium)
Tristagma (springstar)
Triteleia (triteleia)
Triteleiopsis (Baja lily)
Tulipa (tulip)
Uvularia (bellwort)
Veratrum (false hellebore)
Xerophyllum (bear grass)
Zephyranthes (zephyr lily)
Zigadenus (death camas)

Adverse effects

Respiratory

Occupational inhalation of garlic powder can lead to asthma (4).

Nervous system

A spontaneous spinal epidural hematoma resulting in paraplegia in an 87-year-old patient was attributed to chronic excessive use of garlic cloves (5).

Hematologic

Bleeding due to impaired platelet function has been attributed to garlic (6).

- A 54-year-old woman underwent strabismus surgery and had bilateral retrobulbar hemorrhages intraoperatively. In the absence of other possible causes, the authors thought that the bleeding had been due to garlic pills prescribed by a naturopath. On the day of surgery, she had taken five pills, equivalent to about 5 g of fresh garlic bulb. Platelet function, measured 2 weeks later, was normal.

Garlic has well-documented effects on platelet aggregation (7).

Skin

Topical administration of garlic can lead to allergic contact dermatitis or burn-like skin lesions (8).

- A 50-year-old Romanian man was advised by his herbalist to treat his asthma with a compress of freshly crushed garlic (9). He wore the compress on his forehead overnight and subsequently developed second-degree burns in this area. Specific IgE RAST tests for

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garlic were negative. He was treated conservatively and made an uneventful recovery.
- Two Korean patients used topical garlic for pruritus and subsequently developed irritant contact dermatitis of the treated skin areas (10). Withdrawal resulted in full recovery.

Of about 1000 patients with occupational skin diseases, five had occupational allergic contact dermatitis from spices (11). They were chefs or workers in kitchens, coffee rooms, and restaurants. In all cases the dermatitis affected the hands. The causative spices were garlic, cinnamon, ginger, allspice, and clove. The same patients had positive patch-test reactions to carrot, lettuce, and tomato.

Drug interactions

The antiplatelet activity of garlic might lead to over-anticoagulation when garlic and warfarin are administered concomitantly (12). However, evidence of such an effect is scanty (13).

Colchicum autumnale

Colchicum autumnale (autumn crocus) and other *Colchicum* species belong to the family known as the Colchicaceae, a proposed subdivision of the Liliaceae. They contain colchicine and related alkaloids. Other members of the Colchicaceae include *Gloriosa* species and *Merendera* species. *C. autumnale* (autumn crocus) is the traditional source of colchicine, which is covered in a separate monograph.

Another plant subdivision, the Wurmbaeoideae, includes *Androcymbium* species, *Iphigenia* species, and *Wurmbea* species, which also contain colchicine. *Iphigenia indica* (shan cigu) is a traditional Chinese herbal medicine (14).

Ruscus aculeatus

Ruscus aculeatus (butcher's broom, knee holy, knee holly, knee holm, Jew's myrtle, sweet broom, pettigree) has been used topically for vasoconstrictor treatment of varicose veins and hemorrhoids (15), and for chronic venous insufficiency, both alone (16,17) and in the combination known as Cyclo 3 fort, marketed in France, which contains an extract of *R. aculeatus* 150 mg, hesperidin methyl chalcone 150 mg, ascorbic acid 100 mg, and metesculetol.

In a meta-analysis of the efficacy of Cyclo 3 fort in patients with chronic venous insufficiency 20 double-blind, randomized, placebo-controlled studies and 5 randomized comparison studies in 10 246 subjects were included (18). Cyclo 3 fort significantly reduced the severity of pain, cramps, heaviness, and paresthesia compared with placebo. There were also significant reductions in venous capacity and severity of edema.

Adverse effects

Gastrointestinal

Chronic diarrhea has been described with Cyclo 3 fort and attributed to a disturbance of gastrointestinal motility (SEDA-16, 205) (SEDA-17, 244). However, the mechanism may be immunological, since lymphocytic colitis has occasionally been reported (19).

Skin

R. aculeatus can cause allergic contact dermatitis (20).

Veratrum species

The rhizome and root of *Veratrum album* (white hellebore) and the rhizome of *Veratrum viride* (green hellebore) contain many alkaloids, including hypotensive ester alkaloids and jervine. *Veratrum californicum* contains the alkaloids cyclopamine, cycloposine, and jervine.

Adverse effects

Among the major toxic symptoms of the veratrum alkaloids are vomiting, hypotension, and bradycardia.

V. californicum is teratogenic activity in livestock (21).

Drug overdose

Veratrum poisoning can cause heartburn and vomiting, bradydysrhythmias, atrioventricular dissociation, and vasodilatation with hypotension (22,23). It can be fatal (24).

Of 12 patients, aged 20–80 years, with acute hellebore (*V. album*) intoxication, 10 had a sinus bradycardia at about 40/minute, shortening of the PR interval down to 0.08–0.12 seconds and of the QT_c interval down to 0.32–0.36 seconds, transient right and incomplete left bundle-branch block, atrial and ventricular extra beats, nodal rhythm ($n = 1$), and altered ventricular repolarization (25). The authors suggested that the bradycardia due to *V. album* is caused by a reflex increase in vagal tone and responds to atropine.

Five patients with acute accidental poisoning with *V. album* rapidly developed nausea, vomiting, abdominal pain, hypotension, and bradycardia (26). In four cases the electrocardiogram showed sinus bradycardia and in one there was complete atrioventricular block with an ectopic atrial bradycardia and an intermittent idioventricular rhythm. Symptomatic treatment and/or atropine led to recovery within a few hours.

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Lincosamides

General Information

The two established members of the group of antibiotics known as the lincosamides, lincomycin and its semisynthetic derivative clindamycin, have a narrow antibacterial spectrum involving mostly Gram-positive species and some obligate anerobes, such as *Bacteroides*. Like chloramphenicol and erythromycin, they combine with a subunit of bacterial ribosomes and interfere with protein synthesis.

Whereas oral lincomycin has a systemic availability of about 40%, which may be further compromised by food, clindamycin is absorbed from the gastrointestinal tract about 90–100%. Both are eliminated mainly by hepatic metabolism and biliary excretion.

Observational studies

Long-term oral clindamycin therapy has been successfully used in a 36-year-old woman with late-stage AIDS who presented with disseminated, nodular cutaneous lesions and underlying osteomyelitis due to a microsporidial infection with an Encephalitozoon-like species (1).

Comparative studies

In a multicenter, double-blind, randomized trial in 87 patients, clindamycin + primaquine was compared with co-trimoxazole as therapy for AIDS-related *Pneumocystis jiroveci* pneumonia; efficacy was similar. In patients with a PaO_2 under 70 mmHg, clindamycin + primaquine was associated with fewer adverse events and less glucocorticoid use, but more rashes (2).

In a prospective, open, randomized trial clindamycin (600 mg tds) and quinine (650 mg tds) were compared with atovaquone (750 mg bd) plus azithromycin (500 mg on day 1 followed by 250 mg/day) in 58 patients with non-life-threatening babesiosis (3). Bacterial response was complete 3 months after the end of treatment. Adverse effects were reported by 72% of those who received clindamycin and quinine compared with 15% of those who received atovaquone and azithromycin. The most common adverse effects with clindamycin and quinine were tinnitus (39%), diarrhea (33%), and impaired hearing (28%); the symptoms had resolved in 73% of the patients assigned to clindamycin/quinine 3 months after the start of therapy and in 100% after 6 months.

In 233 women with bacterial vaginosis, a 3-day regimen of clindamycin (intravaginal ovules, 100 mg/day) was as effective as a 7-day regimen of oral metronidazole (500 mg bd) and better tolerated (4). Treatment-related adverse events were reported more often with metronidazole, and systemic symptoms, such as nausea and taste disturbance, accounted for most of the difference between the groups.

Placebo-controlled studies

In a 10-week, multicenter, double-blind study 480 patients with moderate to moderately severe acne were

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randomized to receive twice-daily 5% benzoyl peroxide, 1% clindamycin, 5% benzoyl peroxide plus 1% clindamycin, or vehicle, all topically (5). There were significantly greater reductions in the numbers of inflammatory and total lesions in patients who used combination therapy compared with those who used any of its three individual components. The most frequent adverse effect, dry skin, occurred to a similar extent with the combination and with benzoyl peroxide alone.

General adverse effects

The direct toxicity of the lincosamides is relatively low (SED-7, 389) (6). The adverse effects of clindamycin may be well below 1%. In a tertiary care center, adverse reactions to clindamycin were reported in 0.47% of 3896 courses, and in half of these events an effect of other medications could not be excluded (7). However, clindamycin has not been given in as high doses as lincomycin.

The most common adverse effect is diarrhea, which occurs in as many as 10–20% of patients. The most serious gastrointestinal complication is colitis due to *Clostridium difficile*, which occurs with about equal frequency after oral and parenteral treatment (8,9). Skin rashes, urticaria, and angioedema have been reported with lincomycin, but are rare. In contrast, maculopapular and pruritic eruptions occur after 1–2 weeks of treatment in up to 10% of patients taking clindamycin. Clindamycin has also been incriminated in one case of Stevens–Johnson syndrome and in one of anaphylaxis; in the latter, hemagglutinating antibodies were found against clindamycin and lincomycin (10). Leukocytoclastic angiitis associated with clindamycin is rare. If a similar angiitis can also occur in the colon, the question arises whether some cases of antibiotic-associated colitis might be caused by the drug itself rather than by bacterial toxins. Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Rapid intravenous infusion of large doses of lincomycin (600 mg in 5–10 minutes) can cause flushing and a sensation of warmth for about 10 minutes.

- A patient who received 200 mg/kg of lincomycin experienced nausea, vomiting, hypotension, dyspnea, and electrocardiographic changes for 20 minutes (SED-7, 389) (11).

Rapid intravenous infusion of lincomycin 1–2 g can cause phlebitis.

Clindamycin can prolong the QT interval and cause ventricular fibrillation (12). Cardiac arrest associated with rapid intravenous administration of clindamycin has been reported (SEDA-8, 258) (13).

Nervous system

Clindamycin, either alone or in combination with neuromuscular blocking drugs or aminoglycosides, has been associated with neuromuscular blockade.

- A 58-year-old woman who was accidentally overdosed with 2400 mg (40 mg/kg) of clindamycin during anesthesia (with tubocurarine and suxamethonium induction) developed prolonged neuromuscular blockade, unresponsive to intravenous calcium or cholinesterase inhibitors (edrophonium and neostigmine), and required assisted ventilation for 11 hours (14). It seems likely that the large dose of clindamycin used in this case produced sustained neuromuscular blockade in the absence of non-depolarizing relaxants and after full recovery from suxamethonium.

Neuromuscular function

Lincosamide antibiotics can produce neuromuscular block postjunctionally by interacting with the open state of the acetylcholine receptor-channel complex. Lipophilicity, rather than stereochemistry of the molecule, is important for open-channel blockade affecting primarily the "off" rate of channel blocking (15). Neuromuscular blockade after clindamycin has been reported (16).

- A 44-year-old woman with mild asthma and mitral valve prolapse was given intravenous clindamycin 300 mg, methylprednisolone 125 mg, and midazolam 2 mg 30 minutes before surgery. Suxamethonium 120 mg was given and general anesthesia was induced with fentanyl 0.1 mg and propofol 120 mg, and maintained with 60% nitrous oxide in oxygen, desflurane, and a single dose of propofol 80 mg. Five hours after uneventful surgery and about 20 minutes after another intravenous dose of clindamycin 600 mg, she complained of profound weakness and had bilateral ptosis, difficulty in speaking, and rapid shallow respiration. Her weakness rapidly became more profound, and she was given neostigmine 4 mg and glycopyrrolate 0.8 mg, after which her muscle strength returned to normal. Electromyography showed no evidence of neuromuscular disease, and acetylcholine receptor antibodies were negative.

An in vitro study has shown a direct effect of clindamycin on nicotinic but not muscarinic acetylcholine receptors (17). This may explain improvement of tremor on treatment with clindamycin in a patient with Parkinson's disease. On each of three occasions, the tremor almost completely disappeared shortly after the start of therapy with clindamycin but reappeared within 1–3 days after withdrawal.

Sensory systems

In a prospective study subconjunctival injections of clindamycin did not produce any general adverse effects (18). However, conjunctival inflammation and keratitis were observed in one of 13 cases, caused by an error in the administered concentration of clindamycin, which was too high.

Hematologic

Granulocytopenia and thrombocytopenia have been described in a few patients taking lincosamides.

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However, a cause-and-effect relation has not been unequivocally established.

Lymphadenitis has been attributed to clindamycin (19).

- A 54-year-old woman with paraplegia due to spina bifida was treated with clindamycin, ciprofloxacin, and gentamicin for osteomyelitis of the ischium and acetabulum, but developed painful swelling of lymph nodes in the neck, which she said occurred with each dose of clindamycin. Withdrawal of gentamicin had no effect, but withdrawal of clindamycin resolved the adenitis over 7 days; the ciprofloxacin was continued.

Gastrointestinal

Drug-induced esophagitis is rare, accounting for about 1% of all cases of esophagitis. An incidence of 3.9 in 100 000 has been reported. After the first description, there have been more than 250 observations, with more than 50 different drugs. Among those, the principal antibiotics included tetracyclines (doxycycline, metacycline, minocycline, oxytetracycline, and tetracycline), penicillins (amoxicillin, cloxacillin, penicillin V, and pivmecillinam), clindamycin (20), co-trimoxazole, erythromycin, lincomycin, spiramycin, and tinidazole. Doxycycline alone was involved in one-third of all cases. Risk factors included prolonged esophageal passage, due to motility disorders, stenosis, cardiomegaly, the formulation, supine position during drug ingestion, and failure to use liquid to wash down the tablet. Direct toxic effects of the drug (pH, accumulation in epithelial cells, non-uniform dispersion) also seem to contribute to the development of drug-induced esophagitis (21). Clindamycin should be taken with a meal or followed by a glass of water (22).

The most prominent adverse reaction of the lincosamides is diarrhea, which varies from mildly loose bowel movements to life-threatening pseudomembranous colitis (see monograph on Beta-lactam antibiotics). Almost all antimicrobial drugs have been associated with severe diarrhea and colitis; however, lincomycin and clindamycin have been particularly incriminated. The incidence of clindamycin-induced diarrhea in hospital is 23%. Diarrhea resolves promptly after withdrawal in most cases. It seems to be dose-related and may result from a direct action on the intestinal mucosa. Severe colitis due to *C. difficile* is not dose-related and occurs in 0.01–10% of recipients. Clustering of cases in time and place suggests the possibility of cross-infection. Even low doses of clindamycin, in some cases after topical administration, can cause marked alterations in several intestinal functions related to bowel flora (23). There was reduced susceptibility of *C. difficile* to clindamycin in 80% of French isolates in 1997 (24). Lincomycin was among the antibiotics that were most often associated with the development of antibiotic-associated diarrhea in a Turkish study of 154 patients; other associated antibiotics were azithromycin and ampicillin (25).

In a one-year retrospective study at a tertiary hospital in Spain, 17% of 148 episodes of diarrhea associated with *C. difficile* developed after therapy with clindamycin (26). The possible association of toxin-positive *C. difficile*-induced colitis and the use of clindamycin phosphate vaginal cream for bacterial vaginosis has been reported in a 25-year-old white woman postpartum (27).

In a prospective study patients treated with antibiotics, including clindamycin, for 3 days had a significantly lower frequency of antibiotic-associated diarrhea than those treated for longer periods (28).

Restricting the use of clindamycin has been successful in terminating outbreaks of *C. difficile* diarrhea associated with its use (29). Between 1989 and 1992, outbreaks of diarrhea due to a clindamycin-resistant strain of *C. difficile* occurred in different parts of the USA. Resistance was mediated by the ermB gene. The use of clindamycin was a specific risk factor for diarrhea due to this strain (30).

- A young otherwise healthy nurse developed severe diarrhea and vomiting, profuse ascites, pleural effusion, abdominal tenderness, peritoneal irritation, and systemic toxicity 10 days after taking oral clindamycin for a dental infection (31). Although the assay for *C. difficile* was repeatedly negative, features compatible with pseudomembranous colitis were seen at sigmoidoscopy, and the diagnosis was confirmed histologically.

Topical application of clindamycin to the skin has been used in acne vulgaris. However, percutaneous absorption can occur (SEDA-8, 160) and several cases of diarrhea have been reported, including cases of pseudomembranous colitis (32).

Clindamycin can rarely cause antibiotic-associated diarrhea after short-term use as vaginal cream (33).

Liver

Since the lincosamides are eliminated by biliary excretion, toxicity would be expected in patients with liver disease. High doses of clindamycin may be hepatotoxic (34). Abnormal liver function tests during treatment with lincomycin are rare, and only in patients who had taken large doses (over 4 g/day) for more than 3 weeks (6). In another series, intravenous lincomycin 4–18 g/day was not associated with renal or hepatic toxicity (SED-7, 388).

Skin

The most common adverse events in patients using clindamycin/benzoyl peroxide were dry skin, peeling, erythema, and rash (35,36). However, withdrawal rates due to adverse events were low (0–0.8%).

- A 57-year-old Caucasian woman with a history of ocular toxoplasmosis, treated with intravitreal clindamycin (1 mg/0.1 ml) and dexamethasone (0.4 mg/0.1 ml), developed a generalized erythematous macular rash over the scalp, face, arms, thighs, and trunk 2 days after the start of treatment (37).

Precautions are necessary to avoid ultraviolet radiation after taking photoreactive drugs (38). Metabolism of lincomycin can lead to the formation of reactive oxygen species and cause tissue injury and damage to various cellular macromolecules, which can result in phototoxicity. Typical photosensitivity with a maculopapular eruption has been observed with lincomycin in two patients treated intramuscularly (6).

- Toxic epidermal necrolysis has been described in a 50-year-old insulin-dependent diabetic who received

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clindamycin (300 mg 8-hourly) (39). On the seventh day, he developed flu-like symptoms, fever, and an erythematous rash, associated with sloughing of 30% of the body surface after a further 4 days (when Nikolsky's sign became positive). He was given oral methylprednisolone 32 mg and eventually made a full recovery.

Lincomycin can cause acne rosacea (40).

A fixed drug eruption has been reported in a patient taking clindamycin (12).

- In a 38-year-old non-atopic man, a generalized pruriginous maculopapular eruption with lip edema and facial erythema developed after 10 days of treatment with oral clindamycin phosphate (300 mg qds) and amoxicillin (500 mg qds) for bronchopneumonia (24). A patch test was positive 2 months later for clindamycin phosphate but negative for penicillin, amoxicillin, ampicillin, and erythromycin. Prick tests and intradermal tests were all negative. Oral rechallenge with clindamycin phosphate 300 mg was positive.

Acute, generalized, exanthematous pustulosis has been associated with clindamycin (41).

Immunologic

Although the risk of drug hypersensitivity is increased in patients with AIDS, clindamycin hypersensitivity has been considered to be relatively uncommon, despite its widespread use, with rash developing in about 9% of patients. However, in a retrospective survey of 50 patients with AIDS recruited in a European multicenter study of treatment for *Toxoplasma* encephalitis, the incidence of rash in 26 patients given pyrimethamine plus clindamycin was 58%, compared with 75% in those given pyrimethamine plus sulfadiazine, a non-significant difference (42). Treatment was initially continued throughout the duration of hypersensitivity, and was tolerated in all patients taking pyrimethamine plus clindamycin, but had to be withdrawn in half of those taking pyrimethamine plus sulfadiazine. Stevens–Johnson syndrome developed in two patients and fatal toxic epidermal necrolysis in one. Thus, the continuation of treatment despite a rash was more likely to succeed with pyrimethamine plus clindamycin but was potentially hazardous with pyrimethamine plus sulfadiazine.

In a prospective study, true-positive patch tests were seen in four of six patients with known clindamycin hypersensitivity, while 22 healthy controls were negative; there was one false positive and one false negative reaction (43).

Successful desensitization has been described in a 35-year-old woman who developed a generalized rash after taking clindamycin (600 mg 6-hourly) and pyrimethamine for 12 days for AIDS-associated cerebral toxoplasmosis; the rash resolved after withdrawal of clindamycin (44). Subsequent oral rechallenge was performed (without pretreatment with glucocorticoids or antihistamines), starting with three doses of 20 mg on day 1, 40 mg on day 2, 80 mg on day 3, and so on, until a dose of 600 mg qds was reached on day 7. A transient rash lasting 5 hours developed after the second dose of 600 mg. She remained free from adverse reactions for the duration of follow-up (13 months).

Infection risk

Superinfection with resistant strains of *Pseudomonas*, *Proteus*, or staphylococci has been observed with lincosamides. Suppression of *Bacteroides* in the intestinal flora may be related to the proliferation of *C. difficile*, which is important in causing pseudomembranous colitis. Excessive growth of *Candida* on the skin occurred when lincomycin was applied topically (6).

Long-Term Effects

Drug resistance

Staphylococcus aureus, pneumococci, Group A streptococci, and viridans streptococci acquire resistance in vitro to the lincosamides regularly, easily, and quickly (SED-8, 638). In endometrial cultures taken after clindamycin therapy, the occurrence of clindamycin-resistant anerobic bacteria was significantly higher than before therapy (45). Their similar mechanism of action has been used to explain cross-resistance between the macrolide antibiotics and the lincosamides. Among erythromycin-resistant staphylococci, 50% of the isolated strains were also resistant to lincomycin (SED-6, 304). In patients who need long-term suppressive therapy, but who are allergic to penicillin, the development of such combined resistance of the oropharyngeal flora can be a serious clinical problem.

The erythromycin ribosomal methylase (erm) genes encode 23S ribosomal RNA methylases. This modification results in reduced binding of all known macrolides, lincosamides, and streptogramin B to the ribosome (MLS resistance). Novel triazine-containing methyltransferase inhibitors that may reverse erm-mediated resistance are under development (46).

The MLS resistance was found in four of 137 consecutive clinical isolates of *Streptococcus pyogenes* (47). In two, both ermB and ermTR genes were present. In the other two, these genes were not identified, suggesting a new mechanism of high-level resistance to these antibiotics. Erm genes were detected in 45% of 173 strains of *Streptococcus pneumoniae* isolated from surveillance studies in day-care centers in Central Italy (48). From 387 clinical strains of erythromycin-resistant strains of *S. pyogenes* isolated in Italian laboratories from 1995 to 1998, 31% were assigned to the inducible and 17% to the constitutive MLS resistance phenotype (49). Resistance to erythromycin increased to 33% in 1997 among community-acquired isolates of *S. pneumoniae* from central Italy (50). Most carried an erm gene and were also resistant to clindamycin. Regulatory regions located upstream of the erm genes were amplified and sequenced in clinical isolates of enterococci and streptococci with either inducible or constitutive resistance. Expression of constitutive resistance in two strains of *S. pneumoniae* and *Enterococcus faecalis* could be accounted for by a large deletion or a DNA duplication within the regulatory regions respectively (51). In 294 macrolide-, lincosamide-, and/or

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streptogramin-resistant clinical isolates of *S. aureus* and coagulase-negative staphylococci isolated in 1995 from 32 French hospitals, ermA or ermC genes were found in 88% (52). Genes related to linA/linA′ and conferring resistance to lincomycin were detected in one strain of *S. aureus* and 7 strains of coagulase-negative staphylococci.

A resistance gene, named linB, which encodes a lincosamide nucleotidyltransferase catalysing the adenylation of the hydroxyl group in position 3 of the molecules of lincomycin and clindamycin has been characterized in a clinical isolate of *Enterococcus faecium* (53). Expression of linB was also observed in *Escherichia coli* and *S. aureus*, and the spread of this gene in other clinical isolates of *E. faecium* has been suggested.

In *Brachyspira hyodysenteriae* (formerly *Serpulina hyodysenteriae*) isolates, resistance to clindamycin was associated with a transversion mutation in the nucleotide position homologous with position 2058 of the *E. coli* 23S rRNA gene (54).

There was a significant increase in the rate of resistance in clinical strains of *Bacteroides fragilis* from Canada (20% in 1997) (55). This trend was also observed in a prospective multicenter survey from the USA (56).

Among *P. acnes* isolated from acne lesions, a resistance level of 4% (of 50 strains) and 6.8% (of 70 strains) were found in Japanese and German studies respectively (57,58).

Of 302 clinical isolates of *S. pyogenes* from Portugal, 108 were resistant to erythromycin, and 86 also had a constitutive resistance to clindamycin (MLSB phenotype) (59). Four isolates had a phenotype characterized by low-level erythromycin resistance and high-level clindamycin resistance. In another European study of 286 *S. pneumoniae* strains, 7% were resistant to penicillin, and 35% were also resistant to clindamycin (60). Of 3205 group A streptococcal strains from Canada, only 18 and 2 strains respectively showed inducible and constitutive resistance to clindamycin (61). Among 180 strains of the *Streptococcus milleri* group isolated in Spain, 17% were resistant to clindamycin (62).

An increase in resistance to clindamycin has been found in group B streptococcal strains causing neonatal infection (63).

Second-Generation Effects

Pregnancy

In pregnant women with bacterial vaginosis, a 7-day regimen of 2% vaginal clindamycin cream was effective and did not alter the rates of preterm deliveries or peripartum infections (64,65).

Fetotoxicity

Although lincomycin penetrates the fetal circulation, no fetal abnormalities were related to lincomycin administration in 302 women who had completed a course of lincomycin therapy (500 mg every 6 hours) for 1 week; all three trimesters of pregnancy were included (66).

Drug Administration

Drug formulations

Whereas only about 4% of clindamycin from a vaginal cream was systemically absorbed, systemic absorption was in the range of 30% when clindamycin was intravaginally administered as a phosphate ovule (67).

Drug–Drug Interactions

Ciclosporin

In two patients who had lung transplants and were taking an immunosuppressive regimen that included ciclosporin, the addition of clindamycin (600 mg tds) resulted in a significant reduction in ciclosporin concentrations (68).

Ganglion blocking agents

Clindamycin may potentiate the effects of some ganglion blocking agents (69).

Macrolides

Antagonism between the lincosamides and the macrolide antibiotics has been observed in vitro and was explained by binding to the same subunit of bacterial ribosomes (70). This mechanism of bacteriostatic action also suggests that the lincosamides might prevent the bactericidal action of the penicillins and the cephalosporins.

Non-depolarizing neuromuscular blocking drugs

Clindamycin and lincomycin potentiate the action of non-depolarizing neuromuscular blocking drugs, such as pancuronium and D-tubocurarine. The lincosamide-induced block cannot be reliably reversed pharmacologically (71).

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Lindane

General Information

Lindane is a pesticide that is widely used in the treatment of scabies and pediculosis, usually in a 1% lotion (SEDA-5, 154) (1–4). It is the gamma-isomer of 1,2,3,4,5,6-hexachlorocyclohexane. The hazards of excessive industrial exposure and accidental ingestion have been well documented (3).

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Some feel that 1% lindane is safe when used properly (1,5), but precautionary recommendations have been made (3):

(a) a hot soapy bath before treatment is not necessary;
(b) application for 24 hours may be too long, 6 hours having a cure rate of 96%;
(c) a concentration weaker than 1% may be adequate;
(d) lindane should not be repeated within 8 days, and then only if active parasites can still be demonstrated;
(e) lindane 1% should be used with extreme caution, if at all, in pregnant women, very small infants, and people with massively excoriated skin.

There has been concern from animal experiments that lindane may be mutagenic, carcinogenic, and teratogenic; in therapeutic use, however, such hazards are highly unlikely (1,2).

Organs and Systems

Nervous system

In 1976, the US Food and Drug Administration (FDA) published a "Gamma Benzene Hexachloride (Kwell) Alert," based in part on several poorly documented cases of convulsions after topical treatment with lindane (6). Indeed, several authors have reported convulsions (7–9), but in most cases lindane had been inappropriately used (4,7), while another case took place in unusual therapeutic circumstances (prematurity, marasmus, pneumonia, congestive heart failure, ventricular septal defect) (8). A child with convulsions after the application of lindane had tuberous sclerosis and may therefore have had a reduced threshold for convulsions (9).

Hematologic

Anemia, possibly caused by topical lindane, has been described (10).

Urinary tract

Urinary retention has been ascribed to lindane (SEDA-10, 131).

Skin

Acute generalized exanthematous pustulosis has been attributed to topical lindane (11).

Immunologic

Henoch-Schönlein purpura, possibly caused by topical lindane, has been described (12).

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Lipsticks, substances used in

General Information

Branched-chain fatty acid esters, such as glyceryl di-isostearate and di-isostearyl malate, have replaced castor oil and lanolin as major components of lipsticks.

Palmitate-related substances are viscous oils used in cosmetics and topical medicaments. In lipsticks they replace castor oil (1). Allergic reactions to lipsticks have been reported to be caused by a variety of allergens, for example azo dyes, colophony, lanolin, castor oil, sunscreens, and para-tertiary butylphenol.

Organs and Systems

Immunologic

The fatty acid esters have low allergenic potential but cases of contact allergy has been reported, in one case to di-isostearyl malate (patch-tested in 7.7% in petrolatum) (2), and in another case to glyceryl monoisostearate monomyristate in a 23-year-old woman, who had cheilitis from her lipstick (3).

- A 17-year-old woman developed pruritic edematous erythema on her lips after using a lipstick containing isopalmitate (4). A patch test with 10% isopalmitate in petrolatum was positive on day 3, with six negative controls.
- A 27-year-old woman developed papules, scales, and slight swelling of her lips (5). A patch test with isopalmityl diglyceryl sebacate, 10% in petrolatum, was positive.

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Lisinopril

See also Angiotensin converting enzyme inhibitors

General Information

Lisinopril is a non-sulfhydryl ACE inhibitor. It has been used in patients with hypertension, heart failure, myocardial infarction, and diabetic nephropathy.

Organs and Systems

Cardiovascular

An updated and comprehensive review of the use of lisinopril in congestive heart failure has been published (1), including a section on tolerability and details of the ATLAS (Assessment with Treatment with Lisinopril and Survival) trial. The tolerance of high doses of lisinopril (32.5–35 mg od) in heart failure, one of the issues addressed by this trial, was not significantly different from that of low doses (2.5–5 mg od). Since high doses were more effective than low doses, the authors recommended that more aggressive use of ACE inhibitors is warranted (2). However, this conclusion is valid only in the conditions of the trial, with careful and slow dose escalation. With such a strategy, most patients with heart failure can be titrated successfully to high maintenance doses.

Shock after myocardial infarction has been attributed to an ACE inhibitor (3).

- A 42-year-old woman suffered an acute anterior myocardial infarction, initially associated with pulmonary edema. After hemodynamic stabilization she was given lisinopril 10 mg orally. Two hours later she developed circulatory failure in conjunction with acute renal insufficiency. Right heart catheterization showed markedly reduced systemic vascular resistance but a normal cardiac index. After the usual causes of cardiogenic shock had been ruled out, repeated fluid challenges and intravenous noradrenaline failed to improve her hemodynamic status. She was therefore given angiotensin II intravenously (5–7.5 μg/minute), which immediately and markedly raised the systematic vascular resistance and resulted in subsequent regression of shock. She was discharged after an otherwise uneventful course.

Endocrine

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been attributed to lisinopril (4).

- A 76-year-old woman taking lisinopril 20 mg/day and metoprolol for hypertension developed headaches, nausea, and a tingling sensation in her arms. Her serum sodium was 109 mmol/l, with a serum osmolality of 225 mosm/kg, urine osmolality of 414 mosm/kg, and urine sodium of 122 mmol/l. She had taken diclofenac 75 mg/day for arthritic pain for 6 years and naproxen for about 1 month. Propoxyphene napsylate and paracetamol had then been substituted and zolpidem had been started. A diagnosis of SIADH was postulated and thyroid and adrenal causes were excluded. Lisinopril was withdrawn and fluid was restricted to 100 ml/day. The serum sodium gradually corrected to 143 mmol/l.

The authors referred to three other similar cases, in two of which the diagnosis may have been confused by the concomitant use of diuretics in patients with heart failure. However, the present and one other case had occurred without co-existing risk factors for hyponatremia. They discussed a synergistic effect of zolpidem and/or diclofenac, and suggested a potential mechanism involving non-inhibition of brain ACE, which leaves brain angiotensin II receptors exposed to high circulating concentrations of angiotensin which would strongly stimulate thirst and the release of antidiuretic hormone.

Pancreas

Several cases of pancreatitis have been reported with ACE inhibitors, including lisinopril.

- A 67-year-old man without other risk factors developed acute pancreatitis only 3 hours after taking lisinopril. The originality of this case resides in the fact that the patient had experienced a similar but less severe reaction to the medication 3 months before. Thus, this case probably represents the first time a patient was rechallenged with lisinopril and had a more severe adverse reaction (5).
- A 42-year-old woman, who was taking lisinopril, nicardipine, metoprolol, simvastatin, omeprazole, an estrogen, and sublingual glyceryl trinitrate, presented with epigastric pain and vomiting (6). Pancreatitis was diagnosed on the grounds of raised activities of lipase (200 IU/l) and amylase (117 IU/l) and diffuse homogeneous enlargement of the head and body of the pancreas on CT scan. The pancreatic enzyme activities normalized 5 days after lisinopril and simvastatin withdrawal. Two months later she was taking estrogen and simvastatin, but not lisinopril. Her amylase and lipase were normal.

The temporal relation in the second case suggests that lisinopril was causative. The authors raised the possibility that the concomitant use of an estrogen and simvastatin, as well as a history of familial hypertriglyceridemia, may have predisposed her to pancreatitis.

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Skin

Worsening of pre-existing cold urticaria has been associated with lisinopril (7).

- A 43-year-old Caucasian man had a history of mild cold urticaria during the preceding 10 years. Shortly after starting to take lisinopril 20 mg/day and hydrochlorothiazide 25 mg/day for hypertension his condition worsened considerably and he had several bouts of severe cold urticaria. On one occasion, after swimming in water at 24°C, he developed severe urticaria and angioedema, and required emergency hospital admission. Standard ice-cube and cold-water immersion tests were strongly positive within 1 minute. Tests for a variety of causative factors were negative, and a diagnosis of acquired cold urticaria was made. Lisinopril was withdrawn, he was given valsartan 80 mg/day, and the dose of hydrochlorothiazide was reduced to 12.5 mg/day. During the next 24 weeks he had only mild symptoms of cold urticaria. Repeat ice-cube and cold-water immersion tests were negative at 1 and 3 minutes, but positive at 5 minutes.

The authors cited evidence that the kallikrein/kinin system is involved in cold urticaria, that ACE inhibitors increase wheal-and-flare reactions to cutaneously applied bradykinin, and that ACE inhibitor therapy is associated with raised plasma kinin concentrations. They therefore recommended avoidance of ACE inhibitors in patients with cold urticaria.

Erythema multiforme has been attributed to lisinopril (8).

- A 68-year-old man who had taken lisinopril 10 mg/day for several years stopped taking it temporarily because of a cough. It was then restarted in a dosage of 5 mg/day and a few days later he developed several bean-sized non-pruritic erythematous plaques with scales over the whole body, particularly on the chest. The appearance was of seborrheic dermatitis, but histology showed the features of erythema multiforme. The eruptions cleared completely a few days after lisinopril withdrawal. Two months later, a rechallenge test was positive.

Sexual function

Lisinopril 20 mg/day has been compared with atenolol 100 mg/day in a 16-week, double-blind, randomized, controlled trial in 90 hypertensive men aged 40–49 and without a history of sexual dysfunction. The number of occasions on which they had sexual intercourse fell during the first month in both groups (9). Subsequently, sexual activity tended to recover with lisinopril but not atenolol. The authors suggested that lisinopril may cause only a temporary reduction in sexual function.

Drug–Drug Interactions

Clozapine

Raised clozapine blood concentrations have been reported after the introduction of lisinopril (10).

- A 39-year-old man with schizophrenia and diabetes, who had taken clozapine 300 mg/day and glipizide 10 mg/day for a year, took lisinopril 5 mg/day for newly diagnosed hypertension. On several occasions afterwards he had roughly a doubling of his blood concentrations of clozapine and norclozapine. He had typical effects of clozapine toxicity. After replacement of lisinopril by diltiazem, the blood concentrations of clozapine and norclozapine returned to the values that were present before lisinopril was introduced.

The information given here was sketchy and there was no information on the timing of blood samples relative to the dose of clozapine. Clozapine is metabolized by CYP1A2 and CYP3A4, but there is no evidence that lisinopril affects these pathways.

Tizanidine

Hypotension followed the addition of tizanidine to lisinopril (11).

- A 10-year-old boy developed hypotension and reduced alertness. His blood pressure was 56/24 mmHg and his heart rate 88/minute. He had a history of a hypoxic ischemic insult to the central nervous system, subsequent hypertension, and spastic quadriplegia. His blood pressure had been controlled for the last 10 months with lisinopril (dose not stated). Tizanidine had been added 1 week before admission for spasticity. Lisinopril and tizanidine were withdrawn and his blood pressure rose to 149/89 mmHg over the next day. He was discharged and lisinopril was restarted but not tizanidine. He had no further problems with hypotension.

The authors interpreted the finding as a consequence of limited ability of the patient to respond to hypotension because of simultaneous blockade of the sympathetic system with the centrally acting alpha$_2$-adrenoceptor agonist tizanidine.

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Lisuride

General Information

Lisuride is a dopamine receptor agonist that is used as an alternative drug in the treatment of Parkinson's disease. The pattern of adverse effects is similar to that seen with most of the ergot alkaloids (SEDA-10, 118). The adverse effects that occurred after subcutaneous administration were so troublesome that the subcutaneous formulation was eventually unmarketable.

Organs and Systems

Respiratory

In one instance to date, pleuropulmonary disease has been observed. Effusions were present but apparently there was no significant fibrosis, and the condition was almost completely reversible.

Nervous system

Vasoconstriction due to ergot-related dopamine receptor agonists can affect the cerebral circulation (1).

- A 33-year-old woman was discharged from hospital after a normal delivery, taking lisuride 0.2 mg/day for suppression of lactation. Within a day, she complained of throbbing headache, which was followed by right hemiparesis and then a generalized tonic-clonic seizure starting from the right arm. She had widespread segmental vasoconstriction in the cerebral arteries and two intracerebral hemorrhages. She recovered fully within 1 month.

The authors commented that there have been at least seven reported cases of postpartum ergot-related angiopathy with bromocriptine and ergonovine.

Because of its serotoninergic properties, lisuride can cause more psychiatric complications than expected (2).

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Lithium

General Information

Lithium is an alkaline earth element that is used medicinally in the form of salts such as lithium chloride and lithium carbonate. Its main use is in the prevention or attenuation of recurrent episodes of mania and depression in individuals with bipolar mood disorder (manic depression). Lithium also has clearly established antimanic activity, although its relatively slow onset of action often necessitates the use of ancillary drugs, such as antipsychotic drugs and/or benzodiazepines, at the start of therapy. If lithium alone is ineffective for recurrent bipolar mood disorder, combining it or replacing it with carbamazepine or valproate may be of value; reports with lamotrigine and olanzapine are also encouraging.

Lithium also has antidepressant activity in bipolar disorder, has prophylactic value in recurrent major depression, and is a useful augmenting agent for antidepressant-resistant depression. Other uses in psychiatry include schizoaffective disorder, emotional instability, and pathological aggression. The point prevalence of lithium use has been estimated to be as high as 1 in 1000 people in populations in industrial countries. The complex relation between sub-syndromal manifestations of bipolar disorder, particularly cognitive dysfunction, and the role that lithium might play in alleviating or aggravating this problem have been discussed in a thoughtful review (1).

The well-established effectiveness of long-term lithium in reducing manic-depressive morbidity includes a reduced risk of suicide and suicidal behavior. For example, in one study, suicidal acts per 1000 patient-years were 23 before lithium, 3.6 during lithium, 71 in the first year after withdrawal, and 23 in subsequent years (2). In another study, suicide rates during treatment with lithium were 31 per 1000 person-years (emergency department suicide attempts), 11 per 1000 person-years (suicide attempts resulting in hospitalization), and 1.7 per 1000 person-years (suicide deaths); the risk of suicide death was 2.7 times higher during treatment with divalproex than during treatment with lithium (3). A retrospective study divided high-risk patients into excellent, moderate, and poor responders to lithium and showed that no further suicide attempts occurred in 93%, 83%, and 49% respectively (4). The substantial reduction in suicidal tendency in the poor responder group suggested an antisuicidal effect of lithium beyond its mood-stabilizing properties, although the psychosocial benefits of lithium clinic treatment could have been contributing factors.

Since bipolar disorder is a condition for which long-term treatment is usually necessary, both acute and long-term adverse effects are important, especially since patients in remission are often less likely to tolerate them (5). With this in mind, one might consider some speculatively positive findings involving the neurotropic and neuroprotective effects of lithium (6). The concentration of bcl-2, a cytoprotective protein, was upregulated by lithium in both rodent brains and human neuronal cells, as was the concentration of *N*-acetylaspartate, a marker of neuronal viability and function, in human gray matter

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(7). In addition, a 3-dimensional magnetic resonance imaging study with quantitative brain-tissue segmentation showed that treatment with lithium for 4 weeks increased the total volume of gray matter by about 3% in eight of 10 patients in the depressed phase of bipolar I disorder.

Beneficial nonpsychiatric uses of lithium

Some collateral drug effects that are not related to the intended therapeutic effect are potentially beneficial. Several beneficial effects of lithium, besides its action in bipolar disorder, have been described.

Nervous system

There has been a spate of publications describing the neuroprotective effects of lithium. By inhibiting glycogen synthase kinase-3, lithium inhibits tau hyperphosphorylation and protects against β-amyloid-induced cell death, suggesting a possible role in the treatment of Alzheimer's disease (8,9). Studies in mice and cell lines show that lithium reduces gp120-associated neurotoxicity, suggesting that it may be useful in preventing progression of HIV-associated cognitive deterioration (10). Low-dose lithium reduced infarct volume and neurological deficits in a rat model of transient focal cerebral ischemia (11).

Overall, the evidence that lithium has neuroprotective and neurotropic effects through a variety of mechanisms is striking (12), although whether those findings will evolve into therapies of practical clinical value remains to be seen.

Chronic cluster headache has responded to lithium (13).

Sensory systems

In cultured mouse retinal ganglion cells, lithium supported the survival and regeneration of axons (14). This led the authors to the very speculative suggestion that lithium might be useful in treating conditions such as glaucoma, optic neuritis, and other neuron loss disorders.

Endocrine

Lithium blocks the release of iodine and thyroid hormones from the thyroid and has been used to treat hyperthyroidism, as an adjunct to radioiodine therapy (15–18) and in metastatic thyroid carcinoma (19). However, it can also cause hyperthyroidism. Lithium enhanced the efficacy of radioiodine in 23 patients (20), but was ineffective in a larger comparison of lithium ($n = 175$) or radioiodine alone ($n = 175$) (21). In 24 patients with Graves' disease, lithium attenuated or prevented increases in thyroid hormone concentration after methimazole withdrawal and radioiodine treatment (15,22).

Lithium has been used, with several other drugs, to treat four patients with amiodarone-associated thyrotoxicosis, but the drugs were ineffective in two patients, who required thyroidectomy (23). One hopes that the authors actually used milligram amounts of lithium carbonate rather than the microgram amounts listed in the article.

Metabolism

Lithium therapy in a 17-year-old man with Kleine–Levin syndrome led to remission of the characteristic manifestations, including hyperphagia (24).

Hematologic

Lithium has beneficial granulocytopoietic effects (25–27). For example, lithium carbonate (800–900 mg/day) effectively corrected neutropenia due to chemotherapy or radiotherapy in over 85% of 100 cancer patients (28). The potential benefit and possible risks of using lithium to treat clozapine-induced neutropenia/agranulocytosis have been reviewed (29).

- A 29-year-old man with agranulocytosis, who could not tolerate granulocyte-colony stimulating factor, had normalization of peripheral granulocyte counts when he took lithium carbonate 800 mg/day (30).
- A 16-year-old with severe aplastic anemia failed to respond to treatment with corticosteroids plus an androgen and to antilymphocyte globulin, but had a strikingly positive response to the combination of lithium and an androgen derivative (31). Leukopenia and thrombocytopenia recurred 2 months after lithium was withdrawn and responded to reintroduction of the drug.

The potential of lithium to prevent or treat clozapine-induced granulocytopenia has been reviewed (29). In a study of 38 patients on clozapine for schizophrenia or schizoaffective disorder, the addition of lithium increased the leukocyte count (32). A 20-year-old man with olanzapine-induced neutropenia 5 mg/day was able to tolerate 20 mg/day while taking lithium (33).

Skin

Lithium succinate is used topically to treat seborrheic dermatitis (34). A topical 8% lithium gluconate ointment was more effective than a placebo ointment in treating 129 patients with facial seborrheic dermatitis (complete remission in 29 versus 3.8%) (35).

Immunologic and infections

Comments on the generally favorable effects of lithium on immune function have been summarized (36). The antiviral and neuroprotective properties of lithium were mentioned in a review of the immune system and bipolar disorder (37). The potential benefit of lithium in treating AIDS and AIDS-related dementia, owing in part to its cytokine-regulating and neuroprotective effects, has been reviewed (38). Genital *Herpes simplex* infection has responded to lithium (39).

- Lithium had an antiviral effect in a 44-year-old woman whose psychiatric symptoms did not improve but who had complete suppression of *Herpes labialis* for 2 years (after a 30-year history of at least twice-yearly episodes) followed by a recurrence, only 5 days after stopping the drug (40).

Cancers

In one study, there was a lower risk of cancer in both 609 lithium patients and 2396 psychiatric controls compared with the general population, and in the lithium group, there was a nonsignificant trend toward an even lower risk of nonepithelial tumors (41).

Lithium gamolenate, a compound with in vitro antitumor activity, given intravenously or orally, was ineffective in treating advanced pancreatic adenocarcinoma ($n = 278$) (42). Adverse effects attributed to lithium

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(type unspecified) were reported in two of 93 in the oral group (mean serum lithium 0.15 mmol/l), five of 90 with low-dose intravenous administration (mean serum lithium 0.4 mmol/l), and seven of 95 with the high-dose intravenous administration (mean serum lithium 0.8 mmol/l).

Pharmacokinetics

Ionized lithium is readily absorbed from the gastrointestinal tract and is excreted almost entirely by the kidney, which ordinarily clears it at a rate of about one-quarter to that of creatinine clearance (43).

A reduction in glomerular filtration rate (GFR) will reduce lithium clearance, as will a negative sodium balance. Lithium is not metabolized and is not bound to plasma proteins.

Lithium is easily, inexpensively, and accurately measurable in the serum, and serum concentration determination is a useful adjunct to monitoring its therapeutic efficacy and avoiding toxicity (44).

Both immediate-release and modified-release formulations of lithium carbonate are available. Peak blood concentrations are lower and occur more slowly with modified-release formulations than with immediate-release formulations, but all formulations are supposed to deliver equivalent amounts of lithium per millimole. The effectiveness of lithium should not be altered by the formulation used or the number of daily doses (assuming full adherence to therapy), but if it is given once a day the 12-hours serum lithium concentration will be somewhat higher than if the same amount is given in divided doses.

Standardizing the timing of blood sampling to about 12 hours after the last dose (which is preferably taken in the morning) will do much to avoid the vagaries of absorption and should provide a consistency that will allow accurate comparisons across samples (44). Blood concentrations are most useful if a steady state has been reached before sampling (4–5 days after starting treatment or after a dosage change).

Recommended serum lithium concentrations for the treatment of mania and for maintenance treatment are not uniformly agreed on, although differences of opinion are not large. For example, a concentration of 0.5–0.8 mmol/l has been advised for patients starting treatment, with the recognition that both lower and higher concentrations may be necessary. In US product monographs, concentration ranges for acute mania (1.0–1.5 mmol/l) and long-term treatment (0.6–1.2 mmol/l) tend to be higher than currently practiced (mania 0.8–1.2 mmol/l; long-term 0.6–1.0 mmol/l) and considerably higher than concentrations recommended in Europe. While there is uniform agreement that the serum concentration should be kept as low as is compatible with therapeutic efficacy, there is as yet no accurate way to predict this concentration in an individual. Within the target range, one can generally expect efficacy to increase with blood concentration, but at a price—adverse effects are likely to increase. Elderly people will require a lower dosage of lithium to achieve a given serum concentration, and they tend to be more sensitive to adverse effects than younger individuals, but whether they respond better to lower concentrations is unclear.

The frequency with which blood concentrations should be measured varies with the stage of the illness and with a number of patient factors (including age, associated illnesses, concomitant medications, and diet). Generally, concentrations are measured every 5–7 days during the start of therapy, and then less and less often as stability occurs and persists. In reliable patients taking long-term treatment, concentrations may be measured every 3–4 or even 6 months.

Instruction and information

The safe and effective use of lithium is best ensured by close collaboration among patients, physicians, and significant others, all of whom must remain well-informed and up to date about treatment guidelines, benefits, adverse effects, risks, and precautions. While verbal communication and education is invaluable, it should be constructively supplemented with written information (45,46).

Comparative studies

The availability of anticonvulsant mood stabilizers has led to comparative studies with lithium. A review of the comparative efficacy and tolerability of drug treatments for bipolar disorder included tolerability comparisons of lithium versus carbamazepine, lithium versus valproate semisodium, and lithium versus other medications (47).

In 29 patients, the burden of taking lithium ($n = 17$) was compared with that of valproate ($n = 12$) using a visual analogue scale. Adverse effects were common but not significantly different between drugs (48), a finding that contrasts with the common impression that valproate is better tolerated. Indeed, a telephone interview of 11 adolescents taking lithium and 32 taking valproate found more adverse effects, poorer compliance, and greater perceived burden in the lithium group. There was a non-significant trend toward more weight gain with valproate (mean 12 kg) than with lithium (mean 9 kg) (49).

In a 4-week, placebo-controlled study of lithium in 40 hospitalized children and adolescents (mean age 12.5 years) with aggression related to conduct disorder, lithium was "statistically and clinically superior to placebo" (50). Although there were no dropouts related to adverse events, nausea, vomiting, and increased urinary frequency occurred significantly more often in the lithium group. The 55% incidence of vomiting with lithium (versus 20% with placebo) may have been related to the relatively high mean serum lithium concentration of 1.07 mmol/l (range 0.78–1.55 mmol/l).

Lithium versus carbamazepine

In a 2-year, double-blind study, lithium was superior to carbamazepine in prophylactic efficacy, although it caused more adverse effects (Table 1) (51).

Lithium versus divalproex

In a randomized, placebo-controlled, 12-month maintenance comparison of lithium and divalproex in 372 bipolar I outpatients, neither active drug was more effective than placebo on the primary outcome measure—the time to recurrence of any mood episode (52). While a history of intolerance to either lithium or divalproex was an

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Table 1 Adverse effects of lithium and carbamazepine in a double-blind trial (in %)

Adverse effect	Lithium ($n = 42$)	Carbamazepine ($n = 46$)
Difficulty concentrating	45	33
Thirst	41	22
Hand tremor	31	4
Blurred vision	26	11
Reduced appetite	21	9
Increased appetite	17	33
Weakness	14	4

exclusion criterion, it was not stated whether or not prior nonresponders were entered and, if so, how many. The following adverse effects were significantly more frequent:

(a) with lithium than with placebo: nausea, diarrhea, and tremor;
(b) with divalproex than with placebo: tremor, weight gain, and alopecia;
(c) with lithium than with divalproex: polyuria, thirst, tachycardia, akathisia, and dry eyes;
(d) with divalproex than with lithium: sedation, infection, and tinnitus.

Unfortunately, all dropouts were pooled, whether due to adverse events or noncompliance, making overall tolerability comparisons impossible.

General adverse effects

The adverse effects of lithium have been reviewed (5,53–55). The adverse effects of lithium range widely in intensity and can be a major cause of nonadherence to therapy. However, with proper attention to the prevention and management of adverse effects, most patients can be treated effectively and safely. Withdrawal of lithium is almost always followed by resolution of adverse effects, although certain problems can sometimes persist (for example renal).

Adverse effects that can occur at concentrations in the target range, especially in the upper part of the range, include mild cognitive complaints, postural tremor, hypothyroidism, weight gain, leukocytosis, hypercalcemia, loss of appetite, nausea, loose stools, acne, and psoriasis. Renal adverse effects include impaired concentrating ability and polyuria with secondary polydipsia. Cardiac adverse effects are rarely symptomatic and are usually reversible. Lithium does not cause physiological dependence, although there may be an increased risk of early recurrence if it is withdrawn rapidly.

When 60 patients (22 men, 38 women) who had taken lithium for 1 year or more (mean 6.9 years; mean serum concentration 0.74 mmol/l) were interviewed about adverse effects, 60% complained of polyuria–polydipsia syndrome (serum creatinine concentrations were normal) and 27% had hypothyroidism requiring treatment (56). Weight gain was more common in women (47 versus 18%) as were hypothyroidism (37 versus 9%) and skin problems (16 versus 9%), while tremor was more common in men (54 versus 26%). Weight gain of over 5 kg in the first year of treatment was the only independent variable predictive of hypothyroidism.

The severity of lithium toxicity depends on the magnitude and duration of exposure and idiosyncratic factors. Manifestations of acute toxicity range in intensity from mild (tremor, unsteadiness, ataxia, dysarthria) to severe (impaired consciousness, neuromuscular irritability, seizures, heart block, and renal insufficiency), and the sequels of toxicity range from none at all to permanent neurological damage (often cerebellar) to death. Causes of raised serum lithium concentrations include increased intake and reduced excretion (due to kidney disease, low sodium intake, drug interactions). Whether long-term lithium use carries a risk of progressive renal insufficiency in a few patients continues to be debated. Reviews have addressed lithium toxicity in the elderly (57) and lithium intoxication with an emphasis on the kidney (58).

Dose- and time-related adverse effects

During initiation and stabilization of treatment, adverse effects, such as gastrointestinal upset, tremor, dysphoria, fatigue, muscle weakness, unsteadiness, thirst, and excessive urination, are not uncommon, but they usually abate with time. Such adverse effects are more likely to occur at higher dosages or higher serum concentrations and can usually be avoided or attenuated by proper attention to dosage, clinical and laboratory monitoring, and, if necessary, the use of adjunctive medication.

Long-term use of lithium is sometimes associated with weight gain, polyuria and polydipsia, and thyroid dysfunction (see below), but many patients have been treated successfully for several decades without developing treatment-limiting adverse effects. However, long-term success should not breed complacency, since there is an ever-present risk of recurrence (if concentrations are too low) and toxicity (if concentrations are too high).

Treatment of toxicity

Two patients with lithium toxicity (serum concentrations 3.5 and 4.2 mmol/l) had the well-recognized rebound increase in serum concentrations after the end of hemodialysis. Both died during hospitalization from what was cryptically described as "unrelated events" (59).

- A 49-year-old with severe lithium toxicity was treated successfully with continuous veno-venous hemodiafiltration; the serum lithium concentration fell from 3.0 to 0.93 mmol/l after 7 hours and there was no rebound increase after the end of the procedure (60). The maximum lithium clearance was 28 ml/minute which is considerably lower than usually attained with hemodialysis.

An all too common treatment error in the face of severe toxicity is "watchful waiting," during which the patient's condition is more likely to worsen than improve.

Organs and Systems

Cardiovascular

Cardiovascular disease is not a contraindication to lithium, but the risks may be greater, in view of factors such as fluid and electrolyte imbalance and the use of

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concomitant medications. Close clinical and laboratory monitoring is necessary, and an alternative mood stabilizer may be preferred. While long-term tricyclic antidepressant therapy may be more cardiotoxic than lithium, the newer antidepressants (SSRIs and others) seem to be safe.

In two studies of 277 and 133 patients taking long-term lithium, there was no evidence of increased cardiovascular mortality compared with the general population (61,62). While the latter study reported on 16-year mortality, it did not provide information about which patients continued to take lithium after the first 2 years.

Blood pressure

Lithium does not affect blood pressure adversely, nor does it benefit blood pressure, although lithium hippurate was used to treat arterial hypertension in the 1920s.

Cardiac dysrhythmias

Nonspecific, benign ST-T wave electrocardiographic changes are the most common cardiovascular effects of lithium.

- A 13-year-old boy taking lithium developed a "pseudomyocardial infarct pattern" on the electrocardiogram; this may have been an overinterpretation of nonspecific T-wave changes (63).

A very uncommon adverse effect involves sinus node dysfunction (extreme bradycardia, sinus arrest, sinoatrial block), which can be associated with syncopal episodes, perhaps due to hypothyroidism (64,65). In such cases, lithium must either be withdrawn or continued in the presence of a pacemaker. At therapeutic concentrations, other cardiac conduction disturbances have been reported, sometimes in conjunction with hypercalcemia (66), but are uncommon.

Two reviews of the cardiac effects of psychotropic drugs briefly mentioned lithium and dysrhythmias, with a focus on sinus node dysfunction (67,68), reports of which, as manifested by bradycardia, sinoatrial block, and sinus arrest, continue to accumulate in association with both toxic (69) and therapeutic (70,71) serum lithium concentrations. The rhythm disturbance normalized in some cases when lithium was stopped (69,71), persisted despite discontinuation (70), or was treated with a permanent cardiac pacemaker (71). Of historical interest is the observation that the first patient treated with lithium by Cade developed manifestations of toxicity in 1950, including bradycardia (72).

There have been several reports of bradycardia and sinus node dysfunction.

- During an episode of lithium toxicity (serum concentration 3.86 mmol/l), a 42-year-old woman developed sinus bradycardia that required a temporary pacemaker (69). There was marked prolongation of sinus node recovery time. Lithium was withdrawn and the patient underwent hemodialysis once daily for 3 days; sinus node recovery time normalized. The presence of nontoxic concentrations of carbamazepine may have contributed to the condition.
- A 65-year-old man taking lithium for 2 years, with therapeutic concentrations, developed sinus bradycardia (30 beats/minute), which remitted when the drug was stopped and recurred when it was restarted (73). Implantation of a permanent pacemaker allowed lithium to be continued.
- Asymptomatic bradycardia occurred in three of 15 patients treated for mania with a 20 mg/kg oral loading dose of slow-release lithium carbonate (74).
- A 9-year-old boy whose serum lithium concentration was 1.29 mmol/l had a sinus bradycardia with a junctional escape rhythm (40 beats/minute), which normalized at a lower lithium concentration (75).
- A 58-year-old woman with lithium toxicity developed an irregular bradycardia (as low as 20 beats/minute), which resolved during hemodialysis; persistent sinoatrial conduction delay suggested that she was predisposed to the bradydysrhythmia (76).
- A 52-year-old man took an overdose of lithium (serum concentration 4.58 mmol/l) and developed asymptomatic sinus bradycardia with sinus node dysfunction and multiple atrial extra beats, which resolved after hemodialysis (77).
- A 66-year-old woman with pre-existing first-degree AV block, developed sinus bradycardia, a junctional rhythm, a prolonged QT interval, and syncopal episodes (serum lithium concentration 1.4 mmol/l in a 40-hours sample) about 2 weeks after beginning lithium therapy. She was treated successfully with a pacemaker and a lower dose of lithium (78).
- A 36-year-old man became hypomanic after lithium was withdrawn because of symptomatic first-degree atrioventricular block (although, how first-degree block could have caused symptoms is unclear) (79).
- A 44-year-old woman developed atropine-resistant but isoprenaline-sensitive bradycardia (36 beats/minute), thought to be due to sinus node dysfunction related to lithium, fentanyl, and propofol (65).
- A 52-year-old man with a serum lithium concentration of 4.58 mmol/l had sinus node dysfunction with multiple atrial extra beats and an intraventricular conduction delay, which normalized following hemodialysis (77). Two patients, a 58-year-old woman and a 74-year-old woman, developed sick sinus syndrome while taking lithium but were able to continue taking it after pacemaker implantation (80,81).
- A 59-year-old woman with syncope and sick sinus syndrome, which remitted when lithium was withdrawn, recurred when lithium was restarted, and then persisted despite lithium withdrawal; after a pacemaker was implanted she was treated successfully with lithium for 7 years (80).

Lithium can also occasionally cause tachycardia.

- A 59-year-old man was noted to have tachycardia, a shortened QT interval, and nonspecific ST-T changes, while hospitalized with lithium-associated hypercalcemia (82).

An extension of a previously published study (66) added a third comparator group of 18 hypercalcemic non-lithium treated patients and compared them with 12 hypercalcemic lithium patients, 40 normocalcemic lithium patients, and 20 normocalcemic bipolar patients taking anticonvulsant mood stabilizers (83). Both hypercalcemic groups had more conduction abnormalities than the other

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two groups, but did not differ from each other in this regard. While the authors concluded that both lithium and calcium played important roles in the dysrhythmias, their data suggested that hypercalcemia alone was the critical factor.

Cardiac dysrhythmias associated with lithium intoxication in the elderly included sinus node dysfunction and junctional bradycardia (57). A retrospective chart review of patients on lithium who had mild but persistent hypercalcemia ($n = 12$) showed a greater frequency of cardiographic conduction disturbances compared with normocalcemic patients taking lithium ($n = 40$) and normocalcemic bipolar patients taking anticonvulsant mood stabilizers ($n = 20$), although the overall frequency of cardiographic abnormalities did not differ significantly among the groups (66). When 21 patients without cardiovascular disease (mean serum lithium 0.66 mmol/l) were compared with healthy controls using standard electrocardiography, vector cardiography, and electrocardiographic body surface potential mapping, the only abnormality was a reduction in the initial phase of depolarization, a finding of questionable clinical significance (84).

Abnormalities of the QT_c interval have been explored in 495 psychiatric patients (87 taking lithium, but many of them also taking other drugs) and 101 healthy controls (85). There was no association of lithium with QT_c prolongation but it was associated with nonspecific T-wave abnormalities (odds ratio 1.9) and increased QT dispersion (odds ratio 2.9). Caution was suggested if lithium is used with drugs associated with QT_c prolongation, such as tricyclic antidepressants, droperidol, and thioridazine.

Cardiomyopathies

A study of cardiomyopathies found a specific cause in 614 of 1230 patients (the remainder were diagnosed as idiopathic). One was attributed to lithium but no details were provided (86).

In a study of 1230 patients with initially unexplained cardiomyopathies, lithium was implicated in one case (62). Using a data-based mining Bayesian statistical approach to the WHO database of adverse reactions to examine antipsychotic drugs and heart muscle disorders, a significant association was found between lithium and cardiomyopathy, but not myocarditis (87). The authors acknowledged that further study is needed to determine if the association is causal.

- A 78-year-old woman developed a cardiomyopathy while taking lithium, imipramine, amineptine, levomepromazine, and lorazepam; it resolved when the medications were withdrawn (88). Whether lithium was causally involved is not known.

Respiratory

A 60-year-old woman with bipolar disorder since the age of 29 developed idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis) after having taken lithium for 9 years (89). Whether lithium played a causal role is at best highly speculative.

Ear, nose, throat

In two patients, profuse paroxysmal rhinorrhea improved when lithium was withdrawn (90). The rhinorrhea was thought to be a manifestation of mesotemporal lobe epilepsy that had been worsened by lithium.

Nervous system

Reports of overdose-related neurological symptoms abound (91–101). Among these reports, are cases of neurotoxicity at therapeutic serum lithium concentrations (91,99,101) and neurotoxicity associated with nonconvulsive status epilepticus (95,97).

There have been scattered reports of lithium-associated myasthenia gravis, paresthesia, somnambulism (102), seizures and electroencephalographic abnormalities, confusional states, and a reversible Creutzfeldt–Jakob-like syndrome (103). One report rather inconclusively suggested that lithium caused periodic alternating nystagmus in a 61-year-old man (104).

Electroneurographic studies in 34 lithium maintenance patients and controls (both healthy subjects and mood-disorder patients never on lithium) showed statistically significant reductions in sensory and motor conduction in the lithium group (105). None of the decrements was severe enough to be abnormal, and whether these findings have clinical implications is unknown.

Nonreversible lithium neurotoxicity continues to be reported (106,107), including a case of lithium overdose (serum lithium concentration 3.9 mmol/l) with persistent severe ataxia for 9 months that improved markedly when inadvertently treated with high-dose buspirone (120–160 mg/day) (108).

- An 85-year-old woman became gradually toxic (serum lithium 2.9 mmol/l) in a nursing home (109). Despite only conservative management, there was slow but complete resolution of severe neurological symptoms, including coma, fixed pupils, and Cheyne–Stokes respiration.

Twelve patients with mood disorder had electroencephalography before and after taking lithium for an average of 4.4 months (110). Lithium-related changes included:

(a) increased relative power in the delta- and theta-band frequencies;
(b) decreased relative alpha power;
(c) decreased dominant alpha frequency.

The clinical implications of these observations, if any, are unclear.

- A 73-year-old patient had toxic symptoms and moderately severe, generalized slowing on the electroencephalogram at a therapeutic serum concentration (111).

Cerebellar syndromes

Chronic neurological sequelae of intoxication included two patients with a persistent cerebellar syndrome and severe cerebellar atrophy (112), one with subcortical dementia (113), and one with a diffuse sensorimotor peripheral neuropathy (114).

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- An 86-year-old man with a serum lithium concentration of 0.7 mmol/l presented with a several month history of asterixis which resolved fully within 2 weeks of stopping lithium (115).
- Symptoms suggestive of toxicity at therapeutic serum concentrations also occurred in a 49-year-old man taking lithium (0.7 mmol/l), carbamazepine, and trifluperidol, who developed persistent cerebellar deterioration during a febrile episode of lobar pneumonia (116).
- Another patient who developed cerebellar symptoms consistent with lithium neurotoxicity despite a low therapeutic serum concentration (0.5 mmol/l) was more fortunate, as the symptoms resolved promptly when lithium was withdrawn (117).
- Permanent cerebellar sequelae occurred in a 36-year-old man after intoxication at therapeutic lithium concentrations (118).

A literature review of permanent neurological complications of acute lithium toxicity noted that a cerebellar syndrome is quite common and that neuroleptic drugs can worsen toxicity, as might rapid reduction of raised serum lithium concentrations (119). However, the latter point is speculative at best; hemodialysis remains the treatment of choice for severe lithium poisoning.

Convulsions

A proconvulsive effect of lithium was also suggested in two patients purported to have temporal lobe epilepsy, who improved when carbamazepine replaced lithium (90). Twelve cases of status dystonicus of varying causes included a woman with post-traumatic dystonia, who was treated unsuccessfully with lithium. Despite the lack of response, her muscular spasms worsened when lithium was stopped (120).

Five patients taking lithium for unspecified durations developed multifocal action myoclonus without reflex activation, which resolved fully when the drug was withdrawn (121).

- A patient presented with nonconvulsive status epilepticus and a serum lithium concentration of 1.9 mmol/l (122).
- A prolonged seizure occurred after electroconvulsive therapy (ECT) in a 45-year-old man taking lithium, amfebutamone, and venlafaxine (123).

Creutzfeldt–Jakob-like syndrome

A reversible Creutzfeldt–Jakob-like syndrome has been described in patients taking lithium.

- A 65-year-old woman taking lithium, levomepromazine, and phenobarbital developed a Creutzfeldt–Jakob-like syndrome after she had mistakenly increased her lithium dosage (103).
- A 66-year-old man presented comatose with an EEG suggestive of Creutzfeldt–Jakob encephalopathy after an 11-month history of progressive dementia and parkinsonism (124). Lithium (serum concentration 1.3 mmol/l), which he had been taking for 13 years, was withdrawn, and by day 78, clinical examination showed only mild neurological impairment.

Extrapyramidal effects

Parkinsonism

Occasionally, long-term use of lithium is associated with cogwheel rigidity and a parkinsonian tremor (125). More often than not, concurrent or past treatment with an antipsychotic drug is involved. In a review of SSRI-induced extrapyramidal adverse effects, lithium was listed, but not discussed, as a possible risk factor (126). A review of drug-induced parkinsonism provided references to case reports of lithium's "occasionally inducing or exacerbating parkinsonism" (127).

Two patients developed parkinsonism after taking lithium for many years, but did not improve when the drug was withdrawn and a causal relation could not be established (81).

- An 86-year-old man taking lithium monotherapy (serum concentration 0.7 mmol/l) had asterixis for several months; it resolved fully within 2 weeks of stopping lithium (115).
- A 65-year-old woman, after a brief exposure to lithium, developed severe akathisia and disabling parkinsonism; within 4 days of stopping lithium, the symptoms improved, but orofacial dyskinesia appeared; 10 months later both the parkinsonism and the dyskinesia had improved, but were still present (125).

Dystonias

Reversible tardive dystonia has been attributed to lithium (128).

Neuroleptic malignant syndrome

There have been reports of neuroleptic malignant syndrome in patients taking lithium and a neuroleptic drug (129–131). However, while previous reports have suggested an association between lithium and neuroleptic malignant syndrome (132), a case-control study ($n = 12$ with the syndrome, $n = 24$ controls) found no such association (133). Since none of the patients with neuroleptic malignant syndrome was taking lithium, little can be concluded from such a finding.

However, lithium can be associated with the neuroleptic malignant syndrome in patients who are taking neuroleptic drugs, as in the following cases:

- A 63-year-old man taking lithium and amoxapine (129).
- A 23-year-old woman taking lithium, olanzapine, and fluoxetine (130).
- A 39-year-old woman who had overdosed with lithium and who took a single dose of haloperidol (131).

Headache

A 64-year-old woman had a 2-week history of daily bilateral holocranial headache as the presenting complaint of lithium toxicity (serum concentration 2.5 mmol/l); dosage reduction resolved the headache and the extrapyramidal and cerebellar effects (134).

Myasthenia

A 51-year-old man developed a myasthenic syndrome which resolved when lithium was withdrawn (135). The authors referred to three other previously reported cases of lithium-induced myasthenia.

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Pseudotumor cerebri
Pseudotumor cerebri (benign intracranial hypertension) has been linked to lithium in over 30 cases, with headache, papilledema, increased intracranial pressure, reduced vision, and a risk of blindness (136). The condition tends to improve on withdrawal, but surgical intervention may sometimes be necessary. A review of pseudotumor cerebri devoted one paragraph to induction of this condition by lithium and provided six references but no new information (137).

- A 17-year-old woman developed pseudotumor cerebri with headache after she had taken lithium for 6.5 weeks (138). Papilledema and increased intracranial pressure resolved fully when lithium was withdrawn, and she was given acetazolamide.

Serotonin syndrome
Serotonin syndrome has been reviewed twice, but mention of lithium as a possible contributing factor was scanty (139,140).

Somnambulism
After almost a two-decade nap, interest in lithium-induced somnambulism was reawakened by a questionnaire survey of 389 clinic patients that found sleepwalking in 6.9% of those taking lithium alone or with other drugs compared with a 2.5% prevalence in the general population (102).

- A 52-year-old man had a 5-year history of sleepwalking 2–3 times a week beginning 3 months after starting lithium (141). On one occasion, he was injured in a fall when sleepwalking through a second-story window. When lithium was stopped for 3 months, the problem resolved only to recur when it was restarted.

Stuttering
Stuttering worsened in a 48-year-old man while he was taking lithium, with improvement when he was switched to valproate (142).

Tremor
Lithium commonly causes a benign postural tremor, especially early in the course of treatment (143,144) and can enhance physiological tremor (144). Risk factors include higher serum lithium concentrations, a family history of tremor, high caffeine intake, and the use of other drugs that cause tremor (for example antidepressants, valproate). The tremor is often well tolerated, but in some cases, it can be socially or occupationally problematic. In such cases, treatment possibilities include reducing the dose of lithium, the use of a modified-release formulation, reducing caffeine intake, or the addition of a tremor-reducing drug, such as a beta-blocker (145), primidone (146), or possibly gabapentin (147).

Tremor was reported as an adverse effect of lithium in 12 of 22 men and 10 of 38 women who had taken it for at least 1 year (56). In an open study, there was full remission of lithium tremor in four of five patients treated with vitamin B6 (148).

A double-blind study in which 31 patients with breakthrough depression taking lithium received augmentation with either paroxetine or amitriptyline and showed a quantitative increase in tremor activity with combined therapy, but no significant change in tremor frequency (149).

- Severe essential tremor, which was at first mistaken for tardive dyskinesia, occurred in an 80-year-old woman taking lithium; it resolved almost completely when lithium was withdrawn (150).

Neuromuscular function

Lithium has been implicated in impaired athletic prowess in two cases (151).

- A 21-year-old man had muscular incoordination while fast bowling (cricket), which improved when he switched to valproate.
- A 71-year-old woman was unable to serve properly at tennis until she stopped taking lithium.

Sensory systems

Eyes
Lithium can alter retinal sensitivity to light, and concern has been expressed that bright light therapy for seasonal mood disorder can increase the risk of photoreceptor cell damage, although such concerns have not been confirmed clinically (152,153).

Other effects on the visual system attributed to lithium include reduced accommodation, exophthalmos, extraocular muscle abnormalities, nystagmus (most characteristically downbeat), oscillopsia, photophobia, and papilledema with visual impairment (pseudotumor cerebri) (136).

- A 21-year-old woman developed temporary blindness possibly related to lithium toxicity (100).

Ears
The finding of reversible lithium-induced moderate hearing loss (especially low frequency) in guinea pigs has led to speculation that similar findings could occur in humans (154).

Psychological, psychiatric

Neuropsychological testing in a 51-year-old woman with a serum lithium concentration of 2.4 mmol/l showed striking cortical and subcortical deficits, which had only partially resolved when she was retested 4 and 14 weeks later (98).

Cognitive effects
Most people taking lithium have no complaints about its effects on mental processes; they feel normal and function normally. Mild cognitive effects can occur, although it is sometimes difficult to determine whether they are due to the lithium, the resolution of manic euphoria, the presence of mild depression or hypothyroidism, or the effects of other medications. Complaints can include reduced reactivity, lack of spontaneity, loss of emotional tone, and patchy memory impairment. Lithium reportedly has adverse effects on memory, speed of information processing, and reaction time (155,156). It has been suggested that the risk of driving accidents may be increased in patients taking lithium, but there is no evidence that this

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is so. As with any psychotropic drug, patients should be cautious about driving or operating dangerous machinery until they know how they will react to lithium. These mild cognitive adverse effects can be underappreciated by clinicians, yet be a cause of nonadherence to therapy. The action of lithium on the hypothalamic–pituitary–thyroid axis has been discussed in relation to its cognitive effects (157). Although, the English abstract of a Polish review concluded that there is no evidence of significant cognitive deficits caused by lithium (158), others dispute this conclusion (156).

Assessment of cognitive performance in 43 patients with bipolar I disorder showed no correlation between the use of lithium, carbamazepine, or valproate, and full-scale IQ or general and working memory (all of which were impaired by antipsychotic drugs) (159). While a deficit in sustained attention was noted in 19 euthymic patients with bipolar disorder (17 taking medications, 11 taking lithium alone or in combination), there was no difference between those taking and those not taking lithium (160).

In a 3-week, double-blind study of the cognitive effects of lithium (serum concentration about 0.8 mmol/l; $n = 15$) versus placebo ($n = 15$) in healthy subjects, lithium did not impair implicit recall, ability to process two tasks concurrently and simultaneously, short-term memory, or selective attention, but caused impaired learning during repeated administration of memory tests (161). Since neuropsychological testing could not distinguish lithium treatment from pre- and post-treatment in the lithium group, any lithium effects must be considered subtle at best.

It has been suggested that thyroid hormone may minimize the cognitive effects of lithium (157) and a review of this suggested benefit in those patients taking lithium who had subclinical hypothyroidism (157).

Lithium has diverse effects on creativity. While creativity can suffer from the absence of mania or from lithium-induced adverse effects, it can also be improved by the mood stabilization that lithium produces, or may be unaffected by treatment (162).

Four of seventeen studies of the cognitive effects of lithium were deemed to have acceptable methods. Reported adverse effects included effects on memory, speed of information processing, and reaction time (often in the absence of subjective complaints), suggesting that the risk of driving accidents might be increased when patients are taking lithium (155,156). Interventions for lithium-induced cognitive impairment include dosage reduction, use of a modified-release formulation, treatment of thyroid dysfunction, and assessing the role of concomitant illness and medication. When 67 patients who complained of cognitive deterioration while taking lithium were treated with aniracetam, 97% reported subjective improvement (163).

Delirium

In a case-control study, lithium was found to be one of several risk factors for delirium in 91 psychiatric inpatients (odds ratio 2.23), although the authors concluded that this observation may have been confounded by an association with manic episodes (164).

- A 38-year-old woman who had tolerated lithium for 20 years developed delirium following a manic episode, despite therapeutic concentrations of lithium (0.7–1.0 mmol/l); the episode remitted fully after lithium was withdrawn (165).
- A 36-year-old developed a febrile confusional state in the absence of infection while taking lithium (serum concentrations 0.37 and 0.58 mmol/l) and cyamemazine, resulting in a persistent cerebellar syndrome (166).
- A 62-year-old woman became delirious when lithium at therapeutic concentrations was added to valproate, haloperidol, and biperiden (167). The delirium resolved after all drugs were withdrawn, but 6 months later she still had choreoathetoid movements.

Endocrine

Corticotropin (ACTH)

Calcium infusion in lithium patients ($n = 7$) and controls ($n = 7$) caused similar increases in ACTH concentrations across a physiological range of calcium (168).

Prolactin

Serum prolactin concentrations in patients taking long-term ($n = 15$) or short-term ($n = 15$) lithium did not differ from controls (169). In another study, when compared with 17 healthy controls, 20 euthymic bipolar patients who had taken lithium for more than 6 months had significantly lower serum prolactin concentrations (9.72 ng/ml versus 15.56 ng/ml), but prolactin concentrations in short-term lithium users ($n = 15$) did not differ from controls (170). Antipsychotic drugs were not involved.

Diabetes insipidus

Two of ten patients taking long-term lithium therapy were thought to have hypothalamic diabetes insipidus, because of a positive response to desmopressin (171).

Hypothalamic–pituitary–adrenal axis

Hypothalamic–pituitary–adrenal axis function in bipolar disorder has been reviewed, but lithium was mentioned only in passing (172). Two studies ($n = 25$, $n = 24$), possibly reporting many of the same patients, showed that lithium augmentation of antidepressant-resistant unipolar depression increased hypothalamic–pituitary–adrenal axis activity, measured by the dexamethasone suppression test, either alone or combined with the corticotropin releasing hormone test (173,174). However, the tests did not distinguish between lithium responders and nonresponders.

Thyroid

The many effects of lithium on thyroid physiology and on the hypothalamic–pituitary axis and their clinical impact (goiter, hypothyroidism, and hyperthyroidism) have been reviewed (175). Lithium has a variety of effects on the hypothalamic–pituitary–thyroid axis, but it predominantly inhibits the release of thyroid hormone. It can also block the action of thyroid stimulating hormone (TSH) and enhance the peripheral degradation of thyroxine (175). Most patients have enough thyroid reserve to remain euthyroid during treatment, although some initially have modest rises in serum TSH that normalize over time.

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Both goiter and hypothyroidism continue to be reported as complications of lithium therapy (81,176,177).

In a cross-sectional study of 121 patients taking lithium, there was no difference in thyroid function tests among those taking treatment for 0.7–6 months, 7–10 months, or 61–240 months. However, when compared with healthy volunteers ($n = 24$) and prelithium controls ($n = 11$), there was a significant increase in radioiodine uptake in all lithium groups. Serum TSH concentrations were higher in prelithium patients than controls and highest in those taking lithium. Being from an iodine-deficient area appeared to predispose lithium patients to abnormally high TSH values and clinical hypothyroidism (178).

In 1989, in 150 patients at different stages of lithium therapy, thyroid function was assessed and subsequently 118 were reassessed at least once and 54 completed a 10-year follow-up (179). The annual rates of new cases of thyroid dysfunction were subclinical hypothyroidism 1.7%, goiter 2.1%, and autoimmunity 1.4%. While these figures were little different from those found in the general population, the authors acknowledged that lithium was a potential cause of thyroid dysfunction.

Of 42 bipolar patients who had taken lithium for 4–156 months, three had subclinical hypothyroidism, three had subclinical hyperthyroidism, and one was overtly hyperthyroid (177). Ultrasonography showed that goiter was present in 38% and mild thyroid dysfunction was suggested in 48% because of an apparent increased conversion of free T4 to free T3. There was no correlation between the duration of lithium therapy and thyroid abnormalities.

Hypothyroidism

Lithium-induced hypothyroidism has been briefly reviewed (180). Some patients develop more persistent subclinical hypothyroidism (TSH over 5 mU/l, free thyroxine normal) and others overt hypothyroidism (higher risk in women, in those with pre-existing thyroid dysfunction, and those with a family history of hypothyroidism). Since subclinical hypothyroidism is not necessarily asymptomatic, treatment with thyroxine may be necessary in this group (181), as well as in those with more obvious hypothyroidism (182).

The prevalence of thyroperoxidase antibodies was higher in 226 bipolar patients (28%) than in population- and psychiatric-control groups (3–18%). While there was no association with lithium exposure, the presence of antibodies increased the risk of lithium-induced hypothyroidism (183).

Thyroid function tests in 101 lithium maintenance patients were compared with their baseline values and with results in 82 controls without psychiatric or endocrine diagnoses. With hypothyroidism defined as a serum TSH above the reference range, 8 patients were hypothyroid at baseline, and another 40 became so during treatment. Women over 60 years of age were at slightly higher risk and had higher TSH values. Patients with a positive family history of hypothyroidism had raised TSH concentrations sooner after starting lithium (3.7 versus 8.7 years). Whether any patients became clinically hypothyroid was not noted (it was stated that those with grade II hypothyroidism were almost free of symptoms) (184).

Serum TSH concentrations were raised (10 mU/l or more) in 13 of 61 children aged 5–17 years taking lithium and valproate for up to 20 weeks (185).

In a review of lithium-induced subclinical hypothyroidism (TSH over 5 mU/l, free thyroxine normal), a prevalence of up to 23% in lithium patients was contrasted with up to 10% in the general population. It was stressed that subclinical hypothyroidism from any cause can be associated with subtle neuropsychiatric symptoms, such as depression, impaired memory and concentration, and mental slowing and lethargy, as well as with other somatic symptoms. Management guidelines were discussed (181).

An abstract reported that 23% of 61 children and adolescents taking lithium and divalproex sodium for up to 20 weeks had a TSH concentration over 10 mU/l (reference range 0.2–6.0); however, no clinical information was provided (186). Another abstract reported that the prevalence of thyroperoxidase antibodies was higher in bipolar outpatients (28% of 226) than in psychiatric inpatients with any diagnosis (10% of 2782) or healthy controls (14% of 225), but this was not related to lithium exposure; on the other hand, hypothyroidism was associated with lithium exposure, especially in the presence of antithyroid antibodies (187).

When 22 men and 38 women who had taken lithium for at least a year (mean 6.9 years) for bipolar disorder were evaluated for adverse effects, hypothyroidism requiring thyroid supplementation was found in 16 (14 women and 2 men); 9 had a goiter (56). The area from which some of the patients came was known to have a high background incidence of thyroid dysfunction.

The observation that Canada, with ample nutritional iodine, has a relatively high rate of lithium-related hypothyroidism compared with relatively low rates in iodine-deficient countries such as Italy, Spain, and Germany led to the suggestion that ambient iodine may play a role in the genesis of this condition (188). This is reminiscent of the association of amiodarone with hypothyroidism or hyperthyroidism in iodine-replete and iodine-deficient areas respectively (SEDA-10, 148).

Case reports of adverse thyroid effects of lithium have included the following:

- A 56-year-old man taking lithium whose TSH concentration was abnormally high (50 mU/l) (189).
- A 44-year-old woman who had taken lithium for 10 years and who developed swelling of the right lobe of the thyroid and hypothyroidism (65).
- A 63-year-old woman taking long-term lithium who developed subclinical hypothyroidism and primary hyperparathyroidism (190).

Hyperthyroidism

Despite the predominantly antithyroid effects of lithium, thyrotoxicosis continues to be described during treatment and after withdrawal (191–193). In a retrospective review of 201 patients taking lithium (mean duration 6.4 years), hypothyroidism requiring supplemental thyroxine developed in 10% (3.4% of men, 15% of women) after a mean duration of 56 months. Women over 50 years of age tended to have an earlier onset. Two patients developed

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goiter requiring surgery and two others developed thyrotoxicosis (182).

Reports of hyperthyroidism associated with lithium include one in a woman who was also hypercalcemic with a normal parathyroid hormone (PTH) concentration (194) and two discovered while treating lithium toxicity (195).

- A 27-year-old man developed thyrotoxicosis while taking lithium (193).
- A 52-year-old woman became thyrotoxic 2 months after stopping long-term lithium therapy; the authors briefly reviewed 10 previous reports (196).
- A woman with lithium-associated hyperthyroidism lost 2 kg over 3 months, suggesting that lithium may have indirectly caused the weight loss (197).

Thyroiditis

A retrospective record review of 300 patients with Graves' disease and 100 with silent thyroiditis who had undergone thyroid scans showed that the likelihood of lithium exposure was 4.7 times higher in the latter, suggesting a link between lithium and thyrotoxicosis caused by silent thyroiditis (198).

- A 30-year-old man, who had taken lithium for 16 years for bipolar disorder and long-term ciclosporin and prednisolone after a bone-marrow transplant, developed subacute thyroiditis associated with a diffusely enlarged gland that showed heterogeneous echogenicity, but without a clear relation to lithium (199).

Goiter

Euthyroid or hypothyroid goiter can also complicate lithium therapy, although the goiter is seldom of clinical importance and tends to resolve on withdrawal or with thyroxine treatment. In one ultrasound study, there was a 44% incidence of goiter in patients who had taken lithium for 1–5 years compared with 16% in a control group; cigarette smoking was associated with a greater size and frequency of goiter in both groups (200).

Hyperthyroidism has also been associated with lithium use and withdrawal, although a cause-and-effect relation has been more difficult to establish. In fact, lithium has been used with some success to treat hyperthyroidism, particularly in conjunction with propylthiouracil (201) and ^{131}I (16).

Parathyroid and calcium

Mild rises in serum calcium and PTH concentrations have been associated with long-term use of lithium, and, in a review, 27 reports of parathyroid adenoma and 11 of hyperplasia were mentioned (202). The hypercalcemia and raised PTH concentrations are often reversible on withdrawal, but surgical intervention may be necessary. So far, long-term lithium therapy has not emerged as a risk factor for reduced bone mineral density or osteoporosis (203). In one study, there was a greater frequency of electrocardiographic conduction defects in hypercalcemic patients taking lithium than in normocalcemic patients taking lithium (66).

Of 537 patients who had parathyroid glands excised for hyperparathyroidism, 12 (2.2%) had been taking lithium and 11 (2.0%) had been taking it long-term (mean 15.3 years, range 2–30). Manifestations included fatigue, bone pain and fracture, and abdominal pain and constipation. Six had a single adenoma and five had multigland hyperplasia. All resumed lithium, but one had a recurrence after 3 years and one had increased PTH concentrations, but a normal serum calcium. A literature review detected 27 prior reports of parathyroid adenoma and 11 of hyperplasia associated with lithium (202).

When 15 euthymic bipolar patients who had taken lithium for a mean of 49 months were compared with 10 nonlithium euthymic bipolar controls, the former had significantly higher total serum calcium concentrations and intact PTH (iPTH) concentrations (204). The authors advised baseline and periodic serum calcium and iPTH concentrations and bone density measurements in all lithium patients, although whether the benefit outweighs cost is open to question.

Ten patients who had taken lithium for less than 1 year and 13 who had taken it for more than 3 years were assessed for alterations in bone metabolism and parathyroid function (203). There were no differences in bone mineral density, serum calcium concentration, or PTH concentration, but both groups had increased bone turnover and the long-term group had nonsignificantly higher calcium and PTH concentrations (including one hyperparathyroid patient who had an adenoma excised). The authors' conclusion that lithium therapy is not a risk factor for osteoporosis needs to be tempered by the small sample size, the case of adenoma, and the blood concentration trends.

Total serum calcium and iPTH concentrations were measured in 15 patients taking long-term lithium and 10 lithium-naïve patients; both were significantly higher in the lithium group (205). While the number of lithium patients with abnormally high concentrations was not stated, mean iPTH concentrations were almost twice the upper limit of the reference range (102 versus 55 pg/ml).

Parathyroid tumors from nine patients with lithium-associated hyperparathyroidism (six multiglandular, three uniglandular) were compared with 13 nonlithium-associated sporadic parathyroid tumors with regard to gross genomic alterations (206). Gross chromosomal alterations were absent in most of the lithium group and were more common in the sporadic group.

In 53 patients studied prospectively at 1, 6, 12, and 24 months, lithium increased serum PTH concentrations (apparent by 6 months) and increased renal reabsorption of calcium in the absence of a significant change in serum calcium (207). A prospective study of 101 lithium maintenance patients and 82 healthy controls showed higher serum calcium concentrations during lithium treatment than at baseline or in the controls, and higher calcium serum concentrations in those lithium patients over 60 years of age (184).

When compared with 12 healthy matched controls, 13 women who had taken lithium for a mean of 8 (range 3–16) years had higher mean ionized and total calcium concentrations, but mean plasma parathormone concentrations did not differ. In eight of the women taking lithium, the calcium concentration was above the upper end of the reference range, and in one the parathormone concentration was abnormally high (208).

Of 15 patients taking long-term lithium who had surgery for primary hyperparathyroidism, 14 had adenomas

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(11 single, 3 double) and one had four-gland hyperplasia. All restarted lithium successfully after surgery, except one who again developed hyperparathyroidism, resulting in removal of another adenoma (209).

Hyperparathyroidism was considered a possible cause of treatment-resistant manic psychosis in a patient taking lithium (210).

- Hypercalcemia and raised PTH concentrations improved in a woman who had taken lithium for over 20 years after she was switched to divalproex (211).
- A 64-year-old woman who had taken lithium for over 10 years was admitted with altered consciousness, agitation, and disorientation. The serum calcium was 3.35 mmol/l (reference range 2.1–2.6 mmol/l) and the PTH concentration was raised. With hydration and conversion from lithium to valproate, the serum calcium concentration normalized, but 2 years later disorientation and hypercalcemia recurred and a 150 mg parathyroid adenoma was removed surgically (212).
- A 53-year-old woman who had taken lithium for 9 years and carbamazepine for 3 years and had a 3-month history of lethargy was found to be hypercalcemic with a raised concentration of iPTH. She was saved from parathyroid surgery when withdrawal of lithium resolved the hypercalcemia (213).
- A 51-year-old man who had taken lithium for over 10 years presented with nausea, vomiting, anorexia, hypercalcemia (3.1 mmol/l), and increased PTH concentration (iPTH 110 ng/l). Abnormalities resolved after an oxyphilic parathyroid adenoma was excised (214).

Other reports of hyperparathyroidism in patients taking lithium have included the following:

- Three cases among 26 cases of chronic lithium poisoning (215).
- A 78-year-old man who had taken lithium for 30 years who presented with dehydration, azotemia, hypernatremia, hypercalcemia, and increased PTH concentrations (216).
- A 63-year-old woman taking long-term lithium therapy (190).
- A woman who had taken lithium for 15 years who became hypercalcemic and stopped taking lithium, but 2 years later had two parathyroid adenomas removed surgically (217).
- A 42-year-old man who had taken lithium for 17 years and who had raised serum calcium and PTH concentrations which normalized after removal of a parathyroid adenoma (218).
- A 59-year-old man with hypercalcemia and increased PTH concentrations 3 months after starting lithium, which normalized after lithium was withdrawn (82).
- Three cases from Denmark (219) and one from Spain (220);
- A 78-year-old woman who had taken lithium for 25 years (221).
- A 74-year-old man who had an adenoma resected (81).
- Two 77-year-old women who developed hyperparathyroidism which was managed medically (81).
- A 39-year-old (sex unspecified) whose adenoma was resected after taking lithium for 10 years (209).
- A 59-year-old woman with hyperparathyroidism (222).

A lithium chloride solution caused changes in gravicurvature, statocyte ultrastructure, and calcium balance in pea root, believed to be due to effects of lithium on the phosphoinositide second messenger system (223). The implications with regard to human parathyroid function are obscure.

Metabolism

Diabetes mellitus

It has been reported that diabetes mellitus is three times more common in bipolar patients than in the general population (224). However, lithium does not appear to increase the risk of diabetes mellitus, and its use in patients with pre-existing diabetes is generally safe, assuming that the diabetes is well controlled.

When lithium toxicity has been reported in patients with diabetes mellitus, it has been attributed to impaired glucose intolerance (225).

- An increased lithium dosage requirement in a hyperglycemic 40-year-old woman was attributed to the osmotic diuretic effect of glycosuria, increasing lithium excretion (226).
- Two patients with diabetes mellitus developed lithium toxicity (serum concentrations 3.3 and 3.0 mmol/l) in association with impaired consciousness, and hyperglycemia that resolved after intravenous insulin and fluids (227).

While the authors of the second report concluded that impaired glucose tolerance had predisposed to lithium intoxication, the opposite is also possible.

When a 45-year-old man with severe lithium-induced diabetes insipidus developed hyperosmolar, nonketotic hyperglycemia, it was suggested that poorly controlled diabetes mellitus may have contributed to the polyuria (228). Prior contact with a female patient who had developed hyperosmolar coma secondary to lithium-induced diabetes insipidus (229) allowed physicians 4 years later to treat her safely after a drug overdose and a surgical procedure, by avoiding intravenous replacement fluids with a high dextrose content (despite stopping lithium several years earlier, the patient continued to put out 10 liters of urine daily) (230).

Difficulty in attaining a therapeutic serum concentration of lithium despite increased doses was attributed to increased renal clearance due to the osmotic effect of glycosuria in a 44-year-old man with poorly controlled diabetes mellitus (226).

Weight gain

Weight gain, a well-recognized adverse effect of lithium, occurs in one-third to two-thirds of patients (231). It is more common in those with prior weight problems and at higher dosages of lithium. Possible mechanisms include complex effects on carbohydrate and lipid metabolism, mood stabilization itself, lithium-induced hypothyroidism, the use of high-calorie beverages to treat lithium-induced polydipsia, and the concomitant use of other weight-gaining drugs (for example valproate, olanzapine, mirtazapine). Recognizing and managing weight gain early in the course of treatment can do much to ensure continued

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adherence to lithium regimens. Two reviews of weight gain with psychotropic drugs mentioned lithium (232,233).

Risk and magnitude

In a review of psychotropic drug-induced weight gain, the prevalence and magnitude of the problem with lithium was discussed together with risk factors, mechanisms, and management (231). Adolescent inpatients treated with risperidone ($n = 18$) or conventional antipsychotic drugs ($n = 19$) over 6 months gained more weight than a control group but concomitant treatment with lithium was not a contributing factor (234).

A review of psychotropic drugs and weight gain included a brief summary of lithium-related weight gain (235). A retrospective evaluation of 176 patients taking long-term lithium showed that weight gain was an adverse effect in 18%. While 34% of the total did not adhere to treatment because of somatic adverse effects, no specific adverse effect (including weight gain) was associated with nonadherence (236).

The prevalence of overweight (BMI 25–29) and obesity (BMI 30 or more) was determined in 89 euthyroid bipolar patients and 445 reference subjects. The rate of obesity in patients taking only lithium was 1.5 times greater than in the reference population (a nonsignificant difference), compared with a statistically significant 2.5 times greater rate associated with antipsychotic drugs (237).

The prevalence of overweight (BMI 20 or more) and obesity (BMI 30 or more) has been evaluated in 89 euthymic bipolar patients and 445 age- and sex-matched controls (237). The bipolar women were more overweight and more obese than the controls and the bipolar men were more obese but not more overweight. Obesity was clearly related to antipsychotic drug use and less so to lithium and anticonvulsants (but patients taking lithium alone had an obesity rate 1.5 times that of the general population).

A review of the effects of mood stabilizers on weight included a section on lithium in which the authors concluded that lithium-related weight gain occurs in one-third to two-thirds of patients, with a mean increase of 4–7 kg; possible mechanisms were discussed (238).

An open chart review of 74 hospitalized patients showed a mean weight gain of 6.3 kg and an increase in BMI of 2.1 kg/m^2 after they had taken lithium for a mean of 89 days (239). Of 47 lithium-treated patients, 14 gained at least 5% of their baseline BMI, 6 gained over 10%, and 2 gained over 15% during an acute treatment phase of unspecified duration, while during the 1-year maintenance phase 11 gained over 5% and 2 gained over 10% (240).

Comparative studies

In a 1-year, placebo-controlled study of bipolar I prophylaxis ($n = 372$), weight gain with divalproex, but not with lithium, was significantly more common than with placebo (52). A patient who gained 18 kg over 18 months while taking lithium and perphenazine lost 16 kg when the latter was changed to loxapine (she also participated in a weight loss program) (241). Whether lithium played a role in the weight gain was unclear.

In a 12-month maintenance study, weight gain was an adverse event in 21% of patients taking divalproex, 13% of those taking lithium, and 7% of those taking placebo (52). The divalproex/placebo difference was statistically significant, but the lithium/placebo difference was not.

Mechanism

In 15 consecutive patients, serum leptin concentrations were measured at baseline and after 8 weeks of lithium treatment. There was a significant mean increase of 3.5 ng/ml and serum leptin correlated positively with weight gain (5.9 kg), increased BMI (24–27), and clinical efficacy (242). The authors suggested that leptin might play a role in lithium-induced weight gain.

Management

The Expert Consensus Guideline Series, Medication Treatment of Bipolar Disorder 2000, has recommended to "continue present medication, focus on diet and exercise" as the preferred first-line treatment for managing weight gain in patients taking lithium or divalproex. The next approach was to continue medication and add topiramate. Second-line treatments included switching from divalproex to lithium or vice versa, reducing the dosage, and switching to another drug. The addition of an appetite suppressant was a lower second-line recommendation (243).

Nutrition

In a review of naturally occurring dietary lithium (food and water sources), the author acknowledged that human lithium deficiency states have not been identified, but concluded that lithium should be considered an essential element, a conclusion reached on rather shaky grounds (244).

Electrolyte balance

Potassium

Episodes of acute hypokalemic paralysis have been associated with long-term lithium therapy (245).

- A 25-year-old man, who had taken lithium for 5 years, awakened from sleep unable to move his limbs and had a generalized flaccid paralysis with a serum potassium concentration of 2.1 mmol/l (245). Lithium was withdrawn and he responded to treatment with intravenous potassium chloride.

The diagnosis of acute hypokalemic paralysis was attributed to lithium but without confirmation by rechallenge it was unclear whether this was causal or coincidental.

Sodium

Hypernatremia can occur secondary to dehydration in patients taking lithium and is not uncommon in association with lithium poisoning. Lithium-induced diabetes insipidus is often a contributing factor.

Mineral balance

Fluid and sodium balance are important to the safe use of lithium. Both dehydration and a negative sodium balance (for example a low salt intake, diuretic-induced sodium loss) will reduce renal lithium clearance and predispose to toxicity (246). Hyponatremia (for example, secondary to polydipsia or SIADH) may also increase the risk of lithium toxicity (247).

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When nine trace elements were measured in whole blood (oven dried, moisture-free) from controls, pre-lithium, and lithium patients, there were many changes related to lithium, but none appeared to be clinically important (248).

Fluid balance

Edema associated with lithium is uncommon (249,250). It is usually restricted to the legs, and is usually transient or intermittent. If treatment is necessary, the intermittent and cautious use of a loop diuretic may be helpful (but see drug–drug interactions).

Dehydration, secondary to lithium-induced nephrogenic diabetes insipidus, was thought to be the cause of a superior sagittal sinus thrombosis in a 30-year-old woman who presented with confusion, papilledema, and a left hemiparesis (251).

Hematologic

The most common hematological effect of lithium is a benign leukocytosis (252), consisting primarily of mature granulocytes, which is reversible on withdrawal. An increase in platelet count is a much less consistent finding (253), and there are no clinically important effects on erythrocytes. Despite anecdotal reports to the contrary, epidemiological studies have shown no increased risk of leukemia with lithium (254). The leukocyte-inducing effects of lithium have been used with some success to treat granulocytopenia (25,26).

The effects of lithium on hemopoiesis have been studied in 100 patients who had developed chronic granulocytopenia after cancer chemotherapy or radiotherapy (255). The mean leukocyte count rose by 46%, but there were no changes in platelet or erythrocyte counts. However, there was a significant increase in platelet count in those whose baseline values were below 150×10^9/l. Lithium was well tolerated (mean serum concentration 0.59 mmol/l).

Granulocyte counts and granulocyte colony-stimulating factor (G-CSF) concentrations were measured in 18 patients before and after 1 and 4 weeks of lithium treatment, and compared with values in 20 patients taking long-term lithium (256). At week 4, the granulocyte count was significantly higher than at baseline or at week 1, or in the long-term group. There was only a nonsignificant increase in G-CSF concentration at weeks 1 and 4. The granulocyte count in those taking long-term lithium did not differ significantly from the baseline values in the other group.

A retrospective review of inpatients showed higher leukocyte and granulocyte counts in those taking lithium alone ($n = 38$) compared with those taking antipsychotic drugs alone ($n = 207$); lymphocyte counts were not affected. Rises in leukocyte counts above normal occurred in 18% of those taking lithium and 6% of those taking antipsychotic drugs (252). The neutrophil-stimulating effect of lithium was used to advantage to successfully re-treat a patient with clozapine several years after stopping it because of neutropenia (257). Likewise, lithium was used to successfully stimulate neutrophil production in a patient with clozapine-induced neutropenia and in another with clozapine-induced agranulocytosis (recovery was as fast as seen with colony-stimulating factor and twice as rapid as expected spontaneously) (25).

In eight patients with bipolar disorder, lithium for 3–4 weeks increased neutrophil count by 88% and also caused a significant increase in CD34+ cells (although three patients had no increase in either) (258).

- A lithium-treated bipolar patient with acute myeloid leukemia had an unusually great increase in CD34+ cells following administration of G-CSF, suggesting a boosting effect from lithium (259).
- After he had failed to respond to combined treatment with corticosteroids and androgens and to antilymphocyte globulin, a 16-year-old with aplastic anemia responded to lithium combined with an androgen derivative, relapsed when lithium was stopped, and responded again when it was restarted (31).

Of 39 patients taking lithium, 18% had neutrophilia and 15% had raised activity of polymorphonuclear elastase (a marker of granulocyte activation) (260). In keeping with these observations, a chart review of 38 patients taking clozapine showed an increase in leukocyte count when lithium was added (32). A man with olanzapine-induced neutropenia (with a prior history of risperidone-induced neutropenia), which normalized with drug withdrawal, had no difficulty when the drug was reintroduced after the patient had been treated with lithium (33).

When 50 bipolar lithium patients were compared with 30 healthy controls, platelet counts were similar, but the lithium group had higher concentrations of plasma beta-thromboglobulin and platelet factor 4, suggesting lithium-induced platelet activation (253).

A cross-sectional study showed a 20% lower serum vitamin B12 concentration in patients taking lithium ($n = 81$) than in controls ($n = 14$) (serum and erythrocyte folate concentrations were normal) (261).

Mouth and teeth

A comprehensive review of psychoactive drug-induced hyposalivation and hypersalivation included a discussion of lithium-induced dry mouth (common) and sialorrhea (262). A review of dental findings and their management in patients with bipolar disorder briefly mentioned that xerostomia, sialadenitis, dysgeusia, and stomatitis have been attributed to lithium (263). Dry mouth is common and can be due to lithium-induced polyuria, a direct effect on thirst, salivary gland hypofunction, or other drugs (262). Hypersalivation attributable to lithium is rare (264).

A review of drug-induced oral ulceration mentioned lithium as a possible cause, based on two older references (265,266).

- An 8-year-old taking lithium citrate for 6 months developed waxing and waning areas of denuded papillae on her tongue, diagnosed as benign migratory glossitis (geographic tongue) and attributed to lithium (267).

The issue has been raised of whether oral lithium therapy was responsible for failure of titanium dental implants in a 62-year-old man (268).

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Gastrointestinal

Lithium can cause loss of appetite, nausea, and at times vomiting and loose stools, especially early in therapy, but these can be minimized by the passage of time and by making dosage increases gradually (52). Gastrointestinal symptoms can also be an early warning sign of lithium intoxication.

In a 12-month maintenance study, lithium ($n = 94$) was not unexpectedly associated with more nausea (45 versus 31%) and diarrhea (46 versus 30%) than placebo ($n = 94$) (52).

- A 72-year-old man who had recently started to take lithium developed severe nausea, vomiting, and oliguric renal insufficiency which was initially attributed to lithium toxicity, until a serum lithium concentration of only 0.35 mmol/l directed evaluation to the correct diagnosis of acute gastric volvulus (269).
- An 80-year-old woman taking lithium developed constipation, nausea, vomiting, and abdominal pain after starting to take amfebutamone. A diagnosis of acute paralytic ileus was made and attributed to amfebutamone, although an amfebutamone–lithium interaction could not be excluded (270).
- In an 80-year-old woman a 2-month history of diarrhea, nausea, and abdominal distress attributed to irritable bowel syndrome was ultimately determined to be due to early lithium intoxication (271). Her lithium concentration when she was hospitalized was 1.2 mmol/l, although she had taken no lithium for the previous 10 days. Treatment with a thiazide diuretic contributed to the toxicity.

Pancreas

Of 47 cases of drug-induced pancreatitis reported to the Danish Committee on Adverse Drug Reactions between 1968 and 1999, one involved lithium (plus a neuroleptic drug) (272). Whether lithium was causally involved is not known.

- A 78-year-old woman taking lithium had hyperamylasemia and hyperlipasemia in the absence of gastrointestinal symptoms. Ultrasound examination showed the pancreas and liver to be normal. She also had hyperparathyroidism and renal dysfunction (221).

Urinary tract

There have been several reviews of the effects of lithium on the kidney (273–276).

In a retrospective study, 114 patients who had taken lithium for 4–30 years were compared with 94 unmedicated age- and sex-matched controls with regard to changes in creatinine concentrations (277). Of the patients taking lithium, 21% had blood creatinine concentrations that had increased gradually and were now over the top of the reference range. This finding was associated with episodes of lithium intoxication and with diseases and other medications that could also affect glomerular function. Sex, psychiatric diagnosis, duration of treatment, cumulative dose, and serum lithium concentrations did not predict an abnormal creatinine concentration.

Renal function was assessed in 10 patients taking long-term lithium (over 3 years, mean 80 months), 10 taking short-term lithium (3 years or less, mean 16 months), and 10 lithium-naïve patients (171). Blood urea nitrogen and serum creatinine concentrations were within the reference ranges and did not differ among the groups, but 24-hour creatinine clearance was significantly lower in those taking long-term lithium (73 versus 125 and 150 ml/minute). There were no significant differences among the groups in urine osmolality after 8-hour water deprivation and desmopressin, but partial nephrogenic diabetes insipidus was diagnosed in four long-term and two short-term patients and hypothalamic diabetes insipidus in two long-term patients. The authors concluded that long-term lithium therapy is a risk factor for renal impairment.

In a retrospective review of lithium concentrations in 2210 psychiatric hospital patients, 151 (6.8%) had serum lithium concentrations of 1.5 mmol/l or more. Of those with high serum concentrations, 10 (6.6%) had a raised blood urea nitrogen or serum creatinine concentration (278). In a retrospective study of 114 patients who had taken lithium for 4–30 years and 94 matched unmedicated subjects, 21% of those taking lithium had blood creatinine concentrations greater than 1.5 mg/ml [sic]; comparative figures were not given for the controls (277). Raised creatinine concentrations tended to be associated with episodes of lithium toxicity and drugs or diseases that could alter glomerular function.

Renal disease is not a contraindication to lithium, but it does complicate its use, and alternative mood stabilizers should be considered. Despite the diverse effects of lithium on the kidney, most patients find it to be generally well tolerated; nevertheless, monitoring should include periodic testing of renal function. In one case, a psychiatrist and family physician were sued for failing to monitor renal function in a patient who developed renal insufficiency (279). The distribution of monitoring guidelines in the area of Aberdeen, Scotland, led to an increase in the number of lithium patients who had at least once-yearly serum creatinine concentration measurements from 71% to 78%, still leaving 22% without adequate renal function monitoring (280).

To what extent long-term treatment with lithium impairs GFR is a matter of continued study (275). Lithium does not appear to impair GFR consistently, especially if correction is made for age-related changes in kidney function, although in one study there was an age-related reduction in 21% of 142 patients who had taken lithium for at least 15 years (281). There have been a few case reports of progressive renal insufficiency attributed to lithium, but it has not been possible to establish a cause-and-effect relation with absolute certainty.

In a review of the renal and metabolic complications of lithium, the example of a 78-year-old woman taking long-term lithium who had urinary incontinence, moderate renal insufficiency, a 5–7 litres 24-hour urine volume, and thyroid and parathyroid abnormalities was used to set the scene (221).

In a historical cohort study, changes in renal function in 86 patients taking lithium were evaluated first after a median treatment duration of 5.8 years and again after 16 years (282). Maximum plasma osmolality was reduced in nine of 63 patients in the initial study and in 24 of 63 at follow-up. Other findings included increased serum

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creatinine (in one of 76 patients initially and eight of 76 at follow-up) and reduced GFR (in three of 29 patients initially and six of 29 at follow-up); only the latter of these changes was not significant. The authors noted that this progressive impairment in renal dysfunction was greater than expected for age and advised strict surveillance of renal function in patients taking long-term lithium.

In a retrospective review of 6514 renal biopsies, there were 24 patients with renal insufficiency who had taken lithium for a mean duration of 13.6 years (range 2–25 years); the histological changes included chronic tubulointerstitial nephropathy (100%), cortical and medullary tubular cysts (63%) or tubular dilatation (33%), global glomerulosclerosis (100%), and focal segmental glomerulosclerosis (50%) (283). Only two had a history of acute lithium toxicity. Clinical findings included proteinuria (42%), nephrotic syndrome (25%), nephrogenic diabetes insipidus (87%), and hypertension (33%). Despite lithium withdrawal, either seven (abstract) or eight (text) of nine patients with an initial serum creatinine of over 221 μmol/l (2.5 mg/dl) progressed to end-stage renal insufficiency, whereas this occurred in only one of ten with lower creatinine concentrations. The study design was such that the risk of renal insufficiency with long-term lithium therapy could not be established and the possibility of alternative causes could not be excluded.

Two studies in rats have potential implications for humans. In rats with mild to severe lithium-induced nephropathy, urine *N*-acetyl-β-D-glucosaminidase was an early indicator of renal insufficiency (284). Both ^{6}Li and ^{7}Li caused reduced urine concentrating ability and increased urine volume and renal tubular lesions, but ^{6}Li was more nephrotoxic (285). The authors suggested that eliminating ^{6}Li from pharmaceutical products might reduce nephrotoxicity (although ^{6}Li accounts for only about 7% of the lithium in such products).

Concentrating ability

Lithium often impairs renal concentrating ability, an effect that is related in part to both dosage and duration of treatment (273,275). While it is initially reversible on withdrawal, it may eventually become irreversible and indicative of structural tubular damage. Impaired concentration is of no clinical consequence in itself, but it may go hand in hand with polyuria (lithium-induced nephrogenic diabetes insipidus), which can sometimes be a social and occupational nuisance and can increase the risk of toxicity secondary to dehydration. These problems can be minimized if the maintenance serum concentration is low, but whether single daily dosing is kinder to the kidney has yet to be resolved. Since the defect is at the level of the kidney (both before and after the site of cyclic AMP generation and probably involving the water channel protein aquaporin-2, a vasopressin-regulated water channel protein (286)), vasopressin (ADH) is unlikely to be effective. A thiazide and/or potassium-sparing diuretic (especially amiloride) can reduce the urine volume, although serum lithium concentrations can rise at the same time. Avoiding hypokalemia is essential, but whether dietary potassium supplementation can also be helpful is not known. Inositol is no longer considered promising.

In a comparison of patients taking long-term lithium ($n = 10$) or short-term lithium ($n = 9$) and bipolar patients not taking lithium ($n = 10$), there was significantly lower creatinine clearance and renal concentrating ability in the long-term group (287).

Acute and chronic renal insufficiency

Renal insufficiency was attributed to lithium in a 40-year-old who had had nontoxic concentrations for 15 years (interstitial nephropathy on biopsy) (288) and in a 55-year-old woman who had taken lithium for 6 years (serum creatinine 141 μmol/l (289). A few patients develop progressive renal insufficiency that can best be attributed to lithium (275).

Chronic renal insufficiency (creatinine clearance under 80 ml/minute), for which there was no apparent alternative explanation, developed in 53 patients taking long-term lithium (mean 17.7 years); 7 required periodic dialysis (290).

After taking lithium for 6 years, a 55-year-old woman developed mild renal insufficiency (serum creatinine 1.6 mg/dl) and lithium was withdrawn (289).

Interstitial nephritis

Lithium-associated changes in kidney morphology include an acute, reversible, and possibly lithium-specific distal tubular lesion and a chronic, nonspecific, and tubulointerstitial nephritis (291). The differential diagnosis of the latter is extensive, and it is not clear if lithium is causative. Lithium received a brief mention in a review of tubulointerstitial nephritis (291).

- A 48-year-old man taking lithium and chlorprothixene had a creatinine clearance of 60 ml/minute and a renal biopsy showing chronic interstitial nephritis (292).
- Lithium-induced interstitial nephritis (serum creatinine 2.3 mg/dl) occurred in an 89-year-old woman who had taken lithium for 29 years (81).

Nephrogenic diabetes insipidus

There have been several case reports of lithium-related nephrogenic diabetes insipidus, sometimes associated with dehydration and lithium intoxication (216,293–296).

Nephrogenic diabetes insipidus has been specifically reviewed in the context of a case in which resolution did not occur despite withdrawal of lithium (297).

Nephrogenic diabetes insipidus secondary to lithium led to severe dehydration in two patients who required intravenous rehydration followed by a thiazide diuretic to reduce urine volume (294). One patient had persistent polyuria (6.7 l/day) 57 months after stopping lithium (211).

- A 77-year-old woman who had taken lithium for 10 years developed delirium, hypernatremia, prerenal azotemia, and a serum lithium concentration of 1.4 mmol/l; her condition was attributed to dehydration related to partial nephrogenic diabetes insipidus (293).
- Eight years after stopping lithium because of polydipsia and polyuria, a 55-year-old woman was hospitalized with lethargy, coma, and hypernatremia (sodium concentration 156 mmol/l) after her fluid intake had been restricted (297).

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- A 30-year-old woman who became dehydrated secondary to lithium-induced nephrogenic diabetes insipidus developed a superior sagittal sinus thrombosis (251).
- A 78-year-old woman who had taken lithium for 25 years had hypotonic polyuria (4.7 l/day), mild renal insufficiency, and hyperparathyroidism attributed to lithium (221).
- Nephrogenic diabetes insipidus resulted in dehydration and hypernatremia in a 78-year-old man who had taken lithium for 30 years (216).
- Nephrogenic diabetes insipidus in a 63-year-old woman was treated successfully with lithium withdrawal and amiloride (298).

Nephrotic syndrome

Nephrotic syndrome (proteinuria, edema, hypoalbuminemia, hyperlipidemia) is a rare and idiosyncratic complication of lithium therapy; it usually resolves on withdrawal, and can recur on rechallenge (299,300). Lithium-associated nephrotic syndrome occurred in a 59-year-old woman with lithium toxicity (serum concentration 1.9 mmol/l) whose renal biopsy showed focal segmental glomerulosclerosis. Lithium withdrawal led to resolution of edema and marked improvement in proteinuria and albuminemia (300).

- An 83-year-old man developed nephrotic syndrome while taking lithium (301).
- An 11-year-old boy who had taken lithium for an unstated duration developed nephrotic syndrome with focal glomerulosclerosis which remitted fully after lithium was withdrawn (299).
- A 59-year-old woman with lithium-associated nephrotic syndrome (focal segmental glomerulosclerosis on biopsy) had resolution of edema and pleural effusions and marked improvement in albuminemia and proteinuria after withdrawal of lithium (300).

Renal tubular acidosis

Incomplete distal renal tubular acidosis has been attributed to lithium, but appears to be of no clinical significance (302).

Skin

In a review of skin reactions to mood stabilizers, a wide variety of reactions attributed to lithium were mentioned, but the authors did not critically evaluate the data on which the reports had been based (303).

In a review of acute skin reactions to psychotropic drugs, alopecia, psoriasiform, acneiform, and lichenoid eruptions, and drug-induced lupus were attributed to lithium, but critical comment was not provided (304).

There have been anecdotal reports of papular and nonpapular rashes, pityriasis versicolor, hidradenitis suppurativa, and nail dystrophy (305,306), although causal relations are difficult to establish.

In a review of lichenoid drug eruptions, lithium was implicated in one patient with ulcerative oral lesions and in another with ulcerative genital lesions (307).

- A 60-year-old man developed systemic swelling, redness, and pruritus 1 month after starting to take lithium; it was attributed to the drug based on positive patch and challenge tests (308).
- A 55-year-old man who had taken lithium and haloperidol for 11 years developed hyperkeratotic follicular papules on his scalp, extremities, and trunk, which on biopsy were suggestive of follicular mycoses fungoides (309). He also had a 1-year history of scalp, axillary, and pubic hair loss. Following replacement of lithium with valproate, his hair regrew and the papules cleared almost completely in 3 months.

A man and a woman developed vegetating plaques with peripheral pustules (halogenoderma) after taking lithium for 6 and 8 years respectively (310). No follow-up information was provided and it could not be established whether the lesions were caused by, worsened by, or unrelated to lithium.

Acne

Acne can occur or worsen during lithium treatment (311). In a comparison of 51 patients taking lithium with 57 patients taking other psychotropic drugs, there were secondary skin reactions in 45% of the former and 25 of the latter; while acne (33 versus 9%) and psoriasis (6 versus 0%) were more common in the lithium group, the only statistically significant association was acne in males (312).

- Six months after beginning lithium, a man in his late twenties developed severe truncal acne which worsened over 5 years, at which time lithium was withdrawn (313). Nevertheless, the lesions were still present 4 years later, leading to the conclusion that lithium had caused irreversible acne.

In this case, the association could have been coincidental.

Alopecia

Hair loss in psychopharmacology has been reviewed (314). It appears to be an uncommon and unpredictable adverse effect of lithium. Hypothyroidism is occasionally involved. Hair texture can also be altered (315).

- A 36-year-old woman had taken lithium for 4 months when her scalp hair became thinner and stopped growing. She continued to take lithium, and 2 months later was diagnosed and treated for hypothyroidism, after which her hair became curlier but did not grow longer or fuller.

Darier's disease

Darier's disease (follicular keratosis) can be exacerbated by lithium (316,317).

- In a woman who had had keratosis follicularis (Darier's disease) since she was 16, the condition worsened when she was given lithium at age 50 (and improved when she switched to valproate) (317).

However, despite reports that Darier's disease is worsened by lithium, a 52-year-old man noted no exacerbation despite taking lithium for many years (318).

Psoriasis

Psoriasis can occur or worsen during lithium treatment (311). Before psoriasis can be treated effectively, lithium may have to be withdrawn. In a comparison of 51 patients taking lithium with 57 patients taking other psychotropic drugs, there were secondary skin reactions in 45% of the

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former and 25% of the latter; while acne (33 versus 9%) and psoriasis (6 versus 0%) were more common in the lithium group, the only statistically significant association was acne in males (312).

- A 42-year-old woman taking lithium developed psoriasis which resolved when the drug was withdrawn (319). Brief mention was made of two patients (age and sex unstated) taking lithium whose psoriasis improved with oral omega-3 fatty acids (320).
- Lithium worsened psoriasis in a 54-year-old woman; improvement followed withdrawal (321).

Hair, nails, sweat glands

Hair loss in psychopharmacology has been reviewed (314). It appears to be an uncommon and unpredictable adverse effect of lithium. Hypothyroidism is occasionally involved. Hair texture can also be altered (315).

- A 36-year-old woman had taken lithium for 4 months when her scalp hair became thinner and stopped growing. She continued to take lithium, and 2 months later was diagnosed and treated for hypothyroidism, after which her hair became curlier but did not grow longer or fuller.

Musculoskeletal

Despite lithium-induced increases in serum calcium and PTH concentrations, most recent studies have not shown a reduction in bone mineral density or increased risks of osteoporosis or bone fractures (322). In 26 patients who had taken lithium for at least 10 years, bone mineral density did not differ from controls (323).

A patient with a diffuse sensorimotor peripheral neuropathy also developed rhabdomyolysis during the acute episode in association with a serum lithium concentration of 3.1 mmol/l and a serum sodium of 163 mmol/l (114).

Sexual function

Despite occasional reports of reduced libido and erectile dysfunction, lithium causes little in the way of sexual dysfunction in men or women (324). In a brief review of the sexual adverse effects of psychotropic drugs, reduced libido and arousal with lithium were mentioned in passing, particularly when it was combined with other drugs (which, of course, makes it difficult to implicate lithium) (325).

Reproductive system

In a cross-sectional pilot study of 22 bipolar women taking lithium ($n = 10$), divalproex ($n = 10$), or both ($n = 10$), there was an increased number of ovarian follicles in one woman taking lithium, but no evidence of hormonal changes suggestive of polycystic ovary syndrome in any patient (326). The small sample size was a limiting factor.

When 22 women with bipolar disorder (10 taking lithium alone, 10 taking divalproex alone, and 2 taking both) were evaluated for polycystic ovary syndrome, none had typical hormonal screening abnormalities (326). Some type of menstrual dysfunction was present in all ten women taking lithium alone, but it predated use of the drug in all but one.

Compared with 13 women taking placebo, 10 women taking lithium carbonate 900 mg/day for one menstrual cycle had no significant alterations in reproductive hormone concentrations (327).

In an in vitro study, LY294002, a phosphatidylinositol-3-kinase inhibitor, overcame impaired human sperm motility induced by lithium chloride (328).

At blood concentrations within the human target range, oral lithium caused degenerative changes in testicular morphology in spotted munia (*Lonchura punctulata*), a seasonally breeding subtropical finch (329). Lithium at a serum concentration of about 0.6 mmol/l reduced sperm motility, number, and viability, and markedly altered testicular histopathology in *Viscacha*, a nocturnal rodent from the pampas of Argentina (330). How these findings might relate to effects in men is open to question.

Immunologic

Lithium is not an allergen. Allergic reactions that have been reported in patients taking lithium have been attributed to excipients in the formulation (331), as in a case of leukocytoclastic vasculitis (332).

In a brief report, evidence has been presented that short-term exposure to lithium (less than 2 months) caused alterations in the expression of histocompatibility antigens (333).

In 10 healthy volunteers, lithium caused increases in interleukin-4 and interleukin-10 concentrations and falls in interleukin-2 and interferon concentrations (334). In in vitro studies of monocytes from women with breast cancer, lithium chloride suppressed production of interleukin-8 and induced production of interleukin-15 (335,336). The clinical implications of these findings are unclear.

The immunomodulatory effects of lithium have been reviewed (337,338). Lithium

(a) stimulated the production of pro-inflammatory cytokines and negative immunoregulatory cytokines or proteins in nine healthy subjects (339);
(b) altered the expression of human leukocyte antigens (HLA) in 11 of 15 subjects (333);
(c) normalized manifestations of mild immune activation in 17 rapid cycling bipolar patients (340).

The clinical implications of these findings are unclear.

The very complex antiviral and immunomodulatory effects of lithium have been reviewed (341). In 15 inpatients, lithium produced changes in a number of histocompatibility antigens, but whether these have any clinical implications is unknown (342).

Death

The 1997 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System listed nine lithium-associated deaths and provided some clinical details in seven cases, including serum concentrations of 2.4–7.8 mmol/l (343).

Long-Term Effects

Drug abuse

Lithium is not a drug of abuse or dependence, although when one bipolar alcohol abuser was prevented from drinking, he tried to get a "buzz" by increasing his lithium

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dose to the point of toxicity (serum concentration 3.0 mmol/l) (344). The only other suggestion of abuse appeared in 1977 when passing mention to the "fairly recent (over the past 2 years or so) abuse of lithium" by poly-drug abusers (345).

Drug tolerance

In a review of whether the prophylactic efficacy of lithium was transient or persistent, the authors concluded that "the balance of evidence does not indicate a general loss of lithium efficacy" (346). A similar conclusion was reached in a study of 22 patients who had taken lithium for at least 20 years (347). There was no change in affective morbidity over the second 10 years compared with the first 10 years. However, individual exceptions could not be excluded.

Drug withdrawal

Three issues have been addressed:

(a) does rapid withdrawal increase recurrence risk?
(b) how common is post-withdrawal refractoriness to the reinstitution of lithium?
(c) does withdrawal increase the risk of thyrotoxicosis?

Recurrence risk

Abrupt or rapid withdrawal of lithium is not associated with a physical withdrawal reaction, but there does appear to be an increased risk of early recurrence of mania and depression compared with more gradual withdrawal (348,349), although this conclusion has been questioned (350). Data from Italy have suggested that gradual withdrawal of lithium (over 15–30 days) was associated with a markedly reduced risk of early recurrence of mania and depression and a much greater likelihood of prolonged stability compared with rapid discontinuation (over 1–14 days) (348). There was a marked increase in suicidal acts during the first year after lithium withdrawal; after that the risk returned to what it had been before the start of lithium treatment. The increased risk in the first year exceeded that expected from increased affective morbidity alone. There was a 1.95-fold greater risk, during this first year in those who discontinued lithium rapidly, although this was not statistically significant (351).

Of 30 patients with major depressive disorder who had responded to lithium augmentation for antidepressant-resistant depression, 15 were switched to placebo over 1–7 days (352). Two became manic, and it was suggested that lithium withdrawal may have uncovered latent bipolar disorder (353).

When 21 elderly patients with a major depressive episode who had responded to lithium augmentation had lithium withdrawn gradually (over 2–12 weeks), 9 relapsed but none became manic (354). Whether gradual withdrawal protected against withdrawal mania or whether there were no latent bipolar patients in the study is unknown.

A retrospective study of lithium withdrawal in pregnant and nonpregnant women showed similar rates and times of recurrence, including a higher risk of early occurrence with rapid withdrawal (1–14 days) versus gradual withdrawal (15–30 days) (355). How to balance the first trimester fetal risk of greater lithium exposure during gradual withdrawal with the greater maternal risk of potentially devastating relapse after rapid withdrawal remains a challenge.

There is a higher risk of postpartum recurrence of bipolar disorder in women who have discontinued lithium; the protective effect of restarting lithium late in pregnancy or soon after delivery has been emphasized (355).

The observation that rapid or abrupt lithium withdrawal might be associated with a more immediate or higher likelihood of recurrence has gathered further support from a reanalysis of data from a double-blind lithium maintenance study, in which the benefits of low serum concentrations (0.4–0.6 mmol/l) and standard serum concentrations (0.8–1.0 mmol/l) were compared (356). Recurrence rates were greater only in those whose concentrations were abruptly reduced from standard to low at the start of the study. The authors suggested that rapid dosage reduction, rather than a low maintenance concentration itself, accounted for their initial conclusion that standard concentrations were more effective than low concentrations.

Others have concluded that withdrawal mania is "a major and sinister complication of the everyday use of lithium" (357). Withdrawal of effective lithium therapy was associated with an increased risk of suicide and suicidal acts, especially during the first 12 months. Gradual withdrawal (over 15–30 days) was associated with half the rate of suicidal acts compared with more rapid withdrawal (strong trend toward statistical significance) (358).

Refractoriness to retreatment

In 28 patients who had responded to lithium treatment of mania or schizoaffective mania and who had recurrences after withdrawal, there were equally good responses to retreatment with lithium (359). These findings add to the evidence that lithium discontinuation-induced refractoriness is the exception rather than the rule. However, the issue of whether post-withdrawal refractoriness to reintroduction of lithium is a real phenomenon and, if so, how often it occurs continues to be debated (360). Three patients failed to respond to the reintroduction of lithium, despite having had sustained beneficial responses before withdrawal (361).

Risk of thyrotoxicosis

Lithium withdrawal may be associated with an outpouring of thyroid hormone in predisposed individuals; there have been reports of thyrotoxicosis (192) and a thyrotoxic crisis (192) after lithium withdrawal.

- A 37-year-old man who had taken lithium and sulpiride for 14 years and who was a long-time smoker without respiratory symptoms or a history of asthma had lithium withdrawn because of an asymptomatic bradycardia (44 beats/minute) (70). Six weeks later, he developed symptoms of asthma, including nocturnal cough, exertional wheezing, increased airway resistance, and a low FEV1, attributed to lithium withdrawal.

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Mutagenicity

In 18 patients taking benzodiazepines and/or neuroleptic drugs, there were increased chromosomal aberrations and increased sister chromatid exchange, but there were no significant differences between this group and another group of 18 patients taking lithium in addition to benzodiazepines and/or antipsychotic drugs (362).

Tumorigenicity

There is no evidence that lithium causes or promotes the growth of tumors. Since tumors are not rare events over a lifetime, and since lithium is taken for long periods of time, any apparent association is likely to be coincidental.

Second-Generation Effects

Fertility

Intramuscular lithium chloride produced subtherapeutic blood concentrations (by human standards) in male rose-ringed parakeets, but significantly reduced testicular weight and caused widespread degenerative changes in the testes (363). Fertility was not assessed directly.

Pregnancy

The treatment of bipolar disorder during pregnancy and lactation has been reviewed, with reference to lithium-related maternal, fetal, and neonatal toxicity, morphological and behavioral teratogenicity, carcinogenicity and mutagenicity, and miscellaneous effects (364–376). Elsewhere, the effects of lithium, valproic acid, and carbamazepine during pregnancy (377) and drug-induced congenital defects (with only a brief mention of lithium) (378) have been reviewed. A more specific review dealing with the use of drugs during pregnancy in women with renal disease mentioned the need for lithium-dosage reduction in such cases (379).

Pregnancy in bipolar women was found to be a "risk-neutral" condition, in that it neither protected against nor increased episode risk in a comparison of 42 pregnant with 42 nonpregnant women who stopped lithium either rapidly (over 1–14 days) or gradually (over 15–30 days). Stopping lithium was not "risk-neutral," and the risk was especially high in those who stopped rapidly (380) (see also Withdrawal effects). These observations must be balanced against the low but real risk of teratogenesis from first trimester lithium exposure (381).

- A 37-year-old woman with severe bipolar disorder, who continued to take lithium throughout pregnancy, had a normal delivery (382).

Teratogenicity

While there is an increased risk of teratogenesis (particularly cardiovascular) from exposure to lithium in the first trimester, this risk has been overstated initially because of selection bias (380,381,383,384). Subsequently, case-control and cohort studies have substantially reduced, but not eliminated, such concerns (385). The risk of major malformations from exposure to lithium in the first trimester appears to be lower than from exposure to carbamazepine or valproate.

The teratogenic effects of lithium have been reviewed in several articles (364,365,386); two reviews of drug-related congenital malformation briefly mentioned lithium and cardiovascular teratogenesis (378,387). The authors concluded that while the risk of cardiovascular malformation is lower than once believed, it is nevertheless increased.

The cardiovascular teratogenicity of lithium has been summarized in a review of managing bipolar disorder during pregnancy and postpartum (371). While the risk of Ebstein's anomaly is increased, likely 10–20 times more than in the general population, the absolute risk (0.05–0.10%) is small. Fetal ultrasonography was advised at 18–20 weeks of gestation in cases of first trimester lithium exposure (386).

In a review of all pregnancies in Leiden in The Netherlands between 1994 and 2002, none of the 20 children of mothers who had taken lithium had major problems or congenital anomalies (388).

There is no evidence that children exposed to lithium during pregnancy who are born without malformations develop other than normally.

Fetotoxicity

Hypoglycemia, requiring temporary glucagon and glucose supplementation, was noted in a neonate whose mother had taken lithium throughout pregnancy (cord lithium concentration 1.73 mmol/l) (370).

Reports of fetal goiter and a variety of other lithium-related adverse events in newborns have been reviewed (386).

In 20 infants exposed to lithium during labor and delivery, there were higher rates of perinatal complications (65%) and special care nursery admissions (45%) than in nonexposed infants, although most complications were transient (389). An infant who died shortly after birth had oromandibular-limb hypogenesis spectrum which was speculatively attributed to lithium that the mother had taken during most of her pregnancy (390).

A neonate whose mother had taken lithium throughout pregnancy developed a supraventricular tachycardia (240/minute) which was treated successfully with adenosine (391). Another newborn girl exposed to lithium in utero had asymptomatic cardiomegaly that resolved by 1 month of age (226).

Transient polyuria in two newborns was attributed to the lithium their mothers had taken throughout pregnancy (370,391).

Neonates born to mothers taking lithium included a boy with a goiter and chemical hypothyroidism who required temporary treatment with oral thyroxine for 11 weeks (392), a girl with respiratory distress, cardiomegaly, hyperbilirubinemia, nephrogenic diabetes insipidus, and hypoglycemia who responded to various treatments and eventually remitted fully (370), and a preterm infant with a supraventricular tachycardia and temporary polyuria associated with 20% weight loss (391). The mother of the preterm infant developed polyhydramnios during pregnancy, which was attributed to lithium-induced fetal polyuria.

Lactation

Lithium concentrations in breast milk are about 40% of maternal serum concentrations, although the range is

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wide (369,393,394). Because of this, breastfeeding is often discouraged (394), although the authors of a comprehensive review of the use of mood stabilizers during breastfeeding have pointed out that there is a paucity of information to support adverse effects of lithium in breastfeeding infants—one case of toxicity in a 2-month-old with an intercurrent infection (serum lithium 1.4 mmol/l) and one report of lethargy and cyanosis at days 5 and 6 (infant serum concentration 0.6 mmol/l on day 5) secondary to fetal and breast milk exposure. However, there have been only two reports of lithium toxicity attributed to breastfeeding (395,396). Others, however, have stated that "lithium should only be used with great caution . . ." (397); "[breastfeeding by women taking lithium] has been repeatedly discouraged in the literature" (398); ". . . it also seems unwise to expose infants unnecessarily to lithium" (394). Lithium has also been stated to be "an excellent example of a drug that requires monitoring and case-by-case assessment so that nursing mothers can be successfully treated" (393).

In a review of the use of psychotropic drugs during breastfeeding, it was briefly mentioned that lithium was not advisable, but was justified under certain circumstances (399). Lithium was also briefly discussed in a review of xenobiotics and breastfeeding (400).

Breast-milk lithium concentrations were measured in 11 women taking lithium carbonate 600–1,500 mg/day (401). Maternal serum concentrations were available in only three and infant concentrations in two. No infants had adverse effects that could be attributed to lithium, and the authors calculated that infant lithium exposure was low, leading them to challenge the general contraindication to breastfeeding under such circumstances.

In its 2001 Policy Statement, the American Academy of Pediatrics Committee on Drugs modified its earlier contraindication to lithium during breastfeeding by listing it with "drugs that have been associated with significant effects on some nursing infants, and should be given to nursing mothers with caution" (402).

The Motherisk Team in Toronto has recommended use of the Exposure Index (the maternal milk/plasma ratio times 100 divided by the infants' clearance in ml/kg/minute) to determine the advisability of breastfeeding when a mother is taking lithium (396). However, this approach does not seem very practical.

Given the extremely high risk of postpartum recurrence in bipolar patients, the issue is not whether the mother should take a mood stabilizer (she should), but whether the baby should be breastfed. A review of mood stabilizers during breastfeeding reaffirmed that there are only two reported cases of infant lithium toxicity associated with breastfeeding (one of which involved both fetal and breast milk exposure) (395). The following recommendations were made in the case of a mother taking lithium who chooses to breastfeed:

(a) educate her about the manifestations of toxicity;
(b) explain the risks of dehydration;
(c) consider partial or total formula supplements during episodes of illness or dehydration;
(d) suspend breastfeeding if toxicity is suspected;
(e) check infant and maternal serum lithium concentrations.

Susceptibility Factors

Age

Whether elderly patients taking lithium received proper monitoring was questioned in a case note audit of 91 patients, over 40% of whom had deviations from practice standards. These included absence of pretreatment laboratory tests, infrequent monitoring of serum lithium concentrations, lack of adequate adverse effects documentation, and the use of risky concomitant drugs (403). In a placebo-controlled study, there was poor tolerance of lithium augmentation of antidepressants in 76% (13/17) of elderly (mean age 70 years) patients at a mean serum concentration of 0.63 mmol/l, due to tremor and muscle twitches, cognitive disturbance, tiredness and sedation, and gastrointestinal upsets (404).

In a cross-sectional study of 12 octogenarians (average age 84 years) who had taken lithium for an average of 54 months (mean serum concentration 0.42 mmol/l), none became toxic and none had to stop treatment because of adverse effects. Transient renal function abnormalities were noted: one patient developed nephrogenic diabetes insipidus and one became hypothyroidic (405). For lithium therapy in very old people, the authors advised close monitoring in a specialized setting.

Renal disease

While there are no absolute contraindications to lithium, patients with advanced kidney disease or unstable fluid/electrolyte balance may be more safely treated with an alternative mood stabilizer, such as carbamazepine, valproate, lamotrigine, or olanzapine.

Other features of the patient

Factors that put patients at risk of lithium intoxication are those that increase intake (deliberately or accidentally), reduce excretion (kidney disease, dehydration, low sodium intake, drug interactions), or reduce body water (dehydration secondary to fluid restriction, vomiting, diarrhea, or polyuria) (45). Patients with lithium-induced polyuria are at a particular risk of toxicity if their ability to replace fluids is compromised (for example by anesthesia, over-sedation, CNS trauma).

Thyrotoxicosis was considered a possible contributor to lithium toxicity in two patients, possibly by increasing tubular lithium reabsorption through induction of the sodium-hydrogen antiporter (195).

Two patients developed lithium intoxication (serum concentrations 3.3 and 3.0 mmol/l) in association with poorly controlled diabetes mellitus, suggesting that the latter is a risk factor (227).

A review of the effects of obesity on drug pharmacokinetics briefly mentioned that the steady-state volume of distribution of lithium correlated with ideal body weight and fat-free mass but not with total body weight (406). Lithium clearance was greater in those with obesity than in lean controls, suggesting that obese patients may require larger maintenance doses to maintain target serum concentrations.

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Drug Administration

Drug formulations

Despite the availability of modified-release lithium formulations for several decades, there continues to be a paucity of information about their efficacy and tolerability compared with less expensive immediate-release formulations (407).

Brain lithium concentrations (measured by magnetic resonance spectroscopy) after the use of a modified-release formulation (Lithobid SR) or an immediate-release formulation have been compared in a crossover design in 12 patients with bipolar disorder (408). There were higher brain concentrations with the modified-release formulation, but whether this has clinical implications requires further study.

Formulations of lithium carbonate tablets with various binding substances have been discussed (409).

A modified-release formulation (Carbolithium Once-A-Day) produced a reduction in peak/trough lithium ratio compared with a standard formulation (410), and an interim analysis of an open switch to the modified-release formulation suggested better tolerability and efficacy at 4 weeks ($n = 27$) and 6 weeks ($n = 15$) (411). A paucity of detail, however, prevents firm conclusions.

A modified-release multi-particulate lithium capsule has been described consisting of five copolymer-coated prolonged-release tablets and one standard tablet, each 6 mm in size (412).

Following an overdose with a sustained-release formulation (8,000 mg of Teralithe 400 LP), the appearance of clinical symptoms (vomiting and dizziness) was delayed for 35 hours, despite a serum lithium concentration of 2.38 mmol/l at 15 hours and 3.12 mmol/l at 25 hours (413).

A woman taking conventional lithium developed lithium toxicity after two doses of a homeopathic formulation, "Lithium carb. 30"; a paucity of detail allows no conclusions to be drawn from this observation (414).

Drug additives

Gelatin is derived from natural pork and beef products and is present in some lithium formulations. Since certain religions forbid the consumption of gelatin, knowing that it is present in Eskalith capsules and Eskalith CR and absent in Eskalith tablets (not available in the USA) and Lithobid SR might influence prescribing practices under certain circumstances (415). The same would apply to other lithium products.

Drug dosage regimens

In an open-label pilot study of rapid administration of slow-release lithium (20 mg/kg/day in two divided doses) for acute mania, five of 15 patients completed 10 days of treatment, seven improved sooner and were discharged, two withdrew because of adverse effects (bradycardia in one and tremor, fatigue, and diarrhea in the other; and one patient appears not to have been accounted for) two other patients also had asymptomatic bradycardia (74).

A review of loading strategies in acute mania included a section on lithium (416).

A small study of brain lithium concentrations measured by magnetic resonance spectroscopy showed higher brain:serum lithium concentration ratios in subjects taking a single daily dose ($n = 5$) than in those taking a twice-daily regimen ($n = 3$) (417). Even to speculate about the possible clinical implications of this finding would be premature.

Drug administration route

Intravenous

To determine the safety of using lithium chloride dilution to measure cardiac output, the pharmacokinetic and toxic effects of intravenous lithium chloride have been studied in six conscious healthy Standardbred horses (418). The mean peak serum concentration was 0.56 mmol/l. There were neither toxic effects nor significant changes in laboratory studies, electrocardiograms, or gastrointestinal motility. Three horses had increased urine output.

A similar study was performed in patients undergoing cardiac surgery and healthy volunteers; the highest dose of lithium chloride was 0.6 mmol given intravenously five times at 2-minute intervals (419). Unfortunately, no mention was made of tolerability or adverse effects.

When 10 volunteers were given 500 ml of a 0.1% lithium carbonate solution (13.5 mmol of lithium) intravenously over 1 hour, the peak serum concentration was 0.93 mmol/l, the elimination half-life was 7.8 hours, and there were no adverse effects (420).

Drug overdose

There are three forms of lithium overdose:

(a) acute (abrupt overdose in a drug-naïve person);
(b) chronic (gradual accumulation, reaching toxic concentrations);
(c) acute-on-chronic (abrupt overdose by a person already taking lithium), which can also be due to a drug interaction.

Thus, the term overdose (57,421,422) can be misleading, because poisoning can develop not only as a result of overdosage but also by a fall in lithium clearance. Of 205 cases of lithium poisoning reported to the Ontario Canada Regional Poison Information Centre in 1996, 12 were acute overdoses (someone else's tablets), 19 were chronic poisonings, and 174 were acute-on-chronic poisonings. Over 80% had no or minimal symptoms, two patients died, and one had persistent renal sequelae (423). A retrospective study of 97 cases of lithium poisoning treated at a regional center in Australia over 13 years found severe neurotoxicity in 28 cases (26 were cases of chronic and two of acute-on-chronic poisonings) (215). Risk factors were nephrogenic diabetes insipidus, older age, abnormal thyroid function, and impaired renal function.

Early signs of intoxication include ataxia, dysarthria, coarse tremor, weakness, and drowsiness. More advanced toxicity can involve progressively impaired consciousness, neuromuscular irritability (myoclonic jerks), seizures, cardiac dysrhythmias, and renal insufficiency. A reversible Creutzfeldt–Jakob-like syndrome has been described (103). The severity of intoxication depends on both the extent and duration of exposure to raised lithium concentrations, as well as idiosyncratic factors.

When the Marseilles Poisons Centre analysed information on lithium overdose between 1991 and 2000, in

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addition to an unspecified number of suicide attempts and accidental poisonings in children, the next most frequent reports were prescription misinterpretation ($n = 43$), dehydration in the elderly ($n = 35$), renal insufficiency ($n = 15$), and diuretic interactions ($n = 8$) (424).

The 2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System listed six lithium-related deaths (four cases of intentional suicide and two of therapeutic error) and two other deaths in which lithium was not listed as the primary cause (425). A total of 4663 lithium-related exposures were reported, in which death was the outcome in 13 and a major life-threatening event or cause of significant disability in 267.

A chart review of psychiatric hospital admissions between 1990 and 1996 showed that 6.8% of 2210 patients who were given lithium had at least one serum concentration of 1.5 mmol/l or over (43% of these were increased at admission) and of those only 28% had signs and symptoms of toxicity (278).

In another case, following an overdose with a modified-release formulation, the appearance of clinical symptoms (vomiting and dizziness) was delayed for 35 hours, despite a serum lithium concentration of 2.38 mmol/l at 15 hours and 3.12 mmol/l at 25 hours (413).

The distribution of clinical practice guidelines in Northeast Scotland had no impact on whether appropriate action was taken for high serum lithium concentrations (80% before the guidelines, 82% after). There was no significant difference in proper attention to high concentrations between those in primary care alone (77%) and those in shared care (85%) (280).

In a retrospective study of 114 patients admitted to a toxicological ICU with suspected lithium intoxication, 81 had definite intoxication; 78% were deliberate overdoses, and 22% were accidental (due, for example, to renal insufficiency, dehydration, drug interactions, poor compliance, drunkenness). Most were treated conservatively with gastric lavage and forced diuresis; hemodialysis was used only in 3–6%. Two of those who took a deliberate overdose and one of those who took an accidental overdose died (426).

Cases of lithium toxicity in a municipal hospital over a 10-year period involved eight women (mean age 66 years); neurological symptoms were the most common presentations (92). Two were acute overdoses and the rest were chronic intoxications. There was one death (group not specified).

Convincing manifestations of toxicity have occasionally been reported in patients with concentrations within the preferred target range (sometimes called "therapeutic" concentrations) (427). While full recovery is often the case, improvement may lag many days behind the fall in serum lithium concentration. Unfortunately, both persistent neurological damage (characteristically cerebellar) and deaths have occurred. The risk of an adverse outcome from toxicity can be minimized by prompt and comprehensive treatment (428–430), which should include gastric lavage and ion exchange resins for acute overdose, volume expansion to restore fluid and electrolyte balance and improve kidney function, and in severe cases, hemodialysis. Hemodiafiltration has also been used, and while this technique eliminates rebound increases in lithium concentration after dialysis, it is also less efficient than hemodialysis.

The 1998 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System listed three lithium-related fatal exposures (two intentional and one a therapeutic error) and three other fatalities in which lithium was not the primary cause of death. A total of 4486 lithium-related poison exposure cases were reported, in which the outcome was death in five and a major life-threatening event or cause-significant residual disability in 212 (431).

A study of drug intoxication in the south of Brazil reported 2938 cases of drug ingestion, 25 of which involved lithium (including 14 suicide attempts) (432).

Of 133 patients 40 who had begun treatment with lithium died over an observation period of 16 years. Suicide (in 11 cases) was twice as common as in the general population, but it was more likely to occur in lithium noncompliant patients (433). It is important to be aware that suicidal behavior is actually reduced in patients who are compliant with long-term lithium therapy (although still somewhat higher than in the general population).

The 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System included six fatal exposures to lithium, three of which were intentional suicides. A total of 4607 exposures to lithium were reported, and death was the outcome in eight (434). A retrospective review of eight cases of lithium poisoning included one death (92).

Other reports include the following:

- A 71-year-old woman developed lithium toxicity (serum concentration 2.1 mmol/l) because of increased absorption of urinary lithium from the bowel following urinary diversion with ileal conduits for stress incontinence (435).
- A 29-year-old man who overdosed on 8,000 mg of a sustained-release lithium formulation had a serum concentration of 3.12 mmol/l 25 hours later, but only became symptomatic (with vomiting and dizziness) 35 hours later; his symptoms resolved with hemodialysis (413).
- A 72-year-old woman developed an acute confusional state, gait instability, and blepharospasm and apraxia of eyelid opening (24 hours serum concentration 1.8 mmol/l), which resolved after withdrawal (436).
- In the presence of high lithium concentrations (2.6 and 1.6 mmol/l), two patients had high amplitude of the primary complex in median nerve somatosensory evoked potentials, which normalized as concentrations fell (437).
- Two women with lithium toxicity and stormy clinical courses were found to be hyperthyroid (195).
- A 32-month-old boy developed lithium toxicity after ingesting a relative's tablets (438).
- A 46-year-old man became toxic after an initially unrecognized pontine hemorrhage (439).
- A 39-year-old woman took an overdose of lithium tablets, was given a single dose of haloperidol, and developed neuroleptic malignant syndrome (131).
- A 62-year-old woman developed persistent cerebellar and extrapyramidal sequelae at a serum concentration of 3.61 mmol/l (107).

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Management

An all too common treatment error in the face of severe toxicity is "watchful waiting," during which the patient's condition is more likely to worsen than improve.

Hemodialysis (295,440,441), sometimes with additional continuous venovenous hemofiltration dialysis (442,443), continues to be described as a successful intervention for lithium poisoning. Peritoneal dialysis is a far less efficient way to clear lithium from the body. One patient treated in this way had permanent neurological abnormalities and another died; a third toxic patient who also had diabetic ketoacidosis died after treatment with hydration and insulin (444). On the other hand, a 51-year-old woman who took 50 slow-release lithium carbonate tablets (450 mg) had a serum lithium concentration of 10.6 mmol/l 13 hours later, but no evidence of neurotoxicity or nephrotoxicity. She was treated conservatively with intravenous fluids and recovered fully (445). Acute lithium overdose is often better tolerated than chronic intoxication.

Several reports have described severe poisoning responding to treatment that included hemodialysis or hemodiafiltration:

- A 57-year-old man, serum lithium concentration 3.1 mmol/l (446).
- A 52-year-old woman, serum lithium concentration 3.2 mmol/l (446).
- A 58-year-old woman, serum lithium concentration 4.0 mmol/l (76).
- A 52-year-old man, serum lithium concentration 4.6 mmol/l (77).
- A 40-year-old man, serum lithium concentration 5.4 mmol/l (447).
- A 39-year-old man, serum lithium concentration 5.9 mmol/l, with renal insufficiency associated with a polydrug overdose (448).

Some patients recovered from severe intoxication without dialysis:

- A 24-year-old woman, who survived a lithium carbonate overdose (5600 mg; serum concentration 4.0 mmol/l) with conservative treatment (449).
- A 55-year-old woman, serum lithium concentration 4.5 mmol/l, who was left with residual slurred speech (450).
- A 52-year-old woman, serum lithium concentration 10.6 mmol/l after an acute overdose (445).

In a small number of patients for whom hemodialysis was recommended, the outcomes were similar in those who were actually dialysed and those who were not, leading the authors to conclude that dialysis should be reserved for the more severe cases (451).

- Two teenagers with neurological toxicity (serum concentrations 5.4 mmol/l and 4.81 mmol/l) were treated successfully with hemodialysis followed by continuous venovenous hemofiltration, which prevented a post-dialysis rebound in serum lithium concentrations (442).
- An agitated, confused, disoriented 52-year-old woman who took an overdose of lithium recovered fully after high-volume continuous venovenous hemofiltration (452).

In an in vitro study, bentonite was an effective adsorbent of lithium; the authors suggested that it be explored as an overdose treatment (450).

Product monographs written by pharmaceutical companies and published by the Canadian Pharmacists Association in the Compendium of Pharmaceutical Specialties have been reviewed with regard to the adequacy of lithium overdose management advice (453). All five were rated "fair" for listing essential interventions for managing overdose but "poor" for warning against contraindicated interventions, and all contained misleading or dangerous information. All in all, a dismal showing.

Drug–Drug Interactions

General

Drug interactions with lithium have been reviewed (454–458); another review focused on interactions in the elderly (458). A review of drug interactions with lithium considered both pharmacokinetic interactions [for example diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs)] and pharmacodynamic interactions (for example antipsychotic drugs, SSRIs) and summarized the most important ones in tabular form (454).

Alcohol

Excessive use of alcohol can interfere with adherence to lithium therapy. Alcohol does not itself appear to alter lithium pharmacokinetics (459).

Anesthetics

Sinus bradycardia (36/minute) developed in a 44-year-old woman taking lithium who received fentanyl and propofol (65).

Angiotensin converting enzyme (ACE) inhibitors

There have been scattered reports of lithium toxicity associated with the use of ACE inhibitors and attributed to reduced lithium excretion (458,460). This is not a predictable interaction.

- A 57-year-old man developed confusion, lethargy, ataxia, and myoclonus in conjunction with a serum lithium concentration of 2.6 mmol/l 4 days after starting to take captopril 50 mg tds (460).

In rats, ramipril reduced renal lithium clearance and increased fractional lithium reabsorption in association with decreased systolic blood pressure and decreased sodium excretion. These effects were attenuated by icatibant, a specific bradykinin B2 receptor antagonist (461).

Angiotensin-2 receptor antagonists

There have been occasional reports of lithium toxicity in patients taking angiotensin receptor blockers.

- A 58-year-old bipolar woman with previously stable therapeutic lithium concentrations was hospitalized with a 10-day history of confusion, disorientation, and agitation 8 weeks after starting to take candesartan 16 mg/day. Both drugs were withdrawn, the serum

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lithium concentration fell from a high of 3.25 mmol/l, and she was again maintained on her usual therapeutic concentration of lithium (462).
- Lithium toxicity occurred in an elderly patient after the addition of losartan (463).
- A 51-year-old woman developed symptoms of lithium toxicity (serum concentration 1.4 mmol/l) while taking valsartan, which resolved when the valsartan was replaced by diltiazem (serum lithium concentration 0.8 mmol/l) (464).

Anticonvulsants

The combination of lithium with an anticonvulsant mood stabilizer can be beneficial. There have been reports of lithium/carbamazepine neurotoxicity, but on the other hand, lithium can benefit carbamazepine-induced leukopenia. There do not appear to be clinically important pharmacokinetic interactions of lithium with gabapentin (465), lamotrigine, valproate, or topiramate (although one subject did have a 70% fall in lithium concentration) (466). In a review of pharmacokinetic interactions between antiepileptic drugs and psychotropic drugs, there were no clinically significant interactions of lithium with gabapentin, lamotrigine, valproate, or topiramate, although serum lithium concentrations were reduced slightly by topiramate (466).

Although reviews have generally been favorable regarding the combination of lithium with anticonvulsants (466–468), there have been occasional anecdotal reports of possible interactions.

Carbamazepine

Lithium intoxication in a 33-year-old man was attributed to carbamazepine-induced renal insufficiency (469).

A case report suggested an association between lithium and carbamazepine in causing sinus node dysfunction (69).

Lamotrigine

In an open crossover study in 20 healthy men, the serum lithium concentration was slightly lower (0.65 versus 0.71 mmol/l) when lamotrigine 100 mg/day was added for 6 days, but the difference was not statistically significant (470).

Topiramate

In a 42-year-old woman, the serum lithium concentration rose from 0.5 to 1.4 mmol/l after she increased her topiramate dose from 500 to 800 mg/day (471). The authors speculated that topiramate had interfered with lithium excretion. On the other hand, in a crossover study in healthy volunteers, 6 days of treatment with topiramate did not significantly alter serum lithium concentrations; however, the maximum topiramate dose was only 200 mg/day and one subject did have about a 70% fall in lithium C_{max} and AUC (472).

Valproate

In rats, lithium pretreatment reduced the plasma half-life of valproate by 25% and increased urinary excretion of valproate glucuronide (473).

Antidepressants

Adverse interactions of lithium with tricyclic antidepressants, SSRIs, and monoamine oxidase inhibitors have been reviewed (474). In reviews of antidepressants and the serotonin syndrome, a possible contributory role has been suggested for lithium, based on case reports with tricyclic antidepressants, SSRIs, trazodone, and venlafaxine (139,475).

Lithium augmentation of antidepressants is a well-established treatment for resistant depression and is usually well tolerated with all classes of antidepressants, although there have been a few reports of the serotonin syndrome with SSRIs (474). It is possible that shared adverse effects could be magnified by combining lithium with various antidepressants (for example tremor, weight gain, gastrointestinal upset). Hyponatremia secondary to the SIADH has been linked to SSRIs and tricyclic antidepressants, especially in elderly patients, and could predispose to lithium toxicity.

In 28 of 75 patients taking lithium, 24-hour urine volumes were over 3 l/day, and this group had a greater duration of lithium exposure (6.0 versus 3.9 years) (476). There was no relation between polyuria and serum lithium concentrations or dosing regimens, but there was an association with the concurrent use of serotonergic antidepressants (odds ratio 4.25).

Amfebutamone

Although data have suggested that amfebutamone has approximately the same seizure potential as the tricyclic compounds (SEDA-8, 30) (477), the manufacturers reported an increased risk of seizures in patients taking over 600 mg/day in combination with lithium or antipsychotic drugs (SEDA-10, 20) (478).

- A 45-year-old man taking lithium, amfebutamone, and venlafaxine developed a prolonged seizure after ECT, thought to have been caused by a lowering of the seizure threshold due to amfebutamone (although a role of the other two drugs could not be excluded) (123).

Mirtazapine

In a placebo-controlled, crossover study in 12 healthy men, lithium and mirtazapine had no effect on the pharmacokinetics of each other and there was no difference in psychometric testing between the addition of lithium and placebo (479).

Nefazodone

In 12 healthy volunteers, there were no clinically significant alterations in blood concentrations of lithium or nefazodone and its metabolites when the drugs were coadministered (480). The addition of lithium for 6 weeks to nefazodone in 14 treatment-resistant patients produced no serious adverse effects and no dropouts (481). Lithium augmentation of nefazodone in 13 treatment-resistant depressed patients was associated with a variety of annoying adverse effects, but none led to treatment withdrawal (482).

SSRIs

The authors of a thorough literature review of 503 patients treated with lithium and SSRIs (483) acknowledged that

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conclusions would be hedged with qualifications and equivocations but suggested the following:

(a) "when lithium is added to SSRIs new, nonserious, events occur frequently";
(b) "serotonin syndrome is associated with combined lithium/SSRI therapy, but is rare";
(c) "the evidence for the efficacy of lithium add-on to SSRIs is at best provisional".

There was no systematic evidence that SSRIs alter serum lithium concentrations.

Fluoxetine
Lithium toxicity has also been reported during co-administration with fluoxetine (484).

- After 4 hours of mild, intermittent, hot-weather work, a 45-year-old man taking fluoxetine and lithium (serum concentration not mentioned) collapsed, became comatose, convulsed, and was febrile (42°C); consciousness returned after 6 days but cerebellar symptoms and atrophy persisted (485). It was suggested that disruption of temperature regulation had been caused by a synergistic effect of the two drugs (although he had taken neither drug for 36 hours before the episode).

Fluvoxamine
Six patients taking a stable dose of fluvoxamine had a minor increase in plasma fluvoxamine concentration (from 67 to 76 ng/ml) 2 weeks after starting to take unspecified doses of lithium; this is unlikely to be of clinical significance (486).

Paroxetine
Serum lithium concentrations were unchanged when breakthrough depression was treated double blind by the addition of paroxetine (20–40 mg/day, $n = 19$) and the combination was generally well tolerated (487).

- A 20-year-old woman taking lithium and risperidone became catatonic 5–7 days after the addition of paroxetine, leading to speculation that this was due to an interaction between the three drugs (488). Of 17 patients 4 who had paroxetine added to lithium as an adjunctive antidepressant developed symptoms suggestive of emerging serotonin syndrome (for example nausea, vomiting, diarrhea, sweating, anxiety, oversleeping) (489).

Tricyclic antidepressants
Amitriptyline
Serum lithium concentrations were unchanged when breakthrough depression was treated double blind by the addition of amitriptyline (75–150 mg/day, $n = 23$) and the combination was generally well tolerated (487).

- A 34-year-old woman took amitriptyline 300 mg each night for several years (490). Six days after starting to take lithium 300 mg tds, she had several generalized tonic-clonic seizures. A second episode occurred on re-exposure to lithium.

Doxepin
An interaction of lithium with doxepin has been described.

- A 65-year-old man who took lithium and doxepin for 13 years presented with a 6-month history of myoclonic jerking of both arms, which resolved when both drugs were stopped (491).

Whether this represented a drug interaction or a single drug effect is unclear.

Six patients taking a stable dose of fluvoxamine had a minor increase in plasma fluvoxamine concentration (from 67 to 76 ng/ml) 2 weeks after starting to take unspecified doses of lithium; this is unlikely to be of clinical significance (486).

Antimicrobial drugs

Two reviews of drug interactions with antibiotics briefly and incompletely discussed lithium (492,493).

Quinolones

- A 56-year-old man with normal renal function and therapeutic lithium concentrations became toxic (serum concentration 2.53 mmol/l 24 hours after the last dose) with renal impairment (serum creatinine 141 μmol/l; 1.6 mg/dl) within days of starting levofloxacin. Both symptoms and laboratory abnormalities resolved with withdrawal of both lithium and levofloxacin (494).

Trimethoprim

- A 40-year-old woman developed nausea, malaise, impaired concentration, trembling, unsteadiness, diarrhea, and muscle spasm in association with a serum lithium concentration of 2.1 mmol/l while taking trimethoprim 300 mg/day (495).
- A 42-year-old woman developed symptoms of lithium toxicity and a raised serum concentration (2.1 mmol/l) while taking trimethoprim (495).

This interaction may be due to an amiloride-like diuretic effect of trimethoprim, causing lithium retention.

Antipsychotic drugs

In a discussion of drug interactions with antipsychotic drugs, the literature on lithium was reviewed (496). Caution was advised when lithium is combined with antipsychotic drugs, especially with high dosages of high-potency drugs. In a review of acute, life-threatening, drug-induced neurological syndromes, the controversy of whether lithium increases the risk of neuroleptic malignant syndrome was mentioned briefly (497) (see also Nervous system).

While it is still not clear whether there is a unique encephalopathic interaction of lithium with haloperidol, there is a consensus that the judicious use of these two drugs in combination should be safe. In general, caution is advised if lithium is combined with antipsychotic drugs, especially with high dosages of high-potency drugs (496). There have been reports of neuroleptic malignant syndrome in patients taking lithium plus antipsychotic drugs, but a causal relation has not been established (498).

The risk of extrapyramidal adverse effects may be increased when lithium is combined with antipsychotic drugs.

Erythrocyte/plasma lithium concentration ratios were lower in patients taking phenothiazines or haloperidol

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than in those taking lithium alone (499,500), and the former group had a higher incidence of neurological and renal adverse effects (500).

- A 59-year-old man taking lithium, haloperidol, and carbamazepine had impaired memory, impaired attention, and an encephalopathy-like pattern on the electroencephalogram that normalized when haloperidol was withdrawn (501). Olanzapine 5 mg/day was added, and 3 weeks later he became disoriented. Surprisingly, the olanzapine was continued and he remained disoriented.

Amisulpride

In a placebo-controlled, parallel-design, double-blind study in 24 male volunteers, amisulpride 100 mg bd for 7 days did not alter lithium pharmacokinetics (502).

Amoxapine

The neuroleptic malignant syndrome occurred in a 63-year-old man when lithium was added to amoxapine (129).

Aripiprazole

A review of aripiprazole included a brief mention of no apparent pharmacokinetic interaction with lithium (503).

Chlorpromazine

The neuroleptic malignant syndrome in a 49-year-old man was attributed to a combination of lithium and chlorpromazine (504).

Clozapine

Seizures and other neurological effects have been described in a few cases when lithium was added to clozapine (505). Five treatment-resistant patients were treated successfully with a combination of clozapine and lithium with no clinically significant adverse events (506). However, a 59-year-old woman developed neurotoxic symptoms 3 days after lithium was added to clozapine; the symptoms resolved when both drugs were stopped and recurred with rechallenge (507).

- Multisystem organ failure occurred shortly after clozapine was added to a therapeutic dose of lithium in a 23-year-old woman (508). Improvement occurred when clozapine was stopped and the toxicity was attributed to clozapine.

Haloperidol

The neuroleptic malignant syndrome has been described when lithium was added to haloperidol (131).

- A pharmacodynamic drug interaction could not be excluded when a 60-year-old man developed delirium at a serum lithium concentration of 0.97 mmol/l when taking lithium and haloperidol (99).

Olanzapine

The neuroleptic malignant syndrome occurred when lithium was added to olanzapine (130).

- A 13-year-old boy with rhabdomyolysis ascribed to olanzapine was also taking lithium, so that a drug interaction could not be excluded (63).
- A 16-year-old boy developed the neuroleptic malignant syndrome when his olanzapine dose was increased (509).

In a double-blind study of 344 patients inadequately responsive to lithium or valproate who were randomized to olanzapine or lithium for 6 weeks, 21% gained weight on lithium plus olanzapine compared with 4.9% taking lithium and placebo (510). Whether lithium contributed to weight gain in the olanzapine group is unclear.

Quetiapine

In an open study in 10 patients, the addition of quetiapine 250 mg tds did not significantly alter serum lithium concentrations (511).

Risperidone

There were no changes in lithium pharmacokinetics when risperidone was substituted open-label for another neuroleptic drug in 13 patients (512). On the other hand, an 81-year-old man had an acute dystonic reaction 4 days after lithium was added to a regimen of risperidone, valproic acid, and benzatropine (513).

- A 17-year-old man had taken risperidone for 2 years without adverse effects, but 12 weeks after lithium was added, he reported prolonged erections (lasting 1–3 hours) 2–5 times daily; risperidone was tapered and withdrawn and the problem resolved (514).

In an in vitro study, there was no visible precipitate formation when lithium citrate syrup was mixed with risperidone solution (515).

Ziprasidone

In 34 healthy men, ziprasidone did not alter serum lithium concentrations or renal lithium clearance (516).

In a placebo-controlled, open-label study in 25 healthy subjects there were no changes in serum lithium concentration or renal lithium clearance when ziprasidone (40–80 mg/day) was added for 7 days (516).

Anxiolytics

There has been a well-documented case of profound hypothermia in a patient taking lithium and diazepam; it did not occur with either drug alone (517). Otherwise, benzodiazepines and lithium have proven to be compatible.

Calcitonin

Serum lithium concentration should be monitored at the start of calcitonin therapy.

Serum lithium concentrations fell significantly within 3 days of starting calcitonin in four women (518), due to increased renal clearance of lithium (518,519).

After they had received 100 units of salmon calcitonin subcutaneously for 3 days, four patients had a 30% mean reduction in serum lithium concentration, which was attributed to reduced absorption and/or increased renal excretion (518).

Calcium channel blockers

Lithium clearance is reduced by about 30% by nifedipine (520).

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- A 30-year-old man required a reduction in lithium dosage from 1500 to 900 mg/day to maintain his serum lithium concentration in the target range shortly after he started to take nifedipine 60 mg/day (521).

There have been reports of neurotoxicity, bradycardia, and reduced lithium concentrations associated with verapamil (522–524).

Ciclosporin

In rats, lithium chloride alone had no significant renal toxicity, but when it was combined with ciclosporin, the renal toxicity of the latter was worsened (525). There was also a strong ciclosporin dose-dependent increase in serum lithium concentrations (tenfold at the highest dose).

Diuretics

The effects of lithium can be enhanced by sodium depletion caused by any diuretic.

Osmotic diuretics increase lithium clearance, the change being proportional to the increased rate of urine flow.

Acetazolamide increases lithium renal clearance (526).

Furosemide can cause lithium toxicity by inhibiting the tubular excretion of lithium ions (527).

Thiazide diuretics predictably reduce renal lithium clearance and increase the risk of toxicity (528). The same may be true of potassium-sparing diuretics, although this is less well established.

- A 26-year-old woman had been stable on lithium (serum concentration 1.1 mmol/l), but after taking herbal diuretics for 2–3 weeks developed manifestations of lithium toxicity (serum concentration 4.5 mmol/l) (529).

Laxatives

Certain bulk-forming laxatives, such as ispaghula husk and psyllium, can impair the absorption of lithium (530).

Mazindol

There have been reports of lithium toxicity associated with the use of the appetite suppressant mazindol.

- A woman stabilized on lithium developed toxic symptoms 3 days after starting the appetite suppressant mazindol. After 9 days, her serum lithium concentration was 3.2 mmol/l (531).
- A 58-year-old woman developed lithium toxicity (serum concentration 3.2 mmol/l) after the addition of mazindol (532).

Methyldopa

There have been occasional reports of neurotoxic symptoms when methyldopa was combined with lithium, both with and without an increase in serum lithium concentration (533).

Metronidazole

Nephrotoxicity due to lithium was reportedly exacerbated by metronidazole (534).

Neuromuscular blocking drugs

A few cases of potentiation of the neuromuscular blocking effects of suxamethonium and pancuronium were reported about 30 years ago (535,536) and have been reviewed (537).

Nonsteroidal anti-inflammatory drugs

The interaction of NSAIDs with lithium has been reviewed briefly (538). Most NSAIDs, although perhaps not all (for example aspirin, sulindac), if given in sufficient dosages for sufficient time, can increase the serum lithium concentration, sometimes to the point of toxicity (539).

A review of drug interactions with analgesics in the dental literature concluded that NSAIDs should be used briefly, if at all, in patients taking lithium, especially in the elderly (538).

A review of the psychiatric effects of NSAIDs included a section on renal function and lithium clearance (540).

COX-2 inhibitors

In one study, there was a mean increase of only 17% in healthy volunteers taking celecoxib 200 mg bd (541). When celecoxib was co-administered with lithium, celecoxib concentrations were higher for the first 6 hours after the dose but the AUC was not altered significantly (542). In another review it was mentioned that clinically significant interactions with lithium (increased lithium concentrations) had been identified, but no detail was presented (543). Both celecoxib and naproxen reduced the renal clearance of lithium (used as a measure of proximal tubular sodium reabsorption) (544).

There have been several reports of raised serum lithium concentrations and neurotoxic symptoms when COX-2 inhibitors (celecoxib and rofecoxib) were added to an otherwise stable lithium regimen (75)(545,546). In 10 patients taking lithium who took rofecoxib 50 mg/day for 5 days serum lithium concentrations increased in 9 and reached 1.26, 1.47, and 1.63 mmol/l in three (details not provided) (547).

- A 44-year-old woman taking nimesulide and ciprofloxacin developed lithium intoxication (serum concentration 3.23 mmol/l) complicated by renal insufficiency; the interaction was attributed to nimesulide (548).

All in all, the COX-2 inhibitors appear to be similar to non-selective NSAIDs with regard to the likelihood of increasing lithium concentrations.

Diclofenac

Diclofenac increases serum lithium concentrations by impairing its renal excretion (549).

- The serum lithium concentration nearly doubled to 1.3 mmol/l after a 57-year-old woman started to take diclofenac (550).

Ibuprofen

Ibuprofen can increase the serum lithium concentration (SEDA-13, 81) (551,552).

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- A man of unspecified age developed cognitive impairment and a serum lithium concentration of 2.4 mmol/l after taking ibuprofen for shoulder pain (553).

Ketorolac
Reports of lithium neurotoxicity resulting from interaction with ketorolac have been published (SEDA-22, 117) (554). In five male volunteers, ketorolac 10 mg qds for 5 days increased lithium AUC by 24% and increased the incidence and severity of lithium-related adverse effects (555).

Mefenamic acid
Mefenamic acid may have interacted with lithium in a patient with reduced renal function (SEDA-13, 83) (556).

Meloxicam
In 16 subjects, meloxicam 15 mg increased plasma lithium concentrations by 21% (range −9 to 59%) and reduced total plasma lithium clearance by 18% (557).

Naproxen
There were no significant changes in serum lithium concentrations in 12 men taking over-the-counter doses of naproxen (220 mg tds) or paracetamol (650 mg qds) for 5 days (558).

Piroxicam
Piroxicam may interact with lithium (559–561).

Sulindac
Unlike other NSAIDs, sulindac supposedly does not interact with lithium (SEDA-10, 82). However, there has been a report of a toxic increase in serum lithium concentration in a 23-year-old man and a 27-year-old woman (to 2.0 and 1.7 mmol/l respectively) (562).

Tenidap
Tenidap increased serum lithium concentrations by reducing its renal clearance (563).

Plantago species

Plantago seeds are widely used as bulk laxatives under the names of psyllium (from *P. psyllium* or *P. indica*) and ispaghula (from *P. ovata*). The possibility that the intestinal absorption of lithium and other drugs may be inhibited should also be considered (534).

Sumatriptan

The 1996 Canadian Product Monograph for sumatriptan (but not the 1998 US package insert) listed the combination of sumatriptan and lithium as contraindicated. However, in a review, there was little evidence of a severe interaction of sumatriptan with lithium (564).

Xanthines

Renal lithium clearance is increased and serum lithium concentrations are reduced by theophylline and aminophylline (496).

Caffeine increases renal lithium clearance (565), and there have been case reports of caffeine withdrawal leading to increased serum lithium concentrations, assumed to be due to reduced renal lithium clearance (565).

Food–Drug Interactions

In 12 healthy men, there was no food-induced change in the systemic availability of a sustained-release lithium formulation that used an acrylic matrix of Eudragit RSPM as a sustaining agent (566).

Other Environmental Interactions

Dietary restriction of sodium causes lithium retention and an increased risk of toxicity. The same would be true of a diet that markedly restricted fluid intake. In brief, dietary extremes should be avoided.

Electroconvulsive therapy

While electroconvulsive therapy (ECT) does not alter serum lithium concentrations, the risk of prolonged confusion after ECT can be increased in the presence of lithium (567). However, there is no universal agreement about this association (568), and there may be circumstances that justify the continuation of lithium during ECT (569,570).

Interference with Diagnostic Tests

Serum lithium measurement

The inadvertent use of lithium heparin as an anticoagulant in the collection tube will lead to a spuriously high serum lithium determination.

- A 33-year-old woman was admitted to an intensive care unit after ingesting unknown quantities of a variety of medications, including lithium. She remained asymptomatic, except for drowsiness, despite serum lithium concentrations of 2.7, 3.1, 3.6, and 5.6 mmol/l. The latter concentration was discovered to be spuriously high when it was realized that blood had been collected in a lithium-heparin anticoagulant tube. When the test was repeated using the proper collection tube, the concentration was 2.2 mmol/l (571).
- A similar problem occurred in a 20-month-old with recurrent convulsions, who had an apparent serum lithium concentration of 3.2 mmol/l. The absence of lithium in the urine prompted further investigation and the source of the lithium was found to be from the use of a lithium-heparin collection tube (572).

Ageing of ion-selective electrodes has been reported to give inaccurately high serum lithium concentration. In one case, a concentration of 0.4 mmol/l was reported in a patient who was not taking lithium (573). The possibility that other substances could interfere with ion-selective electrode lithium analysis has been briefly reviewed (574).

Contamination of lithium heparin blood culture bottles with *Pseudomonas fluorescens* led to an outbreak of pseudobacteremia and the unnecessary treatment of a

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number of children with antibiotics. Lithium had no direct role in this misadventure (575).

In blood samples from 32 subjects, TSH and free T4 concentrations were no different in collection tubes that contained a lithium heparin anticoagulant compared with dry tubes, but free T3 concentrations were significantly lower (576).

Lithium treatment of adolescents with bipolar disorder and secondary substance abuse improved both conditions (577). It was suggested, however, that lithium-induced polyuria may have diluted urine to the extent that false negative test results were obtained when screening for drugs of abuse (578). While the number of positive urine tests was actually higher (but not significantly so) in those with polyuria (579), there is still a possibility that lithium-induced diabetes insipidus could increase the frequency of false negative urine drug assays, because of urine dilution.

Diagnosis of Adverse Drug Reactions

When a split hair sample from a healthy volunteer was sent to six commercial laboratories in the USA for trace mineral analysis, marked variations in results were found (including lithium concentrations), leading to the conclusion that such analyses were unreliable (580).

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Lobeline

General Information

Lobeline is derived from the plant *Lobelia inflata* (Indian tobacco). It is both an agonist and an antagonist at nicotinic receptors, although it is not structurally related to nicotine (1). It inhibits nicotine- and amphetamine-induced dopamine release by interacting with the tetrabenazine-binding site on the monoamine transporter. It also inhibits dopamine re-uptake. It has been used in smoking cessation, but is ineffective (2).

Nausea, vomiting, coughing, tremor, and dizziness have been noted with an average dose of lobeline. It can also cause nausea, sweating, and palpitation when inhaled from a cigarette.

Drug Administration

Drug overdose

Profuse sweating, paresis, tachycardia, hypotension, hypothermia, convulsions, coma, and death can occur in overdosage.

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Local anesthetics

General Information

Local anesthetics typically contain a hydrophilic tertiary amine group linked to a lipophilic ester or amide. The most commonly used local anesthetics are either amides or esters, as shown in Table 1. The aminoester anesthetics cause adverse reactions more commonly than local anesthetics in the amide group. The esters are typically metabolized by de-esterification by esterases, such as pseudocholinesterase in the plasma or esterases in the liver. Metabolism occurs rapidly, and so these agents have short durations of action after they reach the systemic circulation. The amides are mainly metabolized in the

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liver, by *N*-dealkylation followed by oxidation by CYP isozymes. Metabolism of these drugs occurs more slowly.

The potency of a local anesthetic depends on its lipophilicity (Table 2) (1); the more lipophilic, the more potent.

Local anesthetics can be classified as follows (2):

(a) low potency, short duration of action (for example procaine);
(b) intermediate potency, intermediate duration of action (for example lidocaine, prilocaine);
(c) high potency, long duration of action (for example ropivacaine).

Local anesthetics have a wide range of effects. They inhibit sodium, potassium, and calcium ion channels, alpha-adrenoceptors, and phosphatidylinositol signalling. They also cause dysrhythmias when injected directly into the brain. Local anesthetics are also mitochondrial poisons and impair oxidative phosphorylation.

The adverse effects of local anesthetics are well established (3,4). The safety advantages claimed for newer agents have to be treated with much reserve. With increasing experience, discovery of optimal doses, and understanding of potency differences, the tolerability of newer agents is often found to be similar to that of substances that have been used for much longer.

The adverse effects of local anesthetics fall broadly into four groups (5):

(a) Effects attributable to the technique itself rather than to the agent used, for example needle damage to a vessel or nerve.
(b) Local and regional effects of the drug, which may be related to its anesthetic activity or a consequence of irritation or allergy.
(c) Systemic effects, most usually seen if the agent is inadvertently injected into a blood vessel in sufficient quantities.
(d) Effects of additives, notably vasoconstrictors to prolong the local effect, hyaluronidase to promote penetration, and preservatives to prevent bacterial contamination or degradation (6).

The possibility must always be anticipated that when a local anesthetic is administered, some of it will reach organs or tissues for which it was not originally destined, either because it has been incorrectly administered or because some anatomical or other idiosyncrasy of the patient has resulted in unexpected diffusion or leakage of the agent beyond its intended location. The main problems that result relate either to effects on the nervous system or adverse effects resulting from unintended entry into the general circulation. Very occasionally, infections are transmitted (SEDA-16, 129).

Systemic toxicity is most likely to occur if a local anesthetic is accidentally injected into a vessel in sufficient quantity (7). Even with appropriate local administration, there is inevitably some diffusion of the local anesthetic into the body from the site at which it is applied, varying with local blood flow and the technique; intercostal block, for example, rapidly produces high plasma concentrations, while subcutaneous infiltration leads to much lower concentrations more slowly. The amount of local anesthetic used is another contributory factor.

Although the effects are usually mild, systemic toxicity related to local anesthesia can be fatal: in one study of 53 deaths after the use of local anesthetics there was no evidence of allergy (SED-11, 217) (8). In preventing systemic complications from local anesthesia, such measures as close monitoring of patients, the administration of intravenous fluids before major regional block, the immediate availability of drugs and equipment to treat systemic toxicity, preoxygenation, injection of a test dose, and incremental dosing are important measures.

Some distinction must be made between the main groups of local anesthetics as to the frequency of complications. Hypersensitivity reactions, for example, are relatively less common with the aminoamides, such as bupivacaine, cinchocaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine, than with the aminoesters. However, the systemic toxic effects of individual local anesthetics differ: bupivacaine, cinchocaine, and tetracaine are the most toxic. Furthermore, the individual characteristics of the patient (for example age, sex, body weight, and cardiac, renal, and hepatic function) are important (SEDA-17, 134).

The early recognition of complications can be very difficult if a local anesthetic is administered during

Table 1 Structural groups of some commonly used local anesthetics (durations of action in parentheses)

Amides
Articaine
Bupivacaine (2–8 hours)
Cinchocaine (2–3 hours)
Etidocaine (2–6 hours)
Levobupivacaine
Lidocaine (1–2 hours)
Mepivacaine (1.5–3 hours)
Prilocaine (1–2 hours)
Ropivacaine (4–6 hours)
Esters of benzoic acid
Cocaine
Esters of meta-aminobenzoic acid
Proxymetacaine
Esters of para-aminobenzoic acid
Benzocaine
Chloroprocaine
Oxybuprocaine
Procaine (30–45 minutes)
Propoxycaine
Tetracaine

Table 2 Partition coefficients (*n*-octanol/water) of some local anesthetics

Local anesthetic	Partition coefficient
Benzocaine	1.44
Procaine	2.51
Mepivacaine	2.69
Prilocaine	2.73
Lidocaine	3.40
Bupivacaine	4.05
Etidocaine	4.19
Tetracaine	4.32
Oxybuprocaine	4.38

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general anesthesia, to prevent postoperative pain, since unconscious or sedated patients will not recognize the early signs of problems, such as traumatic paresthesia (9).

In a general review of the systemic toxicity of local anesthetics interesting trends were identified (10). The incidence of systemic toxicity has been falling during the last 20 years, most probably due to increased awareness of the potential cardiotoxicity of long-acting aminoamide local anesthetics. Steps to guard against unintentional intravascular injection have been increasingly used. These include aspiration, incremental injection, dose limitation, and the use of test doses. The most studied test dose is adrenaline 15 micrograms, which reliably produces a tachycardia in healthy subjects within 20 seconds of intravascular injection. Specifically, the incidence of cardiotoxicity has also fallen; several case series of systemic toxicity have been published in recent years, reporting only nervous system toxicity but no cases of cardiotoxicity. This contradicts previous estimates of the risk of cardiotoxicity, which suggested an incidence of 10% of all systemic toxicity reactions, reconfirming the impression of increased carefulness of healthcare professionals.

Organs and Systems

Cardiovascular

Cardiovascular complications are not uncommon in the course of local anesthesia; however, most changes are moderate, involving mild peripheral vasodilatation and reduced cardiac output with a change in heart rate.

Local anesthetics reduce myocardial contractility and rate of conduction (11). They also cause direct vasoconstriction or vasodilatation of vascular smooth muscle (12) and central stimulation of the autonomic nervous system (13).

Cardiac arrest and marked myocardial depression, in which hypoxia plays a critical role, have been reported.

Cardiovascular collapse can be severe and refractory to treatment; most fatal cases involve bupivacaine.

The cardiovascular system is more resistant to the toxic effects of local anesthetics than the nervous system. Mild circulatory depression can precede nervous system toxicity, but seizures are more likely to occur before circulatory collapse. The intravenous dose of lidocaine required to produce cardiovascular collapse is seven times that which causes seizures. The safety margin for racemic bupivacaine is much lower. The stereospecific levorotatory isomers levobupivacaine and ropivacaine are less cardiotoxic, and have a higher safety margin than bupivacaine, but not lidocaine; in the case of ropivacaine this may be at the expense of reduced anesthetic potency (14,15). Toxicity from anesthetic combinations is additive.

A comparison of the cardiotoxicity of the two stereoisomers of ropivacaine and bupivacaine on the isolated heart showed that both compounds had negative inotropic and negative chronotropic effects irrespective of the stereoisomer used, but bupivacaine had greater effects compared with ropivacaine at equal concentrations (16). Atrioventricular conduction time showed stereoselectivity for bupivacaine at clinical concentrations; the R(+) isomer had a greater effect in lengthening atrioventricular conduction time, but the less fat-soluble ropivacaine only showed stereoselectivity at concentrations far greater than those used clinically. Similar to the negative inotropic and chronotropic effects, bupivacaine produced greater effects on atrioventricular conduction time than ropivacaine at equal concentrations. This important study has confirmed speculations that not only the stereospecificity of ropivacaine but also its physicochemical properties contribute to its cardiac safety.

Current concepts of resuscitation after local anesthetic cardiotoxicity have been reviewed (17). Vasopressin may be a logical vasopressor in the setting of hypotension, rather than adrenaline, in view of the dysrhythmogenic potential of the latter. Amiodarone is probably of use in the treatment of dysrhythmias. Calcium channel blockers, phenytoin, and bretyllium should be avoided. In terms of new modes of therapy targeted at the specific action of local anesthetics, lipid infusions, propofol, and insulin/glucose/potassium infusions may all have a role, but further research is necessary.

Nervous system

Central nervous system effects of low concentrations of local anesthetics are mainly sedation and confusion; high concentrations are more likely to cause seizures (18).

The first sign of systemic toxicity can be mild sedation or diminished alertness. Dizziness, tinnitus, metallic tastes, muscle twitching, perioral numbness, visual disturbances, disorientation, and light-headedness are the most frequently reported adverse nervous system effects (19).

However, as the blood concentrations achieved are sometimes higher than one would anticipate, toxicity can occasionally prove much more severe than expected, for example frank convulsions, sometimes progressing to respiratory arrest and loss of consciousness. The management of local anesthetic-induced convulsions has been reviewed (20).

Local anesthetic-induced seizures have been reported more often with bupivacaine, particularly in combination with chloroprocaine (SEDA-20, 123). Ropivacaine-induced seizures have also been reported (21,22).

Severe seizures have been reported after topical use of TAC, a combination of tetracaine, adrenaline, and cocaine, in children (23,24).

Endocrine

Local anesthetics generally have only slight endocrine and metabolic adverse effects, without clinical repercussions.

Hematologic

Methemoglobinemia has been reported with benzocaine, Cetacaine (a mixture of benzocaine, butyl aminobenzoate, and tetracaine), cocaine, lidocaine, novocaine, and prilocaine. Acquired methemoglobinemia can result from exposure to chemicals that contain an aniline group, such as benzocaine and procaine, or to those that are transformed to metabolites that contain an aniline group, such as lidocaine and prilocaine. Toxic blood concentrations of local anesthetics, aberrant hemoglobin, and NADH-methemoglobin reductase deficiency are critical

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factors that favor the onset of methemoglobinemia. However, methemoglobinemia can occur even in the absence of such risk factors. Young children are most likely to experience clinical effects, but topical use (for example of Cetacaine) has very occasionally caused severe problems even in adults (25). Intravenous methylthioninium chloride (methylene blue) 1–2 mg/kg and oxygen are usually recommended when methemoglobinemia exceeds 30%.

There have again been several reports of methemoglobinemia following topical anesthesia (26,27). Most have been associated with topical benzocaine, and the patients recovered fully after the administration of methylthioninium chloride.

- A neonate born at 24 weeks had a rectal biopsy under general anesthesia and was intubated with an endotracheal tube that had been lubricated with lidocaine jelly 1 g and after the biopsy a rectal pack soaked in about 1 g of benzocaine lubricant; 30 minutes after surgery she developed cyanosis, with a methemoglobin concentration of 45% (28).

The authors postulated that either local anesthetic could have been responsible, but that the oxidant effects of the two agents may have been additive. They highlighted the need for awareness of seemingly minor uses of medications in neonates.

Liver

Reduced hepatic clearance, as well as relative overdosage, of local anesthetics can lead to systemic toxicity, as illustrated by three patients who underwent topicalization of the oropharynx for transesophageal echocardiography with lidocaine 10% spray or 2% viscous and subsequently became confused and drowsy (SEDA-21, 135).

Immunologic

Systemic hypersensitivity reactions are not a frequent problem in local anesthesia. Systemic toxicity or allergy to additives (hyaluronidase, bisulfate, parabens) has sometimes been mistakenly classified as hypersensitivity to local anesthetics (SEDA-17, 135) (29). Well-documented case reports are very few, relating particularly to the older aminoesters; this appears to be because these agents have the highly antigenic para-aminobenzoic acid as a metabolite (SEDA-l3, 98). The incidence of true allergy is actually very low, probably less than 1% of all the adverse effects attributable to these substances (SEDA-20, 123).

Allergic reactions to aminoamide local anesthetics are unusual, but type I hypersensitivity reactions are described, and life-threatening anaphylaxis can rarely occur (SEDA-21, 136) (SEDA-22, 134). Cross-reaction between amides also occurs, for example articaine, bupivacaine, lidocaine, and prilocaine (SEDA-22, 134).

Type IV delayed hypersensitivity reactions are uncommon, but allergic contact dermatitis and localized erythema and blistering have been reported (SEDA-21, 136).

- A 58-year-old man with a urological stoma used a catheter lubricated with Braum Monodose ointment (30). After almost 2 years, he developed severe pruritus and squamous erythematous plaques in the peristomal skin. Patch tests were positive with the lubricant ointment and one of its constituents, tetracaine.

Both anaphylactoid reactions and bronchospasm have occasionally been reported, although the latter may have been due to sympathetic nervous blockade leading to unopposed parasympathetic effects (SEDA-18, 143) (31).

Contact hypersensitivity also occurs. Benzocaine is a potent skin sensitizer, and several cases of contact dermatitis to lidocaine have been reported. In many cases there is no cross-reactivity between different local anesthetics.

- A 79-year-old man developed a weeping dermatitis of the perianal skin, buttocks, and proximal thighs (32). In the previous 3 weeks, he had used Proctosedyl cream which contains cinchocaine (dibucaine). Patch tests were positive with Proctosedyl cream and 5% cinchocaine in petrolatum, while benzocaine, lidocaine, and clioquinol were negative.
- A 62-year-old woman had a systemic contact dermatitis several days after topical administration of DoloPosterine ointment for hemorrhoids (33). She had erythematous vesicular lesions on her perianal area and an edematous erythematous rash on her upper thighs, elbow flexures, axillae, and face. Patch tests with the ointment and its constituents were positive with DoloPosterine and dibucaine 5% in petrolatum; patch tests with benzocaine and other local anesthetics were negative.
- A 71-year-old Japanese man developed an itchy erythematous papular eruption after using an over-the-counter medicament for skin wounds (Makiron) for 1 month (34). Patch tests with the constituents showed positive reactions to dl-chlorphenamine maleate and cinchocaine hydrochloride (both 1% in petrolatum). Patch tests with lidocaine hydrochloride and mepivacaine hydrochloride showed no cross-sensitization.

However, some sensitized patients do cross-react with various related local anesthetic agents or chemically similar compounds, including some muscle relaxants (SEDA-15, 117). On the other hand, cross-reactivity between aminoesters and aminoamides seems unlikely and does not appear to be on record. Although cross-reactivity between amide local anesthetics is uncommon, it has been reported.

- A 26-year-old woman, 6 months pregnant, developed local redness and itching after exposure to topical agents containing lidocaine, and a further similar reaction to bupivacaine, also with swelling, 8 hours after injection (35). She had a history of anaphylaxis to an unidentified agent, and a patch test was performed using mepivacaine, lidocaine, and ropivacaine; all resulted in strong reactions after 48 hours, while patch testing was negative with chloroprocaine. She subsequently had a cesarean section under spinal anesthesia with chloroprocaine with no adverse reaction.
- A 39-year-old man was investigated for three episodes of facial swelling following dental procedures over 2 years. The swelling always occurred on the same side as the dental procedure and about 12 hours after it, took a couple of days to resolve, did not respond to

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antihistamines, and was not associated with a rash, laryngeal edema, or bronchospasm. He was admitted twice and treated with intravenous antibiotics for cellulitis. He also reported a history of a rash after penicillin but no previous reactions to local anesthetics. All blood tests, including full blood count, C3 and C4 concentrations, and C1 esterase inhibitor activity and function were normal; an antinuclear antibody test was negative, IgE concentrations were not raised, and latex-specific IgE was not detected. Skin prick, intradermal, and subcutaneous tests were carried out with isotonic saline, lidocaine, prilocaine, and procaine; these did not show immediate reactions, but 2 days later a wheal appeared at the lidocaine site. There was a less intense reaction with prilocaine and none with saline or procaine.

The authors concluded that sensitization to lidocaine must have taken place during previous procedures and that cross-reactivity with another amide type local anesthetic, prilocaine, had also occurred.

Contact dermatitis was reported in three hemodialysis patients who used Emla cream repeatedly as analgesia for AV fistula cannulation (SEDA-21, 136).

Twenty patients with a prior history of generalized and/or local skin reactions after local anesthetics were examined with intradermal testing and patch testing; in 10 of them a lymphocyte transformation test was performed to investigate whether they had T cell sensitization to local anesthetics, which might have been responsible for their symptoms (36). Only two had a positive intradermal test, whereas six had a positive patch test and six had a positive lymphocyte transformation test, suggesting that allergic skin symptoms could be mediated by T cells in some patients who do not have evidence of an IgE-mediated reaction.

- A 20-year-old woman, who had had eight previous uneventful exposures to local anesthetics for dental procedures, received an injection of 1% lidocaine for treatment of an in-growing toenail; 12 hours later she developed widespread urticaria lasting a week accompanied by bronchospasm and abdominal discomfort (37). A skin prick test gave a slight positive reaction, and later a positive intradermal injection provided evidence of a true type I hypersensitivity reaction. Following negative skin and intradermal tests with prilocaine, subsequent dental treatment 12 months later was performed using prilocaine with no untoward effects.
- A 70-year-old woman received a peribulbar block using 10 ml of 2% lidocaine, 0.75% bupivacaine (50/50), and hyaluronidase 500 units for cataract extraction; 12 hours later she awoke with a painful, swollen eye (38). There was marked swelling, erythema, tenderness of the eyelids, and a tense orbit, with reduced visual acuity, marked restriction of eye movements, and conjunctival chemosis. There was no hematoma or evidence of infection, but allergy could not be ruled out. Four days later, she received tetracaine eye drops and local infiltration with lidocaine for further suturing and again developed similar symptoms and signs in that eye, with swelling extending to the cheek; follow-up showed persistent ocular dysfunction.

The second patient had had previous exposure to prilocaine, lidocaine, and bupivacaine without problems. The author proposed a diagnosis of lidocaine allergy, although hyaluronidase as the antigen could not be excluded.

- A 23-year-old woman developed an allergic contact dermatitis after applying an over-the-counter proprietary antipruritic jelly containing 0.1% cinchocaine chloride, and a "caine" mixture (5% benzocaine, 1% cinchocaine hydrochloride, 1% procaine hydrochloride) (39). She had positive patch testing to both components.

Allergic reactions attributed to local anesthetics can be due to excipients in the formulation (40).

- A 69-year-old woman developed hypesthesia of all four limbs lasting several hours after three gastroscopies using lidocaine jelly; although the symptom was not typical of an allergic reaction, intradermal tests and nasal provocation tests were performed. The intradermal tests were negative, but the nasal provocation tests were positive for carboxymethylcellulose, a suspending agent used in lidocaine jelly; this caused ipsilateral nasal congestion and dysesthesia of the tongue and the ipsilateral temporal region within 30 minutes. A drug-induced lymphocyte stimulation test was also positive for carboxymethylcellulose.

Hypersensitivity to carboxymethylcellulose may have contributed to this patient's unusual symptoms.

The use of skin testing to identify a causative drug allergen has been repeatedly advocated by several groups, but their advice has not always been followed. Intradermal testing can be helpful in distinguishing between safe and unsafe agents in patients with a history of allergy to local anesthesia.

Various types of immunodepressant effects of local anesthetics can be detected by laboratory testing, although they may have no clinical significance. Lidocaine dose-dependently inhibits EA rosetting by human lymphocytes. In vitro depression of human leukocyte random motility and phagocytosis has also been reported (SED-11, 220) (41).

When injected into the skin, local anesthetics often cause pseudo-allergic reactions, with similar symptoms to immediate type allergy (42). However, true immediate hypersensitivity to local anesthetics is extremely rare.

- A 50-year-old man had local infiltrations a few days after an injection of lidocaine and dexamethasone (43). Prick and intradermal tests were negative after 20 minutes. However, lidocaine produced a positive patch test after 2 days, with erythema and papules.

Second-Generation Effects

Fertility

The use of in vitro fertilization has raised the question of whether the use of local anesthetics during oocyte removal is innocuous or not. Pharmacological concentrations of anesthetic agents are found in follicular fluid (44). No clinical effects have been noted, but knowledge of the behavioral effects of lidocaine on offspring in rats must cause some concern (SEDA-15, 117).

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Pregnancy

It seems most unlikely that local anesthetics have any adverse effect on the fetus when used during pregnancy (45). However, the risks of local anesthetic toxicity may be greater in pregnancy because an increase in the unbound fraction of local anesthetic and physiological changes increase the transfer of local anesthetic into the central nervous system. The authors of a report of systemic symptoms in a pregnant patient suggested the precautionary use of a lower dose of local anesthetic than usual and a longer tourniquet time, to increase the safety of this technique during pregnancy (46).

Susceptibility Factors

Age

Children

Neonates and infants absorb local anesthetics more rapidly after topical application to the airways, and peak plasma concentrations can be reached within 1 minute of application. In the first few months of life they have a larger volume of distribution, reduced hepatic clearance, and lower concentrations of albumin and alpha$_1$-acid glycoprotein (47).

Drug Administration

Drug administration route

Local anesthetics can be given by many different routes, each of which has its own particular adverse effects. In this section the following routes of administration are covered:

- Brachial plexus anesthesia
- Buccal anesthesia
- Caudal anesthesia
- Cervical plexus anesthesia
- Dental anesthesia
- Digital anesthesia
- Epidural anesthesia
- Intercostal nerve anesthesia
- Interpleural anesthesia
- Intra-articular anesthesia
- Intradermal anesthesia
- Intrathecal (spinal) anesthesia
- Intravenous regional anesthesia
- Laryngeal anesthesia
- Lumbar plexus anesthesia
- Nasal anesthesia
- Neck anesthesia
- Obstetric anesthesia
- Ocular anesthesia
- Oropharyngeal anesthesia
- Otic anesthesia
- Paravertebral anesthesia
- Perianal anesthesia
- Peritonsillar anesthesia
- Respiratory anesthesia
- Sciatic nerve anesthesia
- Stellate ganglion anesthesia
- Subcutaneous anesthesia
- Submucosal anesthesia
- Urinary tract anesthesia

Brachial plexus anesthesia

The systemic complications of brachial plexus anesthesia are similar to those seen with others if sufficient drug enters the circulation. Injections outside the axillary sheath result in higher plasma concentrations of local anesthetic than intrasheath injection (SEDA-22, 135). However, several other complications are specific to this route. Local complications include hematoma and infection. Horner's syndrome, temporary phrenic nerve blockade, and peripheral neuropathies have been reported (SEDA-18, 142).

The adverse effects of ropivacaine and bupivacaine have been compared in 104 patients who received 30 ml of either 0.75% ropivacaine or 0.5% bupivacaine for subclavian perivascular brachial plexus block (48). There were similar incidences of nausea (33 and 28%), vomiting (8 and 14%), and Horner's syndrome (8 and 6%), and one patient who received bupivacaine developed a tonic-clonic generalized seizure 8 minutes after injection, suggestive of systemic toxicity.

Patient-controlled interscalene analgesia (PCIA) with ropivacaine 0.2% has been compared with patient-controlled intravenous analgesia (PCIVA) with an opioid in 35 patients after elective major shoulder surgery (49). Although hemidiaphragmatic excursion on the non-operated side was increased in the PCIA group 24 and 48 hours after the initial block, pulmonary function was similar in both groups. Pain was significantly better controlled in the PCIA group at 12 and 24 and the PCIA group had a lower incidence of nausea and vomiting (5.5 versus 60%).

Cardiovascular

Cardiovascular complications can arise from unintended stellate ganglion block (SEDA-21, 131).

- A 67-year-old man had an axillary plexus block for a right palmar fasciectomy with mepivacaine 850 mg and adrenaline 225 micrograms. Twenty minutes later he became agitated and confused and an electrocardiogram showed fast atrial fibrillation. Rapid systemic absorption of the combination of high-dose mepivacaine and adrenaline in a patient who was also taking amiodarone, sotalol, captopril, and amiloride for pre-existing cardiac disease was felt to be responsible (50).

Pulmonary embolism has been attributed to brachial plexus block.

- A 43-year-old man with end-stage renal disease became acutely hypoxic after an interscalene brachial plexus block with 35 ml of 1.5% mepivacaine for primary placement of an arteriovenous fistula in the left arm (51). He had been undergoing hemodialysis for 1 month using subclavian and internal jugular vascular catheters for temporary access. Immediately after an apparently straightforward block, his oxygen saturation fell from 99 to 85%, he complained of chest pain and shortness of breath, and he developed hemoptysis. A CT scan suggested acute pulmonary embolism.

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The authors proposed that manipulations and vasodilatation related to the interscalene block may have facilitated the dislodgement of a pre-existing thrombus in the arm.

Respiratory

Large volumes (30–40 ml) of local anesthetics for interscalene block cause hemidiaphragmatic paresis in nearly all patients. An interscalene brachial plexus block in 11 volunteers using 10 ml of either 0.25% bupivacaine or 0.5% bupivacaine, both with adrenaline 1:200 000, resulted in significant impairment of lung function (forced vital capacity fell by 75% and FEV_1 by 78%) and in hemidiaphragmatic excursion in those given 0.5% bupivacaine, but not 0.25% bupivacaine (52). The authors suggested that 10 ml of 0.25% bupivacaine provides adequate anesthesia, with only occasional interference with respiratory function.

However, reducing the volume of local anesthetic (1.5% mepivacaine) from 40 to 20 ml, and applying proximal digital pressure, did not reduce the incidence or intensity of diaphragmatic paralysis during interscalene block in 20 patients, in whom arterial oxygen saturation fell significantly (53).

- A 55-year-old man with newly diagnosed non-small-cell lung cancer developed difficulty in breathing, cyanosis, agitation, and confusion, 10 minutes after interscalene supplementation of an axillary nerve block with only 3 ml of 2% mepivacaine with adrenaline (54). He was anesthetized, intubated, and ventilated. Surgery proceeded and postoperative radiographic examination of the lungs showed ipsilateral elevation of the diaphragm with reduced respiratory excursion. Phrenic nerve block after the interscalene injection was the postulated cause of the deterioration in respiratory function. He was successfully extubated at the end of the procedure.

Pneumothorax has occasionally been observed (55). The axillary technique is recommended to prevent this complication (56).

Phrenic nerve palsy, resulting in paralysis of the ipsilateral hemidiaphragm, can rarely cause severe respiratory compromise, depending on pre-existing lung dysfunction. In unpremedicated patients who underwent supraclavicular brachial plexus block for upper limb surgery, blocks were performed using a peripheral nerve stimulator and 0.5 ml/kg of bupivacaine 0.375% (57). Spirometric and ultrasonographic assessments of diaphragmatic function were made at intervals. Of 30 patients, 15 had complete paralysis of the hemidiaphragm, 5 had reduced diaphragmatic movement, and 10 had no change. Those with complete paralysis all had significant reductions in pulmonary function and those with reduced or normal movement had minimal changes. Only one of the patients had respiratory symptoms and the oxygen saturation remained unchanged. This may not be the case, however, in patients with significant pre-existing respiratory disease or in obese people; the authors therefore suggested caution in choosing this approach as a safer alternative to general anesthesia in such individuals.

Two cases of respiratory compromise after infraclavicular brachial plexus blockade have been described (58).

- An 84-year-old woman weighing 74 kg had a past history of hypertension, emphysema, and ischemic heart disease. She had an infraclavicular brachial plexus block with 40 ml (400 mg) of prilocaine 1% and 10 ml (75 mg) of ropivacaine 0.75%, and 20 minutes later developed difficulty in breathing and became desaturated. She had received midazolam 2 mg before the block.
- A 47-year-old woman with a history of hypertension, gastric reflux, and obesity was premedicated with oxazepam 10 mg and had an infraclavicular brachial plexus block with the same doses of ropivacaine and prilocaine as in the first case; 10 minutes later she developed dyspnea and became desaturated.

Each patient's symptoms settled with supplementary oxygen, and surgery proceeded uneventfully. In both instances a chest X-ray showed a raised hemidiaphragm on the side of the block, but pneumothorax was excluded. The respiratory compromise was probably caused by paresis of the ipsilateral diaphragm due to blockade of the phrenic nerve, which is likely to occur after an infraclavicular plexus block but is well tolerated in most patients. Dyspnea in these two patients may have resulted from several factors. Both had been lightly sedated with benzodiazepines (although both were alert and cooperative, so this probably had a minimal contribution). The first had emphysema, which may have been an important factor; in such patients diaphragmatic function is important for sufficient gas exchange and a 50% loss of function can result in significant impairment. The second woman was obese, and obesity is associated with a reduction in functional residual capacity and respiratory function, so she may have had reduced respiratory reserve. The authors suggested that in patients with reduced pulmonary reserve, infraclavicular brachial plexus blockade should be avoided and an axillary approach considered. In addition they speculated that a smaller volume of local anesthetic may reduce the risk of phrenic nerve blockade.

Nervous system

Neurological injury after peripheral blockade has an incidence of less than 1%. However, it has been suggested that for axillary nerve blocks, neurological damage is more likely if paresthesia is the endpoint for location of the nerve sheath, in contrast to the transarterial method. This is probably due to the increased likelihood of direct damage from a needle, intraneural injection of local anesthetic, or toxicity of the local anesthetic to the nerve (59). However, published results on this issue remain contradictory (60).

Ropivacaine is less toxic than bupivacaine. However, there have been reports of brachial plexus blockade after ropivacaine, associated with unusual symptoms of nervous system toxicity; none of the patients recalled the events and there were no subsequent sequelae (61).

- A 46-year-old man received an axillary nerve block using 40 ml of 0.5% ropivacaine with 1:200 000 adrenaline and 45 seconds later developed a sinus tachycardia and started screaming, appearing terrified. He struck out violently with all limbs and sat upright, attempting

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to leave the bed. The pulse oximeter reading (SpO_2) fell to 90% and his symptoms were interpreted as a seizure and treated successfully with 100% oxygen, sodium thiopental, and intubation.

- A 60-year-old woman received an interscalene block using 30 ml of 0.5% ropivacaine with 1:200 000 adrenaline. Immediately after the injection, she sat up and began screaming in a loud high-pitched voice, appearing terrified and enraged. She then attempted to get off the stretcher in an uncoordinated manner and became unresponsive to verbal commands. She had a sinus tachycardia and hypotension. Treatment with 100% oxygen and propofol was effective.
- A 76-year-old woman received an interscalene block using 20 ml of 0.75% ropivacaine with 1:400 000 adrenaline. At the end of the injection, she sat up and appeared extremely terrified; she screamed twice, fell back on the stretcher, and began moving the unblocked arm and both legs in clonic movements, remaining unresponsive to verbal command. She had a sinus tachycardia and hypertension (205/70 mmHg). The seizure abated with thiopental.

The authors suggested that these signs of anxiety, vocalization, and agitation may have been due to the administration of ropivacaine formulated exclusively as the *S*(–) enantiomer, which has a spectrum of nervous system and cardiovascular toxicity different from the racemic mixture.

Reverse arterial flow can cause nervous system toxicity, even during peripheral regional blocks with only small volumes of local anesthetic (62).

- A 47-year-old woman received an axillary brachial plexus block with 3 ml of 1% lidocaine after negative aspiration. She became dysphoric 30 seconds later, with muscle twitching in the face and distal arms, became unresponsive, and required ventilation.

During a study of 104 adults to compare the efficacy and safety of 40 ml of 0.75% ropivacaine (300 mg) and 40 ml of 0.5% bupivacaine (200 mg) for axillary plexus block, significantly more patients reported postoperative dizziness in the ropivacaine group (5 versus 0) (63). However, this occurred 4–5 hours after the injection in two patients and the day after in the other three, and was therefore unlikely to have been due to high serum concentrations. One patient developed dizziness, dysarthria, and unconsciousness, with convulsions shortly after an injection of ropivacaine, indicating an intravenous injection.

In some cases adjuvants should be considered as well as the local anesthetic after a toxic reaction (64).

- A 52-year-old woman received an axillary plexus block with 20 ml of 1% ropivacaine, clonidine 70 micrograms, and 15 ml of 1% mepivacaine with 1:400 000 adrenaline. Generalized tonic-clonic seizure activity developed, even though careful incremental aspiration was performed. She was still comatose 90 minutes later, but this was reversed by intravenous naloxone.

The authors suggested that clonidine could have been responsible for the maintenance of her unconscious state.

Axillary blockade using high-dose mepivacaine with adrenaline was performed in 50 patients, each of whom received 850 mg of mepivacaine; two patients had symptoms of toxicity associated with this combination (euphoria, dizziness, and tinnitus) 13 and 15 minutes after the procedure with doses of 14.1 and 16.4 mg/kg of mepivacaine respectively (65). One patient who received 10.9 mg/kg developed hypertension and atrial fibrillation, became agitated, and lost consciousness 12 minutes after the block was performed, and required beta-blockade and midazolam before waking up 15 minutes later. Another received 6.5 mg/kg, became light-headed, agitated, and hypertensive, and reported whole body numbness 18 minutes later, with resolution of symptoms after 10 minutes with beta-blockade. The author thought that adrenaline had probably been responsible for the reaction in the first patient. As high-dose mepivacaine did not greatly improve the quality of the block and can obviously produce serious systemic reactions, it would be prudent to limit the dose to under 10 mg/kg.

Horner's syndrome is a well-recognized complication of interscalene brachial plexus block, stellate ganglion block, and occasionally epidural blockade. It occurs when the local anesthetic reaches the cervical sympathetic trunk and is usually transient. However, persistent Horner's syndrome is a rare complication, and may represent traumatic interruption of the cervical sympathetic chain. Cases of prolonged Horner's syndrome related to prevertebral hematoma formation at the site of continuous interscalene blockade have been described (66).

- A 48-year-old obese woman had a 22G interscalene catheter inserted under local anesthesia via a short-bevel stimulating needle. Anesthesia was achieved using 0.6% ropivacaine 40 ml followed by an infusion of ropivacaine 0.2% for effective analgesia. On day 3, she reported blurred vision and a painful neck swelling. She had developed a hematoma around the catheter insertion site (confirmed by ultrasound) and had an ipsilateral Horner's syndrome including myosis, ptosis, enophthalmos, ipsilateral anhidrosis, and conjunctival hyperemia.
- An interscalene catheter was inserted in an awake 20-year-old woman for analgesia after shoulder surgery. Analgesia was achieved with ropivacaine 0.2% as a 30 ml bolus followed by an infusion of the same solution. One day later she had visual disturbance and neck swelling due to a hematoma between the prevertebral and scalene muscles.

Neither patient was taking NSAIDs, aspirin, or anticoagulants. Catheters were removed immediately on diagnosis of hematoma formation. There was no neurological or sympathetic fiber damage to the upper limb in either patient, as tested by electroneuromyography and sympathetic skin response. Remission in both cases occurred within 1 year. There has been one previous report of prolonged Horner's syndrome in the absence of any obvious technical complication (67). Further studies into the use of interscalene catheters are needed to assess their propensity to cause this rare complication.

In 60 patients receiving patient-controlled interscalene analgesia with either ropivacaine 0.2% or bupivacaine 0.15%, there was a significant reduction in hand motor function and an increased incidence of paresthesia in the bupivacaine group, with no difference in pain scores (68).

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This finding contrasts with that in a comparison of epidural bupivacaine or ropivacaine, in which there was no difference in motor function between the two groups (69).

Inadvertent injection into the subarachnoid space, occasionally causing cerebral or neurological problems, is a life-threatening complication of brachial plexus anesthesia. It can also cause postdural puncture headache (SEDA-21, 131).

Interscalene block can cause paralysis of the arm.

- A 33-year-old woman received combined regional and general anesthesia for a shoulder repair (70). Preoperatively an interscalene catheter was placed uneventfully. The next day, she had almost complete paralysis of the arm with hypesthesia of dermatomes C5–7. The symptoms persisted and 4.5 months later, during surgical exploration of the brachial plexus, electrical stimulation of the three trunks was possible and there were electrophysiological signs of recovery. Despite extensive neurophysiological tests a clear cause could not be established and there was no improvement at 2 years.

Sensory systems

- An intolerable metallic taste appeared and disappeared in a 48-year-old woman within hours of infusion of bupivacaine via an axillary catheter, and its severity changed with the rate of infusion (71). The mechanism was postulated to be through sodium channels or taste bud disturbances.

Psychological, psychiatric

- A 59-year-old woman, grade ASA I, had psychiatric effects associated with local anesthetic toxicity after receiving bupivacaine 50 mg and mepivacaine 75 mg for an axillary plexus block. She complained of dizziness and a "near death experience" (72).

Hematologic

Methemoglobinemia has been reported in a woman who received a combination of local anesthetics (73).

- A 60-year-old woman with medical problems including severe coronary vascular disease and anemia, taking multiple medications, including isosorbide dinitrate, received axillary plexus blockade with bupivacaine 150 mg + 10 ml of 1% lidocaine injected into the operative field; 90 minutes later her SpO_2 fell to 85–89% on oxygen 10 l/minute. She became drowsy, disoriented, and tachypneic, and an arterial blood gas showed a metabolic acidosis and a methemoglobin concentration of 6.4%. Her mental status improved 10 minutes after methylthioninium chloride and sodium bicarbonate; her SpO2 rose to 96% on air, her methemoglobin concentration fell to 1.6%, and her acidosis partly resolved.

The authors assumed that displacement of lidocaine from protein binding by bupivacaine, in combination with metabolic acidosis and treatment with nitrates, had caused methemoglobinemia.

Susceptibility factors

Mepivacaine toxicity has been studied in 10 patients with end-stage chronic renal insufficiency undergoing vascular access surgery (74). These patients represent a high-risk group for general anesthesia, as they often have concomitant coronary artery disease, hypertension, and diabetes. Brachial plexus block is often used: as well as avoiding systemic effects, it enhances regional blood flow. However, high doses of local anesthetic are required, and this block carries one of the highest rates of seizures. In this study, following axillary block with mepivacaine 650 mg, plasma concentrations were greater than the threshold of 6 micrograms/ml, above which signs of nervous system toxicity reportedly occur. The authors suggested that the absence of nervous system signs may have been due to slow systemic absorption of the local anesthetic. Peak concentrations occurred after 60–90 minutes, but were still high at 150 minutes, raising the question of more prolonged monitoring after these blocks.

Buccal anesthesia

Persistent hiccup, paralysis of cranial nerves, and systemic toxicity are the main complications of local anesthesia in the mouth (75–77). Trismus has been seldom reported (78–80).

Caudal anesthesia

In a study in 60 anesthetized children undergoing minor subumbilical surgery caudal blocks, 0.2% ropivacaine, 0.25% racemic bupivacaine, and 0.25% levobupivacaine (all 1 ml/kg) were compared (81). All the blocks were successful in terms of intraoperative and early postoperative analgesia. Ropivacaine, but not levobupivacaine, was associated with less motor block during the first postoperative hour compared with racemic bupivacaine. However, the lower concentration of ropivacaine will have biased this result.

Caudal block with bupivacaine in children provides adequate analgesia in the early postoperative period, but additional analgesia is often required as the block wears off. Two studies have looked at adjuvants to prolong the analgesic effect.

The first was a randomized, controlled trial in 60 boys undergoing unilateral herniorrhaphy (82). They received 0.25% bupivacaine 1 ml/kg or the same dose of bupivacaine plus 1.5 mg/kg tramadol, or tramadol 1.5 mg/kg alone made up to the same volume. Caudal administration of bupivacaine plus tramadol resulted in more effective analgesia, with a longer period without demand for additional analgesia postoperatively without increases in any adverse effects. The second was a study of the addition of midazolam to caudal bupivacaine in 30 children undergoing genitourinary surgery (83). They randomly received 0.25% bupivacaine 0.5 ml/kg or the same dose of bupivacaine plus midazolam 50 micrograms/kg. There were no untoward events in either group. Fewer required additional analgesia in the first 6 hours postoperatively in the bupivacaine plus midazolam group than with bupivacaine alone: 27% compared with 60%. Midazolam prolonged analgesia with no increase in adverse effects.

In 165 children receiving caudal anesthesia with fentanyl 1 mg/kg and bupivacaine 4 mg/kg, there were adverse effects in only six, two of whom required postoperative ventilation. This was felt to be due to their pathology and not the anesthetic. However, there was no comment on the presence or absence of specific local anesthetic adverse effects, and an unusually high dose of

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bupivacaine was used, 4 mg/kg, twice that recommended by the manufacturers and greater than that used by most pediatric anesthetists (2.5–3 mg/kg) (SEDA-20, 124).

Caudal bupivacaine has been successfully combined with clonidine, ketamine, diamorphine, and buprenorphine, with increased duration of anesthesia and a low incidence of adverse effects (SEDA-20, 124) (SEDA-21, 131).

Awake regional anesthesia for inguinal hernia repair in former preterm infants has been suggested, in order to avoid life-threatening respiratory complications that can occur after general anesthesia. Caudal anesthesia is becoming a more popular technique for this purpose. To prolong the duration of anesthesia and to reduce the postoperative need for analgesics in these infants, caudal clonidine has been considered useful.

- A former preterm infant had two awake caudal anesthetics for herniotomy within 3 weeks (84). The first was uneventful with bupivacaine 0.25% at 35 weeks of age. At 38 weeks, the baby had intraoperative and postoperative bouts of apnea after inadvertent administration of bupivacaine 0.125% plus clonidine.

There has been a report of T wave changes on the electrocardiogram during caudal administration of local anesthetics (85).

- A 4.2 kg 2-month-old baby was given a caudal injection under general anesthesia for an inguinal hernia repair. A mixture of 1% lidocaine 2 ml and 0.25% bupivacaine 2 ml was injected. Every 1 ml was preceded by an aspiration test and followed by observation for electrocardiographic changes for 20 seconds. On administration of the third 1 ml dose, there was a significant increase in T wave amplitude. The aspiration test was repeated and was positive for blood. The caudal injection was stopped and the electrocardiogram returned to normal after 35 seconds. The baby remained cardiovascularly stable with no postoperative sequelae.

Previous reports have suggested that an increase in T wave amplitude could result from inadvertent intravascular administration of adrenaline-containing local anesthetics. This is the first case report of local anesthetics alone causing significant T wave changes.

Inadvertent dural puncture is a recognized complication in up to 1% of caudal anesthetics. It can be due to excessive needle insertion or sacral abnormalities. Potentially serious consequences, such as total spinal anesthesia, can result (SEDA-21, 131).

In eight episodes of toxic methemoglobinemia in seven premature infants after the combination of caudal anesthesia (prilocaine 5.4–6.7 mg/kg) and Emla cream (prilocaine 12.5 mg) for herniotomy, the highest methemoglobin concentration 5.5 hours after anesthesia was 31% (86). All the infants were symptomatic, with mottled skin, pallor, cyanosis, and poor peripheral perfusion. The most severe symptoms occurred at 3–8 hours and disappeared within 10–20 hours. The authors stressed the importance of recognizing the poor tolerance of premature infants to methemoglobinemia and that whereas topical prilocaine is relatively safe, caudal administration is not.

Cervical plexus anesthesia

Nervous system

Deep cervical plexus block can cause ipsilateral phrenic nerve palsy. A patient with pre-existing respiratory disease and a contralateral raised hemidiaphragm developed hypoxia and respiratory distress when given 20 ml of plain bupivacaine 0.375% by this route for carotid endarterectomy (87). Local anesthetic spread resulted in presumed stellate ganglion block, which caused nasal congestion and aggravated the respiratory distress. The symptoms resolved without intubation, but the authors advised against deep cervical plexus block in patients with diaphragmatic motion abnormalities or chronic respiratory disease.

Nerve palsies can occur during deep cervical plexus anesthesia.

- A woman complained of being unable to clear secretions effectively from her throat, had a paroxysm of coughing, and developed a large neck hematoma requiring surgical re-exploration (88).
- A 71-year-old man complained of difficulty in breathing and was desaturated on pulse oximetry for 5 minutes after cervical plexus blockade (89). He required tracheal intubation, was ventilated for 110 minutes, and was then successfully extubated. It was thought that the most likely diagnosis was cardiorespiratory failure exacerbated by phrenic nerve blockade.
- A 67-year-old man developed transient hemiparesis and facial nerve palsy before becoming unconscious and apneic 10 minutes after a right cervical plexus block (89). His trachea was intubated without the need for anesthetic drugs and he was ventilated. Hypotension was treated with intravenous ephedrine. He woke up, started breathing, and was extubated 75 minutes later. The authors postulated brainstem anesthesia following accidental injection of local anesthetic into a dural cuff as a cause of loss of consciousness.

Hemidiaphragmatic paralysis can occur with cervical plexus anesthesia and can be particularly risky in cases of pre-existing airways obstruction (90).

Infiltration of even small doses of a local anesthetic in the region of the carotid artery is likely to cause nervous system toxicity if injected intra-arterially (91).

- A 76-year-old man had already received a deep and superficial cervical plexus block for an awake carotid endarterectomy. One hour later, during manipulation of the carotid artery discomfort was treated with infiltration of 1 ml of 0.5% lidocaine in that region. Immediately he became unresponsive, with generalized tonic-clonic seizure activity of the face and arms. He was given 100% oxygen and within 30 seconds the seizure terminated spontaneously with no sequelae.

This demonstrates the requirement for constant vigilance in a patient undergoing awake carotid endarterectomy.

Dental anesthesia

Dental anesthesia is generally safe and effective. However, it can cause adverse effects, ranging from mild to severe, perhaps a reflection of the number of dental anesthesias performed.

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Systemic effects, such as dizziness, tachycardia, agitation, nausea, tremor, syncope, seizures, and bronchospasm, are a definite risk with local anesthesia in a vascular area. A wide range of patients present for dental surgery, and it is important that an adequate medical history be taken and accurate doses calculated on an individual basis. Low concentrations of adrenaline should be used.

Complication rates increase with premedication at home, and pre-existing disease or risk factors, such as pregnancy, cardiovascular disease, and allergies. Articaine and lidocaine with epinephrine 1:200 000 were associated with a low incidence of complications (3.1 and 0%), whilst mepivacaine and articaine with adrenaline 1:100 000 caused the most frequent complications (7.2 and 6.1%) (SEDA-22, 135).

Cardiovascular

Acute hypertension leading to myocardial infarction and pulmonary edema has been described after the use of mepivacaine with levonordefrin (92).

Nervous system

An unexplained case of permanent neurological deficit, consisting of left facial palsy, right sensorineural hearing loss, gait ataxia, and hemisensory loss in the body and face, has been described after inferior alveolar nerve block (93).

Facial paralysis is occasionally reported and is not necessarily due to poor technique; in one case vascular spasm seemed to provide an explanation (SED-12, 252).

- An 8-year-old girl received prilocaine for a dental procedure performed under 70% oxygen/30% nitrous oxide (94). The dose of 288 mg was 2.7 times higher than the recommended safe dose of 6 mg/kg. Toward the end of the procedure, she became unconscious and had a convulsion.

Two reviews have highlighted the fact that the degree and incidence of neurological damage after dental anesthesia is probably underestimated. Some drugs, such as articaine and prilocaine, seem to cause a higher incidence of paresthesia than others (SEDA-20, 124).

In seven subjects articaine with adrenaline caused distortion of lingual nerve function with effects on vowel pronunciation and therefore the potential to impair speech (95).

- A 49-year-old man developed uvular deviation as a result of palatal muscle paralysis following intraoral mandibular block of the inferior alveolar nerve with 1.8 ml of 2% lidocaine with adrenaline 1 in 100 000 (96). A few minutes after injection he had swallowing difficulties and a foreign body sensation in his throat. There was paralysis of the velum palatinum, with deviation of the uvula towards the non-paralysed side opposite the point of anesthetic infiltration. This resolved after the anesthetic had worn off.

The authors suggest that a high inferior alveolar nerve block can easily affect the mandibular nerve if the anesthetic solution diffuses to the internal trunk of the third trigeminal branch and the supply to the tensor veli palatini.

Sensory systems

Adverse ocular effects, such as ptosis, are on record (SEDA-15, 118). Transient dizziness, diplopia, and partial blindness have been reported after the entry of lidocaine with adrenaline into the ophthalmic artery following mandibular block (97). A similar case after posterior alveolar block resulted in dizziness and diplopia for 3 hours when the patient stood up, possibly due to the entry of local anesthetic into the ophthalmic artery (SEDA-22, 135).

Ophthalmological complications after intraoral anesthesia occurred in 14 cases over 15 years (98). The most common symptom was diplopia. Three patients developed Horner's syndrome, with ptosis, enophthalmos, and miosis on the same side as the anesthesia. Three patients developed mydriasis and ptosis. There was complete resolution in all patients. The authors postulated that direct diffusion of anesthetic solution from the pterygomaxillary fossa through the sphenomaxillary cavity to the orbit had caused the ophthalmological effects.

- A 45-year-old man developed temporary monocular blindness, ophthalmoplegia, ptosis, and mydriasis immediately after a mandibular block injection (99). Unidentified intra-arterial injection into the maxillary artery, with backflow of the local anesthetic solution to the middle meningeal artery was the postulated cause.

Additives

Additives in local anesthetic solutions can cause allergic reactions (100).

- A 34-year-old man developed swelling and redness of the face after receiving lidocaine as Lignospan® for dental treatment. Patch testing showed allergic contact dermatitis due to the preservative disodium ethylenediamine tetra-acetic acid (EDTA).

Digital anesthesia

Digital anesthesia with 1% lidocaine plus adrenaline was performed on 23 patients for surgery to finger injuries; 11 patients received adrenaline 1:200 000, and 12 received 1:100 000 (101). A digital tourniquet was also used, but no patient developed ischemic symptoms. The authors discussed the usefulness of adrenaline as an additive to local anesthetic solutions in prolonging regional block, reducing the dose of local anesthetic required. They stated that an extensive search of the literature had revealed no sound clinical evidence to support the widely held opinion that adrenaline contributes to the risk of gangrene when it is used in digital blocks.

Epidural anesthesia

The accidental transformation of epidural to subarachnoid block can be dramatic, and tracheal intubation and ventilatory support may be necessary (102). Severe hypotension can result after inadvertent intrathecal local anesthesia (SEDA-21, 131). In women in labor, fetal bradycardia can occur. Postdural puncture headache can also be a sign of catheter migration.

Long-term epidural catheters can be highly effective in the management of chronic pain of malignant and non-malignant origin, but they can also cause complications. Infection and extravasation of fluid to the paraspinal

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tissue resulting in inadequate analgesia have been described in a patient with non-Hodgkin's lymphoma (103). Another patient with non-Hodgkin's lymphoma had a tunnelled thoracic epidural for analgesia and presented with spinal cord compression. Laminectomy showed a mass consisting of white chalk-like drug-related precipitate around the catheter tip. As the solvent for bupivacaine contains sodium hydroxide and sodium chloride, the authors assumed that the mass was a precipitate of sodium hydroxide (104).

- A 1-year-old boy inadvertently received ropivacaine 6 mg intravenously over 2 hours when his epidural infusion was incorrectly connected to his intravenous cannula (40). He had already received ropivacaine 28 mg via his epidural catheter. He suffered no overt adverse effects.

In a dose-finding study for the combination of 0.2% ropivacaine with fentanyl for thoracic epidural analgesia in 224 patients undergoing major abdominal surgery, each received fentanyl in concentrations of 0, 1, 2, or 4 micrograms/ml; effective pain relief was provided by all the combinations and the degree of motor block was low overall and did not differ significantly among the groups (105). Hypotension was most common during the first postoperative 24 hours and was most frequent in those given fentanyl 4 micrograms/ml. Although the combination with fentanyl 4 micrograms/ml improved the quality of analgesia, there was a higher incidence of adverse effects, such as hypotension, nausea, and pruritus.

Patient-controlled epidural analgesia is increasingly being used, as it reduces the need for adjustment of epidural infusion rates by anesthetic personnel. In a retrospective survey of 1057 patients who received postoperative patient-controlled epidural analgesia using bupivacaine 0.1% plus fentanyl 5 micrograms/ml, on the first postoperative day 93% of the patients had adequate analgesia and 96% reported no nausea; two patients had an episode of respiratory depression and one patient was unrousable (106). Hypotension occurred in 4.3%, but there were no cases of epidural hematoma or abscess. Despite these adverse events, the authors concluded that patient-controlled epidural analgesia was effective and safe on surgical wards. The large amount of fentanyl in the solution they used is most probably the reason for the rare, potentially life-threatening adverse effects.

The amount of bupivacaine with fentanyl used in patient-controlled epidural analgesia was significantly less than with a continuous infusion of the same mixture in a group of 54 patients (mean age 71 years) after total knee arthroplasty (107). However, 10% of the patients were too confused to use the PCEA device. Despite the advantages of analgesic dosage reductions, a constant infusion may prove more appropriate in this age group.

Patient-controlled epidural analgesia (0.05% bupivacaine and fentanyl 4 micrograms/ml) has been studied prospectively in 1030 patients requiring postoperative analgesia (108). Pruritus was the most common adverse effect, with an incidence of 17%, with two susceptibility factors: age (under 58 years) and increased consumption of analgesia (over 9 ml/hour). The incidence of nausea was 15% and of sedation 13%; female sex was a slight risk factor for both. Hypotension had an incidence of 6.8% and motor block of 2%; lumbar placement of the epidural catheter was the strongest risk factor. Respiratory depression occurred in 0.3%.

The effects of single-dose epidural analgesia with lidocaine and morphine have been studied in 60 women undergoing elective cesarean section (109). The patients received morphine sulfate 4 mg and 2% lidocaine 18–20 ml. Four patients proceeded to general anesthesia owing to failure of the epidural block to reach T6, 48% of patients complained of discomfort during surgery, and 23% needed supplementary analgesia. Perioperative adverse effects were hypotension 29%, bradycardia 3.6%, and shivering 5.4%. Postoperative adverse effects were pruritus 45% and nausea and vomiting 35%. Apgar scores at 1 and 5 minutes were 8 or over. At 2 hours and 24 hours, two babies had transient tachypnea and one had mild respiratory distress. Maternal and neonatal venous concentrations of morphine, measured at delivery, were low. The authors recommended this technique for elective cesarean section in uncomplicated obstetric patients. This study had no control group and reported a high incidence of unwanted effects and a high perioperative failure rate. Mean analgesic duration of morphine was reported as 24 hours. However, 75% of patients required additional analgesia after 12 hours. There was no record of the incidence of postoperative maternal respiratory depression.

Comparative studies

After thoracotomy, 106 patients received a thoracic epidural infusion of either 0.1% or 0.2% bupivacaine, both with fentanyl 10 micrograms/ml, compared with epidural fentanyl alone; there was no difference in the number of episodes of postoperative hypotension (systolic pressure below 90 mmHg) or in the number of interventions for postoperative hypotension, but intraoperative vasopressors were used significantly more in the bupivacaine groups (110). In addition, two patients given 0.2% bupivacaine reported slight weakness of both hands and another a right-sided Horner's syndrome and weakness of the right hand. There was a similar incidence of nausea and pruritus in all the groups; however, the incidence of respiratory depression with fentanyl was high (4.2%).

Random allocation of 150 women in labor to either an intermittent epidural bolus, a continuous epidural infusion, or patient-controlled epidural analgesia with 0.125% bupivacaine and sufentanil 0.5 micrograms/ml resulted in significantly more frequent motor blockade with continuous infusion compared with intermittent boluses (22 versus 4%), with similar frequencies of pruritus, hypotension, and high sensory level in each group (111).

In 52 patients who received either epidural bupivacaine (0.10–0.28 mg/kg/hour) or lidocaine (0.44–0.98 mg/kg/hour), both with epidural morphine, there were no significant differences in the times to mobilize, motor function (as measured by the Bromage grade), and the incidence of hypotension (112). Most of the patients had no motor blockade, and the Bromage grade did not help predict which of them could be mobilized.

In 90 parturients who received epidural analgesia during labor with bolus administration of either 10 ml of 0.125% bupivacaine or 0.125% ropivacaine, each with sufentanil 7.5 micrograms, there were comparable onset times and duration of analgesia in the two groups, but

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patients given ropivacaine had significantly less motor blockade after the third and subsequent epidural injections compared with those given bupivacaine: 93% of those given ropivacaine had no motor impairment compared with 66% of those given bupivacaine (113). There were no differences in hemodynamic effects and pruritus.

An epidural infusion of 0.2% ropivacaine plus sufentanil has been compared with 0.175% bupivacaine plus sufentanil in 86 patients postoperatively after major gastrointestinal surgery; there was no statistically significant difference in the incidence of adverse effects (respiratory depression, sedation, nausea, vomiting, pruritus, and motor blockade), but those given ropivacaine mobilized more quickly (114).

In 60 women who underwent elective cesarean section under epidural anesthesia, 0.5% levobupivacaine or 0.5% bupivacaine (30 ml) were equally efficacious in terms of anesthesia (115). The incidence and severity of motor blockade, hypotension, changes in QT interval, nausea, and vomiting were not significantly different, and neither were the neonatal Apgar scores.

Drug combinations are often used in epidural anesthesia to enhance the analgesic effect and minimize adverse effects. Continuous epidural analgesia (0.125% bupivacaine 12.5 mg/hour and morphine 0.25 mg/hour) has been compared with patient-controlled analgesia (morphine) in 60 patients after major abdominal surgery. Analgesia was superior in the epidural group, satisfaction and sedation scores were similar in both groups, whilst episodes of moderate nocturnal postoperative hypoxemia (SaO_2 85–90%) were more frequent in the epidural group (116).

The addition of opioids to local anesthetic to improve the efficacy of epidural analgesia for cesarean section has been advocated (109,117). A test dose of lidocaine 60 mg was given to 24 patients undergoing elective cesarean section, followed by either bupivacaine 45 mg or bupivacaine 45 mg plus fentanyl 50 micrograms (117). Sensory blockade to T6 was achieved in both groups, but pain scores were significantly lower in the fentanyl group. Rescue fentanyl on uterine exteriorization was required in 40% of the control group, but in none in the fentanyl group. There were no significant differences in adverse effects, specifically pruritus, hypotension, nausea and vomiting, maternal respiratory depression, and Apgar scores.

Cardiovascular

Hypotension is a frequent adverse effect of epidural anesthesia. In a comparison of the effects of bupivacaine and ropivacaine in 60 women undergoing cesarean section, 90% had a fall in blood pressure to below 90 mmHg, or by more than 30% of baseline (118).

Abrupt onset of arterial hypotension is also a complication of cervical epidural anesthesia, particularly in elderly patients (119). However, supplementation with adrenaline in this high-risk group is no longer defensible; it is better to be cautious with dosage and to monitor the patient closely.

- Severe hypotension during a lumbar epidural anesthetic in a 61-year-old woman taking amitriptyline was refractory to high doses of ephedrine and other indirect alpha-adrenergic agents (120). It eventually responded to one dose of noradrenaline 200 micrograms, illustrating the importance of the choice of vasopressor for treating hypotension in the presence of chronic tricyclic antidepressant use.
- A 27-year-old woman developed significant myocardial depression and pulmonary edema after administration of 5 ml of bupivacaine 0.5% via an epidural catheter (121). The bupivacaine followed a test dose of 3 ml lidocaine 2%.

Although initial aspiration on the epidural catheter was negative, the most likely explanation must be inadvertent intravascular administration of lidocaine and bupivacaine.

Unusually, a mother and her child died after repeated administration of a local anesthetic for cesarean section; pulmonary edema was believed to have been the cause (122).

Intracardiac conduction disturbances should not be considered as absolute contraindications to epidural anesthesia: there were only nine cases of sinus bradycardia, easily reversed with atropine sulfate, in 66 patients (123). However, rare cases of complete heart block and complete left bundle branch block have occurred (SEDA-21, 132) (124).

Unexpected cardiopulmonary arrest can result from accidental dural puncture during epidural blockade (SEDA-22, 136).

- Asystolic cardiac arrest has been described in a 55-year-old man who underwent partial hepatectomy under combined general and epidural anesthesia (125). During postoperative recovery he developed asystole followed by ventricular fibrillation. Resuscitation was unsuccessful.

The authors concluded that in the absence of any other abnormality the arrest had been the result of an autonomic imbalance due to spreading sympathetic block, although other postoperative causes of death should not be discarded.

Respiratory

Respiratory depression was noted in 0.24% of patients in a Chinese series of 10 978 epidural blocks (SED-12, 254) (126). Direct paralysis of respiration probably plays an important role. Respiratory depression with adverse cardiovascular effects after miscalculated dose requirements or a misplaced catheter has also been described (SEDA-22, 136).

In 15 patients receiving lidocaine 300 mg plus adrenaline by cervical epidural injection, the upper cervical nerve roots C3, 4, and 5 were anesthetized. None of the patients had pre-existing pulmonary disease. Only one had symptoms of impaired pulmonary function at 20 minutes after epidural, and complained of dyspnea, with a reduction in maximum inspiratory pressure, FEV_1, FVC, and SpO_2. Four patients had a bradycardia requiring atropine, eight complained of nausea, and one developed hypotension requiring ephedrine. At 20 minutes after the epidural, all the patients had a maximum reduction in FEV_1 and FVC, ranging from 12 to 16% of preanesthetic measurements. The authors felt that as the maximum inspiratory pressure was virtually unchanged, this

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suggested that the motor function of the phrenic nerve was mostly intact, despite analgesia of the C3, 4, and 5 dermatomes (127).

Nervous system

Peripheral paresthesia, in 1.13% of patients in a Chinese series (SED-12, 254) (126) and 0.16% of patients in a Japanese study of 15 884 epidurals (128), is the most frequent neurological deficit attributed to spinal and epidural analgesia.

High spinal block has previously been reported as a rare complication of epidural anesthesia.

- A 31-year-old woman in labor had an epidural catheter sited at L3/4 (129). A test dose of 0.25% bupivacaine 10 ml was followed 90 minutes later by another 10 ml. After a further 90 minutes she required cesarean section, had a block to T7, and was topped up with 0.75% ropivacaine 10 ml. Within minutes she developed arm weakness, and over the next 15 minutes developed further ascending block requiring intubation. Three hours later the block had regressed to T8 and she had no further complications.

The cause was thought to be subdural injection, although other mechanisms could not be excluded; for example the catheter could have been partly intrathecal and the ultimate distribution of the dose could have been related to the speed of injection or catheter migration before the final dose was given.

Lumbar extradural analgesia with bupivacaine increases intracranial pressure in some patients, apparently those who already have some reduced intracranial compliance, and who may be at risk (130). A sudden increase in intracranial pressure, due to an increased volume in the caudal space, can precipitate respiratory arrest because of direct midbrain stimulation.

- A watershed cerebral infarct with subsequent full recovery occurred in a 70-year-old man 8 hours after a hypotensive event following an incremental bolus of 1% lidocaine 10 ml via an established epidural catheter (131).

A cause-and-effect relation cannot be established in such cases.

Epidural anesthesia can mask a neurological deficit, such as nerve compression of the femoral nerve and lateral femoral cutaneous nerve of the thigh from the lithotomy position (SEDA-22, 137).

- Neurological effects after accidental intravenous injection of a large dose of levobupivacaine (142 mg) have been described during epidural anesthesia (132).
- A 77-year-old woman had epidural anesthesia, following negative aspiration, with a 3 ml test dose of 0.75% levobupivacaine with 1:200 000 adrenaline and then incremental doses up to a total of 17 ml of 0.75% levobupivacaine. During the final 5 ml of injection, she became disoriented and drowsy, with slurred speech, immediately followed by excitation with shouting and writhing about. She was given thiopental for seizure prophylaxis with high-flow oxygen, and the excitatory signs abated. The catheter was withdrawn 1 cm and blood was freely aspirated. The serum levobupivacaine concentration 14 minutes later was 2.7 micrograms/ml.

Transient radicular irritation

Transient radicular irritation has been reported (SEDA-21, 130) (SEDA-22, 137).

- A 38-year-old woman underwent cystoscopy and urethral dilatation in the lithotomy position under continuous epidural anesthesia at the L3–4 interspace with 3 ml of 1.5% lidocaine with adrenaline 1:200 000 as a test dose, followed by a total of 15 ml of 2% lidocaine with adrenaline 1:200 000 in incremental doses (133). The operation was uneventful, but 4 hours later she developed severe bilateral buttock and posterior leg pain, described as "deep, aching, and excruciating," worse when immobile, and better when standing; there were no other symptoms and ibuprofen gave immediate relief.

The authors stressed that transient radicular irritation can occur after epidural administration, despite the lower concentrations of lidocaine in the cerebrospinal fluid.

- Transient neurological symptoms have been reported in two parturients who received lidocaine 45 mg with adrenaline 5 micrograms/ml as a test dose followed by bupivacaine (134). One patient received a single dose of bupivacaine 12.5 mg and the other received a total of 62 mg bupivacaine administered as two 5 ml and one 3 ml bolus of 0.25% bupivacaine followed by an infusion of 0.125% bupivacaine at 5 ml/hour for 4 hours 40 minutes. Both patients later developed reversible burning lower back, buttock pain, and leg pain; there was nothing to suggest intrathecal administration of local anesthetic in either case. Both patients gave birth in the lithotomy position, which may have been contributory.
- Severe burning pain in the buttocks, thighs, and calves has been described in a 5-year-old boy who was given 0.25% bupivacaine and morphine epidurally for perioperative and postoperative analgesia (135).

Two unexplained cases of back and leg pain have been separately described (SEDA-20, 125).

Motor block

Prolonged profound motor block occurred in two patients using patient-controlled epidural analgesia with 0.1% ropivacaine subsequent to spinal bupivacaine for cesarean section (136). One of them developed pressure sores on both heels. The authors hypothesized that epidural ropivacaine may interact with intrathecal bupivacaine to prolong its effects and advised caution when this combination is used, as unexpected motor block can ensue.

The optimal concentration of lumbar epidural ropivacaine in terms of adverse effects and quality of analgesia has been studied in 30 patients using patient-controlled epidural analgesia after lower abdominal surgery (137). Each solution provided comparable analgesia, but motor block was significantly more common and more intense with 0.2% ropivacaine + 4 micrograms/ml fentanyl than with 0.1% ropivacaine + 2 micrograms/ml fentanyl or 0.05% ropivacaine + 1 microgram/ml fentanyl. The amount of ropivacaine used by the 0.1% ropivacaine group was significantly higher than in the other two groups, implying that the concentration rather than the amount of ropivacaine is a primary determinant of motor block with

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patient-controlled epidural analgesia. The authors recommended the use of ropivacaine in concentrations under 0.2% to reduce motor blockade while still providing effective analgesia.

Epidural solutions containing 0.125% levobupivacaine with and without fentanyl 4 micrograms/ml produced a greater degree of motor blockade only in the first 6 hours of patient-controlled epidural analgesia compared with fentanyl alone in groups of 22 patients after total hip or knee arthroplasty (138).

- An 85-year-old woman undergoing elective right total knee replacement had prolonged motor blockade of her left leg when her epidural ropivacaine (0.2% at 8–10 ml/hour) infusion was discontinued on the third postoperative day; normal motor function had returned by the sixth postoperative day (139).

Paraplegia can result, and can be prevented by early recognition, appropriate investigation, and immediate surgical intervention.

- Delayed onset, prolonged coma, and flaccid quadriplegia occurred in a 22-year-old woman 2 hours after an injection of fentanyl 100 micrograms and 10 ml bupivacaine 0.25%, given in divided doses (4, 3, and 3 ml) via an epidural catheter (140). At the time of the initial attempt at insertion she had complained of severe cervico-occipital pain with loss of resistance to air injection. Despite negative aspiration of CSF, the physician suspected intrathecal injection of air and abandoned the attempt at epidural catheter placement at that level. An epidural catheter was successfully inserted one level higher. Within 1 hour of the original epidural injection, she developed hypotension requiring ephedrine, and a surprisingly high sensory block to T6 with profound lower limb motor blockade. This progressed 2 hours later to upper limb weakness, with respiratory failure requiring intubation and ventilation. She remained unconscious for 9 hours after the initial intubating dose of thiopental. She was able to move all of her limbs 26 hours later and was successfully extubated 43 hours later.

In this case the authors felt that although the initial picture looked like the effects of subdural injection of bupivacaine and fentanyl, the prolonged coma with high motor blockade was more reminiscent of total spinal injection. They postulated that delayed total spinal anesthesia had occurred in this patient as a result of the epidural administration of a large quantity of bupivacaine and fentanyl via a hole made in the dura during the first attempt at epidural insertion.

Accidental subdural block can also lead to rapidly developing high block, patchy block, and symptoms such as myoclonus and anxiety (SEDA-20, 125) (SEDA-22, 136).

Total spinal anesthesia

Permanent or temporary deficits of spinal cord function are caused either by cord ischemia after arterial hypotension, or by cord compression due to an epidural or subdural hematoma or infection, or injury to the spinal cord and nerve roots as a consequence of needle puncture, introduction of a catheter, or chemical irritation.

Total spinal anesthesia is a potentially life-threatening complication of epidural anesthesia.

- A 68-year-old man developed total spinal anesthesia after the administration of 20 ml of ropivacaine 1% without a prior test dose via an epidural catheter, which was inadvertently placed intrathecally (83). Initial aspiration of both the Touhy needle and the catheter failed to identify the intrathecal position of the catheter. The patient noted weakness in his right leg immediately after the end of the injection. This was followed by weakness in his right arm, asystole, apnea, and loss of consciousness. Ventricular escape beats were noted and sinus rhythm returned after mask ventilation with 100% oxygen and the administration of atropine 1 mg and ephedrine 50 mg. He was able to open his eyes, but remained apneic and was therefore intubated and ventilated. Cardiovascular stability was maintained with incremental boluses of ephedrine to a total of 60 mg. He regained consciousness and was successfully extubated 145 minutes later. All sensory and motor deficits had resolved within 8 hours and no neurological deficit or transient neurological symptoms were detected 5 days later.

This complication emphasizes the fact that aspiration is not sufficient to identify an intrathecal catheter position and that a large dose of a local anesthetic should never be administered without a prior test dose.

- Total spinal anesthesia was suspected in a 46-year-old man who was found unconscious and apneic with no palpable cardiac output 20 minutes after a high thoracic (T2/3) epidural injection of 3 ml lidocaine 1% and 3 ml bupivacaine 0.125% (141). Following initial cardiopulmonary resuscitation he was admitted to the intensive care unit, where treatment included mechanical lung ventilation, thiamylal infusion, and cooling to a core temperature of 33–34°C. The thiamylal was withdrawn after 17 days and he was warmed and successfully extubated the next day. He was discharged after a further 4 months of rehabilitation with no relevant neurological consequences.

Horner's syndrome

Horner's syndrome (miosis, ptosis, anhidrosis, and vasodilatation, with increased temperature of the affected side) can result from epidural anesthesia. A report of Horner's syndrome due to a thoracic epidural catheter has highlighted the fact that small doses of local anesthetic can block the sympathetic fibers to the face, particularly when the catheter tip is close to T2 (142). The same symptoms have been reported after obstetric epidural anesthesia (143).

Horner's syndrome has been reported after lumbar epidural block in two other patients who were having lumbar epidural anesthesia for chronic pain treatment (144). The authors suggested that this complication had probably occurred through anatomical changes in the epidural space, leading to a high degree of sympathetic blockade.

A left-sided Horner's syndrome has been reported following a lumbar epidural with ropivacaine for cesarean section (145). The symptoms resolved after 5 hours. The

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most likely cause was high sympathetic block, possibly facilitated by left lateral positioning, leading to cephalad spread of the local anesthetic. The authors also wondered whether the physicochemical properties of ropivacaine favor its effect on sympathetic fibers over bupivacaine.

Metabolism

A small reduction in glucose concentrations, rarely leading to hypoglycemic coma, can occur (SEDA-16, 130). This effect is in keeping with the finding that the catabolic stress response to surgery may be suppressed by epidural analgesia (SED-12, 254) (146). However, in one study, thoracic epidural administration produced a degree of hyperglycemia (SED-12, 252) (147).

- Symptomatic hypoglycemia occurred in a healthy 30-year-old primigravida after a second 5 ml bolus of 0.25% bupivacaine administered epidurally during labor (148). She developed an altered mental state, which responded rapidly to 50 ml of 50% dextrose administered intravenously.

Urinary tract

Epidural anesthesia increases the risk of urinary retention (149).

Musculoskeletal

Occasionally orthopedic patients have developed compartment syndrome postoperatively during epidural infusions of bupivacaine/fentanyl mixtures. However, although "aggressive analgesia" was blamed for the resulting disasters, there seems to have been a remarkable lack of adequate pressure area care, correct positioning, and regular review of both patients and splints (SEDA-22, 136).

Infection risk

Contamination of catheters, with subsequent clinical infection, is a potential hazard of epidural analgesia. But not every suspected infection is what it seems; aseptic meningitis has been described after an intradural injection of bupivacaine with methylprednisolone acetate (150).

Death

Inadvertent intravenous administration, due to the accidental placement of an epidural catheter in a vein, is a high-risk complication; deaths have been reported (151).

Pregnancy

Patient-controlled epidural analgesia using either 0.125% ropivacaine with fentanyl 2 micrograms/ml or 0.125% bupivacaine with fentanyl 2 micrograms/ml was studied in 50 patients during labor. Significantly more patients receiving bupivacaine developed motor blockade; 68% of patients in the bupivacaine group developed minimal motor block (Bromage score = 1), while the majority (68%) of patients in the ropivacaine group had no motor blockade. The incidences of adverse effects were similar in both groups. Hypotension occurred in 24% of the ropivacaine group and 16% of the bupivacaine group. Pruritus occurred in 56% of the ropivacaine group and 52% of the bupivacaine group (152).

In 122 women who received 20 ml of either ropivacaine 7.5 mg/ml or bupivacaine 5 mg/ml for epidural anesthesia during elective cesarean section, there were no significant differences in adverse effects, such as the incidence of hypotensive episodes, bradycardia, or nausea and vomiting; however, there was a greater median fall in systolic blood pressure in those given ropivacaine (24 versus 16%) (153). Efficacy and neonatal tolerability were similar in the two groups. This, together with its lesser cardiotoxicity, favors ropivacaine as an alternative to bupivacaine in this setting.

The possibility of increased maternal mortality is a topic of debate. In 1979 there were 150 maternal deaths (0.27 per 1000 births) in Germany, of which 15–25% were apparently related to regional anesthesia, with such complications as hypotension, systemic toxicity, total spinal block, hematoma, catheter rupture, and uterine injury (SED-12, 253) (154). However, obstetric regional anesthesia is regarded as being safer than general anesthesia, whatever the choice of drug, if competently and carefully performed.

Fetotoxicity

Maternal hypotension and excessive placental transfer of local anesthetics and other drugs, for example narcotics or sedatives, given to the mother before or during delivery are the main causes of neonatal death related to the use of these agents in obstetrics. However, deaths are very infrequent (155).

In about 10% of cases, obstetric use of epidural anesthesia will cause some bradycardia in the fetus, but this is not always a clinical problem (SEDA-15, 119). However, accidental intravenous injection of bupivacaine can lead to both maternal convulsions and severe fetal bradycardia (156).

The question of possible neurobehavioral effects in the child as a consequence of obstetric analgesia is still debated; although impairment of visual and neurological performance, reduced alertness, and alterations in walking and muscle tone have all been reported, most authors have found normal Apgar scores and psychomotor development after obstetric anesthesia (SED-12, 253) (157,158), and any functional defects noted at birth are likely to be transient (159).

The effects of low concentrations of epidural bupivacaine on the developing neonatal brain has been studied in infant rhesus monkeys, to decide if there was a detrimental relation between perinatal analgesia with epidural bupivacaine and later infant development (160). The monkeys, whose mothers had been given epidurals at term (but not during labor) were subjected to a battery of neurobehavioral tests for 1 year. The authors concluded that epidural bupivacaine did not cause neonatal abnormalities or specific cognitive defects, but that it may delay the normal course of behavioral development. It is difficult to extrapolate the results of this small study to human obstetrics.

Susceptibility factors

Epidural infusions of bupivacaine are often used in children. However, there are concerns about the increased incidence of adverse effects in infants, owing to reduced hepatic clearance and serum protein binding. In 22 infants

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aged 1–7 months who received a continuous infusion of bupivacaine 0.375 mg/kg/hour for 2 days during and after surgery, the unbound and total serum concentrations of bupivacaine were measured, along with presurgical and postsurgical concentrations of alpha$_1$ acid glycoprotein (161). The concentrations of alpha$_1$ acid glycoprotein increased markedly after surgery. However, because of reduced clearance unbound concentrations of bupivacaine increased to over 0.2 micrograms/ml in two infants younger than 2 months. The authors proposed a maximum dosage rate of 0.25 mg/kg/hour in infants younger than 4 months and 0.3 mg/kg/hour in older infants.

Intercostal nerve anesthesia

High spinal anesthesia after inadvertent injection is a possible complication of intercostal nerve block (SED-12, 252). Pneumothorax is another reported complication (55).

Interpleural anesthesia

Interpleural administration of local anesthetics has been followed by Horner's syndrome and increased skin temperature, apparently pointing to an effect on the sympathetic nervous system (162). Pneumothorax or infection can also result. Interpleural administration of local anesthetics can produce high serum drug concentrations and a risk of systemic toxicity (SEDA-21, 13), possibly increased by the addition of adrenaline (SEDA-20, 126).

Intra-articular anesthesia

Intra-articular anesthesia has been used successfully in many patients, with few adverse effects (SEDA-20, 126). However, it is not always safe; at least one death has occurred from bupivacaine used in this way (163). Intra-articular anesthesia in the knee joint was followed in one case by necrosis of the knee ligament and the skin, apparently due to localized drug-induced embolism (164).

Intradermal anesthesia

Intradermal local anesthetic solutions can cause considerable pain on injection. Additives, such as hyaluronidase, which are used to enhance the analgesic effect of local anesthetics, can often exacerbate this (165). Infiltration from the inside of a wound can be less painful than through intact skin (166).

The order of injection can affect the pain of local anesthetic infiltration with buffered lidocaine; in a sequence of two injections the second injection was consistently reported to be more painful than the first. This finding has important consequences with regard to trial design in this area of research (167). Buffered lidocaine warmed to 37°C was less painful than warmed plain lidocaine, plain lidocaine, and buffered lidocaine in a randomized controlled trial in 26 volunteers (168).

Intrathecal (spinal) anesthesia

Intrathecal anesthesia has been compared with general anesthesia in 33 patients with pre-eclamptic toxemia undergoing cesarean section (169). The complications after general anesthesia were more serious, with a 4.3% mortality, whereas complications after spinal anesthesia were less serious and easily manageable, notably intraoperative hypotension (47%), difficulty in locating the subarachnoid space (29%), and intraoperative vomiting (6%).

Hyperbaric ropivacaine 0.25% has been compared with hyperbaric bupivacaine 0.25% in a crossover study in 18 volunteers who received an intrathecal anesthetic; the doses were 4, 8, or 12 mg (170). More patients had lumbosacral back pain after intrathecal ropivacaine compared with bupivacaine (5 versus 1), although this difference was not significant; the back pain lasted 3–5 days and was mild to moderate in intensity.

Intrathecal isobaric ropivacaine (15 mg) has been compared with intrathecal isobaric bupivacaine (10 mg) in 100 patients having transurethral resection of the bladder or prostate (171). Median cephalad spread of blocks was two segments higher for both pinprick and cold with bupivacaine compared with ropivacaine. Onset time to anesthesia was the same in both groups. Significantly more patients in the ropivacaine group complained of painful sensations at the surgical site (16 versus 0%). There was no difference in anesthetic duration, the incidence, intensity, onset, and duration of motor blockade, or the incidence of hypotension in the two groups. There were no cases of transient neurological symptoms. The authors concluded that ropivacaine 15 mg is less potent than bupivacaine 10 mg for intrathecal analgesia.

Continuous intrathecal anesthesia with 10 ml of 0.25% bupivacaine over 24 hours has been compared with continuous epidural anesthesia with 48 ml of 0.25% bupivacaine over 24 hours during the first 2 days after hip replacement in 102 patients (172). Continuous spinal anesthesia provided better analgesia and more patient satisfaction, but significantly more patients had motor blockade during the day of surgery and the first postoperative day. There was a significantly higher incidence of nausea and vomiting with continuous epidural anesthesia (39 versus 21).

When a pneumatic tourniquet was used in intrathecal anesthesia, pain was twice as frequent with tetracaine (60%) as with bupivacaine (25%) (173). However, using bupivacaine and tetracaine together seems to produce a more prolonged analgesic effect without inducing more hypotension than either agent alone (SEDA-18, 143).

In 80 patients undergoing lower extremity or lower abdominal surgery randomized to receive hyperbaric bupivacaine 10 mg alone or in combination with fentanyl 12.5 micrograms intrathecally, those given fentanyl had significantly longer duration of analgesia with no reported sedation or respiratory depression (174). Pruritus occurred in 20% of patients given fentanyl and shivering occurred significantly more often in those given bupivacaine only (30 versus 12.5%).

The addition of low doses of clonidine and neostigmine to intrathecal bupivacaine + fentanyl in 30 patients in labor significantly increased the duration of analgesia but was associated with significantly more emesis (175).

In a comparison of intrathecal bupivacaine 10 mg and bupivacaine 7.5 mg combined with ketamine 25 mg, in 30 healthy women there was no extension of postoperative analgesia or reduction in postoperative analgesic requirements in those given ketamine (176). Those given ketamine had a shorter duration of motor blockade, but had an increased incidence of adverse effects, and the study was abandoned after 30 patients.

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Intrathecal blockade with 0.5% isobaric bupivacaine 10 mg has been compared with 0.5% isobaric bupivacaine 5 mg combined with fentanyl 25 micrograms (diluted to 2 ml with isotonic saline) in 32 patients undergoing elective cesarean section (177). The bupivacaine + fentanyl combination was associated with significantly less hypotension than bupivacaine alone (31 versus 94%) and a near 10-fold reduction in the mean ephedrine requirement (2.8 versus 23.8 mg). There were also significant differences in the incidence of nausea (31 versus 69%) and the median time to peak block (8 versus 10 minutes) with bupivacaine plus fentanyl. The authors advised further large-scale studies to quantify the minimum dose of bupivacaine plus fentanyl for single-dose spinal anesthesia.

An isobaric solution of sameridine given intrathecally in doses of 15, 20, and 23 mg has been compared with hyperbaric lidocaine 100 mg in 100 volunteers (178). Sameridine has both local anesthetic and opioid analgesic properties. There was one incident of transient paresthesia with sameridine 20 mg and two cases of bradycardia with lidocaine; the incidence of hypotension was more frequent with lidocaine, but pruritus was more common with sameridine.

Cardiovascular

Hypotension is the most frequent adverse effect of spinal anesthesia; in one very large series it occurred in 22% of the subarachnoid group (179), but the actual figures differ with the anesthetic, its concentration, and the definition of hypotension used. For example single-dose spinal anesthesia causes significantly more hypotension and bradycardia than continuous spinal anesthesia (180). Hypotension may be more of a problem with tetracaine or lidocaine than with bupivacaine in equivalent doses (SEDA-12, 35), and the incidence is less when the patient is in the lateral rather than the sitting position. However, using bupivacaine and tetracaine together seems to produce a more prolonged analgesic effect without inducing more hypotension than either agent alone (SEDA-18, 143). Hypotension is also reported with intrathecal opioids and opioid/local anesthetic combinations; sufentanil appears to predominate in these reports (SEDA-21, 132) (SEDA-22, 137).

Hypotension can be prevented or treated with vasopressors and/or fluids (SED-12, 254) (SEDA-18, 143) (181–183). A comparison of these approaches showed that ephedrine alone is less effective than ephedrine and colloid (184), and metaraminol, with or without colloid, is better than colloid alone (185).

The effect of baricity on the hemodynamic effects of intrathecal 0.5% bupivacaine has been measured by recording invasive systolic blood pressure and central venous pressure in 36 men given plain bupivacaine 0.5%, heavy bupivacaine 0.5% (in dextrose 8%), or a mixture of the two (in dextrose 4%) (186). Heavy bupivacaine caused more rapid falls in central venous pressure and systolic blood pressure than plain bupivacaine. However, it was subsequently remarked that both 4 and 8% dextrose are significantly hyperbaric relative to adult cerebrospinal fluid, implying that the 4% solution should have behaved more like the 8% solution (187).

In 191 women who had had cesarean sections under spinal anesthesia using hyperbaric bupivacaine 12–15 mg and morphine 0.25 mg, who were transferred to the recovery room on a stretcher with the upper body either flexed 30° or supine during transport 10% of each group had a greater than 20% fall in systolic blood pressure unaffected by position (188). The authors recommended routine monitoring of the blood pressure and pulse after transfer to the stretcher, and suggested that raising the head for the comfort of the mother during transport does not increase the risk of hypotension.

Isobaric bupivacaine 4 mg combined with fentanyl 20 micrograms has been compared with isobaric bupivacaine 10 mg alone in 20 patients over the age of 70 undergoing surgery for fractured neck of femur (114). Hypotension was defined as a systolic blood pressure less than 90 mmHg or a fall in mean arterial pressure of more than 25%. Significantly more patients given bupivacaine only had hypotension (90 versus 10%). The mean dosage requirement of ephedrine was higher with bupivacaine only (32 versus 0.5 mg) and two patients in this group required phenylephrine, while no patient given bupivacaine plus fentanyl did. No patient in either group complained of perioperative pain or required supplementary analgesia intraoperatively.

In young infants similar problems with blood pressure occur, and some changes in heart rate may be found, but tend to be transient (SEDA-12, 154) (189).

Intrathecal blockade for cesarean section using 0.5% hyperbaric bupivacaine at three different doses of 7.5 mg, 8.75 mg, and 10 mg has been studied in a double-blind comparison in 60 patients (190). There was no significant difference in maximum block height, but more of the patients who were given the two lower doses had moderate visceral pain requiring rescue ketamine. Bupivacaine 10 mg was associated with significantly more bradycardia, and 7.5 and 8.75 mg with significantly more hypotension. Motor block lasted significantly longer with 10 mg. The outcome was good in all the infants, although one baby whose mother had received bupivacaine 10 mg had an Apgar score below 10 at 5 minutes. The authors concluded that the use of bupivacaine 7.5 mg avoids hypotension, bradycardia, and prolonged block.

Bradycardia occurs in some 3% of spinal anesthetics in adults. Bradycardia can lead to cardiac arrest, either by direct block of the sympathetic innervation of the heart (in unintended high block) or as a consequence of insufficient venous return. In 900 cases of major anesthetic mishaps giving rise to compensation claims, there were 14 cases of cardiac arrest under spinal anesthesia, of which six were fatal (191). Myocardial infarction and cardiac arrest preceded by atrioventricular block have also been described.

- A 68-year-old man was given 0.5% bupivacaine 4 ml or spinal anesthesia, and 5 minutes later complained of nausea and developed hypotension, loss of consciousness, and a tonic-clonic seizure. He had first-degree heart block 4 minutes after subarachnoid injection, followed 1 minute later by third-degree heart block, and then asystole. He was successfully resuscitated. Proposed theories included a reflex bradycardia resulting from reduced venous return and/or unopposed

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vagal tone due to thoracic sympathectomy induced by spinal anesthesia (192).

Bradycardia has been reported to follow spinal anesthesia in association with urinary retention (193).

- A receding spinal block to level L1–2 gave rise to acute bradycardia (34–40/minute) and transient loss of consciousness in a 31-year-old man 5 hours after spinal anesthesia; on waking he complained of severe low back pain, and although he had no symptoms of urinary retention, urinary catheterization yielded 900 ml of urine with immediate relief of symptoms.

Slow injection of hyperbaric bupivacaine 8 mg has been compared with hyperbaric bupivacaine 15 mg used to achieve bilateral block in 30 patients of ASA grades I–II (194). There was significantly greater cardiovascular stability in the patients who had a unilateral spinal block.

Respiratory

Respiratory arrest is one of the most serious potential adverse effects of spinal anesthesia, either due to brainstem depression in high block or rostral spread of opioids after the use of combined techniques (SEDA-21, 132) (SEDA-22, 137).

Immediate respiratory arrest has been reported after the administration of intrathecal bupivacaine and fentanyl (195).

- A 26-year-old woman in labor was given an epidural for analgesia. After 2 hours and total doses of bupivacaine 77.5 mg and fentanyl 190 micrograms, the epidural was removed owing to failure. A subsequent intrathecal injection of bupivacaine 2.5 mg plus fentanyl 10 micrograms was followed 4 minutes later by apnea and loss of consciousness. She was rapidly intubated and regained consciousness after 15 minutes, at which time her sensory level was T8 to pinprick. She was extubated after 30 minutes.

The authors concluded that the respiratory depression had been due to excessive cephalad spread of fentanyl, possibly facilitated by the volume of bupivacaine that had previously been injected epidurally.

Bronchospasm has been reported in two obstetric patients, possibly due to thoracic sympathetic blockade in one and hypersensitivity in the other (SEDA-21, 132).

There is a potential risk that spinal anesthesia will cause apnea in premature infants. However, spinal anesthesia with a sound technique has been used safely in high-risk infants. Tetracaine was used in 142 such cases; only two infants had serious adverse effects, one with unexplained but treatable apnea and one in whom too high a block resulted in respiratory arrest (196).

Two former preterm infants (postconceptual age 38 weeks) both received spinal anesthetics for inguinal herniorrhaphy (block level T4–6) (197). No other medications were given. Both infants had frequent episodes of perioperative apnea and associated bradycardia. One had a 20-second bout of apnea, with an oxygen saturation of 70% and a heart rate of 80/minute, the other a 30-second bout of apnea, with a saturation of 70% and a heart rate of 60/minute. These episodes persisted for 8 hours into the postoperative period in one of the infants.

- A patient who was receiving modified-release morphine for malignant pain had a respiratory arrest after intrathecal bupivacaine 12.5 mg. She recovered after treatment with naloxone. Another patient who was taking modified-release morphine was given intrathecal morphine 10 mg and bupivacaine 7.5 mg. He had respiratory distress and became comatose. Morphine-induced respiratory depression was not diagnosed and the patient subsequently died. In both cases, respiratory distress and sedation was probably due to opioid action in the absence of the stimulating effect of pain on respiration, due to the intrathecal bupivacaine (198).
- A 20-year-old woman who received a combined spinal epidural for labor had a respiratory arrest 23 minutes after the administration of sufentanil 10 micrograms and bupivacaine 2.5 mg (199).

Nervous system

- A 40-year-old woman developed acute aphasia and a change in mental status 15 minutes after the intrathecal administration of sufentanil 10 micrograms and isobaric bupivacaine 2.5 mg as part of a combined spinal epidural anesthetic for analgesia during labor (200). She appeared to be in a dissociated state, had apparent difficulty swallowing, and was aphasic, but able to follow simple commands. She had sensory block to T6 on the right and T8 on the left, with no motor block. The neurological picture resolved about 100 minutes after the anesthetic; an exact etiology could not be established.
- A similar case has been reported 20 minutes after the intrathecal administration of 0.5% hyperbaric bupivacaine 2 ml for cesarean section (201). She became unresponsive then apneic for a short time. There were no changes in heart rate or blood pressure and no loss of airway protection. She slowly regained consciousness over the next hour without any consequences.

The authors were unclear about the cause and suggested subdural injection, as the slow onset, stable hemodynamics, and rapid recovery were suggestive of this complication. However, other causes, including a psychogenic response, are possibilities.

- New onset, severe lightning pain after repeated subarachnoid blockade occurred in a 48-year-old man with pre-existing neuropathic pain after incomplete spinal cord injury, similar to previous reports in patients with phantom limb pain (202).

Postural headache is a common complication of spinal anesthesia (so-called postdural puncture headache). It is caused by CSF leakage through the puncture site. The incidence has been greatly reduced by the use of smaller-gauge and pencil-point spinal needles. However, headache (or psychosis) can be the presenting sign of subdural hematoma, which has twice been observed in women given spinal anesthesia for childbirth (SEDA-18, 143).

- A 30-year-old patient developed aseptic meningitis 24 hours after spinal anesthesia with bupivacaine plus fentanyl; it resolved without sequelae within 48 hours (203).

Conus medullaris syndrome has been reported after consecutive intrathecal injections of hyperbaric 1%

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tetracaine, followed by hyperbaric 5% lidocaine with adrenaline, in a patient with diabetic neuropathy (SEDA-21, 130).

Less frequent neurological complications are bladder dysfunction or sphincter paresis (204), intracranial hypertension, and convulsions, the latter reflecting systemic toxicity.

- A 36-year-old man had two generalized tonic-clonic convulsions after receiving intrathecal tetracaine 8 mg to supplement inadequate block established by intrathecal administration of tetracaine 10 mg (205). His seizures were controlled with intravenous thiamylal sodium. He regained consciousness, but complained of dizziness and blurred vision. He had a sensory block to T4–5.

The authors excluded total spinal anesthesia as a cause of the seizures, on the basis of the sensory level and the lack of hypotension.

Cauda equina syndrome

Cauda equina syndrome is the triad of bilateral paraparesis or paraplegia of the muscles of the legs and buttocks, saddle anesthesia plus sensory deficits below the groin, and incompetence of bladder and rectal sphincters, causing incontinence of urine and feces.

Cauda equina syndrome has been reported after the use of microcatheters for continuous intrathecal anesthesia. The concern was sufficient reason for the FDA to withdraw microcatheters from the US market after 11 cases of cauda equina in 1992 (SEDA-21, 129) (206). It has now become obvious that a confounding factor was the use of hyperbaric solutions pooling around lumbosacral nerve roots, aggravated by the poor mechanics of microcatheters and the use of inappropriate amounts; the authors of one study argued that the problem was not evident with the use of low concentrations of isobaric local anesthetics administered via microcatheters (207).

Six cases of the syndrome have also been reported after "single-shot" spinal anesthesia at the L3–4 interspace with 5% hyperbaric lidocaine (208).

- A 55-year-old man was given 5% hyperbaric lidocaine 100 mg intrathecally in the sitting position for transurethral resection of the prostate in the lithotomy position, with no complications. However, the next day he complained of persistent numbness of the perianal, scrotal, penile, and sacral regions, and both legs. He also had difficulty in defecation and weakness of both quadriceps muscles. Despite normal MRI scanning, electromyography, and electroneurography, he had no neurological improvement, even 1.5 years after the operation.
- A 59-year-old woman received 5% hyperbaric lidocaine 60 mg for an operation on a toe. That evening she complained of urinary and bowel incontinence; 5 months later she had urinary stress incontinence and bowel incontinence, with absent anal reflexes. There was also reduced sensation over the medial side of the foot.
- A 48-year-old woman had spinal anesthesia for hallux valgus surgery and had pain radiating to the left buttock during insertion of the needle. Hyperbaric 5% lidocaine 100 mg was injected, with no associated paresthesia. One month later, she complained of persistent numbness of the perianal and sacral regions and had sensory loss in these regions, which failed to improve over 6 months.
- A 31-year-old man had spinal anesthesia with 5% hyperbaric lidocaine 100 mg for fasciotomy. His systolic blood pressure briefly fell to 90 mmHg and he was given ephedrine. He later complained of persistent numbness of the entire right leg, right scrotum, right side of the penis, and right buttock, and had difficulty in micturition; there was no improvement one month later, and he had reduced pain and temperature sensation in the right leg, intact touch sensation, and weakness of right hip extension. His neurological state did not improve over a year.
- A 37-year-old woman had varicose vein surgery under spinal anesthesia with 5% hyperbaric lidocaine 120 mg in two injections followed by a general anesthesia, because the spinal block was inadequate. Postoperatively she complained of persistent numbness in the right buttock, difficulty in micturition, and bowel incontinence. She had reduced sensation in the perianal region and both labia majora, with a large residual urine volume. An MRI scan was normal, but electromyography, electroneurography, and cystometry 4 months later showed denervation of the pelvic muscles, partial denervation of the detrusor muscle, and signs of reinnervation. After 5 months her condition remained much the same.
- A 59-year-old man had spinal anesthesia for hallux valgus surgery with 5% hyperbaric lidocaine 75 mg. The next day he had persistent perianal numbness, difficulty in micturition, and a large residual urine volume. An MRI scan was normal and he had reduced perianal and scrotal sensation, difficulty in defecation, and erectile impotence. He was no better 5 months later.

The authors stated that at least some of the cases had probably resulted from neurotoxicity of hyperbaric lidocaine, most often in the absence of obvious maldistribution. They recommended that hyperbaric lidocaine should be used in concentrations not exceeding 2% and in a total dose no greater than 60 mg.

- A 75-year-old woman with a history of lumbar laminectomy, but no neurological deficit, received an intrathecal injection of 4 ml of 0.5% bupivacaine with preservatives at the L4–5 level using a 22-gauge spinal needle for a total knee replacement (209). Intraoperatively she complained of severe low back pain, which improved 8 hours later. In parallel, she developed persistent sensory loss to L1 and flaccid paralysis of both legs. An MRI scan was normal, but myelography showed inflammation of the cauda equina; 2 months later she developed hydrocephalus and had adhesive arachnoiditis of the thoracolumbar region. Her neurological condition did not improve over 2 years.

A retrospective review of 603 continuous spinal anesthetics (127 had microcatheters) showed three patients with postoperative paresthesia, one of whom was from

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the microcatheter group (210). One patient, who had received anesthesia via a macrocatheter with 5% lidocaine, developed sensory cauda equina syndrome.

- A 57-year-old man with pre-existing severe vascular disease was given bupivacaine 12.5 mg with 1:1000 adrenaline 0.2 ml for incision and drainage of a thigh abscess (211). After 2–3 minutes he complained of "severely painful warmth" on the anterior of both thighs. The pain resolved with onset of the block, but the next morning he had symptoms of cauda equina syndrome. Some perineal sensation returned over the next few days.

The authors suggested that the neurological deficit had been due to anterior spinal artery insufficiency secondary to intrathecal bupivacaine and adrenaline. They questioned the use of adrenaline in patients with multi-organ vascular disease.

- A man with severe vascular disease was given general and epidural anesthesia with 2% isobaric lidocaine plus adrenaline for a popliteal distal vein bypass graft (212). The epidural inadvertently became a total spinal, which was discovered at the end of the operation. He developed cauda equina syndrome, confirmed by electromyography. He was unable to turn or sit up by himself for a month and at 12 months was walking with a cane and needed self-catheterization and medication for neuropathic pain.

The cauda has a tenuous blood supply, and in this patient with pre-existing vascular disease, perioperative hypotension and the use of intrathecal adrenaline may have precipitated ischemia in an area with very poor reserve. To follow this with an accidental large dose of lidocaine, which is neurotoxic in animals when directly applied and theorized to cause interruption of nerve blood supply, would add insult to injury. The authors questioned the wisdom of performing continuous epidural anesthesia in such patients, when frequent neurological assessments cannot be performed.

Bupivacaine has recently been implicated in two cases of cauda equina syndrome (213). One patient was given 3.6 ml of a hyperbaric 0.5% solution, and the other, 3.5 ml of plain bupivacaine. Spinal stenosis was felt to have contributed to the first case, while the cause of the second was unclear.

- Cauda equina syndrome occurred in a 55-year-old woman who underwent spinal anesthesia with a 22 G needle in the L4–5 interspace (214). On needle insertion, she felt radiating pain in her right leg. The needle was immediately withdrawn and repositioned. Pain-free intrathecal injection of 2.0 ml of hyperbaric cinchocaine 0.24% with adrenaline 66 micrograms resulted in block to L1. Surgery was carried out in the supine position. Three days postoperatively, she had enuresis and reduced perineal sensation, without bowel dysfunction or lower limb symptoms. There was sensory loss at S2–5. The symptoms persisted, required self-catheterization and systemic steroids, and disappeared on the 19th postoperative day.

The cause of this transient neurological deficit was unclear, but the authors suggested that the following factors may have contributed:

- direct nerve damage;
- local anesthetic toxicity;
- adrenaline effects.

Transient radicular irritation

Neurological sequelae of intrathecal anesthesia are rare and usually minor. However, transient radicular irritation can occur with the use of both isobaric and hyperbaric solutions of local anesthetics. Hyperbaric 5% lidocaine is such a persistent offender that there is little to recommend its use in neuraxial blockade (SEDA-20, 125) (SEDA-21, 129) (SEDA-22, 138). However, others have suggested that lidocaine can be used for intrathecal anesthesia if a short-acting anesthetic is desired (215). There have also been reports with most other local anesthetics, including tetracaine and mepivacaine. High concentrations of hyperbaric 4% mepivacaine are likely to cause transient radicular irritation of the same order of magnitude as 5% lidocaine (216). A randomized study with isobaric mepivacaine 2% administered intrathecally to patients undergoing surgery in the supine position showed an incidence of 7.5% compared with 2.5% with isobaric lidocaine 2% (217). There is a low incidence of transient radicular irritation after intrathecal bupivacaine, but a few cases have been reported (SEDA-20, 125). Bupivacaine and tetracaine have toxic effects on chick neuron cultures in vitro (218).

Since the cause of transient radicular irritation after lidocaine intrathecal anesthesia has not been elucidated, and although non-neurotoxic mechanisms must be considered, it has been recommended that the lowest effective doses and concentrations for intrathecal injection should be used (219).

Presentation Transient radicular irritation causes transient pain in the back, buttocks, and lower extremities, without formal neurological signs or symptoms. It can follow single-dose intrathecal anesthesia. Lidocaine has been reported as the predominant culprit. However, transient radicular irritation has also been reported with bupivacaine, mepivacaine, tetracaine, and prilocaine. Osmolarity, the addition of dextrose, and speed of injection do not contribute, and even reducing the concentration of lidocaine does not alter the incidence (220,221).

Cases involving lidocaine (222–224) and mepivacaine (225,226) have been reported.

- A 50-year-old woman had a right knee arthroscopy under spinal anesthesia with 1% lidocaine 4 ml. The anesthetic and procedure were uncomplicated. At 4 hours she complained of a mild cramp in her buttocks and went home at 6 hours. By the next morning the buttock pain was severe, cramp-like in nature, and radiated down the fronts of both thighs. Walking alleviated it, simple analgesics were ineffective, and lying down made the pain worse. Neurological examination was unremarkable and the pain was gone after 36 hours.
- A 74-year-old man who had a cystoscopy performed in the lithotomy position, reported dull pain in the hips, buttocks, and legs, radiating to the toes after a spinal anesthetic with 5% hyperbaric lidocaine 75 mg. The pain occurred 30 hours after the dural puncture and

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disappeared after 18 hours. Three months before he had had a similar anesthetic for a transurethral resection of the prostate and complained of similar but more severe symptoms of transient radicular irritation.

- A 66-year-old woman with unrecognized spinal stenosis had six spinal anesthetics over 3 years. The first five were with lidocaine 2%. After 24–48 hours, she developed pain in the back, hips, buttocks, and thighs, which lasted for 2–3 days. On the sixth occasion she had a spinal anesthetic with 1.5% mepivacaine 4 ml and the next day again had severe back pain radiating bilaterally to the hips and thighs.
- Three patients undergoing minor surgical procedures in the lithotomy position were given a spinal anesthetic with 2% mepivacaine 3 ml. From 6 to 10 hours postoperatively they complained of burning pain in both buttocks radiating to both thighs and calves. Neurological examination in all cases was normal and all symptoms had resolved by 3–5 days postoperatively.
- A 30-year-old man had a left spermatic vein ligature performed in the supine position. He had uncomplicated unilateral spinal anesthesia with 1% hyperbaric bupivacaine 8 mg. Three days later he reported an area of hypesthesia in the L3–4 dermatomes of the left leg. Sensation returned to normal after 2 weeks.

Incidence The incidence of transient radicular irritation varies depending on the local anesthetic used, its baricity, and its concentration. It has been reported to be as high as 37% in patients who receive 5% lidocaine. In a prospective study of 303 parturients undergoing intrathecal anesthesia using 0.75% hyperbaric bupivacaine or 5% lidocaine there were no cases of transient radicular irritation after lidocaine (227). This is remarkable, as significantly more procedures were performed in the lithotomy position in the lidocaine group; the authors wondered if such a low incidence of transient radicular irritation could have been explained by their use of a 1:1 dilution of lidocaine with cerebrospinal fluid.

Transient neurological symptoms have been studied in patients given intrathecal lidocaine 2% or intrathecal prilocaine 2%. In one study of 70 patients transient neurological symptoms occurred in 20% of patients given lidocaine, with no cases in those given prilocaine (228). In another study in 70 patients given intrathecal procaine or lidocaine in a 2:1 dose ratio there were significantly more transient neurological symptoms with lidocaine than with procaine (31 versus 6%) (229). However, in a similar study of 100 patients there was no significant difference in the incidence of transient neurological symptoms, although the trend suggested a lower incidence with prilocaine (4 versus 14.3%) (230).

In 110 patients presenting for knee arthroscopy who were randomized to receive either 1% hypobaric lidocaine 50 mg or 1% hypobaric lidocaine 20 mg + fentanyl 25 micrograms complaints of transient neurological symptoms were nearly ten times more frequent in those given lidocaine 50 mg (33 versus 3.6%) (231). Patients given lidocaine 50 mg also had a greater fall in systolic blood pressure and a greater need for ephedrine.

In a prospective study of 1045 patients receiving spinal anesthesia with 3% hyperbaric lidocaine for anorectal surgery in the prone position, 4 (0.4%) complained of aching, hypesthesia, numbness, and dull pain in both buttocks and legs on the third postoperative day. In three cases the symptoms resolved by day 5 and in one by day 7 (232).

In a retrospective audit of 363 patients receiving spinal anesthesia, of whom 322 received hyperbaric 5% lidocaine 75–100 mg and 41 hyperbaric 0.5% bupivacaine 12.5–15 mg, six patients given lidocaine reported back pain at 24 hours; five of them had undergone arthroscopy. One patient given bupivacaine, who underwent arthroscopy, complained of backache (233).

Over 14 months, 1863 patients received spinal anesthesia, of whom 40% were given bupivacaine, 47% lidocaine, and 13% tetracaine (234). Patients given lidocaine had a significantly higher risk of transient radicular irritation (relative risks 5.1 compared with bupivacaine and 3.2 compared with tetracaine). They were more likely to be men, have outpatient surgery, and have surgery in the lithotomy position. For those who were given lidocaine, the relative risk of transient radicular irritation was 2.6, for those in the lithotomy position 3.6, and for ambulatory surgery 1.6. Most of the patients had resolution of symptoms by 72 hours and all by 6 months.

The incidence of transient radicular irritation with two different local anesthetics used for single-dose spinal anesthesia has been studied in 60 ambulatory patients given spinal anesthesia for knee arthroscopy (235). None of those who were given 1.5% mepivacaine 45 mg developed transient radicular irritation. Six of those given 2% lidocaine 60 mg developed transient radicular irritation, but all symptoms resolved by 1–5 days. The difference between the two groups was significant.

Of 90 patients who received intrathecal hyperbaric lidocaine 5%, mepivacaine 4%, or bupivacaine 0.5%, none in the bupivacaine group developed transient radicular irritation, but 20% in the lidocaine group and 37% in the mepivacaine group complained of a mixture of back and leg pain, classified as transient radicular irritation (216).

When 90 patients received spinal anesthesia for gynecological procedures with 2% lidocaine, 2% prilocaine, or 0.5% bupivacaine (all 2.5 ml in 7.5% glucose), nine of the 30 patients who received lidocaine had transient radicular irritation, defined as pain or dysesthesia in the legs or buttocks, compared with none of the 30 patients who received bupivacaine (236). The symptoms resolved within 48 hours. One of the 30 patients who received prilocaine had transient radicular irritation that lasted for 4 days.

In 200 patients given hyperbaric 5% lidocaine or hyperbaric 5% prilocaine, four developed transient radicular irritation after lidocaine (the patients were supine or prone) compared with one after prilocaine (this patient had a knee arthroscopy) (237). There were no significant differences between the two groups.

When procaine 5% or procaine 5% with fentanyl 20 micrograms was given to 106 patients for spinal anesthesia, the incidence of transient radicular irritation was 0.9% (238). There was nausea and vomiting in 17% of men and 32% of women.

Procaine has been suggested as an alternative to lidocaine for intrathecal use in ambulatory surgery, as it also

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has a short duration of action. In a randomized, double-blind comparison of procaine 10% or lidocaine 5% in glucose 7.5% for spinal anesthesia, transient radicular irritation occurred in 27% of the lidocaine group compared with none of the patients in the procaine group (239). However, the failure rate in the procaine group was 14%. This was perhaps a reflection of the fact that the procaine was glucose-free.

Intrathecal hyperbaric lidocaine 1.5% has been compared with hyperbaric bupivacaine 0.75% for outpatient transvaginal oocyte retrieval (240). The time to voiding of urine and the time to discharge were significantly longer in the bupivacaine group, despite the fact that there were no differences in the time to recovery of sensory and motor function. The incidence of transient radicular irritation in the lidocaine group was 5%, compared with none of the women in the bupivacaine group. The authors concluded that bupivacaine was a useful alternative to lidocaine in outpatient spinal anesthesia.

There have been two studies of transient radicular irritation in the obstetric population. One was a randomized, double-blind comparison of intrathecal hyperbaric lidocaine 5% or bupivacaine 0.75% for postpartum tubal ligation (241). All the patients were supine for surgery. The incidence of transient radicular irritation was 3% with lidocaine and 7% with bupivacaine. The other was a prospective follow-up study of patients who had cesarean sections under spinal anesthesia using hyperbaric 0.5% bupivacaine; the incidence of transient radicular irritation was 8.8% (242).

In a careful meta-analysis, 29 randomized, controlled studies of the incidence of transient radicular irritation were identified (243). Lidocaine and mepivacaine were identified as the two local anesthetics that most commonly cause transient radicular irritation, while prilocaine, bupivacaine, and ropivacaine had the lowest incidences. Owing to insufficient data, definitive statements could not be made about the effects of the baricity of the local anesthetic, the concentration, and the effect of vasoconstrictors, although all these factors seemed not to be relevant. With regard to intrathecal ropivacaine, the incidence in the formal studies was zero. However, there has been one previous report after intrathecal administration, and one report of transient radicular irritation following epidural anesthesia with ropivacaine; the symptoms resolved within 24 hours (244).

Mechanism The cause of transient radicular irritation is unclear but probably multifactorial. Several factors have been implicated (SEDA-21, 130) (220,245):

(a) high concentrations of local anesthetic producing neurological injury;
(b) possibly the high osmolarity and density of some solutions;
(c) the addition of vasopressors that compromise neural blood flow;
(d) pooling of anesthetic around nerve roots;
(e) the patient's position, with a significantly higher incidence in patients positioned for knee arthroscopy and the lithotomy position (stretching lumbosacral nerve roots);
(f) co-existing disease subarachnoid lidocaine;
(g) ambulatory surgery;
(h) stretching of nerve roots.

With the introduction of 25 gauge and 27 gauge spinal needles, it was suggested that slow injection may be an additional factor predisposing to transient radicular irritation, since layering of the hyperbaric fluid in the dependent portion may lead to areas of highly concentrated local anesthetic (246).

The high baricity of the local anesthetic solutions was thought to be chiefly responsible for transient radicular irritation. However, isobaric local anesthetics have also been implicated; commonly the concentrations are 2% or greater. From comparisons of 2 and 5% hyperbaric and isobaric lidocaine and hyperbaric 0.5% bupivacaine, it seems more likely that high concentrations of local anesthetic solutions are responsible for transient radicular irritation rather than the osmolarity of the solutions (247–249). That the concentration of lidocaine is not a contributory factor to transient radicular irritation has been shown in 109 patients who received hyperbaric spinal lidocaine 50 mg, as a 2, 1, or 0.5% solution (250). The incidence of transient radicular irritation did not differ (16, 22, and 17% respectively).

The importance of the patient's position has been illustrated by a study in which transient neurological symptoms occurred in five of 12 volunteers who were given 5% lidocaine 50 mg intrathecally and then placed in the low lithotomy position (251). No consistent abnormalities were detected by prespinal and postspinal electromyography, nerve conduction studies, or somatosensory evoked potentials. This is in line with the current opinion that transient neurological symptoms constitute neither a true neurological syndrome nor an expression of the neurotoxicity of local anesthetics.

In 70 patients undergoing surgery in the supine position, there were transient neurological symptoms in 26% of patients after intrathecal lidocaine, compared with 3% after intrathecal bupivacaine (252). The incidence of transient neurological symptoms after intrathecal lidocaine 5% in patients undergoing surgery in the supine position is therefore similar to the previously reported incidence in the lithotomy position.

Animal studies have highlighted the potential toxic effects of adding adrenaline to local anesthetics for intrathecal injection. In one study the effects of adding 0.01% adrenaline to intrathecal tetracaine 1% and 2% was investigated in rabbits (253). Although adrenaline had no neurotoxic effects when given alone, there was worsening of neurotoxicity when it was given in combination with tetracaine. The same group had previously shown an increase in glutamate concentrations in the CSF and dose-dependent neurotoxicity with tetracaine injected intrathecally in rabbits (254). In another study they looked at the effects of intrathecal lidocaine 5% with and without adrenaline 0.02% on the spinal cord and nerve roots of rats (254). They showed that lidocaine 5% caused persistent sensory impairment and histological damage that was significantly exacerbated by the addition of adrenaline.

Several explanations for the increased neurotoxicity of vasoconstrictors, such as adrenaline and phenylephrine, in combination with local anesthetics have been offered:

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(a) vasoconstrictors may reduce the absorption of local anesthetics and thereby increase anesthetic exposure intrathecally;
(b) a reduction in blood flow caused by vasoconstrictors may cause ischemia in the spinal cord;
(c) bisulfite, used as a preservative in adrenaline formulations, which may have a role, although that would not explain the lack of toxicity seen with adrenaline alone.

A randomized study in 64 patients undergoing urological, gynecological, or lower limb surgery showed no significant difference in the incidence of transient neurological symptoms between hyperbaric tetracaine 0.5% with and without phenylephrine 0.025% (255). In fact, the neurological symptoms that were described (in 6.7% of the patients) occurred in the group without phenylephrine and could possibly have been explained by the patient's position or by the effects of plaster-cast compression postoperatively.

Early ambulation has previously been implicated in transient radicular irritation. However, in a randomized trial there was no difference between early and late mobilization in patients who received intrathecal lidocaine 2% for inguinal hernia repair; the incidence was 23% in both groups (256).

In a prospective audit of 100 patients having intrathecal anesthesia with 5% hyperbaric lidocaine in a mean dose of 73 mg, there was an unusually low incidence of 4% (257). All the patients recovered completely, which led the authors to conclude that 5% hyperbaric lidocaine is acceptable for intrathecal anesthesia in patients in whom rapid recovery from the block is desired. The low incidence in this study might have been due to the fact that the patients were placed in the supine or lateral position, as patient position has previously been reported to be a risk factor for the development of transient radicular irritation, the lithotomy position and knee arthroscopy having a higher incidence, possibly owing to excessive stretching of the nerve roots, leading to ischemic damage.

This impression has been confirmed by three recent reports of patients who developed transient radicular irritation after intrathecal anesthesia, as all these patients had surgery in positions that could have caused excessive stretching of nerve roots.

- A 44-year-old man developed transient pain in the buttocks and thighs 4 hours after 4% hyperbaric mepivacaine had been used to provide anesthesia for knee arthroscopy (258). The symptoms resolved after 2 days.
- A 46-year-old woman had an epidural placed at L4/5 (259). As there was insufficient block 20 minutes after injection of 300 mg mepivacaine, the epidural catheter was removed and an intrathecal injection of 0.5% tetracaine 2 ml dissolved in 5% glucose was performed. She was then placed in the lithotomy position for 30 minutes. One day postoperatively she developed pain and numbness in her left leg, and the numbness spread to the lower back, buttocks, and thighs. The symptoms disappeared after 4 days.
- A 50-year-old man had an intrathecal injection of 2% lidocaine 40 mg diluted to 1% with sterile water, while in the prone jack-knife position for excision of a pilonidal cyst (260). About 7 hours after the start of the block he developed acute sharp lower back pain radiating to the right buttock. There were no accompanying neurological signs. The pain settled with ketorolac and was gone after 5 days.

The last case is the first report of transient radicular irritation after the use of hypobaric lidocaine, but it again suggests the importance of sciatic stretching.

A high concentration of tetracaine given intrathecally in rabbits caused neuronal injury and glutamate release in the CSF (254). The authors postulated that this might give some insight into the mechanisms of neurotoxicity of intrathecal local anesthetics.

An animal study of the histological and physiological effects of intrathecal lidocaine at varying concentrations from 3 to 20% showed the presence of lesions in the posterior roots and columns characterized by axonal degeneration (261). The lesions were severe at higher concentrations, but even at the lower concentration of 7.5% there were mild lesions that did not correlate with the presence of neurofunctional deficit.

In a study of the effect of clinically relevant concentrations of lidocaine, bupivacaine, mepivacaine, and ropivacaine on cultured neurons, the local anesthetics caused destruction of the growth cones, implying that they have a toxic effect on the growth and regeneration of neuronal tissue (262). Lidocaine had the most marked effect and mepivacaine the least. While this might not be of direct relevance to the etiology of transient radicular irritation, the authors pointed out the potential risks of using local anesthetics in very young children, taking into consideration the difficulties of extrapolating from in vitro studies to in vivo use.

Sensory systems

Hearing

In some series, transient hearing loss after anesthesia with bupivacaine was found with intrathecal but not epidural administration (SEDA-13, 99) (SEDA-16, 129)(263). It has been suggested that the cause could be a reduction in CSF pressure transmitted through the cochlear aqueduct (264), a hypothesis that has been both supported and criticized (SEDA-16, 129). Sensorineural hearing loss after spinal anesthesia with bupivacaine has been thought to be due to the entry of bupivacaine into the inner ear, resulting in a direct effect on its functional apparatus (265).

When 44 patients undergoing inguinal hernia repair were given intrathecal anesthesia with 2% prilocaine 6 ml or 0.5% bupivacaine 3 ml, those given prilocaine had an average hearing loss of about 10 dB and 1–3 days postoperatively and those given bupivacaine had an average hearing loss of about 15 dB (266). However, 10 of 22 in those given prilocaine developed hearing loss, compared with four of the 22 given bupivacaine.

Gastrointestinal

Dysphagia has been reported from the cephalad spread of a spinal anesthetic (267).

- A 26-year-old woman underwent cesarean section with an intrathecal injection of 12 mg of 0.75% hyperbaric

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bupivacaine, fentanyl 25 micrograms, and morphine 0.2 mg. After 4 minutes she developed hypotension, which was treated with ephedrine. Another 4 minutes later she became agitated and complained of difficulty in swallowing. At this stage she had a block to T4 with no dyspnea, her facial sensation was normal, and phonation was intact; the dysphagia resolved within 30 minutes.

Urinary tract

Urinary retention as a true transient neurological symptom developed after accidental total spinal anesthesia with mepivacaine, which is often considered to be the best agent for intrathecal anesthesia, owing to its low incidence of transient radicular irritation (268).

- A 71-year-old man received an intrathecal anesthetic with 2 ml of 0.3% hyperbaric mepivacaine using a 25-gauge Quincke needle at the L3–4 interspace, before which he had slight hypesthesia in the L5–S1 dermatomes in the right leg, reportedly having originated from the use of local anesthetic in the lumbar spine 16 years before to treat severe lumbago (269). When he was turned supine he started to complain of severe lightning pain in the region of his hypesthetic segments, which completely resolved 4 hours later.

Musculoskeletal

Profound musculoligamental relaxation by high doses of local anesthetics may contribute to the development of postoperative musculoskeletal pain. Of 60 patients who received either spinal anesthesia with hyperbaric 5% lidocaine (85–100 mg) or balanced general anesthesia with neuromuscular blockade, there was transient radicular irritation in eight patients who received spinal anesthesia and in one who received general anesthesia, a significant difference (270). However, there was non-radiating back pain in ten of the patients who received spinal anesthesia and in six of those who received general anesthesia.

Sexual function

For reasons that are not understood, intraoperative penile erection is sometimes observed with neuraxial blockade; it can be followed by prolonged priapism (SEDA-14, 110).

A long-standing belief that intrathecal anesthesia in young men reduces sexual potency was not confirmed in a retrospective study (SEDA-17, 139).

Intravenous regional anesthesia

Systemic toxic reactions are the most common complications of intravenous regional anesthesia, and they occur soon after the tourniquet is released. In cases of early accidental tourniquet release or rupture, deaths have resulted; prilocaine seems to be the safest agent for this technique (271).

- A 74-year-old woman was given prilocaine 400 mg for carpal tunnel surgery. Within 3 minutes, she developed signs of central nervous system toxicity, sweating, and tachycardia. Twenty minutes later, her symptoms had resolved and the cause was found to be a leak in the tourniquet.

The authors used this case to stress the importance of adequately functioning equipment and the relative safety of prilocaine (272).

Methods of reducing the dose of lidocaine used in intravenous regional anesthesia by adding fentanyl 0.05 mg, pancuronium bromide 0.5 mg, or both, have been evaluated in 60 patients undergoing elective forearm, wrist, and hand surgery; the dose of lidocaine used was 100 mg (273). None of the patients had signs of drug toxicity on release of the tourniquet; those who were given all three agents had better anesthesia and muscle relaxation. A separate group of volunteers, in whom the tourniquet was released immediately after injection of the lidocaine/fentanyl/pancuronium mixture, complained of minor adverse effects including mild dizziness and transient visual disturbances and one case of vomiting and moderate hypotension.

A study of lidocaine toxicity in intravenous regional anesthesia showed that two of 24 patients who were given 0.5% lidocaine 40 ml for carpal tunnel decompression had serum lidocaine concentrations above the target range 2 minutes before and 2, 5, and 10 minutes after distal tourniquet deflation (274). However, no patients had signs of central nervous system or cardiovascular toxicity.

Cardiovascular

Chloroprocaine, because of its rapid onset and ester hydrolysis, should be the ideal agent for intravenous regional anesthesia. However, there are reports that it can cause endothelial damage and dysrhythmias after tourniquet deflation (275).

- Phlebitis seems to have been triggered by intravenous regional anesthesia in a 32-year-old smoker who was also taking oral contraceptives (276).

Nervous system

In 15 volunteers, ropivacaine 1.2 and 1.8 mg/kg produced intravenous regional anesthesia as quickly as a conventional dose of lidocaine (3 mg/kg), but with more prolonged anesthesia (55 minutes before loss of pinprick analgesia) and motor block (120 minutes before return of hand grip strength) at the higher dose, suggesting that ropivacaine can provide a greater degree of residual analgesia (277). All the volunteers given lidocaine and only one patient receiving high-dose ropivacaine developed light-headedness and a hearing disturbance when the tourniquet was released after 30 minutes, but with individual peak arterial plasma ropivacaine concentrations lower than the mean values for the group. The authors pointed out the limitations of this study in terms of a small sample size and their inability to determine the safety of ropivacaine for intravenous regional anesthesia.

- A 56-year-old man developed unexplained acute aphasia when the tourniquet was released 20 minutes after the infusion of 0.75% lidocaine 20 ml for wrist surgery (278). He also had light-headedness, but no circumoral numbness or visual or auditory disturbances. He made a spontaneous recovery 20 hours later with no sequelae.

The correlation of nervous system adverse effects with plasma concentrations after the intravenous

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administration of 40 ml of lidocaine 0.5% plus ropivacaine 0.2% for regional anesthesia has been examined in 10 volunteers (279). The double-cuffed tourniquet was inflated for as long as it could be tolerated. The incidence, duration, and intensity of nervous system adverse effects were recorded at 3, 10, and 30 minutes after tourniquet release and correlated with venous samples. There was a lower incidence and shorter duration of nervous system adverse effects with ropivacaine than with lidocaine; however, the dose of ropivacaine was much lower than that of lidocaine and therefore no clear conclusions can be drawn. In view of the availability of safer and effective alternatives for intravenous regional anesthesia, such as prilocaine and lidocaine, the reasons for using ropivacaine are hard to comprehend.

Sensory systems

Ears

It has been suggested that ropivacaine is a good choice for intravenous regional anesthesia because of its longer duration of action and lower risk of toxicity. In 20 patients scheduled for upper limb surgery who received 40 ml of either ropivacaine 0.2% or lidocaine 0.5% for intravenous regional anesthesia, both agents provided same onset and quality of surgical anesthesia, but ropivacaine gave longer-lasting analgesia in the immediate postoperative period (279). Additionally, one patient in the lidocaine group had tinnitus on release of the tourniquet, while there were no adverse effects in the ropivacaine group.

Taste

When 20 patients each received 40 ml of 0.5% chloroprocaine or 0.5% lidocaine for intravenous regional anesthesia, chloroprocaine caused a significantly higher incidence of a metallic taste (22 versus 0%) than lidocaine; when the study was repeated using alkalinized instead of plain chloroprocaine, there was no significant difference between the groups (280).

Skin

When 20 patients each received 40 ml of 0.5% chloroprocaine or 0.5% lidocaine for intravenous regional anesthesia, chloroprocaine caused a significantly higher incidence of urticaria (28 versus 0%) than lidocaine; when the study was repeated using alkalinized instead of plain chloroprocaine, there was no significant difference between the groups (280).

Laryngeal anesthesia

Local anesthesia to the larynx, for example with 4% lidocaine, is generally safe. Laryngeal edema has been reported in a few cases, perhaps due to the propellant rather than to lidocaine itself (281). An unusual complication is mydriasis if part of the spray is accidentally directed to the eye (SEDA-18, 144).

- A 22-year-old man had a generalized tonic-clonic convulsion and loss of consciousness after an attempted superior laryngeal nerve block using 2% lidocaine 2 ml (282). The seizure was not terminated by intravenous diazepam 10 mg and he was intubated after intravenous thiopental and suxamethonium. He required two boluses of ephedrine 10 mg to maintain his blood pressure. Surgery proceeded uneventfully and he recovered without any sequelae.

The authors postulated vertebral artery injection of local anesthetic as the cause of the seizure and loss of consciousness.

Local anesthesia administered directly into a fracture hematoma can cause systemic absorption and toxicity (SED-12, 252) (283).

Lumbar plexus anesthesia

The combination of lumbar plexus and posterior sciatic nerve block represents an alternative to a neuraxial technique.

- An 80-year-old 41 kg woman was given a combination of a posterior lumbar plexus block and a posterior sciatic nerve block for dynamic hip screw repair of a fractured right neck of femur (284). The lumbar plexus block was technically difficult, requiring three attempts, and 25 ml of ropivacaine 0.75% (187.5 mg), adrenaline (1 in 400 000), and clonidine 50 micrograms was slowly injected, aspirating after every 3 ml. The sciatic nerve block was straightforward, and 20 ml of a solution containing mepivacaine 1.5% (300 mg), adrenaline 1 in 400 000, and clonidine 50 micrograms was injected slowly. She had seizures and dysrhythmias 20 minutes after completion of the block. Cardiopulmonary resuscitation was successful, surgery proceeded under general anesthesia, and she made a full recovery. Blood samples taken 5 minutes after the seizures contained ropivacaine 1.9 micrograms/ml and mepivacaine 3.7 micrograms/ml.

The authors suggested that the timing of events (the neurological signs preceded cardiac toxicity) suggested a toxic reaction to one of the local anesthetics or an overdose from their combination.

Nasal anesthesia

Intranasal 4% lidocaine has been used for migraine and cluster headaches with success and few serious adverse effects: a bitter taste was common and some patients complained of nasal burning and oropharyngeal numbness

Unilateral mydriasis (anisocoria), suggesting serious neurological injury, has been attributed to topical cocaine (285).

- A 51-year-old man developed mydriasis in one eye, with loss of the accommodation reflex, immediately after endoscopic sinus surgery, before which 4% cocaine had been applied to the nasal mucosa on cotton pledglets. There were no surgical or anatomical complications.

The authors suggested a diagnosis of local anesthetic blockade of the nasociliary nerve.

Acute angle closure glaucoma has been attributed to local cocaine (286).

- A 46-year-old woman developed acute angle closure glaucoma 24 hours after the application of topical intranasal 25% cocaine (about 200 mg) for an elective antral washout under general anesthesia. She developed a severe headache around the right eye, with halos and blurring of vision on the same side and associated

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nausea and vomiting. The next day, when she awoke, she had completely lost the vision in that eye.

Neck anesthesia

With regional anesthesia in the neck there is a risk of inadvertent intra-arterial injection; this could explain one report of convulsions in an elderly woman (287). There is also a risk of subarachnoid injection and pneumothorax.

Obstetric anesthesia

When a local anesthetic is used for episiotomy, there is a risk that the needle will enter the child's scalp; in two cases involving prilocaine, this resulted in cyanosis, methemoglobinemia, and hemolytic anemia (288).

Retroperitoneal hematoma has been reported as a complication of pudendal block, probably due to pudendal artery perforation (SEDA-21, 134).

Prilocaine 3% + felypressin 0.03 IU/ml has been compared with lidocaine 2% + adrenaline 12.5 micrograms/ml in 300 women having large-loop excision of the cervical transformation zone (289). Those who received lidocaine had significantly less blood loss, but were more likely to have adverse effects, including shaking and feeling faint.

Ocular anesthesia

A cluster of 25 cases of transient or permanent diplopia occurred after 13 retrobulbar blocks, 10 peribulbar blocks, and two unknown techniques, possibly related to the non-availability of hyaluronidase, highlighting the likely importance of hyaluronidase in preventing anesthetic-related myopathy in the extraocular muscles (290). Other reports of 21 cases of persistent postoperative diplopia following the peribulbar technique (291) and 4 cases following the retrobulbar technique during the period of non-availability of hyaluronidase support this theory (292). Bupivacaine and lidocaine may be contraindicated for peribulbar or retrobulbar injections without hyaluronidase.

Severe sneezing after ocular local anesthetic injection during intravenous sedation has been linked to photic sneezing. However, in 557 patients there was no relation between the two (293). Severe involuntary sneezing occurred after ocular blockade under thiopental sedation overall in 5.2% and only in 7.6% of those with a history of photic sneezing; peribulbar block had a significantly higher incidence of involuntary sneezing compared with retrobulbar block (24 versus 4.5%). Sneezing can occur with many hypnotics and after injections inside the muscle cone and outside the orbit, without pupillary dilatation or lid elevation (294). Awareness of this phenomenon can facilitate recognition and prompt needle withdrawal to avoid serious problems from sudden head movements during injection.

Ocular explosion occurred in seven cases after periocular anesthetic injections (295). To minimize the incidence of ocular explosion, the authors recommended the following:

(a) use a blunt needle and a 12 ml syringe;
(b) aspirate the plunger and wiggle the syringe before injection;
(c) discontinue the injection if corneal edema or resistance to injection is noted;
(d) inspect the globe for evidence of intraocular injection before ocular massage or placement of a Honan balloon.

Retrobulbar anesthesia

Retrobulbar anesthesia, competently administered, is a safe procedure. In 13 000 patients in whom a curved needle technique was used, the only serious complication was a single case of postoperative ischemic neuropathy (296). However, other centers have experienced recurrent problems with chemosis (up to 30%), sub-conjunctival hemorrhage, and lid hemorrhage before perfecting their technique (SEDA-18, 144).

Inadvertent injection into the subarachnoid space surrounding the optic nerve has on various occasions led to bilateral impairment of vision and ophthalmoplegia, with varying degrees of nervous system and respiratory effects, ranging from pulmonary edema (297) to respiratory arrest (SED-12, 254) (SEDA-21, 133) (298). Similar adverse effects result from diffusion of the local anesthetic toward the cerebrospinal fluid (SEDA-14, 110). Several groups have shown that such complications can occur, especially with higher concentrations, independently of any fault in technique (SED-12, 254) (299). Patients must therefore be closely monitored during ocular anesthesia and surgery. Particular care should be taken in patients with orbital roof defects, as there is potential for local anesthetics to move rapidly into the nervous system, with severe toxic effects (SEDA-20, 126).

On the other hand, headache after bupivacaine-induced block has been traced to the use of a vasoconstrictor additive, and is more likely to occur with noradrenaline than adrenaline (300). Unwanted effects on the eye muscles, occurring in some 1% of retrobulbar blocks, extend to ptosis, horizontal rectus muscle palsy, and lagophthalmos; all recover spontaneously within a matter of weeks (301). It has been postulated that local anesthetics can be myotoxic, causing contracture and subsequent diplopia (302). Tissue pressure, causing ischemia, can also lead to muscle damage and subsequent contracture and strabismus (SEDA-22, 139).

Two cases of vitreous hemorrhage have been observed after retrobulbar block in patients with severe diabetic retinopathy (303).

- A retrobulbar injection in a 45-year-old woman with high myopia was complicated by globe perforation with vitreous and submacular hemorrhage (304).
- In another case, retrobulbar hemorrhage and raised intraocular pressure developed after subtenon block with lidocaine (305).

Retinal vascular occlusion is rare, but it can occur in patients with severe vascular disease, without retrobulbar or optic nerve sheath hemorrhage; the mechanism is unclear (SED-12, 254) (306).

There is a risk of traumatic optic nerve injury with retrobulbar block (SEDA-21, 134).

Complications from retrobulbar block can arise from accidental scleral perforation and intraocular injection of local anesthetic.

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- An 86-year-old man scheduled for cataract surgery sustained an inadvertent occult single perforating needle injury with an intraocular injection of 0.5% plain bupivacaine during a retrobulbar block using a long (38 mm) needle (307). He had pain on injection and a raised intraocular pressure, with corneal edema, poor iris detail, and a reduced red reflex. Paracentesis lowered the intraocular pressure and surgery proceeded uneventfully. At 6 weeks, he had a reduction in visual acuity, and a scan identified a vitreous hemorrhage and retinal detachment. Prompt vitreoretinal surgery was performed with reasonable success.

The authors added that retinal toxicity of the local anesthetic agent did not affect the visual outcome in this patient. Scleral perforation is a well-known complication of eye blocks for ophthalmic surgery. The incidence with retrobulbar techniques is 0.075% and with peribulbar blocks 0.0002%. When recognized, ocular perforation usually requires a vitreoretinal procedure and is associated with a poor visual outcome. Risk factors include an anxious or oversedated patient, long sharp needles, superior injection, incorrect angle of needle insertion, and myopic eyes. If the intraocular pressure is increased, paracentesis may acutely reduce it, preventing retinal and optic nerve ischemia and possible permanent visual loss.

Retrobulbar anesthesia can lead to serious systemic toxicity. However, in animal studies accidental intravitreous spread of lidocaine, bupivacaine, or a mixture of the two did not cause long-term retinal damage (308).

Possible techniques to reduce complications include avoiding Atkinson's position, the classical position for retrobulbar block (309), during injection, limiting the volume of solution injected, and the use of shorter needles (310,311).

Retrobulbar anesthesia can be complicated by brainstem anesthesia (312).

- A 79-year-old man received retrobulbar anesthesia using a 1:1 mixture of 2% lidocaine and 0.5% bupivacaine plus hyaluronidase, which was complicated by brainstem anesthesia presenting as dysarthria. Initially there was some resistance to injection and the syringe was withdrawn slightly before injection of 4 ml of solution; 5 minutes later he complained of a strange sensation in his throat, which progressed to difficulty in swallowing and not being able to speak above a whisper. His blood pressure rose to 210/118 and his pulse to 120/minute; he also had signs of involvement of cranial nerves III, VI, and XII. He received glyceryl trinitrate for the hypertension and by 24 hours all the cranial nerve symptoms and signs had resolved.

Two cases of cardiopulmonary arrest after retrobulbar block for corrective squint surgery have been described (313). Both the patients were fit, healthy young men and they received a retrobulbar block with 2% lidocaine 2 ml via a 23G 1.5" needle after negative aspiration. Three minutes later both complained of breathlessness and rapidly became apneic and unresponsive, with unrecordable pulse and blood pressure. Both were resuscitated and became fully alert within 40 minutes. Possible reasons suggested were an allergic reaction, a direct toxic effect, a vasovagal attack, intra-arterial injection, or injection directly into the optic nerve sheath with spread of the local anesthetic into the CSF. The latter seemed to be the most likely in these cases. Since then the authors have altered their technique, including changing the position of gaze and using a short blunt needle. These cases illustrate the need for careful monitoring, knowledge of potential complications, and the ready availability of resuscitation facilities (including appropriately trained personnel familiar with the equipment), even when performing what many regard as minor local anesthetic blocks.

Peribulbar anesthesia

Peribulbar anesthesia is generally considered safer than retrobulbar anesthesia, with a lower incidence of adverse effects. It avoids deep penetration of the orbit and therefore inadvertent subarachnoid injection. It also seems to be safer with regard to the risk of bulb perforation (314).

Cardiovascular

In addition to complications arising from the local anesthetic used during ocular anesthesia, complications can arise as a direct result of the injection. An arteriovenous fistula has been reported (315).

- An arteriovenous fistula of the supraorbital vessels developed in a 75-year-old man after peribulbar anesthesia with a supplementary supranasal injection. He elected to have conservative management and the lesion remained asymptomatic and static in size over 10 months follow-up.

Respiratory

Pulmonary edema has been attributed to lidocaine (316).

- A 74-year-old woman had peribulbar blockade with 4 ml of 2% lidocaine at the inferotemporal approach and then 3 ml at the medial approach. She had a history of mitral stenosis, occasional angina, and possibly myocardial infarction, but denied breathlessness on exertion, nocturnal dyspnea, or orthopnea. She had breathlessness and sweating 10 minutes after the medial injection. She then developed hypoxia and a few minutes later began to cough up pink frothy secretions, required intubation, and developed a sinus tachycardia without acute electrocardiographic or cardiac enzyme changes.

The authors assumed that she had developed neurogenic pulmonary edema, probably worsened by the co-existing myocardial disease.

Sensory systems

Nine patients developed prolonged symptomatic diplopia (predominantly vertical) after peribulbar anesthesia with ropivacaine 1% plus hyalase 750 units (317). The mean time to resolution of the diplopia was 24 hours. The authors stressed the importance of warning patients undergoing peribulbar blockade with ropivacaine of the possibility of prolonged diplopia and queried its future use in routine cataract surgery.

Six cases of global perforation have occurred during routine cataract surgery (SEDA-21, 134). It has incidentally led to contralateral mydriasis, hemiplegic coma, and damage to the infra-orbital nerve (SEDA-18, 144). The contralateral

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eye may exhibit oculomotor weakness (SEDA-16, 130). Three other reports have highlighted problems.

- A 76-year-old man undergoing trabeculectomy developed bilateral amaurosis after a peribulbar block with 6 ml of a mixture of 2% lidocaine, 0.5% bupivacaine, and hyaluronidase (318). The authors thought it unlikely that the optic nerve sheath had been penetrated and suggested that local spread to the optic nerves via the subarachnoid or subdural space had been responsible.
- A 49-year-old woman had a tonic-clonic seizure about 15 minutes after a peribulbar block for left trabeculectomy (319). She recovered and surgery continued uneventfully. However, she had severe permanent visual loss in that eye, and an MRI scan at 4 weeks showed swelling of the left optic nerve. The authors suggested that some prilocaine had been injected into the nerve sheath, causing the convulsions, local optic nerve swelling, and subsequent optic nerve atrophy.

In 60 patients, peribulbar blockade was performed with either 8 ml of 0.75% ropivacaine or a 1:1 mixture of 2% lidocaine and 0.5% bupivacaine (320). Surgical block was achieved after a similar period of time in each group, but ropivacaine provided a better quality of postoperative analgesia, with no pain reported at 24 hours in 26 (87%) compared with 18 (60%) in the lidocaine + bupivacaine group. One patient given ropivacaine reported unbearable pain due to a high intraocular pressure, and the incidence of postoperative nausea and vomiting was under 7% in both groups.

In 54 patients who received peribulbar anesthesia with either 1% ropivacaine or a mixture of 0.75% bupivacaine + 2% lidocaine there was no significant difference in akinesia scores or adverse effects reported the following day, notably headache, dizziness, nausea, scalp anesthesia, and diplopia, the latter occurring in 26% and 30% respectively (321).

Peribulbar anesthesia with 1% etidocaine, 0.5% bupivacaine, and hyaluronidase has been evaluated in 300 patients (322). The mean volume administered was 17 ml. There was adequate analgesia in 85% of cases, and the other 15% required supplementation with a subtenon block. Akinesia occurred in 82% of cases. Two patients developed generalized seizures, and four developed severe hypotension.

- A rare case of hyphema after peribulbar block with 1% lidocaine 8 ml occurred in a 38-year-old woman with a history of Fuchs' heterochromic iridocyclitis (323).

Postoperative strabismus and diplopia occurred in two of 200 patients undergoing cataract extraction under peribulbar anesthesia; the symptoms resolved spontaneously by 6 months (324).

Hematologic

- A 27-year-old woman with diabetes mellitus, complicated by diabetic retinopathy and chronic renal insufficiency with anemia, developed methemoglobinemia (11%) after peribulbar blockade with prilocaine 80 mg, bupivacaine 30 mg, hyaluronidase, and naphazoline (325). She recovered uneventfully after methylthioninium chloride 1.5 mg/kg.

The authors concluded that she may have been at increased risk of methemoglobinemia as a result of the metabolic acidosis associated with renal insufficiency, since impaired protein binding of prilocaine could have increased the concentrations of ionized prilocaine. Furthermore, the patient was also taking isosorbide dinitrate, which may have predisposed her to methemoglobinemia.

Topical anesthesia

Topical anesthesia in the eye is relatively safe in controlled circumstances, when administered correctly (SEDA-20, 127). There does not seem to be any benefit in warming topical local anesthetic solutions before use (326).

Topical anesthetic abuse, mostly unintentional, remains a persistent cause of keratitis and epithelial defects, leading to continuing ocular pain, visual impairment, and at worst enucleation (SEDA-21, 134) (SEDA-22, 140) (327). Mechanisms include direct toxicity of the local anesthetic or preservative and immunological causes.

In 14 patients, 0.5% proxymetacaine had similar efficacy to 0.4% oxybuprocaine and 0.5% tetracaine but was significantly better tolerated (328).

There have been reports of topical ocular anesthetic abuse.

- A 49-year-old woman developed repeated episodes of severe keratitis after radial keratotomy for myopia (329). After 18 months of repeated hospital admissions, several operations, and considerably reduced visual acuity, it eventually transpired that she had been self-medicating with 1% proparacaine mixed with artificial tears to control pain after her surgery.

Abuse of these medications often results in irreversible corneal damage and visual loss (330). Two patients continued to instil their topical 0.5% tetracaine eye-drops, despite medical advice. The result was bilateral corneal perforation in the first case and a large unilateral descemetocele in the second. Surgery was required to correct the perforations, but the long-term anatomical and functional results were poor. A third patient had obtained 0.5% tetracaine hydrochloride drops over the counter to relieve discomfort in his eye after colleagues at work had attempted to remove a foreign body from his eye. He had developed chronic toxic keratitis and was persuaded to discontinue the eye-drops. With appropriate treatment the cornea returned to normal.

Lidocaine gel 2% has been compared with 0.5% tetracaine drops for topical anesthesia in cataract surgery in 25 patients (331). There were no corneal epithelial or ocular surface complications, demonstrating the safety of the gel, which may provide a more practical and efficient method of anesthesia, because it needs to be applied only once as opposed to three applications of the drops.

Differences in the manufacture of unpreserved lidocaine formulations have been postulated as a cause of transient corneal clouding in patients who were given intraocular unpreserved lidocaine 1% as an adjunct to topical anesthesia (332). Independent analysis of the lidocaine solution associated with corneal clouding found it to be hypotonic and not buffered with bicarbonate compared with the solution that did not cause corneal clouding.

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Intracameral anesthesia

Non-preserved intracameral lidocaine 1% is a useful adjunct to topical anesthesia for cataract surgery. In 631 patients, topical anesthesia alone was compared with combined topical and intracameral anesthesia (333) The combination had greater efficacy—only 1% of those given combined anesthesia needing to be converted to general anesthesia compared with 40% of those given topical anesthesia alone. The authors suggest that the key difference between the two methods is reduced sensitivity to the microscope light. Another prospective study in 93 patients showed that intracameral non-preserved lidocaine was both safe and efficacious; four patients reported discomfort and none had measurable endothelial cellular changes (334).

The endothelial toxicity of local anesthetics has been assessed in pigs, as this might be relevant to the safety of agents given by intracameral injection (335). Lidocaine, mepivacaine, and prilocaine were safe, while bupivacaine in clinically effective concentrations resulted in significant cell reduction.

Sub-tenon anesthesia

Sub-tenon infiltration of local anesthesia has recently become increasingly popular for cataract and vitreoretinal surgery; presumed advantages are its safety, speed of onset, and patient compliance. Three cases of persistent diplopia following sub-tenon local anesthesia have been reported (336). Two of the patients were given injections of 4 ml of a mixture of lidocaine 1% or 2% with adrenaline 1 in 100 000 and hyaluronidase 1500 units, and the third was given 4 ml of 0.75% bupivacaine with lidocaine. All had vertical diplopia, consistent with restriction of the inferior rectus muscle, which persisted for 2–9 months. The authors suggested possible mechanisms, including direct trauma to the muscle, inflammation and adhesions, infection, and myotoxicity of local anesthetics. They have since modified their technique, reducing the rate and force of infiltration.

An infectious complication of sub-tenon anesthesia has been reported (337).

- A 63-year-old woman underwent phacoemulsification and lens implantation under sub-tenon block. After the local anesthetic was injected, the eye was prepared with an aqueous solution of povidone iodine and the surgery proceeded uneventfully. At the end, gentamicin and betamethasone were injected subconjunctivally. Over the next few days she developed orbital cellulitis, requiring intravenous antibiotics.

The authors concluded that bacterial contamination of the episcleral space from the ocular surface or skin flora had occurred during or after the sub-tenon injection. They recommended applying topical povidone iodine before the episcleral space is opened, in order to reduce this risk.

Eyelid and conjunctival anesthesia

Local infiltration with prilocaine 2% was significantly more comfortable than lidocaine 2% in a prospective randomized study in 125 patients undergoing minor eyelid procedures (338).

Two cases of transient blindness after subconjunctival injection of 2% mepivacaine 2 ml were reported in patients with advanced refractory glaucoma undergoing diode laser cyclophotocoagulation (339). The authors hypothesized that in patients with advanced optic neuropathy, even subconjunctival anesthesia can result in optic nerve block.

Oropharyngeal anesthesia

Reduced hepatic clearance, as well as relative overdosage, of local anesthetics can lead to systemic toxicity, as illustrated by three patients who underwent topical anesthesia of the oropharynx for transesophageal echocardiography and subsequently became confused and drowsy (SEDA-21, 135).

- Acute bilateral parotid swelling occurred after upper gastrointestinal endoscopy in a 53-year-old woman who had gargled 2% lidocaine solution beforehand; the swelling was associated with difficulty in swallowing and resolved after treatment with intravenous glucocorticoids for 4 days (340).
- A 21-year-old developed seizures, respiratory distress requiring tracheal intubation, severe hypotension, and then bradycardia culminating in asystole and death while gargling with 4% lidocaine 20 ml (800 mg) (341).

The authors strongly advised against exceeding the maximum recommended dose of lidocaine (200 mg), even when using it topically.

Otic anesthesia

Transient vestibular irritation without hearing loss after infiltration of the auditory canal has been incidentally attributed to diffusion of the local anesthetic from the site of injection (342).

Paravertebral anesthesia

Postural headache after thoracic paravertebral nerve anesthesia, and probably reflecting dural entry, has been reported (343). Nerve root damage is another possible complication. Hematuria due to injury to the kidney or ureter is an unusual complication of lumbar paravertebral sympathetic block (344).

An epidural abscess and paraplegia occurred after paravertebral lidocaine infiltration for back pain (SEDA-21, 133).

Among 44 women who received a single paravertebral block with 0.3 ml/kg of 0.5% bupivacaine at the level of T4 for breast surgery, there was one incident of epidural spread of the block with paraparesis for 280 minutes accompanied by unilateral Horner's syndrome for 170 minutes (345).

Post-thoracotomy pain can be treated with thoracic epidural or thoracic paravertebral blockade. In 100 adult patients allocated to receive one of these treatments with preoperative bolus doses of bupivacaine followed by a continuous infusion there was less postoperative respiratory morbidity and significantly better arterial oxygenation in the paravertebral group; nausea (10 versus 2), vomiting (7 versus 2), and hypotension (7 versus 0) were more problematic in the epidural group (346).

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Perianal anesthesia

Local anesthetic ointments are widely used to relieve the symptoms of hemorrhoids and anal fissures. Absorption through the mucosa can be considerable; a case of convulsions as a suspected consequence of such treatment has been cited (SED-12, 253) (347).

Peritonsillar anesthesia

A stroke occurred after infiltration of the tonsillar bed with bupivacaine subsequent to tonsillectomy (348).

- A 16-year-old girl undergoing adenotonsillectomy had cardiac asystole for 10 seconds after injection of her adenoid bed with 0.5% bupivacaine 1 ml with adrenaline 5 micrograms/ml. She had already been given an unstated quantity of bupivacaine with adrenaline 5 micrograms/ml injected into her tonsillar fossae. Her cardiac output returned spontaneously, but she had a central medullopontine infarction, confirmed on MRI and CT brain scans. Magnetic resonance angiography showed an abnormal circle of Willis, with absence of both posterior communicating vessels. The authors were unclear as to the exact cause of the cardiac event and stroke, which resulted in a persistent neurological deficit.

Two cases of medullary injury after injections of local anesthetics intraoperatively have been reported (349).

- A 4-year-old child received injections of lidocaine plus adrenaline into the anterior tonsillar pillars and nasopharynx during adenotonsillectomy. After the procedure, he became agitated and dysarthric, vomited, and had abnormal eye movements. He was unable to stand and walk, owing to ataxia. An MRI scan showed a cavity in the right paramedian medulla.
- A 7-year-old boy underwent tonsillectomy, with an injection of lidocaine plus adrenaline into the operative field. After surgery he was lethargic, and during the next 24 hours he developed respiratory distress requiring mechanical ventilation. He was pyrexial (41.8°C) and had cardiomegaly and a left hemiparesis. A cranial MRI scan showed a hemorrhagic lesion in the right paramedian medulla.

Both patients had lesions in the medial medulla supplied by branches of the anterior spinal and vertebral arteries, and although such cases are rare it seems wise, in the light of these reports, to avoid the routine use of adrenaline as an adjunct to local anesthesia for adenotonsillectomy.

Excessive volumes of local anesthetic in a confined space can lead to life-threatening upper airway obstruction. When glossopharyngeal nerve blocks are used for tonsillectomy, children under 15 kg should be given 1 ml or less of 0.25% bupivacaine per tonsil (350).

Respiratory anesthesia

Topical anesthesia of the airways is commonly used to facilitate endoscopy and sometimes manipulation of the airways. This can result in an increase in airway flow resistance, possibly due to laryngeal dysfunction (351). Lidocaine spray 10%, used for upper airways anesthesia for fiber optic intubation in a grossly obese patient, caused acute airway obstruction. The patient went on to have a percutaneous tracheotomy, and it was postulated that the local anesthetic had abolished laryngeal receptors responsible for airway maintenance, or that laryngospasm and reduced muscle tone due to the lidocaine might have been the cause (SEDA-22, 140).

- Unilateral bronchospasm has been described in a 19-year-old woman after the administration of lidocaine 4% 5 ml into the larynx via a Laryngojet injector (352).

Lidocaine gel is not recommended for lubrication of laryngeal masks. It confers no benefits and increases the incidence of adverse effects such as intraoperative hiccups, postoperative hoarseness, nausea, vomiting, and tongue paresthesia (353).

- A patient due to have a bronchoscopy was given an overdose of lidocaine to anesthetize the airway by an inexperienced health worker. He was then left unobserved and subsequently developed convulsions and cardiopulmonary arrest (354). He survived with severe cerebral damage. His lidocaine concentration was 24 micrograms/ml about 1 hour after initial administration (a blood concentration over 6 micrograms/ml is considered to be toxic).
- A 19-year-old healthy volunteer undergoing bronchoscopy was given about 1200 mg of lidocaine to anesthetize the airway and was sent home after the procedure, despite complaining of chest pain. Shortly afterwards she had a tonic-clonic seizure and cardiopulmonary arrest and died 2 days later. The research protocol had failed to specify an upper dose limit for lidocaine (355).

Sciatic nerve anesthesia

Sciatic nerve anesthesia can cause cardiovascular depression (356).

- A 74-year-old man was to receive a combined sciatic nerve and psoas compartment block for a total hip arthroplasty; the classic Labat's approach was used and 30 ml of 0.75% ropivacaine was injected over 1.5 minutes, after which he suddenly became unresponsive and developed tonic–clonic movements. Propofol was administered and the seizure resolved, but he developed sinus bradycardia with progressive lengthening of the QRS interval, which converted to nodal bradycardia. A ventricular escape rhythm at 20/minute with T wave inversion was treated with ephedrine 10 mg and adrenaline 0.1 mg, resulting in supraventricular tachycardia with transient atrial fibrillation.

The authors pointed out that an equipotent dose of bupivacaine would have resulted in worse cardiovascular depression with less chance of successful resuscitation.

Stellate ganglion anesthesia

Inadvertent spinal anesthesia and subsequent nervous system toxicity, for example with transient paralysis or apnea, are the main complications of stellate ganglion block (SEDA-22, 140). It has been suggested that ultrasound guidance when performing the block might improve safety (357). The use of very small test doses and an anterior approach to the stellate ganglion are recommended preventive measures.

Brachial plexus paresis has been reported (358). Accidental block of the recurrent laryngeal nerve can cause hoarseness and occasionally aspiration of saliva (359).

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In two women with Raynaud's syndrome, the symptoms were aggravated contralaterally after stellate ganglion block (SEDA-18, 145).

Severe hypertension has been reported after a left-sided block, possibly due to vagal nerve block and unopposed sympathetic output (SEDA-21, 134).

Convulsions are a recognized complication of inadvertent intra-arterial injection during stellate ganglion block; two such cases have been described (360).

- A 28-year-old 75 kg woman underwent stellate ganglion block for symptomatic treatment of Raynaud's syndrome. An anterolateral approach was used, guarding the carotid artery and jugular vein. After an aspiration test was negative in two planes, 5 ml of 1% lidocaine was injected over 2–3 seconds using a 20 G needle. However, a second aspiration test was positive for blood, the needle was pulled back, and on reinjection the patient immediately had a severe generalized tonic-clonic seizure. The patient made a rapid recovery with no further treatment and was fully conscious after 2 minutes.
- A 31-year-old 72 kg man with diabetes, who had had a below-knee amputation in the past, developed Buerger's disease affecting his hands, particularly on the right. He underwent his third stellate ganglion block for symptomatic treatment. An anterior paratracheal approach was used with a 20 G 3.5 cm needle; after an aspiration test was negative in two planes, 1 ml of 1% lidocaine was injected every 2–3 seconds. After one injection, he had an abrupt seizure which was treated with diazepam 10 mg. He made a full recovery and later completed his course of stellate ganglion blocks uneventfully.

It was thought that inadvertent vertebral arterial injection had occurred, with subsequent rapid elimination due to high cerebral blood flow. The authors suggested several precautions to minimize this risk, including using a large-diameter needle and using less than the calculated minimum arterial toxic dose of lidocaine (16.8 mg) as the initial test dose; for subsequent doses they suggested 5 mg.

Subcutaneous anesthesia

When infiltrating local anesthetics into the skin there is always a risk of intravascular injection (SEDA-17, 140), but it can be avoided by back-aspiration of the syringe or continuous advancement of the needle during injection.

Skin infiltration with local anesthetics can cause pain. The pain experienced during skin infiltration of lidocaine, chloroprocaine, and buffered solutions of both has been studied in 22 volunteers in a double-blind, randomized study (361). The pH of the solutions was unrelated to the pain score, but both formulations of chloroprocaine were significantly less painful than lidocaine.

A weak solution of lidocaine has sometimes been injected into excess fat before liposuction, so that the procedure can be carried out without general anesthesia. The technique is generally regarded as safe (362). However, deaths are reported, associated with local anesthetic toxicity or drug interactions (363).

Of 30 volunteers who had subcutaneous slow infusion tumescent anesthesia at 250 ml/hour with three solutions containing lidocaine 2 mg/ml, ropivacaine 0.5 mg/ml mixed with lidocaine 1 mg/ml, and ropivacaine 1 mg/ml alone, all containing adrenaline 1:1 000 000, one had a tingling sensation in the tongue after lidocaine and another went into vasovagal shock (364). In the same paper, 5020 surgical procedures were reported in 3270 patients using different strengths of ropivacaine alone (0.05–0.2%) with a maximum dose of 300 mg, or with a mixture of ropivacaine and prilocaine (0.08–0.3%) with a maximum ropivacaine dose of 160 mg and a maximum prilocaine dose of 300 mg. There was no methemoglobinemia and there were no minor or major adverse effects related to the local anesthetic. The maximum plasma concentrations were low, suggesting that higher maximum doses may be possible, provided adrenaline is added.

- Ventricular tachycardia, severe hypertension, and pulmonary edema developed in a 53-year-old woman soon after she had a skin flap infiltrated with 4 ml of 0.5% lidocaine and 0.0005% adrenaline (20 micrograms) (365).

This has been previously described during general anesthesia but not with a local anesthetic alone, and the author emphasized the risk of severe cardiovascular compromise, even with a small dose of adrenaline.

Five patients with complex regional pain syndrome received a subcutaneous infusion of 10% lidocaine, with successful alleviation of many of their symptoms; initially 200 mg/kg was infused but symptoms of vertigo and slurred speech each occurred in four of them and stuttering in three, so the rate was adjusted to 100–190 mg/hour and serum lidocaine concentrations of 0.1–8.1 micrograms/ml (average 3.7 micrograms/ml); other symptoms, such as aphasia, nausea, fatigue, metallic taste, lightheadedness, and perioral numbness, each occurred in over half of the patients (366).

An iatrogenic tension pneumothorax was the result of breast infiltration with lidocaine and adrenaline before an augmentation procedure (SEDA-20, 127).

Infiltration anesthesia has reportedly caused transient paralysis.

- Transient paraplegia occurred after wound site infiltration with bupivacaine in a 35-year-old woman during removal of a lumboperitoneal shunt that had been inserted 2 years previously for benign intracranial hypertension (367). Under general anesthesia with the patient in the left lateral position, a small incision was made over the right flank and the drain was easily removed. The site was infiltrated with 7.5 ml of 0.5% bupivacaine with adrenaline 1 in 200 000. During recovery, she was anxious and moderately hypotensive and had a flaccid paralysis from T4 down. An MRI scan was normal. She gradually recovered motor function, sensation, and pain at the wound site.

The authors concluded that the local anesthetic may have passed down a fistulous track into the subarachnoid space, producing spinal block.

Submucosal anesthesia

Complications noted at various times with submucosal use include allergic reactions to the parabens present in lidocaine, systemic effects due to general diffusion (which

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readily occurs), or necrosis (when adrenaline is included in the formulation) (SEDA-16, 131).

Urinary tract anesthesia

Urethral instillation of anesthetics is most likely to be needed in the elderly, in whom there may be marked absorption from the mucosa, especially if it is diseased or damaged. Seizures after instillation of lidocaine jelly (for example 20 ml of a 2% formulation) have been reported as a consequence of this (368).

Local anesthetic gels and creams used liberally on traumatized epithelium can be rapidly absorbed, resulting in systemic effects, such as convulsions, particularly if excessive quantities are used.

- A 40-year-old woman developed seizures after lidocaine gel 40 ml was injected into the ureter during an attempt to remove a stone (369).

Drug–Drug Interactions

Neuromuscular blockers

The effects of non-depolarizing neuromuscular blocking drugs can be potentiated and their actions prolonged by large doses of local anesthetics, because of depression of nerve conduction, inhibition of acetylcholine formation, mobilization, and release, reduced postsynaptic receptor channel opening times, and reduced muscle contraction (370).

Opioids

Opioids potentiate the analgesic effect of neuraxial local anesthetics, with minimal adverse effects (SEDA-18, 141) (SEDA-20, 121) (SEDA-22, 135), as shown in several studies with clonidine, fentanyl, morphine, or pethidine as the systemic or neuraxial analgesic, and bupivacaine, lidocaine, and ropivacaine as the local anesthetic. The benefits have been shown in relief of long-term pain and postoperative pain, in adults and children (SEDA-18, 141) (SEDA-18, 146).

Sulfones/sulfonamides

Local anesthetics, sulfones, and sulfonamides are all aniline derivatives, exposure to which, particularly to two or three concurrently, can predispose patients to methemoglobinemia (5,371,372).

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Lofepramine

See also Tricyclic antidepressants

General Information

Lofepramine is an imipramine analogue whose animal pharmacology suggests low toxicity (1). Its clinical efficacy is similar to that of imipramine and amitriptyline. Patients on lofepramine report less dryness of the mouth, fewer disturbances of accommodation, and less drowsiness, but a greater incidence of tremor (2).

Lofepramine has apparently not been compared with desipramine, to which it is mainly metabolized. The claim that lofepramine has fewer adverse effects than

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traditional tricyclic compounds must be viewed with skepticism (SEDA-11, 14). However, lofepramine is safer than conventional tricyclic antidepressants in overdose.

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Loganiaceae

See also Herbal medicines

General Information

The genera in the family of Loganiaceae (Table 1) include strychnos and trumpet flower.

Strychnos nux-vomica

The dried ripe seeds of *Strychnos nux-vomica* (nux vomica) contain the alkaloids strychnine and brucine, together with traces of other alkaloids.

Adverse effects

Strychnine is a powerful convulsant, which can cause serious and even lethal poisoning (1).

Maqianzi, the dried ripe seed of *S. nux-vomica* contains 1.0–1.4% each of strychnine and brucine. It has been used as a herbal remedy for rheumatism, musculoskeletal injuries, and limb paralysis.

- A 42-year-old woman with neck pain took 15 g of maqianzi in two doses 7 hours apart (recommended dose 0.3–0.6 g) (2). One hour after she took the second dose she suddenly developed tonic contractions of all her limbs and carpopedal spasm lasting 5 minutes, difficulty in breathing, chest discomfort, and perioral numbness. She complained of muscle pain and tiredness and had hyperventilation and weakness of all four limbs. All her symptoms gradually subsided over the next few hours.

Table 1 The genera of Loganiaceae

Fagraea
Gelsemium (trumpet flower)
Labordia (labordia)
Mitreola (hornpod)
Spigelia (pinkroot)
Strychnos (strychnos)

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Lomefloxacin

See also Fluoroquinolones

General Information

Lomefloxacin is a fluoroquinolone antibacterial drug with actions and uses similar to those of ciprofloxacin.

Organs and Systems

Gastrointestinal

In a multicenter, prospective, randomized study of oral lomefloxacin 400 mg/day in 182 patients with chronic bacterial prostatitis, the most frequent adverse events were gastrointestinal disorders (1).

Skin

Photosensitivity was found in 44 (1.03%) of 4276 patients treated with lomefloxacin in Japan. Most cases were not severe and improved after withdrawal. Risk factors for a sensitivity reaction were age over 60 years with concomitant diseases and complications, total amount of lomefloxacin over 20 g, treatment for longer than 30 days, and previous treatment with a quinolone (2).

In eight patients (mean age 69 years) with eczematous or acute sunburn-like lesions in photo-exposed areas, who took lomefloxacin for 1 week to several months, phototoxicity appeared to be the main mechanism of photosensitivity, particularly in older patients with concomitant diseases and long-term use of the drug (3).

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Lonazolac

See also Non-steroidal anti-inflammatory drugs

General Information

Lonazolac, an arylacetic acid derivative, causes adverse effects like those of other NSAIDs. Gastrointestinal disturbances are followed in frequency by nervous system and skin reactions. The extent of gastrointestinal blood loss is similar to that with diclofenac (1). Cholestatic hepatitis has also been reported (SEDA-8, 106).

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Loperamide

General Information

Loperamide is an opioid whose action is almost completely restricted to the gut. Recognition of its consequent safety, if it is appropriately used, has led to its being released in many countries for sale without prescription. It nevertheless has some central activity, and nausea, dizziness, dry mouth, abdominal pain, ileus, and lethargy all occur in a minority of users, with occasional reports of more serious central reactions, such as a possible association with delirium in a child (1).

The effectiveness of loperamide 4, 8, and 12 mg in reducing symptoms of lactose intolerance has been investigated in an open study in 19 subjects (2). Loperamide 8 mg significantly improved symptom scores to a similar extent as lactase tablets. Four subjects complained of delayed constipation and abdominal cramps related to loperamide.

Organs and Systems

Gastrointestinal

Some cases of necrotizing enterocolitis have been reported in infants with paralytic ileus after treatment for mild diarrhea (3). This is only one of the good reasons to avoid the drug in young children; the most important is that diarrhea in infants should not be suppressed pharmacologically (4).

Second-Generation Effects

Teratogenicity

To determine whether loperamide in pregnancy is associated with an increased risk of birth malformations, birth outcomes in 105 women who had taken loperamide during pregnancy (89 during the first trimester) were compared with the outcomes in women matched for age, smoking, alcohol, and other exposures (5). There were no differences in the frequencies of birth malformations between the two groups. However, 21 of the women had babies that were 200 g smaller than babies in the control group.

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Lopinavir and ritonavir

See also Protease inhibitors

General Information

Lopinavir and ritonavir are nucleoside analogue reverse transcriptase inhibitors that are used in combination in the treatment of AIDS.

The pharmacology, clinical pharmacology, uses, adverse effects, and interactions of lopinavir + ritonavir have been reviewed (1).

Observational studies

In studies of combining ritonavir with fluconazole (2) and ritonavir with mefloquine (3) there were no significant effects, and dosage adjustment is not warranted.

Placebo-controlled studies

In a randomized, double-blind study in 70 patients taking a regimen containing protease inhibitors, lopinavir + ritonavir 400/100 mg or 400/200 mg bd was substituted (4). On day 15 nevirapine 200 mg bd was added and NRTIs were changed to include at least one NRTI not previously taken. Despite a more than four-fold reduction in phenotypic susceptibility to the pre-entry protease inhibitor in 63% of the patients, mean plasma HIV-1 RNA concentrations fell by 1.14 log copies/ml after 2 weeks. At week 48, 86% had plasma HIV-1 RNA concentrations of

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under 400 copies/ml, and 76% under 50 HIV-1 RNA copies/ml. Mean CD4 cell counts increased by 125 cells/μl. The most common adverse events were diarrhea ($n = 16$) and weakness ($n = 4$). There were rises in gamma-glutamyltransferase activity ($n = 18$), total cholesterol ($n = 17$), and triglycerides ($n = 17$), and transient rises in transaminase activities ($n = 11$). Three patients discontinued therapy because of drug-related adverse events.

General adverse effects

In early monotherapy studies, including 62 and 87 patients (5,6), in which the potent antiretroviral effect of ritonavir was first demonstrated, the most common adverse events were nausea, diarrhea, headache, circumoral paresthesia, and altered taste sensation. Nausea, vomiting, and diarrhea are common during the start of therapy and usually disappear over the first few weeks of treatment. These adverse effects can be markedly reduced by using a step-up approach, increasing to the full dose over six days. General weakness, circumoral paresthesia, and taste disturbance occur in 5–10% of patients and are seldom dose-limiting.

Ritonavir does not have a broad therapeutic margin, and patients with higher ritonavir concentrations are at a higher risk of neurological or gastrointestinal adverse effects. It is feasible to individualize the dosage regimen with the aid of plasma concentration measurement and close observation of adverse effects, and there is a close relation between the two; this may enable one to increase substantially the percentage of patients who tolerate ritonavir without risking underdosage (7).

An important consideration in the use of all HIV-1 protease inhibitors, but of ritonavir in particular, is their potential for drug interactions through their effects on cytochrome P450 isozymes. The various interactions of ritonavir with other anti-HIV drugs have recently been reviewed (8).

Organs and Systems

Cardiovascular

Two of 16 patients taking lopinavir + ritonavir developed so-called inflammatory edema, which resolved on withdrawal and recurred after rechallenge (9). In three of eight patients inflammatory edema occurred 1–4 weeks after they started to take regimens that contained lopinavir + ritonavir (10). The edema affected the feet, ankles, and calves and was associated in one case with fever and in another with a transient rash; in one case the left shoulder and groin were also affected. All three recovered completely within 1–4 weeks despite continued drug treatment, but 7 months later one had a relapse that required withdrawal of lopinavir + ritonavir.

From a case in which there was positive dechallenge and rechallenge it has been concluded that edema of the lower limbs can be an adverse effect of ritonavir in some HIV-positive patients (11). The authors suspected a relation to the drug's vasodilatory activity. However, it should also be borne in mind that ritonavir has caused reversible renal insufficiency, which should be looked for in any patient who develops edematous changes.

Nervous system

Myasthenia has been attributed to ritonavir (12).

- A 71-year-old man with an 8-year history of HIV infection developed slurred speech, difficulty in climbing stairs, bilateral ptosis, and lateral rectus weakness 3 weeks after having started to take ritonavir (1200 mg/day). All his signs worsened with prolonged testing, and edrophonium produced improvement in ptosis and speech. Specific electromyographic testing confirmed myasthenia gravis. Computed tomography of the chest was normal. After withdrawal of ritonavir the signs and symptoms partly resolved by 3 months.

A definite causal link with ritonavir could not be established, but the authors speculated that ritonavir may have unmasked myasthenia gravis in this patient.

Sensory systems

Ototoxicity has been attributed to lopinavir + ritonavir (13).

- A 46-year-old man took a regimen containing lopinavir + ritonavir, and 4 weeks later complained of reduced auditory acuity accompanied by lancinating pain. Audiology showed mild to moderate bilateral sensorineural hearing loss. On withdrawal and use of efavirenz his hearing recovered.

Based on the time-course and the effect of withdrawal, lopinavir/ritonavir appears to have been the causative agent in this case.

Gastrointestinal

In a prospective, randomized trial in 100 patients, the most common adverse effects of lopinavir + ritonavir included abnormal stools, diarrhea, and nausea (14).

Urinary tract

In a retrospective analysis of 87 HIV-positive patients taking ritonavir in combination with two nucleoside analogues, serum creatinine increased in 12 cases by 66 (5–242)% from 66 (range 46–102) μmol/l, with a median glomerular filtration rate (GFR) of 116 ml/minute (60–202). Ten of the 12 patients had other risk factors for nephrotoxicity, such as dehydration or use of nephrotoxic drugs (15). It is prudent to monitor renal function in patients receiving ritonavir, particularly in the presence of other risk factors for renal dysfunction.

Three patients developed reversible renal insufficiency 10–12 days after starting treatment including ritonavir (16).

Reproductive system

Four women taking ritonavir developed hypermenorrhea, strongly suggesting that this can occur as a complication of ritonavir treatment (17).

Immunologic

Subcutaneous non-tuberculous granulomatous lesions developed in a 48-year-old HIV-positive man when he was given ritonavir (18).

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Susceptibility Factors

Age

The adverse effects commonly observed with ritonavir in adults are reportedly similar in children (19). Of 51 children aged 6 months to 18 years who took escalating doses of a liquid formulation of ritonavir (from 250 up to 400 mg/m^2 every 12 hours), seven withdrew because of gastrointestinal toxicity and four because of grade three hepatic transaminase rises. Both serum triglyceride and cholesterol concentrations increased significantly from baseline within 12 weeks of treatment.

Drug–Drug Interactions

Carbamazepine

Ritonavir can interact with carbamazepine (20).

- A 49-year-old woman with a long history of HIV infection developed worsening ataxia leading to two falls. Four days before admission she had had her antiretroviral drugs changed from zidovudine, lamivudine, and indinavir to ritonavir, saquinavir, and efavirenz. She was also taking carbamazepine to control generalized seizures resulting from a previous right thalamic infarction. The change in antiretroviral therapy resulted in an increase in serum carbamazepine concentration from 6.9 to 20 μg/ml. Serum concentrations in the usual target range were eventually achieved by a sixth of the dose of carbamazepine that had been required before starting ritonavir.

As saquinavir is only a mild inhibitor of CYP3A4 and efavirenz is an inducer, this effect was attributed to the potent inhibitor ritonavir.

Coumarin anticoagulants

Ritonavir can dangerously increase warfarin concentrations (21).

In contrast, ritonavir has been reported to reduce the effect of acenocoumarol (22).

- A 46-year-old man with prosthetic cardiac valves took acenocoumarol and later started to take stavudine, lamivudine, and ritonavir 600 mg bd. His INR fell markedly. Although the dose of acenocoumarol was progressively increased to three times the original dose, it was impossible to achieve the previous INR, and ritonavir was withdrawn.

Ecstasy

Ritonavir can interact with methylenedioxymetamfetamine (MDMA, ecstasy) (23).

- A 32-year old HIV-positive man who added ritonavir 600 mg bd to his existing antiretroviral regimen of zidovudine and lamivudine became unwell within hours after having ingested two and a half tablets of ecstasy, estimated to contain 180 mg of methylenedioxymetamfetamine. He was hypertonic, sweating profusely, tachypneic, tachycardic, and cyanosed. Shortly after, he had a tonic-clonic seizure and cardiorespiratory arrest. Attempts at resuscitation were unsuccessful. Blood concentrations obtained postmortem showed an concentration of 4.56 μg/ml, in the range of that reported in a patient with a life-threatening illness and symptoms similar to this patient after an overdose of 18 tablets of MDMA.

Ritonavir inhibits CYP2D6, which is the principal pathway by which MDMA is metabolized.

Ergot alkaloids

Ergot alkaloids are among the many medications that are contraindicated in patients taking ritonavir. One patient developed severe ergotism after taking ritonavir and ergotamine for 13 days (24), and other cases of ischemia of the lower limbs or elsewhere in the periphery have been reported in patients taking both ritonavir and ergotamine (25–27).

Fentanyl

By inhibiting CYP3A4, ritonavir can significantly inhibit the metabolism of fentanyl, and considerable caution is needed (28).

Ketoconazole

In 12 patients taking ritonavir and saquinavir for HIV infection, ketoconazole significantly increased the AUC, the plasma concentration at 12 hours, and the half-life of ritonavir by 29, 62 and 31% respectively (29). Similar increases of 37, 94, and 38% were recorded for saquinavir. CSF concentrations of ritonavir were raised by 178% by ketoconazole, but there was no significant change in CSF concentrations of saquinavir.

Methadone

Withdrawal symptoms, and the need to increase the dose of methadone, in a 51-year-old man previously stable on a maintenance dosage, have been attributed to ritonavir (30).

Rifamycins

In a pilot, non-randomized study, HIV-infected patients with tuberculosis were treated with regimens containing rifampicin and ritonavir (31). Despite the effects on CYP3A4, there was no significant interaction; plasma ritonavir concentrations remained sufficiently high and rifampicin concentrations did not rise to the toxic range.

Statins

An interaction of ritonavir with simvastatin reportedly resulted in rhabdomyolysis (32).

- A 51-year-old woman taking zidovudine, lamivudine, indinavir, and simvastatin started to take ritonavir and after 1 week developed diffuse muscle weakness and body aches. Creatine kinase (total and the MB isozyme), lactate dehydrogenase, and transaminases were all raised. There were crystals and hemoglobin in the urine.

Presumably this interaction occurred through inhibition of CYP3A4 by ritonavir.

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Loratadine

See also Antihistamines

General Information

Loratadine is a second-generation antihistamine (SEDA-18, 182) (SEDA-19, 174) (SEDA-22, 178).

Organs and Systems

Cardiovascular

In contrast to astemizole and terfenadine, loratadine is generally believed to be free of adverse cardiac effects. However, there is some evidence that it could be associated

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with atrial dysrhythmias. In human atrial myocytes loratadine rate-dependently inhibited the transient outward potassium current at therapeutic concentrations, possibly providing a basis for supraventricular dysrhythmias (1). However, during prolonged exposure (3 months) of healthy adult men to four times the recommended daily dose (40 mg/day) there was no change in the electrocardiogram that would suggest QT_c prolongation or any evidence of cardiac dysrhythmias (2).

Prolonged QT interval and symptomatic ventricular tachycardia has been described in a patient who took loratadine plus quinidine, but is most likely to have been attributable to the quinidine and the patient's cardiac condition (SEDA-19, 174).

The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup have been studied in 161 children aged 2–5 years (3). A single-dose open study was performed to characterize the pharmacokinetic profiles of loratadine and its metabolite desloratadine, and a randomized, double-blind, placebo-controlled, parallel-group study was performed to assess the tolerability of loratadine syrup 5 mg after multiple doses. Electrocardiographic parameters were not altered by loratadine compared with placebo. There were no clinically important changes in other tolerability assessments.

In healthy adults loratadine 10 mg/day had no effects on the electrocardiogram when co-administered for 10 days with therapeutic doses of ketoconazole or cimetidine (4).

Liver

Two cases of severe hepatotoxicity in patients using loratadine have been reported (5).

Skin

Loratadine caused erythematous, edematous, pruriginous skin eruptions in a 19-year-old woman who complained of at least three episodes of eruptions located at the same sites each time (6). An oral challenge with loratadine was positive, and cetirizine and ebastine caused no cutaneous reaction. Histopathology suggested a fixed drug eruption.

Drug–Drug Interactions

Nefazodone

Nefazodone is a phenylpiperazine antidepressant that is predominantly metabolized by CYP3A. In a randomized, double-blind, double-dummy, parallel-group, multiple-dose study in healthy men and women who were given loratadine 20 mg od or nefazodone 300 mg every 12 hours, the plasma loratadine concentrations were significantly increased by co-administration of nefazodone (7). The mean QT_c interval was unchanged by loratadine alone, but was markedly prolonged with co-administration of nefazodone, and the extent of prolongation correlated with the plasma loratadine concentration.

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Lorazepam

See also Benzodiazepines

General Information

Lorazepam is a benzodiazepine with CNS, depressant, anxiolytic, and sedative properties, used as a hypnotic, sedative, and anxiolytic drug.

Comparative studies

In a multicenter, randomized, double-blind comparison of diazepam (0.15 mg/kg followed by phenytoin 18 mg/kg), lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), and phenytoin (18 mg/kg) in 518 patients with generalized convulsive status epilepticus, lorazepam was more effective than phenytoin and at least as effective as phenobarbital or diazepam plus phenytoin (1). Drug-related adverse effects did not differ significantly among the treatments and included hypoventilation (up to 17%), hypotension (up to 59%), and cardiac rhythm disturbances (up to 9%).

Intramuscular lorazepam 4 mg has been compared with the combination of intramuscular haloperidol 10 mg + promethazine 50 mg in 200 emergency psychiatric patients with agitation, aggression, or violence (2). The treatments were comparably effective and well tolerated overall, but two patients who took lorazepam had moderate adverse effects: one had worse bronchial asthma and one had nausea and dizziness.

Placebo-controlled studies

The use of intravenous benzodiazepines administered by paramedics for the treatment of out-of-hospital status epilepticus has been evaluated in a double-blind, randomized trial in 205 adults (3). The patients presented either with seizures lasting 5 minutes or more or with repetitive generalized convulsive seizures and were randomized to receive intravenous diazepam 5 mg, lorazepam 2 mg, or

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placebo. Status epilepticus was controlled on arrival at the hospital in significantly more patients taking benzodiazepines than placebo (lorazepam 59%, diazepam 43%, placebo 21%). The rates of respiratory or circulatory complications related to drug treatment were 11% with lorazepam, 10% with diazepam, and 23% with placebo, but these differences were not significant.

Organs and Systems

Respiratory

Patients receiving intravenous benzodiazepines must be monitored for respiratory depression, which may demand artificial ventilation during intensive treatment. Lorazepam may cause less respiratory depression than diazepam at equieffective dosages (SEDA-20, 59).

Psychological, psychiatric

Lorazepam causes some rare adverse effects, including a manic-like reaction on withdrawal, delirium, and paradoxical precipitation of tonic seizures or myoclonus in children (SEDA-19, 35). It can both relieve and worsen behavioral disturbances in demented elderly patients (SEDA-20, 32).

The effects of lorazepam on three neuropsychiatric measures of attention and psychomotor performance have been investigated in 40 patients, 20 of whom were given placebo, 10 were given lorazepam 1 mg, and 10 were given lorazepam 2.5 mg (4). Performance on digit cancellation, digit-symbol substitution, and the Paced Auditory Serial Addition Task was significantly impaired by lorazepam (2.5 mg) and this was significantly worse in the middle-aged subjects compared with the younger. These results suggest that older people are more susceptible to these adverse effects.

Lorazepam disinhibits aggression more than its chemically and kinetically similar analogue oxazepam (5).

Cognition

The psychomotor and amnesic effects of single oral doses of lorazepam 2 mg were studied in 48 healthy subjects in a double-blind, placebo-controlled, randomized, parallel-group study (6). The effects were assessed by a battery of subjective and objective tests that explored mood and vigilance, attention, psychomotor performance, and memory. Vigilance, psychomotor performance, and free recall were significantly impaired by lorazepam.

Lorazepam shares with other benzodiazepines the ability to impair explicit memory, but has a distinct further effect on implicit memory as well (7). However, it impairs memory more than its chemically and kinetically similar analogue, oxazepam (8). The effects of lorazepam 2.5 mg and diazepam 0.3 mg/kg on explicit and implicit memory tasks have been examined in 24 men and 24 women randomly allocated to lorazepam, diazepam, or placebo (7). An implicit word-stem completion task and explicit memory tasks of immediate and delayed word recall and word recognition were administered 90 minutes after drug administration. Both diazepam and lorazepam significantly impaired performance on explicit memory measures. Only lorazepam significantly impaired performance on the implicit memory task.

In a separate study, pharmacokinetic–pharmacodynamic modeling of the psychomotor and amnesic effects of a single oral dose of lorazepam 2 mg was investigated in 12 healthy volunteers in a randomized, double-blind, placebo-controlled, two-way, crossover study using the following tasks: choice reaction time, immediate and delayed cued recall of paired words, and immediate and delayed free recall and recognition of pictures (9). The delayed recall trials were more impaired than the immediate recall trials; similar observations were made with the recognition versus recall tasks.

The effects of lorazepam and diazepam on false memories and related states of awareness have been investigated in 36 healthy volunteers, randomly assigned to one of three groups (placebo, diazepam 0.3 mg/kg, lorazepam 0.038 mg/kg) (10). The results suggested that diazepam and lorazepam cause impaired conscious recollection, associated with true, but not false, memories.

Metabolism

Metabolic acidosis and hyperlactatemia have been attributed to lorazepam (11).

- A 34-year-old woman with a history of renal insufficiency induced by long-term use of cocaine developed respiratory failure and was intubated and sedated with intravenous lorazepam (65 mg, 313 mg, and 305 mg on 3 consecutive days). After 2 days she had a metabolic acidosis, with hyperlactatemia and hyperosmolality. Propylene glycol, a component of the lorazepam intravenous formulation, was considered as a potential source of the acidosis, as she had received more than 40 times the recommended amount over 72 hours. Withdrawal of lorazepam produced major improvements in lactic acid and serum osmolality.

Long-Term Effects

Drug withdrawal

Lorazepam has considerable abuse potential, and poses particular difficulties in withdrawal (12). On the other hand, a sizeable sample ($n = 97$) of chronic users who wanted to discontinue were generally able to use stable or decreasing doses on an as-needed basis (13).

The Omnibus Budget Reconciliation Act of 1987 (OBRA '87) regulations (www.elderlibrary.org) specify when antipsychotic drugs can and cannot be used to treat behavioral disturbances in nursing home residents in the USA. Accordingly, antipsychotic drugs can be used in patients with delirium or dementia only if there are psychotic or agitated features that present a danger to the patient or others. Preventable causes of agitation must be excluded and the nature and frequency of these behaviors must be documented. Non-dangerous agitation, uncooperativeness, wandering, restlessness, insomnia, and impaired memory are insufficient in isolation to justify the use of antipsychotic drugs. With this in mind, the effects of withdrawing haloperidol, thioridazine, and lorazepam have been examined in a double-blind, crossover study in 58 nursing home residents (43 women and 15 men, mean age 86 years), half of whom continued to take the psychotropic drugs that had been prescribed,

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while the other half were tapered to placebo (14). After 6 weeks, the drugs were tapered to the reverse schedule for another 6 weeks. There were no differences between drug and placebo in functioning, adverse effects, and clinical global impression. Cognitive functioning improved during placebo. The authors concluded that gradual dosage reductions of psychoactive medications must be attempted, unless clinically contraindicated, in an effort to withdraw these drugs. Similar conclusions have been reached in other studies (SEDA-22, 54).

Drug Administration

Drug administration route

The pharmacokinetics of intranasal lorazepam compared with oral administration have been evaluated in 11 volunteers in a randomized, crossover study (15). Lorazepam had favorable pharmacokinetics for intranasal administration compared with standard methods. Intranasal delivery could provide an alternative non-invasive delivery route for lorazepam.

Drug–Drug Interactions

Caffeine

Caffeine aggravates, rather than attenuates, lorazepam-induced impairment in learning and performance (16). This contradicts popular wisdom that stimulants are useful in perking up patients taking benzodiazepines, and invites research into what may be a very dangerous practice in benzodiazepine users, that of taking caffeine before driving or operating machinery (see also General Introduction in the monograph on Benzodiazepines).

Clozapine

Caution has been recommended when starting clozapine in patients taking benzodiazepines (SEDA-19, 55). Three cases of delirium associated with clozapine and benzodiazepines (17) have been reported. There have been several reports of synergistic reactions, resulting in increased sedation and ataxia, when lorazepam was begun in patients already taking clozapine (18).

Haloperidol

A thorough review of the pharmacokinetics of haloperidol, with special emphasis on interactions, has been published (19). The interactions include one with lorazepam.

Moxonidine

When co-administered with lorazepam 0.4 mg, moxonidine increased impairment of attentional tasks (choice, simple reaction time and digit vigilance performance, memory tasks, immediate word recall, delayed word recall accuracy, and visual tracking). These effects should be considered when moxonidine is coadministered with lorazepam, although they were smaller than would have been produced by a single dose of lorazepam 2 mg alone (20).

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Lorcainide

See also Antidysrhythmic drugs

General Information

The clinical pharmacology, clinical use, efficacy, and adverse effects of lorcainide have been reviewed (1–3).

Organs and Systems

Cardiovascular

Cardiovascular effects of lorcainide are reportedly uncommon (under 1% of cases) and have mostly been associated with intravenous administration. They include hypotension (1) and heart block. Pre-existing sinoatrial disease and heart block are contraindications to the use of lorcainide (4).

Nervous system

Nervous system effects account for most adverse reactions to lorcainide after both intravenous and oral administration. During intravenous treatment patients may complain of vertigo, feeling hot, numbness of the feet (5), dizziness, blurred vision, muscle tremor (6), and tingling sensations in the fingers or tongue (7). All of these effects are transient.

During long-term oral therapy the most frequent adverse effect is sleep disturbance of one kind or another, the frequency being up to 45% (6,8–13). The main types of disturbance are difficulty in falling asleep, nightmares, and lively dreams. In about half of the patients affected there is also excessive sweating (10,11). These effects become less severe after a week or two of therapy, and during that time benzodiazepines may give symptomatic relief (14). In contrast, these patients do not suffer drowsiness or other central nervous system effects during the day.

Seizures and hallucinations have been reported rarely (14).

Endocrine

Lorcainide has been reported to cause hyponatremia, attributed to inappropriate secretion of ADH (15).

Gastrointestinal

Nausea occurs in about 5% of patients during long-term oral therapy. It is probably of central nervous origin (14).

Skin

There have been a few reports of mild allergic skin reactions (14).

Susceptibility Factors

The adverse effects of lorcainide may be partly caused by its active metabolite, norlorcainide, which accumulates during treatment (15).

Drug Administration

Drug overdose

- Lorcainide 2500 mg produced bradycardia, convulsions, and coma in a 15-year-old girl who took a deliberate overdose and died rapidly (16).

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Lorenzo's oil

General Information

Lorenzo's oil is a 4:1 mixture of glyceryl trioleate and glyceryl trierucate. It is used in patients with adrenoleukodystrophy. The dyslipidemia in patients with adrenoleukodystrophy consists of increased blood concentrations of very-long-chain saturated fatty acids, particularly hexacosaenoic acid (C26:0). Treatment with Lorenzo's oil has tended to normalize the abnormality in the blood while the patient deteriorates. Neurological changes are unrelated to the fatty acid changes in the blood, and, moreover, erucic acid does not seem to enter the brain. Owing to lack of controlled trials, it is not known whether it works.

Registration of adverse effects with Lorenzo's oil has been hampered by the absence of controlled trials. In 22 patients treated for at least 12 months, although Lorenzo's oil did not seem to be beneficial, there were possible adverse effects, such as mild increases in liver enzymes (55%), thrombocytopenia (55%), gastrointestinal complaints (14%), and gingivitis (14%). Furthermore, there were falls in hemoglobin concentration and leukocyte count, and an increase in the plasma alkaline phosphatase concentration; the reduction in platelet count did not result in hemorrhage (1). Whether some of the adverse effects of Lorenzo's oil are due to low concentrations of essential fatty acids or caused by reduced dietary fat intake is not known.

Organs and Systems

Hematologic

Lorenzo's oil affected blood platelet counts in 39 patients followed for 1 year (2). Blood platelet aggregation studies in those patients were normal and there were no platelet-associated immunoglobulins. It has been suggested that the thrombocytopenia might be due to platelet activation, resulting from an increase in the concentration of erucic acid in the platelet membrane (1).

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Lormetazepam

See also Benzodiazepines

General Information

Lormetazepam is a short-acting benzodiazepine with effects similar to those of diazepam.

Organs and Systems

Psychological, psychiatric

Auditory hallucinations have been attributed to lormetazepam (1).

- A 45-year-old woman with moderate depression and anxiety took lormetazepam 4 mg/day. After a few days, she noticed musical auditory hallucinations like children's songs. There were no neurological, otological, or psychiatric causes for the hallucinations. When the dose of lormetazepam was reduced to 2 mg the auditory experience changed to "classic tinnitus." The lormetazepam was eventually withdrawn, but a slight degree of tinnitus persisted.

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Lornoxicam

See also Non-steroidal anti-inflammatory drugs

General Information

Data are insufficient to indicate whether the oxicam NSAID lornoxicam is safer for the gastrointestinal tract than other oxicam derivatives (SEDA-16, 113). Headache, dizziness, and gastrointestinal symptoms are the most frequent adverse effects; clinically significant gastrointestinal events include upper gastrointestinal ulceration, with or without hemorrhage or perforation (SEDA-20, 94) (SEDA-21, 107). The profile of drug interactions is similar to the profiles of other NSAIDs (SEDA-21, 108).

Drug–Drug Interactions

Phenprocoumon

Lornoxicam altered the pharmacokinetics of the more potent *S*-isomer of phenprocoumon and to a lesser extent *R*-phenprocoumon, with a reduction in factor II and VII activity (1). In contrast, at the upper limit of the recommended doses lornoxicam did not alter the pharmacokinetics of *R*-acenocoumarol or the anticoagulant activity of acenocoumarol (2).

Warfarin

Lornoxicam increased the mean serum concentration of racemic warfarin and correspondingly increased its anticoagulant effect (3).

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Losartan

See also Angiotensin II receptor antagonists

General Information

Losartan is a non-peptide, selective angiotensin type 1 (AT_1) receptor antagonist. Because it has been suggested that there is a local renin–angiotensin system in the eye, losartan may be useful in treating glaucoma. In a small, well-designed, placebo-controlled, crossover study in four groups of subjects—controls, hypertensive patients with normal intraocular pressure, and patients with primary open-angle glaucoma with and without hypertension—a single oral dose of losartan 50 mg produced a drop in intraocular pressure in all subjects within 2–6 hours after drug intake, proportional to baseline eye pressure (1). Blood pressure fell only in the hypertensive subjects. Thus, the fall in intraocular pressure was independent of the systemic effect on blood pressure. Beyond the potential for using losartan as a therapy for glaucoma, ophthalmologists should take into account concomitant therapy with losartan (and possibly other angiotensin receptor antagonists) when measuring intraocular pressure.

Using the method of prescription event monitoring (PEM), the incidence densities of adverse effects per 1000 patient-months of exposure have been measured in 14 522 patients (2). Most were hypertensive (63%). During treatment months 2–6, the commonest adverse effects were cough (17%), malaise and lassitude (15%), dizziness (15%), headache or migraine (11%), nausea and vomiting (6.0%), rash (5.0%), dyspnea (4.9%), edema (4.8%), dyspepsia (4.2%), and diarrhea (3.7%). These were also the most common reasons for drug withdrawal. The seemingly high incidence of cough may have been due to carry over from previous use of ACE inhibitors. In 1378 patients with mild to moderate hypertension valsartan 80 mg/day has been compared with losartan 50 mg/day and placebo for 8 weeks (3). This study confirmed the excellent tolerance profile, not different from placebo, of both angiotensin II receptor antagonists.

An extensive review of the use of losartan, with special focus on elderly patients, has included an update on the tolerability profile, mainly in clinical trials, but with no significant new information (4).

Organs and Systems

Nervous system

An isolated case of migraine occurring after a single dose of losartan was reported (5). The temporal association during challenge and rechallenge, although in unblinded conditions, argues for a possible causal relation.

Sensory systems

There have been reports of taste disturbance in patients taking ACE inhibitors, tentatively attributed to chelation of metal ions. However, no mechanism for taste loss due to angiotensin-II receptor blockers has been proposed. Reversible loss of taste discrimination has been reported with losartan (6). In two cases dysgeusia occurred some time after switching from an ACE inhibitor to losartan (1 week in one case and 3 months in the other). In both cases the dysgeusia disappeared after withdrawal of losartan (timing not reported in one case, 1 week after in the other) (7). The authors referred to previously reported cases, one with losartan (8) and one with valsartan (9), and to a personal communication from the manufacturer of 12 other cases within a large safety monitoring program.

Hematologic

Anemia in hemodialysis (10) and mainly in renal transplant patients has been reported (11–13). The suggested mechanism is by an action on erythropoietin, similar to that of ACE inhibitors, which produce the same adverse effect. However, in a small uncontrolled but prospective study, losartan given for 3 months to 15 patients on chronic hemodialysis with anemia, neither altered plasma erythropoietin concentrations nor aggravated the anemia (14). In those taking losartan there was no need for higher doses of co-administered r-Hu Epo in order to correct anemia, in contrast to controls.

Liver

Hepatic injury due to losartan is a recognized rare adverse effect (15).

- A 52-year-old woman developed jaundice, right upper abdominal discomfort, and weakness. She had had a similar problem previously, after taking losartan

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50 mg/day for 5 months for hypertension. At that time she was jaundiced with increased serum transaminase activities. The losartan was withdrawn and during the following 3 weeks she improved. Losartan was then reintroduced, and 2 weeks later her symptoms recurred. She was jaundiced, with raised transaminase, alkaline phosphatase, and lactic dehydrogenase activities; tests for viral hepatitis were negative. A liver biopsy showed chronic hepatitis with moderate to severe inflammation and mild fibrosis. Losartan was withdrawn and the laboratory tests returned to normal over a period of 4 months. She was healthy with normal laboratory tests 2 years later.

The authors made a strong case for a causal relation, based on the absence of other causes, the return to normality after withdrawal of losartan, and re-occurrence on rechallenge. A literature search revealed four previous reports of losartan-induced liver damage.

Pancreas

Pancreatitis can occur with losartan (16).

- A 42-year-old woman with insulin-dependent diabetes and chronic renal insufficiency developed pancreatitis 5 days after taking enalapril 2.5 mg and recovered after drug withdrawal. The pancreatitis relapsed one week after her general practitioner had prescribed losartan 50 mg/day, with full recovery after withdrawal. A rechallenge test with losartan was fully positive.

The case was well documented and causality seems to have been very convincingly established. No mechanistic speculation was given by the authors.

Urinary tract

Renal insufficiency has been reported with losartan (17).

- A 69-year-old man with hypertension and heart failure took losartan 25 mg/day, increasing to 50 mg/day after 2 weeks. He also took spironolactone 50 mg/day, furosemide 40 mg/day, digoxin 0.25 mg/day, acenocoumarol, and allopurinol. Two weeks later he developed acute renal insufficiency with a plasma creatinine concentration of 725 μmol/l (previously 115 μmol/l). Within 24 hours after losartan withdrawal (it was not stated whether spironolactone was also stopped) and hemodialysis, he recovered renal function (plasma creatinine 124 mg/l). He was later found to have bilateral renal artery stenosis, which is a contraindication to angiotensin II receptor antagonists.

The authors did not discuss the possible aggravating role of spironolactone.

- Anuric renal insufficiency occurred with losartan in a 70-year-old man with a solitary kidney (18). An interesting feature was that the patient's blood pressure could be controlled with captopril without the development of anuria.

This is in line with a study in dogs, in which there was a greater deterioration in glomerular filtration with angiotensin II receptor inhibition than with ACE inhibition, for the same effect on blood pressure (19).

Skin

Two cases of atypical cutaneous lymphoid hyperplasia have been reported (20). Both occurred after 2 weeks of treatment with losartan 50 mg/day.

Immunologic

Angioedema has been reported with angiotensin II receptor antagonists (21,22).

- An African-American developed swelling of the lips and shortness of breath within 24 hours of starting losartan. However, similar reactions had been noted before, while the patient was taking captopril. It was therefore unclear whether the reaction was related to losartan or was a carry-over reaction to captopril.
- A 45-year-old white man, who had taken losartan, hydrochlorothiazide, allopurinol, and colchicine for 9 months, developed facial urticaria, eyelid swelling, shortness of breath, and upper chest tightness, which resolved quickly with famotidine, methylprednisolone, and adrenaline. He had a recurrence 7 hours later, not having taken another dose of losartan. The patient had no history of allergy and was well after losartan withdrawal.

The late onset and recurrence of symptoms after initial resolution are the unique original features of this case report. Patients with such reactions should be kept under observation after the resolution of initial symptoms.

Second-Generation Effects

Teratogenicity

In the study of 14 522 patients mentioned in the introduction to this monograph (2) three mothers were exposed to losartan during the first trimester of pregnancy. One pregnancy terminated in a spontaneous abortion. The two others were both complicated by hypertension. One baby died with extreme prematurity and growth retardation, and the second survived after having been born prematurely. A woman who took losartan from 17 to 31 weeks of gestation developed oligohydramnios and delivered a stillborn fetus with deformities of the extremities and face (23).

Susceptibility Factors

Renal disease

Losartan was evaluated in 406 patients with end-stage renal insufficiency undergoing hemodialysis (24). Only 15 patients discontinued losartan because of adverse effects. In seven the adverse reaction was hypotension. Two patients reported a possible anaphylactoid reaction on treatment with AN69 dialysis membranes. However, nine patients with a history of previous anaphylactoid reactions on treatment with AN69 have not shown this complication with losartan and AN69.

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Drug Administration

Drug overdose

In a case of accidental overdose in an 80-year-old patient, who was taking 200 mg/day for 2 months, no ill effects were observed (2).

Drug–Drug Interactions

Erythromycin

Because losartan is metabolized by CYP2C9 and CYP3A4 to an active metabolite, E3174, which has greater antihypertensive activity than the parent compound, the effects of co-administration of losartan 50 mg/day and erythromycin, a moderate inhibitor of CYP3A4, have been investigated in a well-designed study in healthy volunteers. There was no significant effect of erythromycin.

Fluconazole

The pharmacokinetic interaction of fluconazole 200 mg/day with losartan 100 mg/day has been investigated in 32 healthy subjects (25). Fluconazole significantly increased the steady-state concentration of losartan by 66% and inhibited the formation of the active metabolite EXP-3174 by 34%.

Another very similar study investigated interactions with itraconazole, an inhibitor of CYP3A4, and fluconazole, which is more specific for CYP2C9 (26). Fluconazole reduced the mean peak plasma concentrations of losartan and E3174 to 30% and 47% of their control concentrations respectively. The half-life of losartan was prolonged by 67%. Itraconazole had no significant effect. The possibility of a reduced effect of losartan when co-administered with fluconazole should be expected.

Grapefruit juice

Administration of grapefruit juice (which inhibits both cytochrome P450 and P glycoprotein) to healthy volunteers resulted in an increased serum concentration ratio of losartan to its active metabolite E3174 (27). As both losartan and its metabolite contribute to the therapeutic effects, the absence of pharmacodynamic measurements in this study obviated conclusions about the clinical implications of this interaction.

Indometacin

Indometacin 50 mg bd for one week did not interfere with the antihypertensive efficacy of losartan 50–100 mg/day in patients with essential hypertension, despite the fact that indometacin caused significant increases in weight and extracellular fluid volume (28). Glomerular filtration rate remained unchanged. Indometacin did not adversely influence peripheral hemodynamics. This is in contrast to the reported effects of indometacin during ACE inhibition, leading to an increase in blood pressure. It suggests that prostaglandins in part mediate vasodilatation during ACE inhibition, a mechanism that is not shared by angiotensin II antagonists. However, the result of this study is in contrast with those of several similar interaction studies with other antihypertensive agents, in which prostaglandin inhibition for 1–4 weeks caused an increase in weight combined with an increase in blood pressure. If indometacin had been given with losartan for more than 1 week, it may have produced a similar increase in blood pressure. Thus, the results of this study should not be taken as an argument against the recommendation that non-steroidal anti-inflammatory drugs should not be combined with angiotensin II antagonists, a recommendation that should be re-emphasized.

Lithium

An interaction of losartan with lithium has been reported (29).

- A 77-year-old woman who had been taken lithium carbonate 625 mg/day with a stable lithium concentration of around 0.6 mmol/l started to take losartan for hypertension. Within 4 weeks she developed ataxia, dysarthria, and confusion, and her serum lithium concentration was 2.0 mmol/l. Her symptoms resolved on withdrawal of losartan.

The authors proposed that this effect had occurred by reduced aldosterone secretion, an effect which is greater with ACE inhibitors than with angiotensin II receptor antagonists. In healthy volunteers losartan did not alter the fractional secretion of lithium (30), so presumably this patient had some susceptibility that caused the interaction.

Rifampicin

A study in 10 healthy volunteers has suggested that rifampicin interacts with losartan (31). The AUCs of both losartan and its active metabolite were markedly reduced (about 30 and 40% respectively) when rifampicin 300 mg bd was given for 1 week.

Because losartan is metabolized by CYP2C9 and CYP3A4 to an active metabolite, E3174, which has greater antihypertensive activity than the parent compound, the effects of co-administration of losartan 50 mg/day and the potent enzyme inducer rifampicin have been investigated in a well-designed study in healthy volunteers. Rifampicin produced 35 and 40% reductions in the AUCs of losartan and E3174 respectively. Losartan oral clearance increased by 44% and the half-lives of both compounds were shortened by 50% (32). Given the magnitude of the effect, this interaction is likely to be of clinical relevance.

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Lovastatin

See also HMG Co-A reductase inhibitors

General Information

The adverse events profile of lovastatin in 8245 patients with moderate hypercholesterolemia has been evaluated in a double-blind, diet- and placebo-controlled trial (1). The difference between lovastatin and placebo in the incidence of adverse events that required discontinuation was small, ranging from 1.2% at 20 mg bd to 1.9% at 80 mg/day. Among a variety of symptoms, only constipation differed significantly between drug and placebo, with a slightly higher frequency in the treated group. The treated patients also gained on average 0.4 kg more weight than controls. Deaths were few. Lovastatin-induced rhabdomyolysis can occur (2), even in the absence of other drug therapy (SEDA-12, 1101) (3).

Organs and Systems

Psychological, psychiatric

In a double-blind study, 209 healthy adults were randomized to placebo or lovastatin 20 mg/day for 6 months (4). Placebo-treated subjects improved between baseline and post-treatment periods on neuropsychological tests in all performance domains (neuropsychological performance, depression, hostility, and quality of life), consistent with the effects of practice on test performance, whereas those treated with lovastatin improved only on tests of memory recall. Comparisons of the changes in performance between placebo and lovastatin showed small but significant differences for tests of attention and psychomotor speed, and were consistent with greater improvement with placebo. Psychological well-being was not affected by lovastatin. The authors concluded that treatment of hypercholesterolemia with lovastatin did not cause psychological distress or substantially alter cognitive function. However, treatment did result in slight impairment of performance in neuropsychological tests of attention and psychomotor speed, the clinical importance of which is uncertain.

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Skin

Ichthyosiform eruptions on the abdomen and back occurred in a Korean patient after 3 months of lovastatin therapy; they disappeared on withdrawal (5). Similar lesions occurred in a 54-year-old Chinese man (6).

Reproductive system

Hypospermia has been reported in a patient taking lovastatin (7).

Immunologic

There were 25 serious hypersensitivity reactions (such as arthralgia and thrombocytopenia) among the first million patients taking lovastatin; at least some of these were considered to be due to the drug (8).

Body temperature

Severe hyperthermia has been attributed to lovastatin (9).

Drug–Drug Interactions

Diuretics

Potassium-depleting diuretics, except indapamide, can attenuate the effect of lovastatin on blood lipid concentrations (10).

Erythromycin

Rhabdomyolysis due to a short course of erythromycin in a 73-year-old man who had taken lovastatin for 7 years was accompanied by signs of multiple organ toxicity so severe as to mimic sepsis (11).

Gemfibrozil

Lovastatin in combination with gemfibrozil caused a rise in creatine kinase activity 234 000 U/l, with complete remission after both drugs had been withdrawn (12).

Quetiapine

Lovastatin caused prolongation of the QT interval in a patient taking quetiapine.

- A 46-year-old African-American woman with schizophrenia, taking quetiapine 800 mg/day and sertraline 100 mg/day, was given lovastatin 10 mg/day for dyslipidemia (13). Although 2 months later her lipid concentrations had improved, a routine electrocardiogram showed prolongation of the QT_c interval to 569 milliseconds; it had been 416 milliseconds 6 months before. There were no electrolyte abnormalities and no history of cardiac conduction abnormalities. The dose of lovastatin was reduced to 5 mg/day and an electrocardiogram the next day showed a normal QT_c interval (424 milliseconds). Later she switched from lovastatin to niacin and subsequent electrocardiograms were all normal.

Probably lovastatin caused an increase in plasma quetiapine concentrations through competitive inhibition of CYP3A4.

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Loxapine

See also Neuroleptic drugs

General Information

Loxapine is a dibenzoxazepine neuroleptic drug.

Organs and Systems

Hematologic

Three cases of leukocytosis attributed to loxapine have been reported; all resolved when loxapine was withdrawn (1).

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Drug Administration

Drug overdose

A review of acute loxapine overdosage suggested that it has a high potential for causing serious neurological problems and cardiotoxicity (2).

In a study of overdosages of different neuroleptic drugs, loxapine had the highest fatality index (the number of deaths divided by the number of prescriptions) (3).

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Loxoprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Data on the safety of loxoprofen are based on an open, multicenter trial of about 4000 elderly patients in Japan (SEDA-17, 112). Adverse effects were mainly gastrointestinal, but other adverse effects, common to every NSAID, included edema, dizziness, skin rashes, pruritus, and a case of eosinophilic pneumonia and liver dysfunction (SEDA-17, 112).

Organs and Systems

Respiratory

A fatal asthmatic attack occurred in a young man with a history of asthma and nasal polyps who took loxoprofen (SEDA-18, 105).

Gastrointestinal

In a retrospective study of NSAID-induced colonic ulceration related to NSAID therapy, five of 14 patients were taking loxoprofen (1). However, this finding does not prove that loxoprofen is more ulcerogenic than other NSAIDs.

Liver

The Japanese Health Authority has tightened the hepatic warnings for loxoprofen after eight reports of serious hepatic adverse events since 1997, including two deaths (2).

Immunologic

Three cases of a type-I hypersensitivity reaction to loxoprofen, characterized by generalized urticarial rash and dyspnea, have been reported (3,4).

Drug–Drug Interactions

ACE inihibitors

Loss of consciousness due to marked bradycardia caused by severe hyperkalemia has been described in an 85-year-old woman who took loxoprofen for several days and long-term imidapril, an ACE inhibitor. The combination of an NSAID with an ACE inhibitor can produce serious adverse effects in high-risk patients (5).

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Lumefantrine

General Information

Lumefantrine is a synthetic aminoalcohol fluorene derivative, related to halofantrine and mefloquine (1). It was highly effective in uncomplicated chloroquine-resistant malaria tropica in an open, non-comparative trial in 102 patients in China when given in four oral doses over 48 hours (2). No significant adverse effects have been reported. It has also been marketed in a combination of artemether (20 mg) plus lumefantrine (120 mg).

In 60 children in the Gambia with uncomplicated malaria tropica, lumefantrine was safe and effective. No neurological, cardiac, or other adverse effects were reported (3).

Lumefantrine was inferior to artesunate + mefloquine in an open, randomized comparison in 617 patients in Thailand with uncomplicated multidrug-resistant malaria tropica, but produced two to four times fewer adverse effects, such as nausea, vomiting, dizziness, sleep disorders, or other neurological symptoms (4).

In another study in Thailand, lumefantrine was less efficacious than mefloquine in a double-blinded, randomized trial in 252 adults (5). The lower efficacy of

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lumefantrine in Thailand may be due to poorer absorption and more resistant parasites in these areas, and the manufacturers have recommended higher doses than were used in these studies (6).

In an open, randomized trial in 260 Tanzanian children, lumefantrine was superior to chloroquine and did not produce major adverse effects (7).

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Lycopodiaceae

See also Herbal medicines

General Information

The family of Lycopodiaceae contains three genera of clubmoss, *Huperzia*, *Lycopodium*, and *Lycopodiella*.

Lycopodium serratum

Lycopodium serratum (clubmoss, Jin bu huan) has been used in Chinese medicine for more than 1000 years. It contains the alkaloid serratidine and triterpenoids, such as oxolycoclavinol, oxoserratenetriol, tohogeninol, and tohogenol.

Adverse effects

Jin bu huan can cause liver damage (1).

- A 49-year-old man developed signs of hepatitis after taking three tablets of Jin bu huan per day for 2 months for insomnia. No other potential causes for the liver damage could be identified. A liver biopsy showed chronic hepatitis with moderate portal and parenchymal lymphocytic inflammation and focal necrosis. The patient stopped taking the herbal remedy and his liver function normalized.

There have been other reports of hepatotoxic effects of Jin bu huan (2).

Overdosage of Jin bu huan can cause central nervous system and respiratory depression with rapid life-threatening bradycardia (3,4).

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Lyme disease vaccine

See also Vaccines

General Information

Lyme disease is a tick-borne, spirochetal zoonosis, characterized by a distinctive skin lesion, systemic symptoms, and neurological, rheumatological, and cardiac involvement, occurring in varying combinations over a period of months to years. *Borrelia burgdorferi* is the causative agent in North America, whereas in Europe three genomic groups (named *Borrelia burgdorferi sensu stricto*, *Borrelia garinii*, and *Borrelia afzelii*) have been identified. Endemic foci have been found in North America, Europe, the former USSR, Japan, and China. In many of these areas, Lyme disease is now the most common vector-borne disease. Because of this epidemiological problem and the severity of the disease, a vaccine was developed. High titers of antibody to outer surface protein A (OspA) of the spirochete prevented *B. burgdorferi* infection in mice and subsequently in immunized hamsters, dogs, and monkeys.

In December 1998, based on many prelicensure clinical trials, the first Lyme disease vaccine (LYMErix, manufactured by the then SmithKline Beecham) was licensed by the Food and Drug Administration (FDA) for individuals aged 15–70 years old (1) and subsequently became commercially available in the USA. In 1999, the Advisory Committee on Immunization Practices (ACIP) made recommendations for Lyme disease vaccine (2), including data on efficacy and safety (SEDA-23, 338). No convincing evidence was found that the vaccine caused serious problems, but discussion about its safety continued and

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the demand for the vaccine did not reach a sustainable level. Therefore, in February 2002 the vaccine was withdrawn by the manufacturers.

In two overviews the results of various clinical and efficacy trials were summarized (3,4) and the safety, immunogenicity, and efficacy of the vaccine were underlined. The authors considered that the intravector mode of action of the vaccine was unique and opened the door to a new method of preventing insect-borne illnesses in humans.

Dr Neal Halsey, head of the Institute for Vaccine Safety at John Hopkins University, explained that the poor sales had resulted from "public misperception and the promotion of false concerns" (5). Lyme disease researchers consider the Lyme vaccine story in the USA to have been a setback in Lyme disease prevention. Vaccines meeting the specific epidemiological situation in Europe are under development. Lyme disease prevention and prophylaxis has been reviewed (6).

Observational studies

LYMErix safety data reported to the Vaccine Adverse Event Reporting System (VAERS) from 21 December 1998 to 31 October 2000 mentioned reports of adverse events associated with Lyme vaccine in prelicensure trials, including injection site reactions, transient arthralgia and myalgia within 30 days of vaccination, fever, and a flu-like illness (7). Allergic reactions were reported to the VAERS and some could have plausibly been linked to the vaccine because of the short latency between vaccination and reaction onset. No clear patterns in age, sex, time to onset, or vaccine dose were identified, although the unexpected predominance of reports of arthrosis in men might warrant further consideration.

Placebo-controlled studies

The results of two efficacy and safety trials using Lyme disease vaccine with or without adjuvant have been reported. In a double-blind trial, 10 305 subjects at least 18 years old, recruited at 14 sites in areas of the USA where Lyme disease was endemic, were randomly assigned to receive either placebo ($n = 5149$) or OspA vaccine ($n = 5156$) (8). The first two injections were given 1 month apart and 7515 subjects also received a booster dose at 12 months. The efficacy of the vaccine was 68% in the first year of the study in the entire population and 92% in the second year among the 3745 subjects who received a third injection. The vaccine was well tolerated. There was a higher incidence of mild, self-limiting, local and systemic reactions in the vaccine group, but only during the 7 days after vaccination (Table 1). There was no significant increase in the frequency of arthritis or neurological events in vaccine recipients. The authors concluded that OspA vaccine was safe and effective in the prevention of Lyme disease.

In another randomized, double-blind trial in 10 936 subjects in areas of the USA in which Lyme disease is endemic, either recombinant *B. burgdorferi* OspA with adjuvant or placebo was given initially and at 1 and 12 months (9). After two injections, 22 subjects given vaccine and 43 given placebo contracted definite Lyme disease; vaccine efficacy was 49% (95% CI = 15, 69%). In the second year, after the third injection, 16 vaccine recipients and 66 placebo recipients contracted definite Lyme disease; vaccine efficacy was 76% (CI = 58, 86%). The efficacy of the vaccine in preventing asymptomatic infection was 83% in the first year and 100% in the second year. Injection of the vaccine was associated with mild to moderate local or systemic reactions lasting a median of 3 days (Table 2).

Table 1 Percentage incidences of adverse effects within 7 days after injection

Adverse effect	Vaccine	Placebo
First injection		
Number of subjects	5156	5149
Any adverse effect	9.8	4.1
Musculoskeletal	6.4	1.3
Myalgia	5.5	0.6
General	1.8	0.9
Pain at injection site	0.3	0.04
Second injection		
Number of subjects	5050	5034
Any adverse effect	6.1	3.1
Musculoskeletal	3.3	1.1
Myalgia	2.5	0.4
General	1.7	0.8
Pain at injection site	0.8	0.1
Third injection		
Number of subjects	3745	3770
Any adverse effect	11.2	5.5
General	7.3	2.6
Tenderness	2.3	0.2
Pain at injection site	1.5	0.2
Unspecified pain	1.0	0.1
Reaction at injection site	0.8	0.2
Swelling	0.6	0.1
Pain in limb	0.5	0.02
Edema at injection site	0.5	0
Rigors	0.2	0
Skin or subcutaneous tissue	2.1	0.2
Erythematous rash	1.9	0.1

Organs and Systems

Musculoskeletal

Suspicions were expressed in the Mealey Publication's Drug and Medical Device Report that the Lyme disease vaccine LYMErix could cause an incurable form of autoimmune arthritis. It was hypothesized that blood concentrations of OspA after three doses of vaccine place vaccinees classified by genetic type HLA-DR4+ at risk of developing treatment-resistant Lyme arthritis. The premarket trials for the vaccine were assessed by an independent advisory committee, which found no link between Lyme disease immunization and autoimmune arthritis (10). However, the committee stressed the need for long-term surveillance and further studies in those over 70 years and in children, and the effect of the vaccine in patients with chronic arthritis; the possible development of autoimmunity deserves further study (11). After licensing of the vaccine, more than 1 million Americans received it and no unusual adverse effects were reported to the manufacturer (10).

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Table 2 Percentages of subjects with symptoms with an overall incidence of at least 1% that were classified as related or possibly related to vaccination or unrelated to vaccination

Symptom	Vaccine	Placebo	*P*-value
Related or possibly related to vaccination[*]			
Local at injection site			
Soreness	24.1	7.6	<0.001
Redness	1.8	0.5	<0.001
Swelling	0.9	0.2	<0.001
Systemic: early (<30 days)			
Total[*]	19.4	15.1	<0.001
Arthralgia	3.9	3.5	0.34
Headache	3.0	2.5	0.14
Myalgias	3.2	1.8	<0.001
Fatigue	2.3	2.0	0.37
Aching	2.0	1.4	0.01
Influenza-like illness	2.0	1.1	<0.001
Fever	2.0	0.8	<0.001
Chills	1.8	0.5	<0.001
Upper respiratory tract infection	1.0	1.1	0.69
Systemic: late (>30 days)			
Total[*]	4.1	3.4	0.06
Arthralgia	1.3	1.2	0.54
Unrelated to vaccination			
Early (<30 days)	27.1	27.9	0.37
Late (>30 days)	53.3	52.6	0.48

[*] Totals include all early or late related or possibly related systemic events, not just those with a frequency of at least 1%.

However, subsequently the FDA received some reports of arthritis and Lyme disease after the use of the vaccine (12). Therefore, on 31 January 2001, the FDA's Vaccines and Related Biological Products Advisory Committee held a meeting to evaluate safety data of LYMErix. Among other information, the experts considered a manufacturer's briefing document as well as safety data reported to the VAERS. The Associated Press Report from 31 January 2001 on the FDA meeting on Lyme vaccine read (in part) as follows: "Vaccine Safety experts found no proof that the LYMErix vaccine is dangerous—the rare cases of arthritis and other symptoms could be coincidence. Many reports are of minor complaints or are not believed to have been caused by the vaccine, but the FDA is studying 133 reports of severe arthritis-like symptoms. That's because of a theory that the vaccine might set off an autoimmune reaction where the body attacks its own tissues, particularly in people who carry a certain gene called HLA-4." The panel said that ultimately "no convincing evidence exists that the vaccine causes serious problems", but the experts urged the FDA and the manufacturer to expedite new safety studies and demanded that the Government should act to ensure that patients are told about the possible risks before inoculation. They also urged that the CDC should aggressively distribute a patient-friendly safety fact sheet about LYMErix (13).

A postmarketing assessment cohort study using automated record linkage was initiated at Harvard Pilgrim Health Care (HPHC) in order to address the theoretical concern that immunization with a vaccine containing OspA might cause an autoimmune arthritis and to evaluate whether exposure to the vaccine is a risk factor for Lyme disease, treatment-resistant Lyme disease, rheumatoid arthritis, certain neurological diseases, allergic events, hospitalization, and death (SEDA-24, 367) [http://www.fda.gov/ohrms/dockets/ac/01/slides/3680s2-05_platt.pdf]. The study involves 25 000 HPHC members who are expected to receive the vaccine and 75 000 non-immunized controls. For the most recent report, matched data were available for 2568 vaccinees and 7497 controls. At this stage, the available results do not suggest that the outcomes of interest were more frequent among vaccinees than among non-vaccinees. Having recognized that enrolment into the database is at a slower rate than anticipated, two additional Health Maintenance Organizations in countries where Lyme disease is endemic have been identified and will contribute.

On 30 November 2000, 1.4 million doses of vaccine had been distributed. From January 1999 to the time of the database query, there was no evidence that the incidence of these arthritic conditions was higher than reported in the general population or that they were associated with an autoimmune process (7).

To address further the question of a possible link between Lyme vaccine and arthritis, the FDA is conducting a telephone survey of individuals who have reported arthritic conditions to the VAERS after receiving the vaccine (7). This survey is a census of available and willing individuals who submitted reports that have been coded as arthritis, arthrosis, rheumatoid arthritis, joint disease, and arthralgia. The goals of the survey are to describe the characteristics of these adverse events, to identify concomitant factors that might influence the characteristics of these events, and to describe the relation of the events to immunization. After this survey phase is complete, the VAERS will identify cases of arthritis and will conduct a case-control study to examine the hypothesis that Lyme vaccine causes arthritis. It is planned to compare people who report arthritis after Lyme disease vaccine with two control groups: people who report arthritis to the VAERS after other vaccines and people who report adverse events to the VAERS other than arthritis after Lyme vaccine. All cases will be age-, sex-, and race-matched with controls. All three groups will be tested for DR HLA haplotypes at the allele level and for peripheral blood lymphocyte responses to OspA and leukocyte function-associated antigen-1 (LFA-1). This is an attempt to determine if people who report arthritis after Lyme vaccine have a higher prevalence of certain HLA alleles that are known to be associated with rheumatoid arthritis and have the same third common hypervariable region, while simultaneously having greater peripheral T cell reactivity to OspA and LFA-1. Given the relatively small number of arthritis cases reported after Lyme vaccine, probably only a very high risk will be detectable.

Four cases of arthritis associated with the administration of Lyme vaccine have been reported (14).

- 15 weeks after a third dose of Lyme vaccine a 9-year-old boy developed arthritis, including both knees, the right elbow, the left hip, the right ankle, and the right thumb; he was probably in an asymptomatic phase of natural Lyme infection.

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- About 3 months after a third dose of Lyme vaccine a 16-year-old boy developed arthritis of both knees.
- 24 hours after a second dose of Lyme vaccine a 53-year-old man developed flu-like symptoms and arthralgia; he later developed swelling of the finger joints and toe joints.
- 24 hours after a second dose of Lyme vaccine a 43-year-old man developed multiple synovitis.

In all cases the disease was self-limiting and to the knowledge of the authors inconsequential in the long term. They considered that the findings supported post-infectious and mimicry models, by showing that OspA, an outer surface protein of the causative organism of Lyme disease, *B. burgdorferi*, could cause acute arthritis, the possibility that it was associated with a more protracted form of arthritis, and that it perhaps had a modulating effect in individuals with concurrent Lyme infection.

Susceptibility Factors

Genetic factors

From reports containing information on HLA types, clinical descriptions of adverse events in those given Lyme disease vaccine are similar in people with DR4 and non-DR4 HLA haplotypes and do not suggest more inflammatory arthritis in people of DR4 haplotype (15) [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3680b2-06.pdf]. The characteristics of adverse events in people with a self-reported history of Lyme disease do not differ substantially from all adverse events after Lyme vaccine.

Drug Administration

Drug dosage regimens

In a randomized study in 956 volunteers aged 17–72 years a shortened immunization schedule of injections at 0, 1, and 2 months were compared with a schedule of injections at 0, 1, and 12 months (16). Adverse events were transient and mild to moderate. Soreness was the most frequently reported local symptom (82%), whereas fatigue (20–22%) was the most frequently reported general symptom. Two volunteers had more serious adverse events: severe chills and shaking in one and an episode of syncope (lasting a few minutes with complete recovery) on the day of the first dose in another. The authors concluded that doses at 0, 1, and 2 months would provide protection during a typical tick-transmission season.

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Lysergide

General Information

Lysergic acid diethylamide (LSD) is a hallucinogen that is usually taken orally. Its initial effects, anticholinergic and sympathomimetic in type, occur within about half an hour and include tachycardia, hyperthermia, mydriasis, piloerection, hypertension, and occasionally nausea and vomiting. The more important psychoactive effects develop 1–2 hours later and can last 24–48 hours. They are principally

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changes in perception, mood, and behavior, leading in many cases to acute panic, hallucinations, delusions, and in some cases a classical psychosis. Perception may be strikingly heightened and distorted, and initial perceptions may mask and overshadow later sensory perception. Users often grossly exaggerate their mental and emotional capacities, attributing to themselves extraordinary powers. Visual hallucinations, loss of appreciation of time and space, and instability of mood are common. Meaningfulness and a sense of universal union often predominate. A significant problem in street purchase is the uncertain quality and likely impurity of the material obtained. Doses of 25 mg and more are sufficient to cause its psychophysiological effects, which are generally dose-related up to 500 mg. The half-life is about 3 hours, but the effects last considerably longer (1).

Acute panic attacks and hallucinogen-induced psychotic disorder often occur when people with preexisting personality disorder or pre-psychotic personalities use hallucinogens. Suicide and self-injury have been reported. Prolonged psychotic disorders can occur, but psychiatric opinion is divided as to whether these occur only in people with pre-existing disorders or in healthy individuals as well. "Flashbacks" occur particularly when there has been prolonged heavy use, but eventually disappear (SED-11, 83) (1,2). Self-injury and suicide can result (3).

Hypersensitivity reactions are exceedingly rare and no reports have been validated. Tumor-inducing effects are possible, as a consequence of various reports from animal and human studies that chromosomal abnormalities may be associated with exposure to LSD. However, its mutagenic effects in practice are questionable, and no useful evidence for or against its potential for carcinogenicity has been produced (4).

Organs and Systems

Cardiovascular

Vasoconstriction, affecting both cerebral and peripheral circulations, has been associated with LSD (5), but it is not usually significant at ordinary doses in people with a normal circulatory system.

Nervous system

Hallucinogen-induced mood disorder is associated with changes in affect, varying from euphoria to manic-like symptoms, panic/fear, and depression, often occurring within minutes and often varying in the same individual on different occasions. Changes in sensory perception, with a loss of ability to distinguish temporal or spatial reality and sensory hallucinations, particularly visual and tactile, are frequent, with a tendency to assume godlike attributes. These features often merge in a psychosis, particularly with repeated use. Whether chronic psychosis after LSD is the result of the drug or of a combination of the drug and predisposing factors is currently unanswerable (6–8).

The repeated use of LSD is associated not only with psychoses, but also with more specific neurological signs and symptoms, including ataxia, incoordination, dysphasia, paresthesia, and tremor. Convulsions have been reported. "Flashback," or the return of hallucinogenic effects, occurs in almost a quarter of those who have used LSD, particularly if they have also used other CNS stimulants, such as alcohol or marijuana (2,9). They can experience distortions of perception of objects, space, or time, which intrude without warning into reality, resulting in delusions, panic, and unusual images. A "trailing phenomenon" has also been reported, in which the visual perception of objects is reduced to a series of interrupted pictures rather than a constant view (10). The frequency of these events may slowly abate over several years, but in a significant number their incidence later increases (1,3).

Sensory systems

Apart from visual hallucinations (discussed under the section Nervous system in this monograph), diplopia, blurred vision, mydriasis, and other visual disturbances occur (11). Pupillary dilatation, combined with altered sensory appreciation, has led to a number of instances of retinal damage after continued direct exposure to the sun (12).

Hematologic

The only hematological effect reported has been an increased rate of blood clotting associated with severe hyperthermia (13).

Gastrointestinal

Retroperitoneal fibrosis has been reported, not unexpectedly, in view of the structural similarity between LSD and methysergide (3).

Body temperature

Hyperthermia can occur but does so very seldom with usual doses (14). It has been produced experimentally with high doses.

Second-Generation Effects

Teratogenicity

Animal studies have not shown that LSD is teratogenic. Various publications have referred to a high incidence of abortions and congenital abnormalities associated with LSD. However, none of these has shown any consistent pattern of abnormality, and neither has there been an acceptable control group (4).

Susceptibility Factors

People who are predisposed to psychosis, schizophrenia, or a family history thereof, may be at considerable risk of developing LSD psychosis (3,8). People with epilepsy may be more prone to convulsions, with a reduction in convulsant threshold.

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Drug–Drug Interactions

Monoamine oxidase inhibitors

Chronic administration of a monoamine oxidase inhibitor causes a subjective reduction in the effects of LSD, perhaps due to differential changes in central serotonin and dopamine receptor systems (15).

Phenothiazines and butyrophenones

Phenothiazines and butyrophenones can counteract the psychoactive effects of LSD and benzodiazepines can depress their effects (16).

Reserpine

Reserpine can accentuate the effects of LSD (17).

Interference with Diagnostic Tests

Ambroxol

A urine sample from a patient with a severe head injury tested positive for LSD (18). The test was carried out using a homogeneous immunoassay CEDIA DAU LSD (Boehringer, Mannheim). Although LSD has a half-life of 3 hours, the patient's urine tested positive for several days. Analysis of the same urine samples using high-performance liquid chromatography (HPLC) failed to detect LSD. LSD screening was then performed in urine samples obtained from ten other patients in the same ward. All samples tested positive for LSD by the CEDIA DAU LSD assay but negative using HPLC. All of the patients were taking ambroxol. Ambroxol was detected in the urine by HPLC. In a volunteer, LSD was not detected in a fasting urine sample. After a dose of ambroxol 15 mg a urine sample obtained 90 minutes later tested positive for LSD. The addition of 50 µl of Mucosolvan juice (which contains ambroxol) to the negative fasting urine sample resulted in a positive test for LSD. The authors concluded that ambroxol should be excluded when LSD screening is performed using the CEDIA DAU LSD test.

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Lysine acetylsalicylate

General Information

Lysine acetylsalicylate is a soluble form of salicylate developed for intravenous administration in acute pain. Its mode of action and scope of adverse effects are similar to those of aspirin (1), although it has a faster onset of action (2) and causes less gastrointestinal bleeding (3).

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Macrolide antibiotics

General Information

The basic structure of the macrolide antibiotics is characterized by a lactonic cycle with two osidic chains, and they are classified according to the number of carbon atoms in the cycle: 14-membered macrolides (for example clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin), 15-membered macrolides (for example azithromycin), and 16-membered macrolides (for example josamycin, midecamycin, spiramycin).

The following macrolides are covered in separate monographs: azithromycin, clarithromycin, dirithromycin, erythromycin, josamycin, midecamycin, rokitamycin, roxithromycin, spiramycin, and troleandomycin (all rINNs).

The antibacterial activity of the macrolides is based on interference with protein synthesis by combining with a subunit of bacterial ribosomes. This generally results in a bacteriostatic effect. They cover a broad range of pathogens. Most are active against Gram-positive cocci and some Gram-negative bacteria, including *Campylobacter* and *Haemophilus*, but not most *Enterobacteriaceae*. However, they are very active against *Mycoplasma*, *Ureaplasma*, *Chlamydia*, *Legionella*, and *Coxiella*. Their activity against *Mycobacterium avium* complex, *Cryptosporidia*, and *Toxoplasma* is variable (1). The macrolide antibiotics have established themselves in the treatment of community-acquired infections. In addition, some have found new indications in the treatment of opportunistic infections in HIV-infected patients (1).

Actions and uses in non-infective conditions

Erythromycin is a motilin receptor agonist (2–4). Azithromycin also produced a significant increase in postprandial antral motility (5). Clarithromycin is also prokinetic, as shown in 16 patients with functional dyspepsia and *Helicobacter pylori* gastritis (6). For this reason, the macrolides have been used to treat gastroparesis (7).

Azithromycin may be useful in reducing ciclosporin-induced gingival hyperplasia in renal transplant recipients (8).

A beneficial effect of low doses of clarithromycin on sputum rheology has been reported in patients with chronic pulmonary diseases, such as chronic bronchitis (9).

In a murine model of virus-induced lung injury, erythromycin significantly improved survival rate (10). This may be explained by inhibition of inflammatory-cell responses and suppression of nitric oxide overproduction in the lungs of the virus-infected mice.

In 202 patients with unstable angina pectoris, roxithromycin prevented death and re-infarction for at least 6 months after initial treatment (11). However, these findings could not be confirmed in another study in 302 patients with coronary heart disease and a seropositive reaction to *Chlamydia pneumoniae* who were treated with azithromycin. While global tests of markers of inflammation improved, there were no differences in antibody titers and clinical events (12).

General adverse effects

Macrolides are in general well tolerated and are used over wide dosage ranges. The rates of adverse reactions are dose-related, as exemplified by the rate of adverse reactions to clarithromycin, which was higher with 2000 or 4000 mg in two doses per day than with 500 or 1000 mg/day (1). Severe toxicity is very rarely observed with macrolides. Most adverse reactions are rated as either mild or moderate, regardless of the macrolide used. Among 245 patients who were hospitalized because of toxic epidermal necrolysis or Stevens–Johnson syndrome, 6 patients had had exposure to macrolides within the week before the onset of the illness (13). The following antibiotics were used: erythromycin, roxithromycin (14), and spiramycin (14). The results of a case-control study suggest that macrolides do not pose an excess risk of this toxic complication (13). Anaphylactic reactions to macrolides are exceedingly uncommon, but anaphylaxis and acute respiratory distress have been reported (15,16). Skin tests with erythromycin were positive for the immediate and/or delayed types of hypersensitivity (17). Tumor-inducing effects have not been reported.

Table 1 and Table 2 summarize the frequencies of adverse reactions and premature withdrawal of the most widely used macrolides.

Pharmacoeconomics

The pharmacoeconomic impact of adverse effects of antimicrobial drugs is enormous. Antibacterial drug reactions account for about 25% of adverse drug reactions. The adverse effects profile of an antimicrobial agent can

Table 1 Frequencies of adverse reactions to macrolide antibiotics

Drug (number of patients)	Adverse reactions (%)	Premature withdrawal (%)	Reference
Erythromycin (112)	33	18.7	(18)
Clarithromycin (4291)	19.6	3.5*	(19)
Roxithromycin (2917)	4.1	0.9	(20)
Azithromycin (3995)	12	0.7	(21)
Dirithromycin (2825)	33.1	3.1	(22)

*at high doses (2000 mg/day) withdrawal rate 22%.

Table 2 Adverse effects of macrolide antibiotics

Drug	Gastro-intestinal (%)	Nervous system (%)	Skin (%)	Reference
Erythromycin (n = 112)	27	4	1	(18)
Clarithromycin (n = 96)	6	2	0	(19)
Roxithromycin (n = 2917)	3.9	0.4	0.7	(20)
Azithromycin (n = 3995)	9.6	1.3	0.6	(21)
Dirithromycin (n = 4263)	5.6	4.5	0.4	(22)

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contribute significantly to its overall direct costs (monitoring costs, prolonged hospitalization due to complications or treatment failures) and indirect costs (quality of life, loss of productivity, time spent by families and patients receiving medical care). In one study an adverse event in a hospitalized patient was associated on average with an excess of 1.9 days in the length of stay, extra costs of $US2262 (1990–3 values), and an almost two-fold increase in the risk of death. In the outpatient setting, adverse drug reactions result in 2–6% of hospitalizations, and most of them were thought to be avoidable if appropriate interventions had been taken. In a review, economic aspects of antibacterial therapy with macrolides have been summarized and critically evaluated (23).

Organs and Systems

Cardiovascular

Cardiovascular reactions are rare if macrolide antibiotics are used in the absence of susceptibility factors, which include drug interactions, increasing age, female sex, concomitant diseases, and co-morbidity (24).

Respiratory

In an animal model, acute lung injury was inhibited by pretreatment with clarithromycin or roxithromycin, which significantly ameliorated bleomycin-induced increases in the total cell and neutrophil counts in bronchoalveolar lavage fluids and wet lung weight (25). Pretreatment with clarithromycin or roxithromycin also suppressed inflammatory cell infiltration and interstitial lung edema. Pretreatment with azithromycin was much less effective.

Nervous system

Table 2 lists the rates of adverse events affecting the nervous system attributed to erythromycin and newer macrolides.

Sensory systems

Eyes

Bilateral ischemic optic neuropathy can develop secondary to macrolides (26).

Ears

The cochlear toxicity of systemic macrolides, azithromycin, clarithromycin, and erythromycin, has been investigated in guinea pigs by measuring transiently evoked otoacoustic emissions (27). A single intravenous dose of erythromycin 125 mg/kg caused no change in evoked otoacoustic emissions, whereas oral azithromycin 45 mg/kg and intravenous clarithromycin 75 mg/kg reversibly reduced the emission response. This could have been caused by transient dysfunction of the outer hair cells.

Psychological, psychiatric

Although there is no evidence that neuropsychiatric complications of macrolides develop more readily in uremic patients, several factors may predispose toward these adverse effects, such as reduced drug clearance, altered plasma protein binding, different penetration of drug across the blood–brain barrier, and an increased propensity for drug interactions.

Two women, aged 49 and 50 years, developed altered mental status a few days after starting to take clarithromycin for eradication of *H. pylori* (28). There was incoherent speech with perseveration, inability to sustain attention, impaired ability to comprehend, coprolalia, euphoria, restlessness, visual hallucinations, anxiety, and inappropriate affect. Similarly, in three cases, a 46-year-old man, a 39-year-old woman, and a 4-year-old boy, treatment with clarithromycin was followed by nervous system and psychiatric symptoms that included euphoria, insomnia, aggressive behavior, hyperactivity, and emotional lability (29).

Hematologic

Clarithromycin and roxithromycin slightly inhibited the down-regulation of L-selectin expression on neutrophils induced by interleukin-8 stimulation (30). Furthermore, clarithromycin strongly inhibited the interleukin-8-induced up-regulation of the expression of Mac-1, an adhesion molecule, on neutrophils.

Hematological changes with macrolides are very rare. Isolated instances of neutropenia are occasionally reported (31).

Gastrointestinal

The gastrointestinal adverse effects are the most common untoward effects of the macrolides (Table 2). Nausea and vomiting associated with abdominal pain and occasionally diarrhea can be minor and transitory or, in a small percentage of patients, become severe enough to result in premature withdrawal. The rate of these adverse effects varies among the different antibiotics. In general, newer macrolides, such as azithromycin, clarithromycin, or roxithromycin, are better tolerated and cause fewer adverse effects than erythromycin.

Erythromycin is a motilin receptor agonist (2–4). This mechanism may be at least partly responsible for the gastrointestinal adverse effects of macrolides.

Based on observations in dogs and rabbits, clarithromycin is significantly less potent than azithromycin and erythromycin as an agonist for stimulation of smooth muscle contraction (32). A lower rate of gastrointestinal adverse events would therefore be expected with clarithromycin than with azithromycin (Table 2). Since most of these data were compiled from several studies, and since most have not been obtained by direct comparison of the various macrolides in single studies, the rates should be interpreted with caution. They most probably provide only an approximate indication of the rate of adverse events. Small differences in rates between individual macrolides will in most cases not be clinically useful indicators of the true risk for the occurrence of adverse events.

In contrast to the macrolides mentioned above, macrolides with a 16-membered lactone ring (acetylspiramycin, josamycin, leucomycin, midecamycin, rokitamycin, spiramycin, tylocin) have little if any motor-stimulating effects (33,34).

Drug-induced esophagitis is rare, accounting for about 1% of all cases of esophagitis. An incidence of 3.9 in 100 000 has been reported. After the first description, there have been more than 250 observations, with more than 50 different drugs. Among those, the principal antibiotics included

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tetracyclines (doxycycline, metacycline, minocycline, oxytetracycline, and tetracycline), penicillins (amoxicillin, cloxacillin, penicillin V, and pivmecillinam), clindamycin, co-trimoxazole, erythromycin, lincomycin, spiramycin, and tinidazole. Doxycycline alone was involved in one-third of all cases. Risk factors included prolonged esophageal passage, due to motility disorders, stenosis, cardiomegaly, the formulation, supine position during drug ingestion, and failure to use liquid to wash down the tablet. Direct toxic effects of the drug (pH, accumulation in epithelial cells, non-uniform dispersion) also seem to contribute to the development of drug-induced esophagitis (35).

Liver

Erythromycin can cause two different types of liver damage (36,37), benign increases in serum transaminases, which may or may not recur on rechallenge, and cholestatic hepatitis. Reports of intrahepatic cholestasis with azithromycin (38), clarithromycin (39,40), and josamycin (41) suggest that the newer macrolides are not free of this adverse effect, although the relative risks compared with erythromycin are unclear. Similar involvement of the liver has been seen with the ester of triacetyloleandomycin, but not with the unesterified antibiotic.

Macrolides such as josamycin, midecamycin, and spiramycin, which do not form stable complexes with cytochrome P450, rarely if ever cause cholestatic hepatitis.

Urinary tract

- A 77-year-old man taking regular captopril, furosemide, salbutamol inhaler, vitamin C, and nasal beclomethasone dipropionate took clarithromycin 250 mg bd for sinusitis and bronchitis and 5 days later developed abdominal pain and intermittent fever (42). Laboratory findings included raised serum creatinine and blood urea nitrogen, aspartate transaminase, amylase, lactate dehydrogenase, and creatine kinase (not of the MB isoenzyme). The cause of the non-oliguric renal insufficiency was diagnosed by renal biopsy as interstitial nephritis with eosinophilic infiltrates. During the course of illness he also developed thrombocytopenia.

Skin

Skin rashes and fixed drug eruptions can occur during treatment with various macrolides but are rare (under 1%) (17).

Immunologic

Immunomodulatory effects of macrolides have been repeatedly reported; for example suppression of the release of chemotactic mediators may be important for the clinical effect of roxithromycin in patients with chronic lower respiratory tract infections (43). Both clarithromycin and azithromycin altered cytokine production in human monocytes in vitro (44).

The suppressive activity of macrolide antibiotics on pro-inflammatory cytokine production has also been shown in human peripheral blood monocytes, in which roxithromycin inhibited the in vitro production of interleukin-1 beta and tumor necrosis factor alpha (45). It also suppressed cytokine production after a prolonged pretreatment period in mice. In another mouse model both roxithromycin and clarithromycin inhibited angiogenesis and enhanced the antitumor activity of some cytotoxic agents, suggesting a beneficial effect when combined with such drugs against solid tumors (46,47). Furthermore, growth suppression of human fibroblasts by roxithromycin has been demonstrated both in vitro and in vivo (48).

Azithromycin has been associated with Churg–Strauss syndrome in a patient with atopy (49).

- A 46-year-old man with asthma was treated with oral roxithromycin 300 mg/day for 5 days for purulent rhinitis and 2 weeks later developed arthritis, mononeuritis multiplex, eosinophilia (64%), eosinophilic infiltrations in the bone marrow, raised IgE concentrations, and transient pulmonary infiltrates. Churg–Strauss syndrome was diagnosed.

A similar course of disease had occurred 1 year before, after the administration of azithromycin (50).

Leukocytoclastic vasculitis associated with clarithromycin has been reported in an 83-year-old woman who was treated for pneumonia. All her symptoms resolved after withdrawal and a short course of glucocorticoids (51).

- Henoch–Schönlein purpura developed in an 84-year-old Indian woman 10 days after she started to take clarithromycin (250 mg bd) for pneumonia (52). She was otherwise healthy and taking no regular medications. Histology confirmed a leukocytoclastic vasculitis of superficial vessels, with extravasation of erythrocytes, and direct immunofluorescence showed immunoglobulin A in superficial dermal vessels. Treatment with prednisone (1 mg/kg/day) was required. Most of the symptoms and signs resolved within a few days, but renal function remained impaired.

The authors identified two previous case reports of clarithromycin-induced leukocytoclastic vasculitis.

- A 39-year-old man developed acute angioedema and urticaria 6 hours after taking erythromycin base 500 mg in enteric-coated pellets for acute sinusitis (53). He remembered having taken erythromycin once before without any problem. He had no known allergies and was taking no regular medications, but he had had chemotherapy for non-Hodgkin's lymphoma several years earlier.

The authors identified five previous reports of erythromycin-associated urticarial reactions. However, it was not possible to exclude a reaction to the ingredients of the coated pellets.

Long-Term Effects

Drug tolerance

An area of increasing concern and clinical importance is the increasing macrolide resistance that has been reported over the last several years with some of the common pathogens, particularly *Streptococcus pneumoniae*, group A streptococci, and *Haemophilus influenzae*, and may result in failure of therapy of pneumonia, pharyngitis, and skin infections (54). High rates of resistance of several groups of streptococci to macrolides have been reported from all parts of the world (55–64).

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Resistance to erythromycin can develop rapidly and is usually associated with bacterial cross-resistance to the other macrolide antibiotics, and also to the chemically unrelated lincomycins. Resistance has been detected in strains of staphylococci, Group A hemolytic streptococci, viridans streptococci, *Streptococcus pyogenes*, *Neisseria gonorrhoeae*, *Bacteroides fragilis*, and *Clostridium difficile* (65,66). It has tended to occur in hospitals, where either erythromycin or the lincosamides were used extensively, but can also result from multiple drug resistance when other antibiotics are used. Subinhibitory concentrations of erythromycin can cause resistance in staphylococci.

In combination with proton pump inhibitors and other antibiotics, macrolides are still successfully used for the eradication of *H. pylori* infection (67,68). However, resistance of *H. pylori* to macrolides has emerged in a number of countries. The first case of *H. pylori* resistance to clarithromycin has now also been documented in Denmark and follows increased use of this macrolide in eradication regimens (69).

Clinical isolates of *N. gonorrhoeae* with reduced susceptibility to azithromycin are commonly found in Uruguay, and one of the mechanisms involved included mutations in the mtrR gene (70).

Resistance of *H. pylori* to clarithromycin appears to have increased in proportion to clarithromycin use. Clarithromycin resistance arises through mutations that lead to base changes in 23S ribosomal RNA subunits. A rapid PCR hybridization assay with a sensitivity of 97% for the detection of clarithromycin resistance of strains of *H. pylori* has been described (71). Resistance to clarithromycin has a serious impact on the efficiency of eradicating regimens that include clarithromycin (72–74). The reported incidences of primary resistance of *H. pylori* to clarithromycin are 6.1% in the USA, 8% in Austria, 8.7% in Bulgaria, 9.5% in Japan, 10% in Spain, 11% in France, 13% in Nigeria, and 23% in Italy (75–82).

Among strains of *Enterococcus faecium*, resistance against tylosin was mainly detected in strains from poultry, but also in some strains from pork. Among strains of *E. faecium* and *Enterococcus faecalis* isolated from pigs and poultry in Denmark, resistance to tylosin was often observed among isolates from places in which these antimicrobials had been widely used, but rarely among isolates from places in which their use had been limited (83).

Second-Generation Effects

Teratogenicity

In a large case-control surveillance study from Hungary in 38 151 pregnant women, oral erythromycin during pregnancy did not present a detectable teratogenic risk to the fetus (84).

Susceptibility Factors

Allergic reactions to antimicrobials are frequent in patients with Sjögren's syndrome. They are especially susceptible to reactions to penicillins, cephalosporins, and sulfonamides, but reactions to macrolides and tetracyclines also seem to be over-represented in these patients (85).

Drug–Drug Interactions

Alfentanil

The metabolism of alfentanil, a potent short-acting narcotic, is inhibited by macrolide antibiotics, resulting in significant changes in half-life and clearance (86).

Antihistamines

Toxic effects of terfenadine and astemizole have been reported in patients taking concomitant macrolides, especially clarithromycin (87–89,116), typically resulting in prolongation of the QT interval and cardiac dysrhythmias (torsade de pointes) (111). The potential interaction of azithromycin with terfenadine has been evaluated in a randomized, placebo-controlled study in 24 patients who took terfenadine plus azithromycin or terfenadine plus placebo (90). However, azithromycin did not alter the pharmacokinetics of the active carboxylate metabolite of terfenadine or the effect of terfenadine on the QT_c interval.

Only a modest increase in QT_c interval has been observed with concomitant use of erythromycin and the antihistamine ebastine (91).

Clarithromycin (500 mg bd for 10 days) significantly increased the steady-state maximum plasma concentration and the steady-state AUC of loratadine (10 mg/day for 10 days) (92). In contrast, the addition of loratadine did not affect the steady-state pharmacokinetics of clarithromycin or its active metabolite, 14(R)-hydroxyclarithromycin. No QT_c interval exceeded 439 ms in any subject.

Benzodiazepines

Interactions of macrolides with triazolam and midazolam are clinically important. Increased serum concentration, AUC, and half-life, and reduced clearance have been documented (93,94,118). These changes can result in clinical effects, such as prolonged psychomotor impairment, amnesia, or loss of consciousness (95). No interactions between ciprofloxacin and diazepam have been reported (96).

Carbamazepine

Significant increases in serum carbamazepine concentrations due to reduced clearance (97) and prolonged half-life (98,122,123) can result in confusion, somnolence, ataxia, vertigo, nausea, and vomiting in patients taking macrolides (100,124,125). Toxicity can occur rapidly after addition of the macrolide and abate quickly on withdrawal (126). However, a retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interaction in patients who were also taking carbamazepine (127,128).

- Carbamazepine toxicity, with dizziness, lethargy, and nystagmus, developed in a 17-year-old boy two days after he started to take clarithromycin 500 mg/day (129). His serum carbamazepine concentration (previously acceptable) rose, but returned to within the target range after withdrawal of clarithromycin.

Ciclosporin

The pharmacokinetics of ciclosporin can be altered by macrolides. Commonly observed changes include increases

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in ciclosporin AUC and peak plasma concentration and reductions in the time to peak and clearance (102,104,130,131). Ciclosporin concentrations should therefore be monitored, to minimize the risk of toxicity in patients taking certain macrolides. When azithromycin is used concomitantly with ciclosporin, blood ciclosporin concentrations need to be monitored (132).

Cytochrome P450

The frequency and pattern of drug interactions with macrolides is influenced by the chemical structure of the individual macrolide. The most important mechanism determining many drug interactions is the effect of macrolides on the hepatic cytochrome P450, which oxidizes macrolides after binding of the drug to oxidized (Fe_3) cytochrome P450 (126). Binding of the macrolide to group IIIA cytochrome P450 can have one of several consequences: oxidation can result in the formation of a stable iron-metabolite complex, causing either induction of cytochrome P450 and increased metabolism of the antibiotic, or inactivation of cytochrome P450 and inhibition of drug metabolism (126).

Structural properties of the macrolides determine whether the drug metabolizing enzyme is induced or inactivated. Macrolides with a 14-membered lactone ring have a greater potential to inhibit cytochrome P450 than bulkier macrolides with 15-membered or 16-membered lactone rings. It is therefore useful to group the macrolides according to their molecular structure and their potential for drug interactions via cytochrome P450 (Table 3).

The differences in interactions of different macrolides with cytochrome P450 are marked. Troleandomycin is a more potent inhibitor of microsomal drug metabolism than erythromycin, while josamycin, midecamycin, and spiramycin have not so far been incriminated (133,134). Azithromycin does not induce or inhibit cytochrome P450 in rats (135).

The occurrence of an interaction in a particular patient is difficult to predict. Hepatic concentrations of CYP3A4, the activity of which can be estimated by an erythromycin breath test (133), vary at least ten-fold among patients (136,137).

Table 3 Molecular structures of macrolides and the extent of their interactions with cytochrome P450

Degree of interaction	Number of carbon atoms in macrolide ring		
	14	15	16
High	Troleandomycin Erythromycin		
Low	Flurithromycin Clarithromycin Roxithromycin		Josamycin Midecamycin Miocamycin
Not incriminated	Dirithromycin	Azithromycin	Rokitamycin Spiramycin

The variability is compounded by the fact that, in addition to the liver, mucosal cells of the small intestine commonly express CYP3A4, where it is responsible for significant first-pass metabolism of orally administered substrates (137).

Drugs that participate in major CYP3A4 interactions with macrolides are listed in Table 4. Other drugs that may be affected include alprazolam (138), the water-soluble artemisinin analogue artelinic acid (139), gallopamil (140), lovastatin (141), nefazodone (142), and risperidone (143). Pharmacokinetic interactions with clarithromycin, erythromycin, and troleandomycin have been reviewed (144).

Digoxin

The interaction between macrolides and digoxin is not a consequence of altered cytochrome P450 activity. Digoxin is metabolized in the gastrointestinal tract by *Eubacterium lentum* in the bowel flora of about 10% of patients (106). The direct antibacterial effect of macrolides reduces digoxin metabolism and increases its systemic availability (134). The resultant increased digoxin plasma concentrations are associated with severe nausea, vomiting, and dysrhythmias (105,145,146).

Table 4 Summary of major interactions with macrolides

Interacting drug	Azithromycin	Clarithromycin	Erythromycin	Roxithromycin	Reference
Alfentanil	ND	ND	++	ND	(99)
Carbamazepine	–	++	++	–	(100,101)
Ciclosporin	+	ND	++	(+)	(102,103)
Digoxin	ND	++	++	ND	(104,105)
Disopyramide	ND	ND	++	(+)	(106,107)
Methylprednisolone	–	ND	+	ND	(108)
Oral contraceptives	ND	–	ND	–	(109,110)
Rifamycins	+?	++	ND	ND	(111–115)
Terfenadine, astemizole	ND	++	++	ND	(116)
Theophylline	–	+	++	(+)	(29)(101)(117)
Triazolam, midazolam	–	ND	++	(+)	(118)
Warfarin	–	–	++	–	(119,120)
Zidovudine	–	+	ND	ND	(121)

++ clinically relevant
+ potentially clinically relevant
(+) probably insignificant interaction
– documented lack of interaction
ND no published data
? insufficient information to judge relevance

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A concomitant clarithromycin-associated interaction with digoxin and warfarin has been reported (147).

- A 72-year-old man was taking regular digoxin (0.25 mg/day) and warfarin (22.5 mg/week) for chronic atrial fibrillation; other medications included furosemide, enalapril, glyceryl trinitrate paste, and a beclomethasone inhaler. He developed signs of digoxin intoxication after taking clarithromycin (500 mg tds) for 12 days and a raised serum digoxin concentration was confirmed. In addition, the INR was well above the target range (7.3 instead of 2.0–3.0).

An interaction with CYP450 enzymes was thought to be involved in the interaction with warfarin, and alteration of gut flora may have been involved in digoxin intoxication. Inhibition of P-glycoprotein by clarithromycin may also have contributed to the interaction with digoxin (148).

Azithromycin

- In a 31-month-old boy with Down's syndrome and Fallot's tetralogy during a 5-day course of azithromycin 5 mg/kg/day the serum digoxin concentration rose and the child had anorexia, diarrhea, and second-degree atrioventricular block with junctional extra beats (149).

The mechanism was not investigated, but it is likely that azithromycin affects *Eubacterium lentum*. When azithromycin is used concomitantly with digoxin, serum digoxin concentrations need to be monitored (132).

Clarithromycin

- In a 72-year-old woman taking digoxin 0.25 mg/day, the addition of clarithromycin caused a rise in the serum digoxin concentration to 4.6 ng/ml (147).

In two other cases in which clarithromycin increased serum digoxin concentrations there was an associated reduction in the rate of renal digoxin clearance, which may be another mechanism for this interaction (150). The authors hypothesized that clarithromycin inhibited P glycoprotein. This was supported by the observation of a concentration-dependent effect of clarithromycin on in vitro transcellular transport of digoxin.

There is anecdotal evidence that this interaction may be clinically important. Digoxin toxicity occurred in a patient taking clarithromycin (151).

Erythromycin

- Digoxin toxicity occurred in a neonate who was also given erythromycin (152). She had bradycardia and coupled extra beats. Digoxin and erythromycin were withdrawn and she was given antidigoxin antibodies. Her plasma digoxin concentration, which had previously been 1.8 ng/ml, had risen to 8.0 ng/ml.

Disopyramide

Severe cardiac dysrhythmias and major hypoglycemia have occurred in patients taking disopyramide with some macrolide antibiotics, especially erythromycin and clarithromycin (153).

Clarithromycin

- In a 76-year old woman, severe prolongation of the QT_c interval and self-terminating torsade de pointes were induced by the combined use of clarithromycin and disopyramide; concomitant hypokalemia may have contributed to the cardiac dysrhythmia (154).
- Symptomatic hypoglycemia developed in a 59-year-old man treated with a combination of disopyramide (50 mg/day) and clarithromycin (600 mg/day) (155).

Additional investigations in the second case suggested enhanced insulin secretion induced by toxic disopyramide concentrations as the probable mechanism.

Erythromycin

Disopyramide alters the protein binding of erythromycin, and this results in increased plasma concentrations in vitro (156). The interaction between erythromycin and disopyramide was potentially fatal in two cases (107).

Roxithromycin

Disopyramide alters the protein binding of roxithromycin, and this results in increased plasma concentrations in vitro (156). However, this effect has not been observed with roxithromycin in vivo.

Glucocorticoids

Some macrolides have a dose- and time-related effect on methylprednisolone elimination, resulting in a prolonged half-life and reduced clearance (157). These changes were considered advantageous (steroid sparing) in patients with asthma (158,159). However, a retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interaction in patients who were also taking methylprednisolone (127,128).

In an open study in six adults with mild to moderate asthma, clarithromycin significantly reduced methylprednisolone clearance, thereby increasing the risk of steroid-induced adverse effects (160). In contrast, prednisolone clearance and mean prednisolone plasma concentrations were unaffected. Frank psychosis due to combined therapy with prednisone and clarithromycin has been reported (161).

Lincomycins

Antagonism in vitro has been described between macrolides and lincomycins (162). Competition for similar binding sites at bacterial ribosomes probably underlies this phenomenon.

Oral contraceptives

Most reports associating cholestatic jaundice with the concomitant use of oral contraceptives and macrolides have implicated troleandomycin (163–166). The exact mechanism of this interaction has not been established. Troleandomycin possibly inhibits the metabolism of estrogens and progestogens (133). In most patients jaundice persisted for more than a month after the antibiotic was withdrawn.

In a non-blinded study in 20 healthy women using Ortho Novum 7/7/7–28, oral dirithromycin 500 mg/day

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for 14 days produced a small (7.6%) but statistically significant reduction in the mean ethinylestradiol 24-hour AUC and an increase in apparent oral clearance (167). No woman ovulated or had compromised effectiveness of the oral contraceptive in this small series, so the clinical importance of this interaction may be negligible.

Risperidone

Drugs that inhibit CYP3A, such as the macrolides, can significantly alter risperidone concentrations, especially in patients with CYP2D6 deficiency (143).

SSRIs

- A 12-year-old boy developed the serotonin syndrome, which is normally associated with the interaction of two or more serotonergic agents, after the co-administration of erythromycin and sertraline.

This could have been due to erythromycin-induced inhibition of sertraline metabolism by CYP3A (168).

Statins

Macrolide antibiotics inhibit the metabolism of statins that are metabolized by CYP3A4 (atorvastatin, cerivastatin, lovastatin, simvastatin) (169). This interaction can cause myopathy and rhabdomyolysis, particularly in patients with renal insufficiency or in those who are concurrently taking medications associated with myopathy. Rhabdomyolysis is a rare disorder that mostly results from adverse drug effects. Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are among the most important drugs causing this disorder, and the risk is increased when gemfibrozil or macrolide antibiotics are concurrently administered. The interaction usually develops within 2 weeks of combination therapy with macrolide antibiotics. Treatment includes drug withdrawal, intravenous fluids, urine alkalinization, and in severe cases dialysis.

Atorvastatin

In 12 healthy volunteers, erythromycin increased both the maximal plasma concentration and AUC of co-administered atorvastatin (170).

Lovastatin

Based on case reports or small studies, the potential for drug interactions between macrolides and lovastatin should be considered (171).

- Rhabdomyolysis, acute renal insufficiency, pancreatitis, ileus, livedo reticularis, and raised transaminase activities developed in a patient who had taken lovastatin for 7 years and took erythromycin before a dental procedure.
- Rhabdomyolysis requiring short-term dialysis occurred in a 57-year-old man with chronic renal insufficiency treated with lovastatin 40 mg/day, gemfibrozil 600 mg bd, and clarithromycin 500 mg tds (172).

In a review of the literature, three other reported instances of erythromycin and lovastatin interaction presenting with rhabdomyolysis, raised transaminase activities, and acute renal insufficiency were identified (173).

Simvastatin

Erythromycin interacts with simvastatin, probably by inhibiting its metabolism by CYP3A4. In a randomized, double-blind crossover study in 12 healthy volunteers, erythromycin significantly increased mean peak serum concentration and AUC for both unchanged simvastatin and its active metabolite simvastatin acid. However, there was extensive interindividual variability in the extent of this interaction (174).

- A 64-year-old African-American man developed rhabdomyolysis resulting from concomitant use of clarithromycin and simvastatin (175).

Theophylline and other xanthines

The most frequent effects of macrolides on theophylline pharmacokinetics are increased half-life and serum theophylline concentration and reduced clearance (133). The interaction with theophylline is mainly seen with higher doses of macrolides and can result in theophylline toxicity (108).

The effect of macrolides on serum theophylline concentration and clearance has been investigated in 53 patients with moderate asthma treated with theophylline (400 mg/day) in a randomized trial reference. Erythromycin (500 mg bd) and roxithromycin (150 mg bd), but not clarithromycin (250 mg bd) or azithromycin (250 mg bd), caused increased serum theophylline concentrations and reduced clearance.

However, a retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interaction in patients who were also taking theophylline (127,128). Furthermore, in two double-blind, placebo-controlled, randomized studies azithromycin did not inhibit the metabolism of theophylline (176,177). However, there has been a report of reduced theophylline concentrations after withdrawal of azithromycin (178). The authors concluded that the mechanism of interaction was best explained by concomitant induction and inhibition of theophylline metabolism by azithromycin, followed by increased availability of unbound enzyme sites as azithromycin was cleared from the system.

Clarithromycin increases the serum concentration of theophylline by inhibiting CYP450 enzymes.

- In a 72-year-old man, the administration of clarithromycin (400 mg/day) plus modified-release theophylline (200 mg/day) resulted in acute rhabdomyolysis with renal insufficiency requiring hemodialysis after 5 days of combined treatment (179).

Verapamil

- A 77-year-old woman taking verapamil and propranolol for hypertrophic cardiomyopathy and paroxysmal atrial fibrillation developed symptomatic bradycardia on two separate occasions within days of taking either erythromycin or clarithromycin. The proposed mechanism of the interaction was inhibition of cytochrome P450, since verapamil is a substrate of an isoenzyme that is inhibited by some macrolides (180,181).

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Severe hypotension and bradycardia after combined therapy with verapamil and clarithromycin has been reported in another case (182).

Warfarin

Azithromycin can increase the effect of warfarin (183), perhaps by inhibiting its metabolism. Despite only modest effects of macrolides on serum warfarin concentrations and increases in prothrombin time (119), morbidity caused by hemorrhage may be significant, as illustrated by several case reports (184–188). It is likely that this interaction is potentiated by other factors, such as old age or dietary restrictions (119). However, a retrospective analysis of 3995 patients treated with azithromycin did not show any pharmacokinetic interaction in patients who were also taking warfarin (127).

- A 71-year old woman, who was taking maintenance warfarin for a prosthetic heart valve, took a 5-day course of azithromycin, and 6 days later her INR rose from 2.5 to 3.5–15 (189).

A concomitant clarithromycin-associated interaction with digoxin and warfarin has been reported (147).

- A 72-year-old man was taking regular digoxin (0.25 mg/day) and warfarin (22.5 mg/week) for chronic atrial fibrillation; other medications included furosemide, enalapril, glyceryl trinitrate paste, and a beclomethasone inhaler. He developed signs of digoxin intoxication after taking clarithromycin (500 mg tds) for 12 days and a raised serum digoxin concentration was confirmed. In addition, the INR was well above the target range (7.3 instead of 2.0–3.0).

An interaction with CYP450 enzymes was thought to be involved in the interaction with warfarin, and alteration of gut flora may have been involved in digoxin intoxication. Inhibition of P-glycoprotein by clarithromycin may also have contributed to the interaction with digoxin (148).

Zafirlukast

Although zafirlukast inhibits CYP3A, it did not have any significant pharmacokinetic effect on single doses of azithromycin or clarithromycin in 12 healthy volunteers (190).

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Macrophage colony-stimulating factor (M-CSF)

See also Myeloid colony stimulating factors

General Information

Macrophage colony-stimulating factor (M-CSF) stimulates the growth and differentiation of the monocyte lineage, and promotes the survival, proliferation, and functions of mature monocytes/macrophages (1). It also enhances myelopoiesis through the amplified production of G-CSF and GM-CSF by monocytes, and has antitumor activity. Purified human urinary M-CSF and recombinant human M-CSF are under investigation in humans.

The safety of human M-CSF (hM-CSF) in allogeneic and syngeneic bone marrow transplantation was evaluated in a randomized, double-blind, placebo-controlled trial in 119 patients (2). There was mild transient fever in 6.7% of patients and there were no significant adverse effects on the platelet count. The incidence of graft-versus-host disease or graft rejection and the leukemic relapse rate were not affected compared with placebo. There was a similar safety profile in patients with autologous bone marrow transplants (3).

Glycosylated mammalian-derived recombinant human M-CSF (rhM-CSF) has been used in several trials. Constitutional symptoms (malaise, fatigue, insomnia, headache, nausea, fever, and chills) sometimes occurred. There was no evidence of long-term toxicity during follow-up of patients who received rhM-CSF after allogeneic bone marrow transplantation (4).

Organs and Systems

Sensory systems

Subclinical conjunctival injection occurred in 50% of patients in one series, with moderate but symptomatic episcleritis and blurred vision in one patient (SEDA-19, 345). Asymptomatic retinal or perilimbal hemorrhages were sometimes noted, but there was no clear correlation with platelet count. Subjective ophthalmological symptoms, ocular inflammation, iridocyclitis, or malaise have also occurred as dose- or treatment-limiting adverse effects in other studies (5,6).

Hematologic

The most significant adverse effect of glycosylated mammalian-derived rhM-CSF is a transient, dose- and schedule-related severe thrombocytopenia, which correlates with monocytosis and typically occurs after 7–10 days of treatment (7). Thrombocytopenia sometimes resolves despite continued administration of rhM-CSF and has usually not been sufficiently severe to cause bleeding. In other cases, a 50% reduction in the dose of rhM-CSF should be considered to allow treatment to be continued. The mechanism of rhM-CSF-induced thrombocytopenia does not involve suppression of hemopoiesis, but rather increased activity of the monocyte/macrophage system in the liver and spleen (8).

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Urinary tract

Acute nephrotic syndrome has been reported in a patient with a previous history of mild proteinuria (SEDA-20, 339), but the origin of the M-CSF (recombinant or human) was not stated.

Skin

Mild local toxicity sometimes occurs after subcutaneous injection of M-CSF (SED-13, 1118) (7). In one patient, multiple subcutaneous nodules consistent with a panniculitis occurred after each administration (SEDA-19, 345).

In one study, severe erythroderma and a dramatic proliferation of blast cells after each dose of hM-CSF were the only significant severe adverse effects, reported in one patient each (SEDA-19, 345).

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Mafenide

General Information

Mafenide is a topical sulfonamide that has been used for the treatment of burns but is now obsolete. Its adverse effects include hyperchloremic metabolic acidosis and (possibly) methemoglobinemia (1). Pulmonary insufficiency has been ascribed to mafenide acetate cream (SEDA-8, 160).

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Magnesium salts

General Information

Magnesium is a bright, silver-white alkaline earth metallic element (symbol Mg; atomic no. 12). It is widely found as different salts in minerals such as boracite (borate), ankerite and dolomite (carbonates), carnallite (chloride), brucite (hydroxide), periclase (oxide), lazulite (phosphate), amphibole, cummingtonite, enstatite, garnierite, hornblende, humite, hypersthenite, iolite, jade, melilite, monticellite, olivine, Pennine, saponite, sapphire, serpentine, talc, and tremolite (silicates), and epsomite, kainite, kieserite, and polyhalite (sulfates).

Uses

Magnesium salts are used in the following ways:

- as antacids (magnesium trisilicate, magnesium hydroxide) usually in combination with an aluminium salt; the combination of magnesium hydroxide and aluminium hydroxide is called co-magaldrox
- as laxatives (magnesium oxide)
- in the treatment of eclampsia (magnesium sulfate)
- to treat cardiac dysrhythmias (magnesium sulfate)
- in urological irrigation solutions, used for dissolution of urinary calculi (magnesium citrate).

General adverse effects

Acute toxicity can arise from overdosage or intestinal or renal disease. The main symptoms of magnesium toxicity are neuromuscular (paralysis) and cardiac (electrocardiographic changes, hypotension, bradycardia, heart block). In more severe cases there will be nervous system or respiratory depression, hypomotility of the bowel, muscle paralysis, and hyporeflexia.

Magnesium sulfate in bolus doses of 2–4 g over up to 5 minutes causes feelings of warmth, flushing, and sometimes sweating (1–3). Transient nausea has also been reported (2,3).

Organs and Systems

Cardiovascular

Circulatory collapse can occur as a symptom of severe hypermagnesemia if magnesium-containing products are taken in large amounts in high-risk patients (4).

Respiratory

Magnesium can be absorbed via the renal pelvis, at least when it is inflamed (5), and it has been suggested that absorption of magnesium through inflamed pelvic mucosa results in hypermagnesemia. Respiratory paralysis is a terminal event in severe hypermagnesemia, and iatrogenic hypermagnesemia with respiratory depression has been reported in patients who received hemiacidrin, a magnesium-containing irrigation fluid, through a ureteric catheter, together with magnesium citrate orally (6). Intravenous calcium directly antagonizes respiratory depression due to magnesium, possibly by displacement by calcium of magnesium from cell membranes (7).

Electrolyte balance

Severe hyperkalemia has been reported in pregnant intravenous drug abusers during prolonged parenteral magnesium sulfate therapy for treatment of toxemia (8). Hypermagnesemia was thought to be responsible.

Some patients develop mild transient hypotension after the administration of bolus doses of intravenous magnesium sulfate (2,3). In patients with suspected myocardial infarction who received magnesium sulphate infusions there was an increased incidence of atrioventricular conduction disturbances (9).

Gastrointestinal

Magnesium salts, given alone or in combination with other antacids, commonly cause diarrhea of osmotic origin (10).

In infants of low birth weight, the use of magnesium-containing antacids has caused hypermagnesemia and intestinal perforation (SEDA-16, 417).

Urinary tract

A Japanese patient taking magnesium silicate developed urolithiasis, the stone consisting of 98% silicate (11); some 15 cases of silica stones have been reported in Japan, but it is not clear how many of these patients had used magnesium silicate.

Skin

A fixed drug eruption during magnesium trisilicate treatment has been reported (SEDA-11, 321).

Susceptibility Factors

Renal disease

In severe renal insufficiency there can be accumulation of magnesium due to reduced excretion, with inhibition of parathyroid function and consequent calcium and phosphorus abnormalities (12).

Drug Administration

Drug administration route

Enema treatment with magnesium salts can cause severe hypermagnesemia (13).

Drug overdose

Magnesium overdose is usually inadvertent, due to high intake of magnesium-containing antacids or laxatives.

- A 42-year-old Hispanic woman with normal renal function took magnesium hydroxide (as milk of magnesia) 30 ml each night with Maalox 30 ml tds for about 5 days for abdominal pain and constipation (14). She developed confusion, vomiting, hypothermia, hypotension, and abdominal distension. Additional medications included lithium carbonate, chlorpromazine, benzatropine, and docusate sodium. Her serum magnesium concentration was 4.5 mmol/l (reference range 0.7–1.0). She was treated with intravenous calcium gluconate and fluids. At surgery for abdominal distension she was found to have adhesions from a previous oophorectomy. On the second postoperative day she developed a cardiac dysrhythmia and died in asystole.
- A 3-week-old girl who was treated with magnesium oxide as a laxative developed severe hypermagnesemia as a result. Treatment was with a combination of hyperhydration, forced diuresis and natriuresis, and administration of intravenous calcium and insulin (15).

Magnesium was administered in high doses to a child as part of an alternative regimen of megavitamin/megamineral therapy (16). The treatment was prescribed by an alternative nutritionist without the knowledge of the pediatrician in charge. The child died of hypermagnesemia.

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Malaria vaccine

General Information

For centuries, attempts have been made to find a vaccine against malaria, especially malaria tropica (1). Most of these attempts have been disappointing (SEDA-13, 822) (SEDA-21, 298). However, the results of a number of field studies have been reported.

SPf66 vaccine is a synthetic polypeptide based on preerythrocyte and asexual blood stage proteins of *Plasmodium falciparum*. A trial in Tanzania, in an area in which malaria is not only endemic, but the parasite load heavy, showed an estimated efficacy of 30% (95% CI = 0, 52%). The vaccine was immunogenic. There was also a difference in mortality between the groups, with one death among the vaccinated children and five in the control group. Adverse effects were in general mild and similar to those in earlier work (2,3).

In Colombia, the vaccine brought about an immune response, and adverse effects were minimal. The first randomized, double-blind, controlled trial in Colombia, in which 1548 volunteers participated, showed an overall efficacy of 39%. In a small, selected group of volunteer soldiers there was a protective effect of 60–80%. In 96% of cases there were no adverse effects and the adverse effects in the remainder were mainly localized erythema, discomfort, and sometimes induration (4,5).

A study in Ecuador showed 67% mean prophylactic efficacy against *P. falciparum*, but the 95% CI were very wide (2.7, 89%). The vaccine was administered in three doses, at zero time and after 30 and 180 days. Adverse effects (local pain, erythema, and local induration) occurred after the first dose in 6.2%, after the second dose in 19%, and after the third dose in 14%. The placebo group had similar adverse effects, but in a lower proportion of subjects and with fewer cases of induration. There was no protection against *Plasmodium vivax* infections (6).

In a Venezuelan study (7), 1442 villagers were vaccinated and vaccination was completed with the three doses in 976 subjects, with a comparison group of 938 subjects from the same area. Antibodies were produced against the vaccine. The adverse effects were as in earlier work, but there was also some contralateral induration, mainly after the third dose of vaccine, which was given alternately into the left and right arms. Five women had generalized pruritus. Bronchospasm was observed in one case.

A new recombinant vaccine has shown promise in vitro and in rabbits. It combines segments of 21 different immunogenic peptides from *P. falciparum* into a single recombinant protein, eliciting a multilayered immune response, including B cell and T cell responses (1).

Organs and Systems

Immunologic

Immediate-type hypersensitivity reactions (acute, systemic urticaria after the third immunization) occurred in two of 39 volunteers immunized with a synthetic multiantigen peptide vaccine (PfCS-MAP1NYU) against *P. falciparum* sporozoites, with detection of serum IgE MAP antibody (8). Immediate pain at the injection site was associated with the adjuvant QS-21, and delayed local inflammatory reactions were associated with high titers of circulating IgG anti-MAP antibody. Skin tests using intradermal injections of diluted MAP vaccine, to identify those who were sensitized to the vaccine, were negative in seven volunteers tested 27 days after the first vaccination, but six of these developed positive wheal and flare reactions when tested 14 or 83 days after the second vaccination; IgE MAP antibody was detected in only one of them. Skin tests may help in identifying individuals who have been sensitized to malaria peptides and who are at risk of developing systemic allergic reactions after revaccination.

On the other hand, delayed-type hypersensitivity testing has been used to test T cell functional activity in 27 volunteers immunized with a synthetic multi-antigen peptide vaccine (MAP) (PfCS-MAP1NYU) against *P. falciparum* sporozoites (9). Intradermal inoculations (0.02 ml) of several concentrations of the MAP vaccine and adjuvant control solutions were applied and induration measured 2 days after. Nine of 14 vaccinees with high serum titers of anti-MAP antibody developed positive skin tests (at least 5 mm induration), which first appeared by 29 days after immunization and persisted for at least 3–6 months after one or two more immunizations. In contrast, skin tests were negative in all of eight vaccinees with no or low antibody titers, and in all of five non-immunized volunteers. Biopsies of positive skin test sites were histologically compatible with a delayed hypersensitivity reaction. The authors concluded that the presence of T cell functional activity is reflected by a positive skin test response to the MAP antigen and may serve as another marker for vaccine immunogenicity.

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Malathion

General Information

Malathion is used for the treatment of lice, a single application of 0.5% in a solution being customary. Used in this way, it is generally safe, although the same compound has caused fatal poisoning when used as a pesticide in the environment.

Four children developed malathion intoxication after hair-washing with a solution containing malathion (50% in xylene) for the purpose of louse control (1). Hyperglycemia and glycosuria were found in all cases. One child, described in detail, was in coma and did not respond to pain stimuli; other symptoms included severe dyspnea, extensive, moist coarse crackles in both lung fields, voluminous frothy saliva, and mucus filling the nose, mouth and pharynx, pinpoint pupils not responding to light, excess lacrimation and fasciculation in the upper eye lids, and flaccid limbs and absent tendon reflexes.

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Malvaceae

See also Herbal medicines

General Information

The genera in the family of Malvaceae (Table 1) include cotton, okra, and various types of mallow.

Gossypium species

Gossypol occurs in certain species of *Gossypium* (cotton), mostly in the seeds and root bark. Clinical studies have confirmed its efficacy as a male contraceptive agent (1).

Gossypol is a racemic mixture of (+)-gossypol and (−)-gossypol. When tested separately in male rats in a dosage of 30 mg/kg orally for 14 days, only the latter enantiomer had a clear anti-fertility effect. Furthermore, (+)-gossypol has less acute toxicity than (−)-gossypol after intraperitoneal administration to mice. In a human study, the enantiomers showed pharmacokinetic differences in half-life; less than 5 hours for (−)-gossypol compared with 133 hours for the (+)-enantiomer.

Adverse effects

The reported adverse effects of gossypol include fatigue, changes in appetite, transient rises in alanine transaminase, and hypokalemia.

Because of the adverse effects of gossypol, The Special Program of Research, Development and Research Training in Human Reproduction (HRP) at the World Health Organization (WHO) decided that gossypol is not acceptable as an antifertility drug (2).

Electrolyte balance

Gossypol causes potassium loss, perhaps by a direct toxic effect on the renal tubules (3), which can cause renal tubular acidosis (4). Hypokalemic paralysis (5) has been reported in about 1% of 8806 volunteers and in China was more common in areas of low dietary potassium intake, such as Nanjing (6); muscular weakness and severe fatigue are prodromal signs (7). Neither potassium supplementation nor triamterene prevented potassium loss in patients taking gossypol (8).

Fertility

Of 151 men from Brazil, Nigeria, Kenya, and China who received gossypol 15 mg/day for 12 or 16 weeks and were then randomized to either 7.5 or 10 mg/day for 40 weeks,

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Table 1 The genera of Malvaceae

Abelmoschus (okra)
Abutilon (Indian mallow)
Alcea (hollyhock)
Allosidastrum (mock fanpetals)
Allowissadula (false Indian mallow)
Althaea (marshmallow)
Anoda (anoda)
Bastardia (bastardia)
Batesimalva (gaymallow)
Billieturnera (false fanpetals)
Callirhoe (poppymallow)
Cienfuegosia (flymallow)
Eremalche (mallow)
Fioria (fanleaf)
Freyxellia (fryxellwort)
Gossypium (cotton)
Herissantia (herissantia)
Hibiscadelphus (hibiscadelphus)
Hibiscus (rose mallow)
Horsfordia (velvet mallow)
Iliamna (wild hollyhock)
Kokia (tree cotton)
Kosteletzkya (kosteletzkya)
Krapovickasia (krapovickasia)
Lavatera (tree mallow)
Malachra (leaf bract)
Malacothamnus (bush mallow)
Malva (mallow)
Malvastrum (false mallow)
Malvaviscus (wax mallow)
Malvella (mallow)
Meximalva (meximalva)
Modiola (bristle mallow)
Napaea (napaea)
Pavonia (swamp mallow)
Pseudabutilon (pseudabutilon)
Rhynchosida (rhynchosida)
Sida (fanpetals)
Sidalcea (checkerbloom)
Sidastrum (sand mallow)
Sphaeralcea (globe mallow)
Thespesia (thespesia)
Urena (urena)
Wissadula (wissadula)

81 had suppression of spermatogenesis (9). Testicular volume decreased, but normalized after withdrawal. Of 19 subjects who took 7.5 mg/day, 12 recovered sperm counts over 20 million/ml within 12 months of discontinuing gossypol; of 24 who took 10 mg/day, sperm counts recovered in only 10. Eight remained azoospermic 1 year after stopping gossypol.

Psoralea corylifolia

Infusions prepared from the seeds of *Psoralea corylifolia* (bakuchi) can cause photosensitivity due to the presence of psoralens (10).

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Manganese

General Information

Manganese is a hard but brittle grayish-white metallic element (symbol Mn; atomic no. 25) that occurs in nature chiefly in the form of its oxides, but is also found as a sulfide (for example in alabandite), carbonate (ankerite, dialogite, and rhodochrosite), niobate and tantalate (columbite), silicate (piedmontite, rhodonite, spessartite, and tephroite), arsenate (synadelphite), and tungstate (wolframite).

Uses

The inorganic manganese salt potassium permanganate is used as a local anti-infective, an astringent, and a powerful deodorant and cleanser.

Manganese is often present in mineral supplements, in hemopoietic formulations, and in some solutions for parenteral nutrition. Trace elements are required in patients receiving long-term parenteral nutrition (1), and the use of manganese has been reviewed (2).

Mangafodipir trisodium (Mn DPDP; Teslascan, Nycomed, Oslo) is a chelate complex containing manganese (II) ion bound to fodipir, used as a hepatobiliary contrast agent (SEDA-22, 246). After injection, mangafodipir trisodium undergoes net transmetalation with endogenous zinc (II) ion and removal of the two phosphate groups to give two metabolites, manganese dipyridoxal ethyldiamine diacetate and zinc dipyridoxal ethylenediamine diacetate. The transmetalation with zinc is associated with a transient reduction in serum zinc concentrations, which normalize within about 24 hours after injection. About 14–20% of the manganese

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is excreted in the urine and 52–61% is excreted in the feces over 4 days. About 92% of fodipir is eliminated within 24 hours. Mangafodipir trisodium is mainly indicated to enhance the MRI T1-weighted images that are used in the detection, localization, and characterization of hepatic lesions. Normal liver parenchyma takes up the manganese and becomes bright, resulting in clear demarcation of abnormal parenchymal lesions.

LumenHance (Bracco Diagnostics Inc, Princeton, NJ) is a gastrointestinal MRI contrast agent based on manganese chloride.

Finally, as with other metallic elements, non-medical exposure to manganese can occur, particularly in occupational settings, and can cause neurotoxicity (3).

General adverse effects

The toxic effects of manganese in dogs (SEDA-21, 239) and humans (4) tend to involve the heart, liver, and nervous system, but some endocrine effects can occur. The general toxicity of manganese (5) and its neurotoxicity (6) have been reviewed.

Two cases of manganese intoxication during intermittent parenteral nutrition have been reported (2). In one case, manganese had been given once or twice a week for 4 years and in the other case twice a month for 5 years. Both patients had mild headache and dizziness. One had mild hepatic dysfunction. After withdrawal of manganese the symptoms all disappeared. Patients should be carefully monitored when receiving long-term parenteral nutrition including manganese, even when the manganese dose is small and administration infrequent.

The best way to monitor excessive exposure to manganese includes serum manganese concentration measurement in combination with brain MRI scanning and perhaps a battery of neurofunctional tests (7). Studies have concentrated on manganese in patients on parenteral nutrition (8) and occupational exposure (9).

In a phase III study 546 patients with suspected or known focal liver lesions received intravenous mangafodipir trisodium 5 μmol/kg before MRI examination (10). There were 195 adverse effects in 123 (23%) patients; only 72 were considered to be related to the contrast medium. Most common were nausea (7%), headache (4%), vomiting and abdominal pain (2% each), chest pain and palpitation (1% each), and hypertension, flushing, vasodilatation, and hypotension (under 1% each). Injection-associated reactions included heat (49%) and flushing (39%). Most of the adverse events (65%) were moderate and 7% were severe. Changes in laboratory values (full blood count, electrolytes, serum creatinine, and liver function tests) and vital signs (pulse, blood pressure) were generally transient, not clinically significant, and did not require treatment. The authors concluded that exposure to mangafodipir trisodium is not associated with short-term risks.

Organs and Systems

Nervous system

Workers who have been exposed to manganese, patients with hepatic disease, and patients undergoing total parenteral nutrition with excessive amounts of manganese (11,12) can accumulate manganese selectively in the globus pallidus of the basal ganglia without immediate neurological effects. Because of its paramagnetic properties manganese can be visualized by MRI, and produces high-intensity, bilateral, symmetrical signals, visible in T1-weighted images. Two indicators of exposure and hyperintensity should be considered: the concentration of manganese in total blood and the pallidal index.

Following occupational exposure, neurobehavioral effects resembling parkinsonism have been observed in a series of manganese workers at exposures well below current occupational standards (13); higher levels of exposure can cause dystonic rigidity and proximal tremor. The late effects of currently asymptomatic exposure are uncertain; however, in Chilean workers with past exposure in manganese mines, hand tremor was detectable (14).

Two cases of manganese intoxication have been reported during total parenteral nutrition including manganese (15).

- A 68-year-old woman developed psychiatric symptoms and gait disturbance. She had received total parenteral nutrition for 3 months for ulcerative colitis, and essential trace elements (Elemenmic), including manganese (20 μmol/day), had been added. She was markedly confused and had parkinsonism, with dysarthria, marked rigidity, hypokinesia with a mask-like facies, and a supranuclear vertical gaze palsy. Her manganese concentrations were raised in both serum (4.2 ng/ml, normal 0.4–2.0 ng/ml) and urine (9.0 ng/ml; normal under 2.0 ng/ml). Serum concentrations of other trace elements (zinc, copper, iron) were normal. An MRI scan showed symmetrical high intensity T1 weighted images in the basal ganglia, especially the globus pallidus. Trace element supplementation was discontinued, levodopa was given, and her psychiatric symptoms and parkinsonism gradually abated. Calcium EDTA 1 g/day for 5 days produced marked urinary secretion of manganese. The high intensity basal ganglia MRI lesions regressed after supplementation had stopped.
- A 70-year-old man was given total parenteral nutrition for 4 months, with essential trace elements (Mineralin), including manganese (20 μmol/day). After 2 months he had progressive gait disturbance and confusion. His manganese was raised (5.1 ng/ml in serum, and 1 ng/ml in the urine). He was markedly confused and had parkinsonism, with marked rigidity, a mask-like facies, hypokinesia, and a slight resting finger tremor. An MRI scan showed symmetrical high intensity signals on T1 weighted images of the basal ganglia, especially the globus pallidus, and T2 weighted images showed multiple high intensity spots in the cerebral white matter, suggesting multiple lacunar infarcts. Trace element supplementation was discontinued, levodopa was given, and his parkinsonism gradually improved. Calcium EDTA daily for 5 days produced marked urinary secretion of manganese. The high-intensity basal ganglia lesions regressed after supplementation had stopped.

It is difficult to distinguish parkinsonism due to manganese from idiopathic parkinsonism by clinical signs only, but positron emission tomography can be helpful in discriminating them.

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- In a 48-year-old welder with parkinsonism an MRI scan showed symmetrical high signal intensities in the globus pallidus (16). The intensities disappeared almost completely 6 months after the last exposure to manganese. Positron emission tomography showed reduced uptake of ^{18}F-dopa in the left putamen, findings that occur in idiopathic parkinsonism.

Another study reports positron emission tomography discriminated between idiopathic parkinsonism and parkinsonism due to manganese in three cases (17).

- A 51-year-old man had a mask-like face, marked postural tremor of the hands, dystonia of the neck and arms, severe retropulsion, and lateropulsion, typical of chronic manganese intoxication. An ^{18}F-dopa scan was normal.
- Two other patients, a 46-year-old man and a 47-year-old man with tremor at rest, rigidity predominantly on the right side, bradykinesia, stooped posture, and postural instability, all of which were typical of Parkinson's disease, had reduced uptake of ^{18}F-dopa in the striatum, particularly in the posterior putamen, predominantly on the left side.

The first patient had pure manganism, while the other two had Parkinson's disease, because loss of nigrostriatal fibers was obvious, with asymmetry in the putamen.

Endocrine

In a series of workers exposed to manganese dust for more than 14 years in a ferroalloy-producing plant, the correlation between prolactin and manganese in blood and in urine was studied (18). In the manganese-exposed workers there was an increase in serum prolactin, which correlated with manganese in both the blood and urine, suggesting impairment of tonic inhibition by tuberoinfundibular dopaminergic neurons.

Gastrointestinal

A phase 3 multicenter study of LumenHance has been reported (19). At a concentration of 40 μg/ml of Mn^{2+} the agent causes the lumen to have high-signal intensity on T1 weighted images and low signal intensity on T2 weighted images. The contrast agent was reconstituted with water and given in three 300 ml doses, 45 minutes, 30 minutes, and immediately before imaging in 226 patients, of whom 48 complained of one or more adverse effects, mainly related to the gastrointestinal tract (nausea was the most common). There were no serious adverse effects and no changes in vital signs or laboratory parameters. Reported adverse effects were not statistically different from placebo, and the authors concluded that LumenHance is a safe and efficacious oral gastrointestinal MRI contrast agent.

Of 30 patients undergoing contrast enhanced MRI scanning for focal liver lesions only two complained of slight nausea during the injection of mangafodipir (20). In all other cases the contrast agent was well tolerated.

Liver

In a series of neonates on total long-term parenteral nutrition, cholestatic disorders were associated with high manganese concentrations (over 360 nmol/1) (21).

Susceptibility Factors

Hepatic disease

Chronic hepatic cirrhosis is associated with manganese overload (not as a rule of medicinal origin), and manganese deposition in the brain may be responsible for hyperintensity of the T1-weighted magnetic resonance imaging (MRI) signal that is consistently seen in the globus pallidus of patients with cirrhosis (22).

- A 14-year-old boy presented with progressive hepatic myelopathy caused by cryptogenic micronodular cirrhosis, associated with persistent polycythemia and large increases in whole blood manganese concentration (23). An MRI scan showed manganese deposition in the basal ganglia and other regions of the brain. The liver manganese concentration was raised. Environmental exposure to manganese was investigated and excluded.

Apparently the liver disorder initiated altered manganese metabolism. However, the patient developed neither liver failure nor parkinsonism.

Other features of the patient

In patients on home parenteral nutrition, hypermanganesemia can be facilitated through (1) cholestatic liver disease and thereby reduced manganese biliary excretion, (2) high nutritional requirements (responsible for increased manganese supply), and/or (3) altered manganese metabolism or body distribution (12).

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Manidipine

See also Calcium channel blockers

General Information

Manidipine is a dihydropyridine calcium channel blocker that can be given once a day for hypertension. In a comparison of manidipine 10 mg/day and amlodipine 5 mg/day in a multicenter, randomized, double-blind study in 530 patients with mild-to-moderate hypertension, the two drugs had comparable antihypertensive effects, but manidipine was associated with a significantly lower incidence of ankle edema (1). Nevertheless, adverse events caused withdrawal from treatment in a similar number of patients, 23 with manidipine and 26 with amlodipine.

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Mannitol

General Information

Mannitol is an osmotic diuretic that has been used in acute oliguric renal insufficiency, acute cerebral edema, and the short-term management of glaucoma, especially to reduce intraocular pressure before ophthalmic surgery. Other indications include promotion of the excretion of toxic substances by forced diuresis, bladder irrigation during transurethral resection of the prostate, and oral administration as an osmotic laxative for bowel preparation. Mannitol is used as a diluent and excipient in pharmaceutical formulations and as a bulk sweetener.

Large doses of mannitol used in treating cerebral edema can alter extracellular fluid volume, osmolality, and composition and can lead under some circumstances to acute renal insufficiency, cardiac decompensation, and other complications (1). The patient's body habitus, age, total body water content relative to body weight, pretreatment plasma sodium concentration and plasma osmolality, and the presence of edema or ascites can influence the degree of extracellular fluid change and the rate of mannitol excretion to a significant degree.

Mannitol is excreted unchanged through the kidneys, and when renal function is impaired it accumulates and the movement of water into the intravascular space results in cellular dehydration. Two patients have been reported who suffered reversible acute oliguric renal insufficiency after mannitol infusion given as treatment for intracranial hypertension (2). Both had nausea and vomiting and became increasingly lethargic with the development of generalized edema. Congestive cardiac

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failure occurred. Laboratory tests showed severe dilutional hyponatremia with hyperosmolality.

The commonly recognized complications of osmotic agents used in patients with acute closed-angle glaucoma are mild headache, neck pain, nausea, and vomiting.

Organs and Systems

Nervous system

Rebound intracranial hypertension can develop as a result of mannitol administration in neurological patients and is associated with an increase in CSF mannitol and osmolality after intravenous administration (3,4). The reported incidence of rebound intracranial hypertension with mannitol varies widely. There is no agreement that osmotic gradients and their reversal are the respective mechanisms of intracranial pressure reduction and rebound after mannitol. Another explanation is that mannitol reduces intracranial pressure by reducing viscosity and compensatory vasoconstriction, thus reducing cerebral blood volume and thereby reducing intracranial pressure. Rebound can then be explained by the delayed increase in viscosity after mannitol-induced diuresis and elimination of mannitol. It is unlikely that this provides a comprehensive explanation for the effects of mannitol. It may be that passage of mannitol across the blood–brain barrier is significantly influenced by the presence and nature of neurological disease. There may be patient subsets, such as those with diffusely increased blood–brain barrier permeability or those with focally increased blood–brain barrier permeability but diffuse distribution of mannitol throughout the cerebrospinal fluid. Such patients might be especially susceptible. These observations need to be regarded as speculative for the time being, but the idea of identifying subsets of patients who are at special risk is challenging.

Psychological, psychiatric

Acute mania has been reported in a patient who was given intravenous mannitol (5).

- A previously well 75-year-old woman without a personal or family history of mental disorders developed severe major depression and was given nortriptyline 50 mg/day. After 10 days a diagnosis of bilateral acute angle-closure glaucoma was made and she was given a continuous intravenous infusion of mannitol 20%, oral acetazolamide 500 mg, and topical pilocarpine 2%, timolol 0.5%, and dexamethasone 0.1% (each 1 drop every 15 minutes). She became euphoric 30 minutes later and remained overactive, overly affectionate, and talkative, telling jokes, with pressured speech and flight of ideas. Her manic state remitted 1 hour after the end of the mannitol infusion and her severe depression recurred dramatically.

Mannitol can cause both acute expansion of extracellular fluid volume and a rapid reduction of intracellular fluid volume with retention of brain electrolytes; these may have been the mechanisms in this case.

Gastrointestinal

Oral mannitol can raise intracolonic hydrogen concentrations sufficiently to cause explosions at diathermy (6).

Urinary tract

Four cases of acute renal insufficiency have been described in men aged 20–42 years who received mannitol 1172 (sd 439) g over 58 (sd 28) hours (7). The onset of acute renal insufficiency was detected 48 (sd 22) hours after the start of infusion. All the patients had dilutional hyponatremia (average 120 mmol/l) and serum hyperosmolarity (osmolar gap 70 mosm/kg water). In the three anuric cases, in which hemodialysis was performed, there was immediate recovery of diuresis. This emphasizes the risk of renal insufficiency with mannitol and stresses the importance of early hemodialysis. Mannitol is dialysable and once its suppressive effect on renal perfusion is eliminated functional recovery is prompt.

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Maprotiline

See also Antidepressants, second-generation

General Information

Maprotiline has a tetracyclic structure, in which the tricyclic nucleus adjoins a fourth ring formed by an ethylene bridge vertical to the major plane of the molecule (SEDA-5, 34). It has a strong inhibitory effect on noradrenaline uptake across cell membranes, and relatively weak effects on serotonergic mechanisms. The half-life averages 43 hours (1), allowing once-daily dosing.

After the release of maprotiline in Britain, information was collected from 10 000 patients treated in general practice during 9 months (2). Patients were given 75 mg/day, preferably at night, and were followed for 3 weeks. By the end of that time 1343 patients had dropped out owing to adverse effects, of which drowsiness was the most common, followed by dizziness and headache. Skin rashes reached a constant peak incidence of about 3%

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after 2 weeks; rashes were reported in some earlier clinical trials (SEDA-2, 12).

Blood concentrations were measured in two trials in general practice (3). On both regimens (single and divided doses), a steady state was reached after 1 week, but there was considerable individual variability (up to ten-fold) in plasma concentrations. In a multicenter study of over 2000 records from more than 500 general practitioners (4) the onset of action usually occurred within the first week of treatment and the effect was complete after 3–4 weeks; roughly half of the total improvement occurred by the end of the first week.

There have been several comparisons of maprotiline with other antidepressants. There was no significant difference in adverse effects compared with doxepin (5), amitriptyline (6), or imipramine (7).

Organs and Systems

Cardiovascular

Maprotiline is among the antidepressants with the lowest reported incidence of tachycardia and postural hypotension.

Respiratory

Exercise-induced bronchospasm has been reported (8).

Nervous system

Information released by the UK Committee on Safety of Medicines showed that maprotiline was associated with a disproportionate risk of seizures (9). Among 186 patients taking antidepressants who were admitted to a medical center during one year only one of 45 patients taking tricyclic compounds and none of the 109 patients not taking antidepressants had a seizure; in contrast, five of 32 patients taking maprotiline had seizures, a significant difference (10). The patients who had seizures were aged 20–66 years and none had a previous history. Dosages of maprotiline were 75–300 mg/day, and each patient had undergone a dosage increase in the week before the seizure. A report based on experience in one hospital, in addition to a review of 87 cases reported to the manufacturer, showed that seizures tended to occur at high doses (regardless of dose escalation or plasma concentrations), and that seizures presented after patients had been taking maprotiline for several weeks (11). Post-marketing surveillance has also shown a higher seizure risk with maprotiline than with tricyclic antidepressants, but since the maximum dose of maprotiline was reduced from 300 to 225 mg, few seizures have been reported (SEDA-17, 22).

So-called speech blockage has been reported with other antidepressants.

- A 54-year-old man developed a stammer and speech blockage while taking maprotiline 75 mg/day (12). It responded to a reduction in dose to 50 mg/day, reappeared with another challenge of 75 mg/day, and did not respond to physostigmine intramuscularly on two occasions. It did not occur when he took desipramine 50 mg/day.

Myoclonus due to maprotiline has been reported (13). Further neuromuscular symptoms that have been reported with maprotiline include cerebellar ataxia in a 54-year-old man with a history of unipolar depression and chronic alcohol abuse who was taking maprotiline 200 mg/day (14). The question of whether his history of alcohol abuse contributed by sensitizing his cerebellum to maprotiline-induced ataxia was unresolved.

Non-convulsive status epilepticus occurred in a 27-year-old woman shortly after starting treatment with clomipramine and maprotiline (15). On withdrawal of medication she gradually improved.

Endocrine

Galactorrhea occurred in a 23-year-old woman 2 weeks after she started to take maprotiline 50 mg/day (increased to 75 mg after 10 days) and resolved after withdrawal (16).

Metabolism

An often troublesome adverse effect of antidepressant medication is weight gain. Two cases of this adverse effect have been reported in patients taking low doses of maprotiline (17).

Hematologic

Neutropenia has been reported in a 51-year-old woman who took 150 mg/day for several months and developed myeloid hyperplasia with a virtual absence of mature granulocytes; she recovered fully with conservative management (18).

Liver

As noted previously (SEDA-10, 21), hepatotoxicity has been described with maprotiline, and two further reports have been published. In one of these, hepatotoxicity was observed in a 54-year-old man treated with maprotiline for chronic head and neck pain (19). The other report described a patient who developed a marked increase in liver enzymes and symptoms during therapy with maprotiline and opipramol; after withdrawal the patient recovered completely (20).

Skin

Ichthyosiform desquamation of the skin and alopecia have been reported (SEDA-17, 22).

Drug Administration

Drug overdose

Reports of overdose with maprotiline relate to doses of 750–3200 mg (21,22). The symptoms included impaired consciousness, convulsions, confusion, disorientation, visual hallucinations, and electrocardiographic changes similar to those seen with tricyclic compounds. Among 41 patients who had taken overdoses of maprotiline cardiotoxicity was equal to or greater than that of tricyclic drugs (23). Mania occurred in one case of maprotiline overdose (SEDA-17, 22).

Fatal overdose has been reported in detail in a 13-year-old girl who took 3000 mg of maprotiline and developed lactic

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acidosis, which the authors believed was responsible for her death (24). Another death due to maprotiline was reported in the USA in a 23-year-old woman who took 4.5–6.0 g (25).

Drug–Drug Interactions

Risperidone

In three patients, plasma concentrations of maprotiline were increased by concomitant treatment with the atypical antipsychotic drug, risperidone (26). The data suggest that risperidone is a modest inhibitor of CYP2D6 and should therefore be used with caution in combination with drugs such as maprotiline, where increased plasma concentrations have the potential to cause serious toxicity.

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Mazindol

See also Anorectic drugs

General Information

Mazindol is a tricyclic compound with central nervous system stimulant properties similar to those of amphetamine. It releases and blocks reuptake of dopamine and noradrenaline (1), and the actions of these catecholamines, not serotonin, are responsible for its anorectic activity. With fairly high doses (6 mg/day) central nervous system effects were reported in 30% of 23 patients (2). Euphoria does not occur at therapeutic doses, but can occur at higher doses. It has a much lower addiction potential than the amphetamines and practically no cases have been reported of a physical withdrawal syndrome.

The most frequent adverse effects in a multicenter open study in 274 subjects in Ireland were dry mouth, nausea, insomnia, constipation, headache, and dizziness. Restlessness and drowsiness were each reported by four patients. The incidence of adverse effects was higher at the beginning of the study, but dropped progressively throughout the 12-week treatment period (SEDA-1, 6).

In a double-blind 12-week study of 50 obese patients, adverse effects consisted of dry mouth and a tendency to constipation, except for one case of angioedema and another of peripheral edema and vomiting (SEDA-1, 6).

In another double-blind study over 12 weeks in 60 obese patients taking mazindol there were minimal adverse effects; in this instance, the complaints were insomnia and nausea (3).

In a double-blind study in 40 obese subjects with stabilized controlled diabetes mellitus and no history of emotional instability, drug dependence, or cardiovascular

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disease, there were single cases of mild dry mouth and vertigo (4).

Organs and Systems

Cardiovascular

In another study, an increase in heart rate, probably due to an amphetamine-like stimulatory effect, was ascribed to mazindol (5).

Nervous system

Impaired concentration, but not mood elevation, was noted in healthy subjects who had taken mazindol for 3 weeks (6). Other reported adverse effects were considered to be more peripheral than central. There was no effect on standing blood pressure and pulse.

Urinary tract

There have been two reports of young adult patients with a "semen-like" urethral discharge during micturition and testicular pain attributed to mazindol (7). The composition of the discharge was not identified. Voiding of the discharge did not recur after mazindol was withdrawn, and rechallenge was not performed.

Susceptibility Factors

Adverse effects of mazindol occur with higher frequency and intensity in patients treated for longer periods of time and when it is combined with a low calorie diet (8).

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Measles, mumps, and rubella vaccines

See also Vaccines

General Information

Measles vaccine

Live measles vaccine

Live measles virus vaccine is available in monovalent (measles only) form and in combinations: measles–rubella (MR) and measles–mumps–rubella (MMR) vaccines. Measles vaccines based on further attenuated strains (beyond the level of the original strain, for example the Edmonston B strain or Schwarz strain) produces a mild or subclinical and non-communicable infection.

Inactivated measles vaccine

Inactivated measles vaccine was not distributed after 1967 (owing to lack of efficacy). Reports of the atypical measles syndrome that can occur after immunization with this vaccine type have been reviewed (SED-11, 679) (SEDA-8, 299) (SEDA-11, 291).

High-titer Edmonston–Zagreb measles vaccine

High-titer Edmonston–Zagreb measles vaccine is more immunogenic in young infants than measles vaccine based on other strains. It was hoped that the use of such vaccines could help to reduce the incidence of measles in infancy in developing countries. However, little was known about the long-term effects of high-titer measles vaccine given early in life. Subsequently, experience gained in Senegal, Guinea-Bissau, and other developing countries showed that child mortality after immunization was significantly higher in those who received high-titer Edmonston–Zagreb vaccine than in those given standard vaccine. The higher risk of death remained significant in multivariate analyses (1,2). There is a reason for concern about the long-term safety of high-titer measles vaccine. The World Health Organization has suspended the use of high-titer measles vaccine. Additionally, the mortality data in all West African trials have been analysed. All children were followed up to at least 3 years of age. Mortality in the high-titer group was significantly higher than in those given the standard vaccine. These results support the decision of the WHO that high-titer measles vaccines should no longer be used (3).

General adverse effects

About 5–15% of vaccinees develop a temperature of >39°C (beginning about the sixth day after immunization and lasting up to 5 days). Transient rashes have been reported in about 5% of vaccinees. Allergic reactions very rarely follow the immunization. Most of these reactions are considered minor and consist of wheal and flare or urticaria at the injection site. Very few cases of immediate allergic reactions in children who had histories of anaphylactoid reactions to egg ingestion have been reported, but these reactions could potentially have been life-threatening (4). This risk of egg allergy is excluded in modern vaccines, in which the virus is propagated in chicken or human fibroblast cell cultures.

In Japan, three further attenuated live measles vaccines are licensed for general use:

1. AIK-Cvaccine
2. Biken-CAM vaccine
3. Schwarz-FFB vaccine.

No significant differences have been reported between the three vaccines regarding either immunogenicity or adverse reactions (5).

Data on adverse effects after measles immunization reported in the framework of the US Monitoring System on Adverse Events Following Immunization to the Centers for Disease Control have been published (SEDA-13, 274). Case reports on suspected encephalitis (including two cases with hearing loss) and convulsions have been reviewed (SEDA-8, 299) (SEDA-9, 284) (SEDA-11, 291) (SEDA-12, 283) (SEDA-16, 388); very rare individual case reports on cerebellar ataxia, diffuse retinopathy, optic neuritis, regional lymphadenitis, thrombocytopenic purpura (70% of cases of thrombocytopenic purpura occur following viral diseases; purpura has been reported also following the receipt of measles vaccine), paroxysmal cold hemoglobinuria, parkinsonism, pityriasis lichenoides et varioliformis acuta, nephrosis, and depression of the tuberculin skin test reaction were cited (SED-11, 679) (SED-12, 811) (SEDA-12, 283) (SEDA-16, 389) (SEDA-17, 376).

A review of the data generated in the last 4 years has amply described the continued efforts of the scientific community to monitor and understand true measles vaccine-associated adverse events (6). The rapidity and clarity of this same community's debunking of the spurious associations with Crohn's disease and autism suggests that those charged with vaccination programs have learned from past mistakes.

The immunogenicity and safety of two live attenuated measles vaccine strains (Schwarz strain and AIK-C strain) have been compared in 9-month-old Taiwanese infants in order to find a candidate for an effective measles immunization in the first year of life (7). Because of persisting maternal measles antibody, the commercially available measles vaccines do not produce a sufficient antibody response when given during the first year of life. However, early protection is particularly required in developing countries with high measles morbidity and mortality in infants. Attempts to find suitable candidates for early immunization, including the use of the high-titer Edmonston–Zagreb measles vaccine strain, failed (SED-14, 1078). The Japanese AIK-C measles vaccine strain (derived from the Edmonston strain) has been given to 67 infants and a measles vaccine based on the Schwarz strain was given to 68 infants. The AIK-C strain vaccine caused seroconversion in 65 infants (97%), whereas only 65 infants (70%) seroconverted with the Schwarz strain vaccine. Adverse effects of the two vaccines were comparable: fever 8.8% (Schwarz strain) versus 19% (AIK-C strain); skin rash 13 versus 13%; rhinorrhea 8.8 versus 12%; cough 7.4 versus 6%; diarrhea 2.9 versus 4.5%; poor appetite 2.9 versus 1.5%; irritability 2.9 versus 6%.

Mumps vaccine

Live mumps virus vaccine is available in monovalent (mumps only) form and in combination with measles (MM vaccine) and with measles and rubella (MMR vaccine). Vaccines based on the following mumps vaccine strains are in use:

- The Jeryl Lynn strain is used mainly in vaccines prepared in the USA. The virus was isolated from a female patient in 1963. Vaccines based on Jeryl Lynn strain are mostly used worldwide.
- The Urabe Am9 strain was attenuated in Japan and has been used for the preparation of MMR and other mumps-containing vaccines in Japan and Europe.
- The Rubini strain was isolated in Switzerland and was attenuated by passage in human diploid cells for use in vaccine production.
- The L-3 (Leningrad) strain was derived by combining five isolates of mumps virus from sick children. The attenuated strain is used for vaccine production, especially in Russia.
- The L-3 strain was further attenuated in Zagreb, Croatia, by adaptation and passage in SPF chick embryo fibroblast cell cultures (mumps vaccine strain L-Zagreb).

The most commonly used vaccines have been based on the Urabe Am9 strain and the Jeryl Lynn strain. However, in September 1992 health authorities worldwide were informed by Smith Kline Beecham Biologicals that the company had decided to suspend the distribution of vaccines containing the Urabe Am9 strain, since alternative vaccines were available to maintain the immunization programs established in the various countries.

General adverse effects

Various authors have investigated the immunogenicity and reactogenicity of different mumps vaccine strains. Among adverse reaction reports, episodes of parotitis and low-grade fever have been most prominent. Rash, pruritus, purpura, and other allergic reactions are uncommon, usually mild, and of brief duration (8). Data on adverse effects after immunization with mumps-containing vaccines collected in the framework of MSAEFI have been published (SEDA-13, 274). There have been reports of febrile convulsions, meningitis, orchitis, parotitis, swollen lymph nodes, and thrombocytopenia (SED-12, 813) (SEDA-16, 389) (SEDA-17, 377).

Rubella vaccine

Rubella vaccine is a live attenuated virus vaccine. Most of the vaccines currently manufactured outside Japan are produced in human diploid cells and are based either on the RA 27/3 strain (the most widely used) or the Cendehill strain. In Japan, five different vaccine strains (for example TO 336 and MEQ 11) are produced in two different non-human substrates. In China, another vaccine strain (BRD-2) has been developed and produced in human diploid cells. Its antigenicity and reactogenicity are comparable to those of the RA 27/3 strain.

General adverse effects

Subcutaneous injection is commonly followed by local soreness and induration. Children sometimes develop

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low grade fever, rash, and lymphadenopathy after immunization. Acute arthritis/arthralgia sometimes occurs.

Measles–mumps–rubella vaccine

In most industrialized countries, measles–mumps–rubella (MMR) vaccine has replaced the former use of single antigen vaccines against measles, mumps, and rubella in childhood immunization programs. Single antigen rubella vaccines are still used in postchildhood rubella prevention. Comparisons of the efficacy and safety of different MMR vaccines and monovalent versus bivalent or trivalent vaccines have been made in various clinical trials (SEDA-14, 285). Minor symptoms (fever, rash, malaise) occurred usually after 5–14 days and lasting for 2–3 days. Occasionally, febrile convulsions have been recorded within 3 weeks of immunization, and mild parotitis occurred rarely in the third week after immunization. On average, the seroconversion rates were between 95 and 99% for measles and rubella, and less for mumps.

In a crossover study among 581 twin pairs aged between 14 months and 6 years only 0.5–4% had adverse reactions to MMR vaccine. The difference between the reaction rate reported in the immunized members of the twin pairs and those reported in the placebo-injected twin sisters or brothers showed that most of the reactions were temporally and not causally related to immunization. Respiratory symptoms, nausea, and vomiting were more frequent in the placebo-injected group than in the MMR-immunized group (9).

General adverse effects

A Vaccine Safety Datalink project has been used to compare adverse events after MMR immunization either at 4–5 years or at 10–12 years (10). Information on events that are plausibly associated with MMR immunization (seizures, pyrexia, malaise/fatigue, musculoskeletal symptoms, rash, edema, induration, lymphadenopathy, thrombocytopenia, aseptic meningitis, joint pain) has been collected from 8514 children who received the vaccine at preschool age and from 18 036 schoolchildren. The results suggested that the risk of events is greater in those aged 10–12 years.

When the MMR immunization program was launched in Finland in 1982, a countrywide surveillance system, including all hospitals and health centers, was established to monitor serious adverse events after immunization. From 1982 to 1996 almost 3 million doses of MMR vaccine were distributed to 1.8 million individuals, mostly children. Most of the reported adverse events were minor or self-limiting events among 437 vaccinees, for example fever, rash, headache, fatigue, nausea, vomiting, transient arthralgia, and swelling of the parotid glands. In all, 173 potentially serious adverse events were evaluated in detail. The assessment of causality is shown in Table 1.

- One 13-month-old boy died 8 days after immunization. Autopsy showed that the cause of death was aspiration of vomit. The most commonly reported neurological adverse events were febrile seizures. Epilepsy was diagnosed in three children; symptoms manifested for the first time 1, 10, and 21 days after immunization. One child was later diagnosed as having severe Lennox–Gastaut syndrome; medical records subsequent to the acute phase were not available for the other two.

In the four cases of encephalitis, a causal relation with MMR vaccine could not be excluded, because no other specific cause was detected. One child with acute

Table 1 Assessment of causality between MMR vaccination and 173 serious events

Event	Number of reports	Number not causally associated with MMR	Possibly causally associated with MMR		
			Number	%	Incidence per 100 000 doses
Respiratory					
Asthma	10	5	5	50	0.2
Pneumonia	12	7	5	42	0.2
Nervous system (*n* = 77)					
Febrile seizures	52	24	28	54	0.9
Epilepsy	3	2	1	33	0.03
Undefined seizure	4	2	2	50	0.07
Encephalitis	4	1	3	75	0.1
Meningitis	4	4	0	0	0
Guillain–Barré syndrome	2	0	2	100	0.07
Transient gait disturbance	5	0	5	100	0.2
Confusion during fever	3	1	2	67	0.07
Metabolism					
Diabetes	3	3	0	0	0
Reproductive function					
Orchitis	7	6	1	14	0.03
Immunologic (*n* = 74)					
Anaphylaxis	30	16	14	47	0.5
Henoch–Schönlein purpura	2	1	1	50	0.03
Urticaria	30	5	25	83	0.8
Stevens–Johnson syndrome	1	0	1	100	0.03
Death (*n* = 1)	1	1	0	0	0

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lymphoblastic leukemia (diagnosed after immunization but with symptoms leading to the diagnosis already present at the time of immunization) developed, during immunosuppressive treatment, measles encephalopathy 54 days after immunization and interstitial pneumonia a few days later; 14 years later the leukemia had not relapsed, but she had developed severe epilepsy. The fourth child had *Herpes simplex* encephalitis, with a temporal association between MMR immunization and encephalitis (11). Idiopathic thrombocytopenic purpura was excluded from the analysis, because it has been analysed before (12).

Organs and Systems

Respiratory

Measles

Measles giant-cell pneumonia after measles immunization has been described in a 21-year-old man with AIDS (13).

- A 21-year-old man developed AIDS followed by *Pneumocystis jiroveci* pneumonia. About a year after a booster immunization with MMR vaccine, he developed measles giant-cell pneumonia, confirmed by transbronchial and thoracoscopic lung biopsies. The entire genome of the isolated strain and that of the currently used vaccine strain Moraten were subsequently sequenced and were almost identical.

Taking into consideration the long interval between measles immunization and pneumonia, the causal relation in this case was doubtful.

Nervous system

Measles

The long debate on the degree of risk to the nervous system presented by measles vaccine, especially encephalitis and encephalopathy, is not completely resolved (14). The problem has been analysed by the CDC, Atlanta, Georgia (4,15,16), the Ministry of Health and Welfare, Japan (5), the National Childhood Encephalopathy Study in the United Kingdom (SEDA-11, 285), and investigators in the Northwest Thames region of England (17). However, most investigators, having critically analysed the studies, have concluded that the incidence of suspected cases of encephalitis/encephalopathy after immunization is still much lower than that of natural infection, suggesting that some or most of the reported neurological disorders may be only temporally and not causally related to measles immunization.

Encephalopathy

Claims that cases of encephalopathy followed by permanent brain injury or death were due to measles immunization, submitted to the US National Vaccine Injury Compensation Program, have been reviewed (SED-13, 920) (18). A total of 403 claims of encephalopathy and/or seizure disorders after measles, measles–rubella, measles–mumps–rubella, mumps, or rubella immunization were identified during the period 1970–93. The medical records of these cases were reviewed by physicians in the compensation program to determine, if possible, the cause of injury and the classification of the findings. The inclusion criteria established by the compensation program were met by 48 claims by patients with acute encephalopathy of undetermined cause 2–15 days after immunization with attenuated measles virus. The clustering and peak onset of encephalopathy occurred in 17 patients on days 8 and 9, and the encephalopathy was followed by permanent brain impairment or death. The patients ranged in age from 10 months to 49 months, with a median age of 15 months. There were no cases of encephalopathy of undetermined cause within 15 days after the administration of mumps or rubella vaccine. Table 2 shows the clinical findings and sequelae among the 48 cases. The authors concluded that manifestations of acute encephalopathy among these 48 children were similar to the clinical features of acute encephalopathy described after natural measles. Vaccine-associated measles encephalopathy may be a rare complication of measles immunization. From 1970 to 1993 in the USA, about 75 million children received measles vaccine by age 4 years. The 48 cases of encephalopathy after measles immunization probably represented under-reporting to this passive compensation system. However, given the generous compensation offered in this program, it is reasonable to conclude that most serious cases temporally related to an immunization have been captured. The incidence of 48 cases of encephalopathy possibly caused by 75 million doses of vaccine can reasonably be described as low.

The clinical features of acute and chronic encephalopathy or death in these 48 patients were classified into three groups based on the initial findings of ataxia in 6, behavioral changes in 8, and seizures in 34. The onset of neurological findings varied in severity from ataxia or behavioral changes to prolonged seizures or coma. Fever preceded the onset of acute encephalopathy by several hours to several days in 43 of 48 children. There was a measles-like rash with a post-vaccination onset from day 6 to day 15 in 13 children.

The 1994 report of the Institute of Medicine concluded that the evidence was inadequate to accept or reject a causal relation between MMR and encephalopathy, and it is known that the incidence of encephalitis after measles immunization of healthy children tends to be lower than the observed incidence of encephalitis of unknown cause. Two large studies have been negative. In a study analogous to the British Childhood Encephalopathy Study there were no increased risks of either encephalopathy or neurological sequelae after measles immunization (19). A retrospective case-control study through the CDC Vaccine Safety Datalink assessing the risk for 300 000 doses of MMR found not a single case of encephalitis/encephalopathy within 30 days of the administration of MMR (20). In contrast, the review mentioned above (18) reported an association between measles vaccine and encephalopathy. However, the conclusion of the report of the Institute of Medicine is still valid, namely that evidence is still inadequate to accept or reject a causal relation between measles vaccine and these diseases.

After the publication of the Institute of Medicine report, a literature search for adverse events after measles immunization, limited to publications published in 1994–98, unearthed a considerable amount of data that strengthened the rare association of measles-containing vaccines with postinfectious encephalomyelitis (6). The report has also been criticized as an attempt to establish an adverse event of a vaccine, without a specific laboratory

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Table 2 Clinical effects of acute encephalopathy in 48 patients 2–15 days after the first dose of measles, measles–rubella, or measles–mumps–rubella vaccine, and sequelae, 1970–93

Clinical onset	Number	Acute illness	Number	Neurological sequelae	Number
With initial ataxia ($n = 6$)					
Irritability	6	Ataxia	6	Ataxia (chronic)	4
Fever	5	Changed behavior	4	Mental retardation	3
Measles-like rash	3	Mental regression	3	Seizure disorder	1
		Hospitalization		Hearing loss	1
With initial behavioral changes ($n = 8$)					
Lethargy	3	Mental regression	8	Mental retardation	6
Irritability	2	Coma	5	Spastic paresis	5
Confusion	2	Hospitalization	6	Seizure disorder	1
Coma	1	Death	2	Choreoathetosis	1
Fever	6			Death (later)	1
Measles-like rash	1				
With initial seizures ($n = 34$)					
Fever	32	Hospitalization	33	Mental retardation	31
Status epilepticus	17	Mental regression	31	Seizure disorder	23
Generalized	14	Coma	29	Spastic paresis	10
Focal	3	Behavioral changes	5	Death (later)	3
Measles-like rash	9	Death	2		

finding, without a specific syndrome, without comparable data for non-immunized children, and by ignoring or minimizing years of descriptive epidemiology on reactions (21). In reply, the original authors reminded their critic that the US Congress had set up the Vaccine Injury Table to avoid disagreements over causation by making temporal association an important eligibility element for listed conditions (22). Although biologic plausibility is an important standard for assessing causation in medicine, it is less important in law. In the case of the National Vaccine Injury Compensation Program, the statute provided for a legal presumption of causation, if encephalopathy began 5–15 days after measles immunization.

Seizures

As with the administration of other agents that can produce fever, some children develop febrile seizures after receiving measles vaccine. Most of these convulsions are simple febrile seizures and do not in themselves increase the probability of subsequent epilepsy or other neurological disorders. There may be an increased risk of convulsions among children with a prior history of convulsions or those with a history of convulsions in siblings or parents. After analysing data on the increased risk of such children, both the US Immunization Practices Advisory Committee (ACIP) and the Committee on Infectious Diseases of the American Academy of Pediatrics have recommended that children with a history of convulsions should be vaccinated because the benefits of immunization outweigh the risks. According to the ACIP, children at risk could receive antipyretics, starting before the expected onset of fever and continuing for 5–7 days. The Committee on Infectious Diseases was reluctant to recommend prevention with antipyretics, though after the onset of fever these are likely to be effective (16,23).

Epilepsy has been attributed to measles vaccine (24).

- A 23-month-old boy developed Lennox–Gastaut syndrome (an epileptic syndrome caused by an acquired organic brain insult) 14 days after measles immunization with Japanese FL-vaccine, based on AIK-C live attenuated measles vaccine strain. The child's prenatal and perinatal histories and his development until 23 months of life were uneventful. His monozygotic twin brother had no epileptic seizures, but it is not clear from the original paper whether or not the twin received the same vaccine.

Subacute sclerosing panencephalitis

Subacute sclerosing panencephalitis (SSPE) can occur after immunization with live attenuated measles vaccine, but the possible role of measles virus vaccine in the pathogenesis of SSPE has been neither proved nor disproved. However, the frequency seems to be lower than after natural measles. A fall in the reported incidence of SSPE in the USA accompanied the reduction in the reported incidence of measles and following it by about 7 years (25). Similar experience has been reported from Israel (26), Japan (27,28), and the eastern part of Germany (29). There is no evidence of an increased risk of SSPE on revaccination. A different note is sounded from Romania, where epidemiological investigation of SSPE indicated a yearly incidence of 5–6 cases per million inhabitants without any change due to a measles immunization program implemented about 10 years earlier (30).

Using RNA-templated sequencing, vaccine-strain measles virus has been implicated as the cause of death in three immunocompromised children with inclusion body encephalitis (6). The authors referred to a case of measles vaccine virus-associated giant cell pneumonia in a patient with advanced HIV infection.

Mumps

Meningitis

The risk of aseptic meningitis is increased after the administration of the Urabe mumps vaccine strain in mumps vaccine or MMR vaccine. Since 1992, most

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vaccine manufacturers have decided to suspend the distribution of vaccines containing the Urabe strain, provided that alternative vaccines were available to maintain the immunization programs established in the various countries. In 1997, a mass immunization campaign with an Urabe vaccine strain-containing MMR vaccine was carried out in the city of Salvador, in North-East Brazil (31). There was an increased risk of aseptic meningitis 3 weeks after mass immunization. The estimated risk of aseptic meningitis was 1 in 14 000 doses of MMR vaccine.

To assess the risk of mumps vaccine-associated meningitis, pediatricians were asked to report to the British Paediatric Surveillance Unit (BPSU) all confirmed and suspected cases during 1990–91. The risk based on confirmed cases was estimated to be 1 per 250 000 doses distributed (32). However, data from one district, based on two confirmed cases and one suspected case identified by the Nottingham Public Health Laboratory, suggested a much higher risk, about 1 in 4000 doses (33). To investigate whether the risk observed in Nottingham was atypical or indicative of substantial under-reporting elsewhere, additional studies were initiated. A laboratory study including four independent laboratories identified 13 cases of vaccine-associated meningitis after immunization with Urabe strain vaccines; in one-third of instances, mumps virus characterized as a vaccine-like virus was isolated. The risk estimate of 1 per 11 000 doses distributed was lower than in the Nottingham study but much higher than in the BPSU surveillance. Furthermore, children with a discharge diagnosis of viral meningitis were identified in the Oxford region and their immunization status ascertained. The estimated risk was 4.7 per 100 000 doses. Because there have been no cases of proven vaccine-associated mumps meningitis with isolation of the Jeryl Lynn vaccine virus in the UK, the decision was taken to change to Jeryl Lynn-containing vaccines (32).

Eight cases of mumps vaccine-associated meningitis have occurred in Canada. Mumps viruses have been isolated and characterized by nucleotide sequencing as Urabe Am9-like strains. Urabe mumps vaccine virus-containing vaccines are no longer licensed for sale in Canada (34).

Forsey and colleagues have examined over 80 mumps viruses from around the world; they included 20 isolates found in the cerebrospinal fluid of children with vaccine-associated meningitis in the UK and Ireland and isolates from parotitis and meningitis following mumps immunization from Australia, Belgium, Canada, France, Germany, and Japan (35). They were characterized by PCR and dideoxynucleotide sequencing for the differentiation of wild from attenuated mumps viruses. The isolates were characterized as Urabe Am9-like vaccine strains. The Jeryl Lynn mumps vaccine strain was found in one vaccinee from Germany, but no virus of this type was isolated from a patient with meningitis. Although one cannot conclude from this that Jeryl Lynn is free of such adverse effects, all the evidence points toward a considerable difference between the mumps vaccine strains in the degree of risk. Virological heterogeneity provides a clue for further investigation (36). Commercial mumps vaccine of the Jeryl Lynn strain contains at least two distinct mumps viruses; it has been suggested that this factor contributes significantly to the safety and efficacy of this vaccine (23).

The Global Advisory Committee on Vaccine Safety has considered a comprehensive review of the world literature on the safety of mumps immunization, with special attention to vaccine-associated meningitis. They found no cases of virologically proven aseptic meningitis after mumps immunization based on the Jeryl Lynn vaccine strain. If mumps vaccines based on vaccine strains such as Urabe Am9, Leningrad-3, or Leningrad–Zagreb are being used in mass immunization campaigns, the committee recommends that the potential for clustering of aseptic meningitis cases after the campaign should be taken into consideration. The available data are insufficient to distinguish between the safety profiles of the Urabe Am9, Leningrad-3, and Leningrad–Zagreb strains with regard to vaccine-associated meningitis (37).

Rubella

Adverse effects on the nervous system that have at least temporally been associated with rubella vaccination include myelitis, myeloradiculitis (SEDA-2, 268) (SEDA-20, 292), meningomyelitis (SEDA-10, 291), encephalitis (SEDA-5, 308), peripheral neuropathy (SEDA-12, 284), facial or peripheral paresthesia (SEDA-11, 295) (SEDA-12, 284), and carpal tunnel syndrome (SEDA-12, 284). In many of these cases the causal relation was doubtful. The authors of the report of the Institute of Medicine, National Academy of Sciences, Washington, DC (1991) entitled "Adverse Effects of Pertussis and Rubella Vaccines" (38) considered that there was insufficient evidence to indicate either the presence or absence of a causal relation between RA 27/3 rubella vaccine and radiculoneuritis and other neuropathies.

- Acute disseminated encephalomyelitis occurred in a 14-year-old boy 22 days after rubella immunization (39). The authors suggested that live rubella vaccine can occasionally trigger immunologically mediated demyelination within the nervous system.

It has been suggested that there is insufficient evidence to indicate either the presence or absence of a causal relation between RA 27/3 rubella vaccine and radiculoneuritis and other neuropathies (38), although cases have been reported.

- A 23-year-old woman developed a mild distal demyelination neuropathy 4 weeks after rubella immunization (40). Immunological studies showed the presence of antibodies to the rubella virus proteins and to the myelin basic protein.

The authors suspected that a virus-induced immune response caused an auto-aggressive reaction responsible for demyelination.

Measles–mumps–rubella

A cranial nerve palsy has been attributed to MMR (41).

- A 13-month-old girl developed a recurrent sixth nerve palsy 1 week after MMR immunization. This resolved completely over 8 weeks and recurred 15 weeks after initial onset. Other causes for the sixth nerve palsy were excluded.

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Meningitis

Vaccine-associated meningitis is a well-known adverse effect of mumps (or MMR) immunization. Until 1991 the reported incidence was low, but in that year Japanese researchers published the result of a nationwide survey, started in 1989, in which the incidence of vaccine-associated mumps meningitis varied from less than 1 case per 7000 to 1 per 405 from prefecture to prefecture. Meningitis was generally mild and there were no sequelae from the illness. The vaccine used contained the Urabe Am9 strain (42,43). In April 1993, the Ministry of Health and Welfare in Japan decided to interrupt the use of MMR vaccine (44).

A retrospective study was carried out to determine the incidence of vaccine-associated meningitis in Japan after the administration of different locally produced MMR vaccines (MHW MMR vaccine, Takeda MMR vaccine, Biken MMR vaccine, and Kitasato MMR vaccine) (45). Among the three MMR vaccines (Biken vaccine excepted) the incidence of meningitis was about 1 in 500–900 vaccinees. The criteria for inclusion of a case of meningitis were symptoms of meningitis and pleocytosis in the cerebrospinal fluid. In a complementary nationwide comparison of four MMR vaccines conducted in Japan by 1255 pediatricians the total number of vaccinees was 38 203 (46). All were arbitrarily given one of the MMR vaccines produced by three manufacturers (Biken, Kitasato, and Takeda) or the standard MMR vaccine made of designated strains (Biken's mumps Urabe Am9 strain, Kitasato's measles AIK-C strain, and Takeda's rubella To336 strain). The rates of virologically confirmed aseptic meningitis per 10 000 recipients were 16.6, 11.6, 3.2, and 0 for the standard MMR, Takeda MMR, Kitasato MMR, and Biken MMR vaccines respectively. The incidence of convulsions was the highest with the standard MMR vaccine, and the incidence of fever associated with vomiting at 15–35 days (symptoms relevant to aseptic meningitis) were also the highest with the standard MMR vaccine. The incidence of parotitis was the lowest with Takeda MMR vaccine.

The finding that the incidences of aseptic meningitis differed after administration of the standard MMR vaccine or Biken MMR vaccine has inevitably raised questions about the consistency of manufacture of the Urabe Am9 mumps virus vaccines. The National Institute of Health found that the biological characteristics of the Urabe Am9 mumps virus contained in the standard MMR vaccine and in the Biken MMR vaccine were different. The Biken Company reported that the mumps vaccine in the standard MMR vaccine was a mixture of two Urabe Am9 mumps vaccine bulks, one identical to that contained in the Biken MMR vaccine and the other produced by a different manufacturing process.

In 1995, a somewhat different note was sounded from France, where all mumps vaccines produced and marketed at that time contained the Urabe vaccine strain. The incidence of vaccine-associated meningitis was estimated using two different data sources: the national network of hospital virology laboratories and the manufacturer's pharmacovigilance department (47). The risk of vaccine-associated meningitis was assessed at one case per 28 400 doses distributed when using the laboratory network data or one case per 13 000–67 200 doses distributed when using the pharmacovigilance data. The French vaccination committee recommended that the vaccine continue to be used whilst awaiting vaccine containing the Jeryl Lynn strain.

Cases of aseptic meningitis occurring 14–26 days after MMR immunization have been reviewed (48). All the patients had been immunized with the L-Zagreb mumps strain, Edmonston–Zagreb measles strain, and the RA 27/3 rubella strain. The incidence of vaccine-associated meningitis was 9 per 10 000 doses. This finding was similar to that reported for the same mumps vaccine strain by Cizman (49), 10 per 10 000 (SEDA-12, 815), but higher than that found by Kraigher (48).

Transmission of Urabe mumps vaccine strain between siblings has been reported (44). A girl developed parotitis after immunization with Urabe mumps strain; 19 days later her older sister developed mumps. The strain isolated showed molecular biological characteristics typical for the Urabe strain.

The reason for the high incidence of vaccine-associated mumps meningitis has been investigated by a comparison of the nucleotide sequence of the hemagglutinin-neuraminidase gene from vaccine virus with the genes of viruses isolated from patients with vaccine-associated meningitis (50). The analysis showed that the Urabe AM9 vaccine strain is a mixture of viruses that differ at nucleotide 1081: a wild type-like variant A and a variant G. Vaccinees who developed vaccine-associated meningitis or parotitis had predominantly variant A (98–100%), indicating strong selection of the wild type-like variant of the mumps virus.

The incidence of aseptic meningitis after immunization with MMR containing the Jeryl Lynn mumps vaccine strain has been assessed in a Vaccine Safety Datalink project (20). The overall rate of confirmed cases in the study population (children aged 1–2 years) was 172 cases per million children, very close to the background rate of 162 naturally occurring cases per million children aged 1–4 years in Olmsted County, MN. The authors concluded that there is no increased risk of aseptic meningitis after vaccination with MMR including the Jeryl Lynn mumps vaccine strain.

Gait disturbance

An analysis of 41 reports of gait disturbance in 15-month-old children in temporal relation with the first MMR immunization, collected in the framework of the Danish surveillance system for adverse events after immunization, has been reported (51). About 533 000 doses of MMR vaccine were administered to 15-month-old children in Denmark during the 10 years from 1987 to 1996. The number of reported cases of gait disturbance corresponded to a frequency of eight per 100 000 doses of MMR vaccine. The authors considered that the symptoms were characteristic of cerebellar ataxia. The high frequency and mainly mild course of gait disturbances might indicate a mumps-related reaction. The symptoms mainly occurred at 7–14 days after immunization, and the duration was on average 1–2 weeks (range 1 day to over 4 months). Most cases were mild and short-lasting and a longer duration of symptoms seems to be predictive of late sequelae. In

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the same period about the same number of doses were used for the second MMR immunization without similar reactions. Disturbance of gait has rarely been reported, and the authors listed in their paper two reports from Sweden and Germany in which symptoms were so mild that no invasive investigations were carried out.

Guillain–Barré syndrome

To test the hypothesis that MMR vaccine can cause Guillain–Barré syndrome, a retrospective study has been carried out in Finland, based on linkage of individual immunization records with nation-wide hospital discharge registers (52). MMR vaccine did not cause any increase in the incidence of Guillain–Barré syndrome over background and there was no clustering of cases at any time after the administration of the vaccine. The authors concluded that there is no causal association between MMR immunization and Guillain–Barré syndrome.

Sensory systems

Rubella

Bilateral optic neuritis (53) and retinal vasculitis (SEDA-20, 292) have been attributed to rubella immunization.

Psychological, psychiatric

Measles–mumps–rubella

The suggestion that measles/MMR immunization can cause autism has not been confirmed. Autism is characterized by absorption in self-centered subjective mental activities (such as day-dreams, fantasies, hallucinations), especially when accompanied by marked withdrawal from reality.

History

The scientific and public response to the 1998 publication of Wakefield and colleagues (54), and Wakefield's subsequent press conference, in which he suggested that immunization with MMR might be associated with Crohn's disease and autism was enormous and controversial. For example, Black and colleagues (55) stated that the publicity generated by this paper was out of proportion to the strength of the evidence it contained; Beale (56) suggested that the Lancet would bear a heavy responsibility for acting against the public health interest that the journal usually aims to promote; O'Brien and colleagues (57) considered that the substantial amount of evidence that contradicts the findings of Wakefield and colleagues did not achieve the same prominence in the popular press.

In replying to these letters, Wakefield (58) defended the clinician's duty to his patients and the researcher's obligation to test hypotheses. For his part, the editor of the Lancet pointed out that the paper had been presented with a commissioned commentary in the same issue; peer review had confirmed that the paper merited publication, with suitable revisions and editing, as an early report; finally, he considered that the press had presented the information in a balanced way (59). However, it was subsequently discovered that the work had been sponsored by a pharmaceutical company which had not been declared at the time (60). Furthermore, the children who were included in the study had been selected other than at random. Subsequently, 10 of Wakefield's colleagues withdrew the findings that they had initially reported and one other could not be traced; only Wakefield did not retract (61).

The Lancet then reviewed the developments in the discussion (62), with emphasis on evidence that contradicts the alleged association and new data presented by Wakefield. The last part of the editorial read as follows:

In a new twist, Wakefield's crusade fuelled further anxiety among parents when he and John O'Leary, director of pathology at Coombe Women's Hospital, Dublin, Ireland, presented unpublished data to the US Senate's congressional oversight committee in Washington on April 6 [2000]. The hearing was called by the chairman, Dan Burton, an Indiana Republican, whose grandson has autism and visited the Royal Free Hospital in November last year. At the hearing, six parents of children with autism gave moving testimonies of their children's illness. ... Scientific evidence was presented by six chosen 'experts'. According to Wakefield's testimony, he has now studied more than 150 children with 'autistic enterocolitis'—an unproven association had become a disease—and a detailed analysis of the first 60 cases is to be published in the American Journal of Gastroenterology later this year.

Wakefield presented uninterpretable fragments of results only and concentrated on refuting studies that had contradicted his findings. His conclusions were surprisingly non-committal: 'the virological data indicate that this may be measles virus in some children'; he added that it would be imprudent to interpret the temporal relationship with MMR as a chance finding, in the absence of thorough investigation. O'Leary explained that gut-biopsy material from 24 of 25 children with autism was positive for measles virus compared with one of 15 controls, and that this material was presented to him by Wakefield using 'blinded protocols'. Since the controls are not further described and the details of these findings remain unpublished, this evidence raises far more questions than it answers.

"Autism is a poorly understood neurodevelopmental-disease spectrum with a heart-breaking personal story behind every case. But parents of such children have not been served well by these latest claims made well beyond the publically [sic] available evidence. A congressional hearing, like a press conference, is no place to make controversial scientific assessments. And if scientists question the safety of vaccines without making their evidence fully transparent, harm will be done to many more children than they purport to protect."

Wakefield and Montgomery subsequently raised doubts about the adequacy of the evidence that secured the license for MMR vaccine (63). Particularly in view of the immunosuppressive properties of the measles virus, they suggested that there is a potential for adverse interactions between the component live viruses. They therefore proposed that spaced monovalent measles, mumps, and rubella immunization should replace the use of the combined MMR vaccine. The continuing publications of Wakefield led to reduced MMR coverage in some parts of the UK and to well-publicized concerns about the potential for measles outbreaks among primary school entrants. In an editorial in the British Medical Journal, Elliman and Bedford replied to Wakefield's paper (64). They

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considered that the current concerns were idiosyncratic and presented reviews confirming the vaccine's safety. The Medicines Control Agency and the Department of Health in the UK rejected any suggestion by Wakefield and colleagues that combined MMR vaccines were licensed prematurely. A review of the licensing of MMR vaccines led to the assurance that the licensing procedure was normal and was based on robust studies (65). This position was shared by the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation. At the end of November 2001, Wakefield left his post at the Royal Free and University College Medical School in London. The college said: "Dr Wakefield's research was no longer in line with the Department of Medicine's research strategy and he left the university by mutual agreement" (66). The WHO strongly endorsed the use of MMR vaccine. The combination vaccine was recommended rather than monovalent presentations. There was no evidence to suggest impaired safety of MMR (67).

In April 2001, the Institute of Medicine's Immunization Safety Review Committee released its report "MMR vaccine and autism". Although scientists generally agreed that most cases of autism result from events that occur in the prenatal period or shortly after birth, there was concern because the symptoms of autism typically do not emerge until the child's second year, and this is the same time at which MMR vaccine is first administered in most developed countries. The committee took also into consideration the papers published by Wakefield and other groups and scientists suggesting evidence of a link between MMR vaccine and Crohn's disease and autism. Following review of the numerous research efforts on the MMR–autism hypothesis the committee concluded in its report "that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders". Epidemiological evidence showed no association between MMR vaccine and autism, and the committee did not find a proven biological mechanism that would explain such a relation. Therefore, the committee did not recommend a policy review at this time of the licensure of MMR vaccine or of the current schedules and recommendations for MMR administration (68).

A conference of the American Academy of Pediatrics on "new challenges in childhood immunizations" was convened in Oak Brook, IL, on 12–13 June 2000 and reviewed data on what is known about the pathogenesis, epidemiology, and genetics of autism and the available data on hypothesized associations with Crohn's disease, measles, and MMR vaccine. The participants concluded that the available evidence did not support the hypothesis that MMR vaccine causes either Crohn's disease or autism or associated disorders. They recommended continued scientific efforts directed to the identification of the causes of autism (69).

The response to a newly published adverse event due to immunization must be rapid. If the reported association is correct, urgent re-evaluation of the immunization program is necessary. Otherwise, if the reported association is false, a credible counter-message is necessary to minimize the negative impact on the immunization program (6). The rapidity of response to the 1998 publication of Wakefield and colleagues, including the convening of an independent review panel in the UK, was very useful.

Evidence

Two studies suggested a link between measles/MMR immunization and autism. Fudenberg reported that 15 of 40 patients with infantile autism developed symptoms within a week after MMR immunization (70). Wakefield and colleagues evaluated 12 children with chronic enterocolitis and regressive developmental disorders (54). The onset of behavioral symptoms was associated with MMR immunization in eight cases, as reported by the parents. Both reports were non-comparative and anecdotal. By chance alone some cases of autism will occur shortly after immunization, and most children in developed countries receive their first measles or MMR vaccination in the second year of life, when autism typically manifests. The imprecision of the interval between immunization and the onset of behavioral symptoms in the study by Wakefield and colleagues made these data suspect, even before their retraction.

Inaccuracies in the study of Fudenberg, for example referring to hepatitis B vaccine as a live vaccine, cast some doubts on the carefulness of the entire report. Developmental delay is likely to be detected by a gradual awareness over a period of time, not on a particular day. Epidemiological studies in various countries (UK, Sweden, Finland), comparing the introduction and use of vaccines and the incidence of autism, have not supported a relation between measles/MMR vaccine and autism (71–74). Wing reviewed 16 studies in Europe, North America, and Japan and found no increase in autism with increasing use of measles or MMR vaccines (75). An analysis of two large European datasets produced similar results (76). In early 1998, experts in various medical disciplines reviewed the work of the Inflammatory Disease Study Group of the Royal Free Hospital in detail and concluded that there is no evidence for a link between measles/MMR vaccine and either Crohn's disease or autism (77).

Data from an earlier study have been reanalysed to test the hypothesis that MMR vaccine might cause autism but that the induction interval needs to be short (78). Evidence for an increased incidence was sought using the case-series method. The study used data on all MMR vaccines, including booster doses. The results of this study, combined with results obtained earlier by the same authors, provided powerful evidence against the hypothesis that MMR vaccine causes autism at any time after immunization.

Metabolism

Measles–mumps–rubella

A total of 20 cases of type I diabetes mellitus suspected to be induced by MMR immunization have been reported to Behringwerke, Marburg, Germany, probably due to the mumps component (79). The earliest case occurred 3 days after receiving the vaccine and the latest 7 months after immunization. Twelve cases were diagnosed within 30 days of immunization. The investigators considered the cases of diabetes mellitus to have a temporal relation to the immunization. For every 5 million children immunized against mumps 50 spontaneous cases of diabetes mellitus are to be expected by random coincidence within

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a period of 30 days after immunization. In fact, only 12 cases were reported within 30 days after immunization. Mainly based on this analysis the Deutsche Vereinigung zur Bekämpfung der Viruskrankheiten (DVV) could not confirm the relation between mumps immunization and diabetes mellitus (80).

Hematologic

Measles

Anemia has been reported after measles immunization (81). The vaccine can cause a significant fall in hemoglobin that can persist for 14–30 days and can be difficult to distinguish from iron deficiency.

Rubella

Thrombocytopenic purpura has been attributed to rubella (82). However, the authors of the report of the Institute of Medicine, National Academy of Sciences, Washington, DC (1991) entitled "Adverse Effects of Pertussis and Rubella Vaccines" (38) considered that there was insufficient evidence to indicate either the presence or absence of a causal relation between RA 27/3 rubella vaccine and thrombocytopenic purpura.

Measles–mumps–rubella

There is a relation between MMR vaccination and thrombocytopenic purpura, but not with the measles component itself (18). Thrombocytopenic purpura after MMR has been reviewed, with discussion of pathogenesis and the vaccines and infections associated with this problem (83). Rubella vaccine is one of the most frequently reported causes of thrombocytopenia in Denmark (84). In France, a retrospective epidemiological survey (1984–92) showed that the rates of thrombocytopenic purpura per 100 000 vaccinees were 0.23 for measles vaccine, 0.17 for rubella vaccine, 0.87 for combination MR vaccine, and 0.95 for MMR vaccine (85). Thrombocytopenia was severe and always associated with purpura. Cases of recurrent thrombocytopenic purpura after repeated MMR immunization have been reported (86,87). The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) has recommended avoiding subsequent doses of MMR when a previous episode of thrombocytopenia occurred in close temporal proximity to the previous immunization, that is within 6 weeks (88,89).

The causal relation between MMR vaccine and idiopathic thrombocytopenic purpura has been confirmed using linkage of immunization records and hospital admission records; the absolute risk within 6 weeks of immunization was 1 per 22 300 doses (90).

Gastrointestinal

Measles–mumps–rubella

The suggestion that measles/MMR immunization can cause Crohn's disease has not been confirmed.

Inflammatory bowel disease (ulcerative colitis and Crohn's disease) is a general term for a group of chronic inflammatory disorders of unknown cause involving the gastrointestinal tract. Despite many attempts to confirm an infectious agent as the cause of disease, no bacterial, viral, or fungal agents have so far been isolated. There is strong evidence for a genetic predisposition.

In 1993 and 1994, researchers in the UK and Sweden suggested that Crohn's disease might be a late result of measles infection at a critical time during early childhood (91,92). In a study of the outcome of maternal measles infection in 25 Swedish babies, three of four children exposed to measles in utero subsequently developed Crohn's disease (93). Whereas wild measles virus was initially implicated, a controversial debate was initiated in 1995, when Thompson and colleagues suggested that attenuated measles vaccine virus might also cause inflammatory bowel disease, having found an increased risk of inflammatory bowel disease in about 3000 immunized individuals compared with about 11 000 non-immunized controls (94). Furthermore, the Inflammatory Bowel Disease Study Group of the Royal Free Hospital, London (Wakefield and colleagues), suggested that measles virus is present in the bowel of patients with Crohn's disease (with evidence from transmission electron microscopy, immunohistochemistry, in situ hybridization, and immunogold electron microscopy) (92,95,96).

Wakefield and colleagues then made two suggestions in a paper in the Lancet (54): that autism is linked to a form of inflammatory bowel disease and that this new syndrome is associated with MMR immunization. Their hypothesis was that MMR vaccine causes non-specific gut injury, allowing the absorption of normally non-permeable peptides, which in turn cause serious developmental disorders. The authors stated that they had not proved an association between measles, mumps, and rubella vaccines and either autism or inflammatory bowel disease. However, there were enough references in the text to lead the reader to the assumption that there is sufficient evidence provided by the study, and by other scientific publications, that there is a link. This paper of Wakefield and colleagues, publicized by a subsequent press conference, resulted in a heated debate and a huge number of letters to the editor of the Lancet, in turn severely criticizing both the article and its implications for immunization programs, blaming the editor for publishing the article, and defending the obligation of clinical researchers to publish provocative findings. Considerable evidence, mainly microbiological and epidemiological, has been collected by others to suggest that the association with MMR does not exist.

The alleged association of measles vaccination with Crohn's disease and autism has also been criticized as being based on poor science and as having been largely refuted by a large volume of stronger work, three types of evidence against the hypothesis (biological, microbiological, and epidemiological) being considered in detail (6).

Several groups have found no evidence of persistence of measles virus in the tissues of patients with Crohn's disease with a very sensitive test (polymerase chain reaction) (97–100). Furthermore, no viral genomic sequences of measles, mumps, and rubella viruses were found in intestinal specimens (100). The results of Iizuka and colleagues (98,101) were particularly interesting—they used the same monoclonal antibody in their immunohistochemical studies that Wakefield and colleagues had used. The antigen recognized could be a measles virus protein, but they

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considered it much more likely that the previous immunochemical observations were accounted for by antigen mimicry between measles virus and a host protein found in the intestinal tissue of patients with Crohn's disease. Serological studies have also shown lower measles complement fixation titers in patients with Crohn's disease than in controls, not supporting an association of measles vaccine with Crohn's disease (102,103).

The major weaknesses of the epidemiological studies reported by the Inflammatory Bowel Disease Study Group have been discussed in a number of letters to the editor (104,105) and editorials (105). On behalf of the World Health Organization's Expanded Program on Immunization, Lee and colleagues (71) questioned the conclusion that there was a temporal association between immunization and the onset of symptoms, because the study of Wakefield and colleagues had provided data on the interval between immunization and the onset of symptoms in only five of their 12 cases of so-called autism-bowel syndrome, and the age at which the vaccine was given was mentioned in only three. Furthermore, Lee and colleagues criticized the study on the grounds that no patient selection had been made by Wakefield and colleagues, other than the 12 patients referred to them; there were no controls and no blinding of the investigators (71). Payne and Mason (106) made the same comment, that the cases reported by Wakefield and colleagues were highly selected and that the underlying population was unclear.

Several epidemiological studies have failed to confirm an association between measles/measles vaccine and Crohn's disease. For example:

- *Copenhagen*: In a study of 25 mothers with measles during pregnancy there were no cases of Crohn's disease in their children (107).
- *Finland*: Peltola and colleagues (108) reported on over a decade's effort to detect all severe adverse events associated with MMR vaccine distributed in Finland. There was no evidence to support the hypothesis that the vaccine could cause pervasive developmental disorders or inflammatory bowel disease. Comparing the incidence of Crohn's disease and the Finnish data for measles and measles immunization, Pebody and colleagues (109) came to the same conclusion, namely that there is no association between Crohn's disease and measles vaccine.
- *Japan*: A nationwide survey of inflammatory bowel disease was carried out in 1979–93 in children under 16 years of age. From 1979 to 1992 the number of cases of inflammatory bowel disease was almost the same (ulcerative colitis rates 0.08–0.12 per 100 000, Crohn's disease 0.04–0.06 per 100 000). In 1992, the incidence of Crohn's disease rose to 0.10 and in 1993 to 0.12 per 100 000; the incidence rate of ulcerative colitis increased in 1993 to 0.18 per 100 000. Measles immunization (implemented in 1968) was 68% until 1993, and during the 1980s and early 1990s was relatively constant at about 70% (110).
- *UK*: In close to 7 million children who received MR vaccine in a catch-up campaign there was no increase in the number of new cases or exacerbation of existing cases of Crohn's disease (111).
- In an international case-control study of 499 patients with chronic inflammatory bowel disease and 998 control patients from nine countries, there was no difference in the risk of inflammatory bowel disease in association with either natural measles or measles immunization (112).

Pancreas

Mumps

Acute pancreatitis after mumps immunization is very rare and has been reported only sporadically in adolescents.

- A 13-month-old boy presented with an acute abdomen and surgery was performed for a suspected perforated appendicitis (113). The appendix was normal but the pancreas was enlarged, edematous, and covered with fibrin, with areas of superficial necrosis. The serum amylase activity was 528 IU (normal under 200 IU).

Unfortunately the authors reported no data on the vaccine used or the interval between immunization and disease onset.

Measles–mumps–rubella

- A 19-year-old woman who received MMR vaccine developed pancreatitis 11 days later (114). Other causes of pancreatitis could not be implicated.

Skin

Measles

- An 11-month-old boy developed hypertrichosis at the injection site (2.5 × 3 cm) 1 month after measles immunization (115). The hypertrichosis and induration persisted during the follow-up period of 3 months.

Measles–mumps–rubella

Gianotti–Crosti syndrome has been reported in a child immunized with MMR (116).

- Three days after MMR immunization a 15-month-old boy developed a rash, initially on the arms but later involving the legs. Six weeks later he had an extensive, symmetrical, non-follicular, papular eruption on his face, arms, and legs, with striking sparing of his trunk. This was labeled Gianotti–Crosti syndrome, a self-healing non-recurrent erythematous or skin-colored papular eruption with symmetrical distribution on the face, buttocks, and extremities in children.

A wide spectrum of infectious diseases has been associated with this syndrome, and preceding immunization against influenza, diphtheria, pertussis, and poliomyelitis has been reported.

- A 13-year-old girl developed toxic epidermal necrolysis 7 days after being immunized with live attenuated MMR vaccine (117).

Musculoskeletal

Rubella

Acute arthritis/arthralgia due to rubella vaccine occurs more often and tends to be more severe in susceptible women than in children, usually involving the small peripheral joints. Joint symptoms generally begin 3–25 days

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after immunization, persist for 1–11 days and rarely recur. Incidence rates are estimated to average 13–25% (118) among adult women after RA 27/3 immunization with much lower rates among children, adolescents, and adult men. The incidence of acute joint symptoms increases with increasing dose. There is also an analogous but chronic complication: in small studies of adult female vaccinees in Canada the incidence of persistent or recurrent arthritis was as high as 5–11%.

Radiological bone changes have also been reported after rubella immunization (118).

The committee responsible for the report of the Institute of Medicine, National Academy of Sciences, Washington, DC (1991) entitled "Adverse Effects of Pertussis and Rubella Vaccines" (38) found that the evidence indicates a causal relation between RA 27/3 rubella vaccine and acute arthritis and the available evidence was weaker but still consistent with a causal relation between RA 27/3 rubella vaccine and chronic arthritis. The section on rubella immunization and chronic arthritis included in the report has been reviewed critically (119). In the authors' opinion it is not justified to conclude on the basis of very limited experience that the evidence is consistent with a causal relation between the RA 27/3 rubella vaccine strain and chronic arthritis in adult women.

Other evidence comes from compensation claims. An analysis of 124 claims to the US National Vaccine Injury Compensation Program relating to chronic arthropathy showed that the onset of symptoms occurred at 1–6 weeks after rubella vaccination in 72 individuals (group 1) and at less than 1 week or more than 6 weeks after vaccination in 52 individuals (group 2). Various conditions developed in the two groups after immunization: unspecified arthritis (29 in group 1, one in group 2), specified arthritis (11 and 19), arthralgia (24 and 7), fibromyalgia (4 and 11), and multiple symptoms with minimal arthralgia or myalgia (4 and 14). The Program and the US Court of Federal Claims accepted that there is a causal relation between rubella vaccine and cases of chronic arthropathy that start at 1–6 weeks after vaccine administration (120).

There have also been reviews of this complication (121). Polyarthropathy associated with rubella vaccine predominantly affects the fingers and knees and usually resolves within 2–4 months. However, the duration of symptoms exceeded 18 months in about 5% of cases. Rubella virus RNA has been identified in the peripheral monocytes of such patients 8–10 months after vaccination. The association between adverse musculoskeletal and neurological events and rubella immunization has also been investigated prospectively in 546 healthy postpartum rubella-seronegative women, who received either monovalent rubella vaccine ($n = 270$) or saline placebo ($n = 276$). There was a significantly higher incidence of acute joint manifestations with rubella vaccine (30%) than with placebo (20%). The frequency of chronic or recurrent arthralgia or arthritis was only marginally significant (SEDA-22, 353).

Data from the VAERS on arthritic reactions (arthralgia, arthrosis, arthritis, and joint disease) after rubella immunization during 1991–98 have been analysed (Table 3) (122). Hepatitis A vaccine-associated arthritic reactions reported to VAERS during 1997–98 were used as controls. The analysis confirmed that rubella vaccine is associated with a large number of arthritic reactions. Among the female subjects given rubella vaccine, these reactions occurred primarily in the adult women. The incidence of arthritic reactions was 126 per million rubella immunizations, whereas the hepatitis A vaccine adult control group had an incidence rate of 3.2 per million immunizations.

Immunologic

Measles

It has been suggested that hydrolysed gelatin, rather than egg protein, is responsible for most episodes of anaphylaxis after measles immunization (6). Egg allergy should no longer be a contraindication to measles immunization. However, a previous anaphylactic reaction to measles or MMR vaccine remains a contraindication.

Toxic shock syndrome was reported to have developed within 3 hours of measles immunization in four children, three of whom died. It was initially seen in women who were using tampons in the presence of vaginal colonization and/or infection with toxin-producing strains of *Staphylococcus aureus*. The hallmarks of toxic shock syndrome are high fever, diarrhea, vomiting, tachycardia, hypertension, mucocutaneous ulceration, rash, conjunctival injection, red palms and soles, and a bleeding diathesis. There was some evidence that a used vial of measles vaccine had been kept in cold water and had thereby become contaminated (123). Similar events from various developing countries have been reported to the World Health Organization. Careful investigation pointed clearly to secondary bacterial contamination as the cause of disease and death (124).

Rubella

It has been suggested that RA 27/3 rubella strain could play a role in the etiology of chronic fatigue syndrome (125). Patients with chronic fatigue syndrome have raised IgG serum antibodies to multiple common viruses. Only IgG rubella antibodies correlate positively with the intensity of symptoms and reach titers that are significantly higher than in healthy controls.

Table 3 Rubella immunization and arthritic reactions reported to the VAERS database

Arthritis reaction type	Number of reports	Women	Men	Mean onset (days)	Mean age (years)	Incidence per million immunizations
Arthralgia	191	170	17	11	40	78
Arthrosis	58	51	4	12	43	24
Arthritis	46	41	2	11	38	19
Joint disease	13	13	0	12	39	5

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Measles–mumps–rubella

There is a controversy about the safety of MMR vaccine in children with adverse reactions to egg. Investigating the vaccine produced by Merck Sharpe & Dohme (virus grown in chicken fibroblasts), some did not detect egg protein (126). However, using a competitive ELISA others detected 74 pg of ovalbumin per ml of the MMR vaccine produced by MSD (127). This extremely low amount of ovalbumin appears to be unlikely to provoke allergic reactions. The results of a study carried out in 15 children with egg-positive skin results confirmed the view that the MMR vaccine does not contain enough egg protein to cause reactions (128).

- Moraten vaccine, Berna (virus grown in human fibroblast cultures and therefore certainly ovalbumin-free) was given to a 2-year-old boy with atopic dermatitis (129). The skin tests were positive to cow's milk and egg. Within a few minutes after the receipt of the vaccine, the child developed severe dyspnea, rhinoconjunctivitis, and lip cyanosis; he was successfully treated for an acute anaphylactic reaction. The case seems to demonstrate that the very rare allergic reactions after the administration of measles and MMR vaccines could be due to causes other than egg protein.
- A 17-year-old woman who had an anaphylactic reaction to MMR vaccine was allergic to gelatin; after eating gelatin she developed ear and throat pruritus and tongue swelling (130). Prick skin tests were positive for MMR vaccine and gelatin. Immunoblotting confirmed the presence of IgE antibodies to multiple gelatin components from a variety of animal sources.

MMR vaccine contains gelatin as a stabilizer. The authors concluded that the anaphylaxis was caused by the gelatin component of the vaccine.

- In 24 of 26 children aged 1–4 years who developed anaphylactic reactions within minutes after the administration of MMR vaccine there were IgE antibodies against gelatin (131).
- In 135 children with suspected or documented systemic allergy (atopic eczema, asthma, cow milk's allergy, severe systemic reactions after previous doses of different vaccines), who were prick-tested with undiluted MMR vaccine before immunization, 122 of 126 prick-test-negative children received the MMR vaccine. No untoward reactions developed, except for mild generalized urticaria or fever in two vaccinees. The author concluded that allergic diseases should not be considered as contraindications to MMR immunization (132).

In a brief review of allergy and MMR vaccine the author concluded that anaphylactic reactions are very rare but potentially life-threatening (133). Immunization personnel must therefore be aware of this possibility and trained in its management. Most severe reactions occur within a few minutes after injection and it is extremely unlikely that a child who appears completely well after immunization will subsequently develop a severe reaction.

Second-Generation Effects

Pregnancy

Measles

Live measles vaccine should not be given to pregnant women. This precaution is based on the purely theoretical risk of fetal infection (134).

Rubella

The risks of rubella infection to the unborn child are well known, and necessarily the question has arisen as to whether rubella vaccine is safer. Based on careful analyses by the CDC since 1979 and evaluation of reports from Germany and the UK showing that infants born to susceptible mothers did not develop the congenital rubella syndrome, the Immunization Practices Advisory Committee (135) has concluded that:

- pregnancy remains as a contraindication to rubella immunization because of the theoretical, albeit small, risk of congenital rubella syndrome
- reasonable precautions should be taken to preclude immunization of pregnant women
- rubella immunization of pregnant women should not ordinarily be a reason to consider interruption of pregnancy.

Continued surveillance in the USA (data collected through the Vaccine in Pregnancy Registry) has not shown evidence that RA 27/3 rubella vaccine, administered during pregnancy, can cause the congenital rubella syndrome (136).

Susceptibility Factors

Measles

Persons who have experienced anaphylactic reactions to measles vaccine or neomycin (measles vaccine contains a small amount of neomycin) should not be immunized (137).

Replication of the measles vaccine virus may be potentiated in patients with immune deficiencies and by the suppressed immune responses that occur with leukemia, lymphoma or generalized malignancy, or during therapy with corticosteroids, alkylating drugs, antimetabolites or radiation; such patients should not be immunized (4).

Of 176 high-risk children with pre-existing damage to the central nervous system who were immunized to protect them against measles during an outbreak, only four developed adverse effects after immunization (convulsions, transient electroencephalographic changes) (138). Comparing the risks of immunization and of natural disease, the authors recommended measles immunization of neurologically high-risk children when an epidemic occurs.

Originally, the Committee on Infectious Diseases of the American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP) recommended that severely immunocompromised patients with HIV infection should not receive measles vaccine (139). However, in 1988, recognizing the severity of measles in immunodeficient individuals, it revised its measles immunization guidelines and recommended that

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children with asymptomatic HIV infection should be immunized and that immunization should be considered for symptomatic HIV-infected children (140). Health authorities in many countries have made similar recommendations. Since then, many HIV-infected children have been safely immunized, and the ACIP recommendation has been expanded to all age groups of HIV-infected persons.

Measles–mumps–rubella

Immunocompromise is a contraindication to the use of live virus vaccines, such as measles, mumps, rubella, and oral poliomyelitis vaccine. It is recommended that rubella or MMR vaccine should not be given to persons who are immunosuppressed because of AIDS or other clinical manifestations of HIV infection. The vaccine can be given to asymptomatic infected people (139).

Drug Administration

Drug additives

There has been a report of an allergic reaction after MMR vaccine (141). The author concluded that gelatin seems to be far more often the cause of allergic reactions to MMR vaccine than egg allergy. In vaccinees who receive DTaP vaccine (some brands contain gelatin) before MMR vaccine, the prior injection of gelatin-containing DTaP may be the cause of sensitization to gelatin and the subsequent reaction to other gelatin-containing vaccines.

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Mebendazole and flubendazole

See also Benzimidazoles

General Information

Mebendazole, a benzimidazole, is poorly absorbed from the gut, although it dependably enters cyst fluid; it is therefore most useful for treating intestinal infections and cyst-forming infestations. It is essentially an antihelminthic drug, being effective against hookworm, ascariasis, enterobiasis, and trichuriasis. Mebendazole is effective against enteric *Strongyloides* but since it is not absorbed it is ineffective against tissue forms (1). However, it is also effective against *Giardia lamblia*, while *Trichomonas vaginalis* is susceptible in vitro. Mebendazole does not interfere with the normal intestinal flora.

Mebendazole has been assessed in a range of doses and durations of treatment. The most usual dose is 100 mg bd for 3 days; absorption is minimal, but there is considerable variation in plasma concentrations; the half-life is 2–9 hours. Much higher doses, up to 60 mg/kg/day, have been used in inoperable cases of cystic echinococcosis infestation, and then unwanted effects are more common.

Flubendazole is an analogue of mebendazole used in intestinal helminthiasis and hydatid disease. In trials of two-dose oral treatment for intestinal helminthiasis, reactions were mild and uncommon. They consisted of nausea, abdominal pain, dyspepsia, and sleepiness (SEDA-6, 281). Subsequent field experience has not suggested that flubendazole differs appreciably from other members of the class as regards adverse effects.

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Comparative studies

Echinococcosis

The use of albendazole and mebendazole in patients with hydatidosis has been evaluated in 448 patients with *Echinococcus granulosis* hydatid cysts who received continuous treatment with albendazole 10–12 mg/kg/day for 3–6 months daily orally in a total dose of (323 patients) twice or mebendazole 50 mg/kg/day (2). At the end of treatment, 82% of the cysts treated with albendazole and 56% of the cysts treated with mebendazole showed degenerative changes. During long-term follow-up 25% of these cysts showed relapse, which took place within 2 years in 78% of cases. Further treatment with albendazole induced degenerative changes in over 90% of the relapsed cysts, without induction of more frequent or more severe adverse effects, as observed during the first treatment period. Adverse effects during the first treatment period consisted of raised transaminases with albendazole (67 of 323 patients) and mebendazole (16 of 125 patients), and abdominal pain in 12 and 11% respectively. With both drugs, occasional patients experienced headache, abdominal distension, vertigo, urticaria, jaundice, thrombocytopenia, fever, or dyspepsia, but most of these are known manifestations of echinococcus infection. Six of 323 patients taking albendazole withdrew because of adverse effects compared with eight of 125 patients taking mebendazole. It appears that albendazole is more effective than mebendazole in the treatment of hydatid cysts caused by *E. granulosis* and that both the intensity and the frequency of the usually mild adverse effects are comparable.

In 78 patients with hydatid disease there was a low recurrence rate of hydatid disease (below 3%) after a postoperative prophylactic course of mebendazole 20 mg/kg/day in three divided doses for 3 months (3). The only adverse effect of mebendazole was excessive loss of hair in two women. The unusual low recurrence rate of hydatid disease after treatment with mebendazole in this study was subsequently questioned and attributed to meticulously careful surgical procedures, with avoidance of spillage of hydatid fluid and complete removal of parasitic components (4).

General adverse effects

With normal doses (100 mg bd for 3 days) very slight headache, dizziness, and nausea or diarrhea are common; in principle allergy can occur. Mild and reversible rises in transaminases can occur and need to be followed, but even in high doses withdrawal is justified in only a few patients (5). Neutropenia has been noted and can be severe and persistent. High doses (up to 50–60 mg/kg) can also cause alopecia and cough. Mebendazole has been associated with extra-intestinal migration of *Ascaris* in heavily infected patients. Apart from the poor therapeutic response obtained in some 25% of cases, drug toxicity (especially at high prolonged dosage) has led to withdrawal in a small proportion of patients. Adverse effects severe enough to lead to withdrawal have included worsening of pre-existing hyperlipidemia (type IV), progressive uremia, and a marked rise in liver enzymes (6). One individual developed a rash accompanied by a striking rise in serum transaminases, which recurred on subsequent re-exposure (7). Experience in the treatment of *Echinococcus multilocularis* infection is similar. One patient with fatal agranulocytosis also had severe, probably unrelated, liver disease (SEDA-8, 292). Some 3–4% develop fever, which can be persistent and accompanied by respiratory symptoms and eosinophilia. Other adverse effects include pain over the site of the cyst, allergic reactions, alopecia, glomerulonephritis, and rashes.

Various authors have reported spontaneous rupture of hydatid cysts with mebendazole, and this is probably more frequent than in untreated individuals. Pleural and peritoneal cysts are more likely to rupture.

Evidence of teratogenicity in rats has not been accompanied by reports that it causes harm in human pregnancy, but the WHO recommends avoidance during the first trimester. It is not known if mebendazole enters the breast milk; no adverse effects have been reported but the issue has not been specifically studied.

Organs and Systems

Liver

All benzimidazoles can cause mild and reversible rises in transaminases, but even in high doses withdrawal is justified in only a few patients (5).

Granulomatous hepatitis with eosinophilia has been attributed with mebendazole (8).

- A 52-year-old man with ascariasis took two 3-day cycles of mebendazole 100 mg bd with a 2-week interval. Within 48 hours of the second course he developed fever (39°C), diarrhea, anorexia, and prostration. Ten days later he had tender hepatomegaly. His liver function tests were abnormal (aspartate transaminase 466 IU/l, alanine transaminase 458 IU/l). The serum alkaline phosphatase and bilirubin were normal and the gamma-glutamyl transferase mildly raised. The white blood cell count was 12.7×10^9/l with 18% eosinophils. Coagulation was normal. Tests for Hepatitis A, B, and C, cytomegalovirus, and Epstein–Barr virus were all negative. Serum ACE was not raised. Antimitochondrial antibodies were negative but antinuclear antibodies (1:60) and antibodies against smooth muscle (1:160) were positive. Extensive tests to exclude other causes of granulomatous hepatitis were all negative. A liver biopsy showed multiple granulomata consisting of epithelioid cells, multinucleated giant cells, plasma cells, and lymphocytes. There was slight fibrosis around the granulomata. There was no evidence of cholestasis. No helminthic ova were found. Ziehl-Nielsen and periodic acid Schiff stains were both negative. After 2 days the fever had subsided without treatment and he felt better. The serum transaminases returned to normal over the next 10 weeks and the eosinophilia disappeared.

Liver damage has been described after treatment with most benzimidazoles, but it is usually cholestatic. The liver damage described in this case was granulomatous. Liver damage after mebendazole in the low dose used in this case is rare, probably because of its poor absorption.

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It is more frequent, although still rare, in the higher doses used in the treatment of human echinococcosis.

Urinary tract

Glomerulonephritis has been observed in five patients from Kenya (9).

Skin

Two cases of exfoliative dermatitis occurred in a total of 131 patients treated (9). In one Indian case, a fixed drug eruption was attributed to the drug (10) and other forms of rash have been seen.

An outbreak of Stevens–Johnson syndrome has been reported in 52 Filipino overseas contract workers (aged 20–30 years, 50 women) working in China who used mebendazole for helminthic prophylaxis (11). All took mebendazole at least once after the appearance of rashes and fever. Three women eventually died, primarily due to septicemia.

Susceptibility Factors

Age

Children aged under 2 years who are infected with helminths are currently excluded from treatment with mebendazole and other antihelminthic drugs on the basis of the manufacturer's instructions. In a double-blind, randomized trial in Tanzania 212 children aged under 2 years were given a total of 653 antihelminthic treatments (317 mebendazole 500 mg; 336 placebo) (12). There were no significant differences in adverse events in the two groups. In the light of the potential nutritional benefit achieved by regular deworming in this age group, the policy that excludes children aged under 2 years from treatment should probably be reconsidered.

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Mebeverine

General Information

Mebeverine is an antispasmodic drug that is claimed to act directly on the colonic muscle and is virtually free of systemic adverse reactions. It has been used to treat irritable bowel syndrome, but its therapeutic effect is poor.

The effectiveness and safety of two formulations of mebeverine hydrochloride (200 mg capsules bd and 135 mg tablets tds) in 213 patients with irritable bowel syndrome have been studied in a randomized, double-blind, general practice study lasting 8 weeks (1). The two formulations were equally effective in relieving abdominal pain. The frequencies of reported adverse events were similar in the two groups and were considered unlikely to be related to the medication.

A meta-analysis of 23 randomized clinical trials assessing the efficacy and tolerance of smooth muscle relaxants in irritable bowel syndrome has shown that these drugs are superior to placebo (2). Six drugs were analysed: cimetropium bromide (five trials), hyoscine butyl bromide (three trials), mebeverine (five trials), otilium bromide (four trials), pinaverium bromide (two trials), and trimebutine (four trials). There was no overall significant difference in the frequency of adverse effects compared with placebo.

Organs and Systems

Gastrointestinal

A case of colonic perforation was described in 1990, but the patient concerned was suffering from the distal intestinal syndrome of cystic fibrosis and may have been at particular risk (SEDA-16, 428).

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Mebhydrolin

See also Antihistamines

General Information

Mebhydrolin is an antihistamine, an ethylenediamine derivative, with antimuscarinic and sedative properties.

Organs and Systems

Hematologic

Cases of agranulocytosis have been attributed to mebhydrolin (1).

Skin

Exacerbation of psoriasis has been attributed to mebhydrolin (2).

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Meclozine

General Information

Meclozine is an antihistamine, a piperazine derivative, with antimuscarinic and moderate sedative properties.

Organs and Systems

Psychological, psychiatric

Loss of memory, confusion, and disorientation has been ascribed to meclozine in an 85-year-old woman (SEDA-13, 132).

Second-Generation Effects

Teratogenicity

Delivery outcome in 16 536 women who had used meclozine in early pregnancy was compared with 540 660 women (1). Maternal diagnoses of pre-eclampsia or diabetes were less frequent when the woman had used meclozine. The twinning rate was increased and preterm births, low birth weights, short body lengths, and small head circumferences were less frequent after meclozine as were congenital malformations.

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Medroxyprogesterone

General Information

Other information on medroxyprogesterone will be found in other monographs that deal with progestogens:

- Hormonal contraceptives—intracervical and intravaginal
- Hormonal contraceptives—oral
- Hormonal contraceptives—progestogen implants Hormonal contraceptives—progestogen injections
- Hormone replacement therapy—estrogens + progestogens
- Progestogens.

Medroxyprogesterone acetate is given in a relatively high dose for hormonal contraception and acts primarily by inhibiting ovulation. However, as with the other progestogen-only contraceptives, other mechanisms probably play a very significant role. It is extremely effective, with less than one pregnancy per 100 woman-years.

Depot medroxyprogesterone acetate is by far the most widely used formulation of this compound; the World Health Organization's assessment of it in 1983 (1) remains valid, as confirmed by later studies and reviews (2–4). By 1994 it was estimated that the drug had been used by 30 million women in more than 90 countries, and at the turn of the century it continues to be used on a large scale.

In addition to its use as a contraceptive, medroxyprogesterone acetate has also been used to treat benign prostatic hyperplasia, in which intermediate doses (for example 150 mg) are used (5), and to stimulate the appetite in patients receiving palliative care for cancer, although little published work can be found to support the latter indication.

General adverse effects

Reports on adverse reactions to lower doses of medroxyprogesterone acetate are not entirely consistent, probably because of differences in pharmaceutical formulation which markedly affect the drug's systemic availability. However, high doses of medroxyprogesterone acetate are extensively used for the treatment of hormone-dependent carcinomas (notably of the breast) and marked adverse effects occur consistently under these conditions (SEDA-12, 343). Such doses are likely to bring out the

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compound's glucocorticoid potency. At a dose of some 800 mg/day, effects are likely to include excessive weight gain (in 4090% of cases), Cushingoid facies (10–20%), worsening of diabetes mellitus (up to 8%), edema (10–20%), and other effects suggestive of Cushing's syndrome. The changes are especially marked in women treated for more than 5 weeks; effects are less severe at lower doses. Smaller numbers of patients can develop rash, thromboembolism, dysuria, nervousness, headache, or nausea and vomiting.

In a condition such as benign prostatic hyperplasia, common complications are reduced libido, a reduced volume of ejaculate, and impotence; within 3 days of starting treatment, serum testosterone can reach castration concentrations.

The contraceptive efficacy of depot medroxyprogesterone acetate does not appear to be affected by interactions with other drugs; some interactions are known (6), but the doses used for contraceptive purposes are sufficient to remain effective even if metabolism is increased, for example by aminoglutethimide or phenytoin.

Organs and Systems

Cardiovascular

To date medroxyprogesterone does not seem to have been associated with thrombosis, but an authoritative review has pointed out that this remains a possible risk (7).

Medroxyprogesterone has been reported to have variable effects on blood pressure. In some studies it had no effect on blood pressure at all (8) or reduced diastolic pressure slightly (9). In 24 women (21 normotensive and three hypertensive) aged 16–35 years who received injections of medroxyprogesterone acetate 150 mg for contraception mean blood pressure fell from 124/79 to 120/75 mmHg; the change was attributable to effects in the women with hypertension (10).

Nervous system

For women with epilepsy, depot medroxyprogesterone acetate is a particularly useful contraceptive method, because it reduces seizure frequency (11). The dosage is so high that reduced efficacy due to enzyme-inducing anti-epileptic medication is not an issue. As with other hormonal contraceptives, some women tend to have headaches and mood changes.

Psychological, psychiatric

Mental or personality changes, a typical glucocorticoid effect, have been reported to be more severe and more frequent with combined aminoglutethimide plus medroxyprogesterone acetate treatment than with monotherapy in patients with bone metastases from breast cancer. The increased frequency of depressive syndromes on the two-drug therapy could not be attributed to the physical adverse effects of the combination, since the mental disorders appeared only during the first weeks of treatment, whereas the Cushingoid features did not become apparent until some 6–8 weeks of treatment had been given (12).

Endocrine

Medroxyprogesterone, while suppressing spermatogenesis, also depresses release of growth hormone induced by insulin or arginine (13).

Medroxyprogesterone reportedly increases basal growth hormone concentrations (14).

Metabolism

Treatment with low-dose medroxyprogesterone acetate (50 and 150 mg/day) for endometriosis reduces HDL cholesterol (15) confined to the HDL2 subfraction, which was lowered by as much as 58% after 24 weeks of treatment; the effect was clearly dose-related in the therapeutic dosage range.

A multicenter study of lipid metabolism conducted by the WHO showed considerable differences in serum lipids and apolipoproteins among the centers, with overall small falls in HDL cholesterol and increases in LDL concentrations (16).

In undernourished lactating women in one developing country, metabolic effects were more pronounced than among healthy users (17); serum cholesterol concentrations were somewhat higher with medroxyprogesterone during their first 6 months of lactation, but there were no alterations in glucose tolerance, serum triglycerides, or total protein concentrations during 1 year of treatment.

There is a disputed effect on carbohydrate metabolism, but it is at most mild and there is certainly no precipitation of diabetes in healthy women. Carbohydrate metabolism was unaffected by medroxyprogesterone in one study in which there was modest impairment of glucose tolerance among users of levonorgestrel-containing, low-dose combined oral contraceptives and progestogen-only tablets (18).

Depot medroxyprogesterone acetate contraception is widely used by women of the Navajo tribe of American Indians, and they constitute a high-risk population for diabetes mellitus. However, medroxyprogesterone can cause weight gain and independently reduce sensitivity to insulin, which would be particularly undesirable in such women. Contraceptive use has been studied in 284 Navajo women with diabetes and 570 non-diabetic controls. Users of depot medroxyprogesterone were more likely to develop diabetes than those who had used combination estrogen + progestogen oral contraception only (OR = 3.8; 95% CI = 1.8, 7.9). The excess risk persisted after adjustment for body mass index and it became more pronounced with longer use (19).

Metabolic effects seen when the drug is used in high doses for other purposes (notably the treatment of breast and endometrial cancer) are unlikely to be seen in contraceptive use. This applies to the glucocorticoid potency that medroxyprogesterone undoubtedly possesses to some degree; at the higher doses adrenal suppression can be observed (20) but not at contraceptive doses (21).

Fluid balance

Medroxyprogesterone acetate has a degree of mineralocorticoid potency (22). However, in 10 patients with advanced hormone-sensitive and non-hormone sensitive tumors high-dose medroxyprogesterone acetate (over

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500 mg/day) had no effects on body weight, lean body mass, blood pressure, plasma sodium concentration, urinary sodium excretion, or the exchangeable sodium pool (8).

Hematologic

Medroxyprogesterone acetate, administered either orally or by injection, has little or no effect on blood coagulation (23).

The suitability of medroxyprogesterone for women with sickle cell disease has been evaluated in a controlled crossover trial, which showed that both hematological and clinical parameters were improved (24).

Liver

No consistent effects of medroxyprogesterone acetate on liver function have been found, and primary biliary cirrhosis and chronic active hepatitis have appeared to improve during treatment (25).

Musculoskeletal

Subgroups of users of depot medroxyprogesterone acetate may have reduced spinal bone density, but this seems to be reversible after withdrawal, even after several years of drug exposure (26). Bone mineral density in one cross-sectional study was lower among users of depot medroxyprogesterone acetate, but withdrawal was followed by complete recovery of normal bone density (26). A current study in the USA is expected to provide further data on this matter in women who have used medroxyprogesterone acetate for as long as 10 years.

Reproductive system

Poor cycle control is a problem with medroxyprogesterone acetate. Most women using the product have at first either irregular or excessive bleeding and spotting or amenorrhea linked to endometrial atrophy (27); however, only one woman in a thousand bleeds sufficiently to warrant aggressive therapy, such as curettage. As the duration of use increases, amenorrhea becomes more common. Depot medroxyprogesterone acetate is associated with greater variability in menstrual patterns than other hormonal contraceptives (28,29). Bleeding/spotting episodes are infrequent but are prolonged when they occur, and the prevalence of amenorrhea increases over time to more than half of users after the first year. Under 10% of users have bleeding patterns defined as fully satisfactory and acceptable, compared with 85–90% of women not using contraception and the majority of women taking appropriate doses of oral contraceptives. However, with appropriate patient selection and counselling, many users view amenorrhea positively and are content to continue with the medroxyprogesterone. Indeed, because they are often amenorrheic, they may experience improvements in such menstrual cycle conditions as menorrhagia and dysmenorrhea and in iron deficiency anemia. Other potential benefits include reduction in the risk of pelvic inflammatory disease, improvement in sickle cell disease parameters, and lessened seizure frequency in women with epilepsy.

Other effects are generally less prevalent with progestogen-only contraceptives than with combined oral contraceptives because of the absence of an estrogen and a lower dose of the progestogen. Headache, breast tenderness, and less commonly nausea and dizziness have been reported by users of progestogen-only contraceptives, but it is not clear whether progestogen-only contraceptives actually play a causal role. Androgenic adverse effects, such as acne, hirsutism, and weight gain, occur, but rarely.

The reduced penetrability of cervical mucus, which contributes to the contraceptive effect, may well provide some small degree of protection against pelvic inflammatory disease. However, this effect is likely to be less than that exerted by combined oral contraceptives, since the expanded cervical ectropion found among combined oral contraceptive users is not present in users of progestogen-only contraceptives.

Immunologic

Anaphylactic reactions to medroxyprogesterone are very rare.

- A 40-year-old woman developed anaphylactic shock after receiving depot medroxyprogesterone acetate 150 mg intramuscularly (30). She was not taking any other medications, and there was no history of allergy to food or cosmetics. She responded fully to immediate resuscitation. She had another episode when she received another dose 12 weeks later.

Long-Term Effects

Tumorigenicity

The effects of depot medroxyprogesterone acetate on reproductive cancers appear to be similar to those of combined oral contraceptives. Most notably, despite initial concerns about breast cancer in beagle dogs that were given large doses of medroxyprogesterone, a pooled analysis of epidemiological studies concluded that women using medroxyprogesterone are not at increased risk of breast cancer (31). Furthermore, the risk did not increase with increasing duration of use. However, women who had begun use within the past 5 years had significantly increased risk, perhaps because of accelerated growth of pre-existing tumors or increased surveillance.

Another review, dating from 1994, concluded that depot medroxyprogesterone acetate has a protective effect against endometrial cancer that is at least as strong as for combined oral contraceptives, but that, based on the limited available evidence, there is no association with ovarian cancer (32). Regarding cervical neoplasia, studies of depot medroxyprogesterone acetate do not show a strong adverse effect, but as with combined oral contraceptives it is uncertain whether there is no association or a slightly increased risk (33).

Second-Generation Effects

Fertility

Return of fertility may be delayed for several months after withdrawal of medroxyprogesterone acetate. The length of the delay is not related to the duration of use. There is no evidence of permanent impairment of fertility (2,34).

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Teratogenicity

If a breakthrough pregnancy occurs during the use of depot medroxyprogesterone acetate, the developing embryo and fetus will continue to be exposed to it for months, and an adverse effect cannot be entirely excluded, but little concrete information has emerged. Clitoral hypertrophy has been described in three infants exposed to medroxyprogesterone in utero. In view of the hormonal spectrum of medroxyprogesterone, this is a conceivable adverse effect, but there is no confirmation, nor is it clear whether the drug harms the fetus in any other way (25).

Lactation

Many studies have shown that lactation is not adversely affected by depot medroxyprogesterone acetate and that breast-milk production may even be increased (35). Because of the low binding affinity of medroxyprogesterone to sex hormone binding globulin, the concentration of steroids in the milk is close to that in the maternal plasma, unlike the 19-nortestosterone derivatives.

Children whose mothers used depot medroxyprogesterone acetate while breastfeeding have been followed up in Thailand for 17 years and in Chile for 4.5 years, with no documented effect on growth or development (36). In undernourished lactating women the metabolic effects seem to be more pronounced than among healthy users (17).

Susceptibility Factors

Depot medroxyprogesterone acetate should not be used in women with breast cancer, genital cancer, undiagnosed uterine bleeding, or suspected pregnancy (37), but these are merely logical precautions.

The only study of depot medroxyprogesterone acetate and HIV infection, conducted among Thai prostitutes, showed an increased risk after adjustment for other variables (38).

Drug Administration

Drug administration route

An injection of medroxyprogesterone acetate 150 mg provides contraception for some 3 months. Peak concentrations in the blood are reached on around the 10th day after injection, but the drug is still detectable in the blood at the 90th day, although with wide interindividual variation.

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Mefenamic acid

See also Non-steroidal anti-inflammatory drugs

General Information

The NSAID mefenamic acid is an anthranilic acid derivative. It has been argued for more than a decade that, since there is a wide range of effective and less toxic drugs, there is no reason for continuing to prescribe mefenamic acid and related drugs (SEDA-5, 93). All the same, some of the figures have been disputed, and, strictly speaking, a comparative controlled study to estimate the incidence of the adverse effects of mefenamic acid is still needed. The main reasons for concern are particular effects that are unexpected of an NSAID, such as hemolytic anemia, and which may therefore take the user by surprise.

Organs and Systems

Nervous system

Epileptic seizures in overdosed patients may indicate a degree of nervous system toxicity. Convulsions in poisoned patients are reported to be more likely with mefenamic acid than with other compounds (1). Other nervous system reactions (such as headache) are less frequent than with the arylcarboxylic acid derivatives. Coma has also been described as a consequence of mefenamic acid overdosage (2).

Sensory systems

Hyperacusia, vertigo, and tinnitus have been described in one patient (SEDA-12, 90).

Hematologic

Several hematological disturbances have been reported, although their overall incidence is probably moderate. They include Coombs' positive hemolytic autoimmune anemia, leukopenia, thrombocytopenia, and agranulocytosis (SED-8, 223) (3–5) (SEDA-4, 68). Neutropenic reactions have also been described (6). Severe neutropenia developed simultaneously with non-oliguric renal insufficiency in two elderly hypothyroid women (7).

Gastrointestinal

Gastrotoxicity due to mefenamic acid is marked. Other than the common adverse effects (nausea, anorexia, vomiting, pain, diarrhea), acute peptic ulcer, intestinal hemorrhage, hematemesis, abdominal distension, and profuse steatorrhea (SEDA-2, 97) have been reported. Mefenamic acid, unlike other NSAIDs, can provoke enteritis and colitis in patients with no known predisposing factors (8). It accelerates bowel transit in healthy volunteers (SEDA-16, 112).

Esophageal injury is a rare adverse effect of NSAIDs. The published evidence comprises only a few specific studies and a small number of single case reports regarding various NSAIDs (SEDA-15, 92). A report of

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esophageal ulceration associated with mefenamic acid capsules has been published (9).

- Five days before he presented with esophageal ulceration, a 35-year-old man took two capsules of mefenamic acid (total dose 500 mg) in bed with a small amount of water. The following morning he noted severe retrosternal pain, which persisted until he was seen 4 days later. Endoscopy showed a 3 cm esophageal ulcer near the aortic arch. Within a few days there was complete resolution of ulceration.

All NSAIDs should be taken while standing or sitting, rather than lying, and with about 200 ml of water.

Pancreas

Pancreatitis has been attributed to mefenamic acid (10).

Urinary tract

Mefenamic acid and other anthranilic acid derivatives are nephrotoxic. Many renal effects have been demonstrated in animals. Acute renal insufficiency, renal papillary necrosis, and non-oliguric renal insufficiency have been reported in man (11,12). Renal biopsies in renal insufficiency have shown interstitial nephritis, mesangial proliferation, and focal pedicle fusion, previously undescribed (13).

Skin

Fixed drug eruption has been described in two patients within hours of taking mefenamic acid (SEDA-12, 90). In another case, a multifocal fixed drug eruption mimicked erythema multiforme (14).

Pseudoporphyria is an infrequent adverse effect of some NSAIDs, including naproxen (SEDA-12, 87), nabumetone (SEDA-16, 111), and oxaprozin (SEDA-21, 106).

- A 22-year-old woman developed pseudoporphyria during long-term treatment with mefenamic acid for menstrual problems. After withdrawal of mefenamic acid, the skin lesions gradually disappeared, and at follow-up after 18 months she did not have any skin lesions and had minimal residual scarring (15).
- An unusual skin reaction characterized by widespread pruritic papules and nodules occurred in a 62-year-old-woman who had taken long-term mefenamic acid for arthritis. The histological findings were consistent with dermatitis herpetiformis, whereas direct immunofluorescence was suggestive of atypical bullous pemphigoid or linear IgA disease. The skin eruption responded to dapsone, but an increase in the dosage of mefenamic acid caused diarrhea and steatorrhea with IgA antigliadin antibodies. A lymphocyte stimulation test with mefenamic acid was positive. Mefenamic acid was withdrawn and all her symptoms disappeared within 2 weeks (16).

Sexual function

Although mefenamic acid can be used to relieve dysmenorrhea, it can delay menstruation for several days (17).

Immunologic

Asthma and anaphylactic shock are the most dangerous acute hypersensitivity reactions. There is cross-sensitivity with other NSAIDs (18). Rash, urticaria, and pruritus accompany more serious reactions.

Susceptibility Factors

Age

The dosage of mefenamic acid that is used in preterm infants to induce closure of patent ductus arteriosus must not exceed 2 mg/kg/day in three divided doses, to avoid the danger of renal insufficiency (SEDA-19, 97). The promotion of mefenamic acid in Pakistan for fever in children, as a drug of "unsurpassed efficacy compared to [paracetamol] in fever control" and "better tolerance", has been criticized by the Medical Lobby for Appropriate Marketing. In fact, there have been no controlled comparisons of mefenamic acid with a reference drug or placebo, and its safety and efficacy have not been established in children (SEDA-19, 97).

Drug Administration

Drug overdose

Mefenamic acid overdosage is characterized by nervous system symptoms, such as generalized seizures, agitation, and confusion, sometimes progressing to coma, gastrointestinal problems (bloody diarrhea, abdominal pain, and vomiting), and renal impairment (SEDA-13, 83) (SEDA-14, 95) (19).

Drug–Drug Interactions

Lithium

Mefenamic acid may have interacted with lithium in a patient with reduced renal function, causing acute symptoms of lithium toxicity (SEDA-13, 83).

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Mefloquine

General Information

Mefloquine, a fluorinated derivative of 4-quinoline methanol, is a product of the US Army's antimalarial research program. It is active against chloroquine-resistant *Plasmodium falciparum*, and has an excellent schizonticidal effect in the blood in experimentally induced *Plasmodium vivax* infections in volunteers. It is not gametocidal. *P. vivax* infections can persist after successful treatment of the falciparum infection with other drugs; the fact that mefloquine is effective against both organisms is thus of practical importance (SEDA-13, 808).

Mefloquine is readily absorbed after oral administration; absorption is influenced by the formulation and is more rapid from an aqueous solution. Maximum serum concentrations occur after 1–4 hours. Absorption is reduced by diarrhea. The half-life varies considerably and has been variously reported to be 7–23 days, 15–30 days, and 8–18 days (SEDA-13, 808) (1), (SEDA-16, 308) (2). Plasma protein binding is high. Sick patients have a prolonged t_{max}.

Mefloquine has a high cure rate after a single dose of 750–1000 mg. The use of combinations of mefloquine with other antimalarial drugs has been advocated in order to reduce the development of resistance. Mefloquine is effective as a prophylactic. Using a weekly dosage schedule, a dose of 250 mg is appropriate in adults. Because early reports also suggested that the drug was without serious adverse effects, mefloquine became widely advocated by various advisory bodies for prophylactic use, starting a week before travel to an endemic area where chloroquine resistance is common, and continuing for 4 weeks after departure from the area (SEDA-16, 306). Regrettably, but as might have been expected, it has also been used for prophylaxis in areas where its use is unnecessary (SEDA-13, 808) (3–5).

Mefloquine remains useful in the treatment of uncomplicated malaria in areas of chloroquine resistance, but recommendations for mefloquine as prophylaxis in travellers are under constant review. In visitors to the Kruger National Park (South Africa), adverse effects were reported in 325 (25%) of 1300 subjects taking mefloquine; gastrointestinal and neuropsychiatric effects were dominant (6). Four subjects required hospital attention for particularly severe neuropsychiatric reactions and 53 changed from mefloquine prophylaxis because of adverse effects. However in the same study chloroquine + proguanil prophylaxis led to reported adverse effects in 720 (29%) of 2488 subjects: one had a convulsion and 69 altered their prophylaxis because of adverse events or the dosing schedule. In this population mefloquine was as well tolerated as chloroquine + proguanil prophylaxis in general terms. This is in contrast to previous studies, in which the use of mefloquine led to higher rates of intolerance and severe adverse effects.

Observational studies

Malaria prevention measures taken by 5626 returning North American and European travellers departing from Kenyan airports have been examined in a cross-sectional questionnaire study. Mefloquine (74%) and chloroquine and proguanil (15%) were the most common drugs used (7). There were adverse events in 20% of the travellers who took mefloquine and 16% of those who took chloroquine and proguanil. Neuropsychological adverse events were reported by 7.8% of those taking mefloquine and 1.9% of those taking chloroquine. Despite adverse events, adherence was better in the mefloquine group (95 versus 81%; OR = 0.25), which may have been due to a lower dosing frequency.

Comparative studies

Atovaquone + proguanil (250/100 mg/day; $n = 493$) and mefloquine (250 mg/week; $n = 483$) have been compared in non-immune subjects attending travel clinics in North America, Europe, and South Africa in a randomized, double-blind study (8). Adverse events were reported by an equivalent proportion of subjects who had taken either drug (71 versus 67%; difference 4.1%, 95% CI = 1.7, 9.9). Those who took atovaquone + proguanil had significantly fewer treatment-related neuropsychiatric adverse events (14 versus 29%), fewer adverse events of moderate

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or severe intensity (10 versus 19%), and fewer adverse events that caused prophylaxis to be withdrawn (1.2 versus 5%), compared with those who took mefloquine. Adherence was better in the atovaquone + proguanil group, which may have been due to the shorter duration of post-travel dosing (1 week versus 4 weeks for mefloquine). There were no confirmed cases of malaria.

Mefloquine (125 or 250 mg/week; $n = 56$) has been compared with proguanil (100 or 200 mg/day; $n = 57$) for short-term (6 months) malaria chemoprophylaxis in Nigerians with sickle cell anemia in a non-blinded, randomized study (9). Efficacy was similar (89% for mefloquine and 82% for proguanil). Adverse events were reported by 32% of those who took proguanil and 20% of those who took mefloquine. Surprisingly, only 3.6% of the mefloquine group reported neuropsychiatric adverse events.

Single-dose pyrimethamine + sulfadoxine (25 mg/kg; $n = 54$) has been compared with mefloquine (15 mg/kg; $n = 48$) in the treatment of uncomplicated *P. falciparum* malaria in an unblinded, randomized study in 102 Malawi children (10). Immediate vomiting was more common in those who took mefloquine (eight cases) than in those who took pyrimethamine + sulfadoxine (one case), with comparable parasite failure rates at 14 days (20 and 22% respectively).

General adverse effects

Although mefloquine is generally well tolerated, particularly when used prophylactically, the list of adverse effects has grown with accumulated experience. With therapeutic doses (for example 750–1500 mg in adults; 20 mg/kg in children) adverse effects are usually mild, but with occasional severe neuropsychiatric derangement. The overall incidence of adverse effects is about the same as with chloroquine, about 40–50%. Events most commonly reported include nausea, diarrhea, abdominal pain, dizziness, strange dreams, and insomnia. Adverse effects are dose-related, with an increase in dizziness and gastrointestinal complaints and fatigue at higher doses. Extensive acute, subacute, and chronic studies of mefloquine in animals have shown that it is not phototoxic, like some of the quinolone-methanols studied, nor was it mutagenic, teratogenic, or carcinogenic in these studies (SEDA-13, 808).

The adverse effects of mefloquine have been extensively reviewed both for prophylaxis (when rare neuropsychiatric adverse effects make its use controversial) and in treatment doses, when it has been linked to an increased incidence of the postmalaria neurological syndrome. A retrospective review of 5120 Italian soldiers showed an overall chemoprophylaxis curtailment rate of less than 1%, which was not significantly different from the combination of chloroquine and proguanil (11). A semi-systematic review also suggested no significant difference in tolerability compared with other antimalarial drugs (12).

The frequency and spectrum of adverse events associated with mefloquine (750 and 500 mg 6 hours apart) has been assessed in 22 healthy volunteers who were monitored for 21 days after drug administration (13). More women than men reported severe adverse reactions. The most commonly reported adverse effects were vertigo (96%), nausea (82%), and headache (73%). The vertigo was severe (grade 3) in 73% and required bed rest and specific medication for 1–4 days. In most cases (17/22) the symptoms resolved within 3 weeks after drug administration. Biochemical and hematological measures stayed within the reference ranges, but there were significant rises in serum sodium, chloride, calcium, bilirubin, gammaglutamyl transpeptidase, and lactate dehydrogenase.

Organs and Systems

Cardiovascular

Sinus bradycardia was seen in 18% of patients taking mefloquine (SEDA-12, 693) (14), occurring some 4–7 days after administration; the bradycardia was asymptomatic and lasted about 3–4 days. Transient sinus arrhythmia was also reported, without a need for treatment (SEDA-12, 808). Asymptomatic dysrhythmias were also recorded in a dosage comparison trial (SEDA-16, 308).

Nervous system

Neurological and psychiatric reactions occur to such an extent, even during prophylactic use, that a general recommendation for the use of mefloquine as prophylaxis has been called into question (SEDA-20, 258), although disabling symptoms occur in under 1% of travellers (SEDA-21, 296). Headaches, dizziness, vertigo, and light-headedness are common (SEDA-12, 693) (14,15), (SEDA-16, 307), the incidence varying between 20 and 90%. Dizziness is to some extent dose-related (16,17). Tinnitus and vertigo are less frequent.

A so-called postmalaria neurological syndrome (convulsions, tremor, confusion) has been described in about 4–5% of patients treated for severe malaria tropica with mefloquine (SEDA-21, 296).

All reports have suggested that the neuropsychiatric reactions to mefloquine are transient. They may be precipitated by alcohol (18).

Penetration into the brain of the (+) enantiomer of mefloquine is much higher than that of the (–) enantiomer (19) whilst plasma concentrations are greater for the (–) enantiomer, potentially providing a way of minimizing neurological adverse effects, which are often significantly overstated (20), by using the less toxic enantiomer. However, chiral separation technology is not sufficiently well developed to be economically realistic for clinical practice in the foreseeable future.

Sensory systems

Three cases of previously healthy patients who developed persisting high-frequency sensorineural hearing loss and tinnitus whilst taking mefloquine have been reported (21).

Psychological, psychiatric

At first thought to occur only after therapeutic doses of mefloquine, it is now clear that neuropsychiatric reactions occur after prophylactic use as well. The incidence is estimated at about one in 13 000 with prophylactic use, but as high as one in 215 with therapeutic use (SEDA-17, 329). Combination with other drugs that affect the

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nervous system can result in unpredictable reactions. The symptoms vary in type and severity: non-cooperation, disorientation, mental confusion, hallucinations, agitation, and impaired consciousness. An acute psychiatric syndrome with attempted suicide was reported in one case. A single dose can be all that is needed to evoke a mental reaction. Convulsions have been reported, with or without psychiatric symptoms; it seems that mefloquine can aggravate and perhaps even provoke latent epilepsy (SEDA-13, 809) (22), (SEDA-16, 307) (SEDA-17, 329).

- A severe psychiatric and neurological syndrome, with agitation, progressive delirium, and generalized rigors, was seen in a 47-year-old man after he had taken mefloquine 1500 mg over 24 hours (23).
- A 7-year-old Indian boy was diagnosed as having "cerebral malaria" and received quinine followed by mefloquine (dose not given) (24). He developed hallucinations and removed his clothes and danced. His symptoms resolved within 24 hours of stopping mefloquine. This case highlights the fact that mefloquine should not be given after quinine in cases of severe malaria.
- A 42-year-old man with no previous psychiatric history suddenly developed visual symptoms after the third dose (total dose 750 mg) of prophylactic mefloquine (25). The symptoms consisted of an impression of focusing on two different planes and of perceiving his surroundings as very far from him. They were associated with slurred speech and altered comprehension. They occurred daily, lasting up to an hour, for 6 months. He had previously taken a course of mefloquine for 7 weeks without any adverse events.
- A 52-year-old woman with no psychiatric history developed anxiety, paranoia, visual hallucinations, confusion, and depressive symptoms after 3 doses of prophylactic mefloquine (250 mg/week) (26). She had previously taken mefloquine prophylaxis intermittently for 4 years with no adverse events.

These case reports illustrate important neuropsychiatric adverse effects of mefloquine in individuals who had previously taken mefloquine safely and had no psychiatric history.

A postal survey of 5446 returning Danish travellers examined the adverse effects of unstated doses of mefloquine, chloroquine, and chloroquine plus proguanil for malaria prophylaxis (27). There were 4158 responses (76%); 1223 travellers took chloroquine, 1827 took chloroquine plus proguanil, and 809 took mefloquine. Overall, although chloroquine and chloroquine plus proguanil were associated with a large number of mild (mainly gastrointestinal) adverse effects, 30–50% had diarrhea and about 20% had nausea or abdominal pain. There was a significantly larger number of reported "unacceptable symptoms" (not defined) with mefloquine: 2.7%, 1.0%, and 0.6% for mefloquine, chloroquine, and chloroquine plus proguanil respectively. Most of the more serious adverse events were in those who took mefloquine. Compared with chloroquine alone the relative risk (95% CI) of "depression," experiencing "strange thoughts," or having altered spatial perception were 5.1 (2.7, 9.5), 6.4 (2.5, 16.1), and 3.0 (1.4, 6.2) respectively. There was also a higher incidence of depression in women than in men. The relative risk of hospital admission or early termination of travel possibly related to prophylaxis was higher with mefloquine than with either chloroquine or chloroquine plus proguanil; the relative risks (95% CI) were 162 (69, 498), 612 (169, 5054), and 261 (127, 649) respectively.

A postal survey of the incidence of psychiatric disturbances in 2500 returning Israeli travellers (28) showed that travellers with this class of adverse effects were more likely to have taken mefloquine than other antimalarial drugs. Of 117 travellers with psychiatric adverse effects, 115 had taken mefloquine compared with 948/1340 for the entire cohort. This was a retrospective postal study with a response rate of 54% (1340 out of 2500), and of those who responded 71% had taken mefloquine, 5% had taken chloroquine, and 24% had taken no prophylaxis. In this study 11% (117) of the respondents reported psychiatric disturbances, mainly sleep disturbance, fatigue, vivid dreams, or "lack of mood." Only 16 of the respondents had symptoms lasting 2 months or more. Those who had had a psychiatric disturbance were also more likely to have been female and to have taken recreational drug use.

Although the above studies were limited by retrospective design, their results are in broad agreement with the results of other studies over the past few years that indicate that women have a higher incidence of psychiatric adverse effects from mefloquine than men (29–32).

In a prospective, double-blind, randomized, placebo-controlled study in 119 healthy volunteers (mean age 35 years), who took either atovaquone 250 mg/day + chloroguanide 100 mg/day or mefloquine 250 mg/week, depression, anger, and fatigue occurred during the use of mefloquine but not atovaquone + chloroguanide (33).

Airline pilots should not take routine prophylaxis with mefloquine because of the small risk of neuropsychiatric reactions.

Endocrine

- A 30-year-old woman took mefloquine, 250 mg/week, and developed abdominal pain, palpitation, and tremor; thyroid function tests were abnormal; 1 month after withdrawal the tests had returned to normal (SEDA-18, 289).

Hematologic

- Agranulocytosis occurred in a 31-year-old man with *P. vivax* parasitemia given an initial dose of mefloquine followed by 500 mg 8 hours later (SEDA-16, 307).

There have been no other reports of hematological toxicity.

Gastrointestinal

Gastrointestinal complaints, such as nausea, vomiting, abdominal discomfort, and (usually mild) diarrhea, have been mentioned in most reports, the incidence being 10–25% (SED-12, 693) (14,15), (SEDA-16, 307). The frequency increases with higher doses, for example 25 instead of 15 mg/kg (17).

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Liver

Acute fatty liver has recently been reported after malaria prophylaxis with mefloquine (34).

- A 46-year-old woman took five, weekly, doses of mefloquine 250 mg before discontinuing treatment because of neuropsychiatric and gastrointestinal symptoms. Over the next month she had watery diarrhea, 11 kg weight loss, dependent edema, and abdominal fullness. On examination the liver was substantially enlarged; ultrasound imaging showed massive hepatomegaly with diffuse high-grade steatosis. Serological investigations for infective and autoimmune causes were negative. Her symptoms abated with fluid, electrolyte, and albumin replacement. A fine-needle liver biopsy showed features of diffuse macrovesicular hepatic steatosis. Clinical and radiological changes subsided without sequelae.

Acute fatty liver in this case may have been an idiosyncratic adverse effect of mefloquine.

Raised transaminases (up to 20 times normal activities) have been seen in a man taking mefloquine prophylaxis; they resolved after withdrawal of mefloquine (35).

Skin

Maculopapular rash, urticaria, and itching have been reported; itching may be more common with mefloquine than with chloroquine. However, there are isolated case reports concerning more serious skin conditions: exfoliative dermatitis (36); cutaneous vasculitis (SEDA-17, 3) and a bilateral facial rash, comprising raised red lesions and flat bullae (SEDA-17, 329).

Mefloquine has been associated with erythema multiforme and its variants Stevens–Johnson syndrome (SEDA-16, 307), and toxic epidermal necrolysis (37).

It has tentatively been suggested that mefloquine can exacerbate psoriasis (as can other antimalarial drugs, such as quinidine, chloroquine, and proguanil) (38).

Skin reactions to mefloquine have been reviewed, in relation to 74 case reports published between 1983 and 1997 (39). Pruritus and maculopapular rash were the most common skin reactions: in some studies, their approximate frequency was 4–10% for pruritus and up to 30% for non-specific maculopapular rashes. Adverse effects less commonly associated with mefloquine included urticaria, facial lesions, and cutaneous vasculitis. There was one case of Stevens–Johnson syndrome and one fatal case of toxic epidermal necrolysis.

Long-Term Effects

Drug tolerance

Instances of mefloquine resistance were reported in Tanzania in 1983, in Thailand in 1989, and in Africa (Malawi) in 1991. Resistance to combinations of mefloquine with sulfadoxine and pyrimethamine was reported in 1985 (SEDA-13, 808) (40–44). The possibility of cross-resistance between mefloquine and halofantrine was raised in 1990 (SEDA-13, 808) (45). Currently there are extensive areas, including Thailand, Cambodia, Laos, Papua New Guinea, and Myanmar, where *P. falciparum* is resistant to mefloquine (46). High-dose mefloquine has been tried in areas with mefloquine-resistant *P. falciparum*; and a dose of 25 mg/kg is effective, even in a multidrug-resistant area.

Early laboratory studies suggested cross-resistance between mefloquine and halofantrine, but in a later rodent model cross-resistance was not absolute (SEDA-12, 700).

Second-Generation Effects

Pregnancy

A review of the use of mefloquine in pregnancy (47) did not suggest that mefloquine has a worse effect in pregnancy than other antimalarial drugs, such as chloroquine and pyrimethamine + sulfadoxine.

A 7-day quinine regimen (10 mg/kg salt, 8-hourly for 7 days) has been compared with oral mefloquine 25 mg/kg plus artesunate 4 mg/kg/day for 3 days in 108 women on the Thai-Burmese border (48). The mefloquine plus artesunate regimen was significantly more effective than quinine (day 63, cure rate 98 versus 67%). There were more episodes of dizziness (RR = 1.93; 95% CI = 1.14, 3.25) and tinnitus (RR = 3.93; 95% CI = 1.98, 7.80) with quinine, but no serious adverse events were attributable to either drug. There were also two mid-trimester abortions with mefloquine plus artesunate and none with quinine. There were no birth defects in either group. Although the numbers were very small, the authors concluded that despite a better parasitological cure rate, the increased risk of abortion associated with mefloquine in pregnancy precluded its routine use. Larger studies are needed to confirm this observation.

Teratogenicity

Mefloquine prophylaxis was studied in a group of 339 pregnant women on the Thai-Burmese border in a double-blind placebo-controlled trial. Infants in the mefloquine group had a lower mean birth weight; there was also a higher rate of stillbirths and congenital anomalies, though these differences were not statistically significant (49,50).

However, a further study of 208 pregnant women on the Thai-Burmese border showed a significantly increased incidence of still-births compared with 1565 women treated with other antimalarial drugs (51). Other adverse effects were no more common than with other antimalarial drugs. The study was performed during a period of emerging mefloquine-resistant malaria, and the findings may also reflect the effect of suboptimal malaria treatment.

In a postmarketing survey by Roche, spontaneous reports from 1267 women who had taken mefloquine during pregnancy showed that there was neither a specific pattern of malformations nor an overall increase in congenital malformations over the 4% prevalence observed among the general population (52). These data have been confirmed by a survey among 72 US Army soldiers who had taken mefloquine during pregnancy (53).

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Susceptibility Factors

Sex

A study of the pharmacokinetics of oral mefloquine in 12 healthy adults (6 men, 6 women) over 10 weeks has given insights into sex differences in mefloquine pharmacokinetics (54). Five weekly doses of mefloquine 250 mg were given to healthy volunteers. After this, half the subjects took 5 weekly doses of mefloquine 125 mg and half continued to have 250 mg per week. By the second week, all the subjects had plasma mefloquine concentrations over 1.5 μmol/l (the effective prophylactic threshold), but it was only after the fourth dose that the trough concentrations reached this threshold. The women had significantly higher values of C_{oax} and $C_{min.ss}$ than the men. Although the dose of mefloquine was reduced to 125 mg, the plasma mefloquine concentration was maintained above 1.5 μmol/l in all subjects. In this small study, the most commonly reported adverse events were headache, insomnia, and vertigo, with most adverse events occurring between weeks 5 and 8, when plasma mefloquine concentrations were highest. Women had significantly more adverse events (number of days with adverse events/total number of days exposed 149/420) than men (43/420).

These results may explain why earlier studies in male military personnel failed to detect a higher proportion of neuropsychiatric problems with mefloquine compared with other prophylactic regimens.

Neuropsychiatric events have been extensively reviewed, but little is known about the sex-related incidence. Of 179 travellers (mean age 39 years) who took mefloquine for a 3-week prophylactic period before travelling, the women reported adverse events significantly more often than the men (55). There was an increase in fatigue exclusively in the women, especially in first-time users of mefloquine.

Drug Administration

Drug overdose

Mefloquine has a relatively wide therapeutic margin, but can cause predictable and sometimes long-lasting toxicity in overdose.

- Accidental ingestion of 5.25 g of mefloquine over 6 days by a 36-year-old woman caused vertigo, difficulty in visual accommodation, myalgia, hypotension, and tachycardia; most of the anomalies disappeared in 2 weeks (SEDA-16, 307).

Two case reports have described how the antifungal drug terbinafine (Lamasil) was confused with Lariam, leading to accidental mefloquine overdosage and neuropsychiatric adverse effects, including ataxia, high-frequency hearing loss, depression, and paresthesia (56).

Drug–Drug Interactions

Alcohol

One case history has suggested that the use of alcohol with mefloquine can precipitate a neuropsychiatric reaction (18).

Other antimalarial drugs

Mefloquine has been given in combination with other antimalarial drugs, with the aim of delaying drug resistance. Empirical combinations have been made with pyrimethamine and sulfa drugs. However, no drug has been proven to be synergistic with mefloquine, which, with its very long half-life, is difficult to match.

The chemotherapeutic response of *Plasmodium berghei* to various combinations of mefloquine with other drugs (sulfadoxine + pyrimethamine, primaquine, floxacrine) have shown that the desired effects are purely additive (SEDA-13, 809), so the adverse effects too are probably only those of the individual compounds. Adverse reactions occurred in 46% of 400 patients treated with Fanimef (mefloquine + pyrimethamine + sulfadoxine) (SEDA-12, 693). Of note were dizziness (29%), nausea (9.5%), vomiting (7.3%), weakness/lassitude (5.8%), abdominal discomfort or pain (5.5%), diarrhea (3.8%), pruritus (3.0%), insomnia (2.0%), and headache (2.0%).

The combination of mefloquine with artesunate improves tolerance to mefloquine and the therapeutic response is faster (SEDA-21, 296).

Rabies vaccine

Reports of a possible interaction between concurrent mefloquine administration and intradermal rabies immunization have not been substantiated. Four cases in which rabies vaccine and mefloquine were accidentally given concurrently all led to good antirabies antibody responses (57).

Valproate

Mefloquine has been reported to oppose the effect of valproate (58).

- A 20-year-old woman with bilateral myoclonus and generalized tonic–clonic seizures which had been controlled with valproic acid was given 2 prophylactic doses of mefloquine and developed generalized tonic–clonic seizures.

The authors suggested a causal relation to the administration of mefloquine.

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Mefruside

See also Diuretics

General Information

Mefruside is a diuretic that is structurally related to furosemide, but with pharmacological actions more similar to those of the thiazide diuretics (SED-8, 488) (1). Its effects on serum lipids (SEDA-11, 196) and serum magnesium (SEDA-10, 188) are also similar to those of the thiazides.

Reference

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Meglitinides

General Information

The meglitinides bind with high affinity to a site, distinct from the sulfonylurea receptor site, on the ATP-sensitive potassium channels in pancreatic beta cells and stimulate insulin secretion. After binding, the ATP-dependent potassium channels are closed, reducing potassium efflux and depolarizing the cell membrane. The meglitinides do not have to be internalized in the membrane, in contrast to the sulfonylureas. This may explain their rapid onset of the action and the end of that action when glucose concentrations are falling. MgADP potentiates the effect in beta cells but not in cardiac cells (1), which may explain the reduced cardiovascular adverse effects of repaglinide in vivo. Meglitinide-stimulated insulin secretion depends on the glucose concentration; insulin secretion is not stimulated in vitro or in fasted animals. Nateglinide (and perhaps repaglinide) reduces the secretion of glycated insulin, which has poor activity, from islet cells; this may contribute to its hypoglycemic action (2).

Repaglinide (rINN) is a carbamoylmethyl benzoic acid derivative, which contains the non-sulfonylurea moiety of glibenclamide, and nateglinide (rINN) is a phenylalanine derivative. Nateglinide acts more quickly than repaglinide, and both act more quickly than sulfonylureas, which stimulate insulin secretion independent of blood glucose concentrations (3). It has been stated (4) that earlier studies (SEDA-22, 478) (SEDA-23, 462) (5) showed that the efficacy in lowering HbA_{1c} is almost equivalent for sulfonylureas and repaglinide and is slightly lower for nateglinide. When a lunch-time meal was omitted (SEDA-23, 462) patients taking glibenclamide had the lowest blood glucose concentrations, often within the hypoglycemic range, in contrast to patients taking repaglinide. Both drugs can cause hypoglycemia.

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Repaglinide has been reviewed (6–8). It stimulates glucose-dependent insulin secretion, amplifying insulin bursts without changing burst frequency, but it does not restore disrupted pulsatile secretion in type 2 diabetes (9). It is rapidly absorbed. It is metabolized by CYP3A4 in the liver and is 90% excreted in the feces. It has a half-life of 32 minutes. Its pharmacokinetics do not differ in young or older healthy persons (10). It can be given as monotherapy (11), and the effective dose is 0.5–8 mg/day, starting with 0.5 mg/day. It has to be given before each meal and can be adapted to irregular food intake or missed meals (12). When given preprandially it improves glucose control without increasing the risk of adverse effects (13). There were no differences in action in healthy younger or older volunteers (14). Repaglinide is short-acting and seems to be associated with significantly fewer episodes of serious hypoglycemia (15). In a short review of a number of clinical studies the following contraindications were reported (16):

- known hypersensitivity to repaglinide or one of the constituents of Novonorm®;
- type 1 diabetes;
- renal or hepatic impairment.

Observational studies

In eight patients with type 2 diabetes, nateglinide given 5 minutes before a meal reduced the postprandial blood glucose excursion by 64% (17). There were no attacks of hypoglycemia even with a dosage of 180 mg/day; other adverse effects were not mentioned.

Comparative studies

In 424 patients in a European multicenter, randomized, double-blind study for 1 year, two-thirds of the patients used repaglinide (0.5–4 mg tds) and the others glibenclamide (1.75–10.5 mg/day) (18). HbA_{1c} first fell but later increased. The same trends were seen in fasting blood glucose. There were no differences in hypoglycemia. A comparable American study of 576 patients (19) showed essentially the same result.

In a 14-week, double-blind, multicenter, randomized, parallel-group trial of repaglinide and glibenclamide in 118 patients with type 2 diabetes with borderline or poor control but still responsive to oral hypoglycemic drugs, HbA_{1c} fell at the same rate in both groups (20). The 2-hour postprandial blood glucose concentration was lower with repaglinide, but fasting and mean glucose concentrations did not differ. Repaglinide was associated with 20 hypoglycemic episodes in nine patients and glibenclamide with 15 episodes in nine patients. There were no serious adverse effects.

The effects of repaglinide and glibenclamide have been compared in 235 patients during Ramadan, when people eat two meals a day (21). Before Ramadan, they were adjusted to optimal treatment with thrice-daily repaglinide or once- or twice-daily glibenclamide. During Ramadan they took twice-daily repaglinide or glibenclamide. After Ramadan they continued to take the pre-Ramadan regimen for 4 weeks. Mid-day hypoglycemia (blood glucose below 4.5 mmol/l) occurred in 2.8% of those who took repaglinide and 7.9% of those who took glibenclamide. There were 19 events reported by 15 patients in the repaglinide group and 35 by 19 patients in the glibenclamide group. During Ramadan the numbers were nine events in seven patients and 12 events in nine patients respectively. Mean serum fructosamine concentrations fell by 17 and 7 μmol/l during Ramadan in those taking repaglinide and glibenclamide respectively.

Insulin lispro and repaglinide were given to seven patients with diabetes related to cystic fibrosis (22). They had normal fasting blood glucose and insulin concentrations, but postprandial glucose concentrations were substantially raised. Insulin lispro had a larger and more sustained effect in lowering postprandial glucose than repaglinide. However, the doses of lispro (0.1 U/kg) and repaglinide (1 mg) may not have been comparable.

Placebo-controlled studies

In a randomized, double-blind, placebo-controlled, multicenter study, 289 patients took nateglinide in doses of 30 mg ($n = 51$), 60 mg ($n = 58$), 120 mg ($n = 63$), and 180 mg ($n = 57$), or placebo ($n = 60$) before main meals (23). Meal-time insulin increased rapidly and meal-time glucose excursions were reduced. HbA_{1c} concentrations were significantly reduced after 12 weeks in those taking 60 mg and more. Fasting plasma glucose was only significantly reduced in those taking 120 mg. The drug was withdrawn in one patient taking 180 mg because of increased liver enzymes; at the next visit the enzymes were normal. There were mild symptoms of hypoglycemia, such as increased sweating, tremor, dizziness, weakness, and increased appetite. Blood glucose concentrations were between 2.7 and 3.3 mmol/l in three patients taking 120 mg/day.

Single doses of nateglinide 120 mg, repaglinide 0.5 and 2 mg, and placebo 10 minutes preprandially or 2 mg repaglinide 1 minute preprandially have been compared in 15 healthy volunteers (24). Nateglinide stimulated early insulin secretion more than repaglinide, and insulin concentrations returned more promptly to the preprandial values. The highest but slowest rise was seen with placebo. There were no episodes of hypoglycemia.

In a randomized, double-blind, placebo-controlled comparison of glibenclamide and nateglinide for 8 weeks in 152 patients, nateglinide produced higher postprandial insulin concentrations (25). Hypoglycemia and low blood glucose concentrations were more common with glibenclamide.

In a multicenter, double-blind, randomized, fixed-dose trial of placebo and repaglinide 1 mg and 4 mg for 24 weeks in 361 patients there were no episodes of severe hypoglycemia (26). Most patients withdrew from the placebo group because of hyperglycemia, hypoglycemia, erythematous rash, headache, diarrhea, fatigue, or abnormal vision. Adverse effects had about the same frequencies in the two groups.

Combinations of oral hypoglycemic drugs

The different mechanisms of action of the various classes of hypoglycemic drugs makes combined therapy feasible: the sulfonylureas and meglitinides stimulate insulin production by different mechanisms, the biguanides reduce glucose production by the liver and excretion from the

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liver, acarbose reduces the absorption of glucose from the gut, and the thiazolidinediones reduce insulin resistance in fat. It is not necessary to wait until the maximal dose of one drug has been reached before starting another. However, sulfonylureas and meglitinides should no longer be used when endogenous insulin production is minimal. Combinations of insulin with sulfonylureas or meglitinides should only be used while the patient is changing to insulin, except when long-acting insulin is given at night in order to give the islets a rest and to stimulate daytime insulin secretion.

Large studies of the effects of lifestyle changes, the effects of drugs in preventing or postponing the complications of diabetes, or the usefulness of various combinations are regularly published. The different mechanisms of action of the various classes give different metabolic effects and different adverse effects profiles (27). Comparative costs of the various therapies in the USA have been presented (28).

This subject has been reviewed in relation to combined oral therapy. In a systematic review of 63 studies with a duration of at least 3 months and involving at least 10 patients at the end of the study, and in which HbA_{1c} was reported, five different classes of oral drugs were almost equally effective in lowering blood glucose concentrations (29). HbA_{1c} was reduced by about 1–2% in all cases. Combination therapy gave additive effects. However, long-term vascular risk reduction was demonstrated only with sulfonylureas and metformin.

The adverse effects of combined drug therapy are attributable to the adverse effects of the single drugs. Increased adverse effects or new adverse effects in patients taking combinations have not been reported.

Meglitinides + biguanides

Patients with type 2 diabetes, with unsatisfactory control after taking metformin for 6 months, were randomized to metformin alone, repaglinide alone, or metformin + repaglinide (each 27 patients) (30). Combined therapy reduced HbA_{1c} after 3 months by 1.4% and fasting glucose by 2.2 mmol/l. Repaglinide alone or in combination with metformin increased insulin concentrations. The most common adverse effects were hypoglycemia, diarrhea, and headache. Gastrointestinal adverse effects were common in those taking metformin alone and body weight increased in both groups taking repaglinide.

In 12 patients with type 2 diabetes, a combination of nateglinide 120 mg or placebo with metformin 500 mg before each meal on two separate days was well tolerated (31). One patient taking nateglinide had a headache. One patient was withdrawn because of a myocardial infarction and had multivessel coronary artery disease on catheterization.

In a prospective, randomized, double-blind, placebo-controlled study for 24 weeks, 701 patients took nateglinide 120 mg before the three main meals, or metformin 500 mg tds, or the combination of the two, or placebo (32). The most frequent adverse effect was hypoglycemia, and it was most common in the combination group. There were no differences between those who took nateglinide only or metformin only and there were no episodes of serious hypoglycemia. Diarrhea was more frequent in those taking metformin or the combination, but infection, nausea, headache, and abdominal pain were comparable in the two groups.

Of 82 patients insufficiently controlled by metformin, 27 continued to take metformin with placebo, 28 took titrated repaglinide with placebo, and 27 took metformin with titrated repaglinide for 4–5 months (33). There were no serious adverse effects. Nine patients taking metformin + repaglinide reported 30 hypoglycemic events and three patients taking repaglinide reported nine events.

Meglitinides + sulfonylureas

Glipizide, nateglinide, and their combination have been compared in a double-blind, randomized, placebo-controlled study in 20 patients with type 2 diabetes not requiring insulin (34). Before a standardized breakfast, they took glipizide 10 mg, nateglinide 120 mg, both, or placebo; 4 hours after the meal, blood glucose concentrations were significantly higher after nateglinide, but peak and integrated glucose concentrations did not differ. Integrated insulin concentrations were higher with glipizide. There were three episodes of hypoglycemia in the glipizide alone group and three in the combined group; three required treatment with glucose.

Meglitinides + thiazolidinediones

In 585 patients in a double-blind, randomized, placebo-controlled, multicenter study lasting 16 weeks nateglinide 40 mg tds alone, troglitazone 200 mg/day alone, and the combination were compared (35). The combination was most effective in lowering HbA_{1c}. The most frequent adverse effects were mild hypoglycemia, most often in the combination group. Three patients (two in the combination group and one in the troglitazone alone group) withdrew because of hypoglycemia. Most of the withdrawals were related to increased liver enzymes and weight gain, known adverse effects of troglitazone. Twelve patients withdrew because of predefined changes from baseline (transaminases more than 200% and alkaline phosphatase and bilirubin more than 100% over baseline); seven were taking troglitazone alone, four combined therapy, and one placebo.

In an open trial, 256 patients with type 2 diabetes with inadequate hypoglycemic control (HbA_{1c} over 7.0% during previous therapy) took repaglinide (0.5–4 mg at meals), troglitazone (200–600 mg/day), or a combination of the two for 22 weeks (36). Combination therapy was most effective. Repaglinide only was more effective than troglitazone only. Mean body weight increased in both groups. Serious adverse events were chest pain, cerebrovascular disorders, malignancies, dysrhythmias, electrocardiographic changes suggesting myocardial infarction, and increased aspartate transaminase activity (in one patient taking troglitazone). The serious adverse effects were similar in the different groups. Hypoglycemia occurred in 4% of the patients taking combined therapy, in 16% of those taking troglitazone only, and in 27% of those taking repaglinide only; none needed assistance. There were changes in liver function tests in three patients in the combined group and in one patient each in the two other groups; the drugs were withdrawn in the

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affected patients and liver function normalized. There were no differences in adverse effects in the different groups. Hypoglycemia occurred in 11 patients taking repaglinide, in seven taking combination therapy, and in one taking troglitazone. Anemia occurred in four patients taking combined therapy and in two taking troglitazone only.

Insulin + meglitinides

In 80 patients taking metformin 850 or 1000 mg tds plus NPH insulin at bedtime, metformin was withdrawn and repaglinide 4 mg tds added in half of the patients for 16 weeks (37). In the repaglinide group the dose of insulin increased slightly and weight gain was 1.8 kg more. Mild hypoglycemia occurred more often in the metformin group; nightly episodes of hypoglycemia occurred only with repaglinide. One patient taking repaglinide had a myocardial infarction, and one had three separate hospitalizations for chest pain (myocardial infarction was excluded). No specific data were presented about gastrointestinal adverse effects or infections.

General adverse effects

The most frequent adverse effect of meglitinides is hypoglycemia. The overall incidence of hypoglycemia with repaglinide is similar to that reported with sulfonylureas, but the incidence of serious hypoglycemia is lower. Other adverse effects are respiratory tract infections and headache. Cardiovascular events and cardiovascular mortality are not different from those in users of sulfonylureas. In Europe, repaglinide is contraindicated in patients with severe liver dysfunction and it is not recommended in people over 75 years old; in America the advice is to use repaglinide cautiously in patients with impaired liver function and there is no restriction on its use in elderly patients. In renal impairment, the half-life of repaglinide is prolonged. Reasons for withdrawal are hyperglycemia, hypoglycemia, and myocardial infarction (38).

Organs and Systems

Metabolism

Repaglinide has a short duration of action and improves postprandial hyperglycemia, a potential risk factor for cardiovascular changes (39). In a double-blind, multiple-dose, parallel-group study repaglinide stimulated mealtime insulin secretion (40). Bouts of hypoglycemia were equally frequent with placebo and repaglinide. When repaglinide was added to NPH monotherapy in patients with HbA_{1c} over 7.1% for 3 months, 38% of the patients had an HbA_{1c} below 7.1% (41). The incidence of hypoglycemia did not change.

When glipizide was compared with repaglinide in 75 patients there were no major hypoglycemic events; minor events were the same in both groups, but after the start of therapy the events occurred much later with repaglinide than glipizide (42).

The effect of a missed meal during repaglinide and glibenclamide therapy has been compared in 83 randomized patients (43). During two meals there were six separate hypoglycemic events in those taking glibenclamide. Blood glucose fell from 4.3 mmol/l to 3.4 mmol/l in those taking glibenclamide when lunch was omitted. There were no changes in blood glucose in those taking repaglinide.

Factitious hypoglycemia has been attributed to repaglinide in an 18-year-old man who had bouts of hypoglycemia for 2 months (44). After glucose administration he recovered promptly and was sent home, but the next night his glucose was 1 mmol/l with high concentrations of insulin (395 pmol/l), C-peptide (2966 pmol/l), and proinsulin (81 pmol/l). The plasma concentrations of repaglinide in three specimens were 4.8–21 ng/ml. Metformin was below the detection limit. He finally admitted to taking repaglinide 4 mg regularly.

Immunologic

- A 62-year-old woman with type 2 diabetes, hypertension, and chronic hepatitis C virus infection developed palpable purpura over her legs and buttocks 3 weeks after starting to take repaglinide 500 mg qds (45). The purpura ulcerated and became infected. Repaglinide was withdrawn and the purpura resolved. A biopsy showed leukocytoclastic vasculitis.

Repaglinide, which is metabolized in the liver, is cleared more slowly in people with liver disease, and hepatitis C may have played a part in this case. Although hepatitis C can cause a leukocytoclastic vasculitis, the clinical correlation and the rapid disappearance of the purpura after the withdrawal of repaglinide makes it likely that this was an adverse effect of the drug. Caution with repaglinide in liver disease is important.

Susceptibility Factors

Renal disease

In renal impairment the half-life of repaglinide is prolonged. Patients with severe renal impairment (creatinine clearance 20–40 ml/minute) had excess accumulation of the drug after taking multiple doses for 5 days (46).

In 235 patients with normal renal function or moderate to severe renal impairment switched from their original therapy to repaglinide (titrated to 0.5–4 mg tds within 4 weeks and continued for 3 months), the number of episodes of hypoglycemia increased with increasing severity of renal impairment during the run-in period but not during treatment (47). The final dose tended to be lower in patients with severe renal impairment. Although the concentrations of repaglinide in the patients with renal impairment were higher, they did not exceed the effective concentrations in people without renal impairment.

Patients with mild to moderate impairment can be treated with repaglinide. However, patients with severe renal impairment have other problems, and it is wise not to use repaglinide in patients with severe renal disease, or at least to adjust the dosage (46).

Hepatic disease

The clearance of repaglinide is reduced and the half-life prolonged (2.5-fold) in patients with chronic liver disease (48).

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Drug–Drug Interactions

Clarithromycin

Clarithromycin, an inhibitor of CYP3A4, increases the plasma concentrations and the effect of repaglinide; this can enhance the blood glucose lowering effect and increase the risk of hypoglycemia (49).

Gemfibrozil

In 12 healthy subjects gemfibrozil raised the AUC of repaglinide 8-fold and itraconazole raised it 1.4-fold; however, the combination increased it nearly 20-fold (50).

Ketoconazole

In healthy subjects, ketoconazole increased mean AUC of repaglinide by 15% and mean C_{max} by 7% (51).

Nifedipine

Concomitant treatment with the CYP3A4 substrate nifedipine altered the mean AUC and mean C_{max} of repaglinide by 11 and 3% respectively (51).

Oral contraceptives

Concomitant treatment with ethinylestradiol + levonorgestrel altered the mean AUC and mean C_{max} of repaglinide by 1 and 17% respectively (51).

Rifampicin

Rifampicin 600 mg reduced the AUC of repaglinide by 57% and shortened its half-life from 1.5 to 1.1 hours in nine healthy volunteers after 5 days (52). The effect may even be greater when rifampicin is used for a longer period. In another study in healthy volunteers, rifampicin reduced the mean AUC of repaglinide by 31% and the mean C_{max} by 26%.

Simvastatin

Concomitant treatment with the CYP3A4 substrate simvastatin altered the mean AUC and mean C_{max} of repaglinide by 2 and 27% respectively (51).

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Melarsoprol

General Information

Melarsoprol is a trivalent arsenical with activity against East African and West African trypanosomiasis. It is the drug of choice in the case of *Trypanosoma rhodesiense* infection with nervous system involvement (stage II disease) and in stage I patients refractory or intolerant to suramin and pentamidine. Melarsoprol administered intravenously can cause a reactive encephalopathy, with a clinical picture consisting of high fever, headache, tremor, convulsions, and on occasion coma and death. The incidence of arsenic encephalopathy varies from 3 to 18% in various series (SEDA-12, 708) (1).

In a case-control study of physical growth, sexual maturity, and academic performance in 100 young subjects (aged 6–20 years) with and without a past history of sleeping sickness, melarsoprol-treated patients weighed less, were shorter, and had sexual maturity ratings significantly different from the corresponding controls (2).

The efficacy and safety of two regimens of melarsoprol have been compared in patients with nervous system involvement from *Trypanosoma brucei gambiense*: a conventional regimen lasting 26 days, starting at 1.2 mg/kg and rising to 3.6 mg/kg ($n = 259$), and a regimen of 2.2 mg/kg for 10 days ($n = 250$) (3). Parasitological cure

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24 hours after treatment was 100% in both groups. Disappointingly, the rates of encephalopathy were no better (in fact marginally worse) with the new schedule, despite using 30% less drug overall, and there were six drug-related deaths in each arm. However, the new schedule is quicker and cheaper, and treatment deviations were significantly fewer in the new schedule arm. In a further detailed prospective study of the drug in eight patients with advanced leukaemia, three developed seizures attributable to the drug at doses broadly comparable to those used in trypanosomiasis.

In 42 patients with late-stage *Trypanosoma brucei gambiense* trypanosomiasis, who relapsed after initial treatment with melarsoprol, a sequential combination of intravenous eflornithine (100 mg/kg every 6 hours for 4 days) followed by three daily injections of melarsoprol (3.6 mg/kg, up to 180 mg) was used (4). They were followed for 24 months. In one case the administration of eflornithine had to be interrupted for 48 hours because of convulsions, but treatment was then resumed without recurrence. Other adverse effects during treatment were abdominal pain or vomiting ($n = 4$ each), diarrhea ($n = 1$), and loss of hearing ($n = 1$). Two patients died during treatment:

- A 37-year-old man died of an acute cholera-like syndrome, with severe diarrhea, vomiting, and dehydration, after the last dose of eflornithine but before receiving his first dose of melarsoprol;
- A 34-year-old man died of an unknown cause after having received all 16 doses of eflornithine as well as the first injection of melarsoprol.

In a randomized trial in 500 patients infected with *Trypanosoma brucei gambiense* treated with 10 daily consecutive doses of melarsoprol 2.2 mg/kg, the adverse effects were: encephalopathic syndrome 5.6%, death from encephalopathy 2.4%, polyneuropathy less than 1%, severe bullous dermatitis 1.2%, severe maculopapular rash 3.2%, severe pruritus 3.2% (5). Milder reactions were fever, headache, and diarrhea.

Organs and Systems

Nervous system

Melarsoprol given intravenously in patients with trypanosomiasis can cause a peripheral neuropathy within 2–5 weeks (SEDA-14, 243). It also causes a reactive arsenical encephalopathy in 3–5% of patients with trypanosomiasis (SEDA-13, 834) (6).

- Myalgia, distal paresthesia, and rapidly progressive weakness in all limbs developed in a young woman treated for 38 days with melarsoprol; there was massive distal Wallerian degeneration in the peripheral nerve, and abnormalities in the dorsal ganglia and spinal cord. Very high concentrations of arsenic were found in the spinal cord. All the findings were typical of toxic arsenic accumulation; in this case, renal dysfunction was probably at the root of the arsenic poisoning (SEDA-16, 316).

In patients with *Trypanosoma gambiense* sleeping sickness, the incidence of drug-induced encephalopathy was increased in patients with trypanosomes present in the nervous system, in patients with high CSF lymphocyte counts, and among those in whom no trypanosomes were found in either the blood or a lymph node aspirate. The authors of this report considered that aggressive therapeutic schemes may result in greater toxicity, especially in patients with impaired blood–brain barrier (SEDA-16, 316). Without data on dosage, renal function, and cerebral involvement before therapy it is impossible to assess this conclusion.

In a large-scale review it was estimated that encephalopathic syndromes occur in 5–10% of patients, and that 10–50% of these die as a result (7).

Encephalopathic syndromes complicating treatment of stage II human African trypanosomiasis with melarsoprol in 588 patients have been reviewed (8). The overall rate of encephalopathy was 5.8% and presented in three ways: coma, convulsions, and psychotic reactions. The overall death rate was 38%. Comatose patients had a death rate of 52% and were commonly co-infected with malaria (14/16). Symptoms during treatment of fever (RR = 11.5), headache (RR = 2.5), bullous eruptions (RR = 4.5), and systolic hypotension (RR = 2.6) were associated with an increased risk of encephalopathic syndromes, especially coma.

In 56 patients with African trypanosomiasis, one treated with melarsoprol (total dose 26 mg/kg) developed a reactive arsenical encephalopathy (9).

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Melatonin

General Information

Melatonin (*N*-acetyl-5-methoxytryptamine) is a neurohormone secreted by the pineal gland from the amino acid precursor L-tryptophan. Its endogenous secretion is photosensitive and has a circadian rhythm—plasma melatonin concentrations are highest at night in both diurnal and nocturnal animals, and fall with age (1). The nocturnal melatonin peak coincides with a drop in body temperature and increased sleepiness in healthy humans. Oral melatonin has a short half-life (30–50 minutes) and extensive first-pass metabolism. Its clearance is reduced in severe liver disease (2).

Uses

Melatonin has been promoted as a treatment for conditions ranging from jet lag to cancer (1,3–5) and is sometimes used for sleep induction (1). Because melatonin is present in small amounts in some foods, it is licensed as a nutritional supplement in the USA.

General adverse effects

Acute exogenous administration of melatonin causes sedation, fatigue, self-reported vigor, confusion, and a reduction in body temperature in healthy subjects. The effects of chronic treatment have not been studied, and adverse effects have not been systematically reported.

Timing is critical for melatonin to be effective: if it is given at the wrong time for sleep disorders or jet lag, it can cause increased daytime sleepiness (5,6) and worsened mental performance (7). Drowsiness and a small fall in body temperature are commonly reported effects (8), particularly after daytime administration, when endogenous concentrations of melatonin are low.

Organs and Systems

Cardiovascular

There was an increase in blood pressure throughout 24 hours in a double-blind, placebo-controlled, crossover study in 47 hypertensive patients who were also taking nifedipine (9). This finding differs from other studies in which melatonin had a mild hypotensive effect (10) and may indicate an interaction between melatonin and nifedipine. Tachycardia, chest pain, and cardiac dysrhythmias have also been reported, although the relation to melatonin was not clearly established (5).

Nervous system

Four of six children with pre-existing severe neurological disorders had increased seizure activity within 2 weeks of starting oral melatonin 5 mg at bedtime (11). Seizure frequency returned to baseline after treatment was stopped, and increased again after rechallenge with melatonin 1 mg. A convulsion during melatonin treatment, which recurred when medication was continued, has been reported to the WHO database but not published (5). Headache, which recovered after melatonin was withdrawn, has also been reported in a few cases (5).

Dyskinesia and akathisia have been reported after withdrawal of long-term melatonin (12).

- A 22-year-old woman of Ashkenazi origin, with spastic diplegia resulting from cerebral palsy and severe mental retardation, had insomnia for 6 years. She had taken melatonin 5 mg each night at 8 p.m. for the past year, with a good response. However, 1 week after melatonin was stopped, because of repeated vomiting, she gradually developed involuntary lip-smacking movements and tongue protrusion, with extreme restlessness, moaning, and shouting. These symptoms continued for 2 weeks, accompanied by marked worsening of insomnia. She was restless, could not sit still, and was shouting, moaning, and grunting. Melatonin was reintroduced in gradually increasing doses, and 2 days after a dose of 5 mg was reached, the involuntary movements disappeared and her agitated state and insomnia improved. A month later, another episode of abdominal pain and vomiting made her discontinue melatonin again. Within 2 days she developed identical involuntary lip and tongue movements and akathisia. Melatonin 5 mg was re-administered and all her symptoms disappeared by the next day. No antiemetic drugs were given during these episodes.

This case raises an important question regarding the dopamine-blocking effect of melatonin. Like dopamine receptor antagonists, melatonin should be used with care, because of the risk of tardive dyskinesia, which has serious morbidity and a low remission rate. Melatonin should be used with special caution in patients with organic brain damage.

Sensory systems

- Loss of visual acuity, reduced color vision, and altered light adaptation developed in a 42-year-old woman 2 weeks after she started to take a high protein diet and melatonin 1 mg/day (13). She had also been taking sertraline for the past 4 years. Her vision improved within 2 months of stopping the melatonin and the high protein diet.

This patient's retinal melatonin concentration may have been boosted by increased serotonin (a melatonin precursor) from the effect of sertraline, the high protein intake, and the exogenous melatonin.

Retinal damage has been briefly reported as an adverse effect of melatonin (8).

Psychological, psychiatric

A severely depressed woman developed a mixed affective state after taking melatonin for 7 days in a clinical trial (14). Confusion, hallucinations, and paranoia temporally related to melatonin have also been described (5).

Endocrine

There was suppression of endogenous melatonin secretion in two of five patients with bipolar disorder after 12 weeks of treatment with high-dose melatonin (10 mg/day) (15).

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Gynecomastia has been attributed to melatonin (8,16).

- A 56-year-old man complained of painful asymmetrical breast enlargement, gradually developing over 3 months (16). He had had amyotrophic lateral sclerosis for 3 years and had taken riluzole 50 mg bd for 2 years and melatonin for 1.5 years (1 mg/day during the first year then gradually increasing to 2 mg/day). He had bilateral painful gynecomastia and homogeneously enlarged breasts. There was no galactorrhea. There were no signs or symptoms of other endocrine dysfunction. Withdrawal of melatonin resulted in complete regression of the gynecomastia within a few weeks.

This is a warning against the uncontrolled use of apparently innocuous substances. The absence of adverse effects in healthy people taking melatonin for various reasons does not mean complete safety, particularly in people who are unwell.

Metabolism

Impaired insulin-dependent glucose utilization occurred in a double-blind study of postmenopausal women given melatonin 1 mg in the morning (17). The authors also cited isolated reports of increased blood glucose in healthy individuals and in two men with Parkinson's disease taking melatonin.

Liver

- Autoimmune hepatitis was diagnosed in a previously healthy, 39-year-old woman 4 weeks after she started to take melatonin 3 mg at bedtime (18).

It is unclear whether this was a direct hepatotoxic effect of melatonin (or a contaminant), or if hepatitis was caused indirectly by an immunomodulatory mechanism.

Skin

Vesicular plaques and erosions developed on the penis in two men after they took melatonin for jet lag: one man had two such episodes 4 months apart (19). The lesions resolved within 10 days without any sequelae, and recurred within 8 hours of rechallenge.

Reproductive system

Melatonin affects reproduction in seasonally breeding animals. In humans, findings of increased endogenous melatonin in hypogonadism and low concentrations in precocious puberty imply an interaction between melatonin and gonadotropins; however, data on the effects of exogenous melatonin are limited (1). In a randomized study in 16 women, melatonin enhanced LH and FSH responses to submaximal GnRH stimuli in the follicular but not the luteal phase of the menstrual cycle (20).

A very high dose of melatonin (300 mg) partially inhibited ovulation in healthy young women: norethisterone enhanced the effect (21).

Immunologic

There has been a single report of a subject in a controlled trial of melatonin who had difficulty in swallowing and breathing within 20 minutes of taking melatonin 0.5 mg. The symptoms resolved without treatment after 45 minutes and recurred in a milder form after rechallenge (22).

Long-Term Effects

Drug withdrawal

There was suppression of endogenous melatonin secretion in two of five patients with bipolar disorder after 12 weeks of treatment with high-dose melatonin (10 mg/day) (15). One woman developed an unentrained sleep–wake cycle after melatonin was withdrawn (not previously a feature of her illness), which persisted for several months.

Involuntary movements of the lip and tongue, restlessness, and insomnia developed twice when chronic melatonin therapy was abruptly withdrawn in a young woman with cerebral palsy: these symptoms resolved when melatonin was restarted, but did not recur with gradual withdrawal over 2 months (12). This again suggests that endogenous melatonin secretion is suppressed after chronic use.

Drug Administration

Drug contamination

The reliability and consistency of commercial melatonin has been questioned (3). One group analysed three commercial melatonin formulations and identified analogues of the contaminant of L-tryptophan compounds implicated in an epidemic of eosinophilia–myalgia syndrome in the 1980s (23). There have been no reports of this condition associated with melatonin consumption, but food supplements are not required to comply with the same manufacturing and monitoring quality control standards as drugs.

Drug overdose

Melatonin overdose has been reported in three patients, all of whom were also taking psychotropic drugs. Drug interactions with antidepressants may have played a part in the resulting symptoms, which were not reported in cancer trials using higher doses of melatonin (1).

- A 73-year-old woman developed an acute psychosis after taking melatonin 30 mg as well as her usual fluoxetine (24).
- A 14-year-old girl became drowsy and dizzy and complained of blurred vision after taking melatonin 24– 36 mg as well as her usual trazodone and paroxetine (25).
- A 66-year old man became lethargic, confused, and disoriented after taking melatonin 24 mg with his usual amitriptyline and chlordiazepoxide (26).

All three patients recovered fully within 24 hours without specific treatment.

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Drug–Drug Interactions

SSRIs

Fluvoxamine increases the systemic availability of oral melatonin, probably by reducing its first-pass clearance (27). In a crossover study in seven healthy subjects, serum melatonin concentrations were increased by fluvoxamine but not citalopram (28). In another study fluoxetine, paroxetine, citalopram, imipramine, and desipramine did not affect the biotransformation of melatonin at therapeutic concentrations in vitro (29).

Warfarin

There have been several reports of altered prothrombin time in patients taking warfarin and melatonin. In some cases bleeding or purpura was the presenting symptom, despite a reduced prothrombin time (5).

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Meliaceae

See also Herbal medicines

General Information

The genera in the family of Meliaceae (Table 1) include mangrove and different types of mahogany.

Azadirachta indica

Azadirachta indica (bead tree, pride of China, margosa, neem or nim tree, holy tree, indiar, lilac tree) contains a variety of steroids, sesquiterpenoids, ester terpenoids, tetranortriterpenoids, and triterpenoids.

Adverse effects

Margosa oil, a long-chain fatty acid that is extracted from the seeds of the neem tree, has been implicated as a

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Table 1 The genera of Meliaceae

Aglaia (Chinese rice flower)
Azadirachta (azadirachta)
Carapa (carapa)
Cedrela (cedrela)
Dysoxylum (mahogany)
Guarea (guarea)
Khaya (African mahogany)
Lansium (lansium)
Melia (melia)
Swietenia (mahogany)
Toona (redcedar)
Trichilia (trichilia)
Xylocarpus (mangrove)

potential cause of Reye's syndrome in 13 infants who developed vomiting, drowsiness, metabolic acidosis, a polymorphonuclear leukocytosis, and encephalopathy within hours of taking margosa oil; liver biopsy in one infant showed pronounced fatty infiltration of the liver (1). In experimental animals given margosa oil there was also fatty infiltration of the proximal renal tubules and cerebral edema. Electron microscopy showed mitochondrial damage.

Reference

1. Sinniah D, Baskaran G. Margosa oil poisoning as a cause of Reye's syndrome. Lancet 1981;1(8218):487–9.

Melitracen

See also Tricyclic antidepressants

General Information

Melitracen is structurally and pharmacologically related to imipramine, with two methyl groups attached to the central ring. It has similar efficacy to amitriptyline, with a somewhat more rapid effect and similar adverse effects (1).

Reference

1. Francesconi G, LoCascio A, Mellina S, et al. Controlled comparison of melitracen and amitriptyline in depressed patients. Curr Ther Res Clin Exp 1976;20:529.

Meloxicam

See also Non-steroidal anti-inflammatory drugs

General Information

Meloxicam, a COX-2 inhibitor, has been marketed in some countries and promoted as having an improved safety profile over current NSAIDs. It has a long half-life, is highly protein-bound, is metabolized to inactive compounds, and is excreted in the urine and feces. Neither hepatic insufficiency nor moderate renal dysfunction affects its pharmacokinetics, but in one study meloxicam plasma concentrations were 26% higher in patients over 65 than in younger patients.

Changes have been made to the Summary of Product Characteristics by the manufacturers of meloxicam (1), in agreement with the type of adverse drug reaction reports received by the Committee on Safety of Medicine in the UK. Warnings about gastrointestinal reactions (perforation, ulceration, and/or bleeding) and skin reactions (including erythema multiforme and Stevens–Johnson syndrome) have been strengthened (2).

Organs and Systems

Nervous system

About 7% of patients have dizziness and headache (3).

Gastrointestinal

Gastrointestinal adverse effects were the most frequently reported (in about 15–20% of patients), but their incidence was lower with meloxicam than with piroxicam, naproxen, and diclofenac in long-term double-blind studies. They were more frequent with a dosage of 15 mg/day than with 7.5 mg/day, were judged to be severe in 1.7%, and led to withdrawal in about 4% of patients. The most frequent symptoms were abdominal pain, dyspepsia, eructation, nausea, and vomiting. Upper gastrointestinal perforation, ulceration, and bleeding occurred rarely with meloxicam; the incidence was dose related and lower than with the comparators (4,5). A double-blind endoscopic microbleeding comparison of meloxicam and piroxicam in healthy volunteers showed better gastrointestinal tolerability with meloxicam. Fecal blood loss and endoscopy scores were higher in piroxicam-treated patients, and six piroxicam volunteers versus one treated with meloxicam withdrew because of severe gastrointestinal toxicity; colitis was reported in one case (6). In a few patients meloxicam suppositories can cause abdominal pain and rectal bleeding.

A large prospective comparison of meloxicam 7.5 mg/day with piroxicam 20 mg/day for a median of 28 days suggested that meloxicam has a lower propensity to cause gastroduodenal adverse events. However, serious gastrointestinal events (that is, ulceration, perforation, or bleeding), albeit rare, had similar frequencies in meloxicam and piroxicam recipients, and furthermore the difference in the incidence of adverse gastrointestinal events, although statistically significant, was clinically less relevant (7). Reports received by the Swedish Adverse Drug Reaction Advisory Committee (SADRAC) have suggested that meloxicam has a similar adverse drug reactions profile to other NSAIDs (8) and reports of gastrointestinal hemorrhage have started to appear (9).

Colitis has been described as an adverse effect of meloxicam (SEDA-20, 94).

- Ischemic colitis occurred in a 49-year-old woman 10 days after she started to take meloxicam 15 mg/day for osteoarthritis; meloxicam was withdrawn and her symptoms completely resolved within 1 week (10).

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Although meloxicam is considered to be a preferential COX-2 inhibitor, its safety profile is not much different from other traditional NSAIDs, especially in high doses (11).

Liver

Acute cytolytic hepatitis has been described in a 46-year-old woman who took meloxicam for 4 days (12).

Urinary tract

Deterioration in renal function, reversible on withdrawal, was rare (0.4%) (3).

Skin

Rash, pruritus, and other skin problems occurred in about 6.5% of patients (3).

The manufacturers of meloxicam have recently included a warning about the possible occurrence of life-threatening skin reactions in the Summary of Product Characteristics (SEDA-23, 120).

- Erythema multiforme has been reported in a 19-year-old man 8 days after he started to take meloxicam for tendonitis; withdrawal and therapy with corticosteroids resulted in complete recovery (13).

Immunologic

Meloxicam may be relatively safe when given to patients with NSAID-induced urticaria/angioedema (14,15). Of 148 NSAID-sensitive subjects with an unequivocal history of urticaria with or without angioedema, who were challenged with increasing oral doses of meloxicam (1–7 mg/day) in a single-blind placebo-controlled trial, only two had a positive test (urticaria in one and urticaria/angioedema in the other); both had chronic idiopathic urticaria (16).

Drug Administration

Drug administration route

Local tolerability with intramuscular administration is reportedly good (17). Serum creatine kinase activity can increase slightly. Gastrointestinal disorders, central nervous system adverse events, and skin rashes have been reported with intramuscular administration.

Drug–Drug Interactions

Methotrexate

In 13 patients with rheumatoid arthritis, oral meloxicam for 1 week had no effect on the pharmacokinetics of a single dose of intravenous methotrexate 15 mg (18).

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Melphalan

See also Cytostatic and immunosuppressant drugs

General Information

Melphalan (L-phenylalanine mustard) is an alkylating agent that has been used to treat a wide variety of solid malignancies, including cancers of the breast and ovary, and multiple myeloma. Intravenous melphalan has been used to treat rhabdomyosarcoma, lymphomas, multiple myeloma, and neuroblastoma (1).

The adverse effects of high-dose intravenous melphalan have been reviewed (2). Two patients who received less than 100 mg/m^2 recovered from marrow aplasia within 3 weeks without major complications. A third patient died 6 days after injection of 290 mg/m^2, probably because of a cardiac dysrhythmia before complete marrow failure had become established. After intravenous administration of more than 125 mg/m^2, gastrointestinal adverse effects, such as hemorrhagic diarrhea, or bowel perforation, can occur. These, together with reduced ADH secretion and electrolyte disturbances are the predominant clinical problems and the reasons for early death before the occurrence of infectious or bleeding complications from prolonged marrow aplasia.

Organs and Systems

Respiratory

Melphalan can cause an acute interstitial pneumonia with hypoxemia (3). This is probably due to a hypersensitivity mechanism and should be distinguished from fibrosing pneumonitis, which melphalan can also cause (4).

Fatal pulmonary fibrosis and atypical epithelial proliferation has been reported in patients with multiple myeloma treated with melphalan (4).

Urinary tract

Acute renal insufficiency has been attributed to melphalan in a patient with third stage ovarian cancer (5).

Reproductive system

Primary ovarian failure has been recognized in adults after intermittent low-dose melphalan, and has also been reported in three adolescents after high-dose melphalan (6).

Drug–Drug Interactions

Busulfan

The possibility that melphalan and busulfan may cause additive lung damage has been discussed in the light of a 59-year-old patient with chronic myeloid leukemia who developed severe interstitial lung fibrosis after short-term sequential treatment with the two drugs (7).

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Memantine

General Information

Memantine is an amantadine derivative that has been studied in patients with Parkinson's disease. Its adverse effects include agitation, restlessness, insomnia, pronounced delirious states, and muscular hypotonia. All were reversible after dosage reduction or withdrawal.

Organs and Systems

Psychological, psychiatric

A toxic psychosis was reported in two patients taking memantine (1).

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Meningococcal vaccine

See also Vaccines

General Information

Meningococcal vaccines have been comprehensively reviewed, distinguishing conventional polysaccharide vaccines, non-polysaccharide group B meningococcal vaccines, and conjugated meningococcal vaccines (1).

Reports of clinical trials in children, adults, and asplenic individuals have been provided (2) and surveyed (SEDA-11, 288) (SEDA-16, 379) (SEDA-17, 370) (SED-12, 813).

Polysaccharide vaccines

Polysaccharide meningococcal vaccines in various combinations against meningococcal disease caused by meningococci of groups A, C, W135, and Y have been commercially available for many years. Studies mostly using a bivalent serogroup A + C vaccine carried out in about 15 countries, including some millions of people, have shown efficacy of 61–99%. Meningococcal group A vaccine is more immunogenic than group C vaccine in infants and small children. However, infants below 6 months of age produce a weak response, and meningococcal group C vaccine should not be used before the age of 2 years. Meningococcal group B polysaccharide vaccine is poorly immunogenic in humans and is therefore not available commercially.

Adverse reactions are infrequent and mild, consisting of local soreness or localized erythema at the injection site, and systemic reactions (transient fever, headache, fatigue), lasting 1–2 days (3,4). With the quadrivalent vaccine used in Canada, fever was reported in less than 1%, local reactions in 6.3%, and rash in 1.6% among those aged 11 years or older. Local reactions were also the most reported adverse effect in other reports.

Non-polysaccharide group B meningococcal vaccines

Considering the poor immunogenicity of polysaccharide group B vaccines, different vaccines have been developed—a Norwegian outer membrane complex group B vaccine and a Cuban vaccine in which the group C polysaccharide is added to a mixture of high molecular weight B outer membrane proteins and proteoliposomes. Both vaccines have been used in clinical trials, mainly in Latin America, but more conclusive studies with these two products are awaited. Adverse reactions with the Cuban vaccine have been studied. Among 16 700 vaccinees, mostly older than 4 years, local reactions were observed in 62%, and systemic reactions in 4.3%.

From studies in 370 infants and children and 171 adults aged 18–30 years, who received three doses of outer membrane protein meningococcal vaccine developed in either Cuba or Norway or a control vaccine (Hib vaccine), the vaccines are promising candidates for the control of epidemics caused by homologous epidemic strains (5). However, the vaccines would not confer protection during a heterologous epidemic. All vaccinees had more pain, induration, and erythema at the injection site than did Hib vaccine recipients; there were no serious adverse events, and 95% of individuals who reported symptoms said that the symptoms did not interfere with their normal activities.

A genetically engineered vaccine containing six meningococcal class I (PorA) outer membrane proteins, representing 80% of group B meningococcal strains prevalent in the UK, has been assessed in 103 infants who received the vaccine at ages 2, 3, and 4 months with routine infant immunization, and a fourth dose at 12–18 months (6). The vaccine was well tolerated, and after the fourth dose there were larger bactericidal responses to all six strains.

Conjugated meningococcal vaccines

Success with the protein-conjugate formulations of *Hemophilus influenzae* vaccines has facilitated research and development on conjugated meningococcal vaccines with preference for monovalent group C or bivalent group A/group C vaccines. Conjugated meningococcal vaccines of serogroup C made by various manufacturers were first licensed in 1999 in the UK and then (at the end of 2000) in many other countries, including some other member states of the European Union (Belgium, Germany, Greece, Luxembourg, Ireland, Portugal, Spain).

Field trials in the UK and the Gambia have shown immunogenicity not only in adults but also in toddlers and even infants. Except for local tenderness in 30–75% of vaccinees, no conjugate vaccine evaluated to date has been associated with significant adverse effects (1).

Vaccine containing oligosaccharides derived from group C meningococcal capsular polysaccharide coupled to CRM197, a non-toxic mutant diphtheria toxin (manufactured by Wyeth Lederle Vaccines and Pediatrics, Pearl River, NY) was given to 114 infants at 2, 3, and 4 months of age; 57 received a vaccine containing 2 μg of oligosaccharide and 5 μg of CRM197, and 57 received a vaccine containing 10 μg of oligosaccharide and 25 μg of CRM197 (7). The infants received DTP and Hib vaccine at the same time. In each group, 25 infants received a polysaccharide vaccine booster at median age of 83 weeks. Antibody concentrations required for protection are estimated to be 1–2 μg/ml. All the infants achieved a concentration of 2 μg/ml by age 4 months after two doses of conjugated meningococcal vaccine, and concentrations of bactericidal antibodies were much higher than after meningococcal polysaccharide vaccines. Antibody concentrations fell significantly by age 14 months. After boosting with polysaccharide vaccine all the children achieved antibody concentrations over 2 μg/ml. Local and systemic reactions were rare after meningococcal conjugate vaccines and were significantly less common at the site of DTP/Hib immunization for all three doses. The high-dose cohort had more systemic reactions than the low-dose cohort (Table 1). One infant required hospitalization for a viral illness soon after the second injection.

The results of a randomized, double-blind trial of safety, immunogenicity, and induction of immunological memory in 182 healthy infants has been published (8). The infants received either conjugated meningococcal vaccine (conjugated to CRM197, a non-toxic mutant of diphtheria toxin) of lot 1 (60 infants) or lot 2 (60 infants) or hepatitis B vaccine as a control vaccine. Diphtheria and tetanus toxoids and whole cell pertussis (DTP) vaccine reconstituted with Hib-tetanus conjugate was co-administered in the other leg. Polio vaccine was given orally. According to the UK immunization schedule, these vaccines were given at 2, 3, and 4 months of age. At 12 months the children received either meningococcal A and C polysaccharide vaccine or conjugated meningococcal serogroup C vaccine. The conjugated meningococcal vaccines were

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Table 1 Adverse effects of a conjugated meningococcal group C vaccine

Reaction	Conjugated meningococcal group C vaccine		DTP/Hib vaccine
	Low dose (2 μg/ml)	High dose (10 μg/ml)	
Erythema ≥2.5 cm	4/171 (2.3%)	5/173 (3.9%)	38/344 (12%)
Swelling ≥2.5 cm	2/171 (1.2%)	6/173 (3.5%)	64/344 (19%)
Fever ≥38°C for up to 3 days	7/171 (4.1%)	8/173 (4.6%)	No data
Systemic reactions in first 24 hours	26/171 (12%)	53/173 (31%)	No data
Crying for >1 hour in first 24 hours	3/156 (1.9%)	2/153 (1.3%)	No data

generally well tolerated and resulted in less tenderness and induration than the routine vaccines (DTP-Hib and hepatitis B) administered in the opposite leg. There was also no significant difference in systemic reactions between any of the vaccine groups. Parents of the children who received meningococcal polysaccharide vaccine as a booster dose reported significantly more local tenderness, general irritability, and change in eating habits than those whose children received conjugate meningococcal vaccine. There was also an increased use of antipyretic drugs in children who received the polysaccharide vaccine. There were no differences in rash, sleepiness, unusual crying, vomiting, or diarrhea. The immunological results suggested that the conjugated vaccines were highly immunogenic and able to induce both a primary response in infants and immunological memory.

A somewhat different conjugated meningococcal vaccine (purified group C meningococcal polysaccharide coupled to purified tetanus toxoid, manufactured by North American Vaccine, Columbia, Maryland, USA) has been evaluated in 30 healthy adults (9). One dose containing 10 micrograms of polysaccharide and 15.5 micrograms of tetanus toxoid was given intramuscularly. All the volunteers developed a four-fold or greater increase in serum bactericidal antibody to group C meningococcus. Most of the local and systemic reactions were mild (Table 2). The only significant local erythema and swelling (over 3 cm) was related to an injection site hematoma, which resolved rapidly.

The results of a phase 1 study in 30 children aged 12–23 months, who received two doses of tetravalent A-C-W135-Y conjugated meningococcal vaccines (conjugated to diphtheria toxoid), have been reported (10). Three different doses were used: 1, 4, and 10 micrograms/ml polysaccharide of each serogroup. The 4 micrograms/ml dose appeared to be immunologically optimal. No children had a temperature of over 39.9°C. Local reactions were reported in 40–60% of children after each injection, with no apparent relation to dose. None of these local reactions was severe. The investigators considered the results as being sufficiently promising for further evaluation of this vaccine in a larger trial in toddlers and infants.

Table 2 Adverse effects of a purified group C meningococcal polysaccharide coupled to purified tetanus toxoid

Reaction	Number ($n = 30$)
Tenderness	15
Erythema	15
Pain	15
Induration	8
Fever ≥38°C	1
Headache	2
Myalgia	1
Arthralgia	0

Combined meningococcal and typhoid fever vaccine

A combined meningococcal and typhoid vaccine (Mérieux) was evaluated in 158 volunteers in a single-blind study (11). Comparing the effects with those in vaccinees receiving monocomponent vaccines or the combination vaccine, there was no significant difference in the reported frequency or duration of local and systemic reactions. However, vaccinees who received the monocomponent typhoid fever vaccine alone were less likely to complain of swelling or pain at the injection site.

Organs and Systems

Nervous system

During an immunization campaign with a polysaccharide vaccine in 130 000 children in Auckland, New Zealand, there were 92 reports of apparent peripheral nerve involvement, including 80 reports of unexplained weakness and 57 reports of paresthesia or dysesthesia (12).

Acute disseminated encephalomyelitis has been reported 4 weeks after immunization with a polysaccharide meningococcal A + C vaccine in a 23-year-old woman; she recovered with glucocorticoid treatment (13).

During an efficacy trial using the Norwegian meningococcal group B vaccine carried out in Norwegian secondary schools from 1988 to 1991, seven of the reported events in vaccinees were classified as serious, among them one case was of acute transverse myelitis which was considered to be most probably a vaccine reaction. The remaining cases could have been triggered by the vaccine without being directly caused by the vaccine (14).

Data on adverse events reported to a passive provincial surveillance system have been evaluated after the mass immunization with a polysaccharide meningococcal vaccine of 1 198 751 people aged 6 months to 20 years in Quebec. A total of 118 reports of severe adverse events were selected. The most frequent were allergic reactions (9.2 per 100 000 doses), followed by few neurological reactions (0.5 per 100 000 doses) and very few anaphylactic reactions (0.1 per 100 000 doses). There were no reports of long-lasting sequelae or of encephalopathy, encephalitis, or meningitis (15).

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Urinary tract

The possible risk of relapse of nephrotic syndrome after administration of meningococcal serogroup C conjugate vaccine to children has been discussed (16). In 106 children with nephrotic syndrome, there were 63 relapses during the 12-month period before immunization and 96 relapses during the equivalent 12-month period after meningococcal immunization. The increase was statistically significant and the risk was especially higher in the first 6 months after immunization. Regarding the possible pathogenesis of the increased rate of relapses the authors discussed the hypothesis that disturbance of cytokines by the conjugated vaccine might mediate the onset of proteinuria. This is the first report of possible serious adverse effects of conjugated meningococcal immunization; further studies are needed before a real risk can be confirmed.

Musculoskeletal

A polyarthropathy has been reported after the administration of a conjugated meningococcal serogroup C vaccine (17).

- A 17-year-old boy developed a widespread rash on his back and the left side of his chest and painful swelling of his left elbow, right knee, and left ankle 4 days after receiving meningococcal serogroup C vaccine. The detection of meningococcal DNA in fluid from his knee made it probable that the disease was due to natural meningococcal infection, as the meningococcal vaccine does not contain nucleic acid. As the serogroup C vaccine protects only against group C infections, natural meningococcal infection of other serogroups, particularly the commonest serogroup B, can still occur.

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Menispermaceae

See also Herbal medicines

General Information

The genera in the family of Menispermaceae (Table 1) include chondrodendron and moonseed.

Stephania species

Various species of *Corydalis* (fumewort, Fumariaceae) and *Stephania* (Jin bu huan) contain tetrahydropalmatine (1), which is the active constituent in Chinese "Jin Bu Huan Anodyne" tablets, sold on the Western market. The package insert suggested that *Polygala chinensis* is the source plant, but in reality this alkaloid comes from a species of *Stephania*. Both l-tetrahydropalmatine and its racemic dl-form are used in Chinese medicine as analgesic and hypnotic agents.

Stephania has been adulterated with *Aristolochia* (2,3), and confusion is possible because of the similarity in their

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Table 1 The genera of Menispermaceae

Calycocarpum (calycocarpum)
Chondrodendron (chondrodendron)
Cissampelos (cissampelos)
Cocculus (coral bead)
Dioscoreophyllum (dioscoreophyllum)
Fibraurea (fibraurea)
Hyperbaena (hyperbaena)
Jateorhiza (jateorhiza)
Menispermum (moonseed)
Stephania

Chinese names: han fang ji (*Stephania*) and guang fang ji (*Aristolochia*).

Adverse effects

The reported adverse effects of Jin bu huan include vertigo, fatigue, nausea and drowsiness, which could make users unfit for driving. Life-threatening bradycardia and respiratory depression occur in small children after unintentional overdosage (4) and acute hepatitis in adults (5).

Nine adults acutely poisoned with tetrahydropalmatine recovered quickly after mild neurological disturbances; tetrahydropalmatine was metabolized rapidly and excreted as polar metabolites in the urine (6).

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Menthol

General Information

Menthol is a cyclic alcohol obtained from the volatile oils of various species of *Mentha*. It occurs naturally as levomenthol (rINN), and racementhol (rINN) can be synthesized.

Menthol is largely used as a flavoring or olfactory agent in a variety of products, including cigarettes, liqueurs, cough drops, mouthwashes, toothpastes, and shampoos. Menthol has been used in different medications to relieve symptoms of asthma and rhinitis and is a constituent of cold remedies and ointments designed to be rubbed on to the chest or applied around and even into the nostrils. Applied to the skin, it acts as a rubefacient and counter-irritant, but substantial concentrations of volatile oil can be inhaled from the skin.

Organs and Systems

Respiratory

In young children, menthol can induce reflex apnea or laryngospasm and application of the compound to the nostrils can result in instant collapse. There have been reports of a relation between menthol in toothpaste and worsening of asthma in some patients, most of them sensitive to aspirin (1,2). Cases of menthol-induced asthma are almost always associated with sensitivity to aspirin (3), but an exception has been reported (4).

- A 40-year-old woman with no personal or family history of asthma had dyspnea, wheezing, and nasal symptoms for 2 years whenever she used toothpaste and/or ingested mint confections. She had no history of aspirin sensitivity, and a challenge test with a menthol solution diluted in alcohol ruled out any possibility that the asthma had been caused by preservatives, dyes, or other additives.

Hematologic

Blood dyscrasias have been attributed to menthol (5).

Skin

There have been reports of perioral dermatitis, urticaria, and stomatitis due to menthol (1,6).

Immunologic

Hypersensitivity reactions to menthol are well recognized and comprise urticaria and flushing. Twelve cases of contact sensitivity to the flavoring agents menthol and peppermint oil were reported in patients presenting with intra-oral symptoms in association with burning mouth syndrome, recurrent oral ulceration, or a lichenoid reaction (6). Nine patients were followed up and six of these described resolution or improvement of their symptoms as a result of avoiding menthol and peppermint.

Drug Administration

Drug overdose

Overdose of menthol, particularly over long periods, can occur with overuse of mentholated cigarettes. Inhalation can result in ataxia, confusion, euphoria, nystagmus, and diplopia (7).

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Mepacrine

General Information

Following the administration of mepacrine in normal doses, adverse effects are usually limited to gastrointestinal upsets, with nausea and sometimes vomiting. Yellow discoloration of the skin and conjunctivae is common, but is usually considered more of a cosmetic problem. The aplastic anemia seen with the use of mepacrine may be caused by a hypersensitivity reaction.

Organs and Systems

Cardiovascular

Mepacrine inhibits phospholipase A2 and subsequently leukotrienes, which are calcium ionophores. Mepacrine also has an inhibitory effect on phospholipase C and subsequent inositol phosphate formation, which mobilizes cytosolic calcium from intracellular stores. It has therefore been suggested that this might influence myocardial contractile function (SEDA-13, 241). However, mepacrine is not cardiotoxic, although problems could arise in the presence of a "sick" myocardium.

Nervous system

Headache and dizziness are not uncommon with ordinary doses of mepacrine and after transcervical administration for sterilization (1).

Signs of central nervous system excitation, including convulsions, have been seen with the use of large parenteral doses of mepacrine in the treatment of malignancies (SEDA-11, 592).

Sensory systems

Yellow discoloration of the conjunctivae and sclerae can occur in patients taking mepacrine. The corneal deposits and mild diffuse cornea edema, which can cause blurring of vision, are reversible.

There have been occasional reports of retinopathy resembling that seen with chloroquine (SEDA-11, 593) (2). However, as a rule mepacrine is non-toxic to the retina (SEDA-14, 241).

Psychological, psychiatric

Acute psychosis has been seen with the use of large parenteral doses of mepacrine in the treatment of malignancies (SEDA-11, 592).

- An acute transient psychosis (screaming, kicking, and hallucinations) was seen in an 11-year-old boy after 5 days' treatment with quinacrine 100 mg tds for *Giardia lamblia* infestation. Recovery occurred after withdrawal (SEDA-16, 309).

Hematologic

Mepacrine used in the prophylaxis of malaria can cause aplastic anemia. The incidence among soldiers during World War II was 2.84 per 100 000 compared with 0.66 per 100 000 in controls. A skin rash or lichenoid eruption often preceded the blood dyscrasia (SEDA-11, 593).

- Aplastic anemia has been reported in a 28-year-old woman given mepacrine for several months for the treatment of lupus erythematosus (SEDA-16, 309).

Liver

Rare cases of hepatitis and even hepatic necrosis have been reported in patients taking mepacrine (SEDA-11, 593).

Skin

Mepacrine causes a marked yellow discoloration of the skin and often also the conjunctivae. This is often combined with a blue–black discoloration of the palate and a curious discoloration of the nails, which can be brownish-black, yellowish-green, or sometimes white fluorescent in appearance. This phenomenon is related to the cumulative dose, though it is occasionally also seen with short-term use. The discoloration disappears after withdrawal. Mepacrine-induced discoloration shows up under Wood's lamp as a brilliant yellow–green fluorescence of the nails and palms of the hands and also of the urine.

Skin changes attributed to mepacrine include lichen planus nodules, wart-like growths, erosions, and ulcerations (3).

In allied soldiers during World War II, the most common adverse effect of mepacrine was a drug eruption, tropical lichenoid dermatitis, which sometimes led to permanent sequelae at an early stage (4). Late sequelae occurred 7–17 years after the war, and malignancies developed in two cases. Mepacrine can cause skin cancers as late as 34 years after administration.

A skin rash or lichenoid eruption often precedes mepacrine-induced aplastic anemia (5).

Sexual function

The local placing in the cornual portion of the fallopian tube of a 250 mg quinacrine pellet caused necrosis of the epithelial lining and an acute inflammatory reaction, with subsequent progressive fibrosis and occlusion of the lumen of the tube; in that particular study it was a desired effect (SEDA-16, 309).

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Reproductive system

In three non-comparative phase I trials of transcervical administration of quinacrine pellets 250 mg in 21 women who were scheduled to undergo hysterectomy, five women reported pelvic/abdominal cramps (1).

Long-Term Effects

Tumorigenicity

The possibility of a relation of mepacrine to the incidence of squamous cell carcinoma was suspected in Australian ex-servicemen, but causality is not clear (SEDA-13, 818) (SEDA-14, 241). Extensive sun exposure could have been a factor, and that would explain the difference in findings around the world.

Smoking

Antimalarial drugs (chloroquine, hydroxychloroquine, or quinacrine) were given to 36 patients with cutaneous lupus, of whom 17 were smokers and 19 non-smokers (6). The median number of cigarettes smoked was one pack/day, with a median duration of 12.5 years. There was a reduction in the efficacy of antimalarial therapy in the smokers. Patients with cutaneous lupus should therefore be encouraged to stop smoking and consideration may be given to increasing the doses of antimalarial drugs in smokers with refractory cutaneous lupus before starting a cytotoxic agent.

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Mepenzolate bromide

General Information

The 25-mg dose of the anticholinergic drug mepenzolate bromide, often given several times a day for gastrointestinal disorders, is sufficient to cause anticholinergic adverse effects, but the compound may itself be a cause of gastric pain, and one must hence realize the risk of creating a vicious circle (1).

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Mepivacaine

See also Local anesthetics

General Information

Mepivacaine is an aminoamide local anesthetic. Systemic toxicity is its major complication and can prove fatal. Vasoconstrictors are not warranted, as they do not alter the rate of systemic reactions.

Organs and Systems

Cardiovascular

Severe bradypnea and bradycardia requiring external ventricular pacing occurred in a previously asymptomatic 30-year-old woman with a known cardiac conduction defect 85 minutes after a paracervical block with mepivacaine 400 mg (1). First-degree atrioventricular block has been reported (2).

Nervous system

Hyperbaric mepivacaine has also been implicated in causing transient radicular irritation after spinal anesthesia, of the same order of magnitude as lidocaine (3,4). Three cases of transient radicular irritation have been reported after spinal anesthesia with isobaric 2% mepivacaine (5).

Immunologic

An allergic reaction has been described in a patient given mepivacaine (6).

Susceptibility Factors

Renal disease

Mepivacaine toxicity has been studied in 10 patients with end-stage chronic renal insufficiency undergoing vascular access surgery (7). These patients represent a high-risk group for general anesthesia, as they often have concomitant coronary artery disease, hypertension, and diabetes. Brachial plexus block is often used: as well as avoiding systemic effects, it enhances regional blood flow.

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Meptazinol

General Information

Meptazinol is a centrally-acting opioid analgesic with an affinity for $OP_3(\mu)$ receptors (1). Common adverse effects are typically opioid in character; vomiting seems to be a problem and abdominal pain can occur in some patients. Euphoria and hallucinations are uncommon.

Organs and Systems

Respiratory

Clinically and statistically significant respiratory depression can occur within 1 minute of the start of a meptazinol infusion 1 mg/kg. Respiratory depression was less than after pethidine 1 mg/kg, but more than after 0.5 mg/kg (2). Other studies have confirmed these effects. In 49 patients who received either PCA with meptazinol (20 mg bolus, maximum 120 mg/hour) or morphine (2 mg bolus, maximum 12 mg/hour) after major orthopedic surgery, there was a tendency for more patients receiving meptazinol to have obstructive apnea and central apnea.

Drug Administration

Drug administration route

Prophylactic administration of intramuscular prochlorperazine 12.5 mg did not prevent meptazinol-induced emesis; in fact, the incidence of vomiting with this combination was twice the expected frequency; cyclizine was an effective antiemetic (3). Prolonged vomiting has followed the use of intravenous meptazinol 50 mg (4).

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Mequitazine

See also Antihistamines

General Information

Mequitazine is a first-generation antihistamine (SED-13, 15) (SEDA-22, 179).

In a comparative study with placebo, there was no significant difference in the incidence of drowsiness, while dry mouth was reported in nine of 23 patients taking mequitazine compared with six of 25 taking placebo.

Organs and Systems

Nervous system

Mequitazine 10 mg, but not 5 mg, has central effects (1). Syncopal attacks occurred in a patient taking mequitazine plus spiramycin for 48 hours.

Sensory systems

Disturbance of accommodation was seen in three patients treated with mequitazine (2).

Liver

Liver damage has been attributed to mequitazine (3).

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Mercaptamine

General Information

Mercaptamine (cysteamine), an aminothiol, is used to reduce tissue cystine content in patients with nephropathic cystinosis, an autosomal recessive lysosomal storage disorder in which intracellular cystine accumulates due to impaired transport out of lysosomes (1). The clinical manifestations include renal tubular Fanconi syndrome in the first year of life, with hypophosphatemic rickets, hypokalemia, polyuria, dehydration and acidosis, growth retardation, hypothyroidism, photophobia, renal glomerular deterioration by 10 years of age, and late complications such as myopathy, pancreatic insufficiency, and retinal blindness. The cystinosis gene, CTNS, codes for cystinosin, a 367 amino acid protein with seven transmembrane domains. More than 50 CTNS mutations have been identified, but about 50% of Northern European patients have a 57257-bp deletion which removes the first nine exons of CTNS. The mainstay of cystinosis therapy is oral mercaptamine, 60–90 mg/kg/day qds every 6 hours, and generally achieves about 90% depletion of cellular cystine, as measured in circulating leucocytes. This delays renal glomerular deterioration, enhancing growth, preventing hypothyroidism, and lowering muscle cystine content. In one study, for every month of treatment before 3 years of age, 14 months' worth of later renal function were preserved.

Mercaptamine is available for oral administration as hydrochloride and bitartrate salts and as sodium phosphomercaptamine. Topical mercaptamine prepared from the oral formulation has been used to treat severe photophobia from corneal crystal deposition in cystinosis (2).

- An 8-year-old boy with nephropathic cystinosis had debilitating and worsening photophobia from corneal crystal deposition (3). After 8 months of topical application of mercaptamine, he has marked improvement, both subjectively and objectively.

Mercaptamine has also been used to treat paracetamol overdose (4).

Adverse effects include lethargy, hyperthermia, and rash (5), and nausea and vomiting (6). The risk of vomiting correlates inversely with body weight (7).

Organs and Systems

Sensory systems

In 93 children with nephropathic cystinosis oral mercaptamine 51 mg/kg for up to 73 months produced 82% cystine depletion from leukocytes and improved creatinine clearance and growth (8). However, 14% of the patients could not tolerate the taste and smell of mercaptamine, which is excreted in the breath.

Hematologic

In a phase I trial myelosuppression was the main adverse effect of mercaptamine in five of 24 patients (9). One had grade 4 thrombocytopenia and two had grade 3 thrombocytopenia; anemia and leukopenia were milder (grade 1 to 2).

Gastrointestinal

In four children with nephropathic cystinosis receiving mercaptamine 14.35 mg/kg qds serum gastrin concentrations up to 90 minutes later rose as did gastric acid output (10). Two of the four subjects had visual and histological evidence of gastric inflammation. The clinical effect of this acid production is unknown.

Skin

Mercaptamine hydrochloride contained in "neutral" permanent-wave preparations has been used in American beauty salons since 1993 and can cause contact dermatitis (11).

- A hairdresser, allergic to mercaptamine hydrochloride, had positive patch-test reactions to mercaptamine hydrochloride, glyceryl thioglycolate, diglyceryl thioglycolate, and *p*-phenylenediamine.

There were negative results with mercaptamine hydrochloride (1.0% in petrolatum) in 64 controls. People whose hair had been waved with mercaptamine hydrochloride were not allergic.

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Mercury and mercurial salts

General Information

Mercury is a silver-colored metallic element in fluid form (symbol Hg; atomic no. 80). Its symbol derives from the Greek name for the element hydrargyros. It is found as the sulfide salt in cinnabar, the source of the pigment vermilion.

With a few exceptions, the use of metallic mercury in medicine is considered to be outdated; the few exceptions include its use in certain preservatives and in dental amalgam. The radioactive nuclides ^{197}Hg and ^{203}Hg have been used diagnostically, but the amount of mercury involved is very small. Even the mercury thermometer is rapidly being replaced by safer alternative devices. The use of mercury in dermatological therapy should be abandoned because of the risk of mercury intoxication (1).

Aryl mercurials that have been used medicinally include phenylmercuric acetate, phenylmercuric nitrate, nitromersol, thiomersal, merbromin (mercurochrome), and mercurobutol. These compounds are variously used as preservatives in drugs, including vaccines, for skin disinfestation, the treatment of infections of the skin and mucosa, and in contraceptive jellies and hemorrhoidal remedies; they have also been used in some cosmetics. The aryl mercurials are better absorbed across the mucous membranes than most inorganic mercury salts.

Regrettably, some therapeutic exposure to mercury continues, more particularly generally outside the Western world. Non-prescription laxatives containing mercurial compounds are still sold in some countries. The presence of mercury may not always be divulged on the label. Mercury poisoning can also occur through consumption of fish that have swum in waters that have been contaminated with methyl mercury from industrial waste (Minamata disease) (2). When it was first described, in May 1956, the marine products in Minamata Bay contained high concentrations of mercury (6–36 ppm). Mercury was also found in the hair of patients, their families, and the inhabitants of the Shiranui Sea coastline (maximum 705 ppm). Typical symptoms include sensory disturbances (glove and stocking type), ataxia, dysarthria, constriction of the visual fields, auditory disturbances, and tremor. Mercury poisoning has also been seen in the children of mothers who have eaten contaminated marine life (congenital Minamata disease).

Acute and chronic mercury poisoning

The characteristic clinical picture of acute mercury poisoning includes sudden profound circulatory collapse with tachycardia, hypotension and peripheral vasoconstriction, vomiting, and bloody diarrhea due to hemorrhagic colitis. Renal insufficiency usually develops within 24 hours and is associated with albuminuria, epithelial cell casts, and red cells in the urine, glycosuria, and aminoaciduria. Oliguria can proceed to complete anuric failure. There is also neutrophilic leukocytosis due to tissue necrosis (SED-11, 483) (3).

Symptoms of chronic mercury poisoning have been reviewed (4–6). The symptoms are listed in Table 1. The urinary tract is very sensitive to poisoning by all forms of mercury, a sensitive indicator of early injury being a rise in the urinary excretion of *N*-acetyl-beta-D-glucosaminidase (NAG) (7).

In 70 patients with psoriasis treated with an ointment containing ammoniated mercury, symptoms and signs of mercury poisoning were detected in 33 (8): albuminuria, headache, gingivitis, erythroderma, nausea, dizziness, precordial pain, contact dermatitis, conjunctivitis, epistaxis, keratitis, tremor, neuritis, hematological changes, metallic taste in mouth, and purpura.

Acrodynia ("pink disease") is thought to be a particular form of mercury hypersensitivity, which can be caused by organic or inorganic mercury; it formerly occurred in young children exposed to teething formulations containing mercury compounds. Typical signs include pink scaling palms and soles, flushed cheeks, pruritus, photophobia, profuse irritability, and insomnia. A modern case of acrodynia involved a patient with congenital agammaglobulinemia who had received merthiolate-containing gammaglobulin injections for 15 years (SEDA-6, 225).

Mercury poisoning has been reported in a child who took a Chinese herbal medicine (9).

- A 5-year-old Chinese boy developed oral ulceration, mainly affecting the left lateral aspect of his tongue, and 5 weeks later motor and vocal tics. Herpetic ulceration was diagnosed and confirmed by the isolation of

Table 1 The symptoms of chronic mercury poisoning

System	Symptom
Cardiovascular	Hypertension, hypotension
Nervous system	Emotional disturbances, irritability, hypochondria, psychosis, impaired memory, insomnia, tremor, dysarthria, involuntary movements, vertigo, polyneuropathy, paresthesia, headache
Sensory systems	Corneal opacities and ulcers, conjunctivitis, hypacusis
Endocrine	Hyperthyroidism
Hematologic	Hypochromic anemia, erythrocytosis, lymphocytosis, neutropenia, aplastic anemia
Mouth	Loose teeth, discoloration of the gums and oral mucosa, mouth ulcers, fetor
Gastrointestinal	Anorexia, nausea, vomiting, epigastric pain, diarrhea, constipation
Urinary tract	Nephrotic syndrome
Skin	Tylotic eczema, dry skin, skin ulcers, erythroderma
Musculoskeletal	Acrodynia, arthritis in the legs
Reproductive system	Dysmenorrhea

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Herpes simplex virus type 1 from a tongue swab. The lesion improved with oral aciclovir (200 mg five times a day for 5 days), but relapsed a few days later. A local pharmacist prescribed a Chinese medicinal herb mouth spray called "Watermelon Frost", said to be useful in controlling pain and healing difficult mucosal wounds. Over the following weeks his oral symptoms improved but he became irritable and cleared his throat frequently. He developed a transient skin rash on his trunk and motor tics (eye blinking, head turning, and shoulder shrugging). His blood lead concentrations was 0.31 μmol/l (normal below 1.5) and his blood manganese concentration was 246 nmol/l (normal 70–280); his urine arsenic concentration was 10 nmol/mmol creatinine (normal <68). His blood mercury concentration was 83 nmol/l (normal for adults <50). The mercury content of the spray was 878 ppm (2% methyl mercury and 98% inorganic mercury). There was a significant difference in mercury content between different brands and between batches of the same brand of the Chinese medicinal herb. The spray was withdrawn and his tics completely resolved within 4 weeks.

Metallic mercury

Metallic mercury (SEDA-21, 239) is poisonous, and prolonged or acute inhalation can be fatal; organic damage results in a severe chemical pneumonitis. Gingivitis, sometimes proceeding to loss of the teeth, is a well-recognized consequence of prolonged low-level exposure to the metal. Inhalation of vapor from broken thermometers by persons allergic to mercury or even skin exposure can give rise to allergic contact dermatitis (10). If the liquid metal enters the system, even a small amount can cause complications (SEDA-22, 248), although much of the metal is likely to remain at the site of entry and some will be trapped by the lymphatic system.

In one remarkable case, a nurse accidentally pierced her hand with a broken mercury thermometer, and developed amyotrophic lateral sclerosis 3 years later; the causal link was uncertain but there was some reason to believe that the metal had activated a latent predisposition to the disorder (11).

- A man who attempted suicide by injecting 40 ml mercury was found to have mercury deposits at the injection site and in the lungs (12).
- A man who injected mercury intravenously developed malaise and weight loss, and a bilateral cervical adenopathy was found (13).

Dental amalgam

Dental amalgam (SEDA-10, 210) (SEDA-15, 233) (14,15) is still used for about 75–80% of single-tooth restorations. The modern amalgam consists of a metallic alloy (silver, tin, and copper, sometimes with small amounts of zinc, indium, and/or palladium) mixed with mercury in a percentage of 40–54% mercury by weight. The resultant plastic mass sets and hardens over a period of 8–24 hours.

Contrary to previous belief, measurable amounts of mercury escape from dental amalgam fillings in the form of vapor, ions, and abraded particles, and individuals who are accustomed to chew their food thoroughly are exposed to particularly high levels of mercury. This finding has led to a widespread belief in some countries, supported by certain scientific workers (16), that mercury released from amalgam may be the cause of some hitherto unexplained diseases, and a demand has arisen for the removal of amalgam fillings. A number of case histories have been published of individuals in whom chronic (primarily neurological) disorders appear to have responded to removal of amalgam.

Although it is acknowledged that occasional individuals are allergic to metallic mercury, the view that it presents any other risk has generally been contested by the dental profession, citing evidence that the mercury released from amalgam will not accumulate in the body as long as there is adequate renal function. A meta-analysis has shown numerous logical and methodological errors in the anti-amalgam literature (17). The author concluded that the evidence supporting the safety of amalgam is compelling. The debate continues (18,19).

There have been reports of allergic reactions to dental amalgam.

- A 32-year-old dentist had multiple exudative erythematous pruritic plaques on his limbs and trunk for 3 years (20). Although the eruptions were seen almost throughout the year, his symptoms tended to be worse in the summer. Topical corticosteroids, white petrolatum, and oral antihistamines had given slight relief, and an oral corticosteroid gave him transient relief from the itchy eruptions. Patch tests showed that he reacted to 1% ammoniated mercuric chloride in petrolatum and to 0.05% mercuric chloride in water. It was suggested that his dental amalgam should be removed and that he avoid contact with amalgam during his work. Two weeks later his skin symptoms had dramatically improved, leaving pigmentation. Thereafter he was free of symptoms for several months. However, when he handled amalgam again, similar but less severe eruptions appeared on his legs the next day. Subsequent strict avoidance of amalgam improved his eruptions.
- A 70-year-old man had multiple coin-sized exudative eczematous plaques on his legs and trunk for several months (20). Various kinds of corticosteroid ointments and white petrolatum as an emollient gave him little relief. Patch tests showed that he reacted to 1% ammoniated mercuric chloride in petrolatum and 0.05% mercuric chloride in water. He had all his dental amalgam removed, and 1 month later his eruption had subsided, leaving pigmentation.
- A 50-year-old man complained of soreness of the left buccal mucosa and the right side of his tongue, made worse by consuming spicy foods and acidic drinks (21). He had a heavily restored dentition, with asymmetrically distributed white striated and red atrophic lesions on the left buccal mucosa and the right and left borders of the tongue. The lesions were in direct contact with the buccal and palatal surfaces of an old corroding and amalgam restoration and the lingual surface of an amalgam restoration. A provisional diagnosis of a lichenoid reaction to amalgam was made and patch tests showed a strong positive response to mercury and a slightly weaker response to amalgam after 72 hours. One amalgam filling was covered with a bonded porcelain crown

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and the other was replaced with glass ionomer cement. Within 2 months he was asymptomatic, and after 12 months the lichenoid lesions had completely resolved.

- A-57-year-old woman (21) had a recurrent urticarial rash on the skin of her face, scalp, and neck precipitated by restorative dental treatment. The reactions were fully established within 12 hours and would resolve over 2–3 days and be completely gone within 1 week. Patch tests showed a strong reaction to mercury. She was advised that alternative dental materials should be used and that existing amalgam should be removed.

Organic salts

Organomercurials have been a common cause of allergic contact dermatitis or rash (22) and even exfoliative dermatitis has been described (23). Some reagents for intracutaneous testing (tuberculin, etc.) may contain thiomersal, which can cause sensitization and thus elicit false-positive delayed-type skin reactions. Mercury compounds inhibit most lymphocyte functions (SEDA-21, 240). An early indicator of an immunological response to mercury exposure, for example in occupational medicine, appears to be a change in the lymphocyte count with a differential increase in T helper cells and a rise in the T helper/T suppressor ratio (24).

Merbromin

Merbromin (mercurochrome, the disodium salt of 2,7-dibromo-4-hydroxymercurifluorescein) is the oldest organic mercurial antiseptic in use, but it is active only as a bacteriostatic agent. In contrast to earlier assumptions, it is absorbed through burned or otherwise absorptive surfaces, and can cause severe and lethal intoxication. High mercury concentrations in blood, urine, and organs have been demonstrated (SED-11, 483). Young children run a particular risk of renal damage from absorption of organic mercury compounds used as antiseptics; in one case, frequent application of merbromin to an omphalocele apparently resulted in anuria, respiratory arrest, and death (SED-8, 520). Neither merbromin nor thiomersal can be considered useful in the management of large omphaloceles.

- A patient developed mercury intoxication, including aplastic anemia, after local application of merbromin to an operation wound (SED-11, 483) (25).
- A 37-year-old patient with burns involving 50% of the body surface was treated by Grob's three-phase method (2% merbromin, 5% tannic acid, and 10% silver nitrate solutions) (26). By day 6 he had pink-coloured urine and progressively developed restlessness, confusion, and coma, with hypothermia on day 8. He died on day 10 with respiratory arrest. The mercury concentration of the urine was 2170 ng/ml on day 6 and 1250 ng/ml on day 9.

The authors pointed out that merbromin should no longer be used in the treatment of burns. However, good results were reported in a retrospective study on the treatment of second-degree burns in 129 children using the same method (solutions with 7% silver nitrate and 2% merbromin). The authors pointed out that the indication is given only in second-degree burns, with burned surfaces of maximally 10–20% of the body surface, preferably in burn injuries of the trunk and non-mobile areas of the extremities. The most important factor seems to be careful attention to the serum sodium concentration and sufficient substitution with infusion therapy (SED-11, 483).

An anaphylactic reaction occurred after local application of merbromin in one patient, and several mercury-sensitive patients had severe local reactions in patch tests (SED-11, 483) (27).

Thiomersal

Thiomersal (*O*-ethylmercurithiobenzoic acid), an organic mercurial, was first added to childhood vaccines as a preservative in the 1930s. It contains 50% ethyl mercury by weight. It was the potential for infants to be exposed to cumulative doses of mercury from thiomersal in vaccines that prompted the European Medicines Evaluation Agency and the UK's Committee on Safety of Medicines (CSM) to recommend that it would be prudent to promote the use of vaccines without thiomersal as a precautionary measure (SEDA-26, 259). Thiomersal is also widely used in cutaneous test solutions and in contact lens cleaners and creams. The danger of toxic effects and the efficacy of thiomersal are similar to those of merbromin. Toxic amounts can be absorbed during omphalocele treatment.

The aryl mercurials, such as thiomersal are particularly likely to elicit hypersensitivity reactions (10,28), including attacks of asthma in patients who have received hepatitis B vaccine (29). Ethyl mercury toxicity and sensitization from thiomersal-containing vaccines have been indecisively discussed (30,31). The toxicity of ethyl mercury has also been discussed (32).

Fatal mercury (and borate) intoxication has been reported after irrigation of the ear with 0.1% thiomersal and 0.14% sodium borate for purulent otitis media, which was refractory to antibiotic therapy over 4 weeks (SED-11, 483) (33).

The histories of 25 patients with chemical burns caused by preoperative skin preparation have been reviewed. Thiomersal was the most common agent implicated. The burns did not occur in the main area of preparation, but more peripherally where the solution was in close contact with the skin in the drapes or was more closely applied to the skin by pressure, either because of the patient's own weight or to tourniquet dressings. No burning occurred under a sterile wound drape (although solutions stagnate at this site and do not evaporate), perhaps because there was no pressure. There are particular risks in patients placed in the lithotomy position to undergo gynecological operations (the burns being on the buttocks), and in those undergoing orthopedic operations (the burns then being on the extremities and under a tourniquet) (SED-11, 483) (34).

Thiomersal is one of the most frequent sensitizers in the world (3,35). It is used as a preservative in vaccines, test solutions, and topically administered applications, for example creams and solutions used on eczematous skin, ear-drops, eye-drops, and cleanser solutions for ocular contact lenses. The concentration of thiomersal varies between 0.0005 and 0.01% in these formulations.

Sensitization can be provoked by immunization with thiomersal-containing vaccines. Even in sensitized

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patients, thiomersal-induced adverse effects due to immunization has not been shown to be a severe risk, and a positive patch test to thiomersal does not represent a contraindication to immunization with thiomersal-containing vaccines. Many of the reactions seen in patch tests with 0.1% thiomersal are probably caused by the irritant nature of thiomersal. It has been pointed out that only half of a series of subjects tested with a solution of 0.1% thiomersal had a positive reaction in patch tests with concentrations of 0.05 and 0.01% (36).

Thiomersal included in patch-test series has given varying frequencies of positive reactions. Cross-reactions occur to a few organic mercurials, but not to inorganic or metallic mercury. The allergic determinant seems to be the ethyl mercury radical in thiomersal.

Frequencies of positive reactions have been reported in the following countries:

- USA: 13.4% in 1967 (37) and 8% in 1972 (38)
- Japan: 5.6 (39) and 16.3% (40)
- Finland: 2.0% (41)
- Denmark: 1.3% (42)
- GDR: 6.9% (43)
- Czechoslovakia: 5.3% in infant inpatients (44)
- France and Belgium: 2.3% in a multicenter study in 200 adult patients submitted to routine patch-testing (45)
- Italy: 5.3% (46)
- Poland: 5.7% (13.8% of all medicinal personnel, tested in this study) (47).

There was a very high peak frequency of positive patch tests in the 20–30 years age group in Sweden (48): 16% of male recruits and 10% of other healthy subjects in nursing schools and among medical students. A common reason for sensitization to thiomersal in the younger generation in Sweden arises from intracutaneous testing with tuberculin containing thiomersal as a preservative. It was shown experimentally that tuberculin could act as adjuvant during sensitization to thiomersal. The iatrogenic occurrence of thiomersal allergy in the Swedish population does not result in eczematous reactions, but merely in false-positive skin tests.

Thiomersal takes second place, after nickel, as a contact allergen in Austria. As in Sweden this high incidence is probably due also to frequent immunization with vaccines containing thiomersal (49).

- A generalized allergic reaction occurred in a 50-year-old nurse with a documented allergy to thiomersal, who received 10 ml of human euglobulin with thiomersal as a preservative.
- A 38-year-old man treated a mild sore throat himself with a thiomersal spray, and about 30 hours after the second application developed a severe laryngeal obstruction, for which emergency tracheotomy was necessary. A subsequent patch test produced a severe disseminated allergic reaction to thiomersal (SED-11, 484) (50).

Serious allergic reactions were reported in 18 patients after the use of a Japanese encephalitis vaccine containing thiomersal (51). Reactions in 15 patients were thought to be related to the product; 13 had urticaria affecting the whole body, one had erythema multiforme, and one had a rash. Fourteen reactions arose after the second immunization. Seven of the 13 urticarial reactions began within 24 hours of vaccination, and the other six within 72 hours. In five patients encephalitis vaccine was the only vaccine given. The thiomersal concentration had been increased from 0.0005% in previous vaccine batches, to 0.0067% in the batch used. However, the concentration of thiomersal was that used in most vaccines.

In topical formulations thiomersal can lead to an allergic contact dermatitis. There was a high incidence of thiomersal allergy in patients with pompholyx, that is vesicular eruptions on the palms and soles (48).

Thiomersal is more soluble and stable than the older mercurials. It does not influence tear-film wetting of cornea or contact lenses, or the stability of the tear film itself. Thiomersal has been known to cause both a blepharoconjunctivitis and a punctate keratitis in contact lens wearers. Thiomersal keratoconjunctivitis accounted for 32 of 312 consecutive referrals to an outpatient department for problems related to contact lenses (52). The typical appearances included non-specific conjunctival changes, limbal follicles, superficial punctate keratopathy, and superior corneal epithelial opacities. Atypical cases presented with superior limbitis, coarse punctate keratopathy, severe keratopathy with visual loss, pseudodendritic corneal lesions, or acute conjunctival hyperemia without keratopathy. In atypical cases, the diagnosis can be difficult but can be aided by the use of topical challenge with thiomersal. The condition can be incorrectly attributed to allergy. However, a large number of cases of allergic conjunctivitis have been attributed to thiomersal as a constituent of a solution for preserving soft contact lenses (SED-11, 484) (53).

- A 26-year-old man with a 2-year history of repeated episodes of dermatitis, swelling of the eyelids, and burning eyes was thought to have delayed contact allergy (54). The original diagnosis was of occupational allergy, but patch tests confirmed that the conjunctivitis was due to thiomersal-containing eye-drops, which had been used to treat the condition.

In an effort to reduce exposure to mercury the FDA have recommended that vaccine manufacturers phase out its use. In response to this, some blood products are also being manufactured free of thiomersal (55). In July 1999 the American Academy of Pediatrics and the US Public Health Service issued a joint statement calling for the removal of thiomersal, a mercury-containing preservative, from vaccines. This action was prompted partly by a risk assessment by the FDA, which consisted of hazard identification, dose–response assessment, exposure assessment, and risk characterization (56). The review showed no evidence of harm caused by the doses of thiomersal in vaccines, except for local hypersensitivity reactions. However, it was noted that some infants may be exposed to cumulative doses of mercury during the first 6 months of life that exceed the Environmental Protection Agency recommendations. In the UK the Committee on Safety of Medicines and the Department of Health reviewed the available data relating to thiomersal in vaccines and possible neurodevelopmental disorders, including autism, an issue that has gained media attention (57). There was no evidence of neurodevelopmental harm, a known effect of acute

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intoxication with mercury, caused by the amounts of thiomersal that are found in vaccines.

The amounts of thiomersal in the UK schedule of childhood vaccination are lower than in the USA. No specific action has been recommended in the vaccination program. European and American regulatory authorities have recommended that vaccine manufacturers should phase out their use of thiomersal whenever possible as a precaution (SEDA-25, 278).

Inorganic salts

Chronic mercurialism with nervous system involvement, renal insufficiency, and progressive colitis has been described after the long-term use of remedies containing inorganic mercury. Such remedies may also explain the persistence of other unexplained disorders, such as pink disease. Inorganic and organic mercury compounds may cause allergic dermatitis (SEDA-22, 247) (28). Frank poisoning from these sources, although uncommon today, is still possible, and occasional case reports appear (SEDA-13, 195); in one instance, injudicious chronic use of an ammoniated mercury ointment led to a peripheral polyneuropathy, which was only partly reversible (SEDA-22, 247). As with other metals, reactions to mercury can occur after occupational or environmental exposure; in one case, a child already known to be hypersensitive to mercurochrome developed a severe rash after wearing plastic boots which were found to contain mercurous chloride (58).

Despite several warnings over many years, the use of mercuric chloride solutions during operations in an attempt to kill cancer cells implanted in healthy tissues persists in some countries. Intraperitoneal administration, when seeding of a visceral cancer is feared, carries the risk of mercury absorption and nephrotoxicity. Death from intoxication after peritoneal lavage with a mercuric chloride solution has been reported (3).

Health authorities in Canada have warned consumers not to use Diana Cream (Diana de Beauté), a product that is used for skin lightening, mainly by Afro-Caribbean communities. The Directorate General of Pharmaceutical Affairs & Drug Control has prohibited the registration, import, and sale of the product, which is manufactured in Lebanon and is being illegally imported. It contains ammoniated mercury, bismuth subnitrate, and salicylic acid. The mercury content poses a high risk of mercury poisoning in adults and a serious health hazard to unborn and nursing infants of women who use the product (59).

Peripheral polyneuropathy as a result of chronic ammoniated mercury poisoning has been studied and followed over 2 years (60).

- A 36-year-old man developed peripheral polyneuropathy after chronic perianal use of an ammoniated mercury ointment. He had very high blood and urine mercury concentrations. Sural nerve biopsy showed mixed axonal degeneration/demyelination. His symptoms improved progressively over 2 years after withdrawal of the ointment, but neurophysiological recovery was incomplete.
- A 4-month-old boy was hospitalized with a weeping eczema covering more than the half of the body surface and complicated by skin hemorrhage and infection by *Klebsiella pneumoniae* and *Proteus mirabilis*. Apart from general therapy, a compound zinc oxide ointment containing, among other ingredients, yellow mercuric oxide 2 g per 40 g of base was applied daily. After 12 days, he rapidly developed cardiovascular collapse, acute pulmonary edema, and coma Stage II, with right hemiparesis, generalized hypertonia, and muscular tremor. The mercury concentrations in blood, urine, and CSF were respectively 120 ng/ml (normal <10 ng/ml), creatinine 260 micrograms/g (normal <5 micrograms/g), and 4.8 ng/ml (normal <0.1 ng/ml). Despite therapy with dimercaprol and vigorous supportive measures, the child's condition deteriorated, he developed *Klebsiella aerogenes* septicemia, and died 6 weeks later (61).

Organs and Systems

Sensory systems

Topical treatment with phenylmercuryl acetate can cause band-shaped corneal opacities (62). Long-term use of eye-drops containing phenylmercuric nitrate as a preservative can cause pigmentation of the anterior lens capsule. In 31 patients who used eye-drops containing phenylmercuric nitrate as a preservative for 3–15 years, a brownish pigmentation of the anterior capsule of the pupillary area developed. Light and electron microscopic studies on two lenses showed deposits of dense particulate material resembling melanin pigment on and in the anterior capsule of the lens in the area of the pupil (63). Electron microprobe analysis and neutron activation analysis established the presence of mercury. However, the pigmentation does not seem to be associated with visual impairment.

The use of mercurials in the eye can lead to a bluish-gray deposit of mercuric oxide on the eyelids, conjunctivae, and Descemet's layer. Phenylmercuric nitrate used in a 0.004% concentration can cause mercuria lentis. Mercurial compounds have been found in the aqueous humor, having penetrated the eye from hydrophilic-gel contact lenses preserved with thiomersal. Although it remains to be established whether deposition of mercury in the eye is clinically important, the concentrations found are similar to those reported in cases of systemic poisoning by organic mercurials (64).

Psychological, psychiatric

There is continuing debate that there is an association between autism and thiomersal-containing vaccines. Some authors believe that review of the literature supports the hypothesis that mercury in vaccines may be a factor in the pathogenesis of autism (65). The World Health Organization's Global Advisory Committee on Vaccine Safety (GACvS) has also kept this issue under review and concluded in November 2002 that there is no evidence of toxicity in infants, children, or adults who have been exposed to thiomersal in vaccines. The CSM is also keeping the issue under close review and studies of the possible toxicology of thiomersal continue to appear (66).

The usual dose of ethyl mercury in pediatric vaccines is small (about 12.5–25 micrograms of mercury). However, the metabolism of ethyl mercury in infants who receive

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vaccines containing thiomersal is unknown. The mean doses of mercury in 40 full-term infants exposed to thiomersal-containing vaccines were 46 (range 38–63) micrograms in 2-month-old children and 111 (range 88–175) micrograms in 6-month-old children. Blood mercury concentrations in the thiomersal-exposed 2-month-old children ranged from less than 3.8 to 21 nmol/l; in 6-month-old children all the concentrations were below 7.5 nmol/l. Only one of 15 blood samples from 21 controls contained measurable concentrations of mercury. Urine concentrations of mercury were low after vaccination, but stool concentrations were high in thiomersal-exposed 2-month-old children (mean 82 ng/g dry weight). The mean half life of ethyl mercury was 7 days.

This study was not designed as a formal assessment of the pharmacokinetics of mercury. However, it showed that the administration of vaccines containing thiomersal did not seem to raise blood concentrations of mercury above safe values in infants. Ethyl mercury seems to be eliminated from the blood rapidly via the stools. The authors concluded that the thiomersal in routine vaccines poses very little risk in full-term infants.

Urinary tract

Membranous glomerulonephritis has been attributed to mercury in a patient with diabetes mellitus.

- A 21-year-old man with a 16-year history of diabetes mellitus, who had been using an ointment containing 10% mercuric ammonium chloride for eczema for about 3 weeks, became tired, with fasciculation in the limbs and poor control of his diabetes (67). Nephrotic syndrome and hypertension were diagnosed 1 month later, and at 2 months he was very weak with tremor of the hands, was almost unable to walk, and had lost 20 kg. His behavior suggested an acute psychosis. The urine mercury concentration was 250 micrograms/l. He was treated with sodium 2,3-dimercaptopropane-1-sulfonate (Dimaval) capsules for 12 days (total dose 6.3 g). The highest urine mercury excretion during antidote treatment was 2336 micrograms/day. He had proteinuria of up to 11 g/day and renal biopsy showed diffuse membranous glomerulonephritis without diabetic nephropathy. Similarly, his neuropathy did not have typical features of diabetic neuropathy. He improved over the next year.

Immunologic

Merthiolate was tested as a matter of routine in an extended standard series of skin tests in patients with different subtypes of eczema and varicose complex (68). Of 880 patients 53% responded positively to one or more allergens, 3.9% to merthiolate. The latest results of skin tests in adults have confirmed the persistence of contact allergy to merthiolate and justify further follow-up and systematic screening.

Attention has been given to mercury as a cause of autoimmune responses, especially in the kidney (69). Exposure to mercury can cause immune responses to various auto-antigens and autoimmune disease of the kidney and other tissues. Although epidemiological studies have shown that occupational exposure to mercury does not usually result in autoimmunity, mercury can cause the formation of antinuclear antibodies, scleroderma-like disease, lichen planus, or membranous nephropathy in some individuals. In experimental animals mercury causes autoimmune disease similar to that observed in humans, with emphasis on the importance of immunogenetic and pharmacogenetic factors.

Homeopathic medicines can cause mercury allergy (baboon syndrome).

- A 5-year-old girl developed an itchy erythematous macular rash, symmetrically distributed in the anogenital area and thighs (70). The lesions developed into a widespread maculopapular vesicular rash in 48 hours, sparing the face, palms, and soles. The eruption cleared after systemic corticosteroids and antihistamines, with scaling and post-inflammatory hypopigmentation. She had had neonatal periumbilical dermatitis associated with the application of merbromin to the cord, and 24 hours before the onset of the rash had taken a single homeopathic tablet (Mercurius Heel), which contained soluble mercury. Allergy tests to a standard series of foods and respiratory allergens were negative and total IgE was normal. Patch-testing to allergens showed positive reactions to thiomersal and metallic mercury.

Previous sensitization and the subsequent development of an allergic contact dermatitis from vaccines that contain thiomersal has received more attention than before (71). Cross-reactivity, exposure factors, and tolerance to vaccines containing thiomersal have been studied in 125 patients sensitized to mercury derivatives in a cross-sectional study (71). Childhood vaccinations, merbromin used as an antiseptic, broken thermometers, and the use of drops were the main sources of previous exposure. There was sensitization to thiomersal in 57 patients and 24 had a positive intradermal reaction. Ammoniated mercury elicited positive reactions in 78% of all patients and merbromin in 66%. In most cases (100/125) there was cross-reactivity among different mercury derivatives. Intramuscular thiomersal caused a mild local reaction in only five patients (4% of the total, 9% of thiomersal positive reactions). Most of the patients had positive tests to both organic and inorganic mercury derivatives. Vaccination with thiomersal is relatively safe, even for individuals with delayed type hypersensitivity, since more than 90% of allergic patients tolerated intramuscular challenge tests with thiomersal. However, in such patients it would be advisable to restrict the use of mercurial antiseptics and mercury thermometers.

Drug Administration

Drug administration route

Mercury toxicity has resulted from the use of an ointment containing mercuric ammonium chloride (67).

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Mescaline

General Information

Mescaline is one of eight hallucinogenic alkaloids derived from the peyote cactus, slices of which (“peyote buttons”) have been used in religious rites by North and South American Indian tribes. Mescaline itself is only one of the alkaloids present in peyote, but it produces the same effects as the crude preparation. Chemically, it is related to amfetamine. In doses of some 300–500 mg it depresses nervous system activity and produces visual and occasionally auditory hallucinations, illusions, depersonalization, and depressive symptoms. The total picture can closely resemble that caused by lysergic acid diethylamide. Its physical effects include nausea, tremor, and sweating.

Organs and Systems

Psychological, psychiatric

The effects of mescaline have been investigated in a psychiatric research study (1). Psychosis induced during the experiment was measured with the Brief Psychiatric Rating Scale and the Paranoid Depression Scale. During use of mescaline neuropsychological measures showed reduced functioning of the right hemisphere. Single photon emission computed tomography (SPECT) studies showed a hyperfrontal pattern, with an emphasis on the right hemisphere. The authors discussed the possible educational value of experimentally induced psychosis in understanding the psychotic state.

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Mesna

General Information

Mesna is used to prevent or ameliorate hemorrhagic cystitis produced by the anticancer drugs cyclophosphamide and ifosfamide. It is excreted by the kidney and binds and detoxifies acrolein in the urine; mesna also prevents the breakdown of acrolein precursors. It is also used as a mucolytic.

Endotracheal instillation of mesna was compared with instillation of saline in mechanically ventilated patients. Following instillation of mesna, there was a significant increase in maximal airway resistance and impairment of oxygenation with a slight increase in $PaCO_2$ (SEDA-20, 183). A single episode of

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bronchorrhea occurred 10 minutes after the instillation of mesna.

In a randomized, crossover study, 25 volunteers received single doses of intravenous mesna and four different formulations of oral mesna (1). One subject withdrew from the study because of ocular inflammation followed by loss of appetite, nausea, and vomiting. Another developed a rash during the period in which three of his four oral doses were given. Two further subjects developed loose stools after one of the oral doses. Another reported dizziness after an oral dose. One reported pain at the site of the intravenous infusion. The adverse effects were all considered to be mild or moderate and resolved spontaneously without treatment.

Organs and Systems

Respiratory

Bronchorrhea due to inhaled mesna may be the result of mucolysis, but could also be caused by stimulation of bronchial secretions. Application by aerosol or nebulizer is occasionally followed by bronchospasm, but mesna is usually well tolerated by people with asthma (SEDA-20, 183).

Drug–Drug Interactions

Platinum cytotoxic agents

Platinum agents are now combined with ifosfamide in the treatment of cancer. The possibility that mesna may interfere with the anticancer effects of platinum has been investigated using cultured malignant glioma cells (2). Mesna protected tumor cell lines from the cytotoxic effect of the platinum agents. This in vitro study emphasizes the importance of specifying in detail the infusion schedules of mesna and platinum agents.

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Mesulergine

General Information

Mesulergine is an 8-alpha-aminoergoline derivative that acts as a dopamine receptor agonist. In a blind, crossover study in six patients with hyperprolactinemia, mesulergine 0.5 mg caused fewer adverse effects than bromocriptine 2.5 mg, while the prolactin release-inhibitory effect of the two was of the same order (1).

The most frequent adverse effect of mesulergine is dyskinesia, mostly in patients who have had similar reactions with levodopa. Orthostatic light-headedness and visual hallucinations are also common. Other adverse effects include anorexia, nausea, drowsiness, ankle swelling, insomnia, confusion, irritability, visual disturbance, chest pain, rash, and augmented body odor.

In one study of 17 patients with mild Parkinson's disease who were given either mesulergine or pergolide, mesulergine impaired the quality of life; frequent adverse effects were vomiting, lassitude, abdominal discomfort, depression, right bundle-branch block, fuzzy-headedness, and increasing insulin requirements in a patient with diabetes (SEDA-13, 113).

Reference

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Mesuximide

See also Antiepileptic drugs

General Information

Mesuximide (*N*,2-dimethyl-2-phenylsuccinimide) is a succinimide anticonvulsant with actions similar to those of ethosuximide. Its activity is mostly due to its main metabolite, *N*-desmethylmesuximide, which has a half-life of about 48 hours (1).

Mesuximide has been used in 112 children with intractable epilepsy taking other anticonvulsants (2). There was a 50% or greater reduction in seizure frequency in 40 patients after 9 weeks. After a mean of 3.7 years, 39 patients were still taking mesuximide and 22 of them had derived long-term benefit. In patients with good seizure control, fasting plasma concentrations of desmethylmesuximide were 25–45 μg/mg. Of the 112 patients 41 developed adverse effects while taking mesuximide treatment, but none was serious or irreversible.

Of 26 patients with complex partial seizures refractory to phenytoin, carbamazepine, phenobarbital, or primidone, mesuximide produced a 50% or greater reduction in seizure frequency in eight after 8 weeks, and five of those continued to benefit after 3–34 months (1). Drowsiness, gastrointestinal disturbances, hiccups, irritability, and headache were the common adverse effects.

Drug Administration

Drug overdose

Mesuximide can cause profound nervous system depression (3). In one patient this responded to charcoal hemoperfusion (1).

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Drug–Drug Interactions

Lamotrigine

In a retrospective study, in which 376 samples from 222 patients were analysed, mesuximide induced the metabolism of lamotrigine and reduced lamotrigine concentrations by about 70% (4).

Valproate

In 17 patients (12 men, 5 women; aged 8–19 years) the mean valproic acid concentration was 82 μg/ml while not taking mesuximide and 56 μg/ml while taking mesuximide (5). In eight patients who stopped taking mesuximide the mean serum concentration increased from 50 μg/ml to 72 μg/ml.

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Metalloporphyrins

General Information

Synthetic tin protoporphyrin is a specific inhibitor of heme oxygenase and reduces plasma bilirubin concentrations in both adults and neonates, thereby preventing jaundice (1–3). A variety of heme analogues, such as tin, zinc, chromium, and manganese metalloporphyrins, act by competitive inhibition of cleavage of heme to biliverdin and carbon monoxide. Stannic porphyrins seem to be the most effective. The adverse effects are few, with only occasional erythema attributable to the phototoxicity of the metalloporphyrins.

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Metamizole

General Information

Metamizole and phenyldimethylaminophenazone are the main derivatives of aminophenazone (amidopyrine) and are expected to provoke the same adverse reactions as aminophenazone itself.

Metamizole is still widely prescribed and openly sold as a headache remedy in some developing countries, but has been withdrawn from the market in many parts of the world. Curiously, in some Western countries it still enjoys a reputation as an injectable product that relieves renal colic. In other places it is entirely unknown and apparently not missed. Although it was German in origin, in 1987 the German authorities decided to subject all metamizole products to prescription-only regulations, a clear message to the regulatory authorities in other countries where it is sold without prescription (SEDA-12, 82). According to the Japanese authorities, suppositories and injectable formulations should be used only as a last resort, and warnings should be included in the package insert (SEDA-12, 83).

Metamizole was the single most commonly used agent causing adverse reactions (mainly hypersensitivity reactions, anaphylactic shock, and two deaths) in India, based on reports to an adverse drug reactions monitoring center by general practitioners (SEDA-16, 108).

Organs and Systems

Cardiovascular

In one case, intravenous injection of metamizole caused arterial hypotension (1).

Fluid balance

Fluid and salt retention have been observed in small children given metamizole (2).

Hematologic

The absolute risk of blood dyscrasias associated with the use of metamizole, particularly agranulocytosis (3), is unacceptably high.

In the International Agranulocytosis and Aplastic Anemia study (4), an epidemiological study organized by the manufacturers (Hoechst) of metamizole, the overall annual community agranulocytosis incidence was 4.4 per million (6.2 including hospital cases), with a fatality rate of 10% and an annual mortality rate of 0.4 per million. Analgesics significantly associated with agranulocytosis were metamizole, indometacin, oxyphenbutazone, and phenylbutazone. The International Agranulocytosis Study has been both criticized (5) and strongly defended (6).

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An analysis of all reports of blood disorders attributed to NSAIDs that were submitted to the Finnish National Board of Health during 1973–85 showed that metamizole was suspected of causing 14 cases of agranulocytosis (three fatal), other pyrazolones four cases, indometacin two cases, and ibuprofen one case (7).

In a study of all spontaneous reports of serious blood dyscrasias associated with metamizole and an analysis of prescription data the incidence was estimated to be at least one in 1439 prescriptions (95% CI = 850, 4684), of which 92% occurred during the first 2 months of treatment (8). These results stimulated comments and criticisms (9,10), but despite criticisms about the small number of cases identified in the study, this result confirms earlier ones (10).

Hemolysis has also been reported with metamizole (11). It is possibly due to cell membrane absorption of drug-antibody immune complexes.

Urinary tract

Nephrotoxicity from metamizole is rare (SEDA-17, 108).

Skin

An active amide group on metamizole has been shown to cause pemphigus vulgaris (12,13).

Drug Administration

Drug overdose

In a retrospective review of 243 patients who had taken an overdose of metamizole, median age 17 years (range 4 months to 83 years), median amount 5 g (250 mg to 45 g), and median time to consultation 2 hours (5 minutes to 48 hours), there were toxic effects in 39 (16%); 57% of these were gastrointestinal and all were mild (14). The time to consultation was longer in the symptomatic patients (4 versus 1.5 hours) and in children (8 versus 3.5 hours in adults). There were no cases of agranulocytosis. Suggested treatment includes gastrointestinal decontamination and supportive measures.

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Metaraminol

General Information

Metaraminol (2–10 mg intramuscularly) is used to treat serious hypotension. It has no noticeable central nervous effects and the beta-adrenoceptors of the heart usually do not react. The maximum effect of a dose is not at once apparent, and one should wait for some 10 minutes before deciding to give a further dose. In two patients an intravenous infusion of metaraminol to treat paroxysmal supraventricular tachycardia resulted in acute hypertension and pulmonary edema (1). Subcutaneous administration is risky and can result in dangerous sloughing.

Drug–Drug Interactions

Guanethidine

Guanethidine and related drugs make adrenoceptors highly sensitive to metaraminol (2).

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Methadone

General Information

Methadone is an OP_3 (μ) receptor agonist with pharmacological properties similar to those of morphine. It is an attractive alternative OP_3 opioid receptor analgesic, because of its lack of neuroactive metabolites, a clearance that is independent of renal function, good oral systemic availability, a longer half-life with fewer doses needed per day, and extremely low cost. It is mainly metabolized by CYP3A4.

Drug studies

Pain relief

Experience with methadone in cancer pain is limited. Its long half-life tends to produce delayed toxicity, especially in older patients, but in chronic renal insufficiency and stable liver disease methadone is safe, unlike morphine.

Methadone is being used increasingly for treating chronic pain and cancer pain (neuropathic and somatic) that is non-responsive or has lost responsiveness because of tolerance to high-dose μ opioid receptor agonists (for example morphine, fentanyl, oxycodone) (1). There are several protocols for converting from morphine to methadone and for initiating and stabilizing maintenance dosages.

In a prospective uncontrolled study, 45 patients with advanced cancer were given 0.1% methadone 2–3 times a day as required (2). Ten had nausea and vomiting, none had drowsiness, and 17 had constipation. In another study, nine of 29 patients in a tertiary level cancer pain clinic could not take opioid analgesics owing to uncomfortable adverse effects: nausea, vomiting, and drowsiness in four and other adverse effects in five (3). The average daily dose of methadone at the end of the titration phase (range 1–79 days) was 208 (range 15–1520) mg. Twenty patients had methadone toxicity during titration. In 12 patients mild drowsiness was a problem, six patients had nausea, and one patient each had confusion and severe headaches. In a third cross-sectional prospective study, 24 patients with advanced cancer pain were rapidly switched form oral morphine to oral methadone using a fixed ratio of 1:5 (4). There was a significant reduction in pain intensity and adverse effects intensity within 24 hours of substitution, although five patients required alternative treatments.

In a prospective, open, uncontrolled study 50 patients with a history of cancer taking daily oral morphine (90–800 mg) but with uncontrolled pain with or without severe opioid adverse effects were switched to oral 8-hourly methadone in a dose ratio of 1:4 for patients receiving less than 90 mg of morphine daily, 1:8 for patients receiving 90–300 mg daily, and 1:12 for patients receiving more than 300 mg daily (5). Methadone was effective in 80% of the patients when comparing analgesic response with opioid-related adverse effects. Ten patients were switched because of uncontrolled pain, eight because of moderate or severe adverse effects in the presence of acceptable pain control, and 32 because of uncontrolled pain with morphine-related adverse effects. In the last 32 there were significant improvements in pain intensity, nausea and vomiting, constipation, and drowsiness, with a 20% increase in methadone dose over and above the recommended starting dose.

In a prospective uncontrolled study of intrathecal methadone in 24 patients with a history of intractable chronic non-malignant pain, methadone was a better analgesic than morphine, with improved quality of life and no adverse effects in 13 patients (6). The final rates of methadone infusion were 20% higher than the preceding morphine rates.

Opioid dependence

An analysis of the balance of benefit to harm during methadone maintenance treatment for diamorphine dependence has shown lower mortality and morbidity with improvement in quality of life (7). The risks of methadone treatment include an increased risk of opiate overdosage during induction into treatment, and adverse effects of methadone in some patients. However, with careful management the benefits of prescribing methadone outweigh the risks.

The validity of self-reported opiate and cocaine use has been studied in 175 veterans enrolled in a methadone treatment program (8). Urine analysis showed higher rates of substance use than the patients themselves reported. The authors encouraged the development of more objective measures for assessing patient progress and the performance of the methadone program.

Organs and Systems

Cardiovascular

A variety of complications following parenteral self-administration of oral methadone were noted, including regional thrombosis, often associated with shock and multiorgan failure (9).

The use of methadone/dihydrocodeine has been linked to an acute myocardial infarction (10).

- A 22-year-old man with a 6-year history of intravenous heroin use was maintained on methadone 60 mg/day and dihydrocodeine 0.5 g/day. He had an extensive anterior myocardial infarction as a result of occlusion of the left anterior descending coronary artery, which was reopened by percutaneous transluminal coronary angioplasty.

This case presents circumstantial evidence only, and the association was probably not a true one.

There has been a report of five cases of episodes of syncope and an electrocardiogram showing ventricular tachydysrhythmias with prolonged QT intervals and episodes of torsade de pointes; all the patients were taking high doses of methadone (270–660 mg/day) with no previous history of cardiac disease (11). Torsade de pointes also occurred when high doses (3 mg/kg) of the long-acting methadone derivative, levomethadyl acetate HCl (LAAM), were given to a 41-year-old woman with a history of heroin dependence (12). She was also taking fluoxetine and intravenous cocaine, which can prolong the QT interval, and fluoxetine and marijuana, which

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inhibit the activity of CYP3A4, which is responsible for the metabolism of LAAM and its active metabolite.

In a retrospective case study in methadone maintenance treatment programs in the USA and a pain management center in Canada, 17 methadone-treated patients developed torsade de pointes during 5 years (13). The dose of methadone was 65–1000 mg/day. Six patients had had an increase in methadone dose in the months just before the onset of torsade de pointes. One patient had taken nelfinavir, a potent inhibitor of CYP3A4, begun just before the development of torsade de pointes. The above two risk factors (increased drug dosage and drug interactions) are important when eliciting the cause of torsade de pointes in patients taking methadone.

Respiratory

In 10 stable methadone-maintained patients (50–120 mg/day) and nine healthy subjects assessed using polysomnography, the methadone-maintained patients had more abnormalities of sleep architecture, with a higher prevalence of central sleep apnea (14). Methadone depresses respiration, probably by acting on μ opioid receptors in the ventral surface of the medulla and possibly on other receptor sites in the lung and spinal cord. All the patients taking methadone also used benzodiazepines and cannabis, which may have influenced the above findings.

Nervous system

Reversible choreic movements of the upper limbs, torso, and speech mechanism developed in a 25-year-old man taking methadone as a heroin substitute (15).

Spastic paraparesis has been attributed to methadone (16).

- A 43-year-old patient taking methadone for pain secondary to a squamous cell carcinoma of the larynx, which progressed despite surgery and radiation therapy, developed reversible spastic paraparesis with prominent extensor spasms in the legs while receiving an infusion of high-dose intravenous methadone 100 mg/hour. On the second day, after 5 hours on 100 mg/hour, he noted weakness in both legs, uncontrollable trembling, bilateral tinnitus, and generalized anxiety. Dexamethasone 6 mg intravenously every 6 hours was started and the methadone was reduced to 60 mg/hour. Dexamethasone was withdrawn when an MRI scan confirmed the absence of metastases in the thoracic and cervical spinal cord. Because of persistent spastic paraparesis, methadone was switched to levorphanol 40 mg/hour intravenously, and there was complete resolution of symptoms 24 hours later.

Methadone can cause movement disorders characterized by tremor, choreiform movements, and a gait abnormality (17).

- A 41-year-old woman with a 15-year history of chronic neuropathic pain was given methadone 5 mg tds and then qds. One month after the final increase she had bilateral tremor spreading from her arm up to her neck, followed by choreiform movements of the torso, a broad-based gait, and staccato-like speech. She was switched from methadone to modified-release oxycodone 60 mg/day, with complete resolution after 3 weeks.

Psychological, psychiatric

In a randomized, double-blind, crossover study of 20 patients on a stable methadone regimen, a single dose of methadone caused episodic memory deficits (18). This was significant in patients with a history of diamorphine use averaging more than 10 years duration. Such deficits can be avoided by giving methadone in divided doses.

Psychomotor and cognitive performance has been studied in 18 opioid-dependent methadone maintenance patients and 21 non-substance abusers (19). Abstinence from heroin and cocaine for the previous 24 hours was verified by urine testing. The methadone maintenance patients had a wide range of impaired functions, including psychomotor speed, working memory, decision making, and metamemory. There was also possible impairment of inhibitory mechanisms. In the areas of time estimation, conceptual flexibility, and long-term memory, the groups performed similarly.

Endocrine

Prolonged therapy with methadone causes increases in serum thyroid hormone-binding globulin, triiodothyronine, and thyroxine, as well as albumin, globulin, and prolactin, and these must be monitored (SEDA-15, 71) (SEDA-17, 81).

Fluid balance

Methadone-induced edema soon after start of treatment is recognized, and distal leg edema after 7 years of treatment has been described (SEDA-17, 81).

Gastrointestinal

In a randomized, double-blind, placebo-controlled trial of the efficacy of intravenous methylnaltrexone (0.015–0.095 mg/kg) in treating chronic methadone-induced constipation in 22 patients attending a methadone maintenance program (oral methadone linctus 30–100 mg/day), methylnaltrexone induced immediate bowel movements in all subjects (20). There were no opioid withdrawal symptoms or significant adverse effects.

Skin

Subcutaneous administration can cause skin erythema and induration at the injection site (SEDA-16, 81).

Parenteral self-administration of oral methadone can cause cellulitis, abscess formation, and necrosis of the skin and deeper tissues (9).

Death

There has been a cross-sectional survey of 238 patients in New South Wales who died during a methadone maintenance program in a 5-year period (21). There were 50 deaths (21%) in the first week of methadone maintenance

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treatment, 88% of which were drug-related. These findings reinforce the importance of a thorough drug and alcohol assessment of people seeking methadone maintenance treatment, cautious prescribing of methadone, frequent clinical review of patients, and tolerance to methadone during stabilization.

In a retrospective study of cases from the Jefferson County Coroner/Medical Examiners Office, Alabama, USA between January 1982 and December 2000 there were 101 deaths in patients in whom methadone was detected in the blood (22). Methadone was the sole intoxicant in 15 cases, with a mean concentration of 0.27 μg/ml. A benzodiazepine was the most frequently detected co-intoxicant in 60 of the 101 cases and the only co-intoxicant in another 30 cases. In 26 cases methadone had been taken with a range of non-benzodiazepine substances, including antidepressants, antipsychotic drugs, antiepileptic drugs, and cocaine. The high incidence of benzodiazepine + methadone related deaths can be explained by synergistic respiratory depression. Higher concentrations of methadone can occur with chronic abuse of methadone plus benzodiazepines, because over time benzodiazepines inhibit the hepatic enzymes that metabolize methadone. This might explain why the mean methadone concentration in the 30 deaths attributed to methadone plus a benzodiazepine was only 0.6 μg/ml.

Long-Term Effects

Drug tolerance

Several methadone studies have focused on opioid-dependent or opioid-abusing subjects. For example, six opioid-dependent individuals maintained on methadone subsequently developed cancer and continued to use methadone, but in a higher dose as an analgesic (16,23). The first five were partly refractory to the analgesic effects of opioids other than methadone, but all six achieved adequate analgesia without sedation or respiratory depression from aggressive upward intravenous methadone titration using an infusion of 100 mg/hour. Methadone was given in divided doses every 6–12 hours rather than once daily, as is customary in maintenance therapy for opioid dependence. The reasons for increasing the methadone dosage and frequency of administration are cross-tolerance to other opioids and the presence in methadone-maintained individuals of hyperalgesia to pain (a low pain tolerance to pain detection ratio) (24). These issues are also relevant to determining whether other drugs are more effective than morphine in managing acute pain in these patients.

Drug withdrawal

Four patients with methadone withdrawal psychosis have been described (SEDA-20, 79).

Second-Generation Effects

Pregnancy

Methadone is extensively used in opioid withdrawal and maintenance programs (see Drug tolerance in this monograph), and has been safely used for this purpose in pregnancy, with only mild effects on the offspring (25). However, fetal exposure to methadone in utero can cause a neonatal abstinence syndrome after delivery.

The outcomes in 100 chronic opiate-dependent pregnant women who received levomethadone substitution treatment have been reported (26). The average gestational age at delivery was 38 weeks and the mean birth weight was 2869 g. The rate of premature labor was 19% and the risk of premature delivery 11%. There were withdrawal symptoms in 74% of the neonates at a mean of 39 hours and all responded well to levomethadone.

Fetotoxicity

A newborn girl born of an HIV-positive mother who took antiretroviral drugs and methadone during pregnancy developed a methadone abstinence syndrome at day 7 (27). She was HIV-negative and was treated symptomatically for 15 days with chlorpromazine. The platelet count was 1049×10^9/l on day 17 and fell progressively to 290×10^9/l at 8 weeks. The authors suggested that the thrombocytosis had been secondary to intrauterine methadone exposure.

Susceptibility Factors

From a literature search and subsequent analysis of data on the relation between methadone prescribing and mortality, it was concluded that (28):

(a) 69% of deaths attributed to methadone occurred in subjects who had not previously received methadone;
(b) 51% of deaths attributed to methadone occurred during the dose-stabilizing period of methadone maintenance treatment;
(c) the dose of illicit methadone exceeded that prescribed for methadone maintenance therapy;
(d) deaths were attributed to discharge from prison and immediate intravenous injection of methadone in people who had lost their tolerance to high doses of methadone when incarcerated.

Subsequent advice related to the above identifiable susceptibility factors included:

(a) restriction of take-home prescriptions with daily supervised consumption of methadone in pharmacy premises;
(b) meticulous evaluation of substance abuse history;
(c) slowing down of increases and tolerance testing during the stabilization period of methadone maintenance; enhanced psychosocial assistance during the first months out of prison;
(d) use of naloxone as an adjunct to methadone syrup.

Drug Administration

Drug dosage regimens

The role of opioid rotation in cancer pain management has been described, highlighting the limitations of equianalgesic tablets and the need for monitoring and individualization of dose. This is particularly important

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when methadone is used as the opioid for conversion. The authors referred to a greater than expected potency of methadone, with excessive sedation and opioid-related adverse effects, if the switch is done on a one-to-one basis. They suggested that the calculated equianalgesic dose of methadone should be reduced by 75–90% and the dose then titrated upwards if necessary (29,30).

Drug administration route

Methadone has been used for intrathecal administration. Although this route can provide prolonged analgesia, the adverse effects have been reported to be unacceptable (SEDA-16, 81).

Of 90 patients undergoing abdominal or lower limb surgery randomly assigned double-blind to two groups, 60 received racemic methadone in initial doses of 3–6 mg followed by 6–12 mg by continuous infusion over 24 hours, and 30 received repeated boluses of 3–6 mg every 8 hours (31). In both groups the highest visual analogue score occurred 2 hours after surgery. From then on the pain diminished gradually and significantly at each recording. Opioid-related adverse effects were not different between the two groups, except for miosis, which was significantly more common in the bolus group. The results suggested that both epidural methadone protocols used in this study provide effective and safe postoperative analgesia. However, the infusion method should be preferred, as the doses of methadone can be reduced after the first day of treatment.

Drug–Drug Interactions

Antiretroviral drugs

Methadone is often used for opioid replacement therapy in intravenous drug abusers. The incidence of HIV infection is significantly higher in this population than in the general public, and interactions with drugs used for the treatment of AIDS are therefore important.

Methadone is predominantly metabolized by CYP3A4. Antiretroviral therapy with a non-nucleoside reverse transcriptase inhibitor (for example efavirenz, abacavir, and nevirapine) and/or a protease inhibitor (for example amprenavir) will induce the metabolism of methadone. This therapeutic combination is becoming increasingly common in HIV-positive substance misusers. Two studies have explicitly shown a significant reduction of methadone concentration by 28–87%. In the first study, 11 patients taking methadone maintenance therapy were given efavirenz and had a mean increase in methadone dosage requirement of 22% (32). In the second study, five methadone-maintained opioid-dependent individuals were given a combination of abacavir and amprenavir; the methadone concentration fell to 35% of the original concentration within 14 days (33).

In a prospective study of 54 patients taking antiretroviral drugs who also took methadone and a further 154 patients who did not take methadone there were similar clinical, virological, and immunological outcomes after 12 months (34). These results support the usefulness of methadone in the management of intravenous drug users with HIV infection.

Ritonavir, indinavir, saquinavir

In an in vitro study of the effects of the HIV-1 protease inhibitors, ritonavir, indinavir, and saquinavir, which are metabolized by the liver CYP3A4, all three protease inhibitors inhibited methadone demethylation and buprenorphine dealkylation in rank order of potency ritonavir > indinavir > saquinavir (35). Clinical studies are required to establish the further relevance of these observations.

Zidovudine

The metabolism of the antiviral nucleoside zidovudine to the inactive glucuronide form in vitro was inhibited by methadone (36). The concentration of methadone required for 50% inhibition was over 8 μg/ml, a supratherapeutic concentration, thus raising questions about the clinical significance of the effect. However, in eight recently detoxified heroin addicts, acute methadone treatment increased the AUC of oral zidovudine by 41% and of intravenous zidovudine by 19%, following the start of oral methadone (50 mg/day) (37). These effects resulted primarily from inhibition of zidovudine glucuronidation, but also from reduced renal clearance of zidovudine, and methadone concentrations remained in the target range throughout. It is recommended that increased toxicity surveillance, and possibly reduction in zidovudine dose, are indicated when the two drugs are co-administered.

Cimetidine

Cimetidine increases the effects of methadone, probably by inhibition of methadone metabolism (38).

Enzyme inducers

Enzyme-inducing drugs, such as carbamazepine, phenobarbital, phenytoin, and rifampicin, enhance the metabolism of methadone, leading to lower serum methadone concentrations (39).

Fluconazole

In a randomized, double-blind, placebo-controlled trial, oral fluconazole increased the serum methadone AUC by 35% (40). Although renal clearance was not significantly affected, mean serum methadone peak and trough concentrations rose significantly, while renal clearance was not significantly altered.

Phenytoin

Phenytoin enhances the metabolism of methadone (40).

Rifampicin

Enzyme-inducing drugs, such as rifampicin, enhance the metabolism of methadone, leading to lower serum methadone concentrations (40). This interaction is thought to have caused acute methadone withdrawal symptoms in two patients with AIDS (SEDA-16, 81).

Selective serotonin re-uptake inhibitors

Fluvoxamine

Fluvoxamine increases the effects of methadone, probably by inhibition of methadone metabolism (41).

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Paroxetine

Paroxetine 20 mg/day, a selective CYP2D6 inhibitor, was given for 12 days to 10 patients on methadone maintenance (42). Eight were genotyped as CYP2D6 homozygous extensive metabolizers and two as poor metabolizers. Paroxetine increased the steady-state concentrations of *R*-methadone and *S*-methadone, especially in the extensive metabolizers.

Use of methadone in opioid withdrawal

A widely used technique for opioid detoxification, pioneered by Isbell and Vogel (43), involves the substitution of methadone for the illicit opioid, followed by a gradual reduction in the amount of methadone taken.

Methadone maintenance treatment was established in 1964 in New York City by Vincent Dole and Marie Nyswander. In the initial studies, subjects who were heavily addicted to heroin were evaluated and stabilized on daily methadone doses as inpatients before transfer to an outpatient clinic for continued treatment. With further experience, it was feasible to drop the inpatient phase (44).

Methadone is used to substitute for a variety of opioid drugs. It is well absorbed after oral ingestion, with peak blood concentrations after about 4 hours. Steady-state concentrations are reached after about 5 days. By virtue of its long duration of action (the half-life with regular dosing is about 22 hours), methadone suppresses opioid withdrawal symptoms for 24–36 hours. In the early stages of treatment patients may report problems such as drowsiness, insomnia, nausea, euphoria, difficulty in micturition, and excessive sweating. With the exception of chronic constipation and excessive sweating, these effects do not generally persist.

Methadone maintenance treatment is considered to be a medically safe treatment with relatively few and minimal adverse effects. However, the danger of serious adverse effects and death with the increasing use of methadone as maintenance therapy in drug addicts has been highlighted. It must be emphasized that a daily maintenance dose of 50–100 mg is toxic in a non-tolerant adult and as little as 10 mg can be fatal in a child. There is an increasing number of reports of the deaths of children of mothers on maintenance therapy from inadvertent ingestion.

British studies have shown that, using methadone, about 80% of inpatients, but only 17% of outpatients, were successfully withdrawn (45,46). However, the technique is not without problems, one being that the methadone reduces but does not eliminate withdrawal symptoms. The withdrawal response has been described as being akin to a mild case of influenza, objectively mild but subjectively severe (47). The fear of withdrawal symptoms expressed by those dependent on drugs should not be underestimated: these factors are associated with the subsequent severity of withdrawal symptoms, and they are more closely related to symptom severity than drug dosage (48). Methadone substitution can result in a protracted withdrawal response, with patients still experiencing significantly more symptoms than controls 2 weeks after withdrawal (49).

In a study of methadone withdrawal, patients who were withdrawn over 10 days had a withdrawal syndrome that began to increase in severity from day 3, with peak severity of symptoms on day 13; in those who were withdrawn over 21 days, symptoms began to increase about day 10 with a peak on day 20 and abated thereafter, although some patients did not recover fully until 40 days after starting withdrawal (50). Thus, the duration of the withdrawal syndrome is much the same for both treatments in terms of symptom severity. It is possible that an exponential rather than linear reduction in dosage may improve the withdrawal response. These results may be of clinical significance, in that patients may feel it important that they recover from withdrawal as quickly as possible, in order to participate fully in other aspects of drug withdrawal programs. However, although there was no difference between the 10-day and 21-day programs regarding completion rates for detoxification (70 and 79% respectively), the dropout rates after detoxification were significantly different. During the 10 days after the last dose of methadone, the dropout rate in the 21-day group was 18% compared with 30% in the 10-day group. These results may also have financial implications in respect of the number of subjects who can be admitted to treatment programs.

In some treatment programs, total abstinence is not considered to be a practical objective and treatment may involve the use of drugs such as methadone as maintenance therapy with the expectation of reducing illicit drug consumption (51). Well-organized methadone maintenance treatment can reduce the intake of illicit opioids in many injecting drug users (52,53).

Outcome studies of methadone maintenance treatment have reported favorable results. High rates of patient retention, reduced criminality, and improved social rehabilitation are reported. Despite its proved effectiveness, it remains a controversial approach among substance abuse treatment providers, public officials, policy makers, the medical profession, and the public at large. Nevertheless, almost every nation with a significant narcotic addiction problem has established a methadone maintenance treatment program.

For patients entering treatment from an institution where they have been drug-free, initial daily methadone doses should be no more than 20 mg. Otherwise initial daily doses of 30–40 mg should be sufficient to obtain the necessary balance between withdrawal and narcotic symptoms. Thereafter, stabilization is achieved by gradually increasing the dose. When methadone is given in adequate oral doses (usually 60 mg/day or more), a single dose in a stabilized patient lasts 24–36 hours, without creating euphoria and sedation. Tolerance to methadone seems to remain steady, and patients can be maintained on the same dose, in some cases for more than 20 years. The methadone dose must be determined individually, owing to individual variability in pharmacokinetics and pharmacodynamics. Maintenance of appropriate methadone blood concentrations is recommended.

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Tolerance to the narcotic properties of methadone develops within 4–6 weeks, but tolerance to the autonomic effects (for example constipation and sweating) develops more slowly.

The major adverse effects during treatment occur during the initial stabilization phase. In addition to constipation and sweating, the most frequently reported adverse effects are transient skin rash, weight gain, and fluid retention. Since the main metabolic pathway of methadone is CYP3A4, numerous drug interactions can be expected. Drugs that interact with methadone are listed in the table in the monograph on opioids.

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Methanthelinium

General Information

Oral doses of 25–100 mg methanthelinium have typical anticholinergic adverse effects. Methanthelinium is considered to be more toxic than propantheline, mainly because its ganglion-blocking activity is relatively more marked than its antimuscarinic effect. Perhaps for this reason, impotence (1) has appeared to be a greater problem with this drug; central nervous adverse reactions, even including psychosis, have been reported in the past.

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Methapyrilene

See also Antihistamines

General Information

Methapyrilene is a first-generation antihistamine with a relatively strong sedative effect. It is therefore a constituent of many sedative and sleep-inducing over-the-counter formulations.

Long-Term Effects

Drug abuse

Owing to easy access and abuse, intoxication with a fatal outcome has been reported with methapyrilene (1).

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Methohexital

See also General anesthetics

General Information

Methohexital is an ultrashort-acting barbiturate that is widely used in dental anesthesia because of its rapid onset and short duration of action.

Of 4379 dental patients who received methohexital, 6.7% experienced restlessness, 5.5% respiratory disorders (respiratory obstruction, hiccuping, laryngeal spasm, apnea, or sneezing), 1.1% venous complications, 1.0%

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delayed recovery, 0.5% excitation, 0.27% nausea and vomiting, and 0.2% other mild reactions (1). Pain at the site of injection occurs in up to 64% of patients; the addition of lidocaine 10 mg significantly reduced the incidence to 22% (2).

A selective inhibitor of neuronal nitric oxide synthase, 7-nitroindazole, prolonged the duration of methohexital-induced narcosis in rats (3). This finding is consistent with previous work showing potentiation of anesthetic agents by non-specific nitric oxide synthase inhibitors.

Organs and Systems

Cardiovascular

Vasodilatation and depressed myocardial contractility are possible hemodynamic consequences of high-dose methohexital anesthesia (4).

Respiratory

Rectal administration of methohexital, sometimes used for children with needle-phobia, can cause apnea, particularly if there are pre-existing nervous system abnormalities (SED-12, 242) (5).

Nervous system

Seizures are a possible but rare complication of methohexital (6); it is inadvisable to use it in a patient with a history of epilepsy.

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Methotrexate

General Information

Methotrexate is a folic acid antagonist that acts by inhibiting dihydrofolate reductase. Owing to its immunosuppressive and anti-inflammatory properties, low-dosage methotrexate (7.5–15 mg/week) has been extensively investigated for other therapeutic purposes characterized by inflammation or cellular proliferation. Since the mid-1980s, methotrexate has become one of the most widely used disease-modifying anti-rheumatic drugs (DMARDs) in rheumatoid arthritis. It also has a significant degree of efficacy in psoriasis, asthma, and inflammatory bowel disease, and may also be effective in systemic lupus erythematosus, giant cell arteritis, and Wegener's granulomatosis. The exact mechanisms by which methotrexate affects these diseases are still uncertain, and its clinical effects probably result from multiple biochemical events at a variety of cellular sites (1).

General adverse effects

Most of the experience regarding the adverse effects of low-dose methotrexate has accumulated in patients with rheumatoid arthritis. Adverse effects are very common during the first year of treatment and reach an incidence of 60–70%. However, they are rarely severe enough to require permanent drug withdrawal, even after very long-term treatment. Based on a cohort study of 152 patients with rheumatoid arthritis, the probability of methotrexate continuation was 30% at 10 years, and adverse effects were the most frequent reason (50%) for drug withdrawal (2). Even though the overall withdrawal rate for methotrexate-induced adverse effects is 7–16%, long-term methotrexate treatment required drug withdrawal because of adverse effects less often than several other second-line DMARDs (SEDA-22, 416). In a retrospective analysis of 437 rheumatoid arthritis patients treated for 3–106 months (mean = 35 months), the most common adverse effects were gastrointestinal disorders (20%), raised liver function tests (13%), respiratory disorders (6.4%), hematological abnormalities (4.4%), weakness (3.4%), central nervous system disorders (2.8%), infections (2.3%), mucocutaneous disorders (2.3%), and arthralgia (1.8%) (3). A Ritchie's index of 10 or less, a low polymorphonuclear leukocyte count, and the absence of rheumatoid factor predicted the occurrence of adverse effects.

In one study, 10 patients (of an original 29) were still taking methotrexate after a mean of 13 years and a mean cumulative dose of 9.7 g (4). The overall drug withdrawal rate was 48%, and the rate of adverse effects, particularly on the gut and central nervous system, fell with time (85% at baseline, 90% at 90 months, 62% at 160 months). It was felt that routine folate supplementation might have contributed to the observed reduction in toxicity, except for mouth ulcers or soreness. Very similar findings were found in another long-term (132 months) prospective study (5).

Raised methotrexate serum concentrations (over 100 nmol/l at 36–42 hours after ingestion) are expected to increase the likelihood of several adverse effects, that is, gastrointestinal and hematological effects, but similar adverse effects can be found even with low methotrexate serum concentrations. Reduced red cell folate concentrations during methotrexate treatment also related to adverse effects and rises in liver enzymes, and red cell folate concentrations above 800 nmol/l protected against common adverse effects and treatment withdrawal (6). Several investigators now advocate the concomitant use of folic acid (5–7 mg/week and up to 27.5 mg/week) to reduce some of methotrexate-associated adverse effects without reducing its efficacy (7).

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Prevention of adverse effects

It is possible to reduce the incidence of several adverse effects of methotrexate by using folic or folinic acid. The usual practice is to give weekly folic acid in patients who are taking weekly methotrexate (on a different day) and daily folinic acid in those who are taking daily methotrexate. Folic acid supplementation is now commonly given to reduce the adverse effects of methotrexate, in particular its mucosal and gastrointestinal toxic effects (SED-14, 1297) (SEDA-23, 406), but less is known about how long this should be continued in patients taking long-term treatment.

In a meta-analysis of 307 patients with rheumatoid arthritis from seven randomized clinical trials, of whom 147 took folate supplementation, hematological adverse effects were not significantly reduced in the folate group (8). However, there was a 79% reduction in mucosal and gastrointestinal adverse effects in patients taking folic acid and a non-significant trend toward a reduction (42%) in patients taking folinic acid. Disease activity was not modified by low doses of folate. Finally, the authors noted that folinic acid is more expensive.

In 75 patients with rheumatoid arthritis taking methotrexate (up to 20 mg/week) and folic acid (5 mg/day), folic acid was withdrawn and the patients were randomized to restart folic acid ($n = 38$) or to take placebo ($n = 37$) double-blind, and were regularly assessed for 1 year (9). There were more withdrawals with placebo (46%) than with folic acid (21%) and more nausea. There were no obvious differences in efficacy. This suggests that folic acid supplementation is still helpful in the long term.

Organs and Systems

Cardiovascular

Cardiovascular adverse effects of methotrexate are extremely rare.

- There has been one detailed report of ventricular dysrhythmias and myocardial infarction, with recurrence of frequent ventricular extra beats on each readministration of methotrexate in a 36-year-old man (10).

It has been suggested that methotrexate increases mortality in patients with rheumatoid arthritis with cardiovascular co-morbidity (11). This assumption was based on a retrospective analysis of 632 patients with rheumatoid arthritis, of whom 73 died. The simultaneous presence of methotrexate and evidence of cardiovascular disease was an independent predictor of mortality. There was no such association with other DMARDs. The authors suggested that this effect may result from a methotrexate-induced increase in serum homocysteine, encouraging atherosclerosis.

Respiratory

Isolated and sustained cough is an unusual adverse effect of methotrexate. Among 13 patients who had a cough, only three met the criteria for methotrexate-induced pneumonitis (12). An irritant effect of methotrexate on the airways was therefore suggested.

Pneumonitis

Acute or subacute interstitial pneumonitis is an important but unpredictable and potentially life-threatening adverse effect of low-dose methotrexate (13–16).

Presentation

In patients with definite or probable methotrexate-induced lung injury, the predominant clinical features include shortness of breath, cough, and fever (13). Pathological examination usually shows an interstitial inflammatory cell infiltrate (sometimes granulomatous or with alveolar damage), and variable degrees of interstitial fibrosis. Unfortunately, confirmatory evidence is sometimes hard to obtain, particularly in patients with rheumatoid arthritis in whom rheumatoid interstitial lung disease can also occur. Infectious pneumonias, particularly viral or *Pneumocystis jiroveci* pneumonia, which resemble methotrexate pneumonitis and can occur as a result of immunosuppression, should also be carefully excluded.

- Pulmonary endoalveolar hemorrhage was a possible complication of pneumonitis in a 57-year-old woman who voluntarily increased her dosage of methotrexate from 7.5 mg once a week to 7.5 mg/day for 15 days (17).

The potential severity of methotrexate pneumonitis was finally exemplified in a careful retrospective multicenter study of 29 patients with definite or probable criteria for methotrexate-induced lung injury (13). Overall, five patients (17%) died, two of them after methotrexate rechallenge.

Frequency

The prevalence of methotrexate pneumonitis has been variably estimated from 0.3 to 18%, with a mean estimated prevalence of 3.3% (14,16). In a review of the respiratory complications of methotrexate, the authors concluded that pneumonitis occurs in 7% of patients, in 25% of whom it is fatal as a result of respiratory failure (18). This can occur with any dose of methotrexate, given via any route; it has occurred after the intrathecal administration of 12 mg given for central nervous system prophylaxis (19). In a review of 194 patients with rheumatoid arthritis and 38 with psoriatic arthritis, the prevalences of pneumonitis were 2.1 and 0.03% respectively (14), which is similar to the 3.2% incidence in a prospective study of 124 patients with rheumatoid arthritis (20). Another analysis performed over 5 years showed that the estimated prevalence of definite or probable pneumonitis was only 0.86% in 1162 patients (10 patients, of whom three died), but this conclusion was based on a limited retrospective identification of cases (21).

Mechanism

Even though methotrexate pneumonitis was first described about 30 years ago, very little is known about the mechanism, and whether it is due to direct cumulative toxicity, hypersensitivity, or an idiosyncratic reaction. In one case, interleukin-8 was speculated to play an important role in the pathogenesis (22).

Susceptibility factors

Susceptibility factors for methotrexate pneumonitis are still poorly understood. In one study, no risk factors were

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identified and periodic pulmonary function tests were not predictive (20). In contrast, advanced age, diabetes, pre-existing rheumatoid pleuropulmonary involvement or previous lung disease, previous use of DMARDs, and hypoalbuminemia were suggested as the most reliable predictors of methotrexate-induced pneumonitis in a large historical case-control study (15,23). The weekly dose, the cumulative dose, and the duration of treatment were not related to its occurrence. A history of drug-induced pulmonary disorders was also thought to favor methotrexate pneumonitis, but this was based on a single case report in a patient who previously had aminorex-induced primary pulmonary hypertension (SEDA-22, 416).

Management

The management of methotrexate pneumonitis primarily requires methotrexate withdrawal and supportive care. Although glucocorticoids are commonly used, there is as yet no evidence that they positively influence the outcome. Any readministration of methotrexate is dangerous, and four of six patients treated again with methotrexate developed recurrent lung toxicity, of whom two died (13).

Based on a report of 9 cases and a careful reanalysis of 123 previously published cases, the clinical spectrum and histopathology of methotrexate-induced pneumonitis have been reviewed (24). The authors stressed that methotrexate pneumonitis should be promptly recognized to avoid a severe outcome, although no specific features could be identified compared with other drug-induced adverse lung effects and no definite pathological findings compared with rheumatoid lung. Diagnostic criteria therefore mostly included a history of exposure, the exclusion of other pulmonary diseases, especially infections, and the presence of pulmonary infiltrates on the chest X-ray. Once methotrexate pneumonitis developed, 13% of the patients died from respiratory failure, clearly underlining the fact that methotrexate pneumonitis is potentially life-threatening. Methotrexate reintroduction should also be strongly discouraged in such cases, because about 25% of patients experience recurrence.

Nervous system

Reports of necrotizing leukoencephalopathy in association with methotrexate have been verified by biopsy or autopsy (25,26). Serial electroencephalography can predict this, since slow-wave activity develops during the administration of high-dose methotrexate. Autopsy has shown widespread necrosis and spongiosis in the cerebral and cerebellar white matter in such cases (25).

Chronic brain edema, multifocal white matter necrosis, and deep brain atrophy have been reported in patients who received high-dose methotrexate therapy, with an incidence of 4% (27). All patients received methotrexate 8–9 g/m^2 intravenously over 4 hours. The encephalopathy began abruptly, an average of 6 days after the second or third weekly treatment, presenting with behavioral abnormalities. These ranged from laughter to lethargy or unresponsiveness. In some patients, there were focal sensorimotor or reflex signs and generalized seizures. The disorder lasted from 15 minutes to 72 hours, and it disappeared as abruptly as it began, without specific treatment.

A rare case of a reversible neurological disturbance associated with focal subcortical white matter pathology has been described after administration of methotrexate 3 g/m^2. In patients who received 8–12.5 g/m^2, the incidence of neurological abnormalities was 4%. All of these patients were also receiving methotrexate intrathecally as well, but the relevance of this is not known (28).

In one case, low-dose methotrexate was implicated in leukoencephalopathy (29).

Treatment with intrathecal methotrexate of children under 5 years of age with acute lymphoblastic leukemia (irrespective of other drugs) has structural and functional effects on the developing neocerebellar–frontal subsystem (30).

Acute dysarthria has been attributed to methotrexate (31).

- A 71-year-old man was given oral methotrexate (15 mg/week) for a cutaneous T cell lymphoma. Within 3 weeks he developed progressive dysarthria and incoordination, and neurological examination showed mild buccofacial dyskinesia. Complete examination was otherwise normal, and he fully recovered 6–8 weeks after methotrexate withdrawal.

This case is reminiscent of other previously reported neurological abnormalities with low-dose methotrexate.

Psychological, psychiatric

There was a significantly higher risk of late cognitive impairment (concentration and memory) in patients ($n = 39$) taking adjuvant cyclophosphamide, fluorouracil, and methotrexate than in controls matched for age, disease, surgery, and radiation dose (32).

In studies of the neurotoxic effects of low-dose methotrexate treatment, dizziness, headache, visual disturbances or hallucinations, lack of concentration, cognitive dysfunction, and depression-like symptoms were detected in 1–35% of patients (33,34). Advanced age and mild renal insufficiency were possible susceptibility factors (34).

Nutrition

Of patients receiving high-dose methotrexate (5–8 g/m^2), 95% developed a significant increase in serum phenylalanine concentrations, probably due to inhibition of dihydropteridine reductase (35). The clinical significance of this is not obvious, although it is possible that it may contribute to the transient neurological disturbance observed in some patients taking high-dose methotrexate.

Hematologic

Significant hematological abnormalities occur in 10–24% of patients who take methotrexate. Mild to moderate leukopenia is the most frequent, followed by thrombocytopenia. Isolated thrombocytopenia and anemia are uncommon (SEDA-22, 416) (36). In a retrospective study in 315 patients, 13 had thrombocytopenia, two of whom also had pancytopenia (37). Thrombocytopenia correlated with the weekly dosage of methotrexate administered on the same day as NSAIDs, and methotrexate was safely reintroduced in patients who developed thrombocytopenia as a result of concomitant administration of

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both drugs, provided that NSAIDs were withheld at least on the day of methotrexate administration.

Pancytopenia is a rare but potentially fatal complication, and numerous reports have been published. The characteristics and incidence of pancytopenia have been carefully re-evaluated from case reports and clinical trials published from 1980 to 1995 (38). Of 70 reported cases, 12 patients died (17%). Impaired renal function was the most important contributing factor (54%), particularly in fatal cases (10/12). Other important susceptibility factors included advanced age (over 65 years), hypoalbuminemia, concurrent infection, and/or concomitant multiple medications (particularly co-trimoxazole). The mean cumulative dosage was 675 (10–4800) mg, and the minimal cumulative methotrexate dose leading to fatal pancytopenia was 10 mg. This confirms that pancytopenia can occur at any time during treatment, even in the absence of known susceptibility factors. Bone marrow biopsy showed megaloblastosis and hypocellularity. Eosinophilia and increased mean corpuscular volume were rarely observed. In an overall review of five long-term prospective studies (511 patients), the calculated incidence of methotrexate-induced pancytopenia was 1.4%. Although severe myelosuppression sometimes required folinic acid, there are as yet no data to determine whether prophylactic folate supplementation can reduce the incidence of pancytopenia.

In a double-blind, placebo-controlled study of the safety and efficacy of methotrexate therapy combined with glucocorticoids in patients with giant cell arteritis over 24 months, adverse events were defined as a new diagnosis of any condition during treatment (39). The combination of methotrexate plus prednisolone reduced the number of relapses and improved the course of the disease. Methotrexate was withdrawn in three patients who had adverse events that were clearly drug-related. One had leukopenia, anemia, and mucositis, one developed pancytopenia, and one oral ulcers. These patients were not taking folic acid or folinic acid supplements.

Gastrointestinal

Gastrointestinal adverse effects (stomatitis, anorexia, abdominal pain, dyspepsia, nausea, vomiting, diarrhea, and weight loss) are very common, particularly after oral administration of methotrexate (up to 50%), and often require dosage adjustment (3). Folic acid supplementation reduces the incidence of several gastrointestinal adverse effects.

Stomatitis can sometimes be particularly harmful and has been reported as the cause of transient or permanent treatment withdrawal in 4.5 and 1.1% of 1539 patients respectively (40). However, one study did not show significant differences in the number of oral lesions or the duration or frequency of stomatitis between patients with rheumatoid arthritis taking methotrexate and those not taking methotrexate (19/51 versus 9/46), although the prevalence of ulceration was higher in the methotrexate group (41).

Liver

Cytolytic hepatitis has been reported in a 58-year-old man being treated with intramuscular methotrexate 10 mg/week (total dose over the previous 4 years 2.3 g); it resolved within 2 weeks of stopping therapy (42).

Hepatic fibrosis and cirrhosis

The main concern over long-term treatment with methotrexate is hepatic fibrosis and cirrhosis. Methotrexate hepatotoxicity was initially reported in children given high daily dose methotrexate for leukemia. After its introduction for the treatment of psoriasis, several papers published in the late 1960s pointed out the possible risk of severe hepatic fibrosis and cirrhosis in patients taking moderate daily doses. Since then many studies have focused on the extent of long-term methotrexate hepatotoxicity in patients taking low-dose methotrexate for psoriasis and rheumatoid arthritis. However, the evidence on the frequency and severity of severe liver disease in these patients is still highly controversial, since there may be liver histological changes before methotrexate treatment, particularly in patients with psoriasis. Furthermore, there are numerous confounding factors (Table 1) which can contribute to histological liver changes, leading several authors to suggest as early as 1990 that methotrexate-induced hepatic fibrosis and cirrhosis is uncommon and only occurs in patients with other susceptibility factors (43).

Frequency

The incidence of liver cirrhosis after a mean dose of 2 g is 7–10%. Once 1.5 g has been administered (44), or 2 years after starting long-term treatment, biopsy should be discussed (45).

Liver failure or cirrhosis were identified among 24 patients in a retrospective survey of more than 16 600 patients with rheumatoid arthritis who had taken

Table 1 Susceptibility factors for hepatotoxicity of methotrexate

Strong association	Previous or concurrent heavy alcohol use
	Pre-existing liver disease
	Daily methotrexate administration
	Renal insufficiency
Probable association	Duration of methotrexate treatment (over 2 years)
	Cumulative methotrexate dose (over 1500 mg)
	Prior treatment with arsenicals
	Obesity with diabetes mellitus
Possible or potential association	Maximum weekly dose over 25 mg
	Obesity alone
	Diabetes mellitus alone
	Heterozygous alpha$_1$ -antitrypsin deficiency
	Felty's syndrome
	Prior treatment with vitamin A
	Concurrent NSAID use
	Concurrent treatment with ciclosporin
	Concurrent PUVA treatment
No association	Sex
	HLA phenotype
	Extent of psoriatic skin involvement
	Duration of rheumatoid arthritis
	Glucocorticoid therapy
Negative association	Concurrent folate supplementation
	Concurrent hydroxychloroquine use

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methotrexate for at least 5 years, giving an estimated 5-year frequency of one in 1000 (46).

No morphological features of methotrexate hepatotoxicity were demonstrated after 2 years of methotrexate treatment in 48 patients with primary biliary cirrhosis (47).

Collectively, the available data suggest that methotrexate rarely causes significant serious liver damage in patients who have been otherwise carefully selected, who present no risk factors for methotrexate-induced hepatotoxicity, and who have received lower weekly dosages with strict monitoring of liver function (for example transaminases) in order to reduce methotrexate doses when liver enzymes are persistently raised (48).

Diagnosis and monitoring

Routine liver function tests do not reliably indicate liver damage, and they may not become abnormal until there is already considerable liver damage. It is therefore common practice to monitor patients by conducting annual liver biopsies. Measurement of the serum amino-terminal propeptide of type III procollagen (PIII PI) has been used as an alternative to liver biopsy; high concentrations correlate with fibrosis on liver biopsy (49). No patient with a normal serum concentration had an abnormal biopsy. An increase in the plasma phenylalanine/tyrosine ratio in children and adolescents can provide clinical evidence of liver damage before the appearance of symptoms in patients who have taken high doses of methotrexate (50).

Methods of monitoring patients for possible methotrexate hepatotoxicity and guidelines have been reviewed (48,51,52). It should be mentioned that the frequent rise in serum transaminases (involving 30–80% of patients) after the start of treatment is transient and does not predict liver damage; only persistently abnormal transaminases are potential indicators of methotrexate hepatotoxicity.

Mechanism

Folate depletion may be a factor in the pathogenesis of methotrexate-induced liver disease. In 30 patients on long-term methotrexate therapy, aimed at determining whether erythrocyte concentrations of folate and methotrexate might provide an indication for liver biopsy, there was no difference between red cell folate concentrations in patients with cirrhosis or progressive liver fibrosis and patients without fibrosis or with non-progressive hepatic fibrosis. Erythrocyte methotrexate concentrations were higher in patients with progressive hepatic disease, but cumulative dose and length of treatment were stronger predictors. In individual cases, erythrocyte folate and methotrexate concentrations were not a reliable guide (53).

Pathology

In patients with rheumatoid arthritis, baseline histological liver abnormalities were less common, with mild fibrosis only in 0–15% of patients. In retrospective studies with no pre-methotrexate liver biopsies, mild fibrosis was found in 3–35% of patients taking methotrexate, moderate or severe fibrosis in 0–10%, and cirrhosis in 0–2%. However, no case of cirrhosis was identified in studies which compared pre- and postmethotrexate biopsies or sequential biopsies while on long-term methotrexate, that is, a mean cumulative dose of 1200–5000 mg (52). Again, both worsening and improvement of histological lesions occurred. The application of guidelines to prevent methotrexate hepatotoxicity may account for these reassuring results. Liver biopsy changes were moderate or absent in patients with juvenile rheumatoid arthritis who took a cumulative dose of over 3000 mg (SEDA-21, 388) (52).

In 22 of 29 patients (76%) who were treated with low-pulse doses of methotrexate for rheumatoid arthritis, liver biopsy specimens showed variability in liver cell nuclear size, glycogenated nuclei, and fatty change. Occasionally there was mild portal infiltration with lymphocytes. There were no significant differences in age, duration of treatment, or cumulative dose amongst the cases. Serial increases in serum transaminases and/or alkaline phosphatase activity and development of hypoalbuminemia during treatment were indicators of development of liver disease (54).

In another study, the pathological lesions found in liver biopsies from patients treated with methotrexate were non-specific, consisting usually of macrovesicular steatosis, nuclear pleomorphism, chronic inflammatory infiltrates in the portal tracts, focal liver cell necrosis, fibrosis, and cirrhosis (52).

The pathological features of methotrexate-induced liver damage have been comprehensively reviewed (52). In patients with psoriasis, baseline liver biopsies were often abnormal, with mild fibrosis, moderate or severe fibrosis, and cirrhosis in 0–30, 0–7, and 0–1.5% respectively. These figures increased after methotrexate use, with fibrosis and cirrhosis in 14–34 and 0–21% respectively.

Ultrastructural studies have sometimes identified Ito cell prominence and collagen deposition in the perisinusoidal space of Disse during the first months of treatment and before the appearance of any signs of fibrosis, but these findings have been disputed in rheumatoid arthritis patients. Using immunohistochemical quantification, increased matrix proteins, collagen and transforming growth factor alpha were also found as possible early markers of methotrexate hepatotoxicity (55).

Susceptibility factors

The susceptibility factors for methotrexate-induced hepatotoxicity are listed in Table 1.

In a meta-analysis of 636 patients from 15 studies, who took chronic low-dose methotrexate for rheumatoid arthritis or psoriasis, the risk of liver toxicity increased with cumulative dose and heavy alcohol intake (56).

In one study, the risk of developing cirrhosis progressively increased with the total cumulative dose of methotrexate, from 13% at 2200 mg to 26% at 4000 mg (57). However, studies that compared sequential liver biopsies in patients on treatment and included specific recommendations for patient selection and the monitoring of methotrexate hepatotoxicity, gave contrasting results, with a lower incidence of cirrhosis even after high cumulative methotrexate doses (up to 5100 mg) (52). In addition, although histological lesions can worsen during treatment, improvement or absence of progression of prior fibrosis/cirrhosis has been found in very long-term follow-up of patients still taking methotrexate after 10 years (58).

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The incidence and susceptibility factors of rises in serum transaminases have been detailed from a retrospective analysis of 66 patients with rheumatoid arthritis (59). There was an asymptomatic increase in serum transaminases in 42 and 49% of patients respectively, an incidence 4–5 times greater than that found in 21 patients taking other DMARDs. Although most of the rises in transaminases were transient and spontaneously reversible, 14 patients had sustained rises. There was a close relation between the incidence of high transaminases and the weight-adjusted dose of methotrexate. In a multivariate regression analysis, only obesity, methotrexate dose (over 0.15 mg/kg/week), and the concomitant presence of gastrointestinal adverse effects were significantly and independently associated with the likelihood of a rise in alanine transaminase. In the 14 patients who had persistently high transaminases, weekly folic acid 5 mg produced a sustained fall in serum alanine transaminase within 3 months, but three patients had to be withdrawn because of exacerbation of rheumatoid arthritis.

Urinary tract

Low-dose methotrexate is usually not regarded as nephrotoxic, and one report of nephrotic syndrome with minimal change disease on renal biopsy should be regarded with caution, since there was recovery after glucocorticoid treatment and withdrawal of concomitant NSAIDs (SEDA-22, 416).

However, renal toxicity occurs with high-dose methotrexate and more likely to occur with concomitant administration of other nephrotoxic agents, such as aminoglycosides, cephalosporins, NSAIDs, and diuretics (60).

The pathogenesis of methotrexate-induced nephrotoxicity is not understood, but it is thought to result from crystallization of methotrexate in the renal tubules. Adequate hydration and urinary alkalinization are necessary to minimize this effect (61). Urinary beta$_2$ microglobulin may be a useful marker of methotrexate nephrotoxicity (62).

When serum methotrexate concentrations are high, leucovorin (folinic acid) rescue may protect against renal damage. Methotrexate concentrations are only transiently lowered by hemoperfusion, and they are unaffected by peritoneal dialysis once there is acute renal insufficiency. Sustained reductions in drug concentrations and recovery of renal function have been reported after charcoal hemoperfusion followed by hemodialysis (63,64).

Co-administration of methotrexate and procarbazine in the treatment of medulloblastomas increases the risk of methotrexate nephrotoxicity. Delayed administration of methotrexate until 72 hours after procarbazine therapy has been given may reduce this risk (65).

Skin

Since the first descriptions of the rapid development of a large number of nodules, also termed "accelerated nodulosis," in methotrexate-treated patients, a number of such reports have accumulated in patients with rheumatoid arthritis or, more rarely, psoriatic arthritis (66–68). Nodulosis is characterized by the development of small, painful, multiple nodules, sometimes disseminated; pulmonary, meningeal, or pericardial nodulosis has also been reported in a few patients (SEDA-21, 387) (67,69,70). Four cases of nodulosis and four of cutaneous vasculitis were noted during a long-term follow-up of 437 rheumatoid arthritis patients (3), but the estimated incidence of accelerated nodulosis was found to be higher in other studies: that is, 8–12% (5,66,70).

The nodules can appear at any time during treatment, with or without concomitant cutaneous vasculitis, and are usually found in patients with erosive disease and a high titer of rheumatoid factor. This has raised the question as to whether they are a reason to modify treatment, and whether they are rheumatic or represent a true adverse effect of methotrexate; certainly, methotrexate-associated nodulosis is very similar to idiopathic rheumatoid arthritis nodulosis and sometimes disappears despite continuation of methotrexate. However, prompt regression on methotrexate withdrawal and recurrence on rechallenge in several patients strongly argue for a causal drug-related effect.

There was a characteristic clinical and histopathological spectrum of skin lesions, distinct from rheumatoid papules, in four patients who took low-dose methotrexate for acute flares of collagen vascular disease (71). These so-called methotrexate-induced rheumatoid papules developed shortly after methotrexate administration consisted of erythematous indurated papules mostly affecting the proximal limbs, and disappeared after methotrexate was withdrawn or tapered. Histology showed inflammatory infiltrates of interstitially arranged histiocytes and a few neutrophils, but no features of leukocytoclastic vasculitis.

Isolated cutaneous leukocytoclastic vasculitis occurs infrequently in patients taking methotrexate, and an immediate-type hypersensitivity reaction has been thought to be involved, in view of prompt recurrence after drug readministration or a positive mast cell degranulation test as recorded in several patients (SEDA-21, 388) (SEDA-22, 417) (72).

Other isolated reports included the occurrence of skin ulceration (SEDA-22, 388) and one fatal case of toxic epidermal necrolysis (SEDA-21, 388).

Persistent hyperpigmentation is an unusual manifestation of weekly administration of methotrexate (73).

- Severely ulcerated psoriatic plaques and acute extensive exfoliative dermatitis occurred in a 37-year-old man who had taken methotrexate for 5 years for psoriasis (74).

In the context of a case of severe reactivation of recent sunburn after a single injection of methotrexate for ectopic pregnancy in a 40-year-old woman, the authors reviewed the literature on methotrexate photosensitivity (75). Photodermatitis reactivation is the only well-documented type of photosensitivity associated with methotrexate. It can occur if methotrexate is given at 2–5 days after excessive exposure to ultraviolet or X-radiation.

A previously unreported skin reaction mimicking Stevens–Johnson syndrome has been reported (76).

- A 61-year-old woman inadvertently took a high dose of methotrexate (10 mg/day) for psoriasis, and developed mucosal ulcers after 3 months. One month later, methotrexate (20 mg/week) was restarted, but she developed

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painful oral ulceration and burning skin lesions 3 days later. She had an erythema multiform-like rash and several buccal ulcers. There was a moderate pancytopenia. Histological examination of the skin showed features consistent with an acute graft-versus-host reaction. All medications except aspirin were withdrawn, and she recovered fully after treatment with calcium folinate and prednisolone.

The authors speculated that concomitant aspirin may have contributed to this severe reaction.

Hair

Mild alopecia is common in patients taking methotrexate (77,78).

Nails

Yellow nail pigmentation without paronychia has been noted in a patient with psoriasis taking methotrexate (79).

Musculoskeletal

Arthralgia and myalgia sometimes occur within 24 hours of methotrexate injections in patients with rheumatoid arthritis. These transient effects, which can be accompanied by fatigue, malaise, and various neuropsychological disorders, have escaped recognition, but they occurred in 10% of patients over 18 months and sometimes resulted in treatment withdrawal (80).

Leg pain and spontaneous fractures attributed to prolonged high-dose methotrexate therapy in pediatric oncology have been recognized since the 1970s, but there have been some cases in patients taking low-dose methotrexate (81,82). All the same, it is still controversial as to whether methotrexate can actually cause changes in bone metabolism (83). There was a significant reduction in bone mineral density in 11 postmenopausal women taking methotrexate for primary biliary cirrhosis compared with 11 matched controls not taking methotrexate (84). Among 133 patients with rheumatoid arthritis, methotrexate without glucocorticoids was not associated with changes in the bone mineral density after 3 years of treatment, but methotrexate plus prednisone (over 5 mg/day) produced greater bone loss than prednisone alone (85). In contrast, another study failed to show accelerated bone loss in methotrexate users compared with non-users, but the study was limited to 10 patients in each group (86).

The possible effects of methotrexate on bone metabolism and bone loss have been discussed in the context of two adults (87) and in relation to a study in children with juvenile rheumatoid arthritis (88) who had delayed bone healing after surgery. The two adults, aged 52 and 62 years, had been taking methotrexate (7.5 and 15 mg/week) for 14 and 15 months when they underwent metatarsal and tibial osteotomy. Because X-ray examination 5 and 6 months after surgery showed non-union, methotrexate was withdrawn; the bone healed promptly in both patients within 2 months. The authors thought that the outcome in these patients without risk factors for bone fragility suggested that temporary methotrexate withdrawal should be considered in cases of delayed bone healing after surgery.

In contrast, in a longitudinal study of 32 patients with juvenile rheumatoid arthritis, there was no evidence of deleterious effects of long-term, low-dose methotrexate on bone mass density (88). The cumulative dose of glucocorticoids, weight, and height were the main determinants of bone mass changes.

Furthermore, there is evidence that it is disease activity rather than methotrexate that accounts for changes in bone mass (89). This 2-year longitudinal study involved 22 patients taking methotrexate and 18 patients taking other DMARDs; it was strictly controlled for the use of glucocorticoids. There were significant and equal reductions in trabecular bone mineral density in both groups. Bone loss was most marked in patients with active disease.

Sexual function

Impotence has very rarely been attributed to methotrexate (90).

Reproductive system

Although the occurrence of gynecomastia requiring surgical excision in two patients might have been coincidental (91), in another patient it disappeared after methotrexate withdrawal and recurred on rechallenge (92).

Immunologic

Immediate hypersensitivity reactions are rare after low-dose methotrexate.

- A 53-year-old woman had three episodes of angioedema while taking methotrexate, with no recurrence after withdrawal (93).

Vasculitis has been infrequently reported in patients taking low-dose methotrexate (SEDA-21, 388) (SEDA-22, 417) (94). Although most cases have been observed in patients with rheumatoid arthritis, suggesting that the underlying disease plays a part, vasculitis has also been described in a patient with ankylosing spondylitis (95). Methotrexate was also reported to have exacerbated pre-existing urticarial vasculitis in a 32-year-old woman; the lesions recurred after rechallenge (96).

Infection risk

Methotrexate-related immunosuppression can be expected to increase the likelihood of infections. The infection rate reported in patients taking low-dose methotrexate has varied from one study to another. In a literature review focusing on patients with rheumatoid arthritis taking methotrexate, the mean infection rate was 1.8% in retrospective studies, 4.6% in open studies, and 11.6% in double-blind studies (97). Infections usually occurred within 1.5 years of starting treatment and mostly comprised common respiratory or cutaneous bacterial infections, *Herpes zoster*, and, more rarely, opportunistic infections. In one comparative study, the overall risk of infections was considered to be low and similar in patients taking methotrexate and azathioprine (97), but others have found a higher prevalence of infections and an increase in antibiotic use in patients with rheumatoid arthritis taking methotrexate as compared to other DMARDs, except cyclophosphamide (98,99).

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An accumulating series of case reports has focused on the possible more frequent occurrence of opportunistic infections despite normal leukocyte counts in patients treated for rheumatoid arthritis or, less often, psoriasis (97,100,101). Various bacterial, fungal, and viral opportunistic infections have been described, with *Pneumocystis jiroveci* pneumonia as the most frequently reported (SEDA-21, 389) (SEDA-22, 417). Although the most severe, sometimes fatal, infectious diseases were usually observed in patients also taking glucocorticoids (SEDA-22, 417) (102,103), severe infections can also occur in occasional patients not taking concomitant glucocorticoids (SEDA-21, 389) (101,104–107).

Acute reactivation of a presumed quiescent chronic hepatitis B infection in one reported case after methotrexate withdrawal suggests that T cell-mediated immunological rebound might lead to rapid destruction of infected hepatocytes (108).

Long-Term Effects

Tumorigenicity

The evidence that methotrexate is carcinogenic is inconclusive and mostly based on case reports or analyses of cohort studies without control groups (100,109). For example, malignant neoplasms (urothelial carcinoma of the bladder, a malignant teratoma, and a dermal squamous cell carcinoma) have been described in three patients taking prolonged courses of methotrexate 7.5–15 mg/week (110).

From a retrospective study in more than 16 000 rheumatoid arthritis patients, the risk of hematological malignancy in methotrexate-treated patients was thought to be very small and not different from that observed in patients who used other DMARDs (111). In 426 patients with rheumatoid arthritis who took methotrexate for a mean of 37 months (follow-up period 4.6 years), the incidence rate of new cancers (4 cases/1000 person-years) was similar to that found in the general population (2.8 cases/1000 person-years) (112). Another preliminary study did not show an excess in the risk of lymphoproliferative disorders in patients with rheumatoid arthritis receiving long-term methotrexate maintenance (113). Earlier studies in patients with psoriasis did not show a higher incidence of cancers in patients on methotrexate compared with the general population (100,114).

In contrast, there have been several isolated reports of methotrexate-induced lymphomas (SEDA-21, 388) (SEDA-22, 417) (115,116). The pathological features in these cases have ranged from benign lymphoid hyperplasia to non-Hodgkin's lymphoma, and more rarely Hodgkin's disease (115), and patients usually had the typical features of lymphoproliferative disorders as found in immunosuppressed patients, that is, transplant patients or patients with congenital or acquired immune deficiency syndromes. Exceptionally, cases of pseudolymphoma have also been reported (SEDA-21, 389).

- Two patients developed lymphomas within 3 years of methotrexate treatment, and the authors suggested that an increase in serum IgE concentrations might anticipate the development of lymphoma in patients with rheumatoid arthritis treated with methotrexate (117).
- A cutaneous B cell lymphoma occurred in a 58-year-old man who had been treated with intramuscular methotrexate 10 mg/week for 4 years (total dose 2.3 g); the lymphoma resolved spontaneously 2 weeks after withdrawal of therapy (118).

A convincing argument implicating methotrexate as the cause of lymphomas is the possible spontaneous remission of lymphoproliferation after methotrexate withdrawal, as reported in several cases (SEDA-22, 389) (115,116). However, the putative pathophysiological mechanisms of methotrexate-induced lymphomas are unclear, and the drug's precise role, as well as that of the underlying disease as a confounding factor, needs to be investigated. The risk of a lymphoma in rheumatoid arthritis probably has more to do with the disease and its activity than with methotrexate treatment (113,119).

Low-dosage methotrexate is also a possible factor in the development of Epstein–Barr virus-associated lymphoproliferative disease, but the role of the Epstein–Barr virus in these cases is unclear. Epstein–Barr virus infection does not appear to be mandatory for the development of lymphoproliferation in patients taking methotrexate, but it was nevertheless found in about one-half of patients who developed lymphomas (SEDA-22, 389) (115,120).

Lymphoproliferative disorders have been observed during treatment of sarcoidosis and connective tissue diseases with low-dose methotrexate.

- A 51-year-old man with systemic sarcoidosis took methotrexate for 36 months and developed a large anal fissure with a diffuse polymorphic infiltrate containing large Epstein–Barr virus-positive lymphoid cells, similar to the classical B cell lymphoproliferative disorders that occur in immunosuppressed transplant recipients of solid organs (121).

This case supports the hypothesis that immunosuppressant therapy may contribute to an increased risk of Epstein–Barr virus-associated lymphoproliferative disorders.

Some of the mechanisms and risk factors of methotrexate-associated non-Hodgkin's lymphoma in patients with rheumatoid arthritis have been reviewed, including an analysis of the characteristic features of 25 detailed published cases (122). Although the epidemiological evidence is limited, several reports of spontaneous remission of lymphomas after methotrexate withdrawal strongly support a cause-and-effect relation.

A second malignancy in a patient taking methotrexate for chronic lymphatic leukemia has been described (123).

- A 55-year-old man with chronic lymphocytic leukemia and rheumatoid arthritis took methotrexate for 4 years and developed a B cell non-Hodgkin's lymphoma in the shoulder and axillary lymph nodes; he had Epstein–Barr viral antigens in the serum. After radiation and chemotherapy had failed, complete remission was achieved with a combination of rituximab and EPOCH (etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin).

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The authors thought that T cell deficiency induced by methotrexate, chronic lymphatic leukemia, and rheumatoid arthritis may have contributed to the development of the B cell lymphoma.

Other malignancies, such as malignant melanoma, multiple myeloma, leukemia or solid cancers, have been seldom reported (SEDA-21, 389) (SEDA-22, 389) (90,124), and the association with methotrexate therapy is uncertain.

Second-Generation Effects

Teratogenicity

Owing to its known teratogenic effects, methotrexate is usually considered to be contraindicated in pregnancy, and several authors have recommended withdrawing methotrexate at least 3 months before a planned pregnancy. Most of our knowledge on the consequences of in utero exposure to methotrexate is derived from oncology patients. In this setting, the fetal methotrexate syndrome mimics the aminopterin syndrome, with central nervous system abnormalities, skeletal defects, and more rarely cardiac abnormalities. The critical period of exposure is 6–8 weeks after conception and the minimal weekly dose is 10 mg (125), but one report suggested that the critical period may extend to week 11 in patients exposed to high-dose methotrexate (SEDA-22, 417).

- A 3-year-old infant born to a woman who had taken methotrexate 37.5 mg/week throughout the first 8 weeks after conception had significant developmental delay with mental retardation, which might therefore be a feature of the fetal methotrexate syndrome (126).

The developmental effects of in utero exposure to methotrexate have been reviewed, including a brief mention of three original cases (127), and a series of pregnancy outcomes in four patients exposed to low-dose methotrexate during early pregnancy has been reported more extensively (128). Of 24 patients available for evaluation, who took 2.5–35 mg/week and were accidentally exposed from the beginning of pregnancy up to 19 weeks gestation, pregnancy ended in spontaneous abortion in four and elective abortion in three (including one case of major malformation). Of the 17 neonates, three had major malformations. The malformations mostly consisted of central nervous system or craniofacial abnormalities and skeletal defects. Three patients had been exposed up to 8 weeks of gestation and one from 8 to 10 weeks, and the methotrexate doses were 12.5–35 mg/week. This is consistent with the threshold dose of 10 mg/week and the timing of exposure previously suggested for fetal methotrexate syndrome.

Susceptibility Factors

Renal disease

Impaired renal function is a susceptibility factor for methotrexate-induced pancytopenia.

- A 57-year-old man who had been on hemodialysis for the past 5 years developed severe pancytopenia 12 days after a single dose of methotrexate 5 mg (129).
- Severe complications, mostly bone marrow suppression and related complications, occurred in three patients on regular hemodialysis for end-stage renal disease (130).

Drug–Drug Interactions

Aspirin

Aspirin and methotrexate compete for renal tubular secretion, and aspirin alters the systemic and renal clearances of intravenous methotrexate (131). However, the clinical relevance of this interaction is not clear. In one study, aspirin (mean dose 4.5 g) in 12 patients did not cause more toxicity than other NSAIDs taken by 22 other patients (132).

Co-trimoxazole

Drugs that inhibit folate metabolism increase the likelihood of serious adverse reactions to methotrexate, particularly hematological toxicity. The additional risk of myelosuppression and subsequent severe pancytopenia has been particularly exemplified by the combination of methotrexate and co-trimoxazole (trimethoprim plus sulfamethoxazole) (133). This should also be taken into account in patients taking trimethoprim alone (SEDA-22, 418).

Etretinate

A case of severe hepatitis has been attributed to the combination of methotrexate with etretinate (134), a finding that was not explained by a pharmacokinetic interaction between the two drugs (135).

Fluorouracil

There is sequence-dependent synergy between fluorouracil and methotrexate. Pre-treatment with methotrexate enhances the formation of fluorouridine monophosphate and hence fluorouridine triphosphate; this enhances RNA-directed toxicity. In studies in which methotrexate has been given 1 hour before fluorouracil, response rates did not differ significantly. However, when it was given 4 hours or more before, there were significantly better response rates (136).

Glucocorticoids

Dexamethasone increased the hepatotoxicity of methotrexate in 57 children with brain tumors (137). The hepatotoxicity was not related to differences in serum concentrations and was independent of bone marrow toxicity or mucositis.

There have been conflicting studies on the interaction between low-dose methotrexate and long-term glucocorticoids. In one study, there was a significantly increased AUC and a reduction in methotrexate clearance compared with patients not taking glucocorticoids (138), and in another there was no change (139). Collectively, the data suggest that the interaction, if any, is of little clinical significance.

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NSAIDs

Theoretically, NSAIDs can increase methotrexate serum concentrations by competition for renal tubular secretion (140). Since the publication of case histories reporting severe toxic effects in patients taking methotrexate and NSAIDs, there has been much concern among patients taking low-dose methotrexate (SEDA-20, 89) (SEDA-21, 100). However, most of the reports related to patients taking doses of methotrexate higher than those recommended in rheumatoid arthritis. From often mutually contradictory data, it appears that co-administration of most NSAIDs and stable low-dose methotrexate is relatively safe and that the supposed risks have little clinical significance in patients with normal renal function who are regularly monitored for hepatic, hematological, and renal toxicity (141).

In one study there was a significant reduction in renal methotrexate clearance and creatinine clearance in patients who took NSAIDs plus a high maintenance dose of methotrexate (16.6 mg/week), but no change in either variable in patients taking a stable maintenance dose of 7.5 mg/week (142). This suggests that patients taking higher doses should be more closely monitored for early signs of renal impairment that could predispose them to methotrexate toxicity.

Penicillin

Concomitant penicillin administration has been reported to exacerbate the hematological toxicity of low-dose methotrexate (143). This could have been due to inhibition of the tubular secretion of methotrexate.

Probenecid

Probenecid competes with methotrexate for renal tubular secretion, and can cause severe hematological toxicity.

- Severe pancytopenia occurred in an elderly patient taking low-dose methotrexate and probenecid (144).

Triamterene

Drugs that inhibit folate metabolism increase the likelihood of serious adverse reactions to methotrexate, particularly hematological toxicity. Bone marrow suppression and reduced plasma folate concentrations resulted from the concomitant administration of triamterene with methotrexate (145).

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Methoxamine

General Information

Methoxamine is a relatively selective alpha$_1$-adrenoceptor agonist that has been used to a limited extent in the management of urinary stress incontinence. It has also been used locally as a nasal decongestant and in the emergency treatment of hypotension. No matter what the route of administration, methoxamine can cause adrenergic effects, including cold limbs, pilomotor stimulation, and a desire to micturate. Tachyphylaxis has been seen in experimental animals.

The effects of methoxamine have been examined in a double-blind, placebo-controlled trial in only six women (1). There was little effect on maximum urethral pressure, the surrogate end-point used in the trial. The drug was given by intravenous infusion at a maximum dose of 1.0 mg/70 kg/minute. There was a significant rise in systolic blood pressure of about 13 mmHg and a fall in pulse rate of some 18 beats/minute. All subjects taking methoxamine had headache, cold extremities, and piloerection. The authors understandably concluded that this is not a very promising treatment for stress incontinence.

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Methoxyflurane

See also General anesthetics

General Information

Methoxyflurane is a volatile halogenated anesthetic.

Organs and Systems

Liver

Hepatitis has been reported (1), with possible cross-allergy between halothane and methoxyflurane.

Urinary tract

The nephrotoxicity of methoxyflurane is well established (2).

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Methoxyphenamine hydrochloride

General Information

Methoxyphenamine is a sympathomimetic drug that has been used as a bronchodilator (1) and to treat nasal congestion. It has been claimed to be relatively free of cardiostimulant and psychomotor effects, but there is little published evidence suggesting marked beta-adrenoceptor selectivity, and the normal oral dose of 50–100 mg can in a minority of cases produce tightness of the chest and palpitation. Drowsiness, mouth dryness, nausea, and faintness have been anecdotally reported.

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Methyldopa

General Information

The presynaptic alpha-adrenoceptor agonists, particularly methyldopa and clonidine, are agonists at presynaptic alpha$_2$-adrenoceptors. Guanabenz, guanfacine, and tiamenidine appear to be qualitatively similar to clonidine; clear evidence of quantitative differences remains to be confirmed.

The mechanism of action of these drugs depends on reducing sympathetic nervous outflow from the nervous system by interference with regulatory neurotransmitter systems in the brainstem. Because none of the drugs was selective or specific for circulatory control systems, the hypotensive effects were invariably accompanied by other nervous system effects. However, the identification of imidazoline receptors has suggested that it may be possible to develop drugs, such as moxonidine and relminidine, with greater selectivity for circulatory control mechanisms and a reduced likelihood of unwanted nervous system depressant effects (1).

Organs and Systems

Cardiovascular

Although postural hypotension is often quoted as a complication of treatment with methyldopa, there is no convincing evidence that this unwanted effect is more likely with methyldopa than with other commonly used antihypertensive drugs.

Complete heart block, which resolved after the withdrawal of methyldopa but recurred on rechallenge, has been reported in two elderly patients and attributed to the central sympatholytic effect of methyldopa (2).

Nervous system

Treatment with centrally acting agents is characterized by a relatively high incidence (up to 60% in some studies) of nervous system depressant effects (dizziness, drowsiness, tiredness, dry mouth, headache, depression), particularly during the initial period of treatment or after dosage increments. Some tolerance develops during long-term treatment, but the insidious presence of these depressant effects may not be fully apparent until the patient is given alternative treatment.

Methyldopa should probably be avoided in patients with parkinsonism, because in theory the production of alpha-methyldopamine can worsen the disease, and there have indeed been reports of exacerbation (3).

Endocrine

Acutely methyldopa promotes the release of growth hormone and prolactin, but the long-term significance of this is unclear. However, there have been reports of hyperprolactinemia, leading to amenorrhea and galactorrhea (4).

Hematologic

Coombs' positivity (in about 20% of cases) and Coombs' positive hemolytic anemia (in about 2%) are well-recognized complications of methyldopa.

- Anemia, reticulocytosis, and a positive Coombs' test were seen in a 64-year-old woman taking methyldopa 1000 mg bd; these problems resolved after withdrawal (5).

Gastrointestinal

Dry mouth occurred twice as often with methyldopa (41%) as with atenolol (21%) in a crossover comparison in 69 hypertensive patients (6).

There is an association between methyldopa and diarrhea.

- An 84-year-old black woman over a period of 7 years was free of diarrhea during periods when methyldopa was stopped but suffered diarrhea as soon as methyldopa was re-introduced (7).
- Similar recurrences on repeated exposure occurred in a 71-year-old man who took methyldopa 250 mg bd (8).

Liver

Hepatotoxicity due to methyldopa is most often an acute hepatitis, which resolves when the drug is withdrawn. It can start at any time after the start of therapy, but it usually occurs within the first few weeks and ranges in severity from a minor disturbance of liver function tests to acute hepatic necrosis.

- Fatal toxic hepatitis occurred in a 22-year-old woman treated with methyldopa in late pregnancy (9).

Sometimes, a more chronic picture develops after treatment for 2 or 3 years, with features of chronic active hepatitis (10).

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Immunologic

Lupus-like syndrome has been attributed to methyldopa, causing hemolytic anemia, arthritis, photosensitivity, and high titers of antinuclear antibody (1:256) and of IgG antibodies to class I histones in a 55-year-old man who took methyldopa 250 mg bd for 13 months; the syndrome resolved spontaneously when methyldopa was withdrawn (11).

Long-Term Effects

Drug withdrawal

A withdrawal syndrome with rebound hypertension has been reported with methyldopa (12). Although it is similar to that associated with clonidine, it is less well defined, less severe, and less frequent.

- Withdrawal of methyldopa has been associated with the development of an acute manic syndrome in a 62-year-old man who had had methyldopa withdrawn 4 weeks before; there had been no previous history of psychiatric disorder (13).

Drug–Drug Interactions

Mianserin

Mianserin has alpha-adrenoceptor activity and so might interact with methyldopa (14). In 11 patients with essential hypertension, the addition of mianserin 60 mg/day (in divided doses) for 2 weeks did not reduce the hypotensive effect of methyldopa. In patients treated with methyldopa, there were additive hypotensive effects after the first dose of mianserin, but these were not significant after 1 or 2 weeks of combined treatment. The results of this study appear to have justified the authors' conclusion that adding mianserin to treatment with methyldopa will not result in loss of blood pressure control.

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Methylenedioxymetamfetamine

See also Amphetamines

General Information

Methylenedioxymetamfetamine (MDMA, ecstasy) is a recreational drug with actions like those of amphetamine. It is the usual and expected constituent of the tablets that are known as ecstasy, although adulteration with other substances is not uncommon (see the section on Drug contamination in this monograph). MDMA and other drugs, such as its *N*-demethylated derivative (MDA), 3,4-methylenedioxyamfetamine (MDA), 3,4-methylenedioxyethylamfetamine (MDEA), *N*-methylbenzodioxazolylbutamine (MBDB), and 4-bromo-2,5-dimethoxyphenylethylamine (2-CB or Nexus), are often grouped together as "ecstasy". Some have used the term "enactogen", meaning "touching within", to describe ecstasy.

In low doses MDMA produces a pleasant altered state of mind, with enhanced emotional closeness, but it is also used in high doses and settings in which toxicity is often reported (1). In the UK, considerable adverse effects have been reported from its use at rave dances. In the 1970s and 1980s its mind-altering effect caused some clinicians to advocate its use as an adjunct to psychotherapy (2).

Concern has been raised about the increasing use of ecstasy in Europe (3), particularly the UK and the Netherlands. The patterns and trends of substance use among college students have been evaluated over a 30-year period (4). Alcohol use remained stable, but illicit drug use peaked in 1978 and fell sharply over the next 20 years. Ecstasy was the exception: its use rose from 4.1% in 1989 to 10% in 1999. Ecstasy was the second most frequently tried illicit drug after marijuana.

Associated with increased physical activity and altered thermoregulation, ecstasy has been reported to cause unconsciousness, seizures, hyperthermia, tachycardia, hypotension, disseminated intravascular coagulation, and acute renal insufficiency, as well as death.

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Ecstasy has a mild stimulant effect and is modestly hallucinogenic. The results of one study suggested that tolerance to its effects develops, but that adverse effects can increase with continued use (5). Recent reports have highlighted some disturbing effects, particularly when it is used while dancing vigorously at rave parties (6). In this setting, with increased physical activity, ecstasy can cause unconsciousness, seizures, hyperthermia, tachycardia, hypotension, disseminated intravascular coagulation, rhabdomyolysis, and acute renal insufficiency (7). Severe complications are also linked to uncontrolled fluid intake, hemodilution, and salt-losing syndromes. Deaths after the use of ecstasy in such settings have been described (8). It has been suggested that severe toxicity from ecstasy can result from altered thermoregulation in the face of excessive activity in warm environments (9).

Deaths related to ecstasy and MDEA in seven young white men, two of whom had hyperthermia, have been reviewed (10). In all cases, autopsy showed striking liver damage with necrosis; five patients had heart damage (contraction band necrosis and cell necrosis with inflammation), and others had brain damage, including focal bleeding, gross edema, and hypoxic changes. In one patient, who died of acute water intoxication, the pituitary gland was necrotic and there was accompanying cerebral edema. The authors proposed that the spectrum of pathological findings suggested more than one mechanism of damage, injury being caused by hyperthermia in some cases and a toxic effect (directly accountable for damage to liver and other organs) in others.

Ecstasy that is sold on the streets is a heterogeneous substancer, with enormous variations in its main active ingredients. It most often contains derivatives of MDMA and 3,4-methylenedioxy-*N*-ethylamfetamine (MDEA). Other amphetamine derivatives that it can contain include 3,4-MDA, *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), and 2,5-dimethoxy-4-bromamfetamine (DOB). The amount of active ingredient in street ecstasy ranges from none to very high. In addition, other amphetamines or hallucinogens can be mixed in. A survey of 3021 young adults (14–24 years old) in Germany showed that regular use of ecstasy by itself is uncommon (2.6%). Among lifetime users, 97% have also used cannabinoids, 59% cocaine, 48% other substances, 46% hallucinogens, and 26% opiates. However, the interviews revealed that the use of ecstasy and hallucinogens is increasing, especially in young people. The authors observed that a large number of first-time users are at risk of regular use (11).

As recreational use of ecstasy has dramatically increased in recent years, deaths related to its use have been reported. In a retrospective review of all violent deaths from 1992 to 1997 in South Australia, six deaths were associated with ecstasy abuse; all occurred after September 1995. Three victims had documented hyperthermia and there was evidence of hyperthermia in another. The authors suggested that individual susceptibility to MDMA may be caused by impaired metabolism by CYP2D6 or through genetically poor metabolism (seen in 5–9% of Caucasians). One woman, who died with a cerebral hemorrhage, had fluoxetine (a CYP2D6 inhibitor) present in her blood. Furthermore, toxicology identified paramethoxyamfetamine (PMA) in all the cases, amfetamine/metamfetamine in four cases, and MDMA in only two cases. PMA, which is sold as an MDMA substitute or is present as a contaminant, is associated with a high rate of lethal complications (12).

- A 35-year-old male criminal died under suspicious circumstances (13). The police had seen him alive about 1.5 hours before the alleged time of death during a patrol visit to his home. Evaluation of the corpse showed an obvious head injury and the body was in an advanced stage of rigor mortis, despite the fact that the alleged time of death had been less than 4 hours earlier. The body temperature was significantly raised (42°C). A witness testified that the deceased had taken ecstasy at various times during the night, after which he had been groaning, before taking off his clothes and thrashing on the floor while hitting his head and bumping into things. When resuscitation had been attempted, his jaw had been locked. Toxicology detected amfetamine, metamfetamine, and PMA in the blood.

The authors suggested that in a subgroup of amfetamine abusers, a triad of amfetamine use, prolonged exertion, and hyperthermia can be potentially lethal. Any temperature above 42°C requires active cooling (to below 38.5°C) and carries a poor prognosis. In this case rigor mortis may have started almost at the time of death. An ecstasy tablet that was allegedly from the same batch contained 50 mg of PMA.

The pharmacological and pharmacokinetic effects of ecstasy have been studied in healthy volunteers (14). In the pilot phase, two subjects each took ecstasy 50, 100, and 150 mg. In the second phase, eight subjects took ecstasy 75 and 125 mg. All were CYP2D6 extensive metabolizers. The ecstasy plasma concentrations were not proportional to dose, probably indicating non-linear kinetics in the dosage range usually taken recreationally. While the results were not conclusive (owing to problems in the study design) and require further exploration, the finding that relatively small increases in the dose of ecstasy ingested can translate to disproportionate rises in ecstasy plasma concentrations, if confirmed, would be important.

Organs and Systems

Cardiovascular

Cardiotoxicity following ecstasy use has been reported (15).

- A 16-year-old boy took three tablets of ecstasy and amfetamine 0.3 g and several hours later had convulsions and a temperature of 40.9°C. His heart rate was 210/minute and his blood pressure 100/75 mmHg. His creatine kinase activity was raised and he had myoglobinuria, renal impairment, hyperkalemia, and hypocalcemia. An electrocardiogram showed ventricular and supraventricular tachycardias but no myocardial ischemia. A diagnosis of serotonin syndrome due to ecstasy ingestion with associated hyperpyrexia and rhabdomyolysis was made. Following active treatment, his condition stabilized, with restoration of sinus rhythm and normal urine output. However, 12 hours later he developed jaundice, raised liver enzymes, and coagulopathy, suggesting acute liver failure due to ecstasy. With supportive treatment, his liver function improved. However, another 12 hours later, he developed

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shortness of breath associated with right-sided chest signs and X-ray changes compatible with aspiration pneumonia, and required emergency intubation 4 days later. He developed pulmonary edema, his pulmonary artery was occluded, and an echocardiogram showed globally impaired left ventricular function with an ejection fraction of 30–35%; there was electrocardiographic T wave inversion. Primary myocardial damage causing cardiac dysfunction was investigated using serial creatine kinase and troponin measurements. He recovered completely with treatment and an echocardiogram showed an ejection fraction of 60%.

The authors reported that this was the first case report of clinical, radiological, biochemical, and echocardiographic evidence of myocardial damage and cardiac dysfunction following ecstasy and amfetamine use.

Transient myocardial ischemia associated with ecstasy has been reported (16).

- A 25-year-old man, a regular alcohol drinker with a history of asthma, had been out drinking 8 pints of lager and 4 gins. His last drink was spiked with a tablet that was presumably ecstasy. He scooped the tablet out, and even though some of the tablet may have dissolved, he finished the drink. He awoke 3 hours later with restlessness, nausea, and abdominal cramps. In the emergency room, his temperature was 37.2°C, and he was sweating. His heart rate was 120/minute and his blood pressure 130/70 mmHg. He had some abdominal discomfort. A diagnosis of ecstasy ingestion was made, although urine MDMA concentrations were not measured. His electrocardiogram on admission showed sinus tachycardia, with T wave inversion in leads I, aVL, and V4–6 and the voltage criteria for left ventricular hypertrophy. The next day the electrocardiogram had returned to normal. An echocardiogram was within normal limits. He was well on discharge.

The authors suggested that this was the first report of transient myocardial ischemia after ecstasy. They reasoned that the myocardial ischemia did not proceed to necrosis or a dysrhythmia because the amount of drug exposure was low.

Cardiovascular autonomic functioning during MDMA use has been investigated in 12 MDMA users and a matched group of non-users (17). Resting heart rate variability (an index of parasympathetic tone) and heart rate response to the Valsalva maneuver (Valsalva ratio, an index of overall autonomic responsiveness) were both reduced in the drug users. Thus, seemingly healthy users of MDMA had autonomic dysregulation, comparable to that seen in diabetes mellitus. In several users there was a total absence of post-Valsalva release bradycardia, a sign of parasympathetic dysfunction. Since no cardiac data were available for these patients before their use of ecstasy, and since all were multidrug users, the findings must be interpreted with caution.

Extensive aortic dissection with cardiac tamponade and mesenteric ischemia has been attributed to ecstasy (18).

- A 29-year-old man who took ecstasy and alcohol at a rave had no immediate adverse effects, slept well later on, and was in good health until he suddenly collapsed to the floor about 2 hours after waking. When seen 36 hours after the last dose of ecstasy he was short of breath and had abdominal pain, diarrhea, and vomiting. He had a loose bloody bowel movement but refused further investigations. He was discharged with a diagnosis of gastroenteritis, only to be readmitted 8 hours later after sudden deterioration and hypertension. Despite extensive efforts, his condition deteriorated and he died 5 hours later. At autopsy, there was a type I aortic dissection, starting at the root and spreading to the bifurcation, which had resulted in cardiac tamponade. The dissection had involved the mesenteric arteries, resulting in bowel ischemia.

Since this condition is rare in young adults, diagnosis can be difficult. The authors believed that this was the first case report of aortic dissection secondary to ecstasy.

Ecstasy has been associated with sudden death and cardiovascular complications. Eight healthy self-reported ecstasy users participated in a four-session, ascending-dose, double-blind, placebo-controlled comparison of the echocardiographic effects of ecstasy and those of dobutamine (19). Ecstasy 1.5 mg/kg increased the mean heart rate by 28 beats/minute, systolic blood pressure by 25 mmHg, diastolic blood pressure by 7 mmHg, and cardiac output by 2 l/minute. The effects of ecstasy were similar to those produced by dobutamine (40 μg/kg/minute), except that ecstasy had no measurable inotropic effects. Thus, ecstasy increases systolic and diastolic blood pressures in the absence of a significant change in cardiac contractility and end-systolic wall thickness. The resulting increase in the tension of the ventricular wall leads to disproportionately higher myocardial oxygen consumption than would be expected from the observed changes in the heart rate and blood pressure. The authors commented that the behavioral and environmental factors accompanying the use of ecstasy—sustained exercise from dancing, often in crowded nightclubs with high ambient temperature and humidity—could further potentiate toxicity. They recommended a combination of beta-blockers and vasodilators for the emergency treatment of ecstasy-associated vascular instability.

Respiratory

Pneumomediastinum after MDMA has been reported.

- Spontaneous pneumomediastinum occurred in a 17-year-old man who presented with chest pain and vomiting after taking two tablets of ecstasy (20).
- A 16-year-old boy took six ecstasy tablets over 2 hours (21). A period of vomiting ensued and he developed chest pain and swelling in the neck. A chest X-ray showed pneumomediastinum. He was managed conservatively and his emphysema settled uneventfully within 2 days.

The authors of the second case reported that five such cases have been reported in the past 4 years in the British literature; the respiratory complications were thought to be due to severe physical exercise or secondary to vomiting. It is therefore possible that this complication may not be due to a direct effect of MDMA, but rather a consequence of repeated Valsalva maneuvers associated with the dance habits of ecstasy users or vomiting induced by the drug.

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Two cases of pneumomediastinum occurred in people who took ecstasy at the same rave party (22).

- A 23-year-old woman developed chest, back, and neck pain, and surgical emphysema over the chest and neck 7 hours after taking ecstasy. She had surgical emphysema in the mediastinum and neck and was given intravenous fluids and antibiotics.
- A 22-year-old man developed anterior chest and neck pain and surgical emphysema over the neck and chest 8 hours after taking four ecstasy tablets. He had surgical emphysema in the mediastinum and neck and contrast swallow showed a leak at the posterolateral aspect of the mid-esophagus. He was given intravenous fluids and antibiotics.

These symptoms were possibly related to the use of ecstasy, but it is also possible that a corrosive additive in the ecstasy was responsible. Ecstasy can cause gastrointestinal dysmotility, which could have resulted in esophageal rupture.

Adverse effects can develop after amphetamines are abused in combination (23).

- A 28-year-old healthy woman had left-sided pleuritic chest pain for 18 hours, having taken one tablet of ecstasy and one tablet of speed (metamfetamine hydrochloride) 4 hours earlier. There was surgical emphysema in her neck. On auscultation there was a crunching cardiac systolic sound. Chest X-ray showed pneumopericardium and pneumomediastinum. She was given analgesics and monitored. The chest pain subsided after 4 days.

Her respiratory problems could have been due to alveolar rupture, caused by an increase in intra-alveolar pressure, due to the exertion while she had been dancing strenuously. Alternatively, it could have been secondary to her use of positive ventilatory pressure after taking the drugs; this is done by a partner, either by direct mouth-to-mouth contact or through a cardboard cylinder, to enhance the user's experience of the stimulant's effects.

Nervous system

Two previously reported cases of cerebral edema associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) after ingestion of ecstasy elicited strong responses (24). The writers questioned the certainty of the clinical diagnosis on the basis of the biochemical details, specifically the plasma and urine osmolalities (25). They pointed out that cerebral edema can occur secondary to severe water consumption without SIADH and suggested that the use of intravenous fluids or water consumption after exposure to MDMA requires close monitoring. The original authors replied that they strongly agreed with the potential risks of unlimited fluid intake in MDMA users.

Dry mouth, with possible increased risk of enamel erosion and dental caries, has also been described (26).

Since the toxic effects of MDMA resemble certain features of both the serotonin syndrome and the neuroleptic malignant syndrome, some have suggested that MDMA may have combined actions on both the dopamine and serotonin systems (27). However, dantrolene (which may be helpful in cases of neuroleptic malignant syndrome) does not appear to be useful in dealing with MDMA toxicity (28).

A report linking ecstasy use and parkinsonism generated considerable discussion (29).

- A 29-year-old man developed difficulty in walking and lost the ability to write or drive 4 weeks after developing clumsiness of his extremities. He was unable to work or live independently. His electroencephalogram, lumbar puncture, and MRI and positron emission tomography (PET) scans were normal. Eleven weeks after the onset of symptoms he had disturbed gait and fine motor coordination; his condition deteriorated and 8 weeks later he had bradykinesia of the face and limbs, absence of blinking, hypokinesia in relation to speech, postural instability, and a markedly parkinsonian gait. However, his cognitive function was intact.

This patient had taken ecstasy 10 times during the year before, the last time about 3 months before the onset of symptoms. Apart from marijuana, he denied using other substances. He was treated with maximal tolerable doses of levodopa and pramipexole, without improvement. The authors reported that they had no explanation for this patient's symptoms, other than the use of ecstasy. They felt that the parkinsonian symptoms most closely resembled MPTP-induced parkinsonism. They further postulated that this could be a delayed neurotoxic effect of ecstasy in the substantia nigra and striatum and could have occurred as a result of neuronal damage by free radicals.

This report brought many responses. The first criticized the authors' conclusion that the neurotoxic effects in their patient were similar to those seen with MPTP (30). They argued that the PET scan was normal, and that the patient's condition did not respond to the use of antiparkinsonian drugs, unlike MPTP-induced damage, which does respond. They further argued that the extensive animal and human experience involving MDMA has not shown damage to the dopaminergic system. Furthermore, MDMA and MPTP are chemically unrelated and share neither precursors nor metabolites. Although the purity of street drugs is suspected and a contaminant could have been responsible, they seriously doubted that MPTP was one of the contaminants ingested.

Another group expressed the concern that although other types of amfetamine can cause dopaminergic neurotoxicity in animals and are sometimes sold as MDMA, they have not been associated with parkinsonism, despite more than 60 years of worldwide therapeutic and illicit use (31). Furthermore, they observed that the pattern in this case, in which symptoms began 8 weeks after drug exposure, did not fit the expected pattern of drug toxicity. They proposed that the problem had either been caused by contaminants or by a highly idiosyncratic reaction. However, if the toxicity had been from a contaminant, a cluster of cases would have been expected, as was seen with MPTP. On the other hand, if this had been an idiosyncratic case, the symptoms would have emerged soon after drug use. They were also puzzled by the absence of hair analysis to confirm MDMA use.

The authors of the original report responded by citing evidence that MDMA can be toxic to dopaminergic

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neurons and can cause lasting changes in neuronal responses to dopamine (32). They further stated that although parkinsonism has not been reported after MDMA, the possibility that such an association exists cannot be excluded. They raised the possibility that clinical evidence of parkinsonism can be missed, particularly when the disorder is mild and, as in their patient, when tremor is absent. They pointed out that with valproate the first full report of parkinsonism did not appear until 18 years after its introduction into the USA, even though those who commonly prescribe it (neurologists and psychiatrists) should have noticed it earlier. The authors clarified that they had mentioned MPTP as an example of a substance that may have a delayed neurotoxic effect on monoaminergic neurons, without intending to suggest that MDMA acts chemically in the same manner as MPTP. They agreed that a contaminant could have played a role, and raised a concern that contaminants also put MDMA users at risks of adverse effects. They countered the argument that all idiosyncratic responses have to be immediate, by quoting examples from the literature to suggest that the course of a reaction depends on the underlying mechanism.

The patient discussed in the case report also responded, alleging that his permission had not been obtained before publication (33). Contradicting the original published report, he stated that he had never used marijuana; the authors defended their data by stating that when the patient's friend, who had accompanied him to the clinic, mentioned cannabis use the patient did not deny it. He also reported using creatine, ephedrine, caffeine, and aspirin, none of which, the authors noted, has previously been associated with parkinsonian symptoms.

Other neurological adverse effects have been reported in a first-time ecstasy user (34).

- A 19-year-old man, an occasional user of benzodiazepines and heroin, developed dizziness and loss of consciousness the morning after taking ecstasy for the first time. He was intubated and ventilated. He had a monocular hematoma, pulmonary edema, and cutaneous emphysema, without focal neurological deficits. There was rhabdomyolysis with renal insufficiency but no rise in temperature. Body fluid toxicological analysis showed only benzodiazepines and amphetamines. After he was weaned from the respirator, although awake, he did not react to noxious stimuli and showed no spontaneous movements. A CT scan of the brain had been normal on admission, but 2 and 3 weeks later it showed multiple hypodense lesions in the white matter. One month after admission, he was in a vegetative state, with marked spasticity, intermittent non-specific reactions to noise, and sustained generalized myoclonus. An electroencephalogram showed generalized slowing with intermittent theta wave activity. An MRI scan showed bilateral severe white matter damage.

Brain damage in this patient was restricted to the white matter. Although hypoxia was present at the time of admission, the authors did not believe that it was the only causative factor. By a process of elimination, they concluded that ecstasy might have caused the toxic encephalopathy, although it was not detected by toxicological analysis. They suggested that myelin damage might be an indirect sequel of MDMA-related metabolic oxidative stress and multiorgan failure due to individual susceptibility. They also entertained the idea of a lipophilic toxic contaminant rather than MDMA as the causative toxic agent.

An unusual case of bilateral sixth nerve palsy associated with ecstasy has been reported (35).

- A 17-year-old man developed horizontal diplopia in all directions of gaze while using ecstasy tablets every 5–7 days for 2 months. A diagnosis of bilateral sixth nerve palsy was confirmed. Ocular motility returned to normal within 5 days without treatment. There was no evidence of inflammation or degenerative disease of the central nervous system.

The authors speculated that the most likely cause of the lesion was either an interaction of ecstasy with serotonergic neurons or cerebral edema (albeit not detected by MRI) secondary to ecstasy.

Psychological, psychiatric

Concerns have been raised about the long-term nervous system effects of MDMA use from animal data, which suggest that the dose of MDMA used for recreational purposes by humans can cause toxic effects in nonhuman primates, especially involving the serotonin system. In a case-control study, 10 long-term MDMA users were compared with 10 controls who had not used MDMA but were drug abusers and were matched for age, sex, education, and premorbid intellect (36). All participated in a single photon emission computed tomography (SPECT) study with a serotonin transporter (SERT) ligand. Dopamine transporter binding was determined from scans acquired 23 hours after injection of the tracer. Hair analysis, which covers about the last 4 weeks of drug use, generally confirmed the drug use history, although two ecstasy users tested negative for both amfetamine and metamfetamine. On neuropsychological testing, both groups showed comparable performances in tests of verbal and spatial memory, psychomotor speed, attention, and executive function. Larger lifetime doses of ecstasy were associated with reduced verbal memory performance on the California Verbal Learning Test and more errors in the Spatial Working Memory Test. Ecstasy users showed a cortical reduction of SERT binding prominently in primary sensorimotor cortex, with normal dopamine transporter binding in the lenticular nuclei. There was also an association between the length of the MDMA-free period (mean 18 days) before the scan and ligand binding in the cingulate. Spatial working memory performance and SERT binding in the left calcarine cortex were negatively correlated with the estimated lifetime dose of MDMA in the ecstasy users. While these results could be coincidental, or reduced SERT binding could be the imaging correlate of a psychobiological predisposition to heavy use of ecstasy, the authors suggested that this study provided evidence for specific albeit temporary serotonergic neurotoxicity of MDMA in humans. If confirmed, these effects on the serotonergic system could underlie psychiatric morbidity in ecstasy users.

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The neurotransmitter systems involved in the psychological and information processing effects of ecstasy have been studied in 16 ecstasy-naïve subjects (37). Ecstasy produced a state of enhanced mood, well-being, increased emotional sensitiveness, little anxiety, moderate thought disturbances, but no hallucinations or panic reactions. It caused thought disturbances, such as difficulty in concentrating, thought blocking, and difficulty in reaching decisions. Women had greater subjective responses to ecstasy than men. For instance, they scored higher on ratings of anxiety, adverse effects, and thought disturbances, suggesting differences in the metabolism of ecstasy. Prepulse inhibition of the startle response was used to measure physiological changes. Prepulse inhibition and startle habituation have been used as operational measures of sensorimotor gating and habituation functions, respectively, in investigations of attention. Moreover, some studies have associated prepulse inhibition with endogenous serotonin release. Ecstasy 1.7 mg/kg increased prepulse inhibition, suggesting that the overflow of endogenous serotonin caused by ecstasy may interfere with the startle response and cause a breakdown of cognitive integrity. This effect further suggests serotonin dysregulation in response to ecstasy.

Reports of adverse neuropsychiatric effects of MDMA have included descriptions of flashbacks, anxiety, insomnia (38), panic attacks (25,39), and psychosis (40). Subacute adverse effects that have been reported following MDMA use include drowsiness, depression, anxiety, and irritability (41). Prolonged or chronic effects have also been reported, including panic disorder (42,43), psychosis (40,44,45), flashbacks (40), major depressive disorder (25,46), and memory disturbance (25). The observation that only certain individuals develop neuropsychiatric disturbances after using ecstasy suggests that certain predisposing psychiatric factors (or high-dose regimens) may make some individuals more vulnerable to these untoward effects.

With increasing use of ecstasy, there is considerable interest in its effects on psychopathology and cognition. The residual effects of ecstasy on psychopathology and cognition have been examined in 18 current regular users, 15 ex-users with an average abstinence of 2 years, 16 ecstasy-naïve polydrug users, and 15 non-drug users (47). Both current and previous users had significantly worse psychopathology than the controls and polydrug users. Ecstasy users had higher scores on the Symptoms Check List SCL-90-R Global Severity Index and the Positive Symptom Distress Index. They also scored significantly higher on eight specific factors on the SCL-90-R: somatization, obsessive-compulsive disorder, anxiety, phobic anxiety, interpersonal sensitivity, depression, paranoid ideation, and altered appetite/restless sleep. Current users had higher scores across more categories, but the values were not significantly different from ex-users. Current and ex-users had lower working memory and verbal learning abilities than the controls and polydrug users, but there were no significant differences between the two groups. Using regression analyses, the investigators found that the best indicator of increased psychopathology was a high consumption of cannabis, while cognitive deficits were best predicted by the amount of previous ecstasy use. Thus, the investigators suggested that ecstasy-induced cognitive impairment may not be reversible over time and with abstinence, suggesting that ecstasy is a potent neurotoxin.

The neuropsychological effects of ecstasy have been studied in 20 polydrug users (48). Various functions and processes throughout the brain, such as verbal fluency, spatial working memory, and attention, were assessed. Ecstasy users showed a significant deficit in complex visual pattern recognition and spatial working memory compared with the polydrug abusers who were not taking ecstasy. Since these tests are sensitive to temporal lobe functioning, the authors suggested that there is a selective temporal lobe deficit in ecstasy users, with relative sparing of executive functioning. Based on previous studies, they postulated that serotonin dysfunction in the temporal lobe may be associated with impaired visuospatial working memory. However, they did not study a drug-free control group and the ecstasy group used higher amounts of drugs in general. In addition, the sample size was small.

Some reports have suggested that the relation between the dose of ecstasy and its complications may not be straightforward (49). Some people have problems with very small amounts.

- A 21-year-old woman developed a protracted psychotic depersonalization disorder with suicidal tendency after taking two tablets of ecstasy for the first time (50).
- A 23-year-old man with no prior psychiatric history developed panic disorder after taking a single dose of ecstasy (42).
- A psychosis occurred in an 18-year-old man who had used ecstasy on an occasional recreational basis (51).

The acute and short-term effects of a recreational dose of MDMA (1.7 mg/kg) given to 13 MDMA-naïve healthy volunteers in a double-blind, placebo-controlled study have been reported (52). MDMA produced a state of enhanced mood, well-being, and enhanced emotional responsiveness, with mild depersonalization, derealization, thought disorder, and anxiety. The subjects also had changes in their sense of space and time, heightened sensory awareness, and increased psychomotor drive. MDMA increased blood pressure moderately, except in one case of a transient hypertensive reaction. The most frequent somatic adverse effects were jaw clenching, poor appetite, restlessness, and insomnia. Lack of energy, difficulty in concentrating, fatigue, and feelings of restlessness during the next day were also described. The authors suggested that MDMA produces a psychological profile different from classic hallucinogens or psychostimulants. The potential risk of hypertensive effects of recreational dosages of ecstasy should also be considered in the safety profile.

Using PET with a radioligand that selectively labels the serotonin (5-HT) transporter, 14 MDMA users who were currently abstaining (for 3 weeks) from use and 15 MDMA-naïve controls were studied (53). MDMA users showed a reduction in global and regional brain 5-HT transporter binding, a measure of the number of 5-HT neurons, compared with controls. Deficiency in SERT correlated positively with the extent of previous drug use. The authors suggested that ecstasy users are susceptible to MDMA-induced serotonin neural injury.

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Panic disorder

A case of ecstasy-related panic disorder has been reported (54).

- A 21-year-old man used increasing dosages of ecstasy (seven tablets or 400–500 mg/day) over a period of 5 months. After taking six tablets on one day, he developed palpitation, chest pain, sweating, vertigo, and a fear of dying. He responded well to alprazolam and was discharged. Several days later, the panic attacks recurred spontaneously. Five weeks later, he had a complete medical work-up that was unrevealing. Since his panic attacks persisted in the absence of any drugs, he was given the SSRI paroxetine 20 mg/day plus alprazolam; his panic attacks gradually abated and stopped 3 months later. The paroxetine was gradually tapered over the next 3 months and he continued to be symptom-free at 6 months.

The authors suggested that this case may have exemplified dose-dependent serotonergic neurotoxicity from ecstasy abuse.

Psychoses

Psychoses, both acute and chronic, have been reported following the use of ecstasy.

- A 26-year-old man without previous psychopathology (except social phobia) unknowingly consumed ecstasy with alcohol and developed an acute psychosis 12 hours later (44,55).

The authors reported that 12 cases of acute psychosis have previously been reported after the use of ecstasy once or twice. Based on a previously suggested hypothesis, they proposed that the psychosis was probably due to the indirect effects of MDMA on the dopaminergic system, secondary to serotonergic deregulation. Most patients who went on to develop a chronic psychosis were either chronic ecstasy users or multiple substance users. However, in the case mentioned here, after 6 months the patient still had symptoms of psychosis. The authors further suggested that genetically slow metabolizers of ecstasy are probably more vulnerable to this adverse effect, even with a single exposure.

Past reports have suggested that ecstasy use is associated with increased scores on self-report measures of depression. The long-term effects of ecstasy consumption on depression have been examined in 29 individuals who had consumed large quantities of the drug in the past, but were now leading relatively drug-free lives (56). They had taken an average of 1.5 ecstasy tablets in the last month, 8.4 in the last 6 months, and 23.3 in the last 12 months. None had taken it in the last 14 days. The former chronic ecstasy users had not taken ecstasy for an average of 26 weeks. The female former users had taken ecstasy more recently than the men (15 versus 31 weeks respectively). The levels of depression, as measured by Beck's depression inventory (BDI), were significantly increased compared with a matched non-drug using control group. The depression scores were independent of alcohol and cannabis use. Peak usage (maximum ecstasy usage in 12 hours) and current levels of perceived stress together significantly predicted depression scores. Thus, former chronic ecstasy users may be at a high risk of developing more severe depression.

Cognitive effects

Several studies have focused on the cognitive effects of ecstasy, and a review of the adverse effects of MDMA in animals has raised concerns about potential toxicity in humans (57). MDMA can selectively damage brain serotonin (5-HT) neurons in animal brains, even at doses within the range of those typically used recreationally. In many studies, lasting reductions in various brain 5-HT markers have been reported in MDMA-treated animals. Axons of 5-HT neurons were damaged in MDMA-treated animals, including monkeys, and neurotoxic effects of MDMA have been observed in every animal species studied so far. In non-human primates, the toxic dose of MDMA closely approaches the dose used by humans.

In 30 regular ecstasy users (drug use 10 or more times per month) and 31 ecstasy-free controls, prospective memory—the process of remembering to do things at some future time—was assessed using a self-report questionnaire (58). Ecstasy users reported global impairment in prospective memory, even after controlling for the use of other drugs. The authors observed that their finding of impairment of cognitive functions, especially memory, in regular ecstasy users is similar to findings in other recent studies. They postulated that serotonergic toxicity secondary to chronic ecstasy exposure can cause cognitive impairment, as serotonergic pathways are involved in memory function.

More support for a relation between memory impairment, serotonin neurotoxicity, and chronic ecstasy use has come from a study of cognitive performance and serotonin function in two groups of 21 men with moderate or heavy ecstasy use and a control group of 20 men who had not used ecstasy (59). Ecstasy users had a broad spectrum of statistically significant but clinically subtle impairment of memory and prolonged reaction times. Heavy users had larger effects than moderate users. Serotonergic function was assessed in a double-blind crossover challenge with dexfenfluramine 30 mg or placebo. Release of cortisol, but not prolactin, after dexfenfluramine was significantly reduced in both groups of ecstasy users compared with controls. According to the authors, these neuroendocrine findings are similar to those observed in animals and humans. Recent exposure to ecstasy, psychosocial profiles, and the use of other drugs did not explain the differences.

The density of serotonin transporters (SERTs) in humans can be measured by neuroimaging techniques, such as SPECT and PET. Two groups of ecstasy users (22 recent but abstinent and 16 ex-users) were compared with ecstasy-naïve controls (60). In subjects who had stopped using ecstasy more than 1 year before the study, cortical densities of SERTs did not differ from those of controls. However, recent ecstasy users had global reductions in SERTs. In addition, individuals who had stopped using ecstasy had a deficit in verbal memory similar to that in current ecstasy users. Higher lifetime doses of ecstasy were associated with greater impairment of immediate verbal memory. The authors suggested that the absence of reductions in SERT densities in ex-ecstasy

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users suggested reversibility of ecstasy-induced changes in brain SERTs. Thus, ecstasy use can lead to neurotoxic changes in human cortical 5-HT brain neurons, but these changes may be reversible. However, functional consequences of ecstasy on cortical brain 5-HT neurons may not be reversible, as seen by impaired memory function in this group, similar to that in current ecstasy users.

The amino acid *N*-acetylaspartate is a robust, non-specific marker of neuronal loss or brain dysfunction. It is detectable by proton magnetic resonance spectroscopy (MRS). The ratio of creatine to phosphocreatine, another marker that remains stable in many brain diseases, can also be assessed using MRS. In a recent study, the ratio of *N*-acetylaspartate to creatine/phosphocreatine was used to determine whether there are memory deficits in ecstasy users and whether there are changes in specific brain regions (61). Eight men with a history of ecstasy use and seven ecstasy-naïve male controls took part. The findings included a significant difference in delayed recall between ecstasy users and ecstasy-naïve controls. There was a strong association between impaired memory function in ecstasy users and neuronal pathology, specific to the prefrontal cortex. Poorer performance on verbal memory testing was associated with greater neuronal loss or dysfunction in ecstasy users. These findings implicate ecstasy as a cause of serotonergic neuronal damage and memory impairment.

Another group has assessed cognitive function in 80 subjects who were non-users, novice users, regular users, or currently abstinent users of ecstasy (62). Compared with the non-users, all three groups of ecstasy users had significantly poorer verbal fluency and immediate and delayed prose recall. Days since last use and total lifetime consumption of ecstasy made separate contributions to the variance in recall scores. Novice and currently abstinent users likewise had significantly poorer immediate recall than non-users. The novice users had milder impairment than the regular users, while those who were currently abstinent performed at a similar level to regular users. These deficits were not attributable either to differences in general reasoning ability or to impairment of working memory. The authors expressed concern that increased use of ecstasy in large numbers of young people and its enduring effects on memory are under-appreciated consequences.

However, cognitive impairment and ecstasy use is a complex association to study, with difficult confounding variables. For example, ecstasy users may consume cannabis to relieve the negative experience that occurs when ecstasy-related euphoria diminishes. In a recent study the concurrent use of cannabis was controlled by the recruitment of 31 drug-naïve controls, 11 ecstasy/cannabis users, and 18 cannabis users (63). Users were instructed to abstain from drug use for 48 hours before testing. The ecstasy/cannabis user group had deficits in learning, memory, verbal word fluency, speed of processing, and manual dexterity compared with the healthy controls. The authors suggested that the deficits in the drug group were not related to ecstasy. They observed that the study group did not perform poorly compared with those who used cannabis only. Moreover, the finding that the ecstasy/cannabis group was no different from the cannabis group suggested that ecstasy does not cause significant cognitive deficits. The poorer performance of the ecstasy/cannabis users was very little affected by the frequency of use or total ecstasy consumption. However, co-varying for indices of cannabis consumption removed most of the significant differences between the groups. On the other hand, ecstasy did affect the measures of working memory, such as forward and backward digit span. The authors raised the question of whether previous evaluations of the effects of ecstasy on cognition had been confounded by the concomitant use of cannabis.

Susceptibility factors

Sex differences in subjective experiences of ecstasy use have been reported. Three previously published controlled studies of the acute effects of ecstasy in healthy subjects with no or single previous ecstasy experience have been summarized (64). There were 74 subjects (54 men and 20 women), aged 20–49 (mean 27) years, of whom 69 were ecstasy-naïve and five had used it on one or two occasions before. All had been screened using a semi-structured interview, and anyone with a personal or family history of mood disorders, schizophrenia, or other psychiatric disorders was excluded. The analysis included psychological and physiological effects of ecstasy in controlled settings. Generally, subjective effects of ecstasy were more intense in women than men. Women had especially higher scores for ecstasy-induced perceptual changes, anxiety, and adverse effects. In contrast, men were slightly activated by ecstasy compared with women and had significantly higher increases in systolic blood pressure. The authors suggested that women may be more sensitive to the effects of ecstasy. Many previous studies have suggested sex differences in markers for serotonergic activity in ecstasy users, with suggestions that serotonergic function is relatively impaired in women compared with men. The authors, based on their findings coupled with data from previous reports, raised the question of whether women might be more susceptible to ecstasy-induced depletion of serotonin.

Electrolyte balance

A death from hyponatremia after ecstasy use has been reported from New Zealand, where it is a commonly used recreational drug (65).

- A 27-year-old woman was admitted to the intensive care unit with coma and respiratory arrest. She had been seen taking two ecstasy tablets while dancing at a nightclub about 5 hours before admission. She had drunk copious amounts of water to cool herself. When she reached the hospital, her Glasgow score was 3 and she was in respiratory arrest with fixed dilated pupils. Her serum sodium concentration was 124 mmol/l with a low serum osmolarity (267 mmol/l) and normal renal function. Her toxicology screen was positive for ethanol, and MDMA was found in her serum. The electrocardiogram showed a sinus tachycardia without ischemia, and a chest X-ray showed gross pulmonary edema. A CT scan of the brain showed generalized cerebral edema, diffuse cerebral swelling, and significantly increased intracranial pressure; the basal cisterns and extracerebral spaces were completely effaced. Brain death was confirmed by cerebral angiography,

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which showed no intracranial flow in the carotid or vertebral arteries. The post-mortem report confirmed marked cerebral edema with signs of cerebellar tonsillar herniation.

The authors reviewed the possible explanations, which included excess water ingestion, SIADH, and the serotonin syndrome. While many ecstasy users drink water to counter its hyperthermic effects, others do it because of "health advice" given at such parties to prevent toxic effects. However, death can occur due to water intoxication, albeit infrequently.

In a retrospective analysis of all cases of hyponatremia associated with ecstasy (SEDA-25, 37) at the London Centre of the National Poisons Information Service from December 1993 to March 1996, 17 patients were identified with a serum sodium concentration under 130 (range 107–128 mmol/l) (66). In 10, ecstasy was identified analytically, and six of them had SIADH. The clinical presentation was very consistent, with initial vomiting and delirium, and 11 had seizures. There was complete recovery in 14, but two died of cerebral edema 5 hours after ingestion.

- A 20-year-old woman attended a "rave", where she took ecstasy and drank large amounts of water (often suggested to prevent dehydration and other life-threatening consequences) (67). She felt drowsy and had a headache. After lying still for 3 hours, she had a tonic-clonic seizure and was brought to hospital, where her plasma sodium concentration was 112 mmol/l and she had cerebral edema. She was treated with hypertonic saline and recovered fully.

These reports show that hyponatremia due to ecstasy occurs primarily due to inappropriate secretion of antidiuretic hormone and relative excess liquid intake, usually in the setting of a warm environment and possible hyperthermic effects of ecstasy. Excess water ingestion should be discouraged in ecstasy users.

Two deaths in patients with hyponatremia after ecstasy intoxication have been reported (68).

- A 15-year-old woman developed impaired consciousness and psychomotor agitation and 10 minutes later reactive bilateral mydriasis and decerebration. A CT scan showed diffuse brain edema and subarachnoid hemorrhage. She had hyponatremia (119 mmol/l) and was considered brain dead 32 hours later.
- A 19-year-old woman became disoriented and had hyponatremia (131 mmol/l) and a serum ethanol concentration of 2.4 mmol/l. Her serum sodium had fallen to 120 mmol/l 10 hours later, and 5 hours later she suddenly deteriorated and had a respiratory arrest, coma, and sinus tachycardia of 180/minute with bigeminy. A CT scan showed diffuse edema in the posterior fossa. She was considered brain dead 23 hours after taking the ecstasy.

Mineral balance

SIADH has been associated with MDMA (69,70).

- A healthy 19-year-old woman complained of nausea and vomited 8 hours after taking unknown quantities of MDMA and beer; 3 hours later, she suddenly clenched her jaw, had tonic contractions of all four limbs, and collapsed. She was obtunded, with occasional moaning and non-purposeful movements of the limbs. Head CT scan showed mild cerebral edema. Her serum electrolytes, including a sodium of 115 mmol/l and a corresponding urine osmolality of 522 mosm/kg, suggested SIADH. Despite treatment, the serum sodium concentration 10 hours later was 116 mmol/l, but 18 hours after treatment, it rose to 125 mmol/l. She became progressively more responsive, with normalization of her sodium concentration, and after 48 hours was awake and alert, with a serum sodium concentration of 136 mmol/l.

The authors reviewed nine other reported patients with MDMA-related SIADH, all of whom were women. They concluded that MDMA-associated SIADH is multifactorial and that MDMA may stimulate vasopressin secretion in susceptible individuals. They further suggested that hyponatremia can also occur secondary to voluntary increases in fluid or water intake aimed at preventing the adverse effects of MDMA. With appropriate treatment, full recovery is possible in almost all cases of this life-threatening condition.

- An 18-year-old woman developed impaired consciousness, psychomotor shaking, hallucinations, tics, and delirium. Her serum sodium concentration was low at 120 mmol/l with a plasma osmolality of 242 mosm/kg and a urine osmolality of 562 mosm/kg, suggesting SIADH. Most other blood tests were within the reference ranges, except for a raised creatine kinase. Urine toxic screen was positive for amphetamines. Treatment with hypertonic saline brought about resolution of symptoms. The patient recalled taking three ecstasy tablets over 6 hours.

Hematologic

Transient anemia has been associated with ecstasy (71).

- A 36-year-old HIV-positive man taking zidovudine, lamivudine, and indinavir was noticed to have a mild asymptomatic anemia (hemoglobin 10.2 g/l, white cell count 10.4×10^9/l with a normal differential count, and platelets 237×10^9/l). The blood film suggested hemolysis. He had taken ecstasy 2 weeks earlier for the first time. The anemia was reportedly "secondary to oxidative stress, probably due to drug toxicity." Three weeks later his hemoglobin returned to normal.

In the absence of other explanations, the authors concluded that this syndrome had probably been caused by ecstasy toxicity.

Mouth and teeth

An unusual adverse effect of MDMA, tooth wear, has been reported (72).

- A healthy 17-year-old boy, who complained of dental sensitivity that occurred only when he consumed fizzy drinks, presented with marked tooth wear. All the teeth were involved, especially the premolars and permanent molars. He ate a poorly balanced diet, with 500 ml carbonated drinks twice daily. He subsequently admitted to frequent MDMA abuse.

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Current health promotions advise that ecstasy users should frequently consume "sports" type or fruit drinks to counteract dehydration and avoid ion imbalances. These particular drinks may be erosive to the teeth. Bruxism and trismus associated with ecstasy use can also contribute to tooth wear.

Liver

Cases of ecstasy-associated hepatotoxicity have been reported.

- A 27-year-old man developed jaundice without fever (73). He used ecstasy regularly and had recently increased his consumption. All other possible causes of acute hepatitis were ruled out. After withdrawal of ecstasy, the condition resolved completely.
- A 17-year-old girl developed progressive jaundice and weight loss (74). Four months before, she had had malaise, anorexia, a sore throat, and tender cervical lymph nodes. Two months later she reported eating "hallucinogenic mushrooms." Five weeks before admission she observed blood clots in her stool. Three weeks later, she ate more mushrooms. She then developed progressive jaundice, with vomiting, dark urine, light-colored stools, and raised aminotransferases. She drank alcohol in binges and reported marijuana use since the age of 15. She had used ecstasy on several occasions during the previous 2 months. She had a minimally tender enlarged liver. Her viral hepatitis screen was negative. Genetic, metabolic, and autoimmune disorders were also ruled out. A urine screen for drugs was positive only for cannabinoids. Abdominal ultrasound showed periportal edema and contraction of the gall bladder, but no gallstones or dilated bile ducts. A CT scan showed moderate amounts of free fluid in the abdomen and pelvis and periportal hepatic edema. Percutaneous liver biopsy showed acute cholestatic hepatitis with cholangitis, eosinophils, and histiocytes, strongly suggesting a hypersensitivity reaction. There was no evidence of chronic liver disease. Within 24 hours after the liver biopsy, her liver enzymes and coagulopathy had begun to improve.
- A 21-year-old soldier had nausea, vomiting, abdominal pain, and fever, having taken 7–8 ecstasy tablets a week (75). He was treated with intravenous fluids and paracetamol (650 mg/day) for 3 days. His symptoms did not improve and he developed jaundice. He had increased transaminase activities and total bilirubin concentrations and all tests for viral hepatitis were negative. He was considered for liver transplantation, but over the next 2 weeks improved spontaneously.

The authors of the last report postulated a hyperthermic effect of ecstasy on the liver or a direct toxic effect of ecstasy on hepatocytes as possible mechanisms.

Cases of successful liver transplantation after ecstasy-induced hepatotoxicity have been reported (68,76,77).

- A 19-year-old man with no significant past history of medical problems took 1½ tablets of ecstasy and some alcohol. Within 2–4 days, he developed tiredness, nausea, malaise, and vomiting and on the fifth day weakness and anorexia; 12 days later, he was admitted to hospital with marked jaundice and weight loss. He deteriorated and developed hepatomegaly and an abnormal prothrombin time; his total bilirubin was 571 (reference range 5–17) μmol/l, aspartate transaminase 213 (14–50) U/l, and alanine transaminase 336 (11–60) U/l. By day 20, his condition had deteriorated, with increased jaundice, somnolence, mild disorientation, and altered glucose metabolism. His total bilirubin was 654 μmol/l, aspartate transaminase 1290 U/l, and alanine transaminase 1932 U/l. A liver biopsy showed swollen hepatocytes, patches of necrosis, and patchy cholestasis. Two days later, he developed a grade III encephalopathy and further disturbances of coagulation. Abdominal ultrasonography showed hepatic atrophy, and a liver biopsy showed massive necrosis. Serological tests for viral infections were negative. The probable diagnosis was toxic hepatitis secondary to MDMA. On day 31, he had a right auxiliary liver transplantation, but there was no clinical and laboratory improvement during the next 48 hours. Histopathology of the transplanted liver showed massive liver necrosis consistent with a "diagnosis of primary non-function". A second liver transplant on day 33 was successful.
- A 17-year-old girl with no history of drug abuse took two tablets of ecstasy at a disco 10 days apart, and reported malaise, constipation, and icterus 6 days after taking the second. She had severe acute hepatic failure. Viral hepatitis was ruled out. Following rapid clinical and neurological deterioration (encephalopathy grade I–II), she had an urgent liver transplant and made a good recovery. In the affected liver, there was submassive centrilobular hemorrhagic necrosis (75–80%) with massive periportal and lobular lymphocytic infiltration (CD 8+) and moderate fatty changes.
- A 25-year-old woman developed abdominal pain, jaundice, and vomiting 5 days after consuming ecstasy. She had hepatocellular failure with a prothrombin ratio of 6.5, cytolysis, cholestasis, renal insufficiency, and encephalopathy. She had a liver transplant 2 days later and recovered fully.
- A 17-year-old man developed toxic subacute hepatitis with grade II encephalopathy and coagulation disorders a few days after consuming ecstasy. Liver transplantation was performed and he recovered fully.
- A 16-year-old woman consumed ecstasy and developed jaundice, hepatic failure, a prothrombin ratio of 9, and grade I encephalopathy. She had a liver transplant and was asymptomatic at 11 months.

Many cases of hepatotoxicity and some deaths have occurred in drug-naïve subjects after the ingestion of relatively small amounts of ecstasy. The authors reported that more than 70 deaths have been reported worldwide between 1990 and 1998 after the onset of severe hepatic damage from ecstasy. Although many patients died after liver transplantation, a significant number recovered. The authors suggested that in emergency care the use of ecstasy should be suspected in young people who present with unexplained jaundice, hepatomegaly, or altered liver function, in the absence of other known substance exposure. Early referral for liver transplantation may be significantly beneficial. The prognosis may be better with grade I–II encephalopathy than grade III–IV, which is

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usually associated with rapid deterioration and a poor prognosis.

Skin

Two cases of facial papules have been reported (78).

- A 20-year-old woman developed diarrhea and a pruritic yellowish skin 7 days after she had taken half a tablet of ecstasy. Her liver was enlarged and tender. Her urine was positive for MDMA. A diagnosis of acute hepatotoxicity after MDMA was made. She rapidly developed reddish papules over the face with a perioral and acne-like distribution.
- A 21-year-old-man developed similar skin lesions after using ecstasy, without hepatotoxicity.

Both patients responded to a low fat diet and 1% metronidazole ointment. The authors suggested that serotonin indirectly affects the nerve endings of the eccrine glands via other peptides, and that the interaction of MDMA with serotonin may have caused the rapid development of pimples in these abusers.

Immunologic

Four healthy male MDMA users volunteered for a randomized, double-blind, double-dummy, crossover pilot study in which they took single oral doses of MDMA 75 mg ($n = 2$) or 100 mg ($n = 2$), alcohol (0.8 mg/kg), MDMA plus alcohol, or placebo to study the effects on their immune system. The doses of MDMA were compatible with those used for recreational use (79). The baseline immunological parameters were within the reference ranges. Acute MDMA use produced time-dependent immune dysfunction, which paralleled MDMA plasma concentrations and MDMA-induced cortisol stimulation kinetics. The changes in the immune system after MDMA peaked at 1–2 hours. Although the total leukocyte count remained unchanged, there was a fall in the ratio of CD4 to CD8 T cells and in the percentage of mature T lymphocytes (CD3 cells), probably because of a fall in both the percentage and the absolute number of T helper cells. The fall in CD4 cell count and in the functional responsiveness of lymphocytes to mitogenic stimulation with phytohemagglutinin A was MDMA dose-dependent. Alcohol produced a decrease in T helper cells, B lymphocytes, and mitogen-induced lymphocyte proliferation. Combined MDMA and alcohol use produced the greatest suppressive effect on CD4 cell count and mitogen-stimulated lymphoproliferation. Immune function was partially restored at 24 hours. According to the authors, these results provided the first evidence that recreational use of MDMA alone or in combination with alcohol alters immunological status. The reaction of the immune system to MDMA appears to be an alteration of physiological homeostasis, similar to that seen in volunteers exposed to acute physiologic stress, suggesting that MDMA could be a "chemical stressor". Moreover, combined MDMA and alcohol use produced additive effects. This is an important finding, since in the general population alcohol and MDMA are commonly taken together.

Because other drugs of abuse can cause immune dysfunction in regular users, the effects of acute administration of ecstasy on the immune system have been studied in both controlled and natural settings (80). In the controlled study, 18 male ecstasy users were given two doses of ecstasy 100 mg at intervals of 4 or 24 hours. There were significant reductions in CD4 T helper cells (30%) and the lymphoproliferative response to phytohemagglutinin mitogenic stimulation (68%) 1.5 hours after the first dose, and a 103% increase in the number of natural killer cells. At 4 hours, CD4 T helper cells and lymphocyte proliferative responses were reduced by 40% and 87%, but natural killer cell numbers increased to 141%. At 24 hours, the second dose augmented the alterations in the numbers of CD4 T helper cells and natural killer cells about threefold. The authors suggested that this large effect after repeated administration of ecstasy increases the interval during which the immune response is compromised, leading to a higher risk of illness and infection in ecstasy abusers.

In the uncontrolled study, 30 recreational users of ecstasy (mean age 24 years) were observed for 2 years and had lymphocyte counts at yearly intervals. The ecstasy users tended to have lower white blood cell counts over time. Lymphocyte counts were significantly lower than in healthy controls by year 1 and significantly lower than that the following year. CD4 and CD19 cell numbers fell significantly from basal to year 1 and from year 1 to year 2. Natural killer cell numbers were always lower than in healthy controls but did not fall with time. The authors extended these results to suggest a possible role of serotonin dysregulation caused by ecstasy in compromising immune function. These findings suggest that ecstasy abusers may be at a significantly higher risk of infectious diseases.

Death

MDMA and MDEA, or "eve," have rapidly become popular drugs of abuse in recent years in Europe and to some extent in other developed countries as well. Over the years, reports of deaths following their use at "rave" parties have generated considerable public concern.

In a study of all ecstasy-positive deaths (22 of 19 366 deaths) in New York City from January 1997 to June 2000, 18 were men, average age 27 years (81). The deaths fell into three categories: acute drug intoxication ($n = 13$), mechanical injury ($n = 7$), and a combination of natural causes and acute drug intoxication ($n = 2$). Only two of the deaths due to acute drug intoxication were caused by ecstasy alone, and one death was caused by a combination of ecstasy and coronary artery disease. Seven deaths were caused by a combination of cocaine/opiates and ecstasy. Acute ecstasy poisoning includes symptoms such as hypertension, hyperthermia, and delirium, and can progress to intracranial hemorrhage, status epilepticus, and death. Based on reports from harm-reduction organizations and previous studies, the authors discussed the lack of standardization of ecstasy tablets and the danger of harmful additives that could react with other drugs to cause life-threatening symptoms.

Death rate

In a report from the UK it was noted that the annual death rate from ecstasy use is uncertain (82). A meta-analysis of surveys of illegal drug use by 15–24-year-old

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individuals in the UK in 1996 showed that 7% had used ecstasy in the previous year and 3% in the previous month, a rate 44% higher than in 1993–1995. But the actual numbers of ecstasy-related deaths are more difficult to ascertain. In Scotland, ecstasy-related deaths are defined as "ecstasy found in the body"; in England, on the other hand, it is defined as "ecstasy written on the death certificate." Using these disparate definitions, 11 deaths were reported in Scotland and 18 in England in the 15–24-year-old category. Based on all available data, the author of the report suggested a 26-fold range (0.2–5.3) of possible ecstasy-related deaths per 10 000 within this age group. To make death estimates more reliable, the author recommended that the definition of "ecstasy-related-death" should be unified, and that surveys should ask directly about regular, sporadic, and first-time drug use, so as to determine which group is at most risk. The author expressed concern that these data (poor as they are) may be used by the courts and policy makers as if they were more valid, citing the example of Switzerland, which has recently liberalized the guidelines on sentencing people who supply ecstasy tablets, in contrast to suppliers of heroin, based on their interpretation of the data that the death rate in ecstasy users is at the lower end of the range.

This report generated two responses. One group felt that estimating such death rates is even more complex than noted (83). They asked whether, if someone purchased ecstasy but instead got a contaminated or a very different compound, causing death, the death would be classified as ecstasy-related or as something else? Furthermore, they wondered if the definition of ecstasy-related death is based on the detection of MDMA (or its metabolites) in the blood or on detection of other compounds (consumed under the presumption of its being ecstasy). Citing their own experience, they suggested that criteria for inclusion should include: "Would the deceased still be alive if (s)he had not abused the substance?" Thus, even deaths from causes such as traffic accidents, when the death was secondary to intoxication with the compound, should be included.

The second group, while agreeing with the original report, raised the concern that surveys that are more frequent would be economically prohibitive (84). They noted that in 1997 The National Program on Substance Abuse Deaths (NPSAD) was established to monitor drug-related deaths in the UK. It uses a "cause of death ratio," which looks at the number of drug-related deaths in specific categories (for example 15–24-year-olds) and the drugs implicated in these deaths. According to the authors, this method allows rapid surveillance of the pattern of deaths over time.

Pathology

Three deaths have been reported after the ingestion of MDMA/MDEA, in which immunohistological studies further elucidated the causes of the deaths (85). One death was caused by MDMA intoxication, one was from MDEA, and the third was from combined intoxication. One case had been reported previously (SEDA-22, 31).

- A 19-year-old man consumed ecstasy for the entire duration of a discotheque party (lasting until morning) and had respiratory difficulty, uncoordinated movements, generalized hypertonia, and hyperpyrexia (40.6°C). The diagnosis was disseminated intravascular coagulation and was treated with heparin but suffered severe blood loss from the oral cavity and injection wounds. He subsequently had a cardiac arrest.
- A 20-year-old man took many ecstasy tablets at a discotheque, returned home complaining of feeling feverish (axillary temperature 40°C), went to bed, and was found dead 10 hours later, his pillow soaked with blood.
- A 19-year-old man was found unconscious near a discotheque. His course progressively worsened, with the appearance of diffuse subcutaneous petechiae. While being treated for hypotension, he developed sustained convulsions and uremia and later died.

In all cases, amphetamines were detected in the urine. The pathological findings showed diffuse subserous petechiae and polyvisceral stasis. The brains showed massive edema and signs of neuronal hypoxia. In two cases, the heart showed coagulative myocytolysis, while one had areas of subendocardial hemorrhage. The lungs showed subpleural and intra-alveolar hemorrhages with severe edema, and in two cases microthrombotic formations inside lung capillaries. In two cases, the liver showed evidence of microvesicular steatosis and in one case centrilobular necrosis. Liver cells in the central zones showed coagulation necrosis with precipitation of fibrin in the whole area affected by necrosis. In the kidney, fibrin thrombi in the renal glomeruli were observed in two of the cases, while acute tubular necrosis was observed in one.

The findings in these three cases were similar to those seen in deaths from hyperthermia and disseminated intravascular coagulation. The myocardial necrosis (coagulative myocytolysis) without infarct necrosis suggested adrenergic overdrive. In two cases the muscle showed the typical pathological changes observed in deaths due to malignant hyperpyrexia. Myoglobin was detected in the proximal tubules in all three cases. The authors interpreted the clinical, histopathological, and toxicological data as indicative of an idiosyncratic response to ecstasy.

Long-Term Effects

Drug dependence

There are few preclinical or clinical data to suggest that repeated use of MDMA is associated with increased tolerance or dependence. However, anecdotal reports suggest that in some individuals, increasing amounts of MDMA are used in order to achieve the same reinforcing psychoactive effects (44,86).

Second-Generation Effects

Pregnancy

Workers in Canada have tried to characterize women who reported gestational exposure to ecstasy (87). The Motherisk Program is a large Teratogen Information Service based in Toronto and receives over 150 calls daily about exposure to various agents during pregnancy. The authors reviewed the data from 1998 to 2000. The

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study group consisted of all pregnant women who had been exposed to ecstasy. The control group was randomly selected pregnant women who visited the Motherisk Clinic during the same week as the subject who called about ecstasy. The 132 ecstasy-exposed women were significantly younger, earlier in gestational age, and weighed less than the non-exposed controls. The ecstasy users had had significantly fewer pregnancies and live births and had a higher rate of therapeutic abortions but not spontaneous abortions. Significantly more ecstasy users reported unplanned pregnancies and were more likely to be single and white. The ecstasy users were more likely than controls to have had alcohol exposure in pregnancy, and significantly more drank heavily. The ecstasy-exposed women were more likely to binge-drink and smoke cigarettes during pregnancy, and more were significantly heavy smokers. Ecstasy users also had a greater tendency to use marijuana, cocaine, amphetamines, ketamine, gamma-hydroxybutyrate, and psilocybin.

Of the 132 women who reported ecstasy use, 129 had used it during pregnancy, of whom 101 reported previous use of ecstasy before their pregnancy, but had discontinued it. The mean gestational age of last ecstasy exposure was 5.0 weeks (range 1–24 weeks). All but three used tablets: two snorted and one used a liquid formulation. The mean dose taken on one occasion was 1.24 tablets. Of the 122 patients whose data were included in the analysis, most (57%) had only one exposure to ecstasy during pregnancy; 10 women had more than five exposures. One 15-year-old girl did not realize she was pregnant until 24 weeks gestation and had used two tablets of ecstasy four times a day. Only seven of the ecstasy group reported exposure to ecstasy alone. Ecstasy-associated adverse events were reported by 33 of 77 respondents. The physical adverse effect most commonly reported was vomiting (23%). The authors raised significant concerns about the potential teratogenic effects in these women, due to clustering of risk factors.

Drug Administration

Drug formulations

In New Zealand, "herbal ecstasy" is a term used for many different herbal formulations, none of which contains ecstasy. Some of the names for these herbs (which can be sold in stores) include "The Bomb", "Reds", and "Sublime". Analysis of "The Bomb" showed substantial amounts of ephedrine; the Ministry of Health in New Zealand removed it from the market. Some symptoms associated with herbal ecstasy include headache, dizziness, palpitation, tachycardia, and raised blood pressure. Thus, in countries where the term "herbal ecstasy" is commonly used, it is important that those who see patients who have taken herbal ecstasy should not confuse it with ecstasy, as toxicity and medical management may be quite different (88).

Drug contamination

It is not uncommon for people to be deceived into consuming other substances, believing them to be MDMA. At dance parties and "raves" for young adults, compounds passed as ecstasy may be more lethal than MDMA, either because they contain more potent amphetamines than MDMA or because of adulteration with other substances. In three fatal cases reported in the USA, the victims (two men aged 19 and 24 and a woman aged 18) believed that they were using MDMA but had in fact taken PMA, a more potent central stimulant with structural and pharmacological similarities to MDMA (89). They became agitated and developed bruxism, severe hyperthermia, convulsions, and hemorrhages. The presence of PMA was confirmed by enzyme immunoassay, and MDMA was not detected. PMA is not a contaminant of MDMA.

Drug–Drug Interactions

Alcohol

The pharmacokinetic and pharmacodynamic interactions of single doses of ecstasy 100 mg and alcohol 0.8 g/kg have been investigated in nine healthy men (mean age 23 years) in a double-blind, double-dummy, randomized, placebo-controlled crossover design (90). Each underwent four 10-hour experimental sessions, including blood sampling, with 1 week between each. For the task used to test the recognition and recording of visual information, the conditions involving ethanol yielded significantly more errors and fewer responses than ecstasy alone or placebo alone. The combination of ecstasy with ethanol reversed the subjective effect of sedation caused by alcohol alone. In addition, the combination extended the sense of euphoria caused by ecstasy to 5.25 hours. The addition of ethanol caused plasma ecstasy concentrations to rise by 13%. These results show that the combination of ecstasy with alcohol potentiates the euphoria of ecstasy and reduces perceived sedation. However, psychomotor impairment of visual processing caused by alcohol is not reversed. This is a concern for road safety, as people who take both drugs would feel sober, but their driving would still be compromised, although the extent of driving impairment under these conditions is not known. The increase in plasma concentrations of ecstasy caused by alcohol could exacerbate the adverse effects of ecstasy.

Ritonavir

An important consideration in the use of all HIV-1 protease inhibitors, but of ritonavir in particular, is their potential for drug interactions through their effects on cytochrome P450 isozymes. The various interactions of ritonavir with other antiretroviral drugs have been reviewed (91). Ritonavir, which inhibits CYP2D6, the principal pathway by which MDMA is metabolized, can also produce clinically relevant interactions with recreational drugs (92).

- A 32-year-old HIV-positive man, who added ritonavir 600 mg bd to his antiretroviral regimen of zidovudine and lamivudine, became unwell within hours after having taken two and a half tablets of ecstasy, estimated to contain 180 mg of MDMA. He was hypertonic, sweating profusely, tachypneic, tachycardic, and cyanosed. Shortly after he had a tonic-clonic seizure and a cardiorespiratory arrest. Attempts at resuscitation were

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unsuccessful. Blood concentrations obtained post-mortem showed an MDMA concentration of 4.56 mg/l, in the range of that reported in a patient with a life-threatening illness and symptoms similar to this patient after an overdose of 18 tablets of MDMA.

A patient infected with HIV-1 who was taking ritonavir and saquinavir had a prolonged effect from a small dose of MDMA and a near-fatal reaction from a small dose of gamma-hydroxybutyrate (93).

Selective serotonin re-uptake inhibitors (SSRIs)

An MDMA-related psychiatric adverse effect may have been enhanced by an SSRI (94).

- A 52-year-old prisoner, who was taking the SSRI citalopram 60 mg/day, suddenly became aggressive, agitated, and grandiose after using ecstasy. He carried out peculiar compulsive movements and had extreme motor restlessness, but no fever or rigidity. He was given chlordiazepoxide and 2 days later was asymptomatic. Citalopram was reintroduced, and 2 days later he reported visual hallucinations of little bugs in the cell. Promazine was substituted for citalopram and his condition improved 2 days later.

The authors suggested that SSRIs such as citalopram can potentiate the neurochemical and behavioral effects of MDMA.

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Methylnaltrexone

See also Opioid antagonists

General Information

Methylnaltrexone is an opioid receptor antagonist that acts peripherally and can be of value in preventing the unwanted effects of opioids while maintaining their central analgesic effects (SEDA-21, 92) (1).

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Methylphenidate

See also Anorectic drugs

General Information

Methylphenidate is a piperidine derivative, structurally related to amphetamine, but a milder central nervous system stimulant. However, large doses produce symptoms of generalized central nervous system stimulation and convulsions. It is more active than amphetamine as an antidepressant, as a treatment for overdosage of depressant drugs, and in exacerbating schizophrenic symptoms. Occasionally, anorexia, nausea, dry mouth, nervousness, insomnia, dizziness, and palpitation have been recorded.

Considerable concern surrounds the use of methylphenidate, and to a lesser extent amphetamine and pemoline, in hyperactive children or those with attention deficit hyperactivity disorder (ADHD), because of possible detrimental effects on general physical and emotional growth and central nervous system development. The Psychopharmacology Pediatric Subcommittee of the FDA in the USA has reviewed the literature relevant to growth suppression by stimulants in the treatment of hyperkinesia. There is clear evidence of temporary retardation in weight increase and a suggestion of temporary slowing of height increase related to dose and absence of drug holidays during the prepubertal period (1–3). Drug holidays allow growth rebound in children who require higher doses.

At an NIH Consensus Conference, one of the conclusions was that "... careful therapeutic use of stimulants is effective in treating the core symptoms of ADHD as long as a child is taking the medication" (4). However, the panel identified "... the need to study the benefits and risk of long-term use of such medications. Although behavioral treatments produced positive short-term results it remains unclear what combinations of these strategies are most effective... Although little information exists concerning the long-term effects of psychostimulants, there is no conclusive evidence that careful therapeutic use is harmful. When adverse drug reactions do occur, they are usually related to dose. It is well known that psychostimulants have abuse potential ...". However, drugs used for ADHD, other than psychostimulants, have their own adverse reaction patterns: "tricyclic antidepressants may induce cardiac arrhythmias, bupropion at high doses can cause seizures, and pemoline is associated with liver damage." Effects associated with moderate doses include reduced appetite and insomnia. These effects occur early in treatment and may abate with continued dosing. There may be negative effects on growth rate, but final height does not appear to be

affected. Rarely, children and adults who take high doses have hallucinogenic responses. The need for long-term follow-up looking for potential adverse effects was highlighted by the conference.

The short-term and long-term efficacy and safety of pharmacological and nonpharmacological interventions in patients with ADHD have been discussed in a systematic review of 92 reports of 78 randomized clinical trials (5). There was substantial heterogeneity in the data, and so a meta-analysis was not performed. In 22 comparisons of stimulants, the drugs did not generally differ in efficacy. The evidence was too limited for a reliable assessment of the effectiveness of stimulant drugs compared with tricyclic antidepressants. Of six comparisons of drugs and non-drug interventions, five showed that stimulants were more effective. In 20 trials of combined interventions there was no compelling evidence to support combination treatment. Of nine comparisons of tricyclic antidepressants with placebo, six showed benefit with desipramine, whereas the effect of imipramine (three trials) was inconsistent. The study with the highest methodological score showed greater benefit with methylphenidate than placebo. Adverse effects, such as sleep disorders, headache, tics, reduced appetite, abdominal pain, irritability, nausea, and fatigue, were assessed in 29 trials. No evidence was available for more severe, long-term adverse effects, such as the risk of addiction with stimulants, liver toxicity with pemoline, or cardiac dysrhythmias with antidepressants. The authors concluded that in patients with ADHD published studies of treatment regimens provide limited information of effectiveness because of small sample sizes, flawed methods, and heterogeneity across outcomes. Thus, pharmacological interventions in ADHD are consistently more effective than nonpharmacological interventions. Combined interventions are not more beneficial than single interventions.

Two reviews have addressed the diagnosis and management of ADHD and have summarized the effects of stimulants, including those of methylphenidate and Adderall® (a mixture of equal components of D-amfetamine saccharate, D,L-amfetamine aspartate, D-amfetamine sulfate, and D,L-amfetamine sulfate, which seems to be gaining popularity in the treatment of ADHD) (6,7).

The results of the National Institute of Mental Health Collaborative Multimodal Treatment Study of children with attention deficit hyperkinetic disorder have been analysed (8). This double-blind, placebo-controlled methylphenidate titration trial identified the optimum dose and replicated previously reported methylphenidate response rates and dose-related adverse events. For parent ratings, the severity of the following adverse events increased as the dose was raised: appetite suppression, dull/listless appearance, stomachache, tearfulness, and trouble sleeping. For teacher ratings, the only significant drug-related adverse event that had a dose-related trend was reduced appetite. Other adverse events reported by teachers were dull/listless appearance, crabbiness, and buccal movement or chewing. However, these teacher-reported adverse events improved with increased methylphenidate dosage. The authors also emphasized that parents report more dose-related adverse events than teachers do, making them better reporters of safety during dosage titration.

As more adults with ADHD are being treated with methylphenidate, the possibility of drug interactions with methylphenidate increases (9). However, based on a study in extensive and poor CYP2D6 metabolizers, it has been suggested that CYP2D6 is not involved in the metabolism of methylphenidate, and that drugs that are inhibitors of CYP2D6 should not affect methylphenidate plasma concentrations (10).

Organs and Systems

Cardiovascular

Significant increases in blood pressure and/or pulse rate after methylphenidate are more frequent when it is given parenterally (11) (SEDA-4, 9).

Cardiac dysrhythmias, shock, cardiac muscle pathology, and liver pathology have all been reported (12).

Ambulatory blood pressure monitoring showed changes in blood pressure and heart rate in boys aged 7–11 years taking stimulant therapy (13). This preliminary study with chronic methylphenidate or Adderall® (dexamfetamine + levamfetamine) for ADHD showed alterations in awake and asleep blood pressures, with profound nocturnal dipping. Modified-release formulations of methylphenidate and Adderall® now allow more sustained blood concentrations in children. The effects of these newer formulations on cardiovascular indices should be evaluated.

Nervous system

A first case of neuroleptic malignant syndrome probably caused by methylphenidate has been reported in a child with multicystic encephalomalacia due to severe perinatal hypoxic/ischemic encephalopathy (14). At 1.5 years of age, because her circadian rhythm was irregular or reversed, methylphenidate (3 mg/day) was given for its antihypnotic effect. The diagnostic criteria of neuroleptic malignant syndrome (15) were fulfilled in this case, including three major manifestations (fever, rigidity, and raised creatine kinase activity) and six minor ones (tachycardia, abnormal blood pressure, tachypnea, altered consciousness, sweating, and leukocytosis). Other predisposing factors, such as pre-existing severe brain damage suggestive of organic fragility and infection, may have contributed.

There is continuing concern about the potential for methylphenidate to precipitate tics or Tourette's syndrome, in subjects with and without pre-existing tics. However, in a placebo-controlled crossover study in 91 children with ADHD, the usual doses of methylphenidate did not produce significantly more tics than placebo in children with or without pre-existing tics (16). This study had limitations of sample size and statistical power. Moreover, these conclusions cannot be generalized to patients who use higher doses of methylphenidate, because a dose-dependent relation between methylphenidate and tics has been proposed (17). Until the effect of methylphenidate in larger populations has been studied with more exacting measures of tics, it would be wise to monitor for tics, especially if higher doses (0.5–1.3 mg/kg) of methylphenidate are required.

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The risk of using methylphenidate for long periods has been highlighted by a case of a stroke in a child (18).

- An 8-year-old boy, who had taken methylphenidate (20 mg/day) for 18 months, suddenly developed paresthesia in his left arm, with spontaneous resolution after a few days. Two months later he had intense paresthesia in the left arm, spreading to the left side of the face; 48 hours later he developed weakness of the arm that extended to the whole of the left side of the body. He remained lucid. The episode resolved spontaneously within 24 hours. After a symptom-free period of 2 months, he had a third episode, similar to the previous ones, but more severe and leaving a residual deficit. Methylphenidate was withdrawn and he did not subsequently relapse. A CT scan showed a hypodense area in the left thalamus, and an MRI scan showed multiple lesions in both thalami. A cerebral angiogram showed enlargement of the basilar artery and the proximal segment of both posterior cerebral arteries.

The authors suggested that in this case the stroke was due to a vasculitis, which has previously been reported with methylphenidate (19).

Episodes of explosive behavior, apparently due to methylphenidate, masquerading as unmanageable ADHD, have been reported (20).

- A 10-year-old boy developed motor and vocal tics and severe obsessive-compulsive symptoms, predominantly about symmetry. These were not evident before he started taking methylphenidate. At 7 years of age he had begun a regimen of methylphenidate 20 mg/day in divided doses. Paradoxically, his impulsive behavior increased and he began to have explosions of aggressive and violent behavior, during which he would lash out at his family or destroy things. After a year of methylphenidate therapy, the tics subsided spontaneously but other symptoms remained. Eventually, because of severe impairment resulting from obsessive-compulsive symptoms, his parents stopped giving him methylphenidate. A few months later there were no further obsessive-compulsive preoccupations and no tics, and he did not have any explosive behavior.

It is well recognized that in vulnerable individuals, methylphenidate can induce or aggravate Tourette's syndrome, most often characterized by motor tics and occasionally vocal tics (21). Moreover, obsessive-compulsive symptoms caused by methylphenidate have also been reported (22,23). However, it is not clear whether explosive episodes associated with Tourette's syndrome are an integral part of the disorder or occur as part of a co-morbid disorder, predominantly ADHD or obsessive-compulsive disorder. In this case the explosive episodes coincided with a period of treatment with methylphenidate. In view of the extreme, sudden, discrete nature of the outbursts and the temporal relation to treatment, it was concluded that the episodes were behavioral problems caused by methylphenidate, rather than a feature of the underlying ADHD.

As with other stimulants, chorea (24) and choreoathetosis (25) can be precipitated in children and adults at methylphenidate doses ranging from therapeutic to abuse levels. These symptoms respond to drug withdrawal or neuroleptic drugs.

Psychological, psychiatric

Methylphenidate-induced obsessive-compulsive symptoms are very rare (26); a second case has been reported (22).

- An 8-year-old boy had unusual difficulties in completing a trial of methylphenidate for ADHD. Methylphenidate 10 mg/day initially improved his school performance, but by the end of the second week of treatment severe obsessive-compulsive behavior began to emerge, requiring drug withdrawal. He eventually refused to eat because he suspected that his food was being poisoned. His parents reported that he became more sensitive and easily upset, appearing increasingly tense and fearful. He continued to have intrusive distressing contamination worries. He had repetitive tic-like movements of his head and neck, frequently rubbed his face with his shirtsleeves, and avoided touching his face directly with his fingers for fear of contamination. His symptoms gradually and completely dissipated over 2–3 months without specific intervention. While very mild symptoms of ADHD persisted, he remained entirely free of symptoms at 1 year. Medication was not restarted.

This case lends further support to existing anecdotal evidence associating methylphenidate with obsessive-compulsive disorder of acute onset. However, rechallenge was not attempted, and causality should be viewed as being uncertain.

In a small percentage of hyperactive children, there were gross behavioral changes with hallucinations after brief administration of modest doses of methylphenidate; the reaction subsided after withdrawal (27).

Endocrine

Methylphenidate has been reported to cause stunting of growth by impairing growth hormone secretion (28).

- A 10-year-old boy with ADHD and chronic asthma, who was using inhaled corticosteroids, developed almost complete growth arrest during methylphenidate treatment. Growth hormone stimulation tests and measurement of growth hormone-dependent growth factors suggested that methylphenidate had altered growth hormone secretion and had impaired growth. Determination of growth velocity was a sensitive marker for the evaluation of growth.

Metabolism

The association between childhood treatment with methylphenidate and adult height and weight has been investigated in 97 boys, aged 4–12 years, who were referred to a child psychiatry out-patients clinic and took methylphenidate for an average of 36 months (29). They were re-evaluated between ages 21 and 23 years. Hierarchical analysis predicted adult height and weight from sets of both nonmedication-related and medication-related variables. Medicated individuals who had attained their final stature did not differ in average height or weight from family, community, or nonmedicated

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controls. In some individuals, nausea and vomiting and the use of higher doses of methylphenidate were associated with growth impairment. It should be emphasized that the correlations in this study do not demonstrate cause and effect relations between medication and ultimate stature.

Gastrointestinal

Methylphenidate can occasionally cause abdominal distress, which can be alleviated either by reduction of the dose or by administering the drug immediately after meals (30,31).

Liver

Increased activities of aspartate transaminase, alanine transaminase, and alkaline phosphatase were reported in a 67-year-old woman with a stroke who had taken methylphenidate 10 mg tds. Nausea, vomiting, and dizzy spells occurred. The drug was withdrawn and liver enzymes returned to normal, but when she was rechallenged with a small dose (2.5 mg), the pathological changes recurred (32).

Long-Term Effects

Drug abuse

Abuse and psychosis

Methylphenidate shares the pharmacological properties and the abuse potential of the amphetamines. When given intravenously, it activates psychotic symptoms in schizophrenic patients if administered during the active phase of their illness, but not after remission. It failed to produce a psychotic reaction in most manic or depressed patients or in healthy subjects (27). Adults with childhood-onset ADHD had an earlier onset of psychoactive substance use disorders, independent of any psychiatric co-morbidity (33). However, bipolar disorders conferred a significantly increased risk for early onset psychoactive substance use disorders independent of ADHD. The question arises as to the contribution of stimulant treatment to psychoactive substance use disorders. There were no differences in medicated versus unmedicated adolescents with ADHD in a review of eight outcome studies comprising 580 adolescents briefly treated with stimulants for six months to five years (34).

In a double-blind study, undesirable personality changes, consisting of lethargic and apathetic behavior, occurred in six of 98 hyperactive children aged 6–12 years and treated with methylphenidate for 16 weeks. Withdrawal resulted in a prompt switch from the characteristic mental depression to normal behaviour (35).

There is large variation in individual responses to methylphenidate among hyperactive children with minimal brain dysfunction. It is therefore advisable to start with small divided doses, since some symptoms (extrapyramidal and seizure-like) could be dose-related.

Complications of abuse

Chronic parenteral injection of methylphenidate hydrochloride tablets intended for oral use has led to cutaneous reactions. Pulmonary granulomata were seen in two patients who died as a consequence of drug abuse (SED-8, 22). In one case, bullous erythema multiforme was described and considered unlikely to be due to the excipients in the tablets. However, cornstarch, talc, and binders cause significant microemboli, noticeable on retinoscopic examination, and can cause pulmonary hypertension (SEDA-4, 9).

Five patients suffered skin abscesses or cellulitis after parenteral methylphenidate abuse (SED-9, 11). Such lesions can arise from local vasospasm and chemical irritation and can be susceptible to secondary infection.

Susceptibility Factors

Untreated ADHD is a significant risk factor for substance abuse disorders in adolescents (36). In contrast, pharmacotherapy, that is stimulants, was associated with an 85% reduction in the risk of substance abuse disorders in youths with ADHD. Most authorities recommend complete assessment and diagnosis of both ADHD and any dual diagnoses before starting stimulant medication.

Drug Administration

Drug formulations

A modified-release, once-daily formulation has been evaluated in 282 children with ADHD in a double-blind, placebo-controlled trial for 28 days (37). For core ADHD symptoms, both once-daily modified-release and thrice-daily immediate-release methylphenidate were superior to placebo and not different from each other. A similar percentage of patients reported at least one adverse event with both formulations. The most commonly reported adverse events were headache and upper respiratory infections, followed by abdominal pain, cough, pharyngitis, vomiting, and otitis media. Of these, only headache and abdominal pain were considered to be related to the study medication. One patient withdrew because of depression with modified-release methylphenidate and one because of tics with placebo. Headache occurred in 14%, 5.8%, and 10% of patients taking modified-release methylphenidate, immediate-release methylphenidate, or placebo respectively, and abdominal pain in 6.7%, 5.8%, and 1.0%. Other adverse events included appetite suppression (modified-release methylphenidate) and insomnia (all three). The results of this study suggest that once-daily modified-release methylphenidate provides efficacy superior to placebo and is not significantly different from thrice-daily immediate-release methylphenidate.

Drug overdose

A death due to intranasal abuse of methylphenidate in a teenager has been reported (38).

- A teenager presented with a history and physical signs characteristic of methylphenidate abuse, including hyperpyrexia and tachycardia. The plasma methylphenidate concentration was less than 0.05 mg/l in the admission sample. However, the concentration of ritalinic acid, the principal metabolite of methylphenidate,

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was 0.4 μg/ml. Ethanol was also found in a concentration of 22 mmol/l (100 mg/dl).

Comparable toxicity with other stimulants is well known (39,40).

Of 289 patients exposed to excessive doses of methylphenidate, 31% had symptoms, including most commonly tachycardia, agitation, and lethargy (41). No patient developed severe symptoms, although there was a less favorable outcome with intentional versus unintentional exposure. Peak exposure occurred in 6- to 9-year-old children, in whom therapeutic error was the most common reason for exposure.

Drug–Drug Interactions

Carbamazepine

Carbamazepine can reduce methylphenidate concentrations markedly (42). Since these drugs are often used together, the authors suggested that the worsening of behavior in a 13-year-old girl with ADHD might have been due to a fall in blood concentration of methylphenidate, resulting from carbamazepine.

Ciclosporin

Potential drug–drug interactions of ciclosporin with methylphenidate and amfebutamone (bupropion) have been described (43).

- A 10-year-old boy with a heart transplant had a potentially life-threatening reduction in ciclosporin blood concentrations with amfebutamone. He subsequently had an increase in ciclosporin concentrations while taking methylphenidate.

These interactions merit further systematic investigation.

Citalopram

There is growing interest in using stimulants, particularly methylphenidate, in the management of elderly depressed patients, either alone (44) or in combination with antidepressants such as citalopram (45). In a preliminary trial in 10 elderly patients a combination of methylphenidate and citalopram was well tolerated.

Clonidine

There has been a scare regarding the use of clonidine in combination with methylphenidate, based on frequently cited cases of four children who died, presumably while taking clonidine together with methylphenidate (46,47). It has been argued that "... cases of fatality in people receiving the combination have a paucity of supporting evidence, with prominent mitigating and extenuating circumstances nullifying any scientific attempts at association. Given that no association can be drawn, there are insufficient data to support any 'causal mechanisms'." Further discussion of the dangers beyond solid evidence does little to ease the task of thoughtfully using medications in the treatment of children and adolescents with psychopathology (48).

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Ethanol

A novel metabolite of methylphenidate, ethylphenidate, has recently been detected in human blood and liver samples obtained from two suicide victims who had taken a large dose of methylphenidate and ethanol (49). The concentrations of ethylphenidate were small relative to those of methylphenidate and ritalinic acid. Nevertheless, given the frequent occurrence of methylphenidate and ethanol co-ingestion, the detection of ethylphenidate warrants further studies on the extent of its formation, as well as any associated toxicity associated with normal doses. A transesterification reaction, analogous to that known to produce cocaethylene after cocaine and ethanol co-ingestion (50), has been described with methylphenidate (51).

Levodopa

Methylphenidate increased some of the motor effects of levodopa in selected patients with Parkinson's disease (52). Changes in self-assessed analogue ratings of mood, anxiety, arousal, or concentration did not differ.

Oral anticoagulants

Methylphenidate slows the rate of clearance of ethylbiscoumacetate and can therefore enhance its anticoagulant action (53).

Phenobarbital

Methylphenidate increases serum concentrations of phenobarbital (54).

Phenytoin

Methylphenidate increases serum concentrations of phenytoin (SED-14, 176).

Tricyclic antidepressants

Hypertensive episodes occurred in three adults who combined methylphenidate with tricyclic antidepressants (SED-9, 11). Methylphenidate increases serum concentrations of imipramine (55).

Valproic acid

Two cases of dyskinesia and bruxism in children have been attributed to an interaction of methylphenidate with valproic acid. These adverse effects were severe, occurred a few hours after the ingestion of methylphenidate 5 mg, and lasted for 4 and 7 hours (56).

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Methylphenobarbital

See also Antiepileptic drugs

General Information

The adverse effects of methylphenobarbital are similar to those of phenobarbital, to which methylphenobarbital is metabolized.

Organs and Systems

Immunologic

Giant cell myocarditis has been reported in a patient taking phenytoin, phenobarbital, and methylphenobarbital, and in one taking primidone (1).

Second-Generation Effects

Teratogenicity

There is an association of methylphenobarbital with oral clefts and cardiac malformations (2).

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Methyl-tert-butylether and monoctanoin

General Information

Methyl-tert-butylether and monoctanoin are solvents that are used for the rapid dissolution of cholesterol gallstones in patients who are not considered suitable for surgery. They are given by direct infusion into the gallbladder (1). However, they are suitable only for cholesterol stones, take too long to act, are often not successful, and have high rates of adverse effects (2).

The results of contact dissolution of gallstones using infusions of methyl-tert-butylether by percutaneous transhepatic gallbladder puncture have been assessed in 803 patients (3). Stones were dissolved in 724 of 761 patients in whom gallbladder puncture was successful. The 30-day mortality was 0.4%. Common complications were biliary leak, fever, leukocytosis, abdominal pain, and mild increases in transaminases. Toxic effects due to ether were not reported.

Fever, abdominal pain, nausea, vomiting, and diarrhea all occur frequently with methyl-tert-butylether and monoctanoin. Activities of serum amylase or liver enzymes can be slightly raised.

In 343 patients treated with monoctanoin there were adverse effects in 67% (4). Abdominal pain was the commonest (in 40%), followed by nausea (25%), vomiting (15%), diarrhea (16%), and fever (5%). One patient with hepatic cirrhosis developed an acidosis and encephalopathy. The adverse effects were usually dose-related and responded to reduction in infusion rate. The effects were life threatening in 12 patients (5%), but there were no permanent sequelae and no deaths.

Of 42 patients, 19 of whom received methyl tert-butylether alone and 23 with bile acid-ethylenediaminetetraacetate, there were mild complications in 40: vomiting in 12, pain at the start of treatment in 32, raised liver enzymes in six, and fever and leukocytosis in five (5). In those given methyl tert-butylether alone, there were two serious complications (gallbladder wall necrosis with

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perforation in one and catheter dislocation in the other). In those given combination therapy there were five serious complications: pericystic extravasation in two and catheter dislocation, sterile perihepatic abscess, and perihepatic biloma in one each. A CT scan with intravenous contrast after treatment was performed in 27 patients and showed gallbladder mural hyperemia and edematous swelling of the pericystic tissue layer in 26 cases.

Organs and Systems

Respiratory

Non-cardiogenic pulmonary edema has been reported with monoctanoin after appropriate intra-biliary use (6). If monoctanoin is injected intravenously in error, fatal respiratory and cardiac arrest can occur (7).

Biliary tract

Cholecystitis can be induced, at least when methyl-tert-butylether is used alongside ethylenediaminetetraacetic acid (SEDA-16, 428). Most such effects are probably attributable to over-rapid infusion.

Necrotizing choledochomalacia has also been described with monoctanoin (8). Gallstone impaction has been described.

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Methylthioninium chloride

General Information

Methylthioninium chloride (methylene blue) has been used for a variety of purposes, including marking of polyps, identification of sinus and fistula tracts, localizing islet cell tumors (1), marking of skin incisions in plastic surgery (2), labelling of vascular malformations, and the treatment of methemoglobinemia. Transient burning and blue discoloration can occur (3).

Organs and Systems

Hematologic

Severe hemolytic reactions have been attributed to methylthioninium chloride (4).

Immunologic

Methylthioninium chloride marking of a colonic polyp resulted in an inflammatory mass with small arteries showing both segmental and circumferential fibrinoid necrosis with thrombosis (5).

- A 68-year-old Hispanic woman had multiple polyps associated with recurrent episodes of hematochezia over several years. All but a single polyp were removed endoscopically. The region of the remaining polyp was labelled with 2 ml of methylthioninium chloride injected in divided doses to aid operative localization. Because surgery was postponed, methylthioninium chloride was again injected. At surgery the polyp and a 5 cm perirectal indurated mass were identified, and there was a blue track from the submucosal to the outer portions of muscularis propria into the adjacent fat. Microscopically, the mucosa was intact and the submucosa was edematous. There were acute inflammatory cells in the submucosa and muscularis propria. Inflammation (acute and chronic), fibroblastic proliferation, and fat necrosis were seen in areas outside the muscularis propria and extending to the connective tissue margin. A prominent finding was fibrinoid necrosis of small arteries, in some cases segmental and in others circumferential. The internal elastic lamina was destroyed and there were thromboses and vessel wall inflammation. There was no evidence of infiltrating carcinoma in the adenomatous polyp or the adjacent colon. The inflammation and vascular changes were only in the mass defined grossly by induration; sections away from this area were unremarkable. The blue track contained blue–black pigment within macrophages.

The mechanisms of the tissue damage and vascular changes in this case were unclear.

Anaphylactic shock has been attributed to methylthioninium chloride (SEDA-22, 526).

Second-Generation Effects

Pregnancy

Significant neonatal morbidity can occur after transabdominal infusion of methylthioninium chloride to diagnose premature rupture of fetal membranes, to stain the amniotic fluid in twin pregnancies, or after postpartum administration of methylthioninium chloride. Toxic manifestations include hyperbilirubinemia, Heinz body hemolytic anemia, and possible desquamation of the skin. In most cases it appears that toxicity was the result of an overdose of methylthioninium chloride (6–9).

Fetotoxicity

Multiple ileal occlusions have been reported in babies born to mothers who had twin pregnancies and who had received methylthioninium chloride administered during amniocentesis (10–12). In a number of cases it was found that methylthioninium chloride had been injected into the amniotic sac of the affected twins.

Methylthioninium chloride phototoxicity may also be related to the high prenatal dose of the dye relative to patient's small size and young gestational age (13).

The fetal death rate appears to increase after the use of methylthioninium chloride during pregnancy. In a retrospective cohort study of all women who had an amniocentesis during twin pregnancy from 1980 to 1991 in New South Wales in Australia, women who were exposed to methylthioninium chloride dye during the procedure were compared with women who had amniocentesis without dye exposure (14). Fetal death occurred in 32% of pregnancies that had exposure to a high concentration of methylthioninium chloride, compared with 15% of pregnancies exposed to a low concentration and 4.3% of pregnancies with no exposure to dye. It was concluded that methylthioninium chloride dye use during mid-trimester amniocentesis in twin pregnancy increases the risk of fetal death.

Drug Administration

Drug administration route

Methylthioninium chloride is sometimes given intrathecally to track the source of a cerebrospinal fluid leak. This procedure involves considerable risk of spinal cord damage, with its attendant neurological consequences (15–17).

- A 59-year-old man had 6 ml of unbuffered methylthioninium chloride injected into the lumbar theca in an attempt to localize the source of cerebrospinal fluid rhinorrhea (18). After injection of the dye he became shocked, and within the next few days developed a mild paraparesis, which subsequently progressed to total paraplegia.

Drug overdose

Overdosage of methylthioninium chloride given intravenously, which has happened inadvertently during urinary tract surgery, can cause shock and pseudocyanosis. The latter is due to the blue tinge of methylthioninium chloride, and it can create confusion as to the patient's circulatory status. Patients receiving methylthioninium chloride should be examined for unstable hemoglobins or an abnormal hexose monophosphate pathway if the risk of methemoglobinemia is to be minimized; this has been described with a normal dose (19).

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Methysergide

General Information

Methysergide is a semisynthetic ergot derivative that is structurally similar to ergometrine. However, its spectrum of activity differs substantially. It is a potent 5-HT receptor antagonist and has been used prophylactically in migraine and to control the symptoms of the carcinoid syndrome. However, it has been replaced by other more effective and safer drugs and should now be regarded as obsolete, given its tendency to cause retroperitoneal fibrosis (1). For any patients who still take it, a program of 3-monthly monitoring, including clinical examination, plasma electrolytes, full blood count, and erythrocyte sedimentation rate, has been recommended. The authors suggested that methysergide should be withdrawn if any abnormalities emerge, and also concurred with the widespread practice of "drug holidays" for 3–6 months, although these are not of proven value. Despite the title of their paper, they did not describe the management of established retroperitoneal fibrosis, and indeed there is no treatment of proven value.

Although a third of patients have some adverse effects, only about 10–15% have to stop treatment acutely for this reason. Mild gastrointestinal upsets, abdominal cramping and a tendency to dizziness, light-headedness, and nervousness are the most frequent complaints. Less frequent but more serious symptoms include those attributable to fibrosis. Its vasoconstrictor and oxytocic effects are generally slight.

Organs and Systems

Cardiovascular

Methysergide can cause tachycardia, postural hypotension, and angina pectoris.

Aortic and mitral valvular fibrosis can lead to congestive cardiac failure; fibrosis rarely affects the endocardium more extensively (extending into the myocardium) or the pericardium (resulting in constrictive pericarditis). Vasospastic effects can occasionally be as severe in susceptible subjects as with ergotamine; especially dangerous are combinations with ergotamine tartrate, as are combinations of ergot alkaloids with beta-blockers (SEDA-9, 128).

Nervous system

Methysergide can cause restlessness, insomnia, drowsiness, and mild psychic changes (2).

Psychological, psychiatric

An LSD-like reaction has been observed with as little as 2 mg (3). There is a risk of dependence and the drug is better avoided in patients with a history of mental disorders.

Hematologic

Hemolytic anemia, neutropenia, and eosinophilia have all been described (4).

Postpartum hemolytic–uremic syndrome has been reported (SEDA-12, 124).

Skin

Various skin disorders have been described in patients taking methysergide (2). In one case, hair loss occurred (5).

Serosae

Serious fibrotic changes occur in about 1% of patients who take methysergide continuously for 1 year or more, and provide the main reason for reducing doses and withdrawing the drug at intervals. Most commonly the fibrosis is retroperitoneal and starts in the pelvis or the lumbar region, where it can constrict the ureters, arteries, veins, and lymph vessels. Both infarction and obstruction of the bowel have occasionally been described. Fibrotic syndromes elsewhere can involve the heart, pleura, chest wall, and lungs.

Drug–Drug Interactions

Sumatriptan

The combination of methysergide with sumatriptan has been associated with vasospasm in the coronary arteries (6).

- A 43-year-old woman with controlled hypertension, but no other known coronary risk factors, had an acute myocardial infarction. She took two oral doses of methysergide 2 mg 12 hours apart, followed by sumatriptan 6 mg subcutaneously. About 10 minutes after the sumatriptan, she complained of chest pain, and on arrival in hospital, an anterior myocardial infarction was diagnosed. Subsequent angiography showed a solitary stenosis in the left anterior descending coronary artery, and it was therefore presumed that she had suffered vasospasm associated with this stenosis. She made an excellent recovery after stenting.

The danger of combining two cerebral and coronary vasoconstrictors needs no emphasis.

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Metirosine

General Information

Metirosine (alpha-methyl-para-tyrosine) inhibits the formation of dopamine (1) and is sometimes used to prepare patients with pheochromocytoma for surgery (2), although not always successfully (3).

Organs and Systems

Nervous system

In one study, metirosine 5.25 g caused reduced happiness, euphoria, energy, talkativeness, vigor, and attentiveness, and increased sleepiness, fatigue, sedation, and eye blink rate (4).

Psychological, psychiatric

In 14 drug-free subjects with a history of depression metirosine 5 g caused marked, transient increases in core depressive and anxiety symptoms (5).

When tested in 21 healthy subjects, metirosine produced panic attacks on several occasions in three of them (6).

Urinary tract

Metirosine can cause crystalluria unless there is a high fluid intake (7).

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Metoclopramide

General Information

Metoclopramide is a dopamine receptor antagonist used in the treatment and prevention of nausea and vomiting. It also has effects on HT_3 receptors in the gut, but at concentrations higher than are generally achieved during routine therapy.

Although metoclopramide has lost some ground to newer congeners, it has been the most widely used of the neuroleptic-type antiemetic drugs and is therefore the one for which the clearest picture of adverse effect, typically neuroleptic and endocrine effects, has emerged. Reactions are generally short-lived provided treatment is withdrawn; the duration of reactions does not always seem to be explained by simple pharmacokinetic considerations.

Organs and Systems

Cardiovascular

Complete heart block (SEDA-12, 939) (1) and supraventricular tachycardia (2), presumably due to a vagolytic effect, have been described with metoclopramide. If there are predisposing conditions, heart failure can be precipitated (SEDA-16, 418). In one study in which 56 patients were treated with metoclopramide, a single case of second-degree atrioventricular heart block was observed (SEDA-20, 316).

- Complete heart block has been reported in a 65-year-old woman with type 2 diabetes, hypertension, and ischemic heart disease, who was given intravenous metoclopramide 20 mg (3).

A hypertensive crisis has been precipitated by metoclopramide in patients with pheochromocytoma (4).

Respiratory

Two cases of acute bronchospasm have been reported after the intravenous administration of metoclopramide, one in a patient with pre-existing asthma (SEDA-16, 419).

Nervous system

Dyskinesias of various types are classic effects of metoclopramide in adults. Tardive dyskinesia and myoclonus have been described (SEDA-9, 312) (SEDA-17, 414). Dyskinesias tend to occur after some months of use. As with the classic neuroleptic drugs, neuroleptic malignant syndrome can occur (5).

Adverse reactions to metoclopramide in 52 children aged 2.5–4.5 years who were admitted to hospital over 6 years have been studied retrospectively (6). All had various dystonic symptoms that occurred several hours after

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taking the drug. The prominent clinical effect was an oculogyric crisis in all cases, while children who took higher doses also became drowsy. All extrapyramidal symptoms were treated successfully with a single intravenous dose of procyclidine hydrochloride 0.1 mg/kg.

Severe parkinsonism has been reported in a 73-year-old woman with tuberculosis of the large intestine who had taken metoclopramide for nausea; she recovered on withdrawal of the drug and treatment with biperiden (7).

The "blue tongue" sign, in which the tongue is blue and swollen and obstructs the upper airway, is an unusual but dangerous manifestation of the same group of adverse effects (SED-12, 940) (8).

Acute dystonia has been reported in three men with AIDS who had received metoclopramide; they recovered on withdrawal and treatment with biperiden or diazepam (9). Dystonic reactions seem to be particularly problematic in the very young and the very old, but the frequency is disputed (10). In one overview acute movement disorders were thought to have occurred in about one in 80 young adults (SEDA-17, 414). When metoclopramide is given by intravenous injection, for example as an aid to gastric emptying imaging, akathisia seems to occur mainly in women or young men, and more often if the injection is more rapid.

The fact that the neurological reactions can be difficult or impossible to distinguish from spontaneous parkinsonism perhaps explains reports of apparently irreversible effects; almost certainly in such cases the disorders were not exclusively due to the drug.

A lengthy withdrawal reaction has also been described after 6 months of treatment, characterized by an alternation of an akinetic state and akathisia reminiscent of the restlessness seen in parkinsonism (11); even after a year of symptomatic treatment the effects had not fully subsided.

Psychological, psychiatric

Supersensitivity psychosis has been reported in two men, aged 74 and 65 years, who had taken metoclopramide 5 mg qds for 6 and 3 months respectively (12). Hallucinations and delusions developed 12 hours after the drug was withdrawn in one patient and 3 days after withdrawal in the other. Both recovered after treatment with risperidone.

Endocrine

Hyperprolactinemia and galactorrhea, sometimes with gynecomastia, are classic complications of metoclopramide that can equally well occur in adults, children, or neonates (13) (SEDA-22, 390).

Vasopressin release has been claimed to be enhanced by metoclopramide, while aldosterone release is impaired (SED-12, 940).

Hematologic

Effects of metoclopramide on the blood are very uncommon, but neutropenia has been reported in circumstances suggesting that a causal link is likely (SEDA-13, 329).

Methemoglobinemia has been reported following gross accidental overdosage of metoclopramide in an infant (SEDA-15, 392).

Liver

Complex liver disorders very occasionally occur with metoclopramide, with cholestasis and opening of arteriovenous shunts in the liver (SEDA-16, 419). In two cases a condition resembling Reye's syndrome has been seen (14).

Susceptibility Factors

Hepatic disease

If there is impaired liver function, metoclopramide can accumulate. In eight patients with severe alcoholic cirrhosis there was a 50% lower clearance than in eight healthy volunteers; the apparent volume of distribution and absolute systemic availability were similar in the two groups (15).

Other features of the patient

Metoclopramide is contraindicated when stimulation of gastrointestinal motility could be dangerous, for example when there is hemorrhage, obstruction, or a risk of perforation.

Patients with pre-existing dyskinesias should not be given metoclopramide, and both the very young and the very old have a greater risk of adverse reactions, as do patients with cardiac disorders or asthma.

Drug Administration

Drug formulations

In a four-way crossover study in 16 healthy men a modified-release formulation of metoclopramide (30 mg) administered fasting and after a high-fat meal, an immediate-release formulation (30 mg) and a short intravenous infusion of 30 mg have been compared (16). The absolute systemic availability of the modified-release formulation was about 17% lower than that of the immediate-release formulation. Food had no significant effect on absorption. Uniform absorption of the drug from modified-release formulations supports their use in long-term treatment.

Seven patients from Peru developed extrapyramidal symptoms when supposedly taking lincomycin: in fact each capsule contained no less than 500 mg of metoclopramide (17).

Drug–Drug Interactions

Alcohol

Intravenous metoclopramide 20 mg accelerated gastric emptying and increased the rate of absorption of alcohol in seven subjects (18). In another similar study the sedative effects of alcohol were enhanced (19).

Ciclosporin

It has been suggested that metoclopramide increases the systemic availability of ciclosporin (SED-11, 783) (20).

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Cisplatin

Metoclopramide reduces renal plasma flow, suggesting that concurrent use could increase the nephrotoxicity of cisplatin (21), an important observation in view of the specific usefulness of metoclopramide to treat cytotoxic drug-induced emesis.

Digoxin

When digoxin is given in a slowly dissolving form, the plasma concentrations achieved are reduced by about one-third if metoclopramide is given at the same time (22); liquid or readily dissolvable solid forms of digoxin are unlikely to be affected.

Paracetamol

In five health subjects intravenous metoclopramide increased the rate of absorption of a single dose of paracetamol 1.5 g (23).

Quinidine

Metoclopramide increases the serum concentrations of quinidine by up to 20% (24).

Theophylline

Metoclopramide reduces serum concentrations of theophylline (25).

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Metocurine

See also Neuromuscular blocking drugs

General Information

Metocurine is a non-depolarizing neuromuscular blocker, a synthetic derivative of D-tubocurarine. No metabolites have been detected and it depends almost entirely on renal function for its excretion; 40–50% of the drug is

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excreted in the urine and about 2% (possibly more) in the bile in 24 hours (1). It is about twice as potent as D-tubocurarine and a quarter as potent as pancuronium, measured during narcotic/nitrous oxide anesthesia. It has similar onset and duration of action and speed of recovery to D-tubocurarine and pancuronium (2).

The dose of metocurine for intubation is 0.3 mg/kg and adequate abdominal relaxation is achieved with 0.1–0.2 mg/kg in most patients. As with all neuromuscular blocking agents, there is great individual variation in response, and if it is desired to give minimal doses, monitoring of the neuromuscular response is advisable. Volatile anesthetics and prior suxamethonium would be expected to reduce dosage requirements, but clinical reports are lacking. Patients with burns require 2–3 times higher doses of metocurine (3) and this phenomenon can persist (in lessening degree) for 1 year or more (4).

Organs and Systems

Cardiovascular

Metocurine has significantly less ganglion-blocking activity than D-tubocurarine (5) and much less of a tendency to provoke histamine release (6,7). It does not block cardiac muscarinic receptors at neuromuscular blocking doses (8). Cardiovascular stability is therefore to be expected (9). Slight tachycardia and fall in blood pressure have been reported in one-third of patients given larger doses (0.4 mg/kg) rapidly, probably as a result of histamine release, but no bronchospasm was seen (2).

Susceptibility Factors

Renal disease

Greatly prolonged duration of paralysis and a reduced rate of return of neuromuscular function can occur in renal insufficiency, because of a reduced plasma clearance and a prolonged half-life (10). Metocurine is not the relaxant of choice when renal function is poor.

Drug–Drug Interactions

Phenytoin

Resistance to metocurine is also described in patients taking long-term phenytoin (SEDA-10, 110) (11).

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Metolazone

See also Diuretics

General Information

Metolazone occupies an intermediate position between the thiazide diuretics and the more potent loop diuretics (1). It is more effective than the thiazides in moderate to advanced renal insufficiency (SED-8, 488) (SED-9, 355). In patients with normal renal function its antihypertensive effect compares favorably with that of bendroflumethiazide. When severe heart failure is refractory to conventional triple therapy (high-dose loop diuretic, digoxin, and angiotensin-converting enzyme inhibitor) metolazone can restore diuresis, with weight loss and clinical improvement.

Organs and Systems

Electrolyte balance

Metolazone causes a greater degree of potassium depletion than thiazides (SED-11, 424). In order to avoid serious electrolyte disturbances when metolazone is introduced in patients taking loop diuretics, the metolazone should be given in low doses to start with in hospital, and at the same time the dosage of the loop diuretic should be reduced under careful biochemical monitoring (SEDA-16, 225).

Long-Term Effects

Drug abuse

Neutropenia is a rare complication of metolazone (2).

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Metoprolol

See also Beta-adrenoceptor antagonists

General Information

Metoprolol is a cardioselective beta-adrenoceptor antagonist with some membrane-stabilizing activity. It is metabolized by polymorphic hydroxylation (1).

Organs and Systems

Liver

Metoprolol was associated with hepatitis in a patient who was a poor metabolizer (2).

Musculoskeletal

A metoprolol-induced polymyalgia-like syndrome (3) has been described.

Susceptibility Factors

Genetic factors

The metabolism of metoprolol varies six-fold higher between poor metabolizers of debrisoquine and extensive metabolizers (1).

Drug Administration

Drug formulations

A modified-release formulation of metoprolol has been associated with more skin reactions, probably due to the succinate component, instead of the tartrate component used in the old fast-acting formulation (SEDA-16, 195).

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Metrifonate

General Information

Metrifonate, which is given orally, is effective in *Schistosoma hematobium* infections in three doses of 7.5–10 mg/kg 14 days apart. When metrifonate was used in daily doses, as in the treatment of *Onchocerca volvulus* infections, it produced muscarinic effects, and in one case there was proximal weakness due to a nicotinic effect. The combination of polyarthritis, fever, and a raised sedimentation rate was described in 11 of 34 patients treated. Metrifonate inhibits blood cholinesterase activity for up to 48 hours, and common reactions that probably result from this effect comprise nausea, vomiting, abdominal pain, diarrhea, dizziness, weakness, headache, and muscle cramps. Because of its prolonged inhibition of brain cholinesterase and increased steady-state concentrations of acetylcholine in the cortex and the hippocampus, it is now also increasingly used in the treatment of Alzheimer's disease.

Metrifonate has been used for the treatment of schistosomiasis for almost 40 years. Its identification as a cholinesterase inhibitor, together with recognition of the cholinergic deficit in Alzheimer's disease, has led to its use in Alzheimer's disease.

The pharmacology and pharmacokinetics of metrifonate and experience with its use in Alzheimer's disease have been reviewed (1).

Two reviews (2,3) of the use of metrifonate in Alzheimer's disease have been published. Both reported a positive effect of metrifonate, with generally mild and usually transient adverse effects, consisting of gastrointestinal symptoms (such as abdominal pain, diarrhea, flatulence, and nausea, probably reflecting cholinergic overactivation) and leg cramps, possibly caused by the overstimulation of nicotinic receptors at the neuromuscular junction. No laboratory abnormalities were reported.

In a randomized, double-blind, placebo-controlled trial in 408 patients with Alzheimer's disease, metrifonate (20 mg/kg/day for 2 weeks followed by 0.65 mg/kg/day for 24 weeks) significantly improved several mental performance scales (4). Of the 273 patients treated with metrifonate 12% discontinued treatment because of adverse effects, compared with 4% of the 134 patients treated with placebo. The adverse effects that led to withdrawal were mainly gastrointestinal in nature. Diarrhea occurred in 18% of the patients treated with metrifonate (leading to withdrawal in 3%) and in 8% of the patients treated with placebo; 2% of the patients treated with metrifonate discontinued treatment because of nausea and vomiting and 1% because of dyspepsia. Nausea occurred in 12% of the patients treated with metrifonate and in 10% of the patients treated with placebo. Vomiting occurred in 7% and 4% respectively.

In a second randomized, double-blind, placebo-controlled trial (5) 480 patients were randomized to receive placebo ($n = 120$), a low dose of metrifonate (0.5 mg/kg/day for 2 weeks followed by 0.2 mg/kg/day for 10 weeks) ($n = 121$), a moderate dose of metrifonate (0.9 mg/kg/day for 2 weeks followed by 0.3 mg/kg/day for

10 weeks) ($n = 121$), or a high dose (2.0 mg/kg/day for 2 weeks followed by 0.65 mg/kg/day for 10 weeks) ($n = 118$). These doses were selected to achieve steady-state erythrocyte acetylcholinesterase inhibition of 30%, 50%, and 70% respectively. There was a significant dose-related improvement in several mental performance scales with metrifonate. Most of the adverse events were mild and transient. Adverse events that occurred more often in the patients treated with metrifonate were abdominal pain (placebo 4%, low dose 3%, moderate dose 11%, high dose 12%), diarrhea (8%, 9%, 11%, 19%, respectively), flatulence (9%, 2%, 8%, 16%), and leg cramps (1%, 1%, 3%, 8%). Bradycardia, presumably related to the vagotonic effect of acetylcholinesterase inhibition, led to withdrawal of treatment in three patients with asymptomatic bradycardia. All three were in the loading-dose phase of the highest metrifonate dosage regimen.

In 16 patients with Alzheimer's disease, adverse effects were dose-related (6). In eight patients who took 2.5 mg/kg/day for 14 days, 4 mg/kg/day for 3 days, and then 2.0 mg/kg/day for 14 days (acetylcholinesterase inhibition 88–94%) treatment had to be withdrawn because of moderate to severe adverse effects in 6 patients on day 28 of the planned 31. In eight patients treated with 2.5 mg/kg/day for 14 days followed by 1.5 mg/kg/day for 35 days (acetylcholinesterase inhibition 89–91%), the frequency of more severe adverse effects was considerably lower despite similar acetylcholinesterase inhibition. The most frequent adverse events in the high-dose group were muscle cramps and abdominal discomfort during the loading-dose phase, followed by increasing gastrointestinal symptoms in the second loading phase, accompanied by headache and muscle aches. The adverse events profile initially improved during the maintenance phase. However, after 11 days of maintenance treatment, six patients complained of generalized moderate to severe muscle cramps, weakness, inability to resume daily activities, and difficulties with coordinations. The adverse events profile was much more favorable with the lower dose, with the same, but much less severe, range of adverse effects. Again, the most frequent adverse effects were gastrointestinal disturbances, muscle cramps, and light-headedness. One patient had increased sweating, dizziness, and palpitation on day 29 and another developed severe abdominal tenderness on day 31, which led to termination of treatment. There were no abnormalities in laboratory parameters. The authors proposed a maximum tolerated dose of 1.5 mg/kg/day of metrifonate for maintenance therapy in patients with Alzheimer's disease.

The Metrifonate Alzheimer's Trial (MALT) was designed to evaluate a wide range of symptoms and efficacy measures in four main clinical domains of Alzheimer's disease: cognition, psychiatric and behavioral features, activities of daily living, and global functioning (7). These are considered key targets for antidementia drugs. This prospective, multicenter, randomized, double-blind, parallel group study was conducted at 71 independent study centers, and 605 patients were randomized to placebo ($n = 208$), metrifonate 40 or 50 mg/day ($n = 200$), and metrifonate 60 or 80 mg/day ($n = 197$); within each treatment group the dose was determined according to body weight, and treatment lasted for 24 weeks. Metrifonate improved a wide range of symptoms across all four clinical domains of Alzheimer's disease in a dose-dependent manner, and was well tolerated at both doses. One patient withdrew from the study during the high-dose loading phase owing to cholinergic effects, resulting in muscle weakness. Metrifonate was also associated with a slight gradual lowering of hemoglobin, hematocrit, and erythrocyte count in both groups during the first 12 weeks; these were nonprogressive, stabilized over the 6-month treatment period, and hence were not considered to be clinically relevant. Metrifonate was associated with a higher incidence of bradycardia (under 50/minute); serious adverse events possibly related to bradycardia (hypotension, postural hypotension, syncope, dizziness, malaise, and accidental injury) occurred in three patients taking placebo, eight taking low-dose metrifonate (three of whom were withdrawn from the study), and two taking high-dose metrifonate.

In patients with mild to moderate Alzheimer's disease metrifonate significantly improved behavior as well as cognition, function in activities of daily living, and global functional status, as shown by a pooled analysis of four prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled trials, meeting FDA guidelines (8).

The safety and tolerability of once-daily oral metrifonate has been evaluated in patients with probable mild to moderate Alzheimer's disease in a randomized, double-blind, placebo-controlled, parallel-group study (9). Metrifonate was given to 29 patients as a loading dose (2.5 mg/kg) for 2 weeks, followed by maintenance dose (1 mg/kg) for 4 weeks; 10 patients received placebo. The proportion of patients who had at least one adverse event was comparable in the two groups: metrifonate 76%, placebo 80%. Selected adverse events, defined as those for which the incidence in the metrifonate and placebo group differed by at least 10%, were diarrhea, nausea, leg cramps, and accidental injury. The adverse events were predominantly mild and transient. Those who took metrifonate had a significantly lower heart rate. Metrifonate had no clinically important effect on laboratory tests, such as liver function tests, and did not affect exercise tolerance or pulmonary function.

Organs and Systems

Nervous system

Patients with Alzheimer's disease taking long-term treatment with metrifonate suffered seizures after abrupt withdrawal of antimuscarinic agents (10).

- A 58-year-old woman was given hyoscyamine for abdominal cramps by her local physician without the knowledge of her neurologists. She had a generalized seizure 36 hours after stopping the drug.
- A 66-year-old woman was treated for a skin allergy with doxepin cream in large doses. Withdrawal of this treatment led to two complex partial seizures.

The authors speculated that the antimuscarinic drugs impaired the cholinergic receptor down-regulation that would normally occur in the presence of the increased concentrations of acetylcholine caused by

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acetylcholinesterase inhibition. Withdrawal of the antagonist therefore abruptly exposed the receptors to high concentrations of the neurotransmitter, leading to seizures.

Second-Generation Effects

Teratogenicity

The birth of a hydrocephalic infant with a large meningomyelocele to a mother who had been treated with metrifonate for an infection with *Schistosoma hematobium* during the second month of pregnancy has been reported, but the report is not recent and the association was probably coincidental (SED-11, 598).

Drug Administration

Drug dosage regimens

The effects of a loading dose on the adverse events of metrifonate 50 mg/day have been studied in Alzheimer's disease. The regimen without a loading dose was better tolerated during the 4-week study period (11).

Drug–Drug Interactions

Organophosphorus insecticides

Theoretically, suxamethonium will be potentiated after administration of metrifonate and, in view of its ability to suppress enzyme activity, metrifonate should be used with great caution in areas where organophosphorus insecticides are used, since they have a similar effect.

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Metronidazole

General Information

Metronidazole is a benzimidazole derivative.

Uses

Metronidazole is effective in the treatment of many protozoal diseases, notably trichomoniasis, amebiasis, schistosomiasis, strongyloidiasis, and giardiasis, and has been in use for over 20 years.

For amebiasis there is still discussion about the use of a single high dose versus repeated lower doses, both as regards efficacy and adverse effects.

The use of metronidazole against infections with anerobic bacteria has increased over the years, and with this indication the use of metronidazole in combination with many other drugs used by patients with conditions likely to develop secondary anaerobic bacterial infections. With increased use there is also a widespread and increasing incidence of resistance of various strains of bacteria. The use of metronidazole as an added medication merely "to make assurance double sure" is to be discouraged. It is to be especially discouraged in immunocompromised patients, because of the risk of emergence of resistant bacterial strains. With increased use there is also an increased number of reports of some more unusual adverse effects. Overall, metronidazole can still be considered safe, if used in generally recommended doses.

Metronidazole has been formulated as a vaginal gel (0.75%) for the treatment of bacterial vaginosis. A single daily 5-day regimen has been approved by the FDA and has been shown to be as effective as oral metronidazole (1).

In the eradication of *Helicobacter pylori,* metronidazole plus bismuth is effective, but causes more adverse effects than omeprazole plus amoxicillin plus either clarithromycin or metronidazole.

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Pharmacokinetics

Metronidazole has excellent systemic availability, and absorption after oral administration is not significantly affected by food. Peak serum concentrations occur about 1 hour after ingestion. Multiple doses every 6–8 hours result in some drug accumulation, the half-life averaging about 8 hours. There is a linear relation between dose and serum concentration. Rectal administration results in serum concentrations about half those seen after oral administration. Systemic absorption after local use in the vagina is slow, maximum serum concentrations being reached only after 8–24 hours; they are only about 20% of those attained after oral administration. Metronidazole is extensively metabolized, and only about 20% of the dose is excreted unchanged in the urine. Tissue concentrations are similar to serum concentrations, and metronidazole penetrates readily into the central nervous system. As with many metabolized drugs, the half-life is markedly prolonged in neonates; there is an inverse relation between gestational age and half-life. Prolonged elimination times are also seen in the presence of serious liver disease (SEDA-13, 831) (SEDA-16, 310) (SEDA-17, 332) (SEDA-18, 294).

Preliminary case reports have suggested that azithromycin or metronidazole can improve ciclosporin-induced gingival hyperplasia (SEDA-19, 350).

General adverse effects

Metronidazole is generally well tolerated. With high doses and high-dose prolonged treatment, nausea, vomiting, and central nervous system symptoms ranging from headache and dizziness to neuritis can occur. The commonest reactions are nausea, a metallic taste in the mouth, furry tongue, and vulvovaginal irritation in patients who take metronidazole for bacterial vaginosis (SEDA-13, 831) (SEDA-18, 295). Reports of pancreatitis, neuropathy, and optic neuritis call for caution. Hypersensitivity reactions are unusual, but rashes have been described.

Organs and Systems

Cardiovascular

Thrombophlebitis can occur after intravenous administration of metronidazole; an incidence of 6% has been cited (SEDA-7, 297) (2).

Respiratory

Pneumonitis has been attributed to metronidazole, with recurrence after rechallenge (SEDA-14, 242).

Nervous system

Central nervous system symptoms can occur with standard doses of metronidazole, but they are mainly seen with high doses and especially when such doses are given for a long time. Under the latter conditions, there was a 25% incidence of such symptoms as headaches, dizziness, tremor, ataxia, and confusion.

A polyneuropathy is a well-recognized adverse effect of metronidazole (3). A 6% incidence of neuropathy has been quoted; polyneuropathy, mainly sensory in nature, has been recorded during the treatment of Crohn's disease, but again in connection with the prolonged use of high doses (SEDA-12, 705) (4,5). This complication is not restricted to patients with Crohn's disease; it is also seen when metronidazole is given for other purposes, such as radiosensitization. Electrophysiological studies have suggested distal sensory axonal degeneration, with loss of sensory nerve potential over the distal segment and normal motor nerve conduction. In some cases the severity of clinical and electrophysiological abnormalities is closely related to the total amount of metronidazole administered (SEDA-14, 242). Metronidazole is structurally similar to thiamine, and thiamine-synthesizing gut flora may synthesize a neurotoxic analogue of thiamine from ingested metronidazole. However, this hypothesis is weakened by the fact that nitroheterocyclic drugs other than metronidazole are also neurotoxic, despite a much weaker structural analogy to thiamine (SEDA-12, 706) (6).

Peripheral neuropathy was associated in one case with intermittent use of metronidazole (2 g/day for 5 days every other month) (7).

- A 65-year-old white woman with small intestine bacterial overgrowth developed persistent numbness and tingling of her upper and lower extremities. She had been taking alternating courses of tetracycline and metronidazole for 5 days every other month for about 1 year. Other medications included amitriptyline, lisinopril, digoxin, omeprazole, and tamoxifen. Serum vitamin B_{12} and folate concentrations were within the reference ranges. She had reduced sensation in a stocking-glove distribution, reduced sensation to touch and pin-prick, intact reflexes, and no weakness. Neuropathy was attributed to metronidazole, which was withdrawn. After 4 months she reported improvement. On follow-up at 5 months, there was no evidence of peripheral neuropathy.

Metronidazole-associated sensory neuropathy usually presents with pain and reduced thermal and pin-prick sensation, but normal strength, proprioception, and tendon reflexes. Four patients with metronidazole-associated sensory symptoms had detailed electrodiagnostic studies and nerve or muscle biopsies (8). All had taken different doses of metronidazole and one (with a mitochondrial myopathy) had only used the drug topically. After withdrawal, sensory complaints persisted without progression in two patients and resolved in one. In the fourth, a lower dosage led to partial resolution. Nerve conduction studies were normal in all four cases, but quantitative sensory testing and quantitative sudomotor autonomic reflex testing showed abnormalities of small-fiber function. A sural nerve biopsy from one patient confirmed some loss of small myelinated axons. Metronidazole probably caused a small-fiber neuropathy in these four cases. The authors also reviewed nerve conduction studies in 30 reported cases of metronidazole-associated neuropathy; they were sometimes normal, suggesting that sensory symptoms related to metronidazole may be caused by a mixture of small-fiber and large-fiber sensory dysfunction.

Aseptic meningitis is a rare, possibly allergic adverse effect of metronidazole; the one published case was well documented, with positive rechallenge (9).

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There has been a report of visual loss and headache after metronidazole (10).

- A 68-year-old man with a tooth abscess had a tooth extraction and received amoxicillin. A few weeks later he developed toothache again and was given amoxicillin and metronidazole 400 mg tds; he took no other drugs. Six hours after the first dose he developed a headache. He continued with metronidazole for a total of three doses, and 6 hours after the last dose the headache resolved. Two days later he noticed flashing lights in both eyes. He then developed a central visual field defect and progressive visual loss. His blood pressure was 220/120 mmHg, but it settled spontaneously. Visual acuity was 6/12 in both eyes and fundoscopy showed marked disc swelling with hemorrhages, without other features of hypertensive retinopathy. Full blood count, plasma viscosity, routine biochemistry, vasculitis screen, anticardiolipin antibodies, angiotensin converting enzyme assay, chest X-ray, CT of the brain and orbits, MRI, and MRA were all normal. CSF examination showed an opening pressure of 24 cm of water and 13 white cells/μl. Over the next few months his visual symptoms slowly improved but he developed secondary optic atrophy.

In this case there was no other obvious cause for visual loss and it could have been caused by metronidazole. The exact mechanism was unclear, but it may have been related to raised intracranial pressure.

Convulsions occurred in an 87-year-old man who had taken metronidazole (11).

Encephalopathy associated with metronidazole has been reported in a patient with chronic renal insufficiency (12).

- A 58-year-old woman with end-stage renal insufficiency secondary to diabetic nephropathy developed abdominal wall cellulitis 4 days after insertion of a peritoneal dialysis catheter. She was given vancomycin, cefepime, and metronidazole in reduced doses (doses not stated) and 2 days later developed dysarthria, an intention tremor, dysmetria, and dysdiadochokinesia. "Routine" biochemical tests were unchanged and a CT scan of the brain was unremarkable, but an MRI scan showed cerebral and cerebellar atrophy with multifocal ischemic glial lesions. Metronidazole was withdrawn and 2 days later her symptoms and signs had completely resolved.

It is difficult to ascribe encephalopathy unequivocally to metronidazole in this case.

Sensory systems

Eyes

Acute myopia occurred after 11 days of treatment with metronidazole for *Trichomonas* infection; it resolved within 4 days after withdrawal but recurred on rechallenge. The combined figures of two major American reporting systems for adverse reactions listed seven cases of retrobulbar or optic neuritis associated with oral metronidazole; two had a concurrent peripheral neuropathy. However, there is insufficient information to evaluate these reports (SEDA-17, 333).

Ears

Two reports of moderate to severe sensorineural deafness after metronidazole therapy, which resolved slowly after therapy ended suggest that this is an additional adverse effect (13). Both cases of deafness were preceded by tinnitus, which may be a warning to withdraw the drug.

Hematologic

Metronidazole can produce leukopenia and neutropenia, usually only associated with prolonged therapy and reversible on withdrawal (SEDA-13, 832). One case each of agranulocytosis and of aplastic anemia have been reported (SEDA-11, 595) and a single case of hemolytic–uremic syndrome in six children (SEDA-15, 298).

Gastrointestinal

Anorexia, nausea, vomiting, abdominal pain, and diarrhea have all been reported in patients taking metronidazole (14). The use of a large single dose most commonly leads to these complaints. A metallic taste also seems to be quite common (14), as is the occurrence of a black tongue (SEDA-13, 832) (15).

Although metronidazole is often used to treat pseudomembranous colitis, it can also occasionally cause it (16,17).

Liver

Raised serum liver enzyme activities were reported in one case about 15 years ago (SEDA-11, 595) (18), but there has been no more recent confirmation.

Pancreas

Pancreatitis has been reported in various individual case histories (SEDA-15, 298), but there is reason to think that some of these cases at least were due to other factors, such as alcohol use (SEDA-13, 832).

- Pancreatitis has been described in a 63-year-old woman with Crohn's disease, coinciding with the administration of metronidazole and disappearing 1–2 days after withdrawal, but even here there was little support for a causal link (19–21).
- Pancreatitis was attributed to metronidazole in a 61-year-old woman given intravenous metronidazole 500 mg 6-hourly (22). The relation between pancreatitis and metronidazole in this case was less convincing than in previously reported cases, as there was no rechallenge.

Urinary tract

Darkening of the urine can occur in patients taking metronidazole (23); this is a harmless discoloration, mostly seen during prolonged treatment.

Skin

Pruritus and rashes have been reported in patients taking metronidazole, including a fixed drug eruption (24) and a pityriasis rosea-like eruption. Urticaria after a single dose has been reported but could have been coincidental (SEDA-17, 333).

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In a case of fixed drug eruption, a provocation test showed cross-reactivity with tinidazole but not with secnidazole (24).

Reproductive system

A genital mucosal erosion occurred in a 38-year-old woman who had taken metronidazole 400 mg tds for 10 days for bacterial vaginitis (SEDA-16, 310).

Long-Term Effects

Drug tolerance

Resistance of *H. pylori* to metronidazole was found in 30% of isolates in the Lebanon (25), 42% in Brazil (26), and 80–90% in Africa (27).

Mutagenicity

Mutagenicity of metronidazole has been demonstrated in some bacterial systems (SEDA-13, 832). Studies on breakages in single-stranded DNA in the lymphocytes of patients treated with metronidazole for *Trichomonas* vaginitis have suggested that such breakages were repaired after withdrawal. Another study reported chromosomal aberrations in the lymphocytes of ten volunteers taking metronidazole (SEDA-21, 301). A mutagenic effect would theoretically be possible in patients with a DNA repair defect (SEDA-16, 310).

There has been concern that metronidazole may be genotoxic, as there have been reports of mutagenicity in several bacterial species. The genotoxic effects of metronidazole (250 mg bd for 10 days) and nalidixic acid (400 mg bd for 10 days) have been assessed in women with *Trichomonas vaginalis* infections (28). The genotoxic potential of these drugs was evaluated using a sister chromatid exchange test in peripheral blood lymphocytes. Metronidazole had no effect but nalidixic acid caused an increase in sister chromatid exchange frequency. This result confirms that there is little evidence of genotoxicity with metronidazole.

Tumorigenicity

Prolonged high-dose exposure of mice to metronidazole leads to an increased incidence of lung tumors, and in one study there was an increase in lymphoreticular neoplasia in female animals. These results, which caused much concern when first published, are probably non-specific and not relevant to humans; these and other neoplasms have also been induced in mice merely by varying the diet. Several long-term follow-up studies in man have failed to demonstrate an excess cancer risk (SEDA-13, 831). There has been a single report of cancers in three patients with Crohn's disease who had taken metronidazole for years (SEDA-11, 595) (29), but they had also taken sulfasalazine and glucocorticoids, and this cannot be regarded as constituting reasonable evidence of a causal link.

Second-Generation Effects

Teratogenicity

Tests for embryotoxicity and teratogenicity in different animal species have been negative, and there have been no reports of adverse effects on the fetus in pregnant women given metronidazole for trichomoniasis. Despite this, it is still wise to avoid metronidazole during the first trimester of pregnancy.

In a retrospective cohort study using the national birth registry in Denmark, comparing 124 women who took the drug with 13 327 who did not, there was no evidence of any increased risk to the unborn child (30).

In a prospective case-control study in Israel of 857 pregnant women seeking telephone advice regarding gestational exposure to prescribed drugs, 228 women who had taken metronidazole were compared with 629 controls exposed to non-teratogenic agents (31). The mean daily dose of metronidazole was 973 mg for a mean duration of 7.9 days; 90% had used the medication orally, 6% by suppository, and 4% intravenously. Most (86%) had been exposed to metronidazole in the first trimester of pregnancy. There was no difference in the rate of major congenital malformations between the groups (1.6 versus 1.4%), even after accounting for terminations due to prenatally diagnosed malformations. Neonatal birth weight was reduced in the metronidazole group (3.2 versus 3.3 kg) and this was not explained by an earlier gestational age at delivery or a higher prematurity rate but may have been due to the underlying conditions for which metronidazole was prescribed. These findings agree with previous meta-analyses showing that the use of metronidazole in pregnancy is not associated with an increased risk of fetal abnormality, despite in vitro evidence of mutagenesis and inconsistent animal evidence of fetal abnormalities caused by metronidazole.

Lactation

Metronidazole is excreted in the breast milk. There were no adverse effects in nursing infants (SEDA-13, 832), but one should still be cautious in using metronidazole in nursing mothers (SEDA-18, 295).

Susceptibility Factors

Age

In a randomized trial in 100 Iranian children, mebendazole (200 mg tds for 5 days, $n = 50$) was compared with metronidazole (5 mg/kg tds for 7 days, $n = 50$) in giardiasis (32). The two drugs were equally effective (over 85% cure rates). There were no adverse effects of mebendazole, whereas nausea, anorexia, and metallic taste were respectively observed in 4.9, 6, and 24% of those taking metronidazole.

Drug–Drug Interactions

Alcohol

Metronidazole has a disulfiram-like effect in users of alcohol, sufficient to justify a warning (SEDA-13, 833).

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An unusual Antabuse-type reaction reported on one occasion seems to have been due to an interaction of metronidazole with the alcohol present in X-Prep (SEDA-15, 398).

Antibiotics

In vitro, the combination of metronidazole with antibiotics has an additive effect against anaerobic bacteria (SEDA-13, 833).

Carbamazepine

Metronidazole can increase the toxicity of carbamazepine (33) by inhibiting its metabolism.

Cephalosporins

The use of high doses of metronidazole in combination with cefamandole and clindamycin has been associated with encephalopathy (SEDA-12, 705).

Ciclosporin

An interaction with metronidazole and ciclosporin, in which ciclosporin blood concentrations rise, has been suggested, though only in isolated case histories (SEDA-19, 351) (34).

It has been confirmed that metronidazole can produce a two-fold increase in blood concentrations of ciclosporin and tacrolimus, with a subsequent increase in serum creatinine in both cases (35).

The interaction of metronidazole with ciclosporin significantly increased blood ciclosporin and tacrolimus concentrations in two patients (35). Since both of these immunosuppressive drugs are toxic in overdosage, and since patients taking them are prone to infections, this is potentially a serious interaction.

Fluorouracil

Pretreatment with metronidazole increased the toxicity of fluorouracil given by a daily bolus dose (36). The clinical significance of this is yet to be determined.

Gentamicin

In guinea pigs, metronidazole augmented gentamicin-induced ototoxicity, determined by the measurement of compound action potentials (37).

Lithium

Metronidazole can increase the toxicity of lithium (38).

Phenytoin

In a patient taking phenytoin, there was a disproportionate increase in the serum concentration of the hydroxylated metabolite of metronidazole, suggesting that phenytoin induces metronidazole-metabolizing enzymes (SEDA-12, 706) (39).

Quinidine

Serum quinidine concentrations rose during concomitant administration of metronidazole (40). The authors speculated that the mechanism was inhibition of cytochrome P_{450}.

Tacrolimus

A possible interaction with metronidazole recently reported is that it significantly increased blood ciclosporin and tacrolimus concentrations in two patients (35). Since both of these immunosuppressive drugs are toxic in overdosage, and since patients taking them are susceptible to infections, this is potentially a serious interaction.

Vecuronium bromide

Metronidazole can potentiate the effects of non-depolarizing muscle relaxants (41).

Serum concentrations of metronidazole rose during concomitant administration of ciprofloxacin and metronidazole (42). The authors speculated that the mechanism was inhibition of cytochrome P_{450} by ciprofloxacin.

Warfarin and other coumarins

The effect of warfarin is potentiated by metronidazole (43,44). The mechanism is stereoselective inhibition by metronidazole of the metabolism of *S*-warfarin, the more potent isomer (43). There is a similar interaction with acenocoumarol (45,46).

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Mexazolam

See also Benzodiazepines

General Information

Mexazolam is a benzodiazepine with effects similar to those of diazepam.

The anxiolytic effects of mexazolam have been compared with those of alprazolam in 64 outpatients with generalized anxiety disorder in a multicenter, double-blind, parallel-group, randomized trial (1). Five mexazolam and nine alprazolam recipients reported mild adverse events: drowsiness in three patients in each group; dizziness in one taking mexazolam and two taking alprazolam; blurred vision in one patient taking mexazolam; and weight gain, nausea, and insomnia in one patient taking alprazolam. Both drugs were effective anxiolytics and both were well tolerated.

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Mexiletine

See also Antidysrhythmic drugs

General Information

Mexiletine is a class Ib antidysrhythmic drug, similar in action to lidocaine, but it can be given orally. Its adverse effects occur in up to 50% of patients (1) and withdrawal is often necessary (2). The most common adverse effects are on the cardiovascular and central nervous systems. The pharmacokinetics, clinical use, and adverse effects and interactions of mexiletine have been reviewed widely (3–8).

In addition to its use as an antidysrhythmic drug, mexiletine has also been used in the treatment of various types of neuropathic pain and dystonias (9,10). The adverse effects in these circumstances have been reported (11–13) and reviewed (14).

Observational studies

In an open study of the antidystonic effect of mexiletine (200 mg/day increasing to a maximum of 800 mg/day) in spasmodic torticollis in six patients, mexiletine produced significant improvement and there were no adverse effects in five of the six patients; in the other patient dizziness occurred at the highest dose and required a reduction in dosage (11).

In studies in patients with diabetic peripheral neuropathy, adverse effects included nausea, hiccups, tremor, headache, weakness and dizziness, tachycardia, and allergic reactions (14).

Mexiletine has been used to treat painful peripheral neuropathy in patients with HIV infection, without any evidence of efficacy (15,16). In one study of 22 patients, nine had adverse effects probably related to mexiletine, including nausea in five, vomiting in four, and abdominal pain, diarrhea, dizziness, insomnia, rises in liver enzymes, and skin rash in one patient each (15). Adverse effects in seven patients required dosage reduction in four cases and withdrawal in three (because of a rash in one case and gastrointestinal effects in two).

In a study in which 48 patients with painful peripheral neuropathy due to HIV infection were treated with mexiletine, 10 had nausea and vomiting that required dosage modification; dosage modification was also occasioned by dizziness in one case and urinary retention in three cases (16).

Comparative studies

In 51 patients with serious ventricular tachydysrhythmias mexiletine alone or in combination with other class Ia drugs (quinidine, procainamide, disopyramide) was ineffective in 41% and there was no difference between those who had mexiletine alone and those who had the combinations (17). The incidence of adverse effects was also the same in both groups (about 70%), despite a lower mean dose of mexiletine in the latter.

The adverse effects of mexiletine have been compared with those of quinidine in a randomized, double-blind comparison in 491 patients (18). The commonest adverse effects in the 246 patients given mexiletine were upper gastrointestinal distress (38%), light-headedness (20%), tremor (13%), and co-ordination difficulties (11%). These all occurred more frequently than with quinidine. However, quinidine more often caused diarrhea (35 versus 7%) and dysrhythmias (19 versus 12 patients). The other reported adverse effects, associated in equal frequency with the two drugs, were fatigue, changes in sleep habit, weakness, headache, angina-like pain, and rash. Visual problems (7 versus 3%) and nervousness (6 versus 2%) occurred slightly more often with mexiletine.

Placebo-controlled studies

In a double-blind, placebo-controlled, crossover study of the use of mexiletine in 20 patients with neuropathic pain with prominent allodynia the dosage was titrated to maximum of 900 mg/day or until dose-limiting adverse effects occurred. Mexiletine produced little beneficial effect and the two most common adverse effects were nausea and sedation (12). Other adverse effects that occurred in one or two patients each included insomnia, trismus, headache, agitation, nightmares, and tremor.

In a double-blind, placebo-controlled, crossover study in 12 healthy volunteers mexiletine, in a dosage that was titrated to a maximum of 1350 mg/day or until there were dose-limiting adverse effects, was used to alleviate capsaicin-induced allodynia and hyperalgesia (13). Mexiletine had no significant effect on any of the major measures of pain or neurosensory thresholds after intradermal capsaicin; however, it did reduce the flare response. All 12 subjects had dose-limiting adverse effects and the mean maximum tolerable daily dose was 850 mg. The adverse effects included nausea, light-headedness, muscle twitching and weakness, blurred vision, headache, tremor, difficulty in concentrating, dysphoria, sedation, pruritus, and rash. These adverse effects occurred at an average daily dose of 993 mg. The three most common adverse effects were nausea, dizziness, and tremor in ten, nine, and four of the subjects respectively.

The analgesic effects of mexiletine 600 mg/day and gabapentin 1200 mg/day have been investigated in 75 patients with acute and chronic pain associated with breast surgery in a double-blind, randomized, placebo-controlled study for 10 days (19). Pain at rest and after movement was reduced by both drugs on the third postoperative day and pain after movement was reduced by gabapentin at 2–5 days postoperatively. Two women given mexiletine withdrew from the study because of adverse events, one with an axillary vein thrombosis and one with nausea and vomiting.

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Organs and Systems

Cardiovascular

Prodysrhythmic effects of mexiletine have been reported in up to 29% of patients, although it has been suggested that on average the incidence is lower than has been reported with other antidysrhythmic drugs (20).

Mexiletine can have major hemodynamic effects in patients with pre-existing impairment of left ventricular dysfunction (21). Circulatory depression with bradycardia and hypotension have been reported (17,22,23).

Other cardiovascular effects include widening of the QRS complex, atrioventricular dissociation, heart block, sinus arrest, and cardiac arrest (23,24).

Respiratory

Mexiletine has been associated with pulmonary fibrosis and eventual respiratory failure (25).

Nervous system

The commonest adverse effects of mexiletine are on the nervous system, and include centrally mediated gastrointestinal distress (38%), light-headedness (20%), tremor (12%), and coordination difficulties (11%). The figures in parentheses are quoted from a study in which mexiletine was compared with quinidine (26). Other reported adverse effects include changes in sleep habit, weakness, headache, visual problems, and nervousness. Slurred speech, dysarthria, diplopia, and ataxia have also been reported (18).

Mexiletine 300–400 mg/day has been used to treat some of the symptoms of multiple sclerosis in 30 patients with painful tonic seizures, attacks of neuralgia, paroxysmal itching, and Lhermitte's sign (27). Mexiletine produced similar therapeutic effects to lidocaine. In one patient, weakness worsened during the administration of mexiletine. In two patients when mexiletine was replaced by placebo there was a suggestion of some rebound in painful tonic seizures.

In three patients with neuropathic pain, mexiletine added to the analgesic regimen caused some improvement in visual analogue scores for pain (10). All three had some symptoms of nausea, and two became depressed. One patient also reported feeling "trembly and shaky" on occasion, but there was no objective evidence of tremor.

Sensory systems

In two patients with neuropathic pain and pre-existing ocular disease, mexiletine caused persistent ophthalmic changes (28).

- A 39-year-old woman took mexiletine 300 mg tds for 3 days and developed transient blindness with residual reduced visual acuity due to an acute pigmentary retinopathy. Her vision improved markedly after withdrawal of mexiletine, but when she restarted it she developed clouding of the vision, which resolved again on withdrawal. The pigmentary changes persisted.
- A man with a history of glaucoma took mexiletine 300 mg tds and developed worsening visual acuity. Mexiletine was withdrawn and he took carbamazepine 200 mg/day instead. However, he started to see red and green spots. The serum carbamazepine concentration was below that usually associated with visual disturbances. No structural abnormalities were detected.

Hematologic

Mexiletine can cause a spuriously low platelet count as a result of clumping of platelets due to antibodies (29); however, it can also cause a true thrombocytopenia (30,31).

Eosinophilia and atypical lymphocytosis associated with liver dysfunction have also been described (32).

Gastrointestinal

Nausea and vomiting are common and probably central in origin, since they occur with intravenous as well as oral therapy (17).

Mexiletine affects the esophagus, and can cause heartburn (1) and esophageal spasm and ulceration (1,33).

Liver

Changes in liver function tests, resolving on withdrawal, have been reported (34). In one case there was histological evidence of cholestasis.

Skin

Mexiletine can occasionally cause generalized rashes (SEDA-17, 224) (26,32), pseudolymphomatous change with erythroderma (35), and contact urticaria (36).

- Exfoliative dermatitis has been reported in a 68-year-old man who had taken mexiletine and diltiazem for 3 weeks (37). Patch tests with 1, 10, and 30% mexiletine and diltiazem in petrolatum were positive, but a lymphocyte stimulation test was negative.
- Drug eruptions occurred in a 56-year-old woman, a 50-year-old man, and a 66-year-old woman, who developed disseminated maculopapular eruptions with high fever after oral mexiletine (38). In all cases the liver transaminase activities were raised and there was an eosinophilia with atypical lymphocytes; in two cases there was a lymphadenopathy. In all cases patch tests were positive.
- An acute exanthematous pustular eruption has been reported in a 56-year-old man who had taken mexiletine 300 mg/day for 1 month (39). There was mild liver dysfunction. Patch tests with mexiletine 10 and 20% were subsequently positive, but a lymphocyte stimulation test was negative.

In addition to these cases, 37 cases of drug eruption due to mexiletine have been reported in Japan, with several common clinical features (37). The interval between initial drug therapy and the start of the eruption was relatively long (48–88 days); there was a high proportion of positive patch tests (86–97%) but a low incidence of positive lymphocyte stimulation tests (23–27%); there were frequent systemic symptoms, such as fever (93–94%) and liver dysfunction (43–78%); finally, some patients had multiple drug eruptions.

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Immunologic

Mexiletine caused an increased incidence of positive antinuclear antibody (ANA) titers in some studies (8,40), but not in others (41,42). The clinical significance of this effect is not clear. For example, there have been no reports of a lupus-like syndrome attributable to mexiletine.

Mexiletine caused increases in the serum activities of aspartate transaminase, alanine transaminase, and alkaline phosphatase in a few patients (8).

Susceptibility Factors

Renal disease

Mexiletine is mainly cleared polymorphically by CYP2D6 in the liver, and poor metabolizers and the slower among the extensive metabolizers have a higher incidence of mild adverse effects (nausea and light-headedness) (43). However, renal insufficiency can also be associated with an increase in plasma mexiletine concentrations (44).

Hepatic disease

Mexiletine is mainly cleared polymorphically by CYP2D6 in the liver, and poor metabolizers and the slower among the extensive metabolizers have a higher incidence of mild adverse effects (nausea and light-headedness) (43).

Drug Administration

Drug overdose

Overdosage with mexiletine resulted in death in two cases due to cardiovascular effects (45,46).

- Status epilepticus was the chief presenting feature in a 17-year-old boy who took an unspecified amount of mexiletine (47). The seizures responded to intravenous diazepam and phenytoin, but he also had agitation and hallucinations, which took 24 hours to abate. A urine specimen was positive for both benzodiazepines and amphetamines, but this was subsequently found to be a false positive result, because of the presence of large amounts of mexiletine, confirmed by thin-layer chromatography. The serum mexiletine concentration was 44 μmol/l, the usual target range being about 4–11 μmol/l.

Drug–Drug Interactions

Antacids

Mexiletine interacts with antacids, but the interaction is unlikely to be clinically important (48).

Antidysrhythmic drugs

Interactions of mexiletine with other cardioactive drugs have been reviewed (48). The most important are beneficial interactions with beta-adrenoceptor antagonists, quinidine, and amiodarone in the suppression of ventricular tachydysrhythmias. During these interactions the adverse effects of mexiletine may also be less common, although this effect is inconsistent (17).

Fluvoxamine

Mexiletine is metabolized by CYP2D6, CYP1A2, and CYP3A4; fluvoxamine inhibits CYP1A2. It is not surprising therefore that fluvoxamine 50 mg bd for 7 days increased the C_{max} and AUC of a single oral dose of mexiletine 200 mg in six healthy Japanese men (49).

Omeprazole

Mexiletine is metabolized mainly by CYP2D6 and CYP1A2. Omeprazole is an inducer of CYP1A2 and might therefore be expected to interact with mexiletine. However, in a study in nine healthy men there was no evidence of an effect of steady-state omeprazole 40 mg/day on the single-dose kinetics of mexiletine 200 mg (50).

Phenytoin

Mexiletine interacts with phenytoin, but the interaction is unlikely to be clinically important (48).

Propafenone

Mexiletine and propafenone are metabolized by the same enzymes, CYP2D6, CYP1A2, and CYP3A4. In 15 healthy volunteers, eight of whom were extensive metabolizers of CYP2D6, administration of oral mexiletine 100 mg bd on days 1–8 and oral propafenone 1 mg bd on days 5–12 significantly reduced the clearance of R(–) mexiletine from 41 to 28 l/hour and of S(+) mexiletine from 43 to 29 l/hour in the extensive metabolizers (51). The new values were no different from the clearance values in the poor metabolizers. Propafenone also reduced the partial metabolic clearances of mexiletine to hydroxymethylmexiletine, parahydroxymexiletine, and metahydroxymexiletine by about 70% in the extensive metabolizers. Propafenone had no effect on the kinetics of mexiletine in the poor metabolizers. There were no electrocardiographic changes during this interaction. Smokers had higher clearance rates than non-smokers, but the effects of propafenone were similar in the two groups. In contrast, mexiletine had little effect on the disposition of propafenone. The authors proposed that these effects could explain at least in part the increased efficacy that sometimes occurs when mexiletine and propafenone are combined in patients in whom a single drug was not effective. They also recommended that the dosages of the drugs should be titrated slowly when they are used together, in order to reduce the risk of adverse effects.

Rifampicin

Mexiletine interacts with rifampicin, but the interaction is unlikely to be clinically important (48).

Sevoflurane

- A 79-year-old woman was given mexiletine 125 mg intravenously over 10 minutes during anesthesia after

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having been given lidocaine 100 mg intravenously, and had a marked drop in blood pressure 1 hour later (52). The blood pressure rose when sevoflurane was withdrawn.

The authors proposed that the effect had been brought about by the combination of mexiletine and sevoflurane, although it is more likely that the effect was due to the combination of mexiletine with lidocaine.

Xanthines

Mexiletine reduces the clearance of theophylline, and this combination has been reported to cause ventricular tachycardia (53). A similar interaction with caffeine has been reported (54).

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Mianserin

See also Antidepressants, second-generation

General Information

Mianserin is a tetracyclic compound, related to cyproheptadine (SEDA-5, 18). It is an effective antidepressant with antiserotonergic properties and a sedative profile, but minimal anticholinergic effect and less action on the cardiovascular system than tricyclic antidepressants (1).

Organs and Systems

Cardiovascular

Cardiotoxic effects are relatively uncommon with mianserin (2). In a placebo-controlled study in 50 patients with a variety of cardiac conditions who were taking anticoagulants, mianserin (up to 30 or 60 mg) had no effects on electrocardiography, blood pressure, or pulse rate after 3 weeks. In a second phase, mianserin (up to 60 mg/day) was compared with amitriptyline (up to 150 mg/day) and placebo in 18 healthy volunteers. Measurements included systolic time intervals, electrocardiography at rest and during exercise, echocardiography, and blood pressure. Amitriptyline had a negative inotropic effect; mianserin increased ejection fraction. The results of both these experiments led the authors to conclude that mianserin is an antidepressant with very low cardiac toxicity.

In another study of the electrocardiographic effects of mianserin and a review of previous experiments with doses up to 120 mg/day, there were no consistent cardiovascular effects, although four patients who took 40 mg/day for 13 months had significant increases in pulse rate, with prolonged PR intervals and reduced T-wave amplitude (3). Fainting and persistent bradycardia were noted in one woman after a single dose of mianserin 60 mg, and her symptoms recurred on rechallenge (SEDA-17, 21).

There have been two instances of possible cardiac effects due to mianserin in elderly patients with pre-existing cardiovascular disorders (4).

- A 71-year-old man with hypertension who took 30 mg/day developed cardiac failure.
- A 66-year-old woman with mitral regurgitation and atrial fibrillation developed hypokalemia and a variety of rhythm disturbances at dosages of 40 mg or more per day.

Nervous system

In 40 patients who had seizures while taking therapeutic dosages of mianserin it was concluded that mianserin is probably no more likely to produce convulsions in therapeutic dosages than tricyclic compounds (5). When it does so, seizures are more likely to occur in the first 2 weeks of treatment in patients with a family or personal history indicative of risk, and after a dosage increase.

Mianserin can cause restless legs (SEDA-14, 15) (SEDA-17, 21).

Hematologic

In 1979 the first case of leukopenia due to mianserin was reported (6), followed by another soon after (7). In July 1980, the Australian Drug Evaluation Committee issued a preliminary caution concerning further cases that had been reported to its National Monitoring Centres and 6 months later published detailed reports of four other cases (8), all of which had occurred within 1 year of marketing in Australia, despite 6 years of use in Europe. Inquiries unearthed reports of seven similar episodes held by drug surveillance organizations in other countries, and the Committee expressed its concern that "if a causal relationship between mianserin and these blood disorders is subsequently confirmed, the incidence of disorders due to mianserin may be significantly greater than that of disorders due either to the phenothiazines or the tricyclic antidepressants" (9). In 1985 the UK Committee on Safety of Medicines issued a statement concerning 15 reports that the Committee had received during 5 years (10). Three of the patients subsequently died, one with aplastic anemia, one with granulocytopenia, and one with both erythrocyte and leukocyte hypoplasia. The New Zealand Department of Health's Clinical Services Letter mentioned three cases of agranulocytosis that occurred in New Zealand in 1982 (11). Another report (12) described thrombocytopenia and leukopenia based on an immune mechanism without generalized marrow depression. A high rate of agranulocytosis has been reported by the IMMP in New Zealand: one case out of 1822 and one fatal case out of 11 537 (12).

Mouth and teeth

The lack of anticholinergic effects reported in clinical studies has been supported by a double blind, placebo-controlled comparison of mianserin (10–60 mg/day) and amitriptyline (25–150 mg/day) in healthy volunteers (13). Mianserin tended to increase saliva flow, while amitriptyline significantly reduced it. However, a further experiment in healthy volunteers showed that single doses of mianserin (50–70 mg) produced a significant 29% reduction of salivation compared with placebo (14). This may account for the glossitis that has previously been reported (SEDA-9, 23).

Liver

Hepatotoxicity from mianserin has been reported in eight cases (SEDA-17, 22).

Musculoskeletal

Mianserin can cause joint symptoms and arthritis (SEDA-16, 11).

Drug Administration

Drug overdose

One of the putative benefits of mianserin is its alleged safety in overdose, which may be related to a reduced risk of cardiovascular adverse effects and convulsions. Data from the UK Committee on Safety of Medicines suggest that mianserin accounts for 11% of reported convulsions and 5.8% of use, putting it intermediate between amitriptyline and maprotiline (15). On the other hand, in the London Poisons Unit survey, involving 84 patients who took mianserin alone (up to 1000 mg), there were no deaths and no patients with convulsions, although this could represent a frequency of up to 3.6% (12).

A survey of 100 cases of overdose with mianserin reported to the London Centre of the UK Poisons Information Service included 54 patients who took mianserin alone in amounts up to and in three cases in excess of 1000 mg (12). Plasma mianserin concentrations were 70–665 ng/l (the usual mean target concentration is 50 ng/l). There were no reports of convulsions, cardiac dysrhythmias, or profound coma in any patient taking mianserin alone, but there were two deaths in patients who took multiple drugs. The authors concluded that in acute overdosage mianserin is less toxic than tricyclic antidepressants.

Drug–Drug Interactions

Clonidine and methyldopa

Mianserin lacks potential for peripheral adrenergic interactions, but since it has α-adrenoceptor activity, it might interact with the centrally acting α-adrenoceptor agonists clonidine and methyldopa. In healthy volunteers, pretreatment with mianserin 60 mg/day for 3 days did not modify the hypotensive effects of a single 300 mg dose of clonidine, and in 11 patients with essential hypertension, the addition of mianserin 60 mg/day (in divided doses) for 2 weeks did not reduce the hypotensive effects of clonidine or methyldopa (16). In patients taking methyldopa, there were additive hypotensive effects after the first dose of mianserin, but these were not significant after 1 or 2 weeks of combined treatment. The results of this study appear to have justified the authors' conclusion that combining mianserin with centrally-acting hypotensive agents will not result in loss of blood pressure control.

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Mibefradil

See also Calcium channel blockers

General Information

Mibefradil is a member of a class of calcium antagonists that specifically block the T-type calcium channel. It was marketed as an antihypertensive and antianginal drug with an adverse effects profile similar to that of placebo (1) and a favorable pharmacokinetic profile, allowing once-a-day dosage (2).

Owing to its attractive pharmacological profile, namely an anti-ischemic action with little or no negative inotropism, mibefradil was tested in a large-scale mortality trial in heart failure (MACH-I, Mortality Assessment in Congestive Heart Failure Trial). However, early in June 1998, only a few months after its launch, Roche Laboratories withdrew mibefradil from the market, after several dangerous interactions with at least 25 drugs had been reported (3,4) associated with rhabdomyolysis and life-threatening cardiac dysrhythmias; these problems were detected by postmarketing surveillance (4). The FDA stated that: "since [mibefradil] has not been shown to offer special benefits (such as treating patients who do not respond to other anti-hypertensive and antianginal drugs), the drug's problems are viewed as an unreasonable risk to consumers."

In the MACH-1 (Mortality Assessment in Congestive Heart Failure) trial, 2590 patients with moderate to severe congestive heart failure were randomized to mibefradil or placebo (5). Mibefradil given for a maximum of 3 years did not affect mortality or morbidity. However, a subgroup analysis by concomitant drugs showed that digoxin, class I antidysrhythmic drugs, amiodarone, and other drugs associated with torsade de pointes increased the risk of death with mibefradil. These worrisome drug–drug interactions were consistent with the results of postmarketing surveillance, which prompted withdrawal of mibefradil from the market by its manufacturers in June 1998, even before complete results of the trial became available.

The safety and efficacy of mibefradil in association with beta-blockers was assessed in 205 patients with chronic stable angina, randomized to placebo or mibefradil 25 or 50 mg/day for 2 weeks (6). Besides an improvement in angina with mibefradil, it dose-dependently reduced heart rate and increased the PR interval. One patient taking mibefradil had an escape junctional rhythm 26 hours after the last dose of 50 mg. The nodal rhythm disappeared on withdrawal of mibefradil, but based on the overall results it was concluded that mibefradil was safe and effective when given for a short time with beta-blockers.

In a Prescription-Event Monitoring study in 3085 patients, mean age 65 years, the commonest reported adverse events and reasons for stopping were malaise/lassitude, dizziness, edema, and headache (7).

Organs and Systems

Cardiovascular

Mibefradil causes slight bradycardia associated with its hypotensive effect. In a Prescription-Event Monitoring study in 3085 patients, mean age 65 years, there were seven reports of serious bradycardia/collapse thought to be possible adverse drug reactions to mibefradil (7). All were in patients over 65 years and six were thought to have resulted from a drug interaction. In all, there were 11 possible drug interactions. Nine (eight reports of bradycardia and one of syncope) involved beta-blockers. Collapse and severe bradycardia occurred in a patient who had started to take a dihydropyridine calcium channel blocker within 24 hours of stopping mibefradil. Palpitation and dyspnea occurred in a patient taking digoxin and sotalol. None of the 53 deaths during the study was attributed to mibefradil.

Abrupt switch of therapy from mibefradil to other dihydropyridine calcium antagonist was reported to cause shock, fatal in one case, in four patients also taking beta-blockers (8).

Drug–Drug Interactions

General

Mibefradil inhibits CYP3A4 (2). Other drugs that are metabolized by this pathway accumulate as a result. Drugs that were commonly affected included amiodarone, astemizole, ciclosporin, cisapride, erythromycin, imipramine, lovastatin, propafenone, quinidine, simvastatin (9), tacrolimus (10), tamoxifen, terfenadine, thioridazine, and drugs that impair sinoatrial node function (for example beta-blockers) (6).

- Severe rhabdomyolysis occurred in an 83-year-old woman who developed progressive immobilizing myopathy, low back pain, and oliguria; she was taking simvastatin and mibefradil (9). The symptoms disappeared completely after 4 weeks of withdrawal.

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Mibefradil was probably responsible for raising plasma concentrations of simvastatin to toxic concentrations.

Beta-blockers

In a Prescription-Event Monitoring study in 3085 patients, mean age 65 years, there were 11 possible drug interactions. Nine involved beta-blockers, with eight reports of bradycardia and one of syncope. One patient developed palpitation and dyspnea while also taking digoxin and sotalol.

Calcium channel blockers

In a Prescription-Event Monitoring study in 3085 patients, mean age 65 years, one patient developed collapse and severe bradycardia after starting to take a dihydropyridine calcium channel blocker within 24 hours of stopping mibefradil (7).

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Miconazole

See also Antifungal azoles

General Information

Miconazole has been evaluated as a topical, oral, and intravenous agent. Its absorption is slightly better than that of clotrimazole, but is still insufficient for use as a systemic agent, particularly in view of its relatively short half-life of around 8–9 hours (1). Miconazole has also been given intravenously and intrathecally. It is highly protein-bound and does not diffuse well into the CSF; however, it does penetrate readily into synovial and vitreous fluids (2).

The indications for miconazole have diminished with the advent of newer antifungal azoles (3) and it has largely been superseded by other azoles; infection with *Pseudallescheria boydii* remains one of the few indications (4).

General adverse effects

Topical miconazole is well tolerated. Parenteral administration carries a higher frequency of adverse effects, some probably being caused by Cremophor (polyethoxylated castor oil, the carrier). Adverse effects include fever, chills, pruritus, rash, nausea, vomiting, diarrhea, hyponatremia, cardiac toxicity, phlebitis, hyperlipidemia, and central nervous system disturbances. Hypersensitivity reactions can occur. Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Local phlebitis is not uncommon after intravenous miconazole (5); the type of intravenous solution used is of importance.

Collapse after rapid intravenous injection has been described, as have some cases of tachycardia, ventricular tachycardia, and even, in a few instances, cardiorespiratory arrest, attributable to the histamine-releasing properties of Cremophor (SED-12, 679) (2).

Nervous system

Arachnoiditis has been described after intrathecal injection (6).

Psychological, psychiatric

Acute toxic psychosis is a rare consequence of miconazole (SED-12, 679) (7).

Endocrine

Hyperlipidemia has been described in many patients given miconazole; this may be caused by the solvent (SED-12, 679) (2).

Skin

Pruritus and rashes have been reported with miconazole but do not seem to be frequent (5).

Drug–Drug Interactions

Anticoagulants

Miconazole can potentiate the effects of coumarin anticoagulants (SED-12, 679) (2). Potentiation of the anticoagulatory effects of acenocoumarol was noted after vaginal administration of miconazole capsules to two postmenopausal patients (8) and after oral administration of miconazole gel in three elderly patients with oral candidiasis (9). In both instances there were no major bleeding complications. However, it appears prudent to consider the use of non-azole topical antifungal agents in patients who are taking CYP3A4 metabolized drugs with a narrow therapeutic index.

Phenytoin

Miconazole can increase serum concentrations of phenytoin (SED-12, 679) (10).

Sulfonylureas

Enhancement of the effects of hypoglycemic sulfonamides has been reported (SED-12, 679) (2).

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Midazolam

See also Benzodiazepines

General Information

Midazolam is used mainly in parenteral form in anesthesia, as a sedative adjunct to medical and dental procedures, and in status epilepticus (1). Its pharmacology and therapeutics have been extensively reviewed (2). It produces greater amnesia than diazepam, useful in terms of its anesthetic use, but carries a risk of cardiorespiratory depression and death (SED-12, 99), particularly at the extremes of age and when combined with the opioid fentanyl (SEDA-22, 42), which can cause accumulation of midazolam (see Drug–Drug Interactions in this monograph). Vomiting has been reported in 10% of children having midazolam sedation before radiology (SEDA-22, 41). Behavioral disinhibition (SEDA-18, 44), acute withdrawal, and hiccups appear to be relatively common (SEDA-22, 41); hallucinations, flumazenil-reversible dystonia, and hypersensitivity have all been observed (SED-12, 99) (SEDA-17, 44).

Clinical electrophysiological procedures can be very complex and prolonged, requiring safe and effective conscious sedation. A study in 700 patients has shown that intermittent midazolam plus fentanyl in electrophysiological procedures is safe and efficacious (3). All the staff were ACLS-certified and had successfully completed conscious sedation training courses, but none was an anesthetist; one team member was dedicated to monitoring conscious sedation and providing rescue defibrillation if required.

The pharmacology and adverse effects of midazolam in infants and children have been reviewed (4).

Midazolam has been carefully evaluated for adverse effects when used in critically ill infants and children; several difficulties, including prolonged obtundation and paradoxical behavioral and withdrawal reactions, have been noted (SEDA-19, 35) (5). Midazolam by the buccal route has been evaluated in children with persistent seizures; it was both effective and well tolerated (6), offering obvious practical advantages to rectal or parenteral administration. The availability of flumazenil, a specific benzodiazepine antagonist, to correct any adverse or overdose effects from injected midazolam should not encourage laxity in its use. Recent reports have highlighted kinetic interactions between midazolam and a variety of other drugs (see Drug–Drug Interactions in this monograph), and its effects can be magnified or prolonged in patients with hepatic or renal insufficiency (SEDA-20, 32).

Midazolam was used in a wide range of doses (0.03–0.6 mg/kg) in 91 children undergoing diagnostic or minor operative procedures with intravenous midazolam sedation (7). Opioids were co-administered in 84% and oxygen desaturation occurred in 32%, most of whom had received high doses of opioids in addition to the midazolam. Other adverse events included airway obstruction ($n = 3$) and vomiting ($n = 1$). The presence of independent appropriate trained personnel not directly involved in performing the procedure, appropriate resuscitation

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equipment, and monitoring were recommended whenever midazolam and opioids are co-administered for intravenous sedation.

A cherry-flavored midazolam syrup was evaluated for premedication in 85 children requiring general anesthesia (8). The patients received a randomly assigned dose of 0.25, 0.5, or 1 mg/kg. All clinicians and observers were blinded to the treatment group. There was satisfactory dose-related sedation in 81%, and 83% had satisfactory non-dose-related anxiolysis at separation from parents and at anesthetic induction. One or more adverse events occurred in 36%, but only 31% of these were judged as possibly related to midazolam (hiccups 6%, hypoxemia 6%, vomiting 5%, hallucinations 4%, drooling 4%, agitation 2%, coughing 2%, diplopia 2%, dizziness 2%, and hypotension 2%). The authors suggested that although adverse effects were common, they were minor.

Intranasal midazolam 0.2 mg/kg and intravenous diazepam 0.3 mg/kg have been compared in a prospective randomized study in 47 children (aged 6 months to 5 years) with febrile seizures that lasted over 10 minutes (9). Intranasal midazolam controlled seizures significantly earlier than intravenous diazepam. None of the children had respiratory distress, bradycardia, or other adverse effects. Electrocardiography, blood pressure, and pulse oximetry were normal in all children during seizure activity and after cessation of seizures.

In a Canadian multicenter, open, randomized trial in 156 patients to determine whether sedation with propofol would lead to shorter times to tracheal extubation and length of stay in ICU than sedation with midazolam, the patients who received propofol spent longer at the target sedation level than those who received midazolam (60 versus 44% respectively) (10). Propofol allowed clinically significantly earlier tracheal extubation than midazolam (6.7 versus 25 hours). However, this did not result in earlier discharge from the ICU.

In a double-blind, randomized, placebo-controlled study during coronary angiography in 90 patients, midazolam with or without fentanyl and local anesthesia provided better hemodynamic stability than placebo (11).

In a randomized study in 301 agitated or aggressive patients, intramuscular midazolam was more rapidly sedating than a mixture of haloperidol + promethazine (12). There was only one important adverse event, transient respiratory depression, in one of the 151 patients who were given midazolam.

Organs and Systems

Cardiovascular

The incidence of hypotension with the use of midazolam for pre-hospital rapid-sequence intubation of the trachea has been assessed in a retrospective chart review of two aeromedical crews (13). The rapid-sequence protocols were identical, except for the dose of midazolam. Both crews used 0.1 mg/kg, but one crew had a maximum dose of 5 mg imposed. This meant that patients over 50 kg received lower doses of midazolam; they also had a higher incidence of hypotension. This relation was also present in patients with traumatic brain injury, implying that cerebral perfusion could be compromised at a critical time in those without dosage restriction.

Midazolam depresses both cardiovascular and respiratory function, especially in elderly patients (14). As little as 0.01 mg/kg can obtund the response to hypoxia and hypercapnia (15). The simultaneous use of opiates (such as fentanyl) commonly produces hypoxia (16).

Hypertension and tachycardia during coronary angiography can cause significant problems. In a double-blind, randomized, placebo-controlled study during coronary angiography in 90 patients, midazolam with or without fentanyl under local anesthesia provided better hemodynamic stability than placebo (11).

Respiratory

Intranasal midazolam is a successful route of administration for sedating children. However, it can cause nasal burning, irritation, and lacrimation (17). In a study of an alternative route of administration, namely inhalation via a nebulizer, bronchospasm developed in two of the 10 patients studied. This formulation of midazolam has a pH of 3.0, and this was thought to be the reason it caused bronchospasm.

Nervous system

Two premature neonates, who already had epileptic manifestations related to severe hypoxic ischemic encephalopathy, developed seizures (one tonic and the other tonic-clonic) within a few seconds of receiving intravenous midazolam (0.15 μg/kg) for sedation (18). In one, the seizure recurred after rechallenge on the same day. Benzodiazepines occasionally cause tonic seizures, especially after intravenous administration to children with Lennox–Gastaut syndrome. This seems to be the first report related to midazolam in newborns.

Involuntary epileptiform movements have been described in three of six premature infants given midazolam for sedation (19). The infants had been born at 24–26 weeks gestation, were aged 23–32 days, and weighed on average 671 g. They were given midazolam 100 μg/kg by slow bolus injection for sedation and then had accentuated myoclonic jerks resembling clonic seizures within 5 minutes. In all cases it was the first dose of midazolam and the cardiorespiratory parameters remained normal. The abnormal movements resolved within 5–10 minutes. There has also been a report of convulsions caused by midazolam in two preterm infants (20). They were of 26 and 28 weeks gestation and were given midazolam 100 and 150 μg/kg intravenously before tracheal intubation. Both were successfully treated with flumazenil 10 μg/kg.

The safety of midazolam in very low birth-weight neonates is being questioned. In 200 children weighing 3–15 kg premedicated with rectal midazolam 0.5 or 1.0 mg/kg before minor surgery, the incidence of hiccups was 22% and 26% respectively (21). The mean age of children with hiccups was 6 months and of children without hiccups 20 months. Intranasal ethyl chloride spray was 100% successful in treating the hiccups. The incidence of hiccups was related to age but not dose. The effectiveness of ethyl chloride was postulated to be via cold nasopharyngeal stimulation.

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The effects of sevoflurane and halothane anesthesia, including the effect of midazolam 0.5 mg/kg premedication, on recovery characteristics have been studied in 100 children aged 6 months to 6 years undergoing myringotomy (22). Children who received sevoflurane had about 50% faster recovery times and discharge-home times than those who received halothane. However, sevoflurane without midazolam premedication was associated with 67% postoperative agitation compared with 40% in the premedicated group. Midazolam delayed early recovery times by about 5 minutes, but had no effect on discharge times. In view of the very high incidence of postoperative agitation in the control group midazolam was seen as an effective premedicant.

Midazolam can cause paradoxical reactions, including increased agitation and poor cooperation (23,24). Often other drugs are required to continue the procedure successfully. Reversal of these reactions by flumazenil, a benzodiazepine antagonist, has been reported.

Sevoflurane often causes postoperative delirium and agitation in children, and this may be severe. The effect of intravenous clonidine 2 μg/kg on the incidence and severity of postoperative agitation has been assessed in a double-blind, randomized, placebo-controlled trial in 40 boys who had anesthetic induction with sevoflurane after oral midazolam premedication (25). There was agitation in 16 of those who received placebo and two of those who received clonidine; the agitation was severe in six of those given placebo and none of those given clonidine.

The effect of a single bolus dose of midazolam before the end of sevoflurane anesthesia has been investigated in a double-blind, randomized, placebo-controlled trial in 40 children aged 2–7 years (26). Midazolam significantly reduced the incidence of delirium after anesthesia. However, when it was used for severe agitation, midazolam only reduced the severity of agitation without abolishing it.

In the presence of acute neurological injuries, midazolam produces a high risk of raised intracranial pressure (27), and the risk of airway obstruction (28) is a further concern.

Recovery after propofol or midazolam has been compared in two studies (29,30). Memory was significantly impaired by midazolam, an effect that was reminiscent of the problems experienced with short-acting oral benzodiazepine hypnotics, such as triazolam.

Psychological, psychiatric

Midazolam can cause an unpleasant state of dysphoria if surgical stimuli are applied to the patient, who may nevertheless appear calm and untroubled. Amnesia is also routinely produced and can be beneficial. Delayed recovery of cognitive function occurs after the use of benzodiazepines as premedication (31).

There was a variety of significant nervous system adverse effects in six of 104 patients who underwent transesophageal echocardiography, including aggression, euphoria, depression, and intense hiccups (32). These effects occurred despite careful titration and relatively low doses of intravenous midazolam (mean 4.8 mg), and were generally reversible with intravenous flumazenil 0.25–0.5 mg.

Hematologic

Fat emulsions affect coagulation and fibrinolysis (33). In 36 patients undergoing aortocoronary bypass operations with midazolam/fentanyl- or propofol/alfentanil-based anesthesia, factor XIIa concentrations and kallikrein-like activity were about 30% higher in the propofol group. The authors suggested that there had been stronger activation of the contact phase at the start of recirculation and stronger fibrinolysis in the propofol group. They also found more hypotension in the propofol group, which they assumed to be due to release of kallikrein, resulting in release of bradykinin. Propofol has not been proven to cause increased perioperative bleeding.

In a 40-month-old boy a withdrawal syndrome with neurological symptoms was accompanied by thrombocytosis, which peaked at 1230×10^9/l (34). Recovery from the withdrawal syndrome was accompanied by normalization of the platelet count. The relevance of this change in platelet count was not clear. The boy had also been given fentanyl, and the authors suggested that the combination of midazolam with fentanyl should be used with caution.

Urinary tract

The conjugates of the main metabolite of midazolam, α-hydroxymidazolam, accumulate in renal insufficiency. In five patients with severe renal insufficiency (creatinine clearance 7 ml/minute or less), in whom prolonged sedation after midazolam was immediately reversed by flumazenil, there were high serum concentrations of glucuronidated α-hydroxymidazolam, even at times when the concentrations of the unconjugated metabolite and midazolam itself were low (35). Glucuronidated α-hydroxymidazolam is about one-tenth as potent as midazolam and unconjugated α-hydroxymidazolam, and accumulation of the conjugated metabolite in renal insufficiency may be important.

Body temperature

Midazolam premedication causes exaggerated perioperative hypothermia in 15 elderly surgical patients compared with 15 young patients (36). The same group also showed that atropine prevents midazolam-induced core hypothermia in 40 elderly patients (37). The thermoregulatory effects of benzodiazepine agonists and cholinergic inhibitors oppose each other, and the combination leaves core temperature unchanged.

Long-Term Effects

Drug withdrawal

The withdrawal of an infusion of midazolam, used as sedation in intensive care units, is associated with occasional severe and bizarre behavioral disturbances, particularly in children (38). These are similar in nature to the withdrawal effects seen with other short-acting benzodiazepines.

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Susceptibility Factors

Age

The pharmacology and adverse effects of midazolam in infants and children have been reviewed (4). The optimal dose of intramuscular midazolam for preoperative sedation has been studied in a double-blind prospective study of 600 patients who were age-stratified (39). The patients received intramuscular atropine 0.6 mg and one of five doses of midazolam 15 minutes before induction of anesthesia. For the age groups 20–39, 40–59, and 60–79 years, the optimal sedative and amnesic effects of midazolam were 0.10, 0.08, and 0.04 mg/kg respectively. The frequency with which the undesirable adverse effects of reduced blood pressure, oxygen desaturation, oversedation, loss of eyelash reflex, and tongue root depression occurred increased with age, and optimal doses for a low incidence of adverse effects were 0.08, 0.06, and 0.04 mg/kg in the same age groups respectively.

Drug Administration

Drug administration route

Midazolam nasal spray 2 mg/kg has been compared with a citric acid placebo for conscious sedation in children undergoing painful procedures (40). Citric acid was added to the placebo, so that the sensation of nasal burning caused by midazolam did not unblind the observers. Parents and nurses judged the procedure to be more comfortable with midazolam, but the children rated the discomfort of the procedure similar in the two groups. Anxiety was significantly reduced by midazolam. There was nasal discomfort in 43% of the midazolam group. The authors concluded that midazolam intranasal spray effectively reduces anxiety, but that its use may be limited by nasal discomfort.

Drug–Drug Interactions

Antifungal azole derivatives

The pharmacokinetics and pharmacodynamics of midazolam are significantly affected by antifungal azoles. The effects of fluconazole (400 mg loading dose followed by 200 mg/day) on the kinetics of midazolam have been studied in 10 mechanically ventilated adults receiving a stable infusion of midazolam (41). Concentrations of midazolam were increased up to fourfold after the start of fluconazole therapy; these changes were most marked in patients with renal insufficiency. During the study, the ratio of α-hydroxymidazolam to midazolam progressively fell. The authors concluded that in ICU patients receiving fluconazole, reduction of the dose of midazolam should be considered if the degree of sedation is increasing.

In a study of the effects of itraconazole 200 mg/day and rifampicin 600 mg/day on the pharmacokinetics and pharmacodynamics of oral midazolam 7.5–15 mg during and 4 days after the end of the treatment, switching from inhibition to induction of metabolism caused an up to 400-fold change in the AUC of oral midazolam (42).

In an in vitro study of midazolam biotransformation using human liver microsomes, midazolam metabolism was competitively inhibited by the antifungal azoles ketoconazole, itraconazole, and fluconazole, and the antidepressant fluoxetine and its metabolite norfluoxetine (43). The degree of inhibition was consistent with the inhibition reported in pharmacokinetic studies, and suggests that in vitro assay is useful for predicting significant interactions.

Diltiazem

Diltiazem caused a 43% mean increase in the half-life of midazolam in 30 patients who underwent coronary artery bypass grafting (44). Similar effects were observed with alfentanil. The proposed mechanism was diltiazem-induced inhibition of benzodiazepine metabolism by CYP3A. Patients taking diltiazem had delayed early postoperative recovery as a result.

Drugs that influence CYP3A

Midazolam is selectively metabolized by CYP3A4, with which several drugs interact, influencing its pharmacokinetics and pharmacodynamics.

Itraconazole, an inhibitor of CYP3A, and rifampicin, an inducer of CYP3A, altered the pharmacokinetics and pharmacodynamics of oral midazolam in nine healthy volunteers (42). The half-life was prolonged from 2.7 to 7.6 hours by itraconazole and reduced to 1.0 hour by rifampicin. These effects were still present, although less marked, at 4 days after withdrawal of itraconazole and rifampicin. Similarly, after acute administration, the period of drowsiness was increased from 76 to 201 minutes with itraconazole and fell to 35 minutes with rifampicin; the effects were again less marked 4 days after withdrawal.

The protease inhibitor saquinavir, propofol, and fluconazole (41,45,46) increased the systemic availability and peak plasma concentrations and prolonged the half-life of midazolam, thus increasing its sedative effects. The dosage of midazolam should be reduced in patients taking these drugs.

Grapefruit juice reduced the metabolism of midazolam; prolonged sedation can be expected in some circumstances (47).

Chronic administration of glucocorticoids, which induce CYP3A4, reduces the sedative effect of midazolam by increasing its clearance; higher doses are therefore required for sedation (48).

Fentanyl

Several adverse effects have been reported with the combined use of fentanyl and midazolam, including chest wall rigidity, making ventilation with a bag and mask impossible (SEDA-16, 79). In neonates, hypotension can occur (SEDA-16, 80), and respiratory arrest in a child and sudden cardiac arrest have been reported (SEDA-16, 80). However, in one study there were no cardiac electrophysiological effects of midazolam combined with fentanyl in subjects undergoing cardiac electrophysiological studies (SEDA-18, 80).

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Glucocorticoids

Chronic administration of glucocorticoids, which induce CYP3A4, reduces the sedative effect of midazolam by increasing its clearance; higher doses are therefore required for sedation (48).

Grapefruit juice

Grapefruit juice reduced the metabolism of midazolam; prolonged sedation can be expected in some circumstances (47).

Halothane

Midazolam produced marked reduction of the MAC of halothane in humans at lower serum concentrations than required to cause sleep (49).

Isoflurane

The effects of the combination of midazolam and isoflurane on memory were studied in a randomized, double-blind study in 28 volunteers (50). Midazolam 0.03 mg/kg or 0.06 mg/kg combined with isoflurane 0.2% almost completely abolished explicit and implicit memory, but there were more variable effects on the level of sedation. The duration of the deficit averaged 45 minutes. The study was remarkable for the very low doses required to abolish memory, owing to synergy of the combination of midazolam and isoflurane and abolition of memory at subhypnotic doses with this combination. However, the subjects did not undergo surgery, so caution must be exercised in extrapolating the result to surgical patients, because painful stimuli increase the dosage required to abolish memory.

Macrolides

Interactions of macrolide antibiotics with midazolam are clinically important. Increases in serum concentration, AUC, and half-life, and a reduction in clearance have been documented (51). These changes can result in clinical effects, such as prolonged psychomotor impairment, amnesia, or loss of consciousness (52).

Erythromycin potentiates the effects of oral midazolam (SEDA-17, 125). Either midazolam should be avoided in patients taking erythromycin or the dose should be reduced by 50–75% (53,54).

Nitrous oxide

The combination of midazolam with nitrous oxide produced retrograde amnesia in 21 women undergoing elective cesarean section (55). All had spinal anesthesia. After delivery the patients received intravenous midazolam, average dose 94 μg/kg, and inhaled nitrous oxide 50%. At the end of surgery, flumazenil was given in 0.1 mg increments until the patient awoke. Another nine women were given only nitrous oxide inhalation after delivery. Of the women who received midazolam and nitrous oxide, 33% could not recall their baby's face, while all of the women not given midazolam could. The results suggest that midazolam plus nitrous oxide can produce retrograde amnesia not reversed by flumazenil.

Pethidine

Rectal pethidine is not advised in children, owing to enormous variability in systemic availability (SEDA-18, 82). When used for sedation in children undergoing esophagogastroduodenoscopy, hypoxia with dysrhythmias was more likely to occur with a combination of pethidine and diazepam than with pethidine and midazolam (SEDA-18, 81).

Rifampicin

In a study of the effects of itraconazole 200 mg/day and rifampicin 600 mg/day on the pharmacokinetics and pharmacodynamics of oral midazolam 7.5–15 mg during and 4 days after the end of the treatment, switching from inhibition to induction of metabolism caused an up to 400-fold change in the AUC of oral midazolam (42).

Saquinavir

Saquinavir substantially potentiates the effects of midazolam by raising its blood concentrations, and this suggests that a parallel interaction could occur with other protease inhibitors (and no doubt certain other benzodiazepines) in similar combinations (46).

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Midecamycin

See also Macrolide antibiotics

General Information

The reported rates of adverse events among 1565 patients treated with midecamycin 900–1800 mg/day are similar to the rates with other macrolides (1). The adverse events profile is also similar, but precise data are not available. In 12 053 Japanese children under 15 years, the rate of adverse events was 0.54% (2). There were adverse events in 0.97% of very young children (under 1 year). These adverse events affected mainly the skin and the gastrointestinal tract. However, this very low rate of adverse events must be interpreted with caution, since lower dosages (21–40 mg/kg/day) were used than are typically prescribed (50 mg/kg/day) (1).

Some drug interactions can be caused by weak induction of cytochrome P450 by midecamycin (3).

Drug–Drug Interactions

Carbamazepine

The half-life of carbamazepine given as a single daily dose (13% increase) and the AUC were significantly affected (4), whereas the trough concentrations and mean AUCs in nine patients treated with carbamazepine 400, 600, or 1200 mg/day increased only minimally (5).

Ciclosporin

Midecamycin 1600 mg/day increased the steady-state concentration of ciclosporin two-fold (6).

Nicoumalone

Midecamycin did not significantly change the pharmacokinetics of acenocoumarol (nicoumalone) in six volunteers (1).

Theophylline

The pharmacokinetics of theophylline were not significantly affected by midecamycin (7).

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Midodrine

General Information

Midodrine is a prodrug, whose active metabolite is relatively selective for vascular postjunctional alpha$_1$-adrenoceptors and therefore increases peripheral resistance by arteriolar constriction, with some venoconstriction in capacitance vessels (1). It has minimal activity in the central nervous system, since it does not cross the blood–brain barrier. It can be given orally and has a systemic availability of over 90% by this route. The half-life of the active deglycinated metabolite is relatively short (2–3 hours). The dosage range is 2.5–10 mg tds, and is usually toward the upper end of this range.

Midodrine has been extensively tested in several of the orthostatic hypotension syndromes, including: neurogenic hypertension due to autonomic neuropathies (2,3); neurocardiogenic syncope (4–8); the controversial syndrome of orthostatic hypotension and tachycardia that may be associated with chronic fatigue (9,10); the hypotension seen during hemodialysis (11); and hypotension due to neuroleptic drugs (12).

Few of the above-mentioned studies have systematically addressed problems of safety and adverse effects, but on the whole the effects described are predictable from the adrenergic properties of the drug and are dose-related. The most common adverse effect, in up to 15% of patients, is piloerection, with or without paresthesia especially of the scalp and face, most commonly in the form of pruritus.

In a 4-week, double-blind, placebo-controlled study in 97 patients with orthostatic hypotension aged 22–86 years (mean age 61 years) midodrine 2.5, 5, or 10 mg was given three times a day for 4 weeks (5). Midodrine 10 mg significantly increased standing systolic blood pressure by

22 mmHg and improved the following symptoms of orthostatic hypotension compared to placebo: dizziness/light-headedness, weakness/fatigue, syncope, low energy, impaired ability to stand, and feelings of depression. The overall adverse effects were mainly mild to moderate. One or more adverse effects were reported by 22% of the placebo group compared with 27% of the midodrine-treated group. Scalp pruritus/tingling, which was reported by 10 of 74 (13.5%) of those given midodrine, was most frequent. Other reported adverse effects included supine hypertension (8%) and feelings of urinary urgency (4%).

Organs and Systems

Cardiovascular

Supine hypertension occurs in up to 3% of subjects, although it is not clear how the underlying pathology of the hypotension influences the likelihood of this reaction.

Nervous system

- A 33-year-old schizophrenic woman took midodrine 4 mg/day because of postural hypotension due to risperidone 6 mg/day (13). She developed an acute dystonic reaction, which recurred several times on rechallenge, and the dose of risperidone had to be halved to minimize the hypotension.

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Mifepristone

General Information

Mifepristone (RU-486) has become best known as an abortifacient. It is a potent antagonist at progesterone receptors and glucocorticoid receptors. The abortifacient effect is thought to be primarily due to blockade of endometrial progesterone receptors, but mifepristone also impedes the production of human chorionic gonadotropin and progesterone in the placenta. When given in a single dose of 10 mg/kg by mouth to induce menses, heavy bleeding was reported in some cases (1).

Whatever the adverse effects of mifepristone, the risks have to be looked at realistically and compared with those of the alternatives available to a particular woman in particular circumstances. Particularly in rural areas in developing countries, the risks of surgical and non-professional abortion are high, whereas, as has been shown in a study in rural India, a regimen of mifepristone plus misoprostol can be used as effectively and safely, through family planning clinics and country hospitals, as in a European environment (2).

Observational studies

The effective oral doses of mifepristone are 100–600 mg, and at any dose the bulk of recipients abort. Of 150 healthy women who received the higher dose, 131 attained a complete abortion. Three women reported bleeding for more than 2 weeks after abortion; 16 women had a reduced hemoglobin concentration of under 11 g/dl, justifying iron therapy. Other adverse effects were uterine contractions and pelvic pain ($n = 4$), transient asthenia ($n = 3$), and nausea ($n = 2$) (3). These findings seem to be typical, even though dosage schemes have varied; as little as 100 mg orally has been used successfully with similar adverse effects (SED-12, 1037) (4).

Placebo-controlled studies

In a double-blind, randomized, controlled trial, 896 healthy women requesting a medical abortion (57–63 days gestation, mean age 25 years) were randomized to a single oral dose of mifepristone 200 mg or 600 mg, both followed in 48 hours by gemeprost 1 mg vaginally (5). The complete abortion rates were similar with the lower and higher doses of mifepristone (92 versus 92%). The

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incidences of adverse effects were similar, with the exception of nausea at 1 week, which was less frequent in the low-dose group (3.6 versus 7.6%).

Organs and Systems

Electrolyte balance

Severe hypokalemia has been attributed to long-term mifepristone (6).

- An extremely ill 51-year-old man with Cushing's syndrome, due to an ACTH-secreting pituitary macroadenoma, which had failed to respond to conventional surgical, medical, and radiotherapeutic approaches, responded dramatically in the short-term and long-term to high-dose mifepristone (up to 25 mg/kg/day) for 18 months. However, she developed severe hypokalemia, attributed to excessive cortisol activation of mineralocorticoid receptors; it responded to spironolactone.

This case shows the potential need for concomitant mineralocorticoid receptor blockade when mifepristone is used to treat Cushing's syndrome, since mineralocorticoid concentrations can rise markedly, reflecting corticotropin disinhibition.

Reproductive system

Long-term mifepristone is primarily used as a means of treating uterine myomas, endometriosis (25–100 mg/day), and possibly inoperable meningiomas (200 mg/day) or inoperable Cushing's syndrome. While it is primarily regarded as an antiprogestogen, some of these uses reflect its antiglucocorticoid and antiproliferative effects. However, there are also data to suggest that, acting as an antiprogestogen, mifepristone can promote an unopposed estrogen milieu, and can thus have a proliferative effect on the endometrium.

- An adolescent girl with Cushingoid features and osteoporosis took mifepristone 400 mg/day for its antiglucocorticoid effect in an attempt to prevent further bone loss (7). Her striae, weight gain, and buffalo hump markedly improved, and further bone loss was halted. However, with each of the two 6-month courses of mifepristone (9 months apart) she developed massive simple endometrial hyperplasia and a markedly enlarged uterus. This reverted to normal after withdrawal of mifepristone.

The authors suggested that interval pelvic imaging may be advisable in women who take long-term mifepristone.

Drug Administration

Drug dosage regimens

There has sometimes been reluctance to use higher doses of mifepristone, because of a supposedly greater risk of severe adverse effects. However, in a randomized comparison of a single oral dose of mifepristone (either 200 mg or 600 mg) followed 48 hours later by oral misoprostol 400 μg the two regimens produced identical results as regards the induction of abortion and the incidence of adverse effects (8).

The optimal dose of mifepristone to secure an abortion without excessive adverse effects is not known. In a study in nearly 900 women there was no appreciable difference between oral doses of 200 or 600 mg, followed after 48 hours by gemeprost 1 mg vaginally (5). The similarity of adverse reactions with the lower and higher doses of mifepristone has been confirmed by others (9). However, in another study mifepristone 0.5 mg, which has sometimes been recommended on supposed safety grounds, was not sufficient to induce abortion (10). The frequencies of various adverse effects of mifepristone in effective doses have emerged from various studies. In one study nausea, vomiting, or diarrhea in women using a standard regimen occurred in 68%, 36%, and 20% respectively (11); these risks are not considered to be problematic. The combination of oral mifepristone and vaginal misoprostol is also effective and safe, has few serious adverse effects, and is well accepted by women (12).

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Milrinone

See also Phosphodiesterase type III, selective inhibitors of

General Information

Milrinone is an inhibitor of phosphodiesterase type III. Although the long-term oral use of such inhibitors is associated with an increase in mortality (SEDA-17, 217), milrinone has been used intravenously in patients with heart failure, both for short-term and longer-term therapy (SEDA-21, 196) (SEDA-22, 203) (SEDA-23, 109). It has been suggested to be particularly useful in tiding patients over while they are waiting for definitive treatment.

- A 48-year-old man with an inflammatory aneurysm of the ascending aorta and severe heart failure due to massive aortic regurgitation was given a continuous intravenous infusion of milrinone 0.5 micrograms/kg/minute (1). His pulmonary arterial pressure fell and his symptoms improved over 7 weeks while he was taking corticosteroids. The diseased tissue was successfully replaced at operation and the milrinone was tapered uneventfully.

The authors suggested that continuous milrinone infusion may be suitable for patients with surgically correctable inflammatory cardiovascular diseases complicating severe heart failure in whom maintenance of optimal hemodynamics is necessary for several weeks before operation.

The disappointing results with positive inotropic drugs in treating acute and chronic heart failure may be due to the fact that they increase both systolic and diastolic calcium concentrations in the myocardium (2).

Observational studies

There has been a study of the use of intermittent intravenous milrinone in 10 patients with end-stage congestive heart failure (3). Some hemodynamic benefit was obtained, but this was an open uncontrolled study and firm conclusions are impossible. There was also some improvement in the quality of life. The drug was well tolerated and only one patient had an increase in dysrhythmias (an increased frequency of ventricular extra beats).

On the premise that phosphodiesterase inhibitors also inhibit the production of cytokines, milrinone has been used in the treatment of nine patients with the systemic inflammatory response syndrome and compared with seven patients with congestive heart failure (4). In both groups milrinone significantly altered cardiac index, pulmonary capillary wedge pressure, and left ventricular stroke work index. In the patients with cardiac failure it also reduced systemic vascular resistance index, and the dose of adrenaline had to be increased substantially during milrinone infusion to counteract vasodilatation.

Placebo-controlled studies

OPTIME-CHF (5) was a randomized, placebo-controlled study in which 951 patients (mean age 65 years; 92% with baseline NYHA class III or IV; mean left ventricular ejection fraction 23%) with acute exacerbations of chronic heart failure in 78 community and tertiary care hospitals in the USA were randomly assigned to a 48-hour infusion of either milrinone (0.5 micrograms/kg/minute initially for 24 hours) or saline (6). The median number of days in hospital for cardiovascular causes within 60 days after randomization did not differ significantly between patients given milrinone (6 days) or placebo (7 days). Sustained hypotension requiring intervention (11 versus 3.2%) and new atrial dysrhythmias (4.6 versus 1.5%) were more common in the patients who received milrinone. There was no difference in hospital mortality (3.8 versus 2.3%), 60-day mortality (10 versus 8.9%), or the composite incidence of death or readmission (35 versus 35%). The authors concluded that these results do not support the routine use of intravenous milrinone as an adjunct to standard therapy in patients with an exacerbation of chronic heart failure.

Comparative studies

In a randomized, open, parallel-group study of the hemodynamic effects of milrinone and glyceryl trinitrate in 119 patients with advanced decompensated heart failure, milrinone was significantly more effective than glyceryl trinitrate (7). Adverse effects caused the withdrawal of milrinone in three of the 58 patients who took it; one had ventricular extra beats, one had renal insufficiency, and one had hypokalemia. Headache was the most common adverse effect in both groups, but was less common in those who took milrinone (12 versus 29%).

In a randomized, open study of milrinone and dobutamine in 120 patients with low cardiac output after cardiac surgery, the two drugs were roughly comparable in efficacy (8). Adverse events were more frequent with dobutamine (77%) than with milrinone (58%). With milrinone cardiovascular adverse events were the most common, including hypertension (13%), hypotension (20%), bradycardia (13%), new atrial fibrillation (5%), and tachycardia (8%). Other adverse events included hemorrhage and oliguria. Adverse events required withdrawal from the study in 20 patients who took milrinone.

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Organs and Systems

Cardiovascular

The main limitations of the short-term use of milrinone is the risk of hypotension and ventricular dysrhythmias (9–12) and sudden death has occurred (10). Acute exacerbation of chronic heart failure has also been reported (13).

In a retrospective view of 63 patients who received intravenous milrinone for more than 24 hours for advanced cardiac failure, the mean dose was 0.43 microgram/kg/minute and the mean duration of therapy 12 (range 1–70) days (14). After 24 hours of therapy there was significant improvement in pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac index. Because of the nature of the study, which was not placebo-controlled, it is impossible to be sure what events could have been attributed to the milrinone. However, the authors reported five cases of asymptomatic, nonsustained ventricular tachycardia, six of symptomatic ventricular tachycardia, and three deaths, one in ventricular tachycardia and two in heart failure. There was no difference in the incidence of these adverse events in patients who received milrinone for more than 7 days compared with the others.

Milrinone can cause tachycardia, partly because of its vasodilatory effects and partly perhaps by a direct effect on the heart.

- A 74-year-old man had a tachycardia of 145/minute during infusion of milrinone after an operation for repair of an abdominal aortic aneurysm (15). The tachycardia was controlled by esmolol on one occasion and more impressively by metoprolol on a second occasion. However, the hemodynamic effects of milrinone were not altered by beta-blockade.

Presumably the beneficial effects of beta-blockade in this case were non-specific, since milrinone does not affect beta-adrenoceptors.

Of 19 children (12 infants and 7 children aged 1–13 years) who were given either two boluses of 25 micrograms/kg followed by an infusion of 0.5 microgram/kg/minute, or a bolus of 50 micrograms/kg followed by a bolus of 25 micrograms/kg followed by an infusion of 0.75 microgram/kg/minute, two infants developed junctional ectopic tachycardia during infusion of milrinone.

Vasopressin has been used to treat hypotension due to milrinone. In seven patients with congestive heart failure who developed hypotension (systolic arterial pressure below 90 mmHg), vasopressin 0.03–0.07 units/minute increased the systolic arterial pressure to 127 mmHg (16). This effect was due to peripheral vasoconstriction, since the systemic vascular resistance increased from 1112 to 1460 dyne.s/cm^5 with no change in cardiac index. Urine output also improved significantly. In three patients in whom milrinone caused hypotension, vasopressin (0.03–0.07 U/minute) increased the systolic arterial pressure from 90 to 130 mmHg and reduced the dosages of catecholamines that were being used (17). The authors hypothesized that vasopressin may have inhibited the milrinone-induced accumulation of cyclic AMP in vascular smooth muscle.

Fluid balance

In one series fluid retention was very common with milrinone (10).

Hematologic

Falls in platelet counts have been seen with milrinone (18) and it can cause thrombocytopenia (SEDA-20, 174). Of 19 children (12 infants and 7 children aged 1–13 years) who were given either two boluses of 25 micrograms/kg followed by an infusion of 0.5 microgram/kg/minute, or a bolus of 50 micrograms/kg followed by a bolus of 25 micrograms/kg followed by an infusion of 0.75 microgram/kg/minute, 11 developed thrombocytopenia, defined as a platelet count below 100×10^9/l, during milrinone infusion (19). Of these, two infants required a platelet transfusion. By comparison, in 128 patients who did not receive milrinone the incidence of thrombocytopenia was 25%, significantly lower than in those given milrinone. The occurrence of thrombocytopenia increased with increasing duration of infusion.

Susceptibility Factors

Renal disease

In six patients with severe congestive heart failure and renal insufficiency being treated with continuous venovenous hemofiltration, the pharmacokinetics of milrinone 0.25 mg/kg/minute by continuous intravenous infusion were different from those that have been previously reported in patients with normal renal function, with a prolonged half-life and a raised mean steady-state concentration, suggestive of reduced clearance (20). The half-life of milrinone was 20 hours, compared with reported half-lives of around 3 hours.

Drug Administration

Drug administration route

Inhaled milrinone has been used to treat patients with pulmonary hypertension after cardiac surgery (21). Milrinone produced a significant dose-related reduction in pulmonary vascular resistance in nine patients. There were no systemic adverse effects.

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Miltefosine

General Information

Miltefosine is an alkylphospholipid that affects cell-signaling pathways and membrane synthesis; it was originally developed as an oral antineoplastic agent but is now licensed for use in visceral leishmaniasis in India (1,2).

Observational studies

In an open, multicenter trial in 120 patients, aged 12–50 years, who took 50, 100, or 150 mg/day of miltefosine for 4 or 6 weeks, there was an initial parasitological cure in all cases (3). Six patients had clinical and parasitological relapses by 6 months after initial treatment. There was a 97% cure rate with miltefosine 100 mg/day. Gastrointestinal adverse effects were frequent (in 62%) but mild to moderate in intensity, and no patient discontinued therapy as a result. In one patient, treatment was withdrawn because of raised aspartate transaminase activity, and in 12 others the aspartate transaminase activity increased to 100–150 U/l during treatment. In one patient, treatment was withdrawn because of a raised creatinine concentration.

Comparative studies

Miltefosine has been compared with the most effective standard treatment, amphotericin, in a randomized, open comparison in India, in which 299 patients, aged 12 years or over, received oral miltefosine (50 or 100 mg) and 99 patients received intravenous amphotericin deoxycholate (1 mg/kg every other day to a total of 15 injections) (4). Vomiting and diarrhea were more common with miltefosine. However, the effects were mild in almost all cases, and only 3–4% of patients needed antiemetic drugs in both groups. One patient who took miltefosine withdrew because of gastrointestinal intolerance and one developed Stevens–Johnson syndrome.

Second-Generation Effects

Fertility

Miltefosine caused infertility in male rats, but not in 211 men (4).

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Minocycline

See also Tetracyclines

General Information

Minocycline, in common with doxycycline, is more lipophilic than other tetracyclines. It is well absorbed after oral administration. Its half-life is 16–18 hours. Its higher affinity for fatty tissues improves its effectiveness and changes its adverse effects profile. Local gastrointestinal irritation and disturbance of the intestinal bacterial flora occur less often than with the more hydrophilic drugs, which have to be given in higher oral doses for sufficient absorption.

Nevertheless, its toxic effects are similar to those of other tetracyclines and arise from accumulation in fatty tissues. Accumulation in a third compartment and the resulting long half-life may contribute to an increased incidence of various toxic adverse effects during long-term treatment, even if lower daily doses are used. This seems also to be the case for pigmentation disorders and possibly for neurological disturbances (1).

Minocycline is predominantly eliminated by the liver and biliary tract (70–90%). Therefore, no change in dose is needed in patients with impaired renal function. However, it should be considered that hepatic elimination of doxycycline might be accelerated by co-administration of agents that induce hepatic enzymes.

Adverse effects of minocycline are reported far more often than adverse effects of other tetracycline derivatives. Whatever the mechanisms underlying this larger number of reports might be, they continue to appear. With increasing use of minocycline in acne and other conditions, adverse reactions may become increasingly common; early recognition is important to prevent further deterioration, to hasten recovery, and to avoid invasive investigations and treatment (2). The authors of this review recommended that safer alternatives be considered in the treatment of acne.

Organs and Systems

Respiratory

Minocycline and nicotinamide therapy for bullous pemphigoid have been associated with severe pneumonitis (3).

Nervous system

The syndrome of pseudotumor cerebri consists of symptoms and signs of raised intracranial pressure in the absence of neuroimaging or cerebrospinal fluid abnormalities. Most cases are idiopathic, but several drugs have been implicated as causative or contributory.

The first description of minocycline-related pseudotumor cerebri was published in 1978 (4). Further data have been published concerning 12 patients who developed pseudotumor cerebri after taking standard doses of minocycline for acne vulgaris (5). Nine developed symptoms within 8 weeks of starting minocycline therapy. Minocycline was withdrawn, and none of the patients developed recurrences for at least 1 year afterwards. However, three patients had substantial residual visual field loss.

It seems reasonable to assume that the mechanisms may be similar to that postulated for tetracyclines, which reduce cerebrospinal fluid absorption, possibly by an effect on cyclic adenosine monophosphate at the arachnoid villi (6). Minocycline crosses the blood–brain barrier more effectively than other tetracyclines, because of its greater lipid solubility. Therefore, a physician who prescribes minocycline should keep his eye on the patient's eyes.

Mouth and teeth

Staining of permanent teeth by tetracyclines takes place during tooth development by well-documented mechanisms. Tetracycline forms a complex with calcium orthophosphate during calcification, which then darkens with exposure to light. With minocycline, however, the staining occurs after eruption in previously normal-colored, fully mineralized adult teeth. For example, adult-onset tooth discoloration coincident with minocycline administration occurred in four of 72 patients (7).

There are at least four theories about the mechanisms of this adverse effect.

1. That minocycline attaches to the acquired pellicle glycoproteins (the "extrinsic theory") (8). This in turn etches the enamel, and cycles of demineralization and remineralization occur. It oxidizes on exposure to air or as a result of bacterial activity, and the final product is insoluble black quinine.
2. That minocycline, bound to plasma proteins, is deposited in collagen-rich tissues, such as pulp, teeth, and bones (the "intrinsic" theory). Minocycline is then slowly oxidized over time with exposure to light (9,10).
3. That a breakdown product of minocycline chelates with iron to form insoluble complexes (7,11).
4. That minocycline is deposited in dentine during dentinogenesis, accelerating or changing the process (12).

Whatever the mechanism(s) might be, staining of adult dentition occurs in 3–6% of patients who take long-term minocycline 100 mg/day (8,13). The onset of discoloration can occur at any time from 1 month to many years after the start of treatment (11,13).

The importance of avoiding permanent staining of the teeth cannot be over-emphasized, as many patients with acne are already prone to negative psychological effects. Minocycline should therefore be prescribed only with great care.

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Liver

Hepatotoxicity associated with minocycline has been reviewed, covering data reported to the WHO Centre for International Drug Monitoring, which had recorded 8025 reactions to minocycline, of which 493 were reactions involving the liver (14). The authors stated that fields available to define indications for use, time of treatment, and outcome subsequent to the reactions were seldom completed. They therefore concentrated on more complete records in patients known to have used minocycline for acne. Patients taking minocycline for reasons other than acne or those given intravenous minocycline were excluded. Altogether, 65 patients were then commented on; 58% were women and 94% were aged under 40 years. Briefly, two types of hepatic reactions were recognized: autoimmune hepatitis associated with lupus-like symptoms occurring after 1 year or more of exposure to minocycline, and hypersensitivity reactions associated with eosinophilia and exfoliative dermatitis occurring within 35 days of therapy.

The authors stated that they did not have any clear information about the absolute and relative risks of hepatitis, whether these were hypersensitivity reactions or autoimmune hepatitis, in patients taking minocycline for varying lengths of time, and that a study of the comparative rates of hepatitis in people exposed to minocycline compared with those not exposed is required. In the meantime, new reports of severe hepatic reactions to minocycline continue to appear (15–17), including one case of autoimmune hepatitis requiring liver transplantation in a woman who had used minocycline 50–200 mg/day for 3 years (17). Another case of liver transplantation has previously been reported in patients with hepatic failure after minocycline therapy (18).

Some patients consider drugs to treat a common dermatological disease such as acne vulgaris to be cosmetics rather than medications. Safer alternatives than minocycline should be considered in the treatment of acne.

Pancreas

Minocycline has been associated with acute pancreatitis (19).

Skin

Long term minocycline often results in pigmentation of skin, nails, bones, thyroid, mouth, and eyes. The bones of the oral cavity are probably the most frequently affected sites of pigmentation. On the skin, the blue-black pigmentation develops most frequently on the shins, ankles, and arms. Other patterns include pigmentation that either is generalized and symmetrical or develops at sites of inflammation. The pigmentation is often permanent when sites other than the skin and oral mucosa are involved (20,21). The pigment is a product of an oxidation reaction. In an experimental rat study, pigmentation of the thyroid gland was prevented by ascorbic acid (9). Laser treatment was successfully used in two cases (22,23).

Fixed drug eruptions are characterized by solitary or multiple, round or oval, erythematous patches of variable size; some of them develop into bullae or superficial erosions. Characteristically they appear in the same site each time the responsible drug is given, usually 30 minutes to 8 hours after administration, and with itching or burning as the first symptoms. Over a period of 1–2 weeks they fade, often with crusting and scaling, followed by hyperpigmentation, which can persist for months.

Antimicrobial drugs, especially co-trimoxazole, ampicillin, and tetracyclines, can cause fixed drug eruptions (24), and cases have been attributed to minocycline (25). There is usually no cross-reactivity (26). However, a case of fixed drug eruption has been reported after minocycline in a patient with a previous eruption due to doxycycline (27).

- A 48-year-old man with urethritis took doxycycline 100 mg bd and developed a fixed drug eruption on the glans penis. Doxycycline was withdrawn and the eruption healed with symptomatic treatment. Eight months later he took minocycline 100 mg/day for rosacea. A few hours after having taken the first tablet he became aware of oval erythematous patches on the glans, prepuce, and scrotum. The patches rapidly became violaceous and developed into superficial erosions. He stopped taking minocycline and the lesions faded.

According to the authors, this is the first report of a fixed drug eruption after minocycline in a patient with a previous eruption due to doxycycline. They advised clinicians to be aware of this potential cross-reactivity when prescribing these two drugs.

A generalized pustular eruption was reported in a patient with acne treated with minocycline (28). Skin prick tests with minocycline were positive at 48 hours.

Immunologic

Immunoallergic reactions have been reported with minocycline and include lupus-like syndrome, autoimmune hepatitis, eosinophilic pneumonia, hypersensitivity syndrome, a serum sickness-like illness (29), and Sweet's syndrome (SEDA-21, 262) (SEDA-22, 271). Over 60 minocycline-induced cases of lupus-like syndrome and 24 cases of minocycline-induced autoimmune hepatitis were found in a review of the literature (30). In 13 patients, both disorders co-existed. These patients had symmetrical polyarthralgia/polyarthritis, raised liver enzymes, and positive antinuclear antibodies; they were also generally antihistone-negative, and only two patients had p-ANCA antibodies. Minocycline-related lupus can also occur in adolescents (31).

Lupus-like syndrome

Drug-induced lupus is a well-known phenomenon, although the mechanisms are unclear. The diagnostic features should include no prior history of systemic lupus erythematosus (SLE) before the start of treatment, at least one clinical feature of SLE, a positive antinuclear antibody during sustained drug therapy, and dramatic symptomatic improvement after drug withdrawal. Since 1970, at least 49 drugs have been reported to be associated with drug-related lupus (32), of which hydralazine and procainamide have been claimed to the most commonly implicated. However, new reports on minocycline-induced lupus continue to appear (33–35) and it is possible that minocycline is now the most common cause.

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In a retrospective nested case-control study in 27 688 young patients with acne, 7136 had used minocycline, of whom 29 had the lupus-like syndrome (36). Minocycline was associated with an 8.5-fold risk of the lupus-like syndrome. The effect was greater in longer-term users, but the absolute risk of developing lupus-like syndrome seemed to be relatively low.

Minocycline-induced lupus usually occurs some months, or even years, after the start of therapy, and it usually resolves when the drug is withdrawn. The diagnosis can easily be overlooked, especially in patients with rheumatoid arthritis (37). It would always be wise to follow the recommendation that a patient's antinuclear antibody be checked before starting minocycline and when drug-induced lupus is suspected.

In a retrospective review of drug safety databases, minocycline was the only tetracycline derivative that caused drug-induced lupus (SEDA-22, 268) (38). The authors proposed that the propensity of minocycline to cause drug-induced lupus may be due to the presence of a functional group that is easily oxidized to a reactive metabolite. However, the chemically modified tetracycline CMT-3, which has also reportedly caused a lupus-like syndrome (39), lacks this group, so another theory is needed.

- A 16-year-old girl, who had taken minocycline for acne for more than 2 years, developed a severe cough with paroxysms (40). She had also a recent history of joint pain with swelling and stiffness, fever, general weakness, and weight loss of 9 kg. She had been treated as an outpatient for presumed pneumonia with multiple antibiotics, but developed progressive dyspnea. Pulmonary lupus was suspected, and minocycline was withdrawn. She was treated with an initial 3-day course of intravenous methylprednisolone 20 mg tds, and then prednisone 40 mg bd for 2 weeks. She improved very rapidly, and the prednisone was gradually reduced over 7 weeks.

According to the authors, the patient fulfilled all the criteria for a diagnosis of drug-induced lupus-like syndrome, that is no history of lupus erythematosus before minocycline therapy, the presence of antinuclear antibodies, at least one clinical feature of lupus erythematosus, and prompt recovery after withdrawal of minocycline. She also had positive antihistone antibodies, compatible with drug-induced lupus-like syndrome.

- A 54-year-old woman with a 2-week history of low-grade fever, dry cough, and dyspnea was given levofloxacin for a presumed community-acquired pneumonia (41). Five days later she developed severe respiratory failure and was mechanically ventilated and given antibiotics (imipenem and clarithromycin). Microbiological examination of tracheobronchial aspirates was negative for pathogenic organisms, as were serological tests for common agents of atypical pneumonia. She progressively improved and was taken off the ventilator after 6 days and discharged about 10 days later, but 14 days later was readmitted with rapidly progressive pulmonary failure requiring mechanical ventilation. It then transpired that 2 weeks before the first episode of respiratory failure, she had started to take oral minocycline for acne vulgaris and had started to take it again 24 hours before the second episode. The minocycline was stopped and she was given intravenous methylprednisolone. She improved rapidly, and for 12 months after minocycline withdrawal she remained free of respiratory symptoms.

It is a good rule of thumb that patients who develop minocycline-induced lupus should never be rechallenged with minocycline, as symptoms tend to recur (34,42,43). If minocycline is used to treat rheumatoid arthritis, the patient should be followed very carefully, as worsening arthritis may be erroneously attributed to the underlying disease. It should also be emphasized that in the search for a cause of joint pains, minocycline should always be considered (44).

Autoimmune hepatitis

In a review of relevant American and European literature, hepatitis and drug-induced lupus were reported in 66 cases after minocycline therapy, mostly after long-term treatment for acne (45).

- Minocycline-induced hepatitis with antinuclear, antimitochondrial, and antismooth muscle antibodies has been reported in a 19-year-old black West Indian woman who had been treated for acne for two years with oral minocycline (50 mg/day) and topical benzoyl peroxide (5%) (46).
- Seven patients (17–22 years old) developed symptoms of arthralgia and arthritis after having taken minocycline 50–100 mg bd for 6–36 months for acne vulgaris (47). Increased titers of perinuclear ANCA were detected in all seven, five had fluorescent antinuclear antibodies, two had antihistone autoantibodies, and one had anticardiolipin antibodies. Symptoms resolved in five patients on withdrawal; the other two were treated with corticosteroids and also achieved remissions.

Autoimmune hepatitis has also been reported (48).

- Three adolescents taking therapeutic doses of minocycline for 12–20 months met the 1993 International Autoimmune Hepatitis Group criteria for autoimmune hepatitis. All had hypogammaglobulinemia and positive antinuclear antibody and antismooth muscle antibody titers. Two underwent liver biopsy that showed severe chronic lymphoplasmocytic inflammation, necrosis, and fibrosis. All other causes of liver disease were excluded. One patient had resolution of symptoms after withdrawal of the drug, while two required immunosuppressive therapy.

Necrotizing vasculitis of the skin and uterine cervix has been reported in a patient taking minocycline (49).

- A 35-year-old woman developed an asymptomatic, erythematous, subcutaneous nodule on the anterior aspect of her left leg. She had been taking minocycline 50–100 mg bd for acne for 2 years, and her only other medication was an oral contraceptive. A presumptive diagnosis of erythema nodosum was made. The nodule was injected twice with triamcinolone acetonide and she was given indometacin 50 mg tds but continued to take minocycline. Some weeks later, after a routine gynecological examination, pathological examination

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of a cervical biopsy showed necrotizing arteritis of the cervix. A biopsy of the pretibial nodule showed a necrotizing vasculitis with fibrinoid necrosis of the vessel walls and thrombosis. Her serum transaminase activities were increased, and an antinuclear antibody test was positive at 1:60 with a nucleolar pattern. Minocycline was withdrawn, and over the next 3 months her liver function tests normalized, the antinuclear antibody became negative, and the pretibial nodule and uterine cervix vasculitis resolved. There was no recurrence over the next 2 years.

Serum sickness

A serum sickness-like reaction clinically similar to classical serum sickness can result from the administration of a number of non-protein drugs, such as tetracyclines, penicillins, cephalosporins (50). Minocycline has been reported to cause serum sickness (29,51).

- A 16-year-old girl taking minocycline for acne developed typical symptoms of serum sickness after 14 days. Minocycline was withdrawn and her symptoms resolved after a short course of systemic steroids for 5 days.
- An 18-year-old woman developed typical symptoms of serum sickness after taking minocycline 50 mg/day for 10 days for acne. Her symptoms resolved gradually after minocycline was withdrawn.

The authors reviewed some other cases of serum sickness after the use of minocycline. They suggested that the syndrome is under-reported, either because of unawareness that it can be an adverse effect or lack of willingness of physicians to document the event.

Polyarteritis nodosa

Two cases of biopsy-proven cutaneous polyarteritis nodosa with positive perinuclear antineutrophilic cytoplasmic antibodies have been reported with long-term use of minocycline for acne vulgaris (50–100 mg/day for 44 months and 100 mg/day for 65 months) (52). In one of the cases, involvement was not restricted to medium-size vessels alone. In both cases the vasculitis disappeared after a short course of prednisone (40 mg/day) and withdrawal of minocycline. Rechallenge was not performed. P-ANCA is usually found in microscopic polyangiitis, a vasculitis of smaller arteries, and its significance in polyarteritis nodosa is not clear.

Susceptibility Factors

Renal disease

Minocycline is almost completely eliminated via the liver and the biliary tract and is therefore safe in patients with pre-existing renal insufficiency.

Drug Administration

Drug administration route

The use of minocycline as an agent for inducing chemical pleurodesis has been reported in only a few patients and there is little information regarding its adverse effects. In a retrospective study, 51 patients with primary spontaneous pneumothorax treated by video-assisted thoracoscopic surgery followed by instillation of minocycline hydrochloride 7 mg/kg into the pleural space through a thoracostomy tube were compared with 51 who underwent surgery only (53). Chest pain was a common complaint after minocycline pleurodesis, but the total doses of analgesics were comparable. The rate of prolonged air leaks was significantly lower after minocycline (7 versus 18%). Patients treated with minocycline had shorter periods of postoperative chest drainage and hospitalization. The ipsilateral recurrence rate was also significantly lower (2.9 versus 9.8%).

Drug–Drug Interactions

Phenothiazines

Black galactorrhea was described in a breastfeeding woman during treatment with minocycline and a phenothiazine (54).

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Minoxidil

General Information

Minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide) is a potent vasodilator effective in severe hypertension irrespective of the cause. Isolated case reports have been published of hair growth in areas of male pattern baldness in patients treated with oral minoxidil, therefore topical minoxidil has been used for the treatment of alopecia areata and alopecia androgenica, with some success.

The pattern of adverse vasodilator effects with minoxidil is similar to, but more severe than, that of hydralazine and fluid retention can be troublesome.

Topical minoxidil stimulates new hair growth and arrests loss of hair in androgenic alopecia. Minoxidil is poorly absorbed through the skin (less than 4%) (1), and plasma concentrations of minoxidil are far less than 10% of the mean minoxidil concentration present 2 hours after oral ingestion of 5 mg, the lowest dose for the treatment of hypertension (2). Its adverse effects after topical application are therefore usually limited to the application site on the scalp. They include irritant contact dermatitis, allergic contact dermatitis, and exacerbation of seborrheic dermatitis. These effects are seen in 5.7% of patients who use a 5% solution and in 1.9% of those who use a 2% formulation (3).

Therapeutic studies

The results with a 2% solution of minoxidil are variable, and experience has suggested that higher concentrations may be more effective. Topical twice-daily minoxidil 2% and 5% have therefore been compared for 48 weeks in a double-blind, randomized, placebo-controlled, multicenter trial in 393 men (aged 18–49 years) with androgenic alopecia (4). The higher concentration of minoxidil was significantly more effective than both the lower concentration and placebo in terms of change from baseline in non-vellus hair count, patient rating of scalp coverage and treatment benefit, and investigator rating of scalp coverage; the response to treatment occurred earlier with 5% minoxidil. However, there was more pruritus and local irritation with 5% minoxidil.

Organs and Systems

Cardiovascular

Minoxidil can cause pericardial effusion (5).

- A 52-year-old man with a history of chronic hypertension presented with worsening dyspnea and leg edema. He had been taking minoxidil for 10 years. The cardiac silhouette was markedly enlarged. Echocardiography and computed tomography showed a large pericardial effusion. Minoxidil was withdrawn and the effusion resolved within 1 month.

A hypertensive crisis occurred in one patient after withdrawal of topical minoxidil (SEDA-16, 158).

Skin

Local adverse effects of topical minoxidil (usually in an alcohol–propylene glycol base) include dryness, irritation, pruritus, contact allergy (SEDA-11, 139), and photocontact allergy (SEDA-11, 139).

Leukoderma has been reported in two men from India who used 2% minoxidil lotion for 2–3 months to treat baldness (6). The depigmentation was localized to the scalp. Other possibilities of leukoderma were ruled out, as was vitiligo. There was repigmentation of the leukodermic area within 3 months of minoxidil withdrawal in both cases.

Hair

A particular feature of minoxidil is excessive hair growth (7), which occurs in about 70% of patients who take oral minoxidil, usually within 2 months of the start of therapy. Severe hypertrichosis, unacceptable even to men, has complicated the otherwise successful antihypertensive treatment of six patients after renal transplantation, for which ciclosporin was also used. Since hypertrichosis has also been described with ciclosporin, there may be an additive pharmacodynamic interaction (8).

Topical minoxidil has been used to treat women with androgenic alopecia. Severe hypertrichosis of the face and the limbs occurred in three women after 2–3 months of treatment with 5% topical minoxidil (9). The hypertrichosis disappeared from the face and arms within 1–3 months of withdrawal and from the legs after 4–5 months.

Immunologic

A "polymyalgia syndrome," characterized by fatigue, anorexia, weight loss, and severe pain in the shoulders and the pelvic girdle, was attributed to minoxidil in four men (10).

In 11 patients allergic to topical minoxidil lotion, patch tests showed that four were positive to minoxidil itself (11). Propylene and butylene glycol are used as solvents for minoxidil in topical formulations. Nine of the 11 patients appeared to have positive patch tests to propylene glycol and one of the 11 reacted to its alternative butylene glycol.

- A 57-year-old man developed a pigmented contact dermatitis after using topical minoxidil 5% for 2 years (12). Patch tests were negative with the European standard series and with a textile and finishes series, but positive with minoxidil 5% on days 3 and 7. However, withdrawal of the minoxidil did not lead to improvement after 10 months.
- A 24-year-old woman with androgenic alopecia became sensitized to topical minoxidil after using minoxidil 4% with retinoic acid in a propylene glycol base (13). She subsequently also became sensitized to saw palmetto (*Serenoa repens*), a topical herbal extract commonly promoted for the treatment of hair loss.
- Allergic contact dermatitis occurred in a 54-year-old man who had used 1% minoxidil on the scalp for 8 months (14). He had positive patch tests to minoxidil in alcohol, but not to minoxidil in petrolatum, piperidine, pyrimidine, or diaminopyrimidine.

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The authors of the last report suggested that the whole structure of minoxidil is required for sensitization and that propylene glycol in the formulation of minoxidil that is used therapeutically increases the penetration of minoxidil into the skin, enhancing the risk of a reaction.

Long-Term Effects

Drug withdrawal

A hypertensive crisis occurred in one patient after withdrawal of topical minoxidil (SEDA-16, 158).

Second-Generation Effects

Teratogenicity

Caudal regression syndrome is a rare anomaly, a continuum of congenital malformations ranging from isolated sacral agenesis to absence of the lumbosacral spine and major visceral anomalies. While the exact cause of this syndrome is unclear, maternal diabetes, genetic factors, teratogens, and vascular anomalies that alter blood flow have been hypothesized to play a role. A case has been attributed to maternal minoxidil exposure (15).

A fetus had an extremely hypotrophic caudal body pole, aplasia of the lower spine, and complete renal agenesis diagnosed in the second trimester by ultrasound. The mother had used minoxidil solution to prevent hair loss for 4 years before and during gestation. She had also taken co-trimoxazole during the first trimester. She was not diabetic and had no history of familial genetic disorders.

Drug Administration

Drug administration route

Despite the poor transdermal absorption of minoxidil, in 7 out of 30 non-hypertensive patients treated with 3% minoxidil solution twice daily, there was a "significant" fall in blood pressure (16).

Some patients using minoxidil solution had increased hair growth outside the area of drug application (SEDA-18, 175), which suggests a systemic effect (17).

The sudden death of a patient using topical minoxidil (18) was probably not drug-related but due to cardiovascular disease and hypertension. Nevertheless, in patients who are known to be hypertensive and who are also receiving other antihypertensive medication extra caution is warranted when topical minoxidil is used (19).

Smoking intolerance possibly related to topical minoxidil has been observed rarely (20).

Drug overdose

In some countries, an extra-strength solution of minoxidil is available over the counter for hair regrowth treatment in men. Ingestion of a large dose in a suicide attempt has been reported (21).

- A 26-year-old woman took 60 ml of minoxidil solution 5% and 1 hour later developed hypotension (75/40 mmHg) and tachycardia (130/minute). She was alert and oriented and physical examination was unremarkable. She was given a saline infusion, oral activated charcoal, and sorbitol, and had worsening hypotension (40 mmHg systolic) and bradycardia (20/minute), developed chest pain and T wave inversion on the electrocardiogram, and lost consciousness. Atropine and dopamine restored a heart rate of 120/minute, but she remained hypotensive (54/36 mmHg). Her blood ethanol concentration was 5.64 mmol/l and other toxicological screening tests were negative. The addition of phenylephrine up to a dose of 200 μg/minute restored her systolic blood pressure to 90–100 mmHg.

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Mirtazapine

See also Antidepressants, second-generation

General Information

The antidepressant mirtazapine is pharmacologically similar to mianserin. It has a slightly weaker blocking action at α_1-adrenoceptors, and this is claimed to give it a dual mode of action, increasing the release of both noradrenaline and serotonin (1). It is claimed to have a more rapid onset of action than some SSRIs, but this may be due to its prominent sedative effect, which improves insomnia from the start of treatment.

Mirtazapine is extensively metabolized in the liver, mainly by CYP1A2, CYP2D6, and CYP3A4. With once-daily dosing, steady-state concentrations are reached after 4 days in adults and 6 days in elderly people.

In major depression, the efficacy of mirtazapine is comparable to that of amitriptyline, clomipramine, doxepin, fluoxetine, paroxetine, citalopram, and venlafaxine.

In placebo-controlled trials the most common adverse effects of mirtazapine were dry mouth (25%), drowsiness (23%), increased appetite (11%), and weight gain (10%) (SEDA 21, 13).

Organs and Systems

Psychological, psychiatric

Some patients appear to develop manic symptoms in response to some antidepressants but not to others. Psychosis was reportedly triggered by mirtazapine in a patient taking long-term levodopa (2) and in another patient hypomania occurred.

- A 45-year-old woman had a long history of dysthymia and depression. She had taken many antidepressants, including tricyclics, SSRIs, amfebutamone, and venlafaxine. She had no history of mania or hypomania. She took sertraline 250 mg/day, with only a transient response, and mirtazapine 15 mg/day was added. Within 4 days she developed clear symptoms of hypomania, with euphoric mood, mild grandiosity, pressure of speech, increased energy, and a reduced need for sleep. Mirtazapine was withdrawn and sertraline continued; within 3 days the hypomanic symptoms had remitted. The depressive disorder then re-emerged (3).

Unlike most other antidepressants, mirtazapine does not inhibit the reuptake of monoamines, but instead blocks inhibitory α_2-adrenoceptors. It is conceivable that this pharmacological mechanism led to hypomanic symptoms in this patient.

Hematologic

During clinical trials two of 2796 patients (0.08%) developed neutropenia, but both recovered after withdrawal. No other cases were detected in postmarketing surveillance of 13 500 patients in the Netherlands (SEDA-21, 14).

Liver

Mirtazapine has been associated with increases in liver enzymes (SEDA-21, 14).

Drug–Drug Interactions

Fluoxetine

In patients who do not respond to SSRI treatment, the addition of mirtazapine is an increasingly popular option. Mirtazapine is an α_2-adrenoceptor antagonist, so its acute pharmacological effects predominantly involve potentiation of noradrenergic function. This might be expected to enhance the serotonergic actions of SSRIs.

- A 48-year-old woman unresponsive to fluoxetine (20–40 mg/day for 8 weeks) was given additional mirtazapine (30 mg/day) (4). Over the next month her depression remitted, but after taking the combined treatment for 7 weeks she slept less, spent more, and was more sociable than usual. She was also argumentative and agitated. Mirtazapine and fluoxetine were withdrawn and valproate introduced as a mood stabilizer. Within 2 weeks her mood had settled but she subsequently became depressed again.

The manic episode here could have been due to mirtazapine alone or to the combination of fluoxetine and mirtazapine. The case also demonstrates the common clinical observation that when an antidepressant treatment has apparently caused mania, withdrawal of antidepressant therapy often results in re-emergence of depressive symptoms, even when mood stabilizer treatment has been introduced.

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Misoprostol

See also Prostaglandins

General Information

Misoprostol, an analogue of PGE_1, is licensed for use in the management of gastroduodenal ulceration. It is an effective myometrial stimulant of the pregnant uterus and is used for the induction of labor and as abortifacient, both alone and in combination with other substances (for example mifepristone). It provides an effective alternative to gemeprost, the most widely used prostaglandin pessaries in combination with mifepristone.

Vaginal misoprostol is more effective and better tolerated than oral misoprostol for induction of first and second trimester abortions after the administration of mifepristone (1,2). It is more effective than either gemeprost or sulprostone combined with mifepristone for induction of first trimester abortion, although uterine rupture has been reported (3).

Intramuscular methotrexate 50 mg/m^2 followed by intravaginal misoprostol was effective in the induction of first trimester abortion. Adverse events following the administration of misoprostol included nausea (12%), vomiting (8.1%), diarrhea (7.4%), and fevers/chills (3.4%) (4).

Observational studies

A single intravaginal dose of misoprostol 800 micrograms can obtain an abortion. The success rate has been assessed in 102 pregnant patients with amenorrhea for less than 42 weeks (5). After 1 day and 3 days of administration the abortion rates were 72 and 87% respectively. A second dose 7 days later increased the cumulative rate to 92%. The main complaints were pain (85%), nausea (21%), and headache (18%). Similar results were obtained in 2295 pregnant women (up to 56 days of gestation), who took a single oral dose of mifepristone (200 mg) and were randomized to self-administer misoprostol 800 micrograms/day at home for 1, 2, or 3 days (6). Complete abortion rates were 98, 98, and 96% among those who took misoprostol for 1, 2, and 3 days respectively. There were similar frequencies of adverse effects in all groups (cramping, nausea, fever/chills, dizziness, vomiting, headache, and diarrhea).

Misoprostol has been used to induce abortions in 150 adolescents (age range 12–17 years) at gestations of 63–84 days (7). They received vaginal misoprostol 800 micrograms/day to a maximum of three doses. Complete abortion occurred in 84%. Adverse effects were more frequent in these adolescents than in adult women, and included nausea (31%), vomiting (41%), diarrhea (48%), dizziness (19%), headache (17%), a subjective feeling of fever (26%), flushing (16%), and chills (49%).

The efficacy and tolerability of sublingual misoprostol has been evaluated in an uncontrolled trial in China in 50 women who requested medical abortions at up to 12 weeks of gestation (8). All received three doses of misoprostol 600 micrograms sublingually 3-hourly, and two more doses of 600 micrograms sublingually if an abortion did not occur. The overall complete abortion rate was 86% and the mean number of doses of misoprostol required was four. There was no significant change in hemoglobin concentration and the median duration of vaginal bleeding was 15 days. Lower abdominal pain, fatigue, diarrhea, fever, and chills were the most common adverse effects, and they occurred more often (from 70 to 100%) than in studies in which repeated doses of vaginal misoprostol were used.

Comparative studies

Different prostaglandins

Extra-amniotic dinoprost ($PGF_{2\alpha}$) and intracervical misoprostol have been compared for termination of pregnancy in 40 women at 16–24 weeks of gestation (9). All the women given dinoprost aborted within 28 hours and 16 within 20 hours; termination of pregnancy was complete in 13 cases. With misoprostol, all the women aborted within 20 hours, 18 within 13 hours; termination of pregnancy was complete in 17 cases. The mean time to induction of abortion was 16 hours for extra-amniotic dinoprost and 10 hours for intracervical misoprostol (significantly quicker). The incidence of prostaglandin-associated pyrexia, vomiting, and diarrhea was significantly higher with dinoprost. Abdominal pain was similar in the two groups.

Oxytocin

Misoprostol and oxytocin have been compared in three trials during vaginal and cesarean delivery. The first trial included 663 women (mean age 25 years, mean parity 2) with uncomplicated vaginal deliveries (10). They were randomized to receive two tablets of misoprostol (total dose 400 micrograms, dissolved in saline 5 ml and given as a micro-enema) or oxytocin (10 IU intramuscularly), with a double-dummy technique. There were no significant differences between the groups in mean hemoglobin and hematocrit, volume of blood loss, or duration of third-stage labor. Shivering (38 versus 15%) and an increased mean temperature were significantly more common among those who received misoprostol.

The second trial included 60 women who were randomized to oral misoprostol (400 micrograms) or intravenous oxytocin (10 IU) during cesarean section (11). Estimated blood loss was 545 ml (95% CI = 476, 614) in those given misoprostol and 533 ml (95% CI = 427, 639) in those given oxytocin. The hemoglobin concentration and hematocrit were similar in the two groups.

The third trial included 2058 patients (mean age 28 years, 53% nulliparous) with a singleton pregnancy, a low risk of postpartum hemorrhage, and vaginal delivery (12). They were randomly assigned to either intramuscular Syntometrine 1 ml (oxytocin 5 units plus ergometrine 0.5 mg) or oral misoprostol 600 micrograms. There were no significant differences between the two groups in mean blood loss, the incidence of postpartum hemorrhage, or the fall in hemoglobin concentration. The need for oxytocic medication was higher with misoprostol, but manual removal of the placenta was required more often. Shivering (30 versus 9.9%) and transient pyrexia (temperature over 38°C, 8.5 versus 1.3%) were more common with misoprostol.

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Misoprostol could be an alternative to oxytocic drugs in reducing postpartum blood loss.

Placebo-controlled studies

Oral misoprostol 400 micrograms has been compared with placebo in the routine management of the third-stage of labor. In this study shivering was a specific adverse effect of oral misoprostol in the puerperium (19 versus 5%; RR = 3.69; 95% CI = 2.05, 6.64) (13).

A systematic review of the use of misoprostol for induction of labor has been published (14). The meta-analysis included all randomized clinical trials registered in the Cochrane Pregnancy and Childbirth Group. Vaginal misoprostol was associated with increased uterine hyperstimulation, both without fetal heart changes (RR = 1.67; CI = 1.30, 2.14) and with associated fetal heart rate changes (RR = 1.45; CI = 1.04, 2.04). There was also an increase in meconium-stained amniotic fluid (RR = 1.38; CI = 1.06, 1.79).

General adverse effects

The most common adverse effects during misoprostol use in labor include pyrexia (temperature over 38°C), shivering, postpartum hemorrhage, nausea, vomiting, diarrhea, hot flushes, headache, and vertigo. When it is used in the first or second trimesters for pregnancy termination, its adverse effects include fever, chills, vomiting, diarrhea, moderate and severe abdominal pain, profuse bleeding, dysfunctional uterine bleeding, dizziness, and headache.

Organs and Systems

Body temperature

Severe hyperthermia has been reported after misoprostol (15).

- A 31-year primigravida had a missed abortion after 12 weeks of amenorrhea and was admitted for evacuation of the uterus. Preoperative cervical priming was done with intravaginal misoprostol 600 micrograms. Within 30 minutes of insertion of the misoprostol tablets she had chills and rigors, felt unwell, and started to have lower abdominal cramps. She was febrile (39.5°C) and her pulse rate was 90/minute. The undissolved misoprostol tablets were removed digitally and her vagina was douched. Ice sponging lowered her temperature. A rectal suppository of diclofenac 25 mg and an intramuscular injection of promethazine 25 mg were given. Her temperature remained high at 38°C for 3 hours and normalized after 5 hours.

Second-Generation Effects

Pregnancy

Cervical laceration associated with misoprostol has been reported in a 33-year-old woman who received four doses of vaginal misoprostol (total dose 100 micrograms) for labor induction. Uterine rupture has occurred during induction of labor with misoprostol, usually in women who have had a previous cesarean section (16,17). Uterine dehiscence occurred in one and uterine rupture in three of 48 women with prior cesarean sections treated with intravaginal misoprostol 50 micrograms for cervical ripening (18). In comparison, uterine rupture occurred in one of 89 women who had an oxytocin infusion and none of 24 patients who received intravaginal alprostadil.

- Transvaginal misoprostol for induction of labor caused uterine rupture in a 26-year-old woman with a previous low transverse cesarean delivery (19).
- In two cases, disruption of prior uterine incisions occurred after misoprostol (20).
- In two cases, uterine rupture occurred after inappropriate use (21). In one case the dose of 200 micrograms was too high. In the other case oxytocin was started 5 hours after the second misoprostol tablet, while the usual recommendation is to wait at least 12 hours. One patient had also had a previous dilatation and curettage for spontaneous abortion, which is a predisposing factor for uterine rupture in labor.

Seven pregnant women who had uterine rupture after intravaginal administration of misoprostol for induction of labor (SEDA-23, 436) had all undergone cesarean section in previous pregnancies (22).

- The first four women (aged 26–36 years) underwent induction of labor at 37–40 weeks of gestation. They received 1–2 doses of intravaginal misoprostol 25 micrograms; three of the women then received intravenous oxytocin. Soon after the first woman began pushing, there was fetal heart rate deceleration and the fetal head could not be palpated in the vagina. Emergency laparotomy showed that the baby was free in the abdominal cavity and the woman had a bladder defect. The bladder and uterine defects were repaired successfully and the mother received a transfusion of packed erythrocytes.
- In the second case, there was sudden fetal bradycardia. Laparotomy showed a large clot overlying the previous uterine incision. Dissection through the hematoma showed complete separation of the uterine incision. After delivery, the uterine rupture site and a cervical laceration were successfully repaired.
- The third woman had sudden-onset severe abdominal pain and fetal decelerations were detected. Emergency laparotomy showed complete separation of the uterine scar; both the fetus and the placenta were free in the abdominal cavity. The uterine defect was repaired and the woman recovered. However, the baby subsequently died.
- The fourth woman began to have extreme pain and fetal bradycardia then occurred. Uterine rupture from the previous incision was found at emergency cesarean section, with the baby's arm extending through the lacerated area. The uterine defect was successfully repaired.
- Uterine rupture also occurred in another three women (ages not stated) after misoprostol (dosages not stated) was used to induce labor. One underwent cesarean section because labor did not progress. During the procedure, the fetal hand and head were outside the uterine cavity (maternal and fetal outcome not stated).

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- The other two women underwent emergency cesarean deliveries because of fetal bradycardia. Both had complete uterine wall separation; one had a stellate laceration involving the previous incision, and the other had a hematoma associated with the scar disruption. Outcomes were good in both cases.

In view of these cases, the authors recommended that there be a moratorium on the use of misoprostol in the setting of a scarred uterus until the relative risks have been thoroughly investigated in appropriately controlled trials.

Uterine rupture has also been associated with misoprostol (200 micrograms vaginally) during second trimester termination of pregnancy. Occasionally, uterine rupture can occur in women who have not had a previous cesarean section, as happened in two women, one of whom had a normal delivery and the other curettage after abortion (23).

Misoprostol is not approved by the FDA for any obstetric indication. In 2000, the manufacturers GD Searle distributed a "Dear Health Care Provider" letter in the USA, emphasizing the fact that misoprostol, by any route of administration, is not intended for the induction of labor or as a cervical ripening agent before termination of pregnancy (24). Searle has become aware of instances in which misoprostol was used for such purposes, in spite of its being specifically contraindicated for use during pregnancy. The following serious adverse events have been reported after such off-label use: maternal or fetal death; uterine hyperstimulation; uterine rupture or perforation requiring surgical repair, hysterectomy, or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding; retained placenta; shock; fetal bradycardia; and pelvic pain. Searle does not intend to study or support the use of misoprostol for pregnancy termination or labor induction. The company is therefore unable to provide complete risk information for misoprostol when it is used for such purposes. Furthermore, the effects of misoprostol on the later growth, development, and functional maturation of children who are exposed to it during induction of labor have not been established.

Teratogenicity

The common phenotypical effects of exposure of the fetus to misoprostol in utero have been defined in 42 infants who were exposed to misoprostol during the first 3 months of gestation, and then born with congenital abnormalities (25). Equinovarus with cranial nerve defects occurred in 17 infants. Ten children had equinovarus as part of more extensive arthrogryposis. The most distinctive phenotypes were arthrogryposis confined to the legs (five cases) and terminal transverse limb defects (nine cases), with or without Möbius' syndrome. The most common dose of misoprostol was 800 (range 200–16 000) micrograms. Deformities attributed to vascular disruption were found in these children. The authors suggested that the uterine contractions induced by misoprostol cause vascular disruption in the fetus, including brainstem ischemia. Information on the effects of taking misoprostol during pregnancy should be made more widely available, to dissuade women from misusing the drug. Additional information on the risk associated with continuing a pregnancy to term after a failure of mifepristone and prostaglandin has been provided (26).

Data from Brazil, where misoprostol has been used orally and vaginally as an abortifacient, have suggested a relation between the use of misoprostol by women in an unsuccessful attempt to terminate pregnancy and Möbius' syndrome (congenital facial paralysis) in their infants (27). The frequencies of misoprostol use during the first trimester by mothers of infants in whom Möbius' syndrome was diagnosed and mothers of infants with neural-tube defects have been compared. There were 96 infants with Möbius' syndrome and 96 with neural-tube defects. The mean age at the time of the diagnosis of Möbius' syndrome was 16 (range 0.5–78) months and the diagnosis of neural-tube defects was made within 1 week of birth in most cases. Of the mothers of the infants with Möbius' syndrome, 47 had used misoprostol in the first trimester of pregnancy, compared with three of the mothers of the infants with neural-tube defects (OR = 30; 95% CI = 12, 76). Of the mothers of the infants with Möbius' syndrome, 20 had taken misoprostol only orally (OR = 39; CI = 9.5, 159), 20 had taken misoprostol both orally and vaginally, three had taken it vaginally, and four did not report how they had taken it. The authors concluded that attempted abortion with misoprostol is associated with an increased risk of Möbius' syndrome in infants.

In another case-control study in Brazil, 93 cases of prenatal exposure to misoprostol and 279 controls were recruited (28). Vascular disruption defects (transverse terminal limb reductions, Möbius and/or Poland sequences, hypoglossia–hypodactyly sequence, arthrogryposis, intestinal atresia, hemifacial microsomia, microtia, and porencephalic cyst) were identified in 32 exposed infants compared with only 12 controls.

In another case-control study in Brazil, congenital anomalies were compared in 34 misoprostol-exposed children and 4639 unexposed controls (29). Misoprostol exposure significantly increased the risk of arthrogryposis (OR = 8.5; 95% CI = 2, 37), hydrocephalus (OR = 4.2; CI = 1.5, 12), terminal transverse limb reduction (OR = 12; CI = 3.5, 41), and limb constriction ring or skin scars (OR = 40; CI = 11, 153). There were 13 different defects not previously described in the misoprostol-exposed cases, but only holoprosencephaly and bladder exstrophy significantly exceeded the expected number.

Mothers who used misoprostol during pregnancy as an abortifacient had an increased risk of having a baby with congenital anomalies (OR = 2.4; 95% CI = 1.0, 6.2), as reported in a case-control study in Fortaleza, Brazil (30). Multiple malformations have been described associated with the use of misoprostol (31).

- A 23-year-old woman took oral misoprostol 600 micrograms/day twice when she was 7 weeks pregnant to induce an abortion. At 12 weeks she developed a *Varicella* infection. At 15 weeks, ultrasound showed a fetus of 14.5 weeks size with several abnormalities. After amniocentesis at 17 weeks, an elective abortion was performed. The fetus had amputation deformities at the proximal interphalangeal joints of four fingers, with

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distal fusion of the proximal finger stumps by thin strands of tissue; the index finger was normal. The left leg had an amputation deformity at the mid-tibial/fibular level. There was an omphalocele. Histological examination of the placenta showed an absence of amnion on the chorionic surface, with reactive changes in the superficial chorionic stroma and "vernix granulomas" on the chorionic surface. These findings are diagnostic of early amnion rupture. There were no features of *Varicella* embryopathy.

Möbius' syndrome in association with congenital central alveolar hypoventilation has been described in Brazil (32).

Misoprostol-induced arthrogryposis has been reported in 15 Brazilian patients (33).

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Mitomycin

See also Cytostatic and immunosuppressant drugs

General Information

Mitomycin is an alkylating agent that is used intravenously to treat upper gastrointestinal and breast cancers and by direct instillation to treat superficial bladder tumors. Its main adverse effects are thrombocytopenia and leukopenia. Rare but severe adverse effects are hemolytic–uremic syndrome, pneumonitis, and cardiac failure.

Organs and Systems

Respiratory

Biopsy-proven mitomycin pneumonitis occurred in five of 44 patients who were given mitomycin in conjunction with low-dose doxorubicin 20 mg/week (1). The picture was of pulmonary infiltrates clinically and radiologically, progressive dyspnea, and hypoxia, and improvement with glucocorticoids. The mean total dose of mitomycin that had been given in the five patients was 89 mg. Mitomycin-induced interstitial pneumonitis occurs in 2–38% of cases (2,3) and at cumulative doses of 20 mg/m^2 or greater, although doses up to 30 mg/m^2 have been used safely. It is characteristically of slow-onset (3).

A fatal case of mitomycin C-induced pneumonitis has been reported in a radiotherapy/chemotherapy trial in 43 patients (4). The dose was 8 mg/m^2 on days 1 and 29, radiotherapy and vindesine being given on the intervening days.

Urinary tract

Hemolytic–uremic syndrome has often been described in patients treated with mitomycin (5–7). Up to 1990 the United States National Cancer Registry received 85 reports of cancer-associated hemolytic–uremic syndrome and 84 had received a cumulative dose of 60 mg mitomycin or more as part of their treatment (8).

Hemolytic–uremic syndrome presents as a Coombs-negative microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency, and the outcome is often fatal. The underlying pathology is thought to be vascular endothelial damage. It occurs 4–7 months after the start of chemotherapy. Blood transfusion can cause clinical deterioration in those affected (9). Histology of the kidney in the hemolytic–uremic syndrome caused by mitomycin shows mesangial proliferative glomerulonephritis with partial thickening and/or splitting of the basement membrane. On electron microscopy there is accumulation of non-homogeneous material in the subendothelial spaces. Neither immunoglobulin nor complement deposition is found (10). Treatment with hemodialysis and immunosuppressive drugs is not always successful. Plasmapheresis is commonly used (11). Prophylactic glucocorticoids can reduce the severity and prevent hemolytic–uremic syndrome in patients receiving mitomycin (12). Erythropoietin is also reportedly beneficial (13).

Mitomycin when administered intravesically causes cystitis of variable severity, which can lead to mucosal ulceration in the worst cases. However, there has also been a report of bladder fibrosis and loss of function in a 74-year-old man who had received 20 mg/week for 8 weeks (14).

Ten cases of bladder wall calcification have been reported after intravesicular administration of mitomycin. These lesions can resemble tumor recurrence in the bladder, and biopsy is advocated to distinguish between the two (15).

Skin

There have been several reports of erythematous blistering skin eruption of the palms and soles affecting patients treated with intravesical mitomycin. This has been attributed to contact dermatitis, but more widespread skin involvement and an association with eosinophilic interstitial cystitis suggest that it may be a more generalized allergic reaction (16–20).

Local extravasation of mitomycin causes inflammation and ulceration, starting within 7–10 days and lasting several weeks. In four cases the onset of tissue necrosis was delayed several weeks or months after exposure (21,22). In one case, ulceration seemed to have been precipitated by drinking ethanol, and in another by exposure to the sun.

Three cases of allergic dermatitis have been described after intravesical mitomycin (23). A type IV hypersensitivity reaction was demonstrated on patch-testing. Six cases of purpuric allergic drug eruption from intravesicular mitomycin have been reported (24).

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Mitotane

See also Cytostatic and immunosuppressant drugs

General Information

Mitotane is an inhibitor of intramitochondrial synthesis of pregnenolone and cortisol, used to produce a chemical adrenalectomy in the treatment of adrenal carcinoma and Cushing's disease and syndrome. Its unwanted effects include increased transaminase and alkaline phosphatase activities, reduced leukocyte, platelet and erythrocyte counts, and myasthenia (1).

Organs and Systems

Sensory systems

A pigmentary retinopathy with macular edema and abnormal electroretinography has been attributed to mitotane (2).

Endocrine

Because it inhibits glucocorticoid synthesis, mitotane can cause acute hypoadrenalism (3).

Metabolism

Mitotane 1–5 g daily for 4 weeks was associated with the development of hypercholesterolemia in three cases; the effect had not reverted to normal 3 months later (4).

Hematologic

Pancytopenia has been attributed to mitotane (5).

In six of seven patients with adrenocortical cancer taking mitotane for 1–2 weeks the bleeding time became prolonged; four had platelet aggregation responses compatible with an aspirin-like defect (6).

Liver

All of 10 patients taking mitotane for Cushing's syndrome had rises in either gamma-glutamyl transpeptidase or alanine transaminase, with a maximum increase six times basal value (7). The only variable that correlated with hepatic increase was the body mass index. In contrast, the severity of the disease, alcohol intake, and other biological characteristics did not correlate with transaminase rises.

In six patients with Cushing's syndrome, including one pregnant woman, who took mitotane 0.5 g/week, there was adrenocortical insufficiency requiring hormone replacement in one patient. The only other significant adverse effect was a reversible increase in gamma-glutamyl transpeptidase activity (8).

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Mivacurium chloride

See also Neuromuscular blocking drugs

General Information

Mivacurium chloride is a non-depolarizing muscle relaxant, a benzylisoquinolinium diester compound with a duration of approximately twice that of suxamethonium. In vitro (1), it is metabolized to a significant extent by plasma cholinesterase, and minimally by acetylcholinesterase. The rate of metabolism in vitro is directly related to plasma cholinesterase activity. In pooled human plasma the rate of hydrolysis of mivacurium was 70% that of suxamethonium. Its half-life is 5–10 minutes compared with 2–5 minutes for suxamethonium. The in vitro hydrolysis of mivacurium by purified human plasma cholinesterase occurs at 88% of the rate for suxamethonium (2). There was a poor correlation between the duration of action of bolus doses of mivacurium and the plasma cholinesterase activity in individual patients (2), a finding that has also been reported by others (3). However, the average infusion rate to maintain around 95% blockade in individual patients correlated significantly with the patients' plasma cholinesterase activities (4). While metabolites have been detected in both urine and bile, mivacurium seems to depend principally on ester hydrolysis for its plasma clearance, so that reduced activity of plasma cholinesterase is likely to result in a prolonged duration of action.

Organs and Systems

Cardiovascular

Benzylisoquinolinium compounds have a tendency to evoke histamine release, the main source of the cardiovascular changes seen with mivacurium. These have been reported as minimal up to and including twice the ED_{95} dose in several studies (3,5–7). At higher dosages (0.2 mg/kg and over) transient hypotension, often associated with facial flushing and lasting only some 2–5 minutes, which correlated significantly with increases in plasma histamine, has been described (5). Reducing the speed of injection to 30 or 60 seconds reduced the degree of hypotension to insignificant levels. Similar findings in 50% of patients given doses of 0.2 and 0.25 mg/kg have been described elsewhere (3). In yet another series, mean arterial pressure fell by more than 20% (24–61%) in seven of 15 patients given rapid bolus injections of 0.2–0.25 mg/kg (6). Pretreatment with oral antihistamines has been suggested as an additional option to reduce histamine-related adverse effects after administration of high-dose mivacurium (8).

In patients scheduled for coronary artery bypass grafting or valve replacement (7), significant hypotension was seen in two patients (out of 27 given higher doses), even when mivacurium was injected slowly (over 60 seconds); the mean arterial pressure fell by 24 and 50% after the injection of 0.2 and 0.25 mg/kg respectively. Beta-blockers, calcium channel blockers, and nitrates were not discontinued preoperatively in this study. The authors concluded that "doses larger than 0.15 mg/kg are probably unnecessary and may contribute to hemodynamic instability at least in cardiac patients."

Susceptibility Factors

Genetic factors

Prolonged neuromuscular blockade, up to several hours duration, has been reported in patients with abnormal plasma cholinesterase activity, who were either homozygous for the atypical gene or the silent gene or heterozygous for the atypical and the silent genes (9–12). This is a particular problem if mivacurium is used for ambulatory anesthesia, after which the patient is expected to return home, since facilities for postoperative ventilatory support may not be available. As patients with atypical cholinesterase are usually not detected by preoperative screening, it has been suggested that the patient's response to mivacurium should be tested by using a very low initial dose. However, complete paralysis for nearly 5 hours has recently been observed after a test dose of mivacurium 14 μg/kg in a patient with atypical serum cholinesterase as diagnosed by standard phenotyping and DNA sequencing (13). The authors concluded that neuromuscular monitoring and facilities for long-term ventilation should always be available when mivacurium is used.

Renal disease

The duration of mivacurium-induced neuromuscular blockade was prolonged in patients with kidney disease (SEDA-17, 25) (14,15). These results are probably due to reduced plasma cholinesterase activity.

Hepatic disease

The duration of mivacurium-induced neuromuscular blockade was prolonged in patients with liver disease (SEDA-17, 25) (16). These results are probably due to reduced plasma cholinesterase activity.

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Drug–Drug Interactions

Bambuterol

Bambuterol has been reported to alter the metabolism of mivacurium (17). Bambuterol has a dose-dependent inhibitory effect on plasma cholinesterase activity and prolongs the effects of suxamethonium. Bambuterol 10 mg was given to 28 patients 2 hours before an elective operation requiring general anesthesia. The patients given bambuterol had a 67–97% fall in plasma cholinesterase activity, leading to reduced clearance of mivacurium. This resulted in a shorter onset and a 3- to 4-fold prolongation of action of the neuromuscular blockade produced by standard doses of mivacurium.

General anesthetics

Inhalation anesthetics potentiate the neuromuscular blocking action of mivacurium, as with other nondepolarizing relaxants. With isoflurane (3) and enflurane (18) the ED_{95} is reduced by about 25% and the duration of action is somewhat prolonged, although the extent of this is not clear. Halothane has much less of an effect (19,20).

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Mizolastine

See also Antihistamines

General Information

Mizolastine is a second-generation antihistamine, a benzimidazole derivative (SEDA-19, 175) (SEDA-20, 163) (SEDA-21, 176). The effectiveness of mizolastine has been demonstrated by the inhibition of histamine-induced weal and flare and in clinical trials with patients with rhinitis or urticaria (1).

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Organs and Systems

Cardiovascular

Erythromycin and ketoconazole both increase mizolastine plasma concentrations and patients with hepatic or renal impairment have altered pharmacokinetics of mizolastine, indicating the need for caution in its use in such individuals (2).

Nervous system

Initial studies with mizolastine strongly suggested that it was free of significant sedative effects in the lower range of clinically useful doses, but a dose of 40 mg was sufficient to produce general behavioral impairment. Subsequently, investigations using tests simulating driving performance showed that even a dose of 10 mg was sufficient to impair performance in divided attention tasks 6 hours after intake and to reduce tracking speed significantly; although direct examination of driving performance showed no changes, these specific measures suggest that caution is justified in using the drug when driving vehicles, particularly because individual sensitivity to such effects of antihistamines varies.

Psychological, psychiatric

Mizolastine in doses up to 10 mg does not differ from placebo with regard to cognitive function and psychomotor performance, but in higher doses, there is dose-dependent impairment (SEDA-19, 175).

Susceptibility Factors

Renal disease

Patients with renal impairment have altered pharmacokinetics of mizolastine, indicating the need for caution in its use in such individuals (2).

Other features of the patient

Patients with hepatic impairment have altered pharmacokinetics of mizolastine, indicating the need for caution in its use in such individuals (2).

Drug–Drug Interactions

Alcohol

Mizolastine did not potentiate the effects of ethanol on psychomotor and driving performance (SEDA-20, 163), but did affect tracking speed and performance in divided attention tests.

Erythromycin

Erythromycin increases mizolastine plasma concentrations (2).

Ketoconazole

Ketoconazole increases mizolastine plasma concentrations (2).

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Mizoribine

General Information

Mizoribine is an immunosuppressive agent that inhibits de novo purine biosynthesis and affects both humoral and cell-mediated immunity. It has been used as an alternative to azathioprine in transplant patients, with a reduced incidence of leukopenia and hepatotoxicity.

Mizoribine is mostly well tolerated when it is used to treat different renal diseases, such as vasculitis, lupus nephritis, or nephritic syndrome (1–3). However, hemorrhagic enteritis and erosive changes in the intestinal mucosa have been found in dogs, and similar adverse effects have been reported in humans (4).

Organs and Systems

Endocrine

There has been a single case report of inappropriate secretion of antidiuretic hormone (SIADH) attributed to mizoribine (5).

A 74-year-old man with rheumatoid arthritis developed nausea and headache 1.5 months after starting to take mizoribine. His serum sodium concentration fell to 118 mmol/l, but his urinary sodium excretion was normal and there was no hypotension or hemoconcentration. His serum antidiuretic hormone concentration was raised at 0.59 pg/ml in spite of a reduced serum osmolality to 254 mosm/kg. He had no organic disease likely to cause SIADH. Despite infusion of hypertonic saline, his serum sodium concentration did not return to normal. Shortly after mizoribine withdrawal, his serum sodium increased from 128 to 139 mmol/l and his plasma osmolality from 265 to 287 mosm/kg.

Additional predisposing factors in this case were the patient's age and difficulty in micturition because of benign prostatic hyperplasia.

Metabolism

In a double-blind, placebo-controlled, multicenter study of mizoribine in 197 children aged 2–19 years with frequently relapsing nephrotic syndrome, transient

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hyperuricemia was the most common adverse event, occurring in 16% (6).

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Moclobemide

See also Monoamine oxidase inhibitors

General Information

Moclobemide was the first selective inhibitor of monoamine oxidase (MAO) type A to become commercially available. It binds reversibly to the enzyme, considerably shortening the duration of its effect. Both of these characteristics reduce the risk of hypertensive crisis (1,2).

The adverse effects of moclobemide have been well reported in several studies, mainly comparisons of moclobemide with standard antidepressants. The consensus has been that moclobemide produces fewer anticholinergic effects and less orthostatic hypotension and dizziness than clomipramine or imipramine. The main problems reported early on were insomnia, agitation, and paresthesia (3–9). The most common adverse effects in controlled trials have been insomnia and nausea (SEDA-18, 15).

In a multicenter comparison of moclobemide, amitriptyline, and placebo, gastrointestinal discomfort, headache, and dizziness occurred in over 20% of moclobemide-treated patients; insomnia was also common (10). In healthy volunteers there were no effects of moclobemide on psychomotor performance. Acute confusion and agitation was reported in one patient who dropped out of a clinical trial owing to this adverse effect (SEDA-16, 7). Hypomania was attributed to moclobemide in two cases (SEDA-17, 16). Aggressive behavior and mild manic symptoms were described in severely depressed patients, refractory to other treatments, who took moclobemide (SEDA-18, 15).

In a controlled multicenter study of 115 in-patients with relatively severe depression, moclobemide was better tolerated but had a weaker therapeutic effect than clomipramine. Nine of the patients taking moclobemide withdrew owing to worsening of depression and suicidality, although it is possible that the dosage of moclobemide (400 mg/day) was inadequate (SEDA-18, 15).

Organs and Systems

Cardiovascular

There have been two reports of single cases of a rise in blood pressure after moclobemide: in one there was a 40 mmHg increase in systolic pressure after one dose only (8), while the other report referred only to "episodes of hypertension" without further comment (4). Interactions were not suggested in either case.

In a prospective drug utilization study in 13 741 patients who received the reversible type A MAO inhibitor moclobemide in a variety of settings, including general practice, psychiatric out-patients, and psychiatric in-patients, there were few episodes of hypertension (0.11%; 95% CI = 0.06, 0.18%) or hypotension (0.04%; 95% CI = 0.02, 0.10%) and episodes were mostly associated with underlying cardiovascular disease (11). These findings suggest that moclobemide in usual therapeutic doses carries a low risk of producing significant changes in blood pressure relative to conventional MAO inhibitors.

Endocrine

A number of antidepressant drugs, particularly SSRIs, can increase plasma prolactin concentrations, although galactorrhea is uncommon. In a prescription event monitoring survey of about 65 000 patients, compared with SSRIs, moclobemide was associated with a relative risk of galactorrhea of 6.7 (95% CI = 2.7, 15) (12). However, this was substantially less than the risk associated with the dopamine receptor antagonist risperidone (relative risk compared with SSRIs 32; 95% CI = 14, 70). Nevertheless, the data suggest that moclobemide may be more likely to cause galactorrhea than other antidepressant drugs.

Liver

Hepatotoxicity has been associated with moclobemide, including fatal intrahepatic cholestasis in an 85-year-old

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woman 7 days after switching to moclobemide from fluoxetine (13).

Sexual function

Most conventional antidepressants lower sexual desire and performance. However, the reversible type A selective MAO inhibitor moclobemide produced intense pathological sexual desire in three men with organic brain disease (two with strokes and one with idiopathic Parkinson's disease) (14). In one man, the hypersexuality was associated with features of pathological jealousy in a paranoid state, but in the other two increased sexuality was an isolated symptom. One of these patients, who had been impotent after the stroke, resorted to telephone sex services, a most uncharacteristic behavior for him. In all cases, the hypersexuality remitted when moclobemide was withdrawn. There have been two previous case reports of moclobemide-induced hypersexuality in women without organic brain disease. This must be a rare adverse effect, but it is possible that in the cases reported here the organic brain disease may have contributed.

There are many other ways in which SSRIs can interfere with sexual function, for example by causing loss of sexual interest and erectile difficulties. In an open, prospective study of 1000 Spanish patients taking a variety of antidepressants, there was an overall incidence of sexual dysfunction of 59% (15). The highest rates, 60–70%, were found with SSRIs (including fluvoxamine) and venlafaxine. The lowest rates were found with mirtazepine (24%), nefazodone (8%), and moclobemide (4%). Spontaneous resolution of this adverse effect was uncommon – 80% of subjects had no improvement in sexual function over 6 months of treatment.

Second-Generation Effects

Lactation

Moclobemide was measured in the milk and plasma of six nursing mothers after single oral doses of moclobemide 300 mg, 3–5 days after delivery (16). The milk plasma ratio was 0.72 and the estimated dose of moclobemide to the infant was at most 1.2% of the weight-adjusted maternal dose.

Drug Administration

Drug overdose

Overdoses of moclobemide alone have been considered less toxic than overdoses of tricyclic antidepressants. Intoxication with moclobemide (0.95–2 g) produced symptoms of drowsiness, disorientation, and hyporeflexia (17,18). Fatal moclobemide overdose when the compound is taken alone is extremely rare (19).

Drug–Drug Interactions

Alprazolam

A 44-year-old man developed the serotonin syndrome after taking moclobemide and alprazolam for 1 year (20). The symptoms developed after 4 days of extreme heat, which was thought to have contributed.

Citalopram and clomipramine

Five fatal cases of serotonin syndrome after combined overdoses of moclobemide with citalopram and moclobemide with clomipramine have been reported (SEDA-18, 16). Several cases of this syndrome have been reported in patients taking moclobemide with drugs that potentiate serotonin function (21–28).

Co-beneldopa

In healthy subjects given co-beneldopa and moclobemide, no hypertension was noted, but the combination was poorly tolerated, headache and insomnia commonly being reported (SEDA-18, 16).

Dextromethorphan

Four healthy volunteers taking moclobemide (600 mg/day for 9 days) had reduced clearance of dextromethorphan, a marker of hepatic CYP2D6 activity (29). These findings suggest that at the higher end of its therapeutic dosage range, moclobemide inhibits the metabolism of drugs that are substrates for CYP2D6, for example antipsychotic drugs and tricyclic antidepressants (SEDA-14, 22).

Indirect sympathomimetics

Moclobemide increased the pressor effect of ephedrine in healthy volunteers, who also had more adverse effects including light-headedness and palpitation (SEDA-18, 16). Thus, moclobemide can potentiate the effect of indirect sympathomimetics; such combinations should be used with caution.

Rizatriptan

Rizatriptan is a 5-$HT_{1B/1D}$ receptor agonist that is metabolized by MAO type A. In 12 young healthy volunteers, moclobemide (300 mg/day for 4 days) potentiated the hypertensive effect of acute rizatriptan (10 mg orally) (30). This was associated with a significant increase in the AUC of rizatriptan and its *N*-monodesmethyl metabolite (by 2.2 and 5.3 times respectively). The authors suggested that moclobemide and rizatriptan should not be given together.

Selegiline

Patients taking moclobemide can usually eat a normal diet, since there is no significant potentiation of tyramine. However, the combination in high doses (20 mg or more) of selegiline and moclobemide potentiates the pressor effects of tyramine (presumably because of simultaneous inhibition of both MAO type A and MAO type B), and a tyramine-free diet is needed if the two drugs are used together (SEDA-20, 6).

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SSRIs

The combination of conventional MAO inhibitors with serotonin-potentiating agents, such as SSRIs, is contraindicated, because of the risk of the serotonin syndrome. Moclobemide may be less likely to cause this interaction, although both case reports and clinical series have suggested that some patients have suffered significant adverse effects consistent with serotonin toxicity (SEDA-20, 6) (SEDA-21, 10). After steady-state therapy with the SSRI fluoxetine (20–40 mg/day for 23 days), 12 subjects took fluoxetine plus moclobemide (600 mg/day) and 6 took fluoxetine and placebo (31). There was no difference in the rates of adverse effects between the two groups and no evidence of serotonin toxicity, although fluoxetine inhibited the metabolism of moclobemide. The authors suggested that patients can be safely switched from fluoxetine to moclobemide without the need for the currently advised 5-week washout (which is necessary to allow the long-acting fluoxetine metabolite, norfluoxetine, to be eliminated). However, case reports have suggested that some patients can develop serotonin toxicity when moclobemide is combined with SSRIs (23,25,28) or clomipramine (26), so great caution is still needed in clinical practice. Overdoses of moclobemide and SSRIs can cause serious and sometimes fatal serotonin toxicity (SEDA-18, 16).

Tyramine

Moclobemide in conventional doses (300–600 mg/day) does not significantly potentiate the pressor effects of oral tyramine, and special dietary restrictions are therefore not usually necessary. However, higher doses of moclobemide are sometimes used to treat patients with resistant depression. Moclobemide 900 mg/day and 1200 mg/day have been compared with placebo in 12 healthy volunteers (32). Neither dose of moclobemide significantly potentiated the pressor effect of 50 mg of tyramine, which has been estimated to be the upper limit of dietary tyramine content, even of large meals containing substantial amounts of cheese. However, one subject taking moclobemide 1200 mg/day had an increase in systolic blood pressure of over 30 mmHg. Individuals have rather different sensitivities to the pressor effects of oral tyramine challenge, and the number studied in this series was small. Accordingly, clinical extrapolation might not be straightforward. Patients taking conventional doses of moclobemide are sometimes advised to restrict their intake of cheese or other tyramine-containing foods, and this advice is clearly prudent if subjects take higher doses.

Venlafaxine

Interactions of moclobemide with venlafaxine, a potent serotonin re-uptake inhibitor, have been reported (25,33).

- A 34-year-old man took 2.625 g of venlafaxine (therapeutic dose 75–375 mg/day) and 3 g of moclobemide, plus an unknown amount of alcohol 1 hour before being admitted to hospital. Within 20 minutes of arrival his conscious level deteriorated and he had increased muscle tone, with clonus in all limbs. He was treated with intubation, paralysis, and ventilation, and sedated with midazolam and morphine. He regained consciousness after 2 days.

This case report confirms the serious consequences of combined overdosage of moclobemide with drugs that potentiate brain serotonin function (see also the monograph on SSRIs).

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Modafinil

General Information

Modafinil is a benzhydrylsulfinylacetamide wake-promoting agent for oral administration (1). It selectively targets neuronal pathways in the sleep/wake centers of the brain. It is well absorbed and its half-life is about 12–15 hours, which largely reflects the half-life of its levorotatory enantiomer. It is metabolized, mainly in the liver, by amide hydrolysis with lesser contributions from CYP-mediated oxidation, and. less than 10% of the dose is excreted as unchanged drug.

In controlled clinical trials, modafinil reduced excessive daytime sleepiness in patients with narcolepsy (2).

In an open, randomized, crossover study in healthy men, concomitant administration of single oral doses of modafinil (200 mg) and dexamfetamine (10 mg), each given separately, produced a slight increase in blood pressure and the cardiovascular effects were more pronounced after concomitant administration (3). These changes were considered not to be clinically relevant and would not necessarily preclude short-term administration of the two drugs together. The most frequent adverse events with modafinil or dexamfetamine were headache, dizziness, insomnia, and dry mouth.

Modafinil was effective in narcolepsy in a 9-week, randomized, placebo-controlled, double-blind, 21-center trial in 271 patients (4). During treatment withdrawal, the patients did not have symptoms associated with amphetamine withdrawal. Nausea and rhinitis were significantly more common in the treatment group; in contrast, in a previous multicenter study in the USA there was a higher incidence of headache (5). Modafinil was also effective in the treatment of somnolence due to pramipexole in a patient with Parkinson's disease (6).

Once-daily modafinil for an average of 4.6 weeks has been evaluated in an open trial in 11 children aged 5–15 years with ADHD (7). This pilot study, with non-blinded ratings, a small number of subjects, and a short duration of treatment, showed significant improvement. Adverse events were responsible for drug withdrawal in one child. The most common adverse event was delayed onset of sleep or sleep disruption, which, in two of three cases, responded to a reduction in dosage. No patient taking modafinil lost weight or had a reduced appetite. A larger-scale, double-blind, placebo-controlled study will be needed to further substantiate the efficacy and safety of modafinil.

In a 9-week, single-blind, placebo-controlled pilot study in 72 patients with multiple sclerosis who took modafinil 200 mg/day for 2 weeks, there was significant improvement in fatigue compared with placebo run-in treatment (8). The most frequent adverse effects were headache, nausea, and anxiety, and these were rated as either mild or moderate.

Long-Term Effects

Drug dependence

The abuse potential of modafinil is very low and differs from that of methylphenidate (9). The data suggest that the subjective effects of modafinil may be similar to those of drugs such as phenylpropanolamine or caffeine, although a direct comparison with these drugs would be required to draw adequate conclusions. Furthermore, modafinil cannot be injected intravenously or smoked, and its once-daily dosing in the management of excessive daytime sleepiness in patients with narcolepsy suggests that it does not carry the same public health or safety concerns for abuse as amphetamines, since drugs that have a long half-life have less of a tendency to produce a "rush" and hence are less likely to be abused. However, the effects of social responses to the availability of

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modafinil can only be determined by post-marketing surveillance.

Drug–Drug Interactions

General

In vitro, modafinil caused reversible inhibition of CYP2C19 in human liver microsomes (1). It also caused a small, but concentration-dependent, induction of CYP1A2, CYP2B6, and CYP3A4 and inhibition of CYP2C9 activity in primary cultures of human hepatocytes. In clinical studies of interactions of modafinil with methylphenidate, dexamfetamine, warfarin, ethinylestradiol, and triazolam, the only substantive interactions were with ethinylestradiol and triazolam, apparently through induction of CYP3A4, primarily in the gastrointestinal tract (1). The results suggested that modafinil can affect the pharmacokinetics of drugs that are metabolized by certain CYP isozymes. Compounds that induce or inhibit CYP activity are unlikely to have major effects on the pharmacokinetics of modafinil.

Clozapine

Clozapine toxicity occurred after modafinil administration to reverse sedation associated with clozapine (10).

- A 42-year-old man with schizophrenia, taking haloperidol, quetiapine, divalproex, gabapentin, benzatropine, and lorazepam, was given clozapine 25 mg at bedtime titrated to 400 mg/day over 13 days. His non-psychotropic medications included levothyroxine, furosemide, potassium, and docusate sodium. All other psychotropic drugs were tapered and withdrawn by day 69. On day 70 the serum clozapine concentration was 761 ng/mL. Because of persistent psychotic symptoms, the dose of clozapine was increased to 450 mg/day on day 77, but this resulted in severe sedation. He was given modafinil 100 mg/day on day 82, titrated to 300 mg/day by day 101; this produced slight improvement in sedation. On day 116 he complained of dizziness, had an unsteady gait, and fell twice. He was afebrile and tachycardic but had a normal blood pressure; his blood oxygen saturation was 86%. His serum clozapine concentration on day 112 was 1400 ng/ml. Clozapine and modafinil were withdrawn. His gait disturbance and hypoxemia resolved. Clozapine 100 mg/day was restarted on day 121 and increased to 300 mg/day by day 122. The clozapine concentration 21 days later was 1236 ng/ml and 5 weeks later 960 ng/ml.

It is possible that inhibition of CYP2C19 by modafinil interfered with clozapine clearance in this case (11). Despite the potential of modafinil for reversing clozapine-associated sedation (12), caution is required when prescribing this drug combination.

Dexamfetamine

The potential for an interaction of modafinil with dexamfetamine, each at steady state, has been investigated in an open, randomized study in 32 healthy subjects (13). All took modafinil orally once daily for 28 days (200 mg on days 1–7 and 400 mg on days 8–28). On days 22–28, half of them also took dexamfetamine 20 mg orally 7 hours after modafinil. The steady-state pharmacokinetics of modafinil and its metabolites, modafinil acid and modafinil sulfone, were unaltered by low-dose dexamfetamine. Adverse events (abdominal pain, headache, and insomnia) were similar in the two groups and mild or moderate in nature. In another open, randomized, crossover study in healthy men, concomitant administration of single oral doses of modafinil (200 mg) and dexamfetamine (10 mg) showed no clinically significant pharmacokinetic interaction (3). Some patients with narcolepsy may require a change from dexamfetamine to modafinil, and arguably such a transition can be made without any washout period.

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Mofebutazone

See also Non-steroidal anti-inflammatory drugs

General Information

Adverse reactions to mofebutazone are similar to those of the parent drug, phenylbutazone, and include skin reactions, including epidermal necrolysis and bullous drug eruption (1). Gastrotoxicity, hepatotoxicity, nephrotoxicity, edema, headache, and hematological adverse effects (SED-9, 145) (2) have been described.

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Molsidomine

See also Antianginal drugs

General Information

Molsidomine is a vasodilator that acts as a nitric oxide donor and has been used in angina pectoris, heart failure, and after myocardial infarction.

In a multicenter, randomized, double-blind, crossover, placebo-controlled study of the efficacy of two regimens of molsidomine in 90 patients with stable angina, beneficial effects on exercise load did not seem to be reduced by 6 weeks of continuous therapy, suggesting lack of tolerance (1). The most frequently reported adverse effect of molsidomine was headache, as for all other nitric oxide donors.

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Monoamine oxidase inhibitors

General Information

All available monoamine oxidase (MAO) inhibitors (excepting moclobemide, toloxatone, brofaromine, and selegiline) act via a "suicide" mechanism, by causing long-lasting, irreversible, competitive inhibition of mitochondrial MAO, which persists until new enzyme is manufactured (1). Most of these drugs also produce a non-specific reduction in the activity of hepatic drug-metabolizing enzymes.

Table 1 lists the MAO inhibitors that are already available or under investigation. These compounds fall into different chemical categories, including compounds that have the following properties: antidepressant (moclobemide), antihypertensive (pargyline), antineoplastic (procarbazine), and antimicrobial (furazolidone).

Antidepressant drugs of various classes (tricyclics, MAO inhibitors, SSRIs) have broad efficacy in generalized anxiety and in panic disorder, but SSRIs are now the treatments of choice (2,3). Selegiline has been used to treat Parkinson's disease. Other drugs that have MAO inhibitory activity, but are not used as such, include debrisoquine, linezolid, and isoniazid.

The monoamine oxidase inhibitors epitomize cyclical fashions in drug use and the impact of adverse effects. They were the first psychotropic drugs for which a clear biochemical action was defined. Early excitement was quickly tempered by reports of liver toxicity with the hydrazine derivatives, leading to synthesis of the cyclopropylamine drug, tranylcypromine, which in turn elicited the food and drug interactions that led to an overall decline in popularity.

Then in the 1980s there was a reappraisal of the benefit-to-harm balance of the MAO inhibitors. This spawned both a search for safer and more selective or rapidly reversible enzyme inhibitors (including moclobemide, toloxatone, and brofaromine), as well as a review and retrial of the older compounds.

The scientific underpinnings of this renaissance have been reviewed (4). Much of the earlier work was conducted using inadequate doses of phenelzine, whose efficacy was later validated using adequate drug concentrations (to produce 85% or more enzyme inhibition) (5). A review of eleven studies conducted in 1963–1982 that compared MAO inhibitors and tricyclic compounds showed that in three studies there was no difference, four favored tricyclic antidepressants, and in three MAO inhibitors were superior (6). The three studies that favored MAO inhibitors were among the four most recently conducted (all since 1979). An article in 1985 entitled "Should the use of MAO be abandoned?" (7) was accompanied by commentaries from six British and US experts in psychopharmacology. The consensus was clearly in favor of continued use, with the recognition that even if a specific responder is difficult to define there are individuals who respond when all other drugs have failed. No clear-cut clinical or metabolic features distinguish such individuals; an earlier claim that the clinical response and susceptibility to adverse effects might be influenced by genetically determined rapid or slow acetylation of phenelzine was not confirmed by a review of seven studies (8).

There have been many studies of the efficacy and toxicity of selective inhibitors of MAO type A (SEDA-16, 7) (SEDA-17, 16) (SEDA-18, 16).

The adverse effects of the MAO inhibitors include hepatocellular damage, similar to that which led to the withdrawal of the earlier hydrazine derivatives, hypotension, often a pronounced adverse effect (possibly due to the accumulation of a pseudotransmitter normally

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Table 1 Monoamine oxidase (MAO) inhibitors that have been studied or are currently commercially available for treating depression or for other purposes (rINNs except where stated)

Compound	Structure	Comments
Fenoxypropazine Iproniazid Mebanazine Pheniprazine Pivhydrazine	Hydrazines	These drugs are earlier compounds that caused liver damage; they are obsolete
Nialamide	Hydrazine	Little used today
Phenelzine (pINN)	Hydrazine	Widely used
Isocarboxazid	Hydrazine	Similar to phenelzine
Tranylcypromine	Cyclopropylamine	Most amphetamine-like High propensity for interactions with foods and drugs
Pargyline	Propinylbenzylamine	Used for hypertension
Furazolidone	Nitrofuran	Antimicrobial (giardiasis)
Procarbazine	Methylhydrazine	Antineoplastic
Clorgiline	Propylamine	Type A MAO inhibitor (serotonin/noradrenaline)
Selegiline	Propinylamine	Type B MAO inhibitor (phenylethylamine)
Moclobemide	Benzamide	Type A MAO inhibitor
Toloxatone	Oxazolidinone	Type A MAO inhibitor
Brofaromine	Piperidine	Type A MAO inhibitor

metabolized by MAO), and autonomic disturbances, such as dryness of the mouth, sweating, constipation, and weight gain.

Differences between MAO inhibitors in adverse effect profiles are poorly substantiated, and are confounded by different usage patterns and drug potencies. The selective MAO inhibitors are considered in other monographs.

Comparative risks of monoamine oxidase inhibitors and tricyclic antidepressants

MAO inhibitors suffered a long period of disfavor, largely because of their troublesome interactions. Their risks still exceed those of the tricyclic compounds, but some experienced clinicians feel that they can be used safely, provided appropriate precautions are taken.

Of particular interest is a chart review of 198 patients, aged 19–64, treated in a university research clinic by psychiatrists who specialized in the pharmacological treatment of affective disorders (9). Most of the patients (130) had atypical depression and participated in a 6- or 12-week double-blind comparison of phenelzine, imipramine, and placebo, with further follow-up. The authors selected 14 adverse effects generally considered to cause "serious medical risk or subjective discomfort great enough to require drug discontinuation." There were serious adverse effects in 14% of the patients taking placebo, 27% of those taking imipramine, 43% of those taking tranylcypromine, and 64% of those taking phenelzine; 38% had two or more serious adverse effects and all but one was taking phenelzine. The differences between imipramine and phenelzine were highly significant. By 33 weeks under half of the patients taking imipramine had had a serious adverse effect, compared with over 90% of those taking phenelzine. Adverse effects were sufficiently severe to require withdrawal in 45%. None of the 14 selected adverse effects was more common in the patients taking imipramine. The serious adverse effects that were more common in patients taking phenelzine included hypomania (10%), hypertensive crisis (8%), weight gain over 15 pounds (8%), and anorgasmia and impotence (22%). In a second article the authors discussed these adverse effects in detail (10). Of the eleven patients who had hypertensive crises, six had eaten tyramine-containing foods "despite meticulous dietary review and cautioning," and three had taken ephedrine-containing medications; four obtained emergency medical treatment in local hospitals and a fifth developed coma with intracranial bleeding due to an unsuspected aneurysm.

Organs and Systems

Cardiovascular

When MAO is inhibited, the concentrations of noradrenaline, dopamine, and serotonin increase in the central nervous system and heart. The concentrations of the precursors of these amines (dihydroxyphenylalanine and 5-hydroxytryptophan) are greatly increased. The effects are similar to those of the postganglionic blocking amines: postural hypotension occurs and cardiac output is reduced, possibly due to the accumulation of a pseudotransmitter.

Hypotension

The hypotensive effects of the MAO inhibitors differ from those of the tricyclic antidepressants, inasmuch as the former affect supine as well as orthostatic blood pressure. This was confirmed both in a study (11) involving tranylcypromine and in an evaluation of blood pressure changes in 14 patients taking phenelzine averaging 65 mg/day for at least 3 weeks (12). The drug-free mean supine systolic blood pressure was 127 mmHg and it fell significantly (mean drop 5 mmHg) by the end of the first week. By contrast, an increase in the orthostatic drop from the mean predrug baseline of 2 mmHg did not reach significance until the end of the second week of treatment, after which the blood pressure continued to fall. Two patients developed profound orthostatic falls of up to 50 mmHg

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after more than 2 weeks of treatment. In one patient the hypotension and related symptoms (light-headedness and ataxia) improved with fludrocortisone, but not in the other, who required drug withdrawal. The authors commented that because orthostatic hypotension can develop late, cautious long-term monitoring is required.

Hypertension

Hypertensive crises usually occur when MAO inhibitors are combined with other drugs or foods that cause interactions (see next subsection).

Autopotentiation of hypertensive effects

In a few cases, a hypertensive crisis appears not to have been provoked by known drug or dietary precipitants (13). From a review of 12 reports of spontaneous hypertension in patients taking tranylcypromine or phenelzine, it has emerged that a family history of hypertension may be a risk factor (SEDA-18, 14). A significant increase in supine blood pressure without similar changes in standing blood pressure after the administration of tranylcypromine has also been described (SEDA-17, 17).

Cardiac arrhythmias

MAO inhibitors can cause bradycardia. A report of two cases of interactions of monoamine oxidase inhibitors with beta-blockers (nadolol and metoprolol) is of interest, and several possible mechanisms were discussed (14).

Nervous system

Autonomic nervous system

A carefully controlled 3-week comparison of phenelzine (up to 90 mg/day, mean 77 mg) and imipramine (up to 150 mg/day, mean 139 mg) showed no significant difference between the drugs in the incidence of dry mouth, blurred vision, constipation, and urinary hesitancy (15).

Central nervous system

Insomnia and daytime somnolence and fatigue have been reported with tranylcypromine, phenelzine, and isocarboxazid (SEDA-16, 8) (SEDA-17, 16). In a comparison of phenelzine and imipramine (15) there were important and significant differences between the drugs: 19% of the patients taking phenelzine reported drowsiness compared with none of those taking imipramine; moreover, 18 patients taking phenelzine had to be withdrawn, compared with one taking imipramine (who developed urinary retention). Central nervous system toxicity was also reported after an abrupt switch from phenelzine to isocarboxazid (SEDA-17, 17).

Parkinsonism

The MAO inhibitors can be used in patients who have Parkinson's disease, for two reasons. First, this is a disorder in which depression is common. Secondly, the selective type B inhibitor selegiline was originally thought to benefit patients with parkinsonism, possibly by increasing brain dopamine concentrations (16).

However, a recent long-term study has shown higher death rates in patients with early mild Parkinson's disease taking combined selegiline and levodopa compared with those taking levodopa alone. The authors concluded that the combination of selegiline with levodopa offers no advantage to patients with early mild Parkinson's disease, and that although selegiline may help symptoms in advanced Parkinson's disease it is best avoided in patients with postural hypotension, frequent falls, confusion, and dementia (17).

Dystonias

Two Italian neurologists have described current theories about the pathophysiology of levodopa-associated motor fluctuations and the use of inhibitors of MAO type B, inhibitors of catechol-*O*-methyl transferase, and modified-release levodopa in minimizing this problem (18).

- Dystonia has been described in a 65-year-old woman who had taken tranylcypromine 10 mg bd for 3 days. She had major long-term depression that had failed to respond to other agents. The dystonia abated 48 hours after withdrawal but recurred on rechallenge (19).

Neuromuscular function

The tendency for MAO inhibitors to produce symptoms related to neuromuscular excitability, the serotonin syndrome, has been recognized in cases of overdose (SEDA-10, 18) and in interactions with other antidepressants or tryptophan (SEDA-10, 16, 17) (20). The authors of a thorough review of the preclinical and clinical literature have drawn attention to these phenomena, which occur at therapeutic doses with a MAO inhibitor alone, and have speculated that the mechanism is related to a combination of increased serotonergic tone and central disinhibition of alpha motor neuron-mediated spinal activity (21). They discussed ten previous reports of myoclonus, hyperreflexia, muscle twitching, and increased muscle tone in patients taking MAO inhibitors. These neuromuscular effects appear to occur in up to 15% or more of patients, and are more likely when tryptophan is given in combination. They usually appear after 10–14 days. Tolerance does not occur, but the effects may abate or disappear with dosage reduction. Symptoms predominate during sleep and are often associated with muscle or joint pains.

Endocrine

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (22) may be the mechanism of action underlying cases of peripheral edema that have been described (SEDA-2, 12) (SEDA-6, 28). Diuretics are not helpful, but dosage reduction produces relief (23).

A number of antidepressant drugs, particularly selective serotonin re-uptake inhibitors (SSRIs), can increase plasma prolactin concentrations, although galactorrhea is uncommon. In a prescription-event monitoring survey of about 65 000 patients, compared with SSRIs, moclobemide was associated with a relative risk of galactorrhea of 6.7 (95% CI = 2.7, 15) (24). However, this was substantially less than the risk associated with the dopamine receptor antagonist risperidone (relative risk compared with SSRIs 32; 95% CI = 14, 70). Nevertheless, the data suggest that moclobemide may be more likely to cause galactorrhea than other antidepressant drugs.

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Hematologic

Leukopenia and agranulocytosis are well-recognized complications of treatment with tricyclic antidepressants and have been reported with some second-generation compounds. In a report of leukopenia in a patient taking phenelzine attention was drawn to five other unpublished cases and to previous published reports involving isocarboxazid, tranylcypromine, and tryptamine (25).

Liver

The early reports of hepatotoxicity with iproniazid led to the synthesis of non-hydrazine inhibitors, and a report from 19 French drug surveillance centers (26) has reaffirmed the frequency and severity of this adverse effect. There were 91 cases of hepatitis due to all antidepressants (11 with iproniazid) over 5 years. Cytolytic reactions occurred in 11 patients treated with iproniazid; 5 died. There was a high titer of antimitochondrial antibodies (M6) in five patients.

Skin

Photosensitivity to MAO inhibitors must be most unusual, but one well-authenticated report has been published (27).

Sexual function

Impotence and delayed ejaculation in men and difficulty in achieving orgasm in two women have been reported with a variety of MAO inhibitors used to treat narcolepsy (28), phobic anxiety (29), and depression (30–32). Sexual symptoms are often dose-related and there is a delicate interplay between psychic and pathophysiological influences. In men with premature ejaculation this effect may even be considered therapeutic.

Immunologic

Rashes have been reported, but their relation to drug ingestion is poorly substantiated. The hepatocellular damage caused by hydrazine derivatives is probably mediated by an immunological mechanism.

Body temperature

Hyperthermia and labile blood pressure, perhaps due to an interaction of clomipramine, phenelzine, and chlorpromazine has been described in one patient (SEDA-17, 17).

Long-Term Effects

Drug withdrawal

The literature on a withdrawal syndrome (SEDA-10, 17) has been expanded by further reports. One of these (33) involved the development of an acute toxic delirium 3 days after withdrawal of phenelzine, and another (34) concerned patients who became manic after withdrawal of isocarboxazid. A withdrawal state similar to that caused by withdrawal from amphetamines has been described after withdrawal of tranylcypromine (SEDA-16, 8) (SEDA-18, 14).

In principle it should be possible to switch from one conventional MAO inhibitor to another without a washout period. However, there have been reports that patients who switched from phenelzine to tranylcypromine had hypertensive reactions, with disastrous consequences (35). Whenever possible, a 2-week washout period when switching from a conventional MAO inhibitor to tranylcypromine seems advisable.

Second-Generation Effects

Pregnancy

Little is known about the use of MAO inhibitors during pregnancy and the postpartum period. There is a literature review along with a case report of phenelzine exposure throughout pregnancy and the postpartum period (36).

Lactation

There are some reports of the excretion of MAO inhibitors in breast milk (37,38).

Susceptibility Factors

Age

Because of the concern expressed about the use of tricyclic antidepressants in elderly people, MAO inhibitors have been studied in this population (39). Patients with dementia benefited in mood (but not cognition), and some non-demented patients also improved. Adverse effects were considered less frequent or troublesome than those due to tricyclic compounds, although one patient taking tranylcypromine became paranoid and another taking phenelzine developed a choreiform movement disorder. The fact that MAO concentrations increase with age supports the use of these drugs in the elderly, but their hypotensive effects and interactions with other drugs and foods suggest that they should be used with extreme caution in people who are exposed to polypharmacy and whose comprehension of and attention to warnings may be impaired.

Other features of the patient

It is inadvisable to give MAO inhibitors to schizophrenic patients, even when they seem to be anergic or depressed, since they may precipitate a psychotic crisis. It is also difficult to ensure that such patients respect the necessary dietary restrictions, that is, avoidance of tyramine-containing foods.

Drug Administration

Drug overdose

The fatal effects of antidepressants in England, Scotland, and Wales during 1975–1984 and 1985–1989 have been compared in retrospective epidemiological studies (40,41). The fatality index (deaths per million prescriptions) for individual drugs or groups of drugs was used to give an indication of the relative effects of the different drugs. There were 24 deaths due to tranylcypromine, 33

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due to phenelzine, and 3 due to isocarboxazid. The fatality index for tranylcypromine was significantly higher than the mean for all antidepressants, while that for the other MAO inhibitors was lower. The majority of all deaths from antidepressant poisoning were due to two tricyclic drugs (amitriptyline and dosulepin), and they, as well as the entire group of older tricyclic antidepressants, had a fatality index significantly higher than the mean (41). It must of course be kept in mind that the fatality index of a drug is influenced by many factors other than its inherent toxicity, including dosage, differences in severity of illness and suicidal tendencies, and prescription for indications other than depression.

The minimum fatal dose of non-selective MAO inhibitors is about 5–10 times the maximum daily dose, although individuals have been reported to survive such amounts. Symptoms of overdosage can be initially mild and deceptive, but can progress over 24 hours to include agitation, tremor, alternating low and high blood pressure, severe muscle spasms, hyperpyrexia, and convulsions. Symptomatic treatment has included the beta-blocker practolol (10 mg intravenously, repeated after 2 hours) and muscle relaxants with assisted respiration (42), which may help reduce pyrexia by abolishing excessive muscle activity. Active elimination techniques are unhelpful, according to a comprehensive review of antidepressant overdosage (43).

In one patient who took 900 mg of phenelzine, there was a marked excess of urinary and plasma catecholamines, analogous to pheochromocytoma, and the patient was successfully managed with alpha-adrenoceptor antagonists (44). In another patient, who probably took about 2000 mg of phenelzine, hyperpyrexia was prominent and responded to dantrolene sodium (45). The authors noted clinical similarities to malignant hyperpyrexia and neuroleptic malignant syndrome.

Drug–Drug Interactions

General

Problems with non-selective irreversible MAO inhibitors arise for two reasons: the large number of amines that are substrates for the enzyme and the fact that these drugs also inhibit non-specific drug-metabolizing enzymes in the liver. Together, these two actions produce a lengthy list of interactions with other substances, the effects of which can be enhanced or prolonged, both during treatment with a MAO inhibitor and for up to 2 weeks afterwards, owing to the irreversible nature of the enzyme inhibition (Table 2).

Amines that serve as substrates include both natural and synthetic ephedrine congeners contained in prescribed and proprietary formulations, and amines such as tyramine, which occur naturally in a variety of protein-containing foods, in which amines are produced by bacterial decarboxylation of amino acids. When these "indirectly acting" amines are ingested, they are normally destroyed by MAO in the intestine or liver; however, after treatment with a MAO inhibitor they gain access to the systemic circulation, resulting in release of noradrenaline from sympathetic nerve terminals. If the amount ingested is sufficient, symptoms similar to those of pheochromocytoma occur, with a paroxysmal increase in blood pressure, sudden severe occipital headache, and cardiac irregularities. In rare instances, fatal cerebral hemorrhage or cardiac failure have occurred. The actions of MAO inhibitors on non-specific hepatic drug-metabolizing enzymes potentiate the effects of a large number of drugs, including narcotic analgesics, barbiturates, and anesthetics. This can complicate elective or emergency surgery in patients taking these antidepressants, with occasional fatal results.

A cause-and-effect relation for interactions between non-selective MAO inhibitors and other substances is often difficult to establish, for two reasons (46). First, MAO inhibitors act by forming an irreversible bond with an enzyme that is continuously being resynthesized. The degree of enzyme inhibition therefore varies with the dosage and duration of treatment, and can persist to some degree for up to 2 weeks after withdrawal. Secondly, any

Table 2 Drug and food interactions with MAO inhibitors

Hypertensive crisis: potentiation of central effects of drugs or food components due to inhibition of monoamine oxidase
Drugs
Amines, prescribed or proprietary
Amphetamine and congeners
Ephedrine and congeners
Levodopa
Reserpine
Tryptophan
Foods
Alcohol (wine, beer)
Amine-containing foodstuffs
Banana (peel)
Broad beans (including pods)
Caviar
Cheese
Chicken livers
Chocolate
Hung meats
Pickled herring
Yeast extracts (Marmite, packeted soups)
Serotonin syndrome
Dextromethorphan
Pethidine (meperidine)
Selective serotonin re-uptake inhibitors
Trazodone and dextropropoxyphene (combined with phenelzine)
Tricyclic antidepressants
Tryptophan
Potentiation or prolongation of other drug effects due to inhibition of hepatic drug-metabolizing enzymes
Alcohol (all types)
Anesthetics
Antihistamines
Antiparkinsonian agents
Barbiturates
Benzodiazepines
Chloral hydrate
Hypoglycemic agents
Opiate analgesics
Thyroid extract
Tricyclic antidepressants

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protein food that contains decarboxylating bacteria can convert amino acids to amines such as tyramine, phenylethylamine, and histamine, and the amine composition of foodstuffs is variable and unpredictable; for example, identical-looking pieces of cheese can vary 100-fold in tyramine content. The diversity and number of substances (listed in Table 2) and unpredictability in the occurrence of adverse effects have contributed to the unpopularity of the MAO inhibitors as therapeutic agents.

Two facts simplify the understanding and use of these drugs.

(1) The interactions listed in Table 2 fall into three categories:

   (a) hypertensive crisis due to the release and potentiation of catecholamines similar to that experienced in pheochromocytoma;
   (b) a serotonin syndrome, caused by excess serotonin availability in the nervous system;
   (c) exacerbation or prolongation of the normal actions of the object drug (sedation or coma due to alcohol, anesthetics, or opioid analgesics; atropine-like central toxicity due to tricyclic antidepressants).

   The consequences of the hypertensive interaction are variable. Many individuals remain unaware of relatively minor increases in blood pressure. However, if the rise is large and rapid (an increase of 30 mmHg or more in systolic pressure within 20 minutes), the patient experiences a sudden severe occipital headache and palpitation, which may be associated in rare instances with subarachnoid hemorrhage or cardiac failure, if the cerebral vasculature or cardiac musculature are already weakened.

   The serotonin syndrome is characterized by three or more of the following symptoms: confusion, hypomania, agitation, myoclonus, hyper-reflexia, hyperthermia, shivering, sweating, ataxia, and diarrhea (47). It is most often seen in patients taking a combination of drugs that increase serotonin availability by different mechanisms. Drug combinations that have been reported to cause the serotonin syndrome have been reviewed and the pathophysiology of the syndrome discussed (45). It is probably mediated by stimulation of 5-HT_2 receptors. In most reported cases the drug combination associated with the syndrome included a MAO inhibitor (see Table 2). The syndrome is rare, although it has been reported more often during the past few years, and is often due to a combination of a MAO inhibitor and a selective serotonin re-uptake inhibitor. In most cases the symptoms are mild and resolve rapidly after drug withdrawal and supportive therapy. It must, however, be borne in mind that this syndrome can be fatal, and if combinations of serotonergic drugs are used they should be used with great caution.

(2) A second factor that can improve the use of these drugs is adequate patient education. Patients must be aware of the name and nature of the drug they are taking and its potential to interact with proscribed foods and prescribed or over-the-counter medications. In addition, patients should understand what symptoms to expect when an interaction occurs, such as unexpected drowsiness (after alcohol or other drugs) or a sudden severe headache (within 2 hours of a meal or medication). Because of the many variables involved, foods or medications that are taken with impunity on one occasion can interact dangerously on another. The director of a British counselling service has reported that of 119 patients taking MAO inhibitors who experienced problems, 35 reported hypertensive crises, 4 fatal (48). Despite warnings, these patients had eaten amine-containing foodstuffs or taken over-the-counter cold remedies. MAO inhibitors should not be prescribed unless the patient is able to understand such instructions and repeat them after explanation; compliance can be confirmed at subsequent inquiry. Those who take multiple medications, who have difficulty with comprehension or compliance (such as the elderly), or who are frightened by such explanations should not be given these drugs.

   The management of a patient who experiences these drug interactions depends on their nature. For symptoms due to exacerbation or prolongation of drug effects, specific or supportive measures (cardiovascular or respiratory) may be indicated. In the case of a hypertensive crisis, symptoms usually abate within 1–2 hours, as the blood pressure falls. If hypertension is seen early, or if it persists or recurs, it can be treated with parenteral phentolamine or chlorpromazine, but the danger of causing hypotension should be weighed carefully.

   The combination of central nervous system stimulants with MAO inhibitors in treatment-resistant depressed patients has been reported (49). However, this use should be restricted to patients in whom there is careful monitoring by specialists, because of the potential for hypertensive crisis.

Buspirone

The combination of buspirone with a MAO inhibitor can cause the serotonin syndrome (50).

Etamivan

Etamivan is contraindicated in patients taking MAO inhibitors (51).

Fenfluramine

Fenfluramine can produce an acute confusional state if it is given together with a MAO inhibitor (SED-9, 9).

Fluoxetine

The problem of the long half-life of fluoxetine, which leads to interactions with MAO inhibitors, even after withdrawal, has been discussed previously (SEDA-13, 12), and caused the manufacturer to circulate a warning to that effect.

Ginseng

Interactions of antidepressants with herbal medicines have been reported (52). Herbal medicines are widely used for their psychotropic properties and patients

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sometimes take herbal formulations in addition to conventional psychotropic drugs, such as antidepressants. Ginseng has been reported to cause mania, tremor, and headache in combination with conventional MAO inhibitors.

Isoniazid

Isoniazid inhibits MAO, and during isoniazid treatment the ingestion of several kinds of cheese can cause flushing, palpitation, tachycardia, and increased blood pressure (53). Similar symptoms occur with isoniazid after the ingestion of skipjack fish (*Thunnidae*) (53). The symptoms, notably headache, palpitation, erythema, redness of the eyes, itching, diarrhea, and wheezing, are thought to be caused mainly by the high histamine content of this fish. The undesirable effects that occur when MAO inhibitors are taken together with isoniazid resemble the symptoms seen after the simultaneous ingestion of these foods.

Lithium

Interactions of lithium with antidepressants have been reviewed: tricyclic antidepressants and MAO inhibitors—no serious problems; SSRIs—a few reports of the serotonin syndrome (54).

Nefazodone

Co-administration of nefazodone with a MAO inhibitor or SSRI can cause the serotonin syndrome (55).

Neuroleptic drugs

Additive hypotensive effects can occur when a MAO inhibitor is combined with an antipsychotic drug (56). However, the combination can be beneficial in treating the negative symptoms of schizophrenia (57).

Opioids

The interactions of MAO inhibitors with opioids, which can lead to sudden and fatal reactions, have been reviewed (SEDA-18, 14).

Dextromethorphan is metabolized by CYP2D6 to dextrorphan, which binds to phencyclidine receptors and is thought to account for the toxic effects of hallucinations, tachycardia, hypertension, ataxia, and nystagmus. Individuals who are slow metabolizers, those who take long-acting dextromethorphan formulations, and those who take serotonin re-uptake inhibitors or MAO inhibitors are at increased risk of adverse effects.

Phenylephrine

Patients taking medications with pressor effects, such as MAO inhibitors, tricyclic antidepressants, and anticholinergic agents, should be monitored closely if phenylephrine is used (SEDA-16, 542).

Sumatriptan

On theoretical grounds sumatriptan should not be used with a MAO inhibitor (58).

Trazodone

Trazodone is related to nefazodone but probably potentiates 5-HT neurotransmission less. Trazodone is often added to MAO inhibitors and SSRIs at low doses (50–150 mg/day) as a hypnotic, but such combinations can rarely provoke the serotonin syndrome.

- The serotonin syndrome occurred in a 60-year-old woman when the addition of trazodone 50 mg/day to nefazodone 500 mg/day caused confusion, restlessness, sweating, and nausea after the third day of treatment (59). The symptoms settled quickly on withdrawal of both antidepressants.

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Monobactams

See also Beta-lactam antibiotics

General Information

In the monobactams there is no second ring fused to the beta-lactam ring. However, the highly active compounds of this group do, as a rule, contain the aminothiazole side chain, known to be associated with good antimicrobial activity and beta-lactamase stability in cephalosporins (1). Aztreonam, marketed in 1984, was the first monobactam.

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Other compounds, such as carumonam, pirazmonam, and tigemonam, have been developed (2), but so far only aztreonam is widely used. Monobactams are almost exclusively active against Gram-negative bacteria, and their clinical usefulness lies particularly in their antipseudomonal activity.

Like 6-aminopenicillanic acid for the penicillins and 7-aminocephalosporanic acid for the cephalosporins, 3-aminomonobactamic acid is the basic compound for the monobactam family.

In clinical trials the safety profile of aztreonam was similar to or better than that of other more conventional beta-lactam antibiotics, in adult patients with both normal renal function (3,4) and impaired renal function (5). These findings have been confirmed in children (6).

Organs and Systems

Hematologic

In a child with typhoid fever, severe leukopenia and neutropenia necessitated withdrawal of aztreonam (150 mg/kg/day) on the 10th day, followed by recovery (7). In another case there was myelosuppression (mainly neutropenia) possibly caused by aztreonam after 10 days of treatment; it resolved within 1 week of withdrawal (8). However, acute reversible neutropenia has been otherwise reported in under 0.1% of patients taking aztreonam (6).

Three of twenty-eight patients taking high-dose aztreonam (300 mg/kg/day) for cystic fibrosis developed mild and transient thrombocytopenia (9).

Liver

The frequency of liver function test abnormalities in patients taking monobactams does not differ from the frequencies in patients taking other beta-lactam antibiotics (3,6,9).

Urinary tract

- Acute renal insufficiency associated with a skin rash and eosinophilia has been reported in a 70-year-old man after 9 days of treatment with aztreonam (10).

However, significant nephrotoxicity has not been documented in trials.

Skin

Aztreonam was the suspected cause of toxic epidermal necrolysis in two patients undergoing bone marrow transplantations (11). Graft-versus-host disease seemed a less likely diagnosis of the cutaneous manifestations.

Immunologic

Aztreonam has minor immunogenicity in animals and was associated with a 2% incidence of all presumably immunologically mediated drug reactions in early phase I and II trials (12).

When *Escherichia coli* was co-cultured with mouse peritoneal macrophages and exposed to aztreonam and ceftazidime, there was enhanced secretion of TNF-alpha; imipenem did not do this (13). Both aztreonam and ceftazidime enhanced LPS release from *E. coli* while imipenem did not, consistent with the observed differences in TNF-alpha release. All three antibiotics increased *E. coli*-induced expression of inducible nitric oxide synthase (iNOS), as assessed by both mRNA and protein.

Negligible cross-reactivity has been reported in both animal and human studies involving hapten inhibition, skin tests, and treatment of penicillin-allergic patients with therapeutic doses of aztreonam (12,14–19). Aztreonam therefore seems to be a safe alternative for patients with penicillin allergy. However, the numbers of safely treated patients reported are still small, and immediate type hypersensitivity to aztreonam has been reported in patients with penicillin allergy (20–23).

Several cephalosporins, for example ceftazidime, have the same aminothiazole side chain as aztreonam. Sensitization with either drug involving side chain-specific antibodies may therefore predispose to allergy to the other. However, clinical data on this problem are currently not available.

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Monoclonal antibodies

General Information

Human monoclonal antibody immunotherapy in clinical medicine has been an exciting prospect for some time, and increasing numbers of such antibodies have gradually become available (1,2).

An illustration of the potential of human monoclonal antibodies was provided by the HA-1A antibody, a human monoclonal IgM specific for the core/lipid A part of endotoxin. Among 291 patients with Gram-negative bacteremia treated with this antibody there was a significant reduction in mortality (3). Since then other patient groups have been treated, and apart from local urticaria, flushing, and mild transient hypotension, no adverse reactions were noted (4,5). No patient has developed antibodies to HA-1A. Although the initial results seem promising, more trials are needed to substantiate the therapeutic efficacy of HA-1A.

Numerous investigators have reported and reviewed the clinical application of monoclonal antibodies in various areas, including organ transplantation, neoplastic diseases, severe sepsis, and chronic inflammatory diseases. Collectively, these antibodies generally did not produce major adverse effects. The rapid development of antibodies against murine monoclonal antibodies is one of the most important clinical limitations to their therapeutic use, but the development of humanized (chimeric human/murine) monoclonal antibodies has improved their safety. Monoclonal antibodies have also been used in non-immune mediated diseases, such as cancer, septic shock, reperfusion, and as antiplatelet drugs. Treatment of neoplastic diseases with monoclonal antibodies is theoretically attractive. Unfortunately none of the monoclonal antibodies available at present has been demonstrated to be strictly tumor-specific, and binding of antibody to normal cells has been shown to be the major unknown factor for toxicity (6).

Monoclonal antibodies that are dealt with in separate monographs are abciximab, alemtuzumab, anti-CD4 antibody, basiliximab, daclizumab, edrecolomab, gemtuzumab ozogamicin, ibritumomab, muromonab-CD3, omalizumab, palivizumab, rituximab, and trastuzumab.

Nomenclature

Modern international non-proprietary drug names have two parts. The suffix, or stem, tells you what group the drug belongs to, ideally chosen to reflect its pharmacological action. For instance, -vastatin denotes HMG Co-A reductase inhibitors (-stat- often being used for enzyme inhibitors); -olol denotes beta-blockers (but beware stanozolol); and -mycins are antibiotics. The prefix is chosen at will. It might reflect the structure or source of the drug (for example diclofenac, virginiamycin), the inventor's love of opera or the cinema (for example, mimimycin, rifampicin (7)), or just whimsy.

The monoclonal antibodies have a prefix and three substems. All, with one exception (muromonab), end in -mab for monoclonal antibody. The penultimate syllable (or substem) indicates the animal source and the prepenultimate syllable indicates the target (Table 1). The prefix (one or two syllables) is chosen at random. Finally, if

Table 1 The components of the names of monoclonal antibodies

Prepenultimate syllable (general target)	Prepenultimate syllable (specific tumor target)	Penultimate syllable (species source)
-ba(c)- = bacterium	-co(l)- = colon	-a- = rat
-ci(r)- = cardiovascular	-go(t)- = gonad (testis)	-e- = hamster
-le(s)- = infectious lesions	-go(v)- = gonad (ovary)	-i- = primate
-li(m)- = immunomodulation	-ma(r)- = mammary	-o- = mouse
-vi(r)- = virus	-me(l)- = melanoma	-u- = human
-pr(o) = prostate		-abo- = rat-mouse hybrid
-tu(m)- = tumor (unspecified)		-xi- = chimeric
		-zu- = humanized

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the antibody is conjugated to a toxin, an extra word is added; aritox, for example, denotes the A chain of ricin.

For example, trastuzumab can be parsed as follows: tras-tu-zu-mab. The -zu- denotes a humanized antibody and the -tu- a tumor target. If you wanted to show that it targets the breast specifically, you could call it tramazumab.

Uses

The uses of some monoclonal antibodies are listed in Table 2.

Several anti-human T cell monoclonal antibodies have undergone preliminary trials in the treatment of renal allograft rejection. Most of these monoclonal antibodies were not effective than muromonab (1). T10B9, an anti-human pan-T lymphocyte monoclonal antibody, had similar efficacy but caused less fever, severe infection, respiratory, gastrointestinal, or neurological symptoms than muromonab (SEDA-22, 409). Other monoclonal antibodies, such as chimeric anti-CD7 and murine anti-ICAM-1 (CD54; enlimomab), were devoid of adverse effects or produced only minimal and transient adverse effects (SED-13, 1134).

Anti-CD4 monoclonal antibodies, for example OKT4A, BF-5, cM-T412 (clenoliximab, keliximab), are continuously being investigated, although in small numbers of patients, after transplantation or in chronic inflammatory diseases, such as rheumatoid arthritis (SEDA-20, 340) (SEDA-21, 379) (2,8,9). Significant clinical immunomodulation has sometimes been obtained, with only transient and self-limiting, first-dose effects, namely headache, fever and chills, gastrointestinal disorders, hypotension, and tachycardia (SEDA-21, 379). Whereas most other adverse effects were not specifically associated with these monoclonal antibodies, mild skin eruptions and transient increases in hepatic enzymes, with one reversible case of liver failure, have been attributed to B-F5, a murine IgG1 CD4 monoclonal antibody (10).

Various monoclonal antibodies have been developed to be used as carrier molecules or as immunoconjugates to target drugs, enzymes, isotopes, or toxins to tumor cells. Some of the available data have been summarized (11), but there is still insufficient evidence of clinical benefit.

Table 2 Some monoclonal antibodies and their uses

Monoclonal antibody	Uses
Abciximab	Prevention of ischemic cardiac complications during percutaneous coronary interventions; short-term prevention of myocardial infarction
Afelimomab	Treatment of sepsis
Alemtuzumab	Chronic lymphocytic leukemia
Apolizumab	Chronic lymphocytic leukemia
Basiliximab	Prevention of acute renal allograft rejection
Clenoliximab	Rheumatoid arthritis
Daclizumab	Prevention of acute renal allograft rejection
Edrecolomab	Adjuvant therapy for cancer after colorectal surgery
Efalizumab	Treatment of severe plaque psoriasis
Enlimomab	Burns; stroke; prevention of acute rejection and delayed onset of graft function in cadaveric renal transplantation
Epratuzumab	Non-Hodgkin's lymphoma
Gemtuzumab	CD33-positive acute myelogenous leukemia
Infliximab	Rheumatoid arthritis; ankylosing spondylitis; Crohn's disease
Inolimomab	Prevention of graft rejection
Keliximab	Rheumatoid arthritis
Muromonab	Prevention of acute renal allograft rejection
Natalizumab	Acute relapse in multiple sclerosis; Crohn's disease
Odulimomab	Prevention of ischemic renal damage during kidney transplantation
Omalizumab	Prevention of allergic asthma and seasonal rhinitis
Palivizumab	Prevention of respiratory syncytial virus infection
Rituximab	Chemotherapy-resistant advanced follicular lymphoma; diffuse non-Hodgkin's lymphoma
Trastuzumab	HER2 receptor-positive breast cancer
Visilizumab	Treatment of glucocorticoid-refractory acute graft-versus-host disease

Rodent monoclonal antibodies

Compared with the therapeutic use of human monoclonal antibodies, the use of rodent (mouse or rat) monoclonal antibodies in vivo is disadvantageous because the xenogeneic antibody can induce immune responses that will mitigate the effectiveness of the antibody and/or cause adverse reactions in the recipient. Thus, the authors of one report concluded that antimouse immunoglobulin responses in human patients have limited the usefulness of murine monoclonal antibodies in more than half of those treated (12). The formation of human antimouse antibodies has been described both when murine monoclonal antibodies are used as a diagnostic tool in vivo and when they are used therapeutically (13–16).

Common adverse effects of treatment with murine monoclonal antibodies include fever, chills, and malaise in 21–23% of cases and urticaria and pruritus in 15–18% (17).

The murine monoclonal antibody muromonab directed against the CD3 structure on T lymphocytes has proved to be an important therapeutic agent with potent immunosuppressive actions, and its extensive use provides examples of the adverse effects of rodent monoclonal antibodies. It is used to reverse acute rejection episodes in kidney, heart, liver, or pancreas allografts and for graft-versus-host disease in bone marrow transplant recipients, when glucocorticoids have failed, or to avoid ciclosporin nephrotoxicity and the inconvenience of polyclonal anti-lymphocyte globulins (18). Despite its efficacy in over 90% of cases, muromonab causes a number of adverse effects, such as fluid retention and acute pulmonary edema (19), while marked early adverse effects include fever, chills, nausea, vomiting, headache, and hypotension, the last being attributed to systemic vasodilatation.

Other rodent monoclonal antibodies against cell membrane markers (CD molecules) have been described. The adverse effects of such antibodies can be ascribed to the general adverse effects of a heterologous protein, or to effects of the cell-targeting mechanisms (for example cell lysis).

General adverse effects

Although the adverse effects of most monoclonal antibodies were very few or benign, the possibility of more severe or unusual late complications should be

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considered, as illustrated by several case reports. In one patient, both immediate and delayed injection site reactions were noted after injections of a type I recombinant human interleukin-1 receptor (rhu IL-1RI), and positive cutaneous tests and specific IgE antibodies strongly suggested an immune-mediated allergic reaction (20).

Severe migratory polyarthritis with fever, an urticarial rash, and renal involvement have been reported after the first dose of CAMPATH-1G, a rat antihuman monoclonal antibody reactive against CDw52 antigens, used before marrow transplantation in a 25-year-old patient (21). In patients with renal transplants or rheumatoid arthritis, alemtuzumab, a humanized monoclonal antibody directed against the CDw52 antigen found on lymphocytes, produced only mild to moderate first-dose symptoms, such as fever and rigors, nausea and vomiting, bone pain, dyspnea, and headache (SED-13, 1134) (SEDA-20, 380). By contrast, there was a high incidence of severe lymphopenia associated with infectious complications during the intravenous administration for low-grade lymphoma (22). Finally, several patients with rheumatoid arthritis treated with infliximab (a chimeric monoclonal anti-TNF-alfa antibody) or CDP-571 (a human anti-TNF-alfa antibody) developed various autoantibodies (23). Although there were no clinical consequences in these patients, the possible delayed development of overt autoimmune diseases should still be considered.

The mechanisms of adverse effects of monoclonal antibodies include sensitization due to the xenogeneic nature of the product, specific suppression of physiological functions, and secondary activation of inflammatory cells or mediators, which might be characterized by the cytokine release syndrome, as observed with muromonab-CD3 or rituximab (24). Although sensitization may be frequent, its clinical relevance is still limited, with only rare cases of allergic reactions. Although this has been strongly debated with muromonab-CD3 (orthoclone) (SED-14, 1309), the available information on the risk of infections or cancers with other monoclonal antibodies is still limited, but does not suggest an increased risk.

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Monosodium glutamate

General Information

Monosodium glutamate, the sodium salt of the amino acid L-glutamic acid, is used as a flavor enhancer in a variety of foods. Average individual daily intake in developed countries is 0.3–1.0 g/day.

The use of monosodium glutamate has been controversial over the past 35 years because of reports of adverse reactions in people who have eaten foods that contain it.

The Chinese restaurant syndrome (Kwok's syndrome)

A triad of symptoms, numbness at the back of the neck radiating to both arms and the back, general weakness, and palpitation, after eating a Chinese meal, referred to collectively as the Chinese restaurant syndrome, was first described by Kwok in 1968 (1). It was suggested that monosodium glutamate triggered these symptoms, which were later extended to include headache, flushing, tingling, weakness, stomachache, visual disturbances, nausea, vomiting, and tightness or pain in the chest.

- A 36-year-old man developed severe weakness, palpitation, and sweating 30 minutes after eating wonton soup (2). He had a ventricular tachycardia, which converted to normal rhythm soon after the administration of intravenous lidocaine.

Many similar reports, most of them anecdotal, were published after the original observation, followed by clinical studies of varying degrees of rigor in experimental design, ranging from uncontrolled open challenges to double-blind, placebo-controlled studies. Challenges in subjects who reported adverse reactions to monosodium glutamate included relatively few subjects and failed to show significant reactions to monosodium glutamate. The results of surveys and of clinical challenges with monosodium glutamate in the general population showed no evidence of untoward effects. In a multicenter, double-blind, placebo-controlled challenge study in 130 subjects, large doses of monosodium glutamate given without food elicited more symptoms than placebo in individuals who believed that they reacted adversely to monosodium glutamate (3). However, the frequency of responses was low and the responses were inconsistent, not reproducible, and not observed when monosodium glutamate was given with food. Some have suggested that the syndrome is more likely in the presence of vitamin B_6 (pyridoxine) deficiency (4).

In a questionnaire survey, 43% of 3222 respondents associated unpleasant symptoms with specific foods and eating environments; however, only 1–2% reported symptoms characteristic of the Chinese restaurant syndrome, and only 0.19% associated the characteristic symptoms with consumption of Chinese food (5). Most respondents who were aware of the syndrome and most of those who believed they had experienced it reported non-specific symptoms.

L-glutamic acid and its ammonium, calcium, monosodium, and potassium salts were evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1988 (6). Because human studies had failed to confirm involvement of monosodium glutamate in the Chinese restaurant syndrome or other reactions, the JECFA classified glutamic acid and its salts under the heading "acceptable daily intake (ADI) not specified." The Scientific Committee for Food (SCF) of the European Commission reached a similar conclusion in 1991, and the conclusions of a subsequent review by the Federation of American Societies for Experimental Biology (FASEB) and the Federal Drug Administration (FDA) did not discount the existence of a sensitive subpopulation but otherwise concurred with the evaluations of JECFA and the SCF.

Organs and Systems

Nervous system

Research on the role in the nervous system of the glutamates has raised questions about the safety of monosodium glutamate (7). Glutamate is an amino acid neurotransmitter in the brain, and there are glutamate-responsive tissues in other parts of the body as well. Abnormal function of glutamate receptors has been linked with certain neurological diseases, such as Alzheimer's disease and Huntington's chorea. Injection of glutamate in laboratory animals has resulted in damage to nerve cells in the brain, but consuming glutamate in food does not have this effect. Although people normally consume dietary glutamate in large amounts, and the body can make and metabolize glutamate efficiently, the results of animal studies conducted in the 1980s raised the question of whether monosodium glutamate and possibly some other glutamates can harm the nervous system.

However, the 1995 report from the FASEB, an independent body of scientists, helped to put these safety concerns into perspective and reaffirmed the FDA's belief that monosodium glutamate and related substances are safe food ingredients for most people when eaten in usual amounts.

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Montelukast

See also Leukotriene receptor antagonists

General Information

Montelukast is a leukotriene receptor antagonist. It has been taken by about 2500 patients in over 40 clinical trials. Its adverse events have not been significantly different from those of placebo.

Montelukast is extensively metabolized to 21- and 36-hydroxylated and dicarboxylic acid metabolites, which are excreted in the bile. The steady-state plasma concentrations of these metabolites are below the limit of detection in adults and children. In vitro studies have shown that high concentrations of montelukast inhibit CYP3A4 and CYP2C9, but in clinical studies the recommended dose of 10 mg/day did not interfere with metabolism of important cytochrome P450 substrates, such as warfarin (1).

The efficacy and safety of montelukast in 689 asthmatic children under 5 years have been studied in an international, multicenter, randomized study (2). The patients were randomly assigned to 12 weeks of treatment with placebo ($n = 228$) or montelukast 4 mg as a chewable tablet ($n = 461$). There were no clinically relevant differences between the groups in the overall frequencies of adverse effects, individual adverse effects, or the frequency of laboratory adverse effects, especially raised serum transaminase activities. Asthma was more frequent in the placebo group. The withdrawal frequency was similar in the two groups. Accidental ingestion of montelukast up to dosages 18 times the recommended daily dose of 4 mg was generally well tolerated. The authors concluded that montelukast is well tolerated in this specific group of preschool children.

The safety and tolerability of montelukast in patients aged 6 years or more have been evaluated in a meta-analysis of pooled data from 11 multicenter, randomized studies and five long-term extension studies (3). In 3386 adults (aged 15–85 years) and 336 children (aged 6–14 years), the overall incidence of clinical and laboratory adverse events was similar among patients taking montelukast and placebo. There were no clinically important differences in individual adverse events between the two treatment groups. There were no dose-related adverse effects of montelukast up to dosages 20 times the recommended daily dose of 10 mg.

Drug Administration

Drug overdose

Since montelukast is a relatively new drug, few data are available on unintentional poisoning. This makes it difficult to determine which dosages require aggressive decontamination or simple monitoring. Acute montelukast overdose with doses up to at least 150 mg/day have been reported in children. In most of the reports no adverse events were reported; when they occurred, symptoms included thirst, somnolence, mydriasis, hyperkinesia, and abdominal pain. In two cases of unintentional poisoning with montelukast there were no symptoms in a 3-year-old child who took 80 mg or in a 5-year-old child who took 135 mg (4).

In adults, montelukast doses up to 20- to 90-fold greater than the recommended dose (10 mg/day), given for longer than 1 week, were well tolerated and no unexpected adverse events occurred (5).

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Moracizine

See also Antidysrhythmic drugs

General Information

Moracizine (moricizine) has Class I antidysrhythmic actions that cannot be easily further subclassified. Its pharmacology, clinical pharmacology, clinical uses, adverse effects and interactions have been reviewed (1–3).

In a retrospective study of 85 patients with recurrent atrial fibrillation (mean left atrial size 46 mm, mean left ventricular ejection fraction 0.51), 69 of whom had structural heart disease, moricizine (mean dose 609 mg/day) was withdrawn because of unacceptable adverse effects in six patients: frequent ventricular extra beats and short runs of non-sustained ventricular tachycardia ($n = 2$); significant widening of the QRS complex ($n = 1$); first-degree heart block ($n = 1$); a significant rise in liver enzymes ($n = 1$); and a severe rash ($n = 1$) (4). Six patients developed transient adverse effects that resolved spontaneously without withdrawal: brief self-limiting episodes of atrial flutter ($n = 2$); a small increase in blood pressure ($n = 1$); generalized weakness and tremor ($n = 2$); and reduced appetite ($n = 1$).

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Organs and Systems

Cardiovascular

The overall risk of dysrhythmias with moracizine seems to be similar to that of other antidysrhythmic drugs, at around 10% (5), although lower rates have been reported. In CAST-II (the Cardiac Arrhythmia Suppression Trial) moracizine increased mortality in patients with asymptomatic ventricular dysrhythmias after myocardial infarction (6).

There have been anecdotal reports of conduction defects (SEDA-17, 225).

Moracizine has little or no effect on hemodynamics, but it sometimes has adverse hemodynamic effects and can exacerbate heart failure (SEDA-17, 225).

Hematologic

Moracizine has an anti-aggregatory effect on platelets, and thrombocytopenia has been reported (7).

Liver

Moracizine can cause increased serum bilirubin concentrations and serum transaminase activities (7).

Susceptibility Factors

Hepatic disease

Moracizine is cleared by the liver, and dosages should be reduced in liver disease (8).

Drug–Drug Interactions

Cimetidine

Cimetidine inhibits the metabolism of moracizine, but the effect is probably clinically unimportant (9).

Diltiazem

Moracizine is an enzyme inducer; it increases the rate of clearance of diltiazem (10). Conversely, diltiazem caused a doubling of the AUC of moracizine (10) in healthy volunteers.

Phenazone (antipyrine)

Moracizine is an enzyme inducer; it increases the rate of clearance of phenazone (antipyrine) (11).

Theophylline

Moracizine is an enzyme inducer; it increases the rate of clearance of theophylline (12).

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Morniflumate

See also Non-steroidal anti-inflammatory drugs

General Information

Morniflumate is an NSAID that is widely prescribed in some countries as an antipyretic analgesic in children.

Organs and Systems

Immunologic

- A 4-year-old girl developed angioedema and urticaria 30 minutes after receiving rectal morniflumate. Her signs and symptoms resolved in 48 hours. Skin prick and intradermal tests to morniflumate were negative, but rechallenge with rectal administration caused a recurrence (1).

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Morphine

See also Opioid analgesics

General Information

Morphine and its two glucuronides may have neuroexcitatory effects and affinity for non-opioid receptors (glycine and/or *N*-methyl-D-aspartate), effects that will not be antagonized by naloxone. Furthermore, these other opioid effects may be related to the mechanism of some adverse effects, including hyperalgesia, allodynia, and myoclonus, which are increasingly being reported after high doses of morphine, but which do not seem to occur after methadone, fentanyl, sufentanil, or ketobemidone (1).

Morphine is the benchmark "step 3" opioid analgesic based on the WHO's concept of an analgesic ladder (2). Revised recommendations for the use of morphine in cancer pain have been published by the European Association for Palliative Care's Expert Working Group on Opioid Analgesics (3). In summary, oral morphine is still the opioid of first choice for moderate to severe cancer pain, every 4 hours for normal-release morphine and 12- or 24-hourly for modified-release morphine. If patients are not able to take morphine orally the preferred alternative is subcutaneous infusion, especially in patients who require continuous parenteral morphine. A small proportion of patients develop intolerable adverse effects with oral morphine, and a change to an alternative opioid (for example hydromorphone, oxycodone, methadone, transdermal fentanyl) or a change in the rate of administration should be considered. If despite optimal use of systemic opioids and non-opioids a patient still has intolerable adverse effects or inadequate analgesia, spinal (epidural or intrathecal) administration of an opioid analgesic in combination with a local anesthetic or clonidine should be considered.

In a randomized, double-blind study in 94 patients with acute renal colic, morphine had equal analgesic efficacy to pethidine and a similar adverse effects profile (4).

Managing the adverse effects of morphine

The strategies used in managing the adverse effects of oral morphine have been reassessed in another special article compiled by the Expert Working Group of the European Association of Palliative Care Network (5). Factors that predict opioid adverse effects include:

(1) *Drug-related factors* There is little evidence suggesting that any one opioid agonist has a substantially better adverse effects profile than any other.
(2) *Route-related factors* There is limited evidence to suggest differences in adverse effects associated with specific routes of systemic administration.
(3) *Patient-related factors* There is evidence to suggest that there is interindividual variability in sensitivity to opioid-related adverse effects; the variables include genetic susceptibility, the presence of co-morbidity, and age.
(4) *Dose-related factors* A dose-response relation is most evident with the CNS adverse effects of sedation, cognitive impairment, hallucinations, myoclonus, and respiratory depression, although there is still interindividual variability in dose responsiveness to these effects; nausea and vomiting are common at the start of therapy but are then unpredictable.
(5) *Starting doses and escalation* The adverse effects of morphine, especially cognitive impairment, occur transiently and abate spontaneously; there are no reports of a relation between the starting dose of morphine or dose escalation and the occurrence of nausea, vomiting, or delirium.
(6) *Drug interactions* Adverse effects of concurrent medications may be synergistic or cumulative with those associated with opioids.

The reviewers also stressed the importance of differentiating opioid-related adverse effects from other causes of co-morbidity that might mimic opioid-induced adverse effects. Examples include cerebral metastases, stroke, metabolic changes, septicemia, bowel obstruction, and iatrogenic factors (other drugs or radiotherapy).

Four different approaches to the management of opioid adverse effects were described in the review:

(1) *Dosage reduction* A reduction in the dosage of the systemic opioid is usually enough to relieve adverse effects. If dosage reduction is accompanied by loss of pain control, a non-opioid analgesic (for example an NSAID) can be added. Specific therapy, such as radiotherapy, chemotherapy, or surgery, that targets the cause of the pain can be helpful, as can a regional anesthetic or neuroablative intervention (for example celiac plexus blockade in patients with pancreatic cancer).
(2) *Symptomatic management of the adverse effects.*
(3) *Opioid rotation.*
(4) *Switching the route of administration.*

The reviewers also examined the symptomatic management of specific adverse effects and commented that most approaches are based on cumulative anecdotal evidence and that there have been few prospective evaluations of the efficacy and toxicity of these approaches over a long period of use. Polypharmacy adds to the burden of adverse effects and drug interactions.

Nausea and vomiting

The authors of two related double-blind, randomized, placebo-controlled studies of the use of dexamethasone prophylaxis for nausea and vomiting after epidural morphine for postcesarean or posthysterectomy analgesia concluded that 5 mg of dexamethasone is an effective dose (6,7). Meanwhile, ADL 8-2698, a trans-3-4-dimethyl-4 piperidine that is a novel opioid antagonist, produced improved gastrointestinal transit time (peripherally mediated opioid activity) without affecting centrally mediated opioid analgesia (8). This contrasts with naloxone or nalmefene, which tend to antagonize central opioid effects, resulting in withdrawal symptoms in up to 50% of patients when used to treat constipation.

Intravenous droperidol 1.25 mg and intravenous dexamethasone 8 mg, given at the end of cesarean section, have been compared in reducing the incidence of nausea and vomiting caused by epidural morphine 3 mg in 120

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women in a randomized, double-blind, placebo-controlled study (9). The incidence of nausea and vomiting was 18% with dexamethasone, 21% with droperidol, and 51% with saline. About 11–13% of the women who were given dexamethasone or droperidol required rescue antiemetic therapy compared with 41% in the saline group. The incidence of pruritus was similar among the three groups (26–42%). Six women (16%) given droperidol reported restlessness compared with none in the other two groups.

Pruritus

The effectiveness of intravenous ondansetron in preventing intrathecal morphine-induced pruritus has been investigated in a randomized, double-blind, placebo-controlled study in 60 consecutive women undergoing cesarean section (10). All were given spinal anesthesia with bupivacaine and intrathecal morphine 0.15 mg and then randomly divided into three groups. Group 1 received intravenous saline injections as placebo, group 2 received diphenhydramine 30 mg intravenously, and group 3 received ondansetron 0.1 mg/kg intravenously. Group 3 had a significantly lower incidence of pruritus (25%) than both group 1 (85%) and group 2 (80%), with no difference in postoperative pain scores between the groups.

In another randomized, double-blind study, 140 patients undergoing cesarean section had anesthesia with epidural bupivacaine 100 mg and adrenaline to which was added morphine 2 mg and droperidol 0, 1.25, 2.5, or 5.0 mg (11). Previous evidence had suggested that intravenous droperidol reduces morphine-induced pruritus, but that the effect disappeared when the dose was increased from 2.5 mg to 5.0 mg (12). However, in this study, epidural droperidol caused a dose-dependent reduction in morphine-induced pruritus even at a dose of 5 mg.

Myoclonus

Gabapentin has been used to treat morphine-induced myoclonus in a 54-year-old patient with gallbladder cancer (13). Effective pain control was maintained with morphine 300 mg, but after 24 hours the patient developed generalized muscular movements while asleep. Gabapentin 300 mg bd produced complete resolution of symptoms after 12 hours. In another case gabapentin 600 mg/day was used to treat a 1-month history of spontaneous jerking of both wrists after an increase in the dose of morphine to 120 mg/day; the myoclonus disappeared over the next 24 hours (8,13).

Organs and Systems

Cardiovascular

Adverse cardiac effects due to morphine are rare. They comprise inappropriate heart rate responses to hypotension, rather than conduction defects. They are not especially associated with inferior myocardial infarction, as was previously thought (SED-11, 142) (14).

Respiratory

Non-cardiogenic pulmonary edema occurred in three cancer patients, all of whom had received rapidly escalating doses of morphine over a short period (15).

Nervous system

A patient with Guillain–Barré syndrome experienced shock with morphine sulfate (16).

- A 69-year-old woman developed interscapular pain after a mild respiratory infection. Non-opioid analgesics were ineffective, so she was given modified-release morphine 10 mg. On day 4 she had rapidly progressive weakness in her legs and on day 5 she was found unconscious with no detectable blood pressure. She recovered with naloxone 0.8 intravenously. Her paralysis persisted. Nerve conduction studies confirmed slowed neurotransmission. Further investigation excluded other potential causes and Guillain–Barré syndrome was diagnosed.

The episode of unconsciousness was attributed to opioid toxicity in a patient in whom autonomic dysfunction may already have been present. It was suggested that opioid analgesics should be used with caution in patients with Guillain–Barré syndrome, because of the risk of hypotension consequent on autonomic dysfunction.

High doses of chronic morphine can cause hyperalgesia or allodynia (pain caused by a stimulus that does not normally provoke pain) (17).

- A 9-month-old girl with an inoperable and partially resected astrocytoma of the hypothalamus had morphine-induced allodynia, and became extremely distressed during routine care, such as nappy changing, feeding, and washing. The allodynia resolved after the dosage of morphine was reduced from 6950 μg/kg/hour to 280 μg/kg/hour.

Intravenous patient-controlled administration of morphine (total 56 mg in 9 hours) was associated with downbeat nystagmus in a 61-year-old man with a Grade 3 adenocarcinoma of the gastro-esophageal junction and a previous small cerebellar infarct (18). Withdrawal of the analgesia led to complete resolution of all signs and symptoms within 12 hours.

Psychological, psychiatric

Hallucinations have been described after the use of morphine in various dosage forms; in one series, patients experienced adequate pain relief and no further hallucinations or nightmares when changed to oxycodone (19). Delusions and hallucinations have been reported in a patient who was also taking dosulepin (20). Restlessness, vomiting, and disorientation were described in two male patients over 60 years of age taking modified-release morphine for relief of pain in advanced cancer (21).

Endocrine

Morphine can cause prolactin release (22); this effect is not antagonized by naloxone.

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Mouth and teeth

There is a clear association between the administration of morphine and dry mouth (23).

Gastrointestinal

Nausea and vomiting are frequent adverse effects associated with the use of PCA opioids. Droperidol and tropisetron may reduce the incidence and severity of nausea and vomiting caused by morphine (SEDA-19, 84).

Morphine reduces the rate of transient lower esophageal sphincter relaxation in patients with reflux disease, thus reducing the number of reflux episodes; the effect was reversed by naloxone (SEDA-22, 12).

Biliary tract

Morphine can cause choledochal sphincter spasm, especially if there is a previous history of cholecystectomy (24).

- A 60-year-old man received intramuscular morphine 10 mg with scopolamine 0.4 mg as premedication and 40 minutes later complained of sharp right upper quadrant pain radiating to the back. The symptoms were identical to the gallbladder pain he had experienced in the past and for which he had had a cholecystectomy 25 years before. He had complete relief from intravenous naloxone 0.9 mg.

Skin

A purpuric rash has been reported in a patient taking morphine (25).

Death

- A 14-year-old boy with infectious mononucleosis was given intravenous morphine 10 mg for pain relief with good effect, but 2 hours later was found unresponsive, lying on his back, and not breathing (26). An autopsy showed marked bilateral tonsillar enlargement with considerable narrowing of the upper airway. The blood morphine concentration was 0.08 μg/ml.

The coroner concluded that the morphine had contributed to respiratory compromise and death.

Long-Term Effects

Drug withdrawal

Acute opioid withdrawal syndrome apparently precipitated by naloxone following epidural morphine has been reported (27).

- A 28-year-old nulliparous woman with no history of opioid exposure underwent elective cesarean section with epidural anesthesia. On delivery she received morphine 2 mg epidurally. At 8 hours after delivery she complained of pruritus and received naloxone 0.14 mg intravenously in fractional doses. After 2 minutes she felt warm in her legs, trunk, and face. Pruritus resolved and analgesia was maintained. After 5 minutes she began to shiver in a waxing and waning pattern every 2 minutes. She was restless and agitated and had tachypnea, lacrimation, and rhinorrhea. Her symptoms resolved in 40 minutes.

Previous reports of opioid withdrawal on single exposure have been described after the administration of intramuscular morphine in healthy individuals. This case suggests that opioid dependence can occur after acute exposure to morphine by the epidural route too. An alternative explanation (28) is that the stress of labor may have led to increased endogenous opioid activity, particularly B-endorphin, and that the antagonistic effect of naloxone on the endogenous opioid system contributed to the clinical effects in this patient. Moreover, the authors pointed out that many symptoms characteristic of the classic opioid withdrawal syndrome were not present in the patient.

Second-Generation Effects

Pregnancy

In a double-blind, randomized, controlled study of analgesia in labor, the addition of morphine 150 μg to an intrathecal combination of fentanyl (25 μg) and bupivacaine (2.5 mg) significantly prolonged analgesia to more than 4 hours without increasing opioid-related adverse effects (29).

Susceptibility Factors

Genetic factors

Accumulation of morphine-6-glucuronide is a risk factor for opioid toxicity during morphine treatment. However, it does not occur in all patients with renal insufficiency, which is the most common reason for accumulation of morphine-6-glucuronide; this suggests that other risk factors can contribute to morphine-6-glucuronide toxicity.

- Two men, aged 87 and 65 years, both with renal insufficiency, took oral morphine 30 mg/day for pain management (30). While the 65-year-old tolerated morphine well despite a high plasma morphine-6-glucuronide concentration of 1735 nmol/l, the 87-year-old had severe sleepiness and drowsiness, even though the plasma morphine-6-glucuronide concentration was only 941 nmol/l.

The patients were screened for genetic polymorphisms in the OPRM1-gene (coding for μ opioid receptors), P glycoprotein, and other candidate genes that code for transporters that may play an important role in determining the central nervous system concentration of morphine or morphine-6-glucuronide. The 65-year-old patient was a homozygous carrier of the mutated G118 allele of the μ opioid receptor gene, which has previously been related to reduced glucuromorphine potency (a protector gene). In contrast, the 87-year-old patient was a homozygous carrier of the wild-type allele A118. This observation implies that a single nucleotide polymorphism, the G118 allele, has a protective effect against morphine-6-glucuronide toxicity.

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Age

Children

Of 44 children undergoing major genitourinary or lower abdominal surgery in a randomized, single-blind study, 24 were given morphine 0.1 mg/kg epidurally and 20 were given the same dose intravenously immediately after intubation (31). Postoperatively PCA boluses were administered to both groups. Both techniques provided sufficient pain relief. Of the children given epidural morphine, one required treatment for pruritus and seven vomited more than once, compared to none in those given intravenous morphine.

A study of PCA in children suggested that the pharmacokinetics of morphine are similar to those in adults, with the exception of young infants (32).

Neonates with reduced capacity for glucuronidation may have reduced efficacy of morphine, because of reduced renal excretion of morphine-6-glucuronide.

In a 7-year, retrospective, multicenter, observational study, 95 children aged 1–19 years with cancer pain and treated with long-acting morphine were investigated for adverse effects and age-dependent analgesic effects (33). The adverse effects most frequently reported were constipation (10 patients at the beginning of treatment, 20 patients during the course of therapy, and 3 patients at the end of data collection), followed by vomiting (five, eight, and two patients), and nausea (two, six, and three patients), especially in children aged 7 years or more. Some of the children repeatedly complained of pruritus (five, eleven, and two patients). There were no cases of respiratory depression. Oral long-acting morphine proved to be safe and effective, even in very young patients with a history of malignancy.

There have been another two studies of the analgesic effect of intrathecal morphine in children (34,35). In a prospective, double-blind study, 30 children (aged 9–19 years) scheduled for spinal fusion were randomly allocated to a single dose of saline or intrathecal morphine 2 or 5 μg/kg; after surgery, a PCA device provided access to additional intravenous morphine (34). The doses of 2 and 5 μg/kg had similar analgesic effectiveness and adverse effects profiles (nausea, vomiting, pruritus). There were no episodes of severe respiratory depression. Low-dose intrathecal morphine supplemented with PCA morphine provides better analgesia than PCA morphine alone.

In a smaller prospective, open, uncontrolled study, 12 children (3–6 years of age) were given either intermittent intrathecal morphine 5 μg/kg qds or a continuous infusion of a mixture of bupivacaine (40 μg/kg/hour) and morphine (0.6 μg/kg/hour) for intense postoperative pain after selective dorsal rhizotomy (35). The bupivacaine/morphine mixture provided better analgesia with fewer adverse effects. The incidence of pruritus was 83% with morphine compared with 33% with bupivacaine/morphine. Otherwise the adverse effects were similar.

Elderly people

Morphine, as an intravenous bolus of 2 or 3 mg every 5 minutes until pain relief or adverse effects occurred, was given to 875 patients who were under 70 years old and 175 patients who were over 70 years old in a prospective, uncontrolled, non-blinded study (36). The total dose of morphine was not significantly different between the groups. There was no significant difference in the incidence of morphine-related adverse effects, the number of sedated patients, and the number of patients in whom dose titration had to be stopped. The results only applied to the immediate and short-term postoperative periods and the patients studied had a variety of surgical procedures unrelated to age. The results suggested that intravenous morphine can be safely given to elderly patients using the same protocol that is used in younger ones. The generalizability of this study is limited because the sample size was small.

Renal disease

There was a higher incidence of adverse effects of morphine in patients with renal insufficiency who receive opioids for some time (37), and in patients with hemolytic uremic syndrome who were given ketamine with subcutaneous morphine postoperatively (38).

Patients with renal insufficiency may experience a stronger and more prolonged effect, because of reduced renal excretion of morphine-6-glucuronide.

Hepatic disease

Morphine is extensively metabolized. Its main metabolite, morphine-3-glucuronide is without analgesic effects, while morphine-6-glucuronide (also called morphine glucuronide) is supposed to be more potent than morphine. In patients with cirrhosis, morphine clearance may be reduced and the half-life prolonged, and dosages should be reduced (SEDA-22, 101).

Other features of the patient

Myoclonus is more likely in patients taking psychotropic or non-steroidal anti-inflammatory drugs as adjunct analgesia (39).

Drug Administration

Drug additives

Low-dose intrathecal morphine (0.3 mg) plus 0.5% spinal bupivacaine and patient-controlled intravenous morphine (given as a 1 mg bolus with a 5-minute lockout period) has been compared with patient-controlled intravenous morphine alone in 38 patients undergoing knee surgery in a randomized, double-blind study (40). The former combination provided effective analgesia with a low and non-significant incidence of emesis, pruritus, and respiratory depression.

Drug dosage regimens

Oral morphine is more effective after repeated rather than single doses. This is probably due to penetration into the central nervous system of morphine-6-glucuronide, the active metabolite (41).

In a dose-response study of the effects of epidural morphine after cesarean section the quality of analgesia increased with the dose of morphine to a ceiling dose of 3.75 mg (42). Adverse effects were not dose-related.

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Perioperative administration of morphine is another way of enhancing its analgesic properties during the transition from total remifentanil-based anesthesia to the postoperative period, when adequate analgesia is sometimes difficult.

In a randomized study in 245 patients undergoing abdominal or urological surgery the effect of perioperative morphine was evaluated (43). Patients were given a bolus of 0.15 or 0.25 mg/kg 30 minutes before the end of surgery. The results suggested that intraoperative morphine administration did not preclude the need for more morphine in the immediate postoperative period. The 0.25 mg/kg dose was slightly more effective but caused more respiratory depression.

Drug administration route

The practical administration of morphine has been reviewed in relation to dose (initial dose with titration and rescue), formulations (indication and costs), routes of administration, and adverse effects (44).

There is a similar frequency of adverse effects between buccal and intramuscular morphine, as well as intramuscular and intravenous infusions.

Two novel routes for the administration of morphine or bupivacaine (intraperitoneal and interpleural) have been studied for the provision of analgesia after laparoscopic cholecystectomy (SEDA-20, 79).

Some patients developed severe local toxicity during the subcutaneous administration of morphine sulfate (and of hydromorphone) via portable pumps (SEDA-16, 82).

Intramuscular morphine has been compared with epidural morphine or epidural sufentanil, both with bupivacaine, in 90 patients undergoing major abdominal surgery (45). Both epidural regimens gave significantly better postoperative analgesia at rest and during movement. The incidence of adverse effects did not differ significantly between the groups, although the intraoperative requirement for ephedrine or dopamine was higher for the epidural group. Itching was significantly less in the intramuscular morphine group than the epidural groups (7 versus 69%) but nausea and vomiting were equally common.

The systemic availability of morphine from an aerosol is low (about 10%). A nasal solution containing morphine and chitosan, a linear polysaccharide, has been tested in a pilot study in healthy volunteers and patients with cancer (46). The formulation was well tolerated and could be a useful delivery system for morphine.

In a double-blind, randomized, uncontrolled study in 150 women to compare intrathecal morphine 100 micrograms plus ketoprofen, intrathecal morphine 200 micrograms, or epidural morphine 3 mg, postoperative nausea or vomiting occurred in 16, 28, and 26% respectively (47). The incidence of itching was least in those given intrathecal morphine 100 micrograms. The results were unequivocal and did not justify preferring any one of the techniques as better or safer.

In a double-blind, randomized study in 60 patients undergoing elective knee arthroscopy, direct intrasynovial injection of morphine 1 mg provided better long-term analgesia (12–24 hours) than intra-articular morphine 1 mg, with no adverse effects (48).

Intrathecal

Intrathecal morphine provides adequate postoperative analgesia in orthopedic surgery, but commonly causes urinary retention, pruritus, and nausea and vomiting. Finding the optimal dose of analgesic effect with minimal adverse effects is still the main objective of most papers published on morphine (49,50).

In a randomized, double-blind study in 143 patients scheduled for total hip surgery the optimal dose of intrathecal morphine was as low as 0.1 mg (51). The patients were allocated to four groups depending on the dose of morphine used (0.025, 0.05, 0.1, and 0.2 mg). The incidence of pruritus, nausea and vomiting, and urinary retention, and the consumption of antiemetics did not differ among the groups.

The use of intrathecal morphine (52) in the management of chronic non-malignant pain has been reported. Eighty-eight patients were originally evaluated followed by 67 patients 6 months later. At the time of follow-up, mean pain relief was 60%, with 74% of respondents reporting increased activity. There were frequent reports of opioid adverse effects, including sexual dysfunction and menstrual disturbances. The reported adverse effects in descending order of frequency were: excessive sweating (62%), weight gain (52%), difficulty in concentrating, thinking, and memory (48%), nausea and vomiting (42%), arthralgia (25%), peripheral edema (25%), and pruritus (21%). Despite these adverse effects, most of the patients expressed satisfaction with intrathecal opioid therapy. The results were limited owing to the retrospective nature of the study, differing rates of response to specific questions, and the lack of objective measures.

Drug–Drug Interactions

Diclofenac

Although spinal morphine provides effective analgesia, different ways of managing and minimizing its troubling adverse effects are constantly sought. Diclofenac, a non-steroidal anti-inflammatory drug, improves the analgesia provided by epidural morphine and may allow dosage reduction. In an investigation of this drug combination, intrathecal morphine was administered either regularly or on demand to 120 women undergoing cesarean section in doses of 0.1 mg, 0.05 mg, or 0.025 mg with diclofenac 75 mg intramuscularly (53). Severe pruritus was significantly more common in those who received morphine 0.1 mg and there was a trend toward less vomiting with smaller doses. There was no respiratory depression. The results suggested that the adverse effects of intrathecal morphine are dose-dependent and that there was no advantage in using doses of morphine larger than 0.25 mg.

Droperidol

A prospective, randomized, double-blind study of 97 women investigated whether droperidol alleviated the adverse effects of epidural morphine after cesarean section (54). All groups received morphine 5 mg epidurally on delivery, accompanied by no droperidol, or droperidol 2.5 mg epidurally, or droperidol 2.5 mg intravenously. Pruritus occurred in 70% of patients, starting at 6 hours

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after epidural morphine, peaking at 17 hours, and with no significant difference between the different treatment regimens. Nausea and vomiting were significantly reduced by intravenous droperidol, but not by epidural droperidol. The authors concluded that droperidol acts systemically to counter the adverse effects of epidural morphine but is not entirely effective, and they suggested that its failure to alleviate pruritus may have been due to the fact that they used larger doses of morphine than some other investigators.

Propofol

Subhypnotic doses of propofol (20 mg) given to 120 women receiving intrathecal morphine after cesarean section had no significant effect on pruritus (55). Higher success rates have been reported for propofol with non-obstetric patients, suggesting that labor-related factors may perpetuate this adverse effect.

Rifampicin

The metabolism of morphine is enhanced by rifampicin, resulting in loss of analgesic effects of morphine (56).

Tricyclic antidepressants

Clomipramine, amitriptyline, and probably other antidepressants that potentiate the serotonergic system, enhance the analgesic effect of morphine.

Interference with Diagnostic Tests

Therapeutic doses of morphine can alter the blood activities of amylase, lipase, lactate dehydrogenase, creatine phosphokinase, and leucine aminopeptidase, BSP retention, and urine glucose concentration (Benedict's) (57–59).

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Moxifloxacin

See also Fluoroquinolones

General Information

Moxifloxacin is an 8-methoxyquinolone with enhanced potency against important Gram-positive pathogens, notably *Streptococcus pneumoniae* (penicillin-resistant and penicillin-susceptible strains), and class activity against Gram-negative bacteria. Its activity is not affected by beta-lactamases. Moxifloxacin may therefore represent a promising alternative for treatment of respiratory tract infections (1).

Dosage adjustment is not required for patients of advanced age or those with renal or mild hepatic impairment (2).

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Drug interactions with moxifloxacin have been reviewed (3–6).

Observational studies

In a phase I trial, single-dose pharmacokinetics of moxifloxacin have been reported after oral administration of 50–800 mg in 45 healthy Caucasian men. Moxifloxacin was well tolerated (7). There were no serious adverse events, dropouts, or deaths. Only weakness was reported more often in the active treatment group. Other adverse events in subjects taking the active treatment included *Herpes simplex* labialis and an ear disorder. There were no changes in laboratory parameters, electrocardiograms, electroencephalograms, or findings on physical examination. Mean maximum concentrations of moxifloxacin in plasma ranged from 0.29 μg/ml (50 mg dose) to 4.73 μg/ml (800 mg dose) and were reached 0.4–4 hours after drug administration (MICs at which 90% of isolates of penicillin-resistant *Streptococcus pneumoniae* were inhibited were below 0.125 μg/ml). Plasma concentrations fell in a biphasic manner: within 4–5 hours, they fell to 30–55% of the C_{max}. A terminal half-life of 11–14 hours accounted for most of the AUC. Protein binding was about 48%. There was partial tubular reabsorption. No major active metabolites were detected. Concentrations in saliva were higher than in the plasma during the absorption phase, whereas in the terminal phase there was a constant saliva:plasma concentration ratio of 0.5–1.

In an open, randomized, crossover study, the absolute systemic availability of a single 100 mg dose of moxifloxacin was 0.92 in 10 healthy men (mean age 29 years) (8). There was no evidence of active tubular secretion. Both the oral and intravenous formulations were well tolerated, with five reported possible or probable drug-related adverse events, including headache, nausea, and localized urticaria.

In a prospective, uncontrolled, unblinded, phase III trial in 254 patients with community-acquired pneumonia diagnosed by culture or serologically, moxifloxacin (400 mg/day orally for 10 days) produced a bacteriological response of 91% (9). Drug-related adverse events were reported in 33% of patients; nausea (9%), diarrhea (6%), and dizziness (4%) were the most common adverse events.

Moxifloxacin (400 mg/day orally for 7 days) in 12 healthy men significantly reduced the normal oropharyngeal microflora (alpha-hemolytic streptococci and *Neisseriae*), whereas the number of Gram-negative anerobic bacteria increased markedly; however, no new colonizing moxifloxacin-resistant strains were isolated (10). Moxifloxacin caused a significant reduction in enterococci and enterobacteria, while the numbers of staphylococci, streptococci, *Bacillus* species, and *Candida albicans* were unaffected. There was no impact on peptostreptococci, lactobacilli, *Veillonella*, *Bacteroides*, or fusobacteria, but bifidobacteria and *Clostridia* decreased during moxifloxacin administration. The microflora normalized after 35 days (11).

In a multicenter, prospective, double-blind, randomized trial in 455 patients with community-acquired pneumonia oral moxifloxacin 200 mg/day or 400 mg/day for 10 days resulted in a bacteriological response of 91% (12). Most adverse events, possibly or probably related to moxifloxacin, were generally mild or moderate and were mostly related to the digestive system: diarrhea, nausea, and abdominal pain with 200 mg/day; diarrhea, liver function abnormalities, and nausea with 400 mg /day. The drugs were withdrawn because of adverse events in seven of 229 patients taking 200 mg/day, and 11 of 224 taking 400 mg/day.

Organs and Systems

Cardiovascular

Moxifloxacin blocks the rapid-component delayed-rectifier potassium channel in the heart, and thus prolongs the QT_c interval by 6 minutes after oral administration and 12 minutes after intravenous administration (13). Moxifloxacin carries a greater risk of QT interval prolongation than ciprofloxacin, levofloxacin, and ofloxacin (14), and although the risk of moxifloxacin-induced torsade de pointes is expected to be minimal when the drug is given in the recommended dosage (400 mg/day) (15), moxifloxacin should be used with caution in patients with prodysrhythmic conditions and avoided in patients taking antidysrhythmic drugs, such as quinidine, procainamide, amiodarone, and sotalol (3).

- A man developed a hypertensive crisis and transient left bundle branch block with QT interval prolongation after taking moxifloxacin (16).
- Sinus tachycardia (120/minute) associated with moxifloxacin has been reported in a 49-year-old man about 45 minutes after he took a single 400 mg dose of moxifloxacin (17).

The underlying mechanism may have been vasodilatation, either directly or indirectly, owing to release of histamine, with reflex tachycardia. These effects have been described for other fluoroquinolones.

Nervous system

Syncope has been reported after the use of moxifloxacin (18).

Gastrointestinal

The most common adverse effects of moxifloxacin are gastrointestinal disturbances (nausea, diarrhea), which are usually mild to moderate in intensity and do not force patients to discontinue treatment (19,20). The frequency of nausea and vomiting is higher than the frequency of diarrhea and abdominal pain (21). Moxifloxacin caused nausea in 7.2% and diarrhea in 5.7% of patients (19).

In a prospective pharmacokinetic study in 12 healthy men the most frequent adverse events, possibly or probably related to moxifloxacin, were generally mild or moderate and were mostly diarrhea, nausea, and abdominal pain (22).

Liver

- A 69-year-old man who took moxifloxacin 400 mg/day for 5 days developed cholestasis (20).

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Skin

Moxifloxacin has a low propensity for causing phototoxic reactions relative to other fluoroquinolones (2,3).

Immunologic

In vitro, moxifloxacin has immunomodulatory activity through its capacity to alter the secretion of IL1-α and TNF-α by human monocytes (23).

Moxifloxacin can cause anaphylactic reactions (24).

A case of simultaneous drug allergies has been reported (25).

- A 32-year-old woman had a generalized urticaria 15 minutes after taking co-amoxiclav and 1 year later developed a non-pruritic micropapular rash some hours after taking moxifloxacin 400 mg.

Drug–Drug Interactions

Antacids

The systemic availability of moxifloxacin is markedly reduced by the co-administration of antacids that contain magnesium or aluminium, unless administration occurs 2 hours before or 4 hours after moxifloxacin (19,26). An interval of 2 hours before or 4 hours after taking antacids ensures that the effect of the interaction is not clinically relevant.

Digoxin

There was no clinically relevant effect of moxifloxacin on the pharmacokinetics of digoxin in combination steady-state conditions (4).

Epoetin

- A 76-year-old man with low-risk myelodysplastic syndrome had a major erythroid response to combination therapy with epoetin and moxifloxacin (27). The immunomodulatory effects of moxifloxacin may have explained the synergy with epoetin.

Iron

Iron salts impair the absorption of moxifloxacin (26).

Probenecid

Concomitant administration of probenecid did not affect the elimination of moxifloxacin (4).

Ranitidine

The systemic availability of moxifloxacin was not affected by concurrent administration of ranitidine (4).

Sucralfate

Drugs that contain sucralfate impair the absorption of moxifloxacin (26).

Theophylline

Moxifloxacin did not affect the pharmacokinetics of theophylline or vice versa (28).

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Warfarin

Moxifloxacin had no effect on the pharmacokinetics of warfarin in combination steady-state conditions (4)

Food–Drug Interactions

The effect of food on the pharmacokinetics of moxifloxacin was not clinically important (29). In another study dairy products had no effect on moxifloxacin kinetics (30).

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Moxisylyte

General Information

Moxisylyte is an alpha-adrenoceptor antagonist with vasodilatory activity (1). It is used orally in the treatment of peripheral vascular disease and by intracavernosal injection in erectile dysfunction.

Organs and Systems

Liver

Three cases of hepatitis have been reported with moxisylyte in separate publications from France in 1991 (SEDA-17, 163).

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Moxonidine

General Information

Moxonidine is a selective agonist at imidazoline I_1 receptors in the rostroventrolateral medulla and has very little alpha$_2$-adrenoceptor agonist activity. It has similar efficacy to other antihypertensive drugs. Its safety has been evaluated in a number of individual studies and in a systematic review of randomized trials (1).

Unlike clonidine, moxonidine does not appear to cause sedation or to impair psychomotor performance or cognitive function. However, possible potentiation of the effect of benzodiazepines can occur. There is no evidence of a withdrawal syndrome or rebound hypertension associated with sudden withdrawal.

Organs and Systems

Mouth

Dryness of the mouth occurs in about 10% of patients who take moxonidine, but it is usually mild and occurs early in therapy. The effect is dose-dependent but shows no tendency to accumulate over time. This effect is consistent with an action of mildly inhibiting salivary flow.

Liver

- Cholestatic hepatitis occurred in an 83-year-old man after 9 months of continuous therapy with moxonidine. No autoantibodies were detected and liver biopsy showed features compatible with drug-induced inflammatory intrahepatic cholestasis. The patient recovered fully and his biochemical data normalized 8 weeks after withdrawal.

In a postmarketing surveillance program none of more than 20000 patients developed cholestatic hepatitis (2).

Drug Administration

Drug formulations

Whereas moxonidine appears to be generally well tolerated in hypertension, in congestive heart failure it was

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prematurely withdrawn because of adverse outcomes on survival in a major trial, the MOXCON trial, in patients with NYHA class II-IV heart failure who were treated with modified-release moxonidine 0.5–3.0 mg/day or placebo (3). An interim analysis of the first 2000 patients enrolled showed that 53 patients taking moxonidine, compared with 29 taking placebo, died in the first 6 months and the trial was stopped prematurely. Excess mortality in the moxonidine arm appeared to be related to sudden death. The reason for this adverse outcome has to be fully elucidated. Although it has not been established that moxonidine caused a higher mortality rate, it is no longer being used in patients with heart failure. From the large database available there is no concern with regard to any adverse effect on survival with the immediate-release formulation used in hypertension.

Drug–Drug Interactions

Lorazepam

When co-administered with lorazepam 0.4 mg, moxonidine increased impairment of attentional tasks (choice, simple reaction time and digit vigilance performance, memory tasks, immediate word recall, delayed word recall accuracy, and visual tracking). These effects should be considered when moxonidine is co-administered with lorazepam, although they were smaller than would have been produced by a single dose of lorazepam 2 mg alone (4).

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Mupirocin

General Information

Mupirocin is an antibiotic that inhibits bacterial protein synthesis by binding to isoleucyl transfer RNA synthetase. It is primarily bacteriostatic at low concentrations, but is bactericidal in the high concentrations and can have activity against organisms reported to be relatively resistant in vitro.

In a randomized, double-blind, placebo-controlled trial, 97 of 2012 patients treated with mupirocin reported adverse effects, such as rhinorrhea and itching at the site of application (1).

Spontaneous rupture of polyurethane peritoneal catheter has been attributed to mupirocin ointment (2).

- An 84-year-old man with diabetic nephropathy and end-stage renal disease began continuous ambulatory peritoneal dialysis and over the next year had four episodes of exit-site infection and peritonitis and used mupirocin ointment. The exit-site catheter became dilated and during an episode of infection for which he used mupirocin on 6 successive days, a longitudinal rupture developed in the peritoneal catheter, which was removed. The peritoneal liquid contained *Escherichia coli* and *Proteus mirabilis* and the catheter tip contained *E. coli* and *Enterobacter cloacae*. He was treated with ciprofloxacin, without complications, and after 1 month a new peritoneal catheter was inserted.

Organs and Systems

Skin

Mupirocin ointment can occasionally cause allergic contact dermatitis (3).

Long-Term Effects

Drug tolerance

Resistant *Staphylococcus aureus* can emerge during treatment with mupirocin.

In 149 patients undergoing chronic peritoneal dialysis, *S. aureus* was isolated from 26 patients, 25 from the nares, axillae, or groins and one from the catheter exit site (4). So-called "high-level" mupirocin-resistant organisms (minimum inhibitory concentration 256 mg/ml or more) were isolated from four patients. Methicillin-resistant organisms (MRSA) were not detected. One patient with high-level mupirocin-resistant organisms had peritonitis due to *S. aureus*, resulting in treatment failure and catheter loss.

Of 36 patients undergoing continuous ambulatory peritoneal dialysis (mean age 55 years; 21 men), who had been applying mupirocin to the catheter exit site once weekly for an average of 3.1 years before the start of the study, three were nasal carriers of *S. aureus*, and there was only one mupirocin-resistant organism (5). Once-weekly application of mupirocin at catheter exit sites led to comparable rates of colonization by mupirocin-resistant *S. aureus* as did thrice-weekly or more frequent application.

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Muramyl tripeptide

General Information

The antitumor properties of muramyl tripeptide are thought to be related to its immunoenhancing effects, in particular on the monocyte/macrophage system. Its most common adverse effect is a flu-like syndrome, usually during the first administration. In one trial in nine patients, four had mild to moderate respiratory distress, two of whom had pre-existing asthma and symptoms suggestive of asthma exacerbation (1).

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Muromonab–CD3

See also Monoclonal antibodies

General Information

Muromonab–CD3 (orthoclone, OKT3) is a murine monoclonal antibody targeted against the human CD3-receptor–T cell complex. This powerful immunosuppressive agent is used in the treatment of acute transplant rejection. Its use during initial rejection prophylaxis is subject to debate because excessive immunosuppression can increase the risk of infections and secondary malignancies (1). Renal transplant patients with a high risk of rejection have been suggested as possible candidates for muromonab prophylaxis (2). Excessive immunosuppression and unexpected over-activation of the immune system are the main adverse effects.

Cytokine release syndrome

A complex of acute systemic symptoms referred to as the "cytokine-release syndrome" is the most typical adverse effect of muromonab (3). A flu-like reaction is the key component of this complex syndrome, including fever, chills, headache, myalgia, tachycardia, and gastrointestinal symptoms. Other systemic and severe manifestations of the syndrome include acute pulmonary edema and neurological, renal, and hematological disorders. Symptoms occur within 1 hour after the initial doses of muromonab and last for several hours. A lower incidence and less severity were observed after subsequent doses (4). The cytokine-release syndrome was also less frequent after low doses or a 2-hour infusion of muromonab (instead of conventional doses or single bolus infusion) and it was thought to be more severe and of longer duration in patients with moderate-to-severe graft rejections (5–9).

Considerable efforts have been made to prevent or control the cytokine-release syndrome and its consequences (10). High-dose methylprednisolone (8 mg/kg) given before muromonab remains the basis of prophylaxis, and two separate doses are more effective than a single bolus (11). In a retrospective comparison of 345 renal transplant patients, other investigators found that the use of diltiazem allowed a reduction in the dosage of methylprednisolone, reduced nephrotoxicity, and reduced both delayed graft function and postoperative intragraft thrombosis (12). Indometacin, even at low doses, has also been successfully used without impairing rejection reversal or renal function (13). In contrast, prophylaxis with pentoxifylline was not supported in one carefully controlled study (14).

Although the release of a wide range of cytokines was increased after muromonab administration, tumor necrosis factor alfa and interleukin-6 were suggested to play a pivotal role, and monoclonal anti-TNF-alfa antibody administration reduced the acute clinical symptoms (15). A role for the activation of complement and neutrophils was also suggested.

Several humanized CD3 antibodies have been produced and tested, with the aim of reducing the adverse effects associated with the murine orthoclone antibody. The first results in renal transplant patients were encouraging, with promising clinical results, no evidence of antiglobulin response, and no or very few and minimal adverse effects attributable to various humanized monoclonal CD3 antibodies (16,17). In particular, careful patient monitoring failed to identify any significant cytokine release syndrome.

Organs and Systems

Cardiovascular

Cardiovascular manifestations are usually observed during the cytokine-release syndrome. They mostly included tachycardia and transient hypertension or hypotension (4). Fluid overload or volume depletion can also play a role. Chest pain or severe dysrhythmias are infrequent (18).

Muromonab has been thought to exert procoagulant activity and activate fibrinolysis, probably as a result of TNF-alfa release of other cytokines and cellular adhesion to the vascular endothelium (19,20). Accordingly, retrospective studies have pointed to an increased risk of intragraft thromboses with thromboses in the renal artery, renal vein, or glomerular capillaries, or thrombotic microangiopathy, leading to a higher incidence of rejection episodes in patients receiving high or conventional doses of muromonab (19,21). Among 231 kidney transplant

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recipients who received muromonab prophylaxis, intragraft thromboses were found in 13 (5.6%), and the use of very high-dose methylprednisolone (30 mg/kg) was suggested to be a major risk factor (22). In contrast, and despite the evidence of procoagulant activity, some investigators have failed to identify evidence that muromonab increases the risk of thromboembolic complications (20,23).

Respiratory

Dyspnea and pulmonary edema sometimes develop during the cytokine-release syndrome. Pulmonary toxicity was mostly observed in patients who had fluid retention and weight gain before receiving muromonab. The incidence has been markedly reduced by the formulation of guidelines for management (3). Cytokine release and complement activation with further neutrophil activation and pulmonary vascular endothelium damage were suggested to be involved (24).

Nervous system

Self-limiting and benign central nervous system manifestations mimicking those of aseptic meningitis, that is fever, headache, nuchal rigidity, cognitive disorders, and photophobia, were observed in 3–10% of patients who received muromonab (3). The symptoms were usually delayed for 2–3 days and resolved spontaneously despite continuation of treatment. More severe neurological disorders requiring withdrawal have been observed in up to 7% of patients (25). The various reported symptoms consisted of slowly reversible diffuse encephalopathy with mental changes, neurosensory hallucinations, tinnitus with reversible hearing loss, transient hemiparesis, cerebral infarction, generalized or focal seizures, cortical blindness, psychotic symptoms, obtundation, and coma (SED-13, 1132) (SEDA-21, 380) (25). Diabetes and severely impaired renal function were possibly significant risk factors (SEDA-19, 353) (SEDA-21, 380). Neurotoxic symptoms were supposedly mediated by cytokine release and potentiated by uremic toxins. Raised concentrations of tumor necrosis factor alfa in the cerebrospinal fluid were suggested to play a major role in muromonab-induced aseptic meningitis and encephalopathy (26).

Muromonab-induced aseptic meningitis is relatively common and is usually benign, with prompt recovery despite continuation of treatment.

- In a 28-year-old man the clinical features of aseptic meningitis were prolonged over 1 month after the administration of muromonab, and persistent severe headaches resolved only after several aspirations of cerebrospinal fluid (27).

This case was described as a syndrome of headache with neurological deficits and CSF lymphocytosis (HaNDL syndrome).

Sensory systems

Eyes

Spontaneously reversible mild conjunctivitis and episcleritis have been noted in 75 and 10% of patients respectively.

Diffuse anterior scleritis responding to an increased dosage of prednisone was mentioned in one patient (28).

Isolated visual loss (persistent in one patient) shortly after muromonab administration is rare (SEDA-20, 340) (29).

Ears

Ototoxicity from muromonab has been described, but the incidence is unknown (SEDA-21, 380). Audiograms performed before and 48–72 hours after administration of muromonab showed sensorineural hearing loss of at least 15 db in five of seven renal transplant patients (30). A third audiogram 2 weeks after muromonab treatment showed amelioration or complete recovery in all four of the patients who were tested.

Hematologic

Acute thrombocytopenia has been reported in one patient (SEDA-21, 380).

Liver

Hepatitis has been attributed to cytokine release from muromonab (31).

- A 31-year-old man underwent renal transplantation for end-stage renal disease secondary to hypertension. He was given basiliximab for induction immunosuppression. At 13 months after transplantation he had evidence of transplant rejection. His creatinine concentration rose acutely from 83 to 165 μmol/l over 1 week. This was his first rejection episode (Banff IIa). There was no evidence of viral infection. He received muromonab with conventional prophylaxis (antihistamines, paracetamol, and corticosteroids) to reduce the severity of cytokine release. This was his first exposure to muromonab. Initially he complained of fever and nausea, and the following day he was somnolent and had right upper quadrant tenderness. Liver function tests, which had been normal on the day of admission, were abnormal. Hepatitis serology showed positive hepatitis B core antibody (IgM and IgG), positive hepatitis A antibody, negative hepatitis surface antigen, and negative hepatitis C antibody. The hepatitis B core antibody (IgM and IgG) had been positive before transplantation 16 months before. Muromonab was withdrawn and he showed signs of clinical and chemical improvement. Rejection was successfully treated with glucocorticoids and antithymocyte globulin.

Urinary tract

Spontaneously reversible increases in serum creatinine concentrations occurred in 8–18% of muromonab-treated patients, and were thought to have resulted from inhibition of renal prostaglandin synthesis and release of cytokines (32,33). There were no adverse consequences on short-term graft survival or graft function (32).

Isolated cases of hemolytic-uremic syndrome have been reported (SED-13, 1133) (SEDA-21, 380).

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Immunologic

An antibody response to muromonab has been detected in 40% of patients undergoing a 14-day induction regimen of muromonab 5 mg/day (10). It has been suggested that the incidence of antimuromonab antibodies depended on the immunosuppressive regimen, but this was based on a retrospective study in a limited number of patients (SEDA-22, 409). Furthermore, sensitization was not relevant in most patients. Only raised IgG anti-idiotypic antibodies in high enough titers (over 1:1000) significantly neutralize the binding of muromonab to the CD3 receptor and reduce clinical efficacy, thus precluding further muromonab administration.

Antimuromonab IgE antibodies have been identified after 10–25 days of treatment in six of 181 patients, and only in those with high titers of antimuromonab IgG antibodies (34). Immediate IgE-mediated anaphylactic reactions, namely anaphylactic shock, bronchospasm, urticaria, have been rarely reported and have sometimes been difficult to differentiate from the cytokine-release syndrome (35,36). Late-onset reactions after the first week of treatment, including cutaneous erythema, a fall in blood pressure, or serum sickness-like reactions, are infrequent (37).

Rare anaphylactic reactions with antimuromonab IgE antibodies have been reported (SED-14, 1309). Anaphylactoid reactions to muromonab can also occur (38).

- A 15-year-old girl underwent uneventful renal transplantation. On the third postoperative day she received her first dose of muromonab for a presumptive diagnosis of graft rejection. Despite premedication with diphenhydramine, paracetamol, and high-dose methylprednisolone, within 20 seconds after intravenous muromonab, she developed shortness of breath, digital paresthesia, facial edema, laryngeal stridor, reduced oxygen saturation, and a fall in blood pressure. She recovered after intubation and appropriate vasopressor administration, but required transplant nephrectomy for hemorrhagic and coagulative necrosis of the transplanted kidney.

This acute reaction was supposedly mediated by nonimmunologic mast cell degranulation, as screening for IgE antimuromonab antibodies was negative.

As with other potent immunosuppressive drugs, muromonab has been suspected to increase the risk of infections. Multiple possible biases in studies of the incidence of muromonab-associated infections have been discussed (3); there were no differences among patients who received muromonab compared with those who received other immunosuppressive regimens. Since then, several other investigators have reported their findings, indicating that this debate continues.

In patients with renal transplants, the overall incidence of infections during the first three posttransplantation months was significantly higher in one trial of patients treated with prophylactic muromonab or ciclosporin (39), but there was no significant difference in the severity of infections in another similar trial (40). Both studies failed to identify any adverse impact of infectious episodes on patient survival. In a comparison of prophylactic ATG-Fresenius with muromonab there were more common minor infections (for example, cutaneous mycosis, *Herpes simplex* virus infections) in the muromonab arm, but a similar incidence of life-threatening or severe infections (41). In contrast to these findings, a large retrospective study showed a significantly higher incidence of infection-related deaths among patients who received muromonab for induction therapy compared with those who did not receive muromonab (42). However, renal graft survival was significantly improved in patients treated with muromonab, and there were no subsequent viral deaths after the routine use of appropriate anti-infectious prophylaxis.

In patient with liver transplants (43,44) or heart transplants (45), retrospective studies have shown that muromonab treatment is an additional or independent risk factor for symptomatic cytomegalovirus infections in cytomegalovirus-seropositive patients or in recipients of cytomegalovirus-seropositive donors, suggesting that cytomegalovirus prophylaxis should be implemented in these patients. It has also been suggested that early muromonab administration in the posttransplant period increases the likelihood of invasive cytomegalovirus disease after liver transplantation (46). In contrast, other investigators failed to show an increased incidence of cytomegalovirus infections after muromonab versus triple drug therapy in heart transplant patients (47). Based on a retrospective study of 154 liver transplant patients, muromonab was suggested as a risk factor for *Pneumocystis jiroveci* pneumonia (48).

These results suggest that the incidence and severity of infections is more likely to be related to the degree of immunosuppression than to the effect of an individual drug.

Long-Term Effects

Tumorigenicity

As expected from its pronounced immunosuppressive activity, muromonab is a significant risk factor for secondary neoplasia, especially when high doses, increased treatment duration, sequential courses, or early retreatment are used (49). Whether the increased risk of neoplasia after muromonab-based immunosuppression is due to the drug itself or reflects the overall degree of immunosuppression is a matter of debate, and conflicting results have emerged. Several retrospective or controlled studies did not show more frequent malignancies after muromonab compared with other immunosuppressive regimens (50–52). On the other hand, the rate of non-Hodgkin's lymphomas was higher in kidney and heart transplant recipients who received muromonab prophylaxis rather than antithymocyte/antilymphocyte globulin (53). Using data from the manufacturers and the literature, the rate of malignancies after muromonab was estimated to be 0.57% (54), but potential under-reporting strongly limited the validity of this estimation. Although the roles of high cumulative doses or repeated courses as risk factors are not definitely proven, it is usually recommended not to exceed 14 days of treatment with cumulative doses of 70 mg (3).

An analysis of the Australia and New Zealand Dialysis and Transplant Registry (7953 patients with 9460 renal

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transplants) has confirmed that immunosuppression with polyclonal and monoclonal muromonab antibodies independently increases the risk of virus-mediated cancer (55). The increased risk was about 60% for non-Hodgkin's lymphoma and 75% for non-Hodgkin's lymphoma plus, in women, carcinoma of the cervix, vagina, and vulva.

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Muzolimine

See also Diuretics

General Information

Muzolimine is a diuretic with a long duration of action, slightly more effective than furosemide. In Germany muzolimine was withdrawn 2 years after its introduction.

Organs and Systems

Nervous system

Of 29 patients with chronic renal insufficiency treated with high doses of muzolimine, five developed a neurological syndrome very similar to multiple sclerosis (1). Other reports of severe neurotoxicity with muzolimine have appeared (SEDA-16, 225).

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MW-2884

See also Non-steroidal anti-inflammatory drugs

General Information

MW-2884 (10-methoxy-4*H*-benzo-(4,5)-cycloheptathiophene-4-glindene acetic acid) is an inhibitor of monokine release. In 12 patients with rheumatoid arthritis it caused gastrointestinal disturbances, temporary liver function impairment, and allergic skin reactions. One patient stopped taking it because of severe urticaria (1).

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Mycophenolate mofetil

General Information

Mycophenolate mofetil, the morpholinoethyl ester of mycophenolic acid (rINN), is an antimetabolite that interferes with the synthesis of nucleic acids and selectively inhibits the proliferation of T and B lymphocytes. It has been used to treat psoriasis and to prevent acute renal allograft rejection in combination with ciclosporin and glucocorticoids.

Uses

In 16 renal transplant patients with suspected ciclosporin nephrotoxicity, the addition of mycophenolate allowed safe reduction in the dosage of ciclosporin, with subsequent improvement in renal function and arterial blood pressure over 6 months (1). It might allow the rapid withdrawal of glucocorticoids in patients taking ciclosporin or tacrolimus, and therefore reduce the incidence of glucocorticoid-induced post-transplant diabetes, hypercholesterolemia, and hypertension (2). There have been several reports of patients with ciclosporin-associated thrombotic microangiopathy/hemolytic-uremic syndrome in whom mycophenolate was successfully substituted (3,4).

When mycophenolate replaced ciclosporin in 17 renal transplant patients with ciclosporin nephropathy, serum creatinine concentrations fell by a mean of 26% (5). There were no cases of acute allograft rejection. Adverse effects of mycophenolate were not mentioned.

There were beneficial effects on blood pressure, lipid profile, and glomerular hemodynamics by switching from ciclosporin to mycophenolate in an open study in 17 renal transplant patients with stable renal function who took ciclosporin and prednisone in two steps (6). In step I mycophenolate was added and the dose of ciclosporin was progressively reduced to produce one-third of the original trough concentration; this took about 20 weeks. In step II, ciclosporin was gradually withdrawn over 6 weeks. During step I, two patients dropped out, one with severe diarrhea which reversed after mycophenolate withdrawal and one with biopsy-proven acute rejection, with recovery after mycophenolate withdrawal and an increase in the dose of ciclosporin. During step II there was no acute rejection. At 1 year after the end of the study, two patients had stopped taking mycophenolate, one because of recurrent upper airway infections (probably not related to mycophenolate) and one because of Kaposi's sarcoma of the leg. In the last case a possible role of mycophenolate could not be ruled out (SEDA-24, 429).

Mycophenolate has also been studied in various chronic inflammatory disorders, such as rheumatoid arthritis, pemphigus vulgaris, and psoriasis. In 70 patients with chronic active Crohn's disease, mycophenolate plus glucocorticoids produced benefit on disease activity comparable to azathioprine plus glucocorticoids (7). Two of the 35 patients randomized to mycophenolate had significant adverse effects that required drug withdrawal, namely rashes and vomiting.

General adverse effects

In three pivotal clinical trials of mycophenolate mofetil in kidney transplant recipients, adverse effects were in accordance with the known antiproliferative effect of mycophenolate, namely gastrointestinal disorders, leukopenia, and opportunistic infections, in particular cytomegalovirus tissue invasive disease (SED-13, 1130) (SEDA-20, 346). Nephrotoxicity was not observed in clinical trials, and renal function significantly improved in six patients converted to mycophenolate for ciclosporin nephrotoxicity (8).

In one patient, mycophenolate mofetil was putatively involved in a constellation of symptoms that included fever, exudative pharyngitis, adynamic ileus, electrolytic abnormalities, and myocardial dysfunction, which resolved on withdrawal (SEDA-20, 346).

Organs and Systems

Respiratory

Interstitial pneumonitis with severe respiratory failure has been reported in two patients (SEDA-21, 389) (SEDA-22, 418). One patient improved after mycophenolate mofetil was withdrawn, but interstitial fibrosis was found on serial lung biopsies. The other patient died from respiratory failure 3 months later. Although other drugs may have been involved in these two patients, one other reported case with recurrence of respiratory failure on each rechallenge of mycophenolate is particularly convincing.

There was a dry cough in five of 45 patients taking mycophenolate, associated with dyspnea and hypoxia in one patient and asthma exacerbation in another (9). As the symptoms reversed only after mycophenolate mofetil withdrawal, the authors suggested that dry cough and dyspnea should be considered as early symptoms of pulmonary toxicity.

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Hematologic

There was a dose-related increase in the incidence of leukopenia in the three pivotal trials.

Abnormalities of neutrophil morphology have been reported with mycophenolate.

- In two transplant patients, changes in circulating neutrophils (nuclear hypolobulation and abnormal clumping of nuclear chromatin) were identified after 4–5 months of treatment with mycophenolate (10). A bone marrow aspirate in one patient showed hypocellularity, abnormal clumping of chromatin beyond the promyelocyte stage, and almost no segmented neutrophils. These morphological abnormalities preceded the appearance of peripheral neutropenia in both patients and normalized after mycophenolate withdrawal.

The authors suggested that neutrophil dysplasia had resulted from inhibition of guanosine nucleoside synthesis.

Gastrointestinal

Mycophenolate mofetil often causes gastrointestinal disorders, most commonly a dose-related diarrhea and more rarely esophagitis, gastritis, duodenal or colonic ulceration, and gastrointestinal hemorrhage (SEDA-22, 418). Diarrhea can be extremely severe for various reasons, such as inappropriate dosage in low-weight patients, renal insufficiency, drug interactions (for example with sulfinpyrazone) interfering with the renal tubular excretion of mycophenolate metabolites. That was the case in two patients who had frequent diarrhea with significant weight loss and electrolyte disturbances requiring parenteral nutrition (SEDA-21, 389).

Pooled data from the tricontinental and the US studies in kidney transplant patients showed incidences of diarrhea of 31 and 36% in patients taking 2 and 3 g/day respectively (11). In a retrospective study, 29% of 109 mycophenolate-treated patients had diarrhea that required hospitalization and 12% developed upper intestinal symptoms (gastritis, esophagitis) (12). Frequent dosage reduction was necessary and only 28% of patients were still taking full doses after 1 year.

Gastrointestinal toxicity was confirmed to be the most frequent adverse effect (53%) in 120 pancreas transplant patients who received a triple immunosuppressive regimen consisting of mycophenolate, tacrolimus, and prednisone (13). As a result, conversion from mycophenolate to azathioprine at 1 year was mostly due to gastrointestinal toxicity, which was significantly more frequent in recipients of pancreas transplantation alone (49%) compared with recipients of pancreas transplantation after previous kidney transplantation (26%) or recipients of simultaneous pancreas and kidney transplants (14%). In another study in 120 kidney transplant patients randomized to receive tacrolimus and prednisone with or without mycophenolate, there was a high rate of mycophenolate withdrawal (43%) during the first 6 months, mostly because of gastrointestinal toxicity (14). In both of these studies, the withdrawal rate was higher than in the pivotal trials in kidney transplant patients (4–10% after 6 months) (11). As both studies used a combination of tacrolimus plus mycophenolate rather than mycophenolate plus ciclosporin, a synergistic effect on the gastrointestinal tract, or more probably higher serum concentrations of mycophenolic acid due to an interaction with tacrolimus, could have contributed (SEDA-21, 390) (SEDA-22, 421).

The mechanism of gastrointestinal toxicity is not well understood.

- A 42-year-old woman with a renal transplant taking triple immunosuppression (azathioprine, ciclosporin, and glucocorticoids) was converted after 7 years from azathioprine plus ciclosporin to mycophenolate (2 g/day) because of ciclosporin nephrotoxicity (15). Within 2 months she had developed severe persistent watery diarrhea (5–10 stools/day) and lost 7 kg over 2 months. Investigations ruled out an infectious cause and there were features of duodenal villous atrophy on histological examination. Diarrhea disappeared after mycophenolate withdrawal and two subsequent duodenal biopsies showed improvement 2 months later and further complete recovery 6 months later.

This report suggests that loss of normal villous structure is one of the possible mechanisms of mycophenolate-induced severe diarrhea.

Diarrhea is the most commonly reported adverse effect in patients with transplants taking mycophenolate. In 26 renal transplant recipients with persistent afebrile diarrhea (daily fecal output over 200 g), prospectively investigated for infections and morphological and functional integrity of the gastrointestinal tract, all but one had an erosive enterocolitis; 70% had malabsorption of nutrients, which contributed to the diarrhea (16). In about 60% an infectious origin was demonstrated and successfully treated with antimicrobial drugs without changing the immunosuppressive regimen. In about 40% there was no infection but a Crohn's disease-like pattern of inflammation. These patients also had less pronounced malabsorption of bile acids but a significantly faster colonic transit time, which correlated with trough concentrations of mycophenolic acid. Withdrawal of mycophenolate was associated with allograft rejection in one-third of these patients.

Ischemic colitis has also been attributed to mycophenolate (17).

- A 49-year-old woman taking ciclosporin, prednisolone, and mycophenolate developed acute refractory rejection 4 days after renal transplantation. After an unsuccessful glucocorticoid pulse, her immunosuppressive regimen was successively changed to muromonab and tacrolimus with mycophenolate maintenance. Twelve days after transplantation she had abdominal pain and watery/bloody diarrhea. Colonoscopy showed multiple ulcers with mucosal injection and colon edema. A biopsy suggested ischemic colitis and cytomegalovirus infection was ruled out. Her symptoms persisted until mycophenolate was withdrawn and further colonoscopy showed complete resolution.

Patients with inflammatory bowel disease unresponsive to azathioprine or intolerant of it may benefit from mycophenolate mofetil. Of 12 patients so treated, three had minor adverse effects (headache, nausea, arthralgia). Three with ulcerative colitis developed rectal bleeding while taking mycophenolate mofetil. Histological features of the mucosa were highly

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suggestive of drug-induced bleeding. Enterohepatic recycling results in high colonic concentrations of mycophenolic acids, which may have a direct toxic effect on the epithelium (18).

Liver

In two renal transplant patients, serum bilirubin concentrations increased to 46 and 63 μmol/l within 3–7 days of mycophenolate treatment, and further increased to 98 μmol/l in one patient after the dose was increased (19). The bilirubin concentration returned to normal or pretreatment values after withdrawal or dosage reduction. Although both patients also received ciclosporin, which has been associated with hyperbilirubinemia, the temporal relation and a possible dose-dependent effect favored a causative role of mycophenolate.

Skin

Mycophenolate-induced eczema has been reported (20).

- A 45-year-old woman with a liver transplant began to take mycophenolate mofetil (2 g/day) before planned ciclosporin withdrawal. After 3 days she developed pruritus and a bullous eruption on her hands and feet. The lesions improved after mycophenolate was withdrawn, but soon reappeared after readministration of a lower dose (500 mg/day). A skin biopsy showed dyshidrotic eczema and a skin test with mycophenolate mofetil produced recurrence.

Hair

Alopecia has been noted in two patients converted from ciclosporin to mycophenolate (SEDA-22, 418).

- Onycholysis with blisters and loose toenails has been observed in a 45-year-old man who took tacrolimus, prednisone, and mycophenolate for 3 weeks after renal transplantation (21). The lesions improved after withdrawal and recurred after two subsequent re-exposures.

Immunologic

Transplant rejection

In a randomized study, 14 patients with liver transplants were given calcineurin inhibitors and 14 were given mycophenolate mofetil monotherapy (22). Those who were given mycophenolate had reversible episodes of acute graft rejection and there were no such episodes in those who were given calcineurin inhibitors.

In 11 patients with orthotopic liver transplants who had adverse effects from ciclosporin or tacrolimus, mycophenolate mofetil monotherapy for 1 year was successful. This was followed by a randomized, controlled trial in 18 patients, of whom nine were given mycophenolate mofetil (23). Five patients completed the 3 month trial. Of these, two had an episode of acute rejection, one after 2 months and one after 3 months, which did not respond to the reintroduction of tacrolimus and intravenous glucocorticoids. One had a glucocorticoid-responsive episode of severe acute rejection after 3 weeks. The other two patients had normal liver function tests after 2 weeks and 2 months respectively, when the trial was stopped. Mycophenolate mofetil allows a reduction of the dose of calcineurin inhibitor, with a low risk of rejection and improvement in renal function. However, it is associated with an unacceptable risk of acute rejection.

Infection risk

The role of mycophenolate in the occurrence of opportunistic infections is debated. In a retrospective comparison of 358 simultaneous pancreas plus kidney transplant patients who received a ciclosporin-based immunosuppressive regimen, the rate of opportunistic infections was similar in patients treated with mycophenolate ($n = 109$) and azathioprine ($n = 249$) (12). However, very few patients taking mycophenolate were available for long-term comparison. In contrast, another retrospective comparison of 135 renal transplant patients (69 for prophylactic treatment and 66 for rescue therapy) showed that the combination of mycophenolate, tacrolimus, and prednisone ($n = 49$) produced fewer rejection episodes, but a significantly higher incidence of infectious episodes than the combination of mycophenolate, ciclosporin, and prednisone (24). In another randomized trial of 120 renal transplant patients, there was a significantly higher rate of asymptomatic or symptomatic cytomegalovirus infection in patients who took mycophenolate, tacrolimus, and prednisone than in patients who took tacrolimus plus prednisone (20 versus 5%) (14). Overall, both of these studies suggest that mycophenolate plus tacrolimus has a more potent immunosuppressive effect, with an increased risk of infections (and theoretically lymphoproliferative disorders), as the counterpart of a possible greater effect on acute rejection prophylaxis.

Bacterial infections

- Staphylococcal septicemia complicated by endocarditis has been reported in a 50-year-old woman after 5 months of treatment with mycophenolate for atopic dermatitis (25).

As the skin of most patients with atopic dermatitis can be colonized with *Staphylococcus aureus*, the authors suggested caution in using mycophenolate, which can also cause leukopenia. This patient had previously taken ciclosporin and azathioprine, which were ineffective, but without apparent infectious complications. A specific role of mycophenolate is therefore debatable and the occurrence of bacterial septicemia may have been purely coincidental.

Mycobacterium hemophilum is a pathogen that is found in immunosuppressed patients, such as those with malignancy, AIDS, and organ transplants. Systemic lupus erythematosus can make patients more susceptible to infection.

- A 25-year-old Chinese woman with systemic lupus erythematosus had a disease course characterized by multiple flares involving the kidneys, central nervous system, and gastrointestinal tract (26). She was given mycophenolate mofetil and multiple courses of antibiotics, with a poor response. After about 9 months she developed a recurrent right leg cellulitis. Two initial skin biopsies yielded negative bacterial and mycobacterial cultures, but histopathology of the muscle of

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her right thigh showed acid-fast bacilli and culture subsequently grew *M. hemophilum*.

The authors concluded that this complication had been due to late diagnosis, multiple antibiotics, and immunocompromise. These points must be taken into consideration when treating a patient with mycophenolate mofetil.

Virus infections

Cytomegalovirus

The role of mycophenolate in the rate and severity of cytomegalovirus infection in transplant patients has been debated (SEDA-23, 407) and is difficult to evaluate in otherwise immunosuppressed patients. Whereas there was a dose-related increase in the incidence of cytomegalovirus disease in the three pivotal trials, a later analysis did not confirm that mycophenolate mofetil is specifically associated with an increased risk of cytomegalovirus infection, and suggested that over-immunosuppression rather than mycophenolate mofetil per se was the main contributing factor (SEDA-22, 418) (27–29).

- Severe cytomegalovirus pancolitis has been reported in a 59-year-old man taking only mycophenolate and prednisone for Wegener's granulomatosis (30).

In a retrospective study of 84 cytomegalovirus-seronegative renal transplant patients who received a kidney from a cytomegalovirus-seropositive donor without cytomegalovirus prophylaxis, the incidence of primary cytomegalovirus infection was similar in the 24 patients who took mycophenolate plus ciclosporin and prednisone, compared with the 60 patients who took ciclosporin and prednisone alone (31). However, the incidence of cytomegalovirus disease was nearly twice as high in the mycophenolate group (67 versus 30%), but with no difference in the severity of the disease. The authors speculated that the more frequent incidence of symptomatic cytomegalovirus disease might have been due to some specific effects of mycophenolate on the primary immune response to cytomegalovirus.

Mycophenolate mofetil has been compared with azathioprine in combination with ciclosporin and glucocorticoids in 65 children after kidney transplantation (32). The main adverse effects of this treatment were infections of the urinary tract and the upper respiratory tract, abdominal pain, and diarrhea. Opportunistic infections with cytomegalovirus or cytomegalovirus syndrome occurred in 20% within the first 6 months and tissue-invasive cytomegalovirus disease in 3.1%. These results were similar to those in adults.

Varicella

A retrospective study in 19 children with renal transplants identified three who developed disseminated varicella, despite a prior history of chickenpox in two and pretransplant varicella vaccination in one (33). The clinical disease was mild and responded promptly to oral aciclovir. Although this was based on very few patients, the incidence of 16% was thought to be unexpectedly higher than that reported in historic controls (0.7–1.9%), and might have resulted from the higher degree of immunosuppression achieved with mycophenolate mofetil.

Herpes simplex

To evaluate whether mycophenolate mofetil is effective in treating moderate to severe atopic dermatitis, an open pilot study was conducted in 10 patients (34). There were no serious adverse effects, but one patient had to discontinue treatment because he developed *Herpes simplex* retinitis, which resolved after treatment with aciclovir. Although there is no direct evidence that mycophenolate mofetil is a major cause of *Herpes* retinitis, in this patient it seems likely that it was due to immunosuppression. In contrast, in vivo and in vitro mycophenolate mofetil strongly potentiates the antiherpetic effects of aciclovir, ganciclovir, and penciclovir (35). It is probably therefore enough to give antiviral therapy only when clinical signs of *Herpes* infection occur.

Fungal infections

There have been two cases of intestinal microsporidiosis (36) and one case of *Nocardia asteroides* brain abscess (37) in adults taking mycophenolate mofetil.

Body temperature

- Isolated and intermittent drug fever with a spiking pattern has been attributed to mycophenolate in a 41-year-old man with a renal transplant (38). The relation to treatment was confirmed by the exclusion of numerous infectious causes, the persistence of fever despite ciclosporin withdrawal, subsidence of fever after mycophenolate withdrawal, and the absence of further episodes of fever during follow-up.

Long-Term Effects

Tumorigenicity

- Kaposi's sarcoma recurred 4 months after starting mycophenolate in a 58-year-old renal transplant patient who 7 years before had had similar lesions that reversed on withdrawal of ciclosporin (39).
- Kaposi's sarcoma has been reported after a mean of 7 months of treatment in three renal transplant patients whose immunosuppressive regimen included mycophenolate mofetil (40).

The investigators of the second case found that the incidence of Kaposi's sarcoma in patients taking regimens containing mycophenolate mofetil was 0.8% (3/371 patients) compared with 0.1% in patients not taking it (2/1464). It was suggested that mycophenolate mofetil might increase the susceptibility to Kaposi's sarcoma.

Second-Generation Effects

Pregnancy

- A 33-year-old woman was given a living related donor kidney transplantation during the first trimester, followed by mycophenolate mofetil, tacrolimus, and prednisone (41). The mother did well, except for mild pre-eclampsia and mild renal insufficiency. The child was born prematurely during the 36th week. The only teratogenic effects detected were hypoplastic nails and a short fifth finger.

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Susceptibility Factors

Age

The adverse effects of mycophenolate mofetil in children have been reviewed retrospectively in 24 renal transplant patients (mean age 14 years) switched from azathioprine to mycophenolate mofetil a mean of 4.8 years after transplantation (42). The mean dose of mycophenolate mofetil was 560 mg/m^2. After a mean of 9.6 months, 13 had to discontinue treatment because of adverse effects, namely severe and partially reversible anemia (10 patients, of whom three required transfusions), neutropenia ($n = 1$), and diarrhea ($n = 2$). The anemia was normocytic and normochromic in nine patients, and such a high incidence of severe anemia was unexpected from the available adult data. Although patients who discontinued treatment had a lower pretreatment-calculated creatinine clearance, this was not significant and probably not the major cause of anemia. The author speculated that the anemia resulted from a disproportionately high unbound plasma concentration of mycophenolate mofetil, due to reduced protein binding and impaired renal clearance.

Drug–Drug Interactions

Ciclosporin

In 52 patients taking mycophenolate mofetil 1 g bd, prednisone, and ciclosporin to a target blood concentration of 125–175 ng/ml for 6 months after transplantation, withdrawal of ciclosporin resulted in almost a doubling of mycophenolic acid trough concentrations (43).

Tacrolimus

Patients taking tacrolimus have higher mycophenolate mofetil plasma trough concentrations than patients taking ciclosporin (44). Compared with the combination of ciclosporin plus mycophenolate mofetil, tacrolimus plus similar doses of mycophenolate produced significantly higher serum concentrations of mycophenolic acid, resulting in a greater degree of in vitro immunosuppression (SEDA-21, 390).

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Myeloid colony-stimulating factors

See also Individual agents

General Information

Around 10 glycoprotein myeloid hemopoietic growth factors or colony-stimulating factors (CSFs) have so far been identified and purified; their genes have been cloned and active recombinant proteins have been produced. Recombinant factors produced by yeast or mammalian cells are glycosylated, as they are in their native state, whereas those expressed in bacterial systems are not. Glycosylation may be clinically relevant with regard to the efficacy and antigenicity of the molecule, although antibody formation has not been observed, even after prolonged therapy (1). Most clinical studies with CSFs have hitherto been performed with granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), although clinical trials of other colony-stimulating factors have also been initiated in a number of centers. GM-CSF leads to a dose-related sustained increase in peripheral neutrophil numbers, with a delayed increase in circulating monocytes and eosinophils. The effect of G-CSF appears to be more restricted to neutrophils. Multi-CSF (IL-3) stimulates the production of all types of leukocytes, as well as platelets and reticulocytes (2).

Both granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been extensively investigated for the treatment of chemotherapy-induced neutropenia, reducing the duration of neutropenia after bone marrow transplantation, or mobilizing peripheral blood progenitor cells after myelosuppressive chemotherapy (3). Other clinical uses are indicated in the monographs on the individual growth factors.

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Two reviews have examined the available data on the effects of hemopoietic growth factors on the duration of neutropenia and mortality in drug-induced agranulocytosis, which mostly consists of isolated case reports or small series of patients (4,5). The authors reached contrasting opinions, suggesting that hemopoietic growth factors might or might not be of interest in patients with severe drug-induced agranulocytosis. Adverse effects were noted in 13 of 118 case reports (4). Although most of them were benign, pulmonary toxicity or acute respiratory distress syndrome occurred in a few patients.

Comparative studies

There were no major differences in the adverse effect profiles in 42 patients with breast cancer randomized to filgrastim (G-CSF) or molgramostim (GM-CSF) (SEDA-22, 407). There were no significant differences in the adverse effects profiles and severity of adverse effects in 181 patients with cancers randomized to receive filgrastim (G-CSF) or sargramostim (GM-CSF) for chemotherapy-induced myelosuppression (6).

The effects and the safety of a 5-day regimen of G-CSF ($n = 9$) or GM-CSF ($n = 8$) have been compared (7). Most patients complained of flu-like symptoms in both groups (six and seven respectively), but rash at the injection site was observed only in four patients treated with GM-CSF. In the G-CSF group, there was a fall in platelet count (below 150×10^9/l) in five patients, raised serum lactic dehydrogenase activity, and raised uric acid concentrations; three patients required transient treatment with allopurinol.

The frequency and severity of adverse effects associated with the prophylactic use of filgrastim or sargramostim have been assessed in a retrospective review of the medical records of 490 cancer patients from ten centers (8). Sargramostim-treated patients had significantly more frequent non-infectious fever, fatigue, diarrhea, injection site reactions, edema, and dermatological adverse effects, whereas skeletal pain was more frequent with filgrastim. In addition, switching to the alternative treatment was more frequent in the sargramostim group (18% of patients) than in the filgrastim group (none of the patients). The authors tried to minimize selection bias, but the strength of the results was limited by the retrospective nature of the study.

Susceptibility Factors

Age

Guidelines for the appropriate use of hemopoietic growth factors in children have been proposed by a panel of European experts, who carefully summarized the potential indications and recommendations, and concluded that adult guidelines are applicable to children in most cases (9). The authors considered that growth factors should be used in children for only a limited number of circumstances: prophylaxis or treatment in low-risk patients treated with chemotherapy, routine use in aplastic anemia, and mobilization of peripheral blood progenitor cells in healthy pediatric donors.

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Myristicaceae

See also Herbal medicines

General Information

There are three genera of the family of Myristicaceae:

- *Horsfieldia*
- *Myristica* (nutmeg)
- *Virola* (virola).

Myristica fragrans

Myristica fragrans (nutmeg) has long been a highly desired spice. In the seventeenth century physicians claimed that a nutmeg pomander was a cure for the bloody flux and the sweating sickness, later called the black plague, and nutmeg was also supposed to have aphrodisiac properties (1). Mace, the dried shell of the nutmeg, is used as a spice; it should not be confused with

chemical Mace, which is a form of tear gas containing 1% chloracetophenone (CN) gas in a solvent of sec-butanol, propylene glycol, cyclohexene, and dipropylene glycol methyl ether; some formulations also include oleoresin *Capsicum* (from peppers).

Myristicin is methoxysafrole, the principal aromatic constituent of the volatile oil of nutmeg. Myristicin is also found in several members of the carrot family (Apiaceae, formerly Umbelliferae), such as *Petroselinum crispum* (parsley) (2). Safrole is a mutagenic and animal carcinogenic monoterpenoid. It is the major component of oil of sassafras, and lesser quantities occur in essential oils from cinnamon, mace, nutmeg, and star anise. Some of its known or possible metabolites have mutagenic activity in bacteria and it has weak hepatocarcinogenic effects in rodents. Experiments in mice have suggested the possibility of transplacental and lactational carcinogenesis. The carcinogenic effect is primarily mediated by the formation of 1′-hydroxysafrole, followed by sulfonation to an unstable sulfate that reacts to form DNA adducts; these metabolites are formed by CYP2C9 and CYP2E1, the latter contributing three-fold more to the metabolic clearance than the former (3).

Adverse effects

Asthma has been attributed to nutmeg (4).

- A 27-year-old man developed rhinitis and asthma 1 year after starting to prepare a certain kind of sausage, having a previous allergy to coconut, banana, and kiwi and allergic rhinitis to horses, cats, dogs, and cows. There was a positive immediate skin prick test with paprika (dry powder of *Capsicum annuum*), coriander (*Coriandrum sativum*), and mace (shell of *M. fragrans*) at concentrations of 10%. There were specific IgE antibodies to paprika, coriander, and mace.

Large doses of nutmeg seed can cause nausea, vomiting, flushing, dry mouth, tachycardia, nervous system stimulation possibly with epileptiform convulsions, miosis, mydriasis, euphoria, and hallucinations (5).

- A 16-year-old youth who had taken nutmeg for recreational purposes developed a number of neurological symptoms and signs along with non-specific electrocardiographic changes and anticholinergic-type symptoms (6).

Among 55 patients with suspected contact dermatitis, skin patch tests that were positive at concentrations of both 10% and 25% were most common with ginger ($n = 7$), nutmeg ($n = 5$), and oregano ($n = 4$); other spices produced no responses or one positive response (7). Positive reactions at only one concentration were more likely at 25%: nutmeg ($n = 5$), ginger and cayenne ($n = 4$), curry, cumin, and cinnamon ($n = 3$), turmeric, coriander, and sage ($n = 2$), oregano ($n = 1$), and basil and clove ($n = 0$).

Contact allergy has been reported with mace (8).

Nutmeg is sometimes abused for its hallucinogenic potential; less than one tablespoon can be enough to produce severe symptoms similar to those seen in anticholinergic poisoning (9,10). It can also cause psychosis, both acute (11,12) and chronic (13).

- A 13-year-old girl took 15–24 g of nutmeg in gelatin capsules over 3 hours and smoked two joints of marijuana (14). She developed bizarre behavior and visual, auditory, and tactile hallucinations, nausea, gagging, hot/cold sensations, and blurred vision, followed by numbness, double, and "triple" vision, headache, and drowsiness. There was nystagmus, muscle weakness, and ataxia. She received activated charcoal 50 g and recovered within 2 days.

Deaths from acute poisoning have been reported (15).

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Myrrh

General Information

Myrrh is an oleo gum resin obtained from the stem of *Commiphora molmol*, a tree that grows in north-east Africa and the Arabian Peninsula. In mice, myrrh showed no mutagenic effects and was a potent cytotoxic drug against solid tumor cells (1). The antitumor potential of *Commiphora molmol* was comparable with that of cyclophosphamide. Studies in hamsters suggested an antischistosomal activity of myrrh (2).

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Observational studies

Facioliasis

The efficacy of myrrh has been studied in seven patients aged 10–41 years (five men, two women) with fascioliasis and 10 age- and sex-matched healthy volunteers (3). Myrrh was given orally in the morning on an empty stomach in a dosage of 12 mg/kg/day for 6 days. All the patients were passing *Fasciola* eggs in their stools (mean 36 eggs per gram of stool). The symptoms and signs of fascioliasis resolved during treatment with myrrh, and *Fasciola* eggs could not be demonstrated in the stools 3 weeks and 3 months after treatment. Antifasciola antibody titers became negative in six of the seven patients. There were no adverse effects.

Schistosomiasis

The efficacy and adverse effects of myrrh and the most effective dosage schedule have been studied in 204 patients (169 men and 35 women) with schistosomiasis aged 12–68 years and 20 healthy non-infected age- and sex-matched volunteers (2). The patients were divided into two groups: 86 patients with schistosomal colitis and 118 with hepatosplenic schistosomiasis, further divided into two subgroups—77 patients with compensated disease and 41 with decompensated disease. All but 12 had received one or more courses of praziquantel. The dosage of myrrh was 10 mg/kg/day for 3 days on an empty stomach 1 hour before breakfast. A second course of 10 mg/kg/day for 6 days was given to patients who still had living ova in rectal or colonic biopsy specimens. The response rate to a single course of myrrh was 92% in 187 patients. The cure rates were 91, 94, and 90% in patients with schistosomal colitis, compensated hepatosplenic schistosomiasis, and decompensated hepatosplenic schistosomiasis respectively. The cure rate was less in patients who had previously taken praziquantel and in patients with impaired liver function. *Schistosoma hematobium* infection was the most responsive ($n = 4$, cure rate 100%), followed by mixed infections ($n = 29$, cure rate 93%). Those infected with *Schistosoma mansoni* had the lowest cure rate ($n = 171$, cure rate 91%). There was no impairment of liver function after treatment with myrrh. In contrast, liver function tests significantly improved in patients with impaired liver function. There were no significant effects of myrrh on the electrocardiogram. Adverse effects of myrrh were reported in 24 of the 204 patients. Giddiness, somnolence, or mild fatigue were the most common (2.5%), and all other adverse effects were minor and less frequent. None of the healthy volunteers reported any adverse effects, nor were there any significant changes in liver or kidney function. A second course of myrrh resulted in a cure in 13 of the 17 patients who did not respond to a single course.

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Myrtaceae

See also Herbal medicines

General Information

The family of Myrtaceae (Table 1) includes guava and various types of gums.

Eucalyptus species

Eucalyptus oil has been used in different medications to relieve symptoms of asthma and rhinitis and is a constituent of cold remedies and ointments designed to be rubbed on to the chest or applied around and even into the nostrils (Vicks Vaporub, Obat Madjan, etc.). Applied to the skin it acts as a rubefacient and counterirritant, but substantial concentrations of volatile oil can be inhaled from the skin. Eucalyptus oil has also been used systemically to treat asthma.

Adverse effects

Fever and headache occurred in a heavy consumer of eucalyptus extract (1).

Table 1 The genera of Myrtaceae

Baeckea (baeckea)
Callistemon (bottle brush)
Calothamnus (net bush)
Calyptranthes (mountain bay)
Chamelaucium (chamelaucium)
Corymbia (corymbia)
Eucalyptus (gum)
Eugenia (stopper)
Feijoa (feijoa)
Gomidesia (gomidesia)
Leptospermum (tea tree)
Lophostemon (lophostemon)
Marlierea (marlierea)
Melaleuca (melaleuca)
Metrosideros (lehua)
Myrcia (rodwood)
Myrcianthes (myrcianthes)
Myrciaria (guava berry)
Myrtus (myrtus)
Pimenta (pimenta)
Pseudanamomis (pseudanamomis)
Psidium (guava)
Rhodomyrtus (rhodomyrtus)
Siphoneugena (siphoneugena)
Syncarpia (turpentine tree)
Syzygium (syzygium)
Tristaniopsis (tristaniopsis)

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Respiratory
Asthma can be exacerbated by eucalyptus (2).

- In a 30-year-old woman the symptoms of asthma and rhinoconjunctivitis were exacerbated by eucalyptus pollens and by ingestion of an infusion containing eucalyptus. There were specific IgE antibodies to eucalyptus pollens but not to common aeroallergens.

Eucalyptus oil has been reported to cause vocal cord dysfunction (3).

- A 46-year-old woman with vocal cord dysfunction associated with exposure to eucalyptus underwent inhalation challenges consisting of water, ammonia, pine oil, and a combination of eucalyptus (dried leaves) and ammonia. Vocal cord dysfunction occurred within minutes of exposure to eucalyptus.

Skin
Contact urticaria has been ascribed to eucalyptus pollen (4).

Drug overdose
Eucalyptus oil has caused death in doses of up to 560 ml in adults and 15 ml in children.

- A 73-year-old woman who deliberately took 200–250 ml of eucalyptus oil was found unconscious in her home after she had vomited and had been incontinent of urine and feces. Despite intensive treatment she developed pneumonitis and aspiration pneumonia to which she ultimately succumbed (5).

In a telephone survey of 109 parents or guardians of children under 5 years who had been involved in actual or suspected ingestion of eucalyptus oil, 90 incidents had involved vaporizer solutions, 15 eucalyptus oil formulations, and the remainder other medicinal products containing eucalyptus oil (6).

In a retrospective analysis of case histories of 109 children admitted to the Royal Children's Hospital, Melbourne, between 1 January 1981 and 31 December 1992 with a diagnosis of eucalyptus oil poisoning, there were clinical effects in 59%; 31 had depression of consciousness, 27 were drowsy, three were unconscious after taking known or estimated volumes of 5–10 ml, and one was unconscious with hypoventilation after taking an estimated 75 ml (7). Vomiting occurred in 37%, ataxia in 15%, and pulmonary disease in 11%. No treatment was given to 12%; ipecac or oral activated charcoal was given to 21%, nasogastric charcoal to 57%, and gastric lavage without anesthesia to 4% and under anesthesia to 6%. All recovered.

Of 42 children with oral eucalyptus oil poisoning, 33 were entirely asymptomatic (8). This group included all of the four children who were reported to have taken more than 30 ml of eucalyptus oil. Only two of the others had symptoms or clinical signs on presentation to hospital. No child required advanced life support. There was no correlation between the amount of eucalyptus oil taken and the presence of symptoms.

Systemic eucalyptus oil toxicity can result from topical application.

- A 6-year-old girl presented with slurred speech, ataxia and muscle weakness progressing to unconsciousness following the widespread application of a home remedy for urticaria containing eucalyptus oil. Six hours after removal of the topical preparation her symptoms had resolved and there were no long-term sequelae (9).

Administrative route
Systemic effects of eucalyptus oil applied locally have been reported (9).

- A 6-year-old girl was treated with a home-made concoction mainly containing 50 ml of eucalyptus oil (consisting of 80–85% cineole oil) for pruritus. As the mixture seemed to relieve her symptoms, the parents applied it more and more generously to the girl's skin. She subsequently developed symptoms of intoxication: slurred speech, unsteady gait, and drowsiness. Eventually she lost consciousness and was unrousable. She was admitted to hospital, where several tests were negative, but her urine sample contained components of eucalyptus oil. She made a full recovery within 24 hours after withdrawal of the external herbal treatment.

Melaleuca species

The undiluted essential oil from the leaves of *Melaleuca alternifolia* (tea tree), which contains the sesquiterpene viridiflorene and the monoterpenoids eucalyptol, limonene, and terpinen-4-ol, has been used as a topical natural cure for bacterial and fungal skin infections.

Adverse effects
Nervous system

- A 23-month-old boy became confused and was unable to walk 30 minutes after ingesting less than 10 ml of T36-C7, a commercial product containing 100% tea tree oil (10). His condition improved and he was asymptomatic within 5 hours of ingestion.

Skin
Tea tree oil can have adverse effects on the skin (11). Several patients developed an allergic contact dermatitis (12), which was most commonly caused by the constituent d-limonene (13). Internal use of half a teaspoonful of the oil can result in a dramatic rash (14), whereas half a teacup can induce coma followed by a semiconscious state with hallucinations (15). Less than 10 ml is sufficient to produce serious signs of toxicity in small children.

- In one case, allergic contact dermatitis to tea tree oil presented with an extensive erythema multiforme-like reaction (16). However, a skin biopsy from a target-like lesion showed a spongiotic dermatitis without the features of erythema multiforme. Five months after treatment with systemic and topical glucocorticoids, patch testing elicited a 3+ reaction to old, oxidized tea tree oil, a 2+ reaction to fresh tea tree oil, a 2+ reaction to colophony, a 1+ reaction to abitol, and a 1+ reaction to balsam of Peru.

Of 1216 patients who were patch tested, 14 with eczema had used products (creams, hair products, and essential oils) containing tea tree oil (17). They were patch tested for a standard panel of allergens, topical emulgents, perfumes, plants, topical medications, metal, gloves, topical

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disinfectants and preservatives, dental products, and rubber derivatives. Seven patients had allergic contact dermatitis due to tea tree oil. Two of them also had delayed type IV hypersensitivity toward fragrance-mix or colophony, suggesting the possibility of cross-reactions or allergic group reactions caused by contamination of the colophony with the volatile fraction of turpentines.

Immunologic

Of 1017 subjects, 16 had positive skin tests to *Melaleuca quinquenervia* pollen extract (18). Six of them were subjected to double-blind nasal challenge with the pollen extract and four to single-blind bronchial challenge; 11 received 34 different *Melaleuca* odor challenges (blossoms, bark, and leaves) through a closed system for up to 30 minutes. Four inhaled an odor from cajeput oil (derived from *Melaleuca* leaves) for 1 hour. One of six nasal challenges and one of four bronchial challenges were positive. All the odor challenges with blossoms, bark, leaves, and cajeput oil were negative. A radioallergosorbent test for *Melaleuca* pollen extract correlated with the skin test results. The authors concluded that the *Melaleuca* tree is not a significant source of aeroallergens and explained the few positive results on the basis of cross-reactivity with pollen extracts from a proven aeroallergen, *Bahia* grass pollen.

Syzygium aromaticum

Syzygium aromaticum (clove) is used as an aromatic spice.

Adverse effects

Of about 1000 patients with occupational skin diseases, five had occupational allergic contact dermatitis from spices (19). They were chefs, or workers in kitchens, coffee rooms, and restaurants. In all cases the dermatitis affected the hands. The causative spices were garlic, cinnamon, ginger, allspice, and clove. The same patients had positive patch test reactions to carrot, lettuce, and tomato.

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Nabumetone

See also Non-steroidal anti-inflammatory drugs

General Information

Nabumetone is a naproxen derivative, whose efficacy is related to its active metabolite, 6-methoxy-2-naphthylacetic acid. Not unexpectedly, a study in 2000 patients, mostly treated for more than 6 months, elicited an adverse events pattern similar to the other derivatives of this class of NSAIDs (SEDA-13, 81). Adverse effects were reported in 18% of patients and 10% stopped taking the drug because of adverse reactions. Diarrhea was the most common problem (13%) followed by abdominal pain (9.9%), dyspepsia (9.3%), nausea (7.8%), and flatulence (4.7%). Ten ulcers were detected. Nervous system reactions, skin rashes, edema, unspecified eye disorders, and liver function test abnormalities all occur (1).

A postmarketing surveillance study in 10 800 patients with osteoarthritis and rheumatoid arthritis, who were followed up at 12 months, reported that 12% of patients discontinued the drug because of adverse events; 11 serious events may have been related to nabumetone and seven of these were gastrointestinal hemorrhage (2). In 6148 patients treated with nabumetone in long-term trials, the 3-month cumulative incidence of clinically detected perforations, ulcers, and bleeding was 0.1% and the 6-month incidence was 0.2% (3).

Organs and Systems

Metabolism

Nabumetone-induced pseudoporphyria has been described (SEDA-16, 11) (SEDA 22, 117), and a further five cases in four adults and a child have been reported (4–6).

Gastrointestinal

Being a non-acidic compound and a weak inhibitor of prostaglandin synthesis, nabumetone was designed as a prodrug that could be administered without causing gastric damage. This theoretical advantage still awaits confirmation. Although there was no gastrointestinal toxicity in animals, in humans gastric problems with NSAIDs are not primarily a local effect but are exerted systemically, so a metabolite formed after gastric passage could still cause gastric problems. Again, although radiochromium evaluation of gastrointestinal blood loss in healthy volunteers and endoscopic studies in patients with rheumatoid arthritis showed that nabumetone provokes less gastric damage than naproxen, the usual defects of such studies limit their clinical relevance (SEDA-13, 81). The same applies to the preliminary results of a long-term study in patients with osteoarthritis and rheumatoid arthritis, which also showed that nabumetone is less gastrotoxic than naproxen, but it was not possible to exclude the possibility that the dosage was lower than was needed for optimal efficacy (7).

Susceptibility Factors

Age

After repeated once-daily doses, nabumetone accumulates in elderly patients but not in others; it is therefore wise to reduce the dose in elderly patients.

Drug–Drug Interactions

Warfarin

Concomitant therapy with warfarin and NSAIDs is of concern, owing to the potential for increasing bleeding.

- In a 72-year-old man the concomitant use of nabumetone and warfarin led to an increased international normalized ratio and hemarthrosis (8).

Previous reports suggested a lack of interaction of nabumetone with warfarin, but close monitoring is advisable when these two drugs are co-administered.

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Naftidrofuryl

General Information

Naftidrofuryl is a complex acid ester of diethylaminoethanol, with direct vasodilatory properties and antagonistic effects on 5-HT (via 5-HT_2 receptors) and bradykinin. It also causes an intracellular increase in ATP concentrations, improves cellular oxidative metabolism (by activating succinate dehydrogenase), and reduces blood and plasma viscosity and fibrinogen concentrations.

Naftidrofuryl has been marketed in Europe for over 20 years for the treatment of peripheral and cerebrovascular diseases and for senile dementia (1). A few placebo-controlled studies have reported increases in

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walking distance in patients with claudication, but no substantial hemodynamic improvement. Subjective improvement with naftidrofuryl was also noted in patients with Raynaud's phenomenon, but it had variable effects on digital blood flow and pressure during cold provocation. In patients with an acute ischemic stroke there was better neurological progress, leading to a shorter stay in hospital in some but not all studies. Several double-blind trials have reported improvements in the deficits associated with mild senile organic brain syndrome.

Oral naftidrofuryl (300–600 mg/day) was generally well tolerated in controlled trials: gastrointestinal complaints were as frequent with placebo as with the drug. Esophageal ulceration has been ascribed to naftidrofuryl in a few patients. Rare cases of reversible liver dysfunction have been reported.

Parenteral naftidrofuryl was withdrawn from the market following reports of severe adverse effects with intravenous or intra-arterial bolus injections, including intracardiac conduction defects, epileptic seizures, severe anaphylactic reactions, and acute renal insufficiency secondary to deposition of oxalate crystals in the tubules (SED-12, 473) (SEDA-17, 244).

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Nalbuphine

See also Opioid antagonists

General Information

Nalbuphine is a partial opioid agonist structurally similar to naloxone. Like naloxone it is an antagonist at $OP_3(\mu)$ receptors, whilst achieving analgesia via an agonist effect at $OP_2(\kappa)$ receptors.

Nalbuphine was approximately equianalgesic with morphine (1) and its hemodynamic and respiratory effects were not statistically significantly different from those of morphine (SEDA-14, 69). Other studies have shown that this also applies to other organ systems. However, unlike morphine, nalbuphine has a "ceiling" effect on respiratory depression, a low incidence of dysphoric effects, and a low addiction potential. Ten patients with a history of cardiac or orthopedic problems who received intravenous nalbuphine (6–20 mg) required additional doses of morphine (15–70 mg) to relieve pain (2). However, this report was not supported by objective physiological measures or recognized pain scores.

Nalbuphine has similar efficacy and incidence of adverse effects to tramadol and paracetamol (acetaminophen) (3). Dysrhythmias and coughing occurred more often with nalbuphine than fentanyl (4).

Cardiac dysrhythmias, hypertension, agitation, nausea, and vomiting occurred when nalbuphine was given to four patients to reverse fentanyl-induced respiratory depression (SEDA-16, 89).

In a double-blind, placebo-controlled study in 24 elderly patients scheduled for elective total hip replacement who were randomized to either intrathecal morphine 160 μg or nalbuphine 400 μg postoperatively, when the pain score was greater than 3 cm on a visual analogue scale, nalbuphine produced significantly faster onset and shorter duration of analgesia (5). Both opioids produced adequate maximal pain relief in all patients. The adverse effects profile was unremarkable in both groups.

Intravenous nalbuphine 3 mg ($n = 101$) has been compared with intravenous propofol 20 mg ($n = 90$) in a double-blind, randomized study, to determine efficacy in the treatment of intrathecal morphine-induced pruritus after cesarean delivery 10 minutes after the drug was administered (6). Nalbuphine was significantly more effective, especially in cases of moderate but not severe pruritus. Adverse effects such as reduced analgesia and increased nausea, vomiting, sedation, and dizziness were not significantly different between the two groups.

Organs and Systems

Respiratory

Although similar respiratory depression occurs with morphine and nalbuphine after single doses, on cumulative dosing there appears to be a ceiling effect with nalbuphine, which may also occur with respect to analgesic efficacy (7). Considerable respiratory depression requiring prolonged monitoring has been reported in children (SEDA-16, 89).

Neuromuscular function

Psychomotor performance and subjective effects seems to be dose-related (SEDA-22, 104).

Psychological, psychiatric

- A 53-year-old man with no past psychiatric history was found by the police walking aimlessly, unclothed, and responding to auditory hallucinations (8). He had slurred speech and generalized tremors. Lumbar puncture, a CT head scan, and urine drug screen were all normal. He responded to risperidone 1 mg bd with dramatic improvement after 2 days. He reported chronic use of nalbuphine, with recent increased use.

Gastrointestinal

The effects of nalbuphine and morphine on gastrointestinal function have been compared in 17 volunteers. Nalbuphine 10 mg prolonged gastric emptying to a greater extent than nalbuphine 5 mg or morphine 5 mg, which were about equal in their effects (9). However, another study (10) showed that nalbuphine produced significantly less inhibition of gastrointestinal activity than morphine.

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Biliary tract

The effect of nalbuphine 20 mg intravenously on biliary tract pressure was examined in 10 patients undergoing surgery for symptomatic cholelithiasis. There was a statistically significant rise in pressure 30 minutes after the administration of nalbuphine, but this did not have any apparent deleterious effects (11). Others have suggested that nalbuphine reverses opioid-induced spasm of the sphincter of Oddi (SEDA-17, 88).

Long-Term Effects

Drug dependence

The development of dependence is unlikely at doses within the usual analgesic range (12).

Second-Generation Effects

Fetotoxicity

Transplacental transfer of nalbuphine was measured in eight mothers who underwent cesarean section and were given nalbuphine 200 μg/kg intravenously along with thiopental and suxamethonium. The umbilical cord/maternal vein ratio was 1.4:1 at delivery, which occurred at 2–10 minutes after nalbuphine injection. Mean Apgar scores at 1 minute were 6.6 and 8.5 at 5 minutes and did not correlate with either the serum nalbuphine concentration or the time between injection of nalbuphine and delivery (13).

Three neonates, whose mothers who had received nalbuphine during labor, developed apnea and cyanosis, which required ventilation within 3 minutes of birth (14,15).

Bradycardia and bradypnea have been reported in babies whose mothers were given nalbuphine a few hours before delivery (SEDA-16, 89).

A case of fetal sinusoidal rate pattern with nalbuphine has been reported (SEDA-17, 87).

Drug Administration

Drug dosage regimens

In a randomized, double-blind, multicenter comparison of three different intrathecal doses of nalbuphine (0.2, 0.8, or 1.6 mg) and a single intrathecal dose of morphine (0.2 mg) for postoperative pain relief after cesarean section in 90 parturients, intrathecal nalbuphine 0.8 mg provided rapid and effective analgesia, with minimal adverse effects but a shorter duration of action, reinforcing morphine's position as an analgesic that provides long-lasting analgesia (16).

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Nalidixic acid

General Information

Nalidixic acid, the first quinolone, first introduced in 1962, is now only rarely used and has been supplanted by the fluoroquinolones. It is almost completely absorbed from the gastrointestinal tract and is rapidly eliminated by the kidneys, resulting in urinary concentrations 4–6 times higher than plasma concentrations. There are better drugs to treat urinary tract infections.

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General adverse effects

The adverse effects of nalidixic acid tend to be toxic rather than allergic. Nervous system toxicity is predominant, including disturbances of sensory perception and benign intracranial hypertension, which is nearly exclusively found in babies and young children. Gastrointestinal toxicity and skin reactions also occur. Immunological and hypersensitivity reactions mainly affect the skin. Drug fever is rare. Hematological and hepatic reactions are very rare. Tumor-inducing effects have not been reported but require further study, since nalidixic acid, as a DNA gyrase inhibitor, damages DNA (1,2). Fluorinated derivatives, but not nalidixic acid, induced unscheduled DNA synthesis in vitro but not in vivo. While specific fluoroquinolones, such as CP-115,953, have cytotoxic effects on eukaryotic cancer cells, the fluoroquinolones designed specifically as antimicrobial agents have extremely low toxicity against eukaryotic cells. This is due to a marked reduction in the affinity for eukaryotic topoisomerases versus prokaryotic topoisomerases (3,4).

Organs and Systems

Nervous system

Benign intracranial hypertension (pseudotumor cerebri) mainly affects babies, especially during the first 3 months of life. Occasionally even older children can be affected, especially when inordinately high doses are used (5). Very rarely, it occurs in adults with renal insufficiency. In infancy, impaired nalidixic acid elimination (due to underdeveloped glucuronidation), overdosage, or prolonged treatment may be responsible. Metabolic acidosis is usually important in adults (6).

The syndrome includes headache, nausea and vomiting, dizziness, tinnitus, papilledema, and visual disturbances caused by scotoma or optic nerve damage. In babies, the first symptoms appear during the first 3 days of treatment; while in older children and adults symptoms may not appear before a second or even later exposure. In adults, peripheral paresis or severe pyramidal and extrapyramidal symptoms, occasionally followed by a transitory psychosis, have been observed (7).

After withdrawal, most symptoms usually subside quickly. Papillary edema and ocular palsy recede more slowly, the latter not always completely.

Functional short-lasting phenomena, such as sensations of over-bright lights, blurred vision, altered color perception, or difficulty in focusing, are dose-dependent and have been observed in about 7% of cases (8). They begin 30–60 minutes after drug intake and subside within 20 minutes to 3 hours.

Convulsions without benign intracranial hypertension have been reported (9). Affected patients usually had preexisting cerebral disease or had taken very high doses. Normal doses in otherwise healthy persons can exceptionally provoke convulsions.

Uncharacteristic general symptoms, such as headache, dizziness, drowsiness, insomnia, or restlessness, can occur (10).

Sensory systems

Occasional cases of tinnitus have been attributed to nalidixic acid (8).

Psychological, psychiatric

Disturbances of body perception, hallucinations, confusion, confabulation, and depression can rarely occur with nalidixic acid (11).

Endocrine

Hyperglycemia associated with convulsions has been observed after the use of high single doses of nalidixic acid (7,12).

Metabolism

Nalidixic acid can cause metabolic acidosis in infants (13). This has also been seen in older children and adults with renal insufficiency and can result from disturbed lactate metabolism. Extreme overdosage can cause metabolic acidosis in subjects with normal renal function (12,14).

Hematologic

Rarely, hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency has been precipitated by nalidixic acid (15,16).

Rarely hemolytic anemia in neonates has been attributed to nalidixic acid in breast milk (15).

Gastrointestinal

Nausea, vomiting, and occasionally diarrhea or abdominal pain occur in about 8% of patients taking nalidixic acid (17).

Liver

Cholestatic hepatitis has been reported in patients taking nalidixic acid (18).

Skin

Skin reactions occur in about 5% of patients taking nalidixic acid (19), including urticaria, erythematous or maculopapular rashes, isolated pruritus, purpura, lesions resembling pityriasis rosea, erythema multiforme, or exfoliative dermatitis. Except for the latter, they usually run a benign course.

Phototoxic reactions occur in animals given nalidixic acid after exposure to light (20) and have been reported in patients taking nalidixic acid, with blistering (21,22). Sometimes the lesions develop only several days after nalidixic acid withdrawal. The eruptions can persist for several months after withdrawal.

Musculoskeletal

Large doses of nalidixic acid cause degenerative inflammatory damage in the large weight-bearing joints in animals, and occasionally arthritis, arthralgia, or myalgia occur in humans (17). However, three retrospective controlled studies showed no evidence of nalidixic acid-associated arthropathy in children (23,24).

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Long-Term Effects

Drug tolerance

Salmonella typhimurium DT104 is usually resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An outbreak of 25 culture-confirmed cases of multidrug-resistant *S. typhimurium* DT104 has been identified in Denmark (25). The strain was resistant to the above-mentioned antibiotics and nalidixic acid and had reduced susceptibility to fluoroquinolones. A swineherd was identified as the primary source (26). The DT104 strain was also found in cases of salmonellosis in Washington State, and soft cheese made with unpasteurized milk was identified as an important vehicle of its transmission (27).

Mutagenicity

The genotoxic effects of nalidixic acid (400 mg bd for 10 days) and metronidazole (250 mg tds for 10 days) have been investigated in a prospective randomized study in 20 patients with *Trichomonas vaginalis* infections (28). Evaluation was by the sister-chromatid exchange test, in which an increased number of exchanges in lymphocytes reflects mutagenic action. Metronidazole had no effect but there was a significant increase with nalidixic acid.

Second-Generation Effects

Teratogenicity

In a case-control surveillance of congenital abnormalities in 22 865 women who had neonates or fetuses with congenital abnormalities, and 38 151 pregnant women who had neonates without any defects, treatment with nalidixic acid during pregnancy was associated with an increased risk of pyloric stenosis (29). Nalidixic acid should be avoided during pregnancy.

Lactation

Very small amounts of nalidixic acid pass into the breast milk. Use during lactation should therefore also be avoided. Rare cases of hemolytic anemia in the newborn have been related to nalidixic acid ingested through breast milk (15).

Drug Administration

Drug overdose

In 18 children with nalidixic acid intoxication, most of whom were aged under 1 year, the clinical effects were neurological disorders of alertness, hypertensive cranial syndrome, and neuronal damage; some had a metabolic acidosis (30). Treatment included gastric lavage, correction of acid-base balance, and control of convulsions.

- A woman survived ingestion of nalidixic acid 32 g despite developing lactic acidosis, hyperglycemia, convulsions, and abnormal behavior (12). The maximum recorded plasma concentration of nalidixic acid was 185 μg/ml and the half-life was 3.2 hours. Carboxynalidixic acid was demonstrated in the plasma.
- A woman developed a severe metabolic acidosis and coma after taking nalidixic acid 28 g (14). She was given sodium bicarbonate 600 mmol and developed a respiratory alkalosis with secondary tetany. She recovered consciousness 9 hours later and the acid–base disturbance resolved after 60 hours.

Drug–Drug Interactions

Urine alkalinizing compounds

Alkalinization of the urine increases the excretion of nalidixic acid (31).

Warfarin

Nalidixic acid can displace warfarin from its plasma albumin binding sites, briefly enhancing its anticoagulant effect (32).

Interference with Diagnostic Tests

Glucose measurements

If reducing agents are given with nalidixic acid, glycosuria and hyperglycemia can be mimicked by the presence of nalidixic and glucuronic acid compounds in blood and urine (33).

Ketosteroids

Urine concentrations of C17-ketosteroids (but not of C17-hydroxysteroids) can be falsely raised by nalidixic acid (34).

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Nalmefene

See also Opioid antagonists

General Information

Nalmefene is a pure opioid antagonist, which is structurally similar to naloxone and naltrexone.

Drug studies

Reversal of opioid-induced adverse effects

In a comparison of the efficacy of naloxone and nalmefene in reversing opioid-induced sedation, vertigo and nausea were observed with nalmefene (1). Three of six healthy male volunteers given nalmefene 0.4 mg/70 kg complained of paresthesia in the midthoracic region (2).

In a randomized, placebo-controlled, double-blind study 120 women undergoing lower abdominal surgery were randomized to receive nalmefene 15 micrograms, nalmefene 25 micrograms, or saline intravenously at the end of surgery (3). The total consumption of morphine and the subsequent adverse effects profiles were recorded. Those given nalmefene used significantly less antiemetic and antipruritus medications during the subsequent 24-hours without a change in the quality of analgesia.

Stroke

The Cervene Stroke Study Investigation Group conducted a phase III study to assess the efficacy and safety of nalmefene (Cervene) in patients with acute ischemic strokes and also the safety of combined recombinant tissue plasminogen activator and nalmefene in a subset of patients (4). It was a randomized, placebo-controlled, double-blind study of a 24-hour infusion of nalmefene on 368 patients who received 60 mg nalmefene administered as 10 mg bolus over 15 minutes and then a 50 mg infusion over 24 hours or placebo. Even though nalmefene appeared safe and well tolerated, the study failed to find any benefit in stroke patients treated with nalmefene within six hours.

Pruritus

The role of opioid antagonists in the treatment of pruritus in cholestatic liver disease has been reviewed (5). Their use is based on the theory that implicates opioid neurotransmission as the cause of itching in this condition, and it has been observed that opioid antagonists, while providing relief from itching in patients with cholestasis, also cause symptoms similar to those seen in the opioid withdrawal syndrome. It has therefore been suggested that

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patients with cirrhosis are chronically exposed to increased concentrations of endogenous opiate receptor agonists.

In 11 patients with cirrhosis-induced pruritus, nalmefene led to relief of itching within 1 month, sustained at 3 and 6 months. However, the first two patients had severe withdrawal reactions that took 3 days to subside. In the light of this experience, the trial was modified so that patients received oral nalmefene 5 mg bd with a gradual increase in dosage over 7–10 days to 20–40 mg/day, and clonidine was administered simultaneously for the first 7 days of nalmefene therapy. Despite these precautions, all patients had withdrawal reactions, including anorexia, nausea, colicky abdominal pain, sweating, tremor, and occasionally visual or auditory hallucinations. These developed within 1 hour of nalmefene therapy and diminished within 2–3 days, despite continuation of nalmefene. This review included reports of two other studies, available in abstract form only, but which appear to have reported a lower incidence of withdrawal symptoms precipitated by nalmefene, although the dose of drug used also appeared to have been lower.

In 14 patients with cholestatic liver disease, oral nalmefene was started at a dose of 2 mg bd and increased until symptomatic relief of pruritus was obtained (6). Five patients were reported to have a transient opioid withdrawal-like reaction that did not preclude continuing with treatment. Other adverse events associated with nalmefene therapy included: perception of pins and needles ($n = 4$), anxiety and depression ($n = 2$), abdominal cramps and nausea ($n = 2$), insomnia ($n = 3$), depersonalization ($n = 2$), and changes in mood ($n = 2$); difficulties in visual focusing, dizziness, chronic goose bumps, mental "fuzziness," anorexia, and nightmares were each reported by one patient only. Of the cases of depersonalization, one occurred after the first dose while the other occurred in the first 2 weeks of therapy. There were no consistent changes in biochemistry with nalmefene. Several patients had a "breakthrough" of pruritus, which was managed by upward adjustment of dose. The authors suggested that this can be explained if nalmefene initially displaced pruritus-mediating ligands from opioid receptors, but then induced an increased density of receptors because of reduced agonist–receptor interactions, allowing further binding of pruritus-mediating ligands to receptors. In a few other patients, exacerbations of pruritus after long-term control on maintenance therapy may have been attributable to the development of tolerance toward nalmefene.

Organs and Systems

Cardiovascular

Pulmonary edema has been described after nalmefene (SEDA-22, 104).

Long-Term Effects

Drug abuse

When nalmefene was given to six men with history of drug abuse, the adverse effects reported were agitation, irritability, muscle tension, and a feeling of hangover (SEDA-17, 88).

Susceptibility Factors

Age

The efficacy and safety of intravenous nalmefene 0.1 mg/ml has been studied in an open trial in 115 children given fentanyl (7). An initial dose of 0.25 microgram/kg (maximum 10 microgram) was infused over 15 seconds, and another dose of 0.25 microgram/kg (maximum 10 micrograms) was given if there was no response after 1.75 minutes. Further doses were given every 2 minutes until a response occurred or a maximum dose of 1 micrograms/kg (maximum 40 micrograms) was reached. Nalmefene was effective and safe, especially in a mean dose of 0.55 microgram/kg; the median number of doses was two. The limitations of this study included the small study sample and the use of a short-acting opioid, fentanyl, so that re-sedation was unlikely even without the use of an antagonist.

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Naloxone

See also Opioid antagonists

General Information

Naloxone is an opioid antagonist devoid of pharmacological activity, except for its reversal of opioid effects.

As naloxone is widely believed to be innocuous, large maintenance doses of opioids are commonly used, in the belief that reversal can be safely achieved at the end of anesthesia.

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Drug studies

Placebo-controlled studies
In a randomized, double-blind study in 40 patients with moderate to severe acute traumatic brain injury, intravenous naloxone, 0.3–4.8 mg/kg/day for 10 days, reduced morbidity and mortality (1).

Reversal of opioid adverse effects
According to the results of one study, it might be expected that in every 1000 patients with drug overdose treated with naloxone, 4–30 serious complications, such as convulsions, asystole, pulmonary edema, and violent behavior, can be expected (SEDA-21, 92).

The use of naloxone has been studied in an open study in 43 patients having combined thoracic epidural and general anesthesia for subtotal gastrectomy, who were randomly assigned to receive a bolus dose of epidural morphine 3 mg followed by a continuous infusion of 3 mg in 0.125% bupivacaine 100 mg with either no naloxone ($n = 18$) or naloxone 0.208 μg/kg/hour ($n = 25$) for 48 hours (2). The time to the first postoperative passage of flatus and feces (indicating restoration of bowel function) and pain intensity (using a visual analogue scale) were assessed. The results suggested that naloxone 0.208 μg/kg/hour adequately reverses hypomotility induced by epidural morphine.

The preliminary results of two pilot schemes to provide take-home naloxone to opiate users have suggested that this provision can save lives (3). This observation needs corroboration by a prospective case-control study of adequate sample size and response rate, with the ability to collate objective data robust enough for analysis (4).

There was complete resolution of a unilateral neurological deficit associated with anesthesia along with complete resolution of postoperative unilateral EEG evidence of ischemia when naloxone was given to reverse residual opioid effects (5).

Pruritus
In a randomized, double-blind, controlled trial in pruritus in cholestatic liver disease, naloxone was effective in most patients, but five had an increase in mean scratching activity during naloxone therapy, three patients had anxiety, and one developed withdrawal symptoms (6).

Stroke
The efficacy and toxicity of a naloxone loading dose of 4 mg/kg followed by 2 mg/kg per day was evaluated in 36 patients with acute stroke (7). The most common adverse effects were nausea and vomiting, which were easily controlled. The most serious effects were bradycardia and hypotension, which occurred in response to the loading dose. One patient developed hypotension and two developed focal seizures, which were ipsilateral to the affected hemisphere; one had myoclonus.

In another study, the safety of naloxone in much higher doses was studied in 38 patients with acute ischemic stroke (SEDA-16, 87). They were given a loading dose of 160 mg/m^2 over 15 minutes followed by a 24-hour infusion at a rate of 80 mg/m^2/hour. There was nausea and/or vomiting in 26 patients, 3 patients had behavioral changes, and in 7 patients naloxone was withdrawn because of adverse effects. The authors concluded that although naloxone is relatively safe in the dosage used, its efficacy in ischemic stroke is unproven.

Tension headaches
Mild adverse effects, such as dizziness, nausea, coolness of the head, and abdominal pain, were reported when moderate doses of naloxone were given to patients with tension headaches (8).

Organs and Systems

Cardiovascular

Doses of naloxone over 1 pg/kg should be given with caution, especially to patients with hypertension. Massive release of catecholamines in response to pain after administration of naloxone can trigger left ventricular failure, partly by causing a shift in fluid from the intravascular to the interstitial space. Thus, alpha-blockers such as phentolamine have been postulated to be beneficial in its management (SEDA-17, 88). A fatal case of pulmonary edema followed the use of naloxone in a young man (9), although the causal link was disputed (10).

Severe hypertension and multiple atrial extra beats have been reported after the administration of naloxone, especially in patients with coronary heart disease (11).

Psychological, psychiatric

Behavioral effects have been noted after high doses of naloxone (2 and 4 mg/kg) in volunteers. Most subjects experienced an initial rush or buzz, tingling or numbness in the extremities, dizziness, a heavy head, and reluctance to move or initiate activities, which usually subsided within 15–30 minutes of administration. Transient sweating and yawning occurred later. Nausea and stomachache were often experienced and in two subjects persisted throughout the day, although in mild form. There were no pupillary changes or sleepiness. Increasing doses of naloxone were associated with increasingly impaired cognitive performance. Violent behavior has been reported after the use of naloxone to reverse sedation (SEDA-17, 88).

Endocrine

Marked changes in physiological functions can occur if naloxone is given when the endorphin system has been modified by opioids. Following the use of naloxone, a reduced plasma prolactin concentration was noted (12).

Second-Generation Effects

Fetotoxicity

Convulsions occurred in a baby born to an opioid-dependent mother. This case is unusual, as convulsions due to neonatal opioid withdrawal do not usually occur in the first 24 hours after delivery; it suggests that naloxone should be used with great caution in children born to opioid-dependent mothers (13).

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Susceptibility Factors

Patients with pre-existing cardiac abnormalities are particularly susceptible to effects such as hypertension, pulmonary edema, atrial and ventricular dysrhythmias, and cardiac arrest, which can occur when naloxone is given to reverse opioid effects.

Drug Administration

Drug administration route

The authors of two review papers both concluded that there is no evidence that subcutaneous or intramuscular administration of naloxone is less effective in restoring respiration in patients with opioid overdose than the intravenous route (14,15).

Drug–Drug Interactions

Captopril

Following the use of naloxone the hypotensive effect of captopril was abolished (16).

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Naltrexone

See also Opioid antagonists

General Information

Naltrexone is an orally-active long-acting pure opioid antagonist with no significant actions of its own. It antagonizes the actions of morphine-like drugs by preferentially binding to opioid receptors in the brain and other tissues, thereby displacing any opioid present and preventing the binding of any pure opioid agonist subsequently administered.

Naltrexone can be used on its own in detoxified individuals to discourage relapse.

The neurotoxic adverse effects of interferon alfa may be mediated by an action at opioid receptors, and naltrexone may antagonize some of this (SEDA-20, 83). Pruritus, probably mediated via enkephalins and opioids, may also be antagonized by naltrexone (SEDA-22, 104).

Gastrointestinal irritation and clinically insignificant increases in blood pressure are commonly reported. Fatigue, irritability, and reduced food intake are also reported.

Drug studies

Opioid dependence

Behavioral disturbances and aversive effects in particular have been observed when naltrexone has been used for treatment of opioid dependence; symptoms noted were loss of energy, gastrointestinal disturbances, and mental depression.

Alcohol dependence

When naltrexone was used in the treatment of alcohol dependence, 5–10% of patients discontinued treatment because of adverse effects (SEDA-20, 83).

A systematic review and meta-analysis of seven double-blind, randomized, placebo-controlled outpatient studies of naltrexone used in the treatment of alcohol dependence between 1976 and 2001 has shown that naltrexone was no more toxic than placebo and was not associated with a significantly greater number of withdrawals because of adverse effects (1). Naltrexone was more effective than placebo in reducing relapses to heavy

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drinking and improving alcohol abstinence in the short term, considering that the studies lasted for only 12 weeks. Additional long-term follow-up studies, with the possibility of studying outcomes of naltrexone treatment programs after stopping the drug and with suitable comparison groups, are necessary. Similar results with similar conclusions were seen in a 12-week randomized controlled trial in 55 alcohol-dependent men treated with naltrexone 50 mg or placebo (2).

To examine the relation between adverse effects profiles, study retention, and treatment outcomes in alcohol-dependent individuals receiving naltrexone for relapse prevention, 92 subjects had their adverse effects monitored weekly and categorized as either neuropsychiatric or gastrointestinal (3). The neuropsychiatric adverse effects had little effect on medication compliance but reduced the length of study retention. In contrast, the gastrointestinal adverse effects significantly affected medication compliance but not study retention.

In an open, single-blind, randomized study, naltrexone (50 mg/day) and acamprosate (1665–1998 mg/day) were used for 1 year by 157 recently detoxified alcohol-dependent men with moderate dependence (4). The time to first relapse was 63 days (naltrexone) and 42 days (acamprosate); after 1 year, 41% of those given naltrexone and 17% of those given acamprosate had not relapsed. Adverse effects were more common with naltrexone and were worse during the first 2 weeks of treatment. They included nausea (25 versus 4%), abdominal pain (23 versus 4%), drowsiness (35 versus 2%), headache (13 versus 6%), and nasal congestion (23 versus 7%).

The Health Technology Board of Scotland has concluded that in people with alcohol dependence, naltrexone reduces drinking (5). In a multicenter, double-blind, placebo-controlled, 12-week study of naltrexone 50 mg/day in 202 patients with alcohol dependence naltrexone was well tolerated, with few adverse effects: abdominal pain (8.6%), headache (7.5%), nausea (6.5%), and dizziness (5.4%); there were no changes in liver function tests (6). However, those who took naltrexone did not have significant improvements in drinking history or fewer relapses.

Pruritus

Naltrexone 50 mg/day has been used to relieve pruritus in cholestatic liver disease in five patients (7). Pruritus scores fell, but two patients developed severe nausea, vomiting, light-headedness, or tremor, requiring withdrawal of treatment. The reviewers commented that these reactions may or may not have been related to opioid withdrawal and that the trial had had several design limitations. They pointed out that one concern relating to the chronic use of high-dose naltrexone is an asymptomatic rise in serum transaminases, although the doses used in this study have not been reported to produce liver function abnormalities.

Organs and Systems

Nervous system

Headache occurred in two children, and an opioid withdrawal syndrome occurred in one child during the first 3 days of treatment when naltrexone was given for protracted apnea in children with increased beta-endorphin concentrations in the cerebrospinal fluid (8).

Psychological, psychiatric

Panic attacks precipitated by naltrexone have been reported (9).

- A 29-year-old woman with bulimia nervosa and a family history of anxiety was enrolled in a trial of naltrexone (100 mg/day). She had no history of opioid use. Within hours of her first dose she experienced alarm, anxiety, chest discomfort, shortness of breath, a fear of dying, sweating, nausea, and derealization. She was unable to remain at home or to go out alone. For 3 days she continued to take naltrexone, with an increasing frequency of panic attacks. On day 4 she was treated with alprazolam (0.5 mg) but relapsed after further naltrexone. Withdrawal of naltrexone led to complete remission of symptoms.

This effect was attributed to an action of naltrexone in removing the endogenous opioid effect at OP_3 (μ) opioid receptors in the locus ceruleus and thus resulting in unchecked noradrenergic hyperactivity.

Acute psychosis secondary to the use of naltrexone has been reported (10).

- A 44-year-old physically healthy woman developed auditory and visual hallucinations and persecutory delusions. She had been given naltrexone hydrochloride 50 mg/day 3 days before the acute psychotic incident in order to prevent relapse of alcohol dependence. Her psychotic symptoms completely resolved 48 hours after withdrawal of naltrexone.

In studies of its use in treating alcohol, opioid, and nicotine dependence, naltrexone has not been reported to cause depression or dysphoria. Patients who complain of naltrexone-associated dysphoria often have co-morbid depressive disorders or depression resulting from opioid or alcohol withdrawal states (11). Co-morbid depression is not a contraindication to naltrexone. Small pilot studies have supported the use of naltrexone in combination with antidepressants for the treatment of patients with co-morbid depression. The risk of non-fatal overdose is significantly increased after naltrexone treatment, as a result of reduced tolerance, compared with patients taking substitution methadone (12).

Hematologic

Idiopathic thrombocytopenic purpura has been attributed to naltrexone (13).

Gastrointestinal

The risk factors for naltrexone-induced nausea have been studied in 120 alcohol-dependent patients in an open trial (14). After 5–30 days of abstinence, they received a bolus dose of naltrexone 25 mg followed by 50 mg/day for 10 weeks. Moderate to severe nausea was reported in 15%. The risk of nausea was significantly predicted by poor medication compliance, intensity of drinking during

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treatment, short duration of abstinence, young age, and female sex.

Gastrointestinal adverse effects of naltrexone were also observed in 183 alcohol-dependent individuals who received either naltrexone or nefazodone (15). These adverse effects predicated early termination of naltrexone used to treat alcohol dependence (16).

Liver

Reversible hepatocellular injury has been reported with naltrexone in doses of up to 300 mg/day, which is five times that usually used for opioid blockade (SED-11, 147) (17). Five of twenty-six patients treated with naltrexone for obesity developed raised serum transaminase activities after 3–8 weeks of treatment. In another study in which 60 obese subjects received naltrexone for 8 weeks, there were abnormal liver function tests in six patients. Three patients failed to complete the course. Nausea and vomiting occurred within the first 24 hours of treatment but responded to a reduction in dose. There were also changes in mentation such as decreased mental acuity, depression, and anxiety, all of which resolved after withdrawal. This is significant, as adverse effects from naltrexone have previously been attributed to mild physical withdrawal syndromes.

Biliary tract

A woman with chronic cholestasis and disabling pruritus had severe but transient opioid withdrawal-like reactions after oral naltrexone 12.5 mg and 2 mg (18). This observation suggests the hypothesis that increased central opioidergic tone is a component of the pathophysiology of cholestasis.

Skin

Skin rashes have been attributed to naltrexone (SEDA-21, 92).

Musculoskeletal

Rhabdomyolysis has been attributed to naltrexone (19).

- A 28-year-old alcoholic was given naltrexone 50 mg/day on the eighth day of a detoxification regimen. On day 17 there was a marked rise in creatine kinase activity (2654 U/l) but no accompanying symptoms of myalgia, weakness, or chest pain. Naltrexone was withheld immediately. The creatine kinase peaked at over 18 000 U/l on day 19 and then fell to within the reference range by day 25. A diagnosis of rhabdomyolysis without accompanying renal insufficiency was suggested.

Long-Term Effects

Drug abuse

Three opiate-dependent individuals abused intravenous naltrexone, believing it to be diamorphine, and developed acute opiate withdrawal symptoms; they were managed with a combined regimen of diazepam, prochlorperazine, and hyoscine (20,21).

Drug Administration

Drug administration route

Six cases of complications loosely related to the use of naltrexone pellet implantation during the highly controversial rapid and ultra-rapid opioid detoxification procedures have been reported (22). These included pulmonary edema, prolonged opioid withdrawal states, drug toxicity, withdrawal from cross-dependence to alcohol and benzodiazepines, aspiration pneumonia, and death. The risk of these controversial procedures and of naltrexone in this novel delivery system are high; a robust scientifically validated program of research is needed to justify such treatment packages.

Drug–Drug Interactions

Clonidine

When naltrexone was given to a group of clonidine-detoxified opioid-dependent subjects, several complained of anorexia and weight loss (23).

Diazepam

The effects of naltrexone on diazepam intoxication were investigated in 26 non-drug-abusing subjects who received either naltrexone 50 mg or placebo and 90 minutes later oral diazepam 10 mg in a double-blind crossover trial (24). Naltrexone was significantly associated with negative mood states, such as sedation, fatigue, and anxiety, compared with placebo, while positive states (friendliness, vigor, liking the effects of diazepam, feeling high from diazepam) were significantly more common with placebo. Naltrexone significantly delayed the time to peak diazepam concentrations (135 minutes) compared with placebo (75 minutes), but there were no significant differences in the concentrations of nordiazepam, the main metabolite of diazepam, at any stage in the study.

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Naphazoline

General Information

Naphazoline is used as a 0.05% intranasal solution. Local irritation, headache, and rebound effects can all occur, and rhinorrhea can follow prolonged use. It has been suggested that such effects are more common with naphazoline than with other decongestants.

Systemic adverse reactions have been reported with ocular administration in young children.

- When nasal drops containing naphazoline were given to an infant of 12 weeks, he had what was apparently severe depression of the nervous system, with pallor followed by apnea, then tachycardia with hypertension; the condition responded to treatment (1).

Although this reaction was unusual, all nasal decongestants should be regarded as contraindicated in young infants.

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Naproxen

See also Non-steroidal anti-inflammatory drugs

General Information

Naproxen sodium, an arylalkanoic acid NSAID, was approved for over-the-counter marketing in January 1994.

The adverse effects of naproxen resemble those of ibuprofen. Any minor differences in frequency cannot be assessed with certainty. In 881 patients who had been followed for more than 3 years, only 8.9% dropped out because of adverse effects. In shorter studies, doses of up to 1.5 g/day produced no more adverse effects than lower or standard doses of other NSAIDs (1).

The safety profile of over-the-counter naproxen has been adequately evaluated, and the incidence of adverse events was similar to the incidence with placebo, ibuprofen, and paracetamol. There were no serious adverse reactions in these studies (SEDA-20, 93).

A comparative case-cohort study on the risk of gastrointestinal tract bleeding associated with naproxen or ibuprofen showed a low incidence of upper gastrointestinal tract bleeding with both drugs, but low-dose naproxen put patients at increased risk of gastrointestinal bleeding compared with low-dose ibuprofen (2). If properly advised, patients can use the over-the-counter formulations without serious risks; patients taking NSAIDs must swallow their tablets with large amounts of water while standing, at least 1 hour before retiring.

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The safety and efficacy of NSAIDs for the relief of symptoms of the common cold have been insufficiently studied. Naproxen did not alter virus shedding or the serum-neutralizing antibody response in healthy young adults with experimental rhinovirus colds but had some beneficial effect on symptoms (SEDA-17, 113).

The fact that its half-life is unchanged in renal insufficiency can be therapeutically useful (3).

Piproxen

Piproxen is a piperazine derivative of naproxen; its adverse effects profile is similar to that of naproxen (4).

Organs and Systems

Respiratory

Eosinophilic interstitial pneumonitis has been reported (5); the incidence is greater with naproxen than ibuprofen, as shown by an FDA survey (SEDA-17, 112).

Exacerbation of asthma in sensitive patients is rare, but has been reported with naproxen (6–8).

Nervous system

Peripheral neuropathy has been reported in a patient with psoriatic arthropathy taking naproxen and hydroxychloroquine (SEDA-12, 87).

Aseptic meningitis has been attributed to naproxen in a healthy young man taking it for neck pain (SEDA-14, 95).

Worsening of parkinsonian symptoms has been described with naproxen (SEDA-19, 99).

Sensory systems

Eyes

Blurred vision, ocular discomfort, and lenticular and corneal changes were observed in a long-term study (1).

Ears

Hearing loss and tinnitus (sudden, bilateral, and permanent) have been associated with naproxen (9).

Psychological, psychiatric

Abnormalities in cognitive capacity and altered behavior have been described in elderly patients taking naproxen (SEDA-8, 107) (10).

Hematologic

Fatal aplastic anemia was reported in a patient taking naproxen as the only drug for 4 months (11). Cases of Coombs' positive and Coombs' negative autoimmune hemolytic anemia (12), agranulocytosis (SEDA-13, 82), and thrombocytopenia (SEDA-15, 102) have also been reported.

- Three men, aged 56, 57, and 71 years developed extensive purpuric hemorrhages involving their legs ($n = 3$), arms ($n = 2$), and abdomen ($n = 1$) 10–20 days after having taken naproxen 250 mg tds for musculoskeletal disorders (13). One patient also had gastrointestinal bleeding. They all had severe thrombocytopenia (platelet counts below 3×10^9/l). Naproxen was withdrawn and prednisone started. The platelet counts normalized within a week. The prednisone was withdrawn and the thrombocytopenia did not recur during follow up. Analysis of their sera showed the presence of IgG antibodies that recognized normal platelets in the presence of the metabolite naproxen glucuronide.

Gastrointestinal

By December 1995 the FDA had received 81 reports of esophageal symptoms and 7 had esophageal ulcers. No hemorrhages were reported (SEDA-22, 117).

Naproxen-induced gastrotoxicity has been reported with varying frequency (SED-9, 152) (1).

There were no differences in the incidence of middle and distal duodenum lesions (14). Esophageal ulceration with bleeding was reported in an elderly woman with esophageal dysmotility (SEDA-17, 112). Esophageal symptoms and esophageal ulcers were reported with naproxen sodium tablets (as opposed to capsules) for over-the-counter use (SEDA-22, 111). Naproxen did not cause reflux and had no significant effect on motility in healthy subjects (15).

Local adverse effects of naproxen suppositories include edema, erythema, and bleeding, which are usually mild.

Acute eosinophilic colitis has been described; it resolved rapidly when naproxen was withdrawn (16).

Liver

Abnormal liver function tests (SED-9, 152) (17) and hepatic injury have been associated with naproxen (18), but no definite cause–effect relation has been established.

Pancreas

Acute pancreatitis has been described in two young women taking naproxen for dysmenorrhea (SEDA-18, 105) (SEDA-20, 93).

Urinary tract

Interstitial nephritis, with rises in serum urea and creatinine, which fell after withdrawal, has been described after treatment for 3 months in adults (19) and in a young boy (SEDA-16, 111).

Oliguric renal insufficiency with the nephrotic syndrome and active interstitial nephritis has been described in a young woman with systemic lupus erythematosus taking intermittent long-term naproxen (SEDA-15, 102).

- A marathon runner, who had taken naproxen until 36 hours before the race, developed acute oliguric renal insufficiency that required hemodialysis 2 days afterwards (SEDA-12, 87).

The kidney can be affected in generalized hypersensitivity reactions to naproxen (3).

Skin

Acne has been reported in a woman with primary dysmenorrhea (20).

The skin can be affected in the course of generalized allergic reactions (21).

Bullous photodermatitis resembling porphyria cutanea tarda has been described in patients taking long-term treatment (SEDA-12, 87).

Hair loss can be induced by naproxen (SEDA-15, 102).

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A photodermatitis, defined as pseudoporphyria, has been reported in 21 children with juvenile rheumatoid arthritis and one with systemic lupus erythematosus after prolonged treatment with naproxen (22) and in another four children with juvenile rheumatoid arthritis (23). This effect is rare, but since naproxen is widely used in juvenile rheumatoid arthritis, it is worth mentioning.

- Linear IgA bullous dermatosis occurred in a 69-year-old man (24). Long-term corticosteroid treatment caused gradual resolution.

Sexual function

Impotence and failure to ejaculate have been described, the latter with positive rechallenge (25).

In women, naproxen, like other NSAIDs, can interfere with menstruation; two young women had interrupted menstrual blood flow after taking the drug (SEDA-15, 102).

At high doses in mid-cycle, naproxen can inhibit ovulation and cause the so-called luteinized unruptured follicle syndrome (SEDA-16, 111).

Immunologic

Generalized reactions (26) include cutaneous necrotizing vasculitis (SEDA-5, 106) (SEDA-17, 113), nephritis, paralytic ileus, and angiitis with cutaneous, muscular, articular, and renal involvement (21).

- A leukocytoclastic vasculitis occurred in a 62-year-old woman with skin, peripheral nerve, and renal involvement (27). Long-term corticosteroid treatment caused gradually resolution.
- Exercise-induced anaphylaxis in a girl who had been taking naproxen for 3 weeks was confirmed by rechallenge (SEDA-21, 106).

Second-Generation Effects

Fetotoxicity

Pulmonary hypertension and severe protracted hypoxemia occurred in babies born to mothers who took naproxen to delay delivery (28). The babies also had disorders of blood clotting, renal function, and bilirubin metabolism. Necroscopy showed subarachnoid hemorrhage, gastric ulcers, and closed ductus arteriosus.

Susceptibility Factors

Age

In an analysis of nine double-blind, controlled studies, adverse reactions to naproxen in older and in younger subjects had similar incidences (29).

Drug Administration

Drug formulations

The suspension and modified-release tablets produce the usual pattern of adverse effects (SEDA-15, 101), although an enteric-coated formulation of naproxen in patients intolerant of NSAIDs caused fewer gastrointestinal adverse effects (SEDA-19, 99).

Drug overdose

Nothing more serious than nausea and indigestion have been reported after 25 g of naproxen (30), whereas 35 g caused an epileptic fit (31). Metabolic acidosis, loss of consciousness, seizures, and apnea have been reported after the ingestion of more than 10 g (32).

Drug–Drug Interactions

Diuretics

Naproxen reduces the actions of diuretics (SEDA-8, 107).

Methotrexate

Methotrexate alters naproxen kinetics and vice versa (33).

Methyldopa

Naproxen reduces the actions of methyldopa (SEDA- 8, 107).

Prebenecid

Naproxen inhibits the metabolism and renal excretion of probenecid, prolonging its half-life (34).

Propranolol

Naproxen reduces the actions of propranolol (SEDA-8, 107).

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Nedocromil

General Information

Nedocromil sodium, a cromone similar to cromoglicate, is classified as an antiallergic drug (1). It is available for inhalation as a metered dose aerosol and is used prophylactically in asthma. Nedocromil is more potent than cromoglicate in inhibiting lung mast cell secretion and stabilizing neutrophils, eosinophils, and platelets; it affects nerve reflexes in the lung in a similar manner to cromoglicate (1). In a number of comparisons of inhaled nedocromil with cromoglicate there was no clinically significant difference between the drugs (2,3).

Nedocromil appears to be as safe as cromoglicate, with an absence of reports of truly severe adverse effects. Nausea (3.8% of patients) and headaches (4.8%) are the most commonly observed adverse effects. These adverse effects were mild and tended to abate during long-term therapy (SEDA-13, 135). Throat irritation is another frequent complaint with nedocromil therapy; less common adverse effects include tremor, chest tightness, production of yellow mucus and dizziness (SEDA-15, 2).

Nedocromil 2% ophthalmic solution is as effective as cromoglicate in allergic conjunctivitis and more effective in peak periods of pollen challenge (4). Headache was the most common adverse effect, but unpleasant taste and nasal congestion also occurred commonly. In cases of vernal keratoconjunctivitis, both cromoglicate (2%) and nedocromil (2%) eye-drops produced improvement without significant adverse effects (5).

Drug Administration

Drug administration route

Ocular irritation, burning, or stinging can occur with nedocromil eye-drops (6). Unpreserved 2% nedocromil sodium eye-drops and placebo were used for 6 weeks in a double-masked comparative study of 45 patients with contact lens-associated papillary conjunctivitis. There was significantly less itching in the nedocromil sodium group compared with placebo, and biomicroscopic assessment showed a significant difference in the amount of mucus on the upper tarsal surface in favor of nedocromil sodium by the end of the study. In the nedocromil group, however, 21 patients had adverse effects, especially taste changes and/or stinging on application of the drops (7).

When nedocromil eye-drops (2%) were used by 1552 patients, 5% noticed a distinctive taste; in another study, 14% of patients reported that nedocromil had a distinctive bitter taste (8). Minor irritation was frequently noted just after application of the drops (4).

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Nefazodone

See also Antidepressants, second-generation

General Information

Nefazodone is a phenylpiperazine antidepressant, structurally related to trazodone, but it has less alpha$_1$-adrenoceptor antagonist activity and is therefore less sedative. It is a potent 5-HT$_2$ receptor antagonist at postsynaptic receptors, and a weak serotonin reuptake inhibitor. In trials it was more effective than placebo and comparable to imipramine.

Commonly reported adverse effects are dry mouth, weakness, somnolence, nausea, dizziness, constipation, light-headedness, amblyopia, and blurred vision (1,2).

Organs and Systems

Nervous system

Nefazodone is unusual amongst antidepressants in that it does not reduce and in fact may increase rapid eye movement (REM) sleep or dream sleep. In a controlled study in depressed patients nefazodone 400 mg/day increased REM sleep, while fluoxetine 20 mg/day produced the opposite effect (3). In addition, nefazodone increased sleep efficiency, while fluoxetine reduced it. The patients' subjective assessments of sleep improved more with nefazodone than with fluoxetine. However, the overall antidepressant effects of the drugs were similar. The function of REM sleep and its relation to depressive disorders is not clear, so it is uncertain whether preservation of REM sleep by nefazodone is likely to be of clinical consequence.

Three men (aged 28–63 years) had troublesome burning sensations, not clearly localized to any one area of the body, 3 days to 3 weeks after starting to take nefazodone (4). The episodes lasted for about 30 minutes and recurred several times each day. The symptoms responded to nefazodone withdrawal or dosage reduction. These unpleasant sensations appeared to be linked to nefazodone, but the mechanism was obscure.

Psychological, psychiatric

- A 55-year-old woman with no previous history of bipolar disorder became manic while taking nefazodone (5).

Metabolism

Hypoglycemia occurred in a 54-year-old woman with diabetes mellitus after she started to take nefazodone (6). She also reported weight loss of 5 pounds.

Liver

There have been several reports of serious hepatotoxicity associated with nefazodone, in some cases leading to liver failure.

- A 27-year-old man developed hepatitis (with raised bilirubin and liver enzymes) without overt jaundice after taking nefazodone 200 mg/day for 12 weeks (7). No other cause for the hepatitis could be established and the abnormal liver function tests settled 4 weeks after nefazodone withdrawal. They became abnormal again 1 week after nefazodone rechallenge and settled once again on withdrawal.
- Four women, aged 16–73 years, developed catastrophic liver failure while taking nefazodone (8,9). Nefazodone was given for 14–28 weeks before the onset of symptoms. The cases had similar histological appearances, with prominent centrilobular necrosis. Three died, one survived after liver transplantation, and one improved sufficiently to obviate the need for transplantation. The duration of nefazodone treatment before the onset of symptoms was 7–28 weeks. The patients had no history of liver disease and other causes were excluded as far as possible.
- An 80-year-old man developed acute fatal liver failure while taking nefazodone 50 mg/day (8).
- A 52-year-old man with a 10-day history of fatigue and jaundice had been taking nefazodone (300 mg/day) for depression for about 6 weeks. Biochemical investigations showed acute liver failure. Infective hepatitis and immune disorders were excluded. He failed to respond to medical treatment, and hepatic transplantation was performed. Histological examination of the liver showed parenchymal necrosis, particularly in centrilobular areas, together with lymphocytic infiltration (10).
- A 46-year-old woman developed fatigue and jaundice about 20 weeks after she started to take nefazodone (300 mg/day). She had raised liver enzymes and bilirubin concentrations. There was no evidence of infectious hepatitis or immune disorders. Liver biopsy showed ballooning degeneration and necrosis of hepatocytes with mixed inflammatory infiltrates. The nefazodone was withdrawn and corticosteroid treatment started. Within 4 months she recovered clinically and her liver function tests returned to normal (11).

These severe reactions, although rare, cause concern.

The cumulative incidence of hepatic adverse reactions associated with antidepressant treatment has been estimated through spontaneous reports to the Spanish Pharmacovigilance System (12). For classical tricyclic

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antidepressants and SSRIs the estimated rate of adverse hepatic reactions was 1.28–4.00 per 100 000 patient years. However, the rate with nefazodone was much higher (29 per 100 000 patient years). This report supports concerns that nefazodone may be more hepatotoxic than other antidepressants. Significant hepatic reactions to nefazodone are relatively rare but can be serious.

Hair

Nefazodone was associated with hair loss in a 40-year-old woman after dose escalation from 100 to 200 mg (13).

Sexual function

Sexual adverse effects seem to occur less often with nefazodone than with SSRIs (SEDA 20, 9).

- A 48-year-old woman developed clitoral priapism on the first day of nefazodone treatment (100 mg) (14). The problem persisted for another day, after which she discontinued the nefazodone and the priapism subsided.

Clitoral priapism has been reported with other antidepressants, including SSRIs both alone and in combination with trazodone. In men, trazodone rather than nefazodone is occasionally associated with priapism (SEDA-21, 14).

Long-Term Effects

Drug withdrawal

Discontinuation of SSRIs causes significant withdrawal symptoms (SEDA-22, 12). Withdrawal reactions have been less often described after discontinuation of nefazodone.

- A 27-year-old man developed withdrawal symptoms (dizziness, nausea, vomiting, sweating, anxiety, insomnia, and restlessness) after nefazodone was abruptly withdrawn after 1 month (15).
- A 22-year-old woman gradually increased her dose of nefazodone to 400 mg/day over 3 weeks (16). One week later she abruptly discontinued treatment. About 48 hours later she began to have nausea, vomiting, fatigue, headache, myalgia, restlessness, dizziness, nightmares, emotional lability, and anxiety. These symptoms continued unabated for a further 48 hours, after which they remitted a few hours after nefazodone was restarted.

These symptoms are very similar to those of severe SSRI-induced withdrawal, as were those described in two further case reports (17,18). As with SSRIs, it seems prudent to withdraw nefazodone slowly and to be aware of the possibility of SSRI-like withdrawal symptoms.

Second-Generation Effects

Lactation

Nefazodone passes into the breast milk and has been reported to cause drowsiness and feeding problems in a breast-fed infant (19).

- The mother of a 7-week-old premature girl became depressed and was given nefazodone 300 mg/day. Two weeks later the infant became drowsy and lethargic and did not feed well. No medical condition was found to account for these symptoms and breast-feeding was stopped. The symptoms improved over the next 3 days. The concentrations of nefazodone in breast milk were about 10 times less than those in maternal plasma, and the total infant dose of nefazodone was calculated to be only 0.45% of the maternal dose.

In this case, nefazodone in the breast milk may have caused the infant's drowsiness and feeding problems, despite the fact that the transferred dose of nefazodone would have been very low, since the low gestational age of the infant might have been associated with impaired hepatic and renal clearance, making her susceptible to even very small quantities of nefazodone.

Drug Administration

Drug overdose

The outcomes of over 1300 cases of poisoning with nefazodone as a sole agent have been reported (20). Generally, the toxic effects were mild, consisting mainly of drowsiness, nausea, and dizziness. Clinical signs developed within 1–4 hours of ingestion and dissipated within the following 24 hours. The most serious toxic effect was hypotension, which occurred in 1.6% of cases. Bradycardia occurred in 1.4% of cases. Only one patient had a seizure and none required intubation. These data suggest that the toxicity of nefazodone in overdose is low. However, in suicide attempts, antidepressants are often ingested with other agents, particularly alcohol and other sedating drugs. This might increase the toxic effects of nefazodone, particularly with regard to respiratory depression.

Drug–Drug Interactions

Carbamazepine

In a controlled study in 12 healthy men the combination of carbamazepine and nefazodone led to increased plasma carbamazepine concentrations and substantially lowered plasma nefazodone concentrations (21). This interaction, which is due to inhibition of CYP3A4 by nefazodone, could lead to difficulties during treatment, since the risk of carbamazepine toxicity would have to be balanced against the loss of therapeutic effect of nefazodone. Except in special circumstances it is probably better to avoid the combination.

Clozapine

When nefazodone (400 mg/day for 3 weeks) was added to clozapine treatment in six patients with schizophrenia there was no significant change in plasma clozapine concentrations (22). This finding suggests that CYP3A4 does not play a major role in the metabolism of clozapine and that nefazodone may be a suitable adjunctive treatment for depression in clozapine-treated patients.

However, in another case the addition of nefazodone appeared to produce clozapine toxicity (23).

- A 40-year-old man had taken clozapine 450 mg/day and risperidone 6 mg/day for several years. Nefazodone

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200 mg/day was added in an attempt to improve persistent negative symptoms, and after a week the dosage was increased to 300 mg/day. One week later, he reported anxiety and dizziness and was hypotensive. The combined concentrations of clozapine and its active metabolite norclozapine had increased from 309 ng/ml before nefazodone to 566 ng/ml. The nefazodone dosage was reduced to 200 mg/day and the anxiety, dizziness, and hypotension resolved over the next 7 days. At the same time plasma concentrations of clozapine and norclozapine fell to 370 ng/ml.

These results suggest that in some individuals CYP3A4 plays a significant role in the metabolism of clozapine and that the combination of nefazodone and clozapine should therefore be used with caution. It is possible that in this case concomitant treatment with risperidone may have increased the effect of nefazodone to reduce the clearance of clozapine.

Selective serotonin re-uptake inhibitors (SSRIs)

Concentrations of nefazodone and its metabolites can be increased by fluoxetine and paroxetine (SEDA-20, 9). Combinations of serotonin agents produce serotonin toxicity, and a case of serotonin syndrome occurred when nefazodone (200 mg/day) was combined with fluoxetine (40 mg/day) in a 50-year-old man (24). The toxic symptoms settled 3 days after withdrawal of both antidepressants.

Statins

Nefazodone can cause myositis and rhabdomyolysis in patients taking pravastatin and simvastatin (25). The postulated mechanism involves inhibition of CYP3A4, leading to reduced clearance of the HMG-CoA reductase inhibitors and muscle toxicity.

Substrates of CYP3A4

Nefazodone is a weak inhibitor of CYP2D6, but a potent inhibitor of CYP3A4, and increases plasma concentrations of drugs that are substrates of CYP3A4, such as triazolam, alprazolam, ciclosporin, astemizole, cisapride, terfenadine, and carbamazepine (26). Co-administration with terfenadine, astemizole, or cisapride should be avoided, because of the risk of cardiac dysrhythmias (SEDA-20, 9).

Terfenadine

Drugs that inhibit CYP3A4 inhibit the clearance of terfenadine, an antihistamine that can prolong the QT_c interval. This can cause potentially dangerous interactions. In a double-blind, placebo-controlled study of the effect of nefazodone (600 mg/day for 1 week) on the pharmacokinetics of terfenadine (120 mg/day for 14 days) and another antihistamine, loratadine (20 mg/day for 14 days), in 67 healthy volunteers, nefazodone significantly reduced the clearance of terfenadine and prolonged the mean QT_c interval (27). In addition, nefazodone produced a similar but smaller decrease in the clearance of loratadine and combined treatment also significantly increased the QT_c interval. This effect of nefazodone on the clearance of terfenadine is predictable, as is the increase in QT_c interval. Loratadine is also partly metabolized by CYP2D6, which probably explains the lesser effect of nefazodone on loratadine clearance. Loratadine by itself does not increase the QT_c interval significantly, but cardiotoxicity may be a possibility when it is combined with nefazodone.

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Nefopam

General Information

Nefopam, an orphenadrine derivative, is a centrally acting non-opioid analgesic. Various adverse effects have been reported, including nausea, vomiting, epigastric pain, dizziness, drowsiness and mental confusion, hypotension, tachycardia, skin rashes, xerostomia, and urinary retention; some of these may be related to its anticholinergic properties (SEDA-11, 100). Its unsatisfactory adverse effects profile was confirmed in two studies of pain control in cancer and rheumatoid arthritis (SEDA-15, 104)

In one study, five of 33 patients (15%) stopped treatment because of the severity of adverse effects attributed to nefopam (1).

In an open trial 120 patients undergoing elective hepatic resection were randomized to receive postoperative intravenous patient-controlled analgesia with morphine either alone or in combination with nefopam (20 mg 4-hourly) or propacetamol (2 g 6-hourly) (2). Nefopam plus morphine was the most effective treatment. Adverse effects, especially sedation, were comparable in the three groups, but there was significantly more nausea in the morphine group and more sweating in the nefopam group (requiring early drug withdrawal in three cases). Tachycardia was seen more often in the nefopam group but did not reach significance.

Organs and Systems

Urinary tract

There have been 53 cases of reversible urinary retention, hesitancy, a poor stream, or dribbling reported to the UK Committee on Safety of Medicines.

Long-Term Effects

Drug abuse

Three cases of nefopam abuse have been reported (3). The patients had the same pattern of a history of chronic pain, concomitant anxiolytic and antidepressant drug therapy, and abuse of nefopam due to its primarily psychostimulant-like symptoms. The recommended dose of nefopam is 20 mg intramuscularly every 6 hours, with a maximum recommended dose of 120 mg/day. Daily consumption in the three patients was 120–1840 mg/day.

Susceptibility Factors

The UK Committee on Safety of Medicines received 12 reports of confusion and 22 of hallucinations and recommended that nefopam be used with caution in the elderly, in patients with symptoms of urinary retention, or in conjunction with other drugs that have anticholinergic activity (4).

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Nelfinavir

See also Protease inhibitors

General Information

Nelfinavir is a non-peptidic inhibitor of the HIV protease. Its most prominent adverse effect is diarrhea, which occurs in up to one-third of individuals. However, the diarrhea is usually mild and can be controlled, if necessary, by antidiarrheal agents (1). Other adverse effects, including rash, nausea, headache, and weakness, are reported in under 5%.

Observational studies

In a multicenter, open, uncontrolled trial of protease inhibitors in conjunction with NRTIs for at least 96 weeks in 32 children, the pharmacokinetics of nelfinavir showed large interindividual differences (2). In all, 17 children suffered adverse events, most of which were mild and occurred early in treatment. The rate of drug-related adverse effects was 0.16 per patient-year in those taking nelfinavir.

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Organs and Systems

Nervous system

Peripheral neuropathy has been reported with nelfinavir (3).

- In a 40-year-old HIV-positive patient nelfinavir 750 mg tds was added to existing combination therapy with stavudine, lamivudine, and loviride. He had taken various drugs during the 4 years before, including zidovudine, zalcitabine, didanosine, stavudine, loviride, ritonavir, and saquinavir. Zalcitabine had been withdrawn 3 years before because of pain and paresthesia in both feet after 4 weeks. Thereafter, he had persisting dysesthesia in the feet. One week after having started nelfinavir, this extended in both legs to the knees. He also had sharp pains in the Achilles tendons and bones and burning in the legs, which made walking impossible. He reduced the dosage to 1500 mg/day and felt an improvement within a few days; nelfinavir was then withdrawn, and his symptoms abated.

Although circumoral paresthesia has been a common adverse effect of ritonavir, peripheral neuropathy has not been previously reported with HIV-1 protease inhibitors. There has been a report of painful neuropathy in two patients who took ritonavir and indinavir respectively (4).

Gastrointestinal

The main adverse event that has been consistently reported with nelfinavir is diarrhea and loose stools in 20–30% of patients. The frequency with which diarrhea is truly dose-limiting is not yet clear, but clinical experience suggests that in many cases treatment can be continued in conjunction with non-specific antidiarrheal medication (SEDA-22, 317) (5,6).

Pancreas

Pancreatitis, if it occurs, can be serious; any doubt as to the causal link has been largely dispelled by a case in which there was positive rechallenge (7).

Urinary tract

Nelfinavir has been reported to cause urinary stones.

- A 37-year-old woman stopped taking indinavir and other antiretroviral drugs because of skin reactions and started to take nelfinavir and delavirdine (8). An unspecified time later she presented with right flank pain, due to nephrolithiasis with hydronephrosis. She was treated with lithotripsy, but 6 months later had another episode of flank pain with microscopic hematuria and crystalluria. There was a large urinary stone in the right renal pelvis and a smaller stone obstructing the ureter. The stone fragments contained nelfinavir 99% and indinavir 1%.

The authors pointed out that nelfinavir is normally only 1–2% excreted in the urine, and they postulated that the indinavir may have started a nidus on which the nelfinavir was subsequently deposited.

Skin

Three HIV-infected patients, who had all taken zidovudine, didanosine, and co-trimoxazole (for *Pneumocystis jiroveci* prophylaxis) for over 12 months, developed generalized urticaria 8–10 days after starting nelfinavir 750 mg tds. Withdrawal of nelfinavir and treatment with antihistamines resulted in the disappearance of the lesions within 4–6 days. One patient restarted nelfinavir 250 mg tds without consulting his physician and had similar symptoms within 5 days. Desensitization by using a dose escalation protocol was attempted in all three patients after withdrawal of nelfinavir. This was successful in two cases; the third patient prematurely discontinued desensitization on his own request. During desensitization two of the patients had mild and transient pruritus and rash, reinforcing the diagnosis of an allergic skin reaction (9).

Patients often develop rashes due to HIV infection or drug allergy. Sulfa desensitization is well documented, but desensitization to other medications is not as well studied. One patient taking nelfinavir developed a severe, pruritic rash; management included nelfinavir desensitization over 12 days (10).

Susceptibility Factors

Age

The pharmacokinetics of three doses of nelfinavir, 15, 30, and 45 mg/kg bd, have been studied in 22 neonates, who were also given stavudine and didanosine for 4 weeks after birth (11). Median values of C_{min} (μg/ml) at 1, 7, 14, and 28 days of age were respectively: 0.19, 1.21, 0.51, and 0.33 (15 mg/kg); 1.02, 3.18, 0.73, and 0.55 (30 mg/kg); and 0.67, 3.21, 0.70, and 0.73 (45 mg/kg). The median values of steady-state AUC (hours.μg/ml) at 14 and 28 days were respectively: 14 and 8.7 (15 mg/kg); 19 and 16 (30 mg/kg); and 23 and 19 (45 mg/kg). There were no serious adverse events. Thus, systemic exposure to nelfinavir fell after 7 days of age, perhaps because of hepatic enzyme maturation, autoinduction of nelfinavir metabolism, and/or changes in nelfinavir absorption. Because of the highly variable kinetics the authors suggested that plasma concentration monitoring was warranted to ensure adequate nelfinavir dosing in neonates.

In a multicenter trial, 128 children were randomly assigned to one of three regimens: zidovudine + lamivudine ($n = 36$), zidovudine + abacavir ($n = 45$), or lamivudine + abacavir ($n = 47$) (12). The children who were free of symptoms ($n = 55$) were also randomized to nelfinavir or placebo, while those with more advanced disease received open-label nelfinavir ($n = 73$). All 13 episodes of diarrhea occurred in those taking nelfinavir. Nelfinavir did not affect serum cholesterol or triglyceride concentrations and there were no cases of lipodystrophy. There were 24 serious adverse events; six were in the symptom-free children (all taking nelfinavir), but all were attributed to the NRTIs.

Drug–Drug Interactions

Cannabinoids

The effects of smoked marijuana (3.95% tetrahydrocannabinol; up to three cigarettes per day) and oral dronabinol (2.5 mg tds) on the pharmacokinetics of nelfinavir 750 mg tds ($n = 34$) have been evaluated in a

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randomised, placebo-controlled study in HIV-infected patients (13). At day 14, marijuana reduced the 8-hour AUC of nelfinavir by 10%, the C_{max} by 17%, and the C_{min} by 12%. However, none of these changes was significant. Dronabinol had no effects.

Methadone

Withdrawal symptoms in a 40-year-old man maintained on methadone, necessitating an increase in dosage, were attributed to nelfinavir (14).

Phenytoin

While one might expect nelfinavir to reduce blood concentrations of certain other drugs by inducing their metabolism, it has been suggested that it might actually increase circulating concentrations of simultaneously administered phenytoin (15). However, a Japanese case has suggested that phenytoin concentrations can indeed be reduced; when the two drugs were co-administered a patient previously stabilized on phenytoin had a generalized convulsion (16).

Statins

Since HMG CoA reductase inhibitors (statins) are partially or completely metabolized by CYP3A4, drug interactions with protease inhibitors can be expected. When nelfinavir was combined with atorvastatin and simvastatin, their AUCs increased by 74 and 505% respectively (17). As myopathy and rhabdomyolysis are concentration-related, simvastatin is contraindicated with any protease inhibitor, not just nelfinavir. Based on the data, the starting dose of atorvastatin should be reduced by about 50%.

Tacrolimus

An interaction of nelfinavir with the macrolide immunosuppressant tacrolimus has been reported in a patient co-infected with HIV and hepatitis C virus who had undergone orthotopic liver transplantation (18). The dose of tacrolimus had to be reduced to a 70th of the normal dose to avoid adverse effects. Nelfinavir serum concentrations were not affected by tacrolimus. The authors suggested that this effect had resulted from inhibition of the metabolism of tacrolimus, because both compounds are substrates of CYP3A4.

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Neuraminidase inhibitors

General Information

The major drawbacks of older drugs for the treatment of influenza (amantadine and rimantadine) include lack of activity against influenza B, a considerable frequency of adverse effects, and probably a higher likelihood of resistance. With the recent development of inhibitors of the viral neuraminidase, a more specific class of drugs has been added to the antiviral armamentarium. After the description of the crystal structure of the viral neuraminidase, a surface glycoprotein, specific inhibitors were designed. Two derivatives of sialic acid, the natural substrate of the neuraminidase, are currently in use, oseltamivir (rINN) and zanamivir (rINN). These drugs were designed to bind strongly to a conserved region of the cleavage site of the virus, which resulted in a class of compounds with limited risk of viral resistance. In fact, resistance is rare during the use of these drugs (1).

Oseltamivir is administered as an oral capsule and zanamivir by inhalation. Inhaled zanamivir has fewer adverse effects than oral oseltamivir, but there are concerns about its use in young and elderly patients, who are generally unable to achieve the inspiratory flow rate needed to ensure adequate lung deposition (2). Oral oseltamivir is more convenient and easier to administer, but needs to be given with food to lower the frequency of gastrointestinal adverse effects.

Oseltamivir

Oseltamivir (GS4104) is an ester prodrug, whose active metabolite (GS4071) is a potent selective inhibitor of influenza virus neuraminidase, to which it is rapidly hydrolysed by hepatic carboxylesterases. The metabolite is then completely excreted by the kidneys by filtration and secretion. In animals oseltamivir had a wide safety margin, with no evidence of teratogenicity or adverse effects on fertility. Oseltamivir has also been studied in the treatment and prevention of influenza A and B, but published results are sparse. To date it has been well tolerated. Headache was the most frequent complaint and mild to moderate gastrointestinal adverse effects (nausea, diarrhea) have been described (3).

Zanamivir

Zanamivir has poor oral systemic availability. Intranasal administration slightly increases its availability, but in mice strongly reduced viral replication (4). In vitro, zanamivir does not significantly inhibit human lysosomal neuraminidases, and so the potential for severe adverse effects is low (5).

Zanamivir has been evaluated in the prevention and treatment of influenza A and B, and was effective against both viruses. In placebo-controlled trials, the adverse events profile, including local nasal irritation, did not differ significantly between zanamivir and placebo (3,6–8). Phase II and III clinical studies have shown that zanamivir by inhalation, either orally or combined orally and intranasally, slightly shortened the duration and severity of influenza symptoms and in high-risk patients reduced the risk of complications (1,9). Typical doses are 10 mg by oral inhalation and 6.4 mg by intranasal inhalation. Dosing frequency is 2–6 times/day. Zanamivir is well tolerated. In placebo-controlled studies its toxicity profile was similar to placebo.

A review of the use of zanamivir in 6000 patients in clinical studies has confirmed its favorable safety profile (10). To date there is still an optimistic impression that the adverse reactions pattern is no different from that of placebo and that interactions are also unlikely, since it does not inhibit cytochrome P450 (11).

Observational studies

In 730 residents of nursing homes who took oseltamivir prophylaxis for a median of 9 days (range 5–12), adverse effects were identified in 30 (4.1%), of whom 20 had one adverse effect and 10 had two (12). The most common adverse effects were diarrhea ($n = 12$), nausea or vomiting ($n = 7$), cough ($n = 5$), and confusion ($n = 4$).

In seven patients with influenza (three type A and four type B) after allografting, inhaled zanamivir (10 mg bd) was used until excretion of virus ceased (median duration 15, range 5–44, days); there was rapid resolution of the influenza and no adverse effects attributable to zanamivir (13).

Organs and Systems

Respiratory

Zanamivir is administered by inhalation of a powder in a lactose vehicle. It can cause bronchospasm (14).

- A 63-year-old man with oxygen-dependent chronic obstructive pulmonary disease was given zanamivir because of an exacerbation attributed to influenza. Shortly after each inhalation of the drug he reported increasing respiratory difficulty and wheezing. After 3 days he developed respiratory distress, hypoxia, and wheezing, and was treated with bronchodilators, glucocorticoids, and antibiotics.

Patients taking zanamivir are advised to stop using it if bronchospasm occurs, and those with underlying lung disease are advised to have a fast-acting bronchodilator to hand. The bronchospasm can be reduced in frequency by using an inhaled β_2-adrenoceptor agonist before zanamivir. Proper drug deposition depends on flow rate and inhaler technique, so young and elderly patients may not be the best to treat in this way (2,15).

Gastrointestinal

Upper gastrointestinal effects (nausea or nausea with vomiting) have been reported more often in those taking oseltamivir in placebo-controlled studies (16,17). Despite this mild gastrointestinal intolerance, withdrawal rates have been low.

The oral capsule of oseltamivir can be used in any patient who can swallow. However, it must be given with food, to reduce the frequency of nausea and gastrointestinal discomfort. Of 695 children aged 1–12 years, 14.3% had vomiting compared with 8.5% of those

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who took placebo; otherwise oseltamivir was well tolerated (18).

In a meta-analysis of trials, there was a reduction in the duration of symptoms of about 1 day (19). Oseltamivir caused significantly more gastrointestinal symptoms (dyspepsia or nausea) than placebo; the effect increased with dose. Similarly, zanamivir caused significantly more gastrointestinal symptoms than placebo (OR = 2.6; 95% CI = 1.6, 4.2).

Drug–Drug Interactions

Amoxicillin

In healthy subjects amoxicillin had no effect on the pharmacokinetics of oral oseltamivir (20).

Cimetidine

In healthy subjects cimetidine had no effect on the pharmacokinetics of oral oseltamivir (20).

Probenecid

In healthy subjects probenecid completely blocked the renal secretion of the active metabolite of oseltamivir after oral administration, increasing its AUC 2.5 times (20). In vitro studies of the metabolite on the human renal organic anionic transporter I (hOAT1) were investigated in Chinese hamster ovary cells stably transfected with the transporter. The metabolite was a low-efficiency substrate for hOAT1 and a very weak inhibitor of hOATl-mediated transport of *para*-aminohippuric acid. Probenecid inhibited the transport of the metabolite, *para*-aminohippuric acid, and amoxicillin via hOAT1.

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Neuroleptic drugs

General Information

Since the introduction of chlorpromazine in the early 1950s, a large number of phenothiazines with neuroleptic properties have been discovered; they include fluphenazine, perphenazine, prochlorperazine, and thioridazine. Several other chemical structures with similar therapeutic properties have also been introduced, including the butyrophenones (such as haloperidol and droperidol) and the thioxanthenes (such as flupenthixol). In recent years the so-called atypical neuroleptic drugs (such as clozapine, olanzapine, and risperidone) have also become available. They have less affinity for dopamine receptors in the basal ganglia than the typical neuroleptic drugs, and therefore cause fewer extrapyramidal adverse effects. The range of usefulness of these agents includes the treatment of schizophrenia (to treat acute episodes and in long-term maintenance treatment), mania, certain organic psychoses, certain depressive states, and a variety of lesser indications. They have also been used to treat autism (1) and psychosis in patients with dementia (2).

Equipotent doses of neuroleptic drugs are listed in Table 1.

General adverse reactions

Neuroleptic drugs can produce a variety of adverse effects in several organ systems. Extrapyramidal reactions and sedation are common; less common are seizures, unwanted behavioral effects, and tardive dyskinesia. Most neuroleptic drugs have anticholinergic effects and commonly produce dry mouth, blurred vision, and constipation. Postural hypotension is common. These effects usually disappear when the drug is stopped or the dosage is reduced.

Table 1 Equipotent doses of neuroleptic drugs (all rINNs)

Drug	Dose (mg)
Typical neuroleptic drugs	
Chlorpromazine	100
Chlorprothixene	100
Fluphenazine hydrochloride	2
Haloperidol	2
Loxapine	10
Mesoridazine	50
Molindone	10
Perphenazine	10
Prochlorperazine	15
Pimozide	1
Thioridazine	100
Tiotixene	5
Trifluoperazine	5
Trifluoperazine	25
Atypical neuroleptic drugs	
Aripiprazole	6
Clozapine	50
Olanzapine	4
Quetiapine	80
Risperidone	1
Ziprasidone	20

Non-specific, usually reversible, cardiographic changes have been reported, but their relation to myocardial toxicity has not been confirmed. Sudden death related to cardiac arrest cannot be fully explained on the basis of the administration of neuroleptic drugs. Weight gain is a common adverse effect. Breast engorgement and galactorrhea can occur in women and even in men. Amenorrhea, gynecomastia, hyperglycemia, hypoglycemia, raised growth hormone, inappropriate ADH secretion, and disturbance of sex hormones have been reliably documented, although they are unusual.

The contraindications to neuroleptic drug therapy include coma, the presence or withdrawal of high doses of other CNS depressants (alcohol, barbiturates, narcotics, etc.), serious hematological conditions (for example bone-marrow suppression), and a previous history of hypersensitivity reactions for example jaundice or severe photosensitivity. Since neuroleptic drugs cause sedation, they can impair mental or physical abilities (including reaction times), especially during the first few days of therapy. A large number of substances can interact with neuroleptic drugs (SED-14, 153) (3).

Hypersusceptibility reactions

Neuroleptic drugs infrequently produce allergic reactions. There are no reports of anaphylactic reactions, but various skin reactions, for example rashes, photosensitivity, and dermatitis, can be viewed as delayed forms of hypersensitivity. Jaundice and blood dyscrasias (hemolytic anemia, agranulocytosis) are rare and may be types of allergic reactions.

Tumorigenicity

Since neuroleptic drugs raise prolactin concentrations, there is concern that this may increase the risk of breast cancer. Although studies have failed to show an association, it would be best to avoid neuroleptic drugs in a patient with a hormone-dependent breast tumor.

Effects on fertility

Amenorrhea and infertility were consequences of the effects of typical neuroleptic drugs and of risperidone. Clinicians should be aware that patients changed from these agents to drugs like olanzapine, quetiapine, or clozapine are therefore at risk of pregnancy (4).

A project group at the Swedish Council on Technology Assessment in Health Care has analysed more than 2000 published manuscripts about neuroleptic drugs (5). They concluded that neuroleptic drug therapy is often accompanied by serious, sometimes permanent, adverse effects. Hence, neuroleptic drugs should be reserved for patients with severe psychoses. Agitated and demented elderly patients should not be treated with neuroleptic drugs unless they have pronounced psychotic symptoms. Nor should neuroleptic drugs be used in young mentally retarded patients and other children and adolescents, except in those with severe autism, Tourette's syndrome, or schizophrenia. In fact, in patients with schizophrenia

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there is increased mortality, and the involvement of neuroleptic drug treatment has been investigated (6).

Severe adverse events associated with neuroleptic drug treatment are epileptic seizures, QT interval prolongation, myocarditis associated with clozapine, neuroleptic malignant syndrome, hypothermia, respiratory arrest, and pulmonary embolism associated with clozapine. To minimize these potential risks, practical prescribing guidelines have recently been proposed (SEDA-21, 42); they recommend careful titration of therapy, checking for a history of cardiac disorders, seizures, neuroleptic malignant syndrome, and hypotension, and regular monitoring for known adverse effects.

Further comparisons of the main features of typical and atypical neuroleptic drugs have emerged (SEDA-22, 45) (7). The review by the Collaborative Working Group on Clinical Trial Evaluations has addressed adverse effects extensively (8). The authors stressed that atypical neuroleptic drugs cause fewer extrapyramidal signs and may have a lower risk of causing tardive dyskinesia than typical neuroleptic drugs. The adverse effects of the atypical drugs of which one should be aware are the following (listed with the drug(s) most likely to cause them):

(a) orthostatic hypotension (clozapine, olanzapine, quetiapine);
(b) myocarditis (clozapine);
(c) pulmonary embolism (clozapine);
(d) seizures (clozapine);
(e) anticholinergic effects (clozapine, olanzapine);
(f) increased prolactin (risperidone);
(g) weight gain (clozapine, olanzapine);
(h) hepatic changes (clozapine, risperidone);
(i) agranulocytosis (clozapine).

Drug interactions can be dangerous or fatal and should be avoided. Patients' individual concerns and health needs must be taken into account when selecting a drug. The atypical drugs, it is said, would be better first-line drugs for patients with specific health concerns.

The Collaborative Working Group has also drawn attention to the interpretation of certain results from clinical trials with novel neuroleptic drugs (8). It has been stated, for instance, that when extrapyramidal signs are not significantly different from those with placebo, it does not necessarily mean that a new neuroleptic drug absolutely lacks extrapyramidal effects. Patients who enter studies of new neuroleptic drugs may have been previously treated with traditional neuroleptic drugs, and extrapyramidal symptoms may have persisted from this prior drug treatment.

A comparison of patients' and prescribers' beliefs about the adverse effects of neuroleptic drugs has been carried out (9). Psychiatrists' estimates of prevalence, but not of distress, correlated significantly with patients' reports. The authors concluded that the apparent lack of understanding of which adverse effects are most likely to cause distress to patients can adversely affect the therapeutic alliance between prescribers and patients.

Patients with good adherence to therapy have a higher incidence of adverse effects (10). Logistic regression analysis identified four factors that discriminate adherent ($n = 48$) from non-adherent ($n = 30$) patients: the course of the illness, the employment status of a key relative, age at onset of the illness, and the presence or absence of adverse effects.

Several atypical neuroleptic drugs are currently considered to be first-line therapies for schizophrenia. However, choosing one can be difficult, because head-to-head comparisons are just beginning to appear and most published trials are comparisons with typical neuroleptic drugs, particularly haloperidol. Several reviews (11,12) and clinical comparisons (13,14) of atypical neuroleptic drugs have been published; a meta-analysis of the efficacy and extrapyramidal effects of the new neuroleptic drugs olanzapine, quetiapine, and risperidone, compared with typical neuroleptic drugs and placebo, deserves particular attention (15). Only randomized, double-blind, controlled trials in patients with schizophrenia or schizophrenia-like psychoses were selected. Combining all Brief Psychiatric Rating Scale (BPRS) comparisons between all neuroleptic drugs and placebo resulted in a mean effect size of 0.25 (CI = 0.22, 0.28; $n = 2477$), which is only a moderate treatment effect. Quetiapine (six studies; $n = 1414$) was as effective as haloperidol. Risperidone (nine studies; $n = 2215$) and olanzapine (four studies; $n = 2914$) were statistically superior to haloperidol. However, the latter two effect sizes (0.06 and 0.07) were very small. The new neuroleptic drugs and placebo were associated with similar use of antiparkinsonian medications, and all were clearly superior to haloperidol in this respect; risperidone had the weakest effect (effect size 0.09 versus placebo and 0.12 versus haloperidol). Many of the trials used relatively high doses of haloperidol, favoring the occurrence of extrapyramidal signs.

Special subgroups have been considered in different studies. Agitated and demented elderly patients should not be treated with neuroleptic drugs, unless they have pronounced psychotic symptoms (SEDA-23, 48). Since some studies have reported the lack of a documented diagnosis associated with the use of neuroleptic drugs, a drug utilization study using a chart review has been carried out in Canada to discover the pattern of use of neuroleptic drugs in a long-term care facility (16). Neuroleptic drugs were prescribed for 86 (19%) of 446 patients from four units of a 360-bed nursing home, mainly for agitation ($n = 21$); their mean age was 84 years and the mean length of time they had been receiving neuroleptic drugs was 37 (7–263) months. The authors thought that this was of definite concern, given the modest benefit that has been observed during long periods of treatment in such patients and the risk of tardive dyskinesia and other adverse effects.

In the light of evidence from large, randomized, double-blind trials, the authors of a thorough review of the role of atypical neuroleptic drugs in the treatment of psychosis and agitation associated with dementia have concluded that low-dose risperidone (0.25–1.5 mg/day) can be used as first-line treatment (17).

A further comprehensive review on the use of atypical neuroleptic drugs in older adults has also been published (18).

Comparisons of neuroleptic drugs

Comparisons of different typical drugs

Amisulpride versus typical neuroleptic drugs

In an extensive review of 19 randomized studies for the Cochrane Library ($n = 2443$), most of the trials were small and of short duration (19). Compared with typical

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neuroleptic drugs, the pooled results of a total of 14 trials suggested that amisulpride was more effective in improving global state ($n = 651$), general mental state ($n = 695$), and the negative symptoms of schizophrenia ($n = 506$). Amisulpride was as effective as typical neuroleptic drugs in relieving positive symptoms. It was less likely to cause at least one general adverse event ($n = 751$), to cause one extrapyramidal symptom ($n = 771$), or to require the use of antiparkinsonian drugs ($n = 851$). There were no clear differences in other adverse events compared with typical drugs. Amisulpride also seemed to be more acceptable than typical drugs, as measured by early withdrawal ($n = 1512$) than typical drugs, but this result may have been overestimated owing to publication bias, which could not be excluded with certainty.

A further meta-analysis of 10 randomized controlled clinical trials of amisulpride in "acutely ill patients" ($n = 1654$) was supported in part by a grant from Sanofi-Synthélabo, the marketing authorization holder (20). Amisulpride was significantly better than typical neuroleptic drugs by about 11% on the BPRS. In four studies in patients with "persistent negative symptoms," amisulpride was significantly better than placebo ($n = 514$), but there was no significant difference between amisulpride and typical drugs (only three studies; $n = 130$). Low doses of amisulpride (50–300 mg/day) were not associated with significantly more use of antiparkinsonian drugs than placebo ($n = 507$), and usual doses caused fewer extrapyramidal adverse effects than typical neuroleptic drugs ($n = 1599$). In four studies in acutely ill patients, significantly fewer patients taking amisulpride dropped out compared with patients taking typical drugs, mainly because of fewer adverse events; in three small studies with conventional neuroleptic drugs as comparators there was only a trend in favor of amisulpride in this regard.

Amisulpride versus flupenthixol

In a randomized, double-blind, multicenter comparison of amisulpride 1000 mg/day ($n = 70$) and flupenthixol 25 mg/day ($n = 62$) for 6 weeks, the two drugs significantly improved the acute psychotic symptoms to a similar extent (21). The total numbers of dropouts were 19 with amisulpride and 25 with flupenthixol. Adverse effects accounted for 8.6 and 18% respectively of the totals. Amisulpride caused significantly fewer extrapyramidal adverse effects. Apart from the extrapyramidal adverse effects, there were treatment-related adverse events in 87% of the patients given amisulpride and 92% of those given flupenthixol. Prolactin concentrations were higher with amisulpride.

Amisulpride versus haloperidol

Fixed doses of amisulpride (100, 400, 800, and 1200 mg/day) and haloperidol (16 mg/day) have been compared in a 4-week, double-blind, randomized trial in 319 patients with acute exacerbations of schizophrenia (22). Amisulpride 400 mg/day and 800 mg/day was effective in treating the positive symptoms of schizophrenia, with fewer extrapyramidal adverse effects than haloperidol, which was associated with the highest proportion of extrapyramidal symptoms. The incidence of extrapyramidal symptoms in patients treated with amisulpride increased with increasing dose (31%, 42%, 45%, and 55% for 100, 400, 800, and 1200 mg/day respectively). The rate of withdrawals due to adverse events was higher with haloperidol (16%) than with amisulpride (0%, 5%, 3%, and 5% respectively).

The long-term safety and efficacy of amisulpride in subchronic and chronic schizophrenia have been assessed in an open, multicenter study in 489 patients randomly allocated to amisulpride (mean dose 605 mg/day; $n = 370$) or haloperidol (mean dose 14.6 mg/day; $n = 119$) for 12 months (23). Improvement in mean total score on the BPRS was significantly greater with amisulpride than with haloperidol. The proportion of patients with at least one treatment-emergent adverse event was similar in the two groups, 69% with amisulpride and 70% with haloperidol, but extrapyramidal symptoms occurred more often with haloperidol (41%) than with amisulpride (26%); endocrine disorders occurred in 4% of those taking amisulpride and 3% of those taking haloperidol. Amenorrhea (6 versus 0%) and weight increase (11 versus 4%) were more frequent with amisulpride. There were serious adverse events in 10% of the patients taking amisulpride and 7% of those taking haloperidol.

Atypical versus typical drugs

There is no clear evidence that atypical neuroleptic drugs are more effective or better tolerated than typical neuroleptic drugs. It has therefore been suggested that typical neuroleptic drugs can be used in the initial treatment of schizophrenia, unless the patient has previously not responded to these drugs or has unacceptable extrapyramidal adverse effects, based on a meta-analysis of 52 randomized comparisons of atypical neuroleptic drugs with typical neuroleptic drugs (12 649 patients) or alternative atypical neuroleptic drugs (24). After correction for the higher than recommended doses of typical neuroleptic drugs that are used in some trials, there was a modest advantage of atypical neuroleptic drugs in terms of extrapyramidal adverse effects, but the differences in efficacy and overall tolerability disappeared, suggesting that many of the perceived benefits of atypical neuroleptic drugs are really due to excessive doses of the comparator drugs used in trials. Other reviews of atypical neuroleptic drugs have not added anything new (25,26). Both types of neuroleptic drugs have serious shortcomings, particularly their adverse effects on the extrapyramidal and endocrine systems. However, quality of life is said to be superior with atypical neuroleptic drugs, from an analysis of seven controlled trials and eight open trials (27).

An independent cross-sectional survey, not sponsored by the pharmaceutical industry, in schizophrenic outpatients clinically stabilized on a neuroleptic drug for a period of 6 months showed that quality-of-life measures and Global Assessment of Functioning did not differ significantly in patients taking typical neuroleptic drugs ($n = 44$) and novel ones (risperidone, $n = 50$; olanzapine, $n = 48$; quetiapine, $n = 42$; clozapine, $n = 46$) (28).

Adverse effects have been studied in people with mental retardation treated with atypical neuroleptic drugs ($n = 17$), typical neuroleptic drugs ($n = 17$), or no drugs ($n = 17$) (29). The patients taking atypical neuroleptic drugs did not have different overall adverse events from those taking no medications, and both had significantly

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fewer overall adverse effects than those taking typical neuroleptic drugs. However, the study had some important flaws: patients taking typical neuroleptic drugs were on average 7 years older than those taking atypical drugs; they had also taken medication for longer and had more stereotypic movement disorders at baseline. This jeopardizes the conclusions.

Atypical drugs versus haloperidol

In a randomized double-blind trial in 157 inpatients with chronic schizophrenia, clozapine ($n = 40$), olanzapine ($n = 39$), and risperidone ($n = 41$), but not haloperidol ($n = 37$), produced statistically significant improvements in total scores on the Positive and Negative Syndrome Scale after 14 weeks (30). Patients who had failed to respond to any typical neuroleptic drug were eligible, including patients who had previously failed to respond to haloperidol. High doses were used (the mean daily doses achieved during the last period of study were: clozapine 525 mg, olanzapine 30 mg, risperidone 12 mg, and haloperidol 26 mg). There was a significant fall in the Extrapyramidal Symptom Rating Score with the three atypical drugs at the end of the study and no change with haloperidol. One patient developed agranulocytosis, two had hypertensive episodes, and four had seizures while taking clozapine.

The results of 11 studies in 1933 patients with schizophrenia, who were randomly assigned to amisulpride ($n = 1247$), haloperidol ($n = 309$), risperidone ($n = 113$), flupenthixol ($n = 62$), or placebo ($n = 202$) have been reviewed (31). Extrapyramidal signs occurred in 15% of those given amisulpride ($n = 579$), 12% of those given risperidone ($n = 113$), and 31% of those given haloperidol ($n = 214$). In contrast, endocrine disorders were more frequent with amisulpride (4%) and risperidone (6%) than with haloperidol (1%). In a subgroup of patients with predominant negative schizophrenia who had at least one electrocardiogram recorded during treatment, there was a relative prolongation of the QT_c interval of at least 60 ms in three of 296 patients treated with amisulpride compared with no cases with both haloperidol ($n = 80$) and risperidone ($n = 91$); however, there were no ventricular dysrhythmias.

Clozapine versus typical neuroleptic drugs

A meta-analysis of 30 randomized controlled comparisons of clozapine with typical neuroleptic drugs ($n = 2530$) has been published (32). Clozapine was more effective in reducing symptoms in patients with both treatment-resistant and non-resistant schizophrenia. In a subset of 13 trials hematological problems tended to be more frequent in patients taking clozapine (OR = 1.93, CI = 0.96, 3.87); hypersalivation was also more frequent (OR = 5.50, CI = 4.26, 7.10), as were fever (OR = 1.89, CI = 1.38, 2.60) and sedation (OR = 1.94, CI = 1.50, 2.50). Xerostomia (OR = 0.29, CI = 0.20, 0.42) and extrapyramidal symptoms (OR = 0.46, CI = 0.28–0.75) were more frequent in the patients treated with typical neuroleptic drugs. There was no difference between the two groups in weight gain (OR = 1.07, CI = 0.37, 3.10), hypotension or dizziness (OR = 1.66, CI = 0.74, 3.71), or seizures (OR = 1.60, CI = 0.84, 3.04). Although there were fewer deaths in the clozapine group, statistical significance was not reached (OR = 0.50, CI = 0.11, 2.30). One of the flaws of this meta-analysis was that there was no information on dropouts.

Clozapine versus chlorpromazine

In 42 elderly patients (mean age 67 years) with schizophrenia randomly assigned to clozapine, titrated to 300 mg/day ($n = 24$), or chlorpromazine, titrated to a maximum of 600 mg/day ($n = 18$), the two medications were equally effective at 5 weeks (33). In each group there was one patient with a serious and potentially fatal adverse effect: agranulocytosis in the clozapine group and paralytic ileus in the chlorpromazine group; both drugs significantly lowered the white cell count.

Clozapine versus chlorpromazine and haloperidol

Clozapine has been compared with typical neuroleptic drugs in seven studies in patients with chronic refractory schizophrenia (34) ($n = 1124$). Of the 10 comparisons of second-generation versus typical neuroleptic drugs ($n = 1801$), there was a significant difference in six favoring second-generation neuroleptic drugs on measures of treatment efficacy; in the other four there was no significant difference between treatments. ANCOVA with the baseline score as a co-variate was performed to compare the efficacy of clozapine with that of typical neuroleptic drugs in terms of BPRS total score; there was a significant reduction in psychopathology in those who took clozapine, and the reduction was greater among those with higher BPRS scores. When the assessment was performed with other scales (BPRS positive symptom subscale, SANS) there were no significant treatment effects for clozapine over typical neuroleptic drugs. The subjects who took clozapine had significantly fewer extrapyramidal effects; tardive dyskinesia occurred equally in the two groups. Weight gain was reported in patients who took chlorpromazine (1%) and clozapine (7.1%), but in none of those who took haloperidol. Patients taking chlorpromazine (3.4%) or clozapine (2.9%) had difficulty in concentrating, but none of those taking haloperidol did. Other adverse events reported in patients taking clozapine included neutropenia (2.0%), enuresis (1.0%), and seizures (0.4%); neuroleptic malignant syndrome developed in 0.5% of the patients who took chlorpromazine. Completion rates were higher for clozapine (70%; $n = 400$) than for the typical neuroleptic drugs (56%; $n = 398$). Despite the superior efficacy of clozapine in the treatment of resistant patients, the extent of this in terms of scope (symptoms improved) and magnitude (effect size) was variable. Using what might be regarded as a non-stringent criterion of a 20–30% reduction in total psychopathology scores, under half of the patients responded in most of the studies.

Clozapine versus haloperidol

Clozapine and haloperidol have been compared in 75 schizophrenic outpatients, who met criteria for residual positive or negative symptoms after being treated for at least 6 weeks with typical neuroleptic drugs, in a 10-week randomized, double-blind, parallel-group comparison (35). There was no evidence of any superior efficacy or

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long-term effect of clozapine ($n = 38$) on primary or secondary negative symptoms compared with haloperidol ($n = 37$). Long-term clozapine was associated with significant improvements in social and occupational functioning, but not in overall quality of life. There were no significant differences between the two groups in adverse effects from previous neuroleptic drug treatment, and dizziness (50 versus 19%), salivation (82 versus 19%), and nausea (37 versus 11%) were significantly more common in patients treated with clozapine. In contrast, dry mouth was significantly more common with haloperidol (62 versus 18%). Patients who completed the double-blind study ($n = 58$) entered a 1-year open clozapine study. Over the course of that year, there was a small reduction in adverse effects, apart from hypersalivation, which increased significantly. Over the first 6 months there was weight gain followed by a plateau.

Clinical predictors of response to clozapine have been examined in 37 partially treatment-refractory outpatients who had been assigned to clozapine in a double-blind, haloperidol-controlled, 29-week study (36). Clozapine responders were rated as less severely ill, had fewer negative symptoms, and had fewer extrapyramidal adverse effects at baseline compared with non-responders.

Olanzapine versus chlorpromazine

In 103 previously treatment-resistant patients with schizophrenia were given a prospective 6-week trial of 10–40 mg/day of haloperidol; 84 failed to respond and were randomly assigned to a double-blind, 8-week, fixed-dose trial of either olanzapine 25 mg/day alone ($n = 42$) or chlorpromazine 1200 mg/day plus benzatropine mesylate 4 mg/day ($n = 39$) (37). There was no significant difference in completion rates. Neither drug produced a substantial change in the level of psychosis from prerandomization baseline, and there were no differences between the groups in efficacy. However, olanzapine had a better adverse effects profile.

Olanzapine versus haloperidol

The global efficacy of olanzapine was not substantially different from that of haloperidol in two of three comparative trials involving 2500 patients, according to a comprehensive review of the safety and efficacy of olanzapine; in addition, the only relevant comparative trial failed to demonstrate superiority of olanzapine over risperidone (38). Olanzapine has fewer adverse neurological effects than haloperidol, but there is no evidence that it differs from other atypical neuroleptic drugs in this respect.

A meta-analysis of four comparisons of olanzapine and haloperidol showed similar efficacy, with fewer extrapyramidal effects with olanzapine (15). Similar conclusions were reached in another meta-analysis of three randomized, double-blind, controlled comparisons of olanzapine and haloperidol (39). Only 15% of olanzapine-treated patients ($n = 1620$, dosage 5–20 mg/day) needed anticholinergic drugs compared with 49% of those treated with haloperidol ($n = 786$, dosage 5–20 mg/day).

Olanzapine has been compared with haloperidol in cannabis-induced psychosis (40), schizoaffective disorder (41), first-episode psychosis (42), and treatment-resistant schizophrenia (43); the two last studies were reanalyses of data from large clinical trials promoted by the manufacturers, Eli Lilly. In all cases olanzapine was better than haloperidol at reducing BPRS scores, but in patients with cannabis-induced psychotic disorders they were similar. Increased appetite was consistently reported more often in olanzapine-treated patients and extrapyramidal signs more often in those treated with haloperidol.

A re-analysis of data from a large double-blind comparison of olanzapine with haloperidol ($n = 1996$) showed that in patients who had an initial response, there was no significant difference between olanzapine and haloperidol when outcome was measured using either 52-week relapse rates or the time to first non-compliance; after 12 months, the estimated mean times to discontinuation were 271 days and 241 days respectively (44). However, while the dose of olanzapine was well within the recommended range, the dose of haloperidol was too high (modal doses 13 and 12 mg/day respectively).

In a double-blind trial, 28 patients with paranoid schizophrenia who had had a partial response to typical neuroleptic drugs were randomized to receive either olanzapine or haloperidol in flexible doses for 14 weeks (45). The two groups showed similar improvement on the Brief Psychiatric Rating Scale positive symptoms subscale, while improvement in the same negative symptoms subscale was significant only with olanzapine. There were no significant differences between the two groups on the Simpson and Angus rating Scale scores, but there was a significant difference in the Barnes Akathisia Rating Scale. No patient taking olanzapine had akathisia, while a few patients taking haloperidol did. Apart from the small sample, patients with a partial response to typical neuroleptic drugs were included, which precludes firm conclusions.

In a double-blind, placebo-controlled, dose-response trial, 270 acutely agitated patients were randomized to receive 1–3 intramuscular injections of olanzapine (2.5, 5, 7.5, or 10 mg), haloperidol (7.5 mg), or placebo within 24 hours (46). Olanzapine had a dose-related effect in reducing agitation; olanzapine was better than placebo but not better than haloperidol; the most frequently reported adverse event was hypotension, which occurred with olanzapine ($n = 7$) but not haloperidol or placebo. Acute dystonias did not occur in patients given olanzapine or placebo but occurred in two patients given haloperidol.

Quality of life is said to be superior with atypical neuroleptic drugs, from an analysis of seven controlled trials and eight open trials (27). However, in a comparison of olanzapine and haloperidol in 335 patients there was no significant change in quality of life (47). Moreover, in all the studies, mean doses of haloperidol were higher than 12 mg/day, and in some studies as high as 28 mg/day. This is in accordance with the results of a double-blind, randomized, comparison of olanzapine (mean dosage 11 mg/day; $n = 159$) and haloperidol (mean dosage 11 mg/day; $n = 150$) in 309 schizophrenic patients (48). There were no significant differences between the groups in positive, negative, or total symptoms of schizophrenia, quality of life, extrapyramidal symptoms, or withdrawals. Olanzapine was associated with less akathisia but there were more reports of weight gain and significantly higher costs.

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Olanzapine and risperidone versus haloperidol

A prospective 6-month open study, promoted by Lilly, the market authorization holder of olanzapine, has been conducted, in which olanzapine ($n = 2128$), risperidone ($n = 417$), and haloperidol ($n = 112$) were compared (49). Age, sex, and duration of disease did not differ among the groups. The initial and overall mean daily doses were respectively: olanzapine 12.2 and 13.0 mg; risperidone 5.2 and 5.4 mg; haloperidol 13.9 and 13.6 mg. The improvements were similar in the three groups. A lower proportion of patients taking olanzapine had extrapyramidal symptoms (37%) compared with risperidone (50%) and haloperidol (76%). Weight gain was significantly more common with olanzapine (6.9%) than risperidone (1.9%) or haloperidol (0.9%).

In other studies, outcome variables have been discontinuation, relapse, and compliance (44) or quality of life (27). A re-analysis of data from two large double-blind comparisons of olanzapine with haloperidol ($n = 1996$) and of olanzapine with risperidone ($n = 336$) showed that in patients who had an initial response, there was no significant difference between olanzapine and haloperidol when outcome was measured using either 52-week relapse rates or the time to first non-compliance; after 12 months, the estimated mean times to discontinuation were 271 days and 241 days respectively (44). There were no differences between olanzapine and risperidone. However, while the dose of olanzapine was well within the recommended range, the dose of haloperidol was too high (modal doses, 13 and 12 mg/day respectively).

Olanzapine versus pimozide

The use of olanzapine in patients with Gilles de la Tourette syndrome has been explored in a 52-week, double-blind, crossover comparison of olanzapine (5 and 10 mg/day) and low-dose pimozide (2 and 4 mg/day) in four patients (aged 19–40 years) with a high frequency of tics (2–10/minute), vocalizations, and lack of co-morbidity (50). There was a highly significant reduction in rating scale scores for the syndrome with olanzapine 10 mg versus baseline and versus pimozide 2 mg, and a significant reduction with olanzapine 5 mg versus pimozide 4 mg; only moderate sedation was reported by one patient during olanzapine treatment while three complained of minor motor adverse effects and sedation during pimozide treatment.

Quetiapine versus haloperidol

A 6-week, multicenter, double blind, randomized comparison of quetiapine (mean dose 455 mg/day) and haloperidol (8 mg/day) has been carried out in 448 patients with schizophrenia (51). By day 42, the total score on the Positive and Negative Symptom Scale (PNSS) was equally reduced in the two groups. There were 69 withdrawals among the 221 patients who took quetiapine and 80 among the 227 who took haloperidol. Of the patients who took quetiapine, 154 (70%) had one or more spontaneously reported adverse events, whereas 171 (75%) of the haloperidol-treated patients reported adverse events. Motor and extrapyramidal effects were much more frequent among haloperidol users. In the quetiapine group the most common adverse events were somnolence (20%), insomnia (13%), and dry mouth (10%); in the haloperidol group the most frequent adverse events were akathisia (20%), insomnia (15%), and hypertonia (13%). The overall mean weight gain was 1.9 kg in those who took quetiapine and 0.3 kg in those who took haloperidol. With quetiapine, there was a fall in prolactin concentration from baseline by more than 16 μg/l and with haloperidol a rise of just under 6 μg/l during the same period. There was one death from acute heart failure in the haloperidol group.

Another similarly designed comparison of quetiapine and haloperidol in patients with schizophrenia with a partial response to other neuroleptic drugs gave similar results (52). Patients with a history of partial response to typical neuroleptic drugs and a partial or no response to fluphenazine (20 mg/day) for 1 month were randomly allocated to haloperidol 20 mg/day ($n = 145$) or quetiapine 600 mg/day ($n = 143$). By 8 weeks the total score on the PNSS was reduced to the same extent in the two groups. Similar numbers of patients withdrew during the randomized phase of the trial in the quetiapine ($n = 32$) and haloperidol ($n = 28$) treatment arms. The proportions of patients who were taking anticholinergic drugs at the end of the study were 44% and 60% for quetiapine and haloperidol respectively. The most frequently reported adverse events with quetiapine were somnolence (9.8%), postural hypotension/dizziness (7.7%), dry mouth (5.6%), increased muscle tone (5.6%), and akathisia (5.6%). In contrast, the most common adverse events with haloperidol were related to extrapyramidal signs: tremor (12%), akathisia (9.0%), hypertonia (6.9%), extrapyramidal syndrome (6.3%), and insomnia (6.2%). The mean increase in body weight was 1.4 kg with quetiapine and 0.7 kg with haloperidol.

In a study funded by Astra Zeneca, the marketing authorization holder of quetiapine, 25 patients with schizophrenia were randomly assigned double-blind to quetiapine 300–600 mg/day ($n = 13$) or haloperidol 10–20 mg/day ($n = 12$) for 6 months; 11 completed the study, 8 with quetiapine and 3 with haloperidol (53). After Bonferroni correction for 34 comparisons, only the beneficial effect of quetiapine on the revised Wechsler Adult Intelligence Scale (WAIS-R) was significant. Three patients had weight gain with quetiapine versus one with haloperidol. Two patients had raised hepatic enzymes with quetiapine. One patient taking quetiapine had tiny subcapsular blebs, which were apparent at baseline as small dots and appeared larger after 8 weeks of treatment.

Risperidone versus haloperidol

In 62 patients with co-existing psychotic and depressive symptoms, risperidone (mean dose 6.9 mg/day) was compared with a combination of haloperidol 9 mg/day and amitriptyline 180 mg/day ($n = 61$) in a multicenter, randomized, double-blind study over 6 weeks (54). The results suggested that haloperidol plus amitriptyline was superior to risperidone alone. The incidence of extrapyramidal adverse effects was slightly higher with risperidone (37%) than haloperidol plus amitriptyline (31%); the use of concurrent anticholinergic drugs was significantly higher with risperidone (37%) than haloperidol plus amitriptyline (20%).

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In patients aged 18–73 years with disturbing extrapyramidal symptoms during previous neuroleptic drug treatment ($n = 77$), there was a greater reduction of parkinsonism over 8 weeks with risperidone ($n = 40$; average dose 7.4 mg/day) than with haloperidol ($n = 37$; average dose 9.9 mg/day) (55). With risperidone the most frequently mentioned adverse effects were headache ($n = 4$), oculogyric crisis ($n = 3$), and hypersalivation ($n = 3$); with haloperidol the adverse effects were sleep disorders ($n = 4$), tremor ($n = 4$), and vomiting ($n = 3$).

The effects of risperidone and haloperidol in preventing relapse in 365 patients with schizophrenia have been compared (56). The patients were randomly assigned to receive risperidone ($n = 177$; median duration 364 days; mean dose 4.9 mg/day) or haloperidol ($n = 188$; median duration 238 days; mean dose 11.7 mg/day). Primary analyses were performed on all subjects who underwent randomization and were assessed at least once during drug treatment. The risk ratio for relapse with haloperidol was 1.93 (95% CI = 1.33, 2.80), and early withdrawal for any reason was more frequent among haloperidol-treated patients (RR = 1.52; 95% CI = 1.18, 1.96). Patients who took risperidone had greater reductions in mean severities of both psychotic symptoms and extrapyramidal adverse effects than those who took haloperidol. There were adverse events in 90% of those who took risperidone and 91% of those who took haloperidol. Events that were reported in more than 10% of subjects in at least one group were somnolence (14% with risperidone; 25% with haloperidol), agitation (10% and 18%), and hyperkinesia (5% and 20%). There was a mean weight gain of 2.3 kg in those who took risperidone—similar in magnitude to the weight gain seen in short-term studies—and a mean loss of 0.73 kg in those who took haloperidol.

A qualitative analysis of extrapyramidal effects has been performed using Extrapyramidal Symptom Rating Scale (ESRC) data reported in 11 double-blind risperidone comparisons with haloperidol or placebo (57). Between-group comparisons showed no differences between placebo and risperidone 1–2 mg/day, but parkinsonism, tremor, akathisia, and sialorrhea were more likely to occur with haloperidol 1–6 mg/day than with placebo or risperidone. At risperidone dosages of more than 8 mg/day, the severity of acute extrapyramidal effects lay between those of placebo and haloperidol; the severity of tardive dyskinesia was greater with placebo than with either drug. However, others emphasized that those who received haloperidol in this study took a relatively high mean modal dose (12 mg per day) and 81% of the patients taking haloperidol took a daily dose of 7.5–20 mg (58–60). Many studies have shown that doses of haloperidol over 3.75–7.5 mg/day have no increased clinical efficacy but are associated with a significantly increased risk of extrapyramidal effects.

In a comparison of risperidone and haloperidol in patients with chronic schizophrenia, those taking risperidone had greater reductions in the mean severity of both psychotic symptoms and extrapyramidal adverse effects than those taking haloperidol (56) (SEDA-26, 53). The conclusion was that "the preponderance of the evidence now supports the use of risperidone as a first-line treatment for patients with schizophrenia" (61). Nevertheless, the use of "higher-than-optimal doses of typical drugs" was also mentioned as a caveat of the study.

A meta-analysis has compared risperidone with haloperidol (62). Six of the nine trials met criteria for inclusion, that is they were randomized and double-blind, had a duration of at least 4 weeks, and used risperidone in schizophrenic patients in a dosage range of 4–8 mg/day or in a flexible dose regimen. Risperidone was associated with higher clinical response rates (mean difference 14%; 95% CI = 5.6, 22), less prescribing of anticholinergic drugs (mean difference 18%; CI = 9.4, 26), and fewer treatment dropouts (mean difference 13%; CI = 9.4, 26). It was concluded that risperidone was more efficacious than haloperidol, suggesting both a lower incidence of extrapyramidal symptoms and improved treatment compliance.

Another meta-analysis has further compared risperidone and haloperidol (63). Almost all the randomized controlled clinical trials of risperidone versus haloperidol (number of studies = 18; number of patients = 3591) used a 20% improvement on the BPRS and PNSS to define a clinical response. However, an overall analysis using a 50% improvement showed that risperidone was better than haloperidol (OR = 1.6; 95% CI = 1.4, 1.8). Meta-regression did not show that the dose of the haloperidol comparator had a significant effect on positive or negative symptoms. The authors stated that previous meta-analyses had underestimated the risperidone-comparator difference, because they included the suboptimal 1 mg or 2 mg dose in their comparisons, which were not included in this one. Others have suggested that the apparent advantage of risperidone in some trials may be explained by the use of doses of typical drugs that are less than optimal, leading to poorer tolerability and effectiveness (61).

Risperidone versus pimozide

Risperidone ($n = 26$, mean dosage 3.8 mg/day) has been compared with pimozide ($n = 24$, mean dosage 2.9 mg/day) in a 12-week, multicenter, double-blind, parallel-group study in patients with Tourette's disorder (64). Tics significantly improved in both groups, as measured by the Tourette's Symptom Severity Scale (TSSS) and there was also significant improvement in scales of Global Assessment of Functioning and Clinical Global Impressions, and in symptoms of anxiety and depressive mood; however, obsessive-compulsive behavior was significantly improved only by risperidone. Fewer patients who took risperidone reported extrapyramidal adverse effects ($n = 4$) compared with those who took pimozide ($n = 8$), and depression, fatigue, and somnolence were the most prominent adverse effects in both groups.

Risperidone versus typical drugs

When compared with typical neuroleptic drugs, risperidone may be more acceptable to those with schizophrenia. It may also have marginal benefits in terms of clinical improvement and its adverse effects profile. The superiority of risperidone in these respects may have been overestimated, owing to possible publication bias in favor of risperidone. Any marginal benefit has to be balanced against the greater cost of risperidone and its

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increased tendency to cause other adverse effects, such as weight gain.

Tiapride versus haloperidol

Tiapride has been assessed for the treatment of agitation and aggressiveness in elderly patients with cognitive impairment in a multicenter, double-blind study, in which patients were randomly allocated to tiapride 100 mg/day ($n = 102$), haloperidol 2 mg/day ($n = 101$), or placebo ($n = 103$) (65). The percentage of responders after 21 days, according to the Multidimensional Observation Scale for Elderly Subjects (MOSES) irritability/aggressiveness subscale, was significantly greater in both of the active treatment groups (haloperidol 63%, tiapride 69%) than in the placebo group (49%). There were 10 dropouts in the tiapride group, 21 in the haloperidol group, and 16 in the placebo group. The number of patients with at least one extrapyramidal symptom was significantly smaller with tiapride (16%) than with haloperidol (34%) and identical to that with placebo (17%); there was no significant difference across the groups in the numbers of patients with endocrinological adverse events. Four deaths were reported: one with placebo (stroke), one with tiapride (pneumonia), and two with haloperidol (stroke and heart failure).

Ziprasidone versus haloperidol

Intramuscular ziprasidone has recently been compared with intramuscular haloperidol in the treatment of acute psychosis for a very short period (66). Patients were randomly allocated to intramuscular ziprasidone for up to 3 days of flexible dosing ($n = 90$; last oral daily dose 91 mg) or haloperidol ($n = 42$; last oral daily dose 14 mg) followed by oral treatment to day 7. Mean reductions from baseline in all efficacy variables were significantly greater with ziprasidone than with haloperidol at the end of the study. The percentage of patients who had any adverse event was lower with ziprasidone (46%) than with haloperidol (60%); most of the adverse effects were mild or moderate. Four patients discontinued ziprasidone owing to adverse events compared with one in the haloperidol group.

Both ziprasidone and haloperidol reduced overall psychopathology in 301 schizophrenic outpatients aged 18–64 years who were randomized to flexible-dose oral ziprasidone 80–160 mg/day ($n = 148$) or haloperidol 5–15 mg/day ($n = 153$) for 28 weeks in a double-blind, multicenter study (67). The median duration of treatment was 113 days with ziprasidone and 139 days with haloperidol; the rates of withdrawal due to insufficient clinical response were the same in the two groups (18%), but twice as many patients discontinued haloperidol (16%) as ziprasidone (8%) because of treatment-related adverse effects; the percentage of patients in whom any movement disorder emerged was markedly higher with haloperidol (41%) than with ziprasidone (15%). Mean changes in body weight from baseline to end-point were small and similar with ziprasidone (+0.31 kg) and haloperidol (+0.22 kg). With regard to electrocardiographic changes, the mean baseline and endpoint QT_c intervals were 398 and 404 ms with ziprasidone and 389 and 387 ms with haloperidol; no patient had a QT_c interval over 500 ms at any time. It must be stated that some patients included in the study had already been taking haloperidol, 26% in the ziprasidone group and 25% in the haloperidol group. The study was funded by Pfizer, the marketing authorization holder for ziprasidone.

Ziprasidone 160 mg/day is as effective as haloperidol 15 mg/day, and is less likely to cause extrapyramidal symptoms. Such was the conclusion of a study in which, after a single-blind washout period of 4–7 days, patients were randomly assigned to one of four dosages of ziprasidone—4 mg/day ($n = 19$), 10 mg/day ($n = 17$), 40 mg/day ($n = 17$), or 160 mg/day ($n = 20$)—or haloperidol 15 mg/day ($n = 17$) for 4 weeks (68). There was less use of benzatropine at any time during the study with ziprasidone 160 mg/day (15%) than with haloperidol (53%). One patient taking ziprasidone 4 mg/day had confusion and hyponatremia, and another taking 40 mg/day had seizures.

Zotepine versus typical drugs

The use of zotepine in short-term trials (4–8 weeks) has been reviewed (69). Comparisons have been carried out with haloperidol (three trials; $n = 212$), chlorpromazine (two trials; $n = 328$), perazine (two trials; $n = 81$), and tiotixene (one trial; $n = 94$). In these double-blind trials, zotepine 150–300 mg/day was as effective as typical neuroleptic drugs in controlling the symptoms of schizophrenia. The results suggested that zotepine may be effective in the management of patients with negative symptoms and in those with treatment-resistant schizophrenia. The most common adverse effects of zotepine were constipation, dry mouth, insomnia, sleepiness, weakness, and weight gain. The incidence of extrapyramidal symptoms was 8–29%, significantly less than with haloperidol and chlorpromazine, but there were no differences between zotepine and some other typical neuroleptic drugs in this respect. There was an increase in the risk of generalized seizures with zotepine at dosages over 300 mg/day.

Zotepine versus chlorpromazine

In a trial funded by Knoll Pharmaceuticals, the market authorization holder, zotepine was compared with chlorpromazine and placebo (70). Patients with exacerbation of schizophrenia were randomly allocated to zotepine 150–300 mg/day ($n = 53$), chlorpromazine 300–600 mg/day ($n = 53$), or placebo ($n = 53$) for 8 weeks. Mean BPRS scores improved statistically significantly more with zotepine than chlorpromazine or placebo. During the study, 14 patients reported extrapyramidal symptoms, 5 taking zotepine, 4 taking chlorpromazine, and 5 taking placebo. In all, 99 patients (zotepine 43; chlorpromazine 33; placebo 23) reported a total of 257 adverse events (zotepine 120; chlorpromazine 85; placebo 52) during the study. The mean weight reduction with placebo (1.4 kg) was significantly different from the mean weight gain with zotepine (2.4 kg) and chlorpromazine (1.4 kg). Two patients (one taking zotepine, one taking chlorpromazine) with suspected myocardial infarction required hospitalization, but both subsequently recovered.

Zuclopenthixol versus typical drugs

Case series and reviews have suggested superior effectiveness of zuclopenthixol acetate in the acute management

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of disturbed behavior caused by serious mental illness. However, this seems not to have been supported by the evidence from an analysis of randomized controlled trials (71). A meta-analysis of five randomized comparisons of zuclopenthixol acetate with other neuroleptic drugs in patients with considerable behavioral disturbance showed that in all studies there was some improvement in mental state scores (BPRS; CGI), but none showed statistically significant differences between zuclopenthixol acetate and "standard treatment." In three studies there was more sedation in those who took zuclopenthixol acetate than in those allocated to haloperidol. With regard to adverse effects, the studies were not homogeneous: one study showed that people who took zuclopenthixol acetate were more likely to need antiparkinsonian drugs (OR = 6.4; CI = 1.5, 17); other studies did not show any differences in this particular outcome.

Comparisons of different atypical drugs

There have been systematic reviews from the Cochrane Collaboration (www.cochrane.org.uk) of head-to-head comparisons of atypical neuroleptic drugs in non-treatment-resistant schizophrenia.

The benefits of the atypical neuroleptic drugs in patients with bipolar disorder and the possibility that risperidone, quetiapine, olanzapine, and clozapine cause tardive dyskinesia have been studied (72), and there has been a retrospective comparison of clozapine (5 trials), risperidone (25 trials), and olanzapine (20 trials) using data from consecutive treatment trials in the Massachusetts General Hospital (73). The overall results suggested equivalent efficacy of the novel neuroleptic drugs according to changes in Clinical Global Impressions Scale scores. Extrapyramidal symptoms occurred in about 29% of cases in all groups. There were no prolactin-related adverse effects. Substantial weight gain of more than 4.5 kg was significantly more frequent in patients taking olanzapine.

Amisulpride versus risperidone

Amisulpride has been compared with risperidone in patients aged 18–65 years with an acute exacerbation of schizophrenia who were randomized double-blind to receive amisulpride 800 mg/day ($n = 115$) or risperidone 8 mg/day ($n = 113$) for 8 weeks (74). The two treatments were equally effective. Antiparkinsonian medication was begun in 23% of patients taking risperidone and in 30% of those taking amisulpride. The only notable difference was that patients taking risperidone had significant weight gain (1.4 kg) compared with those taking amisulpride (0.4 kg).

In another comparison of amisulpride and risperidone ($n = 228$) there were no significant differences in efficacy or acceptability, with the exception of agitation, which was more frequent with amisulpride (19).

Clozapine versus olanzapine

Olanzapine and clozapine have been compared in a double-blind study by Lilly Research Laboratories for 18 weeks in 220 patients with schizophrenia; conclusions were based on the one-sided lower 95% confidence limit of the treatment effect observed from the primary efficacy variable (Positive and Negative Syndrome Scale (PANSS) total score) (75). The two drugs were comparably effective in neuroleptic drug-resistant patients. Significantly fewer olanzapine-treated patients (4%) withdrew owing to adverse effects than their clozapine-treated counterparts (14%). Among spontaneously reported adverse effects, increased salivation, constipation, dizziness, and nausea were reported significantly more often by patients taking clozapine, whereas only dry mouth was reported more often by patients taking olanzapine.

The efficacy and safety of olanzapine and clozapine have been studied in an open 12-week study in 18 patients with Parkinson's disease and dopaminergic drug-induced psychosis (76). All the patients who took clozapine (mean dosage 13 mg/day) completed the study, despite reporting a number of adverse effects, including somnolence, falls, orthostatic hypotension, and syncope. In contrast, early withdrawal was required in three of the nine patients who took olanzapine, owing to severe gait deterioration and drowsiness (mean dosage 3.9 mg/day). Psychotic symptoms improved in both groups. However, parkinsonism improved in the clozapine group according to the Cornell University Rating Scale (with a 20% fall in raw score and a 7.9% fall in weighted score), while the six patients who took olanzapine and who finished the study had worse parkinsonian symptoms (with a 26% worsening in raw score and a 25% worsening in weighted score).

Clozapine versus risperidone

After a baseline period of treatment with fluphenazine for a minimum of 2 weeks, 29 patients with chronic schizophrenia participated in a randomized, double-blind, 6-week comparison of clozapine and risperidone (13). Clozapine was superior to risperidone for positive symptoms and parkinsonian adverse effects. In addition, clozapine produced fewer effects on plasma prolactin than risperidone. The mean daily doses during week 6 of the trial were 404 mg of clozapine and 5.9 mg of risperidone.

Clozapine has also been compared with risperidone in 60 treatment-resistant patients with schizophrenia in India (14). There was clinical improvement (a more than 20% reduction from baseline PANSS scale scores) in 80% of the clozapine-treated patients and 67% of the risperidone-treated patients. The predominant adverse effects with clozapine ($n = 30$) were tachycardia (77%), hypersalivation (60%), sedation (60%), weight gain (43%), and constipation (30%); one patient had a seizure. The adverse effects of risperidone ($n = 30$) were constipation (50%), dry mouth (47%), weight gain (43%), akathisia (37%), insomnia (33%), tachycardia (30%), and impotence (27%). The final mean daily doses after 16 weeks of treatment were 343 mg for clozapine and 5.8 mg for risperidone.

Clozapine and risperidone have been compared in 10 patients with psychosis in Parkinson's disease, who were randomized to risperidone or clozapine for 12 weeks (77). The mean improvement in the total BPRS score was 3.0 with clozapine (mean dose 62.5 mg/day) and 6.0 with risperidone (mean dose 1.2 mg/day). The white blood cell count fell below 3.0×10^9/l after 10 weeks in one

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subject taking clozapine and rose to 5.0×10^9/l after withdrawal. One subject taking clozapine had a marked increase in rigidity and incontinence of urine after 4 weeks, and there were similar effects in a patient who took risperidone for 10 weeks. All three adverse events resolved on withdrawal.

Clozapine and risperidone have been compared in a randomized, open study in patients with schizophrenia for 10 weeks; treatment outcomes were assessed blindly and 19 patients entered the randomized phase (78). There were no significant differences between the groups in baseline or end-point positive or negative symptoms, disease severity, or global or social functioning scores, and patients' opinion on the two drugs did not differ. These results have corroborated previous evidence that risperidone may be as effective as clozapine, but it is probable that this study does not have enough power to detect a difference.

The relation between the anticholinergic effects of clozapine and risperidone and their cognitive adverse effects has been studied in 22 patients (79). Anticholinergic potency was indexed by a reduction in the receptor occupancy rates of quinuclidinyl benzylate. Patients who took clozapine ($n = 15$) had significantly higher anticholinergic concentrations than those who took risperidone ($n = 7$). However, they all had essentially equivalent scores on cognitive measures. These data suggest that anticholinergic activity distinguishes clozapine and risperidone in vivo, but that this effect is not associated with differences in global cognitive functioning.

Olanzapine versus risperidone

Olanzapine and risperidone seem to be broadly similar, according to the numbers of patients who respond to treatment (40% reduction in PANSS scores: $n = 339$, RR = 1.14, 95% CI = 0.99, 1.32) (www.cochrane.org.uk). More of those who took risperidone withdrew early ($n = 404$, RR = 1.31, 95% CI = 1.06, 1.60; NNT = 8, 95% CI = 4, 32) and they had more extrapyramidal adverse effects ($n = 339$, RR = 1.67, 95% CI = 1.14, 2.46; NNH = 8, 95% CI = 5, 33), although comparative doses of risperidone were higher than those recommended in practice.

In an open comparison of risperidone and olanzapine (mean daily doses at follow-up 4.5 and 13.8 mg respectively) in 42 schizophrenic patients, there was a greater reduction in psychotic symptoms after 6 months of treatment with risperidone, although akathisia was more frequent (80).

A re-analysis of data from a large double-blind comparison of olanzapine with risperidone ($n = 336$) showed that there were no differences between the two (44).

Olanzapine ($n = 172$) has been compared with risperidone ($n = 167$) in an international, multicenter, double-blind, parallel-group, 28-week prospective study in 339 patients who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder (81). Both olanzapine (starting dosage 15 mg/day) and risperidone (starting dosage 1 mg bd) were effective in the management of psychotic symptoms. However, olanzapine had greater efficacy for negative symptoms and overall response rate. The most common adverse events were somnolence, headache, insomnia, rhinitis, depression, and nausea. Weight gain was reported significantly more often with olanzapine, whereas nausea, amblyopia, extrapyramidal syndrome, increased salivation, attempted suicide, abnormal ejaculation, back pain, increased creatine kinase, and urinary tract infection were reported statistically significantly more often with risperidone. A significantly greater proportion of patients taking olanzapine had raised alanine transaminase activity at any time than those taking risperidone. Similarly, significantly more patients taking olanzapine had low neutrophil counts at any time (olanzapine 4.3%, risperidone 0.6%).

The results of one of the clinical trials in which olanzapine (Eli Lilly) was compared with risperidone (Janssen Pharmaceutica) (SEDA-22, 64) gave rise to a debate between researchers of the two pharmaceuticals companies on some of the possible flaws (82–87). Since the modal dosage over the 28-week trial was 7.2 mg/day, significantly higher than that used in actual clinical practice (average dose 4.6 mg/day), the higher incidence of risperidone-associated adverse effects could have been explained by this dosage difference.

In other studies, outcome variables have been discontinuation, relapse, and compliance (44) or quality of life (27). A re-analysis of data from two large double-blind comparisons of olanzapine with haloperidol ($n = 1996$) and of olanzapine with risperidone ($n = 336$) showed that in patients who had an initial response, there was no significant difference between olanzapine and haloperidol when outcome was measured using either 52-week relapse rates or the time to first non-compliance; after 12 months, the estimated mean times to discontinuation were 271 and 241 days respectively (44). There were no differences between olanzapine and risperidone. However, while the dose of olanzapine was well within the recommended range, the dose of haloperidol was too high (modal doses 13 and 12 mg/day respectively).

The use of neuroleptic drugs in conditions other than schizophrenia

There is enormous interest in the effectiveness of neuroleptic drugs in conditions other than schizophrenia, such as autism (1) and psychosis in patients with dementia (2). Neuroleptic medication for treatment of psychosis and agitation in patients with dementia was generally effective; in double-blind, placebo-controlled trials; mean improvement rates were 61% with neuroleptic drugs and 35% with placebo. However, the number of well-designed studies in this area has been small so far.

Amisulpride

In a randomized, double-blind, multicenter trial for 8 weeks in 278 patients with depression there were no differences in efficacy or tolerability between amisulpride 50 mg and SSRIs (88).

Clozapine

Special subgroups of patients can benefit from clozapine (SEDA 24, 61). Of 10 adolescent inpatients (aged 12–17

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years) with severe acute manic or mixed episodes, who did not improve after treatment with typical drugs and who were given clozapine (mean dose 143 mg/day), all responded positively after 15–28 days and adverse effects (increased appetite, sedation, enuresis, sialorrhea) were frequent but not severe enough to require reduced dosages (89). Mean weight gain after 6 months was 7 kg (11%), and neither reduced white cell counts nor epileptic seizures were reported during follow-up for 12–24 months.

In a case series in which clozapine was used as add-on medication, two patients with bipolar disorder and one with schizoaffective disorder had marked reductions in affective symptoms after clozapine had been added to pretreatment with a mood stabilizer; transient and moderate weight gain and fatigue were the only adverse effects (90).

Olanzapine

The efficacy and safety of olanzapine in disorders other than schizophrenia have been studied (SEDA-24, 67) (SEDA-25, 64) (SEDA-26, 61). In a 3-week, randomized, double-blind clinical trial, the effects of a flexible dose of olanzapine (5–20 mg/day) and divalproex (500–2500 mg/day) for the treatment of patients with acute bipolar manic or mixed episodes have been compared (91). The olanzapine treatment group ($n = 125$) had significantly greater mean improvements in mania rating and a significantly greater proportion of patients achieved protocol-defined remission. With olanzapine there was significantly more weight gain (12 versus 7.9%), dry mouth (34 versus 6.3%), increased appetite (12 versus 2.4%), and somnolence (39 versus 21%), while more cases of nausea (29 versus 10%) were reported with divalproex.

The efficacy of adding olanzapine to either valproate or lithium alone in acute manic or mixed bipolar episodes has been studied in a 6-week, double-blind, randomized, placebo-controlled trial (92). Compared with valproate or lithium alone, the addition of olanzapine provided better efficacy. Olanzapine was associated with somnolence, dry mouth, weight gain, increased appetite, tremor, and slurred speech.

Olanzapine, mean dose 5.4 mg/day, has been given to 21 patients with apathy in the absence of depression after long-term treatment with SSRIs for non-psychotic depression in an open, flexible-dose study (93). The more frequent adverse effects were sedation ($n = 12$), increased appetite ($n = 8$), stiffness ($n = 7$), edema ($n = 6$), and dry mouth ($n = 5$).

The medical records of 10 patients with a DSM-IV diagnostic of cluster B personality disorder (narcissistic personality disorder) who had received olanzapine 2.5–20 mg/day for 8 weeks have been reviewed (94). The mean Social Dysfunction and Aggression Scale score was 29 for the 8 weeks before olanzapine therapy and improved to 14 after 8 weeks of treatment. Five of the ten patients developed severe weight gain.

Risperidone

Risperidone has been used in bipolar disorder, dementia, disruptive behavior disorder with subaverage intelligence, Tourette's syndrome, and autism (SEDA-23, 69) (SEDA-25, 67) (SEDA-26, 64). The efficacy and safety of low doses of risperidone in the treatment of autism and serious behavioral problems have been studied in 101 children aged 5–17 years with autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior, who were randomly assigned to risperidone for 8 weeks ($n = 49$; dosage 0.5–3.5 mg/day) or placebo ($n = 52$) (SEDA27.6.10) (95). Risperidone produced a 57% reduction in the Irritability Score, compared with a 14% reduction in the placebo group; all other parameters were also significantly improved. Risperidone was associated with an average weight gain of 2.7 kg, compared with 0.8 kg with placebo; increased appetite, fatigue, drowsiness, dizziness, and drooling were more common with risperidone. In two-thirds of the children with a positive response to risperidone at 8 weeks, the benefit was maintained at 6 months.

Organs and Systems

Cardiovascular

Neuroleptic drugs can reduce exercise-induced cardiac output as a result of drug-induced increases in plasma catecholamine concentrations and concurrent alpha-adrenoceptor blockade (96). Cardiomyopathy has been associated with neuroleptic drugs, including clozapine (97–99).

Hypotension

Neuroleptic drugs with alpha-blocking activity can cause hypotension. Those of high and intermediate potency, such as haloperidol and loxitane, have minimal alpha-blocking effects and should be less likely to cause hypotension, although in one report orthostatic changes (a fall of 30 mmHg) were reported with these drugs in 27% and 22% of cases respectively (SED-11, 106) (100). An exception to the relatively safe use of high-potency agents has been noted in the combination of droperidol with the narcotic fentanyl, which can cause marked hypotension (101).

Postural hypotension is particularly hazardous in susceptible patients, such as the elderly and those with depleted intravascular volume or reduced cardiovascular output. The risk of orthostatic hypotension is markedly increased after parenteral administration. The combination of alpha-adrenoceptor blockade and sedative effects may explain the increased risk of falling when taking neuroleptic drugs (SEDA-12, 52).

Significantly more low blood pressures were documented by 24-hour ambulatory blood pressure monitoring compared with typical blood pressure measurement obtained an average of 3.6 times a day in patients treated with psychotropic drugs ($n = 12$), most of which were neuroleptic drugs (102). This finding may be of clinical relevance, in view of the potential hemodynamic consequences of hypotension, especially in older patients taking more than one psychotropic drug.

Cardiac dysrhythmias

Neuroleptic drugs are vagolytic and can increase resting and exercise heart rates. Cardiac dysrhythmias have been reported, and include atrial dysrhythmias,

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ventricular tachycardia, and ventricular fibrillation. Bradycardia is unusual. The risk of cardiac dysrhythmias is dose-related and is increased by pre-existing cardiovascular pathology (SEDA-2, 48), interactions with other cardiovascular or psychotropic drugs (particularly the highly anticholinergic tricyclic antidepressants), increased cardiac sensitivity in the elderly, hypokalemia, and vigorous exercise.

In elderly people it is advisable to avoid low-potency neuroleptic drugs, such as thioridazine, which produce significantly more cardiographic changes than high-potency agents, such as fluphenazine (103). In any patient with pre-existing heart disease, a pretreatment electrocardiogram with routine follow-up is recommended.

QT interval prolongation due to neuroleptic drugs has been reviewed (104). It is not a class effect: among currently available agents, thioridazine and ziprasidone are associated with the greatest prolongation. Dysrhythmias are more likely to occur if drug-induced QT prolongation co-exists with other risk factors, such as individual susceptibility, congenital long QT syndromes, heart failure, bradycardia, electrolyte imbalance, overdose of a QT interval-prolonging drug, female sex, restraint, old age, hepatic or renal impairment, and slow metabolizer status; pharmacokinetic or pharmacodynamic interactions can also increase the risk of dysrhythmias. Prolongation of the QT interval occurs more often in patients taking more than 2000 mg of chlorpromazine equivalents daily (105).

In an open study in 164 patients with schizophrenia of the effect of several neuroleptic drugs on the QT interval, the study drugs were given for 21–29 days and three separate electrocardiograms were obtained after steady state had been achieved and drug concentrations were at their maximum (106). The mean changes in the QT_c interval were:

(a) thioridazine 36 ms (95% CI = 31, 41; $n = 30$);
(b) ziprasidone 20 ms (95% CI = 14, 26; $n = 31$);
(c) quetiapine 15 ms (95% CI = 9.5, 20; $n = 27$);
(d) risperidone 12 ms (95% CI = 7.4, 16; $n = 20$);
(e) olanzapine 6.8 ms (95% CI = 0.8, 13; $n = 24$);
(f) haloperidol 4.7 ms (95% CI = −2, 11; $n = 20$).

Mechanism

Torsade de pointes, first described in 1966 by Dessertenne (107), is a potentially fatal ventricular tachydysrhythmia with a characteristic pattern of polymorphous QRS complexes, which appear to twist around the isoelectric line. It is often associated with ventricular extra beats immediately before the dysrhythmia. Torsade de pointes typically occurs in the setting of a prolonged QT interval, which includes depolarization and repolarization times. Conditions or agents that delay ventricular repolarization, causing long QT interval syndromes, can trigger the dysrhythmia. It has been hypothesized that prolongation of the QT interval is caused by early after-depolarization, which in turn may develop in response to abnormal ventricular repolarization (108–110). Evidence linking QT interval prolongation, potassium channel function, and torsade de pointes to neuroleptic drugs has been reviewed (111).

Among the non-cardiac drugs that can cause QT interval prolongation, torsade de pointes, and sudden death (112) the neuroleptic drugs have particularly been associated with conduction disturbances, torsade de pointes being one of the most worrisome (SED-14, 141) (113,114) (SEDA-20, 36) (SEDA-21, 43) (SEDA-22, 45) (SEDA-23, 49) (115,116). Although the role of neuroleptic drugs in sudden death is controversial (SEDA-18, 47) (SEDA-20, 36), and although there are other non-cardiac causes of this syndrome, including asphyxia, convulsions, or hyperpyrexia, QT interval prolongation and torsade de pointes provide a plausible mechanism of sudden death.

QT_c prolongation has been proposed as a predictor of sudden death, and psychiatrists are encouraged to perform electrocardiograms in patients taking high-dose neuroleptic drugs to detect conduction abnormalities, especially QT_c prolongation. It has been suggested that QT_c prolongation in itself is not necessarily an indicator of the risk of sudden death (117). Instead, QT_c dispersion, the difference between the longest and the shortest QT_c interval on the 12-lead electrocardiogram, is an indication of more extreme variability in ventricular repolarization, which could be regarded as a better predictor of the risk of dysrhythmias.

Epidemiology

Electrocardiographic changes are relatively common during treatment with neuroleptic drugs, but there is a lack of unanimity regarding the clinical significance of these findings. The changes that are generally considered benign and non-specific are reversible after withdrawal. Potentially more serious changes include prolongation of the QT interval, depression of the ST segment, flattened T waves, and the appearance of U waves. Non-specific T wave changes are commonly seen during the mid-afternoon, and may be related to the potassium shift and other changes that result after meals, so that a prebreakfast cardiogram may be more desirable.

The prevalence of QT_c prolongation in psychiatric patients has been estimated, to assess whether it is associated with any particular neuroleptic drug (118). Electrocardiograms were obtained from 101 healthy control individuals and 495 psychiatric patients (aged 18–74 years) in various inpatient and community settings in North-East England. Exclusion criteria were atrial fibrillation, bundle-branch block, and a change in drug therapy within the previous 2 weeks (3 months for depot formulations). The threshold for QT_c prolongation (456 ms) was defined as 2 standard deviations above the mean value in the healthy controls. Values were abnormal in 40 patients. Significant independent predictors of QT_c prolongation in psychiatric patients after adjustment for potential confounding effects were aged over 65 years and the use of tricyclic antidepressants, droperidol (RR = 6.7; CI = 1.8, 25), or thioridazine (RR = 5.3; CI = 2.0, 14). Increasing neuroleptic drug dosage was also associated with an increased risk of QT_c prolongation. Abnormal QT dispersion or T wave abnormalities were not significantly associated with neuroleptic drug treatment. Based on these results, the authors recommended electrocardiographic screening, not only in patients taking high doses of any neuroleptic drug but also in those taking droperidol or

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thioridazine, even at low doses. In other studies, dose and age were similarly found to be predictive factors (105), as was co-administration of carbamazepine (119).

Management

Adverse effects related to QT interval prolongation can be prevented by avoiding higher doses and by avoiding the following patients at risk: those with organic heart disease, particularly congestive heart failure; those with metabolic abnormalities (such as hypokalemia and hypomagnesemia); and those with sinus bradycardia or heart block. Concomitant administration of drugs that inhibit drug metabolism should also be avoided, and the potassium concentration should be controlled. If torsade de pointes is suspected, neuroleptic drugs must be withdrawn.

Magnesium sulfate 2 g (20 ml of a 10% solution intravenously) suppresses torsade de pointes (120). Most patients report flushing during this injection. A case of torsade de pointes related to high dose haloperidol and treated with magnesium has been reported (121).

- A 41-year-old woman, with liver lacerations, rib fractures, and pneumothorax after a motor vehicle accident, was given haloperidol for agitation on day 7. During the first 24 hours she received a cumulative intravenous dose of 15 mg, 70 mg on day 2, 190 mg on day 3, 160 mg on days 4 and 5, and 320 mg on day 6. An hour after the first dose of 80 mg on day 7, she had ventricular extra beats followed by 5-beat and 22-beat runs of ventricular tachycardia. The rhythm strips were consistent with polymorphous ventricular tachycardia or torsade de pointes and the QT_c interval was 610 ms (normally under 450 in women). She received intravenous magnesium sulfate 2 g. Concurrent medications included enoxaparin, famotidine, magnesium hydroxide, ampicillin/sulbactam, nystatin suspension, midazolam, and 0.45% saline with 20 mmol/l of potassium chloride. She had no further dysrhythmias after haloperidol was withdrawn. Eight days after the episode of torsade de pointes she had a QT_c interval of 426 ms.

Cardiomyopathy

The relation between neuroleptic drug therapy and myocarditis and cardiomyopathy has been examined using the international database on adverse drug reactions run by the World Health Organization (122). Myocarditis and cardiomyopathy were reported rarely as suspected adverse drug reactions, and accounted for under 0.1% ($n = 2121$) of almost 2.5 million reports. The association of clozapine with those adverse reactions was statistically significant (231 reports out of 24 730), as was the association with "other antipsychotics" (89 of 60 775).

Venous thromboembolism

Typical neuroleptic drugs have been associated with an increased risk of venous thromboembolism (123). The mechanism may be related to increased platelet aggregation (124).

Respiratory

Gag and cough reflexes can be suppressed by neuroleptic drugs (SED-11, 107). Periodic examination of the gag reflex, particularly in patients with tardive dyskinesia, has been recommended.

Acute respiratory failure, which can be complicated by pneumonia, has been reported in psychiatric patients receiving long-term neuroleptic drugs (SED-11, 107) (125).

Pulmonary embolism without a primary focus was surprisingly frequent in cases of sudden death.

Aspiration asphyxia in patients treated with neuroleptic drugs has been described (SEDA-4, 40) (SEDA-5, 51), and it has been suggested that this could have been due to laryngeal-pharyngeal dystonia (126). Patients with asthma treated with neuroleptic drugs may be at increased risk of serious complications of asthma (127).

Diaphragmatic, laryngeal, and glottal dyskinesias have been described as part of the tardive dyskinesia syndrome and can cause respiratory complications (128,129).

Nervous system

Information on neurological adverse effects in particular groups of patients, such as young patients (130) and those with Alzheimer's disease (131,132), AIDS (133), or Gilles de la Tourette syndrome (134), have been published. The use of neuroleptic drugs in patients with Alzheimer's disease is controversial because of the significant adverse effects profile associated with these drugs. Therefore, other pharmacological and psychological methods should be explored before using neuroleptic drugs in dementia. This was the conclusion of a retrospective study in which 80 patients, 40 with confirmed Alzheimer's disease and 40 with confirmed Lewy body dementia, were assessed for neuroleptic drug use and adverse effects (131). Neuroleptic drugs were used in 15 of the patients with Alzheimer's disease and 21 of those with Lewy body dementia. Only six of the latter (29%) had a definite severe sensitivity reaction to neuroleptic drugs, which included cognitive impairment, parkinsonism, drowsiness, and features of the neuroleptic malignant syndrome. All the reactions occurred within 2 weeks of new neuroleptic drug prescription or a dosage change and were associated with a reduction in survival. Certain motor disturbances, measured before neuroleptic drug treatment was begun, could be used to predict the development and severity of neuroleptic drug-induced parkinsonism in patients with Alzheimer's disease treated with very low-dose neuroleptic drugs (132). Parkinsonism occurred in 67% of the patients with Alzheimer's disease. Pretreatment instrumental, but not clinical, measurement of bradykinesia was a predictor of post-treatment parkinsonism.

Seizures

Neuroleptic drugs cause slowing of alpha rhythm and increased synchronization and amplitude with superimposed sharp fast activity. They also induce discharge patterns in the electroencephalogram similar to those associated with epileptic seizures of the tonic-clonic generalized or focal types (SED-11, 108) (135).

Convulsions associated with typical neuroleptic drugs are relatively rare (probably less than 1%) (SED-9, 81) (136).

Predisposing factors to neuroleptic drug-induced seizures include an abnormal electroencephalogram,

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pre-existing CNS abnormalities, parenteral administration of high doses, and a family history of seizures or febrile convulsions (135).

It has been suggested that the less potent sedative neuroleptic drugs (aliphatic or piperidine phenothiazines) lower the convulsive threshold more than the potent neuroleptic drugs (piperazine phenothiazines) (137). Variable and unpredictable effects on seizure activity related to butyrophenones have been reported (138).

An in vitro technique, claimed to assess the relative risks of neuroleptic drug-induced seizures, was reported to produce striking differences between neuroleptic drugs in spike activity in hippocampal slices. Tentatively, molindone, pimozide, and butaclamol were the safest compounds, based on these in vitro experiments (139).

However, they are more common with clozapine (SEDA-22, 57) and are said to occur in 0.9% of patients taking olanzapine (SEDA-24, 67). Olanzapine has been reported to cause a lowered seizure threshold (140).

- A 30-year-old man with paranoid psychosis for 5 years and seizures for 12 years (two generalized seizures a year) was switched to olanzapine 10 mg/day; he was also taking zuclopenthixol and valproate. He then had more frequent seizures, culminating in a generalized tonic-clonic seizure, which resulted in bilateral humeral head fractures. There were no metabolic or electrolyte disturbances. An electroencephalogram showed multifocal generalized epileptiform discharges similar to those seen with clozapine. They resolved on withdrawal of olanzapine and reintroduction of zuclopenthixol.

Extrapyramidal effects

Neuroleptic drugs cause several different types of extrapyramidal adverse effects:

(a) acute dystonic reactions;
(b) akathisia;
(c) parkinsonism and pseudoparkinsonism;
(d) tardive dyskinesia;
(e) tardive akathisia;
(f) tardive Tourette's syndrome;
(g) tardive dystonia;
(h) rabbit syndrome.

Except for tardive dyskinesia, the extrapyramidal adverse effects are largely reversible by giving anticholinergic drugs and withdrawing or lowering the dosage of the neuroleptic drug. These effects have been reviewed (SED-9, 78) (SEDA-7, 61) (SEDA-16, 40) (SEDA-18, 48) (141).

The dose-response relations for a variety of adverse effects of neuroleptic drugs have been reviewed (142). Although the dose-response relations for extrapyramidal effects are not fully understood, the evidence supports a dose-related effect. The relation is probably not linear and is influenced by several factors, but it is reasonable to conclude that systematic attempts to use the lowest possible clinically effective dosage should be strongly encouraged. It is possible that there are susceptible patients in whom tardive dyskinesia can occur at a relatively low cumulative or average daily dose, while in others increasing doses beyond this range may not lead to a substantially increased risk. Since in most patients high dosages do not lead to better therapeutic effects, but are associated with more frequent and severe adverse effects, the use of the smallest dosage necessary to produce neuroleptic benefit is recommended. When sedation is required, the concurrent use of moderate doses of a neuroleptic drug with a benzodiazepine may be preferable to the use of high dosages of a neuroleptic drug alone.

The CYP2D6 genotype is not a determinant of susceptibility to acute dystonic reactions, but may be a contributory factor in neuroleptic drug-induced movement disorders, including tardive dyskinesia (143).

The hypothesis that extrapyramidal adverse effects result from neurotoxicity due to oxidative damage by neuroleptic drugs has been reviewed (SEDA-20, 39) (144).

Patients with AIDS are sensitive to the extrapyramidal adverse effects of neuroleptic drugs and have evidence of depletion of dopamine in the cerebrospinal fluid (SEDA-22, 52). Of 115 consecutive HIV-infected patients, six developed parkinsonism and three of the cases were precipitated by the use of neuroleptic drugs (133).

Since the gamut of the clinical pharmacology of tics is broad, it is often difficult to differentiate tics from other hyperkinetic movement disorders. Of 373 cases of Gilles de la Tourette syndrome, 18 had both tics and other abnormal movements; 12 were secondary to neuroleptic drug treatment (134). Akathisia was the most common movement disorder.

In 15 schizophrenic inpatients aged 16–55 years, there was a 50% probability that a patient would have a tremor when the plasma concentration of chlorpromazine was 46 ng/ml or more, corresponding to the minimum that has been associated with a good clinical response (145). The use of objective accelerometric recordings was said to improve the accuracy of diagnosis of neuroleptic drug-induced tremor. This conclusion was reached in a study in which repeated accelerometric recordings showed constant and regular waveforms and frequencies (4–7 Hz) in each of 14 patients treated with neuroleptic drugs and diagnosed as having neuroleptic drug-induced tremor (146).

In an Australian psychiatric hospital, a rating of movement disturbances was compared with standardized scales (the Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus, and BARS) and the psychiatrists' clinical assessments of such disturbances in 38 consecutive patients (147). The patients were taking neuroleptic drugs and 47% fulfilled the Simpson-Angus criteria for the presence of parkinsonian symptoms compared with 39% who were rated as having mild, moderate, or severe parkinsonian symptoms by their psychiatrists. When BARS was used, 11% of the patients scored some degree of akathisia versus 17% identified by the psychiatrists. The corresponding figures for dyskinesia when using AIMS were 11 versus 14%. In the light of these results, the authors suggested that standardized measures should be introduced into routine practice.

Several studies have shown a relation between neuroleptic drug dosages, extrapyramidal adverse effects, and the degree of dopamine D_2 receptor occupancy (SEDA-18, 48) (148,149). Atypical neuroleptic drugs, such as olanzapine, quetiapine, risperidone, and sertindole, which have lower affinities for D_2 receptors, cause fewer extrapyramidal effects than typical neuroleptic drugs (150,152,153). However, there are reports of

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extrapyramidal effects associated with these atypical neuroleptic drugs (154–156).

A comprehensive review of neuroleptic drug-induced abnormal movements focused on older patients (157). Since there is no effective treatment for patients with tardive dyskinesia once it develops, attention should be paid to its prevention and close monitoring. It was confirmed that striatal D_2 receptor occupancy is an important mediator of response and adverse effects in neuroleptic drug treatment (158). In a double-blind study, 22 patients with first-episode schizophrenia were randomly assigned to a starting dose of haloperidol 1 or 2.5 mg/day. After 2 weeks, D_2 receptor occupancy was determined with raclopride and positron emission tomography; the clinical response, extrapyramidal adverse effects, and prolactin concentrations were also measured. The patients had a wide range of D_2 receptor occupancy (38–87%). The likelihoods of clinical response, hyperprolactinemia, and extrapyramidal adverse effects and akathisia increased significantly as D_2 receptor occupancy exceeded 65%, 72%, and 78% respectively. Since 65–70% D_2 receptor occupancy was obtained with haloperidol 2.5 mg/day in most of the patients, the authors suggested that a dose of 2–3 mg/day should be the optimal starting dose for first-episode patients, which contrasts with the 10–20 mg/day reported in other studies.

Acute dystonic reactions

Acute dystonic reactions are dramatic, acute-onset muscular spasms that occur within the first 24–48 hours after starting therapy, or in a few cases when the dosage is increased. A circadian pattern of acute dystonic reactions has been described (159). Men are more susceptible than women to this reaction, and the young more so than the elderly (160). Drug-induced dystonia can also be precipitated by emotional arousal (161,162). The muscles of the head and neck are mainly affected: opisthotonos, torticollis, oculogyric crisis, and macroglossia (all of which can occur together) are dramatic effects relieved by the use of intramuscular antiparkinsonian or antihistaminic drugs.

- A man in his late twenties, with a several-year history of intravenous heroin use, developed diplopia after he had received single doses of chlorpromazine 100 mg and ibuprofen 400 mg for anxiety (163). There was no extraocular muscle paresis and neurological examination was unremarkable. The diplopia resolved after 6–8 hours.

Temporomandibular joint dislocation has also been reported (164).

Acute laryngeal dystonia is probably under-reported but it is potentially lethal and can mimic anaphylaxis (165). It can occur within hours to days of starting therapy with neuroleptic drugs and is characterized by sudden onset of difficulty in breathing and swallowing (SEDA-22, 51) (166,167).

- A 26-year-old schizophrenic woman developed throat pain and dyspnea while taking haloperidol.
- A 76-year-old man reported difficulty in starting to swallow after taking haloperidol (6 mg/day), sertraline (200 mg/day), lithium, and temazepam for 6 weeks for recurrent depression.

A prospective study has identified cocaine as a risk factor for neuroleptic drug-induced acute dystonia (168). The study sample consisted of a high-risk group for neuroleptic-induced acute dystonia: 29 men aged 17–45 years who had used high-potency neuroleptic drugs within 24 hour of admission and had not taken neuroleptic drugs in the last month. Nine men developed acute dystonia: six of nine cocaine users and three of twenty non-users, a relative risk of 4.4 (95% CI = 1.4, 14). Cocaine users did not differ significantly in age, mean daily neuroleptic drug dose, or peak dose.

A comprehensive review has strongly advocated immediate intravenous administration of anticholinergic drugs to relieve acute dystonia.

Akathisia

Akathisia is a variant of the restless legs syndrome associated with anxiety and/or dysphoria (SEDA-19, 44) (SEDA-20, 36) (169–171). It can be confused with an exacerbation of the disorder being treated. Suicidal tendencies can occur in psychotic patients who developed neuroleptic-induced akathisia (172). On the other hand, recent evidence suggests that depressive symptoms may not be induced or worsened, and may even be reduced, by prescribing atypical neuroleptic drugs (173–175). Subjects show various degrees of restlessness and an inability to sit or stand still; in severe cases, the presentation can merge with behavioral disorders.

Akathisia has been associated with strong effects of terror, anger, and extreme anxiety, the most serious complication being a feeling of helplessness or being out of control, which might lead to suicidal ideation or attempted suicide. Five reported cases of neuroleptic drug-induced akathisia and suicidal tendencies in psychotic patients have further emphasized these risks (172). Doctors ought to pay attention to these symptoms, as suicidal tendencies disappear when symptoms of akathisia are relieved. Patients should also be told that akathisia is a treatable adverse effect of neuroleptic drugs.

Incidence rates of akathisia are reported to be 25–75%. Most cases occur within the first few days of neuroleptic drug treatment, and dosage increase has been identified as a risk factor (176).

Of 23 patients with bipolar affective disorder taking neuroleptic drugs, 15 developed akathisia and 18 had parkinsonism during their entire inpatient treatment (177). The patients initially received high-potency neuroleptic drugs (maximum 2000 mg/day of chlorpromazine equivalents) and were assessed weekly. Akathisia developed in 44% of the patients with severe headache or nausea who received prochlorperazine 10 mg intravenously ($n = 100$) within 1 hour (178). None of the 40 patients receiving other medications, who served as controls, developed akathisia.

Two cases of acute neuroleptic drug-induced akathisia in patients with traumatic paraplegia have been published (179). The authors emphasized the possibility of drug-induced akathisia when patients with traumatic paraplegia or other physical disabilities develop increasing restlessness and an inability to sit or lie still.

Akathisia observed at any time, whether treated or not, has been associated with a poor outcome.

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Antiparkinsonian agents are sometimes helpful, beta-blockers often more so (SEDA-19, 43) (180–182). Low-dosage mianserin has also been used in the treatment of akathisia (183).

Prevention and treatment

Following the development of akathisia, biperiden 5 mg was given intravenously to 17 patients and intramuscularly to 6 (184). The mean times to onset of effect were 1.6 and 31 minutes, respectively, and the maximum effects occurred at 9.2 and 50 minutes. Adverse effects occurred in six patients after intravenous biperiden (slight or mild confusion, drowsiness, dizziness, palpitation, and dry mouth) and in two after intramuscular biperiden (drowsiness and dry mouth).

In 100 adults who were randomly assigned to receive a 3-minute infusion of diphenhydramine or placebo after receiving intravenous prochlorperazine 10 mg for nausea/vomiting or headache, akathisia developed in 18 of 50 subjects in the control group and in seven of 50 subjects in the diphenhydramine group (185). The only adverse effect of diphenhydramine was sedation. Diphenhydramine may be effective in akathisia by more than just an anticholinergic mechanism, since it crosses the blood–brain barrier and blocks central alpha-adrenoceptors and muscarinic, 5-HT, and H_1 histamine receptors. This is claimed to be the first randomized controlled study of the efficacy of single-dose adjuvant diphenhydramine in preventing intravenous drug-induced akathisia.

Mirtazapine is a tetracyclic antidepressant, similar to mianserin, and is a potent 5-$HT_{2A/2C}$ receptor antagonist. It has been successfully used to treat akathisia. In a double-blind, placebo-controlled study in 26 patients with schizophrenia who were receiving neuroleptic drugs, mirtazapine 15 mg/day for 5 days was associated with less akathisia (186).

- A 28-year-old man with akathisia who was taking haloperidol 10 mg/day for schizophrenia complained of leg restlessness, an inability to sit still, and a constant urge to move (187). Biperiden (4 mg bd for 5 days) with the subsequent addition of diazepam (10 mg/day for 3 days) had no effect. Mirtazapine (15 mg/day for 5 days) produced substantial relief of the subjective component of the akathisia, and the abnormal movements disappeared.

Apart from mianserin, other 5-$HT_{2A/2C}$ receptor antagonists, such as ritanserin and cyproheptadine, have also been used to treat akathisia (186).

In one case, severe akathisia was abolished by passive motion when travelling as a car passenger (188).

- A 48-year-old woman developed akathisia soon after having been treated with chlorpromazine 400 mg/day for a bipolar affective disorder. Although the medication was changed a number of times over the next 4 years, there was no improvement. Fluvoxamine 150 mg/day and fluoxetine 20 mg/day seemed to aggravate the movement disorder; neither orphenadrine 200 mg/day nor procyclidine 15 mg/day affected her akathisia; nor did she experience relief from propranolol up to 320 mg/day. Both the subjective feeling of a need to move and the fidgeting in her legs were abolished within seconds of the car's beginning to move. Other movements (for example rocking in a chair or using an exercise bike) were ineffective, as were relaxation techniques and hypnosis.

Since this case emphasizes the importance of sensory input in akathisia, the authors suggested that the recurrent pacing observed in akathisia may be an attempt to alleviate the condition through sensory stimulation, rather than through motor activity.

Akathisia has been associated with iron deficiency (SEDA-17, 49). However, the rationale for iron supplementation in the treatment of akathisia is poor, and there are potential long-term adverse consequences (SEDA-20, 38). This issue has been addressed in patients with acute psychotic disorders who received neuroleptic drugs; 33 patients who developed akathisia were compared with 23 who did not (189). Serum iron was similar in the two groups but ferritin concentrations were significantly lower in akathisia; nevertheless, iron and ferritin concentrations were within the reference ranges.

Parkinsonism and pseudoparkinsonism

Parkinsonism or pseudoparkinsonism induced by neuroleptic drugs is clinically indistinguishable from post-encephalitic or classical parkinsonism. It begins in the head and neck and causes loss of movement in the muscles, which spreads to the arms, producing varying degrees of akinesia and rigidity. Cases of neuroleptic drug-induced parkinsonism with dysphagia as one of the main features have been reported (SEDA-19, 44) (190–192).

The neuroleptic drugs that elicit parkinsonism are those that bind with higher affinity than dopamine to D_2 receptors, while those that cause little or no parkinsonism (clozapine, melperone, quetiapine) bind with lower affinity (193). Antiparkinsonian drugs are more often required in patients taking typical neuroleptic drugs, but they can cause objective and subjective deficits (194,195).

Parkinsonism has been studied in special groups, such as elderly patients (196), patients with bipolar disorders (177), and patients who have received acute medication (178). The incidence of neuroleptic drug-induced parkinsonism has been examined in 50 older newly medicated psychiatric patients (196). After controlling for spontaneous parkinsonism with two groups of 15 unmedicated patients and 49 healthy elderly individuals, 32% of the patients, who were taking an average of 43 mg/day chlorpromazine equivalents of a typical neuroleptic drug, met strict criteria for neuroleptic drug-induced parkinsonism.

Different strategies for the treatment of neuroleptic drug-induced parkinsonism have been reviewed (SEDA-18, 48) (SEDA-20, 40) (197,198). The WHO has recommended that anticholinergic drugs should not be given routinely to patients who are starting to take neuroleptic drugs.

Olanzapine was effective in extinguishing typical neuroleptic drug-induced tremor (199).

Tardive dyskinesia

DoTS classification (BMJ 2003;327:1222–5)
Dose-relation: collateral effect
Time-course: intermediate or delayed
Susceptibility factors: age; sex

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Originally, tardive dyskinesia was described as comprising spontaneous irregular movements, mainly affecting the mouth and tongue; chewing, licking, and smacking movements of the tongue and lips were involved, including protrusion of the tongue outside the buccal cavity and various abnormal movements of the tongue within the buccal cavity. This condition is now also known to include choreoathetoid movements of the fingers and toes, sometimes associated with rocking movements, and akathisia; truncal muscles and respiratory muscles can be involved. Tardive dyskinesia can affect the neural control of any voluntary muscle (SEDA-22, 50). However, smooth pursuit eye movements were not related to tardive dyskinesia in patients with schizophrenia with ($n = 40$) and without ($n = 25$) the condition (200).

The tongue protrusion test, that is an inability to maintain tongue protrusion, is a measure of severity of tardive dyskinesia, and is present mainly in advanced cases; abnormal movements within the buccal cavity occur over a much wider range of severity, suggesting that abnormal tongue movements may be more helpful in the early detection of tardive dyskinesia (201).

There are insufficient data to support the use of drug holidays in detecting the risk of tardive dyskinesia, but they may help to diagnose the covert type by unmasking dyskinesia (202).

When abnormal involuntary movements occur in a patient taking a neuroleptic drug they are not always an adverse effect of the drug, but may be, at least partly, an inherent part of some psychotic illness. Five of forty-nine neuroleptic-naive patients with a first episode of schizophrenia had spontaneous dyskinesias (203) and they were found in 5.8% of individuals in 18 population studies (SED-11, 109) (204). Even higher rates have been recorded, especially among elderly patients; senile dyskinesias in two studies of drug-free elderly subjects occurred in 9% and 37% of individuals (205,206). There is also evidence that dyskinetic movements can be a feature of severe chronic schizophrenia unmodified by neuroleptic drugs (SED-11, 109) (203,207–211), which could mean that neuroleptic drugs merely trigger already latent dyskinesias in patients with schizophrenia.

Whether certain typical neuroleptic drugs are more likely than others to cause tardive dyskinesia is unknown (202), but virtually all typical neuroleptic drugs have been associated with it (212). Although there is evidence that atypical neuroleptic drugs are associated with a low risk (213,214), this needs to be evaluated in more prospective studies (213,215).

A review of the literature did not support the notion that neuroleptic drugs with central anticholinergic properties are particularly likely to cause tardive dyskinesia. However, anticholinergic antiparkinsonian drugs tend to produce reversible increases in the severity of dyskinetic movements, and the authors suggested that antiparkinsonian agents can be used as pharmacological probes in the evaluation of neuroleptic drug-induced movement disorders (216–218).

Discussion about tardive dyskinesia is necessary in the process of obtaining informed consent to treatment with neuroleptic drugs (SEDA-15, 46) (SEDA-21, 42) (SEDA-21, 45). The effect of education about tardive dyskinesia has been evaluated in 56 patients taking maintenance neuroleptic drugs, who completed a questionnaire assessing their knowledge of the condition (219). Education made patients more knowledgeable at 6 months, but had no effect on the clinical outcome.

In a consensus meeting the risk of tardive dyskinesia with typical and atypical neuroleptic drugs was addressed (220). There is sufficient evidence to conclude that atypical neuroleptic drugs are less likely to cause tardive dyskinesia than typical drugs, and that atypical neuroleptic drugs, apart from clozapine or ziprasidone, should be selected before typical drugs for patients with a first episode of schizophrenia or for patients whose history of response to neuroleptic drugs is not available. However, a meta-analysis has shown that atypical neuroleptic drugs have advantages over typical drugs only in studies in which haloperidol in relatively high doses was used as the comparison drug; when doses of haloperidol were below 12 mg/day, there were no advantages of the newer agents (24). Furthermore, clinical studies have not shown an advantage of haloperidol in dosages over 5 mg/day, which leads to a high occupancy of dopamine D_2 receptors, as demonstrated by positron emission tomography and single-photon emission computed tomography (153).

Incidence

Tardive dyskinesia usually occurs after long-term use of neuroleptic drugs, but some cases of early onset (less than 1 year) have been reported (SEDA-6, 47) (SEDA-7, 61). The incidence among patients with extrapyramidal effects is 2.32 times higher than among those without, and the risk could be even higher during the first 2 years of exposure (221). In a prospective study, the cumulative incidence of tardive dyskinesia was 5% after 1 year, 10% after 2 years, 15% after 3 years, and 19% after 4 years. The authors suggested that prevalence increases with increasing duration of neuroleptic drug exposure and that the increase is linear for at least the first 4–5 years (221). The average incidence rate of tardive dyskinesia has been estimated at 0.053 per year and the 5-year risk was 20% (SEDA-18, 49) (222). In another study, the cumulative incidence in patients over age 45 years was 26, 52, and 60% after 1, 2, and 3 years, respectively (223). Figures vary from center to center. In one study, there was a cumulative incidence of presumptive tardive dyskinesia of 6.3% after 1 year, 12% after 2 years, 14% after 3 years, and 18% after 4 years (224). In patients receiving neuroleptic drugs, the prevalence has been reported as 0.5–65% (225). One reviewer has gone so far as to suggest that the prevalence of tardive dyskinesia among all patients taking neuroleptic drugs is so low as not to justify any alarm (226). No cases of the severe form were found in a 12-year follow-up study of 99 chronically hospitalized patients who had received extensive neuroleptic drug treatment (227). Absence of severe tardive dyskinesia was reported in a group of Hungarian schizophrenic outpatients (216). Prevalences of 8.4–39% were reported in other cross-cultural studies of different ethnic groups (228–231).

A group of 261 neuroleptic drug-naive patients aged 55 years or over (mean 77 years) were identified at the time they were starting to take neuroleptic drugs (232).

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The length of follow-up was 3–393 (mean 115). weeks; 60 developed dyskinesias. The cumulative incidences were 25%, 34%, and 53% after 1, 2, and 3 years respectively of cumulative neuroleptic drug treatment. A greater risk of tardive dyskinesia was associated with a history of electroconvulsive therapy (ECT), higher mean daily and cumulative neuroleptic drug doses, and the presence of extrapyramidal signs early in treatment.

Although there are difficulties in establishing a reference figure for the incidence or prevalence of dyskinesia, Australian psychiatrists seem to underestimate the prevalence of tardive dyskinesia. According to a survey of 139 psychiatrists, 80% estimated the prevalence of "mild reversible" tardive dyskinesia as being 5% of those treated with neuroleptic drugs (233).

These wide variations in incidence are perhaps due to the lack of a precise objective definition of the syndrome. The availability of standardized rating scales (234) and research diagnostic criteria represents a significant advance in resolving these problems (235). A multinational study of tardive dyskinesia in Asians ($n = 982$) found that the overall prevalence of tardive dyskinesia was 17% (range 8.2–22%). There was a significant difference in tardive dyskinesia prevalence from center to center within the same ethnic group. The reasons for such a difference are unclear. Two studies showed that Afro-Americans have a greater incidence of tardive dyskinesia than whites (222,223). However, there is still a lack of convincing evidence that there are true inter-ethnic differences in the prevalence of tardive dyskinesia (236,237).

The risk of tardive dyskinesia with typical and atypical neuroleptic drugs has been addressed in a consensus meeting (220). There is sufficient evidence to conclude that atypical neuroleptic drugs are less likely to cause tardive dyskinesia than typical drugs, and that atypical neuroleptic drugs, apart from clozapine or ziprasidone, should be selected before typical drugs for patients with a first episode of schizophrenia or for patients whose history of response to neuroleptic drugs is not available. However, a meta-analysis has shown that atypical neuroleptic drugs have advantages over typical drugs only in studies in which haloperidol in relatively high doses was used as the comparison drug; when doses of haloperidol were below 12 mg/day, there were no advantages of the newer agents (24). Furthermore, clinical studies have not shown an advantage of haloperidol in dosages over 5 mg/day, which leads to a high occupancy of dopamine D_2 receptors, as demonstrated by positron emission tomography and single-photon emission computed tomography (153).

Susceptibility factors

Considerable information, although not entirely consistent, is available on predisposing factors (SED-11, 108) (202,225,238). The condition is apparently more common in women and the elderly; and elderly women in particular seem susceptible to a relatively severe form of the condition (SED-11, 108) (225,239). It has been suggested that estrogen plays a role (240,241). Here too, however, the epidemiology has been challenged; not all studies have confirmed that women are more vulnerable (242), although the consensus supports this conclusion.

Chronically hospitalized elderly inpatients with schizophrenia ($n = 121$; mean age 74 years) were rated for tardive dyskinesia and cognition (243). Subjects with tardive dyskinesia (60%) were older than those without. In subjects who were taking typical neuroleptic drugs ($n = 119$) there was no difference in dosage between those with and without tardive dyskinesia. Cognitive scores (Mini-Mental Status Examination) were significantly lower in the subjects with tardive dyskinesia affecting the orofacial regions. This raises the question of whether neuroleptic drug-induced brain changes underlie both the dyskinesia and cognitive impairment or whether the cognitive impairment represents a degenerative process that is itself a vulnerability factor for the emergence of tardive dyskinesia.

Conversely, tardive dyskinesia is said to be less common in young than in old patients, and a lower incidence has been observed in a retrospective chart review in 40 adolescents taking neuroleptic drugs (244). After 2 years, the figure was 18%; although comparability of those studies is far from optimal. Average daily dose, non-adherence to therapy, early age of illness, and concomitant use of antiparkinsonian drugs were associated with increased susceptibility.

Of 34 schizophrenic children and adolescents followed after a drug-free period that lasted up to 4 weeks at 2-year intervals, 17 had either withdrawal dyskinesia or tardive dyskinesia at some time. Patients who developed dyskinesia had greater premorbid impairment and a greater severity of positive symptoms at baseline, and there was a trend toward more months of neuroleptic drug exposure.

Negative symptoms of schizophrenia have been associated with the severity of orofacial tardive dyskinesia, and positive symptoms were associated with limb dyskinesia (245).

In a retrospective study in a psychiatric hospital in Curaçao, Netherlands Antilles, 133 Afro-Caribbean inpatients (mean age 52 years), with no organic disorders and a history of current use of neuroleptic drugs for at least 3 months, were assessed for tardive dyskinesia (246). The prevalence was 36%. When the number of interruptions to neuroleptic drug therapy was split into up to two and more than two, the resulting adjusted odds ratio was 3.29 (95% CI = 1.27, 8.49). Thus, the number of interruptions turned out to be the second risk factor after age. Cumulative dosages of neuroleptic or anticholinergic drugs were not risk factors.

Another factor that increases the risk of tardive dyskinesia is prolonged treatment with neuroleptic drugs (242). This has been supported by the preliminary results of a prospective study, but there are conflicting results (202,238); one outpatient study showed that the duration of treatment with neuroleptic drugs did not explain the differences in severity of tardive dyskinesia (239). However, dose may be important; one study showed that while age, sex, diagnosis, and race had no significant effects on presumptive tardive dyskinesia, it was predicted by greater neuroleptic drug exposure: each increase in neuroleptic drug dose of 100 mg

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chlorpromazine equivalents resulted in a 6% increase in the hazard of presumptive tardive dyskinesia (224). Furthermore, a positive correlation between tardive dyskinesia and circulating neuroleptic drug concentrations has been reported (247); however, in one study there was no significant difference in serum concentrations of thioridazine, its metabolites, or radio-receptor activity between patients with and without tardive dyskinesia (248). Histories of more and longer drug-free periods were more common in moderate and severe tardive dyskinesia than in mild forms (249). There was a positive association between neuroleptic drug-free periods and persistent tardive dyskinesia (250).

In one study, previous neuroleptic drug use at study entry was the only significant predictor of tardive dyskinesia (251). Psychiatric outpatients aged over 45 years, who had taken neuroleptic drugs for 0–30 days ($n = 176$), were compared with 131 who had taken neuroleptic drugs for more than 30 days. The cumulative incidences of tardive dyskinesia were 23% and 37% at the end of 12 months. In the patients who had never used neuroleptic drugs before ($n = 87$), the mean cumulative incidence of tardive dyskinesia after the use of typical neuroleptic drugs (median dose 68 mg/day of chlorpromazine equivalents) was 3.4% at baseline and 5.9% at 1 and 3 months.

The relation between handedness and tardive dyskinesia has been studied. The estimated rate ratio, comparing left-handers and mixed-handers with pure right-handers, adjusted for confounders, was 0.25. The handedness effect was stronger for men than for women (252).

There are various other possible risk factors, for example diabetes mellitus (SEDA-16, 47) (253), organicity, affective disorder, and a history of ECT or alcohol abuse (254).

Mechanism

Pharmacogenetic assessments of neuroleptic drug-induced tardive dyskinesia have been reviewed (255). The dopamine D_3 receptor (DRD3) gene has a single nucleotide polymorphism that results in a serine to glycine amino acid substitution (Ser9Gly) in the N terminal and gives rise to allelic differences in dopamine affinity; autosomal inheritance of two polymorphic Ser9Gly alleles (2–2 genotype), but not homozygosity for the wild-type allele (1–1 genotype), was a susceptibility factor (256). The severity of tardive dyskinesia was greater in homozygotes for the glycine variant of DRD3 than in serine/serine homozygotes or serine/glycine heterozygotes.

Another polymorphism has been identified in intron 1 of the CYP1A2 gene; similarly, there is an association between the severity of tardive dyskinesia and one of the corresponding genotypes. It is said that CYP1A2 may be important in neuroleptic drug metabolism after CYP2D6 saturation during long-term treatment.

The hypothesis of oxidative damage to striatal neurons mediated by neuroleptic drug enhancement of glutamatergic neurotransmission has been tested in a case-control study (257). Several markers of excitatory neurotransmission (*N*-acetylaspartylglutamate, *N*-acetylaspartate, aspartate, and glutamate) and of oxidative damage (superoxide dismutase, protein carbonyl content, and lipid hydroperoxides) were measured in the CSF of patients with schizophrenia who had taken neuroleptic drugs chronically, and who had ($n = 11$) or had not ($n = 9$) developed tardive dyskinesia. There was an inverse correlation between CSF concentrations of aspartate and superoxide dismutase activity in tardive dyskinesia, what suggests a causative relation between enhanced excitatory amino acid neurotransmission and the oxidative damage associated with tardive dyskinesia. Another plausible model for the development of tardive dyskinesia is that lower activity of superoxide dismutase renders the striatal neurons more vulnerable to excitatory neurotransmission that is exacerbated by neuroleptic drugs, as shown in a subgroup of patients with schizophrenia.

There are conflicting results on the possible relation between plasma iron concentrations and movement disorders (SEDA-19, 45). A significant correlation between serum ferritin concentrations and the severity of choreoathetoid movements has been observed (258). All 30 subjects had a minimum lifetime cumulative exposure to typical neuroleptic drugs of 3 years. Nevertheless, and as was stated by the authors, it is unclear whether higher body iron stores exacerbate the symptoms of tardive dyskinesia or predispose to its development.

Reversibility

The rate of reversibility of tardive dyskinesia after drug withdrawal is 0–90% (225). Since patients with tardive dyskinesia rarely have subjective complaints (259), periodic assessment of dyskinetic movements is essential in making an early diagnosis and can increase the chance of reversing the disorder. Some reports are relatively encouraging regarding reversibility (260,261); the characteristics of reversible and irreversible forms have been reviewed, but no firm conclusion can be drawn (262). However, the prognosis of tardive dyskinesia was better in patients treated for a shorter duration and in those treated with lower doses (263).

Prevention and treatment

In dealing with the whole problem of dyskinesia, the preeminent role of prevention must be emphasized (254), particularly because treatment is so unrewarding. Various agents have been studied, including agonists and antagonists at various CNS neurotransmitters, and newer dopamine receptor antagonists, which supposedly act only at dopamine D_2 receptors (sites that are not linked to adenyl cyclase). The few supposedly positive results that have been claimed for a number of drugs must be interpreted with great caution (SEDA-18, 49) (264).

Treatment of tardive dyskinesia is often unsatisfactory, especially in severe cases. A large number of treatments have been proposed (SEDA-20, 40), including antiparkinsonian drugs, benzodiazepines, baclofen, hormones, calcium channel blockers, valproate, propranolol, opiates, cyproheptadine, tryptophan, lithium, manganese, niacin, botulinum toxin, ECT, dietary control, and biofeedback training. In an open study, 20 patients (mean age 65 years) with severe unresponsive tardive dyskinesia (mean duration 44 months, mean exposure 52 months) were treated

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with tetrabenazine (mean dose 58 mg/day) (265). The mean score on the AIMS motor subset, determined from videotapes, improved by 54%. Sedation was the only subjective complaint.

Abnormal lipid peroxidation and low lipid-corrected plasma concentrations of vitamin E are associated with tardive dyskinesia (266).Vitamin E has therefore been used for its antioxidant properties (SEDA-21, 47) (267–270). A meta-analysis has summarized eight double-blind, placebo-controlled studies of vitamin E in the treatment of tardive dyskinesia in 221 patients (271). Overall, vitamin E had a better effect than placebo; 28% of those who took vitamin E had a 33% or greater reduction in AIMS scores, compared with only 4.6% in the placebo arm. The number of patients included in any study was very small, never more than 28. The rationale for using vitamin E and for finding a better indicator of vitamin E deficiency has been explored (266). Since much of the vitamin E in plasma is carried in the low-density lipoprotein fraction, relating vitamin E content to the sum of cholesterol and triglycerides in the plasma could produce a high degree of specificity and sensitivity in defining vitamin E deficiency. Patients with tardive dyskinesia had lower concentrations of lipid-corrected vitamin E. However, the authors admitted that the lower concentration of vitamin E could have resulted from, predisposed to, or served as a marker of the susceptibility to tardive dyskinesia. The possible involvement of free radicals and treatment with vitamin E has been extensively reviewed (272). A further study has concluded that the addition of vitamin E to neuroleptic drug medication at the start of treatment can reduce the severity of acute neuroleptic drug-induced parkinsonism (273). This has been observed by comparing two groups of randomly allocated patients treated with neuroleptic drugs ($n = 20$) or with neuroleptic drugs plus vitamin E 600 IU/day ($n = 19$). From days 0–14, there was a mean reduction in SARS scores of 10% in those treated with vitamin E versus an increase of 78% in the comparison group. More recently, vitamin E (alpha-tocopherol), with its antioxidant properties, has been reported to be effective.

A beneficial effect of pyridoxine has been reported (274).

- A 22-year-old man with chronic organic persecutory paranoid ideation and recurrent explosive attacks had received neuroleptic drugs since the age of 7. While taking haloperidol, up to 25 mg/day, and trihexyphenidyl, up to 4 mg/day, he developed involuntary movements that were diagnosed as tardive dyskinesia: blinking, movements of the forehead and eyebrows, tongue-thrusting, licking of the lips, smacking, and chewing. He scored 27 on items 1–7 of the AIMS. He began to take pyridoxine, 200 mg/day, and after 5 days had a drastic reduction in the severity of all his movement disorders.
- A 41-year-old man had dramatic relief from tardive dyskinesia and akathisia with high-dose piracetam (275).

Reserpine has been used with apparent improvement in symptoms, but deterioration followed withdrawal (276), and reserpine has also been reported to cause the condition.

A double-blind study of propranolol showed short-term improvement, and two of four subjects responded to long-term propranolol (277); unfortunately this study has not been replicated.

Tetrahydroisoxazoylpyridinol (THIP), an analogue of gamma-aminobutyric acid (GABA), which is a GABA receptor antagonist, produced no change in tardive dyskinesia, in either a dose-finding study or a 4-week placebo-controlled study, but pre-existing parkinsonism increased significantly and eye-blinking rates fell (278); these are preliminary findings, more than a decade old, and hard to interpret.

Tardive akathisia

Akathisia can occur relatively early, within days or weeks, but sometimes occurs later. A 1986 review (279) considered 24 cases of tardive akathisia seen over a long period; in three of these the condition had appeared after only 1 or 2 months of neuroleptic drug therapy, but the remainder had been treated for at least 1 year, and seven had been treated with neuroleptic drugs for at least 5 years. Whereas tardive dyskinesia most often starts in the bucco-oral region and extends to the fingers and occasionally to the lower limbs and trunk, tardive akathisia most often affects the legs or is described as a generalized sensation throughout the limbs and trunk. Moreover, while a reduction in dosage can induce a temporary worsening of masked tardive dyskinesia and an increased dosage an improvement, the effects of dosage changes on akathisia are less certain.

Tardive Tourette's syndrome

There have been at least seven published cases of Tourette's syndrome ascribed to neuroleptic drugs and emerging either during treatment or after withdrawal. Some authors believe that a tardive Tourette-like syndrome may be a subtype of the more frequent tardive dyskinesia, because it can be masked by an increase in neuroleptic drug dosage and exacerbated by withdrawal. However, the symptoms can readily be confused with exacerbation of the underlying psychosis; misdiagnosis of the condition, at least in some of the published case reports, cannot be completely ruled out.

Tardive dystonia

Tardive dystonia is a rare, late-onset, persistent dystonia associated with neuroleptic drugs, which usually affects young men. It tends to affect the muscles of the neck, shoulder girdle, and trunk, causing opisthotonos. Sometimes, patients can become incapacitated (280,281). The incidence is 1–2% (282). Once developed, it is a very persistent disorder, with a low remission rate of only 14%; withdrawal of neuroleptic drugs increases the chances of remission.

Tardive dystonia has sometimes been thought to be a subtype of tardive dyskinesia (SED-13, 123). However, some features of this condition are clearly different from those of tardive dyskinesia (SEDA-20, 41). The diagnosis of tardive dystonia should meet the following criteria: (a) the presence of chronic dystonia; (b) a history of neuroleptic drug treatment preceding (less than 2 months) or

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concurrent with the onset of dystonia; and (c) exclusion of known causes of secondary dystonia (283).

Tardive dystonia developed at any time between 4 days and 23 years after exposure to a neuroleptic drug in 107 patients who fulfilled these diagnostic criteria (284). Although the majority had a focal onset involving the craniocervical region, tardive dystonia tended to spread over the next 1–2 years and resulted in segmental or generalized dystonia in most cases.

Pleurothotonus (Pisa syndrome) is a special form of tardive dystonia that involves tonic flexion of the trunk to one side accompanied by slight backward rotation, in the absence of other dystonic symptoms. However, it can also occur immediately after the administration of neuroleptic drugs (SED-13, 123). Nine of twenty patients (mean age 40 years) who developed Pisa syndrome while taking neuroleptic drugs (mean duration 12 years) improved within 3 weeks of treatment with trihexyphenidyl 12 mg/day (285). Reduction or withdrawal of the daily dose of the neuroleptic drugs was beneficial to the remaining patients.

Antecollis is a rare form of tardive dystonia, in which there is forward bending of the neck (286). Patients with this disorder are usually quite disabled and distressed, have severe difficulties with vision, speech, swallowing, and inspiratory obstruction, and are unable to lie supine. In three reported cases (286), the patients developed the symptoms after receiving a number of neuroleptic drugs for 4 months to 14 years. Neither withdrawal of neuroleptic drugs nor the administration of anticholinergic agents affected their symptoms.

The differential diagnosis includes idiopathic torsion dystonia, parkinsonism, idiopathic torticollis, Huntington's disease, Wilson's disease, and Meige's syndrome (blepharospasm, oromandibular dystonia). A retrospective evaluation of the records of patients with idiopathic cervical dystonias ($n = 82$) and tardive cervical dystonias ($n = 20$) has been performed, in a search for clinical features that could help separate these closely related disorders (287). Despite the overall similarity, the presence of a dystonic head tremor was strongly suggestive of the idiopathic form, which was present in 42% and did not occur at all in the tardive group. A family history of dystonia (10%) was also exclusive to the idiopathic group.

A thorough and extensive review has addressed the treatment of tardive dystonia (288). For patients taking typical neuroleptic drugs, a switch to clozapine is suggested, or, if clozapine is contraindicated, to risperidone, olanzapine, or sertindole. Other alternatives are anticholinergic drugs, particularly trihexyphenidyl, benzodiazepines, tetrabenazine, reserpine, tocopherol, bromocriptine, and (in children and adolescents) baclofen. Local injection of botulinum toxin, which blocks acetylcholine release at the neuromuscular junction, is effective in the treatment of focal dystonias (SEDA-19, 45) (SEDA-22, 52). The therapeutic effects of botulinum toxin last on average for 2–6 months. In one study, botulinum toxin injections produced symptomatic relief, but benzodiazepines were associated with a poorer outcome, probably because of reverse causality, since non-remitting patients were more likely to use benzodiazepines as a second-line treatment (284). In another study there were no differences in responses to injections of botulinum toxin in patients with tardive oromandibular dystonia ($n = 24$) or idiopathic oromandibular dystonia ($n = 92$) (289). Surgical treatment, such as local denervation myectomy, thalamotomy, and pallidotomy, and deep brain stimulation can be considered only for patients with disabling dystonia and in those in whom medical treatment has failed to provide improvement. The successful treatment of tardive dystonia with low-dose levodopa plus benserazide, 50/12.5 mg tds, has been reported (290).

About 50% of patients with tardive dystonia have retrocollis; if the trunk is involved, most of the patients have back-arching opisthotonos. Five such patients experienced relief with a custom-made mechanical device that delivers constant contact to the occiput and shoulders (291).

Misinterpretation of symptoms has led to ineffective management of dystonia (292).

- A 14-year-old boy with Tourette's syndrome developed withdrawal dystonia while being treated with pimozide 12 mg/day. Increased blinking, facial pain, dystonic movements, and other facial movements at each dose reduction pointed toward withdrawal dystonia rather than toward a worsening of Tourette's syndrome.

Rabbit syndrome

Rabbit syndrome is a late-onset extrapyramidal adverse effect associated with neuroleptic drugs. It is characterized by a rapid tremor of the lips and occasionally the jaw. The movements usually respond well to antiparkinsonian agents and withdrawal of neuroleptic drugs. It has been suggested that the rabbit syndrome is the clinical converse of tardive dyskinesia (293).

Neuroleptic malignant syndrome

DoTS classification (BMJ 2003; 327:1222–5)

Dose-relation:?toxic effect
Time-course: intermediate or delayed
Susceptibility factors: high doses or intravenous administration; psychiatric disorders; dehydration; postpartum

The neuroleptic malignant syndrome (SEDA-11, 47) (SEDA-14, 50) (294,295) is a rare but potentially fatal disorder characterized by muscle rigidity, hyperthermia, altered consciousness, and autonomic dysfunction (296). Severe rigidity may explain the increased body temperature, because of heat generated by the muscles, and it may contribute to a rise in serum creatine kinase activity, reflecting a risk of myoglobinuria and acute renal insufficiency. Hyperthermia can lead to dehydration and electrolyte imbalance, leaving the patient exposed to infections and other consequences. Patients with neuroleptic malignant syndrome are more likely to be agitated or dehydrated before the syndrome develops, they often need restraint or seclusion, and they have often received larger doses of neuroleptic drugs soon after hospitalization. Previous treatment with ECT increases vulnerability (297).

This description applies to most of the cases reported since 1960, but the syndrome is still poorly defined and

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overlaps to some extent with lethal catatonia, neuroleptic drug-induced hyperpyrexia, and sudden death due to cardiac dysrhythmias. Similar symptoms have also been reported in non-schizophrenic patients after exposure to dopamine-depleting drugs (298) and after withdrawal of indirect dopamine receptor agonists (299). There is no consensus about the boundaries, causes, or management of the syndrome (SEDA-18, 50) (300,301). Neuroleptic malignant syndrome without pyrexia has been reported (SEDA-19, 4) (302). The syndrome shares clinical features with malignant hyperthermia, which is genetically acquired, but there does not appear to be a common pathophysiological link between the two (SED-11, 111).

The occurrence of neuroleptic malignant syndrome in a patient with cancer after the use of haloperidol has given rise to some comments: (a) clinical oncologists are not familiar with the neuroleptic malignant syndrome; (b) neuroleptic malignant syndrome is difficult to diagnose, because its presentation resembles that of cancer itself, and sometimes other treatment-related complications (303).

There have been reports of neuroleptic malignant syndrome precipitated by promethazine 100 mg/day to treat neuroleptic drug-induced extrapyramidal symptoms and lorazepam 6 mg/day to treat agitation (304), after the addition of intramuscular haloperidol 23 mg to atypical neuroleptic drugs (305), and in other instances in children and adolescents (306).

Cases of neuroleptic malignant syndrome with different features have been published (307–311).

- A 21-year-old woman had bilateral dislocations after being struck by an automobile (307). Postoperatively, she had signs of delirium and agitated behavior, and was given haloperidol 3–5 mg intravenously or intramuscularly and lorazepam 2 mg intravenously. Her general muscular tone increased during the next several days, leading to spontaneous dislocations/subluxations of multiple joints; there was mild hyperthermia (38.4°C), a raised neutrophil count (12×10^9/l) in the absence of an identifiable source of infection, and a raised creatine kinase activity (361 U/l; reference range 0–150). Neuroleptic malignant syndrome was diagnosed. Haloperidol and droperidol were withdrawn, and she was given dantrolene sodium 1 mg/kg orally every 8 hours for 14 days. Within 24 hours her temperature had fallen and during the next week her spasticity progressively improved.

In two other cases there were features of neuroleptic malignant syndrome within 10 days of autotransplantation, with rapid improvement after withdrawal of the neuroleptic drugs (308). Since neuroleptic drugs are often used during transplantation, it is important to recognize that the use of these drugs in concert with the physiological stress of the operation can result in this drug-related complication. In two other cases of neuroleptic malignant syndrome, computerized tomography showed evidence of cerebral edema, which is claimed not to have been reported before (309).

Acute renal insufficiency has been reported as a severe complication of neuroleptic malignant syndrome (SED-13, 124) (SEDA-21, 49), and a patient who developed severe hyponatremia and progressed to neuroleptic malignant syndrome, myoglobinuria, and acute renal insufficiency deserves attention (310).

- A 42-year-old man with a history of paranoid schizophrenia developed confusion and vomiting. His medications included buspirone and tiotixene. He also had a generalized seizure that resolved spontaneously. His serum sodium concentration was 114 mmol/l, which was thought to be secondary to psychogenic polydipsia and which was corrected. The next day his temperature rose to 40°C and the day after that he became lethargic and non-verbal and developed generalized muscle rigidity. A diagnosis of probable neuroleptic malignant syndrome was made, and he was given dantrolene sodium 1 mg/kg intravenously; neuroleptic drugs were withdrawn. The serum creatine kinase activity was over 234 500 U/l. Urinalysis showed more than 3 g/l of protein, a trace of ketones, and hemoglobin and leukocytes. By the following day, his muscle rigidity and fever had resolved and his mental status had markedly improved.

Two patients developed non-convulsive status epilepticus and neuroleptic malignant syndrome (311). Whether this constitutes one syndrome or merely the co-existence of the two is academic, because it makes no difference to therapy.

The syndrome is reported most often in young men. It can occur suddenly days or weeks after initiating or intensifying drug therapy, and usually lasts 5–10 days after withdrawal. Although it is unusual, the syndrome can occur while neuroleptic drug dosage is being reduced (SEDA-19, 46).

The prevalence has been suggested as being less than 1% (312), but the precise frequency is unknown, and a trend toward fewer reports in recent years suggests that factors such as the use of lower dosages of neuroleptic drugs may be important. In a 1986 review it was argued that the neuroleptic malignant syndrome represents a heterogeneous group of neuroleptic drug-induced extrapyramidal syndromes with concurrent fever, and the existence of neuroleptic malignant syndrome as a discrete syndrome was questioned (313).

There is no consistent evidence that any one neuroleptic drug or class of drugs is more or less likely to produce the syndrome. It has been reported with atypical neuroleptic drugs, such as clozapine (314–320) and risperidone (321–326), although less often than with typical neuroleptic drugs. Neuroleptic malignant syndrome attributed to clozapine (19 cases) and risperidone (13 cases) has been reviewed (327). However, relatively more cases have been associated with high-potency neuroleptic drugs, and the course of the syndrome may be particularly prolonged and difficult to treat when depot forms of these drugs have been used. The authors of one review found insufficient evidence to support the concept of an atypical neuroleptic malignant syndrome with novel neuroleptic drugs (327).

Mechanism

It has been suggested that neurotransmitter abnormalities other than reduced dopaminergic function may be responsible for the neuroleptic malignant syndrome, in the light of three cases in which the syndrome occurred after neuroleptic drug administration during

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benzodiazepine withdrawal (328). Benzodiazepines potentiate GABA transmission and their long-term use is associated with a compensatory reduction in GABA activity; since nigral dopaminergic neurons are modulated through the action of GABAergic projection neurons, reduced GABA could facilitate the occurrence of the syndrome.

Susceptibility factors

Susceptibility factors that have been proposed for the development of neuroleptic malignant syndrome include a history of prior episodes of neuroleptic malignant syndrome, the use of high potency drugs, rapid escalation in dosage or parenteral administration of neuroleptic drugs, dehydration, agitation, catatonia, and certain conditions, including mood disorders, schizophrenia, and mental disorders due to medical conditions (SEDA-22, 52). Acute encephalitis has been suggested to be another susceptibility factor (329). It has been reported in five patients who developed neuroleptic malignant syndrome after being treated with neuroleptic drugs for the psychiatric symptoms associated with encephalitis. HIV encephalitis has in particular been associated with neuroleptic malignant syndrome (SEDA-19, 47).

The postpartum period is said to be a susceptibility factor for neuroleptic malignant syndrome. During 30 months, 11 cases of neuroleptic malignant syndrome were detected in a university general hospital in India (330). Five patients were women and in three the onset was in the postpartum period. One was taking a small dose of oral chlorpromazine (20 mg). In contrast, agitation and ECT, which have been proposed as susceptibility factors (SEDA-22, 52), have been questioned as independent susceptibility factors (331,332). Since catatonia was mentioned without reporting the number of affected patients, the authors suggested that some of the agitated patients would actually correspond to catatonic patients. However, catatonia was present before the onset of neuroleptic malignant syndrome in only one subject from the neuroleptic malignant syndrome group (333). On the other hand, ECT remains, at best, an association that possibly flags the characteristics of the primary psychiatric disorder that prompted the treatment.

Malignant catatonia associated with a low serum iron concentration carries a high risk of evolving into neuroleptic malignant syndrome, going by the results of a retrospective study, in which 39 catatonic episodes in patients with low ($n = 17$) or normal ($n = 22$) serum iron concentrations were compared (334). All had been exposed to neuroleptic drugs. Hypoferremia has previously been related to the neuroleptic malignant syndrome.

Susceptibility factors that have been proposed for the development of neuroleptic malignant syndrome include, among others, a history of prior episodes (SEDA-22, 52). A case report has further illustrated that possibility (335).

- A 19-year-old man with bipolar disorder received intramuscular haloperidol 30 mg/day and chlorpromazine 300 mg/day and developed neuroleptic malignant syndrome; the neuroleptic drugs were withdrawn. One month later he had a recurrence. It transpired that he had discontinued his medication 2 weeks after discharge, but because his manic symptoms recurred his relatives had started to give him haloperidol 10 mg/day again, which led to the recurrence.

Treatment

Early recognition and prompt treatment of the neuroleptic malignant syndrome, in particular immediate recognition of new rigidity, may be the best means of arresting its progress and preventing further complications (300). If there is fever, although other possible causes should be investigated, there should be no delay in instituting appropriate treatment, and in particular anticholinergic treatment of severe rigidity. There is no proven specific treatment, but immediate withdrawal of neuroleptic drugs is essential, followed by supportive therapy and intensive monitoring of respiratory, renal, and cardiac function. Anticholinergic drugs are often used, but when the temperature exceeds 101°F, they can exacerbate fever, and other treatments may be preferred. It should be remembered that the simultaneous withdrawal of neuroleptic and anticholinergic drugs can exacerbate extrapyramidal features and that anticholinergic drugs should if possible be continued for 1 week after the withdrawal of the neuroleptic drug. Carbamazepine (336), amantadine (337), and bromocriptine (338) have been successfully used as empirical treatments in isolated cases. However, dopamine receptor agonists are preferred when the temperature exceeds 101–103°F, and muscle contraction can be further alleviated with dantrolene or benzodiazepines (339). Botulinum toxin was used for preventing muscle contractions in one case (340).

Dantrolene may be effective in reducing muscle rigidity in neuroleptic malignant syndrome (341,342) (SEDA-20, 42), but a reliable regimen has not been established (343).

- A 39-year-old man receiving haloperidol 4 mg and trihexyphenidyl 2 mg for schizophrenia developed a fever of over 40°C and clouding of consciousness 19 days after the start of medication. Neuroleptic malignant syndrome was suspected and dantrolene 40–80 mg/day was given intravenously for 5 days, with no improvement; disseminated intravascular coagulation and acute renal insufficiency developed. Dantrolene 200 mg was given intravenously over 10 minutes. One hour later, his temperature fell to 38.4°C. Continuous intravenous infusion of dantrolene 400 mg/day was started in combination with oral bromocriptine 15 mg/day. Dantrolene was changed to the oral route after 14 days and was withdrawn after 28 days.

Six cases successfully treated with ECT have been reported (344,345).

Five patients had residual catatonia after withdrawal; two recovered gradually with supportive treatment (346). Three patients were treated with ECT; two had an initial positive response, but one died later of intercurrent pneumonia; the third did not respond.

After resolution of symptoms, neuroleptic drugs can be reintroduced safely in most patients (347). In all cases the lowest effective dose of neuroleptic drug should be used, along with anticholinergic therapy or thioridazine, which has anticholinergic effects.

It is said that the risk of recurrence on re-exposure to neuroleptic drugs (about 15–30%) can be minimized by

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delaying rechallenge by 2 weeks or by using a neuroleptic drug of an alternative class.

Meige's syndrome

Meige's syndrome is characterized by blepharospasm and spasm of the lower facial or oromandibular muscles (348).

- A 52-year-old woman developed Meige's syndrome 2 days after the appearance of akathisia. She had taken neuroleptic drugs for years, but her current medication had been changed to bromperidol 18 mg/day and trihexyphenidyl (benzhexol) 6 mg/day; 2 days later she developed akathisia. Oral perphenazine 12 mg and trihexyphenidyl 6 mg dose-dependently reduced the frequency of blepharospasm; the dosages of bromperidol and trihexyphenidyl were gradually reduced to 8 mg/day and 3 mg/day respectively over 3 months, by which time her symptoms had completely disappeared.

Sleep

Oversedation and/or drowsiness is the most common adverse effect of neuroleptic drugs. However, most patients develop tolerance to this effect. Patients with Alzheimer's disease, as well as having impaired cognitive function and a change in personality, have a tendency to develop sleep–wake cycle disturbances that may be aggravated by classical neuroleptic drugs.

- Haloperidol was given to a 54-year-old patient with dementia; 10 days later, the circadian rest–activity cycle began to disintegrate and there was total dysrhythmicity for over 2 months; deterioration was progressive (349). Because of extrapyramidal symptoms, haloperidol 40 mg/day was changed to clozapine 50 mg/day and treatment with donepezil was begun. Two weeks later there was sudden and rapid normalization of the rest-activity cycle, started by an apparent shift of wake-up time to earlier each day, until it attained a new stable timing; orientation and memory also improved.

Other neurological effects

Myasthenia gravis caused by neuroleptic drugs has been reported (SED-11, 110). Such cases may be due to impairment of neuromuscular transmission.

Different degrees of frontal atrophy have been observed in 31 psychotic patients who had taken neuroleptic drugs for 5 years (350). All underwent computed tomography when they were drug-naive and 5 years later. Logistic regression analysis identified neuroleptic drugs as having a significant impact on the development of frontal atrophy, and the estimated risk of atrophy increased by 6.4% for each additional 10 mg of chlorpromazine equivalents.

Sensory systems

Various neuroleptic drugs, particularly low-dose phenothiazines and thioxanthenes, commonly cause blurred vision secondary to their anticholinergic activity. This is primarily a nuisance, except in the rare patient with closed-angle glaucoma.

Of more concern are two distinct types of adverse effects in the eye, which can be produced by various neuroleptic drugs: lenticular and corneal deposits, cataract, and pigmentary retinopathy (141,351,352). Deposits in the lens or cornea probably result from deposition of melanin-drug complexes and are best detected by slit-lamp examination. These deposits are probably dose- and time-related, since they generally occur only after years of treatment. Fortunately, they are in large part benign and reversible, but if undetected they can progress to interfere with vision. They are most often reported with chlorpromazine or thioridazine and can occur in association with pigmentary changes in the skin. Non-phenothiazines appear to have minimal propensity to cause oculocutaneous reactions and may be preferred when these problems have occurred during treatment with a phenothiazine (SED-11, 113), although the patient should still be closely monitored.

- A 46-year-old schizophrenic patient, who had taken chlorpromazine 200 mg/day for 9 years and then 400 mg/day for 7 years, developed ocular pigmentation (353).

The interesting thing about this report was its striking photographs, in which multiple, small, dark pigment deposits in the conjunctiva were seen; in addition, the cornea had multiple, small, discrete, yellowish specks, and both lenses had anterior capsular opacities.

Various rarer ocular effects have been reported, including oculomotor palsies, transient myopia, optic atrophy, blue-green blindness, and night-blindness. For a long time it has been suspected that neuroleptic drugs may increase the risk of cataract (352).

A further case of cataract has been reported (354).

- A 50-year-old woman with schizophrenia had a 1-year history of gradual deterioration of vision in both eyes. For several years she had been taking chlorpromazine 300 mg/day, trifluoperazine 10 mg/day, and trihexyphenidyl 4 mg/day. Slit lamp examination showed fine, discrete, brown refractile deposits on the corneal endothelium in both eyes, and characteristic bilateral stellate cataracts with dense, dust-like brown-yellow granular deposits were noted along the suture lines in the anterior pole of the lens and obscured the visual axis.

Psychological, psychiatric

Although neuroleptic drugs are relatively effective in treating psychiatric symptoms, their mental adverse effects can impair the quality of life of some individuals. The effects of newer neuroleptic drugs on cognitive functioning and the implications for functional outcome have been summarized and methodological and conceptional issues addressed (355).

In 44 stable schizophrenic outpatients, a significant proportion of the variance was explained by a combination of protracted duration of illness and dysphoric subjective responses to neuroleptic drugs (356). In terms of the individual items on the Negative Subjective Response subscale, only the statement "I feel weird, like a zombie on medication" was associated with statistically significant differences in quality of life. Patients who agreed with this statement ($n = 10$) had a significantly poorer quality of life than those who disagreed ($n = 34$). Related to this possible impairment of the quality of life

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is the observation, in 45 patients with chronic schizophrenia, that neuroleptic drugs playing a role in the development of depressive symptoms and negative symptoms (174). Duration of treatment correlated positively with the depressive and the negative symptoms.

Notwithstanding this finding, the differentiation between disease-related and neuroleptic drug-induced negative symptoms, such as flat affect, can be especially difficult in some patients. To investigate the interactions among psychomotor performance, negative symptoms, and neuroleptic drug effects, dopamine D_2 receptor availability (measured by the binding of ^{123}I-iodobenzamide) psychopathology, and psychomotor reaction time have been assessed in eight drug-free and eight neuroleptic drug-treated patients with schizophrenia (357). Negative symptoms increased in the patients taking neuroleptic drugs compared with drug-free patients and correlated positively with neuroleptic blockade of dopamine D_2/D_3 receptors. Furthermore, parkinsonism correlated with a flat affect and psychomotor retardation. There were some limitations to this observational study: the sample size was small; different neuroleptic drugs were used, including risperidone (in seven patients), which may not behave in the same way than others neuroleptic drug owing to its antagonistic effect on 5-HT_2 receptors, although it has been observed that dopamine D_2 receptor occupancy and extrapyramidal adverse effects with risperidone do not differ significantly from those observed with traditional neuroleptic drugs; and the duration of disease was longer in the patients who took neuroleptic drugs.

Psychiatric abnormalities

Neuroleptic drugs can cause a depression-like syndrome. This should be differentiated from neuroleptic-induced akinesia. Long-acting drugs have been particularly implicated (SED-11, 107) (141). However, a double-blind, placebo-controlled, randomized study of long-acting neuroleptic drugs did not support this conclusion (358).

Toxic delirium caused by neuroleptic drugs with potent anticholinergic properties has been widely reported (SED-11, 107), and has been reported with low-dose clozapine (359).

Obsessive-compulsive symptoms have been described with both typical neuroleptic drugs (for example chlorpromazine) and atypical drugs (for example clozapine and risperidone) (SEDA-19, 51) (SEDA-20, 47) (360,361).

Other uncommon effects include psychotic exacerbation, catatonia-like states, and Klüver–Bucy-like syndrome (SED-9, 81) (SEDA-7, 67) (141).

Cognitive effects

The effects of atypical neuroleptic drugs on cognitive functioning and the implications for functional outcome have been summarized and methodological and conceptional issues addressed (355).

Cognitive function is reduced in schizophrenia, and neuroleptic drugs can cause further impairment (362,363). However, the extent to which they do so is disputed. In one study, the more anticholinergic drugs impaired short-term verbal memory (SEDA-18, 48) (364). Another study showed that patients with schizophrenia who took neuroleptic drugs had superior information processing compared with unmedicated patients with schizophrenia; the authors claimed that neuroleptic drugs probably do not cause, and may actually reverse, slow information processing in patients with schizophrenia (365). However, a substantial number of patients with schizophrenia declare that neuroleptic drugs slow their thinking, cause them to forget, and remove interest and motivation. These responses to neuroleptic drugs are claimed to be dysphoric and are often associated with drug-induced extrapyramidal symptoms, particularly akathisia (366). Akinesia can also contribute to feelings of apathy and diminished spontaneity, and can be difficult to distinguish from the negative symptoms of schizophrenia or the psychomotor retardation of post-psychotic depression (367).

Visuomotor testing has been performed in 76 patients with schizophrenia or a schizophreniform disorder receiving haloperidol ($n = 23$; mean dose 10 mg/day), olanzapine ($n = 26$; 10.6 mg/day), or risperidone ($n = 27$; 4.4 mg/day) (363). Cognitive function was better in patients receiving risperidone or olanzapine compared with those receiving haloperidol; patients receiving haloperidol or risperidone had more severe extrapyramidal signs than those receiving olanzapine. The authors concluded that the benefits on cognitive functioning had resulted from a direct effect and were not related to reduced extrapyramidal effects. However, the patients receiving haloperidol were older and had a longer duration of illness than those receiving olanzapine or risperidone; this precludes any firm conclusions.

A comparison between haloperidol ($n = 25$) and atypical neuroleptic drugs (clozapine, $n = 24$; olanzapine, $n = 26$; risperidone, $n = 26$) has been conducted in patients with treatment-resistant schizophrenia in a 14-week, randomized, double-blind trial (368). Global neurocognitive function improved significantly with olanzapine and risperidone, by about 8–9 "IQ-equivalent" points. According to the authors, the finding was not mediated by changes in symptoms, adverse effects, or blood drug concentrations. In the haloperidol group, higher blood concentrations were associated with less improvement in motor function.

In another study, there was a small but significant negative correlation between the dosages of typical neuroleptic drugs and "mental functioning" when the data were controlled for psychopathology; this correlation was also seen for risperidone and clozapine, but there were no significant differences between patients taking low or high dosages of atypical agents. The authors pointed out that the dosage range in patients taking atypical agents was rather narrow and it is possible that higher doses of atypical neuroleptic drugs may give different results (369).

In 207 schizophrenic patients who answered the short form of a questionnaire entitled "Subjective Well-Being under Neuroleptic Treatment" (SWN-S), those taking risperidone ($n = 26$) and olanzapine ($n = 40$) took part in a study with random assignment after a washout period of at least 3 days, whereas patients taking typical neuroleptic drugs ($n = 106$; predominantly haloperidol and flupenthixol) were assessed during treatment (370).

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Endocrine

The effects of neuroleptic drugs on menstrual status and the relation between menstrual status and neuroleptic drug efficacy and adverse effects have been explored (371). In contrast to prior reports (SEDA-18, 50), there was not a high prevalence of menstrual irregularities or amenorrhea in 27 premenopausal women with chronic schizophrenia treated with typical neuroleptic drugs.

Prolactin

Neuroendocrine effects of neuroleptic drugs include a rise in growth hormone, inappropriate ADH and prolactin secretion, and disturbances of sex hormones (SEDA-7, 67). Galactorrhea (SEDA-20, 43) and gynecomastia can follow the rise in prolactin.

A correlation between serum concentrations of neuroleptic drugs and prolactin has been claimed (372,373).

However, no further rise in plasma prolactin concentration was observed with higher dosages of haloperidol (over 100 mg/day), which was explained as being related to saturation of the pituitary dopamine receptors by a modest amount of haloperidol (373). A low prolactin concentration during maintenance neuroleptic drug treatment predicted relapse after withdrawal, and it was suggested that serum prolactin concentration may be helpful in monitoring treatment (374). Hirsutism, amenorrhea, and a false-positive pregnancy test associated with neuroleptic treatment have also been reported (SED-11, 111) (371,375).

The effects of haloperidol and quetiapine on serum prolactin concentrations have been compared in 35 patients with schizophrenia after a 2-week washout period in a randomized study (376). There was no significant difference in prolactin concentration between the groups at the start of the study, although prolactin concentrations were significantly lower with quetiapine than haloperidol. After 6 weeks, the mean prolactin concentration was significantly increased in those taking haloperidol but not in those taking quetiapine. Two patients taking haloperidol had galactorrhea related to hyperprolactinemia.

There is concern that neuroleptic drugs may increase the risk of breast cancer because of raised prolactin concentrations. For a long time, findings did not confirm this association (377), but a Danish cohort study of 6152 patients showed a slight increase in the risk of breast cancer among schizophrenic women (378).

In eight patients receiving neuroleptic drugs, serum prolactin concentrations were grossly raised (379). The time-course of the prolactin increase was examined in 17 subjects whose prolactin concentrations rose during the first 6–9 days of treatment with haloperidol (380). The increase was followed by a plateau that persisted, with minor fluctuations, throughout the 18 days of observation. Patients whose prolactin concentrations increased above 77 ng/ml ($n = 2$) had hypothyroidism, and it is known that TRH (thyrotropin) stimulates the release of prolactin (381). It was concluded that all patients should have had TSH determinations at the start of therapy with neuroleptic drugs.

Sex differences in hormone concentrations have been investigated in 47 patients (21 men and 26 women) with schizophrenia or related psychoses who were using different neuroleptic drugs (382). The median daily dose and the median body weight-adjusted daily dose were twice as high in men as in women. However, neuroleptic drug-induced hyperprolactinemia was more frequent and occurred at a lower daily dose in women. The growth hormone concentration was normal in all patients.

Some patients who take clozapine take another neuroleptic drug, and the consequences of this practice in terms of prolactin have been studied in five patients (383). After the addition of haloperidol (4 mg/day) to clozapine the mean prolactin concentration increased from 9.7 ng/ml to 16 ng/ml at week 4 and 19 ng/ml at week 6. Each subject had an increase in the percentage of D_2 receptor occupancy, and the group mean increased from 55% at baseline to 79% at week 4; the increased prolactin concentrations correlated with receptor occupancy.

The effects of haloperidol and quetiapine on serum prolactin concentrations have been compared in 35 schizophrenic patients after a 2-week washout period in a randomized study (376). There was no significant difference in prolactin concentration between the groups at the start of the study, although prolactin concentrations were significantly lower with quetiapine than haloperidol. After 6 weeks, the mean prolactin concentration was significantly increased in those taking haloperidol but not in those taking quetiapine. Two patients taking haloperidol had galactorrhea related to hyperprolactinemia.

Inappropriate ADH secretion

Polyuria and polydipsia have long been associated with schizophrenia, and neuroleptic drugs appear to aggravate these symptoms, sometimes with an accompanying syndrome of inappropriate ADH secretion. However, water retention and edema occur very rarely during treatment with neuroleptic drugs. Water intoxication has been reported during treatment with thioridazine and may be due to its pronounced anticholinergic properties and/or direct stimulation of the hypothalamic thirst center (384).

Metabolism

The charts of 94 long-term inpatients have been reviewed retrospectively to examine the changes in weight, fasting glucose, and fasting lipids in those taking either risperidone ($n = 47$) or olanzapine ($n = 47$) (385). The patients had increased weight, triglycerides, and cholesterol, and the changes were significantly higher with olanzapine; olanzapine but not risperidone considerably increased glucose concentrations. One case of new-onset diabetes mellitus occurred in a patient taking olanzapine.

Lipid concentrations

In a cross-sectional study in 44 men, olanzapine had a worse metabolic risk profile than risperidone (386). The men (mean age 29 years) took olanzapine ($n = 22$; mean duration 18 months; mean dose 13 mg/day) or risperidone ($n = 22$; mean duration 17 months; mean dose 2.8 mg/day). Those who took olanzapine had significantly higher plasma triglyceride concentrations, significantly higher very low density lipoprotein cholesterol concentrations, a trend to a lower HDL cholesterol concentration, and a trend to a higher cholesterol/HDL cholesterol ratio.

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Despite similar mean body weights (olanzapine 84 kg versus risperidone 81 kg), 32% of those who took olanzapine were characterized by the atherogenic metabolic triad (hyperinsulinemia and raised apolipoprotein B and small-density LDL concentrations) compared with only 5% of those who took risperidone.

Diabetes mellitus

Several cases of de novo onset or exacerbation of existing diabetes mellitus in patients treated with neuroleptic drugs have been reported and were not significantly related to weight gain. These included eight patients treated with clozapine (387,388) and two patients treated with olanzapine (388).

Neuroleptic drug treatment of non-diabetic patients with schizophrenia can be associated with adverse effects on glucose regulation, as has been suggested by the results of a study in which modified oral glucose tolerance tests were performed in 48 patients with schizophrenia taking clozapine, olanzapine, risperidone, or typical neuroleptic drugs, and 31 untreated healthy control subjects (389). Newer neuroleptic drugs, such as clozapine and olanzapine, compared with typical agents, were associated with adverse effects on blood glucose regulation, which can vary in severity regardless of adiposity and age.

Weight gain

Shortly after the typical neuroleptic drugs were introduced in the 1950s, marked increases in body weight were observed, and excessive weight gain has been reported in up to 50% of patients receiving long-term neuroleptic drug treatment (390–396).

However, changes in weight during psychosis are also related to the condition; Kraepelin wrote, "The taking of food fluctuates from complete refusal to the greatest voracity... Sometimes, in quite short periods, very considerable differences in the body weight are noticed ..." (397). It was observed early on that food intake and weight often fell as psychosis worsened, but eating and weight returned to normal or increased when an acute psychotic episode abated. However, since the start of the neuroleptic drug era in the 1950s, a new pattern of sustained increased weight has commonly been detected. The question of whether weight gain is associated with efficacy is important; in one study there was no obvious relation between the magnitude of weight gain and therapeutic efficacy (398).

The association between clozapine-related weight gain and increased mean arterial blood pressure has been examined in 61 patients who were randomly assigned to either clozapine or haloperidol in a 10-week parallel group, double-blind study, and in 55 patients who chose to continue to take clozapine in a subsequent 1-year, open, prospective study (399). Clozapine was associated with significant weight gain in both the double-blind trial (mean 4.2 kg) and the open trial (mean 5.8 kg), but haloperidol was not associated with significant weight gain (mean 0.4 kg). There were no significant correlations between change in weight and change in mean arterial blood pressure for clozapine or haloperidol.

Serum leptin, a peripheral hormone secreted by fat, correlates inversely with body weight; in 22 patients taking clozapine who gained weight, those who had the most pronounced 2-week increase in leptin had the least gain in body weight after 6 and 8 months (400).

Epidemiology

Several reviews have addressed the issue of weight gain (401–405). Comparison of different studies of weight gain during treatment with atypical neuroleptic drugs is hampered by problems with study design, recruitment procedures, patient characteristics, measurement of body weight, co-medications, and duration of therapy. These problems have to be considered when assessing this type of information, particularly figures collected in accordance with the last-observation-carried-forward technique, which is one of the most common approaches taken; this type of analysis can produce marked underestimates of the magnitude of weight gain.

There has been one comprehensive meta-analysis including over 80 studies and over 30 000 patients (406). A meta-analysis of trials of neuroleptic drugs showed the following mean weight gains in kg after 10 weeks of treatment: clozapine, 4.5; olanzapine, 4.2; thioridazine, 3.2; sertindole, 2.9; chlorpromazine, 2.6; risperidone, 2.1; haloperidol, 1.1; fluphenazine, 0.43; ziprasidone 0.04; molindone, −0.39; placebo, −0.74 (407,408). In one study, excessive appetite was a more frequent adverse event in patients treated with olanzapine versus haloperidol (24 versus 12%) (152). Loss of weight has been observed after withdrawal of neuroleptic drugs (409).

The percentages of patients who gain more than 7% of their baseline body weight are highest for olanzapine (29%) and lowest for ziprasidone (9.8%). Although these figures are useful for comparing different drugs, they do not illustrate how weight increases over time, nor the total gain. Body weight tends to increase at first but reaches a plateau by about 1 year; with olanzapine 12.5–17.5 mg/day, patients gained, on average, 12 kg (410).

Risperidone and olanzapine, the two most commonly used atypical drugs, have been compared in trials; patients who took olanzapine gained almost twice as much weight (4.1 kg) as those who took risperidone (2.3 kg) (81). In two groups of inpatients, who took either risperidone ($n = 50$) or olanzapine ($n = 50$) for schizophrenia the mean body weight at baseline was 83 kg in the risperidone group and 85 kg in the olanzapine group; after 4 months of treatment, the mean body weights were 83 and 87 kg respectively (411). The increase in body weight with olanzapine was statistically significant.

In a retrospective chart review of 91 patients with schizophrenia (120 treatment episodes; mean age 38 years), there was weight gain with zotepine (4.3 kg), clozapine (3.1 kg), sulpiride (1.9 kg), and risperidone (1.5 kg), but not in patients treated with typical neuroleptic drugs (mean gain 0.0–0.5 kg) (412). The mean duration of treatment was 28–34 days, the maximum weight gain being in the first 3–5 weeks. The mean increases in weight were 4.3% in the patients with normal weight, 3.0% in those with mild obesity, and 1.9% in those with severe obesity (BMI over 30).

In another retrospective study, 65 patients with schizophrenia who gained weight while taking clozapine for 6 months were followed (413). After that they were

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switched to a combination of clozapine with quetiapine for 10 months: clozapine was tapered to 25% of the current dose and quetiapine was added proportionately. During clozapine monotherapy the mean weight gain was 6.5 kg and 13 patients developed diabetes. At the end of the combination period, the mean weight loss was 9.4 kg; patients who developed diabetes showed significant improvement, resulting in a rapid fall in insulin requirements and/or withdrawal of insulin and replacement with an oral hypoglycemic agent. The mechanism of clozapine-associated weight gain is uncertain.

Mechanism

The mechanisms of weight gain are not known. Olanzapine, for example, affects at least 19 different receptor sites, may have reuptake inhibition properties, and may affect hormones such as prolactin. Animal models do not help to elucidate mechanisms, since they have not shown clear results: some studies have shown weight gain with neuroleptic drugs in rats and others have not.

However, a serotonergic mechanism has been proposed (414). Most of the atypical drugs, which most commonly cause weight gain, interact with 5-HT_{2C} receptors; however, ziprasidone also binds to 5-HT_{2C} receptors with high affinity and does not cause weight gain or does so to a lesser extent. In 152 patients treated with clozapine, Cys23Ser polymorphism of the 5-HT_{2C} receptor did not explain the weight gain that occurred (415), nor was there an association between specific alleles of the dopamine D_4 receptor gene (416). In contrast, in 19-year-old monozygotic twins who gained around 40 kg after taking mainly clozapine, weight gain was related to an unspecified genotype (417). An association between weight gain and a 5-HT_{2C} receptor gene polymorphism has been identified in 123 Chinese Han patients with schizophrenia taking chlorpromazine ($n = 69$), risperidone ($n = 46$), clozapine ($n = 4$), fluphenazine ($n = 3$), or sulpiride ($n = 1$) (418). Weight gain was substantially greater in the patients with the wild-type genotype than in those with a variant genotype (–759C/T), at both 6 and 10 weeks; this effect was seen in men and women.

Susceptibility factors

In general, people with schizophrenia have a greater tendency to be overweight and obese than those who do not have schizophrenia (419). The evidence suggests that weight gain will progress most rapidly during the first 3–20 weeks of treatment with second-generation neuroleptic drugs; there is little evidence that dose affects weight gain. There are no sex differences, but there is a positive correlation between weight gain and age. Smokers treated with neuroleptic drugs may gain less weight than non-smokers (412,420). Patients in hospital are more likely to gain weight than those in the community, perhaps because they have an unrestricted diet and limited physical activity; there is some evidence that those with a lower baseline BMI are likely to gain more weight (402).

However, in the USA, data from a large health and nutrition survey ($n = 17\,689$) and from patients with schizophrenia to be enrolled in a clinical trial ($n = 420$) showed no differences; the mean BMIs were high and a substantial proportion of the population was obese (419).

The genetic basis of some reactions associated with neuroleptic drugs is of particular interest. An important association between weight gain and a 5-HT_{2C} receptor gene polymorphism has now been identified in 123 Chinese Han schizophrenic patients taking chlorpromazine ($n = 69$), risperidone ($n = 46$), clozapine ($n = 4$), fluphenazine ($n = 3$), or sulpiride ($n = 1$) (418). Weight gain was substantially greater in the patients with the wild-type genotype than in those with a variant genotype (–759C/T), at both 6 and 10 weeks; this effect was seen in men and women. In addition, a homozygous non-functional genotype, CYP2D6*4, was found in a 17-year-old schizophrenic patient who developed severe akathisia, parkinsonism, and drowsiness after taking risperidone 6 mg/day for 3 months; he had a high plasma concentration of risperidone and an active metabolite (421).

Clinical features

Obesity is associated with increased risks of dyslipidemia, hypertension, type 2 diabetes mellitus, cardiovascular disease, osteoarthritis, sleep apnea, and numerous other disorders; all these conditions have been associated with increased mortality. In the EUFAMI (European Federation of Associations of Families of Mentally Ill People) Patient Survey undertaken in 2001 across four countries and involving 441 patients, treatment-induced adverse effects were a fundamental problem; of the 91% of patients who had adverse effects, 60% had weight gain, and of these more than half (54%) rated weight gain as the most difficult problem to cope with (422). Furthermore, weight gain can adversely affect patients' adherence to medication, undermining the success of drug treatment for schizophrenia.

A report has illustrated how extreme the problem of weight gain associated with neuroleptic drugs can be (423).

- A 32-year-old man with schizophrenia taking neuroleptic drugs was switched to olanzapine 20 mg/day for better control. He weighed 101 kg and his BMI was 31 kg/m^2. After 6 months he had gained 4.5 kg and after 1 year 17 kg. Because of poor control, risperidone 4 mg/day was added and 16 months later he had had a 34.6 kg increase from baseline and had a BMI of 42 kg/m^2 (that is in the range of severe obesity). He had both increased appetite and impaired satiety. His serum triglycerides were 4.0 mmol/l, and his fasting blood glucose was 6.7 mmol/l. He and his physician agreed on a goal of losing 12 kg over 12 months and he was referred to a dietician. Over the next 5 weeks, he lost 2.7 kg and after 2 years his BMI was 38 kg/m^2 and 1 year later 39 kg/m^2. He was given nizatidine 300 mg bd and 1 year later his weight was 95 kg (BMI 29 kg/m^2). His triglycerides and fasting blood glucose concentrations were within the reference ranges.

Comparative studies

The charts of 94 long-term inpatients have been reviewed retrospectively to examine the changes in weight, fasting glucose, and fasting lipids in those taking either risperidone ($n = 47$) or olanzapine ($n = 47$)

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(385). The patients had increased weight, triglycerides, and cholesterol, and the changes were significantly higher with olanzapine; olanzapine but not risperidone considerably increased glucose concentrations. One case of new-onset diabetes mellitus occurred in a patient taking olanzapine. Weight should be monitored in patients taking maintenance atypical neuroleptic drugs, especially dibenzodiazepines.

Management

Behavioral treatment of obesity has given good results in patients taking neuroleptic drugs (424). More dubious is the use of antiobesity drugs, as some of them can cause psychotic reactions.

Good results have been reported with amantadine, which increases dopamine release (425). In 12 patients with a mean weight gain of 7.3 kg during olanzapine treatment, amantadine 100–300 mg/day over 3–6 months produced an average weight loss of 3.5 kg without adverse effects. In contrast, calorie restriction did not lead to weight loss in 39 patients with mental retardation who were taking risperidone, 37 of whom gained weight, the mean gain being 8.3 kg over 26 months (426).

Electrolyte balance

Care should be taken when treating hyponatremic patients with neuroleptic drugs (427).

Mineral balance

In one controlled study, 12 patients who were receiving various neuroleptic drugs had significantly increased urinary calcium and hydroxyproline concentrations and reduced urinary alkaline phosphatase compared with five controls (428). The possibility of a reduction in bone mineralization (429) may contribute to the increased risk of hip fracture associated with neuroleptic drug treatment in the elderly.

Hematologic

Rarely reported hematological reactions to various neuroleptic drugs include agranulocytosis, thrombocytopenic purpura, hemolytic anemia, leukopenia, and eosinophilia. These are thought to represent allergic or hypersensitivity reactions, although this has been questioned in one detailed case report of chlorpromazine-induced agranulocytosis (430).

The reported incidence of agranulocytosis is variable, ranging from 1 in 3000 to 1 in 250 000. Most cases are seen within the first 2 months after the start of treatment, but there have been a few reports in which agranulocytosis occurred only after many years. Frequent white cell counts are of limited value in monitoring, since counts fall rapidly and abruptly. Careful attention should be given to possible early warning signs, such as fever, sore throat, and lymphadenopathy. Treatment requires immediate withdrawal and preventive measures against infection. Granulocyte colony-stimulating factor (GCSF) has been used to treat neuroleptic drug-induced agranulocytosis (431).

In view of the association of agranulocytosis with clozapine and of aplastic anemia with remoxipride, hemopoietic disorders have been studied using information from the UK monitoring system (432). The Committee on Safety of Medicines and the erstwhile Medicines Control Agency in the UK received 999 reports of hemopoietic disorders related to neuroleptic drugs between 1963 and 1996; there were 65 deaths. There were 182 reports of agranulocytosis; chlorpromazine and thioridazine were associated with the highest number of deaths—27 of 56 and 9 of 24 respectively. The much lower mortality with clozapine-induced agranulocytosis—two of 91 (2.2%)—was explained as a function of the stringent monitoring requirements for this drug, which allow early detection and treatment.

There is greater variability in the reference ranges for all white blood cell indices in patients with schizophrenia than in the healthy population (433). This suggests that abnormal hematological findings in patients with schizophrenia should be assessed in the context of a reference range specifically determined in patients with schizophrenia.

Gastrointestinal

The possibility of fatal intestinal dilatation, although very rare, warrants careful evaluation of persistent complaints of constipation, particularly in patients who also have vomiting and abdominal pain, distension, or tenderness (434). Acute intestinal pseudo-obstruction (Ogilvie's syndrome) has been reported in a patient taking haloperidol plus benzatropine (435).

- A 64-year-old woman started to take oral haloperidol 0.5 mg tds, and 3 days later was given intravenous benzatropine 2 mg for dystonia plus a second dose 1 hour later because she had not responded to the first dose. Her dystonia improved, but she started to develop abdominal distension and discomfort, and within the next 3–4 hours her whole abdomen had become significantly distended. Haloperidol and benzatropine were withdrawn and she was treated with hydration, nasogastric suction, a rectal tube, and frequent change of position. With this conservative therapy, her abdominal distension resolved completely in 24 hour.

Liver

When a neuroleptic drug causes jaundice it generally occurs within 2–4 weeks and has many characteristics of an allergic reaction, being accompanied by fever, rashes, and eosinophilia, although a direct toxic mechanism has also been implicated. Symptoms generally subside rapidly after withdrawal, but cholestasis may be prolonged.

Liver damage due to atypical neuroleptic drugs generally occurs within the first weeks of treatment, but the delay is highly variable, being 1–8 weeks for clozapine, 12 days to 5 months for olanzapine, and 1 day to 17 months for risperidone (436).

There is evidence of a significant hepatotoxic effect of the phenothiazines and in persons under age 50, but not over 50 (437).

Hepatotoxicity may be as frequent with piperidine and piperazine phenothiazines as with chlorpromazine, despite previous suggestions that the toxicity of these compounds is less.

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More common are minor dose-related abnormalities in liver function tests with various neuroleptic drugs.

Urinary tract

Urinary retention, incontinence, or dysuria can occasionally occur with neuroleptic drugs that have marked anticholinergic effects.

Skin

Many skin reactions have been reported with neuroleptic drugs, including urticaria, abscesses after intramuscular injection, rashes, photosensitivity or exaggerated sunburn, contact dermatitis, and melanosis or blue-gray skin discoloration. Skin rashes are usually benign. Chlorpromazine is most often implicated (incidence 5–10%).

Non-phenothiazines, such as haloperidol and loxitane, cause fewer urticarial reactions. As with any other class of drug, patients may be allergic to excipients in various tablet or capsule forms, or to preservatives, for example methylparabens in liquid dosage forms (438).

Abnormal skin pigmentation (SEDA-19, 49) is more common in women and generally occurs on the exposed parts of the body. This reaction may be due to deposition of melanin-drug complexes. It was commonly seen in the decade after the introduction of the phenothiazines, but rarely today (438).

- A 45-year-old schizophrenic woman with blue eyes and blond hair who had received a lifetime exposure of at least 1748 g of chlorpromazine had blue discoloration of the skin by age 36 (439). Chlorpromazine was withdrawn and clozapine substituted (up to a maximum of 600 mg/day). The skin pigmentation resolved over 4 years.

Complications at the site of injection of depot neuroleptic drugs, including pain, bleeding or hematoma, leakage of drug from the injection site, acute inflammatory induration, and transient nodules, have been reported (SEDA-20, 43).

Seborrheic dermatitis has been observed in patients receiving long-term neuroleptic drugs (SEDA-17, 57), and this adverse effect appears to be highly associated with drug-induced parkinsonism.

More serious types of skin reactions are rare, but angioedema, non-thrombocytopenic purpura, exfoliative dermatitis, and Stevens–Johnson syndrome have been reported.

Potentially serious skin reactions are best treated by withdrawing the offending agent and switching to a structurally unrelated neuroleptic drug. When the offending agent is a phenothiazine, non-phenothiazines such as haloperidol or molindone may be preferable to the more closely related thioxanthenes.

Musculoskeletal

Rhabdomyolysis has been described in a handicapped child without other symptoms of neuroleptic malignant syndrome (440).

- A 6-year-old boy who was taking clonazepam 2.6 mg/day, diazepam 10 mg/day, and phenobarbital 50 mg/day was given oral haloperidol (0.3 mg/day) plus biperiden (0.3 mg/day) for choreoathetosis. After haloperidol had been introduced, his mother noticed that his urine sometimes became dark brown. He had myoglobinuria (660 ng/ml; reference range below 10 ng/ml) but no renal insufficiency. Haloperidol and biperiden were withdrawn and 2 days later his urine was normal.

A marked increase in creatine kinase activity without neuroleptic malignant syndrome has been previously described (SEDA-21, 48) and, another report has further emphasized this possibility (441).

- A 19-year-old schizophrenic patient taking risperidone 6 mg/day and olanzapine 20 mg/day had a creatine kinase activity of 6940 U/l without clinical manifestations of neuroleptic malignant syndrome; when he switched to clozapine (dose not stated) the creatine kinase fell to about 300 U/l. Because he developed granulocytopenia, he was given quetiapine instead, and the creatine kinase again rose to 3942 U/l but fell after 4 days to 389 U/l without withdrawal of quetiapine.

The authors concluded that the mechanism by which creatine kinase increases is not comparable for olanzapine, quetiapine, and clozapine, and that the increase can be self-limiting.

Sexual function

The frequency and course of sexual disturbances associated with neuroleptic drugs have been studied in a prospective open study of clozapine 261 mg/day (in 75 men and 25 women, mean age 29 years) and haloperidol 16 mg/day (41 men and 12 women, mean age 26 years) (442). There were no statistically significant differences between those taking haloperidol and those taking clozapine. During 1–6 weeks of treatment with clozapine, the most frequent sexual disturbances among women were diminished sexual desire (28%) and amenorrhea (12%), while among men they were diminished sexual desire (57%), erectile dysfunction (24%), orgasmic dysfunction (23%), ejaculatory dysfunction (21%), and increased sexual desire (15%).

Neuroleptic drug-induced sexual dysfunction, including erectile and ejaculatory dysfunction and changes in libido and the quality of orgasm, appear to be reversible on withdrawal.

Male dysfunction

Although the mechanism involved in neuroleptic drug-induced male sexual dysfunction is not entirely understood, it can occur at several levels, including the cortex, hypothalamus, pituitary gland, and the gonads, involving, for example, gonadotrophins and testosterone. Another mechanism involves the sympathetic and parasympathetic nervous systems and may explain why thioridazine and other highly anticholinergic drugs are mainly responsible for male sexual dysfunction, including impotence and retrograde ejaculation (443,444).

The first report of spontaneous ejaculation associated with the therapeutic use of neuroleptic drugs was described in 1983 (445).

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One study showed a reduction in the strength of erection in men with schizophrenia, further accentuated in those who are taking neuroleptic drugs (SEDA-20, 44).

In 12 men with schizophrenia (mean age 36 years) receiving neuroleptic drugs, amantadine 100 mg/day for 6 weeks improved sexual function (446). All 12 patients, who had a sustained relationship with a female partner, had reported sexual dysfunction. Four areas of sexual function were assessed: desire, erection, ejaculation, and satisfaction; there was an improvement in all but ejaculation. Amantadine had no effect on the symptoms of schizophrenia.

Priapism

Neurotropic drug-induced priapism has been reviewed (447). It is said that neuroleptic drugs are most commonly implicated. A prior history of prolonged erections can be identified in as many as 50% of patients presenting with priapism who are using neuroleptic drugs. According to another review, the frequency of priapism with neuroleptic drugs may be increased by the fact that schizophrenia is said to be accompanied by an increase in sexual activity (448).

In one case, priapism followed the use of first risperidone and then ziprasidone (449).

- A 22-year-old African-American with chronic undifferentiated schizophrenia developed priapism after taking risperidone 4 mg bd, clonazepam 0.5 mg bd, vitamin E 400 IU bd, and a multivitamin for over 6 months. He did not respond to subcutaneous terbutaline 0.25 mg. Irrigation of the corpora with phenylephrine 200 μ resulted in detumescence; risperidone was withdrawn. A few months later he took ziprasidone 20 mg bd for 1 week, clonazepam 1 mg bd, and vitamin E 400 IU bd. The ziprasidone dosage was increased to 40 mg bd, but early the next morning he developed a firm erection with some discomfort that lasted about 2 hour and resolved when he urinated; the next morning he had a similar erection that also lasted 2 hour and resolved.

Priapism in twins suggests a hereditary predisposition (450).

- Identical twin brothers, aged 37 years, had both suffered from bipolar disorder since their early twenties and had been treated with chlorpromazine, haloperidol, lithium, and carbamazepine before developing priapism. One of them developed priapism after taking trazodone 400 mg/day, and in the 2 years after the initial episode he suffered recurrent painless erections. Initially they occurred daily and lasted 4–5 hours. During a relapse of mania at age 37, he was given oral zuclopenthixol 40 mg/day. On the tenth day he presented with priapism of 4 days duration, which persisted despite zuclopenthixol withdrawal, needle aspiration, and phenylephrine instillation, but subsided 2 weeks later with conservative management. The other twin presented with priapism of 75 hour duration and hypomania at age 31 years. He had been taking lithium and chlorpromazine for the preceding 2 years.

Priapism necessitates prompt urological consultation and sometimes even surgical intervention (443,451,452).

Female dysfunction

Female orgasm is inhibited by some central depressant and psychotropic drugs, including neuroleptic drugs, antidepressants, and anxiolytic benzodiazepines (165).

Immunologic

Hypogammaglobulinemia in a 22-year-old woman with brief psychotic disorder has been attributed to neuroleptic drug therapy (453). About 4 months after she had started to receive neuroleptic drugs, her serum concentrations of total protein had fallen to 58 g/l, with an IgG concentration of 3.49 g/l, an IgA concentration of 0.54 g/l, and an IgM concentration of 0.34 g/l.

Antiphospholipid syndrome is a disorder of recurrent arterial or venous thrombosis, thrombocytopenia, hemolytic anemia, or a positive Coombs' test, and in women recurrent idiopathic fetal loss, associated with raised concentrations of antiphospholipid antibodies. In systemic lupus erythematosus, the risk of this syndrome is about 40%, compared with a risk of 15% in the absence of antiphospholipid antibodies (454). However, only half of those with antiphospholipid antibodies have systemic lupus erythematosus, and the overall risk of the syndrome is about 30%. In patients who have antiphospholipid antibodies associated with chlorpromazine, there appears to be no increased risk of the syndrome. In contrast, in the primary antiphospholipid syndrome, the only clinical manifestations are the features of this syndrome.

- Symptomatic antiphospholipid syndrome has been described in a 42-year-old woman treated with chlorpromazine 260 mg/day (455). She presented with sudden right-sided weakness, numbness, and headache. Examination confirmed upper motor neuron signs affecting the right arm, leg, and face, with hemiplegia and hemiparesthesia. Autoantibody screening showed positive antinuclear antibodies, with an IgG titer of 50 and an IgM titer of 1600. Anticardiolipin antibody was positive with a raised IgM titer of 24 (normal less than 9). The symptoms and the serological findings resolved after withdrawal of the phenothiazine.

Drug-induced lupus erythematosus has been reviewed (456,457). Neuroleptic drugs, particularly chlorpromazine and chlorprothixene, have often been associated with this autoimmune disorder. It is recommended that several diagnostic criteria for this condition should be met: (1) exposure to a drug suspected to cause lupus erythematosus; (2) no previous history of the condition; (3) detection of positive antinuclear antibodies; and (4) rapid improvement and a gradual fall in the antinuclear antibodies and other serological findings on drug withdrawal. Rare disorders of connective tissue resembling systemic lupus erythematosus have been reported with chlorpromazine, perphenazine, and chlorprothixene (458).

Body temperature

Neuroleptic drugs interfere with the temperature regulatory function of the hypothalamus and peripherally with the sweating mechanism, resulting in poikilothermy. This can result in either hyperthermia or hypothermia, depending on the environmental temperature.

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Hyperthermia

A series of cases has been reported in which heat stroke occurred during hot weather, probably due to impaired heat adaptation in patients taking benzatropine and ethylbenzatropine (459); this can occur with other anticholinergic and neuroleptic drugs as well.

Hypothermia

Reduced body temperature has been observed in a study of 14 drug-free and 7 patients with schizophrenia taking different neuroleptic drugs (460). The temperature fell by about 0.36°C at 24 hours after the drug-free subjects started to take neuroleptic drugs.

Hypothermia, defined as a body temperature lower than 35°C, has been observed in individual cases.

- A 73-year-old woman with diabetes mellitus and schizophrenia was given haloperidol 8 mg/day instead of zuclopenthixol; she also took levomepromazine 75 mg at night; 10 days later she was found unconscious with a rectal temperature of 31.5°C (461). A few weeks later, she had two further episodes, first with olanzapine 10 mg/day (rectal temperature 31.7°C) and then with thioridazine 40 mg/day (rectal temperature 34°C). She was therefore given dixyrazine 150 mg/day and alimemazine 20 mg at night, and had no more episodes of hypothermia.
- An 83-year-old woman developed a rectal temperature of 33.1°C 3 weeks after starting to take olanzapine 5 mg/day (462).
- A 68-year-old schizophrenic woman with type 1 diabetes mellitus developed a body temperature of 33.4°C 1 week after starting to take quetiapine 100 mg bd (462).

In the two last cases, the most common causes of hypothermia, such as hypothyroidism, infection, and cold exposure, were ruled out.

Death

The role of neuroleptic drugs in sudden death is controversial (SEDA-18, 47) (SEDA-20, 26) (SEDA-20, 36). Cardiac dysrhythmias may be involved, but there may also be multiple non-cardiac causes, including asphyxia, convulsions, or hyperpyrexia.

Long-Term Effects

Drug withdrawal

Various somatic complaints have been reported in patients in whom neuroleptic drugs are abruptly withdrawn (SEDA-20, 44). The incidence of these complaints varies widely in different reports, from 0 to 75%. Common complaints include headache, vomiting, nausea, diarrhea, insomnia, abdominal pain, rhinorrhea, and muscle aches. On rare occasions, the symptoms resemble those of benzodiazepine withdrawal (appetite change, dizziness, tremulousness, numbness, nightmares, a bad taste in the mouth, fever, sweating, vertigo, tachycardia, and anxiety), but it is possible that in some of the reported cases there was actually benzodiazepine withdrawal. Some of these symptoms may also have been linked to the simultaneous withdrawal of anticholinergic drugs (SED-11, 113) (463). Parkinsonism, not explained by withdrawal of anticholinergic drugs, has also been reported as an unusual withdrawal effect of neuroleptic drugs (464).

Worsening of psychotic symptoms and/or dyskinetic movements can occur when dosages are lowered or a neuroleptic drug is withdrawn. A functional increase in mesolimbic and striatal dopaminergic sensitivity has been suggested as an explanation (465). Psychotic relapse is rarely seen in the first 2 weeks after withdrawal, but physical withdrawal symptoms generally begin within 48 hours of the last dose (SEDA-14, 54).

Withdrawal emergent syndrome has been described in children (466,467) and consists of nausea, vomiting, ataxia, and choreiform dyskinesia primarily affecting the extremities, trunk, and head after sudden withdrawal of neuroleptic drugs (468). In one study, there were withdrawal symptoms in 51% of children, twice as many being affected by the withdrawal of low-dose, high-potency compounds compared with other drugs. Symptoms usually appear within a few days to 2 weeks after drug withdrawal; spontaneous remission is likely within the next 8–12 weeks.

The Omnibus Budget Reconciliation Act of 1987 (OBRA '87) regulations (www.elderlibrary.org) specify when neuroleptic drugs can and cannot be used to treat behavioral disturbances in nursing home residents in the USA. Accordingly, neuroleptic drugs can legally be used in patients with delirium or dementia only if there are psychotic or agitated features that present a danger to the patient or others. Preventable causes of agitation must be excluded and the nature and frequency of these behaviors must be documented. Non-dangerous agitation, uncooperativeness, wandering, restlessness, insomnia, and impaired memory are insufficient in isolation to justify the use of neuroleptic drugs. With this in mind, the effects of withdrawing haloperidol, thioridazine, and lorazepam have been examined in a double-blind, crossover study in 58 nursing home residents (43 women and 15 men, mean age 86 years), half of whom continued to take the psychotropic drugs that had been prescribed, while the other half were tapered to placebo (469). After 6 weeks, the patients were tapered to the reverse schedule and took it for another 6 weeks. There were no differences between drug and placebo in functioning, adverse effects, and global impression. Cognitive functioning improved during placebo. The authors concluded that gradual dosage reductions of psychoactive medications must be attempted, unless clinically contraindicated, when trying to withdraw these drugs. Similar conclusions have been reached in other studies (SEDA-22, 54).

There has been a randomized controlled study of the factors that affect neuroleptic drug withdrawal or dosage reduction among people with learning disabilities, who were being treated for behavioral problems with typical neuroleptic drugs (470). Of 36 patients, 12 completed full withdrawal and a further 7 achieved and maintained at least a 50% reduction. Drug withdrawal or dosage reduction was not associated with increased maladaptive behavior. This result reinforces concerns that neuroleptic drug treatment for maladaptive behavior reduction is often ineffective and inappropriate.

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Mutagenicity

There was an increase in markers of genotoxicity in patients receiving long-term neuroleptic drugs in combination with other psychotropic drugs ($n = 36$) compared with controls ($n = 36$) (471). In another study there was an association between the frequency of chromosomal aberrations in lymphocytes and the probability of tumor induction (472).

Tumorigenicity

There is concern that neuroleptic drugs may increase the risk of breast cancer because of raised prolactin concentrations. For a long time, findings did not confirm this association (377), but a Danish cohort study of 6152 patients showed a slight increase in the risk of breast cancer among schizophrenic women (378).

Second-Generation Effects

Fertility

The effects of neuroleptic drugs on fertility are not clear; many of the data are controversial, often being based on animal studies, for example reduction in male rat copulation by chlorpromazine. However, oligospermia, polyspermia, necrospermia, and reduced sperm motility have been reported with various phenothiazines and butyrophenones; these are likely to improve after withdrawal (473). Furthermore, fertility may be impaired by neuroleptic drugs, since they increase prolactin concentrations and can cause amenorrhea (4).

Teratogenicity

There have been reviews of neuroleptic drug use during pregnancy (474–478).

All neuroleptic drugs cross the placenta and reach the fetus in potentially significant amounts. However, most large-scale controlled studies have shown that they can be used safely during pregnancy (141). Nevertheless, there have been isolated case reports of malformations (SEDA-7, 68) (479).

Should a neuroleptic drug be required during pregnancy, a drug such as chlorpromazine or trifluoperazine would be preferred, as there is considerably more worldwide experience with these drugs than with newer drugs (141). However, clozapine caused no serious complications or developmental abnormalities during pregnancy in two cases (480).

Although studies have failed to identify an increased rate of malformations with haloperidol, isolated cases have been reported (481) (SEDA-22, 5) (SEDA-23, 57) (477,478).

Phocomelia associated with neuroleptic drugs has been reported (482).

- A 38-year-old woman was admitted to hospital in the third week after conception and acute schizophrenia was diagnosed. She was given oral haloperidol 1.5 mg at 12-hourly intervals. In the fourth week after conception, intramuscular depot fluphenazine 12.5 was added every 15 days. At 8 weeks of gestation, after the pregnancy had been diagnosed, haloperidol and fluphenazine were withdrawn and trifluoperazine 5 mg was started and continued until 8 weeks before the baby was born. The child was born with phocomelia of the left arm, with an extremely short humerus and an absent forearm.

Fetotoxicity

A variety of pharmacological effects can occur in the infant after birth, particularly when the mother has received these agents in the weeks before delivery. These include postnatal depression and acute dystonic reactions (which may interfere with normal delivery). Hypotonia can persist for months (483) and may respond to diphenhydramine 5 mg/kg/day. Severe rhinorrhea and respiratory distress in a neonate exposed to fluphenazine hydrochloride prenatally has been reported (484). Neonatal jaundice, hyperbilirubinemia, and melanin deposits in the eyes have occurred when neuroleptic drugs were given during the last trimester or longer during pregnancy.

Lactation

Neuroleptic drugs appear in breast milk in very low concentrations, related to maternal dosage. Typical regimens of neuroleptic drugs yield low or negligible concentrations (141,485). In one study, breast-fed infants ingested up to 3% of the maternal daily dose, and small amounts of the drugs were detected in their plasma and urine. In addition, three breast-fed infants had a fall in developmental scores from the first to the second assessment at 12–18 months (486). Until these issues are further clarified, it would be best to avoid breast-feeding by mothers who are receiving neuroleptic drugs.

Susceptibility Factors

Age

Children

Neuroleptic drugs have been prescribed for children in the treatment of psychotic disorders, Tourette's syndrome, attention deficit disorder, hyperactivity, behavioral and psychiatric complications of mental retardation, and pervasive developmental disorders, for example infantile autism (487,488).

Untoward effects of neuroleptic drugs in children are said to be similar to those seen in adults (489).

However, adverse effects of neuroleptic drugs in children can be unpredictable and a suggestion that they can cause sudden infant death remains hypothetical (466). Significant weight gain has been reported in almost 100% of neuroleptic drug-treated children, and there seems to be a relatively high incidence of extrapyramidal adverse effects (467). Since there is little information regarding the pharmacokinetics and pharmacodynamics of neuroleptic drugs in children, careful supervision of treatment is vital; the use of high dosages is inadvisable.

Their use in children and adolescents has been extensively reviewed (490–492). Typical neuroleptic drugs have been assessed in three randomized, double-blind, placebo-controlled studies in 122 patients and atypical drugs in five (one clozapine, $n = 21$; two amisulpride,

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$n = 36$; and two tiapride, $n = 59$). The studies were of short durations, 4–10 weeks. Extrapyramidal signs occurred in 25–73% of those treated with the typical neuroleptic drugs.

Elderly people

There is wide individual variation in the extent to which older people tolerate these drugs, and adverse effects, such as postural hypotension and anticholinergic effects, can be more problematic (493). Caution with neuroleptic drug use in old people is further warranted because several of these drugs are metabolized by CYP2D6, which is inhibited by many commonly used drugs (SEDA-20, 44).

Neuroleptic drugs have often been associated with increased rates of falls (SEDA-19, 40) (494).

Older people are supposedly susceptible to delirium caused by centrally acting anticholinergic drugs. This can take the form of anxiety, agitation, or frank hypomania. Such difficulties are more likely if the patient is also taking neuroleptic drugs (most of which also have a weak anticholinergic effect) or anticholinergic antiparkinsonian drugs.

In a study that was claimed to be the first published placebo-controlled dose comparison of neuroleptic drugs used to treat psychoses and disruptive behavior in dementia, haloperidol 2–3 mg/day was compared with 0.50–0.75 mg/day in 71 outpatients with Alzheimer's disease (495). After 12 weeks, there was a favorable therapeutic effect of haloperidol 2–3 mg/day, although 25% of the patients developed moderate to severe extrapyramidal signs. No patient developed tardive dyskinesia, but neuroleptic drug exposure needs to be considerably longer for that to occur.

Drug Administration

Drug formulations

Depot formulations

Guidelines for depot neuroleptic drug treatment in schizophrenia were developed during a consensus conference held in 1995 in Siena in Italy, since when a thorough review devoted to depot neuroleptic drugs has been published (496). The authors reported that depot neuroleptic drugs are associated with significantly fewer relapses and rehospitalizations than oral neuroleptic drugs. The potential disadvantages of depot drugs include patient reluctance to accept injections or a sense of being too subject to control. In addition, clinicians, and sometimes patients, fear that if adverse effects occur they will be more difficult to manage because of an inability to withdraw treatment rapidly. However, these formulations are not associated with a significantly higher incidence of adverse effects than oral drugs. Some patients have pain or discomfort at the injection site. In some cases the injection site becomes edematous and tender or pruritic, with a palpable mass for up to 3 months. The recommendations are to rotate the injection site, to limit the volume of the injection, and to assure deep intramuscular injection.

Drug administration route

Intramuscular injection of neuroleptic drugs in depot formulations is important for compliance in outpatients with schizophrenia, and the benefits and risks have been emphasized (SEDA-23, 73). In a retrospective study in a tertiary center in Riyadh, of 69 patients (mean age 35 years; mean duration of illness 11 years; 38 men) who had been given depot neuroleptic drugs during 1991–2000, only 24 were still receiving their depot injections regularly in that clinic (497). The authors suggested that negative attitudes of families and society toward mental illness and interference with psychiatric treatment by traditional and faith healers could have accounted for this lack of compliance. Although the use of depot neuroleptic drugs is advocated as maintenance treatment for patients with bipolar disorders, no such patients were identified. The authors pointed out that in spite of the fact that patients had been clinically stable, 7% had been receiving their depot neuroleptic drugs for more than 8 years, with no attempts to reduce the dosage or to increase the interval of administration.

Drug overdose

Suicide is the leading cause of premature death among patients with schizophrenia. The lifetime incidence of completed suicide among patients with schizophrenia is about 10% (498) and 18–55% of patients with schizophrenia make suicide attempts (499), sometimes with neuroleptic drugs. In autopsies and toxicological analyses in Vienna from 1991 to 1997, 97 neuroleptic compounds were detected in 85 fatal intoxications (500). Of these, 17 fatal poisonings were attributed to a single compound, 3 were due to two neuroleptic drugs, 57 to a combination of one neuroleptic drug with other drugs, 7 to two neuroleptic drugs with other drugs, and in one case three neuroleptic drugs combined with other drugs. Relating the number of deaths by a drug to the number of Defined Daily Doses, a fatality index was estimated. At the top of the rating were levopromazine, prothipendyl, and chlorprothixene, which had f-values significantly higher than the mean. However, since the estimates were not adjusted for age or condition, these data should be taken with caution.

In another study there were large differences in fatality from overdosage between different neuroleptic drugs (501). Pimozide had the lowest fatality index (the number of deaths divided by the number of prescriptions) and loxapine the highest.

Although mortality is generally low and infrequently associated with residual impairment (SED-13, 129), important exceptions occur when there is co-ingestion with alcohol, tricyclic antidepressants, or antiparkinsonian agents. In acute overdosage of neuroleptic drugs alone, the most serious complications include shock, seizures, and cardiac dysrhythmias. These can be more problematic when the neuroleptic drugs are of low potency, for example thioridazine and chlorpromazine, but taken in high dosages.

Acute extrapyramidal reactions occur more often after ingestion of high-potency drugs, such as haloperidol and fluphenazine; these respond to parenteral benzatropine, but anticholinergic drugs should be used judiciously, so as

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not to worsen peripheral or central autonomic toxicity. Other serious, but less frequent, complications include paralytic ileus and hypothermia. Acute renal insufficiency has been very rarely reported, but is apparently reversible and can occur secondary to severe hypotension or other causes after acute ingestion (502).

Of 524 inquiries received by the National Poisons Information Service concerning new neuroleptic drugs over 9 months, only 45 cases involved overdose with a single agent (olanzapine, $n = 10$; clozapine, $n = 8$; risperidone, $n = 10$; sulpiride, $n = 16$) (503). There were no deaths or cases of convulsions. Cardiac dysrhythmias occurred only with sulpiride. Symptoms were most marked with clozapine: most patients had agitation, dystonia, central nervous system depression, and tachycardia. Most of the patients who had taken risperidone were asymptomatic.

Neuroleptic drug poisoning in 86 children has been retrospectively studied in two pediatric hospitals in the USA (1987–1997), with about 9000 and 11 000 annual admissions (504). Most (70%) occurred in children under 6 years of age; over two-thirds of the cases (78%) were unintentional. The owner of the medication, when identified (85% of cases), was the grandmother (22%), another family member (21%), the patient (13%), or a non-family caregiver (8%); the most common places where ingestion occurred were the patient's home (64%) or a relative's home (22%). There was a depressed level of consciousness in 91% and a dystonic reaction in 51%; there were no deaths.

- A 46-year-old woman took amisulpride (12 g), alprazolam (40 mg), and sertraline (1 g) with suicidal intent, and 3 hours later was still unconscious and was intubated (505). Her body temperature rose from 37.1°C on admission to 38°C soon after. She was discharged on the third day.
- A 50-year-old man who took an overdose of ziprasidone 3120 mg (52 tablets) had no serious effects; he was a little drowsy and his speech was slightly slurred (506). Ziprasidone blood concentrations were not measured.

Fatal intoxication has been reported with melperone (507).

- A 36-year-old woman was found dead in her flat about 2 days after her last contact with one of her relatives. Besides melperone, she was known to take diazepam and carbamazepine. The police found four empty containers of 100 melperone tablets (100 mg per tablet). Post-mortem blood concentration analysis showed melperone, diazepam, nordiazepam, and carbamazepine; the melperone concentration in venous blood was very high (17.1 μg/ml).

Drug–Drug Interactions

Adrenoceptor agonists

Neuroleptic drugs can reduce or block the pressor effects of alpha-adrenoceptor agonists. When using drugs with both alpha- and beta-adrenoceptor activity, neuroleptic drug blockade of alpha-adrenoceptors can lead to unopposed beta predominance, resulting in severe hypotension (508).

A neuroleptic malignant-like syndrome occurred when norephedrine was combined with neuroleptic drugs (338).

Alcohol

Alcohol-induced CNS and respiratory depression is enhanced by neuroleptic drugs (509), but enhancement can be slight if both are used in reasonable amounts (510).

Alpha-adrenoceptor antagonists

Neuroleptic drugs can intensify the effects of alpha-adrenoceptor antagonists, for example phentolamine, causing severe hypotension (467).

Amfebutamone (bupropion)

Bupropion has about the same seizure potential as tricyclic antidepressants (SEDA-8, 30), but the manufacturers noted an increased risk of seizures in patients taking over 600 mg/day in combination with lithium or neuroleptic drugs (SEDA-10, 20).

Antacids

Antacids containing aluminium and magnesium reduce the gastrointestinal absorption of chlorpromazine and other phenothiazines by forming complexes (511). The clinical significance of this is unknown.

Antihistamines

Drugs with a CNS depressant effect (antihistamines, hypnotics, sedatives, narcotic analgesics, alcohol, etc.) will have an increase in effect caused by interaction with neuroleptic drugs.

Benzatropine

Benzatropine and ethylbenzatropine are particularly likely to interact additively with other drugs with both anticholinergic and antihistaminic activity, such as neuroleptic drugs; complications such as hyperpyrexia, coma, and toxic psychosis have been reported several times when such combinations were used (512–514).

Benzodiazepines

Neuroleptic drugs can potentiate the sedative effects of benzodiazepines pharmacodynamically.

In a brief review, emphasis has been placed on pharmacokinetic interactions between neuroleptic drugs and benzodiazepines, as much information on their metabolic pathways is emerging (515). Thus, CYP3A4, which plays a dominant role in the metabolism of benzodiazepines, also contributes to the metabolism of clozapine, haloperidol, and quetiapine, and plasma neuroleptic drug concentrations can rise.

Intramuscular levomepromazine in combination with an intravenous benzodiazepine has been said to increase the risk of airways obstruction, on the basis of five cases of respiratory impairment in patients who received injections of psychotropic drugs (516). The doses of levomepromazine were higher in the five cases that had accompanying airways obstruction than in another 95 patients who did not.

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Beta-adrenoceptor antagonists

The cardiac effects of neuroleptic drugs can be potentiated by propranolol (517).

In general, concurrent use of neuroleptic and antihypertensive drugs merits close patient monitoring (518).

Bromocriptine

The dopamine-blocking activity of neuroleptic drugs can antagonize the effects of dopamine receptor agonists, such as bromocriptine. Conversely, bromocriptine has been reported to cause exacerbation of schizophrenic symptoms (519).

Caffeine

Neuroleptic drugs can precipitate from solution when mixed with coffee or tea (520), but the clinical significance of this physicochemical interaction is unknown (521).

Caffeine can alter blood concentrations of neuroleptic drugs (SEDA-5, 6).

Excess caffeine can stimulate the CNS, which can worsen psychosis and thus interfere with the effects of neuroleptic drugs (522).

Cannabis

In 10 patients, schizophrenia was acutely worsened after cannabis use, despite verified adequate depot treatment with neuroleptic drugs (523).

Carbamazepine

Plasma concentrations of neuroleptic drugs can be lowered by carbamazepine, and patients should be monitored for reduced efficacy (524).

- A 54-year-old man who had been taking neuroleptic drugs for about 30 years developed neuroleptic malignant syndrome within 3 days of taking add-on carbamazepine (400 mg/day) (525).

This syndrome does not appear to have been described with carbamazepine alone, and it was speculated that its pathogenesis could involve rebound cholinergic activity after a reduction in plasma neuroleptic drug concentrations by carbamazepine.

Cocaine

In a retrospective study of 116 patients taking neuroleptic drugs, 42% of cocaine users versus 14% of non-users developed dystonic reactions (526). This suggests that the use of cocaine may be a major risk factor for acute dystonic reactions secondary to the use of neuroleptic drugs.

This has been confirmed in a 2-year study on the island of Curaçao in the Netherlands Antilles, where cocaine and cannabis are often abused (168). The sample consisted of 29 men with neuroleptic-induced acute dystonias aged 17–45 years who had received high potency neuroleptic drugs in the month before admission; 9 were cocaine users and 20 non-users. Cocaine use was a major risk factor for neuroleptic-induced acute dystonia and should be added to the list of well-known risk factors such as male sex, younger age, neuroleptic dose and potency, and a history of neuroleptic-induced acute dystonias. The authors suggested that high-risk cocaine-using psychiatric patients who start to take neuroleptic drugs should be provided with a prophylactic anticholinergic drug to prevent neuroleptic drug-induced acute dystonias.

Corticosteroids

By reducing gastrointestinal motility, neuroleptic drugs enhance the absorption of corticosteroids (509).

Digoxin

By reducing gastrointestinal motility, neuroleptic drugs increase the systemic availability of digoxin and other inotropic drugs and thereby increase the potential for toxicity (510).

Guanethidine

Phenothiazines may inhibit the hypotensive action of guanethidine (510). This antagonism does not occur with molindone (508).

Hypoglycemic drugs

Because phenothiazines affect carbohydrate metabolism, they can interfere with the control of blood glucose in diabetes mellitus (387,509).

Levodopa

Levodopa and neuroleptic drugs can interfere with the effects of each other at dopamine receptors; the patient should be monitored for deterioration in both parkinsonism and mental state. If an antiemetic is required in a patient taking levodopa, one that does not affect central dopamine receptors should be chosen.

Lithium

Neuroleptic drugs are often used in mood stabilizer combinations. However, there have been few controlled studies of the use of such combinations, and interactions are potentially dangerous. The advantages and disadvantages of all currently used mood stabilizer combinations have been extensively reviewed (527). Some effects are well known: neurotoxicity, hypotension, somnambulistic-like events, and cardiac and respiratory arrest associated with the combination of lithium and traditional neuroleptic drugs considered as a first-line treatment for classic euphoric mania with psychotic features.

Several cases of neurotoxicity have been reported when lithium was combined with thioridazine, and patients should be carefully monitored (528–530).

Occasionally, long-term use of lithium is associated with cogwheel rigidity and a parkinsonian tremor. More often than not, concurrent or past treatment with a neuroleptic drug is involved. Neuroleptic malignant syndrome has also been reported in patients taking lithium and a neuroleptic drug, such as amoxapine (531), clozapine (532), haloperidol (533), olanzapine, (534), and risperidone (535). However, a causal interaction has not been established (536), and it should also be remembered that lithium toxicity itself can cause neuroleptic malignant syndrome (537).

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Lysergic acid diethylamide

Phenothiazines and butyrophenones can counteract the psychoactive effects of lysergic acid diethylamide (LSD) (538).

Metrizamide

The role of chlorpromazine in facilitating metrizamide-induced convulsions has been confirmed in animal studies (539); phenothiazines should be withdrawn at least 48 hours before intrathecal use of metrizamide.

Monoamine oxidase inhibitors

There can be additive hypotensive effects when monoamine oxidase inhibitors are combined with neuroleptic drugs.

Four healthy volunteers taking moclobemide (600 mg/day for 9 days) had reduced clearance of dextromethorphan, a marker of hepatic CYP2D6 activity (540). These findings suggest that at the higher end of its therapeutic dosage range, moclobemide may inhibit the metabolism of drugs that are substrates for CYP2D6, for example neuroleptic drugs and tricyclic antidepressants (SEDA-22, 14).

Narcotic analgesics

CNS and respiratory depression due to narcotic analgesics can be enhanced by neuroleptic drugs (509).

Oral contraceptives

Estrogen-containing formulations can further promote neuroleptic drug-induced prolactin stimulation (509).

Neuroleptic malignant syndrome occurred in a woman taking haloperidol and thioridazine 12 hours after she started to take an oral contraceptive. The authors suggested that this could have been a pharmacodynamic interaction involving dopaminergic neurotransmission (541).

Phenytoin

Chlorpromazine, and in some cases other phenothiazines, has been reported to increase plasma phenytoin concentrations (542–545), to reduce plasma phenytoin concentrations (543–547), or to have no effect (544). In one case co-administration of thioridazine caused phenytoin toxicity (548).

Phenytoin induces hepatic microsomal drug-metabolizing enzymes and thus reduces concentrations of haloperidol (549,550), thioridazine (550), and tiotixene (551). In two patients phenytoin reduced plasma clozapine concentrations and worsened psychosis (552).

Piperazine

High doses of piperazine can enhance the adverse effects of chlorpromazine and other phenothiazines (553).

Quinidine

Concurrent administration of quinidine with neuroleptic drugs, particularly thioridazine, can cause myocardial depression (508).

Sedatives and hypnotics

Neuroleptic drugs increase sedative- and hypnotic-induced sleep time and respiratory depression. Lower dosages of barbiturates or other hypnotics should be used, at least initially, in patients receiving neuroleptic drugs (508).

Sevoflurane

- A 19-year-old taking cyamemazine for schizophrenia had severe dystonia during inhalation of sevoflurane (554). One minute after taking four or five maximum breaths in a closed system filled with 8% sevoflurane in a 50% nitrous oxide/oxygen mixture, the patient being unconscious, torticollic posturing began to develop and the stiffness rapidly extended to the left trapezius and scalenus muscles. This was followed by severe rotation of the head, trismus, and opisthotonos. Muscle spasm resolved with an injection of atracurium 30 mg.

An interaction of sevoflurane with cyamemazine was suggested as a possible explanation, without precluding a role of nitrous oxide.

Spiramycin

Acute dystonia occurred during spiramycin therapy in a patient who was being treated with neuroleptic drugs (323).

SSRIs

Paroxetine and fluoxetine are potent inhibitors of CYP2D6, and can therefore interact with neuroleptic drugs that are metabolized by this enzyme.

- Urinary retention and severe constipation occurred in a patient who started to take sertraline when already taking haloperidol and clonazepam (555). After a week, she discontinued sertraline and her symptoms disappeared in a few days.

Three of fourteen adults with Gilles de la Tourette syndrome had acute severe drug-induced parkinsonism when neuroleptic drugs and SSRIs were used together (556). There were no adverse reactions in almost 75 children receiving similar treatment. The authors suggested that age-related changes in dopamine neurotransmitter systems could confer vulnerability. On the other hand, SSRIs themselves can cause parkinsonism and also inhibit P450 enzymes, leading to increases in plasma concentrations of neuroleptic drugs during combined treatment (SEDA-20, 50) (SEDA-21, 51) (SEDA-22, 55). Surprisingly, in a double-blind, randomized, placebo-controlled study, there were no significant differences in plasma haloperidol concentrations when sertraline ($n = 18$) or placebo ($n = 18$) were added at 2, 4, 6, and 8 weeks (557).

Thiazide diuretics

Combined use of neuroleptic drugs and thiazide diuretics has rarely resulted in severe hypotension (508).

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Tricyclic antidepressants

Various neuroleptic drugs inhibit the metabolism of imipramine, nortriptyline, and amitriptyline (SED-11, 114) (558,559).

Valproate

The combination of valproate and traditional neuroleptic drugs, a first-line treatment for mixed or rapid-cycling episodes or dysphoric mania with psychotic features, is associated with altered mental status and electroencephalographic abnormalities (527).

Smoking

Smoking, common in schizophrenics (SEDA-20, 44), has important effects on plasma concentrations of neuroleptic drugs.

Interference with Diagnostic Tests

Pregnancy testing

Phenothiazines can cause a false-positive pregnancy test, but only with the virtually obsolete Ascheim–Zondek animal test method (SED-11, 115).

Urinary ketones

Phenothiazines can cause increased urinary ketones (ferric chloride test) (SED-11, 115).

Urinary steroids

Phenothiazines can interfere with the measurement of urinary steroids (colorimetry) or oxosteroids (Porter–Silber test) (SED-11, 115).

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Neuromuscular blocking drugs

See also Individual agents

General Information

There are two broad classes of neuromuscular blocking drugs: non-depolarizing agents, of which the prototype is curare (for example, d-tubocurarine, atracurium, metocurine, mivacurium, pancuronium, rocuronium, vecuronium) and depolarizing blockers, such as suxamethonium. This monograph is largely concerned with the former; suxamethonium is the subject of a separate monograph.

Non-depolarizing neuromuscular blocking agents compete with acetylcholine for receptors at the neuromuscular junction and clinical relaxation begins when 80–85% of the receptors on the motor end-plate are blocked. They do not produce depolarization themselves and, by blocking access to the receptors, prevent the normal acetylcholine-induced depolarization. Flaccid paralysis ensues. Their action terminates when acetylcholine again gains access to the receptors, due to diffusion of the relaxant molecules away from the neuromuscular junction. This may be hastened by greatly increasing the number of acetylcholine molecules at the motor end-plate by giving an anticholinesterase such as neostigmine. In contrast, the depolarizing blockers first depolarize the motor end-plate and then prevent further depolarization.

Combining different non-depolarizing neuromuscular blocking agents can result in additive or synergistic effects. When pancuronium is given together with D-tubocurarine or metocurine, the resulting block is greater than would be expected if the effects were purely additive. This potentiation is not seen with the metocurine D-tubocurarine combination (1). Synergism resulting from such combinations is thought to be a postsynaptic effect (2). When different non-depolarizing agents are given consecutively, the neuromuscular blocking action of the second may be considerably modified by the first; the action of vecuronium, for example, lasts longer than expected if pancuronium has been given first (SEDA-11, 124) (3). Caution should therefore be exercised when giving a small dose of a normally short-acting non-depolarizer near the end of an operation when another long-acting agent has been given earlier. The resulting block can be greater than expected and last much longer than desired. Reversal with anticholinesterases can be difficult at the end of surgery if the block is still greater than 90%.

Specialized accounts of adverse effects and interactions in this field are available (4–7), including a review of the older literature (8).

Organs and Systems

Ear, nose, throat

Endotracheal intubation is less traumatic when it is facilitated by a muscle relaxant. Vocal cord hematoma after intubation occurred in six of 36 patients when only fentanyl plus propofol was used, compared with one of 37 when atracurium was added (9).

Nervous system

Drug accumulation will result in paralysis lasting from hours to days. Occasionally, however, paralysis can persist for weeks or even months because of relaxant-associated myopathy (10). Muscle weakness, causing difficulties in the subsequent weaning of such patients from artificial ventilation, has often been described (11–15). This condition has been observed most often after concomitant administration of muscle relaxants and high-dose glucocorticoids, typically in patients with exacerbated asthma requiring mechanical ventilation (16–21). It is not known how these factors combine to produce myopathy; myopathic changes can also occur after either high-dose glucocorticoid therapy or long-term muscle relaxant administration alone. Serial electrophysiological testing, and eventually muscle biopsy, is necessary to diagnose myopathy accurately and to avoid useless trials of weaning the patient from the ventilator. Within some weeks, muscle weakness will resolve sufficiently to allow successful weaning, but extensive rehabilitative measures are required for several months until the patient is independent. In view of the multitude of potential mechanisms of muscle weakness in critically ill patients, it is advisable always to monitor neuromuscular function and to avoid complete paralysis for any length of time in intensive care patients who are treated with muscle relaxants.

Musculoskeletal

Several authors have described heterotopic ossification or myositis ossificans after long-term administration of neuromuscular blocking agents to ICU patients (22–25). However, the causative role of muscle relaxants in the development of this phenomenon has been questioned (26), because of the observation that heterotopic ossification also occurred in critically ill patients not treated with such agents (27). It was suggested that prolonged immobilization is an important factor in the pathogenesis of heterotopic ossification, and that both deep sedation and neuromuscular blockade, by producing complete immobilization, might contribute to the pathophysiology of this severe complication in critical illness, which may require prolonged rehabilitation and surgical removal of ectopic

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bone to allow the patient to be ambulatory and self-sufficient.

Residual paralysis

Residual paralysis after the use of long-acting muscle relaxants, such as pancuronium, is not uncommon and can result in significant pulmonary complications (28). Many anesthetists have assumed that this was less of a problem with agents of intermediate duration. However, a surprisingly high incidence of residual neuromuscular impairment has been reported after a single intubating dose of muscle relaxants of intermediate duration as well (29). Two hours after either rocuronium, vecuronium, or atracurium, the train-of-four ratio was still below 0.7 in 10% of patients and below 0.9 in 37%, which was not reliably detected by clinical evaluation (head lift, tongue depressor test) or qualitative measurements (repetitive nerve stimulation with tactile evaluation of fade). Similar results have been reported by others (30–33). Pharyngeal dysfunction with a risk of aspiration has been observed in partially paralysed awake volunteers at train-of-four ratios below 0.9 (34–35). Therefore, patients with a train-of-four ratio below 0.9 at the end of the operation should receive a cholinesterase inhibitor, such as neostigmine, in order to reduce the impact of residual paralysis. This obviously implies that quantitative monitoring of neuromuscular transmission should be used routinely. Only if this is not possible should a cholinesterase inhibitor be given blindly. This represents a change in our opinion: we had previously stated that anticholinesterase drugs should be used to reverse residual neuromuscular block detected by monitoring of neuromuscular transmission or producing clinical symptoms (SEDA-24, 157). Now we acknowledge that a reversal agent is justified, even in asymptomatic patients, because residual dysfunction of certain muscle groups may still be present. For the time being, there is nothing to support the routine use of an anticholinesterase drug if spontaneous recovery with a train-of-four ratio of 0.9 or above can be demonstrated. We should like to stress that attempts to reverse intense neuromuscular blockade must be avoided. Therefore, some evidence of recovery of neuromuscular transmission (for example spontaneous ventilation, voluntary movements, twitch response to nerve stimulation) should be observed before any anticholinesterase is given. In addition, it should be mentioned that large doses of cholinesterase inhibitors can cause deterioration rather than improvement of neuromuscular function (36,37). It is unnecessary to use more than 2.5 mg of neostigmine or equivalent (38). Neostigmine 1.25 mg or equivalent can be as effective (39) and is associated with a reduced incidence of postoperative nausea and vomiting (40).

Immunologic

Hypersensitivity reactions can occur with all neuromuscular blocking agents, including the newer agents (41–43). Allergic reactions during anesthesia have been reviewed (44).

Frequency

The incidence of life-threatening anaphylactic or anaphylactoid reactions occurring during anesthesia is variably reported as being between one in 1000 and one in 10 000 anesthetics (45,46), and in one survey was one in 6500 (47). The frequency quoted depends on the criteria used. An epidemiological study (48) has suggested that the incidence is somewhat greater than one in 5000 anesthetics. The mortality from such serious reactions is reported to be in the range of 3.4–6% (46–48). Minor systemic reactions attributable to histamine release probably occur in more than 1% of anesthesia (49). Neuromuscular blocking drugs are the triggering agents in 50% or more of these reactions (50–52), and of them D-tubocurarine is the most potent histamine liberator. During the last two decades, however, several large series of patients have been investigated, and the data suggest that suxamethonium is the relaxant most likely to produce life-threatening reactions, if allowances are made for the frequency of usage of the different agents (SEDA-17, 12) (48,50,52–56). Pancuronium has repeatedly been shown to be the relaxant least often associated with anaphylactoid reactions major or minor.

The incidence of allergic reactions to several muscle relaxants has been assessed in relation to the number of vials sold in France (57). In line with a previous publication (58), the proportion of reported reactions to rocuronium was higher than its corresponding market share. Based on that, the authors suggested classifying the risk of allergic reactions to neuromuscular blocking agents as high (suxamethonium, rocuronium), intermediate (pancuronium, vecuronium, mivacurium), and low (atracurium, cisatracurium). This classification is based on the assumption that the ratio of used/sold vials is similar for each agent, which may or may not be true. The authors themselves insisted that they did not recommend one muscle relaxant over another on the basis of their allergic potential (59). As highlighted before (SEDA-26, 150), there are significant methodological and statistical problems when such rare events are compared. What we need is an international network of clinics specialized in investigating patients after suspected intraoperative allergic reactions, and the French GERAP centers are an excellent example of this.

Mechanisms

Much controversy still surrounds the issue of the possible mechanisms by which a neuromuscular blocking agent produces the clinical picture of an anaphylactoid reaction, but new insight into the matter has been gathered (60). In most cases (that is the mechanism is a Type I hypersensitivity reaction) (50,52,56,61,62), even though the frequent lack of previous exposure to relaxants seems to exclude this. Direct histamine release and several other mechanisms have also been postulated (63,64). Non-specific histamine release probably is dose dependent (60). Drug-specific IgE antibodies to suxamethonium and other neuromuscular blocking agents have been demonstrated (52,65,66). It has been hypothesized that such antibodies are directed against quaternary and tertiary ammonium ion determinants (65,66). This would help to explain the phenomenon of cross-reactivity with different relaxants and also suggests that prior sensitization could occur via other quaternary or tertiary ammonium-ion-containing compounds in drugs, cosmetics, disinfectants, and the

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like (50,61). Two quaternary ammonium groups may be necessary for histamine release by neuromuscular blocking agents (62,63).

Diagnosis

Anaphylactoid reactions are easily misdiagnosed during anesthesia (67), since circulatory collapse accompanied by sinus tachycardia may be the only signs (49). These are the presenting features in 70–90% of cases. Mucocutaneous manifestations (erythema, urticaria, angioedema) are reported in 60–80% of reactions, but are often only noticed much later when the acute phase is over. Bronchospasm is present in about 40% of cases. Reactions are more common in women (up to 80%), in atopic patients, and in those who have a history of asthma (who are particularly prone to develop bronchospasm) or allergy, and in patients who have had a previous reaction to anesthetic drugs (50,53); they also seem to be more common in patients under 40 years of age (54).

The diagnosis of an allergic reaction to a muscle relaxant is based on clinical features, measurement of histamine and tryptase concentrations in the plasma during the reaction, and subsequent skin testing a few weeks later. However, during general anesthesia isolated symptoms can occur, most often hypotension or bronchospasm. Therefore, the clinical features of anaphylaxis may not be recognized as such.

The investigation of a reaction during anesthesia requires serial blood samples during the first 24–72 hours and further laboratory tests, such as basophil histamine release, and intradermal skin testing 4–8 weeks later (45,52,53,64,68). Plasma tryptase concentration, measured 30 and 120 minutes after the shock, is a sensitive and relatively specific marker of anaphylaxis (60,69). The possibilities of postmortem diagnosis have now been extended to the use of blood samples taken up to 3 hours after a patient's death and subjected to radioimmunoassay for mast cell tryptase activity and drug-specific IgEantibodies (70). However, histamine and tryptase concentrations may be ambiguous.

Radioallergosorbent tests (RAST) which detect IgE antibodies to specific muscle relaxants have been developed (65,66) and are commercially available for some anesthetic drugs (64,71). However, the sensitivity of IgE testing is variable and reached 90–97% in selected specialized centers only (72).

Skin testing has been used to confirm the diagnosis and to identify the causative agent (73). The sensitivity of skin testing for reactions to muscle relaxants is thought to be greater than 95% (73), although significantly lower for opioids, barbiturates, and synthetic colloids (44). However, opinions differ as to the value and the reliability of intradermal skin testing. The proponents of skin testing emphasize that strict criteria must be used in performing and interpreting the tests (74).

Additional biological tests have been suggested to improve the accuracy further. The leukocyte histamine release test has been found helpful (75) but it is expensive and time-consuming. Several surface molecules have been studied as markers, for example CD63. IgE-mediated degranulation of basophils after incubation of the patient's serum with a neuromuscular blocking agent can be detected by flow cytometry if a relevant proportion of basophils express the surface marker CD63 (76–77). An assay for CD63 and CCR3 was reported to have a sensitivity of 54% compared with 63% for the detection of specific IgE (78). Combined, these tests had a sensitivity of 80% and a specificity of 100%. The authors regarded this as a promising approach to the diagnosis of muscle relaxant allergy in cases where discrepancies between the clinical presentation and the laboratory result.

Morphine, which has a single substituted quaternary ammonium ion group, binds to antibodies that react with neuromuscular blocking drugs. Morphine radioimmunoassay was more sensitive in detecting IgE antibodies to neuromuscular blocking agents than assays specific for the various agents (79). Consequently, morphine radioimmunoassay was suggested as a diagnostic tool in cases of suspected anaphylaxis to neuromuscular blocking agents. In addition, IgE-mediated degranulation of basophils after incubation of the patient's serum with a neuromuscular blocking agent may be detected by flow cytometry if a relevant proportion of basophils express the surface marker CD63 (76,77).

Prevention and treatment

Measures for the prevention and treatment of hypersensitivity reactions have been reviewed (53,54,80,82).

The possibility of cross-reactivity with different relaxants (80,83,84) should also be investigated and the patient issued with an appropriate warning-card. After an anaphylactic reaction during anesthesia, the drug responsible is usually determined by skin testing. Most often in such cases, a neuromuscular blocking drug is found to be the triggering substance, and since cross-sensitivity between neuromuscular blocking agents can occur, a variety of these drugs should be tested. Neuromuscular blocking agents that produce negative skin results are considered safe for future anesthesia. However, there have been descriptions of several patients with previous anaphylactic reactions to neuromuscular blocking agents who had a second severe anaphylactic reaction when skin-test negative agents were used (85,86). The authors assumed that the skin tests had been falsely negative in these patients, but they conceded that newly acquired sensitivity might also have been an explanation. They concluded that all neuromuscular blocking agents should be avoided in patients with previous anaphylaxis to one of these drugs. If that is not possible the patient should be given antiallergic pretreatment and the anesthetic team should be prepared for resuscitation. In addition to standard pretreatment with both H1 and H2 histamine receptor antagonists, monovalent haptens might prove effective in blocking anaphylaxis to neuromuscular blocking agents (80).

Second-Generation Effects

Pregnancy

The pharmacokinetics of neuromuscular blocking agents in pregnancy and the impact on anesthesia for cesarean section have been reviewed (87). Key statements are:

(1) The umbilical/maternal vein concentration ratio of non-depolarizing neuromuscular relaxants varies

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from 7 to 26%. Clinical doses of these drugs can induce partial curarization in neonates.
(2) Despite reduced plasma cholinesterase activity, the duration of effect of suxamethonium 1 mg/kg is usually not significantly increased in pregnant women.
(3) At clinical doses, transplacental passage of suxamethonium is insufficient to produce paralysis of the neonate.

However, inadequate muscular activity requiring ventilatory support has been reported in babies born to mothers with atypical plasma cholinesterase.

Susceptibility Factors

Age

Children

Neonates are said to be more sensitive to non-depolarizing neuromuscular blocking drugs. Neonates have a lower muscle mass per kilogram body weight, maturation of neuromuscular transmission occurs in the 2 months after full-term birth (88,89), and the "margin of safety" for neuromuscular transmission (that is the fraction of receptors that must be occupied before neuromuscular block can be detected) is reduced in infants under 12 weeks of age (90). Thus, smaller doses should be used in the very young. The greater body water content of neonates, however, tends to mitigate the increased sensitivity, so that several authors recommend similar doses to adults (calculated on a body weight basis). Owing to longer elimination half-lives, recovery is slower in neonates and maintenance doses are needed at longer intervals (91), certainly where most of the older, long-acting relaxants are concerned. There are conflicting data about whether the actions of vecuronium and atracurium (and even pancuronium) are prolonged or not (92).

Most investigators concur that neonates and infants require a larger dose per kilogram of suxamethonium (2–4 mg/kg) to achieve an equivalent effect to that seen in adults. In young children the plasma clearance of non-depolarizing relaxants is quicker and their duration of action shorter (93,94), so that doses may have to be given more often.

Interindividual variation in dose requirements is even more marked in neonates and infants than in adults, so that monitoring of neuromuscular function is essential. Small dysmature babies, especially with temperatures below 36°C, are notoriously unpredictable in their response to relaxants.

Elderly people

In elderly people there is much slower recovery from non-depolarizing relaxants (about 60% in patients over 75 years of age given pancuronium), associated with a decreased rate of elimination (probably through reduced glomerular clearance and, to a lesser extent, reduced hepatic blood flow). The potency of relaxants is not altered. While the initial dose required to produce full relaxation is the same as in young adults, smaller maintenance doses are required at much longer intervals (95,96). The duration of action of atracurium is not increased, since termination of its action does not depend on renal or hepatic function.

Other features of the patient

Acid–base and electrolyte changes

It has long been accepted that respiratory acidosis tends to potentiate the blockade produced by non-depolarizing relaxants and respiratory alkalosis produces resistance to their action. This is true for the monoquaternary agents D-tubocurarine, vecuronium, and rocuronium (possibly by increased conversion to the bisquaternary forms at lower pH), but it may not hold for the bisquaternary relaxants metocurine, pancuronium, and alcuronium (97–99).

Protein binding of muscle relaxants is maximal between pH 8 and 9 and this may account for increased dose requirements in alkalosis.

Alkalosis is often associated with hypokalemia, in which the actions of non-depolarizing agents may be increased and those of depolarizing agents reduced. Hyperkalemia has the opposite effects, probably by lowering muscle transmembrane potential.

Variations in serum sodium affect neuromuscular blocking agents in a similar manner to potassium changes. However, serum concentrations of electrolytes do not always reflect intracellular concentrations or, perhaps more important, the intra/extracellular concentration ratios; in addition, changes in pH and the concentrations of potassium, sodium and other electrolytes are linked and have opposing influences at several sites in the processes of neuromuscular function, so that the expected effect of a change, taken in isolation, may not be found. Nevertheless, it is of practical importance that respiratory acidosis may enhance non-depolarizing block and makes its reversal by neostigmine more difficult. Such a vicious circle in the recovery room is best broken by ventilating the patient until the cause of the respiratory depression is removed or corrected.

Hypermagnesemia enhances the actions of both depolarizing and non-depolarizing neuromuscular blocking agents. Lithium may also do this. Hypercalcemia may be associated with prolongation of suxamethonium blockade and reduced potency of non-depolarizing agents.

Body temperature

In hypothermia, a reduction in blood flow to muscle increases the time to onset of neuromuscular blockade. The actions (depth of block and duration) of depolarizing relaxants are increased. The potency of non-depolarizing neuromuscular blocking agents is reduced according to some investigators, while others maintain that potency is increased and the duration of action prolonged (100–102). Hypothermia produces different changes in the twitch (103) and electromyographic (104) responses to nerve stimulation in the absence of relaxants. The excretion and the metabolism of relaxants are reduced by hypothermia.

Hemodilution

Hemodilution (for example the replacement of 1 liter of blood by dextran-40) increased the potencies and prolonged the actions of suxamethonium, pancuronium, D-tubocurarine, and vecuronium (SEDA-17, 151) (105). To avoid this, blood collection should be carried out before the administration of anesthetic drugs.

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Muscle diseases

The neuromuscular blocking effects of muscle relaxants in patients with neuromuscular disorders can differ significantly from those in healthy individuals. This can result in overdose and residual curarization on the one hand or in inadequate muscle relaxation on the other. Patients with Duchenne muscular dystrophy often require surgery for contractures and kyphoscoliosis. The neuromuscular blocking effects of vecuronium in eight children with Duchenne muscular dystrophy (11–15 years old) have been compared with those in eight children (8–18 years old) without this disease (106). After vecuronium 50 microgram/kg, the median train-of-four ratio was 0.14 in the patients versus 0.86 in the controls. The median time for recovery of the train-of-four ratio from 0.1 to 0.25 was 36 minutes in the patients versus 6 minutes in the controls. The authors concluded that patients with Duchenne muscular dystrophy need smaller initial doses of vecuronium. Because of the increased recovery time, patients should be closely observed for signs of residual curarization. Monitoring of neuromuscular transmission is strongly recommended in all patients with neuromuscular disorders who are given neuromuscular blocking agents.

Organ failure

Long-term administration of non-depolarizing muscle relaxants can result in prolonged paralysis, owing to accumulation of the drug itself or of pharmacologically active metabolites (107,108). Patients with renal or hepatic insufficiency are prone to this complication, but prolonged paralysis also has been noted in patients without these risk factors. The incidence of prolonged paralysis can probably be reduced if neuromuscular transmission monitoring is used to guide relaxant administration (109,110). In addition, agents with non-organ-dependent metabolic pathways may be of advantage (111). Residual curarization is only one of the potential reasons for prolonged paralysis after long-term neuromuscular blockade in severely ill patients. The interaction of different agents with other neuromuscular abnormalities, such as relaxant-associated myopathy, critical illness polyneuropathy, or other myopathic changes in the critically ill, still have to be evaluated.

Use in the intensive care unit

In the intensive care unit muscle relaxants are used to facilitate airway management and mechanical ventilation. The duration of administration can range from a single dose to continuous infusions for up to several weeks. Patients in ICU are more likely to have abnormalities of acid–base balance, electrolyte balance, body temperature, and liver and kidney function, predisposing them to the adverse effects of neuromuscular blocking drugs.

The most dangerous adverse effect of muscle relaxants in the ICU is suxamethonium-induced hyperkalemic cardiac arrest (112–117). Prolonged immobilization is believed to result in a spread of immature acetylcholine receptors on the muscle surface, which may mediate massive long-lasting potassium release if suxamethonium is given (118). By this mechanism, cardiac arrest can occur within minutes after suxamethonium administration. Standard resuscitative techniques have often failed, and several patients have died of this complication. Suxamethonium should therefore not be used in patients who are immobilized in the ICU for more than a few days. The shortest period of immobilization reported to be associated with fatal hyperkalemic cardiac arrest after suxamethonium administration was 4 days in a previously healthy young woman with bacterial meningitis (117).

Drug–Drug Interactions

Antibiotics

In very high doses or in sensitive patients (for example in myasthenia), antibiotics can produce paralysis and act additively or synergistically with neuromuscular blocking drugs.

Aminoglycosides

The aminoglycosides have a magnesium-like effect, acting prejunctionally to reduce transmitter release and postjunctionally to increase transmitter release; they also reduce postjunctional sensitivity to acetylcholine. In most cases their effects can be reversed, partly at least by calcium or 4-aminopyridine. Tobramycin is thought also to have a direct effect on muscle.

Beta-lactam antibiotics

Penicillins G and V (119) have been reported to cause neuromuscular block in animal preparations, but only at exceptionally high doses. Calcium is effective in reversal. The acylaminopenicillins augment vecuronium-induced blockade (120). Possible "re-curarization" with piperacillin was successfully reversed by neostigmine (121).

Lincosamides

The lincosamides have prejunctional and postjunctional effects, the principal action probably being on the muscle. This blockade is difficult to reverse with cholinesterase inhibitors or calcium.

Polymixins

The polymyxins probably produce a predominantly postjunctional effect (via ion channel block) and reduce muscle contractility. The block is difficult to reverse, calcium being only partly successful. Neostigmine has been reported to increase blockade produced by polymyxin B and colistin; in such cases 4-aminopyridine might be helpful.

Tetracyclines

The tetracyclines produce a small effect, partly by calcium chelation, thus reducing transmitter release. Reversal is usually, but inconsistently, obtained with calcium or neostigmine.

Peptide antibiotics

An unusually high dose of vancomycin augmented vecuronium-induced block during recovery, thus delaying the detubation of the patient for about 30 minutes (SEDA-16, 7). In another patient vancomycin prolonged the recovery

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from blockade induced by a suxamethonium infusion for some hours (SEDA-18, 14).

Management

If it is suspected that an antibiotic is contributing to prolonged neuromuscular blockade, the patient should be monitored and the effect of calcium (up to 1 g of calcium chloride slowly) should be observed. If this is unsuccessful, neostigmine (maximum dose 5 mg for an adult) or edrophonium (0.5 mg/kg) can be tried, but these agents may intensify a block due to colistin, lincomycin, or polymyxin B. If the other remedies fail, 4-aminopyridine (maximum dose 0.3 mg/kg) can be successful. Artificial ventilation should be continued until adequate spontaneous efforts are achieved and other possible factors, such as acidosis or electrolyte disturbances, are corrected.

This subject has been reviewed (119,122,123).

General anesthetics

Inhalational anesthetics

The volatile inhalational anesthetic agents and cyclopropane potentiate the actions of neuromuscular blocking drugs. The extent depends on the particular relaxant and inhalational agent used and the concentration of the latter. In comparative studies, isoflurane was the most potent in this respect, enflurane almost as potent, and both were 2–3 times more potent than halothane, which was in turn twice as potent as nitrous oxide, the volatile agents being administered at concentrations of 1.25 MAC (mean alveolar concentration) and the relaxant studied being D-tubocurarine (124). Concerning the older agents, the relaxant dose can be reduced by half with ether anesthesia and by one-fifth or more when cyclopropane is used. The degrees of potentiation by ether and cyclopropane probably lie between those of enflurane and halothane.

The higher the anesthetic concentration, the greater the degree of potentiation and the smaller the dose of relaxant needed (125). The full potentiating effect will only be seen when the tissues are saturated by the inhalational agent. Reducing the concentration of the inhalational agent generally reduces the degree of neuromuscular blockade (126), a desirable feature at the end of an operation. However, this maneuver can take some time to be effective (about half-an-hour for enflurane) and will only diminish the "volatile" contribution to the total block. Nevertheless, there may be occasions, such as in patients with myasthenia or renal or hepatic disease, when the advantages of using higher concentrations of inhalational anesthetic and lower doses of relaxants may outweigh the disadvantages (127).

The potentiation of D-tubocurarine block produced by enflurane slowly continues to increase with time, even after the usual equilibration period has passed (SEDA-5, 132) (128). This does not occur with halothane, and the discrepancy is said to mean that more D-tubocurarine will be required in the first hour of enflurane anesthesia than during equipotent halothane anesthesia, but that thereafter less will be required during enflurane anesthesia. It has been suggested that enflurane, unlike halothane, may produce an effect on muscle that takes time to develop. This may also be part of the mechanism, in addition to the greater potentiating action of enflurane, that explains the report that there is slower spontaneous recovery from pancuronium and a greatly impaired antagonistic effect of neostigmine in patients anesthetized with enflurane 1.3–1.4% compared with halothane 0.55–0.65% (end-tidal, in 70% nitrous oxide) (129). The experimental conditions in this last study, however, were somewhat different from usual clinical practice (130).

It is unfortunately not possible to come to a categorical conclusion on precisely how great the potentiation of a given relaxant will be by a particular inhalational anesthetic, because the effects of inhalational agents are multifactorial and diverse, and the numerous studies done have involved different methods (125,127,131–134). Very approximately, isoflurane and enflurane potentiate the longer-acting relaxants, such as D-tubocurarine and pancuronium, by 50–70% and the shorter-acting agents, vecuronium, atracurium, and mivacurium, by 20–25%. However, the degree of potentiation reported for the shorter-acting relaxants varies greatly (from 0 to 70% for vecuronium), depending on the duration of exposure of the skeletal muscles to the inhalational agent, the mode of nerve stimulation, whether the relaxant is given as a single bolus or by cumulative bolus doses or by infusion (steady-state or not), and the nature of the circulatory changes produced. The potentiation produced by halothane is much less than for isoflurane and enflurane.

Muscle relaxants may also contribute to anesthesia. Pancuronium 0.1 mg/kg has been reported to lower the MAC for halothane by 25% (135). It was conjectured that this could be due to a central effect or peripheral effect, through reduction of afferent input from muscle spindles to the reticular activating system. Recently, however, a similar though not identical study (SEDA-15, 124) (136) failed to confirm that pancuronium, vecuronium, or atracurium lowers the MAC for halothane.

Intravenous anesthetics

Intravenous anesthetic agents have much less influence on the neuromuscular blocking effects of relaxants and most have no clinically significant effect. However, ketamine (SEDA-14, 113) has been reported to significantly potentiate atracurium (137), and also D-tubocurarine but not pancuronium (138) in man. Animal studies suggest that all relaxants will be potentiated by ketamine in a dose-dependent manner (139,140). It has been suggested that had Johnston et al. (138) used a higher dose of ketamine (than 75 mg/m^2), they would have seen potentiation of pancuronium. The main effect of ketamine appears to be a reduction in the sensitivity of the postjunctional membrane to acetylcholine, possibly by ion-channel blockade. Propofol has been reported to potentiate vecuronium-induced and atracurium-induced blocks (141).

Laboratory investigations have shown that some benzodiazepines can produce biphasic effects (142,143), higher doses potentiating neuromuscular blocking agents (142,144); however, several human investigations have failed to show a significant effect (145–147). It has been suggested that agents that are added to commercial formulations of some benzodiazepines to render them more water-soluble may mask the benzodiazepine effect (147).

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Nevirapine

See also Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

General Information

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (1). Concerns about the adverse effects of nevirapine have delayed its implementation in preventing perinatal HIV. Decision analysis has been used to compare three strategies: a single dose of nevirapine, a short course of zidovudine, and no intervention (2). The

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authors concluded that nevirapine would prevent more deaths than either zidovudine and no intervention, as long as the rate of nevirapine toxicity did not respectively exceed nine and 42 times that observed in an earlier nevirapine clinical trial (HIVNET). Nevirapine would be economically preferable to zidovudine as long as the rate of toxicity did not exceed 22 times that observed in the clinical trial. They thought that implementation of nevirapine should not be delayed by concerns about its adverse effects.

Observational studies

In 77 HIV-positive subjects randomized to switch from protease inhibitors to nevirapine or efavirenz or to continue taking protease inhibitors, quality of life significantly improved among those who switched (3). Lipid profiles improved in those who took nevirapine but gamma-glutamyltransferase and alanine aminotransferase activities increased significantly and one patient interrupted treatment because of hepatotoxicity.

Organs and Systems

Psychological, psychiatric

Various psychiatric abnormalities (delirium, an affective state, and a psychosis) have been described in three patients who took nevirapine for 10–14 days (4):

- cognitive impairment, clouding of consciousness, and a paranoid episode in a 35-year-old man
- delusions of persecutory and depressive thoughts in a 42-year-old woman
- delusions of persecution and infestation and hallucinations in a 36-year-old woman

All three responded to withdrawal of nevirapine.

Metabolism

Lipodystrophy, well recognized with stavudine, has also been reported in nine of 56 patients taking combined HAART therapy including nevirapine, although there must be some doubt as to which drug or combination was responsible (5).

Hematologic

Two patients developed grade 4 thrombocytopenia (under 25×10^9/l) after 42 and 151 days of treatment with nevirapine (6). In the first patient, zidovudine and intravenous immunoglobulin were added to continued nevirapine, and the thrombocytopenia resolved by day 89. In the second, nevirapine was discontinued and alternative antiretroviral therapy was started, whereupon the platelet count returned to normal within 22 days.

Liver

The most frequent laboratory abnormality during nevirapine treatment is an increase in serum gamma-glutamyl transpeptidase activity, usually without changes in other measures of hepatic function. However, in a randomized, placebo-controlled comparison of zidovudine plus nevirapine, zidovudine plus didanosine, and the triple combination of zidovudine plus didanosine and nevirapine in 151 patients, there were abnormal liver function tests in increased frequency in the patients taking nevirapine (19% and 12% versus 6%) (7). Five of 98 patients taking nevirapine had to stop the drug permanently because of raised alanine aminotransferase activity, after which the laboratory abnormalities resolved completely.

Of 70 HIV-infected patients taking nevirapine 33 developed rises in transaminase activities (8). Higher nevirapine concentrations and hepatitis C virus infection were independent predictors of liver toxicity. In those with chronic hepatitis C, nevirapine concentrations over 6 μg/ml were associated with a 92% risk of liver toxicity. The authors concluded that monitoring nevirapine concentrations, especially in individuals with chronic hepatitis C, may be warranted.

In a prospective study of the incidence of severe hepatotoxicity in 312 patients taking nevirapine, hepatitis C and hepatitis B viruses were detected in 43% (9). There was severe hepatotoxicity in 16%, but only 32% of episodes were detected during the first 12 weeks of therapy. The risk was significantly greater among those with chronic viral hepatitis (69% of cases) and those taking concurrent protease inhibitors (82% of cases). However, 84% of patients with chronic hepatitis C or hepatitis B did not have severe hepatotoxicity.

Severe hepatitis has been attributed to nevirapine (10).

- A 36-year-old woman with HIV and hepatitis C infection developed fever, right upper quadrant pain, headache, confusion, and a generalized skin rash. Her antiretroviral treatment included lamivudine (150 mg bd), stavudine (40 mg bd), and nevirapine (200 mg bd). The dose of nevirapine had been doubled 2 weeks before. Her laboratory results were as follows: white cell count 4.1×10^9/l with 18% eosinophils, aspartate aminotransferase 879 U/l, alanine aminotransferase 1424 U/l, lactate dehydrogenase 3268 U/l, activated prothrombin time 14 seconds, partial thromboplastin time 29 seconds. Abdominal ultrasound was normal. Her antiretroviral medications were stopped. She was given intravenous prednisolone (60 mg 6-hourly) and within 8 hours the signs of sepsis had abated and her liver function began to improve and resolved over the next few days. Several weeks later, she was rechallenged with lamivudine and zidovudine, without recurrence of liver toxicity or rash.

The authors argued that, although the syndrome could not be definitively attributed to nevirapine, several factors suggested that nevirapine was the most likely precipitant, including the fact that hepatic failure coincided with a systemic allergic response, which is commonly associated with nevirapine, especially after dose escalation. The rapid improvement with steroid therapy suggested that the hepatic failure was a manifestation of a systemic hypersensitivity reaction. However, since stavudine has also been associated with hepatitis, a causative role of stavudine cannot be excluded. The fact that lamivudine was given again without recurrence of hepatitis renders it an unlikely culprit.

In another case there was severe hepatic failure, which resolved on withdrawal and in which there was no other obvious cause than the use of nevirapine (11).

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Significant hepatic deterioration, consistent with cholestasis, occurred 5 months into a HAART regimen including nevirapine (12).

- A 49-year-old man with severe factor VIII deficiency and stable chronic hepatitis C infection took stavudine, didanosine, and nevirapine. After 5 months of well-tolerated therapy, during which his viral load fell from 39 550 cpm to under 50 cpm, he developed anorexia, nausea, vomiting, fatigue, agitation, and biochemical evidence of deteriorating liver function. All drugs were withdrawn. There was no evidence of an infective cause and his hepatitis C status had not changed. Transvenous biopsy of the right hepatic lobe showed profound cholestasis and mild sinusoidal fibrosis, consistent with drug-induced cholestasis.

In four men aged 27, 41, 47, and 49 years, nevirapine was associated with a skin rash, malaise, and icteric hepatitis, 4–6 weeks after the start of therapy; resolution occurred after withdrawal of nevirapine (13).

Two health-care workers exposed to HIV developed severe hypersensitivity reactions to nevirapine; one required orthotopic liver transplantation to overcome the complications of acute hepatic failure and coma (14).

Skin

The principal, dose-limiting, adverse effect of nevirapine in adults is a rash, which occurs in 3–20% of patients, and which progresses to Stevens–Johnson syndrome in 0.5–1% of cases (15). Rash appears to be sex-specific; in 95 women and 263 men, women had a seven-fold higher risk of severe rash and were 3.5 times more likely to discontinue nevirapine than men (16).

In a review of the medical records of HIV-positive patients who had taken nevirapine, delavirdine, or both, the frequency of skin reactions was determined, as were the consequences of rechallenge with the same or the alternative agent (17). The overall incidence of rash attributed to the use of one of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) was 37%. While rash due to delavirdine was more common (8/20 versus 25/69), the rash due to nevirapine was more severe and necessitated more frequent hospitalization. Rash recurred in six of eight patients who were rechallenged with the same agent and in seven of 10 who were switched to the alternative agent. The conclusion was drawn that there is little value in attempting to re-treat patients who have had skin reactions to NNRTIs, except possibly those with limited treatment options.

In a multiple dose study, 21 children aged 3 months to 15 years were treated with nevirapine in dosages of 7.5–400 mg/m^2/day for up to 168 days (18). When it was intended to use dosages over 240 mg/m^2/day they were pretreated with a lower dosage (120 mg/m^2/day) for 28 days to reduce the risk of rash. However, a rash developed in one child after 2 weeks of treatment with nevirapine at a dosage of 240 mg/m^2/day, resolved on withdrawal, and recurred on rechallenge with a single dose of 120 mg/m^2.

An unusually high incidence of nevirapine-associated rash has been reported in Chinese HIV-infected patients (19). Of eight Chinese patients, five developed a rash within 4 weeks of treatment, resolving on withdrawal. Since the total number of patients in this report was small, it remains to be shown whether Chinese are indeed at increased risk of hypersensitivity reactions to nevirapine.

Prevention

While skin reactions to nevirapine cannot be prevented by the use of glucocorticoids (6,20), it is possible to induce tolerance to them, enabling treatment to continue (6). All the same, very severe skin reactions, with characteristics of both Stevens–Johnson syndrome and Lyell's syndrome, have occasionally been reported (21).

A 14-day lead-in period reduces the frequency of rash, and other effective interventions include antihistamines and a longer lead-in period (4 weeks) (22). In an attempt to reduce the rate of nevirapine-associated rash, 469 patients were randomly assigned to different schedules of induction therapy (23). Using a standard procedure, 19% developed a rash compared with 11, 8.6, and 7.7% in subjects assigned to a slowly escalating dose, concomitant administration of prednisone, or both. The rate of drug withdrawal was also reduced by a half using the new approaches.

Drug–Drug Interactions

Methadone

When methadone is used in HIV infection (for pain or treatment of opioid dependence) nevirapine given simultaneously can reduce methadone blood concentrations, the effect being sufficient to cause methadone withdrawal symptoms (24,25).

Oral contraceptives

The mutual pharmacokinetic interaction of nevirapine with ethinylestradiol + norethindrone has been studied in 10 women (26). After a single dose of ethinylestradiol + norethindrone, they took oral nevirapine 200 mg/day (days 2–15), followed by 200 mg bd (days 16–29); on day 30 they took another dose of ethinylestradiol + norethindrone. Steady-state nevirapine reduced the AUC of ethinylestradiol by 29% and significantly reduced its mean residence time and half-life. The AUC of norethindrone was significantly reduced by 18%, but there was no change in C_{max}, mean residence time, or half-life. The kinetics of nevirapine were not affected by the oral contraceptive. The authors attributed this interaction to increased clearance of ethinylestradiol and concluded that oral contraceptives should not be the primary method of birth control in women of child-bearing potential who are taking nevirapine.

Protease inhibitors

Nevirapine induces CYP3A4 and therefore interacts with drugs such as protease inhibitors (27).

St John's wort

St John's wort reduced nevirapine concentrations, because of induction of CYP3A4 (28).

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Warfarin

Nevirapine induces the metabolism of warfarin.

- A 38-year-old man with severe primary pulmonary hypertension and AIDS took warfarin 2.5 mg/day while he was taking zidovudine plus didanosine (29). His INR was 2.1–2.4. Later, because of virological failure, he was given a combination of stavudine, lamivudine, and nevirapine, and the INR promptly fell to 1.3. The dosage of warfarin was increased to 5 mg/day and anticoagulant activity was restored. All the antiretroviral drugs were then stopped because of an urticarial eruption, and a few days later stavudine, lamivudine, and saquinavir were given; warfarin 2.5 mg/day produced a stable INR.

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Nicardipine

See also Calcium channel blockers

General Information

Nicardipine is a dihydropyridine calcium channel blocker that has been used intravenously for hypertensive crises in adults, although increase in intracranial pressure was observed in a case series (1).

Organs and Systems

Cardiovascular

Severe bradycardia has been attributed to nicardipine (2).

- A 75-year-old man with atrial fibrillation undergoing surgery for esophageal carcinoma developed hypothermia and bradycardia during anesthesia. In an attempt to reduce his blood pressure of over 190/100 mmHg, he was given intravenous nicardipine 1 mg twice, 3 minutes apart. After the second dose, his blood pressure fell and his heart rate fell to 10/minute. He recovered after cardiopulmonary resuscitation.

The authors suggested that direct suppression of the sinoatrial node by nicardipine in the presence of low sympathetic tone might have been the mechanism of this serious adverse reaction.

Liver

Spider nevi, typical of chronic liver disease, have been seen in patients taking long-term nicardipine (3). The lesions disappeared within 2 weeks of drug withdrawal.

Second-Generation Effects

Pregnancy

Nicardipine has been compared with magnesium sulfate in acute therapy of preterm labor in a randomized trial in 122 women (4). The women treated with nicardipine were less likely to have recurrent preterm labor and adverse effects. Neonatal outcomes were similar in the two groups. The most frequent adverse effect was nausea or vomiting with magnesium sulfate (12/65 women).

Susceptibility Factors

Age

Nicardipine has scarcely been used in children. Intravenous nicardipine was effective in controlling blood pressure in three cases of hypertensive emergency secondary to renal disease (5). Children aged 12–14 years received intravenous infusions of 1–3 μg/kg/minute for 3–27 days, which normalized blood pressure without significant adverse reactions.

Intravenous nicardipine reduced systolic (16%) and diastolic (23%) blood pressures in a retrospective uncontrolled series of 29 children aged 2 days to 18 years (6). Tachycardia was recorded in four patients, palpitation in one, and flushing in one.

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Nickel

General Information

Nickel is a white, magnetic, metallic element (symbol Ni; atomic no. 28) that is found in various ores, including annabergite (arsenate), chloanthite (arsenide), garnierite (silicate), millerite, pentlandite, and pyrrhotite (sulfides), and zaratite (carbonate).

Nickel is used in alloys in dental medicine (1) and implant materials (2). Various medical, surgical, and dental routines expose the body to metallic nickel. Exposure to nickel is not always readily traced. For example, it may be present in contaminated cosmetics (SEDA-12, 531) and it may be used in dialysis apparatus. Non-medical exposure is a well-recognized health risk in occupational medicine, but it also occurs after body-piercing; although gold needles are generally used in body-piercing, cheap body-rings are often nickel-plated. Gold salts used in the treatment of rheumatoid arthritis may be contaminated by nickel, thus causing adverse effects not attributable to gold. Nickel (for example as nickel alloys) is also used in orthodontic and orthopedic appliances and in some prostheses.

Many antidotes to nickel poisoning have been tried. Chelating agents and other substances can be used to bind nickel or reduce its penetration through the skin, and hence to reduce symptoms in subjects with nickel sensitivity (3). Topical use is mostly described, but in some studies chelating agents have been given systemically. The most effective ligand for nickel so far described is 5-chloro-7-iodoquinolin-8-ol.

The toxicity of nickel has been reviewed (4).

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Nickel in metal implants and prostheses

Complications from the use of metal implants and prostheses can arise because of biochemical and histological reactions to some of the materials used (SEDA-22, 250). These include titanium, stainless steel (10–14% nickel, 17–20% chromium), and cobalt chrome alloys (27–30% chromium, 57–68% cobalt, and up to 2.5% nickel). All of these metals can produce sensitization or elicit toxic reactions when they are solubilized and come into contact with tissues; it can be difficult or even impossible to differentiate between hypersensitivity and toxic reactions.

Nickel plays a major role in sensitization of patients. Even the small amounts present in cobalt chrome alloys often suffice to elicit allergic reactions. Reactions to cobalt are more generally toxic in nature (5). An increased rate of allergy to cobalt and nickel has been found in those patients bearing metallic implants who have developed bone infection in the surroundings of osteosynthesis material.

Metals from prostheses can continue to be released into the system for many years. The development of hypersensitivity takes time, and allergic reactions are usually delayed for weeks, months, or 1–2 years. The symptoms can assume a variety of forms. Local reactions can cause loosening of the device or local pain. Dermatological reactions include eczema, bullous pemphigoid, urticaria and "muscle tumors."

- A 35-year-old non-atopic diver with no previous history of metal allergy slipped on a wet pier and sustained a multiple compound trimalleolar fracture of the right ankle (6). The tibia and fibula were immediately surgically realigned and retained by metal plates and screws, and the ankle was immobilized in plaster for 5 weeks. One month later he developed itching, scaling, vesiculopapular dermatitis on several fingers of both hands, which worsened over the next few months. Patch-testing was positive to nickel sulfate, chromate, and cobalt.

The author concluded that the patient had become sensitized to nickel and chromate in the orthopedic metals. It was also apparent that sensitization to cobalt had occurred, even though no cobalt could be shown on analysis. The hand dermatitis improved after removal of the metal from the ankle, but nevertheless continued to relapse.

There have been attempts to predict metal sensitivity in the individual patient so that the choice of material can be made accordingly. In vitro tests for metal allergies have been developed on the basis of lymphokine (MIF) release from sensitized T lymphocytes exposed to metal-protein complexes (7). About 6% of patients without a previous metal implant had positive reactions to nickel, chromium, or cobalt. However, it is still not clear whether such a positive reaction is a reliable predictor of clinical problems. In practice few patients have either local or systemic reactions; when symptoms occur and other causes are ruled out, the implant should be removed. Some workers recommend removal of an implant whenever there is both a positive MIF test and a positive skin test, even in the current absence of a serious reaction. Allergic dermatitis will clear up as soon as the metal has begun to be cleared from the tissue. The type of metal and the amount released into the tissue will affect the time taken for the disappearance of toxic dermatological phenomena.

Organs and Systems

Respiratory

The lungs of nickel workers can be affected by a toxic pneumosclerosis resulting from extrinsic alveolitis, as observed in persons engaged in hydrometallurgic nickel production (8). The pathogenesis of the condition includes changes in lung surfactant, an imbalance between lipid peroxidation and antioxidant activity, immune disorders, and the formation of circulating immune complexes.

Immunologic

Nickel allergy is an adverse effect of the use of nickel-containing medical appliances, such as orthopedic metal alloys, dental materials, and implants (9), and allergic reactions are common. Nickel allergy and contact dermatitis with nickel-based appliances have been reviewed (10).

- A 13-year-old non-atopic girl with a 1-year history of recurrent itchy eyelid inflammation and conjunctivitis in both eyes had been fitted with a removable orthodontic appliance 14 months before (11). The metal wires of the orthodontic appliance were made of steel containing 10–13% nickel and 16–19% chromium. Patch-testing confirmed allergy to nickel. A low nickel diet improved the dermatitis, but it did not clear. She was advised to stop wearing the orthodontic appliance, and the ocular lesions cleared within 2 weeks.

In 700 Finnish adolescents, of whom 476 had a history of orthodontic treatment with metallic appliances and others a history of ear-piercing, the frequency of nickel sensitization was 19% (12); in other studies of adolescent girls, among whom body-piercing was popular, sensitivity has been as high as 30%. A review of the literature concerning nickel hypersensitivity in relation to orthodontic appliances has shown that the risk is very low for patients who are not nickel hypersensitive at the start of the treatment (13).

Occupational exposure explains most cases of nickel-associated asthma (14) and rhinitis (15).

Contact dermatitis as a reaction to nickel is well known but usually reflects continuing non-medical exposure, for example among hairdressers (16); nickel released from injection needles and from Dermojets can, however, also give rise to cutaneous hypersensitivity reactions.

Exceptionally, nickel contained in food has caused recurrence of an earlier contact dermatitis to the metal (17); sensitivity to nickel in food may be caused by a type IV immunological reaction in the gut. The commonly recommended patch test procedure is not fully reliable for diagnosing nickel allergy. The lymphocyte transformation test has been suggested as a useful additional tool (18); an increased incidence of HLA-B21 was found in patients with cutaneous nickel hypersensitivity (19).

Although sensitization to nickel sulfate is common in patients with anogenital contact dermatitis and in patients with dermatitis in other body sites, the relevance to anogenital complaints of sensitization to nickel sulfate should

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always be doubted (20–22). However, direct transmission of nickel between the hands and the anogenital region has to be taken into account, and food can be a rare source of nickel contact in the anogenital area. In these cases relevance can be proved by oral nickel provocation and a nickel-restricted diet for a limited period may be justified (23).

The therapeutic use of intramuscular chrysotherapy has been limited by the high incidence of skin adverse effects. The pathogenic mechanisms of these are unknown, but could include allergic reactions to gold or to nickel as a contaminant. In order to investigate these mechanisms further, 15 patients who developed skin eruptions after chrysotherapy were assessed using skin biopsy and lymphocyte transformation stimulated by gold and nickel salts in vitro (24). Chrysotherapy caused two main cutaneous eruptions: lichenoid reactions and non-specific dermatitis. Peripheral blood mononuclear cells from patients with lichenoid reactions proliferated in response to gold salts in vitro, while those who developed non-specific dermatitis responded mainly to nickel. Nickel was a significant contaminant of the gold formulation (sodium aurothiomalate, Myocrisin, Rhone-Poulenc Ltd), amounting to a total dose of 650 ng over 6 months. The authors suggested that a significant percentage of skin reactions during chrysotherapy are due to nickel contamination.

- A 79-year-old woman had an abdominal aortic aneurysm repaired with a straight Vanguard R stent, mainly composed of nickel (about 55%) and titanium (about 21%) with a reinforcing thread of platinum (25). Three weeks later she developed severe erythema and eczema on the legs with continuous pruritus and excoriated papules. Patch tests were positive to nickel sulfate and cobalt chloride.

The need for preoperative patch-testing for metals is controversial. Enquiry about metal allergy is recommended before endoluminal surgical procedures.

The mobile-phone culture has spread rapidly and possible effects connected with its use may still be underestimated (26).

- A 36-year-old dermatologist with a history of jewellery intolerance developed dermatitis on the right side of the chin, with red pruritic papules. The dermatitis had worsened after prolonged use of her mobile phone. Patch tests were positive to nickel sulfate. She solved the problem by covering the phone with a plastic case.
- A 32-year-old woman developed dermatitis on her left cheek and suggested that it might have been caused or worsened by her mobile phone. Patch tests showed only positive reaction to nickel sulfate. The dimethylglyoxime test for nickel on the side of her phone was positive. The skin lesion resolved rapidly after she covered the phone with a plastic case.

Long-Term Effects

Tumorigenicity

Carcinogenetic effects of nickel, recognized from occupational medicine, can involve the upper or lower respiratory tract.

Drug Administration

Drug overdose

Nickel poisoning is well defined in occupational medicine and is occasionally experienced as a complication of exposure to nickel (or nickel-plated) medical devices. Use of nickel-plated dialysis equipment gave rise to nickel poisoning in 23 patients in one hemodialysis unit. They developed nausea, vomiting, weakness, headache, and palpitation, all of which remitted 3–13 hours after the end of dialysis (SEDA-6, 225).

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Niclofolan

General Information

Niclofolan has been used to treat trematode infections, including clonorchiasis, fascioliasis, and paragonimiasis. Sweating, generalized pains, and transient rises in serum transaminase activities have been reported with niclofolan in the treatment of pulmonary infections due to *Paragonimus uterobilaterali* (SEDA-11, 597) (1).

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Niclosamide

General Information

Niclosamide, widely used in the treatment of tapeworm infestation, is well tolerated in doses of 2 g taken orally before breakfast and is the drug of choice for mass chemotherapy (1). It is has also been used as a molluscicide and in the control of *Schistosoma japonicum* (2).

Niclosamide is not absorbed and reactions consist of mild gastrointestinal disturbances. When treating *Tenia solium* infections an antiemetic is usually given before niclosamide, and patients are subsequently purged to reduce the theoretical risk of cysticercosis, because the dose of niclosamide active against *T. solium* does not destroy ova contained within the tapeworm. Alcohol is usually restricted during treatment, since niclosamide can interfere with its metabolism.

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Nicorandil

See also Antianginal drugs

General Information

Nicorandil is a potassium channel activator. The potassium channel activators include cromakalim and its levorotatory isomer lemakalim, bimakalim, nicorandil, and pinacidil (1). Older drugs with this property include minoxidil and diazoxide. Nicorandil, a nicotinamide derivative, is the only drug in the group to be specifically designed as one of this fourth class of agents in the management of angina pectoris after organic nitrates, beta-blockers, and calcium antagonists. Apart from being an arterial/coronary vasodilator, through modulation of ATP-sensitive potassium channels, nicorandil also contains a nitrate moiety, giving it properties similar to organic nitrates but lacking the disadvantages of drug tolerance. Thus, nicorandil has two major hemodynamic actions. It causes venodilatation, reducing preload, by its nitrate-like effect, and systemic arterial vasodilatation, reducing systemic vascular resistance and afterload, by its potassium channel opening effect. In the heart it has a selective effect on coronary vasculature compared with myocardial muscle (2), and it does not appear to affect the sinus node or atrioventricular conduction in animals (3). It also has a vasospasmolytic action (4), and in animals is cardioprotective in induced myocardial ischemia (5).

Nicorandil is effective in controlling 69–80% of cases of chronic stable angina when used as monotherapy (6,7). However, clinical experience with nicorandil is still limited, although it has been in general use in Japan for over 8 years. A review of toxicity data has been published (8).

General adverse effects

The arterial and venous vasodilatory properties of nicorandil precipitate postural hypotension, leading to dizziness, syncope, palpitation, and headache, through a mechanism similar to that of organic nitrates. Other minor gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea have been reported, as has flushing

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due to cutaneous vasodilatation. There have been no reports of hypersensitivity reactions. Tumor-inducing effects have not been reported in animals or man.

Organs and Systems

Cardiovascular

The systemic hemodynamic actions of nicorandil are occasionally associated with a transient increase in heart rate of up to 18% (9,10). Larger doses are associated with cardiac depression, a dose-dependent fall in sinus rate and atrioventricular conduction velocity (11), and shortening of the cardiac action potential duration (12). However, no prodysrhythmic effects have been observed in man (13,14). Single oral doses over 40 mg have been associated with severe postural hypotension, dizziness, and syncope (10,15).

Respiratory

Experimental asthma caused by IgE antibodies in animals is inhibited by nicorandil (16). The relevance of this to man is not known.

Nervous system

Headache occurs in up to one-third of cases in dosages of 10–20 mg bd (17,18), but it is usually mild to moderate, necessitating withdrawal in about 5% of cases. Headache is more common at the start of therapy and is dose-dependent; it gets better with continued therapy or progressive dose titration (8,19).

Endocrine

Nicorandil suppresses the release of insulin from isolated animal pancreatic cells (20). However, this effect is four times weaker than that of diazoxide, and its effect in man is not known.

Hematologic

Nicorandil has an inhibitory effect on platelet aggregation by increasing intracellular platelet cyclic GMP concentrations (21). Whether this effect will potentiate bleeding or protect against myocardial infarction in patients with coronary heart disease is not known

Gastrointestinal

Nausea, vomiting, gastralgia, diarrhea, and abdominal pains have been reported in some studies (6,10).

Skin

Nicorandil, like minoxidil, appears to enhance the incorporation of cysteine into hair shafts (22). However, hypertrichosis has not been reported.

Anal eczema, which resolved after the withdrawal of nicorandil, has been reported (19).

Sexual function

Nicorandil's potassium channel opening action and its ability to release nitric oxide promotes tumescence in isolated human penile corpus cavernosum (23). This effect has been exploited to provide treatment for erectile dysfunction by local injection. Whether oral nicorandil is associated with enhanced erectile function has not been assessed.

Death

Nicorandil was not associated with an excess of sudden deaths complicating acute myocardial infarction in a Japanese series of 1000 sudden deaths between 1983 and 1987 (24).

Long-Term Effects

Drug withdrawal

Adverse effects have not been observed with the withdrawal of nicorandil after long-term therapy. Unlike organic nitrates, there is no drug tolerance with prolonged use of nicorandil (25), and there does not appear to be any cross-tolerance (26). The effects of organic nitrates depend solely on the activation of cyclic GMP in smooth muscle, but this is not the case with nicorandil. In a comparison of intravenous nicorandil and glyceryl trinitrate it took twice as long for blood concentrations of cyclic GMP to return to baseline after the latter, but the hemodynamic effects of the former continued for longer (27). This may be because of the additional non-nitrate potassium channel opening effect of nicorandil when further formation of cyclic GMP ceases.

Susceptibility Factors

Renal disease

The use of nicorandil in elderly patients with chronic renal insufficiency and in patients with stable hepatic cirrhosis is not associated with any significant alteration in its pharmacokinetics. In addition, its metabolism is not affected by drugs that interfere with drug-metabolizing liver enzymes (28).

Hepatic disease

Nicorandil is denitrated in the liver. Its half-life was slightly prolonged in eight patients with cirrhotic liver impairment given a single intravenous bolus of nicorandil (0.1 mg/kg for 5 minutes, half-life 1.7 versus 1.1 hours in controls) (29). This is unlikely to have any significance in adjusting dosages in patients with stable liver disease.

Other features of the patient

There is a theoretical contraindication to nicorandil in patients with cardiogenic shock, acute left ventricular failure with low filling pressure, and hypotension. A sublingual dose of 20 mg in patients with coronary artery disease and normal left ventricular function was associated with a 12% fall in left ventricular end-systolic pressure, a 3% fall in left ventricular end-diastolic pressure, accentuated diastolic filling, a 13% reduction in mean aortic pressure, and a reduced cardiac output at rest (9,30). However, cardiac output may be augmented by up to 60% in patients with congestive cardiac failure or

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with a previous history of myocardial infarction, principally by reduced preload, reduced afterload, and improved myocardial oxygen supply (31–33).

Drug–Drug Interactions

Beta-blockers

The combination of nicorandil and beta-blockers (atenolol/propranolol) potentiates hypotension, with attenuation of reflex tachycardia (6).

Dipyridamole

The coronary vasodilator response of nicorandil is potentiated by dipyridamole (34).

Food–Drug Interactions

Food reduces the rate but not the extent of absorption of nicorandil after an oral dose (35). Its systemic availability is good and is generally greater than 75% in healthy volunteers, suggesting limited first-pass hepatic metabolism, unlike the organic nitrates (36).

Smoking

Cigarette exposure in animals suppresses and delays the absorption of nicorandil from the gastrointestinal tract (37), but this has yet to be investigated in man.

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Nicotine replacement therapy

General Information

The introduction of nicotine replacement systems and agents is a significant advance in the treatment of nicotine addiction. Nicotine replacement reduces the severity of nicotine withdrawal symptoms during smoking abstinence and improves smoking cessation rates. During cigarette smoking, nicotine is rapidly absorbed, producing peak blood concentrations of about 15 ng/ml within the first few minutes, while a 21-mg transdermal nicotine patch produces peak blood concentrations of about 18 ng/ml 5–6 hours after application. Thus, nicotine concentrations are markedly increased when the patch and smoking are combined especially within the early minutes of smoking.

Comparative studies

In a meta-analysis of 42 nicotine chewing gum studies and nine patch studies, comprising 17 000 subjects, the odds ratios of long-term success were 1.61 for gum and 2.07 for patch compared with placebo (1). However, effective use of nicotine gum requires careful instructions. Transdermal uptake of nicotine from patches is about 1 mg/hour (2). Large multicenter studies using 16-hour and 24-hour nicotine patches in primary care have shown double the success rate of placebo (3).

The main objectives of the Collaborative European Anti-Smoking Evaluation (CEASE) were to examine whether long-term success rates (that is complete abstinence sustained for 1 year) could be increased by using higher than standard doses of transdermal nicotine, and/or by prolonging the patch treatment period (4). There were four cases of myocardial infarction during the study period, which comprised 950 treatment years and 1700 study years. One 59-year-old man had a myocardial infarct during treatment with the 25 mg nicotine patch, and one 48-year-old man and one 50-year-old man had myocardial infarcts after discontinuing treatment with 15 mg; one 66-year-old man who took placebo had a myocardial infarct. This compared with the 10.2 cases expected during the study period, based on calculations using data from the Framingham study (5). The overall incidence of adverse events was low, and they were generally transient. In order to examine possible dose-related adverse events, the occurrence of events during the first 8 weeks of treatment in each of the three groups (25 mg, 15 mg, and placebo) was analysed, and nausea and vomiting were the only reported symptoms, with a higher frequency in the 25 mg group (7.3%) than the 15 mg group (5.4%).

General adverse effects

The pharmacokinetics of nicotine transdermal systems have been documented in several studies. In one study, a number of users had headache and transient itching at the site of application (6). In another study in 37 subjects, three reported itching and headache, and one had allergic reactions to the patch, which disappeared after changing the site of application (7). The subjects in a third study had headache (4%), nausea (4%), and vertigo (4%) slightly more often than the placebo group (8). Skin reactions such as mild itching under the patch, lasting for 15–30 minutes, and erythema and acute eczema, persisting for several days after removal, also occurred. Skin reactions necessitating withdrawal of the patches occurred in 10% in another study (9). In the same report sleep disturbances of varying severity was a commonly reported adverse effect.

The effect of transdermal nicotine on concomitant medications has been reported in an open non-comparative study of 80 smokers (42 men and 38 women) who used 24-hour nicotine patches (10). Adverse effects included itching and local erythema, insomnia, and abnormal taste sensations. Two subjects withdrew because of adverse effects. At 12 weeks, 17 were non-smokers. At 26 weeks, 19 were non-smokers and a further 14 had reduced their use of cigarettes significantly.

Nicotine gum used for smoking cessation in 114 smokers caused sore mouth, hiccups, and abdominal pain and vomiting (11). One subject withdrew from the study because of vomiting. Hot flushes have also been reported (12).

Nicotine (15–25 mg/day) has also been used to treat active ulcerative colitis. The most common adverse effects were nausea, light-headedness, headache, sleep disturbance, dizziness, and skin irritation (13,14).

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Organs and Systems

Cardiovascular

Nicotine can aggravate cardiovascular disease through the hemodynamic consequences of sympathetic neural stimulation, or systemic release of catecholamines, or both (15). Although several cardiovascular events have been ascribed to nicotine patches, including cerebral arterial narrowing with severe headaches and transient neurological deficits (16), relatively few adverse effects have been reported (15). Suicide attempts by means of overdosage using nicotine patches, presumably with the intention of precipitating myocardial infarction, have failed (17), and it would seem that the risk of nicotine replacement therapy is likely to be much less than that of cigarette smoking, even in patients with coronary heart disease (15).

Nicotine can provoke angina in patients with coronary artery disease and can also trigger myocardial infarction. It has been hypothesized that activities associated with increased catecholamine concentrations can both trigger plaque rupture and promote an occlusive thrombus formation that can result in myocardial infarction or sudden cardiac death. By evoking the release of catecholamines (stimulating platelet aggregation and increasing platelet/vessel wall interactions), nicotine could therefore be a potent trigger of myocardial infarction. However, a randomized, double-blind, placebo-controlled trial in 584 patients with at least one diagnosis of cardiovascular disease clearly showed that transdermal nicotine does not cause a significant increase in cardiovascular events in high-risk patients with cardiovascular disease. On the other hand, the efficacy of transdermal nicotine as an aid to smoking cessation in such patients has proved to be very limited and may not be sustained over time (18). In another study (19) from the Pharmacovigilance Division of the Federal Ministry for Health and Consumer Products of Austria, 41 cases of myocardial infarction were associated with the use of nicotine patches.

Atrial fibrillation was described in association with normal or large doses (20,21), suggesting that accumulation can occur when nicotine gum is taken daily.

Respiratory

In one study, 27% of the participants reported coughing, and 15% had irritation of the mouth or throat after 3–5 days (22). At 3 weeks 7% reported coughing and 10% mouth and throat irritation. In another study, 18 healthy subjects inhaled nicotine for 20 minutes (80 inhalations) every hour for 10 hours at three different environmental temperatures (20, 30, and 40°C) (23). Adverse events were twice as frequent at 40°C as at 20°C. Most often reported were coughing, a lump in the throat, and a sore or irritated throat. Belching, hiccups, pressure over the chest, headache, and heartburn were reported occasionally. About one-fifth of the subjects experienced coughing after the first 5–10 inhalations.

Nervous system

In 53 subjects, two- and three-dimensional analyses of nicotine-induced eye movements were performed to evaluate whether they were primarily of vestibular or oculomotor origin (24). Nicotine-induced nystagmus was detected in 27 subjects (51%). These findings suggest that nicotine causes an imbalance in the vestibulo-ocular reflex.

Psychiatric

A woman developed hallucinations and cerebral arterial narrowing after using nicotine patches (16). In another case delusions and hallucinations occurred when a woman who had been using nicotine to try to stop smoking took a cigarette (25).

Gastrointestinal

Smoking is negatively associated with ulcerative colitis and positively associated with Crohn's disease; it is the most striking and firmly established epidemiological factor associated with the two conditions. The first association of nonsmoking with ulcerative colitis was made over 20 years ago (26), and was followed within 2 years by the observation that patients with Crohn's disease were more often smokers (27). Smoking also has opposite effects on the clinical course of the two conditions, with possible benefit in ulcerative colitis (28) and a detrimental effect in Crohn's disease (29). Nicotine is probably the principal active ingredient in smoking responsible for these associations.

In a pilot study of oral nicotine in the treatment of primary sclerosing cholangitis in eight patients, only five completed 1 year of treatment; two had no adverse effects, but three had to temporarily reduce the dose of nicotine because of nausea, dizziness, insomnia, or light-headedness, but later resumed the full dose (30). One patient completed only 4 months of treatment because of dizziness and bouts of palpitation, even at the lowest dose, requiring permanent discontinuation of nicotine. One patient with ulcerative colitis, who was completely asymptomatic at the time of entry, had insomnia and watery diarrhea shortly after starting oral nicotine; however, his ulcerative colitis later responded to transdermal nicotine. One patient had moderately active Crohn's colitis and bloody diarrhea treated with corticosteroid enemas and mesalazine; his bloody diarrhea increased shortly after starting oral nicotine, requiring drug withdrawal and an increased frequency of corticosteroid enemas; nicotine was not restarted.

Skin

Local skin reactions to transdermal nicotine patches have been reported (31). Other local adverse effects, including erythema with edema, erosions, and systemic skin reactions have also been described (32).

Skin tolerability in patients with a history of eczema, psoriasis, or other skin disorders has been studied in 1481 participants (33). The adverse effects reported were erythema, rash, pruritus, irritation, edema at the site of application, musculoskeletal pain related to the application site, dreaming, and other sleep disturbances.

Musculoskeletal

The acetylcholine receptors involved in myasthenia gravis are nicotinergic, and in myasthenia gravis they are reduced in number at the neuromuscular junction, which can lead to functional overdosage after the use of nicotine, similar to a cholinergic crisis. This is comparable to

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the myasthenic syndromes that were described during the Second World War in tobacco chewers without any muscle impairment.

- Myasthenia gravis was worsened by a nicotine transdermal system in a man who used to smoke 40 cigarettes a day without an effect on his myasthenia (34). Two hours after applying a nicotine transdermal system he developed increased bilateral ptosis, total ophthalmoplegia, difficulty in chewing, and generalized weakness. The symptoms improved after the patch was removed.

Immunologic

Leukocytoclastic vasculitis has been ascribed to nicotine patches in two patients (35). Two other patients developed vasculitis in association with the use of nicotine patches (36). The authors concluded that it was likely that the reactions in the two patients were related to the nicotine therapy. However, the possibility of a reaction to the vehicle (coconut oil and polymers) could not be excluded.

Susceptibility Factors

Anecdotal reports of paroxysmal atrial fibrillation, myocardial infarction (37,38), dysrhythmias (39), and stroke in patients taking nicotine have made physicians wary of prescribing nicotine gum or transdermal patches for patients with cardiac disease.

Occlusive dressings covering transdermal patches can increase the risk of adverse effects (40).

- A 40-year-old man with renal carcinoma and extensive lung metastases who had smoked three packs per day for 25 years, had two 21 mg transdermal nicotine patches placed on a clean hairless area of his body. Before he took a shower the next afternoon, the nursing staff covered the patches with a polyvinylidrine chloride occlusive dressing (Saranwrap). During the hot shower he felt nauseated, light-headed, and tremorous, and nearly lost consciousness. Removal of the patches and occlusive dressing alleviated the adverse effects.

The adverse effects experienced by this patient could have been due to the use of an occlusive dressing and exposure to a high temperature, in combination with a high dose of nicotine. Absorption of nicotine through the skin is greater at high temperatures, because of increased blood flow to the skin. A high ambient temperature (77–84°C) significantly increases dermal absorption and plasma concentrations of nicotine in the first hour of heat exposure, starting 5 hours after application of nicotine patches (41).

Drug Administration

Drug administration route

Nicotine has also been administered in a nasal spray. In one study, sneezing, irritation in the throat, and headache were reported after application of nasal spray (42). However, in a larger study (255 subjects, half of whom had been assigned to nicotine nasal spray and the other half to placebo), there were nine cases of sinusitis (five nicotine and four placebo) and two of nose bleeding and occasional spots of blood from the nostrils (one in each group) (43). Two other studies reported irritated throat, hiccups, heartburn, bad taste sensation, dry mouth, and dizziness, nasal irritation, runny nose, watery eyes, sneezing, and coughing as the most frequently reported adverse effects (44,45).

Drug–Drug Interactions

General

The therapeutic effects of many drugs are less predictable in cigarette smokers, since smoking can potentially alter the pharmacokinetics of a drug by reducing its absorption, increasing its plasma clearance, or inducing cytochrome P450 isozymes. Enzyme induction in smokers is probably due to polycyclic aromatic hydrocarbons, as they are potent inducers of cytochrome P450 (46).

Antimalarial drugs

Although rigorous data on the metabolism of antimalarial drugs are lacking, it appears from in vitro and in vivo studies that chloroquine is metabolized by cytochrome P450 (47). It is therefore conceivable that cigarette smoking alters the hepatic metabolism of antimalarial drugs.

Antimalarial drugs (chloroquine, hydroxychloroquine, or quinacrine) were given to 36 patients with cutaneous lupus, 17 smokers and 19 non-smokers (48). The median number of cigarettes smoked was one pack/day, with a median duration of 12.5 years. There was a reduction in the efficacy of antimalarial therapy in the smokers. Patients with cutaneous lupus should therefore be encouraged to stop smoking and consideration may be given to increasing the doses of antimalarial drugs in smokers with refractory cutaneous lupus before starting a cytotoxic agent.

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Nicotinic acid and derivatives

See also Vitamins

General Information

Nicotinic acid is an antilipidemic agent that effectively reduces serum concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, and triglycerides, and increases concentrations of high-density lipoprotein (HDL) cholesterol. It has been suggested that the marked lowering of serum cholesterol seen during treatment of dyslipidemia with nicotinic acid results from hepatotoxicity (1).

Nicotinic acid is also a potent vasodilator, probably by a direct action on smooth muscle cells. It produces cutaneous vasodilatation, itching of the skin, facial flushing, a sensation of feeling hot, pounding in the head, gastric irritation, diarrhea, raised transaminases, hyperglycemia, and hyperuricemia. These unpleasant adverse effects limit its acceptability for many patients. Nicotinic acid as such is not used in the treatment of vascular disorders, but some of its derivatives are, albeit with poor evidence of clinical efficacy.

Modified-release formulations of nicotinic acid do not appear to be better tolerated than regular formulations, flushing and itching being the most common adverse effects (SEDA-19, 206). There have also been several reports of hepatotoxicity with this form of the drug (SEDA-16, 438). Other adverse effects are hepatotoxicity (apparently a dose-related direct toxic effect), hyperglycemia, and hyperuricemia. It has been questioned whether the modified-release formulation, which is available over the counter in some countries, ought to continue to be available for self-medication in view of its serious adverse effects (2,3).

Given its many adverse reactions, the safety of using nicotinic acid continues to be discussed. Some are of the opinion that it should only be given to patients with marked dyslipidemia and under close monitoring, and that the initial expectations of fewer adverse reactions with the modified-release form of the drug do not seem to have been borne out in practice (4,5). Others recommend its continued use (6,7). A general warning against indiscriminate use of nicotinic acid as a vitamin supplement has been given (8).

In two studies of accelerated radiotherapy with carbogen and nicotinamide in patients with cancer the adverse effects of nicotinamide have been documented (9,10). In the first study, 62 patients with stage III–IV laryngeal carcinoma were treated with accelerated radiotherapy (total radiation 64 Gy) combined with carbogen breathing in 11 patients and with both carbogen and nicotinamide (Arcon) in 51 patients. Adverse effects attributed to nicotinamide in the 51 patients were nausea in 35 patients, vomiting in 20, flushing, dizziness, epigastric pain, and headache in 2 patients each, and gastrointestinal bleeding, sweating, fatigue, and emotional disturbances in 1 patient each.

In the second study nicotinamide (Nicobion) 6 g was given in tablet form to 15 patients with advanced head and neck and non-small cell lung carcinomas 90 minutes before radiotherapy. Toxicity (nausea and vomiting) did not correlate with any of the pharmacokinetic parameters, such as t_{max}, C_{max}, half-life, or AUC. Gastrointestinal toxicity reached grade 1 (nausea not requiring antiemetics) in four patients, grade 2 (nausea and/or vomiting requiring antiemetics) in four patients, and grade 3 (nausea and/or vomiting requiring nasogastric intubation or parenteral support) in two patients.

It has been hypothesized that long-term survival after recovery from myocardial infarction could be improved with only 1 g of nicotinic acid daily (11).

Nicotinic acid derivatives

Nicotinic acid derivatives include acipimox, aluminium nicotinate, nicotinyl alcohol, and xanthinol nicotinate.

The adverse effects of these compounds appear to be identical to those of nicotinic acid.

Acipimox (*S*-methylpyrazine-2-carboxylic acid 4-oxide) is structurally related to nicotinic acid. Flushing and gastrointestinal disturbances, but there were no effects on blood glucose or uric acid in 7137 patients, of whom 15% stopped taking the drug because of adverse effects (12). In another open study blood glucose was on average slightly lowered in 3009 patients with type 2 diabetes given acipimox for at least 2 months (13).

Acipimox had to be withdrawn in 10 of 32 patients with hypertriglyceridemia, excessive hypertriglyceridemia, and combined hyperlipidemia because of adverse effects or absence of clinical response (14). The other 22 completed 6 months of treatment with no adverse effects. The authors claimed that acipimox is much better tolerated than nicotinic acid, that it has fewer adverse effects, and can therefore be used as a second-line drug.

Aluminium nicotinate perhaps causes slightly less gastrointestinal distress than nicotinic acid, but the same can be achieved by buffering the acid, and neither approach in fact solves the problem, which is probably not primarily one of acidity.

Severe toxicoderma has been reported with xanthinol nicotinate and confirmed by a provocation test (SEDA-1, 333). Flushing is claimed to be less frequent with xanthinol nicotinate than with nicotinic acid, but has nevertheless been repeatedly observed, and its other adverse effects are likely to be the same as those of nicotinic acid.

Organs and Systems

Cardiovascular

Symptoms observed after high doses of nicotinic acid (such as giddiness, faintness, and vasovagal attacks) result from dilatation of the small arteries and arterioles, resulting in reduced peripheral resistance and blood pressure (6). Flushing occurs transiently in all patients and persists in 10–15% of cases. When starting with a high dose, hypotension can occur (15). The flushing of the skin with pruritus is transitory.

Coronary steal with worsening of myocardial ischemia related to vasodilatation has been reported in a patient taking nicotinic acid (16), which should therefore perhaps be withheld in patients with unstable angina.

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Nervous system

Electroencephalographic abnormalities associated with vitamin B therapy have been reported (SEDA-15, 412) (17). Tingling of the fingertips, faintness, and dizziness have been observed. Peripheral neuropathy has been reported (18). Tingling in the orofacial region has been attributed to a neuropathic effect, but this could have been due to vasodilatation.

Sensory systems

Ocular adverse effects of nicotinic acid include sicca syndrome, blurred vision, and eyelid edema.

A few cases of advanced cystoid macular edema have been reported in the older literature; these took months to resolve once nicotinic acid was withdrawn (SEDA-14, 331) (SEDA-20, 191) (15,19). Four new cases have been added in patients who took nicotinic acid 2–4.5 g/day (20,21). The first symptoms of blurred vision appeared 1–18 months after the start of therapy. Withdrawal of nicotinic acid resulted in improvement of visual acuity and resolution of the cystoid macular edema within 1–2 months. A particular feature that distinguishes this form of maculopathy is the absence of leakage on fluorescein angiography. Retinal edema, when it occurs, will abate on withdrawal of nicotinic acid (15).

Three cases of impaired vision occurred after the administration of high-dose nicotinic acid (22).

- A 51-year-old man increased his dose of nicotinic acid from 1 to 4.5 g/day. Within 4 weeks, he noted blurred vision in both eyes. Nicotinic acid was discontinued and his vision improved within a month.
- A 53-year-old man increased his dose of nicotinic acid from 1 to 3 g/day over a year. After he had been taking 3 g/day for 6 months, he noticed a gradual darkening of vision. His symptoms improved within 3 days of withdrawal.
- A 51-year-old man took nicotinic acid 2 g bd. After 18 months he noted visual symptoms, which resolved within 2 months of withdrawal.

Endocrine

Prolonged administration of nicotinic acid can have a diabetogenic effect and decompensation of previously stable diabetes can occur. Severe hyperglycemia has been precipitated by nicotinic acid treatment of hyperlipidemia (23).

Metabolism

During long-term treatment with nicotinic acid, uric acid concentrations tend to rise slightly, but the change is clinically insignificant (24).

Nicotinic acid has a hyperglycemic action (SEDA-13, 1330), and is therefore not recommended as a first-line hypolipidemic drug in patients with type 2 diabetes mellitus (25).

Lactic acidosis has been observed in patients taking nicotinic acid (SEDA-13, 1330).

Hematologic

- A 55-year-old man with localized prostate cancer was given pravastatin (10 mg/day) and aspirin (325 mg/day) (26). He also took food supplements containing about 30 different ingredients, most notably nicotinic acid 2250 g/day. During preparation for prostate surgery it was discovered that his prothrombin time was slightly prolonged (17 seconds, normal 11.4–14.4 seconds). All prescribed medications were withheld, but his prothrombin time continued to be abnormal (24 seconds).

The authors thought that the high dose of nicotinic acid had caused this abnormality.

Intravenous administration of nicotinic acid or nicotinyl alcohol tartrate can cause short-lived fibrinolytic activity (27).

Mouth and teeth

Two patients complained of dental and gingival pain, not previously reported adverse effects of nicotinic acid (28). The pain abated on withdrawal and in one case recurred on rechallenge.

Gastrointestinal

General gastrointestinal symptoms include heartburn, vomiting, persistent nausea (29), abdominal pain, and hunger pains.

In patients with squamous cell carcinomas of the head and neck, accelerated radiotherapy with carbogen and nicotinamide (ARCON) 6 g/day was carried out to determine the feasibility and the adverse effects of this therapeutic approach (30). Accelerated fractionation was combined with carbogen ($n = 11$), daily nicotinamide ($n = 10$), or both ($n = 17$). There were no significant differences in local adverse effects in the three groups. Systemic adverse effects took the form of nausea or vomiting. The authors concluded that in future ARCON trials a lower dose of nicotinamide will be needed to reduce severe upper gastrointestinal toxicity.

Of 61 patients with ischemic heart disease and dyslipidemia treated with nicotinic acid 1.5 and 3.0 g/day, 32 patients were withdrawn, 18 because of adverse effects and 14 for reasons not related to nicotinic acid (31). Of the 29 patients who finished the study, adverse effects included dryness of the skin (14%), acanthosis nigricans (10%), fatigue (6.9%), nausea (6.9%), abdominal pain (3.4%), diarrhea (3.4%), and anorexia (3.4%); the figures in parentheses were the incidences at 33 weeks. Flushing occurred more often at 18 weeks than at 33 weeks (24 versus 6.9%), as did pruritus (35 versus 28%), suggesting tolerance to these effects.

Liver

Nicotinic acid is hepatotoxic, and it is suspected that the modified-release formulation increases the risk (32) (SEDA-13, 1330).

Late adverse effects include hepatic dysfunction, with altered liver function tests and hyperbilirubinemia. After prolonged use of nicotinic acid and nicotinyl alcohol, histological changes, for example parenchymal cell injury, portal fibrosis, cholangitis, cholestasis, biliary casts, and

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lymphocytic infiltrations around the bile ducts, have occasionally been seen.

Rechallenge with crystalline formulations in people in whom liver damage has occurred with the modified-release formulation has been tolerated (33). However, three cases of hepatic dysfunction in patients taking crystalline nicotinic acid 1.5–3.0 g/day have been reported (1). They were all associated with a reduced ratio of esterified cholesterol to free cholesterol in LDL, a reduction in lecithin cholesteryl acyl transferase activity (LCAT), and other evidence of liver dysfunction, including prolonged prothrombin time. Transaminases were in the reference ranges. On reduction of the dosage or withdrawal of nicotinic acid all the abnormalities resolved within 4 weeks. Others have pointed out that some observations suggest that lipid lowering with nicotinic acid is part of a generalized hepatotoxic effect (1).

A "starry sky liver" has been reported in a patient with nicotinic acid-induced hepatitis (34).

- A 50-year-old man developed recurrent sharp lower abdominal pain and nausea, having taken modified-release nicotinic acid 500–2000 mg/day for 8 weeks for hypercholesterolemia. He had a low-grade fever, tachycardia, and hypotension. Abdominal ultrasonography showed a markedly hypoechoic liver of normal size, with relatively echogenic conspicuous portal triads. Aspartate transaminase activity and prothrombin time were raised. Nicotinic acid was withdrawn and the signs and symptoms resolved within several days.

Nicotinic acid can cause hepatic steatosis and clinical hepatic abnormalities that together can simulate the presentation of hepatobiliary neoplasia (35).

- A 52-year-old man with long-standing tetraplegia, who had been taking oral nicotinic acid 2 g/day for several months, developed nausea, vomiting, and fever, raised liver enzymes and total and indirect bilirubin. Ultrasonography showed several hyperechoic intrahepatic lesions and CT scan showed several hypoattenuating lesions, some of which were associated with interrupted vessels and had convex borders, suggestive of a tumor. Other lesions had CT features typical of fatty infiltration of the liver. Niacin was withdrawn. The liver function tests normalized within 4 days and the nausea and vomiting abated. The hepatic lesions on CT scan improved within 1 month and resolved after 9 months.

Skin

Nicotinic acid disturbs the normal cornification of the skin, occasionally leading to reversible ichthyosis and acanthosis nigricans (SEDA-19, 206). Two mechanisms are advanced to explain this effect: insulin resistance induced by nicotinic acid, with compensatory hyperinsulinemia (which in turn leads to increased insulin binding to insulin-like growth factor receptors and stimulation of keratinocytes), or a disturbance of epidermal lipid homeostasis.

Skin problems can be persistent in a proportion of patients, variously estimated at 10–59%, and this can severely limit adherence to therapy. The skin reaction can be ameliorated by concomitant use of non-steroidal anti-inflammatory drugs such as aspirin and indometacin (SEDA-15, 412). Transient exanthems, pruritus, and sometimes wheals are seen, as well as a uniform dryness and scaling of the epidermis, brown pigmentation, and even on occasion an acanthosis nigricans-like dermatosis (15). Persistent rashes can also occur. Doses in excess of 5 g/day are routinely associated with skin manifestations and can on occasion cause liver damage, gout, and ulcer formation. These reactions can be associated with nicotinic acid rather than nicotinamide, which is sometimes recommended as an alternative (36). Increased hair loss has been described.

Musculoskeletal

Nicotinic acid has been associated with the development of myopathy with nocturnal leg aching and cramps, symptoms that can be exacerbated by simultaneous use of other lipid-lowering drugs associated with similar adverse effects, or alcohol, which also has myopathic effects (SEDA-15, 413) (37).

Immunologic

Anaphylactic shock can occur with nicotinic acid (6).

A pseudoallergic reaction has been reported in a patient who took several nicotinic acid-containing formulations (38).

- A previously healthy 40-year-old woman developed a generalized macular erythematous rash associated with palpitation and light-headedness, recurring every few days. The rash started behind the neck and arms, with a sensation of tingling, progressing to a general feeling of heat. She felt ill and had to lie down until the episode subsided after 45–90 minutes, with residual fatigue for several hours. Laboratory findings were all in the reference ranges. She was taking two multivitamin tablets a day, each containing nicotinic acid 20 mg, one B complex tablet containing nicotinic acid 50 mg, and 1–3 tablets of an antiemetic containing nicotinic acid 50 mg. Thus, she had unknowingly taken nicotinic acid up to 240 mg/day. Graded oral challenge with nicotinic acid 20–200 mg reproduced her symptoms.

Drug Administration

Drug formulations

Since nicotinic acid can cause unpleasant flushing and other symptoms of vasodilatation, attempts have been made to develop modified-release formulations. Modified-released nicotinic acid formulations may be better tolerated than the immediate-release formulation, because they reduce the vasodilatory effects of the drug. However, the low frequency of flushing produced by modified-release formulations may be offset by an increased risk of hepatotoxicity. Some reports have suggested a higher frequency of hepatic dysfunction with traditional modified-release nicotinic acid formulations compared with immediate-release products (2,39).

In a double-blind, placebo-controlled study of a modified-release formulation in 128 patients, pruritus was reported in 10 patients taking nicotinic acid and

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rash in 9 patients; there were no similar effects in those taking placebo (40).

In 517 patients taking a modified-release formulation the most commonly reported adverse events were headache in 92 patients, pain in any part of the body except the abdomen in 46, abdominal pain in 54, diarrhea in 97, dyspepsia in 46, nausea in 72, vomiting in 38, rhinitis in 30, pruritus in 56, and rash in 51 (24).

In a study of the efficacy and tolerability of a modified-release formulation in 269 adults and 230 additional adults for whom short-term safety data were available, 13 of 269 patients (4.8%) withdrew because of flushing (41). During the first 4 weeks about half had flushing. The mean intensity was about 4.0 on a visual analogue scale (representing "none" to "intolerable"). Patients were encouraged to use aspirin prophylactically to minimize flushing. Other nicotinic acid-related adverse effects leading to withdrawal included nausea (3.3%) sometimes with vomiting, other gastrointestinal symptoms (1.5%), and pruritus (2.6%). Once case each of gout, acanthosis nigricans, headache, palpitation, raised glucose concentrations, and shoulder pain led to patient withdrawal. Certain adverse events thought to be associated with nicotinic acid were uncommon in the study group. There was one case of peptic ulcer, amblyopia occurred in three patients, and leg aches and myalgias in one patient taking nicotinic acid with simvastatin, with a normal creatine kinase activity.

The efficacy and adverse effects of a modified-release formulation have been studied in 32 patients with type 2 diabetes (42). Of 22 patients who completed 6 months of therapy, 17 took 1000 mg/day, 3 1500 mg/day, and 2 2000 mg/day. Seven of 32 patients discontinued therapy. Of these, three withdrew after 2, 5, and 6 months because of flushing and itching. Three other patients withdrew within 2 months because of nausea, diarrhea, and dyspepsia. One patient withdrew after 7 days because of increased blood glucose concentrations. There were no significant increases in mean transaminase activities, which remained within the reference ranges in all patients.

The safety and efficacy of escalating doses of modified-release tablets of nicotinic acid (Niaspan) have been evaluated in a multicenter, placebo-controlled study in 131 patients with primary hyperlipidemia (43). The dose of nicotinic acid was initially 375 mg/day, then 500 mg/day, and then increasing in 500 mg increments at 4-week intervals to a maximum of 3000 mg/day. Changes in biochemical measurements in patients taking nicotinic acid were significant only for uric acid and phosphorus. Fasting blood glucose, bilirubin, transaminases, alkaline phosphatase, lactate dehydrogenase, and amylase were not altered. Of the 131 patients, 80 completed the study. Of the patients who withdrew, 31 did so for medical reasons (3% taking nicotinic acid and 11% placebo). Eight of the 26 patients who stopped taking nicotinic acid withdrew because of flushing (all before the 2000 mg/day dose) and 5 because of a rash. These reasons accounted for half of the dropouts with nicotinic acid. The number of patients who had episodes of flushing fell with each dose increment of nicotinic acid, suggesting tolerance. Of other adverse events, only nausea (18 and 9%), vomiting (10 and 2%), pruritus (11 and 0%), and rash (10 and 0%) were more common with nicotinic acid.

Drug–Drug Interactions

Ethanol

An apparent interaction between nicotinic acid and alcohol caused toxic delirium and lactic acidosis (44).

Nicotine

An interaction between nicotinic acid and nicotine transdermal patches has also been observed, causing flushing and dizziness (45).

Statins

Nicotinic acid increased the risk of rhabdomyolysis associated with HMG-CoA reductase inhibitors (SEDA-19, 206) (46).

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Nifedipine

See also Calcium channel blockers

General Information

Nifedipine is a dihydropyridine calcium channel blocker.

A significant fall in pulmonary vascular resistance with high doses of oral calcium channel blockers seems to be associated with an improved prognosis, and potential clinical efficacy in primary pulmonary hypertension. However, significant adverse effects have been reported during acute testing with calcium channel blockers. Therefore, to identify patients who may benefit from long-term calcium channel blockers, there is a need for a safe, potent, short-acting vasodilator. Two studies have been conducted to assess the use of inhaled nitric oxide, a selective pulmonary vasodilator, for predicting the safety of high-dose oral calcium channel blockers and acute hemodynamic responses to them in primary pulmonary hypertension. In one study, 17 patients with primary

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pulmonary hypertension undergoing a trial of nifedipine (20 mg hourly for 8 hours) were assessed for the hemodynamic response to inhaled nitric oxide, 80 parts per million for 5 minutes (1). All nitric oxide responders also responded to nifedipine, and nine of the ten nitric oxide non-responders were nifedipine non-responders. All nitric oxide responders tolerated a full trial of nifedipine without hypotension. There was a highly significant correlation between the effects of nitric oxide and nifedipine on pulmonary vascular resistance. In conclusion, the pulmonary vascular response to inhaled nitric oxide accurately predicted the acute hemodynamic response to nifedipine in primary pulmonary hypertension, and a positive response to nitric oxide was associated with a safe nifedipine trial. In patients comparable to those evaluated, a trial of nifedipine in nitric oxide non-responders appears unwarranted and potentially dangerous.

In another study the acute response to inhaled nitric oxide and high doses of oral nifedipine or verapamil was assessed in 33 consecutive patients with primary pulmonary hypertension (2). Ten patients responded acutely to nitric oxide, nine of whom responded acutely to calcium channel blockers, without any complications. The other 23 patients failed to respond to nitric oxide and calcium channel blockers. In these non-responders there were nine serious adverse effects with calcium channel blockers. There was no clinical or baseline hemodynamic feature that predicted the acute vasodilator response. Long-term oral treatment with calcium channel blockers was restricted to the nine acute responders, and there was a sustained clinical and hemodynamic improvement in only six patients. It was concluded that nitric oxide may be used as a screening agent for safely identifying patients with primary pulmonary hypertension who may benefit from long-term treatment with calcium channel blockers.

Organs and Systems

Cardiovascular

The long-term safety of dihydropyridine calcium channel blockers has been extensively debated since 1995, with reports of conflicting results from observational and randomized clinical studies about possible increases in cardiovascular mortality, myocardial infarction, and neoplastic diseases (SEDA-22, 214). Two studies have contributed to this controversy.

In the INSIGHT (Intervention as a Goal in Hypertension Treatment) study, a prospective, multicenter, double-blind study in 6321 hypertensive patients aged 55–80 years, long-acting nifedipine 30 mg was compared with co-amilozide (hydrochlorothiazide 25 mg plus amiloride 2.5 mg) (3). There were no differences between the two treatments in the primary end-points of cardiovascular death, myocardial infarction, heart failure, or stroke during follow-up for 4 years.

In the Canadian Study of Health and Aging, a population-based prospective study of people aged 65 years or more, 5-year follow-up of 837 subjects who reportedly used at least one antihypertensive or diuretic agent showed that the risk of all-cause and cardiac mortality was significantly higher among nifedipine users than beta-blocker users (4). Compared with beta-blockers, the hazard ratios (95% CI) were:

- loop diuretics 1.84 (1.21, 2.82);
- nifedipine 1.82 (1.09, 3.04);
- ACE inhibitors 0.98 (0.54, 1.78);
- diltiazem/verapamil 0.96 (0.58, 1.60).

Among nifedipine users, the risk of death increased with the average daily dose and with recent initiation of therapy and remained significant for long-acting formulations.

Myocardial ischemia

Ischemic chest pain is an infrequent but well-documented adverse effect of initiating therapy with nifedipine (5). Its mechanism is unclear, but it may arise from reduced overall coronary blood flow or coronary steal (6).

Ischemic electrocardiographic changes without pain have also been reported (7).

There has been a meta-analysis of 60 published, randomized clinical trials that enrolled at least 10 patients with stable angina and that compared any nifedipine formulation, either as monotherapy or combination therapy, with a non-dihydropyridine active drug or a placebo control for at least 1 week (8). There were 3096 subjects and 5571 treatment exposures. There was an increased risk of cardiovascular events in patients allocated to nifedipine. The unadjusted odds ratios for nifedipine versus controls were 1.40 (CI = 0.56, 3.49) for major events (death, non-fatal myocardial infarction, stroke, revascularization procedures) and 1.75 (CI = 0.83, 3.67) for increased angina. Episodes of increased angina were more frequent with immediate-release nifedipine (OR = 4.19; CI = 1.41, 12.49) and with nifedipine monotherapy (OR = 2.61; CI = 1.30, 5.26). The odds ratio for immediate-release nifedipine was significantly higher than that for modified-release nifedipine, and the odds ratio for nifedipine monotherapy was significantly higher than that for nifedipine combination therapy. This meta-analysis suggests that the adverse effects of nifedipine on cardiovascular events in patients with stable angina are primarily due to more frequent episodes of angina when monotherapy with immediate-release formulations is used. Modified-release formulations and concurrent beta-blockade do not appear to be associated with an increased risk.

Hypotension

Sublingual nifedipine, given for hypertensive crises in elderly patients, can cause adverse effects associated with a precipitous fall in blood pressure, even at low doses. In 93 consecutive hypertensive patients without coronary heart disease, aged 65 years or over, nifedipine reduced blood pressure significantly, increased heart rate, and relieved symptoms associated with raised blood pressure (9). However, there were electrocardiographic changes consistent with myocardial ischemia in six of 55 patients with left ventricular hypertrophy and in one patient without left ventricular hypertrophy.

Cardiac dysrhythmias

A reported causal relation between torsade de pointes and nifedipine (10) has been questioned (11).

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Nervous system

Rapid lowering of the blood pressure with nifedipine, particularly sublingually, can precipitate cerebral ischemia, with confusion, loss of consciousness, and stroke. Cases of cortical blindness with macular sparing secondary to occipital lobe infarction have been reported (SEDA-17, 238).

Transient cerebral ischemia, with aphasia and hemiparesis in one patient and cerebellar dysfunction and loss of consciousness in another, has been observed with nifedipine (12). In addition, rapidly progressive hemiparesis, aphasia, and confusion, accompanied by a substantial fall in blood pressure, occurred in a patient whose hypertension (230/136 mmHg) was treated with sublingual nifedipine (13). Transient retinal ischemia, which may be recurrent, has also been attributed to nifedipine (14,15). Hypotension or cerebral steal are the likely mechanisms.

Cerebral vasodilatation from nifedipine might have contributed to a subarachnoid hemorrhage in a 32-year-old woman with a berry aneurysm (16).

Paresthesia of the hands and feet has been reported with nifedipine (SEDA-17, 237).

Electrolyte balance

Nifedipine can increase urinary potassium loss in patients treated with thiazide diuretics (17), but it has no effect on adrenaline-induced hypokalemia (18). In the Treatment of Mild Hypertension Study, 4 years of monotherapy with amlodipine maleate caused no change compared with placebo in the serum potassium, uric acid, aspartate transaminase, or creatinine of 114 hypertensive patients (19).

- A 56-year-old man developed hypokalemia associated with muscle weakness after taking nifedipine for 2 weeks for angina; the potassium concentration rose on withdrawal, but fell rapidly again on rechallenge (20).

Hematologic

In a case-control surveillance of agranulocytosis and aplastic anemia conducted in the metropolitan area of Barcelona, where 178 cases of aplastic anemia were identified, nifedipine was associated with a significant relative risk of aplastic anemia, which translates into an absolute risk of 1.2 per patient-year. Among the 178 patients, 147 were interviewed and compared with 1295 controls. Six cases (4.1%) and 11 controls (0.8%) had been exposed to nifedipine during the window period, as all of them had taken nifedipine for at least 7 months. The multivariate odds ratio was 4.6 (95% CI = 1.5, 15). All six died within 5 months of diagnosis. The authors concluded that the risk of aplastic anemia associated with nifedipine is of a similar magnitude to that associated with chloramphenicol (1.7 per 100 000 patients) and that associated with phenylbutazone (2.2 per 100 000 patients) (21).

Mouth and teeth

Nifedipine and ciclosporin can cause gingival hyperplasia, which is associated with gingival inflammation and can be mitigated by careful oral hygiene, although this has not been clearly shown. In gingival biopsies from nine nifedipine-treated cardiac outpatients, 13 immunosuppressant-treated renal transplant recipients, nine of whom were also taking nifedipine, and 30 healthy individuals, there were significant differences in macrophage and lymphocyte subpopulations in gingival connective tissue from patients with nifedipine-associated gingival lesions compared with healthy individuals (22). For example, the proportion of CD8-labelled cells was significantly higher and the CD4/CD8 ratio was significantly lower in connective tissue beneath the sulcus epithelium in those taking nifedipine. The authors suggested that immune responsiveness may be altered in drug-induced gingival overgrowth.

In another study, gingival samples were collected from 19 healthy individuals, 12 nifedipine-treated cardiac patients, and 22 immunosuppressant-treated organ transplant recipients, 11 of whom were also taking nifedipine (23). Mitotic activity was measured in the basal cell layer, and the results suggested that the increased epithelial thickness observed in nifedipine- and ciclosporin-induced gingival overgrowth is associated with increased mitotic activity.

The true prevalence of gingival overgrowth induced by chronic treatment with calcium channel blockers is still uncertain, since most studies have been small. In a cross-sectional study in 65 patients taking nifedipine and 147 controls in a primary-care center in Barcelona there was a higher prevalence of gingival overgrowth in patients taking nifedipine (34 versus 4.1%) (24).

Gastrointestinal

Acute abdominal pain due to mesenteric ischemia has been described with nifedipine (25).

Two patients developed severe gastric mucosal damage probably due to nifedipine (26).

- A 62-year-old man with gastric hemorrhage had a deep fundal ulcer in which a tablet of nifedipine was firmly embedded. The tablet was removed endoscopically and he was given cimetidine and recovered.
- A 67-year-old man with diabetes and hypertension, taking glibenclamide and nifedipine, developed dysphagia. Gastroscopy showed severe damage to the mid-esophagus. He did not respond to omeprazole and sucralfate, but gradually improved after nifedipine withdrawal, and the lesion disappeared.

Modified-release formulations of nifedipine have been associated in case reports with the formation of bezoars, concretions of undigested material within the gastrointestinal tract, mostly in the stomach. An unusual case of tablet impaction in the duodenum, with gastric outlet obstruction, was discovered 1 year after the patient stopped taking a modified-release formulation of nifedipine (27).

- A 77-year-old woman developed constipation and weight loss. Esophagogastroduodenoscopy showed a deformed pylorus and an elongated duodenal bulb, with numerous impacted tablets and ulceration in the outlet. Since only a few tablets could be recovered by endoscopy, she underwent partial duodenal resection to remove the contents: 25 intact tablets that were confirmed to be modified-release nifedipine.

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Liver

Hepatic steatosis with Mallory inclusion bodies has been reported with nifedipine (28). In patients with liver cirrhosis, nifedipine increases portal pressure due to splanchnic vasodilatation (29); whether this increases the risk of variceal bleeding is unknown.

Urinary tract

Several reports have linked renal dysfunction with nifedipine. In a study of hypertensive diabetics with renal insufficiency, nifedipine increased proteinuria and worsened renal function (SEDA-16, 196). Others have reported mild reversible renal impairment in patients with chronic renal insufficiency taking nifedipine for angina or hypertension; a biopsy in one of the patients, who had heavy proteinuria, showed focal and segmental glomerulosclerosis (30). Immune-complex nephritis was reported in a patient taking nifedipine, but the proteinuria persisted (and indeed worsened) on changing to verapamil (31).

Nifedipine was associated with an apparent diuresis within a short time of the first dose in 14 of 24 patients (32) and with nocturia, which ceased or improved markedly on withdrawal of therapy in nine patients (33). The nocturia was considered to reflect an effect of calcium channel blockade on detrusor function.

Skin

Bullous eruptions secondary to nifedipine include bullous fixed drug eruptions, phototoxic bullous eruptions, erythema multiforme, and pemphigus foliaceus.

Two cases of pemphigus vulgaris, one aggravated and one induced by nifedipine, have been described (34).

- A 54-year-old woman with an 8-year history of pemphigus vulgaris had a flare-up of her disease, refractory to oral glucocorticoids, after taking nifedipine for 2 years for hypertension. The nifedipine was withdrawn and she was given high-dose immunosuppressant treatment with prednisone and azathioprine. The lesions subsided promptly and cleared totally within several weeks.
- A 68-year-old woman had a bullous eruption of pemphigus vulgaris after antihypertensive treatment with nifedipine. She was given high-dose systemic glucocorticoids. However, she was unresponsive and nifedipine was finally withdrawn. Although new lesions did not appear, she died a few days later with uncontrollable sepsis.

Probable nifedipine-induced pemphigoid has also been reported (35).

- A 70-year-old man with hypertension took nifedipine 10 mg bd and 3 months later developed a pruritic eruption on his back, which spread to cover his trunk, limbs, face, and scalp, with involvement of the mouth. His skin deteriorated after the dosage of nifedipine was increased to 20 mg bd 1 year later. Antibodies to the 230 kDa pemphigoid antigen were detected in his serum. His skin improved considerably after withdrawal of nifedipine and the use of topical steroids and oral minocycline.

The findings supported a diagnosis of pemphigoid.

Photosensitivity (36) and a generalized bullous eruption (37) have been attributed to nifedipine, as have telangiectasia and spider nevi (38).

Musculoskeletal

Severe muscle cramps in the legs and hands can occur during nifedipine treatment (39).

Immunologic

Anaphylaxis has been attributed to sublingual nifedipine (40).

- A 71-year-old man with prostatic adenocarcinoma and a pathological vertebral fracture received sublingual nifedipine for hypertension and 15 minutes later became stuporose and complained of pruritus, generalized erythema, dizziness, and nausea. His blood pressure had fallen to 60/40 mmHg, his pulse rate was 120/minute, and his respiratory rate was 30/minute. He had cyanosis and severe bronchospasm with no focal neurological abnormalities. After treatment with subcutaneous adrenaline, intravenous fluids, hydrocortisone, and aminophylline, his blood pressure increased to 125/70 mmHg. During the following days his neurological and pulmonary status rapidly improved.

Second-Generation Effects

Pregnancy

Tocolytic therapy with nifedipine has been reported in several studies to be at least effective as ritodrine, terbutaline, or magnesium sulfate, with fewer maternal adverse effects (SEDA-18, 216) (SEDA-20, 187) (SEDA-22, 217) (SEDA-23, 211). These observations have been confirmed in two trials in 102 and 54 pregnant women of under 34 weeks gestation, randomized to nifedipine or ritodrine. There were no differences in the time of delivery, but significantly fewer maternal adverse effects in those given nifedipine (41,42).

The possibility that calcium channel blockers can cause cardiovascular adverse effects in pregnancy has been widely debated (SED-14, 598) (SEDA-20, 185) (SEDA-21, 208) (SEDA-22, 214). An uncomplicated non-Q wave myocardial infarction has been reported during nifedipine therapy for preterm labor (43).

- A 29-year-old woman was admitted because of preterm rupture of membranes and uterine contractions at 29 weeks. She was given ritodrine and 30 hours later reported chest pain. The electrocardiogram was normal. Ritodrine was withdrawn. Oral nifedipine was started and 4 hours later she reported chest pain. Her blood pressure was 70/50 mmHg and her heart rate 124/minute. The electrocardiogram showed T wave inversion in lead III and the serum creatine kinase activity was raised.

The authors concluded that even if $beta_2$-adrenoceptor agonists can cause myocardial ischemia in pregnant women by further increasing oxygen consumption, acute myocardial necrosis is rare; however, in this case

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nifedipine could have posed an extra risk by causing hypotension and reflex tachycardia.

In a review of almost 800 patients randomized to beta-adrenoceptor agonists or nifedipine, the latter was associated with more frequent prolongation of pregnancy, a lower incidence of respiratory distress syndrome, and lower incidences of maternal and fetal adverse effects (44).

Fetotoxicity

The use of nifedipine during pregnancy and labor has been widely debated, although its effects on child development have not been well evaluated. In one study nifedipine did not affect the development and health of 190 children, aged 18 months, born to women with mild to moderate hypertension who had been randomized to nifedipine, given for 12–34 gestational weeks before delivery, or expectant management (45).

Susceptibility Factors

Treatment of hypertensive emergencies has been the object of a randomized comparison of isosorbide dinitrate aerosol and nifedipine in 60 adults (46). Two patients taking nifedipine had myocardial ischemia early after administration and four patients had rebound hypertension during the follow-up period. Authors who reviewed the role of nifedipine in hypertensive emergencies reached the conclusion that the use of short-acting sublingual or oral nifedipine is no longer recommended for the treatment of these urgencies because it can precipitate serious adverse reactions (47).

There has been a report of cardiovascular collapse after uncomplicated coronary artery bypass surgery in patients taking nifedipine preoperatively (48); the condition responded to intravenous calcium chloride in three patients and adrenaline in four. Nifedipine may facilitate cardiac arrest during induction of anesthesia by sensitizing the carotid sinus (49).

Drug Administration

Drug overdose

Unlike verapamil and diltiazem, overdose with nifedipine is not usually fatal. Multiple case series of pediatric nifedipine ingestion have been published, and none has reported any deaths. However, two fatal cases of ingestion of long-acting nifedipine in children have been reported: a 24-month-old girl who took 20 tablets of nifedipine 10 mg and a 14-month-old girl who took a single tablet of nifedipine 10 mg; neither responded to aggressive supportive care (50).

Drug–Drug Interactions

Alcohol

There is a substantial increase in the systemic availability of nifedipine when alcohol is taken at the same time (51).

Atenolol

The combination of nifedipine with atenolol in patients with intermittent claudication resulted in a reduction in walking distance and skin temperature, whereas either drug alone produced benefits (52).

Ciclosporin

Ciclosporin significantly inhibits the metabolism of nifedipine, leading to increased effects (53).

Fluconazole

A pharmacokinetic interaction between fluconazole and nifedipine has been reported (54).

- A 16-year-old man with neurofibromatosis type 1, a malignant pheochromocytoma with lung and bone metastases, and candidiasis of the gastrointestinal tract with fungemia was taking nifedipine for arterial hypertension. The fungal infection responded to fluconazole, but three attempts to withdraw the fluconazole resulted in recurrence of headache, palpitation, and increased blood pressure.

After careful pharmacokinetic assessment of the effects of fluconazole withdrawal on 24-hour ambulatory blood pressure and nifedipine plasma concentration, the authors concluded that fluconazole can enhance the blood-pressure lowering effects of nifedipine by increasing its plasma concentrations, most likely by inhibiting CYP3A4.

Lithium

Lithium clearance is reduced by about 30% by nifedipine (55).

Melatonin

Melatonin has a hypotensive effect in both normotensive and hypertensive subjects. In a double-blind, randomized, crossover study designed to evaluate whether evening ingestion of melatonin potentiates the antihypertensive effect of nifedipine monotherapy in 50 patients with well-controlled mild to moderate hypertension aged 38–65 years (28 men, 22 women), there was a surprising significant increase in blood pressure and heart rate throughout 24 hours (56). The authors suggested that there was competition between melatonin and nifedipine, with impairment of the antihypertensive efficacy of the calcium channel blocker.

Phenytoin

Increased serum phenytoin concentrations have been reported after the introduction of nifedipine (57,58).

Quinidine

Nifedipine may enhance the elimination of quinidine (59) and cause hypotension and a loss of antidysrhythmic effect (60).

Tacrolimus

Nifedipine can increase the blood concentration of the macrolide immunosuppressant tacrolimus (SEDA-21, 392).

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Food–Drug Interactions

The effect of food on the systemic availability of two modified-release dosage forms of nifedipine for once-daily administration (Adalat OROS, a tablet with an osmotic push–pull system, and Slofedipine XL, a tablet with an acid-resistant coating) has been investigated in 24 healthy men in an open, randomized, crossover study (61). After fasted administration the systemic availability was slightly lower for Slofedipine XL than Adalat OROS, with a point estimate of 82%, mainly resulting from differences in nifedipine concentrations during the first 15 hours after administration. Maximum plasma concentrations were lower after Slofedipine XL compared with Adalat OROS (point estimate 84%). After a high-fat breakfast the differences in availability between the two products were greater than while fasting, with point estimates of 70% for AUC and 81% for C_{max}. Most striking was the lag time after food for Slofedipine XL which was more than 15 hours in 15 of 24 subjects. The availability of nifedipine from Slofedipine XL compared with Adalat OROS was only 28% over the intended dosing interval of 24 hours. The delay in nifedipine absorption when Slofedipine XL is administered may be explained by properties of the formulation, since the acid-resistant coating probably confers delayed absorption, due to prolongation of the gastric residence time, while the osmotic push–pull system is not sensitive to food. The same authors conducted a similar study in 24 healthy subjects, in which they compared Adalat OROS with Nifedicron, a product that consists of a capsule containing several mini-tablets (62). There was a higher rate of availability for Nifedicron in the fasted state, and after a high-fat breakfast the differences between the products became even more pronounced. The most important effect of concomitant food was reflected by a pronounced increase in *C*max after Nifedicron, which resulted in a more than three-fold higher mean concentration than Adalat OROS. This phenomenon may result in safety and tolerability problems.

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Niflumic acid

See also Non-steroidal anti-inflammatory drugs

General Information

The three atoms of fluoride in the niflumic acid molecule may be critically implicated in its adverse effects. However, as niflumic acid has been on the market in many countries for more than a decade, fluoride-induced adverse effects are probably very rare, and they are clinically relevant only if therapy is very prolonged. There are no adequate prospective studies of the comparative advantages and disadvantages of niflumic acid.

Organs and Systems

Nervous system

Headache is a common adverse effect of niflumic acid (SED-8, 223).

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Hematologic

A patient with agranulocytosis and a positive lymphocytic stimulation test recovered after withdrawal (1).

Gastrointestinal

Niflumic acid has the same gastrointestinal adverse effects profile as other anthranilic acids (SED-8, 223).

Liver

Hepatic damage has rarely been reported (SEDA-1, 90). Fatal icteric hepatitis occurred in a patient taking niflumic acid and paracetamol (SEDA-13, 83).

Urinary tract

Nephrotoxic effects have often been reported with niflumic acid, although whether this really indicates a relatively high potential for renal toxicity is an open question. Water retention with edema, oliguria, proteinuria, and increases in urea and creatinine concentrations have been described (SED-8, 223) (2).

Seven children taking niflumic acid for ear, nose, and throat disorders for 1-5 days developed acute renal insufficiency due to immune interstitial nephritis; oedema, oliguria, or anuria occurred at 3–6 days (2). There were signs of hypersensitivity (fever, skin rash, eosinophilia, and/or increased IgE) in all cases, leukocyturia in five, and hematuria in six. Renal biopsy showed interstitial lesions with infiltrates of lymphocytes, eosinophils, and plasma cells, but no tubular cell necrosis. In two patients renal insufficiency was irreversible despite the use of methylprednisolone.

Musculoskeletal

Niflumic acid can provoke rhabdomyolysis (SEDA-14, 95).

There are several accounts of skeletal fluorosis attributable solely to chronic intoxication with fluoride as a result of long-term use of the drug (up to 11 years) (SEDA-6, 99). As each capsule of niflumic acid contains 50.5 mg of fluoride, daily intake could be up to 0.30 g. The skeletal fluorosis was asymptomatic and was discovered only by routine radiology. Homogeneous osteosclerosis was in all cases greatest in the axial skeleton. Urinary fluoride concentrations were high and associated with hypocalcemia, hypocalciuria, and increased serum alkaline phosphatase activity. Bone biopsies showed increased trabecular bone volume, suggesting bone fluorosis. Persistent fluoride ingestion leads to a high bone fluoride content, since fluoride is trapped at the site in the apatite mineral lattice that is normally occupied by the hydroxyl group (3). Exactly how fluoride causes changes in bone structure and why osteocondensation is unevenly distributed is not known. It is not clear whether osteoid stimulation increases bone fragility (4). In view of the dangers of fluoride accumulation in renal insufficiency, niflumic acid should not be given in this condition (5).

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Nifurtimox

General Information

There are still few drugs available for the treatment of late-stage sleeping sickness due to *Trypanosoma gambiense*. Melarsoprol and eflornithine are equally efficacious, but both are toxic, and eflornithine is expensive. High-dose nifurtimox (30 mg/kg/day) has been used in Zaire for the treatment of arsenic-resistant trypanosomiasis; this dose was more effective and also more toxic. Of the 30 patients, one died after a period of confusion and coma and eight developed neurological effects, namely confusion, tremor, vertigo, and convulsions. One developed a rash and 12 had marked weight loss (SEDA-17, 333).

Acute polymyositis and toxic erythema purpura have been described in a young woman treated with nifurtimox for Chagas' disease; she died with respiratory and renal failure (SEDA-11, 598) (1).

Nifurtimox is the only drug approved for use in the USA (for Chagas' disease), but it is available exclusively on request from the Drug Service of the CDC. For treatment of the acute phase of Chagas' disease and in congenital cases the recommended dosage is 8–10 mg/kg/day, divided into two or three daily doses, for 30–60 consecutive days. In acute Chagas' disease, nifurtimox reduces both the duration of symptoms and parasitemia and mortality, but with limited efficacy in the eradication of parasites. The more frequent adverse effects are anorexia, loss of weight, psychic alterations, excitability or sleepiness, and digestive manifestations, such as nausea, vomiting, and occasionally intestinal colic and diarrhea (2). Other common adverse effects include neurological adverse effects (such as paresthesia, polyneuropathy, and convulsions), hematological adverse effects (such as thrombocytopenia and granulocytopenia), and allergic skin reactions (SEDA-13, 836) (3).

Long-Term Effects

Mutagenicity

Chromosomal aberrations were significantly increased in cultures of peripheral lymphocytes from a small group of children with Chagas' disease treated with nifurtimox. G-binding analysis of chromosomal aberration sites

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showed that treated patients presented coincidence in the chromosome regions affected (SEDA-15, 298).

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Nikethamide

General Information

Nikethamide has actions similar to doxapram hydrochloride and was formerly given intravenously, intramuscularly, subcutaneously, or orally for the treatment of overdose due to nervous system depressants. However, it can be dangerous and should not be used.

In addition to generalized restlessness, the adverse effects of nikethamide are itching, flushing, sweating, coughing, nausea, vomiting, muscle twitching, especially of the face, and convulsions (1–3). These are actually toxic effects, the margin between the clinically effective dose and the toxic dose being very narrow.

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Nimesulide

See also Non-steroidal anti-inflammatory drugs

General Information

Nimesulide is a selective COX-2 inhibitor. Data from a postmarketing survey on short-term nimesulide treatment of osteoarthritis in 22 938 outpatients confirmed that its adverse effects profile is similar to the profiles of other NSAIDs (SEDA-16, 114). Evidence that nimesulide is well tolerated in aspirin-sensitive asthmatic patients requires confirmation in more extensive well-conducted studies (SEDA-18, 107).

Organs and Systems

Nervous system

Nervous system adverse effects (nervousness, vertigo) have been reported with nimesulide (1).

Hematologic

Thrombocytopenia in an HIV-positive patient treated with nimesulide regressed rapidly when the drug was withdrawn (SEDA-14, 96).

Mouth and teeth

A fixed drug eruption occurred in the mouth of a young woman who had taken nimesulide (SEDA-17, 114).

Gastrointestinal

Gastrointestinal symptoms (pyrosis, pain, nausea) can occur (1), but in a short-term endoscopic study nimesulide caused less gastric damage than indometacin (SEDA-15, 104).

Liver

Many cases of liver toxicity have been reported with nimesulide.

Of five patients, two died as a result of fulminant hepatic failure while taking nimesulide (2).

Six cases of acute hepatitis occurred in four patients during the first 10 weeks of treatment, and in two after 15 weeks of therapy (3). They were represented by jaundice ($n = 5$), itching ($n = 2$), weakness ($n = 3$), and anorexia, nausea, and vomiting ($n = 2$). Increases in liver enzymes varied from 1.5 to over 30 times the upper limit of the reference range. Liver biopsy showed centrilobular or panlobular bridging necrosis in the four women and intrahepatic cholestasis in the two men. Complete recovery of normal liver function tests ensued at follow-up after interruption of nimesulide therapy.

- Fulminant hepatic failure due to massive hepatic necrosis occurred in a 58-year-old woman who took nimesulide for a few weeks for osteoarthritis (4). In the months before, she had received a first short course of the drug, apparently without problems. When she resumed nimesulide therapy she complained of non-specific symptoms, including nausea, and appeared jaundiced. The drug was withdrawn and liver transplantation was performed, but she died of multiorgan failure.

The previous exposure may have sensitized the patient with accelerated liver injury on re-exposure.

Several other reports of the potential hepatotoxicity of nimesulide have appeared (SEDA-25, 135) (5–7). A wide range of types of liver damage have been documented (8). Some patients have required liver transplantation (9) and deaths have occurred (10). The pathogenic mechanism of these unpredictable, sometimes severe, reactions is uncertain (11,12). In some countries nimesulide has been withdrawn from the market or its use has been restricted.

In some cases the hepatitis is severe (SEDA-23, 121). In one case fatal hepatitis occurred after 8 months of treatment (13) and in another treatment for 5 days precipitated fulminant hepatitis (14).

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The Portuguese Pharmacy and Medicines Institute suspended the pediatric formulation of nimesulide in March 1999 (15). This decision was made because of reports of serious adverse drug reactions, including liver damage, in children taking the drug. Nimesulide should be withdrawn immediately if abnormal liver function tests develop, and rechallenge must be avoided. However, it is not yet clear if the potential for hepatotoxicity of this drug is similar or greater to that found with other NSAIDs (16).

Urinary tract

Acute oliguric renal insufficiency caused by interstitial nephritis was attributed to nimesulide in a 68-year-old woman with diffuse arteriosclerosis but normal renal function (SEDA-22, 119).

A series of 11 spontaneously reported cases in which renal impairment was associated with the use of nimesulide has been described (17). The adverse events were represented by acute renal insufficiency ($n = 2$), acute deterioration of chronic renal insufficiency ($n = 3$), fluid retention ($n = 4$), and oliguria and macrohematuria ($n = 1$ each). The patients had a median age of 57 (range 17–81) years and six had some predisposing condition (chronic renal insufficiency, heart failure, diabetes, use of diuretics) to NSAID-induced functional renal impairment. Apart from one patient, nimesulide was taken for a very short time (less than 8 days). A favorable outcome ensued after withdrawal of therapy in all patients. The acute deterioration of renal function described in these patients pointed to hemodynamically mediated renal impairment in all cases, with the exception of one man in whom interstitial nephritis was suspected.

Skin

Reported cutaneous effects of nimesulide include rash and itching (1) and toxic epidermal necrolysis (SEDA-22, 119).

Second-Generation Effects

Fetotoxicity

Various types of nephrotoxicity have been described with nimesulide (SEDA-22, 119) (SEDA-23, 121). Two reports have illustrated the potential danger of using it as a tocolytic (18) or during late pregnancy (19). In both cases, maternal ingestion of nimesulide was accompanied by irreversible neonatal renal insufficiency. In the second case, renal biopsy showed abnormal tubular differentiation and signs of tubulointerstitial nephritis. The mechanism of this adverse reaction is not known, but it is probably related to fetal COX-2 inhibition. COX-2 is fundamental for nephrogenesis, and is upregulated in fetal membranes and myometrium at parturition.

A report has confirmed the potential danger of using nimesulide as a tocolytic agent (SEDA 24, 123). Nimesulide (100 mg bd) was prescribed for postoperative preterm labor prophylaxis, and severe oligohydramnios was identified 3 weeks later (20). After withdrawal the amniotic fluid volume returned to normal over 2 weeks. There were no adverse neonatal renal effects.

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Nimodipine

See also Calcium channel blockers

General Information

Nimodipine is a dihydropyridine calcium channel blocker.

In the absence of effective neuroprotective treatment for ischemic stroke, a double-blind, randomized, placebo-controlled trial has been performed in 454 patients in primary care (1). Nimodipine 30 mg/day or placebo was started within 6 hours after the onset of the stroke and continued for 10 days. Nimodipine had no effect on all-cause mortality or dependency in daily life. In patients with ischemic stroke documented by CT scan, nimodipine had a borderline significant adverse effect on outcome. Nimodipine was tolerated as well as placebo (7 versus 8 treatment withdrawals respectively), but the lack of benefit does not support the use of any voltage-sensitive calcium channel blocker in ischemic stroke.

It has been suggested that calcium channel blockers can be used to treat cocaine dependence, and some studies have shown reductions in cocaine-induced subjective and cardiovascular responses with nifedipine and diltiazem. The cardiovascular and subjective responses to cocaine have been evaluated in a double-blind, placebo-controlled, crossover study in five subjects pretreated with two dosages of nimodipine (2). Nimodipine 60 mg attenuated the systolic, but not the diastolic, blood pressure rise after cocaine. In three subjects, nimodipine 90 mg produced greater attenuation than 60 mg. The subjective effects of cocaine were not altered by either dosage of nimodipine.

Organs and Systems

Cardiovascular

When nimodipine was given intravenously to 87 patients with proven subarachnoid hemorrhage in a maintenance dosage of 2 mg/hour, it caused significant hypotension in one-third of cases (3). With maintenance oral administration, the incidence of hypotension was much lower. It is therefore recommended that if nimodipine is prescribed, the oral route is preferable, even in intubated patients who should receive it via a nasogastric tube.

Nervous system

Nimodipine has been routinely used to reduce cerebral vasospasm in patients with subarachnoid hemorrhage. A randomized, double-blind, placebo-controlled trial was stopped early because of excess mortality (8/75 versus 1/74 deaths with nimodipine and placebo respectively), which was attributed to an increased incidence of surgical bleeding (4). In addition, its use for cerebral protection in a cardiac valve replacement trial involving cardiopulmonary bypass was also terminated prematurely because of increased cerebrovascular complications and excessive blood loss in a small subgroup of patients (5). In traumatic subarachnoid hemorrhage, a trial in 123 patients showed a significant reduction in unfavorable outcomes (death, vegetative survival, or severe disability) at 6 months with nimodipine (25 versus 46% for placebo) (6).

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Niridazole

See also Benzimidazoles

General Information

Niridazole is used in the treatment of schistosomiasis and of guinea-worm (*Dracunculus medinensis*) infections; it is given in divided daily doses of 25 mg/kg for 5–10 days, depending on the infecting species. Niridazole is well tolerated in *Schistosoma hematobium* infections. It is metabolized in the liver, and its metabolites color the urine dark brown. In the treatment of schistosomiasis it has been largely superseded by newer drugs.

General adverse effects

In the treatment of schistosomiasis adverse effects were seen in 80% of inpatients and 33% of outpatients. Gastrointestinal effects were the most common, with vomiting in 50% of cases. Neurotoxic and psychiatric effects, convulsions, and cardiac effects are less common, except in patients with liver disease. Insomnia, somnolence, vertigo, nightmares, headache, weakness, jaundice, and muscle pains have all been reported (SEDA-12, 244). Toxic reactions are seen more often in *Schistosoma mansoni* infections, especially in patients with poor liver function or portocaval shunts, when neuropsychiatric complications can be expected. Some toxicity is directly related to parasite destruction and liberation of antigen rather than to the drug itself. Allergic reactions related to parasite destruction include urticaria, allergic conjunctivitis, and fever with peripheral eosinophilia. Niridazole is a potent carcinogen in mice, and tumorigenic in hamsters. It

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is not clear what the risks are in man, but it is of course usually given for only a brief period.

Organs and Systems

Cardiovascular

Minor electrocardiographic abnormalities, especially T wave changes, are common but are probably of no functional significance of patients (1). Dysrhythmias with prolongation of the QT interval occur in a small minority of patients (2).

Respiratory

Cough, fever, and dyspnea with pulmonary infiltration have been reported in two cases (3).

Nervous system

Headache, drowsiness, and dizziness are common with niridazole (2,4,5). More severe neuropsychiatric symptoms are more frequent in patients with liver disease, especially those with portosystemic shunts, in whom the drug bypasses the liver (6). Symptoms in these cases include insomnia, anxiety, depression, confusion, hallucinations, and convulsions; the reactions may prove fatal. The electroencephalogram can show slowed alpha rhythms, beta waves, and theta waves, as well as sharp wave and spike forms with niridazole (7). A single case of acute cortical necrosis was recorded in the much older literature, but was probably coincidental (SED-8, 691) (8). Agitation can occur in patients with abnormal liver function.

Hematologic

A peripheral eosinophilia is usual (2). Hemolysis has been reported once in glucose-6-phosphate dehydrogenase (G6PD) deficiency (SED-8, 691) (9).

Gastrointestinal

Bad taste, anorexia, nausea, vomiting, diarrhea, and abdominal pain are common with niridazole (1,2,5). Gastrointestinal bleeding has been seen (10).

Liver

Prolongation of the prothrombin time can occur (11). Niridazole is contraindicated in liver disease.

Urinary tract

Metabolites of niridazole color the urine dark brown (12,13).

Musculoskeletal

Muscle pain, joint pain, and bone pain are commonly reported but may be related to parasite destruction rather than to direct toxicity (5).

Long-Term Effects

Mutagenicity

Niridazole should not be used in pregnancy; mutagenic effects have been seen in bacteria (14).

Second-Generation Effects

Fertility

Transient reduction in spermatogenesis, apparently reversible, can occur (15).

Susceptibility Factors

Genetic factors

Caution is required when using niridazole in individuals with G6PD deficiency (16).

Hepatic disease

Niridazole should not be used in the presence of hepatic disease (17).

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Nitazoxanide

General Information

Nitazoxanide is a thiazolide derivative first described in 1975 and originally developed as a veterinary antihelminthic drug. In vitro it has a documented efficacy against protozoa such as *Giardia lamblia*, *Trichomonas vaginalis*, and *Entamoeba histolytica*, and in vivo in particular against *Cryptosporidium parvum* in patients with AIDS, as well as against nematodes such as *Syphacia obvelata*, *Uncinaria stenocephala*, and *Trichuris vulpis*, and cestodes such as *Dipylidium canimum*, *Tenia pisiformis*, and *Hymenolepis nana* (1,2). Since it is also effective against *Fasciola hepatica* in vitro it has been tried in the treatment of fasciola infections in man.

Pharmacokinetics

Nitazoxanide was given to many patients, before its tolerability and pharmacokinetics were adequately assessed (1,2). In men randomly assigned to one of four treatment groups, in each of which two took a placebo and six took a single oral dose of nitazoxanide 1, 2, 3, or 4 g, first fasted and a week later with a standardized breakfast, there were no significant changes in electrocardiograms, vital signs, or laboratory tests (1). Plasma concentrations increased linearly with dose, although there was a trend to increased systemic availability at a dose of 4 g. Food approximately doubled the concentrations of the metabolites of nitazoxanide, deacetylnitazoxanide (or tizoxanide), and tizoxanide glucuronide, irrespective of dose. Tizoxanide glucuronide was eliminated more slowly than tizoxanide. Tolerability was good up to the maximum dose of 4 g. There were 89 adverse events; all were mild and none required treatment. Minor adverse events were dizziness, fatigue, discolored urine, malaise, and postural hypotension. However, the most frequent adverse events were gastrointestinal—diarrhea ($n = 13$), abdominal pain ($n = 8$), flatulence and nausea ($n = 5$), and vomiting ($n = 3$). Their frequency increased significantly with dose under fed conditions but not fasted.

Observational studies

In a village close to Alexandria in Egypt 137 patients were given nitazoxanide 500 mg bd for 6 days (3). On the 30th day 113 patients (82%) were presumed cured, with stools free of fasciola eggs. Nitazoxanide was extremely well tolerated. Only three patients reported adverse effects: abdominal pain in two and vomiting in one. The symptoms were mild and disappeared without medication or withdrawal of treatment. Together with triclabendazole, nitazoxanide can be considered for the treatment of *Fasciola hepatica* infections in man.

Placebo-controlled studies

Nitazoxanide 0.5 g bd and 1 g bd was given to 16 healthy volunteers for 7 days with food to study its pharmacokinetics and tolerability (2). The pharmacokinetics of both tizoxanide and tizoxanide glucuronide were only slightly influenced by repeated administration of nitazoxanide 0.5 g bd; the treatment group had no more adverse events than the placebo group and there was no accumulation. In contrast, repeated administration of nitazoxanide 1 g bd resulted in a significant increase in adverse events: diarrhea ($n = 9$), abdominal pain ($n = 9$), flatulence ($n = 5$), nausea ($n = 4$), and dyspepsia ($n = 1$). All reported discolored urine. Four subjects in the high-dose group reported headaches. Vital signs, electrocardiograms, and laboratory tests were normal. There was accumulation of nitazoxanide metabolites, because of solubility-limited or transport-limited elimination at the higher dose of nitazoxanide.

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Nitrates, organic

See also Antianginal drugs

General Information

Organic nitrates have been in use for over 135 years, and their adverse effects are therefore well documented. The first compound of this class to be used was amyl nitrite, synthesized in 1844 by Ballard and used to treat angina pectoris by Brunton in 1869. Glyceryl trinitrate was first synthesized by Ascagne Sobrero in 1847 and was used by William Murrell to treat angina pectoris in 1879.

Nitrates have been produced in many chemical forms, but the current choice lies between the rapid-onset, short-acting glyceryl trinitrate (nitroglycerin) and the longer-acting isosorbide mononitrate and isosorbide dinitrate.

Mechanism of action

The nitrates act by releasing nitric oxide, which relaxes vascular smooth muscle. The discovery that endothelium-derived relaxing factor (EDRF) is nitric oxide (1) stimulated new interest in these drugs, as nitric oxide not only controls local vessel wall tension in response to shear stress, but also plays a role in regulating the interaction of platelets with blood vessel walls. The release of nitric oxide from the walls of atheromatous arteries is reduced, because of malfunctioning or absent endothelium. Atheromatous arteries behave differently from healthy arteries, in that these vessels vasoconstrict rather than vasodilate when stimulated by acetylcholine. This impairment of the acetylcholine vasomotor response appears to be related to serum cholesterol concentration (2).

Uses

Traditionally, nitrates have been first-line therapy in angina. They can be given to treat acute attacks, taken prophylactically before exertion or other stimuli known to provoke an attack, or used as continuous prophylaxis over 24 hours. Since angina is an episodic symptom, the first two methods are attractive, as continuous prophylaxis requires treatment over long periods when there are no symptoms. Tempering this argument is the realization that there may be silent myocardial ischemia, especially overnight, and morning angina on waking can be troublesome. In practice, a combination of continuous prophylaxis and as-required therapy is often used.

Nitrates are the drugs of choice in patients with left ventricular impairment, in whom they are of benefit when used in combination with hydralazine (3), and they should be used in preference to the calcium antagonists, which cause deterioration in myocardial function by an as yet unknown mechanism (4). In black patients with congestive heart failure taking ACE inhibitors and beta-blockers, a combination of isosorbide dinitrate plus hydralazine significantly reduced total mortality (5).

The potentially life-threatening hypotension caused by an interaction with sildenafil citrate (Viagra), a treatment for male erectile dysfunction, should be highlighted, especially in patients with coronary heart disease needing regular nitrates (6).

Observational studies

Glyceryl trinitrate can be used to treat anal fissure, as an alternative to surgery. Although glyceryl trinitrate causes resolution of symptoms in some cases, its local use as ointment is associated with frequent adverse reactions, mostly headache and anal burning (7,8). The difficulty in adjusting the dose and time of application, the high frequency of adverse reactions (up to 75% of patients), and the high rate of recurrence make the use of glyceryl trinitrate in non-surgical treatment of anal fissures questionable (9). In one case, a patient reported itching, dyspnea, and hypotension after applying glyceryl trinitrate. This unexplained systemic reaction to topical glyceryl trinitrate was reported as "anaphylactic," without a clear demonstration that it was an allergic reaction (10).

Besides its usual indications, topical glyceryl trinitrate has been used to prevent intravenous infusion failure because of phlebitis and extravasation, which occur in 30–60% of patients and can cause discomfort and harm, such as pulmonary embolism, septicemia, and increased mortality. Local application of glyceryl trinitrate patches was efficacious in several studies (11); the mechanism is probably vasodilatation and increased capillary flow. Glyceryl trinitrate is safe, since it causes only skin rashes and transient headache.

Transdermal glyceryl trinitrate is effective as an analgesic co-adjuvant for cancer pain. In combination with opiates it is well tolerated and reduces the daily consumption of morphine (12). Transdermal glyceryl trinitrate was safe in potentiating the analgesic effect of spinal sufentanil analgesia after knee surgery (13). The effects of glyceryl trinitrate include headache, a feeling of pressure in the head, nausea, vomiting, dizziness, tiredness, blackouts, and possibly penile erection and ageusia (14,15).

Placebo-controlled studies

In a multicenter, randomized, placebo-controlled, double-blind study of 0.2% glyceryl trinitrate ointment in 132 patients with anal fissures over at least 4 weeks, healing rates were similar with glyceryl trinitrate and placebo, but adverse events were more frequent in those who used glyceryl trinitrate: 34% complained of headache and 5.9% had orthostatic hypotension (16).

High-dose transdermal glyceryl trinitrate 50–100 mg given over a period of 12 hours each day for 3 months improved exercise tolerance and left ventricular systolic function in 29 patients with congestive heart failure taking a long-term ACE inhibitor (17). The most frequent adverse effects were skin irritation at the site of patch application and headache, which caused premature glyceryl trinitrate withdrawal in three patients.

Intravenous glyceryl trinitrate (starting rate 50 micrograms/minute uptitrated with blood pressure monitoring) for an average of 63 hours was very effective in preventing adverse ischemic events in 200 patients with unstable angina secondary to restenosis after coronary artery angioplasty, while heparin had no effect (18). In this acute setting, complications and adverse effects were not frequent, even if there was an excess of cases with headache or hypotension with glyceryl trinitrate, never leading to premature discontinuation. This study has shown that glyceryl trinitrate is safe and effective in

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reducing the need for urgent invasive procedures in these patients.

Comparative studies

Glyceryl trinitrate has been used as a tocolytic to prolong gestation, reducing the incidence of preterm labor. When compared with a widely used tocolytic, the beta$_2$-adrenoceptor agonist ritodrine, in a randomized, multicenter trial, transdermal patches of glyceryl trinitrate 10–20 mg had similar efficacy in 245 women with preterm labor. The main adverse effect of glyceryl trinitrate was headache, while with ritodrine palpitation and tachycardia were significantly more frequent. Headache with glyceryl trinitrate could usually be managed with paracetamol. Therefore, glyceryl trinitrate appears to be an alternative to ritodrine and is devoid of dangerous cardiac adverse effects (19).

In 90 patients randomly assigned to surgery (internal sphincterectomy) or topical glyceryl trinitrate, surgery led to a higher rate of healing than glyceryl trinitrate, with fewer adverse events: 29% of surgical patients versus 84% of the patients given glyceryl trinitrate (20). In conclusion, glyceryl trinitrate should not be used to treat anal fissure.

Variceal bleeding is a frequent and serious event in cirrhosis, and carries an increased risk of death (SEDA-22, 218). Therapy to prevent bleeding is therefore essential in these patients. Propranolol alone has been compared with propranolol plus isosorbide-5-mononitrate in a randomized, double-blind study in 95 patients (21). The combined treatment reduced the incidence of variceal bleeding compared with propranolol alone, but without any improvement in survival. Isosorbide-5-mononitrate added to propranolol appeared to be less well tolerated than propranolol alone, since seven patients had to be withdrawn from treatment because of adverse effects (four with feelings of faintness, two with headache, one with angina-like chest pain), compared with one with atrioventricular block taking propranolol alone.

Isosorbide-5-mononitrate has been tested with and without propranolol in a placebo-controlled study in 30 patients with liver cirrhosis and esophageal varices (22). The aim of the study was to assess the severity of previously reported adverse effects (that is renal dysfunction and hepatic encephalopathy) when vasoactive drugs are used to prevent variceal bleeding. Neither isosorbide-5-mononitrate nor propranolol alone or together had any adverse effect on subclinical hepatic encephalopathy or renal function in patients with well-compensated cirrhosis. Severe headache in those taking isosorbide caused three patients to withdraw.

Routes of administration

Nitrates can be administered by various routes. For example, glyceryl trinitrate is used not only as traditional sublingual tablets but also in the form of modified-release tablets, buccal tablets, aerosolized oral spray, intravenous injection, and topical ointment or skin patches for percutaneous absorption (23). These different formulations have been developed largely as a means of controlling the onset and duration of action of glyceryl trinitrate, since in conventional oral form its action is limited by marked hepatic first-pass metabolism.

General adverse effects

The adverse effects of the nitrates are unaffected by the chemical form or by the route of administration. The spectrum and frequency of adverse effects for the individual drugs, such as glyceryl trinitrate, isosorbide dinitrate, and isosorbide-5-mononitrate, appear to be similar.

Generalized vasodilatation predictably produces some common mild adverse effects. These include headache, flushing, and palpitation, which are most often experienced during the early treatment period and to which a degree of tolerance invariably occurs. More severe adverse effects, including syncope, transient cerebral ischemic attacks, and peripheral edema, are less common. Sublingual glyceryl trinitrate tablets produce a characteristic local burning or tingling sensation. Adverse cardiac effects can follow abrupt withdrawal of treatment after long-term exposure or high-dose therapy. Contact irritation and allergic contact dermatitis can occur with cutaneous glyceryl trinitrate in ointment or skin patches, and may be attributed to the drug itself or an inactive excipient, such as an adhesive agent. There was no excess risk of cancer in a historical cohort study in 2023 male fertilizer workers exposed to industrial nitrates at work in Norway during 1945–79 (24).

Amyl nitrite

Amyl nitrite, despite its name, is also used as a nitrate. It is a yellowish liquid taken by inhalation of its vapor for angina pectoris. It has also been used to treat cyanide poisoning, but is nowadays used exclusively as a substance of abuse. Although it is a prescription-only medicine in the UK, it is sold over the counter in glass ampoules to be used as a "room deodorizer" or "incense." It is known under numerous different nicknames and brand names, including snappers, poppers, Rush, Kix, Liquid gold, Locker room, Hardware, Ram, Thrust, and Rock Hard.

Amyl nitrate can cause headache, flushing, hypotension, tachycardia, dizziness, and relaxation of the anal sphincter. Less commonly it causes fainting, stupor, vertigo, incontinence, dyspnea, glaucoma, and methemoglobinemia.

Organs and Systems

Cardiovascular

Hypotension is a frequent adverse effect of nitrates (24), resulting from dilatation of arteries and veins. It can be associated with reflex tachycardia and palpitation, and even syncope on assuming an upright posture. Hypotension occurs particularly in old people, especially those with recurrent falls (SEDA-16, 196), and more commonly with glyceryl trinitrate oral spray than with sublingual tablets, because of its faster onset of action (24). It tends to occur more commonly in those who take nitrates infrequently.

Alternatively, bradycardia can accompany hypotension or syncope (25–27), presumably due to a vagal effect (it is responsive to atropine); complete heart block has also been reported (28). Occasionally, similar events occur in patients without ischemic heart disease (29), suggesting a mechanism similar to vasovagal syncope or coronary artery spasm (30,31) rather than coronary steal.

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Nitrates can precipitate myocardial infarction in susceptible patients (32), and occasionally worsen myocardial infarction, producing asystole (33) or ventricular fibrillation (34,35), possibly due to coronary steal or reperfusion of ischemic myocardium.

Throbbing headache as a result of dilatation of cerebral vessels (36,37) is common, although it often abates as tolerance develops. The once-a-day modified-release formulations of oral isosorbide mononitrate are particularly likely to cause headache on first exposure and have accounted for premature withdrawal in about 1% of cases in some trials (38,39).

Respiratory

Transient hypoxemia can complicate the use of glyceryl trinitrate and has been described after sublingual (40) and intravenous administration (41). In patients with ischemic heart disease this can result in a paradoxical response, with further angina pectoris and ST segment depression on the electrocardiogram (40). A possible explanation is vasodilatation of pulmonary arteries, leading to relative hypoventilation in some areas of the lungs, and it may be especially common and troublesome when glyceryl trinitrate is being tried for pulmonary hypertensive disease (42,43).

Nervous system

Glyceryl trinitrate can reduce cerebral blood flow, and this may explain occasional reports of impaired cognitive function and neurological disturbances in patients with coronary heart disease. Continuous intravenous infusion of glyceryl trinitrate in 12 healthy volunteers reduced blood flow velocity in the middle cerebral artery and increased slow-wave power during electroencephalography (44). Patients with cognitive disturbances receiving glyceryl trinitrate should be carefully monitored.

Transient cerebral ischemic attacks, unrelated to blood pressure changes, occurred with isosorbide dinitrate and glyceryl trinitrate ointment in a patient with previous cerebrovascular disease, and resolved on withdrawal (45). Such changes may be more frequent than is realized and, added to the risk of hypotension, suggest that nitrates should be used with great caution in patients with cerebrovascular disease.

Isosorbide mononitrate precipitated pituitary apoplexy in a patient with an unsuspected pituitary macroadenoma (46). Intracranial hypertension associated with glyceryl trinitrate has been reported and attributed to cerebral vasodilatation (47). However, it may occasionally be a consequence of hyperosmolality, hemolysis, and lactic acidosis caused by the excipient ethylene glycol used with intravenous isosorbide dinitrate. The risk of this may be greatest in patients with renal impairment (48).

Psychological, psychiatric

In an elderly woman, isosorbide dinitrate caused visual hallucinations and subsequent suicidal ideation, thought to be due to hypotension and cerebral ischemia (49).

Sensory systems

Eyes

On the basis of animal experiments it has been suggested that nitrates could increase intraocular pressure and should therefore not be used in the presence of glaucoma (50). However, both intravenous glyceryl trinitrate and oral isosorbide dinitrate actually lower the intraocular pressure, both in healthy individuals and in patients with open-angle and closed-angle glaucoma (51).

Taste

Glyceryl trinitrate in sublingual tablets causes a burning sensation under the tongue, an indication of the activity of the formulation. Altered and later absent taste sensation developed in a patient taking long-term transdermal glyceryl trinitrate patches (15).

Fluid balance

Peripheral edema occurred in patients treated for left ventricular failure with isosorbide dinitrate (52). This disappeared on withdrawal. The mechanism is unclear, in common with fluid retention reported with other vasodilators.

Hematologic

Methemoglobinemia has been reported after overdosage of sublingual glyceryl trinitrate (53) but does not occur with usual doses; prolonged intravenous infusion (up to 128 micrograms/minute) was not associated with pathological concentrations of methemoglobin (54). Higher mean infusion rates (290 micrograms/minute) (55), or occasionally lower rates in a patient with reduced drug clearance (56), can cause the formation of methemoglobin and could conceivably cause a clinical problem; however, recovery is rapid after injection of methylene blue (57).

In contrast, amyl nitrite can cause methemoglobinemia when abused, since it has a 2000 times higher affinity for hemoglobin (58). In vitro both amyl nitrite and glyceryl trinitrate reacted immediately with oxyhemoglobin to effect oxidation to methemoglobin, while for sodium nitrite there was a lag phase before the reaction occurred. The affinity rate constants were:

- 11 400 M^{-1} $minute^{-1}$ for sodium nitrite;
- 74 500 M^{-1} $minute^{-1}$ for amyl nitrite;
- 35 M^{-1} $minute^{-1}$ for glyceryl trinitrate.

Organic nitrates inhibit platelet aggregation in response to a wide variety of stimuli and prolong bleeding time.

Mouth and teeth

An increased frequency of dental caries with the use of buccal glyceryl trinitrate formulations has been reported in Sweden (SEDA-17, 237).

Skin

In a multicenter comparison of two transdermal nitrate delivery systems, there were skin problems at the application site in 20–39% of patients (59).

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Allergic contact dermatitis has been reported with the use of an ointment containing glyceryl trinitrate (60), and its development should be suspected if persistent erythema, vesicles, papules, hyperpigmentation, or edema follow the use of such formulations. Allergy may be due to the drug itself or to an excipient in the ointment base. However, erythema and pruritus produced by glyceryl trinitrate ointment can also result from the pharmacological action of the drug. The use of transdermal nitrate patches has also resulted in allergic contact dermatitis which was attributed both to the active drug (61) and to an inactive component of the delivery system or adhesive (62).

A causal relation between rosacea and the facial flushing seen with vasodilators such as glyceryl trinitrate seems likely (63).

Long-Term Effects

Drug tolerance

There is progressive attenuation of the effects of nitrates within the first 24 hours of continuous exposure. In a review of a transdermal nitrate system, the short duration of action of the formulation was ascribed to tolerance (64).

At first it was thought that tolerance was due to depletion of intracellular endothelial sulfhydryl groups (65), which are necessary for the biotransformation of organic nitrates to nitric oxide. It seems likely that tolerance occurs through several mechanisms, and the precise mechanisms are still uncertain (66). However, one possible mechanism of tolerance has been elucidated (67). Organic nitrates are converted to *S*-nitrosothiols when combined with sulfhydryl moieties in smooth muscles. These compounds activate guanylate cyclase, leading to an increase in the intracellular concentration of cyclic GMP, with resultant vascular relaxation and vasodilatation. As the supply of sulfhydryl within the smooth muscles is limited, prolonged exposure to organic nitrates results in its depletion and hence tolerance (68). Other mechanisms of nitrate tolerance that have been proposed include neurohumoral adaptation and a plasma volume-dependent mechanism (69). A unifying hypothesis, involving the excess production of superoxide anions, has been proposed (70).

In an assessment of how nitrate tolerance might be avoided, the efficacy of thrice-daily buccal glyceryl trinitrate and that of four times a day oral isosorbide dinitrate were compared (71); over 2 weeks, prolonged antianginal efficacy was maintained only with thrice-daily buccal administration. Nevertheless, in another study, transdermal glyceryl trinitrate seemed to offer a prolonged effect, sufficient to wean patients with unstable angina from intravenous nitrate therapy (71).

It has been convincingly shown that a nitrate-free period reduces nitrate tolerance (72). The modern strategy is to have a nitrate-free period when the patient is asleep, although this results in reduced protection from ischemia in the early morning, the time when many episodes of silent ischemia and myocardial infarction occur. Reports that ACE inhibitors (73) or carvedilol (74) reduce nitrate tolerance are as yet unconfirmed (75).

Three published controlled trials of the use of vitamin C in treating nitrate tolerance in 77 subjects overall have been reviewed (76). Vitamin C (3–6 g/day orally or by intravenous infusion) reduced nitrate tolerance for up to 3 days, without causing adverse reactions. However, before making definitive recommendations, studies of longer duration should be done in a larger number of patients.

Drug withdrawal

Adverse reactions to industrial exposure to glyceryl trinitrate were first reported in 1914 (77), and there have been several subsequent reports of symptoms during the weekend resulting from withdrawal of the sustained vasodilator response of nitrates. Exposure to organic nitrates, for example in workers in the explosives industry, can cause profound vascular changes after departure from the environment (78). Vasoconstriction ensues and can cause non-exertional angina pectoris, or myocardial infarction (79), and peripheral ischemia, with Raynaud's phenomenon and gangrene of the extremities (80). The development of tolerance to the vasodilatory effects of glyceryl trinitrate, with arterial spasm when exposure ceases, has been postulated as the mechanism (81).

- A 41-year-old man employed in a munitions factory was admitted with crushing chest pain on a Sunday morning. There was evidence of an acute inferior myocardial infarction, and cardiac catheterization showed 80% narrowing of the proximal right coronary artery, which was reduced to 10% by intracoronary administration of glyceryl trinitrate. The electrocardiogram became normal.

Despite continuing reports of adverse reactions to withdrawal from chronic occupational exposure to nitrates, there is no clear evidence of similar events in patients taking chronic nitrate therapy. However, since this risk cannot be excluded, patients taking chronic nitrates should be carefully advised and monitored.

Tolerance can also occur in patients who are given long-term continuous treatment with nitrates in high dosages for angina pectoris. Harmful withdrawal symptoms can be avoided by gradual dosage reduction, but high doses should be avoided where possible (82). Likewise, abrupt withdrawal of intravenous glyceryl trinitrate in patients with unstable angina precipitates further angina (SEDA-16, 196).

Tumorigenicity

In view of the hypothesis that nitric oxide can have mutagenic or carcinogenic effects, chromosomal alterations have been sought in blood lymphocytes from patients taking chronic nitrates and after in vitro exposure to a nitric oxide donor (83). No structural alterations were found in vivo or in vitro, only an increased frequency of micronucleus formation, a nuclear morphological change that has been suggested to be associated with a risk of cancer. However, this first report of a genotoxic effect of nitrates probably has no clinical relevance.

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Second-Generation Effects

Pregnancy

Glyceryl trinitrate has been used for its relaxing action on smooth muscle during cesarean delivery, with the aim of facilitating fetal extraction. After the publication of reports, a randomized, placebo-controlled trial was performed in 97 patients undergoing elective cesarean delivery after the 34th week of gestation (84). The patients were randomized to receive an intravenous bolus of glyceryl trinitrate (0.25 or 0.5 mg) or placebo. Glyceryl trinitrate did not improve fetal extraction. There were no adverse reactions attributable to glyceryl trinitrate in the neonate or mother.

The safety of glyceryl trinitrate in emergency or elective cesarean delivery has also been documented in a prospective series of 23 women, who received 400–800 micrograms of glyceryl trinitrate spray (85). However, no conclusions about the efficacy of glyceryl trinitrate were possible, owing to the lack of a control group.

Transdermal glyceryl trinitrate 5 mg for 16 hours each day has been compared with placebo in 25 mothers bearing intrauterine growth-retarded fetuses (86). It was applied from week 27 to week 35 of gestation until delivery. Three mothers were excluded from the analysis because they did not use the glyceryl trinitrate correctly. Placental flow, measured by Doppler, was improved by glyceryl trinitrate, and there was a better short-term neonatal outcome. Moreover, a biochemical marker of brain distress, the protein S100B, was normalized after glyceryl trinitrate, without an excess of adverse events in either the neonates or the mothers.

An authoritative overview of the published evidence on the use of glyceryl trinitrate to induce uterine relaxation in obstetric emergencies has shown that it is safe for fetus and mother (87).

Susceptibility Factors

The problems that can complicate the use of nitrates in patients with acute myocardial infarction, severe coronary atherosclerosis, and prior cerebrovascular disease have already been stressed. Hypotension, reflex tachycardia, or bradycardia can all be hazardous in individual patients.

Myocardial infarction

Although meta-analysis of studies in acute myocardial infarction suggested that nitrates protect against death and reinfarction (88), the ISIS-4 study found no such protection for 1 month after infarction (89). However, this study did show that nitrates are relatively safe in suspected myocardial infarction, even though 14% of patients who received nitrates had heart failure. Compared with placebo-treated patients there was an excess of hypotension considered severe enough to withdraw the drug in 15 per 1000 patients; in about half the cases it occurred soon after the start of treatment. The excess risk for headache was 18.7 per 1000 and of dizziness 1.6 per 1000, 0.8 per 1000 being associated with profound hypotension.

Congestive heart failure

The combination of isosorbide dinitrate with hydralazine is safe in systolic heart failure. Only headache and palpitation necessitated drug withdrawal and were more common than with enalapril (90). Headache and dizziness were more common with isosorbide dinitrate plus hydralazine than with placebo in patients taking ACE inhibitors and beta-blockers (5).

Pulmonary hypertension

A paradoxical increase in pulmonary vascular resistance has been reported after intravenous infusion of glyceryl trinitrate, and care is needed when giving potent vasodilators to patients with idiopathic pulmonary hypertension (91).

Hypertrophic obstructive cardiomyopathy

Organic nitrates should be used with caution in patients with hypertrophic obstructive cardiomyopathy, as they reduce afterload and venous return, which can exacerbate intraventricular obstruction and reduce left ventricular filling (SEDA-16, 196).

Exercise

A dramatic rise in plasma glyceryl trinitrate concentrations occurred after exercise in healthy subjects following transdermal administration (92). This altered systemic availability could cause adverse effects.

Drug Administration

Drug administration route

Transdermal

In one case a small explosion occurred when a patient was defibrillated with the paddle placed over a glyceryl trinitrate patch (93). The authors felt that this was probably due to arcing of the electrical current from the aluminium backing of the patch, but they advised that patches and gel should be removed before defibrillation.

An unusual skin burn resulted from the application of a glyceryl trinitrate transdermal patch in a patient who was subsequently exposed to radiation that leaked from a damaged microwave oven. The patient sustained a second-degree burn of the size and shape of his skin patch, probably due to a reaction with a metallic element in the adhesive strip (94).

Anal

Topical nitrates are used as an alternative to surgical treatment of chronic anal fissures. Their often limiting adverse effect is headache, due to vasodilatation, which is why glyceryl trinitrate ointment has been compared with diltiazem cream in a double-blind study in 60 patients with chronic anal fissures (95). After 8 weeks of treatment, 25 of 29 patients who received glyceryl trinitrate and 24 of 31 who received diltiazem had healed or improved; adverse effects were more common with glyceryl trinitrate (21/29) than diltiazem (13/31), the most frequent being headache. The authors suggested that diltiazem might be used as an alternative to glyceryl

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trinitrate in the treatment of chronic anal fissures, since it has similar efficacy with fewer adverse effects.

Drug–Drug Interactions

Aspirin

A retrospective case-control study of 736 consecutive patients admitted with upper gastrointestinal bleeding showed that the combination of aspirin with nitrates may be protective against aspirin-induced gastrointestinal bleeding (96).

Clonidine

The combination of isosorbide dinitrate with clonidine predisposes to postural hypotension (97).

Disopyramide

Disopyramide, by producing xerostomia, can prevent the dissolution of sublingual isosorbide tablets (98).

Ethanol

Alcohol potentiates the hypotensive effects of sublingual glyceryl trinitrate (99).

The presence of high concentrations of ethanol and glycerol in intravenous glyceryl trinitrate formulations has led to alcohol intoxication after high-dose therapy (100–102).

- A 74-year-old man developed Wernicke's encephalopathy, which required treatment with intravenous thiamine after discontinuation of the glyceryl trinitrate infusion.

Thus, high-dose intravenous therapy should be given with caution to patients with prior vitamin deficiency or a history of alcohol abuse (103).

Ethanol has also been implicated as the cause of acute gout in four patients with unstable angina who received intravenous infusions of glyceryl trinitrate (104).

Heparin

There have been reports of heparin resistance associated with glyceryl trinitrate (105) (SEDA-16, 196), but subsequent review of this interaction showed no clinical relevance, provided that heparin anticoagulation is monitored closely (106,107).

Hydralazine

Severe postural hypotension has been observed in patients given both isosorbide dinitrate and hydralazine for chronic heart failure (26), although this has not been a problem in large studies (90).

Lidocaine

Complete atrioventricular block has been reported after the use of sublingual nitrates in patients receiving lidocaine by infusion (108,109) and can result in asystole.

Metoprolol

Dizziness or faintness has been reported to follow the use of sublingual nitrate in patients taking the beta-adrenoceptor antagonist metoprolol (110).

Nifedipine

- A case of laryngeal edema has been reported with the use of isosorbide dinitrate spray followed shortly by sublingual nifedipine in an attempt to reduced high blood pressure (230/130 mmHg) in a 65-year-old woman who presented with coma secondary to a large intracerebral hemorrhage; the same complication recurred when she was rechallenged with the same sequence of drugs (111).

Sildenafil

The combination of organic nitrates and sildenafil citrate (Viagra) can precipitate life-threatening hypotension in patients with angina (112). Sildenafil is a selective inhibitor of cyclic GMP-specific phosphodiesterase type 5, which causes smooth muscle relaxation and vasodilatation, and is an effective treatment for male erectile dysfunction. More than 3.6 million prescriptions have been issued as of August 1998, and so far there have been 69 deaths, 12 of which were attributable to the interaction with nitrates, as reported to the FDA.

The pressure-lowering effect of a step-wise intravenous infusion of glyceryl trinitrate was significantly increased in 12 healthy volunteers treated for 4 days with sildenafil (Viagra) 25 mg tds; episodes of symptomatic hypotension were also more frequent with sildenafil (113). When sublingual glyceryl trinitrate was used, the reduction in systolic blood pressure was four-fold greater in association with sildenafil.

An elderly man with anginal pain died after treatment with glyceryl trinitrate (114). The family physician discovered that the man had also taken sildenafil, and he suggested suicidal intent, since he claimed that the patient was aware of the adverse cardiac events of the association of these two drugs.

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Nitrazepam

See also Benzodiazepines

General Information

Nitrazepam is a long-acting benzodiazepine used primarily for insomnia. However, it has a long half-life (about 24 hours) and poses a substantial risk of residual daytime effects, including sedation, psychomotor and cognitive impairment, and accidental injury (1).

Organs and Systems

Death

Between January 1983 and March 1994, 302 patients with intractable epilepsy were entered into a nitrazepam compassionate plea protocol (2). Nitrazepam increased the risk of death, especially in young patients with intractable epilepsy. The authors suggested that nitrazepam should be used with caution in young children with intractable epilepsy, especially if they have difficulties in swallowing, aspiration, pneumonia, gastroesophageal reflux, or a combination of these.

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Nitrendipine

See also Calcium channel blockers

General Information

Nitrendipine is a dihydropyridine calcium channel blocker.

Drug–Drug Interactions

Ciclosporin

Nitrendipine had a small but significant nephroprotective effect independent of its antihypertensive action in patients treated for 2 years with ciclosporin and no adverse effect on renal allografts (1). Nitrendipine did not affect blood concentrations of ciclosporin. Thus, nitrendipine, in contrast to most other calcium channel blockers, does not affect ciclosporin blood concentrations and can be safely added in transplant recipients.

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Nitric oxide

General Information

Gaseous nitric oxide is a short-lived molecule that has been used in the treatment of patients with primary pulmonary hypertension and is used in subgroups of severely ill and hypoxic children with persistent pulmonary hypertension of the newborn, in preterm infants of less than 34 weeks gestation, and in adults with acute lung injury and adult respiratory distress syndrome. There are some reports of its use for intestinal ischemia, reperfusion injury, thrombotic disorders, and sickle cell crises.

The adverse effects and toxicity of inhaled nitric oxide have been reviewed (1).

Therapeutic studies

The role of nitric oxide therapy in infants with severe acute hypoxemic respiratory failure has been reviewed (2). Inhaled nitric oxide was extremely well tolerated. Inhalation of 80 ppm rapidly improved oxygenation in patients with persistent pulmonary hypertension of the newborn (3). In three randomized, multicenter clinical trials there was a reduction in requirement for extracorporeal membrane oxygenation, with no significant adverse effects. There was no methemoglobinemia, high nitrogen dioxide, or increased rates of intracranial hemorrhage. In the NINOS trial in 235 term neonates (4), the study gas was not withdrawn in any patient because of toxicity. In another study of 58 term neonates receiving inhaled nitric oxide 80 ppm, a reduction in the use of extracorporeal membrane oxygenation (from 71% to 40%) was achieved without significant adverse effects (5).

Organs and Systems

Cardiovascular

There have been several case reports that high doses of nitric oxide (40–80 ppm) reduce pulmonary vascular resistance and increase pulmonary capillary wedge pressure in some patients with left ventricular dysfunction. The acute increase in left ventricular filling pressure that ensues can cause or exacerbate pulmonary edema. The author concluded that in patients with severe left ventricular dysfunction (pulmonary capillary wedge pressure over 25 mmHg) it would be prudent to avoid the use of inhaled nitric oxide.

Systemic hypotension has been reported after the introduction of inhaled nitric oxide (6).

- A 72-year-old woman, who underwent emergency resection of a giant left atrial myxoma, had pulmonary hypertension (pulmonary artery pressure 40 mmHg) and a low cardiac output (2.2 l/minute). Inhaled nitric oxide, 40 ppm, before cardiopulmonary bypass resulted in pulmonary vasodilatation and a fall in pulmonary artery pressure from 39 to 31 mmHg. This was accompanied by a fall in cardiac output from 2.4 to 1.5 l/minute and a fall in mixed venous oxygen saturation. After bypass, inhaled nitric oxide improved pulmonary and systemic hemodynamics and resulted in a rise in cardiac output from 3.0 to 3.5 l/minute.

The authors concluded that inhaled nitric oxide had reduced pulmonary hypertension and pulmonary vascular resistance, but that obstruction by the atrial myxoma had caused the low cardiac output, due to a net reduction in transpulmonary pressure.

Respiratory

In animal and in vitro studies, inhaled nitric oxide has led to surfactant inactivation and promotion of oxidative and nitrosylative lung injury (2). These effects have not been reported during clinical use of inhaled nitric oxide at concentrations less than 80 ppm. In a review of two articles it was noted that nitric oxide does not increase the risk of chronic lung disease of the newborn, despite speculation that it may increase chronic lung disease of prematurity due to the formation of nitrogen dioxide and peroxynitrite, in addition to membrane lipid peroxidation and increased unbound plasma iron in preterm infants (7).

In a randomized, double-blind, placebo-controlled, crossover study of the use of nitric oxide in chronic obstructive pulmonary disease (COPD) 11 patients with documented severe COPD received 25 ppm of nitric oxide combined with supplementary oxygen at a flow rate of 2 l/minute via nasal cannulae (8). Four of the patients reported an increase in cough and a feeling of retrosternal rawness after breathing nitric oxide for 24 hours; two had an increase in dyspnea, and one developed

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wheezing and was unable to perform exercise on a treadmill. There were no significant changes in lung spirometry. The authors noted that one patient had underlying reversible airways obstruction, but did not say if it was this individual who developed the wheezing. Nitric oxide is an irritant and causes inflammatory changes in the airways, so it is possible that nitric oxide could cause bronchoconstriction and aggravate asthmatic inflammation. There was a small but significant beneficial fall in pulmonary vascular resistance (183–137 dyne.s/cm^3) with nitric oxide. This is the first study of the prolonged use of nitric oxide (for 24 hours) in non-anesthetized, non-ventilated patients with COPD.

The role of nitric oxide as salvage therapy to improve pulmonary gas exchange has been studied in children with life-threatening asthma, unresponsive to other therapies (9). Four consecutive patients with hypercapnia or hypoxemia, despite mechanical ventilation, treatment with beta-adrenoceptor agonists, ipratropium bromide, intravenous corticosteroids, magnesium sulfate, and a trial of helium/oxygen mixtures, were treated with incremental concentrations of inhaled nitric oxide up to 80 ppm, after a successful trial in an index case. Four of the five had improvements in gas exchange, with a fall in arterial carbon dioxide tension. Gas exchange was also improved by inhaled nitric oxide 20 ppm, from a baseline PaO_2/FiO_2 ratio of 209 (range 175–276) to 430 (range 139–463). However at the higher dose of inhaled nitric oxide of 40 ppm there was a deterioration in oxygenation, with PaO_2/FiO_2 ratios falling to 163 (range 139–463). One patient did not respond to treatment and had a rise in $PaCO_2$ on treatment with inhaled nitric oxide 40 ppm, so treatment was withdrawn. This study has provided some supplementary evidence that nitric oxide can impair pulmonary gas exchange by causing irritation and further bronchoconstriction in susceptible patients, as noted in the COPD study mentioned above (8). Unfortunately, airways resistance was not measured in this study, but caution should be exercised and close monitoring undertaken when using inhaled nitric oxide in patients with bronchoconstriction.

Nervous system

Of major concern in the treatment of preterm infants is that nitric oxide might increase the incidence or severity of intraventricular hemorrhage. Nitric oxide impairs platelet aggregation and agglutination in vitro by activating guanylate cyclase and so increasing cGMP concentration. In a meta-analysis of randomized, controlled trials of inhaled nitric oxide for the treatment of preterm infants, only three studies were identified (10). In all, 300 infants were included in the analysis and the incidence of intraventricular hemorrhage was comparable between treatment and non-treatment groups, 35 of 111 receiving inhaled nitric oxide compared with 25 of 99 controls (OR = 1.37; 95% CI = 0.69, 2.74). There were no changes in mortality with treatment and no differences in neurological outcomes between nitric oxide and placebo during follow-up. These findings have been supported by a second meta-analysis of the use of nitric oxide in near-term infants with hypoxic respiratory failure, which showed no difference in the rate of neurodevelopmental abnormalities in neonates treated with nitric oxide (11).

In a randomized trial in 248 neonates older than 34 weeks of gestation, 126 of whom received nitric oxide, treatment with nitric oxide afforded no protection against neurodevelopmental abnormalities (12). The only benefits conferred by inhaled nitric oxide treatment in 42 preterm neonates was a reduction in the incidence of chronic lung disease along with improvement in oxygenation (13) and significant reductions in oxygenation index, duration of ventilation, and stay in neonatal ICU (14).

During long-term follow-up of the Neonatal Inhaled Nitric Oxide Study (NINOS), the neurodevelopmental safety of nitric oxide in infants over 34 weeks gestation with hypoxemic respiratory failure was assessed at 18–24 months of age, at which time there was a non-significant increase in disability in infants treated with inhaled nitric oxide (15). Of the 199 surviving infants in the study, 173 were assessed. Sensorineural hearing loss (15 and 13%, controls versus treatment), blindness in one or both eyes (2.2 versus 2.4%), the presence of cerebral palsy (10 versus 12%), and the presence of one or more neurodevelopmental abnormalities (30 versus 35%) were all statistically equivalent between the groups. The only significant difference was a greater rate of seizures after discharge in the control patients (15 versus 4.7% in those given inhaled nitric oxide).

Hematologic

Platelet aggregation

Nitric oxide activates guanylate cyclase and increases cGMP concentrations, thus inhibiting platelet aggregation and agglutination in vitro (1,16). The apparently high rate (63%) of intracranial hemorrhage in preterm neonates given inhaled nitric oxide (17) has not been confirmed in subsequent larger trials or in comparisons with matched controls from a large database (2). In addition, the frequency of bleeding complications in adults and children treated with inhaled nitric oxide has not been significantly increased in comparison with matched controls (16,17). Impaired platelet function and an increased risk of intracranial hemorrhage in preterm infants have not been substantiated in larger trials.

Methemoglobinemia

Nitric oxide oxidizes hemoglobin to methemoglobin, two-thirds of which is reduced by nicotinamide adenine dinucleotide (NAD) methemoglobin reductase (1). Several ethnic groups, such as native Americans, have NAD methemoglobin reductase deficiency. There have been reports of methemoglobinemia after accidental overdosage of inhaled nitric oxide in native Americans and others (1).

- A native American woman developed a rise in methemoglobin from 0.9 to 9.4% over 6 hours of inhaled nitric oxide therapy, 80 ppm; with reduction of the dose to 40 ppm, methemoglobin returned to baseline concentration. A patient who received inhaled nitric oxide through an imprecise delivery device had a methemoglobin concentration of 67%. Another patient who received a dose of 110 ppm had a methemoglobin concentration of 19%.

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In a phase II trial of 177 patients with adult respiratory distress syndrome, four developed a methemoglobin concentration over 5% but none had a concentration over 7%; one received placebo, one received inhaled nitric oxide 40 ppm, and two received 80 ppm.

There may also be partial deficiency of methemoglobin reductase in neonates (1). In the Neonatal Inhaled Nitric Oxide Study the dose of inhaled nitric oxide had to be reduced in 11 of 114 patients (9.6%) because of raised methemoglobin. At doses of 1.25–80 ppm, methemoglobinemia is uncommon; in one study only three of 471 (0.6%) patients discontinued therapy for this reason (17).

The incidence of methemoglobinemia is reduced by the use of low-dose nitric oxide. In a study in which inhaled nitric oxide was used in a dose of 20 ppm for 24 hours, followed by 5 ppm for up to 96 hours, only two infants of 126 randomized to nitric oxide developed methemoglobinemia (12). In 11 children aged 2.6–48 months undergoing surgery for congenital heart defects with associated pulmonary hypertension no infant receiving inhaled nitric oxide up to 80 ppm developed a methemoglobin concentration over 5% (18). Nitrogen dioxide concentrations rose to over 5% in some patients, with resolution once the dose was reduced. There were no adverse effects.

Vitamin B_{12} deficiency

One of the biochemical adverse effects of nitric oxide is inactivation of vitamin B_{12}, with subsequent potentiation of folate deficiency (19). This effect is mediated by irreversible oxidation of the cobalt residue in vitamin B_{12} to its Co^{++} and Co^{+++} forms. This leads to a reduction in methionine synthetase activity, with downstream effects on DNA synthesis. Previous studies have identified five patients with unsuspected vitamin B_{12} deficiency who developed subacute combined degeneration of the spinal cord following inhalation anesthesia with nitrous oxide (20). Nitric oxide has a similar effect on vitamin B_{12}, and its prolonged use could theoretically produce similar disorders in vitamin B_{12} metabolism (19).

Urinary tract

The effect of inhaled nitric oxide 2, 10, or 40 ppm on the frequency of reversal of acute lung injury in nitric oxide responders has been examined in an open-label randomized trial in 268 patients, of whom 180 were responders (PaO_2 increased by more than 20% within 10 minutes) (21). The patients were randomized into equal groups to receive conventional treatment with or without inhaled nitric oxide. Nitric oxide was given in the lowest effective dose until an end point (reversal of acute lung injury or severe respiratory failure) was reached or for 30 days. There was a significantly higher rate of renal insufficiency requiring renal replacement therapy in those given inhaled nitric oxide (25 versus 12%). The reasons for this were unclear. Although the groups were heterogeneous, both groups were similarly matched for risk of renal insufficiency at the start of the trial. The difference could have been due to a true adverse effect or to investigator bias in an open-label study. Owing to the absence of preclinical data suggesting renal toxicity and the absence of a known physiological route that could result in renal impairment, it is reasonable to conclude that the effect may have been due to chance (22).

Long-Term Effects

Drug withdrawal

Acute rebound of pulmonary hypertension and cardiovascular collapse can occur after abrupt withdrawal of nitric oxide. The risk factors for this adverse effect, or its incidence, have not been fully characterized. The incidence, risk factors, and nature of cardiopulmonary deterioration when patients' nitric oxide supply is abruptly withdrawn have been investigated in 56 intubated and mechanically ventilated patients with acute hypoxemic respiratory failure, of whom 39 had improved gas exchange (PaO_2 increased by more than 20 mmHg) during treatment with inhaled nitric oxide (23). After at least 10 hours of treatment (range 10–30 hours), inhaled nitric oxide was abruptly withdrawn and the patients were monitored for the rebound phenomenon and the need for continuing administration of inhaled nitric oxide. The mean dose of inhaled nitric oxide at the time of withdrawal was 22.8 (range 3–80) ppm. There was significant deterioration in gas exchange (decrease in SaO_2 more than 5%) and/or a drop in cardiac output of more than 10% in 23 patients (74%) and 15 (48%) had arterial desaturation within 30 minutes, which responded to reintroduction of inhaled nitric oxide. Eight patients had a rapid fall in cardiac output and/or blood pressure of over 20%, with prompt return to baseline measurements with reintroduction of therapy. Independent predictors of hemodynamic collapse were multiple system organ failure, older age, and an increased initial blood pressure in response to institution of inhaled nitric oxide. Hemodynamic measurements suggested that the acute collapse was primarily due to right ventricular overload. The authors also postulated that nitric oxide therapy causes down-regulation of nitric oxide synthase, and that removal of exogenous nitric oxide leaves the pulmonary vasculature with insufficient vasodilatory influences, allowing vasoconstriction to predominate. This down-regulation has been demonstrated in a rat model, but not in humans (24).

Of 88 patients with adult respiratory distress syndrome treated with inhaled nitric oxide, five developed rebound hypertension and arterial desaturation when inhaled nitric oxide was weaned (25). In an open-label, phase II pilot study of 16 infants over 4 weeks of age with severe bronchopulmonary dysplasia, inhaled nitric oxide, 20 ppm, led to a significant reduction (over 15%) in the concentration of inspired oxygen required to maintain satisfactory arterial oxygen saturation in 11 infants (26). There were no significant adverse effects at doses of 20 ppm. Of the 11 responders, seven developed episodes of desaturation within 10 minutes of withdrawal of inhaled nitric oxide after being weaned to under 8 ppm. Typically, a transient (30 minute) desaturation from 95% to 81% occurred after withdrawal of inhaled nitric oxide. On reinstituting therapy the desaturation rapidly reversed. The authors postulated that this effect may have been due to down-regulation of endogenous nitric oxide synthase.

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In a retrospective case-control study, 12 children with severe pulmonary hypertension were treated with inhaled nitric oxide followed by prostacyclin 10 ng/kg/minute for 24 hours before gradual withdrawal of nitric oxide; the 12 matched controls did not receive prostacyclin (27). Only one of the patients developed rebound hypertension, indicated by arterial desaturation (a 5% or greater fall in SaO_2 within 4 hours of withdrawal), while eight of 12 controls developed the rebound effect.

Severe systemic arterial hypotension has been reported after inadvertent withdrawal of nitric oxide (28).

- A 37-year-old woman with acute respiratory failure due to *Pneumocystis carinii* pneumonia 6 months after allogeneic bone marrow transplantation developed adult respiratory distress syndrome. Because of deteriorating gas exchange, mechanical ventilation and inhaled nitric oxide 10 ppm were given, with improvement in gas exchange and a reduction in mean pulmonary artery pressure from 46 to 36 mmHg. At times of brief withdrawal of nitric oxide rebound pulmonary hypertension occurred, with rapid reversal after reinstitution of therapy. After 6 days of treatment there was a sudden fall in systemic arterial pressure and pulmonary arterial pressure during interruption of nitric oxide delivery and subsequent measurements showed a fall in cardiac index from 3.3 to 2.1 l/minute/m^2.

The authors concluded that after sudden withdrawal of inhaled nitric oxide rebound pulmonary hypertension had contributed to acute right ventricular failure and loss of left ventricular pre-load, with a fall in cardiac output leading to reduced coronary performance and near cardiac arrest.

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Nitrofurantoin

General Information

Nitrofurantoin is a synthetic nitrofuran that belongs to a group of organic substances characterized by a heterocyclic ring consisting of four carbon atoms and one oxygen atom (1). Its mechanism of action is not understood. Nitrofurans enter bacterial cells and interact with several enzymes; thereby inhibiting bacterial growth. Nitrofurantoin is active against many Gram-positive and Gram-negative bacteria. It is particularly useful in treating urinary pathogens, including *Escherichia coli*, *Klebsiella* species, and *Proteus* species. However, *Pseudomonas aeruginosa* is almost always resistant.

After almost complete absorption from the gastrointestinal tract, nitrofurantoin produces high urinary concentrations. Blood and tissue concentrations are low. Nitrofurantoin has been used almost exclusively in the treatment and prophylaxis of urinary tract infections (1). Because of the severity of its adverse effects it should not be used as first choice.

General adverse effects

Harmless gastrointestinal adverse effects are most frequent with nitrofurantoin. Polyneuropathy occurs mainly in patients with renal insufficiency, in whom nitrofurantoin is contraindicated. Rarely, hemolytic anemia and hepatitis occur. Adverse events that are believed to be due to hypersensitivity include rashes, generalized urticaria, and acute pulmonary reactions. Although there are some in vitro data suggesting that nitrofurantoin may be a mutagen, a carcinogenic effect has not been proven in vivo. Teratogenic effects of nitrofurantoin have not been reported. High-dose oral nitrofurantoin may influence spermatogenesis and sperm motility.

Frequency

Drug-related adverse events are rare with nitrofurantoin and occur in fewer patients than with co-trimoxazole or trimethoprim, for example (1–3). The frequency of certain adverse reactions varies in different geographical areas (4,5). Lung reactions are more prevalent in Scandinavia and South Africa than in the UK, whereas polyneuropathies or gastrointestinal reactions are more frequent in the UK than in Sweden. These discrepancies are unexplained.

Organs and Systems

Cardiovascular

Except for cardiovascular collapse in anaphylactic shock, adverse cardiovascular events seem to be extremely rare with nitrofurantoin (4,5). In experimental animals, cardiotoxic effects have been described (6).

Respiratory

Acute respiratory reactions to nitrofurantoin include dyspnea, cough, interstitial pneumonitis, and pleural effusion, while interstitial pneumonitis and fibrosis are common chronic reactions (7). Nitrofurantoin causes acute lung injury more often than any other drug. Since the first well-documented case of an acute lung reaction in 1962 (8), several hundred further observations have been published (5,9). The frequency of acute severe pulmonary disease has been estimated to be one in every 5000 first administrations (10). Women aged 40–50 years are mainly affected. The acute lung reactions are not dose-related, and sensitization occurs at the earliest 1–2 weeks after the onset of exposure during the first course of therapy. Symptoms develop 2–10 hours after administration and consist of severe dyspnea, tachypnea, non-productive cough, high fever (usually with chills), cyanosis, and chest pain. Occasionally, arthralgia, backache or headache, vomiting, rash, collapse, and anaphylactic shock accompany the pulmonary symptoms (9). Lung findings include dense crackles or moist râles, predominantly at the lung bases. X-ray examination may be normal, but more often shows bilateral interstitial lower lobe infiltrates, often with pleural effusion. In one case, transient reverse ventilation-perfusion mismatch was documented by scintigraphy (11). Initially the leukocyte count is normal or raised, with neutrophilia and lymphopenia. Later, eosinophilia is common. When nitrofurantoin is withdrawn, clinical symptoms subside rapidly, usually within 1–3 days (5). However, minor X-ray changes can still be found 2 months later. Re-exposure to nitrofurantoin 50 mg re-induces the syndrome. Single cases of death due to heart failure have been reported in debilitated patients.

Acute lung reactions to nitrofurantoin are extremely rare in children (12). Lung tissue findings in acute reactions have shown minor vasculitis, granulomatous vasculitis (hypersensitivity angiitis), proliferation of endothelial cells, and empty alveoli (13). Rapidly progressing bronchiolitis obliterans with organizing pneumonia (BOOP) has been reported (14).

Chronic lung reactions are 10–20 times less frequent than acute reactions and mainly involve older patients. Reactions serious enough to require hospitalization occur in one out of 750 long-term users (15). Acute reactions do not seem to predispose to the later occurrence of chronic reactions. During long-term treatment, dyspnea and usually a non-productive cough without fever develop (15). Restrictive respiratory impairment is common. X-rays show interstitial infiltrations, often in the middle and basal lung regions. Fibrotic changes, alveolar exudates, and pleural effusions are rare. Histologically, chronic interstitial pneumonitis with varying degrees of fibrosis

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most often is found, and in some instances desquamative alveolitis (15–19).

Several mechanisms for the adverse lung effects of nitrofurantoin have been proposed (20–24). The pathogenesis of the acute lung reactions may be allergic (type III reactions) (18). However, there is also evidence that a cytotoxic immune mechanism (type II reactions), cell-mediated immunity (type IV reactions) (2), or direct toxic injury to lung tissue through the production of oxygen radicals (3,4) may be involved (20,21,24,25). In chronic lung reactions, the causative role of nitrofurantoin is less evident. It is supported by analogy and by the clinical course. Sometimes the skin test is positive, even in chronic lung reactions. Lymphocyte transformation tests give variable results. A polyclonal hypergammaglobulinemia is always present, with IgG predominating. Precipitating serum antibodies have not been found. Recent data have supported a toxic pathogenesis similar to that of the herbicide paraquat.

After nitrofurantoin withdrawal, the clinical symptoms regress rapidly. However, in most cases X-ray findings abate slowly and resolution is incomplete in at least 50% of patients. Occasional deaths due to cardiopulmonary failure have also been reported. The therapeutic benefit of corticosteroids is controversial, but the bulk of experience and anecdotal reports suggest that they are useful.

Atypical courses have been rarely described (5). A mixed type of reaction can occur: after an initial short fever peak, the patient becomes either afebrile or subfebrile, despite continuing to take nitrofurantoin and unabated activity of the lung process, or a typical chronic reaction converts to a typical acute reaction on re-exposure to nitrofurantoin after withdrawal. Acute reactions can occur without clinical symptoms, and can be recognized only on X-ray. Single cases of pulmonary hemorrhage, eosinophilic pneumonia, and interstitial giant cell pneumonia have also been reported (26,27).

In nitrofurantoin-induced pulmonary toxicity, in which high-resolution computed tomography initially showed a widespread reticular pattern and associated distortion of the lung parenchyma, thought to represent established and irreversible fibrosis, follow-up scans after drug withdrawal nevertheless showed resolution of pulmonary changes (28). These findings have been corroborated by a report of two middle-aged women who developed respiratory symptoms after prolonged treatment with nitrofurantoin (29). Both had impaired lung function and abnormal CT scans, and lung biopsies showed features compatible with bronchiolitis obliterans organizing pneumonia. Their condition improved when nitrofurantoin was withdrawn and glucocorticoid treatment was given.

In a patient with nitrofurantoin-induced pulmonary toxicity, in whom high resolution CT scans initially showed a widespread reticular pattern and associated distortion of the lung parenchyma, thought to represent established and irreversible fibrosis, follow-up CT scans after withdrawal of the drug showed resolution of the pulmonary changes.

- An 82-year-old woman developed a productive cough after having taken nitrofurantoin 50 mg/day for 4 years (30). She had impaired lung function and abnormal CT scans, and lung biopsies showed features compatible with bronchiolitis obliterans organizing pneumonia. The condition improved when nitrofurantoin was withdrawn and she was given a glucocorticoid.
- In a 58-year-old woman who took nitrofurantoin 100 mg/day for 11 months, pulmonary toxicity occurred, with bilateral interstitial infiltrates in the lower zones of the chest X-ray and loss of lung volume (31). High resolution CT scans showed ground-glass opacification in the mid-thoracic region, with patchy fibrosis and traction bronchiectasis. After withdrawal of nitrofurantoin and administration of prednisone, a chest X-ray 3 months later showed resolution of the pulmonary changes.

Nervous system

More than 140 cases of toxic polyneuropathy have been reported. The frequency depends on dose, tissue concentration, and renal function: in up to 90% of cases polyneuropathy occurred in patients with renal insufficiency (32). Symptoms usually start 9–45 days (at the earliest 3 days) after beginning nitrofurantoin. The neuropathy starts peripherally, predominantly affects the limbs, and remains more severe distally. Initially, there is sensory loss with paresthesia. Later, motor loss develops, often with severe muscle atrophy. As a rule, no further deterioration occurs after withdrawal of nitrofurantoin, and there may be total regression (34% of cases) or partial regression (45% of cases) (32). In some severe cases there is residual disability. The motor loss resolves more slowly and less completely than the sensory impairment. Single cases of retrobulbar optic neuritis, lateral rectus muscle palsy, and facial nerve palsy have been reported (33).

The lesions comprise degeneration of the myelin sheath of the nerves and nerve roots, with degeneration of the corresponding anterior horn cells and muscle fibers. The pathogenesis is unclear. Impairment of glutathione reductase has been considered. Even in healthy people, nitrofurantoin 400 mg/day for 2 weeks causes a significant increase in motor nerve conduction time. If strict attention is paid to the contraindication of renal insufficiency, the risk of polyneuropathy can be reduced. Careful controls for the initial symptoms of paresthesia can prevent the development of severe disablement.

While taking nitrofurantoin after urinary tract surgery, a 10-year-old girl developed diplopia and ptosis (34). A sleep test confirmed ocular myasthenia. Her signs and symptoms resolved after drug withdrawal.

Single cases of benign intracranial hypertension (pseudotumor cerebri), with and without ocular palsy, have been reported (35,36). Uncharacteristic general symptoms, with dizziness, cephalalgia, or drowsiness, are more frequent.

Trigeminal neuralgia (37) and cerebellar symptoms (38) have been attributed to nitrofurantoin.

Sensory systems

One case of crystalline retinopathy has been associated with long-term nitrofurantoin (39).

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Psychological, psychiatric

Rarely, concomitant dysphoric, euphoric, or even psychotic reactions have been reported in patients taking nitrofurantoin (1).

Metabolism

One case of hyperlactatemic metabolic acidosis together with hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency has been reported (40).

Hematologic

Some cases of hemolytic anemia associated with glucose 6-phosphate dehydrogenase deficiency have been described in patients taking nitrofurantoin (41).

Single cases of nitrofurantoin-induced (or enhanced) hemolytic anemia have occurred in patients with deficiencies of other erythrocyte enzymes (enolase or glutathione peroxidase), as have isolated cases of methemoglobinemia (42).

Nitrofurantoin produces oxidant stress and cellular damage by different mechanisms (43). It can disturb folate metabolism, leading to a megaloblastic component in pre-existing (mostly hemolytic) anemia, which responds to folic acid treatment.

There have been single cases of thrombocytopenia and a severe hemorrhagic diathesis with deficiency of coagulation factors due to a nitrofurantoin-induced hepatic disorder (44). Furthermore, nitrofurantoin experimentally inhibits ADP-induced platelet aggregation (45).

Allergic agranulocytosis or neutropenia have been proven in only a few cases (46,47). Pancytopenia is also rarely seen (5).

Mouth and teeth

Some cases of parotitis, rarely proven by rechallenge, have been associated with nitrofurantoin (48). The symptoms disappear after withdrawal.

Gastrointestinal

Gastrointestinal symptoms are the most common adverse effects of nitrofurantoin. Nausea and anorexia have been most often reported (49,50), whereas abdominal pain and diarrhea are rare. These effects are dose-related and usually harmless. The manifestations occur mostly after absorption of the drug and are mediated by the central nervous system. Measures that delay absorption, such as sugar coating or the use of a macrocrystalline form of the drug, reduce these adverse effects (51).

Liver

Hepatic reactions to nitrofurantoin are rare, and different forms can be distinguished (52–54). They can be associated with fatal liver necrosis (55,56).

Data from The Netherlands suggest that acute reactions are more common than chronic ones. Acute hepatic reactions may be hepatocellular or cholestatic. In the vast majority of subjects, symptoms appear within the first 6 weeks of nitrofurantoin treatment, and in half of the patients they occur within the first week of treatment. Jaundice is most common, followed by abdominal pain, malaise, and nausea. Hepatomegaly has been reported in nearly 50% of cases, fever in 30–65%, eosinophilia in 15–50%, and a rash in 12–60%. An immunological pathogenesis has been proposed (57), but experimental data point to a toxic mechanism involving the formation of glutathione-protein mixed disulfides and/or protein alkylation (58). The prognosis after withdrawal of the drug is good, but fatal courses have been reported when the drug is continued or, rarely, even after it has been discontinued.

Chronic active hepatitis, icteric or anicteric, has been described, almost always in women taking long-term nitrofurantoin. Most patients develop symptoms after a period of about 6 months of nitrofurantoin use. Fever (0–24%), rash (0–3%), and eosinophilia (9–23%) occur rarely compared with acute cases. There is hepatomegaly in 30–60% of chronic cases (54). Sometimes a broad spectrum of autoimmune reactions, a lupus-like syndrome, or mild cholestasis can be present (59,60). Some of these cases have occurred in combination with lung reactions of the protracted acute or chronic type, or in patients with ascites and liver cirrhosis. The clinical symptoms usually improve after withdrawal, but a few cases with extensive hepatocellular necrosis have necessitated liver transplantation or ended fatally (61–64). The histological changes can persist. Re-exposure to nitrofurantoin has reproduced the pathological liver tests.

Granulomatous hepatitis, with a rash or isolated increases in serum transaminase activities, can occur in patients with lung reactions (65). In the protracted acute and in chronic lung reactions liver injury (such as chronic active hepatitis) is more frequent than in acute reactions. Such cases usually show a broad spectrum of serological autoimmune reactions (lupus-like syndrome) (66).

Pancreas

A few cases of nitrofurantoin-induced acute pancreatitis, confirmed by rechallenge, have been reported (67).

Urinary tract

Nitrofurantoin-induced crystalluria, leading to obstruction of indwelling catheters, has been described in a few patients (68).

In rare cases, interstitial nephritis has been observed (69,70).

Skin

Allergic skin reactions occur in 1–2% of patients who take nitrofurantoin and comprise about 21% of all adverse reactions to nitrofurantoin (5,71). They often occur with other reactions, such as drug fever, lung, or liver reactions. The lesions can present as pruritus, as macular, maculopapular, or vesicular rashes, urticaria, angioedema, or erythema multiforme (72). The frequency of serious cutaneous reactions (erythema multiforme, Stevens–Johnson syndrome, or toxic epidermal necrolysis) after nitrofurantoin has been estimated to be 7 cases per 100 000 exposed individuals (71).

Sweet's syndrome has been observed in association with a 7-day course of nitrofurantoin (73).

Transitory alopecia that has been reported in a few cases is dose-related (74).

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Immunologic

About 20 cases of a lupus-like syndrome have been described, mostly in the Scandinavian literature. The clinical picture consisted of arthralgia or, rarely, exacerbation of a pre-existing rheumatoid arthritis and generalized lymphadenopathy, mostly associated with chronic lung and/or liver reactions, such as chronic active hepatitis (19,75,76). In patients with the lupus-like syndrome at least two immunological tests (antinuclear factor, rheumatoid factor, Coombs' test, and antibodies against smooth muscle, thyroglobulin, thyroid cell cytoplasm, or glomeruli) were positive. The lymphocyte transformation test was always positive. However, the LE cell phenomenon was always negative. As in other allergic reactions to nitrofurantoin, circulating albumin IgG complexes were found by immunoelectrophoresis, with tailing of the albumin line (77). The syndrome regresses after withdrawal.

Long-Term Effects

Drug tolerance

Nitrofurantoin is effective against Enterobacteriaceae; the rates of resistance were below 2% in a single-center study (78) and 3.5% in a multicenter study (79).

Mutagenicity

In vitro, nitrofurantoin acts as a mutagen by inhibiting DNA synthetase. In human fibroblast cultures it damages DNA (80). Treatment with nitrofurantoin for 12 months caused a significant increase in chromosome aberrations and sister chromatid exchanges in the lymphocytes of 69 children (81).

Tumorigenicity

Some studies have shown similar metabolism of nitrofurantoin and other (carcinogenic) nitrofurans. Formation of carcinogenic nitrofurantoin metabolites is therefore possible (82). However, a carcinogenic effect has not been proven for nitrofurantoin (83).

Second-Generation Effects

Fertility

High-dose oral nitrofurantoin (10 mg/kg/day) transiently reduces the sperm count in 30% of patients (84). This is due to arrest of maturation. Depression of sperm motility or ejaculate volume can also occur at lower doses (85).

Teratogenicity

Only very small amounts of nitrofurantoin cross the placenta, and teratogenic effects are not known (86). Even when it is used in the first trimester, there have been no associated fetal malformations (87). No teratogenic effects have been associated with nitrofurantoin in Denmark, Finland, Norway, and Sweden (88), or in a Hungarian case-control survey (89).

Fetotoxicity

Hemolytic anemia occurred during the first hours of life in a full-term neonate whose mother had taken nitrofurantoin during the last month of pregnancy (90). It may therefore be wise not to prescribe nitrofurantoin at the end of pregnancy.

Lactation

Nitrofurantoin is actively transported into human milk, achieving concentrations greatly exceeding those in serum. Concern is warranted for suckling infants under 1 month old or for infants with a high frequency of glucose-6-phosphate dehydrogenase deficiency or sensitivity to nitrofurantoin (91).

Susceptibility Factors

Genetic factors

Glucose-6-phosphate dehydrogenase deficiency is decisive for the development of hemolytic anemia in patients taking nitrofurantoin.

Age

Nitrofurantoin is contraindicated during the last trimester of pregnancy and in neonates, because hemolytic anemia can result from immature enzyme systems (90).

Renal disease

The main risk factor for toxic reactions to nitrofurantoin, especially polyneuropathy and gastrointestinal symptoms, is impaired renal function (32).

Drug–Drug Interactions

Estrogens

Nitrofurantoin reduces the enterohepatic circulation of estrogens (92).

Nalidixic acid

Antagonism in antibacterial efficacy between nitrofurantoin and nalidixic acid has been observed (93).

Pyridoxine

Pyridoxine accelerates the renal elimination of nitrofurantoin (94).

Interference with Diagnostic Tests

Glucose measurements

Nitrofurantoin can produce spurious positive urine glucose concentrations or raised blood glucose concentrations if reducing reagents are used (95).

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Nitrosourea cytostatic drugs

See also Cytostatic and immunosuppressant drugs

General Information

The nitrosourea cytostatic drugs are alkylating agents that include carmustine, lomustine, nimustine, and streptozocin (all rINNs).

Carmustine (BCNU) is used to treat myeloma, lymphomas, breast cancer, and brain tumors, Topical carmustine has been used to treat mycosis fungoides (1).

Lomustine (CCNU) is used to treat lymphomas and some solid tumors, particularly brain tumors, often in combination with procarbazine and vincristine (2). In contrast to other nitrosoureas, lomustine can be given orally.

Nimustine (ACNU) is used to treat malignant glioma (3).

Streptozocin (streptozotocin) is produced by *Streptomyces achromogenes*. It is used to treat metastatic islet cell carcinoma of the pancreas, but because of its high nephrotoxic and emetogenic potential it should be reserved for patients with symptomatic or progressive disease.

Organs and Systems

Respiratory

Carmustine pulmonary toxicity is well documented. Eight patients developed interstitial pulmonary fibrosis 12–17 years after exposure to carmustine in a total dose of carmustine of 770–1410 mg/m^2 (4).

Lung fibrosis has been described in a long-term follow up 13–17 years after treatment of 31 children given carmustine for brain tumors; six died, and of eight still available for study, six had upper zone fibrotic changes of their lungs on X-ray (5).

Lomustine can cause pulmonary infiltrates and fibrosis (6–8), and fatal pulmonary toxicity has occasionally occurred (9).

Sensory systems

A 2.7% ocular complication rate in 112 patients treated with a cumulative dose of carmustine 370 mg/m^2 for intracranial tumors has been recorded (10).

Eye pain and blindness due to retinal and optic nerve damage are recognized hazards of intracarotid carmustine therapy reference. They are thought to be due, at least in part, to the ethanol content of the diluent. Nimustine (ACNU) is water-soluble and ethanol-free. In a study of 30 patients with malignant gliomas, 123 infusions of nimustine and 53 of carmustine were administered (11). Eye pain was experienced during all carmustine infusions but not with nimustine, and one patient developed unilateral blindness after carmustine. In another study, carmustine was administered in solution with 5% dextrose in water (12). All the patients experienced ipsilateral orbital pain and scleral erythema, suggesting that carmustine itself contributes to the toxicity. Seven additional patients were treated wearing an ocular compression device to decrease blood flow and had not experienced any ocular complications.

Hematologic

Delayed myelosuppression is an important adverse effect of the nitrosoureas (13). It usually occurs 4–6 weeks after administration and can last for about 1–2 weeks. Thrombocytopenia occurs after about 4 weeks and leukopenia after 5–6 weeks.

Of 91 patients treated with topical carmustine, three developed reversible bone marrow suppression (14).

Urinary tract

Nephrotoxicity can rarely occur with lomustine, and all cases have been associated with cumulative doses greater than 1500 mg/m^2 (15).

Streptozocin is highly nephrotoxic, and renal function must be monitored carefully in all patients who are receiving it. Its effects include uremia, proteinuria, anuria, and proximal renal tubular acidosis (16). Uric acid nephropathy has also been reported (17). Adequate hydration has been recommended to reduce the risk of nephrotoxicity (18).

Skin

Local adverse effects of topical carmustine include tender erythema, superficial denudation or bullae, contact allergy, pigment alterations, and patchy telangiectasia (1).

Immunologic

Topical carmustine can cause hypersensitivity reactions, and three previous cases have been supplemented by a fourth (19).

- A 67-year-old woman used topical carmustine for a stage I cutaneous T cell lymphoma. A second course was started after 6 months and resulted in severe erosive inflammation at the site of treatment. Patch tests with carmustine 0.1, 0.5, and 1% in water all gave positive results; 22 controls were tested with 0.1% carmustine and lomustine and were all negative.

The most common adverse effect of chlormethine is an allergic contact dermatitis (20). Neither reducing the concentration of drug applied nor shortening the time of contact appreciably reduces the frequency of this adverse effect, which occurs in 30–80% of patients, although in

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one study of 203 patients with mycosis fungoides, the use of chlormethine ointment was associated with contact hypersensitivity in under 10% of cases. In an open, prospective study in 39 patients with cutaneous T cell lymphomas or parapsoriasis, chlormethine was applied topically and then washed off after 1 hour (21). There was cutaneous intolerance in 19 patients, six of whom had an allergic contact dermatitis after a mean period of 9.3 weeks, while the other 13 developed irritant contact dermatitis after a longer period. Cutaneous intolerance did not differ significantly according to the number of applications per week or the extent of body area treated. Comparison with published studies showed no significant difference in the number of cases of cutaneous intolerance after short-term application, although their occurrence was delayed. Therapeutic response was decreased appreciably by short-term application as compared with results in the literature.

Second-Generation Effects

Fertility

In 21 boys treated with carmustine or lomustine alone or in combination with procarbazine and vincristine for brain tumors, there were 20 cases of persistent testicular damage (22). From assessment of testicular size it was thought that most of those affected would remain infertile. This supports the idea that germinal epithelium is more susceptible than Leydig cells to cytostatic-induced damage.

Drug–Drug Interactions

Cimetidine

Bone marrow suppression by carmustine may be enhanced by cimetidine (23,24).

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Nitrous oxide

See also General anesthetics

General Information

Nitrous oxide is a relatively potent analgesic but a weak anesthetic, in use since 1842. At body temperature, its blood/gas partition ratio is only 0.47. It is excreted unchanged via the lungs. Because of the large mass of gas delivered to the patient, important physicochemical problems arise. Its ability to diffuse into and expand any air-filled cavity continues to produce new reports. Nitrous oxide is occasionally abused (1).

The continued use of nitrous oxide in anesthetic practice has been questioned on the basis of its serious adverse effects and the availability of potentially safer short-acting potent analgesic drugs, such as xenon and remifentanil (2).

Organs and Systems

Cardiovascular

Although myocardial depression has been described in healthy volunteers after the use of 40 or 50% nitrous oxide in oxygen, it is usually mild. It is likely that nitrous oxide can worsen myocardial ischemia in patients with critical coronary stenosis, although this may not be of clinical significance (3,4).

Homocysteine concentrations

Nitrous oxide inhibits methionine synthase, thereby preventing the conversion of homocysteine to methionine. A high homocysteine concentration has also been identified as an independent risk factor for coronary artery and cerebrovascular disease.

The effect of nitrous oxide on homocysteine concentrations and perioperative myocardial ischemia/infarction has been extensively reviewed (5). Nitrous oxide causes acute rises in postoperative homocysteine concentrations temporally associated with postoperative myocardial ischemia. Preoperative oral folate and vitamins B_6 and B_{12} blunt nitrous oxide-induced postoperative increases in plasma homocysteine (6).

The effect of nitrous oxide on homocysteine concentrations and myocardial ischemia has been studied in a randomized controlled study in 90 patients, ASA grades 1–3, who received a standardized anesthetic consisting of propofol induction, an opioid, and either inhalational isoflurane or isoflurane + 50% nitrous oxide (7). They underwent carotid endarterectomy (average operation duration 3.3 hours). Electrocardiographic monitoring consisted of a three-channel Holter monitor (leads II, V2, and V5), which was later examined for periods of ischemia by a physician blinded to treatment group. Myocardial enzyme activities were not measured. Baseline homocysteine concentrations (12.7 μmol/l) were significantly increased in the recovery room and at 48 hours to 15.5 and 18.8 μmol/l respectively. The concentrations did not increase in those given nitrous oxide. Periods of preoperative and intraoperative ischemia did not differ. Postoperatively the nitrous oxide group had more patients with ischemia (19 versus 11), longer ischemic events in the first 24 hours (54 minutes versus 17 minutes), and more episodes of ischemia lasting more than 30 minutes (23 versus 14). The authors concluded that nitrous oxide is associated with increased myocardial ischemia. However, they conceded that they had not shown causality. Previous studies have not shown this outcome, but were less sensitive, using only two-channel or once-daily 12-lead electrocardiography, or not monitoring patients postoperatively. The subject warrants a major study before a firm conclusion can be drawn.

Respiratory

Although airway conductance may be reduced by nitrous oxide, respiratory depression is unlikely after short-term exposure (8). The respiratory safety of nitrous oxide inhalation in children has been confirmed (9).

The effects of intraoperative air or nitrous oxide on postoperative oxygen saturation (S_aO_2) in blood have been compared in 40 patients of ASA classes 1 and 2 undergoing elective open cholecystectomy. The incidence of hypoxemia was significantly higher in those treated with nitrous oxide than in those given air 48 hours postoperatively (10). Hypoxemia may also have some mechanical origins. Nitrous oxide diffuses into the endotracheal tube cuff, overexpanding it, and can thus provoke upper airway obstruction, hypoxemia, and trauma in intubated patients during general anesthesia (11).

The poor solubility of nitrous oxide may be dangerous for patients with pneumothorax, pneumoperitoneum, ileus, or air embolism.

Nervous system

Nitrous oxide inactivates the enzyme methionine synthetase, and caution is urged in giving nitrous oxide to patients who may be deficient in vitamin B_{12}. Low serum vitamin B_{12} concentrations have previously been reported in patients with sickle cell disease, but the reason for this is uncertain. Three cases of peripheral neuropathy have been reported in patients with sickle cell disease who received nitrous oxide (12–14). All three had a history of frequent painful sickle crises, for which they received nitrous oxide for prolonged periods. Serum vitamin B_{12} concentrations were slightly reduced in two patients and very low in the third. The patients all presented with difficulty in walking and paresthesia. Peripheral sensorimotor neuropathy was confirmed by nerve conduction studies. The patients all responded well to vitamin B_{12} injections and avoiding further exposure to nitrous oxide. Caution is therefore recommended when using nitrous oxide in patients with sickle cell disease or who are suspected of vitamin B_{12} deficiency. Two cases of polyneuropathy have also been reported after the use of nitrous oxide for 80 minutes and 3 hours in patients who were subsequently found to have pernicious anemia. They both responded well to hydroxocobalamin.

Nitrous oxide has a potential for abuse (15), one of the major complications of which is myeloneuropathy. Altered vitamin B_{12} metabolism has been suggested as a mechanism (16), and in some cases the patients concerned have been found to have pre-existing subclinical B_{12} deficiency (17). Nitrous oxide interferes with vitamin B_{12} formation by causing irreversible oxidation of cobalt in

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an essential co-enzyme. Three cases of myeloneuropathy after nitrous oxide anesthesia have been reported in patients with subclinical vitamin B_{12} deficiency (18,19). In 12 patients who were heavily exposed to nitrous oxide either deliberately or professionally for periods ranging from 3 months to several years, numbness in the hands or legs developed initially, followed by Lhermitte's sign, gait ataxia, impotence, and sphincter disturbances (20). Several similar cases have been reported by others (SEDA-11, 110). Numbness and/or muscle weakness were found four times more often among exposed than non-exposed dental personnel (21).

Since nitrous oxide has some effects on the nervous system, it is not entirely surprising to note a further report that under experimental conditions it can affect memory. That memory changes can occur has been known for a long time, but the pattern of the effects now appears to be distinctly odd.

Myelopathy associated with nitrous oxide abuse has been reported (22).

- A 23-year-old man presented with a 5-day history of gait disturbance and incoordination. He had severe loss of proprioception in his legs and could not walk. He was hypomanic. Severe posterior column myelopathy was diagnosed using MRI scanning. His nitrous oxide use had consisted of 40–60 whipped cream bulbs per day for 6 months. He also admitted to intermittent diamorphine abuse, but not for the 3 weeks before admission. He was treated with hydroxocobalamin and methionine, but still had minor abnormalities 3 months later.

The authors noted that although the evidence is scant, treatment should consist of both vitamin B_{12} and methionine.

Two cases of polyneuropathy and myelopathy associated with chronic nitrous oxide abuse have been reported (23,24).

Inhalation of 50 or 70% nitrous oxide in oxygen for 15 minutes impaired driving skill (25). Patients who receive nitrous oxide should be informed that its after-effects can alter their functioning without their being conscious of the fact (26).

Nitrous oxide can diffuse into any cavity that has air inserted or left in situ. Intraoperative subdural tension pneumocephalus arising during neurosurgery has been described (27). Air injected into the epidural space can cause symptomatic pressure effects if nitrous oxide diffuses into the air pocket.

Sensory systems

Eyes

Nitrous oxide is 34 times more soluble than nitrogen in enclosed body cavity gas spaces and it enters such spaces rapidly, causing expansion and a rise in pressure. Vitreoretinal surgery often uses intraocular gases to replace vitreous humor, in order to internally tamponade the neuroretina to the retinal pigment epithelium. Various long-acting inert gases, such as sulfur hexafluoride or perfluoropropane, can be used as intraocular tamponading agents. Several cases of blindness and severe visual loss associated with nitrous oxide in people with intraocular gas bubbles have been reported (28–30). It has been suggested that all such patients should have warning bracelets detailing the presence of intraocular gas and that nitrous oxide be avoided until it has been shown that the gas bubble has been absorbed.

Ears

- Rupture of the tympanic membrane was attributed to nitrous oxide in a 28-year-old woman with a history of tonsillectomy and a recent respiratory tract infection who underwent dilatation and curettage during laparoscopy (31).

Hematologic

The effect of nitrous oxide on vitamin B_{12} and folate metabolism can cause megaloblastic bone marrow changes, the period required depending on the patient's nutritional status (32).

Dyshemopoiesis after exposure to nitrous oxide may be mediated through a direct inhibitory effect (33). Although clinical sequelae have not been reported, the use of nitrous oxide in bone marrow transplantation needs to be evaluated further and cannot currently be recommended (34).

Gastrointestinal

Nausea and vomiting seldom occur. Nitrous oxide had no effect on recovery from laparoscopic cholecystectomy (35).

Liver

Jaundice after general anesthesia in which nitrous oxide was the only anesthetic has been described (36). However, contamination with halothane was not definitely ruled out.

Urinary tract

Renal blood flow is moderately reduced by nitrous oxide (37). Disturbances of kidney function have been described (38).

Body temperature

Malignant hyperthermia is very rare; the possible role of nitrous oxide as a triggering agent has not been confirmed in pigs (39).

Second-Generation Effects

Pregnancy

Nitrous oxide has been widely used in pregnancy and is generally regarded as being safe (40).

Teratogenicity

Some experimental data have suggested a possible teratogenic potential of nitrous oxide, the clinical relevance of which is unclear (41). The interaction with vitamin B_{12} causes changes in DNA synthesis that could be important in the first trimester of pregnancy. Nitrous oxide is the only inhalational anesthetic that has definitely been

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shown to be teratogenic in experimental animals, but epidemiological studies have suggested that it is not teratogenic in human (42).

Drug–Drug Interactions

Halothane

The addition of nitrous oxide to halothane in coronary patients produced hypotension, with a subsequent risk of myocardial damage (43).

Other inhalation agents

The uptake of any other inhalation agent, given at the same time as nitrous oxide, is accelerated by the rate of uptake of nitrous oxide. This is termed the "second gas effect" (44). Direct pharmacodynamic interactions do not occur.

Interference with Diagnostic Tests

Oxygen dissociation

Nitrous oxide inhalation can give false PO_2 measurement results and shift the oxyhemoglobin curve to the left (45).

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Nizatidine

See also Histamine H_2-receptor antagonists

General Information

Nizatidine is a histamine H_2 receptor antagonist. Experience with it is still too limited to make valid comparisons with its earlier congeners. Data sheet warnings of possible adverse effects refer to skin rash, urticaria, somnolence, and thrombocytopenia. Nizatidine is said not to give problems with drug interactions or to affect androgen status.

The efficacy and safety of nizatidine 75 mg/day have been studied in a placebo-controlled trial in 994 individuals with heartburn (1). Nizatidine relieved heartburn significantly faster and/or more consistently than placebo. Nizatidine was well tolerated and the frequencies of adverse events were similar in the two groups.

Drug–Drug Interactions

Dapsone

In a randomized, crossover, open study in 16 healthy volunteers a rise in gastric pH to above 6 by nizatidine did not result in clinically important changes in the rate or extent of absorption of oral dapsone (2).

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Nomifensine

General Information

Nomifensine was first introduced in 1977 and eventually became available in over 70 countries. There has been increasing evidence of problems with adverse effects since 1981 (SEDA-5, 19), when cases of "drug fever" were recorded (SEDA-10, 22); this vague term covers a multitude of sins, the origins of which were finally elucidated at almost the exact moment when nomifensine was approved for release in the USA. Finally, in January 1986, the manufacturers withdrew nomifensine worldwide, citing grave concern elicited particularly by cases of rapid acute hemolytic anemia with intravascular hemolysis (SEDA-10, 22) (1).

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Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

See also Individual agents

General Information

The non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) include delavirdine, efavirenz, and nevirapine (all rINNs). The pharmaceutical chemistry and uses of the first- and second-generation NNRTIs have been reviewed (1).

In a non-randomized study of 694 patients taking two NRTIs, who were also given either nevirapine or efavirenz the reasons for discontinuation were as shown in Table 1 (2). In passing, it should be noted that although

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Table 1 Numbers (%) of patients who discontinued therapy in a follow-up study of two NRTIs plus either nevirapine or efavirenz

Reason for withdrawal	Nevirapine ($n = 460$)	Efavirenz ($n = 234$)
Patient-related reasons*	47 (6.7)	16 (6.8)
Failure of therapy	31 (10.2)	5 (2.1)
Adverse events		
Nervous system	1 (0.2)	12 (5.1)
Metabolism (lipodystrophy)	3 (0.7)	0
Gastrointestinal	12 (2.6)	1 (0.4)
Immunologic	56 (12.2)	5 (2.1)
Laboratory adverse events		
Hematologic	3 (0.7)	1 (0.4)
Liver	9 (2.0)	1 (0.4)

*Poor adherence, patient's decision, or therapy simplification.

this paper contains details of adverse events, there is no way of knowing that from a perusal of the title or abstract. Thus, anyone searching online for data for a systematic review of the adverse effects of these drugs might miss this information. When adverse events data are included in accounts of trials, the fact should be mentioned in the title and/or abstract.

Observational studies

Combinations of NRTIs and NNRTIs

The efficacy and safety of abacavir (NRTI) and efavirenz (NNRTI) plus background therapy have been retrospectively evaluated in 50 patients, who had previously been treated with HAART (3). There was some immunological benefit, albeit limited, in most of the patients. Adverse effects were not mentioned in detail, but the dropout rate during the first 4 weeks of treatment was high, owing to skin rashes and hypersensitivity reactions.

Of 80 injecting drug users who took two NRTIs + nevirapine (NNRTI), 20 discontinued treatment and 20 had treatment failures (4). Adverse events led to withdrawal of therapy in 10 patients: eight had a rash (in one case Stevens–Johnson syndrome), one had liver failure thought to be unrelated to the drugs; and one had "general intolerance." Two patients taking methadone had opioid withdrawal symptoms, presumably due to induction of methadone metabolism by nevirapine.

Combinations of NRTIs, NNRTIs, and protease inhibitors

In an open, 48-week, single-arm, multicenter phase II study in 99 patients abacavir 300 mg bd, amprenavir 1200 mg bd, and efavirenz 600 mg/day were associated with rashes in 50 patients, possibly because of abacavir hypersensitivity; 17 permanently discontinued one or more drugs as a result (5). Other adverse effects included nausea ($n = 41$), diarrhea ($n = 27$), sleep disorders ($n = 27$), dizziness ($n = 25$), fatigue ($n = 23$), hypertriglyceridemia ($n = 18$), neutropenia ($n = 8$), hyperamylasemia ($n = 4$), leukopenia ($n = 3$), hypercholesterolemia ($n = 2$), raised alkaline phosphatase ($n = 1$), and raised aspartate transaminase ($n = 1$).

In infants and children assigned to different combinations of one or two NRTIs plus an NNRTI and/or a protease inhibitor, the numbers of patients with moderate or severe adverse events were as shown in Table 2 (6). In cases of rash, the rash was worse in those who were taking nevirapine-containing regimens.

Organs and Systems

Liver

In 13 patients, studied retrospectively, who were given a combination of two NNRTIs, nevirapine + efavirenz, the most common adverse event was a change in liver function tests, to almost three times the upper end of the reference range in three cases; however, it was directly attributable to the antiretroviral drugs in only one case (7).

The incidence of NNRTI-induced hepatotoxicity in HIV-infected patients and the effect of co-infection with hepatitis B or hepatitis C virus have been studied in 272 patients (8). The NNRTIs used were delavirdine ($n = 40$), efavirenz ($n = 91$), and nevirapine ($n = 141$).

Table 2 Numbers (%) of infants and children with moderate or severe adverse events in a study of one or two NRTIs plus an NNRTI and/or a protease inhibitor

System affected by the adverse event	Regimen			
	Stavudine + nevirapine + ritonavir ($n = 41$)	Stavudine + nevirapine + nelfinavir ($n = 44$)	Stavudine + lamivudine + nevirapine + nelfinavir ($n = 44$)	Stavudine + lamivudine + nelfinavir ($n = 52$)
Respiratory	12 (29)	18 (41)	23 (52)	50 (96)
Hematologic (neutropenia)	17 (41)	9 (20)	14 (32)	23 (44)
Gastrointestinal				
Nausea/vomiting	29 (71)	32 (73)	18 (41)	15 (29)
Other	10 (24)	25 (57)	18 (41)	19 (37)
Liver	12 (29)	14 (32)	18 (41)	23 (44)
Skin	27 (66)	41 (93)*	32 (73)	17 (33)*
Body temperature (fever)	24 (59)	30 (68)*	20 (45)	10 (19)*

*Significantly different from the other groups.

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There were mild to moderate rises in serum aspartate transaminase or alanine transaminase in 81 patients and large rises in three patients, one of whom was taking efavirenz and two nevirapine. Hepatitis B or hepatitis C virus infection did not significantly increase the risk of hepatotoxicity. The authors concluded that NNRTIs cause little hepatotoxicity, despite the presence of co-infection with hepatitis B or hepatitis C viruses.

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Non-steroidal anti-inflammatory drugs (NSAIDs)

See also Individual agents

General Information

Non-steroidal anti-inflammatory drugs (NSAIDs) form a heterogeneous group of organic acids (Table 1) that have analgesic, antipyretic, anti-inflammatory, and platelet inhibitory actions.

Table 1 NSAIDs by structural class

Arylalkanoic acid derivatives
Aceclofenac
Alclofenac
Benoxaprofen
Bromfenac
Bucloxic acid
Bufexamac
Butibufen
Carprofen
Clobuzarit
Dexibuprofen
Dexindoprofen
Diclofenac
Diphenpyramidex
Etodolac
Felbinac
Fenbufen
Fenclofenac
Fenoprofen
Fentiazac
Flunoxaprofen
Flurbiprofen
Ibuprofen
Ibuproxam
Indoprofen
Ketoprofen
Ketorolac
Lonazolac
Loxoprofen
Nabumetone
Naproxen
Oxaprozin
Pirproxen
Pranoprofen
Romazarit
Tiaprofenic acid
Tolmetin
Tropesin
Suprofen
Zomepirac

Anthranilic acid derivatives
Antrafenine
Etofenamate
Floctafenine
Flufenamic acid
Glafenine
Meclofenamate
Mefenamic acid
Niflumic acid
Talinflumate
Tolfenamic acid

Continued

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Table 1 *Continued*

Butazone derivatives
Azapropazone
Bumadizone
Feprazone
Ketophenylbutazone
Monophenylbutazone
Oxyphenbutazone
Phenylbutazone
Pipebuzone
Pyrazine-butazone
Suxibuzone
Trimethazone
Coxibs (COX-2 inhibitors)
Celecoxib
Parecoxib
Rofecoxib
Valdecoxib
Indoleacetic acid derivatives
Acemetacin
Cinmetacin
Clometacin
Glucametacin
Indometacin
Oxametacin
Proglumetacin
Sulindac
Zidometacin

More than 100 NSAIDs are marketed or at an advanced stage of development worldwide. Their use is constantly expanding and the search for more efficacious and better-tolerated compounds is still being pursued, and has received renewed impulse with studies on selective inhibitors of cyclo-oxygenase type 2 (COX-2), nitric oxide-releasing NSAIDs, peroxidase inhibitors, enantiomers of already known NSAIDs, NSAIDs associated with zwitterionic phospholipids, and cytokine-modulating antirheumatic drugs.

Predominantly used in the management of rheumatological conditions, NSAIDs are drugs of choice in the treatment of inflammatory arthropathies. However, their use has also been extended to many non-rheumatological problems (for example dysmenorrhea, pain of different origin, neoplastic fever, migraine, thromboembolic disease, and patent ductus arteriosus; they are also used for tocolysis and in some neoplastic diseases) (1). Several clinical, epidemiological, and animal studies have suggested that NSAIDs can reduce the occurrence or progression of colorectal cancer, polyps, and perhaps other gastrointestinal tumors (2–4). Reports and epidemiological studies have shown that NSAIDs can protect against the risk of Alzheimer's disease (5,6). NSAIDs are used locally in the eye to prevent and treat postoperative cystoid macular edema, to control postoperative ocular inflammation and pain, for example after radial keratotomy or photorefractive keratectomy, and for non-surgically induced inflammatory disorders, such as allergic conjunctivitis.

The range and incidence of these conditions clearly justifies extensive use of suitable drugs, and explains the pharmaceutical industry's interest in exploiting the potential revenues of such a large market.

The effort to find new compounds is medically justified by the unsatisfactory benefit-to-harm balance of the NSAIDs that are currently available.

The adverse reactions profiles of many NSAIDs have proved to be unacceptable. Over the last 20 years, 18 NSAIDs have been withdrawn from the market or their clinical studies have been terminated because of unexpected toxicity (7). Selection of an NSAID can be difficult, since reliable information about their relative efficacy and adverse reactions is usually meager.

Although the physicochemical features, pharmacokinetics, and pharmacodynamics of individual NSAIDs differ, it is not known to what extent these differences are significant in the benefit-to-harm balance in the individual patient (8). Certainly they influence the adverse reactions and the general pattern of action of a particular subgroup of NSAIDs or a specific compound within a class, but this still provides no reliable prediction of what the individual patient will experience.

The acidic nature and lipid solubility of these compounds are important. The lipid solubility of an NSAID determines its penetration into the central nervous system and hence the incidence of nervous system-related adverse effects and perhaps adverse skin reactions (9,10). The weak acid nature affects tissue distribution, which explains why NSAIDs have actions at certain sites (for example synovial tissue of inflamed joints) and also contribute to triggering particular adverse reactions at others (for example the stomach and renal medulla) (11).

Pharmacokinetic aspects can play a critical role in the onset of certain adverse effects in some patients (12). NSAIDs are almost entirely absorbed from the gastrointestinal tract (13). The rate and the site of absorption from the gastrointestinal tract can be important; formulations designed to spare the stomach from NSAID toxicity can instead damage the intestinal wall, which seems to have been the case with Osmosin (SEDA-8, 103). There have been a few studies of the chronopharmacology of NSAIDs (SEDA-20, 90). NSAID absorption is probably better in the morning, but there are more adverse effects than when the drug is taken in the evening.

NSAIDs bind avidly to plasma proteins. High protein binding can theoretically predispose patients to drug interactions, which occur most frequently with certain NSAIDs (for example the butazones) in patients who are concomitantly taking drugs such as hypoglycemic agents or oral anticoagulants. The unbound fraction responsible for the pharmacological action of NSAIDs varies with the plasma albumin concentrations, which can be influenced by active rheumatoid arthritis, genetic factors, sex, age, pregnancy, other drugs, and diseases, particularly when the kidney and liver are involved. A correlation between anti-inflammatory action and dose or plasma concentration has been documented for only a few NSAIDs, and there is no direct evidence that an increase in unbound drug concentration is associated with greater toxicity. However, there is convincing evidence that the dose contributes to certain adverse effects (for example gastrointestinal and renal). A record-linkage study has shown an association between NSAID dosage and upper gastrointestinal bleeding (14).

NSAIDs can be roughly divided into those with short and long half-lives. Although the difference in clinical

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effects between these two categories is poorly understood, half-lives have served as a rough guide for NSAID dosage regimens, compounds with long half-lives being administered only once a day. These NSAIDs also have a greater potential to cause adverse effects, at least in some patients. As the half-lives of this type of NSAID vary widely in different patients, drug accumulation can occur in some individuals. When using an NSAID with a long half-life, loading doses can be given to achieve high drug concentrations quickly, but can be associated with increased adverse effects, particularly gastrointestinal intolerance.

NSAIDs are mainly cleared by the liver, and their clearances would be expected to fall with age (13). Their metabolites are generally inactive and excreted in the urine, which as a rule contains very little unchanged drug. Conversely, several NSAIDs that are themselves inactive can be used as prodrugs, since they have active metabolites; some of these compounds, such as sulindac, undergo enterohepatic recycling. Claims that these prodrugs are less toxic than other compounds are not supported by any firm evidence. Some NSAIDs, including carprofen, fenoprofen, indometacin, ketoprofen, and naproxen are metabolized to acylglucuronides; the metabolites are retained and hydrolysed to re-form the parent compound. This is probably one of the mechanisms of toxicity in patients with renal insufficiency.

Pharmacodynamic mechanisms can also be crucial. The main mechanism of action is inhibition of cyclo-oxygenase (COX) activity and consequently of prostaglandin synthesis (15–17). Two forms of COX have been identified: COX-1, which is constitutively expressed in many cells and tissues, and COX-2, which is selectively induced by proinflammatory cytokines at the site of inflammation. The discovery of a second COX enzyme has led to the hypothesis that the toxicity associated with the clinically useful NSAIDs is caused by inhibition of COX-1, whereas the anti-inflammatory properties are caused by the inhibition of COX-2 (18). A selective COX-2 inhibitor may therefore have better anti-inflammatory activity with greater safety than existing NSAIDs. The in vitro potency of NSAIDs as inhibitors of prostaglandin synthesis, which tends to match their anti-inflammatory potency in vivo, varies from one anti-inflammatory agent to the next (19,20). Other mechanisms that are poorly understood may be implicated in determining both a drug's activity and its adverse effects.

These data provide a basis for the practical use of NSAIDs. There can be no doubt that some NSAIDs are more toxic than others, notably those that have the greatest inhibitory effect on cyclo-oxygenase. NSAIDs that inhibit both cyclo-oxygenase and lipoxygenase are particularly toxic. The fact that some NSAIDs are more toxic to single organs than others seems to depend on the physicochemical and metabolic characteristics of single drugs or groups of similar drugs. Despite numerous studies, reliable comparisons of the adverse effects of the different drugs are scanty. However, some data have been produced from the data bank centers of the Arthritis Rheumatism and Aging Medical Information System (ARAMIS) and have been reviewed (SEDA-17, 102). If selective COX-2 inhibitors are confirmed to have less gastrointestinal toxicity than the old NSAIDs, we should have new drugs with fewer risks. However, doubts are emerging about whether COX-1 inhibition makes a contribution to the anti-inflammatory activity of NSAIDs and whether COX-2 activity is implicated in mucosal healing and protective processes (SEDA-22, 109).

The categories of patients who are at higher risk of adverse reactions when treated with NSAIDs are well known and can largely be deduced from what has been said above. They include the elderly (especially women), pregnant women (and their fetuses), neonates, patients with liver, kidney, or cardiac disorders, and those with hypertension, multiple myeloma, peptic disorders, or active rheumatoid arthritis. Greater awareness of these risk factors among medical practitioners, limiting the use of NSAIDs to cases in which there is a precise indication, informing patients, developing systems for monitoring unwanted adverse effects, and carrying out adequate well-designed experimental studies would do much to ensure better use of these drugs. Many of the adverse effects of NSAIDs are, with negligible differences, common to all of them.

Organs and Systems

Cardiovascular

Hypertension

NSAIDs can cause or aggravate hypertension and interact negatively with the effects of antihypertensive drugs, including diuretics, although contrasting data from experimental and clinical studies have been published (21).

The mechanisms by which NSAIDs affect cardiovascular function are complex and controversial. They may include reduced blood flow, a reduction in the filtered load of sodium, an increase in tubular reabsorption of sodium, and a reduction in the synthesis of PGE-1, which may be associated with raised blood viscosity and increased peripheral vascular resistance. This is perhaps the primary mechanism, which is due to increased renal synthesis of endothelin-1.

Meta-analyses

In a meta-analysis of the hypertensive effects of NSAIDs or aspirin (1.5 g/day or greater) in short-term intervention studies; 54 studies and 123 NSAID treatment arms were included (22). Of the 1324 participating subjects, 92% were hypertensive; they had a mean age of 46 years and none was over 65 years. The major outcome studied was the change in mean arterial pressure. The effects of NSAIDs on blood pressure were found solely in hypertensive subjects; among these, the increase in mean arterial pressure, after adjusting for possible confounders (for example dietary salt intake) was different among different NSAIDs. The increase in mean arterial pressure was 3.59 mmHg for indometacin (57 treatment arms), 3.74 mmHg for naproxen (4 arms), and 0.45 mmHg for piroxicam (4 arms). However, mean arterial pressure fell by 2.59 mmHg with placebo (10 arms), by 0.83 mmHg with ibuprofen (6 arms), 1.76 mmHg with aspirin (4 arms), and 0.16 mmHg with sulindac (23 arms).

Overall, only the effects of indometacin on mean arterial pressure were statistically significantly different from those found with placebo, showing that in this population

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the effects of NSAIDs on blood pressure were modest and varied considerably among different drugs. However, one must take into account the important limitations of the analysis: the patients were mostly young, the studies included in the meta-analysis were small and short-term, and information on possible confounders was incomplete. The significance of the results of this study is therefore doubtful.

Another meta-analysis provided more complete and useful results (23). Its primary aim was to produce an estimate of the overall effect of NSAIDs on blood pressure, and its secondary aims were to evaluate the mechanisms by which NSAIDs alter blood pressure and to determine susceptibility factors. Moreover, as NSAIDs have been associated with raised blood pressure in normotensive individuals and in both treated and untreated hypertensive subjects, the authors tried to discover different effects in these subgroups. Finally, they studied whether different NSAIDs alter blood pressure to the same degree.

In all, 50 randomized placebo-controlled trials and 16 randomized comparisons of two or more NSAIDs met the selection criteria. These studies included 771 young volunteers or patients aged 47 years or younger. The studies were small (the mean sample size per trial was 16); many different NSAIDs and antihypertensive drugs were used, but indometacin was used in more than half of all the trials; the duration of therapy with NSAIDs or antihypertensive drugs was 1 week or longer, but in most studies it was less than 3 months. NSAIDs raised supine mean blood pressure by 5.0 mmHg (95% CI = 1.2, 8.7), but had no significant effect on variables measured to assess possible mechanisms (such as body weight, daily urinary sodium output, creatinine clearance, or urinary prostaglandin excretion). Overall, the data suggested that NSAIDs do not appear to increase blood pressure primarily by increasing salt and water retention, because weight and urinary sodium were not altered by NSAIDs and inhibition of blood pressure control was not more marked in patients taking diuretics compared with other antihypertensive drugs. In addition NSAIDs did not significantly alter plasma renin activity or 24-hour urinary excretion of prostaglandin E_2 and 6-ketoprostaglandin $F_{1\alpha}$. Other factors may therefore contribute to the increase in blood pressure caused by NSAIDs. In particular, a potential effect of NSAIDs on peripheral vascular resistance should be considered (24,25). There is good evidence to suggest an important role for prostaglandins in the modulation of two major determinants of blood pressure, vasoconstriction of arteriolar smooth muscle and control of extracellular volume.

NSAIDs inhibited the effects of all antihypertensive drug categories. However, in patients taking beta-blockers and vasodilators, NSAIDs produced a greater increase in supine mean blood pressure than in patients taking diuretics, but only the pooled inhibitory effect of NSAIDs on the effects of beta-blockers achieved statistical significance. When the data were analysed by type of NSAID the meta-analysis showed that all NSAIDs increased supine blood pressure, and that piroxicam, indometacin, and ibuprofen produced the most marked increases. However, only piroxicam had a statistically significant effect with respect to placebo. Aspirin, sulindac, and flurbiprofen caused the smallest increases in blood pressure.

In conclusion this meta-analysis has provided more clear evidence that, as a group, NSAIDs significantly increase arterial pressure and can antagonize the blood pressure-lowering effect of some antihypertensive drugs, by mechanisms that are still unclear. Although the hypertensive effect of NSAIDs was more marked in hypertensive subjects taking antihypertensive drugs than in normotensive subjects not taking antihypertensive drugs, the difference was not statistically significant and its clinical relevance is unclear. It is worth noting that the effects of NSAIDs on blood pressure were similar in patients taking antihypertensive drugs for months or only a few days.

This study also had two main limitations: first, most of the trials were small, which precluded definitive conclusions about the effects of individual NSAIDs or individual antihypertensive drug classes; secondly, in most studies, therapy was short term and the patients were relatively young, making generalization of the results difficult, as NSAIDs are most often prescribed long term and for elderly people.

Prospective studies

A case-control study of the effects of NSAID therapy on arterial pressure has been performed in subjects aged 65 years and over, drawn from a large database (the State of New England Medicaid Program) to determine whether NSAIDs affect blood pressure (26). The investigators calculated the odds ratio (OR) for the initiation of antihypertensive therapy in patients taking NSAIDs relative to non-users after adjusting for possible confounding factors. The 9411 patients had started taking antihypertensive drugs between 1981 and 1990, and a similar number of controls were randomly selected. The date of the first prescription for an antihypertensive drug was defined as the index date. Of those who took antihypertensive drugs, 41% had taken an NSAID during the year before the index date, compared with 26% of the control subjects. This risk increased with the recency of NSAID therapy, and was greatest among recent users (those with a supply of NSAIDs ending more than 60 days before the index date) (OR = 2.10; 95% CI = 1.95, 2.26). For former users (those with a supply of NSAIDs ending more than 60 days before the index date) the adjusted OR compared with non-users was 1.66 (CI = 1.54, 1.80). There was a dose-response relation, with adjusted ORs of 1.55 (CI = 1.38, 1.74), 1.64 (CI = 1.44, 1.87), and 1.82 (CI = 1.62, 2.05) for low, medium, and high daily doses of NSAIDs respectively. The unadjusted ORs for ibuprofen, piroxicam, meclofenamate, and indometacin, were separately calculable, and for each of these drugs the OR increased with increasing dose. The relation between cumulative duration of NSAID use and the initiation of antihypertensive therapy was also examined in recent users. The risk was greatest in those who had used an NSAID for 30–90 days and was less for those who had used an NSAID for less than 30 days or for more than 90 days.

The results of this study suggest that the effects of NSAIDs on blood pressure in older patients taking NSAIDs may be clinically important. Given that 15% of

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the control group were recent users of NSAIDs, and assuming that the adjusted OR of 1.66 represents a causal association of these drugs with the initiation of antihypertensive therapy, the proportion of cases attributable to the use of these drugs in this sample of elderly population was nearly one in ten.

Despite the high prevalence of the use of minor analgesics (aspirin and paracetamol) there is little information available on the association between the use of these analgesics and the risk of hypertension. A prospective cohort study in 80 020 women aged 31–50 years has provided some useful information (27). The women had participated in the Nurses' Health Study II and had no previous history of hypertension. The frequency of use of paracetamol, aspirin, and NSAIDs was collected by mailed questionnaires and cases of physician-diagnosed hypertension were identified by self-report. During 164 000 person-years of follow-up, 1650 incident cases of hypertension were identified. Overall 73% of the cohort had used paracetamol at least 1–4 days/month, 51% had used aspirin, and 77% had used an NSAID. Compared with non-users of paracetamol the age-adjusted relative risk (RR) of hypertension was significantly increased even in women who had used paracetamol for only 1–4 days/month (RR = 1.22; CI = 1.07, 1.39). There seemed to be a dose-response relation, as the RR of hypertension compared with non-users was 2.00 (CI = 1.52, 2.62) in women who had taken paracetamol for 29 days/month or more. For women using aspirin or NSAIDs at a frequency of 1–4 days/month the RRs were 1.18 (CI = 1.02, 1.35) and 1.17 (CI = 1.02, 1.36) respectively. However, after adjusting for age and other potential risk factors, only paracetamol and NSAIDs, but not aspirin, remained significantly associated with a risk of hypertension. In summary, the data from this study support the view that paracetamol and NSAIDs are strongly associated with an increased risk of hypertension in women, the risk increasing with increasing frequency of use. Aspirin did not seem to be associated with an increased risk. This conclusion contrasts with the results of some short-term studies that have shown no effect of paracetamol on blood pressure (28,29).

However, the results from this study must be interpreted with caution, as there were some limitations: the assessments of analgesic use and hypertension were made using a self-reported questionnaire; relative risk can be influenced by many potentially confounding variables; the results are relevant only for young women and cannot be extrapolated to the general population.

The impact of NSAIDs on blood pressure in elderly people has been evaluated in three epidemiological studies, with similar findings (SEDA-19, 92). The use of NSAIDs was significantly associated with hypertension or the use of antihypertensive drugs. Reliable data are available for hypertension in the elderly. Recent users of NSAIDs have a 1.7-fold increase in the risk of initiating antihypertensive therapy compared with non-users, and the use of NSAIDs significantly predicts the presence of hypertension (OR = 1.4; 95% CI = 1.1, 1.7) (21).

Conclusions

The overall results of these studies have provided convincing evidence that NSAIDs and paracetamol can raise arterial blood pressure in a dose-related fashion, interfere with the actions of antihypertensive drugs, and prompt the need for new antihypertensive therapy.

Even if the increase in mean blood pressure is probably modest (less than 5.0 mmHg) the clinical relevance of such an increase can be large, especially in elderly people. In fact, an overview of randomized clinical trials of antihypertensive treatment has shown that a 5–6 mmHg increase in diastolic blood pressure over a few years can be associated with a 67% increase in the incidence of strokes and a 15% increase in coronary heart disease (30). These effects are apparent in both normotensive and hypertensive patients.

Whether these results apply with certainty to patients taking NSAIDs is not known, because these studies included patients not taking NSAIDs, but it is wise to consider this probability. The type and dose of NSAID may be important, but more studies are needed to document this. Hypertensive and elderly patients seem to be particularly at risk. In patients taking long-term NSAIDs, or even paracetamol, periodic monitoring of blood pressure appears to be warranted.

Congestive heart failure

Much less is known about the risk of congestive heart failure with NSAIDs. The rate of hospitalization for congestive heart failure in more than 10 000 patients over 55 years of age during exposure to both diuretics and NSAIDs was compared with the rate in those exposed to diuretics alone (31). At mean follow up of 4.7 years, there was an increased risk of hospitalization when diuretics and NSAIDs were used concomitantly (RR = 1.8; 95% CI = 1.4, 2.4).

In 600 elderly patients with documented congestive cardiac failure there was a possible or probable link between NSAIDs and heart failure in 27 cases (32). In some, the mechanism was apparently a reduction in the effect of furosemide. In others the NSAID may have caused an imbalance in circulatory homeostasis. Pre-existing renal impairment was not observed in any of the 27 cases. This study suggests that in elderly people congestive heart failure may be a complication of NSAIDs.

In a matched case-control study the relation between the recent use of NSAIDs and hospitalization with congestive heart failure in elderly patients has been analysed (33). Cases (n = 365) were patients admitted to hospital with a primary diagnosis of congestive heart failure; controls (n = 658) were patients without congestive heart failure. Structured interviews were used to obtain information on several possible risk factors, such as a history of heart disease and the type and dosage of NSAIDs used. The use of NSAIDs (other than low-dose aspirin) in the previous week was associated with a doubling of the chance of a hospital admission with congestive heart failure (adjusted OR = 2.5, CI = 1.2, 3.3). The risk was even higher in patients with a history of heart disease, in whom the use of NSAIDs was associated with an increased risk of a first admission with congestive heart failure (OR = 11; CI = 0.7, 45), but not in those without a history of heart disease (OR = 1.6; CI = 0.7, 3.7). In contrast to the results of a previous study (31), the risk of admission to hospital with congestive heart failure was positively related to the

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dose of NSAID consumed in the previous week and was higher with long half-life NSAIDs than with short half-life NSAIDs. The authors estimated that, assuming that these relations were causal, NSAIDs might be responsible for about 19% of hospital admissions with congestive heart failure. If confirmed, this burden of illness resulting from NSAID-related congestive heart failure may rival that resulting from damage to the gastrointestinal tract and would represent an under-recognized public health problem. In any case, this study reinforces the timely suggestion that NSAIDs should be used with great caution in patients with a history of cardiovascular disease. This recommendation must also include the use of the selective COX-2 inhibitors, until more information is available.

Respiratory

As 2–20% of adult asthmatics have aspirin hypersensitivity (34), they must be considered at risk from NSAIDs. The mechanism is related to a deficiency in bronchodilator prostaglandins; prostaglandin inhibition may make arachidonic acid produce more leukotrienes with bronchoconstrictor activity. Oral challenge in asthmatic patients is an effective but potentially dangerous method for establishing the presence of aspirin hypersensitivity (35). Occasionally, bronchospasm may be part of an anaphylactoid reaction to NSAIDs; zomepirac was withdrawn for this reason. Intriguingly bee-keepers may be at increased risk for severe reactions from bee stings if they are taking NSAIDs, and it has been suggested that NSAIDs should be prescribed with particular caution for them (36).

Nervous system

NSAIDs cause headaches and confusion in a relatively small number of patients. Headache and dizziness are common with indometacin, and it has been suggested that its chemical similarity to serotonin, which can cause severe headaches, may be responsible (37). Headache due to long-term use of ibuprofen has been reported in children (38,39).

The Australian Drug Reaction Advisory Committee has reported paresthesia as a class effect of NSAIDs, although it is rare and reversible (40).

Studies on the link between falls in elderly people and NSAIDs have yielded conflicting and inconsistent data (41,42), and an increased risk of falls with NSAIDs is difficult to explain.

Some rarer adverse effects, such as aseptic meningitis, have been reported with ibuprofen, sulindac, and tolmetin (37) in patients with systemic lupus erythematosus. A case-control study showed no increased risk of intracerebral hemorrhage in patients using aspirin or other NSAIDs in low dosages as prophylaxis against thrombosis (43).

Sensory systems

Eye disorders, such as blurred vision, ocular discomfort, irritation, and more severe problems, such as optic or retrobulbar neuritis and papilledema, have been described (SEDA-19, 96).

Psychological, psychiatric

Behavioral changes have been reported with indometacin (44).

- A 92-year-old man with a history of senile dementia of the Alzheimer type, glaucoma, and constipation took indometacin 25 mg for pseudogout. After six doses he became very agitated and confused and was physically and verbally aggressive. Indometacin was withdrawn and he recovered over 10 days with the help of haloperidol 0.5 mg/day (45).

NSAIDs should probably be included as one of the many groups of drugs that can cause confusion in the elderly.

Cognitive function in elderly out-patients was assessed in a large retrospective study by a questionnaire; there were no significant differences in the total scores of users and non-users of NSAIDs (SEDA-17, 106). Another study showed that performance in sensorimotor coordination and short-term memory tests can improve in healthy elderly volunteers who take indometacin (46). NSAIDs have also been associated with a reduced risk of Alzheimer's disease (47).

Electrolyte balance

NSAIDs can interfere with fluid and electrolyte homeostasis, thereby causing edema, hyponatremia, hyperkalemia, and blunting of the natriuretic effects of diuretics (48,49).

Hematologic

NSAIDs have been reported to cause potentially severe hematological disorders: thrombocytopenia, agranulocytosis, aplastic anemia, and hemolytic anemia (50). Thrombocytopenia is generally mild and reversible and has a low case-fatality rate, but deaths from bleeding have been reported, particularly with indometacin, oxyphenbutazone, and phenylbutazone (50).

Pyrazolone derivatives and butazones are most frequently blamed for causing agranulocytosis and aplastic anemia (SEDA-9, 85) (SEDA-11, 89). Unfortunately, no reasonably accurate estimate of the overall incidence of either disease or of the risk associated with the use of any particular NSAID is available. The results of the International Agranulocytosis and Aplastic Anemia study (51) have been reviewed in detail (SEDA-11, 89) (SED-11, 171). This epidemiological study was organized by the manufacturer (Hoechst) of the widely incriminated drug dipyrone. The overall annual community agranulocytosis incidence was 4.4 per million (6.2 including hospital cases), with a fatality rate of 10% and an annual mortality rate of 0.4 per million. Analgesics significantly associated with agranulocytosis were dipyrone, indometacin, and two butazones (oxyphenbutazone and phenylbutazone). Other pyrazolones, such as amidopyrine (which is an acknowledged cause of agranulocytosis), or other NSAIDs could not be evaluated because of the small number of cases.

A population-based, case-control study in patients hospitalized with neutropenia has confirmed both the association between NSAIDs and neutropenia and the differences between different classes of NSAID (52). The data on aplastic anemia are also of interest, since

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this was the first study to provide excess risk estimates of this adverse effect in NSAID users. The overall annual incidence was 2.2 per million, with a 2-year fatality rate of 40%. A significantly increased risk for aplastic anemia was associated with any exposure to three drugs: indometacin (multivariate rate ratio 13), butazones (8.7), and, unexpectedly, diclofenac (8.8). Whatever the interpretations by different manufacturers, the study confirmed that dipyrone can cause agranulocytosis and that indometacin can cause aplastic anemia (53). The high relative risk of diclofenac for aplastic anemia is unexpected and requires confirmation.

Hemolytic anemia has occasionally been associated with NSAIDs; many reports involved mefenamic acid, ibuprofen and sulindac (54). No evidence has been found that any NSAID, except aspirin, constitutes a particular risk for subjects with glucose-6-phosphate dehydrogenase deficiency.

A prospective study on bleeding complications in 23 patients undergoing dermatological surgery has shown that NSAIDs and aspirin need not be withdrawn routinely preoperatively, unless the bleeding time is prolonged (55). Relatively few patients developed a prolonged bleeding time while taking aspirin or other NSAIDs and only few had significant intraoperative blood loss. There is variation in the response of patients for unknown reasons and so the recommendation that NSAIDs should be withdrawn before elective surgery awaits confirmation (SEDA-19, 96).

Gastrointestinal

Peptic ulceration

Prostaglandins have a protective effect on the gastrointestinal mucosa. All NSAIDs that non-selectively inhibit prostaglandin synthesis cause gastrointestinal mucosal damage. Direct NSAID-mediated acid damage has been identified as a mechanism of gastrointestinal toxicity (56). Several in vitro and animal studies have provided evidence of early vascular changes and have highlighted the role of leukocyte adhesion to the endothelium in NSAID-induced gastropathy. The pathogenesis of NSAID-associated gastrointestinal damage has been reviewed (SEDA-17, 104).

Clinical presentation

Features of upper gastrointestinal toxicity during NSAID therapy range from relatively mild symptoms (such as heartburn, dyspepsia, and stomach discomfort) to more severe and potentially life-threatening states (for example gastrointestinal erosion or ulceration, bleeding, or perforation). Although dyspepsia is one of the major factors that limit the use of NSAIDs in patients with rheumatic diseases, it does not necessarily predict mucosal damage. There is no close correlation between objective gastroscopy findings and subjective intolerance of medications, or between acute or chronic damage and complications. Epigastric pain was the most common symptom in patients admitted to hospital with hematemesis and/or melena, whether treated or not with NSAIDs in the 14 days before admission (SEDA-17, 103).

"NSAID gastropathy" is the term proposed by Roth and Bennett to describe upper gastrointestinal lesions associated with NSAID therapy. It has its own specific features (primarily antral and prepyloric localization, especially in elderly women), which differentiate it from classic peptic ulcer disease (57). Damage to the upper gastrointestinal tract can also involve the duodenum and, albeit infrequently, the esophagus.

Frequency

Gastrointestinal damage by NSAIDs is a major health problem. Estimates of the absolute risk vary from about two cases of serious upper gastrointestinal adverse effects per 10 000 person-months (58) to a seven-fold increase in the risk of hospitalization in patients with rheumatoid arthritis (59). Estimates of hospitalization for ulcer complications and the excess of gastrointestinal deaths in the UK have shown that 20–30% of all cases of ulcer complications in subjects aged over 60 which result in hospitalization are directly attributable to the use of NSAIDs, and that some 10% culminate in death (60). For the UK, this means that at least 2000 cases of bleeding are caused every year with about 200 deaths (61), in association with about 11 million prescriptions. The relative risk reported in different studies has generally been in the range of 3:1 to 5:1 (62).

In 2747 patients with rheumatoid arthritis, those taking NSAIDs were five times more likely (hazard ratio of 5.2) to be hospitalized for an upper gastrointestinal event (63). The risk of hospitalization for a gastrointestinal event was 15.8 per 1000 person-years in individuals taking NSAIDs, compared with 3.2 per 1000 person-years for controls. Such figures mean that on average one to two out of every 100 patients taking NSAIDs for 1 year are hospitalized for a gastrointestinal event (most commonly an ulcer).

The conclusion of a meta-analysis of 16 studies was that NSAID users have an approximately three-fold greater relative risk of developing serious adverse gastrointestinal events than non-users (64). This has been confirmed by a review (65).

Several authors have suggested that the upper gastrointestinal toxicity shortly after exposure does not persist (SEDA-22, 108), either because there is adaptation to NSAID-induced mucosal damage or because in these studies susceptible patients were selected. However, a population-based, cohort study has provided evidence that upper gastrointestinal toxicity is constant during exposure to NSAIDs and continues for some time after treatment stops (66).

Susceptibility factors

Case-control and surveillance studies have confirmed that the susceptibility factors for peptic ulcer disease are age, a history of ulcers and/or gastric bleeding, combination with corticosteroids, combination with other NSAIDs, and possibly smoking (SEDA-14, 84). The combination of NSAIDs, smoking, and alcohol increased the risk of gastrointestinal perforation nearly 11 times (OR = 10.7; CI = 3.8, 30) (SEDA-21, 97). Data on patients with rheumatoid arthritis taking NSAIDs show that the predisposition to gastrointestinal events is related to the severity of the disease (63). Other potential risk factors are sex (female), the musculoskeletal diseases for which NSAIDs are used, the NSAID taken, and dosage. The

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presence of gastric mucosal erosions at endoscopy was associated with an increased risk of a gastric ulcer, irrespective of prophylactic treatment (misoprostol versus sucralfate) in chronic NSAID users with osteoarthritis evaluated in a large randomized controlled trial (67). This was confirmed in other studies (SEDA-20, 86) (68,69), suggesting that the presence or absence of erosions is a better predictor of the risk of ulceration than the number of erosions.

The role of *Helicobacter pylori* *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) account for nearly all gastroduodenal ulcers and serious ulcer complications, but the interaction between infection with *H. pylori* and the use of NSAIDs in the pathogenesis of NSAID-induced gastropathy is controversial. In fact, studies that have examined these two susceptibility factors have yielded conflicting results about whether *H. pylori* infection increases the risk of toxicity in NSAID users, has no effect, or may even be protective (70–72).

Since we reviewed this topic 10 years ago (SEDA-16, 103) (SEDA-17, 105) a large amount of information has accumulated and merits further attention.

The pathophysiological mechanisms Among possible common pathophysiological mechanisms of importance are those that compromise the effectiveness of the gastroduodenal mucus–bicarbonate barrier, those that cause recruitment and activation of neutrophils, and those that can interfere with the process of mucosal adaptation (70). Both NSAIDs and aspirin can reduce the effectiveness of mucosal defences, by inhibiting gastroduodenal prostaglandin synthesis and by reducing mucosal blood flow (73). On the other hand *H. pylori* infection can damage the mucus–bicarbonate barrier, by increasing gastric acid secretion and reducing the viscosity of gastric mucus (74). Contrasting data have been reported on the effect of *H. pylori* on mucosal blood flow (75,76) and on mucosal prostaglandin production. However, although *H. pylori* increases mucosal prostaglandin synthesis, the combination of *H. pylori* with NSAIDs or aspirin causes a marked fall in mucosal prostaglandin synthesis, showing that the stimulatory effect of prostaglandin production by *H. pylori* is insignificant in the presence of NSAIDs or aspirin (76,77).

Gastric ulceration induced by NSAIDs is a neutrophil-dependent process (78) and the association of *H. pylori* infection with neutrophil infiltration has also been well documented. Gastric injury by NSAIDs is minimal in neutropenic animals, and the cumulative incidence of peptic ulcers in long-term NSAID users is increased in the presence of neutrophil infiltration in the mucosa of patients who are *H. pylori*-positive, suggesting a possible link between NSAIDs and *H. pylori* in the pathogenesis of peptic ulcers (79,80).

The ability of the gastroduodenal mucosa to adapt to repeated exposure to NSAIDs and aspirin is well documented, and some reports have shown the possible involvement of *H. pylori* in this process (76,81). In one endoscopic study in volunteers, mucosal adaptation to naproxen after 4 weeks of treatment occurred in 53% of *H. pylori*-positive subjects and in 81% in *H. pylori*-negative subjects (82). Similar results were found in another study in volunteers who took aspirin for 2 weeks; mucosal adaptation to the injury caused by aspirin was clearly impaired in the presence of *H. pylori* and was restored after *H. pylori* eradication (83).

In summary, NSAIDs and *H. pylori* can cause adverse effects on gastroduodenal mucosal protective mechanisms in different ways, and so the interaction between these two susceptibility factors might allow damage to occur more readily when NSAIDs are taken in the presence of *H. pylori* infection. However, despite this experimental evidence, the interaction between *H. pylori* infection and use of NSAIDs in the pathogenesis of peptic ulcers and their complications is still unclear from clinical studies.

Clinical studies Most of the early studies of the interaction between *H. pylori* infection and the use of NSAIDs were based on observational studies in long-term NSAID users and gave conflicting results (79, 84–91). In some studies there were significantly more ulcers in NSAID users who were *H. pylori*-positive then in users who were not infected (79,84,85). However, these findings were not confirmed by other investigators (86–89), and they probably reflect a complex relation between *H. pylori* infection and NSAID-associated gastropathy, as well as heterogeneity of methods across studies. For example, differences in population studied (for example the type of NSAID exposure, the age of the patient) and even in the definition of ulcer at endoscopy make direct comparison of results difficult. Most of the few published prospective trials did not show that *H. pylori* is a susceptibility factor for NSAID-induced gastroduodenal damage (77,92–94), and two long-term longitudinal studies (69,95) gave conflicting results, although the data have mostly been derived from studies in small numbers of young healthy volunteers at very low risk of gastropathy, and the results must therefore be treated with great caution. Thus, despite numerous studies we do not have convincing evidence for or against a link between *H. pylori* and NSAIDs in the development of peptic ulcers.

A meta-analysis has helped to clarify this issue (96). The aim was to assess the presence and magnitude of any possible interaction in peptic ulcer disease between these two susceptibility factors, with particular attention to bleeding peptic ulcer disease, the sites of ulceration, and the effect of *H. pylori* eradication. In all, 61 relevant studies were identified, 36 of which were excluded for various reasons. Thus, 25 studies were left for analysis, of which 16 observational studies (eight cross-sectional studies, seven case-control studies, and one cohort study) provided data on the prevalence of peptic ulcer disease in 1633 NSAID users, with data on *H. pylori* status for 1625 patients. The pooled frequency of peptic ulcer disease in NSAID users was 42% in those who were *H. pylori*-positive and 25% in those who were *H. pylori*-negative (OR = 2.12; 95% CI = 1.68, 2.67).

The frequencies of uncomplicated peptic ulcer disease in NSAID users and non-users were compared in eight case-control studies; however, the NSAID users and controls were not matched by age in three studies and so, because *H. pylori* infection is age-dependent, the prevalence of infection was analysed in only five studies.

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Overall, *H. pylori* infection was diagnosed in 47% of the NSAID users and 46% of the controls, but peptic ulcer disease was significantly more common in the NSAID users (36% versus 8.3%; OR = 5.14; CI = 1.35, 20). Compared with patients who were *H. pylori*-negative and were not taking NSAIDs, the risk of ulcer in *H. pylori*-infected NSAID users was very high (OR = 61; CI = 10, 373). *H. pylori* infection increased the risk of peptic ulcer disease in NSAID users 3.53 times in addition to the risk associated with NSAID use (OR = 19). Similarly, in the presence of a risk of peptic ulcer disease associated with *H. pylori* infection (OR = 18) the use of NSAIDs increased the risk of peptic ulcer disease 3.55 times. *H. pylori* infection and NSAID use, respectively, increased the risk of ulcer bleeding 1.79 times and 4.85 times; the risk of ulcer bleeding increased to 6.13 when both factors were present.

From these data we can conclude that both *H. pylori* infection and NSAID use independently and significantly increase the risk of peptic ulcer and ulcer bleeding and that there is synergism in the development of peptic ulcer and ulcer bleeding between *H. pylori* infection and NSAID use.

The meta-analysis also showed that one-third of patients taking long-term NSAIDs have gastric or duodenal ulcers, irrespective of *H. pylori* status and study design. However, peptic ulcer disease was significantly more common in *H. pylori*-infected NSAID users than in non-infected users, suggesting a possible interaction between NSAID use and *H. pylori* infection for the development of peptic ulcers.

Moreover, the meta-analysis clarified another uncertainty: whether in NSAID takers *H. pylori* infection is as important a risk factor for gastric ulcer as it is for duodenal ulcer. A pooled analysis of four studies (75,97–99) showed that *H. pylori* infection is less closely associated with gastric ulcer than with duodenal ulcer in both NSAID users and non-users, and that while NSAID use has a major role in the development of gastric ulcer, duodenal ulcer is more closely related to *H. pylori* infection.

Further convincing evidence for the existence of a possible interaction between *H. pylori* and NSAIDs in the pathogenesis of ulcer has been obtained by investigating the effects of *H. pylori* eradication on the occurrence of NSAID-related ulcers and their complications (for example bleeding), although some divergent findings have been reported from these studies (100,101).

In a prospective, randomized trial of the effect of eradication of *H. pylori* before the start of NSAID therapy on the subsequent risk of ulcer occurrence, patients who required new NSAID treatment and who had *H. pylori* infection but no pre-existing ulcers on baseline endoscopy were recruited (100). Of these patients, 100 were randomly allocated to naproxen for 8 weeks, either alone or preceded by a 1-week course of *H. pylori* eradication. Endoscopy was repeated after 8 weeks or if naproxen was withdrawn early because of adverse effects. The primary end-point of the study was the cumulative rate of gastric and duodenal endoscopic ulcers. At 8 weeks *H. pylori* was eradicated in 40 patients (89%) who took eradication therapy and in none of those who had no pretreatment. Twelve (26%) of those who had no eradication therapy developed ulcers compared with three (7%) who had eradication therapy, two of whom had failure of eradication. Thus, only one patient with successful eradication developed ulcers with naproxen. These data suggest that NSAID-induced ulceration can be reduced by eradication of *H. pylori* before naproxen administration and suggest that *H. pylori* infection is a susceptibility factor for NSAID-induced ulcer disease. Some therefore believe that determination of *H. pylori* infection and eradication in infected patients should be recommended before starting NSAID therapy.

However, the data from this study contrasted with those from another randomized, controlled trial, the HELP study, in which the effect of *H. pylori* eradication was investigated in a different population of 285 patients who had used long-term NSAID therapy, those with current or previous peptic ulcers, or dyspepsia, or both (101). The patients were randomly assigned to omeprazole plus 1 week of eradication therapy ($n = 142$) or to omeprazole plus placebo for 1 week ($n = 143$). They took omeprazole until their ulcer healed or dyspepsia resolved, after which they continued taking the NSAID, with follow-up assessment of ulcer and dyspepsia at 1, 3, and 6 months. The estimated probabilities of being ulcer-free at 6 months were similar in the two groups: 0.56% (95% CI = 0.47, 0.65) with eradication treatment and 0.53 (0.44, 0.62) with control treatment. Moreover, fewer gastric ulcers healed in those who had taken eradication therapy than in the controls (7% versus 100% at 8 weeks). These data suggest that *H. pylori* eradication therapy not only did not reduce the rate of development of peptic ulcer or dyspepsia at 6 months, but actually led to impaired healing of gastric ulcers. On the basis of these results *H. pylori* eradication seems not to be justified.

These conflicting results can probably be explained by important differences in the characteristics of the patients and the study methods. The inclusion criteria in the two studies were mutually exclusive: patients with long-term NSAID use and a history of ulceration were excluded in the first study and included in the second. Furthermore, there were differences in the definition of endoscopic ulcers, the eradication regimen, the definition of *H. pylori* infection, and the length of follow-up.

Data from a later eradication study helped to clarify these uncertainties. The aim of the study was to determine whether among NSAID-naive patients positive for *H. pylori* who have dyspepsia or a history of ulcer and who are about to start long-term NSAID treatment, eradication of *H. pylori* infection reduces the risk of ulcers (102). Bismuth was replaced by omeprazole in the eradication regimen, the observation period was increased to 6 months, and the frequencies of both complicated and symptomless ulcers were assessed. Patients were randomly assigned to omeprazole triple therapy (eradication group, $n = 51$) or omeprazole with placebo antibiotics (control group, $n = 51$) for 1 week. All took diclofenac 100 mg/day for 6 months. The 6-month probability of having ulcers was 12% (95% CI = 3.1, 21) in the eradication group and 34% (21, 48) in the placebo group. The 6-month probability of complicated ulcers was 4.2% (1.3, 9.7) in the eradication group and 27% (15, 40) in the placebo group. These statistically significant differences suggested that screening and treatment for *H. pylori*

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infection significantly reduces the risk of ulceration and bleeding in patients who take long-term NSAIDs.

However, these conclusions may not be valid for patients who take low-dose aspirin for prevention of cardiovascular events, as there are data that suggest that *H. pylori* increases (103), has no effect (104,105), or even reduces (106) the risk of bleeding among users of low-dose aspirin as well as other NSAIDs. This question has been addressed in 400 patients with a history of upper gastrointestinal bleeding who were infected with *H. pylori* and who were taking low-dose aspirin ($n = 250$) or other NSAIDs ($n = 150$) (107). Their ulcers were healed with omeprazole 20 mg/day for 8 weeks. Those who had been taking aspirin were given aspirin 80 mg/day, and those who had been taking other NSAIDs were given naproxen 500 mg bd for 6 months. The patients in each group were then randomly assigned separately to receive omeprazole 20 mg/day for 6 months or 1 week of eradication therapy followed by placebo for 6 months.

Among patients taking aspirin the probability of recurrent bleeding during the 6 months was 1.9% for patients who had taken eradication therapy and 0.9% for patients who had taken omeprazole, a non-statistically significant difference of 1% (95% CI = –1.9, 3.9). Among users of naproxen the probability of recurrent bleeding was significantly greater among patients who had taken eradication therapy (19%) than among those who had taken omeprazole (4.4%). Unfortunately, the absolute reduction in the risk of recurrent bleeding attributable to eradication of *H. pylori* could not be determined, because a placebo group was not included.

This study has therefore shown that in patients infected with *H. pylori* who take low-dose aspirin, eradication of *H. pylori* is as effective as prophylactic therapy with omeprazole in preventing recurrent upper gastrointestinal bleeding. Therefore, patients taking aspirin for cardiovascular prophylaxis could be tested for *H. pylori* infection and treated for it if infection is confirmed. In contrast, omeprazole is superior to eradication of *H. pylori* for the secondary prevention of upper gastrointestinal bleeding in *H. pylori*-infected users of naproxen and presumably other non-aspirin NSAIDs.

Conclusions Whether the eradication of *H. pylori* can reduce the risk of ulcers appears to vary according to the characteristics of the patient. For people who have never taken a non-aspirin NSAID, eradication of *H. pylori* before NSAID treatment is begun reduces the risk of ulcers (100). However, for long-term users of non-aspirin NSAIDs, eradication of *H. pylori* has not been shown to prevent gastroduodenal injury. Moreover, eradication alone is not sufficient to prevent recurrent bleeding in susceptible long-term users.

The divergent outcomes in patients taking aspirin or other NSAIDs suggest that *H. pylori* may have a more important role in ulcer bleeding associated with low-dose aspirin than in bleeding associated with other NSAIDs. A possible explanation is that infection with *H. pylori* impairs gastric adaptation to aspirin (76); eradication restores this capability and increases the mucosal resistance to aspirin.

There are several conclusions from these results.

First, eradication of *H. pylori* is a useful strategy in preventing upper gastrointestinal damage caused by NSAIDs or aspirin in some patients.

Secondly, there are doubts about the correct interpretation and generalizability of the results of some relevant studies on the efficacy of omeprazole and misoprostol in the prevention of gastroduodenal ulcer in chronic NSAID users. In fact in these studies, OMNIUM (108), ASTRONAUT (109), and MUCOSA (110), the patients' *H. pylori* status was not considered and may have modified their outcomes (ulcer recurrence and ulcer healing). Some evidence supporting this hypothesis comes from a reanalysis of the data, taking into account the presence or absence of *H. pylori* (111). The superiority of omeprazole over ranitidine or misoprostol claimed in OMNIUM and ASTRONAUT in preventing NSAID-induced ulcers was markedly affected by *H. pylori* status. In a dosage of 40 mg/day, omeprazole was not superior to the full dose of misoprostol in healing unequivocal NSAID-induced gastric ulcers in chronic NSAID users, but it was superior in those whose NSAID use was complicated by *H. pylori* infection. Duodenal ulcers were markedly overrepresented as a cause of ulcer recurrence in the *H. pylori*-infected patients and most of the effect of omeprazole occurred in this population. Therefore, the therapeutic advantages of using omeprazole to prevent recurrent ulcers or their complications in chronic NSAID users may be different in those with and without *H. pylori* infection.

We have no data on the possible interaction between *H. pylori* status and the ability of COX-2-selective inhibitors to cause gastrointestinal toxicity. However, one would expect that when patients use COX-2 inhibitors *H. pylori* infection would remain a source of continuing ulcer risk, requiring eradication. Although there are no trials, this approach is supported by data from the VIGOR study, in which the residual risk of ulcers in patients taking rofecoxib was approximately doubled in *H. pylori*-infected compared with non-infected patients (112).

Comparative studies of different NSAIDs

Although some reports suggest that some NSAIDs are more gastrotoxic than others, data on individual drugs have been at best fragmentary (SEDA-14, 85). Two well-conducted studies have provided convincing data for clarifying whether some compounds are more likely to cause serious adverse gastrointestinal events (113,114) than others. Ibuprofen was associated with the lowest risk of gastrointestinal toxicity; diclofenac, naproxen, and possibly indometacin were intermediate, while piroxicam and in particular azapropazone had much higher risks. The differences appeared to be due to the fairly low dosage of ibuprofen; there were also dose–response relations for naproxen and indometacin. These results have practical implications. When NSAID treatment is needed the least toxic compound should be selected, on the basis of the data provided by these studies and, because of the substantial increase in risk from low-dose to high-dose NSAID therapy, it is wise to start treatment with low dosages.

The search for less toxic drugs or formulations has been discouraging. Several new formulations may be less

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gastrotoxic than standard formulations in short-term studies, but their long-term merit has not yet been proven. Equally, prodrugs have not protected users against gastric complications (14). Parenteral and rectal administration of NSAIDs does not spare the stomach.

Prevention

Ways of preventing NSAID-induced gastrointestinal damage include the use of histamine H_2 receptor antagonists, the prostaglandin analogue misoprostol, and proton pump inhibitors.

Ulcer-preventing drugs The limited data available indicate that H_2 receptor antagonists do not prevent NSAID-induced gastric ulceration. Two studies on ranitidine, reporting that it reduces the incidence of duodenal ulcers, conflict with others that did not find that it offers protection against gastroduodenal mucosal lesions (SEDA-14, 86). Only high-dose famotidine significantly reduced the cumulative incidence of both gastric and duodenal ulcers in patients taking long-term NSAIDs (68). Other trials gave contrasting results (115,116). A large prospective observational cohort study showed that patients taking antacids and H_2 receptor antagonists in combination with NSAIDs did not have a lower risk of significant gastrointestinal events, and asymptomatic patients who started taking these antiulcer drugs prophylactically had a higher risk of a serious gastrointestinal complication than those who did not (OR = 2.69; 95% CI = 1.36, 5.81) (117). The risk might have been increased because these drugs suppress gastrointestinal symptoms and so encourage the use of higher doses of NSAIDs for longer periods, which finally results in more severe gastrointestinal complications.

Co-administration of misoprostol and NSAIDs significantly reduced the frequency of NSAID-induced gastric ulcer in patients with osteoarthritis (118) and misoprostol reduced serious upper gastrointestinal complications (perforation, gastric outlet obstruction, and perhaps bleeding) by 40% compared with placebo in older patients with rheumatoid arthritis treated with NSAIDs (110,119).

Two studies on the proton pump inhibitor omeprazole (120,121) have provided evidence of effective prophylaxis in patients at low and high risks of developing NSAID-associated ulcers, erosions, or dyspeptic symptoms. Two other trials have shown that in patients with ulcers or multiple erosions in the stomach or duodenum who require continuous NSAID treatment, omeprazole gives greater benefit than ranitidine but not misoprostol (108,109). However, misoprostol may be less effective in healing duodenal ulcers and it is not as well tolerated as omeprazole. A daily dose of omeprazole over 20 mg does not confer any clinical advantage. As far as maintenance therapy is concerned, in patients taking NSAIDs, omeprazole 20 mg od prevents gastroduodenal damage more effectively than ranitidine or misoprostol.

Taking into account the limitations of these studies (SEDA-22, 110), these results should not lead to uncritical prescription of proton pump inhibitors for primary prophylaxis in patients taking NSAIDs. Prophylactic therapy may be justified only in high-risk patients, such as the elderly, patients with a history of peptic ulcer, gastrointestinal bleeding, or concomitant cardiovascular disease, or patients who are concurrently taking warfarin or high-dosage glucocorticoids. Whether patients who start taking NSAIDs should routinely have prophylaxis with antiulcer drugs is not at all clear. The costs of therapy are obviously high (appropriate pharmacoeconomic evaluations on the prophylactic use of omeprazole are lacking), the adverse effects of prophylactic drugs must be taken into consideration, and it would seem logical to limit it to high-risk cases (see below).

Eradication of Helicobacter pylori

See the section on Susceptibility factors under Gastrointestinal in this monograph.

Patient education

The relevance of patient information to the prevention of adverse effects of NSAIDs has been well illustrated in a study of 50 consecutive patients who were admitted to hospital with acute gastrointestinal bleeding and who had taken NSAIDs 3 days before admission, compared with 100 matched control patients who had not bled (122). Despite the limitations of the study (123), it looks as if ignorance of adverse effects can lead to inappropriate compliance and failure to recognize warning symptoms. In fact, if the patients who bled had reduced their intake of NSAIDs in response to epigastric pain to the same extent as the apparently better informed control patients, some episodes of acute gastrointestinal bleeding might have been avoided. Consequently we should consider patient education as one of the main strategies for preventing NSAID-related toxicity.

Esophageal damage

Esophageal damage by NSAIDs, usually considered a rare adverse reaction, has been underestimated, perhaps because the symptoms of esophagitis can be misinterpreted as being of gastric origin. The clinical pattern is characterized by inflammatory changes (erosive and/or ulcerative esophagitis), ulceration with or without bleeding, and/or perforation and strictures. Data suggest that the frequency of erosive/ulcerative esophagitis in patients taking NSAIDs is not as low as was previously thought (SEDA-15, 100). Erosive or ulcerative esophagitis was present in 12 of 60 arthritic patients taking long-term NSAIDs (124). There were esophageal symptoms in 83% of the patients with esophagitis.

Long-term NSAID users have fewer esophageal histological abnormalities than controls (125). However, more epidemiological and experimental prospective studies are needed to define the role of NSAIDs in causing esophageal injury. Data on esophageal function suggest that naproxen does not cause reflux and has no significant effect on motility in healthy subjects (126).

Small bowel damage

The capacity of NSAIDs to cause intestinal damage has been demonstrated in a case-control study (127) as well as by experience with a special formulation of indometacin (Osmosin) (SEDA-15, 93). Severe intestinal damage perforation and bleeding is a very rare complication of

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therapy with conventionally formulated NSAIDs. The expected incidences of lower bowel perforations and bleeding are about ten and seven per 100 000 patients, respectively (127). Uncomplicated intestinal mucosal lesions are more frequent, particularly when NSAIDs are given in the long term (128). Small intestine enteropathy is characterized by inflammation and/or malfunction, with an increase in intestinal permeability. Most patients are asymptomatic, although a few taking long-term treatment have symptoms that mimic the features of Crohn's disease. As NSAIDs can exacerbate Crohn's disease (SEDA-10, 76), the differential diagnosis is difficult in symptomatic patients.

Adverse effects on the small intestine may be more frequent than previously thought and range from asymptomatic enteropathy to severe complications, such as ulceration, bleeding, perforation, and stricture (129). A prospective autopsy study in 713 patients provided an estimate of the prevalence of such lesions (130). Non-specific ulcers in the small intestine were more frequent in the NSAID group than in the control group (8.6 versus 0.6%) and the percentage was slightly higher in long-term users. Most lesions were subclinical, but perforation leading to peritonitis and death was documented in three patients taking long-term NSAIDs. The pathogenesis of NSAID-induced enteropathy is still unknown (SEDA-17, 106).

Whether the "diaphragm disease" (131–133) that is found in a few patients is a distinct NSAID-related disease or only a variant form of congenital intestinal diaphragm remains to be clarified.

Large bowel damage

"Diaphragm disease" has been reported in the ascending colon; these lesions are identical to those in the small bowel and are found only in patients who have taken modified-release NSAIDs for more than a year, because they are probably delivered unabsorbed to the large intestine (SEDA-20, 88) (134).

The causal connection between NSAIDs and large bowel inflammation needs to be confirmed by appropriate epidemiological studies. Many publications have associated NSAID and colonic inflammation (SEDA-10, 77) (SEDA-15, 95), but the differential diagnosis between colonic inflammation arising de novo and exacerbation of underlying inflammatory bowel disease can be difficult, and the role of NSAIDs in aggravating ulcerative colitis or Crohn's disease or other inflammatory bowel disease is controversial (SEDA-10, 76) (SEDA-15, 95). A case-control study showed no association between appendicectomy for acute appendicitis and the use of NSAIDs (SEDA-22, 111).

The evidence that NSAIDs can cause exacerbation of inflammatory bowel disease is at best scanty (SEDA-10, 76) (SEDA-15, 92) (SEDA-17, 102). In the few studies in which drugs as a cause of relapse of chronic inflammatory bowel disease have been investigated, NSAIDs have not been shown to be major contributors.

However, well-documented published series of patients with quiescent inflammatory bowel disease whose colitis became active shortly after they were given NSAIDs make the causal relation probable, at least in some patients (135–138). Because the pathogenesis of inflammatory bowel disease is unknown, it is difficult to say whether episodes of colitis are exacerbations of the underlying disease or unrelated events caused by NSAIDs in predisposed patients.

Two studies of the possible association between NSAIDs and the onset or exacerbation of inflammatory bowel disease have given contrasting results. In the first study (139) the authors interviewed 60 patients (mean age 42 years) with either Crohn's disease or ulcerative colitis who required admission to hospital owing to symptoms of their disease, and 62 matched controls (mean age 46 years) with irritable bowel syndrome who did not require hospitalization. Patients were asked about their use of NSAIDs and the relation in time and duration to the exacerbation or onset of the inflammatory bowel disease. There was an association with the use of NSAIDs in 31% of the patients with inflammatory bowel disease, but in only 2% of those with irritable bowel syndrome. Compared with patients with irritable bowel syndrome the odds ratio (OR) for an exacerbation or new onset of symptoms of inflammatory bowel disease after recent use of NSAIDs (defined as use within 1 month of symptom exacerbation or onset of disease) was 20 (95% CI = 2.6, 160).

In contrast, the second study (140) showed that the use of NSAIDs was not associated with a higher incidence of active inflammatory bowel disease. The authors retrospectively examined the records of 192 outpatients with inflammatory bowel disease: 112 with Crohn's disease (mean age 53 years) and 80 with ulcerative colitis (mean age 61 years). The use of NSAIDs was more common in patients with inactive inflammatory bowel disease than in those with active disease. Of 40 patients with active Crohn's disease, three were using NSAIDs compared with 14 of 72 with inactive disease. Of 58 patients with active ulcerative colitis, eight were using NSAIDs compared with five of 21 patients with ulcerative colitis in remission.

These contrasting results may have been due to different patient populations studied (inpatients versus outpatients) or to other limitations: in the case-control study, the number of patients enrolled was small and the confidence intervals of the odds ratio were very large; in the observational study, the analysis was retrospective and the possibility that some patients had used over-the-counter NSAIDs could not be excluded.

Despite the clinical importance of the problem, we lack a firm answer to the question of whether patients with inflammatory bowel disease should refrain from using NSAIDs.

When administered long-term, the fenamates cause watery diarrhea in more patients than other NSAIDs. Although colonic ulceration has been reported after oral ingestion of several NSAIDs (SEDA-7, 105) (SEDA-10, 77) (SEDA-15, 95), the evidence is not entirely convincing. On the other hand, there is firm reason to conclude that there is a direct causal relation between rectally administered NSAID and rectal ulceration, which seems to occur more frequently when doses are high or treatment is prolonged.

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Liver

Serious liver reactions to NSAIDs are rare and unpredictable (SEDA-17, 107) (141), suggesting that most reactions are due to hypersensitivity. However, the FDA has recognized liver reactions as a class effect of NSAIDs. Severe injury and even deaths have been reported (142).

Because of hepatotoxicity, particularly problematic in the elderly, benoxaprofen was withdrawn from the market in 1982, and ibufenac is not on sale for the same reason. Serious hepatocellular reactions have been well-documented with phenylbutazone and the death rate is high (143). Hepatotoxicity has been reported with all of the structural classes of NSAIDs.

Hepatic reactions are more often reported with the pyrazolone, indole, and propionic acid groups of compounds than with the fenamate and oxicam classes (50). Some national monitoring centers have published their experience on liver toxicity with NSAIDs, and the Swedish and Australian agencies have both drawn attention to an apparently higher frequency of liver reactions with sulindac and diclofenac (144,145). Reactions to sulindac are characterized by cholestasis. Diclofenac is associated with more acute hepatocellular derangement and is recognized as a rare cause of acute hepatocellular damage (146).

Cirrhosis with esophageal or cardiac varices

Aspirin can increase the risk of variceal bleeding in patients with cirrhosis. In fact, according to a case-control study (147), patients with cirrhosis and esophageal or cardiac varices who take NSAIDs are three times more likely to have a first episode of variceal bleeding compared with similar patients who are not taking NSAIDs.

In 125 patients with cirrhosis who were admitted to hospital with a first episode of bleeding related to esophageal or cardiac varices, compared with 75 patients with cirrhosis, but no previous or current history of variceal bleeding, who were admitted to the same hospitals, a questionnaire showed that more patients with a first episode of bleeding had used aspirin, either alone or in combination with other NSAIDs compared with controls (OR = 4.9). This increased risk of bleeding was seen only in patients with grade 2 or grade 3 varices.

The results of this small hospital-based study should be interpreted with caution, but as variceal bleeding is a life-threatening event and in cirrhosis other factors (thrombocytopenia and coagulation defects) can also predispose to bleeding, the possible benefit of therapy with aspirin or other NSAIDs should be carefully weighed against the risks of major gastrointestinal bleeding.

Urinary tract

Many of the NSAIDs are associated with renal disorders arising de novo or by aggravation of existent renal dysfunction. Inhibition of PGE-1 synthesis intrarenally leads to a reduction in the vasodilator activity of this prostaglandin, which normally contributes to maintenance of renal functional balance and protection against the vasoconstrictor effects of noradrenaline and angiotensin-II and the action of antidiuretic hormone.

NSAIDs can produce a spectrum of renal diseases: functional renal insufficiency, nephrotic syndrome with or without interstitial nephritis, renal papillary necrosis and chronic interstitial nephritis, acute tubular necrosis, vasculitis, glomerulonephritis, and obstructive nephropathy.

Incidence

Two studies have suggested that the overall incidence of clinical nephrotoxicity with NSAIDs is small (148,149). However, some patients (see below) are at increased risk of particular effects (SEDA-11, 82), and patients with sickle cell anemia can probably be added to the list (SEDA-15, 97).

Although some compound-related variations do occur, every nephrotoxic effect seems to have been reported with every NSAID at some time and no NSAID is free of nephrotoxic potential. This applies to sulindac as to other NSAIDs, although its renal function-sparing effect is disputed (SEDA-15, 99) (150,151). One study suggested that renal effects were more likely to occur with ibuprofen than with piroxicam or sulindac (152), but it was criticized for flawed experimental design (153). There is other evidence that sulindac is relatively safer: short-term sulindac 400 mg/day had no effect on glomerular filtration rate, renal plasma flow, or renal prostaglandin excretion in ten patients with arthritis and impaired renal function, while naproxen 750 mg/day reduced all three (154). Such short-term evidence clearly does not eliminate the problems of long-term use, which constitute the real challenge.

A study of the risk of chronic renal disease associated with the regular use of NSAIDs showed that it was twice as high in men over 65 years and tended to be even higher in patients with heart disease or other disorders that might compromise renal circulation (155). The results of a second investigation, a case control study of 340 patients with end-stage renal disease on a hemodialysis maintenance program and 678 hospitalized controls, confirmed the trend (SEDA-16, 105), but more reliable epidemiological data are needed to show that regular consumption of NSAIDs increases the risk of chronic renal disease. NSAID-associate analgesic nephropathy has been reviewed (SEDA-18, 100).

The actual risk of NSAID-associated acute renal dysfunction also continues to be the subject of controversy. There is adequate evidence that underlying renal insufficiency, congestive heart failure, or hepatic cirrhosis are conditions that carry a high risk of NSAID-related renal functional impairment. It is still not known whether old age is a risk factor, whether the risk of renal impairment varies with different NSAIDs, or whether renal function continues to deteriorate, stabilize, or even improve in affected patients with continued use of NSAIDs. Three cases of renal insufficiency caused by topical NSAIDs have been described (SEDA-18, 100).

Types of complication

Of all the potentially serious adverse effects of NSAIDs, functional renal insufficiency, which is probably the most common, results from the hemodynamic changes secondary to inhibition of prostaglandin synthesis. Renal insufficiency and interference with fluid and electrolyte homeostasis occur in disease states in which prostaglandins are significant determinants of renal function, such as those characterized by hypovolemic states due to salt

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depletion or hypoalbuminemia and those in which there is pre-existing renal impairment due to age, atherosclerosis, hypertensive renal disease, or other intrinsic renal disease. Although the functional renal insufficiency is usually mild and reversible within a few days of withdrawing NSAIDs, it can also be severe and irreversible, so early recognition is essential. All NSAIDs can cause this complication.

A case-control study on recent use of NSAIDs and functional renal impairment at the time of hospitalization showed that there was a weak association between the use of NSAIDs and renal dysfunction. Patients at higher risk had a history of renal disease or of gout and hyperuricemia. While NSAID dosages were only weakly related to renal impairment, there was a statistically significant difference between compounds with half-lives under or over 4 hours: the OR increased from 1.2 (95% CI = 0.6, 2.4) to 4.8 (CI = 1.5, 16) for compounds with half-lives over 12 hours (156). Therefore, long half-life drugs should be avoided in subjects at risk of renal impairment.

A case-control study provided convincing epidemiological evidence that the use of NSAIDs was associated with the risk of hospitalization for acute renal insufficiency (relative risk about 2.0) (SEDA-19, 95) (157).

Acute interstitial nephritis, which is distinct from the methicillin-like form, is the most important type of organic renal damage caused by NSAIDs. Distinguished by a nephrotic syndrome, often with renal insufficiency, the histological picture is an acute interstitial nephritis combined plus a glomerular lesion with fusion of the epithelial foot process. Patients had usually been taking NSAIDs over a long period of time. Acute interstitial nephritis has been reported relatively often in patients taking fenoprofen.

The acute flank pain syndrome associated with reversible renal insufficiency is very rare. It has usually been reported with suprofen (SEDA-12, 89), but flurbiprofen and ibuprofen have also been implicated (SEDA-18, 100).

Membranous nephropathy is rare and causes the nephrotic syndrome, usually with minimal-change glomerulopathy, with or without interstitial nephritis (SEDA-11, 85). A retrospective study provided more data on the frequency and clinical characteristics of membranous nephropathy associated with NSAIDs (158). It confirmed that it is rare (13 of 125 patients diagnosed during the last 20 years met the strict criteria for NSAID-associated membranous nephropathy), and the nephrotic syndrome is reversible after prompt withdrawal. The pathogenesis is unknown but seems to be immune-mediated, given the characteristic deposition of IgG and C3.

Renal papillary necrosis has been reported after long-term intake or abuse of aspirin and other NSAIDs (SEDA-11, 85) (SEDA-12, 79).

Chronic renal disease

The relation between long-term heavy exposure to analgesics and the risk of chronic renal disease has been the object of intensive toxicological and epidemiological research for many years (SEDA-24, 120) (159). Most of the earlier reports suggested that phenacetin-containing analgesics probably cause renal papillary necrosis and interstitial nephritis. In contrast, there is no convincing epidemiological evidence that non-phenacetin-containing analgesics (including paracetamol, aspirin, mixtures of the two, and NSAIDs) cause chronic renal disease. Moreover, findings from epidemiological studies should be interpreted with caution, because of a number of inherent limitations and potential biases in study design (160). Two methodologically sound studies have provided information on this topic.

The first was the largest cohort study conducted thus far to assess the risk of renal dysfunction associated with analgesic use (161). Details of analgesic use were obtained from 11 032 men without previous renal dysfunction participating in the Physicians' Health Study (PHS), which lasted 14 years. The main outcome measure was a raised creatinine concentration defined as 1.5 mg/dl (133 μmol/l) or higher, and a reduced creatinine clearance of 55 ml/minute or less. In all, 460 men (4.2%) had a raised creatinine concentration and 1258 (11%) had a reduced creatinine clearance. Mean creatinine concentrations and creatinine clearances were similar among men who did not use analgesics and those who did. This was true for all categories of analgesics (paracetamol and paracetamol-containing mixtures, aspirin and aspirin-containing mixtures, and other NSAIDs) and for higher risk groups, such as those aged 60 years or over or those with hypertension or diabetes.

These data are convincing, as the large size of the PHS cohort should make it possible to examine and detect even modest associations between analgesic use and a risk of renal disease. Furthermore, this study included more individuals who reported extensive use of analgesics than any prior case-control study. However, the study had some limitations, the most important being the fact that the cohort was composed of relatively healthy men, most of whom were white. These results cannot therefore be generalized to the entire population. However, the study clearly showed that there is not a strong association between chronic analgesic use and chronic renal dysfunction among a large cohort of men without a history of renal impairment.

The second study was a Swedish nationwide, population-based, case-control study of early-stage chronic renal insufficiency in men whose serum creatinine concentration exceeded 3.4 mg/dl (300 μmol/l) or women whose serum creatinine exceeded 2.8 mg/dl (250 μmol/l) (162). In all, 918 patients with newly diagnosed renal insufficiency and 980 controls were interviewed and completed questionnaires about their lifetime consumption of analgesics. Compared with controls, more patients with chronic renal insufficiency were regular users of aspirin (37% versus 19%) or paracetamol (25% versus 12%). Among subjects who did not use aspirin regularly, the regular use of paracetamol was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of paracetamol. The risk increased with increasing cumulative lifetime dose. Patients who took 500 g or more over a year (1.4 g/day) during periods of regular use had an increased odds ratio for chronic renal insufficiency (OR = 5.3; 95% CI = 1.8, 15). Among subjects who did not use paracetamol regularly, the regular use of aspirin was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of aspirin. The risk increased significantly with an

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increasing cumulative lifetime dose of aspirin. Among the patients with an average intake of 500 g or more of aspirin per year during periods of regular use, the risk of chronic renal insufficiency was increased about three-fold (OR = 3.3; CI = 1.4, 8.0). Among patients who used paracetamol in addition to aspirin, the risk of chronic renal insufficiency was increased about two-fold when regular aspirin users served as the reference group, (OR = 2.2; CI = 1.4, 3.5) and non-significantly when regular paracetamol users were used as controls (OR = 1.6; CI = 0.9, 2.7). There was no relation between the use of other analgesics (propoxyphene, NSAIDs, codeine, and pyrazolones) and the risk of chronic renal insufficiency. Thus, the regular use of paracetamol, or aspirin, or both was associated dose-dependently with an increased risk of chronic renal insufficiency. The OR among regular users exceeded 1.0 for all types of chronic renal insufficiency, albeit not always significantly. These results are consistent with exacerbating effects of paracetamol and aspirin on chronic renal insufficiency, regardless of accompanying disease.

How can we explain the contrasting results of these two studies? A possible explanation lies in the different populations studied. In PHS, relatively healthy individuals were enrolled while in the Swedish study all the patients had pre-existing severe renal or systemic disease, suggesting that such disease has an important role in causing analgesic-associated chronic renal insufficiency. People without pre-existing disease who use analgesics may have only a small risk of end-stage renal disease.

Prevention

While misoprostol has been shown to limit NSAID-induced gastric damage, three studies failed to show that misoprostol prevents NSAID-induced impairment of renal function. However, another showed that it prevents ciclosporin-induced renal damage in renal transplant patients (163). Further studies are therefore required to assess the protective effect of misoprostol on renal function (SEDA-16, 106).

Skin

Skin reactions are often reported with NSAIDs, but the true incidences with individual NSAIDs are unknown. There are very few specific epidemiological studies, and most information comes from single case reports and data from national spontaneous reporting systems. A major study on nearly 20 000 patients showed that 0.3% of 9118 patients taking analgesics and NSAIDs developed skin reactions that could be attributed to these drugs (164).

Although usually mild, skin reactions very often require withdrawal of treatment. At times they can be severe, and isoxicam was withdrawn from the market because of the high frequency of severe adverse skin reactions (SEDA-10, 88).

There are various types of NSAID-induced rashes. The main morphological patterns are urticarial, maculopapular, vesicular, and exfoliative. Skin reactions to NSAIDs are probably of phototoxic origin and can be associated with systemic hypersensitivity or other allergic reactions. More rarely, NSAIDs can exacerbate pre-existing skin disease (for example psoriasis, acne). Phototoxic reactions were very common with benoxaprofen (30–50% of patients treated in the UK), and were one reason why it did not receive licensing approval in Australia or the Benelux countries. Other NSAIDs, such as azapropazone, piroxicam, and fenbufen, have been reported to cause higher than average rates of photosensitivity (165). NSAIDs were among the causal agents of phototoxic reactions most commonly reported to the Australian Adverse Drug Reactions Advisory Committee (166,167).

Widespread use of naproxen, sulindac, diclofenac, and diflunisal probably explains why they were the most frequently implicated, rather than because they have a greater tendency to cause these adverse effects. NSAIDs differ in their ability to cause adverse skin reactions in terms of both frequency and severity: pyrazolones, butazones, and oxicams are most often blamed, and among the arylalkanoic acid derivatives fenbufen and carprofen are most often incriminated.

The types of skin adverse effect also vary with different compounds. The most serious life-threatening reactions, such as erythema multiforme and its variants (Stevens–Johnson syndrome, toxic epidermal necrolysis, exfoliative erythroderma) are uncommon and occur mainly with the butazone derivatives and to a lesser extent with piroxicam, sulindac, and possibly fenbufen. In large series reported in France, Germany, and the USA, NSAIDs are most often implicated: 12 (44%) of the most commonly implicated 29 drugs (168).

Although all NSAIDs can cause urticaria, particularly in aspirin-sensitive patients, it is more common with pyrazolone derivatives. Photosensitivity is principally a problem with azapropazone, carprofen, tiaprofenic acid, and piroxicam (SEDA-9, 84).

The reasons for these different effects of different NSAIDs are poorly understood. The only physicochemical characteristic that seems to be important in determining a particular propensity for adverse skin reactions is lipophilicity (10), which probably affects NSAID distribution to the skin. The longer half-lives of lipophilic compounds may concomitantly facilitate the persistence of skin reactions. Although there are no clear relations between the other pharmacological and kinetic characteristics of NSAIDs and effects on the skin, less lipophilic drugs with short half-lives might be preferable.

There are no clearly identifiable predisposing factors for most adverse skin reactions. Urticaria and photosensitivity are exceptions. Many NSAIDs can cause urticaria (sometimes associated with angioedema) in aspirin-sensitive patients. Probably not immunological in origin, the reaction may be related to prostaglandin inhibition in a patient whose cutaneous mastocytes are more susceptible to the stabilizing effect of prostaglandins. Skin testing in patients with a history of urticarial and/or anaphylactic reactions to analgesics is of little value in identifying patients at risk and can be dangerous (169,170). Skin pigmentation and environmental factors that influence the radiant exposure dose are clearly very important in determining the risk of a phototoxic reaction.

Since the extreme rarity of life-threatening reactions, such as erythema multiforme and toxic epidermal

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necrolysis, suggests individual susceptibility, efforts have been made to identify subjects at risk. In 25 cases of erythema multiforme and toxic epidermal necrolysis there was a slight, non-significant increase in the frequency of the HLA-B12 and DR4 phenotypes, suggesting that genetic factors are involved (171). Genetic predisposition also seems to be confirmed by the finding of a fixed drug eruption in four members of a single family taking feprazone (SEDA-17, 108). From a practical point of view, if a mild reaction occurs it is wise to withdraw treatment, even if the reaction disappears spontaneously in some patients despite continuing treatment. Withdrawal of treatment and prompt referral to hospital is imperative if the reaction is severe and/or tends to progress.

Careful clinical monitoring is probably necessary for all patients with underlying skin diseases (for example acne, psoriasis), as some NSAIDs can exacerbate them (172,173). NSAIDs should not be used for apparently benign inflammatory cutaneous lesions, unless the possibility of infection has been ruled out.

Lichenoid photoeruptions have been reported not infrequently in HIV-positive people, often in association with photosensitizing drugs, especially NSAIDs (174). Facial scars have been described in adults and children treated with NSAIDs, usually in connection with sun exposure (175).

Contact sensitivity to topical NSAIDs

Topical NSAIDs can cause allergic, photoallergic, and phototoxic contact dermatitis. There have been two systematic studies of photosensitivity to these compounds and their cross-reactivity (176,177). Eleven patients with confirmed photocontact dermatitis were photopatch tested with seven topical NSAIDs. Ketoprofen was the commonest cause. In five cases there was cross-sensitivity with fenofibrate, which was explained by a common benzoylketone or benzophenone molecule, and in one patient there was cross-sensitivity to tiaprofenic acid, an arylpropionic acid derivate that is not available in topical form in Europe. There was also one case of photocontact dermatitis from diclofenac, which was discovered by 1% dilution in alcohol, while 5% in petrolatum was negative in the same patient (176). In contrast to these findings, all 12 patients tested in another study reacted to both ketoprofen and tiaprofenic acid, mainly after UVA irradiation, but were negative to other arylpropionic acids (177). Furthermore, there were positive reactions to both ketoprofen and fenofibrate in eight of the 12 patients. The authors concluded that photoallergy to ketoprofen and fenofibrate is due to the molecular benzophenone structure and confirmed cross-reactivity with other benzophenones, used as sunscreens. Cross-reactivity between ketoprofen and tiaprofenic acid was supposed to be due to the benzophenone moiety of ketoprofen, or to the very similar thiophene-phenylketone part of tiaprofenic acid, but not to their arylpropionic function.

The topical use of NSAIDs, such as bufexamac, can provoke contact allergic reactions (178–180) and a case has been reported with bendazac (181).

- A 28-year-old man had been using a bendazac-containing ointment for his atopic dermatitis for 6 months, together with topical corticosteroids. Patch testing showed positive reactions to bendazac in petrolatum on days 2, 3, and 7 and a positive reaction to alclometasone dipropionate.

Contact allergy to topical indometacin has rarely been reported (182).

- A 14-year-old boy had contact allergy to indometacin gel used for a sprained ankle (183). He had previously taken NSAIDs orally, but not topically. Patch tests with the indometacin gel and pure indometacin 1% in petrolatum were positive.

Photocontact allergy to NSAIDs is not uncommon, but the incidence may differ from NSAID to NSAID. A case of photoallergy from local piketoprofen has been reported (184), as have two cases of prolonged photosensitivity after contact photoallergy from ketoprofen, persisting for more than a year after withdrawal (185,186).

Contact pemphigus has been attributed to ketoprofen.

- A 65-year-old Caucasian woman developed a localized skin eruption within hours of using ketoprofen gel on her knees to relieve arthralgia (187). The lesions were pruritic, well-demarcated, and erythematous, and later became studded with vesicles and small bullae. Histology and immunopathology suggested autoimmune pemphigus.

Photosensitivity to topical NSAIDs

The arylpropionic acid derivatives often cause allergic and photoallergic contact dermatitis, and photoallergic dermatitis to ketoprofen, with cross-photosensitivity to benzophenone and tiaprofenic acid, has been reported (188). Photopatch tests to these substances were positive but patch tests were negative.

A case of photoallergic contact dermatitis from aceclofenac has been reported (189). Photopatch tests were positive with aceclofenac 10% in petrolatum, but not with either aceclofenac 1% or 5% in petrolatum or with a series of NSAIDs and other analgesics (benzydamine hydrochloride 3 and 5%, bufexamac 5%, diclofenac 1, 5, and 10%, fepradinol 1%, ibuprofen 5%, indometacin 1, 5, and 10%, ketoprofen 1%, naproxen 5%, paracetamol 1, 5, and 10%, phenylbutazone 1%, piroxicam 1%, salicylic acid 1 and 5%, and thiosalicylic acid 0.1%, all in petrolatum).

Photocontact dermatitis has been reported after topical application of dexketoprofen (Enangel), with positive photopatch tests to dexketoprofen 1% and piketoprofen 2% (190).

Local pharyngeal treatment with benzydamine hydrochloride 0.15% (Tantum verde) by a 67-year-old man resulted in systemic photocontact dermatitis in the third week of treatment (191). Photopatch tests with Tantum verde as is and in 10% aqueous solution were positive: D1+, D2+, D3++.

Photosensitization potentials and cross-reactivities of ketoprofen, suprofen, tiaprofenic acid, and benzophenone have been studied in guinea pigs (192). Ketoprofen and benzophenone were the strongest photosensitizers. Cross-reactivity was most frequent after sensitization with

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ketoprofen. Benzophenone photosensitization did not induce cross-reactivity. The benzoyl radical was identified as the key structure for both photosensitization and cross-reactivity among the NSAIDs.

Pseudoporphyria

Pseudoporphyria is a photodistributed bullous disorder with clinical and histological features similar to those of porphyria cutanea tarda, but without accompanying abnormalities of porphyrin metabolism. Drugs, in particular NSAIDs and sulfur-containing diuretics, often cause pseudoporphyria (193). Pseudoporphyria associated with naproxen (15 mg/kg/day) has been reported in a child (194).

Musculoskeletal

Suspected but unproven harmful effects of NSAIDs on joints, cartilage, and bone have been reviewed (SEDA-11, 87). Inhibition of glycosaminoglycan synthesis in joint cartilage, inhibition of necrotic bone repair by reduced synthesis of vasodilator prostaglandins, which have been shown both in vitro and in animals, and deprivation of protective painful stimuli are possible mechanisms. As these data derive from experimental models, they cannot be extrapolated with certainty to the effects of NSAIDs on the pathophysiological characteristics of the human osteoarthritic joint. Evidence for harmful effects of NSAIDs on the human hip joint comes from single case reports and a small series of clinical observations, two retrospective studies, and two prospective investigations. The first prospective study showed that hip osteoarthritis progressed more rapidly in patients taking indometacin, a potent inhibitor of prostaglandin synthesis, than in those taking azapropazone, a weak inhibitor (195). This suggests that one should be cautious with long-term use of the more potent cyclo-oxygenase inhibitors in patients whose joints are severely compromised by osteoarthritis. The second study showed that the risk of progression of knee osteoarthritis increased in patients treated with indometacin for 1 year (196). Other studies have reported that some NSAIDs have a protective effect on cartilage (197). A study on a small group of patients treated with piroxicam for osteoarthritis of the knee supported the hypothesis that deprivation of painful stimuli lets the patient put more load on the joint, increasing the risk of more rapid progression of the disease (198).

The suggestion that NSAIDs should not be used as analgesics after orthopedic surgery because they might inhibit fracture healing (199) elicited strong disagreement (200,201). The belief that NSAIDs could cause more harm then benefit in patients undergoing orthopedic surgery in based on some experimental data in animals. In diverse rodent models NSAIDs inhibited bone healing, but other animal studies have shown no effect (200,202,203). In humans, published evidence is almost non-existent (200). In the absence of well-designed trials showing important effects on bone healing, NSAIDs should continue to be used as effective analgesics after orthopedic surgery.

Reproductive system

There have been several case reports that non-selective NSAIDs (diclofenac, naproxen, piroxicam) can cause infertility, attributed to "luteinized unruptured ovarian follicles" syndrome (204–206). Women who are trying to become pregnant should avoid taking any NSAIDs if possible, and those who need one for a chronic rheumatic disorder should be aware of possible infertility; in such cases further investigation is not required, as withdrawal of the drug restores fertility.

Immunologic

There is considerable difficulty and controversy in identifying and classifying allergic reactions to NSAIDs, for many reasons (207). First, the difficulty in making a definite diagnosis in patients who have these reactions without provocative challenge with the suspected drug and other NSAIDs. Secondly, reactions are characterized by a large spectrum of target organ responses to NSAIDs, and the same drug may cause different types of reactions in different organs in the same or different individuals. Thirdly, a patient can have a similar reaction to a structurally different NSAID. Finally, reports of these reactions include different, often imprecise, terms, making interpretation difficult.

Anaphylactic or anaphylactoid reactions to NSAIDs are probably relatively rare. Even today, the only data available are from 1981, when the FDA's Division of Drug Experience was notified of 131 cases attributable to various NSAIDs (208). Tolmetin was the most frequently implicated compound. However, the figures are distorted, because some of these drugs are much more widely used than others. A retrospective cohort study using 1980–84 Medicaid billing data from three states in the USA, designed to assess the relative risk of hypersensitivity reactions from different NSAIDs, failed to confirm that tolmetin is associated with a higher risk of hypersensitivity reactions than other NSAIDs (209). However, two drugs (glafenine and zomepirac) have been withdrawn from the market because of their propensity to cause severe hypersensitivity reactions.

The clinical picture of hypersensitivity reactions varies from vasomotor rhinitis, urticaria, and angioedema to serious bronchoconstriction and in some cases anaphylactic shock.

Two pathogenic mechanisms have been proposed: an allergic immunological hypersensitivity reaction and a pseudoallergic reaction characterized by mast-cell degranulation by complement components, histamine liberation by drugs, and interference with endogenous eicosanoid biosynthesis (210). The first mechanism appears to be responsible for anaphylactic shock and/or urticaria after amidopyrine or noramidopyrine, and the second for bronchoconstriction after aspirin, noramidopyrine, or aminophenazone and other pyrazole drugs. It is important to distinguish the two mechanism, since the first type of intolerance is fairly structure-specific and can be avoided by switching from a drug to which the patient has proved sensitive to an NSAID with a distinct structure, whereas pseudoallergic aspirin-sensitive

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patients must avoid all drugs that inhibit fatty acid cyclooxygenase.

There have been reports of exaggerated responses (angioedema and malaise) to bee stings in patients taking NSAIDs (SEDA-11, 88). More recently a report of resensitization to bee stings associated with diclofenac has been received by the Centre for Adverse Reactions Monitoring in New Zealand. The patient, who had been successfully desensitized to bee venom many years before, developed life-threatening anaphylaxis after a bee sting while taking diclofenac (211).

Infection risk

NSAIDs can mask signs of infection, such as fever and pain, which can delay appropriate treatment. Furthermore they can impair the host defence mechanism against infection and can modulate the acute inflammatory response in such a way as to alter the course of infection, predisposing the patient to bacteremia, shock, and multiorgan failure (212,213). Until appropriate studies have defined the relation between NSAIDs and severe soft tissue infections, it is better to avoid using them, if possible, until the cause of the fever is known.

In 11 cases of necrotizing fasciitis (which is usually caused by *Streptococcus pyogenes*) NSAIDs were suspected to have predisposed to the infection and/or to have caused its fulminant evolution (SEDA-12, 79). Sporadic cases continue to be reported (214), but a causal link between this severe infection and NSAIDs is far from proven (215).

Long-Term Effects

Tumorigenicity

Studies on the tumor-inducing effects of heavy use of analgesics, especially those that contain phenacetin, have given contrasting results (SEDA-21, 100) (216,217). There has been a case-control study of the role of habitual intake of NSAIDs on the occurrence of urothelial cancer and renal cell carcinoma (218). In previous studies there was a consistent association between phenacetin and renal cell carcinoma, but inconclusive results with respect to non-phenacetin analgesics. In 1024 patients with renal cell carcinoma and an equal number of matched controls, regular use of analgesics was a significant risk factor for renal cell carcinoma (OR = 1.6; CI = 1.4, 1.9). The risk was significantly increased by aspirin, NSAIDs, paracetamol, and phenacetin, and within each class of analgesic the risk increased with increasing exposure. Individuals in the highest exposure categories had about a 2.5-fold increase in risk relative to non-users or irregular users of analgesics.

Second-Generation Effects

Pregnancy

NSAIDs are among the commonest drugs prescribed for pregnant woman (219). However, the risk of adverse birth outcomes in women who take NSAIDs other than aspirin during pregnancy is largely unknown.

In a comparison, too small to allow firm conclusions, pregnancies in 88 patients with rheumatic diseases in which NSAIDs had or had not been used, there were no differences in pregnancy outcome, duration of labor, complications at delivery, neonatal health, and the health or development of offspring at follow-up (220).

However, there is no doubt that NSAIDs can alter fetal physiology in the last trimester of pregnancy and prolong gestation and labor (SEDA-5, 101) (SEDA-6, 93) (SEDA-7, 108) (SEDA-8, 102) (SEDA-9, 88) (SEDA-11, 88) (SEDA-12, 84) (SEDA-15, 99) (SEDA-21, 96) (SEDA-22, 112).

There has been a study in a Danish county (population about 490 000), including data on all women who between 1991 and 1998 had a live birth or a stillbirth after the 28th week of gestation, or who had a miscarriage (including missed abortions) (221). The researchers performed a case-control study using data from the Danish birth registry, the county hospital discharge registry, and the county's prescriptions database. The risk of miscarriage was examined. The study involved 4268 women who had had their first miscarriage, 63 of whom had filled a prescription for an NSAID in the 12 weeks before being discharged from hospital after the miscarriage, and 29 750 primiparous controls who had live births. There was a significant association with miscarriage both when the prescription for the NSAID was filled during the week before the miscarriage (OR = 7.0; CI = 2.8, 17) and when it was filled at 7–9 weeks before the miscarriage (OR = 2.6; CI = 1.8, 4.0).

The validity of these findings has been challenged on the grounds of possible bias and other methodological problems (222,223). However, according to a statement issued by the UK Royal College of Obstetricians and Gynaecologists (RCOG) NSAIDs should be avoided by women who know that they are pregnant. According to the RCOG, although the study did not establish a causative link between NSAID use and miscarriage, pregnant women should avoid NSAIDs and in the meantime prefer to use effective alternative drugs, such as paracetamol (224).

Teratogenicity

Many NSAIDs have provoked teratogenic effects in animals, but there is no evidence from epidemiological studies that NSAIDs are embryotoxic in humans. The lack of clinical and epidemiological studies makes any firm recommendations about the use of NSAIDs during the first 6 months of pregnancy impossible. However, the possibility of unrecognized dysmorphogenic effects of NSAIDs needs to be considered before prescribing, so it is wise to use compounds with short elimination half-lives and to give them at the longest possible dosage intervals. When NSAIDs are used for dysmenorrhea, administration should be delayed until menstruation has started, so as to avoid ingestion during an unrecognized pregnancy; in any case, there is no need to give them earlier.

There has been a study in a Danish county (population about 490 000), including data on all women who between 1991 and 1998 had a live birth or a stillbirth after the 28th week of gestation, or who had a miscarriage (including

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missed abortions) (221). The researchers performed a cohort study using data from the Danish birth registry, the county hospital discharge registry, and the county's prescriptions database. The risk of an adverse birth outcome (congenital abnormality, low birth weight, and preterm birth) was examined. The study included 1462 women who gave birth after 28 weeks and who had filled a prescription for an NSAID, a total of 1742 prescriptions. The control group consisted of 17 259 pregnant women who did not take any drugs during pregnancy. There was no significant association between the uptake of prescriptions for NSAIDs during pregnancy and the risks of congenital abnormalities, low birth weight, or preterm births.

Fetotoxicity

Several studies have shown that the use of indometacin as a tocolytic agent is associated with severe adverse effects in the fetus (for example fetal ductal constriction, oligohydramnios), which limit this indication (SEDA-16, 108) (225).

Lactation

Although the newer NSAIDs are all secreted into milk, the amounts are probably too small to affect the breast-fed infant. However, serious adverse effects in breast-fed children have been described with pyrazolones and indometacin (SEDA-10, 78). The choice of NSAID, if it is indispensable, should therefore be directed to compounds that have short half-lives. In order to reduce the quantity of drug reaching the child, the mother should take the drug at the time of breast feeding or immediately afterwards, so that the next feed occurs after a time equivalent to the half-life of the drug.

Susceptibility Factors

Genetic factors

Anaphylactic reactions induced by NSAIDs are associated with HLA-DRB1 genes encoding HLA-DR11 molecules, according to the results of a study in 21 patients who suffered from anaphylactic reactions to NSAIDs and 47 patients who had exclusively skin reactions to these drugs (226). A control group of 167 patients was studied. Patients and controls were challenged, single-blind, with aspirin, salsalate, paracetamol, piroxicam, or diclofenac. There were 88 episodes of skin reactions to NSAIDs and 26 episodes of anaphylaxis. The frequency of HLA-DR11 alleles was 59% in the anaphylaxis group compared with 16% in the control group. Neither HLA-DR nor HLA-DQ alleles was associated with NSAID-induced skin reactions.

Drug Administration

Drug administration route

Topical NSAIDs

Despite official approval and wide use as either over-the-counter or prescription drugs, there is skepticism that topical NSAIDs have any action other than as rubefacients (227). There has been a systematic review of the efficacy and safety of these drugs in 86 randomized controlled clinical trials in more than 10 000 patients with acute or chronic pain (228). Topical NSAIDs were significantly more effective than placebo for pain relief. Local tolerability was good: local skin reactions were rare (3.6%) and systemic effects even rarer (less than 0.5%). Local or systemic unwanted effects of sufficient severity to cause withdrawal from the study were also rare (0.5%) and no more common than with placebo.

In two case-control studies, topical NSAIDs were not significantly associated with upper gastrointestinal bleeding or perforation, after adjustment for the confounding effect of concomitant use of oral NSAIDs (229), nor with hospitalization for acute renal insufficiency (157), although renal adverse effects have been described, albeit rarely, with these topical formulations (SEDA-18, 100).

Drug–Drug Interactions

General interactions with NSAIDs

General interactions with NSAIDs are summarized in Table 2 (pharmacokinetic interactions) and Table 3 (pharmacodynamic interactions).

Widespread use of NSAIDs, particularly in the elderly, who often take other drugs at the same time, leads to a high risk of clinically significant drug interactions, both pharmacokinetic and pharmacodynamic. The inhibitory effects of azapropazone, oxyphenbutazone, and phenylbutazone on the metabolism of other drugs, such as oral anticoagulants, oral hypoglycemic drugs, and phenytoin, is an example of a pharmacokinetic mechanism. Other NSAIDs inhibit the renal excretion of lithium (although toxicity is less likely with aspirin, ibuprofen, and sulindac) and methotrexate. Pharmacodynamic mechanisms are exemplified by the interactions between indometacin and other NSAIDs (except perhaps sulindac) and with antihypertensive agents (including beta-blockers, diuretics, and ACE inhibitors). Interactions of NSAIDs with other drugs (230) are summarized in Tables 2 and 3.

To explore the frequency of continuous use of over-the-counter drugs and the potential for harmful interactions between OTC drugs and prescribed drugs, a population-based interview survey was conducted in 10 477 subjects (231). Daily use of over-the-counter drugs was reported by 7% of the subjects and 4% of those who used over-the-counter drugs had taken combinations with potential for clinically significant interactions. Interactions were most common for NSAIDs such as ketoprofen (15% of ketoprofen users), ibuprofen (10%), and aspirin (6%). Unfortunately, this study did not provide information on whether the potential interactions led to actual clinical problems.

Alcohol

The FDA has announced its intention to require alcohol warnings on all over-the-counter pain medications that contain acetylsalicylic acid, salicylates, paracetamol, ibuprofen, ketoprofen, or naproxen. The proposed warnings are aimed at alerting consumers to the specific risks incurred from heavy alcohol consumption

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Table 2 Pharmacokinetic drug interactions with NSAIDs

Drug(s) affected by NSAIDs	NSAID(s) implicated	Effect(s)	Management
Oral anticoagulants	Phenylbutazone Oxyphenbutazone Azapropazone	Inhibition of metabolism of *S*-warfarin, increasing anticoagulant effect	Avoid NSAIDs if possible; careful monitoring when unavoidable (note also pharmacodynamic interactions)
Lithium	Probably all NSAIDs (?except sulindac, aspirin)	Inhibition of renal excretion of lithium, increasing lithium serum concentrations and increasing risk of toxicity	Use sulindac or aspirin if an NSAID is unavoidable; careful monitoring of serum lithium concentration and appropriate dosage reduction
Oral hypoglycemic drugs	Phenylbutazone Oxyphenbutazone Azapropazone	Inhibition of metabolism of sulfonylureas, prolonging half-lives and increasing the risk of hypoglycemia	Avoid these NSAIDs if possible; if not, monitor blood glucose closely
Phenytoin	Phenylbutazone Oxyphenbutazone	Inhibition of metabolism of phenytoin, increasing plasma concentration and risk of toxicity	Avoid these NSAIDs if possible; if not, intensive plasma concentration monitoring
	Other NSAIDs	Displacement of phenytoin from plasma albumin, reducing total concentration for the same unbound (active) concentration	Careful interpretation of serum total phenytoin concentration; measurement of unbound concentration can be helpful, if available
Methotrexate	Probably all NSAIDs	Reduced clearance of methotrexate (mechanism unclear), increasing plasma concentration and risk of severe toxicity	Simultaneous dosing is contraindicated; use of NSAIDs between cycles of chemotherapy is probably safe
Sodium valproate	Aspirin	Inhibition of valproate metabolism, increasing plasma concentration	Avoid aspirin; monitor plasma concentration if other NSAIDs are used
Digoxin	All NSAIDs	Potential reduction in renal function (particularly in the very young and very old), reducing digoxin clearance and increasing plasma concentrations and the risk of toxicity; no interaction if renal function is normal	Avoid NSAIDs if possible; if not, frequent checks of serum digoxin concentration and serum creatinine
Aminoglycosides	All NSAIDs	Reduction in renal function in susceptible individuals, reducing aminoglycoside clearance and increasing plasma concentrations	Careful plasma concentration monitoring and dosage adjustment
Antacids	Indometacin (?other NSAIDs)	Variable effects of different formulations: aluminium-containing antacids reduce the rate and extent of absorption of indometacin; sodium bicarbonate increases the rate and extent of absorption of indometacin	No action required, unless a marked reduction in absorption results in a poor response to the NSAID, in which case dosages may need to be increased or the antacid withdrawn
Probenecid	Probably all NSAIDs	Reduction in the metabolism and renal clearance of NSAIDs and their acylglucuronide metabolites, which are hydrolysed back to the parent drug	Can be used therapeutically to increase the response to a given dose of an NSAID
Barbiturates	Phenylbutazone (?other NSAIDs)	Increased metabolic clearance of NSAIDs	May require higher dosages of phenylbutazone
Caffeine	Aspirin	Increased rate of absorption of aspirin	No action required
Colestyramine	Naproxen and probably other NSAIDs	The anion exchange resin binds NSAIDs in gut, reducing the rate (?and extent) of absorption	Separate dosing times by 4 hours; may need higher than expected dosages of NSAIDs
Metoclopramide	Aspirin	Increased rate and extent of absorption of aspirin in patients with migraine	Can be used therapeutically

and its interaction with analgesics. For products that contain paracetamol, the warning indicates the risks of liver damage in those who drink more than three alcoholic beverages a day. For formulations that contain salicylates or the mentioned NSAIDs three or more alcoholic beverages will increase the risk of stomach bleeding (232).

Antihypertensive drugs

All NSAIDs interfere with hypertension control in patients taking diuretics, beta-blockers, or vasodilators, although contrasting data have been published on the effects of these drugs on blood pressure (233). Moreover, they interact diversely with different

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Table 3 Pharmacodynamic drug interactions with NSAIDs

Drug affected by NSAIDs	NSAID(s) implicated	Effect(s)	Management
Antihypertensive drugs	Indometacin	Reduction in hypotensive effect, probably related to impaired prostaglandin synthesis (causing salt and water retention) and vascular prostaglandin synthesis (causing vasoconstriction)	Avoid all NSAIDs in treated hypertensive patients if possible; if not, use sulindac preferentially; may need additional antihypertensive therapy
Diuretics	Indometacin	Reduction in natriuretic and diuretic effects; can exacerbate congestive cardiac failure	Avoid NSAIDs in patients with cardiac failure; use sulindac; monitor clinical signs of fluid retention
Anticoagulants	All NSAIDs	Gastrointestinal tract mucosal damage; inhibition of platelet aggregation; increased risk of gastrointestinal bleeding in patients taking anticoagulants	Avoid all NSAIDs if possible
Hypoglycemic drugs	Salicylates (high dosages)	Potentiation of hypoglycemic effects (mechanism unknown)	Monitor blood glucose concentration
Combinations with increased risk of toxicity	NSAID(s) implicated	Effect(s)	Management
All diuretics	All NSAIDs	Combination associated with increased risk of hemodynamic renal insufficiency	Avoid combination if possible
Triamterene	Indometacin	Potentiation of nephrotoxicity, including subjects with normal renal function	Combination contraindicated
Potassium-sparing diuretics	All NSAIDs	Potassium retention and hyperkalemia	Avoid combination; monitor plasma potassium concentration

antihypertensive drugs, antagonizing the effect of beta-blockers and ACE inhibitors more than calcium channel blockers, diuretics, and centrally acting alpha-adrenoceptor agonists (234,235). In one study there was no significant change in blood pressure in patients taking calcium channel blockers (verapamil or nifedipine) with NSAIDs (236). Among ACE inhibitors, perindopril reduces blood pressure in patients taking NSAIDs (237).

Ciclosporin

An interaction resulting in additive deterioration of renal function has been documented in patients taking ciclosporin together with different NSAIDs (SEDA-17, 107). The mechanism is still uncertain, but may involve prostaglandin production, and the known effects of NSAIDs on cyclo-oxygenase suggest an additive effect in the kidney. The concomitant use of NSAIDs and ciclosporin requires caution. Sulindac, which may be less toxic to the kidneys, can increase whole blood ciclosporin concentrations by inhibiting hepatic cytochrome P450 (SEDA-17, 107). Inhibition by ciclosporin of diclofenac first-pass metabolism has been hypothesized (SEDA-21, 104).

Methotrexate

Interactions of NSAIDs with methotrexate have been reviewed (SEDA-20, 89). Severe toxicity has been attributed to different dosages of methotrexate in concomitant use with several NSAIDs. The mechanisms are unclear. Both methotrexate and the NSAIDs are secreted by the organic acid secretory pathway in the kidney and both are highly bound to plasma albumin. In a study on the pharmacokinetics of methotrexate in patients with rheumatoid arthritis there was no significant interaction between a single low dose of methotrexate and piroxicam (238). A second study in patients with rheumatoid arthritis showed no significant differences in the pharmacokinetics of methotrexate 7.5 mg/week with or without NSAIDs. At higher dosages (10–25 mg/week) the renal clearance of methotrexate was reduced by both salicylate and non-salicylate NSAIDs (239). These data confirm that simultaneous dosing of methotrexate (over 7.5 mg/week) and NSAIDs must be avoided, since methotrexate toxicity can be severe. Differences between NSAIDs in interactions with methotrexate require other studies (240).

Misoprostol

Two reports of adverse neurological effects (dizziness, unsteadiness in walking, and ataxic symptoms) in patients treated with misoprostol and NSAIDs require confirmation (SEDA-16, 108).

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Noradrenaline

See also Adrenoceptor agonists

General Information

Noradrenaline is a catecholamine with agonist effects mainly at alpha-adrenoceptors. It is still occasionally used to maintain blood pressure in acute emergencies.

Note on nomenclature

Although norepinephrine is the recommended International Non-proprietary Name (rINN), there are good reasons why the name noradrenaline should be preferred, based on usage, history, etymology, and, most importantly, risk of clinical errors (1).

General adverse effects

The systemic adverse reactions of noradrenaline are typically adrenergic, involving primarily the central nervous system and the blood vessels. It has very little effect on beta-adrenoceptors in the heart, but there tends to be some bradycardia as a reflex consequence of the drug-induced rise in blood pressure. Retrosternal pain can occur, as with the amphetamines. A paradoxical but transient engorgement of the thyroid has occurred.

Organs and Systems

Cardiovascular

Like adrenaline, noradrenaline is also sometimes added to local anesthetics (for example in a 1:250 000 concentration) to prolong their effect; it should not be injected into extremities (finger, penis) for this purpose, since dangerous ischemia can result (2).

When infusing noradrenaline the infusion should always be ended very gradually, since otherwise a catastrophic fall in blood pressure can occur.

Drug Administration

Drug administration route

Extraordinary care is needed to avoid local damage at the site of the intravenous infusion, which can readily result in skin necrosis as a consequence of ischemia.

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Norastemizole

See also Antihistamines

General Information

Norastemizole is a metabolite of the second-generation antihistamine astemizole (1). Its major advantage is that it is not cardiotoxic and does not interact with drugs that increase the risk of serious dysrhythmias.

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Norfloxacin

See also Fluoroquinolones

General Information

Norfloxacin is a fluoroquinolone antibacterial drug with properties similar to those of ciprofloxacin, although less potent in vitro.

Norfloxacin inhibits CYP1A2 and can therefore enhance the effects of other drugs by reducing their clearance (1).

Comparative studies

In a double-blind, multicenter study 171 patients who had acute pyelonephritis were given intravenous cefuroxime for 2–3 days, followed by ceftibuten 200 mg bd or norfloxacin 400 mg bd for 10 days (2). There were fewer bacterial relapses after oral norfloxacin than ceftibuten. Adverse events were reported by 47% of the patients taking ceftibuten and by 38% of those taking norfloxacin. This difference was not significant, but diarrhea or loose stools occurred more often with ceftibuten.

Organs and Systems

Sensory systems

A corneal ulcer associated with deposits of norfloxacin in the right eye has been reported in a 40-year-old man with right trigeminal and facial nerve palsies and reduced tear secretion. He stopped using norfloxacin ophthalmic solution and recovered (3).

Psychological, psychiatric

There have been reports of hallucinations with norfloxacin (4).

Hematologic

- Eosinophilia occurred in a 35-year-old man with alcoholic cirrhosis taking norfloxacin 400 mg bd for prophylaxis of spontaneous bacterial peritonitis (5).

Gastrointestinal

In a prospective study in women with urinary tract infections treated with pivmecillinam 400 mg bd for 3 days ($n = 483$) or norfloxacin 400 mg bd for 3 days ($n = 471$), 36% of the pivmecillinam-treated patients and 39% of the norfloxacin-treated patients reported adverse events (6). Gastrointestinal symptoms were most frequent. Of the patients who took norfloxacin 4.3% had vaginal candidiasis.

Liver

Acute hepatitis has been reported with norfloxacin (7,8).

Pancreas

Norfloxacin can cause pancreatitis (9).

Urinary tract

Acute interstitial nephritis, probably related to norfloxacin, has been reported (10).

- A 38-year-old woman took norfloxacin (300 mg/day) and tiaramide hydrochloride (300 mg tds) for an infection with *Mycoplasma pneumoniae*. One day after the start of treatment, her symptoms of cough and fever worsened and she developed lumbago and hematuria. The diagnosis was confirmed by percutaneous renal biopsy. She slowly improved without specific treatment. Lymphocyte stimulation tests were negative, but rechallenge with norfloxacin was followed by bilateral lumbago.

The authors identified two previous reports of acute interstitial nephritis associated with norfloxacin.

Musculoskeletal

Myalgia has been attributed to norfloxacin (11).

- A 33-year-old man developed myalgia and rhabdomyolysis while taking norfloxacin for cystitis. He complained of general muscle fatigue, tendon disorders, and articular pain. When norfloxacin was withdrawn, his symptoms abated, with persistence of slight myalgia for 10 days.

Drug Administration

Drug formulations

The stability of norfloxacin in suspensions prepared from two brands of film-coated tablets has been studied (12). The vehicle consisted of tragacanth, saccharin sodium, sorbitol solution, glycerol, parabens concentrate, peppermint spirit, purified water, and syrup USP, yielding a final concentration of norfloxacin of 20 mg/ml. The resulting suspensions were chemically stable for 28 days when stored in amber glass bottles at room temperature.

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Drug–Drug Interactions

Antacids

Norfloxacin can interact with antacids containing aluminium or magnesium salts, by complexation, reducing its solubility and therefore its absorption; this can result in therapeutic failure. In an in vitro study, dissolution rates were markedly reduced in the presence of all antacids studied; however, this phenomenon was practically avoided when a disintegrant (sodium starch glycolate or crospovidone) was included in the tablet (13).

Ciclosporin

In children undergoing renal transplantation and receiving ciclosporin, the mean daily dose of ciclosporin needed to maintain adequate trough concentrations fell when patients were treated with norfloxacin for urinary tract infections (14).

Oral contraceptives

Plasma concentrations of oral contraceptive steroids were unchanged by norfloxacin (15).

Food–Drug Interactions

The systemic availability of norfloxacin was reduced by 38–52% by dairy products (16).

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Nortriptyline

See also Tricyclic antidepressants

General Information

Nortriptyline is a tricyclic compound which differs from amitriptyline in being monodemethylated (1).

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Noscapine

General Information

Noscapine, which is derived from *Papaver somniferum*, has little analgesic or sedative effect. It is thought to be capable of modifying cough (1), but as with other antitussives, it remains difficult to say whether cough is genuinely suppressed or merely better tolerated. Headache and drowsiness can occur in a minority of patients and a skin rash has been occasionally reported.

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Long-Term Effects

Mutagenicity

In vitro experiments have shown that noscapine can produce spindle inhibition and polyploidy, suggesting that it may be genotoxic or carcinogenic (SEDA-17, 210). The degree of risk to humans when noscapine is used in a cough mixture remains to be established. Nevertheless, as there are alternative drugs, noscapine should not be given to women of childbearing potential.

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Novobiocin

General Information

Novobiocin is an antimicrobial drug that is structurally related to the coumarins. It is active against Gram-positive bacteria, such as *Staphylococcus aureus* (including meticillin-resistant strains) and other staphylococci; the enterococci are usually resistant. Some Gram-negative organisms, including *Haemophilus influenzae* and *Neisseria* species, are also susceptible, as are some strains of *Proteus*, but most of the Enterobacteriaceae are resistant. Its action is primarily bacteriostatic, although it may be bactericidal against more sensitive species at high concentrations. It inhibits DNA gyrase and is effective in eliminating plasmids, but resistance to novobiocin develops readily both in vitro and during therapy.

Although novobiocin has been used alone or with other drugs, such as rifampicin or tetracycline, in the treatment of infections due to staphylococci and other susceptible organisms, it has largely been superseded by other drugs because of the problems of resistance and toxicity.

Organs and Systems

Hematologic

Reports of drug-induced thrombocytopenia have been systematically reviewed (1). Among the 98 different drugs described in 561 articles the following antibiotics were found with level I (definite) evidence: co-trimoxazole, rifampicin, vancomycin, sulfisoxazole, cefalothin, piperacillin, methicillin, novobiocin. Drugs with level II (probable) evidence were oxytetracycline and ampicillin.

Drug–Drug Interactions

Cytotoxic drugs

Novobiocin potentiates the activity of etoposide in vitro by increasing intracellular accumulation of etoposide. A phase I trial showed that the maximum tolerated dose of novobiocin was 7 g/m^2/day when it was given in combination with etoposide; dose-limiting adverse effects consisted of neutropenic fever and reversible hyperbilirubinemia. Novobiocin did not augment the toxic effects of etoposide on the bone marrow or the gastrointestinal mucosa, and nausea, a dose-limiting adverse effect in other trials of novobiocin, was well controlled by 5-HT3 receptor antagonists (2).

However, in a phase II study of the combination of novobiocin and high-dose cyclophosphamide and thiotepa, followed by autologous bone marrow support in women with chemosensitive advanced breast cancer, there was no significant increase in progression-free survival and overall survival compared with historical controls treated with high-dose alkylating drugs alone (3).

Lactoferrin

Lactoferrin can potentiate the activity of novobiocin against some strains of *Escherichia coli* strains (4).

Sodium polyphosphate

The permeabilizer sodium polyphosphate may enhance the activity of novobiocin against *Pseudomonas aeruginosa* (5).

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Noxiptiline

See also Tricyclic antidepressants

General Information

Noxiptiline is a tricyclic compound that differs from amitriptyline in having a longer side-chain, containing an oxyimino-group.

In a double-blind comparison of noxiptiline ($n = 30$) and amitriptyline ($n = 32$) in hospitalized patients with

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primary depressive illness for 3–6 weeks there were no significant differences, but noxiptiline had a faster onset of action (1). A comparison with imipramine also showed no difference in therapeutic efficacy (2).

As regards adverse effects, noxiptiline seemed to cause more mental symptoms, such as delirium (3). In one study in 44 patients, 9 developed delirium, there were mild manic symptoms in 6, dry mouth in 21, disturbed micturition in 2, and difficulty in accommodation in 3 (2), the last 3 being evidence of anticholinergic effects.

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Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

See also Individual agents

General Information

The nucleoside analogue reverse transcriptase inhibitors (NRTIs) include abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, and zidovudine (all rINNs). The following abbreviations have been used and may still be encountered in published papers:

- DDI: didanosine (inosine analog)
- 3TC: lamivudine (cytidine analog)
- D4T: stavudine (thymidine analog)
- DDC: zalcitabine (cytidine analog)
- ZDV: zidovudine (thymidine analog)

The abbreviation AZT should not be used to designate zidovudine, since it can be, and has been, confused with azathioprine (1).

To be converted into an active compound, all the NRTIs have to be phosphorylated intracellularly to the triphosphate form via monophosphates and diphosphates. The triphosphates compete with cellular nucleotides and inhibit HIV reverse transcriptase by introducing a chain terminator into the growing complementary DNA strand during reverse transcription. However, this mechanism also occurs when human DNA is transcribed by the human DNA polymerase. In fact, the first NRTI in clinical use (zidovudine) was initially developed as an anticancer drug, targeting human DNA polymerase in cancer cells. However, all NRTIs have higher specificity for viral reverse transcriptase than for the human DNA polymerase.

Observational studies

Combinations of different NRTIs

In a 24-week open, single-arm trial, 108 antiretroviral therapy-naive, HIV-infected prisoners were given a combination tablet of lamivudine + zidovudine (150 mg/300 mg) and a tablet of abacavir 300 mg bd (2). The plasma HIV-1 RNA concentration remained at 400 copies/ml or less in 85% of the patients and at less than 50 copies/ml in 75%. Nausea was the most common adverse effect ($n = 40$). Four patients withdrew prematurely because of one or more of the following: abdominal discomfort and pain; abdominal distension; neutropenia; malaise or fatigue; nausea and vomiting. Two patients had a suspected hypersensitivity reaction to abacavir and were withdrawn.

A combination of nucleosides analogues, stavudine 2 mg/kg/day plus didanosine 180 mg/m^2/day for 48 weeks, has been assessed in 16 asymptomatic children, median age 6.5 years, with HIV infection (3). They had plasma HIV RNA concentrations below 50 000 copies/ml and CD4 counts above 15%. Plasma HIV RNA was reduced to 400 copies/ml or less in 43% and 44% of cases at 24 and 48 weeks respectively. There were minor adverse effects in two-thirds of the children; none led to drug withdrawal. There were no cases of lipoatrophy. There were no resistance mutations linked to didanosine (L74V or M184V) or stavudine (V75T) nor multinucleoside resistant genotypes (151 complex or 69 inserts). However, four children developed zidovudine-like mutations, T215Y and/or M41L.

Combinations of NRTIs and NNRTIs

The efficacy and safety of abacavir (NRTI) and efavirenz (NNRTI) plus background therapy have been retrospectively evaluated in 50 patients, who had previously been treated with highly active antiretroviral therapy (HAART) (4). There was some immunological benefit, albeit limited, in most of the patients. Adverse effects were not mentioned in detail, but the dropout rate during the first 4 weeks of treatment was high, owing to skin rashes and hypersensitivity reactions.

Of 80 injecting drug users who took two NRTIs + nevirapine (NNRTI), 20 discontinued treatment and 20 had treatment failures (5). Adverse events led to withdrawal of therapy in 10 patients: eight had a rash (in one case Stevens–Johnson syndrome); one had liver failure thought to be unrelated to the drugs; and one had "general intolerance." Two patients taking methadone had opioid withdrawal symptoms, presumably due to induction of methadone metabolism by nevirapine.

Combinations of NRTIs and protease inhibitors

A variable-dose plasma concentration-controlled approach to combination antiretroviral therapy (zidovudine, lamivudine, and indinavir) has been compared with conventional fixed-dose therapy in 40 patients in a randomized, 52-week, open trial (6). Significantly more concentration-controlled recipients achieved the desired concentrations for all three drugs: there was a good response in 15 of 16 concentration-controlled recipients compared with nine of 17 conventional regimen recipients. However, there was no difference in the occurrence

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of drug-related clinical events or laboratory abnormalities between the two regimens. Three patients withdrew because of gastrointestinal adverse effects, one because of a peripheral neuropathy, and one with headache and anemia. There was nephrolithiasis in four cases.

The combination of indinavir + ritonavir 400/400 mg bd plus two NRTIs has been studied in 93 patients in an open, uncontrolled, multicenter trial (7). Raised triglycerides ($n = 78$) and cholesterol ($n = 63$) were the commonest adverse effects, followed by nausea ($n = 22$) and circumoral paresthesia ($n = 9$). Withdrawal was required in four cases of nausea, four of lipodystrophy, one of diarrhea, and one of osteonecrosis.

In a multicenter, open, uncontrolled trial of protease inhibitors in conjunction with NRTIs for at least 96 weeks in 32 children, the pharmacokinetics of indinavir and nelfinavir showed large interindividual differences (8). In all, 17 children suffered adverse events. The most common adverse events in those taking indinavir were diarrhea ($n = 6$), vomiting ($n = 6$), anorexia ($n = 5$), hematuria ($n = 5$), abdominal pain ($n = 4$), and headache ($n = 3$); most were mild and occurred early in treatment. The rates of drug-related adverse effects were 0.4 per patient-year in those taking indinavir and 0.16 per patient-year in those taking nelfinavir.

Combinations of NRTIs, NNRTIs, and protease inhibitors

In an open 48-week, single-arm, multicenter phase II study in 99 patients abacavir 300 mg bd, amprenavir 1200 mg bd, and efavirenz 600 mg/day were associated with rashes in 50 patients, possibly because of abacavir hypersensitivity; 17 permanently discontinued one or more drugs as a result (9). Other adverse effects included nausea ($n = 41$), diarrhea ($n = 27$), sleep disorders ($n = 27$), dizziness ($n = 25$), fatigue ($n = 23$), hypertriglyceridemia ($n = 18$), neutropenia ($n = 8$), hyperamylasemia ($n = 4$), leukopenia ($n = 3$), hypercholesterolemia ($n = 2$), raised alkaline phosphatase ($n = 1$), and raised aspartate transaminase ($n = 1$).

In infants and children assigned to different combinations of one or two NRTIs plus an NNRTI and/or a protease inhibitor, the numbers of patients with moderate or severe adverse events were as shown in Table 1 (10). In cases of rash, the rash was worse in those who were taking nevirapine-containing regimens.

General adverse effects

Almost all NRTIs cause non-specific gastrointestinal and general adverse effects (nausea, sleep disturbances, headache) that are difficult to attribute to a single agent and usually disappear after the first 2–4 weeks of therapy.

Mitochondrial toxicity associated with NRTIs

Initially, most of the adverse effects seen with zidovudine use (in particular hematological effects) were attributed to interference with cellular DNA replication. However, DNA replication also occurs in mitochondria. Mitochondrial DNA encodes some of the enzymes used for oxidative phosphorylation. Only recently has it been hypothesized that inhibition of this pathway could lead to mitochondrial toxicity and be responsible for most of the toxicity seen with NRTIs, including polyneuropathy, myopathy, cardiomyopathy, steatosis, lactic acidosis, exocrine pancreas failure, bone marrow failure, and proximal tubular dysfunction (11). These adverse effects are also a compilation of the clinical features seen in several genetic mitochondrial cytopathies.

In vitro, NRTIs reduce mitochondrial DNA, most likely by inhibiting mitochondrial DNA polymerase gamma. Heterogeneous toxicity profiles of different NRTIs in vivo may be related to variable tissue sensitivity, cell entry, and drug phosphorylation. Therefore, each NRTI has a specific adverse effect profile (Table 2 (11)), but any feature of mitochondrial toxicity must be considered with all NRTIs. A major problem of mitochondrial toxicity is its delayed onset, sometimes after several months of treatment.

Table 1 Numbers (%) of infants and children with moderate or severe adverse events in a study of one or two NRTIs plus an NNRTI and/or a protease inhibitor

System affected by the adverse event	Regimen			
	Stavudine + nevirapine + ritonavir ($n = 41$)	Stavudine + nevirapine + nelfinavir ($n = 44$)	Stavudine + lamivudine + nevirapine + nelfinavir ($n = 44$)	Stavudine + lamivudine + nelfinavir ($n = 52$)
Respiratory	12 (29)	18 (41)	23 (52)	50 (96)
Hematologic (neutropenia)	17 (41)	9 (20)	14 (32)	23 (44)
Gastrointestinal				
Nausea/ vomiting	29 (71)	32 (73)	18 (41)	15 (29)
Other	10 (24)	25 (57)	18 (41)	19 (37)
Liver	12 (29)	14 (32)	18 (41)	23 (44)
Skin	27 (66)	41 (93)*	32 (73)	17 (33)*
Body temperature (fever)	24 (59)	30 (68)*	20 (45)	10 (19)*

*Significantly different from the other groups

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Table 2 Spectrum of adverse effects of nucleoside analogue reverse transcriptase inhibitors

Adverse effects	Didanosine	Lamivudine	Stavudine	Zalcitabine	Zidovudine
Cardiomyopathy	+	−	+	−	+
Neuropathy	++	−	++	++	−
Lactic acidosis	−	−	+	+	+
Bone marrow toxicity	+	−	+	−	++
Hepatic steatosis	−	±	+	+	+
Pancreatitis	−	±	++	+	−
Myopathy	−	−	−	−	++

++ most prominent adverse effect
+ observed adverse effect
± possible adverse effect
− adverse effect typically not observed

Organs and Systems

Cardiovascular

Cardiomyopathy is a rare adverse effect that has been observed in patients treated with didanosine, zidovudine, and zalcitabine (12). In a retrospective, case-control study, cardiomyopathy was 8.4 (95% CI = 1.7, 42) times more likely to develop in children who had previously used zidovudine than in children who had never been exposed to it (13).

Nervous system

Peripheral neuropathy is often observed in patients treated with didanosine, stavudine, and zalcitabine (14,15).

Sensory systems

In a report of ototoxicity in a patient taking three antiretroviral drugs, the authors suggested that nucleoside analogues should be avoided in patients with known neurotoxicity.

- A 23-year-old woman who took stavudine, lamivudine, and nevirapine had nausea and diarrhea during the first few days and within 2 weeks developed sudden bilateral hearing loss, dizziness, and tinnitus (16). The hearing defect was sensorineural. CT and MRI scans were normal. Prednisolone was ineffective.

Metabolism

Lipodystrophy

The prevalence of lipodystrophy has been studied during follow-up for 30 months of previously untreated patients who had been randomized to receive different nucleoside analogue combinations for 6 months in the ALBI–ANRS 070 trial (17). After 30 months 37 of 120 patients who had used nucleoside analogues with or without other antiretroviral drugs had at least one morphological change, and 21 of those had isolated peripheral lipoatrophy; the corresponding values for the patients who used only nucleoside analogues during follow-up were 20 of 66 and 14 of 21 respectively. The factors associated with lipodystrophy were initial assignment to stavudine plus didanosine compared with zidovudine plus lamivudine (OR = 6.7), age below 10 years (OR = 3.6), and HIV RNA concentration at month 30 (OR = 0.4). There were no differences in cholesterol and glucose concentrations. Thus, exposure to stavudine and didanosine was associated with lipodystrophy (predominantly lipoatrophy).

In a well-controlled French comparison of changes in body composition, body fat distribution, and insulin secretion, patients taking stavudine ($n = 27$) or zidovudine ($n = 16$) were compared with controls ($n = 15$) (18). The zidovudine group and the control group had similar body composition and regional fat distribution. Stavudine was associated with a significantly lower percentage of body fat than zidovudine (13 versus 15%), a markedly lower ratio of subcutaneous to visceral fat, and a higher mean intake of fat and cholesterol. Triglyceride concentrations were significantly higher with stavudine than in the controls, but did not differ between stavudine and zidovudine or between zidovudine and controls. Free fatty acids tended to be higher with stavudine. Lipodystrophy was observed in 17 patients taking stavudine, and in three taking zidovudine after a median time of 14 months. The relative risk of fat wasting with stavudine compared with zidovudine was 1.95. Five of twelve patients had a major or mild improvement in their lipodystrophy after stavudine was withdrawn. The authors concluded that lipodystrophy may be related to long-term NRTI therapy, particularly if it includes stavudine.

Lactic acidosis

Lactic acidosis is a severe and potentially fatal form of mitochondrial toxicity. Metabolic stress or vitamin deficiencies (riboflavin, carnitine) might provoke it. There is suggestive evidence of clinical benefit with riboflavin therapy (19).

Antiretroviral nucleoside analogues have been associated with hepatic steatosis and lactic acidosis. These compounds require phosphorylation to active triphosphate derivatives by cellular phosphokinases. The triphosphate nucleotide inhibits the growing proviral DNA chain, but it also inhibits host DNA polymerases, and this can result in compensatory glycolysis and lactic acidosis. Abnormal mitochondrial oxidation of free fatty acids causes the accumulation of neutral fat in liver cells, and this manifests as hepatomegaly with macrovesicular steatosis. Hepatic steatosis and lactic acidosis have been reported previously with zidovudine, didanosine, zalcitabine, Combivir (zidovudine plus lamivudine), and lamivudine.

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Of 349 Australian patients studied for 18 months (516 patient-years) taking NRTIs only two had severe lactic acidosis (20).

Three cases of steatosis/lactic acidosis syndrome associated with stavudine plus lamivudine have been reported (21).

- A 37-year-old HIV-infected woman receiving stavudine, lamivudine, and indinavir developed epigastric pain, anorexia, and vomiting. She had lactic acidosis (serum lactate 4.9 mmol/l), raised liver enzymes, and an increased prothrombin time. She had hepatomegaly and tachypnea and required mechanical ventilation. Her progress was complicated by pancreatitis and acute respiratory distress syndrome. Antiviral medication was stopped and she was treated with co-enzyme Q, carnitine, and vitamin C. The serum lactic acid and transaminases returned to normal over 4 weeks and she was weaned off the ventilator after 4 months.
- A 40-year-old HIV-infected woman receiving stavudine, lamivudine, nelfinavir, and co-trimoxazole developed dyspnea, dysphagia, and vomiting with lactic acidosis (serum lactate 9.4 mmol/l) and hepatomegaly. Despite ventilation for respiratory failure she died after 5 days. Autopsy showed massive hepatomegaly with steatosis.
- A 36-year-old HIV-infected woman who had been receiving stavudine, saquinavir, ritonavir, and didanosine developed lactic acidosis (serum lactate 11.4 mmol/l) and hepatomegaly. She had acute pancreatitis and, despite ventilatory support for respiratory failure, died after 8 weeks.

There have been similar reports related to didanosine plus stavudine (22) and stavudine alone (23).

Routine monitoring of lactate is not recommended, since lactate concentrations do not correlate with symptoms and patients may have asymptomatic lactatemia. Furthermore, technical difficulties in blood collection and processing, and the lack of a standardized definition of lactic acidosis for patients taking NRTIs, prevent any routine monitoring recommendations in the absence of symptoms. In addition, it is possible that NRTIs also cause other forms of mitochondrial dysfunction.

Hematologic

The NRTIs are toxic to hemopoietic progenitor cells in vitro (24) and can cause anemia (25,26), neutropenia (25), and thrombocytopenia (27,28).

Pancreas

Pancreatitis has been observed in patients treated with didanosine, lamivudine, stavudine, and zalcitabine (29), but its incidence is also increased in drug-naive patients with advanced HIV infection (30).

Immunologic

- A man developed several erythematous plaques on his face due to borderline tuberculoid leprosy with a reversal reaction (31). He had severe CD4 T cell lymphocytopenia due to HIV infection and had been given HAART. A fall in viral load and an increase in CD4 count preceded the development of the skin lesions, suggesting immune reconstitution as the underlying mechanism for the reversal reaction.

Paradoxical reactions are often observed in patients with pulmonary and extra-pulmonary tuberculosis being treated with HAART. Clinicians need to distinguish these from other adverse reactions related to drug therapy. Reversal reactions in leprosy are increasingly likely as more patients with HIV infection are treated with HAART in developing countries.

Second-Generation Effects

Pregnancy

Two HIV-1-positive women, both of whom had taken regimens containing stavudine and didanosine for at least 2 years, presented in the third trimester of pregnancy, one with acute lactic acidosis and one with acute pancreatitis and lactic acidosis (32). In the first case both mother and baby died. It is not known whether pregnancy is a risk factor for NRTI-induced lactic acidosis, perhaps in combination with riboflavin deficiency or a metabolic defect in the fetus, or whether NRTIs independently cause lactic acidosis through mitochondrial toxicity.

Drug–Drug Interactions

Methadone

In those who are opioid-dependent, methadone can facilitate adherence to HAART regimens. The pharmacokinetics of the tablet formulations of didanosine and stavudine have been studied in 17 individuals taking stable methadone therapy in comparison with 10 untreated controls (33). Methadone reduced the AUC_{0-6} by 63% for didanosine and by 25% for stavudine and the C_{max} by 66% and 44% respectively. These effects appeared to result primarily from reduced systemic availability. Trough concentrations of methadone were comparable to those seen in historical controls, suggesting that the nucleoside analogues did not affect methadone disposition. The authors concluded that larger doses of the tablet formulation (or another type of formulation) may be necessary to provide HAART in subjects taking methadone.

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Nystatin

General Information

Nystatin, the earliest antifungal drug, is used today primarily by the oral route to treat gastrointestinal mycosis and topically for mucocutaneous candidiasis (SED-11, 576). Absorption from the gut is insufficient to produce systemic activity.

An intravenous multilamellar liposomal formulation of nystatin has been developed. Its pharmacokinetics are unique among polyenes and are characterized by high peak plasma concentrations and a rapid clearance rate. In a phase I study it was tolerated well at doses up to 8 mg/kg. It was efficacious in candidemia, invasive aspergillosis, and as empirical antifungal therapy in patients with cancer and neutropenia (1). However, it was subsequently withdrawn by the manufacturers.

Organs and Systems

Gastrointestinal

Nausea, vomiting, and diarrhea have been reported after oral administration, possibly due to the drug but perhaps also ascribable to the underlying disease. These effects are more marked with doses over 5 MU a day (SED-11, 576) (2).

Immunologic

Allergic reactions to topical use are rare (SED-11, 576) (3).

Contact allergy due to topical nystatin has been reported in a woman using a combination of clobetasol and nystatin (4). The contact allergy was demonstrated with a positive patch test on day 4.

In another case, the patient developed a maculopapular rash over the trunk and limbs, associated with fever, arthralgia, malaise, and diarrhea; nystatin patch tests were positive on days 2 and 4 (5).

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Oak moss resin

General Information

Oak moss resin is an extract of *Evernia prunasti* found in many after-shave lotions and some perfumes (1).

Organs and Systems

Immunologic

Oak moss resin is usually reported as a contact allergen in those who use perfumed products, but is also reported in rural and forestry workers (2). Perfumes are recognized as being potential sensitizers in soluble oils (3), but oak moss as a specific sensitizer within a coolant has not previously been reported.

- A 47-year-old atopic man gave a 3-year history of dermatitis of his hands, forearms, and face (4). He had worked for 24 years as an engineer, grinding components for printing presses. During an enforced absence from work, he noticed that his rash had resolved, but it relapsed within 2 days of his return. Further remissions were noted during his annual holidays, but the rash would always recur within 2 days of returning to work. His skin eruption continued to deteriorate until the coolant used during the grinding process was withdrawn. His rash subsequently resolved and did not recur. Patch testing with standard series, oils and coolants, the constituents of fragrance mix, and his own coolant gave strong positive reactions to fragrance mix, balsam of Peru (*Myroxylon pereirae*), sodium metabisulfite, diethanolamine, and oak moss, and a smaller reaction to his own coolant. The manufacturer of the coolant was contacted for information on the individual constituents of the oil. Further patch tests were then carried out with these components plus the individual components of the fragrance used within it. There were strong positive reactions to oak moss resin and monoethanolamine.

This case highlights the importance of patch testing with individual components of a suspected product in occupational dermatitis. This reduces the chance of false positive reactions and of missing a relevant allergen.

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Ocular dyes

General Information

Fluorescein

Topical fluorescein dye is often used during slit lamp examination, because it helps in identifying corneal epithelial defects (1). Fluorescein retinal angiography was first described in 1961 (2); rapid intravenous injection of fluorescein displays retinal circulation velocity and the fine architecture and integrity of the blood retinal barrier. This is associated with minor adverse events in 21% of cases and potential life-threatening adverse events in 0.5% (3).

Fluorescein angiography using oral sodium fluorescein involves the use of 10 ml of a 10% solution of sodium fluorescein, the same material that is generally used for intravenous injection in conventional fluorescein angiography. Retinal photography starts 15 minutes after ingestion and continues for 1 hour. The camera, the photography, and film processing techniques are the same as those used for conventional fluorescein angiography. In 97% of 2625 eyes, adequate photographs for clinical use were obtained after oral fluorescein (4). Only 1.7% of the patients had minimal itching, discomfort, or nausea after oral sodium fluorescein. There were no anaphylactic or other severe adverse effects.

Complications of the use of fluorescein, all of which were reversible in a few hours or days, have been reported (5,6). Most of the complications were associated with the use of a larger quantity of fluorescein than recommended. The most frequent adverse effect of intravenous fluorescein is nausea; urticaria, hypersalivation, rhinorrhea, and chills have been seen in a few cases.

Serious or fatal accidents during fluorescein angiography have been assessed in an international survey involving 594 687 angiographies. The incidence of fatal accidents was one case per 49 557 angiographies, and of non-fatal but serious accidents one case per 18 020 angiographies. The total number of accidents reported was 45 cases, equal to one per 13 215 angiographies.

Indocyanine green

Indocyanine green, used for infrared angiography of the choroidal vessels, is well tolerated intravenously and its adverse effects are less pronounced than those of intravenous fluorescein (7).

Methylthioninium chloride (methylene blue)

Methylthioninium chloride is somewhat irritating, and topical anesthesia is recommended before its use; prolonged systemic exposure can cause the fundus to turn visibly blue (8).

Rose bengal

Discomfort and irritation are more pronounced with rose bengal than with fluorescein. Discoloration of the skin of the patient's eyelids and the examiner's fingers as well as ocular staining are more persistent than when fluorescein is used (9).

Organs and Systems

Nervous system

Non-convulsive status epilepticus has been attributed to fluorescein.

Hematologic

A study was undertaken to evaluate whether or not fluorescein interferes with erythrocyte properties during the angiographic procedure. In 37 patients, 26 with type II diabetes mellitus with and without retinopathy and 11 without diabetes mellitus, all undergoing fluorescein angiography, blood samples were drawn before and 30 minutes after fluorescein injection. The erythrocyte aggregation index, membrane lipid fluidity, and erythrocyte acetylcholinesterase activity were determined in both groups. After fluorescein injection there was no statistical change in erythrocyte aggregation index or erythrocyte membrane fluidity in either group. However, there was a significant fall in erythrocyte acetylcholinesterase activity, a marker of membrane protein integrity, in the diabetic patients. In other words, in diabetic patients fluorescein seems to interact with the erythrocyte membrane, and may interfere with the blood flow in the microcirculation (10).

Skin

The most common adverse effect of topical fluorescein is local irritation (11).

- A previously healthy 35-year-old man with conjunctival irritation had fluorescein dye instilled using a fluorescein-treated ophthalmic strip and isotonic saline. Within 30 minutes he began to notice a pruritic rash around his eye and on his arms, chest, and legs. His joints felt swollen. He had a diffuse erythematous macular rash with evidence of moderate excoriation over his arms and legs. His wrists and ankles were swollen. There were no oral lesions, and all laboratory studies, including the white blood cell count, were normal. Methylprednisolone succinate 125 mg plus diphenhydramine 50 mg produced rapid improvement.

Three patients out of eighty-four in another study had urticaria, which settled within half an hour of administration of an oral antihistamine, and one had nausea, which subsided without treatment (12). Another case of urticaria due to topical fluorescein has been described (13).

Fluorescein transiently stains the skin and mucous membranes yellow (7).

Immunologic

Most systemic reactions after intravenous fluorescein are allergic, but in the past some were due to contamination with dimethylformamide, an industrial solvent (14). It is difficult to predict adverse effects by intracutaneous testing. A delayed allergic response, developing a few hours after intravenous fluorescein dye injection, can occur (15). It is recommended that a complete allergy evaluation be performed in all patients who have adverse reactions to fluorescein, in order to differentiate true allergic reactions from other types of reactions (16).

Infection risk

Contamination of fluorescein eye drops is a very serious risk (17). *Pseudomonas aeruginosa* is an especially dangerous pathogenic microorganism liable to invade fluorescein eye drops. Fluorescein is most safely dispensed in sterile single-dose units or as sterile fluorescein-impregnated paper strips.

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Ofloxacin

See also Fluoroquinolones

General Information

Ofloxacin is a fluoroquinolone antibacterial drug similar to ciprofloxacin.

Comparative studies

The safety and efficacy of topical ofloxacin ear-drops 0.3% (0.25 ml bd) have been compared with that of co-amoxiclav oral suspension (40 mg/kg/day) for acute otitis media in 286 children aged 1–12 years with tympanostomy tubes in place. Topical ofloxacin was as effective as and better tolerated than systemic therapy with co-amoxiclav. Treatment-related adverse event rates were 31% for co-amoxiclav and 6% for ofloxacin (1).

Organs and Systems

Nervous system

Headache was recorded in 9% taking ofloxacin during short-course treatment of urinary tract infections (2).

Seizures have occurred in patients taking ofloxacin (3).

A Tourette-like syndrome developed in a 71-year-old patient, temporally related to ofloxacin; spitting, profuse swearing, echolalia, echopraxia, orofacial and limb automatisms, and hypersalivation all resolved completely after withdrawal (4).

Sensory systems

Compared with aminoglycosides, which caused significant loss of hair cells in the basal turn of the cochlea, ofloxacin caused no loss of hair cells in rats, even at concentrations higher than are achieved clinically (5). Moreover, auditory brainstem testing showed no change in auditory thresholds in the ofloxacin-treated animals, whereas neomycin-treated animals showed substantial threshold shifts. In human studies, topical ofloxacin 0.3% had no demonstrable adverse effects on middle ear or cochlear function and was not associated with any changes in hearing.

Endocrine

Ofloxacin 200 mg bd caused diabetes insipidus in a 25-year-old man (6).

Mouth

Ofloxacin can impair salivary gland function. In rat parotid and submandibular glands intraperitoneal ofloxacin (20, 40, and 80 mg/kg) reduced flow rate, amylase activity, total protein and calcium concentrations; in parotid saliva, sodium and potassium were increased (7). Sodium and potassium concentrations were also increased by a dose of 80 mg/kg in submandibular saliva. Possible mechanisms of these effects include altered intracellular cAMP and calcium concentrations and suppression of DNA, RNA, and protein synthesis in acinar cells.

Liver

Ofloxacin can cause fatal hepatic failure (8).

Urinary tract

Acute renal insufficiency has been caused by ofloxacin (9).

Antimicrobial chemotherapy against diseases caused by *Escherichia coli* producing Shiga toxin has been implicated as a risk factor for progression to the hemolytic–uremic syndrome.

- A 75-year-old woman took ofloxacin and developed the hemolytic-uremic syndrome (10).

In an in vitro study the addition of ofloxacin to a cell culture increased toxin activity by more than 200-fold (11).

Skin

Ofloxacin has been implicated in a case of toxic epidermal necrolysis (12).

- A 75-year-old white man took 24 g of ofloxacin over 51 days for epididymitis. He had a severe skin reaction, diagnosed as toxic epidermal necrolysis, and died from complications.

Drug Administration

Drug formulations

Chitosan, a positively charged polysaccharide, increases the precorneal residence time of ophthalmic formulations that contain active compounds. Two chitosan products of high molecular weights (1350 and 1930 kDa) and low degrees of deacetylation (50%) significantly increased antibiotic availability compared with controls (13). The duration of efficacy of ofloxacin was significantly increased from about 25 minutes to 46 minutes by the chitosan of higher molecular weight.

Drug–Drug Interactions

Antacids

The systemic availability of ofloxacin is reduced by aluminium-containing antacids, but not by antacids containing magnesium or calcium (14).

Glucocorticoids

The antibacterial activity of polymorphonuclear leukocytes is based on the production of superoxide anions and H_2O_2 in the respiratory burst. Combinations of an antibacterial agent and an anti-inflammatory drug are commonly used in immunosuppressed patients whose respiratory burst of polymorphonuclear leukocytes is impaired. An in vitro study has shown that the combination of a glucocorticoid (dexamethasone, methylprednisolone, betamethasone, hydrocortisone) with ofloxacin 10 mg/ml neutralizes the inhibitory effect of the former on the respiratory burst (15).

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NSAIDs

The antibacterial activity of polymorphonuclear leukocytes is based on the production of superoxide anions and H_2O_2 in the respiratory burst. Combinations of an antibacterial agent and an anti-inflammatory drug are commonly used in immunosuppressed patients whose respiratory burst of polymorphonuclear leukocytes is impaired. An in vitro study has shown that the combination of an anti-inflammatory drug (phenylbutazone or acetylsalicylic acid) with ofloxacin 10 mg/ml neutralizes the inhibitory effect of the former on the respiratory burst (15).

Oral contraceptives

Plasma concentrations of oral contraceptive steroids were unchanged by ofloxacin (16).

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Olanzapine

See also Neuroleptic drugs

General Information

Several reviews have echoed the efficacy and tolerability of olanzapine (1–3). In several reviews it has been emphasized that the most common adverse effects are somnolence and weight gain, since about 40% of patients gain weight (especially if on a high starting dose and if they were underweight before treatment); sexual dysfunction can also be a problem for many patients (4–6).

Clinical trials

A thorough and extensive review has summarized five pivotal clinical trials comprising 3252 patients (7). In some studies olanzapine has failed to show efficacy in treatment-resistant schizophrenia (8,9).

In addition to clozapine (10,11), olanzapine has also been reported to improve tardive dyskinesia (12–14).

- An elderly woman who developed moderately severe neuroleptic drug-induced dyskinetic movements responded to olanzapine 10 mg/day (15).

Placebo-controlled studies

A multicenter, double-blind, placebo-controlled study in patients with Alzheimer's disease and symptoms of agitation/aggression and/or psychosis but few or no psychotic symptoms at baseline, and data from a subgroup of patients have been analysed (16). Three subsets of patients were identified on the basis of their symptoms at baseline: those with no clinically significant hallucinations, those with no clinically significant delusions, and those with no clinically significant delusions or hallucinations. Of the patients without hallucinations or delusions at baseline ($n = 75$), the placebo-treated patients had significantly more of these symptoms than olanzapine-treated patients. Similarly, among the patients without baseline hallucinations ($n = 153$), the placebo-treated patients had higher hallucination scores than olanzapine-treated patients, whereas patients without baseline delusions ($n = 87$) had no significant treatment effects. Abnormal gait, a term comprising leaning, limp, stooped posture, and unsteady gait, occurred in a higher incidence among olanzapine-treated patients (14/72) than placebo-treated patients (0/33). Somnolence was also reported at higher rates with olanzapine (27/72) than placebo (3/33).

Olanzapine has been proposed as a treatment for acute mania. In a randomized, double-blind, placebo-controlled

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study for 3 weeks, patients were assigned to either olanzapine 10 mg/day ($n = 70$) or placebo ($n = 69$) (17). Significantly more olanzapine-treated patients responded (49%) compared with those assigned to placebo (24%). Somnolence, dizziness, dry mouth, and weight gain occurred significantly more often with olanzapine, but there were no statistically significant differences with respect to measures of parkinsonism, akathisia, and dyskinesia.

Observational studies

Olanzapine, mean dose 5.4 mg/day, has been given to 21 patients with apathy in the absence of depression after long-term treatment with selective serotonin reuptake inhibitors for non-psychotic depression in an open, flexible-dose study (18). The more frequent adverse effects were sedation ($n = 12$), increased appetite ($n = 8$), stiffness ($n = 7$), edema ($n = 6$), and dry mouth ($n = 5$).

The efficacy and safety of switching 108 Asian patients from their regimen of neuroleptic medications to olanzapine (initial dose 10 mg/day) for 6 weeks has been studied in an open, multicenter, randomized study (19). They were randomly assigned to one of two groups: the direct switch group ($n = 54$) received only olanzapine, while the start-taper switch group ($n = 54$) received olanzapine and their usual neuroleptic drug in decreasing doses for the first 2 weeks. There were statistically significant improvements from baseline to end-point in both switch groups in the Clinical Global Impressions—Severity of Illness Scale score and the Positive and Negative Syndrome Scale total score. Nevertheless, there were no significant differences between the switch groups in any measure of efficacy. Weight gain occurred in both switch groups and both showed statistically significant improvement from baseline to end-point on the Simpson–Angus Scale and Barnes Akathisia Scale.

In 19 patients previously treated with clozapine, olanzapine was used instead (9). Eight were considered to be responders and the rest decompensated, seven of them enough to require hospitalization. Overall Brief Psychiatric Rating Scale (BPRS) scores increased significantly from baseline to final assessment.

In an open trial to determine the efficacy of olanzapine in the treatment of bipolar mixed state ($n = 9$), the results showed improvement in acute symptoms and the drug was well tolerated (20).

In a study supported by Eli Lilly and Company it was concluded that olanzapine may be effective in a significant number of neuroleptic drug-resistant schizophrenic patients (21). However, of 25 patients who entered an open trial for 6 months, 14 discontinued olanzapine, one because of an adverse effect (depression), two because of lack of compliance, and 11 because of lack of efficacy.

Of 14 consecutive patients with bipolar I disorder, who were inadequately responsive to standard psychotropic agents and who were given olanzapine, 8 improved (22). The most common adverse effects were sedation, tremor, dry mouth, and increased appetite with weight gain.

The response to olanzapine in 150 consecutive patients has been assessed by reviewing their records (23). Patients with a moderate-to-marked response to olanzapine were more likely to be younger, to be female, and to have a diagnosis of bipolar disorder. No information on adverse effects was provided.

The efficacy of olanzapine in treatment-refractory childhood-onset schizophrenia has been examined in eight patients (mean age 15 years) over 8 weeks (24). There was a 17% improvement in the BPRS total score. Olanzapine was moderately well tolerated. The most common adverse events were increased appetite ($n = 6$), constipation ($n = 5$), nausea/vomiting ($n = 6$), headache ($n = 6$), somnolence ($n = 6$), insomnia ($n = 7$), difficulty in concentrating ($n = 5$), sustained tachycardia ($n = 6$), transient rises in liver transaminases ($n = 7$), and increased agitation ($n = 6$).

In contrast, olanzapine was discontinued in five preadolescent children (aged 6–11 years) within the first 6 weeks because of adverse effects or lack of therapeutic response (25). The adverse effects included sedation ($n = 3$), weight gain ($n = 3$), and akathisia ($n = 2$).

Substance abuse is a major complication in the treatment of schizophrenia. Of 60 patients with schizophrenia in an open 7-week trial of olanzapine up to 25 mg/day, there was substance abuse in 23 (26). There were no differences in response between the substance-abusing patients and the others. Baseline rates of extrapyramidal adverse effects did not differ between the groups. Overall the patients did not improve significantly.

The medical records of 151 hospitalized elderly psychiatric patients (mean age 71 years) have been analysed (27). Of 37 patients treated with olanzapine (mean duration of treatment 20 days, mean dose 10 mg/day), 75% responded. Adverse effects were reported in six patients: sedation in four patients and extrapyramidal signs and postural hypotension in one each.

In 16 patients with treatment-resistant schizophrenia (defined as non-responsiveness to at least three antipsychotic drugs from at least two different chemical classes), olanzapine was effective treatment in a significant proportion; no serious adverse events were associated with maintenance doses of 10–40 mg/day, and no subjects dropped out (28).

In five consecutive cases, olanzapine was effective for treatment-refractory psychosis in patients previously responsive to, but intolerant of, clozapine (29).

Olanzapine was effective in an open trial in 10 patients with obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors, who were given additional olanzapine; they had minimal adverse effects, primarily sedation (29).

In 23 patients with obsessive-compulsive disorder who had not responded to a 6-month course of fluvoxamine (300 mg/day), olanzapine (5 mg/day) was added in an open comparison (30). There was a significant reduction in the mean score on the Yale–Brown Obsessive–Compulsive Scale; concomitant schizotypal personality disorder was the only factor significantly associated with a response. The most common adverse effects were mild to moderate weight gain and sedation.

The use of olanzapine for the psychiatric manifestations of hereditary coproporphyria has been studied (31).

In an open study, eight patients with Lewy body dementia associated with psychotic and behavioral difficulties were given olanzapine 2.5–7.5 mg (32). Three of the eight could not tolerate olanzapine, even at the lowest

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dose, two had a clear improvement in psychotic and behavioral symptoms, and three tolerated olanzapine but gained only minimal benefit. The authors concluded that olanzapine in the doses used conferred little advantage over conventional neuroleptic drugs and should be given only with great caution to patients with Lewy body dementia.

In a prospective open 12-week study in eight children, adolescents, and adults with developmental disorders, the most significant adverse effects of olanzapine were increased appetite and weight gain in six patients and sedation in three (33).

The efficacy and adverse effects of high doses of olanzapine (up to 30 mg/day) have been assessed in seven patients with schizophrenia and schizoaffective disorder (34). None discontinued olanzapine because of adverse effects; the only adverse effects were weight gain and self-limited diarrhea. However, poor design and small sample size precluded definitive conclusions.

In an observational prospective study sponsored by Lilly, 2128 patients were treated with olanzapine as monotherapy (mean dose 13 mg/day) or combined with other drugs, and 821 were treated with other neuroleptic drugs as monotherapy or combined with other drugs (control group) (35). Olanzapine was well tolerated and effective, and the overall incidence of adverse events was significantly lower than in controls, although weight gain (6.9%) was significantly more frequent. Dropouts were statistically similar in the two groups.

To evaluate anticholinergic effects, differences among patients taking olanzapine ($n = 12$; average dose, 15 mg/day) or clozapine ($n = 12$; average dose, 444 mg/day) for at least 8 weeks were measured in an unblinded study (36). Altered salivation was significantly more common with clozapine (increased salivation) and olanzapine (decreased salivation), whereas constipation, urinary disturbances, and tachycardia/palpitation were significantly more common with clozapine. There were no global cognitive problems in either group.

Olanzapine has fewer extrapyramidal effects than typical neuroleptic drugs such as haloperidol (SEDA-24, 66). Even some cases of tardive dystonia have been successfully managed with atypical neuroleptic drugs. The antidystonic efficacy of olanzapine has been studied in an open video-blinded study in four patients with tardive cervical dystonia after several years of neuroleptic drug treatment (37). There was moderate to marked improvement in dystonia in all of them, and no serious adverse effects at the maximum dosage reached (7.5 mg/day).

Two patients, one with treatment-resistant rapid cycling bipolar disorder (38) and the other with severe mood changes during corticosteroid therapy (39), improved with olanzapine.

Comparative studies

Comparison with divalproex

The efficacy and safety of olanzapine in disorders other than schizophrenia have been studied (SEDA-24, 67) (SEDA-25, 64) (SEDA-26, 61). In a 3-week, randomized, double-blind trial, the effects of a flexible dose of olanzapine (5–20 mg/day) and divalproex (500–2500 mg/day) for the treatment of patients with acute bipolar manic or mixed episodes have been compared (40). The olanzapine treatment group ($n = 125$) had significantly greater mean improvements in mania rating and a significantly greater proportion of patients achieved protocol-defined remission. With olanzapine there was significantly more weight gain (12 versus 7.9%), dry mouth (34 versus 6.3%), increased appetite (12 versus 2.4%), and somnolence (39 versus 21%), while more cases of nausea (29 versus 10%) were reported with divalproex.

Combination with valproate or lithium

The efficacy of adding olanzapine to either valproate or lithium alone in acute manic or mixed bipolar episodes has been studied in a 6-week, double-blind, randomized, placebo-controlled trial (41). Compared with valproate or lithium alone, the addition of olanzapine provided better efficacy. Olanzapine was associated with somnolence, dry mouth, weight gain, increased appetite, tremor, and slurred speech.

In another study, 30 patients with mania were randomized to olanzapine or lithium in a double-blind 4-week study (42). Olanzapine did not differ from lithium in terms of efficacy or of extrapyramidal adverse effects, as measured by the Simpson–Angus Scale.

Organs and Systems

Cardiovascular

It has been suggested that olanzapine often causes QT interval prolongation (SEDA-25, 64). However, in an analysis of electrocardiograms obtained as part of the safety assessment of olanzapine in four controlled randomized trials ($n = 2700$) the incidence of maximum QT_c prolongation beyond 450 ms during treatment was approximately equal to the incidence of prolongation of the QT_c beyond 450 ms at baseline (43). The authors therefore suggested that olanzapine does not contribute to QT_c prolongation. This has been supported by the report of a patient in whom QT_c prolongation while he was taking clozapine reversed when he switched to olanzapine (44).

Two cases of light-headedness or "fainting" in patients taking olanzapine have been reported (45). Electrocardiograms showed first-degree heart block and AV conduction delay, which normalized after dosage reduction.

- A 44-year-old man took clozapine 10 mg/day and the dose was increased to 50 mg/day, after which he complained of episodes of light-headedness. An electrocardiogram showed prolongation of the PR interval to 227 ms. The dosage was reduced to 30 mg and the PR interval returned to 187 ms within 2 days.
- A 36-year-old man took clozapine 20 mg/day and within 2 weeks began to complain of intermittent, unpredictable "fainting" attacks. An electrocardiogram showed a prolonged PR interval at 230 ms. The dose of olanzapine was reduced to 17.5 mg/day, and a repeat electrocardiogram 1 week later was normal.

Nervous system

Extrapyramidal effects

To ascertain to what extent olanzapine occupies 5-HT_2 and dopamine D_2 receptors, a positron emission

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tomography study has been conducted in 12 patients with schizophrenia randomly assigned to 5, 10, 15, or 20 mg/day of olanzapine (46). Olanzapine is a potent 5-HT_2 antagonist and has higher 5-HT_2 than D_2 occupancy at all doses. Its D_2 receptor occupancy is higher than that of clozapine and similar to that of risperidone. At the usual clinical dose range of 10–20 mg/day, D_2 receptor occupancy is 71–80%, and this restricted range may explain its freedom from extrapyramidal adverse effects. However, doses of 30 mg/day and higher are associated with more than 80% D_2 receptor occupancy and may have a higher likelihood of extrapyramidal adverse effects.

The relation between extrapyramidal adverse effects and the negative symptoms of schizophrenia has been studied (47). Correlation analysis after 6 weeks of treatment showed that extrapyramidal symptoms correlated significantly in patients taking haloperidol ($n = 10$) but not in those taking olanzapine ($n = 13$). The results of multiple regression analysis suggested that ratings of negative signs were confounded by extrapyramidal symptoms in patients treated with haloperidol. This confusion occurred to a lesser extent with olanzapine.

Acute dystonia

Patients taking olanzapine reported a low incidence of dystonias, which may be about 0.3% (SEDA-22, 56). In the light of two new cases of acute dystonia associated with olanzapine in patients with previous history of dystonia or parkinsonism related to antipsychotic treatment, comparative figures have been reported. Acute dystonia occurred in 1.4% of patients who took olanzapine, compared with 5.0–6.3% of those taking haloperidol (48).

Akathisia

Akathisia has been reported in 16% of patients taking olanzapine (SEDA-21, 56). Three patients developed severe akathisia during treatment with olanzapine (20–25 mg/day) (49). In two, the akathisia resolved after withdrawal of olanzapine and in one of those olanzapine was well tolerated when reintroduced in combination with lorazepam. In the third patient, the akathisia was controlled by dosage reduction. A 33-year-old man with AIDS and a prior history of extrapyramidal symptoms with both typical antipsychotic drugs and risperidone developed dose-dependent akathisia with olanzapine 15–19 mg/day; the akathisia responded to dosage reduction and beta-blockade (50).

- A 30-year-old woman with obsessive-compulsive disorder, who took olanzapine 10 mg/day titrated to 15 mg/day, developed severe akathisia after 3 weeks; the condition resolved on withdrawal and reappeared on rechallenge (51).

Restless legs syndrome shares clinical features with akathisia.

- A 41-year-old man complained of paresthesia in both legs at rest, much worse at night, and was relieved by walking around (52). The reaction occurred during the sixth week of treatment, 36 hours after an increase in dose from 10 to 20 mg/day; no other drug was administered.

Neuroleptic malignant syndrome

Several reports of neuroleptic malignant syndrome associated with olanzapine have been published (53–59).

- A 67-year-old man with bipolar disorder became confused, delirious, and manic (60). His only medications were olanzapine 10 mg/day and divalproex sodium 500 mg bd. On day 6, typical neuroleptic malignant syndrome developed. He had a fever (39.9°C), obtundation, rigidity, tremor, sweating, fluctuating pupillary diameter, labile tachycardia and hypertension, hypernatremia, and raised serum creatine kinase. Olanzapine was withdrawn and the syndrome resolved by day 12.

This patient had all of the major manifestations of this condition and there was no other likely explanation for his illness; he had taken no other drug likely to be associated with the syndrome.

- Another case of possible neuroleptic malignant syndrome associated with olanzapine has been reported in a patient who had taken clozapine for 3 years without incident (61). Symptoms suggestive of neuroleptic malignant syndrome appeared 19 days after the addition of olanzapine.

This severe reaction could have resulted from clozapine alone or from an interaction of clozapine with olanzapine.

- A 23-year-old woman had some of the features of the serotonin syndrome (mental status changes, sweating, tremor, and fever); however, the large rise in creatine kinase activity, extreme lead-pipe rigidity, and the abrupt onset suggested neuroleptic malignant syndrome rather than the serotonin syndrome (62).
- An 85-year-old man developed fever, muscle rigidity, and changes in mental state, but his serum creatine kinase activity was not increased (63).
- A 42-year-old man took olanzapine for 3 weeks and developed hyperpyrexia, tremor, labile blood pressure, and mental changes; he had a metabolic acidosis and an escalating creatine kinase activity (64).
- A 78-year-old woman developed fulminant neuroleptic malignant syndrome complicated by pneumonia while taking olanzapine and levomepromazine. When the neuroleptic drugs were withdrawn she recovered; however, when the combination was restarted later, because of severe agitation and hallucinations, the symptoms of neuroleptic malignant syndrome recurred (65).
- A 30-year-old man who had taken olanzapine 20 mg/day for 10 days developed typical neuroleptic malignant syndrome with raised body temperature (39.7°C), obtundation, tremor, rigidity, sweating, fluctuating pupillary diameter, tachycardia, labile hypertension, raised serum creatine kinase activity, and severe hypernatremia (190 mmol/l) (66).
- A 53-year-old man developed atypical neuroleptic malignant syndrome, with fever, altered mental status, and autonomic dysfunction, but without rigidity (a usual feature of this condition) while taking olanzapine (67).

The authors of the last report pointed out that such atypical cases may support either a spectrum concept of neuroleptic malignant syndrome or the theory that neuroleptic malignant syndrome secondary to atypical neuroleptic drugs

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differs from that caused by conventional neuroleptic drugs. They suggested that more flexible diagnostic criteria than currently mandated in DSM-IV may be warranted.

Following a case of olanzapine-associated weight gain, hyperglycemia, and neuroleptic malignant syndrome in a 64-year-old woman the authors suggested that neuroleptic malignant syndrome might occur more often in patients aged 60 years or older (68). However, this patient had previously had well-documented neuroleptic malignant syndrome secondary to haloperidol, and on another occasion fluphenazine decanoate.

In contrast to these cases, a 34-year-old man, who had had clozapine-induced neuroleptic malignant syndrome, was successfully treated with olanzapine (69).

Parkinsonism

Whether treatment with olanzapine is useful in psychotic patients with neuroleptic drug-induced parkinsonism, or even in dopaminergic psychosis in Parkinson's disease, remains unclear. In a retrospective study of 19 patients with parkinsonism, 10 had some worsening of their parkinsonism after taking olanzapine, 3 had some motor benefit, and 7 had improvement in their psychosis (70).

Olanzapine was given to five patients with idiopathic Parkinson's disease and hallucinosis, and after initial treatment for 9 days, the frequency of hallucinations was significantly reduced; during this early phase of treatment, parkinsonian motor disability increased, which resulted in medication discontinuation in two of the patients (71).

Worsening parkinsonism was observed in two patients after treatment with olanzapine 5 mg/day (72). In contrast, coarse tremors induced by fluphenazine or haloperidol disappeared in three patients within days of the start of treatment with olanzapine (10 mg/day), without discontinuation or reduction in the dosage of fluphenazine or haloperidol (73). Olanzapine is active at muscarinic cholinergic receptors, which may account for the observed suppression of neuroleptic drug-induced tremor; however, two of the three patients had been taking benzatropine, an antagonist at muscarinic acetylcholine receptors, with little tremor relief, suggesting that olanzapine could suppress tremor by means of an action other than muscarinic blockade.

Whether treatment with olanzapine is useful in psychotic symptoms in patients with Parkinson's disease is unclear (SEDA-23, 66). Nine patients of twelve with drug-induced psychosis in Parkinson's disease had worsening of motor function while taking olanzapine (2.5 mg/day and increased in 2.5 mg increments as needed); this worsening was considered dramatic in six of these patients, and only one was still taking olanzapine at the time of the analysis (12 months) (74). In addition, two elderly patients, one with and one without pre-existing parkinsonism, had marked rigidity induced by olanzapine 5 mg/day (75).

Tardive dyskinesias

Anecdotal reports of olanzapine-induced tardive dyskinesia have been described as occurring in 1% of treated patients (SEDA-22, 65). Data from three pivotal trials of olanzapine (SEDA-21, 56) have been reanalysed by investigators from the manufacturers, Eli Lilly, with a focus on tardive dyskinesia (76). In a previous study, they had presented the percentage of patients developing dyskinesia without regard to the time to development: tardive dyskinesia occurred in 1.0% and 4.6% with olanzapine and haloperidol respectively (SEDA-22, 65). They subsequently calculated the number of cases per patient exposure time. When patients were stratified by abnormal involuntary movement scale (AIMS) at baseline, the incidence rate ratios for those with AIMS = 0 was 5.67 (CI = 2.45, 13.1) and for those with AIMS > 0 it was 2.55 (CI = 1.15, 5.68), both favorable to olanzapine. However, since only the highest dosages of olanzapine were as effective as haloperidol in the trials, choosing all the patients treated with olanzapine without regard to the dosages yielded an underestimation of the risk. Since olanzapine has a better profile of extrapyramidal adverse effects, it has been proposed as an alternative in the long-term treatment of schizophrenia (77).

Two cases of olanzapine-induced tardive dyskinesia have been described (78).

- A 55-year-old man with Huntington disease took olanzapine 5 mg/day and rapidly developed tardive dyskinesia (79). After 2 months, his chorea improved markedly, but orofacial dyskinesia, which he had never had in the past, appeared. Olanzapine was withdrawn, and 1 week later the orofacial dyskinesia improved while the chorea worsened.

However, olanzapine may also improve pre-existing tardive dyskinesia (SEDA-22, 65) (SEDA-23, 66) (14,80). A case of remission of tardive dyskinesia after changing from flupenthixol to olanzapine has been reported (82).

- A 59-year-old man with a long history of neuroleptic drug exposure improved markedly when given olanzapine (2.5 mg/day, titrated within 5 days to 17.5 mg/day) (14).
- Respiratory dyskinesia, which was conceptualized as a form of tardive dyskinesia, including grunting, tachypnea, and impaired vocalization, improved after the patient started to take olanzapine 2.5 mg/day (80).

Tardive dystonia

- A 40-year-old woman with bipolar disorder developed tardive dystonia after taking olanzapine 10 mg at bedtime for 7 months (82).

Seizures

Fatal status epilepticus occurred in a patient taking olanzapine with no known underlying cause or predisposing factor for seizures.

- A 41-year-old woman developed seizures that progressed to status epilepticus, and died from secondary rhabdomyolysis and disseminated intravascular coagulation (83). She had been taking olanzapine 10 mg/day for 5 months. No other toxic, metabolic, or anatomical abnormalities were identified pre- or postmortem to explain the seizures. However, her medications also included levothyroxine 0.15 mg/day, clonazepam 1.0 mg qds, and propranolol 20 mg tds.

Non-fatal seizures have also been reported.

- A 31-year-old woman with multiple psychiatric and medical disorders, including a generalized seizure

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disorder (a probable confounding factor in this case), developed seizures when she switched from haloperidol to olanzapine (84).
- A 27-year-old woman had a seizure while taking a stable dosage of olanzapine 15 mg/day 1 day after the introduction of quetiapine 100 mg in the evening (85). She suddenly fell to the ground and had generalized shaking and inarticulate vocalization for about 30–60 seconds.

Seizures associated with olanzapine in premarketing studies have been estimated to occur in 0.88% of patients, a reported incidence probably comparable to that found with many conventional agents.

Speech dysfunction

Four patients taking olanzapine developed speech dysfunction (86). The authors suggested that the incidence of speech abnormalities may be higher than listed in the package insert of olanzapine (impairment of articulation 2% and voice alteration less than 1%).

Sleep-related eating disorder consists of partial arousal from sleep followed by rapid ingestion of food, commonly with at least partial amnesia for the episode on the next day; this disorder has been reported, purportedly for the first time, in association with an atypical neuroleptic drug (87).

- A 52-year-old man with bipolar I disorder and a family history of sleepwalking took olanzapine 10 mg/day and after several days had episodes of sleep-related eating disorder, witnessed by his wife; he had no memory of these episodes. After olanzapine withdrawal, the episodes disappeared rapidly.

Sensory systems

Esotropia (an inward squint) has been reported in a patient taking olanzapine and fluoxetine for psychosis; it resolved promptly on withdrawal of olanzapine (88).

- A 14-year-old girl with psychotic depression took fluoxetine 40 mg/day and olanzapine 5 mg/day, and 6 months later developed a severe headache, menorrhagia, diplopia, and eye irritation; her mother had also noted a "lazy eye." She had corrected visual acuity of 20/20 in both eyes, and intermittent esotropia of 14–16 diopters when fixing at 6 meters, and 8 diopters when fixing at 1/3 meters. A month later, her deviation had increased to 20 and 14 diopters respectively. Olanzapine was withdrawn and within 1 week the diplopia and headaches cleared, and the esotropia resolved.
- A 37-year-old man who had taken olanzapine 10 mg/day at bedtime for 1 week developed an excessive whitish discharge from the eyes (89).

The authors suggested that in some patients olanzapine may cause heavy mucus secretion in any of the mucus-secreting surfaces of the body.

Psychological, psychiatric

Hypofrontal symptoms, with problematic discourtesy and socially inconsiderate conduct, occurred in a 31-year-old man shortly after the introduction of olanzapine 20 mg/day; he had taken typical neuroleptic drugs for 13 years without such symptoms (90).

Anxiety and panic attacks

Anxiety has been reported as a common adverse effect (in 36% of patients) associated with olanzapine (SEDA-22, 65).

- A 36-year-old woman taking olanzapine 5 mg tds had new-onset panic attacks, with feelings of severe anxiety, shortness of breath, trembling, palpitation, and sweating, and felt that she was going to die (91). She had no previous history of panic attacks, which responded to the addition of alprazolam. The authors hypothesized that the 5-HT_2 antagonist action of olanzapine had triggered the onset of this condition.

Mania

Mania has rarely been associated with classic neuroleptic drugs, but has been described in patients treated with new antipsychotic drugs, especially risperidone (SEDA-22, 69). Several cases of mania, presumably associated with olanzapine, have been reported (60,92–99). The mechanism is not clear. It has been suggested that olanzapine could lead to manic symptoms in patients with schizophrenia because of its potent anti-$5HT_{2A}$ action.

- An 85-year-old woman with a 3-year history of delusional disorder developed florid manic symptoms, which resolved 2 weeks after withdrawal (100).
- A 36-year-old woman with paranoid schizophrenia was given olanzapine 15 mg/day and 3 weeks later she had a hypomanic episode (Young Mania Rating Scale, YMRS, score 30). The dosage of olanzapine was reduced to 10 mg/day and then to 5 mg/day, with minimal improvement of her manic symptoms (YMRS score 27). Olanzapine was withdrawn and a conventional neuroleptic drug given instead. The manic episode resolved over the next 4 days (YMRS score 5).

Obsessive-compulsive disorder

Olanzapine-induced de novo obsessive-compulsive disorder has been reported in two cases (101). One of the patients developed de novo obsessive-compulsive symptoms with the introduction of olanzapine, whereas in the other case the patient had undisturbing obsessive symptoms before olanzapine treatment.

Olanzapine-induced worsening of obsessive-compulsive symptoms has also been reported.

- Obsessive-compulsive symptoms worsened in a 35-year-old man who had had a similar response to both clozapine and risperidone in previous trials (102).
- A 35-year-old woman developed obsessive-compulsive symptoms after starting to take olanzapine (103). Her symptoms remitted after withdrawal and recurred on rechallenge, which provides evidence for de novo provocation of obsessive-compulsive symptoms by olanzapine.
- A 42-year-old woman with bipolar II disorder who had taken olanzapine 5 mg/day for 5 weeks began to have severe enduring panic-like anxiety and serious obsessive-compulsive symptoms (104).

In three other cases, olanzapine caused significant exacerbation of obsessive-compulsive symptoms in schizophrenia (two cases) and obsessive-compulsive disorder (one case) (105).

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The aims of a prospective study in 113 consecutively hospitalized young patients (mean age 22 years) were to determine whether the severity of obsessive-compulsive symptoms differs during treatment with olanzapine or risperidone and to establish whether the duration of neuroleptic treatment is related to the severity of obsessive-compulsive symptoms (106). At baseline and week 6 assessments, obsessive-compulsive symptoms were found in 32 of 106 evaluable cases and 16 met DSM-IV criteria for obsessive-compulsive disorder, but there were no differences in patients taking olanzapine or risperidone. However, the severity of obsessive-compulsive symptoms was associated with the duration of treatment with olanzapine.

Paranoia

Paranoia and agitation occurred in two patients, a 34-year-old man and a 30-year-old woman, who had taken olanzapine for a few weeks (107). Their symptoms improved when olanzapine was withdrawn.

Endocrine

Prolactin

Olanzapine can cause increased serum prolactin concentrations and galactorrhea, but probably to a lesser extent than haloperidol (SEDA-22, 65).

- A depressed 27-year-old woman taking mirtazapine developed hyperprolactinemia and galactorrhea after taking olanzapine 10 mg/day for 5 weeks (108).
- A 19-year-old woman with mild mental retardation and a history of birth anoxia who took olanzapine 15 mg/day for 3 weeks developed euprolactinemic galactorrhea (109). Laboratory tests were all normal, including a normal thyroid-stimulating hormone concentration and a prolactin concentration of 13 ng/ml (reference range 3–30 ng/ml). She had mild to moderate akathisia. Both the galactorrhea and the akathisia abated after substitution by quetiapine.

The authors stated that the reason why galactorrhea occurred is unclear but suggested that it may have been due to structural damage and greater sensitivity to prolactin resulting from the patient's anoxia at birth.

However, paradoxical cases of improvement in galactorrhea have also been observed (SEDA-23, 67).

Two women with neuroleptic-drug induced hyperprolactinemia, menstrual dysfunction, and galactorrhea had improvement in these adverse effects during treatment with olanzapine (110).

- A 34-year-old woman, who developed amenorrhea while taking risperidone, regained her normal menstrual pattern along with a marked fall in serum prolactin concentration 8 weeks after being switched to olanzapine, whereas amantadine had failed to normalize the menses and had apparently reactivated the psychotic symptoms (111).

The authors suggested that olanzapine may offer advantages for selected patients in whom hyperprolactinemia occurs during treatment with other antipsychotic drugs.

Improvement in galactorrhea has also been observed in a case of trichotillomania refractory to a selective serotonin reuptake inhibitor (112). The patient only had a positive response with risperidone in combination with fluoxetine, but developed hyperprolactinemia and an intolerable galactorrhea. Olanzapine in combination with fluoxetine was started, with significant clinical improvement and without symptoms of galactorrhea; however, the patient had undesired weight gain of 3.6 kg after 22 weeks.

Metabolism

Diabetes mellitus

Hyperglycemia associated with olanzapine has a frequency of 1/100 to 1/1000. Hyperglycemia and diabetes have been associated with olanzapine, and published cases have suggested that these adverse effects may be caused by a mechanism related to weight gain (SEDA-23, 67) (SEDA-24, 69) (SEDA-25, 65). However, several cases of de novo onset or exacerbation of existing diabetes mellitus in patients treated with neuroleptic drugs have been reported and were not significantly related to weight gain. These included patients taking clozapine (113,114) or olanzapine (114,115).

- A 51-year-old woman with an 18-year history of type II diabetes mellitus developed glucose dysregulation with persistent hyperglycemia within 3 weeks of starting treatment with olanzapine, in the absence of weight gain (116).

The author suggested that olanzapine can cause glucose dysregulation by a mechanism other than weight gain.

- A 32-year-old African-American man with no prior history of diabetes mellitus or glucose intolerance had a raised blood glucose concentration after 6 weeks of olanzapine therapy, and required insulin (117). Olanzapine was withdrawn and blood glucose concentrations returned to normal about 2 weeks later. At rechallenge hyperglycemia occurred again.
- A 50-year-old man developed acute ketoacidosis with de novo diabetes mellitus after 8 months of adjunctive olanzapine (118). His dosage was then gradually titrated to 30 mg/day over 6 months, and after withdrawal of olanzapine his diabetes mellitus disappeared completely.
- A 31-year-old man taking olanzapine 10 mg/day, who had no family history of diabetes and had never had any laboratory evidence of diabetes or glucose intolerance, developed diabetic ketoacidosis; obesity was the only predisposing factor, his BMI being 40 kg/m^2 (119).
- A 45-year-old man with a 4-year history of diet-controlled diabetes had hyperglycemia with polyuria, polydipsia, and blurred vision associated with the use of olanzapine 10 mg/day. Within 1 week after olanzapine was withdrawn his blood glucose returned to normal and insulin was discontinued.
- A 54-year-old woman developed severe glucose dysregulation with exacerbation of type 2 diabetes 12 days after starting to take olanzapine 10 mg/day; she also gained 13 kg (120).

The effects of olanzapine on glucose–insulin homeostasis have been studied in 14 patients in an attempt to elucidate the possible mechanisms of olanzapine-associated weight gain (121). Olanzapine caused weight gain of 1–10 kg in

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12 patients and raised concentrations of insulin, leptin, and blood lipids, as well as insulin resistance; three patients developed diabetes mellitus. The authors concluded that both increased insulin secretion and hyperleptinemia may be mechanisms behind olanzapine-induced weight gain. They also suggested that the metabolite *N*-desmethylolanzapine has a normalizing effect on the metabolic abnormalities.

In an open study in seven men and four women taking olanzapine (mean daily dose 12 mg and mean treatment duration 23 months), although the mean fasting triglyceride concentrations and mean fasting plasma glucose concentrations were similar to those found in the previous study, the mean fasting insulin concentrations were lower (143 pmol/l versus 228 pmol/l), and four of the subjects had hyperinsulinemia, compared with ten in the other study (122). However, the small sample sizes precluded any clear conclusions.

Susceptibility factors, such as family history, obesity, and concomitant medications can predispose an individual taking olanzapine to diabetes mellitus. New-onset diabetes mellitus developed after olanzapine was given to a 31-year-old man and a 44-year-old man (123). In both cases, the family history included diabetes mellitus, type unknown. The patients were taking various psychotropic drugs. In the first case body weight increased by about 12 kg (BMI 32 kg/m^2) 6 weeks after starting olanzapine, when his diabetes mellitus started; in the second case (BMI 26 kg/m^2, weight 81 kg) the previous weight was unknown.

Olanzapine-induced non-ketotic hyperglycemia has also been reported in the absence of obesity (124).

- A non-obese 51-year-old man without a history of diabetes mellitus had a serum glucose concentration of 89 mmol/l and was non-ketotic. Treatment with olanzapine had been started less than 6 months before; about 2 months before the event, his blood glucose concentration was 6.0 mmol/l, and 8 days after withdrawal the glucose concentration returned to normal; he no longer required insulin nor any other hypoglycemic drug.

The authors suggested that olanzapine can cause hyperglycemia by a mechanism other than weight gain.

Glucose concentrations have been studied in 47 patients with non-responsive schizophrenia taking olanzapine (125). Three of them, who had taken olanzapine for 3–6 months, had persistently high blood glucose concentrations. However, this is similar to what would be expected on the basis of the prevalence of diabetes mellitus in US adults.

Death from olanzapine-induced hyperglycemia has been reported (126).

- A 31-year-old man took olanzapine 10 mg/day for 1 week, and his fasting blood glucose rose to 11 mmol/l (200 mg/dl). For more aggressive treatment of his psychosis, the dosage of olanzapine was increased to 20 mg/day, and his fasting blood glucose rose to 16 mmol/l (280 mg/dl). He became progressively weaker and developed polydipsia and polyuria and died 3 weeks after starting to take olanzapine. He had no personal or family history of diabetes mellitus and was taking no other drugs at the time of his death. Death was attributed to hyperosmolar non-ketotic hyperglycemia.

The authors recommended including vitreous glucose and gammahydroxybutyrate analysis as part of postmortem toxicology work-up when the drug screen reveals either olanzapine or clozapine.

On the other hand, seven cases of asymptomatic lowered blood glucose concentrations have also been reported in patients with Tourette's syndrome who were taking olanzapine (mean dose 12 mg/day) during an 8-week, open-label trial (127). The mean serum glucose concentration was 4.8 mmol/l at baseline and 4.1 mmol/l during the study; the average weight gain was 4.5 kg. The authors suggested that increased insulin release may have been responsible for the changes observed; however, non-insulin mechanisms, such as a low carbohydrate intake, may also have played a role.

Weight gain

Significant weight gain occurs more often with olanzapine than with either haloperidol or risperidone (SEDA-22, 64).

Weight gain of 38.5 kg occurred in a 15-year-old adolescent who had taken olanzapine 5–10 mg/day for 14 months (128).

The medical records of ten patients with a DSM-IV diagnosis of cluster B personality disorder (narcissistic personality disorder) who had taken olanzapine 2.5–20 mg/day for 8 weeks have been reviewed (129). The mean Social Dysfunction and Aggression Scale score was 29 for the 8 weeks before olanzapine therapy and improved to 14 after 8 weeks of treatment. Five of the ten patients developed severe weight gain.

In 15 patients with excessive weight gain associated with olanzapine the mean weight gain was 11 (range 3.6–25) kg and the mean duration of treatment was 7 (range 2–11) months (130).

In a retrospective study of 16 patients (7 men, 9 women) taking olanzapine (mean dose 14 mg/day, range 10–30) there was weight gain of over 7% in 15 of them; no change in diet, access to food, or change in exercise pattern had occurred (131).

Weight gain was observed in nine patients (seven men, two women, mean age 41 years) treated with olanzapine (mean dose 19, range 10–30, mg/day) (132). The patients had a mean weight gain of 9.9 kg and triglyceride concentrations (reference range 0.3–2.3 mmol/l) increased from a mean of 1.9 mmol/l (range 0.8–4.3) to a mean of 2.7 mmol/l (range 1.5–4.2).

Average weight gain was 8 kg in patients with refractory schizophrenia ($n = 8$) who were taking olanzapine in high doses (20–40 mg over an average of 40 weeks) (133).

In a retrospective chart review, 20 consecutive patients, who requested a switch from their previous neuroleptic drug therapy to olanzapine, were monitored over 12 months to note changes in weight. After 12 months of olanzapine treatment, 13 had a mean weight gain of 7.3 kg and three had no significant change in weight (134). Paradoxically, four patients lost weight when taking olanzapine, and the authors claimed that this is the first report of patients who had weight loss with olanzapine, although in these cases it is difficult to determine which factors contributed to the weight loss.

Taking advantage of this effect on weight, olanzapine 10 mg has been used in an open trial in 20 patients with anorexia nervosa (135). Of the 14 patients who completed

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the 10-week study, 10 gained an average of 3.9 kg and three of these attained their ideal body weight. The other four patients who completed the study lost a mean of 1.0 kg. The most common adverse effects were sedation ($n = 13$), headache ($n = 5$), fatigue ($n = 4$), and hypoglycemia ($n = 4$).

The genetic basis of some reactions associated with neuroleptic drugs is of particular interest. Different polymorphisms have been studied in connection with atypical neuroleptic drug-induced weight gain (SEDA-26, 57). The relation between the CYP2D6 genotype and weight gain in patients taking atypical neuroleptic drugs has been addressed in a study in 11 Caucasian patients taking a fixed dose of olanzapine 7.5–20 mg/day for up to 47 weeks (136). They had their DNA analysed for the CYP2D6*1, CYP2D6*3, and CYP2D6*4 alleles; six had two *1 alleles and the other five had either *1/*3 or *1/*4. Subjects with a heterozygous genotype (*1/*3 or *1/*4) had a statistically significantly larger percentage change in body mass index than those who were homozygous for the *1 allele.

Histamine H_2 receptor antagonists, like nizatidine, can control appetite in overweight patients (137).

- A 23-year-old man, who had had repeated episodes of weight gain during olanzapine treatment, had good control and subsequent weight reduction after 4–5 weeks of therapy with nizatidine.

Electrolyte balance

Hyponatremia has been reported in patients treated with olanzapine (138).

Hematologic

Neutropenia and agranulocytosis

Although hemotoxicity was not observed during premarketing studies of olanzapine (139), cases of neutropenia (neutrophil count below 1.5×10^9/l) (140) or agranulocytosis (neutrophil count below 0.5×10^9/l) (141) have been published.

Six cases of hematological reactions, including leukopenia, granulocytopenia, and neutropenia, were reported in Canada in the 2 years after the approval of the drug in 1996 (142).

- A 20-year-old man with schizophrenia took olanzapine 5 mg/day increasing to 10 mg/day after 3 days (143). His total leukocyte count fell to 3.9×10^9/l on the fifth day, with an absolute neutrophil count of 1.52×10^9/l. Olanzapine was withdrawn and the leukocyte count normalized within 72 hours. A few days later rechallenge was positive. He was given lithium 900 mg/day and continued to take olanzapine 20 mg/day.

Mechanism

Some explanations of the lower risk of agranulocytosis have been advanced after an in vitro cytotoxicity study (144). Like clozapine, olanzapine is oxidized to a reactive nitrenium ion by HOCl, the major oxidant produced in activated neutrophils. However, the olanzapine-reactive metabolite has a lower propensity to cause toxicity to human neutrophils, monocytes, and HL-60 cells than the reactive clozapine nitrenium ion. The lower toxic potential of the olanzapine reactive metabolite, in conjunction with the lower therapeutic plasma concentrations of olanzapine compared with clozapine, may help to explain this difference between the drugs.

Dose relation

In three cases of leukopenia with olanzapine, a reduction in dose was followed by normalization of the leukocyte count and allowed continued treatment (145). Two of the patients had a previous history of neutropenia and agranulocytosis associated with typical neuroleptic drugs and the third developed neutropenia for the first time while taking olanzapine.

Time course

Of two cases of olanzapine-induced neutropenia, one occurred 17 days after the first dose of olanzapine and the other more than 5 months after the first dose (140); in the second patient, re-exposure to olanzapine caused the neutrophil count to fall again. In neither case was there evidence of infection, and the white blood cell counts increased immediately to the reference ranges after withdrawal of olanzapine, no special treatment being necessary. In addition, two cases of reversible leukopenia during treatment with olanzapine have also been reported (146).

Susceptibility factors

Genetic

Susceptibility factors for neutropenia and agranulocytosis have been investigated in two patients, one of whom had neutropenia after taking other drugs and one of whom was also taking amitriptyline (147). The risk of clozapine-induced agranulocytosis was significantly higher in patients with the HLA haplotypes DQB*01, DQB*05, and DQB*02. One of the patients who had neutropenia had HLA-DQB*05 and both patients had haplotype HLA-A2.

If there is an HLA association for olanzapine, it seems to be different from the HLA antigens incriminated for clozapine (SEDA-25, 66).

- In a 46-year-old man taking olanzapine 10 mg/day, leukopenia and neutropenia were associated with HLA types A1 24, B7, B35, DRB1*15, DRB1*11, DRB3*01–03, DRB5*01–02, a haplotype distinct from that previously observed in clozapine-induced hemotoxicity (148).

Cross-reaction with clozapine

Olanzapine-induced blood disorders have been reviewed and compared with clozapine-induced agranulocytosis (149). Whether clozapine-induced granulocytopenia or leukopenia predisposes a patient to hematological adverse effects during treatment with olanzapine is unclear: three patients who had previously stopped clozapine owing to hematologic adverse effects had improvement with olanzapine that equated to a 16–31 point reduction in rating scale scores during 1 year of follow-up without any hematological abnormalities (150). In contrast, one case associated with clozapine worsened when olanzapine was given (151).

- In a 31-year-old woman clozapine monotherapy 75 mg/day caused neutropenia (neutrophil count 1.1×10^9/l);

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5 days after clozapine withdrawal the neutrophil count normalized (2.6×10^9/l). Olanzapine was then introduced at 5 mg/day and the next day increased to 10 mg/day. After a week the neutrophil count fell to 0.9×10^9/l and olanzapine was withdrawn. The neutrophil count was normal 4 weeks after olanzapine withdrawal.

In another case, olanzapine caused agranulocytosis after clozapine had had no effect on the white cell count (141).

- A 27-year-old man taking clozapine, benperidol, and risperidone developed severe extrapyramidal adverse effects and had insufficient antipsychotic effects and was given olanzapine, rapidly increasing to 40 mg/day. After 9 days of treatment with olanzapine, his total white cell count fell from 5.8×10^9/l to 3.4×10^9/l, and olanzapine was withdrawn; 3 days later his neutrophil count was 0.39×10^9/l. He developed a fever of 39.5°C and was treated with granulocyte colony-stimulating factor.

Prolonged granulocytopenia due to olanzapine occurred in a 39-year-old woman after clozapine withdrawal (152). In contrast, two patients with severe clozapine-induced granulocytopenia and agranulocytosis were successfully treated with olanzapine in a dose greater than 25 mg/day (153). Furthermore, a 65-year-old man who had previously developed leukopenia and neutropenia, first with clozapine and then also with risperidone, took olanzapine (20 mg/day for 2 years with only a transient reduction in leukocyte and neutrophil (but not erythrocyte or platelet) counts) during a flu-like illness (154).

Seven patients, after developing eosinophilia ($n = 1$), agranulocytosis ($n = 2$), or neutropenia ($n = 4$) during neuroleptic drug therapy, were given olanzapine, with improvement and without evidence of blood dyscrasias (155,156). In a review it was suggested that this might reflect the fact that olanzapine shares many pharmacological properties with clozapine, which might make it more likely to prolong the clozapine-induced effect on white cells (157).

Thrombocytopenia

Thrombocytopenia, with a platelet count of 20×10^9/l, possibly associated with olanzapine and subsequently with benzatropine mesylate, has been reported, purportedly for the first time, in a 38-year-old woman (158).

Pancytopenia

Pancytopenia associated with exacerbation of motor disability induced by olanzapine (10 mg/day) in a patient with Parkinson's disease has been reported (159). Olanzapine withdrawal increased the neutrophil, total granulocyte, erythrocyte, and platelet counts to normal in 3 weeks, while the motor disability improved only moderately.

Eosinophilia

Eosinophilia occurred in a 30-year-old man taking olanzapine 22.5 mg/day (160). After 5 weeks, the white blood cell count increased to 15×10^9/l, of which 7.9×10^9/l were eosinophils. Olanzapine was withdrawn, and 5 weeks later the white blood cell count was 8.5×10^9/l with 14% eosinophils.

Gastrointestinal

While hypersalivation is a common adverse effect of clozapine (SEDA-22, 60), dry mouth is associated with olanzapine (SEDA-21, 57) (SEDA-22, 64). Drooling as an adverse effect of olanzapine has been reported in a 20-year-old woman (161). Excessive, chalky-white, frothy, sticky salivation has been reported in a 27-year-old man who had taken olanzapine 10 mg/day at bedtime for 4 days (89).

Pancreas

Acute pancreatitis has been reported in a patient who did not take alcohol and who had undergone a cholecystectomy in the past; other medical causes of pancreatitis were ruled out (162).

Acute pancreatitis was subsequently discussed (163,164). The main points of debate were the interpretation of attributability and the use of the Naranjo probability scale in a case in which the patient was taking another drug that could not be completely excluded as at least a partial contributor to the acute pancreatitis.

Urinary tract

Urinary incontinence has been attributed to olanzapine.

- A 61-year-old man with bipolar disorder treated with olanzapine and lithium developed urinary incontinence 4 days later (165). He was successfully treated with ephedrine 25 mg/day.

The authors suggested that the alpha-blocking effect of olanzapine was involved and that an alpha-adrenoceptor agonist (such as ephedrine) would reduce urinary incontinence in such cases.

Sexual function

Priapism has been attributed to olanzapine.

- A 68-year-old taking olanzapine 5 mg at bedtime developed priapism and required emergency surgery (166).
- In a 46-year-old man taking olanzapine 15 mg/day, priapism remitted after withdrawal (167).
- A 27-year-old man had taken olanzapine 15 mg at bedtime for 12 days for hallucinations and then developed priapism (168). Partial detumescence was followed by recurrence, and he required an operation to insert a glandular shunt. He subsequently required mechanical support to achieve an erection.
- Recurrent priapism during clozapine and then olanzapine therapy occurred in a 43-year-old man (169).
- A 26-year-old man, who had previously taken a variety of psychotropic medications, including typical neuroleptic drugs and risperidone, without sexual adverse effects, took olanzapine 10 mg at bedtime (170). Soon after, he developed priapism; 24 hours after withdrawal of olanzapine, the adverse effect disappeared.
- A 51-year-old man developed priapism 16 hours after attempting suicide by taking olanzapine 100 mg and gabapentin 1500 mg (171). Detumescence was produced by two injections of lidocaine and 8 hours later an intracorporeal shunt.

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Immunologic

Hypersensitivity syndrome, defined as a drug-induced complex consisting of fever, rash, and internal organ involvement, has been associated with olanzapine (172).

- A 34-year-old man took clozapine for several months, but developed a cardiomyopathy. Clozapine was withdrawn and olanzapine 20 mg/day was given instead; 60 days later he developed a recurrent high fever, rash, and pruritus. There was bilateral periorbital edema and generalized erythroderma without target lesions or bullae and no mucosal involvement. He also had an eosinophilia and hepatitis.

Drug Administration

Drug overdose

Fatal overdoses in which novel antipsychotic drugs were the sole ingestant have been reported with olanzapine (173). In two cases blood olanzapine concentrations were 237 ng/ml in one and 675 ng/ml in the other (174). The usual target range for plasma olanzapine concentrations is 9–23 ng/ml.

- A 59-year-old woman died after taking an unknown quantity of olanzapine; the blood concentration was 4900 ng/ml (173).
- A 43-year-old man (175) died within hours of ingestion of 600 mg of olanzapine; the drug concentration in a postmortem analysis of the blood was 12 400 ng/ml.
- A 24-year-old man took a presumed cumulative dose of 420 mg of olanzapine and 10 mg of alprazolam (176). He had a cardiac arrest with asystole, from which he was initially resuscitated. Recurrent cardiac arrest, probably caused by hyperkalemia, occurred in the intensive care unit and he died within 1 hour.

Several non-fatal cases have also been published.

- Profound central nervous system depression and tachycardia without other dysrhythmias occurred within 2 hours of an olanzapine overdose (800 mg; the highest serum concentration was 991 ng/ml) (177). The patient recovered after intubation, gut decontamination, and supportive care.
- A patient took an overdose of 1110 mg of olanzapine and had tachypnea, sinus tachycardia, fluctuating blood pressure, and brief hypoxemia; respiratory and cardiovascular function returned to normal within 16 hours of ingestion with minimal interventions (178).
- A patient attempted suicide by taking 120 mg of olanzapine, but had no serious clinical adverse effects, and only fatigue, dizziness, and headache (179).
- A 22-year-old man took about 800 mg of olanzapine; his olanzapine serum concentration reached a maximum of 200 ng/ml (180). His vital signs were stable at all times, but he started to become progressively somnolent, with short periods of aggressive agitation. Gastric lavage was performed and after 10 hours he was alert and oriented.

In four cases of overdose with up to 1000 mg there was significant central nervous system depression and miosis after acute overdosage of olanzapine (181). Olanzapine concentrations were over 250, 59, 54, and 151 ng/ml. All four patients recovered with supportive care and two required advanced airway support. The authors pointed out that all the patients had marked miosis and depressed mental status, findings that are usually associated with intoxication with opioids or alpha$_2$-adrenoceptor agonists.

Several cases of olanzapine overdose have been reported in children.

- An 11-kg, 1-year-old child developed agitation followed by prolonged lethargy after accidental ingestion of an unknown amount of olanzapine (182).
- An 18-month-old boy took 30–40 mg of olanzapine and had respiratory distress and mental status changes (183).
- Prolonged central nervous system depression occurred after a medication error in a 17-kg, 6-year-old girl who was given Zypresa (olanzapine 10 mg) instead of Zyrtec (cetirizine 10 mg) (184).
- In a dispensing error a 14-year-old boy was given olanzapine 80 mg/day, eight times the recommended dose in adults (185).
- A 2.5-year-old boy took one or two tablets of 7.5 mg and exhibited agitation, aggressive behavior, miosis, hypersalivation, tachycardia, and ataxia (186). A similar dose was well tolerated by an 8-year-old autistic boy (187).

Drug–Drug Interactions

General

Pharmacokinetic and pharmacodynamic profiles of olanzapine have been extensively reviewed (188). Olanzapine does not inhibit CYP isozymes, and no clinically significant metabolic interactions were found of olanzapine with aminophylline, biperiden, diazepam, ethanol, fluoxetine, imipramine, lithium, or R/S-warfarin.

Carbamazepine

Patients co-medicated with carbamazepine had a median dose-corrected plasma olanzapine concentration 36% lower than those taking monotherapy (189).

The pharmacokinetics of two single therapeutic doses of olanzapine have been determined in 11 healthy volunteers, before and after carbamazepine (190). The dose of olanzapine given after pretreatment with carbamazepine for weeks was cleared more rapidly than olanzapine given alone. Olanzapine C_{max} and AUC were significantly lower after the second dose, the half-life was significantly faster, and the clearance and volume of distribution were significantly increased. This interaction may be attributed to induction of CYP1A2 by carbamazepine, leading to increased first-pass and systemic metabolism of olanzapine.

The effect of carbamazepine on the glucuronidation of olanzapine has been studied in 30 patients taking olanzapine monotherapy (dosage 2.5–30, median 15, mg/day) and in 15 patients being co-medicated with carbamazepine (dosage 5–50, median 20, mg/day) (191). The median ratio of unbound olanzapine concentration to daily dose in the carbamazepine group was 38% lower than in the monotherapy group, confirming that carbamazepine accelerates the metabolism of olanzapine. Furthermore, in the carbamazepine group, the median glucuronidated olanzapine fraction was 79% of the unbound fraction,

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compared with 43% in the monotherapy group, which suggests that an increased rate of olanzapine glucuronidation contributes to the increased rate of metabolism of olanzapine induced by carbamazepine.

Ciprofloxacin

The plasma concentration of olanzapine doubled in a patient who also took ciprofloxacin, a potent inhibitor of CYP1A2 (192). The magnitude of the interaction was surprising, because available data suggest that CYP1A2-mediated oxidation of olanzapine accounts for only a small portion of the biotransformation of olanzapine relative to glucuronidation.

Diazepam

There were orthostatic changes when olanzapine and diazepam were co-administered (188).

Ethanol

There were orthostatic changes when olanzapine and ethanol were co-administered (188).

Inhibitors of CYP2D6

Of 56 patients, 22 of whom took olanzapine monotherapy and the rest took other psychotropic drugs, those co-medicated with inhibitors of CYP2D6 and other drugs had a median dose-corrected concentration about 40% higher than those taking monotherapy.

Selective serotonin re-uptake inhibitors (SSRIs)

Olanzapine is metabolized by CYP1A2, and fluvoxamine, which inhibits CYP1A2, increases plasma olanzapine concentrations (SEDA-24, 71).

- A 21-year-old woman had a very high olanzapine plasma concentration (120 ng/ml) during co-administration of fluvoxamine 150 mg/day and olanzapine 15 mg/day; her symptoms included slight tremor, rigid movements, and general discomfort (193).

Pharmacokinetic and pharmacodynamic profiles of olanzapine have been extensively reviewed (188). Olanzapine does not inhibit CYP isozymes, and no clinically significant metabolic interaction was found with fluoxetine.

Tricyclic antidepressants

Clomipramine and olanzapine are both metabolized by CYP1A2 and CYP2D6, and it is therefore possible that raised concentrations of both compounds can result from co-administration.

- Seizures in a 34-year-old man were attributed to an interaction of olanzapine with clomipramine (194).

A pharmacodynamic interaction occurred between olanzapine and imipramine (188).

Smoking

Plasma concentrations of olanzapine and clozapine are lower in smokers than in non-smokers, mainly because of induction of CYP1A2. Two patients who smoked tobacco and cannabis have been reported (195). One took olanzapine and had extrapyramidal motor symptoms after reducing his consumption of tobacco. The second, who was taking clozapine, developed confusion after he stopped smoking tobacco and cannabis, related to increased clozapine concentrations. The authors recommended that when patients stop smoking, appropriate dosage adjustments should be made to ensure that the plasma neuroleptic drug concentrations remain within the usual target range.

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Olprinone

See also Phosphodiesterase type III, selective inhibitors of

General Information

Olprinone is an inhibitor of phosphodiesterase type III, and has a positive inotropic effect. It is given intravenously and is mostly eliminated by the kidneys. Its pharmacological effects have been reviewed (1). Its major adverse effects are cardiac dysrhythmias and thrombocytopenia, the latter with a reported incidence of 0.43%.

Reference

1. Mizushige K, Ueda T, Yukiiri K, Suzuki H. Olprinone: a phosphodiesterase III inhibitor with positive inotropic and vasodilator effects. Cardiovasc Drug Rev 2002; 20(3):163–74.

Omalizumab

See also Monoclonal antibodies

General Information

Omalizumab (formerly rhuMab-E25) is a humanized monoclonal antibody against IgE, which blocks the interaction of IgE with mast cells. Several phase I and phase II trials have demonstrated its efficacy in patients with allergic asthma (1–4).

In a placebo-controlled study of subcutaneous omalizumab (50, 150, and 300 mg before the ragweed season and every 3 or 4 weeks during the pollen season) in 536 patients with seasonal allergic rhinitis, injection site reactions were mild and infrequent, there were no clinically significant alterations in laboratory values, and anti-idiotypic antibodies to omalizumab were not detected; there was no evidence of immune complex-related adverse events (5–7).

In another placebo-controlled trial in 525 patients with severe asthma, the adverse effects profiles were similar in the treatment and placebo groups (8).

In an extension study in 225 children there were no anaphylactic reactions or adverse events suggestive of serum sickness or immune complex formation; anti-omalizumab antibodies were not detected (9). In cases of re-treatment there were no severe adverse events related to omalizumab (10).

Organs and Systems

Skin

The safety of subcutaneous omalizumab has been assessed in 334 boys and premenarchic girls aged 6–12 years with moderate to severe allergic asthma requiring inhaled glucocorticoids in a randomized, placebo-controlled, double-blind trial (11). There were no serious treatment-related adverse events, and the frequencies of most adverse events were similar with omalizumab and placebo. However, urticaria was more frequent with omalizumab (4 versus 0.9%). It usually resolved spontaneously or with antihistamine therapy and did not recur with subsequent treatment. Urticaria was also reported in a small number of adults (0.5%) given omalizumab for allergic rhinitis (12).

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Omeprazole

See also Proton pump inhibitors

General Information

Omeprazole is a proton pump inhibitor. Headache, skin rash, and diarrhea have all been recorded by adverse event registries sufficiently often to suggest causal relations (1). Omeprazole is a modest inhibitor of CYP isoforms. Interactions are less likely than with cimetidine and are probably of no practical importance. However, omeprazole reduces the absorption of drugs that require a low gastric pH (ketoconazole, iron salts, ampicillin) and can inhibit the hepatic clearance of some drugs (diazepam, warfarin, phenytoin) (2).

To test whether omeprazole accelerates healing of standardized gastroduodenal lesions in the presence of diclofenac, 12 healthy volunteers took consecutive 2-week courses of omeprazole 40 mg/day or placebo, with diclofenac given in the second week of each course, in a double-blind, crossover study (3). Omeprazole did not accelerate the healing of pre-existing mucosal lesions or prevent the development of small diclofenac-induced mucosal lesions. Omeprazole increased serum gastrin in all subjects.

Organs and Systems

Psychological, psychiatric

- Delirious psychosis has been attributed to intravenous omeprazole 40 mg bd in a 77-year-old woman with Guillain–Barré syndrome, who also had *Helicobacter pylori*-associated gastritis (4). Delirium developed 2 days after omeprazole was begun and resolved completely after drug withdrawal.

Metabolism

In patients with Zollinger–Ellison syndrome, omeprazole causes significant weight gain, perhaps because of shifts in hormonal balance (SEDA-17, 419) (5,6).

Electrolyte balance

Hyponatremia caused by omeprazole has been reported in a 78-year-old woman who was taking omeprazole 20 mg/day for esophagitis, in a 74-year-old man (7), and in an elderly alcoholic (SEDA-17, 419).

Hematologic

- Iron deficiency anemia has been reported in a 49-year-old man eating a normal diet who had taken omeprazole 40 mg/day for 3 years (8). Two months after withdrawal of omeprazole his anemia improved and his serum ferritin concentration normalized after 4 months. During this period he took his usual diet and was not given any iron supplements.

Prolonged suppression of gastric acid, which plays an important role in the absorption of non-heme iron, was thought to have led to iron deficiency.

Hemolytic anemia occurred with recovery after withdrawal of omeprazole (SEDA-17, 419).

Agranulocytosis in a kidney transplant recipient (9) and neutropenia (10) have been associated with omeprazole.

Thrombocytopenia occurred in a man with a history of chronic alcoholism taking omeprazole; the blood disorder appeared on the fourth day of treatment and resolved after drug withdrawal (11,12).

Gastrointestinal

Moderate nausea, diarrhea, or abdominal pain can occur in patients taking omeprazole (13). There is an increased incidence of the severe interstitial and atrophic forms of gastritis, associated with moderate hypergastrinemia and hyperplasia of the argyrophil cells (1). This is not necessarily an adverse effect; it could represent the natural history of chronic gastritis associated with peptic ulcer disease.

Gastric polyps have been observed in a number of patients, but they disappear spontaneously during follow-up (SEDA-18, 373). Most or all patients taking omeprazole have a non-pathological "pseudohypertrophy" of the parietal cells.

The possibility that, as with H2 receptor antagonists, achlorhydria will increase the risk of gastrointestinal infection has been advanced both on theoretical grounds and in the light of a number of cases, including one of esophageal candidiasis (SED-12, 944) (14,15).

Of 33 patients with severe reflux esophagitis prospectively followed up for 5–8 years six were positive for *H. pylori* (16). There was no evidence of significant enterochromaffin-like cell hyperplasia, gastric atrophy, intestinal metaplasia, dysplasia, or neoplastic changes during 185 patient follow-up years during which 137 gastric biopsies were taken.

Omeprazole 20 mg/day and famotidine 20 mg bd for 4 weeks had equivalent ulcer healing rates in a randomized, endoscopist-blinded study in 16 patients who had undergone endoscopic mucosal resection for early gastric cancer (17). Although concentrations of fibroblast growth factor-2 in biopsy specimens were similar in the two treatment groups, fibromuscular hyperplasia was significantly greater in the omeprazole group on day 28.

Liver

Hepatitis occasionally occurs with omeprazole.

- Severe hepatitis occurred on two occasions when a 30-year-old man with advanced renal insufficiency secondary to diabetic neuropathy took omeprazole for esophagitis (18).
- A 34-year-old woman developed jaundice 11 days after starting to take omeprazole for ulcer dyspepsia (19). Her liver function tests suggested acute hepatitis with large rises in transaminases. Investigations excluded virus infections, autoimmune disorders, copper overload, and alpha$_1$ antitrypsin deficiency. On withdrawal of omeprazole, the transaminases gradually normalized.

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Urinary tract

There have been occasional reports of acute interstitial nephritis attributed to omeprazole (SEDA-20, 318).

- A 31-year-old pregnant woman (35 weeks gestation) developed hypercalcemia and interstitial nephritis possibly associated with omeprazole 20 mg/day for over 8 weeks (20). Investigations excluded other causes of hypercalcemia. She recovered after drug withdrawal and treatment with glucocorticoids.
- Renal insufficiency due to acute interstitial nephritis occurred in a 73-year-old man who had taken omeprazole 40 mg/day for 4 months for severe reflux esophagitis (21). He recovered completely after withdrawal of omeprazole.
- A 36-year-old woman who had taken omeprazole 20 mg/day for 3 months developed acute interstitial nephritis (22). The drug was withdrawn and she made a full recovery after 4 weeks of glucocorticoid therapy.

Skin

Cutaneous adverse reactions attributed to omeprazole are uncommon; they include rashes, urticaria, angioedema, acute disseminated epidermal necrolysis, lichen spinulosus, and contact dermatitis.

- Erythroderma has been reported in a 58-year-old woman with scleroderma who had taken omeprazole 20 mg/day for 6 months (23). She made a full recovery after omeprazole was withdrawn. She was then given pantoprazole 40 mg/day, which was well tolerated.

Hair

Several well-documented case reports have suggested an association between omeprazole and diffuse hair loss (SEDA-22, 392), in one case at least confirmed by rechallenge (24).

Sexual function

Painful erections occurred after each dose of omeprazole in an elderly man (SEDA-17, 419).

Reproductive system

There have been occasional reports of gynecomastia in patients taking omeprazole, regressing after drug withdrawal (25).

Immunologic

Angioedema and urticaria triggered by omeprazole, but not by the enteric granules devoid of the capsule shell, has been described (SEDA-18, 373).

- Cutaneous leukocytoclastic vasculitis has been reported in a 71-year-old woman with epigastric pain who had taken omeprazole 20 mg/day for 4 weeks (26). She made a full recovery after omeprazole was withdrawn.

Anaphylaxis has been attributed to omeprazole (27).

- A 35-year-old alcoholic with pancreatitis developed anaphylaxis after an intravenous infusion of omeprazole. He had raised serum tryptase activity 6 hours after the onset of anaphylaxis. Total serum IgE concentrations were also raised. Intradermal tests 2 months later were positive for both omeprazole and lansoprazole, suggesting cross-reactivity.

Yersinia enterocolitica septicemia occurred in a patient taking omeprazole and heavy oral iron supplementation (28). The authors suggested that intra-luminal iron together with a raised intestinal pH resulting from omeprazole may have contributed to the enhanced proliferation and dissemination of this organism. Since treatment with omeprazole arrests the secretion of gastric acid, it increases the risk of overgrowth with small intestinal bacteria in patients with scleroderma (SEDA-20, 318).

Susceptibility Factors

Age

The use of omeprazole in the treatment of acid-related disorders in children has been reviewed (29). Different formulations have been used in children aged 2 months to 18 years for the treatment of erosive esophagitis, gastric and duodenal ulcer, *H. pylori* infection, and related conditions in dosages of 5–80 mg/day (0.2–3.5 mg/kg/day). The initial dose most consistently reported to heal esophagitis and relieve symptoms of gastroesophageal reflux disease appears to be 1 mg/kg/day. Omeprazole was well tolerated during both acute and chronic use.

Omeprazole, in a starting dose of 0.7 mg/kg/day, was effective in the treatment of severe esophageal reflux after failed fundoplication in 18 children (mean age at presentation 7.8 years) over a mean follow-up period of 4.4 years (30). It was also well tolerated. A hyperplastic polyp was noted in one child after 38 months of treatment and persisted without any dysplastic change. One to three gastric nodules were seen in three children after a mean of 45 months; histology of the nodules showed only mucosal edema.

Hepatic disease

The pharmacokinetics of omeprazole during intravenous infusion in patients with varying degrees of liver dysfunction have been examined in an open study in 13 patients with hepatic cirrhosis (31). Each patient received a bolus of omeprazole 80 mg over 30 minutes, followed by a continuous infusion of 8 mg/hour for 47.5 hours. Exposure to omeprazole after intravenous administration was higher in patients with liver dysfunction. However, even in patients with severely impaired liver function, the plasma concentration of omeprazole did not change by more than 100% and the drug was well tolerated. Adverse effects were infrequent and occurred in three patients: epigastric pain, arthralgia, and hepatic encephalopathy; the last was probably unrelated to the drug.

Drug Administration

Drug formulations

To investigate the pharmacokinetics of omeprazole MUPS tablets and its encapsulated form, 38 healthy

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male volunteers were given a single 20 mg oral dose of each formulation in a crossover study (32). Encapsulation did not influence the extent and rate of absorption of the drug, demonstrating bioequivalence. Both formulations were well tolerated. The most commonly reported adverse effect with both formulations was headache.

Drug dosage regimens

The effect on serum gastrin concentrations of omeprazole 20 mg/day and 20 mg on alternate days given long term has been studied in 53 patients with reflux esophagitis in a controlled trial (33). The mean serum gastrin concentration was significantly raised in the first group. Gastrin concentrations in the alternate day treatment group were similar to controls who did not take omeprazole.

Drug–Drug Interactions

Ciclosporin

Omeprazole increases ciclosporin blood concentrations (SEDA-17, 420).

Clarithromycin

In an open, randomized, crossover study of the effects of oral omeprazole 20 mg/day for 7 days on the distribution of co-administered clarithromycin in the gastric juice in 18 male volunteers with *H. pylori*, short-term omeprazole increased the amount of clarithromycin transferred to the gastric juice, confirming synergy between these two drugs (34).

Digoxin

In an acid-free stomach a different and shorter-acting pattern of metabolites of digoxin is produced, which could change its duration of action (35).

Furazolidone

The effect of acid secretion blockade by omeprazole 20 mg/day for 5 days on the systemic availability of oral furazolidone has been investigated in a randomized, crossover study in 18 healthy volunteers (36). Omeprazole significantly reduced the systemic availability of furazolidone. This could partially explain reports of modest *H. pylori* eradication rates (50%) when the two drugs are used in combination, despite the fact that furazolidone is considered to be highly effective against the bacterium, and low resistance to the drug has been reported.

Itraconazole

The effects of omeprazole 40 mg/day on the pharmacokinetics of itraconazole 200 mg have been studied in 11 healthy volunteers (37). Omeprazole reduced the absorption of itraconazole. As the absorption of itraconazole is pH-dependent (it requires a pH of under 3.0 for complete dissolution and absorption) the likely explanation for this interaction is the effect of omeprazole on gastric pH.

Roxithromycin

The effect of omeprazole on roxithromycin concentrations in plasma and gastric tissue has been investigated in 12 healthy volunteers who took omeprazole 20 mg bd with or without roxithromycin 300 mg bd over 6 days (38). The medications were well tolerated, with only mild adverse events. The more frequent adverse events were nausea, bloating, and diarrhea. Omeprazole and roxithromycin did not alter the systemic availability of each other. However, omeprazole increased the local concentration of the antibiotic in the stomach.

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Onagraceae

See also Herbal medicines

General Information

The genera in the family of Onagraceae (Table 1) include evening primrose and fuchsia.

Oenothera biennis

The seeds of *Oenothera biennis* (evening primrose, fever plant, king's cure-all, night willow herb, scabish, sundrop, tree primrose) yield evening primrose oil, which contains gamma-linolenic acid and has been used in various disorders, such as atopic eczema, premenstrual syndrome, and benign breast pain, but is probably not efficacious (1,2).

Adverse effects

Evening primrose oil has generally only minor adverse effects, such as nausea, diarrhea, and headache.

In three patients evening primrose oil triggered temporal lobe epilepsy (3).

Table 1 The genera of Onagraceae

Calylophus (sundrops)
Camissonia (suncup)
Chamerion (fireweed)
Circaea (enchanter's nightshade)
Clarkia (clarkia)
Epilobium (willowherb)
Fuchsia (fuchsia)
Gaura (beeblossom)
Gayophytum (groundsmoke)
Ludwigia (primrose willow)
Oenothera (evening primrose)
Stenosiphon (stenosiphon)

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Opioid analgesics

See also Individual agents

General Information

Classes of substances

Opioids are naturally occurring or synthetic substances that have morphine-like activity. The term opiate refers only to substances with morphine-like activity that are derived from opium. Substances that bind to opioid receptors but elicit little agonist activity are known as opioid antagonists. Some drugs have both agonist and antagonist effects (partial agonists). The opioids and their antagonists can be divided into three groups: (a) opioid agonists (morphine and morphine-like opioids); (b) opioid antagonists (for example naloxone and naltrexone); and (c) opioid partial agonists (for example buprenorphine and nalbuphine).

Three separate categories of endogenous substances with morphine-like activity have been identified. These families of neuropeptides are known as enkephalins, endorphins, and dynorphins. Each family is derived from a distinct precursor polypeptide (pro-enkephalin, pro-opiomelanocortin, and prodynorfin) and has a characteristic anatomical distribution. The enkephalins and dynorphins found co-exist with other neurotransmitters, such as serotonin (5-HT) and noradrenaline, but details of how the peptides modulate the activity of co-transmitters await elucidation.

Finally, several molecules with chemical structures similar to morphine have been found in mammalian brain, but it is not certain if these molecules have been derived from dietary sources or if they are synthesized in the brain.

The word narcotic was previously used to describe substances with morphine-like activity and is now largely obsolete, although it is still used in legal parlance.

Opioid receptors

There are three main types of opioid receptor: OP_3 (μ), OP_2 (κ), and OP_1 (δ) receptors. They are mainly found within the central nervous system but also in the periphery. Subtypes of each have been identified. Opioids interact with these receptors to produce their effects, primarily by exerting presynaptic inhibition, which results in reduced release of excitatory transmitters. It is thought that analgesia is primarily mediated via activation of OP_3 (μ) receptors at supraspinal sites and OP_2 (κ) receptors within the spinal cord. The finding that morphine is ineffective as an analgesic in knock-out mice without μ receptors confirms the importance of this receptor type. However, structural studies in cloned μ receptors have failed to support pharmacological studies that suggest the existence of separate μ receptor subtypes that independently mediate analgesia and respiratory depression.

The identification of opioid receptors and the discovery of opioid peptides in the 1970s led to the hope that greater understanding of fundamental mechanisms would lead to the development of new drugs with all the valued properties of known opioids but without their unwanted effects. However, these hopes have remained unrealized, although a synthetic enkephalin (pentapeptide 443C81), which penetrates the blood–brain barrier poorly, produces dose-related analgesia without causing significant miosis or reducing minute volume on rebreathing carbon dioxide in healthy volunteers (SEDA-16, 86).

Understanding of nociceptive processing has progressed in recent years, and the pain mechanisms and opioid effects on various receptors and transmission systems have been elucidated (1–3), as have tolerance and physical dependence and the influence of NMDA receptors (4,5).

The peptides endomorphin 1 and 2 have been identified in human brain and show selectivity and affinity for μ receptors. In mice, endomorphin 1 and 2 produce spinal and supraspinal analgesia. They appear to act through regulation of calcium entry into the target cell via voltage-gated channels and also to inhibit cyclic AMP production in μ receptor bearing cells. Clinically they mimic the action of other μ opioids. Their clinical relevance and unique adverse effects profiles await further investigation. Similarly the clinical usefulness of newly discovered receptor systems, such as the orphan opioid receptor for nociceptin (ORL1), which produces analgesia, hyperalgesia, and anti-opioid effects in animals, has yet to be defined.

Differences between individual agents

Morphine remains the gold standard against which all other opioids are compared. Most opioids are used as analgesics, although some are used primarily as antitussives, despite the fact that the cough-suppressing effect of codeine and dextromethorphan has not been demonstrated in children (SEDA-22, 98); others, such as loperamide and diphenoxylate, are used exclusively in the treatment of diarrhea; fentanyl and its congeners are primarily used in anesthesia. Fentanyl, the oldest of the anesthetic opioid agonists, and its derivatives alfentanil and sufentanil, are used either as anesthetic supplements or in appropriate doses as complete anesthetics. Butorphanol and nalbuphine have largely replaced pentazocine in analgesia, because they are less likely to have dysphoric effects and, in contrast to the pure agonists, any respiratory depression that follows their use is not dose-related and reaches a ceiling as the dose increases.

The main characteristics and use of opioid drugs are listed in Table 1. Drugs in widespread clinical use each have a separate monograph.

The use of opioid drugs is continuing to increase, mainly because of the development of alternative routes

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Table 1 Major characteristics and uses of some opioid drugs

Drug	Typical dose	Route of administration	Half-life (hours)	Usual indication	Main adverse effects
Agonists					
Morphine (active metabolite morphine-6-glucuronide)	10 mg and upwards 3–4 hourly	Oral, subcutaneous, intravenous, intramuscular, intrathecal	2–4	Severe pain, anesthesia	Sedation, constipation, nausea, vomiting, itching, respiratory depression, tolerance and dependence, euphoria
Alfentanil	30–50 μg/kg	Epidural, intravenous	1.6–4	Analgesia, anesthesia	As morphine
Codeine (metabolized to morphine by CYP2D6)	30–60 μg 4-hourly	Oral	3–4	Cough, diarrhea, moderate pain	As morphine; lack of effect in poor metabolizers by CYP2D6
Dextromethorphan	10–30 mg 4–8 hourly	Oral	2.7–3.3	Dry cough	
Dextropropoxyphene (active metabolite norpropoxyphene)	65 mg 6–8 hourly	Oral	6–32 (norpropoxyphene 24–42)	Moderate pain	As morphine; cardiotoxicity, not reversible by naloxone; convulsions possible, due to norpropoxyphene
Fentanyl	50–200 μg	Epidural, intravenous, transdermal patch	2–7	Acute pain, anesthesia	As morphine
Methadone	10 mg 6–8 hourly; 30–80 mg/day	Oral, intravenous, intramuscular	15–60	Severe pain; opioid dependence	As morphine
Pethidine (meperidine)	50–150 mg 3-hourly	Oral, intramuscular	3.2	Moderate/severe pain	As morphine; excitement and convulsions
Sufentanil	Up to 8 μg/kg	Epidural, intravenous	2.7–6	Severe pain, anesthesia	As morphine
Partial agonists					
Buprenorphine	300–600 μg 6–8 hourly; 2–32 μg	Sublingual, intravenous Sublingual	5–12	Moderate/severe pain Opioid dependence	As morphine, but less pronounced; less well reversed by naloxone
Pentazocine	30–60 mg 3–4 hourly	Oral, intravenous, intramuscular	2–4	Acute pain	As morphine; dysphoria
Antagonists					
Naloxone	1.5–3 μg/kg repeated according to response	Intravenous	1.1	Reversal of opioid-induced respiratory depression	Nausea, vomiting, hypertension, cardiac dysrhythmias, rarely seizures
Nalmefene	0.25 μg/kg repeated according to response	Intravenous	10	Reversal of opioid-induced respiratory depression	Nausea, vomiting, tachycardia, hypertension, fever, dizziness
Naltrexone	25–50 mg/day	Oral	2.7	Adjunct to prevent relapse in formerly opioid-dependent patients	Nausea, vomiting, abdominal pain, dysphoria, joint and muscle pains, dizziness

of administration and increasing use in the very young. Pharmacological maneuvres have been made in order to improve analgesic potency and reduce adverse effects. Benzodiazepines have been used to improve analgesic effects (SEDA-17, 78), and methylphenidate has been given to patients in order to reduce drowsiness (SEDA-17, 78). Combinations of opioids with non-steroidal anti-inflammatory drugs have been used to provide analgesia postoperatively, with the aim of reducing the amounts of opioid required, with consequent reduction in adverse effects (SEDA-18, 79).

The more novel routes of administration of opioids, including oral, nasal, rectal, transdermal, spinal, and by patient-controlled methods, have been outlined (SEDA-17, 78). Oral transmucosal fentanyl administration, avoiding first-pass metabolism, produces analgesia and sedation in both adults and children undergoing short, painful outpatient procedures. The quality of analgesia is good, and the adverse effects are those typical of the opioids.

Degrees of risk

When the opioids are used correctly, their adverse effects are usually minimal. However, when they are used illicitly, they are often adulterated with other substances, which can cause adverse effects.

A strategy for controlling pain caused by malignant disease has been outlined and the classic effects that can be associated with opioid administration have been reviewed (6). These include constipation, nausea, sedation, pruritus, urinary retention, myoclonus, and respiratory depression. The latter can be life-threatening. Particular care is needed in opioid-naive individuals, those with compromised respiratory function, and elderly patients.

The use of opioids in very young patients is increasing. In a review of pain management in children, various routes of administration of opioids and their associated adverse effects have been discussed (SEDA-17, 78). Attention has been drawn to the adverse effects of intravenous codeine in children and to the risk of convulsions with pethidine in neonates, because of accumulation of its metabolite norpethidine. The risk of respiratory depression with morphine was also highlighted, and morphine is recommended for use only in neonates who are being ventilated or intensively nursed. Routine use of pulse oximetry has been recommended in all children receiving opioids (SEDA-21, 86).

The use of patient-controlled analgesia (PCA) (SEDA-15, 68) highlights the importance of adequate monitoring, in order to avoid potentially catastrophic adverse effects, such as respiratory depression. With PCA, patients generally use less morphine but still achieve the same degree of pain control (7). This supports the view that self-administration of opioids does not put patients at risk of over-medication or drug dependence.

It has been suggested that the risk of producing opioid dependence in the medical setting is greater in those who prescribe and administer them than in those who receive them (8). The likelihood of dependence in patients treated with opioids has been examined. In the treatment of cancer pain, tolerance and physical dependence occur but psychological dependence (addiction) is rare (9,10). In 11882 patients who had received at least one opioid, addiction was reasonably well documented only in four (11).

Of 130 patients with chronic malignant and chronic benign pain attending a pain relief unit over 3 years, 9 (18%) were considered to be addicted to analgesics on subjective evaluation (12). Of 71 patients with chronic pain referred to a pain relief center, 86% were taking analgesics, 58% opioids, and 68% psychotropic agents; 49% of those taking opioids were considered to be dependent (13).

These studies emphasize the need to define the meaning of terms such as addiction and dependence correctly and to distinguish between psychological and physical dependence. Failure to do so could lead to unwitting deprivation of opioids in patients for whom they provide undisputed benefit with minimal harm. These results also suggest that patients receiving opioids for less well-defined pain conditions, quite often for longer periods and sometimes along with other drugs with abuse potential, may be at special risk of dependence and abuse. Thus, withdrawal may be important, but may become extremely difficult. The adverse effects encountered during long-term opioid therapy have been reviewed, as well as the evidence that opioids can cause seizures or seizure-like activity (SEDA-22, 97).

Finally, it must be borne in mind that some of the problems with opioids are treatable: for example, naloxone can reverse respiratory depression, but care must be taken in opioid-dependent individuals, as it may precipitate opioid withdrawal.

General adverse reactions

Opioid agonists

Although opioids share many adverse effects, in some respects they are qualitatively and quantitatively different. They all cause constipation by reducing gastrointestinal motility. Respiratory depression, cough suppression, nausea, vomiting, and urinary retention also occur. With the exception of constipation, tolerance to these effects develops. Physical and psychological dependence is also possible. Interaction with monoamine oxidase inhibitors leads to central nervous excitation and hypertension. Hypersusceptibility reactions are rare, although anaphylactic reactions have occurred after intravenous use and skin phenomena can occur. Tumor-inducing effects have not been described in man, but in vitro experiments have suggested a mutagenic effect of papaveretum in mammalian cell lines apparently related to the noscapine content.

The role of opioids in chronic non-malignant pain has been reviewed (14,15), and reports of randomized, double-blind, controlled studies of opioids in chronic non-malignant pain have been identified (15). Opioids appear to be more effective in patients with well-defined nociceptive pain (that is pain associated with clear evidence of tissue damage) than in patients with chronic non-malignant pain of neuropathic origin (i.e. pain associated with injury, disease, or section of the peripheral or central nervous system in the absence of tissue damage) or psychogenic causes (no organic pathology present). Gastrointestinal and CNS adverse effects (sedation, dizziness, cognitive impairment, respiratory depression,

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myoclonus) were frequent and distressing in most of the studies.

Clinical observations suggest that patients often find adverse effects, particularly nausea and vomiting, more distressing than the postoperative pain for which they are prescribed. Some are even willing to endure pain rather than suffer unpleasant adverse effects. This important aspect of opioid-induced analgesia has been investigated in a randomized, double blind, three-way, crossover study of between- and within-patient variability in response to equianalgesic doses of morphine, pethidine, and fentanyl during postoperative PCA (16). In 82 patients undergoing a variety of surgical procedures, the three opioids were equally efficacious from objective measurements in relieving pain and the subsequent incidence and intensity of adverse effects. However, the responses to the three opioids were highly individual, and there were three types of response. One group of patients tolerated all three opioids, another tolerated none, and a third group was sensitive to one or more of the opioids with no preference for any of the opioids used. The authors suggested that it would be good clinical practice to change from one opioid to another in patients who have intolerable adverse effects during PCA, since there is wide variation in subjective interpretation of pain and adverse effects.

Limitations to the use of opioids in cardiac surgery have been reviewed, highlighting the fact that μ receptor agonists cause dose-related respiratory depression through a reduction in carbon dioxide sensitivity in the respiratory centre (17). This depression, with a reduced respiratory rate and hypoxia, outlasts the analgesic effect of μ receptor agonists. Thoracic muscle rigidity on anesthetic induction with high doses of opioids has also been reported and can further compromise respiration. Hypotension through reduced peripheral vascular resistance occurs, while a negative inotropic effect of opioids acting directly on the heart via κ receptors is proposed, based on evidence from in vitro studies. The above effects have limited the role of opiates in patients with coronary artery disease, although they are of less importance in cardiopulmonary bypass surgery, when the heart is quiescent. In such surgery fentanyl partially blocks the expected tachycardia, hypertension, and release of inflammatory mediators that constitute the stress response, although the block is incomplete, owing to a lack of anesthetic effect.

Opioid partial agonists

There is evidence that in the case of partial opioid agonists, such as buprenorphine, the relative clinical activity of agonist and antagonist actions can differ, depending, among other things, on the dose.

The prevention of opioid-induced adverse effects

Prevention of sedation

The use and possible mechanism of amphetamines to counteract opioid-induced sedation has been reviewed (18). Most studies had methodological problems, including small numbers of patients completing short-term trials (under 1 week) and the small number of randomized, placebo-controlled, crossover trials. The quantitative measure of sedation was highly subjective and no uniform cognitive tests were performed to help compare the results of using amphetamines to reduce opioid-induced sedation. The overall conclusion was that more research is needed to determine the exact role of amphetamines. The use of amphetamine and amphetamine derivatives for the treatment of opioid-induced sedation is not recommended.

Prevention of emesis

Another excellent review has focused on the use of prophylactic antiemetics during PCA (19). A systematic search for relevant randomized controlled trails identified 14 studies involving 1117 adults published between 1992 and 1998. Without antiemetic drugs the incidence of opioid-induced nausea was on average 48% and of vomiting 55%, with a 67% chance of having an emetic episode. The most frequently studied antiemetic was droperidol, which was added to morphine PCA in six placebo-controlled trials in 642 adults and to tramadol in another trial. A wide range of doses of droperidol was used, with a constant degree of antiemetic efficacy. Based on this review, the optimal dose of droperidol is said to be less than 0.1 mg of droperidol per mg of morphine or less than 4 mg/day of droperidol. There were few adverse reactions: 56 in 10 000 patients had extrapyramidal adverse effects when droperidol was added to morphine PCA.

The next most frequently used drugs in the prevention of opioid-induced emesis are the 5-HT_3 receptor antagonists (ondansetron and tropisetron). There is no evidence that they prevent nausea, but the effect on vomiting is satisfactory enough for them to be regarded as second-line choices after droperidol. However, in 109 patients undergoing day-case oral surgery there was a higher incidence of nausea with tramadol plus ondansetron compared with three other treatments (fentanyl plus metoclopramide, tramadol plus metoclopramide, and fentanyl plus ondansetron) (20). There was no difference between the groups in analgesic efficacy.

Other prophylactic antiemetic agents include clonidine, promethazine, hyoscine, propofol, and metoclopramide. However, the data on these drugs are either insufficient or non-existent.

In a randomized, double-blind, placebo-controlled study of 80 patients who required epidural morphine after abdominal hysterectomy, 40 received intravenous dexamethasone (8 mg) (21). The incidence of vomiting with dexamethasone group was 5% compared with 25% with placebo; the total incidence of nausea and vomiting was 16% compared with 56%.

Prevention of pruritus

The incidence of opioid-induced pruritus varies widely, and depends on the opioid used and its mode of administration. The highest incidence (up to 80%) is associated with intrathecal morphine. The pruritus is usually localized to the area of the face that is innervated by the trigeminal nerve. A central encephalinergic mechanism has been proposed to explain this localization. The pruritus is often difficult to treat and responds poorly to conventional treatments, except for naloxone and propofol; 10–15% remain unresponsive. Naloxone reversibility of opioid-induced pruritus supports the existence of an

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opioid-medicated central mechanism. However, naloxone will reverse the analgesic effects of the opioids.

Three studies have suggested the use of ondansetron, a 5-HT_3 receptor antagonist, for the treatment of opioid-induced pruritus (22–24). The articles suggested a possible interaction between the opioid and the serotonergic systems. In one prospective, randomized, double-blind, placebo-controlled study, 80 patients undergoing any type of surgery were given intravenous ondansetron 4 mg or 0.9% saline over 1 minute, with alfentanil as the opioid used in the anesthetic technique (22). The study was inconclusive; there was a significant reduction in the incidence of scratching in patients who received ondansetron compared with placebo but a non-significant incidence of itching in the ondansetron group.

In a prospective randomized, double-blind, placebo-controlled study in 100 patients scheduled for elective orthopedic surgery and presenting with pruritus induced by epidural or intrathecal morphine, intravenous ondansetron 8 mg was effective in 70% of cases and placebo in 30% (23). Ondansetron was well tolerated, did not change the degree of analgesia, and was not associated with adverse effects usually associated with ondansetron, such as headache, abdominal pain, and cardiac dysrhythmias.

In a double-blind randomized study of 130 patients given subarachnoid bupivacaine 0.5% with morphine 0.3 mg for surgical and postoperative analgesia, repeated-dose and single-dose ondansetron were compared (24). The overall incidence of pruritus was 73% in the group not given ondansetron, 63% in those who received intravenous ondansetron 4 mg 20 minutes before the spinal analgesia and 2 ml of saline at 12, 24, 26, and 48 hours after surgery, and only 49% in those who received ondansetron 4 mg 20 minutes before the spinal and 12, 24, 36, and 48 hours after surgery. There were methodological problems—the small number of subjects studied and the lack of an objective scoring system—but these results add to the current discussion of pursuing further studies to determine the effective dose of ondansetron in the treatment of opioid-induced pruritus. Further neurobiological research is needed to determine a "human" model of explaining the role and interactions of the central serotonergic system with the opioid system.

In a prospective, randomized, controlled study, 90 women with moderate to severe pruritus due to intrathecal morphine after cesarean section were given intravenous nalbuphine 2 mg, 3 mg, or 4 mg (25). Nalbuphine 2–3 mg relieved morphine-induced pruritus without increasing pain scores or causing other adverse effects.

Organs and Systems

Cardiovascular

Orthostatic hypotension can occur and is common after intravenous administration. Histamine release sometimes contributes to this.

Respiratory

Opioids cause respiratory depression by virtue of a direct effect on brain-stem respiratory centers (26). The nadir depends on the route of administration, and occurs at about 7 minutes after intravenous opioids, but not until about 30 minutes after intramuscular and 90 minutes after subcutaneous injection. The mechanisms of the respiratory effects of opioids (with special reference to their postoperative use) have been reviewed (SEDA-20, 76) (SEDA-21, 85). Pulmonary granulomatosis has occurred (27), and asthma after opioid inhalation has been described (28).

Nervous system

Opioids produce analgesia without loss of consciousness, although drowsiness, changes in mood, and mental clouding occur. Responses to painful stimuli are blocked at several locations in the brain, resulting in both an alteration in the sensation of pain and a change in the affective response. The ability of a patient to perceive pain can remain the same while tolerance to pain is markedly increased (29).

Opioids cause nausea and vomiting by stimulating the chemoreceptor trigger zone in the medulla, although tolerance to this effect usually develops within a few days (30).

Morphine and most opioids cause papillary constriction, which may be due to an excitatory action on the autonomic segment of the nucleus of the oculomotor nerve. Tolerance to this miotic effect is not usual.

Single therapeutic doses of opioids produce a shift toward increased voltage and lower frequencies in the encephalogram, such as occurs in natural sleep or after very low doses of barbiturates. High doses of morphine can cause sleep disturbances in some children (SEDA-17, 78).

Fentanyl and sufentanil can cause epileptiform activity in patients undergoing coronary artery bypass grafting (SEDA-18, 79).

Catatonia is a rare complication of prolonged epidural opioid administration in cancer pain (SEDA-16, 78). Patients with advanced cancer who were taking opioids had significant but transient cognitive impairment when opioid doses were increased (31). This correlates well with studies of the effects of psychotropic medications on ability to drive (32).

The neuropsychiatric syndrome that results from opioid toxicity consists of cognitive impairment, severe sedation, hallucinations, myoclonic seizures, and hyperalgesia (33). Opioid-induced neurotoxicity is most often seen in patients receiving high doses of opioids for prolonged periods, often in association with psychoactive medications (for example benzodiazepines and tricyclic antidepressants), and in older patients with associated dehydration and renal insufficiency. Strategies for reducing the occurrence of opioid-induced neurotoxicity primarily include opioid rotation and dosage reduction and circadian modulation techniques. Drugs such as amphetamines, amphetamine-like derivatives, and neuroleptic drugs like haloperidol can be used to treat hallucinations and delirium as a result of opioid-induced neurotoxicity and when the minimal dose of opioid that can cause sufficient analgesia also causes excess sedation. Proper assessment of the potential risk factors of opioid-induced neurotoxicity with careful monitoring of early signs is the fundamental principle in prevention.

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Opioids and hypnotic drugs are often used to prevent increased intracranial pressure and the subsequent reduction in cerebral perfusion pressure. However, it is still uncertain whether opioids can cause increased intracranial pressure. The effects of a bolus injection and infusion of sufentanil, alfentanil, and fentanyl on cerebral hemodynamics and electroencephalographic activity have been studied in a randomized crossover study in six patients with increased intracranial pressure after severe head trauma (34). All three infusions were associated with a significant increase in intracranial pressure (9, 8, and 5.5 mmHg respectively) 3–5 minutes after the bolus opioid injection. Intracranial pressure gradually fell and returned to baseline after 15 minutes. This increase was associated with significant falls in mean arterial pressure and cerebral perfusion pressure throughout the study period. The electroencephalogram changed from a fast to a reduced activity pattern, with an improvement in background activity. It is therefore advisable to avoid using bolus injections of opioids in patients with head injury and to use continuous infusion for sedation.

Endocrine

Morphine reduces the response of the hypothalamus to afferent stimulation (35). In many species, opioids alter the equilibrium point of the hypothalamic heat-regulatory mechanisms.

In patients undergoing surgery, opioids inhibit the stress-induced release of ACTH (36).

Secretion of luteinizing hormone (LH) and thyrotropin is suppressed by opioids, whereas the release of prolactin and, in some cases, growth hormone is enhanced (37).

Gastrointestinal

Opioids reduce the secretion of hydrochloric acid and have a marked effect on gastrointestinal motility. Gastric emptying is prolonged and the likelihood of esophageal reflux is increased (38). Tone in the antral part of the stomach and first part of the duodenum is increased. The passage of gastric contents through the duodenum can be delayed by as much as 12 hours, retarding the absorption of orally administered drugs (39). In 260 patients with malignant disease, 23–40% vomited and 8–10% felt nauseated (SEDA-17, 79). Transdermal hyoscine (scopolamine) can reduce these problems (SEDA-17, 79).

Biliary and pancreatic and intestinal secretions are reduced by morphine, and digestion in the small intestine is delayed.

Constipation is usual (SEDA-17, 79). The tone of the anal sphincter is increased and the usual reflex relaxation response to rectal distension is reduced.

Biliary tract

Therapeutic doses of opioids constrict the sphincter of Oddi, and biliary tract pressure rises ten-fold. Patients with biliary colic can have exacerbation of pain after morphine. Likewise, opioids such as fentanyl, morphine, and dextropropoxyphene can cause bile duct spasm (SEDA-21, 85).

"It is standard teaching that morphine should not be used to treat patients with pancreatitis because it causes a rise in biliary and pancreatic pressure" (40). From this starting point, this comprehensive review discusses current approaches to opioid analgesia in pancreatitis, pointing out that morphine has been reported to cause biliary colic in individuals without biliary tract disease and that pethidine (meperidine) has become the analgesic of choice. Constriction of the sphincter of Oddi and the basal tone of the sphincter and the frequency of phasic contractions have been measured using endoscopic retrograde cholangiopancreatography (ERCP); an increase in basal tone is believed to be the best indication of sphincter dysfunction. Morphine sulfate in intravenous doses of 2.5–5 micrograms/kg caused increased contractions but no change in basal pressure, while doses of 10 micrograms/kg and over caused a rise in basal pressure. Pethidine increased contractions but not basal tone, while tramadol had no effect on basal pressure in a small study. Among mixed opiate agonist/antagonists, pentazocine increased basal pressure. Buprenorphine, a partial opiate agonist, resulted in no pressure changes, while the antagonist naloxone 0.4 mg intravenously had no effect alone on the sphincter basal pressure and did not stop the increase in pressure caused by morphine. However, case reports have suggested that naloxone reduces sphincter spasm in clinical situations.

Urinary tract

The urinary voiding reflex is inhibited by opioids, and both the tone of the external sphincter and the volume of the bladder increase; urinary retention is therefore common.

Skin

Flushing of the face, neck, and upper thorax can follow therapeutic doses of opioids. These effects may be partly due to release of histamine, which is also implicated in the sweating and pruritus seen after opioid administration. Opioid effects on neurons may partly be involved in the pruritus, as pruritus is provoked by opioids that do not release histamine and is abolished by small doses of naloxone.

Urticaria at the site of injection is due to histamine release. It is seen with pethidine and morphine, but not with oxymorphone, methadone, fentanyl, or sufentanil. Wheal and flare responses to various opioids differ (41).

Sexual function

Although long-term administration of low-dose opioids, especially intrathecally, improves quality of life through improved pain control, it can compromise it by causing impaired sexual function. Low testosterone concentrations have been reported in heroin addicts (42) and subjects in a methadone maintenance program (43).

In prospective non-randomized non-blinded evaluation of the effects of a 12-week course of intrathecal opioids for the control of chronic non-cancer pain on the hypothalamic–pituitary–gonadal axis in 12 men, it was suppressed and serum testosterone concentrations fell (44). This effect not only reduces quality of life through sexual

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dysfunction but can also increase the risk of spinal osteoporosis in men, with an increased risk of vertebral and hip fractures. Patients receiving long-term intrathecal opioid therapy need to be informed of potential hypothalamic–pituitary–gonadal axis suppression as a result of the treatment, and testosterone replacement after hypothalamic–pituitary–gonadal axis surveillance during treatment should be considered if indicated.

Death

Opiates are widely used all over the world, but recently concerns about opiate use (and deaths from such use) have increased in Australia and the UK (45). The rate of opiate overdose deaths in these countries increased dramatically between 1985 and 1995. Throughout that period, it was four to ten times higher in Australia than the UK, but the rate of increase may have been greater in the UK in the latter half of the period, since the difference in rate narrowed substantially during that time. Methadone maintenance treatment, established in Australia in 1969 and in the UK in 1970, has become the main treatment for opiate dependence in both countries. About half of the opiate deaths in the UK were attributed at least in part to methadone. By contrast, considerably fewer (18%) opiate overdose deaths in Australia were attributed to methadone. The authors suggested that the discrepancy in the rates between the two countries could be artefacts of the differences in (a) the documentation of these deaths, (b) the rate of opiate dependence, (c) the route of opiate administration, (d) opiate purity, and, most importantly, (e) the method of delivery of methadone maintenance treatment.

Methadone-related fatalities have been reported from all countries in which methadone has been used for either detoxification or maintenance treatment of opiate users. These fatalities are often defined as cases of poisoning due to methadone or as polydrug intoxication with methadone as the leading cause of death. Methadone maintenance treatment was introduced in Germany in 1989, and 1396 drug-related deaths were reported from 1990 to 1999 in Hamburg (46). While the absolute numbers of drug-related deaths by poisoning did not change over this period, the rise in methadone-associated deaths paralleled a fall in the number of heroin-associated deaths. From 1990 to 1998, the rate of monovalent heroin intoxication in cases of poisoning fell from 60% to 11%, while the rate of polydrug intoxication increased. Poisoning caused by methadone combined with other substances first gained significance 4 years after methadone maintenance treatment was introduced in Hamburg. Since 1994, methadone-related deaths have increased steadily, and by 1997–1998 the numbers had increased exponentially. In the first 6 months of 1999, 60% of all cases of poisoning among drug addicts showed the presence of methadone. When strict guidelines for describing such poisonings were used, 39 poisonings in 1998 (40%) were predominantly caused by methadone, six of them being monovalent methadone intoxication. About two-thirds of all methadone-related poisonings concerned drug addicts who never stayed in methadone maintenance treatment, implying that they obtained methadone from outside of regular treatment. Almost 10 years after the introduction of methadone maintenance treatment in Hamburg, methadone replaced heroin as the leading cause of death due to poisoning. At the same time, however, the absolute number of drug-related deaths and poisonings fell slightly. While methadone maintenance treatment has clearly reduced overall morbidity and mortality in addicts globally, some issues remain unresolved. There are significant differences in the delivery of methadone maintenance treatment from one country to another. The authors reported that in some patients the starting doses of methadone are quite high and potentially lethal. This is especially so when the patients are also using other drugs and attempting to wean off them. Thus, continued polydrug use in treatment is an important risk factor for mortality. Many patients receive take-home doses for a week at a time. While this is useful in a select group of patients, it is not useful in those who sell methadone to buy heroin and combine the two drugs without knowledge of their half-lives and potential complications. The authors suggested changes in methadone maintenance treatment policy, in order to reduce the chances of accidental overdose/poisoning. Specifically, they recommended: a substantial improvement in quality assurance; a more restrictive methadone take-home policy (at least for patients with evidence for concomitant opiate use); and evaluating heroin or long-acting acetylmethadol as alternatives.

Another report from Australia reviewed all the accidental illicit drug deaths that occurred in the Sydney area in 1995–1997 (47). There were 3559 autopsies, of which 4% were considered accidental illicit drug deaths; of these deaths, 121 were men and 22 were women. While the highest number of male deaths occurred in the 25–35 year age group, female deaths were evenly spread from ages 20–35. Almost half (49%) of the deaths occurred from morphine poisoning, 27% from multiple drug toxicity, and 21% from heroin toxicity combined with alcohol. Methadone was detected in 19 cases (13%); 12 of these people were enrolled in a methadone maintenance program. Methadone intoxication alone was responsible for two deaths (1%) only. Methadone was present in the blood in a potentially fatal concentration in 13 cases, while 113 people (80%) had a heroin concentration in the fatal range and 91% had detectable concentrations of heroin. There were no significant neurological findings in the 143 cases studied. More than 50% of those with methadone detected also had heroin in their blood. Unfortunately, this appears to show that some people who participate in a methadone program may still die from accidental heroin overdose. Thus, the authors emphasized the importance of education of heroin users about the risk of accidental overdose.

There is excess mortality in heroin users compared with the general population. The prevalence and experience of heroin overdose in drug users in a general practice in Ireland were examined during 5 months (48). Of the 33 patients identified, 24 agreed to participate. They had had their first overdose on average 5 years after starting to use heroin. Ten had taken an overdose themselves, 23 had witnessed an overdose, 22 knew a victim of fatal overdose, and 4 had been present at a fatal overdose. However, they reported poor understanding of how to deal with an overdose. Despite maintenance treatment

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with methadone, a significant proportion continued to inject heroin; 17% admitted to the use of illicit methadone, but methadone was not implicated in overdose in any case. The authors suggested that overdose prevention and management should become a priority for general practitioners who care for opiate-dependent patients. Factors implicated in overdose include too high a dose, use after a period of abstinence, and mixing with other drugs.

Clostridium novyi type A, a bacterium that was associated with serious infection during the two World Wars, killed 35 injecting heroin users in Britain and Ireland (49). *Clostridium novyi* type A is present in soil and dust and is a well-recognized cause of infection in sheep, cattle, and other animals. Contaminated batches of heroin from a common source were believed to be responsible for the recent outbreak. The bacteria were able to survive the process of preparation for injection. All recent cases occurred after intramuscular injection, which provides the requisite anerobic conditions for infection. This was the first time that this organism caused an outbreak of infection in drug injectors. In all, 74 cases with the same clinical features were reported.

An increase in the number of deaths of all body packers in New York has been associated with an increase in deaths among opiate body packers: of 50 deaths among body packers from 1990 to 2001, 42 were due to opiates (50). Four were related to cocaine and four to both opiates and cocaine. In 37 cases, open or leaking drug packets in the gastrointestinal tract resulted in acute intoxication and death. Five cases involved intestinal obstruction or perforation, one a gunshot wound, one an intracerebral hemorrhage due to hypertensive disease, and one was undetermined. The number of packets recovered was 1–111 (average 46).

An unbound morphine blood concentration of 100 ng/ml or more is considered potentially fatal. However, fatal cases of heroin intoxication occur in patients with blood morphine concentrations below 100 ng/ml. In 62 cases of heroin intoxication, death was associated with unbound morphine heart blood concentrations below 100 ng/ml in 21 cases and 100 ng/ml or over in 41 cases (51). In the 21 with low concentrations, respiratory tract infections occurred more often, and plausible causes of death were identified in 19.

Long-Term Effects

Drug tolerance

The clinical significance of opioid tolerance has been extensively reviewed (4) and the evidence for tolerance in acute and prolonged opioid administration has been presented. The former remains controversial while the latter has been adequately demonstrated. Different patterns of opioid use in chronic cancer-related pain are described, these being essentially escalating prescribing, steady-dose prescribing, and opioid withdrawal. The particular pattern followed by any individual is the result of the balance between physical changes in the level of nociceptive activity, psychological processes, such as increased anxiety and depression, and the degree of tolerance itself. While tolerance to an opiate reduces its clinical effectiveness, the tolerance may be beneficial if it mitigates drug adverse effects. Tolerance to respiratory depression and nausea occurs swiftly, sedation takes longer to resolve, and constipation is relatively resistant to the development of tolerance. Cross-tolerance is partial; hence switching from one opioid to another can relieve particular adverse effects without loss of clinical effect.

Physical dependence on opioids appears to occur in patients who use opioids for long-term pain relief, and cases of addiction have been reported. However, rates of addiction are low and occur mainly in individuals who have a history of substance misuse. The role of long-term opioid medication in non-cancer-related chronic pain remains controversial. "Opiophobia," a fear of the legitimate use of opioid analgesics because of the potential for addiction, remains a significant issue for physicians, patients, and relatives alike. The review is illustrated with a report of a 52-year-old man with multiple myeloma who displayed tolerance to oral morphine over 2 years.

Opioid tolerance in neonates

Tolerance to opioids in neonates has been reviewed (52). There are two forms of neonatal opioid exposure. First, in-utero exposure to opioids of neonates with opiate-addicted mothers; secondly, preterm infants requiring prolonged support in intensive care when opioid administration is used to reduce the stress response. The adverse effects of opioids on neonates are similar to those described in adults (sedation, dysphoria, seizures, nausea and vomiting, urinary retention, reduced intestinal motility, biliary tract spasm, histamine release, and chest wall rigidity), but it has been proposed that differences in the densities of the different opioid receptor subtypes lead to an increased theoretical propensity for respiratory depression with given opioid doses compared with older people. However, clinical studies have not confirmed increased sensitivity to respiratory depression in neonates or young infants. Tolerance may occur more swiftly in neonates due to slower opioid metabolism and a more permeable blood–brain barrier. Opioid withdrawal symptoms in neonates are similar to those for other age groups but can be mimicked by hypoxia, hypercarbia, hypoglycemia, hypocalcemia, or hypomagnesemia. Assessment of tolerance and withdrawal is made using the neonatal abstinence score rating scale and the neonatal withdrawal index.

Management of neonatal opioid withdrawal relies on gradually reducing doses of opioids to reduce the severity of withdrawal symptoms. Paregoric was formerly used as a withdrawal aid but is little used now owing to toxic effects. Tincture of opium (10% solution), consisting of 1 ml in 24 ml of sterile water, 0.05 ml/kg 4-hourly is proposed as the most suitable replacement. Speed of reduction depends on the length of neonatal exposure to opioids and a short reducing regimen (over 2–3 days) can be sufficient. A methadone replacement withdrawal regimen is also discussed, while benzodiazepines, phenobarbital, chlorpromazine, and clonidine are all reviewed as having a potential role in symptomatic relief during withdrawal; however, each has its own associated adverse effects, which limit their usefulness.

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Mechanism

At micromolar concentrations opioids cause an increase in the cell membrane threshold, shortened action potentials, and inhibition of neurotransmitter release. At nanomolar concentrations opioid agonists are excitatory and prolong the action potential via the stimulatory G proteins, which act on the adenylate cyclase/cAMP system and on protein kinase A-dependent ion channels. Tolerance is proposed to be the result of an increase in the association of opioid receptors to stimulatory G proteins, to an activation of *N*-methyl-D-aspartate receptors via protein kinase C, and calmodulin-dependent increases in cytosolic calcium, resulting in cellular hyperexcitability.

Drug withdrawal

Chronic administration of opioids produces physical and psychological dependence. A characteristic withdrawal syndrome occurs when the opioid is stopped abruptly or an opioid antagonist is given. In the case of morphine and other OP_3 receptor agonists with a similar duration of action, lacrimation, rhinorrhea, yawning, and sweating occur about 8–12 hours after the last dose. Symptoms peak at about 24–48 hours after withdrawal, with restlessness, irritability, and insomnia, as well as severe sneezing, weakness, anxiety, and depression. Other symptoms include dilated pupils, anorexia, piloerection, nausea, vomiting, diarrhea, pyrexia, hypertension, muscle cramps, dehydration, and weight loss (53).

Treatment of opioid withdrawal

Various regimens were used in the past in an attempt to withdraw patients from opioid addiction (54). The modern scientific basis for the evaluation of opioid withdrawal regimens was established by Kolb and Himmelsbach (55), who concluded that the methods that produced the least discomfort and the best results were either abrupt or rapid withdrawal of the opioid. Rapid withdrawal consisted of gradually reducing doses of morphine over 4–10 days. Such methods were in regular use until the advent of methadone as a heroin substitute in the 1950s.

Antidepressant, anxiolytic, and neuroleptic drugs can allow some patients to participate in treatment programs, especially when drug abuse is associated with psychiatric disorders such as depression, chronic anxiety, or schizophrenia.

Methadone

A widely used technique, pioneered by Isbell and Vogel (56), involves the substitution of methadone for the illicit opioid, followed by a gradual reduction in the amount of methadone taken. Methadone is used to substitute for a variety of opioid drugs. It is well absorbed after oral ingestion, with peak blood concentrations after about 4 hours. Steady-state concentrations are reached after about 5 days. By virtue of its long duration of action (the half-life with regular dosing is about 22 hours), methadone suppresses opioid withdrawal symptoms for 24–36 hours. In the early stages of treatment, patients may report problems such as drowsiness, insomnia, nausea, euphoria, difficulty in micturition, and excessive sweating. With the exception of chronic constipation and excessive sweating, these effects do not generally persist.

British studies have shown that, using methadone, about 80% of inpatients but only 17% of outpatients were successfully withdrawn (57,58). However, the technique is not without problems, one being that the methadone reduces but does not eliminate withdrawal symptoms. The withdrawal response has been described as being akin to a mild case of influenza, objectively mild but subjectively severe (59). The fear of withdrawal symptoms expressed by those dependent on drugs should not be underestimated: these factors are associated with the subsequent severity of withdrawal symptoms, and they are more closely related to symptom severity than drug dosage (60). Methadone substitution can result in a protracted withdrawal response, with patients still experiencing significantly more symptoms than controls 2 weeks after withdrawal (61).

In a study of methadone withdrawal, patients who were withdrawn over 10 days had a withdrawal syndrome that began to increase in severity from day 3, with peak severity of symptoms on day 13; in those who were withdrawn over 21 days, symptoms began to increase about day 10 with a peak on day 20 and abated thereafter, although some patients did not recover fully until 40 days after starting withdrawal (62). Thus, the duration of the withdrawal syndrome is much the same for both treatments in terms of symptom severity. It is possible that an exponential rather than a linear reduction in dosage may improve the withdrawal response. These results may be of clinical significance, in that patients may feel it important that they recover from withdrawal as quickly as possible, in order to participate fully in other aspects of drug withdrawal programs. However, although there was no difference between the 10-day and the 21-day programs regarding completion rates for detoxification (70 and 79% respectively), the dropout rates after detoxification were significantly different. During the 10 days after the last dose of methadone, the dropout rate in the 21-day group was 18% compared with 30% in the 10-day group. These results may also have financial implications in respect of the number of subjects who can be admitted to treatment programs.

In some treatment programs total abstinence is not considered to be a practical objective and treatment may involve the use of drugs such as methadone as maintenance therapy with the expectation of reducing illicit drug consumption (63). Well-organized methadone maintenance treatment can reduce the intake of illicit opioids in many injecting drug users (64,65).

The methadone maintenance treatment was established in 1964 in New York City by Vincent Dole and Marie Nyswander (see the monograph on Methadone). In the initial studies, subjects who were heavily addicted to heroin were evaluated and stabilized on daily methadone doses as inpatients before transfer to an outpatient clinic for continued treatment. With further experience, it was feasible to drop the inpatient phase.

Outcome studies of methadone maintenance treatment have reported favorable results, with high rates of patient retention, reduced criminality, and improved social rehabilitation. However, despite its proved effectiveness, it remains a controversial approach among substance abuse treatment providers, public officials, policy makers, the medical profession, and the public at large.

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Nevertheless, almost every nation with a significant narcotic addiction problem has established a methadone maintenance treatment program.

For patients entering treatment from an institution where they have been drug-free, initial daily methadone doses should be no more than 20 mg. Otherwise initial daily doses of 30–40 mg should be sufficient to obtain the necessary balance between withdrawal and narcotic symptoms. Thereafter, stabilization is achieved by gradually increasing the dose. When methadone is given in adequate oral doses (usually 60 mg/day or more), a single dose in a stabilized patient lasts 24–36 hours, without creating euphoria and sedation. Tolerance to methadone seems to remain steady, and patients can be maintained on the same dose, in some cases for more than 20 years.

The methadone dose must be determined individually, because of individual variability in pharmacokinetics and pharmacodynamics. Maintenance of appropriate methadone blood concentrations is recommended.

Tolerance to the narcotic properties of methadone develops within 4–6 weeks, but tolerance to the autonomic effects (for example constipation and sweating) develops more slowly.

The major adverse effects during treatment occur during the initial stabilization phase. In addition to constipation and sweating, the most frequently reported adverse effects are transient skin rash, weight gain, and fluid retention. Since the main metabolic pathway of methadone is CYP3A4 numerous drug interactions can be expected. Drugs that interact with methadone and other opioid analgesics are listed in Table 2.

Methadone maintenance treatment is considered to be a medically safe treatment with relatively few and minimal adverse effects. However the danger of serious adverse effects and death with the increasing use of methadone as maintenance therapy in drug addicts has been highlighted. It must be emphasized that a daily maintenance dose of 50–100 mg is toxic in a non-tolerant adult, and as little as 10 mg can be fatal in a child. There is an increasing number of reports of the deaths of children of mothers on maintenance therapy from inadvertent ingestion.

Clonidine

Clonidine appears to ameliorate the opioid withdrawal syndrome by reducing central noradrenergic activity. It has been hypothesized that the opioid withdrawal syndrome is due to increased noradrenergic neuronal activity in areas such as the locus ceruleus, which are regulated by both opioid receptors and α_2-adrenoceptors (66). Opioids and clonidine both act at the locus ceruleus, reducing central noradrenergic function. This common pathway hypothesis is supported by the similarity of clonidine and opioid withdrawal in respect to their effects on vital signs, mood, and noradrenergic hyperactivity (67). Since the actions of clonidine are mediated by α-adrenoceptors they are not antagonized by opioid antagonists.

There have been many reports of the use of clonidine in the treatment of acute opioid withdrawal (68). A dose of 500 micrograms/day for 10 days reduced but did not completely abolish withdrawal symptoms in 50 patients dependent on methadone or heroin. The patients still complained of sluggishness, insomnia, and bone pain, but there were none of the usual complaints associated with opioid withdrawal, such as anxiety, abdominal cramps, chills, muscle spasms, irritability, and anger.

Others have reported good results from the use of clonidine (69,70). Of 25 inpatients physically dependent on methadone, 20 were able to withdraw completely from methadone at the end of 2 weeks. In most patients, 10–11 days of clonidine, in a peak dose of 16 micrograms/kg/day, produced a perceived reduction in symptoms compared with previous attempts to become opioid-free. In these dosages, clonidine significantly reduced standing blood pressure without producing clinical problems.

Table 2 Drug interactions involving opioid analgesics

Object drug	Precipitant drug	Clinical consequences	Proposed mechanism(s)
Carbamazepine	Dextropropoxyphene	Increased effect of carbamazepine	Reduced metabolism
Codeine	Quinidine	Reduced analgesic effect	Reduced liver metabolism of codeine to morphine
Dextropropoxyphene	Ethanol	Increased effect of dextropropoxyphene	Reduced metabolism
Methadone	Carbamazepine	Reduced effect of methadone	Increased metabolism
Methadone	Cimetidine	Increased effect of methadone	Reduced metabolism
Methadone	Phenobarbital	Reduced effect of methadone	Increased metabolism
Methadone	Fluvoxamine	Increased effect of methadone	Reduced metabolism
Methadone	Phenytoin	Reduced effect of methadone	Increased metabolism
Methadone	Rifampicin	Reduced effect of methadone	Increased metabolism
Morphine	Cimetidine	Increased effect of morphine	Reduced metabolism
Morphine	Amitriptyline	Increased effect of morphine	Increased systemic availability
Morphine	Clomipramine	Increased effect of morphine	Increased systemic availability
Nortriptyline	Dextropropoxyphene	Increased effect of nortriptyline	Reduced metabolism
Pethidine	Cimetidine	Increased effect of pethidine	Reduced metabolism
Pethidine	Chlorpromazine	Increased toxicity of pethidine	Altered metabolism
Pethidine	Moclobemide	Increased effect of pethidine	Serotonin syndrome reported
Pethidine	Selegiline	Increased effect of pethidine	Serotonin syndrome reported
Phenobarbital	Dextropropoxyphene	Increased effect of phenobarbital	Reduced metabolism
Phenytoin	Dextropropoxyphene	Increased effect of phenytoin	Reduced metabolism

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Withdrawal symptoms of anxiety, restlessness, insomnia, and muscle aching were still evident.

In a randomized double-blind, placebo-controlled comparison of clonidine with a reducing dose of methadone, there was no difference in success rate: 42% abstinence with clonidine and 39% with methadone (71). However, patients who received clonidine had more self-rated withdrawal symptoms and a higher percentage of days on which symptoms were severe.

Clonidine has been reported to reduce both diastolic and systolic blood pressure by 10–15 mmHg during treatment for opioid withdrawal. Sedation and insomnia have also been noted. However, it is often difficult to distinguish which symptoms are due to the treatment and which are caused by opioid withdrawal. In a comparison of clonidine and methadone, seven of 14 patients in the clonidine group were withdrawn from the study because they had unacceptable adverse effects, compared with one of 11 in the methadone group. Two of those taking clonidine had severe immediate adverse effects that prevented them from continuing beyond 2 days (72).

One of the limitations of clonidine treatment is that it does not appear to reduce the duration of the opioid withdrawal syndrome. In one study, 10 days of clonidine therapy were required to suppress the symptoms of opioid withdrawal from long-acting opioids such as methadone (70).

The effect of clonidine in the management of opioid-dependent individuals undergoing gradual methadone detoxification over 14 days has been studied (73). In those who completed the course, clonidine did not significantly reduce either the symptoms or objective signs of opioid withdrawal. There was a substantial dropout rate, and several subjects were withdrawn from the study because of symptoms related to hypotension. In those who completed detoxification, clonidine did not reduce either the symptoms or the signs of opioid withdrawal. Clonidine therefore seems to have no place as an adjunct to a program of gradual methadone detoxification.

Clonidine plus an opioid antagonist

In a double-blind study using titrated doses of clonidine and naltrexone, combined clonidine and naltrexone treatment allowed 38 out of 40 patients physically dependent on methadone to withdraw completely in 4–5 days (74). For most patients naltrexone was gradually increased from 1 to 50 mg/day over 4 days. The dose of clonidine was 200–600 micrograms every 4 hours. After the first 48 hours the dose was rapidly tapered without recurrence of withdrawal symptoms. Flurazepam was used for night sedation. Although clonidine reduced the intensity of naltrexone-induced withdrawal symptoms, it did not eliminate them completely. On the first day after withdrawal of methadone and initiation of naltrexone and clonidine the frequencies of craving, anxiety, restlessness, insomnia, muscular aching, anorexia, hot and cold flushes, and diarrhea were significantly higher than whilst taking methadone. However, after 4 days of naltrexone, the patients were considerably less symptomatic. Compared with their feelings whilst taking methadone, they complained of significant increases in irritability, unpleasantness, and lethargy during the first 3 days.

The combined use of clonidine and naltrexone appears to allow successful withdrawal from long-term methadone therapy within 4–5 days of its abrupt withdrawal. Although patient selection may be an important consideration, the apparent success rate compares favorably with other methods and is achieved in a much shorter time (70).

Buprenorphine

In a study designed to assess the safety of buprenorphine for the treatment of cocaine and opiate dependence there were no adverse effects or serious interactions with a single dose of intravenous morphine or cocaine during daily maintenance on buprenorphine (SEDA-18, 85).

Second-Generation Effects

Pregnancy

A major review of the problems of drug dependence in pregnancy and the clinical management of mother and child was published in 1979, and its findings remain valid today (SED-11, 138) (75).

Opioids taken in pregnancy by a drug-dependent mother, or administered to the parturient, can cause respiratory depression in the newborn. Abstinence symptoms have been reported in the infants of mothers who are opioid-dependent at term (76).

The adverse consequences for the neonate of drug abuse in pregnancy can be dramatically reduced by comprehensive medical and psychosocial care for the mothers during pregnancy and delivery (SED-11, 138) (77,78). However, without due care during pregnancy problems are likely.

The long-term consequences of maternal opioid dependency on the child have been examined in detail in 89 infants born to mothers addicted to heroin, morphine, and methadone (SED-11, 138) (79); 20% were preterm and 31% were light for gestational age; 85% of the infants had withdrawal symptoms and 12% had convulsions. The somatic and neurobehavioral findings in children in their first 18 months of life, born to methadone-maintained mothers and to a matched drug-free comparison group of mothers, have been reported (SED-11, 138) (80). At 18 months the methadone children had: (a) a significantly higher incidence of otitis media; (b) a significant incidence of head circumference below the third percentile; (c) neurological findings of tone discrepancies, developmental delays, and poor motor co-ordination; (d) a high incidence of abnormal eye findings; and (e) significantly lower scores on the Bayley mental and motor developmental indices. In a study of 72 such children investigated 1–10 years after birth, only 25% were physically, mentally, and behaviorally normal (79).

In 41 children born to methadone-maintained mothers and 23 children from matched controls at 6 months of age, there was delayed motor development in methadone-exposed infants and greater vulnerability of males to adverse environmental conditions; in adult male rats there was a correlation between early methadone exposure and behavioral abnormalities (SED-11, 138) (81).

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Opioid analgesia during the first stage of labor

The 50% and 95% effective doses (ED_{50} and ED_{95}) of intrathecal sufentanil for analgesia in labor have been characterized in several studies (82,83). The same criteria have been applied to fentanyl in 90 women in active early labor (at least 5 cm dilatation), who received a range of doses of intrathecal fentanyl (5–25 micrograms) in a double-blind, randomized study (84). Fentanyl induced rapid and effective dose-dependent analgesia in early labor. Pruritus occurred in 66% of patients and falls in ventilation were dose-related. The ED_{50} and ED_{95} values were 5.5 and 17.4 micrograms respectively.

In 60 women who requested epidural analgesia during labor randomized to sufentanil 10 micrograms, fentanyl 10 μg, or saline in addition to intrathecal bupivacaine 2.5 mg, the combination of sufentanil plus bupivacaine gave a significantly longer duration of analgesia (85). Pruritus was more common in women given sufentanil (80%) and fentanyl (47%) than in those given plain bupivacaine. However, there were no differences in the incidences of gastrointestinal effects, hypotension, or motor blockade between the groups. Adding sufentanil 10 micrograms to intrathecal bupivacaine 2.5 mg provided fast onset, better analgesia for a longer duration than the other treatments.

In another similar study, the adverse effects profile, especially in regard to pruritus, improved if intrathecal sufentanil 2.5 micrograms was added to bupivacaine 1.25 mg and adrenaline 2.5 micrograms, without compromising analgesia in women in the first stage of labor (86).

In 30 women randomized to receive either sufentanil 7.5 micrograms plus bupivacaine 2.5 micrograms, with or without clonidine 50 micrograms, using a combined spinal-epidural technique, analgesia was prolonged in those given clonidine without an increased incidence of adverse effects or worse pain scores (87).

In a prospective, randomized, double-blind comparison of nalbuphine with pethidine in 310 women requiring analgesia during labor, nalbuphine produced a lower incidence of nausea and vomiting (88). There were no differences between the two groups in the other adverse effects of the opioids, and nalbuphine did not afford major analgesic benefits.

Use of opioids in cesarean section

The use of intrathecal or epidural opioids has been recommended for the relief of pain after cesarean section, and there have been several comparisons of intrathecal and epidural opioid use.

In 50 women randomized to intrathecal diamorphine 0.25 mg or epidural diamorphine 5 mg in addition to intrathecal bupivacaine 10 mg, there was no significant difference in the duration or quality of analgesia (89). The incidence of nausea and vomiting was higher in the epidural group (24 versus 4%). There was no difference in the incidence of pruritus, but the incidence was as high as 88% of patients, and it was severe enough to require treatment in 20%.

In a double-blind, randomized study, 55 women undergoing elective cesarean section were allocated to either epidural diamorphine 3 mg or intrathecal morphine 0.2 mg (90). There were no significant differences between the two groups in pain assessed by visual analogue scale or in the incidence of pruritus, sedation, or respiratory depression measured by pulse oximetry during the 28-hour postoperative period. Nausea and vomiting were significantly more common in the intrathecal morphine group (73 versus 41%).

Patient-controlled analgesia with epidural pethidine or a single bolus of epidural morphine 4 mg during the 24 hours after cesarean section has been studied in 78 women (91). There were no differences in the degree of analgesia or opioid adverse effects profiles.

In 66 cesarean section patients the effects of sufentanil (2 micrograms/ml), tramadol (10 mg/ml), or a mixture of the two were compared using patient-controlled extradural analgesia (92). Nausea and vomiting were closely related to the use of tramadol, while pruritus was associated with sufentanil. The combined regimen reduced the dosage requirements of both opioids by 20%. Extradural tramadol cannot be recommended, because of the increased incidence of severe gastrointestinal adverse effects, the high dose required, and inferior analgesia.

Patient-controlled epidural fentanyl (20 micrograms with 10 minute lock-out) has been compared with patient-controlled intravenous morphine (1 mg with a 5-minute lock-out) in 48 women after cesarean section (93). Fentanyl was more efficacious in controlling postoperative pain, with a lower incidence of nausea and drowsiness.

Finally, 60 women undergoing cesarean section were randomly given epidural tramadol 100 mg, epidural tramadol 200 mg, or saline (94). Pain scores and adverse effects were evaluated for 24 hours after surgery. In all three groups there were no opioid-related adverse effects and epidural tramadol 100 mg provided adequate postoperative analgesia.

Fetotoxicity

The pharmacokinetics and effects of various systemically administered analgesics on the uterus, fetus, and neonate have been reviewed (SED-11, 137). Fetal bradycardia lasting up to 7 minutes was reported in 53 of 1910 fetuses (2.7%) after the administration of pethidine (meperidine) 75 mg and promethazine 25 mg intravenously to the mothers during labor (SED-11, 137) (95).

The relation between maternal morphine administration during labor and the Apgar score of the baby at birth has been studied (SED-11, 137) (96). The authors concluded that morphine alone did not seem to cause asphyxia at birth, but that morphine together with other fetal and/or obstetric factors would definitely be a cause for concern with regard to birth asphyxia.

The effect of maternal analgesia on neonatal behavior has been assessed (SED-11, 137) (97). The authors suggested that neonates respond to pethidine in the same way as adults, but the changes observed were relatively subtle, and comparison of these infants with a control group whose mothers had received no drugs showed no differences in behavior.

Opioid analgesia can cause prolonged reductions in the baseline variability of the fetus during monitoring in labor (SEDA-17, 85). This is thought to occur by a direct effect

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on the cardiac centers or fetal myocardium. The danger of this is the risk of misinterpretation of the cardiotocogram as being indicative of fetal distress.

Intramuscular tramadol (50 or 100 mg) during labor is associated with fewer adverse effects than pethidine 75 mg (SEDA-18, 83). Pethidine and the higher dose of tramadol had similar analgesic efficacy, but pethidine was associated with a significantly lower neonatal respiratory rate at birth.

Susceptibility Factors

Age

Neonates, infants, and children are at risk of adverse effects of opioids, owing to pharmacokinetic and pharmacodynamic changes (SEDA-17, 78). Routine use of pulse oximetry is recommended in all children receiving opioids (SEDA-21, 85).

Elderly patients are particularly at risk, as a number of other susceptibility factors can co-exist.

Renal disease

Renal insufficiency can result in clinically significant accumulation of pharmacologically active opioid metabolites and prolonged narcosis; such patients must be monitored for signs of toxicity (SEDA-17, 79) (SEDA-21, 85) (98,99). To date, this effect has only been reported with codeine, morphine, and pethidine. Dextropropoxyphene is not recommended in renal insufficiency, as its metabolite norpropoxyphene, which is eliminated by the kidneys, accumulates, causing cardiac depression (SEDA-17, 79) (SEDA-21, 85).

Other features of the patient

In patients with reduced respiratory reserve, such as those with emphysema, severe obesity, cor pulmonale, and kyphoscoliosis, opioids must be used with caution. The relative benefits and harms of using opioids in patients taking monoamine oxidase inhibitors, those with a history of drug abuse, asthma, hepatic impairment, hypotension, raised intracranial pressure, or head injury, and during pregnancy or breast feeding, should be carefully considered. Dextropropoxyphene, pethidine, and methadone should be used with caution (SEDA-21, 85).

Drug Administration

Drug administration route

Compared with conventional routes, spinal opioid administration carries potentially greater morbidity and can only be justified if it produces equal or superior pain relief compared with conventional methods, with fewer unwanted effects (SED-11, 139).

Although the analgesic effect of spinal opioids is largely due to a spinal effect, the opioid can spread rostrally to the brainstem and higher centers, and can cause delayed adverse effects. Lipid solubility affects the rate at which an opioid is absorbed into the spinal cord from the cerebrospinal fluid (CSF), and therefore predicts the likelihood of rostral spread. Hydrophilic drugs, such as morphine, will linger in the CSF and produce prolonged analgesia that may last 12 hours or more. Such drugs can float rostrally, producing more widespread but less intense analgesia. However, if the drug reaches opioid receptors in the respiratory center in the fourth ventricle, delayed respiratory depression can occur. In contrast to morphine, fentanyl is very lipid-soluble but short-acting; a single dose will produce intense highly segmental analgesia lasting 2–3 hours. These properties make it suitable for continuous epidural infusion.

When an opioid is used as the sole agent by the epidural or intrathecal route, the results are disappointing, because of unwanted adverse effects, such as pruritus, nausea, vomiting, respiratory depression, and effects on the neonate, caused by significant systemic absorption (SEDA-17, 85). Hypotension and changes in fetal heart rate are not uncommon (SEDA-21, 91). Combinations of opioids (alfentanil, fentanyl, morphine, sufentanil) with local anesthetics (for example bupivacaine) have therefore been suggested to yield better results (SEDA-18, 83).

The use of alfentanil with bupivacaine via continuous epidural infusion during labor resulted in a significant reduction in motor blockade compared with bupivacaine alone. There was no respiratory depression in the mothers, although shivering and pruritus were more frequent with alfentanil. There were no differences in the neonatal Apgar scores between the groups (SEDA-18, 83).

There has been a comparison of the effects of fentanyl and sufentanil, combined with bupivacaine and adrenaline, given by PCA after cesarean section (SEDA-18, 83). The numbers of requests were greater in the fentanyl group, but there was no difference between the groups with regard to sedation, pruritus, or nausea. However, those who received sufentanil had a significantly higher incidence of vomiting, light-headedness, and dizziness.

It is uncertain whether the addition of adrenaline to intrathecal sufentanil increases the duration of analgesia during labor. In one study, the addition of adrenaline to intrathecal sufentanil did not prolong the duration of analgesia, but reduced the incidence and severity of pruritus (SEDA-18, 83), whereas in another the addition of adrenaline or morphine to intrathecal sufentanil prolonged the duration of analgesia (SEDA-18, 83). However, those given morphine had significantly more nausea and pruritus.

In another comparison of a single dose of epidural morphine with PCA epidural fentanyl after cesarean section, pain relief and the incidence of nausea were similar, but pruritus was significantly less with fentanyl (SEDA-18, 83).

Epidural methadone and diamorphine are useful analgesics during cesarean section, but oxygen desaturation and nausea are more frequent with diamorphine (SEDA-18, 83).

Combined spinal-epidural administration achieves almost instantaneous analgesia with longer pain relief (100). This method gives a faster onset of analgesia and less motor blockade than standard epidural analgesia (101).

Intrathecal route

Technical problems after intrathecal opioids are rare, although catheter occlusion and leakage of CSF have been reported (SEDA-17, 85) (102–104). In 121 patients with

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mean follow-up of 68 days (maximum 13 months) there was an incidence of less than 10% (105).

Intrathecal opioids used in obstetrics are well tolerated by mother and child (SED-11, 139, 140) (106–108).

Morphine is the opioid most often chosen for intrathecal administration.

Respiratory

Respiratory depression occurs more often after intrathecal than after epidural opioid administration and can be more of a problem in old age or when there is pre-existing respiratory disease (SED-11, 139) (109,110). The time of onset is variable but usually occurs within 6–10 hours of the opioid injection, although delays of up to 11 hours have been reported (111). There have been two cases of prolonged respiratory depression lasting 18 hours after single doses of 3 and 5 mg (111). Repeated doses of naloxone were required, but each incremental dose did not alter the level of analgesia.

It has been suggested that opioid-naive patients may be more susceptible to respiratory depression and that posture may also be important (SED-11, 139) (112).

Return of normal respiration can take up to 23 hours. Peak expiratory flow rate (PEFR) was significantly better in patients who had received intrathecal rather than intravenous morphine after cardiac surgery, but mean $PaCO_2$ was significantly higher in patients given intrathecal morphine 2 mg, rather than intrathecal or intravenous morphine 1 mg (113). The effect was dose-dependent (114).

Nervous system

Central adverse effects are as expected; with the exception of constipation, urinary retention, and respiratory depression, these effects tend to be transient and disappear within a few days of starting therapy.

Drowsiness, miosis, and respiratory depression have been reported after intracerebroventricular administration of morphine in two of 55 patients who received morphine 1–1.5 mg (115). A third patient developed visual hallucinations and behavioral disorders after 1 mg. All effects were rapidly reversed by naloxone.

Myoclonic spasms of the legs have been described after intrathecal morphine, and were abolished by intrathecal bupivacaine (116).

Hyperalgesia and myoclonus were reported after high-dose intrathecal morphine (SEDA-17, 87).

Temporary, totally reversible motor and sensory paralysis has been reported after intrathecal morphine 1.6 mg and was attributed not to a direct spinal action of morphine but to cardiovascular changes occurring as a result of pain relief (117).

Gastrointestinal

There is a high incidence of nausea and vomiting with intrathecal diamorphine, which may not be dose-related (118). Two studies have suggested that the incidence of nausea and vomiting in labor is higher with intrathecal than with epidural opioids (119,120).

Urinary tract

Urinary retention has been described in one of a series of patients who had been given pentazocine 5 mg intrathecally (121); others have since reported similar findings.

Skin

Pruritus is a frequent adverse effect after intrathecal administration, with an incidence of one-third with buprenorphine (122) and diamorphine (123) and over 70% for both diamorphine and morphine (124,125). In one study the incidence of pruritus was higher with morphine than with methadone; analgesia was also superior (124). Pruritus has also been reported with intrathecal pethidine (meperidine). Treatment was not reported to be necessary. This effect is not reported to occur after intrathecal beta-endorphin (126,127). The mechanism of pruritus is not well understood and has been attributed to a disturbance of thiamine metabolism (128) and to a disturbance of afferent input at supraspinal as well as at spinal receptor sites (129).

Infection risk

Reactivation of *Herpes simplex* infection after epidural administration of opioids is well known. However, there have been reports of reactivation of *Herpes simplex* after intrathecal morphine for cesarean section (SEDA-17, 87) (SEDA-18, 84).

Susceptibility factors

Knowledge of the use of spinal opioids in children is limited, but adverse effects are similar to those reported in adults (SEDA-18, 85) (130–132). Dysphoria has also been reported, but attributed to systemic absorption (132).

Epidural route

The adverse effects reported with epidural administration are similar to those reported with the intrathecal route. Again, old age and respiratory disease probably dispose to respiratory depression (133). As can be predicted from pharmacokinetic considerations, delayed respiratory depression is more common with epidural morphine than with fentanyl (134).

Epidural administration of opioids has been reviewed (SEDA-21, 92). Morphine causes less respiratory depression and provides better analgesia when it is given by continuous infusion than by intermittent bolus. The authors concluded that epidural fentanyl offers no advantage over the intravenous route and that the mechanism of analgesia is by a systemic effect due to the vascular absorption of this lipophilic drug. However, the administration of lipophilic opioids together with a local anesthetic offers the advantage of using lower doses of both drugs, giving comparable analgesia with a reduction in adverse effects.

Patient-controlled epidural analgesia (PCEA) with fentanyl gives superior analgesia and reduces opioid doses, but without a reduction in adverse effects. However, PCEA with sufentanil offers no advantage (SEDA-19, 87).

Studies of the use of the partial opioid agonist butorphanol to reduce the adverse effects of epidural morphine have not provided evidence of benefit (SEDA-19, 86). Epidural meptazinol has been described as being well tolerated (135).

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Respiratory

Respiratory depression occurs less often after epidural than intrathecal opioid administration (109,110). It has been suggested that older patients and those with increased intrathoracic or intra-abdominal pressure are particularly at risk and require reduced dosages (133). In a retrospective study, in which over 6000 patients received epidural morphine, 220 epidural pethidine, and 90 intrathecal morphine, respiratory depression requiring naloxone occurred in about 0.33% after epidural morphine and 5.5% after intrathecal morphine (110). Only two of the patients who received epidural morphine had respiratory depression later than 6 hours after the last dose of opioid. Only three of the 22 patients who had respiratory depression after epidural morphine had not received opioids in addition to epidural morphine during or after the operation. Ten were over 70 years old and 10 had thoracic injections. In another study of 2000 women who received 9000 doses of epidural pethidine 50 mg there was only one case of respiratory depression; this was due to migration of the catheter into the subarachnoid space (136).

The time taken for diffusion of poorly lipid-soluble opioids, such as morphine, from the lumbar subarachnoid space to the fourth ventricle is the most likely explanation for the delayed onset of respiratory depression. It has been suggested that the frequency of respiratory depression can be influenced by the position of the patient and the form of administration, as well as by the dosage of the opioid and the volume of the solution (112).

Doxapram has been used to treat respiratory depression after epidural morphine (137). However, the patient still required endotracheal intubation and mechanical ventilation to correct severe hypercapnia.

Markedly lipid-soluble opioids have also been reported to cause respiratory depression. There was profound respiratory depression 100 minutes after the administration of fentanyl 100 micrograms epidurally (138), whilst epidural sufentanil caused apnea within a couple of minutes, reversed by nalbuphine (139). Epidural buprenorphine 150 micrograms produced prolonged time-dependent biphasic depression of carbon dioxide response in six healthy volunteers. The second maximum occurred at 8–10 hours after injection (140). Similar cases have been reported by others.

Respiratory depression occurred 3.5 hours after a 2.5-year-old child had been given a caudal epidural of 100 micrograms/kg of morphine (141). The effects were successfully reversed by intravenous naloxone.

The efficacy of up to two doses of epidural hydromorphine 1.5 mg has been evaluated in 10 women after cesarean section (142). The mean duration of analgesia was 19.3 hours. Adverse effects were pruritus (56–70%), nausea (11–20%), and vomiting (less than 10%). There was a significant increase in venous PCO_2 3 hours after the second dose of hydromorphine. There was no delayed respiratory depression.

Extradural diamorphine 5 mg, extradural phenoperidine 2 mg, and intramuscular diamorphine 5 mg have been compared (143). Extradural diamorphine produced more prolonged and intense analgesia and there were no serious adverse effects.

Epidural opioids have a much better safety margin in patients who are already tolerant to such drugs (144). Tolerance has also not proven to be a problem (145).

Cardiovascular

Both severe hypotension and severe hypertension have occurred after epidural pethidine (146,147).

There were symptoms of shock lasting 2–3 hours in two women with advanced cancer who were given epidural buprenorphine 300 micrograms after becoming tolerant to epidural morphine (148). The buprenorphine was given 12 hours after the last dose of morphine. Symptoms started within 2 hours of administration and remitted spontaneously.

Nervous system

Myoclonic seizures after epidural morphine 25 mg/hour and after intrathecal hydromorphone have been reported (149).

- A 30-year-old known epileptic woman who had undergone cesarean section developed a tonic-clonic seizure 6 hours after epidural morphine (150).

Two cases of Menière-like syndrome (SEDA-16, 83) (151), and vertical nystagmus and blurred vision (SEDA-16, 83) (SEDA-17, 86), have been reported after epidural morphine.

Catatonia has been reported after a continuous infusion of epidural morphine (152). Hallucinations were thought to be an important sign of impending intoxication.

Mechanical difficulties, in the form of backflow of solution from epidural catheters, occurred in 31 of 32 patients and there were neurological complications in a further two of eight patients in whom the catheter had been tunnelled and connected to a subcutaneous access port; epidural fibrosis with compression of the spinal cord was presumed to be the cause (144).

Epidural fibrosis is a reported complication after long-term epidural morphine administration (SEDA-17, 85).

Psychological, psychiatric

Psychomotor symptoms have been noted subsequent to epidural buprenorphine (153).

Gastrointestinal

Whereas a high incidence (50%) of delayed (6 hours) nausea and vomiting has been reported in volunteers who received epidural morphine (154), there is a low incidence postoperatively (155). In another series the incidence of nausea (12%) and vomiting (24%) was similar whether morphine was used intramuscularly or epidurally or saline was injected epidurally (156). In labor the incidence of this adverse effect is low with epidural opioids (136,157) compared with intrathecal opioids (119,120). The incidence appears to fall with repeated dosing and is very low in patients with cancer who require long-term opioids (111,158). Nausea and vomiting have also been reported after fentanyl (159,160) and pethidine (161). The effects are abolished by intravenous naloxone without loss of analgesia (162).

Urinary tract

Current evidence suggests that the urodynamic effects of epidural morphine are not dose-related, and the incidence is similar to that reported after intramuscular injections. Urinary retention is more frequent after the use of epidural opioids in volunteers compared with patients

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(163,166). In one series (154) two patients who had failed to respond to bethanechol 5 mg subcutaneously, responded to intravenous naloxone 400 micrograms, and in other studies all subjects responded to naloxone 800 micrograms (164–167), which suggests that the mechanism involves opioid receptors. There was a 22% incidence of urinary retention in 90 postoperative patients who received epidural morphine (168), and in another series a rate of 39% (112). In a dose–response study of epidural morphine in increments of 0.5–8 mg (169) there was a similar incidence of urinary retention at all doses. These results are similar to those in a volunteer study involving 30 subjects who received 2, 4, or 10 mg of morphine epidurally (164).

Skin

Pruritus has been noted after epidural morphine, pethidine (meperidine), diamorphine (heroin), and fentanyl, with a quoted incidence of 1–100%. Troublesome pruritus occurs in only about 1% of cases (SED-11, 139) (102). In one study of postoperative patients who received morphine 10 mg epidurally, pruritus occurred in 28% of patients (112), but in only 1% of patients in other studies who received 5 and 2 mg morphine (SED-11, 139). With pethidine 50 mg epidurally after cesarean section, there was a 50% incidence of pruritus, but it was troublesome in only one patient (136). Pruritus has been reviewed in relation to parturition (170,171). It occurred in 593 cases (43%) in pregnant women compared with 3050 non-parturients (8.4%). These findings are borne out by other comparative work (137). Pruritus after cesarean section was more common with epidural morphine and fentanyl than with buprenorphine or butorphanol (172).

Suggested mechanisms for the difference in the incidence of pruritus in parturients and non-parturients include high plasma concentrations of maternal endorphins during labor together with more distant spread of morphine within the CSF, competition by estrogens for opioid-binding sites, and hormonal modifications of endogenous opioid concentrations at opioid receptors. It has also been suggested that the incidence of all adverse effects after spinal opioids may be higher in pregnant women, for the reasons stated above.

Various approaches have been used to try to eliminate pruritus with opioids. Substitution of epidural buprenorphine for morphine in combination with bupivacaine relieved severe unremitting pruritus in a single case (173). Injection of 10 mg nalbuphine subcutaneously significantly reduced the pruritus induced by epidural fentanyl within 15 minutes in 24 patients (174). Naltrexone 6 mg by mouth significantly reduced the incidence of pruritus after epidural morphine without affecting analgesia, but a dose of 9 mg was associated with a shorter duration of analgesia (175). Naloxone and propofol can reduce pruritus (SEDA-19, 87) (154), and the addition of droperidol to epidural sufentanil reduced the adverse effects of nausea, vomiting, and pruritus (SEDA-19, 88).

Spinal opioids probably cause widespread alterations in sensory modulation, as it occurs when there is evidence of opioid migration over the entire spinal cord to the brain. The dominant feature of facial pruritus, which is often reported, can be explained by rapid penetration of opioid to the superficially placed caudal portions of the nucleus of the spinal tract of the trigeminal nerve (154).

Pruritus is not due to preservatives in formulations, as it occurs with non-preservative-containing opioid solutions (176). It is unlikely to be due to histamine release, as the effect occurs about 3 hours after spinal or epidural administration (154,177–179) and occurs with fentanyl, which does not cause histamine release, in contrast to morphine (180).

Immunologic

An anaphylactic reaction to epidural fentanyl has been reported (181).

Body temperature

Maternal pyrexia has been reported following epidural opioid analgesia during labor. This may be the result of vascular and thermoregulatory modifications induced by the epidural analgesia (182).

Fetotoxicity

The effect of obstetric epidural administration of a mixture of 8 ml of bupivacaine (0.25%) with fentanyl 50 micrograms has been studied in 40 offspring (183). Fetal distress occurred in 11 babies, five of whom needed resuscitation; there was no correlation between fetal distress and plasma fentanyl concentrations in the neonates.

The use of epidural opioids in labor can pose a risk to the fetus (184), but in a series of 40 parturients who received either epidural morphine 2.0–7.5 mg or bupivacaine (10 patients), the opioid did not produce respiratory depression in the neonate (185).

Drug overdose

Acute opioid poisoning involves marked CNS depression, with drowsiness, loss of consciousness, and coma. Other prominent features are a reduced respiratory rate, hypotension, and symmetrical pinpoint pupils (unless the patient has been hypoxic for some time, in which case the pupils can be dilated). Reduced urine output, hypothermia, flaccid skeletal muscles, and pulmonary edema can also be present. Convulsions have occurred in children.

Rhabdomyolysis in association with myoglobinuric renal insufficiency and cardiac failure has been reported with a variety of agents (SEDA-8, 76) (186).

Respiratory depression can be rapidly reversed by clearing the airway, ventilating the patient, and giving intravenous naloxone. The duration of action of naloxone is generally shorter than that of opioids, necessitating periodic repeated administration.

Drug–Drug Interactions

General

For various interactions, see Table 2.

Opioids can reduce or prolong the gastrointestinal absorption of other drugs. The partial opioid agonists, for example buprenorphine and pentazocine, can antagonize the effect of poor opioid agonists.

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Increased respiratory depression can occur if other respiratory depressant drugs, for example hypnotics, sedatives, or alcohol, are taken concurrently. Muscle relaxants and antihistamines with sedative properties have a similar effect.

Monoamine oxidase inhibitors

Opioid analgesics interact with non-selective monoamine oxidase inhibitors, causing nervous system excitation and hypertension (187).

Concomitant use of some opioid analgesics, such as pethidine or dextropropoxyphene, with the selective monoamine oxidase inhibitors selegiline and moclobemide can enhance their nervous system toxicity (188).

Phenothiazines

Hypotensive effects are increased if opioids and phenothiazines are used together (SED-9, 109).

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Opioid antagonists

See also Individual agents

General Information

Opioids are naturally occurring or synthetic substances that have morphine-like activity. The term opiate refers only to substances with morphine-like activity that are derived from opium. Substances that bind to opioid receptors but elicit little agonist activity are known as opioid antagonists (1–3). Some drugs have both agonist and antagonist effects (partial agonists). The opioids and their antagonists can be divided into three groups:

(a) opioid agonists (morphine and morphine-like opioids);
(b) opioid antagonists (for example naloxone and naltrexone);
(c) opioid partial agonists (for example buprenorphine and nalbuphine).

Individual drugs are covered in seperate monographs.

General adverse effects

The main adverse effects of the opioid antagonists fall into two groups. The first are those caused by a reversal of opioid actions; these include hypotension, pulmonary edema, atrial and ventricular dysrhythmias, and cardiac arrest. The risk of such effects is increased in patients with pre-existing cardiac abnormalities. The second group of effects results from direct actions of the opioid antagonists and their actions on the central nervous system, that is typical opioid effects, including dependence.

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Oprelvekin

General Information

Oprelvekin has thrombopoietic activity and has been licensed to prevent severe thrombocytopenia and reduce the need for platelet transfusion after myelosuppressive chemotherapy (1). Common adverse effects included myalgia and arthralgias, fatigue, headache, and conjunctival injection. Peripheral edema, dyspnea, pleural effusions, tachycardia, and anemia were supposedly the result of oprelvekin-induced fluid retention (SEDA-20, 336) (SEDA-21, 376). Atrial flutter or fibrillation were sometimes noted.

Severe fluid retention resistant to furosemide and fluid restriction was observed in 10 patients randomized to receive subcutaneous oprelvekin 50 μg/kg/day to prevent mucositis and acute graft-versus-host disease after allogeneic stem cell transplantation (2). One patient also had a large but reversible increase in serum transaminases.

A preliminary study of the thrombopoietic effect of oprelvekin (50 μg/kg/day for 21 days) in patients with refractory immune thrombocytopenic purpura was halted, since all of the first seven patients had adverse effects without significant changes in the platelet count (3). Adverse effects consisted of conjunctival injection, diffuse aches and joint pains, marked pedal edema, petechiae, and mild anemia. In addition, one patient had a neuropathy, which resolved more than 1 month after oprelvekin withdrawal.

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Orciprenaline

See also Adrenoceptor agonists

General Information

Orciprenaline is somewhat $beta_2$-selective compared with isoprenaline, but is by no means free of cardiac effects (1). Individual susceptibility to these varies, but it would seem that about one individual in 10 will experience tachycardia after usual therapeutic doses. At normal doses (for example 20 mg qds) "jitteriness" and nervousness are not uncommon, and about one patient in 12 suffers from cramps or numbness in the extremities. Lactic acidosis has been described in one patient as a result of concomitant use of orciprenaline, theophylline, and glucocorticoids. Other susceptibility factors and interactions are as for isoprenaline.

Reference

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Organic solvents

General Information

Lighter fuels, benzene, toluene, cleaning fluids (carbon tetrachloride), petrol, paraffin, and even the fluorocarbon propellants found in various household sprays and medications have all been used, particularly by children, to produce changes in consciousness. They are all inhaled, often with the aid of a plastic bag, and, since they are lipid-soluble, they are readily concentrated in brain tissue. As with many anesthetics there is an early period of hyperactivity, excitement, and intoxication, followed by sedation and confusion. Prolonged or regular use can cause serious toxicity with bone-marrow depression, cardiac dysrhythmias, peripheral neuropathy, cerebral damage, and liver and kidney disorders (SEDA-12, 37) (1).

Reference

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Orgotein

General Information

Orgotein, an enzyme (CuZn superoxide dismutase) that is present in all mammalian cells, is obtained from bovine liver by several steps, including chromatography. It can be given parenterally or topically. Reliable published clinical experience of its properties is limited. In Germany, marketing approval for orgotein was suspended because of severe reactions and deaths, mostly due to hypersensitivity (SEDA-18, 107).

Organs and Systems

Immunologic

Two anaphylactic reactions have been reported, one after intra-articular injection, the other after submucosal bladder injection of orgotein. An IgE-mediated mechanism was demonstrated in the first case (SEDA-12, 94) (SEDA-14, 96).

Drug Administration

Drug administration route

Painful local subcutaneous reactions, erythema, urticaria, and pruritus have been observed after topical administration (1), as have fever and swelling, redness, heat, and pain at the injection site after intravenous administration (2).

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Ornidazole

General Information

Used in single large doses for the treatment of *Trichomonas urogenitalis* or *Giardia* infections, ornidazole can cause gastrointestinal symptoms (SEDA-11, 597) (1).

Organs and Systems

Nervous system

- A meningeal syndrome with fever has been reported in a 65-year-old man on the fourth day of administration of ornidazole (500 mg tds) (2). Spontaneous recovery occurred within a few days and without sequelae.

Liver

Ornidazole can cause hepatotoxic damage resembling acute cholestatic hepatitis (3).

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Orphenadrine

See also Adrenoceptor agonists

General Information

Orphenadrine is related to an antihistamine (diphenhydramine), and appears to have been developed in the hope of producing a greater effect in Parkinson's disease by combining both anticholinergic and antihistaminic effects in a single molecule.

In the doses commonly used, any of the well-recognized anticholinergic effects can occur. Some patients become drowsy, whilst others are stimulated. With increasing dosages, some patients go into coma; others have agitation, convulsions, and marked euphoria, perhaps with hallucinations and disorientation.

Organs and Systems

Cardiovascular

Non-sustained ventricular tachycardia has been attributed to orphenadrine (1).

- A 57-year-old woman had been taking a formulation containing orphenadrine 15 mg and paracetamol 450 mg bd for musculoskeletal pain. She was also taking propafenone 600 mg/day for paroxysmal atrial fibrillation. After 5 days she developed severe palpitation. Holter monitoring showed frequent brief episodes not only of atrial fibrillation but also of non-sustained ventricular tachycardia. After the orphenadrine was withdrawn the palpitation ceased.

The authors pointed out the potential problems of anticholinergic drugs like orphenadrine in patients taking antidysrhythmic drugs.

Long-Term Effects

Drug abuse

Orphenadrine abuse has been described (SEDA-14, 122).

Drug Administration

Drug overdose

In overdosage, orphenadrine has been stated to be relatively toxic (SEDA-3, 124). Although some patients have survived doses grossly in excess of the usual maximum of 400 mg/day, the therapeutic margin can vary. On occasion doses of as little as 2–3 g have produced a fatal outcome within 6–12 hours. The clinical picture of intoxication tends to be characterized by coma with seizures, apnea, disturbances of cardiac rhythm, and shock; physostigmine should only be used cautiously and preferably after the most severe toxic phase has been overcome (2).

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Osmic acid

General Information

Osmic acid is injected into joints for chemical synovectomy and is associated with local pain, effusions, and fever; skin necrosis is less frequent (1). Nerve damage and abnormal urinary findings (hematuria, proteinuria, and leukocyturia) can occur (SEDA-12, 94). A potentially dangerous drug, it certainly should not be given to young patients.

Reference

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Oxaceprol

General Information

Oxaceprol, a hydroxyproline derivative, has been used to treat osteoarthritis (1,2). Gastrointestinal reactions, nervous system reactions (headache, dizziness), and skin reactions have been reported (3), but oxaceprol is reportedly tolerated at least as well as diclofenac (1) or better (2).

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Oxametacin

See also Non-steroidal anti-inflammatory drugs

General Information

The adverse reactions pattern of oxametacin is similar to that of indometacin. In one study, 17% of 771 patients taking oxametacin had adverse effects, which led to withdrawal of treatment in 87. Gastrointestinal adverse effects accounted for 60% and nervous system reactions (headache, dizziness) for 31% (1).

Reference

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Oxamniquine

General Information

Oxamniquine, in doses of 15 mg/kg or in a single oral dose of up to 15 mg/kg bd for 2 days, depending on the sensitivity of *Schistosoma mansoni* in the area concerned, is effective with minimal toxicity. It has no effect in *Schistosoma hematobium*. It is no longer given intramuscularly, because of severe pain at the injection site.

Reactions occur in up to one-third of patients and include dizziness, drowsiness, headache, amnesia, occasional behavioral disturbances (hallucinations, excitement), and even seizures (SEDA-14, 262); there is often some nausea, vomiting, and diarrhea (1). Allergic manifestations include fever and pruritic skin rashes. Minor abnormalities of liver function and creatine kinase, proteinuria, and hematuria have been reported.

Organs and Systems

Cardiovascular

Electrocardiographic and electroencephalographic changes have been reported as rare adverse effects of oxamniquine (SEDA-11, 598) (2).

Nervous system

Oxamniquine can cause neurological adverse effects (3). At high doses, somnolence was reported in 25% of cases. Somnolence is reportedly more common if the drug is given just before a meal. In a comparison of oxamniquine with praziquantel, there were adverse effects in 45% of patients treated with oxamniquine and 71% of patients given praziquantel; somnolence occurred less often (11% of cases) with praziquantel (SEDA-12, 709) (4).

Headache and dizziness have also been reported with oxamniquine (5).

Gastrointestinal

Gastrointestinal complaints are common with oxamniquine, and take the form of anorexia, abdominal discomfort, and diarrhea (4).

Liver

Hepatic enzyme changes, initially reported as rare with oxamniquine, may in fact be frequent if sought. In one study, there were changes in 79% of patients, with raised alkaline phosphatase in 36% and a raised eosinophil count in 52% (SEDA-13, 837) (6).

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Immunologic

Fever occurs in about a quarter of patients taking oxamniquine (SEDA-11, 598) (7), and in some 15% of these, a Löffler-like syndrome with eosinophilia and pulmonary infiltrates was seen when it was specifically looked for.

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Oxaprozin

See also Non-steroidal anti-inflammatory drugs

General Information

In controlled studies, oxaprozin caused adverse effects in 23–58% of patients (1). It was considered better than aspirin and similar to other NSAIDs in long-term studies (2). However, treatment had to be interrupted owing to adverse effects in 8–31% of patients.

Organs and Systems

Nervous system

Headache, dizziness, vertigo, and tinnitus are less frequent with oxaprozin than with indometacin or aspirin (3,4).

Metabolism

Drug-induced pseudoporphyria has been ascribed to oxaprozin (SEDA-21, 106).

Liver

There were minor rises in transaminase activity in 10–20% of patients taking oxaprozin. Liver function should be monitored, especially during the first 6 months of therapy. Fulminant hepatitis has been reported (5).

Urinary tract

Of 847 patients with different rheumatic diseases who took oxaprozin daily for up to 1 year, 6% developed significant rises in blood urea nitrogen or creatinine, but a severe adverse renal effect occurred in only one patient (SEDA-12, 87). Oxaprozin can cause membranous nephropathy with nephrotic syndrome (SEDA-21, 106).

Skin

Under 5% of patients taking oxaprozin develop rashes. Some have phototoxic reactions (SEDA-12, 87).

Toxic epidermal necrolysis occurred in a 71-year-old man after treatment with oxaprozin for shoulder pain (6).

Immunologic

Life-threatening respiratory distress, facial edema, and lethargy occurred in a woman with a history of severe asthma and aspirin allergy (SEDA-22, 118).

Susceptibility Factors

Age

Older patients are more likely to have gastrointestinal and nephrotoxic reactions to oxaprozin. In this respect, it differs little from other NSAIDs.

Drug–Drug Interactions

Cimetidine

The clinical significance of the reduced renal clearance of oxaprozin when it is given concomitantly with cimetidine is not clear (SEDA-12, 87).

Ranitidine

The clinical significance of the reduced renal clearance of oxaprozin when it is given concomitantly with ranitidine is not clear (SEDA-12, 87).

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Oxatomide

See also Antihistamines

General Information

Oxatomide is a second-generation antihistamine (SED-12, 371) (SEDA-18, 185) (SEDA-21, 176).

Organs and Systems

Respiratory

In some cases of asthma exacerbation of bronchospasm has occurred when patients have taken oxatomide (1,2).

Nervous system

Oxatomide caused drowsiness in 37–56% of treated patients (3,4).

Liver

Acute cytolytic hepatitis has been attributed to oxatomide (5). An eruption and liver damage has been described in an elderly woman taking several different antihistamines; oral rechallenge with both terfenadine and oxatomide caused erythema, and there was mild liver dysfunction after oxatomide (6).

Skin

When oxatomide was used topically in a gel in 22 patients with vulvar lichen sclerosus, in a concentration sufficient to relieve pruritus, some patients withdrew from treatment because of a burning sensation (7).

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Oxazepam

See also Benzodiazepines

General Information

Oxazepam is a relatively short-acting benzodiazepine with a half-life of about 9 hours. As well as being used as a drug in its own right, it is a metabolite of temazepam and desmethyldiazepam.

Passiflora incarnata extract has been compared with oxazepam in a double-blind, randomized trial in 26 outpatients with DSM-IV generalized anxiety disorder (1). Both were effective, but oxazepam had a more rapid onset of action and caused significantly more problems relating to work performance.

Organs and Systems

Psychological, psychiatric

An important behavioral adverse effect of benzodiazepines, hostility and aggression in response to provocation, is less common with oxazepam than with its closely related analogue lorazepam (2). In a study of the effects of oxazepam on implicit versus explicit memory processes, as a function of time-course the effects of oxazepam (30 mg) or placebo on directly comparable tests of implicit memory and explicit memory were examined at three times in 60 healthy volunteers. Before the plasma concentration had peaked, oxazepam impaired cued recall performance relative to placebo but did not impair priming. At the time of the peak, oxazepam impaired performance in both memory tasks. After the peak, cued recall performance in the oxazepam group remained significantly impaired relative to placebo. However, oxazepam-induced impairments in priming were only marginal, suggesting that oxazepam-induced impairments in implicit memory processes begin to wane after theoretical peak drug concentrations. The results support the hypothesis that benzodiazepines cause impaired implicit memory processes time-dependently (3).

In 30 subjects who were given an acute dose of oxazepam 30 mg, lorazepam 2 mg, or placebo, both drugs impaired explicit memory relative to placebo. Also, both oxazepam and lorazepam impaired priming performance. The results suggested that episodic memory is time-dependently impaired by both benzodiazepines (4).

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Oxazolidinones

General Information

The oxazolidinones have a unique mechanism of action, involving inhibition of the first step in protein synthesis. The first marketed member of the class, linezolid, has inhibitory activity against a broad range of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate *Staphylococcus aureus* (GISA), vancomycin-resistant enterococci (VRE), and penicillin-resistant *Streptococcus pneumoniae*. It also has activity against certain anerobes, including *Clostridium perfringens*, *Clostridium difficile*, *Peptostreptococcus* species, and *Bacteroides fragilis*. The most frequently reported adverse effects are diarrhea, headache, nausea and vomiting, insomnia, constipation, rash, and dizziness; thrombocytopenia has also been documented in a few patients (about 2%) (1,2).

In controlled phase III studies, linezolid was as effective as vancomycin in patients with infections caused by MRSA and VRE. It is effective both intravenously and orally. Although technically classified as bacteriostatic against a number of pathogens in vitro, linezolid behaves in vivo like a bactericidal antibiotic.

The pharmacokinetics of linezolid in adults are not altered by hepatic or renal function, age, or sex to an extent that requires dose adjustment. Linezolid is metabolized via morpholine ring oxidation, which is independent of CYP450; linezolid is therefore unlikely to interact with medications that induce or inhibit CYP450 enzymes. Plasma linezolid trough concentrations after a 1-hour infusion of 600 mg bd were 0.54–5.3 μg/ml and CSF linezolid trough concentrations were 1.46–7.0 μg/ml; the ratio between CSF and plasma linezolid trough concentrations always exceeded 1 (mean, 1.6; range 1.2–2.3) (3). There was good rapid penetration of linezolid into bone, fat, and muscle (4,5). The mean peak plasma concentration of linezolid was 18.3 μg/ml in six healthy men who took 600 mg orally every 12 hours for five doses. There was good penetration into inflammatory fluid (6,7).

General adverse effects

Linezolid is generally well tolerated (8–10). The most frequently reported adverse events were diarrhea, headache, nausea and vomiting, insomnia, constipation, rash, and dizziness. Thrombocytopenia was also documented in few patients (about 2%). In a phase II, open, multicenter study of intravenous linezolid followed by oral linezolid suspension, both in a dose of 10 mg/kg every 12 hours in 66 children, the most common adverse effects were diarrhea (10%), neutropenia (6.4%), and raised alanine transaminase activity (6.4%) (11).

In children the common adverse events have been similar to those found in adults, although thrombocytopenia has not been as common (12).

Organs and Systems

Nervous system

Peripheral and optic neuropathy occurred in a 76-year-old man after he had taken linezolid for about 6 months (13).

Hematologic

Linezolid has been associated with reversible myelosuppression (14), which appears to be related to the duration of therapy, with a higher risk after more than 2 consecutive weeks of treatment (15). Myelosuppression with red cell hypoplasia has been reported in three patients taking linezolid 600 mg bd. The bone marrow changes were similar to those seen in reversible chloramphenicol toxicity. Another patient had sideroblastic anemia after taking linezolid for 2 months (16,17).

- Red cell hypoplasia and thrombocytopenia occurred in a 66-year-old man who took linezolid 600 mg bd (18).
- Reversible pure red blood cell aplasia occurred in a 52-year-old black man who had taken linezolid for 8 weeks (19).

Pancytopenia in two cases was reported with linezolid 600 mg bd (20).

In 19 patients there was thrombocytopenia in six of those who had taken it for more than 10 days; gastrointestinal bleeding was observed in one patient and four required platelet transfusions (21). Of 71 patients who took linezolid for 1–44 days, 48 took it for more than 5 days; among those 48, thrombocytopenia, with a 32–89% reduction in platelet count, occurred in 23; the platelet count fell to below 100×10^9/l in nine (22).

Susceptibility Factors

Age

In single-dose pharmacokinetic studies children had a greater plasma clearance (0.34 l/hour/kg for children aged 3 months to 16 years) than adults (0.10 l/hour/kg) (12).

Drug–Drug Interactions

Selective serotonin re-uptake inhibitors (SSRIs)

Serotonin syndrome was reported in a 56-year-old white woman who received intravenous linezolid shortly after withdrawal of a selective serotonin reuptake inhibitor, paroxetine (23).

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The serotonin syndrome was reported in a 45-year-old white man who received intravenous linezolid (600 mg 12 hourly) and sertraline (24).

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Oxcarbazepine

See also Antiepileptic drugs

General Information

Oxcarbazepine is the 10-keto analogue of carbamazepine and a prodrug for monohydroxycarbazepine, to which it is rapidly reduced. Its efficacy and tolerability profiles are similar to those of carbamazepine, from which oxcarbazepine differs in kinetic profile (lack of autoinduction, linear kinetics, half-life of 10–20 hours, elimination by glucuronidation), lower allergenicity, greater antidiuretic activity, possibly slightly better central nervous system tolerability, and less potential for drug interactions (1). Like carbamazepine, oxcarbazepine can exacerbate absence and myoclonic seizures (SEDA-21, 73).

Oxcarbazepine has not been associated with hepatotoxicity or hematological toxicity. It is less likely than carbamazepine to cause hypersensitivity reactions, but may be more often associated with hyponatremia. It is less likely than carbamazepine to induce CYP450 isozymes, but it may significantly increase the clearance of oral contraceptives and significantly induce CYP450 at higher doses.

The pharmacology, clinical pharmacology, and adverse reactions and interactions of oxcarbazepine have been reviewed (2–6).

Placebo-controlled studies

The safety and efficacy of oxcarbazepine 600–2400 mg/day as adjunctive therapy for uncontrolled partial seizures have been studied in a randomized, double-blind, placebo-controlled study in 694 patients aged 15–65 years (7). During the double-blind phase, 76%, 84%, 90%, and 98% of patients respectively taking placebo or oxcarbazepine 600, 1200, or 2400 mg/day reported one or more adverse events. The most common adverse events were related to the nervous and gastrointestinal systems.

The safety and efficacy of oxcarbazepine 300 and 2400 mg/day have been studied in patients with refractory partial epilepsy in a double-blind, randomized trial (8). Dizziness, fatigue, somnolence, and nausea, mostly transient and mild to moderate, were the most frequent adverse events.

The safety and efficacy of oxcarbazepine have been studied in a randomized, placebo-controlled trial in 267 children with inadequately controlled partial seizures (9). There was at least one adverse event in 91% of those who took oxcarbazepine and 82% of those who took placebo;

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vomiting, somnolence, dizziness, and nausea occurred more often (two-fold or more) with oxcarbazepine.

Two doses of oxcarbazepine have been compared in a double-blind, parallel-group, randomized trial in patients with uncontrolled partial-onset epilepsy who had previously taken carbamazepine monotherapy (10). After two open phases in 143 patients, 96 were randomized to oxcarbazepine 300 or 2400 mg/day for 126 days. The time to meet an exit criterion was significantly in favor of oxcarbazepine 2400 mg/day. In all, 24 of the 47 non-randomized patients withdrew because of an adverse event, most commonly dizziness, ataxia, headache, nausea, vomiting, or fatigue. Three withdrew because of laboratory abnormalities, one each with leukopenia, hyponatremia, and hyperglycemia. Headache, dizziness, and nausea were the only adverse events that occurred in more than 10% in either group. Similar adverse events were reported in the randomized patients, but none withdrew.

Organs and Systems

Nervous system

- A 31-year-old man developed oculogyric crises after starting to take oxcarbazepine, and the frequency of these episodes correlated with the dosage of the drug (11). Similar episodes had occurred in the past after exposure to carbamazepine. The implantation of a vagus nerve stimulator led to the disappearance of the oculogyric crises.

Electrolyte balance

Hyponatremia occurs in an appreciable proportion of patients taking oxcarbazepine (12), perhaps more often than with carbamazepine; it is usually asymptomatic. Among 2166 oxcarbazepine-treated patients in the manufacturer's database, the incidence of sodium concentrations below 135 mmol/l was 22% (13). There was marked hyponatremia (sodium concentrations below 125 mmol/l) in 2.7% overall and the risk increased with age: 0% below 6 years, 0.5% 6–17 years, 3.4% at 18–64 years, and 7.3% above 65 years. The incidence of adverse events was similar in all sodium categories: the absence of symptoms suggests that the fall in sodium concentrations was not precipitous.

Changes in serum electrolyte balance and underlying regulatory mechanisms have been evaluated in 10 men with epilepsy 2 and 6 months after long-term carbamazepine monotherapy had been replaced with oxcarbazepine (14). Serum sodium concentrations fell in four patients (in two below the reference range) and were unaltered in six. Serum aldosterone rose in the six patients whose serum sodium concentrations did not fall, but not in those with low sodium concentrations during oxcarbazepine. The serum concentration of the N-terminal fragment of pro-atrial natriuretic peptide fell in all patients, reflecting the reduced serum sodium concentrations. Thus, compensatory aldosterone release may prevent hyponatremia in some patients taking oxcarbazepine.

In one series in which there were low serum sodium concentrations in patients taking oxcarbazepine, 25% had concentrations below 135 mmol/l and 3% had concentrations below 125 mmol/l (12). In most patients, the hyponatremia was asymptomatic and only rarely resulted in morbidity or led to drug withdrawal.

In a prospective study, 11 patients with epilepsy and 10 controls taking oxcarbazepine 600–1800 mg/day for 3 weeks were subjected to a water-load test (15). Oxcarbazepine significantly reduced serum osmolality and serum sodium concentration after a water-load test in both healthy volunteers and patients with epilepsy. The hyponatremia was hypotonic and not associated with a significant change in serum concentrations of arginine vasopressin; thus, it could not be attributed to inappropriate secretion of ADH. There was a statistically significant negative correlation between the trough plasma concentration of the monohydroxylated derivative of oxcarbazepine and the percentage of the water load excreted at 1 hour. The hyponatremia appears to result from both a relative inability to dilute the urine and a reduction in the percentage of water excreted. The underlying mechanism might be related to a direct effect of the drug on the renal collecting tubules or enhancement of their responsiveness to circulating antidiuretic hormone.

Susceptibility Factors

- A 28-year-old man with porphyria cutanea tarda took oxcarbazepine without adverse effects, suggesting that oxcarbazepine may be used in patients with this disorder (16); most other antiepileptic drugs cannot.

Drug–Drug Interactions

General

Oxcarbazepine is a weaker enzyme inducer than carbamazepine. When it is substituted for carbamazepine, plasma concentrations of concomitant drugs, such as valproate and neuroleptic drugs, can rise, owing to de-induction, leading to potential toxicity (17,18).

Oxcarbazepine metabolism is unaffected by several inhibitors of carbamazepine metabolism.

Ciclosporin

A possible interaction of oxcarbazepine with ciclosporin has been reported after renal transplantation in a 32-year-old man (19). The ciclosporin trough serum concentration and serum sodium concentration fell after oxcarbazepine was added.

Enzyme-inducing anticonvulsants

Enzyme-inducing anticonvulsants cause a modest reduction in monohydroxycarbazepine concentrations (17).

Felodipine

Oxcarbazepine reduces serum felodipine concentrations, although less than carbamazepine does (20).

Lamotrigine

In a retrospective study, in which 376 samples from 222 patients were analysed, oxcarbazepine induced the metabolism of lamotrigine and reduced lamotrigine concentrations by about 29% (21).

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Phenytoin

In human liver microsomes with cDNA-expressed CYP2C19, oxcarbazepine and its 10-monohydroxy metabolite inhibited CYP2C19-mediated phenytoin metabolism at therapeutic concentrations (22). Thus, co-administration of oxcarbazepine with phenytoin could significantly increase serum phenytoin concentrations.

Steroid oral contraceptives

In a placebo-controlled study in healthy women, oxcarbazepine 900 mg/day reduced the serum concentrations of ethinylestradiol and levonorgestrel by about 50% (23). This confirms that oxcarbazepine may reduce the efficacy of the contraceptive pill, as does carbamazepine. Women taking oxcarbazepine should be given a contraceptive that contains 50 μg of ethinylestradiol and they should be monitored for signs of insufficient contraceptive cover, such as breakthrough bleeding.

Warfarin

Oxcarbazepine does not modify the anticoagulant activity of warfarin (17).

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Oxitropium

See also Anticholinergic drugs

General Information

Oxitropium is an anticholinergic drug that is used in the treatment of asthma.

In a single blind, randomized, crossover study, in 12 patients the bronchodilator effects of salmeterol 50 micrograms and oxitropium 200 and 400 micrograms were compared with placebo. All treatments were taken from a metered dose inhaler. The peak effect of salmeterol was delayed but the effect was more prolonged than the effect of oxitropium. The response to salmeterol 50 micrograms exceeded the response to oxitropium 200 micrograms over 12 hours. Between 3 and 12 hours the response to salmeterol was greater than the response to oxitropium 400 micrograms, but the difference was not

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significant. There were no significant changes in pulse rate, blood pressure, or the electrocardiogram with any of the four treatments. No patients complained of adverse symptoms and none noticed any difference in the taste of the different inhalers (1).

Organs and Systems

Immunologic

Total serum IgE has been measured in 36 patients with allergic rhinitis and 11 healthy subjects given a submaximal dose of oxitropium bromide 600 micrograms by inhalation (2). FEV_1 was greater than 80% of predicted in all subjects. Baseline FEV_1 correlated negatively with serum IgE concentration. Oxitropium bromide inhalation produced an increase in FEV_1 (mean 155 ml) that was significantly greater in allergic patients with high serum IgE than in healthy subjects (64 ml) or in those with allergic rhinitis and low serum IgE (82 ml). The effect of an inhaled $beta_2$-adrenoceptor agonist (orciprenaline) was similar in all three groups. These findings may explain some of the variation in response to inhaled antimuscarinic drugs in patients with asthma. The data also suggested that IgE may itself modify airway tone by an increase in cholinergic responsiveness.

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Oxolamine

General Information

Oxolamine citrate is a synthetic derivative of 3,5-disubstituted 1,2,4-oxodiazole. It has been used to treat cough in some European countries for more than two decades.

Organs and Systems

Psychological, psychiatric

Evidence has accumulated that oxolamine can cause hallucinations in children, especially those under 10 years of age (1,2); some cases have been confirmed by re-exposure to the drug.

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Oxybuprocaine

See also Local anesthetics

General Information

Oxybuprocaine is an ester of para-aminobenzoic acid. It is a popular local anesthetic for use in ophthalmology.

Organs and Systems

Cardiovascular

An episode of severe bradycardia, with no perceptible cardiac output, was reported in a previously healthy patient after one drop of 0.4% oxybuprocaine was applied to each eye (1).

Sensory systems

When used in the eye, oxybuprocaine can enter the anterior chamber, and fibrinous iritis and moderate corneal swelling have been described (SED-12, 257) (2). Abuse has often been reported and can lead to keratopathy, severe visual impairment, and even enucleation (3).

Skin

There have been two reports of patients scheduled for tonometry who developed periorbital dermatitis following the topical instillation of local anesthetic eye drops (4). The first patient reacted strongly positive on patch testing to Thilorbin AT (oxybuprocaine, fluorescein, phenylmercuric borate, polysorbate 20, mannitol) and also to oxybuprocaine alone. The second reacted to Conjucain EDO (oxybuprocaine, sorbitol, sodium hydroxide) and to oxybuprocaine alone. The authors believed these to be the only described cases of a delayed hypersensitivity reaction to oxybuprocaine, an ester local anesthetic commonly used for topical anesthesia in the eye.

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Oxybutynin

See also Anticholinergic drugs

General Information

Oxybutynin is an anticholinergic drug that is used to treat bladder detrusor instability. It can cause all the adverse effects that would be expected from its anticholinergic action (1).

Oxybutynin 15 mg/day has been compared with a newer anticholinergic agent tolterodine 4 mg/day in a randomized, double-blind, placebo-controlled parallel group study in 293 patients with bladder detrusor instability (2). The efficacies were generally similar, but twice as many patients taking oxybutynin withdrew because of adverse effects (17 versus 8%). Dry mouth was by far the most frequent adverse effect, reported by 86% of patients taking oxybutynin and 50% of those taking tolterodine. Although there was still an excess of adverse effects after halving the dose of oxybutynin, it would not be normal practice to start treatment with this drug in a dose as high as 15 mg/day.

Organs and Systems

Sensory systems

Oxybutynin can precipitate acute angle closure glaucoma (3).

- An 80-year-old woman, who was taking oxybutynin 2.5 mg bd, developed acute angle closure glaucoma but did not suffer permanent visual impairment, despite the very high intraocular pressure (56 mmHg) initially found in the affected eye.

Psychological, psychiatric

Neuropsychiatric adverse effects seem to pose a greater problem with oxybutynin than other anticholinergic drugs. A group of pharmacologists involved in pharmacovigilance have described five spontaneous reports of night terrors associated with oxybutinin (4). Four were children, aged 5–8 years, being treated for enuresis, and the fifth was a 77-year-old woman with incontinence. Total daily doses were 8–12 mg in the children and 10 mg in the elderly woman: these are all toward the upper end of the recommended ranges.

Mouth and teeth

There have been several comparisons of tolterodine and oxybutynin. All agree that oxybutynin, in its standard formulation at a dose of 5 mg bd, while of similar efficacy, produces significantly more adverse effects (5). The incidence of dry mouth reached 60%, and over 75% in patients taking the highest dose of 5 mg tds. Direct measurements of saliva production confirmed that oxybutynin 5 mg/day reduces saliva output significantly more than tolterodine 2 mg or a modified-release formulation of oxybutynin 10 mg, all given as single doses (6). In over 300 patients modified-release oxybutynin once-daily produced less dry mouth (28 versus 33%) than immediate-release tolterodine 2 mg bd (7).

Drug Administration

Drug formulations

An extended-release formulation of oxybutynin has been compared with an immediate-release formulation; it had similar efficacy but fewer adverse effects (8). The overall conclusion of an unsystematic review was that, as expected, dry mouth is very common; it occurred in about two-thirds of those taking the extended-release formulation (up to a dose of 30 mg/day) and in nearly 90% of those who took the immediate-release formulation. In about 25% of those who took the extended-release formulation the dry mouth was classified as severe, compared with nearly 50% of those who took the immediate-release formulation. Other adverse effects were very uncommon and significant toxicity was not reported. In total the two comparative trials involved 331 patients, and an open study of 256 patients was also discussed.

Diagnosis of Adverse Drug Reactions

Means of reducing the adverse effects of oxybutynin have been considered in 226 patients (89% women, mean age 59 years) with urge incontinence and known to be responsive to anticholinergic therapy, who were randomized to take either conventional or modified-release oxybutynin (9). The dosage was titrated up to a maximum of 20 mg/day in both groups. Response rates were similar in both groups, as was the incidence of dry mouth (48% in the modified-release group and 59% in the immediate-release group). However, further analysis showed that at any dose significantly fewer patients complaining of dry mouth in the modified-release group, and this was even more apparent in patients with moderate to severe dry mouth.

Another approach is to try to stimulate salivary flow in patients taking oxybutynin. Malic acid pastilles have been used as a salivary stimulant, but the results were not good, although the study has some design problems (10). Of the 67 women enrolled only 32 completed the 8-week study. It is not clear whether there was any attempt to make the trial double-blind.

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Oxycodone

See also Opioid analgesics

General Information

Oxycodone is an opioid analgesic that is 1.5 times as potent as morphine and has a longer duration of action.

Drug studies

Pain relief

The postoperative analgesic effects of intravenous ketamine 10 mg and oxycodone 2 mg have been compared in a randomized, double-blind study in 40 tonsillectomized men (1). There were no significant differences between the two analgesics. The patients found ketamine more acceptable than oxycodone. Oxycodone was associated with more skin problems, especially pruritus. Oxycodone also caused a significantly lower respiratory rate with lower oxygen saturation throughout the recovery period and increased sedation throughout the study.

The effects of modified-release oxycodone in osteoarthritic pain have been evaluated in a placebo-controlled, double-blind trial in 133 patients (2). Oxycodone was effective, and although opioid-related adverse effects were frequent they were considered acceptable by the authors.

In a double-blind, randomized, crossover comparison of the efficacy and safety of modified-release oxycodone bd and immediate-release oxycodone qds in 57 patients with intervertebral disc disease or osteoarthritis, eleven patients withdrew: eight with nausea and constipation while taking modified-release oxycodone and three (one with migraine and two with nausea, vomiting, and headaches) while taking immediate-release oxycodone (3). There were no statistically significant differences in the adverse effects profiles between the two formulations. The overall incidence of adverse effects fell over the three phases of the study: from 89% (51/57 patients) during titration to 77% (36/47 patients) in stage 1 and 62% (29/47 patients) in stage 2. The most common adverse effects were constipation, nausea, pruritus, somnolence, and dizziness, the frequency of which fell with time; the incidence of constipation remained constant.

In a randomized, double-blind, crossover study, previous findings on the adverse effects of oxycodone among sufferers of postherpetic neuralgia were confirmed (4). Oxycodone was analgesic in this group, although 76% of the sample reported adverse effects compared with 49% of the placebo group. Constipation, nausea, and sedation were the most frequently reported adverse effects.

Two studies of oxycodone in patients with cancer pain have been carried out. In the first, modified-release and immediate-release oxycodone were compared (5) in a multicenter, double-blind trial in 180 patients who were given either modified-release oxycodone, mean dose 114 mg bd, or immediate-release oxycodone 127 mg qds, four times a day for cancer-related pain. A 5-day comparison showed no significant difference in the analgesic effects of the two formulations, both of which provided effective relief of pain. However, of the 160 patients who received at least one dose of medication, 104 reported a total of 295 adverse events, significantly fewer being reported with modified-release oxycodone (109) than immediate-release oxycodone (186). Reported adverse effects included: nausea (18 versus 26%), vomiting (11 versus 23%), and constipation (9 versus 17%). With immediate-release oxycodone headache was reported by 7% and anxiety by 5%; neither was reported with modified-release oxycodone. Altogether, 7% of the modified-release group and 11% of the immediate-release group discontinued medication because of adverse effects. It is suggested that the equianalgesic effect is likely to be a factor of the rapid initial release of the modified-release formulation, allowing adequate drug concentrations to establish sufficient receptor activation, followed by a slower release of the remaining drug, which may be responsible for the reduction in adverse effects. Alternatively the peaks achieved with each administration of medication may account for the observed difference in the rates of adverse effects between the two formulations.

The second study was a randomized, double-blind, crossover comparison of the safety and efficacy of oral modified-release oxycodone with modified-release morphine in 32 patients with cancer pain, nine of whom completed the trial (6). The average dose of oxycodone was 47 mg bd compared with 73 mg bd of morphine. There were no significant differences in the degrees of sedation, nausea, or pain intensity experienced by the subjects on the different regimens and the results suggested that oxycodone may be used as an alternative to morphine.

Long-Term Effects

Drug withdrawal

A patient with atypical oxycodone withdrawal had restlessness and delusions (7).

Susceptibility Factors

Age

Children may have a faster rate of clearance of oxycodone than adults, and ventilatory depression may be greater than with comparable opioids in children (SEDA-19, 85).

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Hepatic disease

In end-stage cirrhosis, reduced clearance and prolonged half-life of oxycodone may necessitate dosage reduction (SEDA-22, 101).

Drug Administration

Drug formulations

A double-blind, randomized, crossover comparison of modified-release or immediate-release oxycodone has been carried out in 30 patients with cancer pain (8). There were no significant differences between the two groups with respect to pain intensity or acceptability of therapy. More than 80% of the patients did not require rescue medication. Adverse effects were similar with the two formulations and occurred in relatively low numbers compared with previous morphine studies. The greatest difference in adverse effects was in the incidence of vomiting, which occurred in 6% of those given immediate-release morphine, and none of those given modified-release morphine. The modified-release formulation provided equal analgesia with the benefit of less frequent dosing.

In a systematic review of the safety and efficacy of modified-release oxycodone 16 trials were identified; 7 addressed the safety and efficacy of oxycodone for the treatment of non-cancer pain (9). In these studies, modified-release oxycodone offered no significant advantage over immediate-release oxycodone. There was no consistent beneficial effect on quality of life, despite adequate analgesia. Opioid adverse effects, such as constipation, nausea, vomiting, and drowsiness, were more frequent and severe with oxycodone than with placebo. In six studies, modified-release oxycodone was compared with immediate-release oxycodone in cancer and non-cancer pain. In only one study was modified-release oxycodone superior; in the other five there were no significant differences in analgesic effect. In five randomized, double-blind comparisons there was no advantage in analgesic efficacy nor a consistent reduction in adverse effects with modified-release oxycodone compared with modified-release morphine, hydromorphone, or methadone.

Drug administration route

Oxycodone has been available in oral form for at least 70 years and is rarely given by other routes. In a study of subcutaneous oxycodone hydrochloride 100 mg/ml for opioid rotation in 63 patients with cancer pain (maximum dose 4.5–660 mg in 24 hours for 1–49 days) there was local toxicity in only two cases, and this included central pallor of the skin at the needle site with surrounding erythema and bruising; there was no necrosis (10). The design of the study made it difficult to compare the adverse effects profile of subcutaneous oxycodone with oral oxycodone or other opioids. Randomized controlled trials are needed to support the conclusions that subcutaneous oxycodone is free from adverse effects and is a better vehicle for analgesia in terminal cancer.

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Oxyfedrine

See also Adrenoceptor agonists

General Information

Oxyfedrine is a vasodilator and has been used in angina pectoris and myocardial infarction.

Organs and Systems

Sensory systems

Impairment of the sense of taste is a particular complication of oxyfedrine therapy; 21 such cases have been reviewed since 1985 (1) and they continue to be reported to national monitoring centers. This adverse effect usually occurs within 4 weeks after the start of therapy and is slowly reversible after the drug is withdrawn.

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Oxygen

General Information

The duration and extent of hyperoxygenation during anesthesia are generally limited. However, in intensive care, a patient's exposure to oxygen can become prolonged and dangerous. Oxygen toxicity can cause adverse effects in numerous tissues, including the lungs, nervous system, eyes, red blood cells, and liver, because of their susceptibility to chemical toxicity by mechanisms such as lipid peroxidation (SED-12, 242) (1).

Organs and Systems

Respiratory

The adverse effects of high-dose oxygen on the lungs take the form of an initial exudation of blood and fibrinous fluid into the alveoli followed by proliferation of fibroblasts and alveolar cells (2). The proliferative phase can be permanent (3). It is reflected in a reduced vital capacity and a reduced diffusion capacity (4) and appears to be proportional to the units of pulmonary toxic dose (UPTD) administered; 1 UPTD is equivalent to 1 absolute atmosphere $\times$ 1 minute of exposure. If exposure exceeds 1000 UPTD it can be difficult to predict the outcome (5), owing to inter-patient differences in susceptibility.

Nervous system

High doses of oxygen can cause convulsant activity resembling tonic-clonic seizures (6) and is associated with reduced concentrations of GABA in the brain. Such fits may not be apparent in sedated patients.

Sensory systems

Oxygen toxicity in the eye can cause tunnel vision by an effect on the retina (7) and, in neonates, retrolental fibroplasia (8) (SED-12, 242).

Hematologic

Oxygen toxicity in red blood cells can cause hemolysis (SED-12, 242) (9).

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Oxygen-carrying blood substitutes

General Information

The development of oxygen-carrying blood substitutes, which can act as alternatives for allogenic erythrocyte transfusions, has progressed significantly in the last decade. It is important for the laboratory medicine community to be aware of their effects on routine laboratory testing and the settings in which they might be used (1).

The characteristics of an ideal emulsion for use as a blood substitute are absence of red cell incompatibility, absence of a risk of transmission of infectious diseases, a long duration of conservation, easy access, and rheological parameters similar to those of blood (2).

Oxygen carriers can be divided into two classes: hemoglobin-based oxygen carriers, prepared from hemoglobin of human or bovine origin, and synthetic perfluorocarbons.

Hemoglobin-based oxygen carriers

There are three sources of hemoglobin from which oxygen carriers have been developed: human, bovine, and recombinant. Hemoglobin-based oxygen carriers have benefits, such as the lack of pathogen transmission, no need for cross-matching, and increased stability and storage time; however, compared with erythrocyte transfusions, they have a short half-life. Of various hemoglobin-based oxygen carriers under development, two (Polyheme and Hemopure) have been tested in phase III studies. One product, Hemopure—polymerized hemoglobin of bovine origin—has been licensed for human use in South Africa. The tetrameric hemoglobin easily dissociates in vivo into dimers and monomers that are quickly eliminated by the kidneys. As the administration of tetrameric hemoglobin is associated with renal insufficiency, intermolecular cross-linking of hemoglobin has been performed using different agents to polymerize hemoglobin. Newly developed hemoglobin-based oxygen

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carriers are conjugated hemoglobin or packed hemoglobin in nanocapsules or lipid vesicles (3–6).

Perfluorocarbons

Perfluorocarbons are synthetic, fluorinated hydrocarbons that increase the amount of oxygen dissolved in the fluid phase of the blood. Perfluorocarbon emulsions are heavy, low-viscosity liquids, inert, and optically clear, with a high specific gravity and good surface tension. Their chemical and physical properties make them a suitable temporary intraoperative tool to flatten the retina during surgery, and they have gained wide acceptance in the surgical management of complicated retinal detachment (7). Perfluorocarbons have a transport capacity that is greater than that of blood under hyperoxic conditions (2).

The available formulations include perfluoro-octyl bromide, perfluoro-octylethane, perfluorodichloro-octane, Fluosol-DA (70% perfluorodecalin plus 30% perfluorotripropylamine), Oxygent™ (perflubron, perfluoro-octyl bromide) (5), and LiquiVent (perflubron). Second-generation perfluorocarbons are now used in anemia, trauma, high blood loss surgery, perioperative hemodilution, ischemia, and organ conservation for transplantation. Phase III studies of one of the perfluorocarbons, Oxygent™, are proceeding in cases in which tissue oxygenation is required and when it is desirable to avoid allogeneic blood transfusion.

General adverse effects

Hemoglobin-based oxygen carriers

Hemoglobin-based oxygen carriers bind endogenous nitric oxide, thereby causing transient hypertension, esophageal dysfunction, and abdominal discomfort. In a phase II study using *O*-raffinose cross-linked hemoglobin (Hemolink™) in patients undergoing coronary artery bypass grafting surgery raised blood pressure, probably caused by binding of *O*-raffinose cross-linked hemoglobin to nitric oxide, and jaundice were observed (8). Jaundice was expected, owing to metabolism of cell-free hemoglobin.

Perfluorocarbons

Perfluorocarbon blood substitutes are reported to have several adverse effects, the clinical significance of which is not currently fully understood. They include a dose-related, flu-like illness 4–6 hours after infusion (2,9). Symptoms included back pain, malaise, flushing, and transient fever (10); arterial hypotension, tachycardia, a high leukocyte count, and thrombocytopenia can also occur. These symptoms are most likely cytokine-mediated, as the perfluorocarbon particles are cleared by cells of the reticuloendothelial system (11). The most important adverse effect of LiquiVent is the risk of intravascular passage of the perfluorocarbon. Phagocytosis by alveolar macrophages has been demonstrated by cytology. Larger doses of emulsion particles can lead to hepatic engorgement and temporary impairment of immune defences (2).

Third-generation emulsions are currently in early preclinical development (2). The absence of toxicity of these new emulsions has been demonstrated in endothelial cell cultures and in animal organ preservation studies.

In a phase II study in 25 patients undergoing ardiac surgery a perflubron emulsion (AF0144) was well tolerated (12).

Organs and Systems

Cardiovascular

A modified hemoglobin solution, DCLHb, has been associated with an increase in mean arterial pressure. This has been proposed to be due to binding to nitric oxide, stimulation of the production of endothelin, and sensitization and/or potentiation of beta-1 and beta-2 adrenoceptor responses to catecholamines (2).

It has been suggested that cell-free hemoglobin, particularly low molecular weight hemoglobin, such as tetrameric hemoglobin, has the ability to come more closely to the endothelial cell lining of blood vessels than erythrocytes and to extravasate into the subendothelial space. There, hemoglobin might scavenge nitrous oxide and so induce vasoconstriction and hypertension (3,5,9). A randomized, controlled phase II study has suggested that hemoglobin raffimer (Hemolink) is safe and effective in patients undergoing coronary artery bypass surgery. The incidence of hypertension was higher in the treated group, but blood pressure management prevented serious hypertension-related events (13).

Another hemoglobin substitution product, liposome-encapsulated tetrameric hemoglobin, can exacerbate the manifestations of septic shock (2).

Respiratory

In premature neonates and children with respiratory distress syndrome treated with a perfluorocarbon, pneumothorax has been observed (2).

Sensory systems

Corneal epithelial damage has been attributed to a perfluorocarbon (14).

- An elderly man underwent vitreoretinal surgery for retinal detachment. Perfluorodecalin was used to repair the retina and was left in situ for 8 weeks and removed via the pars plana. One month later he developed a non-healing corneal epithelial defect associated with limbitis. Perfluorodecalin was found under the superior conjunctiva. A biopsy showed vacuoles in the conjunctival stroma surrounded by inflammatory cells. On surgical removal of the perfluorodecalin from the subconjunctival space, the epithelial defect healed.

Although the high surface tension of perfluorocarbons allows closure of retinal breaks and prevents them from flowing into the subretinal space, particularly during intraocular manipulation, they can gain entry into the subretinal space, resulting in residues in the eye (15,16). The removal of perfluorocarbons is recommended at the end of surgery, but they can be left in the eye for limited periods of time (17).

- A 29-year-old man with a high degree of myopia developed a rhegmatogenous retinal detachment due to a giant retinal tear following blunt trauma (18). After

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surgical treatment perfluorodecalin was left in the eye as a tamponade; 2 weeks later it was removed and 20% sulfahexafluoride was injected. On the following day the retina was flat and residual perfluorodecalin was not detected in the vitreous cavity. A week later he developed severe pain in the operated eye and his vision worsened. There was a marked cellular response in the vitreous cavity and total retinal detachment. Examination with retroillumination showed that there was residual perfluorocarbon trapped in the retrolental space. There also appeared to be a precipitate of pigmented cells adherent to the vitreous surface of the posterior lens capsule, as seen on slit lamp biomicroscopy. Posterior capsulotomy removed the obstruction caused by the deposits, confirming the suspicion of the site of the pigmentary infiltration. A small amount of heavy liquid was found subretinally and removed. Although retinal reattachment was not possible due to very severe proliferative vitreoretinopathy, the intravitreal inflammation resolved.

Hematologic

Administration of erythrocytes can cause neutrophil priming, which leads to a dysfunctional inflammatory response. This neutrophil priming, which has been associated with the occurrence of multiple organ failure after trauma, was not observed after administration of Polyheme, a glutaraldehyde-cross-linked hemoglobin product (3).

In a randomized, double-blind, placebo-controlled study in healthy volunteers coagulation responses (using bleeding time) and hemostasis were examined for 14 days after dosing with either saline or perfluorocarbon emulsion (1.2 or 1.8 g/kg) (19). There were no postinfusion changes in bleeding time or differences in in vivo agonist-induced platelet aggregation. There was a fall in platelet count, but this recovered to baseline within 7 days. The intravascular half-life of perfluorocarbon for the first 24 hours was dose-dependent (9.4 hours and 6.1 hours with 1.8 and 1.2 g/kg respectively). The authors concluded that perfluorocarbon does not affect coagulation, at least in healthy volunteers.

Transient thrombocytopenia can occur 3–4 days after perfluorocarbon (10). In several studies the fall in platelet count was 30–40%, and platelet counts returned to normal in 7–10 days. The use of radioactively labelled platelets showed increased platelet clearance, thought to be due to alteration of the platelet surface by the perfluorocarbon emulsion.

Gastrointestinal

Occasionally, gastrointestinal disorders have been related to the use of hemoglobin-based oxygen carriers, possibly through binding of nitrous oxide, causing gastrointestinal smooth muscle spasm (9,20).

Liver

In a single-blind, randomized study, four of 55 surgical patients who were treated with Hemopure developed jaundice without an increase in serum bilirubin (21). Similarly, in a double-blind, randomized study of 98 patients undergoing cardiac surgery, Hemopure was related to some cases of jaundice (22).

Urinary tract

Purification of haemoglobin avoids free hemoglobin, which can cause nephrotoxicity (2).

Skin

In a single-blind, randomized study, two of 55 surgical patients who were treated with Hemopure had ecchymotic rashes (21).

Immunologic

Hemoglobin solutions do not have the antigenic properties of the blood groups.

Drug Administration

Drug contamination

The main limitation of bovine hemoglobin is the risk of transmission of bovine spongiform encephalopathy and the development of antibodies to bovine proteins (2).

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Oxymetazoline and xylometazoline

General Information

Oxymetazoline and xylometazoline are alpha-adrenoceptor agonists, which seem to be better tolerated than other topically used drugs of this sort.

Organs and Systems

Ear, nose, throat

Nasal irritation, with dryness of the mouth and throat, can occur; a rebound effect on the nasal mucosa was found in some 5% of cases studied (1).

Sensory systems

The development of an acute retinal artery obstruction in a young, otherwise healthy man was associated with excessive use of an oxymetazoline nasal spray. Platelet coagulation studies indicated a platelet aggregation hypersensitivity to adenosine diphosphate and adrenaline. Predisposition to sympathomimetic drug-induced platelet fibrin embolus formation may have played a role in this case (2).

Oxymetazoline has a vasoconstrictor effect and this has been reported to have caused an ischemic retinopathy (3).

- A 43-year-old woman with hypertension and diabetes mellitus used 2–3 puffs of oxymetazoline nasal spray and experienced painless blurring of vision in the right eye, with a corrected acuity of 20/400 (20/50 on the left). Apart from background diabetic retinopathy she had edema of the optic disk. Several weeks later she used the spray again and this time developed blurred vision in the left eye. There was disk pallor on both sides and acuities were 20/400 on the right and 20/70 on the left. There were also segmental inferior field defects in both eyes. After 6 weeks both eyes had recovered somewhat, but only to 20/200 and 20/50 respectively: there was no further improvement after a year.

The authors concluded that this was sequential bilateral ischemic retinopathy due to oxymetazoline.

Long-Term Effects

Drug withdrawal

The interruption of a high dose nasal spray therapy precipitated a prolonged panic disorder in a healthy man (SEDA-13, 109).

Second-Generation Effects

Fetotoxicity

Repeated use of an oxymetazoline nasal spray has been associated with changes in fetal heart rate demonstrated as a non-reactive, non-stress test and late decelerations in a patient at 41 weeks of gestation; 6 hours after the last dose these changes gradually disappeared (4).

Susceptibility Factors

Age

Systemic adverse reactions of ocular administration have been reported in young children (5).

Drug Administration

Drug overdose

An unusual response to an overdose of oxymetazoline (0.05% nasal spray) occurred in an elderly patient who used the product several times daily; the patient, who had pre-existing cerebellar degeneration and peripheral neuropathy, developed severe bradycardia and oscillations in systolic pressure between 236 and 60 mmHg. Withdrawal of the spray resulted in complete recovery (6).

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Oxyphenbutazone

See also Non-steroidal anti-inflammatory drugs

General Information

Oxyphenbutazone is a parahydroxylated analogue of phenylbutazone, and is one of its active metabolites. It has the same spectrum of activity, therapeutic uses, interactions, dangers, and contraindications. In April 1985, Ciba-Geigy decided to stop sales of systemic dosage forms of oxyphenbutazone worldwide. They stated that they had reached this decision because a survey had shown that although the recommended limitations on the use of phenylbutazone had been widely respected, the same could not be said of oxyphenbutazone. Evidence that oxyphenbutazone was more likely to cause death due to bone marrow failure than phenylbutazone (1) was provided by data from the UK's Committee on Safety of Medicines. Furthermore, according to Ciba-Geigy's re-assessment in January 1984, deaths per million prescriptions of oxyphenbutazone were 5.5 (USA) to 12.8 (UK) compared with phenylbutazone (3.8–7.6 deaths per million prescriptions) (SEDA-9, 87).

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Oxyphencyclamine

General Information

Oxyphencyclamine is an anticholinergic drug, which is claimed to act for some 12 hours. However, the wide range of oral doses used (10–50 mg/day) indicate doubt about its potency.

Oxyphenonium

See also Anticholinergic drugs

General Information

Like methanthelinium, oxyphenonium is an anticholinergic drug with relatively marked ganglion-blocking effects, but it seems to have little effect on the central nervous system; an oral dose of 5–10 mg given several times a day produces typical anticholinergic effects. Its efficacy is rather poor (1).

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Oxytocin and analogues

General Information

Oxytocin is a hypothalamic nonapeptide that selectively stimulates the smooth muscle of the uterus and mammary glands. It is used in the induction or augmentation of labor and to prevent postpartum hemorrhage, and is well tolerated and effective in a wide range of infusion rates and concentrations. Contraindications to its use include placenta previa or vasa previa, a previous classical uterine incision, pelvic structural deformities, and an abnormal fetal presentation. Large fetal size and high maternal parity are relative contraindications. Prior nonclassical cesarean delivery should not preclude oxytocin therapy.

Uterine contractions and fetal heart rate should be monitored during oxytocin administration (SEDA-13, 1310) (1,2). There is no significant increase in uterine complications or in fetal morbidity or mortality in women with a previous cesarean section, although oxytocin-treated patients had a higher rate of failed trial of labor for reasons that are unclear (3). Oxytocin is structurally similar to vasopressin, and like the latter has water-retaining properties when used in pharmacological doses.

Oxytocin is in common use during induction of labor and in the third stage of labor to prevent uterine atony and postpartum hemorrhage. Carbetocin, a synthetic analogue with a half-life 4–10 times longer than the native hormone, has been studied in trials; both agents cause a small transient fall in blood pressure (less than 4 mmHg) (4). Common mild adverse effects of both drugs include headache, flushing, a feeling of warmth, a metallic taste, and abdominal pain.

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Organs and Systems

Cardiovascular

Tachycardia and a fall in blood pressure are common and usually short-lived after oxytocin administration during labor. There has been one reported maternal death after a hypovolemic woman was given a bolus dose of oxytocin 10 units (5).

In 34 women undergoing cesarean section at full term under spinal anesthesia, heart rate and cardiac output increased significantly within 2 minutes of the rapid administration of either 5 or 10 units of oxytocin, with an associated 10 mmHg fall in mean arterial pressure in those who received 10 units (6). There were significant ST segment changes in 11 of 26 women undergoing cesarean section, with raised concentrations of troponin I in two; however, the relationship to oxytocin administration was not clear in this report (7).

- A previously fit 19-year-old woman had severe ST segment depression and increased troponin concentrations after a bolus dose of oxytocin 5 units (8).

Ventricular tachycardia has been reported in two patients with pre-existing prolongation of the QT interval, immediately after oxytocin was begun (9).

Fluid balance

Fluid retention causing severe hyponatremia and convulsions has been observed in neonates after administration of oxytocin and salt-poor fluids to the mother during labor.

Acute water intoxication has produced maternal cerebral edema and convulsions in under 50 reported cases, both with intravenous and intranasal administration (10). The risk is higher in women given high doses of the drug in combination with salt-poor intravenous fluids. In rare cases this has been fatal.

Hematologic

Maternal oxytocin administration increases the rate of neonatal physiological jaundice in a dose-dependent manner (SEDA-13, 1310) (11). This effect may be due to hemodilution and an increased rate of hemolysis.

Second-Generation Effects

Pregnancy

In a retrospective analysis of 2774 women who had had one prior cesarean delivery, there was a 1% incidence of uterine rupture in women who were given oxytocin, compared with 0.4% in non-augmented controls with spontaneous labor (12). Six women needed emergency hysterectomy. The odds ratio for uterine rupture in the oxytocin-treated women was 4.6 by logistic regression analysis (CI = 1.5,14). The small number of events limited the study: it had only 30% power to detect changes of that magnitude. However, it is reasonable to proceed cautiously, with close clinical observation, given the potentially severe outcome.

- Uterine rupture occurred when oxytocin was started 5 hours after the administration of a second misoprostol tablet for induction of labor, although the usual recommendation is to wait at least 12 hours (13).
- A 36-year-old multiparous woman had a ruptured uterus after labor was induced at 24 weeks with misoprostol 200 μg and augmented with oxytocin (14).

The risk of uterine rupture is increased by previous cesarean section, fetal weight over 4 kg, and the use of oxytocin (SEDA-24, 506) (15,16). In 24 women with uterine rupture after oxytocin, the dose and duration of use of oxytocin were 10% higher than in controls; this difference was not statistically significant, but the power of the study was limited by the small sample size (17).

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Paclitaxel

See also Cytostatic and immunosuppressant drugs

General Information

Paclitaxel is a complex plant product derived from the bark of the yew tree, *Taxus brevifolia*. It has been used for the treatment of metastatic carcinoma of the ovary and breast. It has also been investigated in the treatment of other carcinomas, including non-small-cell lung cancer, malignant melanoma, head and neck cancers, acute leukemias, and Kaposi's sarcoma. The recommended dosage for the treatment of ovarian and breast carcinoma is 175 mg/m^2 given intravenously over 3 hours every 3 weeks. However, various dosage and administration schedules have been investigated.

Mechanism of action

Paclitaxel acts by enhancing microtubule assembly and stabilizing microtubules (1,2). Microtubules consist of polymers of tubulin in dynamic equilibrium with tubulin heterodimers. Their principal function is the formation of the mitotic spindle during cell division, but they are also active in many interphase functions, such as cellular motility, intracellular transport, and signal transmission. Paclitaxel inhibits the depolymerization of tubulin, and the microtubules formed in the presence of paclitaxel are extremely stable and dysfunctional. This stabilization impairs the essential assembly and disassembly required for dynamic cellular processes, and death of the cell results through disruption of the normal microtubular dynamics required for interphase processes and cell division. In tumor cells, cytotoxicity is represented by the appearance of abnormal microtubular bundles, which accumulate during G2 and mitosis, blocking the cell cycle (3).

Pharmacokinetics

Paclitaxel has non-linear kinetics: peak plasma concentrations and drug exposure increase disproportionately with increasing doses and the pharmacokinetics depend on the schedule of administration. Saturation is reached with high-dose short infusions (4). Paclitaxel has been reported to follow both biphasic (5) and triphasic models (6). The half-life has been estimated at 6–13 hours after intravenous administration (7).

After intravenous administration, paclitaxel is extensively distributed, despite extensive binding to plasma proteins (89%), presumably albumin (2). Its routes of elimination have not been fully elucidated, but renal clearance accounts for an insignificant proportion of total systemic clearance, suggesting that metabolism, biliary excretion, or excretion via other routes are responsible for elimination (6). High concentrations of paclitaxel and its hydroxylated metabolites have been found in rat and human bile, suggesting hepatic metabolism (8). In all, 11 metabolites of paclitaxel have been identified, and paclitaxel metabolism to 6-α-hydroxypaclitaxel is an important detoxification pathway (6,9).

The effects of renal and hepatic dysfunction on paclitaxel elimination have not been studied extensively. Since renal clearance accounts for a small proportion of total clearance, dosage modifications are not considered necessary in patients with renal dysfunction.

One study has shown that patients with existing liver dysfunction have a reduced total body clearance of paclitaxel and require dosage reductions (10). A dosage reduction of 50% has been suggested in patients with moderate or severe hyperbilirubinemia or increased serum transaminases (4).

Paclitaxel is formulated in a mixture of ethanol and Cremophor EL (polyethoxylated castor oil). Cremophor reduced the electrophoretic mobility of serum lipoproteins along with the appearance of a lipoprotein dissociation product. After serum was exposed to Cremophor in vitro or in vivo there was substantial binding of paclitaxel to the lipoprotein dissociation product(s), and this could represent an important factor in the distribution of paclitaxel (11).

General adverse effects

A summary of the incidences of the adverse effects of paclitaxel in single-agent studies in 402 patients is given in Table 1 (12).

Organs and Systems

Cardiovascular

Paclitaxel causes disturbances in cardiac rhythm, but the relevance of these effects has not been fully elucidated. Originally, all patients in trials of paclitaxel were under continuous cardiac monitoring, owing to the risk of hypersensitivity reactions, and cardiac disturbances were therefore more likely to be detected. Many trials limited eligibility to patients without a history of cardiac abnormalities and to those who were not taking medications likely to alter cardiac conduction. The incidence of cardiac dysrhythmias in the population under study not treated with paclitaxel is unknown, and it is therefore not always possible to attribute dysrhythmias to paclitaxel in these patients. The Cremophor EL vehicle does not appear to be implicated in the incidence of dysrhythmias, although hypotension associated with hypersensitivity reactions may occur (13).

The most common effect of paclitaxel is asymptomatic bradycardia, which occurred in 29% of patients in one phase 2 trial (14) and in 9% of patients in a further assessment of 402 patients in phase 2 trials (15). One phase 1 trial showed no significant cardiac dysrhythmias (16), while another reported cardiac toxicity in 14% of patients, 74% of these being due to asymptomatic bradycardia (17). Bradycardia is not an indication for discontinuation of treatment, unless it is associated with atrioventricular conduction disturbances or clinically significant effects (for example symptomatic hypotension). More significant bradydysrhythmias and atrioventricular conduction disturbances have been reported during clinical trials, including Mobitz I (Wenckebach syndrome) and Mobitz II atrioventricular block (14,18).

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Table 1 Incidences of adverse effects of paclitaxel

Adverse effect	Incidence (%)
Cardiovascular	
Bradycardia during infusion	10
Hypotension during infusion	23
Severe cardiovascular events	1
Abnormal electrocardiogram (all patients)	30
Abnormal electrocardiogram (patients with normal baseline)	19
Nervous system	
Peripheral neuropathy	
Any symptoms	62
Severe symptoms	4
Hematologic	
Neutropenia $<2 \times 10^9$/l	92
Neutropenia $<0.5 \times 10^9$/l	67
Leukopenia $<4 \times 10^9$/l	93
Leukopenia $<1 \times 10^9$/l	26
Thrombocytopenia $<100 \times 10^9$/l	27
Thrombocytopenia $<50 \times 10^9$/l	10
Anemia <11 g/dl	90
Anemia <8 g/dl	24
Liver	
Bilirubin raised	8
Alkaline phosphatase activity raised	23
Aspartate transaminase (AsT) activity raised	16
Gastrointestinal	
Nausea and vomiting	59
Diarrhea	43
Mucositis	39
Hair	
Alopecia	82
Musculoskeletal	
Myalgia/arthralgia	
Any symptoms	55
Severe symptoms	4
Immunologic reactions (with premedication)	
Any	41
Severe	2

One patient died in heart failure 7 days after receiving paclitaxel by infusion; this patient had no prior history of cardiac problems, apart from mild hypertension (19).

The authors of a review of the cardiac toxicity associated with paclitaxel in a number of studies concluded that the overall incidence of serious cardiac events is low (0.1%) (20). Heart block and conduction abnormalities occurred infrequently and were often asymptomatic. Sinus bradycardia was the most frequent, occurring in 30% of patients. The causal relation of paclitaxel to atrial and ventricular dysrhythmias and cardiac ischemia was not entirely clear. There did not appear to be any evidence of cumulative toxicity or augmentation of acute cardiac effects of the anthracyclines.

In an attempt to clarify further the cardiotoxicity of paclitaxel, its effect on cardiovascular autonomic regulation has been investigated in 14 women (21). The authors concluded that autonomic modulation of heart rate is impaired by paclitaxel, but they were unable to say whether it would return to normal on withdrawal. They also investigated the effect of docetaxel on neural cardiovascular regulation in women with breast cancer, previously treated with anthracyclines (22). They concluded that docetaxel did not impair vagal cardiac control. The changes that they observed in blood pressure suggest that docetaxel changes sympathetic vascular control, although these changes seemed to be related to altered cardiovascular homeostasis rather than peripheral sympathetic neuropathy.

Continuous cardiac monitoring is recommended for patients with serious conduction abnormalities; however, routine cardiac monitoring is considered unnecessary in patients without a history of cardiac conduction abnormalities (7). Further studies are needed to determine the risk in patients treated with paclitaxel with predisposing cardiac risk factors.

Respiratory

Effects of paclitaxel on the respiratory system are generally related to hypersensitivity reactions. One case of pneumonitis was possibly due to a hypersensitivity reaction to either paclitaxel or its vehicle Cremophor EL; treatment with corticosteroids resulted in improvement (23). One patient developed tachypnea and cyanosis and subsequently died of pulmonary edema 7 days after receiving an infusion of paclitaxel (19).

Nervous system

The most common nervous system effect is peripheral neuropathy, although one patient developed tonic-clonic seizures whilst receiving paclitaxel and required treatment with benzodiazepines and barbiturates (14). Motor weakness has occasionally been reported (24).

Neurotoxicity associated with paclitaxel is dose-dependent, cumulative, and characterized principally by a sensory and motor peripheral neuropathy. Neuropathy appears to be related to axonal degeneration and demyelination (25). Neurological toxicity is usually reversible after termination of therapy, and although it rarely requires withdrawal of therapy, it has been the dose-limiting adverse effect in some phase 1 trials (5,26). This effect became more apparent as higher doses of paclitaxel were used, particularly in combination with growth factors, which allow escalating doses of paclitaxel to be administered. A high-dose study has shown dose-related toxicity, with a dose-limiting ceiling at 775 mg/m^2, when paresthesia occurs (27). Patients with co-existing medical illnesses associated with peripheral neuropathy, such as diabetes mellitus and alcohol abuse, may be more prone to develop peripheral neuropathy.

Peripheral neuropathy presents as numbness, burning, and tingling in a glove-and-stocking distribution. Symptoms usually begin 24–72 hours after treatment with paclitaxel, with a symmetrical distal loss of sensation. Most cases occur at doses over 200 mg/m^2 and particularly after multiple courses (24–26). Mild to moderate sensory neuropathy has occurred in 52% of patients treated with doses of 175 mg/m^2, while only 36% experienced neuropathy at doses of at least 135 mg/m^2 (17,24,28,29). At the lower dose of 135 mg/m^2, the effects are usually limited to a mild sensory neuropathy (17,29).

The incidence of peripheral neuropathy increases substantially at doses above 250 mg/m^2 (14,16,18–20,

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25,29–32). Neuropathy was the dose-limiting adverse effect in one phase 1 trial with doses of 275 mg/m^2, and patients experienced grade 2–3 neurotoxicity 1–3 days after treatment (5). The symptoms generally subsided within several weeks to months. A study of adverse effects in patients in phase 2 trials showed that peripheral neuropathy occurred in 62% of 402 patients (15). Of patients receiving higher doses (190 mg/m^2 or more), 80% had symptoms that were mild or moderate. In severe cases of peripheral neuropathy a dose reduction of 20% is recommended for subsequent courses (7).

Previous treatment with other neurotoxic agents may compound the problem. In one study symptoms of neurotoxicity were observed in one patient who received concomitant cisplatin with paclitaxel (33). However, signs and symptoms of neurotoxicity have been insignificant in combination treatments of cisplatin and paclitaxel in other trials (1). Pre-existing neuropathy as a result of previous therapy is not a contraindication to paclitaxel (7).

Tricyclic antidepressants, in particular amitriptyline, and venlafaxine are helpful in relieving symptoms of paclitaxel-induced peripheral neuropathy (1,26,33,34).

Sensory systems

Transient scintillating scotomata have been observed in the visual fields of both eyes in nine patients receiving paclitaxel infusions in doses of 175 and 225 mg/m^2 (35). Involvement of the optic nerve was confirmed, and this is likely to have been related to optic nerve conduction abnormalities associated with the neurological effects of paclitaxel. The abnormalities were not progressive and there was some degree of recovery, although one patient sustained a permanent reduction in vision.

Hematologic

Bone marrow suppression is a dose-limiting adverse effect often encountered with paclitaxel. Neutropenia occurs most commonly 8–10 days after treatment, and recovery usually occurs on days 15–21. Paclitaxel is relatively platelet-sparing, and thrombocytopenia and anemia are rare (26). There is no evidence that neutropenia is cumulative, suggesting that paclitaxel may not irreversibly damage hemopoietic stem cells (1).

Neutropenia is dose- and schedule-related and is less common with shorter infusion schedules. At doses of 110–250 mg/m^2 over 24 hours, neutropenia is usually severe, and grade 4 neutropenia develops in a large proportion of patients. Paclitaxel given as a 3-hour infusion causes less severe neutropenia (17,24,29). An analysis of patients receiving either a 3-hour or 24-hour infusion of 175 or 135 mg/m^2 showed that severe neutropenia was more common with the 24-hour infusions: 75% of patients developed severe neutropenia (absolute neutrophil count below 500×10^6/1) and episodes of fever (29). Doses of 200–250 mg/m^2 also cause severe neutropenia when paclitaxel was given as a 24-hour infusion, but recovery of neutrophil count was fairly rapid (13,14,26,33,36,37).

The duration of neutropenia is usually brief and treatment delays for unresolved adverse hematological effects at day 21 are rare. Paclitaxel-induced neutropenia does not always lead to infectious complications, and therefore a dosage reduction for neutropenia alone is not considered necessary (14,16,18–20,29,30).

Prior myelotoxic chemotherapy and/or radiotherapy appear to be major risk factors in determining the severity of neutropenia (1,13). Doses of 200 and 250 mg/m^2 over short infusion times induce minimal myelosuppression in patients who have had minimal prior therapy (26,30); however, seven patients (1.6%) died because of toxicity in another trial in patients with ovarian cancer who had received extensive previous chemotherapy; deaths were due to sepsis or severe neutropenia (13).

Other data suggest that neutropenia may be related to pharmacological exposure, and phase 1 studies have shown that the severity of paclitaxel-induced neutropenia correlates with the area under the paclitaxel concentration–time curve (36).

The incidence of neutropenia has also been investigated in combination schedules. Patients receiving paclitaxel in combination with cyclophosphamide have severe neutropenia more often than with single treatment (72% of patients). Paclitaxel given as a 24-hour infusion before cyclophosphamide is more likely to cause severe neutropenia compared with patients who receive cyclophosphamide first (31).

Attempts to overcome neutropenia include the use of human granulocyte colony stimulating factor (GCSF). The absolute neutrophil counts are generally higher and the duration of severe neutropenia is shorter when GCSF is given 24 hours after paclitaxel and continued until there is recovery of the neutrophil count. When paclitaxel is given in combination with GCSF, doses of 250 mg/m^2 given over 24 hours every 3 weeks are possible without inducing dose-limiting neutropenia (16). Three-hour infusion schedules have also been successful using doses of 250 mg/m^2 in combination with GCSF and doxorubicin (32). Other dose-limiting adverse effects tend to predominate when paclitaxel is given in higher doses in combination with GCSF.

Recommendations currently specify that patients should not be retreated with paclitaxel until the neutrophil count recovers to 2.5×10^9/1 and the platelet count recovers to over 100×10^9/1 (7).

Gastrointestinal

Severe nausea, vomiting, and diarrhea are uncommon with paclitaxel (1). Although about half of the patients in one study had vomiting or diarrhea, under 5% were severe events (15). In another phase 2 trial, there were 11 episodes of nausea and vomiting in 281 courses (14). Four patients developed diarrhea, but this was not clinically significant. Generally, symptoms of nausea, vomiting, and diarrhea associated with paclitaxel therapy are mild.

Mucositis and stomatitis have been reported with paclitaxel. Mucositis is characterized by ulceration of the lips, pharynx, and oral cavity, occurring 3–7 days after paclitaxel treatment (1,13,14,17,24,26,29,33,36–38). Mucositis appears to be more common during treatment of acute leukemias rather than solid tumors, when doses above 390 mg/m^2 are used (24). Severe mucositis occurred during second and third courses, suggesting a cumulative effect, and was more severe if treatment was given at 15 days or less after previous courses. Patients

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with hematological malignancies are more prone to breakdown of the mucosal barrier, and this may account for the increased incidence of mucositis. Narcotic analgesics are effective in controlling the pain associated with mucositis (1).

Severe abdominal pain occurred in 25 patients treated with intraperitoneal paclitaxel in doses over 175 mg/m^2 (39).

Transient paralytic ileus occurred in two patients in one study (29). Both patients were diabetic, and these symptoms may have been an additional manifestation of autonomic neuropathy.

Postmortem examinations of patients treated with paclitaxel have shown mucosal ulceration of the esophagus, stomach, small intestine, and colon (40). Changes associated with epithelial necrosis and mitotic arrest were most prominent in patients who had recently been treated with paclitaxel. These findings suggest that paclitaxel causes transient mitotic arrest associated with cell necrosis.

Urinary tract

Reversible renal insufficiency has been reported in one patient who was treated with paclitaxel by the intraperitoneal route (39).

Skin

Local venous effects, including erythema, tenderness, and discomfort, can occur at the injection site during paclitaxel infusion (13). Inflammation is evident within hours and usually resolves within 21 days. Inflammation occurs in areas of drug extravasation along with prolonged soft tissue injuries, and necrotic changes have been reported in one patient at the site of extravasation (41). Inflammation is most likely to be due to the drug, but the Cremophor EL vehicle may be implicated, as it produces mild inflammation in animals (41).

There is little information on the treatment of extravasation of paclitaxel, as it has not been common during clinical trials. However, a soft-tissue injury occurred in one patient at the site of previous extravasation after treatment with paclitaxel in a different limb (42). This resolved within 7 days.

Radiation dermatitis has been reported in a patient who received a single infusion of paclitaxel (43). This was attributed to the potentiation of radiation effects by paclitaxel because of the close time relation between the radiotherapy and paclitaxel therapy.

Hair

Alopecia occurs in nearly all patients who receive paclitaxel, but it has unique characteristics. Hair loss is sudden and complete, and many patients often experience loss of all body hair, including axillary and pubic hair, eyelashes, and eyebrows (28,44). The loss of body hair often occurs with cumulative therapy and is more severe after longer infusion times.

Nails

Onycholysis occurred in five of 21 patients who received more than six doses of paclitaxel 100 mg/m^2/week (45). The authors also provided a useful review of onycholysis caused by other chemotherapy.

Musculoskeletal

An arthralgia/myalgia syndrome occurs 2–5 days after chemotherapy in about 20–30% of patients receiving paclitaxel and is possibly dose-related (1). It commonly occurs at doses above 170 mg/m^2 (29). Symptoms of myalgia usually involve the shoulder and paraspinal muscles, while arthralgia is common in the large joints of the arms and legs (1,13). Symptoms can be controlled by nonsteroidal anti-inflammatory drugs (13) and perhaps gabapentin (46). The incidence of arthralgia and myalgia is also increased in patients who receive GCSF, with symptoms occurring more frequently in 86% of patients compared with patients who receive similar doses without growth factor support (28%) (16).

The severity of myalgia and arthralgia correlated significantly with the total cumulative dose of paclitaxel 210 mg/m^2/cycle by 3-hour infusion in 247 patients with a median cumulative dose of 630 mg/m^2 (47).

Immunologic

Acute hypersensitivity reactions were common during phase 1 trials of paclitaxel, and this caused delays in the completion of many trials. Reactions were mild to severe and consisted of cutaneous flushing, bronchospasm, bradycardia, and hypotension; the reactions occurred after either the first or second dose (48). The mechanism of these reactions is uncertain, but they are thought to be non-immunologically mediated, and direct histamine release by mast cells is probably responsible. A large dose of Cremophor EL is used in the formulation of paclitaxel, and this may play an important part in these hypersensitivity reactions; Cremophor EL induces similar reactions in dogs by direct release of histamine (4).

In a study of 32 patients, 84% of those who received paclitaxel developed hypersensitivity reactions characterized by hypotension, respiratory distress, and urticaria (35). These symptoms further confirm that histamine is likely to be the cause of the reaction. The majority of reactions (53%) occurred within 2–3.minutes after the administration of paclitaxel and 78% within 10 minutes. There was one fatal reaction, characterized by hypotension and asystole. Most reactions to paclitaxel occurred after the first or second dose, and hypersensitivity reactions were more common with shorter infusion schedules. Since the duration of the infusion affected the incidence of hypersensitivity reactions, an extension of the infusion duration was investigated. Longer infusion schedules were associated with a reduced incidence of hypersensitivity reactions, the frequency of severe reactions being reduced from 12% or more to 5% with longer infusion times (5,15,49).

Premedication regimens of glucocorticoids and histamine H_1 and H_2 receptor antagonists have been used in an attempt to prevent hypersensitivity reactions in other phase 1 trials. These trials were successfully completed using infusion schedules of 1–120 hours and doses of 135–390 mg/m^2, with a lower incidence of hypersensitivity reactions (15,17,28,29,37,44,48). However, the use of premedication did not completely prevent such reactions.

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There were incidences of 16, 13, and 7% with 3-hour, 6-hour, and 24-hour infusion schedules respectively, despite premedication (48), while only 1.5% of patients developed reactions in a trial with doses of 125–250 mg/m^2 over 24 hours with glucocorticoids and histamine receptor antagonists (29). Only one patient out of 26 developed a hypersensitivity reaction with doses of 150–250 mg/m^2 over 24 hours (26). The relative merits of longer infusion times and premedication are not entirely clear.

In one study of infusion of doses of 175–275 mg/m^2 over 6 hours without premedication, there was only one hypersensitivity reaction in 32 patients (49), while patients who received paclitaxel administered over 1 hour with premedication developed no serious hypersensitivity reactions (37). There were no hypersensitivity reactions in 40 patients who received fractionated doses of paclitaxel administered over 3–5 days, with cumulative doses of 120–250 mg/m^2 (36). In a randomized comparison of two doses of paclitaxel given by 3-hour or 24-hour infusions, premedication alone was sufficient to prevent hypersensitivity reactions with either infusion duration (29).

Premedication, consisting of dexamethasone 20 mg intravenously, 12 and 6 hours before the infusion, and diphenhydramine 50 mg and cimetidine 300 mg, intravenously 30 minutes before the infusion, are now routinely given before patients are treated with paclitaxel, and this, as well as a recommended infusion time of 3 hours, has reduced the incidence and severity of hypersensitivity reactions. A single dose of dexamethasone 16 mg given 30 minutes before paclitaxel was effective in preventing hypersensitivity reactions in 43 patients (38); however, whether a single dose of a glucocorticoid is sufficient for prophylaxis is controversial.

About 2% of all patients who receive paclitaxel with preventive premedication will develop a severe hypersensitivity reaction, characterized by dyspnea, hypotension, angioedema, and urticaria, and requiring treatment. Minor reactions occur in 39% of patients but do not require therapeutic intervention (7).

There was a 9% incidence of clinically important hypersensitivity reactions to paclitaxel in 450 women with gynecological malignancies treated with paclitaxel either alone or in combination regimens (50). There was a significant association between bee sting or animal allergy and paclitaxel hypersensitivity in 57 patients with a variety of tumors (51).

Drug–Drug Interactions

General

Drug interactions with paclitaxel have been reviewed (52). The most important of these are the pharmacodynamic interactions with other cytostatic drugs, but pharmacokinetic interactions have also been described.

Paclitaxel is metabolized by the cytochrome P_{450} isoenzymes CYP2C and CYP3A4 (53), and drugs that inhibit or induce these isozymes would be expected to alter the metabolism of paclitaxel. In vitro ranitidine, diphenhydramine, vincristine, vinblastine, and doxorubicin had little or no effect on the metabolism of paclitaxel, but barbiturates stimulated hydroxylation of the side-chain by induction of CYP3A isoforms (53).

Anthracyclines

The combination of doxorubicin plus paclitaxel is cardiotoxic. Various authors have suggested that after a median cumulative dose of 480 mg/m^2, 50% of patients will have a reduced left ventricular ejection fraction and 20% will develop congestive heart failure.

In 36 women with previously untreated metastatic breast cancer, paclitaxel dose-dependently increased the plasma concentrations of doxorubicin and its metabolite doxorubicinol; this was attributed to competition for biliary excretion of taxanes and anthracyclines mediated by *P*-glycoprotein (54).

Two studies of the combination of epirubicin plus paclitaxel have shown less reduction in left ventricular ejection fraction and no clinical evidence of cardiac failure (55,56).

Ketoconazole

In patients with ovarian cancer, ketoconazole, 100–1600 mg as a single oral dose 3 hours after paclitaxel 175 mg/m^2 as a 3-hour continuous intravenous infusion, did not alter plasma concentrations of paclitaxel or its principal metabolite, 6-alpha-hydroxypaclitaxel (57).

Platinum-containing cytotoxic drugs

In 21 patients with advanced non-small cell lung cancer carboplatin had no effect on the pharmacokinetics of paclitaxel 135–200 mg/m^2 as a 24-hour intravenous infusion (58). Peripheral neuropathy occurred in 13 of 37 patients treated with paclitaxel 175 mg/m^2 and carboplatin (59). The authors concluded that clinically important neurotoxicity increases with every cycle of chemotherapy. The peripheral neuropathy mainly affected sensory fibers without involving motor nerves. The same paclitaxel/carboplatin chemotherapy in 28 women caused no signs of acute central neurotoxicity or neuropsychological deterioration; however, 11 patients had a peripheral neuropathy (60).

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Palivizumab

See also Monoclonal antibodies

General Information

Palivizumab is a humanized monoclonal antibody that inhibits an epitope at the A antigenic site of the F protein of respiratory syncytial virus subtypes A and B (1).

Palivizumab is generally well tolerated (2). Its most common adverse effects (over 5%) are rhinitis, cough, fever, pharyngitis, bronchiolitis, and diarrhea (3).

In 565 patients with respiratory syncytial virus infections palivizumab caused injection site reactions (2.3%), fever (1.5%), and nervousness/irritability (under 1%); no other adverse effects were reported (4).

Organs and Systems

Immunologic

The estimated risk of anaphylactic reactions to palivizumab is under one per 100 000 infants (5). No second-season subjects had a significant antipalivizumab antibody response (titer over 1:80) (6).

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Pancreatic enzymes

General Information

Pancreatic enzyme supplements are used to treat people who lack pancreatic secretions. Pancreatin, the British Pharmacopoeia standard, is an extract of pancreas, and contains enzymes with proteinase, amylase, and lipase activity; most commercial formulations are similar or identical (SEDA16, 358).

The effect of oral pancreatic enzyme supplementation (Creon 10 000 in a dose of 1000 units of lipase per gram of ingested dietary fat) on fat malabsorption has been evaluated in an open study in 24 patients with HIV infection (1). Pancreatic enzyme supplementation was highly effective in reducing fecal fat loss. There were no clinical adverse effects or changes in serum biochemistry attributable to the drug.

Organs and Systems

Metabolism

The effects of pancreatic exocrine supplements (four capsules with meals, two with snacks; each capsule containing lipase 10000 units, protease 37500 units, amylase 33200 units) on glucose metabolism have been studied in a 2-week parallel, randomized, placebo-controlled trial in 29 patients with chronic pancreatitis who had stool fat excretion of over 10 g/day, 18 of whom were diabetic and 15 of whom were malnourished (2). There were major problems with blood glucose control in 28 of the 29 patients.

Gastrointestinal

Colonic toxicity due to pancreatic enzyme supplements in children with cystic fibrosis has been reviewed (3). Since it was first reported in 1994, an increasing number of cases of fibrosing colonopathy due to pancreatic enzymes have been reported in children with cystic fibrosis in the UK, USA, and continental Europe. The disorder is not affected by age or sex, and the age at diagnosis is 9 months to 13 years.

- Fibrotic injury of the entire colon has been reported in an 8-year-old boy with cystic fibrosis who took pancreatic enzymes 12 000 IU/kg at each meal (SEDA23.36.65). He had earlier been taking 5000 IU/kg. The first colonic symptoms occurred 1 year after the increase in dose.

Evidence implicates high-strength formulations, which provide at least 22 000–25 000 IU of lipase per capsule (compared with low-strength and medium-strength formulations which provide up to 10 000 IU), and the association between pancreatic enzymes and colonopathy is clearly dose-related: the higher the dose greater the risk. There are several hypotheses about the pathogenesis of the condition. They include the following:

- toxicity due to the enteric coating (Eudragit L30D-55) used in high-strength pancreatic capsules;
- prolonged exposure of the colon to high-strength pancreatic enzymes because of the abnormally low small intestinal pH in cystic fibrosis, causing delay in dissolution of the enteric coating of the capsule (which occurs only above pH 5.5) until the enzymes reach the distal small intestine or even the large intestine;
- a colon-specific immune-mediated disorder or primary dysregulation of collagen synthesis in the colonic wall.

High-dose pancreatic enzyme formulations are no longer recommended for use in children because of the risk of fibrosing colonopathies (SEDA-19, 330) (SEDA-20, 322). A consensus meeting between the Cystic Fibrosis Foundation and the FDA in 1995 recommended that weight-based dosing should start at 1000 lipase units/kg per meal for children under 4 years and that the upper limit of the usual dosage should be 2500 lipase units/kg per meal and about half for snacks. This translates to a daily intake of 12 000–15 000 lipase units/kg, and the doses of other enzymes, such as protease, would be proportional (SEDA-21, 366).

Having reviewed the available epidemiological data, the UK's then Medicines Control Agency recommended that high-strength pancreatic enzymes coated with Eudragit L-30D-55 should be contraindicated in children under 15 years, that all high-strength formulations should be available only on prescription, and that no formulation should be used in a dosage over 10 000 IU/kg/day.

Pancreas

The effect of high-dose pancreatic enzymes on pancreatic function has been assessed in a double-blind study in 12 healthy volunteers, six of whom were given 18 capsules of Panzytrat (20 000 units of lipase, 18 000 units of amylase, and 1000 units of protease per capsule) daily for 4 weeks (4). There were no morphological or functional changes in the pancreas in those treated. None of the subjects had severe adverse effects. Two had transient mild nausea, epigastric pain, and heartburn. There were no abnormalities in liver function tests.

Drug Administration

Drug contamination

Pancreatic preparations can be bacterially contaminated (5).

Some formulations of pancreatic enzymes contain monohydroxy bile acids, which should not be administered to patients with liver disease (6).

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Pancuronium bromide

See also Neuromuscular blocking drugs

General Information

Pancuronium bromide is a non-depolarizing muscle relaxant (1) with two quaternary ammonium groups on a steroid (androstane) skeleton. It is about 5–7 times as potent as D-tubocurarine. Protein binding occurs to both albumins and globulins, probably only to a relatively slight extent (10–20%), although reports vary from 10 to 90%. In contrast to most other non-depolarizing relaxants, pancuronium is metabolized at about 10–20%. Deacetylation in the liver probably accounts for the greater part of this biotransformation. The major metabolites are 3-monohydroxypancuronium, 17-monohydroxypancuronium, and (3,17)-dihydroxypancuronium; they are active pharmacologically, 3-monohydroxypancuronium being half as potent and the other two having 2% of the potency of pancuronium. About 40–50% of a dose is normally excreted in the urine and 5–10% in the bile over 24 hours as pancuronium plus its metabolites.

Pancuronium is reported to inhibit plasma cholinesterase (2) and this may be partly why the action of suxamethonium, given after a small dose of pancuronium, is prolonged. It also weakly inhibits acetylcholinesterase.

For tracheal intubation the usual dose is 0.1 mg/kg. When given after suxamethonium, 0.05 mg/kg is sufficient for good abdominal relaxation. Further doses of about one-quarter to one-third of the initial dose are given at intervals of 30–40 minutes to maintain relaxation. Reversal is easily achieved with neostigmine, provided there is some spontaneous return of neuromuscular transmission beforehand. If the evoked twitch height is less than 10% of the control value, there can be difficulty in reversing the blockade; this applies to all non-depolarizing relaxants, except perhaps vecuronium and atracurium.

The onset time for complete neuromuscular blockade is similar to that of D-tubocurarine and other non-depolarizing agents, namely 2–4 minutes. However, this is to some extent dose-dependent, and because of the relative lack of cardiovascular effects and histamine release, pancuronium can safely be given in higher dosages, thus producing good intubation conditions within 2 minutes. The dose of D-tubocurarine required to achieve similar conditions in 2 minutes would result in hypotension. As with D-tubocurarine, repeated doses can lead to accumulation and prolonged blockade.

In burned patients resistance to the neuromuscular blocking action of pancuronium may be encountered (3), as with other non-depolarizing relaxants.

Patients in whom pancuronium bromide is of value (4) include:

- patients with hypoxemia resisting mechanical ventilation and so cardiovascularly unstable that the use of sedatives is precluded;
- patients with bronchospasm unresponsive to conventional therapy;
- patients with severe tetanus or poisoning when muscle spasm prohibits adequate ventilation;
- patients with status epilepticus unable to maintain their own ventilation;
- shivering patients in whom metabolic demands for oxygen should be reduced;
- patients requiring tracheal intubation in whom suxamethonium is contraindicated.

Organs and Systems

Cardiovascular

Cardiovascular adverse effects are minimal with pancuronium. Ganglion blockade does not occur. Slight dose-dependent rises in heart rate, blood pressure, and cardiac output are common (5), but are often masked by the actions of other co-administered agents, such as fentanyl or halothane, which cause bradycardia or hypotension. These adverse effects of pancuronium are thus often beneficial and can be deliberately harnessed. Several mechanisms contribute: vagal blockade via selective blockade of cardiac muscarinic receptors (6), release of noradrenaline from adrenergic nerve endings (7), increased blood catecholamine concentrations (8), inhibition of neuronal catecholamine reuptake (9–11), and direct effects on myocardial contractility (12). These have been reviewed (13–15).

Occasionally nodal rhythm, atrioventricular dissociation, and tachydysrhythmias (such as ventricular extra beats or even bigeminy) develop, but these usually occur in association with halothane.

Supraventricular tachycardia has been reported after 8 mg pancuronium in a patient taking aminophylline (800 mg/day) (16).

Nodal rhythm can occur after injection of pancuronium. This dysrhythmia and bradycardia appear to be more common when neostigmine (plus atropine) is given for reversal of pancuronium-induced neuromuscular blockade than for reversal of D-tubocurarine or alcuronium (17); cholinesterase inhibition by pancuronium may contribute to the bradycardia in these circumstances.

Respiratory

Histamine release and bronchospasm are relatively rare with pancuronium but have been reported (SEDA-12, 117) (18–21).

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Nervous system

Accidental injection into the cerebrospinal fluid of 4 mg of pancuronium resulted in generalized hypotonia, weakness, and hypoventilation (SEDA-15, 126) (22). Neostigmine given intravenously led to prompt recovery.

Sensory systems

Neonates with congenital diaphragmatic hernia often develop respiratory failure. To facilitate mechanical ventilation, neuromuscular blocking agents may be used. Sensorineural hearing loss can occur in survivors, with a reported incidence of up to 60%. It has been associated with the use of pancuronium. In a historical cohort study of 37 survivors of congenital diaphragmatic hernia, children with hearing loss had received significantly higher doses of pancuronium during respiratory failure than children without hearing loss (23). In addition, the cumulative dose of pancuronium correlated with the intensity of hearing loss in decibels. There were no differences with regard to oxygenation and ventilation parameters or to the cumulative dose of aminoglycosides, vancomycin, or furosemide, but children with hearing loss had received a higher cumulative dose of etacrynic acid. The authors admitted that the retrospective study design and the small sample size demanded cautious interpretation of their observations. For the time being, this report is not reason enough to avoid pancuronium if neuromuscular blockade is required. However, it should be remembered that the risk of severe neuromuscular disturbances associated with long-term administration of neuromuscular blocking agents militates against the routine use of these drugs in patients in intensive care, both children and adults. If muscle relaxants are given in this setting for more than a few hours, their effect should be monitored by a peripheral nerve stimulator to avoid overdose and drug accumulation. This may prove technically difficult in neonates.

Liver

Significant hyperbilirubinemia has been reported to occur more frequently in critically ill neonates given pancuronium than in a control group (24). The hyperbilirubinemia increased in the 4 days after withdrawal of pancuronium, whereas during the administration period the hyperbilirubinemia was less in the pancuronium group.

Body temperature

Malignant hyperthermia, possibly triggered by pancuronium, has been described (25), although pancuronium is generally considered to be safe in patients who are susceptible to the syndrome (26).

Second-Generation Effects

Fetotoxicity

There is placental transfer of pancuronium, but no untoward effects have been reported in neonates.

In a comparison of the onset and duration of paralysis produced by 0.2 mg/kg pancuronium ($n = 8$) or pipecuronium ($n = 8$) injected into the thighs of fetuses at 30–38 weeks gestational age, tachycardia occurred in four out of eight fetuses given pancuronium, and there was loss of beat-to-beat variability in two. No such changes were observed in any of the eight fetuses given pipecuronium (27).

Susceptibility Factors

Renal disease

Pancuronium appears to depend more on renal function for its elimination than D-tubocurarine does. Its action is, in most cases, significantly prolonged in renal insufficiency (28); in particular, spontaneous recovery is slow and adequate reversal of the block with neostigmine takes much longer than is generally expected (29). The response to pancuronium is much more unpredictable in renal insufficiency, with great interindividual variation in duration of blockade. Occasionally resistance to neuromuscular blockade with pancuronium is encountered (SEDA-13, 103) (28,30). This may be because of an increase in the volume of distribution. High plasma and tissue concentrations of 3-monohydroxypancuronium, sufficient to produce significant neuromuscular blockade, have also been measured in anuria (31). Monitoring of neuromuscular function is required in patients with appreciable renal dysfunction.

Hepatic disease

In hepatic disease, pancuronium seems to be more problematic than D-tubocurarine. Patients with cirrhosis have a prolonged half-life, a reduced clearance, and a markedly increased apparent volume of distribution (32). This is likely to result in the need for larger initial doses for adequate relaxation and prolongation of recovery of neuromuscular function.

Cholestasis can prolong the action of pancuronium, reducing its plasma clearance by 50%. This may be a result of raised bile salts, reducing the hepatic uptake of pancuronium (which is an important factor contributing to the total plasma clearance in normal patients) (SEDA-6, 130).

In patients undergoing liver transplantation, the dosage requirements for pancuronium and vecuronium by intravenous infusion were reduced by 57 and 50% respectively during the anhepatic phase (SEDA-17, 153), whereas atracurium requirements were not altered by exclusion of the liver from the circulation.

Other features of the patient

As with all muscle relaxants, abnormal reactions can occur in patients with neuromuscular diseases. In addition, muscle fibrillation has been reported, possibly due to pancuronium, in a patient with metachromatic leukodystrophy (33).

Pancuronium is relatively contraindicated, particularly in combination with halothane, in patients who may have raised catecholamine concentrations, or who are receiving drugs with sympathomimetic effects. Severe hypertension together with tachycardia can occur when pancuronium is given to a patient with a pheochromocytoma (34,35).

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Caution should also be exercised in patients with thyrotoxicosis and with valvular stenosis, coronary artery insufficiency (36), or other conditions in which a tachycardia is hazardous.

Drug–Drug Interactions

Aminophylline

Aminophylline facilitates neuromuscular transmission, perhaps by increasing neurotransmitter release, through raising cyclic AMP concentrations at the neuromuscular junction via phosphodiesterase inhibition (37). This would account for the antagonism of pancuronium-induced blockade that has been reported in the presence of very high serum concentrations of theophylline (38).

Anticonvulsants

The long-term use of phenytoin has been associated with increased pancuronium requirements during neurosurgical operations (39), although the opposite effect might be expected from the quinine-like membrane-stabilizing activity of phenytoin.

Azathioprine

Azathioprine reduces sensitivity to pancuronium in experimental animals, possibly as a result of phosphodiesterase inhibition, increasing transmitter release (SEDA-4, 87) (40), (SEDA-13, 104).

Carbamazepine

Resistance to pancuronium, with a considerable shortening of recovery time, has been seen in patients taking long-term carbamazepine (SEDA-12, 118) (41); there was an inverse correlation between the daily dose and the recovery time.

Ciclosporin

Ciclosporin can cause considerable prolongation of the neuromuscular paralysis induced by pancuronium (42) in one patient (and also in another given vecuronium). Reversal required both neostigmine and edrophonium. Subsequently, recurarization occurred (SEDA-14, 116). Contributing factors could have been the solvent Cremophor EL in the ciclosporin formulation (Sandimmun) and minor renal dysfunction.

Corticosteroids

Corticosteroids have been reported to antagonize neuromuscular blockade due to pancuronium (43,44). In vitro studies in rats have shown a direct facilitating action of prednisolone on neuromuscular transmission (45), so that one would expect some antagonism of non-depolarizing relaxants in general.

Furosemide

Furosemide (1 mg/kg) shortened the recovery time from pancuronium blockade in neurosurgical patients with normal renal function (46). Phosphodiesterase inhibition and increased pancuronium excretion were suggested as possible explanations.

General anesthetics

Halothane anesthesia increases the risks of tachydysrhythmias when pancuronium is used (47).

Pancuronium lowers the MAC for halothane by 25% (48), although this has been disputed (SEDA-15, 124) (49).

Glyceryl trinitrate

Experiments in cats have demonstrated a significant prolongation and potentiation of the neuromuscular blockade induced by pancuronium during glyceryl trinitrate infusion (1 mg/kg/minute) started before the muscle relaxant was given. No prolongation was seen if suxamethonium, D-tubocurarine, or gallamine were used instead of pancuronium. Neostigmine reversal of the pancuronium block was not affected and neither was the plasma clearance of pancuronium changed over the 2 hours after the injection (50,51). The cause of this phenomenon, and whether it is applicable to humans, remains to be elucidated. However, more recent experiments (also in cats), using only moderate doses of pancuronium (and vecuronium), have failed to elicit any potentiation by glyceryl trinitrate (52).

Lithium carbonate

Prolonged neuromuscular blockade has been reported in patients taking long-term lithium given pancuronium (53). In animal experiments, lithium prolonged neuromuscular block due to pancuronium, suxamethonium, and decamethonium, but not that due to D-tubocurarine and gallamine (54); on the other hand, lithium was reported to have no or minimal effects on the blockade produced by pancuronium or D-tubocurarine (55). The mechanism of this interaction is not known, although possible mechanisms have been discussed (54). Caution, and monitoring are advisable.

Tricyclic antidepressants

The use of both halothane and pancuronium in patients taking tricyclic antidepressant has been reported as resulting in severe tachydysrhythmias. Experiments in dogs have shown that this combination can produce ventricular fibrillation and cardiac arrest (56). Enflurane also resulted in tachycardias in dogs given both imipramine and pancuronium acutely, but not when the imipramine was given chronically for 15 days beforehand. Pancuronium should not be used in patients taking tricyclic antidepressants.

Interference with Diagnostic Tests

Radiography

Complete relaxation in artificially ventilated neonates has resulted in apparent "gasless abdomens" on radiography and confusion in diagnosis. On discontinuation of paralysis, the normal appearance of gas-filled bowel was restored (57).

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Pantoprazole

See also Proton pump inhibitors

General Information

Pantoprazole is a proton pump inhibitor.

Comparative studies

Pantoprazole 40 mg/day and ranitidine 150 mg bd for 8 weeks have been compared in the treatment of grades II and III reflux esophagitis in a randomized, double-blind trial in 256 patients (1). Symptom relief and healing rates were significantly better with pantoprazole. The incidences of adverse effects were similar in the two groups; the most commonly reported were diarrhea and somnolence with pantoprazole (2–3%) and headache, diarrhea, dizziness, increases in liver enzymes, and pruritus (2–4%) with ranitidine.

Pantoprazole 20 and 40 mg/day and nizatidine 150 mg bd for 8 weeks have been compared in the treatment of reflux esophagitis (grade II or worse) in a multicenter, randomized, double-blind trial in 221 patients (2). Both doses of pantoprazole were more effective in relieving symptoms and healing erosive esophagitis than nizatidine. The incidences of adverse effects were similar in the three groups; the most commonly reported were diarrhea and headache.

Pantoprazole 20 mg/day and ranitidine 300 mg/day for 12 months have been compared in the relief of symptoms in a multicenter, randomized, double-blind trial in 307 patients with symptomatic gastro-esophageal reflux disease in primary care (3). Symptom control was significantly more effective and faster with pantoprazole than ranitidine. Adverse effects were similar in the two groups; the most common adverse effects were headache, diarrhea, nausea, constipation, and vomiting.

Pantoprazole 40 mg/day and pantoprazole 40 mg/day plus cisapride 20 mg bd for 8 weeks have been compared in the treatment of gastro-esophageal reflux disease in a multicenter, randomized, double-blind trial in 350 patients (4). The addition of cisapride did not significantly improve symptom control or healing rates. The frequency of adverse effects in the two groups was similar. Compliance was worse in the pantoprazole plus cisapride group.

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Pantothenic acid derivatives

See also Vitamins

General Information

The pantothenic acid derivatives include pantothenic acid (BAN), pantothenol (BAN), dexpanthenol (rINN), and hopantenic acid (rINN).

Pantothenic acid (vitamin B_5) has been proposed as a treatment for hair loss. It has been used to treat pantothenic acid deficiency, acne, and rheumatoid arthritis. Over

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the past 30 years, only mild adverse reactions, such as rash and diarrhea, have been reported.

Hopantenate (calcium D-(+)-4-(2, 4-dihydroxy-3, 3-dimethylbutyramido)butyrate hemihydrate), or calcium hopantenate, is a homoanalog of l-pantothenate and has been used in Japan for the treatment of mental retardation with behavioral abnormalities. It represents one of the many attempts that have been made, so far unsuccessfully, to develop derivatives of substances belonging to the vitamin B group as agents for the treatment of brain or nervous disorders (SEDA-12, 328) (SEDA-13, 347).

Adverse effects, sometimes fatal, have been reported in patients taking calcium hopantenate, notably encephalopathy with metabolic acidosis and semicoma (1) and a Reye-like syndrome (2); this may be due to pantothenic acid deficiency, as hopantenate is a pantothenic acid antagonist. In elderly people, liver dysfunction and gastrointestinal upsets have been reported (3,4). In Japan, where the product was introduced in 1978, the control authorities in 1988 issued a series of warnings with respect to problems caused by hopantenate (5).

Organs and Systems

Cardiovascular

Eosinophilic pleural effusion with eosinophilic pericardial tamponade has been attributed to concomitant use of pantothenic acid and biotin (6).

- A 76-year-old woman developed chest pain and difficulty in breathing. She had no history of allergy and had been taking biotin 10 mg/day and pantothenic acid 300 mg/day for 2 months for alopecia. Chest X-rays showed pleural effusions and cardiac enlargement. Blood tests showed an inflammatory syndrome, with an erythrocyte sedimentation rate of 51 mm/hour and an eosinophil count of 1.2–1.5 $\times$ 10^9/l. Pericardiotomy showed an eosinophilic infiltrate. There was no evidence of vasculitis. Serological studies were negative for antinuclear antibodies, rheumatoid factor, viruses, bacteria, and Lyme disease. Stool examination and parasitological serologies were negative. A malignant tumor was excluded by mammography, thoracoscopy, and a CT scan. Myelography, a biopsy specimen of the iliac crest bone, and the concentrations of IgE, lysozyme, and vitamin B_{12} were also normal. A week after withdrawal of pantothenic acid and biotin she improved dramatically and her eosinophilia resolved.

Metabolism

As a pantothenic acid analogue, hopantenate can affect lactate generation, glucose metabolism, and ammonia disposal, and there have been two fatal cases in elderly people who developed disturbances of consciousness with lactic acidosis, hypoglycemia, and hyperammonemia (7).

Immunologic

Contact allergy to dexpanthenol is rare, but it occurs more often in some patients (for example those with eczema of the lower leg). Between 1992 and 1999, only 163 of 13 216 patients tested in the Information Network of Departments of Dermatology had a positive reaction to dexpanthenol. There have been no previous cases of occupational dexpanthenol sensitization caused by occupational exposure, but one has been reported in a junior nurse (8).

- Six weeks after starting training a 29-year-old nurse developed flushing and pruritus on the back of both hands and fingers, spreading to the forearms. Because of increased skin sensitivity she had been recommended to use skin protection measures; however, she did not use the skin protection cream that was available at the hospital but used a "Hand- und Hautsalbe" that had been designed for use especially in hairdressing salons. In addition to the lesions on her hands and arms she had periorbital shadowing, angular cheilitis, palmar hyperlinearity, and slightly generalized xerosis of the skin. She also reported seasonal rhinoconjunctivitis, intolerability of metals, and rhagades on the ears. After withdrawal of all supposed allergenic substances and local antieczematous therapy, the hand and arm lesions healed within a few days. Skin tests were positive for nickel-II-sulfate, imidazolidinyl urea, phenyl mercury acetate, and the hand cream, in which pantothenol (5% in vaseline) was identified as the allergen. She avoided the cream and the eczema did not recur.

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Papaveraceae

See also Herbal medicines

General Information

The genera in the family of Papaveraceae (Table 1) include a variety of poppies and the greater celandine.

Chelidonium majus

Chelidonium majus (celandine, common celandine, greater celandine) contains a number of alkaloids, including chelidonine, chelerythrine, chelidocystatin, coptisine, sanguinarine, berberine, and sparteine.

Greater celandine was traditionally used to improve eyesight and in modern times has been used as a mild sedative, and antispasmodic in the treatment of bronchitis, whooping cough, asthma, jaundice, gallstones, and gallbladder pain. The latex is used topically to treat warts, ringworm, and corns. A semisynthetic thiophosphate derivative of alkaloids from *C. majus*, called Ukrain, has cytotoxic and cytostatic effects on tumor cells (1).

Adverse effects

Hematologic

Hemolytic anemia has been reported after the oral use of a celandine extract; there was intravascular hemolysis, renal insufficiency, liver cytolysis, and thrombocytopenia; a direct antiglobulin test was positive (2).

Liver

Hepatitis has been attributed to celandine (3).

- A 42-year-old woman had been admitted twice to hospital with hepatitis (4). No toxic agent could be identified during the first episode, but detailed questioning during the second showed that in both cases she had self-prescribed a commercially available medication of common celandine. Withdrawal of this herbal remedy was followed by an unremarkable recovery.

Table 1 The genera of Papaveraceae

Arctomecon (bear poppy)
Argemone (prickly poppy)
Bocconia (bocconia)
Canbya (pygmy poppy)
Chelidonium (celandine)
Dendromecon (tree poppy)
Eschscholzia (California poppy)
Glaucium (horn poppy)
Hunnemannia (hunnemannia)
Macleaya (macleaya)
Meconella (fairy poppy)
Papaver (poppy)
Platystemon (cream cups)
Platystigma (queen poppy)
Roemeria (roemeria)
Romneya (Matilija poppy)
Sanguinaria (bloodroot)
Stylophorum (stylophorum)
Stylomecon (wind poppy)

- A 42-year-old woman developed acute hepatitis several weeks after taking a herbal formulation containing greater celandine and curcuma root for a skin complaint (5). After withdrawal recovery was rapid and hepatic function returned to normal within 2 months.

Ten cases of acute hepatitis induced by formulations of greater celandine were observed over 2 years in a German University hospital (6). Perhaps ironically, this product is popular in Germany for gastric and gall-bladder problems. In five cases there was marked cholestasis but no liver failure. After withdrawal of the product, the symptoms subsided and the liver enzymes normalized within 2–6 months. Unintentional rechallenge led to a further episode of acute hepatitis in one patient.

In addition to about 15 published cases, some 40 cases of liver damage from *C. majus* have been reported to the German regulatory authorities (7). The course of the hepatitis can be severe and can include cholestasis and fibrosis, but acute liver failure has not been observed. Based on these data, celandine has been banned for oral use in several countries.

Skin

Contact sensitivity has been attributed to *C. majus* (8).

Susceptibility factors

Some authors caution that the use of celandine in children should be discouraged because of an early fatal colitis in a 3-year-old boy (9); however, this report does not provide convincing evidence that the victim had indeed taken *C. majus*.

Papaver somniferum

Papaver somniferum (opium poppy) contains a variety of opioid and related alkaloids, including codeine, morphine, noscapine, papaverine, and thebaine. Crude opium is the air-dried latex obtained by incising the unripe capsules of *P. somniferum*. Paregoric is ammoniated tincture of opium (Scotch paregoric) or camphorated tincture of opium (English paregoric). The use of these formulations has largely been replaced by use of the purified compounds.

Adverse effects

The adverse effects of opium are generally the same as those of the pure compounds.

Respiratory

Of 28 workers in a pharmaceutical factory that produced morphine and other alkaloids extracted from the shells of *P. somniferum*, six had symptoms of sensitization and positive skin tests (10). A bronchial provocation test was positive in four of them, and in all six there was a specific IgE, detected by ELISA and RAST tests using an aqueous extract of *P. somniferum*.

Nervous system

- A young man dependent on "Kompot" or "Polish heroin", a domestic product produced from poppy straw or the juice of poppy heads (*P. somniferum*) and given intravenously, developed Guillain–Barré syndrome after severe intoxication induced by home-made heroin, barbiturates, and benzodiazepines (11).

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"Kompot" contains variable amounts of morphine, heroin (diacetylmorphine), 3-monoacetylmorphine, 6-monoacetylmorphine, acetylcodeine, and codeine, in addition to papaverine, thebaine, and narcotine.

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Papaveretum

See also Opioid analgesics

General Information

Papaveretum (Omnopon, Pantopon) is a mixture of several opium alkaloids.

Organs and Systems

Urinary tract

Renal insufficiency has been reported in a 60-year-old patient after the use of papaveretum for perioperative analgesia (SEDA-17, 83).

Second-Generation Effects

Teratogenicity

Because of possible teratogenicity, papaveretum is no longer recommended for women of child-bearing age (SEDA-17, 83).

Susceptibility Factors

Age

There was a 56% incidence of nausea and vomiting with papaveretum in 129 children 24 hours after circumcision with caudal epidural blockade (1).

Reference

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Papaverine

General Information

Papaverine is an alkaloid present in opium, although it is not related chemically or pharmacologically to other opium alkaloids. It has a direct relaxant effect on smooth muscle, partly attributable to inhibition of phosphodiesterase.

Systemic adverse effects reported are hypotension and dizziness and, in rare cases, abnormal results of liver function tests (SEDA-15, 3).

Organs and Systems

Sexual function

Intracavernous administration of papaverine with phentolamine has been used in the diagnosis and treatment of erectile dysfunction. The major local adverse effect is prolonged erection, which usually occurs early during diagnostic testing and is reduced after dose adjustment; furthermore, local hematomas have been reported in a number of patients. It may be that patients most susceptible to priapism can be identified in advance by testing their erectile abilities in response to erotic stimulation (1). Long-term therapy can also cause intracavernous fibrosis but it can also lead to development of tolerance to the desired effect.

Reference

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Parabens

See also Disinfectants and antiseptics

General Information

Parabens (methyl, ethyl, propyl, and butyl esters of parahydroxybenzoic acid) are used as preservatives in concentrations of 0.1–0.3% in pharmaceutical formulations and in concentrations of 0.01–0.1% in cosmetics and foods. In such concentrations they are devoid of systemic toxic effects, but allergic reactions have been reported.

Organs and Systems

Immunologic

Parabens can cause allergic contact dermatitis that can run an insidious course, especially when the parabens are in glucocorticoid ointments. In such cases, treatment leads to a protracted dermatitis without acute exacerbation, so that neither the patient nor the physician suspects parabens as a possible cause. A sensitization index of 0.8% was found in 273 patients with chronic dermatitis (1).

In 1973, in a multicenter study of 1200 individuals carried out by the North American Contact Dermatitis Group, there was a 3% incidence of delayed hypersensitivity reactions to parabens. General allergic reactions have also been reported after the injection of parabens-containing formulations of lidocaine and hydrocortisone and after oral use of barium sulfate contrast suspension, haloperidol syrup, and an antitussive syrup, all of which contained parabens (SEDA-11, 484).

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Paracetamol

General Information

A century after its introduction, acetylsalicylic acid (aspirin) is by far the most commonly used analgesic, sharing its leading position with the relative newcomer paracetamol (acetaminophen), and notwithstanding the fact that other widely used compounds, such as ibuprofen, have in recent years been introduced in over-the-counter versions. Both are also still being prescribed by physicians and are generally used for mild to moderate pain, fever associated with common everyday illnesses, and disorders ranging from head colds and influenza to toothache and headache. However, their greatest use is by consumers who obtain them directly from the pharmacy, and in many countries outside pharmacies as well.

Perhaps this wide availability and advertising via mass media leads to a lack of appreciation by the lay public that these are medicines with adverse effects. Both have at any rate been subject to misuse and excessive use, leading to such problems as chronic salicylate intoxication with aspirin and severe hepatic damage with paracetamol overdose. Both aspirin and paracetamol have also featured in accidental overdosage (particularly in children) as well as intentional overdosage.

In an investigation of Canadian donors who had not admitted to drug intake, 6–7% of the blood samples taken were found to have detectable concentrations of acetylsalicylic acid and paracetamol (1). Such drugs would be potentially capable of causing untoward reactions in the recipients.

To offer some protection against misuse of analgesics, many countries have insisted on the use of packs containing total quantities less than the minimum toxic dose (albeit usually the one obtained for healthy young volunteers and thus disregarding the majority of the population), and supplied in child-resistant packaging. Most important, however, is the need to provide education for the lay public to respect such medicines in general for the good they can do, but more especially for the harm that can arise, but can be avoided. There is a definite role for the prescribing physician, since informing the patient seems to prevent adverse events (2).

The sale of paracetamol or aspirin in dosage forms in which they are combined with other active ingredients offers considerable risk to the consumer, since the product as sold may not be clearly identified as containing either of these two analgesics. Brand names sometimes obscure the actual composition of older formulations that contain one or both of these analgesics in combination with, for example, a pyrazolone derivative and/or a potentially addictive substance. For instance, in Germany, with the EC harmonization of the Drug Law of 1990, the manufacturers of drugs already marketed before 1978 had the opportunity of exchanging even the active principles without being obliged to undergo a new approval procedure or to abandon their brand name. Combination formulations are still being promoted and sold, and not exclusively in developing countries. Consequently the patient who is so anxious to allay all his symptoms that he takes several medications concurrently may without knowing it take several doses of aspirin or paracetamol at the same time, perhaps sufficient to cause toxicity. It is essential that product labels clearly state their active ingredients by approved name, together with the quantity per dosage form (3).

The antipyretic analgesics share with the non-steroidal anti inflammatory drugs (NSAIDs) a common mechanism of action, namely the inhibition of prostaglandin synthesis from arachidonic acid and their release. More precisely their mode of action is thought to result from inhibition of both the constitutive and the inducible isoenzymes (COX-1 and COX-2) of the cyclo-oxygenase pathway (4). However, aspirin and paracetamol are distinguishable from most of the NSAIDs by their ability to inhibit prostaglandin synthesis in the nervous system, and thus the hypothalamic center for body temperature regulation, rather than acting mainly in the periphery.

Endogenous pyrogens (and exogenous pyrogens that have their effects through the endogenous group) induce the hypothalamic vascular endothelium to produce

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prostaglandins, which activate the thermoregulatory neurons by increasing AMP concentrations. The capacity of the antipyretic analgesics to inhibit hypothalamic prostaglandin synthesis appears to be the basis of their antipyretic action. Neither aspirin nor paracetamol affects the synthesis or release of endogenous pyrogens and neither will lower body temperature if it is normal.

While aspirin significantly inhibits peripheral prostaglandin and thromboxane synthesis, paracetamol is less potent as a synthetase inhibitor than the NSAIDs, except in the brain, and paracetamol has only a weak anti-inflammatory action. It is simple to ascribe the analgesic activity of aspirin to its capacity to inhibit prostaglandin synthesis, with a consequent reduction in inflammatory edema and vasodilatation, since aspirin is most effective in the pain associated with inflammation or injury. However, such a peripheral effect cannot account for the analgesic activity of paracetamol, which is less well understood.

The use of paracetamol as an antipyretic increased rapidly once phenacetin was no longer available and has received a boost more recently with wide acknowledgement of the role of aspirin as a causative agent in Reye's syndrome, resulting in the virtual disappearance of children's dosage forms of aspirin. While the incidence of adverse effects is reassuringly low, satisfaction must be tempered by appreciation of the relatively short duration of extensive clinical experience with paracetamol, its close relation to phenacetin, its low potency as an analgesic, and low public awareness of its potential adverse effects.

General adverse reactions

Although paracetamol is acceptably safe in usual dosages, there have been some reports that in patients with significant hepatic dysfunction or those taking substances that induce hepatic enzymes (for example ethanol, phenobarbital, isoniazid) even these doses may aggravate liver dysfunction, sometimes to the point of causing hepatic failure. The problem of overdosage is substantial. Allergic reactions, including urticaria, are seen occasionally. Anaphylactic shock has been reported.

Organs and Systems

Cardiovascular

Despite the high prevalence of the use of minor analgesics (aspirin and paracetamol) there is little information available on the association between the use of these analgesics and the risk of hypertension. A prospective cohort study in 80 020 women aged 31–50 years has provided some useful information (5). The women had participated in the Nurses' Health Study II and had no previous history of hypertension. The frequency of use of paracetamol, aspirin, and NSAIDs was collected by mailed questionnaires and cases of physician-diagnosed hypertension were identified by self-report. During 164 000 person-years of follow-up, 1650 incident cases of hypertension were identified. Overall, 73% of the cohort had used paracetamol at least 1–4 days/month, 51% had used aspirin, and 77% had used an NSAID. Compared with non-users of paracetamol the age-adjusted relative risk (RR) of hypertension was significantly increased even in women who had used paracetamol for only 1–4 days/month (RR = 1.22; CI = 1.07, 1.39). There seemed to be a dose–response relation, as the RR of hypertension compared with non-users was 2.00 (CI = 1.52, 2.62) in women who had taken paracetamol for 29 days/month or more. For women using aspirin or NSAIDs at a frequency of 1–4 days/month the RRs were 1.18 (CI = 1.02, 1.35) and 1.17 (CI = 1.02, 1.36) respectively. However, after adjusting for age and other potential risk factors, only paracetamol and NSAIDs, but not aspirin, remained significantly associated with a risk of hypertension. In summary, the data from this study support the view that paracetamol and NSAIDs are strongly associated with an increased risk of hypertension in women, the risk increasing with increasing frequency of use. Aspirin did not seem to be associated with an increased risk. This conclusion contrasts with the results of some short-term studies that have shown no effect of paracetamol on blood pressure (6,7).

This study suggests that paracetamol can raise arterial blood pressure in a dose-related fashion, interfere with the actions of antihypertensive drugs, and prompt the need for new antihypertensive therapy. However, these results must be interpreted with caution, as there were some limitations: the assessments of analgesic use and hypertension were made using a self-reported questionnaire; relative risk can be influenced by many potentially confounding variables; the results are relevant only for young women and cannot be extrapolated to the general population.

Respiratory

Paracetamol can aggravate bronchospasm in patients who are sensitive to aspirin and other analgesics (8). In severe poisoning, paracetamol depresses respiratory function centrally through metabolic acidosis and coma (9).

An observational study, part of a population-based case-control study of dietary antioxidants and asthma, has shown an association between the regular use of paracetamol and the incidence of asthma and rhinitis in adults (10). After controlling for potential confounding factors the OR for asthma in daily users, compared with never users, was 2.38 (CI = 1.22, 4.64). Not unexpectedly, there was also an association in users and non-users of aspirin, strongest when cases with more severe disease were compared with controls. This adverse effect of paracetamol may be due to depletion of the antioxidant glutathione in the lungs. However, further studies are needed before paracetamol can be blamed for an increase in the prevalence and severity of asthma.

Nervous system

In patients who suffer from recurrent headaches, for example migraine, cluster headache, or tension headache, temporary relief for the constant or intermittent pains is obtained from each analgesic dose, but wears off after a few hours with the arrival of a new episode. The patient gets accustomed to this pattern and may use excessive doses of analgesics. This in turn can cause, worsen, and perpetuate headaches, leading to what is called analgesic-induced or rebound headache. Like

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migraine, analgesic-induced headache is more likely to occur in women and is associated with depression.

It is postulated that the mechanism by which analgesic abuse transforms a primary headache into a rebound headache involves serotonin: both platelet serotonin concentrations and uptake were lower in patients with analgesic-induced headache compared with migraine sufferers and non-headache sufferers. At the same time, there was upregulation of serotonin receptors on the platelet membrane (11,12). Extrapolating these findings to the nervous system, it has been suggested that excessive analgesic use suppresses serotonin pathways, contributing to aggravation of headaches. Paracetamol and codeine were the major culprits of the analgesics investigated.

Analgesic-induced headache has also been described in children. One report (13) described 12 children, aged 6–16 years, who gave a history of headaches on at least 4 days a week, for 3 months to 10 years. Eleven of the children had been taking paracetamol, six in combination with codeine, and one was taking ibuprofen alone. They were taking at least one dose of an analgesic for each headache and eight were taking analgesics every day. The headaches presented with increasing frequency and were related to overuse of analgesics, a typical finding in analgesic-induced headache. The analgesics were withdrawn; in six children the headaches resolved completely, another five children experienced a reduced frequency of headaches, and one resumed analgesic abuse.

A second report (14) was of a retrospective study of patients seen in a pediatric headache clinic. During 8 months, 98 patients were seen for headache; 46 of them suffered from daily or near daily headache and 30 were consuming analgesics daily. Follow-up information was available in 25. The average number of doses of analgesics per week they consumed was 26. The most commonly used medications were paracetamol and ibuprofen. In addition, a minority were taking combinations that contained aspirin, codeine, caffeine, propoxyphene, or butalbital, or other NSAIDs. Abrupt withdrawal of all analgesics concomitant with the use of amitriptyline 10 mg/day (in 22 patients) prompted a significant reduction in the frequency and severity of headache.

The data from these studies are comparable to previous observations reported in adults (SEDA-21, 95) and suggest that daily use of analgesics can cause daily or near daily headaches in children and adolescents. However, additional controlled prospective studies are needed to address the true frequency of analgesics rebound headache among children and to evaluate possible treatments.

Metabolism

Hypoglycemia has been recorded with paracetamol, particularly in children (15).

Hematologic

Agranulocytosis was recorded in a series in France (16), but does not appear to have been a significant clinical problem elsewhere.

Two patients developed immune thrombocytopenia attributed to metabolites of paracetamol (17).

- A 30-year-old man and a 66-year-old woman had taken paracetamol 1 g intermittently for headaches and other non-specific indications. Routine blood testing showed thrombocytopenia (50×10^9/l and 45×10^9/l respectively). They both stopped taking paracetamol, and their platelet counts rose to normal within 7–10 days. Their sera contained antibodies (IgG or IgA) that recognized normal platelets in the presence of the metabolite paracetamol sulfate.

This suggests that in patients with drug-induced immune thrombocytopenia, tests for metabolite-dependent antibodies can be helpful in identifying the responsible agent.

A hemolytic crisis has been recorded in a patient with glucose-6-phosphate dehydrogenase deficiency (18).

Gastrointestinal

In normal doses, paracetamol, in contradistinction to aspirin and the NSAIDs, is well tolerated by the gastrointestinal tract.

Liver

Paracetamol is directly hepatotoxic and can cause severe hepatic damage in dosages over 6–10 g (12–20 tablets).

Biliary tract

Acute biliary pain with cholestasis is an occasional complication (19,20).

Pancreas

Pancreatitis has been reported, but only in overdose (21).

Urinary tract

Apart from renal tubular necrosis, which is usually associated with hepatic toxicity, but is occasionally seen without hepatic damage, there have been reports of a nephropathy similar to that seen with phenacetin, after prolonged use of paracetamol alone or in combination with other NSAIDs (22–27).

Analgesic nephropathy

DoTS classification (BMJ 2003;327:1222–5)

Dose-relation: collateral effect

Time-course: delayed

Susceptibility factors: age (over 65); sex (women)

In a series of papers that appeared from 1950 onwards (28), Spüler and Zollinger in Switzerland recognized analgesic nephropathy as a condition resulting from prolonged excessive consumption of analgesic mixtures, usually containing phenacetin. The disease is characterized by renal papillary necrosis and interstitial nephritis. The prevalence is variable, being especially high when the use of minor analgesics is intensive. The evidence linking the disorder primarily to phenacetin has been reviewed extensively (SED-8, 169) (SED-8, 178) (SED-9, 123) (SED-10, 135) (SEDA-9, 75).

Over the last 50 years there has been a steady evolution in our knowledge of drug-related renal pathology, including the role of prostaglandins in the kidneys and the concept of two cyclo-oxygenase isozymes. In the 1960s a distinct clinical entity was identified, separate from

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NSAID-induced renal toxicity, comprising interstitial nephritis and renal papillary necrosis. The condition, named analgesic nephropathy, was not uncommon and was serious. In a number of cases malignancies in the urinary tract also occurred.

The relation between long-term heavy exposure to analgesics and the risk of chronic renal disease has been the object of intensive toxicological and epidemiological research for many years (SEDA-24, 120) (29). Most of the earlier reports suggested that phenacetin-containing analgesics probably cause renal papillary necrosis and interstitial nephritis.

Nephropathy due to non-phenacetin-containing analgesics

There is no convincing epidemiological evidence that non-phenacetin-containing analgesics (including paracetamol, aspirin, mixtures of the two, and NSAIDs) cause chronic renal disease. Findings from epidemiological studies should be interpreted with caution, because of a number of inherent limitations and potential biases in study design (30). However, two methodologically sound studies have provided information on this topic.

The first was the largest cohort study conducted thus far to assess the risk of renal dysfunction associated with analgesic use (31). Details of analgesic use were obtained from 11 032 men without previous renal dysfunction participating in the Physicians' Health Study (PHS), which lasted 14 years. The main outcome measure was a raised creatinine concentration defined as 1.5 mg/dl (133 μmol/l) or higher and a reduced creatinine clearance of 55 ml/minute or less. In all, 460 men (4.2%) had a raised creatinine concentration and 1258 (11%) had a reduced creatinine clearance. Mean creatinine concentrations and creatinine clearances were similar among men who did not use analgesics and those who did. This was true for all categories of analgesics (paracetamol and paracetamol-containing mixtures, aspirin and aspirin-containing mixtures, and other NSAIDs) and for higher risk groups, such as those aged 60 years or over or those with hypertension or diabetes.

These data are convincing, because the large size of the PHS cohort should have made it possible to examine and detect even modest associations between analgesic use and a risk of renal disease. Furthermore, this study included more individuals who reported extensive use of analgesics than any prior case-control study. However, the study had some limitations, the most important being the fact that the cohort was composed of relatively healthy men, most of whom were white. These results cannot therefore be generalized to the entire population. However, the study clearly showed that there is not a strong association between chronic analgesic use and chronic renal dysfunction among a large cohort of men without a history of renal impairment.

The second study was a Swedish nationwide, population-based, case-control study of early-stage chronic renal insufficiency in men whose serum creatinine concentration exceeded 3.4 mg/dl (300 μmol/l) or women whose serum creatinine exceeded 250 μmol/l (2.8 mg/dl) (32). In all, 918 patients with newly diagnosed renal insufficiency and 980 controls were interviewed and completed questionnaires about their lifetime consumption of analgesics. Compared with controls, more patients with chronic renal insufficiency were regular users of aspirin (37 versus 19%) or paracetamol (25 versus 12%). Among subjects who did not use aspirin regularly, the regular use of paracetamol was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of paracetamol. The risk increased with increasing cumulative lifetime dose. Patients who took 500 g or more over a year (1.4 g/day) during periods of regular use had an increased odds ratio for chronic renal insufficiency (OR = 5.3; 95% CI = 1.8, 15). Among subjects who did not use paracetamol regularly, the regular use of aspirin was associated with a risk of chronic renal insufficiency that was 2.5 times as high as that for non-users of aspirin. The risk increased significantly with an increasing cumulative lifetime dose of aspirin. Among the patients with an average intake of 500 g or more of aspirin per year during periods of regular use, the risk of chronic renal insufficiency was increased about three-fold (OR = 3.3; CI = 1.4, 8.0). Among patients who used paracetamol in addition to aspirin, the risk of chronic renal insufficiency was increased about two-fold when regular aspirin users served as the reference group (OR = 2.2; CI = 1.4, 3.5) and non-significantly when regular paracetamol users were used as controls (OR = 1.6; CI = 0.9, 2.7). There was no relation between the use of other analgesics (propoxyphene, NSAIDs, codeine, and pyrazolones) and the risk of chronic renal insufficiency. Thus, the regular use of paracetamol, or aspirin, or both was associated dose-dependently with an increased risk of chronic renal insufficiency. The OR among regular users exceeded 1.0 for all types of chronic renal insufficiency, albeit not always significantly. These results are consistent with exacerbating effects of paracetamol and aspirin on chronic renal insufficiency, regardless of accompanying disease.

How can we explain the contrasting results of these two studies? A possible explanation lies in the different populations studied. In the PHS study, relatively healthy individuals were enrolled, while in the Swedish study all the patients had pre-existing severe renal or systemic disease, suggesting that such disease has an important role in causing analgesic-associated chronic renal insufficiency. People without pre-existing disease who use analgesics may have only a small risk of end-stage renal disease.

As up to 10% of about 42 000 dialysis patients have suffered from renal insufficiency due to analgesic nephropathy (in the postphenacetin era), German nephrologists have demanded the withdrawal from the market of medications that contain fixed combinations of analgesics (paracetamol, aspirin, or propyphenazone) plus caffeine, following the example of their American colleagues in the National Kidney Foundation (33).

Despite the fact that a careful evaluation of all epidemiological studies on non-narcotic analgesics showed no evidence that phenacetin-free combination drugs are more nephrotoxic than simple analgesics (29), the Belgian Public Health Authorities decided that combination analgesics are to become "prescription only" (34), as they have a "devastating" effect on the kidneys. However, contrasting opinions have been published (30,35).

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The effect of the withdrawal of phenacetin in Germany in 1986 and its replacement with paracetamol in most analgesic mixtures resulted in a significant fall in the incidence of end-stage analgesic nephropathy from 30% in 1981–82 to 21% in 1991–92 and 12% in 1995–97 (36). However, whether this reduction can be taken as proof that only phenacetin and not paracetamol is nephrotoxic in compound analgesics is debatable (37). In fact, the German authors found that other factors, such as advanced age and an increasing prevalence of type II diabetes mellitus, affected the relative frequencies of primary renal disease in patients with end-stage renal disease to such a degree that the observed relative reduction in analgesic nephropathy may not have been related to a change from phenacetin to paracetamol. Thus, the relative reduction in the incidence of analgesic nephropathy cannot be used as an argument for the non-toxicity of compound analgesics that contain paracetamol.

Furthermore, despite withdrawal of phenacetin from the market, analgesic nephropathy has continued to occur. It has been estimated that analgesic-associated nephropathy still accounts for 20% of patients in the USA with interstitial nephritis. As recently as the mid-1990s, a German study showed that up to 10% of dialysis patients had suffered from renal insufficiency owing to analgesic nephropathy (SEDA-20, 89). There is evidence that paracetamol, which replaced phenacetin in analgesic combination formulations, is nephrotoxic as well (38,39). The withdrawal of combination analgesic products from over-the-counter sales in Sweden and Australia has markedly reduced analgesic nephropathy as a cause of end-stage renal disease in those countries (SEDA-21, 99). It is therefore not surprising that nephrologists on both sides of the Atlantic have suggested a ban on the advertising and over-the-counter sales of these medications.

Symptoms and signs

Clinical evidence suggestive of analgesic nephropathy includes nocturia, renal insufficiency with severe acidosis, persistent urinary tract infection with colic, hematuria, and hypertension (40,41). Nocturia resulting from failure to concentrate urine is usually the earliest functional defect, but like the other symptoms it is non-specific, rendering the diagnosis of analgesic nephropathy difficult. A CT scan showing bilateral small kidneys with bumpy contours, and papillary calcification is accepted to be of sufficient specificity (38,39).

Epidemiology

Analgesic nephropathy is mostly diagnosed between the ages of 30 and 70 years, with a peak in the fourth decade, and there is a familial predisposition (SEDA-6, 80).

The prevalence of analgesic nephropathy is particularly high when there is intensive use of analgesics. There is evidence from animal and clinical work to suggest that hypovolemia plays a part, and that the risk of nephropathy is greatest in women and the elderly. Because of the long latent period of over 10 years, the condition has continued to appear despite the withdrawal of phenacetin.

In Australia, where phenacetin was withdrawn from antipyretic analgesic formulations during 1962–75 (42), analgesic nephropathy continued to be a major problem for a considerable time thereafter, reflecting the long latent period before the disorder develops; 22% of patients newly admitted to the Australian Kidney Foundation's dialysis and transplant registry in 1980 had analgesic nephropathy. The consumption of phenacetin-containing analgesics increased the risk of renal papillary necrosis in Australian women some 17-fold compared with non-consumers, while analgesics not containing phenacetin did not increase the risk of kidney damage (43).

In Belgium, the distribution of analgesic nephropathy in patients with terminal renal insufficiency was well correlated with the sale of drugs containing either aspirin + phenacetin or paracetamol + caffeine (SEDA-7, 75), and it is estimated that Belgium, after Australia, had the second highest incidence of analgesic nephropathy in the world.

Statistics published in 1981 from the European Dialysis and Transplant Association on the causes of chronic renal insufficiency suggested that in Europe about 3.1% of cases up to that time had been drug-induced; the figures cited varied from 0.4% in Spain to 17.5% in Switzerland. Some of the best-documented reports were those from Switzerland, where per capita consumption of phenacetin reached a peak of some 10 g annually between 1955 and 1968 (44). Between 1962 and 1978 the proportion of phenacetin users coming to autopsy increased from 1.8 to 3.1%.

In the USA only a very small proportion of phenacetin patients (in one series 2.8%) have a history of analgesic abuse (45).

True geographic differences cannot be proven from such figures, since the variation from country to country is largely due to inconsistent classification and differences in the selection of patients for dialysis and transplantation (46).

By the early 1980s, most countries had severely restricted or entirely prohibited the sale of phenacetin. Subsequent data from several of these countries suggested that the number of new patients with analgesic nephropathy fell as a result of the prohibition of phenacetin in analgesic mixtures.

Cause

It soon became clear that the major causative agent in analgesic nephropathy was phenacetin, improperly used long-term and especially in combinations with other analgesics, and this identification led to its virtual disappearance in the mid-1970s, following regulatory action.

In recent years it has become obvious that many of the NSAIDs are associated with renal disorders arising de novo or by aggravation of existent renal dysfunction. Inhibition of prostaglandin synthesis intrarenally leads to reduced vasodilator activity of PGE_1, which normally contributes to the maintenance of renal functional balance and protection against the vasoconstrictor effects of noradrenaline and angiotensin-II and the action of antidiuretic hormone. Some experimental work suggests a tendency for phenacetin and its metabolite paracetamol to concentrate in the renal medulla, possibly accounting for the papillary lesions most often associated with them.

There is no evidence that short-term use of cyclooxygenase inhibitors has any major deleterious effect on renal function in healthy individuals.

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Although some authors have stressed the possible role of aspirin as a causal factor (SED-8, 169), a study of the safety of long-term ingestion of large cumulative doses did not confirm this (47). The patients in question, with seropositive rheumatoid arthritis, had taken aspirin continuously for 10 or more years (mean total dose per patient 36 kg, range 16–82 kg). Their normal creatinine and BUN concentrations, with maximum recorded specific gravities of urine greater than 1019 in 93% of patients, suggested that long-term salicylate ingestion does not cause renal damage or that the magnitude and long-term clinical significance of such damage is not significant. The fact remains, however, that the overwhelming sale of phenacetin was in the form of fixed combinations with aspirin (and sometimes with caffeine, codeine, and other components), and the possibility of some additive effect cannot retrospectively be excluded.

As the debate developed, the safety of paracetamol and its combination with aspirin, which had only come to the fore on a large scale as phenacetin disappeared, also came to be questioned. The difficulty in assigning specific roles to the various analgesics is partly related to the use of drug combinations but largely because of the prolonged time over which the disorder develops.

Susceptibility factors

The association between analgesic abuse and renal papillary necrosis is well established, but the existence of other unrecognized factors is highly probable (SEDA-6, 80). The female/male ratio of analgesic abusers as a whole in the Australian community is 2:1, but the ratio in analgesic nephropathy is about 6.5:1. Swiss data also point to a higher incidence than expected in women and in elderly subjects (28). Climatic factors and fluid intake have also been incriminated, since dehydration can aggravate the risk. Reports of an association between HLA genotype and analgesic nephropathy might explain why only a few of the many individuals who take large quantities of analgesics develop renal insufficiency (48).

Pathology

The primary renal lesions in phenacetin abusers are those involving the capillaries (49,50). In some 80% of cases there is capillary sclerosis, with reduplication of laminar transformation of the intima, due to reduplication of the basement membrane in the capillaries just below the urothelium in the papillae, renal pelvis, and lower urinary tract. It is these changes that make it possible to diagnose analgesic abuse from surgical or postmortem specimens, even when the clinical history is unknown. A morphological study of 21 transitional cell carcinomas in an Australian histopathology department disclosed 16 cases with papillary changes of the analgesic type. Of these patients, only two were known to be analgesic abusers (SEDA-6, 82).

The renal cortical and medullary tubules are similarly affected, since overuse of analgesic-containing formulations can affect the metabolism of the basement membranes of capillaries and tubules and result in thickening of the walls. In skin biopsy specimens from patients with a history of excessive intake of analgesics, thickening of dermal capillaries suggested that the microangiopathy was not confined to the renal tract but also occurred in other organs (SEDA-6, 81).

Associated disorders

In the prospective Swiss Analgesic Study the risk of bacteriuria was about three times higher in those who abused analgesics heavily than in matched controls (51). The primary causes of mortality in this study were tumors and cardiovascular disease; only 7.5% died from primary renal disease due to pyelonephritis.

Renal papillary necrosis with retroperitoneal fibrosis secondary to analgesic abuse (involving aspirin, propoxyphene, and numerous other analgesics taken in large quantities for many years) has also incidentally been reported (SEDA-7, 94).

Patients with analgesic nephropathy have an increased risk of atherosclerosis. In a retrospective study their serum cholesterol and triglyceride concentrations were significantly higher than in a control group of similar age and with a similar degree of renal insufficiency due to other renal diseases (SEDA-6, 81). Some possible mechanisms of hyperlipidemia in analgesic nephropathy have been discussed, as this phenomenon is not sufficiently explained by end-stage renal insufficiency or by protein loss, as in the nephrotic syndrome (SEDA-7, 94).

Urinary tract tumors Renal carcinoma has been associated with analgesic abuse an order of magnitude greater than in non-abusers (52–54), and the causal association has been recognized since 1965 (SEDA-6, 81) and repeatedly confirmed. In 1984 an authoritative consensus conference in the USA pointed to the evidence that very heavy and sustained use of some analgesic mixtures without phenacetin can also predispose to cancer of the urinary tract, particularly transitional cell carcinoma of the renal pelvis (55).

Of 422 inhabitants of Basel with malignant tumors of the lower urinary tract, 18.5% were users of phenacetin-containing analgesics, which means that carcinomas and sarcomas of the lower urinary tract were nearly 13 times as common in abusers as in non-abusers (54). Carcinoma of the renal pelvis was increased 77-fold, carcinoma of the ureter 89-fold, and carcinoma of the urinary bladder 7-fold. In Australia, in 274 urological patients who had abused phenacetin-containing products, renal symptoms appeared after an average latent period of 10 years; within the last decade of the period studied, 8% of this group (22 patients) had tumors of the urothelium.

In an Australian investigation of renal papillary carcinoma (SEDA-6, 81) the overall crude incidence rate was 1.6 per 100 000 population per year; 47% of the tumors were associated with analgesic abuse and analgesic nephropathy. The risk of renal papillary carcinoma among patients who regularly took analgesics was estimated to be 8 per 100 000 patients per year. Renal papillary carcinoma had a female-to-male ratio among analgesic abusers of 2.6:1, compared with 1:2 among those without analgesic-associated nephropathy. A similar epidemiological study from the USA (53) supported this association between analgesic nephropathy and tumors; 5.2% of patients with transitional carcinoma of the urinary tract diagnosed over 3 years had analgesic-

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associated nephropathy. The patients were predominantly younger women, who had renal pelvis tumors instead of bladder tumors and a higher mortality rate. In a historical prospective study of 146 patients with interstitial nephritis, 84 cases were associated with analgesics and in four patients transitional cell carcinoma developed. None of the 98 nephritic patients without analgesic-associated nephropathy developed transitional cell carcinoma. In 300 urological patients (75% women) in whom renal and extrarenal manifestations appeared after an average latency period of 20 years, 31 patients had a tumor of the urothelium.

Studies on the tumor-inducing effects of heavy use of analgesics, especially those that contain phenacetin, have given contrasting results (SEDA-21, 100) (56,57). Two case-control studies have been published on the role of habitual intake of analgesics on the occurrence of urothelial cancer and renal cell carcinoma.

In the first study, 647 cases of urothelial cancer (571 bladder, 25 ureter, and 51 renal pelvis) and an identical number of controls were enrolled (58). Exposure to compound analgesic (at least 1 kg of analgesic substances lifelong) showed a substance-specific association, with an increased risk ratio for renal pelvis cancer but not for cancers of the ureter or bladder. Among the different analgesics, anilide derivatives (intake over 1 kg) were associated with the highest risks of renal pelvis cancer, with respective odds ratios of 5.28 for phenacetin (CI = 0.34, 81) and 3.27 for paracetamol (CI = 0.25, 43); however, these odds ratios were not statistically significant. This lack of significance was due mainly to two factors, the high proportion of heavy analgesic use in controls and the low number of cases with renal pelvis cancer, which had the highest risk.

The second study (59) was aimed at clarifying the possible relation between analgesic use and renal cell carcinoma. In previous studies there was a consistent association between phenacetin and renal cell carcinoma, but inconclusive results with respect to non-phenacetin analgesics. In 1024 patients with renal cell carcinoma and an equal number of matched controls, regular use of analgesics was a significant risk factor for renal cell carcinoma (OR = 1.6; CI = 1.4, 1.9). The risk was significantly increased by all four major classes of analgesics (aspirin, NSAIDs, paracetamol, and phenacetin) and within each class of analgesic, the risk increased with increasing exposure. Individuals in the highest exposure categories had about a 2.5-fold increase in risk relative to non-users or irregular users of analgesics. However, exclusive users of aspirin who took aspirin 325 mg/day or less for cardiovascular problems were not at an increased risk of renal cell carcinoma (OR = 0.9; CI = 0.6, 1.4).

In contrast to these results, another large case-control study (60) in 1732 patients with renal cell carcinoma and 2039 controls showed no increase in the risk of renal cell carcinoma among regular users of phenacetin, paracetamol, and aspirin. There is no clear explanation of these disparate findings.

Conclusions

The history of analgesic nephropathy must not be dismissed as involving only a drug now obsolete. Phenacetin, alone or in combination with other analgesics, was unwisely taken chronically by a large section of the public, and unless such misuse of analgesics can be avoided, there is much reason to fear that the story will be repeated with other agents and combinations.

If analgesics are discontinued in the early phases of nephropathy, there is a reasonable possibility of a return to normal renal function. It is wise to ensure that the dosage of aspirin or paracetamol, or of any NSAID, is kept as low as possible, that renal function is regularly assessed, and that prolonged use is avoided, especially in patients over 65 years of age, who seem to be at particular risk of analgesic nephropathy and who may also have pre-existing renal dysfunction, including marginally compensated asymptomatic renal insufficiency (40).

There is no evidence that short-term use of single cyclooxygenase inhibitors has any major deleterious effect on renal function in healthy, non-hypovolemic individuals, but even short-term use of a compound of this class is never a guarantee that nephropathy will not occur.

Skin

Rashes, usually erythematous, occur occasionally (61–63).

Paracetamol can rarely cause fixed drug eruptions (64,65), including an unusual non-pigmented fixed drug eruption (66).

Immunologic

Acute hypersensitivity reactions due to paracetamol are rare (SEDA-22, 114), but can be life-threatening (67).

Long-Term Effects

Mutagenicity

Animal studies have indicated a carcinogenic effect when paracetamol has been administered for prolonged periods in relatively high dosages. However, no clinical data are so far available to corroborate this. The matter cannot be dismissed entirely for the time being, in view of a report (68) of the development of chromosomal aberrations after prolonged use.

Second-Generation Effects

Fetotoxicity

Paracetamol crosses the placenta readily. However, there has been no published evidence of a teratogenic effect in the offspring of mothers who have taken paracetamol during pregnancy. A case of fetal death after a maternal overdose of paracetamol (30 g) has been described (SEDA-10, 73), but in another similar case, in which 22.5 g was taken in the 36th week, the fetus survived (SEDA-9, 96). Preliminary data from a longitudinal study have shown no adverse effects of therapeutic doses of paracetamol on either pregnancy or infant development (69).

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Susceptibility Factors

Hepatic disease

It is generally considered inadvisable to use paracetamol in patients with active liver disease or severe liver dysfunction, patients with cachexia, or chronic alcoholics. Stable mild chronic liver disease does not seem to be a contraindication (70).

Drug Administration

Drug overdose

Paracetamol is one of the most commonly ingested medications in deliberate self-poisoning and accidental ingestion by children.

Fulminant hepatic failure occurs in 1–5% of cases of paracetamol overdosage 3–6 days after ingestion (71), with frequent deaths in people who take 20–25 g. There is only a narrow margin between the normal maximum 24-hour dosage and that which can cause liver damage and acute hepatic failure. Undoubtedly, some people are more susceptible than most to paracetamol toxicity, since although 6 g has been reported as toxic in some cases, most toxicity is seen with 12 g upwards (72,73). Nomograms have been developed to show the relation between plasma paracetamol concentrations over time and the risk of a serious outcome (SEDA-18, 94).

Epidemiology

Paracetamol is a widely-used, effective, and well-tolerated analgesic, but thanks also to its ready availability, it is the most commonly used substance in self-poisoning (SEDA-18, 94) (74) and a frequent cause of accidental overdose, especially in children (SEDA-22, 114), although children of 6 years and under are rarely subject to hepatotoxicity, even with accidental overdosage (75), possibly owing to age-dependent differences in paracetamol kinetics (76).

From prospective data (74,77), it has been estimated that around 58 000 people take paracetamol in overdose each year in England and Wales and that these episodes of poisoning prompted 3.3% of inquiries to US regional poisons centers (78), 10% of inquiries to the UK National Poisons Information Service (79), and up to 43% of all admissions to hospital with self-poisoning in the UK (80). Despite the availability of effective antidotes for patients who seek medical intervention early after an overdose, in the USA paracetamol alone accounted for 4.1% of deaths from poisoning reported to American poison centers in 1997 (78).

Paracetamol plus dextropropoxyphene, the combination known as co-proxamol, is available as a prescription-only analgesic in many countries. Self-poisoning can be lethal, as respiratory depression can occur from an excessive dose of dextropropoxyphene. In England and Wales, co-proxamol alone accounts for 5% of all suicides, and overdose is more likely to result in death than overdose with paracetamol alone or tricyclic antidepressants (81). Furthermore, although it is often prescribed, it is no more effective than paracetamol for short-term relief of pain. It should not be prescribed without good reason.

Symptoms and signs

While damage to the liver is effected within hours of ingestion, major clinical manifestations are seldom seen until some 24–48 hours. However, they can be prevented by early treatment. Thus, early history taking, a high index of suspicion, and prompt and repeated assays of plasma paracetamol concentrations are essential in emergency management. Primary signs, when they do appear, are those of liver failure, for example abdominal pain and tenderness, followed by jaundice, raised serum transaminases, and reduced concentrations of coagulation factors, resulting in a prolonged prothrombin time. It may be up to a week before severe liver failure ensues. Consciousness is not usually lost early on, but resistant cerebral edema can intervene in a few days secondary to hepatic failure.

Acute renal tubular damage occurs in association with the liver damage, together with muscle necrosis and hyperkalemia. The muscle necrosis, as demonstrated at autopsy in fatal cases (82), can itself exacerbate the severe electrolyte derangement, particularly marked hyperkalemia, that occurs in liver failure. The measurement of serum concentrations of coagulation factors V (below 10%) and VIII (VIII/V ratio over 30) can have predictive value and can thus be helpful in selecting patients who require liver transplantation (SEDA-17, 99).

- A 29-year-old woman with a psychiatric disorder took an overdose of paracetamol on nine separate occasions. On the last three occasions she developed a dose-dependent, late-onset, delayed hypersensitivity reaction, characterized by an erythematous rash over the entire body (83).

Risk factors

Alcohol

Alcohol abuse can predispose to paracetamol hepatotoxicity (84–91), even in moderate social drinkers who take therapeutic or modestly excessive doses (92), and there have been anecdotal reports of severe hepatotoxicity in chronic ethanol abusers after ingestion of 4 g/day (93). Alcoholics are more likely to exceed the recommended dosage of paracetamol and consequently may be at higher risk of hepatotoxicity than non-alcoholics (91,94).

The theory behind this effect involves induction by alcohol of CYP2E1, which metabolizes about 5% of a typical dose of paracetamol, producing the reactive hepatotoxic metabolite named *N*-acetylparabenzoquinone-imine (NAPQI), which is normally metabolized by glutathione (95). The rest of a therapeutic dose of paracetamol is conjugated to non-toxic forms of glucuronide and sulfate. Saturation of the detoxification pathway occurs with overdose of paracetamol (72), or sometimes in certain individuals who make long-term use of normal dosages (96), in patients with compromised hepatic function, with certain drug combinations, and in other conditions of glutathione deficiency. Ingestion of alcohol induces the activity of CYP2E1 and therefore predisposes the alcoholic patient to injury even at therapeutic doses of paracetamol (97).

Despite this theory, the evidence that therapeutic doses of paracetamol can produce liver injury in alcoholics is scanty (98,99). There has been only one study of the

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hepatotoxicity of paracetamol in therapeutic doses in alcoholic patients, a double-blind, randomized, placebo-controlled study in which 200 long-term alcoholic patients took placebo or paracetamol 1 g qds on two consecutive days (100). Paracetamol was not given until alcohol had been eliminated from the body. Liver injury, documented by increased serum transaminases, was not detected. Mean aspartate transaminase activity on day 4 was 38 U/l with paracetamol and 38 U/l with placebo. Only five patients who took placebo and four who took paracetamol had an increase in serum aspartate transaminase to greater than 120 U/l, and it did not exceed 200 U/l in any patient. Thus, repeated administration of the maximum recommended daily doses of paracetamol to alcoholic patients was not associated with liver damage. An older report also provided evidence that alcoholic patients are not at risk from therapeutic doses of paracetamol (70). The researchers concluded that the usual recommendations that alcoholic patients should use reduced doses of paracetamol or avoid it entirely are not based on firm evidence. However, the study had some limitations, as paracetamol was given for only 2 days in doses that did not exceed the maximum therapeutic daily dose. Moreover, the alcoholic patients enrolled in the study may not have been representative of those who would be at increased risk of paracetamol toxicity (101–103). It therefore seems wise to suggest that caution is still warranted with paracetamol in alcoholic patients.

Other drugs

Analgesic cocktails or the concurrent use of potentially hepatotoxic drugs increase the risk of paracetamol toxicity.

Drugs that induce liver microsomal enzymes, such as phenobarbital, phenytoin, carbamazepine, rifampicin, and isoniazid, can make paracetamol poisoning more severe (104,105). In patients taking such drugs the serum paracetamol concentration should be doubled before consulting the usual treatment nomogram.

Fasting

Potentiation of the toxic effects of paracetamol by fasting has been previously shown in animals. In 21 cases of paracetamol hepatotoxicity not due to intentional overdosage, fasting was significantly more common than recent alcohol use among patients who developed hepatotoxicity after a dosage of 4–10 g/day (SEDA-20, 96).

Prevention

Restricting supplies

The easy availability of paracetamol is reported to be the most common reason for its common use in overdose (106), and so reducing its availability might be an effective strategy. Therefore, in September 1998 legislation was introduced in the UK limiting the pack size of paracetamol to 20 units of 500 mg; at the same time nearly all formulations became available only in blister packs. The justification for this legislation was that analgesic self-poisoning is highly impulsive and is associated with both low suicidal intent and limited knowledge of the possible consequences; it was expected that the number of cases of paracetamol overdose might be reduced by limiting its availability.

The impact of this legislation on mortality from paracetamol overdose has been assessed in a prospective study of mortality from paracetamol overdose before and after the new legislation (107). The evaluation included the number of patients referred to liver units or listed for liver transplantation, the number of episodes of overdose and tablets taken, the plasma concentration of paracetamol, and sales of paracetamol to pharmacies. In the years after the legislation the number of tablets of paracetamol formulations per packet fell markedly, as did the number of deaths from self-poisoning with paracetamol, the number of liver transplants and admissions to liver units with hepatic damage after paracetamol poisoning, and the number of episodes of overdose in which a large number of tablets was taken. On the basis of these results it seems that the legislation was relatively successful. The results suggested that the main factor was the reduction in the number of tablets per pack available for impulsive self-poisoning. However, the study had some limitations. The period assessed may have been too short for a full assessment of the impact of the legislation (108), and the effect of legislation on self-poisoning with other drugs was not examined (109).

It may be that limiting access to one type of drug simply increases the incidence of overdose with other potentially more dangerous medicines. If that is so, unless the availability of other medications is also controlled, the removal of one readily available medication, such as paracetamol, could lead to an increase in the use of other compounds with similar or even greater toxicity (for example aspirin, ibuprofen).

In Australia, paracetamol-containing medications were recalled during two periods in 2000, presenting a unique opportunity for a retrospective observational study of the effect of reduced availability of paracetamol on the incidence of deliberate self-poisoning and accidental pediatric poisoning with paracetamol and other over-the-counter analgesics (110). During the recall periods there was a significant increase in ibuprofen deliberate self-poisoning (RR = 1.86; 95% CI = 1.41, 2.44), while there was no statistically significant change in paracetamol and aspirin deliberate self-poisoning. In children there was a significant increase in the proportion of ibuprofen accidental poisoning but no significant change for aspirin and paracetamol.

These results suggest that reduced paracetamol availability increased poisoning with alternative analgesics (in particular ibuprofen) but had little effect on the incidence of paracetamol poisoning. Restriction of paracetamol-containing medications should be critically reconsidered as an effective strategy for preventing deliberate and accidental poisoning.

Adding antidotes to oral formulations

Because restricting the packet size cannot completely resolve the problem of paracetamol overdose, alternative measures have been proposed (SEDA-22, 114). Because of the beneficial effect of acetylcysteine in paracetamol overdose, it has been suggested that toxicity caused by paracetamol overdoses, whether intentional or not, could

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be prevented by formulating paracetamol with added acetylcysteine. It has been estimated that including 200 mg acetylcysteine for every 500 mg of paracetamol would prevent toxicity (111,112). Methionine has previously been added to oral paracetamol formulations for the same reason. For example, Paradote contains paracetamol 500 mg and methionine 100 mg, and the combination is called co-methiamol. However, adding methionine to every paracetamol tablet prompted contrasting opinions (SEDA-22, 114) (113,114). Pameton (paracetamol 500 mg + methionine 250 mg) was voluntarily withdrawn in the UK because of safety concerns, before any evaluation of its impact on overdose had been carried out (113). Paradote remains available in the UK, but similar formulations are not currently available in the rest of Europe or the USA.

Treatment

Gastric lavage, especially in the first hour after ingestion, is recommended.

Glutathione donors

Since the mechanism of damage appears to be the exhaustion or depletion of sulfhydryl groups, as available in glutathione, treatment consists of early replacement of those groups by administration of an alternative source of glutathione, either oral methionine or, better, *N*-acetylcysteine, either orally or intravenously. To be most effective, a glutathione donor should be given within 8–12 hours of ingestion of the overdosage, but even up to 24 hours administration can improve the outcome (115). Acetylcysteine is usually given intravenously, but a 20-hour treatment protocol for acute paracetamol overdose using oral acetylcysteine has also been proposed (116) and was effective in preventing hepatic injury after an acute overdose of paracetamol when therapy was begun within 8 hours after ingestion.

To reduce the chance of liver damage and death in cases of paracetamol overdosage, guidelines have been produced in many countries (74,117,118) to identify patients at high risk who need to be treated soon with acetylcysteine.

In general, such guidelines recommend that the antidote should be given to all patients with a serum paracetamol concentration over 200 μg/ml (1.32 mmol/l) 4 hours after ingestion. A nomogram, in which this value is joined to an end-point of 25 μg/ml (0.16 mmol/l) at 16 hours, allows identification over this period of the patients who must receive the antidote. If acetylcysteine is not administered, it has been calculated that over 60% of patients with serum concentration of paracetamol above the described treatment line develop serious liver damage and of these about 5% will die (119). No deaths have been reported in any of the major treatment trials, however high the initial serum paracetamol concentrations, provided acetylcysteine was given within 10 hours of paracetamol ingestion. These data support the hypothesis that serious liver damage and death should be very uncommon if treatment guidelines are followed and if the patient presents for medical advice within the critical time of 10 hours from poisoning.

However, a report (119) has described fatal overdose of paracetamol in four patients who presented within 10 hours with serum paracetamol concentrations below the treatment line who, in accord with the established guidelines, were not treated with the antidote and developed fatal acute liver failure. The report generated considerable debate by advocating changing the treatment line for the use of antidotes in patients at standard risk from paracetamol poisoning from that currently recommended to a lower line passing through 150 μg/ml at 4 hours and 30 μg/ml at 12 hours.

A second "high-risk patient" line, at about half the concentration of the conventional treatment line, has already been adopted in some guidelines for patients considered at adjunctive risk of liver damage, such as those taking long-term enzyme-inducing drugs, abusing alcohol chronically, or with poor nutrition and cachexia.

However, an absolute cut-off point between a non-toxic and a toxic paracetamol overdose does not exist. Many factors should be taken into consideration in correctly interpreting the measured serum concentrations. First, the timing of the blood sample in relation to the overdose is often uncertain, and when using treatment nomogram clinicians should assume the longest interval between poisoning and blood sampling that is consistent with the history. Secondly, the current treatment nomogram is useless when paracetamol overdosage has occurred over several hours or more rather than as a single episode. Thirdly, apart from the already mentioned known risk factors, some individual differences in susceptibility to paracetamol are not well understood.

Therefore, owing to these uncertainties, it seems wise to suggest that in judging whether or not to use an antidote, clinicians should always err on the side of caution: "If there is doubt about the timing or the need of treatment, treat" (74).

Other methods of treatment

The only alternatives to glutathione donors are charcoal hemoperfusion and hemodialysis, which can be effective up to 18 hours after dosage. However, the longer the time from ingestion to treatment, the less likely the condition is to be reversible and the more likely a fatal outcome.

Theoretically, inhibitors of cytochrome P450, like cimetidine, might be of value in the treatment of paracetamol overdosage, and preliminary animal data also suggest this (115).

Drug–Drug Interactions

Alcohol

The FDA has announced its intention to require alcohol warnings on all over-the-counter pain medications that contain acetylsalicylic acid, salicylates, paracetamol, ibuprofen, ketoprofen, or naproxen. The proposed warnings are aimed at alerting consumers to the specific risks incurred from heavy alcohol consumption and its interaction with analgesics. For products that contain paracetamol, the warning indicates the risks of liver damage in those who drink more than three alcoholic beverages a day. For formulations that contain salicylates or the mentioned NSAIDs three or more alcoholic beverages will increase the risk of stomach bleeding (120).

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Argatroban

The thrombin inhibitor argatroban had no effect on the pharmacokinetics of five oral doses of paracetamol 1 g 6-hourly in 12 healthy volunteers; the argatroban was given as an intravenous infusion of 1.5 μg/kg/minute from hours 12 to 30 (121).

Oral contraceptives

Oral contraceptives accelerate the renal excretion of paracetamol, reducing its effect (SEDA-9, 90).

Phenytoin

Paracetamol is metabolized in part by CYP2E1, and inducers of CYP2E1 predispose patients to paracetamol hepatotoxicity. However, a possible interaction leading to hepatotoxicity with phenytoin has been reported in a 55–year-old woman taking paracetamol 1300–6200 mg/day over 10 days (122). Phenytoin induces CYP2C and CYP3A4 but not CYP2E1. As CYP3A4 may participate in paracetamol metabolism the induction of this isoform may also be responsible for paracetamol-induced hepatotoxicity.

Rifampicin

The addition of rifampicin in patients taking paracetamol can reportedly cause liver failure and encephalopathy (123).

- A 32-year-old woman, who had been taking paracetamol 2–4 g/day for several weeks, was given rifampicin 600 mg bd, and 2 days later developed agitation, confusion, and laboratory abnormalities indicative of severe liver injury. Both rifampicin and paracetamol were withdrawn and she was given acetylcysteine. Her liver dysfunction resolved.

The severe hepatotoxicity in this case was probably due to induction of CYP3A4 by rifampicin, but rifampicin-induced liver damage could not be excluded.

Warfarin

The anticoagulant effect of warfarin is potentiated by concomitant long-term paracetamol administration.

In an early, double-blind, placebo-controlled study of the interaction between coumarin anticoagulants and paracetamol, there was a statistically significant lengthening of the prothrombin time (124). The effect, although statistically significant, was very small and was considered to be clinically unimportant.

However, in a case-control study of the risk factors for excessive warfarin anticoagulation the investigators studied 289 patients prospectively, 93 with an International Normalized Ratio (INR) over 6.0 and 196 with an INR of 1.7–3.3 during warfarin therapy (125). Paracetamol intake was independently associated with a high INR and the effect was dose-related. At a dosage of about 2–4 g/week the adjusted odds ratio (OR) for having an INR over 6 was 3.5 (95% CI = 1.2, 10) compared with no intake of paracetamol. At an intake of 4–9 g/week the adjusted OR was 6.9 (95% CI = 2.2, 22), and at an intake over 10 g/week the OR was 10 (95% CI = 2.6, 38).

However, the results of this study must be interpreted with caution, for many reasons. First, despite these data and the widespread use of paracetamol as an analgesic in patients taking warfarin, only few reports from the literature have described serious hemorrhagic complications due to potentiation of anticoagulant effect of warfarin or acenocoumarol by paracetamol (126,127). Secondly, numerous factors in the Hylex study were independently associated with an increased likelihood of having an INR over 6.0 and it is therefore possible that overlap could have occurred between these factors and paracetamol intake. Thirdly, the biochemical mechanism by which paracetamol may interfere with warfarin is not well understood. The normal metabolism of warfarin, which occurs via hepatic cytochrome P450, is a complex mechanism that can be competitively and non-competitively inhibited by many drugs. The normal metabolism of paracetamol, particularly when large doses of paracetamol are ingested, also involves cytochrome P450. Thus, paracetamol can exhaust the capacity of cytochrome P450 and prevent the normal metabolism of warfarin. When the normal metabolism of warfarin is prevented by paracetamol, the amount of active, non-protein bound warfarin promptly increases and may double or triple in concentration in the blood. Some pharmacological data, however, makes this explanation uncertain. CYP2E1 and CYP1A2 partially metabolize paracetamol. CYP2E1 is not involved in warfarin metabolism, CYP1A2 partially metabolizes paracetamol and is responsible for metabolism of *R*-warfarin, the less potent anticoagulant of the two warfarin stereoisomers. While *R*-warfarin and paracetamol may compete for metabolism, it is unlikely that a drug that competes for or inhibits metabolism of the less potent *R*-warfarin would significantly increase the INR. Finally, despite sporadic case reports this potential interaction has been suggested to be clinically irrelevant on the basis of the extensive collective experience of many clinicians in managing patients who require anticoagulation (128,129).

Some pharmacokinetic studies have failed to show such an interaction (130). However, if this interaction happens in only a few individuals at risk, a formal pharmacokinetic study in a small number of subjects would probably fail to include enough of such individuals to detect an effect. A case-control study, on the other hand, would be the appropriate design for detecting this type of interaction.

Thus, the key message from this study is that in patients taking a stable warfarin regimen who begin to take repeated doses of paracetamol a possible interaction should be considered. The dose and duration of paracetamol therapy should be as low as possible and INR values should be monitored.

Zidovudine

Concomitant administration of paracetamol and zidovudine leads to inhibition of glucuronidation and to potentiation of the toxicity of each drug (131,132).

Interference with Diagnostic Tests

YSI glucose analyser

Paracetamol can cause false-positive reactions for glucose in serum and blood specimens examined using the YSI glucose analyser. The effect could be of considerable importance in patients admitted with suspected paracetamol overdosage.

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Paraffins

General Information

Paraffin is a name that is commonly used to denote a group of saturated alkane hydrocarbons with the general formula C_nH_{2n+2}, n being greater than 20. They take both solid and liquid forms. The solid form known as paraffin wax was discovered by Karl Reichenbach in 1830. Paraffins are mostly obtained from petroleum. Paraffin oil, used as a fuel, is also known as kerosene.

Hard paraffin

Hard paraffin is a mixture of solid hydrocarbons, also known as paraffin wax. It is used to stiffen ointments and creams and to coat capsules and tablets. At one time it was used for cosmetic enhancement, for example of the breasts, before silicone was introduced. It is also used in bismuth iodoform paraffin paste (BIPP) (see the monograph on bismuth).

Soft paraffins

White soft paraffin and yellow soft paraffin are mixtures of semi-solid hydrocarbons. They are used as bases for ointments, as emollients in skin diseases, and as lubricants in treating dry eyes. Soft paraffin is also known as petroleum jelly, petrolatum, and Vaseline.

Liquid paraffin

Liquid paraffin is a mixture of liquid hydrocarbons. Its main use has been as a lubricant laxative but it is not recommended, because of its adverse effects. Nevertheless, it continues to be used for this purpose and is reportedly as effective as lactulose (1). However, the erstwhile Committee on Safety of Medicines in the UK recommended the following precautions (2):

- pack sizes to be limited to 160 ml;
- liquid paraffin to be used only for the symptomatic relief of constipation;
- prolonged use to be avoided and the package label to state "repeated use is not recommended";
- to be contraindicated in children under 3 years of age.

Liquid paraffin has also been used in ointments, as an emollient in skin diseases, and as a lubricant in treating dry eyes. Injection of liquid paraffin into the pleural cavity (oleothorax) was a widely used treatment for pulmonary tuberculosis before effective antituberculosis drugs became available. Long-term complications continue to be reported (3–10).

Organs and Systems

Respiratory

Liquid paraffin can cause a lipoid pneumonia or pneumonitis if inhaled (11). This has been treated with bronchoalveolar lavage (12). Lipoid pneumonia in a 34-year-old fire-eater who inhaled liquid paraffin was treated with prednisolone, antibiotics, and urinastatin (13).

Nutrition

Liquid paraffin impairs the absorption of fat-soluble vitamins (A, D, E, and K). This has rarely been reported to be of clinical significance, although one case of rickets has been reported (14).

Hematologic

Reticulolymphoblastosarcomatosis with acquired hemolytic anemia and cryoglobulinemia complicated a paraffinoma after 50 years (15,16).

Gastrointestinal

Liquid paraffin leaks from the anus and can cause local irritation.

Immunologic

Although soft paraffin has been used to treat irritant contact dermatitis (17) and to protect the skin from other sensitizers (18), hypersensitivity reactions can occur, but are rare (19–26). Yellow soft paraffin is slightly more antigenic than white soft paraffin (24). Contact sensitization to a neat cutting oil containing chlorinated paraffin occurred in 12 men (27). Contact urticaria mimicking dermatitis has also been reported (28).

Sensitization to soft paraffins can cause false-positive drug patch tests (29).

- A 31-year-old woman with a long history of presumed atopic dermatitis actually had contact dermatitis due to the soft white paraffin that was present in the several medicaments (glucocorticoids, tacrolimus, pimecrolimus, and ciclosporin) that she had used to treat the skin (30).

Long-Term Effects

Tumorigenicity

There have been many reports of so-called paraffinomas, benign tumors due to granulomatous reactions, in patients using paraffin.

Paraffin used for breast enhancement can cause mammary paraffinomas, and there have been many such

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reports in men and women (31–51). The tumors can calcify but are benign; in one case there was no evidence of malignant transformation after 60 years (52), although in another case there was an associated malignancy (53). Lymphatic spread of paraffin has been described (54), as has sarcoid formation (55).

Paraffinomas have also been reported after the use of paraffin to enhance the male and female external genitalia (51,56–71).

When liquid paraffin is used as a laxative, paraffinomas can occur in the colon and rectum (72–75).

Paraffin used as packing after nasal surgery can cause nasal paraffinomas (76–81).

Other tissues in which paraffinomas have been reported include the orbit and eyelids (82–86), the lungs (87–94), the limbs (95–97), sometimes with subsequent calcification (98), the face (99–101), nose (102), and scalp (103), muscle (104), the bladder (105), and the ureter (106).

Although in most cases paraffinomas occur at the site of injection, remote deposition can occur, for example in the mediastinum (107–109).

- A 55-year-old woman, who had undergone intrapleural injection of paraffin for pulmonary tuberculosis 15 years before, developed a large left-sided chest wall mass and spinal paralysis (110). A paraffinoma had invaded the vertebral canal.

Paraffin deposition has also been reported in the retinal fundi, the liver, and the spleen, in addition to the lungs (111).

There is epidemiological evidence linking the use of liquid paraffin to gastrointestinal cancer (112). Malignant transformation of a paraffinoma has occasionally been suggested.

- An 82-year-old woman who had taken long-term liquid paraffin as a laxative, developed a lipoid pneumonia and a mesothelioma (113).

Susceptibility Factors

Age

Liquid paraffin is contraindicated in children under 3 years of age (2).

Drug–Drug Interactions

Anticoagulants

It is often stated that liquid paraffin should interact with oral anticoagulants because it inhibits the absorption of vitamin K. However, no evidence of such an interaction has been published.

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Paraldehyde

General Information

Paraldehyde is the cyclic trimer of acetaldehyde, a colorless or slightly yellow-colored liquid. It has been used as an anticonvulsant, but because of its adverse effects and because it is difficult to use it has been replaced by more modern agents. However, it is still sometimes used to treat status epilepticus that is resistant to first-line drugs (1). The usual adult rectal dose is 10–20 ml.

Paraldehyde is a solvent for rubber, polystyrene, and styrene acrylonitrile co-polymer, and if parenteral administration is required it should ideally be given via a glass syringe (2). Plastic syringes start to break down after exposure of about 2 minutes (3). However, some plastic syringes are resistant to its effects for a few hours (4), and intravenous tubing is reportedly unaffected (5); in an emergency it has been given rapidly by plastic syringe.

Organs and Systems

Cardiovascular

Paraldehyde caused microembolization in a neonate immediately after the injection of 0.3 ml/kg (6). The skin below the waist became red, large purple vesicles formed, and there was loss of skin and sloughing of two toes.

Respiratory

Non-cardiac pulmonary edema has been reported with paraldehyde. In one case it followed the intravenous administration of 23 ml of paraldehyde over 10 hours (7) and in another 2 ml of undiluted paraldehyde followed 30 minutes later by 0.1 ml of a 10% solution (8).

Acid–base balance

Paraldehyde can cause a metabolic acidosis, due to inability of the renal tubules to acidify the urine; several cases have been described (9–15).

- A 35-year-old man who regularly took paraldehyde 15–20 ml/day took 200 ml and developed a metabolic acidosis (pH 7.12) and acute renal insufficiency (12). He was successfully treated with intravenous alkali and peritoneal dialysis.
- A 41-year-old woman took paraldehyde 20–50 g on three different occasions and developed a metabolic acidosis that mimicked diabetic ketoacidosis (13).
- A 49-year-old woman took paraldehyde 100 ml in 4 days; she became comatose and acidotic and required hemodialysis (14).
- A 30-year-old man taking anticonvulsants was given paraldehyde 40 ml intramuscularly; 6 hours later he collapsed and was found to have a lactic acidosis (15).

Drug Administration

Drug formulations

Paraldehyde easily oxidizes to acetic acid and acetaldehyde. It should be stored in an airtight container and protected from the light. It should not be used if it has a brown color or if it smells vinegary. It solidifies when cooled and may need to be warmed before use.

Drug administration route

Paraldehyde can be given orally, rectally, intramuscularly, or intravenously.

Oral and rectal administration can cause gastric and rectal irritation.

Intramuscular administration can cause sterile abscesses (16). Peripheral nerve injury has also been reported (17), but that is a hazard of any intramuscular injection (18).

Intra-arterial administration in one case caused generalized arterial and venous thrombosis (19).

Drug overdose

A 20-year-old man died after taking paraldehyde 16 g (20).

Drug–Drug Interactions

Alcohol

Paraldehyde has been used to treat delirium tremens, but eight patients with alcohol intoxication died unexpectedly after they were given paraldehyde 30–60 ml (21).

Disulfiram

Paraldehyde is metabolized in the liver to acetaldehyde (22), and the metabolism of aldehyde by aldehyde dehydrogenase is inhibited by disulfiram, causing aldehyde toxicity. The adverse effects of this have been shown in experimental animals (23) and there have been reports of confusional psychosis in patients given disulfiram and paraldehyde (24).

Intravenous fluids

About 10–16% of paraldehyde in 5% dextrose or 0.9% sodium chloride is lost when it is delivered from PVC bags through standard intravenous administration sets and burettes over 6 hours (25).

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Parathyroid hormone and analogues

General Information

Both intact parathyroid hormone and smaller *N*-terminal fragments are used. No adverse reactions have been reported with single infusions of up to 60 mg of synthetic human parathyroid hormone in diagnostic procedures (SEDA-13, 1307) (1,2). Although bone resorption increases if the hormone is given continuously or in high doses, it has an anabolic effect on bone when given intermittently. Synthetic parathyroid hormone fragments have therefore been used in the treatment of slow turnover osteoporosis. However, no improvement in fracture risk has been documented, and the anabolic effect may only be present in the first 12 months (3). The use of parathyroid hormone in the treatment of hypoparathyroidism is also under investigation, with the optimum dosage and target calcium concentrations yet to be determined.

The adverse effects of parathyroid hormone that have been reported in clinical trials are mild and include transient bone pain, nausea, and local irritation at the injection site (4).

Parathyroid hormone has potent anabolic effects on the skeleton if given intermittently; being used in clinical trials. Initial concerns about the development of osteosarcoma in rats after prolonged treatment with high doses of parathyroid hormone have not been confirmed in human trials, but surveillance continues (5). In one study there was a mild increase in creatinine, which was thought not to have clinical significance (6). Mild nausea (7) and arthralgia (7,8) have also been reported.

Nausea was reported in 18% and headache in 13% of 552 women who took parathyroid hormone 40 micrograms, compared with 8% of the 544 women who took placebo (9).

Organs and Systems

Cardiovascular

Parathyroid hormone lowers the blood pressure by a direct effect on vascular smooth muscle, and there are isolated instances of hypotension or tachycardia (10). Pre-injection blood pressure was normal in 1093 women randomized to parathyroid hormone ($PTH_{1–34}$), and dizziness was reported infrequently in 541 women taking 20 micrograms/day but not in 552 taking 40 micrograms/day (9).

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Mineral balance

Mild asymptomatic hypercalcemia is common during treatment with parathyroid hormone (11). The hypercalcemia is persistent, and requires dosage reduction in 3% of patients using 20 micrograms/day and in 11% using 40 micrograms/day (12). Transient mild hypercalciuria and increased serum phosphate are common but do not usually limit therapy.

In a randomized study in premenopausal women also treated with nafarelin, four of 23 women randomized to $PTH_{1–34}$ 500 IU/day had a serum calcium concentration over 2.67 mmol/l 4 hours after the injection; the concentration normalized after the dose of parathyroid hormone was reduced and other treatment was continued (7).

In another study, two of 10 men who were randomized to receive subcutaneous $PTH_{1–34}$ 400 IU/day for 18 months had serum calcium concentrations over 2.6 mmol/l after 1 or 3 months; the concentrations normalized after reduction of the dose of parathyroid hormone (8).

Hypercalcemia was present in 11% of 541 women 4–6 hours after parathyroid hormone 20 micrograms/day and in 28% of 552 women after 40 micrograms/day (9). The dose was halved because of hypercalcemia in 3 and 11% of the women taking 20 and 40 micrograms/day respectively. Nine of the women taking 40 micrograms/day stopped treatment because hypercalcemia persisted after dosage reduction.

Combining parathyroid hormone with antiresorptive agents may prevent or minimize hypercalcemia. None of 27 women randomized to estrogen plus parathyroid hormone $PTH_{1–34}$ 25 micrograms/day became hypercalcemic during a 3-year study (13).

Skin

Local reactions at sites of subcutaneous injection are common but are usually limited to transitory redness (7,8).

Subcutaneous nodules at the injection site developed in two of 17 women after more than 2 years of administration in a clinical trial (14). Two of 27 women randomized to parathyroid hormone developed nodules at injection sites; however, this could have been due to a contaminant, as both women received parathyroid hormone from the same batch (13).

Immunologic

Dose-dependent antiparathyroid hormone antibodies developed in under 10% of 1093 women in one study; however, there was no reduction in efficacy (9).

Long-Term Effects

Tumorigenicity

The rate of osteosarcoma in animal and human trials of parathyroid hormone has been reviewed (15). Rats treated with parathyroid hormone for 2 years had a high dose-dependent rate of osteosarcoma, up to 48% in animals given 75 micrograms/kg; human trials were therefore interrupted (16). However, the anabolic effect of parathyroid hormone is much greater and occurs much earlier in rats than in humans, possibly because of fundamental differences in bone biology: moreover, osteosarcoma has never been associated with primary, secondary, or tertiary hyperparathyroidism in humans (15). There has been no evidence of osteosarcoma in several hundred patients involved in parathyroid hormone clinical trials lasting up to 3 years, after 5 years minimum follow-up (15).

Drug–Drug Interactions

Bisphosphonates

Alendronate significantly reduced the anabolic effect of parathyroid hormone when the two were used in combination, both in postmenopausal women (17) and in men (18). It seems likely that this interaction will also apply to other bisphosphonates, although the mechanism has not been determined.

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Parecoxib

See also COX-2 inhibitors

General Information

Parecoxib sodium is an injectable COX-2 inhibitor developed for the treatment of acute pain. It is a prodrug of a sulfonamide-based COX-2 inhibitor, valdecoxib, a potent anti-inflammatory and analgesic drug. The published information on this compound is inadequate to draw any conclusion about its tolerability. Single-dose and multiple-dose studies have not shown any safety problems compared with placebo (1–4). In small short-term endoscopic studies parecoxib was much better tolerated than the non-selective NSAID ketorolac (5,6). However, it should be noted that valdecoxib was withdrawn in 2005 (7).

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Parenteral nutrition

General Information

Parenteral nutrition should be tailored to the needs of the individual, but on average should provide about 25 kcal/kg/day. Solutions for long-term parenteral nutrition should contain:

- about 30% carbohydrate, usually in the form of glucose, providing 60% of the energy requirements
- 30–50% fat in the form of a lipid emulsion such as soya oil
- amino acids, 150–250 kcal/g of nitrogen
- sodium and potassium
- calcium, phosphate, and magnesium
- bicarbonate
- vitamins
- trace elements (chromium, cobalt, copper, fluoride, iodide, iron, manganese, molybdenum, selenium, zinc)

The benefits and safety of parenteral nutrition have been considerably improved in recent years by innovative strategies, such as supplementation with medium-chain triglycerides, glutamine, or branch-chain amino acids.

Observational studies

GAB-88 is an infusion solution containing amino acids (3%), dextrose (7.5%), and electrolytes in a dual-chamber plastic bag. It has been evaluated in 39 non-operative patients who were unable to tolerate oral feeding or to take adequate amounts by mouth (1). When it was given in a daily dose of 1.0–2.5 liters for 7–19 days, there was an improvement in nutritional status without obvious adverse effects. There was mild vascular pain in four patients, but no phlebitis. There were no other clinically significant adverse reactions.

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In 28 Japanese institutions, GAB-88 was infused continuously via a peripheral vein at a rate of 30–45 ml/kg/day for 5 postoperative days after partial gastrectomy for gastric cancer in 92 patients and compared with a similar commercial formulation; no particular adverse events emerged (2,3).

No serious adverse effects were noted in a phase 1 clinical study of GAB-88 aimed at determining its safety and pharmacokinetics in eight healthy men who were given three different doses (0.15 g/kg/hour, 0.3 g/kg/hour, and 0.5 g/kg/hour) at 1-week intervals. Serum electrolytes did not change significantly, except for zinc (4).

General adverse effects

Many of the safety issues in parenteral nutrition relate to the fact that the process is inherently unphysiological (5). Instead of periodic ingestion of nutrients via the gastrointestinal tract resulting in gradual entry of nutrients into the blood, nutrients are infused directly at a constant rate. The gastrointestinal tract as a mediator of nutrient absorption, the periodicity of nutrient administration, and the natural biorhythms of hormone secretion are all lost.

Common problems in the past were fat overload syndrome, metabolic acidosis, hyperglycemia, and hypertriglyceridemia (6). These problems are now rare. Increasing efforts have been made to avoid adverse effects such as central venous catheter infection and hepatic dysfunction. Major developments in the future are likely to be achieved with the identification of nutrients, hormones, or other active compounds that can positively influence outcome beyond the safe provision of 40 essential nutrients in proper amounts, which is what principally has been achieved to date (7). Liver damage is still a major problem. The most common micronutrient deficiency is of thiamine.

In an assessment of the clinical use of nutrients, and the tendency that has been noted in the past to overfeed with carbohydrate, lipid, and micronutrients, attention has been drawn to the adverse effects of oversupply (8).

The emerging discipline of nutritional pharmacology and the related legislative and ethical issues require expert attention and analysis. Scientific study of the nutritional and pharmacological aspects of these substances will provide new and safer forms of therapy in a number of medical conditions.

Organs and Systems

Cardiovascular

Infusion phlebitis presents a problem in parenteral nutrition. Various alternative techniques of administration have been compared in order to identify means of countering this problem (9). Mechanical trauma appears to be a causative factor; it can be reduced by limiting the time of exposure of the vein wall to nutrient infusion and by minimizing the amount of prosthetic material within the vein (10). This is likely to be even more important in small veins. In one study the addition of heparin (500 U/l) and hydrocortisone (5 micrograms/ml) significantly reduced the risk of thrombophlebitis from 0.43 to 0.11 episodes per patient-day, and a reduction in osmolality of the solution resulted in a further ten-fold fall in the incidence of thrombophlebitis (11). Other work has concluded that the incidence of infusion phlebitis is minimized during parenteral nutrition by cyclic infusion of nutrient solutions and by rotation of venous access sites (12).

Respiratory

The clinical differentiation of chylothorax from leakage of parenteral nutrition fluid into the pleural space can be difficult. However, in one case the diagnosis of leakage of parenteral nutrition fluid was made by additional tests of electrolytes, showing very high concentrations of potassium (11.3 mmol/l) and glucose (128 mmol/l), ruling out chylothorax (13).

In an acute experiment, infusion of fat emulsion (Intralipid) for 60 minutes (mean dose 0.07–0.16 g/kg/hour) in neonates with lung disease was found to lead consistently to a 10% fall in transcutaneous PO_2 (transcutaneous oxygen tension). There was no change in PCO_2. This is evidence that Intralipid contributes to the hypoxia of respiratory distress in neonates; it should be used with caution in this group, and not at all in infants with pulmonary disease (14).

Nervous system

Two children developed neurological complications of fat emulsion therapy, including focal and generalized seizures, weakness, and altered mental status, before any systemic findings were in evidence (15). Biopsy and autopsy findings included cerebral endothelial and intravascular lipid deposition. These complications are potentially reversible with alteration of the parenteral nutrition content, highlighting the importance of their early recognition.

- Acute hemiplegia and seizure developed in a 24-year-old patient following accidental catheterization of the right common carotid artery for parenteral nutrition infusion (16). Magnetic resonance imaging of the brain showed lesions in the frontal lobe and putamen, consistent with an ischemic stroke.

Considerable interest has been stimulated in the pathogenesis of critical illness polyneuropathy during artificial nutrition (17). This condition (initially functional, but proceeding to an axonal polyneuropathy, demonstrable postmortem by histological evidence of axonal degeneration) is familiar to intensive care units, and it is an important cause of weaning failure. The neurological disability can last for some 6 months, but it is likely to be reversible if the cause is recognized early and treatment withdrawn before permanent axonal changes occur. There is a strong association with sepsis and multiple organ dysfunction syndrome, the nervous system being yet another focus of organ failure. The autonomic nervous system is commonly involved, and patients are likely to show early cardiovascular instability requiring antihypotensive medication. It seems that artificial feeding after starvation leads to reduced activity of the enzymes involved in glucose oxidation, with the result that nutrient glucose causes accumulation of phosphorylated glycolytic

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intermediates; this in turn causes a block in the energy cascade that is an essential element in the development of axonal polyneuropathies. Although the exact chain of events is not known, there is evidence that there are disturbances of the microcirculation and increased microvascular permeability, which can lead to endoneural edema with resulting primary axonal degeneration of peripheral nerves (18). A sensitive bioassay capable of identifying a low molecular weight fraction toxic to rat spinal motor neurons has been identified in the sera of these patients (19,20).

Cases of Wernicke's encephalopathy caused by thiamine deficiency during parenteral nutrition are reported (21).

- A 13-year-old girl with acute myeloid leukemia received parenteral nutrition and chemotherapy. After a second cycle of chemotherapy she developed persistent nausea and vomiting, nystagmus, ophthalmoplegia, and brisk deep tendon reflexes on the left. Her level of consciousness deteriorated progressively. A CT scan was normal, but an MRI scan showed caudate nucleus lesions, cortical involvement, and typical diencephalic and mesencephalic abnormalities. She was given mannitol and dexamethasone, but without improvement. However, after intravenous thiamine her symptoms gradually improved; she recovered within 1 month and the MRI abnormalities disappeared.

The authors suggested that this case showed how MRI can play a role in the diagnosis of Wernicke's encephalopathy, but that there was unusual involvement of the frontal and parietal cortex and the caudate nuclei.

Metabolism

Ammonium

Hyperammonemia has occurred during parenteral nutrition as a component of therapy for renal insufficiency (22). The hyperammonemia presented as a change in mental status, developing about 3 weeks after initiation of parenteral nutrition therapy; in most cases the episodes are of increasing duration and paroxysmal. In three of the patients, serum amino acid analysis in the acute phase showed reduced concentrations of ornithine and citrulline (the respective substrate and product of condensation with carbamyl phosphate at its entry into the urea cycle). Concentrations of arginine, the precursor to ornithine, were raised.

Carbohydrates

The effects of parenteral nutrition on endocrine and exocrine functions of the pancreas have been investigated in experimental rats (23). The conclusion was that after parenteral nutrition treatment the insulin secretory response to glucose is impaired, the exocrine pancreas is hypoplastic, and the storage pattern of pancreatic exocrine enzymes is altered.

Lipids have an adverse effect on carbohydrate metabolism under basal conditions. The infusion of 20% triglyceride emulsion with heparin during basal insulin and glucose turnover conditions resulted in a rise of plasma free fatty acids from 0.4 to 0.8 mmol/l at a low rate of infusion (0.5 ml/minute for 2 hours) to between 1.6 and 2.1 mmol/l at a high rate (1.5 ml/minute for 2 hours). There were similar increases in plasma concentrations of glycerol, acetoacetate, and hydroxybutyrate. The infusions resulted in significant increases in C-peptide concentrations, but had no effects on any of the other indices of carbohydrate metabolism that were examined (plasma glucose, lactate, and pyruvate concentrations), or on carbohydrate oxidation rates. By blocking the compensatory release of insulin by the intravenous administration of somatostatin and by simultaneous replacement of basal insulin and glucagon concentrations, these workers found that there was a significant increase in plasma glucose and in hepatic glucose output, and reduced glucose clearance. It was concluded that exogenous lipids may have adverse effects on carbohydrate metabolism under basal conditions, and that healthy individuals normally compensate for this by additional secretion of insulin (24).

Preoperative parenteral nutrition can be a major cause of hyperglycemia, which has been associated with an increased risk of postoperative infection. The frequency of hyperglycemia and infectious complications has been studied in a prospective, randomized, controlled, nonblind trial in 40 patients who required parenteral nutrition for at least 5 days (25). They were given either a hypocaloric regimen (1 liter containing nitrogen 70 g and dextrose 1000 kcal) or a standard weight-based regimen begun with similar amounts initially but with gradual increases in calorie and nitrogen contents to 25 kcal and 1.5 g nitrogen/kg, up to one-third of the calories being given as fat. There were no significant differences between the two groups with regard to hyperglycemia or infections. The higher calorie regimen provided significant nutritional benefit in terms of nitrogen balance compared with the hypocaloric regimen.

Some children receiving parenteral nutrition have abnormal glucose tolerance. When this was studied in 12 patients, aged 5.7–19 years, receiving cyclic nocturnal parenteral nutrition, patients with normal glucose tolerance had an insulin response to intravenous glucose tolerance testing similar to that of normal people of the same age (26). Two patients with abnormal glucose tolerance had a reduced capacity to release insulin, whereas insulin sensitivity was unchanged in one of them. Patients with a limited capacity to release insulin, either constitutional or acquired, may not be able to produce enough insulin in these conditions and they may develop glucose intolerance during parenteral nutrition. Insulin sensitivity was not a key factor in the alteration of glucose tolerance in this study.

In five patients with multiple trauma given sodium lactate as part of parenteral nutrition there was a 20% fall in glycemia, a 43% fall in insulinemia, a 34% reduction in net carbohydrate oxidation (assessed by indirect calorimetry), and a 54% fall in plasma glucose oxidation (assessed using $^{13}CO_2$). Respiratory oxygen exchange was increased by 3.7% owing to a 20% thermic effect of lactate, but respiratory CO_2 exchange was not altered. PaO_2 fell by 11.3 mmHg, suggesting that the increased oxygen consumption was matched by an appropriate increase in spontaneous ventilation. Arterial pH increased from 7.41 to 7.46. It appears that sodium lactate given in parenteral nutrition during short intravenous

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nutrition in critically ill patients as a metabolic substrate limits hyperglycemia but contributes to metabolic alkalosis and does not spare ventilatory demand (27).

Lipids

The fat overload syndrome, characterized by a sudden rise in serum triglycerides, hepatosplenomegaly, intravascular coagulopathy, and end-organ dysfunction, is today an uncommon complication of intravenous administration of fat emulsion. Its higher incidence in the past may have been due to the greater phospholipid content of intravenous solutions in use at the time. The syndrome is a consequence of fat sludging within the microvasculature in organs such as the spleen, liver, kidney, lungs, brain, and retina. Necrosis in these organs suggests that emboli are responsible for the clinical symptoms and functional impairment that results. Plasma exchange has been successfully used in a patient with this syndrome who had not responded adequately to conventional medical therapy (28).

Critically ill patients are at greatest risk of fat overload syndrome when they are given lipid emulsions intravenously. Some of these patients already have impaired lipid metabolism and they are at risk of developing fat intolerance. These are the very patients who are likely to be given parenteral nutrition, including fat emulsions. Patients with increased serum triglyceride concentrations (for example, in hypothyroidism, with inborn errors of lipid metabolism, renal insufficiency, and severe sepsis, especially gram-negative sepsis) are at greatest risk. There is impaired metabolism of fats in advanced liver disease. Continuous heparin infusion may also lead to a decreased elimination capacity (29).

Fatty acids

Patients undergoing home parenteral nutrition for severe malabsorption or reduced oral intake can exhaust their stores of essential fatty acids, causing clinical effects, mainly dermatitis. In a comparative study of fatty acid profiles in 37 healthy control subjects and 56 patients receiving home parenteral nutrition, reduced small bowel length was associated with aggravated biochemical signs of essential fatty acid deficiency (30). This applied to total *n*-6 fatty acids and not to *n*-3 fatty acids. There were skin problems in 25 of the 56 patients receiving home parenteral nutrition. Patients receiving home parenteral nutrition had biochemical signs of essential fatty acid deficiency. Parenteral fluids did not increase the concentration of essential fatty acids to values comparable with those of control subjects. However, 500 ml of 20% fat emulsion (Intralipid) once a week was sufficient to prevent an increase in the Holman index (an indicator that reflects optimum proportions of polyunsaturated fatty acids).

Linoleic acid and alpha-linoleic acid are essential fatty acids that are provided in any long-term parenteral nutrition by administering fat emulsions at least twice a week. Fatty acid deficiency is a common complication of severe end-stage liver disease. The ability of short-term intravenous lipid supplementation to reverse fatty acid deficiencies has been studied in patients with chronic liver disease and low plasma concentrations of fatty acids (31). Short-term supplementation failed to normalize triglycerides.

Phospholipids

Although choline is not regarded as an essential nutrient for humans, it has been described as being "conditionally essential" in patients receiving parenteral nutrition. Choline is a methyl-group donor, a component of phospholipids, and a precursor of acetylcholine and lecithin. In animal models and healthy human beings, choline deficiency impairs liver function. Studies in patients receiving long-term parenteral nutrition have shown that low levels of plasma choline are common and are associated with hepatic steatosis.

- Choline deficiency developed in a 41-year-old woman with advanced cervical cancer who underwent prolonged parenteral nutrition (32). Her liver function tests became abnormal and she became jaundiced and complained of nausea and vomiting. The serum choline concentration was 5.77 mmol/l and there was histological evidence of hepatic steatosis. There was steady improvement with oral choline supplementation, 3 g/day, and with oral glutamine 15 g/day. There was a 45% improvement in serum choline concentration over baseline.

Intravenous fat emulsions contain choline, but not in sufficient amounts to prevent choline deficiency (32,33).

Nutrition

Amino acids

Carnitine

In septicemic patients with multi-organ dysfunction syndrome serum carnitine concentrations are in the reference range, and they remain unchanged over treatment for 10 days with parenteral nutrition without carnitine supplementation. This has been established in 28 septicemic patients, mean age 53 years, whose mean APACHE II score on admission was 17. Of these patients, 10 had septicemia with multi-organ dysfunction syndrome and 18 had uncomplicated septicemia. There were no differences in patients given long-chain triglycerides ($n = 16$) and a 1:1 mixture of long-chain and medium-chain triglycerides ($n = 12$). It does not appear from these findings that carnitine deficiency plays a significant role in the pathogenesis of multi-organ dysfunction syndrome complicating septicemia, whether or not parenteral nutrition is given in the acute phase of the illness (34).

Deficiency of carnitine has been described in all of a series of surgical neonates receiving parenteral nutrition (35); carnitine intake was far below the recommended minimal need of 11 mmol/kg per day. Although only three of the infants had clinical symptoms suggestive of carnitine deficiency, the authors recommended carnitine supplementation for all neonates receiving parenteral nutrition for more than 2 weeks. It has been suggested that a deficiency of l-carnitine may be responsible for steatosis and steatohepatitis in patients on parenteral nutrition, but one experimental study in adult women throws much doubt on this theory (36). However, in another series of patients who had depletion of erythrocyte and plasma glutathione peroxidase activity during parenteral nutrition (37), supplementation with selenium resulted in normalization of glutathione peroxidase activity within 3–4 months, which is consistent with the time-course for bone marrow erythrocyte production.

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Glutamine

Animal studies have shown that raised plasma glutamate concentrations increase cerebral edema whenever the blood–brain barrier is disturbed. In a prospective study of 23 neurosurgical patients requiring parenteral nutrition, glutamine-containing regimens were compared with parenteral nutrition regimens that excluded glutamine (38). The former doubled plasma glutamine concentrations compared with controls, and the authors concluded that glutamine-containing solutions cannot be recommended for patients with a disturbed blood–brain barrier.

In a study of the safety and efficacy of l-glutamine when added to parenteral nutrition solutions of patients being treated at home, glutamine was stable in home parenteral nutrition solutions for at least 22 days. Supplementation of home parenteral nutrition solutions with l-glutamine in a dose of 0.285 g/kg for 4 weeks in seven stable patients resulted in increases in hepatic enzymes in two patients, requiring withdrawal of the glutamine/parenteral nutrition mixtures at the end of weeks 2 and 3. A third patient's liver enzymes rose at the end of week 4. These abnormalities subsided after withdrawal. Plasma concentrations of glutamine rose during the first 3 weeks of supplementation, but these increases were not statistically significant. It appears that hepatic toxicity can be associated with supplementation of home parenteral nutrition solutions with l-glutamine, without a demonstrable beneficial effect on intestinal absorptive capacity, as measured by d-xylose absorption (39). Other work seems to confirm the lack of benefit from adding glutamine in the form of its dipeptide, though it proved harmless (40).

Thiamine

Thiamine deficiency has been reported (41).

- A young man developed marked deterioration in his vision and oscillating vision, despite normal optic fundi, during parenteral nutrition; he went on to develop a characteristic Wernicke's encephalopathy, confirmed by characteristic findings on MRI brain scan (42). The serum vitamin B_1 concentration was 110 pg/ml (reference range: 200–500). He responded fully to thiamine 300 mg/day in addition to betamethasone for 4 weeks.
- Parenteral nutrition was used to support a patient requiring autologous blood stem-cell transplantation, but vitamins were excluded (the reason was not identified). After about 28 days, the patient suddenly developed severe metabolic acidosis, heart failure, and deep coma. Thiamine was immediately infused, with rapid improvement.

In the second case, the authors were unsure if the associated graft failure was due to the acute metabolic acidosis or thiamine deficiency, since the absence of thiamine in the diet leads to poor glucose oxidation, resulting in accumulation of lactic acid and metabolic acidosis, which is refractory to any treatment except thiamine supplementation.

Vitamins

More than 40 cases of fulminant beriberi have been described in patients receiving parenteral nutrition (43). The condition becomes evident 4–40 days after the start of parenteral nutrition, and is more likely to develop in patients with malignancies, ulcerative colitis, and short bowel syndrome, and in those receiving chemotherapy. The severity of metabolic acidosis is very high and refractory to bicarbonate administration, but it responds quickly to intravenous thiamine. Rapid intravenous administration of thiamine is imperative, and the patient should be transferred urgently to an intensive care unit when parenteral nutrition-induced fulminant beriberi develops.

A further consequence of thiamine depletion during parenteral nutrition can be severe lactic acidosis (44). Six cases have been described from Japan with associated hypotension, Kussmaul's respiration, and clouding of consciousness, as well as abdominal pain not directly related to the underlying disease. During parenteral nutrition administration there was blockade of oxidative decarboxylation of alpha-keto acids such as pyruvate and alpha-ketoglutarate, resulting in pyruvate accumulation and massive lactate production. None of the patients responded to sodium bicarbonate or other conventional emergency treatments for shock and lactic acidosis. Thiamine replenishment with intravenous doses of 100 mg every 12 hours resolved the lactic acidosis and improved the clinical condition of three patients.

These various reports stress the need to supplement parenteral nutrition with thiamine-containing vitamins unless there is adequate dietary intake, and to monitor serum thiamine and erythrocyte transketolase activity so that supplementary thiamine can be given in good time, if necessary intravenously (45). Giving thiamine will not rectify the various disorders if hepatic function is severely disturbed, because then thiamine is not phosphorylated and hence remains physiologically inactive.

Electrolyte balance

Hyperkalemia in one published case was attributed to combined treatment with octreotide and heparin (enoxaparin) in parenteral nutrition (46). It was suggested that both enoxaparin and octreotide had contributed in this case to the development of hyperkalemia since they reduce urinary potassium excretion.

Mineral balance

Calcium

Calcium is normally considered to be safe in parenteral nutrition, and relatively high quantities are often included in neonatal and pediatric formulations. However, there is a risk of hypercalciuria. The pathogenesis of hypercalciuria is not readily explicable on the basis of endocrine or metabolic effects, but it has been postulated to be due to excessive calcium or vitamin D intake or aluminium overload.

- A 6-year-old girl with Hirschsprung's disease had jejunostomy at 1 month followed by parenteral nutrition (47). Her calcium intake was 1–1.5 mmol/kg/day. Her urinary calcium rose from 3 months of age; her serum calcium concentrations remained within the reference range but started to rise when she was 3–4 years old. At 5–6 years of age she showed growth retardation and deteriorating renal tubular function with bilateral

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nephrocalcinosis. The calcium content of the parenteral nutrition was reduced, her serum and urinary calcium concentrations stayed within the reference ranges, and her renal function and growth rate improved.

After persistent hypercalciuria, osteopenia can develop, causing "metabolic bone disease," pathological fractures, and immobilization. Hypercalciuria can also lead to nephrolithiasis and nephrocalcinosis, factors that can impair renal function. Intravenous chlorothiazide has been successfully used for its hypocalciuric effect, with remarkable effect over a period of 6 months in a 13-year-old child who had received parenteral nutrition for 6 years. Calcium excretion and tubular reabsorption of phosphate returned to normal (48). What is not clear from this study is whether the drug actually has a positive long-term beneficial effect on metabolic bone disease.

Increasing the inorganic phosphorus content of parenteral nutrition formulas reduces hypercalciuria due to parenteral nutrition in experimental animals and humans. Urinary calcium excretion is significantly lower when patients receive higher inorganic phosphorus formulae, without changing the load of ultrafilterable calcium or filtered calcium, but significantly reducing fractional calcium excretion. There were no differences in serum concentrations of ionized calcium, parathyroid hormone, 25-hydroxycolecalciferol, 1,25-dihydroxycolecalciferol, or urinary cyclic AMP between different treatments with inorganic phosphorus formulae. Thus, increasing the inorganic phosphorus content of the parenteral nutrition formula reduces urinary calcium content by increasing renal tubular calcium resorption. This effect is not due to alterations in the parathormone/1,25-dihydroxycolecalciferol axis, but more probably reflects a direct action of inorganic phosphorus on the renal tubules (49).

Phosphate

Since chronic renal insufficiency is frequently complicated by rises in serum potassium, phosphate, and magnesium, parenteral nutrition solutions used to treat malnourished patients with chronic renal insufficiency are usually prepared with little supplementation of these cations. Four patients with chronic renal insufficiency developed significant hypophosphatemia 3–5 days after starting parenteral nutrition. Other electrolyte abnormalities included hypomagnesaemia ($n = 1$) and hypokalemia ($n = 3$) (50). Hypophosphatemia may be the most significant of the electrolyte risks in this clinical setting, and the electrolytes of such patients should be monitored closely when nutritional support is begun.

Hypophosphatemia has received continued attention, resulting in the need to recognize the importance of maintaining awareness of the possibility of low phosphate concentrations, monitoring phosphate concentrations closely during the first week of therapy, and supplementing with phosphate cautiously while serum concentrations remain in the reference range (51,52).

Excess phosphate is only likely to be administered as a result of medical error.

- Hyperphosphatemia complicated by calcification of subcutaneous arteries and skin infarcts has been reported in a patient with sepsis who received an unintended excess of phosphate in parenteral nutrition (53). The patient had unintentionally received total elemental phosphorus infused over a 7-week period in the daily amount of 1.8–4.2 g (median 3.1 g), over three times the normal daily requirement. Serum phosphorus increased to 3.02 mmol/l (reference range 0.76–1.46 mmol/l). Calcification of subcutaneous arteries was complicated by widespread infarcts of the anatomically related skin and subcutis, apparently the result of hypoperfusion of these vessels during an episode of septic shock. The infarcts were characterized by blotchy skin discoloration.

Metal metabolism

Aluminium

Over the years, problems have arisen as a result of the presence of significant amounts of aluminium in parenteral nutrition solutions; in particular they have been held responsible for hypercalciuria and its consequences (54). Parenterally administered aluminium bypasses the gastrointestinal tract, which normally serves as a protective barrier to aluminium entry into the blood. In the past, aluminium contamination of casein hydrolysate, which was used as a source of protein in parenteral nutrition solutions, was associated with low-turnover osteomalacia and with encephalopathy in uremic patients. Premature infants are still at risk of aluminium accumulation as a result of prolonged parenteral nutrition (as are patients receiving plasmapheresis with albumin contaminated in its preparation with aluminium). Metabolic bone disease can result (54).

Deposition of aluminium in bone seems to relate to the appearance of bone disorders (55), although it is probably not the only cause and some studies have failed to detect a clear relation. In one critical study the bone response to parenteral nutrition containing high amounts of aluminium and ergocalciferol (25 micrograms/day), administered for 6–72 months, was compared with that to parenteral nutrition containing amino acids with reduced amounts of aluminium and ergocalciferol (5 micrograms/day) for 9–58 months, and various other solutions. Bone formation varied inversely with both plasma aluminium and bone surface aluminium, suggesting that plasma or bone surface aluminium, acquired during parenteral nutrition, reduces bone formation and leads to patchy osteomalacia (56). One should add, however, that in this study the switch to amino acids rather than casein not only influenced aluminium intake but also that of protein and ergocalciferol, both of which could be relevant to bone responses.

No effective treatment has been established for aluminium-loaded patients other than identifying the primary source of aluminium contamination and reducing or eliminating it with an appropriate substitute constituent. Prospective studies of serum aluminium concentration and urinary aluminium excretion in children receiving long-term parenteral nutrition would allow better definition of the extent to which aluminium loading remains a problem (5).

Copper

Patients who develop cholestatic jaundice during chronic parenteral nutrition can develop significant hematological complications due to hypocupremia.

- A 36-year-old woman with short bowel syndrome developed progressive liver dysfunction 6 months after

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the start of parenteral nutrition (57). Trace elements had been omitted because of cholestasis and persistent hyperbilirubinemia. After 15 months she became dependent on erythrocyte transfusions and her neutrophil and platelet counts fell steadily. After 19 months her serum copper concentration was 4 ng/ml (reference range 11–24 ng/ml, 0.17–0.38 μmol/l). Provision of trace elements for 2 months was associated with increased serum copper concentration and neutrophil and platelet counts, independent of erythrocyte transfusions. When the serum copper concentration reached 30 μmol/l copper was discontinued. Over the next 3 months, the copper concentration fell to 1.6 μmol/l and neutrophil and platelet counts fell precipitously. Once again, the copper concentration and neutrophil and platelet counts recovered with copper supplementation.

Because copper is excreted primarily in the bile, some experts advocate reducing or curtailing copper supplementation in patients with chronic hyperbilirubinemia. The earliest signs of copper deficiency are peripheral blood cytopenias (typically anemia and neutropenia) and occasionally thrombocytopenia, caused by reduced bone marrow production. The authors recommended that serum copper should be monitored quarterly and that copper should be included in the parenteral nutrition mixture three times a week, adjusting the frequency in response to serum copper concentrations.

Three adult cases in which copper deficiency developed during long-term parenteral nutrition without copper supplementation have been described. All three patients were suffering from malabsorption when therapy was instituted, and overt symptoms of copper deficiency developed an average of 5.8 months after the start of parenteral nutrition. Leukopenia with neutropenia and low plasma concentrations of copper and ceruloplasmin were seen in all cases (58).

- Copper deficiency has been reported in a patient with Crohn's disease after removal of copper from the parenteral nutrition because of severe cholestasis (59). The patient developed pancytopenia with severely depressed serum copper concentrations after 8 weeks. Bone-marrow biopsy confirmed the cause as copper deficiency. Although intravenous replacement of copper improved the patient's anemia and other markers, he suddenly died of cardiac tamponade.

Manganese

The dangers of hypermanganesemia as a result of parenteral nutrition are well documented. They are mainly associated with neurological toxicity. The causes of hypermanganesemia are poorly understood, but cholestasis is suspected as a key factor. There has been an attempt to identify the main factors associated with increased plasma manganese in a prospective study in 21 subjects (60). Hypermanganesemia was not only related to increased quantities infused but also to persistent inflammation (which can alter manganese metabolism) and cholestasis (causing reduced manganese biliary excretion). Neurological complications appeared to be marginal, despite the fact that manganese brain deposition is frequent. The authors suggested that manganese status must be regularly monitored during long-term parenteral nutrition.

When oral intake is precluded, the recommended daily parenteral supplementation of manganese is 0.15–0.8 mg. Manganese is mainly excreted in the bile; during cholestasis serum manganese levels may rise, and manganese toxicity can result. Hypermanganesemia after parenteral nutrition when first reported was linked to portosystemic encephalopathy. Patients with liver disease were particularly at risk.

- Manganese deposition in the brain has been reported after 28 days of parenteral nutrition including manganese 20 μmol/day (61). The serum manganese concentration was raised (4.9 μmol/l) 34 days postoperatively, 13 days after stopping parenteral nutrition. MRI scans showed symmetrical hyperintense lesions in the globus pallidus, which gradually improved as serum manganese concentrations fell to normal.

The authors concluded that even short-term perioperative parenteral nutrition can result in manganese deposition, especially if there is liver impairment.

Excess manganese can accumulate in the brain, resulting in toxic psychosis ("manganese madness") and parkinsonism. One striking report involves a middle-aged woman receiving parenteral nutrition supplemented with trace elements from the first postoperative day after a Whipple's procedure; she developed obstructive jaundice, and her serum bilirubin concentration peaked at 179 μmol/l on the ninth postoperative day (62). She simultaneously developed increasing confusion, aggression, and choreoathetoid movements. The serum manganese concentration was 26 ng/ml (reference range below 10 ng/ml). When supplementation of manganese was substantially reduced there was progressive improvement in her confusion and other neurological signs. On the basis of this experience the authors warned against the use of standard dosages of manganese in patients with obstructive jaundice.

In manganese madness, neuroleptic drugs may be ill-advisedly administered. However, they themselves can potentiate manganese toxicity and have serious adverse effects of their own. Trivalent manganese promotes oxidation of phenothiazines, increasing free-radical formation, and may increase a patient's susceptibility to haloperidol (63). MRI brain scans in 13 of 57 children aged 6 months to 10 years receiving long-term parenteral nutrition who were being investigated because of hypermanganesemia showed characteristic increased signal intensity on T1-weighted images in seven cases, with no abnormalities on T2-weighted images. All the patients had increased whole blood manganese concentrations, suggesting that the basis for the MRI abnormality was deposition of manganese within the basal ganglia and other cerebral tissues (64). In other studies these MRI changes disappeared or abated after withdrawal of manganese supplements or exposure, but the Parkinson-like neurological manifestations appear to be permanent.

Serum manganese concentrations are not a reliable indicator of the concentrations attained in the brain. However, in one reported case with neurological complications in which alterations in basal ganglia and cerebral signal intensity had been detected during life by magnetic

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resonance, postmortem showed raised concentrations of manganese in the radiologically abnormal areas (65).

The relation between dose and erythrocyte concentrations of manganese has been studied in patients receiving parenteral nutrition, including manganese 500 micromol/day, for periods varying from a few days to many months (66). While concentrations during short-term parenteral nutrition were normal, patients who had been receiving parenteral nutrition for up to 30 days had raised concentrations. Of 21 patients who had been receiving parenteral nutrition for over 1 month, 15 had raised erythrocyte manganese concentrations, although in this group there was no clear relation with liver test abnormalities or renal function. In three patients there was evidence of neurological damage. The authors recommended that all patients receiving parenteral nutrition for more than 30 days should be monitored for serum manganese concentrations, that the recommended dose of manganese should not exceed 100 micrograms/day, and that manganese should be eliminated from nutrition solutions when the serum concentration is raised. The authors also recommended that manganese should not be added to parenteral nutrition solutions for patients with chronic liver disease.

It is not known with certainty whether manganese accumulation is hepatotoxic in humans, but in rats it causes mild though reversible intrahepatic cholestasis. Manganese may prove to be an overlooked cause of hepatotoxicity, as it is excreted via bile. Of 53 children who had been given parenteral nutrition for over 6 weeks, 35 had biochemical evidence of cholestatic liver disease, and in all those cases the serum manganese concentration was over 360 nmol/l (67). The highest serum manganese concentrations were found in children under 2 years of age; it is possible that biliary excretion of manganese at this age is less efficient.

The possible link between hypermanganesemia and cholestasis has been investigated in patients receiving long-term parenteral nutrition (68). The authors concluded that cholestatic liver disease does not contribute to increased blood manganese concentrations in such patients, and that plasma concentrations reflect recent manganese exposure and impaired excretion when cholestasis is present. They also emphasized that serum concentrations are a poor marker and that erythrocyte manganese concentrations should be used instead.

Selenium

The signs of selenium deficiency include skeletal myopathy and cardiomyopathy, and selenium deficiency continues to be reported in cases in which this essential element has not been added to parenteral nutrition solutions during long-term administration (69).

In a report dating from 1987, low selenium concentrations were found in four children receiving long-term parenteral nutrition. There was erythrocyte macrocytosis ($n = 3$), loss of pigmentation of hair and skin ($n = 2$), raised transaminase and creatine kinase activities ($n = 2$), and profound muscle weakness ($n = 1$). Intravenous supplementation with selenium for 3–12 months resulted in progressive improvement in all these (70).

Selenium deficiency caused by parenteral nutrition can cause heart failure.

- A 38-year-old man with Crohn's disease had been receiving parenteral nutrition for 16 years, from the age of 22 years (71). After 6 years of parenteral nutrition he developed heart failure and ventricular extra beats associated with selenium deficiency. A serum concentration of 62 ng/ml was measured (reference range 80–230). Selenium supplements improved his condition but did not normalize left ventricular function. He was given selenium supplements and was free from heart failure for 11 years, but the echocardiographic findings gradually deteriorated and he died of congestive heart failure at the age of 38 years. At autopsy, his heart showed linear fibrosis in the interventricular septum, confined to the right side. The subendocardial region and the right ventricular free wall were relatively spared.

The authors proposed that the cardiac changes in this case were characteristic of the cardiomyopathy related to selenium deficiency. Once fully developed, left ventricular dysfunction may be irreversible, even after the use of selenium supplements.

Selenium deficiency has also been reported to have caused a myopathy.

- A 35-year-old man developed selenium deficiency after repeated administration of parenteral nutrition for 13 years (72). The deficiency syndrome manifested as muscle weakness but not pain in both arms and legs, especially the thighs. There was a dominant proximal muscle weakness and reduced deep tendon reflexes. There was a progressive rise in serum creatine kinase activity, mainly of the MM type. Serum aldolase and lactate dehydrogenase were significantly raised. Peripheral muscle electromyography showed a myogenic pattern of short duration and amplitude. Muscle biopsy showed myopathic changes, with mild variation in size, regeneration of muscle fibers and muscle cell necrosis. There was no infiltration of inflammatory cells. The serum concentration of selenium was very low (1 ng/ml, reference range 97–160). After treatment for 3 months with selenium infusions the muscle weakness began to resolve and the creatine kinase activity improved. The muscle weakness did not disappear completely and serum selenium concentrations did not return to normal for more than 4 months after treatment. Eventually, and after about 5 months, there was virtually complete resolution of the muscle weakness and serum creatine kinase abnormality.

Selenium is a constituent of glutathione peroxidase, an enzyme that catalyses the oxidation of reduced glutathione by hydrogen peroxide and other hydroperoxides to form oxidized glutathione and water. In addition, glutathione peroxidase reduces phospholipid hydroperoxide in cell membranes. Selenium deficiency, as well as glutathione depletion, reduces resistance against oxidative stress, resulting in lipid peroxidation. Selenium via glutathione peroxidase may be one of the key mediators in response to oxidative stress. Cardiomyopathy and hyperglycemia are additional possible complications of selenium deficiency, but they were not noted in this case.

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Acid–base balance

Lactic acidosis can occur through thiamine deficiency during parenteral nutrition (73).

- A 13-year-old boy underwent bone marrow transplantation and received parenteral nutrition without vitamins. After 15 days he had acute life-threatening lactic acidosis refractory to bicarbonate and Tris. Intravenous thiamine 100 mg produced satisfactory clinical and biochemical responses.

The authors suggested that in any patient receiving parenteral nutrition without added vitamins who develops lactic acidosis, thiamine deficiency should be suspected.

Hematologic

Erythrocytes

The major cause of megaloblastic anemia in children is folate deficiency. The following case indicates the importance of including regular supplementation of parenteral nutrition with folate (74).

- A Japanese boy, born at 34 weeks with congenital microvillous atrophy, was given parenteral nutrition 7 days after birth. The mixture included trace elements and most vitamins, but not folate. At 3 months he became lethargic, with facial pallor and hepatosplenomegaly. He had a hemoglobin of 6.9 g/dl with thrombocytopenia and a normal white blood cell count. Bone marrow showed typical megaloblasts. The serum folate concentration was 0.6 (reference range 2.4–9.8) ng/ml and vitamin B_{12} was 290 (249–938) pg/ml. These findings indicated megaloblastic anemia due to folate deficiency. Daily intramuscular folate 30 micrograms/kg and vitamin B_{12} 40 micrograms/kg improved his anemia and thrombocytopenia and his serum folate concentration returned to normal after 14 days. Both vitamins were then added daily and there was no recurrence of anemia, but he died at 4 months because of sepsis.

It is estimated that the minimum daily requirement of folate is 5 micrograms/kg. Liver stores are about 160 micrograms in premature children, and 220 micrograms in full-term infants. Infants who require parenteral nutrition will rapidly become folate deficient unless folic acid is included in the regimen. Since many multivitamin supplements do not contain folic acid, its inclusion should be ensured by the addition of folic or folinic acid.

Iron deficiency anemia can also be an important adverse effect of long-term parenteral nutrition. It is usually caused by partial or complete absence of iron from the regimen, inadequate absorption if oral iron is substituted, or chronic iron loss from gastrointestinal lesions. In a retrospective study, the records of 55 patients on long-term parenteral nutrition (more than 6 months) were examined for evidence of iron deficiency anemia (75). All had received home parenteral nutrition, comprising amino acids, glucose, and fat emulsion, with appropriate electrolytes, vitamins, and trace elements, but without iron. All had taken substantial amounts of food despite malabsorption. Iron deficiency anemia was identified in patients whose hemoglobin concentration was less than 12 g/dl and who had at least one the following: serum iron less than 600 ng/ml and TIBC less than 3500 ng/ml; iron to TIBC ratio (or transferrin saturation) 16% or less; or serum ferritin less than 15 ng/ml. Iron studies had been monitored at about 3-monthly intervals, reduced to yearly if no problems were found. In 30 patients there was evidence of iron deficiency anemia; ten of these were detected at the start of home parenteral nutrition, and the other 20 developed iron deficiency anemia during treatment. Many had evidence of acute blood loss, for example from the gastrointestinal or genitourinary tracts. The time between the start of parenteral nutrition and the development of anemia was 2–97 (mean 29) months. Mild iron loss from the gastrointestinal tract was identified as the predominant cause. Regular treatment with small amounts of iron (10–15 mg/day had been used in these patients) added to the parenteral nutrition regimen appeared to be safe and efficacious, with no reported adverse effects. In contrast, total dose infusion of iron (for example, iron dextran infusion) had adverse effects in 25% of patients.

Iron is an essential element in nutrition, and its inclusion in any long-term parenteral nutrition regimen should be mandatory. However, it is not included in all trace element formulations, although this varies from country to country; most European products include 20 μmol of iron in trace element formulations. While it might be considered unnecessary to include iron as a daily supplement, because of safety and pharmaceutical considerations, there is ample evidence that the use of iron-containing trace element formulations is both safe and efficacious, with no associated adverse effects.

Histiocytosis

Sea-blue histiocytes containing granulations and hemophagocytosis can be seen on bone marrow smears, and there can be bone marrow sequestration of radiolabeled autologous erythrocytes. The constellation of hematological abnormalities suggests an activation of the monocyte-macrophage system by the fat emulsion (76).

Sea-blue histiocytes have been reported in bone marrow secondary to parenteral nutrition including fat-emulsion sources in seven patients with severe thrombocytopenia undergoing long-term parenteral nutrition required by extensive small-bowel resection (77). All patients received intravenous fat emulsion (Intralipid 20%) for 3–18 months. Bone marrow biopsy showed sea-blue histiocytes dispersed amongst hemopoietic cells or arranged in aggregates adjacent to osseous lamellae and blood vessels or separated from bone trabeculae. The significance of these histological findings in association with parenteral nutrition and thrombocytopenia is not known.

When one young woman on chronic parenteral nutrition for short bowel syndrome presented with hepatosplenomegaly and pancytopenia (78), bone marrow examination showed the sea-blue histiocytes to be lipid-laden macrophages. The total amount of fat in the regimen was subsequently reduced, and there was partial hematological improvement. The condition observed in this patient is analogous to that which occurs in Gaucher's disease and Niemann-Pick disease.

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Leukocytes

Septic complications associated with total parental nutrition may be partly due to neutrophil dysfunction, though this has not been demonstrated (79).

Platelets

Hematological abnormalities have been found to be associated with prolonged administration of intravenous fat emulsion in children on a program of long-term cyclic parenteral nutrition. Recurrent thrombocytopenia is common and platelet lifespan is reduced. In one study (80), thrombocytopenia occurred in 66% of patients, but most of these had taken drugs that might have interfered with platelet function. Hypercoagulability was not found in the majority of cases.

It seems clear that platelet counts should be performed on a regular basis in patients receiving prolonged parenteral nutrition with fat emulsion (Intralipid). If a low platelet count develops, reduction or termination of administration is indicated (76). Clinical findings further point to hyperactivity of the macrophage in the reticuloendothelial system related to long-term treatment with Intralipid.

Coagulation

The activation of coagulation that occurs during parenteral nutrition is thought to be aggravated by coincidental infection; experimental work in healthy humans provides evidence that in patients receiving parenteral nutrition bacterial infection may facilitate the occurrence of venous thrombosis by synergistic stimulation of the coagulation system. Warfarin resistance has been found to develop during high dose propofol infusion, which contains 10% soybean oil as an emulsified preparation (81). Despite increasing the daily dose of warfarin to 30 mg, anticoagulation was not achieved until propofol was withdrawn. Lipid emulsions interfere pharmacodynamically with warfarin activity by enhancing the production of clotting factors, facilitating platelet aggregation, or supplying vitamin K; they may also facilitate warfarin binding to albumin. It follows that where patients with intestinal absorptive deficiencies who receive high-dose lipid emulsions require reliable anticoagulation heparin rather than warfarin should be used. If warfarin is given, the response should be monitored daily.

To test the hypothesis that infection facilitates activation of coagulation during parenteral nutrition, healthy subjects were injected intravenously with endotoxin (2 ng/kg) after they had received either standard parenteral nutrition for 1 week ($n = 7$) or normal enteral feeding ($n = 8$) (82). Compared with enteral feeding, parenteral nutrition was associated with selectively enhanced activation of the coagulation system (plasma concentrations of thrombin-antithrombin III complexes) during endotoxemia. Activation of the fibrinolytic system (plasminogen activator activity, tissue-type plasminogen activator, plasminogen activator inhibitor type 1) proceeded similarly in both groups. Bacterial infection, a common complication in patients receiving parenteral nutrition, may aggravate the occurrence of another common complication (venous thrombosis) by synergistic stimulation of the coagulation system. Lipids were not included in the parenteral nutrition in this study, and it is possible that the shift towards thrombogenesis may be even more pronounced in patients receiving parenteral nutrition containing lipids.

Gastrointestinal

The proportion of patients on parenteral nutrition in whom cholestasis is accompanied by necrotizing enterocolitis has increased markedly in the past ten years. Little is known about the nature of this association. In one study, directed primarily to cases of necrotizing enterocolitis and bowel necrosis or perforation who required surgical intervention, it was found that the incidence of accompanying cholestasis was much higher in those patients who had received parenteral nutrition; necrotizing enterocolitis may make the liver more susceptible to the hepatotoxic effects of parenteral nutrition (83). In an animal study using neonatal piglets (84) parenteral nutrition produced a significant reduction in weight and length of the gastrointestinal tract, particularly in the proximal small bowel. The proximal small-bowel weight was reduced by 67–72% compared with controls; similar, but less marked, differences were found in the distal small bowel. If these findings apply to man they mean that parenteral nutrition, while necessary for survival, is at least temporarily detrimental to intestinal growth and development and thus to enteral absorption of nutrients.

Normal enterally-administered nutrition prevents the development of gut barrier failure through several mechanisms which fail to come into play when nutrition is provided parenterally (85).

Liver

Both short-term parenteral nutrition and long-term parenteral nutrition can cause liver damage (86,87). Some adult patients develop cirrhosis (88), but there is a particularly high prevalence of hepatic complications of parenteral nutrition in children (89). The clinical spectrum includes cholestasis, cholelithiasis, hepatic fibrosis with progression to biliary cirrhosis, and the development of portal hypertension and liver failure in a significant number of children who are totally parenterally fed. The pathogenesis is multifactorial and is related to prematurity, low birth weight, and the duration of parenteral nutrition. The degree and severity of the liver disease is related to recurrent sepsis, including catheter sepsis, bacterial translocation, and cholangitis. Lack of enteral feeding leads to reduced gut hormone secretion, reduced bile flow, and biliary stasis, all of which may be important in the development of cholestasis. Even in the absence of frank gallstones, there is a high incidence of biliary tract sludge and microlithiasis in patients receiving parenteral nutrition, highlighting the necessity for preventive measures and for vigilance for acute pancreatitis (90). There is evidence in rats that hepatic steatosis may be an early marker of liver toxicity caused by parenteral nutrition, preceding biochemical disturbances (91). If so, reversal of early hepatic steatosis should spare the liver from further damage. There is an inverse relation between the incidence of parenteral nutrition-associated cholestasis and both gestational age and birth weight (92).

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Intestinal transplantation is combined with liver transplantation in 46% of cases, because of terminal liver failure (93). Of 78 patients who had received parenteral nutrition for more than 2 years ($n = 66$) and/or had short bowel syndrome and could not be weaned from parenteral nutrition ($n = 12$), 58 developed chronic cholestasis and 37 developed one or more severe liver complication (serum bilirubin concentration 60 μmol/l, factor V (proaccelerin) 50%, portal hypertension, encephalopathy, ascites, bleeding from the gastrointestinal tract, or histological findings consisting of extensive fibrosis and cirrhosis) after 6 (3–132) months and 17 (2–155) months respectively. Liver disease was responsible for deaths in 6.5% of the patients (22% of deaths).

Patients treated with interleukin-2 (IL-2) develop profound anorexia, malaise, loss of energy, mucositis, nausea, and vomiting, which can contribute to poor nutrition. In 21 patients who took a normal diet (controls) and 16 who received parenteral nutrition during IL-2 treatment, parenteral nutrition improved serum calcium and potassium concentrations, particularly during spontaneous diuresis after completion of IL-2 treatment (94). Unexpectedly, parenteral nutrition reduced the frequency and severity of cholestatic jaundice caused by IL-2, the pathophysiological basis of which is unknown. A brief period of parenteral nutrition during IL-2 treatment was well tolerated and it corrected the calorie and protein malnutrition. Parenteral nutrition also improved control of serum electrolytes, particularly calcium, potassium, and magnesium concentrations, although there was more marked hypophosphatemia during IL-2 treatment. The reason for this change is not clear.

Frequency

In a prospective prevalence study of liver disease in 90 patients with permanent intestinal failure receiving parenteral nutrition liver biopsy was performed in 57 (95). Chronic cholestasis developed in 58 patients after a median of 6 (range 3–132) months, and 37 developed complicated liver disease after a median of 17 (range 2–155) months. Chronic cholestasis was significantly associated with a risk of liver disease independent of parenteral nutrition, a bowel remnant shorter than 50 cm, and a lipid intake of 1 g/kg/day or more; liver disease related to parenteral nutrition was significantly associated with chronic cholestasis and a parenteral lipid intake of 1 g/kg/day or more. The authors concluded that the prevalence of liver disease increased with the duration of parenteral nutrition and was one of the main causes of death in patients with permanent intestinal failure. Parenteral intake of long-chain lipid emulsion should be restricted to less than 1 g/kg/day.

Mechanisms and susceptibility factors

Several mechanisms have been proposed to explain the cholestasis that occurs during parenteral nutrition, but there is little direct evidence to support any of them. Nutrient deficiencies that may be critical for hepatic uptake, biotransformation, and secretion of bile may be involved. Deficiency of taurine, which is important for bile acid conjugation, may cause cholestasis in premature infants. Certain amino acids may act as toxins. Reduced hormonal and neural stimulation of hepatic bile secretion may be a factor in patients who are not receiving nutrition enterally. Increased production by intestinal bacteria of lithocholate, which is a hepatotoxic bile acid, or retention of lithocholate in the liver, might account for the cholestasis. It is unclear whether it is the lipid or the carbohydrate component of parenteral nutrition solutions that determines the development of cholestasis during parenteral nutrition (96). In one study in neonates receiving parenteral nutrition the number of operations (amongst other factors) was significantly related to the development of cholestasis, possibly because of the stress of surgery itself or to the repeated administration of anesthetic agents or morphine (97). Some animal work suggests that gallbladder sludge and cholestasis during parenteral nutrition result from a reduction in both the bile salt-dependent and bile salt-independent fractions of canalicular bile flow (98). Another possible causal factor is an accumulation in the body of phytosterols derived from soya oil and/or soya lecithin used to make the intravenous lipid emulsion. There is a close association between phytosterolemia and cholestatic liver disease; animal work provides evidence that increasing the content of phytosterols in cell membranes can interfere with the function of important transport proteins involved in the secretion of bile (99,100). Phytosterol-induced changes in neutrophil function also lead to impaired phagocytosis of bacteria and an increased risk of sepsis; the latter is responsible for further damage to hepatocytes. Finally, in neonates who are at high risk of developing parenteral nutrition-associated cholestasis when receiving a prolonged course of parenteral nutrition lack of gastrointestinal hormone formation, including cholecystokinin, may be responsible. In a prospective controlled study, patients who received cholecystokinin prophylaxis had concentrations of direct bilirubin significantly lower than in the non-treated group (101).

Increased hepatic lipogenesis and reduced transport function are important in the fatty liver associated with parenteral nutrition. Providing ample quantities of essential amino acids mitigates but does not prevent this. This highlights the importance of total caloric intake. If insufficient amounts of amino acids are taken together with adequate non-protein calories, protein deficiency analogous to kwashiorkor can develop. Hepatic lipid accumulates, but lipoprotein synthesis is limited. Carnitine supplementation minimizes fatty infiltration of the liver in patients receiving dextrose-based parenteral nutrition, which supports the idea that carnitine deficiency plays a role in the development of this complication. However, carnitine can ordinarily be synthesized from the essential amino acids methionine and lysine, which are present in all commercially available parenteral nutrition formulae. Hepatic tissue requirements may be increased under conditions of stress, contributing to the development of a fatty liver by impairment of transport and oxidation of fatty acids by mitochondria.

Raised concentrations of lithocholate, portal bacteremia, and/or endotoxemia have all been suggested as contributing to hepatic triaditis in patients with inflammatory bowel disease receiving parenteral nutrition. Toxic amino acids or their metabolic products, excessive calorie administration and a disturbed carbohydrate/protein

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ratio may also influence the development of triaditis. Steatonecrosis is also known to occur when nutritional depletion develops. Inadequate administration of a critical nutrient or combination of nutrients might be involved in the pathogenicity of this lesion.

The high incidence of cholestatic liver disease associated with long-term parenteral nutrition in infants who have undergone major gut resection is linked to high plasma concentrations of phytosterols, compounds that resemble cholesterol but have an alkylated side-chain (99). The phytosterols that accumulate in patients receiving parenteral nutrition are derived from the soya oil and/or soya lecithin that is used to make the intravenous lipid emulsion. There is a strong association between phytosterolemia and cholestatic liver disease, which suggests a possible causative association. Experiments in neonatal piglets have suggested that phytosterols, given without any of the other components of parenteral nutrition, can reduce bile flow. The authors suggested that increasing the content of phytosterols in cell membranes may interfere with the function of important transport proteins involved in the secretion of bile. If a 20% lipid emulsion is infused at a rate of more than 50 ml/kg/week into a premature neonate who has had a major gut resection, and if this rate of infusion is continued for 2 months, the plasma phytosterol concentration is likely to rise to a value close to 25% of the total plasma sterols. The mechanism of the liver injury and effect on bile flow caused by parenteral nutrition is likely to be more complex than a simple sterol-induced change in membrane fluidity. Intravenous lipid emulsions that do not contain phytosterols may be safer.

The possible link between cholestasis and intravenous fat emulsions has been investigated in five patients (aged 2 months to 15 years) receiving parenteral nutrition, all of whom had signs of liver disease (102). In particular, the possible role of phytosterols, natural contaminants of fat emulsions, in causing liver disease was evaluated. Three developed steatosis with non-icteric hepatic dysfunction. High plant phytosterol concentrations in patients receiving parenteral nutrition were related to liver dysfunction and depended on the degree of cholestasis and the dosage of fat emulsion. However, this evidence does not prove that plant phytosterols contribute to the development of liver disease in susceptible individuals, and the authors concluded that in patients with steatosis associated with parenteral nutrition, lipid emulsions should not be withdrawn.

In a retrospective study of the incidence of cholestasis and liver failure in 42 patients with intestinal resection in the neonatal period who subsequently became dependent on parenteral nutrition support, the effect of various associated clinical factors on the incidence and severity of cholestasis was determined (103). Cholestasis developed in 28 while they were receiving parenteral nutrition. In 21 patients, the raised direct bilirubin concentration returned to normal while they continued to receive parenteral nutrition. Seven patients progressed to liver failure. Patients without cholestasis had been dependent on parenteral nutrition for longer than patients with cholestasis. It was clear from this study that cholestasis in neonates with intestinal resection is not simply a function of the duration of exposure to intravenous nutrition. The results instead suggested that infection early in life, when the developing liver may be uniquely sensitive to cholestatic injury and additionally stressed by intravenous nutrition, may play an important role.

The role of lipid emulsions in cholestasis associated with long-term parenteral nutrition has been investigated retrospectively in 10 children with a total of 23 episodes of cholestasis, associated with thrombocytopenia in 13 cases (104). Changes in lipid delivery, associated with increased daily amounts, preceded complications in more than half the cases, while temporary reduction in lipid administration led to normalization of bilirubin in 17 episodes. The authors concluded that lipid supply is one of the risk factors for cholestasis associated with parenteral nutrition. They recommended that when cholestasis occurs, lipid should be temporarily withdrawn, especially if there is associated thrombocytopenia.

In a randomized, controlled study of 244 infants one group ($n = 123$) received lower concentrations of manganese (0.0182 micromol/kg/day as Peditrace 1 ml/kg/day) while the second ($n = 121$) received 1 micromol/kg/day (as Ped-el 4 ml/kg/day) (105). All other components of the parenteral nutrition regimen were standardized. Monitoring comprised whole-blood manganese and serum direct bilirubin concentrations, the indicator for the development of cholestasis being a peak bilirubin concentration over 50 micromol/l. Those who were given extra manganese had higher peak whole blood manganese concentrations and higher peak serum direct bilirubin concentrations, but the differences were not significant. The two groups did not differ in terms of the occurrence of cholestasis (63/121 versus 57/123), but more infants in the high manganese group developed a more severe degree of hyperbilirubinemia. The authors concluded that the pathogenesis of cholestasis during parenteral nutrition is probably multifactorial, and that a high manganese intake is a significant contributory factor.

The link between cholestasis during home parenteral nutrition and inflammatory markers has been investigated in 17 patients on long-term home parenteral nutrition and 10 age-matched and sex-matched controls (106). Liver enzyme concentrations were used as markers of liver disease. Circulating inflammatory and immune markers were determined as measures of inflammatory activity. There were abnormal liver function tests in 14 of the patients. Alkaline phosphatase was positively correlated with markers of persistent inflammation and immune activation. Liver enzyme activities were also related to the amounts of total intravenous calories and calories originating from carbohydrates, but not lipids, in contrast to other recent data. The authors suggested that these results confirm that the number of infused calories contributes to liver toxicity in patients receiving home parenteral nutrition and strongly imply that sustained inflammation is probably a key factor in worsening the associated cholestasis.

Management

There is no effective treatment of liver damage during parenteral nutrition, except for using enteral nutrition as soon as possible. However, the benefits of ursodeoxycholic acid, a naturally occurring non-toxic hydrophilic bile acid,

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have been evaluated in a retrospective chart review of six infants who received oral ursodeoxycholic acid 15–30 mg/kg/day for at least 1 month (107). Ursodeoxycholic acid was safe and led to some early reduction in bilirubin concentrations, although there was no improvement in other markers of liver function. Clearly, the possible benefits have yet to be firmly established. Ursodeoxycholic acid may prevent or reduce the hepatocyte damage and cholestasis caused by high concentrations of hydrophobic bile acids by increasing the concentrations of hydrophilic non-hepatotoxic bile acids in the bile, by reducing histocompatibility antigens displayed by hepatocytes, or by a direct cytoprotective effect (108).

One cause of deteriorating liver function resulting from long-term parenteral nutrition is attributable to excessive or persistent calorie intake. Cyclic parenteral nutrition is a procedure of intermittent delivery (either during the day or at night over 10–12 hours). During the non-infusion period the central venous catheter is heparin-locked. In a prospective study the effect of early use of cyclic parenteral nutrition on deterioration of liver function has been studied in 65 patients with impaired liver function (109). The patients were divided into three groups based on bilirubin concentrations (over 85 μmol/l, 170 μmol/l, and 340 μmol/l). Each of the subgroups was divided into control (continuous parenteral nutrition) or test (cyclic parenteral nutrition). Patients on non-cyclic parenteral nutrition had significantly increased bilirubin and alkaline phosphatase, but the difference between the control and test groups was not significant in those patients with the most severe liver failure before the study. The authors were therefore unable to confirm the possible value of cyclic parenteral nutrition in reducing deterioration in liver function, although the results suggested that, at least in mild or moderate liver failure, there may be some benefit in reducing hepatocellular damage and progressive jaundice.

Urinary tract

There was a profound reduction in renal function associated with very long-term parenteral nutrition (continuing for periods longer than 10 years) in 29 of 33 patients studied: a reduction in estimated creatinine clearance of 0.6–15.4% per year (110). Tubular function, as determined by the tubular reabsorption of phosphate, was impaired in 52%. Although nephrotoxic drug use, bacteremia, fungemia, age, and infection rate accounted for part of the decline in renal function, most of it was unexplained.

In some infants receiving parenteral nutrition nephrocalcinosis occurs. Parenteral nutrition solutions contain the oxalate precursors ascorbate and glycine, and in one study of very low birth weight infants (111) administration of parenteral nutrition protein of about 0.5 g/kg/day was associated with an increased urinary oxalate/creatinine ratio; the effect was dose-dependent. Raised urinary oxalate concentrations may be a factor in the pathogenesis of nephrocalcinosis in these infants.

Musculoskeletal

There is massive evidence that parenteral nutrition therapy itself can affect bone adversely, especially bone density (5,112,113). Depletion of bone mineral is common in patients dependent on long-term parenteral nutrition (114). It is difficult to identify the role of a single nutrient in the development of bone disease during parenteral nutrition. The pathogenicity may be multifactorial and different in patients at different ages: in growing infants increased mineral requirement can be of particular importance, whereas other factors (such as aluminium toxicity) can occur in both adults and children. Since mineral status can be critical, particularly in small preterm infants, non-nutritional factors, including chronic use of potent loop diuretics and altered acid-base status, can affect urine mineral loss, cell metabolism, and consequently bone mineralization. Other factors that can play a role in the pathogenesis of bone disease associated with parenteral nutrition make reports confusing; they include lack of periodic enteral feeding, underlying intestinal disease including malabsorption and inflammation, neoplasm, and drug-induced alterations in calcium and bone metabolism.

In adults receiving long-term parenteral nutrition, despite its anabolic effects on other tissues, there is no improvement in bone density. Infants treated with parenteral nutrition from birth also develop low bone density for age, suggesting that parenteral nutrition treatment in some way contributes to the osteopenia (5). A 17% long-term increase in spinal bone mineral content has been shown in patients who have received parenteral nutrition solutions without vitamin D. However, this rise was nearly balanced by a 15% fall in hip bone mineral content (115). In a Danish study of bone mineral content in adults receiving home parenteral nutrition for short bowel syndrome, despite the fact that all were on free oral intake as a supplement to the parenteral nutrition, 47% had mandibular osteoporosis while 33% had osteoporosis in the forearm and radiographic changes of osteoporotic fractures in the vertebral column. Dental and periodontal tissues were normal (116).

In general, the question of whether parenteral nutrition adversely affects calcium regulation is unclear. Human studies are confounded by uncontrolled variables, including the degree to which food is taken orally; gut absorption; underlying disease; medications that adversely affect bones, including glucocorticoids; and aluminium contamination of parenteral nutrients. Calcium loss in the urine is often described, but the pattern is not consistent. Non-human primate work can provide some insight, but here too the findings are difficult to interpret. In one such study it was not possible to show a negative calcium balance with the use of parenteral nutrition in the absence of underlying disease (114). However, at higher rates of intravenous nutrition negative calcium balance has been demonstrated in such a model (117), while in other work evidence has been obtained that there is initial calciuria (and a negative calcium balance), which improves within 2 weeks (5). Some evidence seems to show that in premature infants receiving parenteral nutrition the mixture should contain higher calcium and phosphorus concentrations in prematurity than in childhood in order to avoid rickets and to promote improvement in existing rickets (118).

Cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor alfa influence bone resorption and have been invoked as a cause of type 1 osteoporosis.

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Parenteral nutrition in experimental rats enhances the catabolic effect of tumor necrosis factor alfa (119). The role of parenteral nutrition-induced cytokine release or activity, especially of IL-1, IL-6, and tumor necrosis factor alfa, in causing hypercalciuria and reduced mineralization in patients receiving parenteral nutrition needs to be clarified (119).

Metabolic bone disease in children receiving parenteral nutrition manifests primarily as osteopenia and, on occasion, fractures (5). The etiology is multifactorial: calcium and phosphate deficiency play a major role in the preterm infant but the part played by aluminium toxicity in this population is unknown. Lack of reference values of bone histomorphometry in the premature infant, as well as lack of reference data for biochemical markers of bone turnover in these patients, contributes to the uncertainty. Other factors that may play a role in the pathogenesis of bone disease associated with parenteral nutrition include lack of periodic enteral feeding; underlying intestinal disease, including malabsorption and inflammation; the presence of neoplasms; and drug-induced alterations in calcium and bone metabolism. However, the true incidence and prevalence of parenteral nutrition-associated bone abnormalities in pediatric patients are unknown.

Sexual function

Priapism has been reported as a complication of parenteral nutrition (160).

- A man developed a persistent painful penile erection 12 hours after the administration of a 12% fat emulsion (120). This was thought to have been caused by venous thrombosis in the corpora cavernosa, and the priapism was immediately relieved by bilateral corpora cavernosa spongiosa shunts, although the patient remained impotent.

Three different mechanisms have been postulated for this complication of parenteral nutrition:

1. an increase in blood coagulability
2. adverse effects on erythrocytes
3. fat embolism

In this case it was felt that the 20% fat emulsion had increased platelet activity, which was already increased before the start of therapy, and that this had predisposed to the development of priapism. The authors pointed out that a shunt procedure should be performed as soon as possible if erectile capacity is to be preserved.

Immunologic

Parenteral nutrition can adversely affect the immune system, thereby increasing the risk of infection and sepsis, for example by impairing neutrophil function, blocking the function of the reticuloendothelial system, and altering cell-mediated immunity. However, much of the evidence has been obtained in experiments using large bolus doses; the immunological effects of more conservative doses administered as continuous infusions over 12–24 hour/day are less clear. As the chylomicron-like lipid is metabolized, increased triglyceride concentrations may alter the function of macrophages by reducing chemotaxis and phagocytic capacity, although this has not been consistently demonstrated. Excessive parenteral administration of lipid may overload the mononuclear cells of the reticuloendothelial system, resulting in an inability to clear bacteria from the bloodstream. Studies of the alterations in cellular immunity associated with intravenous infusions of lipid emulsions have produced mixed results. Increases in B lymphocyte and T lymphocyte counts, increased lymphocyte mitogenesis, and increased production of interleukin-2 have been reported in patients receiving parenteral lipids. Others have reported no change or reductions in natural killer cell counts, helper-to-suppressor cell ratios, and antibody-dependent cellular cytotoxicity compared with patients not receiving intravenous lipids. No significant changes in serum immunoglobulin or complement concentrations have been observed secondary to intravenous lipid administration.

A growing area of interest is the use of intravenous medium-chain triglycerides, which have a different metabolic fate to long-chain triglycerides and may not have similar detrimental effects on the reticuloendothelial function, leukocyte activity, and eicosanoid production. Another focus of research is the differences observed between the various lipid components and fatty acids. The polyunsaturated fatty acid content of cell membranes, an important factor in the structural and functional integrity of the cell, can be altered by the provision of increased amounts of *n*-3 fatty acids in place of *n*-6 fatty acids. In a 1987 study, the effects of different parenteral nutrition solutions on in vitro lymphocyte reactivity and measured lymphocyte responsiveness were investigated in patients during treatment (121). In vitro lymphocyte responses were significantly depressed by a fat emulsion at concentrations similar to those achieved in clinical practice, but were unaffected by dextrose or amino acid solutions. These and similar finding by others indicate that careful consideration should be given before using fat emulsions in patients whose cell-mediated immunity is already impaired.

Immune function has been studied in ten surgical infants (aged under 6 months) requiring parenteral nutrition in two consecutive phases: (a) after 31 days with no enteral feeding (parenteral nutrition) and (b) after 4.7 days from the addition to parenteral nutrition of small volumes of enteral feeding. Host bactericidal activity against coagulase-negative staphylococci, measured by an in vitro whole blood model, was lowest in the patients who received parenteral nutrition, and it increased significantly after the addition of small enteral feeds, approaching the levels measured in controls. Production of tumor necrosis factor-alfa was low during parenteral nutrition and rose significantly after the addition of small enteral feeds in patients on parenteral nutrition. The increase in killing of coagulase-negative staphylococci after the addition of small enteral feeds correlated significantly with the duration of enteral feeding. The mechanism causing impaired immune function during parenteral nutrition is not known, and it is probably multifactorial. Neither is it understood how small additional enteral feeds affect host bactericidal activity (122).

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Allergic reactions

Severe allergic reactions can occur to parenterally administered lipid solutions. Such reactions may be mistaken for symptoms of the underlying disease or adverse effects of cytostatic chemotherapy (123). There is some evidence that the presence of soya bean proteins is responsible.

In 1989 the Perioperative Anaphylactic Reactions Study Group began an epidemiological survey of anaphylactoid reactions during anesthesia. Details recorded about patients who have suffered an anaphylactic reaction include demographic information and the results of allergy testing. In the most recent survey 1750 patients were reported from 27 diagnostic centers during January 1992 to June 1994 (124). Plasma substitutes accounted for 5.0% of the reactions observed. Intravenous infusions carry a comparatively small risk of anaphylaxis in the perioperative period. Other surveys come to a similar conclusion (125).

Allergic reactions have been reported infrequently in children receiving parenteral nutrition. The length of exposure before the reaction, the severity of the response, and the component responsible are variable.

- Anaphylaxis has been reported in a 4-year-old child when parenteral nutrition was resumed after a 5-day interruption in therapy after prior treatment 16 days after surgery for Wilms' tumor.

The authors considered the reaction to have been a type 1 IgE-mediated allergic response, although the causative agent was not identified. It was considered unlikely that individual amino acids had stimulated the allergic response, although the possibility of aggregated amino acids acting as a potential sensitizing agent could not be excluded. A component of the multivitamin mixture was considered the more likely explanation; the substances administered were vitamin E, vitamin K_1, the preservatives butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), and polysorbate emulsifiers (126).

Anaphylaxis linked to vitamin B complex in a parenteral nutrition regimen has been reported (127).

- An 8-year-old girl had a diaphragmatic hernia repaired at 7 days of age and had two episodes of adhesion ileus at 8 months. After laparotomy she was given all-in-one parenteral nutrition and after 21 days developed a reddish rash on her face and chest. The rash was pruritic and resolved quickly after intravenous diphenhydramine. She was readmitted 15 days after discharge because of malnutrition. Parenteral nutrition was restarted and she rapidly became irritable and developed an itchy rash over her face and trunk and swelling of her lips and eyelids. Parenteral nutrition was discontinued, diphenhydramine was given, and her symptoms abated rapidly. The possibility of hypersensitivity to a component of the parenteral nutrition was considered, and by a process of elimination the cause of the reaction was identified as the vitamin product MVI No 1. This was further confirmed by a skin test 1 year after the anaphylactic episode, but using a vitamin B complex solution.

Previous reports of anaphylactic reactions to parenteral nutrition have been identified as being caused by fat emulsion, vitamin K, iron dextran, and in particular multivitamins. This appears to be the first report of a reaction to vitamin B complex injection. However, neither the source of the vitamin B complex test product nor its formulation was identified by the authors, and there is doubt about the specific allergens responsible for the allergic response in this case.

Infection risk

Infection has long been recognized as a risk of parenteral nutrition and it has proved impossible to eliminate it (SEDA-22, 379). Once established, sepsis can increase the risk of fat overload syndrome. In an extensive study in Taiwan there was sepsis with positive blood cultures in 56 of 378 children receiving parenteral nutrition; the risk factors were longer duration of parenteral nutrition, age under 3 months, the use of central venous catheters, gastrointestinal disease as an indication for parenteral nutrition, low birth weight, and short gestational age in prematurity (128).

Various explanations have been offered for the occurrence of sepsis during parenteral nutrition, quite apart from the fact that the solution itself may be contaminated. Phytosterols can cause changes in neutrophil function. Cholestasis may play a role and then be further aggravated by the sepsis, creating a vicious circle. And fat emulsion may reduce hepatic phagocytosis. In vitro evidence using material from preterm infants suggests that administration of Intralipid may interfere with the binding of IL-2 to the specific receptors on their activated lymphocytes, with suppression of the immune response (129).

However, the clinical significance of these various mechanisms has been questioned. Some experimental in vitro work on human white cells suggests that the effect is markedly dose-dependent; it has been suggested that very few inhibitory effects on phagocytic cells will be found if lipid emulsion rates are kept at around 0.08 g/kg/hour (20). It is also notable that in one large series of premature very low birth weight infants in whom the use and duration of treatment with parenteral nutrition were associated with short gestational age and low birth weight, children treated with parenteral nutrition had a higher risk of sepsis usually caused by *Staphylococcus epidermidis* or *Staphylococcus aureus* (130). Thus, although the risk of sepsis in this age group appears to be significantly increased by parenteral nutrition, the causative organisms were fairly benign. It was concluded that the advantages of parenteral nutrition outweighed the risk of sepsis in this group of infants.

The incidences of bacteremia and fungemia during the first month after bone marrow transplantation for hematological malignancies have been studied in a prospective comparison in 512 patients. The patients were randomly assigned to receive 6–8% (low dose) or 25–30% (standard dose) of total energy as a 20% lipid emulsion. An adaptive randomization scheme, stratified for various treatments and transplant type, ensured that confounding treatment variables did not differ between the groups. Of 482 evaluable patients, 55 in the standard-dose group developed bacteremia or fungemia compared with 54 in the low-dose group. There was no association

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between the incidence of bacteremia or fungemia and intravenous lipid. Similar results were obtained when the results were analysed according to intention to treat, when bacterial or fungal infections at all sites were included, and when the observation period was extended to 60 days. These results suggest that moderate amounts of intravenous lipid rich in linoleic acid are not associated with an increased incidence of bacterial or fungal infections in patients undergoing bone marrow transplantation and receiving parenteral nutrition (131).

In infants of very low birth weight, fungal colonization and the association between fungal colonization and systemic fungal diseases was significantly linked to prolonged administration of antibiotics, parenteral nutrition, and fat emulsion (Intralipid) (132). Of 116 infants with birth weights under 1500 g, fungal colonization was detected in 25, of whom 17 developed colonization by 2 weeks of life. *Candida albicans* (61%) and *Candida parapsilosis* (29%) were the two most common organisms. The rectum (76%) was the most frequent site of colonization. Cultures were taken from the oropharynx, rectum, skin (groin and axilla), urine, and endotracheal aspirates in the first 24 hours after birth and weekly thereafter. There was an association between colonization and subsequent fungemia in one infant, representing 4% of colonized infants. It was also noted that although fungal colonization represents a risk factor for invasive candidiasis in infants of very low birth weight, candidiasis in this population is not invariably associated with prior colonization. Factors other than fungal colonization can also contribute to the occurrence of invasive candidiasis.

In a study of the independent risk factors for nosocomial coagulase-negative staphylococcal bacteremia among neonates of very low birth weight, after adjusting for the severity of the underlying illness, there was a significant association between coagulase-negative staphylococcal bacteremia and exposure during hospitalization to intravenous lipids (133). The study was conducted in 590 consecutively admitted neonates with birth weights under 1500 g, in two neonatal intensive care units, with a case-control study of 74 cases of coagulase-negative staphylococcal bacteremia and 74 pairs of matched controls. The independent risk factors for bacteremia were intravenous lipids (odds ratio 9.4), mechanical ventilation (OR = 2.0), and short peripheral venous catheters (OR = 2.6). It would appear that exposure to intravenous lipids at any time during hospitalization remains, and has possibly become an increasingly important risk factor for coagulase-negative staphylococcal bacteremia. In neonates of very low birth weight 85% of these bacteremias are now attributable to lipid therapy. In contrast, the relative importance of intravenous catheters as an independent risk factor has declined. Mechanical ventilation in the week before bacteremia has emerged as a risk factor for bacteremia.

There is evidence that lipid emulsion, which is cleared by the Kupffer cells of the reticuloendothelial system, can adversely affect reticuloendothelial function by reducing its ability to remove blood-borne bacteria. In a study of the blood clearance and organ localization of viable ^{35}S-radiolabelled *Escherichia coli* after slow intraperitoneal and more rapid intravenous administration of 20% fat emulsion in Sprague-Dawley rats, although there was rapid bacterial blood clearance in control and test animals, there was a significant change in the organ localization of bacteria as a result of the administration of lipid emulsion. There was a slight increase in lung localization of bacteria in rats that received intraperitoneal fat emulsion, and a significant increase in lung trapping of bacteria in rats that received intravenous fat emulsion. Liver localization of bacteria was reduced in all groups after fat emulsion. The data are understood to indicate that intravenous fat emulsion reduces hepatic phagocytosis and increases pulmonary localization of *E. coli*, and it is thought that this may produce greater susceptibility to infection. Patients with underlying sepsis are at greatest risk. The capacity of the lungs to kill sequestered bacteria is not known. Thus, increased bacterial lung localization may result in local inflammation and other pulmonary complications, and in the re-emergence into the blood of *E. coli*, with systemic sepsis as a result (134).

Second-Generation Effects

Teratogenicity

The developmental toxicity of a 20% lipid emulsion containing a 3:1 ratio of medium-chain to long-chain triglycerides has been examined in animals. Administration was once-daily intravenously to rats and rabbits during organogenesis. Maternal and embryo/fetal toxicity were also assessed. There were no adverse effects on fetal parameters for rats even in the presence of maternal toxicity. However, embryo and fetal toxicity (resorptions) and skeletal abnormalities were noted in rabbits (135). The adverse fetal effects were probably the result of dietary deprivation, maternal toxicity, or both rather than representing a direct teratogenic effect.

Susceptibility Factors

Age

Since lipoprotein lipase activity is reduced in premature babies and babies who are small for gestational age, and since bacterial and viral infections adversely affect lipoprotein lipase activity and can precipitate fat overload, it follows that fat emulsion should be administered with great caution, or even temporarily withheld, in small infants with proven or suspected sepsis (134).

Cholestatic liver disease is a frequent complication of prolonged parenteral nutrition, especially in preterm infants, with an occurrence rate that can approach 60% after 2 weeks of parenteral nutrition. In a retrospective survey of the incidence of liver dysfunction in 94 children (mean age 5 years) receiving parenteral nutrition over 2 years, liver disease was identified in over 50% of cases, with a nadir during the second week of parenteral nutrition (50). The most closely associated factors were length of parenteral nutrition and sepsis. In premature low birth weight infants hepatobiliary dysfunction with histological changes has been attributed to parenteral nutrition (48). Other risk factors include high baseline serum bile acids, reduced hepatic extraction, and an underdeveloped ileal transport system for conservation of bile acids. These lead to a reduced pool of bile acids and consequent exposure

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of the liver to toxic bile acids. The liver damage is aggravated by sepsis, ischemia, necrotizing enterocolitis, or surgery.

The pattern and prognosis of liver injury in children is distinct from that seen in adults, despite some overlap; liver disease develops in 40–60% of infants who require long-term parenteral nutrition for intestinal failure (89). The longer parenteral nutrition is used in neonates the greater is the risk of developing cholestasis, and the risk approaches 100% in neonates who receive parenteral nutrition for more than 8 weeks, especially if parenteral nutrition has been started very early in life (83,136). The particularly high risk in infants can be explained by factors that are specific to this age group; namely, immaturity of the enzyme systems responsible for hepatic conjugation, disturbance in the physiological patterns of enteral nutrition, and excessive secondary bile acid production and absorption from a contaminated small bowel. The bile of premature and newborn infants differs in its composition from that of adults, and this may account for the differences in solubility (137). Histologically one is likely to find cholestasis (intracellular or canalicular), periportal inflammation, fibrosis, and bile ductular proliferation (138). Sepsis can make cholestasis more severe. The clinical manifestations of cholestasis in infants include a progressively rising conjugated bilirubin concentration starting after 2 weeks of parenteral nutrition. Liver biopsy characteristically shows bile duct proliferation, bile plugs, and congestion. The clinical consequences include increased rates of sepsis, cirrhosis, liver failure, and death (139), though if parenteral nutrition can be withdrawn the condition is in principle reversible (138). Cholelithiasis is much less common in these children, but the administration of large amounts of amino acids and a high ratio of non-protein (kcal/ml) increased the risk of formation of gallstones and sludge. Conversely, these are prevented by the administration of appropriate amounts of fat (140). It has been recommended that ultrasound examination of the gallbladder be performed in children maintained on parenteral nutrition for longer than 30 days, and early elective cholecystectomy performed if parenteral nutrition-associated cholelithiasis develops (141).

A theory has been proposed regarding a possible mechanism by which parenteral lipid solutions injure preterm infants; namely, by free radical-induced lipid peroxidation in the lipid solution (142,143). How this happens is not explained. The result can be pulmonary damage and chronic lung disease. Premature infants are thought to be at particularly high risk. However, others (144,145) have suggested that Cooke's interpretation (142) was not based on solid clinical evidence, and that the data that he derived from his observations should be tested in controlled studies before parenteral nutrition is prescribed for infants of very low birth weights.

Other features of the patient

Thrombosis can occur, especially (for unclear reasons) in patients suffering from AIDS. The incidence of symptomatic central venous thrombosis in patients with AIDS receiving home parenteral nutrition has been estimated at 0.009 per patient-month (80). However, in one retrospective study of malnourished patients with AIDS, none of whom had had a previous venous thrombosis, and who were treated with parenteral nutrition for a long period, the rate of central venous thrombosis in patients taking warfarin was 0.016 thromboses per patient-month, both in those taking warfarin and in those not so treated; in this series no hypercoagulability was found.

In a prospective study of the effects of parenteral medium-chain and long-chain triglycerides on lymphocyte subpopulations and function in severely malnourished patients with acquired immunodeficiency syndrome (AIDS), long-chain triglycerides were compared with a balanced emulsion of long-chain and medium-chain triglycerides (146). Administration was over 6 days. With 2 g/kg/day of lipids, long-chain triglycerides caused significant abnormalities in lymphocyte function, expressed as a reduction in phytohemagglutinin A response. Such abnormalities were not observed with long-chain plus medium-chain triglycerides, which reduced IgM and increased the C3 fraction.

Drug Administration

Drug formulations

Precipitates can develop in parenteral nutrition admixtures because of a number of factors such as the concentration, pH, and phosphate content of the amino acid solutions, the calcium and phosphorus additives, the order of mixing, or the mixing process. The consequences can be serious. In one cohort study of hospitalized patients who received peripheral parenteral nutrition, a subgroup developed unexplained chest pain, dyspnea, cardiopulmonary arrest, or new interstitial infiltrates on chest radiograph. A change in the amino acid source of a parenteral nutrition mixture was associated with respiratory adverse events that ranged from interstitial infiltrates to sudden death. The events apparently resulted from infusion of calcium phosphate precipitate in an opaque admixture, and the deposition of the crystals in the pulmonary microvasculature (147).

The United States Food and Drug Administration issued a safety alert in 1994 regarding the potentially life-threatening formation of precipitates in parenteral nutrition admixtures (148). They had received reports of two deaths and at least two cases of respiratory distress during intravenous infusion of a three-in-one parenteral nutrition mixture (amino acids, carbohydrates, lipids). The mixture contained 10% FreAmine III (amino acids + magnesium acetate + phosphoric acid + potassium chloride + sodium acetate + sodium chloride), dextrose, calcium gluconate, potassium phosphate, other minerals, and a lipid emulsion. The solution may have contained a precipitate of calcium phosphate. Autopsies revealed diffuse microvascular pulmonary emboli containing calcium phosphate.

The FDA has recommended the following steps to decrease the hazard of injury through precipitation (149):

1. The amounts of phosphorus and calcium added to the admixture are critical. The solubility of the added calcium should be calculated from the volume at the time that the calcium is added. It should not be based on the

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final volume. The line should be flushed between the addition of any potentially incompatible components.
2. A lipid emulsion in a three-in-one admixture obscures the presence of a precipitate. Therefore, if a lipid emulsion is needed, either use a two-in-one admixture with the lipid infused separately, or add the calcium before the lipid emulsion according to the recommendations in 1 above. If the amount of calcium or phosphate which must be added is likely to cause a precipitate, some or all of the calcium should be administered separately. Such separate infusions must be properly diluted and slowly infused to avoid serious adverse events related to the calcium.
3. During the mixing process, parenteral nutrition admixtures should be periodically agitated to check for precipitates. This check should be conducted both before and during the infusion. Patients and caregivers should be trained to inspect for signs of precipitation. They should also be trained to stop the infusion and seek medical assistance if precipitates are noted.
4. A filter should be used when infusing either central or peripheral parenteral nutrition admixtures. Data are not available to determine which size filter is most effective in trapping precipitates.
5. Parenteral nutrition mixtures should be administered within the following time frames: if stored at room temperature, the infusion should be started within 24 hours after mixing; if stored at refrigerated temperatures, the infusion should be started within 24 hours of rewarming. Because warming parenteral nutrition mixtures may contribute to the formation of precipitates, once administration begins, care should be taken to avoid excessive warming of the mixture.

Mirtallo has added to the FDA guidelines, stressing the need to ensure that an appropriate dose of calcium is prescribed, to follow appropriate procedures when mixing parenteral nutrition solutions and to use automatic mixing devices strictly in accordance with the manufacturer's instructions (150). He has stressed the fact that more information is needed to substantiate the usefulness of filters in preventing adverse effects caused by the infusion of particulate matter present in parenteral nutrition admixtures.

It has been pointed out that calcium phosphate precipitates more readily in warm than in cold solutions. Precipitation can occur in solution at room temperature, even if an identical cold solution is clear. A precipitate can also form when a clear solution, stored refrigerated or at room-temperature, is warmed to body temperature. Thus, visual inspection and even in-line filters, if they are distal to the side of precipitation, may not prevent infusion of the precipitate (151).

Drug contamination

Since the introduction of parenteral nutrition in hospital care the potential microbiological risks associated with the manufacture, preparation, and administration of these products have abated but not disappeared (133,152). Fatal infectious complications still occur. The parenteral nutrition mixture is a good growth medium for microorganisms, more conducive to microbial growth than glucose or amino acid solutions. Storage of mixtures allows time for microbial multiplication, often to counts of millions per ml. Commonly isolated organisms from parenteral nutrition solutions are coagulase-negative staphylococci, *S. aureus*, *Candida* species, *Serratia* species, and *Enterobacter* species. Infection with *Malassezia furfur* is a rare but serious complication strongly associated with parenteral nutrition in young children, now documented in some 50 reports (153). *Candida* infection is a particular problem in patients receiving parenteral nutrition. Even organisms such as *S. epidermidis* and *Bacillus* species, relatively non-pathogenic in normal circumstances, can multiply in the infusion to such large numbers as to have disastrous effects. Many of these commensal organisms tend to be insensitive to antibiotics. In an open-system aseptic process of preparation the estimated risk of contamination, according to the World Health Organization, is one in 3000. Microbiological and environmental quality control assurance needs to be continuous.

The average rate of episodes of catheter-related bacteremia in patients receiving parenteral nutrition is 3–5%. Higher rates are reported for long-term patients. Patients with a nosocomial infection have an 11-fold higher risk of acquiring an additional nosocomial infection compared with those with no infection. Prompt removal of the catheter and targeted antimicrobial treatment remains the standard approach for febrile episodes in these circumstances. However, many catheter-related infections caused by coagulase-negative staphylococci can successfully be treated with the catheter still in place (154).

Drug administration route

Local extravasation of parenteral nutrition fluid can occur. Two patients developed an intense inflammatory reaction that was successfully controlled with repeated local administration of the hyaluronidase analogue chondroitin sulfatase (155). Although the exact mechanism of tissue toxicity by extravasated parenteral nutrition is not understood, it seems likely to be related to osmolarity, pH, and ions. The area affected may become blistered, with darkening of the skin, or ischemic, depending on whether the skin thickness is partially or fully damaged. In children, extravasation can have devastating consequences, such as deep necrosis, amputation, severe sequelae in the affected limb, or other complications, such as subdural collection of fat emulsion, liporrhachis, and acute abdomen after intra-abdominal extravasation. Children are at special risk, because very young infants and children are unable to communicate the pain that results from the pressure of extravasated fluid. Other individuals in this situation are comatose patients, those under general anesthesia, and patients who are being resuscitated. Other risk factors that predispose to extravasation are related to venepuncture technique, state of the patient, and medication delivery. Special care should be taken when high-osmolarity (1000–1700 mosmol/l) peripheral parenteral nutrition is administered, as fluids of this osmolarity are likely to cause severe tissue damage if extravasated. Fluids should not generally exceed 600–900 mosmol/l in order to minimize the risk of this complication. The position of the catheter needs to be regularly checked. Fat emulsions are harmless to the tissues if extravasated.

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After a preterm infant developed parenteral nutrition ascites after infusion through a low umbilical vein catheter, a follow-up study of eight patients, all of whom developed hypotension and ascites, showed that each had an umbilical vein catheter overlying the liver on plain X-ray (156). The catheters had been in place for a mean of 8.9 days before extravasation. Ultrasound in four patients showed hepatic parenchymal damage around the umbilical vein catheter tip. Parenteral nutrition given through abnormally placed umbilical vein catheters is not without risk, and correct placing of the catheter is paramount.

Drug–Drug Interactions

Glucocorticoids

Infants of very low birth weight have reduced tolerance to intravenous fat emulsions, with consequent hyperlipidemia. Since glucocorticoids are often used to prevent or treat chronic lung disease, and since they can cause hyperlipidemia, this potential drug interaction has been investigated in a randomized double-blind trial (157). The results supported the hypothesis that dexamethasone increases triglyceride serum concentrations, and the authors recommended that low birth weight infants who are receiving both dexamethasone and fat emulsion should be monitored carefully for signs of impairment of lipid tolerance.

Propofol

Drugs with a high lipid content, when given concurrently with lipid-containing parenteral nutrition, can aggravate the problems of lipid overload (29). The anesthetic, propofol, which is used for continuous sedation in a dose of 1–3 mg/kg/hour (an equivalent of 300–500 ml of a 10% fat emulsion), may aggravate the symptoms and pathological effects of fat overload (29).

Warfarin

Warfarin resistance has been described in a patient with short bowel syndrome receiving intravenous lipid (158). Up to 20 mg of warfarin was given daily without increase in the International Normalized Ratio (INR). Although intravenous lipid has been reported anecdotally to account for warfarin resistance, this report suggests that the more likely explanation was the reduced surface area for drug absorption secondary to total surgical removal of the patient's duodenum and gastrojejunostomy. However, several other reports have refuted a correlation between warfarin resistance and short bowel syndrome. Conversely, warfarin resistance has occurred secondary to intravenous lipid administration in a patient with only 12 cm of small bowel; the patient had been given oral warfarin while he received daily fat emulsion (Intralipid) to prevent fatty acid deficiency (159).

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Paroxetine

See also Selective serotonin re-uptake inhibitors (SSRIs)

General Information

Paroxetine is a phenylpiperidine derivative. Its half-life is about 17–22 hours and about 95% of it is bound to plasma proteins. Its metabolites have no more than 1/50 of the potency of the parent compound in inhibiting serotonin re-uptake. The metabolism of paroxetine is accomplished in part by CYP2D6, saturation of which at therapeutic doses appears to account for the non-linearity of paroxetine kinetics at higher doses and increasing durations of treatment. The adverse effects of paroxetine are those of the SSRIs in general. Commonly observed adverse events

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in placebo-controlled clinical trials were weakness, sweating, nausea, reduced appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders. Paroxetine seems to have a higher incidence of withdrawal symptoms than other SSRIs.

Organs and Systems

Cardiovascular

Electrocardiographic changes, with a prolonged QT_c interval and bradycardia, have been reported with paroxetine (1).

Nervous system

Serotonin syndrome

The serotonin syndrome is a recognized complication of SSRI treatment. Usually it occurs as part of a drug interaction, when the serotonergic effects of SSRIs are augmented by medications that also have serotonin-potentiating properties (SEDA-22, 14) (SEDA-25, 16). Occasionally, however, the serotonin syndrome can occur after SSRI monotherapy.

- A 23-year-old Japanese woman with major depression took a single dose of paroxetine (20 mg) and 1 hour later had agitation, myoclonus, mild hyperthermia (37.5 °C), sweating, and diarrhea, symptoms that meet the criteria for the serotonin syndrome; she recovered with supportive treatment over 3 days (2).

Blood concentrations of paroxetine were not obtained, but the authors reported that the patient was homozygous for the 10* form of the CYP2D6 allele, which is associated with low CYP2D6 activity in vivo. While this is an interesting observation, it is unlikely by itself to explain the patient's sensitivity to paroxetine, because this genotype is not uncommon in the Japanese population, and if a lot of Japanese have this genotype, the serotonin syndrome with SSRI monotherapy would be quite common, given the widespread prescription of SSRIs. However, it reinforces clinical advice that in patients new to SSRI treatment it is advisable to start therapy with half the standard dose.

Dystonias

Acute dystonia has been described during the first days of paroxetine treatment (SEDA-17, 19).

Paroxetine-induced akathisia has been described in an 81-year-old man with bipolar depression. The akathisia began one week after paroxetine treatment (20 mg/day) and remitted within 6 days of withdrawal (3).

The authors pointed out that it is important to recognize SSRI-induced akathisia, because increasing agitation and restlessness early in treatment can be mistaken for worsening depression. In addition, case reports have suggested that akathisia can be associated with suicidal impulses.

Sensory systems

Tricyclic antidepressants can precipitate acute glaucoma through their anticholinergic effects. There are also reports that paroxetine can cause acute glaucoma, presumably by pupillary dilatation.

- An 84-year-old woman developed acute closed-angle glaucoma after taking paroxetine for 6 days (SEDA-21, 13).
- A 70-year-old woman taking paroxetine developed acute closed-angle glaucoma (4).
- A 91-year-old developed bilateral acute closed-angle glaucoma after taking paroxetine (5).

Three patients taking paroxetine for interferon-alpha-induced depression developed retinal hemorrhages, including one with irreversible loss of vision (6).

Psychological, psychiatric

In three children (two aged 9 years and one aged 10 years) who took paroxetine 10–20 mg/day for the treatment of childhood obsessive-compulsive disorder, symptoms of mania, including overactivity, pressure of speech, irritability, and antisocial behavior, occurred within 3 weeks of starting paroxetine and remitted after paroxetine withdrawal or dosage reduction (7). Symptoms of mania are rare in childhood, suggesting that the elevated mood in these cases was a direct effect of the paroxetine.

Psychomotor retardation with semistupor has been reported in one patient taking paroxetine; however, she was also taking antipsychotic drugs, which may have contributed (SEDA-18, 20).

Endocrine

Serotonin pathways are involved in the regulation of prolactin secretion. Galactorrhea has been associated with paroxetine (8).

Serotonin pathways are involved in the regulation of prolactin secretion. Amenorrhea, galactorrhea, and hyperprolactinemia have been reported in a patient taking SSRIs.

- A 32-year-old woman taking paroxetine 40 mg/day had a raised prolactin concentration (46 ng/ml) and galactorrhea, both of which resolved a few days after paroxetine withdrawal (9).

Hematologic

Clozapine and SSRIs are often used together, because depressive syndromes are common in patients with schizophrenia. Clozapine carries a relatively high risk of agranulocytosis, but this adverse effect is very rarely seen with SSRIs, although a case of possible fluoxetine-induced neutropenia has been described (SEDA-22, 15). Two cases in which the addition of paroxetine to clozapine was associated with neutropenia have been reported (10). The patients had been taking stable doses of clozapine for 6–12 months and had previously tolerated other SSRIs without adverse hematological consequences. In both cases the white cell count recovered when clozapine was withdrawn, although paroxetine was continued.

Fluoxetine has infrequently been associated with abnormal bleeding, including ecchymoses, melena, and hematuria. Spontaneous ecchymoses have been reported in a woman taking paroxetine (11).

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- A 47-year-old woman who had had bilateral mastectomies for breast cancer became depressed and was given paroxetine 20 mg/day. After 15 days she developed widespread multiple ecchymoses over the arms, legs, and abdomen. Her platelet count, prothrombin time, partial thromboplastin time, and bleeding time were normal. Paroxetine was withdrawn, and 5 days later, the bruising had markedly abated and no new lesions were identified. She was subsequently treated with a tricyclic antidepressant without recurrence of the ecchymoses.

The authors noted two earlier reports of ecchymoses with paroxetine, with normal laboratory values. They speculated that an indirect effect on platelet function through inhibition of platelet 5-HT uptake may be involved.

Paroxetine caused neutropenia in a patient whose white cell count fell to 2.9×10^9/l (neutrophils 1.37×10^9/l) (12). The white cell count gradually recovered over 6 weeks after paroxetine withdrawal.

Liver

Hepatotoxicity associated with paroxetine has been documented in two case reports (SEDA-21, 12). Severe hepatitis has been reported in two young women who took Atrium (febarbamate + difebarbamate + phenobarbital) and paroxetine (13). Liver biopsy showed lesions compatible with drug-related injury. Both recovered completely. The authors suggested that simultaneous treatment with Atrium and paroxetine increased each drug's hepatotoxicity.

Sexual function

Delayed ejaculation associated with paroxetine has been reported (SEDA-18, 21).

Immunologic

A skin reaction consistent with a vasculitis has been reported.

- A 20-year-old woman taking paroxetine 10 mg/day for obsessive-compulsive disorder developed multiple purple lesions on the fingers of both hands after 15 weeks (14). The lesions disappeared after 1 week but returned in 2 days after rechallenge with paroxetine.

Long-Term Effects

Drug withdrawal

Sudden withdrawal of paroxetine has been associated with nausea, dizziness, tremor, insomnia, irritation, and agitation (SEDA-17, 20). In three cases, a withdrawal reaction occurred with paroxetine, despite tapering of the dose for 7–14 days before discontinuation; the symptoms were the same as in earlier reports, but also included in one case myalgia, and in another rhinorrhea and visual phenomena similar to those associated with migraine (15). The authors suggested that cholinergic mechanisms and functional changes in 5-HT may play a role in the mediation of withdrawal symptoms.

Drug Administration

Drug overdose

There were gastrointestinal symptoms and CNS disturbances in patients who took overdoses of paroxetine, the largest amount being 850 mg (16).

Drug–Drug Interactions

Beta-blockers

Paroxetine can cause clinically important increases in plasma concentrations of metoprolol (17).

Clozapine

In a prospective study, paroxetine (20 mg/day), a potent inhibitor of CYP2D6, did not increase clozapine concentrations ($n = 14$), and the authors therefore suggested that CYP2D6 is not an important pathway of metabolism of clozapine (18). However, other studies (SEDA-21, 22) have shown that paroxetine can increase clozapine concentrations, suggesting that this combination should be used with caution.

Linezolid

SSRIs can also cause pharmacodynamic drug interactions for some time after withdrawal, through residual serotonin reuptake blocking activity.

- A 56-year-old woman with a postoperative wound infection developed the serotonin syndrome when she was given the antibiotic linezolid intravenously (19). The dose of paroxetine had been tapered and it had been withdrawn 5 days before.

Linezolid inhibits monoamine oxidase activity and has been reported to cause serotonin toxicity in combination with paroxetine. While some patients have apparently taken the combination of linezolid and an SSRI safely, this report suggests that patients taking combined treatment should be monitored for serotonin toxicity.

Methadone

Methadone-maintenance treatment is now established by controlled trials as effective in managing patients with opioid dependence. SSRIs are often co-prescribed for such patients, and there have been reports that SSRIs can increase methadone concentrations, presumably by inhibition of CYP2D6 (SEDA-25, 15). The effect of adding paroxetine (20 mg/day) to the treatment regimen has been studied in 10 opiate-dependent patients taking methadone maintenance (20). Methadone concentrations increased on an average by about one-third, although there was much individual variation. There were no obvious clinical consequences, presumably because the patients were fairly tolerant to the effects of methadone. However, the authors cautioned that sudden withdrawal of an SSRI in methadone users has the potential to trigger opioid-withdrawal symptoms.

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Tricyclic antidepressants

Paroxetine can cause clinically important increases in plasma concentrations of tricyclic antidepressants (21).

Triptans

Treatment of 12 healthy volunteers with paroxetine (20 mg/day for 14 days) did not alter the pharmacokinetics or pharmacodynamic effects of an acute dose of rizatriptan (10 mg orally) (22). These data are reassuring, but (as with sumatriptan) it is possible that sporadic cases of 5-HT neurotoxicity could still occur when rizatriptan is combined with an SSRI.

Risperidone

The addition of paroxetine 20 mg/day to risperidone 4–8 mg/day in 10 patients with schizophrenia produced a 45% increase in plasma concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone (23). One of the patients developed signs of drug-induced Parkinson's disease following the addition of paroxetine.

The serotonin syndrome occurred in a patient taking paroxetine plus an atypical antipsychotic drug, risperidone (24).

- A 53-year-old man took paroxetine 40 mg/day and risperidone 6 mg/day, having previously taken lower doses of both. Within 2 hours he developed ataxia, shivering, and tremor. He had profound sweating but was apyrexial, and was confused, with involuntary jerking movements of his limbs. He recovered without specific treatment over the next 2 days.

This was the first report of the serotonin syndrome in a patient taking an SSRI and an atypical antipsychotic drug. The reaction was unexpected because risperidone, in addition to being a potent dopamine receptor antagonist, is also a 5-HT_2-receptor antagonist. Subsequent animal studies suggested that 5-HT_2-receptor antagonists increase the firing of serotonergic neurons, perhaps through a postsynaptic feedback loop. This could account for potentiation of the effects of SSRIs by 5-HT_2-receptor antagonists, such as risperidone.

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Passifloraceae

See also Herbal medicines

General Information

The family of Passifloraceae contains the single genus *Passiflora*.

Passiflora incarnata

Passiflora incarnata (apricot vine, grenadille, passion flower, passion vine) is widely touted as a herbal sedative and anxiolytic (1). It contains harman alkaloids.

Adverse effects

Passion flower has reportedly caused prolongation of the QT interval (2).

- A 34-year-old woman developed nausea, vomiting, drowsiness, a prolonged QT interval, and episodes of non-sustained ventricular tachycardia after self-medication with passion flower for 1 day. She made a full recovery after withdrawal of the passion flower.

The authors suggested that the adverse event had been caused by harman alkaloids from *P. incarnata*.

Five patients developed altered consciousness after taking the herbal product Relaxir for insomnia and restlessness, produced mainly from the fruit of the passion flower (3).

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Pazufloxacin

See also Fluoroquinolones

General Information

Pazufloxacin is an injectable quinolone antibiotic with bactericidal effect against cephalosporin-resistant, carbapenem-resistant, and aminoglycoside-resistant strains of bacteria.

Organs and Systems

Skin

In in vivo studies in animal models of phototoxicity, pazufloxacin was less potent than nalidixic acid, ofloxacin, ciprofloxacin, or sparfloxacin, and there was no photoallergenicity (1).

Drug–Drug Interactions

Theophylline

Co-administration of pazufloxacin and theophylline has been studied in rats (2). Pazufloxacin reduced the clearance of theophylline by about 25%. In seven healthy volunteers taking modified-release theophylline, intravenous pazufloxacin mesilate increased serum theophylline concentrations; analysis of the urinary excretion of theophylline and its metabolites suggested that CYP1A2 had been inhibited (2). Theophylline concentrations need to be monitored if pazufloxacin is co-administered.

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Pedaliaceae

See also Herbal medicines

General Information

The genera in the family of Pedaliaceae (Table 1) include sesame.

Harpagophytum species

Harpagophytum procumbens (devil's claw, grapple plant, wood spider) contains the iridoids harpagoside and procumbide. It is used to treat pain in the joints and lower back, although the quality of trials demonstrating efficacy is poor and there is variability from formulation to formulation (1).

Adverse effects

It is sometimes stated that *H. procumbens* should be avoided during pregnancy because of its supposed abortifacient effect, but the oxytoxic properties of the plant remain to be verified. There may be an interaction with warfarin (2).

Table 1 The genera of Pedaliaceae

Ceratotheca (ceratotheca)
Craniolaria (craniolaria)
Harpagophytum (devil's claw)
Ibicella (yellow unicorn plant)
Martynia (martynia)
Proboscidea (unicorn plant)
Sesamum (sesame)

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Pefloxacin

See also Fluoroquinolones

General Information

Pefloxacin is a fluoroquinolone antibiotic that inhibits *Plasmodium falciparum* in vitro. It is effective against *Plasmodium yoelii* infections in mice.

Observational studies

In humans pefloxacin was tested in a dosage of 400 mg every 12 hours for 3 days against chloroquine-resistant *P. falciparum* infections in Madagascar, and proved successful in 9 out of 22 cases; seven further cases responded at first but recrudescence followed. The investigators suggested that pefloxacin should be used as a complementary drug rather than as a primary antimalarial drug.

There was a significant reduction in proteinuria in ten children with idiopathic nephrotic syndrome after pefloxacin therapy (mean dose 2–4.6 mg/kg/day for 4–8 weeks) (1). All had received a course of cyclophosphamide at least 6 months before. One patient discontinued pefloxacin within 2 weeks because of nausea and vomiting, one complained of arthralgia, and one developed nail discoloration.

The efficacy and safety of pefloxacin, 15–20 mg/kg bd for 14–28 days in combination with ceftazidime and amikacin, have been investigated in 21 children (aged 7–16 years) with mucoviscidosis or aplastic anemia (2). Combined therapy had good clinical efficacy. Arthropathy developed frequently and children at risk were over 10 years old and had a history of allergies.

General adverse effects

The adverse effects of pefloxacin are those of the fluoroquinolones, which are generally well tolerated. Gastrointestinal complaints occur in some 3–6%, and have included (in declining order of frequency) nausea, abdominal discomfort, vomiting, and diarrhea. Colitis due to *Clostridium difficile* infection has been reported infrequently. Nervous system effects have been less common, but headache, dizziness, agitation, sleep disturbances, and more rarely seizures, delirium, and hallucinations have been reported. Allergic reactions are infrequent. Photosensitivity reactions have been reported. The quinolones cause cartilage erosion in weight-bearing joints in young growing animals, and the long-term use of pefloxacin in growing children, such as would be required for prophylaxis, should be avoided. In bacteria that have developed resistance to fluoroquinolones, cross-resistance with chemically unrelated antibiotics, such as tetracycline and chloramphenicol, is possible.

Organs and Systems

Musculoskeletal

In vitro, pefloxacin was more toxic to tendons than ofloxacin, ciprofloxacin, or levofloxacin (3). In rodents, pefloxacin (400 mg/kg for several days) caused oxidative damage to the type I collagen in the Achilles tendon; these alterations were identical to those observed in experimental tendinous ischemia and a reperfusion model (4). Oxidative damage was prevented by the co-administration of *N*-acetylcysteine (150 mg/kg). Several cases of rupture of the Achilles tendon have been reported during or shortly after the use of fluoroquinolones, including five case in which pefloxacin was used (5).

The efficacy and safety of pefloxacin, 15–20 mg/kg bd for 14–28 days in combination with ceftazidime and amikacin, have been investigated in 21 children (aged 7–16 years) with mucoviscidosis or aplastic anemia (2). Combined therapy had good clinical efficacy. Arthropathy developed frequently and children at risk were over 10 years old and had a history of allergies.

In patients with mucoviscidosis treated with pefloxacin the most common adverse event was arthropathy, and the symptoms disappeared 3 days to 3 months after drug withdrawal (6).

Immunologic

Pefloxacin in suprabactericidal concentrations (2.0 mg/ml and 0.4 mg/ml) markedly suppressed T lymphocyte proliferation in blast transformation; 0.08 mg/ml did not (7). Pefloxacin in a maximal effective dose (200 mg/kg) suppressed delayed hypersensitivity skin reactions in mice.

Susceptibility Factors

Renal disease

In moderate impairment of renal function, prolongation of the dosage interval of pefloxacin should be considered; pefloxacin should be avoided in severe renal impairment (8).

Drug–Drug Interactions

Theophylline

Pefloxacin inhibits theophylline metabolism (9).

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Pemirolast

General Information

Pemirolast is a mast-cell stabilizer, like cromoglicate, used in eye-drops for the treatment of allergic disorders (1). It has also been used to prevent coronary artery restenosis after the insertion of a stent (2).

In a 7-day, double-blind, single-dose, crossover, parallel-group study, 45 adults with asymptomatic eyes were randomized to bilateral pemirolast, cromoglicate, or ketorolac at each of three visits (1). Overall discomfort was significantly less with pemirolast than with cromoglicate or ketorolac. Burning/stinging and tearing were also significantly less with pemirolast than with cromoglicate.

In a 1-day, randomized, double-blind, single-dose study in which 48 subjects received pemirolast in one eye and nedocromil in the other, overall discomfort was significantly less with pemirolast than with nedocromil (1).

The most common adverse effects of pemirolast are headache, rhinitis, and mild cold- or flu-like symptoms. After ocular administration for 2 weeks, plasma concentrations were detectable, but with no significant accumulation (SEDA-24, 534).

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Pemoline

General Information

Pemoline has similar actions to dexamfetamine and is used in the management of hyperactivity disorders in children (1).

Organs and Systems

Liver

During the past two decades there have been many reports of liver failure resulting in death or transplantation in patients being treated for ADHD with pemoline. However, a descriptive meta-analysis of the existing scientific literature and drug reporting databases showed that current assumptions of the risk of acute hepatic failure posed by pemoline alone are overestimates.

- A 7-year-old boy with Duchenne muscular dystrophy and attention deficit hyperactivity disorder (ADHD) developed acute hepatic failure, with features of autoimmune hepatitis (2). The only medications he had taken were pemoline (56 mg/day) and cyproheptadine (2 mg/day). Pemoline was withdrawn after 8 months as the presumed cause of his raised transaminases. Two weeks later he developed an altered mental state, jaundice, and encephalopathy. The histological features of the liver and his autoimmune antibody panel were consistent with autoimmune hepatitis. He was treated with corticosteroids and azathioprine and recovered.
- A 9-year-old boy with ADHD taking pemoline developed signs and symptoms of liver failure requiring liver transplantation (3).

The evidence linking pemoline to life-threatening liver failure prompted the Food and Drugs Administration to require the manufacturer to add a black box warning to the package insert, whereas in the UK the Committee on Safety of Medicines withdrew marketing approval for pemoline, citing safety and a lack of adequate evidence of efficacy as the reason (4).

Drug Administration

Drug overdose

There has been a report of pemoline-induced acute movement disorders after presumed overdose (5).

- Two 3-year-old identical male twins were found playing with an empty bottle of pemoline that had originally contained 59 tablets. They had a history of attention deficit disorder previously unsuccessfully treated with methylphenidate, but no history or family history of movement disorders. Choreoathetoid movements began 45 minutes to 1 hour after ingestion. The children received gastrointestinal decontamination and high doses of intravenous benzodiazepines but continued to have choreoathetosis for about 24 hours and were discharged at 48 hours.

Five children who took excessive amounts of pemoline have been described (6). They had a relatively benign course and their symptoms appeared to be primarily accentuated pharmacological effects on the central nervous and cardiovascular systems. Sinus tachycardia, hypertension, hyperactivity, choreoathetoid movements, and hallucinations were most commonly observed, consistent with previous reports.

Possible rhabdomyolysis occurred after overdose, accompanied by raised serum creatine kinase activity in three of four patients in whom it was measured; this appears to be common in acute pemoline poisoning. After ingestion, symptoms occurred within 6 hours and lasted up to 48 hours in all cases.

Gastric lavage and activated charcoal are considered to be effective decontamination measures, whereas ipecac-induced emesis should be avoided after massive ingestion, because of the risk of seizures. Aggressive use of benzodiazepine is a reasonable first choice to treat associated involuntary movements, tremor, hyperactivity, and agitation. Chlorpromazine or haloperidol can also be used, especially for serious, life-threatening symptoms, including hypertensive crises and severe hyperthermia, and labetalol or sodium nitroprusside are reasonable choices for rapid stabilization of blood pressure.

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Penicillamine

General Information

Penicillamine is dimethylcysteine or 2-amino-3-mercapto-3-methylbutyric acid, a sulfur-containing amino acid. It has three functional groups: an alpha-amine, a carboxyl, and a sulfhydryl, which largely determine its pharmacological effects. Because the levorotatory isomer, L-penicillamine, is a pyridoxine antagonist and toxic, the racemic mixture has been replaced for medicinal purposes by purified D-penicillamine. Here "penicillamine" refers to the D-isomer unless otherwise specified.

Acetylpenicillamine is a weaker chelating agent than penicillamine, has no effect on collagen cross-links, and is not effective in rheumatoid arthritis. It has been used in the treatment of mercury poisoning (1).

As its name suggests, penicillamine is a degradation product of penicillin. There have been several reviews of the chemistry, pharmacokinetics, and pharmacology of penicillamine (SED-12, 537) (2). After oral administration about two-thirds (50–70%) of a dose of penicillamine is absorbed. As much as 33% can be degraded in the gut before absorption can take place. With a half-life of less than 1 hour, penicillamine is rapidly cleared after oral administration, largely by formation of disulfides with plasma albumin and with low-molecular weight thiols, such as cysteine and glutathione. Low-molecular weight disulfides constitute the major urinary metabolites. The penicillamine-albumin disulfide, on the other hand, has a long half-life. The consequence of this is slow accumulation: in healthy volunteers pseudo-steady-state plasma concentrations of penicillamine-albumin disulfide are not reached until the second week of daily administration. Peak plasma concentrations of penicillamine occur at 1.5–4 hours after ingestion and range from 5 μmol/l after 150 mg to 28 μmol/l after 800 mg (when conventional-release oral formulations are used). About 80% of penicillamine is protein-bound; about 7% occurs as L-cysteine-D-penicillamine disulfide, 5% as penicillamine disulfide, and 6% as free penicillamine. A large proportion is rapidly excreted in the urine, mainly as the disulfide or as the disulfide metabolite conjugated with cysteine; formation and excretion of the latter can cause cysteine depletion. Some penicillamine is converted to *S*-methyl-penicillamine and is either excreted by the kidneys or metabolized in the liver. Although S-methylation is a quantitatively minor elimination pathway, *S*-methyl-penicillamine is a potential substrate for sulfoxide formation, and patients with rheumatoid arthritis who form the sulfoxide at a reduced rate are at greater risk of adverse effects (3). The concentrations of penicillamine and its metabolites within cells and at the cell surface are largely unknown, but may be relevant to variability in response in regard to cellular sites of action.

Uses

Penicillamine is mainly used in the treatment of rheumatoid arthritis, Wilson's disease, and cystinuria. Although penicillamine and gold compounds were both originally used in rheumatoid arthritis on the basis of erroneous pharmacological hypotheses, they have been strongholds in the treatment of debilitating rheumatoid arthritis for more than a quarter of a century (4). Whereas they do not have much effect on the progression of joint damage, they have unexpectedly been found to be associated with a remarkable diversity of serious adverse reactions. In hindsight, they have played central roles in improvements in the understanding of the pathology of rheumatoid arthritis and of the methods of studying the benefits and harms of therapeutic strategies in rheumatoid arthritis and other chronic progressive diseases.

General trends in the treatment of rheumatoid arthritis in the past decade have been more aggressive treatment in early disease with disease-modulating antirheumatic

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drugs (DMARDs) (5) and the use of combinations of DMARDs (6). Strategies for improving the long-term outcome in rheumatoid arthritis include early specialist referral for DMARD treatment and the avoidance of NSAID-induced gastrointestinal and renal toxicity (7). However, a 28-year observational study in Austria of the patterns of use of DMARDs has illustrated how penicillamine has given way to other drugs, in particular methotrexate and sulfasalazine (8,9). The advent of novel drugs with different mechanisms of action, such as cytokine antagonists, has empowered rheumatologists with effective new instruments (10–12).

Some believe that early, aggressive, and continuous use of DMARDs and of combinations thereof slows joint destruction, modifies the natural course of the disease, and improves outcome (13,14). On closer inspection, however, the evidence still seems thin. Schemes for treatment and monitoring are variable and complex, and none is demonstrably superior to any other. It is in any case always important to tailor treatment to the needs of the individual patient rather than following rigid guidelines.

In other reviews, the conclusion has again been reached that the long-term use of DMARDs, including penicillamine, is limited by both frequent loss of response and serious adverse reactions, and that the advantages of combination DMARDs treatments remain controversial (15,16) (SEDA-19, 229) (SEDA-20, 219) (SEDA-25, 266). In particular, the treatment of juvenile rheumatoid arthritis is difficult, since DMARDs are often poorly active in children and some (gold compounds, sulfasalazine) cause special adverse reactions, such as the macrophage activation syndrome (which in turn can lead to severe infections) (17). There is still much to be achieved and improved. As Fries has put it (16): "Determining the most clinically useful DMARD combinations and the optimal sequence of DMARD use requires effectiveness studies, Bayesian approaches and analyses of long-term outcomes. Such approaches will allow optimization of multiple drug therapies in rheumatoid arthritis, and should substantially improve the long-term outcome for many patients." In the same paper it was emphasized that patients taking penicillamine should have blood cell counts and urine protein measurements every 2 weeks during drug titration and then about monthly for as long as treatment lasts.

Since the recognition of the superior effectiveness of methotrexate and the publications of the Pediatric Rheumatology Collaborative Study Group, penicillamine has been used infrequently in juvenile rheumatoid arthritis. The maximum daily dose is about 10 mg/kg (750 mg/day) (18). This dosage is reached in three equal steps, each of 6–8 weeks' duration. Perhaps more than gold, penicillamine acts slowly, taking 9 months to 3 years for maximum effectiveness.

In a small trial, penicillamine together with metacycline was not effective in progressive multiple sclerosis (19).

Observational studies

In an Austrian study, patients with rheumatoid arthritis were followed for a mean of 10 years (20). Of 27 courses of penicillamine, 13 were discontinued because of adverse effects, 12 because of lack of effectiveness, and two because of remission. Furthermore, an analysis of the reasons for DMARD withdrawal in patients in the Czech and Slovak Republics has underlined the fact that lack of effectiveness is, in addition to adverse effects, an important reason for stopping penicillamine (21).

General adverse effects

In clinical trials about 50% of patients experienced one or more adverse effects and withdrawal was necessary in about one-third (22–26). A mucocutaneous reaction (for example a rash or stomatitis) is the most frequent reason for discontinuing the drug (27). Long-term follow-up studies have shown that many patients (up to 80%) stop taking penicillamine, either because of adverse effects or lack of efficacy (27–31).

Adverse effects are less common when small doses are used, when increments are made only slowly, when patients are closely monitored, and when penicillamine has been tolerated for some years. However, in a meta-analysis of a large series of clinical trials, dose was not a strong determinant of the risk of adverse effects (dose range 500–1250 mg/day) (26). With regard to the safe use of penicillamine the words of Huskisson (1981) are still true (32): "Perhaps the most important aspect of the surveillance of patients receiving penicillamine is the need for the physician and patient to be able to contact each other. The physician must find the patient if his blood count changes. The patient must find the physician if he becomes ill. Disasters have occurred when patients consulted physicians who were unaware of the problems of penicillamine and instituted unwise therapy for them. Penicillamine can only be used by those who know how to use it and skilful management [of its adverse effects] is a most important aspect, perhaps the most important aspect of the treatment."

In patients with rheumatoid arthritis, delayed disease complications or serious intercurrent disorders can be mistaken for complications of treatment with penicillamine or other drugs (SEDA-21, 252). Anyone responsible for a patient taking penicillamine must bear in mind that serious adverse reactions can occur suddenly and at any time during treatment, even with very small doses (as low as 125 mg/day) and after many years. Penicillamine can be the unexpected cause of serious adverse reactions as an additive to Chinese herbs (33).

Early effects are gastrointestinal upsets and, more characteristically, loss of taste. Although a fall in the number of platelets is common, serious thrombocytopenia is less frequent. After long-term use of high doses, skin collagen and elastin are impaired, resulting in increased friability and sometimes in disorders such as perforating elastoma or cutis laxa; the latter has also been observed in neonates.

Hypersensitivity reactions are frequent early in a course of penicillamine, with urticarial or maculopapular rashes, fever, and lymphadenopathy. Cross-allergy to penicillin can occur. In addition, the use of penicillamine can be complicated by a unique variety of often serious autoimmune reactions, involving the skin, kidneys, liver, lungs, muscles, or other organs. Proteinuria is found in more than 10% of patients and sometimes develops into the nephrotic syndrome. Pemphigus, myasthenia gravis, polymyositis, or a lupus-like syndrome occur in smaller percentages.

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Reactions such as aplastic anemia, Goodpasture's syndrome, or thrombotic thrombocytopenic purpura (Moschcowitz's syndrome) are rare but serious.

Although lymphatic malignancies have been described in a few patients using penicillamine (SEDA-11, 212) (SEDA-8, 237), a causal relation is considered unlikely.

Combinations with other drugs used in rheumatoid arthritis

Adding chloroquine or hydroxychloroquine to penicillamine in the management of rheumatoid arthritis probably offers no therapeutic advantages, produces more adverse effects, and may even be less effective (SEDA-10, 223) (34–37). A combination of penicillamine and sulfasalazine seems to be more effective, although the extent of the advantage is uncertain, and adverse effects may be more frequent (34). In one study penicillamine and intramuscular gold together produced much earlier improvement, but efficacy and adverse effects did not differ significantly compared with either drug alone. In an open, uncontrolled study, the combination of penicillamine and intramuscular gold yielded the highest proportion of remissions in patients with refractory rheumatoid arthritis (34). The possible consequences of previous intolerance to gold compounds in association with adverse reactions to penicillamine administration have been reviewed (SEDA-8, 236); at present no firm conclusions can be made. Penicillamine does not chelate gold stores in the body.

Comparisons with other drugs used in rheumatoid arthritis

In an outpatient study in New Zealand, the changing patterns were studied in the use of "slow-acting" antirheumatic drugs (38). There were increases in the use of methotrexate and of drugs in combination, whereas there was a marked reduction in the use of auranofin. Penicillamine had the highest "average toxicity" score. However, despite the increased popularity of sulfasalazine and immunosuppressive drugs, drugs such as penicillamine continue to be used worldwide. In a long-term follow-up study, the proportion of patients who continued to take their first DMARD or who were in remission at 5 years was 53% for penicillamine, compared with 34% for aurothiomalate, 31% for auranofin, and 30% for hydroxychloroquine (39). Of the 179 patients who used penicillamine, 36 stopped taking it because of adverse effects (see Table 1). In an open, randomized, follow-up study of patients with rheumatoid arthritis, 98 were allocated to penicillamine (median daily dose 750 mg, range 375–1000 mg) and 102 to sulfasalazine (40). Over follow-up for 12 years as many as 95 patients (48%) died, four from peptic ulcer disease complications, illustrating the prevalence of premature mortality in patients with rheumatoid arthritis. Only four of the 98 patients continued to take penicillamine. Major reasons for withdrawal of penicillamine, other than death, were adverse effects ($n = 47$) and lack or loss of effect ($n = 36$) (see Table 1). In neither study was any of the deaths thought to have been related to penicillamine. The picture given in Table 1 illustrates the remarkable diversity and seriousness of the adverse reactions pattern of penicillamine.

Table 1 Adverse effects leading to the withdrawal of penicillamine in two studies

Reference	(40)	(39)
Total number of patients	98	179
Patients with adverse effects	47 (48%)	37 (20%)
Proteinuria	17	8
Rash, pruritus, or mouth ulcers		16
Nausea/vomiting	7	2
Rash	9	
Abdominal pain/dyspepsia	2	4
Thrombocytopenia	4	1
Leukopenia	2	2
Mouth ulcers	4	
Malaise	1	1
Exacerbation of joint pains		1
Myasthenia gravis		1
Pemphigus		1
Lupus-like syndrome	1	

A diagnostic and monitoring database program called DIAMOND runs across a network of personal computers throughout the Staffordshire Rheumatology Centre (41). For about 10 years, drug histories, blood test results, and clinical correspondence files for about 2000 patients have been accessible, and the system is linked to the main hospital pathology database. The DIAMOND system has been used to study adverse reactions and durations of treatment for commonly prescribed DMARDs, including penicillamine (combination treatments excluded). With a median survival time of 34 months, penicillamine held an intermediate position, between methotrexate (<96 months) and azathioprine (13 months) at the extremes; 38% of the patients continued to take penicillamine after 5 years. There were strong associations between penicillamine and both proteinuria and thrombocytopenia, both well-established adverse effects of penicillamine. Myasthenia gravis occurred in eight of 582 penicillamine users (1.4%) and not in patients using other DMARDs.

Prevention

Some 15 years ago, a more aggressive "sawtooth" strategy (early continual serial use) for the treatment of rheumatoid with disease-modifying drugs (DMARDs) was advocated (SEDA-19, 229). There is now evidence that DMARDs, when carefully monitored, are both less toxic and less effective than previously thought (42). Apparently, the sawtooth strategy has not changed the balance of benefit and harm of these drugs. No single DMARD or combination of DMARDs stood out favorably with respect to efficacy, toxicity, or survival. Ineffectiveness, rather than toxicity, was the main reason for drug withdrawal. A Canadian study has added to the evidence that the long-term results of treatment with DMARDs, such as penicillamine and gold, are disappointing, as well as in patients treated early in the course of their disease (43). After 3 years, only 30% were still taking penicillamine. After 6 years only 20% of patients had not been withdrawn, and there were no substantial differences between the drugs.

The effect of a patient education program, taught by rheumatology nurse practitioners, on adherence of patients to treatment with penicillamine has been studied

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(44). The program significantly and persistently increased adherence over a period of 6 months in 51 patients compared with 49 controls (who used penicillamine without the educational program). Most of the patients (in both groups) had adverse effects, including thrombocytopenia in two and myasthenia gravis in one. The number of patients who asked to have penicillamine withdrawn was far higher in the control group ($n = 12$) compared with the patient education group ($n = 2$). Taste disturbances, for example, led to self-withdrawal in four patients, all in the control group. On the other hand, the patients in the patient education group were much more reluctant to withdraw, even in the event of serious adverse effects.

Dose relation

In a comparison of high doses (750–1000 mg/day) and low doses (125 mg every other day) of penicillamine in the treatment of early diffuse systemic sclerosis, there were no differences in efficacy (45). However, 16 of the 20 adverse event-related withdrawals were in the high-dose group. Seven of the 34 patients in the high-dose group had proteinuria (over 1 g/day) compared with only one of the 32 patients in the low-dose group. On the other hand, and in accordance with previous experience (SED-14, 723), other recorded adverse reactions, including myasthenia gravis, flu-like illness, thrombocytopenia, stomatitis, and rash, were only slightly more common in the high-dose group.

Time-course

Certain adverse effects occur predominantly during the first few months of treatment, for example taste alterations and non-specific hypersensitivity reactions, whereas others are more frequent during the second half-year of treatment (thrombocytopenia, proteinuria) or become apparent even later (for example collagen insufficiency). However, almost the entire spectrum of possible adverse reactions can occur at any time and without warning throughout a course of treatment with penicillamine. Although different schemes may be used, the monitoring of penicillamine treatment usually includes regular testing of platelet and white cell counts, a blood smear, proteinuria, and hematuria.

Organs and Systems

Cardiovascular

Penicillamine has no direct effect on the cardiovascular system. However, penicillamine-associated polymyositis can involve cardiac muscle and cause dysrhythmias, Adams–Stokes attacks, and death. Necrotizing vasculitis can occur as an immunological reaction to penicillamine (46). The effect of penicillamine on collagen and elastin fibers, which causes characteristic skin lesions, also includes the vascular wall, but effects of vascular insufficiency have not been reported.

Respiratory

Although penicillamine has no direct effects on the lungs (47), its use is associated with a spectrum of pulmonary injury: interstitial and alveolar reactions, pulmonary fibrosis, bronchiolitis obliterans, and pulmonary/renal syndromes (48–52). However, the differentiation between drug reactions and pulmonary disorders secondary to rheumatic or other underlying diseases is often difficult. The clinical presentation of bronchiolitis obliterans is acute, with cough, shortness of breath, and other non-specific respiratory complaints. The prognosis is often poor. Two separable but overlapping groups have been described: acute and chronic cellular bronchiolitis with less conspicuous scarring, and constrictive bronchiolitis, with histology varying from fibrotic and inflammatory lesions to complete small airway obliteration (SED-12, 539) (51,53–55).

In addition, several autoimmune reactions to penicillamine can secondarily affect pulmonary function. Penicillamine-induced polymyositis (56) or myasthenia gravis can cause respiratory failure, even requiring ventilatory support (57). The diagnosis and management of lupus-induced pleurisy have been reviewed (58).

Alveolar hemorrhage can occur with penicillamine, usually as part of a life-threatening pulmonary-renal syndrome resembling Goodpasture's syndrome (59,60).

Rhinitis, bronchospasm, and asthma can occur as a manifestation of hypersensitivity to penicillamine (SEDA-5, 248) (61–63) and rarely of the Churg–Strauss syndrome (64). Rhinitis can also be a symptom of penicillamine-induced pemphigus (65). In one patient a large pulmonary cyst developed concomitantly with skin lesions characteristic of the use of large doses of penicillamine (66). Microscopic derangement of the elastic fibers predominated. Although the frequency is uncertain, penicillamine can be associated with recurrent respiratory tract infections, that is secondary to IgA deficiency (67,68) or as part of the "yellow nail syndrome" (SEDA-9, 223).

Nervous system

Penicillamine, both L-penicillamine and the racemic mixture, strongly inhibit pyridoxal-dependent enzymes, cause pyridoxine deficiency in animal experiments, and are neurotoxic. Although this effect is much weaker with D-penicillamine, a few case reports have shown that D-penicillamine can also occasionally cause a polyneuropathy, as either a toxic or an allergic reaction (69–72). Rarely, an optic neuropathy (73) or a polyradiculoneuropathy (Guillain–Barré syndrome) (74,75) can occur.

When penicillamine is started in patients with Wilson's disease, pre-existing neurological involvement can acutely worsen; convulsions, muscle spasms, and coma can occur and death can follow (76–81). Worsening of neurological symptoms after starting therapy with penicillamine can occur in up to 50% of neurologically affected patients with Wilson's disease (79,80) and penicillamine can precipitate serious neurological injury in previously asymptomatic patients (82,83). It is uncertain if this results from alterations of copper distribution at submolecular, subcellular, transcellular, or transorganic levels, or whether it results from some other property of penicillamine (for example its capacity to donate sulfhydryl groups). Since the initial damage may be caused by copper decompartmentalization, it has been suggested that pretreatment with lipid-soluble antioxidants, such as vitamin E, may be useful (77), whereas at least some of these effects may reflect secondary pyridoxine deficiency. Supplementary oral pyridoxine may be advisable (80).

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Two patients have been described with the internuclear ophthalmoplegia syndrome, probably induced by penicillamine. In one it was secondary to serious progressive intracerebral necrotizing vasculitis (46), in the other the underlying condition was a myasthenic reaction (84). Isolated cases have been described of neuromyotonia (85) and diffuse fasciculations (86), attributed to penicillamine.

Myasthenia

Penicillamine can induce a myasthenia gravis-like reaction, indistinguishable from idiopathic myasthenia gravis (33,57,82,87–101). It develops in up to 4% of patients using penicillamine, is most often described in patients with rheumatoid arthritis, but can also occur with other indications (for example biliary cirrhosis (102) or eosinophilic fasciitis (103)). However, it reportedly does not occur in Wilson's disease (104). The reaction often starts with involvement of ocular muscles, but any striated muscle can become involved. In contrast to other drug causes, it is characteristic of penicillamine-related myasthenia that about 90% of patients have antiacetylcholine receptor antibodies (101). The antigenic properties of circulating acetylcholine receptor antibodies in penicillamine-induced and idiopathic myasthenia are similar to those in recent-onset cases of spontaneous myasthenia gravis (92,99). Antistriational and antinuclear antibodies (105) can be present, and a sensitive immunoassay for striational autoantibodies can be used to monitor patients taking penicillamine for the development of myasthenia (94). In one study, measurement of acetylcholine receptor antibodies was considered to be of little or no use in routine monitoring of patients using penicillamine, because in 20% of patients antibodies were detected at least on one occasion, although none of the patients had signs or symptoms of myasthenia, and the antibody tests returned to normal despite continuation of the drug (106). Others have advised annual monitoring of every patient taking penicillamine, to detect subclinical changes in neuromuscular transmission and by acetylcholine receptor antibody testing (107,108).

- A 68-year-old woman, with HLA type DR1+, had been taking penicillamine (dose not specified) for 9 months for erosive seropositive rheumatoid arthritis (109). T cell clones were highly specific for D-penicillamine, but not for L-penicillamine or D-cysteine, and were restricted to HLA DR1. They responded well to blood mononuclear cells prepulsed with D-penicillamine but not to autologous B cell lines pulsed with D-penicillamine.

Apparently, penicillamine can couple directly to distinctive peptides resident in surface DR1 molecules on circulating macrophages or dendritic cells. In another article, apparently concerning the same patient, the same group described the selection of T cell clones specific for the ϵ (rather than the α or γ) subunit, responding to peptide ϵ 201–219 (110). They were restricted to HLA-DR52a (a member of the strongly predisposing HLA A1-B8-DR3 haplotype). Since these T cells had a pathogenic Th1 phenotype with the potential to induce complement-activating antibodies, they could be important targets for selective immunotherapy. In another patient, penicillamine-related myasthenia gravis developed simultaneously with polymyositis and pemphigus (111).

In spite of the similarities, there are some differences between spontaneous and penicillamine-induced myasthenia in respect to genetics. Myasthenic reactions to penicillamine appear to occur in a special genetic subgroup of patients, in whom there is a higher prevalence of the HLA antigens DRI and Bw35, and a lower prevalence of the antigens DR3 (which is associated with idiopathic myasthenia) and DR4 (which is increased in rheumatoid arthritis) (112,113).

Myasthenia usually improves rapidly after withdrawal of penicillamine, but it may have a protracted course. Fatal cases have occurred. Unrecognized myasthenia can present with prolonged paralysis after general anesthesia. For this reason, for patients taking penicillamine undergoing anesthesia the same precautions are advisable as for patients known to have myasthenia gravis (114). Penicillamine unexpectedly caused myasthenia gravis when present as an unrecognized adulterant in Chinese herbs (33).

Sensory systems

Alteration or loss of taste is a characteristic adverse effect of penicillamine. Depending on the dose used, taste impairment (dysgeusia) occurs in 10–25% of patients and when daily doses in excess of 900 mg are used this increases to over 50% (SED-11, 466) (23,115). It usually develops in about the sixth week of treatment. Patients complain of requiring increasing amounts of sugar and spices. Food does not taste normal, but salty or metallic, or like cotton wool or blotting paper. Identification of certain foods becomes difficult. Absolute taste loss can ensue but the sense of smell is unaltered. Spontaneous recovery usually follows within 6–8 weeks, despite continuation of the drug. Dysgeusia can occur at any time and can be persistent (116).

In a review of drug-induced olfactory disorders, penicillamine was mentioned as a cause of abnormal smell (117). However, there may have been confusion with its effect on taste.

In patients with Wilson's disease, penicillamine is rapidly attached to copper and, although higher doses are used, taste disturbances develop in a lower frequency, about 4% (SED-8, 536). It has been suggested that dysgeusia is related to deficiency of copper or zinc, but a strong connection between taste impairment and urinary copper excretion has not been demonstrated (118). Serum copper concentrations remained within normal limits and copper supplements were not effective in prevention (119).

In another study, there was an association with reduced serum zinc concentrations, and taste recovered after zinc supplements were given, although it should be remembered that spontaneous recovery occurs in most patients (120).

Taste alterations have been reported with other sulfhydryl compounds, including pyritinol, captopril, and propylthiouracil (121), suggesting that the thiol moiety is involved. However, dysgeusia has not been observed in many studies on the use of penicillamine in children (SEDA-7, 258) (122).

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Optic neuropathy has only rarely been reported in association with penicillamine (73). In one patient, blurred vision occurred as a result of the development of bilateral choroidal hemorrhage complicating penicillamine-induced thrombocytopenia (123).

Ocular pseudotumor has been described in one patient as part of an ANCA-positive vasculitis (124).

Endocrine

A few patients are on record with suspected penicillamine-induced thyroiditis, one case being associated with a myasthenic reaction (125,126).

Metabolism

Penicillamine had a small effect on urinary glucaric acid excretion in patients with rheumatoid arthritis (127). This effect was thought to be the result of an indirect effect on hepatic metabolism and not to be related to disease activity.

Anti-insulin antibodies and hypoglycemia

One of the remarkable autoimmune phenomena that penicillamine can cause is the induction of anti-insulin antibodies, with resultant hypoglycemia (autoimmune hypoglycemia) (128,129). In these patients, there are high concentrations of immunoreactive insulin, despite undetectable free insulin. When penicillamine is withdrawn antibody titers fall sharply. The occurrence of hypoglycemia rather than hyperglycemia is not fully understood (130).

In two previously well-controlled diabetic patients taking penicillamine who developed hypoglycaemia, no reference was made to anti-insulin antibodies (131).

In a study using a competitive radiobinding assay, as many as 43% of patients with rheumatoid arthritis using penicillamine had autoantibodies against insulin (132). These antibodies did not appear to affect pancreatic beta-cells, as the response to intravenous glucose was normal and there were no episodes of hypoglycemia. Other sulfhydryl compounds that have occasionally been reported to cause autoimmune hypoglycemia are tiopronin, pyritinol, and thiamazole (methimazole) (133).

Enzyme inhibition

In in vitro studies penicillamine inhibited angiotensin-converting enzyme (ACE) and carboxypeptidase (134). Penicillamine interferes with the functions of the copper-containing enzyme ceruloplasmin, and some of the penicillamine- and copper-containing complexes formed in vivo have a superoxide dismutase effect (2). In patients with scleroderma, penicillamine normalized collagen metabolism, by inhibiting beta-galactosidase activity (135).

Nutrition

L-penicillamine strongly inhibits pyridoxal-dependent enzymes and causes pyridoxine deficiency in animals. Although D-penicillamine is much less active in this respect, there is some reduction in pyridoxine, and in a report of penicillamine-associated polyneuropathy, pyridoxine supplements for patients receiving D-penicillamine were advised (69).

Metal metabolism

Penicillamine is a potent chelator of metals. The stability of complexes of metals with penicillamine varies in the following order (from highest to lowest): mercury, lead, nickel, copper, zinc, cadmium, cobalt, iron, manganese (136–138). Most human data refer to copper, lead, and mercury.

Because of the strong affinity of penicillamine for copper and other metals, it is used in the treatment of Wilson's disease and lead poisoning. In other patients, however, this effect may sometimes cause deficiencies (SED-8, 531), especially of copper (SEDA-10, 223). Copper deficiency has been thought to play a role in the occasionally reported alopecia and in the loss of taste that is often experienced by patients with rheumatoid arthritis taking penicillamine (but rarely in Wilson's disease), but this could not be confirmed (118).

Penicillamine-induced deficiency of both copper and iron has been held responsible for the development of anemia (139), but serum iron concentrations do not usually change in patients using penicillamine (SED-8, 535).

The influence on metals such as copper and zinc may be difficult to assess, since penicillamine not only increases the excretion but also the absorption of these metals (140). A zinc deficiency syndrome, with skin lesions, alopecia, granulocytopenia, and eye damage, has been described in association with penicillamine (141).

Hematologic

The pathogenesis of hematological reactions to penicillamine is uncertain, but the available evidence suggests that pharmacological as well as immunological processes may be involved (142–144).

In the ARAMIS PMS Program, hematological events regarded as adverse effects of penicillamine, calculated per 1000 person-years, were as follows: pancytopenia 10, low white blood cell count 8, low platelet count 18, and polycythemia 2 (145). Serious blood dyscrasias, although rare, are among the most important adverse effects of penicillamine (SED-12, 541) (146,147). The assessment of the frequency of penicillamine-related hematological reactions can be hindered by the use of other potentially hemotoxic drugs, such as analgesics or gold compounds.

Eosinophilia can occur in up to 25% of patients using penicillamine, but is of little value in predicting serious hypersensitivity reactions (148).

Thrombocytopenia occurs in about 10–16% of patients and requires withdrawal in up to 10% (22,23,115), but these percentages vary considerably, presumably reflecting the use of different doses of penicillamine and different definitions of thrombocytopenia. In a series of 309 spontaneous case reports of drug-related thrombocytopenia, penicillamine was the fifth most common cause (18 cases, 6%) (149). The fall in platelet count is usually transient, but it is occasionally a warning of impending profound and dangerous thrombocytopenia or other serious hematological reactions, such as aplastic anemia or thrombotic thrombocytopenic purpura. Thrombocytopenia mainly develops during the first 6 months of penicillamine administration and appears to be associated with certain HLA antigens (DRA4, A1, C4BQO). Platelet counts fall to some extent in about 75% of patients taking penicillamine

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and it can be difficult to decide when to withdraw it. Platelet counts are recommended initially at 2-weekly intervals and subsequently each month, in addition to clear instructions to the patient. Weekly checks are needed when counts fall to between 100 and 70×10^9/l, and daily checks when below 70. If the platelet count falls progressively or falls below 70×10^9/l penicillamine should be immediately withdrawn (150).

In all but one of 26 children with Wilson's disease who were treated with penicillamine 20 mg/kg/day, there were fewer adverse reactions than expected: two patients developed a rash, one patient had to stop taking the drug because of a lupus-like syndrome, and another had thrombocytopenia, which resolved after treatment with prednisone (151).

Concurrent thrombocytopenia and anemia have been attributed to penicillamine (152).

- A 66-year-old woman had taken penicillamine 200 mg/day for 8 months for long-standing systemic sclerosis, together with erythromycin (800 mg/day) for prophylaxis of pulmonary infection. Her platelet count was 39×10^9/l and her hemoglobin concentration 7.3 g/dl. The leukocyte count was 3×10^9/l with a normal differential count. There was no hemolysis. A bone marrow aspirate showed mild hypoplasia and reduced megakaryopoiesis. Incubation with penicillamine produced inhibition of erythroid and megokaryocyte burst-forming units, but not of granulocyte/macrophage colony-forming units, suggesting a selective effect of penicillamine on erythropoiesis and megakaryopoiesis. The blood cell counts recovered gradually on withdrawal of both penicillamine and erythromycin, treatment with corticosteroids, and a blood transfusion.

The authors did not make reference to the effects of incubating the bone marrow with erythromycin.

There have been several cases of thrombotic thrombocytopenic purpura or Moschcowitz's syndrome, characterized by intravascular coagulation, thrombocytopenia, and hemolysis, as a rare but life-threatening complication of penicillamine (153–156). There is one case report of Evans' syndrome, thrombocytopenic purpura in combination with autoimmune hemolytic anemia, in suspected association with penicillamine (157). In this patient antiplatelet antibodies as well as antibodies against erythrocytes were detected.

Penicillamine can cause other serious hematological reactions such as agranulocytosis and aplastic anemia (27,144,146,158–167).

- Pure red-cell aplasia developed in a 40-year-old woman as a rare idiosyncratic hematological reaction to penicillamine (105). Withdrawal of the drug, which had been taken in a daily dose of 500 mg for rheumatoid arthritis, and a short course of glucocorticoids was followed by permanent recovery.

Sideroblastic anemia has been attributed to penicillamine (168).

Because of its effect on ceruloplasmin and, in turn, the utilization of stored iron, penicillamine is considered to be able to cause iron deficiency anemia (139,169,170).

Penicillamine can also cause hemolytic anemia (SEDA-8, 535) (171), although good clinical evidence of this is lacking. A positive Coomb's test can occur as part of a lupus-like syndrome (172).

Polycythemia (145), leukocytosis, and thrombocytosis have been mentioned in association with penicillamine, but data are lacking.

Mouth and teeth

Stomatitis is a troublesome adverse effect of DMARDs. Ulcers of the oral mucosa are not uncommon in patients taking penicillamine (188,173) and lead to withdrawal in 3.1% of patients (174). However, stomatitis may be a consequence of multiple factors, including hematinic deficiency, virus or Candida infection, recurrent aphthous ulceration, or Sjögren's syndrome. Moreover, aphthous stomatitis often occurs in users of non-steroidal anti-inflammatory drugs (175).

When high doses are used, stomatitis may reflect impaired collagen synthesis. In one patient, mucosal ulcers were associated with leiomyomatosis in the peripheral serosa, which in turn caused intestinal obstruction (176). In another patient taking penicillamine for Wilson's disease, the removal of an impacted maxillary third molar was followed by the development of an oroantral fistula, presumably as a result of impaired collagen synthesis and disturbed wound healing (177). Furthermore, oral ulcers may be an important warning sign of penicillamine-induced agranulocytosis.

Cheilosis has also been reported (178). Oral lesions in patients using penicillamine may be due to pemphigus, cicatricial pemphigoid, or lichen planus, even in the absence of lesions outside the oral cavity. In 56 consecutive patients taking penicillamine, oral lichen planus was found in as many as seven (179). Penicillamine-induced cicatricial pemphigoid can be associated with oral ulcers as well as lesions of the esophagus, and stenosis can develop.

Gastrointestinal

Gastrointestinal complaints, including nausea, vomiting, heartburn, abdominal distress, and diarrhea, occur in up to one-third of patients starting penicillamine and may account for up to half of the withdrawals in the first 3 months of treatment (SED-12, 541) (22,23,173). However, penicillamine is not known to be ulcerogenic (SED-8, 535) (SEDA-2, 217) (180), and the nature of gastrointestinal effects is not clear. Gastrointestinal symptoms are less frequent with initially low doses that are slowly increased. Taking penicillamine with food improves tolerance but reduces its absorption.

- A woman taking penicillamine developed dysphagia, heartburn, and weight loss; numerous large aphthoid ulcers were found in the esophagus (181).

Sulfhydryl compounds can damage the gut mucosa, but examination of the mucosa of cysteinuric patients who reported gastrointestinal upsets while taking penicillamine showed no evidence of structural damage (182).

Although less well documented than with gold, penicillamine can also occasionally cause life-threatening colitis (183).

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Liver

Several case reports have demonstrated that penicillamine can cause liver damage (SEDA-13, 199) (184), mainly cholestatic hepatitis, often associated with other signs of hypersensitivity such as fever, rash (185), and pulmonary (159,186) or hematological reactions (162). In two children with Wilson's disease, penicillamine was thought to have caused persistence of a pre-existing increase in aminotransferase activity (187).

- A 30-year-old Japanese man with polyarthritis, in whom sodium aurothiomalate for 3 years had been ineffective, was given penicillamine 200 mg/day (188). After 10 days he became febrile and 2 days later jaundiced. A lymphocyte stimulation test against penicillamine was positive, suggesting type IV hypersensitivity. Later on he had a good response to tiopronin, without further adverse reactions.

In 29 Chinese patients, there was evidence in one that DMARDs and chronic viral hepatitis have synergistic hepatotoxic effects (189). However, the relevance of this anecdotal observation is uncertain.

Copper and iron are both capable of electron exchange and play a complex role in oxygen utilization. Copper proteins are critical in the transfer and transport of iron (190). In four patients with Wilson's disease, the fall in serum ceruloplasmin concentrations after treatment with penicillamine was associated with increased hepatic iron content; in two of these patients serum ferritin was increased (191). In another patient a liver biopsy taken after 15 years of treatment with penicillamine and zinc showed iron-laden hepatocytes, whereas histochemically detectable iron had been absent from an initial biopsy (192). The copper-containing protein ceruloplasmin and its membrane-bound homolog hephaestin are pivotal in iron metabolism. In addition there are intracellular transfer proteins ("chaperones") that deliver copper to ferroxidase proteins. Intracellular ferroxidase proteins accelerate the efflux of iron through stimulating the conversion of Fe^{2+} to Fe^{3+} and subsequent binding to transferrin. Presumably, excess loss of copper due to penicillamine or penicillamine plus zinc can reduce ferroxidase activity and cause intracellular iron deposition and paradoxical deterioration in liver function. Therefore, during treatment of Wilson's disease when the non-ceruloplasmin-bound copper falls to within the reference range (<150 ng/ml), the maintenance dose of penicillamine should be reduced to the minimum needed; temporary withdrawal of penicillamine may even be indicated (190).

Pancreas

There have been three poorly documented cases of pancreatitis attributed to penicillamine (SED-8, 385) (SEDA-2, 217).

Urinary tract

Penicillamine is often associated with renal damage. Proteinuria occurs in about 10–25% of patients taking penicillamine (SED-11, 464) (22,23,115,145,193–196) and occurs in 50% of patients with cysteinuria (SEDA-8, 236). However, microalbuminuria is common in patients with rheumatoid arthritis and may reflect either rheumatoid nephropathy or renal injury caused by penicillamine (or other drugs, such as gold compounds) (197). In about 5% of patients, proteinuria is the reason for withdrawing penicillamine. To avoid renal damage, response-dependent prescribing is recommended in rheumatoid arthritis, starting with a low dose and making increments at intervals of at least 1–2 months. Frequent urine testing is necessary, particularly during the first 18 months. Mild proteinuria (<1 g/day) occurs most frequently, is often transient, and may be coincidental. Moderate proteinuria may be penicillamine-induced but need not be progressive or clinically harmful; close monitoring is indicated in such cases, and a temporary reduction in dose is advisable, although withdrawal of penicillamine may not be needed. When proteinuria increases, nephrotic syndrome can develop, necessitating withdrawal (198). In cysteinuria it is advisable to withdraw penicillamine when proteinuria exceeds 5 g/day (199), but in rheumatoid arthritis a lower limit of 2 g/day has been proposed (200). Nephropathy mainly develops during the second 6 months of treatment with penicillamine (200). It is more frequent in patients with a low sulfoxidation capacity (3,201) and with the HLA antigens DR3 and B8 (SEDA-11, 212) (202). Although nephropathy is thought to be rare in Japanese people (SEDA-8, 235) (25), it has been encountered in Japan (203).

In a comparison of high doses (750–1000 mg/day) and low doses (125 mg every other day) of penicillamine in the treatment of early diffuse systemic sclerosis, seven of the 34 patients in the high-dose group had proteinuria (over 1 g/day) compared with only one of the 32 in the low-dose group (45). Rheumatoid arthritis is a risk factor for renal disease, and the distinction from adverse drug reactions can be difficult in these patients (SED-14, 729).

On the basis of experience in one patient and 10 published case histories, the "scleroderma-pulmonary-renal syndrome," a rare and usually fatal complication of systemic sclerosis, characterized by fulminant alveolar hemorrhage and rapidly progressive renal insufficiency, has been reviewed (204). In their patient penicillamine was continued, and the disease progressed. Five of the 11 patients in their review had been using penicillamine.

In a prospective study of renal disease in 235 patients with early rheumatoid arthritis, persistent proteinuria and a raised serum creatinine concentration were predominantly related to drugs, including penicillamine and other DMARDs, whereas isolated hematuria was more directly associated with the activity of the disease process (205). Risk factors for drug-induced proteinuria were raised C-reactive protein, raised erythrocyte sedimentation rate, and age over 50 years.

Of 44 patients with rheumatoid arthritis, 24 had proteinuria (206). Two of these had drug-related nephropathy (penicillamine and gold, respectively); both had nonselective tubuloglomerular proteinuria, type V.

The principal renal lesion associated with proteinuria is membranous glomerulopathy or minimal-change glomerulopathy (196,201,207,208), characterized by minor thickening of the basement membrane or no change on light microscopy, but striking disturbances of the glomerular

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structures on electron microscopy (fusion of epithelial cell foot processes, subepithelial electron-dense deposits, and mesangial cell hyperactivity). Immunofluorescence microscopy shows granular deposits that contain IgG and C3 (209). These immunoglobulin deposits are not the result of precipitation of circulating immune complexes, as was previously thought. The available evidence suggests that the nephritogenic antigen, although still not identified, is expressed in the glomerulus and the immune complexes are formed in situ (207,210). Although proteinuria may be profound, serum creatinine is usually unaltered and penicillamine glomerulopathy usually has a good prognosis. Proteinuria can nevertheless continue for longer than 12 months after withdrawal and microscopic lesions can persist for longer. Although penicillamine nephropathy is more frequent when high doses are taken, it can also occur with small doses (for example 125 mg/day). On rechallenge, nephropathy does not necessarily relapse (SEDA-10, 218), and a history of previous gold nephropathy is not thought to be a risk factor (203). In one study, titers of antigalactosyl antibodies were correlated with the prior development of penicillamine (or gold) nephropathy (211).

Occasionally, penicillamine-associated renal injury is proliferative and progressive, extending beyond the basement membrane, with crescent formation in the glomeruli, and encompassing other renal structures, for example in the case of renal vasculitis, IgM nephropathy (212), or as part of a more general reaction; persistent renal insufficiency can develop and death can follow (196,213–218).

Penicillamine-induced lupus-like syndrome can be associated with proliferating glomerulonephritis with mesangial involvement and interstitial infiltrates (213,219). In such cases antibodies to native DNA can be found.

A rare but life-threatening complication of penicillamine is the development of a Goodpasture's syndrome-like reaction, characterized by alveolar hemorrhage, crescentic glomerulonephritis, and fever (59,220–224). In contrast to genuine Goodpasture's syndrome, circulating antiglomerular basement membrane antibodies are not detected (222), perhaps because the antigen concerned is not present in the test extracts used (223). Patients who have taken immunosuppressive therapy have a comparatively good outcome, but plasmapheresis and hemodialysis may be needed (220).

Serious renal injury can develop as a late complication of pre-existing benign penicillamine nephropathy (220,225). Unfortunately, microscopic hematuria has limited predictive value for imminent serious renal injury, since in most patients who take penicillamine it is a transient or coincidental finding (SEDA-7, 260). The diagnosis of penicillamine-induced renal injury is often difficult because of the frequent association of rheumatoid arthritis with renal disorders (198,204,226–228), including spontaneous membranous glomerulopathy (229), or with injury caused by concomitant analgesics (230).

In a comprehensive study of 158 Japanese patients with rheumatoid arthritis, there was an obvious relation between membranous nephropathy and exposure to disease-modifying antirheumatic drugs (DMARDs) in 40 of 49 patients (231). In this study penicillamine (15%), bucillamine (67%), and gold compounds (17%) clearly predominated.

A patient with nephrotic syndrome that developed soon after the start of treatment with penicillamine has been described in detail (232).

- A 12-year-old boy with a history of a generalized pruritic rash after penicillin took penicillamine up to 500 mg/day for Wilson's disease. He had a rash after using penicillamine for 1 week. The penicillamine was stopped for 3 days. He developed nephrotic syndrome 2 weeks after restarting penicillamine. On electron microscopy, there was the typical picture of minimal change disease with extensive foot process effacement.

In rare cases penicillamine can cause extracapillary glomerulonephritis with more extensive and serious glomerular injury leading to progressive and persistent renal insufficiency. One such patient has been described with a review of 26 similar published cases (233).

- A 51-year-old woman, who used penicillamine, maximum dose 600 mg/day, for systemic sclerosis, developed microscopic hematuria after 11 months. The penicillamine was withdrawn. Three months later she had progressive renal insufficiency. A biopsy showed extracapillary glomerulonephritis, with central fibrinoid necrosis and segmentary mesangial proliferation, and marked tubulointerstitial lesions. After treatment with glucocorticoids, cyclophosphamide, and 12 plasma exchanges her renal function improved slightly.

In half of the 26 patients renal damage was associated with alveolar hemorrhage (233). In eight patients plasma exchange treatment was performed. Seven patients died, including four with alveolar hemorrhage; 12 ended up with more or less chronic renal insufficiency. Only seven patients regained normal renal function; five of these had had plasma exchange.

- Acute renal insufficiency together with diffuse alveolar hemorrhage and bilateral pulmonary infiltrates was suspected to have been caused by penicillamine (500 mg/day for 6 months) in a 34-year-old white woman, who took penicillamine for progressive systemic sclerosis (234). Because of disseminated intravascular coagulation, a biopsy was not made and the role of penicillamine remained uncertain.

Hemolytic–uremic syndrome has been described in a patient with paradoxical rapid progression of systemic sclerosis (235).

- A 58-year-old man with a complex history of Hashimoto's thyroiditis and mixed cellularity Hodgkin's disease in complete remission developed systemic sclerosis involving the skin and the lungs but not the kidneys. He was given penicillamine 250 mg/day and prednisone 60 mg/day. After a few weeks there was rapidly progressive skin thickening, spreading from the hands to the trunk. However, his treatment was not altered, and 4 months later he developed hemolytic–uremic syndrome with microangiopathic hemolytic changes, thrombocytopenia, and acute renal insufficiency, with proteinuria, hematuria, and granular casts in the urine. The renal insufficiency persisted and he died with fulminant sepsis.

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Three case reports from Belgium and France have illustrated the fact that rarely proliferative crescent-forming extracapillary glomerulonephritis and renal insufficiency can also occur (236,237). All three patients had taken penicillamine for systemic sclerosis. Antimyeloperoxidase antineutrophil cytoplasm antibodies were found in all three; one patient also had alveolar hemorrhage (that is Goodpasture's syndrome).

A clinical algorithm for the management of hematuria, for example in patients taking penicillamine or NSAIDs, has been published (238). It should be borne in mind that in such patients hematuria may be symptomatic of underlying pathology (for example a tumor of the urinary tract).

In one study in children with low-level lead poisoning, urinary incontinence was mentioned as a suspected adverse effect of penicillamine (239).

Skin

There is probably no other medicine that causes skin reactions with such a high frequency and of such striking diversity as penicillamine (see Table 2).

During the first few weeks of treatment, allergic reactions occur in about one patient in five (SED-11, 465) (25).

Maculopapular or urticarial rashes are frequent and can be associated with pruritus, edema, lymphadenopathy, arthralgia, fever, and eosinophilia. Patients with previous hypersensitivity to penicillin are more likely to experience a rash when taking penicillamine. Cross-allergy to penicillin can occur, but the risk of a severe allergic reaction to penicillamine in penicillin-allergic patients is thought to be low (240,241). Skin reactions may be more common in the presence of the HLA antigen DRw6 (242), and rashes and febrile reactions were more frequent in patients with anti-Ro(SSA) antibodies (243). Early allergic reactions do not usually necessitate permanent withdrawal of penicillamine, and can often be overcome by lowering the dose or by timely withdrawal of the drug and the use of a glucocorticoid. On the other hand, a non-specific eruption can be the first sign of a serious penicillamine-induced skin disorder, for example pemphigus.

Table 2 Penicillamine-associated skin disorders

Maculopapular or urticarial rashes
Seborrheic dermatitis
Lichen planus-like eruptions
Psoriasiform eruptions
Erythema annulare
Photosensitivity
Pemphigus (erythematosus, foliaceus, vulgaris)
Bullous pemphigoid
Cicatricial pemphigoid
Dermatomyositis
Graft-versus-host reactions
Systemic lupus-like syndrome
Discoid lupus; subacute cutaneous lupus
Erythema multiforme and toxic epidermal necrolysis
Tardive dermopathy (friability, miliary papules, hemorrhagic bullae)
Elastosis perforans serpiginosa
Pseudoxanthoma elasticum
Cutis laxa (hyperelastica)
Cutaneous pseudolymphoma
Acantholytic dermatosis (Grover's disease)

There were no serious adverse reactions in 55 children who received 66 courses of low-dose penicillamine (about 15 mg/kg/day for a mean period of 77 days) for mild to moderate lead poisoning (244). However, in three children penicillamine was withdrawn because of a transient rash.

Paradoxically, penicillamine is occasionally involved in the development of rare diseases for which it is also sometimes used, such as systemic sclerosis-like lesions (245) and circumscribed scleroderma (or morphea) (246,247).

A rash or photosensitivity can also occur as part of the penicillamine-induced lupus-like syndrome (248–250). Type II bullous systemic lupus erythematosus (251) and necrotizing vasculitis (46) have been attributed to penicillamine. In one report, a hypersensitivity reaction to penicillamine with a skin rash and fever was associated with low back pain (252).

Erythema multiforme and toxic epidermal necrolysis are considered to occur as adverse reactions to penicillamine (SEDA-12, 465) (167).

Various other skin lesions have been described.

- In one inconclusive case report acantholytic dermatosis (Grover's disease) was described as a suspected adverse reaction to penicillamine (253). This is a papulovesicular eruption in elderly people, characterized histologically by focal acantholytic dyskeratosis.
- In a female patient acne and hirsutism developed in association with breast enlargement, probably induced by penicillamine (254).
- In a 31-year-old Korean woman with Wilson's disease, high doses (1–2 g/day) of penicillamine led to the development of a dermopathy, with mildly itchy, matchhead-sized, cream-colored papules on top of dark reddish plaques on both knees and elbows (255).

Penicillamine can cause localized scleroderma (also known as morphea), which has been reviewed (257). Bullous lesions can occur in scleroderma (localized, generalized, or systemic), and this highlights the diagnostic problems in such patients (258). In one of the four case histories presented in this paper, the bullous eruption, in a patient taking penicillamine for systemic sclerosis, was diagnosed as penicillamine-induced pemphigus foliaceus.

- A man with a history of penicillin allergy developed a hypersensitivity reaction of the penis when his wife was taking penicillamine (259).

Effects on collagen and elastin

When penicillamine is administered for a long time and in high doses (for example for Wilson's disease) it can cause a characteristic delayed skin eruption, with increased friability, hemorrhagic bullous lesions, and miliary papules (66,260–266). The lesions develop predominantly in those parts of the skin that are often exposed to trauma. This disorder is a manifestation of the effects of penicillamine on collagen and elastin. Occasionally, these eruptions imitate other rare

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dermatological diseases and take the shape of elastosis perforans serpiginosa, cutis hyperelastica (cutis laxa) (267), or pseudoxanthoma elasticum (268–270); however, the histological and ultrastructural characteristics of the penicillamine variants differ from those of the spontaneous disorders.

In delayed penicillamine skin disorders, abnormal elastic tissue also exists in non-lesional skin, and has occasionally been documented in other organs (lungs, blood vessels, ileum, visceral adventitia, joint tissue), but the clinical implications of these findings are uncertain. In one study, multiple lymphangiectases and bloodvessel-lymphatic anastomoses were observed (263). Clinically manifest impairment of collagen and elastin has been reported in association with much lower penicillamine doses than had previously been recognized (271–273). In five of eight patients receiving penicillamine for rheumatoid arthritis, there was elastic fiber damage in joint capsules, suggesting that penicillamine-associated collagen injury may be common (273), although in only one case there was also elastic fiber damage in a skin biopsy. The fact that the lesions in delayed penicillamine skin disorders concentrate in flexural areas (neck, axillae, antecubital fossae, and buttocks) may reflect the accelerated turnover rate of elastin in these areas, secondary to shearing stresses and stretching. Perhaps impairment of collagen interferes with wound healing.

Presumably, the mechanism underlying penicillamine dermopathy is inhibition by penicillamine of cross-linkage of collagen fibers. In addition, the enzyme lysyl oxidase, required for the cross-linking of collagen fibers, is copper-dependent and may be inhibited by copper chelation by penicillamine. Another argument for a possible role of copper deficiency is the fact that cutis laxa is common in Menke's disease, a rare genetically determined disturbance of copper metabolism. Perforating elastoma occurs when abnormal elastic fibers accumulate, cause a foreign body reaction, and are transepidermally eliminated. Although the patient was also thought to have elastolytic involvement of the lining of the upper respiratory tract, there was no objective evidence of this.

Elastosis perforans serpiginosa, cutis laxa, and pseudoxanthoma elasticum

In rare cases, penicillamine dermopathy mimics elastosis perforans serpiginosa, cutis laxa, or pseudoxanthoma elasticum.

Elastosis perforans serpiginosa

Elastosis perforans serpiginosa starts as red umbilicated papules that coalesce to form annular (serpiginous or arcuate) lesions with clear centres. There are microscopically thickened coarse elastic fibers, extruding through narrow epidermal channels.

- A 37-year-old Japanese woman, who was taking penicillamine (500 mg/day) for systemic sclerosis, developed papules distributed in characteristic arcuate patterns of the skin of her neck (274). Histologically there was transepidermal elimination of degenerative elastic particles.

Cutis laxa

Cutis laxa presents with loose redundant skin folds, reduced elasticity of the skin, and connective tissue involvement.

- An 84-year-old woman, who had been taking penicillamine 1.2 g/day for 50 years for Wilson's disease, developed generalized, rapidly progressive, acquired cutis laxa (275). Faulty production of collagen and elastin fibers lead to gross folding of the skin, giving it an appearance reminiscent of the folds of the cerebral cortex.

In one patient the characteristic features of both of elastosis perforans serpiginosa and cutis laxa developed (276).

- A 36-year-old man, who had had Wilson's disease since the age of 4 years, had used penicillamine for about 13 years in a dosage of 2–3 g/day. He developed an itching papular eruption, which initially resolved after withdrawal of the drug but recurred and progressed 6 months later. Generalized cutis laxa developed, with perforating elastolytic nodules on the neck and elastosis perforans serpiginosa over the shoulders. A biopsy showed perforating channels from the dermis through the epidermis, with a surrounding inflammatory infiltrate and horseshoe-shaped multinuclear giant cells phagocytosing abnormal elastic fibers. Van Giesen staining showed a lumpy-bumpy appearance of elastin fibers, typical of penicillamine dermopathy, as originally described by Bardach et al. (SED-14, 730).

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum is characterized by coalescent yellow waxy papules with a "plucked chicken" appearance (because of the prominence of follicular orifices in the papules) and a marked laxity and wrinkling of the skin, resulting in redundant skin folds. In delayed penicillamine skin disorders gross abnormalities of elastic and collagen fibers are seen on electron microscopy. Elastic fibers have "moth-eaten," "saw-toothed," or "bramble bush thorns" appearances. Collagen fibers show large differences in thickness. Elastic tissue stains show an increase in the number of elastic fibers and irregular serrated fibers. The elastin content of lesional skin is three times greater than normal, whereas the number of elastin cross-links is only 15% of normal. In electron photomicrographs, dermal elastic fibers are studded with multiple perpendicular buds of different sizes and shapes, described as "lumpy-bumpy" and show varying degrees of fragmentation. Aggregations of granular elastinophilic material surround the central core of normal mature elastic tissue. In contrast to spontaneous pseudoxanthoma elasticum there is no calcium deposition in elastic fibers.

- A 47-year-old man had been using penicillamine 1.5 mg/day for 18 years for Wilson's disease. He developed pseudo-pseudoxanthoma combined with dysphagia and dyspnea. Biopsy specimens showed systemic involvement of elastic fibers, including skin, lung, esophageal muscle, gum, and pharyngeal and cervical connective tissue. All biopsies showed abnormal elastic fibers, consisting of a central core of uneven thickness with many lateral arborizations. There were branches at

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right angles to the main fibers, with perpendicular lateral arborizations off these, producing a stag-horn or fractal appearance. On the other hand, the adjacent collagen fibers were normal in structure.

Pseudo-pseudoxanthoma elasticum, caused by the use of high doses of penicillamine, has also been described (277).

Wound healing

In the past, penicillamine, because of its effects on collagen synthesis, has been suspected of interfering with normal wound healing. Experience of 217 operations in 150 patients did not show such effects, and consequently, there does not seem to be a need for stopping penicillamine before surgery (278). On the other hand, a few reports have suggested that penicillamine can, at least in some patients, have deleterious effects on wound healing (177,279).

Pemphigus

Pemphigus is a bullous autoimmune disorder of the skin, characteristically associated with antidesmoglein antibodies. Although many different drugs have been described as a cause of pemphigus, there is a remarkably strong predominance of penicillamine (and other sulfhydryl compounds) (280–283). Three groups of pemphigus-inducing drugs can be distinguished (284):

1. thiol drugs (for example penicillamine);
2. "masked thiol drugs" (sulfur-containing drugs that undergo metabolic changes to form thiol groups, for example piroxicam, beta-lactam compounds);
3. drugs with an active amide group (for example dipyrone, enalapril).

Thiol-related pemphigus usually presents as the foliaceus variant, with comparatively few immunofluorescence findings and a good prognosis, whereas drugs with an active amide group can provoke pemphigus vulgaris with a less favorable prognosis on drug withdrawal. A pemphigus-like eruption (284–297) develops in 1–2% of the users of penicillamine (SEDA-11, 213). Penicillamine is by far the most frequent cause of the drug-related variant.

- A 71-year-old woman taking penicillamine (dosage not specified) developed pemphigus vulgaris rather than pemphigus foliaceus, which is the usual form of pemphigus that penicillamine causes (298). She presented with pustular bullae (due to secondary infection with *Pseudomonas aeruginosa*), and the indication for penicillamine was not rheumatoid arthritis but systemic sclerosis.
- A 64-year-old woman, who had used penicillamine 500 mg/day for 3 years for rheumatoid arthritis, developed a bullous skin eruption affecting her neck and limbs (299). After treatment with prednisolone (dose not specified) she improved, but relapsed when the dose was reduced below 10 mg. Eleven months after the onset of blistering, penicillamine was discontinued and within 2 months the prednisolone was also stopped, with no recurrence of the eruption during 12 months follow-up. Direct immunofluorescence was positive for immunoglobulin G and complement component C3, and indirect immunofluorescence was positive on the roof of the NaCl split skin preparation.

A consultation of the database of the Committee on Safety of Medicines in London showed that 41 cases of bullous pemphigoid have been reported in suspected connection with penicillamine, suggesting that this adverse reaction is less rare that the published literature suggests.

Pemphigus usually recedes when penicillamine is stopped, but can persist for many years (286,296), and recur on rechallenge (300); fatal cases have occurred (301,302). Pemphigus that continues after drug withdrawal is referred to as triggered pemphigus, whereas a reaction that clears soon after withdrawal is called induced pemphigus (285). Although it is usually rapidly reversible, penicillamine-induced pemphigus can run a protracted course (SED-14, 730). In a report from the Netherlands, penicillamine-related pemphigus foliaceus was highly resistant to treatment for 7 years (303). Eventually the intravenous administration of low doses of normal human immunoglobulin (40 mg/kg/day for 5 days in cycles of 3 weeks), together with dexamethasone pulse therapy, led to remission.

The entire clinical and pathological spectrum of pemphigus can occur in association with penicillamine, that is pemphigus erythematosus, pemphigus foliaceus, pemphigus vulgaris, and bullous pemphigoid (297). In this order of sequence the level of blister formation descends from the superficial layers to the deeper layers of the epidermis toward the basement membrane and subepidermal tissue. Penicillamine-induced pemphigus is predominantly of the foliaceus type. As in spontaneous pemphigus, antidesmoglein antibodies are present, although they may not be found in early stages. In pemphigus vulgaris antibodies react with desmoglein 3 and in pemphigus foliaceus with desmoglein 1, suggesting that different antigens are involved (304,305). The antibody reactivity of patients with idiopathic and penicillamine-related pemphigus appeared to be the same (284), which is suggestive of a similar basic molecular mechanism. Sometimes the characteristic lesions of different eruptions, for example pemphigus, bullous or cicatricial pemphigoid, lupus erythematosus, discoid lupus, or seborrheic dermatitis, can be seen in one and the same patient taking penicillamine (SEDA-11, 213) (SEDA-15, 239) (300). This suggests differences in the pathogenic process rather than the simultaneous occurrence of different reactions.

Penicillamine has epidermotropic properties and accumulates in the skin. There are several possible mechanisms involved in penicillamine-induced pemphigus (SED-12, 544):

- penicillamine may cause acantholysis by direct destruction of epidermal intercellular attachment (without pemphigus antibodies) (306–308);
- the drug may induce autoantigens through modification of epidermal differentiation or interaction with epidermal tissues;
- penicillamine may change immunological tolerance, influence T-suppressor cells, and elicit autoimmune responses (280,281).

There is still uncertainty about the precise underlying processes. Apart from a reduced frequency of the rheumatoid arthritis-associated antigen B15, penicillamine-induced

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pemphigus does not appear to be strongly associated with a characteristic HLA antigen pattern (309,310).

Penicillamine-induced pemphigus can pose diagnostic difficulties, for example because it can present as a nonspecific rash, seborrheic dermatitis, erythema annulare (311), isolated stomatitis, or even rhinitis (65). Because of the friability of the superficial blisters, the bullous nature of pemphigus erythematosus and pemphigus foliaceus may be overlooked.

Since beta-lactam antibiotics also appear to be associated with pemphigus, especially ampicillin and amoxicillin, an earlier hypothesis (SEDA-5, 244) that this (and perhaps other reactions) to beta-lactam antibiotics may in fact be induced by the hydrolytic metabolite penicillamine has received attention (280,283).

A rare but potentially serious skin reaction to penicillamine is cicatricial pemphigoid (312,313). These patients can have symblepharon and entropion of the eyes, ulcers in the mouth, and blistering lesions on the trunk, extremities, and perineum (314). Involvement of the esophageal or vaginal epithelium can cause stenosis.

Ulcerative lesions of the vagina can occur in patients taking penicillamine, as a manifestation of pemphigus or cicatricial pemphigoid, or following impaired collagen synthesis (SED-8, 533) (315).

Graft-versus-host-like eruptions

Although rarely described, skin reactions that mimic graft-versus-host disease are an established complication of penicillamine (SED-14, 731). The similarity of the pathology of these drug-induced eruptions to those that occur after bone marrow transplantation has been reviewed (316). The drug-related eruptions may have different manifestations and can, for example, resemble smallpox, lichen planus (317), eczema, or other eruptions (318). However, their histological features are similar to those seen in cutaneous graft-versus-host disease, in particular eruptions in which liquefactive necrosis is seen at the interface between the epidermis and the cutis. One of the possible mechanisms involved in hypersensitivity reactions to sulfhydryl-containing drugs is based on the immune response of T cells to the sulfhydryl group, which arises when binding of IL-2 to the IL-2 receptor induces autoreactive T cells (319). The concentrations of IL-2 and IL-2 receptor were closely associated with the onset and severity of cutaneous graft-versus-host disease, suggesting an etiological similarity between the disease and skin eruptions induced by sulfhydryl-containing drugs. Proliferation of autoreactive T cells is induced by the binding of IL-2 to its receptor in these patients.

With seven cases in 56 consecutive patients taking penicillamine in one study, oral lichen planus may be fairly frequent (179). Most patients have erosive oral lichen planus, but bullous, plaque-like, or "classic" lichen planus can occur. Rarely a psoriasiform eruption has been reported with penicillamine (320).

Hair

Alopecia has occasionally been reported in association with penicillamine (145), but is ill-understood; hair loss can occur in association with polymyositis (321).

Nails

The peculiar yellow nail syndrome (SEDA-9, 223), characterized by dystrophy of the nails, lymphedema, pleural effusion, and bronchial involvement, has occasionally been reported in association with penicillamine and also with bucillamine (SEDA-9, 223) (SED-13, 612) (322–325). It has been suggested that penicillamine and bucillamine, because of their structural similarity to cysteine, might disturb nail growth by interfering with keratin synthesis. Although the nail changes and injury to other organs probably develop by different mechanisms, in patients with nail changes a careful search for possible systemic disorders is needed.

Monosymptomatic nail changes, with longitudinal ridging, transverse or longitudinal defects of the nail plate, absence of lunulae, and a tendency toward onychoschizia, can also occur as adverse effects of penicillamine (326).

Musculoskeletal

Joint symptoms in patients taking penicillamine vary from "creaking" and subjective discomfort and worsening of joint pain to severe arthralgia (327–329). Paradoxical acute severe exacerbation of rheumatoid arthritis has been reported in three patients, probably induced by penicillamine (330). Arthritis can also be a manifestation of penicillamine-induced systemic lupus erythematosus.

Although rare, Wilson's disease may itself be associated with a polyarthritis resembling rheumatoid arthritis and when it develops during the use of penicillamine it can be mistaken for an adverse reaction to the drug (331). Demineralization osteopathy has been reported in a study on the use of D-penicillamine in Wilson's disease (SED-8, 536).

- Progressive eosinophilic fasciitis with muscular involvement in a 35-year-old Brazil woman has been attributed to penicillamine (250 mg/day) (332).

In a prospective analysis of 74 women with systemic sclerosis, low bone mineral density and densitometric osteoporosis were related to the menopause and not to the previous use of penicillamine or other drugs (333).

Reproductive system

Gigantism of the breasts (macromastia) can occur in patients using penicillamine (SEDA-8, 238) (255,334–338). It usually develops in women and very rarely as gynecomastia in men (337,339). There is resemblance to the pubertal form of massive breast enlargement. It can be painful and has been encountered in pre- and postmenopausal women, with normal and increased prolactin concentrations. Histological examination mainly shows increased connective tissue and no changes in the glandular tissue.

- In one patient, the breasts were tender and grew progressively larger during each menstrual period.
- A 55-year-old premenopausal woman took penicillamine 1 g/day for 2 years for localized scleroderma (340). She used no other drugs. She noticed a gradual enlargement of her breasts, from a size B to size D+ bra cup. There were no palpable masses or tenderness. The only abnormal laboratory test finding was a positive test

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for homogeneous antinuclear antibodies (titer < 1:80), which is often found in patients with scleroderma. Serum prolactin was normal. Penicillamine was withdrawn and the breast enlargement regressed over 3 months; the bra cup size reverted to B.

- In a 25-year-old woman with Wilson's disease, treatment with penicillamine (1.5 g/day) was first followed by the development of hirsutism, mainly of the face (255). After she started to use an oral contraceptive, her breasts enlarged rapidly and she experienced cyclic mastodynia; in addition, gingival hyperplasia developed. All symptoms improved on withdrawal of penicillamine, but additional mammoplasty was needed.

The sequence of events in the last patient suggested that the use of the oral contraceptive contributed to the development of macromastia.

In one case breast enlargement was accompanied by systemic lupus erythematosus (341).

- A 37-year-old woman with a 7-year history of rheumatoid arthritis had taken penicillamine for about 1–2 years (dose not specified). When she presented at the Cambridge Breast Unit she had had rapidly increasing painful enlargement of the breasts for 7 months. The breasts were symmetrically enlarged (from an A cup to DD) and had thickened and erythematous skin. There were several palpable masses; mammography showed no evidence of malignancy and an ultrasound scan showed large hypo-echoic nodules with engorged vessels. Histology of a large lump in the left breast showed a fibroadenoma. Immunohistochemistry for estrogen receptors showed 50% nuclear staining. She had stopped taking penicillamine 2 months before because of a lupus-like syndrome with thrombocytopenia, lymphopenia, and positive ANA and DNA antibodies (whether single-stranded or double-stranded was not stated).

Although breast gigantism is a rare manifestation of idiopathic SLE, in this case autoimmune substances could have stimulated mammary duct proliferation or mimicked estrogen or other growth factors in the breast.

Immunologic

Several experimental studies in humoral and cell-mediated immune systems have demonstrated numerous effects of penicillamine on the immune system; these findings are in keeping with a reduction in the overactivity of helper T lymphocyte that is found in rheumatoid arthritis (2,342). There is a fall in the numbers of immunoglobulin-secreting cells, and cultured mononuclear cells produce less IgA, IgG, and IgM. There is suppression of the autologous mixed lymphocyte reaction (343) and reduced hydroxyl radical generation from polymorphonuclear leukocytes (344). Penicillamine reduces the clearance of immune complexes and inhibits the complement cascade (345).

Penicillamine is uniquely likely among therapeutic drugs to cause autoimmune reactions (see Table 3).

Clinically and pathologically these variants of autoimmune disorders are closely similar to or indistinguishable from the spontaneous diseases. A major difference is that the patients usually recover when penicillamine is withdrawn. Differences in HLA configurations also suggest that penicillamine-induced and spontaneous autoimmune disorders occur in different populations.

Table 3 Autoimmune-like reactions reported in suspected association with penicillamine

Pemphigus (erythematosus, foliaceus, vulgaris)
Bullous pemphigoid, cicatricial pemphigoid
Graft-versus-host-like skin eruptions
Myasthenia gravis
Dermatomyositis/polymyositis
Glomerulonephritis
Lupus-like syndrome
Goodpasture's syndrome
Autoimmune hypoglycemia
Thyroiditis
Sjögren's syndrome
Aplastic anemia
Thrombocytopenia
Agranulocytosis
Thrombotic thrombocytopenic purpura (Moschcowitz's syndrome)
Evans' syndrome
Churg–Strauss syndrome
Necrotizing vasculitis
Guillain–Barré syndrome

During penicillamine treatment autoantibodies develop in a high proportion of patients without clinical disease (346). For example, penicillamine can be associated with the development of anticentromere antibodies (347,348). Although these are usually a marker of serious autoimmune diseases, in association with penicillamine, the phenomenon was not accompanied by clinical symptoms and disappeared after stopping the drug.

In the serum of three patients with acute hypersensitivity reactions to penicillamine, complement-binding antibodies against penicillamine were detected (349). Patients with Wilson's disease are not known to have an abnormal immune status. The striking variability of penicillamine-induced pathology, including autoimmune reactions such as SLE, is also seen in patients with Wilson's disease, but the proportion of these patients in whom withdrawal is necessary is smaller, about 2–8% (72,79,80,350).

An unusual case report showed that low back pain can be a manifestation of drug hypersensitivity (253).

Anaphylaxis

Although hypersensitivity reactions are frequent, systemic anaphylaxis has only been reported rarely (351).

ANCA-positive vasculitis

Various vasculitic diseases, including Wegener's granulomatosis, microscopic polyangiitis, Churg–Straus syndrome, and crescentic glomerulonephritis, are associated with antineutrophil cytoplasmic antibodies (ANCA) or leukocytoclastic vasculitis. In drug-induced ANCA-positive vasculitis antimyeloperoxidase antibodies are most often found; they produce a perinuclear pattern of staining by indirect immunofluorescence (pANCA), but antiproteinase 3 (anti-PR3) antibodies can also occur (cANCA).

The possible drug causes of ANCA-positive vasculitis with high titers of antimyeloperoxidase antibodies in

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30 new patients have been reviewed (124). The findings illustrate that this type of vasculitis is a predominantly drug-induced disorder. Only 12 of the 30 cases were not related to a drug. The most frequently implicated drug was hydralazine (10 cases); the rest involved propylthiouracil (three cases), penicillamine (two cases), allopurinol (two cases), and sulfasalazine.

- A 49-year-old woman with systemic sclerosis, taking penicillamine 750 mg/day, developed a vasculitis, with an orbital pseudotumor and, 2 months later, fatal alveolar hemorrhage. She also had antinuclear antibodies with a homogeneous pattern.
- A 56-year-old woman with systemic sclerosis taking penicillamine 750 mg/day had homogeneous antinuclear antibodies and antibodies to native DNA. Her manifestations of vasculitis were glomerulonephritis with renal insufficiency, pulmonary hemorrhage, and bilateral hemothorax (that is similar to Goodpasture's syndrome).

As the authors pointed out, practically all drugs known to cause ANCA-positive vasculitis (including penicillamine) have also been associated with a lupus-like syndrome, suggesting the possibility of a similar underlying mechanism. However, the presence of discriminating markers (such as anti-elastase and antilactoferrin antibodies) in drug-induced ANCA-positive vasculitis, but not in idiopathic cases, is suggestive of different pathways in these conditions.

In three Japanese patients with penicillamine-associated glomerulonephritis, antimyeloperoxidase ANCA assays were strongly positive (352). These patients had been taking penicillamine for rheumatoid arthritis in daily doses of 100, 200, and 300 mg for 32, 42, and 39 months respectively. All three had proteinuria, hematuria, anemia, and rapidly progressive renal insufficiency. Histological examination showed crescentic glomerulonephritis with granular deposits of IgG, IgM, IgA, C1q, and C3 in the mesangium. Penicillamine was withdrawn and the patients were given steroid pulse therapy, warfarin, and in two cases cyclophosphamide. Renal function gradually improved and the antineutrophil cytoplasmic antibodies disappeared.

- In a 69-year-old man with penicillamine-induced crescentic glomerulonephritis ANCA tests were repeatedly negative (353). He had been taking penicillamine up to 750 mg/day for systemic sclerosis.

Churg–Strauss syndrome

The Churg–Strauss syndrome is a rare disease, with eosinophilia, vasculitis, and granulomas, involving many organ systems (skin, lungs, kidneys, gastrointestinal tract, joints, heart, and central nervous system); rhinitis and asthma are often early manifestations. In one of two patients with the syndrome, penicillamine might have triggered its development (64); however, withdrawing the drug had no effect on the course of the disease and the relation was therefore uncertain.

Dermatomyositis and polymyositis

Penicillamine can cause other serious autoimmune reactions involving the muscles: dermatomyositis, with its characteristic facial rash (354), and polymyositis (56,95,96,321,355–366). Effects vary from only biochemical abnormalities, through moderate muscular weakness, to severe polymyositis with myolysis and sometimes myocarditis. There can be dysrhythmias, heart block, and Adams–Stokes attacks (362) and deaths have occurred (96). Muscle weakness can cause secondary respiratory failure (56,321). The clinical, pathological, and electromyographic features are similar to those of idiopathic polymyositis.

Antinuclear antibodies are found in about 90% of cases of penicillamine-induced polymyositis, a finding that may be helpful in distinguishing this condition from true polymyositis (357). In one patient anti-Jo-1 antibodies were found, which was thought to be an epiphenomenon and not pathogenic (78). Myositis occurs in about 1% of patients taking penicillamine and appears to be relatively common in Japanese and Indian patients (SEDA-15, 240) (23,355,363). HLA investigations showed that the antigens DR2 and DQwl are increased in patients with penicillamine-induced myositis, suggesting that myositis occurs in a specific genetic subgroup (363). Of interest is the report of a patient with penicillamine-associated polymyositis who had a relapse after administration of ampicillin (358).

In penicillamine-induced polymyositis, weakness can be the presenting symptom and it may at first be mistaken for myasthenia (56).

The diagnostic pitfalls of penicillamine-induced polymyositis have been reviewed in the light of a report of a patient in whom postural changes were at first mistaken for possible ankylosing spondylitis (367).

IgA deficiency

IgA deficiency is a rare penicillamine-induced immune disorder, which can be accompanied by recurrent upper respiratory tract infections (67,68,368). IgA deficiency is more likely to develop when there is improved rheumatic disease activity, together with other adverse effects (for example rash, thrombocytopenia, proteinuria).

Lupus-like syndrome

Serological features of systemic lupus erythematosus develop in about 7% of patients taking penicillamine (172,227,249–251,369). A clinical lupus-like syndrome is less frequent (about 2%) and is as frequent in rheumatoid arthritis as in Wilson's disease. Characteristic phenomena are polyarthropathy, rash, pleurisy, fever, leukopenia, thrombocytopenia, antinuclear antibodies, and LE cells. The syndrome can be associated with antibodies to native DNA, renal damage, and neurological symptoms. The disorder usually improves in a few weeks or months after stopping penicillamine, but serological tests may remain abnormal for a longer period. Also, type II bullous systemic lupus erythematosus has been attributed to penicillamine (252). Penicillamine is no longer used in juvenile rheumatoid arthritis, in particular because of lack of effect and the possibility of inducing a lupus-like syndrome (370).

- A 6-year-old Taiwanese girl, who had taken penicillamine (dosage not specified) for Wilson's disease for 17 months, developed arthralgia, fever, and oral ulcers (371). She had antinuclear antibodies with a homogeneous pattern at a dilution of 1/5120, and a direct

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Coombs' test was positive. On the other hand, anti-DNA antibodies were within the reference range and antibodies against non-histone nuclear antigens (Sm, RNP, SS-A/Ro, SS-B/La, Scl-70) were all negative. She improved with prednisolone, and penicillamine was continued in a lower dosage.

Sjögren's syndrome

There have been two reports of Sjögren's syndrome (keratoconjunctivitis sicca, xerostomia, swelling of the parotids) in suspected association with penicillamine (372,373). In one study, reference was made to a patient with a Henoch–Schönlein-like syndrome as a suspected adverse reaction to penicillamine, but no details were given (374).

Multiple autoimmune reactions

Penicillamine often elicits multiple adverse reactions in the same patient, illustrating its immunomodulatory actions. Examples are listed in Table 4.

In a long-term prospective study of 69 patients taking penicillamine (750 mg/day) for progressive systemic sclerosis, 27 had adverse effects requiring either temporary reduction or complete withdrawal of therapy. Five of these had two, or, in one case, three different reactions (115).

- A 47-year-old woman developed concurrent pemphigus and myasthenia gravis (with ptosis and diplopia), apparently induced by penicillamine (500 mg/day for rheumatoid arthritis) (376).

In another patient, pemphigus, polymyositis, and myasthenia gravis developed simultaneously (111).

- A 67-year-old patient with rheumatoid arthritis had taken penicillamine 600 mg/day for 15 months when a skin eruption developed. Although no intercellular substance or basement membrane antibodies were found, a biopsy showed characteristic intraepidermal blistering. Direct immunofluorescence showed anti-IgG and anti-C3 antibodies, and desmoglein immunolabelling (32–2B) favored drug-induced pemphigus. In addition, acetylcholine receptor antibodies were found. After the withdrawal of penicillamine there was rapid improvement of pemphigus and myasthenia. However, polymyositis was progressive, required high doses of corticosteroids for about 18 months, and improved only slowly.

Table 4 Examples of simultaneous multiple reactions reported with penicillamine

Pulmonary alveolitis, pancytopenia, cholestatic hepatitis, stomatitis, proctitis, skin rash, proteinuria, renal insufficiency (52)
Cholestatic hepatitis with allergic pneumonitis (186)
Pemphigus and nephrosis (minimal change nephropathy) (375)
Pemphigus and myasthenia gravis (376)
Thyroiditis and myasthenia gravis (125)
Polyradiculopathy and nephrosis (70)
Aplastic anemia and cholestatic hepatitis (162)
Gingival hyperplasia, acne, hirsutism, breast gigantism (255)
Agranulocytosis and toxic epidermal necrolysis (167)

Desensitization

The National Taiwan University Hospital has reported successful desensitization with prednisolone in a patient with hypersensitivity to penicillamine (377).

- A 14-year-old boy with Wilson's disease had a rash, fever, and angioedema repeatedly after the administration of penicillamine (600 mg/day). He was given prednisolone 30 mg/day for 2 days and then 20 mg/day. He was given penicillamine in an initial dose of 300 mg/day, which was increased to 600 mg/day in increments of 150 mg over 3 days and subsequently to 900 mg/day. Prednisolone was gradually discontinued over a 4-week interval, and penicillamine was increased to 1.2 g/day without further problems.

Infection risk

In a nested case-control study in Mexican patients with rheumatoid arthritis encompassing 1274 patient years, the risk factors were determined for acquiring infectious diseases (378). In addition to the cumulative doses of methotrexate and the duration of corticosteroids use, the mean daily dose of penicillamine was a risk factor. In one patient the infection was secondary to neutropenia. Tests for a possible immunoglobulin deficiency were not performed.

Long-Term Effects

Mutagenicity

In one experimental study it has been suggested that penicillamine may be mutagenic (379).

Tumorigenicity

There are a few case reports of lymphatic malignancies in patients using penicillamine, but epidemiological data in support of the association are lacking (SEDA-7, 259) (380–382).

Second-Generation Effects

Teratogenicity

Whereas the benefits of penicillamine outweigh the risk in patients with Wilson's disease and probably cysteinuria, there have been a few reports of congenital injury attributed to the use of penicillamine, notably congenital cutis hyperelastica with a fatal course in three infants. Penicillamine should be withdrawn during pregnancy in patients with rheumatoid arthritis (383–385). It should be added, however, that in Wilson's disease it is also worth considering if it is possible to control copper metabolism with less penicillamine or without it altogether.

- A baby with a bilateral cleft lip with total cleft palate was born at 41 weeks to a 22-year-old mother who had taken penicillamine (dosage not specified) throughout an uncomplicated pregnancy for Wilson's disease (386). The child did not have a lax skin.

This case was found as part of a case-control study of 24696 mothers of malformed infants. It was the only case of penicillamine exposure in the entire series.

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However, cleft lip has not previously been observed in association with maternal use of penicillamine, and there is little reason for suspecting the drug.

Susceptibility Factors

Genetic factors

Several studies have shown an increased frequency of penicillamine adverse effects in patients with low sulfoxidation activity, especially with regard to proteinuria and probably thrombocytopenia and myasthenia gravis (SED-12, 547) (3,196,387,388). The sulfoxidation capacity is expressed as the sulfoxidation index, calculated as the percentage of administered *S*-carboxymethyl-L-cysteine (750 mg), excreted as sulfoxides in the urine in 8 hours. A sulfoxidation index above 6% is taken as indicative of relative impairment of sulfoxidation capacity.

Certain adverse reactions to penicillamine are associated with increased or decreased frequencies of HLA antigens (SEDA-8, 235) (SEDA-11, 212) (22,389–396). Most consistently reported are the associations between proteinuria and the antigens B8 and DR3 and between thrombocytopenia and DR4. These associations are not strong enough to include HLA typing into the routine of treatment with penicillamine. The relative risk of toxicity for patients possessing either HLA-DR3 or poor sulfoxidation appeared to be 25 as compared with those possessing neither; if these tests could be simplified, a valuable opportunity would become available for identifying patients at risk (202,387). Racial factors may be involved: proteinuria is less frequent in Japanese people, whereas polymyositis occurs at an increased frequency in India and Japan (202,330).

Age

Although published experience in children is limited, penicillamine has the same pattern of adverse effects as in adults. However, an interesting difference is that taste dysfunction has so far not been reported in children (SED-10, 221) (SEDA-14, 198). In two children with Wilson's disease, penicillamine was thought to have caused persistence of a pre-existing increase in amintransase activity (187).

Other features of the patient

Patients with previous hypersensitivity to penicillin are more likely to experience a rash when taking penicillamine. Cross-allergy to penicillin can occur, but the risk of a severe allergic reaction to penicillamine in penicillin-allergic patients is thought to be low. An important measure to reduce the frequency of adverse reactions of penicillamine is to start with a small dosage (for example 125 mg/day in rheumatoid arthritis), to increase the dosage only slowly, and to maintain treatment with the lowest effective dosage. Nevertheless, serious complications such as nephrosis, pemphigus, alveolitis, and polymyositis have occurred while only 250 mg/day or less was used (SEDA-8, 235) (50,182,355).

The absorption of penicillamine can be significantly altered by alimentary factors. Changing habits, for example taking penicillamine between meals instead of with food, or stopping iron supplements, can precipitate adverse reactions by increased absorption.

Early hypersensitivity reactions are usually transient, and although there is undoubtedly an increased risk, in patients with a history of previous adverse reactions to penicillamine (or gold), re-exposure may not be followed by a relapse (SEDA-10, 218). In the case of serious complications, such as agranulocytosis, profound thrombocytopenia, polymyositis, or Goodpasture's syndrome, the repeated use of penicillamine carries unacceptable risks. Commencing penicillamine in patients with Wilson's disease can aggravate or even precipitate neurological involvement.

Antibodies to the Ro(SSA) cellular antigen (244,397) and circulating cryoglobulins (244) are risk factors for adverse reactions to penicillamine. AntiRo (SSA) antibodies characterize a distinct group of patients with rheumatoid arthritis who are almost exclusively female, express more activated B cell function, have a high prevalence of Sjögren's features, and commonly develop adverse reactions to penicillamine. Rashes and febrile reactions were especially associated with anti-Ro(SSA) antibodies, and renal pathology was more frequent in men (244).

Drug–Drug Interactions

Antacids

Antacids that contain aluminium or magnesium can reduce the absorption of penicillamine by up to 45%, presumably because increased gastric pH favors oxidation to the poorly absorbed disulfide (182,398,399).

Iron compounds

Iron compounds reduce the systemic availability of penicillamine to about 35% and copper excretion to about 28%, probably as a result of catalysis of the oxidation of penicillamine to its disulfide (2,398,400). Even the iron present in certain multivitamin formulations can be sufficient to cause interference, and when a patient who has regularly taken iron stops taking it, increased absorption of penicillamine and adverse effects can ensue (401,402).

Probenecid

When probenecid is co-administered with penicillamine in cystinuria, the efficacy of the penicillamine is significantly reduced (403).

Interference with Diagnostic Tests

Alpha-1 antitrypsin

Penicillamine can cause an artificially abnormal alpha-1 antitrypsin protein pattern, which can result in diagnostic errors (404).

Diagnosis of Adverse Drug Reactions

Reporting adverse reactions

The organization and preliminary results of an intensified voluntary reporting system for rheumatologists in the UK

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West Midlands for studying the safety of DMARDs have been described (405).

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Penicillins

See also Beta-lactam antibiotics

General Information

The basic structure of the penicillins consists of a thiazolidine ring, the beta-lactam ring, and a side chain. The beta-lactam ring is essential for antibacterial activity. The side chain determines in large part the antibacterial spectrum and pharmacological properties of a particular penicillin. The rapid emergence of bacteria, particularly *Staphylococcus aureus*, that produce beta-lactamases (penicillinase) has been partly countered by the development of compounds that resist hydrolysis by beta-lactamases and compounds that are more active than penicillin G against Gram-negative species. This has led to the production of many semisynthetic penicillins, the first of which was meticillin, active against beta-lactamase-producing *S. aureus*; followed by ampicillin, active against selected Gram-negative bacilli; carbenicillin, which has activity against *Pseudomonas aeruginosa*; and subsequently many agents with different pharmacological and antimicrobial properties. Some of the more important penicillins are listed in Table 1. Another method of combating beta-lactamase-producing organisms has been the development of beta-lactamase inhibitors.

Clinical experience with penicillins, especially penicillin G and the aminopenicillins, is extensive. These substances are rarely toxic, even when they are given in an extended range of dosages, making them invaluable for use in pregnant women and children. Their major limitation is their propensity to cause allergic reactions.

Use in non-infective conditions

In spite of the fact that most trials of antibiotics in pregnancy have shown that antibiotic administration prolongs pregnancy, the mechanism is unclear. However, it is well established that several antibiotics can alter intracellular calcium concentrations (1–3) or inhibit some enzymes, including various phospholipases (4). It is also well established that bacterial products, such as phospholipases and

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Table 1 Some penicillins (all rINNs except where stated)

Beta-lactamase sensitive penicillins	Broad-spectrum penicillins	Beta-lactamase resistant penicillins	Antipseudomonal penicillins
Benzylpenicillin (penicillin G)	Ampicillin	Flucloxacillin	Piperacillin
Benzylpenicillin benethamine	Amoxicillin	Meticillin (pINN)	Ticarcillin (pINN)
Penicillin G procaine	Azlocillin	Oxacillin	
Phenoxymethylpenicillin (penicillin V)	Mezlocillin	Cloxacillin	
	Piperacillin	Dicloxacillin	

endotoxins, can stimulate prostaglandin biosynthesis and release by the human amnion (5). Therefore, because prostaglandin biosynthesis depends on the action of phospholipase A2, a calcium-dependent enzyme (4), it has been hypothesized that antibiotics that interfere with phospholipase A2 might affect prostaglandin biosynthesis and release by the amnion. This hypothesis has been tested by evaluating the effect of ampicillin on the release of prostaglandin E from human amnion (6). The results were clear: ampicillin dose-dependently inhibited the release of prostaglandin E from human amnion in vitro. Moreover, ampicillin reversibly counteracted the rise in prostaglandin E induced by arachidonic acid or oxytocin. The authors concluded that inhibition of prostaglandin E release from amnion is a mechanism whereby ampicillin might prevent some cases of premature delivery, even in the absence of infection.

General adverse effects

Non-allergic reactions to penicillins occur mainly with high doses or are related to renal insufficiency. They consist of convulsions or electrolyte disturbances, with hyperkalemia or sodium retention. The penicillinase-resistant and broad-spectrum penicillins can cause specific adverse reactions. Leukopenia, agranulocytosis, liver damage, and some cases of nephropathy are considered to be due to toxic rather than to allergic mechanisms. Diarrhea is a common complication, whereas severe antibiotic-associated colitis is rare. Hypersensitivity reactions are of great importance and are dealt with in the monograph on beta-lactam antibiotics. They range from mostly harmless skin reactions to life-threatening immediate reactions, including anaphylactic shock, acute bronchial obstruction, and severe skin reactions. Tumor-inducing effects have not been described.

Organs and Systems

Respiratory

Bronchospasm may be a consequence of penicillin allergy (7–12). Acute severe dyspnea with cyanosis has also been observed without symptoms of bronchial obstruction or pulmonary edema (13). Specific mechanisms for such cases have yet to be identified.

Allergic pneumonitis and transient eosinophilic pulmonary infiltrate (Loeffler's syndrome) are rare. These syndromes have also been observed with penicillin hypersensitivity (14–16). In one case, an alveolar allergic reaction, probably due to ampicillin, showed features of an adult respiratory distress syndrome (17).

Nervous system

High doses of penicillins, in the order of several million units/day of penicillin G, can produce myoclonic jerks, hyper-reflexia, seizures, or coma. Drowsiness and hallucinations can occur occasionally (18–20). Such reactions are due to a direct toxic effect and are more likely with high concentrations, as seen with intravenous administration (21,22) and with cardiopulmonary bypass in open-heart surgery (23,24).

Myasthenia gravis can be aggravated by ampicillin (25), a reaction that is well described with aminoglycosides and some other antibiotics.

Intrathecal instillation of more than 10 000 units of penicillin and the topical application of high concentrations of penicillin to the nervous system, especially the brain, during surgery have produced comparable reactions (26). All penicillin formulations can produce this kind of reaction.

Benign intracranial hypertension is an extremely rare reaction to penicillins, possibly allergic (27).

Metabolism

Lipoatrophy can occur after the injection of some drugs, including penicillin (28).

- A 2-year-old boy developed a non-tender, hypopigmented, atrophic patch measuring about 2 × 6 cm on his right buttock. He had been well until 5 months before, when he had received an injection of penicillin into the right buttock.

The incidence of this adverse effect is unknown, as is the mechanism.

In six healthy subjects, ampicillin caused an increase in urinary uric acid excretion; this effect was attributed to competition for active renal tubular reabsorption of urate (SEDA-13, 212).

Electrolyte balance

Potassium penicillin G can significantly alter potassium balance when given in very high doses; 20 million units of potassium penicillin G contains about 30 mmol of potassium, and in patients with renal insufficiency this amount can decisively aggravate potentially lethal hyperkalemia. Similarly, large doses of sodium penicillin G, carbenicillin, or ticarcillin can cause hypernatremia (29,30).

High doses of sodium penicillin can cause urinary potassium loss, presumably by acting as a non-absorbable anion in the distal tubule (30). Apparently by analogous mechanisms a variety of semisynthetic penicillins, including carbenicillin, cloxacillin, mezlocillin, nafcillin,

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piperacillin, and ticarcillin, caused hypokalemia, mainly in severely ill patients (30–36).

Urinary loss of potassium and interstitial nephritis are well-recognized adverse effects of piperacillin. Since patients in ICU may have increased risks of renal complications, serum electrolyte concentrations have been measured in 43 patients before and after piperacillin administration and in 40 patients who were given other antibiotics (37). The groups were comparable in regard to age and severity of disease and all had normal serum creatinine concentrations before the study. Serum concentrations of magnesium, potassium, and, to a lesser degree, calcium fell significantly 36 hours after the start of therapy in patients who were given piperacillin, but not in patients who were given other antibiotics. The fall was most pronounced in the subgroup of patients who were also given furosemide. The authors concluded that treatment with piperacillin can cause or aggravate electrolyte disorders and tubular dysfunction in ICU patients, even when serum creatinine is normal and that the mechanism is probably exacerbation of pre-existing tubular dysfunction. Serum concentrations of electrolytes, including magnesium, should be regularly monitored and, if necessary, supplements should be given to patients in ICU who are receiving piperacillin. This may hold true for all patients receiving piperacillin.

Hematologic

Since the days when chloramphenicol was more commonly used, it has been recognized that many antimicrobial drug are associated with severe blood dyscrasias, such as aplastic anemia, neutropenia, agranulocytosis, thrombocytopenia, and hemolytic anemia. Information on this association has come predominantly from case series and hospital surveys (38–40). Some evidence can be extracted from population-based studies that have focused on aplastic anemia and agranulocytosis and their association with many drugs, including antimicrobial drugs (41,42). The incidence rates of blood dyscrasias in the general population have been estimated in a cohort study with a nested case-control analysis, using data from a General Practice Research Database in Spain (43). The study population consisted of 822048 patients aged 5–69 years who received at least one prescription (in all 1 507307 prescriptions) for an antimicrobial drug during January 1994 to September 1998. The main outcome measure was a diagnosis of neutropenia, agranulocytosis, hemolytic anemia, thrombocytopenia, pancytopenia, or aplastic anemia. The incidence was 3.3 per 100000 person-years in the general population. Users of antimicrobial drugs had a relative risk (RR), adjusted for age and sex, of 4.4, and patients who took more than one class of antimicrobial drug had a relative risk of 29. Among individual antimicrobial drugs, the greatest risk was with cephalosporins (RR = 14), followed by the sulfonamides (RR = 7.6) and penicillins (RR = 3.1).

An immunologically induced hemolytic anemia due to penicillin or its congeners occurs but is rare (44–47). It typically occurs during treatment with high doses (over 10 million units/day) of penicillin for more than 2 weeks (44,45,48). The dose- and time-dependence of this reaction appear to be explained by the underlying mechanism. During penicillin treatment the erythrocytes are normally coated with penicillin, thereby forming a penicilloyl bond on their surface (49). A drug-specific IgG antibody is directed against the complete antigen, that is the penicillin–erythrocyte complex, and can be shown in direct and indirect Coombs' tests. Clinical hemolysis therefore requires both sufficient coating of erythrocytes and high anti-penicilloyl IgG titers.

Besides this "hapten" or "penicillin-type" of drug-induced hemolysis, a second less frequent mechanism, the so-called "innocent bystander" mechanism can occur (46,49,50). Penicillin–antibody complexes are only loosely bound to erythrocytes and activate complement, which can be detected on the erythrocyte surface with the complement antiglobulin test ("complement" or "non-gamma" type). This mechanism plays a part in immune hemolytic anemias due to various drugs other than penicillins. The hemolytic reaction can continue for weeks after withdrawal of penicillin, that is as long as sufficient penicillin-coated erythrocytes and specific antibodies remain in circulation.

That any penicillin derivative can cause hemolytic anemia is emphasized by the following case (51).

- A 34-year-old woman with cystic fibrosis took piperacillin 6 g tds for respiratory distress. She had no known allergies, although she had previously had pruritus while taking ceftazidime and tingling in her hands with azlocillin. She had completed courses of amoxicillin and flucloxacillin without adverse effects. After about 2 weeks she complained of headache and nausea and passed pink urine. A diagnosis of hemolytic anemia was established and piperacillin was withdrawn. She was given a blood transfusion, prednisone, and folic acid, with good effect.

Various antibiotics, including azlocillin, aztreonam, cefuroxime, ceftazidime, chloramphenicol, colistin, flucloxacillin, gentamicin, imipenem, meropenem, piperacillin, tazobactam, temocillin, and ticarcillin, were incubated with this patient's serum. Only piperacillin and piperacillin + tazobactam caused agglutination in an indirect agglutination test. The authors concluded that the hemolytic anemia had been caused by piperacillin.

Penicillin has been rarely suspected to cause hemolytic–uremic syndrome (52).

Agranulocytosis and leukopenia are discussed in the monograph on beta-lactam antibiotics. Over the years, several cases of neutropenia after treatment with piperacillin with or without tazobactam have been described, especially in children (53–55).

- A 77-year-old man with chronic obstructive lung disease and pneumonia received piperacillin 4 g + tazobactam 0.5 g every 6 hours (56). The neutrophil count gradually fell to zero after 24 days. Piperacillin + tazobactam was withdrawn and lenograstim was given. Within 4 days, the number of neutrophils started to increase. Lenograstim was withdrawn, and the number of neutrophils returned to normal within a week. He made a full recovery.

Whether the rate of hematological adverse effects is higher for piperacillin + tazobactam than for other penicillins is unclear, as is the question of whether

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neutropenia is more frequent in children than in adults or more frequent in patients with cystic fibrosis than in patients with other conditions (51). It would anyway be wise to follow patients treated with piperacillin, either alone or in combination with tazobactam, with particular attention.

Thrombocytopenia with penicillins has very rarely been reported (57–61). In two cases with mezlocillin (62) and piperacillin + azobactam (63) antibodies became attached to the platelets in the presence of the incriminated drug. The second of these cases is of particular interest, since drug-dependent antibodies were found in the presence of piperacillin but not tazobactam.

- A young woman developed microangiopathic hemolysis and thrombocytopenia in temporal relation to three separate courses of penicillin or ampicillin (64).

Bleeding disorders with penicillins are discussed in the monograph on beta-lactam antibiotics.

Disseminated intravascular coagulation has been reported during long-term administration of piperacillin (65).

- A 51-year-old man was given piperacillin 2 g bd for osteomyelitis. After close to 4 weeks he developed acute renal insufficiency and superior mesenteric venous thrombosis. His coagulation profile showed disseminated intravascular coagulation. Withdrawal of piperacillin and anticoagulation therapy resulted in clinical improvement and normalization of the laboratory data.

Gastrointestinal

Antibiotic-induced colitis and diarrhea and non-specific gastrointestinal symptoms are discussed in the monograph on beta-lactam antibiotics.

Liver

Penicillin-induced hepatotoxicity may not be as uncommon as has been thought. There have been three reviews. The first was a comparison of the assessment of drug-induced liver injury obtained by two different methods, the Council for International Organizations of Medical Sciences (CIOMS) scale and the Maria & Victorino (M&V) clinical scale (66). Three independent experts evaluated 215 cases of hepatotoxicity reported using a structured reporting form. There was absolute agreement between the two scales in 18% of cases, but there was no agreement in cases of fulminant hepatitis or death. The authors concluded that the CIOMS instrument is more likely to lead to a conclusion compatible with the specialist's empirical approach.

In the second review some syndromes of drug-induced cholestasis were outlined, with lists of typical examples of which drugs cause what (67). The authors stated that the treatment of drug-induced cholestasis is largely supportive and that the offending drug should be withdrawn immediately.

In the third review the authors' intention was to give new insights into basic mechanism of bile secretion and cholestasis (68). Some drug-induced forms of cholestasis appear to be associated with certain HLA class II haplotypes in patients taking co-amoxiclav (SEDA-24; 276). Whether or not this holds true for hepatotoxicity due to other beta-lactam antibiotics is not known.

Co-amoxiclav

Transient rises in serum transaminases are not uncommon after the use of co-amoxiclav, and hepatic dysfunction with jaundice can also occur. Since this effect is thought to be largely due to the clavulanic acid that co-amoxiclav contains rather than the amoxicillin, it is covered in the monograph on beta-lactamase inhibitors.

Isoxazolyl penicillins

Flucloxacillin is the most important cause of antimicrobial drug-induced hepatotoxicity in various countries (69–71). The risk has been estimated in some countries to be in the range of 1 in 10000 to 1 in 30000 prescriptions (72–74). The hepatic injury is often severe and deaths have occurred (73). The course can be prolonged. Cholestasis is the most frequent and prominent feature and the so-called "vanishing bile duct syndrome" can develop. Female sex, increasing age, and duration of therapy are risk factors (75). High daily doses increase the risk (74).

Chronic hepatitis has been reported in a patient with a history of flucloxacillin-induced hepatitis (76).

- A 55-year-old woman with psoriasis was treated with oral 5-methoxypsoralen and UVA photochemotherapy. After 40 treatments over 5 months she became unwell and complained of headaches, nausea, and abdominal pain. Laboratory tests confirmed a diagnosis of hepatitis. Six years earlier she had had flucloxacillin-induced hepatitis.

Hepatitis after 5-methoxypsoralen is supposedly very rare, and the authors gave only one reference, although there have been several more reports after the use of 8-methoxypsoralen. Without discussing possible mechanisms underlying this difference, it might be wise to remember that a previous history of drug-induced hepatitis should be a reminder of the need to consider hepatotoxic reactions in any patient who develops unexplained symptoms while using another drug.

The other isoxazolyl penicillins, that is cloxacillin, dicloxacillin, and oxacillin, can cause similar hepatotoxicity (77–82). However, it is not known whether the incidence is as high as with flucloxacillin. Nor is it known whether the clearly dose-dependent "oxacillin hepatitis" (83–85) is an identical reaction.

In isolated cases, glucocorticoids (77) and ursodeoxycholic acid (86) apparently improved the outcome of hepatitis related to isoxazolyl penicillins.

Other penicillins

Other penicillins have been only very rarely associated with hepatotoxicity. There are isolated reports involving, among others, penicillin G (87), penicillin V (88), ampicillin and amoxicillin (89,90), carbenicillin (91), and nafcillin (92).

- A 28-year-old woman developed upper abdominal pain, weakness, and dark urine 5 days after a single injection

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of benzylpenicillin 2 million units for suspected streptococcal pharyngitis (93). Liver dysfunction persisted for up to 18 months.

The authors rated the likelihood that benzylpenicillin had caused cholestasis as probable and referred to three previous reports in which penicillin was claimed to cause hepatotoxicity.

- A 20-year-old man with abdominal trauma received a single dose of piperacillin (1 g) followed by nine doses of imipenem + cilastatin (500 mg tds for 3 days) and 2 weeks later developed jaundice, fatigue, and pruritus (94). A liver biopsy showed centrilobular cholestasis, portal infiltration with eosinophils, and cholangitis. Lymphocyte transformation tests for piperacillin and imipenem/cilastatin were positive, suggesting an immunological mechanism. He made a full clinical and biochemical recovery after 3 months.

The authors concluded that short-term therapy with piperacillin, imipenem + cilastatin, or the combination could cause the same type of liver damage as described with co-amoxiclav and antistaphylococcal penicillins.

Pancreas

The list of agents associated with pancreatitis is long and diverse and is growing. Drugs such as glucocorticoids, estrogens, diuretics, and cancer chemotherapeutic agents have all been implicated, as have various antibiotics, including tetracyclines, rifampicin, and isoniazid (95). Cases of pancreatitis have been reported after the administration of ampicillin (96) and a penicillin derivative (97).

- A 7-year-old boy developed epigastric pain, nausea, and vomiting, starting 10 days after a course of oral penicillin (dose and derivative not stated). His serum amylase activity was 1260 U/l and lipase 528 U/l; electrolytes and liver functions tests were within the reference ranges. Ultrasonography showed a normal liver, spleen, and gallbladder, but his pancreas was diffusely enlarged.

Urinary tract

Acute tubulointerstitial nephritis has been reported in relation to various penicillins, including penicillin G, ampicillin, and amoxicillin (98–102), dicloxacillin (103), meticillin (104–109), nafcillin (110,111), oxacillin (107), and piperacillin (112–114). However, meticillin is the prototype that has caused this reaction more often than any other beta-lactam.

Meticillin-induced acute interstitial nephritis follows a similar pattern of dose-dependence and time-dependence to that of neutropenia (104,105). This reaction occurred in 16% of all children treated with high-dose meticillin (115). Nephritis occurred after a mean of 17 days and a mean cumulative dose of 120 g.

Fever and hematuria (macroscopic or microscopic) are the dominating symptoms. Rash, eosinophilia in the blood, possibly eosinophiluria, and signs of non-oliguric renal insufficiency can occur but are not always present (107). Acute anuric/oliguric renal insufficiency is rare.

Hemorrhagic cystitis has been observed in connection with meticillin (116) and carbenicillin (117).

A very high dose of amoxicillin (250 mg/kg/day for *Listeria monocytogenes* meningitis) combined with an aminoglycoside led to crystal-induced acute renal insufficiency after 14 days (118).

Drug-induced nephrolithiasis, often seen during the sulfonamide era, is nowadays rare, especially in patients taking beta-lactams. However, it can still occur with penicillins (119).

- A 48-year-old woman with pneumococcal meningitis developed acute oliguric renal insufficiency after taking high-dose amoxicillin (320 mg/kg/day) for 4 days. Amoxicillin crystallization was documented by infrared spectrometry. The outcome was favorable after dosage reduction, a single hemodialysis, and adequate hydration.

As was true for the sulfonamides, the risk of crystalluria due to penicillins is increased by high doses, a low urinary pH, and low urine output.

Skin

Skin reactions are the commonest adverse effects of therapeutically administered penicillins (120). Penicillin-contaminated milk or meat can cause itching or generalized skin reactions (121) or even anaphylaxis (122,123).

Incidence

The overall annual incidence of severe erythema multiforme (toxic epidermal necrolysis and Stevens–Johnson syndrome) is about one case per million, antibiotics being involved in 30–40% (124,125). The clinical differentiation between these syndromes can be difficult (126). Allergic contact dermatitis is usually caused by topical drugs, but is also seen in connection with ingestion, injection, or inhalation (127–129).

The increased frequency of contact eczema due to cloxacillin and bacampicillin may be because they are intensely irritant and lipophilic (130).

Mechanisms

Mechanisms of non-immediate reactions are unclear; but may be immunological and non-immunological. Delayed reactions of the IgE type are known (131). Aminopenicillins seem to be an important cause of non-immediate reactions (132–134). The morbilliform rash that begins 1–10 days after amoxicillin can be caused by a delayed cell-mediated immune reaction (135) as can fixed drug eruptions (136,137), toxic epidermal necrolysis (138–140), bullous erythroderma (141), and contact eczema (142). Investigation of these disorders should include delayed readings of skin tests (135). In patients with chronic urticaria, penicillin allergy was demonstrated by cutaneous tests.

Presentation

In contrast to other drugs, penicillin-induced skin reactions can occur after more than 1 week of therapy (60). The typical presentation is a maculopapular, erythematous, symmetrically disposed rash on the legs, buttocks, and trunk.

In very rare cases, certain penicillins can cause pemphigus vulgaris (143) or pemphigoid-like reactions (144,145).

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Linear IgA disease is an acquired subepidermal bullous disease characterized by linear deposits of IgA at the cutaneous basement membrane zone and by circulating IgA anti-basement membrane antibodies. Although the cause of linear IgA disease is usually unknown, a few cases have been reported to follow ingestion of drugs, especially vancomycin and diclofenac. A patient with penicillin G-induced linear IgA disease who had circulating IgA antibodies showed specificity against type VII collagen (146).

- A previously fit, 76-year-old man developed pneumococcal pneumonia and acute confusion. He was given oxygen, digoxin, furosemide, and penicillin G 9.6 g/day. Because his symptoms of infection continued he was then given higher doses of penicillin, together with intravenous dexamethasone, and his condition slowly improved. After 10 days of treatment with penicillin (cumulative dose 125 g), he developed a maculopapular truncal eruption compatible with a drug rash. Penicillin was withdrawn and the eruption faded over several days, but 1 week later he developed a localized blistering eruption with tense clear bullae and erosions on the penis, scrotum, and inner thighs. This became generalized, affecting most of the body, and he developed large erosions over pressure-bearing sites, oral ulcers, and hemorrhagic nasal crusting. He was given oral prednisolone. His blistering abated within a month, steroid therapy was withdrawn after 3 months, and his disease remained in remission at follow-up 12 months later. Histology of the affected skin showed subepidermal bullae and a mixed inflammatory infiltrate in the dermis. Direct immunofluorescence showed linear IgA deposition along the basement membrane. Anti-basement membrane antibodies were demonstrated by indirect immunofluorescence and were identified by Western blotting to be against a 250 kDa antigen in dermal extracts. Monoclonal antibodies to collagen VII co-migrated to the same spot.

Collagen VII is the major target antigen of epidermolysis bullosa acquisita (147). Consequently, it is open for discussion whether such patients should be classified as having IgA epidermolysis bullosa acquisita or collagen VII linear IgA disease. The authors stated that their patient did not have the clinical phenotype of epidermolysis bullosa acquisita, and the diagnosis of drug-induced collagen VII linear IgA disease seems to have been well validated (95).

Allergic contact urticaria has been attributed to amoxicillin (148).

- A 40-year-old male nurse developed facial angioedema, dyspnea, rhinoconjunctivitis, dysphonia, and dysphagia immediately after opening a sachet containing amoxicillin and clavulanic acid (149). Skin prick tests were positive for both amoxicillin and ampicillin, and an open test with amoxicillin resulted in a severe immediate-type reaction with large localized wheals and erythema at 10 minutes. Six months later, when he was asymptomatic, erythema was observed during open tests with ampicillin 5%.

Consort urticaria has been attributed to penicillins and may occur more often than recognized.

- A 22-year-old woman had labial urticaria with oropharyngeal edema some minutes after kissing her boyfriend, who had taken amoxicillin some minutes before kissing her (150). A few months before, she had had generalized urticaria several minutes after taking amoxicillin. A prick test with amoxicillin was positive and a similar test with penicillin G was negative. Total serum IgE was 90 kU/l and a RAST test for amoxicillin was positive (4.74 kU/l).
- Two episodes of urticarial angioedema occurred in a 45-year-old woman (151). The first episode occurred 1 hour after she had taken a fifth dose of bacampicillin 1200 mg. In the second episode, she had mild itching and edema of the lips and moderate cutaneous itching and swelling about 30 minutes after making love with her husband, who was taking bacampicillin 1200 mg bd and had taken a tablet about 2 hours before. He had used a condom as contraception, and so the only contact between their mucosae was by kissing. Her symptoms disappeared 2 hours after she took cetirizine 10 mg. Some months later, her husband took placebo or bacampicillin 120, 360, or 520 mg on different days, and 2 hours after taking the tablets kissed his wife. She developed mild intraoral itching and itching and wheals on the face and arms 20 minutes after kissing her husband after he had taken bacampicillin 360 mg.

Kissing can cause an allergic reaction if one of the lovers is sensitized to a compound that has just been taken by the other. This holds true for both drugs and food (152,153). Whether a similar reaction can occur if the lovers have intercourse without using a condom has neither been reported nor investigated. However, allergic reactions to penicillin during in vitro fertilization and intrauterine insemination are possible, and the authors recommended that in patients who are penicillin-sensitive, penicillin should not be used during transfer of gamete and embryo for assisted reproductive procedures (154).

Pustular drug eruptions due to penicillin (155), amoxicillin (156), ampicillin (157), bacampicillin (158), or imipenem + cilastin (159) seem to form a distinct clinical entity that has to be differentiated from pustular psoriasis, which can be drug-induced as well (159). A history of drug exposure, rapid disappearance of the eruption after the drug is stopped, and eosinophils in the inflammatory infiltrate argue in favor of pustular drug eruptions.

Pseudoallergic reactions are reactions that mimic immunoallergic reactions, but in which a specific immune-mediated mechanism is not involved. The so-called "ampicillin rash," which also occurs with amoxicillin, another aminopenicillin, is an example of a pseudoallergic reaction, which looks like a typical type III allergic rash, but usually occurs at 7–12 days after the start of administration rather than 3–10 days (160). Some major mediators of pseudoallergic reactions have been reviewed (161). The roles of newer putative mechanisms, involving cytokines, kinins, and other host-derived substances, remain to be ascertained. Most important is the fact that currently there are no standardized and validated animal models for predicting pseudoallergic reactions (162). In patients with infectious mononucleosis, the aminopenicillins evoke rashes in a much higher percentage

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than usual (163). The incidence of rashes in infectious mononucleosis without antibiotics is 3–15%, compared with 40–100% with ampicillin. The underlying mechanism is speculative.

Although several reports have described fixed rashes due to amoxicillin, palmar exfoliation has rarely been described (164).

- Five patients (one man, four women, aged 30–72 years) developed intense palmar rashes and itching during treatment with amoxicillin (doses not stated). All the episodes began after several days of treatment with amoxicillin, either alone or in combination with clavulanic acid. Three of the patients had repeated episodes, and the interval between treatment and onset was shorter each time (down to 5 hours on the third occasion). In all cases the rash was followed by exfoliation and cleared in 7–10 days without residual lesions. Skin prick tests, intradermal tests, and patch tests were performed with several beta-lactams, including amoxicillin, and all were negative. A challenge test with amoxicillin was performed in one patient, and the erythema recurred in 3–4 hours. All five patients tolerated cefuroxime and ceftazidime. Cefalexin was given to one patient only, and palmar exfoliative erythema developed a few days later.

Diagnosis

A maximum of 20% of subjects with a history of allergy-like reactions after administration of a penicillin antibiotic have positive skin or RAST tests (165–167). Tests using benzylpenicillin derivatives or semisynthetic penicillins can almost double positive test results (168,169). Patients with a positive history but negative skin tests run a 1–3% risk of an IgE-mediated reaction and 60% of test-positive patients had evidence of an immediate reaction, including urticaria and angioedema (165).

Management

Penicillins should be avoided in any patient who gives a history of a skin reaction or anaphylaxis to any penicillin derivative. To prevent mild skin reactions becoming severe when they occur, it is advisable to withdraw the culprit antibiotic not only when a type I reaction is suspected but in all kinds of common rashes, in view of a possible epidermolytic process. A diet free of dairy products was curative in 30 of 70 patients with positive tests (170).

Immunologic

Type I reactions

Anaphylactic shock can occur, even after oral administration of penicillin and skin testing. However, anaphylactic shock is less common after oral than parenteral administration (171). In one study the incidence of anaphylactic shock was 0.04% of all patients treated with penicillin (7). It is also low in patients receiving long-term benzathine penicillin (1.2 million units every 4 weeks). Four episodes of anaphylaxis occurred in 0.012% of injections (1.2 reactions to 10 000 injections) (172). Anaphylactic shock resulting in death occurred in 0.002% of all patients treated with penicillin (7) and in 0.003% of those treated with benzathine penicillin (172).

In nearly half of the cases, the course of anaphylactic shock, especially that induced by penicillin and other small molecular substances, is that of a cardiovascular reaction without any other effects suggestive of an allergic mechanism (173–175). There is an extensive list of articles on anaphylactic shock to penicillins (7–10,173,174,176,177). General anesthesia does not inhibit the development of anaphylactic shock in penicillin allergy (178).

Diagnosis

The two most important elements in the evaluation of an individual for the presence or absence of beta-lactam hypersensitivity are the drug history and skin tests. Other diagnostic tools, such as measurement of drug-specific antibodies and lymphocyte transformation tests, are investigational or restricted to specialized laboratories. Standardized and widely used protocols for skin testing only exist for the penicillins and allow assessment of IgE-mediated hypersensitivity. The most commonly used reagents are penicilloyl-polylysine (PPL, which contains multiple penicilloyl molecules coupled to a polylysine carrier) and fresh penicillin followed by minor determinant mixtures (MDM), containing penicilloate, benzylpenicilloate, and benzylpenilloate (179). A survey conducted among members of the American Academy of Allergy and Immunology reported the use of penicilloyl-polylysine and fresh penicillin by 86% and minor determinant mixtures by 40% of those responding to the questionnaire (180).

Skin tests are first applied as a prick test for safety. In the absence of a local or systemic reaction, an intradermal test is performed and interpreted as described elsewhere (181,182). Experience with skin testing in penicillin allergy has been reviewed (176,183). Properly performed sequential testing is considered a safe procedure, and only an estimated 1% or less of penicillin allergic patients will have systemic symptoms while undergoing skin tests. However, at least three deaths have been reported with both epicutaneous and intradermal testing (184).

In a collaborative study in the National Institute of Allergy and Infectious Diseases (NIAID), hospitalized patients were tested with major and minor skin test reagents in order to assess the predictive value of skin testing. Among 600 history-negative patients, 568 had negative skin tests and none had a reaction to penicillin. Among 726 history-positive patients, 566 had a negative skin test and received penicillin, seven of whom (1.2%) had a possibly IgE-mediated reaction. Nine of the 167 patients with positive skin tests were exposed to penicillin, two of whom had reactions compatible with IgE-mediated reactions. These data suggest that overall, 99% of patients with negative skin tests to penicilloyl-polylysine and minor determinant mixtures can safely receive penicillin. A history of a previous reaction slightly increases the risk of an adverse reaction, to 1.2%. Most positive skin tests were detected with penicilloyl-polylysine with or without minor determinant mixtures, and a further 16% reacted to minor determinant mixtures alone (166).

In another study in an outpatient clinic for sexually transmitted diseases, 5063 consecutive patients were

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tested with penicilloyl-polylysine with and without minor determinant mixtures (167). The role of the history of a previous penicillin reaction was emphasized in this study: 1.7% of history-negative subjects had a positive skin test; in contrast, 7.1% of history-positive patients had a positive skin test, and a previous history of anaphylaxis or urticaria was associated with positive skin tests in 17% and 12% respectively. Penicillin was safe in more than 99% of patients with a negative history and a negative skin test. Reactions were more common (2.9%) in patients with a positive history and a negative skin test. The reactions were mild and self-limiting. Two patients with a history of severe IgE-mediated reaction had mild anaphylactic reactions.

Relatively safe doses for skin testing, provided that one begins with a prick test, are 25 nmol/ml of penicilloyl-polylysine and purified benzylpenicillin. Positive skin tests of the immediate type with penicilloyl-polylysine are usually obtained 2 weeks to 3 months after the clinical reaction (185).

The safety of such an approach has been challenged in a description of three patients who were negative in skin tests with penicilloyl-polylysine and minor determinant mixtures and who tolerated therapeutic doses of benzylpenicillin, but reacted to amoxicillin (173). In an extension of that study, 177 patients who were allergic to beta-lactams were identified using the clinical history, a skin test panel including penicilloyl-polylysine, and minor determinant mixtures, as well as ampicillin and amoxicillin and drug-specific radio-allergosorbent tests. Fifty-four patients (31%) tolerated penicillin G but reacted to amoxicillin with anaphylaxis, urticaria, or angioedema. Skin tests with penicilloyl-polylysine and minor determinant mixtures failed to detect those patients, but tests with amoxicillin were positive in 63% (168).

Canadian data have partly confirmed these findings (169). Benzylpenicillin derivatives and semisynthetic penicillins were applied to 112 patients with a history of an allergic reaction to penicillins. The tests were positive in 21 patients (19%), of whom 10 reacted against the semisynthetic penicillin reagents only. Reports of subjects allergic to flucloxacillin (186), cloxacillin (187), and cefadroxil (188), but not penicillin, lend further support to the concept of side chain-specific allergic reactions (see the monograph on beta-lactam antibiotics).

Management

Fearing penicillin anaphylaxis, many clinicians overdiagnose penicillin allergy in patients who have not had a true allergic reaction. Consequently, penicillins are withheld from many patients who could safely receive them. This was the background to a study whose objectives were to determine the likelihood of true penicillin allergy, taking into consideration the clinical history, and to evaluate the diagnostic value added by appropriate skin testing (189). The authors searched MEDLINE for relevant English-language articles dated 1966 to October 2000. Bibliographies were searched to identify additional articles. Original articles describing the precision of skin tests in the diagnosis of penicillin allergy were included, and studies that did not use both minor and major determinants were excluded; 14 studies met the inclusion criteria. At least three authors independently reviewed and abstracted the data from all the articles and reached a consensus about any discrepancies. Some of their conclusions are worth remembering:

- 80–90% of all patients who report penicillin allergy have negative skin tests, suggesting that penicillins are withheld from many patients who could safely receive them;
- patients who develop a rash while taking penicillins should not be automatically labeled as allergic without considering other possibilities, including rashes due to ampicillin distinct from allergic rashes, and rashes caused by the infection being treated or by other drugs;
- for patients with a history of immediate (type I) penicillin allergy who have a compelling need for penicillin, skin testing should be performed;
- at least 98% of patients with positive histories of penicillin allergy and negative skin test results can tolerate penicillin without any sequelae.

Desensitization

Patients with a history of penicillin allergy should undergo skin testing with both penicilloyl-polylysine and minor determinant mixtures. Patients with positive skin tests should be treated with another immunologically unrelated compound or should undergo desensitization. The management of patients with a negative skin test but a history of a severe IgE-mediated reaction has to be individualized; options include the use of an alternative compound, desensitization, or the controlled administration of a test dose.

Acute drug desensitization is commonly described as the process by which a drug-allergic individual is converted from a highly sensitive state to a state in which the drug is tolerated. The procedure involves cautious administration of incremental doses of the drug over a short period of time (hours to a few days). In the past it has mainly been considered to be of value in patients in whom IgE antibodies to a particular drug are known or assumed to exist and no alternative treatment agent is available. In clinical practice, most of the desensitization protocols have involved penicillins (190). However, the principle has been applied successfully to other agents as well (191,192), including other antibiotics, insulin, chemotherapeutic agents, vaccines, heterologous sera, and other proteins.

Mechanism It has been stated that in patients with penicillin-specific IgE antibodies who underwent successful penicillin desensitization, the data suggest that anti-specific, mast cell desensitization is responsible for the tolerant state and that mediator depletion plays no role (190). Additionally, the clinical observation that wheal-and-flare skin responses to penicillin often become negative with successful desensitization, while IgE responses to other antigens remain unchanged, also supports an involvement of an antigen-specific mechanism. Furthermore, both clinical reactivity and skin-test reactivity return within a few days, unless a tolerant state is maintained by continued drug administration. The author stressed that these findings show that the desensitized state depends on the

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continuous presence of antigen and that clinical sensitivity returns rapidly in the absence of antigen.

However, the underlying mechanisms responsible for the antigen-specific desensitized state are still unclear. It has been hypothesized that IgE receptor aggregation may generate counter-regulatory forces that, instead of causing cell activation, actually extinguish activating signals (191). The key point is that during desensitization, the drug is introduced very slowly and the drug concentration rises gradually. The slow rate of possible receptor aggregation caused by the gradual increase in drug concentration, along with suppression of cellular activation signals, may lead to antigen-specific desensitization and clinical tolerance. It has also been long thought that during desensitization, univalent drug-hapten protein conjugates are formed and may act by inhibiting the cross-linking of drug-specific IgE molecules on mast cells. It is slightly surprising that this prospect has not come into routine therapy.

Procedure Beta-lactam desensitization should be done in an intensive care unit and any concomitant risk factors for anaphylaxis, such as use of beta-blockers should be corrected. Protocols based on incremental use of the drug orally or parenterally have been described (190,193). The oral route is preferable and is associated with a lower incidence of adverse events, but mild transient reactions are frequent (171,194,195). Pregnant women with limited antibiotic choices have been treated with immunotherapy (196). Repeated administration will maintain a state of anergy, which is often lost after withdrawal (197). At the conclusion of therapy, patients must be informed that after withdrawal, they may once again become allergic to penicillin, with a new reaction to the first subsequent application (197).

Desensitization is not effective in non-IgE-mediated reactions and should therefore not be attempted, for example in cases of serum sickness-like syndromes or Stevens–Johnson syndrome.

Treatment of acute anaphylaxis
For acute anaphylaxis, immediate treatment is essential, with adrenaline followed by intravenous histamine H_1 receptor antagonists, glucocorticoids, fluids, and electrolytes. In view of the frequency of cardiac dysrhythmias and conduction disturbances in patients with anaphylactic shock, they should immediately be monitored (198,199).

Type III reactions
Serum sickness was first described by von Pirquet and Schick in 1905 and was regarded as a syndrome resulting from the administration of heterologous serum or other foreign proteins. The immunopathology of classic serum sickness results from antigen–antibody complex formation with a foreign protein as the antigen. Characteristic symptoms include fever, cutaneous eruptions, edema, arthralgia, and lymphadenopathy. The incidence of classical serum sickness has fallen secondary to the refinement of foreign proteins. However, a serum sickness-like reaction that is clinically similar to classical serum sickness can result from the administration of a number of non-protein drugs, such as tetracyclines, penicillins, and cephalosporins (200). The reaction typically occurs within 1 month of the start of therapy and resolves after withdrawal.

Serum sickness has been associated with penicillins (201).

- A 39-year-old woman developed the characteristic symptoms for serum sickness, having completed a 5-day course of amoxicillin for a perilingual infection 1 week before. She was treated with prednisone 60 mg/day and diphenhydramine 25–50 mg tds. Her symptoms gradually resolved and the prednisolone dose was tapered over 2 weeks.
- A 29-year-old woman complained of fever, rash, throat and facial swelling, abdominal pain, and increasing joint pain, leaving her wheelchair-bound. Her symptoms started a week after she had completed a 10-day course of penicillin V for a dental abscess. She was given oral methylprednisolone, 40 mg every 6 hours, and over the next few days her symptoms gradually resolved.
- A 29-year-old woman developed symptoms of serum-sickness 2 weeks after completing a 21-day course of co-amoxiclav for sinusitis. She responded to prednisone 40 mg/day.

The authors suggested that serum sickness may be more common than has previously been described and that the reaction may be under-reported or unrecognized.

Second-Generation Effects

Teratogenicity

Early animal studies suggested that malformations could be caused by penicillins. However, this was not confirmed in later, more extensive evaluations (202). Penicillin G, ampicillin, and probably most other penicillins can be safely used in pregnant women and children. Experience with the newer semisynthetic penicillins is not extensive enough to allow definite conclusions regarding their safety for mother and fetus during pregnancy.

Fetotoxicity

Increased antenatal administration of ampicillin for the prevention of neonatal group B streptococcal disease may be responsible for the higher incidence of more severe neonatal sepsis with ampicillin-resistant non-group B streptococci, without a change in the overall infection rate (203,204).

Lactation

The transfer of penicillins (ampicillin, pivampicillin, phenoxymethylpenicillin) into the breast milk of nursing mothers with puerperal mastitis to the breastfed infant is minimal (205). The risk of adverse drug reactions due to penicillins is therefore negligible, unless the infant has penicillin allergy (SEDA-14, 215).

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Susceptibility Factors

Renal disease

Toxic effects of penicillins can occur in patients with renal insufficiency if the dosage is not altered (206).

Other features of the patient

Toxic reactions can occur in patients with pre-existing cerebral damage or during cardiopulmonary bypass. Embolic reactions can have severe consequences in patients with pre-existing cardiac or pulmonary disease.

Drug Administration

Drug formulations

Embolic-toxic reactions to penicillin depot formulations were first described in patients with syphilis (207). The symptoms include fear of death, confusion, acoustic and visual hallucinations, and possibly palpitation, tachycardia, and cyanosis (SEDA-8, 559) (175,207–211). Generalized seizures or twitching of the limbs have been observed in children and adults (210,212–216). As a rule, the symptoms abate and disappear within several minutes to an hour. They rarely persist for up to 24 hours. If a cardiovascular reaction with a fall in blood pressure occurs simultaneously with typical symptoms, a combination with anaphylactic shock must be considered (217,218).

Such reactions have been called "pseudo-anaphylactic reactions" or "acute non-allergic reactions" (174,208–210,219–223), "panic attack syndrome," and "acute psychotic reactions" (212,224). In several countries, the term "Hoigné syndrome" is used.

The frequency of such reactions is about 1–3 reactions per 1000 intramuscular injections of penicillin G procaine, the usual dose being about 0.6–1.2 million units (175,213,225–227). Eight of 920 patients with venereal diseases had a definite toxic-like reaction with a dose of 4.8 million units of penicillin G procaine, corresponding to about one in 120 patients (228). In a series of 7700 intramuscular injections with only 400 000 units of penicillin G procaine, there was not one episode (221).

The mechanism is probably embolic (172,207,219,222,225), as has been shown in one case at autopsy, in which emboli of benzathine penicillin crystals were found in the lungs (219).

Some reports suggest that the procaine component may be especially important (213,222). Plasma procaine esterase activity was low in patients with systemic toxic reactions (213). The same symptoms occurred in three patients after erroneous administration of penicillin G procaine by intravenous infusion (222), but also in two after procaine-free antihistamine penicillin was injected intramuscularly (172,225). However, observations of similar symptoms with a procaine-free antihistamine penicillin argue against a central role of the procaine component (SED-8, 560) (175,217,220,221,225).

Drug administration route

Intramuscular injection of high doses of depot formulations of penicillins can lead to painful swelling, especially when over 600 000–1 000 000 units are given at a single site (229,230). Such reactions occurred in two of 878 patients (0.2%) with intramuscular penicillin G procaine (231). Arthus phenomenon seems to be rare (127,232).

Nicolau syndrome (embolia cutis medicamentosa) is a very rare complication of intramuscular injections, in which there is extensive necrosis of the injected skin area, perhaps due to accidental intra-arterial and/or para-arterial injection (233). It usually occurs in children: in a review of 102 patients, 80 were under 12 years of age (234). Complications can include everything from an ischemic syndrome with local necrosis of the skin, subcutaneous tissue, and muscle, often combined with vascular and nervous system involvement, intestinal and renal hemorrhage, necrosis of the entire leg, and even paraplegia from spinal cord damage (235–241). Necrosis of the forearm has been described in two patients after inadvertent intra-arterial administration of dicloxacillin (242).

Special emphasis should be put on the precautionary measures to be taken when injecting long-acting penicillins or other drugs in crystalline suspensions intramuscularly.

Repeated intramuscular injections into the thighs of newborns and infants can cause severe and widespread muscular contractures of the quadriceps femoris (SEDA-8, 560). In some cases, penicillin was implicated.

Drug–Drug Interactions

Allopurinol

The risk of rashes caused by aminopenicillins does not seem to be increased by parallel treatment with allopurinol (243), as had been suggested before (244).

Aminoglycosides

High doses of parenteral penicillin can inactivate aminoglycosides (245). In patients receiving low doses of aminoglycosides because of reduced renal function this can be clinically important (246,247). Parenteral administration of these drugs in neonatal dosages does not seem to produce relevant inactivation, and so temporal separation of the infusions is not required (248).

Piperacillin protected against aminoglycoside nephrotoxicity without reducing its blood concentration; this was possibly a protective effect of co-administered mineral salts (249).

Ciclosporin

In a study in lung transplant recipients, ciclosporin nephrotoxicity was potentiated by nafcillin (111).

Methotrexate

Beta-lactams are weak organic acids that compete with the renal tubular secretion of methotrexate and its metabolites and reduce their clearance, leading to methotrexate toxicity (250,251). Consecutive aplastic crises have been described, particularly in patients with impaired

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renal clearance (250,252,253). In contrast, co-administration of flucloxacillin in another study produced a significant but not clinically important reduction in methotrexate AUC (254).

The more basic interactions between piperacillin and methotrexate and its major metabolite 7-hydroxymethotrexate have been studied in rabbits (255). The interaction was mainly caused by reduced renal clearance of both methotrexate and its metabolite. The authors concluded that renal function in patients taking this combination should be monitored, with adequate fluid intake, especially in elderly patients, because dehydration may accelerate the occurrence of toxicity.

Phenytoin

Competitive albumin binding of drugs with high serum protein affinity can increase pharmacologically active unbound concentrations and enhance the metabolism of low clearance drugs. In vitro data suggest a significant increase in unbound phenytoin concentration by high doses of oxacillin, especially with hypoalbuminemia or uremia (256).

Interference with Diagnostic Tests

Pseudoproteinuria

Patients who take penicillin G or ureidopenicillin derivatives in doses over 5 g/day develop pseudoproteinuria. Proteinuria should be evaluated by a bromphenol blue test (Albustix) or after urine dialysis (SEDA-3, 219).

17-ketosteroids

High-dosage penicillin produces abnormally high concentrations of 17-ketogenic steroids in the blood and high concentrations of 17-ketosteroid in the urine (257).

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Pentagastrin

General Information

Pentagastrin is a short peptide that stimulates the production of gastric acid from the stomach by a direct action on gastrin receptors and of calcitonin from thyroid C cells (1). It also acts on cholecystokinin receptors centrally and stimulates the release of adrenocorticotropin (ACTH) and hence the production of glucocorticoids (2).

Pentagastrin was originally used to test for suppression of gastric acid in patients who had had a vagotomy, and has been used to study gastric physiology and to test the effects of drugs that inhibit gastric acid secretion. It has also been used in the diagnosis of medullary carcinoma of the thyroid because it stimulates the production of calcitonin.

General adverse effects

Pentagastrin often causes adverse effects, which limit its use. Nausea, abdominal cramps, headache, drowsiness, and giddiness can occur. The effect on the stomach is largely dissociated from these unwanted effects. In one series 38 of 40 patients had a feeling of chest tightness (3). In 50 patients parenteral pentagastrin 6 micrograms/kg caused nausea in 14, tremor in 12, and a hot sensation in 11 (4). These effects occurred immediately after injection and continued for several minutes. In four subjects the test had to be stopped because of collapse.

Organs and Systems

Cardiovascular

Pentagastrin causes small transient increases in blood pressure and pulse (5), autonomic effects that are prevented by inhibiting cholecystokinin receptors (6). Atrial fibrillation has been observed (7).

Psychological, psychiatric

In a double-blind placebo-controlled study intravenous pentagastrin led to panic attacks in nine of 19 patients with social phobia, seven of 11 with panic disorder, and two of 19 healthy controls (8). Anxiety, blood pressure, and pulse increased in all three groups.

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In a double-blind, placebo-controlled study in seven patients with obsessive-compulsive disorder and seven healthy controls, intravenous pentagastrin 0.6 microgram/kg produced panic-like reactions in six (86%) of the seven patients and only two (29%) of the controls (9).

The anxiety caused by pentagastrin is prevented by inhibiting cholecystokinin receptors (6).

Hematologic

In one case thrombocytopenia was attributed to pentagastrin (10).

Pancreas

- Acute severe abdominal pain occurred in a 25-year-old patient with recurrent duodenal ulcers after subcutaneous injection of pentagastrin (11). Laparotomy showed acute hemorrhagic pancreatitis. Healing and freedom from complaint occurred rapidly with drug therapy.

The authors postulated the following mechanisms: acute exacerbation of chronic pancreatitis, a direct effect of pentagastrin on the pancreas, increased pancreatic secretion due to stimulation by gastric acid, reflux of duodenal contents or bile, arterial hypotension with local acidosis in the pancreas.

Drug–Drug Interactions

Cimetidine

In 150 subjects some, but not all, of the somatic symptoms caused by pentagastrin were abolished by cimetidine; however, the combination of pentagastrin and cimetidine produced a significant incidence of dizziness (12).

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Pentamidine

General Information

Pentamidine, an aromatic diamine, has been known since the late 1930s as a treatment for trypanosomiasis and some forms of leishmaniasis. In recent times it has been extensively used in the treatment of *Pneumocystis jiroveci* pneumonia. Its mechanism of action is probably related to inhibition of dihydrofolate reductase and inhibition of oxidative phosphorylation and nucleic acid synthesis, as well as an effect on aerobic glycolysis.

Pharmacokinetics

The pharmacokinetics of pentamidine are incompletely known. It is not absorbed after oral administration and needs to be given parenterally or by aerosol. After intramuscular injection peak concentrations are seen after about 1 hour, and the serum concentration stays about the same for 24 hours. A study of multiple dosing over 2 weeks showed progressive accumulation in the plasma during that time. After multiple intravenous doses the half-life was 12.5 days. After a course of treatment decreasing amounts of pentamidine can be found in the urine for as long as 8 weeks. It seems that pentamidine is stored or bound in the tissues and excreted slowly in the urine and the amount excreted changes only marginally with repeated doses. The highest tissue concentrations have been found in the kidney, followed by the liver and then other tissues, but pentamidine was not found in the brain. Serum concentrations after aerosol therapy are markedly lower than after intravenous therapy. Uptake via the lungs is limited, which explains the lack of serious systemic toxicity seen with aerosol treatment, but also explains the reported occurrence of extrapulmonary *Pneumocystis* infections.

These pharmacokinetic data merit attention, because they may be helpful in preventing toxicity, which seems to be dictated by tissue accumulation rather than serum concentrations; major toxic reactions usually occur only

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after the first week of parenteral treatment. The pharmacokinetics may also explain the varied response to treatment with aerosolized pentamidine and the more satisfactory results of prophylaxis with the aerosol after initial parenteral treatment (SEDA-13, 824) (SEDA-16, 312). A retrospective study showed efficacy of intravenous pentamidine in AIDS patients with *Pneumocystis jiroveci* pneumonia, the most frequent toxic effects being gastrointestinal, especially nausea (SEDA-21, 299).

Observational studies

In an uncontrolled study in French Guiana, intramuscular pentamidine isethionate (two 4 mg/kg injections 48 hours apart) in 198 patients with cutaneous leishmaniasis produced a cure rate of 87%; 80% of treatment failures responded to an identical second course (1). Compared with published studies, adverse events were relatively mild: pain on injection (54%), gastrointestinal effects (53%), and hypotension (8%). There were no dysrhythmias or glucose abnormalities. This may reflect the brief course of pentamidine used.

Pentamidine is the drug of choice for the treatment of cutaneous leishmaniasis in Surinam. Pentamidine mesylate in 235 patients and pentamidine isethionate in 80 patients have been compared in a retrospective study; the cure rate (healing without relapse) was nearly 90% in both groups (2). Relapses occurred in about 10% of patients in both groups. Minor adverse effects, such as pain at the injection site, bitter taste, and nausea, occurred with both drugs in about 65% of patients. Respiratory tract problems occurred in under 10% of patients who took pentamidine isethionate but were uncommon in those who took pentamidine mesylate.

General adverse effects

Pentamidine in therapeutic doses has a high rate of adverse effects (over 50%). Toxicity seems to occur more often in patients with AIDS. Hypotension subsequent to injection or infusion, hypoglycemia, and nephrotoxicity are the major adverse effects. Hepatotoxicity and neutropenia are not uncommon. Compared with the general population there is a high incidence of pancreatitis in patients with AIDS, particularly during aerosol treatment. Hypoglycemia has also been seen after aerosol treatment. Intermittent prophylactic aerosol use causes few adverse effects, apart from cough and bronchial irritation after inhalation. There is a higher incidence of spontaneous pneumothorax with aerosol prophylaxis. There is also a higher incidence of extrapulmonary infections with *P. jiroveci* in patients treated with aerosolized pentamidine. Another disturbing finding was the higher incidence of other opportunistic infections with pentamidine aerosol versus placebo, while pentamidine aerosol was associated with a markedly lower recurrence rate of *P. jiroveci* pneumonitis in a placebo-controlled pentamidine aerosol study of prophylaxis after initial treatment (SEDA-13, 824). Intramuscular administration of pentamidine brings its own adverse effects: localized pain, erythema, and sterile abscesses are frequent and troublesome (SEDA-13, 824) (3). The use of the Z-track technique for injection mitigates the local effects. Allergic reactions have been reported. There is no information about tumor-inducing effects.

Organs and Systems

Cardiovascular

Severe hypotension can occur after a single intramuscular injection of pentamidine or with rapid intravenous administration, but has been seen with slow infusion as well. Infusing the drug over 60 minutes or more may reduce this risk. Facial flushing, breathlessness, dizziness, and nausea and vomiting can occur at the same time.

Cardiac dysrhythmias, including ventricular tachycardia, have been reported during treatment (SEDA-13, 824) (SEDA-16, 331) (4,5). Prolongation of the QT interval, which usually precedes the development of ventricular dysrhythmias with pentamidine, occurs in one-third of patients, usually within 2 weeks of starting therapy. Torsade de pointes has been described. Any dysrhythmia can recur many days after the pentamidine has been discontinued, which is not surprising, in view of the long half-life and tissue accumulation. Electrolyte abnormalities, including low serum magnesium concentrations, have been noticed at times of dysrhythmias (SEDA-16, 315) (SEDA-17, 331) (4–6).

- Torsade de pointes has been reported in a 48-year-old HIV-positive woman treated with intravenous pentamidine (7).

Local thrombophlebitis can occur after injection of pentamidine, but problems are more often seen at the injection site after intramuscular injection.

Respiratory

Inhalation of pentamidine can cause intolerable coughing. Bronchospasm can occur, especially in cases of asthma; tolerance of inhaled pentamidine is increased in nearly all patients by pretreatment with inhaled $beta_2$-adrenoceptor agonists (SEDA-16, 313) (SEDA-17, 330) (SEDA-18, 290) (4).

In lung function tests, high-dose aerosolized pentamidine (600 mg/month) was associated with an increased pulmonary residual volume, reduced flow rates, and increased airway reactivity (SEDA-18, 291).

There is an increased incidence of spontaneous pneumothorax after the administration of pentamidine by aerosol, which may be connected with the effect on airway resistance. There was a particularly high frequency of spontaneous pneumothorax in people with hemophilia; the authors suggested that *P. jiroveci* infection and treatment resistance had played a role (SEDA-16, 313).

Acute eosinophilic pneumonia after one dose of inhaled pentamidine of 300 mg has been reported; the reaction subsided within 2 weeks but recurred on rechallenge (SEDA-18, 292).

Dissemination of lung infection is a potentially serious matter, especially when using pentamidine by the aerosol route. While high alveolar drug concentrations can be reached in the most accessible parts of the lung, systemic absorption is minimal and the organism can spread through the lung and beyond, despite containment of the initial pulmonary infection; in some cases there has been extensive spread of *P. jiroveci* into major organs and the bone marrow (SEDA-16, 313) (SEDA-17, 332). Patients who have been treated with parenteral

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pentamidine are at a lower risk of disseminated *P. jiroveci* infection than those given aerosol prophylaxis only (SEDA-16, 313) (SEDA-17, 322).

Nervous system

Mild dizziness can occur with pentamidine, but nervous system adverse effects are uncommon.

Psychological, psychiatric

Confusion and hallucinations have occasionally been reported with pentamidine. Magnesium deficiency may affect mental function; a flat affect, slow speech, and mental withdrawal are some of the typical effects (SEDA-13, 825) (6). The symptoms of hypomagnesemia can be ill defined; unexplained symptoms, despite improvement of the *P. jiroveci* infection, demand measurement of the serum magnesium concentration.

Metabolism

Hypoglycemia can be a serious and life-threatening effect of pentamidine and is seen in 10–30% of cases, mainly with parenteral use, although it can also occur with inhalation. In one 21-day study it was equally common with either form of therapy. Higher doses and longer durations of treatment increase the likelihood, as does prior treatment with pentamidine (SEDA-16, 314); uremia also increases the risk. In one study there was nephrotoxicity in all cases with hypoglycemia. The hypoglycemia is the result of a direct toxic effect on the pancreatic beta cells, resulting in insulin release and transient hypoglycemia, which is followed by beta cell destruction and insulin deficiency, which in turn can eventually lead to an irreversible state of diabetes mellitus (SEDA-13, 825) (SEDA-16, 315) (SEDA-17, 331) (4).

Mineral balance

Hypocalcemia has been attributed to pentamidine but not explained (8).

Hypomagnesemia (related to excess urinary excretion of magnesium due to pentamidine) and clinical signs of magnesium deficiency can have psychiatric consequences. Magnesium deficiency itself can affect mental function; a flat affect, slow speech, and mental withdrawal are some of the typical effects (SEDA-13, 825) (6). In one case (6) hypomagnesemia was still present 2 months after intravenous pentamidine treatment, although aerosolized pentamidine was being continued and could have caused hypomagnesemia. Some patients are particularly sensitive to this effect, and previous renal damage (for example by other drugs) can be a risk factor (SEDA-13, 825).

Hematologic

Anemia, leukopenia, or thrombocytopenia occur in less than 5% of cases (SEDA-13, 825). Thrombocytopenia is more likely to occur during prolonged therapy than initially.

Megaloblastic bone marrow changes can occur with prolonged therapy (SEDA-11, 598). Low blood cell counts have been reported even after aerosolized pentamidine.

- Intravenous pentamidine caused megaloblastic anemia in a 38-year-old woman with *Pneumocystis jiroveci* pneumonia (9).

In one patient with AIDS with severe but reversible thrombocytopenia after intravenous pentamidine, the serum during the acute phase contained antiplatelet antibodies that reacted with glycoprotein IIb/IIIa, similar to the reactions observed with quinine-induced thrombocytopenia (SEDA-18, 292). This suggests that even aerosol treatment or environmental exposure will need to be avoided in such patients.

Gastrointestinal

Gastrointestinal complaints due to pentamidine are usually minor. Nausea and vomiting can occur. Dysgeusia has been reported in a few cases with intravenous therapy, but one study of aerosol administration specifically noted its absence (SEDA-13, 825).

Liver

Occasionally, abnormal liver function tests have been seen in patients receiving pentamidine (10).

Pancreas

Episodes of acute pancreatitis and of hemorrhagic pancreatitis have been reported. This may or may not be combined with evidence of damage to pancreatic beta cells (SEDA-13, 825) (SEDA-16, 315) (SEDA-17, 331) (4). However, pancreatitis has also been seen in patients with AIDS who did not receive pentamidine. The risk of pancreatitis seems to be greater in children with CD4 counts under 100×10^6/l. In a case-control study 12 of 44 patients with AIDS and pancreatitis had used pentamidine (SEDA-20, 264).

Urinary tract

Nephrotoxicity is common with pentamidine. In one study, serum creatinine concentrations increased in nine of 10 patients with *P. jiroveci* infection during 2–3 weeks of treatment. The incidence is 20–35% (SEDA-13, 825), and in AIDS higher still, for example 50–65% (SEDA-17, 331) (4). Renal toxicity is more pronounced in patients with diarrhea and probably more severe with intramuscular use, perhaps because of dehydration, which is more readily corrected if the drug is given by infusion. In one study there was evidence of renal toxicity in all patients with pentamidine-induced hypoglycemia, in contrast to an incidence of 38% in the group who remained euglycemic. Because of the marked accumulation of pentamidine, it is conceivable that after an initial period of daily administration a modified treatment regimen, every other day or even twice a week, may prevent renal and pancreatic permanent damage (SEDA-13, 825).

Skin

Rashes can occur with pentamidine but are not common (11).

Local pain at the injection site, local infiltration, and sterile abscesses have been reported after intramuscular pentamidine (2,3).

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There have been reports of a Herxheimer reaction and of skin lesions resembling toxic epidermal necrolysis, both in children (SEDA-13, 825).

Musculoskeletal

- Two patients (aged 31 and 38 years) with cutaneous leishmaniasis given intramuscular pentamidine 600 mg twice in 48 hours developed rhabdomyolysis (12). They recovered with fluid replacement and alkaline diuresis.

Drug Administration

Drug formulations

The administration of nebulized pentamidine has an environmental impact; handling the nebulizer, cleaning and preparing it for use, and assisting the patient exposes health-care workers to pentamidine (13). Adverse reactions, such as ocular and pulmonary irritation and irritation of exposed skin, have been reported in health care workers (14).

Drug–Drug Interactions

Potassium-sparing diuretics

Pentamidine is structurally similar to amiloride and can cause severe hyperkalemia if co-prescribed with potassium-sparing diuretic (15). This is a particularly important interaction in patients with AIDS.

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Pentamorphone

See also Opioid analgesics

General Information

Pentamorphone is a potent opiate with a rapid onset and short duration of action, similar to that of fentanyl, which has been reported to produce analgesia with limited depression of ventilation (1).

Subjective symptoms in 23 male volunteers who received pentamorphone were pain on injection, headache, tiredness, euphoria, dizziness, visual disturbances, and nausea (2).

Organs and Systems

Cardiovascular

There was no effect on blood pressure or heart rate with pentamorphone doses of 0.015–0.48 micrograms/kg (2).

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Pentaquine

General Information

Pentaquine is an 8-aminoquinoline that has been used to treat malaria (1,2) and trypanosomiasis (3,4). It has adverse effects very similar to those of primaquine.

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Pentazocine

General Information

The adverse effects of pentazocine in effective doses are largely typical of its class (1,2), with some quantitative exceptions.

Pentazocine 30 mg had no effect on motor skills but impaired sensory processing and extraocular muscle imbalance (3). Other effects reported in this study were slight respiratory depression (enhanced by concurrent amitriptyline) and feelings of clumsiness, drowsiness, friendliness, and contentedness, and a muzzy head.

The effects of pentazocine were studied in 16 non-abusing volunteers recruited via posters and local newspaper advertisements and were compared with the effects of morphine (4). Pentazocine had dose-related effects on subjective, psychomotor, and physiological variables, and the clinically relevant dose of 30 mg produced a greater magnitude of dysphoric subjective effects than morphine 10 mg and, unlike morphine, impaired psychomotor performance. With pentazocine, peak ratings from the adjective checklist were significantly increased for "dry mouth," "sweating," and "turning of stomach." Compared with morphine, pentazocine led to higher ratings for "drunk," "feel bad," "having pleasant bodily sensations," and "having unpleasant bodily sensations."

Organs and Systems

Psychological, psychiatric

Perceptual disturbances are generally thought to occur more often with pentazocine than with other opioids. Objective definition of such phenomena is difficult, but in a study of postoperative dreaming after the use of pentazocine and morphine as premedicants there was no statistically significant difference between the two drugs (SED-11, 148) (5).

Hematologic

There have been reports of pentazocine-induced agranulocytosis in the absence of other predisposing factors (SED-11, 148) (6).

Skin

Two distinct types of skin lesions have been described in patients taking pentazocine: scleroderma-like changes, subcutaneous abscesses, cellulitis, ulceration, muscle atrophy and granulomas (all of which are well-recognized consequences of pentazocine abuse), and a generalized erythematous desquamative rash.

Severe renal insufficiency associated with toxic epidermal necrolysis has been reported (7).

Long-Term Effects

Drug abuse

Abusers sometimes adulterate the pentazocine with tripelennamine (T's and blues). Medical and psychiatric complications can include seizures, abscesses, depression, psychosis, dysphoria, confusion, and hallucinations (8,9).

Drug dependence

Pentazocine dependence is associated with a mild opioid–like withdrawal syndrome (8,9).

Drug withdrawal

A neonatal withdrawal syndrome has been described, with verification by the detection of pentazocine and its metabolites in the urine of both mother and baby. Within 4 hours of birth the child was irritable, jittery, and hypertonic, with a high-pitched cry, a voracious appetite, and frequent bowel movements. The symptoms improved over 3 days. The mother had abused parenteral pentazocine (23–46 mg) for the previous 10 years and injected the last dose of 46 mg some 10 hours before delivery (10).

Susceptibility Factors

Renal disease

A fatal nephrotic syndrome occurred in a 33-year-old man with renal glomerular disease dependent on pentazocine (SEDA-17, 88).

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Other features of the patient

There is evidence that heavy smoking can increase the elimination of pentazocine; thus heavy smokers may require larger doses than non-smokers.

Drug Administration

Drug administration route

Fibrous myopathy and necrotic ulceration can occur at the injection site after repeated parenteral administration (1). Myocutaneous sclerosis and extensive calcinosis at the injection site have also been reported (SEDA-17, 88).

- A 58-year-old nurse who was given parenteral pentazocine developed large sclerotic and infected areas with multiple depressed atrophic scars at sites of prior ulceration; unsterile injection technique could not be excluded as a cause (11).
- A 47-year old woman with a 4-year history of injections of pentazocine into the legs developed very hard thigh and buttock muscles with hard, shiny, hairless overlying skin (12). Imaging showed fibrosis and calcification of the muscles and biopsy showed fibromyopathy. There were associated clinical and electrophysiological polyradiculopathy and multiple mononeuropathy of the lower extremities.
- A 26-year-old woman presented with progressive thickening and tightening of the skin over both her shoulders and buttocks, with resulting movement restrictions (13). She had a 5-year history of multiple intramuscular pentazocine injections for abdominal pain. The site of skin tightening was initially localized to the injection site. The affected areas increased progressively. There was an ill-defined area of hyperpigmented, indurated, "woody hard" skin bound to underlying structures and over her shoulders and buttocks. The diagnosis was pentazocine-induced widespread cutaneous fibrosis and myofibrosis. There was no evidence of scleroderma or dermatomyositis.
- A 38-year-old man, with a painless progressive restriction of flexion around both knee joints for 4 years, had been injecting pentazocine 1–2 ml intramuscularly for 18–20 years (14). The diagnosis was pentazocine-induced fibromyositis and contracture.

Drug overdose

Pentazocine in overdose can cause generalized tonic-clonic seizures, hypertension, hypotonia, dysphoria, hallucinations, delusions, and agitation, with a poor response to naloxone (15). Others have reported status epilepticus, coma, respiratory depression, acidosis, severe hypotension, and ventricular dysrhythmias.

Drug–Drug Interactions

Alcohol

There is increased toxicity in patients who take pentazocine with alcohol, antihistamines, or CNS depressants; one patient developed opioid pulmonary edema and one died (15).

Rhabdomyolysis and acute renal necrosis occurred in a 26-year-old man after concomitant use of pentazocine and alcohol (16).

Methylphenidate

Intravenous injection of a mixture of methylphenidate and pentazocine intended for oral use resulted in death due to granulomatosis associated with pulmonary hypertension (17).

Monoamine oxidase inhibitors

Opioids interact with monoamine oxidase inhibitors, causing CNS excitation and hypertension (18).

Serotonin re-uptake inhibitors

A serious excitatory interaction between fluoxetine and pentazocine has been reported (SEDA-16, 89). The authors commented on the similarity of this syndrome to the reported dangerous interactions between monoamine oxidase inhibitors and narcotic analgesics, and suggested that increased central 5-HT activity may be the basis of the observed interaction.

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Pentetrazol

General Information

Pentetrazol (pentylenetetrazol) is a central and respiratory stimulant, similar to doxapram hydrochloride. It is a $GABA_A$ receptor antagonist and is anxiogenic (1). It has been used in respiratory depression and has also been included in multi-ingredient formulations for respiratory tract disorders, including cough, and for the treatment of hypotension and pruritus. However, the general consensus is that pentetrazol does not have a place in the treatment of respiratory depression (2).

Adverse reactions were mild in a controlled study of the efficacy of pentetrazol, alone and in combination with nicotinic acid, in 30 chronic hospitalized elderly patients. Improvement was better with the combined treatment, and only one subject, a 71-year-old woman, developed restlessness, anorexia, and weight loss (3).

Irritability, altered consciousness, and autonomic reactions, together with improvement in thought content and memory testing were noted in a double-blind, placebo-controlled study of pentetrazol 200 mg/day in 20 elderly patients. Nine of the ten patients lost weight (4).

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Pentoxifylline

General Information

Pentoxifylline (oxipentifylline) is a methylxanthine that antagonizes the vasoconstrictor effects of catecholamines and increases cyclic AMP concentrations, causing smooth muscle to relax. It has also been claimed to correct impaired microcirculation, by improving various factors that disturb blood rheology, and to reduce the generation of toxic free radicals from leukocytes during ischemic leg exercise in patients with intermittent claudication. Pentoxifylline has been used to suppress overproduction of tumor necrosis factor alfa in conditions such as falciparum malaria and rheumatoid arthritis and in transplant recipients, with varied success.

Comparative studies

In 52 adults with cerebral malaria who were randomized to either quinine dihydrochloride alone ($n = 32$) or a combination of quinine and pentoxifylline ($n = 20$), the addition of pentoxifylline significantly improved coma resolution time from 64 to 22 hours and reduced mortality from 25% to 10% (1). Three days after therapy, serum tumor necrosis factor alfa concentrations fell significantly in those who received pentoxifylline. Pentoxifylline caused no serious adverse effects that necessitated withdrawal.

Placebo-controlled studies

The efficacy of pentoxifylline in treating claudication has been evaluated in double-blind, controlled trials in Europe and the USA. Several of these trials have shown that pentoxifylline 400 mg tds increases the walking distance significantly more than placebo in patients with claudication. However, critics remain skeptical about the real value of pentoxifylline, because of a negative correlation between the trial sample sizes and its effects, reflecting an overestimate of drug effect in highly selected trial populations (2). In a trial in almost 300 patients with acute ischemic stroke, the neurological deficit improved more rapidly with pentoxifylline in the initial phase, but the difference was not significant at the end of 1 week (3).

In a placebo-controlled trial in 114 patients with critical limb ischemia, twice-daily intravenous pentoxifylline 600 mg produced unimpressive results (4).

Unwanted effects of pentoxifylline recognized in the double-blind studies were gastrointestinal symptoms (chiefly nausea, vomiting, and bloating) and dizziness. Although common, they required drug withdrawal in only about 3% of patients.

Organs and Systems

Nervous system

Aseptic meningitis has been reported in a patient taking pentoxifylline (5).

- A 37-year-old woman with mixed connective tissue disease took pentoxifylline 400 mg/day for Raynaud's

phenomenon. After 12 days she complained of headache, myalgia, and neck pain and developed a fever. She recovered promptly after withdrawal of the drug. A few weeks later, she took a single tablet of pentoxifylline and within 1 hour developed the same symptoms together with chills, vomiting, and diarrhea. Neurological examination was normal, but the cerebrospinal fluid contained a large number of leukocytes. Bacteriological and virological tests were negative.

A diagnosis of aseptic meningitis was made and pentoxifylline was thought to have played a causative role because of the suggestive symptoms after first exposure, the close temporal relation on rechallenge, and the quick recovery after withdrawal. The authors argued that the underlying disease may have had a predisposing role, since aseptic meningitis secondary to pentoxifylline has never been reported in the thousands of patients who have used it for peripheral arterial disease. On the other hand, aseptic meningitis occurs with NSAIDs in patients with connective tissue diseases.

Psychological, psychiatric

Rare cases of hallucinations in elderly people have been ascribed to a stimulant effect of pentoxifylline on the central nervous system (SEDA-18, 219).

Hematologic

A single case of bleeding duodenal ulcer after a single dose of pentoxifylline was reported as being possibly secondary to disturbed platelet function induced by the drug (6). However, the effects of pentoxifylline on platelet function have not been very consistent, and the use of pentoxifylline may have been purely coincidental.

Immunologic

In an open, randomized, controlled trial in 56 children with cerebral malaria, the 26 children who received pentoxifylline 10 mg/kg/day by continuous infusion had significantly shorter periods of coma than the controls. The pentoxifylline recipients showed a trend toward a lower mortality. Pentoxifylline has an inhibitory effect on the synthesis of tumor necrosis factor alfa. The better outcome in the treated group was associated with a fall in tumor necrosis factor alfa serum concentrations on the third day of treatment in a few subjects; this was not seen in the controls (7).

However, in a later, randomized, placebo-controlled trial pentoxifylline neither reduced tumor necrosis factor alfa serum concentrations nor affected the clinical course in 51 patients who received it as adjunctive treatment to standard antimalarial therapy in a dosage of 20 mg/kg/day over 5 days (8).

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Pergolide

General Information

The adverse effects of pergolide, a dopamine receptor agonist, resemble those of bromocriptine (SEDA-10, 118) (SEDA-13, 113).

It is almost universally accepted that directly acting dopamine receptor agonists have less efficacy than levodopa, although the reasons are not clear. Neurologists from London have sought to question this assumption by using cabergoline ($n = 11$) and pergolide ($n = 7$) at considerably higher doses than recommended (1). The actual mean doses were 8.8 and 9.4 mg/day, compared with recommended maxima of 6 and 5 mg/day respectively. The high doses were tolerated by the patients for 2.3–2.5 years; mild dyskinesias ($n = 7$), ankle edema ($n = 3$), and hallucinations ($n = 1$) were the only reported adverse effects. The authors concluded that the therapeutic window for these drugs is apparently much greater than is generally accepted, and that higher doses can be given safely with potentially enhanced efficacy.

In 41 patients with Parkinson's disease who took pergolide, confusion and hallucinations were the adverse effects that were most likely to result in withdrawal of pergolide (2). Symptoms suggestive of dose-related angina pectoris occurred in four patients in the open phase and two patients in the earlier double-blind phase; these symptoms were easily controlled by dosage reduction or withdrawal of pergolide without sequelae. There was leukopenia in one patient.

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Organs and Systems

Cardiovascular

Symptoms suggestive of dose-related angina pectoris were observed in a number of patients, either early or late in treatment, but they were easily controlled by dose reduction without sequelae (2).

Pergolide can cause severe hypotension in patients already receiving antihypertensive agents (3).

Respiratory

Pleuropulmonary disease, especially with a fibrotic component, has been reported with all the ergot alkaloids after long-term use.

- A 65-year-old man, who had been taking pergolide 3.5 mg/day for 3 years to treat restless legs syndrome, presented with progressive weight loss, fatigue, and dyspnea (4). The history was of at least 2 years duration. A chest X-ray showed a loculated right hydropneumothorax, and a bloody pleural exudate was aspirated with no cytological evidence of malignancy. An open biopsy showed inflammatory changes and fibrosis. After withdrawal of pergolide and a short course of corticosteroids he made a full clinical and radiological recovery.
- A 73-year-old man who had taken pergolide 1.5 mg/day for 4 months developed dyspnea, bilateral pleural effusions, and severe edema of the legs up to the scrotum (5). There was no pleural thickening or any evidence of cardiac failure or nephrotic syndrome. These clinical features were resistant to diuretic therapy but resolved completely within a month of withdrawal of pergolide. The mechanism of this type of very rare reaction is totally unknown.

Nervous system

Long-term assessment pointed to confusion and hallucinations as the adverse effects most likely to occur requiring withdrawal of the drug (SEDA-15, 3) (2). Owing to its potency as a dopaminergic drug in patients with Parkinson's disease, dyskinesias can occur.

Sleep disorders can occur with pergolide, as with other dopamine receptor agonists.

- A 57-year-old woman and a 61-year-old man taking pergolide 4.5 mg/day and 5 mg/day respectively both suffered sleep disorders; the woman did not suffer from sleepiness but had abrupt sleep episodes, while the man was sleepy for much of the day (6). These were high doses and a reduction to 3 mg/day led to cessation of sleepiness in both patients.

Hematologic

Dose-related leukopenia developed in one patient (2).

Serosae

Most of the dopamine receptor agonists in current use are ergot derivatives, and these are known to cause serosal fibroinflammatory syndromes.

- Three men aged 61–70 years, who had taken pergolide 1–3.75 mg/day for 18–24 months for Parkinson's disease developed pericardial, pleural, or retroperitoneal fibrosis (one case of each) (7). Despite drug withdrawal, one patient needed pericardial exploration, one was left with residual evidence of severe ureteric obstruction, and one was left with persistent pleural disease.
- Pergolide 3 mg/day has been associated with retroperitoneal fibrosis in an 83-year-old woman after 18 months (8). She required ureteric stents, which were removed 2 years later, after her renal function had remained stable. Because of deterioration in her Parkinson's disease the non-ergot dopamine receptor agonist ropinirole was started and treatment was uneventful after 12 months.
- A 63-year-old British woman with Parkinson's disease was given pergolide in an attempt to minimize motor fluctuations in response to levodopa (9). After taking 4.5 mg/day for 8 months she developed shortness of breath and ankle swelling. This gradually deteriorated over the next year, despite diuretic therapy, and by that time her serum creatinine was 807 μmol/l and her hemoglobin was 8 g/dl. She had bilateral hydronephrosis on ultrasound scanning and a CT scan confirmed retroperitoneal fibrosis, which was successfully treated with nephrostomy and stenting, with resolution of the hydronephrosis. Pergolide was discontinued.

Dutch authors have described four patients, men aged 63–65 years, who had been treated for Parkinson's disease for 3–5 years with various doses (not all specified) of pergolide (10). In three cases pleural fibrosis was demonstrated on biopsy, while in the fourth there was pleural effusion with no histological evidence. On drug withdrawal there was clinical and radiological improvement in three cases but not in the fourth. On reviewing reports of similar adverse drug reactions the authors noted that the age and male preponderance of their patients was in keeping with previous reports. They observed that the dosage was generally higher in patients with retroperitoneal fibrosis compared with those with pleuropulmonary fibrosis. The duration of drug exposure was also a significant risk factor. Clearly, the fact that changes are often irreversible emphasizes the need for early detection and high levels of awareness of these problems.

- A 67-year-old man developed pericardial fibrosis and thickening while taking pergolide for Parkinson's disease (11). The symptoms and signs of heart failure emerged after 11 months, but the possible causative role of the drugs was not suspected for some months while the pericardial changes progressed, as did cardiac failure.

In this case the changes appeared to be wholly reversible on drug withdrawal.

Hair

Treatment with pergolide has very rarely been associated with reversible alopecia (12).

Sexual function

Czech neurologists have described seven men, aged 35–70 years, in whom sexual behavior was greatly increased and who had frequent spontaneous penile erections (13). All had been taking levodopa, to which pergolide 3 mg/day had been added, and all had advanced fluctuating

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Parkinson's disease. In one case the dosage of pergolide was halved and in two others ropinirole or entacapone were used as alternatives, in all cases with reduction of the hypersexual symptoms. The other four patients continued to take pergolide, with persistence of the symptoms, to which they and their partners adjusted.

Second-Generation Effects

Teratogenicity

Parkinson's disease is very rare in pregnancy, but has been described (14).

- A 36-year-old woman with a 4-year history of Parkinson's disease, who had been taking pergolide 3 mg/day and levodopa 200 mg/day continued to take it during pregnancy. The end-of-dose wearing-off effect completely disappeared, and reappeared at their previous intensity after delivery. There were no adverse effects in the mother. The baby was healthy at birth and remained so at the time of the report, at the age of 13 months.

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Perindopril

See also Angiotensin converting enzyme inhibitors

General Information

Perindopril is a prodrug ester of perindoprilat, an ACE inhibitor that has been used in patients with hypertension and heart failure. An updated review of its use in hypertension has appeared (1).

A large French open postmarketing study in 47351 hypertensive patients treated with perindopril for 12 months did not show unexpected adverse effects. The safety profile was similar to that of ACE inhibitors as a class (2).

Organs and Systems

Respiratory

Two cases of pneumonitis have been reported with perindopril (3). The second case was more convincing, because of the result of involuntary rechallenge, but the two cases had typical features of drug-induced pneumonitis. The authors referred to two previous reports of less typical but very likely cases of pneumonitis with captopril.

Skin

UVA photosensitivity induced by perindopril has been reported (4).

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Peroxides

See also Disinfectants and antiseptics

General Information

Solutions of hydrogen peroxide containing 5–7% H_2O_2 are used for cleaning wounds and ulcers. The disinfectant and deodorant actions of hydrogen peroxide occur by oxidation of cell materials during the rapid release of oxygen while hydrogen peroxide is in contact with the tissues. The solution does not penetrate well, but the effervescence provides a mechanical means for detaching

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necrotic tissue from inaccessible parts of wounds. It should not be used in closed body cavities. The germicidal action of hydrogen peroxide is relatively weak and of short duration.

Residues on insufficiently rinsed equipment disinfected by hydrogen peroxide can provoke local irritation, burns, and general reactions. Non-specific inflammation has been reported, with instantaneous blanching and effervescence on the surfaces of the intestinal mucosa during endoscopy (1).

Organs and Systems

Respiratory

Pneumomediastinum caused by subcutaneous emphysema has been reported in a 30-year-old man after the application of hydrogen peroxide solution to a root canal. The patient had acute pulpitis of the lower right third molar, treated by extirpation followed by irrigation with 3% hydrogen peroxide solution. Soon after irrigation, subcutaneous emphysema developed (2).

Hematologic

Hemolysis was reported after hemodialysis therapy with a dialysis fluid inadvertently contaminated with hydrogen peroxide (3).

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Perphenazine

See also Neuroleptic drugs

General Information

Perphenazine is a phenothiazine neuroleptic drug.

Organs and Systems

Hematologic

Aplastic anemia, defined by the presence of pancytopenia and a hypocellular bone marrow in the absence of any abnormal blood cells, is a serious reaction that has been attributed to perphenazine in a single case (1).

- A 23-year-old man with schizophrenia taking perphenazine 4 mg bd, benzatropine mesylate 2 mg/day, lithium carbonate 600 mg each morning and 900 mg at bedtime, and famotidine 40 mg/day developed fatigue, shortness of breath, dizziness, light-headedness, and general debility. He had a pancytopenia, which persisted in spite of blood transfusions. Bone-marrow aspiration showed hypocellularity, absent megakaryocytes, reduced erythropoiesis and myelopoiesis, increased iron storage, and a relative excess of lymphoid cells. All medications were withdrawn and he was given lorazepam 2 mg bd. He recovered after 8 months.

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Pertussis vaccines

See also Vaccines

Note on abbreviations

DTP = Diphtheria + tetanus toxoids + pertussis
DTaP = Diphtheria + tetanus toxoids + acellular pertussis
DTwP = Diphtheria + tetanus toxoids + whole cell pertussis

General Information

Whole-cell and acellular pertussis vaccines have been reviewed, with emphasis on the protectivity of the various virulence factors and antigens (1). The authors summarized their review as follows: although *Bordetella pertussis* has at least five proteins required for virulence and an additional two "toxic" components, only serum neutralizing antibodies to pertussis toxin have been shown to confer immunity to pertussis.

Acellular pertussis vaccine

Quality control of acellular pertussis vaccines presents particular problems related to the various methods used for preparation of the active components, the different compositions of the final formulations, and different amounts of antigen. Researchers in the National Institute for Biological Standards and Control in the UK have presented a strategy capable of addressing the key problem areas likely to be encountered with all existing types of acellular pertussis vaccines and combinations (2). Their proposal could be considered as a starting point for improvement of quality control programs for these vaccines.

An overview of clinical trials with a special diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine has been published (3). The vaccine contains as pertussis components purified filamentous hemagglutinin, pertactin, and genetically engineered pertussis toxin. The vaccine induces high and long-lasting immunity and is at least as efficacious as most whole-cell pertussis vaccines and similar in efficacy to the most efficacious acellular

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pertussis vaccines that contain three pertussis antigens. The vaccine is better tolerated than whole cell vaccines and has a similar reactogenicity profile to other acellular vaccines.

A vaccine containing diphtheria and tetanus toxoids and acellular pertussis with reduced antigen content for diphtheria and pertussis (TdaP) has been compared with a licensed reduced adult-type diphtheria–tetanus (Td) vaccine and with an experimental candidate monovalent acellular pertussis vaccine with reduced antigen content (ap) (4). A total of 299 healthy adults (mean age 30 years) were randomized into three groups to receive one dose of the study vaccines. The antibody responses (anti-diphtheria, anti-tetanus, anti-pertussis toxin, anti-pertactin, anti-filamentous hemagglutinin) were similar in all groups. The most frequently reported local symptom was pain at the injection site (62–94%), but there were no reports of severe pain; redness and swelling with a diameter of 5 cm or more occurred in up to 13%. The incidence of local symptoms was similar after TdaP and Td immunization. The most frequently reported general symptoms were headache and fatigue (20–50%). The incidence of general symptoms was similar in the TdaP and Td groups. There were no reports of fever over 39°C. No serious adverse events were reported.

Japanese studies of acellular vaccines

The first generation of the new acellular vaccines was developed in Japan in the late 1970s (Sato). Since late 1981, acellular vaccines have replaced the whole-cell pertussis vaccines for use in the Japanese immunization program. Two types of acellular pertussis vaccine have been produced by six Japanese manufacturers (5,6) (SEDA-12, 276) (SEDA-13, 283) (SEDA-14, 279). No doubt as a result of these measures the rate of reported serious reactions has decreased in Japan. During the period 1975–81, when whole-cell vaccines were given, the rate was 0.4 per million doses, compared with a rate of 0.25 per million doses during the period 1982–84 (7). In 1988, Kumura and Kuno-Sakai (8) summarized the experience gained in Japan since the introduction in 1981 of the new DTP vaccines containing acellular pertussis components. Acellular vaccines seem to be effective in Japan, since in parallel with their wider use the numbers of reported cases of pertussis and pertussis deaths have declined. Reactogenicity (as expressed by fever or local reactions) was very low. Kimura and Kuno-Sakei cited reports of Quincke's edema-like swelling of the whole arm following the third injection (0.17% of vaccinees) and the booster injection (2.61%), respectively. Data on more severe adverse events have been collected from 1970 to 1986 in the framework of the National Adverse Reaction Compensation System (SED-12, 818). Kimura and Kuno-Sakei considered the vaccines to be safe and effective enough to eliminate pertussis in Japan in the future (8).

European studies of acellular vaccines

The epidemiological circumstances in Sweden and in parts of Germany and Italy, where the immunization programs against pertussis using whole-cell vaccine had been discontinued or reduced because of public concern about rare severe adverse events, offered good opportunities to assess the clinical efficacy and safety of acellular pertussis vaccines. In Germany, both controlled field trials and a household contact study were carried out. Different mono-component and multi-component acellular vaccines from European and US manufacturers were used in European trials. They comprised a mono-component vaccine composed only of detoxified pertussis toxin (toxoid); a two-component vaccine composed of pertussis toxin and filamentous hemagglutinin; a three-component vaccine composed of pertussis toxin, filamentous hemagglutinin, Pertactin; and another five-component vaccine composed of pertussis toxin, filamentous hemagglutinin, Pertactin, and fimbriae antigens 2 and 3. In some instances they were compared directly with whole-cell pertussis vaccines. In general, the acellular vaccines were found to be immunogenic, epidemiologically effective, and less reactogenic than the whole-cell pertussis-component vaccines as assessed in terms of fever, pain, fretfulness, and local reactions at the injection site. Based on the results, acellular pertussis vaccines have since been licensed in many countries of the world both for primary and booster immunization. Details regarding the results and conclusions of the large-scale field trials completed in 1994 and 1995 in Germany, Italy, and Sweden have been reviewed (SEDA-19, 298), as have reports on other clinical trials using acellular pertussis vaccines (SED-12, 818) (SEDA-12, 277) (SEDA-13, 283) (SEDA-14, 279) (SEDA-15, 350) (SEDA-16, 382) (SEDA-17, 370) (SEDA-18, 332) (SEDA-20, 289) (SEDA-21, 230). The optimal composition of acellular vaccines has not yet been determined: the number of antigens still varies from one to five, and antigen amounts are also different. Post-licensing studies will therefore be of the utmost importance in studying the induction of herd immunity and possible rare events.

Local effects of acellular vaccines: effect of number of injections

Data on the use of a single DTaP vaccine for four-dose or five-dose series are limited, but the available data show a substantial increase in the frequency and magnitude of local reactions with successive doses. The accompanying tables show reactions after the fourth dose (Table 1) and fifth dose (Table 2). The original data and references are included in the supplementary recommendations of the Advisory Committee on Immunization Practices (ACIP) on the use of DTaP vaccines in a five-dose series (9). Reports from Alberta and British Columbia provinces, Canada, have suggested that the incidence rates of severe local adverse reactions may increase with each dose (third, fourth, fifth) in preschool children (10).

Limb swelling after booster doses of acellular vaccines

Swelling involving the entire thigh or upper arm has been reported after booster doses of different acellular pertussis vaccines, for example in a German study during April 1993 to November 1994 using a fourth dose of Infanrix. There was an increase in thigh circumference in 1.2–3.2% of children; swelling began within 48 hours of a booster dose and the mean duration was 3.9 (range 1–7) days; the

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Table 1 Reactions after the fourth dose of DTaP given at 2 or 3 years of age

Local and systemic reactions	ACEL-IMUNE	Tripedia	Infanrix*	Certiva
Pain		19%	26%	19
Erythema	10% ≥2.4 cm	30% ≥2.54 cm	14% ≥2 cm	6% ≥3 cm
Swelling		29% ≥2.54 cm	11% ≥2 cm	5% ≥3 cm
Induration	9% ≥2.4 cm			
Tenderness				
Fever = 38°C	26%		26%	6.3%
Fever = 38.3°C		5.5%		

*To be compared with reactions after the first dose: pain 2%, erythema 0%, swelling 0%, fever ≥38°C 6.3%

Table 2 Reactions after the fifth dose of DTaP administered at entry to school

Local and systemic reactions	ACEL-IMUNE	Tripedia	Infanrix
Pain		2.1% severe pain	1.6% severe pain
Erythema	20% >2–2.4 cm	31% >5 cm	
Swelling		25% >5 cm	30% >5 cm
Induration	14%		21% >5 cm
Tenderness	38%		

mean increase in circumference was 2.2–5.0 cm; in a few children, the swelling interfered with walking.

Similar swelling and substantial local reactions have been observed in fourth-dose and fifth-dose follow-up studies from the Multicenter Acellular Pertussis Trial, which examined 12 different DTaP vaccines, and in recent studies of the fifth dose of Tripedia and Infanrix in Germany. The pathogenesis of both substantial local reactions and limb swelling is unknown. Associations with pertussis toxoid, diphtheria toxoid, or aluminium in the vaccine have been discussed. Because reports to date have suggested that the reactions are self-limited and resolve without sequelae, and in recognition of the benefits of a fifth dose of DTaP, the ACIP has recommended that a history of extensive swelling after the fourth dose should not be considered to be a contraindication to a fifth dose of DTaP. Parents or caregivers of children who receive fourth and fifth doses of a DTaP series should be informed of the increases in reactogenicity that have been observed (9).

Whole-cell pertussis vaccine

Pertussis whole cell vaccine is an adsorbed suspension of inactivated pertussis bacteria. The vaccine is available in monovalent form or in combination with diphtheria and tetanus toxoids (DTP). DTP vaccine is the preparation of choice in routine immunization practice.

Local reactions are common after DTP immunization (40–70% of the vaccinees) but are usually self-limiting (10). A nodule may be palpable at the injection site of adsorbed products for several weeks. Abscess at the injection site has been reported (6–10 per million vaccinees). Mild to moderate fever (38.0–40.4°C) occurs frequently (about 50% of vaccinated infants), generally within several hours of administration, persisting for 1–2 days. Fever and other systemic symptoms are much less common following immunization with preparations not containing the pertussis component. Arthus-type hypersensitivity reactions occur, particularly after booster doses. Rarely, severe systemic reactions (urticaria, anaphylaxis) have been reported.

The non-neurological adverse effects of whole-cell immunization have been reviewed (SED-12, 815) (SEDA-16, 379) (SEDA-17, 370) (SEDA-18, 330). The most frequent are mild fever, drowsiness, and reduction in appetite; a very small percentage of vaccinees experience more severe fever, redness, swelling, pain, "fussiness", or vomiting.

A follow-up study has been carried out in 105 children with collapse (a hypotonic-hyporesponsive episode or a shock-like syndrome) after their first immunization with DTwP + IPV vaccine (11). Information about subsequent immunizations, health, and development in 101 of the children was supplied by child health-care units. The parents of one child refused further immunization, 16 children completed their schedule with the combination diphtheria + tetanus + poliomyelitis vaccine (DT-IPV), and the other 84 children received further pertussis vaccine (DTP-IPV), totalling 236 doses; 74 children received the complete series of three additional doses. None of the children had recurrent collapse, and other adverse events were only minor. About half were given paracetamol prophylactically for the first subsequent dose; most of them did not take it for further doses. The authors suggested that it is unnecessary to withhold further doses of pertussis vaccine in a child with collapse after a previous dose. It has been suggested that the threat of natural pertussis in non-immunized children should be taken much more into account than the fear of developing a collapse reaction (12). In another study (13) in the USA, one of the 14 children not completely immunized because of a hypotonic-hyporesponsive episode after a previous dose later developed natural pertussis, which lasted for 3 months and was transmitted to both her parents.

Acellular pertussis vaccine versus whole-cell pertussis vaccine

In a randomized, double-blind trial to determine the efficacy of vaccination against *Bordetella* infection, a

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multi-component acellular pertussis has been compared with a whole-cell product and diphtheria + tetamus toxoids (DT) in 8532 infants aged 2–4 months, who received four doses of either DTwP or DTaP vaccine at 3, 4.5, 6, and 15–18 months of age, and 1739 controls, who received three doses of DT vaccine at 3, 4.5, 15–18 months of age (14). All the vaccines were generally well tolerated. However, adverse reactions were significantly less common after DTaP compared with DTwP vaccine. Persistent inconsolable crying was four times more common in DTwP recipients than in DTaP recipients. High fever, 40.5°C or over, was three times more common in DTwP vaccinees than in DTaP vaccinees. Only one DTaP recipient had a convulsion in temporal relation to immunization.

The 2000 Childhood Immunization Schedule, proposed by the Advisory Committee of Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians, recommended that acellular pertussis vaccines be exclusively chosen for routine use in the USA (15).

One evaluation of the results of two studies in a total of 182 children primed either with acellular or with whole-cell pertussis vaccines at 2, 4, and 6 months of age and boosted with an acellular vaccine has shown that booster doses of acellular vaccine are safe and immunogenic (16). Local adverse reactions after booster immunization with acellular vaccine were more common in children primed with acellular vaccine than in those primed with whole-cell pertussis vaccine (68 versus 33%). In another and similar study, children primed with acellular or whole cell pertussis combined with DT vaccine have been boosted with a recombinant acellular pertussis vaccine combined with DT vaccine. The vaccine was highly immunogenic and safe (17).

From 1991 to 1993 about 27 million doses of DTP vaccine and 5 million doses of DTaP (that is acellular) vaccine were distributed in the USA. The results of a postmarketing comparison of the safety of acellular pertussis vaccines with whole-cell pertussis vaccines have been published. The rates of reported adverse events per 100 000 immunizations were significantly lower after the administration of DTaP vaccine than after DTP vaccine for the following outcomes: all reports (2.9 versus 9.8); fever (1.9 versus 7.5); seizures (0.5 versus 1.7); and hospitalizations (0.2 versus 0.9) (18).

The safety and immunogenicity of 12 acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fourth dose have been compared in 1293 children aged 15–20 months. In general, DTaP vaccines were associated with fewer adverse events than a US-licensed DTwP vaccine (SEDA-22, 342).

A randomized, controlled comparison of two-component, three-component, and five-component acellular pertussis vaccines and a whole-cell pertussis vaccine has been carried out in 82 892 infants who were immunized either at age 3, 5, and 12 months, or at 2, 4, and 6 months. High fever and seizures occurred more often after whole-cell vaccine than after any of the acellular vaccines. Hypotonic-hyporesponsive episodes also occurred significantly more often in the whole-cell group and were more frequent in the acellular groups than previously reported (SEDA-22, 342).

An informal consultation of invited epidemiologists, infectious disease clinicians, immunologists, representatives of regulatory agencies for biological products, and other scientists and public health officials was held in Geneva on 18–19 May 1998 on the control of pertussis using whole-cell and acellular pertussis vaccines. The consultation was called jointly by the Children's Vaccine Initiative and the World Health Organization Global Program on Vaccines. The report of the meeting including the conclusions at full length has been summarized (SEDA-22, 341). The main conclusions read as follows. Whole-cell vaccines of documented quality have proved to be highly effective tools for preventing pertussis. Acellular pertussis vaccines are valuable alternatives to whole-cell vaccines for immunization in infancy. Because of their safety profiles, acellular vaccines may be preferred alternatives in industrialized countries, in which pertussis vaccination with whole-cell vaccines is not widely accepted. In each country, recommendations for the use of pertussis vaccines will be based on local risk–benefit and cost–benefit analyses. The use of acellular vaccines in many circumstances can be further considered for booster doses (fourth and fifth doses) in improving pertussis control after evaluation by local authorities of the epidemiological, cost, and programmatic issues. Additional data on the potential benefit of booster doses using acellular pertussis vaccines in adolescence or older ages are needed. The current control regulations and recommendations for pertussis vaccines (whole-cell and acellular) needs thorough review in the light of recently available scientific data, and appropriate revisions should be made (19).

Comparisons of DTP and DT

An older study in the USA compared the rates of both minor and more serious reactions in 15 752 children 0–6 years of age to DTP vaccine and in 784 children to DT vaccine. The frequencies of minor reactions associated with DTP and DT are shown in Table 3. The reactions after DT were not only less frequent, but also less severe. Convulsions and hypotonic-hyporesponsive episodes each occurred in one per 1750 immunizations (20).

Data from the Monitoring System for Adverse Events Following Immunization (MSAEFI) (SEDA-13, 274) show that the adverse effects rate for DTP vaccine was twice as high as that for DT vaccine. The most reported adverse effect was fever (59% of all reports) followed by

Table 3 Frequencies of minor reactions associated with DTP and DT

Adverse effect	DTP (%)	DT (%)
Fitfulness	53	23
Pain	51	9.9
Fever	47	9.3
Local swelling	41	7.6
Local redness	37	7.6
Drowsiness	32	15
Anorexia	21	7.0
Vomiting	8.2	2.6
Persistent crying	3.1	0.7
High pitched unusual cry	0.1	0

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local reactions (36%) (21). Similar results have been published by Dittmann (13.5 severe adverse effects per million vaccinees after DTP immunization and 4.8 reactions per million vaccinees after DT immunization) (22) and by Miller and colleagues (23).

Tetravalent, pentavalent, and hexavalent immunization

DTaP or DTwP vaccine can be combined with other antigens, such as *Haemophilus influenzae* type b (Hib), inactivated poliovirus (IPV), and hepatitis B vaccine. In children DTaP or DTwP vaccines form the basis for such combinations, while in adults it is mostly Td vaccine. Current safety concerns regarding combination vaccines have been defined and reviewed (24). The author concluded that there is no evidence that adding vaccines to combination products increases the burden on the immune system, which can respond to many millions of antigens. Combining antigens usually does not increase adverse effects, but it can lead to an overall reduction in adverse events. Before licensure, combination vaccines undergo extensive testing to assure that the new products are safe and effective.

The frequency, severity, and types of adverse reactions after DTP-Hib immunization in very pre-term babies have been studied (25). Adverse reactions were noted in 17 of 45 babies: nine had major events (apnea, bradycardia, or desaturation) and eight had minor reactions (increased oxygen requirements, temperature instability, poor handling, and feeding intolerance). Babies who had major adverse reactions were significantly younger at the time of immunization than the babies who did not have major reactions. Of 27 babies immunized at 70 days or less, nine developed major reactions compared with none of those who were immunized at over 70 days.

The Hexavalent Study Group has compared the immunogenicity and safety of a new liquid hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and *Haemophilus influenzae* type b (DTP + IPV + HB + Hib vaccine, manufactured by Aventis Pasteur MSD, Lyon, France) with two reference vaccines, the pentavalent DTP + IPV + Hib vaccine and the monovalent hepatitis B vaccine, administrated separately at the same visit (26). Infants were randomized to receive either the hexavalent vaccine ($n = 423$) or (administered at different local sites) the pentavalent and the HB vaccine ($n = 425$) at 2, 4, and 6 months of age. The hexavalent vaccine was well tolerated (for details, see Table 4 and Table 5). At least one local reaction was reported in 20% of injections with hexavalent vaccine compared with 16% after the receipt of pentavalent vaccine or 3.8% after the receipt of hepatitis B vaccine. These reactions were generally mild and transient. At least one systemic reaction was reported in 46% of injections with hexavalent vaccine, whereas the respective rate for the recipients of pentavalent and HB vaccine was 42%. No vaccine-related serious adverse event occurred during the study. The hexavalent vaccine provided immune responses adequate for protection against the six diseases.

Organs and Systems

Nervous system

The question of nervous system complications and persistent brain damage after whole-cell pertussis vaccination has been argued for a long time. During the 1980s it was debated by physicians as well as by the general public in several countries. Reports, publications, and national evaluations of the matter led some countries to change their national pertussis immunization policy. In the autumn of 1981, Japan replaced the whole-cell vaccine with acellular pertussis vaccine developed by Sato in Japan. Sweden ended its pertussis (whole-cell vaccine) immunization program in 1979. As a result of the prominence accorded

Table 4 Percentage rates of local adverse events within 72 hours of immunization in infants given a hexavalent vaccine (Hexavac) or separate injections of the reference vaccines

Events	Hexavac				Pentavac				Hepatitis B Vax II			
	First dose	Second dose	Third dose	All[a]	First dose	Second dose	Third dose	All[a]	First dose	Second dose	Third dose	All[a]
Number of injections	423	420	418	1261	424	418	417	1259	424	418	417	1259
Any local reaction	23[b]	18	20	20	14[b]	16	18	16	3.3	2.6	5.5	3.8
Skin redness ≥2 cm	10	12	14	12	3.5	7.9	9.1	6.8	0.7	1.0	2.9	1.5
Skin redness ≤5 cm	2.8	1.2	1.0	1.6	0.5	0.7	1.0	0.7	0	0	0	0
Skin induration ≥2 cm	15	14	14	15	11	14	16	14	2.6	2.4	4.8	3.3
Skin induration ≥5 cm	2.6	1.5	0.7	1.6	0.3	1.0	0.7	0.6	0	0	0.3	0.1
Other local reactions[c]	2.8	0.5	1.2	1.5	0.9	0.2	0.7	0.6	0.5	0	0.2	0.2

[a] At least one reaction to any of the three primary doses.
[b] Statistically significant between the groups.
[c] Other local reactions: hematoma, injection site pain, local maculopapular rash, local heat.

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Table 5 Percentage rates of systemic adverse events within 72 hours of immunization in infants given a hexavalent vaccine (Hexavac) or separate injections of the reference vaccines

Events	Hexavac				Pentavac and Hepatitis B Vax II			
	First dose	Second dose	Third dose	All[a]	First dose	Second dose	Third dose	All[a]
Any systemic events (%)	52[b]	47	38	46	45[b]	42	40	42
Fever >38°C	6.9	19	18	15	4.7	17	22	15
Fever 38.0–38.9°C	6.4	18	14	13	4.2	17	18	18
Fever 39.0–39.9°C	0.5	1.4	3.6	1.8	0.2	0.2	3.4	1.3
Fever >40°C	0	0	0	0	0.2	0	0.5	0.2
Drowsiness	17	9.5	7.7	11	14	9.3	6.0	9.9
Irritability/unusual crying	33	27	21	27	29	23	20	24
Inconsolable crying >3 hours	0.2	0.2	0.2	0.2	0	0	0	0
Vomiting/diarrhea	7.3	5.7	5.0	6.0	6.8	4.3	6.5	5.9
Insomnia	6.1	5.2	3.1	4.8	4.5	4.1	5.0	4.5
Loss of appetite	13	8.3	6.5	9.3	9.2	9.1	7.4	8.6
Other systemic events[c]	4.3	5.0	7.7	5.6	3.8	4.1	6.2	4.7

[a] At least one reaction to any of the three primary doses.
[b] Statistically significant between the groups.
[c] Minor childhood illnesses (for example respiratory or gastrointestinal disorders).

to the risks involved, the pertussis vaccine coverage rates in the UK fell sharply at the beginning of the 1980s, but were increasing again when some large pertussis epidemics occurred as a result of diminished population immunity. In the 1980s, in the erstwhile Federal Republic of Germany, pertussis immunization was only recommended for children at special risk but from 1991 onwards the approach changed again and use of DTP was advised throughout what was now a united Germany. Severe neurological adverse effects of whole-cell pertussis immunization has been reviewed in detail, including reports on the legal cases brought in the English High Court pertussis vaccine trials (SED-12, 817).

It would now seem that the long debate has been resolved. The first step toward its resolution was taken in a review of all information available worldwide which was presented in a report produced in 1991 by the Institute of Medicine of the National Academy of Sciences, Washington (27) (SED-12, 817). It was concluded that:

- there is evidence indicating a causal relation between DTP vaccine and anaphylaxis, febrile seizures and inconsolable crying;
- there is weaker evidence pointing to a relationship between DTP vaccine and acute encephalopathy and hypotonic-hyporesponsive episodes;
- there is no reason to believe in an association between vaccination and the occurrence of infantile spasms, afebrile seizures, hypsarrhythmia, Reye's syndrome, or sudden infant death syndrome;
- there is insufficient evidence to indicate either the presence or absence of a causal relation between DTP vaccine and chronic neurological damage, epilepsy, aseptic meningitis, erythema multiforme or other rash, Guillain–Barré syndrome, hemolytic anemia, juvenile diabetes, learning disabilities and attention-deficit disorder, peripheral mononeuropathy, or thrombocytopenia.

In 1993, Miller and colleagues (28) and Madge and colleagues (29) presented the results of a 10-year follow-up study of the National Childhood Encephalopathy Study (NCES) carried out in 1976–79. The findings suggested a small excess risk of severe acute neurological events within 7 days of pertussis immunization, but the risk of permanent damage due to the vaccine, if any, was slight. Follow-up of cases and controls from this study for some years has shown that significantly more children with such illnesses die or suffer subsequent educational, behavioural, or neurological deficits than expected by comparison with controls, but the number of cases associated with pertussis vaccine was small and statistically vulnerable.

The committee responsible for the report of the Institute of Medicine concluded in 1994 that the recent findings from the NCES necessitated a review of the conclusion that the evidence is insufficient to indicate a causal relation between DTP and permanent neurological damage. After having reviewed the new NCES data, the committee declared that the balance of evidence was consistent with a causal relation between DTP vaccine and the forms of chronic nervous system dysfunction described in the NCES in children who have a serious acute neurological illness within 7 days after receiving DTP vaccine. This type of serious acute neurological response to DTP is rare. The estimated excess risk ranged from 0 to 10.5 per million immunizations. The evidence remains insufficient to indicate the presence or absence of a causal relation between DTP vaccine and chronic nervous system dysfunction under any other circumstances (30).

Finally, Gangarosa and colleagues have reviewed in detail the so-called pertussis vaccine encephalopathy. Seven epidemiological studies have been conducted; they show that neurological reactions are exceedingly rare with whole-cell pertussis vaccines (SEDA-21, 329).

Susceptibility factors

The (US) Immunization Practices Advisory Committee (ACIP) has recommended that a personal history of a prior convulsion should be evaluated before initiating or continuing immunization with vaccines containing a

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pertussis component. The presence of an evolving neurological disorder contraindicates pertussis immunization. Other contraindications to the receipt of pertussis vaccine are hypersensitivity to vaccine components or a history of a severe reaction following an earlier dose (31). Reviewing the data on the relation between a family history of convulsions and immunization with pertussis-containing vaccines, both the ACIP as well as the US Committee on Infectious Diseases considered that a family history of convulsions in parents and siblings was not a contraindication to pertussis immunization. The ACIP and other authors, believe that the use of an antipyretic (for example paracetamol given at a dose of 15 mg/kg at the time of DTP immunization and again 4 hours later) in conjunction with DTP vaccine may be reasonable in children with personal or family histories of convulsions since it will reduce the incidence of post-immunization fever (32,33).

Skin

Bullous pemphigoid has been attributed to DTP-IPV vaccine (34).

- A previous healthy 3.5-month-old infant developed bullous pemphigoid 3 days after receiving a first dose of DTP-IPV vaccine. *Staphylococcus aureus* was isolated from purulent bullae. The lesions resolved rapidly after treatment with antibiotics and methylprednisolone.

The authors mentioned 12 other cases of bullous pemphigoid, reported during the last 5 years, that had possibly been triggered by vaccines (influenza, tetanus toxoid booster, and DTP-IPV vaccine).

Immunologic

Data from the Third National Health and Nutrition Survey (1988–94) have been used to analyse the possible effects of DTP or tetanus immunization on allergies and allergy-related symptoms among 13 944 infants, children, and adolescents aged 2 months to 16 years in the USA (35). The authors concluded that DTP or tetanus immunization increases the risk of allergies and related respiratory symptoms in children and adolescents. However, the small number of non-immunized individuals and the study design limited their ability to make firm causal inferences about the true magnitude of effect.

It has been suggested that the development of a sterile abscess represents an idiosyncratic reaction of some individuals, perhaps genetically determined, which causes a granulomatous response to antigens, irrespective of the location of the vaccine (36). Others maintain that it is caused by a contaminated needle track or to vaccine material coating the outside of the needle, resulting from the lack of a proper injection technique.

Susceptibility Factors

Age

Details regarding the age-related efficacy of the use of paracetamol and the inefficacy of prophylactic paracetamol given in a single dose have been published (SEDA-14, 277).

Drug Administration

Drug formulations

In a study of local and systemic reactions following 9920 DTP immunizations there were significant differences relating to different manufacturers and different vaccine lots (37).

Drug additives

Eight children developed urticaria within 30 minutes after administration of a diphtheria + tetanus + acellular pertussis (DTaP) vaccine that contained gelatin as a stabilizer (38). None of the children had anti-gelatin IgE, and only two had detectable concentrations of anti-toxoid IgE to diphtheria and pertussis toxoids. No methods to measure anti-thiomersal and anti-alum IgE were available. The authors recommended the development of such methods, which could improve research into the causality of adverse effects of this sort.

Drug administration route

The "two-needle strategy," based on the hypothesis that changing the needle on the syringe after drawing up the DTP vaccine and before injecting reduces local reactions by eliminating deposition of aluminium adjuvant in the subcutaneous track of the needle, has been evaluated (39). When immunizing 223 children using this strategy and 200 others using the "one-needle strategy," there was no significant difference in the occurrence of local or systemic reaction.

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Pethidine

General Information

Pethidine (meperidine) is about one-tenth as potent as morphine in terms of analgesia. It is metabolized in the liver by hydrolysis and conjugation, either directly or via *N*-demethylation to norpethidine. Norpethidine (normeperidine) is significantly less analgesic, with a longer half-life (15–20 hours).

There has been a systematic review of the postoperative analgesic efficacy and adverse effects of pethidine and ketorolac compared with placebo in published randomized, controlled, double-blind studies (1). The authors reviewed studies of moderate to severe postoperative pain relief and the use of single doses by injection (intravenously or intramuscularly) or orally. Studies of epidural, intrathecal, or intravenous administration using patient-controlled analgesia were excluded. Of the 24 placebo-controlled pethidine studies, only 8 met the inclusion criteria and these generated 10 pethidine versus placebo comparisons and 254 patients given pethidine 50 mg or 100 mg intramuscularly. No studies of oral or intravenous pethidine at any dose met the inclusion criteria. Only the eight comparisons of pethidine 100 mg versus placebo ($n = 203$) had sufficient information available for analysis of adverse effects. The overall conclusion was that opioids carry a small but finite risk of serious adverse effects, such as respiratory depression, and a greater risk of minor adverse effects than single-dose injected or oral NSAIDs like ketorolac. Analgesia from the injected opioid or NSAID was equivalent to that achieved with oral NSAIDs. For those who cannot swallow, the choice is injected opioids like pethidine.

In a double-blind, randomized, placebo-controlled study, 40 patients who were scheduled for elective cesarean section under spinal anesthesia were given intrathecal 0.5% hyperbaric bupivacaine 2 ml together with either 5% pethidine 0.2 ml or isotonic saline (2). The pethidine group had a significantly greater incidence of intraoperative nausea or vomiting, with significantly better immediate postoperative analgesia, which was not sustained 4 hours after surgery.

In a randomized, controlled study in 611 mothers, 310 were randomized to intramuscular pethidine up to 300 mg and 301 to epidural 0.25% bupivacaine 10 ml with an infusion of 0.125–0.25% bupivacaine (3). There were no significant differences in analgesic efficacy, adverse effects, or the incidence of backaches.

Organs and Systems

Cardiovascular

- A 70-year-old patient with a metastatic carcinoid tumor of the liver presented with a hypertensive crisis after being given pethidine 10 mg/hour by continuous intravenous infusion (4). The patient remained hypertensive with a systolic blood pressure of 210 mmHg, even after chemoembolization of the tumor. The blood pressure fell when pethidine was withdrawn and nitroprusside was given. The serum 5-HT concentration was 15 μmol/l (reference range 0.17–0.26) and the urine 5-hydroxyindoleacetic acid concentration was 1311 mg/g of creatinine (reference range less than 10).

The authors postulated that the hypertensive crisis had occurred from the release of 5-HT from the tumor and blockade by pethidine of 5-HT re-uptake.

When used for sedation in children undergoing esophagogastroduodenoscopy, hypoxia with dysrhythmias was more likely to occur with a combination of pethidine and diazepam than with pethidine and midazolam (SEDA-18, 81).

Nervous system

Cases of severe reversible neurotoxicity and parkinsonism are on record (SED-11, 143) (SEDA-18, 82) (5,6). Severe nervous system syndromes may also result from interactions (see the monograph on Opioid analgesics).

Although seizures are uncommon, several cases have been reported, including when pethidine was used in PCA. The metabolite norpethidine is considered to be of significant importance in provoking seizures. Risk factors are renal insufficiency, sickle-cell anemia, high doses of pethidine, and concurrent administration of phenothiazines or drugs that induce hepatic enzymes (SEDA-16, 85) (SEDA-18, 82) (SEDA-19, 85). Myoclonus can occur (7). Norpethidine is twice as likely as pethidine to cause convulsions. The seizures occur at a norpethidine concentration range of 0.38–9.9 μg/ml, and only few reports have described convulsions within the first 24 hours of pethidine treatment.

- A 35-year-old woman, who was admitted for elective laparotomy and ileostomy formation was given patient-controlled analgesic with pethidine for postoperative analgesia (8). The device was set to deliver 20 mg of pethidine with a 5-minute lock-out period and no hourly limit. At 4 hours postoperatively she did not have pethidine-related neurotoxicity, but at 23 hours she had myoclonic jerks and facial twitching followed by a brief generalized tonic-clonic seizure and postictal sequelae. The pethidine was withdrawn and there was no further seizure activity. She had self administered a total of 2700 mg. The norpethidine concentration was 1.8 μg/ml.

Two of three patients with seizures due to norpethidine toxicity (9–11) had renal disease.

- A 46-year-old woman with previous extensive urological problems, including ureteric stricture and recurrent urinary tract infections, was given pethidine in a total cumulative dose of 1500 mg postoperatively over 12 hours when she presented with a single tonic-clonic seizure that lasted 30 seconds. The pethidine concentration was 1200 ng/ml and the norpethidine concentration 2100 ng/ml.
- A 72-year-old patient with end-stage renal insufficiency undergoing peritoneal dialysis developed myoclonic contractions and a generalized tonic-clonic seizure 48 hours after having been given pethidine in a total cumulative dose of 250 mg intravenously and 600 mg

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orally. The neurotoxicity resolved after withdrawal of pethidine and 4 hours of hemodialysis.
- A 2-month-old boy presented with muscle rigidity of the arms and legs, catatonia, and an exaggerated startle reflex after being erroneously given a single dose of pethidine 1 mg/kg. The symptoms subsided without any active intervention.

Two case reports have highlighted the potential danger of injecting pethidine into the lateral thigh region, which can cause injury to the femoral nerve branch to the vastus lateralis, causing muscle atrophy (12).

In a retrospective survey of 355 medical records of patients who received intravenous PCA pethidine between 1988 and 1994 the mean consumption by patients who had used over 600 mg/day of pethidine was 13.3 mg/kg/day in asymptomatic patients and 16.9 mg/kg/day in the 2% of patients who presented with central nervous system excitatory signs and symptoms (muscle twitches, jitteriness, agitation, and hallucinations) (13). The authors recommended a maximum safe dose of pethidine by PCA of 10 mg/kg/day for no more than 3 days.

Gastrointestinal

A study in which it was intended to recruit 90 women in labor for a comparison of intrathecal bupivacaine 2.5 mg, fentanyl 25 μg, pethidine 15 mg, and pethidine 25 mg was stopped prematurely after only 34 had been recruited, because of a significant increase in the incidence of nausea and vomiting in the patients who received the two doses of pethidine (14).

Immunologic

Pethidine causes histamine release (7). Of 16 patients given pethidine (mean dose 4.3 mg/kg), 5 had signs of the effects of histamine (hypotension, tachycardia, erythema) and raised histamine concentrations (7).

- A 42-year-old patient presented with generalized pruritus, erythema, urticaria, facial angioedema, dysphagia, dysphonia, and dizziness 15 minutes after a single intramuscular dose of pethidine 100 mg for severe renal colic (15). Prick tests and intradermal tests with pethidine and other compounds confirmed an allergic reaction to pethidine.

Long-Term Effects

Drug dependence

The interaction between the drug-dependent patient and health professional has been investigated in a retrospective study of the medical records of 20 patients with chronic organic pain and perceived as being dependent on pethidine (16). The fact that the patients were perceived as being addicted may have influenced the adequate management of their chronic intractable pain, precipitated poor staff–patient relationships, created a lower pain threshold or tolerance due to anxiety and depression, and led to overuse of placebo, leading to inadequate analgesia. All of these factors may then have led to craving-like behavior and demands for more analgesics, further fuelling the negative stereotyped perception of the addicted personality. The authors suggested that people with dependence-related problems should be evaluated for suicidal intent; concurrent psychiatric illnesses should be treated; and precipitating factors that make pain worse should be identified. Medical and other staff should be educated about the use of opiate analgesics and concepts of dependence, in order to reduce negative judgmental attitudes and misconceptions.

Second-Generation Effects

Fetotoxicity

Pethidine is commonly used in some countries as an analgesic in maternal labor. The analgesic and adverse effects of intramuscular pethidine 5 mg plus diamorphine 100 mg in labor have been studied in a randomized, double-blind, controlled study in 64 multiparous and 69 nulliparous women (17). There was a significantly higher incidence of low Apgar scores at 1 minute after pethidine compared with diamorphine. The study also confirmed that for women who requested intramuscular narcotic analgesia, neither diamorphine nor pethidine provided good pain relief, suggesting that there is a need to consider alternatives.

Pethidine 50 mg plus promethazine 25 mg given intravenously to 14 mothers in labor caused a significant change in fetal heart rate indices 40 minutes after administration (18). There were significant changes in fetal heart rate acceleration of at least 10 beats/minute, acceleration of at least 15 beats/minute, time spent in episodes of high variation, and short-term variation.

Susceptibility Factors

Renal disease

Norpethidine (normeperidine) accumulates in cases of renal insufficiency (19), leading to symptoms of overdosage.

Hepatic disease

Patients with cirrhosis and acute viral hepatitis can have a 50% reduction in pethidine clearance (SEDA-19, 85).

Drug Administration

Drug dosage regimens

In a double-blind study of 60 patients undergoing elective carpal tunnel release given pethidine 0, 10, 20, 30, 40, or 50 mg in addition to intravenous regional anesthesia with lidocaine 0.5%, the duration of analgesia increased dose-dependently with 0, 10, 20, and 30 μg (20). In those given pethidine 30, 40, and 50 μg there was a significantly higher incidence of sedation, pruritus, nausea, vomiting, and respiratory depression with no increase in analgesic effect. These results support an optimal dose of pethidine 30 mg when used with 0.5% lidocaine for postoperative analgesia.

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In a prospective, randomized, single-blind study in 45 men undergoing lower abdominal surgery using one of three doses of intrathecal pethidine (1.2, 1.5, or 1.8 mg/kg) there was no difference in the incidence of adverse effects among the three groups (21). The authors postulated that increasing the dose of pethidine from 1.2 to 1.5 mg/kg increased the duration of analgesia but not the level of sensory block, without an increase in adverse effects.

In 40 patients undergoing prostatectomy with spinal anesthesia with lidocaine 5% (75 mg) intrathecally, either alone or co-administered with pethidine 0.15 or 0.30 mg/kg, the higher dose of pethidine reduced the requirement for parenteral analgesics with a non-significant incidence of pethidine-related adverse effects (22).

Drug administration route

Epidural versus intravenous

In a double-blind, randomized, controlled study, 17 patients undergoing gastrectomy were given epidural PCA pethidine (10 mg bolus and a 4-hourly maximum dose of 3 mg/kg) and were compared with 20 patients after gastrectomy who were given the same regimen intravenously (23). The mean pethidine consumption in the first 24 hours was 33% less in the epidural group than in the intravenous group. Pain scores, adverse effects profiles, patient satisfaction, and patient outcome were similar. However, the sample size was small, and even though the study was intended to be double-blind, the route of pethidine administration and the patient's perception of an intravenous and epidural injection might have caused bias.

Rectal

Rectal pethidine is not advised in children, owing to enormous variability in systemic availability (SEDA-18, 82).

Drug overdose

Cardiac arrest occurred after pethidine overdose (24).

- A 2-month-old boy had a cardiac arrest when he was given a combination of pethidine, promethazine, and chlorpromazine in 10 times the recommended dose by the wrong route (intravenously rather than intramuscularly). Within seconds he became apneic and stiff. Cardiopulmonary resuscitation was instituted, including two intravenous doses of adrenaline 0.06 mg and naloxone 0.6 mg, with recovery 7 minutes after the incident and complete resolution 24 hours later.

Drug–Drug Interactions

Cimetidine

The hepatic metabolism of pethidine can be inhibited by cimetidine, leading to respiratory depression and sedation (25,26).

Phenytoin

Phenytoin enhances the metabolism of pethidine (27).

Selegiline

A syndrome resembling the serotonin syndrome has been reported in a patient taking pethidine plus selegiline (28).

- A woman with Parkinson's disease, taking selegiline 5 mg bd, pergolide 0.75 mg bd, co-careldopa 440 mg qds, imipramine 175 mg qds, and desipramine 25 mg qds, was given pethidine, 325 mg over 3 days, and hydroxyzine for pain. After 2 days she became restless and irritable, and after 4 days she developed delirium, muscle rigidity, sweating, and fever. The symptoms resolved when selegiline was withdrawn.

The authors did not discuss the role of the tricyclic antidepressants in this presentation.

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Phenazone

General Information

Phenazone, commonly known as antipyrine, is still used therapeutically in some countries, although it is now used mainly as a marker of hepatic enzyme drug metabolizing activity. It is an old compound with little recent investigation, usually taken in combination with other analgesics, and an exact analysis of its adverse effects is impossible. Phenazone seems to have a low toxicity index, in correspondence with its weak anti-inflammatory effect. Allergic reactions are very rare (SEDA-6, 92) (SEDA-14, 92) (SEDA-16, 108), but subjects undergoing the phenazone test should be informed of the potential risk.

Organs and Systems

Hematologic

Hemolysis can occur in patients with glucose-6-phosphate dehydrogenase deficiency. An immediate reaction after a single test dose, in the form of latent leukopenia, has also been reported (1), with previous sensitization to pyrazolone derivatives as the most probable explanation. Agranulocytosis has been observed in six women after the use of a phenazone-containing cream (SEDA-18, 101).

Gastrointestinal

Only chronic abuse of phenazone, probably together with other more aggressive antipyretics, can cause gastric symptoms (2).

Urinary tract

Phenazone nephrotoxicity is well-established, but information is limited. Experimental papillary necrosis can easily be provoked; analgesic nephropathy is probably a real danger with antipyrine, especially when it is combined with a stronger inhibitor of prostaglandin synthesis. The effect is probably toxic, since inhibition of prostaglandins is not a marked characteristic of phenazone. Two reports have suggested a causal link between phenazone and renal carcinoma, as is well-known for phenacetin (3,4), but this has not been confirmed.

Skin

Urticarial rashes and erythema are the most common adverse effects of phenazone, followed by maculopapular eruptions, erythema multiforme, erythema nodosum, or even angioedema (5).

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Phenazopyridine

General Information

Phenazopyridine, an azo dye, is used as a urinary tract analgesic. However, because of toxicity, the standard use of phenazopyridine as part of a fixed-dose combination no longer seems justified.

Organs and Systems

Nervous system

Aseptic meningitis was diagnosed in a patient who had three distinct episodes of fever and confusion after taking phenazopyridine (SEDA-13, 84).

Hematologic

Hematological adverse effects of phenazopyridine include methemoglobinemia and hemolytic anemia, particularly after overdosage (1,2).

Liver

Liver toxicity has been reported with phenazopyridine (3).

Urinary tract

Because of nephrotoxicity (oliguria, cylindruria, and reduced creatinine clearance, with crystal deposits in renal tubules and interstitial tissue) (4) phenazopyridine should not be used in patients with suspected renal disease and insufficiency, or in patients with glucose-6-phosphate dehydrogenase deficiency. Bladder stones have also been described (5).

Skin

Yellow discoloration of the nails has been attributed to long-term therapy with phenazopyridine (6).

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Phencyclidine

General Information

Phencyclidine or 1-(1-phenylcyclohexy-1) piperidine (known as PCP or "angel dust") was originally developed as an anesthetic, but was abused as an illicit drug from the late 1960s onwards. It is an antagonist at the *N*-methyl-d-aspartate (NMDA) subtype of glutamate receptors and a dopamine receptor agonist. It has anticholinergic properties through blockade of ion channels in acetylcholine receptors. It is still used in some countries as an antiparkinsonian agent (SED-11, 86) (1–3).

The psychoactive effects of phencyclidine are stimulant and similar to the effects of hallucinogens. Hallucinations are often bizarre, frightening, and challenging. Aggressive behavior, usually with amnesia, is common. Self-destructive actions are also seen. Overdosage is associated with paresthesia, slurred speech, ataxia, and later catatonia, dilated pupils, and coma, with tachycardia, hypertension, and dysrhythmias. Seizures and deaths have occurred (SED-11, 86) (4).

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Phenelzine

See also Monoamine oxidase inhibitors

General Information

Phenelzine is a non-selective monoamine oxidase (MAO) inhibitor.

Organs and Systems

Nervous system

A potential risk of using a non-selective inhibitor in patients with Parkinson's disease is illustrated by separate reports of the appearance of parkinsonism in patients taking phenelzine (1,2).

- Speech blockage, so called, has been reported in a 34-year-old woman who had taken phenelzine 45 mg/day for 2 months (3). The adverse effect disappeared on

withdrawal and did not recur when her depression was successfully treated with maprotiline 175 mg/day.

Psychological, psychiatric

In a carefully controlled 3-week comparison of phenelzine (up to 90 mg/day, mean 77 mg) and imipramine (up to 150 mg/day, mean 139 mg), four patients developed antisocial behavior, three overt paranoid psychosis, and one a hypertensive crisis, despite all precautions to avoid interacting foods and drugs (4).

There has also been a report of delusional parasitosis with phenelzine (SEDA-17, 14).

Dose-related visual hallucinations have been reported in a patient with macular degeneration taking phenelzine (the Charles Bonnet syndrome); the authors discussed the possibility that deprivation-induced visual phenomena had been intensified by increased central monoamine concentrations (5).

Nutrition

Authors who reported a case of carpal tunnel syndrome due to pyridoxine deficiency in a patient taking tranylcypromine (SEDA-9, 21) later collected data (6) on six patients taking phenelzine (up to 75 mg/day for up to 4 months). All developed low concentrations of pyridoxine and a variety of symptoms, including numbness, paresthesia, and edema of the hands, as well as an "electric shock" sensation in the head, neck, and arms. The symptoms resolved completely after the addition of pyridoxine 150–300 mg/day to the treatment regimen.

Hematologic

Leukopenia and agranulocytosis are well-recognized complications of treatment with tricyclic antidepressants and have been reported with some second-generation compounds. In a report of leukopenia in a patient taking phenelzine, attention was drawn to five other unpublished cases and to previous published reports involving isocarboxazid, tranylcypromine, and tryptamine (7).

Long-Term Effects

Drug withdrawal

In a study of the use of phenelzine in continuation therapy after recovery from an acute episode of depression, relapse rates were higher in patients subjected to tapered withdrawal than in those who continued taking the therapeutic dose (8).

In a study of the effects of sudden drug withdrawal in 34 patients taking phenelzine and 17 taking tricyclic antidepressants who had been treated for a mean duration of over 9 months, depressed patients taking phenelzine had significantly more symptoms than depressed patients taking tricyclic antidepressants, and a third of them relapsed, compared with a quarter taking the tricyclic (9). At 3 months follow-up 47% of the patients taking phenelzine had resumed treatment compared with 23% taking the tricyclic. An attempt to distinguish between withdrawal symptoms and relapse on the basis of the rapidity and severity of symptoms was unsuccessful, but about a third of the patients in both groups developed new symptoms of adrenergic hyperactivity, including anxiety and perceptual disturbances.

Acute psychotic symptoms have been reported in two young women shortly after withdrawal of long-term phenelzine 90 mg/day (10).

Tumorigenicity

A single case of angiosarcoma in the liver has been reported in a patient taking phenelzine (11); similar tumors have occurred in mice treated with phenelzine.

Drug–Drug Interactions

Amantadine

A possible hypertensive interaction of phenelzine with amantadine in Parkinson's disease has been reported (SEDA-10, 17).

Clonazepam

A flushing reaction has been associated with an interaction of phenelzine with clonazepam (SEDA-17, 17).

Venlafaxine

There have been reports of serotonin toxicity when venlafaxine was combined with therapeutic doses of conventional MAO inhibitors (SEDA-20, 21). The serotonin syndrome has been reported in four patients who were switched from the MAO inhibitor phenelzine to venlafaxine (12). In two of them, the 14-day washout period recommended when switching from phenelzine to other antidepressant drugs had elapsed.

- A 25-year-old woman, who had taken phenelzine (45 mg/day) for refractory migraine and tension headache, suffered intolerable adverse effects (weight gain, edema, and insomnia). Phenelzine was withdrawn and 15 days elapsed before she took a single dose of 37.5 mg of venlafaxine. Within 1 hour she developed agitation, twitching, shakiness, sweating, and generalized erythema with hyperthermia (38°C). Her symptoms resolved within 3 hours with no sequelae.

This suggests that even after the recommended 2-week washout from MAO inhibitors, venlafaxine can provoke serotonin toxicity in some patients.

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Phenindamine

See also Antihistamines

General Information

Phenindamine is an antihistamine that is reputed to cause stimulation rather than sedation in some patients. However, in one small study the central nervous system effects of phenindamine were intermediate between those of terfenadine and diphenhydramine (1).

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Pheniramine

See also Antihistamines

General Information

Pheniramine is a first-generation antihistamine.

Organs and Systems

Skin

Skin reactions with parenteral pheniramine maleate are uncommon. Relapsing generalized multiple evanescent pruritic erythematous weals after antihistamine and steroid injections have been reported in a 29-year-old woman (1).

Cutaneous reactions have also been reported with pheniramine in eye-drops (2).

- A 30-year old woman who used pheniramine eye-drops for allergic oculorhinitis developed eyelid dermatitis (2). Patch testing showed positive reactions on days 2 and 3.

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Phenmetrazine and phendimetrazine

See also Anorectic drugs

General Information

Phenmetrazine and phendimetrazine are central stimulants and indirect sympathomimetics related to dexamfetamine. Phendimetrazine is about 30% rapidly metabolized to phenmetrazine (1). Their reported adverse effects include glossitis, stomatitis, dry mouth, nausea, abdominal pain, cramps, constipation, difficulty in micturition, and headache.

Organs and Systems

Cardiovascular

A dilated cardiomyopathy has been associated with chronic consumption of phendimetrazine (2).

Nervous system

The main adverse effects of phenmetrazine reflect central nervous system stimulation and resemble those of other stimulants. There have been reports of encephalopathy as a result of phenmetrazine toxicity. There were also two cases of damage to the central nervous system after long-term treatment with phenmetrazine; in one, there were disseminated lesions, and in the other, hemiparesis and sensory motor aphasia (3).

Urinary tract

Phendimetrazine has reportedly caused acute interstitial nephritis (4).

Long-Term Effects

Drug abuse

There are many reports of abuse of phenmetrazine. Nervousness, hyperexcitability, euphoria, and insomnia,

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although less frequent than with amphetamines, have been observed with average doses. Dizziness, headache, nausea, dryness of the mouth, and urticaria have also been recorded. With large doses these adverse reactions were more pronounced. Paranoid psychosis was produced in addicts, and with chronic ingestion psychotic manifestations were evident as with amphetamine.

In Sweden, phenmetrazine has been extensively abused and misused, sometimes with intravenous use. Addicts who had previously been taking morphine stated that phenmetrazine gave them a sense of well-being and overconfidence. There was a high incidence of criminal activity in phenmetrazine users whose primary objective was obtaining money for the drug. Their average doses were 3060 tablets at a time, repeated 4–5 times a day (SED-9, 15).

Second-Generation Effects

Teratogenicity

Very rarely, congenital defects in the newborn have been associated with phenmetrazine consumption by the expectant mother.

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Phenobarbital

See also Antiepileptic drugs

General Information

Because it is cheap and of unquestioned efficacy, phenobarbital is still widely prescribed around the world, although in developed countries its use has fallen since the introduction of drugs that are better tolerated. Its most common adverse effects are sedation (to which partial tolerance develops), cognitive dysfunction, and in children hyperkinesia and other behavioral disturbances.

In a randomized trial in newly diagnosed patients, adverse effects leading to withdrawal were more common with phenobarbital (22%, mostly drowsiness and lethargy) than with all other drugs combined (carbamazepine 11%, phenytoin 3%, valproate 5%) (1).

Pretreating patients with phenobarbital can reduce the impact of adverse events when primidone is introduced. Of 30 patients with intractable partial epilepsy pretreated with phenobarbital before starting primidone (500 mg/day increasing by 125–250 mg/day every 3 weeks until adverse events or a seizure-free state was reached), 26 tolerated the introduction of primidone with minimal or no adverse events (2). Only one patient had to discontinue primidone during the initial 4 weeks because of severe dizziness. Three other patients had dizziness severe enough to interfere with their activities and this disappeared in two patients after the dose was lowered.

Organs and Systems

Nervous system

Unusual manifestations of neurological toxicity of phenobarbital include regression of developmental milestones mimicking a neurodegenerative disorder in young children (SEDA-19, 72) and unilateral choreiform hyperkinesia as a possible withdrawal symptom (SEDA-22, 82).

In a 12-month trial in 109 epileptic children randomized to monotherapy with phenobarbital (maintenance dosage 3.0 mg/kg/day) or phenytoin (5.0 mg/kg/day) in rural India there were no significant differences in either efficacy or toxicity (3). In particular, behavioral adverse effects were not more common with phenobarbital. The findings suggest that phenobarbital is an acceptable first-line agent for childhood epilepsy in rural settings in developing countries.

In 114 patients, of whom 72% took phenobarbital, one had ataxia due to phenobarbital toxicity (4).

Psychological, psychiatric

Phenobarbital-induced behavioral disturbances, especially hyperkinesia, are especially common in children, with an incidence of 20–50%; drug withdrawal is required in 20–30% of cases. It is unclear whether and to what extent adults are affected in this way.

Skin

Rare effects of phenobarbital include erythroderma and an atypical lymphocytosis that mimics cutaneous T cell lymphoma (SEDA-18, 67).

Toxic epidermal necrolysis has been reported in a 62-year-old woman and a 72-year-old man who had taken phenobarbital 100 and 150 mg/day respectively (5).

Musculoskeletal

The incidence of barbiturate-induced Dupuytren's contracture, frozen shoulder, Ledderhose syndrome, Peyronie's disease, fibromas, and joint pains may be up to 10% (6). Most affected patients develop connective tissue changes in the first year, although these become disabling at a later stage. These complications should be recognized early, since they are often reversible (SED-12, 137) (7).

Immunologic

Giant cell myocarditis has been reported in a patient taking phenytoin, phenobarbital, and mephobarbital and in one taking primidone (8).

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Death

The efficacy of a single intramuscular dose of phenobarbital (20 mg/kg) in preventing seizures in childhood cerebral malaria has been the subject of a randomized, placebo-controlled study in 340 children in Kenya (9). Seizure frequency was significantly lower with phenobarbital than placebo: 18 versus 46 children had three or more seizures of any duration (OR = 0.32; 95% CI = 0.18, 0.58). However, mortality was doubled (30 versus 14 deaths; OR = 2.39; CI = 1.28, 4.64). The frequency of respiratory arrest was higher with phenobarbital than with placebo, and mortality was greatly increased in children who received phenobarbital plus three or more doses of diazepam (OR = 32; CI = 1.2, 814). The authors felt that although phenobarbital was effective, the risks were too high to recommend using it.

Second-Generation Effects

Teratogenicity

There is an association of phenobarbital with oral clefts and cardiac malformations (10). This is also the case for methylphenobarbital (10).

Fetotoxicity

After prenatal exposure to anticonvulsants, small head size has been observed in neonates and cognitive impairment in infancy. However, it is currently unknown whether these effects are permanent or disappear later in life. Head size and cognition have been studied in adults who had been exposed in utero to phenobarbital plus phenytoin and who as neonates had a significantly smaller occipitofrontal circumference than neonates who had been exposed to phenobarbital alone or controls (mean difference 0.7 cm) (11). There was no difference in cognitive functioning between the exposed and the control groups, and most of the exposed subjects had normal intellectual capacity. However, 12% of the exposed subjects versus 1% of the controls had persistent learning problems. In addition, more of the exposed subjects were mentally retarded. The authors concluded that the combination of phenobarbital plus phenytoin reduced neonatal head size, which was not associated with reduced cognitive functioning in adulthood, but was associated with learning problems and mental retardation.

Susceptibility Factors

Patients with brain metastases treated with radiotherapy seem to have increased susceptibility to phenobarbital-induced toxic epidermal necrolysis (SEDA-19, 72). In a 53-year-old man taking phenobarbital, eruptions were limited to the sites of radiation, which were multiple (12).

Drug–Drug Interactions

Clozapine

Compared with 15 patients taking clozapine alone, seven patients taking similar dosages in combination with phenobarbital had significantly lower plasma clozapine concentrations (232 versus 356 ng/ml) (13). Plasma norclozapine concentrations did not differ between the two groups, whereas clozapine *N*-oxide concentrations were significantly higher in the phenobarbital group. These findings suggest that phenobarbital stimulates the metabolism of clozapine, probably by inducing its *N*-oxidation and demethylation. Although the clinical implications remain to be defined, an increase in clozapine dosage requirements may be considered in patients co-medicated with phenobarbital.

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Phenols

See also Disinfectants and antiseptics

General Information

Phenol is a benzyl alcohol and a major oxidized metabolite of benzene that was introduced into medicine as an antiseptic (1). Although it can be prepared in an aqueous solution or in glycerine, it appears to be more effective when mixed in aqueous compounds. At a concentration of 0.2% it is bacteriostatic and at over 1% bactericidal (2). In addition to its uses as an antiseptic and disinfectant, phenol is also used as a sclerosant, as a local anesthetic on the skin, and as an analgesic, by injection into nerves or spinally, but its use was limited by severe adverse effects. Current medical uses include cosmetic face peeling, nerve injections, and topical anesthesia. It is also an ingredient of various topical formulations, and is used as an environmental disinfectant.

Systemic adverse effects can occur through absorption from intact skin or wounds, by ingestion, or by absorption of vapor through the skin or via the lungs. They include central nervous stimulation followed by depression, seizures, coma, tachycardia, hypotension, dysrhythmias, pulmonary edema, metabolic acidosis, and hepatic and renal injury. Serious adverse reactions due to percutaneous absorption can occur and death has been described several times. The signs and symptoms of phenol toxicity have been reviewed (3–7) and are listed in Table 1.

Nonoxynols are ethoxylated alkyl phenols that are synthesized from alkylbenzene nonoxynol by reacting it with ethylene oxide to produce ethylene oxide polymers of various lengths. Each nonoxynol is followed by a number that indicates the approximate number of ethylene oxide groups it contains. In cosmetic products, nonoxynols are used as emulsifying, wetting, foaming, and solubilizing agents. They are used in hair and skin products, and in bath, shaving, and fragrance formulations (8). The non-ionic surfactant properties of nonoxynols allow them to be used in a wide variety of industrial, household, agricultural, and pharmaceutical products. Nonoxynol-9 and nonoxynol-10 are surface-active agents used in antiseptic formulations, such as Hibitane solution, Betadine solution, Hexomedine transcutanée, and Hexomedine ointment. They are the most commonly used spermicidal contraceptives and have been recommended in the prevention of sexually transmitted diseases and in human immunodeficiency virus prophylaxis (9).

Table 1 The signs and symptoms of phenol toxicity

System	Symptoms
Cardiovascular	Cyanosis, cardiac dysrhythmias, electrocardiographic abnormalities, circulatory failure, collapse
Respiratory	Respiratory failure
Nervous system	Dizziness, coma
Sensory systems	Darkening of the cornea
Hematologic	Methemoglobinemia
Gastrointestinal	Abdominal pain
Urinary tract	Hemoglobinuria
Skin	Darkening of the face and hands

Pentachlorphenol is a disinfectant that is used in commercial laundries. In 1967 a hospital laundry accidentally used a product containing sodium pentachlorphenolate for a final rinse in the laundering of diapers and infants' bed linen. Twenty newborn infants developed sweating, tachycardia, tachypnea, hepatomegaly, and metabolic acidosis. Six children with severe reactions were subjected to exchange blood transfusion and in each instance there was a dramatic improvement. Two babies died before exchange transfusion could be carried out; postmortem examination showed fatty change in the liver and hydropic and fatty degeneration in the renal tubules and myocardium. There were toxic concentrations of pentachlorphenol in the serum of one patient and autopsy tissue of another.

The phenol derivatives paratertiary butylphenol and amylphenol are used in proprietary germicides.

The permeability of the human epidermis to many phenolic compounds correlates with their lipophilic pattern. However, phenolic compounds appear to produce denaturation in the skin, and an additional increase in permeability is attributed to the resulting damage to the epidermis. Complications of topical phenol, notably cardiac dysrhythmias, including death, can be caused by phenol face peels (10).

Phenol is so rapidly absorbed through the skin that severe systemic effects and even death can result within minutes to hours.

- A 90% solution of phenol spilled over the left sole and shoe of a 47-year-old tanker driver (11). He neither removed his soaked shoe nor attempted to decontaminate himself. He continued driving for 4.5 hours, after which he had vertigo and faintness. Fire fighters removed him from the vehicle, took off his shoes and clothes, and thoroughly washed his leg with copious amount of water. On admission to hospital he was alert but confused, his heart rate was 146/minute, his blood pressure 160/100 mmHg, and there was tense swelling and blue-black discoloration of his left foot, ankle, and distal part of the leg (3% total body surface area), with hypalgesia and hypesthesia over the affected area. His leg was irrigated with large amounts of water, longitudinal incisions of his left foot were performed, and he was transferred to the intensive care unit. Shortly afterwards, he developed rapid atrial fibrillation, ventricular extra beats, reduced blood pressure (90/60 mmHg), and fever of 38.3°C. He was treated with intravenous crystalloids, verapamil, dopamine, and phenylephrine. All the systemic symptoms resolved in 24 hours. Blood and urine cultures were negative. Over the next 3 weeks he was treated with 0.25% troclosene dressings and 1% micronized silver sulfadiazine, until the swelling resolved and the wound had healed. On discharge from hospital and at a 4-month follow up, only blue-black discoloration was noted.

Phenol can be applied percutaneously by the use of a monopolar needle electrode or by open injection when the nerve is exposed surgically. In addition, main nerve trunks or motor branches can be injected, depending on the clinical indication.

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Organs and Systems

Cardiovascular

Phenol is cardiotoxic, and various cardiac dysrhythmias have been noted after application to the skin, or less commonly when it has been used for neurolysis. Ventricular extra beats occurred during topical application of phenol and croton oil in hexachlorophene soap and water for chemical peeling of a giant hairy nevus (12). Three of sixteen children treated with motor point blocks for cerebral palsy with a phenolic solution under halothane anesthesia developed cardiac dysrhythmias (13). Severe cardiac dysrhythmias followed by circulatory arrest occurred in an elderly patient with pancreatic cancer, injected with a phenolic solution to produce splanchnic neurolysis (14). The authors recommended that ethanol should replace phenol for this purpose.

In New Zealand, a patient died with brain damage after a cardiac arrest after being exposed to a chemical face peeling solution containing 64% phenol, Exoderm (15). The New Zealand Ministry of Health issued a public statement concerning the safety of phenol solutions.

Respiratory

Acute life-threatening epiglottitis developed in one patient after the use of a throat spray containing the equivalent of 1.4% phenol. The reaction may have been anaphylactic or a direct toxic effect (16).

Nervous system

Early reports suggested that phenol caused selective damage only to small sensory nerve fibers (17). However, later studies showed that in concentrations of 1–7% it caused indiscriminate damage to efferent and afferent nerve fibers (18). At concentrations under 1%, phenol appears to have a local anesthetic affect, which is fully reversible (19). However, at higher concentrations it causes both Wallerian degeneration and axonal demyelination, leading to muscle denervation. After injection of 2% aqueous phenol there can be damage to the microcirculation around nerves, leading to occlusion of small blood vessels and fibrosis in the injected area (20).

The most common adverse effect of phenol injection is pain during injection, often described as a burning or stinging sensation. It can be associated with edema several hours after injection. The application of ice and the use of non-steroidal anti-inflammatory drugs often help to minimize the discomfort. In some studies, lidocaine mixed with phenol has been used to help diminish the local pain response associated with injection (21).

The most worrying adverse effect related to phenol injection is dysesthesia, caused by involvement of sensory nerve axons when perineural injection is attempted. Dysesthesia has been reported from a few days to about 2 weeks after injection; most patients describe a neuropathic component, including a burning pain with light tactile stimulation and involvement of only a small portion of the sensory distribution of the nerve that was blocked (22).

Sensory loss or loss of voluntary motor strength are not uncommon in the first few days after chemical neurolysis with phenol (23), but permanent loss, other than motor changes associated with the reduction in hypertonia, is less frequent (24,25). A muscle that is already weak is more susceptible to further weakening with chemical neurolysis (26).

- Loss of all sensation and strength after chemical neurolysis occurred in the distribution of the posterior tibial nerve after mixed sensorimotor block of this nerve, in this case after five blocks of the nerve or its motor branches over several years. Some strength and partial sensation returned after surgical lysis of excessive fibrous tissue at the site where the injection had been performed (27).

Chemoneurectomy with aqueous phenol injection in 116 selected patients with spastic cerebral palsy, in whom 246 peripheral nerves were blocked, caused complications in 11 patients (28). Five patients, in whom the posterior tibial nerve was blocked, developed paresthesia: one had complete loss of sensation, which recovered spontaneously after a couple of days; and three had pain at the site of injection or in the distribution of the injected nerve, lasting for a few days to a month. In another study there was a 3% complication rate in 98 blocks (29), while adverse effects occurred in nine of 150 blocks, with muscle weakness in eight cases and painful paresthesia in one (30).

Liver

Neonatal jaundice has been associated with the use of phenolic disinfectants in nurseries, not only when used in excessive concentrations, but also when applied in the recommended dilution (SEDA-5, 258) (SEDA-8, 246) (SEDA-11, 484).

Chronic liver disease has been attributed to long-term household poisoning with pentachlorphenol (31).

Skin

Phenol-related contact pemphigus has been described (22).

- A 32-year-old otherwise healthy woman developed oral erosive lesions of 6 weeks duration and a bullous eruption on her legs, back, and chest of 2 weeks duration. She had bullae and erosions on the left thigh and bullae on the legs, back, abdomen, and chest. There was no family history of pemphigus. Pemphigus vulgaris was diagnosed, and she was given prednisone 100 mg/day. She went home for weekends during hospitalization, and returned to hospital each time with worse lesions. She reported working with a cleaning agent that she had begun using before the onset of the disease. The cleaning agent contained nonyl phenol, and she challenged herself at her next visit home by putting the same agent on her hands for a full day. As a result, new bullae appeared in the mouth. She was advised to stop using the product and was discharged a few days later taking prednisone 80 mg/day, which was tapered as the disease subsided. No new lesions appeared after 1 year of follow-up.

Depigmentation has been attributed to germicides (O-Syl® and Ves-Phene®), containing a mixture of the

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phenol derivatives paratertiary butylphenol and amylphenol, in five hospital workers and seven other patients who had used them as household disinfectants. Patch tests with the phenolic components of the disinfectants on the patients and controls showed that virtually any moderately irritating phenolic compound can depigment the skin, but of those tested, paratertiary butylphenol and amylphenol most often depigmented the skin without producing toxic inflammation. Initial signs of depigmentation appeared 6 months after using the phenolic mixtures. Within 1 year, two of five patients noted a spontaneous return of pigment; another continued to use the product and there was no evidence of repigmentation (SEDA-11, 485) (32).

Musculoskeletal

Intramuscular injection of phenol can cause pain and swelling in the muscle (33,34). Sometimes, a firm nodular swelling develops in the calf 1–3 weeks after intramuscular neurolysis (35), particularly when larger quantities of phenol are injected into the intramuscular branches of the tibial nerve. This can usually be avoided by limiting the quantity of phenol injected to the minimum necessary and by applying cold packs to the injected area after the procedure.

Muscle necrosis and round cell infiltrates have been seen in histological studies of animal muscle recently injected with phenol, but not after a few months have passed (36).

Immunologic

Contact dermatitis in patients exposed to nonoxynols was initially considered to result from irritation, but allergic reactions have also been reported (37). Nonoxynol contact allergy has been described in two patients who developed contact photosensitivity to nonoxynol-l0 in the antiseptic product Hexomedine transcutanée (38). Among 32 control subjects, 13 had positive photopatch tests to Hexomedine transcutanée and four had positive photopatch tests to nonoxynol-10. Surprisingly, the authors observed that only undiluted nonoxynol was phototoxic. In another study, nonoxynol-9 was found to be rarely sensitizing and compatible with latex and silicone lubricants used in condoms (39).

There is evidence of immunosuppressive effects due to interference by dibenzo-p-dioxin and/or dibenzofuran with the chemical properties of pentachlorphenol (SEDA-11, 485) (40).

Death

Phenol can be fatal in the newborn.

- A 1-day-old child died 11 hours after 2% phenol had been applied to the umbilicus. The postmortem blood concentration of phenol was 125 µg/ml (SEDA-11, 485)(7).
- A 6-day-old child developed cerebral symptoms, circulatory failure, and methemoglobinemia after application of a phenol camphor solution (30% phenol, 60% camphor) to a skin ulcer. The child recovered after exchange transfusion (SEDA-11, 485)(7).

Drug Administration

Drug administration route

A phenol solution of 89% was mistakenly sprayed into the nostrils of a 79-year-old man (41). Immediately, blanching and local erythema developed. It was expected that the patient would develop a significant local burn and possibly systemic toxicity, but neither developed. This may have been due to the amount sprayed or the relatively small body surface area covered by the phenol.

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Phenoperidine

General Information

Phenoperidine is a potent opioid analgesic often used in neuroleptanalgesia and as a respiratory depressant in ventilated patients.

Organs and Systems

Cardiovascular

Intracranial hypertension occurred within 1 minute in a patient with a severe head injury who received phenoperidine 1 mg intravenously. It was associated with a reduction in arterial blood pressure. A similar reaction occurred when a second 1 mg bolus was given 8 hours later (SED-11, 146) (1).

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Phenoxybenzamine

General Information

Phenoxybenzamine is a non-selective irreversible alpha-adrenoceptor antagonist. It is given orally in total daily doses up to 60 mg in pheochromocytoma, and lower doses have been used to relieve bladder obstruction before surgery. The maximum effect may be delayed because of irregular absorption, and even after intravenous use it may not be attained for 1 hour. Some of the most severe effects, that is hypotension and syncope with tachycardia, can therefore occur unexpectedly. In a review of published reports from 1966 to 2002 phenoxybenzamine improved bladder function in adult men with retention due to inguinal hernioplasty, in women with retention caused by vaginal repair, and in children with myelomeningocele, in whom there was also a reduced incidence of urinary tract infections (1). The most common adverse events were dizziness, impotence and ejaculatory dysfunction, and nasal stuffiness. No drug-related tumors were reported. Phenoxybenzamine can also cause miosis, lassitude, and gastrointestinal upsets.

Organs and Systems

Cardiovascular

In patients with myocardial infarction, in whom phenoxybenzamine has been used to improve circulation, it can cause or aggravate pulmonary edema; this could be explained by severe hyponatremia during treatment with phenoxybenzamine (SEDA-13, 113).

Psychological, psychiatric

Panic attacks have been described in one case, a week after withdrawal of the drug; the causal association was not certain (SEDA-17, 163).

Susceptibility Factors

Renal disease

Because a large proportion is renally excreted, dosages should be reduced in renal disease.

Other features of the patient

In view of the nature of its effects, phenoxybenzamine should be used sparingly in cardiovascular disease.

Drug Administration

Drug administration route

When phenoxybenzamine is injected intradermally or when it is extravasated during intravenous administration, it can cause both extremely severe necrotic reactions and an allergic response.

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Phentermine

See also Anorectic drugs

General Information

Despite the withdrawal of the fenfluramines, the appetite suppressants phendimetrazine and phentermine have remained in widespread use for the treatment of obesity.

With phentermine, adverse effects due to stimulation of the central nervous system are less than with dexamfetamine, although in one study withdrawal because of adverse effects was as high as 16 of 177 patients (9%); 2 of 13 healthy young volunteers withdrew because of unacceptable stimulation (1).

Organs and Systems

Cardiovascular

In a systematic review of 1279 patients taking fenfluramine, dexfenfluramine, or phentermine, evaluated in seven uncontrolled cohort studies, 236 (18%) and 60 (5%) had aortic and mitral regurgitation respectively (2). Pooled data from six controlled cohort studies yielded, for aortic regurgitation, a relative risk ratio of 2.32 (95% CI = 1.79, 3.01) and an attributable rate of 4.9% and, for mitral regurgitation, a relative risk ratio of 1.55 (95% CI = 1.06, 2.25) with an attributable rate of 1.0%. Only one case of valvular heart disease was detected in 57 randomized controlled trials, but this was judged unrelated to drug therapy. The authors concluded that the risk of valvular heart disease is significantly increased by the appetite suppressants. Nevertheless, valvulopathy is much less common than suggested by previous less methodologically rigorous studies.

Spontaneous rupture of a retroperitoneal aneurysm occurred in a 70-year-old woman who had been taking phentermine hydrochloride, 30 mg/day, for about 1 month (3). Other long-term medications included fluoxetine and amitriptyline, and she had no history of coronary artery disease, hypertension, diabetes, or complications of pregnancy. Although it is plausible that phentermine could have contributed to the ruptured aneurysm, other possibilities should be considered, particularly rupture of an anomalous retroperitoneal blood vessel.

Fatal pulmonary hypertension occurred in a 32-year-old man who had been taking phentermine in unknown doses for 4 months (SED-9, 16).

Nervous system

Insomnia is one of the most common adverse effects of phentermine. In a survey in Edinburgh, 20% of the subjects taking phentermine reported insomnia compared with 6% of those taking placebo (SED-9, 13).

Urinary tract

Phentermine can cause allergic interstitial nephritis (4).

- A 47-year-old mildly obese woman began a weight reduction program that included anorectic therapy with phentermine and phendimetrazine. She had normal renal function at the start of therapy. After 3 weeks of treatment she fell ill and discontinued treatment. She was subsequently found to have leukocyturia, a rash on her face and chest, and a rise in serum creatinine from 67 to 175 μmol/l (0.8–2.1 mg/dl). Renal biopsy confirmed the diagnosis of acute interstitial nephritis. She was treated with corticosteroids, and her renal function returned to normal.

Long-Term Effects

Drug abuse

Some cases of toxic psychosis have been reported with abuse doses of phentermine (5).

Drug–Drug Interactions

Fluoxetine

Following the withdrawal of the fenfluramines, alternative combinations have been explored as appetite suppressants. In an open study of a combination of phentermine + fluoxetine in 16 obese patients with

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binge-eating disorder, in the setting of cognitive behavioral therapy, there were significant reductions in weight, binge frequency, and psychological distress by the end of treatment; however, the patients regained most of the weight within 1 year (6). At follow-up at 18 months there was still a reduction in binge eating in patients who continued maintenance treatment. The results did not support the long-term value of adding phentermine + fluoxetine to cognitive behavioral therapy for binge-eating disorder. It is worth emphasizing that it is not known whether phentermine + fluoxetine is also associated with cardiac valvulopathy. Moreover, the recognition that phentermine is a monoamine oxidase inhibitor (7) raises further concerns about its safety.

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Phentolamine

General Information

Phentolamine is a non-selective alpha-adrenoceptor antagonist. It is used to treat hypertensive crises attributable to the effects of noradrenaline, as in pheochromocytoma and during the interaction of monoamine oxidase inhibitors with amine-containing medicaments and foods (1). Its adverse effects are similar to those of phenoxybenzamine.

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Phenylbutazone

See also Non-steroidal anti-inflammatory drugs

General Information

Phenylbutazone was originally a solubilizing agent for aminopyrine and was first used to treat rheumatoid arthritis and allied disorders in 1949. Phenylbutazone and its related compounds were used worldwide until the early 1980s when, following growing concern about their safety, Ciba-Geigy published its own international assessment on phenylbutazone (Butazolidine) and oxyphenbutazone (Tanderil), which summarized reports on 1182 deaths associated with them from their initial use until 1982 (SEDA-9, 85). The report showed that the percentage of serious unwanted effects was high for both drugs, and in both cases the most frequent problems were dermatological and hematological, closely followed by gastrointestinal disorders.

Since 1983 phenylbutazone and oxyphenbutazone have been removed from the market in many countries or have been limited to specific indications. In 1985, Ciba-Geigy decided to stop sales of systemic dosage forms of oxyphenbutazone worldwide and to reduce the indications for phenylbutazone (SEDA-9, 85) (SEDA-10, 78). Nevertheless, phenylbutazone is still to be found in many places. Phenylbutazone and its congeners are now used only for ankylosing spondylitis and sometimes for acute gout, psoriatic arthritis, and active rheumatoid arthritis in patients who have not responded to other therapy, including other NSAIDs. For other indications, less toxic alternatives suffice (1,2).

All combinations of butazone derivatives and a corticosteroid have been removed from the market, even in Germany, one of the most lenient countries in the regulation of phenylbutazone use.

Significant adverse effects can affect up to 40% of patients (3).

Pyrazinobutazone is pyrazine phenylbutazone, which is metabolized to phenylbutazone (4).

General adverse effects

Most of the adverse effects of phenylbutazone are on the gastrointestinal system; they include symptoms ranging from gastric irritation to ulcer perforation and bleeding. Salt and water retention leads to edema, which is undesirable in older patients, and even to congestive heart failure. Hematological adverse effects include blood dyscrasias, lymphadenopathy, and agranulocytosis. Hepatotoxicity and nephrotoxicity occur (5). Headache is common, but other nervous system effects are mild. Acute poisoning can be successfully treated by hemoperfusion (6). Hypersensitivity reactions can be very severe (7); asthma and systemic lupus erythematosus have been reported. Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Salt and water retention (see the section on Fluid balance in this monograph) are particularly dangerous for patients

with impaired cardiac function. Hypertension due to increased plasma volume readily occurs.

Respiratory

Left ventricular failure can result in pleural effusions. Asthma can be provoked. Cross-reactivity with aspirin has been noted (8). A picture resembling allergic alveolitis has been described (9).

Nervous system

Therapeutic doses of phenylbutazone can be followed by headache, dizziness, and vertigo (10). Overdose can cause coma and convulsions (11).

Sensory systems

Phenylbutazone can damage the eyes. Conjunctivitis, damage to the cornea with vascularization and scarring, adhesion of the lids to the eyeballs, amblyopia, retinal hemorrhage, and even blindness have been reported (12).

Psychological, psychiatric

Psychomotor reactions to phenylbutazone when driving have been reported (13).

Endocrine

Because of interference with iodine uptake, hypothyroidism and goiter can result (14). The condition is reversible, but an obstructive syndrome due to thyroid enlargement has been observed (14).

Fluid balance

As many as 10% of patients show signs of salt and fluid retention and edema (7). Increased intravascular fluid volume is responsible for dilution anemia and increasing cardiac load (SED-8, 216). There is still no explanation for the water-retaining effect, but it might reflect increased production of antidiuretic hormone.

Hematologic

Phenylbutazone causes blood dyscrasias (SED-8, 213) (SEDA-2, 92) (7,15). The most serious adverse effect is aplastic anemia which, according to Swedish and British sources, ends fatally in almost 50% of cases (15,16,17). More than 1100 deaths are on record with the principal manufacturer (SEDA-8, Essay).

Specific anti-platelet antibodies can cause thrombocytopenic purpura (18), which can be fatal. The increased risk of leukemia after phenylbutazone could be secondary to bone marrow depression (SED-9, 143) (19).

Agranulocytosis and liver injury have been described in a patient with Reiter's syndrome who took pyrazinobutazone for 6 weeks (20). Other causes of agranulocytosis and hepatic damage were excluded and a lymphocyte transformation test showed significant lymphocyte proliferation in response to pyrazinobutazone.

Gastrointestinal

A potent gastric and intestinal irritant, phenylbutazone can cause ulcers and bleeding. In one study in 1975, when the drug was widely used, 19% of 241 cases had acute gastrointestinal bleeding due to phenylbutazone (21). According to the UK's Committee on Safety of Medicines, 120 of 1967 adverse reactions attributed to phenylbutazone and its metabolite oxyphenbutazone involved gastrointestinal bleeding, and 32 ended fatally (22). The risk of developing a peptic ulcer during phenylbutazone therapy is estimated at 1–3% (SED-8, 214). Perforation has also been repeatedly observed (21,23). Other adverse effects are nausea, vomiting, abdominal pain, heartburn, diarrhea, and abdominal discomfort.

Even rectal and enteric-coated formulations can cause adverse reactions in the upper gastrointestinal tract. In one double-blind, crossover trial, plain naproxen caused fewer gastrointestinal adverse effects than enteric-coated phenylbutazone (Butacote) (24).

Phenylbutazone suppositories can cause rectal irritation, with mucosal defects, severe hemorrhagic proctitis (25), perforation of the large bowel, and necrotizing colitis (26).

Gastrointestinal toxicity has been reported in a patient treated short-term with pyrazinobutazone (27).

Liver

Hepatotoxicity has been clearly documented (28). Phenylbutazone causes three types of liver damage through three separate pathogenic mechanisms:

1. acute hepatic necrosis after overdosage, related to the hepatotoxicity of phenylbutazone and/or its metabolites;
2. mild hepatocellular damage (with or without cholestasis) and granulomas (sometimes also found at extrahepatic sites, with varying degrees of steatosis); these changes are the result of hypersusceptibility and possibly a certain degree of toxicity;
3. more pronounced hepatocellular damage with cholestasis but without granulomas; toxicity plays a more important role than hypersusceptibility.

Concomitant treatment with other hepatotoxic agents can predispose to phenylbutazone-induced liver toxicity.

Urinary tract

Although adverse renal effects can occur with any NSAID, phenylbutazone-induced nephrotoxicity has mainly been reported when the drug was taken in association with other anti-inflammatory agents (SED-8, 215) or when taken alone in a high dose (29).

Skin

Skin eruptions, Quincke's edema, and even epidermal necrolysis (SEDA-5, 100) (30,31) can develop during or after phenylbutazone therapy.

Considerable local irritation and pain at the site of injection are sometimes followed by necrosis. Sterile abscess formation has also been reported (32).

Long-Term Effects

Mutagenicity

Phenylbutazone infusion for 10 days induced chromosomal abnormalities in patients with rheumatoid arthritis (33), although the significance of this finding is not clear.

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Second-Generation Effects

Lactation

If phenylbutazone is taken during lactation, only small amounts are found in the milk (34).

Susceptibility Factors

Age

The risk of adverse reactions to phenylbutazone increases with age (SED-8, 213) (17).

Other features of the patient

The specific risks of salt and water retention in cardiac and renal disease have already been mentioned. The potential for ulcerogenic activity should be kept in mind if phenylbutazone is given to a patient with a history of peptic ulceration. Patients who are hypersensitive to other drugs (especially aspirin) should be carefully monitored when taking phenylbutazone.

Drug Administration

Drug overdose

Acute intoxication with phenylbutazone is dominated by metabolic acidosis, which can progress to coma, seizures, hypotension, shock, and oliguria. Kidney and liver reactions, acute bone marrow depression, and acute perforation of peptic ulcer have all been described (5,11,35).

Drug–Drug Interactions

Antihypertensive agents

Inhibition of the effect of antihypertensive agents by phenylbutazone can probably be explained by salt and water retention (36).

Aspirin

Phenylbutazone interferes with the tubular excretion of aspirin (3).

Coumarin anticoagulants

Phenylbutazone displaces warfarin from binding sites on serum albumin, temporarily increasing its effects before the clearance of warfarin increases because of an increase in the unbound fraction (37). If that were the only mechanism, this interaction would not be important. However, phenylbutazone also inhibits the metabolism of *S*-warfarin and induces the metabolism of *R*-warfarin (38); the half-life of racemic warfarin is unchanged, but because the *S* isomer is more potent than the *R* isomer, the action of warfarin is potentiated (SED-9, 144) (36,39).

Oral hypoglycemic drugs

Phenylbutazone can potentiate the hypoglycemic effects of the sulfonylureas acetohexamide (40), chlorpropamide (41), tolbutamide (42), and glibenclamide (43). One mechanism of this interaction is interference with tubular excretion (3).

Penicillins

Phenylbutazone interferes with the tubular excretion of penicillins (3).

Phenytoin

Phenylbutazone can reduce the clearance of phenytoin by inhibiting CYP2C9 (44).

Sulfonamides

Phenylbutazone can displace sulfonamides from protein-binding sites (SED-9, 144) (45).

Interference with Diagnostic Tests

Thyroid function tests

Phenylbutazone inhibits thyroid uptake of iodine and/or competes for protein-binding sites with thyroxine (SED-9, 145) (46,47), and can thus interfere with the use of thyroid function tests.

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Phenylephrine

General Information

Phenylephrine is seldom given systemically but is still commonly used as a mydriatic for both diagnostic and therapeutic purposes. Ocular application of phenylephrine 10% in pledget form is used to produce hemostasis in laser-assisted in-situ keratomileusis (LASIK) surgery and other ophthalmic surgical procedures. Phenylephrine is in some countries available in a non-prescription concentration of 0.12% for use as an ocular decongestant. Phenylephrine (up to 10 mg intramuscularly) has similar properties and uses to other alpha-adrenoceptor agonists.

The incidence of adverse effects is high with 10% phenylephrine, but less with lower concentrations. Systemic reactions also increase with increased frequency of use and when phenylephrine is applied in a pledget. The package inserts for 10% phenylephrine in the USA and Australia require that the drug should not be used more often than once an hour. A large number of severe

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systemic reactions, including death, have been reported in more than 20 articles in peer-reviewed ophthalmic journals. For this reason 10% phenylephrine eye-drops should be used with caution in patients with cardiac disease, significant hypertension, or advanced arteriosclerosis, and in frail elderly people.

It can never be emphasized enough that the eyes are a potential route for systemic drug administration. This has been illustrated by a British case of pulmonary edema in a child, apparently attributable to systemic absorption of phenylephrine eye-drops (1).

- An 8-year-old boy was admitted for unilateral retinal detachment surgery. Phenylephrine 2.5% and cyclopentolate 1% as premedication were prescribed but not given. In theatre the assistant surgeon administered 2–5 drops of 10% phenylephrine to the right eye. During the operation the boy developed bradycardia and was given glycopyrrolate, but shortly afterwards the systolic arterial pressure rose to 211 mmHg and the pulse rate to 160 beats/minute, with multifocal atrial and ventricular ectopic beats. Labetalol was given and the pulse and blood pressure fell to normal, but he then developed clinical and radiological signs of pulmonary edema, which resolved spontaneously.

The management of this case was subsequently criticized by correspondents in the same journal (2). They suggested that a lower ocular dose of phenylephrine should be used routinely, that oxymetazoline might in any case be safer, and that labetalol might have been hazardous, owing to its beta-blocking properties. In their reply the authors pointed out that they used the lowest concentration of phenylephrine available for ocular use, that oxymetazoline is not licensed for use as a mydriatic agent, and that the patient had tachycardia and ventricular extra beats, which made the beta-blocking properties of labetalol clinically desirable.

It is always wise to advocate nasolacrimal occlusion by digital compression of the lacrimal drainage system when using phenylephrine eye-drops in patients at risk or in patients in whom higher concentrations are necessary (3).

Organs and Systems

Cardiovascular

The FDA and the National Registry of Drug-induced Ocular Side Effects (Casey Eye Institute, Portland, Oregon) have received 11 reports of adverse systemic reactions to a single dose of topical ocular phenylephrine 10% applied in pledget form (4). There were eight men and three women, aged 1–76 years. Most of the patients noted systemic effects within minutes of applying phenylephrine, and the adverse systemic reactions included severe hypertension, pulmonary edema, cardiac dysrhythmias, cardiac arrest, and subarachnoid hemorrhage. Ophthalmologists should be warned not to apply phenylephrine in this way, which is believed to be contraindicated in ophthalmic surgery, especially when other medications may be used (SED-14, 1643).

A 10% solution of phenylephrine has sometimes caused extremely severe cardiovascular complications, including myocardial infarction.

In newborn infants the benefit of accurate assessment of gestational age by examination of the anterior vascular capsule of the lens and the value of funduscopic examination in ill premature babies must be weighed against the possible risks of the associated increase in blood pressure produced by the pupillary dilators. Since there is no increase in mydriatic effect with repeated instillation or increasing concentration, and their small body mass places premature neonates at increased risk of phenylephrine overdose, it is prudent to use the lowest possible concentration, as well as the most effective combination of mydriatics for indirect ophthalmoscopy in premature infants when such examination is absolutely necessary. The hypertensive effect is likely to be maximal at some time within the first 20 minutes, and whenever possible (or when risk factors are present) the blood pressure should be monitored.

- A child developed cardiac dysrhythmias, severe hypertension, and pulmonary edema after the intraoperative administration of ocular phenylephrine (1).
- A 2-month-old child given perioperative phenylephrine drops during cataract extraction developed ventricular extra beats, very severe hypertension, and pulmonary edema requiring intensive therapy (5). Extubation was possible within 3 hours, and she recovered with no untoward consequences.

The authors commented that changes in arterial blood pressure are well described with phenylephrine eye-drops, especially in infants. Clearly precise dosage is difficult in these very young patients and they suggested that microdrops might be a safer mode of administration.

Ear, nose, throat

When used as a nasal decongestant, phenylephrine can cause local nasal irritation and even perforation of the anterior nasal septum.

- A 69-year-old woman developed perforation of the nasal septum after overuse of a common over-the-counter nasal spray containing phenylephrine (6).

The authors attributed this effect to both vasoconstriction and physical irritation.

Nervous system

It has been suggested that sodium bisulfite, a preservative in phenylephrine solutions for injection, may have been responsible for transient neurological symptoms that have been observed in some patients (7). However, the original authors rejected this, since the dose of bisulfite was small and since there is uncertain evidence whether the compound is neurotoxic in any case. Another correspondent commented that tetracaine itself may be more toxic than other local anesthetics: the authors did not address this point in their reply (8).

Sensory systems

With phenylephrine, several cases of allergic blepharoconjunctivitis have been seen, even at low concentrations; the reaction begins 3–4 hours after drug application, persists for 12 hours, and regresses gradually within 72 hours

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(9). Biopsy of the conjunctiva reveals marked infiltration with cells of various types; there is some evidence that a sensitization mechanism is involved.

However, blepharoconjunctivitis can occur (SEDA-17, 162), as can other complications.

- Acute periorbital dermatitis and conjunctivitis occurred in a 69-year-old man given phenylephrine 5% eye-drops for ophthalmological examination (10). Subsequent patch-testing was strongly positive for phenylephrine eye-drops.

There have been responses to last year's report of occurring after the addition of phenylephrine to tetracaine spinal anesthesia. It has been suggested that sodium bisulfite, a preservative in phenylephrine solutions for injection, may have been responsible for transient neurological symptoms that have been observed in some patients (7). However, the original authors rejected this, since the dose of bisulfite was small and since there is uncertain evidence whether the compound is neurotoxic in any case. Another correspondent commented that tetracaine itself may be more toxic than other local anesthetics: the authors did not address this point in their reply (8).

Skin

There have been a few reports of allergic contact dermatitis caused by phenylephrine, and little is known about cross-reactivity between the phenylephrine, adrenaline, and ephedrine.

- A 62-year-old man developed contact dermatitis after using phenylephrine eye-drops (Neosynerphin POS) (11). The inflammation affected both eyelids symmetrically and resolved rapidly on withdrawal of the eye-drops and application of topical glucocorticoids. Skin-testing confirmed hypersensitivity to phenylephrine but no cross-sensitization to ephedrine or adrenaline.

Immunologic

Phenylephrine was the drug that most often caused sensitization in patients with contact allergy after the application of mydriatic eye-drops. Since several eye-drops are often used in the same patient, it is always important to find out which drug or preservative is the allergen (10–13).

Long-Term Effects

Drug abuse

Abuse of alpha-adrenoceptor agonist nose-drops can cause a chronic rhinitis (14) and psychoses (15).

Susceptibility Factors

Phenylephrine should be used cautiously in elderly people and in patients with hypertension, coronary heart disease, aneurysms, and diabetic autonomic neuropathy (SEDA-21, 487).

Drug–Drug Interactions

Monoamine oxidase inhibitors

Patients taking monoamine oxidase inhibitors, anticholinergic drugs (such as tricyclic antidepressants), propranolol, reserpine, guanethidine, and methyldopa should be monitored closely if phenylephrine is used (SEDA-16, 542) (16).

Tetracaine

When phenylephrine was used together with tetracaine in spinal anesthesia, 10 of 80 patients developed transient dysesthesia (SEDA-22, 155). Provocation of myocardial ischemia (17), acute edema of the lung (18), and ischemic colitis (SEDA-22, 155) were not so clear-cut.

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Phenylpropanolamine (norephedrine)

General Information

In the past, phenylpropanolamine was marketed extensively in over-the-counter products for a variety of indications, and dietary supplements were marketed with no premarket safety evaluation, at least by the Food and Drug Administration (FDA), since for dietary supplements that include an ingredient marketed in the USA before 15 October 1994 no FDA review is required. Because many of these products were promoted as foodstuffs, consumers may have assumed that they are safe (SEDA-21, 5). It has been used as an anorectic agent in doses of 3–25 mg/day.

However, adverse effects from therapeutic and toxic doses of phenylpropanolamine have often been reported (SEDA-9, 2) (SEDA-10, 3) (SEDA-11, 1), and recently it has been implicated as a cause of stroke and other neurological events. In November 2000, the US FDA asked all manufacturers to recall the product voluntarily.

Organs and Systems

Cardiovascular

Much of the concern over the free sale of phenylpropanolamine relates to its cardiovascular effects. Although the commonly recommended 75 mg dose has no significant effect on blood pressure in healthy volunteers, 150 mg causes significant albeit transient hypertension lasting several hours (1). Hypertensive crises have been reported, for example after a 600 mg overdose (SEDA-18, 158). However, field experience suggests that, because of individual variations in sensitivity, the risks to some patients are greater than these findings suggest. In single doses of 50 mg, phenylpropanolamine increased diastolic blood pressure to over 100 mmHg in 12% of adults.

Phenylpropanolamine can also, on occasion, cause cardiac dysrhythmias in mild overdosage.

A transient cardiomyopathy without hypertension occurred in a girl of 14 who had taken only a small overdose (2) and another in an adult woman (SEDA-17, 163).

A warning was issued by the Swiss Pharmaceutical Association that phenylpropanolamine can cause severe sympathomimetic adverse effects, including hypertensive crises, dysrhythmias, and tachycardia (3) (SEDA-5, 11) (SEDA-7, 12).

Nervous system

Although it has been thought to have relatively little stimulant effect on the central nervous system, phenylpropanolamine can produce restlessness, anxiety, insomnia, and tremor; its central stimulant effects are in practice often masked by manufacturers' practice of combining it with an antihistamine.

In a consecutive stroke registry since 1988, 22 patients (10 men and 12 women) had strokes associated with over-the-counter sympathomimetic drugs (4). There was intracerebral hemorrhage in 17, subarachnoid hemorrhage in 4, and ischemic stroke in 1. Stroke was associated with the use of phenylpropanolamine (75–675 mg) in 16 patients.

- Stroke occurred in an 8-year-old boy on chronic peritoneal dialysis after he took phenylpropanolamine (5). He developed occipital infarcts and was found to have extremely high concentrations of phenylpropanolamine in his blood and dialysis fluid. Although the voluntary recall was in effect, the family already had a bottle of phenylpropanolamine at home.

In a case-control study, 2078 men and women (702 patients and 1376 controls), age range 18–49 years, were recruited from 43 US hospitals if they had had a subarachnoid or intracerebral hemorrhage within 30 days before enrolment and no previously diagnosed brain lesion (6). For women, the adjusted odds ratio was 17 (95% CI = 1.5, 182) for the association between the use of appetite suppressants containing phenylpropanolamine and the risk of a hemorrhagic stroke. For men and women combined, the adjusted odds ratio was 16 (1.4, 184). The authors suggested that phenylpropanolamine in appetite suppressants is an independent risk factor for hemorrhagic stroke in women. There was a trend toward an increased risk of stroke with cough and cold remedies in women (OR = 3.1; CI = 0.9, 11).

- A 37-year-old woman took an over-the-counter formulation containing phenylpropanolamine 100 mg (7). About 90 minutes later she developed very severe bilateral headache resistant to analgesics. Her blood pressure was 180/100 mmHg but fell rapidly to 110/70 mmHg. A CT scan showed multiple small frontal and parietal hemorrhages, and angiography showed extensive segmental vasospasm. She was treated with nimodipine and prednisolone, followed by verapamil. She made an uneventful recovery, and there was angiographic resolution of the vascular lesions.

The authors reviewed a number of other case reports of phenylpropanolamine-induced cerebral vasospasm associated with hemorrhages and drew a parallel with similar effects of amfetamines.

Psychological, psychiatric

Psychosis has been attributed to phenylpropanolamine (8,9). Risk factors include symptoms or a history of

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mood spectrum disorder, a history of psychosis, female sex, and a family history of psychiatric disorder.

Although irritability and insomnia are frequent in adults, behavioral disturbances (restlessness, irritability, aggressiveness, and sleep disturbances), seizures, and delirium with hallucinations have been most often observed in children (SEDA-11, 1) (10).

Immunologic

Phenylpropanolamine can give rise to severe allergic reactions with dyspnea, urticaria, and facial swelling (11).

Long-Term Effects

Drug abuse

As with several other sympathomimetics, phenylpropanolamine is often sold illegally in special packages as a look-alike for more euphoriant/alerting stimulants. Both the absolute increase in use and the changes in the type of user have been associated with many reports of overdose consequences, including hypertension, cardiac dysrhythmias (SEDA-9, 10, 11), cerebral hemorrhage (SEDA-11, 2) (12,13), neuropsychiatric symptoms, including agitation and acute psychosis, and seizures (SEDA-9, 4) (14).

Susceptibility Factors

Age

Children appear to be sensitive to therapeutic doses of pseudoephedrine in the development of hallucinosis as well as irritability and insomnia syndromes (15,16).

Drug–Drug Interactions

Caffeine

Pharmacokinetic and pharmacodynamic interactions between caffeine 250 mg and phenylpropanolamine 25 mg have been investigated in six healthy subjects in a double-blind, placebo-controlled study. Coadministration of caffeine and phenylpropanolamine produced an additive increase in blood pressure, not attributable to a pharmacokinetic interaction and despite the fact that phenylpropanolamine attenuated the responses of adrenaline and renin to caffeine (17).

However, in another study in 16 healthy subjects who took caffeine 400 mg plus phenylpropanolamine 75 mg, the peak plasma–caffeine concentration was significantly higher than after caffeine alone. There were greater increases in both systolic and diastolic blood pressures, and adverse effects were more frequent after the combination than after either drug alone or after placebo (18).

Indinavir

A hypertensive crisis has been reported in a patient receiving triple therapy for HIV prophylaxis, including indinavir (19).

- A 28-year-old female medical resident was given zidovudine, lamivudine, and indinavir after a needle-stick injury involving an HIV-positive patient. She had a long history of sinus complaints and was taking a phenylpropanolamine-containing formulation intermittently. Ten days after starting prophylactic therapy she took phenylpropanolamine, although the dose was not stated, and 6 hours later developed right-sided headache, weakness of the left arm, and a blood pressure of 220/120 mmHg. CT and MRI scans of the brain were normal. Her blood pressure and neurological signs resolved during treatment with nimodipine and aspirin, though the weakness returned briefly.

It seems very likely that the protease inhibitor indinavir inhibited the metabolism of phenylpropanolamine by cytochrome P450 (predominantly CYP3A4), increasing circulating concentrations, and causing systemic and cerebral vasoconstriction.

Indometacin

Severe systemic hypertension developed in a patient who took indometacin shortly after taking an appetite suppressant (Trimolets) containing phenylpropanolamine (20). The hypertension was attributed to inhibition of prostaglandin synthesis by indometacin, which exacerbated the sympathomimetic effects of phenylpropanolamine. However, in 14 young, healthy, normotensive women who were randomized double-blind to modified-release phenylpropanolamine 75 mg/day or placebo for 4 days, modified-release indometacin 75 mg bd had no significant effect on mean systolic or diastolic blood pressures (21).

Neuroleptic drugs

Neuroleptic malignant-like syndrome has been reported when phenylpropanolamine was combined with neuroleptic drugs (22).

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Phenytoin and fosphenytoin

See also Antiepileptic drugs

General Information

Phenytoin is the only widely used hydantoin and, unless otherwise specified, effects discussed here refer to phenytoin. Other hydantoin derivatives include ethotoin (rINN), mephenytoin (rINN), and albutoin (rINN) (all of which are obsolete), and fosphenytoin (rINN). The latter is a water-soluble prodrug that is rapidly hydrolysed to phenytoin after intravenous or intramuscular injection. It causes fewer adverse reactions near the injection site (pain, phlebitis, tissue necrosis, purple hand syndrome) than phenytoin.

The effects of phenytoin have been studied in 39 patients with acute mania (1). One patient dropped out because of tachycardia and one required a dosage reduction because of nystagmus.

Comparative studies

Intravenous phenytoin and intravenous fosphenytoin have been compared in an open, randomized study in 256 emergency department patients who were given 279 doses (2). The mean phenytoin-equivalent dose was similar in the two groups. Adverse events occurred with similar frequencies, but slightly more often with fosphenytoin (phenytoin 9.1%, fosphenytoin 16%). The most common events were pruritus, pain on infusion, and paresthesia. Only one patient developed hypotension, with fosphenytoin. Thus, this study has not demonstrated obvious advantages of fosphenytoin.

General adverse reactions

Phenytoin can cause vestibulocerebellar, oculomotor, and cognitive dysfunction. It can also cause gingival hyperplasia, hirsutism, and acromegaly-like facial features. Movement disorders, symptoms of peripheral neuropathy, and endocrine changes are uncommon. Interstitial nephritis, interstitial pneumonia, and hepatotoxicity are rare. High intravenous doses are cardiotoxic.

Hypersusceptibility reactions

Hypersusceptibility reactions range from relatively common mild rashes to life-threatening Stevens–Johnson syndrome and toxic epidermal necrolysis. Hepatic, cardiac, muscular, pulmonary, hematological, reticuloendothelial, and renal reactions and systemic lupus erythematosus are uncommon.

Tumorigenesis

Pseudolymphoma and a condition resembling malignant lymphoma are very rare.

Organs and Systems

Cardiovascular

Intravenous phenytoin can cause cardiac dysrhythmias, hypotension, and potentially fatal cardiovascular collapse, especially if the highest recommended infusion rate (50 mg/minute or 1 mg/kg/minute in children) is exceeded. One case of hypersensitivity myocarditis was probably initiated by phenytoin, although carbamazepine may have contributed (SED-13, 142) (3).

After intravenous use, the most common vascular complication is the so-called purple-glove or purple-limb syndrome, defined as the progressive development of edema, discoloration, and pain in the limb; sequelae include soft-tissue necrosis and limb ischemia. Retrospective analysis of data from 152 patients treated with intravenous phenytoin identified nine (6%) who developed this syndrome: they had received a greater mean initial dose of phenytoin (500 versus 300 mg) and a larger dose over 24 hours (800 versus 500 mg), and they tended to be older (72 versus 49 years) than those without the complication (4). In one case surgical therapy was required; the others resolved conservatively within 1 month. Extravasation of intravenously injected phenytoin has caused tissue necrosis requiring amputation (SEDA-18, 67). Purple glove syndrome has generally been reported after intravenous phenytoin.

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- In a 49-year-old otherwise healthy woman undergoing craniotomy for aneurysm clipping, inadvertent overdose with phenytoin (1500 mg) by rapid infusion caused intraoperative sinus arrest, which was managed successfully with standard resuscitative measures (5).

This report highlights the cardiovascular risk of intravenous phenytoin, particularly when high infusion rates are used.

However, the purple-glove syndrome can also occasionally occur after oral administration.

- A 10-year-old boy took phenytoin 100 mg/day and his seizures were well controlled (6). However, a pharmacist gave him about 1000 mg of phenytoin instead of the prescribed dose, and several hours later he became drowsy and his hands and feet turned dark purple with marked swelling. Phenytoin was withdrawn after 4 days and the swelling and discoloration of his hands and feet improved gradually and disappeared 11 days later.

The incidence of purple-glove syndrome associated with intravenous phenytoin has been assessed in a prospective review of 179 consecutive exposures (7). There were only three mild cases (1.7%).

However, the purple-limb syndrome was recorded in 20 of 67 patients who received intravenous phenytoin over a 5-month period (8). Affected cases tended to be older (median age 70 years versus 57 years in non-affected cases), and all resolved spontaneously within 3 weeks. These data suggest that the incidence of the syndrome may have been underestimated in the past, possibly owing to its delayed onset, frequent occurrence in patients with impaired communication abilities, and its usually mild self-limiting course.

In 775 patients who received intravenous phenytoin, valproate, or placebo, intravenous site reactions occurred in 25% of patients who received phenytoin (9). Most of the events (70%) occurred in the first intravenous site, and all occurred in peripheral administration sites. When patients who received the drug by central line were excluded, the estimated incidence was 30%. There were fewer adverse events when phenytoin was given alone than when it was given together with valproate.

Fosphenytoin-induced QT interval prolongation has been reported (10).

- A 23-year-old man was given intravenous fosphenytoin (equivalent to phenytoin 1500 mg or 20.5 mg/kg) over 85 minutes. He was normocalcemic before the infusion. During the infusion he had prolongation of the QT interval and reductions in the concentrations of total and ionized serum calcium. Plasma phenytoin concentrations were within the target range during the electrocardiographic changes, and the blood pressure was stable.

Fosphenytoin is metabolized by phosphatases to yield phenytoin plus inorganic phosphate. Binding of calcium by phosphate could have lowered the serum concentration of ionized calcium.

Respiratory

Interstitial pneumonitis is extremely rare with phenytoin (11). The clinical features are fever, dyspnea, hypoxemia, and bilateral radiographic infiltrates. It responds to withdrawal and corticosteroids. Bronchiolitis obliterans organizing pneumonia in the context of a severe hypersensitivity syndrome also improved rapidly with high-dose steroids (SEDA-22, 90).

Nervous system

Ataxia, dysarthria, fatigue, dizziness, tremor, and nystagmus are relatively common in patients with phenytoin intoxication. Sedation occurs only at high serum drug concentrations; however, toxic effects at relatively low serum concentrations can occur when drug binding to plasma proteins is impaired (SEDA-18, 67). Uncommon effects include seizure exacerbation (12), reversible monoplegia or hemiplegia (13), reversible spastic rigidity, hyper-reflexia and clonus, hyperkinetic disorders, choreoathetosis (14), hemiballismus (15), hemichoreiform movements, local dystonia in the foot, myoclonus (16), and reversible parkinsonism (SED-13, 143).

- A 13-year-old girl developed left partial motor status epilepticus with severe postictal hemiparesis (15). An MRI scan showed a right frontoparietal hyperintense T2-weighted signal. Treatment with phenytoin, carbamazepine, and phenobarbital caused the seizures to abate but left choreic-like flinging movements, consistent with hemiballismus, 2 days later. On phenytoin withdrawal, the symptoms gradually abated, with mild residual dystonia at 14 months.

The authors speculated that the lesion might have rendered the cortex more susceptible to phenytoin, causing unilateral toxicity.

Three patients with severe myoclonic epilepsy in infancy developed choreoathetosis after an increase in phenytoin dosage; it resolved when the phenytoin dosage was reduced (17). In one, an ictal SPECT showed reduced perfusion in the basal ganglia contralateral to the unilateral choreoathetosis. Polypharmacy, including carbamazepine and zonisamide, may have facilitated the onset of choreoathetosis.

Phenytoin can aggravate symptoms and worsen outcome in patients with Baltic myoclonic epilepsy (SED-13, 140) (18) and susceptibility to neurological complications can be increased in patients with organic brain disorders.

Long-term phenytoin can cause cerebellar degeneration, but this is probably rare (SED-13, 143) (19), (SEDA-19, 73); irreversible cerebellar atrophy after acute intoxication is extremely rare (SEDA-21, 73).

- Distal lower extremity paresthesia in stocking distribution and motor weakness with loss of the Achilles tendon reflex, associated with reduced sensory conduction velocity, occurred in an 18-year-old girl a few hours after the administration of phenytoin (7.5 mg/kg) (20). The condition regressed after phenytoin withdrawal.

Peripheral neuropathy is a known adverse effect of phenytoin, but this is the first report of an acute neuropathy within less than 1 week of treatment.

Cerebellar atrophy has been reported in association with phenytoin intoxication (21).

Pre-existing myasthenia gravis can be aggravated by phenytoin (SEDA-7, 78).

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Sensory systems

Taste

- Ageusia occurred in a 52-year-old man within a few hours of an intravenous infusion of phenytoin 750 mg for the control of seizures (22). The condition persisted for 2 weeks during oral phenytoin treatment and cleared in about 1 week when phenobarbital was substituted.

The time course in this case strongly suggested that phenytoin was responsible.

Psychological, psychiatric

Phenytoin has been implicated in psychiatric adverse effects with or without other signs of toxicity, and at serum concentrations above or below the upper limit of the target range, but the actual incidence of these reactions is unknown (23).

- A 9-year-old boy with seizures developed intermittent complex visual hallucinations during therapy with fosphenytoin and, on a separate occasion, carbamazepine (24).

Five patients with Down's syndrome and dementia, aged 44–67 years, taking phenytoin had progressive cognitive decline (25). This resolved once the drug was withdrawn. Cognitive decline was not related to high serum concentrations. Older patients with Down's syndrome might be especially sensitive to the effects of phenytoin.

Endocrine

Phenytoin can cause a rise in growth hormone concentration (26).

Phenytoin can cause acromegaly-like facial features, possibly related to its osteogenic actions (SEDA-20, 65).

Hematologic

Megaloblastic anemia and pancytopenia have been rarely attributed to phenytoin (27,28), whereas aplastic anemia has been observed with mephenytoin (29).

Single cases of a hemophilia-like disorder (SED-13, 144) (30), hemolytic anemia associated with renal insufficiency (31), and pure red cell aplasia (SED-12, 129) (32), have been reported.

Mouth and teeth

Gingival hyperplasia is a well-known adverse effect of phenytoin. It occurs in at least one-third of patients, although it can be prevented by careful dental hygiene (SED-13, 144) (33), and does not occur in edentulous mouths. In one case generalized palatal hyperplasia occurred in a patient in whom retained roots and teeth were suspected of having perpetuated a pre-extraction lesion; a subsequently placed complete denture initiated a midpalatal hyperplasia (34).

In 114 patients, of whom 20% took phenytoin, 5 taking phenytoin had gingival hyperplasia (35), which can on occasion be extensive.

- A 17-year-old boy took phenytoin 300 mg/day unsupervised for 2 years and developed coarsening of the facial features, extensive gingival hyperplasia, and cerebellar ataxia (36). The gingival hyperplasia resolved within 3 months of withdrawal but the ataxia persisted.

Gastrointestinal

Phenytoin was implicated in a case of reversible hypertrophy of the submandibular salivary gland, but cause and effect were speculative (SEDA-18, 67).

Liver

Chronic hepatitis is rarely caused by phenytoin (SEDA-18, 67). When it occurs, the signs of hepatotoxicity usually appear after 1–8 weeks in acute cases, and after 4 months to several years in chronic cases (37). Among 16 acute cases, there was fever in 75%, rash in 63%, jaundice in 44%, hepatomegaly in 13%, and lymphadenopathy and splenomegaly in 60% (37). Less common symptoms included sore throat, malaise, chills, myalgia, and pruritus. The condition can be fatal.

- A 51-year-old woman developed hepatitis while taking phenytoin 300 mg/day (38).

The authors did not discuss the possible role of paracetamol, which was co-administered in a dosage of 4 g/day (see Paracetamol section under Drug–Drug Interactions in this monograph).

Urinary tract

There has been one report of autoimmune interstitial nephritis associated with tubular deposits of phenytoin and circulating antitubular basement-membrane antibodies (SED-13, 144) (39).

Skin

Acne and hirsutism are not uncommon in patients taking phenytoin. Of 61 women who had taken phenytoin 100–300 mg/day for 1–5 years, more than half had coarse facial features from a combination of several degrees of acne, hirsutism, and gingival hyperplasia (40).

Skin rashes occur in about 10% of patients. They are generally mild and their incidence varies seasonally (SED-13, 144) (41).

Diffuse fasciitis with eosinophilia (a variant of scleroderma) (42), reversible nodular cutaneous pseudolymphoma, acromelanosis (43), hypertrophic retroauricular folds, and severe forms of erythema multiforme (Stevens–Johnson syndrome and toxic epidermal necrolysis) (44,45) are all rare (SED-13, 144) (SEDA-22, 90) (33).

- Toxic epidermal necrolysis has been reported in a 28-year-old woman who had taken phenytoin for 20 days (46). Phenytoin was cytotoxic in vitro to the patient's lymphocytes.
- A 49-year-old man with post-traumatic epilepsy taking phenytoin developed severe rhinophyma; he also had gingival hyperplasia (47).

Nothing in the history of this case pointed definitively to a cause and effect association.

Subacute cutaneous lupus erythematosus has been reported in a patient taking phenytoin (48).

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- A 73-year-old woman who had taken phenytoin for 5 years developed erythematous, macular, annular lesions over her upper chest, back, and arms. She was also taking propafenone and nifedipine. Routine hematology and biochemistry were normal, except for leukopenia and a raised gamma-glutamyltranspeptidase. There were no antinuclear antibodies, but antibodies against Ro, La, and histone proteins were detectable. A skin biopsy was consistent with subacute cutaneous lupus erythematosus. She was given topical steroids, and all medications, apart from phenytoin, were withdrawn. However, as her eruption persisted, the phenytoin was tapered and withdrawn. Her rash cleared within 6 months. Over the next year there was no photosensitivity or recurrence, but Ro and La antibodies remained positive.

Interpretation of this report is confounded by the presence of concomitant treatments and the lack of quick resolution of the symptoms on phenytoin withdrawal. Furthermore, the autoantibodies did not normalize at 6 months.

Reproductive system

- An 18-year-old man with heterozygous point mutation in the defective allele of CYP2C9 and CYP2C19 (two enzymes involved in phenytoin metabolism) developed gynecomastia about 1 month after phenytoin dosage was increased from 175 to 190 mg/day, resulting in a serum phenytoin concentration of 68 μmol/l (49).

Phenytoin has been rarely implicated in gynecomastia, and whether the cytochrome P450 genotype played a contributory role was unclear. The patient was also taking zonisamide, which has also rarely been associated with gynecomastia.

Immunologic

The phenytoin hypersensitivity syndrome ranges from a simple rash to a fulminant fatal illness with exfoliative dermatitis, vasculitis, and disseminated intravascular coagulation. Features include variable combinations of fever, eosinophilia, lymphadenopathy, hepatosplenomegaly, atypical lymphocytes, blood dyscrasias, serum sickness, hepatitis, and renal insufficiency.

Angioimmunoblastic lymphadenopathy, systemic lupus erythematosus, polymyositis, and serum sickness have been noted in individual cases (SED-13, 144) (50,51).

IgA depression is seen in about 10% of patients (52). There has been one report of deficiency of IgG2 and IgG4 (SEDA-17, 73) and one of panhypogammaglobulinemia (SEDA-16, 73).

- A 32-year-old man developed acute lung injury and renal insufficiency after 4 days of starting to take phenytoin (53). The symptoms mimicked a renopulmonary syndrome, and resolved completely after withdrawal of phenytoin and the addition of steroids.

Giant cell myocarditis has been reported in a patient taking phenytoin, phenobarbital, and mephobarbital and in one taking primidone (54).

Lupus-like syndrome has been attributed to phenytoin (55).

- A 67-year-old white man who had taken phenytoin 300 mg/day for about 15 years developed fever, pericarditis, severe abdominal pain, malaise, and weight loss. He had a positive antinuclear antibody in a titer of 1:80 in a homogeneous pattern, a strongly positive antihistone antibody test, a raised erythrocyte sedimentation rate (115 mm/hour), and a neutrophilia (21×10^9/l). All these abnormalities resolved within a few weeks of withdrawal. Rechallenge was not performed.

The long delay between the start of therapy in this case and the clinical presentation makes it highly likely that phenytoin was not implicated and that recovery was spontaneous.

There has been a report of hypersensitivity to phenytoin (which had been previously well tolerated) after a hypersensitivity reaction to carbamazepine (56).

- A 19-year-old man with partial epilepsy took phenytoin 300 mg/day for over 6 months. Carbamazepine was introduced and after about 6 weeks (while taking phenytoin 300 mg/day and carbamazepine 600 mg/day) he developed fever, anorexia, a sore throat, bloody diarrhea, a diffuse, erythematous, maculopapular rash and palatal petechiae, tender cervical lymphadenopathy, and mild splenomegaly. His liver enzymes were raised and he had a leukocytosis with eosinophilia. Phenytoin and carbamazepine were withdrawn, and he was given prednisone and sodium valproate 1000 mg/day. The rash resolved, as did other manifestations of what was thought to be a hypersensitivity reaction. About a year later, phenytoin was reintroduced starting at 100 mg/day. He developed a sore throat after taking the first dose and a widespread rash after the second dose. There was no evidence of hepatic or hematological dysfunction. Phenytoin was withdrawn and the rash resolved in 1 week.

Cross-sensitivity among aromatic antiepileptic drugs occurs in about 50% of patients with a hypersensitivity reaction. It has previously been described on first exposure to each of the offending drugs (57). However, this patient developed an allergic rash on his second exposure to phenytoin, having previously tolerated it for 6 months. This suggests that carbamazepine may have altered his response to phenytoin.

Long-Term Effects

Mutagenicity

Neuroblastoma has been rarely reported in association with the fetal hydantoin syndrome. Phenytoin can cause pseudolymphoma and rarely a condition resembling malignant lymphoma (SED-13, 142). Pseudolymphoma is usually characterized by lymphadenopathy, fever, and a diffuse erythematous macular skin eruption, although a presentation without fever and rash has been described (SEDA-20, 65).

Tumorigenicity

Pseudolymphomatous reactions, pseudomalignant histiocytosis, a reaction resembling mycosis fungoides, and

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malignant lymphoma have been noted in individual cases (SED-13, 144) (58,59).

Susceptibility Factors

Genetic factors

- A 40-year-old man who developed toxic signs and a high serum phenytoin concentration (130 μmol/l) on a low dosage (187.5 mg/day) was found to be heterozygous for the Leu359 allele of CYP2C9 and for the *3 allele of CYP2C19 (60).

Phenytoin is metabolized by both cytochromes and the mutations probably explained the adverse reaction.

Other features of the patient

Patients receiving cranial irradiation and patients with malignant gliomas may be at particular risk of severe skin reactions to phenytoin (SEDA-18, 68) (SEDA-20, 58). Neurological adverse effects can be enhanced in patients with a recent history of severe traumatic brain injury.

Several reports have suggested that patients with brain tumors who undergo radiation therapy while taking phenytoin may be at increased risk of developing Stevens–Johnson syndrome. A 47-year-old black man (61) and four other patients, including one who died (62), were seen in a 24-month period in one department. A review of 20 similar reported cases showed no relation to the dosage of phenytoin or radiation therapy, or to the histological type of the tumor.

Drug Administration

Drug contamination

Phenytoin poisoning has been reported in a patient who took Chinese proprietary medicines containing phenytoin, carbamazepine, and valproate (63). The manufacturer's information leaflet did not mention any of these prescription drugs.

Drug administration route

Intravenous phenytoin has been associated with fatal hemodynamic complications and serious reactions at the injection site, including skin necrosis and amputation of extremities. Fosphenytoin, a phenytoin prodrug, has the same pharmacological properties but none of the injection site and cardiac rhythm complications after intravenous administration (64).

The extent of absorption and tolerability of intramuscular fosphenytoin has been assessed in a double-blind study in which patients received 10 mg/kg dose of intramuscular fosphenytoin in one gluteus muscle and intramuscular saline in the other (65). More than half the patients had serum concentrations in the target range at 30 minutes. There was no pain at either the fosphenytoin or saline injection sites in 46% of patients and no difference in pain at 60 minutes and thereafter.

Drug overdose

The saturable kinetics of phenytoin results in an increased half-life in overdose and a protracted clinical course, which can last a week or more (66). The most common initial finding in mild toxicity is nystagmus. As concentrations increase, ataxia, decreased coordination, hyperreflexia, slurred speech, and diplopia can occur. Progressive increases result in confusion, lethargy, and coma. Various attempts to increase elimination, including dialysis, hemoperfusion, diuresis, and plasmapheresis, have been ineffective and are not without risk. Meticulous supportive care, including ventilation if necessary, should provide a good clinical outcome. Multiple-dose activated charcoal may be helpful in shortening the duration of symptoms.

Severe poisoning in a hypoalbuminemic neonate responded unusually to peritoneal dialysis, possibly because of reduced phenytoin binding to plasma proteins (SEDA-16, 73).

Serum phenytoin concentrations in overdose have been studied in nine patients aged 20–66 years (67). The serum phenytoin concentrations were initially 136–230 μmol/l and fell linearly (that is with zero-order kinetics); the elimination rate varied from 19 to 41 μmol/l/day. In those with the highest serum concentrations at presentation there was a delay before the fall in concentrations began.

- The apparent effectiveness of charcoal hemoperfusion has been reported in a 19-year-old woman who took about 5 g of phenytoin (68). The plasma concentrations of total and unbound phenytoin fell rapidly, from 160 and 14 μmol/l to 65 and 6 μmol/l respectively, after 3 hours of hemoperfusion. The total phenytoin half-life was 3.9 hours. The protein-bound fraction was constant (91%) throughout.

Drug–Drug Interactions

Atorvastatin

In a 50-year-old woman with familial hypercholesterolemia and epilepsy, the addition of phenytoin caused a marked reduction in the lipid response to atorvastatin, an effect that was reversible after withdrawal of the anticonvulsant (69). It is likely that phenytoin reduced the efficacy of atorvastatin by inducing its metabolism.

Cimetidine

The combined use of cimetidine and phenytoin led to severe thrombocytopenia in four of 1512 neurosurgical patients (70).

Cyclophosphamide

In three patients treated with cyclophosphamide, phenytoin co-medication increased the formation of the *S*-enantiomer (but not the *R*-enantiomer) of the dechloroethylated cyclophosphamide metabolite (71). The findings also suggested that phenytoin increased the clearance of both *R*- and *S*-cyclophosphamide to 4-hydroxycyclophosphamide (the activation pathway). The clinical relevance of these findings is unclear.

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Isradipine

Isradipine, an inhibitor of CYP450, provoked phenytoin intoxication in one patient (72).

Lamotrigine

Choreoathetosis is a rare adverse effect of some anticonvulsants, but has especially been associated with phenytoin. In a retrospective survey, three of 39 adults and one of 38 children developed choreoathetosis acutely when lamotrigine was added to phenytoin or vice versa (73). The effect was reversible by withdrawing one of the drugs. It was calculated that the risk of choreoathetosis is increased more than 50-fold when these drugs are combined, possibly owing to a pharmacodynamic interaction.

Losartan

The interaction of losartan with phenytoin has been studied in a randomized, crossover study in 16 healthy volunteers (74). Losartan, a CYP2C9 substrate, had no effect on the pharmacokinetics of phenytoin. However, phenytoin inhibited the CYP2C9-mediated conversion of losartan to its active metabolite, thus potentially reducing its efficacy.

Nelfinavir

In a 30-year-old man stabilized on phenytoin, the addition of nelfinavir was associated with a fall in serum phenytoin concentration and seizure recurrence (75). However, other drugs were also added or withdrawn during the observation period and the role of nelfinavir in this possible interaction is speculative.

Paracetamol

It has been proposed that phenytoin can exacerbate the hepatotoxic effects of paracetamol (76).

- A 55-year-old woman with a community-acquired pneumonia had unexplained moderate rises in hepatic enzyme activities while taking paracetamol 1300–6200 mg/day and phenytoin 350 mg/day. Paracetamol was withdrawn, and her chemistry normalized within 2 weeks.

The authors suggested that induction of CYP3A4 by phenytoin had encouraged the formation of a hepatotoxic metabolite of paracetamol.

Simvastatin

- In a 50-year-old woman with familial hypercholesterolemia and epilepsy, the addition of phenytoin caused a marked reduction in the lipid response to simvastatin, an effect that was reversible after withdrawal of the anticonvulsant (69).

It is likely that phenytoin reduced the efficacy of simvastatin by inducing its metabolism.

Ticlopidine

A careful study in six patients showed that ticlopidine 250 mg bd caused a two-fold increase in the Michaelis–Menten constant of phenytoin, indicating inhibition of phenytoin metabolism (77). These results are consistent with the known inhibitory activity of ticlopidine on CYP2C19, and suggest that phenytoin dosage requirements can be reduced by ticlopidine.

Valproate

The pharmacokinetic interaction of phenytoin with valproate is complicated (78–80). Initially, the total serum phenytoin concentration falls, because valproate displaces phenytoin from protein binding sites and so the unbound fraction increases, with a consequent increase in clearance. Because of the change in unbound fraction the total plasma concentration effect curve is shifted to the left, and a lower total concentration is as effective as the total phenytoin concentration was in the absence of valproate. However, valproate also inhibits the metabolism of phenytoin and so the serum phenytoin concentration then starts to rise and there is a risk of toxicity.

Phenytoin reduces serum valproate concentrations by inducing its metabolism (81). This may cause the formation of a hepatotoxic metabolite of valproate (82).

In 775 patients who received intravenous phenytoin, valproate, or placebo, intravenous site reactions occurred in 25% of patients who received phenytoin (9). Most of the events (70%) occurred in the first intravenous site, and all occurred in peripheral administration sites. When patients who received the drug by central line were excluded, the estimated incidence was 30%. There were more adverse events when phenytoin was given together with valproate than when it was given alone.

Food–Drug Interactions

The interaction of oral phenytoin with enteral feeding formulations has been reviewed (83). Four prospective, randomized, controlled trials in healthy volunteers showed no interaction. However, numerous anecdotal reports and studies have shown dramatic reductions in serum phenytoin concentrations in patients receiving enteral feeding formulations. The authors therefore concluded that this interaction occurs in patients but not in healthy volunteers.

Diagnosis of Adverse Drug Reactions

The usual target range for plasma concentrations is 40–80 μmol/l (10–20 μg/ml).

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Phosphates

General Information

Sodium phosphates are considered to be dangerous (1), particularly because of their effects on electrolyte balance. An oral solution of sodium phosphates (dibasic sodium phosphate + monobasic sodium phosphate) is used as a laxative for the relief of occasional constipation and is used as part of a bowel-cleansing regimen in preparing patients for surgery or colonoscopy.

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The FDA has limited the container size for oral solutions of sodium phosphates to not more than 90 ml in over-the-counter laxatives, because of reports of deaths associated with overdosage of oral solutions of sodium phosphates when the product was packaged in a larger container and a larger than intended dose was taken inadvertently. The agency has also required warning and direction statements to inform consumers that exceeding the recommended dose of oral and rectal sodium phosphates products in a 24-hour period can be harmful.

In 194 patients randomized to receive either sodium picosulfate or fleet phosphate soda before barium enema, there was no difference in the quality of bowel preparation, but picosulfate was easier to take and better tasting and it provoked less nausea and vomiting (2).

Organs and Systems

Endocrine

A 39-year-old woman with oncogenic osteomalacia caused by an osteosarcoma of the right scapula developed tertiary hyperparathyroidism after taking oral phosphate and vitamin D (3). The uniqueness of this case was the co-existence of hyperparathyroidism and oncogenic osteomalacia. All patients previously reported as having developed tertiary hyperparathyroidism with phosphate supplements had taken them for 10–14 years before diagnosis, but this patient had taken it for only 2 years. The proposed mechanism is that exogenous phosphate stimulates parathyroid activity through sequestration of calcium.

Electrolyte balance

From 1987 to October 31, 2001 the Canadian Adverse Drug Reaction Monitoring Program received 10 reports of serious electrolyte disturbances (hypocalcemia, hyperphosphatemia, hypernatremia, and hypokalemia), acidosis, dehydration, renal insufficiency, and tetany in patients who had taken more than 45 ml of the solution, in patients at risk of these complications, and/or in patients using multiple purgatives for bowel preparation (4). In view of these reports, Johnson & Johnson, Merck Consumer Pharmaceuticals, and Pharmascience Inc, in consultation with Health Canada, each issued a letter to all health professionals, giving information related to the safe use of sodium phosphates oral solution. The identification, characterization, and management of drug-related adverse events depend on the active participation of health care professionals in adverse drug reaction reporting programs. Health care professionals are asked to report any suspected adverse reactions in patients who have taken sodium phosphates oral solution.

The Austrian Adverse Drug Reactions Advisory Committee received three reports of severe electrolyte disturbances associated with an oral bowel-cleansing solution containing sodium phosphate solution (Fleet Phospho-Soda Buffered Saline Laxative Mixture), used as a bowel preparation for colonoscopy (5). Prescribers are advised to be aware of complications of the use of phosphate enemas, particularly in infants, elderly or debilitated patients, patients with congestive heart failure, and patients with impaired renal function.

Gastrointestinal

Four cases have suggested an association between oral sodium phosphate and microscopic focal cryptitis (6). The three men and one woman, aged 31–56 years, all had symptoms suggestive of irritable bowel syndrome and had not taken any antibiotics, NSAIDs, or immunosuppressive drugs before the onset symptoms. Colonoscopy was normal. There was no microbiological evidence of an infective cause, and routine biochemistry and hematology laboratory tests were normal. Histology was distinct from infective, ischemic, or inflammatory bowel disease. However, rebiopsy after withdrawal of the drug was not performed in any patient.

Rectal necrosis has been described in a child after phosphate enemas (7).

Susceptibility Factors

Age

Children

Although phosphate enemas are used in preparing children's bowels for colonoscopy and have been described as being safe and ideal for this purpose (8), in children under 5 years they carry risks of significant morbidity due to hyperphosphatemia, hypocalcemia, hypokalemia and dehydration (9). Phosphate toxicity associated with enteral sodium phosphate has been reported in more than 20 children (10,11). Two died, and one had severe neurological sequelae; these three children had either gastrointestinal or renal abnormalities, and one was very premature. Fatal phosphate toxicity has been reported in a 17-month-old child who had no apparent renal or gastrointestinal abnormality after a relatively small dose of hypertonic phosphate enema (12). Hypocalcemic tetany developed in children after the administration of phosphate enemas (10,11). The authors advised against the use of phosphate enemas in children under 2 years, and they recommend use only with extreme caution in children aged 2–5 years, especially when there is underlying bowel disease or renal dysfunction.

Elderly people

In elderly patients, phosphate enemas (Fleet Enema) have caused serious adverse effects.

- A 77-year-old patient with diverticular disease, who received phosphate enemas in preparation for a barium enema, developed hyperphosphatemia and hypocalcemic coma (13).

This case suggests that caution is required in administering phosphate enemas to patients with abnormal colonic mucosa.

- A Fleet Enema was given to a 91-year-old patient who lapsed into coma and died a few hours afterwards, despite treatment with phosphate binders and calcium (14).

Another similar case has been described (15).

Renal disease

Adults with normal excretory functions should not be at risk, but those with renal failure are likely to experience complications (SEDA-17, 425) (SEDA-18, 374).

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Drug Administration

Drug overdose

A 46-year-old woman, with hepatic encephalopathy complicating cirrhosis due to hepatitis B and C infection, developed fatal hypernatremia, hyperphosphatemia, and hypocalcemia following the erroneous administration of a total of six sodium phosphate enemas (133 ml each) over 36 hours (16).

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Phosphodiesterase type III, selective inhibitors of

See also Individual drugs

General Information

There is a range of bipyridines that are selective inhibitors of a specific isoenzyme of phosphodiesterase, F-III. These include amrinone, enoximone (fenoximone), milrinone, pimobendan, sulmazole, and vesnarinone. Their clinical pharmacology has been reviewed (1).

The pharmacology, clinical pharmacology, uses, therapeutic value, and adverse effects of positive inotropic drugs other than digitalis have been reviewed (2–6), as has the suggestion that their long-term use may be deleterious (6). Apart from the selective inhibitors of phosphodiesterase type III, these drugs include some beta-adrenoceptor agonists and partial agonists, such as dobutamine, dopamine, ibopamine, pirbuterol, prenalterol, and xamoterol, and calcium sensitizers.

The under-reporting of the results of clinical trials in patients with heart failure has been reviewed (7). Some trials that have been unpublished or published only in abstract or preliminary form have involved drugs with positive inotropic effects, such as the phosphodiesterase inhibitor vesnarinone (SEDA-23, 195), the beta-adrenoceptor partial agonist xamoterol, and the dopamine receptor agonist ibopamine.

Although the phosphodiesterase inhibitors are effective in the treatment of acute cardiac failure in various settings, overall mortality during long-term treatment of heart failure is increased, and these drugs should not be used for that purpose (8).

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Photochemotherapy (PUVA)

General Information

Photochemotherapy, which consists of oral (and sometimes topical) administration of psoralens (the furocoumarins 5-methoxypsoralen, 8-methoxypsoralen, and trioxysalen) plus long-wave ultraviolet radiation, known as PUVA, is a well-established effective treatment for psoriasis, which has also been used for vitiligo (1), mycosis fungoides, alopecia areata, dyshidrotic eczema, atopic dermatitis, and certain other skin diseases. Guidelines for treatment have been recommended (2,3).

Bathwater delivery of psoralens ("Bath PUVA") is an attractive alternative to oral administration, since it virtually lacks systemic adverse effects and the rapid decline of photosensitivity after bath PUVA enables the patient to pursue daily activities without restrictions (4). Trioxysalen bath PUVA does not have carcinogenic effects (5).

Guidelines for topical PUVA therapy, including bath and local immersion PUVA therapy, have been published by the British Photodermatology Group (6).

Short-term reactions are not uncommon. They include erythema, burns, nausea, pruritus, headache, and dizziness. Hypersensitivity reactions, which are uncommon, include drug fever, skin rashes, and bronchial asthma. Long-term treatment increases the risk of non-melanoma skin cancers and possibly of cutaneous melanoma.

Organs and Systems

Cardiovascular

A rise in ambient temperature can have cardiovascular effects. In high-risk conditions, cardiovascular monitoring during treatment has been advised (SEDA-6, 148), although patients with cardiovascular disease and hypertension are also reported to tolerate PUVA therapy without evidence of cardiovascular stress (7).

Edema of the legs has been noted occasionally.

Respiratory

Bronchial asthma and coughing attacks have been attributed to methoxsalen allergy (8).

Nervous system

Dizziness, headache, and itching are well-known immediate adverse effects (SEDA-3, 132). Persistent skin pain can be serious (9).

Sensory systems

Although several cases of cataracts presumably or probably induced by PUVA have been reported (10,11), the risk appears to be small when recommendations to prevent ocular complications (12) are strictly adhered to (13).

Other ocular symptoms after PUVA include photophobia, conjunctivitis, keratitis, and dry eyes (SEDA-7, 166). Adequately protecting the eyes from the sun reduces the risk of acute toxic effects on the cornea and conjunctivae (14).

Visual field defects have been described in some patients (15).

Metabolism

Severe hyperlipidemia possibly related to PUVA has been observed once (SEDA-19, 155).

Hematologic

There have been reports of acute leukemia (SEDA-10, 125) and neutropenia (SEDA-5, 151) during PUVA and one dubious report of preleukemia (SEDA-4, 105). Transformation of stable chronic myelomonocytic leukemia to acute myeloid leukemia has been attributed to PUVA (SEDA-14, 124). These events may all have been purely coincidental and not causally related, as PUVA does not appear to increase the risk of non-cutaneous malignancies (16).

Gastrointestinal

Nausea and diarrhea sometimes occur (17).

Liver

Slight transient rises in liver enzymes have been reported during PUVA treatment, but they were usually attributable to pre-existing liver disease or the use of alcohol or other drugs. However, there have been two reports of liver damage clearly attributable to PUVA (18,19). It is rare for liver enzymes to rise after topical 8-methoxypsoralen (20).

Urinary tract

In 12 of 106 patients treated with PUVA an increase in serum creatinine to abnormal values was noted. In one patient a renal biopsy showed uncharacteristic glomerulonephritis (SEDA-5, 151).

Nephrotic syndrome has been reported in a patient treated with PUVA for polymorphic light eruption (SEDA-9, 132).

Skin

Phototoxicity with erythema, burns, localized edema, and blistering can occur in up to 11% of patients treated with PUVA (SEDA-22, 165) (21). Other cutaneous adverse effects that are related or possibly related to PUVA are listed in Table 1.

PUVA can cause pemphigus vulgaris, bullous pemphigoid, and pemphigus foliaceus. In one case intermittent flares continued for 2 years after the withdrawal of PUVA (22).

Immunologic

Concerns that PUVA therapy can cause systemic lupus erythematosus (SLE) and other connective tissue diseases, such as giant cell arteritis (SEDA-6, 147), have been raised by several reports (SED-12, 336) (30), (SEDA-15, 139) (SEDA-17, 183). There have been several studies of the incidence of serum antinuclear antibodies in patients who have received PUVA, with both

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Table 1 Adverse effects of PUVA on the skin, hair, and nails

Acne (SEDA-3, 132)
Actinic lichenoid dermatitis (SEDA-12, 130)
Allergic contact dermatitis to methoxsalen (8-methoxypsoralen)
Allergic cutaneous vasculitis (SEDA-6, 146)
Bacterial infections, such as folliculitis and erysipelas
Bowen's disease and Bowenoid lesions
Bullous eruptions, including phototoxic bullae, acrobullous eruptions, and (rarely) bullous pemphigoid (SEDA-21, 160) (23)
Dermatomyositis (SEDA-19, 155)
Disseminated epidermolytic acanthoma (SEDA-12, 130)
Disseminated superficial actinic porokeratosis (SEDA-6, 147) (SEDA-11, 136)
Epidermal dystrophy
Exacerbation of polymorphic light eruption
Generalized exanthematous pustulosis (SEDA-20, 153)
Granuloma annulare (SEDA-4, 105)
Herpes simplex infection
Herpes zoster infection
Hirsutism (SEDA-6, 146)
Hypertrichosis
Kaposi's varicelliform eruption
Keratoacanthoma (SEDA-9, 131)
Lichen planus (SEDA-6, 147)
Lupus erythematosus (SEDA-15, 140) (SEDA-17, 183)
Lymphomatoid papulosis (SEDA-16, 151)
Mycosis fungoides, inflammatory flare-up (SEDA-20, 153)
Nail pigmentation (SEDA-8, 152)
Neurofibroma (SEDA-15, 142)
Papular phototoxic reaction
Pemphigus vulgaris (24)
Photoallergic dermatitis (SEDA-15, 141)
Photo-oncolysis (SEDA-3, 152) (SEDA-4, 105)
Pigment alterations, notably PUVA lentigines (SEDA-9,130); absence of PUVA lentigines may be an indicator of a lower risk of PUVA malignancy (25)
Psoriasis of the nails
Pustular psoriasis
PUVA keratoses (26)
Rosacea
Scleroderma-like changes
Seborrheic dermatitis of the face
Senile elastosis
Subungual bleeding
Suppression of induction and expression of delayed cutaneous hypersensitivity (27)
Urticaria (28)
Verruciform xanthoma (SEDA-20, 153)
Vitiligo (SEDA-22, 165) (29)

positive and negative results. Current evidence suggests that frequent evaluation of antinuclear antibodies during treatment of patients with uncomplicated psoriasis with an initially negative antinuclear antibody test and with no symptoms of connective tissue diseases is unnecessary (31).

Hypersensitivity reactions occur infrequently and have included drug fever, skin rashes, and bronchial asthma. Anaphylaxis to 5-methoxypsoralen has been reported (32).

- A 36-year-old woman had been treated for a polymorphic light eruption with two annual courses of PUVA, three times weekly for 6 weeks, plus oral 5-methoxypsoralen 60 mg, without any adverse effects. However, during the fourth course, 30 minutes after taking 5-methoxypsoralen 60 mg, she developed intense pruritus of the palms, spreading to the body. This was followed by erythema of the palms and symmetrical erythematous patches and urticarial lesions on the trunk. She had dizziness and slight difficulty in breathing. Her symptoms cleared within an hour after intravenous administration of an antihistamine and cortisone. Two months later skin prick tests with 5-methoxypsoralen were negative, but placebo-controlled oral provocation with 5-methoxypsoralen 20 mg resulted in symptoms similar to those she had experienced during PUVA.

Body temperature

Influenza-like symptoms have been attributed to psoralens (33).

- A 54-year-old man treated with photochemotherapy for disabling hand eczema developed flu-like symptoms, which lasted for 48 hours and occurred repeatedly within 2 hours after oral methoxsalen 50 mg. In addition to a fever up to 39°C, he had headache, nausea and vomiting, fatigue, dyspepsia, and muscle aches.

Although no attempt was made to isolate any viruses, the multiple positive rechallenges, in combination with a time-course compatible with methoxsalen pharmacokinetics, suggested a drug-related event.

Long-Term Effects

Tumorigenicity

Cutaneous carcinogenicity

In a review of the English language literature on the risk of non-melanoma skin cancer from photochemotherapy in the treatment of psoriasis (34) the following were the conclusions:

(a) PUVA is an independent dose-related carcinogen in humans and can initiate and promote the formation of squamous cell carcinoma (35). The relation of basal cell carcinoma to PUVA alone is not well established.
(b) The carcinogenic risk of PUVA is not simply dose-related and skin type; geographic location and other well-established co-carcinogenic risk factors must be taken into account.
(c) Three factors are important co-carcinogens with PUVA: a history of arsenic exposure, ionizing radiation therapy, and skin cancer. Other factors believed to be related to increased risk include skin types I and II.
(d) Factors that appear to be associated with little or no risk of PUVA-related carcinogenesis include methotrexate (although a study from Sweden (36) has suggested otherwise), topical tar, and ultraviolet B (UVB). Exceptions to this include simultaneous use of methotrexate and PUVA, and high exposure of the genital skin to UVB/tar. Retinoids may prove to be negatively correlated with skin cancer.
(e) The dose-related increased risk of cutaneous squamous cell carcinoma from PUVA is independent of

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skin type (I–IV), although the absolute risk is much higher in skin types I and II.

(f) Men treated with PUVA without genital protection are at high risk of developing dose-related invasive squamous cell carcinoma of the penis and the scrotum (SEDA-15, 141).

(g) PUVA-induced squamous cell carcinoma is not biologically aggressive. Nevertheless, metastases have been observed in some patients, emphasizing the need for continued monitoring (37).

(h) There is no definitive degree of cumulative PUVA exposure above which carcinogenicity can be predicted. However, the risk of squamous cell carcinoma is less in patients with skin types II, III, and IV, no risk factors, and a cumulative exposure below 1000 J/cm^2. Of patients treated with over 2000 J/cm^2, even those without risk factors, at least 20% will develop squamous cell carcinomas and 50% atypical squamous keratoses (35). Patients with skin type I should be monitored more rigorously than others.

The following recommendations were made

(a) Whenever possible, exclude patients with a history of ionizing radiation therapy, skin cancer, or arsenic exposure.

(b) Shield the male genital skin at all times during PUVA treatment.

(c) Use the European dosage protocol (lower doses and less frequent irradiations than the US protocol) whenever possible.

(d) Reduce PUVA dosage by combining or cycling with other treatments. Avoid maintenance therapy if possible.

(e) Use PUVA in younger patients only when necessary.

(f) Monitor patients with skin type I closely.

(g) Monitor patients prospectively and at least annually for keratoses and cutaneous carcinoma, particularly after cumulative exposure of more than 1000 J/cm^2.

Risk of melanoma

The PUVA Follow up Study was a prospective evaluation of 1380 patients who started using PUVA for psoriasis in 1975 and 1976. There was a modest but significantly increased risk of malignant melanoma in PUVA-treated patients ($n = 822$), beginning 15 years after first exposure (SEDA-22, 166) (38,39). Incidence rates during 1996–1999 were 10-fold higher than those expected from incidence data in the general population (data available only for 1992–1996). There was a non-significant trend toward a higher incidence of melanoma in patients who had received more courses of PUVA (over 200). High degrees of exposure to PUVA, a period of at least 15 years from the time of the first exposure, or both are required before the risk of melanoma increases substantially. Despite the fact that melanoma is lethal if left untreated, this observation does not necessitate abandonment of PUVA (40). This risk should be weighed against the substantial efficacy of PUVA therapy in severe psoriasis. However, it does suggest that the guidelines for treating psoriasis with PUVA should be rigidly observed (41). Patients receiving long-term treatment should be carefully followed throughout their lives and those who are at increased risk of melanoma should not be given this treatment.

Non-cutaneous cancers

Long-term PUVA does not increase the risk of non-cutaneous cancer, including lymphomas or leukemia (16).

Second-Generation Effects

Pregnancy

Although PUVA therapy should not be begun during pregnancy or lactation, the theoretical mutagenic and teratogenic effect of PUVA does not carry any significant risk of abnormal delivery (42,43).

Susceptibility Factors

Relative contraindications to PUVA therapy include a history of arsenic intake, previous ionizing radiation, long-term use of cytostatic drugs, skin cancer, cataracts, and severe cardiovascular disease. In patients with photosensitive dermatoses and in patients who are using systemic photosensitizing drugs, PUVA should be administered with caution. The possible long-term adverse effects should be taken into consideration, especially when young patients are candidates for photochemotherapy. Uncontrolled use of psoralens may lead to life-threatening burns (27).

Drug–Drug Interactions

Emollients

The use of emollients before PUVA can significantly interfere with UV light transmission during photochemotherapy (44).

Phenytoin

Phenytoin can reduce the serum concentrations of methoxsalen, probably by inducing its metabolism (45).

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Physical contraceptives—intrauterine devices

General Information

Intrauterine contraceptive devices (IUCDs) have been reviewed (1,2). Most are composed of bland synthetic materials or contain in addition a small amount of metallic copper. Others are designed to release either progesterone or a synthetic progestogen (for example levonorgestrel) (3,4). IUCDs that release levonorgestrel are somewhat more effective than copper-containing devices, while those that release progesterone are less effective (5).

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Copper-containing IUCDs (6,7) became popular because local inflammatory reactions in the endometrium are more marked and the contraceptive effect is thus more pronounced (SEDA-21, 234) (8). In addition, copper ions released from IUCDs reach concentrations in the luminal fluids of the genital tract that are toxic to spermatozoa and embryos. The ability of copper to induce the generation of free radicals and the formation of malonaldehyde may be involved in its contraceptive effect.

Migration of IUCDs

Migration of IUCDs is relatively rare, although they have been found in the omentum, rectosigmoid, peritoneum, bladder, appendix, small bowel, adnexa, and iliac vein. Most authors have recommended removal of copper-containing devices, because of the potential for inflammatory reactions, which can cause bowel obstruction and perforation (9). Two cases of migration of IUCDs to the bowel have been reported.

- A 29-year-old woman who had had a Copper 7 IUCD inserted 3 years before developed amenorrhea (10). The intrauterine contraceptive was not in the uterine cavity and X-ray showed that it was positioned over the sacrum just to the right of the midline and outside the uterus. It later moved to the cecum and became completely embedded in the muscular layer after penetrating the serosal surface.
- A Copper-T IUCD migrated to the rectal lumen in a 36-year-old woman with menorrhagia for 3 month and a history of Copper-T insertion 6 years before (11).
- A 28-year-old pregnant woman developed an ileal perforation 4 weeks after the insertion of a Multiload-Cu 375 IUCD (12).

The last report documents the shortest interval between insertion and proven bowel injury by an IUCD.

Organs and Systems

Skin

Perimenstrual dermatitis has been attributed to a copper-containing IUCD (13).

- A 41-year-old woman had a 2-year history of a recurrent, self-healing skin rash associated with abdominal pain. She had had cholinergic urticaria since 1995 and had had a copper-containing IUCD inserted 12 years before. The eruption followed a cyclical pattern, invariably appearing 3–7 days before the menses and tending to improve spontaneously with the onset of bleeding. This non-itchy rash was associated with abdominal distension and cramps that followed a similar course. She had multiple non-itchy symmetrical erythematous papules on the upper trunk, neck, and arms. Patch-testing was positive for copper sulfate. The IUCD was removed and the abdominal symptoms subsided at the following cycle. Progressive resolution of the dermatitis was observed. No cutaneous eruption was observed after 8 months and no new lesions developed after a further 5 months.

Reproductive system

Although the effect of a progestogen in an IUCD is primarily local, the amounts released are sufficient to have some systemic effects. In particular, there are partial and variable effects on ovulation, which seem to cause a greater risk of functional ovarian cysts (14,15).

Menstrual disturbances

The authors of a balanced review of hormone-releasing intrauterine systems concluded that while with large-size devices that release high doses (for example 20 micrograms/day) pregnancy rates and the incidence of ectopic pregnancy are extremely low, users are more likely to have amenorrhea and device expulsion (16). Compared with users of a subdermal hormonal implant (Norplant-2), women who used LNG-20 were more likely to have oligomenorrhea but less likely to have prolonged bleeding and spotting.

The fibrinolytic activity of menstrual blood in wearers of Lippes loops exceeds that of patients with menorrhagia, while the values in users of the Cu-T (200) are in the same range as in normally menstruating and untreated women. In users of Lippes loops no fibrin was found in the endometrial stroma. This may explain the increased blood loss associated with the use of the Lippes loop, which can be severe enough to cause anemia (17).

Oligomenorrhea is a common adverse effect of IUCDs; during the first year after insertion; some 16% of users experience 90 days or more of amenorrhea, which is substantially more common than with a bland IUCD.

Early experience in 22 women who used a device releasing both copper and norgestrel ("Gynefix-Norgestrel") suggested that it was well tolerated and that the amount of menstrual bleeding was less than with the conventional copper-only "Gynefix" product (18).

In women who used a variant that released levonorgestrel 20 micrograms/day from a polymer cylinder covered with a membrane that controlled the rate of release, both the volume of menstrual blood loss and the number of bleeding days were reduced, and during the first year of use 20% of women developed amenorrhea (19). There was an initial increase in the mean number of bleeding and spotting days, but in 3–6 months the number of bleeding and spotting days was the same as observed in users of copper IUCDs. The variation between individuals was wide and unpredictable, but the method was claimed to be well accepted by users, with typical annual continuation rates above 80% in various studies. However, premature removal of the system was often required because of unwanted effects; in a nationwide study in Finland, the continuation rates at 1, 2, 3, 4, and 5 years were 93, 87, 81, 75, and 65% respectively (20). The symptoms most strongly associated with premature removal were excessive bleeding and spotting, infections, and pain. The risk of premature removal was markedly lower among women who had occasional or total absence of menstruation. Premature removal was less likely in the oldest age group. British experience showed a clear need to counsel women in advance about the possibility of early disruption of the bleeding pattern, including the chance of oligomenorrhea or amenorrhea, if they are not to become discouraged and abandon the treatment entirely (21).

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The FibroPlant is a levonorgestrel-releasing device derived from the earlier GyneFix principle. Experience with two forms of this frameless "fibrous delivery system," which releases smaller doses (10 or 14 micrograms/day), suggested that it was as effective and well tolerated as other types of device (22). However, the irregular bleeding that can occur with devices of this type can complicate and delay the recognition of endometrial cancer (23).

Ectopic pregnancy

It is not known whether the risk of ectopic pregnancy is increased in women using an IUCD (24,25). The proportion of such pregnancies has been reported as 6–8%, or higher. Primary ovarian pregnancies also develop in IUCD users, suggesting that ovarian implantation is not fully prevented (26).

The proportion of pregnancies that are ectopic is higher with devices that release either levonorgestrel or progesterone than with copper IUCDs, although the rates vary inversely with the hormonal content; at the most common dosages, the ectopic pregnancy rate for progesterone-containing devices (releasing 65 mg/day) was three times that with IUCDs containing levonorgestrel (releasing 20 mg/day).

Use of a variant that released levonorgestrel 20 micrograms/day from a polymer cylinder covered with a membrane that controlled the rate of release resulted in extrauterine pregnancies in one per 5000 users per year (19).

Chronic inflammatory and degenerative changes

There is a positive correlation between high copper loss from an IUCD and the development of menorrhagia or pathological lesions, such as cervical dysplasia and endometrial cytopathology (27). Evidence of endometrial carcinoma was not found in endometrial aspirates from 189 women who had used Copper-T-200 devices for 1–10 years, but five cases of endometrial hyperplasia (2.67%) were encountered in women in the series, all of whom had worn copper devices for 6 years or more. Inflammatory changes in the endometrial cells were found in 12 cases (6.2%), 11 of 12 having worn the device for over 3 years. It is possible that constant exposure to copper may be responsible for persistence of chronic inflammatory changes in endometrial cells, which could be the precursors of hyperplastic changes. It is not clear whether the dissolved copper is also responsible for the temporarily increased predisposition to bacterial contamination and the somewhat increased risk of pelvic inflammatory disease, seen especially in young nulliparous women using this type of contraceptive method.

In endometrial specimens in which copper-containing IUCDs had been embedded there was evidence of severe, degenerative changes in abnormal cells on the surface of the device and also in the endometrium and occasionally also in the muscle layer of the uterus (28,29). These were characterized by pyknosis of the endometrial cells and altered intracellular components. There were relatively few microtubuli in the endometrial cells. Copper ions escaping to the surface of the device may have been responsible for local endometrial damage.

Uterine and extrauterine infections

Progesterone-releasing devices have to be replaced annually, and since there is always a risk of microbacterial contamination of the endometrium on IUCD insertion this brings with it some risk of pelvic inflammatory disease. The risk is less with an IUCD that releases levonorgestrel 20 mg/day, which remains effective for several years. There is even some evidence of an actual protective effect against pelvic inflammatory disease (30); in a comparative study, the 36-month rate of pelvic inflammatory disease was significantly lower for a levonorgestrel device (0.5 per 100 woman-years) than for a copper-releasing IUCD (2.0 per 100). The pregnancy rate in this study was also very significantly lower (0.3 for the progestogen device compared with 3.7 for the copper device), as was the rate of ectopic pregnancies (0.03 compared with 0.25). The rate of expulsion was similar, while the rates of removal because of amenorrhea and the hormonally related adverse effects were significantly higher with the levonorgestrel-releasing device than the copper IUCD.

If copper-containing fragments of IUCDs perforate the uterine wall and enter the peritoneal cavity, acute inflammatory reactions and peritoneal adhesions can occur. Laparoscopic removal is then not only as a rule impossible but may also be dangerous because of the marked peritoneal reaction surrounding the copper part of the device. Laparotomy has therefore been suggested as the primary measure in such cases. Whether copper devices result more commonly in perforation than non-copper devices is not entirely clear, nor is the question answered whether copper increases the risk of extrauterine pregnancies, although older evidence suggested this as a risk (SED-9, 371).

Immunologic

Immunological and hypersensitivity reactions beyond the uterus are uncommon, but they can occur. Rashes, including generalized urticaria and eczematoid eruptions, have occurred as a result of allergy to the copper released from IUCDs, although they are extremely rare (SEDA-11, 204) (SEDA-12, 186) (SEDA-21, 235). One woman who had worn a copper-containing device for 12 months developed widespread urticaria and angioedema of the eyelids and the labia majora and minora for about 6 months (31). She also had persistent symptoms of premenstrual and postmenstrual spotting and leukorrhea for about 6 months. A patch test was positive with 1% copper sulfate, as was an in vitro lymphocyte-stimulating test with copper. An endometrial biopsy showed vulvovaginitis, with hyperplasia of the cervical canal and T cell and eosinophilic granulocyte infiltration. Removal of the device caused complete remission.

The incidence of salpingitis and other pelvic inflammation is believed to be higher in users of IUCDs. A study of cervical smears in women using IUCD contraception compared with others using other methods of contraception showed that the incidence of cervical inflammation was higher in the former (32).

Genital tract actinomycosis has come increasingly to the fore (33,34). In one study in Britain, the pelvic smears of nearly one-third of women using plastic devices were positive for *Actinomyces*-like organisms, compared with

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two of 165 women using copper-loaded IUCDs and none in a series of oral contraceptive users. There was a highly significant correlation between the presence of these organisms on smear and pain or other symptoms of pelvic inflammatory disease.

Current users of IUCDs suffer more often from acute rather than chronic pelvic inflammatory disease (1.51 compared with 0.54 times per 1000 woman-years). In ex-users the situation was reversed, chronic pelvic inflammatory disease being more common (0.95 compared with 0.48 times per 1000 woman-years) (35).

Second-Generation Effects

Fetotoxicity

Although copper-containing IUCDs are very effective, pregnancies do occur and the question of possible second-generation effects has to be considered. In one case the neonate showed significantly increased copper and ceruloplasmin concentrations, whereas maternal concentrations were within the reference range. Whether such exposure to copper can cause harm is not clear; because of the pharmacological effects of copper, it has been suspected of having mutagenic and carcinogenic potential. Until now, there is no clear evidence that harm is actually done. Five published cases scattered throughout the literature in which incomplete closure of the neural tube was found (36) could have been coincidental, bearing in mind the large number of pregnancies in which exposure to copper must occur in this way. In various species of animals which have been studied (rat, rabbit, hamster, sheep) no teratogenicity of intrauterine copper was detected (SED-11, 442).

Drug–Drug Interactions

Immunosuppressants

Two pregnancies (with normal outcomes) have been described in renal transplant patients using an IUCD. It seems that an intact immune system is needed for effective contraception by IUCD, and that immunosuppressive therapy can render an IUCD ineffective. Immunosuppressed patients should be advised to use another means of contraception (37).

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Physical contraceptives—spermicides

General Information

Modern spermicides are produced in a variety of formulations, including gels, foams, creams, suppositories, pessaries, capsules, foaming tablets, and melting films. Spermicides are also used in conjunction with other methods, such as diaphragms, condoms, and sponges, but also with intrauterine contraceptive devices and methods based on fertility awareness (1).

Contraceptive sponges are controversial: do they act by delivering spermicides or as barriers? However, it has been shown conclusively that the newest forms of sponges, which provide not one but a combination of three active spermicides, act much more like spermicides than as simple vaginal barriers.

Spermicides are relatively inexpensive and widely available over the counter in most countries. All currently used formulations contain the non-ionic detergent nonoxinol-9, usually in a dose of 70–230 mg, but the newest formulations may contain octoxynol or benzalkonium chloride (2). All chemical agents used in spermicides disrupt the sperm cell membrane and finally rupture the cell.

Spermicides, especially in certain communities, have important advantages over the more modern methods of contraception: they are immediately reversible, are available over the counter without prescription, can be used by breastfeeding women, and are under direct female control.

However, spermicides also have adverse effects. They can cause local irritation in the woman or her partner, especially if they are used several times a day and can very rarely cause local allergic reactions in the woman or her partner.

Nonoxinols

Nonoxinols (ethoxylated alkyl phenols) are synthesized from alkylbenzene nonoxinol by reacting it with ethylene oxide to produce ethylene oxide polymers of various lengths. Each nonoxinol is followed by a number that indicates the approximate number of ethylene oxide groups it contains. In cosmetic products, nonoxinols are used as emulsifying, wetting, foaming, and solubilizing agents. They are used in hair and skin products, and in bath, shaving, and fragrance formulations (3). The non-ionic surfactant properties of nonoxinols allow them to be used in a wide variety of industrial, household, agricultural, and pharmaceutical products. Nonoxinol-9 and -10 are surface-active agents used in antiseptic formulations, such as Hibitane (chlorhexidine), Betadine (povidone-iodine), and Hexomedine (hexamidine). They are the most commonly used spermicidal contraceptives and have been recommended in the prevention of sexually transmitted diseases and in human immunodeficiency virus prophylaxis (4).

Carbomers

Carbomers are acrylic acid polymers that are used for a variety of purposes. They are used in pharmaceutical processes as suspending agents, gel bases, emulsifiers, and binding agents. They are also used as artificial tears. Carbomer 974P is a carbomer that is the major non-aqueous component (5% polymer, 94% water) of a proprietary formulation called BufferGel, which also contains dibasic potassium phosphate, magnesium sulfate, dibasic sodium phosphate, sorbic acid, monobasic sodium phosphate, and disodium EDTA. It is a buffering agent, a microbicide, and a spermicide. It is formulated in an aqueous gel at pH 3.9, which acidifies twice its volume of semen to a pH of 5 and maintains the protective acidity of the vagina. It is used vaginally as a spermicide that also protects against HIV infection and possibly other sexually transmitted diseases.

The safety of BufferGel has been evaluated in a high-dose tolerance trial in 98 women, of whom 91 (26 sexually abstinent and 65 sexually active) completed the study (5). Reasons for withdrawal included: an inability to adhere to the protocol ($n = 1$); breakthrough menstrual bleeding ($n = 2$); the presence of yeast on day 7 (two

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asymptomatic cases and one symptomatic case); and refusal to continue ($n = 1$). The percentage of women with at least one sign or symptom judged by a clinician as potentially related to the product was 29% in India, 33% in Thailand, 35% in Malawi, and 33% in Zimbabwe. There were no differences in the proportions of sexually abstinent and sexually active women with at least one potentially product-related sign or symptom at each study site. In all, there were 45 potentially product-related signs and symptoms. Two were judged to be definitely related to the product (vaginal itching after product insertion) and 43 as possibly or probably related. All were categorized as mild (84%) or moderate (16%). Excluding participants who withdrew by day 7, 71% of the signs and symptoms resolved during the trial and 24% within 3 days of product withdrawal at the end of the trial; 5% persisted at the end of the trial (one woman was given treatment for a yeast infection and one was not re-evaluated for itching). Minor self-reported symptoms of irritation of limited duration accounted for 64% of reported signs and symptoms and were approximately equally distributed across study sites. They included vulvar and vaginal itching or burning, burning when urinating, and genital rash. The overall rate of symptoms of irritation for all sites combined was 0.58 events per woman-week of observation (95% CI = 0.3, 0.88). Other signs and symptoms included lower abdominal pain or backache, symptomatic yeast infection, and vaginal discharge.

Organs and Systems

Urinary tract

Urinary tract infections are quite common, although not very serious adverse effects of spermicides. For several years, the rate of urinary tract infections in young, sexually active women caused by the use of spermicides has been uncertain and has not been thoroughly evaluated. Since this phenomenon was observed, special surveys have been carried out and several have confirmed a higher risk of urinary tract infection among women who use a diaphragm with spermicides, compared with sexually active women who use other types of contraception (6). Finally, women who use spermicides are at higher risk of urinary tract infection than women who use other methods of contraception. Users of diaphragms and other barrier methods (including spermicide-coated male condoms) in conjunction with spermicides have increased degrees of introital and periurethral colonization with coliform organisms and *Staphylococcus saprophyticus*, leading to urinary tract infection (7).

In a large case control study in the USA, 96 sexually active young women with acute urinary tract infections caused by *S. saprophyticus* and 629 control patients without urinary tract infections were interviewed (7). Exposure to spermicide-coated condoms during the previous month was associated with a higher risk of urinary tract infections. Younger age, intercourse frequency, prior urinary tract infections and frequency of exposure to spermicide-coated condoms were independent predictors. Among women exposed to spermicide-coated condoms, 74% of urinary tract infections caused by *S. saprophyticus* were attributable to this exposure. The authors concluded that spermicide-coated condoms were associated with an increased risk of urinary tract infections caused by *S. saprophyticus*.

Skin

Contact dermatitis in patients exposed to nonoxinols was initially considered to result from irritation, but allergic reactions have also been reported (8). Nonoxinol contact allergy has been described in two patients who developed contact photosensitivity to nonoxinol-l0 in the antiseptic product Hexomedine transcutanée (hexamidine) (9). Among 32 control subjects, 13 had positive photopatch tests to Hexomedine transcutanée and four had positive photopatch tests to nonoxinol-10. Surprisingly, the authors observed that only undiluted nonoxinol was phototoxic, and in another study, nonoxinol-9 was found to be rarely sensitizing and compatible with latex and silicone lubricants used in condoms (10).

Second-Generation Effects

Teratogenicity

Use of spermicides in the year before pregnancy or during pregnancy has been associated with adverse reproductive outcomes, including spontaneous abortion and Down syndrome. In a preliminary analysis, an association was found between spermicide use at conception and tetraploid and hypertriploid conceptions (11). An association between the use of vaginal spermicides and birth defects has been suggested (12).

Spermicide use for more than a year at any time before conception was more common in cases aborting a trisomic conception than in controls. The association varied with maternal age, and was confined to women aged 30 years or older (13). However, it has since been concluded that there is no convincing evidence of an increased risk of fetal abnormalities in women who become pregnant while using spermicides, or in women who have used them before realizing that they were pregnant (14).

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Phytolaccaceae

See also Herbal medicines

General Information

The genera in the family of Phytolaccaceae (Table 1) include pokeweed.

Phytolacca americana

Phytolacca americana (pokeweed) contains powerful mitogens (pokeweed mitogen), including phytolacain, used to study cell function.

Adverse effects

Severe emesis and diarrhea, accompanied by tachycardia, have been observed after ingestion of raw leaves and after drinking tea prepared from the powdered root of *P. americana* (pokeweed).

Table 1 The genera of Phytolaccaceae

Agdestis (agdestis)
Gisekia (gisekia)
Petiveria (petiveria)
Phytolacca (pokeweed)
Rivina (rivina)
Stegnosperma (stegnosperma)
Trichostigma (alpine clubrush)

In one case Mobitz type I heart block was associated with vomiting due to pokeweed, which resolved after intravenous promethazine (1). The authors suggested that the heart block had been due to increased vagal tone associated with severe gastrointestinal colic.

Reference

1. Hamilton RJ, Shih RD, Hoffman RS. Mobitz type I heart block after pokeweed ingestion. Vet Hum Toxicol 1995; 37(1):66–7.

Picenadol

General Information

Picenadol is a racemic mixture of an *N*-methyl-4-phenylpiperidine derivative. It has mixed agonist–antagonist properties, because the dextrorotatory isomer is a potent opioid agonist and the levorotatory isomer is an opioid antagonist. Picenadol also has anticholinergic activity. Its adverse effects include drowsiness, dizziness, and lightheadedness (SEDA-16, 90). In a double-blind comparison of the analgesic potency and adverse effects profiles of a single oral dose of picenadol 25 mg with codeine 60 mg and placebo, few adverse effects were reported. Drowsiness was the most frequent, with an incidence of 16% (1).

Picenadol 75 mg was reportedly distinguishable from morphine by sedation, dysphoria, and hallucinatory activity, probably due to anticholinergic activity; at lower doses it was morphine-like (SEDA-16, 90).

Reference

1. Brunelle RL, George RE, Sunshine A, Hammonds WD. Analgesic effect of picenadol, codeine, and placebo in patients with postoperative pain. Clin Pharmacol Ther 1988;43(6):663–7.

Picibanil

General Information

Picibanil (OK 432) is derived from *Streptococcus pyogenes* and has been used in the treatment of cancers, lymphangiomas, and viral infections. Low-grade fever, nausea and vomiting, and an inflammatory reaction at the injection site were commonly reported, whereas joint pain and mild liver dysfunction were seldom described.

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Organs and Systems

Fluid balance

Hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been attributed to picibanil (1).

- A 59-year-old woman with a previous history of squamous cell carcinoma of the esophagus developed a metastatic lung tumor 4 years later. A right lower lobectomy was performed, and intrapleural picibanil was instilled on postoperative days 4, 5, and 9 for pulmonary fistula with prolonged air leakage. On day 13 she had fatigue, nausea, and drowsiness. Her serum sodium concentration was 106 mmol/l and there was a 2.5-fold increase in serum antidiuretic hormone concentration. She recovered completely after fluid restriction and sodium supplementation.

The author thought that SIADH had resulted from severe pleurisy secondary to intrapleural administration of picibanil rather than to direct stimulation of antidiuretic hormone release.

Hematologic

Hemolytic anemia, presumably of immune origin, has been reported in a patient taking picibanil (2).

References

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2. Nomura S, Kanoh T. Immune hemolytic anemia associated with streptococcal preparation OK-432. Cancer 1987;59(8):1409–11.

Picrotoxin

General Information

Picrotoxin is a non-nitrogenous plant derivative that is a powerful stimulant of all parts of the central nervous system, acting on the chloride ionophore–aminobutyric acid complex in a manner opposite to that of barbiturates (1). Its adverse effects resemble those of nikethamide; picrotoxin 20mg can cause severe poisoning.

Reference

1 Obata K. The inhibitory action of aminobutyric acid, a probable synaptic transmitter. Int Rev Neurobiol 1972; 15:167–87.

Piketoprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Piketoprofen is an NSAID that has been used topically as the hydrochloride salt.

Organs and Systems

Skin

A photoallergic contact dermatitis followed topical administration of piketoprofen in a 46-year-old man after 3 days; photopatch testing for piketoprofen was positive (1).

Reference

1. Bujan JJ, Morante JM, Guemes MG, Del Pozo Losada J, Capdevila EF. Photoallergic contact dermatitis from piketoprofen. Contact Dermatitis 2000;43(5):315.

Pilocarpine

General Information

Pilocarpine is an antagonist at acetylcholine receptors (1). While it is mainly used in the eye in the treatment of glaucoma, pilocarpine is still occasionally used for other purposes, for example for treating salivary gland hypofunction and xerostomia. When used in this way, cardiovascular tolerance was good but there was a high incidence of sweating, flushing, increased frequency of micturition, increased nasal secretion, and lacrimation (SEDA-18, 174).

Reference

1. Wiseman LR, Faulds D. Oral pilocarpine: a review of its pharmocological properties and clinical potential in xerostomia. Drugs 1995;49(1):143–55.

Pimecrolimus

General Information

Pimecrolimus is a non-steroidal ascomycin derivative with topical anti-inflammatory activity. In a 1% cream it is effective and safe in atopic dermatitis in infants, children, and adults (1–3), although its efficacy has been questioned (4).

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Organs and Systems

Skin

The main adverse effect of pimecrolimus is local skin irritation, with a stinging or burning sensation, which occurs in 30% of patients. Typically, children have less skin irritation than adults. Adverse effects such as local immunosuppression and an increased risk of local bacterial and viral infections (notably eczema herpeticum) are less common than with topical glucocorticoids (5). In addition, there is a lack of skin atrophy (6,7). However, topical corticosteroids have the advantage of better skin penetration than pimecrolimus and will therefore continue to be used for more heavily keratinized skin such as in psoriasis (8).

Tinea incognito has been attributed to pimecrolimus (9).

- A 6-year-old boy developed a small, erythematous, slightly scaly, pruritic plaque near his right eye, which was treated with twice-daily pimecrolimus cream. After 2–3 days, the itching and erythema completely resolved, but a rough scaly plaque persisted. After 1–2 weeks, the itching gradually returned and the lesion began to increase in size. Multiple similar lesions appeared several centimeters from the initially affected area. Pimecrolimus was withdrawn and topical nystatin + triamcinolone ointment was prescribed. The eruption continued to spread, with multiple annular scaly papules and plaques with central clearing. There was excoriation and mild inflammation around all affected areas. A potassium hydroxide examination of the lesions showed numerous hyphae. The nystatin + triamcinolone was withdrawn and oral griseofulvin was prescribed. The eruption improved dramatically after 3 weeks and eventually cleared completely after 5 weeks of treatment. Topical 2% ketoconazole cream was applied twice a day during the final 2 weeks of treatment.

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Pimobendan

See also Phosphodiesterase type III, selective inhibitors of

General Information

Pimobendan is an inhibitor of phosphodiesterase type III with calcium sensitizing properties in the myocardium. It has been associated with a worrisome albeit non-significant increase in mortality in patients with chronic congestive heart failure (1).

Reference

1. Lubsen J, Just H, Hjalmarsson AC, La Framboise D, Remme WJ, Heinrich-Nols J, Dumont JM, Seed P. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. Heart 1996;76(3):223–31.

Pimozide

See also Neuroleptic drugs

General Information

Pimozide is a diphenylbutylpiperidine neuroleptic drug, structurally similar to the butyrophenones.

Organs and Systems

Cardiovascular

Pimozide can cause QT interval prolongation and torsade de pointes; a total of 40 reports (16 deaths) of serious cardiac reactions, mainly dysrhythmias, were reported to the Committee on Safety of Medicines in the UK from 1971 to 1995 (1).

Drug Administration

Drug overdose

In a study of overdosages of different neuroleptic drugs, pimozide had the lowest fatality index (the number of deaths divided by the number of prescriptions) (2).

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Drug–Drug Interactions

Clarithromycin

In 12 healthy volunteers given oral pimozide 6 mg after 5 days of treatment with clarithromycin (500 mg bd) or placebo, pimozide significantly prolonged the QT_c interval in the first 20 hours in both groups (maximum changes in QT_c 16 and 13 ms respectively) (3).

References

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Pinaverium bromide

General Information

Pinaverium bromide is an anticholinergic drug (1). Like emepronium bromide, it can cause inflammation and ulceration in the mouth and esophagus (SEDA-6, 143).

Reference

1. Guslandi M. Profilo farmacologico-clinico del pinaverio bromuro. [The clinical pharmacological profile of pinaverium bromide.] Minerva Med 1994;85(4):179–85.

Pindolol

See also Beta-adrenoceptor antagonists

General Information

Pindolol is a beta-adrenoceptor antagonist with $beta_2$-adrenoceptor agonist action and some membrane-stabilizing activity (1).

Organs and Systems

Nervous system

Pindolol can cause resting tremor in some patients (2).

References

1. Aellig WH, Clark BJ. Is the ISA of pindolol $beta_2$-adrenoceptor selective? Br J Clin Pharmacol 1987; 24(Suppl 1):S21–8.
2. Hod H, Har-Zahav J, Kaplinsky N, Frankl O. Pindolol-induced tremor. Postgrad Med J 1980;56(655):346–7.

Pipebuzone

See also Non-steroidal anti-inflammatory drugs

General Information

Pipebuzone is a combination of phenylbutazone with piperazine, produced in an unsuccessful attempt to improve the tolerance of phenylbutazone. Typical phenylbutazone reactions (abdominal, hematological, renal, allergic, and rectal irritation from suppositories) were common (SED-9, 145) (1–3).

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1. Poulain D. Bilan de l'utilisation de l'élarzone dausse en chirurgie gynécologique et obstétricale. A propos de 228 cas. Arch Med Ouest 1976;8:117.
2. Chovelon R, Hovasse BM. Expérimentation de l'élarzone-dausse, nouvel antiinflammatoire, dans les affectations des voies respiratoires chez les personnes âgées. Med Int Pol 1975;10:179.
3. Pelissier P, Colas IJ, Beaulieux J. Expérimentation de l'élarzone dausse dans un service de chirurgie vasculaire. J Méd Lyon 1974;55:709.

Pipecuronium bromide

See also Neuromuscular blocking drugs

General Information

Pipecuronium bromide is a bisquaternary steroid analogue of pancuronium. In vitro pipecuronium reversibly inhibits both human red cell acetylcholinesterase and human plasma cholinesterase to an extent that might have clinical implications (1). Its potency is similar to that of pancuronium and its onset and duration are also approximately the same. Accumulation can occur (2), and maintenance doses should be one-quarter to one-sixth of the initial dose to achieve a similar effect, depending on the anesthetic technique used.

From animal investigations hepatic uptake appears to be a factor in the drug's total plasma clearance, but renal excretion seems to be the main route of elimination. Ligation of renal pedicles in dogs (3) resulted in reduced elimination of pipecuronium, with a four-fold increase in mean residence time and a four-fold increase in hepatobiliary elimination, which did not compensate for the loss of urinary excretion. In humans, about 40% of

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pipecuronium is excreted unchanged in the urine together with another 15% as 3-hydroxypipecuronium in 24 hours (4). The half-life is around 135–160 minutes.

Organs and Systems

Cardiovascular

No histamine release has been reported with pipecuronium, and vagolytic or sympathomimetic effects are not seen in the usual dose range. Rarely, significant hypotension has been reported (2), but this was transient and occurred during an unstable phase of anesthesia. Bradycardia has also been seen (2) but is usually mild (5), and probably due to the vagotonic effects of co-administered drugs, as is seen with vecuronium and atracurium (that is a minor disadvantage of the relaxant's lack of vagolytic or sympathomimetic effects). Usually, no significant changes in heart rate or blood pressure are seen (6–8), even with doses up to three times the ED_{95} (9,10). Cardiovascular stability has also been reported in cardiac patients (11), including patients in ASA classes II and III about to undergo coronary artery bypass grafting who received doses up to 0.15 mg/kg (12) and those who received high-dose fentanyl anesthesia (13). The absence of tachycardia in these high-risk cardiac patients, in whom any increase in myocardial oxygen demand is unwanted, was considered an advantage of pipecuronium.

Susceptibility Factors

Renal disease

As expected, renal dysfunction is associated with an increase in volume of distribution, a decrease in plasma clearance (1.6 versus 2.4 ml/kg/minute), and an increase in half-life (263 versus 137 minutes) compared with patients with normal renal function (14). In the latter study there was no statistically significant prolongation of the mean duration of action of pipecuronium, but there was a much greater variation in those with renal insufficiency, with 25% recovery times (after 0.07 mg/kg) of 30–267 minutes (controls 55–198 minutes). These patients were also undergoing renal transplantation and most of the replacement kidneys would be expected to have some function and some glomerular excretion of pipecuronium. Prolongation of pipecuronium blockade should be expected in patients with renal insufficiency.

Drug–Drug Interactions

Barbiturates

Thiobutobarbital prolongs the duration of action of pipecuronium in dogs (15), but no interaction with barbiturates has been reported in man.

General anesthetics

In patients who have been exposed to volatile anesthetic agents for 30 minutes or so there is an increase in potency of pipecuronium to such an extent that doses can be reduced by about one-third with isoflurane (16) or enflurane (10) compared with those required for balanced anesthesia. Halothane appears to be associated with relatively minor changes in potency (16). When the same doses of pipecuronium are given, the duration of blockade is significantly longer during isoflurane anesthesia than during neuroleptanesthesia (17); halothane is also associated with a prolonged action but to a lesser extent.

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3. Khuenl-Brady KS, Sharma M, Chung K, Miller RD, Agoston S, Caldwell JE. Pharmacokinetics and disposition of pipecuronium bromide in dogs with and without ligated renal pedicles. Anesthesiology 1989;71(6):919–22.
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non-depolarizing relaxant, pipecurium bromide, in anaesthetized dogs. Arzneimittelforschung 1980;30(2a):358–60.
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Piperaceae

See also Herbal medicines

General Information

The family of Piperaceae contains three genera:

1. *Lepianthes* (lepianthes)
2. *Peperomia* (peperomia)
3. *Piper* (pepper).

Piper methysticum

The rhizome of *Piper methysticum* (kava kava) has been used for hundreds of years in the South Pacific islands as a recreational drug, the main constituents of which are non-alkaloidal pyrone derivatives. These compounds cause sedation and centrally induced muscle relaxation. Kava has also been marketed in the West as a herbal pharmaceutical for use in the treatment of anxiety, for which it seems to be effective (1). However, the formulation used indigenously is an aqueous extract, while the pharmaceutical formulation is prepared from a lipid extract. Thus, the formulation that has been used in the West may contain compounds that are not present in the drink that is commonly prepared in the South Pacific and may therefore have different adverse effects (2). This may explain the risk of liver damage that has been seen in the West, not having previously been reported.

Kava contains the pyridine alkaloid pipermethystine, the chalcone flavokavain, the norsesquiterpenoid dihydrokavain, and the pyran tetrahydroyangonin.

Adverse effects

The acute and chronic effects of kava were first described by the 19th-century German toxicologist Louis Lewin (3) in his book *Phantastica* (1924).

> A carefully prepared kava beverage taken in small quantity occasioned only slight and agreeable modifications of sensibility. In this form it is a stimulating beverage after the imbibition whereof hardships can be endured more easily. It refreshes the fatigued body and brightens and sharpens the intellectual faculties. Appetite is augmented, especially if it is taken half an hour before meals . . . After doses that are not too strong a state of happy carelessness, content, and well-being appears without any physical or mental excitation. It is a real euphoric state which is accompanied by an increased muscular efficiency. At the beginning speech is fluent and lively and the hearing becomes more sensible to subtle impressions. Kava has a soothing effect. Those who drink it are never choleric, angry, aggressive and noisy, as in the case of alcohol. Both natives and whites look upon it as a sedative in case of accidents. Reason and consciousness remain unaffected. After the consumption of greater quantities, however, the limbs become weary, the muscles seem out of control of the will, the gait is slow and unsteady, and the subject appears half drunk. An urgent desire to lie down manifests itself. The eye sees objects before it but is unable to identify them with exactness. In the same way the ears hear everything, but the individual is unable to account for what he hears. Everything becomes more and more diffuse. The drinker succumbs to fatigue, and experiences a desire to sleep which is stronger than all other impressions. He becomes somnolent and finally falls asleep. Many Europeans have themselves experienced this action of kava which paralyses the senses like magic and finally leads to deep sleep. Frequently a state of somnolent torpor accompanied by incoherent dreams and occasionally erotic visions remains without sleep supervening.
>
> The sleep is similar to that produced by alcohol, out of which the individual can be awakened only with difficulty. If moderate quantities have been consumed it occurs twenty to thirty minutes later, and lasts from two to eight hours according to the degree of habituation of the subject. If the beverage is concentrated, that is contains a large amount of the resinous components of kava, intoxication comes on much more rapidly. The drinkers are found lying in the very places where they have been drinking. Occasionally a short state of nervous trembling occurs before they fall asleep. No excitation precedes these symptoms.
>
> The kava drinker is incessantly tormented with the craving for his favourite beverage, which he cannot prepare for himself. It is a repugnant spectacle to see old and white-haired people, degenerate through prolonged abuse of the drug, going from house to house in order to beg for freshly prepared kava and often meeting with a refusal. Mental weakness has also been stated to follow from kavaism. It is said that old kava habitues have red, inflamed, bloodshot eyes, dull, bleary, and diminished in their functions. They become extremely emaciated, their hands tremble, and finally they cannot bring the drinking vessel to their mouths. Numerous cutaneous diseases of the natives of the South Seas, especially a kind of scaly eruption which results in a parchment-like state of the skin, have been attributed to the abuse of kava.

Nervous system

In a pilot study, 24 patients with stress-induced insomnia were treated for 6 weeks with kava 120 mg/day, followed by a 2-week washout period and then treatment with valerian 600 mg/day for another 6 weeks (4). Stress was measured in three areas, including social, personal, and life events, and insomnia was assessed by evaluating the time taken to fall

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asleep, the number of hours slept, and waking mood. Total stress severity and insomnia were significantly improved by both compounds, with no significant differences. The most commonly reported adverse events were vivid dreams with valerian (16%) and dizziness with kava (12%).

In 24 patients treated with kava for generalized anxiety disorder for 4 weeks in an open, crossover, randomized trial, two dosage schedules were compared: 120 mg od and 45 mg tds (5). There were significant reductions in mean Hamilton Anxiety Rating Scale scores, irrespective of dose schedule, treatment order, or sex. The impact of adverse effects was relatively low, and only one patient had to withdraw from the study (tds schedule) because of nausea. There was daytime drowsiness in 33% of patients taking the thrice-daily regimen compared with 9% in those taking a once-daily dose.

Parkinsonism has been attributed to kava (6).

- A 45-year-old woman with a family history of essential tremor developed severe and persistent parkinsonism after taking kava extract for anxiety for 10 days. Her symptoms improved with anticholinergic drugs.

The authors concluded that kava derivatives can produce severe parkinsonism in individuals with a genetic susceptibility.

Liver

There have been reports of liver damage with lipid kava extracts (1), and it has therefore been banned in several countries.

- A 39-year-old woman had been treated for toxic hepatitis of unknown cause (7). When she represented with hepatitis-like symptoms and high liver enzymes, toxic hepatitis was diagnosed. Other causes for the liver pathology were excluded and it was noted that before both exacerbations, she had self-prescribed kava. When the kava was withdrawn, the liver pathology normalized and she made an uneventful recovery.
- A 60-year-old patient, who had taken no medications other than kava extract, developed liver and kidney failure and progressive encephalopathy (8). Viral, metabolic, and autoimmune causes were excluded. Liver biopsy was consistent with toxic liver damage. The patient eventually received an orthotopic liver transplant and made a good recovery.
- A 50-year-old man developed jaundice. He had noticed fatigue for a month, a "tanned" skin, and dark urine (9). The medical history was unremarkable, apart from slight anxiety, for which he had been taking three or four capsules of kava extract daily for 2 months. He took no other drugs and did not consume alcohol. Liver function tests showed very large increases in transaminases. He subsequently developed stage IV encephalopathy but made a good recovery after liver transplantation.
- A 34-year-old woman developed toxic hepatitis after taking kava-kava (10). Ultrasound showed an enlarged echogenic liver, and histology showed centrilobular necrosis and periportal inflammation. After withdrawal of the kava the changes resolved completely. This case illustrates the high hepatotoxic potential of kava-kava.
- A 33-year-old woman took a kava extract equivalent to 210 mg of kavalactones daily for 3 weeks (11). She developed malaise, loss of appetite, and jaundice. Her liver enzymes were raised 3-fold to 60-fold. Viral hepatitis was excluded and liver biopsy confirmed toxic hepatitis. Kava was withdrawn, and within 8 weeks the liver enzymes returned to normal. A lymphocyte transformation test showed strong concentration-dependent T cell reactivity to kava. Phenotyping of CYP2D6 activity showed that she was a poor metabolizer.

The authors of the last report concluded that the liver damage in this case was due to an immune-mediated reaction, possibly mediated by a reactive metabolite of kava, even though she was a poor metabolizer.

Kava has been associated with toxic liver damage in six cases reported from Switzerland (12). In one patient, the liver damage was so extensive that liver transplantation became necessary. Histological data from four patients were consistent with an allergic mechanism. In several cases, other medications with hepatotoxic potential had been taken concurrently. Symptoms generally occurred at between 3 weeks and 4 months and involved daily doses that contained kavapyrones 60–210 mg. Most instances involved acetone extracts. The leading kava extract, Laitan, was subsequently withdrawn from the Swiss market.

Australia's Therapeutic Goods Administration initiated a voluntary recall of all complementary medicines containing kava after the death of a woman who used a medicine containing kava (13). Sponsors and retailers were asked to remove all products containing kava from the market immediately. Consumers were advised to discard kava-containing products in their possession.

The Federal Institute of Germany has withdrawn all products that contain kava and kavaine from the German market because of the risk of hepatotoxicity and insufficiently proven efficacy. The regulation included homeopathic products with dilutions up to D4. The German regulation applies to all kava-containing pharmaceutical formulations. Moreover, following a provisional opinion from the UK Committee on Safety of Medicines (CSM), the Medicines and Healthcare products Regulatory Agency (MHRA) has consulted on a proposal to prohibit the sale, supply, or importation of unlicensed medicinal products containing kava in the UK. The CSM reviewed the issue of kava-associated liver toxicity following the emergence of safety concerns in Europe. At that time, stocks of kava were voluntarily withdrawn by the herbal sector while the safety concerns were under investigation. Currently the MHRA is aware of 68 cases worldwide of suspected kava-associated liver problems, including 6 cases of liver failure that resulted in transplant, and 3 deaths. In the UK there have been three reports of kava-associated liver toxicity. The CSM has advised consumers to stop taking medicinal products containing kava, and to seek medical advice if they feel unwell or have concerns about possible liver problems.

Finally, the FDA has advised consumers of the potential for liver injury by kava-containing dietary supplements. People who have liver disease or liver problems or who are taking medicines that can affect the liver have been advised to consult a physician before using kava-containing supplements (14). Consumers who use kava-containing dietary supplements and who have signs of illness associated with liver disease should also consult

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a physician. The FDA has issued a letter to healthcare professionals informing them of the consumer advice and has urged consumers and healthcare professionals to report injuries that may be related to the use of kava.

The incidence of liver damage with kava seems to be less than one case per million daily doses (15). The mechanism of the effect is currently unclear. It has been suggested that supervised, monitored, short-term medication with kava would still do more good than harm (16). However, the FDA will continue to investigate the relation, if any, between the use of dietary supplements containing kava and liver damage.

Skin

Allergic skin reactions (17) and other adverse effects, including dermatological problems and neurological symptoms, have been described in individuals using such formulations. Heavy chronic consumption of kava-kava can lead to a pellagroid dermopathy that appears to be unrelated to niacin deficiency (18).

- A 36-year-old woman developed a generalized rash, severe itching with erythema, and papules 4 days after discontinuing a kava formulation (Antares), which she had taken in a dosage of 120 mg/day for 3 weeks (19). The condition improved with glucocorticoids and antihistamines, but the itching lasted several weeks. Patch tests with the kava extract were positive.

Musculoskeletal

Rhabdomyolysis has been attributed to kava (20).

- A 29-year-old man developed severe diffuse muscle pain and passed dark urine a few hours after taking a herbal combination product containing guaraná 500 mg, Ginkgo biloba 200 mg, and kava 100 mg. His blood creatine kinase activity and myoglobin concentration were raised and there were no signs of an underlying metabolic myopathy. His condition improved within 6 weeks.

The authors suggested that the methylxanthine-like effects of guaraná and the antidopaminergic and neuromuscular blocking properties of kava had caused the rhabdomyolysis in this patient.

Drug overdose

- A 34-year-old Tongan man complained of sore eyes, headache, generalized muscle weakness, and abdominal pain (21). He was disoriented and hallucinating. His family reported that he had been drinking large quantities of kava daily for about 14 years. Chronic kava intoxication was treated with intravenous Plasmalyte (a crystalloid solution) and he recovered within a day.

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Piperaquine

General Information

Piperaquine is a synthetic 4-aminoquinoline with high blood schizonticidal activity, similar to that of chloroquine (SEDA-13, 810). There is some evidence that piperaquine is active against chloroquine-resistant *Plasmodium falciparum*, but laboratory studies suggest a degree of cross-resistance. Piperaquine 600 mg/month

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was well tolerated. Its reported adverse effects included headache, dizziness, vomiting, and diarrhea.

Organs and Systems

Gastrointestinal

The novel combination (Artekin™) of dihydroartemisinin and piperaquine has been assessed in 106 patients (76 children and 30 adults) with uncomplicated *P. falciparum* malaria in Cambodia (1). The respective doses of dihydroartemisinin and piperaquine, which were given at 0, 8, 24, and 32 hours, were 9.1 and 74 mg/kg in children and 6.6 and 53 mg/kg in adults. All the patients became aparasitemic within 72 hours. Excluding the results in one child who died on day 4, there was a 97% 28-day cure rate (99% in children and 92% in adults). Patients who had recrudescent infections used low doses of Artekin. Adverse effects, most commonly gastrointestinal complaints, were reported by 22 patients (21%) but did not necessitate premature withdrawal.

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Piperazine

General Information

Piperazine is an antihelminthic drug that selectively blocks the neuromuscular cholinergic receptors of worms. It is readily absorbed, but has a highly variable half-life. The adult oral dose of 4 g of piperazine hydrate has been used extensively in the treatment of ascariasis. A very old drug, it is still considered sufficiently safe for use, although in most developed countries it has been abandoned, primarily because of concerns about possible carcinogenicity and electroencephalographic changes (SEDA-12, 267).

General adverse effects

In most patients, piperazine is free of adverse reactions. Mild gastrointestinal disturbances may occur; neurotoxicity is rare. Eczematous skin reactions, lacrimation, rhinorrhea, joint pains, productive cough, and bronchospasm can develop after sensitization, especially with occupational exposure. Urticaria has also been reported. When hypersensitivity reactions occur it should be withdrawn and not used again in the same patient. Mononitrosylation of piperazine can occur in the stomach, releasing the potential carcinogen *N*-mononitrosopiperazine, but there is no direct proof of risk in human subjects.

Organs and Systems

Cardiovascular

Cardiac conduction defects have been described in patients taking piperazine (1).

Respiratory

Allergic respiratory reactions can occur in patients taking piperazine, resulting in cough and bronchospasm (2).

Nervous system

Headache, dizziness, and somnolence occur in a small proportion of individuals who take piperazine (3). More serious neurological reactions occur rarely, but tend to be reported in young children, in people with neurological or renal disease, or after overdosage. Symptoms in such cases include ataxia, paresthesia, undue clumsiness, myoclonus, and nystagmus. Choreiform movements and an electroencephalogram with prominent slow waves have been reported as well as an exacerbation of petit mal (4) and absence seizures (5). In a child, horizontal nystagmus and hypotonia have been reported after a normal dose (6).

- A previously well 23-month-old girl was given piperazine 65 mg/kg/day for 7 days for a suspected worm infestation and developed cerebellar ataxia after 8 days (7). Over the next 48 hours her symptoms gradually settled. She made a complete recovery 5 days later.

Sensory systems

Piperazine can cause a range of visual effects, including dry eyes, bulging eyes, difficulty in focusing, and double vision (8).

Reports of cataract after piperazine have not been authenticated (9).

Hematologic

One suspected case of hemolysis after piperazine treatment was published but it appeared as long ago as 1971 and the patient had G6PD deficiency (10).

A case of temporary thrombocytopenia has been described (11), probably due to prior sensitization by ethylenediamide (a stabilizer in some creams), with which piperazine cross-reacts.

Gastrointestinal

Nausea, vomiting, abdominal pain, and diarrhea can occur occasionally with piperazine (12).

Liver

A single incident resembling viral hepatitis after piperazine and recurring after further dosage has been reported (13).

Skin

Erythema and rarely allergic reactions can occur in patients taking piperazine (12).

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Second-Generation Effects

Teratogenicity

There is no evidence that piperazine has any second-generation effects; it has been used extensively in pregnancy without untoward incidents, but as a precaution WHO advises against administration in the first trimester.

Drug–Drug Interactions

Chlorpromazine

High doses of piperazine can enhance the adverse effects of chlorpromazine and other phenothiazines (14,15).

Pyrantel

Piperazine can antagonize the antihelminthic efficacy of pyrantel and vice versa (16).

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Piperidolate

General Information

Piperidolate is an anticholinergic drug that has been used to treat premature labor and digestive disorders (1). Doses of 50 mg are usual for treating pyloric spasm. The effects and adverse effects at this dose are both small.

Reference

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Piracetam

General Information

Piracetam is a so-called "nootropic" drug, one of a class of drugs that affect mental function (1). In healthy volunteers it improves the higher functions of the brain involved in cognitive processes, such as learning and memory. Its mechanisms of action are not known but may include increased cholinergic neurotransmission.

A meta-analysis of 19 double-blind, placebo-controlled trials in elderly patients with dementia or cognitive impairment showed significant improvement with piracetam (2).

Piracetam has also been used to treat fetal distress during labor, but there is insufficient evidence to assess its efficacy (3).

Organs and Systems

Nervous system

Piracetam 80–100 mg/day for 4 months has been evaluated in a randomized, double-blind, placebo-controlled, crossover study in 25 children with Down syndrome (4). Piracetam did not enhance cognition or behavior but was associated with adverse events: 18 children completed the study, 4 withdrew, and 3 were excluded at baseline. The adverse events were related to the nervous system and included aggression ($n = 4$), agitation/irritability ($n = 2$), sexual arousal ($n = 2$), poor sleep ($n = 1$), and reduced appetite ($n = 1$).

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Pirazolac

See also Non-steroidal anti-inflammatory drugs

General Information

Pirazolac, a pyrazoloacetic acid derivative, caused heartburn, upper abdominal pain, cutaneous adverse effects (rashes, exacerbation of pre-existing eczema), and eosinophilia in early clinical studies (1). In two comparative studies it was withdrawn in 15–20% of patients, that is more often than the comparator NSAIDs (indometacin, sulindac) (SEDA-16, 111).

Reference

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Pirenzepine

General Information

Pirenzepine is an anticholinergic drug with selective effects on muscarinic M_1 receptors. It therefore inhibits gastric acid secretion in the stomach. When it was introduced it was claimed that in the doses necessary to affect gastric acid secretion it would be almost entirely free of other muscarinic (atropine-like) effects. However, although muscarinic adverse effects, such as dry mouth and difficulty in accommodation, are less common with pirenzepine than with atropine, they can still occur in about half the patients who take the drug (1). Cardiac conduction effects resulting in sinus tachycardia, atrial fibrillation, and nodal tachycardia can also occur.

Granulocytopenia and thrombocytopenia are on record (SED-12, 944) (2).

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Piretanide

See also Diuretics

General Information

Piretanide is a close relative of furosemide, with diuretic and kinetic properties very similar to those of furosemide and bumetanide (1,2). Its potency lies somewhere between the two. As with some other diuretics, attempts have been made to show specific advantages for piretanide, for example that it is a "potassium-stable" diuretic. However, there is no good evidence that it has such advantages (SEDA-10, 188) (SEDA-15, 213).

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Piribedil

General Information

Piribedil is a piperazine derivative, a dopamine receptor agonist, which has been mainly used for the treatment of depression and Parkinson's disease. It has also been recommended for the treatment of patients with intermittent claudication, without convincing evidence.

Somnolence is a common adverse effect and can occur at low doses (SED-10, 346) (SEDA-10, 119). Among 50 patients with Parkinson's disease who had recently taken piribedil, 3 satisfied the clinical description of sleep attacks (1).

At higher doses gastrointestinal effects (anorexia and nausea) occur in 13% of patients taking a gradually increasing dose up to 120 mg/day (2). At very high doses (240 mg/day), changes in liver function tests occasionally occur. After intravenous administration (1.5–3.0 mg/hour for 6 hours) drowsiness, cold extremities, and spontaneous erections are common (SED-9, 317) (SEDA-2, 185) (SEDA-5, 207).

In 49 Filipino patients with Parkinson's disease and motor fluctuations the most common adverse effects of piribedil in a dosage of up to 150 mg/day were hallucinations (20%), dyskinesias (20%), dizziness (8%), and sleepiness (6%) (3).

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Piridoxilate

General Information

Piridoxilate, an equimolar mixture of glyoxylic acid and pyridoxine, is marketed in a few countries (for example France) for peripheral arterial occlusive disease and functional venous disorders.

Organs and Systems

Urinary tract

A few reports have dealt with the occurrence of calcium oxalate renal calculi associated with long-term administration of piridoxilate.

- A 23-year-old man developed acute renal insufficiency due to hyperoxaluria and intratubular deposits of oxalate crystals after attempting suicide with an overdose of piridoxilate (SEDA-11, 180).
- An old woman developed end-stage chronic renal insufficiency and histological evidence of renal oxalosis ascribed to 10 years of piridoxilate treatment; renal function did not improve after withdrawal of the drug, and chronic hemodialysis was required (1).

Reference

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Piritrexim

General Information

Piritrexim is a lipid-soluble analogue of methotrexate that has been used to treat methotrexate-resistant tumors (1). It is given with leucovorin (folinic acid) to minimize hematological toxicity. Myelosuppression is the major dose-limiting adverse effect. In 35 patients with urothelial carcinomas there was WHO grade 3/4 thrombocytopenia in four, granulocytopenia in one, and anemia in three; grade 3 non-hematological toxicity consisted of neuropathy in five patients, hepatotoxicity in two, nausea in two, and pulmonary toxicity and rash in one each (2). Piritrexim also causes facial flushing, periorbital edema, and pruritus, and anaphylactic shock has been reported (SEDA-18, 289).

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Piroxicam

See also Non-steroidal anti-inflammatory drugs

General Information

Piroxicam was the first of the oxicam compounds, and is by far the most widely used. It is an inhibitor of prostaglandin synthesis and platelet aggregation. Its long half-life (36–48 hours) allows it to be given in a single daily dose. Adverse effects data from 46 trials in 3827 patients, 2716 on short-term treatment (less than 12 weeks), have been reviewed (SEDA-6, 1) (1). In 20 controlled trials in 816 patients, adverse effects occurred in 27%, causing withdrawal in 2.2%. However, an uncontrolled study registered adverse effects in only 16% of patients. Allowing for all analyses and reviews, the overall adverse effects profile of piroxicam seems to be qualitatively the same as that of other NSAIDs, with gastrointestinal complaints at the top of the list.

Reactions involving the gastrointestinal system occur in up to 40% of patients. The approximately 1% incidence of peptic ulcer appears to be dose-related, as it rises to 7% in patients who take dosages higher than 20 mg/day for several weeks (2). Nervous system reactions are the second most frequent types of adverse effect. Changes in laboratory findings (creatinine, aspartate transaminase, alanine transaminase) are frequent, but they have little clinical relevance. Hypersensitivity reactions do not seem to be a problem with piroxicam treatment, although skin or mucosal reactions have been reported. Shock has been described. Tumor-inducing effects have not been reported.

Cinnoxicam is the cinnamate ester of piroxicam; its adverse effects are similar. Gastrointestinal effects (81%), nervous system effects (4%), and cutaneous effects (4%) were most common in a multicenter post-marketing surveillance study of 2969 patients; 12% had adverse effects (SEDA-16, 113). Cinnoxicam cream can cause itchy erythema, edema, vesicles, and exudation (SEDA-20, 94).

Organs and Systems

Respiratory

In two cases piroxicam caused pulmonary infiltrates and eosinophilia (SEDA-19, 99).

Nervous system

Adverse effects in about 11% of patients include headache, dizziness, drowsiness, fatigue, and sweating (3).

Sensory systems

Eyes

Blurred vision and burning eyes have been described with piroxicam (SEDA-5, 107).

Ears

Permanent sensorineural hearing loss and tinnitus have been described with piroxicam (4).

Electrolyte balance

Severe hyponatremia, characterized by increasing confusion and disorientation, has been reported (SEDA-13, 83).

Hyperkalemia has often been linked to prolonged use of piroxicam, especially in the elderly (SEDA-8, 110) (SEDA-10, 87).

Hematologic

Piroxicam can cause thrombocytopenia, including a case of thrombocytopenic purpura due to an immunological mechanism (SEDA-13, 83). As an inhibitor of prostaglandin synthesis, piroxicam also inhibits platelet aggregation and prolongs bleeding time.

Leukopenia has been reported; the leukocyte count returned to normal after withdrawal (5). Agranulocytosis in a woman who took piroxicam for 3 days disappeared rapidly after withdrawal (SEDA-14, 95).

Aplastic anemia, which resolved fully after withdrawal, has been described (SEDA-17, 114).

Gastrointestinal

Gastrointestinal effects are the most frequent adverse effects of piroxicam. Although epigastric distress, nausea, abdominal pain, constipation, flatulence, and diarrhea have all been reported, they rarely interfere with treatment.

Esophageal lesions have been recorded in young healthy volunteers taking piroxicam (6).

An unusual case of gastrocolic fistula occurred in an old man who had taken piroxicam for 2 months (7).

Peptic ulceration and gastrointestinal bleeding were recorded in 1–1.4% of patients taking piroxicam 20 mg/day, and the incidence of ulceration increased to 6.9% at a dosage of 40 mg/day. A comparative study of gastrointestinal blood loss after aspirin 972 mg qds for 4 days versus different doses of piroxicam (20 mg od, 5 mg qds, and 10 mg qds) showed that piroxicam did not increase fecal blood loss, whereas aspirin did. Gastroscopic evidence of irritation was also greater with aspirin (8). The debate on the ulcerogenicity and relative safety of piroxicam continues, as new reports are published (SEDA-10, 85) (SEDA-11, 97) (SEDA-12, 91). As the perfect epidemiological study has yet not been carried out, the only thing that can be said is that piroxicam's ulcerogenicity increases with dosage and that 20 mg/day constitutes high-dose therapy, especially in elderly women.

Piroxicam can cause diaphragm-like strictures of the intestinal tract (9).

- A 65 year-old woman who had taken piroxicam for the previous 3 years presented with frequent episodes of abdominal bloating and cramping, sometimes associated with nausea and vomiting, and loss of weight. Small bowel examination showed several mid-ileal strictures associated with proximal dilated bowel.

Liver

Transient rises in aspartate transaminase and alanine transaminase can occur (10). Biopsy-proven hepatitis was noted in one patient who was also taking other medications (SEDA-5, 107). Cases of acute hepatitis have been described. Two elderly women developed acute hepatocellular injury, which progressed to fatal subacute hepatic necrosis (SEDA-12, 93) (11,12).

Urinary tract

Piroxicam reduces renal blood flow by inhibition of renal prostaglandins. It can cause transient and probably insignificant rises in urea or blood urea nitrogen, without increases in serum creatinine concentrations. Renal function should be monitored during long-term therapy and piroxicam should be avoided in renal insufficiency. An occasional patient develops edema and dysuria.

Hematuria with purpuric rash and Henoch–Schönlein purpura have been described (13).

Fatal acute renal insufficiency due to diffuse interstitial nephritis has been described in a young man (SEDA-14, 95).

Skin

Minor, often transient, skin rashes are relatively common, as with other NSAIDs. Light-induced skin eruptions have been reported to national ADR monitoring centers in several countries and generally occur only 1–6 days after the start of therapy. They are characterized by pruritic, papulovesicular, or bullous eruptions, usually restricted to exposed areas. Clinical, histological, and provocation studies are not conclusive in distinguishing the eruptions as photoallergic or phototoxic (SEDA-13, 76) (SEDA-15, 103) (14). Cross-reactivity between thiosalicylic acid and piroxicam supports the hypothesis that piroxicam-induced photosensitive reactions have a photoallergic mechanism and occur soon after starting therapy when patients have previously been sensitized to thiosalicylate (SEDA-16, 113) (15). The wide range of adverse skin effects include several types of rashes, urticaria, vasculitis, and life-threatening reactions (toxic epidermal necrolysis, erythema multiforme, and pemphigus) (SEDA-8, 110) (SEDA-11, 192) (SEDA-13, 77). Fixed drug eruptions have also been described (SEDA-16, 113).

- After piroxicam intake and sun exposure a patient with Sjögren's syndrome developed the typical cutaneous lesions and serological markers of systemic lupus erythematosus, despite drug withdrawal (16).

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Susceptibility Factors

Renal disease

Reduced piroxicam excretion increases the risk of gastrointestinal adverse effects. Most reports of these effects refer to elderly women, since impaired renal function in the elderly can lower excretion of the drug by 33%. Dosages should be as low as possible, and certainly not above 20 mg/day in these patients.

Drug Administration

Drug formulations

The adverse effects profile of suppositories, soluble tablet formulations, and standard capsules are similar (SEDA-13, 83). A parenteral formulation of piroxicam caused somnolence more often than diclofenac in a double-blind study, but diclofenac provoked more gastric discomfort and nausea than piroxicam. Local adverse effects of both drugs were pain, burning, and induration at the site of injection (SEDA-15, 103).

In an attempt to reduce gastric toxicity, piroxicam has been complexed with cyclodextrins. In healthy volunteers piroxicam beta-cyclodextrin is less toxic than either piroxicam or indometacin; gastrointestinal adverse effects were the most frequent (SEDA-16, 113).

A fast-dissolving form of piroxicam that can be taken under the tongue infrequently causes local adverse effects, including stomatitis, mucosal erythema, and dysesthesia (SEDA-20, 95).

Drug–Drug Interactions

Furosemide

Furosemide natriuresis and kaliuresis can be reduced by short-term treatment with piroxicam in hypertensive patients with impaired renal function (SEDA-16, 113).

Lithium

Piroxicam can increase the risk of lithium toxicity (17).

Phenazone

The half-life of phenazone (antipyrine) was prolonged and its metabolic clearance significantly reduced in proportion to the dose of piroxicam administered to healthy young volunteers (SEDA-16, 113).

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Pirprofen

See also Non-steroidal anti-inflammatory drugs

General Information

In an open, non-comparative trial in 1506 patients, the adverse effects of pirprofen were mainly gastrointestinal, and consisted mostly of epigastric pain. There were single cases of an attack of asthma, iron deficiency anemia, leukopenia, and an increase in serum transaminases to more than 10 times normal (1). In a long-term trial, 9.7% of over 3000 patients stopped treatment because of poor tolerability. The manufacturers decided to discontinue marketing it worldwide, saying that this was a commercial decision (SEDA-16, 111).

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Organs and Systems

Liver

Laboratory signs of hepatic damage were documented in 37 patients, including three cases of hepatitis (2); pirprofen can definitely be considered hepatotoxic.

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Pizotifen

See also Antihistamines

General Information

Pizotifen is a 5-HT receptor antagonist chemically related to the tricyclic antidepressants, with a five-membered third ring containing a sulfur atom. It has been suggested that pizotifen has effects and adverse effects resembling those of amitriptyline (1). However, it is pharmacologically similar to the antihistamine cyproheptadine and shares its adverse effects, including drowsiness and increased appetite. When used in migraine it causes increased weight; conversely, when it is used to improve appetite, sleepiness and dizziness are common.

Organs and Systems

Metabolism

In 47 patients with severe migraine unresponsive to clonidine, pizotifen 1.5 mg for 6 months more than halved the incidence of attacks in 30 patients and 12 became headache-free. Weight gain was a problem in some subjects (2). In an open, multicenter study of the use of pizotifen 1.5 mg at night to prevent migraine in 834 patients, the most frequent adverse effects were drowsiness, although in one-third of the affected patients this was transient, and weight gain, with an average increase of 0.7 kg over 2 months (3).

Long-Term Effects

Drug withdrawal

Severe weight loss has been reported after withdrawal of chronic pizotifen (4).

Drug Administration

Drug overdose

An acute overdose of 30 mg pizotifen caused pyrexia and anticholinergic effects, with resolution after 10 hours (5).

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Placebo

General Information

Since the first paper in 1945 (1), thousands of papers have been published on placebos. However, little attention has been paid to data on placebos in clinical pharmacology studies. The conditioning model of placebo has been elegantly illustrated in a crossover study in hypertensive patients (2). The use of placebos has been reviewed (3).

The impact of experimental conditions on the results of 109 double-blind, placebo-controlled clinical pharmacology studies conducted in 1228 healthy volunteers has been reported (4). The subjects were young (aged 18–40 years) or old (65–80 years). The treatment was oral placebo (capsules, tablets, or suspension) and the adverse effects were spontaneously reported and/or observed by the investigators. The overall incidence of adverse effects was 19%, with an increased number of complaints in the elderly subjects. After single dosing of placebo, the most common events were headache, drowsiness, and weakness. After repeated dosing, there was an increased incidence of weakness, reaching 7% (compared with 2.5% after a single dose), while the incidences of the other major symptoms were unchanged. A lower overall incidence (7%) of adverse events has been reported after free interviews (5), while in another study there was a higher frequency (6).

Experimental conditions in phase I trials have been described as being potentially responsible for changes in serum transaminase activities (7,8), perhaps ascribable to dietary factors and rest.

Bed-rest experiments have previously shown changes in homeostasis (for example, glucose-induced insulin release) but no change in plasma catecholamine concentrations.

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Plague vaccine

See also Vaccines

General Information

Plague vaccine is a suspension of the formaldehyde-killed encapsulated form of *Yersinia pestis*. Primary immunization involves three doses given intramuscularly.

The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of plague as a biological weapon against a civilian population (1). They concluded that an aerosolized plague weapon could cause fever, cough, chest pain, and hemoptysis, with signs consistent with severe pneumonia 1–6 days after exposure. Rapid evolution of disease would occur in the 2–4 days after the onset of symptoms and would lead to septic shock with a high mortality if early treatment was not instituted. They advised early treatment and prophylaxis with streptomycin or gentamicin or one of the tetracycline or fluoroquinolone classes of antimicrobials.

General adverse effects

General malaise, headache, fever, mild lymphadenopathy, or erythema and induration at the injection site have been reported following the administration of plague vaccine (10% of vaccinees); these effects are more common with repeated injections. Sterile abscesses and hypersensitivity reactions (urticaria, asthma) occur rarely (2).

Organs and Systems

Immunologic

Known allergy to any of the plague vaccine constituents (beef protein, soya, casein, phenol) contraindicates immunization. Severe local or systemic reactions following previous doses contraindicate revaccination (2).

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Plantaginaceae

See also Herbal medicines

General Information

The family of Plantaginaceae contains two genera:

1. *Littorella* (littorella)
2. *Plantago* (plantain).

Plantago species

Plantago species have traditionally been used for many purposes in folk medicine (1,2). Plantain seeds are widely used as bulk laxatives under the names of "psyllium" (from *Plantago psyllium* or *Plantago indica*) and "ispaghula" (from *Plantago ovata*). They are covered in the monograph on laxatives.

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Plasma products

General Information

Plasma products are used to substitute plasma proteins and in plasma exchange. Fresh frozen plasma is used as a source of coagulation factors in deficiency, if no purified factors are available.

Intensive plasma exchange has been studied in the treatment of numerous diseases, above all in Waldenström's macroglobulinemia, hypercholesterolemia, hyperviscosity syndrome, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia

gravis, hemolytic-uremic syndrome, Goodpasture's syndrome, Guillain–Barré syndrome, and several other autoimmune diseases. Its potential benefit is attributable to the removal of a variety of harmful substances from plasma, such as antibodies, antigens, immune complexes, toxins, or abnormal plasma components. If the circulating substance is a cause of the disease, the plasma exchange can be effective. However, its therapeutic potential in many diseases has not yet been precisely defined.

The performance of intensive plasma exchange (removal from an adult of 2–3 liters of plasma with substitution of fresh plasma to maintain the patient's blood volume) requires separation of plasma from cells, so that the patient's own cells can be returned. There are two methods of plasma separation: centrifugal flow separation and flow filtration (1,2).

Intensive plasma exchange is relatively safe. It is generally well tolerated, and only a few serious complications have been reported. The potential complications (3–5) include transient hypotension, nausea, urticaria, abdominal discomfort, fever, hypothermia, air or microaggregate embolism, hypocalcemia (citrate effect) with paresthesia, tetany, and cardiac depression, thrombocytopenia (often observed), coagulation factor depletion and depletion of various intravascular proteins, visual scotomata, hepatitis, vasovagal reactions, and reactions associated with phlebotomy (phlebitis, hematoma).

The fluid volume and protein removed by plasmapheresis must be replaced. Among the solutions available for replacement therapy are fresh frozen plasma and human albumin solutions.

Fresh frozen plasma

Fresh frozen plasma is defined as the fluid portion of 1 unit of human blood that has been centrifuged and separated and then frozen at −18°C (or below) within 6 hours of collection. It is used to reverse the effects of oral anticoagulants (for example during surgery or bleeding episodes) (6). Its use has increased considerably in most countries within the past 20–25 years (7), in spite of mounting evidence of its potential risks, such as the transmission of viral infections. Allo-immunization occurs infrequently, with the formation of Rh antibodies in response to contaminating stroma of red blood cells, and as with any intravenous administered fluid, hypervolemia and cardiac failure can occur (8). Anti-A and anti-B in the plasma can hemolyse the recipient's red cells if ABO-compatible fresh frozen plasma is not used (9). Other disadvantages of fresh frozen plasma are the large volume that needs to be given, the risk of viral transmission, and the variable quantities of clotting factors it contains. Quarantine fresh frozen plasma, when the unit is used after the next consecutive donation of the same donor has been found to be negative in virus screening assays, is a safe alternative.

Organs and Systems

Cardiovascular

Hypotension is a sometimes severe adverse effect of the administration of plasma proteins. It may be associated with the presence of a potent prekallikrein activator, the Hageman factor degradation product, which is thought to initiate the production of kinin from fibrinogen in the recipient's blood. The kinin then produces systemic hypotension.

In five of eight patients treated with fresh frozen plasma to achieve rapid correction of anticoagulation after warfarin-related intracranial hemorrhage, there were complications of fluid overload (10). In two of these patients congestive heart failure developed, resulting in myocardial infarction and renal insufficiency respectively. Two patients had supraventricular tachydysrhythmias and one developed pulmonary edema.

Respiratory

The incidence of transfusion-related acute lung injury is 0.16–0.24% per transfusion of blood products and is the cause of 15% of all fatal complications of blood transfusion (11). Specific antigen–antibody reactions involving donor antibodies specific for leukocyte antigens of the recipients cause activation of neutrophils and aggregation in small pulmonary vessels (11). The complement and cytokine cascade is activated, leading to capillary leakage.

- In a 58-year-old man transfusion of a unit fresh frozen plasma resulted in acute lung injury, caused by antibodies of the donor specific for the neutrophil antigen NB1 (11).

NB1 has a phenotype frequency of 97%.

Immunologic

Immunological adverse effects of the administration of plasma range from mild urticaria and flushing to fatal anaphylaxis. Such reactions can occur either during the infusion or some minutes after. Mild reactions often start locally and have a tendency to spread. In more severe cases dyspnea, arthralgia, and fever occur. Stabilizers or other additives in plasma protein preparations may be of significance in provoking these reactions. In addition, protein aggregates in the preparations may participate in anaphylactoid reactions, including acute pulmonary injury. Severe reactions have occasionally been encountered.

Development of an antibody response

The development of an antibody response against a deficient or genetically different protein can cause post-transfusion complications. The main problems are antibodies against antihemophilia factors, for example directed against factor VIII or factor IX, which may be produced in hemophiliacs after repeated transfusions and inhibit the therapeutic effect. Another problem arises when antibody formation occurs in IgA-deficient subjects who receive IgA-containing products and produce anti-IgA antibodies. Inhibitors of coagulation proteins and antibodies to IgA are described in the monographs on coagulation proteins and immunoglobulins.

Body temperature

Fever can occur 10–15 minutes after the start of an infusion of plasma. It is often accompanied by headache,

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nausea, and shivering. These symptoms often disappear when the infusion is discontinued.

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Platelet glycoprotein IIb/IIIa antagonists

General Information

Platelet membrane glycoprotein IIb/IIIa receptor inhibitors have been approved in various countries for the treatment of patients scheduled for percutaneous transluminal coronary angioplasty or coronary atherectomy to prevent ischemic complications (1). They are antagonists at an adhesion receptor on the platelet membrane, the glycoprotein IIb/IIIa, which binds some ligands implicated in platelet aggregation, fibrinogen, and von Willebrand factor, and is involved in the common final pathway whereby various stimuli cause platelet activation. They therefore reduce platelet aggregation regardless of the mechanism by which the platelet is activated, and are currently the most powerful inhibitors of platelet aggregation available.

The first drug to be developed in this family was the monoclonal antibody abciximab, which is covered in a separate monograph. Other GP IIb/IIIa blockers include peptides (eptifibatide) or small molecules such as tirofiban and lamifiban. Other small molecules that are orally active are in development (2).

For the drugs so far used in major clinical trials (eptifibatide, tirofiban, lamifilan, roxifiban, and sibrafiban) the available data suggest that the commonest adverse events are episodes of bleeding, mostly minor and essentially at the vascular access site, without an excess of intracranial hemorrhage. There is also a low incidence of thrombocytopenia with these non-antibody drugs; two cases were reported in a study of the use of roxifiban in 98 patients with chronic stable angina pectoris (3).

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Platinum-containing cytostatic drugs

See also Cytostatic and immunosuppressant drugs

General Information

Although the main platinum-containing cytotoxic drugs, cisplatin (rINN), carboplatin (rINN), and oxaliplatin (rINN), share some structural similarities, there are marked differences between them in therapeutic uses, pharmacokinetics, and adverse effects profiles (1–4). Compared with cisplatin, carboplatin has inferior efficacy in germ-cell tumors, head and neck cancers, and bladder and esophageal carcinomas, whereas the two drugs appear to have comparable efficacy in ovarian cancer, extensive small-cell lung cancers, and advanced non-small-cell lung cancers (5–7).

Oxaliplatin belongs to the group of diaminocyclohexane (DACH) platinum compounds. It is the first platinum-based drug that has marked efficacy in colorectal cancer when given in combination with 5-fluorouracil and folinic acid (8,9).

Nedaplatin has been registered in Japan, whereas other derivatives, like satraplatin (JM216, which is the only orally available platinum derivative), ZD0473, BBR3464, and SPI-77 (a liposomal formulation of cisplatin), are still under investigation (10–13).

Other platinum-containing compounds under investigation include dexormaplatin, enloplatin, eptaplatin, iproplatin, lobaplatin, miboplatin, miriplatin, ormaplatin, picoplatin, sebriplatin, spiroplatin, and zeniplatin.

The adverse effects of platinum compounds have been reviewed (14).

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Mechanism of action

Although the precise mechanism of the cytotoxic action of the platinum-containing compounds has not been fully elucidated, they are thought to act by causing interstrand and intrastrand cross-links in DNA, particularly including two adjacent guanine or two adjacent guanine-adenine bases (15–18). In comparison with cisplatin- or carboplatin-induced DNA lesions, diaminocyclohexane (DACH) platinum DNA adduct formation has been associated with greater cytotoxicity and inhibition of DNA synthesis. In addition, there appears to be a complete lack of cross-resistance between oxaliplatin and cisplatin, which may be related to the bulky DACH carrier ligand of oxaliplatin, hindering DNA repair mechanisms within tumor cells (8,9).

Pharmacokinetics

There are significant pharmacokinetic differences among cisplatin, carboplatin, and oxaliplatin. Cisplatin is the most highly protein-bound (>90%), followed by oxaliplatin (85%) and carboplatin (24–50%).

The negligible nephrotoxicity of oxaliplatin and carboplatin compared with cisplatin may be related to their slower rates of conversion to reactive species. As a result, intensive hydration is not warranted during carboplatin or oxaliplatin infusion, in contrast to cisplatin (1,8–10). In the case of macromolecular platinum-protein complex formation, decomposition proceeds rather slowly, which may explain why the urinary excretion of total platinum is increased for a long time after treatment, particularly in patients who have been given cisplatin (19,20).

In contrast to cisplatin, carboplatin is primarily eliminated (about 75%) by glomerular filtration, whereas tubular secretion appears to be of minor importance (2–4). It has therefore been recommended that the dose of carboplatin be adjusted according to the individual glomerular filtration rate, in order to avoid high plasma drug concentrations when the dose is calculated according to body surface area (21–23). Individualized carboplatin therapy helps to avoid abnormally high drug concentrations in patients with renal dysfunction and subtherapeutic concentrations in patients with an unexpectedly high glomerular filtration rate (24,25).

Pharmacokinetic-pharmacodynamic correlations between AUC, response rates, and the extent of myelosuppression have been examined retrospectively in patients with advanced ovarian carcinoma (21,24). AUC values below 4 minutes/mg/ml and exceeding 7 minutes/mg/ml cannot be recommended; the former is associated with low response rates and the latter is associated with more pronounced neutropenia and thrombocytopenia without higher response rates. Doses of carboplatin are generally calculated by the Calvert formula (26):

$$\text{Carboplatin dose} = \text{AUC (minutes.mg/ml)} \times (\text{GFR} + 25)$$

However, it is still debatable which method most accurately predicts individual values of glomerular filtration rate or creatinine clearance. Whereas the Cr-EDTA method is the most accurate method of estimating glomerular filtration rate, most clinicians do not use it routinely, and prefer to collect urine for estimation of creatinine clearance. Alternatively, the use of special formulae has been proposed, for example Wright's formula and the formulae of Cockcroft & Gault or Jelliffe (27–29). However, calculation of the glomerular filtration rate or creatinine clearance using such formulae has been associated with some bias in different ranges, regardless of which formula has been used.

After intravenous administration of oxaliplatin, about 33% and 40% of the dose is bound to erythrocytes and plasma proteins. The half-life averages 26 days, which is in accordance with the normal life expectancy of erythrocytes (12–50 days). Oxaliplatin undergoes rapid non-enzymatic biotransformation to form a variety of reactive platinum intermediates, which bind rapidly and extensively to plasma proteins and erythrocytes. The antineoplastic and toxic properties appear to reside in the non-protein bound fraction, whereas platinum bound to plasma proteins or erythrocytes is considered to be pharmacologically inactive. Biotransformation produces DACH-platinum dichloride, 1,2-DACH-platinum dicysteinate, 1,2-DACH-platinum diglutathionate, 1,2-DACH-platinum monoglutathionate, and 1,2-DACH-platinum methionine. The erythrocyte contains only thiol derivatives, whereas all derivatives can be recovered from the plasma.

The platinum-containing metabolites of oxaliplatin are predominantly excreted in the urine (about 50% of the dose within 3 days), whereas drug excretion via the feces is of minor importance (about 5% of the dose after 11 days). The mean total platinum half-life averages 9 days after oxaliplatin administration (130 mg/m^2 intravenously) (8,9). There is a strong negative correlation between the mean plasma concentration of unbound oxaliplatin and renal function; however, moderate renal impairment does not increase the risk of acute toxicity associated with oxaliplatin (30).

General adverse effects

The comparative toxicity and mutagenic effects of platinum anticancer drugs have been reviewed (31).

Of the clinically established platinum compounds, cisplatin has the most toxic effects on organs like the nervous system, the organ of Corti, and the kidneys in a dose-dependent fashion. The dose per cycle has therefore usually been limited to 100–120 mg/m^2 intravenously, in order to avoid drug-induced irreversible organ dysfunction (12,13). The complete spectrum of late or long-term adverse effects of cisplatin in survivors of testicular cancer has been reviewed (32).

In contrast to cisplatin, myelotoxicity represents the most prominent adverse effect of carboplatin. Based on its lower organ toxicity and its better predictable pharmacokinetic behavior, carboplatin has extensively replaced cisplatin in combination chemotherapy for the treatment of ovarian cancer and extensive small cell and non-small cell lung cancer. For other indications, one has to weigh the possibly inferior efficacy of carboplatin against the more pronounced undesirable adverse effects of cisplatin, which may limit its long-term use. Based on its marked organ toxicity, high-dose cisplatin-containing regimens

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are not feasible, in contrast to carboplatin, which is part of several dose-intensified combination chemotherapy regimens (12,13).

Like carboplatin, oxaliplatin does not usually cause nephrotoxicity. In addition, both drugs are only moderately emetogenic, in contrast to cisplatin. The most important dose-limiting adverse effect of oxaliplatin is a sensory peripheral neuropathy, which has two different forms:

1. a unique acute peripheral sensory (and motor) toxicity that often occurs during or within hours after drug infusion and which is rapidly reversible and aggravated by cold;
2. a peripheral sensory neuropathy related to the cumulative dose, which is generally moderate and slowly reversible, in contrast to the forms that have been described after cisplatin administration.

BBR3464

BBR3464 is the first congener of a novel group of platinum compounds, the so-called cationic trinuclear platins. It binds to DNA more rapidly than cisplatin, which results in long-range interstrand and intrastrand cross-links. It is more potent than cisplatin, and very low dosages were effective in phase I trials. With a 1-hour intravenous infusion of 1.1 mg/m^2 every 28 days, diarrhea (preceded by abdominal cramps), nausea/vomiting, and neutropenia were the most prominent drug-related adverse effects. There were no signs of drug-related nephrotoxicity, neurotoxicity, or lung dysfunction (12,13,33).

Heptaplatin

Heptaplatin (cis-malonate[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II), SKI-2053*R*, Sunpla) has high antitumor activity against various cancer cell lines, including cisplatin-resistant tumor cells. Preliminary results suggested that it is less nephrotoxic than cisplatin. However, a comparative trial showed that intravenous heptaplatin 400 mg/m^2 was more nephrotoxic than intravenous cisplatin 60 mg/m^2 in terms of uremia and proteinuria, which occurred despite the use of hyperosmolar mannitol and appropriate concomitant hydration (fluid intake at least 3500 ml/day) (34,35).

Nedaplatin

Nedaplatin (cis-diammineglycolatoplatinum, CDGP, 254-S) has some structural similarities to cisplatin and carboplatin. Since 1995 it has been available for therapeutic use in Japan. In phase II trials, it had promising antineoplastic activity in patients with head and neck cancers, non-small cell lung cancers, esophageal cancer, testicular tumors, and cervical cancer. A distinct number of patients with ovarian cancer have responded to nedaplatin (for example 100 mg/m^2 intravenously) even after relapsing following treatment with cisplatin/carboplatin and cyclophosphamide. Its pharmacokinetic behavior is similar to that of carboplatin. It causes less nephrotoxicity than cisplatin, but hematological toxicity is dose-limiting. Other adverse effects include nausea/vomiting and mild peripheral neuropathy (12,13,36). Although nedaplatin is less nephrotoxic than cisplatin, incidental cases of severe nephrotoxicity have occurred. In addition, ototoxicity, similar to that observed after cisplatin, has been documented. Nedaplatin is excreted primarily unchanged by glomerular filtration, and there is a formula for predicting the clearance of unbound platinum after its administration (37).

Satraplatin

Satraplatin (bis-acetato-ammine-dichloro-cyclohexylamine-platinum, JM 216, BMS-182751) is the first oral platinum compound among the third-generation platinum complexes with activity in platinum-sensitive and some platinum-resistant preclinical models. Adverse effects were generally modest (grades I and II), including nausea, fatigue, anorexia, diarrhea, and altered taste. In addition, myelosuppression and rare cases of grades II and III increases in serum creatinine were reported. During phase II trials satraplatin was given in a dose of 120 mg/m^2/day for 5 consecutive days every 3 weeks in untreated patients with lung cancer or 30 mg/m^2/day for 14 consecutive days every 5 weeks in patients with metastatic squamous cell carcinoma. There was no nephrotoxicity or neurotoxicity (38–40). Pharmacokinetic studies showed that very little intact parent compound reached the systemic circulation after oral administration, perhaps because of extensive metabolic biotransformation or rapid reaction of platinum(II) species with DNA or other compounds. One of the intermediate compounds released during biotransformation is JM118, which has a longer half-life than the parent compound. Its particular role in the overall activity of satraplatin is still being investigated (41).

SPI-77

SPI-77 is a stealth liposomal dosage form of cisplatin. One of the main features of stealth liposomes is that they are pegylated on the liposomal surface. Compared with conventional liposomes (for example DaunoXome or Myocet) the half-life of the liposome and its embedded drug in plasma is significantly increased by this modification, because degradation by cells of the mononuclear phagocytic system is impaired; the cells are thereby, as it were, tricked. Liposomal encapsulation of cisplatin has been suggested to reduce systemic drug exposure and may help to increase drug delivery into tumor tissue. Pharmacokinetic studies have shown a slow rate of release of cisplatin from the liposomes, resulting in low systemic exposure to unbound drug. In contrast to conventional cisplatin, the incidence of gastrointestinal toxicity after SPI-77 was low, and so prophylactic antiemetics could be avoided. In addition, renal toxicity has not been observed, which also makes hydration before or after chemotherapy unnecessary. Extensive neurological measurements did not show any adverse effects. In conclusion, the toxicity profile of SPI-77 is encouraging compared with conventional cisplatin. However, despite its favorable pharmacokinetic behavior, enhanced platinum accumulation in tumor tissue has not yet been detected (42–44).

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Tetraplatin

The further development of the third-generation platinum derivative tetraplatin (ormaplatin, *trans*-D, L-1,2-diaminocyclohexane tetrachloroplatinum) has been abandoned, because drug-induced severe motor and sensory peripheral neuropathy occurred even at low cumulative doses. The high neurotoxic potential of tetraplatin may be associated with its pharmacokinetics: it is rapidly metabolized to 1,2-DACH-platinum dichloride, which was 3.8 times more neurotoxic than oxaliplatin in a neurite outgrowth assay (45).

ZD0473

ZD0473 (formerly AMD473, JM473) was developed in order to overcome acquired or intrinsic (de novo) resistance to cisplatin. Based on the steric bulk of its methyl-substituted pyridine moiety, thiol substitution and drug inactivation is hindered compared with cisplatin. In several in-vitro studies, ZD0473 was active even in cisplatin-refractory tumor cells, whose key mechanism of resistance was based on thiol substitution. In addition, ZD0473 is also active in cisplatin-resistant tumor cells, in which resistance is based on altered drug transport mechanisms or enhanced DNA repair.

Based on encouraging preclinical results, ZD0473 entered clinical phase I/II trials in several solid tumors, including non-small cell lung cancers, mesothelioma, head and neck cancers, and ovarian carcinoma. Its most prominent adverse effects included myelosuppression and nausea/vomiting. Thrombocytopenia and neutropenia were the dose-limiting adverse effects at intravenous doses of 130–150 mg/m^2. In contrast to cisplatin, neurotoxicity, ototoxicity, and renal toxicity have not yet been reported during or after treatment with ZD0473 (12,13,33,36).

Organs and Systems

Cardiovascular

Asymptomatic sinus bradycardia (for example 30–40/minute) is observed within 30 minutes to 2 hours after the start of cisplatin infusion. When cisplatin is withdrawn normal rhythm is restored. Because patients who receive platins are not routinely monitored, drug-induced sinus bradycardia may not be detected in practice. However, several case reports have included heavily pretreated patients, which makes a direct relation between cisplatin administration and the onset of cardiotoxic symptoms much more difficult to assess. In conclusion, no dosage adjustment appears to be warranted in patients with cisplatin-induced sinus bradycardia; however, attention should be paid to patients with resting bradycardia or those using medications known to slow the heart rate (46,47).

- A 60-year-old woman with a squamous cell lung carcinoma developed a paroxysmal supraventricular tachycardia during administration of cisplatin 20 mg/m^2 and etoposide 75 mg/m^2. The dysrhythmia appeared to be related to cisplatin since normal rhythm was restored after cisplatin was withdrawn (48).

Orthostatic hypotension was reported in "several" of 126 patients given cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 as part of treatment for lung cancer in combination with etoposide and chest radiotherapy (49).

There have been 21 reports of life-threatening disease affecting large arteries in patients treated with cisplatin, bleomycin, and vinblastine in combination for germ cell tumors (50,51). Five patients died during or after therapy, three from acute myocardial infarction, one from rectal infarction, and one from cerebral infarction. Other patients who developed major vascular disease, including coronary artery and cerebrovascular disease, have been reported. Symptoms occurred acutely in some (within 48 hours of starting therapy), and after months or years had elapsed in others.

Reduced peripheral circulation, Raynaud's phenomenon, and polyneuropathy have been described after the combined use of cisplatin, bleomycin, and vinblastine for testicular tumors. Of eight cases with polyneuropathy that were investigated, it was not possible to confirm a causative association between Raynaud's phenomenon and the chemotherapy (52).

Platinum compounds have rarely been described to cause phlebitis after intravenous administration (53).

Respiratory

Seven patients died from irreversible respiratory failure after receiving combined cisplatin plus bleomycin chemotherapy; five had raised serum creatinine and all received cisplatin before the bleomycin (54). The authors recommended extreme caution with this combination, and suggested that bleomycin should precede the cisplatin infusion.

Ear, nose, throat

- A 67-year-old white woman with a small cell lung cancer was given six courses of cisplatin and etoposide once every 4 weeks and after the last course developed acute shortness of breath, hoarseness, and stridor, due to bilateral vocal cord paralysis (55).

Nervous system

The neurotoxicity of platinum-containing compounds has been reviewed (56,57), as has the prevention of cisplatin-associated neurotoxicity (58). In experimental measurements of sensory nerve conduction velocity: oxaliplatin caused the most impairment, followed by cisplatin, carboplatin, and satraplatin (JM216) (59). The cumulative incidence of grade 2 peripheral sensory neuropathy with oxaliplatin was 19% (60).

Conventional dosages of carboplatin have been associated with the lowest risk of peripheral neuropathy (for example mild paresthesia) among the approved platinum compounds. It has been estimated that about 4–6% of patients who receive carboplatin develop a peripheral neuropathy. Patients over 65 years of age or patients pretreated with other neurotoxic agents may be at a slightly higher risk (61).

A 47% incidence of peripheral neuropathy of all grades has been reported with cisplatin (62), and a 31% off-therapy deterioration of peripheral neuropathy presenting as muscle cramps and demyelination syndromes has been described (63). Cisplatin causes a well-recognized reversible sensory

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peripheral neuropathy, starting with depressed deep tendon reflexes and loss of vibration sense, progressing to a sensory ataxia (64). This may be age-related, as the use of high-dose cisplatin in children with neuroblastoma has not been associated with peripheral neuropathy (65). Motor nerves are spared (66). There have also been case reports of cerebral herniation and coma, severe encephalopathy, tonic-clonic seizures with concomitant visual disturbances and changed mental state, insomnia, anxiety, and parkinsonian symptoms. The symptoms generally resolved within several weeks (67–71). In some studies, the nervous system effects were the consequence of cisplatin-induced electrolyte disturbances (for example hyponatremia, hypocalcemia, or hypomagnesemia), rather than a direct action of the platinum derivative in the nervous system (72–74). For example, mental status improved in one patient who was given 3% sodium chloride in order to increase the serum sodium from 118 to 128 mmol/l, whereas diazepam, phenytoin, phenobarbital, and dexamethasone were ineffective (75).

Presentation

In about 90% of patients, oxaliplatin is associated with acute neurosensory toxicity, including dysesthesia and paresthesia. Neurosensory toxicity affects the fingers, toes, perioral and oral regions, and the pharyngolaryngeal tract (in about 1–2% of cases), which is generally induced or aggravated by coldness. As a result, patients should be instructed to avoid exposure to cold. Such symptoms can occur during or shortly after the first course of oxaliplatin. The symptoms are commonly mild and disappear within a few hours or days. Some patients also develop muscle cramps or spasms. The risk of acute neuropathy appears to be lower if oxaliplatin is given in a dosage of 85 mg/m^2 every 2 weeks rather than 130 mg/m^2 every 3 weeks. A further strategy to reduce the risk of acute recurrent pseudolaryngospasm is to increase the infusion duration from 2 to 6 hours during subsequent cycles (76,77). The prophylactic use of infusions containing calcium and magnesium sulfate before and after oxaliplatin can prevent acute neurotoxic symptoms (78).

- A woman developed bilateral blindness and lumbosacral myelopathy within 1 month of having received an autologous bone marrow transplant, cisplatin 55 mg/m^2, carmustine 600 mg/m^2, and cyclophosphamide 1875 mg/m^2 (79).

In addition to the acute neurotoxic symptoms caused by oxaliplatin, about 10–15% of patients develop a moderate neuropathy, particularly after cumulative intravenous doses of 700–800 mg/m^2. The symptoms of cumulative neuropathy include non-cold-related dysesthesia, paresthesia, superficial and deep sensory loss, and eventually sensory ataxia and functional impairment, which persists between treatment cycles. Most of these symptoms usually resolve a few weeks or months after oxaliplatin withdrawal. Lower cumulative doses (for example 510–765 mg/m^2) and higher cumulative doses exceeding 1020 mg/m^2 have been associated with incidences of cumulative grade 3 neurotoxicity of 3.2% and 50% respectively (8,9,76,77). In addition, higher cumulative doses, exceeding 1000 mg/m^2, have been associated with severe, atypical neurotoxic symptoms, such as micturition disturbances and Lhermitte's sign, mimicking cord disease. However, these signs have been observed in only a few patients so far (3.3% in phase 3 trials). Both symptoms appear to be reversible after oxaliplatin withdrawal (80). In some patients oxaliplatin treatment is feasible for as long as 18 months (for example cumulative oxaliplatin dose over 3000 mg/m^2) with no signs of dysesthesia or paresthesia causing functional impairment, indicating high interindividual variability with respect to sensitivity to oxaliplatin-induced cumulative neuropathy (76,77). Whether cumulative sensory neuropathy can occur as a result of accumulation of dichloro-DACH-platinum, a biotransformation product of DACH-platinum, in the axonal and dorsal root ganglia neurons, needs further investigation (45).

Persistent Lhermitte's sign (an electric-like sensation induced by flexion of the neck) suggestive of irreversible spinal cord toxicity has been reported in a patient taking cisplatin and etoposide (81). Of four patients with oxaliplatin neurotoxicity, two presented with Lhermitte's sign, one had urinary retention, and one had both (82). All had received cumulative doses of 1248–2040 mg/m^2, which is more than the generally accepted neurotoxic threshold for oxaliplatin (1000 mg/m^2).

Peripheral paresthesia has been reported 5 years after adjuvant cisplatin-based treatment for stages I and II testicular cancer (83).

Four of eight children developed acute neurological toxicity. Three had seizures and one had transient blindness after high-dose cisplatin (200 mg/m^2) given by continuous infusion over 5 days, followed 10 days later by a further 2 days with 40 mg/m^2/day. These children had the greatest deterioration in renal function, and they may have had impaired clearance of and increased exposure to cisplatin (84).

Peripheral neuropathy with clinical signs and/or symptoms was found in 80% of patients who had received a cumulative dose of 576 mg/m^2 of cisplatin. There was a dose-related reduction in sensory action potential amplitudes (85). The clinical and neurophysiological time progression of the severity of cisplatin polyneuropathy during and after treatment with cisplatin up to a cumulative dose of 600 mg/m^2 has been described (86).

The paraneoplastic neuropathy experienced by women with epithelial ovarian cancer receiving cisplatin has been attributed in certain cases to the drug (87).

- A woman with cancer of the ovary and a man with oat cell carcinoma both developed paresthesia of all four limbs, reduced control of fine movements, and unstable gait after receiving a cumulative dose of 500 mg/m^2 of cisplatin (88). There was distal hypesthesia, with conservation of temperature and pain sensation, areflexia, and sensory ataxia. The woman also had continuous pseudoathetosis. Neurophysiological studies showed absence of peripheral and central sensory potentials and of H-reflexes, normal electromyography, normal motor conduction, and normal mixed silent period.

The target organ in cisplatin neurotoxicity is the dorsal root ganglion. This patient had a syndrome that clinically and neurophysiologically suggested diffuse neuropathic involvement of the dorsal ganglion, in which absence of sensory and H-reflex potentials showed that the small

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myelinic cells were not altered, consistent with the preservation of pain and temperature sensation.

- A woman developed bilateral blindness and lumbosacral myelopathy within 1 month of having received an autologous bone marrow transplant, cisplatin 55 mg/m^2, carmustine 600 mg/m^2, and cyclophosphamide 1875 mg/m^2 (79).

Encephalopathy has also been reported.

- A 50-year-old woman with carcinoma of the cervix was treated with radiotherapy and six courses of cisplatin (75 mg/m^2 every 3 weeks; total dose 810 mg) (89). The therapy was completed with no obvious acute complications, but 12 weeks after the last course, she developed sudden blindness associated with occipital headache. She had mild global cognitive deficits and intermittent myoclonic jerking of both arms. Her visual acuity was limited to light perception in both eyes; her pupils were symmetrical with no afferent pupillary deficit. Anterior segment examination and dilated fundoscopy were normal; no ocular movements were elicited when a large plain mirror was held in front of her. The rest of the neurological examination was normal. Serum magnesium was reduced to 0.1 mmol/l (reference range 0.7–1.2 mmol/l). Electroencephalography showed diffuse slowing confirming an encephalopathy.
- An 84-year-old woman with adenocarcinoma of the ovary had two fully reversible episodes of non-convulsive encephalopathy, each following a course of cisplatin-based chemotherapy, confirming a causal relation (90). She developed acute confusion, a partial left homonymous hemianopia and a left extinction hemiparesthesia 7 and 10 days after treatment. Brain MRI showed long-standing cerebral microvascular changes and an electroencephalogram showed right-sided parieto-occipital periodic lateralized epileptiform discharges over a generalized background slowing of activity.

In view of the similarity to posterior leukoencephalopathy, the second case suggests regional endovascular injury rather than direct cerebral toxicity as the initial event in the evolution of encephalopathy.

Strokes have been reported in patients receiving cisplatin.

- A 21-year-old woman with a mixed germ cell tumor of the left ovary was given intravenous chemotherapy including etoposide 100 mg/m^2 on days 1–5, cisplatin 20 mg/m^2 on days 1–5, and bleomycin 30 units on days 2, 8, and 15, all of which she tolerated very well (91). Three weeks later she received a second cycle, which was complicated by an episode of dizziness on day 8. The following day she had an episode of transient dysphasia for 10 minutes. Her third course was uneventful until day 7, when she collapsed with a severe right-sided hemiparesis and dysphasia. Left-sided total anterior circulation infarction was confirmed on MRI scan.
- A 31-year-old man with a seminoma had an orchidectomy, followed by chemotherapy with cisplatin, etoposide, and bleomycin (92). A day after the end of the second course of chemotherapy he became comatose with a heart rate of 150/minute and a systolic blood pressure of 80 mmHg. Cranial angiography showed a thrombosis of the basilar artery and a cranial CT scan showed cerebellar infarction but no brain metastases.

However, the use of other drugs in these patients makes it difficult to assign causality to cisplatin.

Infusions of cisplatin into the axillary artery have led to a bronchial plexopathy rather than the more commonly described lumbosacral nerve plexus lesion (93).

In five patients cerebral herniation followed cisplatin therapy (94). However, all had evidence of an intracerebral tumor with mass effect and the herniation of the brain was thought to be multifactorial rather than directly attributable to cisplatin.

Auditory brainstem responses have been used to detect ototoxicity from cisplatin and carboplatin when used in combination therapy (95).

Mechanism and susceptibility factors

The mechanism of cisplatin-induced neurotoxicity has not been fully explained. Cisplatin appears to affect neurons in the dorsal root ganglia. It has also been suggested that it can act as a calcium channel blocker, altering intracellular calcium homeostasis and leading to apoptosis of exposed neurons, such as those of the dorsal root ganglia. Cisplatin-induced sensory neuropathy is predominantly characterized by symptoms such as numbness and tingling, paresthesia of the upper and lower extremities, reduced deep-tendon reflexes, and leg weakness with gait disturbance. The first symptoms are often observed after a cumulative dose of 300–600 mg/m^2. Risk factors include diabetes mellitus, alcohol consumption, or inherited neuropathies. Advanced age has not been identified as an independent risk factor when there is no co-morbidity (67–70).

The acute neurotoxic effects of oxaliplatin may result from drug-related inhibition of voltage-gated sodium currents (96). It has been suggested that oxalate ions, which are released during oxaliplatin metabolism, might be responsible for the inhibitory effects on the voltage-gated sodium channels, because of their calcium-chelating activity. Whether there are calcium-sensitive, voltage-gated sodium channels that can be affected by oxalate-induced calcium depletion or whether an indirect effect through changes in intracellular calcium-dependent regulatory mechanisms contributes to oxaliplatin-induced sensory neuropathy needs further investigation (97).

The risk of oxaliplatin-induced neurosensory toxicity may be increased after surgery. Of 12 patients with metastatic colorectal cancer, seven reported immediate postoperative aggravation of pre-existing neurotoxicity. Before surgery, they had only acral paresthesia without any functional impairment, whereas after surgery they complained of major worsening of symptoms, including loss of hand grip strength, leading to dependence in dressing, eating, and use of the toilet, or loss of sensitivity, interfering with walking, which could persist for several months (98). The authors speculated that perioperative hemolysis had caused an increase in unconjugated bilirubin and the release of ultrafilterable oxaliplatin, which had previously been confined to the intraerythrocytic compartment. In addition, diffusion of ultrafilterable

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oxaliplatin out of erythrocytes into the plasma during hemodilution can contribute to the undesirable perioperative increase in unbound oxaliplatin in the plasma.

There is a correlation between the total dose of cisplatin and the vibratory perception threshold of the hand (99).

Dose-relatedness

When three different schedules of cisplatin were evaluated with regard to the drug's neurotoxicity, using the same dose of 450 mg/m^2 for each of the schedules, it was found that cisplatin-induced peripheral neuropathy depended on both total-dose and single-dose intensity (100).

Neurotoxicity in 22 adolescents was related to the prior cumulative dose of cisplatin that had been received; the relative risk increased 3.2-fold up to a dose of 600 mg/m^2, and 4.1-fold up to a dose of 1340 mg/m^2 (101).

By comparing 50 mg/m^2 weekly with 75 mg/m^2 3 times weekly, using detailed neurological and neurophysiological examination, it has been concluded that cisplatin neuropathy is either of sensory or axonal type, and that both are related to total and single doses (102). However, others have suggested that cisplatin-induced peripheral neurotoxicity is related to dose intensity rather than to the total dose received (103).

A 4-year follow-up of comparison of a combination of cyclophosphamide with cisplatin either 50 mg/m^2 or 100 mg/m^2 in ovarian cancer has been reported (104). Peripheral neuropathy was dose-limiting and persistent. Ten of 31 patients had significant toxicity in the high-dose group compared with one of 24 in the low-dose group.

High-dose cisplatin therapy

The use of aggressive hydration using hypertonic saline and sodium thiosulfate, with dose-scheduling, reduces the risks of dose-limiting nephrotoxicity of cisplatin, and this has made possible the use of high-dose cisplatin (over 200 mg/m^2/course). However, such doses can cause severe chronic peripheral neuropathy, ototoxicity, and myelosuppression, although these effects can be reduced by lengthening the infusion time of cisplatin (65). Peripheral neuropathy is the commonest manifestation of cisplatin neurotoxicity; with high-dose administration the incidence and severity increase with the total dose, and it appears to be age-related. It was not seen in 47 children treated with high-dose cisplatin (40 mg/m^2/day for 5 days) for neuroblastoma (105). Autonomic neuropathy, motor neuropathy, and denervation changes in muscles occur occasionally.

In a clinical and electrophysiological study of eight patients treated with high-dose cisplatin (800–1400 mg) plus etoposide and bleomycin, all developed a peripheral sensory neuropathy (106). A reduction in vibratory sensation was the earliest manifestation of the neuropathy and the findings were compatible with primary damage to the dorsal root ganglia with a central-distal axonopathy. No motor nerve abnormalities were detected, apart from one patient with carpal tunnel syndrome, but two patients had prolonged brain-stem auditory-evoked potentials, indicating a central transmission defect. In another clinical and electrophysiological study of seven patients treated with cisplatin, the sensory neuropathy was also axonal, with considerable involvement of proprioception (107). Postmortem study in one case showed degeneration of the posterior columns of the spinal cord and evidence of neuronal loss in the lumbar spinal ganglion.

Eleven patients referred for neurological evaluation after cisplatin infusion into the internal or external iliac arteries for pelvic or lower limb tumors all developed symptoms within 48 hours of nerve or plexus dysfunction within the territory supplied by the cannulated artery (108). The lumbosacral plexus was affected in nine patients, the femoral nerve in one, and the peroneal nerve in one. The doses of cisplatin ranged from 50 to 160 mg/m^2 and they did not correlate with the severity or course of the neuropathy. Small-vessel injury and infarction or a direct toxic effect are likely explanations.

Time-course

In a study of the time-course and prognosis of cisplatin-induced neurotoxicity (for example sural nerve sensory action, conduction velocity, and vibration threshold in the left big toe) in 29 patients with metastatic germ cell tumors, the onset of paresthesia was delayed (109). After completion of chemotherapy (3–4 cycles) only 11% of the patients had neurotoxic symptoms, whereas 3 months later the proportion was 65%. Cisplatin-induced neurological disorders should therefore be evaluated at 1–4 months after the end of weekly cisplatin administration, because during this time the most severe form of cisplatin neurotoxicity is to be expected. There was resolution of symptoms in most of the patients over the next 12 months, suggesting that in some individuals a long period of regeneration is required to restore axonal sensory function. In patients with mild signs of cisplatin-related neuropathy, retreatment is generally feasible after several months (110,111).

Management

Among several thiol compounds, glutathione may provide neuroprotection in patients treated with cisplatin without altering its antineoplastic activity. This protective role may be based on blockade of the accumulation of p53 protein in response to platinum in dorsal root ganglia, thereby hindering platinum-based apoptosis (57,112).

The melanocortin Org 2766, an ACTH analogue, which is not yet available for clinical use, alleviates neurotoxicity due to vinca alkaloids and cisplatin, perhaps by enhancing neural repair. However, whereas preliminary results suggested some neuroprotection in women with ovarian cancer treated with cisplatin, these results were not confirmed in a randomized, multicenter, double-blind, placebo-controlled dose-finding study, even with higher doses of Org 2766 (113).

There is evidence that amifostine can reduce the frequency of cisplatin-induced peripheral neuropathy, allowing higher mean cumulative doses to be used. However, some of the results should be interpreted with caution, because the studies included patients who differed in respect to treatment regimen, disease states, and pretreatment status. The underlying protective effect of amifostine may be based on its capacity to scavenge

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free radicals and prevent cisplatin DNA adduct formation in several organs, including the dorsal root ganglia (57).

In a pilot study in 15 patients, subcutaneous amifostine was given 20 minutes before oxaliplatin, in order to counteract oxaliplatin-induced peripheral neurosensory toxicity. In 10 patients, this regimen reduced the severity of cumulative neuropathy without compromising antitumor efficacy; the amifostine was well tolerated (114).

There is increasing evidence that acute oxaliplatin-induced neurotoxicity can be improved by intravenous infusion of calcium gluconate 1000 mg and magnesium sulfate heptahydrate 1000 mg before and after oxaliplatin. It has recently been shown that this strategy could reduce the incidence of acute neurotoxic symptoms, including laryngopharyngeal dysesthesia. Of 101 patients with advanced colorectal cancers who received folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin (85 mg/m^2/2 weeks, 20 patients; 100 mg/m^2/2 weeks, 22 patients; 130 mg/m^2 /3 weeks, 59 patients), 63 received infusions of calcium and magnesium (1 g each) before and after oxaliplatin administration (treatment group); 38 patients (control group) did not receive infusions of calcium + magnesium. The median cumulative dose of oxaliplatin was 910 (range 255–2340) mg/m^2 in the calcium/magnesium group and 650 (range 255–1450) mg/m^2 in the control group. At the end of treatment, 27% had neuropathy (any grade) compared with 75% in the control group; 1.6% and 26% had pharyngolaryngeal dysesthesia; and 5% and 24% had grade 3 neuropathy. However, further studies are warranted before this regimen can be generally recommended for reducing the risk of acute neurosensory symptoms associated with oxaliplatin infusion (77,115).

Carbamazepine is a potent sodium channel blocker and has therefore been studied in the prevention of oxaliplatin-induced neuropathy (116). The doses of carbamazepine were adjusted to produce serum concentrations in the range 30–60 μg/ml. None of the patients who took carbamazepine reported symptoms of peripheral neurotoxicity; however, two patients (one who forgot to take carbamazepine and one who stopped taking it because he felt tired) developed grade-1 peripheral sensory neurotoxicity. These symptoms were abolished when carbamazepine was restarted. One can therefore speculate that the concomitant use of carbamazepine may allow the use of a higher cumulative dose of oxaliplatin without the occurrence of grade-4 neuropathy. However, a multicenter trial is warranted to confirm these encouraging preliminary results (117).

In 15 patients with metastatic colorectal cancer who were given gabapentin (100 mg bd or tds) if neuropathic symptoms developed with oxaliplatin, the symptoms disappeared in all patients, even in those who received up to 14 courses of oxaliplatin. Withdrawal of gabapentin resulted in recurrence. However, a controlled trial is required to verify these encouraging preliminary results.

It has been suggested that chronomodulated delivery of oxaliplatin might reduce the incidence of platinum-induced neurotoxicity (118,119). In a randomized, multicenter trial in patients with previously untreated metastases from colorectal cancer, 93 patients were assigned chronotherapy and 93 were assigned constant-rate infusion (120). Chronotherapy reduced the rate of severe mucositis five-fold and halved the rate of functional impairment from peripheral sensitive neuropathy. Median and 3-year survival times were similar in the two groups.

Preliminary results have suggested that glutathione may be neuroprotective in patients receiving oxaliplatin (121).

Sensory systems

Eyes

Ocular effects, including optic neuritis, papilledema, and retrobulbar neuritis, are uncommon adverse effects of cisplatin-containing cancer chemotherapy. The risk of retinal toxicity is restricted to high-dose cisplatin therapy (for example 200 mg/m^2 over 5 days) and can result in blurred vision and altered color perception, which can persist for several months. In contrast to cisplatin, carboplatin is seldom involved in drug-induced visual disturbances. In two cases there was a relation between the administration of carboplatin (800–1200 mg/m^2) and the occurrence of clinical cortical blindness (122). However, both patients had impaired renal function before the start of therapy with carboplatin.

- Ocular toxicity of cisplatin has been reported in a 47-year-old woman who experienced rapid uncontrollable eye movements associated with hypomagnesemia and hypocalcemia in the presence of renal tubular damage (123).

Ears

Cisplatin is ototoxic (95).

Frequency

In serial audiometric testing in 66 patients receiving cisplatin 100 mg/m^2 per course, of 39 evaluable patients, 54% had no or mild hearing loss, 36% developed early hearing loss and 10% had late loss. If early hearing loss occurred and treatment was nevertheless continued, the speech frequencies were eventually affected in 71% of patients (124).

Dose-relatedness

Tinnitus and bilateral high-frequency hearing loss (threshold 3000 Hz) have been observed in up to 31% of patients treated with initial intravenous doses of cisplatin of 50 mg/m^2. There is considerable individual variation in susceptibility to cisplatin-induced ototoxicity, and both peak plasma concentrations and cumulative dose are important. Transient reversible tinnitus occurs commonly, even after low doses, but hearing impairment is more dose-dependent and affected by age, renal function, preexisting inner ear damage and concomitant loop diuretic and/or aminoglycoside treatment. In in-vitro studies, selective damage to hair cells in the cochlea and in the supporting cells in the cochlear and vestibular parts of the labyrinth has been shown, with arrest of morphogenesis and cytodifferentiation. Morphological changes in the stria vascularis have been noted (125).

An attempt has been made to quantify the ototoxic effects of cisplatin in children by cumulative platinum dose and decibel hearing loss at certain predetermined frequencies. The findings provide useful insight into this

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toxicity (126). In a study of cisplatin ototoxicity in children it was concluded that 77% experienced ototoxicity with a median cumulative dose of 360 mg/m^2 (127). However, when cisplatin was given by continuous infusion rather than bolus administration in 39 children with germ cell tumors, only one, who had received a total cumulative dose of 500 mg/m^2, had evidence of significant ototoxicity over 6 years after diagnosis (128).

In a series of 154 audiograms, ototoxicity increased with cumulative dosage of cisplatin and low-dose or monthly regimens caused the lowest toxicity (129). Patients who were given high doses over short periods of time, or who developed tinnitus and hearing loss in the speech frequencies, were at the highest risk. In a small series of patients it was confirmed that pretreatment hearing loss does not increase the risk of cisplatin ototoxicity (130). It has been postulated that cisplatin ototoxicity is inversely related to the patient's age (131). A 600 mg/m^2 plateau dose of cisplatin, beyond which hearing loss shows no apparent further deterioration in children and adolescents, has been described (132).

Presentation

Progressive hearing loss develops as a result of repeated administration of cisplatin, until a threshold plateau is reached at 3000–8000 Hz (133). Hearing loss greater than 20 dB with frequency as 5% at 1000 Hz, 31% at 2000 Hz, 59% at 4000 Hz, and 95% at 8000 Hz is described (132). This is the result of damage to the organ of Corti. The ototoxicity is bilateral, symmetrical, progressive, and irreversible. Following one course of cisplatin (150–225 mg/m^2) the mean hearing loss recorded was 27 dB at 8000 Hz, 21 dB at 6000 Hz, and 11 dB at 4000 Hz. Development of hearing loss is independent of pretreatment hearing function (134). Sudden bilateral deafness without tinnitus has been described after a single course of cisplatin at a dose of 120 mg/m^2; the patients showed only slight improvement after 4 weeks (135).

Of 186 women receiving cisplatin 50 mg/m^2 4-weekly for gynecological cancers, 40 developed significant hearing loss of at least 15 dB, but there was no significant loss in the speech frequency range (125). Prior hearing acuity did not influence the incidence or extent of the deterioration.

Susceptibility factors

Susceptibility factors include young age, previous cranial irradiation, pre-existing renal dysfunction or inner ear damage, and the concomitant use of other potentially ototoxic agents, such as aminoglycosides, loop diuretics, or tirapazamine (129,136–142). Previous use of an aminoglycoside increases the risk of ototoxicity. Younger patients and patients who had undergone prior cranial irradiation are more particularly susceptible to audiological changes, which progress in severity with increasing dose (143).

Mechanisms

The mechanisms of cisplatin-induced damage to the outer hairy cells of the cochlea may include the formation of highly reactive oxygen radicals and depletion of glutathione (144). The role of amifostine and glutathione in preventing cisplatin-induced ototoxicity has therefore been studied (145,146). The data are not sufficient to support the use of glutathione in this indication. In contrast, there is some evidence that amifostine may provide protection (147). No ototoxicity developed in 18 patients who received amifostine over 15 minutes, 15–20 minutes before the intravenous administration of cisplatin 50–120 mg/m^2 over 20 minutes. There was transient hearing loss and mild persistent audiometric abnormalities in only 30% of the patients who received cisplatin 150 mg/m^2.

Animal experiments show that cisplatin is only weakly vestibulotoxic (148), and clinical vestibular toxicity is found less often than hearing loss. Of 10 patients who received 80–550 mg cisplatin, clinical features of vestibulotoxicity were analysed in addition to hearing, and patients underwent audiometry, body sway, caloric, and optokinetic and pendular rotation testing (149). Four patients sustained significant hearing loss, five had tinnitus, and three complained of dizziness, giddiness, and/or unsteadiness rather than vertigo. These symptoms were transient, and they occurred usually after several weeks of administration; they were not consistently dose-related. Spontaneous nystagmus was observed in seven and positional nystagmus in six. Caloric and body sway tests were abnormal in the early stages in several patients. The findings were suggestive of a cumulative toxic effect.

In an in-vitro study of the adverse effect of cisplatin on hair cells and other inner ear structures, aimed at determining whether selective damage occurs in inner ear hair cells and whether morphogenesis and cytodifferentiation are influenced by low cisplatin concentrations, even at low cisplatin concentrations (0.1 μg/ml) there was selective damage to hair cells. Incubation at a cisplatin concentration of 1 μg/ml caused morphological damage in the supporting cochlear and vestibular cells, and 10 μg/ml caused total collapse of the membranous labyrinth. Drug exposure arrested morphogenesis as well as cytodifferentiation (150).

Auditory brainstem responses have been used to detect ototoxicity from cisplatin and carboplatin when used in combination therapy (95). The method can detect early high frequency damage due to these drugs up to two or three cycles earlier than conventional audiometry.

The ototoxicity of cisplatin has been studied using distortion-product otoacoustic emissions (DPOAEs) and conventional pure-tone audiometry (151). Cisplatin ototoxicity was detected on average one cycle earlier with DPOAEs than with pure-tone audiometry. The authors suggested that this was because DPOAEs are more sensitive to outer hair cell damage.

Carboplatin and oxaliplatin

In one study only 1.1% of evaluable patients taking carboplatin had ototoxic symptoms, such as tinnitus, or subclinical audiographic changes (152). However, in a series of closely monitored patients there was an incidence of 27% (129). It has also been estimated that 19% of patients receiving carboplatin have significant hearing loss greater than 30 dB; the hearing loss is cumulative and maximum at 8000 Hz; the authors reported two of these patients with hearing loss greater than 10 dB at

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1000 Hz. The overall conclusion is that with low-dose, short-schedule, carboplatin therapy, routine audiometry is not justified (152).

After otoacoustic emission testing in 19 children who received cisplatin the authors suggested that this is better at detecting the early cochlear damage associated with cisplatin ototoxicity than traditional pure-tone audiometry, particularly in children, in whom early detection is of the utmost importance (153). In patients who receive high-dose carboplatin, preliminary results suggest that there may be a correlation between the risk of ototoxicity and carboplatin serum concentrations (AUC) during the first course. Patients with high-grade ototoxicity had higher median carboplatin AUCs than patients without any symptoms (122,154).

In another study, carboplatin-induced ototoxicity was reported in 32% of exposed patients. This was similar to cisplatin ototoxicity, although at a lower frequency (4000–8000 Hz) than the often-quoted 6000–8000 Hz for cisplatin. The extent of otic damage was proportional to the dose of carboplatin (155).

Audiological testing has been recommended for patients receiving high-dose carboplatin therapy, following hearing problems in a series of 10 patients with ovarian cancer (156).

There is no evidence that oxaliplatin causes ototoxicity (157).

Smell

About 30% of patients treated with cisplatin have been reported to have some degree of anosmia, which in 1% is severe or complete; the sense of smell returns to normal within 3–4 months of completing cisplatin therapy (158).

Endocrine

The endocrine effects of cisplatin-based chemotherapy were studied in 22 men 9–24 or more months after completion of treatment for germ cell tumors (159). Mean basal FSH and stimulated LH and FSH concentrations were increased but serum testosterone concentrations were similar to untreated controls. Younger patients (under 25 years old) appeared more resistant to these effects of chemotherapy, and the hormonal abnormalities recovered with time.

The long-term effects on Leydig cell function of chemotherapy in 244 patients with germ cell tumors have been studied by measuring concentrations of sex hormone-binding globulin, luteinizing hormone, and follicle-stimulating hormone at least 74 months after chemotherapy (160). The population was divided into groups by cumulative cisplatin exposure (above and below 400 mg/m^2). Low-dose cisplatin exposure had no effect on Leydig cell function, but cumulative high-dose chemotherapy caused persistent impairment.

Metabolism

- Hyperosmolar non-ketotic hyperglycemia occurred in a 61-year-old patient 6 days after a first cycle of cisplatin therapy (161). The patient recovered with conventional conservative management.

Electrolyte balance

Hyponatremia is rare, and persistent hyponatremia very rare in patients taking cisplatin (162). In a detailed description of the biochemical abnormalities that can result from renal tubular dysfunction after cisplatin therapy, it was noted that hypocalciuria is more common than hypomagnesemia, and that there tends to be a state of reduced serum bicarbonate. The most severe renal tubular damage caused by cisplatin is characterized by hypocalciuria, total body magnesium deficiency, and hypokalemic metabolic alkalosis (163).

Other electrolyte disturbances induced by cisplatin include hypocalcemia, hypophosphatemia, hyponatremia, and hypokalemia (164,165). However, these changes are rarely associated with symptoms (166,167).

Metal metabolism

Magnesium

About 75% of patients treated with cisplatin develop hypomagnesemia (serum concentrations below 1.5 mmol/l), which appears to be associated with drug-induced renal tubular damage (168–171). The symptoms include tetany, muscular weakness, tremulousness, dizziness, personality changes, and perioral and peripheral paresthesia (172). Magnesium supplementation is generally recommended during treatment courses with cisplatin (168,170). Sometimes, hypomagnesemia resolves rather slowly and can last several weeks. A significant reduction in serum magnesium and other effects associated with progressive renal dysfunction appear to correlate with high cumulative doses of carboplatin (for example a median cumulative dose of 2590 mg/m^2 in children or in adults undergoing high-dose chemotherapy with peripheral blood stem cell support).

Renal magnesium wasting is the main mechanism responsible for the hypomagnesemia associated with cisplatin (172), and it can be associated with enhanced tubular reabsorption of calcium and consequent hypocalciuria (173). This dissociation in the renal handling of calcium and magnesium is similar to what is found in Bartter's syndrome. The site of the renal tubular defect in these conditions is not known, but there is evidence that active renal tubular transport systems are disrupted.

In a prospective study of 28 patients who received a total of 82 doses of cisplatin, hypomagnesemia occurred in all patients and was associated with significant and prolonged dose-related magnesium wasting. Serum magnesium was 1.8 mg/dl after the fourth dose. Examination of the urine sediment 2–4 days after each dose of cisplatin showed renal tubular epithelial cells, suggesting that cisplatin directly injures the tubules, leading to reduced tubular reabsorption of magnesium, renal magnesium wasting, and hypomagnesemia (174). In another study, patients receiving cisplatin and concomitant magnesium supplementation developed significantly less renal tubular damage, as assessed by urine *N*-acetyl-β-D-glucosaminidase (175). No patient developed clinical signs of hypomagnesemia when intravenous or oral supplementation of magnesium was given as soon as the serum magnesium fell to or below 0.45 mmol/l. In patients receiving intracavitary cisplatin in high doses (100–200 mg/m^2), together with

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intravenous thiosulfate, there was a lower incidence of hypomagnesemia as a result of the thiosulfate; thiosulfate probably inactivated cisplatin before it reached the kidney, by complex formation (176).

Hypomagnesemia secondary to cisplatin administration can be severe enough to present as generalized seizures (172). It more commonly presents with muscular weakness, tremulousness, peripheral paresthesia, tetany, and personality changes. It is dose-related and schedule-related. Loss of magnesium can be prevented by prophylactic magnesium infusion before and during cisplatin administration (177), but this is not universally recommended because of the risk of acute uremia (178).

Zinc

Hyperzincuria and hypozincemia can occur concurrently in patients treated with cisplatin, due to variable excretion of zinc in these cases (179).

Hematologic

Compared with cisplatin and oxaliplatin, carboplatin has the highest myelotoxic potential. Carboplatin-induced myelosuppression is dose-related and results in thrombocytopenia and neutropenia. At conventional doses (AUC 4–7 minutes/μg/ml) about 20–40% of patients develop thrombocytopenia (platelet counts below 50×10^9/l). In contrast, severe neutropenia is less pronounced with conventional doses; about 16–21% of patients develop neutrophil counts less than 1×10^9/l. The lowest leukocyte and platelet counts usually occur at 14–28 days after drug administration. The hemoglobin concentration was below 11 g/dl in 71–91% of patients and below 8 g/dl in 8–21% (155). The severity of drug-induced thrombocytopenia is inversely correlated with the endogenous formation and release of thrombopoietin, which is an important cytokine for de novo platelet formation in the bone marrow. In contrast to conventional dosages, high-dose chemotherapy containing carboplatin is generally associated with severe and life-threatening forms of hematological toxicity, requiring the prophylactic use of recombinant hemopoietic growth factors, such as G-CSF, and peripheral blood stem cell support (180).

Underlying risk factors, which predispose patients to more severe forms of myelosuppression, include lower initial blood cell counts, renal impairment, poor performance status, extensive prior chemotherapy, and advanced age. There is a strong correlation between carboplatin pharmacokinetics and the severity of myelosuppressive adverse effects; an AUC-adapted dosage of carboplatin is therefore highly recommended during conventional dose chemotherapy (22,23,155).

Cisplatin belongs to the most important causative agents for the induction of treatment-related anemia requiring the prophylactic use of erythropoietin or intermittent transfusion of erythrocytes, whereas drug-induced leukopenia and thrombocytopenia are generally mild and transient (180,181). In a pharmacokinetic study, non-protein-bound platinum concentrations in patients with significant falls in hemoglobin (3 g/dl or more) were significantly higher (mean 53 ng/ml) than in patients who did not have significant falls in hemoglobin. The authors suggested that early and simple platinum pharmacokinetic control on the day after first drug administration might be useful in targeting patients who are likely to develop more severe forms of cisplatin-related anemia (182).

Myelosuppression caused by oxaliplatin is generally mild. Grade 3/4 anemia, neutropenia, and thrombocytopenia are observed in only 2–3% of patients. In combination with fluorouracil/folinic acid, the frequency is slightly higher, depending on the dose of fluorouracil (8,9).

Cisplatin causes an increase in erythropoietin, but anemias associated with platinum therapy are independent of this mechanism (183).

Forty patients with lung cancer, treated with a combination of cisplatin, mitomycin, vinblastine, doxorubicin, cyclosphosphamide, and methotrexate, had a significant post-treatment increase in fibrinopeptide A and a fall in fibrinolytic activity, reflected by a fall in functional tissue activator; this appeared to be cumulative, depending on the extent of drug exposure (184).

Gastrointestinal

Of the approved platinum compounds, cisplatin has the greatest emetogenic potential (185). Whereas about 65–94% of patients who receive conventional dosages of carboplatin complain of mild to moderate nausea or vomiting, more than 90% of those who receive cisplatin can have more than 10 vomiting episodes within the first day of administration in the absence of effective antiemetic therapy. An emetogenic episode occurring within 24 hours after drug administration is usually classified as acute emesis; nausea and vomiting that occur thereafter are classified as delayed emesis and may persist over several days. There appears to be a correlation between the time of cisplatin administration and the severity of drug-induced vomiting (186). When cisplatin was given in the morning (0500 hours) vomiting was greater than when it was given in the evening (1700 hours). However, the prophylactic use of a 5-HT_3 receptor antagonist reduced the time-of-day dependency. 5-HT_3 receptor antagonists, such as dolasetron, granisetron, ondansetron, palonosetron, or tropisetron, particularly in combination with dexamethasone, reduce the severity of acute emesis occurring within the first 24 hours after cisplatin. In contrast, the satisfactory prevention of delayed emesis remains a challenge. There is increasing evidence that the introduction of a novel class of antiemetic agents, the neurokinin-1-receptor antagonists, such as MK869 (aprepitant), may be associated with additional benefit in combination with a 5-HT_3 receptor antagonist in reducing cisplatin-induced nausea and vomiting, both acute and delayed (187).

Nausea, vomiting, and diarrhea are common adverse effects of oxaliplatin and carboplatin, but they are generally mild to moderate, and both are less emetogenic than cisplatin. However, patients who have previously received cisplatin may be at greater risk of vomiting with carboplatin or oxaliplatin (1,8,9).

In an endoscopic study of the acute gastroduodenal toxicity of intravenous cisplatin 10 mg/m^2 and etoposide 107 mg/m^2 (mean dose) given for three doses, a significant number of patients developed gastroduodenal lesions, several of which progressed (188).

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Liver

Mild reversible increases in liver function tests can occur in patients who have received platinum compounds (189). However, the platinum compounds are generally not classified as hepatotoxic drugs.

Urinary tract

Cisplatin

Of the approved platinum compounds, cisplatin has the greatest nephrotoxic potential, and the nephrotoxicity is often dose-limiting (190). If dosages exceed 100 mg/m^2 per course or per day, nephrotoxicity is the most severe drug-related adverse effect. It is mainly due to proximal tubular dysfunction (191), with hydropic degeneration, necrosis, and occasional tubular atrophy. Fragments of distal tubular cells have been demonstrated in the urine of patients receiving chemotherapy that included cisplatin (192). The risk is reduced by adequate hydration, which lowers drug concentrations in the renal tubules. Impaired renal function can persist for at least 6 months after treatment has been withdrawn. Indicators of cisplatin-related renal tubular toxicity include changes in creatinine clearance or in urinary alanine aminopeptidase and *N*-acetyl-*β*-D-glucosaminidase activities. Blood urea nitrogen and serum creatinine are poor indicators of early renal damage. The nephrotoxicity of cisplatin is primarily tubular, although changes in renal blood flow and glomerular filtration also occur, and hypomagnesemia is common (SEDA-12) (193,194).

The mechanisms of cisplatin-induced nephrotoxicity have not been fully elucidated. Like several nephrotoxic heavy metals (for example mercury), cisplatin can accumulate in the kidney, where it can interact with sulfhydryl compounds, resulting in increased membrane fragility and depletion of intracellular glutathione. There is some evidence that cisplatin can induce apoptosis and necrosis of kidney cells dose-dependently. In vitro studies have suggested that the constitutive expression of antiapoptotic proteins (for example *bcl*-X) might be inversely correlated with the sensitivity of renal tubular cells (146,195–197).

Cisplatin-induced nephrotoxicity can be detected by a rise in blood urea or by a fall in creatinine clearance. Tubular dysfunction can cause hyponatremia (72), hypokalemia, hypomagnesemia (173), and hypophosphatemia. Inappropriate ADH secretion may be partly responsible for hyponatremia (191).

In experiments in mice, the trace element selenium, which interacts with heavy metals, reduces the renal, intestinal, hepatic, and hematological toxicity of cisplatin without affecting its antitumor activity (198).

Regarding prolongation of infusion, it has been suggested that there is a correlation between higher plasma platinum concentrations and the risk of cisplatin-induced nephrotoxicity. If platinum concentrations exceed 6 μg/ml, more patients develop nephrotoxicity. These drug concentrations were measured shortly after the end of infusion (for example 5 minutes after intravenous infusions of 100–120 mg/m^2), suggesting that high blood concentrations rather than trough concentrations may be predictively important. As a result, prolongation of cisplatin infusion (for example 6 hours) has been proposed to reduce the risk of cisplatin-induced renal insufficiency (147,199). However, in practice, a 1-hour infusion remains the common standard.

In 35 children who had taken cisplatin for a maximum of 2 years, nephrotoxicity was not related to total dose but was less severe in children who received cisplatin in doses below 40 mg/m^2/day (200). During follow-up for 2 years there was partial but significant recovery of renal function.

The effect of age on nephrotoxicity after treatment with ifosfamide or cisplatin has been studied (201). Children aged 5 years or less had more severe proximal tubular toxicity associated with ifosfamide than older patients. They also had significantly lower plasma phosphate concentrations and a higher fractional excretion of glucose. There was no evidence of glomerular or distal renal tubular damage after ifosfamide and there was no difference between the older and younger children in any other aspect of renal function. In general, age predicts independently the likelihood and severity of genitourinary toxicity caused by cisplatin in combination chemotherapy (202).

Several supportive measures have been proposed in order to circumvent cisplatin-induced nephrotoxicity. These include:

- adequate hydration before and during cisplatin administration and afterwards, in combination with an osmotic diuretic such as mannitol (the current standard method);
- prolongation of the infusion time (for example 6 hours instead of 2 hours);
- fractionation over several days;
- the use of a chronomodulated schedule;
- the use of nephroprotective agents, such as organic thiosulfate compounds.

Sodium thiosulfate protects against cisplatin-induced nephrotoxicity by reacting covalently with cisplatin in the renal tubules. Other protectors include probenecid, orgotein, fosfomycin (203), amifostine (2-[3-aminopropyl) amino]ethylphosphorothioic acid, WR-2721, ethyofos), and anthiol. Experimental study drugs that may be useful in renal protection include BNP7787 (dimesna), selenium, and silibinin (146,204–212). The beneficial role of furosemide is uncertain.

Amifostine is an organic thiophosphate. It is a prodrug, because dephosphorylation by tissue-bound alkaline phosphatase is necessary to form its active metabolite, WR-1065. It protects normal tissues against the toxic effects of radiation, cisplatin, and alkylating agents in animals, perhaps through free radical scavenging, hydrogen ion donation, and the prevention or removal of DNA platinum adducts (213). Amifostine has been used in the pretreatment of patients with metastatic melanoma before administration of cisplatin 60–150 mg/m^2 in an uncontrolled trial of 36 patients (214). There was a response rate of 53% and a low incidence of nephrotoxicity; transient nephrotoxicity occurred in 4% of 82 courses of amifostine given with cisplatin 120 mg/m^2.

In a randomized study, 242 patients with advanced ovarian cancer received intravenous cisplatin 100 mg/m^2 and cyclophosphamide 1000 mg/m^2 once every 3 weeks with or without amifostine 910 mg/m^2. Besides a

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significant reduction in chemotherapy-induced neutropenia and thrombocytopenia, amifostine produced significant protection against cisplatin-induced nephrotoxicity. Creatinine clearance fell by more than 40% in 60% of the control group compared with 12% of those in the treated group. In addition, the incidence of cisplatin-related hypomagnesemia was less pronounced in the patients who received amifostine.

Dose fractionation over several days has been associated with less kidney damage. The glomerular filtration rate was maintained in patients who received cisplatin 20 mg/m^2/day over 5 consecutive days (215,216). However, patients still had a significant increase in sensitive urinary markers, such as low molecular weight proteins, *N*-acetyl-β-D-glucosaminidase (NAG), and α–1-microglobulin, showing that conventional approaches can reduce but not completely prevent nephrotoxicity (146,195).

Chronomodulated administration of cisplatin can also reduce drug-induced organ toxicity, for example nephrotoxicity (217,218). Administration of cisplatin in the evening caused markedly less nephrotoxicity and neurotoxicity than morning administration. There is also increasing evidence that all platinum-based anticancer drugs are better tolerated if they are given in the late afternoon or early evening, with less frequent and severe nephrotoxicity, thrombocytopenia, and cumulative peripheral neuropathy after cisplatin, carboplatin, and oxaliplatin. As chronomodulated scheduling appears to affect the adverse effects of all platinum compounds, the mechanism may be based on circadian variation in renal tubular excretion and plasma filtration of platinum compounds, increased plasma protein binding, and reduced tissue susceptibility at about 1600 hours (217–219).

In several studies, intravenous amifostine (910 mg/m^2) preserved glomerular filtration rate when it was co-administered with cisplatin-containing regimens (213). Even after two cycles containing intravenous cisplatin 50 mg/m^2 plus intravenous ifosfamide and etoposide or paclitaxel, glomerular filtration rate can fall by more than 30%, but concomitant use of amifostine prevented this. Even lower dosages of intravenous amifostine (for example 740 mg/m^2) may be effective (220,221).

Because preclinical results suggested that intracellular glutathione may be involved in the modulation of cisplatin-induced toxicity, several trials (two uncontrolled and two randomized) have been conducted to evaluate the efficacy and tolerability of standard doses of cisplatin with concomitant glutathione. In some studies, glutathione reduced cisplatin-related toxicity without impairing its antineoplastic activity (113). However, a cisplatin dose-escalation study with concomitant administration of glutathione had to be terminated prematurely because of unacceptable ototoxicity. Glutathione has not yet received FDA approval for chemoprotection.

Carboplatin

When carboplatin is used in doses that cause similar hematological toxicity to cisplatin, it has negligible renal, neurological, and auditory toxicity (222,223). In combination with other cytotoxic agents, the maximum tolerated dose is less than normal because of the risk of myelosuppression (224). However, if the dose is increased, as in acute non-lymphocytic leukemia, high-tone hearing loss and renal impairment can occur (225). In this study, all but one patient who developed these adverse effects had also received aminoglycoside antibiotics.

Concomitant intravenous hydration and monitoring is not needed when carboplatin is given in conventional dosages. However, during dose-intensified treatment with carboplatin, the risk of impaired renal function increases. In addition, other nephrotoxic drugs, such as ifosfamide, are often part of those high-dose combination regimens. During a study of the use of high-dose carboplatin (1500 mg/m^2/day or more) on 3 consecutive days, the nephrotoxic profile was comparable to a standard single dose of cisplatin (216).

Ultra-high-dose carboplatin can be safely administered as long as clinicians individualize and adjust the therapy to renal function using ^{51}Cr-EDTA glomerular filtration rate; there was only one death attributed to carboplatin in 31 patients who died of acute renal insufficiency (226).

Mild to moderate reduction in creatinine clearance with rises in serum urea and creatinine were reported in 14% of patients receiving carboplatin in a dose of 400 mg/m^2 for gynecological malignancies. Of the patients who received carboplatin 400 mg/m^2 with vincristine but without hydration for lung cancer, 19% developed renal changes.

During a 2-year follow-up of 23 children receiving carboplatin there were falls in both glomerular filtration rate to 22 ml/minute and serum magnesium concentration to 0.17 mmol/l (166). The authors thought that the fall in glomerular filtration rate, although statistically significant, was not clinically significant, but they were unsure about the long-term clinical effects of the low magnesium.

Intensified carboplatin-containing regimens can predispose patients to drug-induced renal dysfunction when cisplatin has previously been used or when renal function is already impaired (167,227).

In a randomized study of the prophylactic use of amifostine during dose-intensified chemotherapy including carboplatin and ifosfamide, patients in the control arm had a median loss of glomerular filtration rate of 37% compared with baseline after one cycle, and 35% of these patients had glomerular filtration rates below 60 ml/minute on day 10 after treatment. In patients who received amifostine during dose-intensified chemotherapy, the glomerular filtration rate fell only by a median of 10% and no patient developed a glomerular filtration rate below 60 ml/minute by day 10 (228).

Oxaliplatin

Oxaliplatin, when given alone or in combination with fluorouracil, is considered not to be nephrotoxic (166,167,227). There has been a single case of acute tubular necrosis probably caused by oxaliplatin and not related to dehydration or pre-renal insufficiency (229).

Skin

Even in cases of accidental extravasation, the risk of skin ulceration is low. Severe cisplatin-related extravasation injury appears to be primarily restricted to the use of

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high concentrations (for example 0.75 mg/ml) and infusion over a short time. In such circumstances it is advisable to give a local injection of isotonic thiosulfate solution (0.16 mol/l). Since carboplatin is more slowly activated than cisplatin to active DNA binding moieties and is more water-soluble, there have been no reports of severe carboplatin extravasation and no antidote is necessary (230,231).

- Accidental subcutaneous administration of oxaliplatin resulted in a red-brown painful swelling and sclerosis of the skin within 8 days (232). The symptoms were worst 1 week after extravasation and lasted for about 5 weeks, but the patient, a 52-year-old woman, recovered fully. Acute intervention included local fluid instillation to dilute the extravasation, removal of the cannula, cold packs, and a gel containing aescin and diethylamine salicylate.

Two other cases of oxaliplatin extravasation have been reported (233). Both occurred when the intraport needle disconnected. The initial symptoms were swelling and tenderness at the port site. The patients developed severe inflammation after 3 days. Treatment included local cool packs, diclofenac ointment, and oral indometacin, morphine, or dexamethasone. The authors avoided saline instillation because sodium chloride and oxaliplatin may be incompatible in combination (119). Both patients recovered without any sign of local necrosis and long-term sequelae (233)

Sexual function

Sexual function in men can be compromised by cisplatin + vinblastine + bleomycin chemotherapy. Of 54 patients, 29 had disorders of sexual function 2 years after completion of treatment (234). Ejaculatory dysfunction was tentatively linked to chemotherapy in 30% of those affected. There was reduced libido, usually reversible, in 40 at the time of chemotherapy.

Reproductive system

A cumulative dose–response toxic effect of cisplatin affects gonadal function when the drug is used in children around puberty; this damage is reversible in girls, but not in boys (235).

Immunologic

Cisplatin can cause anaphylactic shock, asthma, or urticaria (236). Hypersensitivity reactions, probably of type I, have also been reported after the administration of cisplatin, carboplatin, and oxaliplatin (237–243). Life-threatening allergy to cisplatin has also been reported after 16 doses of cisplatin 20 mg/m^2/week (244). These allergic reactions can include respiratory dysfunction (for example wheezing, dyspnea), gastrointestinal discomfort (for example abdominal cramps, diarrhea), and rashes (for example pruritus, urticaria, facial erythema, and swelling). The risk of exfoliative dermatitis is very low. In most patients, the first signs of hypersensitivity reactions usually occurred after the administration of multiple intravenous courses containing platinum compounds. Whether patients who are hypersensitive to one platinum compound also react to another cannot be excluded, since some case reports have suggested possible cross-reactions among platinum compounds (245). Sometimes, successful retreatment may be feasible through premedication with glucocorticoids and antihistamines (240).

The frequency of carboplatin-induced hypersensitivity reactions is 2–9%. Of more than 200 patients 16 had allergic reactions to carboplatin (246). According to one retrospective analysis, mild carboplatin-related hypersensitivity reactions, with itching and mild erythema, occurred in 20 of 194 patients, whereas 12 patients developed severe forms of reactions, including diffuse erythroderma, rigor, facial swelling, throat and chest tightness, tachycardia, bronchospasm, and hypertension or hypotension (243). The most important interventive measures in patients with severe forms of hypersensitivity reactions include intravenous adrenaline, glucocorticoids, and antihistamines.

Severe anaphylaxis has been reported in five patients who had already received several cycles (5–12) containing oxaliplatin 100 mg/m^2 every 2 weeks (241). The predominant symptoms included reduced systolic blood pressure, flushing, sweating, headache, tachycardia, and respiratory distress. If retreatment with the causative platinum compound is required in such cases, premedication with a glucocorticoid and antihistamine may prevent recurrence. However, symptoms can occur despite premedication, making drug withdrawal necessary.

There was a 12% incidence rate of hypersensitivity reactions in 205 women who received carboplatin as part of their treatment for gynecological malignancies (247). In trying to characterize these reactions, the authors noted that in about half of the patients, the reaction developed after more than half of their carboplatin had been infused, with a median number of exposures to carboplatin of eight cycles before the reaction.

An effective carboplatin desensitization protocol has been reported in a child with hypersensitivity, allowing additional months of carboplatin treatment (248). After premedication with diphenhydramine, ranitidine, and methylprednisolone, eight dilutions of carboplatin (0.01–50.0 mg) were given intravenously at 15-minute intervals at a rate of 1 mg/minute. Subsequently, carboplatin 600 mg was given as a continuous infusion over 3 hours without adverse effects. Whether desensitization is generally suitable for overcoming allergic adverse events should be tested prospectively (249).

The term "oxaliplatin-induced hypersensitivity reaction" can refer to:

1. acuteneurosensory symptoms;
2. a cytokine release syndrome related to increased plasma concentrations of interleukin-6 and tumor necrosis factor alfa;
3. an immunological reaction involving antibody formation and histamine release (238).

In order to prove an underlying allergic disorder, an intradermal skin test with commercial formulations of the platinum compound in different concentrations (for example 0.003–1 mg/ml) can be done (250).

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Body temperature

Oxaliplatin is generally well tolerated. Some patients develop fever, which appears to be related to a transient increase in cytokines, particularly interleukin-6 and tumor necrosis factor alfa. In one study the oxaliplatin-induced increase in body temperature correlated with a marked increase in interleukin-6 serum concentrations (peak 133 pg/ml) (251). Interleukin-6 is a proinflammatory cytokine, which stimulates acute phase proteins and B lymphocytes. Premedication with metamizol, dexamethasone, and clarithromycin, which interferes with interleukin-6, did not prevent the fever. The roles of interleukin-6 and tumor necrosis factor alfa in the development of fever is strengthened by the observation that their serum concentrations fell during resolution of the fever (252).

Death

- Fatal acute tumor lysis syndrome has been reported in a 74-year-old woman who received cisplatin (50 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 by continuous infusion for 5 days) for vulvar carcinoma (253).

Whilst this is a well known complication of chemotherapy, particularly with hematological tumors, it is extremely rare as a complication of neoadjuvant chemotherapy for gynecological tumors.

Long-Term Effects

Tumorigenicity

There is some evidence that platinum compounds are mutagenic in bacteria and can cause chromosomal aberrations in animal cells in tissue culture (254). The risk of secondary leukemia in 28 971 patients with ovarian cancers receiving platinum-based chemotherapy has been evaluated; 96 developed a secondary leukemia (255). The authors concluded that the risk of developing a secondary leukemia while receiving a platinum-based protocol may be increased four-fold. The relative risks for carboplatin and cisplatin were estimated at 6.5 and 3.3 respectively. The relative risks of leukemia after cumulative doses of platinum of less than 500, 500–749, 750–999, and 1000 mg were 1.9, 2.1, 4.1, and 7.6 respectively. The delay between the start of platinum-containing chemotherapy and the occurrence of secondary malignancies was 2.8–7.7 years. In children who received an average cumulative dose of cisplatin of 600 mg/m^2, the estimated incidence of chemotherapy-induced leukemia was 1.5% (256). Concomitant radiation therapy or administration of other carcinogenic agents increases the risk.

Second-Generation Effects

Fertility

There is experimental evidence that several anticancer drugs can cause abnormalities of sperm chromosomes. Preliminary data have suggested that after platinum-containing chemotherapy for testicular cancer, penetration of oocytes can be severely impaired. Cytogenetic study of the spermatozoa has shown that many of the abnormalities correspond to structural aberrations that may not have a pathogenic effect in the production of abortions or children with chromosome abnormalities (257).

In men receiving chemotherapy, the sperm count will return to normal within 2 years of discontinuing chemotherapy in 78% of cases; however, intensive treatment, such as with doses of cisplatin in excess of 500 mg/m^2, reduces the probability of full recovery of normal spermatogenesis (258).

A Danish study group has reported a fertility problem of 53% in patients with unilateral germ cell tumors, but there was no significant difference between orchidectomy and cisplatin-based chemotherapy or subdiaphragmatic irradiation (259). Eight patients remained infertile despite evident recovery of spermatogenesis, and all 22 children conceived post-treatment were born normal and without malformations.

Gonadal function was evaluated in 59 men and 31 women after successful treatment of germ-cell tumors with the POMB/ACE regimen (cisplatin, vincristine, methotrexate, and bleomycin + dactinomycin, cyclophosphamide, and etoposide) (260). Most of the patients recovered fertility; 81% of the men who did not receive para-aortic radiotherapy, whose original tumor bulk was less than 5 cm in diameter, and whose duration of chemotherapy was less than 6 months recovered, compared with 32% who had larger tumors or who received longer courses of chemotherapy, or both. Fertility and pregnancies were undisturbed in 24 women with invasive trophoblastic tumors treated with methotrexate alone, with methotrexate and dactinomycin in combination, or with other combination chemotherapy (261). There were nine subsequent pregnancies, with the birth of eight healthy babies, and one woman requested a termination of pregnancy.

The long-term prognosis for sperm counts after chemotherapy with and without radiation in 71 males treated for non-Hodgkin's lymphoma on the CHOP-Bleomycin combination has been studied (262). Pelvic radiotherapy and cumulative cyclophosphamide dosages of greater than 9.5 g/m^2 are associated independently and in combination with a greater risk of permanent sterility.

Teratogenicity

Cisplatin and related compounds cross the placenta and can therefore cause fetal damage. Cisplatin is teratogenic in mice and embryotoxic in mice and rats. The platins should only be used during pregnancy in life-threatening situations. The patient should be informed of the potential hazard to the fetus (263).

Drug Administration

Drug administration route

There have been several reports of local neurotoxicity after intra-arterial cisplatin. In 63 patients pretreated with low-dose cisplatin given by arterial infusion for head and neck cancer (up to 25 mg/day for 1–10 days), before definitive local treatment, cranial nerve palsies developed on the same side as the cannulated artery in

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four cases (264). There was ipsilateral involvement of the 9th, 10th, 11th, and 12th cranial nerves in two patients, and the 7th and 12th nerves alone were affected in the other two patients. The palsies appeared at the end of treatment or up to 10 days later and only the 12th nerve palsy in one of the patients with multiple cranial nerve involvement recovered completely. In each patient, no other cause for paresis was found and CT scans showed that the nerves were not infiltrated by tumor. The cumulative dose of cisplatin administered to these four patients was less than that received by the unaffected 59 patients (median 200 mg, range 160–250; compared with 250 mg, range 160–400).

Drug overdose

Irreversible renal insufficiency has been described after accidental overdosage with cisplatin.

- In a 68-year-old woman who received an accidental overdose of cisplatin (480 mg), there was severe vomiting and myelosuppression, irreversible renal insufficiency, and deafness; other effects included seizures, hallucinations, loss of vision, and hepatotoxicity (265).

Drug–Drug Interactions

Antiepileptic drugs

Plasma concentrations of antiepileptic drugs (for example carbamazepine, valproic acid, phenytoin) should be measured more frequently during cisplatin-containing cancer chemotherapy (266,267).

- Cisplatin caused subtherapeutic carbamazepine and valproic acid concentrations in a 38-year-old woman with epilepsy undergoing cytotoxic cancer chemotherapy with doxorubicin and cisplatin, resulting in tonic-clonic seizures; the mechanism was not clear (266).

Etoposide

- A 52-year-old patient with glioblastoma developed severe ocular and orbital toxicity after receiving intracarotid etoposide phosphate and carboplatin (268). Acutely non-pupillary block angle-closure glaucoma developed secondary to uveal effusion in the ipsilateral eye. Four days later, severe orbital inflammation resulted in reduced visual acuity, proptosis, optic neuropathy, and total external ophthalmoplegia.

Fluorouracil

The combination of cisplatin 100 mg/m^2 with 5-fluorouracil 1000 mg/m^2 for 7 days caused angina and ischemic electrocardiographic changes, suggesting synergistic cardiotoxicity (269). There have also been cases of arterial occlusive events (270) and myocardial infarction (271,272), in some cases with evidence of coronary vascular spasm (273,274).

In 39 patients given low-dose continuous fluorouracil and cisplatin 20 mg/m^2/week for 8 weeks, there was a very low incidence of renal toxicity, although electrolyte abnormalities, particularly hyponatremia and hypomagnesemia, were as expected (244).

Irinotecan

The concomitant use of irinotecan as a 1-hour infusion immediately following a 2-hour infusion of oxaliplatin resulted in more severe hypersalivation and abdominal pain than irinotecan monotherapy (275). Acute intervention with atropine alleviated these adverse effects. When the drugs were separated by 1 day, the cholinergic symptoms were not exacerbated. The authors postulated that oxaliplatin might have some acetylcholinesterase inhibitory activity.

Lithium

Some data have suggested that cisplatin-containing chemotherapy can alter lithium clearance through impaired renal function, and lithium therapy should be closely monitored during treatment with cisplatin-containing regimens (276).

Mesna

Platinum agents are combined with ifosfamide in the treatment of cancer. The possibility that mesna may interfere with the anticancer effects of platinum agents has been investigated using cultured malignant glioma cells (277). Mesna protected tumor cell lines from the cytotoxic effect of the platinum agents. This in-vitro study emphasizes the importance of specifying in detail the infusion schedules of mesna and platinum agents.

Methotrexate

A patient with no other risk factors developed irreversible nephrotoxicity after four cycles of carboplatin 300 mg/m^2 and methotrexate 50 mg/m^2 (278). This appears to have been an additive effect of drugs that are not individually nephrotoxic until much higher doses.

Nephrotoxic drugs

Based on its considerable nephrotoxic potential, cisplatin should be given after, rather than before, other anticancer drugs and other drugs with a low therapeutic index (for example aminoglycoside antibiotics or bleomycin) that are primarily excreted in the urine in unchanged form. Concomitant use of potentially nephrotoxic agents (for example conventional amphotericin, tacrolimus) with cisplatin should be avoided (279,280).

Neurotoxic drugs

The concomitant or previous use of potentially neurotoxic drugs (for example paclitaxel, vinca alkaloids, or hexamethylmelamine) can increase the risk of peripheral neuropathy due to platinum compounds (68,69).

Paclitaxel

There is some evidence that there is a clinically significant pharmacokinetic interaction of paclitaxel with cisplatin. When cisplatin was given before paclitaxel, the clearance rate of paclitaxel was 25% less than when the two drugs were given in the opposite sequence. In consequence, neutropenia was more profound with the former schedule (281). In addition, in experimental studies, cytotoxicity increased when human ovarian carcinoma cells were

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exposed to paclitaxel before cisplatin, whereas the interaction was antagonistic when a 1-hour exposure to cisplatin was followed by a 20-hour exposure to taxol, or when the cells were exposed to cisplatin and taxol for 1 hour concurrently (282). The biochemical basis of this interaction has not been elucidated. The pharmacodynamic interaction may be related to cisplatin-induced alterations in cell-specific and non-specific binding sites for paclitaxel (283). In view of these results, paclitaxel should be given before cisplatin (284). There does not appear to be a similar interaction of paclitaxel with carboplatin (285).

Both cisplatin and paclitaxel are neurotoxic, the toxicity being dose-limiting and cumulative; neurotoxicity due to the combination has been suggested to be synergistic; after five cycles of chemotherapy, 96% of 44 patients had grade 1 toxicity and 52% grade 2 toxicity; 18% with grade 2 or 4 toxicity were withdrawn (286).

Vincristine

In 86 patients treated with cisplatin-based chemotherapy for testicular cancer, cumulative exposure (over 400 mg/m^2) and a previous history of noise exposure were significant susceptibility factors for irreversible ototoxicity; high doses of vincristine (greater than 6 mg/m^2) significantly increased the risk of reversible ototoxicity (287).

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Pneumocandins

General Information

The pneumocandins are a class of anti-*Pneumocystis* agents, thought to act by inhibiting the synthesis of beta-1,3-glucan, a component of the *Pneumocystis jiroveci* cyst wall. Chemical modification of the poorly water-soluble pneumocandins resulted in L-693,989, which can be given by aerosol. In rats, this compound prevents *P. jiroveci* pneumonia after daily or weekly administration, without evidence of toxicity. Since there is no counterpart for beta-1,3-glucan synthesis in humans, there are no obvious reasons to suspect mechanism-based toxicity with this class of compounds. More effective compounds are being studied (1).

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Pneumococcal vaccine

See also Vaccines

General Information

Two types of pneumococcal vaccine are available, polysaccharide vaccine and conjugated polysaccharide vaccine.

Pneumococcal vaccine is composed of a saline solution containing the purified capsular polysaccharides of 23 types of *Streptococcus pneumoniae*. The improved 23-valent vaccine, which replaced a 14-valent vaccine at the beginning of the 1980s, contains antigens to pneumococcal types that are responsible for about 85% of bacteremic pneumococcal pneumonia.

Pneumococcal vaccines produced by different manufacturers are currently available, for example "Pneumovax 23" produced by Merck Sharp & Dohme and "Pnu-Imune 23" produced by Lederle Laboratories. Each vaccine dose (0.5 ml) contains 25 μg of each polysaccharide antigen. Immunization is recommended for people who are at increased risk of developing pneumococcal disease because of underlying chronic health conditions and for older people. About 50% of vaccinees develop mild adverse effects, such as erythema and pain at the injection site. Fever, myalgia, and severe local reactions have been reported in under 1% of vaccinees. Severe systemic reactions, such as anaphylaxis have been rarely reported.

Incidental case reports relate to small vessel vasculitis after combined pneumococcal-influenza immunization (1), severe febrile reactions with leukocytosis (2), Sweet's syndrome (3), thrombocytopenia (4,5), and keratoacanthoma at the injection site (6).

Patients with AIDS have an impaired antibody response to pneumococcal vaccine. Adverse effects in symptomatic and asymptomatic HIV-infected vaccinees were not different from those in HIV-negative persons (7).

Note on abbreviations

DtaP = Diphtheria + tetanus toxoids + acellular pertussis
DTwP = Diphtheria + tetanus toxoids + whole cell pertussis
Hib = *Haemophilus influenzae* type b
OPV = oral poliovirus vaccine
PPV = pneumococcal polysaccharide vaccine

Pneumococcal polysaccharide vaccine

The question of whether revaccination with 23-valent pneumococcal polysaccharide vaccine (PPV) at least 5 years after the first vaccination is associated with more frequent or more serious adverse events than those after the first vaccination has been studied in patients aged 50–74 years who had never been vaccinated with PPV ($n = 901$) or who had been vaccinated once at least 5 years before enrolment ($n = 513$) (8). After one dose of PPV, local injection site reactions and prevaccination concentrations of type-specific antibodies were measured. Those who were re-vaccinated were more likely than those who received their first vaccinations to report a local injection site reaction of at least 10.2 cm (4 in.) in diameter within 2 days of vaccination (55/513 versus 29/901, or 11 versus 3%). The reactions resolved by a median of 3 days after vaccination. The highest rate was among revaccinated patients who were immune competent and did not have chronic illnesses: 15% (33/228) compared with 3% (10/337) among comparable patients receiving their first vaccinations. The risk of these local reactions correlated significantly with prevaccination geometric mean antibody concentrations. The authors concluded that physicians and patients should be aware that self-limited local injection site reactions occur more often after revaccination compared with a first vaccination; however, this risk does not represent a contraindication to revaccination with PPV in recommended patients.

Pneumococcal conjugated polysaccharide vaccines

Pneumococcal polysaccharides are not immunogenic in infants, but improved immunogenicity of polysaccharide-protein conjugates has been demonstrated. One of the major problems in developing a successful vaccine against *S. pneumoniae* is the large number of different serotypes involved. More than 83 serotypes of the bacterium are known to cause disease, although about 10 of these account for up to 70% of disease in young children. The frequency of the serotypes can vary from year to year, from one age group to another, and on a geographical basis. Various conjugated vaccines that include different serotype variations are already licensed (the heptavalent conjugated vaccine Prevnar/Prevenar), under development or undergoing clinical trial (9- and 11-valent

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conjugated vaccines). If the vaccines prove to be successful, it is estimated that their use could reduce child deaths from pneumococcal pneumonia by up to 25%, saving over 250 000 lives a year worldwide. The development of conjugate pneumococcal vaccines has also been driven by the high incidence of inner ear infections and the severity of meningitis due to *S. pneumoniae* in industrialized countries. The results of some clinical trials with different vaccines of this type have been reviewed (SEDA-22, 344).

The immunogenicity of 7-valent pneumococcal-conjugate vaccine plus 23-valent pneumococcal vaccine in 11 children has been compared with the immunogenicity of 23-valent vaccine alone in 12 children up to 2 years of age with sickle cell disease (9). IgG pneumococcal antibody concentrations were higher with combined administration, with no increase in adverse effects after immunization with 23-valent vaccine.

In 2000, the first heptavalent conjugated pneumococcal vaccine, Prevnar, which contains polysaccharides of pneumococcal serotypes 4, 6B, 9V, 14, 19F, and 23F, and oligosaccharide of serotype 18C, conjugated to the protein carrier CRM 197 (non-toxic variant of diphtheria toxin), was licensed in the USA (covering 90% of pneumococcal serotypes found in young children in the USA) and in all EU member states, as well as in selected other countries in 2001. In a randomized, double-blind study, 302 healthy infants in the Northern California Kaiser Permanente Health Plan received either the pneumococcal vaccine or meningococcal group C conjugate vaccine as a control at 2, 4, and 6 months of age and a booster at 12–15 months of age (10). The immunogenicity and safety of simultaneous administration of vaccines used in the routine immunization program of children (DTwP or DTaP, Hib and OPV or hepatitis B vaccine) were also evaluated. Local reactions after pneumococcal, DTwP-Hib, and DTaP plus Hib vaccine were statistically less severe at the pneumococcal vaccine site than at the DTwP-Hib sites (Table 1). There were 12 emergency room visits and 8 hospitalizations that occurred soon after immunization (otitis, febrile illness, urinary tract infection, burns), but none was thought to be related to the vaccine. One hypotensive-hyporesponsive episode 15 minutes after pneumococcal vaccine, DTwP-Hib/HB, and OPV, with complete recovery within 1 hour, was considered to have been vaccine-related. After the booster dose of pneumococcal vaccine, the geometric mean titers of all seven serotypes increased significantly (compared with the values after dose 3 and before dose 4) to antibodies considered as protective. When vaccine was administered at the same time as the booster dose of DTaP and Hib vaccines, there were lower antibody titers for some of the antigens than the antibody response when the pneumococcal vaccine was given separately. Because the geometric mean titers of the booster responses were all generally high and all subjects achieved similar percentages above predefined antibody titers, these differences were considered to be probably not clinically significant. Summarizing their results the authors concluded that the pneumococcal vaccine was safe and immunogenic.

Table 1 Local reactions within 48 hours of injection in infants given conjugated pneumococcal, DTwP-Hib, and DtaP + Hib vaccines

Reaction	Number of children	Infants		Toddlers
		Pneumococcal vaccine (%)	DTwP-Hib (%)	DtaP + Hib (%)
Redness				
Dose 1	183	17	18	
Dose 2	159	18	29	
Dose 3	160	16	22	
Dose 4	110	9.1		6.1
Swelling				
Dose 1	183	10	19	
Dose 2	159	11	20	
Dose 3	160	9.0	21	
Dose 4	110	6.4		3.7
Tenderness				
Dose 1	183	24	27	
Dose 2	159	21	26	
Dose 3	160	23	28	
Dose 4	110	16		9.8

A comprehensive technical overview on the epidemiology and prevention of pneumococcal disease, including the use of polysaccharide and conjugate vaccines has been provided (11).

Further results of field trials on the efficacy, safety, and immunogenicity of heptavalent conjugated pneumococcal vaccine have appeared. Between October 1995 and August 1998, 37 868 infants were included in a double-blind trial (12). At 2, 4, 6, and 12–15 months of age they were randomly assigned to receive either the pneumococcal conjugate vaccine or meningococcal conjugate vaccine. More than 95% of pneumococcal vaccine recipients developed = 0.15 μg/ml antibodies against all serotypes included in the vaccine. As of April 1999, a vaccine efficacy of 97% (prevention of invasive pneumococcal disease caused by vaccine serotypes) was calculated; in addition, there was a significant impact on otitis media. Data on reactogenicity of the conjugate pneumococcal and meningococcal vaccines are provided in Table 2 and Table 3. Local reactions were analysed separately for children who had received DTaP and DTwP vaccine simultaneously. Local and systemic reactions were generally relatively mild with either vaccine, and more severe local and systemic reactions were uncommon and self-limiting. There were significant differences in outpatient clinic visits for seizures (11 pneumococcal vaccine recipients versus 23 controls), but none of the subcategories of seizure (febrile seizures, epilepsy, afebrile seizures) was significantly different. There were four cases of sudden infant death syndrome (SIDS) (0.2/1000) in the pneumococcal vaccine group and eight in the controls (0.4/1000). This rate is similar to the rate of 0.5/1000 children observed in the general infant population of California.

Recent advances in conjugated pneumococcal vaccines selected from current literature have been reviewed, including studies with experimental tetravalent and pentavalent conjugated vaccines and vaccines conjugated to various proteins (13).

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Table 2 Local reactions comparing pneumococcal conjugate (PNCRM7) and meningococcal conjugate (MnCC) as well as each of these with DtaP

Reaction	PNCRM7 (%)	DTaP (%)	P value	MnCC (%)	DtaP (%)	P value	PNCRM7 versus MnCC (P value)
Redness							
Dose 1	10	6.7	<0.001	6.5	5.6	0.345	0.124
Dose 2	12	11	0.512	7.6	11	0.011	0.003
Dose 3	14	11	0.143	9.3	8.2	0.557	0.011
Dose 4	11	3	0.004	4.5	4.0	0.999	0.226
Redness >3 cm							
Dose 1	0.3	0.0	0.500	0.1	0.3		0.999
Dose 2	0.0	0.2	0.999	0.2	0.4	0.999	0.481
Dose 3	0.2	0.2		1.3	0.8	0.999	0.105
Dose 4	0.6	0.6	0.999	0.0	0.0	0.625	0.255
Swelling							
Dose 1	9.8	6.6	0.002	4.2	4.3	0.999	0.013
Dose 2	12	11	0.312	5.1	7.4	0.080	0.001
Dose 3	10	10	0.999	6.9	8.3	0.473	0.001
Dose 4	12	5.5	0.013	4.5	3.4	0.688	0.247
Swelling >3 cm							
Dose 1	0.1	0.1		0.0	0.0		0.999
Dose 2	0.4	0.6	0.999	0.2	0.0	0.999	0.999
Dose 3	0.5	1.0	0.500	0.3	0.5	0.999	0.999
Dose 4	0.6	0.6	0.999	0.0	0.0		0.224
Tenderness							
Dose 1	18	16	0.053	18	19	0.265	0.970
Dose 2	19	17	0.080	15	16	0.677	0.069
Dose 3	15	13	0.265	12	12	0.999	0.280
Dose 4	23	18	0.096	15	15	0.999	0.052

Table 3 Fever within 48 hours of vaccination among infants receiving PNCRM7 or MnCC vaccine*

Reaction	PNCRM7		MnCC		P value
	%	Number	%	Number	
Fever ≥38°C					
Dose 1	15	709	9.4	710	0.001
Dose 2	24	556	11	507	0.001
Dose 3	19	461	12	414	0.003
Dose 4	21	224	17	230	0.274
Fever >39°C					
Dose 1	0.9	709	0.3	710	0.178
Dose 2	2.5	556	0.8	507	0.029
Dose 3	1.7	461	0.7	414	0.180
Dose 4	1.3	224	1.7	230	0.999

*Concomitantly with DTaP and other recommended vaccines; MnCC, meningococcal conjugate.

23-valent pneumococcal polysaccharide vaccine

The efficacy of polysaccharide vaccine in preventing invasive pneumococcal disease, pneumonia, and death has been assessed in a double-blind, randomized, placebo-controlled trial in 1392 HIV1-infected adults in Uganda (14). The vaccine was well tolerated. However, it was ineffective and is not recommended for use in HIV1-infected individuals. Reassessment of recommendations for polysaccharide vaccine immunization may be necessary in some countries. The authors suggested that the vaccine causes destruction of polysaccharide-responsive B cell clones.

In another clinical trial the immunogenicity and safety of polysaccharide vaccine has been assessed in 21 renal transplant recipients (15). Protective antibody titers were reached at 6 and 12 weeks after immunization in all recipients, bar one. No local or systemic adverse effects were observed.

Organs and Systems

Immunologic

Arthus reactions and systemic reactions have commonly been reported after booster doses of polysaccharide vaccine and are thought to result from antigen–antibody reactions involving antibodies induced by the previous immunization (16). Data on revaccination of children are not yet sufficient to provide a basis for recommendation.

An allergic reaction has been described to 23-valent polysaccharide pneumococcal vaccine (17).

- A 2-year-old child developed bronchospasm and cutaneous and laryngeal edema immediately after the injection of a 23-valent polysaccharide pneumococcal vaccine. The symptoms resolved within 1 hour of treatment with antihistamines, glucocorticoids, and aerosols. Skin tests and specific IgE tests showed that the pneumococcal antigens were responsible for the anaphylaxis.

Susceptibility Factors

Age

In an evaluation of simultaneous immunization in 85 elderly subjects, pre-immunization pneumococcal antibodies were

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associated with more reactions, both local and systemic, after vaccination (18). A rise in temperature (9% of vaccinees), and pain at the injection site (5% of vaccinees) were significantly associated with raised preimmunization pneumococcal polysaccharide antibody concentrations.

Other features of the patient

The immunogenicity and safety of pneumococcal polysaccharide vaccine have been studied in renal allograft recipients, dialysis patients (19), children and adolescents with sickle-cell anemia (SED-11, 682) (SEDA-12, 277), people with diabetes mellitus (SED-11, 682), and children with nephrotic syndrome (20). When comparing the results with healthy persons there were no significant differences.

The problems connected with pneumococcal disease and its prevention in HIV-infected individuals have been reviewed (21). Pneumococcal disease occurs significantly more often in HIV-infected individuals, with pneumococcal pneumonia rates 5.5–17.5 times greater than population-based estimates in the USA, and the increasing rate of penicillin-resistant strains of *S. pneumoniae* highlight the need for improved prevention strategies. Studies of pneumococcal disease in HIV infection have repeatedly shown that over 85% of the isolates from bacteremic patients, in both the USA and Africa, are of serotypes included in the 23-valent vaccine. However, the proportion of HIV-positive individuals who respond to 23-valent pneumococcal polysaccharide vaccine has been shown in some but not all studies to be slightly reduced compared with age-matched controls but comparable to other high-risk groups, such as elderly people, in whom clinical efficacy has been established. Some studies have suggested a trend toward a lower response rate as the CD4 cell count falls. The reason for concern about the safety of pneumococcal immunization in HIV-infected individuals is the reported association between immunization and increasing HIV virus load.

Much of this concern arises from extrapolation from published data on influenza immunization. However, there are some data on pneumococcal immunization alone. In 32 HIV-positive patients with a median CD4 cell count of 242×10^6/l, who received Pneumovax and tetanus toxoid there was no change in plasma HIV-1 RNA at 20–56 days after immunization (22). In contrast there were marked increases in plasma viral RNA (1.6–586 times) reported in 12 asymptomatic HIV-positive individuals (mean CD4 cell count 374×10^6/l). More recently, a study of patients with more advanced disease found that HIV-1 RNA and DNA were unaffected by either conjugate or polysaccharide pneumococcal vaccine up to 309 days after immunization (23). In summary, the authors of the review (21) recommended that HIV-infected individuals be immunized with pneumococcal vaccine and that immunization should be carried out as early as possible in the course of HIV infection.

Drug–Drug Interactions

Influenza vaccine

In a study of the interaction between 23-valent pneumococcal polysaccharide vaccine and influenza vaccine, 152 adults with chronic respiratory disease were randomized to receive both vaccines either simultaneously or at an interval of 1 month (24). There were no significant differences in serological responses between the groups. The incidence and severity of both local and systemic adverse effects were also similar: there were mild local reactions in 38 and 36% and systemic reactions in five and three of the vaccinees respectively.

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Poaceae

See also Herbal medicines

General Information

The genera in the family of Poaceae (Table 1) include bamboo, barley, cane, fescue, lawn grass, oats, pappus, and rice.

Anthoxanthum odoratum

Anthoxanthum odoratum (sweet vernal grass) contains anticoagulant coumarins, which cause bleeding in cattle that consume the grass.

Adverse effects

In 125 Turkish patients with rhinitis and/or symptoms of asthma reactivity to *Dermatophagoides* as an indoor

Table 1 The genera of Poaceae

Achnatherum (needle grass)
Achnella (rice grass)
Acrachne (goose grass)
Aegilops (goat grass)
Aegopogon (relax grass)
Agropyron (wheat grass)
Agropogon (agropogon)
Agrostis (bent grass)
Aira (hair grass)
Allolepis (Texas salt)
Alloteropsis (summer grass)
Alopecurus (foxtail)
Ammophila (beach grass)
Ampelodesmos (Mauritanian grass)
Amphicarpum (maidencane)
Amphibromus (wallaby grass)
Andropogon (blue stem)
Anthaenantia (silky scale)
Anthephora (oldfield grass)
Anthoxanthum (vernal grass)
Apera (silkybent)
Apluda (Mauritian grass)
Arctagrostis (polar grass)
Arctophila (pendant grass)
Aristida (three awn)
Arrhenatherum (oat grass)
Arthraxon (carp grass)
Arthrostylidium (climbing bamboo)
Arundinaria (cane)
Arundinella (rabo de gato)
Arundo (giant reed)
Avena (oat)
Axonopus (carpet grass)

Bambusa (bamboo)
Beckmannia (slough grass)
Blepharidachne (desert grass)
Blepharoneuron (drop seed)
Bothriochloa (beard grass)
Bouteloua (grama)
Brachiaria (signal grass)
Brachyelytrum (short husk)
Brachypodium (false brome)
Briza (quaking grass)
Bromus (brome)
Buchloe (buffalo grass)

Calamagrostis (reed grass)
Calamovilfa (sand reed)
Calammophila (calammophila)
Catabrosa (whorl grass)
Cathestecum (false grama)
Cenchrus (sandbur)
Chasmanthium (wood oats)
Chloris (windmill grass)
Chrysopogon (false beard grass)
Chusquea (chusquea bamboo)
Cinna (wood reed)
Cladoraphis (bristly love grass)
Coelorachis (joint tail grass)
Coix (Job's tears)
Coleanthus (moss grass)
Cortaderia (pampas grass)
Corynephorus (club awn grass)
Cottea (cotta grass)
Crypsis (prickle grass)
Ctenium (toothache grass)

Continued

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Table 1 Continued

Cutandia (Memphis grass)
Cymbopogon (lemon grass)
Cynodon (Bermuda grass)
Cynosurus (dogstail grass)

Dactylis (orchard grass)
Dactyloctenium (crowfoot grass)
Danthonia (oat grass)
Dasyochloa (woolly grass)
Dasypyrum (mosquito grass)
Deschampsia (hair grass)
Desmazeria (fern grass)
Diarrhena (beak grain)
Dichanthelium (rosette grass)
Dichanthium (blue stem)
Dichelachne (plume grass)
Diectomis (folded leaf grass)
Digitaria (crab grass)
Dinebra (viper grass)
Dissanthelium (Catalina grass)
Dissochondrus (false brittle grass)
Distichlis (salt grass)
Dupontia (tundra grass)

Echinochloa (cockspur grass)
Ehrharta (veldt grass)
Eleusine (goose grass)
Elionurus (balsam scale grass)
Elyhordeum (barley)
Elyleymus (wild rye)
Elymus (wild rye)
Enneapogon (feather pappus grass)
Enteropogon (umbrella grass)
Entolasia (entolasia)
Eragrostis (love grass)
Eremochloa (centipede grass)
Eremopyrum (false wheat grass)
Eriochloa (cup grass)
Eriochrysis (moco de pavo)
Erioneuron (woolly grass)
Euclasta (mock bluestem)
Eustachys (finger grass)

Festuca (fescue)
Fingerhuthia (Zulu fescue)

Garnotia (lawn grass)
Gastridium (nit grass)
Gaudinia (fragile oat)
Glyceria (manna grass)
Gymnopogon (skeleton grass)
Gynerium (wild cane)

Hackelochloa (pitscale grass)
Hainardia (barb grass)
Helictotrichon (alpine oat grass)
Hemarthria (joint grass)
Hesperostipa (needle and thread)
Heteropogon (tanglehead)
Hierochloe (sweet grass)
Hilaria (curly mesquite)
Holcus (velvet grass)
Hordeum (barley)
Hymenachne (marsh grass)
Hyparrhenia (thatching grass)
Hypogynium (West Indian bluestem)

Ichnanthus (bed grass)
Imperata (satin tail)
Isachne (blood grass)
Ischaemum (muraina grass)
Ixophorus (Central America grass)

Jarava (rice grass)

Karroochloa (South African oat grass)
Koeleria (June grass)

Lagurus (hare's tail grass)
Lamarckia (goldentop grass)
Lasiacis (small cane)
Leersia (cut grass)
Leptochloa (sprangle top)
Leptochloopsis (limestone grass)
Leptocoryphium (lanilla)
Lepturus (thin tail)
Leucopoa (spike fescue)
Leymus (wild rye)
Limnodea (Ozark grass)
Lithachne (diente de perro)
Lolium (rye grass)
Luziola (water grass)
Lycurus (wolf's tail)

Melica (melic grass)
Melinis (stink grass)
Mibora (sand grass)
Microchloa (small grass)
Microstegium (brown top)
Milium (millet grass)
Miscanthus (silver grass)
Molinia (moor grass)
Monanthochloe (shore grass)
Monroa (false buffalo grass)
Muhlenbergia (muhly)

Nardus (mat grass)
Nassella (tussock grass)
Neeragrostis (creeping love grass)
Neostapfia (Colusa grass)
Neyraudia (neyraudia)

Olyra (carrycillo)
Opizia (opizia)
Oplismenus (basket grass)
Orcuttia (Orcutt grass)
Oryza (rice)
Oryzopsis (rice grass)

Panicum (panic grass)
Pappophorum (pappus grass)
Parapholis (sickle grass)
Pascopyrum (wheat grass)
Paspalidium (watercrown grass)
Paspalum (crown grass)
Pennisetum (fountain grass)
Phalaris (canary grass)
Phanopyrum (savannah panic grass)
Pharus (stalk grass)
Phippsia (ice grass)
Phleum (timothy)
Phragmites (reed)
Phyllostachys (bamboo)
Piptatherum (rice grass)
Piptochaetium (spear grass)
Pleuraphis (galleta grass)
Pleuropogon (semaphore grass)
Poa (blue grass)
Polypogon (rabbit's foot grass)
Polytrias (Java grass)
Psathyrostachys (wild rye)
Pseudoroegneria (wheat grass)

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Pseudelymus
(foxtail wheat grass)
Pseudosasa (arrow bamboo)
Ptilagrostis (false needle grass)
Puccinellia (alkali grass)

Redfieldia (blowout grass)
Reimarochloa (reimar grass)
Rostraria (hair grass)
Rottboellia (itch grass)
Rytidosperma (wallaby grass)

Saccharum (sugar cane)
Sacciolepis (cupscale grass)
Sasa (broad leaf bamboo)
Schedonnardus (tumble grass)
Schismus (Mediterranean grass)
Schizachne (false melic)
Schizachyrium (little bluestem)
Schizostachyum
(Polynesian 'ohe)
Sclerochloa (hard grass)
Scleropogon (burro grass)
Scolochloa (river grass)
Scribneria (Scribner's grass)
Secale (rye)
Setaria (bristle grass)
Sinocalamus (wide leaf bamboo)
Sorghastrum (Indian grass)
Sorghum (sorghum)
Spartina (cord grass)
Sphenopholis (wedge scale)
Sporobolus (drop seed)
Steinchisma (gaping grass)
Stenotaphrum (St. Augustine grass)
Swallenia (dune grass)

Taeniatherum (Medusa head)
Themeda (kangaroo grass)
Thinopyrum (wheat grass)
Thuarea (Kuroiwa grass)
Torreyochloa
(false manna grass)
Trachypogon (crinkle awn grass)
Tragus (burr grass)
Trichoneura (Silveus' grass)
Tridens (tridens)
Triplasis (sand grass)
Tripogon (five minute grass)
Tripsacum (gama grass)
Trisetum (oat grass)
Triticum (wheat)
Tuctoria (spiral grass)

Uniola (sea oats)
Urochloa (signal grass)

Vahlodea (hair grass)
Vaseyochloa (Texas grass)
Ventenata (North Africa grass)
Vetiveria (vetiver grass)
Vulpia (fescue)

Willkommia (willkommia)

Zea (corn)
Zizania (wild rice)
Zizaniopsis (cut grass)
Zoysia (lawn grass)

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allergen was 50% ($n = 63$); in pollen allergic patients ($n = 100$) sensitivity to Poaceae was the most common (69%), and among them positivity to *A. odoratum* was 45% (1). Sensitivity to grass pollen was the same in patients from urban and rural areas (72 versus 71%).

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Podophyllum derivatives

General Information

Podophyllum is a powerful skin irritant and antimitotic agent, widely used in the topical treatment of condylomata acuminata. The anticancer topoisomerase inhibitors, tenoposide and etoposide, are podophyllotoxins.

The signs and symptoms of systemic toxicity (1,2) (SED-9, 240) include:

- cyanosis, tachycardia, electrocardiographic changes;
- stertorous respiration;
- polyneuritis, ataxia, coma, agitation, delirium, confusion, lethargy, muscular weakness, paresthesia;
- leukopenia, leukocytosis, thrombocytopenia, anemia;
- nausea, vomiting, abdominal pain, paralytic ileus;
- raised liver enzymes;
- oliguria, anuria, hematuria;
- urticaria;
- fever.

Intrauterine death and teratogenicity have not been demonstrated convincingly.

Podophyllum emodi (Indian podophyllum)

Proresid (mitopodozide), a mixture of more than 20 derivatives of *Podophyllum emodi*, has been used for many years in some countries as a disease-modifying agent in rheumatoid arthritis. A microtubulin antagonist, it is comparable with colchicine and griseofulvin. Its use has been limited because treatment is often complicated by severe diarrhea, abdominal pain, nausea, and vomiting. Leukopenia and thrombocytopenia have been reported (3,4).

Etoposide and teniposide are semisynthetic derivatives of podophyllin, which was originally isolated from the root of the Indian podophyllum plant. They inhibit topoisomerase II and are dealt with in a separate monograph.

Podophyllum peltatum (American mandrake)

The resin prepared from the dried rhizome and roots of *Podophyllum peltatum* contains podophyllotoxin, α-peltatin, and β-peltatin. When applied topically, it is a strong irritant to the skin and mucous membranes and can lead to poisoning because of systemic absorption. When taken by mouth, it has a drastic laxative action and produces violent peristalsis. Ingestion of large doses can result in

severe neuropathic toxicity (SEDA-11, 426). The oral and local use of the resin should be avoided during pregnancy, as this has been associated with teratogenicity and fetal death.

- A 31-year-old man took an unknown amount of *Podophyllum peltatum*, thinking it to be *Mandragora officinarum*; he developed severe nausea and vomiting and recovered uneventfully (5).

Dysosma pleianthum (bajiaolian)

Dysosma pleianthum (bajiaolian), a species of mayapple, has been widely used for thousands of years in China as a general remedy and for the treatment of snake bite, weakness, condyloma acuminata, lymphadenopathy, and tumors. Podophyllotoxin is one of its main ingredients. Five people who drank infusions of bajiaolian developed nausea, vomiting, diarrhea, abdominal pain, thrombocytopenia, leukopenia, abnormal liver function tests, sensory ataxia, altered consciousness, and persistent peripheral tingling or numbness (6).

Long-Term Effects

Tumorigenicity

Etoposide and teniposide are prominent causes of secondary malignancies, particularly secondary myeloid and lymphoid leukemias. The risk appears to be related to both the schedule and the cumulative dose, and it may be aggravated by addition of alkylating agents and/or radiotherapy (7,8). There are differences between the chromosomal abnormalities and the subsequent acute myeloid leukemia associated with the alkylating agents and those following topoisomerase inhibition by epipodophyllotoxins (9). The alkylating agents cause abnormalities of chromosomes five and seven, singly or together, and the epipodophyllotoxins damage the 11q23 chromosome locus (10).

Second-Generation Effects

Teratogenicity

Podophyllum is likely to be teratogenic (11,12) because of its effects on topoisomerase.

- A woman who applied podophyllum resin five times for a duration of 4 hours from the 23rd to the 29th week of pregnancy gave birth to a child with a simian crease on the left hand and a preauricular skin tag (11).

Drug Administration

Drug overdose

Fatal podophyllum toxicity has been reported.

- When a 59-year-old man took 10 g of podophyllum in a fatal suicide attempt he did not develop symptoms until 10 hours later, with loss of reflexes, coma, and marked lactic acidosis; there were nuclear and cytoplasmic changes in circulating leukocytes (1). Despite hemoperfusion, he died after 39 hours.

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Poldine methylsulfate

General Information

Poldine methylsulfate is an anticholinergic drug that has been used to reduce gastric acid secretion in patients with peptic ulceration (1) and has been administered by iontophoresis in the treatment of palmar and plantar hyperhidrosis (2). Its adverse effects are those expected of an anticholinergic drug.

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Poliomyelitis vaccine

See also Vaccines

Note on abbreviations

DTP = Diphtheria + tetanus toxoids + pertussis
DtaP = Diphtheria + tetanus toxoids + acellular pertussis
Hib = *Haemophilus influenzae* type b
IPV = inactivated poliomyelitis vaccine
OPV = oral poliovirus vaccine
PRP-T-Hib = conjugated Hib vaccine (tetanus toxoid linked to Hib capsular polysaccharide)

General Information

There are two types of poliomyelitis vaccines available. One is prepared from polioviruses that as a rule have been inactivated by formaldehyde. Inactivated poliomyelitis vaccine (IPV) is given parenterally. The second group of polio vaccines comprises attenuated strains of live polioviruses (oral poliomyelitis vaccine, OPV), which are given orally; these live vaccines are the most widely used.

Inactivated poliomyelitis vaccine

Inactivated poliomyelitis vaccine produced by improvements in manufacturing technology (potency-enhanced IPV-eIPV was licensed in 1987) is used for routine immunization in an increasing number of countries (for example in Finland, France, Germany, Iceland, the Netherlands, Norway, Sweden, and certain provinces of Canada) and is recommended in other countries for certain specific purposes, for example for persons with underlying immunological disorders or non-immunized adults exposed to high risk. A few countries (for example Denmark, Hungary, Italy, Lithuania, and Israel) use a mixed schedule, starting primary immunization with IPV followed by OPV.

The US 2000 childhood immunization schedule, proposed by the Advisory Committee of Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians, recommended an all-IPV schedule for routine use in the USA, aimed at the elimination of the rare vaccine-associated paralytic poliomyelitis (1). Since 1 January 2000, all children have received four doses of IPV at ages 2 months, 4 months, 6–18 months, and 4–6 years.

Some other industrialized countries that use OPV in their routine immunization programs, and which had no wild poliomyelitis cases for many years but some vaccine-associated poliomyelitis, are reassessing their immunization strategy. They are considering new concepts of shifting from OPV to IPV or from OPV to mixed schedules. This change could help to prevent vaccine-associated poliomyelitis mostly occurring after the first dose of OPV immunization.

Serious adverse effects after IPV immunization have not been documented (2). Because IPV contains streptomycin and neomycin, there is a possibility of allergic reactions in those who are sensitive to these antibiotics. Although it has been postulated that IPV, like some viral infections, might trigger Guillain–Barré syndrome, there is inadequate evidence to accept or reject such an association (3); in this respect it may differ from the oral vaccine.

Oral polio vaccine

In contrast to IPV, OPV causes important problems, including vaccine-associated polio and prolonged polio virus excretion.

Combination vaccines

The safety, immunogenicity, and lot consistency of five-component pertussis combination vaccine (DtaP + IPV + PRP-T-Hib) in infants have been compared to those of a whole-cell pertussis combination vaccine (DTwP + IPV + PRP-T-Hib), as have separate and combined injections of DTP + IPV and Hib. The combination vaccine DtaP + IPV + Hib were comparable or superior regarding safety and immunogenicity to the combination vaccine containing the whole cell pertussis component. There was no interaction between acellular pertussis and PRP-T-Hib, a feature that distinguishes this combination vaccine from some others, which depress anti-PRP responses. The combination vaccine DtaP + IPV + Hib produced significantly lower rates of local and systemic reactions than did the combination vaccine containing the whole-cell pertussis component. Local reactions, such as redness, swelling, and tenderness occurred two to three times more often after combination vaccine containing whole cell pertussis than after combination vaccines with acellular pertussis components. Fever was three times more common after whole cell combination vaccine. Fever over 40°C was rare in all vaccinees, because of the use of paracetamol prophylaxis. Systemic reactions, such as fussiness, crying, reduced activity, and anorexia, were about twice as frequent with whole cell vaccine as with acellular pertussis vaccine. Both local and systemic reactions persisted longer after whole cell vaccine than after acellular pertussis vaccine. There were no significant differences between reaction rates among infants given DtaP + IPV vaccine combined with PRP-T-Hib vaccine in the same syringe compared with those given separate injections, except for local redness after the first dose (4).

Hexavalent immunization

The Hexavalent Study Group has compared the immunogenicity and safety of a new liquid hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and *Haemophilus influenzae* type b (DTP + IPV + HB + Hib vaccine, manufactured by Aventis Pasteur MSD, Lyon, France) with two reference vaccines, the pentavalent DTP + IPV + Hib vaccine and the monovalent hepatitis B vaccine, administrated separately at the same visit (5). Infants were randomized to receive either the hexavalent vaccine ($n = 423$) or (administered at different local sites) the pentavalent and the HB vaccine ($n = 425$) at 2, 4, and 6 months of age. The hexavalent vaccine was well tolerated (for details see the monograph on Pertussis vaccines). At least one local reaction was reported in 20% of injections with hexavalent vaccine compared with 16% after the receipt of pentavalent vaccine or 3.8% after the receipt

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of hepatitis B vaccine. These reactions were generally mild and transient. At least one systemic reaction was reported in 46% of injections with hexavalent vaccine, whereas the respective rate for the recipients of pentavalent and HB vaccine was 42%. No vaccine-related serious adverse event occurred during the study. The hexavalent vaccine provided immune responses adequate for protection against the six diseases.

Polio vaccines as a possible cause of AIDS

There is a hypothesis that the HIV virus might have jumped the species barrier from monkey to people via a contaminated polio vaccine because the vaccine was manufactured in primary monkey kidney tissue known to be sometimes contaminated with monkey viruses. The existing evidence, including tests of poliovirus seed stocks, more than 20 vaccine lots, and serum samples from vaccine recipients makes this hypothesis highly improbable (6,7).

Contamination of polio vaccines with simian papovavirus 40 (SV40)

The problem of early polio vaccines produced in the 1950s and early 1960s, and, in some instances, contaminated with the monkey virus SV40 (simian virus 40) has been discussed (8). From 1954 to 1962, millions of people were immunized with polio vaccines, which during that period contained SV40 as an unrecognized contaminant. Some studies sought to investigate possible causation between the receipt of the vaccine and the development of tumors. The results were not convincing (SEDA-15, 355) (SED-12,821). At a workshop in 1997 some of the scientific questions concerned were again considered (9). The presentations by polio vaccine manufacturers and the UK National Institute for Biological Standards and Control provided convincing evidence that currently used polio vaccine was free of SV40.

Critical assessment of virological and epidemiological data suggests a probable causative role for SV40 in certain human cancers, but that additional studies are necessary to prove etiology (8). To help answer these issues, the World Health Organization has provided the following statement (10): "Investigations from several medical research institutions have detected the presence of simian virus 40 (SV40) genome in certain rare human tumors, notably mesotheliomas, osteosarcomas, and brain tumors. SV40, which is known to induce tumors in laboratory rodents, is a polyomavirus identified in 1960 as a contaminant of some batches of primary rhesus monkey kidney cells used to produce polio vaccine in the 1950s. Soon after its discovery, measures to exclude the virus from polio and other vaccines were rapidly introduced into WHO Requirements for the Manufacture and Quality Control of Polio Vaccines, and these have been rigorously applied by vaccine manufacturers. For over 30 years now, polio vaccines made in primary monkey kidney cells have been shown to be free of live SV40."

The use of new and highly sensitive polymerase chain reaction (PCR) techniques for the detection of the SV40 genome in batches of oral polio vaccines from several manufacturers has confirmed that the measures taken have been effective in excluding SV40 from vaccines. There is no doubt that the early batches of polio vaccine that were used between 1955 and 1963 contained SV40. Epidemiological studies between 1960 and 1974 failed to show an association between exposure to SV40-contaminated vaccines and human tumors. More recent epidemiological data from tumor registers, involving more than 60 million person years of observation, have likewise found no differences in tumor incidence that could be attributable to SV40-contaminated polio vaccines. The latest data published in the Journal of the National Cancer Institute, USA, suggest that SV40 may be present in humans more commonly than had previously been thought, and raises the possibility of transmission of the virus among humans. Whether the antibodies that have been detected are due to exposure to SV40 or to cross-reacting human polyomaviruses is not known. Neither is it certain that SV40 strains now present in the human population originated from the use of the early polio vaccines. Despite almost 40 years of observation, there is still no evidence that SV40 contamination of some early batches of polio vaccine has had any adverse effect on human health.

"The River" by Edward Hooper

The hypothesis that oral polio vaccine played a key role in the current AIDS epidemic was raised again by Edward Hooper, who has worked many years for the BBC and the UN in Africa and some years ago wrote a book called "Slim," in which he described the AIDS epidemic in East Africa. His book "The River. A journey to the source of HIV and AIDS," published in 1999 (11), raised great public attention and was discussed in BBC Press Releases and in the New York Times. Leading experts in virology and AIDS research published comments in Science and other scientific journals. "The River" is a thoroughly researched, well-written book and deserves to be taken seriously. Hooper carefully collected data and events describing the first phases of HIV infection and AIDS, as well as the early development and implementation of polio vaccines. His book reflects some hundreds of interviews, including the leading researchers in the related fields, and he has documented more than 4000 references.

The hypothesis is based on the following facts and assumptions. In 1957 and 1958, Koprowski, from the Wistar Institute in Philadelphia, was administering oral polio vaccine in Africa (pre-licensure field trials in Burundi, Rwanda, and the North-East Congo) near Stanleyville (now Kisangani) in Congo. Not far from the base, chimpanzees for use in medical research were housed in Camp Lindi and might have carried a primate immunodeficiency virus (PIV). Chimpanzee kidneys for hepatitis research were shipped from Camp Lindi to the Virological Department of the Children Hospital in Philadelphia in 1958 and 1959. Hooper suggests that "it could be that [kidneys from these chimpanzees] ended up at the Wistar", the laboratory in Philadelphia where polio vaccines were manufactured, where they contaminated vaccines with PIV. The polio vaccine that was supposed to be contaminated with PIV was then used in the Congo, transmitting the virus that evolved into HIV-1, the starting point of the worldwide HIV-1 epidemic. Over

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the next 20 years, infected humans progressed to AIDS, and the disease became visible in central Africa in the mid-to-late 1970s.

Does Hooper prove his hypothesis beyond a shadow of doubt? No, but he makes a powerful case for soberly and squarely addressing the issue.

There are also strong arguments against the hypothesis. Polio vaccines were first propagated in kidney cultures of rhesus and cynomolgus macaques, and later in African green monkeys. Plotkin and Koprowski categorically stated in a letter to the editor of the New York Times (7 December 1999) that no chimpanzee tissues were used in the Wistar Institute for polio vaccine production. They added that two independent analyses of the probable timing of the crossover of HIV from chimpanzees into humans give dates earlier than 1957–59, the years in which the Wistar polio vaccine was used in the Congo (12). It should also be mentioned that the vaccine manufactured in Wistar at that time was not only used in Africa but also in Sweden, Poland, and the US. One vial of Wistar's oral polio vaccine stored in Stockholm has already tested negative. Garrett and colleagues in England experimentally examined the survival of human and simian immunodeficiency viruses in oral polio vaccine formulations; no live retrovirus came through the procedure. Wistar declared that they would release lab specimens from a polio vaccine project carried out at the end of the 1950s in Africa for examination in two independent laboratories, in order to dispel claims that Wistar scientists inadvertently caused the AIDS epidemic.

It should be mentioned that the majority of scientists believe that the AIDS epidemic began after the simian immunodeficiency virus was transmitted from chimpanzees to humans during the slaughter of chimpanzees as early as the 1930s (13–16).

Finally, it is worth repeating the statement of the US Centers for Disease Control and Prevention, issued in 1992 but still valid (17): "The suggestion that HIV, the AIDS virus, originated as a result of inadvertent inoculation of an HIV-like virus present in monkey kidney cell cultures used to prepare polio vaccine is one of a number of unsubstantiated hypotheses. The weight of scientific evidence does not support this idea and there is no more reason to believe this hypothesis than many other which have been considered and rejected on scientific grounds."

Nevertheless, there are important lessons to be learned from Hooper's book. For many years, virologists and regulatory authorities have been worried that using permanent cell lines for vaccine virus propagation may somehow transfer cancer-causing properties and animal viruses. African green monkey kidneys are still used as the main cell substrate for oral polio vaccine. Millions of doses have been made from simian immunodeficiency virus (SIV)-positive monkeys before screening was introduced. Now there are well-tested non-oncogenic cell substrates, and it is time to reopen the debate on the use of primary cells versus cell lines for live attenuated virus vaccines. There is also a need to strengthen research on the sources of AIDS. However, the main focus of AIDS research should be prevention and treatment.

Global eradication of poliomyelitis and immunization

Using oral vaccine, the global campaign to eradicate polio achieved a more than 90% reduction in the number of polio cases worldwide in the 11 years since it was launched, and is on track to eradicate polio (18). It is to be expected that in a few years both poliomyelitis and polio vaccines will be confined to history books and science museums. Polio immunization will stop for good. When the final goal of global eradication is achieved, a decision on when and how to stop polio immunization will be necessary. Such a decision has not yet been prepared. Different scenarios are under discussion: continuation of universal immunization programs, sequential removal of one or two of the Sabin strains of OPV, change to an all-IPV program, and discontinuation of OPV immunization simultaneously worldwide or selectively country by country (19). The Technical Consultative Group for the World Health Organization on the Global Eradication of Poliomyelitis has the task of elaborating a proposal for final approval by the World Health Assembly (20).

Organs and Systems

Cardiovascular

Myopericarditis has been attributed to Td-IPV vaccine (21).

- A 31-year-old man developed arthralgia and chest pain 2 days after Td-IPV immunization and had an acute myopericarditis. He recovered within a few days with high-dose aspirin.

The authors discussed two possible causal mechanisms, natural infection or an immune complex-mediated mechanism. Infection was excluded by negative bacterial and viral serology and a favorable outcome resulted within a few days without antimicrobial drug treatment.

Nervous system

Vaccine-associated poliomyelitis

There is no doubt that OPV can cause poliomyelitis in a minority of recipients and their contacts. The risk is very low, but the seriousness of such a complication is evident. Various case reports and national surveys of vaccine-associated poliomyelitis, as well as studies quantifying this risk for OPV, have been published (SED-12, 820) (SEDA-16, 390) (SEDA-18, 336). The main conclusions from the field study that WHO conducted over a period of 15 years in 13 countries were as follows:

- The type 1 strain is almost never implicated in vaccine-associated poliomyelitis cases.
- The type 2 strain is an occasional cause of paralysis, commoner in contacts of the vaccine than in recipients.
- Most of the very small number of cases that do occur are due to type 3, both in vaccine recipients and in contacts.

In general, the risk of vaccine-associated poliomyelitis is less than one per million children immunized. The type 1 strain has been confirmed to be as safe and effective as any biological substance can be. The type 2 strain is safe for recipients of the vaccine but on rare occasions can

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cause paralysis in contacts, so that any contact whose immunization status is doubtful should be immunized at the same time as the original vaccinee. The type 3 strain is much less stable genetically than the two strains and requires constant monitoring in the laboratory and in the field (22).

Frequency

The risk of vaccine-associated poliomyelitis has remained exceedingly low but stable since the mid-1960s. In all, 260 cases of vaccine-associated poliomyelitis were reported in the USA between 1961 and 1989. Cases of vaccine-associated poliomyelitis appeared to occur randomly in time and space. One potential cluster of vaccine-associated poliomyelitis consisting of six cases occurring over an 18-month period in Indiana was investigated during the period 1980–89. These cases were not shown to be epidemiologically related.

Using the total number of 80 vaccine-associated poliomyelitis cases in the USA from 1980 to 1989 as a numerator, the overall risk of vaccine-associated poliomyelitis was one case per 2.5 million doses of trivalent OPV distributed. The overall risk of vaccine-associated poliomyelitis was 9.7 times greater after the first dose of OPV than after all subsequent doses. The overall risk of recipient vaccine-associated poliomyelitis was one case per 6.8 million doses. The risk among OPV recipients was 29.0 times higher after the first dose than after subsequent doses. Comparing the first dose of OPV to subsequent doses, the lowest relative risk was found in immunologically abnormal persons. Whereas the average annual rate of vaccine-associated poliomyelitis for the period 1980–89 was 0.34 cases per million population, the annual incidence of vaccine-associated poliomyelitis among immunologically competent infants, who were used as the reference group, was 7.6 cases per 10 million population. Children under 1 year of age with a primary immunodeficiency were at highest risk of vaccine-associated poliomyelitis (annual rate of 16 216 cases per 10 million population, or 0.16%), which is more than 2000 times higher than the rate in the reference group. Among household contacts of children below 6 years of age, the annual rate of contact vaccine-associated poliomyelitis was 0.45 cases per 10 million population. For the remaining US population, the annual rate of vaccine-associated poliomyelitis was 0.14 cases per 10 million population. Summarizing their experience (23), the authors of the 1980–89 study distinguish three groups at risk of vaccine-associated poliomyelitis:

- recipients of OPV, especially infants receiving their first dose of OPV;
- persons in contact with OPV recipients, mostly unimmunized or inadequately immunized adults;
- immunologically abnormal individuals.

There has been a retrospective cohort study of cases of acute flaccid paralysis reported to the Ministry of Health in Brazil between 1989 and 1995 (24,25). For the first dose of OPV the estimated risk was one case of vaccine-associated paralytic poliomyelitis per 2.39 million doses; for total doses of OVP the risk was one case in 13.03 million doses. Most of the cases of vaccine-associated paralytic poliomyelitis were in children with a mean age of 1 year. Paralysis of the lower limbs caused by poliovirus type 2 was dominant.

Poliomyelitis caused by vaccine-derived polioviruses Between 12 July and 18 November 2000, a total of 19 people (aged between 9 months and 21 years) with acute flaccid paralysis were identified in the Dominican Republic; one case occurred in Haiti (August 2000) (26). The case in Haiti and three of the cases in the Dominican Republic were laboratory-confirmed with poliovirus type 1 isolates. All cases were either unimmunized or incompletely immunized. The outbreak was unusual, because the virus is derived from oral polio vaccine virus, with 97% genetic similarity to the parental OPV strain. Normally, vaccine-derived isolates are more than 99.5% similar to the parent strain. In contrast, wild polioviruses normally have less than 82% genetic similarity to OPV. The differences in nucleotide sequences suggest that the virus causing the outbreak has been circulating for about 2 years in the area in which immunization coverage is very low, and that the virus had accumulated genetic changes that restored the essential properties of wild poliovirus. A mass immunization with OPV brought the outbreak under control.

Causative strains

In an outbreak in Egypt during 1988–93, 32 cases of polio were associated with vaccine-derived poliovirus type 2 (27). Nucleotide sequence analysis performed during 1999 showed that all isolates were related (93–96% similarity) to the OPV 2 vaccine strain. The isolates were not related (less than 81% similarity) to the wild poliovirus type 2 that had been indigenous in Egypt. OPV was probably low in the affected communities.

Between 15 March and 26 July 2001, three cases of acute flaccid paralysis associated with vaccine-derived polioviruses type 1 were reported in the Philippines (28). There was a 3% genetic sequence difference between OPV type 1 virus and the vaccine-derived isolates.

Mechanism

The molecular biological findings connected with the occurrence of vaccine-associated poliomyelitis have been summarized (29). There is convincing evidence that the Sabin 2 and 3 viruses themselves can revert to a neurovirulent phenotype on passage in man. The authors report that a point mutation in the 5′-non-coding region of the genome of the poliovirus type 3 vaccine consistently reverts to the wild type in viruses isolated from cases of vaccine-associated poliomyelitis.

Prolonged poliovirus excretion

Molecular studies of poliovirus isolates have suggested that viral replication of vaccine-related polioviruses may have persisted for as long as 7 years in a patient with vaccine-associated paralytic poliomyelitis, in whom common variable immunodeficiency syndrome had previously been diagnosed (SEDA-21, 336).

DTP injections

The risk of DTP injection in provoking paralytic poliomyelitis during a large poliomyelitis outbreak in Oman

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has been evaluated (30). Health center immunization records for 70 children aged 5–24 months with confirmed poliomyelitis and 692 control children were reviewed. A significantly higher proportion of case-patients received a DTP injection within 30 days before onset of paralysis compared with controls (43 versus 28%). All the patients for whom this information was available had paralysis of the injected limb. This study, which provided the first quantitative estimate in this respect, confirmed that injections are an important cause of provocative poliomyelitis and stressed the recommendation to avoid unnecessary injections during poliomyelitis outbreaks.

Multiple injections

Studies in 1994–95 in Romania produced evidence that multiple (unnecessary) injections may actually increase the risk of vaccine-associated poliomyelitis (SEDA-19, 302).

Between 1976 and 1985, seven cases of neurological disease were reported to have occurred in Germany among young children after simultaneous administration of oral poliovirus vaccine and diphtheria–tetanus toxoids or diphtheria–tetanus–pertussis vaccine (31). However, the virological data were incomplete; only one case was confirmed by the isolation of a vaccine-like polio virus, and in three cases the clinical symptoms did not correspond to poliomyelitis. The author concluded that in some cases the simultaneous administration of injectable vaccines cannot be excluded as a cause for paralysis.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis associated with polio vaccine has been reported (32).

- A 6-year-old girl developed acute disseminated encephalomyelitis, and polio vaccine virus type 2 was isolated from her cerebrospinal fluid and pharynx. The virus was sequenced throughout the 5′ non-coding region of the genome by polymerase chain reaction and was determined to have undergone various mutations at nucleotides 481, 500, 795, and 1195. The clinical signs of disease had completely disappeared 2 months later.

Guillain–Barré syndrome

Coincident with the mass nationwide campaign of OPV immunization that interrupted the transmission of wild poliovirus in Finland in 1985, with 4.5 million doses of OPV being administered, there was an unexpected rise in the occurrence of Guillain–Barré syndrome. In 10 cases of Guillain–Barré syndrome with onset of symptoms within 10 weeks after OPV immunization, no specific agents were found (33). The authors concluded that live attenuated polioviruses might trigger Guillain–Barré syndrome.

The authors of a report of the Institute of Medicine concluded that the evidence favored a causal relation between OPV and Guillain–Barré syndrome, but considered the evidence inadequate to accept or to reject a causal relation between OPV and transverse myelitis (SEDA-18, 325) (3).

The available reports on a possible association between polio vaccine and Guillain–Barré syndrome have been reviewed (34). The conclusion of a 1994 US Institute of Medicine committee that the evidence favored acceptance of a causal relation was mainly based on two reports from Finland (35,36). An earlier study of Guillain–Barré syndrome and oral polio vaccine has been extended to include hospital reports from the whole of Finland for 1981–6, during which time an oral polio vaccine campaign was carried out to control an outbreak of poliomyelitis (37). The rise in the numbers of cases of Guillain–Barré syndrome started before the immunization campaign. Because there had also been an influenza epidemic during that time, the researchers acknowledged that the increase in the incidence of Guillain–Barré syndrome could also have been associated with influenza. Data from the Americas are also not supporting an association between oral polio immunization campaigns and Guillain–Barré syndrome (38).

Sensory systems

Optic neuritis has been attributed to Td-IPV vaccine (39).

- Ten days after receiving Td-IPV vaccine a 56-year-old woman developed acute unilateral optic neuritis. Complete remission occurred within 6 weeks of prednisolone treatment. No other causes were found.

Gastrointestinal

Intussusception probably causally related to rotavirus vaccine (SEDA-23, 354) prompted studies to answer the question of whether polio vaccine could also cause intussusception. A workshop held in Atlanta on 15–16 June 2000 brought together experts from various fields with the primary investigators of the studies. The participants concluded that the available evidence favored rejection of a causal relation between OPV and intussusception (40).

Skin

Bullous pemphigoid has been attributed to DTP-IPV vaccine (41).

- A previously healthy 3.5-month-old infant developed bullous pemphigoid 3 days after receiving a first dose of DTP-IPV vaccine. *Staphylococcus aureus* was isolated from purulent bullae. The lesions resolved rapidly after treatment with antibiotics and methylprednisolone.

The authors mentioned 12 other cases of bullous pemphigoid, reported during the last 5 years, that had possibly been triggered by vaccines (influenza, tetanus toxoid booster, and DTP-IPV vaccine).

Second-Generation Effects

Pregnancy

Pregnancy is not a contraindication to the use of IPV. Although there is no convincing evidence documenting adverse effects of OPV on the developing fetus, and some evidence points to safety, it is widely considered prudent to avoid immunizing pregnant women, especially during the first 4 months of pregnancy. However, if immediate protection against poliomyelitis is needed, poliomyelitis immunization is recommended (42,43).

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In order to interrupt poliovirus transmission during an outbreak of wild poliomyelitis in Israel in 1988, some 90% of the population, including pregnant women, were immunized with trivalent OPV. In a study of the abortions that occurred within 4 months of immunization compared with figures from a similar period in the previous year, the number of spontaneous abortions did not differ between women immunized during the first trimester of pregnancy and the controls (44). The authors concluded that OPV administered during early pregnancy has no adverse effect on the embryo or placenta that would cause increased fetal deaths or spontaneous abortions, nor does it seem to cause a higher rate of congenital anomalies.

An analysis of the OPV mass campaign in Finland suggested that OPV during early pregnancy had no harmful effects on fetal development (45). There were no significant deviations from the baseline prevalence for all malformations. However, when the vaccine is administered later in pregnancy the prospects may be different.

- Irreparable damage to the anterior horn cells of the cervical and thoracic cord occurred in a 20-week-old fetus whose mother was immune to poliomyelitis before conceiving but who was inadvertently given OPV at 18 weeks gestation (46).

Susceptibility Factors

There are no known contraindications to the use of IPV. OPV should not be given to persons who are immunocompromised due to immunodeficiency diseases, leukemia, lymphoma or generalized malignancy or who are immunosuppressed due to therapy with glucocorticoids, alkylating drugs, antimetabolites, or radiation. If poliomyelitis immunization is indicated in such persons, IPV should be used. OPV should also be avoided when immunizing household contacts of immunocompromised patients.

In the view of the WHO, live vaccines should in general not be given to immunocompromised individuals, but in developing countries, the risk of poliomyelitis in nonimmunized infants is high and the risk from these vaccines, even in the presence of symptomatic HIV infection, appears to be lower (47).

The Immunization Advisory Committees of many developed countries recommend that OPV should not be given to children and young adults who are immunocompromised due to AIDS or other clinical manifestations of HIV infection. OPV can be given to asymptomatic infected persons. However, because family members may be immunocompromised due to AIDS or HIV infection, it seems prudent to use IPV (48).

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Polyacrylonitrile

General Information

Polyacrylonitrile is a constituent of dialysis membranes (1).

Organs and Systems

Immunologic

Non-IgE-mediated anaphylactic reactions to polyacrylonitrile membranes have been reported (2,3). The effects are enhacing in those using ACE inhibitors (4,5), perhaps because of an effect of bradykinin (6), which is released by the membranes (2,8,9) and whose metabolism is inhibited by ACE inhibitors. The effects also occur to a lesser extent in those taking angiotensin receptor antagonists (7) and in those with C1 esterase inhibitor deficiency (10). Treating the membranes with polyethyleneimine prevents bradykinin release (11).

The FDA has issued a safety alert about life-threatening anaphylactoid reactions associated with the concurrent use of angiotensin converting enzyme (ACE) inhibitors and polyacrylonitrile dialyzers (12). The warning was followed by increased reports in the literature and to the FDA of severe, sudden and sometimes fatal reactions. Symptoms include nausea, abdominal cramps, burning, angioedema, and shortness of breath, leading rapidly to severe hypotension. When these symptoms are recognized, dialysis should be stopped immediately and aggressive treatment for anaphylactoid reactions begun. Antihistamines do not relieve the symptoms. The mechanism of this interaction has not been

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established, and the incidence and scope of the problem are unknown.

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Polygeline

General Information

Polygeline is a plasma volume expander used as a 3.5% solution with electrolytes in the management of hypovolemic shock. It is also used in extracorporeal perfusion fluids, as a perfusion fluid for isolated organs, as fluid replacement in plasma exchange, and as a carrier solution for insulin.

Organs and Systems

Urinary tract

The effects of two modified gelatin preparations (Plasmion and Haemaccel) on renal function have been studied in 15 patients (1). In both groups proteinuria appeared as soon as perfusion began, with a peak as high as 6 g/l at the third hour. At the same time, low-molecular weight proteinuria (<30 kDa) was observed. $Beta_2$-microglobulinuria was significantly increased. The authors suggested that proteinuria was due either to inhibited tubular reabsorption of filtered protein, caused by gelatin, or to the amino acids, arginine and lysine, which are released as a result of gelatin hydrolysis. The pathological significance of this finding is unexplained.

Immunologic

Anaphylactic reactions associated with parenteral gelatin products are relatively common. The number of reports to the UK licensing authority now approaches 300, involving 127 patients, with 7 deaths. Most of these reactions are associated with multiconstituent gelatin-containing products, such as Gelofusine. An anaphylactic reaction due solely to the use of Gelofusine in a patient with non-hemorrhagic hypovolemia has been reported (2).

- A 57-year-old man presented with a 3-day history of lower abdominal pain and vomiting. He was hemodynamically stable but febrile, with tenderness and guarding in the lower abdomen. He was given intravenous fluids and antibiotics and mini-laparotomy was performed. Although 6 liters of crystalloids were given, his urine output was minimal, so 500 ml of Gelofusine was prescribed. Within 10 minutes he developed an urticarial rash, with wheals on his face and chest and difficulty in breathing. The infusion was stopped and replaced with crystalloids via a new administration set. Intravenous chlorphenamine and hydrocortisone improved his condition and the operation was completed without further complications.

Anaphylactic reactions to gelatins occur in about 0.1% of patients. Such reactions are more common in atopic patients and men and often occur within 10 minutes of starting the infusion. The authors recommended the use of allergy identification jewellery in such individuals, to reduce the possibility of life-threatening reactions.

The allergic reactions that have been described in association with polygeline are thought to be caused by direct histamine release as a result of allergenic stimulation of mast cells. These cases raise the questions of whether polygeline is appropriate for bronchoreactive patients and whether such patients should be protected by histamine receptor blockade.

- A 46-year-old man with diabetes mellitus and a history of allergy to penicillin, seafood, and soap had spinal anesthesia, and his systolic blood pressure fell to 90 mmHg (3). He was given 500 ml of gelafundin. Within minutes, he complained of pruritus along the drip site. There was no rash or urticaria, but the infusion was stopped immediately. He became restless, had copious oral secretions, complained of dyspnea, quickly

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lost consciousness, and was bradycardic and hypotensive, with a systolic blood pressure of 65 mmHg. He was given Hartman's solution, Haesteril 6%, adrenaline, and atropine. He had a markedly raised IgE concentration (16 000 IU/ml). He eventually recovered.

The authors suggested that the sequence of events strongly suggested an anaphylactic reaction to gelafundin, and they concluded that while polygelines are useful volume substitutes they should be used carefully in atopic individuals or those with previous drug allergies. Etherified starch is considered a safer alternative in such patients.

- Suspected polygeline-induced anaphylaxis occurred in an 83-year-old woman within 1 minute of receiving an infusion of about 10 ml (exact dose not stated) of polygeline after induction of anesthesia for left thoracotomy (4). Her arterial blood pressure fell to 30 mmHg and there were no palpable pulses and no detectable cardiac output, but she was successfully resuscitated. About 1 month later she showed a strongly positive reaction to polygeline on skin testing. It is believed that modification of the manufacturing process of polygeline has reduced the incidence of associated adverse reactions, although there have been no large-scale studies to estimate the current incidence.

Three cases of acute anaphylactoid reactions to polygeline have been described from Australia. The reactions were serious and the explanation for them was unclear. All three patients were either normovolemic or mildly hypovolemic at the time of the event (5).

In a comparison of 4% human albumin solution, gelatin, and dextran 40, given as replacement fluids during plasma exchange, the gelatin solution induced two immediate allergic reactions and one delayed reaction (among 37 patients exposed). There was no cross-reactive allergy between the two colloids. Dextran 1000 injections were well tolerated. Gelatin infusions were associated with 10 times more episodes of hypovolemia (5.6 compared with 0.62%). This difference is probably explained by the faster elimination of gelatin from the vascular compartment, and it suggests that a larger volume of gelatin is required compared with dextran 40 for the same volume of plasma exchanged (6).

An IgE-mediated anaphylactic reaction to polygeline (Haemaccel, Hoechst Marion Roussel) has been reported (7).

- A 33-year-old woman with supraventricular tachycardia and a history of cadaveric renal transplantation for end-stage renal insufficiency, who was taking an immunosuppressant, enalapril, and simvastatin, was given intravenous adenosine and polygeline 500 ml. After 30 minutes she developed generalized urticaria. Promethazine and hydrocortisone did not ameliorate her symptoms and an hour later she developed angioedema of the lips and tongue, but no airway obstruction, bronchospasm, or hypotension. The reaction resolved with subcutaneous adrenaline. Skin prick tests 2 weeks later showed hypersensitivity to polygeline but not to latex (a possible contaminant).

The authors suggested that the positive skin prick reaction showed that the cause was an IgE-mediated anaphylactic reaction, rather than an anaphylactoid reaction, although this was not confirmed by independent tests.

Susceptibility Factors

Patients with underlying bronchial asthma and pheochromocytoma are thought to be particularly at risk of acute histamine release due to polygeline.

- A 45-year-old woman, who had used salbutamol and budesonide inhalers and oral theophylline for asthma and who had developed bronchospasm during induction of general anesthesia 6 weeks before, was readmitted for surgery under spinal anesthesia (8). During the procedure she developed two episodes of hypotension, which was corrected with fluids and intravenous mephentermine 6 mg. When blood loss reached 750 ml she was given an infusion of polygeline 3.5%, and 10 minutes later complained of respiratory difficulty and developed severe respiratory distress. Polygeline was withdrawn and she was given 100% oxygen with halothane by face mask. The oxygen saturation fell by more than 80% and she developed severe bradycardia and ventricular fibrillation. She was resuscitated.

The authors concluded that the severe reaction in this case had been due to polygeline, despite careful preparation of the patient with glucocorticoids and antihistamines. They recommended that polygeline should be avoided in any patient with reactive airway disease. Preoperative antihistamines and glucocorticoids may not prevent reactions induced by polygeline administration in such patients.

Drug Administration

Drug formulations

Using a computer-aided model for the prediction of pseudoallergic reactions from prospective data collected from 581 patients in a controlled clinical trial with an outdated formulation of polygeline, accurate prediction of 86% of the patients who had a systemic reaction was possible (9). The data were handled by multivariate analysis using the independence Bayes model. The predictive accuracy of other reactions was poor. A history of allergy was recorded in 26% of the patients who had systemic reactions and in 12 and 13% of the patients with no systemic or skin reactions. However, these differences were not statistically significant.

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Polygonaceae

See also Herbal medicines

General Information

The genera in the family of Polygonaceae (Table 1) include buckwheat and rhubarb.

Table 1 The genera of Polygonaceae

Antenoron (antenoron)
Antigonon (antigonon)
Aristocapsa (spiny cape)
Brunnichia (buckwheat vine)
Centrostegia (centrostegia)
Chorizanthe (spineflower)
Coccoloba (coccoloba)
Dedeckera (July gold)
Dodecahema (spineflower)
Emex (three-corner jack)
Eriogonum (buckwheat)
Fagopyrum (buckwheat)
Gilmania (golden carpet)
Goodmania (spine cape)
Hollisteria (hollisteria)
Homalocladium (homalocladium)
Koenigia (koenigia)
Lastarriaea (lastarriaea)
Mucronea (spine flower)
Muehlenbeckia (maidenhair vine)
Nemacaulis (cottonheads)
Oxyria (mountain sorrel)
Oxytheca (oxytheca)
Polygonella (jointweed)
Polygonum (knotweed)
Pterostegia (pterostegia)
Rheum (rhubarb)
Rumex (dock)
Stenogonum (buckwheat)
Systenotheca (spineflower)

Polygonum species

Some species of *Polygonum* (knotweed) contain stilbene phytoestrogens, including resveratrol. *Polygonum tinctorium* contains indirubin, an isomer of indigo, which inhibits interferon-gamma production by human myelomonocytic HBL-38 cells and interferon-gamma and interleukin-6 production by murine splenocytes with no effect on the proliferation of either cells (1). *Polygonum multiflorum* contains compounds that inhibit calmodulin-depleted erythrocyte calcium-dependent ATPase (2). *Polygonum pennsylvanicum* contains vanicosides, glycosides that inhibit protein kinase C (3).

Adverse effects

Hepatitis has been attributed to *P. multiflorum* (4).

- *Polygonum multiflorum* (Shou wu Pian) was prescribed by a Chinese herbalist for a 46-year-old woman with graying hair (5). After taking it for 2 weeks she developed signs and symptoms of hepatitis. The history revealed no plausible cause for hepatitis and viral infection was ruled out. After withdrawal of the *P. multiflorum* her liver enzymes normalized and she recovered fully.
- A 31-year-old pregnant Chinese woman developed hepatitis after consuming Shou wu Pian; tests for viral hepatitis were negative and there was no evidence of other systemic disease (6).

Rheum palmatum

Rheum palmatum (rhubarb) contains the anthranoids sennosides and rhein. In a study of patients taking regular doses of rhubarb-containing Kampo medicines (extracts or decoctions) and patients taking excess doses there was tolerance to initial stimulant pain in the abdomen during excess use (7). The authors proposed that the absence of tenderness on pressure over the umbilical region could predict increasing or excess use of rhubarb.

In 14 616 patients who used various Kampo medicines, some of which contained rhubarb, there was no association between the use of rhubarb and the development of gastric carcinoma (8).

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Polyhexanide

See also Disinfectants and antiseptics

General Information

Polyhexanide is a polymerized form of chlorhexidine, used as a disinfectant (1).

Organs and Systems

Immunologic

Severe anaphylaxis occurred in an 18-year-old woman and a 15-year-old man when polyhexanide was used to clean surgical wounds (2). Immediate-type hypersensitivity to polyhexanide was suggested by positive skin prick tests. Both patients had previously been exposed to chlorhexidine, but skin tests with chlorhexidine were negative.

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Polymyxins

General Information

The polymyxins are antibacterial agents that are produced from different strains of *Bacillus polymyxa*. Because of their poor tissue distribution and their substantial nephrotoxicity and neurotoxicity, they are mainly restricted to topical use. However, they can be considered for serious systemic infections caused by multidrug-resistant Gram-negative bacteria (1–4).

The polymyxins that are used clinically are polymyxin B (rINN) and colistin (pINN, formerly known as polymyxin E). Colistimethate sodium (rINN, also called colistin methanesulfonate and colistin sulfomethate sodium) is prepared from colistin.

The polymyxins are cationic, basic, and amphipathic polypeptides that interact with lipopolysaccharides in the outer membrane of bacilli. They potently neutralize endotoxin, reduce blood endotoxin concentrations in patients with septic shock during direct hemoperfusion over immobilized polymyxin B fibers, and are bactericidal for many Gram-negative rods, even in resting bacteria. Alteration of the cell wall is also thought to be the mechanism of damage to renal epithelia and to the nervous system.

The polymyxins are effective against Gram-negative bacteria, with the exception of *Proteus* and *Neisseria* (*Branhamella*). They have in the past been used particularly to treat infections due to *Pseudomonas*, including inhalation therapy in patients with cystic fibrosis (5). They are prescribed in mg or units; 1 mg of polymyxin B corresponds to 10 000 units and 1 mg of colistin corresponds to 20 000–30 000 units.

After intravenous colistimethate (5 mg/kg/day) the CSF concentration was 25% of the serum concentration in a patient with meningitis (6). For life-threatening meningitis due to such organisms, polymyxins can also be given intrathecally as adjunctive therapy (7). Polymyxins are also used in regimens of selective decontamination of the digestive tract (8).

Observational studies

In a randomized study of the effects of a triple antibiotic ointment (polymyxin B + bacitracin + neomycin) and simple gauze-type dressings on scarring of dermabrasion wounds, the ointment was superior to the simple dressing in minimizing scarring; the beneficial effect on pigmentary changes was especially pronounced (9).

General adverse effects

Even in patients with normal renal function, adverse reactions have occurred in up to 25%, contributing to death in 5% (10). At therapeutically equivalent doses, suggestions of differences in nephrotoxicity or neurotoxicity between polymyxin B and colistin are not convincing. In view of their potential for adverse effects, the polymyxins have now been largely replaced by other antibacterial drugs.

Organs and Systems

Respiratory

The polymyxins are bronchial irritants, probably by histamine release (11). This reaction can be very rapid and resistant to bronchodilators.

In 58 children with bronchoconstriction in response to nebulized colistin, FEV_1 was significantly reduced for 15 minutes (12). In 20 children the reduction was greater than 10% from baseline FEV_1 and was still at that level in five children after 30 minutes. Subjective assessment, baseline FEV_1, and serum IgE did not distinguish susceptible children.

In 62 children with cystic fibrosis there was increased dyspnea in seven and pharyngitis in three in response to nebulized colistimethate (80 mg dissolved in 3 ml of preservative-free isotonic saline, by inhalation twice daily for 4 weeks) (13).

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Nervous system

During treatment with any of the polymyxins, neurotoxicity can occur in up to 7% of patients with normal renal function. Circumoral paresthesia, vasomotor instability, ataxia, dizziness, convulsions of varying severity, and apnea have been reported. Of 31 patients with cystic fibrosis 21 had one or more adverse effects attributed to colistin (14). The most common reactions involved reversible neurological effects, including oral and perioral paresthesia ($n = 16$), headache ($n = 5$), and lower limb weakness ($n = 5$). All of these effects, although bothersome, were benign and reversible. There was no relation between the occurrence of any colistin-associated adverse effect and plasma colistin concentration or colistin pharmacokinetics.

Meningeal irritation rarely occurs in daily doses of 50 000 units (5 mg) given intrathecally, but higher doses can cause a stiff neck with CSF pleocytosis (15).

In animals the polymyxins can cause neuromuscular blockade similar to that observed with the aminoglycosides, aggravated by curare, ether, and suxamethonium, and antagonized by calcium. This can be noted first as fatiguability 1–26 hours after dosing, and can progress to severe muscular weakness, including respiratory paralysis (11). This complication has been reported both in neurologically normal subjects exposed to high plasma concentrations of the polymyxins, and also in some individuals with concentrations that were considered to be in the target range. Particularly at risk are patients with myasthenia gravis, who may require increased doses of neostigmine.

In patients with chronic pulmonary disease, polymyxin-induced neuromuscular block can result in fatal apnea. Finally, after anesthesia involving muscle relaxants the polymyxins can cause relapse of muscle weakness and inadequate ventilation (16).

Effective treatment of polymyxin-induced neuromuscular blockade requires awareness of the complication, with appropriate supervision and immediate ventilatory support, if required. Calcium gluconate and neostigmine are not of proven efficacy and should not be relied on (11).

Sensory systems

The polymyxins are occasionally ototoxic (17).

Electrolyte balance

Hyponatremia, hypokalemia, and hypocalcemia, with corresponding clinical manifestations, have occurred in patients treated for 3 weeks with doses of polymyxin B over 2 g/m^2 body surface (18,19). These abnormalities were interpreted as consequences of polymyxin-induced nephrotoxicity. Hyperchloremia and a negative anion gap seem to result from the polycationic properties of polymyxin B (20).

Urinary tract

Adverse reactions involving the kidneys occur in about 20% of patients receiving polymyxins (10). The potential for kidney damage seems to be related to age. Whereas in neonates and young infants colistimethate 20 mg/kg may be well tolerated, children over 2 years should not receive more than 10 mg/kg/day and adults even less.

Nephrotoxicity occurs more often in patients with preexisting impairment of renal function. Doses must be adjusted in patients with renal insufficiency, because colistin is excreted principally by the kidneys, and raised blood concentrations can further impair renal function (21).

Intermittent proteinuria was observed on urinalysis in 14 of 31 patients with cystic fibrosis, and one patient developed reversible, colistin-induced nephrotoxicity (14). There was no relation between the occurrence of any colistin-associated adverse effect and plasma colistin concentration or colistin pharmacokinetics.

Skin

Topical polymyxin B was the predominant allergen in patients who underwent patch-testing for evaluation of eczema of the external ear canal (22).

Immunologic

Compared with their toxic effects, allergic reactions to the polymyxins are relatively unimportant. Nevertheless, drug fever and maculopapular eruptions and other skin lesions have been observed in few patients (23,24).

In 145 patients with eczema of the external ear canal, allergic contact dermatitis was diagnosed in one-third; topical therapeutic agents, especially neomycin sulfate and probably polymyxin B, were the dominating allergens (22).

Long-Term Effects

Drug resistance

The Gram-negative organism *Burkholderia pseudomallei* is the pathogen that causes melioidosis. This bacterium is intrinsically resistant to the killing action of cationic antimicrobial peptides, including polymyxins. An in vitro study has now identified genetic loci that are associated with resistance to polymyxins in a virulent clinical isolate (25). In patients with cystic fibrosis *Pseudomonas aeruginosa* synthesized specific lipid A structures containing palmitate and aminoarabinose, which were associated with resistance to cationic antibiotics and increased inflammatory responses (1).

A two-component regulatory system has been characterized that is involved in the resistance of *P. aeruginosa* in response to external magnesium concentrations (26). Similarly, the PmrA/PmrB two-component system of *Salmonella enterica* that mediates modifications in the lipopolysaccharide, resulting in resistance to polymyxins, has been characterized in more detail (27). The pqaB locus affected polymyxin B resistance in *Salmonella typhi* (28).

All hemolytic and cytotoxic *Aeromonas* species that have been isolated from water samples from various sources were resistant to polymyxin B (29). Resistance to polymyxin B was also found in *Vibrio vulnificus* (30).

Resistance to colistin has been analysed in 44 adults with cystic fibrosis treated with inhaled colistin. Five developed polymyxin resistance (31). After therapy *P. aeruginosa* became sensitive to polymyxins within a few months, enabling the reintroduction of colistin for antibacterial treatment.

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Second-Generation Effects

Teratogenicity

Colistin, and probably also polymyxin B, crosses the placenta (32). Although there is no evidence that the polymyxins are teratogenic, they should be avoided in pregnancy.

Drug Administration

Drug formulations

A food additive (flavored BMI-60) may help to mask the bitter taste of polymyxin B sulfate tablets (33).

Drug administration route

Bolus intravenous colistin (160 mg in 10 ml of saline tds) has been studied in a phase I open study during acute respiratory exacerbations in adults with cystic fibrosis and chronic *P. aeruginosa* infection; patients without total indwelling venous access systems had mild to moderate injection-like pain (34).

Intramuscular injection of the sulfates of polymyxin or colistin often causes pain at the site of injection; with sodium colistimethate this adverse reaction is largely absent (35).

In a study of the intrathecal administration of colistin adverse events were not reported (36). This may be an effective alternative treatment of bacterial meningitis caused by multidrug-resistant Gram-negative rods.

During sepsis, toxins (for example released from bacteria) can cause shock, disseminated intravascular coagulation, multiorgan dysfunction, and death. Apheresis may be a way of reducing the amounts of toxins and other harmful compounds in the circulation, and polymyxin B may serve as an adsorber. In three patients with septic shock, direct hemoperfusion using a polymyxin B-immobilized fiber column was carried out after antibacterial and antishock therapy. As a result, cardiovascular instabilities improved without increasing the supply of catecholamines (37). Furthermore, in seven patients with endotoxic shock after laparotomy undergoing hemoperfusion with the polymyxin B-immobilized fiber, there was an early increase in urine volume, attributable to increased glomerular filtration independent of systemic hemodynamic factors (38).

Drug overdose

If patients have high plasma concentrations of polymixins, neither hemodialysis nor peritoneal dialysis is effective in eliminating them (39). Exchange transfusion has been proposed (40,41).

Drug–Drug Interactions

Neuromuscular blocking drugs

There may be difficulty in reversing neuromuscular blockade if polymyxin is given in combination with neuromuscular blocking drugs (42).

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Polystyrene sulfonates

General Information

Polystyrene sulfonic acid has been used as sodium, potassium, and calcium salts. Sodium polystyrene sulfonate has been used to treat hyperkalemia in patients with renal insufficiency and as an adjuvant during hemodialysis. It can be given orally or rectally in all age groups (1). It has also been added to feeding formulae and nutritional supplements to reduce their potassium contents and so prevent hyperkalemia; however, the reduction in potassium content was more than balanced by a concomitant increase in sodium content, presumably because of exchange of the sodium with calcium and magnesium (2,3). The uses and adverse effects of sodium polystyrene sulfonate have been reviewed (4,5).

Potassium polystyrene sulfonate has been used to treat hypercalciuria and renal calculi. Calcium polystyrene sulfonate has been used to treat hyperkalemia, particularly in patients who cannot tolerate the extra sodium that would be provided by the sodium salt.

A confection containing sodium polystyrene sulfonate resin 5.0 g per piece was used to treat six chronic dialysis patients with predialysis serum potassium concentrations of 5.2 mmol/l or more (6). Over 2 weeks the mean serum potassium fell by 0.7 mmol/l. However, the effectiveness of sodium polystyrene sulfonate in lowering serum potassium concentrations in patients with renal insufficiency has been questioned (7). A cathartic alone (phenolphthalein) in six patients caused an average fecal potassium output of 54 mmol. The addition of sodium polystyrene sulfonate had no further significant effect on total potassium output. With placebo the average serum potassium concentration increased slightly (0.4 mmol/l) during 12 hours. This rise was attenuated by sodium polystyrene sulfonate, perhaps in part because of extracellular volume expansion caused by the absorption of sodium. Phenolphthalein was associated with a slight rise in serum potassium concentration (similar to placebo), perhaps because of extracellular volume contraction

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produced by a sodium-rich diarrhea and acidosis secondary to bicarbonate loss. None of the regimens reduced the serum potassium concentration, compared with baseline.

Organs and Systems

Respiratory

Pneumonitis has been reported in a woman taking sodium polystyrene sulfonate (8).

Electrolyte balance

Sodium polystyrene sulfonate can cause hypokalemia, hypocalcemia, and hypernatremia (4,5).

Calcium polystyrene sulfonate can cause hypokalemia and hypercalcemia (4,5).

Acid–base balance

Cation-containing antacids and laxatives (for example magnesium hydroxide, calcium carbonate) can reduce the effect of polystyrene sulfonate and metabolic acidosis can develop. This has been reported in both children (9,10) and adults.

- A patient with end-stage renal disease undergoing long-term maintenance hemodialysis developed moderately severe metabolic alkalosis in the absence of vomiting or gastric drainage (10). The cause of the acid–base disorder was the oral administration of exogenous alkali, in the form of "non-absorbable" antacids (aluminium hydroxide and magnesium hydroxide), neutral phosphate, and sodium polystyrene sulfonate.
- In a patient with chronic renal insufficiency, chronic hypocalcemia plus severe metabolic alkalosis due to combined administration of sodium polystyrene sulfonate and magnesium hydroxide caused a generalized tonic-clonic seizure (11).

Hematologic

Thrombocytopenia has been attributed to sodium polystyrene sulfonate (Kayexalate) (12).

- An 84-year-old man with diabetes mellitus and hypertension had gradually worsening renal insufficiency with hyperkalemia and was given oral sodium polystyrene sulfonate (Kayexalate). After 7 days he developed gradually worsening thrombocytopenia, and 12 days later his platelet count, which had initially been 207×10^9/l, fell to 86×10^9/l. The thrombocytopenia rapidly improved after withdrawal of the sodium polystyrene sulfonate. At a later date readministration of sodium polystyrene sulfonate for the treatment of hyperkalemia again caused thrombocytopenia. Bone marrow aspiration biopsy showed normal numbers of nucleated cells and megakaryocytes with no increase in blast count. No other disorders which could have caused thrombocytopenia were seen in this patient.

Gastrointestinal

After oral administration the polystyrene sulfonates commonly cause anorexia, nausea, vomiting, and constipation (4,5).

Esophagus, stomach, and duodenum

Upper gastrointestinal damage associated with sodium polystyrene sulfonate in sorbitol is reported far less often than colonic damage. However, endoscopic appearances were markedly abnormal in 11 patients with crystals of sodium polystyrene sulfonate in biopsies from the esophagus ($n = 7$), stomach ($n = 6$), and duodenum ($n = 2$), in some cases closely mimicking other diagnoses, including esophageal carcinoma, *Candida* esophagitis, and gastric bezoar (13). There was histological and/or endoscopic evidence of mucosal injury in the form of an ulcer or erosion in nine patients, and in four patients with mucosal injury, no other cause could be identified.

Esophageal ulceration has occasionally been attributed to sodium polystyrene sulfonate (14).

- An 83-year-old man with septic shock and renal insufficiency after prostatectomy was given sodium polystyrene sulfonate for hyperkalemia and developed a 3 cm esophageal ulcer. Crystals of sodium polystyrene sulfonate were found in a biopsy.

In five infants of extremely low birth weights, who were given either sodium polystyrene sulfonate or calcium polystyrene sulfonate orally for hyperkalemia, masses were palpable in the left upper quadrant of the abdomen and visible radiographically as opaque masses in the stomach (15). At autopsy, the palpable mass was identified as a solid chalk-like concretion and X-ray diffraction showed that the material was Brushite. The authors suggested that oral exchange resins should not be used in critically ill, extremely low birth-weight infants.

Small bowel

In 15 patients who were given sodium polystyrene sulfonate (Kayexalate) in sorbitol as an enema or orally to treat hyperkalemia, sodium polystyrene sulfonate crystals were observed in specimens from gastrointestinal surgical resections ($n = 9$) or endoscopic biopsies ($n = 7$) (16). There was necrosis in seven of eight surgical resection specimens and three of five endoscopic biopsy specimens; four also had necrosis of the small intestine. Four patients with colonic necrosis in the initial resection specimen developed progressive necrosis of the small intestine or rectum, and five died within 1 day to 6 weeks. There were sodium polystyrene sulfonate crystals in upper gastrointestinal tract specimens from four patients, including one with hemorrhagic gastritis.

The incidence of intestinal necrosis has been estimated in 752 hospitalized patients who had received sodium polystyrene sulfonate, of whom 117 were exposed within 1 week of surgery (17). There were two cases of intestinal necrosis, both in patients who had received oral sodium polystyrene sulfonate in sorbitol. Based on these two cases, the postoperative incidence of intestinal necrosis associated with sodium polystyrene sulfonate was 1.8%. In 862 patients, who had undergone hemodialysis, renal transplantation, or cardiac transplantation, but had not received sodium polystyrene sulfonate, there were no cases of idiopathic intestinal necrosis.

With high doses, intestinal impaction can occur and this has been associated with perforation (18).

- A 650-g, 24-week-old neonate with hyperkalemia was given sodium polystyrene sulfonate enemas and

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developed cecal impaction and perforation. Abdominal radiographs showed radiodense impacted resin outlining the bowel. Pathological examination showed sodium polystyrene sulfonate crystals in a cecal abscess.

Large bowel

After rectal and oral administration, intestinal ulcers and necrosis have occurred (13,19). Several cases affecting the large bowel have been reported and critically ill and uremic patients are at particular risk.

- A 67-year-old man underwent laparotomy for a ruptured abdominal aortic aneurysm (20). Postoperatively he was treated with hemodialysis because of acute renal insufficiency. Hyperkalemia was treated with sodium polystyrene sulfonate, after which he developed ulceration of the colon and required a hemicolectomy because of intractable blood loss.
- Two patients, who had died after cardiac surgery, were in renal insufficiency, and had received sodium polystyrene sulfonate in sorbitol, had colonic luminal crystals of sodium polystyrene sulfonate associated with underlying mucosal necrosis, submucosal edema, and transmural inflammation (21).
- In a patient who developed near-total colonic necrosis shortly after renal transplantation, the onset of symptoms was temporally related to the administration of sodium polystyrene sulfonate plus sorbitol enemas (Kayexalate) for hyperkalemia (22).
- In another case, colonic necrosis presented as an acute abdomen within 24 hours of administration of sodium polystyrene sulfonate in sorbitol (23). After prompt surgical resection of the necrotic transverse colon there was rapid recovery of bowel function.
- A 53-year-old woman took sodium polystyrene sulfonate 15 g twice, 8 days apart, and 15 days later developed colonic necrosis and perforation; there were crystals of sodium polystyrene sulfonate in the inflammatory debris (24).
- An 81-year-old woman with chronic renal insufficiency, who had taken sodium polystyrene sulfonate 2 spoons/day, developed a 3–4 cm ulcer at 45 cm from the anal margin, with crystals of sodium polystyrene sulfonate in the biopsy (25).
- A 74-year-old woman with chronic renal insufficiency, who had taken sodium polystyrene sulfonate 1–2 spoons/day, developed cecal ulceration, with crystals of sodium polystyrene sulfonate in the biopsy (25).
- A giant diverticulum in the sigmoid colon has been attributed to inflammation due to sodium polystyrene sulfonate crystals in a 44-year-old man who had taken 15 mg/day for 2 years (25).

Colonic perforation has been attributed to calcium polystyrene sulfonate in a premature infant (26).

- A boy delivered at 28 weeks was given calcium polystyrene sulfonate 0.2 mg rectally for hyperkalemia (7.1 mmol/l). His abdomen, already distended, became larger with abdominal wall discoloration. An X-ray showed distended loops of bowel and at laparotomy he was found to have a perforation at the rectosigmoid junction.

While crystals of sodium polystyrene sulfonate, which are purple, irregular, and jagged, can be an incidental finding and are not known to cause injury, they are a helpful histological clue to the possibility that sorbitol has been administered (16). Five cases of extensive mucosal necrosis and transmural infarction of the colon have been reported after the use of sodium polystyrene sulfonate (Kayexalate) and sorbitol enemas to treat hyperkalemia in uremic patients (27). The authors also studied the effects of Kayexalate sorbitol enemas in normal and uremic rats and concluded that sorbitol was responsible for colonic damage and that the injury was potentiated in uremic rats. When sorbitol alone or Kayexalate sorbitol was given, extensive transmural necrosis developed in 80% of normal rats and in all the uremic rats. Because uremia and the concomitant use of sorbitol appear to be common denominators in the pathophysiology of this complication, some have suggested that Kayexalate enemas be avoided in renal transplant patients (22). Following reports of colonic necrosis, the Pharmaceutical Affairs Bureau of Japan revised the product information for enemas of polystyrene sulfonate cation exchange resin suspension in sorbitol solution for potassium removal (28).

Two other cases of neonatal bowel opacification secondary to oral and rectal sodium polystyrene sulfonate have been reported (29). Abdominal radiography showed a faint homogeneous increase in density within the bowel lumen.

Hematochezia in a neonate who had been given sodium polystyrene sulfonate enemas prompted a review of the use of such enemas in 20 of 2317 patients (30). Of these 20 patients, four had evidence of hematochezia temporally related to the use of the enemas. There were no episodes of bleeding in infants who were older than 29 weeks or over 1250 g birth weight. In one case, an autopsy performed within 2 days of the enema showed extensive vascular congestion in the mucosa and submucosa, with focal areas of hemorrhage. Sorbitol 20% (1098 mosm/l) was the vehicle for suspension of the sodium polystyrene sulfonate, and the authors thought that the hyperosmolarity of sorbitol had contributed to the colonic damage in these children.

Drug Administration

Drug formulations

Drugs that have similar names are not infrequently confused. The name of Sanofi-Synthelabo's brand of sodium polystyrene sulfonate, Kayexalate, could be confused with the names of proprietary brands of potassium chloride, such as Kay-Cee-L and Kay-Ciel. Furthermore, some formulations of potassium chloride are formulated in packaging that resembles that of Kayexalate. There have been two deaths when potassium chloride was given instead of sodium polystyrene sulfonate for hyperkalemia (31).

Drug–Drug Interactions

Iron

It has been suggested that sodium polystyrene sulfonate might be useful in treating iron overdose, since it binds iron in vitro with high affinity (32). However, in a placebo-controlled crossover study in six healthy adults

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sodium polystyrene sulfonate 30 g had no significant effect on the kinetics of an oral dose of elemental iron 10 mg/kg (33).

Lithium

Sodium polystyrene sulfonate binds lithium in vitro (34); it is more effective than charcoal, but has a higher affinity for potassium (35). In healthy volunteers who took a single dose of lithium carbonate 600 mg, sodium polystyrene sulfonate 30 g reduced the area under the lithium serum concentration-time curve by 11%, reduced the mean C_{max} by 0.07 mmol/l, and delayed the t_{max} by 2.04 hours (36). In six young healthy volunteers who took lithium carbonate 0.5 mmol/kg (18.5 mg/kg), sodium polystyrene sulfonate 857 mg/kg in 4 ml of water/g taken 1 hour later reduced the mean AUC by 15% and the C_{max} by 0.20 mmol/l (37). There was no significant difference in 24-hour urine lithium excretion or in serum sodium and potassium concentrations. Both of these results suggest that sodium polystyrene sulfonate reduces the absorption of lithium. Furthermore, sodium polystyrene sulfonate increased the clearance of oral lithium in a volunteer when given 30 minutes after each dose of lithium (38). For these reasons it has been used to treat lithium overdose (39,40). However, it can cause hypokalemia and is not currently recommended as routine therapy (41).

Tetracyclines

Since calcium salts can bind tetracyclines, leading to reduced absorption (SED-14, 910), an interaction of this kind might be expected with calcium polystyrene sulfonate, but it does not seem to have been reported.

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Polytetrafluoroethylene

General Information

Polytetrafluoroethylene (Polytef) is widely used in industry. "Teflon" is used in household appliances to avoid sticking of food. Polytef paste is used for a variety of medical purposes, including replacement grafts in vascular surgery, vocal cord or fold augmentation, and correction of vesicoureteric reflux and urinary incontinence.

The use of polytetrafluoroethylene has become controversial because of reports of granulomatous reactions and distant migration of the material. Foreign body giant cell responses to the polytetrafluoroethylene implant ("teflonoma") have become a serious complication, and animal models have clearly shown a classic foreign body reaction with multinucleated giant cells, granuloma formation, and migration of Teflon into surrounding muscle after Teflon injection (1). Teflon-related granuloma occurred in 1.3% of a series of 155 patients with trigeminal neuralgia treated by microvascular decompression using Teflon (2). Such granulomas can cause compression syndromes at various locations after varying periods of time.

- A patient who had previously undergone suboccipital microvascular decompression for hemifacial spasm presented 3 years postoperatively with a progressive asymmetric sensorineural hearing loss. At surgery a granuloma was found displacing the structures of the internal auditory canal. Histologically, there was evidence of a Teflon fiber-induced giant cell granuloma (3).

Postoperative failure after Teflon sling repair of a rectal prolapse is probably due to poor technique (4).

Organs and Systems

Cardiovascular

Teflon injected in a young woman for urinary incontinence migrated to the pulmonary vascular system (5).

Particles of Teflon can detach from cardiac valve prostheses, producing embolic complications (6).

Nervous system

Periureteral injection of Teflon has been linked to stroke in a previously healthy child 1 year after the procedure (7).

Urinary tract

Refluxing ureters can be treated endoscopically with subureteric injection of polytetrafluoroethylene paste (Polytef), the "STING" procedure. However, ureteric obstruction has been described as a complication (8). Urinary incontinence has also been treated by periurethral or submucosal injections of Polytef, but reports of urinary obstruction (9,10) and poor long-term success (11,12) have limited the range of indications for this treatment. Other reported complications of Teflon injection for stress urinary incontinence include periurethral abscess, urethral diverticulum, Teflon granuloma with urethral wall prolapse (13), and microembolization (14).

Skin

Skin migration following periurethral polytetrafluoroethylene injection for urinary incontinence has been reported (15).

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Musculoskeletal

Interposition of Teflon-Proplast implants for internal derangement of the temporomandibular joint has been used, although cases of osseous destructive changes have been reported (16).

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Polyurethanes

General Information

Polyurethanes are organic polymers that are formed by reacting a polyol (an alcohol with more than two reactive hydroxyl groups per molecule) with a diisocyanate or a polymeric isocyanate in the presence of suitable catalysts and additives. Flexible polyurethane forms are used in upholstery, mattresses, chemical-resistant coatings, adhesives, sealants, and packaging. Rigid foams are used in insulation for buildings, water heaters, refrigerated transport, and commercial and residential refrigerators.

In medical practice, polyurethane is used in implants. Complications of polyurethane implants are not uncommon, mainly due to foreign-body reactions (1), such as with microporous polyurethane (Mitrathane) cardiac patch implants and with breast implants.

Long-Term Effects

Tumorigenicity

In a study of the mortality (1958–98) and cancer morbidity (1971–94) in a cohort of 8288 male and female employees from 11 factories in England and Wales engaged in the manufacture of flexible polyurethane foams, mortality from lung cancer in female employees was significantly increased (standardized mortality ratio 181) (2). There was no excess among male employees (standardized mortality ratio 107). There were no significantly increased cause-specific standardized mortality ratios among the subcohort ($n = 1782$) with some period of isocyanate exposure.

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Polyvidone

See also Disinfectants and antiseptics

General Information

Polyvidone (polyvinylpyrrolidone, povidone) is a variable-weight polymer of the monomer *N*-vinylpyrrolidinone. When it enters the body, it causes histologically characteristic reactions in tissues with which it comes into contact (1,2).

Polyvidone co-polymers are used in cosmetics as antimicrobials, antistatics, binding compounds,

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stabilizers of emulsions, and film-forming, viscosity-controlling, hair-fixing, skin-conditioning, and skin-protective agents. It is used as a component of hair sprays and as a retardant for subcutaneous injections. It was formerly used as a plasma expander (3) and has been inappropriately used for intravenous injection as a "blood tonic," especially in Asian societies. Some products intended for parenteral administration contain polyvidone as an excipient. Polyvidone is widely used as a suspending and coating agent in tablets, for its film-forming properties in eye drops, and as a carrier molecule for iodine in disinfectants. About 20% of all tablets on the market contain polyvidone. It is also used in the cosmetics industry as a dispersing agent and as a lubricant in ointments.

Povidone-iodine

Povidone-iodine is a macromolecular complex (poly-I(I-vinyl-2-pyrrolidinone)) that is used as an iodophor. It is formulated as a 10% applicator solution, a 2% cleansing solution, and in many topical formulations, for example aerosol sprays, aerosol foams, vaginal gels, ointments, and mouthwashes. Because it contains very little free iodine (less than 1 ppm in a 10% solution), its antibacterial effectiveness is only moderate compared with that of a pure solution of iodine.

Systemic absorption

The extent of systemic absorption of povidone-iodine depends on the localization and the conditions of its use (area, skin surface, mucous membranes, wounds, body cavities).

Healthy skin

Repeated surgical skin antisepsis and hand washing did not increase serum iodine concentrations, but produced a small increase in iodine content in the 24-hour urine (4).

Burns

The use of povidone-iodine for the treatment of burns, for peritoneal lavage in the treatment of purulent peritonitis, or as a rinsing solution for body cavities can increase serum iodine concentrations associated with increased urinary excretion of iodine. In people with burns, the extent of iodine absorption depends on the extent of the burned body surface. It is not uncommon for serum iodine concentrations to rise to more than 1000 μg/ml. If renal function is intact, iodine elimination in the urine can be adequate. The serum iodine concentration returns to normal about 1 week after the last application.

The penetration of povidone-iodine has been studied in vivo in rabbits (5). The penetration from third-degree burns on the back was measured autoradiographically in tissues, blood, urine, and bandages. The results showed that about 20% of iodine is absorbed through fresh necrosis, whereas only 5% is absorbed through a clean wound or 24-hour-old necrosis. The passage through burn necrosis was faster than through vital tissue.

In repeated topical use on burns, the extent of absorption seems to decrease with the treatment time.

Wounds

Povidone-iodine inhibits leukocyte migration and fibroblast aggregation in wounds. The effect on the wound healing process has been studied in 294 children undergoing surgery, 283 of whom had undergone appendectomy (6). In a first series using 5% povidone-iodine aerosol for preoperative disinfection, the postoperative wound infection rate was 19% in the test group and only 8% in the controls. When a 1% povidone-iodine solution was used, only 2.6% of the patients were infected (control group 8.5%). Using a drain with a cellulose viscose sponge, 5% povidone-iodine by aerosol inhibited leukocyte migration, but no cell aggregates or fibroblasts were detected. A 5% solution allowed better cellular movement and attachment to the framework, polymorphonuclear leukocytes predominating. The excipients in the aerosol formula must be more toxic to the cell than those in the solution. If a 1% povidone-iodine solution was absorbed by the sponge, the aggregation phenomenon was only slightly averted and cell morphology was similar to that of the saline control.

Povidone-iodine reduced the number of wound infections only in patients with appendicitis in whom neither peritonitis nor a periappendicular abscess had yet developed (SEDA-11, 489).

Mucous membranes

The effect of a povidone-iodine mouthwash on thyroid function has been studied in 16 medically healthy volunteers. After they had used the mouthwash four times daily for a period of 14 days, all thyroid tests were significantly changed, but there was no suppression of thyroid function. However, this was not to be expected, considering the short test period.

Body cavities

When povidone-iodine is used as a rinsing solution in body cavities, absorption of the whole macromolecular complex is possible. The complex has a molecular weight of about 60 000 and cannot be eliminated by the kidneys or metabolically. It is filtered by the reticuloendothelial system (4,7,8).

Although povidone-iodine is no longer used in dialysates, a povidone-iodine-containing cap is used to seal the Tenckhoff catheter during the day. Iodine-induced hypothyroidism occurred in a 3-year-old boy and an 18-month-old girl, in both cases due to the sealing cap (9). The povidone-iodine inside the cap diffused into the catheter and flushed into the peritoneal cavity at the next dialysis session.

Intravaginal administration

Systemic iodine absorption can occur after intravaginal administration of povidone-iodine (10). There were increases in serum iodine, protein-bound iodine, and inorganic iodine, but not serum thyroxine, after a 2-minute vaginal administration of povidone-iodine in non-pregnant women (11).

Guidelines for the safe use of povidone-iodine complexes

In 1985, a working group of the Federal German Medical Association issued a number of recommendations for the

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safe use of povidone-iodine complexes (12). They remain valid and can be summarized as follows:

1. The application of povidone-iodine formulations cannot be recommended for surgical hand disinfection, since active iodine-free formulations are available.
2. The activity of povidone-iodine in preoperative skin disinfection in adults is well proven.
3. Povidone-iodine is appropriate for skin disinfection before an incision, a puncture, with use of intravenous or arterial catheters, and for the prophylaxis of iatrogenic *Clostridia* infections.
4. In the case of superficial wounds, povidone-iodine can be applied occasionally or repeatedly in spite of increased iodine absorption through the broken skin surfaces.
5. Lavage of wound and body cavities with povidone-iodine or its instillation is not indicated because of increased iodine absorption.
6. Routine body washing of patients in intensive care units is not cost-beneficial.
7. Vaginal administration of povidone-iodine is not recommended.
8. Povidone-iodine is contraindicated in premature babies and neonates; this also applies to prophylactic disinfection of the umbilical stump.
9. The clinical usefulness of povidone-iodine in the treatment of burns is well proven.
10. Local mouth antiseptics serve no therapeutic purpose; this is also true for povidone-iodine.

Organs and Systems

Nervous system

- A 62-year-old man, treated with continuous mediastinal irrigation with a 1:10 solution of povidone-iodine, developed seizures on the fifth day of drainage (13). After the seizure, his serum iodine concentration was raised (120 μg/ml). Renal insufficiency developed at the same time. The electroencephalogram showed no evidence of epileptic activity or other abnormalities. The povidone-iodine irrigation was replaced by continuous irrigation with a solution of neomycin and polymyxin B. Renal function improved and the creatinine concentration returned to normal 3 days after the seizure.

Endocrine

Extensive iodine absorption can cause transient hypothyroidism, or, in patients with latent hypothyroidism, the risk of destabilization and thyrotoxic crisis (SEDA-20, 226) (SEDA-22, 263). Especially at risk are patients with an autonomous adenoma, localized diffuse autonomy of the thyroid gland, nodular goiter, latent hyperthyroidism of autoimmune origin, or endemic iodine deficiency (4).

Povidone-iodine-induced hyperthyroidism is rarer than hypothyroidism (SEDA-20, 226), but a history of long-term use of iodine-containing medications should be considered when investigating the cause of hyperthyroidism (14).

- A 48-year-old woman developed palpitation and insomnia. The clinical history, physical examination, and laboratory tests supported hyperthyroidism. Since July 1994, she had been combating constipation by improper use of an iodine-containing antiseptic cream for external use only. She had inserted povidone-iodine into her rectum by means of a cannula. The iodine-containing cream was withdrawn and she was given a beta-blocker. The palpitation resolved within 2 weeks and her plasma thyroid hormone concentrations normalized within 1 month.

Hyperthyroidism in this patient was probably triggered by improper long-term use of an over-the-counter iodine-containing cream.

Thyrotoxicosis related to iodine toxicity in a child with burns occurred after alternate-day povidone-iodine washes (15).

- A 22-month-old boy was admitted to a pediatric intensive care unit after partial and full thickness burns over 80% of his body surface area. After debridement he was given alternate-day povidone-iodine (Betadine) washes. He became increasingly tachycardic, hypertensive, and hyperpyrexic, with sweating, agitation, and diarrhea and developed neutropenia. Daily sepsis screens were negative. Thyroid function tests showed evidence of iodine-induced thyrotoxicosis. He was given propranolol and carbimazole, and chlorhexidine was substituted for povidone-iodine. His tachycardia, hypertension, and diarrhea slowly improved and his neutropenia resolved. By day 42 his free thyroxine concentration was normal and he was given thyroxine. On day 63 the carbimazole, propranolol, and thyroxine were withheld. However thyroid function tests 1 week later showed hypothyroidism, and thyroxine was restarted. Repeat plasma and urine iodine concentrations on day 57 (a month after withdrawal of povidone-iodine) continued to show marked urinary excretion of iodine (urine concentration 65 μmol/l, reference range 0.39–1.97) with high but falling plasma iodine concentrations (5.9 μmol/l, reference range 0.32–0.63).

Hematologic

Severe neutropenia occurred in a patient in whom deep, second-degree burns, involving about 50% of the body surface, were being treated with Betadine Helafoam twice a day (16).

Liver

There have been reports of liver damage from polyvidone (17).

Urinary tract

Povidone-iodine sclerosis has been suggested to be safe and effective in treating lymphoceles after renal transplantation, with only minor complications of the procedure, such as pericatheter cutaneous infections. However, a case of acute renal tubular necrosis has been reported (18).

- In a 23-year-old woman, a kidney allograft recipient with recurrent lymphoceles treated with povidone-iodine irrigations (50 ml of a 1% solution bd for 6 days), a metabolic acidosis occurred and renal function

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deteriorated. After a few days, despite suspension of irrigation, the patient developed oliguria, and dialysis was needed. A renal biopsy showed acute tubular necrosis.

Iodine-induced renal insufficiency has also been reported after the use of topical povidone-iodine on the skin and after intracavity irrigation.

- A 65-year-old man with second- and third-degree burns covering 26% of his body was given intravenous lactated Ringer solution and topical silver sulfadiazine in addition to debridement and skin grafting (19). However, he developed a wound infection with *Pseudomonas aeruginosa*, which was treated successfully with topical povidone-iodine gel. Persistent nodal bradycardia with hypotension, metabolic acidosis, and renal insufficiency occurred 16 days later. Iodine toxicosis was suspected and the serum iodine concentration was 206 μg/ml (reference range 20–90 μg/ml). The povidone-iodine gel was therefore withdrawn immediately. His family refused hemodialysis and he died 44 days after admission.
- A 57-year-old man developed renal insufficiency after triple coronary bypass grafting, 7 days after povidone-iodine mediastinal irrigation and required 3 days of renal replacement therapy (20). Complete resolution occurred within 8 days and followed a short non-oliguric phase (4 days).

Although other common causes of acute renal insufficiency were present in the second case, the only significant change in management at the time of onset of renal insufficiency was the use of povidone-iodine.

Skin

Povidone-iodine causes concentration-dependent damage to cells and clusters. The effect is most pronounced for isolated cells, but it is also detectable in more complex tissues. Clinical experience with burn victims cannot rule out the possibility that the healing process may be slightly retarded. However, this deficiency may be balanced by an appropriate microbicidal effect on the healing edge (21).

Polyvidone storage disease

Polyvidone molecules that weigh less than 20 kD can be excreted by a normally functioning kidney, whereas larger polymers are phagocytosed and permanently stored in the mononuclear phagocytic system, causing so-called polyvidone storage disease. Polyvidone storage disease occurs in patients who have received polyvidone for prolonged periods of time. The large polymers deposit in the histiocytes and cause them to proliferate and infiltrate histiocytes in the reticuloendothelial system, including osteocytes. There is generally no significant damage to these organs, except that prolonged administration can cause bone destruction, skin lesions, arthritis, and polyneuropathy.

The first cutaneous case of polyvidone storage disease, reported in 1964 (22), was caused by local injection of polyvidone-containing posterior pituitary extracts for the treatment of diabetes insipidus. Similar cases, including those following local injection of porcine polyvidone to treat neuralgia, were documented, mostly in European reports (23,24). Localized cutaneous polyvidone storage disease was then known as Dupont-Lachapelle disease (25).

Five cases of polyvidone storage disease with cutaneous involvement have been documented (26). Two patients presented with skin eruptions mimicking collagen vascular disease and chronic pigmented purpuric dermatosis. In one, polyvidone was found in a metastatic tumor and in the other in a pemphigus lesion. The fifth case was seen in a blind skin biopsy specimen taken to exclude Niemann-Pick disease after examination of a bone marrow smear. The latter patient and the patient with a collagen vascular-like disease also had severe anemia and serious orthopedic and neurological complications due to massive infiltration of polyvidone-containing cells in the bone marrow, with destruction of the bone.

Polyvidone storage disease can easily be diagnosed by its histopathological features. Skin biopsy specimens show a variable number of characteristic blue–gray vacuolated cells around blood vessels and adnexal structures, and stain positively with mucicarmine, colloidal iron, and alkaline Congo red and negatively with periodic acid Schiff and Alcian blue.

Musculoskeletal

Pathological fractures of several bones and destructive lesions seen radiologically in other bones have been reported in patients who had received repeated intravenous injections of polyvidone for many years (27,28). Biopsies of the fracture sites showed both intracellular deposits of polyvidone and mucoid changes in the affected cells. If of sufficient severity, this may cause a virtual "melt down" of osseous tissue.

Immunologic

Polyvidone has been reported to cause anaphylaxis (29).

- A 32-year-old man took paracetamol (in Doregrippin) for flu-like symptoms and about 10 minutes later developed generalized urticaria, angioedema, hypotonia, and tachycardia, and became semiconscious. His symptoms were rapidly relieved by intravenous antihistamines and steroids. This was the first time he had taken Doregrippin, but he had previously taken paracetamol-containing formulations, which had been well tolerated. He was not taking any regular medications. Subsequent testing of the various constituents of the analgesic tablets identified polyvidone as the cause of the anaphylactic reaction.

This report demonstrates a rare case of a type I allergic reaction toward a commonly used ingredient of tablets and widely used disinfectants.

In principle, all forms of the well-known iodine-induced allergic reactions, such as iododerma tuberosum, dermatitis, petechiae, and sialadenitis are possible with povidone-iodine, but the incidence seems to be very low (SEDA-11, 489) (SEDA-12, 586) (4,30,31).

- A severe anaphylactoid reaction occurred immediately after the instillation of a 10% solution of povidone-iodine into a hydatid cyst cavity during surgery. Severe bronchospasm developed immediately and was

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followed by a coagulopathy and subsequent liver and renal insufficiency (32).

There have been only a few reports of contact allergy to povidone-iodine, despite its widespread use. In two cases there were positive patch test reactions on days 2, 3, and 7 to povidone-iodine (5% aqueous) and iodine (0.5% in petrolatum), but negative reactions to povidone itself (33).

Second-Generation Effects

Pregnancy

Routine vaginal douching with povidone-iodine during pregnancy causes maternal iodine overload and markedly increases the iodine content in amniotic fluid and of the fetal thyroid, as soon as the trapping mechanism of iodine by the thyroid has started to develop. Vaginal use of povidone-iodine is therefore not recommended during pregnancy (34,35) and labor (36).

The fetal thyroid starts to store iodine between the 10th and 13th weeks of gestation, and to secrete thyroid hormone between the 18th and 24th weeks. Especially after intravaginal administration during pregnancy, povidone-iodine can cause congenital goiter and hypothyroidism in newborn infants. However, hyperthyroidism can also occur.

In 99 of 9320 newborns, TSH concentrations were above the reference range (20 mU/ml) on the fifth day of life, but between the 10th and 21st day, all these infants had normal TSH concentrations and normal thyroid function (37). In 76 of the newborns with hyperthyrotropinemia, urinary iodine excretion was significantly raised (above 16 μg/ml). Most of them were born in obstetric departments where iodophores were routinely used for disinfection during labor.

In 66 mothers and their infants, povidone-iodine was given during labor and delivery as a 1 or 2% solution pumped intravaginally through a plastic catheter until delivery (for 5–30 hours), urinary iodide concentrations on the first and the fifth day, and serum iodine concentrations at birth were significantly raised in the mothers as well as in the neonates (38). At birth, the TSH concentrations in the mothers and infants were no different from those in the controls, but on the third and fifth days they were significantly higher. Thyroxine concentrations were significantly lower in the exposed mothers and infants (at birth and on the third and the fifth days). One-fifth of the infants had high TSH concentrations (above 20 μU/ml) and low thyroxine values (below 7 μg/ml), which is suggestive of hypothyroidism. However, none of the infants developed clinical symptoms, and on the 14th day the values were normal again. In the iodine-exposed mothers and infants, tri-iodothyronine (T3) concentrations were significantly reduced at birth, but not thereafter. The concentrations of reverse T3 did not differ from the controls at birth, but were significantly lower on succeeding days. This reduction in reverse T3 in the iodine-exposed infants was probably due to reduced thyroxine concentrations, causing a lack of substrates for monodeiodination to reverse T3.

Iodine concentrations in breast milk and in random urine in neonates and the serum concentrations of neonatal TSH and free thyroxine on day 5 after delivery were measured after the use of povidone-iodine for disinfection after delivery (36). Iodine concentrations in the breast milk and neonatal TSH were significantly raised.

Perinatal iodine exposure causes transient hypothyroidism in a significant number of neonates, in whom careful monitoring and follow-up of thyroid gland function are needed. It is better to avoid the use of iodine-containing antiseptics in pregnancy and neonates, especially if follow-up cannot be guaranteed.

Susceptibility Factors

Age

Neonates

Hypothyroidism in neonates has been related to the use of small doses of iodine as an antiseptic. The high vulnerability of the neonatal thyroid is a reason for avoiding povidone-iodine for care of the umbilical stump or omphaloceles (SEDA-11, 488) (SEDA-12, 585) (39).

Serum TSH and thyroxine concentrations have been measured 57 days after birth in 365 healthy newborns whose umbilical stump had been treated with 10% povidone-iodine (40). The prevalence of high TSH concentrations was significantly higher in this group than in the general population (3.1 versus 0.4%), as was the rate of transient hypothyroidism (2.7 versus 0.25%). All the children were normal when retested 1 week later.

Transient hypothyroidism due to skin contamination with povidone-iodine occurred in a neonate with an omphalocele (41).

The postnatal iodine overload, measured as urinary iodine concentration, has been studied in ill neonates after the cutaneous application of povidone-iodine (0.96% I_2; Betadine) (SEDA-11, 488) (39). The mean iodine overload was 1297 μg/day in one povidone-iodine group and 1253 μg/day in a second group; in the control group, 64% of the newborns had iodinuria of less than 100 μg/day, and of the 10 others (mean ioduria 1212 has been studied in ill neonates) three were born by cesarean section: in these cases the mothers received an iodine-containing curariform agent. There were 12 cases of hypothyroidism among the neonates exposed to iodine-containing antiseptics, but none in the control group.

Very low birth weight infants admitted to a neonatal intensive care unit who had been given chlorhexidine-containing antiseptics ($n = 29$) were compared with infants in a comparable unit who had been given iodinated antiseptic agents ($n = 54$) (42). The latter had an up to 50-fold higher increase in urinary iodine excretion than the controls. The median serum TSH concentration was significantly higher in the iodine-exposed infants (4.6 mU/ml) than in the control infants (2.4 mU/ml). On day 14, TSH concentrations in nine of the 36 iodine-exposed infants were above 20 mU/ml, their mean thyroxine concentration was significantly lower (44 nmol/1) than the mean thyroxine concentrations (83 nmol/l) in both the exposed infants with normal TSH concentrations and the controls.

Renal disease

Since iodine is eliminated by the kidneys, renal insufficiency increases the risk of toxicity, and the risk may be further increased by metabolic acidosis (43,44).

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Drug Administration

Drug contamination

Bacterial contamination of povidone-iodine formulations has been reported. *Pseudomonas cepacia* was discovered in the blood cultures of 52 patients in four hospitals in New York over 7 months, and of 16 patients in a Boston hospital over a 10-week period in 1980 (45). A contaminated povidone-iodine solution produced by one manufacturer was implicated as the source of the bacteria. It is not clear why this solution was contaminated, whereas other marketed povidone-iodine solutions containing equivalent amounts of available or free iodine remained sterile.

Interference with Diagnostic Tests

Povidone-iodine gives a positive reaction with an orthotoluidine reagent used to detect blood in the urine, for example Hematest reagent tablets or dipsticks (SEDA-11, 488) (46).

Povidone-iodine used for skin disinfection before skin puncture blood was taken altered serum concentrations of potassium, phosphate, and uric acid.

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Posaconazole

See also Antifungal azoles

General Information

Posaconazole is similar in structure to itraconazole. It was well tolerated and as effective as fluconazole 100 mg in two large randomized comparisons in HIV-infected patients with oropharyngeal candidiasis. In a salvage study in patients with a variety of invasive fungal infections, there were response rates of 44–80% in patients with aspergillosis, fusariosis, cryptococcosis, candidiasis, and pheohyphomycoses after 4–8 weeks of therapy (1,2).

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Potassium chloride

General Information

Oral potassium chloride is used to prevent or correct potassium depletion due to diuretic use or other conditions. Potassium chloride is available not only for medicinal purposes but also as a food supplement and salt substitute.

The main adverse effects of oral potassium salts are hyperkalemia, particularly when they are used in combination with potassium-sparing drugs, such as spironolactone and ACE inhibitors, and gastrointestinal ulceration and perforation, particularly with modified-release formulations. The problems surrounding enteric-coated potassium chloride tablets are unresolved. Despite recommendations that they be withdrawn, some are still available. The risks seem to be less with slow-release potassium chloride tablets.

Simple dietary measures provide adequate potassium intake, and it is questionable whether for most patients potassium supplementation in any pharmaceutical form is necessary, as opposed to the use of potassium-sparing drugs.

Organs and Systems

Cardiovascular

When potassium chloride is given by intravenous infusion for the treatment of potassium depletion (for example in diabetic ketoacidosis) there is a risk of cardiac dysrhythmias if the infusion is too rapid. The rate of infusion should be no greater than 20 mmol/hour.

Electrolyte balance

Hyperkalemia is a risk of potassium chloride administration whether medicinal or not. The wide availability of potassium salts can contribute to accidental fatal hyperkalemia. Hyperkalemia has been reported after ingestion of salt substitutes (1,2) and over-the-counter potassium supplements (3).

Gastrointestinal

Potassium chloride is irritating to the gastrointestinal tract, even to the extent of causing perforation (4). In a retrospective study at surgical clinics in Stockholm County there were 22 cases of small-bowel ulceration in which a connection with slow-release potassium chloride tablets was probable (5). Most of the ulcers had caused stenosis of 1–2 cm of gut, and in four cases there was also perforation of the bowel wall. Five patients had perforation without signs of stenosis. Mortality was 27%. The pathology of the ulcers was similar to that described after use of enteric-coated potassium chloride tablets. The frequency of potassium-induced ulceration is low (about 3 cases per 100 000 patient-years of slow-release tablet use), but this complication can be serious.

Susceptibility Factors

Renal disease

The risk of hyperkalemia from potassium chloride is increased in patients with renal insufficiency (6).

Drug Administration

Drug formulations

Microencapsulated potassium chloride tablets have been reported to be less irritating to the gastrointestinal tract than other forms of potassium chloride. In a comparison of a microencapsulated potassium chloride formulation and a wax-matrix formulation in 48 healthy volunteers, the latter were associated with a higher incidence of upper gastrointestinal lesions determined by endoscopy after 1 week (7). The lesions were not accompanied by epigastric symptoms. Glycopyrrolate, given to some volunteers to reduce gastric emptying, aggravated the effects of potassium chloride.

Drug–Drug Interactions

Potassium-sparing drugs

The risk of hyperkalemia with potassium chloride formulations increases when they are given in combination with drugs that are potassium sparing (8), such as ACE inhibitors and angiotensin II receptor antagonists (9), canrenone, spironolactone (10), amiloride, and triamterene (11).

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Potassium perchlorate

General Information

Potassium perchlorate is a thyrostatic drug that is still used (in a dose of 1000 mg/day or more) as an alternative to the thionamides, especially in cases of allergy. It has also been used to treat the iodine-induced form of thyrotoxicosis, such as type 1 hyperthyroidism due to amiodarone (qv).

Compared with the thionamides, potassium perchlorate has two disadvantages:

1. treatment cannot be directly changed to radioiodine therapy, since perchlorate elimination lasts for some weeks;
2. brief high-dose iodine therapy cannot be used as a preoperative thyrostatic measure.

Potassium perchlorate produces goiter, as do the thionamides, but its effects on the hematological system are the main reason for using it sparingly.

Organs and Systems

Hematologic

Agranulocytosis and aplastic anemia have been described in patients taking potassium perchlorate (SED-8, 897) (1). Deaths have been recorded as a result (2,3).

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Skin

Erythema nodosum associated with lupus erythematosus cells has been described as an adverse effect of potassium perchlorate (SED-8, 897) (1).

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Practolol

See also Beta-adrenoceptor antagonists

General Information

Practolol is a highly cardioselective beta-adrenoceptor antagonist with partial agonist activity.

Although practolol has long been withdrawn from general oral use (because of the oculomucocutaneous syndrome and sclerosing peritonitis) (1), it is still available for intravenous administration in some countries. The practolol syndrome included a psoriasiform rash, xerophthalmia due to lacrimal gland fibrosis, secretory otitis media, fibrinous peritonitis, and a lupus-like syndrome (SED-8, 444) (SEDA-3, 161) (SEDA-2, 170). The pathogenesis of this adverse effect is unknown, but it appears to be unique to practolol.

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Pramipexole

General Information

Pramipexole is a non-ergot dopamine agonist similar to bromocriptine, used in the management of Parkinson's disease as an adjunct to levodopa.

In a systematic review of randomized controlled trials of pramipexole and ropinirole, dizziness, nausea, hypotension, hallucinations, and somnolence were common adverse effects (1). In 306 patients adverse events secondary to pramipexole that occurred in over 10% included dyskinesias, asymptomatic orthostatic hypotension, dizziness, insomnia, and hallucinations (2).

Organs and Systems

Cardiovascular

Orthostatic hypotension is common during oral pramipexole therapy (2).

Peripheral edema has occasionally been described as an adverse effect of dopamine agonist therapy and has been reported in 17 of 300 patients treated with pramipexole (3). The mean dose at onset of edema was 1.7 mg/day and the time after initiation of therapy was 2.6 months. In all cases the edema disappeared after the drug was withdrawn but reappeared on rechallenge. Although the condition was dose-dependent in affected individuals its occurrence was idiosyncratic with no obvious predisposing features. Response to diuretics was minimal.

Nervous system

Drowsiness, dizziness, and insomnia are relatively common adverse nervous system effects of pramipexole in patients with early Parkinson's disease (2).

Worsened dyskinesia is the most common outcome in patients with advanced disease taking concomitant levodopa therapy. In a systematic review of four randomized, placebo-controlled trials of pramipexole in 669 patients with idiopathic Parkinson's disease and long-term complications of levodopa therapy, there were no significant changes in a dyskinesia rating scale, but dyskinesia as an adverse event was reported more often with pramipexole (4).

Eight men aged 54–83 years, who had taken pramipexole 1–4.5 mg/day for Parkinson's disease for an average of 7 months, all fell asleep while driving, resulting in accidents but no injuries (5). They described sudden irresistible sleepiness, with virtually no warning, and four had had similar episodes during other activities. In six patients pramipexole was withdrawn, and in the other two the dose was reduced.

However, doubt has been cast on the existence of sleep attacks, that is acute episodes of sleep that occur without warning, with the newer dopamine receptor agonists (6). In the view of the authors of this review underlying somnolence is always present, even if the patient is not aware of it. They did not attempt to differentiate the risk associated with different agents, but noted that pramipexole doses below 1.5 mg/day are usually adequate and much less likely to cause this problem than higher doses. In general they stressed the importance of keeping doses of all the agents as low as possible and of warning patients about the risk, particularly when driving. They also commented that the possibility of an underlying sleep disorder should be considered in these circumstances.

A study of the effects of pramipexole was generally in agreement with these conclusions (7). In a double-blind study 22 patients were randomized to pramipexole monotherapy (mean 4.4, range 1.5–6, mg/day) and 18 to placebo. Six patients taking pramipexole reported somnolence (one moderate, five mild), compared with two patients taking placebo (one moderate, one mild).

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In an open extension of the study, 21 of 37 patients reported somnolence, including 11 with moderate and 3 with severe symptoms. The onset of symptoms occurred at a mean dosage of 4 mg/day and patients had been taking treatment for 10 months on average at the time of the worst symptoms. Of the 14 patients with moderate to severe symptoms, 12 were interviewed in detail; 7 reported falling asleep while driving and 2 had been involved in minor accidents. Most of the patients reported continuous drowsiness as a background, but three said that they experienced sudden waves of irresistible sleepiness, although with some prodromal symptoms. The symptoms resolved on drug withdrawal or dosage reduction (though details of this were not given), and the comments on dosage from the previous paper are surely relevant. In patients taking pramipexole patient education is clearly of vital importance.

The pathophysiology of the restless legs syndrome is poorly understood, but it often responds well to dopaminergic therapy. However, augmentation of symptoms has also been described, especially with levodopa. Of 60 patients (mean age 58 years) with this syndrome who were treated with pramipexole (0.25–1.0 mg/day) 5 had augmentation of symptoms over a period of at least 6 months during continuous treatment and 4 had what was described as a secondary syndrome, in other words with co-existing and possibly causative neurological disease (8). There was no relation to the initial severity of the syndrome or to the dosage of drug, although the authors suggested that the very low dose of 0.25 mg/day is probably optimal.

Psychological, psychiatric

Hallucinations occur in about 10% of patients with Parkinson's disease, regardless of the stage of disease (2).

Fluid balance

Peripheral edema and weight loss have been reported occasionally during pramipexole therapy. Of 300 patients taking pramipexole, 17 had mild to severe peripheral edema attributable to the drug (3). The mean dosage was 1.7 (range 0.75–3.0) mg/day when the edema first appeared and 2.6 (range 1.5–3.0) mg/day when it was at its worst. In all cases, the edema rapidly abated on withdrawal, and rapidly returned on rechallenge.

Gastrointestinal

Gastrointestinal symptoms have tended to be more frequent in patients with early Parkinson's disease compared with those with advanced disease during pramipexole therapy. In patients with early disease, the most common effects have been nausea (up to 20% of patients), dry mouth (up to 10%), and constipation (7%), whereas less frequent ones, such as dyspepsia, anorexia, dysphagia, and flatulence, have been observed (9). In patients with advanced disease, the overall incidence of adverse gastrointestinal effects is usually 5% or less, and includes constipation, dry mouth, and flatulence (10). Abdominal pain and vomiting occasionally occur.

Hair

Hair loss has been attributed to dopamine receptor agonists.

- Two women in New York, aged 66 and 68 years, took pramipexole 15 and 3.5 mg/day (11). Both developed progressive hair loss 2–12 months later. When pramipexole was withdrawn, there was partial regrowth of hair. Ropinirole and levodopa did not provoke hair loss in these women.

The authors noted that this problem appears to be confined to women, at least according to published reports. The mechanism is unknown.

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Pranlukast

See also Leukotriene receptor antagonists

General Information

Pranlukast is a leukotriene receptor antagonist. It was developed primarily for the Japanese market and there is little international experience of it. To date, adverse events have occurred in under 1% of patients and gastrointestinal effects were the most common, accounting for 4.7% of reported adverse events (1).

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Organs and Systems

Respiratory

Lung injury with interstitial pneumonitis has been attributed to pranlukast (2).

- A 62-year-old woman with severe asthma took oral pranlukast 450 mg/day and oral prednisolone 80 mg/day for a severe asthmatic attack. After oral prednisolone was tapered and subsequently withdrawn by day 35, she was maintained on pranlukast only and 5 days later had fever, deteriorating pulmonary symptoms, hypoxemia, and bibasal reticulonodular pulmonary infiltrates on chest CT. A transbronchial biopsy was consistent with drug-related interstitial pneumonitis. A lymphocyte stimulation test was positive for pranlukast. Her fever abated and her pulmonary symptoms markedly improved 3 days after withdrawal of pranlukast, and 5 months later the pulmonary infiltrates had completely resolved.

Immunologic

The association of cysteinyl leukotriene receptor antagonists with eosinophilic conditions, especially Churg–Strauss syndrome, has generated widespread interest. However, evaluation of the few data is hampered by poor understanding of the underlying pathophysiology of the syndrome as well as by the limited knowledge of the effect that cysteinyl leukotriene has on the immune response and the possibility of interacting genetic polymorphisms (3).

- A 26-year-old asthmatic woman had severe acute necrotizing eosinophilic endomyocarditis while taking pranlukast, inhaled beclomethasone, and oral theophylline (4). Oral prednisolone had been replaced by pranlukast 9 months before the event. Cardiac injury was accompanied by peripheral eosinophilia, cardiogenic shock, and pulmonary infiltrates, suggesting atypical Churg–Strauss syndrome. She recovered after intensive treatment, steroid pulse therapy, and withdrawal of pranlukast.
- A 53-year-old asthmatic woman developed p-ANCA-positive vasculitis while taking pranlukast 450 mg/day (5). Inhaled beclomethasone dipropionate had previously been tapered from 1200 to 800 µg/day over the previous 17 months. She had a mononeuritis multiplex, eosinophilia, and sinusitis. A lymphocyte stimulation test was negative for pranlukast.

In the second case, because p-ANCA had been positive before the patient started to take pranlukast, the authors suggested that her Churg–Strauss syndrome had occurred either through unmasking of a previously unrecognized forme fruste, through tapering the inhaled corticosteroid, or had been coincidental with the natural course of a pre-existing progressive Churg–Strauss syndrome.

In an NIH workshop summary report on the relation between asthma therapy and Churg–Strauss syndrome, the authors concluded that no one compound or class of antiasthmatic agents was solely implicated. An association was found for pranlukast, montelukast, zafirlukast, the 5-lipoxygenase inhibitor zileuton, inhaled corticosteroids, and salmeterol. As corticosteroids constitute the principal therapy of Churg–Strauss syndrome, tapering of these agents may allow incipient Churg–Strauss syndrome to become manifest. In patients who develop Churg–Strauss syndrome and do not receive corticosteroids (6–8), these various antiasthmatic medications might be used to treat asthmatic symptoms but not the underlying Churg–Strauss syndrome (3).

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Pranoprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Pranoprofen is an arylalkanoic acid NSAID (1).

Respiratory

Acute eosinophilic pneumonia has been attributed to pranoprofen in a 48-year-old man (2).

Gastrointestinal

Multiple small bowel ulcers and massive bleeding occurred in a patient taking oral pranoprofen and rectal indometacin (SEDA-17, 113).

Urinary tract

Hemolytic urenic syndrome has been reported in a 25-year-old woman on two separate occasions (3).

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Pravastatin

See also HMG Co-A reductase inhibitors

General Information

In a placebo-controlled study of 1142 hypercholesterolemic patients treated with pravastatin for 8–16 weeks, the numbers of "adverse drug experiences" were similar in the treated and untreated individuals (1). Rash was the only adverse clinical event that was different (4.0 versus 1.1%). However, in the same patients withdrawal of therapy during follow-up was thought to be necessary in 3.2% of those given pravastatin alone. Myopathy was observed in one instance only, and increases in creatine kinase activity in those taking pravastatin did not differ significantly from controls. There were marked persistent increases in transaminases in 1.1%, with no cases of symptomatic hepatitis. Pravastatin is believed to have a particularly low potential for nervous system-related adverse effects, as it has not been shown to enter the cerebrospinal fluid, and clinical experience suggests that muscle toxicity occurs less often with pravastatin than with lovastatin (2).

Organs and Systems

Respiratory

- A 41-year-old man, who had been taking pravastatin for 2 years, developed a hypersensitivity pneumonitis with eosinophilia; the symptoms gradually resolved after withdrawal of pravastatin (3).

Metabolism

- After short-term treatment with pravastatin, a 77-year-old woman transiently developed symptoms diagnosed as porphyria cutanea tarda (4).

Liver

Acute cholestatic hepatitis occurred after 7 weeks of pravastatin 20 mg/day. There was no evidence of allergy (5). It is possible that pravastatin enhances the toxicity of simultaneously administered drugs, for instance, metoprolol in the present case.

- A 64-year-old woman who was twice treated with pravastatin had cholestasis on both occasions with minimal hepatocellular injury (6).

Musculoskeletal

Although myopathy is rarely seen with pravastatin in clinical trials, it does occur.

- Rhabdomyolysis was suspected in a 67-year-old obese man with an acute myocardial infarction (7).
- A 37-year-old man with sarcoidosis developed marked myotonia during several years while he was taking pravastatin 20 mg/day (8). On drug withdrawal his symptoms improved after 2 months.

This association does not prove a causal relation. The authors of the second report pointed to previous observations of myotonia both in sarcoidosis and during the administration of various drugs.

Reproductive system

- A man taking pravastatin 20 mg/day for 3 months reported gynecomastia, which regressed after withdrawal of the drug; he was also taking allopurinol (9).

Drug–Drug Interactions

Fibrate

Rhabdomyolysis can occur when pravastatin is combined with a fibrate (SEDA-21, 460) (10).

Warfarin

With concurrent administration of warfarin and pravastatin there was no evidence of an interaction as assessed by prothrombin time (11).

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Praziquantel

General Information

Praziquantel, initially introduced as a veterinary cesticidal drug, was found to have efficacy against all the human species of schistosomes (including cerebral forms), fasciolopsiasis, cysticercosis, paragonimiasis (lung fluke), *Clonorchis sinensis* (oriental liver fluke), and *Opisthorchis viverrini* infections. It is used in a single oral dose of 40 mg/kg, except in infestations with *Schistosoma japonicum*, *Clonorchis*, and *Paragonimus*, for which more prolonged administration is required, doses varying from 40 to 70 mg/kg/day depending on the infecting species. Evaluation of the result of praziquantel treatment has shown a lower laboratory rate of success than reported for clinical response (SEDA-16, 311).

Praziquantel is effective in human cysticercosis in doses of 10–100 mg/kg for 3–21 days (1). Initially, longer courses of praziquantel were advocated, but even shorter treatment regimens are equally effective: a complete course can be administered in a single day with comparable efficacy as conventional therapy of 15 days. Praziquantel was originally introduced as a racemic mixture; there is evidence that the levorotatory isomer is relatively more effective, but has the same incidence of adverse reactions (2).

Praziquantel is well absorbed and penetrates cyst walls, but it undergoes first-pass metabolism, especially when given together with glucocorticoids and anticonvulsants.

Observational studies

Echinococcosis

The management and operative complications in 70 patients with hydatid disease aged 10–78 years have been studied retrospectively to assess the impact of albendazole and praziquantel compared with surgery (3). In all, 39 patients received albendazole and praziquantel in combination and 19 received albendazole alone; none was treated with praziquantel alone. The combined use of albendazole and praziquantel preoperatively significantly reduced the number of cysts that contained viable protoscolices.

Neurocysticercosis

Praziquantel is generally used to treat neurocysticercosis in an oral dose of 50 mg/kg/day (divided into three doses) for 15 days. Sedation can be marked and driving should be avoided. Liver enzymes sometimes increase. Ocular cysticercosis should not be treated with praziquantel, because destruction of the parasite within the eye can cause irreparable lesions.

A one-day intensive course of praziquantel has been used experimentally, but results vary, and when there are multiple brain cysts present the outcome is poor (4). When used for this purpose in a dose of 25 mg/kg at 2-hour intervals, adverse effects included mild headache, dizziness, nausea, and vomiting. All the adverse effects remitted with analgesics or dexamethasone 0.2 mg/kg/day and continued for 2 days.

Paragonimiasis

Paragonimiasis is a food-borne parasitic disease common in Southeast Asia, especially in Japan, Korea, The Philippines, Taiwan, and parts of China. In Japan, paragonimiasis is caused by either *Paragonimus westermani* or *Paragonimus miyazakii*. Traditionally biothionol was used to treat paragonimiasis, a food-borne zoonosis that is endemic in limited areas of the world. However, owing to the need for long-term administration and moderate to severe adverse effects, such as nausea and diarrhea, biothionol has been replaced by praziquantel. At a dose of 75 mg/kg/day for only 2–3 days, praziquantel has the advantage of an easier dosing schedule in combination with excellent therapeutic efficacy. Adverse effects of praziquantel in paragonimiasis, if any, are mild and transient (5). In patients with pleural effusion, pleural fluid must be drained before starting chemotherapy; insufficient drainage often causes complications, such as chronic empyema or insufficient inflation of the lungs. Praziquantel is also effective for cutaneous, cerebral, or any form of extrapulmonary paragonimiasis.

The radiological features and treatment of paragonimiasis have been described in 13 patients (10 men, three women, aged 25–77 years) (6). All were treated with praziquantel 75 mg/kg/day for 2–3 days. One patient with empyema was also given bithionol. There was mild urticaria in two patients and no serious adverse effects.

Tenia infections

In a report from India the efficacy and safety of treatment of niclosamide-resistant *Tenia saginata* infections with praziquantel 10 mg/kg orally has been confirmed in 185 consecutive patients (7). Follow-up stool examinations at 4 and 12 weeks showed a cure rate of 96%. Eleven patients were lost to follow-up, and eight still produced proglottides at the end of 12 weeks. None passed the worm in their stools, since praziquantel destructs the worm, after which the scolex and worm are digested. Thirty patients (16%) reported minimal adverse effects, such as nausea ($n = 4$), abdominal discomfort ($n = 10$), and giddiness ($n = 16$).

Comparative studies

Praziquantel 100 mg/kg in three divided doses has been compared with albendazole 15 mg/kg/day for 1 week in the treatment of neurocysticercosis in 20 patients (8). In the patients treated with albendazole the number of cysts fell from 64 to 7 and in the patients treated with praziquantel it fell from 59 to 24. The difference was not

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statistically significant. All the patients were concomitantly treated with high doses of glucocorticoids. Nine of the ten patients treated with praziquantel had seizures, headache, and dizziness, and two had hemiparesis before treatment. A few hours after the last dose of praziquantel six patients had adverse reactions, including headache and vomiting in five patients, seizures in one patient, and worsening of the pre-existing motor deficit in one. Analgesics and antiemetics improved the symptoms in four patients. In two patients treatment with mannitol was needed to relief symptoms of increased cranial pressure. The results suggested that single-day treatment with praziquantel of neurocysticercosis may be a useful option. The observed adverse effects were considered to be the result of the inflammatory reaction following the dying of worms and not a toxic effect of the drug itself.

Placebo-controlled studies

In a double-blind, randomized, placebo controlled trial of praziquantel in 42 patients with clonorchiasis and an open study in 32 patients, the adverse effects of praziquantel were transient and included nausea and vomiting (15%), vertigo (12%), hepatomegaly (4.5%), headache (1.5%), rash (1.5%), and hypotension (1.5%) (9). Of 20 patients who received placebo, one developed a transient skin rash, fever, and chills. There were minor and transient, albeit statistically significant, changes in hemoglobin and serum concentrations of total protein, uric acid, cholesterol, and bilirubin.

General adverse effects

Although adverse effects are common they tend to be mild and it is rarely necessary to withdraw praziquantel for this reason; even when used in relatively high doses, as in schistosomiasis, praziquantel has, according to the *British National Formulary* (September 2005), "the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity [of all antihelminthic drugs]." The most common problems relate not so much to direct adverse effects of the drug as to allergic and inflammatory reactions in the host to the presence of dying parasites. Fever, headache, meningism, and exacerbation of neurological symptoms have all been noted; these symptoms tend to be more severe when the pretreatment parasitic infection is widespread and intense (SEDA-20, 282) (SEDA-21, 318). The main direct adverse effects of praziquantel are abdominal discomfort, diarrhea, nausea and vomiting, dizziness, and somnolence (SED-13, 837) (10), (SEDA-16, 310). Among children somnolence was seen in 11%. Headaches, skin rashes, and fever are less common (SED-13, 837). Non-specific effects observed in a minority of patients taking praziquantel include generalized weakness, swelling of the legs, epigastric area, scrotum, or more generally, fatigue (SEDA-16, 354).

Organs and Systems

Respiratory

Acute respiratory failure with exudative polyserositis has been reported in a patient taking praziquantel (11).

Nervous system

An important aspect of drug treatment in neurocysticercosis is the simultaneous use of glucocorticoids with cysticidal drugs (12,13). This combination has been recommended to avoid the secondary effects of treatment due to destruction of parasites within the brain parenchyma. However, these reactions are usually mild and transient and may be ameliorated with analgesics or antiemetics, questioning the need for corticosteroids in every case. Glucocorticoids are currently indicated for patients who develop intracranial hypertension during treatment with cysticidal drugs. This can be anticipated in patients with multiple lesions. However, some forms of neurocysticercosis should not be treated with cysticidal drugs (12,13). Both albendazole and praziquantel can exacerbate the syndrome of intracranial hypertension observed in patients with cysticercotic encephalitis, and are contraindicated during the acute phase of the disease (1). In patients with mixed forms of neurocysticercosis, including hydrocephalus and parenchymal brain cysts, cysticidal drugs should only be used after prior ventricular shunt placement to avoid a further increase in intracranial pressure after treatment. When this precaution is not taken, a further increase in intracranial pressure precipitated by praziquantel can prove fatal (14).

- A 66-year-old man with neurocysticercosis treated with glucocorticoids and praziquantel developed headache and confusion. He did not have a ventricular shunt inserted. A contrast-enhanced CT scan showed multiple focal enhancing lesions with mild edema. An MRI scan of the head was reported as being most consistent with neurocysticercosis. He was given dexamethasone 2 mg bd and praziquantel 50 mg/kg/day. A few days later his headache worsened, with nausea and drowsiness. After 2 weeks he became stuporose and had to be ventilated. A CT scan showed multiple areas of deep subcortical focal edema near the areas of previously enhancing cysts, a striatocapsular stroke, and obstructive hydrocephalus. Two weeks after the last dose of praziquantel and despite a ventriculostomy tube he died.

The authors reported that deaths related to praziquantel in neurocysticercosis are rare. However, this case had characteristics suggestive of a high risk of post-treatment complications. Death was attributed to a sudden increase in intracranial pressure, with multiple foci of edema, meningeal inflammation, and stroke, and occurred despite the concomitant use of glucocorticoids.

In patients with neurocysticercosis treated with praziquantel in increasing doses of 10–50 mg/kg/day for the first week and maintenance therapy during the second week, 27 (60%) presented with adverse effects, three requiring interruption of therapy. Increased intracranial pressure occurred in two cases (one fatal). Exacerbation of CSF pleocytosis was recorded in 26 patients (57%) (SEDA-16, 311).

A delayed reaction, with central nervous system involvement, has been described in patients with cerebral cysticercosis; papilledema, hemorrhages, focal seizures, motor weakness (SEDA-13, 242), and in one case hemiplegia from a vasculitic infarct occurred (SEDA-14, 243). The possibility that this reaction is caused by a

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massive inflammatory response was discussed (SEDA-14, 243). If this hypothesis is correct, glucocorticoid treatment could be contemplated. A review has suggested that the use of glucocorticoids, although still controversial, is generally accepted as a means of alleviating inflammatory complications; however, simultaneous use of a glucocorticoid seems to reduce the plasma praziquantel concentration significantly. According to one group of investigators, no delayed reaction was seen in patients with cerebral schistosomiasis (SED-13, 837).

Dose-dependent dizziness is a recognized effect in some 14% of cases at higher doses of praziquantel (SEDA-12, 267). Patients predisposed to epilepsy may develop convulsions, probably as a reaction to the death of the parasite (15). Headache (40%) and drowsiness (25–40%) have been common in some studies and the manufacturers warn against driving or operating machinery while taking praziquantel.

Most patients treated for neurocysticercosis with praziquantel develop an early cerebrospinal fluid reaction; a similar late reaction, some 2 weeks after treatment has finished, has also been described (16). In both cases clinical signs and symptoms can include papilledema, headache, nausea, vomiting, neck stiffness, and even focal seizures. Glucocorticoids can usually prevent or relieve both the early and late reactions, but they can also reduce efficacy by lowering plasma concentrations of the drug by some 50% (17).

There is a risk that if patients treated with praziquantel for a disease other than neurocysticercosis do in fact also have neurocysticercosis, serious neurological reactions (notably seizures) can occur as the parasite is killed and toxins are released (18).

Sensory systems

Praziquantel should not be used in ocular cysticercosis, because of the risk of inoperable lesions from destruction of the parasite within the eye (19).

Gastrointestinal

Praziquantel can cause dose-related nausea, vomiting, heartburn, and abdominal pain. For example, at doses of 30 mg/kg in schoolchildren there was stomachache in some 16% (SED-12, 775), while in a study with 40 mg/kg 35% of users had abdominal pain (20).

Bloody diarrhea occurs in some patients, but it can be difficult to distinguish this as an adverse effect from pretreatment symptoms; one Ethiopian study of the use of praziquantel in suspected schistosomiasis found that before treatment there was blood in the stool in 55% of cases, diarrhea in 61%, and abdominal discomfort in 80%, and the figures recorded the next day after treatment were not very different (21).

The efficacy and adverse effects of treatment with a single oral dose of praziquantel 40 mg/kg, in relation to egg counts and morbidity, have been studied in 611 primary schoolchildren infected with *Schistosoma mansoni* in Northeastern Ethiopia (22). Before treatment 40% of the patients had no symptoms and 30–40% complained of nausea, abdominal cramps, and/or bloody diarrhea. The symptoms before treatment were not related to nutritional status, intensity of *S. mansoni* egg excretion, or the presence of concomitant intestinal parasites. In the first 4–6 hours, 90 children (15%) developed severe gastrointestinal symptoms, with vomiting, abdominal cramps, and/or bloody diarrhea. They had higher mean pretreatment egg counts than the children who did not have these symptoms. The day after treatment 529 children (87%) were reviewed. Adverse effects were reported by 92% and consisted of abdominal cramps (87%), bloody diarrhea (50%), dizziness (31%), and vomiting (29%). Skin rashes and edema were observed in four individuals. The combination of abdominal cramps with vomiting, bloody diarrhea, and general weakness was significantly more common in the malnourished children and in the children with higher pretreatment egg counts. The overall cure rate after treatment with praziquantel was 83% after 5 weeks, but this rate fell with increasing pretreatment egg counts. These findings confirm that praziquantel is effective in the treatment of *S. mansoni* infections but that treatment may be associated with severe abdominal adverse effects, which may reduce drug compliance in population chemotherapy.

This point has been further evaluated in a larger double-blind, placebo-controlled study of the concurrent administration of albendazole and praziquantel in over 1500 children with high prevalences of schistosomiasis and other helminthic diseases in China and the Philippines, including two strains of *S. japonicum*, and two different areas of Kenya, one each with *S. mansoni* or *Schistosoma hematobium* (23). There was no difference in the rate of adverse effects after treatment with albendazole compared with placebo, but after treatment with praziquantel the children had significantly more nausea, abdominal pain, and headache. These adverse effects, although considered mild, were more common in children with schistosomiasis, which suggests a reaction to dying schistosomes rather than a toxic effect of the drug itself. There was a very high rate of complaints in Kenya, but both the history and the reactions after placebo suggested that many of the adverse effects reported after treatment reflected complaints before treatment.

Liver

It has been suggested that praziquantel can cause hepatomegaly and splenomegaly in children with schistosomiasis (22), but hepatomegaly and splenomegaly have also been described as complications of the disease in these young patients, and they regress with effective treatment (24).

Immunologic

Allergic reactions to praziquantel can be due to parasite death and include fever, urticaria, pruritic skin rashes, and eosinophilia. In one violent reaction there was marked eosinophilia, pleuritic chest pain, cardiac effusion, and ascites, pointing strongly to an exudative polyserositis (11).

Long-Term Effects

Drug tolerance

Diminished susceptibility to praziquantel of *S. mansoni* was reported in an area in Northern Senegal (25).

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Second-Generation Effects

Lactation

Praziquantel is excreted in the breast milk, and mothers should not breastfeed for 72 hours after a dose (26).

Drug–Drug Interactions

Cimetidine

Praziquantel is well absorbed after oral administration and undergoes extensive first-pass metabolism, especially when it is given simultaneously with corticosteroids and anticonvulsants (1). Cimetidine significantly increases praziquantel serum concentrations by inhibiting its first-pass metabolism (27). The concurrent administration of cimetidine with praziquantel in neurocysticercosis allows simplification of the effective praziquantel regimen from 50 mg/kg/day for 2 weeks to a one-day regimen of three doses of 25 mg/kg at 2-hour intervals; this regimen increases the time over which the parasite is exposed to high drug concentrations and produces similar benefits, and also reduces the cost, length of treatment, and total dose used (28). It has also been proposed that simultaneous administration of praziquantel and cimetidine could improve the efficacy of single-day therapy with praziquantel for cysticercosis and other parasitic diseases, such as schistosomiasis (29).

Grapefruit juice

A single dose of grapefruit juice 250 ml significantly increased the AUC and C_{max} of a single dose of praziquantel without changing the t_{max} or half-life, suggesting increased systemic availability (30).

Food–Drug Interactions

Serum praziquantel concentrations increase when a carbohydrate-rich diet is administered (1).

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Prazosin

See also Alpha-adrenoceptor antagonists

General Information

Prazosin is an alpha$_1$-adrenoceptor antagonist.

Organs and Systems

Cardiovascular

Postural hypotension and reflex tachycardia, particularly on standing, are features of the first-dose response to prazosin, but adaptive receptor responses lead to resetting of the reflex mechanisms within the first few days of treatment, and there are therefore generally no significant changes in heart rate during long-term treatment. An orthostatic component to the hypotensive response persists during long-term treatment, and this may be significant and symptomatic if high dosages are used. It is less frequent with modified-release prazosin.

Metabolism

Prazosin and other quinazolines are associated with small but significant changes in plasma lipid profiles. Generally these are potentially beneficial changes, with reductions in LDL cholesterol, total cholesterol, and triglycerides, and increases in HDL cholesterol.

Urinary tract

Blockade of alpha$_1$-adrenoceptors in the urinary tract leads to smooth muscle relaxation and improvement in urinary flow, and this pharmacological action has been used to ameliorate the urinary symptoms of benign prostatic hyperplasia. Prazosin can occasionally lead to urinary incontinence, particularly stress incontinence in women (1).

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Sexual function

There is some evidence that male sexual dysfunction occurs less often with alpha-blockers than with other types of antihypertensive drugs (2). For example, in a comparison of the effects of prazosin and hydrochlorothiazide on sexual function in 12 hypertensive men, plethysmographic measurements and subjective assessments showed less dysfunction with prazosin than with hydrochlorothiazide (3). There is no evidence that this effect can be used therapeutically, but cases of priapism have been reported: for example, a 55-year-old man presented with priapism having taken prazosin 7.5 mg tds for 4 months. After a further 3 months, prazosin was discontinued and erectile function became normal (4).

Drug–Drug Interactions

Alcohol

In a well-controlled study in 10 Japanese patients with mild hypertension, the blood pressure reduction caused by alcohol 1 ml/kg was significantly increased by concurrent treatment with prazosin 1 mg tds (5). At 2–4 hours after ingestion the blood pressure fell by 18/12 mmHg without prazosin and by 24/18 mmHg with prazosin. These results raise the possibility that heavy drinking may cause symptomatic hypotension in patients taking prazosin.

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Prenalterol

General Information

Prenalterol has dobutamine-like positive inotropic effects and has been used in severe heart failure (1). It can cause cardiac dysrhythmias (SEDA-6, 135).

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Prenylamine

See also Calcium channel blockers

General Information

Prenylamine is a coronary vasodilator that depletes myocardial catecholamine stores and has some calcium-channel blocking activity. It has been used in the treatment of angina pectoris, but it often causes ventricular dysrhythmias and has been superseded by less toxic drugs.

Organs and Systems

Cardiovascular

Ventricular tachycardia associated with QT prolongation (torsade de pointes) has often been described with prenylamine (1,2).

Drug–Drug Interactions

Iothalamate

Ventricular tachycardia has been reported after the intravenous administration of sodium iothalamate in a patient taking prenylamine (3). Both drugs can prolong the QT interval.

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Preservatives

General Information

Preservatives that are often found in cosmetics include formaldehyde, quaternium-15, imidazolidinyl urea, diazolidinyl urea, parabens mix, 5-chloro-2-methyl-4-isothiazolin-3-one + 2-methyl-4-isothiazolin-3-one (MCI/MI, Kathon CG), and methyldibromoglutaronitrile (MDBGN, Euxyl K400). Polyhexamethylenebiguanide, a biocide structurally related to hexamidine, is added to cosmetics as a preservative.

Organs and Systems

Immunologic

Preservatives are important causes of allergic contact dermatitis in cosmetics. In a 10-year analysis in 16 centers in 11 countries, 73 818 consecutive patients were patch-tested for the preservatives listed above. There were several cases of contact allergy to formaldehyde and MCI/MI. These preservatives are currently avoided in cosmetics. However, the frequency of positive reactions to MDBGN has risen, from 0.7% in 1991 to 3.5% in 2000. The authors suggested that the concentration of this preservative should be reduced in leave-on cosmetic products (1).

DMDM hydantoin is a preservative that is used mainly in cosmetics. In 1808 consecutive patients DMDM hydantoin was patch-tested in a concentration of 2% in petroleum, and in a further 34 321 patients it was tested in a concentration of 2% in water. The proportion of positive reactions was 0.39–0.65%, with no evidence of a significant time trend. In the 180 positive cases cosmetics (30%) or topical drugs (22%) were considered causal (2).

Hexamidine (0.15% petrolatum) (SEDA-10, 128) has rarely been reported to cause a contact allergic reaction (3,4). Of 1554 patients tested with polyhexamethylenebiguanide 2.5% in aqua, 6 (0.4%) had a positive reaction, indicating a very low sensitization rate (5).

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Prilocaine and Emla

See also Local anesthetics

General Information

Prilocaine is an aminoamide local anesthetic. It can be used on its own, but it is also included in Emla in a eutectic combination with lidocaine (25 mg/ml each), which is widely used as a local anesthetic in topical administration for, for example, superficial surgery and venepuncture.

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Emla cream causes minor local adverse effects, such as itch, burning, and localized purpura (SEDA-19, 131) (SEDA-20, 127) (SEDA-22, 140). A meta-analysis of the use of Emla cream in the elderly (over 65) showed that the technique is generally safe, with only mild transient effects (pallor, redness, and edema) at the application site; there were no systemic effects (1).

However, if large amounts are applied, particularly under occlusion, it can be sufficiently well absorbed to cause systemic effects. Three of 1648 children who received measles vaccination with Emla 1 g had adverse reactions 10–20 minutes later; all required adrenaline for similar symptoms of weakness and dizziness with a cold clammy skin and no pulse or a weak pulse (2). One went on to wheeze markedly and had peripheral cyanosis and shivering, improving with hydrocortisone. The authors proposed that these unusual reactions could have been due to a biphasic local reaction to Emla, with vasodilatation leading to increased absorption and further toxicity.

Organs and Systems

Nervous system

Particular care must be taken with Emla in children, since seizures can occur.

- A 5-year-old child had 35 g of Emla applied under an occlusive dressing to eczematous skin in preparation for cryotherapy for molluscum contagiosum (3). Within 1 hour, the child had a generalized seizure that lasted 10 minutes. The plasma concentrations of lidocaine and prilocaine 30 minutes later were 5.5 and 2.0 μg/ml, respectively, and 6 hours later, the methemoglobin concentration was 19%. The child was given vitamin C 500 mg intravenously, and 2 days later had a methemoglobin concentration of 0.3%.

Errors by pharmacists or parents continue to contribute to severe complications, such as seizures, after overdose of Emla cream in children (4).

- A 21-month-old girl had four generalized tonic-clonic seizures after inadvertent overuse of Emla before curettage of skin lesions of molluscum contagiosum. Because of a pharmacy error, 30 g tubes of Emla were dispensed instead of 5 g tubes. The toddler's mother applied 75 g under occlusive dressing, covering about 350 cm^2 of the child's surface area. This dose significantly exceeds the recommendations for a 14 kg child—maximum 10 g on a maximum area of 100 cm^2. Two doses of intravenous lorazepam (0.1 mg/kg) did not control the seizures, which stopped only after phenobarbital (20 mg/kg) was given. The child then required intubation and ventilation for respiratory depression. The lidocaine concentration 4 hours after the first application of Emla was 2.5 μg/ml and the methemoglobin concentration was 8%.

Seizures have also been reported in adults.

- An 84-year-old woman had three generalized tonic-clonic seizures after repeated applications of Emla (17 applications of 10 g over 23 weeks) (5,6).

Sensory systems

Emla cream can cause severe eye irritation (7).

- Emla cream 30 g was applied to both periorbital and proximal nasal sidewall areas for laser treatment in a 20-year-old woman. Despite the use of a right eye shield for corneal protection, the next day she developed right eye pain and blurred vision and remembered that Emla cream had accidentally entered her right eye before treatment. This caused immediate discomfort, which subsided and then recurred several hours later. She had severe conjunctival injection with loss of epithelium from over 90% of the surface of her cornea, in a pattern more suggestive of chemical than mechanical damage. Treatment with a bandage contact lens and prophylactic antibiotics was effective and her visual acuity returned to baseline.

Hematologic

Methemoglobinemia as an adverse effect of prilocaine (8) has been reported more often than with any other local anesthetic. It is caused by a metabolite and is a particular problem in neonates, who have an immature methemoglobin reductase system and residual fetal hemoglobin, increasing the risk of symptomatic methemoglobinemia.

Neonates and small children who have penile block with prilocaine, for circumcision can develop severe methemoglobinemia (9,10). A report has emphasized the severity of methemoglobinemia in infants especially if premature, when even a small dose of prilocaine is used for infiltration (11).

- A 1.3 kg premature neonate of 30-week gestation, having required ventilation over the first 3 days for respiratory distress syndrome, required reintubation on day 12 of life for recurrent apnea. He developed a pneumothorax requiring an intercostal drain; 0.5 ml of 1% prilocaine was used for infiltration, after which his oxygen requirements overnight went from 28 to 100%; his SpO_2 was 90% and he turned pale gray. His PaO_2 was 23 kPa (170 mmHg) and his methemoglobin concentration was 15%. He was given methylthioninium chloride, and within 8 hours, his methemoglobin concentration was 0.5% and his SpO_2 96%.

Methemoglobinemia can occur with overdosage of prilocaine (SEDA-20, 129) and after inadvertent intravenous administration, particularly in neonates and children (SEDA-11, 221) (12).

- In a 6-year-old boy, 10 ml of a 2% solution given for bilateral percutaneous nephrostomy produced a degree of cyanosis that demanded methylthioninium chloride treatment (13).

In adults, even those with anemia, the shift in methemoglobin concentrations from prilocaine, while measurable, is not of clinical significance (SEDA-12, 257) (14).

Despite concerns that Emla cream can cause methemoglobinemia in neonates and preterm babies, a French study of 116 infants in neonatal intensive care, who were treated with small amounts of Emla once a day before skin puncture, showed that methemoglobin concentrations never exceeded 5% and were not related to

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gestational age or duration of application (SEDA-20, 127). Two other studies on the use of Emla as analgesia for neonates and low birth weight infants showed localized pallor, but no evidence of methemoglobinemia (SEDA-22, 140).

However, high doses of Emla have been responsible for two cases of methemoglobinemia in neonates. In one, 3.5 g of Emla was used before circumcision, and in the other 25 g of cream had been applied to a buttock hemangioma by the parents before laser therapy (SEDA-22, 140).

- A 3-year-old girl with multiple lesions of molluscum contagiosum had Emla applied to the lesions before curettage (15). She became lethargic and hypoactive 2 hours later, with periorbital discoloration and cyanosed lips. Her SaO_2 was 85%, systolic blood pressure 185 mmHg, pulse 144/minute, and her methemoglobin concentration 21%. Her caregiver had applied about 25 g of cream to her entire torso, a massive dose of prilocaine (about 625 mg).

This report reinforces previously described problems arising from carers' lack of understanding of instructions when using Emla in children or babies.

- A 4-day-old boy developed methemoglobinemia (16%) after the application of Emla cream to his penis before circumcision (16).
- A 7-month-old girl was ventilated with inhaled nitric oxide 40 ppm and developed methemoglobinemia after the application of Emla to an 8 cm^2 area of skin for 5 hours (17). Shortly after removal she developed cyanosis, with a methemoglobin concentration of 16%, which resolved with two doses of methylthioninium chloride.

In these cases, the prolonged duration of Emla application was thought to be the cause, but concomitant use of inhaled nitric oxide may have contributed.

Skin

The adverse effects of Emla include localized blanching or erythema, burning or itching sensations, irritant and allergic reactions, and purpura (18).

In 29 children with atopic dermatitis who were given Emla cream before curettage of molluscum contagiosum, there were no adverse reactions, apart from mild transient application site reactions, such as pallor, redness, and edema. No systemic reactions were reported, but the authors emphasized that Emla can be rapidly absorbed through atopic skin, and they therefore recommended that when Emla is applied under occlusive dressing, the maximum dose should be 10 g for 30 minutes (19).

The analgesic effects of single and repeated applications of Emla over six consecutive days have been studied in 11 patients with post-herpetic neuralgia (20). There was no evidence of systemic adverse effects, but four patients developed mild erythema at 30 minutes, which may have been due to the occlusive dressing, and one patient had pruritus on day 7.

Two children developed petechial eruptions after the application of Emla for treatment curettage of molluscum contagiosum (21). Neither became systemically unwell, and subsequent reapplication of Emla in one child did not elicit a petechial eruption.

There has been a report of hyperpigmentation following the use of Emla cream (22).

- A 12-year-old black child developed a patch of hyperpigmentation on his forehead where Emla cream had been used for cutaneous anesthesia before local infiltration with lidocaine for removal of a nevus. This persisted, although fading, for at least 4 months. No other cause could be found.

Hypopigmentation has also been reported with Emla (23).

Contact dermatitis was reported in three hemodialysis patients who used Emla cream repeatedly as analgesia for AV fistula cannulation (SEDA-21, 136).

- A 6-year-old boy developed contact dermatitis following the application of Emla for a skin biopsy to diagnose graft-versus-host disease (24). The histopathological features of the contact dermatitis were similar to graft-versus-host disease.

The use of Emla to provide topical anesthesia should be documented in order to avoid misdiagnosis.

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Primaquine

General Information

The 8-aminoquinolines were the first synthetic antimalarial drugs to be introduced into medicine. Pamaquine (Plasmochin) was the first to be marketed in 1926, but primaquine proved to have the highest chemotherapeutic index of the many compounds tested.

Primaquine is rapidly absorbed, extensively distributed, and predominantly cleared by non-renal elimination. Its principal metabolite is carboxyprimaquine. While primaquine itself is rapidly eliminated from the plasma, the drug is effective when given once daily or even once weekly (SEDA-13, 810). The pharmacokinetics in children, pregnant women, and patients with renal or hepatic dysfunction are unknown.

Primaquine is mainly used to eradicate the exoerythrocytic stages of *Plasmodium vivax* and *Plasmodium ovale*, which if untreated cause late relapse (SEDA-18, 287). There is growing concern about primaquine resistance in *P. vivax* (SEDA-21, 296).

Observational studies

Primaquine base 0.5 mg/kg/day in the prophylaxis of *Plasmodium falciparum* and *P. vivax* malaria for a year did not cause noteworthy adverse effects. General complaints were less than in the placebo group but about the same as in those treated with chloroquine. None of the volunteers (smokers or non-smokers) had a methemoglobin concentration greater than 13% (1).

A randomized, placebo-controlled trial of supervised malaria prophylaxis with primaquine (30 mg/day for 20 weeks) in 97 non-immune adults with normal glucose-6-phosphate dehydrogenase (G6PD) concentrations in Papua New Guinea showed 93% protective efficacy of primaquine against malaria (95% CI = 71, 98%) (2). The most common adverse events were headache, abdominal pain, cough, and nausea, but these were not more frequent than with placebo. Transient rises in methemoglobin concentrations (mean 3.4% on the last day of prophylaxis, resolving by day 18) were asymptomatic.

Supervised treatment of *P. vivax* malaria with chloroquine (600 mg on day 1, 450 mg on days 2 and 3) and primaquine (15 mg/day for 14 days) has been studied in 50 patients in a non-endemic area of Brazil in a prospective open trial (3). G6PD status was not checked. The relapse-free cure rate at 6 months was 86%. There were no important adverse events. Risk factors for relapse included lower doses of primaquine. In patients over 60 kg in weight, the dose of primaquine can fall short of recommendations (0.25–0.3 mg/kg/day), and this can contribute to the risk of relapse.

Combination therapy

Primaquine + clindamycin

Primaquine on its own has some effect against *Pneumocystis jiroveci*, but in dosages of 0.25 or 0.5 mg/kg, primaquine alone was ineffective in rats, confirming earlier clinical experience. Clindamycin alone was also ineffective. The combination was effective both in vitro and in animals for treatment and prophylaxis.

Intravenous clindamycin, 900 mg every 8 hours, with oral primaquine 26.3 mg, was effective in a number of patients with active disease. A maintenance oral dose of clindamycin 150 mg four times daily plus primaquine 26.3 mg/day was adequate. The drugs are thought to be synergistic. In a second study, clindamycin 600 mg qds was used intravenously, with a maintenance dose of 300–400 mg orally and primaquine base orally, 15 mg/day. Tolerance was reasonably good; the most frequent adverse effect, in half the patients, was a generalized maculopapular rash after 10–12 days. Rash was accompanied by fever in three cases. Other adverse effects were leukopenia ($n = 2$), nausea ($n = 2$), and diarrhea ($n = 1$) (SEDA-12, 703) (4). In a third study with higher doses of primaquine, methemoglobinemia was a major adverse effect. In a fourth study, clindamycin was given 900 mg tds with primaquine 30 mg/day, except in three of 28 episodes of *P. jiroveci* pneumonia treated in a total in 26 patients, who received primaquine 15 mg/day (two) or 30 mg on alternate days (one). In 11 episodes the patients had been intolerant of standard therapy, in 13 episodes conventional therapy had failed, and in four episodes there had been treatment failure and intolerance. Of the 28 episodes, 24 were successfully treated with clindamycin/primaquine, the most common adverse effect being rash (5). With the use of higher doses of clindamycin, gastrointestinal effects, especially diarrhea and colitis,

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can be expected. The primaquine component can cause hemolytic anemia and methemoglobinemia. Patients should be screened for G6PD deficiency.

Organs and Systems

Psychological, psychiatric

Severe mental depression and confusion was reported in one patient who had been treated with chloroquine beforehand; all the symptoms disappeared on withdrawal (SEDA-11, 588).

Hematologic

Mild anemia, methemoglobinemia, and leukocytosis have been mentioned occasionally, as well as a very occasional case of agranulocytosis, usually associated with overdosage (6).

Primaquine and its congeners can cause hemolytic anemia in people with G6PD deficiency. The effects are more pronounced in the B type (the Mediterranean type) than in the A type. In a 28-year-old Thai soldier, who developed a hemolytic anemia, G6PD deficiency was not mentioned (SEDA-16, 308), but four patients reported in Vanuatu in 1992 had G6PD deficiency; all developed acute intravascular hemolysis resulting in anemia, hemoglobinuria, and systemic illness after a single dose of the drug (SEDA-17, 328).

Gastrointestinal

The most common adverse effects of primaquine are gastrointestinal: mild to moderate abdominal cramps and occasional gastric distress. In those without G6PD deficiency, primaquine is well tolerated as a prophylactic at doses of 15 mg/day (7), with only 1/106 patients withdrawing because of gastrointestinal upset in one study.

Liver

Primaquine can cause dose-dependent hepatotoxicity, as illustrated by a case of acute liver failure (with spontaneous recovery) caused by accidental overdosage (1260 mg on the second day of treatment for *P. vivax*) (8).

Drug–Drug Interactions

Dapsone

The combination of primaquine with clindamycin is used as second choice in the treatment or prevention of *P. jiroveci* pneumonia. If the patient has been treated immediately beforehand with dapsone, methemoglobinemia can result, especially in patients infected with HIV (SEDA-21, 296).

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Primidone

See also Antiepileptic drugs

General Information

Primidone, a deoxybarbiturate, is partly metabolized to phenobarbital, which is responsible for most of its pharmacological effects. During chronic dosing, the adverse effects of primidone are identical to those of phenobarbital. However, at the start of treatment, primidone can cause a transient intolerance reaction with malaise, dizziness, nausea, vomiting, headache, and other symptoms.

Primidone can cause various idiosyncratic reactions, including systemic lupus erythematosus, a syndrome resembling diabetes insipidus, lymphadenopathy, toxic epidermal necrolysis, thyroid enlargement, and edema.

The use and adverse effects of primidone in the treatment of essential tremor has been reviewed (1). Acute reactions include vertigo, nausea, and unsteadiness; chronic reactions include worsening of depression.

At the start of treatment, primidone can cause a transient intolerance reaction with malaise, dizziness, nausea, vomiting, headache, and other symptoms. To minimize this problem, which is more prominent in patients not exposed to other anticonvulsants, primidone should be started in a low dosage (for example 62.5 mg/day) and increased slowly according to response.

Pretreating patients with phenobarbital can reduce the impact of adverse events when primidone is introduced. Of 30 patients with intractable partial epilepsy pretreated with phenobarbital before starting primidone (500 mg/day increasing by 125–250 mg/day every

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3 weeks until adverse events or a seizure-free state was reached), 26 tolerated the introduction of primidone with minimal or no adverse events (2). Only one patient had to discontinue primidone during the initial 4 weeks because of severe dizziness. Three other patients had dizziness severe enough to interfere with their activities and this disappeared in two patients after the dose was lowered.

Organs and Systems

Immunologic

Giant cell myocarditis has been reported in a patient taking phenytoin, phenobarbital, and mephobarbital and in one taking primidone (3).

Susceptibility Factors

Like phenobarbital, primidone should not be given to patients with acute intermittent porphyria (4).

Drug Administration

Drug overdose

After overdosage, massive crystalluria can occur, due to overload of the urine with hexagonal primidone crystals (SED-13, 154) (4).

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Probenecid

General Information

Probenecid is a uricosuric agent. It is generally well tolerated. Soreness of the gums, gastrointestinal irritation, skin rashes, pyrexia, and the nephrotic syndrome have been reported (1).

Drug interactions with probenecid arise, because it is an inhibitor of the renal tubular secretion of acids and bases (2).

Drug–Drug Interactions

Antibiotics

Probenecid inhibits the renal tubular secretion of various penicillins (3–6) and many cephalosporins (6–20). Ceforanide is not affected (21).

Aspirin

In low dosages (up to 2 g/day), aspirin reduces urate excretion and blocks the effects of probenecid and other uricosuric agents (22,23). However, in 11 patients with gout, aspirin 325 mg/day had no effect on the uricosuric action of probenecid (22). In higher dosages (over 5 g/day), salicylates increase urate excretion and inhibit the effects of spironolactone, but it is not clear whether these phenomena are of importance.

Chloroquine

Probenecid may increase the risk of chloroquine-induced retinal damage (24).

Dapsone

Probenecid increases plasma dapsone concentrations by inhibiting its renal clearance (25).

Indometacin

Interactions with indometacin have been documented through inhibition of renal tubular excretion (26,27). In 17 patients with rheumatoid arthritis, probenecid 500 mg bd improved the therapeutic response to indometacin 25 mg tds over 3 weeks (28). There were changes in the pharmacokinetics of indometacin, which the authors attributed to a reduction in the non-renal clearance of indometacin, possibly because of reduced biliary clearance.

Methotrexate

Probenecid reduces the renal tubular secretion of methotrexate, enhancing its effect (29) and may reduce its plasma protein binding (30).

Sulfinpyrazone

Probenecid reduces the renal tubular secretion of sulfinpyrazone but there is no change in the uricosuric effect (31).

Zidovudine

Probenecid reduces the renal tubular secretion of zidovudine (32,33).

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Probucol

General Information

The adverse effects of probucol have been reviewed (1). As the Probucol Quantitative Regression Swedish Trial (PQRST) showed no improvement in lumen volume of the femoral artery in patients given probucol plus colestyramine, as compared with those given colestyramine alone, doubt has been raised about its efficacy (2).

Organs and Systems

Cardiovascular

Prolongation of the QT interval has been seen and 16 cases of tachydysrhythmias, especially torsade de pointes, have been reported in association with probucol, 15 cases in women (SEDSA-13, 1331) (3,4).

Gastrointestinal

According to long-term studies covering 7–9 years, probucol seems to be well tolerated with a reasonably low incidence of adverse effects. All the documented adverse effects were concentrated in the gastrointestinal tract. The incidence of diarrhea fell from 19% in the first year to 5% in the next. Only in some 3% of cases do symptoms such as diarrhea or abdominal pain lead to withdrawal of treatment. Diarrhea and flatulence, which resolve after a few months, are common.

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Procainamide

See also Antidysrhythmic drugs

General Information

In a prospective study of 488 inpatients there were adverse reactions in 45 cases (9.2%), thought to have been life-threatening in 7 (1.4%), none of whom died (1). The seven patients all had cardiovascular effects. Common adverse effects included gastrointestinal upsets (19 cases) and fever (8 cases). Reactions were more common at daily dosages of 3 g and more.

Comparative studies

The adverse effects of intravenous procainamide (400 mg up to three times infused over 10 minutes) have been reported in 60 adults with atrial flutter or fibrillation in a comparison with ibutilide (2). The adverse effects were headache in 11%, hypotension in 11%, flushing in 3.1%, dizziness in 3.1%, and hypesthesia in 3.1%. The mean fall in systolic blood pressure was about 20 mmHg and occurred at 30–35 minutes after infusion; the corresponding fall in diastolic blood pressure was 10 mmHg. However, in seven patients there was severe hypotension, with a fall in diastolic blood pressure of up to 67 mmHg; in three cases withdrawal of the infusion was required and these patients were treated with intravenous fluids, dopamine, or both. In the severe cases the hypotension occurred during or immediately after the infusion of procainamide.

A comparison between procainamide and propafenone in 62 patients, who had undergone coronary artery bypass grafting or valvular surgery within 3 weeks and developed sustained atrial fibrillation, showed that both drugs converted the dysrhythmia to sinus rhythm in up to 76% of cases, but that propafenone did it more quickly (3). Symptomatic arterial hypotension occurred more frequently with procainamide (nine of 33 patients) than with propafenone (two of 29 patients). Other adverse effects of procainamide were nausea ($n = 2$) and junctional escape rhythm ($n = 2$).

General adverse effects

The adverse effects of procainamide are predominantly on the heart. It causes reduced myocardial contractility and hypotension, and prolongs the QT interval, with consequent dysrhythmias and conduction defects. The lupus-like syndrome most commonly causes polyarthralgia, myalgia, fever, and pleurisy. Neutropenia has been relatively commonly reported in patients taking modified-release formulations. Other adverse effects are uncommon; these include muscle weakness, ataxia, mental confusion, cholestasis, and skin rashes. Hypersensitivity reactions include fever and hematological reactions, including neutropenia, pancytopenia, and pure red cell aplasia. Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Procainamide has a negative inotropic effect and can cause hypotension after both intravenous and oral administration (4,5). When given intravenously it should therefore be infused slowly, at no more than 20 mg/minute. In patients with poor cardiac function procainamide can worsen heart failure, and it may reduce survival after myocardial infarction (6).

Procainamide prolongs the QT interval (7) and can cause dysrhythmias. It can also impair cardiac conduction and can cause bradycardia and heart block (1). In the sick sinus syndrome it can alter sinus node recovery time (8), although the clinical significance of this is not clear.

Pericarditis and tamponade have been reported as rare complications of procainamide-induced lupus-like syndrome (9).

Respiratory

Procainamide can cause lung damage in the context of a lupus-like syndrome (SEDA-17, 226).

Nervous system

Procainamide rarely causes nervous system effects. Acute confusion (10), cerebellar ataxia (11), tremor (12), and muscle weakness (13–16) have all been occasionally reported. In high dosages procainamide has anticholinergic effects (17).

Procainamide has been reported to cause a chronic inflammatory demyelinating polyradiculoneuropathy (18).

- A 68-year-old man took procainamide 500 mg qds for 3 years and developed distal paresthesia and dysesthesia in the legs, followed by progressive muscle weakness, mainly affecting the legs. His gait became unsteady and was wide-based. He had antinuclear antibodies directed against histones in a titer of 1:320, but no antibodies to double-stranded DNA. He had a circulating lupus anticoagulant. The serum procainamide concentration was 3.3 μg/ml (target range 4–8). Nerve conduction studies showed a reduction in sensory nerve action potential amplitudes, a mild reduction in sensory nerve conduction velocity, prolongation of distal motor latencies, and reduced conduction velocities, but no conduction block or temporal dispersions. Electromyography was normal. A left sural nerve biopsy showed perivascular inflammation around a single vessel, without evidence of vasculitis. Myelinated

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nerve fibers were reduced, and scattered nerve fibers showed thin myelin sheaths. About 30% of the fibers showed randomly distributed demyelinated or remyelinated segments. Procainamide was withdrawn and prednisone was given in combination with six plasma exchanges over 2 weeks; after 1 month there was clinical improvement.

This case of polyneuropathy was attributed to a lupus-like effect of procainamide.

Sensory systems

Scleritis has been reported as part of a procainamide-induced, lupus-like syndrome (19).

Psychological, psychiatric

Acute psychosis has been attributed to procainamide (20).

- A 45-year-old woman developed an acute psychosis within 72 hours of starting to take procainamide 75 mg intravenously, followed by a continuous infusion of 2 mg/minute for atrial fibrillation. The plasma procainamide concentration was 8.2 μg/ml and the plasma concentration of the main acetylated metabolite, acecainide, was 4.6 μg/ml. She was then given oral procainamide 500 mg qds, and 2 days later her trough concentrations of procainamide and acecainide were 4.5 and 4.9 μg/ml respectively. The following day she had visual hallucinations and was later found wandering the hospital asking about the babies under her bed. She had no previous history of psychiatric illness and she recovered completely 24 hours after withdrawal of procainamide.

There have been a few previous reports of similar adverse effects with procainamide in therapeutic dosages, and in most cases the plasma concentrations of procainamide and acecainide have been within the usual target ranges, as in this case.

Hematologic

Hematological abnormalities can occur in the absence of a lupus-like syndrome. Hemolytic anemia (21), a circulating anticoagulant (22), thrombocytopenia (23), granulocytopenia (24), and pancytopenia (25) have all been reported occasionally. Thrombocytopenia may be more common in patients taking modified-release formulations (23). Pure red cell aplasia has also been reported (26,27), but it was not clear whether or not there was an associated lupus-like syndrome.

The most common adverse hematological effect of procainamide is neutropenia, which has often been reported, particularly in patients taking modified-release formulations. In one case-control study 4.4% of 114 patients taking modified-release formulations had neutropenia, compared with none in a control group of 509 patients (28). However, a larger subsequent case-control study failed to confirm this association (29). Nevertheless, reports of neutropenia attributed to procainamide continue to appear (30).

There was a positive direct antiglobulin (Coombs') test in about 20% of elderly patients taking procainamide (31). Although a positive Coombs' test can occur in association with a lupus-like syndrome, there was no relation in these cases between positive tests and the presence of antinuclear antibodies. Three of the patients had an autoimmune hemolytic anemia.

Gastrointestinal

Nausea, vomiting, and diarrhea in response to procainamide are common with dosages of 4 g/day or more (32). Pseudo-obstruction has been attributed to the use of a modified-release formulation of procainamide, perhaps due to its anticholinergic effects (33).

Liver

Procainamide can cause intrahepatic cholestasis, perhaps as part of a hypersensitivity reaction (34).

Skin

Lichen planus has been attributed to procainamide as part of a lupus-like syndrome (35).

Procainamide has been reported to cause urticarial vasculitis, although it was not clear whether or not this was part of a lupus-like syndrome (36).

- A 70-year-old man developed a maculopapular skin rash on the trunk 10 days after starting to take procainamide 1.5 g/day (37). Resolution occurred soon after the withdrawal of procainamide and a similar skin rash occurred on rechallenge. In addition to the maculopapular rash, there was swelling and erythema around the eyes and a purpuric rash on the legs. At the time of rechallenge he also had an eosinophilia.

Musculoskeletal

Procainamide can cause an arthropathy as part of a lupus-like syndrome, and the histological findings are indistinguishable from those in idiopathic SLE (38).

Procainamide has occasionally been reported to cause muscle weakness (SEDA-14, 152) (SEDA-16, 183), and it can also cause or exacerbate myasthenia gravis (39).

Necrotizing myopathy of the diaphragm has been reported, perhaps as part of a lupus-like syndrome (40).

Immunologic

Lupus-like syndrome

DoTS classification (BMJ 2003;327:1222–5)
Dose-relation: collateral effect
Time-course: delayed
Susceptibility factors: genetic (slow acetylators)

Procainamide is one of the common causes of drug-induced lupus-like syndrome (41), which is contrasted with idiopathic lupus erythematosus in Table 1.

Frequency

About 29–35% of patients taking procainamide for at least a year are affected and the effect is dose-related. The average age of onset is 59–68 years and 35–58% of the subjects are women. The syndrome can come on within a few weeks, but has been reported as late as 9 years after starting treatment.

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Table 1 The contrast between drug-induced lupus-like syndrome and idiopathic lupus erythematosus

Feature	Idiopathic lupus erythematosus	Drug-induced lupus-like syndrome
Age and sex	Typically young women	Any (depends on use)
Acetylator status	Any	More likely in slow acetylators
Organs involved	Any	Kidneys usually spared
Antinuclear antibody	Usually present	Usually present
Complement	Can be reduced	Usually normal
Anti-DNA antibodies	Usually present (native DNA)	Only to single-stranded DNA

Mechanism

The mechanisms whereby procainamide causes this lupus-like syndrome are not clear. Procainamide is associated with the production of many antibodies, including anti-histone, antiguanosine, anti-DNA, and antiphospholipid antibodies (42). The production of autoantibodies may be due to one of two major mechanisms: first, procainamide may act as a hapten, binding to DNA, nuclear protein, or some membrane constituent, the hapten-protein complex stimulating the production of antibodies; secondly, it may alter suppressor cell function (43). There is also evidence that procainamide can combine with ribonucleoprotein from damaged myocardium after myocardial infarction, thus precipitating the production of antibodies to ribonucleoprotein (44).

Thymus function in 10 patients with symptomatic procainamide-induced lupus has been compared with that in 13 asymptomatic patients who only developed drug-induced autoantibodies (45). Newly generated T cells were detected in all the subjects. Although there was no overall quantitative difference between the symptomatic and asymptomatic patients, there was a correlation between the level of T cell receptor rearrangement excision circles in peripheral lymphocytes and serum IgG antichromatin antibody activity in patients with drug-induced lupus. These results support the hypothesis that the thymus is important in the genesis of drug-induced lupus-like syndrome and that the production of autoreactive T cells starts in the thymus when procainamide hydroxylamine alters T cell tolerance.

In procainamide-induced lupus there is an increase in the number of B cells in both blood and pleural fluid to about 80% (normal 10–25%). Concentrations of IL-6 and soluble IL-2R are also increased (46).

IgG antibodies to the (H2A–H2B)-DNA complex are common in patients with immunological reactions to procainamide (SEDA-20, 178). In a prospective study of 62 patients who had taken procainamide for a mean duration of 23 months (range 1 month to 16 years), and excluding patients with pre-existing systemic lupus erythematosus or who were taking other drugs that have been associated with the lupus-like syndrome, nine developed evidence of lupus-like syndrome and were compared with the other 53 (47). The mean dosage in the patients with lupus-like syndrome was 3.7 g/day compared with 3 g/day in the others, and the durations of administration were 8.8 and 38 months respectively. All four patients who had polyarticular arthritis and/or pleural effusions were positive for the IgG antibodies and four of the other five, who had significantly lower IgG concentrations, presented with the more typical manifestations of vasculitic rashes, pericarditis, or agranulocytosis. In all cases the symptoms and signs either improved markedly or resolved within 3 weeks of withdrawal of procainamide. Seven asymptomatic patients had IgG concentrations comparable with those seen in the patients with lupus-like syndrome, and high concentrations of antibody, although not as high as the two highest in the latter group. Anti-double-stranded DNA antibodies were not detected in any patients. In 33 control subjects there were no detectable antibodies of any kind. The authors therefore suggested that the (H2A-H2B)-DNA IgG antibody is not a useful marker for the occurrence of lupus-like syndrome in patients taking procainamide, although they conceded that the presence of IgG antibody supported the diagnosis of lupus-like syndrome when the main clinical manifestations were arthritis or pleurisy. The significance of the presence of IgG antibodies in asymptomatic patients is not clear, but the authors suggested that it meant that those patients merited careful observation.

The lupus-like syndrome in patients taking procainamide is thought to be due to the procainamide itself, since it has rarely been reported when the main metabolite of procainamide, acecainide, has been administered itself (SEDA-18, 206). Alternatively, the syndrome may be due to a different metabolite of procainamide, and a hydroxylated derivative has been implicated (SEDA-15, 178) (48). CYP2D6 is the major isoform of cytochrome P450 that is involved in the hydroxylation of procainamide, and in the production of some other metabolites (49). It remains to be seen whether extensive CYP2D6 metabolizers are more likely to develop lupus-like syndrome than poor metabolizers.

Susceptibility factors

The lupus-like syndrome is more likely to occur in slow acetylators than in fast acetylators (50), and the rate of development of antinuclear antibody depends on acetylator status (51).

Presentation

The most common feature is arthralgia, in about 77% of cases, with pleural or lung involvement in about 75%. Other common features include myalgia, fever, hepatomegaly, pericarditis, arthritis, and splenomegaly. Skin rashes, adenopathy, and Raynaud's phenomenon occur in 5–10% of cases, and neuropsychiatric and renal involvement are rare. Thrombotic problems can occur because of the properties of anti-DNA and antiphospholipid antibodies (discussed in the next case report). The so-called lupus anticoagulant can be detected in people taking procainamide, even without clinical evidence of lupus

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(52). Angioedema has been reported in a patient who had no history of hereditary angioedema (53).

A lupus-like syndrome with an antiphospholipid syndrome has been attributed to procainamide in a patient with pre-existing systemic sclerosis (54).

- A 51-year-old Korean man with systemic sclerosis was given procainamide 2–3 g/day for suppression of ventricular dysrhythmias. About 2 years later he noticed a new skin ulcer on one of his toes. His dorsalis pedis arteries were not palpable and there was tenderness over the proximal interphalangeal and metacarpophalangeal joints. He had a pancytopenia, prolonged coagulation (with prolongation of the activated partial thromboplastin time and prothrombin time and reduced concentrations of factors XI and XII), an increase in the plasma concentration of von Willebrand factor, a raised serum creatinine concentration, a raised serum C-reactive protein concentration, hypergammaglobulinemia, and hypocomplementemia. He had positive circulating immune complexes and mixed-type cryoglobulinemia, antinuclear antibodies, anti-DNA topoisomerase I antibodies, and a positive LE cell preparation. He had anti-DNA antibodies with a high titer of antibodies to single-stranded DNA and a slightly raised titer of antibodies to double-stranded DNA. Anti-U1 ribonuclear protein, anti-Sm, and anticentromere antibodies were negative. There were high titers of beta$_2$-glycoprotein-I-dependent IgG anticardiolipin antibodies and the lupus anticoagulant test was positive. There were antihistone antibodies. Procainamide was withdrawn and prednisolone and azathioprine given. The pancytopenia, coagulopathy, and renal dysfunction resolved, and his general condition improved; serum concentrations of several of the antibodies returned to normal.

The authors suggested that the pre-existence of systemic sclerosis in this case and the presence of allele HIA-DQBP1* 0303 had increased the patient's susceptibility to the lupus-like syndrome and antiphospholipid syndrome.

Diagnosis

The antinuclear antibody is positive in virtually all cases and the ESR is often raised. Antihistone antibodies are also present in most cases. The prevalence of serum autoantibodies to high-mobility group (HMG) proteins in the serum of patients with drug-induced lupus-like syndrome varies from protein to protein: 67% for HMG-14 and/or HMG-17 compared with 21% for HMG-1 and/or HMG-2. Procainamide-induced lupus is also associated with antibodies to the H2A–H2B dimer (55,56).

Antinuclear antibody is usually present (in 83% of cases), but antibodies to native DNA are not found, although there may be antibodies to single-stranded DNA. Patients taking procainamide can have antinuclear antibodies without developing a lupus-like syndrome.

Management

The syndrome usually regresses rapidly after withdrawal of procainamide, but in a few patients recovery may be delayed; if there are serious effects oral glucocorticoid therapy may be required.

Body temperature

Fever occasionally occurs in patients taking procainamide (SEDA-1, 155) and has been attributed to an allergic reaction (57).

Susceptibility Factors

Renal disease

Maintenance dosages should be reduced in the presence of renal or hepatic impairment, including hepatic congestion due to cardiac failure (58).

Hepatic disease

Maintenance dosages should also be reduced in the presence of renal or hepatic impairment, including hepatic congestion due to cardiac failure (58).

Other features of the patient

Care must be taken in patients with pre-existing connective tissue disease or heart failure. Loading dosages should be reduced in cardiac failure, because of a lowered apparent volume of distribution (58).

Drug Administration

Drug overdose

Procainamide overdose has been reported.

- A 14-year-old boy took about 21 g of procainamide and developed abdominal pain, weakness, blurred vision, dry mouth, pain on swallowing, and headache (59). His pupils were dilated, his skin dry and pale, and his mucous membranes dry. His blood pressure was 106/49 mmHg, his heart rate 91/minute. Following a tonic-clonic seizure his blood pressure was 125/57 mmHg and his heart rate 136/minute in sinus tachycardia. He became lethargic with slurred speech. He was given repeated doses of activated charcoal and made a full recovery. The serum procainamide and acecainide (*N*-acetylprocainamide) concentrations were 63 and 80 μg/ml respectively.
- A 79-year-old man took about 19 g of procainamide and developed lethargy, vomiting, a wide-complex tachycardia, hypotension, and coma (60). His serum procainamide concentration was 77 μg/ml at 3 hours. He was treated with vasopressors and peritoneal dialysis.
- A 67-year-old woman took about 7 g of procainamide and developed nausea, vomiting, lethargy, a junctional tachycardia, hypotension, and oliguria (61). She was treated with hemodialysis.

Drug–Drug Interactions

Amiodarone

The effects of procainamide on the QT interval may be potentiated by other drugs with this action, for example amiodarone (62).

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The pharmacokinetics of procainamide are altered by amiodarone, with a reduction in clearance of about 25% due to changes in both renal and non-renal clearances (62).

Cimetidine

The renal clearance of procainamide is inhibited by cimetidine (63,64).

Class I antidysrhythmic drugs

The effects of procainamide on the QT interval can be potentiated by other drugs with this action, for example other class I antidysrhythmic drugs (62).

Glucose

Procainamide interacts with glucose in vitro to form glucosylamines (63). The reaction was pH-dependent, with a maximum rate of association at a pH of 3.0 and a maximum rate of dissociation at a pH of 1.5. The authors suggested that the loss of procainamide in an intravenous solution of glucose could be marked.

Ofloxacin

The renal clearance of procainamide is inhibited by ofloxacin (66).

Trimethoprim

The renal clearance of procainamide is inhibited by trimethoprim (67).

Monitoring Therapy

The use of serum procainamide concentration measurements in monitoring therapy has been reviewed (58,68). Serum concentrations of 4–10 μg/ml are associated with therapeutic benefit in over 90% of patients with ventricular tachydysrhythmias, and toxicity becomes highly likely over 12 μg/ml. However, the main metabolite of procainamide, acecainide, has antidysrhythmic activity of its own; thus, because metabolism varies widely between individuals, and because acecainide is eliminated by the kidneys, serum concentration measurement of procainamide alone has limited usefulness, particularly in renal insufficiency. There is currently little information on the interpretation of combined measurement of the two compounds.

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Procaine

See also Local anesthetics

General Information

Procaine is an aminoester local anesthetic. It is most widely used as a component of procaine penicillin.

Organs and Systems

Nervous system

Rare cases of tonic seizures have been reliably attributed to the presence of procaine in procaine penicillin (1).

Skin

The incidence of pruritus has been evaluated in a retrospective study of patients receiving procaine, lidocaine, or bupivacaine in combination with fentanyl for spinal anesthesia for a variety of different surgical procedures (2). Procaine plus fentanyl and bupivacaine plus fentanyl produced a higher incidence of pruritus than lidocaine plus fentanyl. The severity of pruritus was also greater in those given procaine plus fentanyl. The incidence and severity of pruritus was not related to the dose of fentanyl. Although this may represent an interaction between fentanyl and ester local anesthetics that differs from the synergy occurring between fentanyl and amide local anesthetics, this was an observational study and was neither randomized nor blinded. Furthermore, the doses of local anesthetic or fentanyl were not standardized. Further prospective randomized studies are therefore required to confirm or refute these claims.

Drug–Drug Interactions

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors inhibit the hydrolysis of procaine and concomitant use can cause procaine toxicity (3).

Suxamethonium

Procaine is hydrolysed by plasma cholinesterase and may therefore competitively enhance the action of suxamethonium (4).

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Procarbazine

See also Cytostatic and immunosuppressant drugs

General Information

Procarbazine is an alkylating agent that is used in the treatment of Hodgkin's disease in regimens such as MOPP (chlormethine (mechlorethamine), vincristine (Oncovin), procarbazine, and prednisolone) and BEACOPP (bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine, and prednisone) (1). It is also used to treat glioblastoma multiforme.

Organs and Systems

Respiratory

The permanent and acute reversible forms of lung disease attributed to procarbazine have been reviewed (2). Pneumonitis has rarely been reported (3).

Drug–Drug Interactions

Antiepileptic drugs

In a retrospective cohort study in 83 patients with primary brain tumors who were treated with procarbazine, 20 patients had procarbazine hypersensitivity reactions (4). There was a significant association between exposure to antiepileptic drugs and the development of procarbazine hypersensitivity reactions. The authors suggested that this association may have been due to a reactive intermediate generated by induction of CYP3A.

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Prochlorperazine

See also Neuroleptic drugs

General Information

Prochlorperazine is a phenothiazine derivative.

Organs and Systems

Nervous system

In 192 consecutive patients attending an emergency department for nausea/vomiting or headache, akathisia occurred in 16% of those treated with prochlorperazine (5–10 mg intravenously or intramuscularly); 4% (all of them women) developed dystonias (1).

Slow infusion of prochlorperazine has been used to try to minimize the risk of akathisia in 160 patients randomly assigned to two groups; akathisia developed in 31 of 84 who were given a 2-minute infusion and in 18 of 76 patients who were given a 15-minute infusion (2).

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Procyclidine

See also Anticholinergic drugs

General Information

Procyclidine is an anticholinergic drug (1). The usual oral dose, which lies between 20 and 30 mg/day, is likely to produce only mild anticholinergic adverse effects, but involuntary movements, with chewing and sucking, have been described in some patients (SEDA-1, 120). Even small doses have produced toxic confusional states when procyclidine was combined with phenothiazines for schizophrenia. Procyclidine is more likely to produce sedation than stimulation.

Reference

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Progabide

General Information

Progabide is an antispasticity drug that is also used in the treatment of epilepsy (1). Together with its metabolites, it acts as an agonist at both $GABA_A$ and $GABA_B$ receptors.

A high proportion of patients suffer from transient minor adverse effects, such as drowsiness, nausea, weakness, or dizziness.

Organs and Systems

Liver

The most serious adverse effect of progabide is hepatotoxicity. In one study, seven of 30 patients given doses up to 45 mg/kg/day had significant disturbances of liver function tests (which returned to normal on withdrawing the drug) (2). In another study, abnormal liver function tests were reported in 8.4% of 1164 patients; clinical hepatotoxicity occurred in 0.5% and three patients died. Monitoring liver function is recommended and drug withdrawal is indicated if liver transaminases exceed twice normal (SED-13, 155).

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Progestogens

See also Individual agents

General Information

Most aspects of progestogens are dealt with in the monograph on hormonal contraception. For a complete account of the adverse effects of progestogens, readers should consult the following monographs as well as this one:

- Hormonal contraceptives—intracervical and intravaginal
- Hormonal contraceptives—oral
- Hormonal contraceptives—progestogen implants
- Hormonal contraceptives—progestogen injections
- Hormone replacement therapy—estrogens + progestogens
- Medroxyprogesterone.

While the progestogens have certain characteristic effects of their own, notably on the female menstrual cycle, the spectrum of adverse effects of any particular progestogen (particularly when given in high doses) is likely to depend heavily on the extent to which it also has glucocorticoid, mineralocorticoid, estrogenic, or androgenic properties.

The natural endogenous progestogen is progesterone (rINN), but most progestogens are semisynthetic. Progestogens belong to two main families:

- hydroxyprogesterone derivatives, which include hydroxyprogesterone caproate, dydrogesterone, medroxyprogesterone, chlormadinone, and cyproterone acetate (all rINNs), and which tend to be antiandrogenic
- ethisterone derivatives, which include norethisterone, norgestrel, levonorgestrel, desogestrel, and gestodene (all rINNs), which have some androgenic activity, and norgestimate (rINN), which has some estrogenic activity.

Water retention occasionally occurs and may reflect a degree of deoxycortone acetate (DOCA)-like activity; virilization of a female fetus is more likely to occur with a product that has some androgenic activity, and breast tenderness with a product that has estrogenic activity.

Some individuals taking progestogens for breast cancer will therefore experience, for example, not only painful swelling of the breast and prolonged amenorrhea (which are progestogenic), but also weight gain and hypercalcemia (which are likely to be glucocorticoid effects). Patients who take progestogens during pregnancy are said to be susceptible to prolonged postpartum bleeding, but this probably reflects the pregnancy disorder for which these drugs were at one time given, for example habitual or threatened abortion. Virilization of the female fetus has been described after administration of various progestogens in early pregnancy and is presumably an androgenic effect.

Progestogens given alone for contraceptive purposes can cause a number of adverse effects, some of which may reflect their other hormonal properties while others are non-specific. Headache, nausea and vomiting, breast tenderness, and pain in the back or abdomen can occur.

Animal studies cannot be regarded as providing a reliable indicator of the spectrum of activity of individual compounds; suggestions that derivatives of hydroxyprogesterone (such as megestrol acetate, medroxyprogesterone acetate) are more "natural" (because of their progesterone-like structure) than derivatives of 19-nortestosterone (such as norgestrel, lynestrenol, ethynodiol acetate, norethisterone, and allylestrenol) are not reflected in any biological findings. Experience, too, can be misleading; there is some suggestion that hydroxyprogesterone caproate can have adverse effects on the fetus when used in pregnancy, while similar reports about allylestrenol (used for the same purpose) are lacking, but one must bear in mind the anecdotal nature of such evidence and especially the fact that hydroxyprogesterone caproate appears to have been more widely used than allylestrenol and is hence more likely to have given rise to reports of adverse reactions.

Progestogens belonging to the ethisterone family (norethisterone, levonorgestrel, desogestrel) have some androgenic activity; those in the hydroxyprogesterone family (hydroxyprogesterone caproate, chlormadinone, cyproterone acetate) tend to be antiandrogenic, while norgestimate seems to be somewhat estrogenic. Water retention occasionally occurs and may reflect a degree of DOCA-like activity; virilization of a female fetus is more likely to occur with a product that has some androgenic activity, and breast tenderness with a product that has estrogenic activity.

In a multicenter, prospective, double-blind, randomized, parallel group study undertaken by general practitioners to compare progesterone pessaries with placebo in the relief of symptoms of premenstrual syndrome, spontaneous reports of adverse events were recorded (1). The 41 patients were randomized to treatment or placebo groups. Patients taking active therapy reported more frequent vaginal pruritus, headache, and irregularities of menstruation. However, when cyclical treatment with progestogen alone was given to postmenopausal women, there was no greater degree of endometrial hyperplasia than in untreated women (2).

Semisynthetic progestogens

Desogestrel (rINN)

Desogestrel, one of the so-called third-generation progestogenic steroids intended for use in oral contraceptives, is metabolized to estrogen. It was developed and introduced because of its relatively favorable effect on blood lipids in experimental work; this led to the hope that it might, in the long run, have a relatively favorable effect on the risk of atherogenesis. However, it is not clear that this does in fact happen, and the third-generation progestogens have been associated with an increased risk of thromboembolism.

Gestodene (rINN)

Gestodene is a third-generation progestogen that has been implicated in an increased risk of thromboembolism.

Gestonorone caproate (rINN)

Gestonorone (17-hydroxy-19-norprogesterone) has been used in doses of 200 mg intramuscularly weekly for benign prostatic hyperplasia (3). Mild adverse effects included loss of appetite and mild fever, but more remarkable were significant reductions in erythrocyte count, hemoglobin, and hematocrit, which normalized after drug withdrawal (4).

Hydroxyprogesterone caproate (rINN)

High doses of hydroxyprogesterone and the related norderivative have been used to treat benign prostatic hyperplasia. Very striking is the high incidence of impotence recorded in these studies, which can affect two-thirds of patients and seems to persist in some patients after withdrawal (5).

Levonorgestrel (rINN)

Extensive clinical trials and premarketing studies were conducted before the Norplant (levonorgestrel) implant was registered and approved, in order to elucidate its mode of action, effectiveness, and adverse effects. However, none of these trials included either teenagers under 18 years of age or nulligravid women.

In an 18-month observational study of 136 adolescents (13–18 years) and 542 adults (19–46 years) who were given Norplant levonorgestrel contraceptive implants problems were reported by 110 patients, mostly irregular bleeding (53% of the adolescents and 38% of the adults) (6). Removal of the implant was requested by 11% of both

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adolescents and adults, most commonly for intolerable menstrual cycle changes, and in 6% of all the adults for irregular bleeding; the time from insertion to removal was 3–15 months for the adolescents and 1–17 months for the adults. Other problems that led to removal (in 5% of adolescents and 7.5% of adults), apart from a desire to become pregnant, included headache, weight gain, and acne.

Lynestrenol (rINN)

Lynestrenol is one of the older progestogens used in oral contraceptives and has been very widely and successfully employed for nearly 40 years; as monotherapy it has been used to treat irregularity of the menstrual cycle.

In a Finnish study analysis of the association between the prolonged use of lynestrenol (to suppress menstruation in mentally retarded women) and arterial disease detected at autopsy, the conclusion was that such treatment, here given for a mean of more than 6 years, increases the risk of arterial disease and that such treatment must be very carefully considered (7).

Medroxyprogesterone acetate (rINNM)

Medroxyprogesterone acetate is the subject of a separate monograph.

Megestrol (rINN)

Megestrol acetate, like medroxyprogesterone acetate, is used for metastatic breast cancer in postmenopausal women. Its commonest adverse effects are typical of the progestogens as a group, but glucocorticoid-like effects are less prominent than with medroxyprogesterone acetate. Typical effects and incidence figures for effective doses in cancer patients (SED-12, 1036) (8,9) have been cited as including weight gain in some 81–88% of cases, mild edema in up to 34%, and hypertension in up to 25%. There are lower but appreciable occurrences of constipation, dyspnea or chest tightness, heartburn, hyperglycemia, and increased urinary frequency; a few cases of phlebitis or thrombosis have been described. Vaginal bleeding, nervousness, sweating, vertigo, gastrointestinal symptoms, skin rash, pruritus, and thrombocytopenia have also been incidentally recorded.

Megestrol acetate has also proved of value in patients with metastatic prostatic cancer, epithelial ovarian cancer, or malignant melanoma and is therefore used in both sexes. The adverse effects are very similar in men to those seen with oncological doses in women; loss of libido and potency is likely to occur in male patients. In one clinical study of 43 men with recurrent and metastatic cancer of the prostate given megestrol acetate 160 mg/day orally, five developed a symptomatic rise in liver enzymes but it resolved during further treatment. In three patients, increasing bone pain occurred, no doubt relating to changes in bony metastases and requiring analgesia. Another patient developed hypercalcemia and one patient developed convulsive epilepsy (10). These latter problems are characteristic of the primary condition as it responds, and not typical for megestrol acetate. The glucocorticoid-induced gain in body weight when it occurs is often linked to improved appetite (11), which can be a positive advantage in cachectic patients with advanced cancers.

When megestrol acetate was used alongside diethylstilbestrol or ethinylestradiol in men with previously untreated metastatic carcinoma of the prostate, there was a high incidence of feminizing adverse effects (70–74%), no doubt attributable to the estrogens; a higher than expected rate of cardiovascular complications (18%) and an unexplained need for cortisone replacement (13%) were also observed (12).

Organs and Systems

Cardiovascular

Progestogens with a degree of mineralocorticoid activity will tend to cause water and salt retention and to increase blood pressure in susceptible subjects. However, effects on blood pressure can be variable; for example, medroxyprogesterone has been variously reported to cause a fall in blood pressure in some initially hypertensive patients while rapidly increasing diastolic pressure in some other women, or to have no effect on blood pressure at all.

Since thromboembolic complications can occur with progestogens, there may be a danger in using them in patients in whom there are other risk factors for thromboembolism. A Spanish group had to deal with patients with AIDS in whom megestrol acetate seems to be helpful in countering AIDS-related anorexia or cachexia. However, advanced HIV infection is itself a risk factor for thromboembolism, as is tuberculosis, which readily occurs in this population. Of 199 patients with AIDS followed for 2 years, 25 took megestrol 320 mg/day. Deep vein thrombosis occurred in seven patients in the entire series, four of them being in the megestrol group and three having tuberculosis. The duration of hormonal therapy up to the moment of thrombosis averaged 98 days. Tuberculosis was an independent risk factor. Statistical analysis led to the conclusion that in this high-risk population the use of megestrol had increased the risk of thrombosis by a factor of 7.6 (13).

Thromboembolism and third-generation progestogens

In October 1995 the UK Committee on Safety of Medicines (CSM) issued a warning that oral contraceptives containing the third-generation progestogens gestodene or desogestrel carry a higher risk of venous thromboembolism, and that women using these should consider changing to another brand (14).

The warning was based on three unpublished studies that had not at the time been formally peer reviewed. All three showed about double the risk of venous thromboembolism with gestodene and desogestrel products compared with oral contraceptives containing other progestogens. The first, a large WHO collaborative case-control study of cardiovascular disease and oral contraceptives was undertaken in 17 countries. It was completed in July 1995, and involved 829 cases of venous thromboembolism and 2641 controls from nine countries in which third-generation oral contraceptives had been used (15). The second, from the Boston Collaborative Drug Surveillance Program, was an analysis of the occurrence of venous thromboembolism in a UK general practice cohort of 238 130 women who had received a

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prescription for an oral contraceptive containing levonorgestrel, gestodene, or desogestrel (16). The third was a transnational case-control study conducted in five European countries, funded by Schering, the leading manufacturer of gestodene (17).

The WHO study was undertaken because the association between oral contraceptive use and venous thromboembolism had not been examined since the 1970s, when oral contraceptives contained higher doses of estrogen and progestogen than now, and because none of the earlier studies had been done in developing countries. The finding of a higher risk of venous thromboembolism with gestodene and desogestrel came as a surprise, and this, together with publicity in the media, prompted the CSM to commission the UK cohort study. The transnational study was set up at the request of the German regulatory authority to follow up German spontaneous reporting data that in 1990 had strongly suggested higher risks of thromboembolism with gestodene-containing oral contraceptives. This led to much controversy in the press and television. Schering had argued that highly publicized deaths had stimulated selective reporting, and that the claimed higher risk was an artefact.

The sudden announcement by the CSM in October 1995 caught prescribers and users of oral contraceptives completely unprepared. What some General Practitioners described as the "pill panic" in the media (18) drove thousands of women to consult their doctors (18–20), who had not been briefed. A heated debate ensued over whether the CSM's decision was justified, whether its announcement should have been delayed until the data were published, and over the dramatic and confusing way in which it was issued. Before long there was general agreement that the decision was necessary and correct, but that its communication had been handled badly, and the Health Minister said that the Government would review the incident to learn from it. Important suggestions for getting this kind of communication correct have subsequently been made (21–23). Official actions in other countries ranged from the imposition of stronger restrictions (in Germany) to decisions in the Netherlands and Canada to wait and consider the published studies, and in the USA not to advise switching to other products (24). The European Union's Committee on Proprietary Medicinal Products also decided to wait and see.

Although doubts about the relative safety of gestodene emerged in 1990, regulators did not publicly acknowledge them. Nor did they help independent scientists to examine all the relevant data (including prescribing figures, essential to provide denominators for the calculation of risk), perhaps because they were insufficient and might have been wrongly interpreted. In Germany, the regulatory authority privately asked Schering to undertake a case-control study; in the UK the Medicines Control Agency considered the available evidence inadequate and dismissed the doubts. Whether the CSM was consulted at that time or only later remains a minor official secret. The attitude changed early in July 1995, when the CSM saw the early results of the WHO Collaborative Study, and a highly critical UK television programme about gestodene-containing oral contraceptives was broadcast (Granada, "World in Action," 10 July). The CSM asked workers from the transnational case-control study to "expedite their results," and commissioned the cohort study using data routinely collected from General Practitioners. The analysis of venous thromboembolism in the transnational study was completed on 8 October, and was promptly discussed with members of the Medicines Control Agency and the CSM. The CSM quickly made its decision (17) and announced it on 18 October. The relevant data from the WHO study and the GP cohort study were published on 16 December; those from the transnational study were published on 13 January 1996 (25). A searching independent analysis of these three studies, and of a fourth (26) that the CSM had not considered, supported the decision (27).

In retrospect, what could the CSM and other authorities have done to alert the world to the potential problem during the 5 years of growing doubts about the relative safety of gestodene? To know about the doubts would have helped women and their doctors. They could then have begun to discuss among themselves whether to act on them or not, in order to weigh any real advantages of their gestodene oral contraceptive against the doubt and potential risk. A joint statement by regulators and manufacturers about their plans for further investigations would have made it clear that there was a problem to be resolved, instead of appearing to ignore or deny it. This would have allowed prescribers and independent experts to rethink their prescribing policies, for example deciding in what circumstances gestodene oral contraceptives should no longer be the first choice. That would not have pleased the manufacturers, since it would almost certainly have reduced the sales of their leading product in an uncontrollable way. The position of desogestrel creates additional complications, since its relative safety was not questioned until the data from the WHO study appeared in July 1995. If doubts had been officially expressed about the gestodene-containing products Femodene and Minulet, these oral contraceptives would meanwhile have lost some market share to Marvelon and Mercilon, the desogestrel-containing products. But greater openness from the start could have minimized the alarm and confusion.

Liver

The progestogens as a group have little effect on the liver. However, some progestogens can increase nonconjugated bilirubin (28); norethisterone acetate has been implicated in this effect (29).

Skin

Progestogens have very occasionally been reported to cause hypersensitivity reactions or skin disorders. Pemphigus has been reported (30).

- A 34-year-old woman with a 3-month history of dysphagia, odynophagia, and conjunctivitis with bulbar injection, who had been taking an oral contraceptive containing a progestogen for 7 months, developed typical bullous lesions on her trunk and nose, typical of pemphigus. Ceftriaxone and ampicillin, which can aggravate pemphigus, exacerbated the lesions. There was reason to believe that the patient had a genetic predisposition to the disorder.

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The circumstances pointed strongly to a drug association, but the identity of the oral contraceptive was not stated; it is likely to have contained a synthetic progestogen and not progesterone itself.

However progesterone-induced dermatitis certainly does occur.

- A 68-year-old woman who took a formulation containing hydroxyprogesterone acetate + conjugated estrogens had for many years an autoimmune dermatitis (31).

Other complications (acne, alopecia, and pruritus) have been associated with Mirena, an intrauterine system containing levonorgestrel.

- Rosacea accompanied the use of Mirena in a 36-year-old woman for 2 years and disappeared within 6 months of removal (32).

However, one is bound to wonder whether this was a direct reaction to levonorgestrel or a stress reaction to the absence of menstrual periods. Like many other users of Mirena, this woman had amenorrhea associated with facial flushing and pustules; conditions such as urticaria, eczema, pompholyx, and erythema multiforme occur cyclically in some women in the second half of the menstrual cycle, irrespective of contraceptive use.

Long-Term Effects

Tumorigenicity

The effects of adding a progestogen on the carcinogenic effects of estrogens are discussed in the monograph on estrogens.

Second-Generation Effects

Teratogenicity

For a number of years from about 1950 onwards, progestogens were used in cases of threatened and habitual abortion. They were largely abandoned for this purpose because of the general conclusion that they were ineffective. There was no general conclusion as to any adverse effects that might have resulted, although some of the progestogens were suspected of having virilizing effects on the fetus. Subsequently, progestogens (usually natural progesterone) were used to provide "luteal support" for some 4 weeks after in vitro fertilization. In 283 women treated for this reason with injectable progesterone 300 mg/day, oral micronized progesterone 90 mg/day, or a sustained-release transvaginal gel, among the offspring there were incidental cases of facial teratoma associated with a cleft palate, a respiratory distress syndrome, and Pierre–Robin syndrome; there was no clear indication that in this respect one formulation was safer than another or that the effects observed were other than might have been anticipated in untreated controls with a similar history (33). Women who received the injectable progesterone tended to complain of drowsiness, reduced libido, dyspareunia, and vaginal irritability.

With regard to progestogens given alone to prevent threatened or habitual abortion, there is no good evidence that they are beneficial, and much evidence to the contrary; however, effects on the sexual development of the fetus cannot be excluded (34).

Tumors may possibly be induced in the second generation. Neuroblastoma in four infants has been attributed to pregnancy or to gonadotropins, clomiphene citrate, or progestational hormones (35), because these drugs result in increased exposure of the early pregnancy to estrogenic or progestogenic influences. Most of these neuroblastomas regress spontaneously, but when regression does not occur they may become malignant. Children born to women who have taken hormonal preparations in early pregnancy should therefore be screened for urinary vanillylmandelic acid concentrations at the age of 6 months.

Drug Administration

Drug formulations

As with estradiol, a case has been made for using natural progesterone, rather than synthetic analogues, largely because it is assumed that as a physiological substance it will be safer. Progesterone is unsuitable for oral use (unless given in a special micronized form), but it is used by other routes. These include systemic and intra-articular injection (36), an intranasal ointment (37), transdermal formulations (38), and intravaginal formulations (39). Apart from local irritation, the wanted and unwanted effects produced when using these modes of administration are the familiar manifestations of progestogen treatment and are proportional to the amount of the drug that actually enters the circulation.

Micronized oral formulations

The fact that progesterone when given by mouth has poor systemic availability can be largely overcome by micronization, and the first product based on this concept was marketed in France as long ago as 1980. Studies and reviews have appeared, particularly since 1997, suggesting that it is indeed less likely to cause adverse effects than the synthetic progestogens are (40). The most frequently reported adverse reactions are stated to be dizziness or drowsiness, which could be related to the pregnenolone metabolites and do not seem to reflect vasoactive changes. It has been argued theoretically that there might be altered sodium metabolism, but no hypertensive effects have been seen. Unusually high doses of micronized progesterone given in pregnancy (in the hope of avoiding premature labor) have been suspected of causing intrahepatic cholestasis, at least in women with a genetic predisposition, but these doses are much higher that those in normal use. No changes in lipid profile appear to occur.

With these very positive conclusions it is not clear why micronized progesterone has not been more widely used. Commercial factors may well have played a role in maintaining the overwhelming dominance of the patented synthetic progestogens. On the other hand, despite the fact that there are estimated to be 500 000 current users of micronized progesterone in France alone, the worldwide scope of experience is still limited compared with that of the synthetic analogues, and one must be prepared for surprises if this product should ever be used more widely. It

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is a fact that in the 1970s, when studies in beagle dogs gave rise to much concern regarding progestogens and the induction of mammary tumors, the same effect was also observed with natural progesterone if sufficient doses were administered. Even a natural substance can have unpleasant effects when used in a manner not foreseen in nature.

Intrauterine release systems

The fiber-based ("frameless") FibroPlant delivery system for levonorgestrel has been tested in an open study in 32 women as a means of relieving menorrhagia or for contraceptive purposes (41). The period of exposure was 1–23 months. This system, which releases levonorgestrel 14 micrograms/day, appeared to be effective for both purposes, and there were no cases of infection, expulsion, or perforation.

An alternative intrauterine delivery system (LNG-IUS) consists of an adapted Nova-T device with a silastic reservoir attached to the vertical arm; the reservoir is impregnated with levonorgestrel and is covered with a rate-limiting silastic membrane. The release rate of levonorgestrel is about 20 micrograms/day for at least 5 years. In a 5-year study in which 1821 women used the combined device and 937 others used the plain Nova-T device, the Pearl index (the number of unwanted pregnancies occurring in 100 couples using a given method for a period of one year) was 0.09/100 woman-years for the LNG-IUS and the ectopic pregnancy rate was 0.02/100 woman-years (42). There were fewer withdrawals because of bleeding problems and pelvic inflammatory disease with LNG-IUS compared with Nova-T, but there were more withdrawals because of hormonal adverse effects and absence of bleeding. One of the advantages claimed for LNG-IUS is that there will be less menstrual blood loss. However, all women who used LNG-IUS had some change in their bleeding pattern after the device had been inserted, and some had many days of spotting. Of another 30 women who used the LNG-IUS system to relieve menorrhagia and who were followed for a year, 13 reported one or more pelvic adverse event; there were six complaints of irregular bleeding, four of abdominal pain, three of breast tenderness, and occasional cases of headache, mood changes, or acne (43).

A systematic review of Mirena, an intrauterine progestogen release system (44), has attracted correspondence (45,46). Like other devices, Mirena releases levonorgestrel, in this case 20 micrograms/day. Since it had no greater efficacy than the Copper T device and was very much more costly, the debate has turned on safety. Amenorrhea is common with this device, as with others like it, and correspondents have pointed out that this is regarded by many women as an unwelcome complication.

Transdermal administration

An older 19-norprogesterone (ST 1435, Merck Darmstadt) was used experimentally in a transdermal form as a possible hormonal contraceptive. A dose of 0.8–1 mg/day was needed to inhibit ovulation in all subjects. There was some irregularity of bleeding, and some subjects had breast tenderness (47).

Vaginal gel

To provide luteal support in ovarian stimulation protocols, especially when following the long procedure, progesterone can be administered by various routes. The oral route is relatively ineffective, since progesterone has a low oral systemic availability (below 10%), which may result in adverse effects such as somnolence. Intramuscular administration is painful and inconvenient. Some workers have therefore given progesterone in the form of an 8% vaginal gel, which is effective and better tolerated than alternative approaches. The gel adheres to the vaginal epithelium, and leakage is substantially less than when using capsules or suppositories; there are no local complications (48). No adverse reactions have been reported with the use of a modified-release vaginal gel containing polycarbophil-based progesterone (49).

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Proglumetacin

See also Non-steroidal anti-inflammatory drugs

General Information

Proglumetacin, an indoleacetic acid derivative, is particularly associated with gastrointestinal adverse effects: in different trials 18–41% of patients had adverse effects, but not to the extent that they interfered with treatment. Comparisons of proglumetacin with indometacin and oxyphenbutazone showed that it is equally effective and usually better tolerated (SEDA-5, 103). In an uncontrolled, open, multicenter, short-term study in patients with cervical or low back pain treated with proglumetacin, the most frequent adverse effects were gastrointestinal, while adverse effects on the nervous system were rare (1).

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Proguanil and chlorproguanil

General Information

Proguanil is one of the antimalarial drugs most widely used for prophylactic purposes, usually in combination with chloroquine or atovaquone in malaria prophylaxis, and with atovaquone in malaria treatment (SEDA-21, 297). A biguanide, it is rapidly absorbed in standard doses and mainly excreted by the kidneys. Its antimalarial effect is due to its metabolite cycloguanil. However, its metabolism varies individually, and this is reflected in a variable degree of efficacy (SEDA-17, 328).

A derivative, chlorproguanil, is similarly effective in chemoprophylaxis of malaria tropica (SEDA-20, 260).

No serious adverse effects of proguanil have been reported in otherwise healthy patients (SEDA-13, 811) (SEDA-17, 328). Skin rashes and hair loss can occur. Mouth ulcers have been mentioned, as have abdominal discomfort and vomiting. The incidence of mouth ulcers in a group of soldiers was 24% in those taking proguanil only and 37% in those taking proguanil 200 mg plus chloroquine either 300 or 150 mg weekly (SEDA-13, 811). With the use of large doses hematuria has been seen.

Organs and Systems

Hematologic

Since chlorproguanil + dapsone exerts lower resistance pressure on *Plasmodium falciparum* than does pyrimethamine + sulfadoxine, a randomized trial in outpatients with uncomplicated falciparum malaria was conducted in Africa in 910 children (1). Treatment failure was more common with pyrimethamine + sulfadoxine. Despite the rapid elimination of chlorproguanil + dapsone, children treated with this combination did not have more episodes of malaria than those who were treated with pyrimethamine + sulfadoxine. However, there was a higher incidence of anemia.

Liver

Hepatitis with mild jaundice has been attributed to proguanil (2).

Susceptibility Factors

Genetic factors

The major limitation of proguanil is that in most ethnic groups there are individuals who have limited ability to metabolize proguanil to the active metabolite cycloguanil. Consequently, poor proguanil metabolizers treated with combination drugs are effectively taking monotherapy. Poor metabolizers also have an increased incidence of adverse effects with proguanil, especially gastrointestinal effects (3).

Renal disease

The urinary excretion of proguanil may mean that caution is advisable when treating patients with renal disorders. Two patients with renal insufficiency became severely ill while taking standard doses of proguanil (SEDA-12, 694) (4). One developed anorexia, dizziness, vomiting, diarrhea, mouth ulcers, a low white cell count, and a low platelet count. The other developed extensive purpura, epistaxis, and vomiting. Bone marrow studies showed hypoplasia and gross megaloblastic changes. The relation of these findings to proguanil therapy is nevertheless questionable, and whether the drug was or was not causative is not known. While it is tempting to seek an explanation in the fact that these biguanides interfere with (plasmodial) folate synthesis, the serum folate and vitamin B_{12} concentrations were normal in both patients.

Drug–Drug Interactions

Cimetidine

Cimetidine co-administration increased the C_{max} of proguanil, and significantly reduced the C_{max} and AUC of cycloguanil, presumably by inhibiting the metabolism of proguanil; co-administration is probably inadvisable (5).

Coumarin

Proguanil potentiates the response to warfarin (6), perhaps by inhibiting CYP2C19 (7).

Levothyroxine

A rise in serum TSH has been described after antimalarial prophylaxis with chloroquine and proguanil in patients taking levothyroxine (SEDA-22, 469). In one case there was a marked increase in serum TSH in the same patient on two occasions after several weeks of antimalarial prophylaxis with chloroquine and proguanil, the likely mechanism being enzyme catabolism (8).

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Prolintane

General Information

Prolintane, an amfetamine-related substance, is a central nervous system stimulant with similar structure and properties to dexamfetamine. Prolintane hydrochloride is available mainly in many formulations with multivitamin supplements in many European countries, Australia, and South Africa.

Organs and Systems

Nervous system

The adverse effects of prolintane include insomnia, nervousness, irritability, euphoria, headache, dizziness, and psychotic reactions (1).

Psychological, psychiatric

Prolintane can cause visual hallucinations (2).

Drug Administration

Drug overdose

Acute overdose can produce cardiorespiratory arrest and death (SEDA-22, 7).

Drug–Drug Interactions

Diphenhydramine

An interaction of prolintane with diphenhydramine has been reported (2).

- A young man developed visual hallucinations after taking prolintane and diphenhydramine. He had started to take prolintane 20 mg/day before 2 months, in order to enhance his intellectual performance and academic grades. Soon afterward he had sleep disturbance and resorted to a hypnotic containing diphenhydramine 25 mg. Despite this, insomnia preceded the acute psychotic episode. Prolintane and diphenhydramine were withdrawn, and he was given oral haloperidol and clorazepate. The symptoms gradually abated.

Pharmacological kindling resulting from increased dopaminergic activity could have explained this psychotic episode (3).

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Promethazine

See also Antihistamines

General Information

Promethazine is a first-generation antihistamine (SEDA-15, 158) (SEDA-21, 176). In vitro studies suggest that CYP2D6 is a key enzyme for the metabolism for promethazine, which could lead to interaction problems (SEDA-21, 176).

Organs and Systems

Nervous system

Neuroleptic malignant syndrome has been associated with promethazine (1).

- A 42-year-old man took promethazine 50 mg every 4–6 hours for 2 days and developed hyperthermia (42.4°C). He died 3 days later despite intensive care and treatment with bromocriptine.

Promethazine intoxication from topical application has been observed in children (2) and adults (3). Symptoms include disorientation, hallucinations, hyperactivity, convulsions, and coma.

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Propafenone

See also Antidysrhythmic drugs

General Information

Propafenone is both a class I antidysrhythmic drug and a beta-adrenoceptor antagonist. Its pharmacological effects, clinical pharmacology, therapeutic uses, adverse effects, and interactions have been reviewed (1–5).

The main adverse effects of propafenone are cardiovascular (27%), central nervous (21%), and gastrointestinal (20%) (6). Other adverse effects occur in under 6% of cases. The overall risk of non-cardiac effects is around 14%. These adverse effects are dose-related: the incidence is 11% at 300 mg/day, 22% at 450 mg/day, 33% at 600 mg/day, and 48% at 900 mg/day (6).

Observational studies

In 87 patients with atrial fibrillation who were given propafenone 2 mg/kg intravenously over 10 minutes, four had hypotension at 8–45 minutes after the start of infusion (7). In two cases this was accompanied by sinus bradycardia, nausea, and slight malaise. In all cases the hypotension resolved rapidly with saline infusion; the drug was withdrawn in only one case. In two cases atrial fibrillation was transformed to asymptomatic atrial flutter with 2:1 atrioventricular conduction.

Quinidine has been added to propafenone with the intention of inhibiting propafenone metabolism via CYP2D6 in the hope of improving outcome (8). Of 60 patients with paroxysmal atrial fibrillation given propafenone 300–450 mg/day for 8 weeks there were 19 refractory cases, who were then randomized double-blind to receive either a higher dose of propafenone (450–675 mg/day) or the standard dose of propafenone with extra low-dose quinidine (150 mg/day), each for 8 weeks, with subsequent crossover to the alternative. Patients who even then were not adequately controlled were given the standard dose of propafenone plus a standard dose of quinidine (600 mg/day) for a further 8 weeks. The plasma propafenone concentrations during the four phases were as follows:

1. standard-dose propafenone alone 128 ng/ml;
2. standard-dose propafenone plus low-dose quinidine 259 ng/ml;
3. high-dose propafenone alone 336 ng/ml;
4. standard-dose propafenone plus standard-dose quinidine 490 ng/ml.

The beneficial effects were related to these plasma concentrations, as were the time to the first bout of atrial fibrillation, the frequency of bouts of atrial fibrillation, and the time between episodes. However, when atrial fibrillation occurred there was no difference in the ventricular rate in the different groups. Adverse effects necessitated drug withdrawal in four patients; one had heart failure and two had gastrointestinal symptoms. These effects were not dose-related, although there were too few occurrences for a definitive conclusion. The authors suggested that this stepwise approach, with increasing doses of propafenone and increasing doses of quinidine could be beneficial in the treatment of paroxysmal atrial fibrillation.

Comparative studies

Amiodarone

Amiodarone 30 mg/kg orally for the first 24 hours plus, if necessary, 15 mg/kg over 24 hours has been compared with propafenone 600 mg in the first 24 hours plus, if necessary, 300 mg in the next 24 hours in 86 patients with recent onset atrial fibrillation (9). Conversion to sinus rhythm occurred faster with propafenone (2.4 hours) than amiodarone (6.9 hours). However, by 24 hours and 48 hours the same proportions of patients were in sinus rhythm; one patient given amiodarone had a supraventricular tachycardia and one a non-sustained ventricular tachycardia.

Of 136 patients with atrial fibrillation treated with either amiodarone ($n = 96$) or propafenone ($n = 40$), 15 developed subsequent persistent atrial flutter, nine of those taking amiodarone and six of those taking propafenone (10). In all cases radiofrequency ablation was effective. It is not clear to what extent these cases of atrial flutter were due to the drugs, although the frequencies of atrial flutter in previous studies with propafenone have been similar. Atrial enlargement was significantly related to the occurrence of persistent atrial flutter in these patients.

Procainamide

A comparison between procainamide and propafenone in 62 patients, who had undergone coronary artery bypass grafting or valvular surgery within 3 weeks and developed sustained atrial fibrillation, showed that both drugs converted the dysrhythmia to sinus rhythm in up to 76% of cases, but that propafenone did it more quickly (11). Symptomatic arterial hypotension occurred more frequently with procainamide (nine of 33 patients) than propafenone (two of 29 patients). Other adverse effects of procainamide were nausea ($n = 2$) and junctional escape rhythm ($n = 2$). Other adverse effects of propafenone were hot flushes ($n = 1$), nausea ($n = 3$), bronchospasm ($n = 1$), and junctional escape rhythm ($n = 2$).

Quinidine

A placebo-controlled study of the use of propafenone 450–600 mg orally, either alone or in combination with digoxin, has been carried out in 176 patients with atrial fibrillation; a further 70 patients were given digitalis plus quinidine (12). There were no significant differences across the groups in terms of percentage conversion to sinus rhythm,

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although conversion occurred more quickly in those given digoxin plus propafenone; this catch-up of the other treatments was attributed to spontaneous conversion in those groups. There were no serious adverse effects in this study. The QT_c interval was slightly prolonged by digitalis plus quinidine and not by the other treatments. In six patients taking propafenone alone there were mild non-cardiac effects, including sickness in two, headache in one, gastrointestinal disturbances in two, and paresthesia in one. Four patients taking propafenone plus digitalis had either sickness or dizziness, and nine patients taking digitalis plus quinidine had gastrointestinal disturbances, sickness, dizziness, or headache. There were no major dysrhythmias; four of the patients who took digitalis plus propafenone had asymptomatic ventricular extra beats, as did one patient who took digitalis plus quinidine. In nine patients who took digitalis plus quinidine there were asymptomatic short-lasting episodes of atrial flutter with atrial ventricular conduction of at least 2:1 immediately before the restoration of sinus rhythm; this happened in 13 patients who took propafenone, 12 patients who took digitalis plus propafenone, and three patients who took placebo. There were two cases of complete left bundle branch block in patients who took digitalis plus quinidine, in three patients who took propafenone, and in two who took digitalis plus propafenone. In two patients who took digitalis plus quinidine and two who took propafenone there was reversible asymptomatic sinoatrial block of Wenckebach type II. Transient mild hypotension occurred in one patient taking digitalis plus quinidine, five taking propafenone, one taking digitalis plus propafenone, and one taking placebo, but the hypotension was transient and not severe. The authors concluded that the addition of digitalis to propafenone hastened cardioversion from atrial fibrillation, although they conceded that the balance of other evidence suggests that digitalis is not effective in restoring sinus rhythm and were unable to explain the efficacy of the combination of digitalis with propafenone.

Sotalol

In a randomized, double-blind, placebo-controlled comparison of propafenone (mean dose 13 mg/kg/day; $n = 102$) and sotalol (mean dose 3 mg/kg/day; $n = 106$) in maintaining sinus rhythm after conversion of recurrent symptomatic atrial fibrillation in 300 patients, efficacy was comparable (13). Tolerable adverse effects in those who took propafenone were gastrointestinal discomfort ($n = 15$), neurological disturbances ($n = 9$), a metallic taste ($n = 4$), and generalized weakness ($n = 1$); nine patients withdrew owing to adverse effects, four with gastrointestinal disorders, three with dizziness, and two with headache; there were no prodysrhythmias.

Propafenone 450 mg/day and sotalol 240 mg/day have been compared in a placebo-controlled study of 300 patients with atrial fibrillation (14). The two drugs had similar efficacy. There were adverse events in 38 of the patients who took propafenone, compared with 12 of those who took placebo. These included gastrointestinal discomfort, neurological disturbances, asymptomatic bradycardia, a metallic taste, and general weakness. In nine patients the adverse effects were sufficient to cause withdrawal of propafenone.

Placebo-controlled studies

In controlled trials in patients with recent-onset atrial fibrillation without heart failure, oral propafenone (450–600 mg as a single dose) had a relatively quick effect (within 3–4 hours) and a high rate of efficacy (72–78% within 8 hours) (15).

The adverse effects of propafenone in placebo-controlled trials in patients with atrial tachydysrhythmias have been reviewed (16). The following effects were reported after single intravenous oral doses to produce conversion of atrial fibrillation to sinus rhythm. Non-cardiac adverse effects included mild dizziness. Mild hypotension was also noted, but only required withdrawal of propafenone in one of 29 patients in one study. There have been prodysrhythmic effects in several studies, including atrial flutter with a broad QRS complex, which can occur in up to 5% of cases; in some cases atrial flutter can have a rapid ventricular response due to 1:1 atrioventricular conduction, which has been attributed to slowing of atrial conduction and reduced refractoriness of the atrioventricular node. Other prodysrhythmic effects in a few patients included sinus bradycardia with sinus pauses and effects on atrioventricular conduction.

In patients taking long-term propafenone for supraventricular dysrhythmias adverse effects were more common and have been reported in 14–60% of cases. Cardiac adverse effects were more common in patients with structural heart disease. The non-cardiac effects were either gastrointestinal (nausea, vomiting, taste disturbances) or neurological (dizziness). Adverse effects are dose-related. In one large study there was no difference between propafenone and placebo in the risk of death.

The use of propafenone in atrial fibrillation (SEDA-23, 202) has been studied in a randomized, double-blind, placebo-controlled trial in 55 patients (17). The dose of propafenone was chosen according to body weight: 450, 600, and 750 mg for those weighing 50–64, 65–80, and over 80 kg respectively. Propafenone converted atrial fibrillation to sinus rhythm significantly more quickly than placebo, and most patients given propafenone had converted by 6 hours. However, by 24 hours there was no significant difference between the two groups. Four patients had hypotension after propafenone, in three cases transiently. The patient with sustained hypotension had poor left ventricular systolic function, but it responded promptly to the administration of fluids and electrical cardioversion. In one patient with transient hypotension there was a brief episode of sinus bradycardia and in another an isolated sinus pause.

Organs and Systems

Cardiovascular

Cardiovascular adverse effects have been reported in 13–27% of patients taking propafenone and ventricular dysrhythmias in 8–19% in small studies. However, in large studies the risk has been reported to be about 5%.

Conduction disturbances are common with propafenone and can result in sinus bradycardia, sinoatrial block, sinus arrest, any degree of atrioventricular block, and right or left bundle-branch block (SEDA-10, 151) (SEDA-15, 179).

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The adverse effects of a single oral dose of propafenone for cardioversion of recent-onset atrial fibrillation have been evaluated in a systematic review (18). The adverse effects were transient dysrhythmias (atrial flutter, bradycardia, pauses, and junctional rhythm), reversible widening of the QRS complex, transient hypotension, and mild non-cardiac effects (nausea, headache, gastrointestinal disturbances, dizziness, and paresthesia).

Dysrhythmias can occur; these include ventricular tachycardia, ventricular flutter, and atrial fibrillation (19–21). Hypotension and worsening of heart failure have occasionally been reported (SEDA-10, 151) (22).

- Wide-complex tachycardias occurred in two elderly patients (a 74-year-old man and an 80-year-old woman) who had taken propafenone for atrial fibrillation (23). In the first case the dysrhythmia was due to atrial flutter with 1:1 conduction.

Although drugs of class Ic, such as propafenone, can slow atrial and atrioventricular nodal conduction in patients with atrial fibrillation or atrial flutter, they do not alter the refractoriness of the atrioventricular node, and this allows 1:1 atrioventricular conduction as the atrial rate slows. This happens despite prolongation of the PR interval.

Class Ic drugs can also convert atrial fibrillation to atrial flutter, reportedly in 3.5–5% of patients. Of 187 patients with paroxysmal atrial fibrillation who were treated with flecainide or propafenone, 24 developed atrial flutter, which was typical in 20 cases (24). These patients underwent radiofrequency ablation, which failed in only one case. All the patients continued to take their pre-existing drugs, and during a mean follow-up period of 11 months, the incidence of atrial fibrillation was higher in patients who were taking combined therapy than in those taking monotherapy. The authors suggested that in patients with atrial fibrillation who developed typical atrial flutter due to class Ic antidysrhythmic drugs, combined catheter ablation and continued drug treatment is highly effective in reducing the occurrence and duration of atrial tachydysrhythmias. They did not report adverse effects.

In controlled trials of oral propafenone (450–600 mg as a single dose) in patients with recent-onset atrial fibrillation without heart failure, atrial flutter with 1:1 atrioventricular conduction occurred in only two of 709 patients (0.3%) who received propafenone (15).

Respiratory

Since propafenone is a beta-adrenoceptor antagonist it can cause shortness of breath or worsening of asthma (25).

Nervous system

Adverse effects on the nervous system are common with propafenone and include somnolence, weakness and disorientation, global amnesia (26), dizziness and vertigo, tremor, visual disturbances, and convulsions (SEDA-10, 151).

- Peripheral neuropathy has been reported in a 41-year-old man who took propafenone 450 mg/day for about a year (27).

Ataxia has been reported in patients taking propafenone (28).

- An 80-year-old man taking propafenone 150 mg tds for paroxysmal atrial fibrillation developed progressive generalized ataxia and weakness 4 days after starting treatment. He had a bilateral symmetrical ataxia, unclear speech, impairment of gait, altered hand coordination, and tremor. The ataxia resolved completely within 3 days of withdrawal.
- A 73-year-old woman taking propafenone 150 mg tds for paroxysmal atrial tachycardia underwent cardioversion during an attack, and the dose of propafenone was increased to 300 mg tds. After 5 days she developed severe ataxia and progressive weakness. The ataxia was symmetrical and there was severe impairment of gait, altered hand coordination, and tremor. The dose of propafenone was reduced to 600 mg/day and the ataxia resolved completely within 6 days. A year later, when the dose of propafenone was increased to 900 mg/day, progressive ataxia again developed after 2 days and became severe within 1 week. Propafenone was withdrawn and the ataxia resolved within a few days.
- An 85-year-old woman took propafenone 150 mg tds for paroxysmal atrial fibrillation and 2 months later developed a progressive ataxia and recurrent falls. The ataxia was symmetrical and there was altered hand coordination, impairment of gait, and tremor. The propafenone was withdrawn and the ataxia resolved completely within 4 days.

Endocrine

Propafenone can cause hyponatremia due to inappropriate secretion of ADH (29).

Hematologic

Propafenone can occasionally cause neutropenia, with a calculated incidence of about one in 10 000 prescriptions per year (30).

Gastrointestinal

Unwanted gastrointestinal effects are the most common adverse effects of propafenone, occurring in up to 30% of cases. They include anorexia, nausea and vomiting, dry mouth, a metallic or bitter taste in the mouth, abdominal discomfort, and constipation (SEDA-10, 151).

Liver

Propafenone can increase the serum activities of transaminases and other enzymes associated with liver function (31). There have also been reports of cholestatic jaundice (32).

Skin

Skin rashes have been reported occasionally (29); these include an acneiform rash and urticaria.

Sexual function

Impotence has occasionally been reported, in one case with a reduced sperm count (33,34).

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Immunologic

Propafenone can cause a rise in antinuclear antibody titers (34) and has once been reported to have caused a lupus-like syndrome (35).

Body temperature

Drug fever without agranulocytosis has been attributed to propafenone (36).

Second-Generation Effects

Pregnancy

When a pregnant woman was given propafenone from the fifth month to term in a dosage of 300 mg tds her dysrhythmias responded satisfactorily and the neonate was healthy (37).

Susceptibility Factors

Genetic factors

Poor and extensive oxidation phenotypes for CYP2D6, which metabolizes propafenone, have been studied in 42 patients, aged 36–75 years, with paroxysmal atrial fibrillation (38). Efficacy was 100% in poor metabolizers, 61% in extensive metabolizers, and 0% in very extensive metabolizers. There was a significant correlation between oxidation phenotype and the ability to maintain sinus rhythm.

Age

The incidence of adverse effects of propafenone in children has varied from study to study, but has sometimes been as high as 25%, requiring withdrawal in 6% of cases (39). Elderly people are at increased risk of adverse effects.

The safety of oral propafenone in the treatment of dysrhythmias has been studied retrospectively in infants and children (40). There were significant electrophysiological adverse effects and prodysrhythmia in 15 of 772 patients (1.9%). These included sinus node dysfunction in four, complete atrioventricular block in two, aggravation of supraventricular tachycardia in two, acceleration of ventricular rate during atrial flutter in one, ventricular prodysrhythmia in five, and unexplained syncope in one. Cardiac arrest or sudden death occurred in five patients (0.6%); two had a supraventricular tachycardia due to Wolff–Parkinson–White syndrome; the other three had structural heart disease. Adverse cardiac events were more common in the presence of structural heart disease and there was no difference between patients with supraventricular and ventricular dysrhythmias.

Drug Administration

Drug dosage regimens

Three different regimens of oral propafenone have been compared in patients with paroxysmal atrial fibrillation (41). In 48 patients who took 600 mg followed 8 hours later by 150 mg there was a higher rate of early successful cardioversion with a lower incidence of adverse effects than in two other groups who took either 300 mg three times over 8 hours ($n = 82$) or four doses of 150 mg over 9 hours ($n = 58$). The rates of conversion were around 80%, similar to those found in other studies. There was QRS prolongation in all three groups, and four of those who took a total of 900 mg developed a broad complex tachycardia.

Drug overdose

About 60 cases of propafenone poisoning have been reported. Even low doses can lead to serious poisoning. Some symptoms, such as gastrointestinal or neurological symptoms, are misleading. Cardiovascular abnormalities include bradycardia, atrioventricular block, abnormal intraventricular conduction, shock, and electromechanical dissociation. The simultaneous presence of neurological symptoms (especially seizures) and abnormal cardiac conduction suggests serious poisoning.

The mortality from propafenone overdose is 23%, according to a retrospective series of 120 patients in Germany over 14 years (42). Severity was related to cardiac conduction disorders and cardiac hyperexcitability.

Seizures have been reported in cases of overdose.

- A 24-year-old woman who took an overdose of propafenone 2.7 g had a convulsion and complete heart block (43). The plasma propafenone concentration 4 hours after ingestion was 2930 ng/ml (target range 400–1600 ng/ml). She was given activated charcoal 50 g, mannitol 200 ml, and clonazepam 1 mg intravenously. By 19 hours after ingestion the electrocardiogram was normal and the plasma propafenone concentration was 858 ng/ml.
- A 22-year-old woman took an overdose of propafenone (amount unknown) and developed tetany and then generalized convulsions requiring intravenous clonazepam (44). She had a low blood pressure and first-degree atrioventricular block associated with prolonged intraventricular conduction. She was intubated and given intravenous fluids, equimolar sodium lactate, dopamine, and adrenaline. Her cardiac conduction returned to normal.

Treatment is symptomatic. Sodium lactate may be required for abnormal intraventricular conduction. Plasma exchange has been successfully used to treat propafenone overdose (45).

- An 18-year-old woman took 35 tablets of propafenone, 300 mg each. She had dilated, non-reactive pupils and greatly increased activity of neuron-specific enolase. She had atrioventricular and intraventricular conduction disorders, and repeated resuscitation was necessary. Propafenone was eliminated by plasma exchange, and the conduction disturbances disappeared rapidly during treatment.

Drug–Drug Interactions

Metoprolol

Propafenone reduces the apparent oral clearance of metoprolol, but it is not clear whether the mechanism is by reduction of true clearance or an increase

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in systemic availability (46). In addition the beta-blocking action of metoprolol is increased by propafenone; this could be due either to reduced clearance of metoprolol or to a true pharmacodynamic interaction between the two drugs, since propafenone has beta-blocking activity.

Monitoring Therapy

Therapeutic benefit is most likely when the plasma propafenone concentration is in the range 0.5–2.0 mg/ml, although the correlation is poor (47), and there is a large overlap between therapeutic and toxic concentrations (32). The therapeutic effect of propafenone correlates better with prolongation of the PR and QRS intervals (48).

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Propanidid

See also General anesthetics

General Information

Propanidid was used as an intravenous anesthetic for rapid induction and for maintenance of general anesthesia of short duration. However, it was withdrawn because of safety considerations regarding the solvent used, polyethoxylated castor oil (Cremophor EL) (SED-11, 211) (1).

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Propantheline

See also Anticholinergic drugs

General Information

Propantheline is an anticholinergic drug. Oral doses are 7.5–30 mg, the latter being used at bedtime; injections of 15 mg have been used in radiology. The persisting doubt as to the incidence of adverse reactions probably reflects the poor and variable systemic availability of the oral form, which also seems to account for conflicting reports about its efficacy. All typical anticholinergic effects can occur if effective doses are given, but central nervous and ocular effects are relatively slight. Propantheline, like others of this type, is not contraindicated in glaucoma or prostatic hyperplasia, but it can influence the response of these conditions to other treatment and hence should be used with some caution.

Drug–Drug Interactions

Digoxin

The interactions of propantheline are similar to those of atropine; for example it increases the rate of absorption of digoxin (1).

Nitrofurantoin

Propantheline increases the rate of absorption of nitrofurantoin (2).

Paracetamol

Propantheline reduces the rate of absorption of paracetamol (3).

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Propiram

General Information

Propiram is an orally active opioid analgesic with weak antagonist activity and effects typical of its class (SED-11, 150) (1,2).

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Propiverine

See also Adrenoceptor agonists

General Information

Propiverine is an anticholinergic drug, used mainly for its effects on the bladder. It is effective in detrusor hyperreflexia and in patients with symptoms of an overactive bladder. Adverse effects occur in about 13% of patients (1).

Organs and Systems

Nervous system

A report of parkinsonism due to propiverine combines a clinical observation with basic pharmacology (2).

- A 72-year-old man had taken propiverine 20 mg/day for nocturia. The exact symptoms are difficult to define, because of the rather curious terminology used in the report, but it appears that he rapidly developed parkinsonian symptoms soon after the start of treatment and was given levodopa 3 months later, with a limited response. After 1 month it was decided to withdraw propiverine and his symptoms disappeared within 2 weeks.

The authors then studied the effect of propiverine on the induction of catalepsy in mice, comparing it with oxybutynin, pentoxyverine, and etafenone, using haloperidol as a reference. They also examined dopamine receptor binding in the striatum. They concluded that any of these agents could cause catalepsy in mice, and that propiverine had greater potency than oxybutynin but less than the others. It was also noted that all the drugs had sub-micromolar affinity for striatal dopamine D_2 receptors. The authors suggested that any drug, such as these, that has a diethylaminomethyl moiety has the potential for extrapyramidal effects, because of interaction with dopamine receptors in the basal ganglia.

Sensory systems

The effect of propiverine on the eye has been investigated in normal and glaucomatous eyes. There was considerable reduction in accommodation in younger individuals in both groups. The drug should therefore be given to younger patients only on very strict indications (3).

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Propofol

See also General anesthetics

General Information

Propofol is a short-acting intravenous induction agent, which is dissolved in a mixture of long-chain triglycerides and soya bean emulsion. It is now in general use in day-care anesthesia and is being increasingly used in infusions in intensive care units. Recovery from anesthetic doses compares favorably with that after enflurane and isoflurane (1).

It has been claimed that propofol produces good recovery after anesthesia. A review of the literature has shown that, for operations that last under 30 minutes, propofol seems to give the best recovery, but for longer operations isoflurane gave better quality recovery (2).

Comparative studies

Propofol versus midazolam

A combination of midazolam plus propofol has been compared with midazolam only for sedation in colonoscopy (3). Midazolam alone produced less profound amnesia, and patients took longer to recover. There

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were no differences in cardiovascular or respiratory parameters. Oxygen saturation was poor in both groups, with saturations less than 85% in 22% of patients given midazolam and in 19% of patients given propofol, although the patients did not initially receive supplementary oxygen. In a similar comparison of midazolam and propofol as sedative agents for diagnostic endoscopy in 80 patients, endoscopy was judged successful in 98% of patients given propofol (mean total dose 354 mg) and 80% of patients given midazolam (mean total dose 8 mg) (4). Patients in the propofol group recovered consciousness more quickly and had complete amnesia. One patient in the propofol group suffered an apneic phase with impaired circulation, requiring manual ventilation and drug therapy.

In a Canadian multicenter, open, randomized trial in 156 patients to determine whether sedation with propofol would lead to shorter times to tracheal extubation and length of stay in ICU than sedation with midazolam, the patients who received propofol spent longer at the target sedation level than those who received midazolam (60 versus 44% respectively) (5). Propofol allowed clinically significantly earlier tracheal extubation than midazolam (6.7 versus 25 hours). However, this did not result in earlier discharge from the ICU.

Anesthetist-administered midazolam and patient-controlled propofol have been compared for sedation during vitreoretinal surgery (6). The patients received propofol 15–18 mg according to age, with a 1-minute lockout, or 0.25–0.5 mg of midazolam as judged necessary by the anesthetist. Few patients were amnesic for the procedure and both techniques produced satisfactory sedation and comfort. Non-anesthetists need to be extremely wary if using propofol for sedation, since propofol has a low therapeutic index and commonly causes unconsciousness, respiratory depression, and cardiovascular collapse, particularly when it is used in combination with either midazolam or alfentanil (7). Adequate staff, training, and facilities for resuscitation of patients must be available before considering propofol sedation. Propofol can cause deep sedation, and the episode reported in one of these studies is not surprising. Extreme caution must be exercised in recommending these techniques to non-anesthetists.

Organs and Systems

Cardiovascular

Propofol is a cardiodepressant and resets the baroreflex set-point, with a tendency to bradycardia (which occurs in some 5% of cases), hypotension (16%), or both (1.3%) (8). The hypotension may be brought about by peripheral vasodilatation, reduced myocardial contractility, and inhibition of sympathetic nervous system outflow (9). Four deaths due to cardiovascular collapse during induction have been reported in patients aged 78–92 years given propofol 1.1–1.8 mg/kg (10). The patients were of ASA classes 3 or 4.

Total intravenous anesthesia with propofol resulted in a reduced heart rate and a higher frequency of oculocardiac reflex bradycardia than thiopental/isoflurane anesthesia, with a higher sensitivity of children younger than 6 years in all groups (11).

Hemodynamic effects

The cardiovascular effects of propofol have been examined in a randomized trial in 40 healthy subjects using transthoracic echocardiography (12). Propofol was given to the same total dose (2.5 mg/kg) at two different rates, 2 mg/second or 10 mg/second. In both groups, global and segmental ventricular function was unchanged, but propofol caused a markedly reduced end-systolic quotient, presumably related to reduced afterload. With the higher infusion rate, there was a significant reduction in fractional shortening, thought to be related principally to reduced preload.

There has been a prospective, double-blind, controlled comparison of propofol, midazolam, and propofol + midazolam for postoperative sedation in 75 patients who received low-dose opioid-based anesthesia for coronary bypass grafting (13). Mean induction doses of propofol and midazolam used alone were 2.5 times higher than when both were used together. The single agents caused significant reductions in blood pressure, left atrial filling pressure, and heart rate after induction. These hemodynamic changes returned to normal after 15 minutes with midazolam and after 30 minutes with propofol, except for the bradycardia, which remained for the duration of the sedation. The combination of propofol + midazolam had no significant hemodynamic effects, but was also associated with bradycardia lasting the duration of the sedation. There was a greater than 68% reduction in maintenance doses with the combination. Propofol and propofol + midazolam were associated with comparable times to awakening and extubation, while with midazolam alone recovery was slower. This study clearly showed a reduction in adverse effects from exploiting the sedative synergism between propofol and midazolam.

In a placebo-controlled study of induction of anesthesia with a combination of propofol + fentanyl in 90 patients aged over 60 years, prophylactic intravenous ephedrine 0.1 or 0.2 mg/kg given 1 minute before induction of anesthesia significantly attenuated the fall in blood pressure and heart rate that is usually observed (14). Prophylactic use of ephedrine may be useful in preventing the occasional instances of cardiovascular collapse recorded after induction of anesthesia using these agents in elderly people.

The hemodynamic effects of combining ephedrine with propofol in an effort to prevent hypotension and bradycardia have been investigated in 40 elderly patients of ASA grades III and IV, who received ephedrine 15, 20, or 25 mg added to propofol 200 mg (15). The hypotensive response to propofol was effectively prevented, but marked tachycardia in the majority of patients meant that the technique may not be beneficial, given the high incidence of ischemic heart disease in this age group.

The effects of giving calcium chloride 10 mg/kg after induction of anesthesia with propofol, fentanyl, and pancuronium have been investigated in 58 patients undergoing elective coronary artery bypass grafting (16). Calcium chloride reduced the fall in arterial blood pressure and prevented the reductions in heart rate, stroke volume index, cardiac index, and cardiac output, compared with placebo. Propofol reduces the availability of calcium to the myocardial cells, and calcium chloride effectively minimizes the hemodynamic effects of

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propofol. However, given that intravenous calcium can be locally toxic when given via peripheral veins, the technique may have limited applicability.

Cardiac dysrhythmias

Propofol causes bradydysrhythmias by reducing sympathetic nervous system activity.

- A four-year-old patient developed a nodal bradycardia while receiving propofol 6 mg/kg/hour + remifentanil 0.25 microgram/kg/minute (17). The bradycardia responded to atropine 0.3 mg.
- Complete atrioventricular heart block occurred in a 9-year-old boy with Ondine's curse who received a single bolus injection of propofol (18).

The authors questioned the safe use of propofol in congenital central hypoventilation syndrome, which is a generalized disorder of autonomic function.

- Propofol caused marked prolongation of the QT_c interval in a 71-year-old woman with an acute myocardial infarction who required ventilatory support (19). Substituting midazolam for propofol was associated with normalization of the QT_c interval. Rechallenge with propofol was associated with further prolongation. There were no malignant ventricular dysrhythmias.

Pain on injection

Propofol can cause severe pain on injection, especially when injected into a small vein (20); the incidence is 25–74% (21). Administration of the lipid solvent in which propofol dissolved has confirmed that the solvent is responsible for this adverse effect (22).

- Severe pain on injection of propofol occurred in a 36-year-old man with severe Raynaud's phenomenon, including a history of skin ulceration when he was given a 2% propofol + lidocaine mixture into a vein on the back of his hand (23).

The author suggested that selecting a larger antecubital vein might be a wiser choice in these patients.

The effectiveness of lidocaine in preventing pain on injection has been confirmed, and a concentration of 0.1% was optimal (24). The kallikrein inhibitor nafamostat mesilate was as effective as lidocaine.

A controlled study in 100 women showed that pretreatment with intravenous ketamine 10 mg reduced the incidence of injection pain from 84 to 26% of patients (25).

Warming propofol to 37°C had no effect on the incidence of pain (26,27).

The effects of different doses of ketorolac, with or without venous occlusion, on the incidence and severity of pain after propofol injection have been studied in a randomized, double-blind study in 180 patients (28). Pretreatment with intravenous ketorolac 15 mg and 30 mg reduced the pain after propofol injection. A lower dose of ketorolac 10 mg with venous occlusion for 120 seconds achieved the same effect.

Ondansetron, tramadol, and metoclopramide were less effective than lidocaine in preventing pain on injection (29–31). Ondansetron and tramadol have been compared in patients being given propofol in a randomized, double-blind study in 100 patients (32). Tramadol 50 mg intravenously was as effective as ondansetron 4 mg intravenously with 15 seconds of venous occlusion at preventing propofol injection pain. However, there was significantly less nausea and vomiting in those given ondansetron.

Respiratory

Respiratory depression due to propofol is well recognized; apnea can result, especially with rapid injection (33).

Pulmonary fat embolism after the use of propofol has been attributed to the milky emulsion in which the propofol was dissolved (34).

Two cases of propofol-induced bronchoconstriction have been reported (35). Both patients had allergic rhinitis and had taken antihistamines during the hay fever season, but were otherwise healthy.

Nervous system

Dystonias

Dystonic movements induced by propofol occurred in a patient undergoing elective cardioversion (36). Benzatropine 2 mg intravenously terminated the abnormal movements. The authors also reviewed all other reports of abnormal movements after propofol.

- Acute dystonia has been reported in a 14-year-old girl after the administration of propofol 150 mg + fentanyl 50 mg for dental anesthesia (37). The intraoperative course was uneventful, but she developed non-rhythmic and non-symmetrical shaking in her upper limbs, unresponsive to diazepam and paraldehyde. A CT scan of the brain was normal. Her symptoms were eventually relieved by procyclidine 2.5 mg.

This adverse effect has been reported many times with propofol in adults, but rarely in children.

Seizures

Myoclonus and opisthotonos, especially in children (38), and choreoathetosis (39) have been attributed to propofol. However, in experimental studies propofol has been shown to be effective against drug-induced seizures (40,41). It has been suggested that propofol inhibits efferent inhibitory neurons in the midbrain and reticular activating system, producing movements that originate subcortically and in the spinal cord (42).

- An otherwise healthy 63-year-old man was anesthetized with propofol 2 mg/kg + fentanyl 1 micrograms/kg followed by an infusion of propofol 6 mg/kg/hour (43). Three minutes after induction he developed myoclonus in his legs. This continued for 10 minutes and the anesthetic was abandoned. When he awoke 10 minutes later, the myoclonus stopped. A repeat anesthetic with propofol soon after caused the same response. When the procedure was performed 12 days later under regional block with propofol infusion for sedation, the myoclonus recurred, and lasted for 2 hours. The patient was alert after each anesthetic and did not appear to be post-ictal. An MRI scan of the spinal cord was normal.

Myoclonus after propofol does not appear to be associated with an adverse outcome.

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Convulsions have been reported in two patients with no history of epilepsy after induction of anesthesia with propofol (44). However, in a crossover comparison in 20 epileptic patients undergoing cortical resection, in which the effects on the electrocorticogram of either propofol or thiopental during isoflurane + nitrous oxide anesthesia were studied, propofol caused no greater proconvulsive effect than thiopental, which is used to treat status epilepticus (45). In spite of occasional reports, a true epileptogenic effect of propofol remains to be proven.

A generalized tonic–clonic seizure has been attributed to propofol in a patient with tonic–clonic seizures after surgery for subarachnoid hemorrhage (46).

Psychological, psychiatric

The association of propofol with a range of excitatory events is well recognized. Behavioral disturbances with repeated propofol sedation have been reported in a 30-month-old child (47). Propofol was well tolerated initially, but the child then became increasing irritable, aggressive, and uncooperative during awakening from subsequent sedations, including screaming, kicking, hitting, and biting. The next two sedations were performed using methohexital and were not followed by any behavioral disturbances.

Prolonged delirium after emergence from propofol anesthesia has also been reported (48).

A psychotic reaction has been reported (49).

- A 37-year-old man who had abused metamfetamine, paint thinner, psychotomimetic drugs, and alcohol for 20 years was given chlorpromazine, haloperidol, and flunitrazepam just before surgery. After spinal anesthesia he was given propofol 5 mg/kg/hour intravenously. However, euphoria and excitement occurred 10 minutes after the start of the infusion and he had excitement, hallucinations, and delirium. His symptoms were suppressed by intravenous haloperidol 5 mg.

The authors speculated that propofol may produce psychotic symptoms when it is used in patients with a history of drug abuse.

Metabolism

Hyperlipidemia

Five cases of hyperlipidemia have been reported in 12 patients who received propofol infusions 3–8 mg/kg/hour for 10–187 hours for sedation in an intensive care unit (50). Propofol was their only source of lipids.

Propofol 2% has been compared with midazolam for sedation in 63 ventilated patients in intensive care (51). They were randomly assigned to either propofol 1.5–6.0 mg/kg/hour or midazolam 0.10–0.35 mg/kg/hour. Sedation was considered a failure if greater rates were required or if triglyceride concentrations were over 5.7 mmol/l (500 mg/dl) on one occasion or greater than 4.0 mmol/l (350 mg/dl) on two occasions. Hemodynamic, respiratory, and neurological variables were similar. Sedation failure occurred in 15 patients given propofol, three with increased triglyceride concentrations and 12 with poor sedation. In comparison, sedation failed in only one of the patients given midazolam. Average serum triglyceride concentrations were higher in the propofol group. In a separate retrospective comparison, triglyceride concentrations were lower than in similar patients treated with 1% propofol, and the sedation failure rate was lower using 2% propofol (9 versus 36%). The authors concluded that 2% propofol is safe but may be less efficient than midazolam. It should be noted that the dose ranges that they used may not have been comparable, leading to an artificially high rate of failure to provide adequate sedation in the propofol group.

Lactic acidosis

There have been several reports of lactic acidosis with and without rhabdomyolysis after propofol infusion, and two fatal cases have been reported (52).

- Two men, aged 7 and 17 years, presented with refractory status epilepticus. Both were treated with high-dose propofol infusions to achieve burst suppression on the electroencephalogram. During the second day of propofol infusion there was progressive severe lactic acidosis, hypoxia, pyrexia, and rhabdomyolysis, followed by hypotension, bradydysrhythmias, and renal dysfunction, leading to death. The total doses of propofol were 1275 mg/kg over 2.7 days and 482 mg/kg over 2 days.

Lactic acidosis and rhabdomyolysis have been reported in a child receiving an infusion of propofol for sedation in an intensive care unit (53).

- A previously healthy 10-month-old boy with an esophageal foreign body was given endotracheal intubation to protect his airway. Midazolam and morphine did not produce satisfactory sedation and he was given propofol by infusion, increased from 3.5 to 7 mg/kg/hour over 2 hours to a total dose of about 500 mg/kg over the next 2 days. Other drugs given included cefotaxime, flucloxacillin, and ranitidine. He developed green urine, triglyceridemia of 907 mg/dl (10 mmol/l), and lactic acidosis, with a peak lactate concentration of 18 mmol/l. He also developed hypotension, with first-degree atrioventricular block and right bundle branch block, unresponsive to atropine, external cardiac pacing, or isoprenaline. Continuous venovenous hemofiltration was instituted. He slowly improved over the next 2 days, but developed a raised creatine kinase activity (over 30 000 U/l) and myoglobinuria. A liver biopsy showed 10% necrosis of zone 3, with fatty infiltration characteristic of a toxic effect. A muscle biopsy showed large areas of muscle necrosis. Extensive investigations showed no underlying infectious or metabolic causes. He slowly recovered over 10 days and appeared to have completely recovered at 3 months.

Lactic acidosis without rhabdomyolysis has been reported in another case (54).

- A 61-year-old woman undergoing mitral valve surgery received fentanyl, midazolam, nitrous oxide, and propofol infusion 3 mg/kg/hour during a 5-hour anesthetic. She developed lactic acidosis soon after the completion of surgery and required reintubation and ventilation. The peak lactate concentration, which occurred 1 day later, was 14.3 mmol/l. There was also mild disturbance of liver function. She eventually recovered.

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These cases are important because, unlike previous reports of metabolic acidosis after propofol infusion, the patients had no documented infections and, in at least one case, extensive investigation showed no other causes of the acidosis. The role of propofol in causing the metabolic problems appears to have been more likely in these than in previous reports. In the first three cases the doses of propofol used, both per hour and in all, were extremely high compared with normal therapeutic practice. The subject has also been reviewed, and it was pointed out that, although suggestive, the association of fatal metabolic acidosis with propofol infusion in sick patients is as yet unproven and to date hinges on 11 case reports of patients who had multiple problems (55).

Porphyria

An acute attack of porphyria has been reported in association with propofol (56).

- A 23-year-old man, with a past history of Fallot's tetralogy repaired at age 2, had catheter ablation of an aberrant conduction pathway causing right ventricular tachycardia, a procedure that took 16 hours. He was sedated with propofol at an average rate of 100 micrograms/kg/minute, and required intubation for respiratory insufficiency half way through the procedure. He also received caffeine and isoprenaline during the procedure to induce ventricular tachycardia. After the procedure he could not be roused or extubated for a further 10 hours and remained drowsy for a further day. He had weakness of an arm and a leg and had lancinating abdominal and shoulder pains. Urinary concentrations of porphyrins, aminolevulinic acid, porphobilinogen, and coproporphyrin III were markedly raised. He made a good recovery after administration of dextrose.

Propofol is regarded as being safe in patients with different types of porphyria. This is the first reported case in which propofol had a possible role in causing raised porphyrin concentrations perioperatively. However, severe illness can also precipitate porphyria, so the association with propofol may have been incidental.

Hematologic

In 10 patients, propofol, but not intralipos, its solvent, inhibited platelet aggregation both in vivo and in vitro (57). This defect was not associated with a change in bleeding time, and it was assumed that the effect is not clinically significant. The cause was probably suppression of calcium influx and release from platelets.

Fat emulsions affect coagulation and fibrinolysis (58). In a study of 36 patients undergoing aortocoronary bypass operations with midazolam + fentanyl or propofol + alfentanil anesthesia, factor XIIa concentrations and kallikrein-like activity were about 30% higher in the propofol group. The authors suggested that there had been stronger activation of the contact phase at the start of recirculation and stronger fibrinolysis in the propofol group. They also found more hypotension in the propofol group, which they assumed to be due to release of kallikrein, resulting in release of bradykinin. Propofol has not been shown to cause increased perioperative bleeding.

Gastrointestinal

Propofol in subhypnotic doses is a potent antiemetic. In a double-blind, randomized study, a small dose of propofol (0.5 mg/kg) was compared with droperidol (20 micrograms/kg) or metoclopramide (0.2 mg/kg) given at the completion of surgery performed in 90 patients under standard anesthesia with thiopental, fentanyl, and sevoflurane (59). Follow-up was to 24 hours. The incidence of emesis at 24 hours was significantly lower in those who received propofol (10 versus 33% and 40% for droperidol and metoclopramide respectively).

Liver

Hepatocellular injury has been reported after the sole use of propofol for outpatient anesthesia (60).

- A young woman with multiple allergies underwent femoral hernia repair and the next day developed acute hepatitis, with severe nausea and vomiting and diffuse abdominal tenderness. She had very high transaminase activities and the prothrombin time was slightly raised. No viral cause could be demonstrated. Antinuclear antibody and smooth muscle antibody titers were not raised and the ceruloplasmin concentration was normal. Abdominal ultrasound did not show gallstones or any other abnormality. The urine was normal and did not contain porphyrins or porphobilinogen. She recovered spontaneously and refused liver biopsy.

Pancreas

There have been several reports of postoperative pancreatitis in association with propofol-induced anesthesia (61–63). In view of the very widespread use of propofol for induction of anesthesia, the very rare reports, and the complexity of establishing the cause of acute pancreatitis, a causal relation between propofol and pancreatitis has not been clearly established.

- A healthy 35-year-old man developed acute pancreatitis a few hours after receiving a 15-minute propofol anesthetic for laser treatment of a urethral stricture (64). He spent 3 weeks in an intensive care unit, requiring both respiratory and renal support. There was no evidence of gallstones on abdominal imaging. There was no defect of lipid metabolism.
- A 51-year-old woman with a past medical history of a seizure disorder, schizophrenia, and asthma, who had been admitted with pneumonia, was sedated using a propofol infusion to assist mechanical ventilation (65). Over 7 days she received a total of 26.5 g of propofol at a maximum rate of 0.2 mg/kg/minute. When pancreatitis, which was associated with hypertriglyceridemia, was diagnosed, the propofol infusion was stopped. In addition to raised amylase activity, serum triglyceride concentrations peaked at 17 mmol/l and lipase activity at 564 U/l. She recovered over the next 7 days. On day 17 she underwent tracheostomy revision, during which

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she received propofol 200 mg. The subsequent postoperative period was complicated by another episode of pancreatitis, this time without associated hypertriglyceridemia. She recovered over the next several days. An ultrasound examination ruled out gallstone pancreatitis, despite the presence of cholelithiasis.

- A healthy 21-year-old woman developed acute pancreatitis a day after an anesthetic that lasted 138 minutes, with propofol for induction (66). She recovered after supportive therapy for 6 days. There was no evidence of gallstones on abdominal imaging and there was no defect in lipid metabolism.

The association between propofol and pancreatitis has been listed as "probable" in 25 reports of pancreatitis associated with propofol to the FDA registry. However, the features of this case, which included resolution of pancreatitis on drug withdrawal and recurrence on rechallenge, suggested that the association should be upgraded to "definitely causal."

Skin

A fixed drug eruption has been attributed to propofol (67).

Musculoskeletal

In an in vitro experiment using uterine muscle strips from 10 consenting parturients undergoing cesarean section, therapeutic concentrations of propofol had no effect on isometric tension developed during contraction of the muscle (68). However, higher than therapeutic concentrations did reduce the peak muscle tension that developed. These results confirm that propofol is free of this adverse effect, which is a known cause of postpartum bleeding after the use of volatile anesthetic drugs.

Rhabdomyolysis

Rhabdomyolysis has been reported in two patients receiving propofol for sedation while being ventilated for severe asthma (69).

- A 47-year-old woman had an infusion of propofol 200 micrograms/kg/minute for 4 days. On day 2 she developed hematuria, and laboratory investigations showed renal insufficiency with hyperkalemic metabolic acidosis. She died as a result of rhabdomyolysis with cardiac involvement.
- A 41-year-old man, who received propofol at rates of up to 222 micrograms/kg/minute for 2 days, developed oliguria, and the propofol was withdrawn. He was also receiving fentanyl and low molecular weight heparin for prophylaxis of deep vein thrombosis. He subsequently developed a very high creatine kinase activity (over 170 000 IU/l). Echocardiography showed globally depressed myocardial dysfunction. He subsequently recovered. The rates of propofol infusion were high and this was thought to be a contributing factor.

A similar death, possibly relating to propofol, has been reported.

- An 18-year-old man suffered multiple trauma (70). He was sedated for 98 hours with propofol 530–700 mg/hour. On day 5 he developed a metabolic acidosis with hyperkalemia and his serum was lipemic. An echocardiogram showed global hypokinesia. He deteriorated and died shortly afterwards.

Although in none of these cases was a definitive link between propofol and the pathology established, the authors pointed out that several other cases have been reported, especially in children. Clinicians should be more aware that propofol may cause rhabdomyolysis, which appears to occur particularly at high doses.

Rhabdomyolysis and the propofol infusion syndrome

The propofol-infusion syndrome consists of a metabolic acidosis, rhabdomyolysis, and cardiovascular collapse. It occurs after prolonged infusion of propofol (over 48 hours) and has generally been reported in children, but also occasionally in adults.

Propofol infusion syndrome mimics the mitochondrial myopathies, in which there are specific defects in the mitochondrial respiratory chain. The clinical features of mitochondrial myopathy result from a disturbance in lipid metabolism in cardiac and skeletal muscle. These patients generally remain well until stressed by infection or starvation, although subclinical biochemical abnormalities of mitochondrial transport can be demonstrated. It has been suggested that early management of critically ill children may not include adequate calorific intake to balance the increase in metabolic demands, and that in susceptible children the diversion of metabolism to fat substrates may cause the propofol infusion syndrome. It is unclear if the dose or duration of propofol infusion alters this effect. As adults have larger carbohydrate stores and require lower doses of propofol for sedation, this may account for the relative rarity of the syndrome in adults. The authors suggested that adequate early carbohydrate intake may prevent the propofol infusion syndrome (71).

- Five adults with head injuries inexplicably had fatal cardiac arrests in a neurosurgical intensive care unit after the introduction of a sedation formulation containing an increased concentration of propofol (72). There were striking similarities with the previously reported syndrome of myocardial failure, metabolic acidosis, and rhabdomyolysis in children who received high-dose propofol infusions for more than 48 hours.

In a subsequent retrospective cohort analysis the odds ratio for the propofol infusion syndrome was 1.93 (95% CI = 1.12, 3.32) for every 1 mg/kg/hour increase in mean propofol dose above 5 mg/kg/hour. The authors suggested that propofol infusion at rates over 5 mg/kg/hour should be discouraged for long-term sedation.

- A 13-year-old girl with a head injury, who received a high-dose infusion of propofol for 4 days, developed the propofol infusion syndrome (73).

In an accompanying editorial, aspects of the propofol infusion syndrome were reviewed, and the author suggested that prolonged high-dose propofol infusions (over 4.8–6.0 mg/kg/hour for over 48–72 hours) should be avoided and that if high-dose metabolic suppression is required for more than 3 days in head injury, the alternative of a barbiturate should be considered (74). However, these long-acting agents have well-known potent myocardial depressant effects of their own, which are difficult to manage.

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- A 2-year-old boy with a gunshot head injury developed the propofol infusion syndrome after receiving propofol in an average dosage of 5.2 mg/kg/hour for 72 hours (71). On the fourth day he became oliguric, with raised potassium, urea, and creatinine concentrations, and then developed a nodal bradycardia (28 minute). Propofol was withdrawn and an isoprenaline infusion was started, but only emergency transvenous pacing restored his heart rate. Hemofiltration was begun, on the basis of another case report, and the acidosis cleared and cardiovascular function was restored. In a blood sample taken before hemofiltration malonylcarnitine, C5-acylcarnitine, creatine kinase, troponin T, and myoglobinemia were raised. The child made a complete recovery and 9 months later all markers of fatty-acid oxidation were normal.

These findings are consistent with impaired fatty-acid oxidation: reduced mitochondrial entry of long-chain acylcarnitine esters due to inhibition of the transport protein (carnitine palmityl transferase 1) and failure of the respiratory chain at complex II. Another previously reported abnormality of the respiratory chain in propofol-infusion syndrome is a reduction in cytochrome C oxidase activity, with reduced complex IV activity and a reduced cytochrome oxidase ratio of 0.004. Propofol can also impair the mitochondrial electron transport system in isolated heart preparations.

Sexual function

Sexual illusions and disinhibition were a problem in two women (aged 20 and 47 years) after sedation with propofol (75).

Immunologic

True anaphylaxis to propofol has been observed (76).

Infection risk

Soon after the introduction of propofol in 1989, clusters of infections related to its use were reported, and there have since been several reports (77,78). The complications include hypotension, tachycardia, septic shock, convulsions, and death. Ethylenediaminetetra-acetic acid (EDTA) was added to the formulation to retard microbial growth. However, there have been concerns over the effects of this additive on trace element homeostasis, particularly when it is used in intensive care units for long-term sedation. Five randomized controlled trials have been reviewed, and minimal or no effects have been found on zinc, magnesium, or calcium homeostasis. However, there is no evidence to suggest that cluster infection has been or will be reduced with this formulation and there is still a need for care with sterility when using this product.

Long-Term Effects

Drug withdrawal

Excitation, including generalized tonic–clonic seizures, has been observed on withdrawal of a propofol infusion in intensive care (79).

Susceptibility Factors

Age

Propofol has previously been associated with death after prolonged infusion in seriously ill children. An in vitro study of the effects of propofol on GABA neurons in a cell culture showed evidence of toxicity after exposure for 8 hours (80). The authors proposed that this toxicity could be the cause of the problems observed in children.

In 21 critically ill children aged 1 week to 12 years, who were also receiving morphine by infusion, propofol kinetics were altered in very small babies and in children of all ages recovering from cardiac surgery (81). Increased volume of distribution and reduced metabolic clearance caused a prolonged half-life. The combination of morphine 20–40 micrograms/kg and 2% propofol 4–6 mg/kg/hour for up to 28 hours appears to be safe.

Drug Administration

Drug formulations

Propofol is formulated as a 1% solution in Intralipid 10% (82). This formulation has been associated with hyperlipidemia, especially raised triglycerides, when given by prolonged infusion to the critically ill, particularly children or patients with liver disease. A formulation of propofol 6% in lipofundin (medium-chain + long-chain triglycerides 10%) has been developed to reduce the risk of hyperlipidemia. In 24 patients who received an induction dose of propofol 2.5 mg/kg over 60 seconds of either the new formulation in 6% or 1% solution and of the original 1% formulation, the pharmacokinetics, induction time, dosage requirements, and safety profile of the three agents were similar. Pain on injection was reported by 17% of the patients, and did not vary between formulations. The 6% solution may be safer for long-term infusion, when reducing the fat load is important.

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Propranolol

See also Beta-adrenoceptor antagonists

General Information

Propranolol is a lipophilic, non-selective, pure antagonist at beta-adrenoceptors, with membrane-stabilizing action.

Organs and Systems

Cardiovascular

An unusual dysrhythmia has been attributed to propranolol: alternating sinus rhythm with intermittent sinoatrial block. The authors suggested that this was

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accounted for by the existence of sinoatrial conduction via two pathways, the first with 2:1 block and the second with a slightly longer conduction time and intermittent 2:1 block (1).

Immunologic

Propranolol has been implicated in hypersensitivity pneumonitis (2,3), although other beta-blockers have also been associated with this complication.

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Propylhexedrine

General Information

In the form of the volatile base, propylhexedrine is used in nasal inhalers; it is also a component of some liquid decongestant mixtures. When inhaled, and especially if over-used, it can cause nasal irritation, rebound congestion, and chronic rhinitis.

Long-Term Effects

Drug abuse

There have been several reports of abuse of propylhexedrine by addicts, who extract the contents of the cotton wad (250 mg propylhexedrine with added aromatics) and take them either orally or intravenously (1). In a few reported cases, deaths have occurred in abusers because of myocardial infarction or pulmonary hypertension, and psychoses of the amphetamine type have been induced (SED-9, 216).

- A 25-year-old white man tried to inject his right internal jugular vein with "home-made crank" [propylhexedrine] (2). After injection, he developed right-sided neck pain, followed by fever, chills, inspiratory stridor, and respiratory distress. He had edema extending from his anterior chest to the right parotid. Neck radiography showed extensive paracervical swelling with displacement of the trachea. At surgery his neck contained extensive necrotic tissue that was debrided. In spite of treatment with antibiotics, he developed progressive renal insufficiency and hypotension unresponsive to fluid therapy, followed by cardiopulmonary arrest and death.

There have been cases of definite brainstem dysfunction and five of transient diplopia secondary to intravenous abuse of Benzedrex, a nasal decongestant that contains propylhexedrine (3). All seven had transient diplopia within seconds after injection. One had a right-internuclear ophthalmoplegia and another had a depressed right gag reflex and paralysis of the right half of the tongue. The deficits in these two patients persisted for many months.

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Propyphenazone

General Information

Propyphenazone is a pyrazolone derivative that has been incorporated into many over-the-counter analgesic combinations in many countries. There is no evidence that it has a lower incidence of adverse effects than phenazone (antipyrine), as was originally supposed, since neither compound has been widely studied alone.

In a systematic review of comparisons of Saridon (propyphenazone 150 mg + paracetamol 250 mg + caffeine 50 mg), paracetamol 500 mg + aspirin 500 mg + ibuprofen 200 mg, and placebo in 500 healthy adults, of whom 329 (66%) had moderate and 171 (34%) severe acute dentoalveolar pain, more of the patients who received Saridon reported "pain gone/partly gone" and fewer reported "pain unchanged or worse" at 30 and 60 minutes (1). There were adverse events in 20 patients (4.0%), with no significant differences between the groups. The most common adverse events were gastrointestinal disorders, followed by nervous system, skin, subcutaneous tissue, respiratory, cardiac, and general disorders.

Organs and Systems

Immunologic

Severe type I hypersensitivity reactions have been reported (SEDA-16, 108). Serious generalized urticaria with angioedema has occurred (2). Rechallenge with oral propyphenazone caused a severe anaphylactic reaction in a patient with a negative skin test. Although the report stressed the importance of oral challenge, it also drew attention to its risks (SEDA-12, 83).

In 44 of 53 patients, all of whom developed symptoms suggestive of IgE-mediated anaphylaxis within 30 minutes of taking propyphenazone, skin tests showed typical

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wheal and flare reactions and significant amounts of propyphenazone-specific serum IgE was detected in 31 (3). In seven of nine patients with negative skin tests, propyphenazone-specific IgE was detected.

Drug Administration

Drug overdose

In overdose, propyphenazone, like other pyrazolones, mainly affects the central nervous system, causing coma and convulsions, and the liver; dysrhythmias and cardiogenic shock can occur; hemoperfusion has been recommended for patients with severe pyrazolone intoxication (4).

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Prostaglandins

See also Individual agents

General Information

Eicosanoids are the oxygenated metabolites of 20-carbon unsaturated fatty acids found in the phospholipids of cell membranes (Greek eikosi = 20). The eicosanoids include the prostaglandins, thromboxanes, and leukotrienes. Precursor fatty acids include arachidonic acid C20:4*n*–6 (for 2-series prostaglandins and thromboxane and 4-series leukotrienes), dihomogammalinolenic acid C20:3*n*–6 (for PGE_1), and eicosapentaenoic acid C20:5*n*–3 (for 3-series prostaglandins and 5-series leukotrienes). Naturally occurring eicosanoids are predominantly metabolites of arachidonic acid, reflecting the dominance of *n*–6 fatty acids in the terrestrial food chain.

The principal biologically active, naturally occurring prostaglandins are prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostacyclin (PGI_2), and thromboxane (TXA_2). These agents have various, sometimes opposed, biological actions (1). Their half-lives are short, owing to their rapid breakdown (a few minutes for PGE_2 and $PGF_{2\alpha}$, a few seconds for PGI_2) (2). Prostaglandins thus have principally local biological actions. Analogues (mostly methyl derivatives) have been synthesized and are more slowly inactivated. The adverse reactions encountered when prostaglandins are used therapeutically will depend on the indications (see Table 1), since these will determine the dose and route of administration and hence the type of reaction likely to occur. Many of the problems experienced are attributable to their main pharmacological effects (Table 2).

Table 1 Indications for prostaglandin therapy

In obstetrics
First- and second-trimester abortion
Cervical reopening
Induction of labor
Augmentation of labor
Postpartum hemorrhage
Ectopic pregnancy
Lactation suppression
In gastrointestinal disease
Peptic ulceration
Liver transplantation
Chemotherapy-induced mucosal lesions
In cardiovascular disease
Congenital cardiac malformations
Raynaud's syndrome
Chronic obstructive pulmonary disease
Adult respiratory distress syndrome
Pulmonary hypertension
Arterial occlusive disease
Extracorporeal circulation
In urology
Erectile dysfunction
Cystitis after radiation or chemotherapy
In ophthalmology
Glaucoma

Nomenclature

The names of prostaglandins are generally abbreviated to a three-letter abbreviation with a subscripted number. The first two letters are always PG; the third is E, F, or I. The recommended International Non-proprietary Names (rINNs) of various prostaglandins are given in Table 3. The convention is that, for example, PGE_1 is the name given to the endogenous prostaglandin and alprostadil is the name given to the same compound available for exogenous administration.

Synthetic analogues of PGE_1, PGE_2, PGF_1, $PGF_{2\alpha}$, and PGI_2

Synthetic analogues of prostaglandins are listed in Table 4. Their use allows reduction of dosages and adverse effects. In general, they cause fewer adverse effects than their naturally occurring counterparts, although this depends on the method of administration. Newer analogues (3) and oral forms (4) are in development.

General adverse effects

The most prominent and frequent adverse effects of prostaglandins are those on the gastrointestinal tract. However, the most dangerous are likely to be the cardiovascular effects, which in predisposed patients can sometimes cause life-threatening collapse and heart failure. Hyperthermia and headache are frequent nervous

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Table 2 Actions of prostaglandins

Prostaglandin E series
Increased hormone secretion
Growth hormone, corticotropin, thyrotropin, luteinizing hormone, thyroid hormone, insulin, glucocorticoids, progesterone, erythropoietin, renin
Increased body temperature
Sensitization of pain-mediating nerve fibers
Increased force of myocardial contraction
Increased blood flow in gastric mucosa, liver, kidney, and placenta
Increased renal secretion of sodium, potassium, and water
Antagonistic action against antidiuretic hormone
Increased intraocular pressure
Increased permeability of blood capillaries
Increased gastrointestinal motility
Reduced gastrointestinal secretions
Reduced blood pressure
Bronchodilatation
Inhibition of bronchial secretions
Sedation
Contraction of the non-pregnant uterus
Induction of abortion and labor
Prostaglandin F series
Bronchial constriction, especially in patients with asthma
Reduced pulmonary blood flow and increased pulmonary blood pressure
Increased erythropoietin secretion
Increased neurotransmission at sympathetic nerve endings
Increased gastrointestinal motility
Reduced blood pressure
Sedation (effects on the central nervous system)
Luteolytic effects in mammalian species (except man)
Induction of abortion and labor
Prostaglandin I series
Reduced platelet aggregation
Reduced mean arterial pressure
Reduced total peripheral and pulmonary resistances
Increased heart rate
Increased renal secretion of sodium (tubular effect)

system effects. Epileptiform convulsions occur rarely. When used for termination of pregnancy, uterine hyperstimulation and, less often, uterine rupture can occur (5). Hypersensitivity to prostaglandins can cause skin reactions, bronchospasm (also seen as a direct pharmacological effect), and occasionally anaphylaxis. Tumor-inducing effects have not been reported. There have been a few reports of infants with limb deformities with and without Möbius sequence after exposure to misoprostol (a PGE_1 analogue) in the first trimester.

Prostaglandins in cardiovascular disease

Maintenance of the ductus arteriosus

PGE_1 and PGE_2 are effective in maintaining the patency of the ductus arteriosus in the initial management of congenital cardiac malformations (6,7). The most frequent adverse effects during prolonged treatment are diarrhea, necrotizing enterocolitis, cortical hyperostosis (8–10), fever, respiratory depression and apnea, and seizure-like activity (11). The frequency of adverse effects is not necessarily reduced with low-dose intravenous or oral administration (12). Maternal/fetal hyperglycemia due to reduced insulin secretion is rare, except in the infants of diabetic mothers (13). Less common adverse effects include gastric outlet obstruction due to antral hyperplasia (14).

Raynaud's phenomenon and digital ischemia

Studies of PGE_1 infusion for treatment of Raynaud's syndrome have shown variable changes in frequency of attacks and of healing ischemic digital ulcers (15–18). Prostacyclin

Table 4 Synthetic analogues of prostaglandins (rINNs except where stated)

PGE_1 analogues
Enisoprost
Limaprost
Mexiprostil
Misoprostol
Ornoprostil
Rioprostil
Rosaprostol
PGE_2 analogues
Arbaprostil
Enprostil
Gemeprost
Meteneprost
Nocloprost
Sulprostone
Trimoprostol
Viprostol
PGF_1 analogues
Prostalene (pINN)
$PGF_{2\alpha}$ analogues
Alfaprostol
Bimatoprost
Carboprost
Cloprostenol
Fenprostalene
Fluprostenol
Latanoprost
Luprostiol
Tiaprost
Travoprost
Unoprostone
PGI_2 analogues
Beraprost
Cicaprost
Ciprostene
Iloprost

Table 3 Recommended International Non-proprietary Names (rINNs) and chemical names of the major prostaglandins

Prostaglandin	rINN	Chemical name (omitting stereochemical information)
PGE_1	Alprostadil	11,15-dihydroxy-9-oxoprosta-13-en-1-oic acid
PGE_2	Dinoprostone	11,15-dihydroxy-9-oxoprosta-5,13-dien-1-oic acid
$PGF_{2\alpha}$	Dinoprost	9,11,15-trihydroxyprosta-5,13-dien-1-oic acid
PGI_2 (PGX, prostacyclin)	Epoprostenol	6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid

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infusion (using PGI_2 or its synthetic analogue iloprost) appears to have beneficial effects, both in reducing the severity and frequency of attacks and healing ischemic digital ulcers. Adverse effects are common and include headache, flushing, jaw pain, nausea, vomiting, diarrhea, and inflammation and pain at the injection site (19,20). Iloprost has also been used effectively in the treatment of local gangrene secondary to chemotherapy (21). Application of a PGE_2 analogue to the skin produced both subjective and objective improvement in patients with Raynaud's syndrome and produced only minor self-limiting adverse effects (headache, flushing, and diarrhea) (22).

Peripheral vascular disease

Synthetic PGI_2 has been used in arterial occlusive disease as an anti-aggregatory drug (23–28). Adverse effects are common (85%). Headache, fever, nausea, anorexia, diarrhea, pain at the infusion site, and arthralgia are the most prominent. A single study has suggested an increased risk of thromboembolism after the use of iloprost in peripheral vascular disease (29).

Beraprost, an epoprostenol (PGI_2) analogue, has been studied in intermittent claudication. Adverse events include gastrointestinal disorders, headaches, skin disorders, and fever (30).

Primary pulmonary hypertension

Initial studies of continuous intravenous prostacyclin infusion in patients with primary pulmonary hypertension have shown sustained improvement in pulmonary artery pressure, exercise capacity, and survival compared with historical controls (31,32). Minor complications (diarrhea, jaw pain, flushing, photosensitivity, and headache) were dose-related. Serious complications were related to problems with the drug delivery system, including catheter thrombosis, sepsis, and temporary interruption of the infusion, resulting in abrupt deterioration (31).

Regulation of pulmonary vascular perfusion in advanced respiratory disease

PGE_1 significantly reduces right ventricular pulmonary after-load in patients with pulmonary hypertension due to chronic obstructive airways disease (33). PGE_1 can also be useful in the treatment of adult respiratory distress syndrome (34). Preliminary studies using aerosolized prostacyclin showed a reduction in pulmonary artery pressure and improved arterial oxygenation with reduction in intrapulmonary shunt in ventilated patients with adult respiratory distress syndrome (35) and severe community-acquired pneumonia (36). However, ventilated patients with severe community-acquired pneumonia and pre-existing fibrosis required much higher doses, with a reduction in systemic vascular resistance and an increase in intrapulmonary shunting (36). A single report described improved oxygenation, mainly due to reduction of intrapulmonary shunting, in two neonates with pulmonary hypertension treated with aerosolized prostacyclin (37).

Other uses

PGI_2 has been used to reduce the re-stenosis rate during transluminal coronary angioplasty (38).

Prostacyclin infusion (using PGI_2 or its synthetic analogue, iloprost) has been used during extracorporeal circulation to prevent blood clotting in the dialyser coil (39). The risk of severe hypotension can be avoided by carefully controlling the infusion rate.

Prostaglandins in gastrointestinal disease

Peptic ulceration and NSAID-induced gastropathy

Prostaglandins of the E series (misoprostol, enprostil) have antiulcer activity in the upper gastrointestinal tract (40). They inhibit gastric acid secretion at modest doses and provide mucosal protection against noxious agents, including non-steroidal anti-inflammatory drugs, smoking, alcohol, and chemotherapy. They have been used to prevent NSAID-induced gastroduodenal lesions (41,42). They may also be effective in preventing NSAID-induced renal impairment (43).

The cure rate for gastric and duodenal ulcers is comparable to the results with H_2-receptor antagonists (44–46). Relapses appear to be fewer with prostaglandin therapy (44,45). Healing of duodenal ulcers refractory to H_2-receptor antagonists has been described.

Diarrhea (4–38%), abdominal pain or cramp, flatulence, and nausea or vomiting account for most of the adverse effects reported. No biochemical or hematological adverse effects have been noted.

These agents are contraindicated in women of childbearing age, unless they are using adequate contraceptive measures, because of uncertain abortifacient effects. They have been used as illegal abortifacients in some countries (47).

Prostaglandins in liver disease

Liver failure and transplant dysfunction

Prostaglandins of the E series (both intravenous and oral formulations) have been used to treat fulminant hepatic failure, primary non-function following orthotopic liver transplantation, and recurrent hepatitis B infection after orthotopic liver transplantation in open trials (48–50). Adverse effects are almost universal. They include gastrointestinal symptoms (abdominal pain and cramping, watery diarrhea), which affect 33–100% and are more common with oral formulations and possibly amongst those with raised blood glucose concentrations. Cardiovascular effects, which affect about 33%, include migraine, hypotension, peripheral edema, and myocardial infarction (in those with pre-existing risk factors). Painful clubbing and cortical hyperostosis (92–100%) developed 10–60 days after the start of intravenous or oral therapy. Arthritis/arthralgia developed in 8% of those receiving intravenous and 92% of those taking oral PGE_1 or PGE_2. All adverse reactions appear to be dose-related and resolve with reductions in dose. Two patients developed calcium oxalate stones after 1 year of oral therapy (51).

Prostaglandins in urology

Prostacyclin infusion in men with persistent pain associated with Peyronie's disease was of little value but produced marked adverse effects (bradycardia, hypotension, nausea, flushing) (52).

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A single dose of PGE_1 into the corpus cavernosum is highly effective in inducing artificial penile erection in cases of erectile dysfunction. The reported adverse effects include pain and a burning sensation, prolonged penile erection, and local fibrosis. The incidence of pain was high (75%) in older studies (53), while later data improved to 13–44% (54–57). Pain is cited as a prominent factor in non-adherence to therapy and in the dropout rate of patients from self-injection programs, although the incidence may fall with time (57). An alprostadil sterile powder formulation had a lower incidence of pain after penile injection (6.6%), attributed to lower doses and the lack of alcohol in the formulation (58). Burning and pain can be reduced by using a lower initial dose, with incremental increases until a satisfactory erection is produced (59).

Although the incidence of priapism varies in different studies, depending on its definition (erection lasting anywhere from 2 to 11 hours), an analysis of 48 studies in 8090 patients showed an overall incidence of 1% (55).

Prolonged erections induced by PGE_1 usually require drainage and phenylephrine irrigation, although a small percentage can be managed with oral terbutaline or oral pseudoephedrine if treated within 3 hours of PGE_1 injection (56). Local fibrosis is infrequent, occurring in 2% at 6 months and in 8% at 18 months (60). A single case of Peyronie's-like plaque and penile curvature deformity has been reported after repeated PGE_1 use (61).

Complications of alprostadil injections include hematoma and ecchymoses (8%) and systemic effects (6%), which mostly occur in the urogenital system (testicular pain and swelling, scrotal pain and edema, changes in urinary frequency, hematuria, and pelvic pain) (62). In 1% there were symptoms related to hypotension.

Massive diffuse hemorrhage due to cyclophosphamide-induced or radiation cystitis has been treated successfully with intravesicular PGE_1, PGE_2, and carboprost. Febrile reactions and severe bladder spasm are dose-dependent (63–65).

Prostaglandins in ophthalmology

Topical PGE_2 and $PGF_{2\alpha}$ significantly reduce intraocular pressure for at least 24 hours and are used in the treatment of glaucoma. Derivatives of the isopropyl ester of $PGF_{2\alpha}$ appear to be the most effective. Transient ocular adverse effects include conjunctival hyperemia, local irritation, intermittent photophobia, and pain in the eye (66–68). Newer derivatives, such as latanoprost, travoprost, and bimatoprost, appear to be better tolerated, with less severe and less frequent adverse effects (69). They reduce intraocular pressure by increasing uveoscleral outflow. The ocular pressure-lowering effect of latanoprost appears to be additive with timolol, with mild transient hyperemia in 50% of those treated with latanoprost alone (70).

Latanoprost, travoprost, and bimatoprost cause increased pigmentation of the iris in some patients after prolonged treatment (3.0–4.5 months) (71). Most data have been obtained with latanoprost, and it appears that there is a predisposition to iris pigmentation in patients with eyes of hazel or heterochromic color. As latanoprost and travoprost are selective agonists at $PGF_{2\alpha}$ receptors, it is likely that the phenomenon is mediated by these receptors. Latanoprost stimulates melanogenesis in iris melanocytes, and transcription of the tyrosinase gene is upregulated. No evidence of harmful consequences of this adverse effect has been found, and the only disadvantage appears to be potential heterochromia between the eyes in unilaterally treated patients: the heterochromia is likely to be permanent, or very slowly reversible (72–74).

The adverse effects of travoprost include gradual darkening of the color of the iris and the eyelid skin, increased thickness, number, and darkness of the eyelashes, conjunctival hyperemia, and ocular pruritus (75).

Cystoid macular edema, iritis, *Herpes simplex* keratitis, periocular skin darkening, and headaches have been described in patients treated with prostaglandin analogues. These adverse effects occur rarely, and cystoid macular edema, iritis and *H. simplex* keratitis occur in eyes with risk factors. Repeated rechallenge with masked controls is required to establish a causal relation. However, even without firm establishment of a causal relation, caution is advised with the use of prostaglandin analogues in the eyes of patients with risk factors for macular edema, iritis, and *H. simplex* keratitis (76).

The ocular adverse effects of latanoprost include conjunctival hyperemia, iris pigmentation, periocular skin color changes, anterior uveitis, and cystoid macular edema in pseudophakic patients (77,78). *H. simplex* dendritic keratitis has been reported after treatment with latanoprost (79). In patients with uveitic glaucoma, latanoprost can cause increased intraocular pressure and recurrence of inflammation (80).

Exacerbation of angina pectoris has been described in association with latanoprost (81). $PGF_{2\alpha}$ is a vasoconstrictor, and systemic absorption of topical latanoprost can cause vasoconstriction in coronary arteries.

Three patients had new-onset migraine after using latanoprost, perhaps through activation of the trigeminal vascular system (82).

Prostaglandins in obstetrics

Prostaglandins of the E and F series are widely used in obstetrics for ripening the uterine cervix and stimulating uterine contraction at any stage of pregnancy. They are used in first- and second-trimester abortions, cervical priming, the induction and augmentation of labor, and postpartum hemorrhage (83–89). The route of administration can be vaginal, cervical, extra-amniotic, intra-amniotic, oral, intramuscular, or intravenous, and varies according to indication. Mifepristone (RU 486), a synthetic 19-norsteroid and progesterone antagonist, has been used in combination with synthetic prostaglandins in the induction of abortion.

A less well-established use involves intratubal injection of $PGF_{2\alpha}$ for ectopic pregnancy (90,91). Oral PGE_2 can be used to suppress lactation, for which it is as effective as bromocriptine, and causes less breast tenderness (92).

Organs and Systems

Cardiovascular

Both PGE_2 and $PGF_{2\alpha}$ commonly cause a fall in blood pressure and a degree of bradycardia (1,93). PGE_2 can cause vasodilatation of small vessels and $PGF_{2\alpha}$ can cause

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vasoconstriction (94). These changes are common but often mild. However, angina pectoris and myocardial infarction have been reported with prostaglandins of all types, particularly after inadvertent intramyometrial injection (95–98). A single case of pulmonary edema after the infusion of PGE_1 has been reported (99). In patients with pre-existing cardiovascular disease, the risk of serious aggravation is very real, and both pre-existing hypertension and states of shock can be worsened. A severe rise in maternal blood pressure occurred in a few cases in which fetal death was associated with unresolved pre-eclampsia.

Respiratory

People with asthma are more sensitive than healthy subjects to bronchoconstriction induced by $PGF_{2\alpha}$ (100,101).

Nervous system

Increased body temperature, pyrexia (both intra- and postpartum), and chills are thought to result from central stimulation of temperature regulatory centers by prostaglandins (102,103). Headache and migraine are the most common adverse effects on the central nervous system (5,104).

Prostaglandin therapy can cause electroencephalographic abnormalities (105). Convulsions, which occur occasionally, are a particular risk in epileptic patients (5,104,105). The combination of prostaglandins and oxytocin can be complicated by tonic-clonic seizures (106).

Enhancement of the pain sensation may reflect a direct effect on nerve fibers. The presence of pain correlates well with the effect on the uterus.

Sensory systems

Increased intraocular pressure and miosis have been reported (5,104).

Mouth and teeth

Gingivitis has been associated with obstetric prostaglandins (5).

Gastrointestinal

Nausea, vomiting, diarrhea, and abdominal pain (107) occur in about 90% of all patients given prostaglandins systemically. The frequency and duration of these adverse effects depend on the mode of application, the dosage, and the molecule used, and are very variable (108).

Reproductive system

Uterine hypertonia and hyperstimulation are well-recognized adverse effects of induction of abortion and labor with prostaglandins. Cervical rupture and uterine rupture have been reported with every prostaglandin and analogue, even in previously unscarred uteri (5,109–116). The risks can be minimized by using lower doses (0.5 mg intracervically or 3 mg intravaginally), by allowing longer intervals between re-applications, and by avoiding combination with oxytocin, which has a potentiating effect. However, there is a single case report of uterine rupture in a multiparous woman with unscarred uterus following low-dose (1.5 mg) intravaginal PGE_2 (117). In the event of uterine hyperstimulation, $beta_2$-adrenoceptor agonists may reduce uterine contractility. Intensive monitoring of uterine activity and fetal condition is mandatory, since the rate of absorption of PGE_2 after intravaginal or cervical administration is unpredictable.

Second-Generation Effects

Teratogenicity

Seven Brazilian infants were born with limb deficiencies both with and without Möbius sequence after exposure to misoprostol in the first trimester during unsuccessful abortion attempts (118).

Fetotoxicity

Like oxytocin, prostaglandins have been responsible rarely for fetal distress and even fetal death (119,120). The risk of fetal death underlines the importance of cardiotocography during prostaglandin (pre)induction. Prostaglandins should be used with extreme caution if there is a risk of placental insufficiency (120).

The incidence of neonatal jaundice was not increased after induction of labor with prostaglandins (47).

Susceptibility Factors

When PGE_2 and $PGF_{2\alpha}$ are used for induction of labor and abortion, the following contraindications must be respected and (until proven otherwise) also apply to the methyl analogues of these two prostaglandins:

- previous cesarean section or hysterotomy (because of the risk of rupture) (110);
- previous major abdominal surgery;
- prior abnormal delivery;
- a history of severe abdominal inflammation and/or infection;
- a predisposition to uterine cramps or tetanus uteri.

However, uneventful vaginal deliveries have been reported in patients with two previous cesarean sections in whom labor was induced with vaginal PGE_2 (121). Women with a history of six or more deliveries and anomalies of the fetus (for example hydrocephalus causing cephalopelvic disproportion) must also be excluded.

Predispositions to glaucoma, epilepsy, pre-eclampsia, hypertension, asthma, and ischemic heart disease are relative contraindications.

Drug Administration

Drug administration route

Intrauterine infusion

Intrauterine infusion (intra-amniotic or extra-amniotic) has been reported to be associated with fewer gastrointestinal symptoms and less fever than parenteral or intravaginal administration (122). In intra-amniotic use, the puncture must be guided by ultrasonography, and before injection a control aspiration of some amniotic fluid is required in order to avoid intrauterine or intravascular

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injection. Uterine rupture has been described with intra-amniotic treatment.

Intramuscular or intradermal injection

Inflammation and pain are common at the site of injection when prostaglandins are given intramuscularly or intradermally (123,124).

Intravenous injection

Prostaglandins have been used intravenously, both for induction of mid-trimester abortion and for induction of labor in cases of intrauterine death. The same adverse effects as described above occur, and are usually very pronounced. Routine premedication with an antiemetic and an antidiarrheal agent significantly reduces gastrointestinal adverse effects.

Inhalation

Intravenous epoprostenol increases exercise tolerance, improves pulmonary hemodynamics, and improves survival in patients with primary pulmonary hypertension. However, there are limitations to intravenous administration, and a significant proportion of patients develop catheter-related problems, such as thrombosis, pump failure, and catheter-related sepsis. In an attempt to improve delivery, several trials of aerosolized prostacyclin have been undertaken, primarily in patients with primary pulmonary hypertension.

There has been a sequential comparison of inhaled nitric oxide 40 ppm with aerosolized iloprost 14–17 micrograms in 35 adults with primary pulmonary hypertension (125). Five of the patients had minor headache and facial flushing during inhalation of iloprost, but these symptoms were short-lived and abated a few minutes after the inhalation ended. One patient had mild jaw pain after aerosolized iloprost, but again this was short-lived. There was an unexpected increase in pulmonary artery pressure in 10 patients and vascular resistance in six patients who received nitric oxide. The authors were uncertain of the cause of this increase, as nitric oxide generally behaves as a vasodilator, but they noted that nitric oxide is a vasoconstrictor in certain conditions, such as the presence of hemolysate (126).

There has been a trial of aerosolized iloprost in 24 patients with primary pulmonary hypertension and New York Heart Association class III or IV disability, who were refractory to conventional medical treatment (127). They were given aerosolized iloprost in a total daily dose of 100–150 micrograms (in 6–8 divided doses, given every 2–3 hours while awake) over 12 months. The treatment was generally well tolerated, except for coughing during inhalation, which was common initially but resolved spontaneously in all patients within the first 4 weeks. Five patients reported symptoms of flushing, headache, and jaw pain at the end of inhalation, but all rated the symptoms as mild and none discontinued treatment because of adverse effects. There was an asymptomatic but significant fall in systemic arterial pressure (from 98 to 90 mmHg) and vascular resistance at 3 and 12 months compared with baseline.

The effects of aerosolized iloprost have been reported in three patients with severe pulmonary hypertension (mean pulmonary artery pressure 50 mmHg or more) who were already being treated with intravenous epoprostenol (10–16 micrograms/kg/minute) (128). The aim of the study was to replace continuous intravenous epoprostenol with intermittent aerosolized iloprost (150–300 micrograms/day in 6–18 divided doses). All three patients had gradual weaning of intravenous epoprostenol (1 micrograms/kg/minute every 3–10 hours) under close supervision and hemodynamic monitoring in intensive care. All three had initial falls in pulmonary arterial pressure and improved right ventricular function with inhaled iloprost. The first could not be fully weaned from epoprostenol, because of right ventricular failure with dyspnea and hypoxemia, accompanied by a three-fold increase in serum bilirubin and lactate dehydrogenase and echocardiographically demonstrated right ventricular failure. The second and third patients both tolerated complete withdrawal of epoprostenol. However, one developed right ventricular failure within 2 hours of withdrawal. The third was successfully discharged from hospital taking aerosolized therapy, but presented 2 weeks later with severe right ventricular failure. Thus, caution should be taken in patients who have been previously maintained on intravenous prostacyclin when trying to convert to aerosolized therapy, as there appears to be a high chance of treatment failure, which can occur abruptly.

Platelet function after inhaled prostacyclin has been measured in a randomized, double-blind study in 28 patients undergoing elective cardiothoracic surgery (129). They were given aerosolized prostacyclin (5 or 10 micrograms) for 6 hours postoperatively. All the patients, regardless of dose, had a lower rate of platelet aggregation in response to adenosine diphosphate (ADP) than controls. There were no differences in clinically significant indices, such as chest tube drainage or bleeding time. This study has shown that prostacyclin, given as an aerosol, can cause measurable alterations in platelet function, with a possibly higher risk of bleeding.

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Protamine

General Information

Protamine, derived from salmon sperm, combines with and neutralizes heparin through an acid-base interaction. It is most commonly used as the sulfate, but chloride and hydrochloride salts are also occasionally used.

The relative insolubility of protamine–insulin suspension in water slows the subcutaneous resorption of the hormone, and consequently prolongs its biological activity.

In a prospective study of patients undergoing cardiopulmonary bypass, 10.7% of patients receiving protamine sulfate had adverse reactions of varying types (1).

Protamine sulfate regularly induces hypotension, bradycardia, transient flushing, and a feeling of warmth when administered too rapidly. These non-allergic effects are not severe, provided the injection is given slowly (50 mg, the maximum recommended dose, over 10 minutes).

Comparative studies

In a double-blind, randomized trial, 167 patients undergoing aortocoronary bypass graft surgery received either heparinase I (maximum 35 μg/kg) or protamine (maximum 650 mg) for heparin reversal (2). Although the two treatments had similar efficacy, protamine had a better safety profile. Those given heparinase I had longer hospital stays, were more likely to have a serious adverse event, and were less likely to avoid transfusion. A composite morbidity score was not different, and there were similar rates of hemodynamic instability.

Organs and Systems

Cardiovascular

Severe acute pulmonary vasoconstriction with cardiovascular collapse was identified in 1983 and subsequent studies showed that the incidence of protamine-induced pulmonary artery vasoconstriction was about 1.5% after cardiac surgery (3). Protamine-induced pulmonary artery vasoconstriction is accompanied by generation of large quantities of thromboxane A_2, a potent vasoconstrictor (3).

The precise mechanisms that explain protamine-mediated systemic hypotension are unknown, but there is evidence that it may be mediated by the endothelium and dependent on nitric oxide/cyclic guanosine monophosphate; it has been suggested that methylthioninium chloride (methylene blue) may be of use in treating hemodynamic complications caused by the use of protamine after cardiopulmonary bypass (4).

Immunologic

Although protamine itself was for a long time not generally considered allergenic, allergic reactions can occur in susceptible individuals. Attributed to residual fish antigens that remained after purification, they are characterized by flushing, urticaria, wheezing, angioedema, and hypotension, and they can occur even after slow intravenous administration. True anaphylaxis with bronchospasm and/or anaphylactic shock is very rare (5).

It now seems to be widely believed that, exceptionally, protamine itself can act as an allergen. There were positive skin tests with protamine in patients who had anaphylaxis and who had all previously received protamine (5). Cases of anaphylactic shock after slow intravenous administration of protamine sulfate to patients with diabetes mellitus suggested cross-allergy to protamine present in protamine zinc insulin (6–8), especially in patients with serum antiprotamine IgE or IgG antibodies (9). Insulin-dependent patients with diabetes who use protamine insulin may be at greater risk of adverse effects when they receive protamine sulfate. A retrospective study in patients who received protamine sulfate to reverse the effects of heparin during catheterization procedures or cardiac surgery showed a relative risk of anaphylaxis four times higher in patients with diabetes who had used protamine insulin than in non-diabetic controls (10). In these patients, the risk of anaphylaxis on administration of protamine sulfate is about 1%.

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Protease inhibitors

See also Individual agents

General Information

All the HIV protease inhibitors have in common a specific effect against the aspartic HIV protease that cleaves viral proteins to yield structural proteins. Competitive inhibition of this process by the protease inhibitors results in the production of immature, non-infectious virus particles. These drugs are also characterized by their high specificity, being more than a thousand-fold more active against viral than human aspartic proteases.

Combination therapy including a protease inhibitor resulted in the first breakthrough of antiviral treatment in the mid-1990s, since when several protease inhibitors have been developed. However, results from in vitro and clinical studies clearly showed that these drugs share a cross-resistance pattern, probably due to secondary conformational changes of the protease outside the active binding site of the protease inhibitor. Nevertheless, some patients may benefit from a second protease inhibitor if therapy is promptly switched before multiple mutations have accumulated.

Drug interactions with protease inhibitors

Drug interactions with protease inhibitors, which are potent inhibitors of CYP3A4 and CYP2D6, have been comprehensively reviewed (1), and an updated summary of interactions is presented on the World Wide Web by the University of Liverpool (http://www.hiv-druginteractions.org); the drugs that should not be co-administered with protease inhibitors are summarized in Table 1.

Interactions between protease inhibitors

Evidence suggests that some protease inhibitors can inhibit the metabolism of others. For example, ritonavir inhibits CYP3A4 and CYP2D6 and has been used to enhance the actions of other protease inhibitors, by inhibiting their clearance (2).

In an open, randomized study of amprenavir combined with indinavir, nelfinavir, and saquinavir (3), saquinavir lowered the amprenavir AUC by 32%; amprenavir did not alter the pharmacokinetics of saquinavir. The amprenavir AUC increased by 35% when it was combined with indinavir, and indinavir concentrations also fell, suggesting that this protease inhibitor combination should be avoided. There was no significant interaction of amprenavir with nelfinavir.

In attempts to lower the amprenavir capsule burden, low-dose ritonavir has been used as a pharmacokinetic booster. When ritonavir was added to amprenavir, the amprenavir AUC increased 3–4 times (4), which should allow the total daily capsule burden to be reduced. Adverse effects included diarrhea, nausea, paresthesia, rash, increased cholesterol, and increased triglycerides. The frequency of adverse events correlated with the dose of ritonavir.

In nine patients who received amprenavir 750 mg bd for at least 3 weeks plus one of two doses of lopinavir + ritonavir, the trough concentration of amprenavir was 0.35–2.54 with lopinavir + ritonavir 400/100 mg bd ($n = 5$) and 1.92–2.83 with lopinavir + ritonavir 532/133 mg bd ($n = 4$); the corresponding trough concentrations of lopinavir were 0.35–2.54 and 4.74–6.71 (5).

A pharmacokinetic model has been developed to describe the interaction of amprenavir with ritonavir (6). A two-compartment linear model with first-order absorption fitted the amprenavir data best, while a one-compartment model best described the ritonavir data. Inhibition of the elimination of amprenavir by ritonavir was modelled with an E_{max} inhibition model. Simulation of drug regimens based on the model suggested that in patients who fail to respond to a traditional amprenavir regimen, amprenavir 600 mg plus ritonavir 100 mg bd would produce similar C_{min}:IC_{50} ratios to amprenavir 1200 mg bd alone.

Using ritonavir as a booster allows indinavir to be given twice daily and with food. In a cohort survey of 100

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Table 1 Drugs that should not be co-administered with protease inhibitors

Drug	APV	ATV	IDV	LPV	NFV	RTV	SQV
Alprazolam			x				
Amiodarone			x	x	x	x	x
Astemizole	x	x	x	x	x	x	x
Atazanavir			x				
Bepridil		x				x	x
Cisapride	x	x	x	x	x	x	x
Clorazepate						x	
Diazepam	x					x	
Ergot derivatives	x	x	x	x	x	x	x
Estazolam						x	
Flecainide	x	x	x	x		x	x
Flurazepam	x					x	
Halofantrine	x	x	x	x	x	x	x
Indinavir		x					
Lovastatin	x	x	x	x	x	x	x
Lumefantrine	x	x	x	x	x	x	x
Midazolam	x	x	x	x	x	x	x
Pethidine						x	
Pimozide	x	x	x	x	x	x	x
Piroxicam						x	
Propafenone	x	x				x	x
Quinidine		x			x	x	x
Rifabutin							x
Rifampicin	x	x	x	x			x
Simvastatin	x	x	x	x	x	x	x
St John's wort	x	x	x	x	x	x	x
Terfenadine	x	x	x	x	x	x	x
Triazolam	x	x	x	x	x	x	x
Vardenafil			x			x	
Vitamin E	x						
Voriconazole						x	
Zolpidem						x	

APV = amprenavir and fosamprenavir
ATV = atazanavir
IDV = indinavir
LPV = lopinavir
NFV = nelfinavir
RTV = ritonavir
SQV = saquinavir

patients the combination of indinavir plus ritonavir (400 mg/400 mg or 800 mg/100 mg bd) was a safe and effective option to reduce the tablet burden and improve adherence (7).

Observational studies

Combinations of NRTIs and protease inhibitors

A variable-dose plasma concentration-controlled approach to combination antiretroviral therapy (zidovudine, lamivudine, and indinavir) has been compared with conventional fixed-dose therapy in 40 patients in a randomized, 52-week, open trial (8). Significantly more concentration-controlled recipients achieved the desired concentrations for all three drugs: there was a good response in 15 of 16 concentration-controlled recipients compared with nine of 17 conventional regimen recipients. However, there was no difference in the occurrence of drug-related clinical events or laboratory abnormalities between the two regimens. Three patients withdrew because of gastrointestinal adverse effects, one because of a peripheral neuropathy, and one with headache and anemia. There was nephrolithiasis in four cases.

The combination of indinavir + ritonavir 400/400 mg bd plus two NRTIs has been studied in 93 patients in an open, uncontrolled, multicenter trial (9). Raised triglycerides ($n = 78$) and cholesterol ($n = 63$) were the commonest adverse effects, followed by nausea ($n = 22$) and circumoral paresthesia ($n = 9$). Withdrawal was required in four cases of nausea, four of lipodystrophy, one of diarrhea, and one of osteonecrosis.

Combinations of NRTIs, NNRTIs, and protease inhibitors

In an open, 48-week, single-arm, multicenter phase II study in 99 patients abacavir 300 mg bd, amprenavir 1200 mg bd, and efavirenz 600 mg/day were associated with rashes in 50 patients, possibly because of abacavir hypersensitivity; 17 permanently discontinued one or more drugs as a result (10). Other adverse effects included nausea ($n = 41$), diarrhea ($n = 27$), sleep disorders ($n = 27$), dizziness ($n = 25$), fatigue ($n = 23$),

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Table 2 Numbers (%) of infants and children with moderate or severe adverse events in a study of one or two NRTIs plus an NNRTI and/or a protease inhibitor

System affected by the adverse event	Regimen			
	Stavudine + nevirapine + ritonavir ($n = 41$)	Stavudine + nevirapine + nelfinavir ($n = 44$)	Stavudine + lamivudine + nevirapine + nelfinavir ($n = 44$)	Stavudine + lamivudine + nelfinavir ($n = 52$)
Respiratory	12 (29)	18 (41)	23 (52)	50 (96)
Hematologic (neutropenia)	17 (41)	9 (20)	14 (32)	23 (44)
Gastrointestinal				
Nausea/vomiting	29 (71)	32 (73)	18 (41)	15 (29)
Other	10 (24)	25 (27)	18 (41)	19 (37)
Liver	12 (29)	14 (32)	18 (41)	23 (44)
Skin	27 (66)	41 (93)*	32 (73)	17 (33)*
Body temperature (fever)	24 (59)	30 (68)*	20 (45)	10 (19)*

*Significantly different from the other groups

hypertriglyceridemia ($n = 18$), neutropenia ($n = 8$), hyperamylasemia ($n = 4$), leukopenia ($n = 3$), hypercholesterolemia ($n = 2$), raised alkaline phosphatase ($n = 1$), and raised aspartate transaminase ($n = 1$).

In infants and children assigned to different combinations of one or two NRTIs plus an NNRTI and/or a protease inhibitor, the numbers of patients with moderate or severe adverse events were as shown in Table 2 (11). In cases of rash, the rash was worse in those who were taking nevirapine-containing regimens.

Organs and Systems

Nervous system

In a randomized comparison of a protease inhibitor-containing regimen and an efavirenz-containing regimen, nervous system adverse effects were specifically sought (12). Patients were randomized to two NRTIs plus one or more protease inhibitors ($n = 49$) or two NRTIs plus efavirenz ($n = 51$). The patients who took the protease inhibitors reported the following at week 4: light-headedness (8%), dizziness (5%), difficulty in sleeping (4%), nervousness (4%), and headaches (3%). They reported the following at week 48: difficulty in sleeping (4%), nervousness (3%), headaches (3%), and light-headedness (2%). Three patients withdrew because of adverse events: diarrhea ($n = 2$) and nephrolithiasis ($n = 1$).

Sensory systems

- Lipemia retinalis and pancreatitis have been reported in a 39-year-old man with HIV infection associated with protease inhibitor therapy (13). He developed lipemia retinalis after switching to an antiretroviral regimen including ritonavir and saquinavir (together with zalcitabine and delavirdine). He had previously been taking zidovudine, lamivudine, and indinavir.

The ophthalmoscopic changes of lipemia retinalis include a milky-white discoloration of the retinal vessels, beginning at the periphery but progressing to involve the posterior pole as the triglyceride concentration rises. The fundus can appear salmon-colored, owing to the effect of triglycerides on the choroidal circulation. Experience from HIV-negative patients with hyperlipidemia has shown that plasma triglyceride concentrations must be at least 28 mmol/l (2500 mg/dl) for lipemia retinalis to occur (reference value below 1.52 mmol/l). This patient had a plasma triglyceride concentration of 53 mmol/l. On withdrawal of ritonavir and saquinavir the appearance of his retinal vessels returned to normal in parallel with a fall in his plasma triglycerides.

Endocrine

Two case reports have suggested that when a protease inhibitor is used with a glucocorticoid the tendency to adverse corticosteroid effects is potentiated (14,15). Two HIV-positive patients developed severely disfiguring skin striae within 3 months of starting indinavir therapy (16).

Metabolism

Metabolic changes that protease inhibitors can cause after prolonged therapy include raised serum lactate, hypogonadism, hypertension and accelerated cardiovascular disease, reduced bone density, and avascular necrosis of the hip. Two large prospective studies in 1207 patients (17) and 3191 patients (18) have clarified the spectrum and incidence of metabolic changes in HAART and have explored the relative importance of protease inhibitors. In addition, data on fat redistribution from a postmarketing review of HIV-infected individuals taking indinavir have been published (19).

Blood glucose concentration

Protease inhibitors can cause a rise in blood glucose concentration, although only a few cases have been reported. Patients with a family history of diabetes mellitus may be at a greater risk, and they demand especially close monitoring, for example with both baseline and quarterly glucose determinations, at least during the first 6–12 months of treatment (20,21).

Dyslipidemias

While abnormal concentrations of circulating lipids are common in patients with HIV infection (usually

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hypercholesterolemia and moderate hypertriglyceridemia), there is no doubt that some members of this group of drugs can cause much more marked changes. The possible differences between the effects of various protease inhibitors on the lipid spectrum have been characterized in 93 HIV-infected adults taking ritonavir, indinavir, or nelfinavir, alone or in combination with saquinavir (22). There was a rise in plasma cholesterol concentration in all those who took a protease inhibitor, but it was more pronounced with ritonavir than with indinavir or nelfinavir. Plasma HDL cholesterol was unchanged. Ritonavir, but not indinavir or nelfinavir, was associated with a marked rise in plasma triglyceride concentrations. The combination of ritonavir or nelfinavir with saquinavir did not further alter plasma lipid concentrations. There was a 48% increase in plasma concentrations of lipoprotein(a) in those taking a protease inhibitor, with pretreatment values exceeding 200 μg/ml. There were similar changes in plasma lipid concentrations in six children taking ritonavir. The risk of pancreatitis and premature atherosclerosis as a consequence of such dyslipidemia remains to be established.

- A 35-year-old HIV-positive man developed a serum cholesterol concentration of 38 mmol/l and a fasting serum triglyceride concentration of 98 mmol/l after he started to take ritonavir, saquinavir, nevirapine, and didanosine (23). All other medications had been stable during this time; the condition resolved with antiretroviral drug withdrawal and lipid-lowering therapy. It was striking that the raised cholesterol and triglyceride concentrations did not recur when therapy was restarted in modified form with nelfinavir, saquinavir, nevirapine, and didanosine; the hyperlipidemia was therefore attributed to ritonavir.

In 19 consecutive HIV-positive men examined before and during treatment with a protease inhibitor (nelfinavir, ritonavir, or indinavir) and two nucleoside analogue reverse transcriptase inhibitors (NRTI), median treatment duration 22 (range 7–40) weeks, the predominant feature of dyslipidemia was an increase in triglyceride-containing lipoproteins (24). This observation is in accordance with the hypothesis of increased apoptosis of peripheral adipocytes, release of free fatty acids, and subsequent increased synthesis of VLDL cholesterol. The lipid profile, based on the ratio of total cholesterol to HDL cholesterol and the ratio HDL2 to HDL3, is significantly more atherogenic than normal.

Lipodystrophy

Soon after the introduction of highly active antiretroviral combination treatments (HAART), lipodystrophy was associated with the use of protease inhibitors, and several reports have confirmed that a syndrome of peripheral lipodystrophy, central adiposity, breast hypertrophy in women, hyperlipidemia, and insulin resistance with hyperglycemia is an adverse event associated with the use of potent combination antiretroviral therapy, particularly including HIV-1 protease inhibitors (25–30).

Peripheral lipodystrophy in patients is characterized by fat wasting of the face, limbs, buttocks, and upper trunk, while central adiposity can cause an increase in belly size ("Crix-belly" or "protease pouch") and an increase in the dorsocervical fat pad, creating the appearance of a "buffalo hump" (31–33). These effects may be related to a glucocorticoid-like action. The increase in belly size is often associated with symptoms of abdominal fullness, distension, and bloating. This is probably due to a change in body fat distribution, with selective accumulation of fat intra-abdominally (34).

Lipodystrophy is not limited to patients taking protease inhibitors (35,36). Nevertheless, protease inhibitors are strongly associated with metabolic alterations and with lipodystrophy, while NRTIs are associated with low-grade lactic acidosis and less markedly with lipodystrophy. Some reports have speculated a link between mitochondrial dysfunction and lipodystrophy. It is clear, however, that the syndrome is related to total duration of antiviral therapy and inversely related to viral load.

In a longitudinal study from an Aquitaine cohort of more than 1400 subjects, hypertriglyceridemia was significantly associated with age, low viral load, and protease inhibitors, but not NRTIs or NNRTIs. However, lipodystrophy also occurred in patients naive to protease inhibitors (37).

- "Buffalo neck" was described in a middle-aged man taking indinavir who developed a lipomatous formation in the retrocervical area; abdominal fat also increased in volume, while the subcutaneous fat on the lower limbs decreased (38).

Of 494 patients during median follow-up of 18 months, 17% developed lipodystrophy (39). Study limitations included the short time of follow-up and the lack of a standardized and accepted definition of lipodystrophy.

Hematologic

There is still no clear explanation for a series of seven patients in whom treatment with various protease inhibitors was associated with early thrombosis (40). Hematological or vascular effects conducive to thrombosis are not recognized as a complication with this group of compounds; the only previous similar cases were associated with prolonged therapy.

In contrast, a detailed report on a large series of patients has provided impressive evidence that the use of protease inhibitors in HIV-infected patients with hereditary bleeding disorders can lead to an increased bleeding tendency (41). This effect, which is most likely to occur when ritonavir is used, is also unexplained.

Liver

In a retrospective study of patients taking one protease inhibitor ($n = 39$) or two ($n = 27$) who discontinued protease inhibitor therapy as a result of hepatotoxicity, the proportions of patients with raised alanine transaminase activity to at least five times the upper limit of the reference range (26 versus 19%) and hyperbilirubinemia (38 versus 30%) were similar (42). Rates of withdrawal due to hepatotoxicity were also similar.

Pancreas

- Lipemia retinalis and pancreatitis have been reported in a 39-year-old man with HIV infection associated with protease inhibitor therapy (13). His plasma triglyceride concentration was 53 mmol/l.

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Urinary tract

In a randomized comparison of a protease inhibitor-containing regimen and an efavirenz-containing regimen in 100 patients, six patients taking protease inhibitors developed nephrolithiasis; one withdrew as a result (12).

Musculoskeletal

The results of a questionnaire survey of 878 people with HIV infection treated with antiretroviral drugs also suggested that other protease inhibitors can cause arthralgia; indinavir and the combination of ritonavir + saquinavir were particularly implicated (43).

Immunologic

A man developed several erythematous plaques on his face due to borderline tuberculoid leprosy with a reversal reaction (44). He had severe CD4 T cell lymphocytopenia due to HIV infection and had been given highly active antiretroviral therapy (HAART). A fall in viral load and an increase in CD4 count preceded the development of the skin lesions, suggesting immune reconstitution as the underlying mechanism for the reversal reaction. Paradoxical reactions are often observed in patients with pulmonary and extra-pulmonary tuberculosis being treated with HAART. Clinicians need to distinguish these from other adverse reactions related to drug therapy. Reversal reactions in leprosy are increasingly likely as more patients with HIV infection are treated with HAART in developing countries.

Drug–Drug Interactions

See also General information and Table 1.

Ecstasy

A patient infected with HIV-1 who was taking ritonavir and saquinavir had a prolonged effect from a small dose of methylenedioxymetamfetamine (MDMA, ecstasy) and a near-fatal reaction from a small dose of gammahydroxybutyrate (45).

Gammahydroxybutyrate

A patient infected with HIV-1 who was taking ritonavir and saquinavir had a prolonged effect from a small dose of MDMA and a near-fatal reaction from a small dose of gammahydroxybutyrate (45).

Statins

There has been a study of the effects of ritonavir 400 mg bd plus saquinavir soft-gel capsules 400 mg bd on the pharmacokinetics of pravastatin, simvastatin, and atorvastatin (40 mg/day each), and of the effect of pravastatin on the pharmacokinetics of nelfinavir in a randomized, open study in 56 healthy HIV-negative adults (46). Ritonavir + saquinavir reduced the steady-state AUC of pravastatin, markedly increased the AUC of simvastatin, and slightly increased the AUC of total active atorvastatin. The AUCs of nelfinavir and its active M8 metabolite were not altered by pravastatin. The authors concluded that simvastatin (and by implication lovastatin, which in common with simvastatin inhibits CYP3A4) should be avoided and atorvastatin should be used with caution in people taking ritonavir and saquinavir, that dosage adjustment of pravastatin may be necessary with concomitant use of ritonavir + saquinavir, and that concomitant use of pravastatin with nelfinavir appears to be safe.

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Protein hydrolysates

General Information

Protein hydrolysates are added to hair-care products, such as shampoos and conditioners, and are supposed to "repair" damaged hair. Hydrolysed proteins are also used in other body-care products, for example soaps, bath gels, and creams.

Organs and Systems

Immunologic

Occasionally single reports of contact urticaria and of allergic contact dermatitis due to hair conditioner and skin cleanser have been published (SEDA-21, 166) (1). Protein hydrolysates used in hair-care products have been tested in 11 hairdressers with hand dermatitis, in 2160 consecutive adults with suspected respiratory disease, and in 28 adults with chronic atopic dermatitis (2). The hairdressers underwent both scratch tests (1% aqueous) and patch tests (5% aqueous) with 22 protein hydrolysates (collagen, keratin, elastin, milk, wheat, almond, silk). Skin prick tests with one to three hydrolysates (1% aqueous) were conducted in the other patients. All 2199 patients were tested with hydroxypropyl trimonium hydrolysed collagen (Crotein Q). There were positive scratch/prick test reactions in 12 patients to three protein hydrolysates. Remarkably, all were women with atopic dermatitis. They reacted at least to hydroxypropyl trimonium-hydrolysed collagen (Crotein Q) and 11 had positive reactions to one or more allergens in a standard prick series. In three patients, clinical relevance could be confirmed by open tests with both undiluted and diluted hair conditioner containing Crotein Q (one hairdresser with contact urticaria on the hands, two cases of contact urticaria on the head, face, and upper body from a hair conditioner containing Crotein Q). Furthermore, in seven of eight sera studied, specific IgE to Crotein Q was detected, while 11 control sera were negative. These results show that protein hydrolysates in hair-care products may be underestimated causes of contact urticaria, particularly in patients with atopy.

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Prothrombin complex concentrate

See also Coagulation proteins

General Information

Prothrombin complex products contain constant amounts of clotting factors II, VII, IX, and X, bypassing the need for factor VIII in the clotting cascade. They are used to reverse the effects of oral anticoagulants (for example during surgery or bleeding episodes) (1) and to treat bleeding episodes in hemophiliacs with inhibitors of factor VIII (2). Prothrombin complex achieves more rapid and effective reversal of acquired coagulation defects than fresh frozen plasma. However, a potential disadvantage is the risk of thromboembolism.

Organs and Systems

Cardiovascular

Thromboembolic events in relation to activated prothrombin complex products include deep venous thrombosis and pulmonary embolism (3–5). So far, the exact mechanism of how thromboembolic events are stimulated by prothrombin complex products is not known. It has been postulated that the presence of activated clotting factors VII, IX, and X, as well as procoagulatory phospholipids in prothrombin complex products, are responsible (6).

In 42 patients who required immediate reversal of oral anticoagulant therapy by prothrombin complex concentrate, no laboratory and clinical evidence for coagulation activation was found (7). The authors suggested that the concentration of protein C within the prothrombin complex concentrate is an important factor for preventing thrombosis. The activated form of protein C is an important natural anticoagulant.

Myocardial necrosis has been described after the administration of a prothrombin complex products, probably because of excessive kininogen in the product.

Hematologic

The administration of prothrombin complex concentrate to reverse anticoagulant treatment has been associated with thrombotic complications, such as disseminated intravascular coagulation (8). However, such complications have typically occurred in patients with liver failure or after repeated treatment, such as in patients with hemophilia B treated with prothrombin complex concentrate (9).

Hypofibrinogenemia has been observed immediately after infusion of one of the activated prothrombin complex products (such as Autoplex). It has been advised that antifibrinolytic substances should be avoided in conjunction with Autoplex.

Skin

An erythematous pruritic eruption has been described after infusion of Autoplex (3).

Immunologic

In about 5% of patients with hemophilia A with antibodies to factor VIII treated with an activated prothrombin

complex product (Autoplex), there was a significant increase in antibody titer (10).

Susceptibility Factors

Relative contraindications for prothrombin complex concentrate are liver disease, coronary heart disease, and factors that predispose to thrombosis (11). It is contraindicated in disseminated intravascular coagulopathy and hyperfibrinolysis.

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Protirelin

General Information

Protirelin is a synthetic tripeptide that stimulates the hypophyseal secretion of thyrotrophin (thyroid-stimulating hormone, TSH). It is used mainly for diagnostic purposes in dynamic tests of pituitary and hypothalamic function, but its use in the assessment of hyperthyroidism has been superseded by sensitive assays of thyrotrophin (SED-13, 1311) (1). Protirelin has neurotransmitter properties and has been used to treat a variety of neurological disorders, including intractable epilepsy (2). Some experiments have also been performed to evaluate its effects in mental disorders.

Protirelin is generally given intravenously (as a bolus of 200 micrograms), as absorption after oral and intranasal administration is unpredictable.

Comparative studies

Protirelin has been given antenatally in combination with a glucocorticoid, to accelerate fetal lung maturation in an attempt to reduce the incidence of infant respiratory distress syndrome. However, there was no improvement in outcome and the mothers experienced more adverse effects (particularly flushing, headache, nausea, and vomiting) in the protirelin group in two large prospective studies (3,4). The infants were reported to have mild developmental delay at 12 months of age (5): this finding was initially criticized because of methodological problems and there was no consensus that protirelin induces harmful effects in these infants (6).

Subsequently, the addition of protirelin to glucocorticoid therapy was the subject of a meta-analysis (7). In 1134 premature infants the serum TSH concentration was increased for the first 6 hours after the last maternal dose of protirelin, then suppressed for 36 hours before returning to control values (8). The largest controlled trial (in 1368 infants) reported a small delay in development at 12 months (5). However, developmental assessment was by questionnaire, with incomplete ascertainment, and these findings have been questioned (6). In the mothers, there was a three-fold increase in nausea, vomiting, or flushing and a two-fold increase in hypertension compared with glucocorticoid therapy alone.

General adverse effects

The adverse effects of protirelin are usually mild. These include facial flushing, urinary urgency, vaginal sensations, nausea, chest pain, and altered taste sensation (9).

Organs and Systems

Cardiovascular

A transient rise in blood pressure occurs immediately after the administration of protirelin (10). In very rare cases, transient amaurosis and bronchospasm have been reported, thought to be due to either vasopressor syncope or cardiac arrhythmias (11–13).

Nervous system

The most serious adverse effect of protirelin is pituitary apoplexy (pituitary hemorrhage or infarction, characterized by severe headache, visual loss, and often by pituitary failure, hypotension, and coma). This complication has been described in 15 cases after pituitary function testing with protirelin. Pituitary macroadenoma was present in all cases. Although insulin and gonadorelin were also used in these patients, protirelin was considered to be

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the most likely agent responsible, owing to its vasoactive properties (SED-13, 1311) (14).

- A woman developed severe bifrontal headache and visual blurring 5 minutes after the intravenous administration of protirelin 200 micrograms to investigate her pituitary macroadenoma (15). The symptoms resolved in less than 2 hours without sequelae.
- A patient developed a severe headache, nausea and vomiting, visual disturbance, and altered mental function 88 hours after a protirelin/gonadorelin stimulation test to investigate a pituitary macroadenoma (16). Bleeding into the tumor was seen on CT scan. The patient died 9 days later of pneumonia.

Loss of consciousness or convulsions occurred in a few patients who received high doses (400 micrograms) of protirelin intravenously.

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Proton pump inhibitors

See also Individual agents

General Information

Proton pump inhibitors inhibit the H/K-ATPase (proton pump) in oxyntic cells of the stomach, the final common pathway in the secretion of gastric acid in response to a variety of stimuli, such as gastrin and histamine. Their use in acid-related disorders has been extensively reviewed (1–3).

Comparative studies

Comparisons between proton pump inhibitors

Lansoprazole 15 mg/day and omeprazole 10 mg/day for 4 weeks have been compared in the relief of heartburn and epigastric pain in a randomized, double-blind, parallel-group study in 609 patients with acid-related dyspepsia (4). Low-dose lansoprazole was more effective in controlling symptoms. There were no significant differences in adverse events between the two groups, although there was a trend toward a higher incidence of more severe adverse events with omeprazole. Most of the reported adverse events were difficult to relate to the treatments.

An unblinded questionnaire survey has been carried out to determine patients' perceptions of differences in the efficacy, adverse effects, and value of omeprazole versus lansoprazole for gastro-esophageal reflux disease maintenance therapy (5). The patients had been taking omeprazole for at least 2 months and then switched to lansoprazole for a minimum of 2 months. There was no significant difference between median symptom scores with the two drugs, but 64% of patients preferred omeprazole to lansoprazole. The most commonly reported adverse effects with both drugs were flatulence, headache, and diarrhea. Significantly more patients reported adverse effects with lansoprazole than with omeprazole.

Rabeprazole 20 mg/day has been compared with omeprazole 20 mg/day in a randomized, double-blind, multicenter study in 205 patients with active duodenal ulcers (6). Rabeprazole produced healing rates equivalent to omeprazole at 2 and 4 weeks of treatment (69 versus 61% and 98 versus 93% respectively) and greater improvement in day-time pain. Both drugs were well tolerated; adverse effects were similar, and included

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headache, infections, diarrhea, gastritis, stomatitis, rash, and sweating. Serum gastrin concentrations increased over time in both groups. There was a statistically significant difference between the groups in the mean change in fasting serum gastrin from baseline to end-point; +40 pg/ml with rabeprazole and +19 pg/ml with omeprazole. However, mean values at the end of the study were in the reference range in both groups.

Rabeprazole 20 mg/day and omeprazole 20 mg/day have been compared in the treatment of erosive or ulcerative esophagitis in a double-blind, multicenter study in 202 patients (7). Overall healing rates for rabeprazole and omeprazole at 4 and 8 weeks of treatment were equivalent (81 versus 81% and 92 versus 94% respectively), as was symptom relief. Both drugs were well tolerated, and there was no significant difference in reported adverse events, except for flatulence, which was only reported by patients taking omeprazole (4%). Other adverse effects included headache, diarrhea, rash, flu-like syndrome, gastroenteritis, raised aspartate transaminase and gamma-glutamyltransferase, weakness, myalgia, somnolence, and hypertension. Serum gastrin concentrations increased over time in both groups; however, there was no significant difference between the treatment groups in the mean change in fasting serum gastrin concentrations from baseline to end-point.

The proton pump inhibitors produce a higher intragastric pH in the presence of *Helicobacter pylori* than after eradication. The mechanism of this effect is unclear, but possible explanations are reduced production of ammonia or other neutralizing substances after eradication of the infection or the development of gastritis during omeprazole therapy in the presence of *H. pylori*, leading to reduced acid secretion. In a double-blind, crossover study in 13 subjects with *H. pylori*, pumaprazole (BY841) 100 mg bd, a reversible proton pump inhibitor, which (unlike omeprazole) does not require activation in the acid compartment of the parietal cell, produced a similar rise in intragastric pH to that produced by omeprazole before and after eradication of *H. pylori* (8). Adverse events during the study were mild and assessed as probably not related to the drugs. They included headache, abdominal pain, and diarrhea. Serum gastrin concentrations rose during pumaprazole therapy and were higher than during omeprazole therapy, both before and after eradication of *H. pylori*.

The common adverse events during treatment with proton pump inhibitors used in general practice in England have been reviewed in a prescription event monitoring study in 16 205 patients taking omeprazole, 17 329 taking lansoprazole, and 11 541 taking pantoprazole (9). The commonest adverse events in all three groups were diarrhea, nausea/vomiting, abdominal pain, and headache. There was little difference in the adverse event rates between the three groups. However, diarrhea was more commonly associated with lansoprazole compared with omeprazole, particularly in elderly people.

To assess acid control, esomeprazole 20 or 40 mg/day has been compared with omeprazole 20 mg/day for 5 days in a double-blind, crossover study in 38 patients with symptoms of gastro-esophageal reflux disease (10). Pharmacokinetic variables and 24-hour intragastric pH were measured on day 5 of each dosing period. Esomeprazole provided more effective acid control than omeprazole. Both dosages of esomeprazole were well tolerated, and the profile and incidence of adverse events were similar to that observed with omeprazole. The most common were abdominal pain, nausea, diarrhea, respiratory infection, and headache.

Esomeprazole 20 or 40 mg/day and omeprazole 20 mg/day for 8 weeks have been compared in the treatment of gastro-esophageal reflux disease in a multicenter, randomized, double-blind trial in 1960 patients (11). Symptom control and healing rates were significantly better with either dose of esomeprazole than with omeprazole. There was no significant difference in reported adverse events between the treatment groups. The most commonly reported were headache, abdominal pain, and diarrhea.

The results of a therapeutic interchange program, in which 78 patients with acid peptic disease requiring proton pump inhibitor therapy (both newly diagnosed patients and those previously stabilized on omeprazole) were treated with lansoprazole, have been retrospectively analysed (12). Although the switch was associated with considerable pharmaceutical savings, there was an overall lansoprazole-associated failure rate of 28%. Reported lack of efficacy required withdrawal of lansoprazole in 15%, while adverse effects required withdrawal of lansoprazole in 13% of patients (versus none with omeprazole). The main adverse effect was diarrhea.

The clinical and fiscal impact of replacing omeprazole with lansoprazole as the only proton pump inhibitor has been assessed by reviewing the medical records of 3833 patients requiring long-term proton pump inhibitor therapy (2224 were started on lansoprazole and 1479 were converted from omeprazole to lansoprazole) (13). There were considerable pharmaceutical savings. The true lansoprazole failure rate (requiring conversion to omeprazole) was 5.3%. Withdrawal of lansoprazole was due to poor symptom control (in 69%) and/or adverse effects (in 22%). The most common adverse effects were diarrhea (10%), abdominal pain (5%), and urticaria (1%).

Omeprazole 40 mg/day for 6 weeks and lansoprazole 30 mg bd have been compared for symptom control in a randomized study in 96 patients with gastro-esophageal reflux disease who had earlier failed to respond to lansoprazole 30 mg/day (14). The two drugs were equally effective in symptom control. There were no significant differences in adverse events between the two groups. The most frequent adverse events reported were diarrhea, abdominal pain/discomfort, bloating/gas, vomiting, and headache.

Omeprazole multiple unit pellet system (MUPS) 20 mg/day and pantoprazole 40 mg/day for 8 weeks were more effective than lansoprazole 30 mg/day in relieving heartburn in a randomized, double-blind trial in 461 patients with symptomatic reflux esophagitis (15). Patient satisfaction and adverse effects were similar in the three groups. The most common adverse effects were diarrhea, headache, and nausea.

In a multicenter, double-blind, crossover study in primary care in 240 patients with acid-related disorders, omeprazole 20 mg/day and rabeprazole 40 mg/day for 4 weeks provided similar symptom control (16). The adverse effect profiles were also similar in the two groups. However, more patients preferred rabeprazole to omeprazole.

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Omeprazole 40 mg/day and rabeprazole 20 mg/day for 4 weeks have been compared in a randomized, double-blind trial in 251 patients with erosive esophagitis (17). The two treatments had similar efficacy in relieving symptoms on day 4 and healing esophageal lesions, but rabeprazole had a faster onset of action in patients with severe heartburn. Both drugs were well tolerated and gave rise to similar frequencies of adverse effects, commonly involving the gastrointestinal tract (10%) and nervous system (4.4%).

Rabeprazole 10 or 20 mg bd and omeprazole 20 mg/day have been compared in the healing of erosive gastro-esophageal reflux disease in a double-blind, multicenter study in 310 patients (18). Overall healing rates for rabeprazole (both dosage regimens) and omeprazole at 4 and 8 weeks of treatment were equivalent. The drugs were equally well tolerated, and there was no significant difference in reported adverse events. The more frequent were abdominal pain, pharyngitis, bronchitis, headache, and diarrhea.

Esomeprazole 40 mg/day and omeprazole 20 mg/day for 8 weeks have been compared in the treatment of erosive esophagitis in a multicenter, randomized, double-blind trial in 2425 patients (19). Significantly more patients were healed with esomeprazole. There was no significant difference in reported adverse events between the treatment groups. The most commonly reported were headache, diarrhea, and nausea.

The effects of omeprazole 40 mg/day and esomeprazole 40 mg/day for 5 days on intragastric acidity have been compared in an open, crossover study in 130 patients with symptoms of gastro-esophageal reflux (20). Esomeprazole provided more effective acid control than twice the standard dose of omeprazole. Adverse effects were similar with the two drugs, and the most commonly reported were headache, nausea, and abdominal pain.

Pantoprazole 20 mg/day and omeprazole 20 mg/day for 8 weeks have been compared in the treatment of grade I reflux esophagitis in a multicenter, randomized, open trial in 328 patients (21). Symptom relief and healing rates were similar and both treatments were well tolerated. There was no significant difference in reported adverse events between the groups. The most commonly reported were nausea, diarrhea, and headache.

Lansoprazole 30 mg/day and omeprazole 20 mg/day for 8 weeks have been compared in the relief of heartburn in a multicenter, randomized, double-blind trial in 3510 patients with erosive esophagitis (22). Symptom control was significantly more effective and faster with lansoprazole than omeprazole. Both drugs were well tolerated. The most common adverse effect was diarrhea.

Rabeprazole 10 mg bd or 20 mg/day, omeprazole 20 mg/day, and placebo for 7 days in reducing esophageal acid exposure have been compared in a multicenter, randomized, double-blind trial in 82 patients with symptomatic gastro-esophageal reflux disease (23). Esophageal pH was monitored for 24 hours before treatment and on day 7. Esophageal acid exposure was significantly reduced in all the treatment groups compared with placebo, with no significant difference in efficacy. Both rabeprazole and omeprazole were well tolerated. The most commonly reported adverse effects were diarrhea, abdominal pain, nausea, and headache.

Comparisons between proton pump inhibitors and H_2 receptor antagonists

The effects of famotidine 20 mg bd and omeprazole 20 mg/day for 8 weeks have been compared in the treatment of reflux esophagitis in a randomized trial in 56 patients (24). Omeprazole was more effective in healing esophagitis and providing symptom relief. Adverse events, which were rare, were similar in the two groups, and consisted of nausea, palpitation, abdominal pain, and mild abnormalities of liver function tests.

Lansoprazole 30 mg/day, lansoprazole 15 mg/day, and ranitidine 150 mg/day have been compared in a randomized, double-blind, multicenter trial in the prevention of relapse of duodenal ulcer and symptom control over 12 months in 359 patients (25). Both doses of lansoprazole were superior to ranitidine. There was no significant difference between the two lansoprazole groups, although there was a trend in favor of lansoprazole 30 mg/day. There were no differences in adverse effects profiles in the three groups. The adverse effects included diarrhea, abdominal pain, viral infections, headache, and vomiting.

Lansoprazole 30 mg/day, lansoprazole 15 mg/day, and ranitidine 150 mg bd for 8 weeks have been compared in a randomized, double-blind, multicenter trial in the healing of NSAID-associated gastric ulceration in 353 patients (26). Both doses of lansoprazole were superior to ranitidine in healing gastric ulcers. Healing rates were similar between *H. pylori* infected and non-infected patients, again with significantly better healing rates with lansoprazole than ranitidine. There were no differences in adverse effects profiles in the three groups. The most commonly reported adverse effect was diarrhea.

Lansoprazole 15 or 30 mg/day and ranitidine 150 mg bd for 8 weeks have been compared in the treatment of non-erosive gastro-esophageal reflux disease in two double-blind, multicenter trials in 901 patients (27). Overall symptom control was significantly better with either dose of lansoprazole than with ranitidine or placebo. There was no significant difference in reported adverse events between the treatment groups. The more commonly reported were abdominal pain and diarrhea.

Pantoprazole 20 mg/day (low dose) and ranitidine 300 mg/day (standard dose) have been compared in the treatment of mild gastro-esophageal reflux disease in a double-blind, multicenter trial in 201 patients (28). Overall symptom control and healing rates were significantly better with pantoprazole. There was no significant difference in reported adverse events between the treatment groups. The more commonly reported were diarrhea, headache, and abdominal pain.

General adverse effects

The adverse effects profile of the proton pump inhibitors during short-term administration (under 12 weeks) is similar to that reported with short-term use of histamine receptor antagonists. The type and frequency of adverse effects reported with lansoprazole, omeprazole, pantoprazole, and rabeprazole are comparable. The most common adverse effects include headache, diarrhea, nausea, abdominal pain, constipation, dizziness, and skin rashes.

Proton pump inhibitors can interact with other drugs by increasing gastric pH, inhibiting hepatic cytochrome

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P450, or inducing specific isoforms of this enzyme system. However, drug interactions involving these isoenzymes and omeprazole or lansoprazole are uncommon and generally appear to be clinically unimportant. Pantoprazole seems to have a lower drug interaction potential than either omeprazole or lansoprazole.

Organs and Systems

Cardiovascular

Reversible peripheral edema has been reported in five women taking the proton pump inhibitors omeprazole, lansoprazole, or pantoprazole for 7–15 days for peptic disorders in recommended standard doses (29). Edema disappeared within 2–3 days of withdrawal and reappeared in all five patients after re-exposure. High-dose intravenous infusions of omeprazole and pantoprazole (8 mg/hour) caused peripheral edema in three of six young female volunteers and two of six female volunteers respectively. The edema disappeared within 24 hours of stopping the infusion. Similar high doses of omeprazole did not produce edema in male volunteers. Subsequent studies performed on 10 female volunteers to elucidate the cause of the edema did not show any changes in concentrations of serum hormones or C1 esterase inhibitor.

Long-Term Effects

Tumorigenicity

There has been concern about the potential for proton pump inhibitors to cause enterochromaffin-like cell hyperplasia, gastric carcinoid tumors and gastric cancers, colorectal polyps and adenocarcinoma, atrophic gastritis, and intestinal metaplasia in patients with *H. pylori* infection, and bacterial overgrowth.

Carcinoid nodules were detected in the stomach of rats given large doses of omeprazole over prolonged periods. A variety of evidence, however, suggests that these findings were neither specific to omeprazole nor likely to indicate material risks to man (30), and that other arguments for a tumor-inducing effect of proton pump inhibitors are equally unconvincing. Firstly, similar carcinoid change has been detected with secretory antagonists and the fibrates, which are anti-secretory in rats. Secondly carcinoidogenesis can be inhibited by antrectomy, presumably by removing an antral gastrin drive, and it can be enhanced by partial fundectomy, when relative anacidity increases antral gastrin release. Thirdly, although omeprazole treatment can raise serum gastrin levels quite markedly in man, they do so by a level of magnitude less than in pernicious anemia, in which carcinoid tumors are recorded, albeit rarely. Fourthly, despite close searching, carcinoids have not been detected complicating ordinary ulcer treatment in man. Others have claimed on the basis of tissue work in vitro that omeprazole may itself be a mitogen or mutagen; it has been counter-claimed that the technique used in the studies concerned is inherently unreliable and that other standard techniques have failed to reveal mutagenic potential (SED-12, 943). Finally, selective and important actions on a cytochrome which would activate carcinogens have been claimed, but seem unlikely experimentally. This is one of the situations in which there is inherent difficulty in disproving a postulated relationship. Currently it seems very unlikely that an appreciable risk exists, but most experts would now recommend that any patient requiring long-term treatment with a proton pump inhibitor should take treatment to eradicate *H. pylori* infection (SEDA-20, 318).

Therapeutic doses of proton pump inhibitors usually produce somewhat higher serum gastrin concentrations than histamine receptor antagonists. However, except for small intestinal bacterial overgrowth, there is no convincing evidence yet to implicate proton pump inhibitors in the development of malignant or premalignant lesions in the human gastrointestinal tract. Nevertheless, although omeprazole has been used for more than 14 years and lansoprazole for more than 10 years, longer-term data are required to completely rule out the possibility of increased risk of gastric tumor formation.

An increasing number of gastric polyps is being reported in patients taking proton pump inhibitors. Although these may be coincidental and may only account for a minority of sporadic cases (31), it is too early to disregard the possibility that they are treatment induced (32). Long-term prospective controlled trials including investigation of the effects of stopping and restarting proton pump inhibitors on the evolution of gastric polyps will have to be done before a firm causal relation can be established.

An uncontrolled retrospective study of patients who had taken proton pump inhibitors for an average of 33 months found gastric polyps in 17 of 231 patients who underwent two or more endoscopies for complicated gastro-esophageal reflux disease (33). The polyps were generally small (under 1 cm), sessile, and multiple, and were present in the proximal or mid gastric body. Of the 15 polyps removed endoscopically, nine were fundic gland type, four were hyperplastic, and two were inflammatory. None had any dysplasia or carcinoma.

A gastric carcinoid tumor, detected during long-term anti-ulcer therapy with a histamine receptor antagonist and proton pump inhibitors, has been reported (34).

- A 31 year old Japanese man with recurrent duodenal ulcer was treated with famotidine, omeprazole, and lansoprazole at different times over 3 years. Gastroscopy showed a small carcinoid tumor in the upper cardia after 35 months. The lesion became larger while the patient was taking lansoprazole.

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Proxymetacaine

See also Local anesthetics

General Information

Proxymetacaine is an ester of meta-aminobenzoic acid. It is often used in ophthalmology.

Organs and Systems

Skin

Proparacaine has been reported to cause contact dermatitis.

- A 49-year-old ophthalmologist developed fissuring and bleeding of his finger-tips (1). Skin patch tests using a series of standard and preservative allergens showed only mild reactions to some. Various treatments were attempted, with minimal success, and skin patch testing was repeated using 32 specific formulations that he had contact with in his practice; he had a severe reaction to proxymetacaine hydrochloride 0.5%. Subsequent removal of proparacaine from his practice resulted in resolution over 6 months.
- An ophthalmologist developed chronic finger pad dermatitis with fissuring and scaling, which mainly affected his thumbs for 3 years (2). Patch testing confirmed that "ophthetic solution" (proxymetacaine hydrochloride 0.5%, glycerine, and benzalkonium chloride 0.01%) was the sensitizing agent. He was instructed to change to tetracaine, to which he had had a negative patch test. However, 2 years later his symptoms recurred and a repeat patch testing was carried out. This was now positive to both tetracaine 1% and proxymetacaine 0.5%.

Cross-sensitization between proxymetacaine and tetracaine is thought to be rare. Moreover, the chemical structure of proxymetacaine is sufficiently different from tetracaine to make cross-reactivity unlikely. This case suggests, however, that some degree of cross-sensitization can occur.

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Proxyphylline

General Information

Proxyphylline is a theophylline derivative used as a bronchodilator. It is readily absorbed from the gastrointestinal tract and is not converted to theophylline.

In 12 patients with chronic obstructive pulmonary disease, intravenous proxyphylline 16 mg/kg lowered airway resistance by 30% in 9 patients and by 40% in 7 (1). There were no serious adverse effects and, in particular, no adverse cardiovascular effects or muscle tremor.

In a short-term, double-blind, crossover study in 10 adult asthmatics, a modified-release formulation of proxyphylline (2400 mg/day) was compared with theophylline (800 mg/day) and placebo (2). There were no significant differences between the treatments with regard to relief of asthma symptoms, the need for additional medication, or the incidence and intensity of adverse effects. The adverse reactions included loss of appetite, palpitation, headache, nausea, stomach ache, muscle tremor, and sleep disturbances.

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2 Mosbech H, Paulsen H, Soborg M. Controlled-release theophylline and proxyphylline in asthmatics: a comparative study. Pharmatherapeutica 1984;3(9):626–30.

Pyrantel

General Information

Pyrantel is an antihelminthic drug that is effective against intestinal nematodes, including roundworms (*Ascaris lumbricoides*), threadworms (*Enterobius vermicularis*), *Trichostrongylus* species, and the tissue nematode *Trichinella spiralis*. Although it is effective against hookworms, it is less effective against *Necator americanus* than against *Ancylostoma duodenale*.

Pyrantel is usually given as the embonate or pamoate in a single dose of 10 mg/kg, and adverse reactions rarely

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impede treatment. They include gastrointestinal disturbance (nausea, anorexia, abdominal pain, diarrhea), headache, and vomiting, which are usually mild but can occur in up to 20% of patients.

Organs and Systems

Nervous system

Myasthenia gravis has reportedly been aggravated by pyrantel pamoate (1).

Liver

In children aged 5–10 years pyrantel caused mild transient changes in liver function tests (2).

Drug–Drug Interactions

Theophylline

An interaction of pyrantel with theophylline has been reported (3).

- An 8-year-old boy with status asthmaticus was given intravenous aminophylline and then switched to modified-release oral theophylline on day 3, when his serum theophylline concentration was 15 μg/ml. On day 4 he was given a single dose of pyrantel 160 mg (for *A. lumbricoides* infection) at the same time as his second oral dose of theophylline. About 2.5 hours later his serum theophylline concentration was 24 μg/ml, and a further 1.5 hours later it had risen to 30 μg/ml. No further theophylline was given and no theophylline toxicity occurred.

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Pyrazinamide

See also Antituberculosis drugs

General Information

Pyrazinamide is a pyrazine analogue of nicotinamide. It is bactericidal for *Mycobacterium tuberculosis* in an acid environment and within macrophages (1). Regimens that include pyrazinamide produce significantly more rapid rates of sputum conversion than any other combination. Pyrazinamide is therefore especially appropriate in the initial phase of treatment. In the 6-month regimen of the American Thoracic Society, pyrazinamide was used together with isoniazid and rifampicin for the first 2 months (2).

Pyrazinamide is distributed throughout the body. Peak plasma concentrations are reached 2 hours after oral administration. Excretion is primarily by glomerular filtration. Serum concentrations are generally 30–50 μg/ml with daily doses of 20–25 mg/kg. The maximum daily dose should not exceed 3 g, regardless of weight. At a pH of 5.5, the minimal inhibitory concentration of pyrazinamide for *Mycobacterium tuberculosis* is 20 μg/ml (1).

Observational studies

The combination of pyrazinamide plus levofloxacin is first-line treatment for multidrug-resistant latent tuberculosis. In 17 Canadian patients there were important adverse reactions affecting the musculoskeletal and central nervous systems; hyperuricemia, gastrointestinal effects, and dermatological effects were also common (3). This combination may be used with careful monitoring for adverse effects.

General adverse effects

Most of the adverse effects of pyrazinamide are toxic effects. Reactions involving the liver, hyperuricemia with and without gout, and symptoms of pellagra have particularly been recognized. Fever and urticaria are described. Sideroblastic anemia, thrombocytopenia, anorexia, nausea and vomiting, dysuria, malaise, and aggravation of peptic ulcer can occur (SEDA-13, 261). Allergic reactions and tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Acute symptomatic hypertension consistently followed the administration of pyrazinamide to a 65-year-old woman with pulmonary tuberculosis (4).

Metabolism

Pyrazinamide interferes with the renal excretion of urate, resulting in hyperuricemia. Acute episodes of gout or arthralgia have occurred. Arthralgia responds better to NSAIDs than to uricosuric drugs (5).

Pyrazinamide can aggravate porphyria (1).

Liver

Liver damage is the most common adverse effect of pyrazinamide (6). It varies from asymptomatic alteration of liver function detectable only by laboratory tests, through a mild syndrome characterized by fever, anorexia, malaise, liver tenderness, hepatomegaly, and splenomegaly, to more serious reactions with clinical jaundice, and finally the rare form with progressive acute yellow atrophy and death. As most patients take a combined regimen of pyrazinamide with isoniazid and rifampicin, it is difficult to determine which of the three drugs causes the hepatotoxicity; it could be due to a combined effect (7). As with isoniazid and rifampicin, hepatic function should initially be monitored every few weeks.

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Skin

Pyrazinamide can cause pellagra. However, prophylactic nicotinamide is not generally recommended. In cases of pellagra, a dosage of 300 mg/day should be given (8).

In one case, erythema multiforme and urticaria occurred together after administration of pyrazinamide, and there were circulating immune complexes (9).

Photosensitization has been rarely described in patients taking pyrazinamide (10).

Susceptibility Factors

Age

00Although pyrazinamide is a part of conventional combination therapy for children with tuberculosis, as in adults (11), there is little published information on its safety. In those with raised transaminases before the start of therapy there was no increase during therapy, and the activities normalized in all patients after its conclusion.

Hepatic disease

Pyrazinamide should be avoided in patients with liver disease and porphyria (1). Liver function tests should be repeated at frequent intervals during the entire period of treatment.

Other features of the patient

Pyrazinamide should be used with extreme caution in patients with a history of gout, especially in elderly people, in whom urinary urate stones can cause renal insufficiency.

In patients with hemoptysis, the possibility that pyrazinamide may have an adverse effect on blood clotting time or vascular integrity should be borne in mind (12,13).

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Pyridoxine

See also Vitamins

General Information

Pyridoxine (vitamin B_6) requirements vary with protein intake: the daily Average Requirement is 13 micrograms/g protein intake and the Population Reference Intake is 15 micrograms/g protein intake. In adults this translates into a daily Average Requirement of 1.3 mg/day for men and 1.0 mg/day for women, and a Population Reference Intake of 1.5 mg/day for men and 1.1 mg/day for women.

Uses

Pyridoxine is used to prevent the adverse nervous system effects of isoniazid (1). Adherence to therapy is improved by prescribing combined tablets containing 20 mg of pyridoxine per 100 mg of isoniazid.

Megadoses of pyridoxine are commonly used to treat homocystinuria, cystathioninuria, and primary oxalosis type I (2,3). In some diseases pyridoxine is used empirically, including rheumatic diseases, degenerative joint diseases, carpal tunnel syndrome, Chinese restaurant syndrome, and premenstrual syndrome. A rare form of neonatal seizures, reported as early as 1954, seems to respond only to large doses of pyridoxine (4,5). Occasionally, the condition can appear up to 2 years after birth. Affected patients can have abrupt seizure cessation and dramatic improvement in the electroencephalogram after receiving an intravenous dose of pyridoxine 50–100 mg. The mechanism of this rare condition is unclear. It has been suggested that in these infants there is a shift in the balance of glutamate and GABA in the central nervous system; giving pyridoxine increases the co-enzyme pool, offsetting the adverse kinetics that result from altered glutamate decarboxylase binding. One adverse consequence

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of the large dose of pyridoxine required is a diffuse inhibitory state, with effects ranging from excessive drowsiness to coma and electrocerebral silence. Resuscitation equipment should be on hand if this treatment is used.

Extremely high doses of pyridoxine, even up to 6000 mg/day, have also sometimes been used therapeutically. While few problems arise from controlled application of high doses of pyridoxine under medical supervision, self-medication in doses exceeding 300–500 mg/day can lead to adverse effects, especially when continued over a long period of time. Many patients have self-medicated with more than 2000 mg/day for long periods of time (SEDA-10, 334) (6,7).

In many countries, pyridoxine is a component of "vitamin B complex" products, administered orally or parenterally as "tonics," commonly because of their supposedly beneficial effects on the nervous system.

General adverse effects

Under the headline "Still time for rational debate about vitamin B_6" the controversial debate on the safety of pyridoxine has been revived (8). Pyridoxine is marketed for stress in general, for depression associated with premenstrual syndrome and oral contraceptives, and for carpal tunnel syndrome, although it is doubtful that it has more than a placebo effect. It is legitimately prescribed in general deficiency states in doses starting at 150 mg/day. Adverse events include sensory neuropathy at oral doses about 2–3 g/day or more.

The editorial refers to the attempts of the UK Government's Committee on Toxicity to find the safe level of daily consumption of pyridoxine. In July 1997 the committee recommended that the sale of pyridoxine in, for instance, health-food shops would be restricted to doses of 10 mg/day. Doses between 10 and 50 mg would be restricted to sale at pharmacies; and doses of 50 mg and above would be available only on prescription. Contrary to these UK recommendations the Committee of the US National Academy of Science concluded that there were no convincing reports of adverse events at doses of up to 200 mg/day. Paying attention to the fact that recommendations tend to be more cautious than might seem necessary from the available evidence, the US experts halved the 200 mg/day dose to define their limit as 100 mg/day.

The author of the editorial found fault with the fact that the US experts have based their recommendations on the slimmest of evidence. The main human study was a self-recall series of 172 patients presenting to a private practice in London (9). In a letter to the editor, Beckett (10) pointed out that daily doses of 200 mg or less have been taken by millions of people worldwide for several decades without evident toxicity and that testimonials from clinicians expert in the use of pyridoxine have attested to its safety in these doses (11). Referring to the editorial, the author of the study in question stated that their study referred to 172 women with raised blood concentrations of pyridoxine that reverted to normal within 4 days of stopping pyridoxine, and was not a "self-recall series." In a recent follow-up of these women who had raised blood concentrations, compared with controls from the same practice who had had a blood test in 1985–86 and whose record showed that they were not taking pyridoxine or multivitamins at that time or since, 16 of 50 respondents had subsequently had autoimmune disease, compared with one of the 38 controls. The autoimmune diseases included thyroid disease ($n = 5$), rheumatoid arthritis ($n = 3$), diabetes ($n = 2$), Sjögren's syndrome ($n = 2$), primary biliary cirrhosis ($n = 1$), polymyalgia rheumatica ($n = 1$), and polyarteritis nodosum ($n = 1$). In the controls there was one case of diabetes.

In another letter to the editor (12) it was mentioned that the suspicion of partiality about the Committee on Toxicity becomes more plausible when one considers the issue of homocysteine. This intermediate metabolite may well turn out to be of greater importance as a risk factor for cardiovascular disease than cholesterol and blood pressure. Raised homocysteine concentrations appear to be accessible to treatment with pyridoxine (100 mg/day) together with vitamin B_{12} and folic acid (13). Furthermore, the statement that there is no good evidence for the efficacy of pyridoxine in any disease, apart from depression, was criticized, because this ignores important studies in autism, pregnancy outcome, asthma, and sickle-cell anemia (12).

In a systematic review on the efficacy of pyridoxine in the treatment of premenstrual syndrome, adverse effects were reported in 63 patients (6.7%) (see Table 1) (14). In another study of 940 women one had a neuropathy associated with pyridoxine toxicity (15).

Table 1 Adverse effects of pyridoxine in the treatment of premenstrual syndrome

Number taking		Dosage and duration	Adverse effects	Number with adverse effects	
Pyridoxine	Placebo			Pyridoxine	Placebo
204	230	10–200 mg/day	Tingling in the fingers	11	8
49	70	200 mg/day*, four cycles		5	1
46	59	100 mg/day*, four cycles		5	2
14	8	600 mg/day, three cycles		1	0
31	–	150–600 mg/day*	Gastrointestinal	5	–
630	–	4–200 mg/day	Indigestion (7), nausea (5), breast soreness (3)	15	–
336	–	Over 200 mg/day	Nausea (8), dizziness (5), mild tingling or numbness (6)	21	–

*In a multivitamin formulation

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Organs and Systems

Nervous system

Pyridoxine has both dopamine-enhancing and dopamine-blocking properties: on the one hand pyridoxine (like dopamine) depresses the release of prolactin from the pituitary gland; on the other hand, in oral doses of 10–20 mg it rapidly reverses the therapeutic effect of dopamine (16). This should be borne in mind if pyridoxine is prescribed for nursing mothers or for patients treated with levodopa for Parkinson's disease or syndrome, although the problem does not seem to arise when using the combination of levodopa with decarboxylase inhibitors.

Reviews of sensory neuropathies and pyridoxine toxicity have been published (17–19). Sensory neuropathy has been described in certain individuals taking high daily doses of pyridoxine on a long-term basis. Although it is generally reversible, a chronic painful neuropathy can occur. Besides individual patient susceptibility, the risk of neurotoxic effects of pyridoxine is related to both the daily dose and the duration of administration. Peripheral neuropathy did not develop in individuals taking 500 mg/day for up to 2 years, whereas it did develop almost universally in patients who took more than 1000 mg/day for variable periods (17). In an adult, a daily dose of 500 mg/day is about 7.1 mg/kg/day. Therefore a child with pyridoxine-dependency taking 5 mg/kg/day may not be at risk of neuropathy. Only one patient with pyridoxine-dependent seizures in whom a sensory neuropathy developed has been described (20). It is recommended that patients with this disorder who will require life-long pharmacological doses of pyridoxine should be assessed for signs of a sensory peripheral neuropathy.

Sensory neuropathy was reported as an adverse effect in eight patients with homocystinuria who took 600–1200 mg/day of pyridoxine for 4–22 years. Nerve conduction studies of the sural nerve in five affected patients showed abnormalities in four (21). Neuropathies have been observed in women taking doses as low as 50–500 mg/day for one to several months (22,23).

Neurotoxicity can be associated with pyridoxine megavitamin therapy (24), the main symptom being a peripheral sensory neuropathy (see Table 2) (25,26).

Table 2 Peripheral sensory neuropathy during pyridoxine megatherapy

Authors	Cases	Daily dose	Duration of treatment
Schaumburg et al. (1983)	7	2–6 g	2–40 months
Berger and Schaumburg (1974)	1	500 mg	1 year
Vasile et al. (1984)	1	3 g	6 months
De Zegher et al. (1985)	1	1 g	Not specified
Dalton (1985)	23	50–300 mg	Not specified
Parry and Bredesen (1985)	16	200–5000 mg	1–36 months
Podell (1985)	1	500 mg	8 years
Baer and Stillman (1984)	1	4 g	4 years (dermatosis)
Friedman et al. (1986)	1	2 g	1 year (dermatosis)

Hematologic

Reduced serum folate concentrations have been demonstrated in patients with homocystinuria taking pyridoxine. The mechanism of this effect may involve removal of substrate inhibition of the enzyme, *N*5-methyltetrahydrofolate homocysteine methyltransferase, due to pyridoxine-induced reduction of the substrate, homocysteine (27).

Skin

Pyridoxine-induced photosensitivity has been reported in a patient with hypophosphatasia (28).

- A 30-year-old woman, a heterozygote for hypophosphatasia, who had been taking two tablets of a multivitamin formulation (pyridoxine hydrochloride 100 mg, riboflavin butyrate 30 mg, nicotinamide 40 mg, biotin 0.05 mg, ascorbic acid 100 mg) once daily for 6 years, had severe skin eruptions and pruritus on exposure to the sun. The minimum erythema doses for UVB (20 mJ/cm^2) and UVA (4 J/cm^2) were lower than normal only for UVB (reference ranges 60–100 mJ/cm^2 for UVB and below 10 J/cm^2 for UVA). Patch and photopatch tests with the constituents of the tablets produced reactions to pyridoxine and pyridoxal phosphate only.

The authors suggested that photosensitivity in this patient may have been caused by abnormal metabolism of pyridoxine because of hypophosphatasia. Pyridoxine (given alone or in combination with vitamin B_{12}) can aggravate acne vulgaris or eruption of an acneiform exanthema (29). Excessive doses of pyridoxine appear to cause a metabolic defect that impairs the structural integrity of the skin, especially during the summer months (30). There are some case reports of photosensitive dermatitis caused by pyridoxine hydrochloride (31–33). Vesicular skin lesions on the hands and feet have also been reported, possibly as a symptom secondary to the neurological disturbances (34).

Contact hypersensitivity to pyridoxine is rare. Only three cases of allergy to pyridoxine have been reported: in hair lotion (35), a glucocorticoid cream (36), and a skin cream (Iruxol) (37). There have also been a few reports of photosensitivity due to pyridoxine hydrochloride (30,31,33).

Occupational systemic contact dermatitis with photosensitivity has been attributed to pyridoxine (38).

- A 45-year-old man developed eczema over the back of his hands, the back and sides of his fingers (sparing the little fingers), the forearms, and the face. This lasted for 6 years, with recurrences and remissions. He was tested with allergens, supplemented with a drop each of various injectable medicaments (streptomycin, benzylpenicillin, ampicillin–cloxacillin, oxytetracycline, vitamins B_1, B_2, and B_{12}, gentamicin, amikacin, and analgesics). Patch tests were positive to nitrofurazane and three different B vitamins. Reactivation of lesions on the hands, face, and neck was noted during patch-testing, and subsided within 1 week. After a further 6 weeks he was tested on the forearms with B_1, B_6, and B_{12}, each in 10% propylene glycol, resulting in a ++ reaction for B_6. Prick testing with B_1, B_2, and B_6 gave negative results. Another 2 months later oral provocation with two tablets each containing B_6 100 mg was performed. Before taking the

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second tablet he started to itch, and 18 hours later he developed itching and severe erythema over the face, neck, back of the hands, forearms, and the distal half of the upper arms (sun-exposed areas). Reactivation of previous positive patch test sites (on the back and forearms) and a negative prick test site were also observed.

Rosacea fulminans is a rare variant of rosacea conglobata and is seen almost exclusively in postadolescent women. It is characterized by the sudden appearance of abscess-forming nodules and draining sinuses. The lesions are usually limited to the center of the face and are precipitated by marked seborrhea. The cause is unknown. Rosacea fulminans temporally associated with the ingestion of high-dose vitamin B supplements has been reported (39).

- A 17-year-old woman with a 5-week history of a facial rash took minocycline (100 mg/day for 14 days) without effect. She had been taking vitamin B supplements (pyridoxine 80 mg, which is over 40 times the recommended daily allowance) and vitamin B_{12} (20 micrograms, which is 20 times the recommended daily allowance) for 2 weeks before the onset of the eruption. She had had low-grade acne vulgaris since puberty and a tendency to facial flushing after drinking alcohol and eating spicy food. There were numerous confluent nodules and pustules on a livid erythematous background on the cheeks and chin, and a few pustules on the neck. There was seborrhea on the affected skin areas. There was an indolent lymphadenopathy in the submandibular region. Histology showed a superficial and deep inflammatory infiltrate with perifollicular distribution, from the upper dermis down to the septa of the subcutaneous fat. Routine laboratory tests showed no abnormalities. There were no pathogenic organisms in bacteriological or mycological cultures from the pustules on the face. She stopped taking the nutritional supplement and was given warm compresses and clobetasol propionate cream twice daily for 2 weeks, methylprednisolone 60 mg/day for 2 weeks, followed by isotretinoin 60 mg/day. Her skin changes resolved within 4 months, with no residual scarring.

Second-Generation Effects

Teratogenicity

- A malformed infant was born to a mother who had taken daily doses of pyridoxine during pregnancy (50 mg for the first 7 months) and unknown doses of lecithin and vitamin B_{12}. The girl was born with near-total amelia of her left leg at the knee (40).

Although this case may have been coincidental, as a precaution, megadoses of pyridoxine should be avoided during pregnancy.

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Pyrimethamine

General Information

Pyrimethamine

Pyrimethamine is the most active antimalarial of the 2–4-diaminopyrimidines, its effect being due to inhibition of the conversion of folic acid to its active form, folinic acid. It is also effective in toxoplasmosis. Its antiprotozoal and antimalarial activity is enhanced by the addition of sulfonamides.

Pyrimethamine is well absorbed in healthy subjects; the half-life is 80–95 hours (SEDA-13, 811). Absorption after intramuscular injection is slower; this may be of importance in patients with reduced muscle blood flow (SEDA-17, 328). Pyrimethamine penetrates the cerebrospinal fluid.

With the usual antimalarial prophylactic dosage of 25 mg/week, adverse reactions are generally slight or absent. With intensive treatment in high cumulative doses, as used in the treatment of toxoplasmosis, gastrointestinal intolerance, neurological symptoms, and depression of hemopoiesis can occur. Allergic reactions have not been reported. Tumor-inducing effects have also not been reported.

Pyrimethamine + azithromycin

Azithromycin is efficacious in animal models of toxoplasmic encephalitis. In a Phase I/II dose-escalation study of pyrimethamine (50 mg/day) plus azithromycin (900, 1200, or 1500 mg/day) for induction and maintenance treatment in 30 patients with AIDS and definite or suspected *Toxoplasma* encephalitis, the overall response rate was 67% after 6 weeks of induction therapy (1). However, maintenance therapy for 24 weeks with this combination was associated with a high relapse rate (47%); only six patients successfully completed induction and maintenance therapy. Adverse events were common (particularly in those taking azithromycin 1500 mg) and included hepatotoxicity, bone marrow suppression, ototoxicity, and gastrointestinal disturbances, which led 20% of patients to withdraw. All adverse events resolved on withdrawal.

In a prospective, randomized, open, multicenter trial of pyrimethamine + azithromycin versus pyrimethamine + sulfadiazine for the treatment of ocular toxoplasmosis in 46 patients with sight-threatening ocular toxoplasmosis, the two regimens had similar efficacy; however, the adverse effects were significantly less common and severe with pyrimethamine + azithromycin (2).

Pyrimethamine + clarithromycin

Clarithromycin, a macrolide, and other macrolide and lincosamine antibiotics (azithromycin, clindamycin, spiramycin, and roxithromycin) have been used in combination with pyrimethamine in the treatment of *Toxoplasma gondii* infections, especially cases of *Toxoplasma* encephalitis.

Clarithromycin 2 g plus pyrimethamine 75 mg/day has been given for 6 weeks to a few AIDS patients with encephalitis (SEDA-13, 814). The adverse effects were many and severe: severe thrombocytopenia, anemia, neutropenia, liver toxicity of varying degree, nausea, vomiting, skin rashes, and hearing loss were found in two of three patients tested in a group of 13. The dose of clarithromycin in this study was the maximum dosage used in an earlier investigation of the treatment of mycobacterial infections in HIV-infected patients.

Pyrimethamine + clindamycin

Pyrimethamine 50 mg/day has been used in combination with clindamycin for the treatment of *Toxoplasma* encephalitis in AIDS. Adverse effects were common (rash, diarrhea, nausea), but the incidence of hematological reactions was lower than with the combination of sulfadiazine and pyrimethamine (SEDA-16, 309).

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Pyrimethamine + dapsone

Pyrimethamine and dapsone are available in two fixed combinations:

1. 12.5 mg of pyrimethamine + 100 mg of dapsone = Maloprim.
2. 25 mg of pyrimethamine + 100 mg of dapsone = Deltaprim.

A "dapsone syndrome" was reported in a 30-year-old woman after 4 weeks of treatment with Maloprim and chloroquine base 300 mg/weekly. The symptoms comprised fever, joint and muscle pains, dry cough, and a diffuse red urticarial rash, followed by generalized lymphadenopathy, a painful exudative tonsillitis, and a prominent atypical lymphocytosis.

In Britain, the retrospective reported rate for serious reactions with Maloprim was one in 9100, the incidence of blood dyscrasias being one in 20 000. These figures are lower than those reported with Fansidar (pyrimethamine + sulfadoxine) (SEDA-16, 309).

Pyrimethamine + sulfadoxine

Pyrimethamine 25 mg plus sulfadoxine 500 mg is available in the combination formulation known as Fansidar. This combination, while effective in the prevention and treatment of *Plasmodium falciparum* malaria, carries a high frequency of adverse effects; hematological and serious skin reactions occur, but there are also reports of polyneuritis, vasculitis, and hepatotoxicity. Most of the severe skin reactions and the cases of vasculitis developed within under a month (SEDA-13, 812). The use of Fansidar for malaria prophylaxis has therefore been virtually abandoned (SEDA-21, 297). However, Fansidar is being increasingly used for the treatment of *P. falciparum* malaria in Africa. With the higher dosage used for that purpose, an increase in adverse effects, particularly hematological, can be expected. In Britain the retrospective reported rate for all serious reactions to Fansidar was one in 2100 prescriptions and for skin reactions one in 4900 prescriptions, the death rate being one in 11 100 (SEDA-16, 309).

Observational studies

In a single-arm, open, prospective study between 1990 and 1995 (before HAART) the prophylactic efficacy of Fansidar was evaluated in 95 HIV-infected patients with successfully treated *Pneumocystis jiroveci* pneumonia and no history of *Toxoplasma* encephalitis (3). Patients took Fansidar with folinic acid (15 mg) twice weekly and were followed for a median of 19 (range 1–72) months. Five patients had a *Pneumocystis* relapse, but three had not taken their therapy. Of the 69 patients positive for anti-*Toxoplasma* IgG antibodies, only one developed toxoplasma encephalitis after 50 months. A rash developed in 16 patients after a median of 3 weeks, and required withdrawal in six. Two developed Stevens–Johnson syndrome after three or four doses. There was no significantly increased risk of adverse reactions to Fansidar in patients with previous hypersensitivity reactions to co-trimoxazole. The results of this study are of particular relevance to areas in which HAART is unavailable and where the antimalarial activity of Fansidar may confer additional benefit.

Placebo-controlled studies

In a placebo-controlled study of chemoprophylaxis for malaria, 701 Tanzanian infants were assigned to intermittent pyrimethamine + sulfadoxine (under 5 kg, a quarter of a tablet; 5–10 kg, half a tablet; over 10 kg, one tablet; each tablet contained pyrimethamine 25 mg plus sulfadoxine 500 mg) alongside routine childhood immunizations and iron supplementation at 2, 3, and 9 months of age (4). The combination was well tolerated, with no reported adverse events. Episodes of clinical malaria fell by 59% (95% CI = 41, 72) and the incidence of severe anemia by 50% (95% CI = 8, 73%) in the first year of life. Contrary to previous studies involving continuous prophylaxis in infants, there was no increase in the frequency of rebound episodes of malaria up to 18 months of age, suggesting that the development of malaria-specific immunity was unimpaired. Responses to vaccines were unaffected.

Pyrimethamine + sulfadoxine + mefloquine

Pyrimethamine (25 mg), sulfadoxine (500 mg), and mefloquine (250 mg) are available in the combination formulation known as Fansimef. The adverse effects characteristic of all three components can be expected.

Pyrimethamine + trimethoprim

With the combination of pyrimethamine plus trimethoprim the risk of megaloblastic anemia is higher than with pyrimethamine alone, which on theoretical grounds might be expected. Concomitant administration of folic acid has been recommended (SEDA-11, 590), but the effect of folic acid on efficacy is not known.

Organs and Systems

Respiratory

Pyrimethamine

Non-cardiogenic pulmonary edema has been reported with pyrimethamine alone (SEDA-13, 811).

Pyrimethamine + sulfadoxine

Dyspnea and pleurisy have been described. Of 52 travellers with adverse reactions to Fansidar in Sweden, six had pulmonary infiltrates accompanied by fever (SEDA-13, 241). Such infiltrates have also been described in the past, and in one case a diagnosis of eosinophilic infiltration was made (SEDA-11, 590). A case of non-cardiogenic pulmonary edema was reported in 1989 (SEDA-13, 813).

Nervous system

High doses of pyrimethamine can cause rapid development of neurological symptoms such as ataxia, tremor, and convulsions, probably by a direct toxic effect (SEDA-11, 588).

Hematologic

Pyrimethamine

Leukopenia, agranulocytosis, and thrombocytopenia have been reported and, as might be expected in view of folate antagonism, megaloblastic anemia. The latter is more

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common when high doses are used or when pyrimethamine is given in combination with a drug such as trimethoprim. The bone marrow depression can be reversed using folic acid (SEDA-18, 287).

Pancytopenia has been reported after the use of pyrimethamine alone, but is more often the result of its use in combination with dapsone or sulfonamides (SEDA-11, 589) (SEDA-14, 241) (SEDA-17, 328).

Although the hematological complications of pyrimethamine are generally a consequence of therapeutic use, long-term prophylactic treatment with pyrimethamine and dapsone in malaria could well involve an increased risk of megaloblastic anemia in patients whose nutritional state is not optimal (SEDA-13, 812).

Pyrimethamine + dapsone

The combination of pyrimethamine plus dapsone causes a higher incidence of blood dyscrasias than pyrimethamine alone; in particular, the occurrence of agranulocytosis increases and even deaths have been reported (SEDA-13, 812) (SEDA-18, 287).

Dapsone (alone or in combination with pyrimethamine) can cause methemoglobinemia and hemolytic anemia. These complications tend to be dose-related and are more often encountered in G6PD-deficient subjects (SEDA-18, 287).

When the pyrimethamine + dapsone combination was used in the prophylaxis of *Pneumocystis jiroveci* pneumonia in 173 patients with AIDS, there was anemia in about 20, and in all 117 cases for which data were available, serum haptoglobin concentrations had fallen (SEDA-18, 287).

Pyrimethamine + sulfadoxine

The hematological adverse effects of the combination of pyrimethamine plus sulfadoxine are largely those known from pyrimethamine, that is leukopenia, agranulocytosis, thrombocytopenia, and pancytopenia, but the literature gives the impression that when using this combination these effects are more marked, with lower cell counts (5).

Intermittent iron supplementation with pyrimethamine + sulfadoxine has been investigated in 328 anemic but symptom-free Kenyan children, who were randomly given either iron (ferrous fumarate suspension 6.25 g/l twice a week) or placebo and pyrimethamine + sulfadoxine (25 mg and 1.25 mg/kg once every 4 weeks) or placebo (82 in each group) (6). After 12 weeks, those who took iron and pyrimethamine + sulfadoxine, iron alone, or pyrimethamine + sulfadoxine alone had higher hemoglobin concentrations than those who took the double placebo. No adverse effects were reported.

Severe megaloblastic anemia has also been described (7).

- Hemolytic–uremic syndrome was reported in a 24-year-old man with glucose-6-phosphate dehydrogenase (G6PD) deficiency (SEDA-18, 288).

Gastrointestinal

Gastric disturbances due to pyrimethamine are dose-related; the high doses used in the treatment of toxoplasmosis caused abdominal pains, vomiting, and dizziness (8). Gastrointestinal bleeding related to thrombocytopenia has also been reported (SEDA-11, 589).

Liver

Pyrimethamine + sulfadoxine

Liver function abnormalities with Fansidar (pyrimethamine + sulfadoxine) vary from raised serum transaminase activities to more marked disturbances, with jaundice and granulomatous hepatitis. An occasional case of fatal hepatic failure has been reported; this was the case in a young white American woman who had taken three doses of Fansidar with chloroquine (SEDA-12, 242). Hepatic symptoms may be part of a vasculitis syndrome or can be seen in association with skin reactions (SEDA-13, 241).

Skin

Pyrimethamine

Photosensitivity has been attributed to pyrimethamine (9).

Hyperpigmentation is a very rare adverse effect of pyrimethamine.

- A 29-year-old woman (HIV-negative) developed hyperpigmentation after taking pyrimethamine 25 mg bd for 40 days (10). The hyperpigmentation regressed 15 days after withdrawal of pyrimethamine.

Pyrimethamine + dapsone

Skin rashes are uncommon with the combination of pyrimethamine + dapsone. A lichen planus type of skin reaction has been described (11).

Pyrimethamine + sulfadoxine

Severe skin reactions have been reported with the combination of pyrimethamine + sulfadoxine (Fansidar) from various countries. These include erythema exudativum multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, cutaneous vasculitis, lichen planus, a single case of ectodermosis pluriorificialis, and some cases of photosensitivity.

The incidence of skin reactions seems to vary regionally: there is a low incidence in Switzerland (12), but a high incidence has been reported by the US Centers for Disease Control. The latter reported skin reactions in 1:5000 to 1:8000 cases, with fatal reactions in 1:10 000 to 1:25 000 users (SEDA-12, 242). In Britain the retrospective reporting rate for all serious reactions was 1:2100 and for cutaneous reactions one in 4900 prescriptions, with a fatality rate of one in 11100 (SEDA-16, 309).

In a spontaneous reporting system of individuals who had been exposed to Fansidar in 27 countries, an estimated 117 million users, there were 126 reports: 87 cases of erythema multiforme or Stevens–Johnson syndrome and 39 cases of toxic epidermal necrolysis; 86% of the cases were reported in Europe or North America (13). The fatality rates were 36% for toxic epidermal necrolysis (95% CI = 21, 53) and 9% for erythema multiforme/Stevens–Johnson syndrome (4, 18). The overall SCAR risk was 1.1 (0.9, 1.3) per million. For developing countries with mainly single-dose use, the risk was estimated at 0.1 (0.0, 0.1) per million. For Europe and North America, with mainly prophylactic use, the risks were 10 (8, 12) and 36 (23, 48) per million respectively.

The prevalence of oral lichenoid reactions was 4.8% in 186 Malay army personnel who used Fansidar for 9 weeks, 0.5% in 186 army personnel who had stopped using Fansidar

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for 2 months, and 0% in 143 army personnel (control group) who had not used Fansidar for at least 4 months (14).

- Exudative erythema multiforme with chronic proliferation of the conjunctiva causing blindness was described in a 24-year-old man who had taken one tablet of Fansidar at 6-day intervals on three occasions (SEDA-16, 309).

Immunologic

Pyrimethamine + dapsone

Maloprim given for antimalarial prophylaxis was associated with immunosuppression: in military personnel in Singapore (15). The incidence of upper respiratory tract infections was 64% higher than in the non-treated group.

Three patients developed a hypersensitivity syndrome after taking pyrimethamine 12.5 mg + dapsone 100 mg weekly as malaria prophylaxis (16). The diagnosis was based on the presence of fever, lymphadenopathy, a maculopapular rash, and hepatitis. A mild Coombs'-positive hemolytic anemia was also observed in one of the patients. All the clinical, hematological, and biochemical abnormalities normalized within 3 months of tapering regimens of moderate-dose prednisolone.

Pyrimethamine + sulfadoxine

Generalized vasculitis was reported in two cases in Sweden; one developed fever, jaundice, orchitis, and gastrointestinal bleeding after 2 weeks, the other cutaneous vasculitis and rapid progressive nephritis after 3 weeks (SEDA-13, 241).

An illness resembling Sézary syndrome was seen after combined treatment with chloroquine 150 mg every third day (total seven tablets) plus Fansidar one tablet weekly (total six tablets); the symptoms comprised fever, diarrhea, erythroderma, jaundice, lymphadenopathy, and hepatosplenomegaly (SEDA-12, 696).

The safety and efficacy of a fixed combination of pyrimethamine 25 mg + sulfadoxine 500 mg, supplemented with folinic acid 15 mg, both twice a week, as primary prophylaxis of *Pneumocystis* pneumonia and *Toxoplasma* encephalitis has been evaluated in 106 patients infected with HIV in a single-arm, open, prospective study (17). There were allergic reactions in 18 patients and permanent withdrawal was required in seven. One patient who took continued prophylaxis despite progressive hypersensitivity reactions developed a serious adverse reaction (Stevens–Johnson syndrome).

Long-Term Effects

Drug tolerance

Resistance to pyrimethamine has been reported from the Amazon region and Southeast Asia (SEDA-21, 297).

Second-Generation Effects

Pregnancy

Pyrimethamine + dapsone

A stillborn male child with a severe defect of the abdominal and thoracic wall and a missing left arm was delivered at 26 weeks to a woman who had used Maloprim on days 10, 20, and 30 after conception (SEDA-11, 589). The case was anecdotal and the relation to medication uncertain.

Teratogenicity

Pyrimethamine

Pyrimethamine is an inhibitor of dihydrofolate reductase and causes tetrahydrofolate deficiency. It is teratogenic in animals: in rats it produces limb defects, cleft palate, and brachygnathia, and in chick embryos micromelia. Fetal death has been seen in rats and hamsters. However, in toxoplasmosis, pyrimethamine, with or without a sulfonamide, has been given to pregnant women without evidence of subsequent abnormalities. Supplementation with folic acid has been advocated to prevent or reduce adverse effects (SEDA-13, 812), but it is not known if this could impair efficacy.

Pyrimethamine + sulfadoxine

Malaria during pregnancy is associated with an increased risk of severe anemia and babies of low birth weight. Effective intermittent therapy with pyrimethamine + sulfadoxine reduces parasitemia and severe anemia and improves birth weight in areas in which *P. falciparum* is sensitive to this combination. In an open, prospective trial in 287 pregnant women in the Gambia who were exposed to a single dose of a combination of artesunate and pyrimethamine + sulfadoxine there was no evidence of a teratogenic or otherwise harmful effect (18).

Susceptibility Factors

Pyrimethamine

Pyrimethamine should not be given to patients with depleted folic acid reserves (19).

Pyrimethamine + sulfadoxine

Sulfonamide and/or pyrimethamine sensitivity, pregnancy, and G6PD deficiency are contraindications. Use in young infants is considered inadvisable; the history of an 8-month-old infant with *P. falciparum* malaria who developed high fever, tachycardia, hypotension, chills, jaundice, and splenomegaly 48 hours after a single parenteral dose of Fansidar (pyrimethamine + sulfadoxine) (SEDA-16, 309) seems to confirm the wisdom of this advice. It has been advocated that Fansidar should not be used prophylactically if exposure to malaria will last less then 3 weeks, in view of the incidence of severe skin reactions during the first month.

Drug–Drug Interactions

Chloroquine

Pyrimethamine + sulfadoxine

The combined use of Fansidar (sulfadoxine + pyrimethamine) with chloroquine has been reported to result in more severe adverse reactions (20). However, an increased risk has not been reported in recent studies (21).

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Liver metabolized drugs

Pyrimethamine + sulfadoxine
Both pyrimethamine and sulfonamides are liver enzyme inhibitors, and can cause interactions with drugs that are normally metabolized in the liver.

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Pyritinol

General Information

Pyritinol is a sulfhydryl-containing compound, a dimer of 5-thiopyridoxine. It was used from 1961 onwards as a psychostimulant of doubtful efficacy, but apparently without adverse effects, and then largely abandoned. When it was re-introduced in some countries for rheumatoid arthritis, adverse effects were registered in 25% of patients.

Cross-allergy with D-penicillamine has been hypothesized to explain the apparently higher frequency of adverse effects of pyritinol in patients with rheumatoid arthritis (1).

In usual doses, 600–800 mg/day, pyritinol has a profile of adverse reactions reminiscent of that of penicillamine (2,3). Some 40% of users have adverse reactions, leading to withdrawal in about 23% of the total. The most common are non-specific rashes and stomatitis; in addition, pemphigus, lichen planus, and photosensitivity have occurred. Gastrointestinal symptoms (diarrhea, gastralgia, nausea, loss of taste) can occur, but are less frequent than with penicillamine. Thrombocytopenia, reversible extramembranous glomerulonephritis with nephrotic syndrome (4), a myasthenia-like picture, and acute polymyositis with positive rechallenge have also been described (5).

In a collaborative study of the French Pharmacovigilance Centers there were 23 reports of suspected reactions to pyritinol, including four cases of pemphigus, three of agranulocytosis (but other drugs taken were oxyphenbutazone or clomipramine), two of nephrosis, and two of a lupus-like syndrome (6).

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Comparative studies

In a multicenter, double-blind study, patients with rheumatoid arthritis took pyritinol 600 mg/day or auranofin 6 mg/day for 1 year (7). Of 139 patients randomized to pyritinol, 61 (44%) dropped out because of adverse events or response failure compared with 44 (31%) of the 142 patients randomized to auranofin. Among the rest, adverse events occurred in 64% of patients taking pyritinol and in 58% of patients taking auranofin: the main events were mucocutaneous symptoms (pyritinol 36%, auranofin 23%) and gastrointestinal complaints (pyritinol 30%, auranofin 37%). There were single cases of proteinuria, hepatic abnormalities, and hematological abnormalities in both groups.

Organs and Systems

Metabolism

Autoimmune hypoglycemia with detectable anti-insulin antibodies, probably caused by pyritinol, has been described in one patient (8). This syndrome has previously been reported in connection with other thiol compounds, (penicillamine, methimazole, and tiopronin).

Liver

Pyritinol-induced acute hepatitis has been described (9).

Pancreas

Pancreatitis has been attributed to pyritinol.

- A 23-year-old student had three episodes of acute pancreatitis after the occasional ingestion of pyritinol for better performance in examinations. Immunological investigations pointed to a probable T cell-mediated hypersensitivity reaction (10).

Immunologic

A high titer of antinuclear antibodies and anti-double-stranded native DNA antibodies occurred during treatment with pyritinol 400 mg/day in a woman with rheumatoid arthritis (11). A clear temporal relation and a reduction in antinuclear antibody titers and disappearance of anti-DNA antibodies after drug withdrawal strongly suggested a causal relation.

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Pyrrolizidine alkaloids

General Information

Pyrrolizidine alkaloids occur in a large number of plants, notably the genera *Crotalaria* (Fabaceae), *Cynoglossum* (Boraginaceae), *Eupatorium* (Asteraceae), *Heliotropium* (Boraginaceae), *Petasites* (Asteraceae), *Senecio* (Asteraceae), and *Symphytum* (Boraginaceae) (Table 1). Certain representatives of this class and the plants in which they occur are hepatotoxic as well as mutagenic and hepatocarcinogenic. They can produce veno-occlusive disease of the liver with clinical features like abdominal pain with ascites, hepatomegaly and splenomegaly, anorexia with nausea, vomiting, and diarrhea. Sometimes there is also damage to the pulmonary region.

The German Federal Health Office has restricted the availability of botanical medicines containing unsaturated pyrrolizidine alkaloids (1,2). Herbal medicines that provide over 1 mg/day internally or over 100 mg/day externally are not permitted; herbal medicines that provide 0.1–1 mg/day internally or 10–100 mg/day externally may be applied for only a maximum of 6 weeks per year, and they should not be used during pregnancy or lactation.

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Table 1 Pyrrolizidine alkaloids in various genera

Genus	Pyrrolizidine alkaloids
Crotalaria albida	Croalbidine
Crotalaria anagyroides	Anacrotine, methylpyrrolizidine
Crotalaria aridicola	Various dehydropyrrolizidines
Crotalaria axillaris	Axillaridine, axillarine
Crotalaria barbata	Crobarbatine
Crotalaria burha	Croburhine, crotalarine
Crotalaria candicans	Crocandine, cropodine
Crotalaria crassipes	Retusamine
Crotalaria crispata	Crispatine, fulvine
Crotalaria dura	Crotaline
Crotalaria fulva	Fulvine
Crotalaria globifer	Crotaline, globiferine
Crotalaria goreensis	Hydroxymethylenepyrrolizidine
Crotalaria grahamiana	Grahamine
Crotalaria grantiana	Grantianine
Crotalaria incana	Anacrotine
Crotalaria intermedia	Integerrimine, usaramine
Crotalaria laburnifolia	Crotalaburnine, hydroxysenkirkine
Crotalaria madurensis	Crotafoline, madurensine
Crotalaria mitchelii	Retusamine
Crotalaria mucronata	Mucronitine, mucronitinine
Crotalaria nana	Crotaburnine, crotananine
Crotalaria novae-hollandiae	Retusamine
Crotalaria retusa	Retusamine
Crotalaria semperflorus	Crosemperine
Crotalaria spectabilis	Retronecanol
Crotalaria stricta	Crotastrictine
Crotalaria trifoliastrum	Various alkylpyrrolizidines
Crotalaria usaramoensis	Usaramine, usaramoensine
Crotalaria virgulata	Grantaline, grantianine
Crotalaria walkeri	Acetylcrotaverrine, crotaverrine
Cynoglossum amabile	Amabiline, echinatine
Cynoglossum glochidiatum	Amabiline
Cynoglossum lanceolatum	Cynaustine, cynaustraline
Cynoglossum latifolium	Latifoline
Cynoglossum officinale	Heliosupine
Cynoglossum pictum	Echinatine, heliosupine
Cynoglossum viridiflorum	Heliosupine, viridiflorine
Eupatorium cannabinum	Echinatine, supinine
Eupatorium maculatum	Echinatine, trachelantimidine
Heliotropium acutiflorum	Heliotrine
Heliotropium arguzoides	Trichodesmine
Heliotropium curassavicum	Angelylheliotridine
Heliotropium dasycarpum	Heliotrine
Heliotropium eichwaldii	Angelylheliotrine
Heliotropium europeum	Acetyl-lasiocarpine, helioitrine
Heliotropium indicum	Acetylindicine, indicine, indicinine
Heliotropium lasiocarpum	Heliotrine, lasiocarpine
Heliotropium olgae	Heliotrine, incanine, lasiocarpine
Heliotropium ovalifolium	Heliofoline
Heliotropium ramosissimum	Heliotrine
Heliotropium strigosum	Strigosine
Heliotropium supinum	Heliosupine, supinine
Heliotropium transoxanum	Heliotrine
Petasites japonicus	Fukinotoxin, petasinine, petasinoside
Senecio adnatus	Platyphylline
Senecio alpinus	Seneciphylline
Senecio amphibolus	Macrophylline
Senecio angulatus	Angulatine
Senecio aquaticus	Aquaticine
Senecio argentino	Retrorsine, senecionine
Senecio aureus	Floridanine, florosenine, otosenine
Senecio auricula	Neosenkirkine
Senecio borysthenicus	Seneciphylline
Senecio brasiliensis	Brasilinecine
Senecio campestris	Campestrine
Senecio cannabifolius	Senecicannabine
Senecio carthamoides	Carthamoidine
Senecio cineraria	Jacobine, seneciphylline
Senecio cissampelinum	Senampelines
Senecio crucifolia	Jacobine
Senecio doronicum	Doronine
Senecio erraticus	Erucifoline, floridanine
Senecio filaginoides	Retrorsine, ionine
Senecio franchetti	Franchetine, sarracine
Senecio fuchsii	Fuchsisenecionine
Senecio gillesiano	Retrorsine, senecionine
Senecio glabellum	Integerrimine, senecionine
Senecio glandulosus	Retrorsine, senecionine
Senecio glastifolius	Graminifoline
Senecio hygrophylus	Hygrophylline, platyphylline
Senecio ilicifolius	Pterophine, senecionine
Senecio illinitus	Acetylsenkirkine, senecionine
Senecio incanus	Seneciphylline
Senecio integerrimus	Integerrimine, senecionine
Senecio isatideus	Isatidine, retrorsine
Senecio jacobaea	Jacobine, jacoline, jaconine, jacozine, otosenine, renardine
Senecio kirkii	Acetylsenkirkine, senkirkine
Senecio kubensis	Seneciphylline
Senecio latifolius	Senecifolidine, senecifoline
Senecio leucostachys	Retrorsine, senecionine
Senecio longibolus	Integerrimine, longiboline, retronecanol, retrorsine, riddelline, senecionine, seneciphylline
Senecio macrophyllus	Macrophylline
Senecio mikanoides	Mikanoidine
Senecio nemorensis	Nemorensine, oxynemorensine
Senecio othonnae	Floridnine, onetine, otosenine
Senecio othonniformis	Bisline, isoline
Senecio palmatus	Seneciphylline
Senecio paucicalyculatus	Paucicaline
Senecio petasis	Bisline
Senecio phillipicus	Retrorsine, seneciphylline
Senecio platyphylloides	Neoplatyphylline, platyphylline, sarracine, seneciphylline
Senecio platyphyllus	Platyphylline, seneciphylline
Senecio pojarkovae	Sarracine, seneciphylline
Senecio procerus	Procerine
Senecio propinquus	Seneciphylline
Senecio pseudoarnica	Senecionine
Senecio pterophorus	Pterophine
Senecio ragonesi	Retrorsine, senecionine, uspallatine
Senecio renardi	Renardine, seneciphylline
Senecio retrorsus	Senkirkine
Senecio rhombifolius	Isatidine, retrorsine, neoplatyphylline, platyphylline sarracine, seneciphylline
Senecio Riddellii	Riddelline
Senecio rivularis	Angeloyloxyheliotrine
Senecio rosmarinifolius	Rosmarinine

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Genus	Pyrrolizidine alkaloids
Senecio ruwenzoriensis	Ruwenine, ruzorine
Senecio sarracenicus	Sarracine
Senecio scleratus	Isatidine, scleratine
Senecio seratophiloides	Senecivernine
Senecio spartioides	Seneciphylline, spartoidine
Senecio squalidus	Senecionine, squalidine
Senecio stenocephalus	Seneciphylline
Senecio subalpinus	Seneciphylline
Senecio subulatus	Retrorsine, senecionine
Senecio swaziensis	Swazine
Senecio triangularis	Triangularine
Senecio uspallatensis	Senecionine, uspallatine
Senecio vernalis	Senecivernine
Senecio vira-vira	Anacrotine, neoplatyphylline
Senecio viscosus	Senecionine
Senecio vulgaris	Senecionine
Symphytum asperum	Asperumine, echinatine
Symphytum caucasicum	Heliosupine, echinatine
Symphytum officinalis	Lasiocarpine, symphytine, viridiflorine
Symphytum orientale	Echinatine, heliosupine
Symphytum tuberosum	Lasiocarpine, symphytine
Symphytum uplandicum	Viridflorine, anadoline, heneicisane, tricosane, acetylintermedine, acetyllycopsamine, uplandicine

Organs and Systems

Liver

In a South African study 20 children were identified as suffering from hepatic veno-occlusive disease thought to be caused by the administration of traditional remedies (3). The predominant clinical presentation was ascites and hepatomegaly. Nine children died. The surviving patients progressed to cirrhosis and portal hypertension. In four cases early urine specimens were available, and in all of these the presence of pyrrolizidine alkaloids was confirmed.

Second-Generation Effects

Fetotoxicity

It is prudent to avoid exposing unborn or suckling children to herbal remedies containing pyrrolizidine alkaloids. Animal studies have shown that transplacental passage and transfer to breast milk are possible, and there is a human case on record of fatal neonatal liver injury, in which the mother had used a herbal cough tea containing pyrrolizidine alkaloids throughout her pregnancy.

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Pyrvinium embonate

General Information

Pyrvinium is a deep-red insoluble dye used as an antihelminthic drug. It is well tolerated in doses up to 5 mg/kg. Nausea, vomiting, diarrhea, and cramping abdominal pain are more frequent at higher doses. Feces and vomit are stained red. Isolated cases of severe allergy (1), transient photosensitivity, and Stevens–Johnson syndrome (2) have been reported.

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Quazepam

See also Benzodiazepines

General Information

Quazepam is a long-acting benzodiazepine with effects similar to those of diazepam.

Food–Drug Interactions

The disposition of quazepam 20 mg, in the fasting state and 30 minutes after the consumption of meals containing different amounts of dietary fat, has been studied in a three-arm, randomized, crossover study in nine healthy men (1). Plasma concentrations of quazepam and its metabolite, 2-oxoquazepam, were measured for up to 48 hours after dosing. The peak concentrations of quazepam 30 minutes after low-fat and high-fat meals were 243% and 272%, respectively, of those in the fasted state. The AUCs of quazepam from 0 to 8 hours and from 0 to 48 hours were increased by both the low-fat and high-fat meals by 1.4–2 times. Quazepam was well tolerated, with no significant difference in the Stanford Sleepiness Scale between fasted and fed conditions. Thus, food significantly increased the absorption of quazepam but did not prolong the half-life. Quazepam is lipophilic; it would therefore be more highly dissolved in a fatty meal and more available for absorption.

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Quetiapine

See also Neuroleptic drugs

General Information

The pharmacology, efficacy, and safety of quetiapine, an atypical neuroleptic drug, have been extensively reviewed (1). Quetiapine interacts with a broad range of neurotransmitter receptors and has a higher affinity for serotonin ($5\text{-}HT_{2A}$) receptors than dopamine (D_2) receptors in the brain. In a meta-analysis, quetiapine was as effective as haloperidol with fewer extrapyramidal adverse effects (2).

Data from short-term clinical trials (6 weeks) suggest that quetiapine may be useful for the management of psychotic disorders in patients who do not tolerate the adverse effects of the typical antipsychotic drugs or clozapine (3). The most common adverse effects of quetiapine were dizziness, hypotension, somnolence, and weight gain. Raised hepatic enzymes have also been reported. In addition, two patients with idiopathic Parkinson's disease and psychosis were treated with quetiapine for 52 weeks (4). Psychotic symptoms were successfully controlled without worsening of motor disability.

Organs and Systems

Nervous system

Although quetiapine seems to cause a lower incidence of extrapyramidal symptoms, a case of neuroleptic malignant syndrome has been described (5).

- A 40-year-old man with chronic schizophrenia and borderline intelligence presented with acute psychotic decompensation. He had previously taken several different neuroleptic drugs and had had significant extrapyramidal symptoms but never neuroleptic malignant syndrome. He was given quetiapine 25 mg bd, increasing to 250 mg bd by day 13. He then had increasing symptoms of restlessness, agitation, and episodic sweating. Loxapine 25 mg and lorazepam 2 mg were added. On day 14 he developed confusion, lead-pipe muscle rigidity, a temperature of 38.2°C, a labile blood pressure, tachypnea, and tachycardia; creatine kinase activity was 18 354 IU/l and he had myoglobinuria. Quetiapine was withdrawn and supportive treatment was instituted. He recovered 5 days after withdrawal.

Endocrine

The effects of haloperidol and quetiapine on serum prolactin concentrations have been compared in 35 patients with schizophrenia during a drug-free period of at least 2 weeks in a randomized study (6). There was no significant difference in prolactin concentration between the groups at the start of the study, and control prolactin concentrations were significantly lower with quetiapine than haloperidol. No patients taking quetiapine had galactorrhea.

Dose-dependent decreases in total T3 and T4 and free T4, without an increase in TSH, have been reported (7,8). Such changes have not been observed with other neuroleptic drugs.

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Quinagolide

General Information

Quinagolide is a non-ergot benzoquinoline dopamine D_2 receptor agonist. Reported adverse effects include gastrointestinal upsets, anorexia, weight loss, and episodes of fainting (1).

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Quinapril

See also Angiotensin converting enzyme inhibitors

General Information

The pharmacology, therapeutic uses, and safety of the ACE inhibitor quinapril have been reviewed (1).

Organs and Systems

Psychological, psychiatric

Depression has been attributed to quinapril (2).

- A 90-year-old man with a history of peripheral arterial disease and mild heart failure presented with reduced appetite, insomnia, anhedonia, reduced energy, and suicidal ideation. His symptoms had started a month before, when he had begun to take quinapril 10 mg/day. He was also taking furosemide 20 mg/day and digoxin. He was alert, coherent, and cognitively intact, but depressed with a flat affect. He had no psychotic symptoms. Quinapril was withdrawn. He improved within 48 hours and recovered fully in 5 days.

The authors cited several reports of depression, mania, and psychosis with various ACE inhibitors.
Acute psychosis has been attributed to quinapril (3).

- A 93-year-old woman with heart failure was given quinapril 2.5 mg bd. Two hours after the first dose she became confused, disoriented, and anxious. During the night, she made many frantic telephone calls to her daughter and other family members complaining that she was being assaulted. Her anxiety, disorientation, and visual hallucinations continued for 5 days. She had had an episode of hallucinations 2 years before, while taking a beta-blocker. Quinapril was withdrawn. She recovered over the next day.

The authors commented on three previous cases of visual hallucination with other ACE inhibitors.

Pancreas

A possible association between quinapril and pancreatitis has been reported in an 85-year-old woman, very similar to other previously reported cases with other ACE inhibitors (4).

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Quinethazone

See also Diuretics

General Information

Quinethazone is chemically related to the thiazides; early work suggested that it was in all essential respects identical (SED-8, 488), and there is no newer evidence that it has any special characteristics.

Quinfamide

General Information

Quinfamide acts on the trophozoites of *Entamoeba histolytica*, making the trophozoite incapable of propagation. It is not active against amebic cysts. In doses of 100–1200 mg adverse effects have been frequent but

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mild, mainly comprising headaches and nausea (SEDA-12, 705) (1).

Reference

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Quinidine

See also Antidysrhythmic drugs

General Information

Quinidine is a class I antidysrhythmic drug. Its actions, clinical use, interactions, and adverse effects have been reviewed (1).

In 652 consecutive inpatients 91 adverse reactions to quinidine occurred in as many patients (14%); of these, 51 were gastrointestinal, 16 dysrhythmic, 11 febrile, six dermatological, and one hematological; there were six cases of cinchonism (2). Although there were four cases of potentially fatal dysrhythmias, there were no deaths.

In a study of 245 patients, the most common adverse effects were diarrhea (35%), upper gastrointestinal distress (22%), and light-headedness (15%). Other common adverse effects included fatigue (7%), palpitation (7%), headache (7%), angina-like pain (6%), weakness (5%), and rash (5%) (3).

Comparative studies

Quinidine and sotalol have been compared in a prospective multicenter trial of 121 patients after conversion of atrial fibrillation (4). Patients with low left ventricular ejection fractions (below 0.4) or high left atrial diameters (over 5.2 cm) were excluded. After 6 months the percentages of patients remaining in sinus rhythm were similar in the two groups (around 70%), but when the dysrhythmia recurred it occurred later with sotalol than with quinidine (69 versus 10 days). There was also a difference between patients who had been converted from recent-onset atrial fibrillation, in whom sotalol was more effective than quinidine, and in patients who had had chronic atrial fibrillation for more than 3 days, in whom quinidine was more effective. There were significant adverse effects requiring withdrawal of therapy in 17 patients, of whom nine were taking quinidine; three patients had gastrointestinal symptoms, two had central nervous symptoms, two had allergic reactions, one had undefined palpitation, and one had QT interval prolongation. One patient taking quinidine, a 65-year-old man, had frequent episodes of non-sustained ventricular tachycardia.

General adverse reactions

Gastrointestinal symptoms, including anorexia, nausea, and vomiting, are common. Quinidine has a negative inotropic effect on the heart and can cause heart failure and hypotension. It prolongs the QRS complex and QT interval and can cause cardiac dysrhythmias, which can result in syncope (so-called "quinidine syncope"). "Cinchonism" is the term used to describe a cluster of adverse effects that occur at high dosages, including nausea, vomiting, diarrhea, tinnitus, dizziness, and blurred vision; in severe cases there may be deafness and toxic amblyopia in addition to cardiac abnormalities. Other adverse effects that have been described include dementia, psychosis, esophagitis, sometimes resulting in stricture, and exacerbation of myasthenia.

Various hypersusceptibility reactions have been attributed to quinidine, including fever, skin rashes, various types of hematological abnormalities (particularly thrombocytopenia), hepatitis, asthma, and anaphylactic shock. Quinidine has rarely been reported to cause a lupus-like syndrome. Tumor inducing effects have not been reported.

Organs and Systems

Cardiovascular

Quinidine prolongs the QRS complex and QT interval, the effect being related to plasma quinidine concentrations (5) and being greater in women (6). As a result, torsade de pointes or other ventricular tachydysrhythmias can occur and may lead to syncope ("quinidine syncope"). The minimum risk of torsade de pointes has been estimated at 1.5% per year (7).

The relation between serum quinidine concentrations and QT interval dispersion has been studied in 11 patients with atrial dysrhythmias and subtherapeutic or therapeutic serum quinidine concentrations (1.48 and 3.78 μg/ml respectively) (8). The baseline QT_c interval was 430 ms. At subtherapeutic and therapeutic serum quinidine concentrations, mean QT_c intervals were 451 and 472 ms respectively. Mean QT dispersion was 47 ms at baseline, 98 ms at subtherapeutic concentrations, and 71 ms at therapeutic concentrations. Despite QT interval lengthening with increasing serum quinidine concentrations, QT dispersion was greatest at subtherapeutic concentrations.

Quinidine has also been incriminated in cases of sinoatrial block and sinus arrest, but it was not clearly established that quinidine was responsible (9,10). The anticholinergic effects of quinidine can increase the risk of dysrhythmias (11).

Treatment of tachydysrhythmias secondary to quinidine is problematic. Other class I antidysrhythmic drugs are theoretically contraindicated. Some success has been reported with bretylium and with a combination of a beta-adrenoceptor antagonist and phenytoin (12,13). Overdrive pacing has also been reported to be of value (14).

Quinidine has a negative inotropic effect on the heart and causes peripheral vasodilatation. Hypotension can occur secondary to these effects (15).

Nervous system

Quinidine rarely causes effects on the nervous system when used in therapeutic dosages, although there have been occasional reports of dementia (16–18). However, in toxicity it can cause vertigo and tinnitus (19).

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Sensory systems

Quinidine rarely affects vision, but can cause scotomata, impaired color vision, and toxic amblyopia (20), altered vision (21), sicca syndrome (22), keratopathy (23), and granulomatous uveitis (24).

Hematologic

Hypersusceptibility reactions to quinidine include thrombocytopenia, hemolytic anemia, and neutropenia.

The overall annual incidence of acute thrombocytopenia has been estimated at 18 cases per million (25), and two possible mechanisms have been invoked:

1. direct combination of quinidine with platelets, causing the production of antibodies, which then cause platelet lysis;
2. formation of quinidine-antibody complexes, which are then deposited on the platelet (the so-called "innocent bystander" mechanism).

There is evidence in favor of both of these mechanisms (26).

Other hematological effects are much less common, and include hemolytic anemia (26,27), neutropenia (28,29), and eosinophilia (30).

Withdrawal of quinidine and the administration of corticosteroids is the usual treatment for thrombocytopenia (31), although intravenous immune globulin has also been used (32).

In a review of all English-language reports on drug-induced thrombocytopenia, excluding heparin, 561 case articles reporting on 774 patients were analysed (33). A definite or probable causal role for the drug used was attributed in 247 case reports, and of the 98 that were implicated quinidine was mentioned in 38 cases. The next most common drugs involved were gold salts (11 cases) and co-trimoxazole (10 cases).

Mouth and teeth

A blue–black pigmentation of the oral mucosa has been reported with quinidine (34).

Gastrointestinal

Anorexia, nausea, vomiting, and diarrhea are common adverse effects of quinidine and occur in up to 30% of patients (2,35). These effects can be minimized by the use of modified-release formulations (36).

In one series diarrhea was reported commonly (37), and it can occur late in treatment (38).

Quinidine sometimes causes esophagitis (39,40), especially when there is some abnormality of the esophagus or cardiomegaly. This sometimes results in esophageal stricture (41).

The quinidine derivative hydroquinidine had some beneficial effects in 10 patients with myotonic dystrophy with slow saccadic eye movements, apathy, and hypersomnia (42,43). However, two patients had nausea and epigastric pain and withdrew while taking the active treatment. Although there were no cases of cardiac abnormalities, the authors raised the concern that in patients with myotonic dystrophy, who have a high frequency of cardiac disturbances, the risk of cardiac dysrhythmias with quinidine derivatives may be too high to take.

Liver

Hypersusceptibility reactions to quinidine include granulomatous hepatitis. In one retrospective series of 487 patients, 32 had evidence of hypersusceptibility, 10 of whom had hepatotoxicity (44). In another series of 1500 patients, quinidine-induced hepatitis was identified in 33 (2.2%) (45); these represented one-third of all cases of drug-induced hepatitis in those patients. In all cases the liver damage resolved on withdrawal.

Urinary tract

Glomerulonephritis has been reported in association with Henoch–Schönlein purpura (46) and nephrotic syndrome, possibly as part of a lupus-like syndrome (47).

Skin

Skin rashes are uncommon (48), but can occur as part of a hypersusceptibility reaction. In a review of drug-induced skin disorders, from a list of 26 drugs or groups of drugs, only quinidine was mentioned of all antidysrhythmic drugs (49). The reaction rate was quoted as 12 per 1000 recipients. Several different kinds of rash have been reported, including photosensitivity (50), which can result in a variety of types of rash, contact dermatitis (51), pigmentation (52), urticaria (53), exfoliative dermatitis (54,55), granuloma annulare (56), and exacerbation of psoriasis.

Musculoskeletal

Quinidine is a neuromuscular blocking drug and can exacerbate myasthenia gravis (57). It can also cause an increase in the serum activity of the muscle-specific isozyme of creatine phosphokinase (58–60).

- A 56-year-old man who took quinidine 324 mg five times daily for prevention of paroxysmal atrial fibrillation developed a syndrome similar to polymyalgia rheumatica which settled on drug withdrawal (60).

Quinidine can cause polyarthropathy (61), both in association with and independent of a lupus-like syndrome.

Immunologic

A variety of immune syndromes have occasionally been reported with quinidine, including a lupus-like syndrome, polymyalgia rheumatica, and vasculitis (SEDA-20, 179) (SEDA-23, 202).

Life-threatening vasculitis has been attributed to quinidine in a healthy volunteer taking part in a clinical trial (62).

- A 58-year-old man took quinidine 200 mg tds for 7 days as part of an interaction study with a new alpha-blocker. He developed widespread maculopapular purpuric lesions on the limbs, trunk, and ears. His temperature rose to 38.4°C and some of the lesions on his fingers, toes, ears, and nose became necrotic. He had peripheral edema with a bluish purpuric discoloration of the hands and feet. There was mucous membrane involvement

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with purpuric, partially necrotic lesions on the tongue and palate. A skin biopsy showed necrotizing vasculitis with focal leukocytoclasia. Direct immunofluorescence showed microgranular deposits of IgA, IgM, and C3 around the superficial skin vessels. Quinidine was withdrawn and he was given intravenous methyl prednisolone followed by oral prednisone for one month. He recovered completely within 3 weeks.

There has been a report of a dermatomyositis-like illness in a man taking quinidine (63).

- A previously healthy 63-year-old man, who had taken quinidine gluconate 972 mg/day for 9 months, developed diffuse edematous erythema on the extensive surfaces of the hands, arms, and face, with marked accentuation over the joints. His nail-fold capillaries were dilated and the shoulder abductors were slightly weak. His erythrocyte sedimentation rate was slightly raised (29 mm/hour) and there was a positive ANA titer (1:640) with a speckled pattern. There were no antibodies to Sm, ribonucleoprotein, SSA or SSB antigens, or histones. There was no evidence of inflammatory myopathy on electromyography, and a skin biopsy showed a mild, superficial, perivascular, lymphocytic inflammation with positive direct immunofluorescence for IgG and IgM at the dermoepidermal junction. There was no evidence of malignancy. All these abnormalities resolved rapidly after quinidine withdrawal.

Lupus-like syndrome

A lupus-like syndrome has occasionally been reported in patients taking quinidine (60,61,64). It usually presents with polyarthralgia, a raised erythrocyte sedimentation rate, and a raised antinuclear antibody titer. It can occasionally be associated with antihistone antibodies and a circulating coagulant. In two cases (65) the syndrome was associated with quinidine and not with procainamide. Lupus anticoagulant has been reported with the use of quinine and quinidine, and an associated antiphospholipid syndrome has been described (66).

Susceptibility Factors

Age

Maintenance dosages should be reduced in elderly people (67).

Sex

The effect of quinidine on the QT interval is greater in women than in men at equivalent serum concentrations (6). In 12 men and 12 women who received a single intravenous dose of quinidine (4 mg/kg) in a randomized, single-blind, placebo-controlled, crossover study, total and unbound serum concentrations of quinidine and 3-hydroxyquinidine were measured and QT intervals were corrected for differences in heart rate using Bazett's method. The QT interval at baseline was longer in women than in men (407 versus 395 ms). The slope of the relation between the serum concentration of quinidine and the change in the QT_c interval from baseline was 44% greater in the women than in the men. However, there were no significant differences between the men and the women in the disposition of quinidine, apart from a small reduction in the unbound fraction of 3-hydroxyquinidine in the men (0.47 versus 0.53). The authors proposed that estrogens and androgens differentially affect the expression and activity of potassium channels in the heart, and that a lower density of potassium channels could contribute to a larger effect of quinidine in the women. They suggested that women are at greater risk of quinidine-induced cardiac dysrhythmias and that altering dosages according to weight would not correct for this difference. They also pointed to the fact that in the SWORD study the risk of excess mortality in those taking D-sotalol was greater in the women than in the men.

Hepatic disease

Maintenance dosages should be reduced if hepatic metabolism is reduced, for example in congestive cardiac failure and hepatic disease and in elderly people (67).

Other features of the patient

Care must be taken in patients with pre-existing conduction tissue disease or heart failure. Loading doses should be reduced in cardiac failure, because of a lowered apparent volume of distribution (67).

Drug Administration

Drug overdose

In acute overdosage the chief effect of quinidine is profound hypotension, due to the combination of peripheral vasodilatation, and a negative inotropic effect on the heart (68,69). Charcoal hemoperfusion has been successfully used in the treatment of quinidine overdose (70).

Drug–Drug Interactions

Amiloride

Quinidine has a pharmacodynamic interaction with amiloride, further prolonging the duration of the QRS complex, but not the QT interval (71).

Amiodarone

Quinidine prolongs the QT interval and will therefore potentiate the effects of other antidysrhythmic drugs that have the same effect (for example amiodarone) (72).

Antacids

The interactions of quinidine with antacids have been reviewed (73). Although the data are inconclusive, it has been suggested that at least 2 hours should elapse between quinidine and antacid doses.

Class I antidysrhythmimc drugs

Quinidine prolongs the QT interval and will therefore potentiate the effects of other antidysrhythmic drugs that have the same effect (for example Class I antidysrhythmic drugs). Specific interactions of this kind have

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been reported with tocainide (74) and mexiletine (75); in these cases the interactions were reported to be beneficial in terms of antidysrhythmic effects.

Diclofenac

In human liver microsomes, diclofenac inhibited testosterone 6-beta-hydroxylation with characteristics that suggested that it inactivated CYP3A4 (76). Quinidine, which stimulates CYP3A4-mediated diclofenac 5-hydroxylation, did not affect the inactivation of CYP3A4 assessed by testosterone 6-beta-hydroxylation activity but accelerated the inactivation assessed by diazepam 3-hydroxylation activity.

In 30 healthy young men the pharmacokinetics of a single oral dose of quinidine 200 mg were studied before and during the daily administration of diclofenac 100 mg (a substrate of CYP2C9) (63). The clearance of quinidine by *N*-oxidation was reduced by diclofenac, but only by 27%. This small effect of diclofenac suggests a minor role for CYP2C9 in the metabolism of quinidine.

Digoxin

Quinidine reduces the renal and non-renal clearance of digoxin and reduces its apparent volume of distribution. The combination should be avoided. This interaction is discussed fully in the monograph on cardiac glycosides.

Enzyme-inducing drugs

The metabolism of quinidine is enhanced by drugs that induce hepatic microsomal drug-metabolizing enzymes (67), such as rifampicin (77) and phenytoin and phenobarbital (78). This leads to an increase in the first-pass metabolism of quinidine, and thus increased requirements of oral quinidine but little change in intravenous dosages.

Inhibitors of CYP3A4

There is in vitro evidence that the oxidation of quinidine to 3-hydroxyquinidine is catalysed by CYP3A4. However, the extent to which other cytochrome P450 isoforms, such as CYP2C9 and CYP2E1, are involved in the oxidation of quinidine is not clear. In 30 healthy young men the pharmacokinetics of a single oral dose of quinidine 200 mg were studied before and during the daily administration of diclofenac 100 mg (a substrate of CYP2C9), disulfiram 200 mg (an inhibitor of CYP2E1), three inhibitors of CYP3A4 (grapefruit juice, itraconazole, and erythromycin), and probes of other enzyme activities, namely caffeine (CYPA2), sparteine (CYP2D6), mephenytoin (CYP2C19), and tolbutamide (CTP2C9) (63). The clearance of quinidine by *N*-oxidation was reduced by 27% by diclofenac. Itraconazole, grapefruit juice, and erythromycin all reduced the clearance of quinidine, including its partial clearance by 3-hydroxylation and *N*-oxidation, by up to 84%, confirming the involvement of CYP3A4 in the in vivo oxidation of quinidine. Specifically, itraconazole reduced quinidine total clearance, partial clearance by 3-hydroxylation, and partial clearance by *N*-oxidation by 61, 84, and 73% respectively. Thus, it is likely that inhibitors of CYP3A4 will cause significant drug interactions with quinidine.

Metoprolol

Quinidine inhibits drug hydroxylation and can thus convert extensive hydroxylators to poor hydroxylators, as in the case of metoprolol (79). Inhibition of hydroxylation does not occur in poor hydroxylators.

Neuromuscular blocking drugs

Quinidine is a non-depolarizing muscle blocker and potentiates the effects of neuromuscular blocking drugs (80).

Timolol

The combination of quinidine with timolol causes an increased risk of bradycardia (81).

Warfarin

Quinidine potentiates the effects of warfarin by a pharmacodynamic effect (82).

However, it has also been reported that quinidine increased the 4′-hydroxylation of *S*-warfarin and the 10-hydroxylation of *R*-warfarin in human liver microsomes and intact hepatocytes by stimulation of CYP3A4 (83). The increases were concentration-dependent and respectively maximized at about three and five times control values. In contrast, warfarin did not affect the 3-hydroxylation of quinidine. These results are consistent with previous findings suggesting that there is more than one binding site on CYP3A4 through which interactions can occur.

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Quinine

General Information

Quinine was originally extracted from the bark of the *Cinchona* tree (Peruvian bark or Jesuits' bark) and was used to treat ague, that is fever, usually due to malaria. It fell out of fashion with the advent of other antimalarial drugs, but has once again become the drug of first choice for malaria originating in areas with multiresistant *Plasmodium falciparum*. To be effective, quinine plasma concentrations greater than the minimal inhibitory concentration must be achieved and maintained.

Pharmacokinetics

Quinine given orally is well absorbed; the half-life is 11 hours. Clearance is predominantly by hepatic metabolism; urinary clearance accounts for only 20%. Information on pharmacokinetics in healthy volunteers can be misleading, since plasma quinine concentrations are higher in the presence of malaria infection than in healthy subjects given the same dose (SEDA-13, 814). The dosage regimen therefore needs to be adapted to the severity of the illness and amended as improvement occurs.

A population pharmacokinetic study of intramuscular quinine (loading dose 20 mg/kg salt diluted 1:1 in water) in 120 Ghanaian children with severe malaria showed predictable profiles, which were within the target range for quinine (15–20 μg/ml) and independent of clinical and laboratory variables (1). Adverse events included skin induration or abscesses at the injection site (12%), all of which resolved without surgical intervention, and hypoglycemia (10%), a special risk in children who were hypoglycemic at presentation.

Adverse effects of quinine are common at plasma concentrations over 10 μg/ml. The dose often recommended, 10 mg/kg intravenously over 10–20 minutes, may be too high in patients with cerebral malaria (SEDA-14, 240). In the USA, intravenous quinine has been discontinued in favor of quinidine (SEDA-17, 329). In some areas, a high rate of recrudescence is seen after short-term treatment with quinine. The addition of specific antibiotics may improve the cure rate.

Placebo-controlled studies

A double-blind, placebo-controlled trial of a 3-day combination regimen of quinine (8 mg/kg tds) and clindamycin (5 mg/kg tds) ($n = 53$) versus 7-day quinine (8 mg/kg tds intravenously for 3 days, then orally; $n = 55$) to treat uncomplicated imported falciparum malaria showed no significant differences in the parasite and fever clearance

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times or the 28-day cure rate (100 versus 96%) (2). The frequencies of mild adverse events (tinnitus and nausea) were similar in the two groups. There were two serious adverse events that necessitated treatment withdrawal: one patient taking quinine alone had a hemolytic episode and another a "severe toxic rash."

General adverse effects

Quinine is not pleasant to take, and adverse effects, including nausea, tinnitus, dizziness, and hypoglycemia, are well recognized and common compared with other antimalarial drugs (3) in the doses used to treat malaria, although not in the smaller doses used to prevent leg cramps, when classical allergic reactions can still occur (4). Most serious adverse effects are due to the prodysrhythmic properties of quinine, and its effects as a hypoglycemic agent, especially in pregnant women with severe malaria. The prolonged use of normal or low doses of quinine can lead to "cinchonism" in sensitive individuals; this in mild form consists of tinnitus, headache, nausea, and visual disturbances (SEDA-13, 814). Overdosage can cause marked gastrointestinal intolerance, central nervous system disturbances (especially vertigo), visual disorders (very occasionally involving sudden blindness), and cardiovascular problems related to impaired intracardiac conduction. A major risk with quinine is that of direct intravenous injection given too fast. Allergic reactions are not uncommon. They are usually limited to fever and rashes, but angioedema and asthma have been seen. Thrombocytopenic purpura and thrombocytopenia are, at least in some cases, caused by an allergic reaction, and the amounts of quinine present in some "tonics" are sufficient to trigger thrombocytopenia in such patients. Anaphylactic shock has been reported in rare cases (SEDA-13, 814).

Organs and Systems

Cardiovascular

Quinine can cause atrioventricular conduction disturbances. In sensitive patients, such changes can occur with normal dosages given over a prolonged period; however, in most cases cardiac effects are due to overdosage.

Electrocardiographic changes, such as prolongation of the QT interval, widening of the QRS complex, and T wave flattening, can be seen with plasma concentrations above 15 μg/ml (SEDA-11, 590) (SEDA-14, 239).

Quinine, and more profoundly quinidine, its diastereomer, can cause ventricular tachycardia, torsade de pointes, and ventricular fibrillation by prolonging the QT interval (SEDA-20, 261).

- An 8-year-old child given an incorrect dose of quinine had ventricular tachycardia and status epilepticus after 48 hours; the plasma quinine concentration was 20 μg/ml (SEDA-18, 288), compared with the target range of 1.9–4.9 μg/ml.

Respiratory

Quinine can cause allergic asthmatic reactions.

- A 45-year-old woman with long-standing rheumatoid arthritis developed wheeze, severe anxiety, breathlessness, cough, orthopnea, mild fever, chills, and pleuritic chest discomfort after taking a single dose of quinine for nocturnal leg cramps (5). A chest X-ray showed diffuse, bilateral pulmonary infiltrates suggestive of pulmonary edema. No cause other than acute quinine ingestion was identified despite thorough cardiac and infectious disease evaluation.

Quinine poisoning can cause respiratory depression.

Nervous system

Tinnitus and vertigo are not uncommon with quinine, especially at higher dosages (6,7).

Headache and tinnitus occur in chronic toxicity (cinchonism) (8).

Acute intoxication can be followed by convulsions and coma (9).

- A general organic brain syndrome was observed in a 24-year-old woman with tropical malaria after the third day of treatment with quinine sulfate 500 mg tds; her symptoms were headache, blurred vision, vertigo, tinnitus, impaired hearing, increasing apathy, disorientation, speech changes, incoherent thinking, and disorientation with respect to time and place; recovery followed withdrawal (SEDA-16, 305).

A quinidine-induced myopathy has been reported (10).

Sensory systems

Eyes

Amaurosis connected with damage to the retina is most common with high plasma concentrations, and thus follows high dosages and especially overdosage. The outdated, but still practiced, use of quinine to induce abortion is probably the most common cause. Quinine initially affects the photoreceptor and ganglion cell layers; retinal vascular changes are secondary. The first sign may be widely dilated pupils that still respond to light; later, visual field contraction and loss of vision can occur. In milder cases, vision can return, but possibly with a residual disturbance of dark adaptation and/or restricted visual fields. However, loss of vision can be permanent. In cases of permanent damage, the classic late appearance of the fundus after quinine intoxication, with marked pallor and vascular narrowing, appears after some months (SEDA-13, 815). Loss of vision occurs mainly at serum concentrations over 10 μg/ml. Such concentrations are thought not to be toxic in patients with malaria, who have high circulating concentrations of alpha$_1$-acid glycoprotein, resulting in a lower fraction of unbound drug in the plasma (SEDA-17, 329).

Ocular toxicity with vasospasm has been described after poisoning with 4.5 g of quinine 24–36 hours before (11). Therapy for vasospasm using nimodipine, hemodilution, and hypervolemia was instituted, with subsequent resolution of the symptoms.

Blindness has been attributed to quinine (12).

- A 43-year-old Ghanaian man with a mild attack of malaria due to *P. falciparum* received quinine 750 mg intravenously over 5 hours and another identical

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infusion 3.5 hours after the end of the first infusion. Half an hour after the start of the second infusion he wakened and reported complete blindness. The infusion was immediately stopped, and ocular examination showed fixed, dilated pupils, complete blindness, and normal fundi. A CT scan of the brain, electroencephalography, and retinal fluorescein angiography were all normal. Serum quinine concentrations continued to rise after the end of the infusion, but this effect was mitigated by an increase in the serum concentration of alpha$_1$-acid glycoprotein, to which quinine binds. Six hours after the end of the infusion of quinine his sight began to improve.

In a case of quinine poisoning, stellate ganglion block was performed immediately on the basis of the clinical history of visual disturbance without waiting for physical signs to develop. There was no residual field defect despite the presence of toxic concentrations of the drug. The authors suggested that stellate ganglion block may prevent development of visual field defects due to quinine toxicity (13). However, in other cases it was ineffective (14,15). The effectiveness of this treatment may be a function of the speed with which it is instituted.

Ears

Tinnitus is a fairly frequent complaint and is not only seen after quinine overdosage. Permanent impairment of hearing has long been thought to be a possible consequence of long-term use of quinine, but this belief has recently been challenged, and the original description of it is questionable (SEDA-13, 816); the complication is certainly rare (16).

Serial audiometry in 10 patients receiving quinine for acute falciparum malaria showed a reduction in high-tone auditory acuity in all patients, resulting in flattening of the audiogram. The onset of the effect was rapid and it resolved completely after the end of treatment; only seven of these patients reported tinnitus. Hearing impairment was investigated in six volunteers after single doses of quinine at 5, 10, and 15 mg/kg. A clear effect on hearing was found, but with high variability (SEDA-17, 306).

Metabolism

Clinical signs and symptoms of hypoglycemia are reported occasionally; most cases are subclinical, but severe cases have been described (SEDA-13, 815). A study of the effect of quinidine on glucose homeostasis in Thai patients with malaria showed a near doubling of plasma insulin concentrations and a corresponding fall in serum glucose concentrations. An additional factor may have been impaired nutritional status and the effects of parenteral quinine in severely ill patients not taking food (SEDA-13, 815) (SEDA-14, 240) (SEDA-18, 288).

Hematologic

Thrombocytopenia is often reported with quinine. It is probably due to hypersusceptibility rather than a toxic effect, since even the ingestion of minimal amounts of quinine, such as those present in commercial tonic waters, can cause it. A drug–antibody complex has been demonstrated (SEDA-11, 591). In some cases of quinine-induced thrombocytopenia, there was autoantibody-binding to glycoprotein Ib-IX, IIb, and IIIa complexes. In three published cases, quinine-dependent autoantibodies to glycoproteins Ib-IX and IIb/IIIa were associated with both thrombocytopenia and a hemolytic–uremic syndrome (SEDA-16, 305) (SEDA-17, 329). Two other patients had recurrent febrile illnesses characterized by hypotension, pancytopenia, coagulopathy, and renal insufficiency, and both had high titers of quinine-dependent antibodies, which showed cross-sensitivity with quinidine. In one case there was a link with tonic water, while the other had taken quinine sulfate for leg cramps before each episode (17). A list of nine earlier published cases with antibody findings was added to these two case histories.

Isolated thrombocytopenia after the use of quinine for malaria or leg cramps has been described in isolated cases. The FDA's Center for Drug Evaluation and Research received 141 reports of isolated thrombocytopenia in association with quinine from 1974 to December 2000 (18). After elimination of cases that were confounded by acute or chronic disease or concomitant drug therapy, 64 reports of quinine-associated thrombocytopenia were analysed. Thrombocytopenia occurred soon after the start of therapy (median 7 days) and was often severe (hospitalization reported in 55 of the 64 cases).

Since 1972, the Australian Adverse Drug Reactions Advisory Committee has received 198 reports of thrombocytopenia associated with quinine, four of which had a fatal outcome (19). In 17 of the 20 reports received since the beginning of 2000, patients had platelet counts of 0–14 $\times$ 10^9/l; most of them required hospitalization and treatment with platelet transfusions, glucocorticoids, or immunoglobulin. In most cases the platelet count normalized within 1 week of quinine withdrawal. As quinine-induced thrombocytopenia has an immune-based mechanism, the Committee suggested that patients who develop this reaction should subsequently avoid all products that contain quinine, including drinks such as tonic water. They also reminded prescribers that quinine is no longer recommended for the treatment of nocturnal cramps; the FDA withdrew nocturnal cramps as an indication for all quinine products in 1995 because of lack of evidence of efficacy, and the Australian Medicines Handbook advises against its use for this indication.

Glycoprotein epitopes involved in quinine-induced thrombocytopenia have been characterized (20).

Acute intravascular hemolysis with renal involvement and even renal insufficiency can occur with quinine and can follow relatively small doses. Quinine-induced hemolysis has probably played a role in the clinical syndrome of blackwater fever in the past.

- The combination of renal insufficiency with cortical necrosis, thrombocytopenia, intravascular coagulation, and deposition of fibrin was seen in a 63-year-old woman who had drunk tonic water. She had had two previous episodes of acute renal insufficiency also associated with quinine-containing drinks; this most certainly reflected a hypersensitivity reaction (SEDA-13, 815).

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- A 65-year-old man, who had taken a single dose of quinine 300 mg for leg cramps, developed both acral necrosis and hemolytic–uremic syndrome, which resolved promptly after treatment with glucocorticoids (21).

Lupus anticoagulant has been reported with the use of quinine and quinidine, and an associated antiphospholipid syndrome has been described (22).

Disseminated intravascular coagulation has been attributed to quinine (23).

- A 79-year-old woman developed disseminated intravascular coagulation. She had taken a dose of quinine for leg cramps 3 months before and on the day before admission. Her only other medication was bendroflumethiazide. Investigations showed a platelet-associated immunoglobulin with positive immunofluorescence on exposure to quinine sulfate.
- Quinine-induced disseminated intravascular coagulation and hemolytic–uremic syndrome occurred in a 78-year-old woman who took quinine 150 mg for leg cramps; this is the first report of the two diseases occurring simultaneously after quinine (24).

In a retrospective survey of thrombotic thrombocytopenic purpura with hemolytic–uremic syndrome reported to the Oklahoma TTP/HUS Registry, 17 of 225 cases were associated with quinine (doses not stated) taken long-term for leg cramps (25). Patients typically presented with an acute onset of fever, chills, nausea, vomiting, diarrhea, and abdominal pain within hours of quinine ingestion. Laboratory findings included thrombocytopenia, microangiopathic hemolytic anemia, and liver and renal dysfunction. This is an immune-mediated reaction associated with quinine-dependent antiplatelet antibodies and a high mortality (three of the 17 patients). It can be triggered by small amounts of quinine, such as those present in tonic water.

Gastrointestinal

Nausea and abdominal pain can occur with quinine (26). With high doses, diarrhea has been seen (26).

Liver

Granulomatous hepatitis has been reported in a patient taking quinine sulfate for night cramps (27). Cholestatic jaundice was reported in another patient who had taken quinine for night cramps (SEDA-13, 815). Except for the occasional anecdotal case, there is no evidence that true hepatotoxicity occurs with quinine.

Urinary tract

Renal damage accompanies acute hemolysis due to quinine. Renal insufficiency in cases of quinine poisoning is probably due to circulatory collapse. Allergic reactions underlie at least some cases. The picture can be complex, with the renal insufficiency coming in association with cortical necrosis, thrombocytopenia, intravascular coagulation, and deposition of fibrin.

Skin

Rashes are common in allergic reactions. Photosensitivity induced by quinine has been reported; some of the cases occurred in elderly persons taking quinine for night cramps (28). Another form of hypersensitivity to quinine is cutaneous neutrophilic vasculitis, which is a form of photosensitivity (SEDA-16, 305). Local pigmentation has been described after intramuscular injection (SEDA-13, 815).

Immunologic

Quinine can cause a variety of immune-mediated syndromes, most commonly isolated thrombocytopenia, but rarely microangiopathic hemolytic anemia with thrombocytopenia and acute renal insufficiency (hemolytic–uremic syndrome). Two reports of immune-mediated syndromes following the use of quinine for leg cramps have helped to provide an immunopathological explanation for the diversity of such presentations (29,30).

- One patient presented with thrombocytopenic purpura, presumed to be idiopathic (which responded to glucocorticoids and intravenous immunoglobulin) and subsequently presented again with hemolytic–uremic syndrome, and required intensive renal replacement and immunosuppressive therapy. Analysis of serum samples from the isolated thrombocytopenic stage of the presentation showed the presence of quinine-dependent antibodies specific for platelet surface glycoprotein GPIb/IX. Quinine-dependent antibody targets widened to include glycoprotein IIb/IIIa during the hemolytic–uremic phase of the illness, with additional binding to neutrophils and lymphocytes.
- In another case of acute systemic allergy to quinine, which mimicked septic shock, with little hemolysis or renal involvement, the patient presented twice with a virtually identical clinical picture: sudden fever, rigors, and back pain, followed by hypotension, metabolic acidosis, granulocytopenia, and disseminated intravascular coagulation. On each occasion clinical and laboratory indices recovered spontaneously within 36 hours. A retrospective analysis of the patient's serum showed the presence of neutrophil-specific, quinine-dependent antibodies.

A quinine-induced lupus-like syndrome, including pericarditis and polyarthralgia, and positive antinuclear and anti-cardiolipin antibodies, and a polymyalgia rheumatica-like syndrome have been described with quinine or quinidine (SEDA-20, 261) (SEDA-21, 298).

Second-Generation Effects

Teratogenicity

Quinine crosses the placenta and can be found in relatively high concentrations in cord blood; it is also excreted in the breast milk. Data about possible teratogenicity related to the therapeutic use of malaria are scanty (SEDA-14, 239). Hypoplasia of the optic nerve and deafness have been reliably described in children born after failure to induce abortion with the drug.

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Susceptibility Factors

Age

Children under 2 years are more vulnerable to quinine toxicity as measured by prolongation of the QRS interval at 2–4 hours after intravenous quinine (SEDA-20, 261).

Renal disease

A pharmacokinetic study in adults with renal insufficiency showed that concentrations of the main metabolite, hydroxyquinine, rose to 45% of the concentrations of the parent compound, and may contribute up to 25% of the cardiac effects of quinine (31).

Other features of the patient

The use of quinine to treat cerebral malaria, and to a lesser extent severe malaria, has always been considered more risky than treatment of common cases of malaria. The changes in the pharmacokinetics of quinine caused by the malaria provide an explanation: the standard dose of 10 mg/kg is usually well tolerated in patients with uncomplicated malaria but causes markedly higher plasma serum concentrations in patients with cerebral malaria. Total quinine clearance and total apparent volume of distribution are significantly lower in severe malaria, and after recovery, the pharmacokinetics return to normal. Probably the first loading dose should be as generally advised, but with a reduction in subsequent doses until the general condition has improved. Monitoring of plasma or red cell concentrations of quinine would of course be ideal, but this luxury is rarely available (SEDA-13, 816).

Drug Administration

Drug overdose

Early symptoms of intoxication with quinine are unremarkable, except for mild visual and auditory complaints (32,33). The principal sign is the sudden onset of bilateral pupil dilatation. Other symptoms are tinnitus, mild deafness, vertigo, mild drowsiness, vague disturbances of consciousness, headache, nausea, vomiting, and abdominal pain. The electrocardiogram may show prolongation of the QT interval and ST abnormalities. Deafness can occur within hours or days of the acute symptoms. Visual disturbances do not necessarily occur early on. Acute intoxication can be seen after ingestion of doses of 4–12 g, but a dose of 8 g can prove lethal. Death is commonly caused by respiratory arrest, but is sometimes due to renal insufficiency. In five children with quinine overdosage, there were serious neurological and cardiac effects, such as seizures, ventricular tachycardia, and cardiac arrest (SEDA-20, 261).

Repeated oral administration of activated charcoal reduces plasma quinine concentrations and mitigates toxicity (34).

Drug–Drug Interactions

Anticoagulants

Quinine can increase the action of anticoagulants, possibly by inhibition of prothrombin synthesis (35).

Carbamazepine

Quinine inhibits the metabolism of carbamazepine (36).

Chloroquine

Chloroquine antagonizes the action of quinine against *P. falciparum* in vivo (37). However, no such evidence of antagonism was found in a study in which Malawian children with cerebral malaria were treated with quinine. There was no difference in survival and rate of recovery in patients who had also been given chloroquine compared with those who had not (SEDA-13, 816).

Clindamycin

The combination of quinine with clindamycin improved the cure rate after a short course of quinine (38). This combination enhances parasite clearance and recovery from fever and is of value in combating bacteremia (39).

Codeine

Quinidine inhibits the metabolism of codeine by CYP2D6 in extensive but not in poor metabolizers (40).

Digoxin

Quinine reduces the clearance of digoxin by inhibiting its biliary excretion (41). There may also be a small effect on renal digoxin clearance (42).

Enzyme inhibitors and inducers

Enzyme inhibitors, such as cimetidine and ketoconazole, increase the toxicity of quinine or quinidine (43), while enzyme inducers, such as rifampicin, reduce the toxic effects (44).

Erythromycin

Erythromycin is a competitive in-vitro inhibitor of quinine 3-hydroxylation and may therefore interact with quinine (45).

Flecainide

Flecainide is metabolized by CYP2D6, and is subject to polymorphic metabolism. In extensive metabolizers its clearance is reduced by quinine (46).

Halofantrine

Quinine should not be combined with halofantrine, since both drugs impair atrioventricular conduction and since quinine can enhance the cardiotoxic effects of halofantrine by inhibiting its metabolism (47).

Phenobarbital

Quinine inhibits the metabolism of phenobarbital (36).

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Tetracycline

The antimalarial effect of tetracycline is well known. The combination of quinine with doxycycline improved the cure rate (38,39). However, none of the patients taking quinine in combination with either clindamycin or tetracycline had high-grade resistant *P. falciparum* infections. The drawback of combining quinine with tetracycline is the longer time required for adequate treatment, which in most cases demands supervision. Furthermore, tetracycline should not be given to young children or pregnant women. The combination can be used in multiresistant and mefloquine-resistant *P. falciparum* malaria. When quinine is combined with doxycycline, the effects of the antibiotic itself may be enhanced.

Theophylline

Quinine raised serum theophylline concentrations in an elderly patient (48).

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Rabeprazole

See also Proton pump inhibitors

General Information

The benefits and risk profile of rabeprazole, a proton pump inhibitor, have been reviewed (1,2). It has been well tolerated in both short-term and long-term studies. The overall rate of drug withdrawal because of adverse effects was 3%. Common adverse effects included diarrhea, headache, and rash.

Observational studies

Rabeprazole 10 and 20 mg/day in the morning were effective in erosive or ulcerative gastro-esophageal reflux disease, gastric and duodenal ulcers, and long-term maintenance of gastro-esophageal reflux disease healing (1). Healing rates were equivalent to those with omeprazole and superior (gastro-esophageal reflux disease healing and duodenal ulcer healing) or equal (gastric ulcer healing) to ranitidine.

In an open study in 189 patients rabeprazole 20 mg/day for 4 weeks was effective in functional dyspepsia (3). The incidence of adverse events was 8%, and included dysgeusia, diarrhea, constipation, and headache.

In a crossover study in 24 healthy volunteers, rabeprazole 10, 20, and 40 mg produced significant dose-related reductions in intragastric acidity associated with a significant rise in serum gastrin concentration (4). There were no serious adverse effects. After taking into account increases in serum gastrin concentrations and interindividual variation in the antisecretory response, 20 mg appears to be the preferred dose for routine clinical use. Similar potent dose-related gastric acid inhibition and rises in serum gastrin were found with rabeprazole 5–40 mg/day in the morning for 7 days in 38 subjects infected with *Helicobacter pylori* (5). There was less than 50% recovery of acid by 48 hours after the seventh dose. In this study the optimal acid inhibitory dose appeared to be 20 mg/day, and there were no serious adverse effects.

The safety and efficacy of rabeprazole have been evaluated in 124 patients aged 65 years and over being treated for a variety of acid-related disorders (6). Rabeprazole controlled symptoms and healed mucosal lesions. The incidence of adverse effects was 4.9%, and adverse effects were more common in the presence of hepatic dysfunction and with increasing duration of treatment.

The efficacy and tolerability of rabeprazole 10 mg/day for 8 weeks in the treatment of reflux esophagitis has been assessed in an open, postmarketing surveillance investigation in 61 patients (7). Rabeprazole was well tolerated and was effective in relieving symptoms and healing esophagitis. Two patients developed slight rises in liver enzymes, which resolved after treatment.

In an open, multicenter trial in 2579 patients with erosive gastro-esophageal reflux disease, rabeprazole 20 mg/day for 8 weeks relieved symptoms in most patients (in over 60% by day 1 and over 80% by day 7) (8). Rabeprazole was well tolerated, and the most common adverse effects were headache, diarrhea, abdominal pain, and nausea, each reported by under 2% of the patients.

In another open, multicenter study in 92 patients with erosive esophagitis, rabeprazole 20 mg/day was effective in healing esophageal lesions and relieving heartburn (9). Adverse effects (diarrhea, headache, and nausea) were attributed to the medication in four cases.

Placebo-controlled studies

In a double-blind, placebo-controlled study in 288 patients with previously treated erosive or ulcerative gastro-esophageal reflux disease rabeprazole 10 or 20 mg/day was significantly more effective than placebo in preventing relapse of erosive or ulcerative gastro-esophageal reflux disease and was well tolerated (10). Commonly reported adverse events were abdominal pain, nausea, diarrhea, rhinitis, pharyngitis, a flu-like syndrome, and back pain. Rabeprazole had no clinically significant effects on laboratory values, thyroid function tests, the electrocardiogram, vital signs, or body weight.

General adverse effects

Rabeprazole was generally well tolerated in both short-term and long-term studies of up to 2 years. Headache was the most important reported adverse effect. Other commonly reported adverse effects were diarrhea, rhinitis, nausea, pharyngitis, abdominal pain, and flatulence. The changes in serum gastrin concentrations were consistent with proton pump inhibitor pharmacology, and no study has reported mean values at end-point that were outside the reference range. In controlled trials, the frequency of abnormalities of hepatic aminotransferases was similar to that of placebo. Scoring of enterochromaffin-like cells in gastric biopsies taken prospectively from patients in studies of up to 2 years have shown some hyperplastic changes, but no evidence of adenomatous, dysplastic, or neoplastic changes.

Organs and Systems

Liver

- Acute fulminant hepatitis occurred in a previously healthy 46-year-old man who took rabeprazole and terbinafine (11). His condition improved gradually after withdrawal of both drugs.

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Rabies vaccine

See also Vaccines

General Information

Rabies vaccine was for a long time prepared from infected brain tissue, and neurological complications were likely to occur in as many as one in 300 cases. A second-generation vaccine prepared from duck embryo tissue has been found to be better tolerated in this respect, and third-generation vaccines prepared in non-neural tissue cultures or in human diploid cell (HDC) vaccines with a progressive improvement in safety have now become the vaccines of choice where they are available.

Any rabies vaccine can apparently cause mild local discomfort and swelling, and either of the animal preparations can result in hypersensitivity reactions, for example pyrexia, serum sickness, or urticaria; sensitization can occur.

Third-generation rabies vaccines include a purified vero-cell rabies vaccine (PVRV) and HDC vaccine purified by zonal centrifugation. In clinical trials (SEDA-12, 284) (SEDA-15, 357) the improved vaccines were well tolerated. In 1988, Rabies Vaccine Adsorbed (RVA), a new cell culture-derived rabies vaccine (Kissling strain of rabies virus adapted to a diploid cell line of the fetal rhesus lung cells in medium-free of human albumin and adsorbed on aluminium phosphate) for human use was licensed in the USA. Reactions after primary immunization are similar to those observed with HDC. Systemic allergic reactions have been reported at a rate <1% (HDC 6%) (1).

Organs and Systems

Nervous system

Brain tissue rabies vaccine

There are many countries that still use first-generation brain tissue rabies vaccine because of limited financial resources and where neurological complications after immunization still occur. The neurological effects produced by this type of vaccine are very variable. Sometimes a peripheral neuropathy occurs, while other vaccinees develop encephalomyelitis, dorsolumbar myelitis, ascending myelitis, hemiplegia, or general subjective neurological symptoms, such as stiffness of the neck or physical weakness.

It has been argued that there may be a risk of transmitting scrapie (spongiform encephalopathy of sheep, similar to bovine spongiform encephalopathy of cattle) through blood donation from individuals who have been immunized against rabies with sheep brain rabies vaccine still used in developing countries (2).

Duck embryo rabies vaccine (DEV)

Nervous system complications after administration of DEV occurred, but in much lower frequency than after brain tissue rabies vaccines. Reports of transverse myelitis and other neurological complications have been published (SEDA-8, 300). There have been some efforts to develop a more purified version of DEV, but improvements in third-generation vaccines have made these the vaccines of choice when they can be afforded, much reducing the motivation to develop duck embryo vaccines further.

Human diploid cell (HDC) vaccines

The major advantage of third-generation rabies vaccines prepared in non-neural tissue cultures or in human diploid cells is the greatly reduced risk of neurological complications. Millions of doses of these vaccines have been administered worldwide since 1974, and only a few neurological complications have been reported. The overall risk of neurological complications is estimated to be less than 1 per 150 000 (SEDA-15, 356), and complications after the administration of third-generation rabies vaccines cultured in non-neural tissues have been very rarely reported. However, those that have been published are of various types.

Isolated case reports of Guillain–Barré syndrome after HDC vaccine have been published (SED-11, 684) (SEDA-15, 356) (3). Polyneuropathy and oculomotor nerve impairment have been reported after Russian cell-culture vaccine (SEDA-12, 284).

- Two weeks after the second injection of HDC vaccine a 45-year-old farmer developed meningoradiculitis. The symptoms regressed spontaneously (4).
- A 25-year-old veterinary practitioner developed an inflammatory demyelinating process affecting the

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central nervous system 8 days after the second HDC vaccine immunization (5).
- Acute disseminated encephalomyelitis developed in a 15-year-old boy after HDC vaccine immunization (SEDA-21, 337).
- A 14-year-old boy had a seizure after the administration of human diploid rabies cell vaccine simultaneously with rabies immune globulin. The symptoms developed within minutes after injection. After treatment and about 2 hours later, his mental status returned to normal (6).

Immunologic

In recipients given primary courses of third-generation rabies vaccines, only mild local and systemic reactions were reported by about 20%. Systemic allergic reactions have occurred in 11 per 10 000 vaccinees (7). However, 2–21 days after the administration of HDC vaccine, about 5% of patients receiving booster injections for pre-exposure prophylaxis and a few receiving postexposure primary immunization develop an immune complex (serum sickness-like) reaction, including urticaria, fever, malaise, arthralgias, arthritis, nausea, and vomiting. This syndrome may prove to be less common with RVA, but direct comparisons are lacking.

Anaphylaxis has been reported rarely after HDC vaccine prophylaxis (3).

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Racecadotril

General Information

Racecadotril is an orally active potent inhibitor of enkephalinase, which has an antihypersecretory effect without increasing intestinal transit time.

Racecadotril 100 mg tds has been compared with loperamide 2 mg tds in a single-blind study in 945 outpatients with acute diarrhea in 21 centers in 14 countries (1). Racecadotril resolved acute diarrhea as rapidly and as effectively as loperamide and produced more rapid resolution of abdominal symptoms and less constipation. The incidence of adverse effects attributable to medication was less in the racecadotril group (9 versus 18%). Common adverse effects were constipation, abdominal distension, anorexia, headache, and abdominal pain.

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Radioactive iodine

General Information

Three radioactive isotopes of ^{127}I are currently used in clinical medicine:

1. ^{131}I (radioactive half-life of 8 days and a high-energy emitter), used mainly in the therapy of hyperthyroidism and thyroid cancer.
2. ^{123}I (radioactive half-life 13 hours) has replaced ^{131}I for diagnostic purposes; however, for in vivo imaging meta-stable technetium-99 (^{99m}Tc) is often preferred, because of its lower radiation dose, availability, and cost.
3. ^{125}I (radioactive half-life of 60 days and a low energy emitter), previously used in the treatment of hyperthyroidism, but now replaced by ^{131}I because of disappointing therapeutic results (1,2).

Radioactive isotopes of iodine are handled by the thyroid in the same way as stable iodine and are therefore actively concentrated, incorporated into thyroglobulin, stored, metabolized, and secreted as thyroid hormones. Small amounts of radioactive iodine are therefore ideal probes to analyse the uptake of iodine, the distribution of iodine in the gland, and possibly even its turnover and incorporation into thyroid hormones. Larger amounts of radioactive iodine selectively radiate the thyroid gland and therefore selectively impair the function of the follicular thyroid cells and eventually destroy them.

Doses

Three dosage ranges for radioactive forms of iodine are used:

1. For diagnostic purposes usually much less than 1 mCi (37 MBq) is given with thyroid radiation doses of a few rads of ^{123}I up to 50–200 rads (0.5–2.0 Gray) (^{131}I).
2. In the treatment of hyperthyroidism the dose of ^{131}I is usually a few millicuries and is either roughly estimated or calculated according to the size of the thyroid gland, the uptake of a tracer dose of iodine, and the type of thyroid disorder (diffuse or nodular), with doses ranging from 80 to 150 microCi (3.0–5.5 MBq) per gram of thyroid tissue (3,4).

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3. In thyroid cancer, ^{131}I can be used to eliminate tumor tissue that cannot be removed surgically but still captures iodine; in such circumstances, amounts of 100 mCi (4000 MBq) of ^{131}I or more are not unusual; with such high amounts, other tissues besides the thyroid gland can also receive substantial amounts of radiation.

The administration of ^{131}I requires safety measurements to reduce to a minimum the irradiation of medical personnel and to avoid contamination of rooms and relatives of patients. Capsules containing ^{131}I are therefore to be preferred to liquid iodine. At doses above 25 mCi (555 MBq), usually intended only for treatment of patients with thyroid cancer, isolation in a specially constructed room of a service for nuclear medicine is necessary. Waste disposal should also be carefully managed so as to avoid overall contamination (5,6).

General adverse effects

Radiation thyroiditis is an infrequent complication resulting in swelling and localized pain over the thyroid gland which subsides spontaneously or with anti-inflammatory or corticosteroid therapy (SEDA-1, 314).

Acute exacerbation of hyperthyroidism, resulting particularly in cardiac complications (arrhythmias or decompensation) or even "thyroid storm," has been reported several times (SEDA-1, 314) and should be avoided by treating very severely hyperthyroid patients with antithyroid drugs prior to the administration of ^{131}I. A temporary increase in serum triiodothyronine and l-thyroxine without clinical symptoms of exacerbation of hyperthyroidism, however, occurs much more frequently (SEDA-1, 314). In 71 patients given ^{131}I for differentiated thyroid carcinoma, short-term adverse effects included gastrointestinal complaints, salivary gland swelling with pain, change in taste and headache (7).

Organs and Systems

Cardiovascular

In a series of thyrocardiac patients, of those dying primarily from thyrotoxicosis more than 21% did so within 3 weeks of ^{131}I treatment (8), presumably reflecting too sudden a change in metabolic activity for patients with existing cardiac complications.

Respiratory

Acute respiratory embarrassment due to thyroid swelling or subsequently due to cicatrization occurs only rarely.

Nervous system

Although aseptic meningitis has been associated with the use of radioactive iodine, the products used were albumin complexes (^{131}I-RISA); this complication is almost certainly attributable to the protein content or to pyrogens rather than to the radioactive iodine itself (8).

Sensory systems

Several papers have reported that radioiodine therapy can lead to worsening of ophthalmopathy, possibly because of the release of thyroid antigens during the inflammatory reaction after ^{131}I therapy. The worsening can be prevented by glucocorticoid therapy (9).

Endocrine

The calcitonin-producing cells of the thyroid are usually destroyed by ^{131}I (SEDA-14, 369).

Both hyperfunction (10) and hypofunction of the parathyroid glands have been described after the use of ^{131}I (11).

Hypothyroidism

There is an increased incidence of late hypothyroidism in patients with autoimmune hyperthyroidism, but the risk increases markedly after extensive thyroid surgery and especially after ^{131}I treatment. Analysis of the cumulative incidence of hypothyroidism shows two phases: an early phase of radiation death of thyroid cells, depending on the ^{131}I dosage and occurring during the first 1–2 years after treatment; a second period of a lower (0.5–3.5% per year) but life-long risk of developing hypothyroidism for a variety of reasons (natural history of the disease, autoimmune processes) (see Table 1) (12–14).

The total incidence of hypothyroidism can therefore be reduced by lowering the therapeutic dose, but at the expense of a higher incidence of more prolonged or recurrent hyperthyroidism. Calculation of the therapeutic dose according to thyroid gland size, iodine uptake, or biological half-life and type of thyroid disorder can help to reduce the total incidence of hypothyroidism, although this is less well documented than many believe (15,16). Moreover, the occurrence of hypothyroidism after the use of ^{131}I should not be dramatized, since treatment is much

Table 1 The risk of hypothyroidism after ^{131}I

N	^{131}I dose (mCi)	Total follow-up period (years)	Incidence of hypothyroidism (%)				Total annual cumulative incidence (% per year)	Reference
			One-year follow-up		End of follow-up			
			Diffuse goiter	Nodular goiter	Diffuse goiter	Nodular goiter		
4473	8–20	26	8	3	77	64	3	(12)
1369	9	17	6	3	26	14	3.5	(13)
248	6–10	10	38	11	70	18	0.5	(14)

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simpler than abandoning the patient first to the prolonged risk of recurrent hyperthyroidism and thereafter to lifelong follow-up for hypothyroidism. Hypothyroidism after ^{131}I can also be transient, and replacement therapy should not be started too early (17).

Hematologic

Leukemia does not occur more often in patients treated with ^{131}I for hyperthyroidism than in similar patients treated by surgery. After use of the high doses used in the treatment of thyroid cancer there was a definite increase in the incidence of leukemia (18).

Salivary glands

In 71 patients given ^{131}I for differentiated thyroid carcinoma, salivary gland swelling with pain occurred in 50% (7); women had a significantly higher incidence than men.

Gastrointestinal

Of 71 patients given ^{131}I for differentiated thyroid carcinoma, 65% had gastrointestinal complaints: appetite loss, nausea, and vomiting occurred in 61, 40, and 7.6% respectively and increased significantly in the patients who received doses above 55.5 MBq/kg and with rises in TSH (7).

Reproductive system

Large amounts of ^{131}I, as used in thyroid cancer therapy, can cause testicular damage as documented from hormonal and sperm analysis (19), but long-term results are nevertheless reassuringly normal (20).

Long-Term Effects

Mutagenicity

Mutagenic effects on the sexual organs are difficult to determine in practice. However, while the radiation dose to the ovary and testes is rather small after ^{131}I treatment for hyperthyroidism (maximum 5 roentgens) it can be substantial after the higher amounts of ^{131}I that are used for thyroid cancer. In any case, children born to mothers previously treated with ^{131}I did not have an increased incidence of congenital malformations. The number of such observations is too small, however, to allow definite conclusions about its safety (21). In patients treated for thyroid carcinoma there was no differences in fertility rate, birth weight, prematurity, or congenital malformations compared with healthy subjects, providing reassurance about the use of radioiodine to treat hyperthyroidism in women of child-bearing age (SEDA-20, 394).

Tumorigenicity

The total number of case reports of thyroid cancer after ^{131}I is very small (under 30 cases) (22) in relation to the estimated number of patients treated with ^{131}I since 1941 (over 1 000 000 patients). Moreover, systematic follow-up or retrospective studies did not show an increased risk of thyroid carcinoma in patients treated with ^{131}I for hyperthyroidism. The results of two such studies are shown in more detail in Table 2 (23) and Table 3 (24).

Table 2 ^{131}I treatment and thyroid cancer: a comparison with thyroidectomy and antithyroid drugs

Incidence of thyroid cancer	Thyroidectomy (n = 11 732)	^{131}I (n = 21 714)	Antithyroid drugs (n = 1238)
Within 1 year of treatment	50	9	0
After 1 year of treatment	4	19	4
Total	54 (4.6%)	28 (11.3%)	4 (3.2%)
Number of deaths from thyroid cancer	4	6	0

Table 3 ^{131}I treatment and thyroid cancer

Number of patients treated with ^{131}I	3000
Mean age	57 years
Mean dose of ^{131}I	13.3 mCi
Mean observation period	13 years
Thyroid cancer	
Observed incidence	4%
Expected incidence	3.2%
Thyroid cancer more than 5 years after ^{131}I	
Observed incidence	2.1%
Expected incidence	3%

In another follow-up study of 1005 women treated with ^{131}I there was no increase in total morbidity or in the incidence of thyroid cancer (20).

In 10 552 Swedish patients (mean age 57 years) who received ^{131}I for hyperthyroidism (mean follow-up 15 years) there were increases in overall cancer mortality and deaths due to carcinoma of the stomach, lung, and kidney. While the findings for stomach cancer may be of significance, for tumors at other sites, because of an association with time after ^{131}I treatment (58 cases at 10 years or more of follow-up against the expected 44 cases), the lack of a relation between cancer mortality and either the time from radioiodine treatment or the dose administered argues against a carcinogenic effect of radioiodine (SEDA-17, 475) (25).

The use of very high amounts of ^{131}I for thyroid cancer imposes special care and risks: the frequency of radiation thyroiditis is much higher (more than 20%) and similar symptoms of pain and swelling can also be observed in the salivary glands. Nausea and vomiting may also occur. The incidence of leukemia is increased: 15 cases being reported in 5000 patients treated with ^{131}I for thyroid cancer (18); it therefore seems wise to limit the total dose of ^{131}I in a single patient to 500 mCi unless the thyroid disease activity permits higher long-term risks. It is also important to keep such patients well hydrated to allow rapid elimination of ^{131}I not retained by thyroid tissue. The radiation dose to the ovaries is not negligible, being approximately 200 roentgens after 500 mCi of ^{131}I, a dose sufficient to increase slightly the subsequent risk of miscarriage or congenital abnormalities. However, no apparent increase in the rate of abnormalities has been observed in the outcome of pregnancies among women previously treated for thyroid cancer.

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The use of ^{131}I in children is different from its use in adults. Experience worldwide is much more limited as regards both the number of children treated and the total number of years of observation (SEDA-20, 394). The risk of eventual tumor-inducing effects in the thyroid or other tissues is real. The young thyroid is very sensitive to external radiation or to nuclear fall-out: 66% of young adults developed thyroid lesions 25 years after such exposure (26). One report on a high prevalence of hypothyroidism after ^{131}I showed no cases of thyroid or other malignancies after a mean follow-up period of almost 15 years (27). However, others found an increased frequency of thyroid nodules: among case reports on thyroid cancer after ^{131}I in the world literature the younger age group is largely over-represented, owing to the frequency of ^{131}I use in this age group (22). In view of the small number of long-term results in a young population with probably higher susceptibility for thyroid tumors it seems unwise to use ^{131}I as preferred treatment for adolescents or young adults with hyperthyroidism. Much longer follow-up periods will be necessary, preferably with central registration to allow a definite conclusion about treatment (21,18). However, many experts consider the current follow-up period sufficiently long to extend the use of ^{131}I to all patients with Graves' disease above the age of 25 (SEDA-14, 368) (28). There are, however, large discrepancies in treatment strategies globally.

Second-Generation Effects

Pregnancy

Radioactive iodine passes the placenta and accumulates in the fetal thyroid where the concentration probably exceeds that in the maternal thyroid. Detailed studies show that the fetal dose of iodine is virtually nil before the 90th day of gestation but sharply increases thereafter (29). This alone is sufficient reason to avoid the use of ^{131}I in pregnancy, but there is also some controversial evidence that various congenital deformities have been produced by the isotope (30).

Teratogenicity

Concern about possible second-generation effects of ^{131}I is difficult to allay but has not been substantiated, since there is an absence of obvious birth defects or genetic changes in the offspring of patients treated with ^{131}I (20,22,24,31,32). Moreover, the radiation dose to the ovaries in ^{131}I therapy for hyperthyroidism is usually below three roentgens and thus comparable to the radiation due to common radiographic abdominal examinations. If ^{131}I is given during pregnancy, fetal hypothyroidism and chromosomal aberrations can occur (33).

Lactation

^{131}I is transferred in the milk and should not be given during lactation. Even the diagnostic use of radioisotopes of iodine should be avoided (34).

Interference with Diagnostic Tests

Detection of pulmonary embolism

Injections of ^{131}I given to detect pulmonary embolism can result in false-negative results in the ^{125}I-labeled fibrinogen test for venous thrombosis.

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Radiopharmaceuticals

General Information

Radioactive substances may be used in medicine as tracers, the quantities used in this case being merely sufficient to enable them to be detected, or as therapeutic agents, in which case the quantities employed and the amount of radiation emitted may be considerable. Risks resulting from the radiation itself fall outside the scope of this volume.

Radio-iodine is covered in a separate monograph.

General adverse effects

Radiopharmaceuticals have a good safety record. The prevalence of adverse reactions is approximately 1000-fold than less than that occurring with iodinated contrast media and drugs. The Society of Nuclear Medicine has maintained a register of adverse reactions to radiopharmaceuticals occurring in USA since 1976. The frequency of reactions appears to be falling because of improved quality control of radiopharmaceuticals. Many of the earlier adverse reactions were attributed to iron-containing formulations, gelatin-stabilized formulations, materials such as albumin contaminated with pyrogens, and other products no longer in use. The overall incidence of reactions for the year 1978 was estimated to be 1–6 per 100 000 examinations (1).

In order to determine the prevalence of adverse reactions to radiopharmaceuticals, a 5-year prospective study (1989–94) was performed in 18 institutions in the USA (2). The reported incidence rate was 0.0023%. No adverse reaction required hospitalization or had significant sequelae. The adverse reactions and types of radiopharmaceuticals are shown in Table 1.

Another study was undertaken to determine the prevalence of adverse reactions to positron-emitting radiopharmaceuticals through a prospective 4-year study in 22 institutions. PET radiopharmaceuticals have an excellent safety record because no adverse reactions were reported in over 80 000 administered doses in this study (3).

In a review of UK reports of adverse reactions to radiopharmaceuticals from 1977 to 1983, there was a changing distribution pattern with time (Table 2) (4). This was partly due to elimination of some of the earlier, more toxic formulations and partly due to changing usage, more particularly the increased use of phosphonate formulations. The authors estimated that only 10% of reactions were reported and that the probable

Table 1 Adverse reactions to 783 525 radiopharmaceutical doses in 1989–94 in the USA

Radiopharmaceutical	Adverse reaction	Number
^{67}Gallium citrate	Rash	1
[^{131}I] Iobenguane (MIBG)	Chest discomfort, light-headedness	1
^{99m}Tc-macroaggregated albumin	Rash	1
^{99m}Tc-medronate (MDP)	Rash/nausea/mild anaphylaxis	2/1/1
^{99m}Tc-oxidronate (HDP)	Rash/sweating	4/1
^{99m}Tc-pentetate (DTPA)	Rash	1
^{99m}Tc-sestamibi	Rash	1
^{99m}Tc-sulfur colloid	Nausea, vomiting, rash, headache	1
Stannous pyrophosphate (non-radioactive)*	Mild anaphylaxis/ light-headedness	2/1
Total		18

*Given intravenously to allow in vivo radiolabeling of erythrocytes and considered part of the final radiopharmaceutical.

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Table 2 Major groupings of adverse reactions to radiopharmaceuticals reported in the UK from January 1977 to December 1983

Period	Colloids	Phosphonates	Albumin particulates	Others
1977 to mid-1980	12 (48%)	2 (8%)	5* (16%)	8* (28%)
Mid-1980 to 1983	8† (21%)	15† (45%)	3 (10%)	8* (24%)
Total	20† (33%)	17† (28%)	8* (13%)	16* (26%)

*1 case or †2 cases considered to be "unlikely to be due to the radiopharmaceutical".

incidence rate was between one in 1000 and one in 10 000. There was one death associated with a hypotensive reaction to colloid in a severely ill patient. One elderly patient had a cardiac arrest after injection of macroaggregated albumin but was resuscitated. In a European prospective survey during 1996, there was a prevalence of 11 events per 105 administrations of radiopharmaceuticals. No serious or life-threatening events were reported (5).

^{99m}Technetium

The widespread use of ^{99m}Tc-DTPA (diethylaminetriaminepenta-acetate), mostly used for renal imaging, has brought with it a number of reported DTPA adverse reactions. Typical symptoms include low pressure, loss of consciousness, feeling faint and occasionally skin rash and bronchospasm. In Europe, a patient with a history of asthma developed severe bronchospasm and died within a matter of minutes (6). A series of very serious problem developed following intrathecal injection of ^{99m}Tc-DTPA in what turned out to be, strictly speaking, a misformulation incident. Almost all currently used DTPA formulations contain the mixed calcium/sodium salt of DTPA. However, one particular manufacturer used the trisodium salt. This form is capable of chelation of cerebrospinal fluid calcium and magnesium and causing gradual onset of severe neurological signs and severe paresthesia (7).

^{99m}Tc-labeled serum albumin microspheres have in one case caused collapse, apparently because the patient in question had earlier been sensitized by blood transfusions (SEDA-2, 376).

A case of anaphylaxis occurred after the injection of a leukocyte suspension labeled with ^{99m}Tc-hexamethyl propylene amine oxime (8).

Inhalation of Technigas (an ultrafine suspension of ^{99m}Tc-labeled carbon particles) for ventilation scintigraphy, in a series of patients led to a temporary reduction in oxygenation in 87% of cases, often in sufficient degree to cause some discomfort (SEDA-17, 539) (9). Injection of ^{99m}Tc-MAA for perfusion scintigraphy similarly tended to cause a decrease in oxygenation, but insufficient to cause symptoms.

Others

Aseptic meningitis has been reported after isotope cisternography with indium diethylenetriaminopentaacetic acid (SEDA-2, 376).

Dipyridamole-^{201}thallium imaging has been used to assess cases of suspected coronary disease (SEDA-15, 506) (SEDA-16, 537) (SEDA-17, 539). It is difficult to distinguish the adverse effects of dipyridamole from those of the pharmaceutical agent (dipyridamole-^{201}thallium), since dipyridamole can cause bronchospasm. In one series of 400 examinations, there was severe chest pain due to myocardial ischemia in 9% of cases, milder chest pain (probably not associated with cardiac events) in 21%, and severe hypotension in 2.5% (10). Others have reported instances of cardiovascular collapse (SEDA-15, 506).

Second-Generation Effects

Lactation

Many radiopharmaceuticals are excreted in breast milk, and two reviews have discussed the implications of nuclear medicine examinations in the nursing mother (11,12).

Iodides are excreted in high concentrations in breast milk. The use of the short half-life ^{123}I in preference to ^{131}I partly overcomes this problem, but iodide or perchlorate, which is used to block thyroid uptake in the mother can be excreted in the milk. Likewise, furosemide or cholecystokinin, which can be used to alter the distribution of radiopharmaceuticals, can be excreted in breast milk.

Technetium compounds are the most widely used radiopharmaceuticals; the highest excretion in breast milk occurs with sodium pertechnetate and the lowest with technetium diethylenetriaminepenta-acetic acid, which is rapidly excreted by the kidneys. Depending on the type of examination and the dose of radiopharmaceutical, the mother should be advised to withhold breastfeeding for 12–24 hours. Advice may also be required concerning external radiation when the mother holds the child.

Before deciding to perform nuclear medicine tests in young women, it is important to consider the possibility of future lactation. Only essential investigations should be performed: the most appropriate radiopharmaceutical should be selected, and the dose reduced to the minimum compatible with obtaining a diagnostic result. According to the radiopharmaceutical in question, interruption of breastfeeding may be necessary. Breastfeeding is contraindicated for ^{201}thallium chloride, ^{67}gallium citrate, ^{131}iodide, ^{75}selenomethionine, and ^{125}I fibrinogen (13).

Drug–Drug Interactions

Heparin

The use of heparinized catheters for in vivo erythrocyte labelling with ^{99m}Tc-pyrophosphate occasionally produces adverse reports, such as diminution of cardiac activity and increase of renal activity due to the formation of a technetium-heparin complex which localizes avidly in the kidneys. A few cases reported the possibility of reaction of radiopharmaceuticals with the components of a syringe or needle.

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Drugs that interfere with the radiolabeling of blood cells

There is evidence that some drugs can adversely affect the radiolabeling of leukocytes. In a survey for the years 1981–97 of instances of unusually low labelling efficiencies of leukocytes labelled with ^{111}In-tropolone and ^{99m}Tc-HMPAO, respondents were asked to ascertain which drugs were being taken on the day of the test (14). Fifty adverse reports were received during that period. Many patients were taking drugs that are known to affect leukocyte function, including azathioprine, cephalosporins, cyclophosphamide, heparin, iron salts, nifedipine, prednisolone, and sulfasalazine. The author used Bradford–Hill's criteria (15) to assess whether the association between two variables was also one of causation, and thought that there was a high probability that these drugs had caused the low labeling efficiency.

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Raloxifene

General Information

Raloxifene is a non-steroidal so-called "selective estrogen receptor modulator" (SERM), that is it binds to estrogen receptors, but this binding produces agonist effects at some sites and antagonist effects at others (1). It has estrogen agonist effects on bone and lipid metabolism but estrogen antagonist effects on the breast and endometrium; it is also claimed by its protagonists to have cardioprotective effects, perhaps through an effect on endothelial cells and a reduction in homocysteine concentrations (2).

Reports of adverse reactions to raloxifene should be considered alongside those reported for tamoxifen and other anti-estrogens. However, earlier reports have pointed to a considerable increase in thromboembolism, as has some recent large-scale work (3), and it would be premature to draw final conclusions about the conditions in which it can safely be used.

Raloxifene has been studied for its ability to reduce bone loss in postmenopausal women (4). Some specialized SERMs could reduce the risk of osteoporosis after the menopause without having other troublesome hormonal effects (5), but much more work is needed to determine whether they will fulfill this hope.

In a critical review of raloxifene, published in France, it was concluded that the compound has no advantages compared with a traditional estrogen, and that in view of certain findings in animal studies there is a possibility that it might increase the risk of ovarian cancer; there is also a need to determine whether it is sufficiently safe in women with a history of (or predisposition to) breast cancer (6).

One also finds a critical view expressed in the USA, where a survey of the literature up to the end of 1999 concluded that while raloxifene might carry a lesser risk of breast cancer than estrogen replacement therapy, it was also less effective in maintaining bone density, and that as regards cardiovascular risk the estrogenic treatment produced a more favorable outcome (7).

The use and adverse effects of raloxifene have been reviewed (8–10). Many centers continue to examine this and other SERMs, for example in countering menopausal bone loss (11), in the hope that they can take the place of tamoxifen and provide a means of avoiding the risks of such complications as endometrial cancer, cataract, and stroke (12–14).

Organs and Systems

Cardiovascular

In one published study there was a two- to three-fold rise in the incidence of thromboembolism, similar to that seen

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with estrogen treatment. There were also some cases of leg cramps and hot flushes (15).

There have been conflicting reports on the incidence and severity of symptoms such as hot flushes (also known as hot flashes) during long-term treatment with raloxifene for the prevention of osteoporosis. In fact the difference between raloxifene and placebo does not seem to be very great. In a review of three identical randomized trials in which raloxifene 60 mg was given for long periods to healthy postmenopausal women of various ages it was concluded that after 30 months the cumulative incidence of hot flushes was 21% for placebo and 28% for raloxifene, but the difference in frequency was confined to the first 6 months of therapy (16). There was no difference between placebo and raloxifene in the maximum severity of symptoms or the rate of early discontinuation, while the period during which hot flushes continued was only a little shorter in the raloxifene group. In a US study in more than 1100 postmenopausal women who took raloxifene 30–150 mg/day the only significant adverse effect of therapy was hot flushes (25% with 60 mg/day and 18% in the placebo group) (17).

Metabolism

LDL cholesterol and total cholesterol concentrations fell significantly in women taking raloxifene compared with placebo, but there was no change in HDL cholesterol or triglyceride concentrations, nor was endometrial thickness affected; the incidence of vaginal bleeding was not increased (18).

Reproductive system

Several sources have suggested that raloxifene can on occasion either cause uterine endometrial polyps or cause pre-existent polyps to enlarge considerably (19).

Drug–Drug Interactions

Warfarin

To assess the potential for an interaction between raloxifene and warfarin, 15 healthy postmenopausal women each received single doses of warfarin 20 mg before and during 2 weeks of dosing with raloxifene 120 mg/day (20). Raloxifene reduced the oral clearance of *R*- and *S*-warfarin respectively by 7.1 and 14% and the oral volume of distribution by 7.4 and 9.8%. Raloxifene reduced the maximum prothrombin time by 10% and the area under the prothrombin versus time curve from 0–120 hours by an average of 8%. The authors concluded that raloxifene may produce a small increase in systemic warfarin exposure but a reduced pharmacodynamic effect. Since the effects are slight this interaction is unlikely to have clinical consequences.

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Raltitrexed

See also Cytostatic and immunosuppressant drugs

General Information

Raltitrexed is a specific inhibitor of thymidylate synthase. It is used to treat colorectal cancers.

In about 1000 patients with advanced colorectal cancer, the dose-limiting toxic effects in phase 1 studies were gastrointestinal toxicity, myelosuppression, and weakness; adverse events during phase 2 and 3 studies were similar to those seen during phase 1 (1). In all comparative studies, mucositis and leukopenia were markedly less common and less severe in patients treated with raltitrexed than with bolus fluorouracil + leucovorin. Thrombocytopenia was more common with raltitrexed but it was not associated with an increase in clinically significant hemorrhage. In contrast, raltitrexed-related myelosuppression was more severe than with fluorouracil + leucovorin when the antimetabolite was given by continuous infusion. Raised transaminases were common with raltitrexed but were usually reversible with continued dosing and were not associated with clinical sequelae.

Organs and Systems

Hematologic

In 21 patients with advanced colorectal cancer, intravenous raltitrexed 3 mg/m^2 plus mitomycin 6 mg/m^2 was associated with WHO grade 3/4 anemia in 2, and neutropenia and thrombocytopenia in one each (2).

Liver

Raltitrexed-induced hepatotoxicity is usually characterized by a transient and self-limiting increase in transaminases. However, it can occasionally be fatal.

- A woman aged 76 years and a man aged 56 years were given raltitrexed as adjuvant treatment of colorectal carcinoma and as palliative therapy for advanced biliary carcinoma respectively (3). Both developed fulminant liver failure with rapid deterioration after the second and sixth cycles of chemotherapy respectively, and both died within 24 hours. Autopsy showed signs of acute necrosis involving roughly 50% of the liver without signs of subacute liver damage.

In 130 patients treated with raltitrexed 3 mg/m^2 ($n = 52$) or raltitrexed plus oxaliplatin ($n = 78$), of whom 78 had liver metastases and 25 had raised transaminases, hepatotoxicity caused delays of a week or more in 60 of 584 chemotherapy cycles and was the reason for withdrawal of chemotherapy in eight patients (4). Raised baseline transaminases, the number of chemotherapy cycles, the cumulative dose of raltitrexed, short intervals between courses, and the addition of oxaliplatin predicted hepatotoxicity, while sex, age, creatinine clearance, previous chemotherapy, and the presence of liver metastases did not. Whether glutathione and ademethionine are hepatoprotective is unclear.

Skin

Two patients, aged 75 and 65 years, were given raltitrexed for colorectal cancers. After 5 and 7 days they developed erythematous, edematous, and purpuric skin reactions associated with weakness, diarrhea, and moderate fever (5). The lesions were painful and pseudocellulitic. They were generalized in the first case and localized to the legs in the second. They subsided 15 days after drug withdrawal.

Immunologic

Of 52 patients with colorectal cancer treated with a median of six 3-weekly cycles of raltitrexed 1.5–3.0 mg/m^2 combined with oral carmofur 300–400 mg/m^2 on cycle days 2–14, 39 had a fever on days 2–9 after receiving raltitrexed, 49 had fatigue, and 49 had a raised serum C-reactive protein concentration without a documented infection (6). Median concentrations of C-reactive protein, interleukin-6, interleukin-8, and tumor necrosis factor-alfa were higher 7 days after raltitrexed or raltitrexed + carmofur than at baseline. The authors suggested that patients with colorectal cancer treated with raltitrexed may develop drug-related systemic inflammation, which may be difficult to distinguish from infection.

Susceptibility Factors

Age

Of 90 patients treated with raltitrexed 3 mg/m^2 every 3 weeks, of whom 50 were aged over 70 years, 437 cycles of chemotherapy were administered and grade 3–4 toxicity was reported in under 10% (7). There were no significant differences between younger and older patients, apart from grade 3–4 weakness, which was reported by three of the older patients and none of the younger. This was despite a significantly lower calculated mean creatinine clearance in the older patients.

Renal disease

The pharmacokinetics of raltitrexed, and hence its toxic effects, particularly on the bone marrow and gut, are directly related to creatinine clearance (8). It is recommended that the dose be reduced and dosage interval increased in patients with mild to moderate renal impairment, based on the fact that raltitrexed is mainly excreted unchanged in the urine.

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Ramipril

See also Angiotensin converting enzyme inhibitors

General Information

Ramipril is an ACE inhibitor, a prodrug that is rapidly hydrolysed after absorption to its active metabolite ramiprilat. It has been used in patients with hypertension, heart failure, and myocardial infraction.

Organs and Systems

Metabolism

Hypoglycemia has been attributed to several drugs in a complicated sequence of effects (1).

- A 64-year-old man with type II diabetes, hypertension, and bilateral renal artery stenosis presented with confusion and dysarthria related to profound hypoglycemia (2.2 mmol/l). He was taking naproxen 500 mg bd, ramipril 2.5 mg/day, glibenclamide 2.5 mg bd, metformin 850 mg bd, a thiazide diuretic, terazosin, ranitidine, paracetamol, and codeine. His plasma creatinine concentration, previously 185 μmol/l, was 362 μmol/l and it fell to 210 μmol/l after the withdrawal of ramipril and naproxen.

The authors discussed the possible role of renal insufficiency, resulting from co-prescription of naproxen and ramipril in the presence of volume depletion, which may have increased the risk of hypoglycemia related to glibenclamide plus metformin.

Gastrointestinal

Two cases of severe vomiting, dyspepsia, and headache, with falls in body weight and plasma albumin, have been reported in patients on chronic peritoneal dialysis (2). Both occurred a few days after they started to take ramipril (dose not reported) and totally resolved after withdrawal. Both patients subsequently took losartan, which was well tolerated. This led the authors to suggest that the mechanism was mediated by bradykinin and/or prostaglandins, through an interaction with gastrointestinal motility, which may also be affected by peritoneal dialysis.

Diarrhea is a recognized infrequent adverse effect of ACE inhibitors. A convincing case of diarrhea associated with ramipril has been reported (3).

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Ranitidine

See also Histamine H_2-receptor antagonists

General Information

Ranitidine is a histamine H_2 receptor antagonist. Compared with cimetidine, it inhibits hepatic metabolism of other substances only to a very slight extent and is not anti-androgenic. In most other respects it is similar to cimetidine.

Comparative studies

Effervescent ranitidine 150 mg bd has been compared with as-needed calcium carbonate antacids 750 mg in a randomized study in 115 subjects who frequently self-treated heartburn (1). Effervescent ranitidine was significantly more effective than antacids in reducing heartburn, healing erosive esophagitis, alleviating pain, and improving quality of life. The overall incidences of adverse events were not significantly different in the two groups; 12% in the antacid group and 3% in the ranitidine group had adverse events related to the gastrointestinal system: nausea, vomiting, diarrhea, constipation, gas, fecal incontinence; and 1% in the antacid group and 4% in the ranitidine group had adverse events related to the central nervous system: headache, dizziness, insomnia, malaise, fatigue, weakness, nervousness.

Placebo-controlled studies

The efficacy of low-dose ranitidine for the relief of heartburn has been studied in a double-blind, placebo-controlled trial (2). Subjects with heartburn were

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randomized to ranitidine 75 mg ($n = 491$), ranitidine 25 mg ($n = 504$), or placebo ($n = 494$), to be taken as needed up to four times a day for 2 weeks. Ranitidine 75 mg was significantly more effective than placebo and provided prompt relief of heartburn lasting up to 12 hours. The most common adverse effects were nausea, diarrhea, and headache, which occurred in under 2% of patients in each group.

In a randomized, placebo-controlled, four-way, crossover study of the effects of low-dose ranitidine and an antacid on meal-induced heartburn and acidity in 26 subjects, ranitidine 75 mg significantly reduced gastric but not esophageal acidity, calcium carbonate 420 mg significantly reduced esophageal but not gastric acidity, and ranitidine plus calcium carbonate reduced both esophageal and gastric acidity (3). Both drugs given alone reduced heartburn severity compared with placebo.

Organs and Systems

Cardiovascular

Atrioventricular block has been attributed to ranitidine (4).

- A 20-year-old man taking ranitidine 300 mg/day had a brief episode of syncope. The only abnormal finding was first-degree atrioventricular block, which disappeared after withdrawal of ranitidine. Rechallenges on two separate occasions produced recurrence of asymptomatic first-degree atrioventricular block, but cimetidine 400–800 mg/day and famotidine 40–80 mg/day caused no electrocardiographic abnormalities.

The authors hypothesized that this patient may have been abnormally susceptible to the cholinergic or cholinergic-like effect of ranitidine, unrelated to its histamine H_2 blocking action. However, the ability of ranitidine to release histamine may also have contributed.

Bradycardia occurred in a 4-day-old full-term male neonate 2 hours after the intravenous injection of ranitidine and resolved over 24 hours (5).

Respiratory

H_2 receptor antagonists can increase the risk of respiratory infections, and the possible significance of this effect has been studied best with ranitidine; there seems to be no reason for concern in most patients, but the risk can be considerable in some older patients with pre-existing health problems rendering them unduly susceptible to infection (SEDA-18, 372).

Nervous system

Chorea has been reported occasionally with ranitidine (6). Headache and lethargy have been described in a neonate (SEDA-18, 372).

Psychological, psychiatric

Depression has been estimated to occur in 1–5% of patients taking ranitidine (SEDA-17, 418) (7).

Occasional confusion and behavioral disturbances have been attributed to ranitidine (8–10).

Hematologic

Pancytopenia and agranulocytosis have been documented with ranitidine (11).

Liver

There seem to be individuals with a metabolic idiosyncrasy who develop serious but probably fully reversible liver damage when exposed to ranitidine. The Netherlands Centre for Monitoring of Adverse Reactions has published data on six cases, in most of which other causal factors could be excluded (12), and a fatal case of liver injury has been reported from France (SEDA-16, 422).

Cholestatic liver damage due to ranitidine has been reported (13).

- A 29-year-old man developed cholestasis (confirmed histologically) having taken ranitidine 150 mg bd for about 2 weeks. The drug was withdrawn and he was treated with glucocorticoids and ursodeoxycholic acid. Three months later he had recovered completely. Rechallenge was not attempted.
- Cholestatic jaundice has been reported in a 73-year-old woman who had taken ranitidine 150 mg bd (14). She developed pruritus 4 days after starting to take the drug and jaundice after 3 weeks. Her liver function tests returned to normal 50 days after ranitidine was withdrawn.

Hepatitis associated with ranitidine is rare.

- Drug hypersensitivity hepatitis with progression to fulminant hepatic failure and death has been reported in a previously healthy 66-year-old woman who had taken ranitidine for 14 days before the onset of jaundice and for 5 days after hepatitis was diagnosed (15).
- A 45-year-old woman with multiple sclerosis developed severe liver injury after taking ranitidine 300 mg/day (16).

Pancreas

In one case where pancreatitis occurred without identifiable cause other than ranitidine, it was confirmed by rechallenge on two occasions (SEDA-16, 422).

Urinary tract

As with cimetidine, acute interstitial nephritis has been documented in a few cases (17).

- Acute interstitial nephritis in a cadaveric renal allograft occurred in a 44-year-old man who had taken ranitidine 150 mg bd for 2 days (18). Allograft function improved rapidly and returned to normal after ranitidine was withdrawn.

Skin

- Stevens–Johnson syndrome has been reported in two patients, a 62-year-old woman and a 58-year-old man, with severe liver disease and jaundice, who had taken ranitidine 150 mg bd; both recovered on withdrawal (19).

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Persistent UVB photosensitivity due to ranitidine (300 mg/day) has been reported (20).

Sexual function

Several cases of impotence have been described in patients taking ranitidine, strongly suggesting that this is an effect that all H_2 receptor antagonists can have on occasion (21).

Long-Term Effects

Tumorigenicity

- A gastric carcinoid tumor was found in a man of 62 taking ranitidine (22). The dosage had been unusually high and there was pre-existing chronic renal insufficiency as well as diabetes, but the tumor was similar in type to that seen in animals; it was successfully removed by partial gastrectomy and did not recur.

Susceptibility Factors

Age

The pharmacokinetics and pharmacodynamics of a single dose of ranitidine 75 mg have been evaluated in a randomized, double-blind, placebo-controlled trial in 29 children aged 4–11 years with gastro-esophageal reflux disease (23). Ranitidine significantly increased the intragastric pH in children, and the pharmacokinetics and pharmacodynamics were similar to those in adults. The drug was effective in the control of intragastric acidity for 5–6 hours. Adverse effects were reported only in children taking ranitidine, and included nausea, vomiting, abdominal pain, dizziness, intermittent headache, and lightheadedness.

Renal disease

In renal impairment, the risk of adverse reactions with intravenous ranitidine is doubled (SEDA-18, 371).

Drug Administration

Drug dosage regimens

Different doses of ranitidine (150 mg bd and 300 mg bd for 8 weeks) have been compared in resolving heartburn in 271 patients with gastro-esophageal reflux disease who had been symptomatic after 6 weeks of therapy with ranitidine 150 mg bd (24). Less than 20% of the patients in either group had complete resolution of heartburn at 4 and 8 weeks; there was no significant difference in the efficacy between the two treatment groups. At least one adverse event was reported by 38% of the patients in each group. They included sinusitis, nausea, abdominal pain, dyspepsia, constipation, and increased liver enzymes.

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Ranunculaceae

See also Herbal medicines

General Information

The genera in the family of Ranunculaceae (Table 1) include anemone, buttercup, columbine, hellebore, larkspur, marsh marigold, and pasque flower.

Aconitum species

Species of aconite contain a variety of diterpene alkaloids; *Aconitum napellus* (monkshood) contains isonapelline, luciculine, and napelline.

Adverse effects

Aconite roots can produce serious heart failure. Among the other symptoms of aconite poisoning are numbing of mouth and tongue, gastrointestinal disturbances, muscular weakness, incoordination, and vertigo (1). A review from Hong Kong reported 17 cases of aconite poisoning after the administration of Chinese herbal mixtures. The toxicity of raw aconite can be reduced substantially by decoction, as this process leads to a change in alkaloid composition (2).

Table 1 The genera of Ranunculaceae

Aconitum (monkshood)
Actaea (baneberry)
Adonis (pheasant's eye)
Anemone (anemone)
Aquilegia (columbine)
Caltha (marsh marigold)
Ceratocephala (curveseed butterwort)
Cimicifuga (bugbane)
Clematis (leather flower)
Consolida (knight's-spur)
Coptis (gold thread)
Delphinium (larkspur)
Enemion (false rue anemone)
Eranthis (eranthis)
Helleborus (hellebore)
Hepatica (hepatica)
Hydrastis (hydrastis)
Kumlienia (false buttercup)
Myosurus (mousetail)
Nigella (nigella)
Pulsatilla (pasque flower)
Ranunculus (buttercup)
Thalictrum (meadow rue)
Trautvetteria (bugbane)
Trollius (globe flower)
Xanthorhiza (yellow root)

Cimicifuga racemosa

Cimicifuga racemosa (black bugbane, black cohosh, black snakeroot, rattleroot, rattletop, rattleweed) contains a variety of cycloartane triterpene glycosides, some of which have cytotoxic effects (3).

Cimicifuga racemosa has been used to relieve symptoms of menopause, although with little evidence of efficacy (4).

Adverse effects

Liver damage has been attributed to black cohosh, which contains diterpenoids that cause liver damage in animals, either via reactive metabolites or by an autoimmune mechanism. However, causality was not demonstrated beyond reasonable doubt.

- A 47-year-old woman took an extract of *C. racemosa* for 1 week to treat menopausal symptoms; she developed jaundice and raised liver enzymes (5). No other causes of liver damage were found. She required liver transplantation.

Delphinium species

Delphinium species contain complex diterpenoid alkaloids that cause acute intoxication and death in cattle (6). The alkaloids and their concentrations vary with the species and plant part involved, which causes variability in toxicity. In *Delphinium consolida* (larkspur) there are toxic alkaloids in the non-medicinal plant parts (root, seed, herb), but they are purportedly absent in the medicinal part (the flower).

Hydrastis canadensis

The root of *Hydrastis canadensis* (golden seal) contains isoquinoline alkaloids, including the quaternary base berberine and the tertiary base hydrastine. As the latter can stimulate uterine contractions, it is prudent to avoid golden seal root during pregnancy, even though the actual risk of premature labor still has to be verified.

Adverse effects

In man berberine has positive inotropic, negative chronotropic, antidysrhythmic, and vasodilator properties (7).

Cardiovascular

There is experimental evidence that berberine can cause arterial hypotension (8,9).

Nervous system

Berberine displaces bilirubin from albumin and there is therefore a risk of kernicterus in jaundiced neonates (10).

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Gastrointestinal
In a study of the effect of berberine in acute watery diarrhea, oral doses of 400 mg were well tolerated, except for complaints about its bitter taste and a few instances of transient nausea and abdominal discomfort. However, patients with cholera given tetracycline plus berberine were more ill, suffered longer from diarrhea, and required larger volumes of intravenous fluid than those given tetracycline alone (11).

Skin

- A 32-year-old woman had a phototoxic reaction after taking a dietary supplement containing ginseng, golden seal, bee pollen, and other ingredients (12). She had a pruritic, erythematous rash, localized to the sun-exposed surfaces of her neck and limbs. She had no significant past medical history and was not taking any other medications. The skin rash slowly resolved after withdrawal of the supplement and treatment with subcutaneous and topical glucocorticoids.

Although the individual ingredients in this dietary supplement have not been associated with cases of photosensitivity, it is possible that the combination of ingredients may have interacted to cause this effect.

Drug interactions
Golden seal root inhibits various isoforms of cytochrome P450, including CYP3A4 (13). However, in a crossover study, goldenseal root (1140 mg bd for 14 days) had no effect on the pharmacokinetics of a single oral dose of indinavir 800 mg (14).

Pulsatilla species

Pulsatilla (pasque flower) species are widely used in homeopathic medicine. Some of them contain podophyllotoxins. High doses of *Pulsatilla vulgaris* (meadow windflower) can irritate the kidneys and urinary tract. Pregnancy is a contraindication.

Ranunculus damascenus

Ranunculus damascenus (buttercup) is used topically for abscess drainage, hemorrhoids, and burns.

Adverse effects
Ranunculus damascenus has been reported to cause skin damage (15).

- A 45-year-old Turkish woman developed open wounds on the abdomen, right knee, and neck. She had used buttercup topically and orally for pain relief. She was treated with antibiotics and adequate wound care. Complete healing was achieved within 10 days.

The authors argued that protoanemonin, a constituent of *R. damascenus*, which inhibits mitosis in plants, had caused this severe reaction.

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Rapacuronium

See also Neuromuscular blocking drugs

General Information

Rapacuronium, an aminosteroid non-depolarizing neuromuscular blocking agent with a rapid onset and a comparatively short duration of action (1,2), was withdrawn from the US market in March 2001 and subsequently worldwide. The manufacturers informed the FDA in an open letter about postmarketing reports of severe bronchospasm and some deaths of unknown origin associated with rapacuronium. The severity of the incidents recently reported to the manufacturers was impressive enough to cause fears about patient safety. This event highlights the need for continued surveillance, not only during clinical trials but also during the routine use of approved drugs.

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Organs and Systems

Cardiovascular

A major adverse effect of rapacuronium is an increase in heart rate (3). Plasma histamine concentrations may increase after rapacuronium injection, but this was not correlated with changes in blood pressure or heart rate (4).

Respiratory

In a study of the effects of rapacuronium on respiratory function, performed while rapacuronium was still on the market in the USA, the authors observed statistically significant reductions in peak inspiratory flow rate, peak expiratory flow rate, and dynamic compliance, and increases in peak inflating pressure when rapacuronium 1.5 mg/kg was given under steady-state conditions to patients who were already anesthetized, intubated, and ventilated (5). In five of the 10 patients these changes amounted to more than 25% from baseline and were considered clinically relevant. As rapacuronium is no longer available this has no direct clinical impact. However, while discussing the mechanisms of rapacuronium-induced bronchospasm the authors speculated that differential effects of the drug on several subtypes of muscarinic acetylcholine receptors might be responsible. As raised histamine concentrations were not found in seven patients with rapacuronium-induced bronchospasm in another study (4), they reckoned that histamine release was an unlikely explanation. Referring to the observation that pipecuronium, another non-steroidal muscle relaxant, blocked pilocarpine-stimulated prejunctional M_2 receptors in vitro (6), they suggested that a similar effect might result in rapacuronium-induced bronchospasm. Prejunctional M_2 receptors are thought to have a role in negative feedback and inhibition of further acetylcholine release, thereby reducing smooth muscle relaxation. These aspects will need to be taken into account when new substances are considered for clinical use.

Second-Generation Effects

Pregnancy

Some controversy has been raised by the use of rapacuronium for rapid sequence induction in elective cesarean section (7). The authors reported that intubating conditions 60 seconds after rapacuronium 2.5 mg/kg were comparable with those after suxamethonium 1.5 mg. The percentage of the drug that crossed the placenta to the fetus was low (umbilical/maternal vein concentration ratio 0.088) compared with other non-depolarizing agents, and there were no adverse effects on the fetus. Others, however, would not use rapacuronium or other non-depolarizing agents for cesarean section, referring to the longer duration of action, which might be a problem in cases of failed intubation (8). Rapid sequence induction with thiopental plus suxamethonium is still standard for cesarean section. Rapacuronium should be considered for cesarean section only in patients in whom suxamethonium is contraindicated. In such cases, induction with propofol plus alfentanil without a neuromuscular blocking agent may be an alternative, which still awaits evaluation with regard to maternal and fetal safety.

Susceptibility Factors

Renal disease

Rapacuronium plasma clearance was reduced in patients with renal insufficiency, but this did not result in an increased duration of action (9).

Hepatic disease

Although not completely understood, hepatic uptake is assumed to be the reason for the short duration of action of rapacuronium. However, neither recovery time nor drug half-life after a single bolus of rapacuronium was prolonged in patients with liver cirrhosis compared with healthy controls (10).

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Ravuconazole

See also Antifungal azoles

General Information

Ravuconazole is similar in structure to fluconazole. It has a long half-life suitable for once-daily dosing.

The safety and efficacy of ravuconazole have been studied in a randomized, double-blind comparison with fluconazole in 71 patients with esophageal candidiasis; ravuconazole was as effective as fluconazole and there were no apparent differences in adverse effects (1,2).

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Reboxetine

See also Antidepressants, second-generation

General Information

Reboxetine is a selective noradrenaline re-uptake inhibitor with low affinity for α-adrenoceptors and muscarinic receptors. In controlled trials the following adverse events occurred significantly more often with reboxetine than with placebo: dry mouth (27%), constipation (17%), increased sweating (14%), insomnia (14%), urinary hesitancy (5%), impotence (5%), tachycardia (5%), and vertigo (2%) (SEDA-21, 13).

Organs and Systems

Electrolyte balance

Hyponatremia has been reported with reboxetine (1,2).

- A 72-year-old man with diabetes mellitus and cardiovascular disease developed major depression. He was taking aspirin (100 mg/day), enalapril (20 mg/day), and glibenclamide (5 mg/day). His serum sodium was 133 mmol/l (reference range 134–146 mmol/l). He started to take reboxetine (4 mg/day) and after 8 days experienced malaise and nausea, at which time his serum sodium had fallen to 118 mmol/l. The reboxetine was withdrawn, and both his symptoms and the low serum sodium remitted over the next 6 days. Rechallenge with reboxetine produced a recurrence of both the low sodium and the accompanying symptoms.

It appears that, like SSRIs, reboxetine can cause sodium depletion in elderly people. However, in this case the contributions of concomitant general medical illness and its treatment were uncertain.

Urinary tract

One of the adverse effects of reboxetine is difficulty in passing urine (SEDA-21, 13). Eight patients taking reboxetine (4–8 mg/day) had troublesome urinary hesitancy (3). They were successfully treated with tamsulosin (0.4 mg/day), and in two patients tamsulosin was withdrawn after 2 weeks without recurrence of the urinary symptoms. Reboxetine is a selective noradrenaline re-uptake inhibitor and may therefore produce urinary symptoms by activating α_1-adrenoceptors in the bladder, which tamsulosin would be expected to reverse. However, tamsulosin is also effective for urinary symptoms caused by other mechanisms, for example benign prostatic hyperplasia. Whether its apparent effectiveness in reboxetine-induced dysuria represents specific pharmacological antagonism is therefore uncertain.

Drug–Drug Interactions

Fluoxetine

In the pharmacological management of patients with treatment-resistant depression, it is a common strategy to combine a drug that selectively inhibits noradrenaline re-uptake (for example reboxetine) with one that selectively inhibits the re-uptake of serotonin (for example an SSRI). As well as the hoped-for pharmacodynamic interaction, a kinetic interaction can also occur, because of the effect of SSRIs on CYP450 enzymes. The effect of combined treatment with reboxetine (8 mg/day) and fluoxetine (20 mg/day) has been compared with each treatment given alone for 8 days in 30 healthy volunteers in a parallel design (4). There was no potentiation of adverse effects by the combination. Fluoxetine increased the plasma AUC of reboxetine by 20%, but this was not statistically significant. The authors suggested that the combination of fluoxetine and reboxetine should have minimal adverse impact in depressed patients. However, the major metabolite of fluoxetine, norfluoxetine, is also an inhibitor of CYP3A4 and would not have reached steady-state concentrations during the time of the study. This suggests that caution might still be needed during longer-term use of this combination in depressed patients.

Ketoconazole

Reboxetine is metabolized by CYP3A4. In 11 healthy volunteers ketoconazole, an inhibitor of CYP3A4, increased the plasma AUC of reboxetine by about 50% and prolonged the half-life (5). The adverse effects profile of reboxetine was not altered by ketoconazole, but the finding suggests that reboxetine should be used with caution in combination with drugs that inhibit CYP3A4, for example nefazodone and fluvoxamine.

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Remacemide

See also Antiepileptic drugs

General Information

Remacemide hydrochloride is a low-affinity, non-competitive *N*-methyl-D-aspartate (NMDA) channel blocker that has been used in epilepsy, Parkinson's disease, Huntington's chorea, and neuroprotection after stroke. Its pharmacology, clinical pharmacology, uses, and adverse effects and interactions have been reviewed (1,2).

The adverse effects of remacemide have been studied in 40 patients with refractory epilepsy randomized to placebo or ascending weekly doses of remacemide in a twice or four times a day regimen for up to 1 month (3). There were adverse events in 38 patients; the most common were dizziness, abdominal pain, headache, diplopia, fatigue, dyspepsia, and abnormal vision.

Observational studies

The efficacy of adjunctive therapy with remacemide has been evaluated in 11 children (4). Remacemide was well tolerated in doses up to 13.5 mg/kg/day. The most common adverse events were dizziness, ataxia, and gastrointestinal events. One patient died after a suspected seizure, which was unlikely to have been related to remacemide.

Placebo-controlled studies

The efficacy, safety, and pharmacokinetics of adjunctive remacemide have been investigated in a randomized, double-blind, placebo-controlled, crossover study in 28 adult patients with refractory epilepsy (5). The mean plasma carbamazepine concentration increased by about 15%. Three patients withdrew owing to adverse events (two remacemide, one placebo). Adverse events that occurred more often with remacemide than placebo included dyspepsia, dizziness, abnormal gait, diplopia, abnormal vision, somnolence, chest pain, and fatigue.

In a randomized, double-blind, placebo-controlled study of remacemide in 200 patients with early Parkinson's disease who were not yet taking levodopa or dopamine agonists, remacemide did not produce improvement in signs or symptoms (6). Significantly fewer patients taking remacemide 600 mg/day were able to tolerate 5 weeks of their assigned treatment on a twice-daily schedule compared with patients taking placebo (64 versus 94%). However, most patients who had intolerable adverse effects with the twice-daily schedule could tolerate the same daily dosage given in four parts during the day. The most common adverse events were dizziness and nausea. There were no serious adverse events or clinically significant treatment-related changes in vital signs, laboratory values, or electrocardiograms.

In a double-blind, randomized study of remacemide in 262 patients with partial seizures there was a trend for efficacy, but not significantly different from placebo (7). The most frequent adverse events were headache, fatigue, dizziness, diplopia, and somnolence. There were no significant changes in vital signs, electrocardiograms, or biochemistry. In another double-blind, placebo-controlled study in patients with refractory epilepsy undergoing in-patient video-electroencephalographic monitoring, the pattern of adverse events was similar (8).

Drug–Drug Interactions

Levodopa

Remacemide delays the absorption of levodopa and increases the concentrations of drugs that are metabolized by CYP3A4 (2).

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Remifentanil

General Information

Remifentanil is a pure OP_3 (μ) opioid receptor agonist with a very short duration of action. It therefore has to be given by continuous intravenous infusion and is used as a supplement to general anesthesia during induction and as an analgesic during maintenance of anesthesia. It has the familiar adverse effects of opioids: respiratory depression, sedation, nausea and vomiting, muscle rigidity, bradycardia, and pruritus. These are short-lived and are antagonized by naloxone. The onset of muscle rigidity and apnea can be alarmingly rapid. Bradycardia occurred more often with remifentanil than alfentanil in patients undergoing abdominal surgery and in children undergoing strabismus surgery; the oculocardiac response was more marked with remifentanil than alfentanil (1).

Drug studies

Pain relief

Three studies have focused on the analgesic use of remifentanil (2–4). In a double-blind, crossover, randomized study 20 healthy volunteers received an infusion of either remifentanil or saline (2). Thermal sensory testing of the heat pain threshold was performed every 5 minutes and the dose of remifentanil was increased by 0.01 micrograms/kg/minute every 5 minutes. Remifentanil produced a dose-dependent increase in the heat pain threshold, and a dose of 0.05 micrograms/kg/minute was suggested as an effective and safe increment in healthy volunteers. The rate of adverse effects (nausea, vomiting, and pruritus) was comparable with previous reports; there were no cardiovascular adverse effects.

General surgery

Mixtures of remifentanil and sevoflurane have been used in two prospective, open, randomized studies (5,6), which showed that adding remifentanil results in a reduced requirement for sevoflurane for maintenance of anesthesia, leading to faster and easier recovery.

In a double-blind, randomized study a continuous infusion of remifentanil (1 microgram/kg followed by 0.5 micrograms/kg/minute) was compared with alfentanil (25 micrograms/kg followed by 1 microgram/kg/minute) during anesthesia in patients undergoing major abdominal surgery (7). Both systolic pressure and heart rate were significantly lower with remifentanil, with a higher incidence of hypotension (53 versus 39%) and bradycardia (10 versus 3%).

Bronchoscopy

In a randomized study, remifentanil 0.5 micrograms/kg/minute was compared with fentanyl 2 micrograms/kg in 22 patients undergoing rigid bronchoscopy (8). The results suggested that remifentanil attenuated the hemodynamic response to bronchoscopy without significantly increasing the incidences of hypotension or bradycardia. Four patients given remifentanil developed ST segment depression compared with eight patients given fentanyl.

Colonoscopy

Remifentanil by infusion ($n = 49$) has been compared with titrated boluses of pethidine ($n = 51$) in a randomized, double-blind study in 100 patients undergoing outpatient colonoscopy (9). The incidences of tachycardia, hypotension, and nausea were significantly less with remifentanil than with pethidine, but there were higher anxiety and pain scores with remifentanil. However, the study was a comparison of two opioids with different pharmacokinetic profiles, which makes it very difficult to achieve equipotent doses for the purpose of comparison.

Lithotripsy

In two randomized, double-blind, controlled comparisons of anesthetic techniques for extracorporeal shock wave lithotripsy remifentanil infusion had no advantage over the combination of fentanyl bolus plus propofol infusion, but caused more adverse effects (nausea and vomiting) (10). In another study remifentanil infusion provided comparable analgesia and caused less respiratory depression and fewer gastrointestinal symptoms than intravenous boluses of sufentanil (11).

Cardiac surgery

In a prospective multicenter, double-blind, randomized study in 297 patients undergoing elective coronary artery bypass surgery, remifentanil infusion 1 microgram/kg/minute was compared with a loading dose of fentanyl 15 micrograms/kg (12). The most common adverse effects were nausea and vomiting, which occurred equally often in the two groups. Hypertension and shivering were significantly more common with remifentanil (12).

Obstetrics and gynecology

The role of remifentanil-based anesthesia in gynecological and obstetric procedures has been reviewed (13).

In a double-blind, randomized comparison of remifentanil (0.25/0.5 micrograms/kg/minute) and alfentanil (50 micrograms and 0.5 micrograms/kg/minute) in 35 patients undergoing total abdominal hysterectomy, remifentanil provided more stable analgesia during anesthesia but caused significantly more hypotension (14).

Orthopedic surgery

Intravenous remifentanil 0.3 micrograms/kg with propofol 2 micrograms/ml has been compared with propofol 2 micrograms/ml alone in a double-blind, randomized study in 86 day-case adults undergoing elective orthopedic surgery (15). The study was designed to assess whether remifentanil improves conditions for laryngeal mask airway insertion. Those given remifentanil had a better quality of airway patency, with minimal cardiorespiratory changes.

Orthopedic and urological surgery

The respiratory depressant and gastrointestinal adverse effects of remifentanil have been observed in a randomized, single-blind study of 125 patients undergoing elective orthopedic and urological surgery under spinal or brachial plexus anesthesia (16). They were randomized to either remifentanil (a bolus of 0.5 micrograms/kg plus an infusion of 0.1 micrograms/kg/minute) or propofol

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(a bolus of 500 micrograms/kg plus an infusion of 50 micrograms/kg/minute). Owing to a significantly higher rate of respiratory depression with remifentanil (46%) than with propofol (19%), the mean remifentanil infusion rate was reduced to 0.078 ± 0.028 micrograms/kg/minute. The incidence of intraoperative nausea and vomiting with remifentanil was 27% compared with 2% with propofol. Postoperatively there was no significant difference in the incidence of gastrointestinal symptoms. Remifentanil may be considered as an alternative if propofol is contraindicated (for example because of amnesic episodes).

Vascular surgery

In a double-blind, randomized, placebo-controlled study in 28 adults undergoing carotid endarterectomy, remifentanil provided adequate analgesia, and supplementary local anesthetics were not needed (17). The remifentanil infusion rate was as low as 0.04 micrograms/kg/minute and there were no episodes of respiratory depression or hemodynamic instability.

In 60 patients receiving cervical plexus block during carotid endarterectomy who were given either remifentanil 3 micrograms/kg/hour or propofol 1 mg/kg/hour there was a higher incidence of adverse respiratory effects with remifentanil and a similar sedative effect (18). The authors suggested that when using remifentanil for sedation in patients undergoing carotid endarterectomy, the initial dose of remifentanil should be reduced to 1.5–2 micrograms/kg/hour to minimize cardiovascular and respiratory adverse effects.

Ophthalmological surgery

The analgesic effects of remifentanil and alfentanil have been compared during ophthalmological nerve block in a randomized, double-blind, parallel-group study in 79 patients (19). Remifentanil (as a single dose of 1 microgram/kg or as a loading dose of 1 microgram/kg followed by an infusion of 0.2 micrograms/kg/minute) was more effective than alfentanil (as a single dose of 7 micrograms/kg). Of the patients given remifentanil, three had mild nausea and three had transient muscle rigidity that resolved spontaneously within 1 minute. There were no adverse effects of alfentanil. The authors suggested that remifentanil 1 microgram/kg given over 30 seconds is a useful alternative to alfentanil 7 micrograms/kg as an analgesic before ophthalmological nerve block.

Anesthesia in ischemic heart disease

In a prospective randomized comparison of combined sevoflurane plus remifentanil with combined fentanyl plus etomidate for induction of anesthesia in 10 patients with ischemic heart disease, 3 of the 20 patients given sevoflurane plus remifentanil developed severe bradycardia (heart rate less than 40) and one developed asystole, but the difference between the two groups did not reach statistical significance (20). Therefore, in patients with ischemic heart disease remifentanil should be used with caution, and concurrent administration of glycopyrrolate 0.2 mg is advisable to reduce the incidence of bradycardia, hypotension, or both, without increasing the heart rate.

Organs and Systems

Cardiovascular

Three groups of 20 women due to undergo elective surgery were recruited into a randomized, double-blind study (21). Group 1 received a bolus dose of remifentanil 1 microgram/kg and an infusion of remifentanil (0.5 micrograms/kg/minute); groups 2 and 3 received remifentanil 0.5 micrograms/kg and an infusion of 0.25 micrograms/kg/minute. Groups 1 and 2 received pretreatment with glycopyrrolate 200 micrograms whilst group 3 did not. Cardiovascular responses to laryngoscopy and orotracheal intubation were measured. There were no significant differences in the three groups, except that there was a significantly lower heart rate in group 3 after induction of anesthesia and after intubation.

The hemodynamic effects of bolus intravenous remifentanil 0.2, 0.33, and 1 microgram/kg/minute have been studied in patients scheduled for coronary artery bypass grafting (22). The study was terminated after only eight patients had been recruited, because of severe hypotension, bradycardia, and/or evidence of myocardial ischemia. The authors concluded that remifentanil should not be given as a bolus dose of 1 microgram/kg but as an infusion at a low rate. An editorial response to this article suggested that the hemodynamic instability reported may have resulted from other contributing factors, such as hypovolemia, impairment of venous return, or excessive anesthesia due to remifentanil toxicity (23).

In a prospective study in 12 men undergoing elective coronary artery bypass grafting, remifentanil 0.5 and 2.0 micrograms/kg/minute combined with propofol preserved hemodynamic stability and reduced myocardial blood flow and metabolism to a similar extent (24).

Asystole has been attributed to remifentanil (25).

- A 78-year-old man with laryngeal cancer developed asystole 1 minute after an intravenous bolus of remifentanil 0.5 micrograms/kg followed by a continuous infusion of 0.5 micrograms/kg/hour. The asystole was unresponsive to intravenous atropine 1 mg. The remifentanil infusion was stopped and cardiac sinus rhythm resumed after two precordial thumps.

The authors postulated that rapid-sequence induction of anesthesia with sevoflurane had blunted sympathetic tone and allowed uncompensated parasympathetic activation by remifentanil.

Remifentanil-induced bradycardia and asystole may be useful as a protective effect in patients with atrial fibrillation (26).

- A 90-year-old woman with atrial fibrillation was given digoxin for 3 days before surgery for a pelvic mass. Following anesthesia, induced with thiopental and atracurium, her heart rate rose to 105/minute and her electrocardiogram showed fast atrial fibrillation and ST segment depression. She was given remifentanil 0.25 micrograms/kg/minute and her heart rate fell to 95/minute.

Nervous system

Seizures have been attributed to remifentanil (27).

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- A 42-year-old woman asked for an intravenous opioid as analgesia during paracervical block and was given an intravenous infusion of remifentanil 1.0 microgram/kg/minute. After 3 minutes she became unresponsive, with upward deviation of gaze and tonic-clonic contractions of the arms. The infusion was discontinued and after another 3 minutes of generalized seizure activity she was given intravenous propofol 80 mg and intravenous suxamethonium 60 mg; she recovered completely 15 minutes later.

Psychological, psychiatric

In 201 patients scheduled for day-case surgery, those who received remifentanil had significantly fewer responses to surgical stimulation and had better psychomotor and psychometric function during the recovery period, although there was no significant difference in time to recovery room or hospital discharge (28).

Second-Generation Effects

Pregnancy

Six patients admitted at 36 weeks pregnancy with pre-eclampsia received patient-controlled intravenous analgesia with remifentanil for labor (3). Remifentanil was delivered as continuous background infusion of 0.05 micrograms/kg/minute and boluses of 25 micrograms with a 5-minute lockout period. The procedure did not cause adverse maternal or neonatal adverse effects and this small uncontrolled study suggests that patient-controlled intravenous analgesia with remifentanil might be an effective alternative when epidural analgesia is contraindicated.

In a dose-finding study in 17 healthy pregnant women in the first stage of labor, the PCA bolus of remifentanil was increased from 0.2 micrograms/kg in 0.2 micrograms/kg increments during 60 minutes until analgesia was considered adequate (29). The median effective dose of remifentanil was 0.4 (range 0.2–0.8) micrograms/kg and consumption was 0.066 (range 0.027–0.207) micrograms/kg/minute. All the women reported slight sedation; five had slight to moderate nausea throughout the study. Supplementary oxygen 2 l/minute via nasal cannula was given to three women who had repeated episodes of oxygen desaturation. Two women reported difficulties in reading and visual focusing and one woman had difficulty in swallowing toward the end of remifentanil administration. In five cases there were changes in fetal heart rate indices within 30 minutes of the first dose. The neonates had Apgar scores of 8–10. The authors concluded that remifentanil is a potentially effective obstetric analgesic but that adverse effects will limit its use.

A similar observation was made in an open pilot study in 36 women randomized during the early stages of labor to either intramuscular pethidine 100 mg or remifentanil given as patient-controlled analgesia (20-microgram bolus over 20 seconds) (30). Remifentanil provided better pain relief but a higher risk of lower oxygen saturation compared with pethidine. Remifentanil was given only a cautious welcome by the authors, owing to its respiratory depressant effects.

Susceptibility Factors

Age

In maintenance of anesthesia in 62 children vomiting occurred in 31% (31). However, the dose of remifentanil was twice the ED_{50} in adults and may have been much larger than required.

The effects of remifentanil on vomiting and the quality of emergence from anesthesia have been studied in children undergoing dental restoration and extraction (32). The children received desflurane with or without remifentanil 0.2 micrograms/kg/minute. The two groups did not differ in adverse effects profile or quality of recovery.

Seven randomized controlled trials and one descriptive trial using infused remifentanil as part of an anesthetic technique in children between 1997 and 2000 have been reviewed (33). The general consensus is that a bolus dose of remifentanil 0.5–1 microgram/kg appears to be well tolerated when it is given over at least 60 seconds. However, a loading dose is not required if the infusion can be started at least 10 minutes before the skin incision is made. Infusion rates of 0.25–0.5 micrograms/kg/minute provide hemodynamic stability when propofol or a volatile agent is also given. The authors advised that infants who receive remifentanil should be paralysed and mechanically ventilated, because of the possible risk of respiratory depression due to chest wall rigidity in non-paralysed patients.

Remifentanil is liable to cause respiratory depression in children (33,34), as well as muscle rigidity, hypotension, and bradycardia, without increasing the incidence of gastrointestinal symptoms (35).

The adverse effects profiles of remifentanil in neonates and infants undergoing pyloromyotomy have been investigated (36,37).

The hemodynamic responses, recovery profiles, and perioperative and postoperative respiratory patterns in 38 children given remifentanil plus nitrous oxide and 22 given halothane plus nitrous oxide have been studied in a multicenter, open, randomized comparison (36). There were no cases of bradycardia or dysrhythmias. There were hypertensive responses at the time of incision in 24% of those given remifentanil and 18% of those given halothane and vomiting in 34 and 45% respectively. None of those who were given remifentanil developed new-onset postoperative apnea compared with three of those who were given halothane. All other adverse effects had similar incidences in the two groups.

Remifentanil 0.1 micrograms/kg/minute by infusion was safe and efficacious in 55 patients (aged 2 months to 12 years) undergoing cardiac catheterization (38).

Drug Administration

Drug dosage regimens

In a double-blind, randomized study of 178 patients scheduled for major thoracic, intra-abdominal, and orthopedic surgery, a high dose of remifentanil (bolus dose of 1 microgram/kg followed by 1 microgram/kg/minute) was compared with a low dose (bolus dose 1 microgram/kg followed by 0.5 micrograms/kg/minute) (39). In this study, intraoperative hypotension (30% and 27% respectively)

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and bradycardia (9% and 7% respectively) were equally frequent in the two groups. The authors proposed that infusion rates of remifentanil over 0.4 micrograms/kg/minute provide satisfactory analgesia throughout surgery but can cause significant hypotension. Prolonged infusion of remifentanil for several hours of surgery does not delay recovery or cause respiratory depression.

The postoperative analgesic efficacy and safety of two continuous constant-dose intravenous remifentanil infusions have been investigated in a double-blind, randomized study in 30 patients scheduled to undergo elective abdominal or thoracic surgery (4). The patients were randomly assigned to intravenous remifentanil 0.05 micrograms/kg/minute or 0.1 micrograms/kg/minute. There were no cases of respiratory depression, and nausea and vomiting occurred in one patient in each group. There was adequate analgesia in 75% and 78% of the patients in the low-dose and high-dose groups respectively and pethidine rescue analgesia was required in 26% and 6% respectively. Remifentanil 0.1 micrograms/kg/minute was therefore effective and safe for postoperative pain.

Drug overdose

A nurse was found dead at home with a syringe and empty vials of remifentanil (2 mg) and midazolam (1 mg/ml); toxicological studies showed that she had not been a chronic user of remifentanil (40).

Drug–Drug Interactions

Propofol

In eight subjects the concentration of remifentanil was significantly increased when therapeutic concentrations of propofol were present in the body (41). The combination of propofol and remifentanil can cause cardiovascular depression. As with other opioids, remifentanil competes with propofol for hydrophobic binding in the lungs and heart.

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Repirinast

General Information

Repirinast is an antiallergic prodrug whose active metabolite has a stabilizing action on mast cells that resembles that of sodium cromoglicate (1).

When repirinast was given to 56 asthmatic patients for 6 months, it was effective in 47% and moderately effective in 81%. Two patients complained of sleepiness, but repirinast was continued with or without dosage reduction (SEDA-17, 205).

Organs and Systems

Skin

Solar urticaria has been attributed to repirinast in a 72-year-old woman who had taken it for 20 months (2). She developed urticaria immediately after irradiation with 1.5 J/cm^2 of UVA, and a provocation test confirmed that repirinast was responsible for the urticarial reaction, with a spectrum of 320–350 nm.

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Reserpine

General Information

The Rauwolfia alkaloids, including reserpine, are now little used. They act by depleting neurotransmitter stores of catecholamines and reducing sympathetic nervous activity, but their effects are non-specific, and nervous system adverse effects (depression, drowsiness, tiredness, confusion) are prominent. There is also a troublesome incidence of diarrhea, hyperprolactinemia, gynecomastia, and a possible withdrawal syndrome.

Organs and Systems

Psychological, psychiatric

Depression is a very common adverse effect of reserpine (SED-9, 328) (1).

- A 66-year-old woman was admitted to hospital suffering from an agitated depressive psychosis. This settled with standard antipsychotic therapy. It was subsequently found that she had been taking reserpine in an over-the-counter formulation and had

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stopped this a week before her admission (2). Her doctor felt that the syndrome had occurred as a result of nervous system hypersensitivity after reserpine withdrawal.

Endocrine

In women reserpine causes a small increase in circulating concentrations of prolactin (3), which could be related to the small increase in the risk of breast cancer. In 27 hypertensive men reserpine 0.25 mg/day for 3 months had no effect on testosterone, dihydrotestosterone, estradiol, luteinizing hormone, or prolactin (4).

Long-Term Effects

Drug withdrawal

Acute psychosis has been reported after the withdrawal of reserpine (2,5). During long-term therapy in animals reserpine causes denervation sensitivity to dopamine in the basal ganglia and chemotactic trigger zone in man and to catecholaminergic agents in the basal ganglia and mesolimbic system; withdrawal could lead to rebound supersensitivity of these systems to endogenous catecholamines, causing the reported symptoms.

Tumorigenicity

Early retrospective studies suggested that reserpine was associated with breast cancer, but prospective studies and meta-analyses of case-control studies have shown only a weak association (6). In vitro studies have shown that rauwolfia alkaloids are not genotoxic or mutagenic (7).

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Resorcinol

General Information

Resorcinol, which was formerly used to treat leg ulcers, is nowadays mainly used in the treatment of acne vulgaris as a peeling agent. In the older literature (1), several cases of systemic toxicity from percutaneous absorption were reported and there were deaths (2). The use of resorcinol in the treatment of acne is considered safe (SEDA-9, 142).

Signs and symptoms of resorcinol intoxication (1,2) include:

- pallor, dizziness, cold sweat, collapse, cyanosis;
- tremor;
- hypothyroidism;
- methemoglobinemia, hemolytic anemia;
- hemoglobinuria, violet-black urine;
- maculopapular eruptions;
- ochronosis.

Organs and Systems

Immunologic

Systemic allergic reactions have been reported in eight patients after topical application of a wart formulation containing resorcinol (3). All developed a marked eczematous, sometimes bullous reaction, localized to the site of application; in four cases there were generalized urticaria and angioedema, in one pompholyx eczema, and in three generalized eczema with pompholyx. In all cases there were positive patch tests with resorcinol.

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Rhamnaceae

See also Herbal medicines

General Information

The genera in the family of Rhamnaceae (Table 1) include buckthorn and jujube.

Rhamnus purshianus

The bark of *Rhamnus purshiana* (cascara sagrada) contains laxative anthranoid derivatives, which occur primarily in various laxative herbs (such as aloe, cascara sagrada,

Table 1 The genera of Rhamnaceae

Adolphia (prickbush)
Alphitonia (alphitonia)
Auerodendron (auerodendron)
Berchemia (supplejack)
Ceanothus (ceanothus)
Colubrina (nakedwood)
Condalia (snakewood)
Frangula (buckthorn)
Gouania (chewstick)
Hovenia (hovenia)
Karwinskia (karwinskia)
Krugiodendron (krugiodendron)
Maesopsis (umbrella-tree)
Paliurus (Jeruselem thorn)
Reynosia (darlingplum)
Rhamnus (buckthorn)
Sageretia (mock buckthorn)
Smythea
Ziziphus (jujube)

medicinal rhubarb, and senna) in the form of free anthraquinones, anthrones, dianthrones, and/or *O*- and *C*-glycosides derived from these substances.

Adverse effects

The anthranoids produce harmless discoloration of the urine. Depending on intrinsic activity and dose, they can also produce abdominal discomfort and cramps, nausea, violent purgation, and dehydration. They can be distributed into breast milk, but not always in sufficient amounts to affect the suckling infant. Long-term use can result in electrolyte disturbances and in atony and dilatation of the colon.

Respiratory

Cascara sagrada can cause IgE-mediated occupational asthma and rhinitis (1).

Liver

Cascara sagrada has been reported to cause liver damage (2).

- A 48-year-old man developed cholestatic hepatitis and hypertension shortly after he started to use the herbal laxative cascara sagrada. He took one capsule (425 mg of aged cascara sagrada bark) tds for 3 days and subsequently developed right upper quadrant pain, nausea, abdominal bloating, anorexia, and jaundice. The cascara was withdrawn, but his symptoms persisted and his liver function tests were abnormal. One week later, he developed ascites and jaundice and underwent liver biopsy, which showed moderately severe portal inflammation, intracanalicular bile stasis, portal bridging fibrosis, and mild steatosis. He gradually improved without specific treatment and 3 months later his ascites and jaundice had resolved.

Tumorigenicity

Several anthranoid derivatives (notably the aglycones aloe-emodin, chrysophanol, emodin, and physicon) are genotoxic in bacterial and/or mammalian test systems (SEDA-12, 409), and two anthranoid compounds (the synthetic laxative dantron and the naturally occurring 1-hydroxyanthraquinone) have carcinogenic activity in rodents. In an epidemiological study, chronic abusers of anthranoid laxatives (identified by the presence of pseudomelanosis coli) had an increased relative risk of 3.04 (95% CI = 1.18, 4.90) for colorectal cancer (3). The German health authorities therefore restricted the indication of herbal anthranoid laxatives to constipation which has not responded to bulk-forming therapy (which rules out their inclusion in slimming aids). In addition, they imposed restrictions on the laxative use of anthranoid-containing herbs (for example not to be used for more than 1–2 weeks without medical advice, not to be used in children under 12 years of age, and not to be used during pregnancy and lactation) (3,4).

Zizyphus jujuba

The fruit of *Ziziphus jujuba* (dazao) is often consumed in Eastern Asia as food or as a tonic and sedative.

Adverse effects

Angioedema has been described after the oral ingestion of dazao (5).

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Ribavirin

General Information

The synthetic triazole nucleoside, ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, tribavirin, virazole), has a broad spectrum of antiviral activity, including DNA as well as RNA viruses (1). Ribavirin closely resembles guanosine and is converted intracellularly to mono-, di-, and triphosphate derivatives, which inhibit the virally induced enzymes involved in viral nucleic acid synthesis by different mechanisms that are not fully understood (2). Of the DNA viruses, ribavirin is active against *Herpes simplex* virus and hepatitis B virus; among the RNA viruses, good activity has been observed against hepatitis C virus, orthomyxoviruses,

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paramyxoviruses, arenaviruses, and bunyaviruses. Although active against HIV in vitro and in vivo (3), ribavirin is not widely used in the treatment of HIV infection. So far, drug resistance has not been described.

Oral ribavirin has been successfully used in the treatment of Lassa fever (4), Crimean Congo hemorrhagic fever (5), and in combination therapy with interferon alfa for hepatitis C infection (6,7). Several publications have suggested enhanced efficacy of the combination of interferon alfa with ribavirin when compared with monotherapy with interferon alfa. There is also evidence that re-treatment with the combination may succeed in controlling or eliminating viremia when monotherapy has failed. Although the combination may lead to some increase in the adverse effects normally associated with interferon alfa (dyspnea, pharyngitis, pruritus, nausea, insomnia, and anorexia) (SEDA-23, 315), there is no doubt that oral ribavirin adds to the overall toxicity of the combination by causing hemolytic anemia, which is usually mild.

Ribavirin is well absorbed orally, but it can be given in aerosol form for the treatment of respiratory syncytial virus (RSV) infections in immunocompromised patients, and in those with cardiopulmonary abnormalities, or in infants receiving mechanical ventilation (8,9).

The adverse effects and other safety aspects of interferon and ribavirin in the treatment of hepatitis C infection have been reviewed (10).

Comparative studies

Two, large, randomized, placebo-controlled comparisons of interferon alfa-2b alone with the combination of interferon alfa-2b plus ribavirin have been published. In the initial treatment of chronic hepatitis C, 912 patients were randomly assigned to receive standard-dose interferon alfa-2b alone or in combination with ribavirin (1000 or 1200 mg/day orally, depending on body weight) for 24 or 48 weeks (7). As expected, dosage reduction for anemia was necessary in 8% of patients taking the combination therapy and in none of those treated with interferon alone. Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were adverse effects that were reported more often during combination therapy with ribavirin (7). In patients whose chronic hepatitis had relapsed after therapy with interferon alfa-2b alone, 345 patients were randomized to receive standard-dose interferon alfa-2b alone or in combination with ribavirin (1000 or 1200 mg/day orally, depending on body weight) for 6 months (6). Dosage reduction for anemia was required in 12/173 patients assigned to combination therapy and in none assigned to interferon alone. As was the case in the initial therapy study, dyspnea, nausea, and rash were significantly more common in patients treated with the combination of interferon and ribavirin (6).

Ribavirin 15 mg/kg/day plus interferon alfa in 12 teenagers has been compared with interferon alone in 10 (11). There was no difference in dropout rate, but viral clearance was achieved in 50% of the patients who took the combination treatment versus 30% of those who took monotherapy. Adverse events were similar in the two groups. There was mild hemolytic anemia at the end of the first month in most of the children who took ribavirin, but four had moderate to severe hemolysis and two had to stop taking ribavirin. Severe hemolysis in a patient with thalassemia warranted withdrawal of ribavirin within 3 months.

Organs and Systems

Hematologic

Ribavirin accumulates in erythrocytes, resulting in hemolysis by an unknown mechanism, perhaps related to oxidative damage to the erythrocyte membrane. Time-dependent and dose-dependent hemolytic anemia (eventually associated with hyperbilirubinemia and a high reticulocyte count) is the only major toxic effect associated with oral or intravenous ribavirin and is reversible on withdrawal. There was a fall in hemoglobin concentrations below 10.0 g/dl in 9% of patients with hepatitis C treated with ribavirin and interferon alfa (6,7).

In 140 patients with Nipah virus infection there was no difference in the incidence of adverse effects between those who elected to have ribavirin treatment and those who refused (12). Dosing was based on recommendations used to achieve the same approximate concentrations as those seen with 100–1200 mg/day in the treatment of hepatitis C. Anemia occurred in 37% of the ribavirin-treated patients and in the same number of controls, suggesting that ribavirin was equally well tolerated in the two groups.

In patients taking ribavirin plus interferon alfa-2b the average fall in hemoglobin is 2–3 g/dl. Of 57 patients taking ribavirin 800 mg/day 28 were randomized to a high dose of peginterferon alfa-2b once a week (3 micrograms/kg for 1 week, 1.5 micrograms/kg for 3 weeks, and 1.0 microgram/kg for 44 weeks) and 27 patients were randomized to receive a low dose (0.5 micrograms/kg) for 48 weeks; three patients required reduced doses of ribavirin because of anemia (13).

In a randomized controlled trial of high-dose interferon alfa-2b plus oral ribavirin for 6 or 12 months in 50 patients with chronic hepatitis C, the sequential effects of treatment on hemoglobin, leukocytes, and platelets were recorded (14). There was a fall in hemoglobin, and the lowest concentrations were recorded after 6 months of treatment in both groups. All hematological measurements returned to normal after the end of treatment.

Detailed studies of the effects of ribavirin on erythrocyte ATP content and on the hexose monophosphate shunt have been conducted in vitro. ATP concentrations were significantly reduced and the hexose monophosphate shunt increased, suggesting erythrocyte susceptibility to oxidation. In vivo, ribavirin, alone or in combination with interferon, was associated with significant reductions in hemoglobin concentrations and a marked increase in absolute reticulocyte counts. Erythrocyte Na/K pump activity was significantly reduced, whereas K/Cl co-transport and its dithiothreitol-sensitive fraction and malondialdehyde and methemoglobin concentrations increased significantly. Ribavirin-treated patients showed an increase in aggregated band 3, which was associated with significantly increased binding of autologous antibodies and complement C3 fragments,

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suggesting erythrophagocytic removal by the reticuloendothelial system (15).

A low pretreatment platelet count, the dose of interferon alfa, and the haptoglobin phenotype are risk factors for ribavirin-induced anemia, and the fall in hemoglobin is independent of dose in the therapeutic range (16). In five patients with chronic hepatitis C on hemodialysis who received subcutaneous interferon alfa-2b and oral ribavirin for 40 weeks, the dose of ribavirin was titrated based on hemoglobin, with bone marrow support by erythropoietin (17). There was significant bone marrow toxicity in all five. A dose of 200 mg/day produced a steady-state AUC comparable to that obtained with 1000–1200 mg/day in historical controls with normal renal function. More severe anemia was possibly due to chronic renal insufficiency in addition to the prolonged effects of ribavirin.

Treatment of ribavirin-induced hemolytic anemia with recombinant human erythropoietin has been described in 13 patients (18). The hemoglobin concentration increased from a nadir of 10.2 g/dl to a median of 11.5 g/dl and ribavirin treatment did not have to be withdrawn.

Liver

As part of a multicenter, randomized, double-blind, placebo-controlled trial of ribavirin in 59 patients with hepatitis C virus infection, liver biopsies were studied for iron deposition (19). Increased total iron deposition, preferentially in hepatocytes, occurred during a 9-month course of ribavirin. The deposition had no apparent effect on the biochemical or histological response to ribavirin therapy.

Skin

Photosensitivity after administration of ribavirin has been described (20). A well-documented photoallergic reaction in a woman who was taking both ribavirin and interferon alfa provided evidence that ribavirin is a potential photosensitizer for UVB, a problem that may become increasingly relevant in patients with chronic hepatitis C taking combination therapy for 6–12 months with interferon alfa and ribavirin (20).

Transient acantholytic dermatosis (Grover's disease) was first described by Grover in 1970 as a pruritic, self-limiting, popular, or papulovesicular eruption, mainly distributed on the trunk of white middle-aged men. The histopathological hallmark is suprabasal acantholysis at different levels of the epidermis. Its origin is uncertain; most cases are related to sunlight, heat, or sweating. Grover's disease has been attributed to ribavirin (21).

- A 55-year-old man with chronic hepatitis C presented with a pruritic papular eruption on the trunk lasting 2 weeks. He had multiple, erythematous, excoriated papules on the neck, trunk, upper arms, and thighs. The lesions appeared 2 weeks after combination therapy with oral ribavirin and subcutaneous interferon alfa-2b. He had previously been treated with interferon alfa alone (in the same dosage). On withdrawal of ribavirin the lesions gradually faded, but they returned 1 week after reintroduction.

Second-Generation Effects

Teratogenicity

Ribavirin is teratogenic and embryotoxic in laboratory animals and should not be given to pregnant women. Concern has been expressed about the safety of people in the same room as patients being treated with ribavirin by aerosol, particularly women of child-bearing age. However, no ribavirin was detected in the urine, plasma, or erythrocytes of 19 nurses exposed to ribavirin administered via ventilator, oxygen tent, or oxygen hood over 3 days (22).

Drug–Drug Interactions

Didanosine

Multisystem organ dysfunction and lactic acidemia occurred in two of 15 patients with HIV and hepatitis C infections who received interferon alfa, didanosine, and ribavirin (23). Co-administration of didanosine with ribavirin can lead to increased toxicity secondary to raised intracellular concentrations of phosphorylated didanosine (ddA-TP) (24,25). Thus, the evidence suggests that the combination of didanosine plus ribavirin increases the risk of lactic acidosis.

Warfarin

An interaction of warfarin with ribavirin has been reported (26).

- In a 61-year-old white man with chronic hepatitis C, who took interferon plus ribavirin, the dosage of warfarin had to be increased by about 40% (from 45 to 63 mg/week) in order to maintain the desired degree of anticoagulation. This effect was reproduced on rechallenge with ribavirin.

The mechanism of this supposed interaction is not known. For example, ribavirin is cleared by intracellular phosphorylation and its metabolites by the kidneys, warfarin by cytochrome P450 isozymes in the liver; warfarin is highly protein bound, ribavirin is not. However, an effect on warfarin absorption or its action on clotting factor synthesis is possible.

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Riboflavin

See also Vitamins

General Information

The Average Requirement of riboflavin is 1.3 mg/day for men and 1.1 mg/day for women, the Population Reference Intake 1.6 and 1.3 mg/day respectively, and the Lowest Threshold Intake 0.6 mg/day for both.

Riboflavin is poorly absorbed and adverse reactions are almost unknown.

Because it can be detected fluorimetrically in the urine it has been used as a tracer to mark adherence to therapy (1,2).

Organs and Systems

Immunologic

Anaphylaxis has been reported in a boy who took a multivitamin tablet containing riboflavin (3).

- A 15-year-old boy developed flushing and a generalized papular rash after taking one multivitamin tablet, followed by dizziness, dyspnea, nausea, and severe angioedema of the face 40 minutes later. He became drowsy and developed hypotension (67/48 mmHg) and tachycardia (131/minute). He was given subcutaneous adrenaline, intravenous isotonic saline, and diphenhydramine and hydrocortisone, and after 30 minutes his vital signs became stable; he recovered consciousness shortly after. He had no history of atopic diseases or adverse drug reactions, but reported that he had had dizziness many times after drinking one particular yellow-colored brand of soft drink and that he had lost consciousness twice after drinking it about 5 years before. Intradermal skin tests with the vitamins

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and determination of in vitro histamine release showed a strong positive response to riboflavin. He was advised to exclude riboflavin-containing products from his diet and to carry adrenaline for self-administration. During the next 13 months he had no further adverse reactions.

The multivitamin tablet that this boy took contained 100 mg of vitamins B_1, B_2, and B_6, cyanocobalamin concentrate 500 micrograms, and vitamin C 500 mg. The soft drink contained vitamin B_1 (0.6 ppm), vitamin B_2 (8.9 ppm), and vitamin C 200 micrograms/ml.

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Ribonucleic acid

General Information

Ribonucleic acid has been used to enhance immune function in patients with cancer. Of 83 patients who received subcutaneous injections of ribonucleic acid (10 mg every other day) for various skin diseases, three developed an erythematous edematous reaction around the injection sites after the 7th to 15th injections (1). Although patch tests were negative in all three patients, lesions were reproduced after intradermal injection in one patient.

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Rifamycins

See also Antituberculosis drugs

General Information

The rifamycins are a group of macrocyclic antibiotics that were originally derived from a culture of *Streptomyces mediterranei*, the products of which were named after the French film "Rififi chez les hommes" (director Jules Dassin).

Rifampicin

Rifampicin (rINN) is a semisynthetic derivative of rifamycin B. By suppressing the initiation of chain formation in RNA synthesis, it inhibits the DNA-dependent RNA polymerase of mycobacteria and other microorganisms (1). It inhibits the growth of most Gram-positive and many Gram-negative bacteria: *Escherichia coli*, some strains of *Pseudomonas*, *Proteus*, *Klebsiella*, *Staphylococcus aureus*, *Neisseria meningitidis*, *Hemophilus influenzae*, and *Legionella* species. *Mycobacterium tuberculosis*, *Mycobacterium kansasii*, *Mycobacterium scrofulaceum*, and *Mycobacterium intracellulare* are suppressed with increasing concentrations between 0.005 and 4 μg/ml. Rifampicin is bactericidal for *Mycobacterium leprae* in a concentration of less than 1 μg/ml. *Mycobacterium fortuitum* is not susceptible. Primary resistance is very rare, but secondary resistance among mycobacteria and meningococci develops very rapidly when rifampicin is used as a single drug (1).

In a prospective, randomized trial in 12 high-risk adult patients, the use of polyurethane, triple-lumen, central venous catheters impregnated with minocycline and rifampicin (on both the luminal and external surfaces) is associated with a lower rate of infection than the use of catheters impregnated with chlorhexidine and silver sulfadiazine (on the external surface only) (2). There were low rates of catheter-related bloodstream infection (0.3%) and catheter colonization (7.9%) with the use of catheters impregnated with minocycline and rifampicin. This favorable result may be explained either by differences in the coating of the catheters (internal and external surfaces versus external surface only), by microbiological advantages of minocycline and rifampicin over chlorhexidine and silver sulfadiazine, or even by an effect unrelated to the antibacterial activity. The additional costs of preventing an infection and a death would be about $3125 and $12 500 respectively (3).

Pharmacokinetics

Rifampicin is distributed to nearly all organs and body fluids in adequate antibacterial concentrations. The rifamycins are concentrated several-fold in alveolar macrophages (4). This explains their efficacy against intracellular bacteria. Peak concentrations of up to 7 μg/ml are reached within 2–4 hours after a dose of 600 mg before a meal. After gastrointestinal absorption, rifampicin is quickly eliminated in the bile, following enterohepatic circulation. It is also excreted in various fluids, and causes orange–red discoloration of the urine, feces, saliva, tears, sputum, and sweat (SED-10, 576) (5). Rifampicin is progressively deacetylated. Its half-life varies between 2.5 and 5 hours and is prolonged to various degrees by isoniazid and hepatic disorders (1). There is a progressive shortening of the half-life of rifampicin by about 40% during the first 14 days of treatment, owing to self-induction of the hepatic microsomal enzymes that metabolize it (6).

Because rifampicin is a potent inducer of hepatic microsomal drug-metabolizing enzymes, it has been implicated in reducing the effectiveness of many drugs that are metabolized in the liver (SEDA-21, 313). Interactions continue to be recognized, reflecting the

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extension of the use of rifampicin from an antituberculosis agent to an antistaphylococcal drug, particularly useful in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and when prostheses are infected.

General adverse effects

Rifampicin given in usual doses (for example 10 mg/kg/day) is well tolerated and causes adverse effects in only about 4% of patients. Adverse reactions are predominantly hepatic and allergic. Gastrointestinal symptoms are generally transient. Risk factors are age, alcoholism, and hepatic disorders (1). As a potent microsomal enzyme inducer, rifampicin shortens the half-lives of many other drugs (1). This effect occurs after about 7 days and persists for a few days after withdrawal. Allergic reactions can cause rashes (in 0.8%), fever, a flu-like illness (malaise, headache), eosinophilia, and much less often hemolytic anemia, hemoglobinuria, and kidney damage with acute renal insufficiency. These reactions occur especially during intermittent treatment (less than twice weekly) or after re-introduction of rifampicin. Anaphylactoid reactions to rifampicin have been described in HIV-positive patients (7). Light-chain proteinuria and concomitant kidney damage are attributed to an immunological process (SEDA-10, 273). Rifampicin antibodies have been found using an antiglobulin test (8). Hemolysis as an adverse effect seems to be mainly of the immune-complex type, exceptionally of the IgG-antibody type (9). The drug-induced lupus-like syndrome has been linked to rifampicin in a few cases. Tumor-inducing effects and chromosome aberrations have not been noted with rifampicin or during the combined use of isoniazid and rifampicin (SEDA-9, 276).

A flu-like illness, with fever, headache, malaise, and bone pain, can occur shortly after the administration of rifampicin, and was observed in a man who had taken rifampicin 600 mg monthly for multibacillary leprosy (10). However, the reaction usually occurs with higher doses given weekly or twice weekly. The usual procedure is to reduce the dose or increase the frequency of treatment. Antipyretic drugs can be used to provide symptomatic relief.

Intermittent rifampicin therapy introduces risks of hematological and renal adverse reactions, probably through immunological mechanisms. Restarting rifampicin after a drug-free interval has to be carefully guided using small initial dosages of about 75 mg/day and increasing to a final dosage of about 500–600 mg/day. It is essential to monitor blood counts, coagulation factors, and kidney function. The authors of a comprehensive review of the adverse effects of rifampicin (11) have made the point that these are likely to increase, because reactions such as hemolysis, thrombocytopenia, and flu-like syndromes are more likely in patients who take rifampicin intermittently, a pattern of treatment that is becoming recognized as the best way to manage tuberculosis in developing countries and in patients everywhere whose compliance cannot be relied upon, since it is impractical to administer directly observed therapy (DOTS) more often than two or three times a week.

Some drug interactions with rifampicin have been reviewed (SEDA-21, 313) (SEDA-24, 354).

Rifabutin

Rifabutin (rINN), a spiropiperidyl derivative of rifamycin, is more effective in vitro against *M. tuberculosis* than rifampicin. It has a longer half-life, better tissue penetration, and causes less enzyme induction than rifampicin. Rifabutin is well absorbed from the gastrointestinal tract and reaches a peak serum concentration of about 0.5 μg/ml 4 hours after a single dose of 300 mg.

A 300 mg dose of rifabutin is usually well tolerated. Adverse effects include neutropenia, thrombocytopenia, rash, and gastrointestinal disturbances (nausea, flatulence). Myositis (12) and uveitis (13) are rarely observed. The drug-induced lupus-like syndrome has been linked in a few cases with rifampicin and rifabutin.

In a multicenter study from the National Institute of Allergy and Infectious Diseases in the USA, azithromycin (600 mg/day) plus rifabutin (300 mg/day) was poorly tolerated by 31 patients with or without HIV infection (14). Gastrointestinal symptoms and neutropenia were the major adverse effects. There was no significant pharmacokinetic interaction between the two drugs.

Rifamycin SV

Rifamycin SV (rINN), a semisynthetic macrocyclic antibiotic derived from natural rifamycin B, has been used in the therapy of tuberculosis and in some European countries as a topical antibiotic. Anaphylaxis has been reported after systemic administration, and rarely after topical application.

Organs and Systems

Cardiovascular

Shock and a flu-like illness (fever, chills, and myalgia) have been observed most often in patients taking intermittent rifampicin, dosages over 1000 mg/day, or on restarting treatment (1,15). Shock and cerebral infarction have been reported in an HIV-positive patient after re-exposure to rifampicin (16).

Local thrombophlebitis can occur during prolonged intravenous administration (17).

Respiratory

Respiratory symptoms from rifampicin are very rare. They can be part of a flu-like illness with bronchial obstruction (18,19).

Rifampicin-induced pneumonitis is rare.

- An 81-year-old man with smear- and culture-positive pulmonary tuberculosis developed clinical and radiological features of localized interstitial pneumonitis 1 week after starting to take rifampicin, isoniazid, and ethambutol (20). The bronchoalveolar lavage fluid contained 83% lymphocytes with a CD4/CD8 ratio of 10.5. Antituberculosis treatment was withheld and he was treated with methylprednisolone for 3 days because of progressive respiratory failure. A drug lymphocyte stimulation test showed a high stimulation index with rifampicin (370%). He was subsequently treated with streptomycin instead of rifampicin. Rechallenge with rifampicin was not undertaken.

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Sudden clinical and radiological worsening during treatment for pulmonary tuberculosis may be due to bronchogenic spread of infection, immune reconstitution producing a paradoxical reaction, drug-induced hypersensitivity pneumonitis, or other unrelated causes, such as pulmonary embolism. Allergic pneumonitis with rifampicin is most unusual, as is the high CD4/CD8 ratio observed in the bronchoalveolar lavage fluid.

Nervous system

Rifampicin is widely used in tuberculous and meningococcal meningitis, since it passes into the cerebrospinal fluid (21). Rifampicin-induced neurological effects include drowsiness, headache, dizziness, ataxia, generalized numbness, pain in the extremities, muscular weakness, confusion, inability to concentrate, delusions, disorientation, hallucinations, and agitation (1,22).

Sensory systems

Drug-induced uveitis is rare. Antibiotics that have been implicated include rifabutin and sulfonamides. Furthermore, nearly all antibiotics injected intracamerally have been reported to produce uveitis (23).

In one study, the most important adverse effect of rifabutin was uveitis, which occurred in 24 of 63 patients taking rifabutin 600 mg/day and three of 53 patients taking 300 mg/day (24). No patients taking quadruple therapy developed uveitis (25). Initially, uveitis was thought to occur only with dosages of rifabutin over 1200 mg/day. However, a review of 54 cases has shown that it can occur at dosages of 300–600 mg/day and is more likely to occur in patients with a low body mass (26). The patients presented with uveitis 2 weeks to 7 months after starting therapy. In all cases they were also taking fluconazole and clarithromycin, drugs that inhibit cytochrome P450 drug metabolism, leading to increased blood concentrations of rifabutin. Rifabutin is less likely to cause uveitis when it is used in combination with azithromycin 500 mg/day than with clarithromycin. If rifabutin is combined with clarithromycin 1 g/day the dose of rifabutin should be limited to 300 mg/day—advice which has been endorsed by the UK Medicines Control Agency (27).

Topical administration of a glucocorticoid and a cycloplegic drug (such as atropine) is suitable as initial treatment. Withdrawal of causative drugs is not always necessary (28).

Endocrine

In patients taking glucocorticoids for Addison's disease, rifampicin may necessitate an increase in glucocorticoid dosage. Thus, incipient adrenal insufficiency can be unmasked by rifampicin (SEDA-13, 261). The phenomenon is due to liver enzyme induction (29).

A significantly raised concentration of TSH during therapy with rifampicin has been reported in a man taking levothyroxine; TSH concentrations returned to baseline 9 days after withdrawal of rifampicin (30).

Metabolism

The combination of rifampicin and isoniazid reduces serum concentrations of 25-hydroxycholecalciferol. Rifampicin acts by induction of an enzyme that promotes conversion of 25-hydroxycholecalciferol to an inactive metabolite, and isoniazid acts by inhibiting 25-hydroxylation and 1-hydroxylation (SEDA-14, 258). Children or pregnant women with tuberculosis have increased calcium requirements independent of rifampicin administration (31). In 132 children of Afro-Asian origin there was a significant increase in serum alkaline phosphatase activity. This was more pronounced in patients taking both isoniazid and rifampicin than with isoniazid alone (32). The rise in alkaline phosphatase could reflect an effect on either liver or bone. The possibility of a link between this effect and osteomalacia is unclear.

Rifampicin-induced porphyria cutanea tarda has been described in one case, combined with altered liver function (33).

Hematologic

Hemolysis (34,35), agranulocytosis (36), leukopenia (37), and thrombocytopenia (38) have been reported in patients taking rifampicin (SED-10, 578) and constitute contraindications to continuation of therapy.

Hemorrhagic states have been induced by rifampicin in pregnant women and their offspring because of drug-induced hepatic breakdown of vitamin K (39).

Disseminated intravascular coagulation has been attributed to rifampicin (40).

- A 46-year-old woman died of severe disseminated intravascular coagulation after her third monthly dose of rifampicin, given with daily dapsone for the treatment of leprosy (41).

Erythrocytes

Isolated cases of massive hemolysis, with or without renal insufficiency, have been observed in patients taking rifampicin (42–44). Whereas rifampicin given repeatedly and in the usual dose is quite safe, it can cause intravascular hemolysis when given intermittently (45).

Antibodies to rifampicin have been found in several studies, with a positive Coombs' test in the presence of the drug (SEDA-5, 291), more often of the immunocomplex type (46,47) than with IgG or IgM antibodies (43,44).

- In one case, hemolysis started after the second dose of rifampicin, and the patient's blood contained rifampicin-dependent IgG and IgM antibodies, which caused erythrocyte lysis through an interaction with the I antigen on the erythrocyte surface (35). This antigen is also expressed on renal tubular epithelium and the hemolysis was accompanied by acute renal insufficiency.

Intermittent or interrupted treatment appears to predispose to this complication.

Leukocytes

There were four cases of agranulocytosis due to antituberculosis drugs (rifampicin, isoniazid, ethambutol, streptomycin, or pyrazinamide) among about 6400 patients who underwent chemotherapy from 1981 to 2002; the incidence rate of agranulocytosis was estimated at 0.06% (36).

In 140 patients who took Rimapen (Orion, Finland) there were 11 cases of leukopenia, while in 132 patients

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who took Rimactan (Ciba-Geigy, Switzerland) there was only one case, a statistically significant difference (37).

Platelets

Reports of drug-induced thrombocytopenia have been systematically reviewed (48). Among the 98 different drugs described in 561 articles, the following antibiotics were found with level I (definite) evidence: co-trimoxazole, rifampicin, vancomycin, sulfisoxazole, cefalothin, piperacillin, methicillin, novobiocin. Drugs with level II (probable) evidence were oxytetracycline and ampicillin. There is an increased frequency of thrombocytopenia with intermittent therapy (40).

Immune thrombocytopenia during rifampicin therapy has been attributed to drug-dependent binding of an IgG antibody to platelets; the binding epitope of the antibody was found in the glycoprotein Ib/IX complex (38).

Gastrointestinal

Nausea, vomiting, epigastric pain, diarrhea, loss of appetite, abdominal cramps, and meteorism are often restricted to the beginning of rifampicin therapy. However, gastric burning can oblige some patients to take the drug after meals. Hemorrhage from gastric erosions is a rare complication (49).

- Tablet-associated esophagitis has been reported in a 70-year-old white man on the fourth day of antibiotic therapy with vancomycin, gentamicin, and oral rifampicin for *Staphylococcus epidermidis* prosthetic valve endocarditis (50).

The authors noted that age, bedridden state, gastroesophageal reflux disease, simultaneous administration of several medications, and nasopharyngeal obstruction may have increased the risk of esophagitis. They found a second case of tablet-associated esophagitis caused by rifampicin in their review of the published literature.

Histologically confirmed pseudomembranous colitis has been reported in patients taking rifampicin. Bacteriology showed mainly *Clostridium difficile* resistant to rifampicin and several other antibiotics. Withdrawal of rifampicin and the use of vancomycin has been helpful (SEDA-6, 275) (SEDA-7, 310) (51).

Liver

Rifampicin is rarely used as monotherapy. The risk of hepatotoxicity appears to be very low in patients with normal liver function, especially if rifampicin is given continuously. When given with isoniazid, rifampicin can cause a fulminant liver reaction. This may be attributable to enhancement of isoniazid hepatotoxicity as a result of enzyme induction by rifampicin. In some cases, jaundice occurred within 6–10 days after beginning isoniazid plus rifampicin (52). High serum transaminase activities, disturbances of consciousness, and centrilobular necrosis were found. All the patients recovered.

Hepatotoxicity of combined therapy for leprosy has been reported in 39 patients treated with dapsone, protionamide, and rifampicin. There were similar findings in 50 patients treated with dapsone, clofazimine, rifampicin, and protionamide. Deaths probably related to the drugs occurred in both groups after 3–4 months of treatment (53). The drug responsible for liver injury may have been protionamide, although rifampicin administered simultaneously could also have contributed (53).

Among 50 000 patients treated prophylactically with rifampicin, there were 16 deaths associated with jaundice (0.03%) (SED-10, 578) (54,55).

Raised transaminases in children commonly cause withdrawal of therapy (56).

Transaminase activities and other liver function tests should be measured weekly in cases with liver dysfunction and every 4 weeks in patients with no known liver disease.

Severe itching is often a distressing symptom in patients with primary biliary cirrhosis and in cholestatic jaundice due to other causes. Rifampicin has been recommended for controlling this symptom, even though it is known to be hepatotoxic. Rifampicin-induced hepatitis has been reported in three of 41 patients with primary biliary cirrhosis (7.3%; 95% CI = 2.5, 19) (57). This risk is greater than the risk of hepatitis during rifampicin monotherapy for latent tuberculosis. Pre-existing liver disease is a recognized risk factor for drug-induced hepatitis, and these patients need to be monitored carefully during rifampicin therapy.

Biliary tract

Total serum bile acid concentrations were raised in 72% of 61 patients treated with rifampicin and isoniazid; in some patients, the concentrations were as much as 40 times above normal, but in only four was the serum bilirubin raised (58).

Skin

Pruritus, rashes, and urticaria have been reported. Rifampicin-induced rashes often resolve spontaneously, even without drug withdrawal, although in others they can be severe and can be accompanied by systemic symptoms, in some cases amounting to anaphylaxis (11).

Acne occurs more often in patients taking rifampicin and isoniazid combinations than those without rifampicin (SEDA-9, 270).

- A patient developed pemphigus foliaceus induced by rifampicin and improved after withdrawal (72).
- Another patient developed an exacerbation of pemphigus vulgaris during rifampicin therapy, which improved after withdrawal (73).

Severe bullous reactions have been associated with subepidermal detachment typical of toxic epidermal necrolysis (74).

After intravenous rifampicin, a severe cutaneous hypersensitivity reaction has been described, similar to the pattern known as the red man syndrome seen after rapid infusion of vancomycin. The reaction responded to a histamine H_1 receptor antagonist (75).

Rifampicin can cause a fixed drug eruption (76).

Musculoskeletal

Of 26 patients who received rifabutin 600 mg/day in combination with ethambutol, streptomycin, and either clarithromycin (500 mg bd; $n = 15$) or azithromycin (600 mg/day; $n = 11$), there were rifabutin-related

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adverse events in 20; these included a diffuse polyarthralgia syndrome in 5 (77).

Immunologic

There is no evidence that rifampicin causes clinically significant deleterious effects on the immune system in humans (78), whereas it can cause immunosuppression in animals (79). Rifampicin partially suppresses cutaneous hypersensitivity to tuberculin and T cell function (80). In 33 patients with leprosy treated with a rifampicin drug combination, a flu-like illness or antibodies to rifampicin-conjugated proteins were not observed (81).

A possible explanation of the association of allergic reactions with intermittent therapy is that during daily regimens the antigen–antibody complexes are continuously cleared from the plasma without reaching a critical concentration, whereas in intermittent regimens, antibody titers can increase markedly during the drug-free days. This is supported by the observation that anti-rifampicin antibodies, measured by the indirect Coombs' test, developed more commonly during intermittent than during daily therapy and that antibodies may disappear from the serum when patients change from intermittent to daily regimens.

Severe anaphylaxis has been reported in two patients with infected wounds that had been treated with topical rifamycin for several months (82). There was urticaria, angioedema, and hypotension in one case, and urticaria, wheezing, dyspnea, and hypotensive shock in the other. In both cases, prick tests with 10% rifamycin solution were positive, while there were no positive reactions in 20 controls.

- A 36-year-old woman developed generalized urticaria during a second course of treatment with rifamycin eyedrops within a month and a 49-year-old man had systemic urticaria, bronchospasm, and hypotension shortly after his surgical wound had been washed with a solution of rifamycin (83). Both patients had positive skin prick tests to rifamycin (1 mg/ml) when tested several weeks after the acute episode, while 10 healthy volunteers had negative tests. The woman also had a positive skin prick test to rifampicin 2 mg/ml, although she had never taken it before.

An HIV-infected patient who developed an anaphylactic reaction to rifampicin tolerated treatment with rifabutin without any adverse event.

The lupus-like syndrome has been reported in seven patients, six of them women who were taking rifampicin ($n = 4$) or rifabutin ($n = 3$) in standard dosages for mycobacterial infections (84). None was HIV-1 positive, none was also taking isoniazid, and although they were taking other antimycobacterial drugs, their symptoms disappeared after withdrawal of the rifamycin alone. All had two or more episodes of fever, malaise, myalgia, and arthralgia, and all had positive antinuclear antibodies. All were also taking either ciprofloxacin or clarithromycin, and the authors speculated that these drugs, which are cytochrome P_{450} enzyme inhibitors, could have increased the serum concentrations of the rifamycins.

Desensitization protocols can be helpful in patients who have had anaphylactic reactions, and the detection of IgE antibodies to rifampicin may be helpful in clarifying pathogenesis. A switch to a daily regimen, when administration was previously intermittent, may allow resumption of rifampicin without further problems. In 35 HIV-positive patients with previous allergic reactions to rifampicin, oral desensitization was safe and allowed the reintroduction of rifampicin in 60% of cases (85). However, the flu-like syndrome, hemolytic and thrombocytopenic crises, and acute renal insufficiency are not IgE-mediated, and when rifampicin is thought to be indispensable, a course of treatment may be completed under glucocorticoid cover. Four patients with reactions to rifampicin, one with rash, fever, and lymphadenopathy and one with hepatitis, completed courses of antituberculosis therapy for nervous system infections under glucocorticoid cover (86).

Second-Generation Effects

Pregnancy

Rifampicin is currently recommended by the WHO for the treatment of tuberculosis during pregnancy. On the other hand, drug companies advise against the use of rifampicin during the first 3 months of pregnancy, even though deleterious effects on the fetus have not been confirmed in man.

Induction of hepatic microsomal enzymes by rifampicin is believed to be the cause of vitamin K deficiency in pregnancy, leading to hemorrhagic disturbances in pregnant women and their neonates. Prophylactic vitamin K should therefore be given to all mothers and their offspring when the mother has taken rifampicin during late pregnancy. Blood coagulation tests should be done on both (SEDA-8, 288).

Teratogenicity

Rifampicin crosses the placenta, and although teratogenicity is uncertain, it may not be as innocuous during pregnancy as isoniazid or ethambutol (SEDA-6, 277) (87).

Lactation

Lactation is not a contraindication to rifampicin; only small amounts pass into the milk with no relevant effects on the newborn (88).

Susceptibility Factors

Renal disease

Impaired renal function has to be taken into consideration when calculating the dosage of rifampicin (89).

Hepatic disease

Pre-existing liver damage has to be taken into consideration when calculating the dosage of rifampicin (90).

Other features of the patient

Chronic alcoholism is an important risk factor for adverse effects of the rifamycins. In 79 consecutive patients taking rifampicin in combination with isoniazid and another drug, there was a high incidence of acute clinical liver

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disease; about half of the patients were advanced alcoholics and almost all the cases of hepatitis came from this group (91). Most of those with pretreatment abnormalities of liver function had abnormalities in liver biopsies, not attributable to alcohol. In one patient, active chronic hepatitis was attributed to rifampicin.

However, in 531 eligible patients enrolled in a US Public Health Service Cooperative Trial of Short-Course Chemotherapy of Pulmonary Tuberculosis, of whom 58% were classified as alcoholic, although the alcoholics had more abnormal concentrations of aspartate transaminase before and during therapy, there was no significant difference between the alcoholics and non-alcoholics in the incidence of adverse reactions, including hepatotoxic reactions (92). The authors concluded that in the absence of clinically significant and persistent pretreatment abnormalities of hepatic function tests, rifampicin and isoniazid are not contraindicated in patients categorized as alcoholic.

In patients with suspected disorders of vitamin D and calcium metabolism, caution has to be taken (SEDA-9, 269).

Drug Administration

Drug overdose

Severe overdosage has been observed in inadvertent administration of an excessive dose of rifampicin in children (93) and also in suicide attempts (94,95). It can also occur when there is impaired hepatic function or severe renal insufficiency. Symptoms are nausea, vomiting, headache, abdominal pain, diarrhea, and pruritus.

Drug–Drug Interactions

Amiodarone

Rifampicin has been reported to reduce the effects of amiodarone (96).

- A 33-year-old woman was given rifampicin to suppress an MRSA infection of a pacing system that could not be removed. She was already taking amiodarone which, with the pacing system, was intended to manage her complex dysrhythmias. The introduction of antibiotic therapy was followed by an increase in bouts of palpitation and in shocks from her defibrillator. Her amiodarone concentrations had fallen and returned to the target range, with disappearance of her symptoms, when the rifampicin was withdrawn.

The authors discussed the possible reasons for this interaction, including a reduction in systemic availability of amiodarone or induction of metabolism by rifampicin.

Antacids

Antacids, particularly aluminium hydroxide gel, magnesium trisilicate, and sodium bicarbonate, reduce the systemic availability of rifampicin (97).

Antiretroviral drugs

The recommendations of the Center for Disease Control and Prevention in Atlanta regarding the use of antituberculosis drugs in combination with antiretroviral drugs have been published (98). In general, the use of rifampicin in patients taking protease inhibitors is contraindicated, except in the following circumstances:

- patients taking the NNRTI efavirenz and two NRTIs;
- patients taking the protease inhibitor ritonavir and one or more NRTIs;
- patients taking a combination of the two protease inhibitors ritonavir and saquinavir.

However, Roche Pharma have recommended that rifampicin should not be used in patients who are taking ritonavir + saquinavir, because of the results of a study in which 11 of 28 patients who took rifampicin 300 mg/day with ritonavir 100 mg bd + saquiniavir 1000 mg bd developed severe hepatotoxicity [http://www.fda.gov/medwatch/safety/2005/Saquinavir-Rifampin_deardoc_Feb05].

The use of rifampicin with the protease inhibitors indinavir, nelfinavir, and amprenavir is contraindicated. However, these agents can be used with rifabutin after appropriate dosage reduction. Failure to reduce the dosage of rifabutin can result in toxic manifestations, such arthralgia and uveitis.

Rifamycins can be used with the NNRTIs nevirapine or efavirenz, but not with delavirdine.

Data on drug pharmacokinetics and drug interactions in patients taking treatment for HIV infection and tuberculosis are scanty, and the current recommendations are almost certain to be modified in the near future. Furthermore, it may be prudent to monitor rifampicin concentrations in the event of intolerance or adverse drug reactions.

Barbiturates

Barbiturates, which induce liver drug-metabolizing enzymes, increase the rate of metabolism of rifampicin (99).

Cardiac glycosides

In eight healthy volunteers rifampicin reduced digoxin plasma concentrations (100), mirroring clinical experience. The authors hypothesized that this effect may be brought about by induction of P-glycoprotein, which increases excretion of digoxin into the gut lumen; however, renal digoxin clearance, which is also mediated by P-glycoprotein, was not affected. In these healthy volunteers, rifampicin reduced digoxin concentrations by about 50%, so the interaction is likely to be clinically important.

Digitoxin plasma concentrations can be reduced by rifampicin, and the dosage should be adjusted according to the serum concentration (SEDA-10, 272).

Ciclosporin

Increased dosages of ciclosporin are recommended when patients take rifampicin (SEDA-21, 314). In one study it was necessary to increase the dosage of ciclosporin from 225 to 800 mg/day during treatment with rifampicin and for 7 days afterwards in order to maintain therapeutic concentrations (101). Low ciclosporin blood

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concentrations and acute graft rejection have been observed in a renal transplant recipient during prophylactic rifampicin therapy (102).

Clarithromycin

Severe interactions have been observed when rifabutin and clarithromycin were given simultaneously (103). The mean concentrations of rifabutin and 25-*O*-desacetyl-rifabutin in healthy subjects who took clarithromycin and rifabutin concomitantly were respectively more than 4 times and 37 times greater than the concentrations recorded when rifabutin was administered alone. Neutropenia was detected in 14 of 18 subjects taking rifabutin. Myalgia and high fever were also common. In another study, clarithromycin increased the AUC of rifabutin by 76% (104). Physicians should be aware that recommended prophylactic doses of rifabutin can be associated with severe neutropenia within 2 weeks after the start of therapy, and all patients taking rifabutin, especially with clarithromycin, should be monitored carefully for neutropenia.

Clofibrate

The interaction of rifampicin with clofibrate has been reviewed (105). Rifampicin induces the metabolism of clofibrate, and in five subjects rifampicin 600 mg/day caused a 35% fall in steady-state serum clofibrate concentrations (106).

Clonidine

Rifampicin 600 mg/day had no effect on the pharmacokinetics of clonidine 0.4 mg/day in six healthy subjects (105,107).

Clozapine

Rifampicin can reduce plasma concentrations of clozapine and exacerbate psychotic symptoms (108).

Contrast media

Excretion of contrast media through the bile can be impaired by rifampicin (1,82).

Corticosteroids

Rifampicin enhances the catabolism of many glucocorticoids. For example, it increases the plasma clearance of prednisolone by 45% and may reduce the amount of drug available to the tissues by as much as 66% (SEDA-8, 288). Glucocorticoid therapy for concomitant diseases should therefore be adjusted in the light of plasma concentrations and clinical effects during rifampicin treatment (SEDA-10, 272). For example, rejection of a kidney transplant occurred after 7 weeks of rifampicin therapy (109).

Co-trimoxazole

In patients taking co-trimoxazole, rifampicin in a standard oral antituberculosis regimen (600 mg/day plus isoniazid 300 mg/day and pyrazinamide 30 mg/kg for more than 12 days) reduced the steady-state AUC of trimethoprim and sulfamethoxazole by 47 and 23% respectively (110). The same authors had previously reported reduced efficacy of co-trimoxazole in the prevention of toxoplasmosis in HIV-infected subjects (111). The reduction in prophylactic efficiency was more pronounced in subjects who took a single double-strength tablet.

There have been no reports on the risk of *Pneumocystis jiroveci* pneumonia in patients taking rifampicin plus co-trimoxazole prophylaxis. Until such time as more data are available, it is prudent to use double-strength co-trimoxazole tablets twice daily for prophylaxis of toxoplasmosis and *P. jiroveci* pneumonia in patients taking concomitant rifampicin.

Coumarin anticoagulants

Coumarin anticoagulants undergo accelerated metabolism in patients taking rifampicin (112). Rifampicin greatly increases the clearance of warfarin by inducing hepatic enzymes, and difficulty in achieving an optimal INR despite an increase in the dose of warfarin has been highlighted (113). In patients taking rifampicin, warfarin should be started in dosages of 20–30 mg/day for two days, subsequently adjusting the dose according to the prothrombin time; a daily maintenance dose of 20 mg may be required (114) and close monitoring is required during the initial weeks to achieve a therapeutic INR (115). Offset of the interaction when rifampicin is withdrawn can take as long as 4–5 weeks, during which time the dose of warfarin should be reduced gradually to avoid a high INR and bleeding complications.

Dapsone

The interaction of rifampicin with dapsone has been reviewed (105). In seven patients with leprosy, rifampicin shortened the half-life of dapsone by 50% (116).

Diazepam

The interaction of rifampicin with diazepam has been reviewed (105). The mean half-life of diazepam fell from 58 to 14 hours in seven patients who took isoniazid, rifampicin, and ethambutol (117).

Fluconazole

Fluconazole increased the AUC of rifabutin by 76% (104).

Haloperidol

Blood concentrations of haloperidol are reduced during rifampicin administration, owing to shortening of the half-life of haloperidol (SEDA-12, 258) (118).

Ketoconazole

Ketoconazole interacts with rifampicin, and the serum concentrations of both drugs are reduced (SEDA-9, 269).

Methadone

Methadone metabolism is increased and a withdrawal syndrome has been reported (1).

Mexiletine

The interaction of rifampicin with mexiletine has been reviewed (105). The mean half-life of a single dose of mexiletine 400 mg fell from 8.5 to 5 hours in eight healthy subjects who took rifampicin 600 mg/day for 10 days (119).

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Nifedipine

The elimination of nifedipine is enhanced by rifampicin (SEDA-14, 259).

Oral contraceptives

The serum concentrations of ethinylestradiol and similar steroids used as contraceptives are reduced during rifampicin therapy; it is therefore not surprising that unexpected pregnancies have occurred (120). The effects of rifampicin have been compared with those of rifabutin (increasingly used for the treatment of atypical mycobacterial infections) in a double-blind, crossover study in 12 women who were taking a stable oral contraceptive regimen containing ethinylestradiol and norethindrone (121). Rifampicin had the greater effect in reducing the mean AUC, but none of the subjects ovulated during the cycle in which either of the rifamycins was administered.

Oral hypoglycemic agents

Oral hypoglycemic agents (glibenclamide, gliclazide, repaglinide, and rosiglitazone) undergo accelerated metabolism in patients taking rifampicin (112).

The addition of rifampicin to glimepiride (metabolized by CYP2C9) produced only a modest reduction in AUC and no significant effect on blood glucose (122).

Phenazone

Rifampicin significantly reduces the half-life of phenazone (antipyrine) (123).

Probenecid

Probenecid can increase the serum concentration of rifampicin; this can reduce costs and hepatotoxicity in long-term therapy (124). Interactions of rifampicin with probenecid have been reviewed (105).

Propranolol

The metabolism of propranolol is enhanced by rifampicin (SEDA-9, 269).

Quinidine

Quinidine plasma concentrations can be lowered by rifampicin because of enzyme induction (125).

Repaglinide

Co-administration of rifampicin with repaglinide considerably lowers the concentration of repaglinide and alters its therapeutic effect in diabetes mellitus (126). In nine healthy volunteers, the maximum reduction in blood glucose after a single 0.5 mg dose of repaglinide fell from 1.6 to 1.0 mmol/l after pretreatment with rifampicin for 5 days. This presumably occurred by induction of CYP3A4.

Statins

In healthy subjects taking rifampicin the C_{max} and AUC of simvastatin were greatly reduced (127), presumably by enzyme induction. It is likely that other HMG-CoA reductase inhibitors, including lovastatin and atorvastatin, also have clinically significant interactions with rifampicin.

Tacrolimus

An interaction of rifampicin with tacrolimus has been documented (128,129).

- A 61-year-old Chinese renal transplant recipient, who had taken tacrolimus for 1 year after an episode of rejection had failed to respond to ciclosporin, took rifampicin and 12 days later had an episode of biopsy-proven graft rejection, associated with very low serum tacrolimus concentrations.
- A 50-year-old woman, a renal transplant recipient, developed a brain abscess due to *Nocardia otitidiscaviarum* after craniotomy and was given meropenem and rifampicin. The dose of tacrolimus had to be increased three-fold to maintain adequate trough concentrations.

Theophylline

Rifampicin increases the metabolic clearance of theophylline by 45%, especially after intravenous use (130,131).

Thyroxine

Induction of cytochrome P_{450} may be the explanation for a modest increase in the clearance of levothyroxine (10–15%) which may necessitate an increase in dosage. In two cases, rifampicin led to significant increases in TSH concentrations in patients being treated for hypothyroidism (30).

Trimethoprim

The interaction of rifampicin with trimethoprim has been reviewed (105). Rifampicin has a small effect on the clearance of trimethoprim but it is not clinically significant (132,133).

Interference with Diagnostic Tests

von Jaksch test

Rifampicin metabolites in urine can cause a false positive test for melanin when assessed with the von Jaksch test (134).

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Rilmenidine

General Information

Rilmenidine is an imidazoline derivative that lowers blood pressure by an interaction with imidazoline (II) receptors in the brainstem and kidneys (1).

In a number of trials in hypertension the adverse effects profile of rilmenidine was qualitatively similar to that of clonidine, although the overall incidence of adverse events appeared to be lower. The main complaints were of dry mouth, drowsiness, and constipation (2–4). In one of these reviews, in which the impact on vigilance was particularly examined, it was concluded that although there were dose-related effects there was no statistically significant difference between rilmenidine and placebo in relation to sedation and drowsiness. However, these results consistently showed a rank order among placebo, rilmenidine, and clonidine, leading to progressively greater degrees of sedation (5).

Organs and Systems

Skin

A photosensitivity reaction has been attributed to rilmenidine (6).

- A 51-year-old woman developed erythema and swelling on sun-exposed areas and complained of a local burning sensation and pruritus 10 days after she started to take rilmenidine 1 mg/day for mild hypertension. She recovered fully 1 week after rilmenidine withdrawal and treatment with prednisolone. The chronology and the results of patch and photopatch tests suggested a phototoxic reaction to rilmenidine.

The authors suggested that this may have been related to the double bond in the oxazoline ring of the drug.

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Rimantadine

General Information

Rimantadine hydrochloride, an alpha-methyl derivative of amantadine (alpha-methyl-1-adamantane methylamine hydrochloride), is more active than amantadine against influenza A viruses in vitro and in laboratory animals. It is an alternative to amantadine for the prevention and treatment of influenza A virus infections in adults and for the prevention of influenza in children. Adverse effects have been considered to be less common with rimantadine (SEDA-8, 143), and it is generally tolerated better than amantadine, because it causes fewer nervous system adverse effects (1). Unfortunately, rimantadine is more costly, which has led many institutions to develop influenza treatment guidelines. Both drugs work by blocking the M2 ion channel, which is needed to affect a pH change that helps to initiate viral uncoating.

In a systematic review of seven trials of amantadine versus placebo ($n = 1797$), three of rimantadine versus placebo ($n = 688$), and two of amantadine versus

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rimantadine ($n = 455$) in the prevention of influenza A illness, there was a relative odds reduction of illness of 64% with amantadine compared with placebo, a 75% reduction with rimantadine compared with placebo, and no significant difference between the two drugs (2). There was a significantly higher risk of central nervous system adverse reactions and premature withdrawal with amantadine compared with placebo, but not with rimantadine compared with placebo. However, there was a significant increase in the risk of gastrointestinal adverse events with rimantadine compared with placebo (OR = 3.34, 95% CI = 1.17, 9.55).

Organs and Systems

Nervous system

The major advantage of rimantadine is a lower risk of central nervous system effects, such as light-headedness, difficulty in concentrating, nervousness, and insomnia, which can be a significant problem with amantadine, particularly in older patients. The English-language literature from 1966 to 1994 has been reviewed (3). In 598 elderly patients, nervous system adverse effects were more common with higher dosages (4.9% at 100 mg/day to 12.5% at 200 mg/day).

Gastrointestinal

The English-language literature from 1966 to 1994 has been reviewed (3). Gastrointestinal effects, including nausea, loss of appetite, diarrhea, and dry mouth, occurred in 8.4% of children under 10 years of age, in 3.1% of adults, and in 2.9% of elderly patients taking 100 mg/day and 17.0% taking 200 mg/day.

Long-Term Effects

Drug tolerance

Emergence of resistance of influenza A virus to rimantadine in vivo has been reported (4), but the incidence of resistance in field isolates appears to be extremely low (5).

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Rimazolium

General Information

Rimazolium is a non-narcotic analgesic that strongly potentiates the analgesic and antagonizes the respiratory depressant effect of morphine alkaloids in animals and prevents the development of tolerance to morphine in animals and humans (1). Although rimazolium is not a new drug, experience with it is very limited.

Organs and Systems

Nervous system

Vertigo, drowsiness, and nausea have been attributed to rimazolium (SED-10, 172) (SEDA-7, 117) (2).

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Risperidone

See also Neuroleptic drugs

General Information

Risperidone is an atypical benzisoxazole neuroleptic drug. It is a dopamine D_2 receptor antagonist, with antagonistic actions at 5-HT_2 receptors, alpha-adrenoceptors, and histamine H_1 receptors.

Placebo-controlled studies

Patients with bipolar disorder may benefit from risperidone, but this conclusion has mostly come from open studies with small sample sizes (SEDA-23, 69). Experience with risperidone has been reviewed with data from Canadian studies (1).

In a 6-week open study of risperidone (mean dosage 4.7 mg/day) in combination with mood-stabilizing treatments (usually lithium, carbamazepine, or valproate) for the treatment of schizoaffective disorder in 102 patients, 95 of whom completed the trial, at week 4 most patients had improved symptom severity and 9.3% were completely symptom-free (2). There were no statistically significant differences between baseline and week 4 in the severity of extrapyramidal symptoms, as measured by the UKU Side-Effect Rating Scale subscale for neurological adverse effects; other adverse effects included depressive symptoms ($n = 13$), exacerbation of mania ($n = 5$), drowsiness ($n = 3$), and impotence ($n = 2$).

The efficacy and safety of risperidone (mean dose 2.9, range 1.5–4 mg/day) have been examined in a double-

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blind, randomized, parallel-group, 6-week study of the treatment of aggression in 35 adolescents with a primary diagnosis of disruptive behavior disorder and subaverage intelligence (3). Risperidone significantly improved aggression, and extrapyramidal symptoms were absent or very mild; there was transient tiredness in 11 of the 19 drug-treated subjects compared with one of the 16 placebo-treated subjects; other adverse effects were sialorrhea ($n = 4$ for risperidone, $n = 0$ for placebo), nausea ($n = 3$ for risperidone, $n = 0$ for placebo), and weight gain (mean of 3.5% of body weight with risperidone). There were no clinically important changes in laboratory parameters, electrocardiography, heart rate, or blood pressure.

In a double-blind, placebo-controlled study of the addition of low-dose risperidone (mean dosage 2.2 mg/day) to a 5-HT re-uptake inhibitor in refractory obsessive-compulsive disorder in 70 adults, 18 of 20 risperidone-treated patients had at least one adverse effect (4). The adverse effects in both groups included sedation ($n = 17$ for risperidone, $n = 8$ for placebo), increased appetite (6 and 3), restlessness (6 and 6), and dry mouth (5 and 5).

The results of two major controlled clinical trials of risperidone in patients with dementia were not conclusive, but risperidone was more effective than placebo in agitated and demented patients (SEDA-25, 68). The long-term data have been reviewed and they suggest that although in the two pivotal previous comparisons of risperidone with placebo the risk of adverse events was similar in the two groups when risperidone was given in the optimal dosage (1 mg/day), during a 12-month open extension of these studies, the incidence of de novo tardive dyskinesia was very low, and there were no clinically important adverse events or changes in vital signs or laboratory signs (5).

Risperidone has been used in bipolar disorder, dementia, disruptive behavior disorder with subaverage intelligence, Tourette's syndrome, and autism (SEDA-23, 69) (SEDA-25, 67) (SEDA-26, 64). The efficacy and safety of low doses of risperidone in the treatment of autism and serious behavioral problems have been studied in 101 children aged 5–17 years with autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior, who were randomly assigned to risperidone for 8 weeks ($n = 49$; dosage 0.5–3.5 mg/day) or placebo ($n = 52$) (6). Risperidone produced a 57% reduction in the Irritability Score, compared with a 14% reduction in the placebo group; all other parameters were also significantly improved. Risperidone was associated with an average weight gain of 2.7 kg, compared with 0.8 kg with placebo; increased appetite, fatigue, drowsiness, dizziness, and drooling were more common with risperidone. In two-thirds of the children with a positive response to risperidone at 8 weeks, the benefit was maintained at 6 months.

Risperidone was also effective and well tolerated in 118 children aged 5–12 years with subaverage intelligence and severely disruptive behavior in a 6-week, multicenter, double-blind, randomized trial (7). Risperidone produced significantly greater improvement than placebo on the conduct problem subscale of the Nisonger Child Behavior Rating Form from week 1 (respective reductions in score of 15 and 6). The most common adverse effects of risperidone (mean dose at end-point 1.16 mg/day) were headache and somnolence; the extrapyramidal symptom profile of risperidone was comparable to that of placebo, and there were respective mean weight increases of 2.2 and 0.9 kg.

Table 1 The results of two 12-week, randomized, double-blind studies of risperidone in elderly patients with behavioral symptoms associated with dementia (28,29)

Mean age (years)	Number	Dose (mg/day)	Response (%)	Extrapyramidal symptoms (%)
81	344	Risperidone (1.1)	54	15
		Haloperidol (1.2)	63	22
		Placebo	47	11
83	625	Risperidone (1)	45	13
		Risperidone (2)	50	21
		Placebo	33	7.4

Adults with autistic disorder ($n = 17$) or pervasive developmental disorder not otherwise specified ($n = 14$) participated in a randomized, 12-week, double-blind, placebo-controlled trial of risperidone (8). Among those who completed the study, risperidone ($n = 14$) was superior to placebo ($n = 16$) in reducing the symptoms of autism, and the most prominent adverse effect was mild transient sedation during the initial phase of drug administration. Abnormal gait was reported in one patient taking risperidone.

According to a thorough review, risperidone is more effective than placebo in patients with dementia (9). Nevertheless, the results of the two major controlled clinical trials have not been conclusive (see Table 1). There was no statistical difference between the treatments in the first study, although there was in the second; extrapyramidal symptoms were notably more common with risperidone. In both studies, there was a high rate of placebo response, which implies that these patients responded favorably to the increased care that is given during a clinical trial. Long-term data in patients with dementia are lacking, but they are crucial in identifying tardive dyskinesia.

Observational studies

In a Prescription Event Monitoring study of the safety of risperidone in 7684 patients treated in general practice, information on risperidone prescriptions issued to patients in England was gathered between July 1993 and April 1996 (10). After 6 months, 76% of the patients for whom data were available were still taking risperidone. Drowsiness/sedation was the most frequent reason for stopping risperidone and the most frequently reported event (4.6 cases per 1000 patient-months). Extrapyramidal symptoms were rarely reported, the incidence being 3.2 per 1000 patient-months; they were more frequent in elderly patients (7.8 per 1000 patient-months). There were only four reports of dyskinesias and one report of tardive dyskinesia, which resulted in withdrawal of risperidone. Eight overdoses of risperidone alone were reported, with no serious clinical sequelae. Nine patients took risperidone during ten pregnancies, with seven live births and three early therapeutic terminations. There were no abnormalities among the live births.

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Long-term data on the efficacy and tolerability of risperidone are scant, as most of the clinical trials have been of short duration (no longer than 12 weeks). However, some additional data from open studies have emerged. In one study, 386 patients with chronic schizophrenia took risperidone 2–16 mg/day for up to 57 weeks; 247 patients were treated for at least 1 year (11). All but 48 patients (88%) had been treated with antipsychotic drugs before entering the study. At the end of the study, 64% of the patients were rated as having improved on the Clinical Global Impression change scale, and extrapyramidal symptoms (scored on the Extrapyramidal Symptom Rating Scale, ESRS) tended to be lower in severity or remained unchanged over the course of risperidone treatment; 27% of the patients required antiparkinsonian medication during the study, and 6.5% discontinued treatment prematurely because of adverse events. One or more adverse events were reported by 221 patients (57%) during risperidone treatment. Extrapyramidal symptoms occurred in 23%. Insomnia and anxiety were reported by 13% and 12% of patients. Two patients died during the 1-year study: one patient drowned and another committed suicide by hanging after 3.5 months. At the end of the study the mean increase in body weight was 1.8 kg.

In a retrospective study of 97 patients taking risperidone, under 30% of the patients were still taking risperidone after a mean period of follow-up of 102 (range 13–163) weeks (12). Reasons for discontinuation included not achieving the desired therapeutic effect ($n = 39$), non-compliance ($n = 22$), adverse effects ($n = 26$), the patient's not liking the drug and requesting a change to a different medication ($n = 17$), and symptom remission ($n = 6$). The authors stated that in routine clinical practice, the use of risperidone is plagued by many of the same problems of older antipsychotic drugs.

The efficacy and safety of risperidone have been examined in special groups of patients, such as those with psychotic depression (13), autistic disorders (8), bipolar disorder (14), mental retardation (15), and children and adolescents (16).

Patients with bipolar disorders may benefit from risperidone. This has been observed in an open trial of ten patients with rapid cycling bipolar disorder who were refractory to lithium carbonate, carbamazepine, and valproate; eight improved after 6 months of treatment. One patient dropped out through non-adherence to therapy and one because of adverse effects (agitation, anxiety, insomnia, and headache) (14). There was a similar beneficial effect in eight adults with moderate to profound mental retardation (15). Risperidone was associated with a significant reduction in aggression and self-injurious behavior, whereas adverse effects were primarily those of sedation and restlessness.

Eight of a heterogeneous group of eleven children and adolescents (mean age 9.8, range 5.5–16 years) with mood disorders and aggressive behavior, improved with a low dose of risperidone (0.75–2.5 mg/day) (16). Treatment was stopped in two children because of drowsiness; the most bothersome adverse effect of risperidone was weight gain in two cases (mean increase 4 kg).

The medical records of 151 hospitalized elderly psychiatric patients (mean age 71 years) have been analysed (17). Of 114 patients treated with risperidone (mean duration of treatment 17 days; mean dose 3 mg/day), 78% responded. Adverse events were reported in 20 patients, including new-onset extrapyramidal effects in four; tremor in four; sedation in three; hypotension in three; diarrhea in two; tardive dyskinesia in two; and chest pain, anxiety, restlessness, itching, insomnia, and falls in one each.

A review of both core information and new findings concerning risperidone concluded that it can be associated with transient drowsiness (probably no greater than that observed with haloperidol), postural hypotension (which is avoided by dose titration), weight gain, reduced sexual interest, and erectile dysfunction. Risperidone can also cause dose-dependent hyperprolactinemia (which can cause amenorrhea, sexual dysfunction, and galactorrhea). Risperidone tends not to cause extrapyramidal signs at therapeutic doses (the optimal dose being 6 mg/day) but they do occur dose-dependently (18).

In an 8-week open prospective study of risperidone in 20 patients, mean age 34 (range 19–53) years, adverse effects included giddiness ($n = 3$), headache ($n = 2$), and agitation ($n = 2$); one woman reported galactorrhea and another developed obsessive-compulsive symptoms; 16 of 20 patients were taking antiparkinsonian drugs before the study, compared with 12 patients at the end (19).

Objections have been raised on the ways in which some clinical trials are interpreted (20). Furthermore, it has been stated that a major problem with the risperidone literature is that the original data can be very difficult to decipher or even obtain. Huston and Moher have described their frustration in trying to perform a meta-analysis of the effects of risperidone; they found "obvious redundancy in the results of a single-center trial being published twice," as well as problems with "changing authorship, lack of transparency in reporting, and frequent citation of abstracts and unpublished reports" (21). These concerns were reiterated in an editorial (22).

In a prospective, 6-week open trial in 31 Chinese patients with acute exacerbation of schizophrenia, risperidone doses were titrated to 6 mg/day (if tolerated) over 3 days, but were reduced thereafter if adverse effects occurred (23). Efficacy and adverse effects were assessed on days 0, 4, 14, 28, and 42. End-point steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone were analysed. Of the 30 patients who completed the trial, 17 tolerated the 6 mg dose well, while the other 13 received lower final doses (mean 3.6 mg) for curtailing adverse effects. At end-point, 92% of the 13 low-dose patients had responded to treatment (a 20% or more reduction in the total score on the Positive and Negative Syndrome Scale), compared with 53% of the 17 high-dose subjects. There were no significant between-group differences in other minor efficacy measures. End-point plasma concentrations of the active moieties (risperidone plus 9-hydroxyrisperidone) were 40 ng/ml in the low-dose group and 50 ng/ml in the high-dose group; this difference was not significant, suggesting that the different responses were pharmacokinetic in origin. The results of this preliminary trial suggest that up to 6 mg/day of risperidone is efficacious in treating patients with an acute exacerbation of schizophrenia. Nearly 60% of the patients tolerated 6 mg/day; in the others, reducing the dosage to relieve adverse effects still yielded efficacy.

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The efficacy and safety of long-term risperidone have been assessed in children and adolescents ($n = 11$) in a prospective study (24). Subjects with autism or pervasive developmental disorder not otherwise specified took risperidone for 6 months, after which their parents were given the option of continuing for a further 6 months. Weight gain was common, although the rate of increase abated with time. After 6 months two patients developed facial dystonias, which disappeared after reducing the dosage in one case and after withdrawal in the other. Amenorrhea was also observed, but there were no changes in liver function, blood tests, or electroencephalography. The authors concluded that risperidone may be effective and relatively safe in the long-term treatment of behavioral disruption in autistic children and adolescents.

Youths with behavioral disorders (25,26), and patients with disturbing neuroleptic drug-induced extrapyramidal symptoms (27) have been studied. Ten youths (aged 6–14 years) were randomly assigned to receive placebo and 10 to receive risperidone (0.75–1.50 mg/day) for conduct disorder in a preliminary study lasting 10 weeks (25). Of those assigned to risperidone, six completed the course; three completed placebo. Those who took risperidone were significantly less aggressive during the last weeks of the study than those who did not. Eight youths who took risperidone and four who took placebo had at least one adverse effect, including increased appetite ($n = 3$ for risperidone), sedation ($n = 3$ for risperidone; $n = 2$ for placebo), headache ($n = 1$ for risperidone; $n = 1$ for placebo), insomnia ($n = 1$ for risperidone), restlessness ($n = 1$ for risperidone), irritability ($n = 1$ for risperidone), enuresis ($n = 1$ for placebo), and nausea/vomiting ($n = 1$ for risperidone; $n = 1$ for placebo). These adverse effects were mild and transient.

There was marked reduction in aggression in 14 of 26 subjects (10–18 years old) in an open study of risperidone (0.5–4 mg/day) for 2–12 months (26). Two subjects had marked weight gain (8 and 10 kg) in the first 8 weeks; another participant who took lithium (1400 mg/day, serum concentration 0.9 mmol/l) presented with moderate akathisia and hand tremor; in seven, tiredness and sedation occurred after week 8.

Organs and Systems

Cardiovascular

Cardiac arrest was attributed to risperidone in a patient with no history of cardiac disease (30).

One of two children aged 29 and 23 months with autistic disorder developed a persistent tachycardia and dose-related QT_c interval prolongation while taking risperidone (31).

Cardiotoxicity of risperidone has recently been discussed (32) in the light of a death in a patient taking a therapeutic dose (SEDA-22, 68).

Nervous system

Seizures

Stuttering, a rare adverse effect of neuroleptic drugs, is thought to be a harbinger of seizures. Stuttering without seizures has been attributed to risperidone (33).

- A 32-year-old Korean man with delusions took oral risperidone 1.0 mg/day and lorazepam 0.5 mg bd. The dose of risperidone was increased to 4 mg/day over 4 days. On day 5, he began to stutter and could not articulate what he wanted to say without stuttering. The dose of risperidone was increased to 8 mg/day and the stuttering became more pronounced. However, after 1 year of continuous treatment, he did not stutter any more.

The authors suggested that since the patient had a history of stuttering risperidone had reactivated the speech pattern.

Extrapyramidal effects

Risperidone produces dose-related extrapyramidal adverse effects, but at concentrations lower than those of conventional antipsychotic drugs (SEDA-21, 58); at equieffective doses it has fewer such effects than haloperidol (SEDA-21, 57) (SEDA-22, 67) (SEDA-23, 68). The relation between the degree of receptor occupancy and the presence of extrapyramidal symptoms is not clear, as observed in a SPECT study in 20 patients (34). The frequency of risperidone-induced extrapyramidal signs, on the other hand, is intermediate between clozapine and conventional antipsychotic drugs, according to an open study in patients treated for at least 3 months with clozapine ($n = 41$; mean dose 426 mg/day), risperidone ($n = 23$; 4.7 mg/day), or conventional antipsychotic drugs ($n = 42$; 477 mg/day chlorpromazine equivalents) (35). The point prevalence of akathisia was 7.3% in those who took clozapine, 13% in those who took risperidone, and 24% in those who took conventional antipsychotic drugs; the point prevalences of rigidity and cogwheeling were 4.9% and 2.4% respectively with clozapine, 17% and 17% with risperidone, and 36% and 26% with conventional antipsychotic drugs.

A combined analysis of 12 double-blind studies in schizophrenic patients comparing the use of risperidone ($n = 2074$) with placebo ($n = 140$) or haloperidol ($n = 517$) has further stressed the dose-related extrapyramidal effects associated with risperidone (36). After covariance analysis to adjust for baseline ESRS (Extrapyramidal Symptom Rating Scale) scores, sex, race, age, height, duration of symptoms, age at first hospitalization, hospitalization status, and diagnosis, the effects of the maximum dose of risperidone on the mean shift to worse ESRS total scores were 1.4 (CI = 0.73, 2.03) at 1–4 mg/day ($n = 319$); 2.1 (CI = 1.65, 2.50) at 4–8 mg/day ($n = 932$); 3.3 (CI = 2.61, 3.89) at 8–12.5 mg/day ($n = 439$); and 3.8 (CI = 2.99, 4.55) at 13 mg/day or more ($n = 361$). The results also showed a significant dose-dependent increase in the use of antiparkinsonian drugs; the percentages of those requiring antiparkinsonian drugs were 14% at 1–4 mg/day ($n = 319$); 25% at 4–8 mg/day ($n = 900$); 27% at 8–12.5 mg/day ($n = 407$); and 31% at 13 mg/day or more ($n = 335$). Of 882 patients who took risperidone for at least 12 weeks, based on unsolicited reports, two developed tardive dyskinesia.

In an international, multicenter, double-blind study in 183 patients with a first psychotic episode treated with flexible doses of risperidone or haloperidol for 6 weeks, the severity of extrapyramidal symptoms and the use of antiparkinsonian drugs were significantly lower in patients taking low doses (up to 6 mg/day) than high doses (over

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6 mg/day) of risperidone or haloperidol (37). These findings are consistent with the suggestion that patients with a first psychotic episode may require low doses of antipsychotic drugs. Furthermore, the severity of extrapyramidal symptoms was significantly lower in the risperidone-treated patients. Also, risperidone-treated subjects were significantly less likely than haloperidol-treated subjects to require concomitant anticholinergic drugs after 4 weeks (20 versus 63%); they had significantly less observable akathisia (24 versus 53%) and significantly less severe tardive dyskinesia. This was observed in a randomized double-blind comparison of risperidone 6 mg/day ($n = 34$) and haloperidol 15 mg/day ($n = 33$) (38).

In a 9-week open study of risperidone for agitated behavior in 15 patients with dementia (modal dose 0.5 mg/day), extrapyramidal symptoms developed at some point during the trial in 8 patients, and cognitive skills were impaired in 3 patients (39). Similarly, in 22 patients with dementia and behavioral disturbances, treated with risperidone 1.5 mg/day (range 0.5 mg qds to 3 mg bd), 50% had significant improvement, but 50% had some extrapyramidal symptoms (40). A further case of a severe extrapyramidal reaction in an old patient with dementia further illustrated these susceptibility factors (41).

Although several cases of sensitivity to risperidone with extrapyramidal signs in Lewy body dementia have been published (SEDA-20, 52), a case of successful treatment without extrapyramidal adverse effects has also been reported (42).

- A 74-year-old man with Lewy body dementia treated with a combination of donepezil (5 mg in the evening) and risperidone (0.25 mg/day) had significant improvement, objectively and subjectively, within 2 weeks.

Akathisia

Restless legs syndrome has been reported in association with risperidone (43).

- A 31-year-old woman with schizoaffective disorder taking risperidone 6 mg/day complained of uncomfortable tingling and tearing sensations deep inside the calves and less severe sensations in her arms after 5 days; the symptoms vanished after replacement by quetiapine 400 mg/day.

Parkinsonism

Intolerable exacerbation of parkinsonism with risperidone has been reported (SEDA-20, 52), and even a 12-year-old boy reportedly developed parkinsonian tremor while taking risperidone (44). However, in contrast, eight patients (five women, three men) with advanced Parkinson's disease, motor fluctuations, and levodopa-induced dyskinesia took part in an open study with a low dosage of risperidone (mean 0.187 mg/day); after an average of 11 months all the patients had moderate to pronounced reductions in levodopa-induced dyskinesias (45).

Whether risperidone should be used in patients with Parkinson's disease is a subject of debate (46,47).

The efficacy and safety of risperidone have been evaluated in 44 patients (25 women and 19 men) with Parkinson's disease (48). There was either complete or near-complete resolution of hallucinations in 23, but an unsatisfactory response ($n = 6$) or worsening of parkinsonism ($n = 6$) in 12. Excluding patients with diffuse Lewy body disease, there was no significant worsening of scores on the Unified Parkinson's Disease Rating Scale after either 3 or 6 months of treatment, and the presence of dementia did not predict the response to treatment.

The long-term effect of risperidone on basal ganglia volume, measured by MRI scanning, has been studied in 30 patients with a first episode of schizophrenia who took risperidone, 12 patients taking long-term typical neuroleptic drugs, and 23 healthy controls (49). Treatment with risperidone for 1 year (mean dosage 2.7, range 1–6 mg/day) did not alter basal ganglia volume, although there were movement disorders in both groups of treated patients, suggesting effects of both illness and medications.

Tardive dyskinesia

Tardive dyskinesia has occasionally been reported with risperidone (SEDA-20, 53) (SEDA-21, 59) (SEDA-22, 68) (50–55).

The incidence of tardive dyskinesia in patients with chronic schizophrenia taking risperidone is said to be 0.34% per year. Advanced age and dementia may be contributing factors (SEDA-21, 59) (SEDA-22, 68) (SEDA-23, 70).

Tardive dyskinesia/dystonia developed in four patients treated with risperidone at an early intervention facility for young people with psychosis (56). Other cases that have emerged were in:

- a 13-year-old young girl treated with risperidone 6 mg/day (57);
- a 21-year-old woman without previous exposure to other neuroleptic drugs or systemic illnesses that affected the central nervous system (58);
- a 58-year-old man with chronic alcoholism who developed tardive dyskinesia after exposure to risperidone that was aggravated by olanzapine (59).
- a 16-year-old girl who developed buccolingual masticatory tardive dyskinesia after taking risperidone 6 mg/day (60); when she restarted risperidone 2 mg/day, increasing to 6 mg/day later on, the dyskinesia improved.
- a 74-year-old woman who developed persistent tardive dyskinesia following a short trial (3 weeks) of a low dose (0.5 mg bd) of risperidone (61).

Tardive dyskinesia was studied in 330 elderly patients with dementia (mean age 83 years) (62). They were enrolled in a 1-year open study, in which the modal risperidone dose was 0.96 mg/day and the median duration of use was 273 days. The 1-year cumulative incidence of persistent tardive dyskinesia among the 225 patients without dyskinesia at baseline was 2.6%, and patients with dyskinesia at baseline had significant reductions in severity.

Attention deficit hyperactivity disorder (ADHD) may be a susceptibility factor for risperidone-induced tardive dyskinesia and withdrawal dyskinesia. Both conditions have occurred in patients with a past or recent history of attention deficit hyperactivity disorder.

- A 34-year-old woman developed dyskinesia after starting risperidone, with a marked increase in prolactin concentrations (63).

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- A 13-year-old boy developed mild mouth movements, neck twisting, and intermittent upward gaze approximately 2 weeks after withdrawal of risperidone (1.5 mg and then 0.5 mg) (64).

Tardive dystonia

Dystonia and tardive dystonia have been attributed to risperidone.

- A 23-year-old man taking risperidone 8 mg/day developed blepharospasm (65).
- A 25-year-old man, who had never taken any other psychotropic medication, developed tardive dyskinesia with severe blepharospasm and tardive dystonia 2 months after withdrawal of risperidone (66).
- Possible risperidone-induced tardive dystonia has been reported in a 47-year-old man (67).

Marked improvement of tardive dystonia after replacing haloperidol with risperidone in a schizophrenic patient has been reported (68).

Pisa syndrome, a tardive axial dystonia with flexion of the trunk towards one side, is a rare reaction that occurs during treatment with neuroleptic drugs (SED-14, 146) (SEDA-24, 57). Two cases related to risperidone have been published.

- A 24-year-old woman with mental retardation and an unspecified psychosis took risperidone 2 mg/day and trihexyphenidyl 2 mg/day and after 2 weeks developed symptoms that included tilting of her body backwards and to the left and tremors and cogwheel rigidity of the limbs (69). Risperidone was withdrawn and olanzapine 5 mg/day started; after 4 weeks there was no improvement and she was then lost to follow-up.
- A 25-year-old man with auditory hallucinations took risperidone 7 mg/day for 15 months plus biperiden 6 mg/day (70). He then complained of leaning to the right and being unable to straighten up. He had tonic flexion of the trunk to the right with slight backward axial rotation. After 5 months of risperidone withdrawal, the condition had not resolved; it later improved with co-beneldopa 400/100 mg/day and then after the addition of cabergoline 0.75 mg/day.

Rabbit syndrome

Rabbit syndrome has been reported in patients taking risperidone.

- A 27-year-old man took risperidone 6 mg/day and after 4 months the dosage was reduced to 4 mg/day; 7 months after the start of treatment he developed fine rapid pouting and puckering of the lips (71). These movements were accompanied by a strange, irritating, involuntary popping sound. The dosage of risperidone was reduced to 2 mg/day and an anticholinergic drug was added. Within days, there was symptomatic improvement, but a trial withdrawal of the anticholinergic drug resulted in worsening of the symptoms and treatment was renewed.
- A 38-year-old man with major depressive disorder and psychotic features developed rabbit syndrome after taking risperidone 4 mg/day and paroxetine 40 mg/day for 4 months; he was also taking simvastatin 10 mg/day, thiamine 100 mg/day, and folic acid 1 mg/day (72).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been reported in patients taking risperidone (73,74); most cases occurred within the first months, and even as early as 12 hours (SEDA-22, 68) (SEDA-23, 70).

Delayed risperidone-induced neuroleptic malignant syndrome has been reported in a 27-year-old man after 21 months (75), and in a 17-year-old girl who took risperidone 0.5 mg bd (76). Risperidone-induced neuroleptic malignant syndrome has also been reported in a 63-year-old woman with probable Lewy body dementia, who had previously had an episode of neuroleptic malignant syndrome with trifluoperazine (77).

A patient with schizoaffective disorder, who developed risperidone-related neuroleptic malignant syndrome, responded satisfactorily to supportive management and vitamin E plus vitamin B6 (78).

Catatonia

Catatonia has been reported in relation to risperidone (SEDA-23, 72) (79,80).

- Catatonia occurred in a 61-year-old woman who was taking risperidone 5 mg/day for prominent paranoid delusions after a post-frontal lobotomy some 35 years ago. The catatonic disorder was dose-dependent and resolved immediately after changing to clozapine.

Pseudotumor cerebri

Two patients with hydrocephalus and learning difficulties developed headache, nausea, vomiting, drowsiness, lethargy, and episodes of collapse after starting to take risperidone for aggressive outbursts; the condition mimicked increased intracranial pressure (81). Withdrawal of the drug resulted in complete resolution of all the symptoms within 72 hours. The authors pointed out the striking degree of overlap between the adverse effects profile of risperidone and the symptoms of raised intracranial pressure due to shunt malfunction, which has not been previously highlighted.

Psychological, psychiatric

Anxiety and behavioral stimulation, characterized by anxiety, insomnia, and restlessness, during risperidone treatment have been reported (SEDA-20, 53) (SEDA-21, 59) (SEDA-23, 71) (82). Six of thirteen outpatients who took part in a 10-week open trial of risperidone had a good initial response, followed by intolerable effects, including feelings of agitation and depression and periods of crying and insomnia (83). The patients who developed this syndrome had a significantly higher mean baseline rating on the Brief Psychiatric Rating Scale anxiety subscale.

Visual distortion with generalized anxiety and panic attacks has been attributed to risperidone (SEDA-22, 69). Visual disturbance resembling hallucinogen persistent perception disorder occurred after each of three consecutive risperidone dosage increases in a 55-year-old woman; there was absence of substance abuse (84).

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It has been speculated that the antiserotonergic properties of risperidone could lead to obsessive and depressive symptoms, since a patient taking risperidone 4 mg/day developed major depression and obsessions, which resolved with fluoxetine 29 mg/day, relapsing when fluoxetine was withdrawn (85).

Mania

Mania has rarely been associated with typical neuroleptic drugs, but has been described in patients treated with new antipsychotic drugs, especially risperidone (SEDA-22, 69) (SEDA-23, 71) (86). Risperidone-induced mania occurred in a 23-year-old man and a 21-year-old woman, who developed acute mania with euphoria, psychomotor agitation, and hypersexuality, at dosages of 4–8 mg/day (87).

Nevertheless, risperidone has been used in the treatment of mania in combination with mood stabilizers (SEDA-23, 69) (SEDA-26, 64).

Obsessive-compulsive disorder

Obsessive-compulsive symptoms associated with risperidone have been reported (SEDA-22, 69).

- Obsessive-compulsive symptoms developed in a 26-year-old Chinese woman taking risperidone for a chronic schizophrenic illness (88). She had no history of obsessive-compulsive symptoms. Risperidone 2 mg/day, benzhexol 2 mg/day, and diazepam 10 mg at night had been prescribed after she had had adverse effects with other antipsychotic drugs.
- A man who had taken risperidone 4 mg/day for 18 months developed an obsessional image of a person's face that repeatedly appeared in his mind as he went about his activities; the recurrent images disappeared after the dosage of risperidone was reduced to 3 mg/day (89).

In one case, reintroduction of risperidone did not cause obsessive-compulsive symptoms to re-emerge in a 29-year-old man who had previously developed obsessive-compulsive features when first treated with risperidone (90).

Endocrine

Prolactin

There was a significant rise in baseline serum prolactin concentration in 10 patients after they had taken risperidone for a mean of 12 weeks compared with 10 patients who were tested after a neuroleptic drug-free wash-out period of at least 2 weeks (91). A non-significant increase in serum prolactin has also been observed in an open comparison of risperidone with other neuroleptic drugs in 28 patients (92). However, in a meta-analysis of two independent studies ($n = 404$), prolactin was greatly increased by risperidone (mean change 45–80 ng/ml), a larger effect than with olanzapine and haloperidol (93).

Five patients (four women and one man, aged 30–45 years), who were evaluated for risperidone-induced hyperprolactinemia, had significant hyperprolactinemia, with prolactin concentrations of 66–209 μg/l (94). All but one had manifestations of hypogonadism, and in these four patients, risperidone was continued and a dopamine receptor agonist (bromocriptine or cabergoline) was added; in three patients this reduced the prolactin concentration and alleviated the hypogonadism.

The relation of prolactin concentrations and certain adverse events has been explored by using data from two large randomized, double-blind studies ($n = 2725$; 813 women, 1912 men) (95). Both risperidone and haloperidol produced dose-related increases in plasma prolactin concentrations in men and women, but they were not correlated with adverse events such as amenorrhea, galactorrhea, or reduced libido in women or with erectile dysfunction, ejaculatory dysfunction, gynecomastia, or reduced libido in men. Nevertheless, in five patients risperidone (1–8 mg/day) caused amenorrhea in association with raised serum prolactin concentrations (mean 122 ng/ml, range 61–230 ng/ml; reference range 2.7–20 ng/ml) (96).

Furthermore, risperidone-induced galactorrhea associated with a raised prolactin has been reported (97,98), as have amenorrhea and sexual dysfunction (18).

- Galactorrhea associated with a rise in prolactin occurred after a few weeks of treatment with risperidone in two women aged 24 and 39 (97). One of them was switched to thioridazine, with an improvement in the galactorrhea, and the other continued to take risperidone owing to a robust response; her galactorrhea was partially treated with bromocriptine.
- A 34-year-old woman, who developed amenorrhea while taking risperidone, regained her normal menstrual pattern along with a marked fall in serum prolactin concentration 8 weeks after being switched to olanzapine, whereas amantadine had failed to normalize the menses and had apparently reactivated the psychotic symptoms (99).

The authors suggested that olanzapine may offer advantages for selected patients in whom hyperprolactinemia occurs during treatment with other antipsychotic drugs.

- Galactorrhea and gynecomastia occurred in a 38-year-old hypothyroid man who took risperidone for 14 days (100).

The authors suggested that men with primary hypothyroidism may be particularly sensitive to neuroleptic drug-induced increases in prolactin concentrations.

- A 17-year-old man developed galactorrhea and breast tenderness within weeks of starting to take risperidone.

The authors suggested that patients who have galactorrhea, amenorrhea, or both while taking risperidone should be gradually switched to olanzapine, quetiapine, or clozapine (101). Indeed, when 20 women with schizophrenia who were taking risperidone and had menstrual disturbances, galactorrhea, and sexual dysfunction (SEDA-24, 72) (SEDA-26, 65) were switched from risperidone to olanzapine over 2 weeks and then took olanzapine 5–20 mg/day for 8 further weeks, serum prolactin concentrations fell significantly (102). Scores on the Positive and Negative Syndrome Scale, Abnormal Involuntary Movement Scale, and Simpson–Angus Scale for extrapyramidal symptoms at the end-point were also significantly reduced. There were improvements in menstrual functioning and patients' perceptions of sexual adverse effects.

Amenorrhea presumed to have been induced by risperidone has been successfully treated with

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Shakuyaku-kanzo-to, a Japanese herbal medicine that contains *Peoniae radix* and *Glycyrrhizae radix* (103).

Metabolism

Diabetes mellitus

There has been a report of diabetic ketoacidosis in a 42-year-old man, without a prior history of diabetes mellitus, who took risperidone (2 mg bd) (104). The authors pointed out that in premarketing studies of risperidone, diabetes mellitus occurred in 0.01–1% of patients.

Weight gain

Pathological weight gain has been increasingly identified as a problem when atypical neuroleptic drugs are given to children (SEDA-21, 57) (SEDA-22, 69). In one case, unremitting weight gain, triggered by risperidone, was eventually curbed through the use of a diet containing slowly absorbed carbohydrates and a careful balance of carbohydrates, proteins, and fats (105).

- A 9-year-old boy with autism and overactivity was unresponsive to several drugs. Risperidone 0.5 mg bd was effective, reducing his Aberrant Behavior Checklist score from 103 to 57 by the end of the first week. Four weeks later his weight had risen from 34.6 to 37 kg. This rate of weight gain (0.6 kg/week) continued over the next 12 weeks. His weight was then contained by the use of the "Zone" diet, with an emphasis on slowly absorbed carbohydrates (examples include apples, oatmeal, kidney beans, whole-grain pasta, and sweet potatoes) in a calorie-reduced diet containing 30% proteins and 30% fats.

In 37 children and adolescent inpatients treated with risperidone for 6 months, compared with 33 psychiatric inpatients who had not taken atypical neuroleptic drugs, risperidone was associated with significant weight gain in 78% of the treated children and adolescents compared with 24% of those in the comparison group (106). Risperidone dosage, concomitant medicaments, and other demographic characteristics (such as age, sex, pubertal status, and baseline weight and body mass index) were not associated with an increased risk of morbid weight gain.

In contrast, in a multicenter, open study in 127 elderly psychotic patients (median age 72, range 54–89 years) taking risperidone (mean dose 3.7 mg/day) there was no significant weight gain after 12 months (107).

Risperidone-induced obesity can cause sleep apnea (108).

- A 50-year-old man with schizophrenia gained 29 kg over 31 months and developed diabetes while taking risperidone 6 mg/day. He reported difficulty in sleeping and frequent daytime napping that left him unsatisfied, and his wife reported prominent snoring and apnea at night.

Nasal continuous positive airway pressure produced improvement.

Electrolyte balance

Polydipsia with hyponatremia has been reported in patients taking risperidone (109,110).

- A 28-year-old man complained of unbearable thirst 2 weeks after starting risperidone 8 mg/day, and would drink 4–5 liters of water within a variable period of a few minutes to 8 hours; he did not develop hyponatremia (111). The condition lasted about 2 years and remitted after withdrawal of risperidone. After a drug-free interval of 2 weeks, clozapine was started and the condition had not recurred after 6 months.

The mechanism of this effect was unclear. The authors thought that SIADH was unlikely, considering the features of polyuria, a low urine osmolality (172 mosmol/kg), and absence of hyponatremia during polydipsia.

Hematologic

Agranulocytosis, leukopenia, neutropenia, lymphopenia, and thrombocytopenia have been reported in patients taking risperidone (112–115).

- A 40-year-old woman developed agranulocytosis after taking risperidone for 2 weeks (114). She had also developed agranulocytosis after treatment with several other antipsychotic drugs (chlorpromazine, haloperidol, and zuclopenthixol).

Mouth and teeth

Hypersalivation or sialorrhea has been reported with all neuroleptic drugs, and has been associated with risperidone as one of the most frequently mentioned adverse effects in patients with disturbing extrapyramidal symptoms during previous neuroleptic drug treatment (SEDA-25, 68). Hypersalivation is a troublesome adverse effect that can contribute to non-adherence to therapy, but it can be treated with clonidine.

- Hypersalivation in a 22-year-old man was rapidly and markedly reduced by clonidine 0.1 mg bd over 3 days (116).

Liver

Several cases of hepatotoxicity have been reported in adults (117) and boys (SEDA-22, 69) taking long-term risperidone.

- Hepatotoxicity occurred in an 81-year-old man who took only two doses of risperidone 0.5 mg (118).
- In a 25-year-old woman, liver function tests were 2.6–7.4 times higher than the upper limit of the reference range during risperidone therapy (119).
- A 13-year-old girl developed liver enzyme rises and fatty liver infiltration in the context of pre-existing obesity after taking risperidone 0.5 mg/day for 3 days (120).
- Transient increases in liver enzymes induced by risperidone occurred in two men aged 19 and 22 (121).
- Cholestatic jaundice occurred in a 37-year-old man taking risperidone (122).

Urinary tract

Hemorrhagic cystitis has been associated with risperidone (123).

- An 11-year-old boy developed acute dysuria and increased frequency accompanied by gross hematuria. He was taking fluoxetine, valproic acid, benzatropine,

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haloperidol, clonidine, trazodone, and nasal desmopressin. One week before presentation, risperidone had been introduced instead of haloperidol to improve behavioral control. The risperidone was discontinued and haloperidol resumed, and his symptoms resolved during the following week.

Several cases of urinary incontinence have been associated with risperidone, and the manufacturers report that this adverse effect occurs in up to 1% of patients (SEDA-22, 70). The authors of a report of two patients, in both of whom the adverse effect was clearly temporally related to the drug, stated that at least 28% of patients developed transient urinary incontinence after starting risperidone (124).

Skin

Photosensitivity has been attributed to risperidone.

- A 69-year-old woman taking risperidone developed an erythematous rash with areas of blistering and early desquamation. It was most pronounced in exposed areas, although there was some spread beyond (125).

Sexual function

Prolonged erection has been reported with risperidone (126) (SEDA-24, 71).

- Priapism associated with risperidone occurred in a 19-year-old man who had taken 2 mg/day for 4 days (127).

In one case priapism followed the use of first risperidone and then ziprasidone (128). In two other cases, presumed to be due to risperidone (129,130), penile irrigation with isotonic saline and phenylephrine injection resulted in detumescence. Risperidone has a high affinity for alpha-1 adrenoceptors, and alpha-1 blockade leads to direct arteriolar dilatation, which results in increased blood inflow and reduced outflow secondary to effacement and subsequent obstruction of emissary veins.

Ejaculatory dysfunction has also been associated with risperidone in two cases.

- A 21-year-old patient with bipolar schizoaffective disorder developed absent ejaculation with normal orgasm 3 weeks after starting to take risperidone (131).
- A 37-year-old man with paranoid schizophrenia had ejaculatory difficulty during sexual intercourse with his wife, compatible with retrograde ejaculation, 1–2 weeks after starting to take risperidone (132). He reported complete failure to emit semen but a normal desire, erection, and sense of orgasm. Semen was seen in postcoital urine. The dosage of risperidone was reduced to 3 mg/day and anterograde ejaculation was partially restored.

Immunologic

Risperidone has been rarely associated with allergic reactions (SEDA-22, 70).

Long-Term Effects

Drug withdrawal

Serious withdrawal effects have occasionally been reported with risperidone (SEDA-21, 60) (SEDA-22, 70). Both manic and psychotic symptoms have been described in a patient with chronic schizophrenia after risperidone withdrawal (133).

- A 38-year-old Chinese man responded to risperidone monotherapy for 2 weeks after 19 years of resistance to typical neuroleptic drugs. Three days later he lost his medicine and 2 days later his auditory hallucinations and persecutory delusions recurred. Meanwhile, vivid manic symptoms (such as heightened mood, irritability, reduced need for sleep, hyperactivity, pressured speech, flight of ideas, and grandiosity) emerged for the first time throughout the history of his illness.
- Dyskinesia occurred for 5 days in an 82-year-old woman after withdrawal of risperidone and citalopram, which she had taken for about 3 months (134).

It is not clear whether this was a withdrawal effect or a tardive dyskinesia in response to risperidone.

Second-Generation Effects

Teratogenicity

All neuroleptic drugs cross the placenta and reach the fetus in potentially significant amounts; the best recommendation is to avoid any drug during the first trimester and only to use drugs thereafter if the benefits to the mother and fetus outweigh any possibility of risk (SED-14, 152) (SEDA-22, 54). Risperidone has been used in two women before and throughout pregnancy without developmental abnormalities in the children after 9 months and 1 year; the dosages started at 2 mg/day and were increased to 4–6 mg/day (135). In a large postmarketing study of 7684 patients who took risperidone, nine women took it during ten pregnancies; there were seven live births and three therapeutic terminations of pregnancy (SEDA-23, 69) (136).

Lactation

The distribution and excretion of risperidone and 9-hydroxyrisperidone into the breast milk of a young woman with puerperal psychosis, who was treated with risperidone, has been reported (137).

- A 21-year-old woman with a 2-year history of bipolar disorder stopped all of her medication when she discovered that she was pregnant; she was given risperidone 2.5 months after childbirth, gradually increasing to a steady-state dosage of 6 mg/day. Risperidone and 9-hydroxyrisperidone concentrations in plasma and breast milk were measured, and calculations indicated that a suckling infant would receive only 0.84% of the maternal dose as risperidone and 3.46% as 9-hydroxyrisperidone.

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Susceptibility Factors

Genetic factors

Impaired metabolism of risperidone can increase the risk of adverse effects.

- A homozygous non-functional genotype, CYP2D6*4, was found in a 17-year-old patient with schizophrenia who developed severe akathisia, parkinsonism, and drowsiness after taking risperidone 6 mg/day for 3 months; he had high plasma concentrations of risperidone and an active metabolite (138).

Age

Elderly people

Elderly patients with dementia have been said to be at particular risk of developing extrapyramidal adverse effects, even with very low doses.

Delirium occurs in 1.6% of elderly patients newly treated with risperidone (SEDA-22, 70), and cases have been reported in patients of advanced age (139,140). It is suggested that in these patients, treatment should begin with low dosages (0.25–0.5 mg/day) and that the dosage be gradually increased over several days, with close monitoring.

The safety, tolerability, and efficacy of risperidone have been assessed in 103 patients with schizophrenia (52 men and 51 women) aged 65 years or older in an open, multicenter, 12-week study (141). The mean risperidone dose at end-point was 2.4 mg/day. Adverse events occurred in 91 patients and included dizziness ($n = 23$), insomnia ($n = 17$), agitation ($n = 15$), somnolence ($n = 15$), injury ($n = 12$), constipation ($n = 11$), and extrapyramidal disorders ($n = 10$); 11 patients withdrew because of adverse events. Among the 91 patients with normal baseline QT_c intervals (below 450 ms), 9 had a prolonged QT_c interval during the study (range 450–516 ms).

Adverse effects leading to dosage reduction or discontinuation were also observed in a retrospective study in 57 patients mean age 84 (range 66–97) years, who took risperidone (doses 0.5–4 mg/day) for more than 1 year (average 2 years) for dementia-related behavioral disturbances (142). Adverse effects included hypotension ($n = 4$), agitation ($n = 6$), and sedation ($n = 5$), and six patients developed a new movement disorder.

In a retrospective study, a substantial proportion of patients who needed antiparkinsonian medication while taking risperidone (mean daily dose 4.4 mg) were identified. Twelve of fifty-five elderly inpatients (aged over 65 years) taking risperidone received antiparkinsonian drugs (143).

A large proportion of new or worsened extrapyramidal adverse effects (32%) was observed in a review of the charts of 41 patients with dementia (mean age 75 years) treated with risperidone (mean 1.8 mg/day) (144).

Children

There was a high incidence (44%) of new movement disorders in 36 children and adolescents who were treated with risperidone (the highest dose of risperidone was 6 mg/day and the average maintenance dose was 4 mg/day) (145). The higher incidence reported in the latter series has been countered by a contrasting report that the most common adverse effect was excessive weight gain ($n = 10$) in a series of 30 children and adolescents (aged 6–21 years) taking risperidone (0.5–6 mg/day) for attention-deficit disorder (146). Vomiting and drowsiness each occurred in one patient; one patient had withdrawal dyskinesia, but the reintroduction of risperidone and slower withdrawal produced no recurrence.

Other features of the patient

Hypothermia associated with hypothalamic and thermoregulatory dysfunction has been reported in a patient with Prader–Willi syndrome taking risperidone and olanzapine (147). Hypothermia in response to these drugs is said to result from 5-HT_2 receptor blockade, and it is recommended that patients with hypothalamic dysfunction should be carefully monitored if risperidone or olanzapine are used.

Drug Administration

Drug dosage regimens

The safety and tolerability of a rapid oral loading regimen for risperidone, developed to achieve therapeutic doses within 24 hours, have been evaluated (148). Risperidone was begun in a dose of 1 mg, increasing by 1 mg every 6–8 hours up to 3 mg. Dose increases were contingent on the tolerance of the last administered dose. Of 11 consecutive inpatients who were treated with this protocol, seven tolerated the most rapid titration, achieving a dose of 3 mg bd in 16 hours; three required slightly slower titration and achieved the target dose in 24 hours; one could not tolerate the 3 mg dose but tolerated 2 mg tds; no patient had serious extrapyramidal adverse effects, sedation, or any other adverse event during the rapid titration, and in no case did risperidone have to be withdrawn. The authors concluded that aggressive dosing with risperidone is well tolerated in most psychiatric inpatients.

A randomized double-blind comparison of two dosage regimens of risperidone, 8 mg od and 4 mg bd for 6 weeks, in 211 patients has provided further information (149). Neither efficacy nor ESRS scores differed significantly. At least one adverse event was reported in 72 of the patients taking once-daily therapy and 87 of the patients taking twice-daily therapy. The most frequently reported were insomnia, anxiety, extrapyramidal symptoms, agitation, and headache. The only statistically significant difference between the groups was in the incidence of anxiety, which was reported by 31% of those taking twice-daily therapy and 17% of those taking once-daily therapy.

The optimal dose of risperidone in first-episode schizophrenia has been studied in 17 drug-naive patients (12 women, 5 men; mean age 29 years) (150). The mean optimal dosage of risperidone was 2.70 mg/day. All the patients reached the optimal dose before developing extrapyramidal adverse effects; four developed parkinsonism and one developed akathisia at a mean dosage of 5.20 mg/day. In contrast, acute exacerbations of schizophrenia may require a higher dose.

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Drug overdose

During 13 months, a regional poisons center gathered information by telephone on 31 patients with reported risperidone overdose (151). Risperidone was the sole ingestant in 15 cases (1–180 mg). The major effects in this group included lethargy ($n = 7$), spasm/dystonia ($n = 3$), hypotension ($n = 2$), tachycardia ($n = 6$), and dysrhythmias ($n = 1$). One patient who co-ingested imipramine died of medical complications, but symptoms resolved within 24 hours in most of the others; all the patients were asymptomatic at 72 hours after ingestion.

- A 41-year-old man who took risperidone 270 mg developed a prolonged QT_c interval (480 ms) and sinus bradycardia (44/minute), without hemodynamic compromise. After 9 hours, he had episodes of asymptomatic supraventricular tachycardia with a maximum frequency of 150/minute. After 30 hours he was in sinus rhythm with a normal QT_c interval (360 ms). He was discharged 72 hours after admission, asymptomatic and with a normal electrocardiogram.
- A 15-year-old who took 110 mg of risperidone in a suicide attempt developed only transient lethargy, hypotension, and tachycardia without any other significant effects (152).

Drug–Drug Interactions

Carbamazepine

Carbamazepine induces CYP3A, and the metabolism of risperidone, which mainly involves CYP2D6, may also involve CYP3A. Carbamazepine can therefore reduce risperidone plasma concentrations (SEDA-22, 71). However, since carbamazepine alters the biotransformation of many agents, non-specific enzyme induction has been suggested for the risperidone and carbamazepine interaction (153).

Plasma concentrations of risperidone and 9-hydroxyrisperidone were measured in 44 patients (aged 26–63 years) treated with risperidone alone ($n = 23$) or comedicated with carbamazepine ($n = 11$) (154). Carbamazepine markedly reduced the plasma concentrations of risperidone and 9-hydroxyrisperidone.

Mean plasma concentrations of risperidone and 9-hydroxyrisperidone (5 ng/ml and 35 ng/ml) fell significantly during carbamazepine co-administration (2.5 ng/ml and 19 ng/ml) in 11 schizophrenic patients taking risperidone 6 mg/day and then carbamazepine 400 mg/day for 1 week; the changes in risperidone concentrations correlated positively with the concentration ratio of risperidone/9-hydroxyrisperidone, which was closely associated with CYP2D6 genotype (155).

Conversely, carbamazepine concentrations can increase when risperidone is added; when risperidone 1 mg/day was added in eight patients taking carbamazepine (mean dose 625 mg/day) carbamazepine plasma concentrations increased from 6.7 μg/ml at baseline to 8.0 μg/ml 2 weeks later (156).

- A 23-year-old man had raised 9-hydroxyrisperidone concentrations in association with carbamazepine dosage reduction and concomitant fluvoxamine therapy (157).
- In a 50-year-old man with deficient CYP2D6 activity, the addition of carbamazepine to pre-existing risperidone therapy resulted in a marked reduction in the plasma concentrations of risperidone and 9-hydroxyrisperidone and an acute exacerbation of his psychosis (158).

Clozapine

Risperidone increases plasma clozapine concentrations (159). The effects of risperidone 3.25 mg/day on cytochrome P450 isozymes have therefore been assessed in eight patients by determination of the metabolism of caffeine (for CYP1A2), dextromethorphan (for CYP2D6), and mephenytoin (for CYP2C19) (159). The results suggested that risperidone is a weak in vivo inhibitor of CYP2D6, CYP2C19, and CYP1A2. The authors concluded that inhibition by risperidone of those isozymes is an unlikely mechanism to explain increased clozapine concentrations.

HIV protease inhibitors

An interaction of risperidone with ritonavir and indinavir has been reported (160).

- A 34-year-old man with AIDS took risperidone 4 mg/day for a Tourette-like tic disorder. Ritonavir and indinavir were added, and 1 week later he developed significantly impaired swallowing, speaking, and breathing, and worsening of his existing tremors.

The authors hypothesized that inhibition of CYP2D6 and CYP3A4 by ritonavir and indinavir may have resulted in accumulation of the active moiety of risperidone.

Lithium

Dystonia occurred in an 81-year-old man who took lithium in addition to risperidone 1 mg/day, valproic acid 2250 mg/day, and benzatropine 4 mg/day (161).

Maprotiline

In three patients, maprotiline plasma concentrations increased when risperidone was added (162). The rise was explained by inhibition of CYP2D6, by which maprotiline is mainly metabolized.

Opioids

Two patients who were hospitalized with a diagnosis of opioid dependence received concomitant treatment with methadone 50 mg/day in one case, and levorphanol 14 mg/day in the other, each in association with risperidone. After several days, both had symptoms of opioid withdrawal despite having no change in their opioid doses (163). The withdrawal symptoms resolved soon after risperidone was withdrawn. According to the authors, this finding suggests that risperidone may precipitate opioid withdrawal in opioid-dependent patients.

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Phenytoin

An interaction between risperidone and phenytoin resulted in extrapyramidal symptoms (164).

SSRIs

The possibility of a pharmacodynamic interaction between risperidone and serotonin re-uptake inhibitors has been discussed (165–167). Published cases of amelioration and deterioration have perpetuated the debate. Amelioration was observed in four patients with depression that had responded inadequately to selective serotonin re-uptake inhibitors by the addition of risperidone 1 mg bd ($n = 2$) or 0.5 mg at night ($n = 2$) (168).

Fluoxetine

A pharmacokinetic interaction of risperidone with fluoxetine has been reported (SEDA-22, 71). When 10 schizophrenic patients stabilized on risperidone 4–6 mg/day took fluoxetine 20 mg/day for concomitant depression the mean plasma risperidone concentration increased from 12 to 56 ng/ml at week 4; the concentration of 9-hydroxyrisperidone was not significantly affected (169). One patient dropped out after 1 week because of akathisia associated with a markedly increased plasma risperidone concentration.

In an open, 30-day trial, the pharmacokinetics, safety, and tolerability of a combination of risperidone 4 or 6 mg/day with fluoxetine 20 mg/day were evaluated in 11 psychotic inpatients (170). CYP2D6 genotyping showed that three were poor metabolizers and eight were extensive metabolizers. The mean AUC of risperidone increased from 83 and 398 h.ng/ml to 341 and 514 h.ng/ml when risperidone was co-administered with fluoxetine in extensive and poor metabolizers respectively. However, despite this pharmacokinetic interaction, the severity and incidence of extrapyramidal symptoms and adverse events did not increase significantly when fluoxetine was added; 10 of the 11 patients improved clinically.

- Catastrophic deterioration, with the severity of obsessive-compulsive symptoms returning to pretreatment levels, was observed in a 21-year-old man when risperidone was added to fluoxetine in a dosage that was stepped up to 3 mg/day (171).

Fluvoxamine

- A 24-year-old woman with auditory hallucinations taking risperidone 6 mg/day developed neuroleptic malignant syndrome after adding fluvoxamine 50 mg/day (172).

Paroxetine

The serotonin syndrome has been reported during treatment with paroxetine and risperidone (173). A case of edema in a patient taking risperidone and paroxetine has also been reported (174).

The effects of paroxetine 20 mg/day for 4 weeks on steady-state plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone have been studied in 10 patients taking risperidone 4–8 mg/day (175). During paroxetine administration, mean plasma risperidone concentrations increased significantly, while 9-hydroxyrisperidone concentrations fell slightly but not significantly; after 4 weeks, the sum of the risperidone and 9-hydroxyrisperidone concentrations increased significantly by 45% over baseline, and the mean plasma risperidone/9-hydroxyrisperidone concentration ratio was also significantly changed. However, the drug combination was generally well tolerated, with the exception of one patient who developed parkinsonian symptoms during the second week, and whose total plasma risperidone and 9-hydroxyrisperidone concentrations increased by 62%.

Venlafaxine

In eight patients with major depressive disorder without psychotic features, who did not respond to serotonin re-uptake inhibitors therapy when risperidone was added, all improved within 1 week. Furthermore, risperidone also seemed to have beneficial effects on sleep disturbance and sexual dysfunction (176). In an open study in 30 healthy subjects who took risperidone 1 mg orally before and after venlafaxine dosing to steady state, the oral clearance of risperidone fell by 38% and the volume of distribution by 17%, resulting in a 32% increase in AUC; renal clearance of 9-hydroxyrisperidone also fell by 20% (177). The authors concluded that these small effects were consistent with the fact that venlafaxine is unlikely to alter the clearance of risperidone, which is mainly by CYP2D6.

Tetracycline

- A possible interaction of risperidone with tetracycline has been reported in a 15-year-old adolescent with Asperger's syndrome, Tourette's syndrome, and obsessive-compulsive disorder (178). Acute exacerbation of motor and vocal tics occurred when tetracycline 250 mg bd was introduced for acne; withdrawal of tetracycline resulted in an improvement in the tics.

Thioridazine

A 23-year-old man had high risperidone plasma concentrations secondary to concurrent thioridazine use (157).

Valproate

Plasma concentrations of risperidone and 9-hydroxyrisperidone were measured in 44 patients (aged 26–63 years) taking risperidone alone ($n = 23$) or co-medicated with sodium valproate ($n = 10$) (154). Valproate had no major effect on plasma risperidone concentrations.

However, an anecdotal report has suggested that some individuals may be susceptible to an interaction.

- Catatonia occurred in a 42-year-old woman taking valproic acid, sertraline, and risperidone (79). The catatonic features evolved for the first time after a single dose of valproate and were alleviated by lorazepam; the same catatonic signs recurred after a second dose of valproate and again remitted after lorazepam.

The authors considered that this was a possible interaction, since catatonia has not been reported with valproate alone.

The addition of risperidone 10 mg/day over 2 months to valproate and clonazepam in a 40-year-old woman

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provoked marked edema in the legs and moderate edema in the arms (179). The authors considered that this was a possible interaction, since edema has not been reported with either of these drugs separately.

In contrast, a beneficial interaction has been observed when valproic acid was added to risperidone; the previous addition of valproic acid to treatment with chlorpromazine had no effect on psychotic symptoms (180).

Diagnosis of Adverse Drug Reactions

A therapeutic target range for serum risperidone concentrations has not been established, but in 20 of 22 patients taking 6 mg/day, which is considered the optimum dosage for most patients, risperidone serum concentrations were 50–150 nmol/l (181). Steady-state serum concentrations of risperidone and 9-hydroxyrisperidone, the active moiety, were also measured in 42 patients; there was no correlation between the serum concentration of the active moiety and adverse effects.

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Ritanserin

General Information

Ritanserin, a selective 5-HT_2 receptor antagonist, increases slow-wave sleep in healthy volunteers (1). It improved sleep in middle-aged poor sleepers (2), but on withdrawal after 20 days treatment there was rebound sleep impairment, which was at its worst 3 nights after withdrawal, consistent with its long half-life (40 hours). Ritanserin is thus not a useful hypnotic, but analogues with more appropriate kinetics will be of interest.

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Ritodrine

See also Beta$_2$-adrenoceptor agonists

General Information

Ritodrine is a beta$_2$-adrenoceptor agonist used in the treatment of premature labor.

The hemodynamic effects of ritodrine have been assessed in 12 fetuses by cardiac and extracardiac Doppler sonography (1). Ritodrine significantly increased maternal and fetal heart rates, left cardiac stroke volume, and cardiac output. There was also an increase in the pulsatility index of the middle cerebral artery and a fall in the pulsatility index of the umbilical artery during ritodrine infusion. The authors suggested that ritodrine vasodilates fetal vessels in the placenta.

Organs and Systems

Cardiovascular

Ritodrine can cause bradycardia instead of the expected tachycardia (SEDA-8, 145); an unexpected hypertensive crisis has also been reported (SEDA-8, 145). ST segment depression is a consistent finding in patients during ritodrine infusion, and should therefore not always be

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interpreted as an indication of myocardial ischemia. The electrocardiographic changes are unrelated to the more generally accepted changes in heart rate, glucose, and potassium concentrations and are probably an intrinsic effect of the drug.

Endocrine

Brief infusions of ritodrine (0.15 mg/minute for 4 hours) rapidly increased plasma melatonin concentrations in healthy women (2).

Metabolism

There are two well-documented independent reports of severe ketoacidosis in non-diabetic pregnant subjects; both the beta-agonist therapy and inadequate dietary intake could have played a role (3).

Hematologic

Agranulocytosis has been documented in a pregnant woman given ritodrine (SEDA-17, 165).

Skin

Palmar erythema was observed in 12 of 209 patients who were treated with ritodrine for more than 7 days (SEDA-12, 123).

Immunologic

A petechial rash due to vasculitis has been documented in a pregnant woman given ritodrine (SEDA-17, 165).

Second-Generation Effects

Fetotoxicity

Neonatal jaundice is more frequent in the babies of mothers who received ritodrine during the second or third trimesters of pregnancy (4).

Magnetocardiography has been used to detect fetal cardiac dysrhythmias in 84 pregnant women with normal pregnancies and in 68 women receiving ritodrine for preterm labor (5). There were dysrhythmias in 3.5% of the fetuses in the normal pregnancy group and in 16% in the ritodrine-treated group.

Drug–Drug Interactions

Atropine

When ritodrine is used to alleviate fetal distress and surgical intervention (cesarean section), atropine premedication must be avoided. The vagolytic action of atropine is synergistic with the action of ritodrine, resulting in severe maternal tachycardia and systolic hypertension (6).

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Rituximab

See also Monoclonal antibodies

General Information

Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen of normal and malignant B lymphocytes, produces prolonged depletion of B lymphocytes. It has been used to treat refractory or relapsing follicular non-Hodgkin's lymphoma and has been tried in other B cell malignancies, including low-grade non-Hodgkin's lymphoma and diffuse large B cell lymphoma. There has also been interest in its use to treat autoimmune diseases (1–3) and in reducing anti-HLA antibodies in patients awaiting renal transplantation (4).

A wide range of adverse events has been reported in most patients (5). A transient flu-like syndrome is very common (50–90%), particularly after the first infusion of rituximab, and is often associated with various hypersensitivity-like symptoms (5–20%). In the most severe cases, patients had life-threatening cytokine release syndrome with dyspnea, bronchospasm, hypoxia, hypotension, urticaria, and angioedema. Deaths have been reported in eight of 12 000–14 000 patients after drug launch.

Severe reactions to rituximab are rare, but are seen in patients with bulky tumors or with leukemic involvement with high numbers of CD20 positive cells (6,7) and were ascribed to a rapid tumor lysis syndrome (6,8,9). In 11 patients with malignant B cell leukemia, first-dose reactions were significantly more severe in patients whose baseline lymphocyte count was higher than 50×10^6/l and were also associated with raised peak serum concentrations of tumor necrosis factor alfa and interleukin-6 (10).

Organs and Systems

Cardiovascular

Cardiac dysrhythmias have been reported in 8% of patients treated with rituximab in patients with lymphomas (11).

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Respiratory

Desquamative alveolitis has been reported in a 55-year-old woman with mantle-cell lymphoma given rituximab (12).

Sensory systems

A variety of ocular adverse effects, including conjunctivitis, transient ocular edema, and visual changes, occurred in 7% of patients receiving rituximab (11).

Hematologic

The factors associated with toxicity in patients with B cell lymphoma receiving rituximab have been studied in Japan (13). By univariate analysis overall non-hematological toxic effects (grade 2 or greater) were more frequent in patients with extranodal disease and especially in those with bone marrow involvement. Fever was more frequent in patients with raised LDH activity, whereas chills/rigors and vomiting were more frequent in patients with extranodal disease. Patients with raised LDH activity or extranodal disease may therefore require closer monitoring. Hematological toxic effects of grade 3 or worse were more common in women.

- A 26-year-old woman with a diffuse large B cell lymphoma received CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin, and prednisone), rituximab, and radiotherapy (14). She developed a transfusion-dependent anemia. Bone marrow biopsy confirmed pure red cell aplasia and parvovirus infection. She had no antibodies to parvovirus, suggesting that she never had a previous exposure. Intravenous immunoglobulin resulted in a reticulocytosis and recovery of her hemoglobin.

The authors suggested that rituximab had depleted her primary B cells, resulting in an inability to mount a primary immune response to parvovirus infection. Parvovirus is pathogenic to red cell precursors, causing their destruction before release from the bone marrow.

Depletion of B lymphocytes by rituximab was suggested as a likely explanation for the occurrence of chronic parvovirus B19 infection complicated by pure red cell aplasia in a 45-year-old patient (15).

Thrombocytopenia leading to gastrointestinal bleeding has been attributed to rituximab (16).

Skin

Stevens–Johnson syndrome has been attributed to rituximab (17).

- A 33-year-old man with a follicular non-Hodgkin lymphoma entered a phase II trial of rituximab. The first two cycles were given without infusion-related toxicity, but during the second cycle mucositis was noticed. Before the third cycle he developed a pruritic rash on the trunk, grade 2 mucositis, and weight loss. He was given oral fluconazole, aciclovir, and antihistamines, which led to improvement. One week after the third infusion of rituximab he had grade 3 orogenital mucositis and the maculopapular rash on the trunk worsened, with areas of ulceration. Rituximab was withdrawn. Stevens–Johnson syndrome was confirmed by biopsy.

Immunologic

Infusion reactions with rituximab are generally well tolerated, as with most monoclonal antibodies. Most reactions are limited to the first infusion, including nausea, chills, and fever. They occur in over 90% of patients. More serious is the cytokine-release syndrome, which occurs within 60–90 minutes and is characterized by fever, chills, rigors, bronchospasm, hypoxia, hypotension, urticaria, and angioedema. Infusion must be discontinued, and the patient carefully monitored with chest radiography and fluid and electrolyte assessment and treated with oxygen and bronchodilators.

A rapid tumor clearance syndrome can occur within 30–60 minutes, with similar symptoms. Lymphocytes rapidly disappear from the peripheral blood and uric acid and lactate dehydrogenase increase markedly. Treatment includes interruption of the infusion, hydration, allopurinol, oxygen, and bronchodilators. It mainly occurs in patients with high white blood cell counts, such as those with chronic lymphatic leukemia.

Severe viral infections/reactivation that have been reported in patients given rituximab have included fulminant hepatitis B (18), parvovirus-induced red cell aplasia (15), and fatal *Varicella zoster* infection (19). There was a high incidence of reactivation of cytomegalovirus and *V. zoster* virus when rituximab was combined with high-dose chemotherapy in high-risk patients with non-Hodgkin's lymphoma (20).

Long-Term Effects

Tumorigenicity

A second cancer is possible when treating a tumor by mutagenicity or immunosuppression. There may be a link between the therapy given and the development of Merkel cell carcinoma (21).

- A 54-year-old man with stage I follicular lymphocytic lymphoma with cervical lymph nodes underwent splenectomy followed by chemotherapy with chlorambucil and had a partial response. Five months later, when he developed generalized lymphadenopathy and bone marrow involvement, he received fludarabine, cyclophosphamide, and rituximab, with complete remission. Ten months later he developed a Merkel cell carcinoma involving the liver and lymph nodes. The disseminated tumor was chemoresistant and he died. His lymphoma remained in complete clinical remission throughout this time.

Two patients developed a peripheral T cell non-Hodgkin's lymphoma after rituximab therapy, one after 15 months and the other after 18 months (22).

Rituximab was suggested as a possible cause of aggressive peripheral T cell lymphoma in two patients 15 and 18 months after the use of rituximab for low-grade B cell non-Hodgkin's lymphoma (23,24).

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Second-Generation Effects

Pregnancy

There are few data on the use of rituximab in pregnancy, but one case has been reported.

- A pregnant woman with relapsed follicular non-Hodgkin's lymphoma took rituximab unintentionally during the first trimester (25). The disease stabilized and following an uncomplicated pregnancy a healthy child was born at full term. Careful hematological and immunological monitoring showed no adverse effects from exposure to rituximab.

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Rivastigmine

General Information

Rivastigmine (1) was the second drug after donepezil in a class of second-generation acetylcholinesterase inhibitors to become commercially available. It is now marketed in over 60 countries worldwide, including those in Europe and South America and the United Kingdom. It has central selectivity, suggesting fewer peripheral adverse effects. These include nausea, vomiting, abdominal pain, and anorexia (2,3). Daily doses up to 12 mg were tolerated and produced improvement in patients with Alzheimer's disease (4).

Although therapy with newer as well as older cholinesterase inhibitors can prevent cognitive decline, psychiatric and behavioral disturbances, and impaired ability to perform basic activities of daily living, and improve global state of patients with mild-to-moderately-severe Alzheimer's disease, more potent therapies are needed, particularly for modifying the rate of disease progression. Future research efforts need to focus on identifying predictors and better measures of response, timing of treatment, optimum dosage regimens, longer-term follow-up, and establishing how and when acetylcholinesterase inhibitors should be stopped (5,6).

A meta-analysis of various drugs approved for the treatment of Alzheimer's disease in the USA and Canada has suggested that rivastigmine can delay cognitive impairment and deterioration in global health for at least 6 months in patients with mild-to-moderate Alzheimer's disease (7). Patients taking active treatment will have more favorable ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive) scores for at least 6 months, after which their scores will begin to converge with those who are taking placebo. The cost-effectiveness data were inconclusive.

In two studies of rivastigmine, 38% of users suffered from nausea, 23% from vomiting, and 24% from vertigo (8). Over 6 months there was a dropout rate of 25%. The gastrointestinal effects led to significant loss of weight. The positive response rate was only 10%, compared with a 6% response to placebo.

The efficacy and safety of rivastigmine have been investigated in several subsequent studies (9–12). Neurologists generally titrated this drug more slowly than recommended in the prescribing information (9). In daily practice, over 50% of the patients were unable to tolerate rivastigmine, mainly because of cholinergic gastrointestinal adverse effects (10), whereas others have found that the adverse events were most frequently mild and transient (11,12). It has been suggested that early treatment with rivastigmine (6–12 mg/day) is associated with sustained long-term (up to 52 weeks) cognitive benefit in patients with Alzheimer's disease (12).

Organs and Systems

Cardiovascular

Based on an electrocardiographic analysis of pooled data from four 26-week, phase III, multicenter, double-blind, placebo-controlled trials of rivastigmine (n = 2791), there were no adverse effects on cardiac function (13). Rivastigmine can therefore be safely given to patients with Alzheimer's disease, without the need for cardiac monitoring.

Psychological, psychiatric

Three patients with dementia, with no prior psychiatric history, deteriorated while taking rivastigmine (14). The time course suggested an association with rivastigmine, and each improved after withdrawal.

Gastrointestinal

Potentially fatal rupture of the esophagus has been associated with untitrated use of rivastigmine tablets in a patient with Alzheimer's disease (15).

- A 67-year-old Caucasian woman had a 2-year history of progressive memory loss. She had arterial hypertension successfully controlled with lisinopril and no history of ethanol abuse. A diagnosis of probable Alzheimer's disease was made, and she was given rivastigmine 1.5 mg/day, increasing to 9 mg/day by weekly increments of 1.5 mg. During the titration period, there were no significant adverse effects. After 13 weeks, weight loss was observed and rivastigmine was withdrawn. After 8 weeks she developed marked cognitive deterioration, and she and her carer were advised to restart rivastigmine 1.5 mg/day. However, she mistakenly took one tablet of 4.5 mg. About 30 minutes later she started to vomit several times. Nearly 2 hours later, she complained of severe chest pain, followed by high-grade fever. A chest X-ray showed mediastinal and soft-tissue emphysema, and a contrast X-ray showed rupture of the distal part of the esophagus. Emergency surgery was performed and she recovered.

Rivastigmine and other acetylcholinesterase inhibitors can produce chest pain because of increased esophageal contractions, although consequent rupture of the esophagus has not previously been reported. In this case, the failure to titrate the dosage of rivastigmine could have resulted in rupture secondary to severe vomiting. This confirms the need for careful titration of the dose of rivastigmine, even when restarting treatment.

The transient use of centrally acting antiemetics during rivastigmine titration may be useful in combination with dose-withholding and titration strategies to allow more patients to reach higher doses, resulting in a rapid and robust therapeutic effect. Patients who were treated with trihexyphenidyl and trimethobenzamide were more likely to be able to maintain or to increase their dose of rivastigmine than patients who were treated with glycopyrrolate or ondansetron (16).

Drug–Drug Interactions

General

Rivastigmine did not interact significantly with a wide range of concomitant medications prescribed for elderly patients with Alzheimer's disease, based on an analysis of 2459 patients (rivastigmine 1696, placebo 763) from four randomized placebo-controlled studies (17). However, the Breslow–Day analysis used in this study detected only differences in the odds ratios of rivastigmine versus

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placebo among patients taking concomitant medications. Thus, these results have to be cautiously interpreted.

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Rocuronium bromide

See also Neuromuscular blocking drugs

General Information

Rocuronium is a steroidal agent related chemically to vecuronium. It is less potent than vecuronium and has a quicker onset of action. The plasma clearance of rocuronium is primarily due to liver uptake and biliary excretion (1). About one-third of an injected dose is excreted unchanged in the urine (1). Good intubating conditions may be expected 90–120 seconds after the injection of 0.6 mg/kg rocuronium. Increasing the dose to 1 mg/kg will give acceptable intubating conditions at 60 seconds. There were no increases in plasma histamine concentrations with doses up to 1.2 mg/kg (2).

Organs and Systems

Cardiovascular

Rocuronium has virtually no cardiovascular adverse effects (2–4). Minor increases in heart rate can occur with higher doses owing to its mild vagolytic properties.

There are several reports of pain during injection of rocuronium (5,6). Eight of 10 patients complained of severe pain, one complained of moderate pain, and another reported an unpleasant sensation (5). This suggests that rocuronium will almost invariably cause pain. The mechanism of this phenomenon is not clear, but there appear to be some similarities to propofol injection pain. Several authors have suggested that rocuronium should not be given to awake patients (5,6). On the other hand, small doses of rocuronium have been used, with some success, to prevent fasciculations and myalgia after suxamethonium (7–10). With regard to the severity of injection pain, rocuronium pretreatment in awake patients does not seem advisable.

Immunologic

Several allergic reactions to rocuronium have been reported (11–20). Based on data from the UK, Australia, and France, it had been suggested that the incidence of such reactions after rocuronium administration parallels its frequency of use, as assessed by its market share, implying that rocuronium does not have unusual allergenic properties (15,21,22). In one hospital, the incidence of such reactions was 1 in 3000 (15) and in another 1 in 6000 (11). Also, the incidence of

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hypotension, tachycardia, or reduced oxygen saturation (which might suggest an anaphylactoid reaction) was relatively low after rocuronium administration compared with other muscle relaxants in a computerized analysis of 47 295 anesthetic records in one hospital (23).

However, the French Group on the Study of Perianesthetic Anaphylactoid Reactions (GERAP) has reported that the proportion of anaphylactoid reactions to rocuronium was similar to suxamethonium in relation to the individual market shares of these agents (22). There were 41 cases among 452 reported cases of anaphylaxis due to neuromuscular blocking agents that were attributed to rocuronium (24). This would make rocuronium look unfavorable, taking into account the fact that suxamethonium is believed to trigger anaphylactoid reactions more often than any non-depolarizing neuromuscular blocker. The authors assumed that their figures might have been partly due to anesthetists' paying more attention to the effects of drugs that had become available more recently, especially in cases of mild reactions. Reporting bias has also been offered as one possible explanation of 29 reports of anaphylaxis to rocuronium among 150 000 patients in Norway, in contrast to 8 cases among 800 000 patients in the other Scandinavian countries (25). This observation has prompted the Norwegian Medicines Agency to recommend that rocuronium be temporarily withdrawn from routine practice and that it be used for rapid-sequence induction only.

It is difficult to understand why such an increase in the number of reported cases should only be observed in France and Norway and not in other countries in which rocuronium is widely used. For the time being, it is not possible to decide whether anaphylactoid reactions are more common with rocuronium than with other non-depolarizing muscle relaxants. To get a clearer picture, a large longitudinal survey would be needed (26), which is unlikely to be performed, owing to the large number of cases that would be required. We shall probably have to rely on national surveys, like the French one cited above. International networking and pooling of data might be the way forward. All of this will depend on clinicians chasing every case of a suspected anaphylactoid reaction by immunological testing and reporting all confirmed cases to appropriate bodies.

The Norwegian Medicines Agency has recommended that rocuronium bromide should be withdrawn from routine practice, referring to 29 reported cases of anaphylaxis or anaphylactoid reactions among 150 000 administrations over 2.5 years. In response, and with regard to the paucity of reported cases of anaphylaxis to rocuronium in other Nordic countries, the statistical problems of surveying such rare adverse drug reactions have been highlighted (25).

One patient died after developing multiorgan failure due to a reaction to rocuronium (27).

- A 64-year-old obese man, scheduled for a hernia repair, had had previous episodes of venous thromboembolism, for which he was still taking an oral anticoagulant. Previous general anesthesia had been uneventful. General anesthesia was induced with sufentanil 15 μg and propofol 400 mg. He was given rocuronium 50 mg to facilitate endotracheal intubation, and shortly after developed bronchospasm, severe hypotension, tachycardia, and generalized erythema. He was resuscitated with adrenaline, hydrocortisone, and colloid infusion. However, his further course after admission to the intensive care unit was complicated by persistent hypotension, acute respiratory distress syndrome, acute renal insufficiency, disseminated intravascular coagulation, and pancreatitis, and he died 7 days after the incident. Blood samples drawn at 30 and 60 minutes after the initial presentation showed increased concentrations of histamine and tryptase. Specific IgE antibodies against quaternary ammonium groups were detected, with a positive radioimmunoassay inhibition by rocuronium.

Death caused by an anaphylactic reaction to a muscle relaxant seems to be rare, although mortality rates from intraoperative anaphylaxis in the range of 3.4–6% have been reported (28–31). The incidence of cardiac arrest was 4.9% among patients with anaphylactic reactions to muscle relaxants referred to the French GERAP centers for further testing, but these patients all survived (22).

Second-Generation Effects

Fetotoxicity

The maternofetal transfer or rocuronium, as indicated by a fetal/maternal plasma concentration ratio of 0.16, is between that of vecuronium and pancuronium (32). When rocuronium was used for cesarean section, no adverse effects on the fetus were observed (32). With regard to the duration of rocuronium-induced paralysis and the relatively high incidence of failed intubations in obstetric patients, however, it was agreed that rocuronium should be considered for rapid-sequence intubation for cesarean section only if suxamethonium is contraindicated (33–35).

Susceptibility Factors

Age

In elderly patients, because of reduced hepatic elimination, the duration of action of rocuronium can be prolonged (36,37).

Renal disease

Despite the predominantly biliary elimination of rocuronium, reduced clearance and a prolonged half-life have been reported in patients with chronic renal insufficiency requiring hemodialysis (38,39); however, the duration of action was not longer than in healthy controls (38).

Hepatic disease

The duration of action of rocuronium was significantly prolonged in patients with liver cirrhosis, which might be explained either by a larger central volume of distribution or by a lower plasma clearance (40,41).

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Drug–Drug Interactions

Anticonvulsant drugs

The duration of action of rocuronium can be reduced during long-term therapy with anticonvulsants (42). In one study the mean times to recovery of twitch height to 25% of baseline after rocuronium 0.6 mg/kg were 21 minutes in patients taking either carbamazepine or phenytoin versus 45 minutes in controls (43). It was suggested that the dose of rocuronium should be increased in patients taking antiepileptic drugs.

General anesthetics

The neuromuscular blocking effects of rocuronium are potentiated by halothane, enflurane, and isoflurane (44–46).

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Rofecoxib

See also COX-2 inhibitors

General Information

Rofecoxib is a selective inhibitor of COX-2. Although it was originally introduced with the expectation that it would be safer than conventional NSAIDs, because of less gastrointestinal bleeding, the benefit to harm balance is now considered to be unfavorable during long-term treatment, mainly because of an increased risk of cardiovascular disease (heart attacks and strokes; see the monograph on COX-2 inhibitors), and it has been voluntarily withdrawn by its manufacturers.

Organs and Systems

Nervous system

Aseptic meningitis is a rare adverse effect of non-selective NSAIDs in patients with or without connective tissue disease or rheumatological disease. Rofecoxib has been implicated in five patients (four women and one man), in each case occurring within 12 days of the start of rofecoxib therapy (1). The clinical presentations and cerebrospinal fluid findings were typical of aseptic meningitis. One patient had rheumatoid arthritis. After drug withdrawal and recovery, two consecutive rechallenges in one patient led to relapses.

Urinary tract

Acute renal insufficiency has been reported after the use of rofecoxib in patients with predisposing conditions, such as chronic renal insufficiency, renal transplantation, heart disease, liver cirrhosis, and dehydration (2–5). COX-2 inhibitors should be used with great caution, if at all, in patients with medical problems that are associated with prostaglandin-dependent renal function. From this point of view they do not differ from traditional NSAIDs (6).

- Rofecoxib 12.5 mg bd for arthritic pain was associated with biopsy-proven acute tubulointerstitial nephritis in a 67-year-old woman.

Drug–Drug Interactions

Methotrexate

Methotrexate is often prescribed for the management of rheumatoid arthritis, and some NSAIDs have been reported to interact with it, causing increased plasma methotrexate concentrations, associated with impaired renal function. The safety of concurrent rofecoxib and oral methotrexate has been studied for 3 weeks in 25 patients with rheumatoid arthritis (7). Rofecoxib 12.5–50 mg/day had no effect on the plasma concentrations or renal clearance of methotrexate, but supratherapeutic doses of rofecoxib (75 and 250 mg) caused a significant increase in the plasma methotrexate AUC and reduced its renal clearance.

Warfarin

Significant increases in International Normalized Ratio (INR) have been reported in patients who took rofecoxib and warfarin; in some, the increase in INR was accompanied by a bleeding event (8,9). Careful monitoring of the INR in patients taking warfarin and concomitant rofecoxib is mandatory.

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Rokitamycin

See also Macrolide antibiotics

General Information

Rokitamycin is a semisynthetic 16-membered ring macrolide. It is more hydrophobic, and has better bacterial uptake and slower release, more cohesive ribosomal binding, and a longer post-antibiotic effect than other 14-, 15- and 16-membered ring macrolides (1).

Organs and Systems

Immunologic

- Churg–Strauss syndrome has been reported in an 18-year-old woman taking cysteinyl leukotriene receptor antagonists and oral rokitamicin 400 mg bd for 10 days (2).

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Romazarit

See also Non-steroidal anti-inflammatory drugs

General Information

Romazarit, a slow-acting drug for use in rheumatoid arthritis, was well tolerated in pharmacokinetic studies. It is structurally similar to clobuzarit, which was withdrawn because of four possible cases of Stevens–Johnson syndrome (SEDA-17, 114).

In a double-blind placebo-controlled study in 224 patients with rheumatoid arthritis romazarit 200 mg or 450 mg bd for up to 24 weeks reduced the rate of progress of the disease. Adverse effects were not reported (1). In a double-blind placebo-controlled in 24 patients with rheumatoid arthritis romazarit 100 mg tds, 350 mg bd, or 350 mg tds was associated with adverse events that were mainly trival and similar in incidence to placebo (2).

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Ropinirole

General Information

Ropinirole is a dopamine receptor agonist.

Organs and Systems

Cardiovascular

Supraventricular extra beats have rarely been reported after low doses of ropinirole and have also been reported after pergolide and levodopa (1). Symptomatic postural hypotension has occurred after even low oral doses of ropinirole (2–5), related to peripheral dopaminergic activity. Hypotensive effects occur within 3 minutes of standing, usually between 2 and 4 hours after an oral dose, associated with non-specific malaise (2). Dizziness occurred in up to 40% of patients in clinical trials. Related symptoms include faintness, malaise, and yawning (2). Bradycardia has occasionally accompanied postural hypotension (4). Syncope has been reported.

Nervous system

Somnolence occurred in 20–40% of patients in clinical trials. Drowsiness or euphoria has occurred in some patients taking oral ropinirole (3,4,6). Dyskinesia

occurred in 34% of patients with advanced Parkinson's disease in clinical trials.

Gastrointestinal

Nausea, usually mild and not associated with vomiting, has been reported after oral doses of ropinirole, in both supine and standing positions (1–5). Nausea is related to peripheral dopaminergic activity and has been controlled by pretreatment with domperidone (20 mg) (2,3). In one study in healthy subjects, nausea was not reported in the supine position after oral ropinirole; however, nausea with malaise was common on standing (orthostatic symptoms) (2).

Sexual function

Penile erections have been described with ropinirole (7).

- A 49-year-old man with Parkinson's disease was treated with ropinirole, and the dosage eventually reaching 3 mg tds. He had penile erections 20–30 minutes after each dose, lasting for 10–15 minutes. They were not associated with arousal and were very uncomfortable: he had no history of sexual dysfunction. Their frequency diminished with a reduction in drug dosage, but they stopped completely only on drug withdrawal.

Drug–Drug Interactions

Ciprofloxacin

Ciprofloxacin, an inhibitor of CYP1A2, the major enzyme whereby ropinirole is metabolized, increased the risk of ropinirole-induced adverse effects (nausea, somnolence, dizziness) (8).

Warfarin

Ropinirole has been reported to enhance the effects of warfarin (9).

- A 63-year-old man taking co-careldopa and warfarin 4 mg/day (it is not entirely clear why) was also given ropinirole 0.75 mg/day to allow levodopa sparing. After 9 days of ropinirole his INR had increased to 4.6 from a previously stable value of 1.8–2.1, little changed in 2 years. There was no clinical evidence of bleeding. Warfarin was withheld for 4 days and then restarted at 25% of its previous dose. The ropinirole was then withdrawn because of gastrointestinal adverse effects and the warfarin dosage was restored to its previous level.

The mechanism of this interaction has not been elucidated. Ropinirole is metabolized by CYP1A2, but that is not the major isoform involved in warfarin metabolism.

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Ropivacaine

See also Local anesthetics

General Information

Ropivacaine is an enantiomeric aminoamide local anesthetic, structurally related to bupivacaine but with a wider margin of safety between concentrations that cause nervous system and cardiovascular effects (1). It is mainly metabolized by CYP1A2.

The safety, pharmacokinetics and efficacy of two doses of ropivacaine (300 and 375 mg) for wound infiltration after surgical incision have been studied in an open non-randomized study of 20 men undergoing elective hernia repair (2). Efficacy was similar. There were wide variations in mean plasma concentrations of ropivacaine, the highest individual plasma concentration of total drug being 3.0 μg/ml for the 375 mg dose. One patient in the low-dose group had two episodes of bradycardia at 2 and 12 hours after drug administration. The first episode corresponded to a total plasma drug concentration of 1.3 mg/ml. Three patients in the high-dose group had several recorded episodes of sinus bradycardia. Two of these were within the first hour of ropivacaine administration and corresponded to plasma concentrations of 2.5 and 2.9 μg/ml. One patient in the 300 mg group complained of dizziness at 12 and 21 hours and of nausea at 12 hours. Another patient in the same group vomited 4 hours after the injection of ropivacaine. Two patients had transient hypesthesia in the leg on the operated side, thought to be due to partial block of the femoral nerve. The authors felt that systemic toxicity due to ropivacaine was unlikely to be a cause of any of these adverse effects and they concluded that high-dose ropivacaine is safe for wound infiltration.

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Organs and Systems

Cardiovascular

The effects on the cardiovascular system of ropivacaine are similar to those of bupivacaine, although direct cardiotoxicity is less severe with ropivacaine than bupivacaine in both man and animals (SEDA-22, 143). Hypotension and bradycardia are prominent adverse effects when ropivacaine is used epidurally, particularly with concentrations of ropivacaine over 0.5% (SEDA-20, 129) (SEDA-22, 143); in one series, hypotension was observed in 30% of patients who received ropivacaine, but in only 13% of those given an equivalent dose of bupivacaine (3).

Nervous system

Convulsions have occurred after inadvertent intravenous injection of ropivacaine during regional anesthesia (4,5). CNS adverse effects from ropivacaine occur before or without severe cardiovascular toxicity, as there have been several similar reports of CNS toxicity, but not yet one with severe or fatal cardiotoxicity. This reinforces the claim of increased safety from cardiovascular toxicity with this enantiomeric local anesthetic compared with racemic bupivacaine.

Two episodes of central nervous system toxicity without significant cardiovascular toxicity have been described in a patient who had brachial plexus blocks with excessively high doses of ropivacaine 6 weeks apart (6).

- A 45-year-old woman with rheumatoid arthritis asked for regional anesthesia for arthrodesis of her wrist. An interscalene block was performed with ropivacaine 300 mg (6 mg/kg). After 3 minutes she complained of circumoral numbness and twitching in her throat. She developed irrational speech and perioral twitching and 15 minutes after injection developed involuntary clonic twitching in her left upper arm. She was anesthetized with thiopental and ventilated with 100% oxygen via a bag and mask. She regained consciousness within 20 minutes and at 135 minutes was fully conscious, with complete sensorimotor block of her left upper limb. Six weeks later she had an axillary nerve block with ropivacaine 225 mg (4.5 mg/kg) and lidocaine 200 mg (4 mg/kg) with adrenaline. After 25 minutes she complained of a strange feeling in her tongue and became dysarthric and unresponsive to voice. She was anesthetized with propofol and the arthrodesis was performed under general anesthetic. Postoperatively she had a complete brachial plexus block, which resolved after 6 hours. In both instances the only cardiovascular effect noted was sinus tachycardia (150–170/minute).

A single seizure after epidural ropivacaine has been reported (7).

- A 26-year-old primigravid woman in labor had an epidural anesthetic with ropivacaine (a background infusion of 18 mg/hour and three bolus doses totalling 44 mg, followed by an infusion of 24 mg/hour). She failed to progress and another three boluses totalling 150 mg were given. She received a total of 279 mg of ropivacaine over 5 hours. Immediately after the final bolus she developed oculogyric movements and slurred speech and then twitching of her face and arms. The seizure ceased with thiopental and the operation was carried out uneventfully under general anesthesia. Her serum ropivacaine concentration 1 hour later was 3.5 mg/l check units; in previous studies, symptoms of toxicity during intravenous infusions occurred at plasma concentrations of 1–2 μg/ml.

This shows that it is important to leave adequate time between bolus doses to detect adverse effects.

Inadvertent intravenous injection of ropivacaine resulted in systemic toxicity in two cases (5–8).

- A 13-year-old boy weighing 44 kg was given a bolus of 20 mg of ropivacaine through an 18 G Tuohy needle. No cerebrospinal fluid or blood had been aspirated. However, he immediately complained that his face "felt different," and within 1 minute developed a tonic-clonic seizure and a tachycardia of 160/minute. In a blood sample taken about 35 minutes later the plasma concentration of ropivacaine was 1.4 mg/ml, consistent with intravascular injection. In humans, symptoms of toxicity occur at plasma concentrations of 1–2 mg/ml. The authors thought that the rate of injection of epidural local anesthetic should be slower, which would give a greater safety margin between the onset of facial numbness and seizures.
- A ropivacaine-induced seizure occurred in a 23-year-old woman undergoing postpartum tubal ligation. An epidural that had been inserted for labor the evening before the procedure was used to give ropivacaine 120 mg in increments over 11 minutes. She complained of nervousness and within a few seconds had a generalized tonic-clonic seizure and a sinus tachycardia of 120/minute.

In both of these cases reasonable precautions had been taken to ensure correct catheter placement, but nevertheless systemic toxicity occurred. However, neither patient had any serious cardiotoxicity. However, it is worth emphasizing that large doses of local anesthetics should be given slowly and in divided doses and that lidocaine, one of the least toxic of the commonly used local anesthetics, has more obvious prodromal symptoms than ropivacaine, and could be a useful marker for intravenous injection (9).

Three patients suffered convulsions as a result of inadvertent intravascular injection of ropivacaine during placement of local blocks.

- A 75-year-old woman received ropivacaine 160 mg intravenously through an epidural catheter (10). After completion of the injection, she suddenly became unresponsive and had a generalized tonic-clonic convulsion accompanied by a sinus tachycardia of 120/minute but no other cardiac dysrhythmias.
- A 56-year-old 70 kg woman with a Colles fracture received a brachial plexus block at the humeral canal with 0.75% ropivacaine 40 ml using a nerve stimulator (11). The local anesthetic was administered slowly with negative intermittent aspiration. However, 15 minutes later she had two generalized convulsions, which were treated with diazepam. The total venous ropivacaine concentration measured 2 hours after the block was 2.3 μg/ml.
- A 25-year-old man received ropivacaine 75 mg intravenously during sciatic nerve block (12). The nerve was

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located using a nerve stimulator and the injection was performed after elicitation of a distal extensor response. Numerous aspirations were performed during the procedure, but 1 minute after injection he suddenly became unresponsive and developed a tonic-clonic seizure, which resolved after treatment with midazolam and propofol. The only cardiovascular effect was a sinus tachycardia of 130/minute.

In the last case, the authors noted that the motor response to stimulation was maintained throughout the injection; it is generally felt that the motor response to stimulation should disappear after the injection of the first milliliters of local anesthetic; if the response does not disappear the injection should be stopped. In all three cases nervous system toxicity occurred with minimal or no cardiovascular toxicity, which is in keeping with previous reports, confirming the relative safety of ropivacaine; there has still not been one single fatal outcome reported with this agent.

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Rosaceae

See also Herbal medicines

General Information

The genera in the family of Rosaceae (Table 1) include avens, cotoneasters, hawthorn, and roses, and a variety of fruits such as apples, loquats, pears, plums, quince, and strawberries.

Table 1 The genera of Rosaceae

Acaena (acaena)
Adenostoma (chamise)
Agrimonia (agrimony)
Alchemilla (lady's mantle)
Amelanchier (serviceberry)
Amelasorbus (amelasorbus)
Aphanes (parsley piert)
Argentina (silverweed)
Aruncus (aruncus)
Cercocarus (mountain mahogany)
Chaenmeles (flowering quince)
Chamebatia (mountain misery)
Chamaebatiaria (fernbush)
Chamaerhodos (little rose)
Coleogyne (coleogyne)
Comarum (comarum)
Cotoneaster (cotoneaster)
Crataegus (hawthorn)
Cydonia (cydonia)
Dalibarda (dalibarda)
Dasiphora (shrubby cinquefoil)
Dryas (mountain avens)
Duchesnea (duchesnea)
Eriobotrya (loquat)
Exochorda (pearlbrush)
Fallugia (Apache plume)
Filipendula (queen)
Fragaria (strawberry)
Geum (avens)
Heteromeles (toyon)
Holodiscus (ocean spray)
Horkelia (horkelia)
Horkeliella (false horkelia)
Ivesia (mousetail)
Kelseya (kelseya)
Kerria (kerria)
Luetkea (luetkea)
Lyonothamnus (lyononthmnus)
Malacomeles (false serviceberry)
Malus (apple)
Mespilus (mespilus)
Neviusia (snow wreath)
Oemleria (oemleria)
Osteomeles (osteomeles)
Peraphyllum (peraphyllum)
Petrophyton (rock spiraea)
Photinia (chokeberry)
Physocarpus (ninebark)
Porteranthus (porteranthus)
Potentilla (cinquefoil)
Prunus (plum)
Pseudocydonia (Chinese-quince)

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Purshia (bitterbrush)
Pyracantha (firethorn)
Pyrus (pear)
Quillaja (quillaja)
Rhodotypos (rhodotypos)
Rosa (rose)
Rubus (blackberry)
Sanguisorba (burnet)
Sibbaldia (sibbaldia)
Sibbaldiopsis (sibbaldiopsis)
Sorbaria (false spiraea)
Sorbus (mountain ash)
Spiraea (spiraea)
Stephanandra (stephanandra)
Vauquelinia (rosewood)
Waldsteinia (barren strawberry)

Crataegus species

Crataegus species (hawthorn, maybush, whitethorn) contain a variety of flavonoids, including rhamnosides, schaftosides, and spiraeosides. They have a positive inotropic effect on the heart by a mechanism different from that of cardiac glycosides, catecholamines, and the phosphodiesterase type III inhibitors (1) and are effective in mild heart failure (2).

Adverse effects

The main adverse effects of *Crataegus* are dizziness and vertigo (3).

It has been suggested that the flavonoids in *Crataegus* inhibit P glycoprotein function and might therefore interact with drugs that are substrates of P glycoprotein, such as digoxin. However, in a randomized, crossover trial in eight healthy volunteers *Crataegus* special extract WS 1442 (hawthorn leaves with flowers) had no effect on the pharmacokinetics of digoxin 0.25 mg/day for 10 days (4).

Prunus species

The raw pits or kernels of various *Prunus* species (such as apricot, bitter almond, choke cherry and peach) are promoted as health foods. However, they contain the cyanogenic glycoside, amygdalin, which yields hydrogen cyanide after ingestion.

During the late 1950s, and for about 20 years afterwards, laetrile (l-mandelonitrile-beta-glucuronoside), which is related to amygdalin, was touted as a cure for cancer (http://www.quackwatch.org/01QuackeryRelatedTopics/Cancer/laetrile.html). However, in 1982 Arnold Relman, then Editor of the New England Journal of Medicine, pronounced that "Laetrile has had its day in court. The evidence, beyond reasonable doubt, is that it doesn't benefit patients with advanced cancer, and there is no reason to believe that it would be any more effective in the earlier stages of the disease. . . . The time has come to close the books." (5). Nevertheless, it is being so touted again today.

Adverse effects

When ingested in sufficient quantities *Prunus* species cause cyanide poisoning. For instance, a total consumption of about 48 apricot kernels produced forceful vomiting, headache, flushing, heavy sweating, dizziness, and faintness before vomiting was induced in the emergency room, whereafter the symptoms rapidly subsided. In another case accidental poisoning was fatal (6).

- A 67-year-old woman with lymphoma presented with a neuromyopathy following treatment with laetrile. She had high blood and urinary thiocyanate and cyanide concentrations (7). Sural nerve biopsy specimen showed a mixed pattern of demyelination and axonal degeneration, the latter being prominent. Gastrocnemius muscle biopsy specimen showed a mixed pattern of denervation and myopathy with type II atrophy.

Besides the risk that a large dose can lead to acute cyanide poisoning, there is also the question whether continued ingestion of cyanogenic pits or kernels can cause chronic intoxication.

An outbreak of congenital malformations in swine has been retrospectively associated with the eating of the fruit, leaves, and bark of *Prunus serotina* (wild black cherry) (8). Prospective experimental evidence of teratogenicity was not available at that time, but amygdalin was later reported to be teratogenic in hamsters (9).

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Rotavirus vaccine

See also Vaccines

General Information

Rotavirus is the most common cause of severe gastroenteritis in infants and young children aged under 5 years in the USA, resulting in approximately 500 000 physician visits, 50 000 hospitalizations, and 20 deaths each year. Worldwide, rotavirus is a major cause of childhood death, accounting for an estimated 600 000 deaths annually among children aged under 5 years. Rotavirus vaccines offer the opportunity to reduce substantially the occurrence of this disease.

Various oral rotavirus vaccines (live attenuated rotavirus vaccines, including rhesus rotavirus and bovine rotavirus strains; serotype 1 bovine-human rotavirus reassortant vaccine; and both rhesus rotavirus monovalent and tetravalent reassortant vaccines) have been evaluated in clinical trials (SEDA-21, 292).

On August 31, 1998, a tetravalent rhesus-based rotavirus vaccine (RRV-TV) (Rotashield) was licensed in the USA. The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians all recommended routine use of the vaccine in healthy infants. Rotashield was the first rotavirus vaccine to be licensed.

Observational studies

The safety and immunogenicity of two human-bovine reassortant rotavirus candidate vaccines have been evaluated in infants, children, and adults (1). One candidate vaccine contained a single human rotavirus gene, while the other candidate vaccine contained two human rotavirus genes. The remaining genes for both vaccines were derived from bovine rotavirus strain UK. Each of these vaccines was well tolerated and immunogenic. This was also the case in the important group of infants under 6 months of age after a single dose of vaccine.

Placebo-controlled studies

The safety, immunogenicity, and efficacy of a live oral human rotavirus vaccine 89–12 has been assessed in 213 US infants in a randomized, placebo-controlled, double-blind, multicenter trial (2). The infants received two doses of vaccine or placebo and were followed up through one rotavirus season. There was an immune response to vaccine in 94.4% of vaccinees, and vaccine efficacy was 89%. Adverse reactions were mild. Low-grade fever after the first dose was the only adverse effect that was significantly more common with the vaccine than with placebo.

Organs and Systems

Gastrointestinal

Natural rotavirus itself is a causative agent for intussusception (3). In rotavirus disease in Japan, hyperplasia of the intestinal lymphoid tissue is a common pathological finding in necropsy cases, and is identical with that observed in patients who receive the tetravalent rhesus-based rotavirus vaccine.

During the period from 1 September 1998 to 7 July 1999, 15 cases of intussusception among infants who had received rotavirus vaccine were reported to the Vaccine Adverse Event Reporting System (VAERS). Of the 15 infants, 13 (87%) had developed intussusception after the first dose of the three-dose RRV-TV series, and 12 had developed symptoms within 1 week of receiving any dose of RRV-TV. Thirteen of the 15 had received other vaccines concurrently. Intussusception was confirmed radiographically in all 15 patients. Eight infants required surgical reduction, and one required resection of 18 cm of distal ileum and proximal colon. Histopathological examination of the distal ileum showed lymphoid hyperplasia and ischemic necrosis. All the infants recovered. The dates of onset ranged from 21 November 1998 to 24 June 1999. The median age of patients was 3 (range: 2–11) months. Ten were boys. Topographically the cases were scattered, being reported from seven states. Of the 15 cases reported to VAERS, 14 were spontaneous reports and one was identified through active postlicensing surveillance.

The rate of hospitalization for intussusception among infants aged less than 12 months during 1991–97 (before RRV-TV licensure) was 51 per 100 000 infant-years in New York. The manufacturer had distributed about 1.8 million doses of RRV-TV as of June 1 1999, and estimated that 1.5 million doses (83%) had been administered. Given this information, 14–16 intussusception cases among infants would be expected by chance alone during the week after the administration of any dose of RRV-TV. Fourteen of the 15 case-patients were vaccinated before June 1 1999, and of those, 11 developed intussusception within 1 week of receiving RRV-TV.

In prelicensure studies of Rotashield, five cases of intussusception had occurred among 10 054 vaccine recipients and one of 4633 controls, a difference that was not statistically significant. Three of the five cases among vaccinated children occurred within 6–7 days of receiving rotavirus vaccine. On the basis of these data, intussusception was included in the package insert as a potential adverse reaction, and the ACIP recommended postlicensure surveillance for this adverse event following vaccination. In addition, because of concerns about the findings in prelicensing trials, VAERS data were analysed early in the postlicensure period (4).

Although the number of reported intussusception cases occurring within 1 week of receiving any dose of vaccine is in the expected range, it must be borne in mind that reporting of suspected adverse events to VAERS is far from complete, and the actual number of intussusception cases occurring among RRV-TV recipients may be substantially greater than that reported. The data available to date suggest but do not establish a causal association between receipt of rotavirus vaccine and intussusception. However, based on these results, use of the vaccine was suspended in July 1999, pending a review of the data by the Advisory Committee on Immunization Practice (ACIP) (5). In further studies more cases of intussusception (including two deaths) were associated with the administration of Rotashield. Based on the results of an expedited review of the scientific data (indicating a strong

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association between Rotashield and intussusception) presented to the ACIP, it was recommended in 22 October 1999 that Rotashield should no longer be used. The recommendation was made in cooperation with the FDA, NIH, and Public Health Service officials, along with the manufacturer, Wyeth-Lederle (6). In late 1999 the CDC recommended postponing administration of RRV-TV to children scheduled to receive the vaccine before November 1999, including those who had already have begun the RRV-TV series (4).

The epidemiology of hospitalizations and deaths associated with intussusception among US infants has been described (7). Such data could be useful for further clinical trials with newly developed rotavirus vaccines.

Further studies have confirmed that there is an increased risk of intussusception associated with the use of rhesus rotavirus tetravalent vaccine (RRV-TV). The association has been assessed in infants in 19 states of the USA (8). Each infant hospitalized with intussusception between 1 November 1998 and 30 June 1999 was matched according to age with four healthy controls who had been born at the same hospital. The authors estimated that one case of intussusception would occur for every 4670–9474 infants immunized.

In a retrospective cohort study in 10 managed care organizations there was an increased risk of intussusception in immunized children (9). The risk was greatest at 3–7 days after the first dose of RRV-TV.

In an editorial in the journal Emergency and Office Pediatrics the critical role of physicians in the early detection of adverse events was stressed. Despite the demands of busy clinical practice, all physicians are obliged to be alert to unusual circumstances and to seek answers when unexpected findings—especially related to new drugs, vaccines, or procedures—seem to be more than just coincidence. It is incumbent on them to report these findings and to learn if their experience can be confirmed by colleagues (10).

Current prelicensure trials of newly developed rotavirus vaccines are taking into consideration the experiences gained during the licensure process of Rotashield. Phase 3 clinical trials have included over 10 000 volunteers in order to exclude the potential risk of intussusception.

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Roxithromycin

See also Macrolide antibiotics

General Information

Roxithromycin is a macrolide antibiotic with actions and uses similar to those of erythromycin.

Observational studies

In 2917 adults, adverse effects of roxithromycin occurred in 4.1% at a dosage of 150 mg/day (1). Nausea (1.3%), abdominal pain (1.2%), and diarrhea (0.8%) were the most frequently reported events, whereas rash, vomiting, headache, dizziness, pruritus, urticaria, and constipation were reported only rarely. Treatment had to be withdrawn in 0.9% of the patients because of adverse effects.

In an uncontrolled study in 24 HIV-infected patients, roxithromycin (300 mg bd for 4 weeks) was effective against cryptosporidial diarrhea (2). The most limiting adverse effects were abdominal pain (two patients), raised hepatic enzymes (two patients), and abdominal pain with raised hepatic enzymes (one patient). Minor symptoms occurred in nine patients.

In 304 infants and children under 14 years adverse effects occurred in 6.9% (3). Treatment was withdrawn in 10 children (two with vomiting, two diarrhea, and six rashes).

In 480 elderly patients (over 65 years), there were adverse events in 3.1% and treatment was withdrawn in 1.9%. The gastrointestinal tract was most often affected, whereas laboratory changes (increases in bilirubin, aspartate transaminase, alanine transaminase, and alkaline phosphatase) were seen in under 0.7%.

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Organs and Systems

Cardiovascular

- Torsade de pointes has been reported in an 83-year-old man who developed severe prolongation of the QT interval after taking roxithromycin 300 mg/day for 4 days (4).

Respiratory

Eosinophilic pneumonia of acute onset has been attributed to roxithromycin (5).

- A 21-year-old woman developed a fever of 39°C, a generalized pruritic macular rash, odynophagia, and intense weakness, in conjunction with respiratory difficulties 8 days after starting to take roxithromycin 150 mg bd. Her leukocyte count was 15.4×10^9/l with 9.8% eosinophils and an erythrocyte sedimentation rate of 32 mm/hour. Peripheral infiltrates were evident on the chest X-ray and CT scan, with multiple areas of consolidation and an air bronchogram, mainly peripherally distributed. Bronchoalveolar lavage showed 50% eosinophils. She improved with glucocorticoids and 6 months later was free of respiratory symptoms; a chest X-ray was normal.

Hematologic

In one study lymphopenia or eosinophilia were observed in two of 37 patients (6). However, this finding could not be confirmed in other studies.

Gastrointestinal

During long-term use of roxithromycin 300 mg/day for 2–66 months in nine patients with chronic diffuse sclerosing osteomyelitis of the mandible, diarrhea and stomach discomfort occurred in one case and liver dysfunction in another (7).

Liver

- Cholestatic and hepatocellular liver damage occurred in a previously healthy 20-year-old woman after she took roxithromycin 150 mg bd for 4 days (8).
- Hepatic failure occurred in a previously healthy 5-year-old boy after he was given roxithromycin 50 mg bd for 5 days (9). He developed a non-pruritic, non-urticarial, erythematous, maculopapular, generalized rash, and occasional vomiting. Three days later he became jaundiced, and after 8 days underwent liver transplantation.

Skin

Allergic dermatitis with characteristic distribution pattern called "baboon syndrome" has been reported (10).

- A 58-year-old man developed a pruritic skin eruption after he had taken roxithromycin 300 mg/day for 3 days. Large erythematous plaques covered his buttocks. Roxithromycin was immediately withdrawn and following treatment with oral antihistamines and topical corticosteroids the rash resolved within a few days.

Urticarial rashes have been attributed to roxithromycin.

- Roxithromycin-induced generalized urticaria and tachycardia with a positive prick test and a cross-reaction to erythromycin and clarithromycin has been reported in a 31-year-old woman (11).
- Angioedema and urticaria occurred in a 22-year-old woman a few hours after a second dose of roxithromycin 150 mg for a sore throat (12). The lesions subsided within 12 hours of drug withdrawal and there was no relapse after 3 months of follow-up. A skin prick test was positive for roxithromycin (1 mg/ml) and negative for erythromycin and clarithromycin in the same concentrations.

Immunologic

Roxithromycin had an immunomodulatory action on peripheral blood mononuclear cells in patients with psoriasis (13). The anti-inflammatory activity of roxithromycin is due to reduced production of proinflammatory mediators, cytokines, and co-stimulatory molecules, as has been shown in animal studies (14).

Drug–Drug Interactions

Antacids

Roxithromycin did not interact with antacids containing hydroxides of aluminium and magnesium (1).

Carbamazepine

Roxithromycin did not alter the pharmacokinetics of carbamazepine (15) or interact with warfarin, ranitidine, or antacids containing hydroxides of aluminium and magnesium (1).

Oral contraceptives

Plasma concentrations of oral contraceptive steroids were unchanged when roxithromycin was co-administered (16).

Ranitidine

Roxithromycin did not interact with ranitidine (1).

Statins

In an open, randomized, crossover study in 12 healthy volunteers, roxithromycin did not alter the pharmacokinetics of lovastatin in such a way that dosage adjustment of lovastatin should be necessary during co-administration (17).

- Myopathy occurred in a 73-year-old woman taking simvastatin 80 mg/day and gemfibrozil 600 mg bd 4 days after she started to take roxithromycin 300 mg/day (18).

Theophylline

Roxithromycin altered the pharmacokinetics of theophylline, mainly increasing the C_{max}, prolonging the half-life, and increasing the renal clearance (15). However, while these changes were statistically significant, they were considered clinically irrelevant. There was no effect of roxithromycin on trough concentrations of theophylline.

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Warfarin

Roxithromycin did not interact with warfarin (1).

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Rubiaceae

See also Herbal medicines

General Information

The genera in the family of Rubiaceae (Table 1) include cinchona and coffee.

Table 1 The genera of Rubiaceae

Anthocephalus (anthocephalus)
Antirhea (quina)
Asperula (woodruff)
Bobea (ahakea)
Bouvardia (bouvardia)
Calycophyllum (calycophyllum)
Canthium (canthium)
Casasia (casasia)
Catesbaea (lilythorn)
Cephaelis (cephaelis)
Cephalanthus (buttonbush)
Chiococca (milkberry)
Chione (chione)
Cinchona (cinchona)
Coccocypselum (coccocypselum)
Coffea (coffee)
Coprosma (mirrorplant)
Crucianella (crucianella)
Cruciata (bedstraw)
Crusea (mountain saucerflower)
Diodia (buttonweed)
Erithalis (blacktorch)
Ernodea (ernodea)
Exostema (exostema)
Faramea (false coffee)
Galium (bedstraw)
Gardenia (gardenia)
Genipa (genipa)
Geophila (geophila)
Gonzalagunia (gonzalagunia)
Guettarda (guettarda)
Hamelia (hamelia)
Hedyotis (starviolet)
Hillia (hillia)
Hintonina
Houstonia (bluet)
Ixora (ixora)
Kelloggia (kelloggia)
Lasianthus (lasianthus)
Lucya (lucya)
Machaonia (machaonia)
Mitchella (mitchella)
Mitracarpus (girdlepod)
Morinda (morinda)
Neolaugeria (neolaugeria)
Neolamarckia (neolamarckia)
Neonauclea
Nertera (nertera)
Oldenlandia (oldenlandia)
Oldenlandiopsis (creeping-bluet)
Paederia (sewer vine)
Palicourea (cappel)
Pentas (pentas)

Continued

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Table 1 Continued

Pentodon (pentodon)
Phialanthus (phialanthus)
Pinckneya (pinckneya)
Psychotria (wild coffee)
Randia (indigoberry)
Richardia (Mexican clover)
Rondeletia (cordobancillo)
Rubia (rubia)
Sabicea (woodvine)
Schradera (schradera)
Scolosanthus (scolosanthus)
Serissa (snowrose)
Sherardia (sherardia)
Spermacoce (false buttonweed)
Strumpfia (strumpfia)
Timonius
Uncaria (uncaria)
Vangueria (vangueria)

Asperula odorata

Asperula odorata (sweet woodruff) is rich in coumarins.

Cephaelis ipecacuanha

The root of *Cephaelis ipecacuanha*, also known as *Psychotria ipecacuanha*, is the source of ipecacuanha, which contains the emetic alkaloids emetine and cephaeline. Ipecacuanha is covered in a separate monograph.

Hintonia latiflora

Hintonia latiflora (copalchi bark) has been advocated as a hypoglycemic agent, an effect that has been attributed to the neoflavonoid coutareagenin (1). Its use has been associated with liver toxicity but a causal relation could not be established (2).

Morinda citrifolia

Morinda citrifolia (noni) is one of the most important traditional Polynesian medicinal plants, which has a large range of therapeutic claims, including antibacterial, antiviral, antifungal, antihelminthic, antitumor, analgesic, hypotensive, anti-inflammatory, and immune enhancing effects (3,4).

Adverse effects

The juice of *M. citrifolia* has been reported to cause hyperkalemia (5).

- A man with chronic renal insufficiency who followed dietary restriction of potassium developed a raised serum potassium concentration (5.8 mmol/l). He insisted that he had followed his dietary regimen as usual, except for taking noni juice, purchased from a health food store. He was treated with sodium polystyrene sulfonate and told to stop taking noni juice. At the next check-up his potassium was still raised; he said that he would never stop taking noni juice and that his physicians did not understand its healing power.

The potassium concentration in noni juice samples was 56 mmol/l.

Rubia tinctorum

The use of herbal medicines prepared from the root of *Rubia tinctorum* (madder) is no longer permitted in Germany. Root extracts have shown genotoxic effects in several test systems, which are attributed to the presence of the anthraquinone derivative lucidin. One of the other main components, alizarin primeveroside, is transformed into 1-hydroxyanthraquinone when given orally to the rat, in which this metabolite has carcinogenic activity (6).

Uncaria tomentosa

Uncaria tomentosa (cat's claw), an herb from the highlands of the Peruvian Amazon, contains the spiroindole alkaloids isopteropodine and rynchophylline; it has immunomodulatory properties and has been used to treat arthritis and inflammatory bowel disease (7).

Adverse effects

- A 59-year-old woman with mantle-cell lymphoma and no hepatic involvement took a range of unconventional medicines (8). During a routine check-up she had raised liver enzymes, and self-medication with cat's claw was deemed the most likely cause. Cat's claw was withdrawn and her liver tests normalized within 60 days.

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Rutaceae

See also Herbal medicines

General Information

The genera in the family of Rutaceae (Table 1) include citrus fruits (citrons, oranges, grapefruit, lemons, limes, tangerines, etc.), angostura, kumquat, pilocarpus, and rue.

Agathosma betulina

Agathosma betulina (buchu) contains diosmin (venosmine), and a synthetic form of diosmin is also available. It has been used to treat the pain and bleeding of hemorrhoids (1).

Adverse effects

Diosmin can rarely cause nausea and epigastric discomfort (SEDA-3, 181) and somnolence (2).

In 12 volunteers, diosmin 500 mg/day for 9 days significantly increased the AUC and C_{max} of metronidazole 800 mg without a change in t_{max}; this effect was attributed to inhibition of CYP3A4 (3).

Table 1 The genera of Rutaceae

Acronychia (acronychia)
Aegle (aegle)
Agathosma (agathosma)
Amyris (torchwood)
Boronia (boronia)
Casimiroa (sapote)
Choisya (Mexican orange)
Citrofortunella (citrofortunella)
Citroncirus (citroncirus)
Citrus (citrus)
Clausena (clausena)
Cneoridium (cneoridium)
Correa (Australian fuschia)
Cusparia (cusparia)
Dictamnus (dictamnus)
Eremocitrus (eremocitrus)
Esenbeckia (jopoy)
Flindersia (flindersia)
Fortunella (kumquat)
Galipea (galipea)
Glycosmis (glycosmis)
Helietta (helietta)
Limonia (limonia)
Melicope (melicope)
Microcitrus (microcitrus)
Murraya (murraya)
Phellodendron (cork tree)
Pilocarpus (pilocarpus)
Platydesma (platydesma)
Poncirus (poncirus)
Ptelea (hoptree)
Ravenia (ravenia)
Ruta (rue)
Severinia (severinia)
Thamnosma (desert rue)
Triphasia (triphasia)
Zanthoxylum (prickly ash)

Citrus auranticum

Volatile plant oils (often incorrectly termed "essential oils") are used in aromatherapy and are usually applied by gentle massage. The oil of *C. auranticum* (bergamot) is often used in this way. It has photosensitive and melanogenic properties and is potentially phototoxic and photomutagenic.

Adverse effects

- Two patients had localized and disseminated bullous phototoxic skin reactions 48–72 hours after exposure to bergamot aromatherapy and ultraviolet light (4). One developed bullous skin lesions after exposure to aerosolized aromatherapy oil in a sauna.

Citrus paradisi (grapefruit)

Grapefruit juice is unusual in that it is not used therapeutically but can cause many drug interactions, since an unidentified constituent of grapefruit inhibits CYP3A4. The drugs most commonly involved are dihydropyridine calcium channel blockers and HMG-CoA reductase inhibitors (5).

Both whole grapefruit and grapefruit juice have been implicated, and the wording used on a warning label in New Zealand to alert patients to potential drug interactions with grapefruit is "Do not take grapefruit or grapefruit juice while being treated with this medicine" (6). Health Canada has advised the public not to take grapefruit or its juice (fresh or frozen) with certain drugs (7). Health Canada has also issued several communication documents to remind health professionals of possible interactions of grapefruit with therapeutic drugs and has worked with drug manufacturers whose products are adversely affected by grapefruit to ensure that the relevant information is printed on the product label.

Of the several hundred chemical entities in grapefruit juice (8), psoralens, mainly 6,7-dihydroxybergamottin, are thought to be the components in grapefruit that are responsible for these interactions, although the flavonoid naringenin, which was originally suspected, cannot be excluded and may have a minor role (9).

The ability of grapefruit to increase the plasma concentrations of some drugs was accidentally discovered when grapefruit juice was used as a blinding agent in a drug interaction study of felodipine and alcohol (10). It was noticed that plasma concentrations of felodipine were much higher when the drug was taken with grapefruit juice than those previously reported for the dose of drug administered. In another study, (11) concurrent administration of grapefruit juice and felodipine increased the AUC, causing increased heart rate, and reduced diastolic blood pressure. Similarly, parallel administration of the juice with midazolam altered psychometric performance tests, while with nisoldipine or nitrendipine there was an increase in heart rate.

Table 2 lists some drugs whose effects are altered by grapefruit juice.

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Table 2 Drug–grapefruit juice interactions

Drug	Effect of grapefruit	Reference
Benzodiazepines	Pronounced nervous system effects	(12)
Ciclosporin	Inhibits metabolism and increases blood concentration	(13,14)
Coumarins	Interferes with the analysis of coumarins	(15)
Diazepam	Increases concentration	(16)
Felodipine	Enhances the effects and can cause increased blood pressure and heart rate, headache, flushing, and light-headedness	(17)
Lovastatin	Greatly increases serum concentration	(18)
Nifedipine	Increases plasma concentration	(19)
Nisoldipine	Increases plasma concentration	(20)
Quinidine	Delays absorption and maximal effect on QT interval	(21)
Saquinavir	Increases AUC and C_{max}	(9)
Terfenadine	Increases systemic availability, with cardiotoxicity at higher doses of grapefruit juice concentration	(22)
Triazolam	Increases plasma concentrations	(23)

Dictamnus dasycarpus

Dictamnus dasycarpus (densefruit pittany) contains rutaevin, terpene glycosides (dasycarpusides), sesquiterpene glycosides (dictamnosides), and phenolic glycosides. *D. dasycarpus* is a common ingredient of the complex traditional Chinese herbal medicines that have been associated with liver damage; however, a causative role remains to be established (24–27).

Adverse effects

The UK hepatologists have described two cases of severe liver damage, one fatal, attributed to Chinese herbal mixtures for minor complaints (28). *D. dasycarpus* was implicated in one. There have been other reports of hepatotoxicity due to *D. dasycarpus* (28).

Dermatitis has been attributed to *D. dasycarpus* (29).

The root bark of *D. dasycarpus* is mutagenic in bacteria, due not to dietary flavonoids, but to the furoquinoline alkaloids dictamnine and gamma-fagarine. The clinical relevance of this finding remains to be established.

Pilocarpus species

The leaves of *Pilocarpus* species, including *Pilocarpus jaborandi* (jaborandi) and *Pilocarpus racemosus* (aceitillo), contain pilocarpine or isopilocarpine as major alkaloids as well as a variety of minor alkaloids. Pilocarpine (see separate monograph) is an agonist at acetylcholine receptors, which enhances salivary flow, sweating, and gastrointestinal motility. It can interfere with asthma therapy and the effect of anticholinergic drugs.

Ruta graveolens

Ruta graveolens (rue) contains acridone alkaloids, such as furacridone and gravacridone, quinoline alkaloids, such as graveoline and graveolinine, the furanoquinoline dictamnine, coumarins, such as gravelliferone, isorutarin, rutacultin, rutaretin, and suberenone, and the furanocoumarins 5-methoxypsoralen (bergapten) and 8-methoxypsoralen (xanthotoxine). It has been used as an abortifacient and emmenagogue (30).

Adverse effects

The essential oil of rue can cause contact dermatitis and phototoxic reactions (31,32) and severe hepatic and renal toxicity. Therapeutic doses can lead to depression, sleep disorders, fatigue, dizziness, and cramps. The sap from fresh leaves can produce painful gastrointestinal irritation, fainting, sleepiness, a weak pulse, abortion, a swollen tongue, and a cool skin.

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Salbutamol

See also Beta$_2$-adrenoceptor agonists

General Information

Salbutamol (albuterol) is a beta$_2$-adrenoceptor agonist used to treat asthma. It is available in various formulations:

- oral formulations (tablets of 2 and 4 mg, a modified-release tablet of 4 or 8 mg, and a syrup 5 mg/ml);
- a multidose pressurized aerosol, which delivers 100 micrograms per puff;
- dry powder form ("Rotacaps" 200 micrograms per capsule, "Accuhaler" 200 micrograms, "Turbuhaler" 100 or 200 micrograms, "Ventodisk" 200 or 400 micrograms per delivered dose);
- individual doses for nebulization ("nebulas") containing 2.5 ml of either 1 or 2 mg/ml salbutamol;
- a multidose vial of respirator solution containing 30 ml (concentration 5 mg/ml);
- formulations for injection, 50 micrograms/ml (5 ml) and 50 micrograms/ml (1 ml), and an intravenous infusion formulation of 1 mg/ml (5 ml).

All of these formulations are used in the treatment of asthma and the intravenous infusion is also used to manage premature labor.

Since salbutamol and its congeners are not entirely selective in their beta$_2$-stimulating action, they retain some stimulant effects on the heart, central nervous system, and carbohydrate and fat metabolism; these only become troublesome with relative overdosage or in particularly susceptible subjects. Adverse effects occur through stimulation of extra-pulmonary beta$_2$-adrenoceptors; they consist of:

- vasodilatation with reflex tachycardia;
- at high doses: direct cardiac stimulation;
- tremor;
- increased blood glucose concentration;
- a fall in serum potassium concentration.

The adverse effects of salbutamol have been reviewed (1).

Organs and Systems

Cardiovascular

Peripheral vasodilatation and palpitation have been reported in patients using salbutamol. These effects usually appear with rapid administration of high doses. Inhalation of 0.4 mg did not affect the heart rate, whereas inhalation of 5 mg raised it by 15/minute (2). Infusion of salbutamol at 0.025 mg/minute had a similar effect. Slight tachycardia can result in a mild rise in blood pressure, whereas at higher doses vasodilatation was more marked and the blood pressure fell. Infusion at 0.125 mg/minute reduced blood pressure by 30 mmHg. Salbutamol 10 puffs, administered from a pressurized aerosol using a spacer, produced significant bronchodilatation without adverse effects in mechanically ventilated patients. Heart rate rose significantly after 28 puffs (SEDA-21, 182).

Patients with severe hypoxemia and low serum potassium have an increased risk of developing extra beats and cardiac dysrhythmias (SEDA-2, 121).

Salbutamol causes an increase in the activity of the MB isoenzyme of creatine kinase, which has been interpreted as meaning that it might be cardiotoxic (3).

The systemic vascular changes produced by the combination of hypoxia and inhaled salbutamol in eight healthy men with mild asthma in a randomized, double-blind, placebo-controlled, crossover trial have been briefly reported (4). Forearm blood flow was measured non-invasively to obtain a measure of forearm vascular resistance (equating with systemic vascular resistance) after inhalation of placebo or salbutamol 800 micrograms under normoxic or hypoxic conditions. Both salbutamol alone and hypoxia alone produced small non-significant falls in forearm vascular resistance, but the combination of salbutamol and hypoxia resulted in a dramatic fall (30%). The authors pointed out that this fall in forearm vascular resistance was equivalent to the effects of glyceryl trinitrate 0.6–0.9 mg sublingually or felodipine 10 mg orally. This study emphasizes the marked cardiovascular changes that can occur with even small doses of salbutamol in people with mild asthma when hypoxia is present and confirms the importance of supplementary oxygen in these patients.

Intravenous and intracoronary salbutamol (10–30 and 1–10 micrograms/minute respectively) and intravenous isoprenaline (1–5 micrograms/minute), a mixed beta$_1$/beta$_2$-adrenoceptor agonist, were infused in 85 patients with coronary artery disease and 22 healthy controls during fixed atrial pacing (5). Both salbutamol and isoprenaline produced large increases in QT dispersion (QT_{onset}, QT_{peak}, and QT_{end}), more pronouncedly in patients with coronary artery disease. Dispersion of the QT interval is thought to be a surrogate marker for cardiac dysrhythmia (6). The authors concluded that beta$_2$-adrenoceptors mediate important electrophysiological effects in human ventricular myocardium and can trigger dysrhythmias in susceptible patients.

In a blind, randomized study, 29 children aged under 2 years, with moderate to severe acute exacerbations of hyper-reactive airways disease, were treated with either a standard dose of nebulized salbutamol (0.15 mg/kg) or a low dose of nebulized salbutamol (0.075 mg/kg) plus nebulized ipratropium bromide 250 micrograms (7). Standard and low-dose nebulized salbutamol was given three times at intervals of 20 minutes and nebulized ipratropium bromide was given once. Clinical improvement, measured as oxygen saturation and respiratory distress, was similar in both groups. QT dispersion was measured at baseline and after treatment and was significantly increased only by the standard dose of nebulized salbutamol.

Respiratory

Although salbutamol generally improves respiratory activity in asthma, arterial hypoxemia can be aggravated if it is used in excess or if parenchymal lung infection is present (8). In patients with bronchiectasis, salbutamol may aggravate hemoptysis (SEDA-9, 125). A feeling of "thick neck," chest heaviness, erythema, and edema of

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the face experienced in one reported case after the third dose could be reproduced by re-administration of the drug (SEDA-10, 116). Pulmonary edema can occur, even hours after discontinuation of $beta_2$-adrenoceptor stimulants (SEDA-13, 110).

Paradoxical bronchoconstriction has rarely been reported in patients with asthma after the inhalation of $beta_2$-agonists (9).

- A 22-year-old woman with mild asthma developed severe laryngospasm and bronchoconstriction after a fourth and subsequent doses of nebulized salbutamol, given during an acute episode of asthma. Her symptoms responded to adrenaline, but recurred after supervised rechallenge with nebulized orciprenaline (metaproterenol) sulfate. Indirect laryngoscopy excluded vocal cord dysfunction, suggesting that her symptoms of severe wheeze, respiratory distress, and hypoxia were due to bronchoconstriction.

Nervous system

Fine muscle tremor is common, especially when salbutamol is given orally or by injection. With nebulized salbutamol (2.5 or 7.5 mg) tremor was experienced by 14% of patients, and occurred more commonly with the higher doses (SEDA-21, 182). Shaking and nervousness were pronounced enough for 84% of patients taking oral salbutamol 5 mg tds to guess their treatment status correctly (SEDA-21, 180). At high doses agitation has been reported (SED-13, 362); in susceptible persons, hallucinations can develop, particularly in children, but also very occasionally in adults (10). A few patients experience headache.

The often reported observation by parents of asthmatic children that salbutamol causes hyperactivity has been investigated in 19 children before and after the inhalation of 5 ml of a nebulized solution (isotonic saline or salbutamol 5 mg); there was no statistically significant difference in activity (11). The authors hypothesized that the supposed effect on the children's activity might be dose-related or might reflect a propellant effect rather than being a consequence of salbutamol itself.

Sensory systems

Salbutamol has been applied to the eye for glaucoma, but often produces local irritation (12).

Metabolism

With inhaled salbutamol there is as a rule no significant effect on carbohydrate metabolism, but there were significant rises in blood glucose and insulin when intravenous salbutamol infusions were given to healthy pregnant women at term. The rise in blood glucose was significantly greater in pregnant women who were diabetic (SED-13, 363). Oral salbutamol 8 mg bd given for 14 days had no effect on glucose tolerance, but total cholesterol fell significantly by 9%; low-density lipoprotein cholesterol fell by 15%, and HDL increased by 10% (SEDA-21, 182).

Transient lactic acidosis/lactatemia has been reported as an adverse effect of inhaled salbutamol. In five patients who received 5 mg salbutamol by inhalation serum lactate concentrations were 3.2–8.0 mmol/l and arterial blood pH values 7.34–7.43; after 24 hours serum lactate concentrations returned to normal without specific treatment (13). In two other cases, high-dose salbutamol caused lactic acidosis, contributing to respiratory failure in one patient and complicating the assessment and management of acute severe asthma in the other (14). Respiratory compensation for this primary metabolic acidosis, characterized by increased respiratory rate and effort, may be mistaken for increased respiratory distress due to asthma. Lactic acidosis in acute asthma can therefore lead to problems in asthma management, including unwarranted intensification of $beta_2$-adrenoceptor agonist therapy and the initiation of premature or unnecessary mechanical ventilation.

Electrolyte balance

High doses of salbutamol, both intravenously and by nebulizer, can cause hypokalemia (15–17). This occurs by at least two mechanisms. First, $beta_2$-adrenoceptor agonists stimulate the Na/K pump in cell membranes, increasing the influx of potassium (18). Secondly, plasma renin activity and angiotensin II concentrations rise; angiotensin causes release of aldosterone, which is potassium-wasting in the kidney. In eight patients with mild asthma, nebulized salbutamol caused falls in serum potassium concentration from 4.4 mmol/l by a maximum of 0.85 mmol/l 45 minutes after 5 mg and by 1.16 mmol/l after 10 mg (SEDA-22, 189).

When three doses of nebulized salbutamol (0.15–0.3 mg/kg) were given at 30-minute intervals to 46 children with acute severe asthma, aged 10 months to 12 years, the mean potassium concentration fell marginally from 3.9 to 3.7 mmol/l. There was a fall in potassium concentration in 57% of the children and hypokalemia (potassium below 3.5 mmol/l) occurred in 39%. Hypokalemia was more likely to occur in children who had received oral salbutamol in the preceding 7 days. It was concluded that hypokalemia can occur in up to 33% of patients treated with three doses of nebulized salbutamol, particularly if they had previously taken oral salbutamol (SEDA-21, 182). Plasma concentrations of salbutamol correlate with changes in plasma potassium (19).

Musculoskeletal

The question of whether salbutamol can cause a myopathy has been discussed (20).

- A 76-year-old asthmatic woman developed increasing weakness, proximal muscle cramps, and fatigue. She had been using salbutamol spray (600 micrograms/day) and tablets (10 mg/day) for 2 years, and for 6 months had also used inhaled formoterol 24 micrograms/day. There were increases in creatine kinase (494 IU/l; reference range 0–130 IU/l), lactate dehydrogenase (350 IU/l; 0–300 IU/l), and aldolase (10 IU/l; 0–7.5 IU/l). Myopathy was confirmed electrophysiologically and histologically. The three medications were withdrawn and 2 days later her condition began to improve; the muscle pain and weakness disappeared within 3 weeks.

The authors concluded that $beta_2$-adrenoceptor agonist activity had been responsible for the deleterious muscle effects and they proposed that $beta_2$-adrenoceptor

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agonists should be added to the list of drugs that can cause myopathies. However, the exact effects of beta$_2$-adrenoceptor agonists on human skeletal muscle are not clear. They have also been reported to increase muscle strength and have been used in patients with muscle weakness, including spinal muscular atrophy (21).

- A 47-year-old man presented with severe myalgia and a raised creatine kinase MM isoenzyme (from skeletal muscle) while taking salbutamol from a multidose pressurized inhaler (SEDA-21, 182). The MM creatine kinase activity returned to normal when he stopped salbutamol and rested. When salbutamol was taken by inhaler or orally, the enzyme activity rose. When salbutamol was combined with exercise, even higher concentrations of creatine kinase resulted. A muscle biopsy specimen was consistent with a myopathy.

Immunologic

Hypersusceptibility reactions to salbutamol are extremely rare, but one well-documented allergic reaction has been described (SEDA-13, 109).

Long-Term Effects

Tumorigenicity

Tumor-inducing effects have not been reported in man. Chronic administration to rats produces mesovarian leiomyomas, a form of tumor not known in human subjects. The findings might reflect a species-specific consequence of prolonged beta$_2$-adrenoceptor stimulation of the rat estrous cycle; no tumors developed in mice similarly treated (SEDA-3, 118).

Second-Generation Effects

Pregnancy

Should an abortion occur in pregnant asthmatic patients taking salbutamol, the relaxant effect on the uterine wall is likely to result in marked bleeding (22).

Fetotoxicity

When salbutamol is used to arrest premature labor, effective doses are likely to produce mild fetal tachycardia (for example an increase of 20/minute) (23). In one case, supraventricular tachycardia occurred in the fetus in the 34th week of pregnancy after the mother had been treated with salbutamol; digoxin with and without propranolol was ineffective, but amiodarone controlled the tachycardia (24).

Susceptibility Factors

Age

A modified-release formulation of salbutamol (Proventil Repitabs) 12 mg bd was well tolerated in children. There were no serious adverse events and no changes in vital signs or the electrocardiogram (SEDA-21, 182).

Continuous salbutamol nebulization is relatively safe in children with severe asthma and impending respiratory failure. No chest pain, dysrhythmias, or signs of deterioration occurred (SEDA-21, 183). In one center, children presenting to an emergency department with severe asthma were initially given nebulized salbutamol 2.5–5 mg and intravenous corticosteroids. Children who did not improve continued to receive nebulized salbutamol and in addition 0.015 mg/kg of intravenous salbutamol. There were no clinically important adverse effects, although the children who were given intravenous salbutamol developed more tremor (SEDA-22, 190).

Renal disease

In patients with renal insufficiency (creatinine clearances 7–53, average 24 ml/minute) the clearance of an intravenous dose of salbutamol was more than halved (25). The dosage of salbutamol should be reduced in patients with impaired renal function.

Other features of the patient

Because of the cardiac and metabolic effects of salbutamol, it should be given cautiously with appropriate monitoring in patients with cardiovascular disease, diabetes, and hyperthyroidism.

Drug Administration

Drug formulations

Adverse effects are generally more likely when salbutamol is given by injection. At therapeutic doses, the pressurized aerosol and dry powder inhalers produce equivalent bronchodilatation without significant adverse effects (SEDA-22, 191). Patients with severe asthma tolerate large doses of nebulized salbutamol. In severe asthma there is a reduction in early lung absorption of salbutamol after inhalation, which does not occur in mild asthma. This results in lower plasma concentrations of salbutamol and less tremor (SEDA-22, 191). This is consistent with the findings in 323 patients who attended emergency departments because of severe asthma. Initial treatment with nebulized salbutamol 7.5–10 mg or up to 3.5 mg by pressurized aerosol in 1 hour caused no serious adverse effects. Tremor was noted in about 15% of the patients. About one-third of these patients failed to achieve an adequate therapeutic response to salbutamol. The most serious adverse effect of high-dose salbutamol would be failure to intensify treatment in the non-responders, that is an error of omission (SEDA-22, 190).

The efficacy and safety of salbutamol inhaled using a dry powder inhaler has been compared with salbutamol inhaled using a pressurized metered-dose inhaler (pMDI) in a randomized, open, crossover study in 12 patients with moderate to severe asthma. A total of 1600 micrograms of salbutamol was given on two separate days in a cumulative dose fashion in increments of 100, 100, 200, 400, and 800 micrograms at 3-minute intervals. FEV_1 rose progressively with each increment. The dose–response curves showed that powdered salbutamol was 3.0 times as potent (CI = 1.8, 5.8) as salbutamol from

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the pMDI. Systolic and diastolic blood pressures did not change. Powdered salbutamol caused a greater rise in heart rate. The maximum heart rate was seen at 25–30 minutes after the last dose on each study day. The average maximum heart rate was 95/minute (range 78–109) for the powder and 89/minute (range 76–106) for the pMDI. The relative dose potency of the powder versus the pMDI was 2.0 (CI = 1.3, 3.6) for lowering the serum potassium concentration. The lowest serum potassium concentration in an individual patient was 3.7 mmol/l after 1600 micrograms of the powder. No adverse events were reported on either study day. Four patients reported tremor. In one patient tremor was reported after each dose of powder as well as after 1600 micrograms inhaled from the pMDI. Cumulative doses of 800 and 1600 micrograms of powder caused tremor in the other three patients and two noted tremor after 1600 micrograms inhaled from the pMDI. Tremor was objectively measured and the dose–response curves showed a relative dose potency for the powder versus pMDI of 2.3 (CI = 1.5, 4.4). Thus, salbutamol powder was more potent than salbutamol pMDI for extrapulmonary effects and even more potent as a bronchodilator. It was concluded that use of the dry powder inhaler resulted in greater lung deposition of salbutamol, causing a higher concentration not only in the airways but also in the systemic circulation.

Drug additives

Additives to drug for inhalation, such as disodium edetate or benzalkonium chloride, can cause bronchoconstriction (26). This can lead to reduced therapeutic effectiveness of bronchodilators, for example salbutamol (or ipratropium). Some products do and others do not contain these additives, and an unexpected reduction in response to a bronchodilator may be the result of a change of product.

Drug overdose

After the ingestion of doses of salbutamol averaging 10 times the therapeutic oral dose, tachycardia, widened pulse pressure, agitation, nausea, and vomiting can occur (27–29).

A dose of 200 mg taken by mouth resulted in agitation, tachycardia, and peripheral vasodilatation; these effects were successfully treated with beta-blockers and benzodiazepines (SED-13, 362).

- A 28-year-old woman took an overdose of oral salbutamol (100 mg of salbutamol BP solution) (30). She developed diabetic ketoacidosis, with a serum glucose concentration of 17 mmol/l (308 mg/dl). Diabetic ketoacidosis induced by salbutamol overdose is uncommon in patients without diabetes; however, this patient had a family history of diabetes.
- A 4-year-old girl with accidental salbutamol intoxication (2.3 mg/kg) developed fever (38°C) besides the classical signs of salbutamol intoxication (31). Since she had no identifiable focus of infection the possibility of a thermogenic effect induced by increased adrenergic stimulation due to salbutamol intoxication was considered.

Drug–Drug Interactions

Beta blockers

The effects of salbutamol are antagonized by beta-blockers (32).

Corticosteroids

The risk of hyperglycemia or hypokalemia is increased if corticosteroids are given simultaneously (for example for asthma). In 24 healthy subjects randomized to salbutamol 5 mg, fenoterol 5 mg, or isotonic saline before and after a course of prednisone 30 mg/day for 1 week, changes in plasma potassium and glucose after the nebulized beta-agonist were significantly greater after treatment with prednisone (33). Baseline potassium concentration fell from 3.75 to 3.50 mmol/l. The lowest mean plasma potassium occurred 90 minutes after fenoterol with prednisone pretreatment (2.78 mmol/l).

Diuretics

Treatment with bendroflumethiazide, and presumably other diuretics, augments the hypokalemic and electrocardiographic effects of high-dose inhaled salbutamol; the dysrhythmogenic potential of this interaction can be important in patients with acute exacerbations of chronic airflow obstruction, who have concomitant hypoxemia and ischemic heart disease (SEDA-15, 134).

Formoterol and salmeterol

The interaction of formoterol and salmeterol with salbutamol has been studied in a randomized, double-blind, crossover study in 16 asthmatic patients (34). The patients were taking regular inhaled corticosteroids and were responsive to methacholine challenge, with a PD20 (that is the dose of methacholine that produced a fall in FEV_1 of 20%) of less than 500 micrograms. The patients had methacholine challenges performed 12 hours after a single dose of formoterol 12 micrograms, salmeterol 50 micrograms, placebo, and either a low dose (400 micrograms) or a high dose (1600 micrograms) of salbutamol. With placebo, challenge after high-dose salbutamol resulted in a higher PD20 than after low-dose salbutamol (as expected). However, after both formoterol and salmeterol, the higher dose of salbutamol did not give as great an increase in PD20 over the lower dose of salbutamol. This suggests that prior treatment with formoterol and salmeterol can antagonize the protective effect of salbutamol against bronchoconstriction. This effect may be important in patients with acute asthma.

Theophylline

Salbutamol has additive effects with theophylline, which can potentiate the hypokalemic effect (SEDA-17, 164). In 14 healthy volunteers, theophylline increased salbutamol-induced hypokalemia and in some individuals there was profound hypokalemia (less than 2.5 mmol/l) (35). Combining theophylline with salbutamol increased the tachycardia resulting from the salbutamol infusion. Salbutamol infusion caused a fall in diastolic and a rise in systolic blood pressure, which was not altered by theophylline.

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Salicaceae

See also Herbal medicines

General Information

The family of Salicaceae contains two genera:

1. *Populus* (cottonwood)
2. *Salix* (willow).

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Table 1 Some plant sources of salicylates

Salicylate	Plant species	Common name	Family
Methyl salicylate	*Gaultheria procumbens*	Wintergreen, Eastern teaberry	Ericaceae
	Spiraea alba	White meadowsweet	Rosaceae
Salicin	*Salix songorica*		Salicaceae
Salicylic acid	*Salix alba*	White willow	Salicaceae
	Burchardia multiflora	Milk maids	Colchicaceae
	Callicarpa integerrima		Verbenaceae
	Falcaria vulgaris	Sickleweed	Apiaceae
	Flemingia laevicarpa		Fabaceae
	Genista lucida		Fabaceae
	Populus pseudosimonii		Salicaceae
Saligenin	*Populus pseudosimonii*		Salicaceae

Salix species and salicylates

The barks of various species of *Salix* contain glycosides of saligenin (salicylalcohol), namely the simple O-glycoside salicin and more complex glycosides such as salicortin (1). When taken orally, these glycosides undergo intestinal transformation to saligenin, which is rapidly absorbed and converted by the liver to salicylic acid. When willow bark preparations are used according to current dosage recommendations, they will not provide sufficient salicylic acid to produce acute salicylate poisoning. However, the risk of hypersusceptibility reactions, such as skin reactions and bronchospasm, in sensitive individuals cannot be excluded.

Other natural sources of salicylates are listed in Table 1. There are separate monographs on acetylsalicylic acid (aspirin), benorilate, diflunisal, lysine acetylsalicylate, and salsalate. Methyl salicylate is covered under *Gaultheria procumbens* in the monograph on the Ericaceae.

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Salicylanilides

See also Disinfectants and antiseptics

General Information

The halogenated salicylanilides, which include closantel, niclosamide, oxyclozanide, rafoxanide, and resorantel, have antiparasitic activity in animals (1). Closantel and rafoxanide are widely used for the control of infestation with *Hemonchus* species and *Fasciola* species in sheep and cattle and *Estrus ovis* in sheep. Niclosamide is used as an anticestode in a wide range of animals. Other parasites that are susceptible include hematophagous helminths and external parasites such as ticks and mites. Many halogenated salicylanilides, including dibromosalicylanilide, tribromosalicylanilide, and tetrachlorosalicylanilide, have been used in disinfectants.

Organs and Systems

Skin

Photocontact dermatitis can occur after the use of halogenated salicylanilides, such as tribromosalicylanilide in soaps (2) and bithionol in first-aid creams (3). Tetrachlorosalicylanilide caused many cases in the 1960s and was withdrawn, after which there was a striking reduction in the numbers of patients with positive photopatch tests (4). The authors concluded that these results were most likely to have been due to removal from the market of the more potent photosensitizing chemicals and increased familiarity of physicians with this effect. Photosensitivity has also been reported to other analogues in widespread use, such as the dibromo and tribromo derivatives. The photoallergy is localized, but transient generalized reactions can occur.

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Salicylates, topical

General Information

Salicylic acid is widely used in dermatology because of its keratolytic properties. Methylsalicylate (the main constituent of oil of wintergreen) is a topical analgesic that is also a constituent of Red Flower Oil and White Flower Oil formulations, popular herbal analgesics used topically in Southeast Asia (1). Some users take small amounts of the oil orally to enhance its analgesic effects. It has been responsible for rare cases of allergic skin reactions.

Salicylism

Many reports have described "salicylism," intoxication due to percutaneous absorption of salicylates, such as methyl salicylate (2). The first symptoms of salicylism are pallor, fatigue and drowsiness, and altered respiration, which becomes more frequent and at the same time deeper, and which can be heard from a distance. Other early signs of intoxication with salicylic acid are nausea, vomiting, changes in the ability to hear, and mental confusion. Several deaths have been recorded, mainly in children.

Other signs and symptoms of salicylism (3–5) include:

fatigue, changes in hearing ability, nuchal rigidity, fever, profuse sweating, and pallor (6);
frequent deep respiration, Cheyne-Stokes respiration, dyspnea, hyperpnea;
drowsiness, mental confusion, stupor, hallucinations, headache, dizziness, tinnitus, slurred speech, agitation, disorientation, lethargy, delusions, aggression, retrograde amnesia, depression, coma, somnolence;
hypoglycemia (SEDA-16, 158) and metabolic acidosis (6); nausea, vomiting, thirst, anorexia, diarrhea.

Accidental ingestion of methylsalicylate in young children has resulted in severe salicylate poisoning, in one case with laryngeal edema (7). A suicide attempt by deliberate ingestion of about 100 ml resulted in severe salicylate poisoning (8).

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Salmeterol

See also Beta$_2$-adrenoceptor agonists

General Information

Salmeterol is a selective beta$_2$-adrenoceptor agonist that is more potent and has a significantly longer duration of action than salbutamol (SEDA-21, 184). It is used as a supplement to inhaled glucocorticoids for sustained bronchodilatation. It has a much slower onset of effect than salbutamol and is not effective in acute attacks of asthma. It is available as a multidose-pressurized aerosol 0.025 mg/puff, and as a dry powder, Diskhaler or Accuhaler 0.05 mg per dose. The adverse effects profile of salmeterol is the same as that of salbutamol and other beta$_2$-agonists (SEDA-21, 185).

Observational studies

There has been a systematic review of the literature and of unpublished trials with single and chronic doses of inhaled salmeterol 100 micrograms from the GlaxoSmithKline databases (1). The analysis covered data available until early 1999. Of 44 trials that included salmeterol 100 micrograms, data on systemic effects were available from 19 trials that were subsequently included in a pooled weighted analysis. In the chronic dose studies in 1504 patients who took salmeterol for more than 7 days, tremor was reported in 5.6%, palpitation in 1.7%, reduced serum potassium in 0.9%, electrocardiographic events in 0.6%, and increased serum glucose in 0.3%. The smaller systemic effects after chronic administration compared with single salmeterol dosing possibly reflected tachyphylaxis to the systemic cardiovascular and metabolic effects of the drug. The mean systemic effects of salmeterol 100 micrograms are small and of doubtful clinical relevance; unintended use of twice the dose of salmeterol is unlikely to affect patients adversely.

Placebo-controlled studies

In a randomized, double-blind, placebo-controlled, multicenter evaluation of the clinical efficacy and safety of salmeterol 42 micrograms bd in 538 asthmatic patients, mean peak flow rate improved significantly in the patients who used salmeterol (2). The use of supplementary salbutamol, asthma symptom scores, and FEV_1 were

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significantly improved by salmeterol. There were no clinically significant adverse events.

In a double-blind study in 49 stable asthmatic patients who were taking inhaled glucocorticoids, randomized to either salmeterol 50 micrograms or placebo bd for 4 weeks, the bronchodilator response to cumulative doses of inhaled salbutamol was measured before and 12 and 36 hours after the last dose (3). There were no significant differences between salmeterol and placebo in maximal FEV_1 or peak expiratory flow rate responses to inhaled salbutamol at 12 and 36 hours. Asthma control, as judged by lung function and diary card parameters, was significantly better in the patients who took regular salmeterol. There were no serious adverse events. The incidence of non-serious adverse events was similar in the two groups, 56% with salmeterol and 50% with placebo. The most commonly reported adverse events were headache and rhinitis.

Salmeterol 50 micrograms bd and salbutamol 400 micrograms qds have been compared in 165 patients with mild to moderate bronchial asthma in a double-dummy, placebo-controlled, crossover study (4). Relative to placebo, mean morning peak expiratory flow rate increased by 30 l/minute with salmeterol but did not change with salbutamol; evening peak expiratory flow rate increased by 25 l/minute. Salmeterol improved the asthma score compared with placebo, but salbutamol produced no overall difference. Only daytime symptoms were improved by salbutamol. The asthma score fell over time with salbutamol. Both minor and major exacerbation rates were significantly less when patients used salmeterol. Major exacerbations lasted for significantly longer in patients taking salbutamol compared with those taking placebo. Tolerance did not develop to either drug; after withdrawal there was no rebound worsening of asthma control, fall in lung function, or increase in bronchial reactivity to inhaled methacholine. Although salbutamol improved daytime symptoms, there was deterioration in asthma control over time.

The effect of salmeterol on asthma control in 506 patients requiring inhaled corticosteroids has been evaluated in a randomized, double-blind, placebo-controlled study (5). The patients received either salmeterol 42 micrograms bd via a metered-dose inhaler or placebo for 12 weeks. Salmeterol was superior to placebo when assessed by asthma quality-of-life score, global score, asthma symptoms, and improvement in FEV_1, peak expiratory flow rate, and use of supplementary salbutamol to treat exacerbations. Adverse events were reported in 53% of patients taking salmeterol and 51% of patients taking placebo. Most adverse events were not related to treatment. Treatment-related adverse events occurred in 13 patients (5%) taking placebo and 11 patients (4%) taking salmeterol. Twelve patients (2%) did not complete the study because of adverse events, five taking placebo and seven taking salmeterol. In only three patients were the adverse effects considered to be potentially related to the treatment: salmeterol—chest tightness; placebo—shortness of breath and chest pains. Respiratory failure occurred in one patient taking salmeterol and was judged to be possibly related to the drug. Exacerbation of asthma occurred in 59 patients (22%) taking placebo and 53 patients (20%) taking salmeterol. The most common reason cited for exacerbation of the asthma was respiratory infection.

In a double-blind, multicenter trial in primary care, 911 patients with asthma, who were already receiving maintenance anti-inflammatory therapy, were randomized to treatment with salmeterol (50 micrograms bd) or placebo for six months (6). As expected, the patients treated with salmeterol had higher mean peak expiratory flows, used less rescue salbutamol, and had less disturbed sleep than the patients treated with placebo. The most important result from this study was that the number of severe exacerbations was the same in both groups; in other words, salmeterol did not increase the frequency of severe exacerbations.

Salmeterol 42 micrograms bd has been compared with inhaled ipratropium bromide 36 micrograms/day and inhaled placebo in a randomized, double-blind study for 12 weeks in 405 patients with chronic obstructive pulmonary disease (6). Both salmeterol and ipratropium bromide significantly increased the peak expiratory flow rate compared with placebo. Non-specific ear, nose, and throat symptoms (for example sore throat and upper respiratory tract infections) were more common with salmeterol and ipratropium than placebo. There were no significant differences between the groups in the total number of ventricular and supraventricular extra beats. There was no tolerance to the bronchodilating effects of salmeterol.

In a randomized, double-blind, parallel-group study, 911 asthmatic patients in primary care were randomly assigned to inhaled salmeterol 50 micrograms bd or placebo bd for 24 weeks (7). They continued to use their anti-inflammatory maintenance therapy throughout. Salmeterol produced a significant improvement in peak expiratory flow rate and a reduction in the use of short-acting $beta_2$-agonists. Salmeterol did not increase the number of severe exacerbations of asthma.

Comparative studies

Salmeterol has been compared with several other bronchodilators.

Formoterol

Salmeterol dry powder 50 micrograms bd and formoterol dry powder 12 micrograms bd have been compared in 425 asthmatic patients treated for 6 months in a randomized, open, parallel-group study. Improvements were similar in the two groups, although evening predose peak expiratory flow rate showed a trend in favor of formoterol, statistically significant at 2, 3, and 4 months (8). Both treatments were well tolerated: 193 patients taking salmeterol and 190 taking formoterol reported adverse events. This was not unexpected in a 6-month trial. The most frequent adverse events included viral infections, asthma exacerbation, headache, rhinitis, and chest infections. Exacerbation of asthma was reported as an adverse event by 54 (22%) taking salmeterol and 41 patients (17%) taking formoterol. Adverse events, assessed as possibly/probably drug-related, were reported in 21 (9%) taking salmeterol and 32 (13%) patients taking formoterol. The most frequent drug-related adverse event was headache, reported by 11 patients taking salmeterol and seven taking formoterol. Other adverse events

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included tremor in two taking salmeterol and five patients taking formoterol, exacerbation of asthma in four patients in each group, and palpitation in four patients taking formoterol.

The relative efficacy of the long-acting beta$_2$-adrenoceptor agonists formoterol and salmeterol has been studied in a randomized, double-blind, crossover trial in 15 patients with asthma taking regular corticosteroids and salbutamol (9). The patients had methacholine challenges performed after varying single doses of formoterol (12, 60, and 120 micrograms) and salmeterol (50, 250, and 500 micrograms). The maximal protective effect of salmeterol against methacholine challenge was reached at 250 micrograms, whereas formoterol showed a dose–response relation, with maximum protection at the highest dose. This confirmed the authors' hypothesis that salmeterol is a partial agonist at beta-adrenoceptors compared with formoterol. The higher affinity of formoterol for beta-adrenoceptors also produced more adverse effects. There was a significant fall in serum potassium concentration after 60 micrograms of formoterol but not after 250 micrograms of salmeterol. The serum potassium concentration was also significantly lower with the highest dose of formoterol compared with the highest dose of salmeterol (minimum concentration 3.1 mmol/l). The highest dose of formoterol also resulted in more tremor than the highest dose of salmeterol. The increases in heart rate and QT_c interval were similar with the two drugs. It should be noted that the doses used in this study were higher than recommended. It remains unclear whether the partial agonist activity of salmeterol is clinically important, but this seems unlikely.

Salbutamol

The effects of single inhaled doses of salmeterol 0.1, 0.2, and 0.4 mg and salbutamol 0.4 mg from a multidose pressurized inhaler have been compared in healthy volunteers (10). At all doses tested, salmeterol produced statistically significant changes in pulse rate, tremor, blood glucose, and plasma potassium concentrations. Tremor, awareness of heartbeat, and headache were reported by the subjects after salmeterol administration.

Theophylline

Inhaled salmeterol 50 micrograms bd has been compared with oral modified-release theophylline in 178 patients with mild to moderate chronic obstructive pulmonary disease (8). Salmeterol caused a significant improvement in mean morning peak expiratory flow rate compared with theophylline and significantly increased the percentage of symptom-free days and nights with no additional requirement for salbutamol. Adverse events occurred in 50% of the patients who took salmeterol, and 49% of those who used theophylline. Adverse events due to the pharmacological properties of the drug were less frequent with salmeterol (4%) than with theophylline (15%).

In a randomized, double-blind study, 943 patients with chronic obstructive pulmonary disease were treated over 12 weeks with either inhaled salmeterol 42 micrograms bd via a metered-dose inhaler or oral modified-release theophylline bd, titrated to serum concentrations of 10–20 micrograms/ml, or with a combination of the two drugs (11). Adverse events potentially related to the study drug were significantly more common in those who took theophylline compared with salmeterol alone. This was most evident for adverse gastrointestinal events (nausea, gastric upset, vomiting, diarrhea). Adverse cardiovascular events occurred in 1–4% and were comparable among the groups. Theophylline-related toxicity was considerable, as nearly 16% of the patients withdrew during the theophylline titration period owing to adverse events.

Organs and Systems

Cardiovascular

No cardiovascular effects are seen at the recommended daily dose. At a dose of 0.1 mg of salmeterol twice a day no change in heart rate or rhythm was seen on a 24-hour electrocardiogram (Holter). No change in blood pressure was seen and no electrocardiographic abnormality related to myocardial ischemia was recorded during 24-hour monitoring (12).

Skin

A single case of a pruritic burning maculopapular rash has been documented and confirmed by patch-testing with the active component (SEDA-17, 165).

Death

When salmeterol was given for one year to 15 407 patients there were no unexpected major adverse events. There were 1022 (6.6%) deaths; 73 patients died of asthma and 39 used salmeterol during the last month of life. Analysis showed that the majority of deaths were due to natural causes. In four of the 39 subjects who died of asthma and who had taken salmeterol the authors thought it possible that death had been related to the use of salmeterol (13).

Long-Term Effects

Drug tolerance

Current guidelines recommend the use of formoterol and salmeterol in addition to inhaled corticosteroids for optimal management of asthma. Both drugs are highly selective beta$_2$-adrenoceptor agonists, with minor pharmacological differences. Several studies have shown that regular use of both formoterol and salmeterol results in the development of tolerance to their bronchoprotective effects, even with treatment periods as short as 1 week. The significance of this tolerance is unclear, but it is potentially important clinically.

Previous studies over periods of up to 8 weeks have established that the bronchoprotective effect of salmeterol abates with regular use, even after only 1 week of regular treatment. The effects of longer-term use of salmeterol on airway hyper-responsiveness have been examined in a randomized, double-blind, placebo-controlled trial in 408 patients with mild asthma (14). These patients were not using inhaled corticosteroids and took salmeterol (42 micrograms bd) or placebo for 24 weeks. Methacholine challenges were performed at 4, 12, and 24 weeks. At 4 weeks

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salmeterol provided protection against methacholine of about one doubling dose and there was no further change in this protection over the study period. As expected, regular salmeterol produced significant improvements in asthma symptoms. Adverse events were similar in the two groups, apart from headache, which was reported in 14 of 202 patients treated with salmeterol and seven of 206 patients taking placebo. The loss of bronchoprotection that develops with regular salmeterol did not appear to worsen over a 24-week period.

The effect of inhaled budesonide on the loss of bronchoprotection with regular salmeterol has been studied in a randomized, double-blind trial in 18 patients with mild asthma, taking no regular medications (15). After 1 week of regular salmeterol (50 micrograms bd) 12 patients developed tolerance to its protective effect against airway allergen. After another week of salmeterol combined with either inhaled budesonide (500 micrograms bd) or placebo, the patients who took budesonide showed some recovery of the protective effect of salmeterol against airway allergen compared with placebo. The authors suggested upregulation of beta-adrenoceptors as a potential mechanism.

The effect of a bolus of inhaled budesonide on formoterol-induced subsensitivity in airway beta-adrenoceptors has been studied in a randomized, double-blind, crossover study in 10 asthmatic patients taking regular inhaled glucocorticoids (16). Challenge testing with AMP was performed at baseline and after one week of regular formoterol (24 micrograms bd). Before the second challenge the patients were given either a dose of inhaled budesonide (1600 micrograms) or placebo via a dry powder inhaler. After one week of formoterol, the PC_{20} for the second challenge fell significantly (by a factor of 3.9). However, when the second challenge was performed after a bolus of budesonide, there was no fall in the PC_{20}, suggesting protection against formoterol-induced tolerance. Lymphocyte beta-adrenoceptor density fell with regular formoterol, but not after a bolus of budesonide. These results have implications for the treatment of acute severe asthma in patients taking regular long-acting $beta_2$-adrenoceptor agonists. It may be appropriate to give a bolus dose of inhaled glucocorticoids to these patients early in an acute asthma attack, particularly if they are poorly responsive to initial therapy with short-acting bronchodilators.

Drug Administration

Drug formulations

Combination formulations of fluticasone with salmeterol delivered through a dry powder inhaler are intended to provide a combination of an inhaled glucocorticoid and a long-acting $beta_2$-adrenoceptor agonist in one dose, simplifying the treatment regimen and so possibly improving compliance.

Salmeterol 50 micrograms plus fluticasone 500 micrograms bd delivered via a combination inhaler (plus a placebo inhaler) have been compared with the same drug regimen delivered by separate inhalers in a randomized, double-blind trial over 28 weeks in 503 asthmatic patients already taking inhaled glucocorticoids (17). There was also an arm treated with inhaled fluticasone alone. Outcome variables were peak flow and asthma symptoms. Both combination and concurrent therapy with fluticasone plus salmeterol resulted in significantly better symptom control and higher peak flows than fluticasone alone. There were no significant differences in the effects of fluticasone plus salmeterol delivered in a combination inhaler versus separate inhalers. Drug-related adverse effects were similar in all three treatment groups: most were asthma-related, but hoarseness, dysphonia, and throat irritation were the commonest adverse effects attributed to therapy (1–4%).

The effects of salmeterol 50 micrograms plus fluticasone 250 micrograms delivered via a combination inhaler and via separate inhalers have been compared in 371 asthmatic patients (18). There were equivalent improvements in peak flows and asthma symptoms. Candidiasis, dysphonia, and throat irritation were the commonest adverse effects attributed to treatment and occurred equally in the two groups (35%). Palpitation and tremor, which may have been related to salmeterol, occurred in 2% (for each symptom) of the combination group and in 1% and under 1% of the separate inhaler group. In both of these studies compliance was measured by dose counters on the inhalers and was equivalent in the two groups.

It appears that treatment with fluticasone plus salmeterol delivered via a combination inhaler is as effective as the same drugs given in separate inhalers and has a similar adverse effects profile. Whether treatment with a combination inhaler improves compliance is not yet proven.

Drug–Drug Interactions

Salbutamol

Experimental studies continue to show that regular treatment with either formoterol or salmeterol in patients with asthma can produce subsensitivity to the bronchodilator effects of salbutamol (19,20). This bronchodilator subsensitivity can be partly reversed by a bolus dose of inhaled or systemic corticosteroids. The clinical relevance of these experimental findings is unclear.

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Salsalate

General Information

Salsalate is a compound that contains two salicylate molecules joined by a diazo bond, which is hydrolysed after absorption, yielding two molecules of salicylate.

Organs and Systems

Mouth and teeth

Salicylates can cause ulceration in the mouth from local contact (1).

- A 77-year-old man developed three ulcerated lesions on his tongue because he had difficulty in swallowing salsalate tablets. He was taught how to swallow tablets and instructed to take them with water to avoid prolonged contact of salsalate with the tongue. Three weeks later, his lesions had healed and no new ones had appeared (2).

Gastrointestinal

There is some evidence that salsalate causes less gastric toxicity than aspirin, but salsalate can produce dyspepsia and occult bleeding when used therapeutically in effective doses. In an open study in 66 patients taking salsalate 3 g/day for 6 weeks, three patients were withdrawn because of gastrointestinal upsets; the most common adverse effect was dyspepsia (3).

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Saperconazole

See also Antifungal azoles

General Information

Saperconazole is an experimental, water-insoluble, lipophilic, fluorinated triazole. Its structure resembles that of itraconazole and it has a long half-life. It has a broad antifungal spectrum, including *Cryptococcus* Species and *Aspergillus* species. In early studies in cases of compassionate use, only a few adverse effects were described, including hepatotoxicity (1,2), and its adverse effects were expected to resemble those of itraconazole (3). However, the manufacturers stopped developing it because of concerns about toxicity.

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Sapindaceae

See also Herbal medicines

General Information

The genera in the family of Sapindaceae (Table 1) include akee and lychee.

Blighia sapida

Blighia sapida (akee) contains a large amount of a potent hypoglycemic amino acid, glycylglycylglycine, known as hypoglycin.

Adverse effects

Akee poisoning (Jamaican winter vomiting sickness or toxic hypoglycemic syndrome) is a potentially fatal illness. During an outbreak in 1991, symptoms included vomiting (77%), coma (25%), and seizures (24%) (1). In 29 African children, all of whom died in 2–48 hours, there were intense thirst (38%) and hypotonia (97%) and the effects were more severe in those with malnutrition.

Chronic poisoning can cause cholestatic jaundice (2).

- A 27-year-old Jamaican man developed jaundice, pruritus, intermittent diarrhea, and right upper quadrant abdominal pain after chronic ingestion of akee fruit. Liver biopsy showed centrilobular zonal necrosis and cholestasis. There was no evidence of another cause.

An anaphylactic reaction to akee has been described (3).

Table 1 The genera of Sapindaceae

Alectryon (alectryon)
Allophylus (allophylus)
Blighia (akee)
Cardiospermum (balloon vine)
Cupania (cupania)
Cupaniopsis (carrot wood)
Dimocarpus (dimocarpus)
Dodonaea (dodonaea)
Exothea (exothea)
Harpullia (harpullia)
Hypelate (hypelate)
Koelreuteria (koelreuteria)
Litchi (lychee)
Matayba (matayba)
Melicoccus (melicoccus)
Nephelium (nephelium)
Paullinia (bread and cheese)
Sapindus (soapberry)
Schleichera (schleichera)
Serjania (serjania)
Thouinia (thouinia)
Ungnadia (ungnadia)
Urvillea (urvillea)
Xanthoceras (xanthoceras)

Paullinia cupana

Paullinia cupana (*guaraná*) contains the xanthines theobromine and theophylline as well as flavone glycosides. The crushed seeds of *P. cupana* are made into a dried paste called guaraná, from which a beverage is prepared. All of its effects are directly related to its high content of caffeine-like substances.

Adverse effects

US authors have reported two cases of ventricular extra beats associated with the intake of supplements containing guaraná (4). In both cases the supplements also contained multiple other ingredients, and causality was therefore not certain.

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Saquinavir

See also Protease inhibitors

General Information

Of all protease inhibitors, saquinavir is the most potent in vitro. However, owing to poor systemic availability (less than 4%), it is the least potent of all protease inhibitors in use, although a formulation with increased availability has been marketed. However, when saquinavir is given together with ritonavir, the strong inhibitory effect on CYP3A4 of the latter results in high plasma concentrations of saquinavir. This interaction has been exploited, with favorable results, both in

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first-line protease therapy and as salvage treatment in patients with virus resistant to a regimen containing a protease inhibitor. Using 400 mg/400 mg and 800 mg/200 mg, the saquinavir soft gelatin capsule AUC increased by 17–23 times compared with saquinavir alone (1). Saquinavir had no clinically significant effect on the pharmacokinetics of ritonavir. Ritonavir as a booster allows a much higher saquinavir concentration to be obtained, allowing twice-daily dosing and a reduced capsule burden.

General adverse effects

Hitherto, no particular or frequent adverse effects attributable to saquinavir have been reported from trials in which saquinavir was used at the licensed dosage of 600 mg tds (2). Diarrhea, usually of only moderate severity, occurring in 3–4% of patients, is the most common single adverse effect (SEDA-22, 310).

As with other HIV-1 protease inhibitors, saquinavir may be associated with drug interactions as a result of the effect of saquinavir on the hepatic cytochrome P450 oxidase system. Although compared with other HIV protease inhibitors, saquinavir has less of an inhibitory effect on cytochrome P450 isozymes; clinically relevant interactions can nevertheless occur. Drug interactions with saquinavir have been reviewed (3).

Organs and Systems

Psychological, psychiatric

Saquinavir can occasionally be associated with acute paranoid psychotic reactions (4).

- A 41-year-old woman took zidovudine and didanosine for HIV-1 infection after an acute seroconversion illness. Zidovudine and didanosine had to be withdrawn because of neutropenia and nausea, so she was given stavudine plus lamivudine without any adverse effects. Saquinavir (600 mg tds) was added 12 months later because of weight loss and a falling CD4 cell count. Within 24 hours of starting to take saquinavir she developed agitated depression with paranoid ideation. After drug withdrawal her mental health returned to normal over 5 days. Over the next 6 weeks stavudine and lamivudine were reintroduced without any adverse effects and continued for a further 11 months. Saquinavir was then reintroduced at the previous dosage, and within 2 days she again became extremely mentally agitated with paranoid ideation. Saquinavir was withdrawn and she recovered within 7 days. She was later given indinavir without problems. Her mother had a history of major depressive illness.

Endocrine

Gynecomastia has been reported in a series of men taking saquinavir (5). In these cases the association was clear (particularly since there was positive dechallenge), but this is a rare effect and has not previously been reported with either this or other protease inhibitors, although it has been associated with the nucleoside analogue reverse transcriptase inhibitor stavudine.

Gastrointestinal

Diarrhea, usually of only moderate severity, which occurs in 3–4% of patients, is the most common single adverse effect of saquinavir (6–8).

Urinary tract

A renal stone has been attributed to saquinavir (9).

- A 42-year-old HIV-positive man with a prior history of *Pneumocystis jiroveci* pneumonia who had been treated with zidovudine and dideoxycytidine started to take saquinavir 600 mg tds. His CD4 cell count rose from 28×10^3/l to 101×10^3/l and zidovudine and dideoxycytidine were replaced by stavudine and lamivudine, because of mild peripheral neuropathy. Saquinavir was continued unchanged. A few months later he developed left-sided loin pain and hematuria and a left renal calculus was seen on ultrasound. A month later the same signs and symptoms recurred and a few weeks later he passed a small black stone in the urine. Ultrasonic lithotripsy was performed, with a good result. Saquinavir was discontinued, after which he had no further renal problems.

This case suggests that saquinavir, like indinavir, may be associated with renal calculus formation in some individuals.

Skin

Adverse skin reactions to saquinavir are exceptional, but erythema multiforme has been reported (10).

- A 32-year-old HIV-positive man, who had been treated with didanosine and lamivudine, added saquinavir (600 mg tds) because of a rising plasma HIV-1 RNA viral load. Five days later he presented with a generalized maculopapular skin eruption, the lesions being centered on a bulla, and erosive lesions on the palate. Histological examination was compatible with erythema multiforme. Saquinavir was discontinued and all the mucocutaneous lesions healed within 15 days. Rechallenge was not attempted.

Long-Term Effects

Tumorigenicity

- Eruptive angiolipomata occurred in a 49-year-old woman after she had taken stavudine 30 mg bd, lamivudine 150 mg bd, and saquinavir 600 mg 8-hourly for 3 months (11). This has also been reported with other protease inhibitors (12,13) and the mechanism is not known. In one case lipomata regressed after the introduction of indinavir (14).

Drug Administration

Drug formulations

A soft gelatin capsule formulation of saquinavir with greater systemic availability than the hard gelatin capsule has been developed. Of 442 patients who used the soft gelatin capsule 1200 mg tds, for 48 weeks, 8% withdrew because of adverse events, which were not necessarily

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related to saquinavir. No new adverse effects or laboratory abnormalities emerged compared with those previously observed with the hard gelatin capsule. The most frequent adverse effects were gastrointestinal, diarrhea being the most common (15).

Drug–Drug Interactions

Ciclosporin

In an HIV-1-positive kidney transplant recipient, saquinavir increased the trough concentration of ciclosporin three-fold, resulting in fatigue, headache, and gastrointestinal discomfort. Ciclosporin, like saquinavir, is metabolized by CYP3A. Saquinavir plasma concentrations were likewise increased by ciclosporin. All the symptoms disappeared after downward adjustment of the doses of both ciclosporin and saquinavir (16).

Cytotoxic drugs

In 37 patients with HIV-associated non-Hodgkin's lymphoma who were treated with a 96-hour continuous intravenous infusion of cyclophosphamide + doxorubicin + etoposide, severe (grade 3 or 4) mucositis occurred in eight of 12 patients who received concomitant saquinavir (600 mg tds) compared with three of 25 who did not receive saquinavir. Although the authors did not measure saquinavir plasma concentrations, they suggested that this finding may have been explained by inhibition of the metabolism of one or more of the cytotoxic drugs by saquinavir (17).

Erythromycin

In 11 healthy men, erythromycin 250 mg qds increased the AUC of saquinavir (given as a soft gel capsule 1200 mg tds) by 69% when both were given for 7 days (18).

Ketoconazole

In 12 healthy men, ketoconazole 400 mg/day increased the AUC of saquinavir (given as a soft gel capsule 1200 mg tds) by 190% when both were given for 7 days (18).

Midazolam

Saquinavir substantially potentiates the effects of midazolam by raising its blood concentrations (19).

Rifamycins

In 14 healthy men, rifampicin 600 mg/day reduced the AUC of saquinavir (given as a soft gel capsule 1200 mg tds) by 46% when both were given for 14 days; this reduction can be counteracted by the addition of ritonavir (18).

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Satranidazole

General Information

Satranidazole is a highly active amebicidal agent with a slightly wider spectrum than metronidazole against micro-aerophilic and anaerobic bacteria; it is also

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effective against *Giardia* and *Trichomonas*. It is less toxic than metronidazole, nimorazole, secnidazole, and ornidazole. Gastrointestinal tolerability was good in early studies. Therapeutic doses did not cause an adverse interaction with alcohol (SEDA-12, 707) (1,2).

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Sclerosants

General Information

In sclerotherapy an irritant is introduced into varicose veins and esophageal varices, causing a local inflammatory reaction and obliteration of the veins concerned. Sclerosing agents include lauromacrogol 400, monoethanolamine oleate, sodium morrhuate, and sodium tetradecylsulfate.

Lauromacrogol 400 (polidocanol)

Lauromacrogol 400 is a solvent and non-ionic emulsifier. In medicaments it is used as topical anesthetic, an antipruritic, and a sclerosing agent (1).

Monoethanolamine oleate

Monoethanolamine oleate is an alkaline viscous liquid that is irritant and is used as a sclerosant.

Sodium morrhuate

Sodium morrhuate is a fatty acid extract of cod liver oil; its sclerosant effect was discovered with the use of the agent in treating leprosy (2). Sodium morrhuate is cytotoxic, as demonstrated by autopsy studies in 10 patients (3).

Sodium tetradecylsulfate

Sodium tetradecylsulfate is an anionic surfactant used as a sclerosant.

Treatment of esophageal varices

Bleeding esophageal varices are treated by inserting a needle-tipped catheter through an endoscope to the site of the varices, and injecting a sclerosing agent directly into the bleeding varix. The common mechanism of action of all sclerosing agents is destruction of endothelial surfaces, with subsequent thrombosis, leading to intimal fibrosis and obliteration of the vessel lumen (4).

Adverse effects occur in 10–15% of patients. These include severe local edema and necrosis at the site of sclerosis (5), bacterial peritonitis (6), and pneumococcal bacteremia (7). Fever, chest pain, and odynophagia are common after esophageal sclerotherapy, but they tend to be of short duration (8).

In one review (9) complications of endoscopic variceal sclerotherapy were studied retrospectively in 267 patients who had been treated with endoscopic variceal injection for esophageal variceal hemorrhage in the period 1988–94. Local complications were: transient dysphagia (73%), chest pain (65%), esophageal ulceration (63%), ulcerogenic bleeding (14%), post-therapeutic hemorrhage (13%), esophageal strictures (10%), pleural effusions (9%), subfebrile temperatures (6.4%), pericarditis (0.4%), and esophageal perforation (0.4%). No patient died from sclerotherapy-induced adverse effects.

Sclerotherapy has also been used in the extremities for treating varicose and telangiectatic leg veins (10,11). Telangiectatic matting can develop bluish areas due to post-treatment neovascularization, in which new blood vessels, less than 0.2 mm in diameter, appear distally to the treated site, most commonly on the thigh. The incidence of this has been reported to be between 5 and 35%. Resolution often occurs spontaneously over 3–12 months, although in some patients it may be permanent or require further sclerotherapy to which it can be resistant (12).

Organs and Systems

Cardiovascular

Vascular thrombosis due to sclerosants is due to direct damage to vascular endothelium and red cells, aggregation of platelets, and aggregation of granulocytes at the venous wall endothelium. Where sodium morrhuate is concerned, these effects probably derive from its surfactant properties and its high arachidonate content (13). Other sclerosant agents in current use (lauromacrogol 400, monoethanolamine oleate, and sodium tetradecylsulfate) cause effects similar to sodium morrhuate.

Cardiac arrest has been reported in a child who received lauromacrogol 400 to sclerose a symptomatic peripheral venous malformation (14).

- A 5-year-old child with Klippel–Trenaunay syndrome, a cutaneous capillary malformation in the right leg, and a venous malformation of the lateral and posterior aspects of the right thigh and buttock had an injection of 4 ml of 1% lauromacrogol 400 into the malformation in the leg after oral premedication with midazolam 5 mg and atropine 0.5 mg and anesthesia with thiopental 80 mg and vecuronium bromide 2 mg for tracheal intubation. Shortly after the injection the patient developed rapidly progressive sinus bradycardia with eventual asystolic cardiac arrest. Anesthesia was discontinued and cardiopulmonary resuscitation, with 100% oxygen, external cardiac message, and intravenous orciprenaline 0.05 mg, was successful.

Respiratory

Fever and pneumonia have been reported after the use of sodium morrhuate sclerosant solution (SEDA-14, 456).

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Gastrointestinal

Following the use of sclerosants, such as monoethanolamine oleate 5%, to treat esophageal varices, patients commonly experience early dysphagia and retrosternal pain, as might be expected. More serious complications can arise later if the fibrosis that is a natural consequence of the treatment extends too far, or if the sclerosant escapes from the veins that are being treated. Complications can include fibrosis (leading, for example, to esophageal stricture) as well as perforation, sepsis, and respiratory problems. Mediastinal pain can be precipitated by excessively deep or large injections. Mesenteric thrombosis has been claimed to occur as a complication and would not be unexpected; chylothorax and cerebral embolism have also been described.

Immunologic

Contact allergic reactions to lauromacrogol 400 have been reported (15). Patch testing with lauromacrogol 400 may yield irritant reactions. In a retrospective study of 8739 patients tested with a topical drug patch test series, 3186 patients were tested with 0.5% lauromacrogol 400 in water (16). There was slight irritation in 0.88%, weakly positive reactions in 0.97%, and strongly positive reactions in 0.25%. In 6202 patients tested with lauromacrogol 400 3% in petrolatum, there was slight skin irritation in 0.48%, weakly positive reactions in 1.77%, and strongly positive reactions in 0.34%. Among the 649 patients tested with both formulations, concurrence was moderate.

Long-Term Effects

Tumorigenicity

A number of case reports have suggested that sclerosant therapy could be carcinogenic (SEDA-15, 401).

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Secnidazole

General Information

Secnidazole is more active and gives more prolonged blood concentrations than metronidazole; it is effective in hepatic amebiasis. Gastrointestinal adverse effects are less common (SEDA-11, 597) (1).

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Secretin

General Information

Secretin is a peptide hormone that stimulates pancreatic secretion. It has been used to treat autism, without success (1–3).

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Synthetic porcine secretin and biologically derived porcine secretin have been compared in a double-blind, randomized, crossover study in 12 volunteers (4). The two formulations had identical effects and were safe and well tolerated. One subject reported transient mild flushing with both formulations. Otherwise, physical examination, clinical laboratory assessments, and electrocardiograms were normal.

In 10 healthy volunteers secretin suppressed peptone-stimulated gastric acid secretion and serum gastrin and inhibited acid output (5). There was a significant correlation between percentage inhibition of acid secretion and plasma secretin concentrations, which were greatly above those seen physiologically. Serum lipase and trypsin activities increased significantly. Most of the subjects lost fluid from diuresis and diarrhea, and serum sodium and total protein concentrations increased significantly.

Organs and Systems

Mineral balance

In seven healthy controls, seven patients with duodenal ulcer, seven with primary hyperparathyroidism, and one with an excluded gastric antrum, intravenous secretin 3 U/kg/hour for 90 minutes increased total protein and the protein-bound calcium fraction but did not alter the ionized calcium fraction (6).

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Selaginellaceae

See also Herbal medicines

General Information

The family of Selaginellaceae contains the single genus *Selaginella*.

Selaginella doederleinii

Selaginella doederleinii (spike moss) has been used as an alternative anticancer treatment.

Adverse effects

- A 52-year-old woman with cholangiocarcinoma developed severe bone marrow suppression after taking *S. doederleinii* daily for 2 weeks (1). She developed severe pancytopenia with skin ecchymoses and gum bleeding. A bone marrow smear and biopsy showed severe hypocellularity without malignant cell infiltration. One week after withdrawal her blood count became normal.

Reference

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Selective serotonin re-uptake inhibitors (SSRIs)

See also Individual agents

General Information

The selective serotonin re-uptake inhibitors (SSRIs) that are currently available are fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. They are widely marketed and are in many countries a major alternative to tricyclic antidepressants in the treatment of depression. The SSRIs are structurally diverse, but they are all inhibitors of serotonin uptake, with much less effect on noradrenaline. They have slight or no inhibitory effect on histaminergic, adrenergic, serotonergic, dopaminergic, and cholinergic receptors (1).

The SSRIs are eliminated mainly through hepatic metabolism. Their half-lives are about 1 day for fluvoxamine, paroxetine, and sertraline (2–5), 1.5 days for citalopram (6), and 2–3 days for fluoxetine (7). Norfluoxetine, the main metabolite of fluoxetine, is a potent and selective serotonin re-uptake inhibitor, and since this metabolite also has a very long half-life (7–15 days) it contributes significantly to the clinical effect. Norsertraline, the desmethylated metabolite of sertraline, is also an inhibitor of serotonin re-uptake, but

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with much lower potency than sertraline; although its half-life is about 2.5 times longer than that of sertraline, it is not considered to contribute to the clinical effect (3). The main metabolite of citalopram, desmethylcitalopram, is pharmacologically active but has much lower potency than the parent compound (1). The metabolites of fluvoxamine and paroxetine are inactive with respect to monoamine uptake (2). Escitalopram oxalate is the *S*-enantiomer of citalopram (8). The therapeutic activity of citalopram resides in the *S*-isomer and escitalopram binds with high affinity to the human serotonin transporter; *R*-citalopram is about 30-fold less potent. The half-life of escitalopram is 27–32 hours. Escitalopram and citalopram have negligible effects on CYP isozymes.

The major advantages of SSRIs over the tricyclic antidepressants are their less pronounced anticholinergic adverse effects and lack of severe cardiotoxicity. However, some studies have shown some degree of nervousness or agitation, sleep disturbances, gastrointestinal symptoms, and perhaps sexual adverse effects more commonly in patients treated with SSRIs than in those treated with tricyclic antidepressants. SSRIs may also be associated with an increased risk of suicide, particularly in children under 16 (9).

There seems to be little difference between SSRIs with respect to frequency and severity of adverse effects. The most common adverse effects are gastrointestinal disturbances (nausea, diarrhea/loose stools, constipation; incidence 6–37%), nervous system effects (insomnia, somnolence, tremor, dizziness and headache; 11–26%), and effects on the autonomic nervous system (dryness of the mouth and sweating; 9–30%) (2,10). Weight gain or weight loss have been documented relatively infrequently (2). A high frequency of sexual disturbances has been reported. SSRIs may selectively inhibit hepatic enzymes, causing pharmacokinetic interactions with other drugs that are metabolized by these enzymes; a pharmacodynamic interaction can also occur when SSRIs are given in combination with other serotonergic drugs, which may give rise to serotonergic hyperstimulation, the "serotonin syndrome." The SSRIs are safer than the tricyclic antidepressants in overdose.

A meta-analysis of 20 short-term studies of five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) has been published (11). There were no overall differences in efficacy, but fluoxetine had a slower onset of action. Analysis of tolerability showed the expected adverse effects profile, the most common adverse event being nausea, followed by headache, dizziness, and tremor. The rate of withdrawal from treatment because of adverse effects was significantly greater with fluvoxamine (RR = 1.9; CI = 1.2, 3.0). Data available from the UK Committee on Safety of Medicines suggested that withdrawal reactions were most common with paroxetine and least common with fluoxetine (presumably because of the long half-life of its active metabolite norfluoxetine). There were more gastrointestinal reactions to fluvoxamine and paroxetine. This pattern was reflected in prescription-event monitoring data. Citalopram and sertraline were least likely to cause drug interactions, but citalopram was implicated more often in fatal overdoses.

Organs and Systems

Nervous system

Movement disorders

Extrapyramidal symptoms (including akathisia, dystonia, dyskinesia, tardive dyskinesia, parkinsonism, and bruxism) have been reported in association with SSRIs, especially in the presence of predisposing factors (SEDA-14, 14) (12). Current data suggest that SSRIs should be used with caution in patients with parkinsonism (see the monograph on fluoxetine). Concomitant treatment with neuroleptic drugs and high concentrations of SSRIs seems to predispose to extrapyramidal symptoms. Elderly patients and women are also at increased risk.

It is believed that SSRIs produce movement disorders by facilitating inhibitory serotonin interactions with dopamine pathways. While all SSRIs are potent inhibitors of serotonin re-uptake, they have other pharmacological actions that might contribute to their clinical profile. Sertraline has an appreciable affinity for the dopamine re-uptake site, and for this reason might be presumed less likely to cause movement disorders than other SSRIs. However, there is little clinical evidence to support this suggestion and a case of sertraline-induced parkinsonism has been reported (13).

SSRI-induced movement disorders have been comprehensively reviewed (14). The use of SSRIs was associated with a range of movement disorders, the most frequent of which was akathisia. However, clinician-based reports of adverse events solicited from SSRI manufacturers suggested that parkinsonism might occur with an equal frequency but with a later onset during treatment. As suggested before (SEDA-22, 12), concomitant treatment with antipsychotic drugs and lithium, as well as pre-existing brain damage, predisposes to the development of movement disorders with SSRIs. Case reports have suggested that akathisia can be associated with suicidal impulses.

Spontaneous reports received by the Netherlands Pharmacovigilance Foundation between 1985 and 1999 have been analysed in a case-control study (15). Relative to other antidepressants, SSRIs were about twice as likely to be implicated in spontaneous reports of extrapyramidal reactions (OR = 2.2; 95% CI = 1.2, 3.9). The risk was greater in patients who were also taking neuroleptic drugs. This result suggests that SSRIs have a modestly increased risk of producing extrapyramidal reactions compared with other antidepressants. However, increased reporting can be influenced by increased awareness. In addition, no account was apparently taken in this study of relative prescription rates of different antidepressants.

Withdrawal of SSRIs usually results in remission of symptoms of extrapyramidal movement disorders. However, occasionally, SSRIs can unmask a vulnerability to Parkinson's disease, and can also worsen established Parkinson's disease (SEDA-22, 23) (see monographs on citalopram and sertraline) (16).

Serotonin syndrome

The serotonin syndrome is a well-established complication of SSRI treatment. It is usually associated with high

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doses of SSRIs or the use of SSRIs in combination with other serotonin-potentiating agents, such as monoamine oxidase inhibitors (SEDA-22, 24).

- A 45-year-old man had definite symptoms of serotonin toxicity (hypomania, myoclonus, sweating, and shivering), first when taking a low therapeutic dose of citalopram (20 mg/day) and then with low-dose sertraline (25 mg/day); he was also taking zolpidem (17).

The authors speculated that the combination of zolpidem with an SSRI might have predisposed to the serotonin syndrome. It is also possible that some people (for example poor metabolizers) are idiosyncratically vulnerable to serotonin toxicity at low doses of SSRIs.

Sleep

SSRIs can cause insomnia and daytime somnolence; however, the symptoms seem to reflect a sleep–wake cycle disorder. It is conceivable that disruptions in the normal pattern of melatonin secretion, particularly a delay in the normal early morning fall in plasma concentrations could be involved in the pathophysiology of these symptoms. The fact that fluvoxamine is the SSRI that is most likely to cause sleep disorders supports a role of melatonin, which is increased by fluvoxamine but not by other SSRIs (18).

Sensory systems

Tricyclic antidepressants can precipitate acute glaucoma through their anticholinergic effects. There are also reports that SSRIs can cause acute glaucoma, presumably by pupillary dilatation (see the monograph on paroxetine and fluoxetine).

Psychological, psychiatric

Like other antidepressants, SSRIs are occasionally associated with manic episodes, even in patients with no history of bipolar disorder. Some argue that the affected patients may have had an underlying predisposition to bipolar illness.

In a retrospective chart review of 167 patients with a variety of anxiety disorders, excluding patients with evidence of current or previous mood disorder, manic episodes were recorded in five patients, a rate of 3% (19). While this might suggest a clear effect of SSRIs to induce mania, two of the patients were taking clomipramine, a tricyclic antidepressant, albeit a potent serotonin reuptake inhibitor. In addition, all the affected patients had additional diagnoses of histrionic or borderline personality disorder, known to be associated with mood instability. It is still therefore plausible that SSRIs cause mania only in patients with an underlying predisposition, although this may be more subtle than a personal or family history of bipolar illness.

Visual hallucinations are rare during antidepressant drug treatment, except after overdosage.

- A 38-year-old man with a history of chronic depression developed on waking visual hallucinations of different geometric shapes after treatment with both sertraline and fluoxetine. Eventually he responded to treatment with nefazodone, which did not cause hallucinations (20).

Many drugs that cause visual hallucinations (for example lysergic acid diethylamide) have agonist activity at 5-HT_2 receptors, and it is conceivable that in these patients both sertraline and fluoxetine caused sufficient activation of post-synaptic 5-HT_2 receptors to produce this visual disturbance. Although nefazodone can increase 5-HT neurotransmission, it is also a 5-HT_2-receptor antagonist, so presumably does not activate 5-HT_2 receptors.

Endocrine

Serotonin pathways are involved in the regulation of prolactin secretion. Amenorrhea, galactorrhea, and hyperprolactinemia have been reported in patients taking SSRIs (see the monographs on fluoxetine, fluvoxamine, paroxetine, and sertraline).

Electrolyte balance

SSRIs can reportedly cause hyponatremia (SEDA-18, 20) (SEDA-26, 13). In a case-control study of hyponatremia in 39 071 psychiatric inpatients and outpatients, the incidence of antidepressant-induced hyponatremia was 2.1% (21). SSRI users had a three times higher risk of developing hyponatremia relative to users of other antidepressant drugs (OR = 3.1; 95% CI = 1.3, 8.6). Additional risk factors included older age and concomitant treatment with diuretics.

SSRIs can cause hyponatremia in elderly patients (SEDA-18, 20, 21).

- A 45-year-old woman developed hyponatremia complicated by rhabdomyolysis while taking citalopram and the antipsychotic drug chlorprothixene for depressive psychosis (22). The hyponatremia became apparent 2 weeks after the dose of citalopram was increased to 40 mg/day, when she complained of weakness and lethargy.

SSRI-induced hyponatremia is unusual in non-geriatric populations, but the chlorprothixene may have played a role in this case.

There have been other reports of hyponatremia with SSRIs (23,24). Hyponatremia is probably more common with SSRIs than with tricyclic antidepressants and predominantly but not exclusively affects older patients. Most reports involve fluoxetine, but this might represent greater patient exposure. All SSRIs and venlafaxine can produce this adverse effect (SEDA-23, 21) (SEDA-25, 14). According to published reports, the median time to the onset of hyponatremia is 13 days (range 3–120) and the presentation is of inappropriate secretion of antidiuretic hormone (23). Symptoms, such as lethargy and confusion, can be non-specific, so awareness of the possibility of SSRI-induced hyponatremia, particularly in elderly people, is needed.

Fluid balance

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a possible adverse effect of the SSRIs (SEDA-14, 14) (SEDA-18, 20) (SEDA 21, 11) (25). The mechanism is not known. Several of the affected

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patients have been elderly, and old people may be at greater risk.

Hematologic

SSRIs have in rare cases been reported to produce bruising, bleeding, prolonged bleeding time, increased prothrombin time, and other hematological disturbances (SEDA-24, 15) (see the monographs on fluoxetine, fluvoxamine, paroxetine, and sertraline). The suggested mechanism of these adverse effects is reduced granular storage of serotonin in platelets, leading to disturbances of platelet function, especially in predisposed patients with mild underlying platelet disorders (26,27). An alternative mechanism is increased capillary fragility. Some patients appear to have a pre-existing susceptibility, for example, by virtue of treatment with other medications that might predispose to bleeding.

Five children, aged 8–15 years, developed bruising or epistaxis 1–12 weeks after starting SSRI treatment (28). In all cases the bleeding problem resolved when the SSRI was withdrawn or the dose lowered. In a review of 30 cases of SSRI-induced bleeding disorders the most common events were bruising, petechiae, purpura, and epistaxis, though gastrointestinal hemorrhage was also reported (29). The mean age of the affected patients was 42 years and the female:male ratio was 3:4. Symptoms were sometimes associated with prolonged bleeding time or platelet aggregation disorders, but often these indices were normal.

Gastrointestinal

Gastrointestinal adverse effects are one of the major disadvantages of SSRIs. The most common is nausea, and the incidence is said to be 20% or more for paroxetine (30,31), sertraline (32), fluvoxamine (5), fluoxetine (33), and citalopram (10,34). Although nausea can lead to drug withdrawal, it usually disappears after a few weeks. Other gastrointestinal symptoms that occur commonly with fluoxetine and sertraline are loose stools and diarrhea (32,33,35), while constipation has been more often reported with fluvoxamine (5) and paroxetine (30,31).

In a case-control study, current exposure to SSRIs was associated with an increased risk of upper gastrointestinal bleeding (RR = 3.0; CI = 2.1, 4.4) (36). The risk was substantially greater in subjects taking both SSRIs and non-steroidal anti-inflammatory drugs (NSAIDs) (RR = 16; CI = 6.6, 37). However, there was also an increased risk of bleeding with trazodone (RR = 8.6; CI = 2.1, 35), which does not block the uptake of 5-HT in therapeutic doses. Thus, the association between certain kinds of antidepressant drugs and upper gastrointestinal bleeding appears to be real.

Liver

SSRIs are rarely hepatotoxic and have only occasionally been reported (see the monographs on fluoxetine, paroxetine, and sertraline).

Skin

Skin reactions to SSRIs have been reported (SEDA-17, 20) (SEDA-18, 20), including Stevens–Johnson syndrome (37), and rash due to fluoxetine occurs in a few percent of patients (38) (see also the monographs on fluoxetine, fluvoxamine, and sertraline).

Sexual function

Impaired sexual function

The adverse sexual effects of SSRIs have been reviewed (39). The use of SSRIs is most often associated with delayed ejaculation and absent or delayed orgasm, but reduced desire and arousal have also been reported. Estimates of the prevalence of sexual dysfunction with SSRIs vary from a small percentage to over 80%. Prospective studies that enquire specifically about sexual function have reported the highest figures. Similar sexual disturbances are seen in patients taking SSRIs for the treatment of anxiety disorders (40), showing that SSRI-induced sexual dysfunction is not limited to patients with depression. It is not clear whether the relative incidence of sexual dysfunction differs between the SSRIs, but it is possible that paroxetine carries the highest risk (39).

The ability of SSRIs to cause delayed ejaculation has been used in controlled trials of men with premature ejaculation (41,42). Of the SSRIs, paroxetine and sertraline produced the most benefit in terms of increase in time to ejaculation, but fluvoxamine did not differ from placebo. Clomipramine was more effective than the SSRIs but caused most adverse effects. From a practical point of view many patients might prefer to take medication for sexual dysfunction when needed rather than on a regular daily basis, and it would be of interest to study the beneficial effects of SSRIs on premature ejaculation when used in this way.

Laboratory studies have shown that fluvoxamine differs from paroxetine, sertraline, and fluoxetine in not delaying the time to ejaculation. The effect of citalopram to delay ejaculation is also relatively modest (43). There are, however, many other ways in which SSRIs can interfere with sexual function, for example by causing loss of sexual interest and erectile difficulties. In an open, prospective study of 1000 Spanish patients taking a variety of antidepressants, there was an overall incidence of sexual dysfunction of 59% (44). The highest rates, 60–70%, were found with SSRIs (including fluvoxamine) and venlafaxine. The lowest rates were found with mirtazapine (24%), nefazodone (8%), and moclobemide (4%). Spontaneous resolution of this adverse effect was uncommon—80% of subjects had no improvement in sexual function over 6 months of treatment. This study suggests very high rates of sexual dysfunction in patients taking SSRIs and venlafaxine. However, in investigations of this nature, it can be difficult to tease out the effect of the drug from that of the underlying disorder. Nevertheless, while depressive symptoms should improve in most patients over 6 months of treatment, the sexual dysfunction in these subjects tended not to remit, suggesting that the antidepressant was the main culprit.

Increased sexual function

Occasionally, SSRIs are associated with increased sexual desire and behavior.

- A 27-year-old married woman with a borderline personality disorder was admitted to hospital with

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depression and suicidal ideation (45). Over 3 weeks she was given fluvoxamine in doses up to 150 mg/day, but because of lack of response the dosage was increased to 200 mg/day; 3 days later she reported that her sex drive was greater than it had ever been before and that she felt she could not control it. There was no evidence of mania. Within a week of withdrawal of fluvoxamine her sexual desire had returned to its previous level.

Patients with borderline personality disorder may behave in a sexually disinhibited manner and have mood swings. In this patient, however, it did not appear as though the hypersexuality was part of a manic syndrome, and she was clear that the sexual feelings were unusually great for her. Support for a role of the SSRI in this adverse effect comes from a series of five patients (four taking citalopram and one paroxetine) who had an unusual increase in sexual interest, with preoccupation with sexual thoughts, promiscuity, and excessive interest in pornography (46). In some of the cases symptoms such as diminished need for sleep suggested the possibility of a manic syndrome.

These reports suggest that occasionally SSRIs can be associated with increased sexual desire and behavior. This might be associated with mood instability, for example in a manic or mixed affective state, but in some people personality factors are likely to be important.

Treatment of sexual dysfunction due to SSRIs

Various treatments have been advocated to ameliorate sexual dysfunction in SSRI-treated patients, including 5-HT_2-receptor antagonists (cyproheptadine, mianserin, nefazodone) and 5-HT_3-receptor antagonists such as granisetron (39). One of the most popular remedies is the use of dopaminergic agents, such as amfebutamone.

In a prospective study, 47 patients who complained of SSRI-induced sexual dysfunction took amfebutamone (bupropion) 75–150 mg 1–2 hours before sexual activity (47). If this was unsuccessful they were titrated to a dosage of 75 mg tds on a regular basis. Amfebutamone improved sexual function in 31 patients (66%). Anxiety and tremor were the most frequently reported adverse events, and seven patients discontinued for this reason. However, it should be noted that more serious adverse events (panic attacks, delirium, and seizures) have been reported when amfebutamone (bupropion) and SSRIs are combined (39).

In a placebo-controlled, parallel-group study of buspirone and amantadine in 57 patients with fluoxetine-induced sexual dysfunction, there was an overall improvement in all three treatment groups and no significant differences between them (48). These data suggest that anecdotal reports of treatment benefit in SSRI-induced sexual dysfunction should be regarded with caution.

Reproductive system

Vaginal bleeding and menorrhagia have been rarely reported with SSRI treatment and the mechanism is uncertain. SSRIs have been associated with bleeding diatheses, which might explain these observations (SEDA-24, 15) (SEDA-25, 14). Another possibility is an action of serotonin pathways on the neural regulation of gonadotropin release. More cases have been reported.

- A 67-year-old woman developed vaginal bleeding after taking sertraline 25 mg/day for 3 days (49). The sertraline was withdrawn and the bleeding stopped 48 hours later.
- A 41-year-old woman developed vaginal bleeding after taking venlafaxine 75 mg/day, a dose at which selective serotonin blockade is the predominant pharmacological action (50). The vaginal bleeding stopped 24 hours after venlafaxine withdrawal and occurred again on rechallenge.

Immunologic

Infection risk: three cases of *Herpes simplex* reactivation associated with fluoxetine have been described (SEDA-16, 10).

Death

Severe adverse reactions to SSRIs that were reported to Health Canada's database in 1986–1996 have been reviewed (51). There were 295 severe adverse reactions with 87 deaths. Of the fatal cases, 65 were due to intentional overdose. The other 22 deaths were due chiefly to other forms of suicide or were accidental or indeterminate (12 cases). Of the rest there were three cases of neuroleptic malignant syndrome and individual cases of cardiac or respiratory disease in which the role of SSRIs was less clear.

This report shows that the major causes of death in patients taking SSRIs are related to the risks of depression itself, particularly self-harm. SSRIs themselves appear to be relatively safe. It is possible, however, that the cases of neuroleptic malignant syndrome could have been misdiagnosed forms of the serotonin syndrome, which, like the neuroleptic malignant syndrome, can present with hyperthermia and changes in consciousness and is usually produced by pharmacodynamic interactions between SSRIs and other serotonin-potentiating compounds (SEDA-25, 24). In general, the risks of SSRIs are increased by co-prescription, and fatal overdose with SSRIs usually involves a mixture of psychotropic drugs and/or alcohol.

Sudden death has been reported in three elderly women with pulmonary disease and atrial fibrillation who had recently started taking fluoxetine. The authors recommended caution in such patients, although no causal link with fluoxetine was established (SEDA-17, 19).

Long-Term Effects

Drug withdrawal

Reports of withdrawal reactions after abrupt withdrawal of SSRIs continue to accumulate, and several reviews have summarized case reports of withdrawal symptoms (52,53).

SSRIs with shorter half-lives, such as fluvoxamine and paroxetine (qv), have a higher incidence of withdrawal symptoms than long-acting ones, but withdrawal effects have been reported, albeit rarely, after withdrawal of

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fluoxetine (qv) (SEDA-20, 8) (54) and citalopram (55). Patients taking high doses, long-term treatment, or both are at increased risk of developing withdrawal symptoms (54,56).

In a randomized, placebo-controlled trial, sudden withdrawal of paroxetine produced significant withdrawal symptoms by as early as the second day, while patients taking fluoxetine remained asymptomatic for the five-day withdrawal period (57). Patients taking sertraline had an intermediate level of abstinence symptoms. Both paroxetine- and sertraline-treated patients reported impaired functioning during the withdrawal period, while those taking fluoxetine did not. These findings are consistent with earlier reports that suggested that acute withdrawal symptoms after fluoxetine withdrawal are unusual, presumably because of the long half-life of its active metabolite, norfluoxetine.

Second-Generation Effects

Teratogenicity

Tricyclic antidepressants appear to be generally free of teratogenic effects, but the status of newer antidepressants is unclear. Since 1993 four controlled prospective studies of antidepressant exposure during pregnancy have been published, involving about 400 women, most of whom took fluoxetine at various stages during pregnancy (58). There was no evidence that fluoxetine or other SSRIs caused an increase in intrauterine death, significant birth defects, or growth impairment. Follow-up behavioral studies of infants exposed to SSRIs during pregnancy also showed no difference from controls.

Fetotoxicity

An increasing number of women are being exposed to SSRIs during pregnancy. It is therefore important to establish as carefully as possible whether SSRIs have teratogenic effects (SEDA-24, 15). In a retrospective study of the impact on birth outcome of the timing of fluoxetine exposure in 64 pregnant women there were no major differences between infants exposed to fluoxetine early in pregnancy (the first or second trimesters only) and those exposed to fluoxetine throughout the third trimester and delivery (59). However, the infants in the late-exposed group were about twice as likely to be admitted to a special-care nursery. No specific pattern of neonatal difficulties could be found to account for this difference, and it is possible that the excess of neonatal problems in the late-onset treatment group was due to worse depression in the women who took antidepressants at around the time of delivery.

Withdrawal effects of SSRI treatment may be apparent in neonates shortly after delivery. These include jitteriness, hypoglycemia, hypothermia, and respiratory distress (60).

Lactation

The benefit : harm balance of breast-feeding during antidepressant treatment is difficult to compute and must be done on an individual basis. In general, breast-feeding with SSRIs is regarded as safe, as the amount of drug ingested by the infant is very low. However, adverse effects in the child are reported occasionally (SEDA-25, 15) and it is difficult to exclude completely the possibility of long-term effects on brain development in the infant. Clearly, the lower the concentration of SSRI in the infant the less likely are problems of acute and longer-term toxicity. In two cases treatment of breast-feeding mothers with fluvoxamine (300 mg/day) was associated with undetectable concentrations of fluvoxamine (below 2.5 ng/ml) in the plasma of both infants (61). These results are encouraging, but further data will be needed before it can be concluded that fluvoxamine has an advantage over other SSRIs in this respect. Because fluoxetine has a long half-life it may be advisable not to use it in breast-feeding women.

Drug Administration

Drug overdose

The SSRIs are in general considered to be less toxic in overdose than tricyclic antidepressants. From a review of cases of overdose with SSRI during 10 years it was concluded that SSRIs are rarely fatal in overdose when taken alone (62). In moderate overdoses of up to 30 times the daily dose, symptoms were either minor or absent. In higher doses, typical symptoms included drowsiness, tremor, nausea, and vomiting. At extremely high doses (over 75 times the usual daily dose), there were more serious toxic effects, including seizures, electrocardiographic changes, and disturbances of consciousness. When an SSRI overdose was taken in combination with alcohol or other drugs, toxicity increased, and almost all deaths involving SSRIs were in combination with other drugs.

Drug–Drug Interactions

General

For the SSRIs there are two types of interaction of major concern: SSRIs can selectively inhibit hepatic drug metabolizing enzymes, giving rise to pharmacokinetic interactions (SEDA-22, 13), and pharmacodynamic interactions can occur when SSRIs are given in combination with other serotonergic drugs, which can cause serotonergic hyperstimulation: the "serotonin syndrome." Fluoxetine gives rise to special concern, since reactions can occur weeks after withdrawal, owing to the long half-life of both parent compound and metabolite. Of the various SSRIs, citalopram seems the least likely to produce this effect. Paroxetine and fluoxetine can cause interactions with tricyclic antidepressants, neuroleptic drugs, and some antidysrhythmic drugs that are metabolized by CYP2D6.

In 31 healthy men and women (mean age 28 years) the ability of four SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) to inhibit CYP2D6 activity was assessed in vivo, as judged by the dextromethorphan test (63). All were extensive metabolizers of dextromethorphan. After 8 days treatment at therapeutic doses, four of eight paroxetine-treated and five of eight fluoxetine-treated subjects had become poor metabolizers, presumably because of the inhibitory effect of the two SSRIs

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on CYP2D6 activity. In contrast, none of the eight fluvoxamine-treated or seven sertraline-treated subjects showed this effect. This in vivo study has confirmed the potent inhibitory effect of fluoxetine and paroxetine on CYP2D6 and the relative sparing by fluvoxamine and sertraline. However, fluvoxamine is a potent inhibitor of CYP1A2 and CYP3A3/4 (SEDA-22, 13). In addition, at higher doses (over 100 mg/day at steady state) sertraline can inhibit CYP2D6.

The drugs that can cause a serotonin syndrome when they are combined with SSRIs include monoamine oxidase inhibitors (including reversible inhibitors of monoamine oxidase types A and B), dextromethorphan, tryptophan, lithium, pentazocine, and carbamazepine (SEDA-17, 23) (SEDA-18, 22) (64).

Buspirone

The serotonin syndrome can occur with therapeutic doses of SSRIs (see above), but it occurs most commonly when SSRIs are co-administered with other drugs that also potentiate serotonin function. Recent case reports have suggested that there is a risk of the serotonin syndrome when SSRIs are combined with buspirone (65).

Dextromethorphan

SSRIs inhibit hepatic CYP isozymes and can thereby increase the activity of co-administered drugs that are metabolized by this route (SEDA-22, 13) (SEDA-24, 15). In healthy volunteers randomly allocated to fluoxetine (20 mg/day), sertraline (100 mg/day), or paroxetine (20 mg/day) the activity of CYP2D6 was measured by dextromethorphan testing once steady state had been achieved and the medication was withdrawn (66). Extrapolated calculations showed that the mean time for full CYP2D6 recovery after fluoxetine (63 days) was significantly longer than that for sertraline (25 days) or paroxetine (20 days). Accordingly, even after SSRIs have been withdrawn, the potential for drug interactions persists for substantial periods of time, particularly in the case of fluoxetine.

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors, including reversible inhibitors of monoamine oxidase types A and B, can cause a serotonin syndrome when they are combined with SSRIs (SEDA-17, 23) (SEDA-18, 22) (64).

Nefazodone

The serotonin syndrome can occur with therapeutic doses of SSRIs (see above), but it occurs most commonly when SSRIs are co-administered with other drugs that also potentiate serotonin function. Recent case reports have suggested that there is a risk of the serotonin syndrome when SSRIs are combined with nefazodone (67).

Neuroleptic drugs

Interactions of SSRIs with neuroleptic drugs have been reported (68–70).

Sibutramine

The serotonin syndrome has been attributed to a combination of citalopram and sibutramine.

- A 43-year-old woman who had taken citalopram 40 mg/day for 2 years was given sibutramine for obesity and a few hours after the first dose of 10 mg had irritability, racing thoughts, pressure of speech, agitation, shivering, and sweating (71). These symptoms persisted for 3 days, during which time she continued to take sibutramine. The day after sibutramine was withdrawn the symptoms resolved.

The serotonin syndrome can present with hypomanic features, and the clinical picture and rapid onset in this case suggested that the addition of sibutramine to citalopram provoked serotonin toxicity. Sibutramine blocks the re-uptake of serotonin, dopamine, and noradrenaline. Whether the serotonin toxicity seen here resulted purely from the combined effects of both citalopram and sibutramine in blocking serotonin re-uptake is unclear. It is possible, for example, that potentiation of dopamine and noradrenaline activity by sibutramine might also have been involved.

Tricyclic antidepressants

Interactions of SSRIs with tricyclic antidepressants have been reported. For example, plasma concentrations of tricyclic antidepressants rise after the addition of fluoxetine (72,73), fluvoxamine (74,75), and sertraline (76).

Triptans

Drugs used in the treatment of acute migraine, such as sumatriptan and rizatriptan, are 5-$HT_{1B/1D}$-receptor agonists and could theoretically interact pharmacodynamically with SSRIs to cause serotonin toxicity. Triptans are metabolized mainly by monoamine oxidase, which makes pharmacokinetic interactions with SSRIs unlikely. Although case series have suggested that sumatriptan can be safely combined with SSRIs (SEDA-22, 14), there are occasional reports of toxicity.

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Selegiline

See also Monoamine oxidase inhibitors

General Information

Selegiline is a relatively selective and irreversible inhibitor of monoamine oxidase type B, which has been used in the treatment of Parkinson's disease. It was originally suggested that selegiline may be neuroprotective. However, in a prospective double-blind study no such action was seen (1). On the other hand, selegiline does delay the start of disability, determined by the need for levodopa and progression of parkinsonian signs and symptoms (2).

However, the Parkinson's Disease Research Group in the UK reported that after a mean follow-up period of 5.6 years, mortality was increased in randomized patients with Parkinson's disease who took levodopa together with selegiline compared with patients who took levodopa alone (2). This unexpected conclusion was interpreted as a result of methodological failures. In a meta-analysis of five long-term, prospective, randomized trials of selegiline, the treated group did not have an increase in mortality (3).

Organs and Systems

Cardiovascular

Unwanted effects of selegiline on cardiovascular regulation have been investigated as a potential cause for the

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unexpected mortality in the UK Parkinson's Disease Research Group trial (4). Head-up tilt caused selective and often severe orthostatic hypotension in nine of 16 patients taking selegiline and levodopa, but had no effect on nine patients taking levodopa alone. Two patients taking selegiline lost consciousness with unrecordable blood pressures and another four had severe symptomatic hypotension. The normal protective rises in heart rate and plasma noradrenaline were impaired. The abnormal response to head up tilt was reversed by withdrawal of selegiline. The authors proposed that these findings might be due to either non-selective inhibition of monoamine oxidase or effects of amfetamine and metamfetamine.

Nervous system

Selegiline is metabolized to amfetamine and metamfetamine, and can therefore cause insomnia (SEDA-17, 167).

Gastrointestinal

Selegiline has rarely re-activated pre-existing peptic ulcer disease (5).

Sexual function

Hypersexuality has been attributed to selegiline (6).

- A 72-year-old man who had taken levodopa for over 20 years started to take selegiline 10 mg/day. He developed a strong impulse for cross-dressing, which he had never experienced before. The behavior ceased when the selegiline was withdrawn.

It is not clear whether this effect was due to an interaction of levodopa with selegiline or due to a direct effect of selegiline itself.

Drug–Drug Interactions

Dopamine

An interaction of selegiline with dopamine has been described (7).

- A 75-year-old critically ill man taking selegiline 10 mg/day was given intravenous dopamine 3.5 micrograms/kg/minute. Within 50 minutes his systolic pressure had risen from 105 to 228 mmHg. Within 30 minutes of stopping the infusion his systolic blood pressure fell to 121 mmHg. Rather surprisingly, two rechallenges were attempted on that day and the next, at doses of 1.03 and 0.9 micrograms/kg/minute. Severe hypertension occurred on both occasions, with return to normal pressures very soon after the dopamine was discontinued.

As the authors pointed out, the selectivity of selegiline for monoamine oxidase type B may be less than was once thought, and co-administration of the drug with dopamine may be risky.

Fluoxetine and paroxetine

When given alongside fluoxetine selegiline can produce a sudden increase in blood pressure. The combined use of selective serotonin re-uptake inhibitors, such as fluoxetine or paroxetine, with selegiline has reportedly caused muscle rigidity, autonomic instability, and agitation or delirium. However, these possibilities are rare, and the serotonin syndrome is even rarer.

Levodopa

The Parkinson's Disease Research Group in the UK have reviewed an earlier report that there was excess mortality in patients with early disease treated with a combination of levodopa and selegiline (8). They have confirmed that there was about a 35% greater mortality in those on combined treatment compared with patients treated with levodopa alone. The excess deaths were all attributed to Parkinson's disease. The authors did not present any explanation for these findings, but they very reasonably suggested that the combination is inappropriate in early disease and should be used only with caution if at all in the later stages of the disease.

Tricyclic antidepressants

The combined use of tricyclic antidepressants and selegiline has been associated with hyperpyrexia, tremors, agitation, restlessness, reduced level of consciousness, and in rare instances death (9).

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Selenium

General Information

Selenium is a non-metallic element (symbol Se; atomic no. 34) that was discovered by Berzelius in 1817.

The major functions of selenium can be attributed to its antioxidative properties and its role in the regulation of thyroid hormone metabolism. Selenium is important as a nutritional factor, and the US Food and Nutrition Board's Committee on Dietary Allowances has, perhaps somewhat arbitrarily, proposed a recommended daily intake of 50–200 micrograms/day.

Selenium has functions in many selenoproteins and also in relation to the immune response. There is an association between low plasma selenium concentrations and oral cancer (1). Selenium compounds inhibit tumorigenesis in a variety of animal models, and added selenium in human diets might reduce the risk of cancer (SEDA-21, 240).

Uses

Selenium-based drugs show some promise in several diseases, as orally active antihypertensive, anticancer, antiviral, antimicrobial, and immunosuppressive drugs, and organoselenium compounds reduce oxidative tissue damage and edema (2).

Selenium sulfide is used as an antiseborrheic agent and as a shampoo in the treatment of *Tinea versicolor*. Selenite is also found in mineral supplements and is used in parenteral nutrition. However, selenium has gained undeserved popularity as a constituent of health foods and alternative tonics, perhaps because selenium deficiency has been implicated in the pathogenesis of some forms of malnutrition in children. However, even in children with selenium deficiency the benefit to harm balance has not been established. Indeed, in protein deficiency it seems to be particularly toxic. Nor is there any serious basis for its reputation as a remedy for cystic fibrosis, to prevent aging, or as a sexual stimulant.

General adverse effects

As is evident from veterinary practice and animal studies, selenium has both acute and chronic toxic effects on many organs. Endemic selenium poisoning of populations in an area of China produced a picture resembling arsenic poisoning (3). It is not possible to say what effects have gone unrecorded, or perhaps what effects irregular use in alternative medicines might have at various ages. In countries where selenium is in vogue, physicians should be aware of its potential risks and should enquire about the possible use of selenium products in the home, either in adults or children.

An FDA overview has described 12 cases of selenium intoxication in the USA due to ingestion of "superpotent" selenium tablets, the estimated total ingested doses ranging from 27 to 2310 mg (4). Nausea, vomiting, nail changes, fatigue, and irritability were the most common symptoms; some subjects had watery diarrhea, abdominal cramps, dry hair, paresthesia, and a garlic-like odor on the breath. Many of these symptoms resembled the pattern of endemic poisoning seen in China (3). In one case, selenium poisoning resulted from a gross underestimation of the selenium content of a nutritional supplement.

Various aspects of selenium have been reviewed, including its toxicology and selenium deficiency (5–7) and its protective effects against cancer (8).

Organs and Systems

Neuromuscular function

The incidence of amyotrophic lateral sclerosis has been studied in some 5000 residents in an area of Italy in which they had accidentally been exposed to drinking water with a high selenium content for 9 years (9). The findings pointed to a possible association between overexposure to environmental selenium and amyotrophic lateral sclerosis.

Endocrine

One report suggests that therapeutic use of selenium in the form of selenite could precipitate hypothyroidism, but the circumstances were complex and iodine deficiency seems to have played a major role (10).

Urinary tract

Selenium 400 micrograms/day for 2 weeks in a boy of 17 and 25 micrograms/day for 2 weeks in an 11-month-old infant were thought to have caused renal damage, manifested primarily by sodium loss (11). However, there is little evidence that selenium is nephrotoxic, and the patients in question had cystic fibrosis, which could have caused sodium depletion.

Skin

Selenium sulfide can cause local irritation (SED-12, 685). Photosensitive dermatitis (pityriasis versicolor) occurred in an adult man after a second application of 2.5% selenium sulfide (12).

Reproductive system

Suppression of lactation has been ascribed to the use of selenium sulfide shampoo, but the causal relation was not proven (SEDA-16, 158).

Immunologic

Selenium can cause allergic reactions (12–14).

Drug Administration

Drug overdose

Fatal suicidal selenium poisoning has been described (15), although the patient had ingested not only selenious acid 90 mg/kg but also cupric sulfate 60 mg/kg. At autopsy, pulmonary edema, congestion of the kidneys, and hemorrhagic and erosive gastric mucosa were found.

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Drug–Drug Interactions

Cisplatin

Selenium appears to accentuate the nephrotoxic effects of cisplatin and its vascular toxicity (SEDA-21, 241).

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Sertindole

See also Neuroleptic drugs

General Information

Sertindole is an antipsychotic drug that was approved in several countries in 1997, but was suspended in January 2000, following concerns about reports of cardiac dysrhythmias and sudden death (SEDA-22, 71) (SEDA-25, 71) (1). To gather further information, data collected for prescription-event-monitoring (PEM) studies have been analysed (2). Patients taking sertindole ($n = 462$; 5482 months of observation) were compared with patients taking risperidone or olanzapine ($n = 16\,542$; 139 987 months of observation). There were seven deaths in the sertindole group and 415 in the other, and the death rates were not significantly different, although the confidence intervals were wide because of the relatively small number of patients in the sertindole group. There were six cases of prolonged QT_c interval in the patients taking sertindole and one in the controls. The authors concluded that the sertindole group was too small to rule out an association between sertindole and cardiovascular deaths.

On 28 June 2001 an ad hoc expert committee was convened to review the available clinical and preclinical data related to the cardiovascular activity of sertindole and to consider whether such data supported the then current marketing authorization status of sertindole (3). Based on a re-evaluation of all the available data, including additional data submitted by the Marketing Authorization Holder, it was concluded that the re-introduction of sertindole could be supported by further clinical safety data, strong safeguards (including extensive contraindications and warnings for patients at risk of cardiac dysrhythmias), a reduction in the recommended maximum dose from 24 mg to 20 mg in all but exceptional cases, and extensive electrocardiographic monitoring before and during treatment. The Committee for Proprietary Medicinal Products (CPMP) of The European Agency for the Evaluation of Medicinal Products later recommended lifting the ban on sertindole-containing medicinal products on the basis of additional data provided by the marketing authorization holders (see monthly report from October, 2001: www. emea.eu.int).

Organs and Systems

Cardiovascular

Sertindole was associated with 27 deaths (16 cardiac) in 2194 patients who were enrolled in premarketing studies; further fatal cases have been collected, and the Committee on Safety of Medicines has described reports of 36 deaths (including some sudden cardiac deaths) and 13 serious but non-fatal dysrhythmias also associated with sertindole (4).

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Sertraline

See also Selective serotonin re-uptake inhibitors (SSRIs)

General Information

Sertraline hydrochloride has an average half-life of about 26 hours, and mean peak plasma concentrations occur at 4.5–8.4 hours. The dosage is 50–200 mg/day orally. Its major metabolite, *N*-desmethylsertraline, is less active than sertraline. Adverse effects are as for the SSRIs in general.

Organs and Systems

Cardiovascular

Angina occurred in an elderly woman shortly after she started to take sertraline and on rechallenge (1).

Nervous system

Parkinsonism

Sertraline has an appreciable affinity for the dopamine re-uptake site, and for this reason might be presumed less likely to cause movement disorders than other SSRIs. However, there is little clinical evidence to support this suggestion and cases of sertraline-induced parkinsonism have been reported (2).

- A 70-year-old woman, who had been taking sertraline 100 mg/day for 7 months, gave a 6-month history of resting tremor and loss of dexterity in the right hand. She had mild bradykinesia and cogwheel rigidity in the right arm and leg. She had not taken any other medications. A brain MRI scan was normal. The sertraline was withdrawn and within 1 month all the neurological symptoms and signs had remitted.
- An 81-year-old woman took sertraline 100 mg/day for depression and 6 months later presented with tremor and difficulty in moving her right arm and leg (3). A diagnosis of right hemiparkinsonism was made and the sertraline was withdrawn. Her extrapyramidal symptoms resolved within 3 months, but 14 months later she developed parkinsonism and was treated with levodopa and carbidopa.
- A 70-year-old man developed parkinsonian symptoms 1 month after starting to take sertraline 100 mg/day (4). Withdrawal of sertraline resulted in amelioration but not complete remission of his symptoms which then required treatment with carbidopa and levodopa.

In these cases presumably the sertraline prematurely precipitated Parkinson's disease. Two cases of sertraline-induced akathisia have been reported (SEDA-18, 19).

Serotonin syndrome

Treatment with serotonin-potentiating drugs in usual therapeutic doses can sometimes produce the serotonin syndrome. There are also case reports of this reaction with single doses of SSRIs (see also the monograph on fluvoxamine) (5).

Serotonin syndrome after a single dose of sertraline 100 mg has been reported in a 16-year-old girl (6). It responded to a single 4 mg dose of the serotonin antagonist cyproheptadine.

There was therapeutic benefit from cyproheptadine in a case of serotonin syndrome in a 2-year-old girl who accidentally swallowed ten 50 mg tablets of sertraline (7).

Endocrine

Serotonin pathways are involved in the regulation of prolactin secretion. Galactorrhea has also been reported in a patient taking sertraline, in whom lactation ceased after withdrawal (SEDA-18, 20) and in another case (8).

Hematologic

Prolonged bleeding time has been reported with sertraline (9).

Sertraline has been associated with agranulocytosis (10).

Liver

Hepatitis has been associated with sertraline (11).

Hepatitis has also been reported with paroxetine (SEDA-21, 12).

Skin

Stevens–Johnson syndrome has been reported in a 96-year-old woman who had taken sertraline (dosage not stated) for 3 weeks (12). The lesions involved the skin, oral mucosa, and conjunctiva. The eruption disappeared within 7 days of sertraline withdrawal.

Hair

Hair loss has been associated with sertraline (13).

Sexual function

Sexual disturbance has also been associated with sertraline (14), and a high frequency of such adverse effects has been reported in studies in which high doses were used. In a double-blind, placebo-controlled study of sertraline and amitriptyline in patients with major depression, male sexual dysfunction, mainly ejaculatory disturbance, was reported significantly more often with sertraline (in 21% of the patients) (15). Male sexual dysfunction in 15% of sertraline-treated patients has also been reported (16).

Priapism is occasionally associated with the use of psychotropic drugs, such as trazodone, that are α_1-adrenoceptor antagonists. It has also been reported in a man taking sertraline (17).

- A 47-year-old man presented with a 4-day history of priapism and moderate pain. Several brief but otherwise similar episodes had occurred during the previous month. He had a history of depression and had been taking sertraline 200 mg/day and dexamfetamine 10 mg/day. He received intracorporeal methoxamine, but when this proved ineffective he was treated with intracorporeal adrenaline and a shunt procedure. However, detumescence was incomplete. At follow-up after several weeks the priapism had resolved and he had not become impotent (a significant risk in cases of

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prolonged priapism). He was given nefazodone with no recurrence of erectile dysfunction.

The dosage of sertraline used in this case was high and the combined use of dexamfetamine may also have been relevant.

Long-Term Effects

Drug withdrawal

Withdrawal symptoms have been reported with sertraline (18). All the symptoms, including gastrointestinal discomfort, insomnia, and influenza-like symptoms, remitted when sertraline was reinstituted.

Drug Administration

Drug overdose

In 40 patients who took up to 8 g of sertraline there were no serious sequelae (19).

One of the largest overdoses of sertraline has been reported (20).

- A 51-year-old woman took about 8 g of sertraline, about 80 times the usual daily dose. On admission to hospital she was somnolent but rousable. Her electrocardiogram showed a transiently prolonged QT_c interval (510 ms falling to 470 ms). On the third day she developed agitation, disorientation, myoclonus, and pyrexia (38.5 °C), was treated with supportive measures, and recovered over the next 3 days.

While cardiac toxicity was not prominent in this case, the patient developed clear evidence of the serotonin syndrome, which proved self-limiting.

Drug–Drug Interactions

Carbamazepine

Sertraline is a substrate for a number of CYP450 isozymes, including CYP2C9, CYP2C19, and CYP3A4. Several case reports have shown loss of antidepressant activity of sertraline at usual therapeutic doses when depressed patients have also taken drugs that induce CYP3A4, including carbamazepine (21).

Erythromycin

Drug interactions leading to the serotonin syndrome usually result from pharmacodynamic mechanisms. However, the antibiotic erythromycin may have precipitated the serotonin syndrome in a patient taking sertraline by a pharmacokinetic mechanism (22).

- A 12-year-old boy, who had taken sertraline 37.5 mg/day for 5 weeks for obsessive-compulsive disorder, started to take erythromycin 200 mg bd. Within 4 days he began to feel anxious; this was followed over the next 10 days by panic, restlessness, irritability, tremulousness, and confusion. These symptoms resolved within 72 hours of withdrawal of sertraline and erythromycin.

The authors proposed that in this case erythromycin had inhibited sertraline metabolism by inhibiting CYP3A. This could have led to increased concentrations of sertraline and signs of serotonin toxicity. Unfortunately sertraline concentrations were not measured to confirm this suggestion.

Rifampicin

Sertraline is a substrate for a number of CYP450 isozymes, including CYP2C9, CYP2C19, and CYP3A4. Several case reports have shown loss of antidepressant activity of sertraline at usual therapeutic doses when depressed patients have also taken drugs that induce CYP3A4, including rifampicin (23).

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Sevoflurane

See also General anesthetics

General Information

Sevoflurane is an isoflurane-related anesthetic, which is pleasant to breathe and has a rapid onset and offset of action. It can be used for both the induction and maintenance of anesthesia.

It has become popular in day surgery, despite little evidence of clear advantages over current alternatives.

Inhalational induction of anesthesia is common in children, and sevoflurane is challenging the tradition of halothane induction in children. Deep anesthesia with sevoflurane can be obtained rapidly, and recovery is also faster than with halothane.

Compound A

Compound A is a haloalkene degradation product of sevoflurane metabolism by carbon dioxide absorbers, and it has been suggested that prolonged low-flow closed-circuit anesthesia with sevoflurane may maximize exposure to the degradation product. Compound A can cause convulsions and neural damage in rats (1). It also causes nephrotoxicity and hepatotoxicity in rats, particularly if barium hydroxide lime is used (2).

Organs and Systems

Cardiovascular

In 28 subjects given either sevoflurane + nitrous oxide or enflurane + nitrous oxide anesthesia, sevoflurane caused fewer cardiodepressant effects than enflurane (3). Nevertheless, in 10 healthy subjects atrial contraction and left ventricular diastolic function, including active relaxation, passive compliance, and elastic recoil were impaired by sevoflurane (1 MAC) (4).

Sevoflurane has a similar effect on regional blood flow to other halogenated anesthetics, although it is perhaps slightly less of a coronary artery vasodilator than isoflurane. It reduces myocardial contractility and does not potentiate adrenaline-induced cardiac dysrhythmias (5). It also reduces baroreflex function, and in that respect is similar to other halogenated anesthetics. Coronary artery disease is not a risk factor for the use of these agents (6).

In contrast to isoflurane and desflurane, sevoflurane tends not to increase the heart rate, and is usually well tolerated for induction of anesthesia in young children. However, profound bradycardia was reported in four unpremedicated children aged 6 months to 2 years during anesthesia induction with sevoflurane 8% and nitrous oxide 66% (7). The episodes were not associated with loss of airway or ventilation. In three of the children there was spontaneous recovery of heart rate when the sevoflurane concentration was reduced; the other child received atropine because of evidence of significantly reduced cardiac output. In a previous study of sevoflurane induction of anesthesia in children with atropine premedication there was also a low incidence of this complication (8), which is probably due to excessive sevoflurane concentrations.

The effects of sevoflurane on cardiac conduction have been studied in 60 healthy unpremedicated infants (9). They received sevoflurane either as a continuous concentration of 8% from a primed circuit or in incrementally increasing doses. Nodal rhythm occurred in 12 cases. The mean duration of the nodal rhythm was 62 seconds in the incremental group and 90 seconds in the 8% group. All of the dysrhythmias were self-limiting and there were no ventricular or supraventricular dysrhythmias. No adverse events occurred as a result of the dysrhythmias. This study highlights the importance of using electrocardiographic monitoring when inducing anesthesia with volatile agents.

- Complete atrioventricular block occurred in a 10-year-old child with a history of hypertension, severe renal dysfunction, incomplete right bundle branch block, and a ventricular septal defect that had been repaired at birth (10). After slow induction with sevoflurane and nitrous oxide 66%, complete atrioventricular block occurred when the inspired sevoflurane concentration was 3% and reverted to sinus rhythm after withdrawal of the sevoflurane. The dysrhythmia recurred at the end of the procedure, possibly caused by lidocaine, which had infiltrated into the abdominal wound, and again at 24 hours in association with congestive cardiac failure following absorption of peritoneal dialysis fluid.

Congenital or acquired forms of the long QT syndrome can result in polymorphous ventricular tachycardia (torsade de pointes). Many drugs, including inhalational anesthetics, alter the QT interval, and sevoflurane prolongs the rate-corrected QT interval (QT_c). In a randomized study of whether sevoflurane-associated QT_c prolongation was rapidly reversed when propofol was used instead, 32 patients were randomly allocated to one of two groups (11). All received sevoflurane induction and maintenance for the first 15 minutes. In one group, sevoflurane was then withdrawn, and anesthesia was maintained with propofol for another 15 minutes; the other group continued to receive sevoflurane for 30 minutes. Sevoflurane-associated QT_c prolongation was fully reversed within 15 minutes when propofol was substituted.

A case of torsade de pointes has been attributed to sevoflurane anesthesia (12).

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- A 65-year-old woman, who had had normal preoperative serum electrolytes and a normal QT interval with sinus rhythm, received hydroxyzine and atropine premedication followed by thiopental and vecuronium for anesthetic induction. Endotracheal intubation was difficult and precipitated atrial fibrillation, which was refractory to disopyramide 100 mg. Anesthesia was then maintained with sevoflurane 2% and nitrous oxide 50%. Ten minutes later ventricular tachycardia ensued, refractory to intravenous lidocaine, disopyramide, and magnesium. DC cardioversion resulted in a change to a supraventricular tachycardia, which then deteriorated to torsade de pointes. External cardiac massage and further DC cardioversion were initially unsuccessful, but the cardiac rhythm reverted to atrial fibrillation 10 minutes after the sevoflurane was switched off. Two weeks later she had her operation under combined epidural and general anesthesia, with no changes in cardiac rhythm.

In this case the role of excessive sympathetic drive as a result of the difficult intubation and the lack of opioid use during induction must be considered, even if sevoflurane played a role in precipitating the dysrhythmia.

Respiratory

In a randomized study of the respiratory effects of high concentrations of halothane and sevoflurane in 21 healthy boys undergoing inguinal or penile surgery, there was similar respiratory depression with each agent (13). Minute ventilation fell by about 50% as a result of a reduction in tidal volume, despite an increase in respiratory rate.

Nervous system

Despite a fall in mean arterial pressure, with a consequent reduction in cerebral perfusion pressure, sevoflurane should be a suitable agent for neuroanesthesia (14). Even in patients with ischemic cerebrovascular diseases, both the CO_2 response and cerebral autoregulation were well maintained during sevoflurane anesthesia (0.88 MAC) (15).

A case of acute dystonia has been reported during induction of anesthesia with sevoflurane (16).

- A 19-year-old man with schizophrenia, who was taking cyamemazine (a phenothiazine) 75 mg/day, and dihydroergotamine 180 mg/day to avoid neuroleptic drug-induced hypotension, had no history of involuntary movements, and neurological examination was normal preoperatively. Anesthesia was induced with midazolam 5 mg oral premedication and an inhalational induction using 4–5 maximum breaths of sevoflurane 8% and nitrous oxide 50% in oxygen. One minute after loss of consciousness, he developed a torticollic posture and stiffness, rapidly extending to the left trapezius and scalene muscles. There was severe rotation of the head accompanied by trismus and opisthotonos. An intravenous injection of the muscle relaxant atracurium 30 mg resolved the muscle spasms. Subsequent anesthesia was uneventful.

Dystonia after inhalational anesthesia is rare and is presumably due to an alteration in the dynamic relation between dopaminergic and other receptors in the brain.

Sevoflurane can cause epileptiform activity on the electroencephalogram, especially during emergence from anesthesia. It has also been associated with epileptiform discharges in volunteer studies, but clinical convulsions appear to very be rare. Two cases of epileptiform activity during sevoflurane anesthesia have been reported in healthy volunteers (17). They were taking part in a study of the effects of sevoflurane on regional cerebral blood flow and received twice the minimum alveolar concentration (MAC) of sevoflurane (4.4%). The only other drug administered was rocuronium, a muscle relaxant. Sevoflurane was used at up to twice its MAC, to induce burst suppression of the electroencephalogram. One of the subjects had partial motor seizure activity in the form of slight clonic movements in the right and then later in the left leg. There was an associated increase in heart rate (from 65 to 79 beats/minute) and systolic blood pressure (from 85 to 106 mmHg) and rhythmic epileptiform discharges on the electroencephalogram. The second subject had epileptiform activity on his electroencephalogram, consisting of partial and secondarily generalized discharges lasting for 2 and 3 minutes respectively. There were no clinical signs of an epileptic seizure. Burst suppression appeared on the electroencephalogram in both subjects before the seizure activity, and the Bispectral Index increased dramatically during the epileptiform discharge to maximum values of 44 and 73 respectively. As expected, regional cerebral blood flow and regional metabolism of the epileptic focus fell interictally and increased ictally. Although the concentrations of sevoflurane used in this study were high compared with usual anesthetic practice, further human studies are warranted, because prolonged epileptiform discharge is known to be harmful.

In another case, epileptiform activity was reported during sevoflurane anesthesia, but not with propofol in the same individual (18).

- A 62-year-old woman with no personal or family history of seizures had general relaxant anesthesia for plastic surgery using a total intravenous anesthetic technique with propofol, remifentanil, and cisatracurium, after benzodiazepine premedication. Routine electroencephalographic monitoring showed continuous slowing followed by burst suppression (consistent with very deep anesthesia), but no epileptiform activity. At a second procedure, and following identical benzodiazepine premedication and induction with propofol, anesthesia was maintained with sevoflurane (plus remifentanil for analgesia and cisatracurium for neuromuscular blockade). During the procedure, sevoflurane was increased from 2% to 8%. After 5 minutes, at an end-tidal concentration of 5.9%, there was epileptiform activity on the electroencephalogram. There were no hemodynamic changes.

Epileptiform activity on the electroencephalogram in association with sevoflurane induction has also been reported in a prospective study of 20 non-premedicated healthy children in whom electroencephalographic monitoring was started before sevoflurane induction (19). At 2

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MAC there was epileptiform activity in two boys, with spontaneously resolving myoclonic movements.

Epileptiform activity on the electroencephalogram in association with sevoflurane has also been reported in two children aged 3 and 5 years in a center in which electroencephalographic monitoring is routine (20). In both cases the activity occurred after several minutes of anesthesia, when the sevoflurane concentrations were increased to 7–8%. The epileptiform activity resolved after a reduction in sevoflurane concentrations. No seizure activity was noted.

In a prospective, observational study in 30 children undergoing adenoidectomy anesthesia was induced with midazolam and thiopental (both potent anticonvulsants) and maintained with sevoflurane; no electroencephalographic epileptiform activity was observed (21).

Generalized tonic–clonic seizures have been reported in association with the use of sevoflurane.

- Generalized tonic–clonic seizure-like movements lasting 40 seconds occurred in a healthy 32-year-old man after emergence from sevoflurane-based anesthesia (22).
- A 19-year-old man with a history of metamfetamine abuse 3 weeks earlier, but no personal or family history of seizure activity had anesthesia induced with midazolam 1 mg, nitrous oxide 50%, and sevoflurane 8% (23). The sevoflurane was subsequently reduced to 2%. After radical orchidectomy the sevoflurane and nitrous oxide were withdrawn and oxygen 100% was given and 2 minutes later rhythmic jerking movements began in the legs and quickly spread to the rest of the body. The movements were accompanied by an arched back and a stiff neck. Arterial oxygen saturation dropped to 50% and ventilation was controlled, again using sevoflurane 8%. The duration of the seizure was about 4 minutes. The sevoflurane was again withdrawn 3 minutes later, and a similar seizure occurred. This time it was controlled with midazolam 1 mg and propofol 30 mg. Recovery was marked only by mild disorientation. Postoperative computerized tomography showed a ganglioneuroma in the posterior cortex. The electroencephalogram was normal.

These reports show that clinicians need to be aware of the possibility of generalized seizures, especially in patients who are predisposed to seizures.

Peripheral neuropathy has been reported in two healthy men anesthetized with 1.25 MAC sevoflurane at 2 l/minute fresh gas flow for 8 hours. Their average concentrations of compound A were 45 and 28 ppm. Both had had previous minor injuries in the regions in which the neuropathies were reported. The authors suggested that compound A, or other factors associated with sevoflurane anesthesia, may predispose patients to peripheral neuropathy. Both men were volunteers for earlier published studies comparing the nephrotoxic properties of sevoflurane and desflurane, sponsored by Baxter PPD, New Jersey, the manufacturer of desflurane, a rival inhalational anesthetic agent; these reports need to be regarded with caution.

Neuromuscular function

Prolongation of rapacuronium-induced neuromuscular blockade by sevoflurane has been studied in a randomized, placebo-controlled comparison with suxamethonium in 40 children (24). Patients received sevoflurane and nitrous oxide anesthesia followed by rapacuronium 2 mg/kg. The study was stopped after only seven patients had been recruited, because the mean time to return of twitch height to 25% of baseline was 26 minutes. This time represents a stage at which neuromuscular blockade can be reversed and in this case it was twice as long as predicted from experience in adult patients. The authors suggested that the prolonged neuromuscular relaxation was due to the interaction of sevoflurane with rapacuronium, because such prolongation has not been observed using other inhalation agents.

Psychological, psychiatric

Delirium during emergence from sevoflurane anesthesia has often been documented. Four patients, an adult and three children aged 3–8 years, who were able to recount the experience, have been reported (25). They had full recall of postoperative events, were terrified, agitated, and distressed, and hence presented with acute organic mental state dysfunction which was short-lived. Two were disoriented and had paranoid ideation. They were not in any pain or were not distressed by pain if it was present. The authors hypothesized that misperception of environmental stimuli associated with sevoflurane's particular mode of action may have been the underlying cause of this phenomenon. Anxiolytic premedication and effective analgesia did not necessarily prevent the problem.

The effect of intravenous clonidine 2 micrograms/kg on the incidence and severity of postoperative agitation has been assessed in a double-blind, randomized, placebo-controlled trial in 40 boys who had anesthetic induction with sevoflurane after oral midazolam premedication (26). There was agitation in 16 of those who received placebo and two of those who received clonidine; the agitation was severe in six of those given placebo and none of those given clonidine.

The effects of intravenous and caudal epidural clonidine on the incidence and severity of postoperative agitation have been assessed in a randomized, double-blind study in 80 children, all of whom received sevoflurane as the sole general anesthetic for induction and maintenance (27). A caudal epidural block was performed before surgery for analgesia with 0.175% bupivacaine 1 ml/kg. The children were assigned randomly to four groups: (I) clonidine 1 microgram/kg added to the caudal bupivacaine; (II) clonidine 3 micrograms/kg added to the caudal bupivacaine; (III) clonidine 3 micrograms/kg intravenously; and (IV) no clonidine. The incidences of agitation were 22, 0, 5, and 39% in the four groups respectively. Thus, clonidine 3 micrograms/kg effectively prevented agitation after sevoflurane anesthesia independent of the route of administration.

The effect of a single preoperative dose of the opioid oxycodone on emergence behavior has been studied in a randomized trial in 130 children (28). Oxycodone prophylaxis had no effect on post-sevoflurane delirium.

The effect of a single bolus dose of midazolam before the end of sevoflurane anesthesia has been investigated in a double-blind, randomized, placebo-controlled trial in 40 children aged 2–7 years (29). Midazolam significantly

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reduced the incidence of delirium after anesthesia. However, when it was used for severe agitation midazolam only reduced the severity without abolishing agitation. The authors concluded that midazolam attenuates, but does not abolish, agitation after sevoflurane anesthesia.

Liver

Sevoflurane can be used to induce hypotension during neurosurgery. Hypotensive anesthesia has little effect on postoperative liver function (30).

- A 3-day-old boy underwent inguinal herniorrhaphy under sevoflurane anesthesia, and 2 days later developed vomiting, anorexia, and fever (31). His aspartate transaminase, alanine transaminase, and lactate dehydrogenase activities were increased and peaked 12–16 days after the operation. Viral markers were negative, as was a lymphocyte stimulation test with sevoflurane. Toxic (not allergic) liver damage due to exposure to sevoflurane was considered to be the most probable diagnosis.

In a randomized study of the renal and hepatic effects of prolonged low-flow anesthesia with sevoflurane or isoflurane in patients undergoing prolonged operations (over 8 hours), using a technique that maximized compound A production, there were no differences in markers of hepatocellular injury at 24 or 72 hours (32).

The effect of minimal-flow (as opposed to low-flow) anesthesia with sevoflurane and isoflurane has been examined in a randomized trial in 76 patients (33). There were no significant differences between the groups in blood chemistry markers of hepatic function, despite high exposure to Compound A in the patients who received sevoflurane.

Plasma activity of alpha-glutathione *S*-transferase activity (αGT) is a more sensitive and specific marker of hepatocellular injury than transaminase activity and it correlates better with hepatic histology. Anesthesia with halothane leads to transiently raised αGT activity, but propofol and isoflurane do not. In a randomized study of plasma αGT activity during and after low-flow anesthesia with sevoflurane or isoflurane, there were no significant differences in αGT activities between the two groups during or after anesthesia (34).

Thus, the evidence suggests that sevoflurane is as safe as isoflurane in low-flow anesthesia with respect to liver dysfunction.

Urinary tract

The effects of sevoflurane, isoflurane, and desflurane on macroscopic renal structure have been studied in 24 patients undergoing nephrectomy (35). All anesthetics were administered using a fresh gas flow of 1 l/minute and a sodium hydroxide absorber and had an average duration of 3 hours. No injury to nephrons was observed by pathologists blinded to which anesthetic agent had been used. Postoperative creatinine concentrations and urine volumes did not differ significantly between the groups.

- Transient renal tubular dysfunction has been reported in a patient with asthma requiring mechanical ventilation who received sevoflurane for 9 days (36). Soda lime was not used, and the cumulative dose was 298 MAC-hours. Serum and urinary inorganic fluoride concentrations reached maximum concentrations of 71 and 2047 μmol/l respectively. Markers of renal tubular injury were also greatly raised (urinary *N*-acetyl-beta-D-glucosaminidase and $beta_2$-microglobulin). However, urine volume, creatinine clearance, and serum creatinine and urea concentrations were unaffected.

There has been a meta-analysis of 22 controlled trials in 3436 patients (82% ASA I or II, 16% ASA III, and 2% ASA IV) (37). The trials had compared sevoflurane for anesthesia maintenance with isoflurane, propofol, or enflurane. Serum creatinine and blood urea nitrogen were used to assess preoperative and postoperative renal function. The duration of anesthesia was 0.5–11 hours. Most patients (97%) were exposed to less than 4 MAC-hours of volatile agent. Falls in the serum creatinine and blood urea nitrogen were significantly smaller with isoflurane than with sevoflurane. In patients who received concurrent aminoglycosides, sevoflurane was associated with a small increase in serum creatinine. The following factors had no effect on renal function: the type of anesthetic circuit, the choice of carbon dioxide absorber, the inorganic fluoride ion concentration, the duration of anesthesia, the use of nitrous oxide, or how sick patients were. When all patients were considered, the incidences of clinically significant increases in serum creatinine were the same between agents. In patients with baseline creatinine values greater than 132 μmol/l (1.5 mg/dl), the incidence of clinically important increases in serum creatinine was significantly higher in both treatment groups compared with baseline. This meta-analysis has provided strong evidence that sevoflurane does not contribute to clinically significant renal insufficiency.

Renal impairment often follows cardiac surgery, but in a randomized trial in elective coronary artery surgery in 354 patients, sevoflurane did not produce greater increases in serum creatinine concentrations than isoflurane or propofol (38).

The role of compound A

Sevoflurane is metabolized to compound A by carbon dioxide absorbers. It is nephrotoxic in rats, but nephrotoxicity in humans has not been proven. The accumulation of compound A is greatest with low fresh gas flows and barium hydroxide absorbers, both of which cause higher temperatures in the absorber. Current anesthetic practice is to use sodium hydroxide for carbon dioxide absorption, because it produces less compound A than barium hydroxide.

There has been controversy over whether compound A causes significant renal damage in humans. The potential for renal damage using sevoflurane was investigated in 42 patients without renal disease scheduled for surgery lasting more than 4 hours (39). The patients were given low-flow sevoflurane or isoflurane (fresh gas flow 1 l/minute/m^2) or high-flow sevoflurane (6 l/minute/m^2). None of these increased blood urea nitrogen concentrations, creatinine concentrations, or creatinine clearance.

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There were no significant differences in $beta_2$-microglobulin, a marker of tubular function, or urinary glucose concentrations. However, there was an increase in the 24-hour urinary excretion of *N*-acetyl-beta-glucosaminidase, a marker of proximal tubular necrosis, with both doses of sevoflurane but not with isoflurane. There were no significant differences in the serum and urinary fluoride concentrations between the two sevoflurane groups, despite the higher concentration of compound A (29 versus 3.9 ppm) in the expired gases of those who received low-flow sevoflurane. The maximum 24-hour protein excretion was higher with low-flow sevoflurane compared with the other two groups.

The effect of the nephrotoxic aminoglycoside antibiotic amikacin on renal function during low-flow sevoflurane anesthesia has been studied in a randomized study in 37 men undergoing orthopedic surgery (40). Markers of renal tubular injury (urinary *N*-acetyl-beta-D-glucosaminidase and $beta_2$-microglobulin) were not abnormally raised, and urine volume, creatinine clearance, and serum creatinine and urea concentrations were unaffected. The duration of anesthesia and compound A concentrations were similar in the two groups.

In a randomized study of the renal and hepatic effects of prolonged low-flow anesthesia with sevoflurane or isoflurane in patients undergoing prolonged operations (over 8 hours), using a technique that maximized compound A production, there were no significant differences between the groups in serum creatinine or urea concentrations, creatinine clearance, or urinary protein or glucose excretion at 24 or 72 hours (32). Proteinuria and glycosuria were common in both groups. There was no correlation between exposure to compound A and any measure of renal function. There were no differences in markers of hepatocellular injury. There was no evidence of nephrotoxicity of sevoflurane even at high degrees of exposure to compound A for as long as 17 hours.

The effect on renal function of minimal-flow (as opposed to low-flow) anesthesia with sevoflurane and isoflurane has been examined in a randomized trial in 76 patients (33). There were no significant differences between the groups in blood chemistry markers of renal or hepatic function or in urinary markers of tubular injury, despite high exposure to compound A in the patients who received sevoflurane.

These studies have confirmed earlier findings that although there is biochemical evidence of renal damage after sevoflurane anesthesia, there are no clinically significant effects.

The role of fluoride

Serum and urinary inorganic fluoride concentrations can rise after inhalation of sevoflurane, because of hepatic metabolism (41). The authors concluded that lengthy sevoflurane anesthesia could alter renal function, although there was no other evidence of nephrotoxicity. Although patients with normal renal function are probably not at risk during normal anesthesia with sevoflurane, those with pre-existing renal impairment may be at risk.

A randomized, open study in 26 patients with renal dysfunction who received either isoflurane or sevoflurane for operations lasting up to 6 hours showed no significant differences in postoperative creatinine clearances. However, there was a significant increase in the plasma fluoride ion concentration with sevoflurane (42). In 10 adults who were given repeat high-flow sevoflurane anesthesia there was no evidence of renal or hepatic injury and no increases in serum or urine fluoride concentrations that would indicate an increase in sevoflurane metabolism with repeated use (43).

Renal function has been assessed after low fresh gas flow anesthesia (1 l/minute or less) with either sevoflurane or isoflurane in a multicenter study of 254 patients (44). The mean duration of anesthesia was 3.0 MAC-hours in both groups. Peak serum fluoride concentrations were significantly higher (40 μmol/l) after sevoflurane compared with isoflurane (3 μmol/l), and 26 patients had peak fluoride concentrations over 50 μmol/l, a concentration that is associated with renal dysfunction after methoxyflurane anesthesia. There were no significant differences in the renal function of the two groups, as measured by serum creatinine, urea, glycosuria, proteinuria, urine pH, or specific gravity. Absence of renal dysfunction, despite high serum fluoride concentrations after sevoflurane anesthesia, was consistent with previous reports. It appears that low fresh gas flow anesthesia with sevoflurane is not associated with clinically significant renal damage.

The role of aquaporins

Aquaporin-2 is a protein involved in regulation of water permeability in the kidneys. The effects of sevoflurane- and propofol-based anesthesia on urine concentrating ability and aquaporin-2 concentrations have been compared in 30 patients undergoing major surgical procedures given sevoflurane + nitrous oxide or propofol + nitrous oxide (45). Sevoflurane caused a transient 25% fall in aquaporin-2 concentrations 90 minutes after surgery, rather than the usual 40% increase, which occurred in the propofol group. By 3 hours after surgery the aquaporin concentrations in the sevoflurane group had increased and were similar to those in the propofol group. There was a 40% fall in urine osmolarity in the sevoflurane group, but recovery occurred by 3 hours postoperatively. This effect is the likely cause of the occasional cases of polyuria reported in association with sevoflurane anesthesia, rather than nephrotoxicity caused by fluoride ion or compound A.

Musculoskeletal

There have been reports of rhabdomyolysis after anesthesia with halothane, enflurane, and isoflurane in patients with muscular dystrophy, in whom suxamethonium was not used. Rhabdomyolysis has also been reported after sevoflurane anesthesia (46).

- An 11-year-old boy with Duchenne's muscular dystrophy underwent strabismus repair. He also had asthma, for which he was taking prednisone 25 mg/day and theophylline. He underwent inhalational induction with sevoflurane 4% and nitrous oxide 64%; tracheal intubation was then performed without the use of a muscle relaxant. Anesthesia was maintained using sevoflurane 1.5–3.0% and nitrous oxide 64%. He also

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received hydrocortisone 100 mg and diclofenac 25 mg. The operation lasted 51 minutes and anesthesia was uneventful. He suffered heel pain during the first few hours postoperatively, and 3 hours postoperatively passed 300 ml of dark red urine, containing large amounts of myoglobin. His serum enzymes increased from preoperative values, serum aspartate transaminase from 76 to 458 IU/l, alanine transaminase from 136 to 254 IU/l, and creatine kinase from 4430 to 55 700 IU/l. He was treated with dantrolene 1 mg/kg and recovered over the next day.

The history and finding in this case are strongly diagnostic of rhabdomyolysis. The most likely cause of rhabdomyolysis in this patient was thought to be inhalation of sevoflurane.

Rhabdomyolysis triggered by sevoflurane in a child with Duchenne muscular dystrophy has been reported in one case (47).

Body temperature

Malignant hyperthermia has occurred in people treated with sevoflurane.

- In the case of a 4-year-old girl, dantrolene was effective; susceptibility to malignant hyperthermia was later confirmed by muscle biopsy (48).
- A 28-year-old man, who developed malignant hyperthermia after anesthesia induced with isoflurane and maintained with sevoflurane, died 4 days later, despite cooling and intravenous dantrolene (49).

Other cases of malignant hyperthermia have been reported in patients who received sevoflurane (50,51). Although it is highly likely that sevoflurane caused malignant hyperpyrexia in these cases, suxamethonium was also given and was also a suspect.

Of two other cases (52,53), the second was remarkable, in that the specific-treatment dantrolene was not available, and yet the patient survived with aggressive active cooling and general supportive measures, including sodium bicarbonate.

In more than 3000 cases in Japan, there were two cases of malignant hyperthermia, one fatal (49). In this case isoflurane had been used early in anesthesia, and could have been at least in part responsible. There was some reason to consider that the patient, a 12-year-old girl, had a family propensity to malignant hyperthermia, as indicated by higher resting Pi/Pcr values. However, sevoflurane itself can trigger malignant hyperthermia in swine (54).

Susceptibility Factors

Renal disease

It has been thought that patients with chronically impaired renal function might be at increased risk of nephrotoxicity due to sevoflurane, because of an increased fluoride load due to reduced excretion. However, this was not confirmed in 41 patients undergoing elective surgery, with a stable increased preoperative serum creatinine concentration, who were randomly allocated to receive sevoflurane ($n = 21$) or enflurane ($n = 20$) at a fresh gas inflow rate of 4 l/minute for maintenance of anesthesia (55). Peak serum inorganic fluoride concentrations were significantly higher after sevoflurane than after enflurane anesthesia. Laboratory measures of renal function remained stable throughout the postoperative period in both groups. No patient had permanent deterioration of pre-existing renal insufficiency and none required dialysis.

Other features of the patient

Insulinoma

- A 56-year-old woman with insulinoma, operated under sevoflurane anesthesia, had an uneventful perioperative course, and the authors suggested that sevoflurane suppressed the spontaneous release of insulin (56).

Sevoflurane may therefore be useful for anesthesia in patients with insulinoma.

Transplantation

- A 29-year-old man was anesthetized after renal transplantation with sevoflurane + nitrous oxide + oxygen for replacement of the head of the left femur (57). His serum fluoride concentration was always below 40 μmol/l and sevoflurane had little effect on the transplanted kidney.

It seems therefore that sevoflurane might be suitable for patients with renal transplants.

Drug–Drug Interactions

Dexmedetomidine

In 45 adult patients undergoing elective surgery, the α_2-adrenoceptor agonist dexmedetomidine in a concentration of 0.7 ng/ml reduced the minimum alveolar concentration of sevoflurane required to suppress movement to skin incision by 17%, but a plasma concentration of 0.39 ng/ml had no effect (58). The larger reductions in isoflurane requirements found in earlier studies of dexmedetomidine were probably due to the use of potent opioids and intravenous induction as part of the anesthetic.

Fentanyl

The minimum alveolar concentrations of sevoflurane required to suppress movements and adrenergic responses to surgery in the presence of the potent opioid fentanyl have been quantified in 226 adults (59). Fentanyl 3 ng/ml and 6 ng/ml reduced sevoflurane requirements to suppress movement to pain by 61% and 74%, respectively, and requirements to suppress the adrenergic responses to pain by 83% and 91%, respectively. There was no further reduction in sevoflurane requirements at concentrations of fentanyl above 6 ng/ml. The degree of interaction was similar to that seen in previous studies of other volatile anesthetic + opioid combinations.

Ketorolac

Ketorolac, which can cause renal vasoconstriction by inhibiting cyclo-oxygenase, is often given to patients anesthetized with sevoflurane, which is also potentially

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nephrotoxic. The effect of ketorolac has been assessed in a placebo-controlled, randomized study in 30 women undergoing breast surgery with sevoflurane anesthesia (60). There were no differences in several markers of renal injury in those who did or did not receive ketorolac.

Probenecid

The effect of the uricosuric agent probenecid in prolonged sevoflurane anesthesia has been examined in 64 patients randomized to receive high-flow or low-flow anesthesia with sevoflurane with or without preoperative oral probenecid (61). There were no differences in urea, creatinine, or creatinine clearance among the treatments. However, patients who received low-flow sevoflurane had some evidence of renal tubular injury (raised urinary markers) compared with those who received either high-flow anesthesia or probenecid.

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Sfericase

General Information

Sfericase is a crystallized alkaline protease that breaks down various protein bases. It is given in enterolytic tablets containing 10 000 units of sfericase. It is prescribed in a dose of two tablets to be taken three times a day. In 73 patients with chronic respiratory diseases there were no significant adverse effects (1).

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Sibutramine

See also Anorectic drugs

General Information

Sibutramine is an appetite suppressant that inhibits the re-uptake of noradrenaline and serotonin. It is used in the adjunctive management of obesity in individuals with a body mass index (BMI) of 30 kg/m^2 or more (and no associated co-morbidity) or in individuals with a BMI of 27 kg/m^2 or more in the presence of other risk factors such as type 2 diabetes or hypercholesterolemia.

The safety and efficacy of sibutramine 10 mg/day in 109 obese patients (BMI over 30 kg/m^2, ages 16–65 years) has been evaluated in a double-blind, placebo-controlled, parallel-group, prospective study over a period of 6 months (1). There was a significant loss of body weight and significantly reduced BMI and waist measurement. There were 45 adverse events in 32 patients taking sibutramine; the most frequent were dry mouth ($n = 19$), increased blood pressure ($n = 5$), constipation ($n = 5$), and tachycardia ($n = 5$); two patients withdrew owing to adverse events. There were 29 adverse events in 23 patients taking placebo, mainly increased blood pressure ($n = 11$) and dry mouth ($n = 10$). In contrast, in an earlier study (2) there was no significant increase in systolic or diastolic blood pressures or heart rate.

Although serious adverse events have not been reported, there is no evidence of the long-term safety of sibutramine (3). Several new randomized clinical trials have assessed long-term weight reduction efficacy, tolerability, and safety of sibutramine. In a 1-year placebo-controlled study in primary care, sibutramine 10 mg/day ($n = 122$) or 15 mg/day ($n = 123$) with dietary advice produced and maintained more weight loss than dietary advice alone (4). None of the patients taking sibutramine or placebo ($n = 114$) was withdrawn because of a raised blood pressure.

There were comparable results in 44 patients who took sibutramine 10 mg/day for 12 months in a double-blind, placebo-controlled, crossover design (5). After sibutramine withdrawal, the patients gained weight but did not reach baseline body weight. There were no significant adverse events of sibutramine withdrawal. Early sibutramine administration produced better effects than administration after a period of dieting.

Further trials have confirmed the efficacy of sibutramine as a weight-loss agent in doses of 10–20 mg/day. The benefit of sibutramine is not only in its ability to induce weight loss, but also in its ability to maintain the weight loss effect for up to 2 years. However, once sibutramine is withdrawn, weight gain commonly occurs. Thus, sibutramine is considered effective in the management of obese patients who require pharmacotherapy as part of a multimodal approach to weight reduction (6).

In a multicenter, double-blind, randomized, parallel-group, placebo-controlled trial in 22 European centers for specialist diabetes care over 6 months, sibutramine, in conjunction with moderate caloric restriction, enabled obese patients with type 2 diabetes taking sulfonylureas to achieve clinically significant weight loss (7). This was associated with additional improvement in glycemic control in a limited number of patients who lost at least 10% of their baseline body weight.

Sibutramine was approved in Italy in April 2001 but was taken off the market there on 6 March 2002, after 50 reported adverse reactions (mainly tachycardia, hypertension, and dysrhythmias, in seven cases serious), and two deaths from cardiac arrest (8). Subsequently, the Secretariat of the European Medicines Evaluation Agency began a comprehensive benefit : harm balance assessment of sibutramine, which remains on the market in several European countries; these include the UK (where there were 215 reports of 411 adverse events, 95 serious and 2 deaths) and France (where there were 99 reports of adverse events, 10 serious but no deaths). From February 1998 to September 2001, the Food and Drug Administration (FDA) in the USA received reports of 397 adverse events (143 cardiac dysrhythmias and 29 deaths, 19 due to cardiovascular causes, 10 involving people under 50 years of age, and 3 involving women under 30 years of age) (9). In Canada, 28 adverse reactions (mainly hypertension and dysrhythmias, but no deaths) were reported from December 2000 to February 2002, including one case of chest pain, one of stroke, and two of eye hemorrhage; in three of these cases, the patients were concurrently taking a contraindicated antidepressant (10). The safety of sibutramine needs further postmarketing surveillance.

In a placebo-controlled study, sibutramine 10 mg/day for 6 months caused weight loss and a reduction in left ventricular mass in 86 obese hypertensive patients, with no changes in blood pressure or antihypertensive therapy (11). Baseline investigations included echocardiography, 24-hour ambulatory blood pressure monitoring, and hepatic enzyme measurements. Compared with placebo, sibutramine produced a greater weight loss, an increase in heart rate, and a reduction in left ventricular mass/height index. The two groups had comparable increases in alkaline phosphatase activity and comparable adjustments in antihypertensive therapy. The most frequent adverse effects associated with sibutramine were dry mouth and arthralgia; higher frequencies of insomnia and irritability, as suggested in other studies, were not found. The alterations reported in alkaline phosphatase may be associated with mobilization of visceral adipose tissue (12) and cannot be attributed to the use of sibutramine.

Organs and Systems

Cardiovascular

Cardiovascular risk factors associated with obesity, including dyslipidemia, particularly raised triglyceride concentrations and reduced high-density lipoprotein concentrations, can be improved with weight loss during sibutramine treatment (4,5,13). In general, improvements in serum lipids are proportional to the degree of body weight loss, whether that weight loss occurs with sibutramine or with placebo (13,14).

In a study of the efficacy and safety of sibutramine in obese white and African Americans with hypertension, the most common adverse event resulting in withdrawal

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among those taking sibutramine was hypertension (5.3 versus 1.4% of patients taking placebo) (15).

The observation that sibutramine, which blocks the re-uptake of noradrenaline and serotonin and to a lesser extent dopamine (6), causes a raised blood pressure has been a cause of concern (1,16). Some insight into this problem and its magnitude comes from two recent studies (17,18). Most studies have shown a positive relation between blood pressure and weight (19). The failure of the blood pressure to fall with weight loss in normotensive and hypertensive patients treated with sibutramine differs from the fall seen with orlistat (20–22) or weight loss induced by life-style modifications (23,24). In the case of sibutramine, the potentially detrimental effect due to the failure of the blood pressure to fall with weight loss may be offset by the reductions in lipids, insulin, and uric acid that occur with weight loss (25).

Intermittent use of sibutramine has been proposed to reduce potential concerns about its effect on blood pressure. An alternative strategy would be to identify those patients who respond to sibutramine with weight loss but who have minimal changes in blood pressure (25).

The effects of sibutramine on weight loss, blood pressure, and pulse rate in hypertensive obese patients, whose blood pressure was well controlled with a beta-blocker either alone or with a thiazide diuretic, have been evaluated in a 12-week, double-blind, placebo-controlled, parallel-group, randomized study in 69 patients (17). Sibutramine was effective and well tolerated and did not exacerbate pre-existing hypertension controlled with beta-blockers. Despite the presence of apparently effective beta-blockade, there were modest increases in pulse rate in those who took sibutramine, suggesting that mechanisms other than increased sympathetic tone may, at least in part, mediate this effect. Based on the potential for increased blood pressure and pulse rate, obese patients with well-controlled hypertension who are taking sibutramine should be monitored periodically (17).

In a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 220 hypertensive patients with obesity (BMI 27–40 kg/m^2), whose hypertension was well controlled with an angiotensin converting enzyme (ACE) inhibitor with or without a thiazide diuretic, sibutramine 20 mg/day safely and effectively achieved weight loss without compromising blood pressure control (18). Blood pressure remained in the target range in patients who took sibutramine or placebo, although sibutramine was associated with a small mean increase in blood pressure and a modest increase in pulse rate.

Drug–Drug Interactions

Citalopram

Hypomania in a unipolar depressed woman has been attributed to concomitant use of sibutramine and citalopram (26). The close temporal relation between the onset and the disappearance of hypomania with the introduction and withdrawal of sibutramine suggested a causal link. This report suggests that combining sibutramine with a serotonin re-uptake inhibitor could cause hypomania in people with unipolar major depressive disorder with a family history of bipolar disorder.

Finasteride

Soon after the introduction of finasteride to treat alopecia, a 30-year-old man taking sibutramine developed paranoid psychotic behavior (27). This drug interaction was demonstrated by careful clinical follow-up and the use of Naranjo's algorithm.

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Sildenafil

General Information

Sildenafil is a potent inhibitor of phosphodiesterase type V, and therefore of the breakdown of cyclic guanosine monophosphate (cGMP) in the corpora cavernosa. The increased concentration of cGMP leads to nitric oxide-mediated relaxation of the smooth muscle cells and vasodilatation in the corpus cavernosum, which is essential for normal erection. Thus, sildenafil increases the penile response to sexual stimulation and is effective in erectile dysfunction (1,2).

The main adverse effects reported in clinical studies were flushing, headache, dyspepsia, visual disturbances, and rhinitis, some of which show that vasodilatation is not confined to the corpora cavernosa. They were mild, and only 1–2% of the patients discontinued sildenafil because of adverse effects.

The adverse effects of a single dose of sildenafil 50 mg have been evaluated in a placebo-controlled study in 40 young healthy volunteers (3). The most commonly reported adverse effects with sildenafil and placebo respectively were flushing (75 and 0%), headache (50 and 5%), and dyspepsia (15 and 5%). This adverse effects profile was similar to that observed in clinical trials. Heart rate changed significantly, but blood pressure did not.

There have been several case reports of the use of sildenafil to ameliorate rebound pulmonary hypertension (4).

- A six-week-old 3.1 kg girl developed severe pulmonary hypertension and systemic hypotension after the removal of a bilateral pulmonary vein obstruction due to a left atrial membrane. Nitric oxide 20 ppm reduced the pulmonary arterial pressure from 57 to 33 mmHg, and plasma cGMP concentrations increased from 12 nmol/l at baseline to 28 nmol/l with nitric oxide. After three unsuccessful weaning attempts, due to rebound, sildenafil 1 mg was given via a nasogastric tube and nitric oxide was withdrawn 90 minutes later, with minimal increase in pulmonary artery pressure and a rise in cGMP concentration to 45 nmol/l.
- A 3.5 kg newborn girl, who underwent corrective surgery for an infradiaphragmatic totally anomalous pulmonary venous connection, had postoperative systemic hypotension, low cardiac output, and pulmonary hypertension. Inhaled nitric oxide 20 ppm improved her pulmonary hemodynamics but could not be withdrawn by the third postoperative day, owing to reflex pulmonary hypertension. Sildenafil 1 mg via nasogastric tube again allowed withdrawal of nitric oxide, with preservation of plasma cGMP concentrations above baseline.
- A 4-month-old 4.1 kg boy with severe bilateral pulmonary vein stenosis developed moderate pulmonary hypertension after surgical revision. Sildenafil 1.1 mg via nasogastric tube did not increase the plasma cGMP concentration or reduce the rebound effect.

The authors suggested that in this case the effect of sildenafil may have been reduced by impaired gastrointestinal absorption. They speculated that exogenous nitric oxide inhibits nitric oxide synthase activity, with a consequent reduction in pulmonary vascular smooth muscle cGMP concentration. Phosphodiesterase type V inhibitors, such as sildenafil, increase cGMP concentration and ameliorate the rebound effect.

Organs and Systems

Cardiovascular

In several reviews, in which the same data have been analysed, sildenafil has been rated as being well tolerated

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(5,6) and extremely safe (7). Concerns about its cardiovascular safety profile have stemmed primarily from sporadic reports of myocardial infarction and stroke.

- One patient without a history of previous chest pain or risk factors for cardiovascular disease, developed a well-documented myocardial infarction 30 minutes after he took sildenafil 50 mg and before any attempt at sexual intercourse (8).

The interpretation of these sporadic cases is controversial, although some have argued that the reported cardiovascular adverse effects occur more often with sildenafil than with other pharmacological treatments of erectile dysfunction. It is at present unclear whether there is an increased risk with sildenafil. For example, in placebo-controlled trials there have been no differences in the incidences of myocardial infarction, angina, or coronary artery disorders between sildenafil and placebo (9). Exclusion criteria in clinical trials may have prevented the inclusion of patients who are at increased risk of adverse events. On the other hand, sexual activity itself increases cardiac workload and the risk of myocardial infarction. Patients with cardiovascular disease should be cautious in their use of sildenafil.

Cardiac dysrhythmias have been reported in patients who have taken sildenafil.

- A 54-year-old man with hypertrophic cardiomyopathy, for which he took verapamil, felt unwell after a single tablet of sildenafil (10). Holter monitoring after repeat sildenafil showed an increase in ventricular extra beats and episodes of non-sustained ventricular tachycardia. On echocardiography, left ventricular dimensions were reduced and the subaortic gradient was markedly increased.
- Two other patients with severely depressed left ventricular function developed ventricular tachycardia (11).

Ear, nose, throat

Two men developed prolonged epistaxis a few hours after taking sildenafil 50 mg to enhance their sexual performance (before the nose bleeding started); both had well-controlled hypertension (12). Epistaxis is not an unusual problem in elderly people with hypertension, and venous engorgement is thought to be the main causative factor. Whether this is amplified by sildenafil (and/or by sexual activity) is an open question.

Nervous system

Clinical trials of sildenafil have not shown increased risks of stroke or myocardial infarction. However, postmarketing drug surveillance programs have mentioned strokes associated with sildenafil, and case reports have been published.

- A 50-year-old man took sildenafil 50 mg, and 2 hours later developed a right-sided hemiparesis and altered hemibody sensation, a right-facial paresis, and slurred speech (13). The symptoms gradually disappeared 4 hours later, but recurred the next week when he took sildenafil 100 mg. On the second occasion the symptoms did not resolve, and an MRI scan showed a recent infarct in the left internal capsule and lateral thalamus. No other cause of the stroke was found by evaluation of the heart and extracranial vessels. The symptoms gradually improved over 6 months.
- A 44-year-old man developed a severe headache and vomiting after taking four tablets of sildenafil (of unknown strength) followed by sexual intercourse (14). A CT scan showed a left-sided temporal intracranial hemorrhage. He died of cerebral edema and pneumonia a few days later. Autopsy showed no vascular abnormality.
- A 67-year-old man took two tablets of sildenafil 25 mg 1 hour apart (15). He complained of headache, confusion, and nervousness after the first tablet, his symptoms increased, and he developed language difficulty after the second tablet. He did not have sexual intercourse. A few days later, an MRI scan showed a large left temporal subcortical hemorrhage. The symptoms resolved partially over a few days.

Whereas the suspected mechanism for ischemic stroke is analogous to that leading to myocardial infarction (hypoperfusion distal to a critical lesion), intracerebral bleeding (14,15) may be more difficult to explain. The authors considered the likelihood of sildenafil-induced spontaneous intracerebral hemorrhage due to the vasodilatory effects of the drug on the cerebral vasculature (as evidenced by headache, flushing, and nasal congestion).

- A third-nerve palsy occurred 36 hours after a second dose of sildenafil in a 56-year-old man.

The authors suggested that sildenafil had caused systemic hypotension sufficient to cause neurological dysfunction, but 36 hours is a long lag time for a drug with a half-life of only a few hours (16).

Unexpected functional disturbances, which occur shortly after the use of sildenafil, are likely to be attributed to the drug.

- A 51-year-old man had transient global amnesia 30 minutes after taking sildenafil 25 mg (17).
- A 79-year-old man had acute vertigo, vomiting, and tinnitus resembling vestibular neuronitis 2 hours after first taking 50 mg; the symptoms lasted for 24 hours (18).
- Generalized tonic-clonic seizures have been reported after a first 50 mg tablet in two men aged 54 and 63, neither of whom had organic brain lesions on imaging; one had tonic-clonic seizures again on rechallenge with the drug 3 months later (19).

Sensory systems

Sildenafil has weak inhibitory effects on phosphodiesterase type V in the retina, leading to temporary changes in the perception of color hue and brightness. The importance of reversible changes in the electroretinogram observed in volunteers after sildenafil 100 mg, ascribed to inhibition of phosphodiesterase type 5 in the retina, is unclear (20–22).

There have been reports of a temporal association between vascular events in the eye and sildenafil administration.

- A fit, healthy, 69-year-old man presented with sudden painless loss of vision in the left eye a few hours after taking sildenafil 100 mg (23). Fundus examination

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showed occlusion of a branch of the retinal artery. No cardiovascular abnormality was detected.
- A 52-year-old man developed sweating, headache, and blurred vision in his left eye 1 hour after a first dose of sildenafil 50 mg (24). The same symptoms recurred on the next night, after a second dose of sildenafil. Fundoscopy a few days later showed an ischemic optic neuropathy.
- A 42-year-old man presented with anterior ischemic optic neuropathy, leading to a visual field defect in that eye within 24 hours of having taken sildenafil (25).

Anterior ischemic optic neuropathy is a disorder whose pathophysiology is poorly understood. The difference between the intraocular pressure and the perfusion pressure in the posterior ciliary arteries determines the circulation in the optic disc, and a reduction in this difference may contribute to ischemia.

Several other cases of non-arteritic ischemic optic neuropathy have been reported in men taking sildenafil (26,27).

Liver

- A 68-year-old man with alcoholic cirrhosis and small esophageal varices (degree of severity classified as Child I) started bleeding after taking sildenafil 25 mg for the first time (28).

Sudden overload of the portal venous system related to splanchnic vasodilatation was a possible provoking factor in this case. Gastroesophageal reflux secondary to a lower esophageal sphincter tone and causing mucosal erosion was an alternative explanation.

Sexual function

Whereas priapism has not been reported with sildenafil in controlled clinical trials, it is being mentioned in postmarketing drug surveillance programs, and two case reports have appeared in a healthy young man and a patient with sickle cell trait (29,30).

Death

There has been debate on the risk of death after sildenafil: can it be entirely attributed to co-existing cardiovascular disease with an inherent high risk of mortality, particularly during sexual activity, or does the drug contribute (31,32).

- A 44-year-old man developed an acute myocardial infarction after taking sildenafil but before sexual intercourse (33).

This case appears to point to the drug as a potential trigger in people with unknown critical coronary lesions

A postmarketing survey over the first 6 months of sales of sildenafil in the USA (April to the middle of November 1998) has reported details on 130 patients who died after having been given sildenafil (over 3.5 million having received a prescription for it). As expected, deaths were mostly cardiovascular. There was a close time relation to the administration of sildenafil (within 4–5 hours) in 44 patients, 27 of whom died during or immediately after sexual intercourse. The disturbing finding was that 16 men also either took or were given glyceryl trinitrate, contrary to product labeling and to several warnings (34). A survey conducted in the UK on recreational use of sildenafil among night-club customers detected combined use of sildenafil with amyl nitrate. As both drugs are vasodilators, combined use may expose users to the same risk as the combination with glyceryl trinitrate (35).

Long-Term Effects

Drug tolerance

Potential tachyphylaxis with long-term use of sildenafil has been discussed following a survey in which 200 patients were questioned twice, 2 years apart, about the effects of sildenafil; on the second occasion 20% of them reported needing an increased dose, and 17% had discontinued therapy because of lack of effect (36). However, others have commented that more likely reasons for the loss of effect over time included worsening of the disease (37–41), reducing testosterone concentrations with age (38,39), or lack of proper arousal (42). Although the mRNA for phosphodiesterase type 5 is down-regulated in the retina by long-term administration of sildenafil in rats (43), it is not known whether that happens in human corpus cavernosum, nor whether long-term sildenafil use is associated with tachyphylaxis.

Drug Administration

Drug overdose

A case of suspected overdose of sildenafil has been reported (44).

- A 56-year-old man with a history of diabetes mellitus and hypertension was found dead at home, with an empty package of sildenafil (12 tablets of 50 mg) near the body. The concentration of sildenafil in postmortem blood was high. Autopsy showed a dilated cardiomyopathy and diffuse coronary atherosclerosis, but an overdose of sildenafil was suspected to have provoked a fatal ventricular dysrhythmia.

Drug–Drug Interactions

Calcium channel blockers

Retrospective analysis of clinical trials has suggested that the concomitant use of antihypertensive drugs did not lead to an increase in adverse events in patients also taking sildenafil (45).

Hypertensive patients taking amlodipine, in contrast to glyceryl trinitrate, had only a minor supplementary fall in blood pressure when challenged with a single dose of sildenafil, and a few had a mild to moderate headache (46).

Diltiazem is metabolized by CYP3A4 and was held responsible for unanticipated prolonged hypotension after sublingual glyceryl trinitrate in a patient who underwent coronary angiography 2 days after last using sildenafil (47).

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Indinavir

A drug interaction between sildenafil and HIV antiretroviral drugs is suspected, since both are metabolized by and act as inhibitors of the same cytochrome P450 isoforms (48). A pharmacokinetic study of sildenafil in HIV-positive patients taking indinavir has shown that the AUC of sildenafil was 4.4 times higher than data from historical controls (49). The magnitude of the interaction suggested that a lower starting dose of sildenafil may be more appropriate in patients taking indinavir.

Nitrates

The concomitant use of nitrates and sildenafil can precipitate a hypotensive reaction, and this combination should therefore be avoided (50,51). More than 3.6 million prescriptions for sildenafil were issued as of August 1998; of 69 deaths, 12 were attributable to the interaction with nitrates, as reported to the FDA.

Potentiation by sildenafil of the hypotensive effects of glyceryl trinitrate and amlodipine has been investigated. The fall in systolic blood pressure with glyceryl trinitrate was amplified four-fold by sildenafil in healthy subjects.

The pressure-lowering effect of a step-wise intravenous infusion of glyceryl trinitrate was significantly increased in 12 healthy volunteers treated for 4 days with sildenafil 25 mg tds; episodes of symptomatic hypotension were also more frequent with sildenafil (52). When sublingual glyceryl trinitrate was used, the reduction in systolic blood pressure was fourfold greater in association with sildenafil.

Tacrolimus

The effects of sildenafil can be potentiated by drugs that are metabolized by CYP3A4. Tacrolimus is an example. When sildenafil was given to patients with kidney transplants taking regular tacrolimus, peak concentrations were much higher and the half-life much longer than expected from data in healthy volunteers (53). However, an effect of the underlying disease and other concomitant drugs obviously could not be excluded.

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Silicone

General Information

Silicones are polymers of alternating atoms of silicon and oxygen, whose viscosity depends on the molecular weight: the longer the molecule the more viscous.

When silicones were used for the first time, more than 35 years ago, they were proposed as excellent, inert, seemingly harmless compounds (1) and they have been used in various medical applications, including the construction of joint prostheses and breast implants and in tissue augmentation procedures. However, reports of silicone-induced granulomatous reactions in man and animals subsequently appeared (2,3) and silicones were prohibited in many countries as cosmetic materials. However, silicones are nevertheless still used (4). The FDA has issued a ruling requiring the filing of a premarket approval application or a notice of completion of a product development protocol for silicone inflatable breast prostheses, a generic type of medical device intended to or reconstruct the female breast. This device is made of a silicone shell that is inflated with sterile isotonic saline (5). The agency has taken this action because the requirement of premarket approval will provide an opportunity to assess more fully the risks and benefits of these devices, in order to determine whether there is reasonable assurance of their safety and effectiveness, or what regulatory course should be taken in the absence of such assurance. Silicone gel-filled breast prostheses have already been subjected to this requirement.

Local complications have been associated with both types of breast prostheses, including rupture, pain, capsular contracture, disfigurement, and serious infection, which may lead to medical interventions and repeated surgery. The practice of injecting liquid silicone has largely been abandoned by plastic surgeons (6), but unfortunately there are still people who perform these injections injudiciously (7).

- A 26-year-old male-to-female transsexual received an injection of 100 ml of liquid silicone of unknown grade into her upper lateral thighs to gain female contours (8). Four years later she developed pain and a massively swollen right ankle with signs of inflammation. An MRI scan showed massive diffuse and localized silicone infiltration throughout the soft tissues of the legs.

This case provides further evidence that severe morbidity can be associated with the subcutaneous injection of large volumes of liquid silicone.

Silicone implants sometimes provoke systemic adverse effects. More than 20 women developed muscle pain, joint pain and swelling, pulmonary disease including pleural effusions, pulmonary infiltrates, and reduced pulmonary diffusing capacity, dry eyes, dysphagia, bladder dysfunction, neurological abnormalities, and skin disease (including localized and diffuse scleroderma-like changes) (9).

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Organs and Systems

Sensory systems

Silicone oil injection has been used to treat retinal detachment. Six patients who had had previous silicone oil injection had the oil extracted, partial introduction of perfluorocarbon liquids, extraction of epiretinal membranes, endodiathermy, retinotomy, retinectomy, complete filling of the intraocular cavity with perfluorocarbon, endophotocoagulation, and silicone oil injection (10). All maintained the reattached retina. One developed a macular epiretinal membrane. Another developed a macular epiretinal membrane with subfoveal perfluorocarbon and a relapse of the retinal re-detachment when the silicone oil was extracted and it had to be re-introduced. Four of the patients developed different degrees of cataracts; the other two were aphakic.

Other reported complications include pupillary block glaucoma, secondary glaucoma, and corneal complications, including band-shaped keratopathy (11). Pupillary block in aphakic eyes can be prevented by placing peripheral iridectomy at the 6 o'clock position, since silicone is lighter than water.

After silicone injection, glaucoma is more common in diabetic aphakic eyes than in phakic or non-diabetic eyes; on the other hand, corneal complications are less frequent in diabetic than in non-diabetic eyes; in non-diabetic eyes the complications are more frequent in aphakic than in phakic eyes (11). In a 2-year-follow up study of 105 eyes (including 27 aphakic eyes), operated on for retinal detachment by silicone oil injection after pars plana vitrectomy, cataract was a constant complication in all phakic eyes (12). Intraocular hypertension was common in both phakic and aphakic eyes (30 and 33% of cases respectively) and responded poorly to medical or surgical treatment. Other complications occurred less often; they were corneal edema, conjunctival hyperemia, and uveitis. Pain required evisceration of 2 eyes.

A heavier-than-water fluorinated silicone oil was used in the treatment of 30 selected cases of complicated retinal detachment due to proliferative vitreoretinopathy ($n = 19$), proliferative diabetic retinopathy with traction detachment ($n = 2$), giant retinal tears ($n = 5$), ruptured globe with retinal detachment ($n = 2$), massive choroidal effusion with retinal detachment ($n = 1$), and acute retinal necrosis with retinal detachment ($n = 1$) (13). Initial retinal reattachment was achieved in all cases. Complications included redetachment ($n = 7$), cataract ($n = 6$), raised intraocular pressure ($n = 4$), hypotony ($n = 4$), keratopathy ($n = 3$), uveitis synechia formation ($n = 3$), phthisis ($n = 2$), choroidal hemorrhage ($n = 1$), and vitreous hemorrhage ($n = 1$).

Skin

Foreign body giant cell granulomas were first reported after liquid silicone injection in 1965 (14) and are usually observed near silicone-injected areas (15). There have been many reports of cysts and granulomatous reactions to silicone at application sites and distal sites after hematogenous or lymphatic migration (15–17).

- An otherwise healthy 59-year-old woman had received acupuncture for a sprained ankle several times over the previous year (18). She had numerous 2–5 mm waxy orange-brown papules on the dorsal aspects of both feet and ankles. A punch biopsy of one of these showed a mixed lichenoid, spongiotic, and granulomatous dermatitis. Macrophages, including many foreign body-type giant cells, were arranged in a granuloma annulare-like pattern around dermal collagen with focal mucinous alteration. Ultrastructural examination showed macrophages containing amorphous foreign material consistent with silicone. The acupuncturist had switched to silicone-plated acupuncture needles over the recent months, and she was believed to have cutaneous granulomas secondary to silicone deposition (18). She was treated with potent topical steroids and continued acupuncture with non-coated needles. The lesions slowly resolved over the ensuing months.

This case raises the possibility of silicone deposition from cutaneous manipulation with silicone-coated instruments over a relatively short duration of time. In addition, the case is remarkable in that the latency from exposure to the foreign material to the onset of lesions was relatively short (6–12 months).

Facial granulomatous lesions and a connective tissue-like disorder have been attributed to silicone deposition following injection of silicone into the breasts (19).

- A 56-year-old Japanese woman developed eyelid edema and erythema on her face and arms and 2 weeks later annular erythema on both arms, sicca syndrome, and progressive loss of sweating on her forehead. Laboratory studies, including muscle enzymes, antinuclear antibodies, and serum immunoelectrophoresis, were unremarkable. One month later, she developed skin lesions around the eyelids that resembled lupus miliaris disseminatus faciei. A biopsy showed non-caseating epithelioid granulomas in the mid-dermis, especially around the sweat glands. A CT scan of the chest showed fibrous implant capsules in each breast, due to silicone injections 30 years before. Electron microscopy of a nodule from the lower eyelid showed particles of silicone within the granulomas. The silicone was thought to have been derived from the material that had been injected into her breasts. After subcutaneous mastectomy and axial lymphadenectomy the facial edema disappeared rapidly, but the nodules remained.

Silicone gel breast prostheses are associated with a mild foreign body response resulting in the formation of a collagenous capsule around the prosthesis (20,21). Although many such patients may have evidence of a microscopic granulomatous foreign body reaction on examination of the capsular material at explantation of a prosthesis, it is unusual to have large palpable granulomas, even in the presence of rupture or leakage (22). Nevertheless, rare patients have had severe local inflammation and complications resulting from silicone migration to the axilla, arm, or abdominal wall (23,24). Three patients had significant problems with deforming granulomas after implant rupture (25). More importantly, they suffered the consequences of silicone gel migrating down the arm. Once silicone gel leaves the implant it is not biologically inert and in some people it can elicit profound pathological responses.

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Silicone granulomas are usually observed near silicone-injected areas (15).

Siliconized dressings can cause pigmentation abnormalities (26).

Musculoskeletal

Foreign-body reactions to silicone can complicate silicone elastomer joint prostheses, manifesting as synovitis and/or lymphadenopathy, sometimes at remote locations (27).

Silicone can cause fibromyalgia (SEDA-22, 526).

Immunologic

There is a possible association between silicone breast implants and underlying connective tissue diseases (9,28–30).

In patients with symptoms of connective tissue diseases it has been assumed that rupture of the gel-filled prosthesis was the most likely cause of the symptoms. Although the prosthesis was intact in some patients, amorphous silicone-like material was identified by light microscopy in surgically removed fibrous tissue. In one study (31), granulomatous inflammatory reactions developed when silicone elastomers were used as skin expanders. This was attributed to leakage of particles of the plastic material through the expander wall. Lymphadenitis and destructive synovitis following silicone implants (especially joint prostheses) have been described before (32,33), while use of silicone in dialysis tubing also led to dissemination of silicone causing splenomegaly and deposits in liver, bone marrow, skin and visceral lymph nodes. Exposure for less than 53 months did not elicit these complications (34,35).

Immunological abnormalities in the form of increased autoantibodies, specifically antinuclear antibodies, antithyroid antibodies, rheumatoid factor, and increased immune complexes, have been evaluated and documented (36). In addition, abnormalities in lymphocyte subsets have been reported, with reduced lymphocytic mitogenic response, as well as abnormalities in the ratios of T-helper to T-suppressor cells (37). Several mechanisms have been suggested, among them that silicone oozes through the intact capsule of the implants, enters the lymphatic system, and causes an immunological reaction (38); this reaction causes further development of autoimmune disease through an adjuvant effect, with possible immune dysregulation (39).

More evidence for the antigenicity of silicone has been provided in studies that have shown specific silicone antibodies directed against silanized albumin in the sera of two patients exposed to silastic tubing (40). In 520 patients, aged 28–65 years, who had had silicone breast implants for 3–22 years, the most common symptoms were fatigue (96%), myalgia (86%), morning stiffness (86%), insomnia (77%), attention deficit (74%), night sweats (43%), cervical lymphadenopathy (78%), and axillary lymphadenopathy (55%).

Clinical, histopathological, and fibroblast studies have been carried out in 30 patients given subcutaneous injections of silicone (41). The mean time between the injection and the onset of symptoms was 6 years. All the patients had sclerodermatous skin changes, subcutaneous nodules, edema, and/or hyperpigmentation at the site(s) of injection(s); five individuals also had skin changes at sites far from the injection; 13 patients had clinical features of an autoimmune disease; 11 patients gave a history of arthralgias, including four who had symmetrical non-erosive polyarthritis; 20 of 28 patients had positive antinuclear antibodies. This report confirms the association between the injection of silicon and the development of autoimmune disease (human adjuvant disease). Pneumonitis and pulmonary edema following subcutaneous injection of silicone have been reported earlier (42–44).

In an evaluation of the frequency and clinical characteristics of the underlying connective tissue disorders associated with silicone breast implants, 300 women with silicone breast implants were studied (45). In addition to a history and physical examination, C reactive protein, rheumatoid factor, and autoantibodies were determined. Criteria for fibromyalgia and/or chronic fatigue syndrome were met by 54%; connective tissue diseases were detected in 11%; and undifferentiated connective tissue disease or human adjuvant disease in 10.6%. A variety of disorders, such as angioedema, frozen shoulder, and a multiple sclerosis-like syndrome, were also found. Several other miscellaneous conditions, including recurrent and unexplained low grade fever, hair loss, skin rash, symptoms of the sicca syndrome, Raynaud's phenomenon, carpal tunnel syndrome, memory loss, headaches, chest pain, and shortness of breath were also seen. Of 93 patients who underwent explantation, 70% reported improvement in their systemic symptoms.

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Silver salts and derivatives

General Information

Silver is a white precious metal (symbol Ag; atomic no. 47). The symbol derives from the Latin word argentum. It is found in various minerals, including argyrodite, cerargyrite, chlorargyrite, dyscrasite, iodyrite, and sylvanite.

Silver compounds are still used in medicine to a limited extent, notably in dermatological formulations, nose-drops,

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and eye-drops, the essential effect being to precipitate protein. If sufficient silver is absorbed, for example from long use or application to extensive burns, there can be accumulation in many tissues (1). Although silver is well tolerated, the frequency of exposure results in frequent reports of complications (SEDA-22, 250).

Silver nitrate

Silver nitrate is used as a caustic, antiseptic, and astringent agent. The silver ion is precipitated by the chloride in tissue fluids, so that it does not readily penetrate.

Silver nitrate is effective in vitro against *Neisseria gonorrheae* and *Staphylococcus aureus* in a concentration of about 0.1% and against *Escherichia coli* in a concentration of about 0.01%. It is effective in vivo against most strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* and also has activity against *Pseudomonas aeruginosa*, but is less active against other gram-negative species, such as *Enterobacter* and *Klebsiella* (2). It does not penetrate eschar to any significant degree. The non-histotoxic concentrations of 0.5% used in burns are bacteriostatic. Thick cotton dressings saturated with the solution are applied to thoroughly debrided areas. The dressings must be re-wetted every 23 hours with fresh solution to prevent development of histotoxic concentrations over 2% at the wound surface. In the treatment of burns, silver nitrate has been largely replaced by silver sulfadiazine.

Silver sulfadiazine

Silver sulfadiazine (3) is a white, highly insoluble compound synthesized from silver nitrate and the sulfonamide sodium sulfadiazine. It is used in burns as a 1% formulation in a water-soluble cream base. It has in vitro activity against a wide range of burn wound microbial pathogens, including *S. aureus*, *E. coli*, *Klebsiella* species, *P. aeruginosa*, *Proteus* species, other Enterobacteriaceae, and *Candida albicans*. Its penetration into eschar is considered to be better than that of silver nitrate. Silver from silver sulfadiazine cream is rapidly absorbed and deposited in large amounts throughout the body (4).

Uses of silver compounds

Silver nitrate and silver sulfadiazine are used to treat burns (5,6).

Ophthalmic use of silver nitrate solution for prophylaxis of ophthalmia neonatorum due to gonorrhea should be considered as obsolete; silver nitrate is highly irritant and antibiotics provide better alternatives.

Silver is used in various medical devices. There is concern about the use of silver-containing formulations of uncontrolled composition (for example colloidal silver) with supposed activity in a host of microbial diseases. Despite the supposed anti-infective efficacy of silver-coated medical prostheses, in the majority of studies these prostheses have not been proven to be infection-resistant (7).

Silver fluoride has been used in dental care for the treatment of deep caries. However, application of 40% silver fluoride to deep carious lesions or its use as a spot application agent can cause 3–4 mg of fluoride to reach the systemic circulation (8). It has therefore been suggested that solutions of lower strength (1–4%), which may be as effective as a 40% solution, should be used. Similarly, the high concentration is contraindicated in children because of systemic access of fluoride (9).

Silver has been used in anti-smoking formulations designed to alter taste sensation. In 21 adults who use silver acetate chewing gum for 12 weeks as a smoking deterrent, serum concentrations of silver rose and quickly returned to normal after withdrawal (10). In most cases the number of silver granules in skin biopsies, observed by autometallography, increased after the gum had been used for 12 weeks. However, no-one developed clinical signs of argyria.

Over-the-counter products containing colloidal silver or silver salts have been marketed for use in adults and children for a wide variety of diseases, including AIDS, cancer, tuberculosis, malaria, systemic lupus erythematosus, syphilis, scarlet fever, herpesvirus infections, pneumonia, typhoid, tetanus, and many others. The US Food and Drug Administration has issued a ruling that a colloidal silver product for any medical use will first have to be approved by the FDA under drug application procedures (11).

Argyria

Argyria is a characteristic smoke-gray discoloration of the skin and a bluish discoloration of the mucous membranes reminiscent of cyanosis (12,13). The discoloration is permanent. The deposited pigment may be partly silver sulfide and partly metallic silver, formed by photoactivated reduction.

Accumulation in the deeper tissues occurs at the same time, but as a rule has no clinical consequences (14). One disputed report dating from 1984 (15) concerned two patients with what was regarded as systemic argyria following the uncontrolled use for several years of nose-drops containing silver salts; they had dyspnea, palpitation, weakness, a slightly reduced CO_2 diffusion capacity and in one case "functional adrenal hypofunction."

Delayed wound healing has been suggested as one adverse effect of presence of silver in the system.

Argyria has followed the use of dietary supplements containing colloidal silver protein (16).

- A 56-year-old man developed blue color changes of his fingernails. His face had a dusky appearance, and there was no scleral or conjunctival discoloration or hyperpigmentation of the gums. His fingernails had a blue-gray proximal band of discoloration, as did the lunulae of both thumbnails. His toenails were not involved and the rest of his skin showed no discoloration. His serum silver concentration was 85 (reference range below 5) ng/ml. He had taken colloidal silver for the previous 3 years as an allergy and cold medication, following the recommended regimen of 1 teaspoon of a 200 ppm silver solution tds.

Generalized argyria has occurred in patients treated with eye-drops containing silver nitrate. In one case the diagnosis was confirmed by a skin biopsy showing deposits of metallic silver in the dermis (17). Argyria should be considered in the differential diagnosis of focal pigmented conjunctival lesions (18).

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- An 82-year-old woman with strabismus amblyopia, for which she had had surgery as a child, developed an asymptomatic pigmented conjunctival lesion in the right eye, mainly involving the underlying subconjunctival connective tissue and the insertion of the lateral rectus muscle; there was no scleral thinning. Biopsy of the conjunctiva and lateral rectus muscle showed numerous extracellular black pigment granules, many of which were aligned in a linear array along the muscle fibers. Energy dispersive X-ray microanalysis showed the pigmentation to be due to silver deposits. During strabismus surgery a silver clip had probably been used to shorten the lateral rectus muscle.

Vaginal argyria has been attributed to a combination of silver sulfadiazine and Aci-Jel (a buffered acid jelly containing acetic acid) (19).

- A 67-year-old woman with a sore vulva applied Flamazine cream (containing 1% silver sulfadiazine) topically for nearly 10 years and then Aci-Jel. She developed widespread black deposits in the vagina consistent with argyria. There were dark pigmented areas around the urethral meatus, Skene's ducts, and hymeneal remnants, and a circumferential deposit around the upper third of the vagina. Biopsies showed mild acanthosis and a mild chronic inflammatory infiltrate in the upper dermis, with black pigment granules 0.5–2 μm in size in the superficial dermis. Electron probe analysis confirmed the presence of silver. The creams were withdrawn and 6 months later the vagina showed no signs of argyria.

It is likely that reducing agents in the gel base of Aci-Jel interacted with the silver sulfadiazine, causing deposition of silver and discoloration of the vagina.

- A patient with schizophrenia developed systemic argyria from chronic and excessive ingestion of an anti-smoking formulation that contained silver (20). Seizures developed after he had taken the pills for 40 years. There was an extremely high concentration of silver in the serum.

The authors suggested that systemic silver can cause seizures.

Argyria and hepatotoxicity has been reported after the use of a silver-coated wound dressing, Acticoat, in the treatment of 30% mixed depth burns in a 17-year-old boy (21). Silver concentrations were high in the plasma (107 μg/kg) and urine (28 μg/kg).

Organs and Systems

Cardiovascular

A chronic inflammatory reaction in a prosthetic valve has been attributed to silver (22).

- A prosthetic mitral valve (St Jude Medical Silzone) that had been implanted in a 72-year-old woman became partially detached 4 months later, causing acute cardiac failure. The mitral annulus was ulcerated and there were multiple erosions in the tissues in contact with the valve. Histology showed chronic inflammation, with hemosiderin deposits and giant cells. She was not allergic to silver.

The silver-coated sewing cuff had caused a chronic inflammatory reaction because of a toxic reaction to silver. The Silzone valve was withdrawn from the market in January 2000.

Nervous system

Peripheral neuropathy from long-term treatment of venous leg ulcers with silver sulfadiazine cream has been observed in one patient (13).

Sensory systems

The use of 1% silver nitrate eye-drops in prophylaxis of ophthalmia neonatorum has been periodically reviewed and compared with other prophylactic measures. There seems to be no case in which permanent damage to the eye was actually proven to have been caused by a single application of a correctly used 1% silver nitrate solution (23). However, silver nitrate has largely been replaced by antimicrobial drugs.

The reaction of the tissues in the front of the eye during the first 5 days after delivery has been examined in a double-blind study in 40 neonates with and without prophylaxis with silver nitrate solution (24). There was no significant difference in the frequency of pathological changes in the palpebrae, conjunctiva bulbi et tarsi, or cornea between the two groups and the same frequency of palpebral edema and conjunctival hyperemia. Repeated application of silver nitrate solutions in low concentrations can cause discoloration of the conjunctiva due to argyria (25).

Several cases of chemical burns of the eyes in newborn babies have been reported (26) but most of these complications followed incorrect administration of the formulation.

The clinical significance and incidence of chemical conjunctivitis due to silver nitrate has been investigated in 1000 newborn infants (27). Rinsing after instillation does not reduce the conjunctival irritation. Although 90% of the infants had conjunctivitis in the first 6 hours of life, in most cases it cleared within 24 hours. Chemical conjunctivitis did not increase the incidence of secondary infections. In 1980 the American Academy of Pediatrics pointed out the need for continued prophylaxis for all newborn infants, and proposed a 1% silver nitrate solution in single dose ampules or single-use tubes of an ophthalmic ointment with 1% tetracycline or 0.5% erythromycin. However, in infants of mothers with clinically apparent gonorrhea aqueous crystalline penicillin G should be injected.

In a double-blind, controlled study of a possible causal relation between 1% silver nitrate solution and 1% tetracycline solution in prophylaxis of ophthalmia neonatorum there was no statistically significant difference in the incidence of nasolacrimal duct obstruction between the two groups at either 2 weeks or 2 months of age (28).

Concentrations of silver nitrate of 5–50% applied accidentally to the eye have caused severe injuries with permanent corneal opacification and cataract in some cases (25).

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Psychological, psychiatric

In one case there was a rapid decline in mental function at silver concentrations of 191 ng/ml, but the patient was seriously ill in other respects and although high concentrations of silver were found in the brain postmortem, it is not at all clear that the silver was responsible for the mental state (29).

Nutrition

Failure to thrive in a child has been attributed to silver toxicity (30).

- A 12-month-old girl with failure to thrive had been treated with various supplements and alternative therapies (including a blend of kelp, *Lactobacillus acidophilus*, wheat, rye, and barley) or colloidal silver. The silver was given in the form of a suspension and was thought to be effective in boosting immunity. The serum silver concentration was 3.4 (reference range below 0.02) μmol/l. Silver was withdrawn and her serum silver concentrations normalized some months later.

Electrolyte balance

Electrolyte disturbances are the major adverse effect of the use of silver nitrate in burns, since the distilled water vehicle used to carry the silver nitrate is hypotonic, and since the silver salts that are formed in the tissues, primarily silver chloride and silver sulfide, are insoluble (31). The hypotonicity produces absorption of large amounts of water into the body, with a dilutional effect and the leaking of significant quantities of body minerals, including sodium, potassium, magnesium, calcium, and chloride. Deficiency of chloride is caused by the formation of silver chloride on the treated surface. Up to 350 mmol/day of sodium can be lost per square meter of treated body surface area. Problems occur particularly in patients with burns that exceed 20% of the body surface and in infants, unless a regular replacement schedule is established. Maximum deficiency can occur within a matter of 6–8 hours after the start of therapy. Continuous oral or intravenous electrolyte supplementation and careful monitoring of electrolyte balance are necessary.

Hematologic

Methemoglobinemia due to silver nitrate occurs via bacterial reduction of nitrate to nitrite, which is subsequently absorbed (32). The diagnosis should be suspected if the skin or blood appears cyanotic or gray in the presence of normal arterial PO_2. The diagnosis should always be confirmed with measurement of blood methemoglobin concentration. In the treatment of burns with silver nitrate solutions, the possible occurrence of methemoglobinemia must be considered, especially when organisms are cultured from the wounds. The silver nitrate should be withdrawn if this complication occurs. Treatment of the methemoglobinemia with reducing agents is rarely required.

- Fatal methemoglobinemia occurred in a 3-year-old Caucasian girl who had burns involving 82% of the body surface and had been treated by painting the burns with silver nitrate solution (33). By the fourth day, low-grade fever was evident and *Aerobacter cloacae*, which was resistant to silver nitrate 0.5%, was cultured from the scar tissue. The child became cyanotic and died after 27 days. Methemoglobin constituted 70% of her hemoglobin; there was no other evident cause of death. The *A. cloacae* cultured from the skin was tested and reduced nitrate to nitrite.
- A 12-month-old girl, with necrotizing fasciitis at the site of a cutaneous infection on her left trunk, became unresponsive, lethargic, and in shock, and underwent immediate aggressive tissue debridement (34). Later wound irrigation was carried out with a solution of silver nitrate 0.5% and 20 days later she became cyanotic and dyspneic. Her methemoglobin concentration was 38%. Intravenous methylene blue restored her oxygen saturation and reduced the dyspnea and cyanosis. Her methemoglobin concentration fell to 0.8%.

Transient leukopenia with a disproportionate reduction in neutrophilic leukocytes has been reported during treatment with sulfadiazine silver (35). This adverse effect appears to run a typical course: sulfadiazine-induced leukopenia reaches a nadir within 2–4 days of starting therapy, with a characteristic fall in the neutrophil count and a relative increase in the number of band forms. The erythrocyte count is not affected. By 2–3 days after the onset of leukopenia, the leukocyte count returns to normal. The leukocyte count tends to recover whether or not the silver sulfadiazine is withdrawn and may also be an intrinsic response to burn injury and unrelated to the use of silver sulfadiazine.

The use of silver sulfadiazine has been associated with acute hemolytic anemia (22).

Fatal pancytopenia has been reported from the extensive use of topical silver sulfadiazine.

- An 11-month-old infant with second- and third-degree burns over 30% of the body was treated topically with silver sulfadiazine (36). From day 2 there was significant neutropenia, maximal at day 3. The silver sulfadiazine was withdrawn. The neutropenia was followed by anemia, which was maximal on day 5. Finally, thrombocytopenia developed. In spite of blood transfusions and recovery of the neutropenia and thrombocytopenia, infection occurred and the patient died from respiratory failure.

Mouth and teeth

In one case severe ulceration of the anterior ventral surface of the tongue was caused by ill-advised cautery of a small ulcer with a silver nitrate stick (37). Only silver nitrate solutions of 5–10% should be used to cauterize mucous membranes or when a strong germicidal action is desired.

Urinary tract

Intrapelvic instillation of silver nitrate is sometimes still used in the treatment of essential hematuria. In one case ureteric stenosis developed as a consequence (38).

Nephrotic syndrome following topical therapy with silver sulfadiazine has been reported once (39).

Anuria has occurred after silver nitrate irrigation for intractable bladder hemorrhage caused by cyclophosphamide chemotherapy (40). The level of obstruction was the ureterovesical junction on the one hand, and the collecting ducts of the renal papillae on the other. Therapy

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consisted of rigorous endoscopic evacuation of deposited coagulate from the bladder, after which the urinary output rapidly returned to normal.

Skin

Three infants treated for umbilical granuloma with silver nitrate suffered chemical burns to the periumbilical area; conservative treatment led to good outcomes (41).

- A 29-year-old woman complained of increasing black discoloration of the tip of her left middle finger, resembling gangrene (42). She had been applying silver nitrate to her finger for the treatment of a small granuloma and had developed localized tissue necrosis, secondary to application of the silver nitrate, on withdrawal of which she recovered completely.

In consequence, it is recommended that the practice of unsupervised local application of silver nitrate to the fingers should be discontinued.

Höllensteinstift 10 (Pharma Winter, Leipzig, Germany) is a stick that contains 90% silver nitrate and 10% potassium nitrate, and has corrosive, germicidal, and astringent characteristics; it is used in the treatment of hypergranulation and common warts.

- A 28-year-old woman used Höllensteinstift 10 inappropriately (43). Intending to treat her periorbital folds, she removed the outside layer of paraffin, moistened the tip, and applied the stick to the lower parts of the lids, accidentally transferring parts of the corrosive agent to the skin in the periorbicular region. After some time, she felt a burning sensation, rinsed her face with water, and so distributed the agent widely to both cheeks and increased the pain. Self-treatment with several ointments did not bring relief. On the next day she developed brown discoloration of the facial skin, particularly in the periorbital region, pain, and torsion of the skin in the affected area. Initial treatment consisted of soap solution (to wash out the silver particles) and panthenol ointment (to support the process of healing). The lesions disappeared completely.

Cutaneous sensitivity reactions, typically maculopapular rashes, occur in under 5% of patients who use silver sulfadiazine and rarely require withdrawal (44).

Immunologic

A meta-analysis of the clinical and economic effects of chlorhexidine and silver sulfadiazine antiseptic-impregnated catheters has been undertaken (45). The costs of hypersensitivity reactions were considered as part of the analysis, and the use of catheters impregnated with antiseptics resulted in reduced costs. The analysis used the higher estimated incidence of hypersensitivity reactions occurring in Japan, where the use of chlorhexidine impregnated catheters is still banned (46).

Susceptibility Factors

Renal disease

If silver sulfadiazine is used in a patient with impaired renal function, accumulation of silver can occur.

- In a patient with end-stage renal disease, there was a marked increase in serum silver concentration during treatment with silver sulfadiazine cream 200 g/day for 2 weeks (29). The serum concentration of silver reached a maximum of 291 ng/ml and there was rapid deterioration of mental status. Silver sulfadiazine was withdrawn, but the patient died after 4 months. At autopsy, there were very high concentrations of silver in the brain tissues (617 and 824 ng/g in the cerebrum and cerebellum respectively).

In this patient both plasma exchange and hemofiltration were effective in reducing the serum silver concentration, and their effects were additive, but hemodialysis was ineffective. However, none of these maneuvers affected brain silver concentrations.

Drug Administration

Drug formulations

A modification of silver sulfadiazine by the incorporation of cerium nitrate is believed to enhance its efficacy. In 60 patients with moderate and severe burns randomly assigned to topical silver sulfadiazine either alone ($n = 30$) or in combination with cerium nitrate ($n = 30$), there were four deaths in those who were given sulfadiazine alone and only one in those who were given the combination (47). Wound infection did not differ significantly between the groups. The rate of re-epithelialization of partial thickness burns was faster by 8 days in those given the combination, and the relatively dry shell-like eschar allowed planned excisions with immediate autologous grafting and the tissue underneath was ready to accept grafting 11 days earlier. There was a higher incidence of transient stinging pain with the combination, but this was effectively managed with analgesics when necessary.

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Simvastatin

See also HMG Co-A reductase inhibitors

General Information

Simvastatin is an HMG Co-A reductase inhibitor. Its most serious adverse effect is rhabdomyolysis, which is enhanced by other drugs that inhibit CYP3A4 (1).

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Organs and Systems

Cardiovascular

Transient hypotension attributable to simvastatin may have been related to reduced production of corticosteroids (2).

Respiratory

Hypersensitivity reactions can occur with statins (SEDA-13, 1328) (3), and an otherwise unexplained case of interstitial lung disease and pleural effusion developed during treatment with simvastatin for 6 months; the number of eosinophils in the bronchoalveolar lavage fluid normalized a few days after withdrawal (4).

Psychological, psychiatric

In the 4S study there were five suicides in the simvastatin group and four in controls (5).

Endocrine

In 521 patients taking simvastatin 40–80 mg/day, serum cortisol concentrations were on average reduced by 3–7% (6). In the men there was a 10% fall in serum testosterone. However, there were no reports of sexual dysfunction.

Simvastatin up to 40 mg/day was given to 98 boys and 75 girls, aged 10–17 years, for 48 weeks without any adverse effects beyond a small fall in dehydroepiandrosterone (7). Of special note was the observation that simvastatin had no adverse effects on growth or pubertal development.

Metabolism

- A 53-year-old man taking simvastatin 40 mg/day developed rhabdomyolysis and hepatitis and had a raised serum lactate concentration (8.3 mmol/l; reference range 0.5–2.2) (8). Everything resolved 7 days after drug withdrawal.

Lactic acidosis in this patient supports the view that interference with the mitochondrial respiratory chain may play a role in the toxicity of the statins.

Hematologic

Thrombocytopenia is a rare adverse effect of simvastatin (9).

- Severe thrombocytopenia occurred in a 75-year-old woman taking simvastatin 5 mg/day and was resistant to therapy until she developed pneumonia. Recovery from the thrombocytopenia coincided with an increased interleukin concentration in the blood (10).
- There was a close temporal association with thrombotic thrombocytopenic purpura in a 43-year-old man after his second dose of simvastatin (11).

Other cases have been reported (12–15).

Liver

Cholestatic hepatitis occurred in a man with cirrhosis of the liver given simvastatin 20 mg/day (16).

Pancreas

Pancreatitis has been reported with simvastatin (17–22).

Urinary tract

It has been claimed that physicians should bear in mind the nephrotoxic potential of this drug (23), but there is no definite evidence that simvastatin is associated with the development of proteinuria (24).

Skin

- A 66-year-old man had persistent photosensitivity after using simvastatin intermittently (25). The clinical, histopathological, and photobiological features met the criteria for chronic actinic dermatitis.

Musculoskeletal

Rhabdomyolysis has been reported in patients taking simvastatin (26,27). Of 66 patients who took simvastatin for 1 year, two had myalgia and weakness with creatine kinase activity above 3000 (normally less than 100) (28).

- Simvastatin 5 mg/day caused rhabdomyolysis in a 61-year-old man not taking interacting drugs (29).

In a meta-analysis of megatrials with simvastatin, the overall incidence of myopathy was 0.025% (30). The authors suggested that potent inhibitors of CYP3A4 greatly increase the risk, but that weak inhibitors do not. Episodes of gout occurred in three of nine patients with chronic renal insufficiency who took simvastatin (31).

Immunologic

Lupus-like syndrome has been associated with simvastatin, with antibodies to double-stranded DNA in the serum (32).

- Simvastatin-induced lupus erythematosus was suspected in a 79-year-old white man after 3 months (33). He had signs of pleuropericarditis that resolved within 2 weeks of withdrawal.

Second-Generation Effects

Teratogenicity

Of 169 women exposed to simvastatin during pregnancy, three delivered babies with malformations and there were two fetal deaths (34). These results are comparable to what would be expected in the general population. However, based on a general consideration of risk, statins should not be used during pregnancy and only in exceptional circumstances should they be given to any woman of childbearing age.

Drug–Drug Interactions

Calcium channel blockers

In a meta-analysis of megatrials of simvastatin, the overall incidence of myopathy was 0.025%; the same proportion of those with myositis had used calcium channel blockers as the proportion overall, suggesting that there is no important interaction between these two groups of drugs (30).

However, diltiazem interacts with lovastatin although not with pravastatin (SEDA-24, 511), and an interaction has also been observed with simvastatin in a 75-year-old

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man who developed impaired renal function (35). He had extreme weakness and muscle pain.

Ciclosporin

In a patient with glucocorticoid-resistant nephrotic syndrome taking simvastatin and ciclosporin, there was an increase in lactic dehydrogenase activity, suggesting tissue injury, in the absence of an increase in creatine kinase (36).

Clarithromycin

Lovastatin has been reported to interact with clarithromycin (SEDA-14, 1531) (37), and a similar reaction has been observed with simvastatin (38).

- A 64-year-old African-American man developed worsening renal insufficiency, raised creatine kinase activity, diffuse muscle pain, and severe muscle weakness. He had been taking simvastatin for about 6 months and clarithromycin for sinusitis for about 3 weeks. He was treated aggressively with intravenous hydration, sodium bicarbonate, and hemodialysis. A muscle biopsy showed necrotizing myopathy secondary to a toxin. He continued to receive intermittent hemodialysis until he died from infectious complications 3 months after admission.

Gemfibrozil

- Severe rhabdomyolysis occurred in a 52-year-old woman taking a combination of gemfibrozil and simvastatin (39).

Grapefruit juice

Simvastatin should be avoided in patients using grapefruit juice (40).

Itraconazole

Itraconazole probably inhibits simvastatin metabolism (SEDA 21, 459).

Rifamycins

Rifampicin greatly reduced the plasma concentrations of simvastatin and simvastatin acid in 10 healthy volunteers in a randomized, crossover study (41). Because the half-life of simvastatin was not affected by rifampicin, induction of CYP3A4-mediated first-pass metabolism of simvastatin in the intestine and liver probably explains this interaction.

Warfarin

An interaction with warfarin with resulting acute rhabdomyolysis has been observed in a patient taking simvastatin (42). This has not been observed with other statins.

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Sirolimus

General Information

Sirolimus is a macrocyclic lactone immunosuppressant that has anti-rejection activity through inhibition of T cell activation. In contrast to tacrolimus and ciclosporin, sirolimus has no effect on calcineurin activity.

Sirolimus is being investigated for the prophylaxis of renal rejection in combination with ciclosporin and glucocorticoids (1).

Comparative studies

In a 12-month study in 719 patients with renal transplants, the combination of sirolimus, ciclosporin, and prednisone in 558 patients (284 taking sirolimus 2 mg/day and 274 taking 5 mg/day) produced significantly more acne, diarrhea, dyslipidemia, headache, hirsutism, hyperkalemia, hypertension, lymphocele formation, and thrombocytopenia compared with 161 patients who took azathioprine, ciclosporin, and prednisone (2). Serum creatinine concentrations were significantly higher at 6 and 12 months in those who took sirolimus. Most of these adverse effects were thought to represent exacerbations of ciclosporin adverse effects, except for diarrhea (8–32%), dyslipidemia (30–42%), lymphocele formation (12–15%), and thrombocytopenia (9–18%), which were more probably related to sirolimus.

That the adverse events profile of sirolimus is different from that of ciclosporin has been further suggested in 83 patients taking primary immunosuppressant regimens containing sirolimus (41 patients) or ciclosporin (42 patients) (3). Arthralgia (20%), hypercholesterolemia (44%), hypertriglyceridemia (51%), leukopenia (39%), thrombocytopenia (37%), and pneumonia (17%) were significantly more frequent in patients taking sirolimus, particularly during the first 2 months of treatment, that is until sirolimus trough concentrations were carefully monitored. Serum creatinine concentrations were lower in the sirolimus group, confirming that sirolimus probably has no direct nephrotoxic effect.

Organs and Systems

Respiratory

Progressive diffuse interstitial pneumonitis has been reported as a possible adverse effect of sirolimus (4), and by 2000 the FDA was aware of at least 34 cases (5). Although the reports were insufficient to conclude that sirolimus was responsible in most cases, eight patients recovered after sirolimus withdrawal.

Bronchiolitis obliterans with organizing pneumonia has been attributed to sirolimus in two renal transplant patients (6). Both improved rapidly after sirolimus withdrawal or dosage reduction.

Metabolism

The most striking consequence of treatment with sirolimus is dose-dependent hyperlipidemia with significant increases in both cholesterol and triglyceride serum concentrations, which resolve after dosage reduction or sirolimus withdrawal (7).

In a 1-year follow-up of 40 renal transplant patients treated with various dosages of sirolimus (0.5–7 mg/m^2/day) in addition to a ciclosporin-based regimen, there were significant increases in serum cholesterol and triglycerides, and significant falls in white blood cell and platelet counts, compared with historical controls (1). These effects correlated with sirolimus trough concentrations but not dosages. One patient had to discontinue sirolimus because of hyperlipidemia refractory to treatment.

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In six patients with renal transplants treated with sirolimus, mean total plasma cholesterol, triglyceride, and apolipoprotein concentrations increased (8). The authors suggested that sirolimus increases lipase activity in adipose tissue and reduces lipoprotein lipase activity, resulting in increased hepatic synthesis of triglycerides, increased secretion of VLDL, and increased hypertriglyceridemia.

Hematologic

Thrombocytopenia, probably related to sirolimus, as well as significant reversible reductions in platelet and white blood cell counts have been found (SEDA-20, 346).

In 119 patients taking sirolimus, thrombocytopenia (defined as a platelet count below 150×10^9/l) and leukopenia (white blood cell count below 5.0×10^9/l) occurred in 78 and 63% respectively (9). The incidence, but not the severity, of these effects correlated with sirolimus whole-blood trough concentrations. Most cases occurred within the first 4 weeks of treatment and the severity was usually limited. There was spontaneous resolution in 89% of the patients and sirolimus dosage reduction or temporary withdrawal was necessary in only 7% and 4% of the patients respectively. None of the patients required permanent withdrawal.

Immunologic

Two reports have recently suggested that sirolimus can produce features of the capillary leak syndrome in patients with psoriasis (10).

- A 53-year-old woman with severe psoriasis for 3 years, who had previously taken ciclosporin, sulfasalazine, and topical glucocorticoids, was given sirolimus 8 mg/m^2/day, and 3 days later had fever, leg edema, dyspnea, weight gain, anemia, and hypotension. A chest X-ray showed pulmonary congestion and cardiomegaly. Empirical antibiotics were unsuccessful, and all symptoms progressively disappeared after sirolimus withdrawal.
- A 58-year-old man took sirolimus 8 mg/m^2/day for severe psoriasis with arthritis. He also took ibuprofen, co-trimoxazole, and paracetamol. Within 1 month he developed nocturnal fever, dizziness, orthostatic hypotension, leg edema, and anemia. All his symptoms subsided after sirolimus withdrawal, furosemide treatment, and erythrocyte transfusion.

No other causes were found, and the authors noted that of 34 psoriatic patients given sirolimus, three had leg edema and a reduced hematocrit. Based on limited in vitro findings, they suggested that sirolimus might enhance apoptosis of activated lymphocytes and thereby cytokine release.

Drug–Drug Interactions

Ciclosporin

Combination of sirolimus with ciclosporin virtually eliminates acute rejection. However, the adverse effects of both drugs are potentiated, increasing the nephrotoxicity of ciclosporin (11).

In a single-dose, open, crossover study in 15 men and six women, the systemic availability of sirolimus 10 mg was markedly increased by concomitant ciclosporin 300 mg, C_{max}, t_{max}, and AUC being increased by 116, 92, and 230% respectively (12,13). However, when sirolimus was given 4 hours after ciclosporin, the increases were only 37, 58, and 80%. Ciclosporin did not affect the half-life or mean residence time of sirolimus. Sirolimus did not significantly affect the systemic availability of ciclosporin.

Diltiazem

In 18 healthy subjects, in a randomized, crossover study of the pharmacokinetics of a single oral dose of sirolimus 10 mg, a single dose of diltiazem 120 mg, and the combination, diltiazem increased exposure to sirolimus, presumably by inhibiting its first-pass metabolism (13).

Tacrolimus

Combination of sirolimus with tacrolimus virtually eliminates acute rejection. However, the adverse effects of both drugs are potentiated, increasing the nephrotoxicity of tacrolimus (11).

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Sitafloxacin

See also Fluoroquinolones

General Information

Sitafloxacin is a quinolone antibiotic that is effective against methicillin-resistant *Staphylococcus aureus*.

Organs and Systems

Liver

In a phase II, open, multicenter, randomized study sitafloxacin 400 mg/day caused mild transient increases in alanine transaminase and alkaline phosphatase in 69 patients but no effects on other enzymes (1).

Skin

Data obtained in albino mice have suggested that the phototoxic potential of sitafloxacin is milder than that of lomefloxacin or sparfloxacin (2).

Drug Administration

Drug formulations

After oral administration sitafloxacin 500 mg is rapidly absorbed, with a systemic availability of 89% (3). By 48 hours, about 61% is excreted unchanged in the urine after oral administration and about 75% after intravenous administration. For both routes, the high renal clearance of sitafloxacin implies active tubular secretion.

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Sitamaquine

General Information

Sitamaquine (1) is an 8-aminoquinoline that has been used to treat kala-azar (visceral leishmaniasis) (2) and is being tested for activity against *Pneumocystis jiroveci* (1).

In a phase-II, open, dose-escalating safety and efficacy study in 22 Brazilian patients with kala-azar, five groups were given different oral regimens, containing 1.0–3.25 mg of sitamaquine, for 28 days (3). There was nephrotoxicity with 2.5 mg/kg/day in two patients and in the single patient who took 3.25 mg/kg/day. Interstitial nephritis with acute tubular necrosis was proven by biopsy in two patients. Headache and gastrointestinal adverse effects occurred in under 5%. Methemoglobinemia of less than 6% after 7 days was common.

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Smallpox vaccine

See also Vaccines

General Information

The last case of smallpox occurred in 1977, and the eradication of smallpox was declared complete by the World Health Assembly in 1980. Since then, routine smallpox vaccination has ceased in all countries, because it is no longer required and because serious adverse reactions sometimes occur after both primary vaccination and revaccination (SED-8, 709) (SED-11, 685) (SEDA-1, 247) (SEDA-3, 262) (SEDA-4, 227) (SEDA-6, 289) (SEDA-13, 289) (SEDA-15, 357) (1–5). However, the threat of bioterrorism has made it necessary to consider prevention and control

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Table 1 Frequencies of some complications per 1 000 000 smallpox vaccinations

Complication	Primarily vaccinated	Revaccinated
Vaccinia gangrenosa	0.9	0.7
Eczema vaccinatum	10.0	0.9
Generalized vaccinia	23.4	1.2
Accidental infections	25.3	0.8

strategies through vaccination and the potential hazards associated with the administration of smallpox vaccine.

Adverse reactions to smallpox vaccination vary from what may be called a "normal" reaction via anomalous reactions to real complications. These can be divided into two categories (6):

1. complications in which sequelae or a fatal outcome are rare (sensitivity, rashes, generalized vaccinia, and autoinoculation vaccinia);
2. complications that may well be fatal or have permanent sequelae (postvaccinial encephalomyelitis, vaccinia necrosum, eczema vaccinatum).

Both categories of complications are much less common after revaccination than after primary vaccination. *Vaccinia* virus can also spread by contact to other subjects and cause adverse effects (7,8).

In an Australian survey of 5 000 000 vaccinations carried out between 1960 and 1976, the frequency of all complications was 188 per million and the death rate 1.5 per million. The ratio of reactions in women to reactions in men was 1.6, increasing with age. Paradoxically, of eight reports of cardiac complications seven concerned men (9).

The frequencies of some complications in 1968 in the USA per 1 000 000 smallpox vaccinations in primarily vaccinated and revaccinated subjects are shown in Table 1 (7).

Recombinant DNA technology using *Vaccinia* virus

Because of its great genetic potential, *Vaccinia* virus is an ideal medium for recombined genes originating from different organisms. In order to use *Vaccinia* virus, efforts have been made to attenuate it further, either by inactivating the genes responsible for virulence (SEDA-15, 357) or by introducing human lymphokine genes into its genome.

Vaccinia DNA can tolerate large insertions into nonessential regions of the genome, and this opens the door to the making of polyvalent live *Vaccinia* recombinations. A major obstacle to their use as vaccines is that severe complications can occur after vaccination, especially in immunodeficient individuals. On the other hand, there is evidence that recombinant *Vaccinia* viruses have reduced pathogenicity. A genetically engineered *Vaccinia* virus expressing murine interleukin-2 has been described (10), and it has been shown that athymic nude mice infected with the *Vaccinia* virus recover from the virus infection rapidly, whereas mice infected with a control virus develop progressive vaccinia.

One attempt to develop safe and efficacious live recombinant vaccines is the use of low neurovirulent strains of vaccinia virus: LC 16 m O (m O) or LC 16 m 8 (m 8). A recombinant *Vaccinia* virus vaccine (RVV) expressing hepatitis B surface antigen likely to form the basis of a safe live RV vaccine against hepatitis B has been constructed (11).

Little is known of the ways in which orthopoxviruses are maintained in nature (12). There is a possibility that strains of *Vaccinia* used as vaccines may become established in nature, as *Vaccinia* may have become established in Indian buffaloes, and/or undergo genetic hybridization with existing orthopoxviruses (12). Enthusiasm for these new prospects should not be allowed to compromise the requirement for obtaining additional scientific information essential to ensure safety, efficacy, and the exercise of all reasonable caution in mounting field investigations (13).

There have already been accusations that two patients with AIDS, treated with an experimental vaccine prepared using a *Vaccinia* virus that had apparently been inactivated and genetically engineered to express HIV proteins, may have died from vaccinia gangrenosa (14,15). On the other hand, there is evidence that recombinant *Vaccinia* viruses have reduced pathogenicity (SEDA-13, 289).

Protection of laboratory workers exposed to orthopoxviruses

In 1980, the US Public Health Service first recommended the use of *Vaccinia* (smallpox) vaccine to protect laboratory workers occupationally exposed to orthopoxviruses. In 1991, the Centers for Disease Control, Atlanta, Georgia, published recommendations on *Vaccinia* vaccine. From 1983 to 1991, 4649 doses of smallpox vaccine were administered, of which 57% were given in 1989–91. The proportion of primary vaccinations increased from 4% in 1983–88 to 14% in 1989–91. Of vaccinees 93% reported no signs or symptoms after vaccination. Reported adverse reactions were mild: lymphadenopathy, fever or chills, and tenderness at the site of vaccination. No severe adverse effects were reported. However, one vaccinee reported a spontaneous abortion 5 months after primary vaccination (16).

A somewhat different note has been sounded from the Committee on Occupational Medical Practice of the American College of Occupational and Environmental Medicine. The committee pointed out that risks to laboratory workers resulting from spontaneous infection are presumably similar to those involved in vaccination. The positive aspect of immunization is that it renders possible control over the time and initial site of entry of the virus. In the Committee's opinion, it is important for scientists and technicians to understand the US Public Health Service recommendations and to have the opportunity to receive *Vaccinia* immunization. They should also understand the possible drawbacks and have the opportunity to refuse vaccination (17). These different recommendations in the USA are also reflected in different national recommendations in other countries.

Accidental needle-stick inoculation of *Vaccinia* virus has been reported (18).

- A 26-year-old laboratory worker, who had been vaccinated against smallpox in childhood, developed a pustule and erythema on his left thumb 3 days after an accidental needle-stick while working with *Vaccinia* virus. Further pustules occurred on the fourth and fifth fingers of the same hand, accompanied by a large

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erythematous lesion on the left forearm, secondary bacterial infection, and axillary lymphadenopathy. After surgical excision of the necrotic tissue, he improved slowly and the lesions healed in about 3 weeks.

Smallpox and bioterrorism

The threat of bioterrorism has made it necessary to consider again prevention and control strategies through vaccination and the potential hazards associated with the administration of smallpox vaccine. Guidelines for prevention and control of smallpox have been elaborated in many countries. The guidelines distinguish between pre-event vaccination programs (worldwide no re-emergence of smallpox) and postevent vaccination programs (re-emergence of smallpox confirmed). Taking into account the risk of smallpox vaccination, most countries have elaborated plans for postevent vaccination programs. During the US pre-event vaccination program, in 1 per 20 000 members of the military who received primary smallpox vaccination, cardiac inflammation (myocarditis and/or pericarditis), including one death (myocardial infarction), has been reported. Compared with the rate reported in an unvaccinated military population during 1998–2000, the rate of myocarditis/pericarditis was substantially increased. However, there were no cases after revaccination. In 2003, among 38 257 civilian health-care and public health workers vaccinated against smallpox, 17 suspected and 5 probable cases of myocarditis/pericarditis were reported. The other adverse events include one case of suspected encephalitis, three of generalized *Vaccinia*, three of ocular *Vaccinia*, and 21 of inadvertent inoculation.

During the US pre-event smallpox vaccination program, there were no reports of eczema vaccinatum, progressive *Vaccinia*, or fetal *Vaccinia* (19,20).

During a meeting in June 2003, the Global Advisory Committee on Vaccine Safety considered two expert reports on the safety of smallpox vaccination in detail. They concluded that there is a real risk of serious adverse events, including safety issues that have not previously been recognized. Therefore, if the vaccine is being used in mass campaigns, it would be very important to include adverse events monitoring. The committee found that the available data were insufficient to define the risk after primary vaccination compared with the risk of revaccination after a long interval (21).

Organs and Systems

Cardiovascular

Acute myocarditis after vaccination against smallpox has been reported (22). Fatal myocarditis is rare, but electrocardiographic evidence of myocarditis has been found more frequently; this adverse effect is probably not always noticed (23–25). Pericarditis after smallpox vaccination has also been described (26).

All case reports of myocarditis/pericarditis after smallpox vaccination have been carefully evaluated. It was concluded that the data are consistent with a causal relation between myocarditis/pericarditis and smallpox vaccination; however, no causal association between ischemic cardiac events and smallpox has been identified (19,20).

- A 57-year-old woman with a history of hypertension, a transient ischemic attack, and carotid endarterectomy died 22 days after smallpox vaccination. Histopathological evaluation showed no evidence of cardiac inflammation.

Pericarditis after smallpox vaccination has been described (26).

The Advisory Committee on Immunization Practices (ACIP) has recommended that people who have underlying heart disease, with or without symptoms, or who have three or more known major cardiac risk factors (that is hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking) should be excluded from the pre-event smallpox vaccination program (27).

During the period of routine smallpox vaccination, only rare reports of cardiac inflammation (pericarditis, fatal myocarditis, and electrocardiographic evidence of myocarditis) were published in the world literature (SED-8, 709). To determine the risk of cardiac death after smallpox vaccination, death certificates were analysed from a period in 1947 when 6 million New York City residents were vaccinated after a smallpox outbreak; the incidence of cardiac deaths did not increase after the vaccination campaign (28).

Respiratory

Pneumonia has been observed after smallpox vaccination (2).

Nervous system

Neurological complications of smallpox vaccination can cause paralysis; of 26 patients with such symptoms, most were children under 2 years (29).

The most dreaded complication of smallpox vaccination is postvaccinial encephalitis or encephalomyelitis, which is said to occur even without a cutaneous vaccination reaction (30), although this occurs rarely, if at all (2,31). It is mainly a complication of primary vaccination. There is increased morbidity with increasing age, especially around puberty. It is rare after revaccination.

Two conditions must be distinguished: a histopathological picture characterized by diffuse perivenous focal encephalitis and a condition based on a disturbance of the blood–brain barrier, that is an encephalopathy that characteristically occurs in infants. The incubation period of postvaccinial encephalomyelitis is 9–13 days. Its onset is mostly sudden. The clinical picture varies. Mortality is high (30–50%). Recovery may be complete, but there are often neurological sequelae, such as paresis and extrapyramidal disturbances.

The frequency of postvaccinial encephalomyelitis in different countries has varied considerably. Per million primary vaccinations 68 cases were recorded in Bavaria, 48 in the Netherlands, 15 in the UK, and 1.8 in the USA. The frequency increases with age beyond the first year (5). In 53 034 primarily vaccinated army recruits in the Netherlands there were 11 cases (1:5000) (32). In 1968 the frequency in the USA was 2.8 per million primarily

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vaccinated. There were no cases among 8.5 million revaccinations (8). In very young infants sudden death can occur (33), but information about frequency is difficult to assess, because of the occurrence of sudden unexplained deaths ("cot" deaths).

The risk of postvaccinial encephalomyelitis is reduced by simultaneous administration of hyperimmune *Vaccinia* gamma globulin (32) or by pre-immunization with an antigen from formol-inactivated *Vaccinia* virus (34,35). However, cases of postvaccinial encephalomyelitis have been described even after these procedures (32,36).

- A 13-year-old girl died of neuromyelitis optica. By inoculation of rabbits it was shown that the brain tissue contained *Vaccinia* antigen. Moreover, there were high titres against *Vaccinia* virus in both sera and spinal fluid. In infancy this patient had been vaccinated against smallpox (37).
- Accidental administration of 10 doses of smallpox vaccine to an already vaccinated girl resulted in a clinical picture characterized by neuraxitis with general tonic-clonic convulsions. Complete cure was attained after treatment with hyperimmune antivaccinia globulins and methisazone (38).

Polyneuropathy (39) and bacterial meningitis (40) have been described after smallpox vaccination.

Sensory systems

Ears

Disturbances of hearing and balance are described after smallpox vaccination (41).

Eyes

Vaccinial lesions on the eyelids and the conjunctivae are seen after secondary infection with *Vaccinia* virus by scratching (42,43). From these lesions a keratitis can develop, which sometimes extends to deeper layers of the cornea, with concomitant iridocyclitis. Papillitis with myelitis has been described after revaccination (44).

Metabolism

Diabetes mellitus occurred in a 1-year-old child about 4 weeks after smallpox vaccination (45).

Hematologic

Thrombocytopenic purpura is a rare complication of smallpox vaccination (46). Postvaccinial lymphadenitis can occur (47).

Mouth and teeth

Of 2568 people who were given oral vaccination, five bit open the vaccine-containing capsule or tablet, with release of the virus, and developed vaccinia lesions on the tongue, gums, or nares (48).

Urinary tract

Nephritis is a very rare complication of smallpox vaccination (49).

Skin

A 20-year-old man had active eczematous lesions on both wrists. After vaccination widespread *Vaccinia* developed in non-eczematous skin around the eyes and mouth, while the eczematous regions were unaffected. The possible reason was the use of a glucocorticoid ointment (50).

Skin reactions after smallpox vaccination can cause the following complications (2,3):

- Ectopic pocks near the vaccination site (vaccinia serpiginosa).
- Secondary vaccinia, which is caused by spreading of Vaccinia virus from the vaccination site to other body sites by scratching.
- Generalized vaccinia (vaccinia generalisata). Here the *Vaccinia* virus is spread by the blood stream and vaccinial lesions can develop all over the body some 9–10 days after vaccination.
- Eczema vaccinatum. This serious complication occurs most often in infants with active infantile eczema and occasionally in adults who have eczema or some other skin disease. It is seen after vaccination or contact with vaccinated persons with vaccinial lesions. The first symptoms are observed at the eczematous spots 3–4 days after vaccination. In many cases generalization of the vaccinial lesions follows. The estimated mortality is 25–30%.
- Progressive vaccinia (vaccinia gangrenosa). About 7 days after a normal vaccinial reaction the lesion extends, penetrates the underlying tissue, and becomes necrotic. Ulcers are formed, and the process spreads to adjacent areas of the skin. Secondary bacterial infection is common. This rare complication may be due to some abnormality of serum proteins, interfering with immunity, such as agammaglobulinemia or hypogammaglobulinemia. Mortality is high (51–53).
- Keloid from vaccinial scars.

Abnormal hair growth (54), herpes virus infections (55), and malignant changes in smallpox vaccination scars have also been observed (56,57). Allergic skin reactions sometimes occur, for example urticaria and purpura (58) and possibly photosensitivity reactions.

Musculoskeletal

Osteomyelitis and periosteitis are exceedingly rare sequels to smallpox vaccination (59,60).

Acute arthritis has been described after smallpox vaccination (61).

Death

In France 4 113 109 primary vaccinations during 1968–77 have been surveyed. There were 30 deaths that could have been associated with the vaccine, 23 in the first year of life (62). The relation was considered certain in one case, probable in 5, possible in 6, and doubtful in 18. In the certain case there may have been immunodeficiency. In the second group there were three cases of acute encephalitis. Among the doubtful cases were 12 patients who had neurological symptoms.

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Second-Generation Effects

Pregnancy

The incidence of abortions is said to be higher in women who have recently received smallpox vaccination; in some cases the aborted fetus showed evidence of *Vaccinia* infection (63).

Fetotoxicity

Although routine smallpox vaccination of infants was discontinued in the UK in 1971, some 20–28 cases of complications of vaccination continue to be reported yearly to the Committee on Safety of Medicines (64), including both cross-infection and fetal infection (64).

Susceptibility Factors

HIV infection is a risk factor for vaccinia generalisata, making it important to have *Vaccinia* immune globulin available for outbreak control (65).

- Vaccinia generalisata developed after smallpox vaccination (co-administrated with other vaccines) of an army recruit with asymptomatic HIV infection (66). After 2–3 weeks he developed cryptococcal meningitis, and a diagnosis of AIDS was made. While being treated for the meningitis he developed generalized vaccinia. He was treated with *Vaccinia* immune globulin and recovered from his vaccinia generalisata.

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Snakebite antivenom

See also Vaccines

General Information

Snakebite is an important medical emergency in some parts of the rural tropics. In most tropical countries it is an occupational disease of farmers, plantation workers, herders, and hunters. Every year thousands of people die in Africa, Central America, South Asia, and South-East Asia because of envenomation after snakebite. In India alone, an estimated 15–20 000 people die each year due to snakebite. In Sri Lanka, the overall incidence of snakebite exceeds 400 per 100 000 population per year, one of the highest in the world.

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Antivenom (also known as antivenin, antivenene, and antisnakebite serum) is the concentrated enzyme-refined immunoglobulin of animals, usually horses or sheep, that have been exposed to venom. It is the only specific treatment currently available for the management of snakebite envenoming and has proved effective against many of the lethal and damaging effects of venoms. The most widely used antivenoms are F(ab')2-equine polyspecific antivenoms, raised against the venoms of many poisonous snakes. In the management of snakebite, the most important clinical decision is whether or not to give antivenom, because only some snake-bitten patients need it, it can produce severe reactions, and it is expensive and often in short supply.

Antivenom is most effective by intravenous injection. The range of venoms neutralized by an antivenom is usually stated in the package insert. If the biting species of snake is known, the appropriate monospecific antivenom should be used. In countries where several species produce similar signs, snakebite victims are treated with polyspecific antivenom, which contains a lower concentration of specific antibody to each species than the monospecific antivenom.

Organs and Systems

Immunologic

Antivenom treatment can be complicated by early reactions (anaphylaxis), pyrogenic reactions, or late reactions (serum sickness-type). The incidence and severity of early reactions is proportional to the dose of antivenom and the speed with which it enters the blood stream (1,2). These reactions usually develop within 10–180 minutes of starting antivenom therapy. The reported incidence of early reactions after intravenous antivenom in snakebite patients, which ranges from 43% (3) to 81% (4), appears to increase with the dose and decrease when refined antivenom is used and administration is by intramuscular rather than intravenous injection. Unless patients are watched carefully for 3 hours after treatment, mild reactions can be missed and deaths misattributed to the envenoming itself. In most cases symptoms are mild: urticaria, nausea, vomiting, diarrhea, headache, and fever; however, in up to 40% of cases severe systemic anaphylaxis develops, with bronchospasm, hypotension, or angioedema. However, deaths are rare (5).

Early reactions respond well to adrenaline given by intramuscular injection of 0.5–1 ml of a 0.1% solution (1:1000, 1 mg/ml) in adults (children 0.01 ml/kg) at the first sign of trouble. Antihistamines also should be given by intravenous injection to counteract the effects of histamine released during the reaction.

Pyrogenic reactions result from contamination of antivenom by endotoxin-like compounds. High fever develops 1–2 hours after treatment and is associated with rigors, followed by vasodilatation and a fall in blood pressure. Febrile convulsions can occur in children. Patients should be cooled and given antipyretic drugs by mouth, powdered and washed down a nasogastric tube, or by suppository.

Late (serum sickness-type) reactions develop 5–24 days after treatment. Symptoms include fever, itching, urticaria, arthralgia (which can involve the temporomandibular joint), lymphadenopathy, periarticular swellings, mononeuritis multiplex, albuminuria, and rarely encephalopathy. This is an immune complex disease which responds to antihistamines or, in more severe cases, to glucocorticoids.

Early antivenom reactions are not usually Type I IgE-mediated reactions to equine serum proteins and are not predicted by hypersensitivity tests. Several methods have been used to reduce acute adverse reactions to antivenom. A small test dose of antivenom to detect patients who may develop acute adverse reactions to the antivenom has no predictive value, can itself cause anaphylaxis, and is no longer recommended (5). Prophylactic use of hydrocortisone and antihistamines before infusion with antivenom is also practiced widely, although the theoretical basis for their use is unclear. Antihistamines counter only the effects of histamine after its release and do not prevent further release; one small randomized controlled trial showed no benefit from the routine use of antihistamines (6). Hydrocortisone takes time to act and may be ineffective as a prophylactic against acute adverse reactions that can develop almost immediately after antivenom treatment, which is very often administered urgently to snakebite victims. One study has suggested that intravenous hydrocortisone is ineffective in preventing acute adverse reactions to antivenom, but if given together with intravenous chlorphenamine it can reduce these reactions (7). However, this trial recruited only 52 patients and was not designed to study the efficacy of chlorphenamine alone, making it difficult to give a clear interpretation of the results and recommendations on pretreatment with glucocorticoids and antihistamines to prevent acute reactions to antivenom. In one study of 105 patients, low-dose adrenaline given subcutaneously immediately before administration of antivenom to snakebite victims significantly reduced the incidence of acute adverse reactions to the serum (3). However, this trial did not enroll sufficient participants to establish safety adequately, a major concern regarding the use of adrenaline in a prophylactic role, particularly the risk of intra-cerebral haemorrhage. Therefore, further studies on the safety of this treatment are required before it can be recommended routinely. For the present, the only available alternative to prevention is the early detection of adverse reactions to antivenom and the ready availability of drugs such as adrenaline for their prompt treatment.

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Sodium hypochlorite

See also Disinfectants and antiseptics

General Information

Sodium hypochlorite is widely used as a cleaning agent and to deal with blood spillages. Chlorine gas is released during the use of hypochlorite. Alkaline hypochlorite solutions with 0.25% "available chlorine" have been used to clean and disinfect wounds.

Accidental injection

Local injection

A patient developed ulceration and paresthesia of the lip with facial swelling after accidental injection of Milton solution (sodium hypochlorite 1%, sodium chloride 16.5%) into the upper lip when a sharp needle was used for irrigation (1). The ulceration healed within 6 weeks, the paresthesia within 3 months. In similar cases hypochlorite solution (25 mg NaClO) was accidentally injected into periapical tissue (2), and into the mandibular branch of the facial nerve (90 mg NaClO) (3).

Intraperitoneal infusion

Accidental intraperitoneal infusion of hypochlorite solution on two occasions (the first time about 10 ml of a 5% solution the second time more diluted) has been reported (4). After the infusion the patient felt severe abdominal pain accompanied by nausea but not by vomiting. Raised peritoneal solute transport rates and reduced ultrafiltration gradually subsided, but they did not return to pre-infusion values.

Intravenous infusion

Accidental intravenous infusion has been reported (5–7).

- A 68-year-old man received an accidental infusion of a 1% sodium hypochlorite solution. After 1 hour and an infusion volume of 150 ml the infusion was stopped. By this time he had a slow heart rate, mild hypotension, and an increased respiratory rate. The blood cell count, hemoglobin, serum electrolyte, creatinine, and urea concentrations, and transaminase activities were normal and hemolysis did not occur. Treatment with NaCl 0.9% and dextrose at an infusion rate of 300 ml/hour was started immediately with the goal of maintaining an adequate diuresis. Furosemide and dopamine hydrochloride were also administered. His blood pressure and respiratory rate promptly returned to normal, but the bradycardia persisted for 3 days despite atropine sulfate (5).
- During dialysis a patient received an accidental infusion of 30 ml of a 5.25% solution of hypochlorite. This led to cardiorespiratory arrest and massive hemolysis with hyperkalemia, although the patient eventually recovered (7).
- In a third case, intravenous infusion of 60 ml of an oral and 0.3 ml of a parenteral 5.25% solution in a suicide attempt did not result in any serious effects (6).

Organs and Systems

Respiratory

Chlorine gas, released during the use of hypochlorite, can cause mucous membrane irritation, bronchospasm, pneumonia, and pulmonary edema. It is believed that when hypochlorite is used as a cleaning substance in low concentrations it does not cause respiratory damage, but in a comparison of pulmonary function tests in 23 cleaning workers and 14 technical personnel, as a control group, even low concentrations of hypochlorite affected pulmonary function, causing irritation in the airways (8).

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Solanaceae

See also Herbal medicines

General Information

The genera in the family of Solanaceae (Table 1) include deadly nightshade, henbane, jimson weed, peppers, petunia, and tobacco.

Anisodus tanguticus

Anisodus tanguticus (Zangqie), a traditional Chinese herbal medicine, contains hyoscyamine and related toxic tropane alkaloids (1). Its active ingredient anisodamine has been used to treat snakebite (2).

Brugmansia species

Brugmansia candida (*Datura candida*, angel's trumpet) and *Brugmansia suaveolens* (*Datura suaveolens*, angel's tears) are ornamental flowers that have been used for hallucinogenic effects. Both contain tropane alkaloids, such as hyoscine, hyoscyamine, meteloidine, and norhyoscine, which have anticholinergic properties.

Table 1 The genera of Solanaceae

Acnistus (acnistus)
Atropa (belladonna)
Bouchetia (bouchetia)
Browallia (browallia)
Brugmansia (brugmansia)
Brunfelsia (rain tree)
Calibrachoa (calibrachoa)
Capsicum (pepper)
Cestrum (jessamine)
Chamaesaracha (five eyes)
Datura (jimson weed)
Goetzea (goetzea)
Hunzikeria (hunzikeria)
Hyoscyamus (henbane)
Jaborosa (jaborosa)
Jaltomata (false holly)
Leucophysalis (leucophysalis)
Lycianthes (lycianthes)
Lycium (desert thorn)
Mandragora (mandrake)
Margaranthus (margaranthus)
Nectouxia (nectouxia)
Nicandra (nicandra)
Nicotiana (tobacco)
Nierembergia (cupflower)
Nothocestrum (aiea)
Oryctes (oryctes)
Petunia (petunia)
Physalis (ground cherry)
Quincula (quincula)
Salpichroa (salpichroa)
Salpiglossis (salpiglossis)
Schizanthus (schizanthus)
Scopolia
Solanum (nightshade)
Solandra (solandra)
Streptosolen (streptosolen)

Adverse effects

Anticholinergic toxicity can result from the alkaloids that *Brugmansia* species contain (3).

- A 53-year-old woman was admitted to hospital with vertigo, blurred vision, palpitation, mydriasis of the right eye, and tachycardia (120/minute) (4). She reported that she had been cutting leaves from an angel's trumpet when a drop of sap had entered her right eye.
- A 76-year-old man drank 3 teaspoons (15 ml) of a homemade wine made from *B. suaveolens* over 1 hour and about 1.5 hours later developed respiratory distress and weakness (5).

There have been reports of young men who had confusion and other signs of central nervous system involvement after taking angel's trumpet (6).

After ocular exposure to sap from *B. suaveolens*, seven patients developed unilateral mydriasis, at least three also had ipsilateral cycloplegia, and one developed transient tachycardia (7).

Capsicum annuum

Capsicum annuum (chili pepper) contains a variety of carotenoids, including capsanthin, capsorubin, beta-carotene, cryptoxanthin, lutein, phytofluene, and xanthophyll, and steroids, including capsicoside. One of the main constituents is capsaicin, which produces an intense burning sensation when it comes into contact with the skin, eyes, or mucous membranes and which gives peppers their burning taste. A hot shower or bath before topical application to the skin intensifies the burning sensation. Capsaicin is used internally for various conditions, including colic and for improving peripheral circulation, and externally for unbroken chilblains. A cream for topical application has been used to relieve the pain of postherpetic neuralgia and other pain syndromes.

Adverse effects

Sensitization to *C. annuum* has been reported in a patient who was allergic to latex (8).

Taken orally in regular high doses capsaicin can act as a carcinogen and could promote gastric cancer, but in low doses it seems to have anticarcinogenic activity (9).

Datura stramonium

Datura stramonium (Jimson weed) is a naturally occurring plant that is ingested to induce hallucinogenic effects. Toxicity after ingestion is due to an atropine-containing alkaloid that is present in all parts of the plant but is particularly concentrated in the seeds.

Adverse effects

Intoxication with *Datura* species is often reported (10–12). Eleven patients aged 13–21 years ingested large quantities of Jimson weed pods and seeds (13). The signs and symptoms were classical of atropine poisoning. In milder cases there was asymptomatic mydriasis and tachycardia and in the more severely affected agitation, disorientation, and hallucinations. Nine of the 11 were admitted for observation. None died and none required pharmacological intervention with physostigmine to reverse the anticholinergic symptoms.

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Lycium barbarum

Lycium barbarum (Chinese wolfberry) contains a variety of steroids. A tea prepared from it is used in China as a general tonic.

Adverse effects

An interaction of *L. barbarum* with warfarin has been described.

- A 61-year-old woman, who had taken warfarin for atrial fibrillation in weekly doses of 18–19 mg for years and had been completely stable, developed a raised INR after she consumed a tea made from Chinese wolfberry (14). Four days after drinking the tea (180 ml/day), she had an INR of 4.1. After withdrawal of the herbal tea her INR returned to within the target range and remained stable.

Although an extract of *L. barbarum* inhibited CYP2C9 in vitro, the effect was weak and the authors thought that another mechanism must have been involved.

Mandragora species

Mandragora (mandrake) species contain toxic tropane alkaloids, such as hyoscyamine and/or scopolamine.

Adverse effects

The tropane alkaloids in *Mandragora* species are powerful anticholinergic agents and can cause peripheral symptoms (for example blurred vision, dry mouth) and central effects (for example drowsiness, delirium) (15). They can potentiate the effects of synthetic drugs with similar pharmacological activity.

In 15 patients anticholinergic effects were due to poisoning by *Mandragora autumnalis* intermingled with leaves of chard (*Beta vulgaris*) and spinach (*Spinacia oleracea*) (16). The latency from the time of ingestion was 1–4 hours. There was no correlation between latency and severity. All had blurred vision and dryness of mouth, nine had difficult in micturition, nine dizziness, nine headache, eight vomiting, two difficulty in swallowing, and two abdominal pain. All had blushing, a reactive mydriasis, and tachycardia. The skin and mucosae were dry in 14. There was hyperactivity/hallucination in 14 and agitation/delirium in nine. One patient developed a florid psychotic episode. Prostigmine (2–6 mg) was given to 11 patients and physostigmine (0.5–2 mg) to six. The time to a definite response was variable (3–36 hours). The patients treated with physostigmine had better reversal of the psychoneurological symptoms.

In some cases of poisoning, formulations of ginseng may have been adulterated with *Mandragora officinarum* (17).

Anaphylaxis has been reported after the administration of a homeopathic preparation of mandragora (18).

Nicotiana tabacum

The leaves of *Nicotiana tabacum* (tobacco) contain the toxic alkaloid, nicotine as a major constituent and several other pyridine alkaloids as minor constituents. Although tobacco enemas have been abandoned in official medicine because of their life-threatening toxicity, unorthodox self-medication with this agent has not completely died out. A case report in the 1970s described nausea and confusion, followed by hypotension and bradycardia, due to an enema apparently prepared from 5 to 10 cigarettes. Transdermal nicotine is now widely used as an aid to smoking cessation. Nicotine is covered in a separate monograph.

Scopolia species

Scopolia species (scopola) contain tropane alkaloids, such as atropine, hyoscine (scopolamine), hyoscyamine, and tropane. They can cause anticholinergic symptoms (19).

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Somatostatin and analogues

General Information

Somatostatin was first isolated from the hypothalamus, and was shown to inhibit growth hormone release. It has since been found in neuroendocrine tissues throughout the body. It has multiple effects, via five distinct receptors, and acts as a neurotransmitter, in the regulation of growth hormone and thyrotropin release, as a regulator of gastrointestinal and pancreatic function, and as an immune modulator. Synthetic analogues are selective for receptor subtypes 2 and 5, and have different clinical and adverse effects profiles to the native hormone, as well as having longer half-lives. Analogues of somatostatin include depreotide, edotreotide, ilatreotide, lanreotide, octreotide, pasireotide, pentetreotide, and vapreotide (all rINNs).

Octreotide, an octapeptide somatostatin analogue, is usually given subcutaneously in three divided doses per day. Longer-acting analogues with similar efficacy and adverse effects to octreotide, but which can be given every 14–28 days, have been developed (1,2). The therapeutic indications and adverse effects of octreotide have been reviewed (SEDA-13, 1309) (3).

Organs and Systems

Cardiovascular

Both somatostatin and octreotide cause transient increases in mean arterial pressure and mean pulmonary pressure when given intravenously to patients with cirrhosis, more marked with bolus administration than with continuous infusion (4). This may be either direct or mediated by inhibition of gut vasodilatory peptides (SEDA-24, 505) (5) and is not usually associated with significant clinical effects.

Severe hypertension with associated headache, nausea, and vomiting was reported within 2 weeks of administration of octreotide LAR 20 mg in a 26-year-old diabetic woman with autonomic neuropathy (5). Rechallenge with octreotide 75 µg resulted in a transient hypertensive episode lasting 3 hours.

- Exacerbation of pre-existing hypertension was also reported in a 22-month-old boy during octreotide infusion (6).

There has been one report of acute pulmonary edema during octreotide and intravenous fluid therapy for variceal bleeding (7).

Sinus bradycardia (less than 50/minute) is reported in up to 25% of acromegalic patients taking octreotide, and conduction abnormalities are also commonly reported in these patients. This adverse effect is reported only rarely in other recipients of somatostatin or octreotide, probably reflecting the high rate of cardiac abnormalities due to acromegaly (8).

Nervous system

Dizziness occurred in 7.4% of 68 patients randomized to somatostatin and 8.2% of 73 randomized to octreotide, both by rapid infusion, to control variceal bleeding, in which the effectiveness of somatostatin and its analogues is probably via a transient reduction in heart rate and cardiac output (9).

Metabolism

Somatostatin and its analogues inhibit insulin secretion in the short term, before receptor down-regulation. Mild hyperglycemia occurs during octreotide infusion in up to 23% of adults (10,11), and occasionally in children (12). This is not usually clinically significant (3). However, in an open, retrospective comparison of octreotide and lanreotide in 38 patients with acromegaly, one patient in each group stopped therapy because of worsening glycemic control (13).

In a meta-analysis of trials for variceal bleeding, hyperglycemia occurred in 41 of 310 patients who received somatostatin, octreotide, or vapreotide, compared with 26 of 318 patients who received placebo (14).

Reports of the effects of octreotide on glucose metabolism in acromegaly are inconsistent and are complicated by the high prevalence of insulin resistance and overt diabetes in acromegaly. In 10 patients with acromegaly who used modified-release lanreotide for 19 months followed by modified-release octreotide for 21 months after a 3-month washout period, mean fasting glucose, the glucose response to oral glucose tolerance testing, and glycated hemoglobin all increased after octreotide but not lanreotide (15). However, the study was small and the order of the two medications was not randomized.

In patients with insulinoma, octreotide can cause clinically important hypoglycemia, because of suppression of counter-regulatory hormone secretion (16).

Hematologic

- A 42-year-old woman, treated with octreotide infusion 50 mg/hour for cirrhosis-related gastrointestinal bleeding on two occasions 9 months apart, had an immediate fall in platelet count on both occasions, resolving after octreotide withdrawal (17). The thrombocytopenia was not severe (nadir platelet counts 62 and 55×10^9/l) and did not require specific treatment.

The rapid fall in platelet count in this case suggests an immunological mechanism, although this was not directly demonstrated.

Gastrointestinal

Transient gastrointestinal symptoms (nausea, diarrhea, abdominal discomfort, and flatulence) occur in up to 50% of patients during the first few days of treatment, but usually resolve spontaneously after the first 1–2 weeks of treatment (13,18). Nausea and vomiting occur in up to 25% of patients after somatostatin and are also common

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after octreotide (19). Two of 15 patients in a phase I trial of malignant gastrinoma had to stop using long-acting octreotide because of severe nausea (20).

Diarrhea is common soon after starting octreotide but usually resolves within 2 weeks without specific treatment. In a randomized, double-blind, placebo-controlled trial in 203 mostly postmenopausal women with locally recurrent or metastatic breast carcinoma, all of whom were also taking tamoxifen, and who had estrogen-receptor positive and/or progesterone-receptor positive tumors, octreotide was added to the basic treatment in 99 cases (21). The adverse events experienced by 10% or more of the patients and attributed to octreotide were gastrointestinal: diarrhea (53%), nausea (16%), and abdominal pain (11%); diarrhea occurred in only 11% of the controls.

One of 10 patients with rheumatoid arthritis in an open study stopped using long-acting octreotide because of severe diarrhea and weight loss of 3 kg (22). These effects are dose-related and are similar in healthy volunteers, acromegalic patients, and patients with gastrointestinal tumors (3).

Octreotide 100 μg given subcutaneously to five healthy subjects 30 minutes before meals for 7 days increased fecal fat excretion; however, steatorrhea occurred in only two cases; fecal bile acid excretion fell to about 25% (23)

Biliary tract

Biliary sludge and gallstones are frequent adverse effects of both octreotide (2) and its longer acting analogues, compared with 10–25% of the general population (24). Cholelithiasis develops in up to 20% of patients in the long term, secondary to reduced gall-bladder contractility, but only 1% of patients develop symptoms per year of treatment (25). There is prospective evidence that gallstones develop earlier in patients on higher doses of octreotide (24). Rebound gall-bladder hypermotility can occur on withdrawal of octreotide and can be associated with biliary colic or pancreatitis (SEDA-13, 1309) (26,27).

Patients treated with octreotide have impaired meal-stimulated gall-bladder emptying and altered bile chemical composition, similar to spontaneous cholelithiasis. In 16 patients with acromegaly the serum deoxycholic acid concentration increased in proportion to large bowel transit time (28). In 11 patients gall-bladder emptying was slower in patients given octreotide LAR than lanreotide SR, but was impaired in both groups compared with pretreatment values (29).

Fasting gall-bladder volume increased progressively in seven patients with acromegaly treated with once-monthly long-acting octreotide; gallstones formed de novo in six patients within 8 months and one had symptomatic biliary colic (30). Gallstones have also been reported in children receiving prolonged octreotide therapy (12).

Ursodiol appeared to reverse gall-bladder abnormalities in seven of 10 patients. Data from this study also showed earlier development of sludge in recipients of higher doses of octreotide (24).

Hair

Reversible hair loss has been reported in a few patients after both octreotide (31) and lanreotide (32).

Immunologic

Antibodies to somatostatin analogues have been reported only rarely. However, in one study octreotide antibodies were demonstrated in 63 (27%) of 231 patients treated with subcutaneous octreotide for more than 3 years, rising to 57% after 5 years and 72% after 8 years (33). The antibodies did not reduce clinical efficacy.

- A 64-year-old woman, who had had monthly intramuscular injections of long-acting octreotide in the buttocks for 6 years, had increased uptake of ^{111}In-pentetreotide in both buttocks, thought to represent granuloma formation at the injection sites (34). Localized granulomas have previously been described in isolated cases after intramuscular somatostatin analogues, and somatostatin receptors are expressed in high density in activated lymphocytes.

Allergic reactions to somatostatin are rare. Of 97 cirrhotic patients randomized to subcutaneous octreotide, one stopped therapy because of erythematous itchy skin, which then resolved (11).

Second-Generation Effects

Pregnancy

Octreotide is a small peptide that can pass the placental barrier, and it is not recommended for use in pregnant women.

Placental transfer was significant in the first reported pregnancy with long-acting octreotide (35). The dose of octreotide was reduced after an ultrasound suggested intrauterine growth retardation. The female infant had a low birth weight (11th percentile) but caught up to the 50th percentile by 3 months of age. Her development was normal during 18 months of follow-up.

Of seven women who took somatostatin analogues during pregnancy, five stopped taking it when the pregnancy was diagnosed (36). One had a single injection of modified-release lanreotide before pregnancy was diagnosed, with no apparent adverse effects on the infant (37). No fetal malformations or delay in postnatal development have been reported.

Susceptibility Factors

Age

Children are generally not given long-term octreotide because of concerns about its effect on growth. Although growth was reported as normal in a few case series, "catch-up" growth was also described after octreotide was withdrawn (12).

Drug–Drug Interactions

Erythromycin

Pretreatment with octreotide enhanced the gastric prokinetic effects of erythromycin in eight healthy subjects, suggesting that octreotide may be clinically useful

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in patients with tachyphylaxis to this effect of erythromycin (38).

Midodrine

In a controlled study of octreotide and midodrine (an alpha-adrenoceptor agonist) in patients with orthostatic hypotension, the pressor effect of the two drugs was synergistic (39).

Morphine

Somatostatin and its analogues have been reported to be OP_3 (μ) opioid receptor antagonists (40). Somatostatin infusions significantly reduced the effectiveness of morphine analgesia in a case report of three patients with cancer.

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Somatropin

General Information

Established indications for somatropin (growth hormone) include growth hormone deficiency in children, Turner's syndrome, Noonan's syndrome, and renal insufficiency in children. Other well-studied indications include idiopathic short stature, adult growth hormone deficiency, osteoporosis, and catabolic states associated with acute and chronic illness and injury. Body composition, respiratory muscle function, physical strength, and height improved in a 12-month trial of somatropin in 54 children with Prader–Willi syndrome (1).

The adverse effects of somatropin differ between adults and children. In adults, adverse effects are commoner in men, in heavier patients, and in adult-onset growth hormone deficiency. Efficacy is no greater in those who develop adverse effects. The higher rate of adverse effects is due to the higher dose of somatropin when calculated according to body weight, and also to lower sensitivity to somatropin in women than in men (2–4). Rapid dose escalation also increases the rate of adverse effects. To minimize adverse effects, it is recommended that treatment be started at a low dosage, that is 0.4–0.8 U/day, and titrated according to the age-specific concentration of IGF-1 (2,3,5).

Adverse effects are commoner in patients using higher doses. Starting at a low dose, increasing the dose gradually, and titrating individual doses against age-specific IGF-I concentrations may minimize adverse events.

Organs and Systems

Cardiovascular

The effect of somatropin on cardiovascular risk is complex, as growth hormone reduces visceral fat and total cholesterol and increases HDL cholesterol concentrations (6–8).

Edema, both generalized and peripheral, is common in adults given somatropin, as is hypertension. Symptoms are usually mild and resolve in many patients despite continuing treatment (9). Increased left ventricular wall thickness has been reported in both adults and children, although in children this is thought to reflect an increase in overall mass and is not thought to be of clinical significance (10,11).

In an open study in five patients with severe dilated cardiomyopathy given high-dose somatropin 4 IU/day (1.3 mg/day) for 3 months, ventricular dysrhythmias worsened in all patients during treatment, from Lown class 2 or 3 to 4A or 4B, and returned to baseline when treatment was stopped (12).

- A 7-year-old boy developed cardiomegaly and edema within a month of starting somatropin, 0.7 IU/kg/week; when the dose was reduced to 0.35 IU/kg/week his heart size returned to normal (13).

This is a reminder that the adverse effects of somatropin are dose-related within the therapeutic range and that dose escalation should be gradual.

Nervous system

Somatropin extracted from cadaveric human pituitaries was used to treat growth hormone-deficient patients until several cases of the fatal degenerative neurological disorder Creutzfeldt–Jakob disease were reported in the mid-1980s. Of 267 cases of iatrogenic Creutzfeldt–Jakob disease, 139 were caused by human cadaver-derived somatropin (SEDA-25, 479).

This disease develops when an abnormal prion protein present in the cadaveric material induces a cascade of conformational changes in host protein. Creutzfeldt–Jakob disease in recipients of somatropin differs from the sporadic form, in that it usually presents with cerebellar signs rather than cognitive impairment, and also in the prominence of prion protein amyloid plaques in nervous tissue (14). In a review, 139 cases of Creutzfeldt–Jakob disease were identified worldwide in people treated with cadaveric somatropin before recombinant human growth hormone became available in the mid-1980s (15). The prevalence of this fatal neurodegenerative condition in recipients of somatropin ranges from 0.3% in the USA

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to 4.4% in France. Creutzfeldt–Jakob disease has been reported to start at 4–30 years after therapy with cadaveric somatropin (14), so that further cases are anticipated and continue to be reported (16).

- A case has been reported in Brazil, 28 years after somatropin therapy (17).
- An 18-year-old man from Qatar presented with a 3-month history of unsteadiness, dysarthria, and left-sided weakness, followed by visual, hearing, and memory loss, 13 years after somatropin therapy (18).

This is the first case from Qatar, but it is possible that other cases there have not been reported.

People exposed to a contaminated batch of somatropin have about a 6% chance of developing Creutzfeldt–Jakob disease (19), although there are no reliable predictors of risk in an individual. The risk varies to some extent with the mode of preparation of the product, but it seems unlikely that it can be entirely eliminated. The natural product was therefore withdrawn from the market in most countries, but was rapidly replaced by biosynthetic somatropin preparations

Carpal tunnel syndrome due to somatropin is probably dose-dependent and was reported in 4.8% of subjects in a double-blind trial (9).

Headache is a common adverse effect of somatropin. It often occurs early in treatment and usually responds to temporary dosage reduction followed by gradual re-escalation (1,20). It can be an early indicator of the rare complication pseudotumor cerebri (idiopathic intracranial hypertension), particularly in high-risk groups, such as children with renal insufficiency, and may require further investigation. Headache was reported in 13% of 75 prepubertal children treated with a modified-release formulation of somatropin over 12 months (21).

Somatropin can cause idiopathic intracranial hypertension (pseudotumor cerebri), characterized by headache, papilledema, visual disturbance, and sometimes nausea and vomiting (22). Less common features include extraocular palsy, present in up to 48% of affected patients (22), mood changes, and somnolence. There have been 30 cases reported worldwide (23); chronic renal insufficiency, Turner's syndrome, obesity, and biochemical growth hormone deficiency are all associated with an increased risk. About half of the reported cases occurred within the first 8 weeks of treatment, and all responded to dose reduction or withdrawal of human growth hormone. Fundoscopy is recommended before starting somatropin and regularly during the first few months, although the absence of papilledema does not exclude the diagnosis. Up to 48% of children with intracranial hypertension due to somatropin also develop a sixth nerve palsy (23).

- A non-obese 6-year-old girl with Ullrich–Turner syndrome developed headache, vomiting, and blurred vision, with papilledema and increased cerebrospinal fluid pressure 5 months after starting somatropin 0.9 IU/kg/week (24). The cerebrospinal fluid pressure normalized after somatropin was withdrawn, and increased again when therapy was restarted. Her visual acuity was reduced to less than 30% in the right eye.

According to the authors there have been 40 cases of pseudotumor cerebri associated with somatropin therapy worldwide, owing to stimulation of cerebrospinal fluid production or reduced drainage.

Sensory systems

Retinal changes, clinically indistinguishable from diabetic retinopathy, were reported in two non-diabetic recipients of somatropin (25).

- An obese 31-year-old man developed non-proliferative retinopathy and macular edema with reduced visual acuity after 14 months' therapy, which improved after somatropin was withdrawn.
- An 11-year-old girl with Turner's syndrome developed unilateral neovascularization after receiving somatropin for 22 months.

These patients improved but did not completely resolve after somatropin was withdrawn.

Somatropin concentrations correlate with retinopathy in patients with diabetes. There are no prospective clinical reports of retinal findings in adult recipients of somatropin, and these are awaited to determine the true frequency of this complication.

Endocrine

Thyroid function tests are often altered by somatropin because of increased conversion of T4 to T3, but this is clinically insignificant at low doses (SEDA-21, 453). One child with Prader–Willi syndrome had a fall in serum thyroxine concentration during somatropin therapy and needed thyroxine replacement (26). Hypothyroidism developed in 11 of 46 growth hormone-deficient children treated with somatropin (27). Prior abnormalities in hypothalamic-pituitary function and alterations in thyroid hormone metabolism, probably both, contributed to the high incidence of hypothyroidism, which was similar to that in previous studies.

Three adolescent boys with chronic renal insufficiency, treated with somatropin during the pubertal growth spurt, developed severe hyperparathyroidism (28). It is unclear whether this was coincidental or whether growth hormone and sex steroid hormones had a synergistic effect.

There have been occasional reports of gynecomastia attributed to somatropin (SEDA-21, 453).

Metabolism

Hyperinsulinemia is common in recipients of somatropin, but the long-term effects are controversial. This issue is becoming increasingly important as more adult patients are treated and the duration of therapy is extended. Growth hormone deficiency is itself associated with insulin resistance (29). Plasma concentrations of glucose and hemoglobin A_{1C} increase, especially in the first 6–12 months, indicating relative insulin resistance (30,31); the increases are often within the reference ranges (4,32).

Plasma glucose is inconsistently described as showing a sustained increase within the reference range, a transient increase, or no change. This reflects both the small non-controlled populations reported and possible selection bias, with exclusion of some patients because of hyperglycemia before the start of a cohort study (32). Hyperglycemia has occasionally been reported in patients

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receiving very high doses of human growth hormone for catabolic conditions, but has usually not required specific treatment (33). In a 6-month randomized study of 74 men and 57 women aged over 65 years, diabetes or glucose intolerance developed in 18 men treated with somatropin compared with seven controls (34).

Diabetes mellitus was previously not thought to be more common in recipients of somatropin than in the general population (SEDA-13, 1308) (35). However, longer-term observations have shown a three-fold incidence compared with predicted rates of type II diabetes, probably representing a younger age of onset rather than an increase in de novo cases (36).

In 78 children treated with somatropin for 7 years the mean fasting glucose concentration increased significantly compared with baseline after both 1 and 6 years of somatropin treatment, but remained the reference range and was not higher at 6 years than at 1 year (30).

In a 5-year study, 67 children treated with somatropin all had a sustained increase in fasting and oral glucose-stimulated insulin concentrations. This was most significant in children on dialysis and with renal transplants (37). In another study, insulin secretion in response to intravenous glucose was increased in 14 children with renal insufficiency, but returned to baseline after 12 months. However, increased insulin concentrations persisted in nine girls with Turner's syndrome (38). Concomitant glucocorticoid and somatropin treatment in children with juvenile arthritis caused a small but significant rise in blood glucose and glycosylated hemoglobin, which returned to pretreatment concentrations after somatropin was withdrawn (39).

Of 21 children, 15 developed hyperglycemia in a study of high-dose somatropin (0.2 mg/kg/day) for burns (40). In another study of 29 children with renal insufficiency (a group known to have insulin resistance), integrated insulin concentrations increased significantly in the first year of somatropin treatment, with no associated change in plasma glucose or glycated hemoglobin (41).

In a retrospective study, the fasting glucose:insulin ratio, a marker of insulin resistance, fell more in girls with Turner syndrome than in children with idiopathic short stature during somatropin therapy. The lower glucose:insulin ratio was due to increased fasting insulin and correlated with increased body mass index (42).

- Diabetes occurred 2 months after somatropin was begun in a 14 year-old girl, with restoration of normoglycemia after it was withdrawn (43).

In a postmarketing review of over 20 000 patients, type II diabetes was three times more common than expected, probably because at-risk individuals became diabetic at an earlier age than predicted (36). In a postmarketing review of 23 333 children and adolescents (52 375 treatment years), the incidence of type I diabetes was not significantly increased. However, type II diabetes occurred in 46 and 28 per 100 000 treatment years in children aged 10–19 and 6–14 years respectively (six times greater in both age groups than published reference values). There was no difference in incidence between boys and girls. A further 42 children developed abnormal glucose tolerance (44). Diabetes and glucose intolerance did not resolve after somatropin was withdrawn. Children who became diabetic were usually pubertal and had received somatropin for a longer period. Obesity, a risk factor for type II diabetes in the general population, was uncommon in these children.

Experience in adults is more limited, and monitoring is essential (45). Studies of somatropin in adults have consistently shown increased plasma concentrations of glucose, glycated hemoglobin, and insulin (46,47). Glucose intolerance and frank diabetes mellitus have been frequently reported in small series (46,48). Hyperglycemia not requiring specific treatment has been reported more often in adult patients (9) and in patients receiving high-dose somatropin to treat wasting associated with burns or HIV infection (33,49), but the overall incidence has not been compared with that in the general population.

In 25 patients a depot formulation of somatropin was associated with a non-sustained increase in glucose and insulin concentrations, more pronounced in men (50).

In a double-blind, placebo-controlled study of 24 growth hormone-deficient adults treated for 4 months with somatropin 2 IU/day, the treated patients had a significant increase in fasting plasma glucose and insulin concentrations, and increased insulin resistance, determined by insulin AUC during oral and intravenous glucose tolerance testing (8). Similarly, a group of 30 adolescents who were not growth hormone-deficient, and who were treated with somatropin for a mean of 7.9 years, had significantly reduced insulin sensitivity and raised plasma glucose concentrations during treatment, returning to control concentrations after somatropin was withdrawn (51). One of these patients developed glucose intolerance.

In a study of high-dose somatropin (0.1 mg/kg/day) in 20 patients with severe burns (a condition that causes insulin resistance), 60% of the treated patients required insulin therapy for hyperglycemia compared with 25% of the controls (52). This study was limited by the fact that the treated patients had more severe burns than the controls.

In a high-dose study in eight HIV-positive men, oral glucose tolerance worsened in the first month of human growth hormone 3 mg/day, then improved toward baseline. Mild glucose intolerance was still present after 6 months, despite a reduction in visceral fat. One man with pre-existing glucose intolerance developed symptomatic diabetes within 2 weeks of starting somatropin (53).

- Acanthosis nigricans, which is characterized by dark velvety thickening of the skin on the nape of the neck and in the groins and axillae, has been described in a non-obese 10-year-old boy with achondroplasia who received somatropin 3–4 IU/week for 7 years (54).

There has been one previous report of acanthosis nigricans in a woman who received human pituitary extract (55). This condition is usually seen in hyperinsulinemic states, including diabetes mellitus and acromegaly; overstimulation at the IGF-I receptor is probably the final common pathway.

Mineral balance

Hypercalcemia, usually mild and not requiring specific treatment, was reported in 43 of 100 patients receiving high-dose somatropin in intensive care (SEDA-13, 1308) (56).

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Fluid balance

Edema is three times more frequent with a dose of somatropin of 0.025 mg/kg/day than 0.0125 mg/kg/day (57). In a randomized, controlled study of 33 obese women, three of nine who received somatropin and two of seven who received somatropin plus insulin-like growth factor-1 withdrew from the study, because of intolerable edema, compared with none in the placebo group. Most patients receiving somatropin required diuretic treatment for edema in this study, in which dose was calculated according to body weight (58). In a randomized, placebo-controlled trial of growth hormone replacement in 166 hormone-deficient adults, 48% of the treated group and 30% of the placebo group reported mild to moderate edema, which resolved in 70% of subjects despite continued treatment (9).

Hematologic

Leukemia has been reported in several patients treated with somatropin. However, when other risk factors are accounted for, there is no current evidence that it increases the risk significantly above population levels (SEDA-23, 468) (59).

- Acute myelogenous leukemia was diagnosed in a 25-year-old man with hypopituitarism, 4 months after he started to use somatropin three times a week (60).

The time interval in this case was too short to implicate somatropin as a definite cause.

Gastrointestinal

Nausea, which did not require specific treatment, occurred within 72 hours after an injection of long-acting somatropin in six of 25 patients (50).

Skin

Injection site reactions to somatropin are common and include nodules, pain, and erythema. They usually resolve spontaneously (21,27). In a 2-year study of once- or twice-monthly injections of a modified-release formulation of somatropin in 56 prepubertal children, injection site reactions were common, especially in the first year of treatment. These included skin nodules in 56% of injections, erythema in 49%, and lipoatrophy in 12% (61).

- A 12-year-old boy developed lipohypertrophy at the site of somatropin injection (62). Site rotation gave partial resolution.
- A 51-year-old woman with both panhypopituitarism and liver disease developed localized abdominal lipohypertrophy during somatropin therapy (63).

The authors of the second report speculated that hepatic IGF-1 secretion was compromised and that peripheral somatropin reached supraphysiological concentrations.

Lipoatrophy, a transient loss of subcutaneous fat identifiable as skin dimpling, occurred in 11% of injections in 75 children who were given modified-release somatropin for 12 months (21) and in one of 68 children in another study (27). Site rotation is recommended to prevent lipodystrophy.

Non-neoplastic pigmented nevi may increase in number in patients treated with somatropin (SEDA-21, 453).

Musculoskeletal

Arthralgia and proximal myalgia are common with somatropin, especially with large doses or rapid dose escalation (3,49,57,58).

A slipped capital femoral epiphysis was reported in 26 of 16 500 patients in one study: it is less common in children with idiopathic short stature than those with a known cause of growth failure (64).

Growth acceleration makes scoliosis more apparent in less than 1% of children treated with somatropin, many of whom also receive spinal irradiation. A causative role for somatropin has not been substantiated (65).

There are conflicting reports on a possible increased risk of fractures in children with osteogenesis imperfecta treated with somatropin, many of whom have a qualitative defect in collagen (66,67).

- A boy with osteogenesis imperfecta, with no previous fractures, who received somatropin from age 5 to 14, had four fractures during his pubertal growth spurt, similar to two previous case reports (68).

Immunologic

Patients treated with recombinant somatropin commonly develop antibodies against growth hormone; the incidence is 22–88% (69). There were low titers of antigrowth hormone antibody, with no reduction in growth response, in 44% of children who used modified-release somatropin once a month and in 68% who used it twice a month (21). Antibodies almost never have clinical significance, but the fourth case of reduced growth due to neutralizing antibodies against growth hormone has been reported in a 9-year-old boy; growth resumed after he was changed to a methionyl-free human formulation of somatropin (69).

Systemic allergic reactions to somatropin are very rare, but can be overcome by desensitization (SEDA-13, 1308) (70). Although early studies suggested a higher rate of renal transplant rejection in recipients of somatropin than in controls (SEDA-21, 452), this was not confirmed in a long-term prospective study (71).

- In a 15-year-old boy with previously quiescent lupus nephritis, laboratory markers of disease activity rose during somatropin treatment and returned to baseline concentrations within 3 months after withdrawal (72).

Long-Term Effects

Tumorigenicity

The incidence of malignancy is increased in acromegaly, in which growth hormone is present in excess. Patients treated with growth hormone have therefore been carefully monitored. The first report of leukemia in Japanese children treated with growth hormone (73) prompted a worldwide survey. There have been reports of 44 new cases of leukemia in growth hormone recipients, of which only 20 were acute lymphoblastic leukemia. This is much less than the expected 80–85% of new childhood leukemia (74).

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A review of Japanese patients found that of the 15 patients who had developed hematological malignancies since 1975, 6 had other risk factors for leukemia, such as Fanconi's syndrome or prior chemotherapy or radiotherapy. The incidence of leukemia in this study was 3 per 100 000, similar to that in the general population of the same age (59). The National Cooperative Growth Study (NCGS—a postmarketing database that includes 19 846 patient-years since the time of growth hormone exposure) similarly reported no increase in the incidence of new leukemia when patients with other risk factors were excluded from the analysis (75).

The recurrence rate of intracranial tumors has been addressed in a number of large observational studies. Reports from the NCGS database (which includes 1262 children with brain tumors) and from England have shown no increase in intracranial tumor recurrence in patients treated with growth hormone (76,77). For patients with craniopharyngioma, postoperative irradiation reduced the recurrence rate, but growth hormone therapy did not increase the risk (78).

In the NCGS study extracranial non-leukemia malignancy rates were similarly not increased in patients treated with growth hormone compared with those who were not (79).

Despite theoretical concerns, there is no evidence that either intracranial or extracranial malignancy, new or recurrent, is increased in subjects treated with growth hormone (76,78,79). Despite this, certain precautions are still recommended for children who have previously been treated for cancer. The diagnosis of growth hormone deficiency should be clearly established (74) and it is recommended that treatment be delayed for at least 1 year after tumor therapy has been completed (36).

In a cohort study in 1848 British patients who received human pituitary-derived growth hormone from 1959 to 1985 (30 000 patient-years), there were two cases of colorectal cancer (0.25 expected) and two cases of Hodgkin's disease (0.85 expected); the standardized mortality ratios were 10.8 and 11.4 respectively (80). However, the number of cancers was small and the doses used were higher than typically today, and these results should be interpreted with caution.

Second-Generation Effects

Teratogenicity

Only a few pregnancies have been reported in women treated with somatropin. Eight women with hypopituitarism were followed prospectively during 12 pregnancies at a mean daily pregestation dose of 0.5 mg/day. The dose of somatropin was gradually reduced during the second trimester and withdrawn at the start of the third trimester. No congenital abnormalities were observed and weight and length at birth were normal (81).

Susceptibility Factors

Age

Most of the information about the long-term safety of somatropin in children has been derived from databases voluntarily maintained by two pharmaceutical companies; thus, there may be under-reporting. Other trials have generally been of short duration, with few participants, and may thus have been subject to type II error. The effectiveness and safety of somatropin in children has been the subject of a systematic review (82).

Sex

Somatropin is being increasingly prescribed for growth hormone-deficient adults. Men have more adverse effects than women, probably because of a greater IGF-1 response (83). This was also seen in 74 elderly men and 57 elderly women in a controlled trial, and was not influenced by concomitant sex steroid therapy (34).

Drug Administration

Drug dosage regimens

One recommended regimen is to start somatropin in a dosage of 0.15 mg/day and titrate upward (SEDA-14, 1521). Very high dosages (0.1–0.2 mg/kg/day, 10–20 times higher than replacement dosages given to adults with growth hormone deficiency) were given to 532 critically ill patients in intensive care units in two placebo-controlled trials (84). Mortality was significantly higher in the treated group than in the placebo group (42 versus 18%). Morbidity was also increased in somatropin recipients, who needed longer ventilator times.

Early studies using doses of somatropin that have been derived from pediatric experience had a high rate of adverse effects, and doses have been progressively reduced. In a 6-month, multicenter, randomized study, 302 adults were given somatropin 3 micrograms/kg/day, increasing to 6 micrograms/kg/day after 3 months, and 293 were given 6 micrograms/kg/day, increasing to 12 micrograms/kg/day (85). The lower dose was associated with significantly fewer adverse events (in particular, arthralgia in 12 versus 20%). However, 78% of women or patients with childhood-onset growth hormone deficiency had subnormal IGF-1 concentrations, suggesting that treatment should be titrated to IGF-1 concentrations and adverse effects.

Drug–Drug Interactions

Ciclosporin

Growth hormone increases the activity and regulates the gene expression of hepatic CYP3A4 (86). Mean blood concentrations of ciclosporin were lower during somatropin therapy in an open study in 16 prepubertal kidney transplant recipients, despite stable weight-related doses, suggesting that the metabolism of ciclosporin was increased by somatropin. Two patients had acute episodes of rejection during somatropin therapy; one of these may have been related to the fall in ciclosporin concentration (87).

Estradiol

In eight postmenopausal growth hormone-deficient women randomized to estradiol, either orally 2 mg/day

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or transdermally 100 micrograms/day, together with incremental doses of somatropin in an 8-week, crossover study, oral but not transdermal estrogen reduced IGF-1 concentrations, protein synthesis, and postprandial lipid oxidation rates (88). This confirms the results of a previous report (89). The mechanism is not known, but high portal estrogen concentrations after oral estrogen administration probably alter hepatic growth hormone metabolism.

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Sotalol

See also Beta-adrenoceptor antagonists

General Information

Sotalol is a non-selective beta-adrenoceptor antagonist with no partial agonist or membrane-stabilizing activity. It is also a class III antidysrhythmic drug. The beta-adrenoceptor antagonist properties of D,L-sotalol reside in the L-isomer, the D-isomer having class III antidysrhythmic activity and no clinically significant beta-blocking action (1).

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Quinidine and sotalol have been compared in a prospective multicenter trial of 121 patients after conversion of atrial fibrillation (2). Patients with low left ventricular ejection fractions (below 0.4) or high left atrial diameters (over 5.2 cm) were excluded. After 6 months the percentages of patients remaining in sinus rhythm were similar in the two groups (around 70%), but when the dysrhythmia recurred, it occurred later with sotalol than with quinidine (69 versus 10 days). There was also a difference between patients who had been converted from recent onset atrial fibrillation, in whom sotalol was more effective than quinidine, and in patients who had had chronic atrial fibrillation for more than 3 days, in whom quinidine was more effective. There were significant adverse effects requiring withdrawal of therapy in 17 patients, of whom nine were taking quinidine; three patients had gastrointestinal symptoms, two had central nervous symptoms, two had allergic reactions, one had undefined palpitation, and one had QT interval prolongation. One patient taking quinidine, a 65-year-old man, had frequent episodes of nonsustained ventricular tachycardia.

Organs and Systems

Cardiovascular

Sotalol prolongs the QT interval and can predispose to torsade de pointes (3), sustained ventricular tachycardia, and cardiac arrest, especially in those taking 160 mg/day or more (SEDA-16, 191). Torsade de pointes has been reported in 1.2% of those exposed (data on file, Bristol-Myers Squibb, Princeton, New Jersey). In a review it was concluded that torsade de pointes is also more likely in patients with depressed left ventricular function and a history of sustained ventricular tachydysrhythmias (4).

Several publications involving 962 patients treated with an intravenous infusion of racemic sotalol have been reviewed, with the aim of describing the risk of torsade de pointes (5). Torsade de pointes occurred in only one case (0.1%; 95% CI = 0.003, 0.6), which is less often than with oral sotalol (2–4%). This difference can be explained by the shorter duration of treatment. The other reported complications were hypotension (0.3%), severe bradycardia (0.2%), and atrioventricular block necessitating drug withdrawal (0.03%).

In a survey of 1288 patients taking sotalol, dysrhythmias occurred in 56, in 24 cases torsade de pointes (3). There was no relation between these dysrhythmias and previously associated factors, such as bradycardia, a long QT interval, and hypokalemia, but in patients on hemodialysis even a low dosage (40 mg bd) can be associated with torsade de pointes (6). Similar prodysrhythmic effects have been reported in children (7).

Death

A trial of the efficacy of D-sotalol in patients with left ventricular dysfunction (8) was discontinued early when an interim analysis of 2762 patients showed an overall mortality of 3.9% in the D-sotalol group, compared with 2% in the placebo group (9).

Susceptibility Factors

Some patients with thyrotoxicosis have occult cardiac dysfunction. However, the use of beta-blockers in the treatment of thyrotoxicosis can have severe consequences in terms of severe cardiac dysfunction (10).

- A 52-year-old woman developed atrial fibrillation with a ventricular rate of 220/minute. She had had thyrotoxicosis 20 years before, but was taking no medications. She had an 8-month history of weight loss with a normal appetite. During the previous month she had had excessive sweating, palpitation, and exercise intolerance. The diagnosis was thyroid storm. She was given intravenous sotalol 1 mg/kg over 15 minutes and within 5 minutes sinus rhythm was restored, with improvement of symptoms. However, immediately after the infusion she had an episode of ventricular tachycardia followed by sinus bradycardia, with a resultant fall in blood pressure, followed by an asystolic cardiac arrest. She underwent endotracheal intubation and was treated with inotropes. Right-heart catheterization showed severe cardiac dysfunction (cardiac index 1.2 l/minute). She made an uneventful recovery.

Patients with severe hyperthyroidism can have an occult cardiomyopathy that makes them extremely sensitive to beta-blockers. The long duration of action of sotalol in this case necessitated prolonged inotropic and vasopressor support. A shorter-acting beta-blocker, such as esmolol, could theoretically be safer in such cases.

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Sparfloxacin

See also Fluoroquinolones

General Information

Sparfloxacin is a fluoroquinolone with activity against the major respiratory pathogens and atypical pathogens that cause pneumonia. Photosensitivity, nausea, and diarrhea have been the most common adverse events reported in trials, and sparfloxacin is contraindicated in patients with QT interval prolongation (1).

In an in vivo study in rats, endotoxin reduced the biliary excretion of sparfloxacin and its glucuronide, probably owing to impairment of hepatobiliary transport systems and renal handling (2).

Observational studies

The efficacy and safety of sparfloxacin (400 mg loading dose followed by 200 mg/day for 10 days) in the treatment of acute bacterial maxillary sinusitis have been evaluated in 253 patients (3). The overall success rate was 92%. The majority of adverse events were mild or moderate and the most frequent were photosensitivity reactions, headache, nausea, and diarrhea.

Comparative studies

Analysis of safety data from six multicenter phase III trials in 1585 patients comparing sparfloxacin with standard drugs (cefaclor, ciprofloxacin, clarithromycin, erythromycin, and ofloxacin) showed that 25% of patients treated with sparfloxacin and 28% of patients treated with the other drugs had at least one adverse event considered to be related to the study medication (4). Photosensitivity reactions were seen in 7.4% of treatment episodes with sparfloxacin, compared with 0.5% of episodes with the other drugs. Gastrointestinal reactions, insomnia, and alterations in taste were more common in patients taking the comparator drugs. The mean change from baseline QT interval corrected for heart rate (QT_c) was significantly greater with sparfloxacin, but no ventricular dysrhythmias were detected. Study medication was withdrawn in 8.9% of patients taking the comparator drugs and in 6.6% of those taking sparfloxacin.

Organs and Systems

Cardiovascular

Some quinolones can prolong the QT interval, with a risk of cardiac dysrhythmias.

Sparfloxacin causes greater prolongation of the QT interval than other quinolones (5), as has been shown in in vitro comparisons. Compared with grepafloxacin, moxifloxacin, and ciprofloxacin, sparfloxacin caused the greatest prolongation of the action potential duration (6), and in an in vitro comparison of sparfloxacin, ciprofloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sitafloxacin, tosufloxacin, and trovafloxacin, sparfloxacin caused the largest increase in QT interval (7). In an in vivo study in conscious dogs with stable idioventricular automaticity and chronic complete atrioventricular block, oral sparfloxacin 60 mg/kg caused torsade de pointes, leading to ventricular fibrillation within 24 hours, while 6 mg/kg did not (8). In halothane-anesthetized dogs, intravenous sparfloxacin 0.3 mg/kg prolonged the effective refractory period, and an extra 3.0 mg/kg reduced the heart rate and prolonged the effective refractory period and ventricular repolarization phase to a similar extent, suggesting that a backward shift of the relative repolarization period during the cardiac cycle may be the mechanism responsible for the dysrhythmogenic effect of sparfloxacin. Data from in vitro electrophysiological studies of the effect of sparfloxacin, ofloxacin, and levofloxacin on repolarization of rabbit Purkinje fibers indicate that the prolongation of the action potential is observed only with sparfloxacin (9).

In a double-blind, randomized, placebo-controlled, crossover study of a single oral dose of sparfloxacin in 15 healthy volunteers, prolongation of the QT interval was about 4% greater with sparfloxacin than with placebo (10). An independent Safety Board concluded from the results of various phase I and phase II studies that the increase in the QT_c interval associated with sparfloxacin is moderate, averaging 3%, and that the few serious adverse cardiovascular events that have been reported during postmarketing surveillance all occurred in patients with underlying heart disease (11).

In 25 patients taking sparfloxacin for multiresistant tuberculosis, there were six cases of moderate prolongation of the electrocardiographic QT interval (30–40 ms compared to baseline) without clinical symptoms (12).

- A 37-year-old woman who was taking sparfloxacin as part of modified antituberculosis drug therapy developed torsade de pointes (13).

Sensory systems

Abnormal taste developed in 17 of 175 patients treated with clarithromycin 250 mg bd for 10 days for community-acquired pneumonia, compared with three of 167 patients treated with sparfloxacin (14). Mild to moderate gastrointestinal disturbances were the most common adverse events and were reported in 13 and 11% respectively.

Skin

During the first 9 months of marketing of sparfloxacin, 371 severe phototoxic reactions were reported to the French pharmacovigilance system or the manufacturers, reporting rate of 0.4 per thousand treated patients (about 4–25 times that reported with other fluoroquinolones) (15).

Phototoxicity occurred in four of nine patients with multidrug-resistant tuberculosis treated with a combination of sparfloxacin (400 mg/day), ethionamide, and kanamycin (initially for 3–4 months) (16). It occurred after several months of treatment and was presumably due to

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the sparfloxacin. Sparfloxacin more commonly causes photosensitivity than ciprofloxacin, levofloxacin, or ofloxacin, which are also effective antituberculosis drugs (15,17). Skin reactions can be severe enough to require withdrawal of sparfloxacin in some patients. In view of this, other fluoroquinolones, particularly ofloxacin, are preferable to sparfloxacin in the management of multidrug-resistant tuberculosis.

In 25 patients taking sparfloxacin for multidrug-resistant tuberculosis, there were five mild phototoxic reactions (12).

Long-Term Effects

Mutagenicity

DNA damage produced by sparfloxacin and UVA in retinal pigment epithelial cells in vitro was remedied by antioxidants, suggesting a possible in vivo strategy for preventing or minimizing retinal damage in humans (18).

Susceptibility Factors

Patients with a history of cardiac disease and patients taking other medications with effects on cardiac repolarization should not be given sparfloxacin, in order to prevent any cumulative inhibitory effect on cardiac repolarization.

Drug–Drug Interactions

Antacids

The absorption of sparfloxacin is impaired by antacids containing aluminium or magnesium (19). In an open, single-dose (400 mg), randomized, four-way crossover study in 20 male volunteers (aged 18–38 years), Maalox (30 ml) given 4 hours after sparfloxacin did not cause a statistically significant reduction in the rate and extent of sparfloxacin absorption. In contrast, Maalox given 2 hours before or 2 hours after sparfloxacin did reduce its absorption: AUC fell by 23 and 17% respectively and mean C_{max} by 29 and 13% (20).

Cisapride

Concomitant administration of cisapride increased the rate of absorption and increased the peak concentration of sparfloxacin without having a significant effect on systemic availability (21,22).

Sucralfate

Co-administration of sucralfate leads to a 44% reduction in the systemic availability of sparfloxacin (22). In eight healthy Japanese, the absorption of sparfloxacin (300 mg orally) was reduced when sucralfate (1.5 g orally) was administered concurrently or 2 hours after sparfloxacin, but not 4 hours after sparfloxacin (23).

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Sparteine

General Information

Sparteine is a major quinolizidine alkaloid found in a variety of plants:

- *Ammodendron conollyi*
- *Anagyris fetida*
- *Baptisia australis*
- *Baptisia tinctoria*
- *Chelidonium majus*
- *Cytisus scoparius*
- *Genista lucida*
- *Lupinus argentus*
- *Lupinus laxus*
- *Lupinus luteus*
- *Lupinus niger*
- *Lupinus polyphyllus*
- *Sarothamnus scoparius*
- *Sophora pachycarpa*
- *Sophora secundiflora*
- *Spartium junceum*
- *Spartium scoparium.*

Sparteine has been used as a marker of the metabolic activity of CYP2D6 (1). Pharmacokinetic studies have shown that its metabolic oxidation exhibits genetic polymorphism and that about 6–9% of the Caucasian population are poor metabolizers. Quinidine, haloperidol, and moclobemide are all potent inhibitors of the oxidative metabolism of sparteine (2).

Among the reported effects of sparteine are reduced cardiac conductivity, stimulation of uterine motility, circulatory collapse, and respiratory arrest. Sparteine was contained in a slimming aid ("Herbal Slimming Aid," UK). It was formerly used to induce labor; at the very least it should be considered contraindicated during pregnancy.

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Spectinomycin

General Information

Spectinomycin is an aminocyclitol antibiotic, distinct from the aminoglycosides. It has been used mainly in single-dose treatment of gonorrhea (2 g intramuscularly), and for treating organisms with multiple antibiotic resistance (1–3). Apart from induration at the site of injection, tolerance in otherwise healthy individuals has been good, even with doses of 8 g/day for 21 days. Allergic reactions have been observed, but are rare. Spectinomycin-resistant gonococci have been found (4,5).

Long-Term Effects

Drug tolerance

Aminoglycoside adenylyltransferase (aadA) genes mediate resistance to streptomycin and spectinomycin. In a pathogenic porcine *Escherichia coli*, the novel aaA5 has now been described integrated with a trimethoprim resistance gene (6). The aadA6 gene has been sequenced from *Pseudomonas aeruginosa* and can confer high-level resistance to spectinomycin in *E. coli* (7). All strains of multidrug resistant *Vibrio cholerae* O1 El Tor isolated in Albania were resistant to spectinomycin, and resistance to this antibiotic was mediated by the aadA1 gene cassette located in the bacterial chromosome within a class 1 integron (8). Another class 1 integron that contained aadA2 was found in pathogenic *Salmonella typhimurium* isolates from France and was also chromosomally located (9). An aadA gene has also been described in *Enterococcus faecalis* (10).

Resistance of *E. coli* isolates from chicken in Saudia Arabia was 96% compared with 71% among human isolates (11). Serotyping showed an overlap between human and chicken strains, suggesting that these animals may serve as a resistance pool for humans.

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Spiramycin

See also Macrolide antibiotics

General Information

Spiramycin is a macrolide antibiotic with activity primarily against *Staphylococcus aureus*, beta-hemolytic streptococci, and viridans streptococci. Since spiramycin is retained in bone and the salivary glands and reaches prolonged high concentrations in the saliva, it is used mainly by dentists and otorhinolaryngologists. Because of high concentration in the tonsillar lymphoid tissue it has been proposed that spiramycin be used in the prevention of meningococcal infections. It does not reach the cerebrospinal fluid. Its toxicity is relatively low. Adverse effects include nausea, vomiting, diarrhea, and skin rashes (1).

Organs and Systems

Cardiovascular

QT interval prolongation (2) and torsade de pointes (3) occur rarely in patients taking spiramycin.

Hematologic

Hematological toxicity, including bone marrow suppression (4) and hemolysis (5), has been observed, especially during combined treatment with spiramycin and pyrimethamine for toxoplasmosis.

Liver

Cholestatic hepatitis occurred in a patient taking spiramycin (6).

Immunologic

A peculiar hypersensitivity reaction was reported in an employee of a pharmaceutical company who developed attacks of sneezing, coughing, and breathlessness while working with spiramycin; he had immediate positive skin prick tests to spiramycin and developed blood eosinophilia during asthma attacks (7).

Henoch–Schönlein purpura occurred in a patient taking spiramycin (8).

Drug–Drug Interactions

Neuroleptic drugs

Acute dystonia was observed during spiramycin therapy in a patient who was being treated with neuroleptic drugs (9).

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Spironolactone

See also Diuretics

General Information

Spironolactone is a competitive antagonist at aldosterone receptors. It acts through its active metabolite, canrenone. Canrenone itself has also been used as a potassium-sparing diuretic for intravenous use and its potassium salt has been used orally, in the hope of avoiding the hormonal adverse effects of spironolactone.

Spironolactone has been used as a potassium-sparing diuretic in cardiac failure and in the management of ascites and edema associated with hepatic cirrhosis with secondary hyperaldosteronism. It is also used to treat hyperaldosteronism due to adrenal tumors or adrenal hyperplasia. It has a weak positive inotropic effect and a modest antihypertensive effect, in keeping with its natriuretic action.

Although spironolactone has been available for more than 30 years, its efficacy and safety in patients with heart failure have only recently been recognized in the Randomized Aldosterone Evaluation Study (RALES), in which it reduced mortality (1). Based on this and numerous smaller trials, the use of spironolactone, in conjunction with ACE inhibitors, other diuretics, and possibly beta-blockers or digoxin, represents a promising strategy for patients with severe heart failure. Its main adverse effects are hyperkalemia and antiadrenergic complications (SED-14, 675).

General adverse effects

The major limitation to the use of spironolactone is its liability to cause (sometimes lethal) hyperkalemia, particularly in the elderly, in patients with reduced renal function, and in patients who simultaneously take potassium supplements or ACE inhibitors. As with other diuretics, hyponatremia and dehydration can occur. Other less frequent adverse effects are gastrointestinal intolerance, neurological symptoms, and skin rashes. Hypersensitivity rashes and a lupus–like syndrome have been reported rarely. A few cases of mammary carcinoma have been reported and potential human metabolic products of spironolactone are carcinogenic in rodents. Second-generation effects have not been reported.

Organs and Systems

Nervous system

Central nervous system effects, such as weakness, drowsiness, and confusion, have been reported in patients taking spironolactone. Because most patients with such adverse effects were taking spironolactone for edema and ascites in hepatic cirrhosis, it is not yet clear whether they were caused by the drug itself or by hepatic encephalopathy. The incidence of these complaints in such patients is quite high (9.8%) (SED-9, 357).

Electrolyte balance

The beneficial effects of spironolactone in congestive cardiac failure and hypertension are additive to those of ACE inhibitors. In the RALES, patients taking an ACE inhibitor who were randomized to spironolactone 25–50 mg/day had only a 0.3 mmol/l increase in median potassium concentration (1). Although the difference between the spironolactone and placebo groups was statistically significant, the mean increase was not clinically important, and the incidence of serious hyperkalemia was minimal in both groups of patients.

However, since the publication of RALES the incidence of hyperkalemia attributable to spironolactone has increased. Trends in the rate of spironolactone prescriptions and the rate of hospitalization for hyperkalemia in ambulatory patients before and after the publication of RALES have been examined in a population time-based series analysis (2). Among patients treated with ACE inhibitors who had recently been hospitalized for heart failure, the spironolactone prescription rate increased immediately after the publication of RALES, from 3.4% in 1994 to 15% in late 2001. The rate of hospitalization for hyperkalemia rose from 0.2% in 1994 to 11% and the associated mortality rose from 0.3 to 2.0 per 1000 patients. These increases were particularly marked in elderly people.

It is essential to identify patients who are likely to develop serious hyperkalemia during combined treatment and to evaluate the associated morbidity and mortality. Spironolactone is used in patients with end-stage renal disease undergoing either peritoneal (3) or maintenance hemodialysis (4), although there is scant experimental evidence to support such use in advanced dialysis-dependent renal disease. Carefully selected dialysis patients exposed to doses of spironolactone ranging from 25 mg three times a week to 25 mg/day appeared not to have an increased frequency of hyperkalemia. However, these studies were preliminary and the results should not be extrapolated to the general dialysis population. If spironolactone is contemplated in patients with end-stage renal disease, periodic surveillance is necessary and other causes of hyperkalemia, such as ACE inhibitor therapy and/or a high potassium intake, should be controlled.

Close laboratory monitoring and judicious use of spironolactone is needed to reduce the risk of hyperkalemia. The excess of hyperkalemia in clinical practice compared with RALES can be explained largely by the use of higher doses of spironolactone and the inclusion of patients with lower glomerular filtration rates and whose aldosterone-mediated compensatory distal tubular potassium excretion is already attenuated (5). Such patients include elderly people, people with diabetes, and those taking beta-blockers, non-steroidal anti-inflammatory drugs, potassium salts, potassium-sparing diuretics, or trimethoprim.

Hematologic

Rare cases of agranulocytosis have been reported in patients taking spironolactone (SEDA-22, 239).

- Agranulocytosis occurred in an 87-year-old man with congestive heart failure who took spironolactone 25 mg/day for 3 weeks (6). The agranulocytosis rapidly

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reversed after withdrawal of spironolactone and a short course of granulocyte-colony-stimulating-factor.
- A 43-year-old woman with cirrhosis and hepatocellular carcinoma took spironolactone for 7 days before leukopenia was detected (7). The leukocyte count returned to normal 8 days after withdrawal of spironolactone.

In general, the onset of agranulocytosis with spironolactone ranges from 4 days to 5 weeks and it takes 5–7 days to resolve without the aid of a growth factor.

Gastrointestinal

Nausea and vomiting are more common with spironolactone than with other diuretics (SED-9, 358) and were reported in 11% of patients in the Boston Collaborative Drug Surveillance Program (8). These symptoms can be reduced in patients taking high doses by spreading the dose out during the day.

Liver

Two cases of spironolactone-induced parenchymal hepatitis have been reported. The patients recovered uneventfully (SEDA-20, 205).

- A 50-year-old woman taking spironolactone for androgenic alopecia developed hepatitis with minimal cholestasis 6 weeks after starting therapy (9). After withdrawal of spironolactone, her symptoms resolved and liver function tests improved. She was not rechallenged.

Skin

Rashes (sometimes with eosinophilia), lichen planus (SED-9, 358), and a lupus–like syndrome with a positive rechallenge (SEDA-5, 230) have been reported, but on the whole skin reactions seem to be rare.

Cutaneous vasculitis has been attributed to spironolactone (SED-11, 430). It is unclear whether a patient presenting with erythema annulare centrifugum while taking spironolactone (10) had a similar reaction.

Other reported adverse effects of spironolactone include urticaria, alopecia, and chloasma (SEDA-14, 185).

- A 76-year-old patient developed eczema-like lesions and severe pruritus; histological and immunological investigations showed pemphigoid (11). The skin lesions regressed spontaneously within 15 days of spironolactone withdrawal and no relapse was noted over the next 30 months.

Sexual function

Because of its antiandrogenic action, spironolactone causes gynecomastia, reduced libido, and erectile failure in 4–30% of men. These effects seem to be both dose- and time-dependent.

Reproductive system

Spironolactone causes breast tenderness and enlargement, mastodynia, infertility, chloasma, altered vaginal lubrication, and reduced libido in women, probably because of estrogenic effects on target tissue. Menstrual irregularities were experienced by almost all women taking spironolactone 400 mg/day and most developed amenorrhea at doses of 100–200 mg/day. Normal menstruation was resumed within 2 months of withdrawal.

Very high doses of spironolactone (over 450 mg/day) can cause infertility, but such doses are rarely used. As with other diuretics, studies with spironolactone have mostly been small, not placebo-controlled, and often anecdotal (SEDA-18, 235).

In patients with hepatic cirrhosis, gynecomastia was twice as common during treatment with spironolactone than with potassium canrenoate (42 versus 20%) at equiactive doses (12). This difference may be related to structural characteristics unique to metabolites of spironolactone, namely a thiol group at the 7-alpha position (SEDA-11, 200).

Long-Term Effects

Tumorigenicity

Spironolactone is antiandrogenic and increases the peripheral metabolism of testosterone to estradiol (13). It often causes gynecomastia in men and breast enlargement and soreness in women. Five cases of mammary carcinoma have been reported. Potential human metabolic products of spironolactone are carcinogenic in rodents, and the UK Committee on Safety of Medicines in 1988 restricted the approved indications for the drug, removing the indications of essential hypertension and idiopathic edema (14).

Susceptibility Factors

Age

It has been argued that potassium-sparing diuretics present a real risk of renal insufficiency when they are used in elderly people (15). In large-scale studies in elderly hypertensive patients there is indeed some slight increase in the incidence of renal insufficiency when combinations including potassium-sparing diuretics are used. Although the overall incidence of nephrotoxicity is quite low, elderly patients and those with prior renal dysfunction are at particular risk. Special care is necessary in these circumstances.

Renal disease

In patients with renal insufficiency there is an increased risk of hyperkalemia with spironolactone; serum potassium should be monitored regularly.

Hepatic disease

Hepatic failure carries an unwarranted risk unless serum potassium is regularly monitored (16).

Drug–Drug Interactions

ACE inhibitors

Co-administration of potassium-sparing diuretics with ACE inhibitors can cause severe hyperkalemia (SED-14, 674).

The effects of ACE inhibitors plus spironolactone have been evaluated in 25 patients (11 men, 14 women, mean age 74 years, five with diabetes mellitus) with a mean serum potassium concentration of 7.7 mmol/l (17). The mean

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serum creatinine was 336 μmol/l, the mean arterial pH 7.3, and the mean plasma bicarbonate 18 mmol/l. The main causes of acute renal insufficiency were dehydration ($n = 12$) and worsening heart failure ($n = 9$). The mean dose of spironolactone was 57 mg/day and 12 patients were also taking other drugs that can cause hyperkalemia. Two patients died and two were resuscitated and survived. Hemodialysis was necessary in 17 patients. The mean duration of hospitalization was 12 days. The combination of ACE inhibitors and spironolactone should be used cautiously in patients with chronic renal insufficiency, diabetes, older age, worsening cardiac failure, a risk of dehydration (for example diarrhea), and in those who are taking other drugs that can cause hyperkalemia (18). A dose of spironolactone of 25 mg/day should be exceeded only with caution. In four similar elderly patients with underlying renal insufficiency taking spironolactone there was an increased risk of hyperkalemia associated with diarrhea (19).

In a population-based, nested, case-control study, all patients aged 66 years or over who were taking an ACE inhibitor and who had been hospitalized for hyperkalemia were evaluated for interacting medications (20). Compared with controls taking ACE inhibitors who did not have hyperkalemia, before adjusting for confounding variables, the patients were 27 times more likely to have received a prescription for a potassium-sparing diuretic (type not specified) in the week before hospitalization. There was no such association between hospital admission for hyperkalemia and the use of indapamide in patients taking ACE inhibitors.

Angiotensin receptor antagonists

In eight healthy subjects, treatment with spironolactone and losartan increased mean plasma potassium concentration by 0.8 mmol/l (up to 5.0 mmol/l) and reduced mean urinary potassium excretion from 108 to 87 mmol/l (21). Until more data are available, it is prudent to consider angiotensin II receptor antagonists similar to ACE inhibitors as risk factors for hyperkalemia in patients taking potassium-sparing diuretics.

Antipyrine

Spironolactone has a weak enzyme-inducing effect and enhances the metabolic breakdown of phenazone (antipyrine) (SED-9, 358).

Aspirin

The renal tubular secretion of canrenone, the main metabolite of spironolactone, is blocked by aspirin (22), abolishing the diuretic response, although the antihypertensive effect is apparently not affected (23).

Carbenoxolone

Spironolactone abolishes the ulcer-healing properties of carbenoxolone (24).

Colestyramine

Colestyramine in combination with spironolactone has been reported to cause severe hyperkalemia (25), presumably because it causes exchange of chloride for bicarbonate in the small bowel, predisposing to hyperchloremic acidosis.

Digitoxin

Spironolactone has a weak enzyme-inducing effect and enhances the metabolic breakdown of digitoxin (SED-9, 358) (26). However, this effect may not be significant, because in six healthy subjects spironolactone prolonged the half-life of digitoxin from 142 to 192 hours (27).

Digoxin

Spironolactone increases steady-state digoxin concentrations by about 30%, probably by inhibiting the renal tubular secretion of digoxin by P glycoprotein. There may also be a pharmacodynamic interaction with digoxin. The clinical importance of these observations is uncertain (SEDA-9, 209).

NSAIDs

Some non-steroidal anti-inflammatory drugs, notably indometacin and mefenamic acid, inhibit the excretion of canrenone (28).

Warfarin

It has been suggested that spironolactone may reduce the anticoagulant effect of warfarin (SED-11, 430).

Interference with Diagnostic Tests

Radioimmunoassay of digoxin

Overestimation of the digoxin concentration

Spironolactone can alter the results of some digoxin radioimmunoassays, because it and its metabolites, such as canrenone and 7-alpha-thiomethylspironolactone, are immunoreactive with some forms of antidigoxin antibody (29–31). This results in an overestimate of the true digoxin concentration, because the assay reads the interfering substances as digoxin.

In a study of the use of the TDx II assay in 80 children and adults, there was apparent digoxin immunoreactivity in 3.7% of healthy subjects ($n = 80$), 3.6% of pregnant women ($n = 28$), 10% of patients with renal transplants ($n = 31$), and 23% of immature infants ($n = 40$) (32).

Underestimation of the digoxin concentration

In contrast to this, it has also been reported that spironolactone and its metabolite canrenone caused falsely low readings in a common assay for digoxin (AXSym MEIA) because of negative cross-reactivity (33). Misleading subtarget concentrations were repeatedly reported, and falsely guided increases in drug doses, resulting in digoxin intoxication.

In another study canrenoate interfered with the immunoassay of digoxin (33), reducing the apparent digoxin concentration. The effect was largest with the AxSym MEIA II assay, and there was also some interference with the EMIT assay. However, the TDx assay was not affected. Spironolactone also caused some interference in the AxSym assay but less than canrenoate. In this case the failure to measure high digoxin concentrations resulted in

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clinical toxicity in a 71-year-old man who was given 3.8 mg over 11 days.

In nine assays (AxSYM, IMx, TDx, Emit, Dimension, aca, TinaQuant, Elecsys, and Vitros) interference by spironolactone, canrenone, and three metabolites was sought in vitro, and all routine digoxin measurements using the AxSYM system over 16.5 months ($n = 3089$) were reviewed (34). There was a reduction in the expected concentrations by canrenone (3125 ng/ml) in the following assays: AxSYM (42% of expected), IMx (51%), and Dimension (78%). There was positive bias in aca (0.7 ng/ml), TDx (0.62 ng/ml), and Elecsys (>0.58 ng/ml). Of 669 routinely monitored patients, 25 had falsely low results and 19 of them actually had potentially toxic digoxin concentrations; this was attributable to concurrent therapy with spironolactone, canrenone, hydrocortisone, or prednisolone. However, standard doses of spironolactone (up to 50 mg/day) in patients with heart failure produced less than 11% inhibition.

Although several modern digoxin assays suffer from potentially negative interference from spironolactone and canrenone (34), there are assays that are less susceptible to interference by spironolactone (35). Laboratories should determine the false negative potential of the analytical method that they use.

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Stavudine

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Stavudine is a nucleoside analogue reverse transcriptase inhibitor. Its most important adverse effects are peripheral neuropathy and increases in hepatic transaminases, both of which usually resolve on withdrawal.

Organs and Systems

Nervous system

The principal toxic effect of stavudine is a peripheral neuropathy, with symptoms similar to the neuropathy associated with didanosine and zalcitabine (1,2). The development of this neuropathy depends on the duration of treatment, with an increasing risk after 12 weeks of treatment. A prior history of neuropathy increases the risk of stavudine-induced neuropathy. After withdrawal, the symptoms usually improve within 2 weeks, although they can persist for several months.

Metabolism

Lipodystrophy, a syndrome characterized by fat redistribution, hyperglycemia/insulin resistance, and dyslipidemia, can be associated with long-term HIV infection or with highly active antiretroviral therapy (HAART). In 1035 patients, those who took stavudine were 1.35 times more likely to report lipodystrophy (3). However, the study was retrospective, and other factors unrelated to specific drug therapy may have had a greater effect on the adjusted odds ratio.

Hematologic

A modest dose-related macrocytosis without an associated anemia can occur during treatment with stavudine (1,2).

Liver

Asymptomatic increases in hepatic transaminases, which are not clearly dose-related, can occur during treatment with stavudine, requiring dosage modification because of moderate or severe toxicity in about 10% of patients (1,2).

Urinary tract

Renal tubular dysfunction and hypophosphatemia occurred in a patient who was taking both stavudine and lamivudine (4).

Sexual function

Painful bilateral gynecomastia and hypersexuality, possibly related to the use of stavudine, have been reported (5).

- A 25-year-old HIV-infected man reported hot flushes and headaches during the first days of treatment with stavudine (40 mg bd), followed by swelling and tenderness under both nipples. He also reported increased libido, premature ejaculation, and persistent erections. He denied illicit drug use. He had bilateral gynecomastia. Luteinizing hormone and testosterone concentrations were within the reference ranges, excluding primary causes of gynecomastia. One month after withdrawal of stavudine, the swelling and tenderness had abated and his sexual symptoms had resolved. He was not rechallenged with the drug.

The authors argued that although idiopathic gynecomastia could not be ruled out, the temporal relation between withdrawal of the drug and improvement in his symptoms suggested a causative role of stavudine.

In a Swiss case-control study gynecomastia was associated with stavudine in 47 cases. Blood concentrations of luteinizing hormone were above the reference range in 40% of the cases and 29% had reduced testosterone concentrations (6).

Drug–Drug Interactions

Isoniazid

A distal sensory neuropathy is the commonest neurological complication in HIV-infected individuals, and has been documented in up to 30% of patients with AIDS. There is evidence from a retrospective case-note review in 30 individuals that co-administration of stavudine and isoniazid increases the incidence of distal sensory neuropathy. Of 22 patients taking stavudine in combination with other drugs, all took isoniazid for tuberculosis and 12 developed a distal sensory neuropathy, with a median time to onset of 5 months (7). Those taking stavudine alone had an incidence of 11%.

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Stem cell factor

General Information

Stem cell factor amplifies the proliferation and mobilization of myeloid, erythroid, and megakaryocyte colonies when combined with a lineage-specific hemopoietic growth factor (for example G-CSF, IL-3). Stem cell factor, added to other recombinant hemopoietic cytokines, is used to increase the mobilization of peripheral blood progenitor cells.

In preliminary trials, transient allergic-type reactions, that is urticaria, respiratory symptoms, and injection-site reactions, resulting from dose-dependent mast cell degranulation, were easily prevented by classical premedication (1).

In 102 patients with multiple myeloma, stem cell factor plus G-CSF produced more frequent injection site reactions and more frequent skin reactions (25 versus 2%), namely rash, erythema, urticaria, pruritus, and abnormal pigmentation, compared with G-CSF alone (2). These reactions occurred despite systemic prophylactic antihistamines. Other adverse effects occurred with similar frequency in the two groups of patients.

Organs and Systems

Immunologic

Stem cell factor produces direct mast cell stimulation with subsequent allergic-type reactions. Despite careful premedication with diphenhydramine, ranitidine, inhaled salbutamol, and pseudoephedrine, such reactions were still observed in 3% of patients (3).

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Stepronin

General Information

The adverse effects of stepronin, a sulfhydryl compound, which is used in rheumatoid arthritis, are similar to those of penicillamine. In a long-term open study, treatment had to be interrupted in 30% of 36 patients because of severe adverse effects (1). Seven patients had mucocutaneous reactions (dermatitis, pruritus, stomatitis, glossitis, ageusia), three proteinuria, and one thrombocytopenia and leukopenia.

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Sterculiaceae

See also Herbal medicines

General Information

The genera in the family of Sterculiaceae (Table 1) include cola, theobroma, and sterculia.

Table 1 The genera of Sterculiaceae

Ayenia (ayenia)
Brachychiton (brachychiton)
Chiranthodendron (chiranthodendron)
Cola (cola)
Firmiana (parasol tree)
Fremontodendron (flannel bush)
Guazuma (guazuma)
Helicteres (helicteres)
Heritiera
Hermannia (hermannia)
Kleinhovia (kleinhovia)
Melochia (melochia)
Pentapetes (pentapetes)
Sterculia (sterculia)
Theobroma (theobroma)
Waltheria (waltheria)

Sterculia species

The family of *Sterculia* plants (sterculia) yield a fiber that has bulk laxative effects. It is covered in the monograph on Laxatives.

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Stiripentol

See also Antiepileptic drugs

General Information

The clinical pharmacology and adverse effects of stiripentol have been reviewed (1).

The effects of stiripentol have been studied in 41 children with severe myoclonic epilepsy in infancy in a randomized, placebo-controlled, add-on trial (2). There were adverse effects in 21 patients taking stiripentol (drowsiness and loss of appetite) compared with five taking placebo, and the adverse effects disappeared when the doses of other antiepileptic drugs were reduced in 12 of the 21 cases.

Drug–Drug Interactions

Clobazam

When stiripentol 50 mg/kg was given to 20 children taking clobazam, mean serum clobazam and norclobazam concentrations increased about two-fold and three-fold respectively; a mean 25% reduction in clobazam dose was required because of adverse effects (3).

Valproic acid

Serum concentrations of concomitantly administered valproic acid rose by about 20% (3). These findings are in agreement with evidence that stiripentol is a potent metabolic inhibitor.

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Streptogramins

General Information

Pristinamycin (rINN) is a synergistic combination of streptogramin A (pristinamycin IIA) and streptogramin B (pristinamycin IB). It is active against the main bacteria that cause respiratory tract infections and could be useful in the treatment of acute or recurrent sinusitis, community-acquired pneumonia, or periodontal infection with *Actinobacillus actinomycetemcomitans* (1–5).

Quinupristin (rINN) and dalfopristin (rINN) are two semisynthetic pristinamycin derivatives that are given in combination parenterally. The combination has a broad spectrum of activity against Gram-positive bacteria, including multidrug resistant bacilli. A comprehensive review has been published (6). Quinupristin + dalfopristin can be used to treat macrolide-resistant streptococci, staphylococcal infections after failure of conventional therapy, or vancomycin-resistant *Enterococcus faecium* (and probably *Enterococcus raffinosus*), but not vancomycin-resistant *Enterococcus faecalis*, *Enterococcus avium*, *Enterococcus casseliflavus*, or *Enterococcus gallinarum* (7–19). Adverse effects include arthralgia, myalgia, and pain at the infusion site (20).

Observational studies

In a small, open, phase II pilot study, low-dose quinupristin + dalfopristin (5 mg/kg intravenously every 8 hours; $n = 11$) and high-dose quinupristin + dalfopristin (7.5 mg/kg intravenously every 8 hours; $n = 15$) were compared with vancomycin (1 g intravenously every 12 hours; $n = 13$) in the treatment of catheter-related staphylococcal bacteremia (21). In patients with a baseline pathogen, the outcome was comparable in all groups. Adverse clinical events in the quinupristin + dalfopristin group consisted of arm and chest pain, chills, fever, arthritis, and phlebitis or pain at the injection site; quinupristin + dalfopristin was withdrawn in 12% of patients (compared with 15% of vancomycin-treated patients).

In healthy volunteers receiving quinupristin + dalfopristin, 7.5 mg/kg infused over 1 hour bd, mean fecal antibiotic concentrations were 291 and 42 µg/g of feces for quinupristin and dalfopristin respectively by the fifth day of treatment (22).

Comparative studies

The pooled results of two multicenter, phase III, randomized comparisons of quinupristin + dalfopristin (7.5 mg/kg intravenously every 12 hours; $n = 450$) with established comparators (cefazolin, oxacillin, vancomycin; $n = 443$) for complicated skin and skin structure infections have been reported (23). The success rate was equivalent in the two groups: 63% of patients given quinupristin + dalfopristin (versus 54%) reported at least one adverse event, most commonly nausea, vomiting, rash, pain, or pruritus. Although most of the adverse events were mild to moderate, the drug was withdrawn in 19% of patients treated with quinupristin + dalfopristin (versus 4.7%) owing to an untoward event. Adverse venous events (atrophy, edema, hemorrhage, hypersensitivity, inflammation, thrombophlebitis, pain) were reported by 66% of patients treated with quinupristin + dalfopristin (versus 28%) and required withdrawal of the drug in 12% of these patients (versus 2%).

General adverse effects

The adverse effects of quinupristin + dalfopristin include arthralgia, myalgias, reversible rises in serum alkaline phosphatase, itching, diarrhea, vomiting, and pain at the infusion site; adverse effects occurred in 2.5–4.6% of patients (24–31).

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Organs and Systems

Electrolyte balance

The combination of quinupristin + dalfopristin has been associated with hyponatremia, probably secondary to inappropriate secretion of antidiuretic hormone (32).

- A 67-year-old woman with peripheral neuropathy, IgM paraproteinemia, and chronic obstructive pulmonary disease developed dyspnea and hyponatremia, and a small-cell lung cancer was diagnosed. She was given 3 cycles of chemotherapy (etoposide, cyclophosphamide, and doxorubicin). Her serum sodium concentrations normalized. On day 103, she was given quinupristin + dalfopristin (7.5 mg/kg every 8 hours) because of septicemia with vancomycin-resistant *E. faecium*. The serum sodium concentration thereafter fell (day 110: 117 mmol/l; serum osmolarity: 268 mosm/l; urine osmolarity: 426 mosm/l). Therapy was withdrawn on day 111, and the sodium concentration gradually returned to normal.

Gastrointestinal

In a multicenter, open, randomized trial in 204 patients with erysipelas treated with either oral pristinamycin 1 g tds or intravenous then oral penicillin, adverse events related to treatment were significantly more common with pristinamycin; they were mostly mild or moderate and mainly involved the gastrointestinal tract (33).

Pristinamycin can cause pseudomembranous colitis.

- An 85-year-old woman developed a severe illness (severe diarrhea and vomiting, abdominal tenderness, peritoneal irritation, and systemic toxicity) 8 days after receiving pristinamycin 3 g/day for 10 days (34). An assay for *Clostridium difficile* was positive. She was treated with metronidazole and her symptoms resolved after 72 hours.

Liver

In 25 liver transplant recipients who received intravenous quinupristin + dalfopristin 7.5 mg/kg 8-hourly for vancomycin-resistant *E. faecium* infection, hyperbilirubinemia developed, but there was no evidence of drug-specific histological injury (35).

Skin

In a retrospective study of children taking quinupristin + dalfopristin, rash (2%) was the most frequent adverse event, but only one patient with rash discontinued quinupristin + dalfopristin because of it (31).

Patch tests can be used to confirm pristinamycin-induced drug eruptions. In 11 patients with cutaneous drug reactions after oral pristinamycin, patch tests (with pristinamycin diluted to 20% aqueous and 20% petrolatum) were performed 1–3 months after treatment with pristinamycin (36). There were positive patch tests in nine, and there was no relapse of the drug eruption during patch-testing; 30 control patients had negative tests.

Mean antibiotic concentrations of pristinamycin in dermal interstitial fluid (from suction bullae) are low; nevertheless, the concentrations achieved should theoretically inhibit the growth of group A streptococci (37).

Musculoskeletal

Of seven patients with end-stage renal insufficiency who received quinupristin + dalfopristin, two developed myalgias (38).

Of 32 patients who received quinupristin + dalfopristin, at least 15 developed arthralgias and/or myalgias (39).

Immunologic

The combination of quinupristin + dalfopristin reduces cytokine production in stimulated monocytes from healthy volunteers, suggesting significant immunomodulatory activity (40).

Long-Term Effects

Drug resistance

The relative frequency of resistance to macrolides, lincosamides, and streptogramins (MLS resistance) has been assessed in a series of 2091 staphylococcus isolates collected during a 3-week period in 1995 in 32 French hospitals. A total of 294 strains (144 *Staphylococcus aureus*, 150 coagulase-negative staphylococci) exhibited resistance to at least one of these groups of antibiotics. Resistance to pristinamycin was phenotypically detected in ten *S. aureus* strains (seven isolates from the same hospital and possibly of the same clone) and three coagulase-negative staphylococcus isolates. It was associated with resistance to type A streptogramins encoded by vat or vatB genes and was associated with the erm genes (41).

A short report demonstrated the absence of a reliable correlation between killing kinetics and normal laboratory tests for pristinamycin susceptibility testing of some pneumococci (42). Eight selected multiresistant clinical isolates and two reference pristinamycin-resistant *Streptococcus pneumoniae* strains were studied. Disk diffusion susceptibility and MICs were determined by the agar dilution method, and all clinical isolates appeared to be susceptible to pristinamycin, whereas the two reference strains were not. In contrast, time-kill experiments identified a limited bactericidal effect of pristinamycin in three clinical and both reference strains. These three strains had been classified as pristinamycin-resistant by the Vitek-II system, which uses a kinetic turbidimetric measurement of bacterial growth. Epidemiological information is hindered by the use of highly selected strains for the study.

The in vitro activity of pristinamycin has been evaluated in 200 isolates of *S. pneumoniae* strains with various degrees of susceptibility to penicillin G and erythromycin (43). All the strains were susceptible to pristinamycin, irrespective of their susceptibility to penicillin G or erythromycin.

After 5 days administration of quinupristin + dalfopristin 7.5 mg/kg infused over 1 hour bd, the fecal microflora in 20 healthy volunteers increased significantly during treatment and returned within 12 weeks to baseline concentrations after the end of treatment. There were anerobes and enterococci resistant to erythromycin or to quinupristin + dalfopristin, but glycopeptide-resistant enterococci did not emerge (22).

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The relevance of resistance to virginiamycin

Virginiamycin is a streptogramin that has been used in animals as a growth-promoter. Increasing use of virginiamycin has been associated with a high rate of resistance to quinupristin + dalfopristin (44). Acquired resistance to virginiamycin, which is active against Gram-positive lactic acid-producing bacteria, can be detected in *E. faecium* and *E. faecalis* strains isolated from animals and food (45), including strains from poultry, in which high resistance against virginiamycin was found in Belgium (46). Streptogramin resistance is associated with the resistance genes vatA and vatG in *E. faecium* of both animals and man (44). Because virginiamycin has been used in animals and streptogramins have been used infrequently in man, an animal origin of resistance has been suggested, and spread of resistance via the food chain to humans is probable (47).

Susceptibility Factors

Renal disease

The disposition of quinupristin, dalfopristin, and their primary metabolites was similar in eight non-infected patients on peritoneal dialysis compared with eight matched healthy volunteers after the administration of quinupristin + dalfopristin 7.5 mg/kg (48). Since dialysis clearance was insignificant, the combination was thought to be inadequate for the therapy of dialysis-associated peritonitis.

The pharmacokinetics of a single intravenous injection of quinupristin + dalfopristin (7.5 mg/kg over 1 hour) have been assessed in 13 patients with severe chronic renal insufficiency (creatinine clearance 6–28 ml/minute/1.73 m^2) (49). Although the mean peak plasma drug concentration and AUC of quinupristin plus its active derivatives and of both unchanged dalfopristin and dalfopristin plus its active derivatives were about 1.3–1.4 times higher than in healthy volunteers, the authors concluded that no formal reduction in the dosage of quinupristin + dalfopristin is necessary in patients with chronic renal insufficiency.

Drug–Drug Interactions

CYP3A4

Quinupristin + dalfopristin can inhibit the metabolism of agents that are metabolized by CYP3A4 (50).

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Strychnine

General Information

Strychnine is an alkaloid that is found in *Nux vomica*. It causes excitation of all parts of the central nervous system, with a characteristic motor pattern. Strychnine is a competitive antagonist at inhibitory neurotransmitter glycine receptors in the spinal cord, brain stem, and higher centers. It thus increases neuronal activity and excitability, leading to increased muscular activity. Since strychnine convulsions also occur in decerebrate animals, the convulsion is termed a "spinal convulsion," but other parts of the central nervous system are also stimulated

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by doses that produce motor manifestations in a decerebrate animal. Strychnine does not selectively stimulate the medulla and cannot therefore be regarded as a useful analeptic drug (1).

The features of strychnine poisoning occur at 15–30 minutes after ingestion. They include heightened awareness, muscle twitches and spasms, and hypersensitivity to stimuli. In severe toxicity, painful generalized convulsions can occur without loss of consciousness. Respiratory arrest secondary to respiratory muscle spasm also occurs and is the usual mode of death. Prolonged muscular spasm can lead to hyperthermia, lactic acidosis, rhabdomyolysis, and acute renal insufficiency due to myoglobinuria.

Drug Administration

Drug overdose

Two cases of strychnine poisoning with characteristic signs and symptoms have been described (2,3). Management included gastric lavage, the administration of activated charcoal, sedation with midazolam and phenobarbital, and paralysis with vecuronium, along with respiratory support and forced hydration. In some countries strychnine is available as a pest control agent, resulting in occasional poisoning. Early diagnosis and prompt management can save the patient, despite the consumption of a large dose of strychnine.

- A 33-year-old man attempted suicide by self-injection of strychnine intramuscularly (4). A few seconds after the first injection he developed dizziness and light-headedness. Ten minutes after the second injection he had seizures, opisthotonos, and tetany. He was rescued with a benzodiazepine and ventilatory support.

A case of fatal poisoning due to strychnine has been described, and the concentrations of strychnine in various body fluids and organs have been detailed (5). The half-life of strychnine in a case of poisoning in a 42-year-old man who survived was 12 hours (6).

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Substances that affect the skin: Contact allergy

General Information

Contact allergy is the most frequently described adverse effect of topical drugs and cosmetics; the diagnosis can be established by patch-testing (1–4) and review articles (5).

In allergic contact dermatitis due to topical medicaments (6), any constituent of the formulation can be responsible for the adverse event—the vehicle, preservative, emulsifier, perfume, or the active drug. Hence, patch tests should be carried out with all active and supposedly inactive ingredients of the incriminated topical drug.

When cosmetic allergy is suspected (SEDA-11, 142) (SEDA-13, 117) (7), the patient should be tested with the suspected products. Skin care products can be tested as the marketed formulation. However, some cosmetics, notably those that contain detergents such as soaps, shampoos, and bath foams, can cause false-negative and false-positive patch test reactions. Their ingredients should therefore preferably be tested separately when contact allergy to such products is strongly suspected (8). Natural botanical extracts are being increasingly used in cosmetics. Consumers tend to regard these natural substances as safe. However, patients with positive patch tests to *Aloe vera*, arnica, *Centella asiatica*, chamomile, cucumber, lavender oil, peppermint, rosemary, sage, St John's wort (photosensitivity), tea tree oil, and witch hazel have been reported (9).

Ingredient labeling, which has been mandatory in the European Union since 1 January, 1997, has greatly facilitated the investigation of patients with suspected cosmetic dermatitis (SEDA-22, 159) (10).

There have been useful review articles on cosmetic allergy (8), preservatives (11), fragrances (SEDA-20, 149) (12), topical drugs (6), glucocorticoids (13), and antihistamines (14).

Table 1 lists alphabetically a large number of ingredients of cosmetics and topical drugs that can act as sensitizers; some drugs are accidental contactants, for example in the pharmaceutical industry or in health personnel. For each compound, the concentration and vehicle for patch-testing, known or generally held to be adequate, are mentioned.

Substances that are not listed in any standard table should be patch-tested with great caution; control tests are mandatory when positive reactions are obtained, so as to exclude false-positive irritant patch test reactions.

We have attempted to estimate the sensitizing potential of each particular drug using the following scale:

1—sensitization is common;
2—sensitization can occur;
3—sensitization is unusual;
4—sensitization is rare.

These estimates are based on literature data and personal experience (4).

Table 1 Patch test concentrations and vehicles for skin testing of ingredients of topical drugs and cosmetics

Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Acetarsone	1–5% petrolatum	4	(SEDA-20, 158)	
Acetylsalicylic acid	2% petrolatum	4	(SEDA-18, 164) (36)	
Aciclovir	5% petrolatum	4	(SEDA-14, 125)	
Adrenaline[3]	0.1–1% aqua	4	(3)	
Aescin	2% aqua	4	(SEDA-17, 188)	
Alcohol[1]	10% aqua, pure	4	(SEDA-12, 133) (37)	b, d
Alkylammonium amidobenzoate	0.1 and 0.01% petrolatum	4	(SEDA-17, 188) (38,39)	
Amalgam	5% petrolatum	3	(SEDA-19, 158)	
Ambroxol hydrochloride	0.5% aqua	4	(SEDA-14, 125)	
Amcinonide[2]	1% epi (45% alcohol, 10% propylene glycol, 45% isopropyl alcohol)	3	(SEDA-15, 140)	
Amerchol CAB	Pure	2	(SEDA-17, 188)	
Aminoethanolamine	0.005, 0.1, and 0.5% in aqua		(40)	
ϵ-Aminocaproic acid[3]	1% aqua	4	(SEDA-17, 189)	
3-(Aminomethyl)-pyridyl salicylate	1% aqua	3	(SEDA-14, 125)	
4-Amino-3-nitrophenol	2% petrolatum		(41)	
Amlexanox	0.01–1% aqua or petrolatum	3	(SEDA-16, 155)	
Ammoniated mercury	1% petrolatum	2	(SEDA-19, 159)	d
Ammonium bisulfate[1]	0.1 and 0.5% aqua	4	(SEDA-21, 165)	
Ammonium persulfate	2.5% petrolatum	3	(3)	e, b
Amorolfine	1% petrolatum or aqua	4	(SEDA-21, 165)	
Ampicillin	5% petrolatum	4	(SEDA-9, 136)	b
α-Amylcinnamic alcohol[4]	2% petrolatum	2	(SEDA-8, 158)	
α-Amylcinnamic aldehyde[4]	2% petrolatum	2	(SEDA-8, 158) (42)	
Anethole	5% petrolatum		(43)	
Apomorphine	0.05% aqua	4	(SEDA-17, 188)	
Arnica, tincture of	20% petrolatum	3	(3)	
Atropine sulfate[3]	1% petrolatum	4	(3)	
Auranofin	0.2% petrolatum	2	(SEDA-19, 158)	
Avocado oil	Pure	4	(SEDA-12, 134)	
Azidamfenicol	5% petrolatum	4	(SEDA-12, 132)	
Azulene	1% petrolatum	4	(SEDA-20, 157)	
Bacitracin[3]	20% petrolatum	2	(SEDA-18, 171)	b
Basic blue 99	0.5% petrolatum	4	(3)	b
Basic red 22	1% aqua		(44)	
Beclomethasone dipropionate[2]	5% petrolatum	4	(SEDA-15, 140)	
Beeswax	30% petrolatum	2	(SEDA-21, 165)	
Befunolol	1% aqua	3	(SEDA-17, 188)	
Benzalkonium chloride[1,3]	0.05% aqua	3	(SEDA-7, 161)	
Benzarone	2% petrolatum and pure	4	(SEDA-10, 127)	
Benzocaine[3]	5% petrolatum	1	(3)	a, b, d
Benzoic acid[1]	5% petrolatum	2	(3)	b
Benzoin tincture	10% alcohol or glycerol	3	(SEDA-10, 127)	b
Benzophenone	Not reported		(45)	
Benzophenone-2	2% petrolatum		(46)	
Benzophenone-3 (oxybenzone)	2% petrolatum	3	(SEDA-2, 137)	a
Benzophenone-10 (mexenone)	2% petrolatum	3	(SEDA-18, 171)	a
Benzoxonium chloride[1]	0.05% aqua	3	(SEDA-13, 127)	
Benzoyl peroxide	1% petrolatum	2	(SEDA-9, 152)	b, e
Benzydamine hydrochloride	5% petrolatum	3	(SEDA-17,188) (36)	a
Benzyl alcohol[1]	5%petrolatum	3	(SEDA-8, 154)	b
Benzyl benzoate[4]	5% petrolatum	3	(SEDA-8,154)	
Benzyl salicylate[4]	1% petrolatum	3	(3)	
Betamethasone-17-valerate[2]	5% petrolatum	3	(SEDA-15, 140)	
Betamethasone sodium phosphate[2]	5% petrolatum	4	(SEDA-15, 140)	
Betaxolol hydrochloride	1–5% aqua	4	(SEDA-17, 188)	
Bifonazole	1% alcohol or methylethylketone	4	(SEDA-20, 156)	
Bismuth tribromophenol	Pure	4	(SEDA-9, 136)	
Black iron oxide	5% petrolatum		(47)	
Boric acid	2% aqua	4	(SEDA-19, 162)	
Bornelone	5% petrolatum	4	(SEDA-9, 140)	
2-Bromo-2-nitropropane-1,3-diol[1]	0.25–0.5% petrolatum	2	(SEDA-9, 136)	

Continued

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Table 1 Continued

Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Bronopol (2-bromo-2-nitropropane-1,3-diol)	Not stated	1	(48)	
Budesonide[2]	1% petrolatum	2	(SEDA-17, 185)	
Bufexamac	5% petrolatum	2	(SEDA-22, 169) (36)	
Buphenine hydrochloride	1% alcohol	4	(SEDA-10, 127)	
Bupivacaine			(SEDA-18, 172)	
Butoxyethyl nicotinate	2.5% petrolatum	4	(SEDA-15, 146)	
tert-Butyl alcohol	70% aqua	4	(SEDA-8, 159) (37)	b
tert-Butyl hydroquinone	1% petrolatum	4	(SEDA-9, 140)	
Butyl aminobenzoate	2% petrolatum	2	(SEDA-16, 155)	
Butylated hydroxyanisole[1]	2–5% petrolatum	3	(3)	
Butylated hydroxytoluene[1]	2–5% petrolatum	3	(3)	
1,3-Butylene glycol	5% aqua	4	(SEDA-22, 171) (49)	
Butylhydroxyanisole	2% petrolatum	2	(50)	
Butylmethoxybenzoylmethane	2% petrolatum	3	(SEDA-18, 171)	
Calcipotriol	0.4–10 μg/ml isopropyl alcohol	4	(SEDA-21, 164) (51)	d, e
Capric/caprylic triglyceride	1% (vehicle not stated)		(52)	
Carboxyvinyl polymer	0.2% aqua	4	(SEDA-20, 158)	
Carmustine	0.1% aqua	1	(53)	
Carprofen	10% petrolatum	4	(SEDA-18, 164) (36)	a
Carvone[4]	1–5% petrolatum	4	(SEDA-20, 157) (54)	
Castor oil	Pure	3	(SEDA-21, 165)	
Centelase	1% powder in petrolatum	3	(SEDA-12, 132)	
Ceramide, hydrophilized	0.25% petrolatum	1	(55)	
Cetrimide	0.1% aqua	1	(56)	
Cetrimonium bromide[1]	0.05% aqua	3	(SEDA-8, 126)	c
Cetyl alcohol	30% petrolatum	3	(3)	b
Cetylpyridinium chloride	0.05% aqua	3	(SEDA-9, 136)	
Cetylstearyl alcohol (Lanette)	30% petrolatum	3	(SEDA-9, 136) (57)	
Chamomile, oil of	25% olive oil	3	(3)	
Chitosan gluconate	10% aqua	4	(SEDA-19, 162)	
Chloral hydrate	1-5 MEK	4	(SEDA-12, 132)	
Chloramphenicol[3]	1% alcohol or 5–10% petrolatum	2	(SEDA-10, 127)	b
Chlordantoin	0.1–1% petrolatum	4	(3)	
Chlorhexidine[1,3]	1% aqua	3	(SEDA-13, 125)	a, b, e
Chlorhexidine digluconate	0.5–1% alcohol	1	(58)	
		1	(59)	
Chloroacetamide[1]	0.2% petrolatum or aqua	3	(SEDA-20, 157)	
p-Chloro-*m*-cresol[1]	1–2% petrolatum	3	(3)	b
2-Chloro-*p*-phenylenediamine	1% petrolatum	2	(60)	
Chloro-2-phenylphenol[1]	1% aqua	3	(3)	a
Chloroxylenol[1]	0.5–1% petrolatum	3	(SEDA-15, 148)	
		1	(61)	
Chlorphenesin	1% petrolatum	4	(SEDA-22, 171)	
Chlorphenamine maleate[3,5]	2% petrolatum	4	(SEDA-17, 191)	f
Chlorquinaldol	5% petrolatum	3	(SEDA-9, 136)	
		1	(62)	
CI 12010 (solvent Red 3)	1% petrolatum	4	(SEDA-16, 156)	
CI 12085 (D and C Red No. 36)	2% petrolatum	3	(SEDA-11, 140)	
CI 26100 (D and C Red No. 17)	2% petrolatum	4	(SEDA-7, 164)	
CI 47000 (D and C Yellow No. 11)	0.1% petrolatum	3	(SEDA-14, 129)	
Cicloproxolamine	1% petrolatum	1	(63)	
Cinchocaine	5% petrolatum	4	(SEDA-20, 158)	
Cinnamic alcohol[4]	1% petrolatum	2	(SEDA-2, 140) (42)	
Cinnamic aldehyde[4]	1% petrolatum	2	(SEDA-22, 168) (42)	a, b
Cinoxicam	2% petrolatum	4	(SEDA-18, 164) (36)	
Clindamycin phosphate	1% aqua	3	(SEDA-20, 158)	d
Clobetasol-17-propionate[2]	0.05–10% petrolatum	3	(SEDA-15, 140)	b
Clobetasone butyrate[2]	0.5–1% petrolatum	3	(SEDA-9, 137)	
		1	(64)	
Clonidine	1% petrolatum	1	(SEDA-15, 144) (65,66)	d
Clotrimazole	1% methylethylketone or alcohol	4	(SEDA-20, 158)	

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Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Cloxyquine (5-chloro-8-hydroxyquinoline)	5% petrolatum	4	(SEDA-20, 158)	
Cocaethylene	10% petrolatum	1	(67)	
Cocamide DEA	0.5% petrolatum	4	(SEDA-12, 134)	
Cocamidopropyl betaine	1% aqua	2	(SEDA-19, 151)	
Cocamidopropyl hydroxysultaine	1% aqua	1	(68)	
Cocamidopropyl PG-dimonium chloride	2.5% aqua	4	(SEDA-21, 165)	
Cocobetaine	2% aqua	4	(SEDA-8, 158)	
Codeine	0.001–0.033% aqua	4	(SEDA-11, 139)	
Colistin sodium methanesulfonate	1–10% petrolatum	4	(SEDA-21, 165)	
Colophony (rosin)	30% petrolatum	1	(SEDA-22, 171)	
Crocein scarlet MOO and solvent yellow 3	1% plastibase	1	(69)	
Croconazole	2% petrolatum	3	(SEDA-21, 166)	
Crotamiton	10% aqua	4	(SEDA-15, 146)	
Cyclomethycaine	1% petrolatum	3	(3)	
Cyclopentolate	0.5–1.0% aqua	4	(SEDA-21, 165)	
Cyclopyroxolamine	10% petrolatum or 1% alcohol	4	(SEDA-20, 158)	
Decyl oleate	1% petrolatum	4	(SEDA-17, 188)	
Desoximetasone[2]	1% epi (45% alcohol, 10% propylene glycol, 45% isopropyl alcohol)	4	(SEDA-15, 140)	a
Dexchlorpheniramine maleate	1% aqua	4	(SEDA-15, 146)	
Dexpanthenol	5% petrolatum	3	(SEDA-22, 171)	f
Diazolidinyl urea[1]	2% aqua or petrolatum	3	(SEDA-19, 158)	
Dibromopropamidine	5% petrolatum	4	(SEDA-13, 125)	
Dibutylphthalate	5% petrolatum	4	(SEDA-17, 188)	
		1	(67)	
Dicaprylyl maleate	10% (vehicle not stated)	2	(52)	
Dichlorodifluoromethane	Pure	4	(SEDA-19, 162)	
Dichlorophene[1]	1% petrolatum	4	(SEDA-20, 157)	a
Diclofenac sodium	2.5–10% petrolatum	3	(SEDA-18, 164) (36)	
		1	(70)	
Diethyl sebacate			(SEDA-22, 171)	
	5% petrolatum	4	(SEDA-24, 173)	
	30% alcohol	1	(71)	
	30% alcohol	3	(SEDA-22, 171)	
Diethylstilbestrol	1% petrolatum	4	(3)	b, d
Diflucortolone 21-valerate[2]	1% petrolatum	4	(SEDA-10, 127)	
2,7-Dihydroxynaphthalene	0.1% aqua	4	(SEDA-22, 171)	
Dihydrostreptomycin	1% petrolatum	3	(3)	
Dihydroxyacetone	10% aqua	4	(SEDA-16, 155)	
Diisopropanolamine	1% petrolatum	4	(SEDA-15, 146)	
Diisopropyl sebacate	3–10% alcohol	4	(SEDA-16, 155)	
Dimethindene maleate[5]	Commercial preparation	4	(SEDA-18, 172)	
Diphenhydramine[5]	1% petrolatum	3	(SEDA-21, 164)	a, d
Dipicolinic acid	0.1% petrolatum	4	(SEDA-14, 125)	
Dipivalyl adrenaline hydrochloride	0.5% aqua	4	(SEDA-17, 188)	
Dipropylene glycol	0.5% petrolatum or aqua	4	(SEDA-20, 158)	
Disodium cocoamphodipropionate	0.3–1% aqua	4	(SEDA-21, 165)	
Disodium ricinoleamido MEA sulfosuccinate	0.1% aqua	4	(SEDA-21, 165)	
Dithranol (cignolin, anthralin)	0.03% acetone	4	(SEDA-7, 161)	e
Dodecyl (=lauryl) gallate	0.25% petrolatum	3	(SEDA-12, 132) (72)	
Dodecyl malamic acid	1% petrolatum	4	(SEDA-8, 154)	
Dorzolamide	0.01–10% aqua and petrolatum		(73)	
Doxepin	0.05–5% petrolatum	1	(SEDA-19, 158) (SEDA-19, 159)	a, d
		1	(74,75)	
Drometrizole	5% petrolatum	4	(SEDA-9, 140)	
Dyclonine hydrochloride	1% petrolatum	4	(SEDA-10, 128)	
Econazole nitrate	1% alcohol or MEK	3	(SEDA-20, 156)	

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Table 1 Continued

Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Enilconazole	1% alcohol or MEK	4	(SEDA-20, 156)	
Enoxolone (18-glycyrrhetinic acid)	10% petrolatum	4	(SEDA-17, 188)	
	10% petrolatum	1	(76)	
Eosin (tetrabromofluorescein)	1% petrolatum	4	(SEDA-20, 158)	
Epinephrine, see adrenaline				
Erythromycin	5% petrolatum	3	(SEDA-8, 154)	a
Erythromycin lactobionate	1–10% petrolatum	4	(SEDA-21, 165)	
Esculin	1% petrolatum	4	(SEDA-5, 155)	
Essential oils[4]	2% petrolatum	2	(SEDA-17, 189)	
17-β-Estradiol	1% petrolatum or alcohol 96%	3	(SEDA-21, 165)	d
Estradiol benzoate	0.05% MEK	4	(SEDA-14, 126)	b, d
2-Ethoxyethyl-*p*-methoxycinnamate	2% petrolatum	3	(SEDA-18, 171)	a
Ethoxyquine	0.5% alcohol or petrolatum	2	(SEDA-9, 137)	
Ethyl chloride	Pure	4	(SEDA-19, 162)	
Ethylenediamine tetraacetate (EDTA)	1% petrolatum	3	(SEDA-12, 132)	
Ethyl diglycol (carbitol) chitosan gluconate	Unknown		(77)	
Ethylhexylglycerine	10% petrolatum	1	(78)	
Ethyl lactate	1% petrolatum	4	(SEDA-13, 125)	
Ethyl mercuric chloride[1]	0.05% petrolatum	2	(SEDA-18, 174) (79)	d
Ethyl sebacate	1% petrolatum	4	(SEDA-15, 146)	
Etofenamate	2% petrolatum	4	(SEDA-18, 164) (36)	b
Eucalyptol (*Malaleuca alternifolia*)	1% petrolatum	1	(80)	
Eucerin	Pure	3	(3)	
Eugenol[4]	5% petrolatum	1	(SEDA-20, 157) (42)	b
Eumulgin L	10% aqua or petrolatum	4	(SEDA-22, 171)	
Eusolez 8021	2% petrolatum	2	(SEDA-7, 164)	
Fenticonazole	5% petrolatum	4	(SEDA-20, 158)	
Fepradinol	5% DMSO or 2% alcohol	3	(SEDA-18, 172)	
Feprazone	5% petrolatum	4	(SEDA-18, 164) (36)	
Flufenamic acid	2–5% petrolatum	4	(SEDA-18, 164) (36)	
Fluocinolone acetonide[2]	1% petrolatum	4	(SEDA-9, 137)	
Fluocortin butyl[2]	1% alcohol	3	(SEDA-15, 140)	
5-Fluorouracil	5% petrolatum	4	(SEDA-10, 128)	a, e
Flurandrenolide	1% petrolatum	3	(SEDA-10, 128)	
Gallate esters	0.1–1% petrolatum	3	(3)	
Gentamicin[3]	20% petrolatum	2	(SEDA-14, 126)	b, d
Gentian violet	0.25% aqua	4	(SEDA-22, 171)	b, d
Geraniol[4]	2% petrolatum	2	(SEDA-7, 164) (42)	
Glucocorticoids[2]	1% alcohol 94%	1	(SEDA-21, 158) (13)(81,82)	d, e
Glutaraldehyde[1]	1% aqua	3	(SEDA-8, 155)	
Glycerol	10% aqua	4	(3)	
Glyceryl diisostearate	2% petrolatum	4	(SEDA-18, 172)	
Glyceryl PABA	5% petrolatum	3	(SEDA-2, 137)	a
Glyceryl stearate	10–30% petrolatum	4	(SEDA-14, 128)	
		1	(83)	
Glyceryl thioglycolate	1% petrolatum	2	(SEDA-10, 128)	
Glyceryl trinitrate	2% petrolatum	3	(SEDA-15, 144)	d
Glyceryl trinitrate (Percutol)	2% petrolatum	1	(65,66)(84)	
Glyceryl trinitrate TTS	0.2% aqua 0.5% ethanol	1	(85)	
Guaiazulene	1% petrolatum	4	(SEDA-21, 157)	
Henna	10% petrolatum	4	(SEDA-22, 171)	b, d
Heparin	Commercial preparation	4	(SEDA-14, 126)	
Hexachlorophene[1]	1% petrolatum	4	(3)	a, d, e
Hexamidine	0.15% aqua	3	(SEDA-10, 128)	
cis-3-Hexenyl salicylate[4]	3% petrolatum	4	(SEDA-8, 158)	
Hexetidine	0.1% petrolatum	4	(SEDA-7, 161)	

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Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Hexyl laurate	30% petrolatum	4	(SEDA-15, 146)	
Hinokitiol	0.1% alcohol	4	(SEDA-8, 158)	
Hirudin	20% alcohol extract	4	(SEDA-21, 165)	
Homomenthyl salicylate (homosalate)	2% petrolatum	4	(SEDA-3, 131a)	
4-Homosulfanilamide (mafenide)	5% petrolatum	2	(SEDA-17, 189)	d
Hydrocortisone acetate[2]	25% petrolatum	3	(3)	a
Hydrocortisone-17-butyrate[2]	1% alcohol	2	(SEDA-17, 185)	
Hydrogen peroxide	3% aqua	4	(SEDA-19, 162)	
Hydroquinone	1% petrolatum	4	(SEDA-22, 171)	
		1	(86)	
Hydroxycitronellal[4]	5% petrolatum	1	(SEDA-2, 140) (42)	
Hydroxyethyl salicylate	1% petrolatum	4	(SEDA-20, 158)	
	5% aqua	1	(87)	
17-α-Hydroxyprogesterone	1% alcohol	3	(SEDA-18, 170)	
Hydroxypropylcellulose	5% aqua	4	(SEDA-13, 125)	
Ibuprofen	5% petrolatum	3	(SEDA-18, 164) (36)	f
Ibuprofen piconol	1–5% petrolatum	3	(SEDA-13, 125)	
Ibuproxam	2.5% petrolatum	3	(SEDA-18, 164) (36)	
Ichthyol (ichthammol)	5% petrolatum	3	(SEDA-9, 136)	
Idoxuridine[3]	1% petrolatum	3	(SEDA-7, 162)	
Indometacin	5% petrolatum	4	(SEDA-18, 164) (36)	
Interferon-β-hydrochloride[3]	Eye drops pure and diluted 1:32	4	(SEDA-16, 155)	
Iodine, tincture of	0.5% aqua (open test)	3	(3)	b, d, e
Iodoform	10% petrolatum	3	(88)	
3-Iodo-2-propynyl-butylcarbamate	0.1% petrolatum	3168	(89)	
Isoconazole	1% alcohol or methylethylketone	3	(SEDA-20, 156)	
Isoeugenol[4]	5% petrolatum	1	(42)	
Isopropyl alcohol[1]	20% aqua	3	(SEDA-7, 162) (37)	b
Isopropyl dibenzoylmethane	2% petrolatum	2	(SEDA-18, 171)	a, b
Isopropyl myristate	20% petrolatum	4	(3)	
Isopropyl palmitate	2% petrolatum	4	(SEDA-8, 155)	
Isostearyl alcohol	5% alcohol and pure	4	(SEDA-12, 135)	b
Isothipendyl hydrochloride	1% petrolatum	4	(SEDA-9, 137)	
Isotretinoin	0.05–0.01% petrolatum	4	(SEDA-21, 165)	
Jasmin synthetic[4]	10% petrolatum	2	(3)	
Jojoba oil	20% olive oil	3	(SEDA-7, 164)	
Kanamycin[3]	20% petrolatum	3	(3)	
Kathon CG[1]	100 ppm aqua	1	See methyl(chloro)-isothiazoline	
Ketoconazole	1% alcohol or methylethylketone	4	(SEDA-20, 156)	
Ketoprofen	5% petrolatum	3	(SEDA-22, 170) (90)	a, f
Kojic acid	1–5% aqua	2	(SEDA-20, 156)	
Krameria triandra (red rhatany)	1% petrolatum 2% ethanol		(91)	
Lactic acid	3% aqua	4	(SEDA-18, 172)	
Lanette wax	30% paraffinum liquidum	3	(SEDA-2, 139)	
Lanoconazole	0.1, 1, and 10% (?)	4	(SEDA-21, 166) (92)	
Lanolin	Pure	3	(3)	
Laurylpyridinium chloride[1]	0.1% aqua	4	(SEDA-13, 127)	
Lawsone(2-hydroxy-1,4-naphthoquinone)	5% petrolatum	4	(SEDA-12, 135)	
Levobunolol hydrochloride[3]	1% aqua	3	(SEDA-17, 189)	
Lidocaine	2% aqua	3	(SEDA-18, 172)	b, d
Lilial[4]	1% petrolatum	4	(SEDA-8, 159)	
Linalool[4]	30% petrolatum	3	(SEDA-9, 140)	
Lincomycin hydrochloride	1% aqua	4	(SEDA-10, 128)	
Mandelic acid	5% petrolatum	4	(SEDA-18, 172)	
Masoprocol (nordihydro-guaiaretic acid)	1% "cream"	2	(SEDA-18, 171)	e
Matricaria chamomilla (German chamomile)	1% (?)		(93)	

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Table 1 Continued

Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Mechlorethamine hydrochloride (nitrogen mustard)	0.02% aqua (open test)	1	(SEDA-22, 172) (94)	b
Melia azadirachata (Psorigon)	1–10%, vehicle not stated		(95)	
Mephenesin	5% petrolatum	3	(SEDA-22, 170)	
Mepivacaine	1% aqua	4	(SEDA-16, 155)	
Mercuric chloride[1]	0.05% petrolatum	2	(SEDA-17, 186)	d
Mercuric oxide, yellow	1% petrolatum	3	(SEDA-21, 165)	d
Mesulfen	5% petrolatum	4	(SEDA-8, 155)	e
Metaoxedrine, see phenylephrine				
Methoxypolyethylene glycol/ 17-dodecyl glycol copolymer (Elfacos OW 100)	10% petrolatum		(96)	
8-Methoxypsoralen	0.1% alcohol	4	(SEDA-19, 162)	a
4-Methylbenzylidene camphor	2% petrolatum	3	(SEDA-18, 171)	a
Methylbutetisalicylate	30% petrolatum		(97)	
Methyl(chloro)isothiazolinone (Kathon CG)[1]	100 ppm aqua	1	(98)	a
Methyldibromoglutaronitrile[1]	0.3–0.5% petrolatum	1	(SEDA-19, 152) (99)	
Methylglucose dioleate	5% petrolatum	4	(SEDA-20, 159) (100)	
Methylglucose sesquistearate	5% petrolatum	4	(SEDA-10, 130)	
Methylionone[4]	10% petrolatum	4	(SEDA-14, 128)	
Methyloctine carbonate[4]	1% MEK	4	(SEDA-13, 125)	
6-Methylprednisolone aceponate[2]	1% alcohol	4	(SEDA-22, 171)	
Methylsalicylate[4]	2% petrolatum	4	(3)	b
Metipranolol[3]	2% aqua	4	(SEDA-13, 125)	
Metoprolol[3]	3% aqua	4	(3)	
Metronidazole	1% petrolatum 50% petrolatum	4	(SEDA-22, 171) (101)	
Miconazole nitrate	1% alcohol or MEK	3	(SEDA-20, 156)	
Microcrystalline wax	Pure	4	(SEDA-10, 130)	
Minoxidil	1% alcohol 2% ethanol	3	(SEDA-11, 139) (102)	a, d
Monobenzylether of hydroquinone	1% petrolatum	3	(3)	
Mupirocin	1–10% petrolatum	4	(SEDA-20, 159)	
Musk ambrette[4]	5% petrolatum	3	(SEDA-7, 164)	a
Mycanodin	2% petrolatum	4	(3)	a
Myristyl picolinium chloride	1% petrolatum	4	(SEDA-20, 159)	
Myrrh	Unknown		(103)	
Naftifine	1% petrolatum or 5% alcohol	3	(SEDA-20, 159)	
Neo-ballistol	1% (?)		(104)	
Neomycin[3]	20% petrolatum	2	(3)	b
Neticonazole	1–10% petrolatum	4	(SEDA-22, 171)	
Nicotine	10% aqua	2	(SEDA-18, 170)	a, b
Nifuratel	1% acetone	3	(SEDA-15, 147)	
Nitrocellulose	10% isopropyl alcohol	4	(SEDA-22, 171)	
Nitrofurazone	1% petrolatum	2	(3)	
Nonoxynols	2% aqua	3	(3)	
Noxurol	(?)		(105)	
(Clostridiopeptidase A)			(106)	
Nystatin	100 000 U/g in PEG-400	3	(3)	
Oak moss[4]	2% petrolatum	1	(42)	
Octyl dimethyl PABA	2% petrolatum	3	(SEDA-18, 171)	a
Octyl dodecanol	5–10% paraffinum liquidum	4	(SEDA-22, 171)	
Oleamidopropyl dimethylamine	0.1% petrolatum	2	(SEDA-14, 128)	
Oleth-3-phosphate	1% petrolatum	4	(SEDA-22, 171)	
Oleyl alcohol	10% petrolatum	3	(SEDA-22, 172)	
Olive oil	Pure	4	(SEDA-15, 147) (107)	
Omeprazole	0.25–1% petrolatum	4	(SEDA-12, 133)	
Oxiconazole	1% alcohol or MEK	4	(SEDA-20, 156)	
Oxybenzone			See benzophenone-3	
Oxyphenbutazone	1% petrolatum	3	(SEDA-18, 164) (36)	b, f

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Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
PABA (para-aminobenzoic acid)[3]	2–5% petrolatum	2	(SEDA-18, 171)	a
Palmitoyl hydrolysed milk protein	10% petrolatum	4	(SEDA-13, 126)	
Parabens	Parabens mix European Standard Series		(108)	
Patchouli oil	10% petrolatum	4	(SEDA-17, 189)	
D-Panthenyl ethyl ether[4]	30% petrolatum	4	(SEDA-9, 141)	
Pentaerythritol ester of rosin	10–20% petrolatum	3	(SEDA-19, 162)	
Petrolatum	Pure	4	(SEDA-9, 138)	
Phenobarbital	0.1% aqua or 20% propylene glycol	4	(SEDA-12,133)	
Phenothiazine derivatives[5]	2% petrolatum	1	(3)	a
Phenoxybenzamine	1% aqua	4	(SEDA-1, 136)	c
Phenoxyethanol[1]	1% petrolatum	4	(SEDA-10, 128)	
Phenylbutazone	5% petrolatum	3	(SEDA-22, 170) (36)	
Phenyldimethicone	2% petrolatum	4	(SEDA-10, 130)	
Phenylephrine	0.5–1% petrolatum 5% aqua	4	(SEDA-19, 162) (109) (3)	
Phenylmercuric acetate[1]	0.01% aqua	2	(3)	b, d
Phenylmercuric borate[1]	0.01% aqua	2	(3)	b, d
2-Phenyl-5-methylbenzoxazole	2% petrolatum	4	(SEDA-14, 128)	a
Phenylsalicylate (Salol)	1% petrolatum	4	(SEDA-20, 157)	
Phthalic anhydride/trimellitic anhydride/glycols co-polymer	1% petrolatum	1	(110)	
Picric acid	1% aqua	4	(SEDA-16, 155)	
Pigment red 57:1	1% petrolatum	4	(SEDA-18, 172)	
Piketoprofen	1–5% petrolatum	4	(SEDA-20, 159)	
Pilocarpine[3]	4% petrolatum	4	(SEDA-18, 172)	
Piperazine	1% petrolatum	3	(SEDA-8, 156)	c
Piroxicam	0.5% petrolatum	2	(SEDA-18, 164) (36)	a
Pivampicillin	5% petrolatum	1	(SEDA-17, 189)	c
Polidocanol	5% petrolatum	3	(3)	d
Polyethylene glycol	Pure	3	(SEDA-15, 144)	b
Polymyxin B[3]	3% petrolatum	4	(3)	
Polyoxyethylene oleylether	1% petrolatum		(111)	
Polysorbate 40 (Tween 40)	5% petrolatum	3	(SEDA-2, 139)	
Polysorbate 80 (Tween 80)	10% petrolatum	3	(SEDA-2, 139) (57)	
Polyvinylpyrrolidone/eicosene co-polymer	1% petroleum	1	(112)	
Polyvinylpyrrolidone/1-triacontene co-polymer	10% petrolatum		(113)	
Potassium coco-hydrolysed animal protein	5 and 30% aqua	4	(SEDA-14, 129)	
Povidoneiodine	10% aqua or petrolatum	3	(SEDA-18, 172)	b, d
Pramocaine	2% aqua	4	(SEDA-9, 138)	
Prednicarbate	10% ethanol 1% ethanol		(114)	
Prednisolone (pivalate)[2]	1% epi (45% alcohol, 10% propylene glycol, 45% isopropyl alcohol)	3	(SEDA-13, 126)	
Prilocaine	2% aqua	3	(SEDA-18, 172)	d
Prime yellow carnauba wax	50% mineral oil	1	(67)	
Procaine[3]	1% petrolatum	1	(3)	a
Proflavine dihydrochloride	1% petrolatum	1	(SEDA-13, 126)	
Promethazine hydrochloride[5]	1% petrolatum	1	(3)	a, b, d
Propantheline bromide	55 petrolatum	3	(SEDA-9, 141)	
Propolis	10% petrolatum	2	(SEDA-17, 181)	
Propylene glycol	2% petrolatum	3	(SEDA-9, 159) (115)	b, e
Propyl gallate	1% petrolatum	3	(SEDA-22, 172)	a
PVP/hexadecene co-polymer	5% petrolatum		(116)	
Pyrazinobutazone	1–5% petrolatum	4	(SEDA-17, 191)	f
Pyridoxine 3,4-dioctanoate	1% petrolatum	4	(SEDA-8, 159)	
Pyridoxine hydrochloride	10% petrolatum	4	(SEDA-10, 128)	
Pyrocatechol	2% petrolatum	4	(SEDA-14, 129)	

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Table 1 Continued

Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Pyrrolnitrin	1% petrolatum	3	(SEDA-9, 138)	
Quaternium-22	0.1 and 0.01 aqua		(117)	
Quinidine sulfate	1% aqua	3	(SEDA-7, 163)	a, c
Quinine	1% aqua	4	(SEDA-18, 173)	a, c
Resorcinol	2% petrolatum	3	(SEDA-21, 165)	b, d, e
Rhus aculeatus	0.8–1.6% alcohol	4	(SEDA-2, 138)	e
Rifamycin	0.5% petrolatum	4	(SEDA-11, 139)	b
Salbutamol sulfate	5% petrolatum	4	(SEDA-18, 173)	
Salicylic acid	2% petrolatum	4	(SEDA-2, 137)	b, d, e
Scopolamine[3]	1% petrolatum	3	(SEDA-15, 144) (65,66)	d
Sertaconazole	1–5% petrolatum	4	(SEDA-20, 159)	
Sesame oil	Pure	3	(SEDA-13, 127)	
Shellac	20% alcohol and pure	4	(SEDA-12, 135)	
		6	(118)	
Silicic acid	5% petrolatum and pure	4	(SEDA-14, 133)	
Silver nitrate	1% aqua	4	(SEDA-17, 189)	
Silver sulfadiazine cream	Pure	3	(SEDA-10, 129)	
Sisomicin sulfate	1–10% petrolatum	4	(SEDA-21, 165)	
Sodium benzoate[1]	1–2% aqua or petrolatum	3	(SEDA-17, 189)	b
Sodium cromoglicate[3]	2% aqua	4	(SEDA-14, 127)	
Sodium dihydroxyacetyl phosphate	5% petrolatum		(119)	
Sodium fusidate	2% petrolatum	3	(SEDA-8, 156)	
Sodium metabisulfite	2% petrolatum	1	(64)	
Sodium myristoyl sarcosinate	1% aqua	1	(120)	
Sodium ricinoleamido MEA-sulfosuccinate	5% petrolatum	4	(SEDA-15, 148)	
Sodium sulfite	2–5% petrolatum	3	(SEDA-17, 190)	b
Sorbic acid[1]	2% petrolatum	3	(SEDA-17, 190)	b
Sorbitan laurate	5% aqua	4	(SEDA-9, 139)	b
Sorbitan oleate	5% petrolatum	4	(SEDA-8, 156) (57)	
Sorbitan sesquioleate	2% petrolatum	3	(SEDA-18, 173) (57)	
Sorbitan stearate	5% petrolatum	3	(57)	
Soybean extract	1, 10, and 20% petrolatum		(121)	
Spearmint (*Mentha spicata*)	2% (?)		(105,106)	
Spearmint oil	1–5% petrolatum		(122,123)	
Spiramycin	10% aqua or petrolatum	3	(3)	c
Spironolactone	1% alcohol or petrolatum	3	(SEDA-19, 162)	
Squaric acid dibutyl ester	0.05% acetone	1	(SEDA-9, 138)	b
Stearic acid	5–10% petrolatum	4	(SEDA-14, 129)	
		1	(83)	
Stearyl alcohol	30% petrolatum	3	(3)	b
Stearyl alcohol in Efudix cream	(?)		(124)	
Storax (styrax)	2% petrolatum	2	(3)	
Streptomycin	1% petrolatum	2	(3)	b
Sulconazole	1% alcohol or methylethylketone	4	(SEDA-20, 156)	
Sulfonamides	5% petrolatum	1	(3)	a
Suprofen	0.1% petrolatum	3	(SEDA-18, 164) (36)	a
Tacalcitol	0.0002% alcohol	4	(SEDA-20, 157)	
Tannin	1–10% petrolatum or aqua	4	(SEDA-19, 162)	
TEA-PEG-3 cocamide sulfate	1% aqua	4	(SEDA-10, 130)	
Tea tree oil	15 petrolatum and pure	3	(SEDA-22, 172) (125)	f
Tetracaine	1% petrolatum	2	(SEDA-9, 138)	
Tetrahydroxypropyl ethylenediamine	10% petrolatum		(126)	
Thiabendazole	2% petrolatum	4	(SEDA-17, 190)	a
Thiomersal[1,3]	0.1% petrolatum	1	SEDA-19, 160) (115,127)	b, d
Thioxolone	0.5% alcohol	4	(SEDA-13, 126)	
Thuja essential oil	Pure	4	(SEDA-18, 173)	
Thymol	1% petrolatum	4	(SEDA-20, 157)	
Tiaprofenic acid	1% petrolatum	3	(SEDA-18, 164) (36)	a, f
Timolol maleate	0.5% petrolatum	4	(SEDA-16, 156)	

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Chemical	Patch test concentration and vehicle	Frequency of sensitization	References	Comments
Tioconazole[3]	2% petrolatum or alcohol	2	(SEDA-21, 164)	
Tiopronin	6.66 mg/ml solution	4	(SEDA-20, 157)	
Tixocortol pivalate[2]	1% petrolatum	1	(SEDA-17, 185)	
Tobramycin	20% aqua or petrolatum	3	(SEDA-15, 147)	
Tocopherols	10% petrolatum	3	(SEDA-19, 162)	b
Tocopheryl linoleate	10% petrolatum	2	(SEDA-19, 165)	
Tolazoline[3]	<10% aqua	4	(SEDA-11, 139)	
Tolnaftate	1% petrolatum	4	(SEDA-20, 157)	
Tosufloxacin tosilate	20% petrolatum on previously affected site		(128)	
Tosylamide/formaldehyde resin	10% petrolatum	1	(SEDA-17, 186)	
Transdermal therapeutic systems (TTS)		1–4	(65,66)	
Tretinoin	0.005% alcohol	4	(SEDA-21, 165)	d, e
Triamcinolone acetonide[2]	1% alcohol	2	(3)	
Triclosan[1]	2% petrolatum	3	(129)	a
Trideceth-2-carboxamide monoethanolamine	0.5% aqua	1	(130)	
Triethanolamine	1–55% petrolatum	3	(SEDA-15, 143) (131)	
Triethanolamine polypeptide oleate condensate	1% petrolatum	4	(3)	
Triethanolamine stearate	5% petrolatum	4	(SEDA-8, 159)	
Trifluorothymidine	1% petrolatum	4	(SEDA-6, 149)	
Trilaureth-4-phosphate	0.5–1% petrolatum	4	(SEDA-10, 130)	
Trimebutine	0.15–4.8 mg/ml aqua		(132)	
Triphenylmethane dyes	2% aqua	4	(3)	d
Tromantadine hydrochloride	1% petrolatum	2	(SEDA-9, 138)	
Tropicamide	5% aqua	4	(SEDA-18, 173)	
Tylosin	5% petrolatum	3	(SEDA-9, 138)	
Tyrothricin	20% petrolatum	3	(3)	
Undecylenamide DEA	0.1–1% aqua	4	(SEDA-17, 190)	
Undecylenic acid	2% petrolatum	4	(3)	
Usnic acid	1% petrolatum	4	(SEDA-20, 157)	
Virginiamycin	5% petrolatum	3	(3)	b
Vitamin A (retinol palmitate)	0.1% petrolatum	4	(SEDA-21, 165)	
Vitamin B_1	10% petrolatum	4	(3)	c
Vitamin E	10% petrolatum	3	(SEDA-21, 165)	c
Vitamin K_4	0.1% petrolatum	4	(3)	c
Witch hazel	10% alcohol distillate	4	(SEDA-19, 162)	
Xanthocillin	1–10% petrolatum	3	(3)	
Zinc pyrithione	1% petrolatum	3	(SEDA-10, 130)	a
Zinc ricinoleate	Commercial preparation	4	(SEDA-12, 135) (133)	

[1] For allergy to preservatives, see (11,134,135).
[2] For glucocorticoid allergy, see (13,81,82) and (SEDA-21, 158). For patch-testing glucocorticoids, a 1% concentration in 70% alcohol can be adequate. However, as alcoholic solutions can only be kept in storage for 1–2 months and can cause irritation, petrolatum is the usual choice of vehicle (SEDA-21, 159).
[3] For allergy to ophthalmic drugs, see (136).
[4] For allergy to fragrances, see (12) (SEDA-20, 149).
[5] For allergy to antihistamines, see (14).

In the column "Frequency of sensitization" the following scale for the occurrence of sensitization is used:

1 = common;
2 = can occur;
3 = unusual;
4 = rare.

In the column "Comment" the following symbols are used:

a = photosensitivity reported;
b = immediate contact reactions reported;
c = accidental contactant;
d = see also separate monograph;
e = has also caused irritant dermatitis;
f = systemic contact dermatitis reported.

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Contact allergy in the anogenital region

Allergic contact dermatitis is a common anogenital disease. The predominant complaints are itching and burning. Scratching, mainly at night, and lichenification can lead to painful erosions. Topical medicaments, body care products, popular remedies, and sanitary products are the main sources of contact allergens in the anogenital area.

Epidemiology

During 1992–1997, 1008 patients with anogenital complaints (2% of the whole test population of 54 500 patients) were patch-tested in the Departments of Dermatology of the Information Network of Dermatological Clinics (IVDK). The standard series recommended by the German Contact Dermatitis Research Group (DKG) was tested in 978 of these patients. Other specific allergens were tested according to each patient's history. In most cases topical drugs, ointment bases, and preservatives were included, and in 466 cases patients' own products were also patch-tested. In 351 patients (35%), the final diagnosis of allergic contact dermatitis was confirmed (15). Similar numbers were reported from the UK, where anogenital dermatosis was diagnosed in 201 women in a contact dermatitis clinic over 14 years. In 79 cases (39%) the diagnosis of allergic contact dermatitis was confirmed by patch tests with the European standard series, a medicament series, a glucocorticoid series, and the patients' own medicaments, if necessary. In another UK study, 39 of 135 patients tested (29%) with persisting vulval symptoms had contact hypersensitivity (16). There is evidence that the vulval region and the perianal region should be considered separately, since patients with dermatosis that only involves the vulva have positive patch tests less often than patients with dermatosis of the vulva and the perianal area or patients who have only perianal involvement (17).

Allergens and sources

The most frequent allergens in the study of the IVDK are listed in Table 2, and Table 3 gives information about the patch test results obtained with topical drugs, ointment bases, and preservatives.

All allergens that led to positive reactions in at least 1% of the patients tested are listed (15).

Although the spectrum is comparable to that of all patients tested between 1992 and 1997, there are some allergens of pronounced significance for the anogenital region. Cinchocaine HCl ranked fourth among contact allergens

Table 2 The most frequent allergens among patients with anogenital complaints

Allergen	Number tested	Number with a positive reaction (%)[1]	Number with a positive reaction (%)[2]	IVDK total 1992–7 (%)[3]
Nickel sulfate	962	86 (8.9)	12.6	16–17
Balsam of Peru	962	74 (7.7)	6.6	6.5–8
Fragrance mix	960	71 (4.7)	7.2	10–13
Cinchocaine HCl (dibucaine HCl)	592	50 (4.8)	7.4	*
Thiomersal	961	48 (5.0)	5.6	5–7
Methyldibromoglutaronitrile/ 2-phenoxyethanol	958	39 (1.4)	3.1	2–3
Paraphenylenediamine	959	39 (1.4)	3.7	4–5.5
(Chloro)methylisothiazolinone (CMI/MI)	951	32 (3.4)	3.7	~2.5
Benzocaine	962	31 (2.3)	2.7	~1.5
Phenylmercuric acetate	736	28 (3.8)	4.0	4–8
Neomycin sulfate	962	23 (2.4)	2.1	~2.5
Wool wax alcohol	962	22 (2.3)	2.1	2.5–4
Amerchol L-101	561	21 (3.7)	2.9	*
Colophony (rosin)	961	19 (2.0)	2.3	2.5–3.5
Mercury amide chloride (ammoniated mercury)	962	19 (2.0)	1.7	~2.5
Propolis	598	17 (2.8)	2.5	*
Parabens mix	962	17 (1.8)	1.6	~1.5
Benzoylperoxide	218	15 (6.9)	7.6	*
Octylgallate	560	15 (2.7)	2.8	*
Methyldibromoglutaronitrile	508	14 (2.8)	2.1	*
Cobalt chloride	960	13 (1.4)	2.0	4.5–5
Propylene glycol	744	12 (1.6)	1.5	*
Formaldehyde	961	12 (1.2)	1.5	~2
Hexylresorcinol	476	11 (2.3)	2.1	*
Para-*tert*-butylphenol Formaldehyde resin (PTBP-FR)	955	11 (1.2)	1.4	~1
Thiuram mix	961	11 (1.1)	1.1	~2.5

[1]Percentage of positive reactions.
[2]Age- and sex-standardized frequency of sensitization.
[3]Range of the age- and sex-standardized frequency of sensitization in all patients tested ($n = 54\,500$).
*Allergens were tested in selected patients only; so a comparison in this way makes no sense.
All allergens that led to positive reactions in more than 1% of the total population (that is 10 patients) are listed.
Source: IVDK 1992–1997 ($n = 1008$) (15).

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Table 3 Patch test results obtained with topical drugs, ointment bases, and preservatives

Allergen	Test formulation	Number tested	Number with a positive reaction (%)
Bufexamac	5% petrolatum	534	9 (1.7)
Framycetin sulfate	20% petrolatum	268	7 (2.6)
Lidocaine HCl	15% petrolatum	524	6 (1.1)
Tincture of *Arnica montana*	20% petrolatum	241	5 (1.2)
Clotrimazole	5% petrolatum	272	5 (1.8)
Iodochlorhydroxyquin (clioquinol)	5% petrolatum	303	5 (1.7)
Chamomile extract	2.5% petrolatum	173	5 (2.9)
Tetracaine HCl (amethocaine HCl)	1% petrolatum	306	4 (1.3)
Panthenol	5% petrolatum	323	4 (1.2)
Chloramphenicol	10% petrolatum	244	3 (1.2)
Mafenide	10% petrolatum	299	3 (1.0)
tert-Butyl hydroquinone	1% petrolatum	710	8 (1.1)
Benzalkonium chloride	0.1% petrolatum	740	8 (1.1)
Bronopol	0.5% petrolatum	728	7 (1.0)
Chloroacetamide	0.2% petrolatum	743	7 (0.9)

in this region. Furthermore, there were more positive patch test results to (chloro)methylisothiazolinone (CMI/MI) and to benzocaine among patients with anogenital complaints compared with the whole test population (15).

Topical local anesthetics play an important role in anogenital contact allergy (15–19). Cinchocaine is commonly used in topical antihemorrhoidal formulations and is a well-known sensitizer (20). Although benzocaine is not as widely used in topical anesthetic formulations in Germany, patients with anogenital dermatitis were at higher risk of sensitization. Amide-type local anesthetics, like lidocaine HCl and tetracaine, are less potent sensitizers (21). Contact allergy to local anesthetics is more often observed among patients with perianal complaints than patients with perianal and vulval or only vulval dermatitis (17).

Topical antibiotics are often used in the treatment of dermatitis with bacterial superinfection. However, in Germany sensitization to the aminoglycoside antibiotic neomycin was less frequent in patients with anogenital dermatitis (15) compared with the UK, where 15 of 79 patients with positive patch tests and anogenital complaints were positive to neomycin (17). Framycetin contact sensitivity was frequent in the UK, partly through cross-reactivity with neomycin (16).

Another important substance in hemorrhoidal formulations is bufexamac, a non-steroidal anti-inflammatory drug that is a well-known sensitizer and sometimes elicits severe dermatitis (22). Bufexamac should therefore always be included in patch tests for anogenital dermatitis.

Glucocorticoid contact allergy is well known (SEDA-21, 158) and has to be particularly suspected in chronic conditions affecting the perianal area (17), after long-term topical medication, and in cases of failure to ameliorate dermatitis with corticosteroids. Patch tests should then be performed both with the recommended markers, budesonide (0.1% petrolatum) and tixocortol pivalate (1% petrolatum), and with the patient's own formulations.

Antifungal drugs are comparatively rare contact allergens in the anogenital region in relation to their widespread use. Clotrimazole and nystatin are preferred. In the study of the IVDK, patch tests with clotrimazole were performed in only 272 patients, leading to five positive reactions (15). In the UK study on anogenital dermatosis, five women out of 201 patients tested had positive reactions to antifungal drugs, but was unfortunately not specified in the article (17). If sensitization to nystatin is suspected, polyethylene glycol should be used as a vehicle for patch-testing (23). Imidazoles can cross-react with one another (SEDA-20, 156). Most cases of contact allergy occurred with miconazole, econazole, tioconazole, and isoconazole (24).

Moist toilet paper is a rare source of contact allergens. The most important allergens in moist toilet paper are preservatives, such as CMI/MI and dibromoglutaronitril + 2-phenoxyethanol (Euxyl K 400) (25–27). These substances were also incriminated in the study of the IVDK (15) and are also found in body care products. In Germany, when CMI/MI was replaced by iodopropyl butylcarbamate (IPBC) in moist toilet paper, one case of contact allergy to IPBC was soon described (28).

Other sources of preservatives are topical medicaments and body care products. Parabens, chloracetamide, and formaldehyde-releasing preservatives, like diazolidinyl urea, imidazolidinyl urea, bronopol, and quaternium 15, should also be considered (15).

Ointment bases do not seem to cause contact allergy in the anogenital region too often, despite wide use. Wool wax alcohol and amerchol L-101 are the most important (15,17). Contact sensitivity to balsam of Peru and fragrance mix is not infrequent and reflects the ubiquitous presence of these substances (16).

Topical remedies are very popular in self-treatment and patients will often not report this, since they do not regard them as medicaments. Furthermore, patients often do not suspect that "natural" remedies cause adverse effects. Some substances lead to a considerable number of allergic reactions, for example chamomile extract and tincture of *Arnica montana* (15). Propolis also has pronounced sensitizing capacity (29), and sensitization to aged tea tree oil is being reported with increasing frequency (30).

Contact allergy from rubber additives in condoms is sometimes suspected, and there are anecdotal reports (31). However, in the study of the IVDK, condoms were patch-tested in 17 patients without positive results (15).

Although sensitization to nickel sulfate is common in patients with anogenital contact dermatitis and in patients with dermatitis in other body sites, the relevance to

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anogenital complaints of sensitization to nickel sulfate should always be doubted (15,16,32). However, direct transmission of nickel from the hands to the anogenital region has to be taken into account, and food can be a rare source of nickel contact in the anogenital area. In these cases relevance can be proved by oral nickel provocation and a nickel-restricted diet for a limited period may be justified (33).

Prediction of contact allergens

Certain chemical substructures, so-called toxophores, can be associated with an increased risk of skin sensitization. These have been codified in a set of 57 rules known as the DEREK (Deductive Estimation of Risk from Existing Knowledge) knowledge-based computer system (34). This rulebase has been subjected to extensive validation and continues to be refined. The predictive ability of the sensitization rule set was assessed by processing the structures of the first 84 chemical substances in the list of contact allergens issued by the German Federal Institute for Health Protection of Consumers (BgVV). The rules identified toxophores for skin sensitization in the structures of 71 of the 84 chemicals. After refinement, by extension of the scope of the existing rules and by generation of new rules with a sound mechanistic rationale for the biological activity, the rules identified toxophores for skin sensitization for 82 of the 84 chemicals.

Conclusions

Contact allergy should always be suspected in patients with anogenital dermatitis, especially if the perianal area is involved. In patients with other chronic inflammatory diseases of the anogenital region, for example lichen sclerosus, contact allergy should also be excluded, since long-term use of topical medicaments on compromised skin carries an increased risk of sensitization.

Patch tests in patients with anogenital eczema should include the standard series: cinchocaine HCl, propolis, bufexamac, and other ingredients of topical formulations according to the patient's history. In cases of doubt, the repeated open application test (ROAT) is recommended. Patients should be advised to apply the suspected product three times a day for 3 days to an area of healthy skin on measuring 5 cm × 5 cm the flexural site of the forearm (35).

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Substances that affect the skin: Contact urticaria

Contact urticaria (1–4) refers to a wheal-and-flare response to the application of chemicals to the intact skin. Various cutaneous and extracutaneous symptoms and signs have been described, justifying the term "contact urticaria syndrome." The broad spectrum of clinical manifestations is classified in Table 1. The symptoms usually develop within 20–30 minutes after contact with the offending chemical, but later reactions after several hours have also been recorded.

Most cases of contact urticaria are of non-immunological origin, presumably due to the direct release of histamine, slow-reacting substance of anaphylaxis (SRS-A), bradykinin, or other vasoactive substances. Topical drugs and ingredients of cosmetics that have caused non-immunological contact urticaria are listed in Table 2.

Contact urticaria of immunological origin is less common, although many topical drugs have caused it in previously sensitized individuals. In several reports, passive-transfer tests were positive, and specific antibodies have occasionally been demonstrated, indicating an immunological phenomenon. Topical drugs and ingredients of cosmetics that have caused immunological contact urticaria are listed in Table 3; in most of these cases, the contact urticaria was of probable immunological origin.

Some cases of contact urticarial reactions cannot be ascribed with certainty to either immunological or non-immunological mechanisms; the classical example of this category of contact urticaria of uncertain mechanism is that caused by the bleaching agent ammonium persulfate. Also belonging to this category are several topical substances that have caused contact urticaria on patch-testing, the clinical significance of which is uncertain, for example nickel sulfate, butylated hydroxyanisole (BHA),

Table 2 Agents that have caused non-immunological contact urticaria (1,4)

Alcohols	Eugenol
Balsam of Peru	Formaldehyde
Benzaldehyde	Iodine
Benzocaine	Methyl green
Benzoic acid/benzoin tincture	Methyl salicylate
Camphor	Monoethyl fumarate (SEDA-16, 153)
Cantharides	Nicotinic acid esters (SEDA-17, 187)
Capsaicin	Parabens
Chlorocresol	Phenol
Cinnamic acid	Propylene glycol (SEDA-19, 159)
Cinnamic aldehyde (SED-9, 249)	Resorcinol
Cinnamon oil	Sodium benzoate
Diethyl fumarate (SEDA-16, 153)	Sorbic acid
Dimethylsulfoxide (SED-9, 249)	Sulfur

Table 1 Staging and symptoms of the contact urticaria syndrome (3,4)

Cutaneous reactions only		Extracutaneous reactions	
Stage 1	Localized urticaria Dermatitis/dermatosis Non-specific symptoms (itching, tingling, burning, etc.)	Stage 3	Bronchial asthma Rhinoconjunctivitis Otolaryngeal symptoms Gastrointestinal symptoms
Stage 2	Generalized urticaria	Stage 4	Anaphylactoid reactions

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Table 3 Agents known or believed to have caused immunological contact urticaria (1–4)

Acetylsalicylic acid
Acrylic acid (SEDA-18, 175)
Albendazole
Aminophenazone (aminopyrine)
Ampicillin
Amyl alcohol
Bacitracin
Balsam of Peru
Basic blue 99
Benzocaine
Benzoic acid
Benzophenone
Benzoyl peroxide
Benzyl alcohol
Buserelin acetate
Butyl alcohol
Butylated hydroxyanisole (BHA)
Butylated hydroxytoluene (BHT)
Caraway seed oil
Cefotiam hydrochloride (SEDA-19, 163)
Cephalosporins
Cetyl alcohol
Chamomile
Chloramine
Chloramphenicol
Chlorhexidine (SEDA-21, 166)
Chlorocresol (SEDA-12, 137)
Chlorproethazine (SEDA-17, 187)
Chlorpromazine (6)
Clioquinol (iodochlorhydroxyquinoline) (SEDA-5, 152)
Clobetasol 17-propionate (SEDA-8, 153)
Colophony
Corn starch
Denatonium benzoate
Diethyl fumarate
Diethyl toluamide (SEDA-8, 153)
1,3-Diiodo-2-hydroxypropane
Dinitrochlorobenzene
Diphenylcyclopropenone (SEDA-14, 132)
Dipyrone
Disodium cromoglicate (SEDA-12, 137)
Emulgade F
Estrogen cream
Ethyl alcohol
Ethylenediamine dihydrochloride
Etofenamate
Formaldehyde (SEDA-8, 153)
Gelatine
Gentamicin (SEDA-12, 139)
Gentian violet
Glyceryl trinitrate
Hamamelis
Henna
Hexanetriol
Hydrolysed protein (SEDA-21, 166)
Isopropyl alcohol
Isopropyl dibenzoylmethane
Labetalol
Lanolin alcohol (SEDA-5, 152)
Latex
Lidocaine (SEDA-15, 149)
Lindane
Mechlorethamine hydrochloride (SEDA-22, 172)
Menthol
Merbromin
Mercurochrome (SEDA-19, 163)
Metamizole
Methotrimeprazine
Methylethylketone
Mexiletine hydrochloride (SEDA-18, 175)
Mezlocillin (SEDA-15, 149)
Monoamylamine
Myrrh
Neomycin
Nickel sulfate
Nicotine
Nicotinyl alcohol
Nifuroxime
Orthophenylphenate
Oxyphenbutazone
Para-aminodiphenylamine (SEDA-5, 152)
Parabens
Parahydroxybenzoic acid
Paraphenylenediamine derivatives (SEDA-21, 166)
Penicillin
Pentamidine isethionate
Phenylmercuric salts
Polyethylene glycol
Polypropylene (Polysorbate 60)
Povidone iodine (SEDA-20, 157)
Pristinamycin
Procaine hydrochloride
Promethazine hydrochloride
Propipocaine hydrochloride (SEDA-15, 149)
Propyl alcohol
Propylene glycol
Protein hydrolysate (SEDA-15, 149)
Pyrazolone derivatives (SEDA-9, 139)
Pyrethrin (SEDA-15, 149)
Rifamycin (SEDA-17, 191)
Salicylic acid
Sisomycin (SEDA-12, 139)
Sodium hypochlorite
Sodium sulfite
Sorbitan laurate (SEDA-9, 139)
Squaric acid dibutyl ester
Steartrimonium hydrolysed animal protein (SEDA-21, 166)
Stearyl alcohol
Streptomycin
Sulfur
Tetracycline (SEDA-9, 139)
Thiomersal
Thuja
α-Tocopherol
Tropicamide
Vanillin
Virginiamycin

butylated hydroxytoluene (BHT), ethyl vanillin, potassium bichromate, parabens, and ethylenediamine (5).

The diagnosis of contact urticaria can usually be confirmed by an open test. However, such tests should be performed with great caution, since anaphylactoid reactions due to the testing procedure have been described (3,4).

Reports of contact urticaria to ingredients of drugs and cosmetics are listed in Table 4 and Table 5 (7–11).

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Table 4 Contact urticaria to ingredients of topical drugs and cosmetics

Allergen	Allergen-containing product	20-minute patch test	Skin prick test	Reference
Cyclopentolate hydrochloride	Eye drops (Colircursi cicloplejico 1%)	Eye drops +	Not performed	(12)
Di(2-ethylhexyl) phthalate (DOP)	PVC grip cotton gloves	Rubbing with PVC grip+	Gas chromatography extracts + DOP + Di-*n*-butylmaleate +	(13)
Glyceryl thioglycolate	Hair permanent fluid	1% in petrolatum +	Not performed	(14)
Panthenol	Hair conditioner	Hair conditioner Panthenol 30% in petrolatum	Hair conditioner + Panthenol +++	(15)
Wheat hydrolysate	Body cream	Body cream ++	Wheat hydrolysate ++	(16)

Table 5 Contact urticaria to relatively rare antigens in drugs and cosmetics

Allergen	Allergen-containing product	Patch tests	Skin prick tests	Reference
Benzophenone 3	Sunscreens	Benzophenone 3 + (concentration not stated)	Not done	(17)
Benzyl alcohol	Bacteriostatic saline	10 cm wheal after 24 hours (concentration not stated)	Not done	(18)
Cyclopentolate hydrochloride	Eye drops	Eye drops 1% +	Not done	(12)
Di-(2-ethylhexyl) phthalate (DOP)	PVC grip cotton gloves	Rubbing with PVC +	Gas chromatography extracts + DOP + Di-*n*-butylmaleate	(13)
Geraniol	Various cosmetics	Geraniol + (concentration not stated)	Not done	(19)
Glyceryl thioglycolate	Hair permanent fluid	1% in petrolatum +	Not done	(14)
Panthenol	Hair conditioner	Panthenol 30% in petrolatum –	Hair conditioner + Panthenol +++	(15)
Phenoxyethanol	Body lotion	Phenoxyethanol 1% pet + Euxyl K 400 1.5% + Own cosmetics + Not done	Phenoxyethanol 1%+ Euxyl K 400 1.5%+ Body lotion +++ Euxyl K 400 ++ Phenoxyethanol 1%+, 5%+,10%++	(20) (21)
Potassium persulfate	Hair dye	Nickel sulfate	Potassium persulfate (dilution not stated) 5 mm wheal	(22)
Wheat hydrolysate	Body cream	Body cream ++	Wheat hydrolysate ++	(16)

+, ++, +++ indicate increasing intensity of reaction.

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Substances that affect the skin: Discoloration, necrosis, and miscellaneous adverse effects

Drugs that cause discoloration of the skin, nails, and mucous membranes are listed in Table 1. Pigmented contact dermatitis has been reviewed (1).

Drugs that cause necrosis of the skin and mucous membranes are listed in Table 2.

Other adverse effects of topical drugs and cosmetics are listed in Table 3.

Table 2 Drugs that have caused necrosis of skin and mucous membranes

Drug	References
Adrenaline	(SEDA-10, 131)
Arsenious oxide	(SED-9, 249)
Cetrimonium bromide	(SED-9, 249)
Dequalinium	(26)
Fluorouracil	(SEDA-5, 155)
Fuchsin–silver nitrate	(27)
Gentian violet (crystal violet)	(SEDA-12, 138)
Glucocorticoids	(SEDA-7, 166)
Phenol	(SED-9, 250)
Povidone iodine	(SEDA-5, 152)

Table 1 Discoloration of the skin and appendages

Drug	Adverse effect	References
Amorolfine nail lacquer	Bluish or yellow-brown discoloration of the nail plate	(SEDA-21, 166)
Benzoyl peroxide	Discoloration of hair and postinflammatory pigmentation; hypopigmentation	(2,3)
Butylated hydroxyanisole	Depigmentation	(4)
Butylated hydroxytoluene	Depigmentation	(5)
Carmustine (BCNU)	Pigmentation	(6)
Chlorhexidine	Discoloration of the teeth and tongue	(SED-9, 249)
Cinnamic aldehyde	Depigmentation	(SEDA-6, 153)
Clioquinol	Red discoloration of white hair	(SEDA-9, 143)
Coal tar dyes	"Pigmented cosmetic dermatitis"	(7)
Diethylstilbestrol	Brown discoloration of nipples and linea alba; systemic effects caused by percutaneous absorption	(SEDA-9, 250)
Dihydroxyacetone	Brown pigmentation ("sunless tanning")	(8)
Dinitrochlorobenzene	Yellow discoloration of grey hair	(SEDA-4, 107)
Diphencyprone	Triggering of vitiligo	(SEDA-14, 132)
Dithranol	Brown-purplish discoloration of skin, nails, and hair	(9,10)
Fluorouracil	Hyperpigmentation of the skin and nails (melanonychia)	(SEDA-5, 155) (11)
Glucocorticoids	Hyperpigmentation and hypopigmentation	(12)
Glutaral (glutaraldehyde)	Brown discoloration	(SED-9, 249)
Hydroquinones	Pigmentation and depigmentation; nail staining	(SEDA-8, 161) (13–15)
Iron salts	Brown discoloration (sometimes permanent)	(16,17)
4-Isopropylcatechol	Depigmentation	(18)
Mechlorethamine hydroquinone	Pigmentation	(19)
Mercury compounds	Depigmentation	(20)
Perfume ingredients	Contact allergy has caused pigmentation of the face	(21)
Petrolatum	Hyperpigmentation	(22)
Phenols	Depigmentation and hyperpigmentation	(SEDA-7, 166)
Resorcinol	Darkens fair hair; orange-brown discoloration of lacquered nails	(23)
Selenium sulfide	Green hair discoloration	(SEDA-22, 173)
Silver nitrate	Slate grey discoloration (argyria)	(24)
Thiotepa	Periorbital leukoderma	(SEDA-5, 155)
Tretinoin	Hypopigmentation	(25)

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Table 3 Miscellaneous adverse effects of topical drugs (for additional references see SED-9, 249)

Drug	Common uses	Adverse effects	References
Benzonyl peroxide	Acne treatment	Co-carcinogen (?)	(SEDA-7, 168)
Benzyl benzoate	Antiscabetic drug	Pemphigoid (?)	(28)
Cetrimonium bromide	Antiseptic	Matting of hair	(29)
Clonidine patches	Antihypertensive	Activation of *Herpes simplex*; hyperpigmentation	(SEDA-13, 128)
Coal tar	Psoriasis; eczema	Carcinogen (?)	(30,31)
Dinitrochlorobenzene	Treatment of alopecia areata	Yellow discoloration of grey hair; enhancement of allergy to non-related allergens; mutagen (?); carcinogen (?)	(SEDA-4, 107) (SEDA-6, 149) (32) (SEDA-10, 131) (SEDA-109, 195)
5-Fluorouracil	Topical antimitotic drug	Telangiectasia; bilateral cicatricial ectropion; exacerbation of *Herpes labialis*; pain, edema, livedo reticularis; erosions	(SEDA-7, 166) (SEDA-7, 166) (SEDA-5, 155)
Fusidic acid	Antibacterial agent	Acanthosis nigricans	(SEDA-17, 192)
Idoxuridine	Antiviral drug	Carcinogen (?); mutagen (?); teratogen (?)	(33–35)
Lindane	Antiscabetic drug	Morphea	(SEDA-16, 159)
Mechlorethamine hydrochloride	Nitrogen mustard; topical antimitotic drug	Carcinogen; suppression of immunological defences; Stevens–Johnson syndrome	(SEDA-22, 172) (19)
Nicotinic acid	Treatment of alopecia	Acanthosis nigricans	(SEDA-11, 142)
Petrolatum	Vehicle constituent	Acne; lipogranulomata	(36) (SEDA-6, 154)
Phenol	Face peeling; antipruritic	Milia; persistent erythema; skin pore prominence; telangiectasia; scarring; pigment alterations	(SEDA-7, 166)
Podophyllin	Treatment of condylomata acuminata	Carcinogen (?)	(37)
Polyethylene glycol	Vehicle constituent	Carcinogen (?)	(SEDA-6, 153)
Salicylic acid	Keratolytic drug	Thinning of the skin, telangiectasia, and (de)pigmentation after prolonged use	(SEDA-15, 151)
Selenium sulfide	Antiseborrheic drug	Reversible hair loss; structural hair defects (?); oiliness of the scalp	(38)
Tretinoin	Acne treatment	Ectropion Eruptive pyogenic granuloma	(SEDA-17, 185) (SEDA-15, 151)

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Substances that affect the skin: Photocontact dermatitis

Photocontact dermatitis can be toxic or allergic in nature (1–4). Phototoxicity can occur in anybody if enough light energy and photosensitizer are present in the skin. Photoallergy is due to a cell-mediated hypersensitivity response, and therefore occurs in sensitized individuals only.

Compared with contact allergy, photocontact allergy is uncommon, although many chemicals have been responsible for photoallergic reactions.

The British Photodermatology Group has provided a summary of the methods and clinical use of photopatch-testing. The following potential photoallergens have been suggested as standard series for routine testing in all patients suspected of photosensitivity:

(a) benzophenone-3;
(b) butyl methoxydibenzoylmethane;
(c) 2-ethylhexyl-para-methoxycinnamate;
(d) musk ambrette;
(e) octyl dimethyl para-aminobenzoic acid;
(f) para-aminobenzoic acid (PABA).

Patients' own products, diluted as appropriate, should be tested as well (5). Currently, UV filters (and to a lesser extent fragrances) are the main photosensitizers, notably benzophenone-3. Sunscreen photosensitization occurs especially in patients with photodermatoses and photoaggravated dermatoses (3). The UV filter isopropyl dibenzoylmethane caused so many cases of photosensitization that it was withdrawn.

In a review of photopatch-testing in 2390 patients with rashes that were confined to sun-exposed areas, about 70% of 4374 positive reactions were classified as photoinduced reactions, of which 222 (5%) were photoallergic reactions (6). NSAIDs, disinfectants, and phenothiazines were the main photoallergens. Photosensitive reactions to antimicrobial drugs, including topical agents, have been reviewed (7).

Topical photosensitizers are listed in Table 1 (1–4,8).

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Table 1 Topical photosensitizers

Aceclofenac (9)	A
6-Acetoxy-2,4-dimethyl-m-dioxane (SEDA-10, 131)	T
Amyl dimethyl PABA (SEDA-10, 131)	T
Balsam of Peru (SEDA-19, 162)	T
Benoxaprofen (10)	A
Benzocaine (11)	A, T
Benzophenone-3 (oxybenzone) (SEDA-22, 170, 172)	A
Benzophenone-4 (sulizobenzone) (SEDA-19, 162)	A
Benzophenone-10 (mexenone) (SEDA-22, 170)	A
Benzydamine (SEDA-18, 164)	A
Bithionol (12)	A
Brilliant lake red	A, T
5-Bromo-4′-chlorsalicylanilide	A
Buclosamide (Jadit)	A, T
Butyl methoxydibenzoylmethane (SEDA-22, 170, 172)	A
Cadmium sulfide	A
Carbimazole (SEDA-10, 131)	A
β-Carotene (SEDA-5, 153)	A
Chloramphenicol (13)	T
Chlorhexidine (14)	A
Chlormercaptodicarboximide	A
Chloro-2-phenylphenol	A
Cinchocaine (dibucaine) (SEDA-5, 155) (SEDA-23, 167)	A
Cinnamates (15)	A
Cinnamic aldehyde (SEDA-8, 153)	A, T
Cinoxate (2-ethoxyethyl-para-methoxycinnamate)	A, T
Clarithromycin (16)	T
Clindamycin (13)	T
Coal tar derivatives (SEDA-8, 160)	A
Coumarin derivatives (SEDA-4, 106)	T
Desoximetasone (SEDA-14, 130)	T
Dibenzthione (sulbentine)	A
Dibromsalan	A
Dichlorophene	A, T
Diclofenac (17)	A
Digalloyl trioleate	A
Dimethoxane	A
Dimethoxydibenzoylmethane	A, T
Diphenhydramine hydrochloride (18,19)	A, T
Doxepin (SEDA-19, 159)	A
Dyes, for example methylthioninium chloride, fluorescein (SEDA-15, 150), rose Bengal, acridine orange, acriflavin, neutral red	A
Erythromycin (13)	T
Essential oils: bergamot oil, cedar oil, citron oil, lavender oil, lime oil, neroli oil, petitgrain oil, sandalwood oil (SEDA-10, 131) (SEDA-12, 134)	A
Fenofibrate (SEDA-22, 170)	A, T
Fenticlor (SEDA-14, 130)	A
Fepradinol (SEDA-23, 167)	T?
Fluorouracil	A
Formaldehyde (SEDA-19, 162)	T
Furocoumarins (20)	A
Glyceryl para-aminobenzoic acid (SEDA-10, 131)	A
Hexachlorophene (21)	A
Homosalate (homomenthyl salicylate) (22)	A
Hydrocortisone (23)	A
Isoamyl-para-methoxycimamate (SEDA-22, 172)	A
Isobutyl para-aminobenzoic acid	A, T
Isopropyl dibenzoylmethane (SEDA-22, 172)	A, T
Ketoprofen (SEDA-22, 170) (24)	A
Lithiol red-CA (D and C Red No. 11)	T
5-Methoxypsoralen (SEDA-23, 167)	A, T
8-Methoxypsoralen (methoxsalen) (SEDA-15, 150) (SEDA-17, 187)	A, T
4-Methylbenzylidene camphor (SEDA-22, 172)	A
6-Methylcoumarin (SEDA-17, 187)	A
Minoxidil (SEDA-11, 139)	A, T
Musk ambrette (SEDA-15, 150)	A
Musk moskene (25)	A
Musk xylene (26)	A
Mycanodin (27)	A
Octyl dimethyl PABA (SEDA-19, 161)	A
Octyl methoxycinnamate (SEDA-22, 172)	A
PABA (para-aminobenzoic acid and derivatives) (SEDA-22, 172)	A
Paraphenylenediamine (18)	A, T
Permanent orange (D and C Orange No. 17)	A
Phenothiazines (28)	A
Phenylbenzimidazole sulfonic acid (SEDA-22, 172)	A
2-Phenyl-5-methylbenzoxazole (Witisol)	A
Piroxicam (SEDA-15, 150) (24)	A
Procaine hydrochloride	A
Selenium disulfide (SEDA-16, 157)	?
Sulfanilamide (29)	A, T
Sulfisoxasole (30)	T
Suprofen (SEDA-18, 164) (24)	A
Tar (31)	T
Tetrachlorosalicylanilide (12)	A, T
Tetracyclines (13)	T
Tiaprofenic acid (SEDA-15, 150) (24)	A, T
Thiocolchicoside (32)	A
Toluidine red (D and C Red No. 35)	A
Tribromsalan (12)	A, T
Triclocarban (14)	A, T
Triclosan (12)	A, T
Zinc pyrithione	A?

A = photoallergy; T = phototoxicity

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Succimer

General Information

Succimer is the meso isomer of 2,3-dimethylmercaptosuccinic acid (DMSA). It is used as a lead chelator for oral administration (1). Nausea, vomiting, diarrhea, and anorexia are common. Rashes, sometimes necessitating withdrawal, have been reported in up to 10% of adults and 5% of children, and mild transient rises in serum transaminase activity in 6–10% (mostly adults) (2,3). Life-threatening hyperthermia occurred on two occasions in one subject, but no details were given. Iron can be safely and effectively given to patients taking succimer, which (unlike dimercaprol) does not appear to deplete iron stores or to form a toxic chelate that would preclude the parenteral administration of iron (3).

The manufacturers have accumulated data on about 200 children treated with succimer, of whom about 10% had an adverse event (1). Gastrointestinal symptoms and raised serum transaminases were most frequently observed.

In a UK study, single oral doses of succimer or dimercaptopropane sulfonic acid in different combinations with or without acetylcysteine and potassium citrate were given to 191 patients considered to have mercury toxicity from amalgam dental fillings (4). After a single dose, about 5% of patients complained of mild gastrointestinal discomfort, fatigue, mental fuzziness, headache, and diuresis. These usually cleared within 6 hours of the dose and were considered to be due to heavy metal mobilization. There were no cases of hypersensitivity.

Organs and Systems

Hematologic

Mild to moderate neutropenia (5) and episodes of granulocytopenia, possibly related to succimer, have been reported (1,6).

In animals thrombocytopenia has occurred (7).

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Sucralfate

General Information

Sucralfate, a basic aluminium salt of sucrose octasulfate, probably acts by binding to inflamed surfaces; it is possible, however, that its binding properties are more generalized, and it has been used as an intra-alimentary phosphate-binding agent in uremic patients.

Organs and Systems

Metal metabolism

Plasma aluminium concentrations rise in patients with renal insufficiency and one might expect aluminium to accumulate with long-term use of sucralfate (1); it is therefore unwise to use sucralfate in such patients (2).

Gastrointestinal

Bezoar formation has been recorded more than once in patients taking sucralfate, with esophageal obstruction by inspissated drug (SEDA-17, 421) (SEDA-18, 374) (3), and a gastric bezoar can be formed when tube feeds include sucralfate; the formation of bezoars reflects the binding of sucralfate to protein in the food. The French System of Pharmacovigilance on sucralfate has reported bezoars in 16 adults and five neonates (4). All the children were of low birth weights and developed bezoars in the stomach. The adults developed esophageal bezoars around nasogastric tubes. The risk factors for bezoar formation were severe illness, gut hypomotility, dehydration, overdosage with sucralfate, and nasogastric tube feeding. At a pH below 4, there is extensive polymerization of sucralfate, and a sticky viscid gel is formed, which may lead to the formation of a bezoar. In view of this, it has been recommended that sucralfate be used with caution in premature babies and in adults in intensive care who are being fed via a nasogastric tube.

Drug–Drug Interactions

Digoxin

Sucralfate may reduce the absorption of digoxin (5).

Fluoroquinolone antibiotics

The absorption of all fluoroquinolones is significantly impaired when they are co-administered with sucralfate (6).

In a man with prostatitis, co-administration of ciprofloxacin and sucralfate resulted in treatment failure, presumably because of impaired absorption of ciprofloxacin (7).

In an open, randomized, crossover study in 127 healthy volunteers, sucralfate 2 g reduced the AUC of a single oral dose of gemifloxacin 320 mg by 53% and the C_{max} by 69% (8). However, sucralfate had no effect when it was given 2 hours after gemifloxacin.

In two separate crossover studies in eight healthy volunteers sucralfate 1 g reduced the systemic availability of both norfloxacin 400 mg and ofloxacin 400 mg (9). However, sucralfate had no effect when it was given 2 hours after the antibiotics.

Phenytoin

In nine healthy subjects sucralfate reduced the AUC of a single oral dose of phenytoin 500 mg by 10% (10), and in another study it reduced the AUC of a single dose of phenytoin 300 mg by 20% (11). However, in six healthy volunteers sucralfate 1 g qds for 7 days had no effect on steady-state serum phenytoin concentrations (12).

Quinidine

Sucralfate may reduce the absorption of quinidine (5).

Warfarin

Concurrent sucralfate treatment has been claimed to reduce warfarin systemic availability (SEDA-12, 945) (5).

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Sufentanil

General Information

Sufentanil, a fentanyl analogue, is a highly lipid-soluble synthetic opioid with high affinity for OP_3 (μ) opioid receptors and a potency some 5–10 times that of fentanyl. It is a short-acting analgesic.

Its adverse effects include pruritus, sedation, nausea and vomiting, dizziness, urinary retention, lightheadedness, miosis, and shivering (SEDA-16, 86). Respiratory depression also occurs (SEDA-21, 89). Motor neuron blockade, acute hypotension, and muscle weakness are rare, affecting under 1% of patients (SEDA-16, 86).

Drug studies

Placebo-controlled studies

In 41 patients undergoing abdominal hysterectomy randomly allocated in a double-blind, controlled study to sufentanil 50 micrograms for 8–16 hours via a lumbar epidural catheter before or at the end of surgery, the pre-emptive group ($n = 20$) used less sufentanil than the control group ($n = 21$) (1). The frequency of adverse effects was similar in the two groups; nine patients in the pre-emptive group and ten in the control group complained of nausea or vomiting and four patients in the pre-emptive group and five patients in the control group complained of mild pruritus.

Comparative studies

Bupivacaine

Intrathecal sufentanil and epidural bupivacaine were compared individually and in combination to establish dose-responsiveness for analgesia in labor in 100 women (2). There was no dose-responsiveness for doses of sufentanil between 2 and 10 micrograms. The ED_{50} for sufentanil was 2.3 micrograms alone (higher than that reported above (3)) and 0.85 micrograms in combination with epidural bupivacaine. Adverse effects included pruritus (incidence 70–90%), nausea, and mild somnolence (10–30%). Transient fetal bradycardia was reported in two cases.

In a double-blind, randomized, placebo-controlled study in 80 patients of the analgesic efficacy of different subarachnoid applications of sufentanil and/or bupivacaine using a microcatheter for easy postoperative pain relief, sufentanil 10 micrograms, bupivacaine 5 mg, or a combination of sufentanil 2.5 micrograms and bupivacaine 2.5 mg provided immediate and adequate postoperative analgesia for 2–3 hours (4). The group who received only sufentanil had the highest incidence of pruritus and respiratory depression. The limitations of this study were highlighted in a letter, which questioned the value of the above procedure when other tried and tested perioperative pain management methods are available (5).

Clonidine

In a double-blind study of the effect of clonidine on intrathecal sufentanil, 53 nulliparous women received sufentanil 5 micrograms intrathecally either alone or with clonidine 30 micrograms (6). The addition of clonidine increased the incidence of hypotension (12% with sufentanil alone, 63% with clonidine) and sedation (23% with sufentanil alone and 46% with clonidine). There was no significant difference in the incidence of pruritus (88%). Again, no motor blockade was observed.

In another randomized, double-blind study in 40 primiparous women in labor at less than 5 cm cervical dilatation who requested epidural analgesia, the addition of clonidine 75 micrograms to epidural sufentanil 20 micrograms did not provide any advantages in analgesic efficacy or adverse effects (7).

Dextrose

The addition of 3.5% dextrose to sufentanil 10 micrograms given intrathecally in a randomized, double-blind study of 48 women in early labor produced a significant reduction in the incidence of clinically important pruritus (8). Dextrose did not compromise the quality and duration of analgesia.

Lidocaine

The analgesic efficacy of intrathecal sufentanil with or without lidocaine has been examined in two groups of outpatients undergoing lithotripsy or gynecological laparoscopy in order to determine optimal analgesia with rapid recovery and discharge (9,10). In a retrospective case-record study of 62 shock-wave lithotripsy procedures, the 25 cases performed using intrathecal sufentanil alone had better outcomes, significantly shorter postanesthesia care unit time, and time for ambulation compared with 37 procedures performed with intrathecal lidocaine; pruritus was significantly more common with sufentanil (9). A double-blind, randomized study in 13 patients undergoing gynecological laparoscopy, who received either lidocaine 10 mg with sufentanil 10 micrograms or intrathecal sufentanil 20 micrograms, was terminated early owing to unacceptably frequent adverse

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effects and inferior analgesia in those given intrathecal sufentanil (10).

Piritramide
Sufentanil 1 microgram/ml plus 0.1% ropivacaine by epidural infusion has been compared with intravenous patient-controlled analgesia with piritramide in a double-blind, randomized study in 24 patients undergoing elective total hip replacement (11). The PCA group had significantly more adverse effects than the epidural group, including hypotension, nausea, and vomiting. There were no cases of respiratory depression, pruritus, hypertension, or dysrhythmias in either group. Epidural sufentanil was a better analgesic.

Combination studies
Adrenaline
In a randomized, double-blind, controlled study, the addition of adrenaline (100 micrograms/ml) significantly reduced the incidence of sedation and light-headedness after epidural sufentanil (40 micrograms) in 43 women who received epidural analgesia during early labor (12). However, adrenaline did not help in preventing maternal oxygen desaturation.

Bupivacaine
In a prospective dose-finding study, 170 women with cervical dilatation of 3–5 cm were randomized to receive intrathecal sufentanil 0, 2.5, 5.0, 7.5, or 10 micrograms combined with bupivacaine 5 mg (13). Bupivacaine combined with 2.5 micrograms sufentanil provided analgesia comparable to higher doses with a lower incidence of nausea and vomiting and less severe pruritus.

Bupivacaine and adrenaline
In a randomized, double-blind study in 243 parturients who received three doses of sufentanil (0.5, 0.75, and 1 microgram/ml) in combination with bupivacaine 0.625 mg/ml and adrenaline 1.25 micrograms/ml by continuous epidural infusion there were no differences in analgesic effects, but there was significantly more pruritus in those who received the highest dose of sufentanil (14). The authors suggested using the lowest dose of sufentanil (0.5 micrograms/ml) with bupivacaine solution to minimize the risk of adverse effects on the mother and neonate, with optimal analgesia.

Ropivacaine
In a randomized, double-blind study in 120 patients undergoing major abdominal surgery the combination of sufentanil 0.75 micrograms/ml with ropivacaine 0.2% provided optimal postoperative patient-controlled epidural analgesia with the fewest adverse effects of the regimens used (ropivacaine alone, ropivacaine and sufentanil 0.5, 0.75, or 1.00 microgram/ml) (15).

Organs and Systems

Cardiovascular

The incidence of hypotension with sufentanil is 7% and that of hypertension 3%. In a double-blind comparison of morphine, pethidine, fentanyl, and sufentanil in balanced anesthesia, patients who received sufentanil had the least hemodynamic disturbances. In high doses, adverse effects such as bradycardia and hypotension can lead to complications in some patients (SEDA-16, 85). Sudden hypotension occurred on induction of anesthesia with sufentanil in four patients, in whom the dose was 8.4–22.7 micrograms/kg (16). Other workers noted similar findings at doses of 1 and 1.5 micrograms/kg.

Clinically significant bradycardia or asystole occurred on induction when sufentanil was used in conjunction with vecuronium (17,18).

The effect of sufentanil was examined in 10 healthy men to find out whether it has the same hemodynamic and sensory effects as when it is used in women in labor. Details of the method of recruitment of volunteers for this double-blind study were not provided, but they received either saline or sufentanil 10 micrograms intrathecally (19), and blood pressure, heart rates, oxyhemoglobin saturation, cold and pinprick sensation, motor block, and visual analogue scales for sedation pruritus and nausea were all measured. Pruritus and sensory changes to pinprick and cold occurred only in the sufentanil group and there were no significant hemodynamic changes in either group. In view of the frequency and severity of pruritus when sufentanil is used in labor, it is interesting that all five of the male volunteers experienced this symptom, three of them severely. These findings suggested that the hypotension observed with the use of intrathecal sufentanil during labor and the sensory changes may not be mediated by the same pathway. The authors proposed that the hypotension observed in such studies is a direct result of pain relief, which is not an issue in the pain-free men in this investigation.

Respiratory

Apneic episodes have been reported in patients given sufentanil (SEDA-20, 81) (SEDA-21, 89). Respiratory arrest occurred 55 minutes after epidural and intrathecal sufentanil and bupivacaine (SEDA-18, 82).

- A healthy 22-year-old woman at 41 weeks gestation presented for urgent cesarean section following fetal heart rate deceleration (20). She was given sufentanil 10 micrograms plus 0.1% bupivacaine 10 mg intrathecally and 8 minutes later became unrousable and apneic. After 3 minutes spontaneous ventilation resumed.

The authors suggested that giving the local anesthesia first and then the sufentanil later might have contributed to this presentation of spontaneous reversal of short-lived early-onset respiratory arrest.

When nasal sufentanil was used to induce anesthesia in children, ventilatory compliance was mildly or markedly reduced and one child required suxamethonium, oxygen, and positive pressure ventilation (SEDA-16, 86).

Respiratory depression has also been described after intrathecal sufentanil 5 micrograms (21).

- An 83-year-old woman scheduled for bilateral knee replacement surgery received midazolam 7.5 mg preoperatively. Continuous spinal anesthesia was planned, with combined general anesthesia.

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Anesthesia was maintained with 0.3–0.5% of inspired isoflurane in 36% oxygen and 70% nitrous oxide while 5 mg of 0.5% bupivacaine was introduced into the subarachnoid space via an insertion at L3–4. Anesthesia extended to T11. During the procedure two top-up doses of bupivacaine 2.5 mg were administered. Postoperatively she was extubated immediately and was fully conscious on transfer to the recovery room, but 75 minutes later she had violent pain in both knees and received sufentanil 5 micrograms intrathecally. Analgesia was achieved in 10 minutes. At 15 minutes pruritus occurred and at 30 minutes she became unresponsive to verbal and painful stimuli and stopped breathing. Blood pressure was 120/60 mmHg, heart rate 72/minute, and oxygen saturation 97%. Ventilation with 100% oxygen via a facemask started immediately and naloxone 160 micrograms was injected intravenously, with full recovery of consciousness and respiration in 10 minutes.

This report is the first of respiratory depression after intrathecal sufentanil in a non-obstetric patient. Previous obstetric cases had occurred earlier and with larger doses of sufentanil. The site of action of sufentanil in this case is likely to have been supraspinal, by either direct cephalad migration in the CSF or through a systemic effect after vascular absorption.

Respiratory arrest has been reported in labor (22).

- A 20-year-old parturient received sufentanil 10 micrograms and bupivacaine 2.5 mg intrathecally as part of combined spinal-epidural analgesia and developed pruritus 15 minutes after the injection, followed by a sleepy feeling at 20 minutes. After 25 minutes she became unresponsive and apneic; her systolic blood pressure was 130 mmHg and her heart rate 60. The fetal heart rate was 86. She was ventilated manually with 100% oxygen and naloxone 0.4 mg was given with prompt recovery of consciousness and respiratory effort. Drowsiness persisted, and a naloxone infusion was initiated after top-up doses of naloxone had failed to relieve it. Subsequent analgesia was with bupivacaine alone. A vacuum-assisted vaginal delivery was performed after 3 hours. The infant's Apgar score was 8 at 1 minute and 9 at 5 minutes. The mother and baby were subsequently well.

This case highlights the low doses at which arrest may occur.

Violent coughing in young children and adolescents exposed to small doses of sufentanil (1 microgram/kg or less) has been reported (23). Specific cases were not alluded to and the literature remains divided on the significance and mechanism of this age-related effect.

Nervous system

An unexpected transient neurological deficit has been described in neurosurgical patients (SEDA-16, 85).

There have been three reports of neurological changes after the intrathecal administration of sufentanil plus bupivacaine (24,25).

- A 40-year-old pregnant woman developed acute confusion, aphasia, increased salivation, and difficulty in swallowing 15 minutes after intrathecal administration of sufentanil 10 micrograms with bupivacaine 2.5 mg (25). There was spontaneous resolution 1 hour later with no need for pharmacological intervention.
- An 18-year-old nulliparous woman with an uncomplicated pregnancy developed difficulty in swallowing, respiratory abnormalities, and excessive tiredness 13 minutes after receiving sufentanil 5 micrograms with bupivacaine 1.25 mg as a spinal analgesic and disappearing over 20 minutes (24).
- A 36-year-old nulliparous woman complained of dyspnea and sensory block extending to the face 15 minutes after an intrathecal injection of sufentanil 5 micrograms with bupivacaine 1.25 mg (24).

In neither of the last two cases was there motor blockade or neonatal sequelae. Such adverse effects can be caused by sufentanil, bupivacaine, or both. Regardless of which drug caused these events, the intrathecal administration of a hypobaric solution to a patient in the sitting position might have contributed, since rostral spread of intrathecal drugs is accelerated in this setting. The use of smaller doses of sufentanil (2.5 or 5 micrograms) will also prevent such adverse effects.

Musculoskeletal

There have been isolated reports of chest wall rigidity after sufentanil (26).

Second-Generation Effects

Pregnancy

The effects of intrathecal and epidural sufentanil as an analgesic during labor have been described in 50 nulliparous patients in a randomized double-blind study, in which they received sufentanil 1–10 micrograms in preservative-free saline (27). The ED_{50} was 1.8 micrograms, based on those who requested further analgesia after 30 minutes. The incidence of adverse effects was similar in all groups (that is was not dose-related in this dosage range) and included pruritus of a similar intensity in all groups. There was no respiratory depression, but blood pressure and oxygen saturation fell. Other adverse effects included changes in temperature sensitivity at 30 minutes in 19 of the 50 subjects. One woman who received 5 micrograms of sufentanil had a fall in oxygen saturation to 90–92% with a respiratory rate of 16 breaths/minute 10–15 minutes after injection, but recovered spontaneously at 20 minutes. Fetal monitoring showed no significant bradycardia and there were no significant differences in 5-minute Apgar scores. It was suggested that hypotension was due to the effect of intrathecal opioid rather than to an effect on the autonomic nervous system and that the temperature sensitivity changes were due to a concentration-dependent local anesthetic effect of opioids. A drop in oxygen saturation in one subject indicated the need for observation for respiratory changes when sufentanil is given intrathecally.

Combined spinal epidural analgesia has been associated with reports of increased operative deliveries, possibly due to reduced perineal sensation and motor weakness. In a comparison of combined spinal epidural

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analgesia (intrathecal sufentanil 10 micrograms followed by epidural bupivacaine and fentanyl at their next request for analgesia) with intravenous pethidine analgesia (50 mg intravenously on demand up to a maximum of 200 mg in 4 hours) in 1223 randomly assigned healthy parturients there was no significant difference in the rates of cesarean delivery for dystocia (28). Maternal hypotension and pruritus requiring treatment occurred in 14% and 17% respectively of patients who received combined spinal epidural analgesia. Fetal heart rate deceleration occurred in 21% of patients who received pethidine compared with 18% of patients who received combined spinal epidural analgesia, and in each group most cases resolved spontaneously. However, profound fetal bradycardia (fetal heart rate of less than 60/minute, lasting 60 seconds or more), necessitating emergency cesarean section, occurred within 1 hour of administration of sufentanil in 8 of 400 mothers, while no such events occurred with pethidine. None of the cases responded to conservative management and none was associated with maternal hypotension. Immediate postnatal neonatal outcomes were similar between the two groups, as judged by Apgar scores and umbilical artery blood gases. These findings are significant, in that an increase in cesarean deliveries due to fetal bradycardia has not previously been reported, but findings in this study must be regarded with an element of caution, as fetal monitoring was more extensive in those given combined spinal epidural analgesia. The authors suggested that fetal bradycardia might have been due to uterine hyperstimulation, associated with intrathecal opioids (although they did not consistently monitor for this), and that fetal bradycardia resulted from reduced placental perfusion secondary to uterine tetany. Alternatively, since sufentanil is highly lipid soluble, it can be detectable in plasma within 39 minutes of intrathecal administration of 15 micrograms. Once in the plasma, transplacental transfer can occur and the drug can have a direct vagotonic effect on the fetus. However, they believed that the most probable explanation for the bradycardia was a direct consequence of hypoperfusion of the placenta secondary to maternal hypotension, although they pointed out that none of their cases was associated with this hemodynamic change in the mother.

In a double-blind, randomized study the analgesic efficacy of sufentanil 0.25 micrograms/ml with 0.125% bupivacaine was compared with fentanyl 2 micrograms/ml with 0.125% bupivacaine in 226 patients in labor with a patient-controlled epidural analgesic device (29). Overall analgesia was good, with no observed difference between the two groups. There was a significant difference in the occurrence of mild pruritus, with 10 cases in the fentanyl group ($n = 105$) and only two in the sufentanil group ($n = 101$). There were no gastrointestinal adverse effects. Sufentanil was deemed preferable owing to a lower incidence of adverse effects for equal analgesic potency.

An epidural mixture of sufentanil with ropivacaine has been used in a double-blind, randomized study in 100 women in the first stage of labor (30). They were randomized to receive 0.2% ropivacaine 12 mg either alone or with sufentanil 5, 10, or 15 micrograms. With combined sufentanil plus ropivacaine the duration of analgesia was about 40 minutes longer than with ropivacaine alone. There were no differences in analgesic efficacy or the incidence of opioid-related adverse effects in the three sufentanil groups. Sufentanil 5 micrograms plus ropivacaine 0.2% was therefore recommended.

Fetotoxicity

When epidural sufentanil is used for labor and delivery, the neonates can have subtle neurological signs of drug depression, including mild hypotonia, poor primary reflexes, and poor habituation to repeated stimuli at 1 and 4 hours of life (SEDA-16, 86).

The absence of motor block associated with combined spinal epidural analgesia using sufentanil has also been reported in an investigation in which intrathecal sufentanil 10 micrograms was compared with epidural lidocaine, adrenaline, and sufentanil 40 micrograms in early labor (31). Adverse effects were not significantly different between the groups, except for more frequent and severe pruritus in the intrathecal group. Although three subjects in each group had transient changes in fetal heart rate within 30 minutes of medication, no intervention was necessary.

Drug Administration

Drug dosage regimens

In a dose-finding, prospective, double-blind study, 60 men scheduled for unilateral extracorporeal shock-wave lithotripsy were randomized to receive 12.5, 15, 17.5, or 20 micrograms of intrathecal sufentanil (32). The results suggested that 15 micrograms of sufentanil may be the optimal intrathecal dose, since 20 micrograms produced significantly more pruritus than the lower doses and those who were given 12.5 micrograms needed significantly more supplementary analgesia.

Drug administration route

Serious consequences (respiratory arrest and hypotension) related to the use of intrathecal sufentanil have been described in parturients (SEDA-22, 101).

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Sulfamazone

See also Non-steroidal anti-inflammatory drugs

General Information

Sulfamazone is a pyrazolone derivative. It causes benign intracranial hypertension in children (SEDA-5, 100) (1).

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Sulfinpyrazone

General Information

Sulfinpyrazone, a pyrazolone derivative, is used both as a uricosuric agent and as an anti-platelet drug. It has similar adverse effects to those of phenylbutazone when taken for long term (SEDA-6, 104). In a large number of patients who took the drug for secondary prevention of myocardial infarction (an indication that was not subsequently accepted), the incidence of adverse effects was not high (1).

Organs and Systems

Respiratory

Sulfinpyrazone can precipitate bronchoconstriction in some aspirin-sensitive patients (2). There is no cross-sensitivity with dipyrone.

Hematologic

Prolonged treatment with sulfinpyrazone produces a high incidence of thrombocytopenia and granulocytopenia. After withdrawal, these effects are completely reversible (SED-9, 157) (3). Sulfinpyrazone also inhibits platelet aggregation (4).

Sulfinpyrazone has been implicated in the development of myelomonocytic leukemia and multiple myeloma when given with colchicine (3).

Urinary tract

Impairment of renal function and even acute renal insufficiency can follow sulfinpyrazone treatment, by various mechanisms: immunoallergic-induced acute interstitial nephritis, inhibition of renal prostaglandins, and precipitation of uric acid stones. These changes are probably reversible, since there have been cases in which renal impairment spontaneously normalized on withdrawal (5).

Susceptibility Factors

The antinatriuretic effects of sulfinpyrazone could be dangerous in patients with impaired cardiac function (6).

Drug–Drug Interactions

Aspirin

In low dosages (up to 2 g/day), aspirin reduces urate excretion and blocks the effects of sulfinpyrazone. In higher dosages (over 5 g/day), salicylates increase urate excretion.

Beta-blockers

Sulfinpyrazone interferes with the antihypertensive action of beta-blockers (7).

Phenylbutazone

Sulfinpyrazone has a biphasic interaction with phenylbutazone (enhancement followed by antagonism).

Warfarin

By reducing the metabolic clearance of warfarin, sulfinpyrazone enhances its hypoprothrombinemic effect, with life-threatening consequences (8).

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Sulfites and bisulfites

See also Disinfectants and antiseptics

General Information

Sulfites and bisulfites have been used extensively as preservatives in the food industry and also in drugs and bronchodilator inhalant solutions (1,2) as preservatives. Sodium metabisulfite is used commonly as an antioxidant in foods and drugs. As an additive in various pharmaceutical products, metabisulfite can cause unpleasant adverse reactions.

Organs and Systems

Respiratory

Status asthmaticus and acute bronchospasm have been linked to the use of metabisulfites (3).

Hematologic

Preservatives in subconjunctival gentamicin were identified as the cause of conjunctival chemosis and capillary closure (4). Patients undergoing cataract surgery were

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divided into three groups: one was given a subconjunctival injection of a preservative-free solution of gentamicin at the end of the cataract procedure, another received a subconjunctival injection of gentamicin containing sodium metabisulfite and disodium edetate as preservatives, and the third was the control group not given a subconjunctival injection. There was a significant difference in the severity of conjunctival chemosis between patients who received gentamicin with and without preservatives (4).

Immunologic

The major symptoms of an adverse reaction to a sulfite are flushing, acute bronchospasm, and hypotension (SED-11, 492) (SEDA-10, 232) (SEDA-11, 221) (5). The incidence of sulfite sensitivity in an asthmatic population is estimated at about 10%. Sulfites have therefore been withdrawn from the composition of several medicines intended for asthmatic patients.

Metabisulfite-induced anaphylaxis through an IgE-mediated mechanism has been described in a patient who developed urticaria, angioedema, and nasal congestion following provocative challenge with sodium metabisulfite (6).

The presence of sodium metabisulfite as an antioxidant in commercial lidocaine with adrenaline significantly increased discomfort during injection (7).

Anaphylactic shock occurring during epidural anesthesia for cesarean section has been attributed to sodium metabisulfite (8).

Reports of contact allergy to topical medicaments containing sodium metabisulfite are rare (9). In two cases, a topical corticosteroid formulation that contained sodium metabisulfite (Trimovate cream) caused contact allergy; patch tests were positive with both sodium metabisulfite and Trimovate cream (10).

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Sulfonamides

General Information

The term "sulfonamide" is generic for derivatives of para-aminobenzenesulfonamide (sulfanilamide), which is similar in structure to para-aminobenzoic acid (PABA), a co-factor required by bacteria for folic acid synthesis. The sulfonamides act by competitive inhibition of the incorporation of PABA into tetrahydropteroic acid. Sulfonamides have a higher affinity for the microbial enzyme tetrahydropteroic acid synthetase than the natural substrate PABA. Sulfonamides have a wide range of antimicrobial activity against both Gram-positive and Gram-negative organisms (1). In therapeutic dosages they have only a bacteriostatic effect, and as single agents therefore have a limited role in drug therapy (1). Sulfonamides have been combined with trimethoprim or trimethoprim analogues, since such combinations result in a bactericidal effect (2). Adverse reactions during the administration of sulfamethoxazole + trimethoprim (co-trimoxazole, BAN) can be due to either compound. Although sulfonamides are thought to cause adverse reactions more often than trimethoprim, the culprit in the individual patient can only be determined by re-exposure to the individual agents.

Based on their pharmacological properties and clinical uses, sulfonamides can be classified into four groups (1):

1. short- or medium-acting sulfonamides;
2. long-acting sulfonamides;
3. topical sulfonamides;
4. sulfonamide derivatives used for inflammatory bowel disease.

Short- or medium-acting sulfonamides include the earliest varieties of azosulfonamides (Prontosil, Neoprontosil), sulfapyridine (Dagenan), sulfathiazole (Cibazol), sulfanilamide, and sulfadiazine. With the exception of sulfadiazine, these compounds are no longer used. Sulfadiazine and more recent compounds, including sulfafurazole (sulfisoxazole), sulfamethoxazole, sulfametrole, sulfacitine, and sulfamethizole, are rapidly absorbed and rapidly eliminated. Compared with the older generation they are more soluble, less toxic, and probably less allergenic. Sulfamethoxazole is a medium-acting sulfonamide that is often combined with trimethoprim (as co-trimoxazole). Long-acting sulfonamides include sulfametoxydiazine, sulfadimethoxine, and other compounds, of which many are no longer available, as they were associated with severe hypersensitivity reactions. Although these compounds have the advantage of long administration intervals, their long half-lives (over 100 hours) can be deleterious

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in case of adverse reactions. A long-acting drug that is still widely used is sulfadoxine (*N*-(5,6-dimethoxy-4-pyrimidinyl)-sulfanilamide). It is primarily used in combination with pyrimethamine (Fansidar) for the treatment and prophylaxis of malaria.

The topical use of sulfonamides has been discouraged, because of the high risk of sensitization. Nevertheless, sulfacetamide and sulfadicramide are still used topically for eye infections. Topical silver sulfadiazine (see monograph on Silver) is widely and successfully used in treating burns and leg ulcers (3,4). Since sulfonamides are easily absorbed through skin lesions, the same adverse reactions can occur as after systemic use.

A sulfonamide derivative with special use is sulfasalazine (salicylazosulfapyridine), which has been widely used to treat ulcerative colitis and regional ileitis (Crohn's disease). It is a compound of sulfapyridine and 5-aminosalicylate, linked by a diazo bond. Sulfasalazine is broken down in the large bowel to sulfapyridine, which is absorbed systemically, and 5-aminosalicylate, which reaches high concentrations in the feces (5). Sulfasalazine is not used for the antibacterial properties of the sulfapyridine, but for the local anti-inflammatory effect of 5-aminosalicylate in the gut. Because most of the adverse reactions are thought to be due to the absorbed sulfapyridine, the combination has largely been replaced in clinical practice by newer drugs that contain only 5-aminosalicylic acid (mesalazine), such as mesalazine itself and diazosalicylate (olsalazine) (5). The aminosalicylates are covered in a separate monograph.

Observational studies

In an open trial in 25 patients treated with sulfamethoxypyridazine (1 g/day) for mucous membrane pemphigoid unresponsive to topical steroid treatment, 12% of patients were withdrawn, 4% because of allergic reactions, the others because of significant hemolysis (6).

In children with acute uncomplicated *Plasmodium falciparum* malaria, pyrimethamine + sulfadoxine (25 mg + 500 mg) and artesunate (4 mg/kg) were well tolerated, and no adverse reactions attributable to treatment were recorded (7).

Comparative studies

In a randomized, open, multicenter study in 46 patients with sight-threatening ocular toxoplasmosis, those who took pyrimethamine + sulfadiazine had significantly more adverse events, especially malaise, than those who took pyrimethamine + azithromycin (8).

General adverse effects

The frequency and severity of the adverse effects of sulfonamides correspond to those seen with other antibacterial agents (2–5%). Dose-related effects, which tend to be more troublesome than serious, include gastrointestinal symptoms, headache, and drowsiness. Crystalluria can occur, but urinary obstruction is rare. Hematological adverse effects due to folic acid antagonism occur primarily in combination with trimethoprim. Hemolytic anemia occurs in patients with enzyme deficiencies and abnormal hemoglobins. Hypersensitivity is thought to be the mechanism of many adverse effects of the sulfonamides. They can be life-threatening, and immediate withdrawal is recommended. The most important reactions include anaphylactic shock, a serum sickness-like syndrome, systemic vasculitis, severe skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis), pneumonitis, hepatitis, and pancytopenia. Sulfonamides should not be used in the third trimester of pregnancy. In premature infants, they displace bilirubin from plasma albumin and can cause kernicterus. Carcinogenicity has not been reported with the use of sulfonamides.

Sulfanilamide and the history of adverse drug reactions

The first major drug catastrophe in the 20th century history of the public control of drugs occurred in 1937 in the USA. A pharmacist introduced Elixir Sulfanilamide, which consisted of sulfanilamide dissolved in diethylene glycol. It had been tested for flavor, appearance, and fragrance, but not for safety. After taking the drug, over 100 patients died in severe pain; many were children, who were given Elixir Sulfanilamide for sore throats and coughs. Public outrage created support for proposed legislation to reinforce the public control of drugs that was pending in the US Congress (9). This led to the US 1938 Food, Drug, and Cosmetic Act, which is still the country's legal foundation for the public control of drugs and devices intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or animals. It has been a model for similar legislation in many other countries.

The 1938 Food, Drug, and Cosmetic Act prohibited traffic in new drugs, unless they were safe for use under the conditions of use prescribed on their labels. The Act also explicitly required the labeling of drug products with adequate directions for use.

The burden of proof of harm of new drugs was laid on the Federal Food and Drug Agency (FDA). Companies that wanted to manufacture and sell new drugs in interstate commerce had to investigate their safety and report to the FDA. Unless the FDA, within a specified period of time, found that the safety of a drug had not been established, the company could proceed with its marketing. The FDA was also authorized to remove from the market any drug it could prove to be unsafe (10).

The US Supreme Court also established in 1941, in a legal case over drug adulteration, that responsible individuals in a company can be held personally accountable for the quality of the products manufactured by the company, and that distributors of pharmaceuticals are responsible for the quality of their products, even if they are manufactured elsewhere (11).

After World War II, the pharmaceuticals market changed radically, as many companies started industrial production of drugs that had previously been manufactured in pharmacies. Announcements of new industrially produced drugs were hailed as part of technological advancement, as significant a sign of progress as the launching of satellites and putting a man on the moon. However, public safeguards against the risks

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of drugs remained unchanged in most countries. Thus, control of the effects of drugs largely lay in the hands of the manufacturers, even though the responsibility for taking precautions rested with pharmacists and doctors.

Organs and Systems

Cardiovascular

Of 98 patients with drug-induced long QT interval, one taking sulfamethoxazole carried a single-nucleotide polymorphism (SNP; found in about 1.6% of the general population) in KCNE2, which encodes MinK-related peptide 1 (MiRP1), a subunit of the cardiac potassium channel I_{Kr} (12). Channels with the SNP were normal at baseline but were inhibited by sulfamethoxazole at therapeutic concentrations, which did not affect wild-type channels.

Cardiovascular reactions can be due to sulfonamide myocarditis or systemic vascular collapse, owing to severe adverse events such as widespread skin disease. Sulfonamide myocarditis has been described in relation to earlier sulfonamides and occurs in combination with other hypersensitivity reactions (13).

Respiratory

Respiratory reactions to sulfonamides include migratory pulmonary infiltrates, chronic pneumonia, asthma, and pulmonary angiitis. These reactions are thought to be mainly due to hypersensitivity, although the precise mechanisms are not well understood (14–16). The link to the drug has been proven in most cases by recurrence after re-exposure to the same sulfonamide or to co-trimoxazole.

Pulmonary reactions have been described with most sulfonamides. Pyrimethamine + sulfadoxine, used in malaria prophylaxis and treatment, also rarely causes pulmonary reactions (17–19). The sulfapyridine moiety of sulfasalazine, used in inflammatory bowel disease, can produce adverse pulmonary reactions (20).

The time between the last drug exposure and the first clinical symptoms varies from hours to a few days, and the lung pathology disappears in most patients within a few days after withdrawal. Most commonly, pulmonary involvement presents with fever, dyspnea, cough, and shortness of breath. Clinical examination reveals râles in the lungs, and there may be pulmonary infiltrates in the chest X-ray. Pulmonary function tests may show bronchial obstruction (18–21), and arterial blood gases show hypoxemia (19,20). Whereas bronchial obstruction is probably an immediate reaction (type I), pulmonary infiltrates may correspond to a type III reaction, similar to the mechanism responsible for extrinsic allergic alveolitis (20,21). Eosinophilia is present in 8–58% of cases (14,16,18,19,21,22). Histologically, the lung tissue is infiltrated by inflammatory cells, and in most cases the alveoli contain numerous macrophages and eosinophils in a protein-rich edema fluid.

Based on the predominant symptoms and their duration, four categories of sulfonamide-related pulmonary hypersensitivity reactions can be distinguished (23–25):

1. transient or migratory pulmonary infiltrations associated with eosinophilia (Loeffler's syndrome) (22,26–28)
2. chronic eosinophilic pneumonia (23,27)
3. asthma with pulmonary eosinophilia (14–16,21)
4. allergic angiitis with pulmonary involvement (25).

In the first three of these, the adverse reaction is limited to the lung, whereas in the fourth the lung involvement is part of a systemic reaction. Syndromes such as allergic granulomatosis and angiitis (Churg–Strauss syndrome) or Wegener's granulomatosis are not associated with the use of sulfonamides (25).

Nervous system

Neurological disturbances that have been attributed to sulfonamides include polyneuritis, neuritis, and optic neuritis (29,30). Tremor and ataxia have been described with co-trimoxazole (31,32). Aseptic meningitis can be separately caused by sulfonamides and trimethoprim. The occurrence of meningitis has been verified in most patients, with recurrence on re-exposure (33–42).

Sensory systems

Eyes

Drug induced uveitis is rare. Antibiotics that have been implicated include rifabutin and sulfonamides. Furthermore, nearly all antibiotics injected intracamerally have been reported to produce uveitis (43). Topical administration of a corticosteroid and a cycloplegic (such as atropine) is suitable as initial treatment. Withdrawal of causative drugs is not always necessary (44).

Transient myopia can be caused by topical or systematic sulfonamides (45–47).

Corneal ring formation has been described simultaneously with an erythematous skin rash in a patient known to have skin hypersensitivity (48).

Taste

In unmedicated young and elderly volunteers and HIV-infected patients, sulfamethoxazole applied to the tongue was described as sour by young subjects but bitter by elderly subjects (49).

Psychological, psychiatric

Headache, drowsiness, lowered mental acuity, and other psychiatric effects can be caused by sulfonamides (50). However, these adverse effects are rare, and the causative role of the drug is usually not clearly established.

Metabolism

Several sulfonamides, including co-trimoxazole in high doses, can produce hyperchloremic metabolic acidosis. This has even been seen in patients with extensive burns receiving topical mafenide (51). Mafenide (Sulfamylon) and its metabolite *para*-sulfamoylbenzoic acid inhibit carbonic acid anhydrase, resulting in reduced reabsorption of bicarbonate and thus bicarbonate wasting.

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Electrolyte balance

Although co-trimoxazole in therapeutic doses can cause hyperkalemia (52), it is thought to be caused by the potassium-sparing effects of trimethoprim (53).

Hematologic

Sulfonamides have adverse effects on all bone marrow–derived cell lines. The resulting disturbances include hemolytic anemia, folate deficiency anemia, neutropenia, thrombocytopenia, and pancytopenia. While adverse effects on erythrocytes are rare, the rates of leukopenia, neutropenia, and thrombocytopenia are highly variable. In a hospital drug monitoring program, leukopenia or neutropenia occurred in 0.4% of 1809 patients treated with co-trimoxazole (54), and thrombocytopenia of mild-to-moderate degree in 0.1% (54,55), similar to figures recorded in other studies (56,57). Pancytopenia is an extremely rare form of adverse reaction to sulfonamides (58).

There were similar findings in children (59). It is generally believed that trimethoprim is primarily responsible for neutropenia due to co-trimoxazole.

Severe neutropenia often occurs in HIV-infected patients taking co-trimoxazole (60). It seems to be due to either folic acid deficiency or immunological mechanisms.

Erythrocytes

Sulfonamides rarely have adverse effects on erythrocytes. However, there are various mechanisms by which sulfonamide-induced hemolytic anemia can occur (61):

- abnormally high blood concentrations, due to large doses or reduced excretion of the drug in patients with renal disease (62)
- acquired hypersusceptibility, as reflected by the development of a positive Coombs' test (63,64)
- genetically determined abnormalities of erythrocyte metabolism, for example deficiency of glucose-6-phosphate dehydrogenase or of diaphorase (65,66)
- the presence of an abnormal, so-called "unstable", hemoglobin in the erythrocyte, for example hemoglobin Zürich (67,68), hemoglobin Torino (69), hemoglobin Hasharon (70), and hemoglobins H and M (66).

Simple and readily available in vitro methods have been used to demonstrate the pathogenetic mechanisms, including Coombs' test, Harris's test (71), a quantitative assay or screening for glucose-6-phosphate dehydrogenase activity after recovery (72,73), a test for Heinz bodies, the buffered isopropanol technique (74) to detect abnormal hemoglobins, and hemoglobin electrophoresis (61,66). The direct antiglobulin (Coombs') test can be negative in spite of an immune mechanism. If such a mechanism is suspected and the direct Coombs' test is negative, the indirect Coombs' test on the patient's serum with the addition of the suspected sensitizing agent can be of diagnostic value (75). Heinz bodies in the erythrocytes can be important for early differentiation of a sulfonamide-induced reaction, which could further progress to hemolytic anemia (76). This result can also be of help in distinguishing this from other kinds of anemia.

Sulfonamides are not directly associated with folate deficiency and megaloblastic anemias. Sulfasalazine can affect the absorption of folates, but inflammatory bowel disease can also be responsible for reduced folate absorption. Only in combination with trimethoprim are sulfonamides thought to deplete folate stores in patients with pre-existing deficiency of folate or vitamin B_{12} (77).

Leukocytes

Since the days when chloramphenicol was more commonly used, it has been recognized that many antimicrobial drug are associated with severe blood dyscrasias, such as aplastic anemia, neutropenia, agranulocytosis, thrombocytopenia, and hemolytic anemia. Information on this association has come predominantly from case series and hospital surveys (78–80). Some evidence can be extracted from population-based studies that have focused on aplastic anemia and agranulocytosis and their association with many drugs, including antimicrobial drugs (81,82). The incidence rates of blood dyscrasias in the general population have been estimated in a cohort study with a nested case-control analysis, using data from a General Practice Research Database in Spain (83). The study population consisted of 822 048 patients aged 5–69 years who received at least one prescription (in all 1 507 307 prescriptions) for an antimicrobial drug during January 1994 to September 1998. The main outcome measure was a diagnosis of neutropenia, agranulocytosis, hemolytic anemia, thrombocytopenia, pancytopenia, or aplastic anemia. The incidence was 3.3 per 100 000 person-years in the general population. Users of antimicrobial drugs had a relative risk (RR), adjusted for age and sex, of 4.4, and patients who took more than one class of antimicrobial drug had a relative risk of 29. Among individual antimicrobial drugs, the greatest risk was with cephalosporins (RR = 14), followed by the sulfonamides (RR = 7.6) and penicillins (RR = 3.1).

Agranulocytosis was not infrequent in the early sulfonamide era. The first cases were observed in association with sulfanilamide (84,85), Prontosil (84), sulfapyridine (85,86), sulfathiazole (87), sulfadiazine (87), and sulfasalazine (88). Even with topical silver sulfadiazine, agranulocytosis as a consequence of systemic absorption has been reported (89).

Special observations in patients with agranulocytosis favor an immunological/allergic mechanism rather than a toxic one. Several points justify this view:

1. the sulfonamide is well tolerated by most patients during the initial phase of treatment
2. sulfonamide concentrations in the serum, when determined, are not particularly high in patients with hematological complications
3. in some patients, skin rash, fever, and arthritis start concomitantly with or even before the appearance of leukopenia or agranulocytosis
4. re-exposure to a single dose can be followed by a second episode of severe agranulocytosis
5. an agglutinin for leukocytes has been identified in patients' serum shortly after withdrawal of the drug (86)
6. using in vitro techniques, positive reactions to the drug with the lymphocyte transformation test or inhibition of colony growth in bone marrow have been found (90,91); however, the results of lymphocyte transformation tests must be interpreted with caution—sometimes they are positive in patients who have been exposed to the drug without any evidence of a hypersensitivity reaction.

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Platelets

Reports of drug-induced thrombocytopenia have been systematically reviewed (78). Among the 98 different drugs described in 561 articles the following antibiotics were found with level I (definite) evidence: co-trimoxazole, rifampicin, vancomycin, sulfisoxazole, cefalotin, piperacillin, methicillin, novobiocin. Drugs with level II (probable) evidence were oxytetracycline and ampicillin.

In another retrospective analysis of drug-induced thrombocytopenia reported to the Danish Committee on Adverse Drug Reactions, 192 cases caused by the most frequently reported drugs were included and analysed (92). There were pronounced drug-specific differences in the clinical appearance. Early thrombocytopenia was characteristic of cases caused by sulfonamides and co-trimoxazole. These drugs also often caused hemorrhage. Accompanying leukopenia was observed in some cases associated with co-trimoxazole. There were no patient-specific factors responsible for the heterogeneity of the clinical appearance, and factors related to the physician seemed to be of little significance.

Acute thrombocytopenia is rarely associated with the newer sulfonamides (4,93,94). The structurally related sulfonylureas and thiazide diuretics can also cause allergic thrombocytopenia (95). Although some in vitro tests have been reported to predict the occurrence of thrombocytopenia, none of these has been used routinely (96,97). Furthermore, a negative test result with a drug does not definitely exclude it as the responsible allergen.

Mouth

Salivary gland enlargement on repeated exposure to sulfafurazole (sulfisoxazole) has been described (98).

Gastrointestinal

Nausea, vomiting, and anorexia occur in a few patients taking sulfonamides (1). They are usually related to dosage, the disposition of the individual patient, and how the question concerning adverse effects is asked.

Liver

Increased activities of alanine transaminase and aspartate transaminase to over five times the upper limit of the reference range were reported in a randomized trial of sulfadiazine in toxoplasmic encephalitis (99).

Co-trimoxazole-induced hepatitis has been repeatedly reported. However, trimethoprim alone can also cause acute liver injury (100). Three forms of liver injury may be related to sulfonamides:

1. hepatitis of the hepatocellular type (101–105)
2. hepatitis of the mixed hepatocellular type accompanied by cholestatic features (106)
3. chronic active hepatitis, possibly leading to cirrhosis (107).

The number of cases of sulfonamide hepatitis published annually fell markedly after 1947, with the introduction of the newer short-acting derivatives (106).

Children can also be affected by drug-induced liver disease (108).

Hitherto, the connection with a sulfonamide has always been investigated by administering a test dose. Immunological in vitro methods that show sensitization to the drug, for example the lymphocyte transformation test, are of limited value. In some patients the hepatic injury develops in connection with a general reaction, such as serum sickness-like syndrome, generalized vasculitis, or rash (109,110). In patients with hypersensitivity, re-exposure can result in generalized malaise, nausea, back pain, and chills within one to several hours (103,107). However, symptoms can be delayed for as long as several days (106). Daily monitoring of liver function on re-exposure seems to be important, since subjective signs can be absent despite rising activities of serum transaminases and alkaline phosphatase (102).

Even in patients with chronic active hepatitis, the histopathology of the liver damage was indistinguishable from non-drug-induced pathology. The degree of piecemeal necrosis usually varies from one area to another. Antinuclear factor and lupus erythematosus factor were positive in some cases (107). Early recognition of drug-induced liver disease is of great importance, since liver injury can be completely reversible after withdrawal.

Pancreas

Pancreatitis has been attributed to sulfonamides. Sulfamethizole (34) and sulfasalazine (111) have been implicated by re-exposure. The 5-aminosalicylic acid moiety of sulfasalazine may also be responsible (112,113).

Urinary tract

Renal complications that occur in relation to sulfonamide administration include crystalluria, tubular necrosis, interstitial nephritis, and glomerular lesions as part of a vasculitis syndrome.

Sulfonamides and their metabolites are excreted in large amounts in the urine. They are relatively insoluble in the acid environment and tend to precipitate in the collecting tubules, calyces, and pelvis of the kidney, and possibly in the ureters. The course is typically benign but adequate hydration and alkalinization may be required (114). Nephrocalcinosis can cause hematuria, renal colic, or acute renal insufficiency (115). Urinary obstruction with anuria/oliguria was seen primarily with the earlier, less soluble sulfonamides. With the newer and more soluble sulfonamides crystal formation is rare, as is acute renal insufficiency due to other mechanisms. During recent years renal complications have been seen more often in patients with AIDS, because of the use of large doses of sulfonamides combined with trimethoprim against infection with *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) or *Toxoplasma* encephalitis. Reduced fluid intake and low urinary pH favor crystal formation, and so both adequate fluid intake (about 2 l/day for adults) and urine alkalinization are encouraged when larger doses of sulfonamides are used (60,115–120). For the diagnosis of sulfonamide crystalluria, the Lignin test is recommended. At room temperature crystals can even be found in the urine of patients taking sulfamethoxazole, which is readily soluble (121).

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Other renal complications reported with sulfonamides are:

- acute tubular necrosis or tubulointerstitial nephritis (117,122);
- interstitial nephritis (123), in some cases combined with granulomatous lesions (124,125);
- acute vasculitis (126);
- acute renal insufficiency in association with a serum sickness-like syndrome, generalized vasculitis, or rashes in combination with hepatic damage (109).

Acute anuria or oliguria is often the first symptom, not only in patients with tubular necrosis or tubulointerstitial nephritis, but also in those with allergic vasculitis. Non-oliguric renal insufficiency can also occur. It is not yet clear whether tubular necrosis in association with sulfonamides is a toxic, collateral, or hypersusceptibility reaction. The unstable hydroxylamine metabolites of some sulfonamides can act as direct renal toxins.

In a French analysis of 22 510 urinary calculi performed by infrared spectroscopy, drug-induced urolithiasis was divided into two categories: first, stones with drugs physically embedded ($n = 238$; 1.0%), notably indinavir monohydrate ($n = 126$; 53%), followed by triamterene ($n = 43$; 18%), sulfonamides ($n = 29$; 12%), and amorphous silica ($n = 24$; 10%); secondly, metabolic nephrolithiasis induced by drugs ($n = 140$; 0.6%), involving mainly calcium/vitamin D supplementation ($n = 56$; 40%) and carbonic anhydrase inhibitors ($n = 33$; 24%) (127). Drug-induced stones are responsible for about 1.6% of all calculi in France. Physical analysis and a thorough drug history are important elements in the diagnosis.

Skin

Rashes are common during sulfonamide administration, and the rate increases with duration of therapy. Maculopapular reactions are most common and occur in about 1–3% of patients (128–132). In a survey of 5923 pediatric records, 3.46% of prescriptions for sulfonamides were followed by the development of a rash, although none was severe enough to require hospitalization (133).

Urticaria, fixed drug eruptions (131,134–137), erythema nodosum (138), photosensitivity reactions (139), and generalized skin reactions involving light-exposed areas (139–141) are less common. Topical silver sulfadiazine cause local reactions, consisting of rash, pruritus, or a burning sensation in 2.5% of patients (4,51).

- Fixed drug eruption has been described in a patient treated with the non-thiazide sulfonamide diuretic indapamide; an oral challenge test showed cross-reactivity to sulfamethoxazole and sulfadiazine (142).

Generalized cutaneous depigmentation after sulfamide therapy occurred in a 41-year-old man (143). Melanocytes were not seen on electron microscopy, but there were clear cells with the characteristics of Langerhans cells along the basal layer.

Other skin eruptions seen with sulfonamides include erythema multiforme, vesicular and bullous rashes, and exfoliative dermatitis (144). In erythema multiforme, linear depositions of IgA at the dermoepidermal junction have been suggested to play a pathogenic role (132).

- Linear IgA dermatosis with erythema multiforme-like clinical features has been reported in a 19-year-old man several days after completion of a 5-day-course treatment with sulfadimethoxine (500 mg bd) for a flu-like syndrome (134). Treatment with methylprednisolone (150 mg) with gradual dosage reduction was started. Slow improvement was followed by a flare-up after reduction to 80 mg/day. Therapy was changed to dapsone 100 mg/day, and there was a dramatic improvement.

The most severe skin reactions associated with sulfonamides are the severe forms of erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis (144–152). In a study from Cameroon, eight of ten patients with toxic epidermal necrolysis had taken sulfonamides (five sulfadoxine, three sulfamethoxazole); two patients died after taking sulfadoxine (153).

Mortality in drug-induced toxic epidermal necrolysis has been estimated to be about 20–30% (154,155), and in Stevens–Johnson syndrome 1–10% (33,146–148,151). Some severe skin reactions start with a maculopapular rash or generalized erythema. The culprit drug is often either a long-acting formulation or a short-acting drug that has been continued over a long period. In both toxic epidermal necrolysis and Stevens–Johnson syndrome immediate withdrawal of the sulfonamide and all other non-essential drugs is required, as well as adequate supportive therapy with fluids, proteins, and electrolytes, in order to prevent renal insufficiency and respiratory distress syndrome (154,155). Occasionally, toxic epidermal necrolysis must be distinguished from staphylococcal scalded skin syndrome (Lyell's syndrome) by histology. In toxic epidermal necrolysis, there is subepidermal cleavage of the skin at the level of the basal cells, resulting in full-thickness denudation, whereas in scalded skin syndrome the split occurs in the upper epidermis near the granular layer just beneath the stratum corneum (156).

The role of sulfonamides as an etiological factor in the Stevens–Johnson syndrome is extremely difficult to evaluate, except for patients with re-exposure or in situations where the drug was given prophylactically for meningitis (146) or pneumonia (147,148,151,152). In the first epidemiological study in 1968, 100 000 individuals were given prophylactic sulfadoxine (Fanasil) and 997 (1.0%) had skin reactions (146). Of these, about 100 had severe reactions, such as erythroderma with jaundice, Stevens–Johnson syndrome, or toxic epidermal necrolysis; 11 died from these complications, that is about one in 10 000 patients treated with the probably causative drug. It is not known how many would have had similar skin reactions unrelated to the drug. However, the benefit to risk balance of meningitis prophylaxis clearly favored the use of sulfonamides (146). A second report (147) showed an incidence of three cases of Stevens–Johnson syndrome in 480 healthy, newly recruited Bantu mineworkers treated prophylactically with sulfadimethoxine. In a third epidemiological study in Mozambique in 1981, 149 000 inhabitants in one town were given a single dose of sulfadoxine as mass prophylaxis in an attempt to stem an outbreak of cholera (148); 22 patients with typical Stevens–Johnson syndrome were admitted to hospital over 18 days; three died.

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In one case toxic epidermal necrolysis caused by cotrimoxazole improved with high-dose methylprednisolone (157). However, previous studies of the use of glucocorticoids in toxic epidermal necrolysis have given contradictory results.

The combination of pyrimethamine and sulfadoxine, used for prophylaxis of chloroquine-resistant malaria (*Plasmodium falciparum*), causes severe skin reactions in one per 5000–8000 users, with fatal reactions in one per 11 000–25 000 users (158). Even at the stage of early rash or generalized erythema, this therapy should be withdrawn (129).

In an open prospective study in 95 HIV-infected patients with successfully treated *Pneumocystis jiroveci* pneumonia, pyrimethamine + sulfadoxine (25/500 mg) was given twice weekly to prevent relapse (159). There were allergic skin reactions in 16 patients, resulting in permanent withdrawal in six. Two patients developed serious adverse reactions (Stevens–Johnson syndrome), both of whom had continued to take prophylaxis despite progressive hypersensitivity reactions.

Most of the cutaneous adverse reactions to sulfonamides are associated with increased in vitro reactivity to sulfonamide metabolites, such as unstable hydroxylamines (160,161). In some cases glutathione deficiency has been proposed as a major mechanism. This seems to be important in patients with AIDS, in whom glutathione deficiency is frequent, and in whom skin rashes are much more common than in other patients (160,162). A predominance of slow acetylator phenotype has also been observed among patients with sulfonamide hypersensitivity reactions, and an association with the phenotypes HLA-A29, B-12, and DR-7 in patients with bullous cutaneous reactions (161,163–165).

A mechanism for generalized drug-induced delayed skin reactions to sulfamethoxazole may be perforin-mediated killing of keratinocytes by drug-specific CD4+ lymphocytes (166). The requirement of interferon gamma pretreatment of keratinocytes for efficient specific killing might explain the increased frequency of drug allergies in generalized viral infections such as HIV, when interferon gamma concentrations are raised.

Immunologic

Sulfa allergy refers to a specific hypersensitivity response to a group of chemicals containing a sulfonamide moiety covalently bound to a benzene ring; drugs structurally similar to sulfonamides may cross-react, for example sulfonylureas, thiazides, and furosemide (167). Sulfa allergy is most consistent with an immune-mediated reaction with delayed onset, 7–14 days after the start of therapy, characterized by fever, rash, and eosinophilia. IgG antibodies may be present and directed against proteins in the endoplasmic reticulum (about 80% of patients) or against the drug covalently bound to protein (about 5% of patients). High-dose methylprednisolone sodium succinate (250 mg every 6 hours for 48 hours) may not only alleviate the signs but also markedly attenuate the antibody response, as reported in a 19-year-old man (168).

Hypersusceptibility to sulfonamides has been proposed to be the mechanism for many adverse reactions, including anaphylactic shock, serum sickness-like syndrome, systemic allergic vasculitis, drug fever (up to 1–2% in some series), lupus-like syndrome, myocarditis, pulmonary infiltrates, interstitial nephritis, aseptic meningitis, hepatotoxicity, blood dyscrasias (agranulocytosis, thrombocytopenia, eosinophilia, pancytopenia), and a wide variety of skin reactions (urticaria, erythema nodosum, erythema multiforme, erythroderma, toxic epidermal necrolysis, and photosensitivity).

Urticarial and maculopapular rashes are the most frequent adverse reactions to sulfonamides after gastrointestinal symptoms. Although hypersusceptibility is suspected to be the mechanism for these adverse effects, type I allergic reactions, which are induced by IgE antibodies, have been confirmed only rarely. It appears that with the older sulfonamides severe reactions were more frequent. In some patients who have immediate hypersensitivity reactions to sulfonamides, IgE has been found that can bind to an N4-sulfonamidoyl determinant (N4-SM) (169).

Prediction

It is desirable to predict hypersusceptibility reactions to sulfonamides. IgE-induced in vitro reactions to sulfonamides have mainly been studied in the last 15 years (169–171). A lymphocyte toxicity assay showed a positive result in about 70% of patients with a maculopapular rash, an urticarial reaction, or erythema multiforme (172). This biochemical test determines the percent of cell death due to toxic metabolites. The same in vitro reaction using the hydroxylamine metabolite of sulfamethoxazole gave significantly different results in six patients with fever and skin rash with or without hepatitis than in control patients (160). Unfortunately, in most adverse reactions it is not known whether the reaction is dose-related or allergic. Individual differences in metabolism predispose to idiosyncratic reactions, for example sulfonamides are metabolized by *N*-acetylation (mediated by a genetically determined polymorphic enzyme) and oxidation to potentially toxic metabolites (164,165). Fever and rash were observed significantly more often in slow than in fast acetylators (164,165). Systemic glutathione deficiency, with a consequently reduced capacity to scavenge such toxic metabolites, might contribute to these adverse reactions, particularly in patients with AIDS (173,174). In a child with dihydropteridine reductase deficiency, a variant of phenylketonuria, adverse drug reactions occurred to cotrimoxazole (175). Unfortunately, there are no reliable in vitro tests to predict idiosyncratic reactions in vivo (160,161,164,165,174).

Cross-reactivity

The immunogenicity of sulfonamide antimicrobials may be due to the presence of an arylamine group at the N4 position of the sulfonamide molecule. Thus, allergic cross-reactions between different sulfonamides can occur. Therefore, in cases of known hypersusceptibility to a specific sulfonamide exposure to other sulfonamides should be avoided. Cross-reactions can even occur with *para*-aminosalicylic acid and local anesthetics of the procaine type; however, the real frequency of these cross-sensitivities is not known and their significance is undetermined. It should be noted that as many as 50% of

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patients with rash have recovered in spite of continued treatment with the same drug (176), and even agranulocytosis did not occur after later re-exposures to the causative agent (162).

Susceptibility factors

In an in vitro study, plasma from HIV-positive patients was less able to detoxify nitrososulfamethoxazole than control plasma, suggesting that a disturbance in redox balance in HIV-positive patients may alter metabolic detoxification capacity, thereby predisposing to sulfamethoxazole hypersensitivity (177).

Types of reaction

Type I reactions

Anaphylactic shock occurs rarely with sulfonamides (160,169,170,178,179). Anaphylaxis to a central venous catheter (ARROWg+ard Blue Catheter) coated with chlorhexidine and sulfadiazine has been reported in a 50-year-old man (180).

Type III reactions

A serum sickness-like syndrome has been observed during sulfonamide administration. This diagnosis should be limited to patients with at least three of the symptoms of classical serum sickness, that is fever, rash, allergic arthritis, lymphadenopathy, and possibly leukopenia or neutropenia. Histologically, severe serum sickness-like syndrome seems to correspond to an allergic vasculitis (126,181). Most of the descriptions of serum sickness-like syndrome with histopathological documentation have been associated with older sulfonamides that are no longer used (182). In some severe forms of serum sickness-like syndrome, the reaction can be complicated by a number of unusual organ manifestations, including plasmacytosis, lymphocytosis, monoclonal gammopathy (183,184), interstitial myocarditis (13,33), allergic pneumonitis, nephropathy, liver damage, and nervous system disorders (126,181).

Lupus-like syndromes

Sulfonamides can cause three different clinical and biological syndromes similar or identical to systemic lupus erythematosus (185,186):

1. exacerbation of pre-existing lupus erythematosus
2. triggering of lupus erythematosus in a susceptible patient
3. serum sickness-like syndrome resembling lupus erythematosus clinically and serologically.

There may be positive LE cells and antinuclear factors. In exacerbation or triggering of lupus erythematosus, two pathogenetic mechanisms may be involved:

1. a reaction to the pharmacological properties of the drug, such as occurs with other drugs, such as hydralazine, diphenylhydantoin, procainamide, isoniazid, and practolol (185–190);
2. a hypersensitivity reaction (186,191,192).

In type I reactions, exposure time, and especially re-exposure time, are usually longer than 1–2 months. In type II reactions, exposure is more variable, lasting from hours to days or up to 1–2 months (185–187). Some patients with ulcerative colitis have developed arthropathy, possibly polyserositis, hematological abnormalities, and even loss of consciousness with positive LE cell and antinuclear antibody tests during treatment with sulfasalazine (187,189).

Diagnosis

No diagnostic tests are available to confirm sulfonamide hypersensitivity, and while avoidance of the drug is generally appropriate when a previous hypersensitivity reaction is suspected, desensitization protocols are available for use in HIV patients in whom *Pneumocystis jiroveci* pneumonia prophylaxis or treatment is indicated (193).

Desensitization

Desensitization has been tried with sulfonamides and especially co-trimoxazole. Desensitization with the combination seems to be essential in patients with AIDS, since co-trimoxazole is the first choice against *Pneumocystis jiroveci* pneumonia and toxoplasmosis. Desensitization is successful in 75% of patients with AIDS (194–196). However, the procedure is not completely safe and even anaphylactic shock can occur (170).

Body temperature

Drug fever due to sulfonamides is usually accompanied by a skin reaction; however, fever without other manifestations can occur (164,165).

Long-Term Effects

Drug resistance

Salmonella typhimurium DT104 is usually resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An outbreak of 25 culture-confirmed cases of multidrug-resistant *S. typhimurium* DT104 has been identified in Denmark (197). The strain was resistant to the abovementioned antibiotics and nalidixic acid and had reduced susceptibility to fluoroquinolones. A swineherd was identified as the primary source (197). The DT104 strain was also found in cases of salmonellosis in Washington State, and soft cheese made with unpasteurized milk was identified as an important vehicle of its transmission (198).

Second-Generation Effects

Fertility

Male infertility with oligospermia has been reported during treatment with sulfasalazine (199,200). However, inflammatory bowel disease can also affect the maturation of spermatozoa (201).

Teratogenicity

The sulfonamides appear to have little if any effect on early human development. This is indicated by the absence of case reports or epidemiological survey data

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during pregnancy. In one study of 50 282 mother–child pairs, 1455 were exposed to sulfonamides during the first 4 months; there was no increase in the relative risk of any malformation (202,203).

Malaria during pregnancy is associated with an increased risk of severe anemia and babies of low birth weight. Effective intermittent therapy with pyrimethamine + sulfadoxine reduces parasitemia and severe anemia and improves birth weight in areas in which *Plasmodium falciparum* is sensitive to this combination. In an open, prospective trial in 287 pregnant women in the Gambia who were exposed to a single dose of a combination of artesunate and pyrimethamine + sulfadoxine there was no evidence of a teratogenic or otherwise harmful effect (204).

Fetotoxicity

Sulfonamides should not be given to pregnant women in the third trimester of pregnancy. They can displace bilirubin from plasma albumin and cause kernicterus (bilirubin encephalopathy) (205–208). For the same reason, the administration of sulfonamides to lactating women or premature infants should be avoided. Successful treatment of neonatal hyperbilirubinemia with higher bilirubin concentrations has been established using exchange transfusion and phototherapy.

Susceptibility Factors

Genetic factors

The acetylator phenotype of a patient can affect the frequency and severity of adverse reactions to drugs that are metabolized by acetylation (66,164,165).

In patients with porphyria, sulfonamides should not be used (209).

Other features of the patient

Although patients with HIV infection are more likely to develop generalized skin reactions to sulfonamides, they can be used for prophylaxis and therapy.

Relative contraindications to sulfonamides are systemic lupus erythematosus and a known predisposition to lupus-like reactions. Allergic reactions to antimicrobials are frequent in patients with Sjögren's syndrome. They are especially susceptible to reactions to penicillins, cephalosporins, and sulfonamides, but reactions to macrolides and tetracyclines also seem to be over-represented in these patients (210).

Drug Administration

Drug administration route

Sulfacetamide sodium (Albucid) in solutions stronger than 5% can cause burning and stinging when applied to the eyes, but this brief discomfort is usually tolerated without serious complaints. Sulfacetamide still compares favorably with newer antibiotics since it is effective against superficial ocular infections caused by a variety of microorganisms. However, serious allergic reactions can develop after ocular treatment (211).

The sulfonamides have a bacteriostatic rather than a bactericidal action. Many local anesthetics used in the eye are esters of *para*-aminobenzoic acid, and such drugs will interfere with the action of sulfonamides. Thus, to obtain the maximum effect from instillation of sulfonamide eye-drops, these drugs should not be used until the effect of the local anesthesia disappears.

Drug–Drug Interactions

Alkalis

Urine alkalinization increases the urinary excretion of sulfonamides (212,213).

Barbiturates

Sulfafurazole enhances the anesthetic effect of short-acting intravenous barbiturates, by competitive displacement from binding sites on plasma albumin (214).

CYP2C9

The inhibitory effect of sulfonamides on tolbutamide metabolism is mediated by CYP2C9, and therefore other drugs with narrow therapeutic ranges that are metabolized by CYP2C9, such as phenytoin and warfarin, deserve attention when certain sulfonamides (for example sulfaphenazole, sulfadiazine, sulfamethizole, and sulfafurazole) are co-administered (215).

Phenytoin

Attention is warranted when certain sulfonamides (for example sulfaphenazole, sulfadiazine, sulfamethizole, and sulfafurazole) are co-administered with CYP2C9 substrates with narrow therapeutic ranges, such as phenytoin.

Sulfonylureas

Hypoglycemia, often during the first hours of combining the two drugs, is the result of an important interaction between sulfonylureas and sulfonamides (216–219). For example, the half-life of tolbutamide was increased from 9.5 to 29 hours by chronic sulfaphenazole and from 9.2 to 26 hours by a single dose of sulfaphenazole (220). Interference by sulfonamides with the protein binding of sulfonylureas may contribute.

Most reports of this interaction have described hypoglycemia with tolbutamide in combination with sulfaphenazole (216,217,220,221), sulfafurazole (217), or co-trimoxazole (219,222). The inhibitory effect of sulfonamides on tolbutamide metabolism is mediated by CYP2C9 (215).

Chlorpropamide produces the same interaction (223).

The combination of gliclazide, fluconazole, and sulfamethoxazole can cause severe hypoglycemia (224).

Warfarin

Attention is warranted when certain sulfonamides (for example sulfaphenazole, sulfadiazine, sulfamethizole, and sulfafurazole) are co-administered with CYP2C9 substrates with narrow therapeutic ranges, such as warfarin (215).

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Interference with Diagnostic Tests

Folate measurement

Sulfonamides, in contrast to trimethoprim, do not interfere with the microbiological assay of folate (77).

Theophylline

Sulfamethoxazole distorts the results of high performance liquid chromatography used for detection of theophylline plasma concentrations; the antibiotic should be withdrawn 24 hours before the procedure (SEDA-6, 7).

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Sulfonylureas

General Information

Sulfonylureas act by inhibiting ATP-sensitive potassium channels (K_{ATP} channels) in pancreatic beta cells, increasing the amount of insulin released. The beta cells of patients taking these drugs are chronically stimulated. Changes in the pattern of insulin secretion and increased peripheral resistance to insulin both result in increased output of glucose from the liver. A rise in the number of insulin receptors, amelioration of the postbinding defect, and inhibition of the increased glucose output from the liver have been described (SEDA-5, 391), mostly in in vitro or animal experiments of short duration. The K_{ATP} channels in the beta cells and other tissues have been reviewed, including a discussion of the effects of various sulfonylureas (1). Enhanced action on beta cells by the addition of ADP suggests that the action of sulfonylureas varies with the metabolic state of the islet. Chlorpropamide and glibenclamide have high islet- binding specificity, while glibenclamide also binds with high affinity to extra-pancreatic binding sites.

Increased insulin release reduces blood glucose and glycosuria and contributes to a reduction in energy loss. This leads to increased storage of body fat when more is eaten than is necessary to meet daily energy needs and provokes feelings of hunger. Traditionally therefore, the sulfonylureas have been regarded as being unsuitable for overweight diabetics, who primarily need to lose weight. However, the results of the Diabetes Control and Complications Trial (DCCT) (2) and the UK Prospective Diabetes Study (UKPDS) (3) have shown that a sustained increase in the blood glucose concentration accelerates the development of secondary complications of diabetes mellitus. Being overweight may therefore be the price to be paid for normalization of blood glucose. However, not all secondary changes, such as macroangiopathy, seem to depend directly on the blood glucose concentration.

The potencies and the durations of action of oral hypoglycemic drugs vary (see Table 1). Oral drugs may make the cell more sensitive to insulin, and it is difficult to predict how long the hypoglycemic effect will last. The blood concentration does not always determine the duration of action. When the concentration is falling, stimulation of insulin secretion can continue for some time.

There have been reviews of oral hypoglycemic drugs (4–8).

Maturity-onset diabetes of the young (MODY) is characterized by type 2 diabetes at or before adolescence. It is a genetically heterogeneous disease, for which at least five different genes have been identified. MODY3, one of the most common forms, is characterized by a mutation in the hepatocyte nuclear factor (HNF)-1α gene. MODY3 can be very sensitive to sulfonylureas (SEDA-22, 475) (9,10).

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Table 1 Doses, durations of action, and half-lives of sulfonylureas

RINN	Dose (mg)		Duration of action (hours)	Half-life (hours)	
				Renal function	
	Mean/day	Maximum/day		Normal	Anuric
Acetohexamide	250–1000	1500	12–24	16	48
Carbutamide[a]	500–1500	2500			
Chlorpropamide	100–500	1000	20–60	35	200
Glibenclamide (glyburide)	2.5–10	20	12–18	5–8	11
Glibornuride	12.5–100		10–15		
Gliclazide	40–240	240	12–18	8–11	
Glimepiride	1–4	6	12–20	5–8	
Glipizide	2.5–20	30	6–12	3–5	Unchanged[b]
Gliquidone	15–90	120	6–12	6–10	Unchanged[b]
Glisoxepide	2–12	15	5–10		
Glymidine (glycodiazine)	500–1500	3000	6–12		
Tolazamide	100–500	1000	12–16	8–10	
Tolbutamide	500–2000	3000	6–12	3–5	48

[a] Obsolete
[b] Hypoglycemia occurs despite the unchanged half-life

Three new cases have been presented, all with a mutation in the HNF-1α gene; low-dose glibenclamide was the best treatment in all cases (11).

The UK Prospective Diabetes Study (3) has shown that timely treatment, by reducing blood glucose concentrations before subjective complaints develop, reduces secondary complications in type 2 diabetes mellitus.

Combinations of oral hypoglycemic drugs

The different mechanisms of action of the various classes of hypoglycemic drugs makes combined therapy feasible: the sulfonylureas and meglitinides stimulate insulin production by different mechanisms, the biguanides reduce glucose production by the liver and excretion from the liver, acarbose reduces the absorption of glucose from the gut, and the thiazolidinediones reduce insulin resistance in fat. It is not necessary to wait until the maximal dose of one drug has been reached before starting another. However, sulfonylureas and meglitinides should no longer be used when endogenous insulin production is minimal. Combinations of insulin with sulfonylureas or meglitinides should only be used while the patient is changing to insulin, except when long-acting insulin is given at night in order to give the islets a rest and to stimulate daytime insulin secretion.

Large studies of the effects of lifestyle changes, the effects of drugs in preventing or postponing the complications of diabetes, or the usefulness of various combinations are regularly published. The different mechanisms of action of the various classes give different metabolic effects and different adverse effects profiles (12). Comparative costs of the various therapies in the USA have been presented (13).

This subject has been reviewed in relation to combined oral therapy. In a systematic review of 63 studies with a duration of at least 3 months and involving at least 10 patients at the end of the study, and in which HbA_{1c} was reported, five different classes of oral drugs were almost equally effective in lowering blood glucose concentrations (14). HbA_{1c} was reduced by about 1–2% in all cases. Combination therapy gave additive effects. However, long-term vascular risk reduction was demonstrated only with sulfonylureas and metformin.

The adverse effects of combined drug therapy are attributable to adverse effects of the individual drugs. Increased adverse effects or new adverse effects in patients taking combinations have not been reported.

Sulfonylureas + meglitinides

Glipizide, nateglinide, and their combination have been compared in a double-blind, randomized, placebo-controlled study in 20 patients with type 2 diabetes not requiring insulin (15). Before a standardized breakfast they took glipizide 10 mg, nateglinide 120 mg, both, or placebo; 4 hours after the meal blood glucose concentrations were significantly higher after nateglinide, but peak and integrated glucose concentrations did not differ. Integrated insulin concentrations were higher with glipizide. There were three episodes of hypoglycemia in the glipizide alone group and three in the combined group; three required treatment with glucose.

Sulfonylureas + thiazolidinediones

Troglitazone 100 or 200 mg/day or placebo was given for 16 weeks to 259 patients already taking sulfonylurea therapy (16). HbA_{1c} was 0.4 and 0.7% lower and blood glucose concentrations fell. The most common event was hypoglycemia, but this did not occur more often when troglitazone was added. Liver enzymes increased to the same extent in the three groups and never rose above normal. No patients withdrew because of drug-related effects.

Organs and Systems

Cardiovascular

Early studies suggested that tolbutamide caused excessive cardiovascular deaths (17) as reported in the University Group Diabetes Program (UGDP) (SEDA-4, 301), but

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the UK Prospective Diabetes Study did not find different mortality in patients treated with insulin, glibenclamide, or chlorpropamide (3).

This effect of tolbutamide has been attributed to prevention of ischemic preconditioning, a protective manoeuvre that reduces myocardial damage after temporary stoppage of coronary blood flow (18). Transient myocardial ischemia augments post-ischemic myocardial function and prevents dysrhythmias. K_{ATP} channels play a role in this so-called ischemic preconditioning. In 48 atrial trabeculae, obtained during catheterization, the recovery of the developed muscle force in patients treated with a sulfonylurea was only half of what was found in non-diabetics or diabetics treated with insulin. This suggests that inhibition of K_{ATP} channels by oral sulfonylureas might contribute to increased cardiovascular mortality (19). The question of whether the findings obtained mainly with glibenclamide can be generalized to all sulfonylureas has been discussed, since sulfonylureas differ greatly in their ability to interfere with vascular or cardiac K_{ATP} channels (20). Both glimepiride and glibenclamide (21) improved glycemia in 29 patients in a randomized, double-blind, placebo-controlled, crossover study of a number of susceptibility factors for ischemic heart disease (plasminogen activator inhibitor activity, plasminogen activator inhibitor antigen, LDL cholesterol, C peptide, proinsulin, des-31,32 proinsulin, etc.), but K_{ATP} channels were not investigated.

Glibenclamide prevented the increase in tolerance to myocardial ischemia normally observed during the second of two sequential exercise tests (22).

Respiratory

- A 76-year-old man who had taken glibenclamide for 2 weeks, having switched from voglibose, developed pneumonitis; a lymphocyte stimulation test was positive for glibenclamide (23).

Sensory systems

A change in taste sensation has been reported with glipizide (24).

Metabolism

In 36 Japanese patients who were relatively lean but had excess abdominal fat, glibenclamide and voglibose caused loss of weight and abdominal fat (25). The loss of abdominal fat was related to glycemic control. The ratio of subcutaneous to abdominal fat shifted toward subcutaneous fat only in those who took voglibose. Both voglibose and glibenclamide improved insulin sensitivity and the acute response to insulin.

Hypoglycemia

DoTS classification (BMJ 2003;327:1222–5)
Adverse effect: Hypoglycemia due to sulfonylureas
Dose-relation: toxic effect
Time-course: time-independent
Susceptibility factors: disease (impaired liver or kidney function, alcoholism); drug interactions; reduced food intake; exercise

Hypoglycemia is the most frequent complication in patients with diabetes taking oral hypoglycemic drugs (26–28).

Presentation

In general, hypoglycemia caused by oral hypoglycemic drugs is more dangerous and of longer duration than hypoglycemia caused by insulin (29), and the most dangerous hypoglycemic attacks are those that result from long-acting drugs, such as chlorpropamide, and later sulfonylureas, such as glibenclamide (SEDA-4, 303). Sulfonylureas are mostly used by elderly people, and the characteristic warning symptoms of hypoglycemia (dizziness, breathlessness, sweating, and a feeling of hunger) are often absent or not well-interpreted.

Neurological symptoms are common and hypoglycemia can cause hemiplegia, which can be confused with neurological symptoms of other origin (transient ischemic attack, stroke, etc.). A bilateral case has been reported (30).

- A 68-year-old man started to take glibenclamide and 1 week later developed a blurred voice and right-sided hemiplegia with a blood glucose of 1.4 mmol/l. Ten minutes after intravenous glucose 50 g his motor function returned to normal. Six hours later he developed slurred speech and left-sided hemiplegia; his blood glucose was 1.9 mmol/l. During glucose administration his deficit resolved.
- A 75-year-old man taking gliclazide 80 mg bd and metformin 850 mg tds became hypoglycemic and was treated successfully (31). All hypoglycemic drugs were withdrawn, but he received more through his doctor's prescription computer and again became hypoglycemic on two occasions. On the second he became unconscious for 4.5 hours and his plasma glucose was 1.2 mmol/l. After resuscitation his abbreviated mental test was 5/10 and did not improve. He later became very aggressive and died of bronchopneumonia.

Three patients became comatose due to hypoglycemia (32):

- an 83-year-old woman who took two times 5 mg glibenclamide bd;
- a 61-year-old man who took 2 mg glimepiride bd and 500 mg metformin bd;
- a 79-year-old woman who took 5 mg glibenclamide tds and metformin 850 mg bd.

All of these patients had general malaise, reduced food intake, and vomiting; glucose had to be given for a long time and one patient died with pneumonia.

Frequent attacks of hypoglycemia can result in encephalopathy, and after withdrawal of the hypoglycemic drug cerebral injury can persist. It is not exceptional for prolonged hypoglycemic coma to end fatally (33,34). In 494 cases of severe hypoglycemia, 10% of the patients died and 9% had permanent sequelae (35).

Factitious hypoglycemia can take a long time to diagnose.

- A 20-year-old woman with unexplained hypoglycemia had an exploratory laparotomy with pancreatic biopsy, which showed a histological picture compatible with hyperplasia (36). Glipizide was detected in the blood at a concentration of 0.72 (usual target

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range 0.1–0.49) μg/ml. The diagnosis was factitious hypoglycemia.

- A 33-year-old nurse with unexplained hypoglycemia had only small increases in insulin and C-peptide, and glibenclamide was found in her serum (37). However, she denied using it and did not want psychiatric therapy.

Reported cases again illustrate that hypoglycemia induced by tablets tends to relapse and that long-term observation after normalizing the blood glucose concentration is necessary.

Hypoglycemia has been reported in a worker, not wearing a mask, working with a machine preparing ultrafine sulfonylurea powder (38).

Incidence

In 13 963 sulfonylurea users over 65 years of age, there were 255 severe attacks of hypoglycemia during 20 715 patient-years of use (39).

In an open comparative study in 57 patients acarbose and gliclazide had the same effects on HbA_{1c}, blood glucose, and lipids, although the ratio of HDL:LDL cholesterol increased during acarbose therapy (40). Of those who took gliclazide 10% reported at least one mild hypoglycemic reaction.

In an 8-week, non-interventional cohort study in 22 045 patients with type 2 diabetes, of whom 4.9% discontinued therapy, adverse advents occurred in 2.3% (41). There were attacks of hypoglycemia in 0.3%. Of the 6547 patients taking glimepiride, 2.5% had adverse reactions and 0.4% had hypoglycemic reactions.

In an open, multicenter study, 849 patients with poorly controlled diabetes were treated with glimepiride monotherapy for 6 months in doses that were titrated from 1 to 6 mg (42). The authors tried to identify factors that could predict the response to glimepiride. Patients who achieved a fasting blood glucose below 7.7 mmol/l and HbA_{1c} below 7.5% or a reduction in fasting blood glucose of over 20% and/or in HbA_{1c} of at least 10% were defined as responders (57% of the 849 patients). Earlier treatment with other oral hypoglycemic drugs or long-standing diabetes increased the rate of non-responders. In 9.2% of the patients there were episodes of hypoglycemia, 1.4 per patient, and third-party or medical assistance was required five times as often. A family history of type 2 diabetes doubled the risk; a high HbA_{1c} reduced the risk.

In a retrospective study in Hong Kong, drug-induced hypoglycemia accounted for 0.5% of admissions; 50% of the episodes were related to sulfonylureas (43). These patients were older, predominantly female, in poorer general health, and needing assistance in daily activities, including feeding. Co-morbidities, such as macrovascular complications, renal insufficiency, and concurrent infections, were common. Low plasma albumin concentrations probably reflected poor nutritional status. Of those who had recurrent admissions, 67% lived in old peoples' homes, compared with 22% in those without previous admissions. The prognosis in this group was poor: 23% died within 1 year. Patients taking gliclazide ($n = 13$) or glipizide ($n = 10$) accounted for 37% of the episodes. They had more vascular complications than patients who used glibenclamide or chlorpropamide. They had a higher frequency of previous admissions (47 versus 19%) and a higher mortality rate (1 year, 47 versus 10%; 5 years, 72 versus 34%).

In a period of 12 months 23 episodes of severe hypoglycemia were recorded in those taking a sulfonylurea in a district with a population of 367 051 (8655 with diabetes) (44). The total cost of emergency treatment was estimated to be up to $92 078/year.

Causes and susceptibility factors

Most sulfonylureas are at least partly metabolized in the liver (SEDA-9, 709) (45), and hence liver insufficiency, liver disease, and liver enzyme inhibition (alcohol) or induction (drugs) can alter the half-life of the drug and its duration of action.

Renal dysfunction is another cause of hypoglycemia (46). Some sulfonylureas, such as chlorpropamide (30%) and tolbutamide (50%), are excreted by the kidney. Other drugs, such as acetohexamide, glibenclamide (glyburide), glibornuride, and glymidine, are mainly metabolized, but some of their metabolites also have a hypoglycemic effect and are excreted by the kidneys, so that renal insufficiency can prolong their hypoglycemic actions. The reduction in insulin metabolism in diseased kidneys (nephropathy) can contribute to hypoglycemia, since it increases the half-life of insulin.

Hypoglycemia can also result from drug interactions, with the simultaneous use of drugs that have glucose-lowering effects or that inhibit the clearance of oral hypoglycemic drugs.

The conclusion (SEDA-22, 475) (47) that fasting is well tolerated and that old age is no contraindication to sulfonylurea therapy has not been accepted by others (48,49), as the previous study included only a small number of relatively healthy patients with type 2 diabetes.

Hypoglycemia can result from overdosage of sulfonylureas (50,51). Factitious hypoglycemia induced by tablets is difficult to diagnose, since C peptide concentrations will be high and not suppressed. Reduced intake of food or alcohol can also play a role (52).

Severe hypoglycemia induced by long-acting and short-acting sulfonylureas in Basel, Switzerland (200 000 inhabitants), has been analysed in a retrospective study in 28 patients (median age 73 years) (53); 11 men and 5 women (2.24 per 1000 person-years) were taking long-acting sulfonylureas (15 glibenclamide, 1 chlorpropamide) and 2 men and 10 women (0.75 per 1000 person-years) short-acting sulfonylureas (10 glibornuride, 2 gliclazide). Metformin was only involved when combined with a sulfonylurea. There were no deaths. Reduced food intake ($n = 9$), increased activity ($n = 2$), impaired renal function ($n = 2$), alcohol ($n = 2$), too many tablets ($n = 3$), and no obvious factor ($n = 10$) were the causes.

Drug-induced hypoglycemia in 102 non-alcoholic, non-epileptic patients has been reviewed (54). There were susceptibility factors for hypoglycemia in 94; 84 were over 60 years old, of whom 70 were over 70 years; 66 had renal impairment, of whom 28 also had reduced energy intake, 10 had reduced energy intake, 30 had infections, 5 had liver cirrhosis, and 10 had malignant neoplasia; 14 had used hypoglycemia-potentiating drugs, such as beta-blockers ($n = 8$), cimetidine ($n = 2$),

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co-trimoxazole ($n=2$), and aspirin ($n=2$). Forty patients had protracted hypoglycemia lasting 12–72 hours. Head trauma ($n=4$), skeletal injury ($n=3$), seizures ($n=8$), transient asymptomatic myocardial ischemia ($n=2$), and transient right hemiplegia ($n=1$) were seen. Five patients died. Ten used glibenclamide + metformin, 14 used glibenclamide + insulin, and 53 used only glibenclamide.

To study the impact of Munchausen's syndrome, 129 patients with unexplained hypoglycemia in France had blood tests for sulfonylureas, which were found in 22 cases—glibenclamide in 19 patients and gliclazide in 3 (55). The concentrations were usually higher than the usual target concentration: in seven cases they were five times higher and the highest value was 18 times higher. In most cases an insulinoma was suggested and pancreatectomy was planned.

Management

Treatment of sulfonylurea-induced hypoglycemia and of overdose with sulfonylureas has been reviewed (56). If intravenous dextrose is insufficient, octreotide is recommended (57) but not diazoxide. In patients with insulin reserve, dextrose can stimulate insulin secretion and paradoxically worsen the condition. Patients with drug-induced hypoglycemia should not be given glucagon, since it will stimulate insulin secretion. Hypoglycemia can last for up to 5 days. Continued observation is important, because recurrence after temporary recovery is common.

Nutrition

In patients taking maximal doses of sulfonylureas, plasma homocysteine concentrations were raised during secondary failure with poor metabolic control, which may indicate increased vascular risk (58). The concentrations correlated inversely with endogenous insulin concentrations.

Electrolyte balance

Mild hyponatremia has been reported with sulfonylureas, most commonly with chlorpropamide (59,60). The mechanism with chlorpropamide is secretion of ADH (61).

In 70 non-insulin-dependent patients with diabetes, taking one of five different oral hypoglycemic drugs, 21% of prescriptions were associated with a low plasma sodium concentration, but it was lower than 129 mmol/l in only 8% (62). Every oral hypoglycemic agent was associated with a low plasma sodium concentration, which normalized on withdrawal. Extreme hyponatremia was only seen with chlorpropamide and, in one case, with glibenclamide.

Fluid balance

Water retention with oliguria, uremia, and edema has been reported with gliclazide (63). Resistance to diuretics can be caused by chlorpropamide (64) or, to a lesser extent, tolbutamide. Changing to a sulfonylurea without an antidiuretic effect (glibenclamide) or to one that enhances water excretion (acetohexamide, glipizide, or tolazamide) (65) may be advisable.

Hematologic

The most dangerous adverse reaction of sulfonylureas is agranulocytosis. Aplastic anemia (66), red cell aplasia (67), pure white cell aplasia (68), bone marrow aplasia, and hemolytic anemia have been described during treatment with chlorpropamide (69), glibenclamide (70), or tolbutamide (71).

Thrombocytopenia has been described with chlorpropamide (72), tolbutamide (73), glibenclamide (74), and glimepiride (75).

- A 68-year-old man, who had taken pipotiazine and trihexyphenidyl for 12 years for chronic psychosis, took glimepiride for hyperglycemia. No platelet counts were performed before or during this. He had no symptoms of bleeding. He developed a petechial rash and hematomas on his trunk, legs, and face, hemorrhagic bullae in his mouth, and gingival bleeding. There was thrombocytopenia (1×10^9/l), with no malignant cells in a bone marrow aspirate and no serological evidence of recent viral infection. All medications were withdrawn and he was given prednisone and human immunoglobulin. After 7 days the hemorrhagic syndrome abated, although his platelet count was still 2×10^9/l. After four weeks the platelet count was 23×10^9/l and the prednisone was gradually withdrawn. After 6 months the platelet count was normal (346×10^9/l).

Glibenclamide can cause hemolysis by a non-immune mechanism (76).

- A 68-year-old man with a long history of type 2 diabetes and a slowly progressive myelodysplastic syndrome for 2 years took glibenclamide 5 mg/day for more than a year, buformin 150 mg/day, and voglibose 0.6 mg/day. His hemoglobin was 8.4 g/dl. No other cause of hemolysis was found and glibenclamide was withdrawn. His hemoglobin rose to 11.1 g/dl.

Eosinophilic infiltrations have been described with tolbutamide (SEDA-8, 917) (77), and chronic eosinophilic pneumonia has been described with chlorpropamide (78) and tolazamide (79).

Gastrointestinal

Gastrointestinal tract disturbances are frequent with sulfonylureas. They comprise nausea, vomiting, heartburn, dyspepsia, a metallic taste, and abdominal pain (80). They are less troublesome when the drug is taken after meals.

Liver

The risk of hepatotoxicity with the sulfonylureas varies with both the drug and the dosage. It has been described with chlorpropamide (81), tolazamide (82), tolbutamide (83), glipizide (84), and glibenclamide (85). Anicteric, cytolytic hepatitis has been described after glibenclamide (86).

Hepatic granulomas have been reported as a hypersensitivity reaction to chlorpropamide (87). Cholestatic jaundice from sulfonylureas is also probably of allergic origin; it is rare and has been described with glibenclamide (88), also in combination with hepatorenal syndrome (89), acetohexamide (90), chlorpropamide (91), gliclazide (92), and tolazamide (93).

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- A 64-year-old man who had taken glibenclamide 10 mg/day for 4 years developed cholestasis (94). There was no extrahepatic obstruction on ERCP and serological tests for hepatitis A, B, and C, *Helicobacter pylori*, and antimitochondrial or antinuclear antibodies were all negative. Liver biopsy showed portal and periportal inflammation, edema, and prominent centrilobular hepatocanalicular cholestasis. When glibenclamide was withdrawn and insulin given, the laboratory values normalized within 8 weeks. Rechallenge was considered unethical.

Hepatitis has been described with glibenclamide (95) and gliclazide (96).

- A 60-year-old woman with normal liver function tests developed acute hepatitis 6 weeks after starting to take gliclazide. No viruses, autoimmune factors, or metabolic factors that could have caused hepatitis could be found. A lymphocyte transformation test was not performed. A liver biopsy was compatible with drug-related acute hepatitis. When gliclazide was withdrawn she improved. She took glibenclamide and recovered fully within 6 weeks.
- A 64-year-old man who took gliclazide 160 mg bd for 3 months developed hepatitis (97). No other cause could be detected. Gliclazide was withdrawn. A liver biopsy after 2 weeks showed resolving acute hepatitis, consistent with a drug reaction, and 3 months later the liver profile was normal.
- A 42-year-old woman with newly diagnosed diabetes and no other known diseases developed a slightly abnormal liver profile (98). Good glycemic control was obtained with metformin 850 mg bd and gliclazide 80 mg bd. After 4 weeks she developed a pruritic skin rash, which resolved after 4 days of treatment with fexofenadine. A liver profile 2 weeks later was abnormal. Metformin was withdrawn, but 3 days later she was icteric and gliclazide was withdrawn. A liver biopsy was consistent with cirrhosis and there were moderate inflammatory infiltrates. The liver function tests improved and after 3 weeks she was rechallenged with metformin without exacerbation.

In the last case cirrhosis may have contributed to the adverse effect of gliclazide.

Pancreas

A possible relation between 2 years of treatment with a sulfonylurea and damage to the islets of Langerhans has been reported (99). A fatal case of pancreatitis has been attributed to glibenclamide (100).

In a case-control study in 1.4 million people in Sweden, 462 who were hospitalized for pancreatitis without gallbladder disease were compared with 1781 randomly selected controls; 6% of the cases and 3% of the controls had diabetes (101). Diet and insulin therapy were not associated with an increased risk, but the risk of pancreatitis with glibenclamide had a crude odds ratio of 3.2 and was higher in people aged over 70 years and in those taking beta-blockers.

Urinary tract

Nephrotic syndrome and immune complex glomerulonephritis have been attributed to chlorpropamide (102).

Skin

Photosensitization has been described with carbutamide (103), tolbutamide (104), chlorpropamide (105), and glibenclamide (106), sometimes combined with porphyrinuria.

Allergic skin reactions have been described with all sulfonylureas. They include pruritic rashes, erythema nodosum, urticaria, blisters (86), erythema multiforme, exfoliative dermatitis, Quincke's edema, erythroderma, and itching, while lichenoid drug reactions with ulceration have occurred after chlorpropamide and tolazamide (107). More generalized hypersensitivity reactions may prove fatal, but rarely.

Erythema multiforme has been attributed to glibenclamide (108).

- A 69-year-old woman, who had taken gliclazide 40 mg/day for 3 months, was switched to glibenclamide 2.5 mg/day. She had malaise for 2 days, followed by anorexia, fever, and 2 days later erythema multiforme over her whole body. She also had liver dysfunction, renal impairment, and rhabdomyolysis. A lymphocyte stimulation test was positive for glibenclamide, which was withdrawn; the rash improved and the laboratory tests normalized within 4 days.

Pigmented purpuric dermatosis has been attributed to glipizide (109).

- A 66-year-old man took glipizide for 4 weeks and developed brownish, non-pruritic, purpuric, scaling patches on his upper legs and buttocks. Biopsy showed dilated capillaries with surrounding extravasated erythrocytes, perivascular lymphocytic infiltrates, and areas of hemosiderin deposition. After withdrawal of glipizide the rash cleared.

Immunologic

Hypersensitivity vasculitis has been described with glibenclamide (110). Glibenclamide contains a sulfa moiety and can cause allergic reactions in someone who is allergic to sulfonamides.

- A 57-year-old man with a previously undocumented sulfa allergy used atenolol 100 mg/day, hydrochlorothiazide 25 mg/day, docusate sodium 100 mg/day, and ranitidine 300 mg bd for several months (111). He started to take celecoxib 200 mg/day, and 1 month later developed erythema multiforme and difficulty in breathing caused by swelling of the throat. He improved after withdrawal of his drugs and further treatment. He was then instructed to reintroduce his previous drugs one a day. One day later, after taking glibenclamide 5 mg, he developed new lesions and dyspnea. After 3 weeks he had another relapse when he reintroduced hydrochlorothiazide. He omitted glibenclamide, celecoxib, and hydrochlorothiazide, but continued to use insulin, metformin, ranitidine, and psyllium. The urticarial lesions disappeared.

Celecoxib and hydrochlorothiazide also have sulfa moieties and could have contributed in this case.

Death

Of 2275 diabetic patients aged 45–74 years with proven coronary artery disease, followed for 7.7 years, 990 were

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treated with diet alone, 79 with metformin, 953 with glibenclamide, and 253 with a combination of metformin and glibenclamide (112). They were compared with 9047 non-diabetics. Mortality was lowest in the non-diabetics; death rates in the others were: diet alone 26%, metformin 32%, glibenclamide 34%, and combined therapy 44%.

Second-Generation Effects

Pregnancy

Sulfonylureas ($n = 68$) and metformin ($n = 50$) have been compared retrospectively with insulin ($n = 42$) in pregnancy (113). There were no severe attacks of hypoglycemia, no jaundice, and no differences in neonatal morbidity. However, in those who took metformin, pre-eclampsia and perinatal deaths were more common. Since metformin was given to obese women, and since obesity contributes to pre-eclampsia and perinatal mortality, this may have been an effect of obesity.

In 404 pregnant women at 11–33 weeks of gestation, with a fasting blood glucose of 5.3–7.8 mmol/l, randomly assigned to insulin or glibenclamide, there were no differences in perinatal outcome (114). Glibenclamide was not found in cord blood. The data were analysed separately for women with mean glucose concentrations at home above and below 5.8 mmol/l. In the high blood glucose group there were large children for gestational age in 19% (insulin) and 17% (glibenclamide), compared with 10% (insulin) and 11% (glibenclamide) in the low glucose group; it is not clear whether these differences were significant. There were no other differences (for example macrosomia, insulin in cord blood) between the groups.

Teratogenicity

There is anecdotal evidence of a risk of teratogenicity of sulfonylureas, and on theoretical grounds it is inadvisable to give sulfonylureas to women of fertile age. In women using self-administered hypoglycemic drugs during pregnancy, chlorpropamide, glibenclamide, and tolbutamide were associated with serious malformations, such as microtia, deafness, facial deformities, ventricular septal defect (with or without aortic rotation), atrial septal defect, and a single umbilical artery (115). Of 332 children of women using a sulfonylurea during the first week of pregnancy, 12% had major and 5% had minor abnormalities, related to the increase in HbA_{1c} (116). An effect of high blood glucose could not be excluded. Chromosomal damage is described with chlorpropamide (117), which may have contributed to the development of a cleft palate in another case (118). The choice for pregnant women with diabetes is between insulin given frequently in a short-acting form to avoid overdosage, or a continuous insulin infusion system, since overdosage of insulin can harm the developing fetus.

Fetotoxicity

Hypoglycemia has been reported in a neonate whose mother had taken tolbutamide (119).

- A woman with pre-existing hypertension took labetalol 600 mg/day and tolbutamide for gestational diabetes and had long-standing hypoglycemia. She had started to take tolbutamide 500 mg/day in week 23 and increased the dosage to 1500 mg/day in week 29. Her HbA_{1c} concentration was 5.0–5.8%. She felt no intrauterine movements during week 34 and an emergency cesarean section was performed. The baby had diabetic fetopathy (details not specified) and a blood glucose concentration of 0.8 mmol/l. Despite the administration of 20% glucose 10 ml as a bolus and then 8 ml/hour, the blood glucose remained below 1 mmol/l, and 10 hours after birth octreotide, a somatostatin analogue, was given. Intravenous glucose was discontinued after 3 days and octreotide on day 9. There were no signs of encephalopathy. C peptide, proinsulin, and insulin concentrations in the child were inappropriately high. Serum tolbutamide in the child was 141 μmol/l at 3 hours and the half-life was 46 hours.

The half-life of tolbutamide in this case was much longer than the reported half-life in adults of 7 hours, but the normal half-life in neonates is not known. The activity of CYP2C9, which metabolizes tolbutamide, may be reduced in the first 2 days of life.

Transient diabetes insipidus was seen in a child born to a mother who took chlorpropamide during pregnancy (120).

Neonatal thrombocytopenia and congenital malformations have been associated with administration of tolbutamide to the mother (121).

Susceptibility Factors

Age

Old age increases sensitivity to sulfonylureas and the frail elderly are at greatest risk (122).

Renal disease

Glimepiride (6), which is metabolized in the liver, was given for 3 months to two groups of diabetic patients with renal impairment: those with creatinine clearances of 30–60 ml and 10–30 ml (123). The goal was to reach a fasting blood glucose concentration below 10 mmol/l. There was recurrent hypoglycemia in one patient who did not need further drug therapy. There was one "silent" myocardial infarct. There were no other adverse effects. Serum insulin and C peptide concentrations did not change. There was increased clearance of glimepiride in the group with low creatinine clearances, probably caused by altered protein binding, increasing the unbound fraction available for hepatic metabolism.

Other features of the patient

Hypopituitarism, hypoadrenalism, and hypothyroidism all increase sensitivity to sulfonylureas because of reduced secretion of counter-regulatory hormones.

In insuloma, sensitivity to sulfonylureas is increased because insulin secretion from the tumor cells is greater than from normal islet cells.

Exercise training can force a reduction in the dose of various drugs in the treatment of diabetes (124). The hypoglycemic action of exercise in combination with

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sulfonylurea on postabsorptive glucose concentration is mainly caused by greater inhibition of glucose production in the liver (125).

Prolonged hypoglycemia in patients with end-stage renal disease prompted a search for predisposing factors in such patients with type 2 diabetes taking oral therapy only (126). Seven patients with and 31 without prolonged attacks of hypoglycemia, all on hemodialysis, were studied. All were using glibenclamide, except for three controls who took tolbutamide. The hypoglycemic episodes lasted 28–256 hours and glucose 83–2000 g was given for each episode. A recent fall in food intake, previous hypoglycemic episodes, longer duration of episodes, and a history of cerebrovascular disease were associated with prolonged hypoglycemia. There were no relations to age, sex, beta-blockers, ACE inhibitors, or drug doses. There were no cases of liver disease or alcohol abuse. Glibenclamide is seven times more highly concentrated in the pancreatic islets than other sulfonylureas, it has a long half-life, and its degradation products have hypoglycemic activity (SEDA-14, 1510).

Drug Administration

Drug formulations

New formulations of some sulfonylureas offer the possibility of once-daily therapy. They include gliclazide MR (SEDA-25, 511) and glipizide GITS (SEDA-22, 444) (SEDA-23, 475).

Gliclazide is available in various formulations with different kinetics in vivo and in vitro (127). Gliclazide MR is a modified-release formulation that allows once-a-day dosing. In a double-blind study 800 patients were randomized to gliclazide or gliclazide MR; there were no differences in adverse reactions or hypoglycemia (128). When comparing identical doses of Diamicron™ and Diabrezide™ in an open, crossover study, Diabrezide had a larger acute and mid-term hypoglycemic effect than Diamicron (129).

In a small study, gliclazide MR 30–120 mg/day had similar efficacy to 80–320 mg/day of the immediate-release formulation. The most commonly observed adverse events were arthralgia, arthritis, back pain, and bronchitis, which may not all have been directly related to the drug, as they also occurred with placebo. There was symptomatic hypoglycemia in about 5%.

Glipizide GITS was also studied in 19 patients with type 2 diabetes in an open, randomized, two-way, crossover study for 5 days, comparing 20 mg/day and 10 mg bd (130). Despite lower serum concentrations with glipizide GITS, the effects on serum concentrations of glucose, insulin, and C-peptide were the same. This may explain the low overall rate of hypoglycemia and lack of weight gain with glipizide GITS.

From time to time, drug names are confused and the wrong drug is prescribed or dispensed instead of the one intended. Of all the errors that occur, sulfonylureas are often implicated (131). Examples include chlorpropamide instead of chlorpromazine, chloroquine or etodolac instead of chlorpropamide, glyburide instead of thyroxine, and oxybutynin hydrochloride or acetohexamide instead of acetazolamide (SEDA-16, 490) (SEDA-17, 495) (SEDA-18, 414) (SEDA-19, 395) (SEDA-21, 443).

Drug dosage regimens

There were no differences in episodes of hypoglycemia, concentrations of glucose, insulin, HbA1c, or lipids, or body weight when glibenclamide was given in one daily dose instead of divided doses (132).

Drug overdose

A suicide attempt with chlorpropamide has been reported (50).

- A 23-year-old woman took chlorpropamide 5–10 g. She needed assisted respiration and cardiac pacing for bradycardia (probably due to blockade of potassium channels), fluid infusion, and forced diuresis for 3 days. Notwithstanding continuous glucose infusion and glucose boluses she relapsed into severe hypoglycemia with convulsions. Only on day 27 was her urine free of chlorpropamide and her blood glucose normal.

Chlorpropamide is the longest-acting sulfonylurea. The high doses of glucose this patient was given may have stimulated further insulin secretion, thus contributing to the long period of fluctuating hypoglycemia. In the preceding 5 years 12 fatal cases of chlorpropamide poisoning with 3–15 g were seen in the same institution.

- Glibenclamide self-poisoning has been reported in a 48-year-old man with von Willebrand disease, Prinzmetal angina, hepatitis C, and depression (51). He had frequent hypoglycemic attacks, which were not reduced by reducing the dose of glibenclamide. Laparotomy for an insulinoma was considered until a glibenclamide concentration of 0.32 μg/ml was found, although glibenclamide was supposed to have been withdrawn.

Permanent right-sided hemiplegia, dysphasia, and hepatitis occurred after a suicide attempt with gliclazide (133).

- A 14-year-old non-diabetic girl took 15 tablets of gliclazide (1200 mg) and had gastric lavage 6 hours later. She developed lethargy, vomiting, and generalized tonic-clonic convulsions. Her blood glucose concentration was 0.8 mmol/l, aspartate transaminase 147 U/l (2.45 μkat/l), alanine transaminase 102 U/l (1.07 μkat/l), bilirubin 78 μmol/l (direct 31 μmol/l), and alkaline phosphatase 63 U/l. Electroencephalography showed voltage suppression in the left hemisphere and generalized slow-wave activity. A CT scan showed cerebral edema. Hypoglycemia was controlled within 24 hours with intravenous glucose. The convulsions could not be controlled with phenytoin, dexamethasone, or mannitol, given for cerebral edema, but they stopped on day 9. After 3.5 months of follow-up she could perceive words but could not speak and was severely hemiplegic.

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Drug–Drug Interactions

General

Drug mechanisms that result in potentiation of the hypoglycemic effects of the sulfonylureas include:

- prolongation of the half-life by inhibition of metabolism or excretion (phenylbutazone, coumarins, chloramphenicol, doxycycline, bezafibrate, probenecid, sulfaphenazole, naproxen, fenyramidol);
- competition with plasma protein binding sites (NSAIDs, salicylates, and sulfonamides);
- potentiation of their hypoglycemic action by inhibition of gluconeogenesis, enhancement of oxidation of glucose, or stimulation of insulin secretion (beta-adrenoceptor antagonists, monoamine oxidase inhibitors, salicylates).

Examples are given in Table 2.

ACE inhibitors

In a retrospective case-control study, a primary diagnosis of hypoglycemia was identified in 413 patients registered as diabetic in 1993 (134). Five controls of the same age and sex, without hypoglycemia, were selected for each case from the same cohort. The relative risks of hypoglycemia with ACE inhibitors, beta-blockers, calcium antagonists, and salicylates were determined. There was an association between enalapril and sulfonylureas. However, other ACE inhibitors could not be identified as a risk factor. There was no interaction with beta-blockers, calcium channel blockers, or salicylates.

The interaction of ACE inhibitors with sulfonylureas has also been illustrated in case reports (135,136).

- A 67-year-old man using glucocorticoids for asthma, ranitidine 300 mg/day, and enalapril 5 mg/day developed a low blood glucose (1.2 mmol/l) within 48 hours of starting to take glibenclamide 5–10 mg/day.
- A 64-year-old man, who used, amongst other drugs, glibenclamide 2.5 mg/day and metformin 850 mg bd, lost consciousness after a week of dwindling appetite and loose stools. His blood glucose was 2.2 mmol/l. He had renal impairment (creatinine 362 μmol/l). He also used ranitidine and ramipril 2.5 mg/day, which could have contributed to both the hypoglycemic effect and renal insufficiency.

In the second case, renal insufficiency could have reduced the clearance of the active metabolites of glibenclamide.

Table 2 Drug interactions with oral hypoglycemic drugs

Interactions	Mechanisms
Enhanced hypoglycemia	
ACE inhibitors	7
Alcohol	3
Allopurinol	1 or 6
Azapropazone	2
Beta-adrenoceptor antagonists	3
Bezafibrate	7
Chloramphenicol	1
Cimetidine	7
Coumarin anticoagulants	7
Isoniazid	7
Levodopa	3
Naproxen	2
Perhexiline	3
Probenecid	1, 2, or 6
Pyrazolones	1, 2, or 6
Salicylates	2 or 6
Sulfonamides	1, 2 or 6
Reduced hypoglycemia	
Acetazolamide	7
Furosemide	7
Glucocorticoids	5
Oral contraceptives	5
Phenothiazines	7
Rifampicin	4
Sulfamethoxydiazine	7
Thiazide diuretics	5

Key to mechanisms:
[1]—Inhibition of drug-metabolizing enzymes
[2]—Displacement of drug from protein-binding sites
[3]—Impairment of glucose homeostatic mechanism
[4]—Induction of metabolizing enzymes
[5]—Increased insulin resistance
[6]—Reduced renal secretion
[7]—Unknown

Alcohol

A disulfiram-like effect after use of alcohol has been described with chlorpropamide, but also with gliclazide, glipizide, and acetohexamide. However, the hepatic effects of sulfonylureas include inhibition of the enzymatic degradation of ethanol, an effect that is only partly comparable with the action of disulfiram, which blocks the degradation of aldehyde but not that of ethanol itself. This interaction results in a vasomotor reaction, with giddiness, tachycardia, headache, angina pectoris, and skin reactions. The most prominent drug to elicit these effects is chlorpropamide, but tolbutamide and other drugs can also do it. The specific effect of alcohol and chlorpropamide has been propagated to be of use as a genetic marker, but this has not been confirmed (SEDA-7, 407).

Excessive use of alcohol, sometimes found in older persons living alone, may also contribute to changes in sensitivity to oral hypoglycemic drugs. Low doses of alcohol (4.35 mmol/l/kg, comparable to one or two drinks) in fasting diabetics taking glibenclamide 20 mg/day in a randomized, double-blind, placebo-controlled study caused a greater fall in blood glucose concentrations than saline and increased counter-regulatory hormone concentrations (137).

Clarithromycin

Two men aged 82 and 72 years with impaired renal function and taking glibenclamide 5 mg/day and glipizide 15 mg/day, respectively, became comatose due to hypoglycemia within 48 hours of starting to take clarithromycin (138). Clarithromycin inhibits cytochrome CYP3A4. It should be used carefully in patients with diabetes and reduced renal function taking oral drugs.

Diltiazem

The interaction of tolbutamide with diltiazem has been studied in eight healthy men (139). Tolbutamide had no

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effect on diltiazem, but diltiazem increased the AUC of tolbutamide by 10% without an effect on blood glucose concentrations.

Hydroxychloroquine

The addition of hydroxychloroquine to sulfonylureas has been investigated in a placebo-controlled study in 125 adipose patients whose diabetes was not well enough controlled with a sulfonylurea alone (140). During the first six months HbA_{1c} was significantly reduced by 1.02%. There were no significant differences in adverse effects, but those who took hydroxychloroquine had a greater incidence of minor corneal changes.

Rifampicin

Reduced efficacy of gliclazide has been attributed to induction of CYP2C9 by rifampicin (141).

- A 65-year-old man who had taken gliclazide 80 mg/day for 2 years took rifampicin for an infection with *Mycobacterium gordonae*, after which the dose of gliclazide had to be increased to 120 mg/day and later to 160 mg/day. After 75 days of combined therapy, gliclazide 80 mg/day gave a plasma concentration of 1.4 μg/ml; 7 months after stopping rifampicin it increased to 4.7 μg/ml. Gliclazide was then reduced to 80 mg/day.

It is important to check the blood glucose concentration if rifampicin is given in combination with oral hypoglycemic drugs.

Sulfonamides

Tolbutamide is mainly metabolized by CYP2C9, which also has a role in the metabolism of sulfonamides. Of various sulfonamides, sulfaphenazole had the largest inhibitory effect on the metabolism of tolbutamide in vitro (142). This gives a theoretical basis for being careful when tolbutamide and sulfonamides are co-administered.

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Sulindac

See also Non-steroidal anti-inflammatory drugs

General Information

There is still no firm evidence that by acting through an active metabolite, sulindac has any distinct advantage over other members of the group of NSAIDs that are

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related to indometacin. However, its good tolerance in elderly patients has been stressed (1). Its pattern of adverse effects is similar to that of indometacin (2), with an incidence ranging from 17 (3) to 50% (4). Sulindac causes fewer gastrointestinal adverse effects than aspirin, but in some studies the incidence equalled that of ibuprofen (5), fenoprofen (6), and indometacin (7).

Organs and Systems

Cardiovascular

Several cardiac abnormalities have been reported, including congestive heart failure, dysrhythmias, and palpitation (8).

Respiratory

Pulmonary infiltrates were described in a woman with osteoarthritis who had been taking sulindac for 6 months (9).

Nervous system

Adverse effects on the nervous system were found in 2.5–6.5% of patients in one study (4). Dizziness, drowsiness and headache, somnolence, vertigo, insomnia, and blurred vision, that is all adverse effects described with indometacin, have been observed. Acute reversible encephalopathy with rash and fever has been described.

Like other NSAIDs, sulindac can cause aseptic meningitis in patients with systemic lupus erythematosus (SEDA-7, 109). Recurrent aseptic meningitis, described in a patient with no underlying connective tissue disease who had tolerated other NSAIDs, suggested immunological hypersensitivity to sulindac (10).

Psychological, psychiatric

Psychiatric symptoms, bizarre behavior, and paranoia have been attributed to sulindac (11).

Electrolyte balance

The risk of severe hyperkalemia with sulindac has been documented in a series of four cases (12).

Hematologic

Agranulocytosis (probably due to toxicity rather than hypersusceptibility) can be caused by sulindac (13), as can bone marrow aplasia (14) and severe thrombocytopenia (15,16), which may be the consequence of autoimmune platelet destruction in the presence of sulindac or its metabolite (SEDA-7, 109). Immune-mediated hemolytic anemia with a positive direct antiglobulin test has been reported (SEDA-18, 103).

Aplastic anemia in a woman with osteoarthritis taking sulindac relapsed 3 years later during therapy with fenbufen, suggesting that extreme caution should be exercised before giving NSAIDs to a patient with a history of NSAID-related aplastic anemia (17).

Gastrointestinal

Sulindac can cause all of the gastrointestinal adverse effects that are associated with indometacin, from dyspepsia to peptic ulcer. Nausea and abdominal pain are the most frequent, followed by constipation (18). Surprisingly, a study in healthy volunteers showed no gastroscopic mucosal damage after 7 days (19). This recalls past papers showing a lack of mucosal damage in short-term therapy, even with NSAIDs known to be gastrotoxic. A giant esophageal ulcer has been described (20). A preterm neonate developed fatal hemorrhagic gastritis with oral sulindac (21).

Ulcers in an ileal pouch with chronic bleeding have been described (22).

Sulindac reduces the number and size of rectal and colon polyps (23) and colon-mucosal synthesis of prostaglandin E_2 and 6-keto-prostaglandin $F_{1\alpha}$ is markedly reduced in patients taking sulindac. As this occurs concomitantly with the regression of polyps, it supports the hypothesis that prostaglandins are implicated in the regulation of colonic polyp growth (24). These observations have been confirmed in two other studies. Low-dose rectal sulindac produced complete adenoma remission in 87% of 15 colectomized patients with familial adenomatous polyposis. Polyp number and size fell significantly in 22 patients who took sulindac 150 mg bd for 3 months (25). After rectal administration of sulindac two patients had histologically proven mild gastritis (26).

Liver

Sulindac can cause toxic hepatitis, and several cases, some with positive rechallenge, have been described (27,28). A retrospective cohort study with secondary case-control analysis suggested that sulindac has a higher incidence of acute liver damage than all other NSAIDs, although the calculated risk is very low (27 per 100 000 prescriptions) (29). Liver function impairment is generally mild and reversible. Analysis of spontaneous reports to the FDA and the Danish Committee on ADRs (SEDA-18, 103) has confirmed these data.

Abdominal pain, nausea, high fever with chills, icterus, high liver enzyme activities, and hepatomegaly are characteristic and are probably caused by hypersensitivity. The occurrence of fever, rash, and/or eosinophilia in 35–55% of patients seems to confirm a hypersensitivity mechanism (SEDA-18, 103).

Cholestatic jaundice (30) and acute cholangitis in combination with acute pancreatitis (SEDA-13, 79) have been described.

Pancreas

There are several reports of pancreatitis associated with sulindac (SEDA-4, 66) (SEDA-7, 109). Symptoms resembling acute pancreatitis appeared after 3–90 days. Rechallenge was positive in one case (31). Acute cholangitis in combination with acute pancreatitis has been described (SEDA-13, 79).

Urinary tract

Sulindac may be less likely to cause renal toxicity than other NSAIDs (32), at least when it is used in low dosages, but there is some disagreement on this point (33–35), and five cases of nephrotic syndrome and renal insufficiency have been described (36,37).

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Analysis of small renal and biliary stones has shown that sulindac or its metabolite was present in the material (SEDA-15, 99), and the labeling of sulindac was revised in 1989 to warn physicians of this phenomenon. However, despite the presence of sulindac or its metabolites in some renal stones, patients taking long-term sulindac are not at risk of an increased incidence of renal stone formation compared with those taking other NSAIDs (38).

Skin

The Stevens–Johnson syndrome has been reported in women who all recovered after the drug was withdrawn and corticosteroids given (SEDA-6, 95). Toxic epidermal necrolysis has also been reported (39–41).

A reaction like lupus pernio, with purple discoloration, swelling, red papules, and desquamation of the distal parts of several toes, which resolved after drug suspension and recurred after resumption, has been observed (42), as have subcutaneous fat necrosis (SEDA-11, 92), and fixed drug reaction (SEDA-12, 84).

Immunologic

Several types of proven or suspected hypersensitivity have already been mentioned, for example in connection with the liver, but the exact mechanism of a particular adverse effect has not always been clear. One case of fever, pharyngitis, cervical lymphadenopathy, leukopenia, liver abnormalities, proteinuria, pulmonary infiltrates, and abdominal pain has been described. Another patient who previously took sulindac without problems developed pruritus, dyspnea, perioral edema, and lethargy after taking a single dose of sulindac 150 mg.

Pneumonitis is probably part of a general hypersensitivity reaction (SEDA-6, 94) (9,43).

An anaphylactic reaction has been described (44). Sulindac is also thought to have been responsible for a severe multisystem reaction (possibly again anaphylactic) involving the cardiovascular, hepatic, pulmonary, and hematological systems in a patient with quiescent systemic lupus erythematosus (45).

Second-Generation Effects

Fetotoxicity

The use of oral sulindac for closure of patent ductus arteriosus has been evaluated in a prospective comparison with intravenous indometacin. Sulindac promoted ductal constriction without compromising renal function in preterm infants, but its use was associated with severe gastrointestinal complications (46).

Susceptibility Factors

Patients with sodium depletion are at risk of developing hyponatremia with all NSAIDs. Sulindac also provoked hyponatremia in an elderly patient taking a salt-restricted diet (47).

Drug Administration

Drug overdose

Agranulocytosis of short duration was described after an overdose of sulindac 12 g (48). Eight cases of sulindac overdose have been reported to the UK National Poisons Information Service; all the patients remained asymptomatic (SEDA-9, 89).

Drug–Drug Interactions

Furosemide

Data on sulindac inhibition of the diuretic effect of furosemide are contradictory (49).

Lithium

Unlike other NSAIDs, sulindac does not seem to interact with lithium (SEDA-10, 82). However, in one case it may have increased serum lithium concentrations (50).

Propranolol

Like indometacin, sulindac interacted with propranolol and a thiazide diuretic in a hypertensive patient (SEDA-6, 95).

Thiazide diuretics

Like indometacin, sulindac interacted with propranolol and a thiazide diuretic in a hypertensive patient (SEDA-6, 95).

Topical dimethylsulfoxide

Two cases of peripheral neuropathy attributed to a combination of oral sulindac and topical dimethylsulfoxide have been reported (SEDA-9, 89).

Warfarin

Potentiation of warfarin effects by sulindac has been reported (51).

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Sulmazole

See also Phosphodiesterase type III, selective inhibitors of

General Information

Sulmazole is an inhibitor of phosphodiesterase type III.

Sulmazole commonly causes adverse gastrointestinal effects; dose-related anorexia, nausea, and vomiting have been reported in about 50% of patients given an intravenous infusion (1,2) and also after single oral doses (3). Cardiac dysrhythmias, mostly ventricular, have been reported occasionally with sulmazole (4). Other reported adverse effects in small numbers of patients include headache (1), temporary visual disturbances (2,5), discoloration of the urine (attributed to a metabolite) (2,6), and a small reduction in platelet count (1).

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Sulpiride and levosulpiride

General Information

Sulpiride and its levorotatory isomer levosulpiride are dopamine receptor antagonists. The pharmacology, efficacy, and tolerability of levosulpiride for dyspepsia and emesis have been reviewed (1).

Levosulpiride has been evaluated in 15 double-blind, randomized trials in patients with dyspepsia (1818 patients in all, of whom 676 were treated with levosulpiride) and in 11 trials in patients with emesis (718 patients in all, of whom 383 were treated with levosulpiride) (1). Levosulpiride was effective in the treatment of dyspepsia and emesis. The incidence of adverse effects was 11% in 840 patients with dyspepsia. Most of them were mild and resulted in treatment withdrawal in only 0.9% of cases. The common adverse effects were drowsiness, breast tenderness, and hoarseness.

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Sulprostone

See also Prostaglandins

General Information

Sulprostone is a synthetic prostaglandin analogue of PGE_2 used for inducing uterine contraction.

In large series, sulprostone has had good tolerability with a very low complication rate. The most severe complication is myocardial infarction secondary to coronary spasm, with a frequency of one in 20 000, usually in smokers and women over 35 years of age with cardiovascular disease (SEDA-23, 436).

Organs and Systems

Cardiovascular

Several experimental studies have provided support for the hypothesis that coronary spasm plays a major role in the pathophysiology of myocardial infarction during the administration of sulprostone. However, the possibility of myocardial infarction is not mentioned in the product information.

- Two cases of myocardial infarction (one fatal) have been reported in patients receiving sulprostone with mifepristone (1,2).
- Myocardial infarction has been reported in a woman aged 35 years with normal coronary arteries and good left ventricular function (3).
- A 30-year-old woman developed uterine atony and bleeding after induced abortion because of fetal death at 17 weeks of gestation (4). Sulprostone was given intravenously at a rate of 500 micrograms/hour. When additional sulprostone was injected into the uterine cervix, the patient sustained a myocardial infarction, with ventricular fibrillation and cardiocirculatory arrest, most probably due to coronary artery spasm. She was resuscitated and recovered completely.

Sulprostone should be used with care, particularly in patients with cardiac risk factors, and only in settings equipped to manage complications.

Cardiac dysrhythmias have been reported after the administration of misoprostol.

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- A 38-year-old woman developed complete heart block, ventricular fibrillation, and subsequent asystole about 7 minutes after intravenous sulprostone 30 micrograms over 5 minutes, after she had previously been given a total dose of intramyometrial sulprostone 500 micrograms at seven different points for postpartum hemorrhage after cesarean section (5).

The time-course suggested that the most likely cause of the arrest was the intravenous sulprostone. Contributory causes may have been hemorrhagic shock, electrolyte abnormalities, and hypothermia (from massive blood transfusion).

- Cardiac arrest occurred in a 39-year-old woman 3.5 hours after the administration of sulprostone 250 micrograms directly into the uterine wall for postpartum hemorrhage after manual removal of the placenta (6). She had specific contraindications to sulprostone, as formulated by the French authorities: age over 35 years, heavy cigarette smoking, and cardiovascular risk factors.

In the Netherlands, sulprostone is registered for intravenous administration only. The authors strongly advised against administration directly into the uterine wall.

Nervous system

Seizures have been described during pregnancy termination induced by sulprostone (7).

Liver

Sulprostone has been associated with minor abnormalities of liver function (8).

Urinary tract

Sulprostone has been associated with minor abnormalities of kidney function (8).

Reproductive system

Sulprostone can cause rupture of the uterine cervix (9).

- A 43-year-old woman, who had previously had a first trimester miscarriage that required evacuation of the uterus and a normal vaginal delivery at term 4 years before, was admitted for an abortion at 16 weeks. Ripening of the cervix was started with a pessary of gemeprost 1 mg. After 3 hours, when the cervix was 1 cm dilated, an intramuscular injection of sulprostone 500 mg was given. After 30 minutes she developed persistent abdominal pain, which became a continuous cramping and then a shooting pain; a male fetus of 170 g was aborted. There was a 3 cm longitudinal cervical rupture located posteriorly that reached the posterior fornix.

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Sultiame

See also Antiepileptic drugs

General Information

Sultiame is a carbonic anhydrase inhibitor that has been used as an antiepileptic agent in most forms of epilepsy except absence seizures.

In 86 patients there was a good correlation between the weight-related dose of sultiame and the sultiame serum concentration (1). The half-life was 8.7 hours. In children the half-life was shorter and the clearance higher than in adults, and sultiame concentrations in children were lower than in adults, dose for dose.

Sultiame as monotherapy has been studied in a double-blind, placebo-controlled trial for 6 months in 66 children with benign childhood epilepsy with centrotemporal spikes (2). The number of adverse events per day of exposure was similar with sultiame and placebo, and no patient withdrew because of adverse effects.

The most common adverse effects of sultiame are gastrointestinal disturbances, ataxia, dizziness, headache, paresthesia, anorexia, weight loss, sedation, behavioral disorders, and metabolic acidosis (SEDA-21, 74) (3). There have been rare reports of neuropathy and acute tubular necrosis (3).

Organs and Systems

Psychological, psychiatric

- A 9-year-old boy with rolandic epilepsy developed impaired vigilance, depressed mood, fatigue, loss of drive, and listlessness when given sultiame 5 mg/kg/day

(4). All his symptoms disappeared within a few days of withdrawal.

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Sunscreens, substances used in

General Information

Solar UV rays are classified into three groups: UVA rays have the longest wavelength and account for 90% of the total; UVB rays have higher energy and are the most damaging; UVC rays are filtered out by the ozone layer.

Topical sunscreens

Topical sunscreens are made up of constituents that either absorb or reflect incident radiation; absorbents are organic chemicals, reflectants are inorganic chemicals.

The commonest absorbents are *para*-aminobenzoic acid (PABA) and its derivatives, cinnamates, benzophenones, and salicylates, none of which offers significant protection against UVA. Dibenzoylmethane derivatives and anthranilates, which also work by absorbing radiation, are more effective UVA filters.

Reflectant inorganic components, such as zinc oxide and titanium dioxide, provide significant UVA protection, as well as good UVB protection. However, they are opaque and can leave a visible white film, despite the use of "microfined" particles in most products, and some users find them cosmetically less acceptable.

The Sun Protection Factor (SPF) is the ratio of the amount of UVB radiation that is just enough to produce sunburn on protected skin to the amount that will produce the same effect on unprotected skin. For example, skin protected by a sunscreen with an SPF of 10 should be able to withstand a given intensity of UVB rays for 10 times as long as unprotected skin before burning. As no assessment of UVA protection is included, the SPF should not be used as the basis for recommending a sunscreen to a patient who is sensitive to UVA.

Some products also carry a star rating system to indicate UVA protection, four stars representing the greatest; this rating is not an absolute measure, but indicates UVA protection relative to UVB, and its usefulness is controversial. Objective testing of widely available sunscreen agents has shown UVA protection to be significantly less than for UVB.

People vary in their susceptibility to sunburn, as follows:

I— Always burns, never tans
II— Burns easily, sometimes tans
III— Tans easily, burns rarely
IV— Always tans, never burns

Those who burn easily (types I and II) should be advised to choose a preparation with a high SPF (15 or more) that will provide good protection against UVB and adequate protection against UVA. Darker subjects (skin types III and IV) can safely use sunscreens with a lower SPF (around 10).

General adverse effects

Ultraviolet-absorbent organic sun filters, particularly derivatives of PABA, dibenzoylmethane, and anthranilates, can cause both allergic and photoallergic contact dermatitis. PABA-containing formulations can stain clothing yellow and cause stinging or drying of the skin.

Organs and Systems

Immunologic

Photopatch-testing with sunscreens in Sweden has been reviewed (1). Between 1990 and 1996, 355 patients with suspected photosensitivity were photopatch-tested with seven sunscreens (benzophenone-3 (Eusolex 4360), isopropyldibenzoylmethane (Eusolex 8020), butylmethoydibenzoylmethane (Parsol 1789), octylmethoxycinnamate (Parsol MCX), PABA, phenylbenzimidazole sulfonic acid (Eusolex 232), 4-methylbenzylidene camphor (Eusolex 6300); 2% petrolatum). There were 42 allergic reactions in 28 patients. The most common allergen was benzophenone-3 (Eusolex 4360), with 15 photocontact and one contact allergic reaction, followed by eight photocontact and four allergic contact reactions to isopropyl dibenzoylmethane (Eusolex 8020). In six cases, photocontact reactions were due to butylmethoxydibenzoylmethane (Parsol 1789). Phenylbenzimidazole sulfonic acid (Eusolex 232) caused two cases of photocontact allergy, and benzophenone-3 caused contact urticaria in one patient (1). There was a similar frequency of photocontact dermatitis to Eusolex 4360, Eusolex 8020, and Parsol 1789 in an Italian study, in which nine of 36 patients had positive reactions when photopatch-tested with sunscreens (UVA 10 J/m^2) (2).

In 19 patients with positive photopatch tests to sunscreens among all the patients that were photopatch-tested between 1992 and 1999 (total not stated) there were 21 positive photopatch tests to sunscreen agents (3). Nine patients reacted to oxybenzone, eight to butylmethoxydibenzoylmethane, three to methoxycinnamate, and one to benzophenone. There were no reactions to *para*-aminobenzoic acid (PABA), reflecting the increased use of PABA-free sunscreens. Six patients also had positive patch tests to components of the

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sunscreen base, such as fragrances, which can complicate the diagnosis.

Oxybenzone is the most frequently used benzophenone in sunscreens, estimated to be present in 20–30% of commercial products. Phototoxicity and allergic contact dermatitis have been described, but reports of immediate-type hypersensitivity are scarce.

- A 22-year-old woman with a history of atopy had anaphylaxis 10 minutes after widespread application of an oxybenzone-containing sunscreen (4). Blinded patch tests with the sunscreen and its ingredients yielded wheal and flare reactions after 15 minutes to the sunscreen and to oxybenzone. Some days before skin testing the woman had had contact urticaria on the face after kissing a friend who had applied the same sunscreen.

A positive patch test to polyvinylpyrrolidone/eicosene (10% in petrolatum on days 2 and 4) was found in a patient who had used a sun block (5).

Photo-induced contact urticaria to benzophenone-3 and benzophenone-10, possibly in combination with delayed hypersensitivity, has been described (6). Urticaria occurred within minutes of UVA irradiation (10 J), 24 hours after the application of the benzophenones.

Octyl triazone is a UVB absorber structurally unrelated to the benzophenones. Photocontact allergy to this agent in a sunscreen has been described (7).

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Suprofen

See also Non-steroidal anti-inflammatory drugs

General Information

Suprofen, alpha-methyl-4-(2-thienylcarbonyl)-phenylacetic acid, was specifically promoted as a non-narcotic analgesic for many painful conditions, and was withdrawn from the market worldwide in 1987. It caused an unusual clinical syndrome of acute flank pain and nephrotoxicity (SEDA-12, 89). It is still available as a 1% ointment in some countries.

Organs and Systems

Urinary tract

The pathogenesis of suprofen nephrotoxicity in young healthy volunteers involved a transient reduction in renal plasma flow and glomerular filtration rate, possibly due to intratubular precipitation of uric acid (1).

Skin

Suprofen ointment can cause photodermatitis (SEDA-17, 113).

Susceptibility Factors

A case-control study identified as susceptibility factors for adverse effects of suprofen male sex, hay fever and asthma, exercise, and alcohol consumption (2).

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Suramin

General Information

Suramin is a trypanocide that has been used in the treatment of African trypanosomiasis and onchocerciasis, and has been studied in AIDS (SEDA-10, 277) (SEDA-15, 335). However, the high doses that are required for a worthwhile effect are extraordinarily toxic. It is particularly likely to cause adverse effects in the malnourished and has therefore largely been abandoned for the treatment of trypanosomiasis and onchocerciasis, but it still seems uniquely capable of killing the adult onchocerciasis worm, although results are sometimes incomplete even in that respect (SEDA-20, 283).

Suramin is mainly used now in the treatment of hormone-refractory prostate cancer, in which it has shown some antitumor effect, although accompanied by extensive and sometimes severe adverse effects (1), and in the treatment of high-grade glioma. Since it suppresses adrenocortical function it is usually given in conjunction with glucocorticoids. The concomitant use of glucocorticoids and anti-androgen withdrawal usually makes it difficult to establish the true response to suramin.

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Observational studies

AIDS

For a time, unsuccessful attempts were made to treat AIDS with suramin (2), because of its proven ability to impair the in vitro infectivity (and inhibit the cytopathic effect) of human T cell lymphotropic virus type III (HTLV-III) or lymphadenopathy-associated virus (LAV). However, it is no longer used for this indication. Its adverse effects were more severe and numerous than in its traditional field of use: two-thirds of patients had malaise, fever, and raised transaminases, and a quarter had adrenal insufficiency. Erythematous drug eruptions (particularly on sun-exposed surfaces) were common; some patients had a burning sensation of the skin, particularly on the limbs. The most common laboratory abnormalities were proteinuria, microscopic pyuria, trace hemoglobinuria, and occasional granular casts. There were rises in hepatic transaminase activities in some patients, usually during the second and third weeks, and others had eosinophilia (maximum 14%) during a drug eruption. There was a high incidence of keratopathy (SEDA-14, 263).

Hormone-refractory prostate cancer

Much work relating to the use of suramin in prostatic cancer involves drug combinations, including aminoglutethimide, epirubicin, and hydrocortisone, with or without androgen deprivation, and in these studies it is hardly possible to determine which drug was responsible for a given adverse effect.

The adverse effects of suramin that were reported in a group of 69 patients with hormone-refractory prostate cancer were anorexia (19%), malaise and fatigue (40%), paresthesia (10%), weakness (9%), and skin rash (6%). In another group of patients there were higher frequencies of adverse effects: fatigue occurred in 70% and neuropathy in 16%. Hematological abnormalities occurred often, but were mostly mild and consisted of neutropenia (30%), anemia (74%), thrombocytopenia (26%), and coagulopathy (30%). Other common adverse effects have included uremia (21%), increased serum transaminase activities (19%), nausea and vomiting (30%), constipation (9%), edema (33%), dysrhythmias (7%), mild hyperglycemia (86%), and rash (60%) (SEDA-20, 283).

In 81 patients intravenous suramin (peak plasma concentration 300 μg/ml trough concentration 175 μg/ml) combined with aminoglutethimide 250 mg qds in patients with progressive androgen-refractory prostate cancer after antiandrogen treatment had been withdrawn, effectiveness was limited, whereas most adverse effects were attributed to suramin (3). There were 38 episodes of grade 3 and 4 toxic effects in 29 patients. Severe thrombocytopenia occurred in four patients. There were four episodes of atrial fibrillation. One patient developed uremia which required dialysis. One patient developed grade 3 neurosensory changes, but none had neuromotor changes. There was one episode of grade 4 rash, which was probably attributable to aminoglutethimide, consisting of diffuse erythematous exfoliating papules over the chest, back, arms, and face. All adverse effects were reversible.

The efficacy and adverse effects of treatment with suramin for hormone-refractory prostate cancer have been evaluated in 27 patients (4). The treatment regimen consisted of a loading phase, targeted to reach suramin serum concentrations of 180–250 μg/ml using a dose of 1.4 g/m^2 at 3-day intervals. Constant suramin concentrations were obtained with a dose of 0.5–1 g/m^2 every 7–10 days. Six patients did not complete the suramin loading phase because of adverse effects and were withdrawn. About one-third of the assessable patients had a more than 50% reduction in prostate specific antigen and/or serum alkaline phosphatase. Two of these also had a reduction in metastases on bone scan. Another 48% of the patients had unchanged prostate specific antigen or serum alkaline phosphatase during treatment with suramin, suggesting stable disease. The mean survival time was 41 weeks. Responders had a survival of 70 weeks compared with 12 weeks among non-responders. However, the adverse effects were substantial. The most common adverse effects were renal impairment (18 patients), 10 of whom had a mild increase in serum creatinine and seven had a moderate increase. One patient died of multiorgan failure, including renal shutdown. Suramin treatment was interrupted for 7–14 days when the creatinine clearance was under 40 ml/minute, which resulted in improvement in renal function. A sensimotor polyneuropathy occurred in 18 patients and typically presented as paresthesia involving the limbs, combined with reduced nerve conducting velocity. Mild and moderate sensorimotor polyneuropathy occurred in 14 patients. Severe polyneuropathy occurred in two cases and led to the withdrawal of suramin. These effects were only partially reversible. Eleven patients had no neurotoxic symptoms. Allergic rashes occurred in 30% of patients and consisted of a moderate, diffuse, morbilliform rash during the loading phase of suramin treatment, usually disappearing within a few days without further therapy. Two patients with more severe and prolonged rashes were treated with high-dose corticosteroids with a beneficial effect. Hematological toxicity consisted of anemia in 22% of the patients, who all needed blood transfusions, leukopenia in 15%, of whom one with a severe leukopenia was successfully treated by granulocyte-macrophage colony stimulating factor, and thrombocytopenia, which occurred in 15% of patients and led to spontaneous bleeding in two. The platelet count returned to normal in both cases after the withdrawal of suramin. Vortex keratopathy occurred in 15% of the patients. Corneal changes were always minimal and vision was not affected. One patient had a retinal bleed, which led to withdrawal. Severe infections occurred in 26% of the patients, and also led to the withdrawal of suramin and required intravenous antibiotics. These results have further confirmed that suramin has a limited but statistically significant effect in the treatment of hormone-refractory prostate cancer. Although the severity of adverse effects were somewhat less than in previous studies they were still substantial. The toxicity of suramin seems to be closely related to the cumulative dose, peak concentration, and treatment regimen, and toxicity may be reduced by reducing daily doses and giving additional treatment-free intervals.

Suramin has been combined with epirubicin in 26 patients with hormone-refractory prostate cancer (5). No additional therapeutic effect was found compared with

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suramin or epirubicin alone. Suramin was given in an initial daily dose of 350 mg/m^2, with weekly infusions thereafter, targeted to maintain suramin plasma concentrations at 200–250 μg/ml for a maximum of 6 months. Cortisone acetate was added after 4 weeks in order to prevent adrenal insufficiency. Epirubicin was given as a weekly intravenous bolus from the start, also for a maximum of 6 months. The median duration of therapy with suramin and epirubicin was 9 (2–29) weeks. The toxic effects of this combined treatment included grade 1–2 nausea and vomiting (54%), fatigue (54%), anorexia (58%), stomatitis (52%), diarrhea (8%), mild rash (11%), neutropenia, usually mild (65%), low-grade fever (26%), mild increases in serum creatinine concentrations (27%), proteinuria (58%), and peripheral neurotoxicity (mild 23%, severe 4%); alopecia was caused by the epirubicin in 58%.

The use of suramin plus hydrocortisone and androgen deprivation and the use of multiple courses of suramin have been assessed in 59 patients with newly diagnosed metastatic prostate cancer (6). Suramin (doses aimed at plasma concentrations between a trough of 150 μg/ml and a peak of 250 μg/ml) was given in a 78-day fixed dosage schedule (one cycle) and suramin treatment cycles were repeated every 6 months to a total of four cycles. There was significant broad-spectrum toxicity throughout the study, leading to withdrawal of treatment in 33 patients. Cardiovascular events (dysrhythmias, hypotension, and congestive heart failure), neurotoxic effects, and respiratory effects were more frequent than expected. In consequence, repeated courses of suramin could be given in a minority of cases only. The authors felt that in the light of the relatively non-toxic palliation achieved with standard hormonal therapy, suramin in this dosage schedule has only limited use in patients with newly diagnosed metastatic prostate cancer.

The effects of fixed-dose suramin plus hydrocortisone have been studied in 50 patients with hormone-refractory prostate cancer (7). Suramin was initially given as a 30-minute test infusion of 200 mg. In the absence of allergic reactions, additional 24-hour intravenous infusions of 500 mg/m^2 were given daily for the next 5 days. Thereafter, 2-hour intravenous infusions (350 mg/m^2) were given weekly on an outpatient basis for 12 weeks or until disease progression. The median duration of response was 16 weeks and the median time to disease progression 13 weeks. Fatigue and lymphopenia were the most commonly reported adverse effects, in 27 patients (54%) and 39 patients (78%) respectively. Skin rash occurred in 12 patients (24%). Suramin was withdrawn in three patients because of acute renal insufficiency ($n = 2$) and Stevens–Johnson syndrome ($n = 1$).

In a randomized study in 390 patients suramin has been given in a fixed low dose (3.192 g/m^2), intermediate dose (5.320 g/m^2), or high dose (7.661 g/m^2) to determine whether its efficacy and toxicity in the treatment of patients with hormone-refractory prostate cancer is dose-dependent (8). There was no clear dose–response relation for survival or progression-free survival, but toxicity increased especially with the higher dose. There were neurological adverse effects in 40% of the patients and cardiac adverse effects in 15%. This raises questions about the usefulness of suramin, particularly in high doses, in advanced prostate cancer. However, in another phase I study of suramin with once- or twice-monthly dosing in patients with advanced cancer, suramin was relatively safely administered without using plasma concentrations to guide dosing (9). Dose-limiting toxic effects included fatigue, neuropathy, anorexia, and renal toxicity. Diffuse colitis, erythema multiforme, and hemolytic anemia were reported as unusual effects.

High-grade glioma

The efficacy, toxicity, and pharmacology of suramin have been studied in 12 patients with recurrent or progressive recurrent high-grade gliomas aged 26–67 years (10). Suramin was given in doses similar to those used in patients with hormone-refractory prostate cancer. Treatment-related adverse effects were usually mild and reversible. Three patients developed transient grade 3–4 toxicity (leukopenia, a rise in serum creatinine, and diarrhea). There was no coagulopathy or central nervous system bleeding. All patients reached target suramin concentrations. The pharmacology of suramin was not affected by anticonvulsant therapy. Median time to progression was 55 days (range 17–242) and median survival was 191 days (range 42–811). There were no partial or complete remissions at 12 weeks. However, the clinical outcome in three patients suggested that effect of suramin may be delayed. One patient who progressed after 12 weeks had a subsequent marked reduction in tumor size and maintained an excellent partial response for over 2 years without other therapy. The two others had disease stabilization and lived for 16 and 27 months respectively. Based on these observations, suramin and radiotherapy are now being used concurrently in patients with newly diagnosed glioblastoma multiforme to study survival as the primary outcome.

Renal cell carcinoma

Suramin was not effective in one phase II study in advanced renal cell carcinoma, in which it was given in a fixed dose plus hydrocortisone to 22 patients (19 men, three women, aged 30–74 years) (11). Three patients had grade 4 toxicity (hypersensitivity, urethral obstruction, hypotension, and neutropenic sepsis). Eleven developed grade 3 toxicity, mainly abdominal pain, anemia, diarrhea, erythema, dyspnea, fatigue, and fever.

Placebo-controlled studies

The antitumor effect of suramin has been evaluated in a prospective randomized trial in 458 patients with hormone-refractory prostate cancer and significant opioid analgesic-dependent pain (12). Reduction of pain and opioid requirements served as surrogates for tumor responsiveness. The patients were given either suramin (aiming at sustained plasma concentrations of 100–300 μg/ml) plus hydrocortisone (40 mg/day) or placebo plus hydrocortisone. Patients treated with suramin plus hydrocortisone had greater reductions in combined pain and opioid analgesic intake. Suramin did not reduce the quality of life or performance status. However, overall survival was similar. Most of the adverse events were mild or moderate and were easily managed medically.

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Frequent adverse effects of suramin were rash, chills, fever, and taste disturbance. In contrast to the results of earlier studies, in which different suramin dosage regimens were used, neurological, renal, hepatic, and coagulation abnormalities were rare.

Organs and Systems

Nervous system

The neurological adverse effects of suramin have been reviewed in the context of a broad review of neuropathies associated with malignancy and chemotherapy (13).

Neurotoxicity is a dose-limiting adverse effect of suramin and there are two distinct types of neuropathy: a mild, length-dependent, axonal polyneuropathy, and a more serious subacute demyelinating, Guillain–Barré-like polyneuropathy. The reported incidence of neuropathy is 25–90% with a mean of about 50%. Various neuropathies were noted in four of 38 patients infused with suramin for various malignancies (14).

The milder axonal polyneuropathy is the most common neurological adverse effect of suramin and causes distal paresthesia, reduced pain and vibration sensation in the feet, weak toe extensors, and absent ankle jerks; this neuropathy is largely reversible. Milder neuropathies occurred in 50–70% of patients with plasma concentrations below 300 μg/ml, and severe motor neuropathy was rare in this category of patients.

The more severe demyelinating neuropathies appear to be dose-related and occur when peak suramin plasma concentrations are maintained above 350 μg/ml; the effective serum concentration in cancers is about 250 μg/ml (SEDA-20, 283) (15,16). A Guillain–Barré-like polyradiculoneuropathy occurs in 10–20% of patients after 1–5 months of treatment, with a maximum at 2–9 weeks after the start of treatment. The first symptoms are distal limb and or facial paresthesia, followed by diffuse, symmetrical, proximal weakness and areflexia. About 25% of these patients eventually require ventilation. The CSF protein content may be raised.

In 24 patients with hormone-refractory prostate cancer given suramin twice weekly intravenously targeted to reach plasma concentrations of 50–100, 101–150, 151–200, or 201–250 μg/ml plus doxorubicin, fatigue occurred in 18 and was dose-limiting in two (17). Eight developed neurological symptoms, of whom three, all receiving the highest dose, developed grade 3 toxicity. There were five cases of neuropathies. Two patients had evidence of a demyelinating neuropathy, one of whom developed a Guillain–Barré-like syndrome and inflammatory myopathy. A further patient had a mixed axonal and demyelinating peripheral neuropathy. Two patients developed a motor neuropathy that exacerbated pre-existing neurological defects. Other frequent adverse events were proteinuria, leukopenia, and alopecia. However, the respective roles of suramin and doxorubicin in causing these adverse effects were uncertain.

Evidence of an underlying distal axonal polyneuropathy can be detected by electromyelography (18). Electroencephalography shows slow motor conduction velocities and electromyography shows reduced recruitment in both proximal and distal muscles. In the more severe cases denervation emerges. Sural nerve biopsies have shown a reduced density of the large and small myelinated fibers, occasional axonal degeneration, and demyelination. Epineural and endoneural mononuclear inflammatory cell infiltrates are sometimes seen. After withdrawal of treatment symptoms may deteriorate further for several weeks with recovery, sometimes incomplete, after 1–2 months.

The precise mechanism of the neurotoxicity of suramin is unknown, although both inhibition of the effects of nerve growth factors and a possible immune-mediated effect, consistent with the many immunomodulating effects, have been suggested. In a recent experimental study in dorsal root ganglion cell cultures suramin disrupted the transport and metabolism of glycolipids, with accumulation of the GM1 ganglioside and ceramide, leading to cell death (19).

Sensory systems

Photophobia, lacrimation, and palpebral edema are recognized late effects of suramin, and there is evidence of a late optic atrophy of suramin (20).

High-dose treatments for cancers seem to produce changes in most patients consistent with a vortex keratopathy (SEDA-21, 320), although it can be entirely symptomless. Other cases have a hyperoptic refractory shift leading to blurred vision. Of 114 patients, 19 developed ocular symptoms and signs while taking suramin sodium for metastatic cancer of the prostate (21). Of these, 13 developed bilateral corneal epithelial whorl-like deposits, in 10 cases associated with a foreign body sensation and lacrimation. Symptoms in all cases resolved with topical lubricants. Three patients developed asymptomatic corneal deposits. Seven had blurred vision and had a mean hyperopic shift in refractive error of 1.13 (range 0.75–2.00) diopters, which persisted throughout treatment. None of these patients had a reduction in best-corrected visual acuity. At the very least, ophthalmological surveillance is necessary when suramin is used.

Suramin has been used in the treatment of AIDS and adrenal carcinoma, in both of which there was a high incidence of keratopathy (SED-13, 836).

Endocrine

The adrenal glands are sensitive to the toxic effects of suramin; both glucocorticoid and mineralocorticoid functions can be impaired at doses normally used, necessitating replacement therapy (22).

Hematologic

Occasional cases of hemolytic anemia and agranulocytosis have been reported in patients taking suramin (SED-13, 836). Severe neutropenia has been attributed to suramin in six cases (23). Plasma concentrations of platelet-derived growth factor-AB (PDGF-AB) and fibroblast growth factor basic correlated with the time-course of the neutropenia, which was unpredictable and occurred both during and after withdrawal of suramin. Plasma concentrations of suramin and G-CSF did not correlate

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with the neutropenia, but there was a rapid response to G-CSF.

Blood coagulation can be altered by suramin, which causes accumulation of glycosaminoglycans, which have heparin-like properties (24). In patients who had received suramin intravenously for 2 weeks there was inhibition of factors V, VIII, IX, X, XI, and XII, while thrombin, prothrombin, and factor VII were unaffected (25). The inhibition of factor V was virtually irreversible, although the effect of suramin on the other factors is readily reversed by dilution.

In one patient with cancer, immunological complement-mediated destruction of circulating platelets was induced by suramin, demanding urgent treatment (26).

Gastrointestinal

Suramin can cause vomiting (27).

Liver

In three men with severe chronic active hepatitis, suramin treatment prolonged the prothrombin time in all three, caused a rise in bilirubin in two, and may have led to hemorrhage from esophageal varices in one patient and to hepatic encephalopathy in another (28).

Urinary tract

Suramin can cause acute renal failure (29,30).

Skin

Skin effects were prominent in patients treated with the high doses needed in malignancies, including morbilliform rashes in 67%, UV recall in 35%, urticaria in 18%, and keratotic papules in 12% (31). Late reactions include various skin eruptions, hyperesthesia and paresthesia (particularly affecting the palms and soles of the feet); erythema multiforme as part of a generalized skin reaction has been well documented in some individual cases (32) and toxic epidermal necrolysis has been reported (33).

A single dose of intravenous hydrocortisone 200 mg was protective against skin complications in another small group of patients.

Second-Generation Effects

Teratogenicity

Suramin has generally been avoided in pregnancy because its safety is uncertain; it is teratogenic in experimental animals (34–36).

Drug–Drug Interactions

Furosemide

In 26 patients treated with suramin for hormone-refractory prostate cancer, furosemide reduced the total body clearance of suramin by 36% (37). In view of the increased risk of severe adverse effects after treatment with higher plasma concentrations of suramin, it would be prudent to alter dosage schemes in patients treated with both suramin and furosemide.

Warfarin

In 13 men with advanced hormone-refractory prostate cancer the interaction between suramin and warfarin was studied because of potential worries that suramin may affect blood coagulation (38). After initial stabilization to an International Normalized Ratio (INR) of about 2.0 suramin plus hydrocortisone was started, after which warfarin requirements fell by 0.50–0.78 mg/day. The difference did not reach statistical significance. There were no bleeding problems. These results suggest that suramin and warfarin can be safely co-administered, provided that coagulation status is monitored.

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Suriclone

General Information

Suriclone, a cyclopyrrolone analogue of zopiclone, has similar pharmacology to the benzodiazepines, binding close to the same site of the GABA receptor–chloride channel complex. It is effective as an anxiolytic and has the notable advantages of minimal sedation and cognitive toxicity, and milder withdrawal effects than those of diazepam or lorazepam (1). Its withdrawal from further development is a mystery.

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Suxamethonium

See also Neuromuscular blocking drugs

General Information

Suxamethonium consists of two acetylcholine molecules linked together. Initially, it acts like acetylcholine by depolarizing the motor end-plate. However, unlike acetylcholine, which on dissociation from the receptor is immediately destroyed by acetylcholinesterase present in the neuromuscular junction, suxamethonium is hydrolysed by a (pseudo)cholinesterase present in the plasma but not at the neuromuscular junction. Most of an injected dose of suxamethonium is normally destroyed before it reaches the neuromuscular junction. If the activity of plasma cholinesterase in a particular patient is reduced, more of the suxamethonium reaches the neuromuscular junction and its action is proportionately prolonged. The molecules of suxamethonium that reach the acetylcholine receptor sites interact repeatedly with them, producing prolonged depolarization of the motor end-plate, which becomes surrounded by an electrically inactive zone. The end-result is flaccid paralysis. The action of suxamethonium is terminated by diffusion away from the neuromuscular junction. Hydrolysis results in choline and succinylmonocholine, which has a very weak competitive blocking action and is further slowly hydrolysed by plasma cholinesterase to choline and succinic acid.

About 10% of an intravenous dose of suxamethonium is excreted unchanged in the urine with a half-life of 1–2 minutes (1). The half-life is prolonged in patients with pseudocholinesterase deficiency or an abnormal pseudocholinesterase.

The usual adult dose of suxamethonium chloride is 0.5–1.5 mg/kg, which provides clinical relaxation for some 4–9 minutes. However, the normal response is highly variable and relaxation for up to 15 minutes can result from normal doses. Suxamethonium iodide has about two-thirds the potency of the chloride.

General adverse effects

Suxamethonium has several unwanted and potentially dangerous adverse effects. Generalized muscle fasciculations are associated, to a varying degree, with muscle pain, an acute rise in serum potassium, which under certain conditions can result in dysrhythmias and cardiac arrest, raised intraocular and intragastric pressures, and rhabdomyolysis and myoglobinuria with a rare risk of renal insufficiency. Bradycardia and junctional rhythms are relatively common. Normal doses can cause prolonged paralysis (on rare occasions for several hours) in patients with congenital or acquired plasma cholinesterase abnormality or deficiency.

Anaphylactoid reactions have been documented, and signs suggestive of histamine release are not uncommon. These are mostly mild such as flushing of the skin. Occasionally bronchospasm and/or hypotension can lead to circulatory arrest. Suxamethonium is the relaxant most commonly associated with the syndrome of malignant hyperthermia.

Tumor-inducing effects have not been reported.

Tachyphylaxis and resistance

Tachyphylaxis to the neuromuscular blocking effects of suxamethonium is associated with repeated doses. Prolonged exposure of the neuromuscular junction to suxamethonium (resulting from repeated bolus injections or during an infusion of the drug, or as a consequence of delayed hydrolysis subsequent to genetic or acquired plasma cholinesterase deficiency) is accompanied by the development of a phase II block, with non-depolarizing characteristics and a variably prolonged recovery. This depends on both the dose and the duration of exposure to suxamethonium. A cumulative dose of 3–4 mg/kg and an exposure time of 20–30 minutes can be sufficient during halothane anesthesia (2). However, there is wide variation between patients (3), and monitoring of neuromuscular transmission (train-of-four or post-tetanic count) is advisable with cumulative doses greater than 3 mg/kg.

Resistance to suxamethonium has been seen in von Recklinghausen's disease (4) and nemaline myopathy (5).

Organs and Systems

Cardiovascular

Bradycardia and other dysrhythmias are common (80% in some series) and occur after the first and subsequent injections of suxamethonium in infants and children. In adults, these effects are seen more commonly after second or later injections, particularly when the interval between the doses is 2–5 minutes. However, it has been suggested that bradycardia and asystole may now be more frequently seen than previously in adults after a single injection of suxamethonium, as a result of the increased use of fentanyl or the omission of atropine beforehand (6). Nodal rhythm and wandering pacemaker are frequent. The bradycardia is sometimes extreme (asystolic periods of 15–30 seconds duration have been reported). Usually these minor dysrhythmias revert to normal after a few minutes. Halothane can prolong their presence. The incidence of bradycardic asystole is not known, as atropine (the effective therapy) is usually quickly given.

Over the years cardiac arrest in apparently healthy children has occurred unexpectedly, most cases having been attributed to suxamethonium-induced hyperkalemia in patients with previously undetected myopathies (7–17). Several children have died of this complication. A diagnosis of Duchenne dystrophy or another unspecified progressive myopathy was made in 80% of the patients reported to the American Malignant Hyperthermia Registry who were subsequently tested for myopathies (18). Pointing out that hyperkalemia was detected in 72% of the patients from whom blood samples were taken, the authors suggested that calcium, sodium bicarbonate, hyperventilation, and glucose and insulin should be considered for the treatment of anesthesia-related cardiac arrest in children. This is certainly good advice. Standard resuscitative efforts in such cases are often ineffective, as severe hyperkalemia prevents the restoration of a stable cardiac rhythm. It should be stressed that resuscitative efforts should not be stopped until hyperkalemia has been aggressively treated. Excessive doses of adrenaline, calcium, sodium bicarbonate, and glucose/

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insulin may be required. Peritoneal dialysis (19), hemodialysis (20), and cardiopulmonary bypass (21) have been used successfully to treat suxamethonium-induced hyperkalemic cardiac arrest.

Regarding the risk of this rare but life-threatening complication in children with undetected myopathy or muscular dystrophy, it has been suggested that the routine use of suxamethonium in pediatric anesthesia be abandoned. It should be reserved for emergency intubation or when immediate securing of the airway is necessary.

Tachycardia and a rise in blood pressure are occasionally seen. Other supraventricular and ventricular dysrhythmias are much less common. Ventricular fibrillation associated with suxamethonium is usually the result of hyperkalemia, but has also been reported in hypercalcemia (22) and is often seen in the course of malignant hyperthermia. Atropine, especially when given intravenously just before suxamethonium, is the most effective agent for the prevention of dysrhythmias. Hexafluorenium, D-tubocurarine, pancuronium, and other non-depolarizer blockers have also been reported as being effective in prevention. Severe hypotension can occur in patients with anaphylactoid reactions.

On theoretical grounds, suxamethonium, being akin to acetylcholine, should produce effects not only at the neuromuscular junction, but also at autonomic ganglia, at muscarinic receptors, and at postganglionic parasympathetic receptors. However, these other types of cholinoceptors are not so sensitive to its action. Nevertheless, stimulation of sympathetic ganglia has been invoked as being possibly responsible for the tachycardia and rise in blood pressure that sometimes occur transiently after its use. Likewise, stimulation of parasympathetic ganglia or direct stimulation of cardiac muscarinic receptors may be responsible for bradycardia. Differences in resting sympathetic and vagal tone have been said to account for the more frequent occurrence of tachycardia in "vagotonic" adults and bradycardia in "sympathotonic" children. The transient mild rise in blood pressure is possibly the result of the initial fasciculation, inducing an increase in venous return, which may also reflexly result in a slowing of the heart rate. Stimulation of afferent receptors in the carotid sinus has also been claimed to cause reflex bradycardia. Small doses (20–25 mg) are said to convert nodal to sinus rhythm, and larger doses to depress the sinoatrial node and so to cause bradycardia and nodal rhythm. Fasciculation probably produces an increase in afferent discharge from muscle spindles, which may account for the reported arousal pattern on the electroencephalogram; this in turn is postulated as a cause of tachycardia and a rise in blood pressure.

It has been hypothesized that suxamethonium modulates noradrenaline release from postganglionic sympathetic nerve terminals by presynaptic nicotine (+) and muscarinic (−) receptors on these nerve terminals (23). The refractory period of these presynaptic nicotinic receptors is postulated as being longer than that of the muscarinic receptors, which results in a net muscarinic effect (bradycardia) after a second injection of suxamethonium within 4–5 minutes of the first. To explain the occurrence of bradycardia after an initial injection of suxamethonium in young children, it is postulated that sympathetic nerve terminals mature later, so that muscarinic (bradycardic) effects are unopposed by noradrenaline secretion in younger patients.

Some controversial correspondence has followed the report of four cases of fatal cardiac arrest among 150 patients who were given suxamethonium by paramedics in out-of-hospital emergencies (24). The authors suggested that this might militate against suxamethonium-facilitated endotracheal intubation in this setting. Others, however, have argued that there was no evidence for a causal role of suxamethonium in those cases (25). Patients with critical conditions, such as respiratory failure requiring endotracheal intubation, may have a cardiac arrest without being given suxamethonium. Furthermore, undetected esophageal intubation was considered to be an alternative explanation of cardiac arrest. Indeed, when endotracheal intubation is attempted in these often dramatic and stressful circumstances by health-care providers who have no routine experience in this, there may be a high rate of esophageal intubation. In one study 18 of 108 patients who had been intubated by paramedics were found to have the tube in their esophagus (26). So the role of suxamethonium in the above report is questionable. On the other hand, suxamethonium is part of the protocol for emergency intubation in many centers worldwide and suxamethonium-associated cardiac arrest, apart from anecdotal instances, has not been reported to be a relevant problem (27). Suxamethonium may increase the success rate of emergency intubations while reducing the incidence of traumatic intubations (28). Therefore, rapid-sequence intubation with an induction agent such as etomidate and suxamethonium is probably still the technique of choice for airway management in emergencies. Whoever uses this technique must be aware of contraindications to suxamethonium and must have frequent practice in endotracheal intubation.

Respiratory

Apnea of variable duration results from muscle paralysis. The return of spontaneous respiration is normally rapid, but it may be delayed if phase II block develops. This will only be of consequence if it is not detected and spontaneous respiration is permitted before it is adequate. Exacerbation of muscle weakness in Duchenne muscular dystrophy after injection of suxamethonium can lead to delayed respiratory failure postoperatively (29).

Bronchospasm is a feature of about one-third of anaphylactoid reactions to suxamethonium and laryngeal edema can also occur, producing intubation problems (30) or respiratory distress and cyanosis after extubation (31).

Nervous system

An arousal pattern can occur on the electroencephalogram, possibly as a result of increased afferent traffic from muscle spindles. This has been speculated as the cause of perioperative dreaming in children in whom an intermittent-suxamethonium technique has been used during light anesthesia (SEDA-13, 102) (32). Suxamethonium must be used with caution in neurological disease and is better avoided altogether when there is a risk of a dangerous rise in serum potassium. A transient rise in intracranial pressure has been observed after injection of

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suxamethonium, probably as a result of increased cerebral blood volume (33,34). This might be regarded as noxious in patients with intracranial lesions. However, when suxamethonium was given to patients with markedly raised intracranial pressure who received artificial ventilation on the intensive care unit, no adverse effects were observed (35).

Patients with severe head injuries require endotracheal intubation and controlled ventilation. Rapid-sequence intubation using an intravenous anesthetic plus suxamethonium is the standard technique for this, as the patient may have a full stomach. However, suxamethonium has been suggested by some to have a negative effect by causing increased intracranial pressure. The literature on this has been reviewed (36). The authors found only two studies that specifically addressed the effects of suxamethonium on intracranial pressure in patients with head injuries (35,37). In both studies suxamethonium was given to patients who were already being ventilated in the intensive care unit. There were no adverse effects of suxamethonium on intracranial pressure or cerebral perfusion pressure. However, when suxamethonium was given to lightly anesthetized patients undergoing resection of intracranial tumors, there were significant increases in intracranial pressure (38,39). These could be prevented by pretreatment with a small dose of a non-depolarizing muscle relaxant (39). The importance of an adequate level of anesthesia for intubating patients at risk of intracranial hypertension should be stressed. A lightly anesthetized patient will have large increases in intracranial pressure during intubation, no matter which muscle relaxant is used, because of a stress response that includes venous vasoconstriction and a massive increase in central venous pressure, resulting in impaired venous outflow from the cranium and thereby increased intracranial blood volume.

Neuromuscular function

Muscle pain

The depolarization of the motor end-plate receptors produced by suxamethonium (either directly or via repetitive discharge generation by the motor nerve terminals) (40) results in generalized and desynchronized contraction of skeletal muscle fibers. These fasciculations result in aching muscle pain (in up to 90% of patients), most commonly in the neck, pectoral region, shoulders, and back. The pain is most often experienced the day after operation and is worse in ambulatory patients. It is more common in women than in men. Children, elderly patients, athletes, and pregnant women (41) complain less often. Africans also seem to be less susceptible (42).

Mechanism

The cause of the pain is unknown, although there are many hypotheses such as damage to muscle (43,44) resulting from asynchronous contractions of adjacent muscle fibers (45), irreversible damage to muscle spindles (46), potassium flux (47), lactic acid (48), serotonin (49), calcium influx-associated damage to muscle spindles (50), and prostaglandins (51,52). The pain appears not to be related to the extent or intensity of the observed fasciculations.

Prevention

Various preventive measures have been recommended, but none is effective in all cases. One reliable method is the injection of a small non-paralysing dose of a non-depolarizing neuromuscular blocker 2–3 minutes before the injection of suxamethonium (53–57) in preventing fasciculations, but the patient must be carefully observed, since an unexpected degree of paralysis occasionally ensues (SEDA-6, 130).

Other measures, much disputed, include the prior injection of diazepam (58,59), procaine or lidocaine (57), vitamin C, suxamethonium itself (10 mg), and aspirin (51,52). The combined use of atracurium 0.05 mg/kg and lidocaine 1.5 mg/kg reduced the incidence of postoperative myalgia to 5% compared with 75% in controls (57). Thiopental, injected immediately beforehand, is also said to have some effect, as is giving the suxamethonium slowly.

Myotonic reactions

Rarely, on injecting suxamethonium, contracture, instead of the usual relaxation, of skeletal muscles ensues. In denervated muscles the postulated mechanism is direct activation of the contractile mechanism by suxamethonium because of the widespread chemosensitivity of the muscle fiber membranes.

Paradoxical contracture is most often associated with myotonia dystrophica and myotonia congenita. A myotonic reaction has also been reported in a patient with hyperkalemic periodic paralysis (60). Suxamethonium is therefore contraindicated in these conditions, even though normal responses are sometimes seen. Contracture has also been reported as a result of denervation in Pancoast's syndrome and after plexus injuries and, rarely, in patients with amyotrophic lateral sclerosis or multiple sclerosis (61–63).

Failure of relaxation and generalized muscular rigidity after suxamethonium is sometimes also seen in patients who develop the syndrome of malignant hyperthermia. Isolated masseter muscle rigidity can occur after the administration of suxamethonium, being reported particularly in children given both suxamethonium and halothane. Most experts define masseter muscle rigidity as a major increase in masseter muscle tone severe enough to make mouth opening impossible and to prevent laryngoscopy and endotracheal intubation. Referring to the high incidence of positive results with halothane-caffeine contracture testing, some believe that up to 50% of patients with masseter muscle rigidity are susceptible to malignant hyperthermia (64–67). Others are not convinced of such a high degree of correlation (68) and hold that divers other factors are responsible for the majority of cases (69–71). While severe masseter muscle rigidity is rare (72), smaller increases in jaw tension of about 60 seconds duration occur almost invariably after suxamethonium administration (73,74). Such increases in masseter muscle tone can be attenuated by using propofol as an induction agent and by precurarization, that is pretreatment with a small dose of a non-depolarizing muscle relaxant (74) This might be important during rapid sequence induction of anesthesia.

A hypothesis has been offered to explain muscle hyperexcitability in response to suxamethonium (75). Voltage clamp experiments on alpha subunits of human muscle

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sodium channels, heterologously expressed in HEK 293 cells, showed that succinic acid, a metabolite of suxamethonium, shifted steady-state activation in the direction of more negative membrane potentials. The EC_{50} for this effect was 0.39 mmol/l. This might lead to muscle hyperexcitability in vivo. Clearly, it is not currently possible to claim any direct clinical implications of this study, but two facts should be considered. After the administration of a routine dose of suxamethonium, blood concentrations of 0.17 mmol/l have been reported (76) Thus, equimolar concentrations of succinic acid are to be expected, given that cholinesterase activity is not impaired. Moreover, succinic acid is a citric acid cycle intermediate, ubiquitous in body tissues. In conditions of ischemia and hypoxia, tissue and serum concentrations of succinic acid increase up to 0.2 mmol/l (77,78). Thus, the administration of suxamethonium to a hypoxic patient may well lead to succinic acid concentrations that affect muscle sodium channel excitability in vitro.

Rhabdomyolysis

Myoglobinuria (79) and raised serum creatine kinase activity (44) have been reported after suxamethonium and appear to be evidence of muscle damage, probably resulting from fasciculation. Repeated bolus doses of suxamethonium result in higher plasma myoglobin concentrations (80) and creatine kinase activities (44). Myoglobinemia seems to be much more common in children than in adults (SEDA-10, 107) (SEDA-11, 121) (81) and is more marked when halothane is used (82). On occasion, myoglobinuria results in renal insufficiency (83–88).

There is an association between (latent) muscular dystrophy (usually of the Duchenne or Becker type) and the production of rhabdomyolysis by suxamethonium (84,85,89,90). Suxamethonium can cause excessive muscle damage in these patients, as manifested not only by severe myoglobinemia and raised serum creatine kinase activity but also by acute exacerbation of muscle weakness postoperatively (SEDA-11, 121) (7,29,84,91,92). Massive potassium release can result in hyperkalemic cardiac arrest. Such patients may also develop features suggestive of the syndrome of malignant hyperthermia (93,94). Suxamethonium should not be used in patients with Duchenne muscular dystrophy or who have a family history suspect for the condition.

Prolonged paralysis

Prolonged paralysis can result from idiosyncrasy, overdose, or reduced or abnormal plasma cholinesterase activity. There are geographical and racial differences in sensitivity to suxamethonium (SEDA-6, 129) (95,96); some of these differences arise from dietary and other environmental factors and others result from variations in plasma cholinesterase genotypes. Genotypically normal patients may be paralysed by a usual (1 mg/kg) dose of suxamethonium for as short a time as 2 minutes or (rarely) as long as 20 minutes, and the duration in general inversely reflects plasma cholinesterase activity (97).

Prolonged paralysis after suxamethonium has also been reported in von Recklinghausen's disease (98), but resistance to suxamethonium has also been seen (4).

Sensory systems

Shortly after the introduction of suxamethonium it was noted that it can increase intraocular pressure (99), an observation that has subsequently been confirmed in several other studies (100–114). The increase in intraocular pressure occurs promptly after intravenous injection of suxamethonium, peaks at 1–2 minutes, and returns to baseline after 6–10 minutes (102,109). The mean increase is about 4–8 mmHg, with a range of 5–15 mmHg.

Mechanism

Several mechanisms have been suggested to explain the effect of suxamethonium on intraocular pressure. One of the first ideas was to blame fasciculation and contraction of the extraocular muscles of the eye (115). However, a study in humans undergoing enucleation showed that suxamethonium produces an increase in intraocular pressure even after detachment of the extraocular muscles (116). So activity of the extraocular muscles may increase intraocular pressure, but there must be other factors. Observing that suxamethonium administration was almost invariably followed by retraction of the eyeball, some investigators suggested increased tone of intraorbital smooth muscles as a mechanism (117), but in fact there is very little intraorbital extraocular smooth muscle in humans. This idea has therefore not been widely accepted. There appears to be some effect of suxamethonium on the intraocular smooth muscles, as indicated by the observation that there is a rapid rise in anterior chamber thickness and a diminution of lens thickness after suxamethonium administration (118). These changes could be explained by a relaxing effect of suxamethonium on the ciliary muscle, which would in turn result in increased aqueous humor outflow resistance and a consequent increase in intraocular pressure (116). However, this mechanism would not be expected to produce pressure increases of the magnitude observed after suxamethonium injection. A vasodilatory effect on conjunctival vessels has been observed (119), and this has been interpreted as indirect evidence of choroidal vasodilatation (120). On the other hand, an increase in ocular blood flow has not been detected after suxamethonium administration but after subsequent endotracheal intubation (121). In conclusion, there is no satisfactory explanation for the suxamethonium-associated increase in intraocular pressure, but increased tone of extraocular muscles, increased aqueous humor outflow resistance, and increased choroidal blood volume are probably important elements.

Prevention

Many efforts have been made to find a technique to prevent the suxamethonium-associated increase in intraocular pressure. Some attenuation of the pressure response has been demonstrated with defasciculation doses of non-depolarizing muscle relaxants (122), but this could not be reproduced in subsequent studies (100–102,123). The same is true for self-taming, that is

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pretreatment with a small dose of suxamethonium (124,125). Other drugs that have been used with some effect are diazepam (105,126,127), lidocaine (107,114,121,128,129), glyceryl trinitrate (130), nifedipine (131), and beta-blockers (132), but none of these completely prevented increases in intraocular pressure.

The most effective method of attenuating the intraocular pressure response to suxamethonium plus endotracheal intubation is to provide a deep level of anesthesia by using intravenous anesthetics and opiates (133–137). In 60 patients who received thiopental/suxamethonium, propofol/suxamethonium, or propofol/alfentanil/suxamethonium for anesthesia induction, the increase in intraocular pressure after suxamethonium plus endotracheal intubation was completely blocked by propofol plus alfentanil (137). Combining an intravenous anesthetic with a rapid-onset opioid, such as alfentanil, prevents increases in intraocular pressure (137). When the ultra-short-acting opioid remifentanil (1 microgram/kg) was given in combination with propofol (2 mg/kg) and suxamethonium (1 mg/kg) for endotracheal intubation during induction of anesthesia the highest intraocular pressure recorded was 18 mmHg, whereas peak values up to 35 mmHg occurred in the control group without remifentanil (138).

Implications for surgery

A particular problem is the clinical impact of a rise in intraocular pressure during operation in cases of penetrating eye injury, which is usually performed as an emergency, when it is often not clear whether the patient has eaten recently. While it is commonly accepted that anesthesia in these patients should be induced in a rapid-sequence technique, that is by giving an hypnotic and suxamethonium followed rapidly by endotracheal intubation, in order to reduce the risk of pulmonary aspiration of gastric contents, there is considerable controversy about what to do in the case of penetrating eye injuries. As suxamethonium provokes an increase in intraocular pressure in intact eyes, there is concern that its use could result in loss of intraocular contents and damage to the eye if the eyeball is opened. This, however, has not hitherto been observed, either in clinical studies or in animal experiments (139–141). Several experts regard suxamethonium as being appropriate for rapid-sequence intubation in patients with penetrating eye injuries (142–146).

Similarly, there are difficulties in strabismus surgery, which is commonly performed in children, with the goal of correcting the optical axes of the eyes by shortening certain extraocular muscles. The "forced duction test" can be used to differentiate between a paretic muscle and a restrictive force that prevents ocular movement. Suxamethonium, by increasing the tone of the extraocular muscles, can produce considerable alterations in the results of that test, sometimes lasting as long as 20 minutes (147). Suxamethonium should therefore be avoided in strabismus surgery. Furthermore, in a retrospective study there was an increased incidence of masseter muscle rigidity in patients with strabismus (148). A positive halothane-caffeine contracture test was subsequently found in 25% of the adults and 50% of the children in whom masseter rigidity had occurred (64–67). In line with that, there were more patients with strabismus in a group of patients who had experienced an episode of malignant hyperthermia than in the general surgical population in the USA (149). Based on these observations, it has been assumed that patients with strabismus might have an increased risk of malignant hyperthermia (146,150), which has been regarded as another reason for avoiding suxamethonium in strabismus surgery (151). On the other hand, the incidence of strabismus was not different in two groups of patients, with or without a positive halothane–caffeine contracture test (152). In conclusion, there are some indirect clues to an increased risk of malignant hyperthermia in patients with strabismus, but for the time being there is not enough evidence to contraindicate suxamethonium. However, there are reasons for reserving its use for special circumstances, such as rapid-sequence induction in patients with an increased risk of pulmonary aspiration. First, the surgical procedure can be impaired by increased tone in the extraocular muscles. Secondly, patients with strabismus may have a higher risk of suxamethonium-associated masseter muscle rigidity. Thirdly, most patients with strabismus are children, in whom the suxamethonium is best avoided (SEDA-19, 139).

Electrolyte balance

An immediate rise in serum potassium occurs after the administration of suxamethonium. The rise is normally small, 0.5 mmol/l or less (4). However, in some cases it can be larger, and cases of cardiac arrest associated with hyperkalemia have been reported in critically ill patients after prolonged immobilization (153–161). Cardiac arrest also occurred in a patient with wound botulism (162).

- A 28-year-old previously healthy man was admitted with a 4-week history of progressive symmetrical muscle weakness that had started in his neck and descended to both arms and legs. He also complained of diplopia, dysphonia, and dysphagia. On the day of admission, he noted difficulty in breathing. He had a history of intermittent diamorphine abuse, and had been injecting "black tar" heroin subcutaneously for the past month. Several hours after admission he had to be intubated, and was given etomidate 20 mg plus suxamethonium 80 mg. Within 60 seconds he developed a wide complex tachycardia, which degenerated into ventricular fibrillation refractory to electrical countershock and standard resuscitative measures. His serum potassium concentration 10–12 minutes after the onset of cardiocirculatory arrest was 6.8 mmol/l, having been 4.7 mmol/l several hours before. Calcium chloride, sodium bicarbonate, and glucose/insulin were given, and 25 minutes after the arrest began the heart rhythm converted to sinus tachycardia. The electrocardiogram subsequently showed no structural abnormalities. A serological test taken on the day of admission was positive for botulinum toxin type A. He eventually survived without any residual deficits and was discharged from hospital after 63 days.

The authors suggested that suxamethonium should be avoided in patients with suspected botulism and in patients with muscle weakness of unknown origin. Wound botulism had been observed before in drug users

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who have injected black tar heroin (163). Botulinum toxin inhibits presynaptic acetylcholine release, resulting in muscle weakness. In animals chronic administration of botulinum toxin caused an increase in the number of postsynaptic acetylcholine receptors with distribution across the muscle surface (164) and postsynaptic acetylcholine receptors converted into the immature type with prolonged channel opening times (165). With huge numbers of muscle fibers altered in that way, suxamethonium may cause hyperkalemic cardiac arrest by producing massive potassium efflux.

One major concern for anesthetists is suxamethonium-associated hyperkalemia in apparently fit patients without obvious risk factors. Life-threatening hyperkalemia occurred in three Japanese women who underwent cesarean section (166).

- Cardiac arrest occurred in a 34-year-old woman who was given suxamethonium 120 mg. She had been immobilized and treated with high-dose magnesium sulfate and ritodrine for 5 weeks before the event because of preterm uterine contractions. Her preoperative creatine kinase activity was 4050 IU/l. After rapid-sequence induction of anesthesia and injection of suxamethonium she became cyanotic and pulseless and the electrocardiogram showed ventricular fibrillation. The serum potassium concentration after 25 minutes of cardiopulmonary resuscitation, which included the administration of adrenaline, sodium bicarbonate, and calcium chloride, was 5.7 mmol/l. During resuscitation vaginal vacuum delivery was performed. Finally, she was defibrillated successfully and made a full recovery.
- Two other patients had been immobilized and treated with magnesium and ritodrine for several weeks. Preoperative creatine kinase activities were 2120 IU/l and 630 IU/l. In both cases, serum potassium increased by 2.3 mmol/l within 2–3 minutes after suxamethonium injection (from 4.0 to 6.3 mmol/l and from 4.9 to 7.2 mmol/l). This was accompanied by tall peaked T waves and a short period of ventricular tachycardia in one case and by tall peaked T waves and widened QRS complexes in the other.

The authors suggested that the combined effects of immobilization and prolonged magnesium administration might have resulted in a denervation-like state of large groups of skeletal muscles. The drawback of that explanation is that an awake and healthy person will always move normally even when confined to bed. As long as muscle cells receive physiological stimulation via the neuromuscular junction in patients without muscle weakness, denervation-like changes should not occur to a significant extent. In addition, denervation alone is not known to be associated with an increase in plasma creatine kinase activity, a strong indicator of muscle cell damage, which was found in all the patients reported here. Unfortunately, the authors did not document creatine kinase activities or myoglobin concentrations after suxamethonium, which might have given some idea about additional suxamethonium-induced rhabdomyolysis.

It can be assumed that these three patients had some form of myopathy, either acquired during their previous course or pre-existing. It would have been interesting to know if they had any clinical symptoms, such as muscle pain or weakness. Pre-existing myopathy would be unlikely if plasma creatine kinase activities had been normal before. However, this information was not given in the paper. On the other hand, myopathy could have been acquired during the course of pregnancy and hospital treatment. Various drugs and toxins have been associated with myopathies (167). Hypermagnesemia can produce muscle weakness but magnesium sulfate has not so far been reported to cause myopathy. Therefore, the role of ritodrine in these cases should be questioned. This selective beta$_2$-adrenoceptor agonist has previously been linked to myopathic changes in a patient treated for preterm labor (168). In addition, glucocorticoid treatment, probably used to promote fetal lung development, might be a contributory factor. Long-term glucocorticoid treatment is associated with myopathic changes (167).

In the end, the exact mechanism of suxamethonium-associated hyperkalemia in these cases cannot be determined. Given the huge numbers of patients who receive suxamethonium during rapid-sequence induction of anesthesia for cesarean section, even after some time of treatment for preterm labor without adverse effects, it would be overzealous to call for a restricted use of suxamethonium in these patients. Rather, this report is in support of preoperative screening of plasma creatine kinase activity. Probably suxamethonium should not be used in patients with raised plasma creatine kinase activity. It is a good idea to check creatine kinase activity preoperatively in women due to undergo cesarean section after prolonged immobilization and pretreatment with magnesium sulfate and a beta$_2$-adrenoceptor agonist such as ritodrine.

Mechanism

The underlying mechanisms of and mortality from suxamethonium-associated hyperkalemic cardiac arrest have been reviewed (169). The rise in serum potassium probably results from repetitive opening of receptor-linked ion channels and suxamethonium-induced fasciculation, although it can occur in the absence of visible fasciculation. Muscle injury with excessive leakage of potassium is postulated as a cause of the hyperkalemia. Reuptake of potassium into muscle cells may also be hindered. It has been shown that denervation results in a spread of the normally small receptor area of the motor end-plate over the entire muscle fiber membrane, so that eventually the whole membrane surface is directly excitable by depolarizing agents such as acetylcholine or suxamethonium (170). The immature extrajunctional receptor-linked ion channels so formed remain open for a longer time than those at normal motor end-plates. Depolarization by suxamethonium thereby results in an excessive efflux of potassium from ion channels spread over the entire muscle fiber membrane and not just, as normally occurs, from the circumscribed motor end-plate region (171–173). Prolonged immobilization can also result in extrajunctional receptor spread (174) and a greater increase in serum potassium than usual after suxamethonium.

Rhabdomyolysis is also a mechanism for hyperkalemia, and it has been said that almost all reported cases of hyperkalemic cardiac arrest considered to have resulted from rhabdomyolysis occurred in children and

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adolescents with underlying muscular dystrophies (169). Hyperkalemia during rapid acute rhabdomyolysis is more likely to result in unsuccessful resuscitation than hyperkalemia due to the potassium efflux that results from upregulation of acetylcholine receptors.

Susceptibility factors

The rise in serum potassium can be prolonged (SEDA-11, 122) (175) and exaggerated (SEDA-10, 108) (176) in patients taking beta-blockers. In renal insufficiency the rise after suxamethonium is similar to that in healthy patients (177) and is only dangerous if the serum potassium is already high (above 5.5 mmol/l). However, several conditions can lead to a massive rise in serum potassium, resulting in ventricular fibrillation and cardiac arrest. These include burns (178,179), massive trauma (180,181), and neurological diseases or injuries, especially when denervation is a feature, such as spinal cord injury (182), hemiplegia, multiple sclerosis, or muscular dystrophy (183), peripheral nerve injuries (62,184) and polyneuropathy (185,186). Hyperkalemia has also been reported after suxamethonium in patients with tetanus (187), encephalitis (188), Parkinson's disease (SEDA-6, 129) (189), muscle wasting secondary to chronic arterial insufficiency (190), metastatic embryonal rhabdomyosarcoma (SEDA-14, 114) (191), ruptured cerebral aneurysms (SEDA-5, 134) (192), hyperparathyroidism (22), and in patients with severe and long-lasting sepsis (193,194).

There are times when patients are most susceptible to hyperkalemia. In patients with burns or trauma this is generally between 10 and 60 days after the injury, or longer if there is persistent infection and delayed healing. In neurological diseases or injuries the danger period is usually from 3 weeks to 6 months after onset. However, in some cases, such as patients with transverse spinal lesions and tetraplegia, dangerous hyperkalemia has been reported as early as 24–48 hours after the injury, and likewise severe potassium rises have been reported more than 6 months after injury or onset of disease, particularly in patients with progressive lesions (SEDA-6, 128) (183).

Extrajunctional spread of acetylcholine receptors and expression of the immature type of these receptors with prolonged channel opening times have been shown after burns, which may be why there can be massive potassium release after suxamethonium administration. As the increase in acetylcholine receptor density on the muscle surface takes some time to develop, there should be an interval after the accident during which suxamethonium can be safely given. However, the length of this interval is controversial. Referring to a lack of reports of hyperkalemic complications during the first week after the injury, it has been suggested that suxamethonium can be given safely during the first 6–7 days after major thermal injury (195). However, based on the results of animal experiments, suxamethonium might be safe for up to 48 hours after the injury only (195).

The use of suxamethonium in intensive care units has been critically reviewed (196). Several cases of hyperkalemic cardiac arrest after suxamethonium have occurred in intensive care patients (153,155–157,159,160). Of particular concern is the risk of hyperkalemic cardiac arrest when suxamethonium is given to critically ill patients after a period of immobilization (154). The exact mechanism is not known, but extrajunctional spread of acetylcholine receptors is believed to play a major role. It is strongly recommended that suxamethonium should not be given to patients who have been immobilized in the intensive care unit for more than a few days.

In yet another report of suxamethonium-induced fatal hyperkalemic cardiac arrest in an intensive care unit it was assumed that severe mucositis after cancer chemotherapy might have contributed to the hyperkalemic response (197).

- A 37-year-old woman with acute myelogenous leukemia was admitted to an intensive care unit (ICU) with mental status changes and progressive dyspnea due to pneumonia. Intubation was performed before ICU admission using a sedative without neuromuscular blockade. She had received chemotherapy with cytarabine, daunorubicin, and intrathecal methotrexate for brain metastases. After chemotherapy and before ICU admission her course was complicated by continuous neutropenic fevers and by painful mucositis causing dysphagia and bleeding. After 10 days of ventilator treatment in the ICU and treatment with ceftazidime, gentamicin, metronidazole, vancomycin, amphotericin, and aciclovir, her condition improved, allowing withdrawal of ventilator support and extubation. A few hours later, however, she gradually developed severe respiratory distress and required reintubation. The serum potassium concentration before intubation was 4.3 mmol/l. For endotracheal intubation she received intravenous etomidate 14 mg and suxamethonium 100 mg. Immediately after intubation she developed a broad-complex tachycardia and her blood pressure could not be measured. Chest compression and advanced cardiac life support were started. Her serum potassium concentration was 13.1 mmol/l. Intravenous calcium chloride, sodium bicarbonate, and insulin/glucose were therefore given. The serum potassium fell to 6.5 mmol/l but rose to 7.4 mmol/l 15 minutes later, despite additional antihyperkalemic treatment. She finally died.

Despite this having been a case of suxamethonium-induced hyperkalemic cardiac arrest after several days of ventilator treatment on the intensive care unit, the authors did not believe that upregulation and extrajunctional spread of acetylcholine receptors were the underlying mechanisms. They implied that mobilization and daily physiotherapy would have both prevented these typical denervation-like changes and ruled out a neuromuscular disorder. Rather they suggested that severe generalized mucositis had resulted in a state that they compared to an "internal burns injury." However, these speculations were not substantiated by additional data. In particular, they gave no information on the presuxamethonium neuromuscular state of the patient. Some form of polyneuropathy and/or myopathy could have been present, and this was not ruled out by the fact that the patient could breathe spontaneously and sit in a chair. While it is true that severe mucositis represents a state of widespread cellular damage similar to severe burn injuries, it is not clear why this itself should result in hyperkalemia after suxamethonium. To our knowledge suxamethonium only has effects on excitable cells. Even in patients with severe thermal injuries, no case of hyperkalemia after suxamethonium has been

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reported within the first 48 hours after the accident, and suxamethonium-induced hyperkalemia in burned patients is believed to result from upregulation of acetylcholine receptors, owing to thermal damage of nerve fibers (structural denervation) and immobilization (functional denervation) (170). Apart from immobilization due to the severity of the illness it is very unlikely that mucositis should have similar effects. Mucositis itself should therefore not be regarded as a risk factor for suxamethonium-associated hyperkalemia.

In a survey of intensive care units in the UK, more than two-thirds of the respondents would have chosen suxamethonium in a clinical scenario requiring re-intubation in a patient with abdominal sepsis and weaning failure after 20 days of ICU stay (198). The authors concluded that there is a lack of appreciation of the dangers of suxamethonium in critically ill patients in intensive care units.

The use of suxamethonium in patients with renal insufficiency was controversial in the 1970s, after some cases of hyperkalemic cardiac arrest in such patients. As several studies did not show exaggerated potassium release, suxamethonium is now considered safe for patients with renal insufficiency, if preoperative hyperkalemia is excluded. The observation of some cases of postoperative hyperkalemia recently prompted a review of the literature (199). The authors found sufficient evidence to support the current consensus: suxamethonium can be used in patients with renal insufficiency, but it should not be given if there is pre-existing hyperkalemia; doses of suxamethonium should not be given repeatedly, as this can result in sinus bradycardia.

Suxamethonium is said to be contraindicated in patients with hyperkalemia (that is a serum potassium concentration over 5.5 mmol/l). This, however, has been questioned (200). In an analysis of their anesthetic database, the authors identified 38 patients with a preoperative serum potassium concentration over 5.5 mmol/l who subsequently received suxamethonium. In no case were dysrhythmias or any complications documented and there were no deaths. While they admitted that minor complications might not have found their way into the database, the authors felt that major problems caused by suxamethonium in these patients were unlikely. They suggested that the use of suxamethonium in patients with serum potassium concentrations above 5.5 mmol/l may be acceptable when other muscle relaxants have inappropriate profiles. As their analysis included only a few patients with serum potassium concentrations above 6.0 mmol/l they recommended the use of antihyperkalemic treatment before suxamethonium in these patients.

Prevention

It has been claimed that non-depolarizing drugs given before suxamethonium attenuate the rise in potassium, but this has been repeatedly shown to be unreliable. It seems advisable to avoid the use of suxamethonium completely in such patients. This subject has been extensively reviewed (201,202).

Gastrointestinal

Suxamethonium can increase intragastric pressure. This is probably a result of fasciculation of the abdominal muscles (203), although a vagal effect can also contribute. The rise is highly variable, ranging from zero to more than 85 cm H_2O according to many different investigations (204–207). The intragastric pressure at which the lower esophageal sphincter opens is also variable, with a mean of about 28 cm H_2O, depending partly on the angle between the esophagus and the cardia of the stomach (208,209). There is therefore a danger that the suxamethonium-induced rise in intragastric pressure may produce incompetence of the lower esophageal sphincter and result in regurgitation. This risk is likely to be increased in patients with hiatus hernia, gastric and intestinal dilatation, ascites, and intra-abdominal tumors. Pregnant patients are especially susceptible, as the tonus of the lower esophageal sphincter can also be reduced in pregnancy. It has been suggested, however, that suxamethonium causes, either by a direct action on the lower esophageal sphincter or indirectly through a pinch action of the diaphragm, increased resistance to opening of the lower esophagus, which counteracts the increased intragastric pressure (210). Attenuating fasciculation by giving small doses of non-depolarizing blockers reduces the rise in gastric pressure (203,206,211).

Urinary tract

In severe renal disease, suxamethonium should only be given if the serum potassium is below 5.5 mmol/l. The excretion of neostigmine and pyridostigmine can be impaired in renal insufficiency, and this has been reported to have resulted in prolongation of the action of suxamethonium given some hours later (212).

Myoglobinuria resulting from suxamethonium administration can cause acute renal insufficiency (83,84,213).

Musculoskeletal

The problem of suxamethonium-associated postoperative myalgia has been reviewed (214). Key statements are:

- there is no correlation between the severity of muscle fasciculation, changes in serum creatine phosphokinase or serum potassium, and postoperative myalgia;
- although not proven, mechanical muscle damage is still assumed to be an underlying mechanism;
- several classes of pretreatment drugs reduce the incidence and severity of myalgia; combining two agents may be the most useful method;
- so far, the lowest incidence of post-suxamethonium myalgia has been reported when a small dose of a non-depolarizing neuromuscular blocking agent was given together with lidocaine as pretreatment.

In addition, there was a reduced incidence and intensity of post-suxamethonium myalgia when anesthesia had been maintained by propofol infusion compared with isoflurane (215).

Immunologic

From the results of intradermal injections, suxamethonium has only 1% of the histamine-releasing activity of D-tubocurarine (216). However, through the years there have been many reports of reactions, varying from flushing and urticaria to bronchospasm (217,218) and severe

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shock (219–222). That suxamethonium was responsible was suggested in some cases by the fact that the patients reacted on different occasions with raised plasma histamine and catecholamine concentrations (223–225). The association was confirmed in other cases by repeatedly injecting the drug, thereby producing bronchospasm several times in the course of the one anesthetic (226,227). Skin testing has also yielded confirmation, although this can be dangerous (220). Analysis of large series of patients (228–233) who have had severe anaphylactoid reactions during anesthesia, using more sophisticated laboratory and immunological investigations in addition to intradermal skin tests, suggests that suxamethonium may be much more commonly associated with such reactions than was previously believed. In 18 cases (234) cardiovascular collapse was the predominant feature in 72% and bronchospasm in 33%; cardiac arrest occurred in five patients. In addition, two reports (235,236) of anaphylactic reactions involving both thiopental and suxamethonium have raised the question of "aggregate"-induced reactions (235) occurring when drugs are given in such a way that they can interact in the injection system.

Body temperature

The syndrome of malignant hyperthermia can be triggered by suxamethonium. Mortality is more than 60% in untreated patients. This syndrome is reported as occurring once in every 15 000–150 000 anesthetics. It may be more common in the Japanese. However, there are also abortive forms of malignant hyperthermia, and many of the typical signs may be produced by other conditions, so that it is difficult to ascertain the precise incidence. Autosomal dominant inheritance, with reduced penetrance and variable expressivity, is the proposed genetic basis. The cause is unknown, but it is thought to be associated with a rise in free ionized myoplasmic calcium, possibly owing to a failure of the sarcoplasmic reticulum to bind calcium. As a result, aerobic and anaerobic metabolism are increased, resulting in the typical features of the syndrome. Halothane and suxamethonium are the most frequent triggers, although almost all of the inhalational anesthetic agents have been incriminated. While other muscle relaxants (pancuronium, D-tubocurarine) have been suggested as triggers in a few cases, and many other drugs used in anesthetized patients also, convincing evidence is lacking. It has been suggested that stress plays a role in the development of malignant hyperthermia (237).

Dantrolene (238,239) is the agent of choice for treatment of malignant hyperthermia and greatly reduces the mortality to under 10% if given in time (240) together with general supportive measures. Dantrolene itself has adverse effects that are mostly minor in nature, such as nausea and vomiting, when it is used acutely. However, a report has suggested that it may have contributed to uterine atony, with resulting excessive hemorrhage when given prophylactically after a cesarean section (241), and muscle weakness associated with its oral prophylactic use in a patient with compromised respiratory function is reported to have exacerbated postoperative respiratory depression to such an extent that artificial ventilation was required (SEDA-14, 114) (242). The combination with calcium channel blockers, such as verapamil, may result in severe cardiovascular depression and hyperkalemia (SEDA-12, 113) (243,244), so that extreme care is required.

Second-Generation Effects

Pregnancy

Maternal doses of suxamethonium up to 200 mg have been reported as not resulting in detectable concentrations in neonates. Very large bolus doses (300–500 mg) have produced umbilical vein concentrations up to 2 micrograms/ml, but the neonates showed no adverse effects (245,246). Extreme reduction in plasma cholinesterase activity, either caused by organophosphorus poisoning (247) or genetically determined (SEDA-15, 123) (248,249), has resulted in weakness and respiratory depression in neonates after normal or small (247) maternal doses.

Susceptibility Factors

Genetic factors

Plasma cholinesterase deficiency can be hereditary or acquired. The hereditary form is believed to account for two-thirds of suxamethonium-sensitive patients. Genetically determined plasma cholinesterase variants hydrolyse suxamethonium much more slowly. About 96% of the population are homozygotes for the normal "typical" gene, one in 25 are heterozygotes ("typical"/"atypical") and have a slightly prolonged (about 2–4 times normal) response to suxamethonium, and one in 2000–3000 are homozygotes for the "atypical" gene and have a markedly prolonged response (2–3 hours). The "silent" gene is much rarer and homozygotes (about 0.0006% of the population) have virtually no plasma cholinesterase activity; in them complete paralysis after suxamethonium lasts many hours.

Acquired plasma cholinesterase deficiency is clinically less important, since paralysis from suxamethonium seldom lasts for more than 20–30 minutes. However, this can be avoided by not using suxamethonium in patients known to be at risk. Clinically important prolongation of suxamethonium-paralysis is only to be expected, with the exception of some drug-induced effects, in patients with more than one cause for a reduction in pseudocholinesterase activity. In malnutrition and liver disease (250,251) the synthesis of plasma cholinesterase in the liver is reduced. Neonates have about 50% of normal adult plasma cholinesterase activity. In pregnancy there is a rapid fall in plasma cholinesterase activity of about 25% in the first trimester, which only returns to normal some 6–8 weeks postpartum (252–254). Occasionally much larger falls occur. The lowest average values have been reported during the first week of the puerperium (SEDA-5, 135) (255,256). Similar changes have been reported in gestational trophoblastic disease (hydatidiform mole) (257). Cancer is sometimes associated with lower plasma cholinesterase activity (SEDA-5, 136) (258). There is also a report of multiple esterase

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deficiencies in Hodgkin's disease (259). Plasma cholinesterase activity has also been reported to be reduced by up to 70–80% in patients with renal disease and burns. Plasmapheresis (SEDA-5, 135) (260,261) removes cholinesterase, along with other proteins, from the plasma.

Numerous drugs also reduce plasma cholinesterase synthesis or activity, for example estrogens, glucocorticoids, phenelzine, organophosphorus compounds (such as ecothiopate eye-drops, insecticides), carbamates (insecticides, bambuterol), cytotoxic drugs, metoclopramide, the ester-type local anesthetic drugs, and pancuronium. Anticholinesterases also prolong the action of suxamethonium. Several reviews are recommended for detailed information about plasma cholinesterase and its relevance in anesthetic practice (96,262–264).

Hepatic disease

In severe liver dysfunction the synthesis of plasma cholinesterase may be reduced to such an extent that the action of suxamethonium can be prolonged (SED-8, 282). This is usually not more than 2 or 3 times the normal duration.

Other features of the patient

Suxamethonium-induced fasciculation or increased muscle tone can be dangerous in patients with fractures or dislocations (especially vertebral, when the drug is relatively contraindicated), in patients with open-eye injuries or after the eyeball is opened surgically, when an increase in abdominal pressure must be avoided (pheochromocytoma, aortic aneurysm, full stomach, ileus), and in patients in whom a rise in arterial pressure may be catastrophic (cerebral aneurysm, raised intracranial pressure). Prolonged paralysis, occasionally lasting hours, is a risk if the patient is, or has been, taking certain drugs.

Pregnancy

In pregnancy the risk of regurgitation has to be weighed against the advantage of rapid intubation. The use of "precurarization" with small doses of non-depolarizing drugs may reduce the intensity of the fasciculation, but is by no means reliable. If possible, relaxation is better achieved by using a non-depolarizing agent alone.

Muscle disorders

Patients with muscle disorders (dystrophia myotonica, myotonia congenita, myasthenia gravis, and hyperkalemic periodic paralysis) tend to react unpredictably to suxamethonium. In myasthenia gravis, small doses of suxamethonium may be tried and the resulting effect monitored. In the other diseases listed non-depolarizers, cautiously used, are preferable. Cardiac arrest has been reported in patients with pseudohypertrophic muscular dystrophy (Duchenne type) and excessive muscle damage may be produced by suxamethonium in this condition.

Myasthenic syndromes

In myasthenia gravis responses to suxamethonium are unpredictable (265–268). Resistance has been reported and the development of a phase II block can occur more readily, occasionally leading to prolonged paralysis. The measures used to treat the condition, for example plasmapheresis or anticholinesterases, further complicate the picture. Patients with the Eaton–Lambert syndrome are very sensitive to all relaxants.

Asthma or allergic reactions

In patients with asthma or a history of previous allergy, suxamethonium should be used with caution, in view of its potential for causing allergic reactions and bronchospasm. When a patient or a relative has had a previous adverse reaction to an anesthetic, the possibilities of an atypical cholinesterase genotype or malignant hyperthermia should also be considered. Patients with certain musculoskeletal and developmental abnormalities, such as a tendency to joint dislocations, squint, ptosis, hernias, some forms of cryptorchidism, pectus excavatum, kyphosis, foot deformities, and myopathic features, and also those who have reacted to a previous injection of suxamethonium with generalized muscle rigidity or masseter spasm, may be more prone to malignant hyperthermia. Dantrolene should be available to every area where anesthetic agents are used.

Patients at risk of aspiration

The choice of muscle relaxants for rapid sequence induction of anesthesia in patients at risk of aspiration has been controversial for many years. Suxamethonium has been used for decades, because it has a fast onset and a short duration of action, although it can have severe adverse effects. Alternatives have been suggested, all of which have their own pros and cons, but suxamethonium has withstood the test of time and is still widely used. On this background, the use of rocuronium versus suxamethonium has been subjected to a Cochrane review, in which 40 studies addressing the issue were identified, 26 of which were combined for analysis (269). For rocuronium, the relative risk of excellent intubating conditions was 0.87 (95% CI = 0.81, 0.94) compared with suxamethonium. In a subgroup of patients who had been given propofol as an induction agent, there was no difference between rocuronium and suxamethonium. The reviewers concluded that overall suxamethonium creates excellent intubation conditions more reliably than rocuronium and should still be used as a first-line muscle relaxant for rapid sequence intubation. Rocuronium, when used with propofol, reliably created excellent intubation conditions and was consequently suggested as a second-line alternative to suxamethonium. In addition, some have suggested that intubating under deep anesthesia without a neuromuscular blocker is an acceptable third-line alternative if neither suxamethonium nor rocuronium is considered appropriate. To allow rapid-sequence intubation of the trachea without a muscle relaxant, adequate doses of propofol (2.0–2.5 mg/kg) or etomidate (0.3 mg/kg) and a fast-onset opioid, such as alfentanil (50 micrograms/kg) or remifentanil (4 micrograms/kg) are required (270–275).

Drug–Drug Interactions

Antidysrhythmic drugs

Quinidine potentiates not only non-depolarizing muscle relaxants but also depolarizing drugs (276).

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Verapamil can potentiate the block produced by both types of neuromuscular blocking agent (277).

Beta-blockers can prolong and possibly exaggerate the rise in serum potassium resulting from the injection of suxamethonium (SEDA-10, 108) (SEDA-11, 122) (175,176).

Aprotinin (Trasylol)

Aprotinin (Trasylol) slightly reduces plasma cholinesterase activity and would only be expected to prolong the action of suxamethonium in combination with other factors. However, re-paralysis has been reported when this agent was used after operations during which suxamethonium had been given alone or in combination with normal doses of D-tubocurarine (278).

Bambuterol

Bambuterol, a $beta_2$-adrenoceptor agonist that is used to relieve bronchospasm, approximately doubles the duration of action of suxamethonium (SEDA-14, 114) (279). Plasma cholinesterase activity was reduced significantly even 10–12.5 hours after a single dose of 30 mg had been given to patients. The interaction is due to the binding of carbamate groups to plasma cholinesterase.

Cardiac glycosides

Cardiac glycosides and suxamethonium can interact, resulting in an increased risk of dysrhythmias (280), perhaps through alterations in intracellular calcium (22). In 24 patients with ischemic heart disease taking digoxin who underwent abdominal surgery ventricular extra beats with bigemini or severe bradycardia were recorded in two patients and episodes of torsade de pointes occurred in two others during endotracheal intubation (281). The authors suggested that endotracheal intubation in digitalized patients should be performed without suxamethonium. However, considering the frequency with which digitalized patients receive suxamethonium and the paucity of reports of clinical problems, this interaction is probably of minor importance.

Cytotoxic and immunosuppressive drugs

Nitrogen mustard and related alkylating agents, such as cyclophosphamide, chlorambucil, triethylmelamine, and thiophosphoramide, prolong the action of suxamethonium (282,283). Plasma cholinesterase activity is reduced, possibly by alkylation of the enzyme. It has been suggested that azathioprine may potentiate suxamethonium by inhibition of phosphodiesterase activity (SEDA-4, 87) (284).

Donepezil

Donepezil acts primarily as a reversible inhibitor of acetylcholinesterase with a half-life of over 70 hours. Prolonged paralysis lasting several hours and requiring postoperative mechanical ventilation in the intensive care unit has been reported after the use of suxamethonium in a patient taking long-term donepezil (285).

- An 85-year-old woman with a history of mild Alzheimer's disease and hypertension underwent abdominal hysterectomy. Anesthesia was induced with suxamethonium 100 mg and 40 minutes later pancuronium 2 mg. After 2 hours, when surgery was finished, train-of-four stimulation elicited three twitches, and neostigmine 5 mg plus glycopyrrolate 1 mg was given to reverse neuromuscular block. She was subsequently able to follow commands and was breathing adequately; four twitches were observed during train-of-four stimulation. Several minutes after extubation she became apneic and had to be reintubated. Further neostigmine 1 mg was given, but neuromuscular block persisted without any response to peripheral nerve stimulation. In a blood sample taken 60 minutes after the second dose of neostigmine plasma cholinesterase activity was 2.1 (reference range 7.1–19) U/ml. The dibucaine number was 45 (reference range 81–87)%, and the fluoride number was 84 (44–54)%.

The authors of this report subsequently tested the effect of donepezil on plasma cholinesterase activity in vitro. Supratherapeutic concentrations (0.02 mg/ml) reduced plasma cholinesterase activity to 53% of baseline. Dibucaine and fluoride numbers were not affected by neostigmine or donepezil. Others have shown previously that therapeutic doses of donepezil inhibit acetylcholinesterase by 64% (286). Prolonged paralysis in this case may have been due to the combined effects of atypical plasma cholinesterase and additional inhibition of plasma cholinesterase activity by donepezil. Unfortunately, preoperative plasma cholinesterase activity was not known and low cholinesterase activity was detected under the influence of neostigmine, which inhibits both plasma cholinesterase and acetylcholinesterase. Because a very high dose of neostigmine resulted in intensification rather than reversal of neuromuscular block, overdose of neostigmine may have caused paradoxical neuromuscular block (287). Hypothetically, paradoxical block is a combination of desensitization and open channel block (SEDA-13, 298). So the additional dose of neostigmine should have been omitted. In addition, an excess of acetylcholine at the end-plate might have been the result of combined inhibition of acetylcholinesterase by both donepezil and neostigmine. Until more is known, neostigmine and other cholinesterase inhibitors should be used with caution in patients taking donepezil.

- A 72-year-old woman with a symptomatic hiatus hernia, osteoarthritis, and Alzheimer's disease was taking fluoxetine 20 mg/day, donepezil hydrochloride 10 mg/day, nimesulide 12.5 mg/day, and omeprazole 20 mg/day (288). There still was no twitch response to peripheral nerve stimulation 20 minutes after rapid-sequence induction of anesthesia with propofol 2.5 mg/kg and suxamethonium 1 mg/kg. She then gradually developed a weak twitch response, and 50 minutes after induction of anesthesia four twitches with a fade were elicited by train-of-four stimulation. No additional medication was given and after the end of the procedure 10 minutes later she was extubated uneventfully. She refused further blood testing and so her plasma cholinesterase activity at that time is not known. However, her anesthetic notes from a previous operation did not reveal any problems with prolonged paralysis after suxamethonium.

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It is not proven that donepezil was the cause of the prolonged duration of action of suxamethonium in this case. However, a case with some similarities has been reported before (285). In addition, there has been another report linking donepezil therapy to both prolonged duration of action of suxamethonium and reduced sensitivity to atracurium (289). Recovery of neuromuscular function should therefore be monitored when suxamethonium is given to patients taking donepezil. The withdrawal of donepezil 2–3 weeks before an operation cannot be supported, because this might have adverse effects on cognitive function. The issue has been highlighted in a recent letter, and the author concluded that "a brief prolongation of muscle relaxation is very rarely a problem (although its mismanagement may be)" (290).

Ecothiopate

Ecothiopate eye-drops, used in the treatment of glaucoma, prolong the action of suxamethonium considerably (291,292). Ecothiopate is a long-acting anticholinesterase that inhibits the activity of both acetylcholinesterase and plasma cholinesterase. Plasma cholinesterase activity may be reduced to 5% or less and on withdrawal requires 1–2 months for recovery to normal values (293,294). The prolonged anticholinesterase effect is due to conversion of the enzyme to its stable phosphoryl derivative. If a patient has used ecothiopate eye-drops in the previous 2 months or so, suxamethonium should not be given, unless normal plasma cholinesterase activity can be demonstrated. Various organophosphorus insecticides, such as parathion and malathion, may also result in prolonged paralysis after suxamethonium due to reduced free cholinesterase activity (247,295), produced in a similar manner to that in the case of ecothiopate.

Estrogens and estrogen-containing contraceptives

Estrogens and estrogen-containing contraceptives prolong the action of suxamethonium. Plasma cholinesterase activity is reduced, possibly by estrogenic inhibition of the hepatic synthesis of plasma cholinesterase, and its isozymes are modified (262,296,297). Diethylstilbestrol, included in this group, is reported to have caused paralysis for 3 hours in a patient with other aggravating factors (SEDA-4, 89) (298). One would, however, expect little prolongation of suxamethonium paralysis since the decrease in plasma cholinesterase activity (after contraceptives, at least) averages only about 20%. Prednisone, cortisol, and dexamethasone also reduce plasma cholinesterase activity to a mild or moderate degree (SEDA-15, 122) (299–301).

General anesthetics

When mixed in solution, thiopental will hydrolyse suxamethonium, owing to a pH effect. Ketamine may prolong the action of suxamethonium slightly (302,303); a phase II block might be prolonged more significantly (303), although there is no clinical experience reported. Decreased presynaptic acetylcholine synthesis or release has been postulated as the mechanism (304). In another study there was no significant shift in the dose–response curve for suxamethonium with ketamine (305). Inhalational agents potentiate muscle relaxants, which is of more clinical importance with regard to non-depolarizing agents. Tachyphylaxis and phase II block develop earlier and after smaller total doses of suxamethonium when volatile agents such as halothane, enflurane, or isoflurane (306,307) are used instead of balanced anesthesia. Halothane can increase the incidence of cardiac dysrhythmias, especially bradycardia and nodal rhythm, after suxamethonium. Atropine and glycopyrrolate, particularly when given intravenously just before, afford some protection (SEDA-5, 136) (308).

Lithium carbonate

Lithium carbonate delays the onset and prolongs the action of depolarizing relaxants (309,310). The principal mechanism of action is disputed. Factors suggested have been the development of dual block, reduced sensitivity of the end-plate for suxamethonium, diminished synthesis or release of acetylcholine, and plasma cholinesterase inhibition (310–312). The clinical importance is also disputed.

Local anesthetics

Procaine and cocaine are esters that are hydrolysed by plasma cholinesterase and can therefore competitively enhance the action of suxamethonium (313). Chloroprocaine may have a similar action. Lidocaine also interacts, although the mechanism is not clear unless very high doses are used (314).

Magnesium sulfate

Magnesium sulfate is used mostly in the treatment of toxemia of pregnancy. Serum magnesium concentrations may be raised and, as magnesium inhibits the release of acetylcholine and reduces the sensitivity of the postjunctional membrane, the action of non-depolarizing agents will be prolonged. It is not so clear, however, why the action of suxamethonium is also prolonged (315–318). Suxamethonium-induced fasciculation are reportedly prevented (SEDA-5, 135) (319). It has been suggested that the administration of intravenous magnesium sulfate should be stopped 20–30 minutes before muscle relaxants are given. Monitoring with a nerve stimulator is advisable.

Metoclopramide

Metoclopramide inhibits the activity of plasma cholinesterase and can prolong the action of suxamethonium (SEDA-14, 115) (320–322).

Neostigmine

Neostigmine inhibits both plasma cholinesterase and acetylcholinesterase, so that if any suxamethonium is still circulating, its action will be prolonged (by about a factor of two). This may present problems when neostigmine is administered to antagonize phase II block (323) (in which hypothetical desensitization block and open channel block elements may also be intensified) or shortly after suxamethonium is given. In renal insufficiency both neostigmine and pyridostigmine can cause prolongation (by 1–2 hours) of the action of suxamethonium given several hours after renal transplant operations.

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Non-depolarizing muscle relaxants

Non-depolarizing muscle relaxants and suxamethonium are mutually antagonistic. These agents are often given in small non-paralysing doses before suxamethonium to reduce fasciculation and other adverse effects. Gallamine is slightly more effective than D-tubocurarine, and both are more effective than pancuronium. This precurarization tends to prolong the onset of action of (probably by direct antagonism) and to shorten (D-tubocurarine) or lengthen (pancuronium) its duration of action (324). The latter effect may well be due to inhibition of plasma cholinesterase by pancuronium. When compared with pancuronium, pretreatment with either atracurium or vecuronium was associated with a significantly shorter time to 90% twitch recovery after a standard dose of suxamethonium (325). When non-depolarizing agents are given after suxamethonium, even more than 30 minutes later, their action is considerably potentiated and prolonged (89,326,327). This effect (and also the production of a phase II block when suxamethonium is used alone in high or frequently repeated doses) may be the result of inhibition of transmitter release through a prejunctional action of suxamethonium (328). Suxamethonium given some time after a paralysing dose of a non-depolarizing agent (for example for peritoneal closure) produces varying effects depending on the depth of residual curarization and on the dosage of suxamethonium (SEDA-21, 141) (329–331). As it is uncertain what type of block results, this practice cannot be recommended, although few problems with subsequent reversal have been reported.

Phenelzine

Phenelzine, a monoamine oxidase inhibitor, has been reported to cause significant prolongation of suxamethonium paralysis due to depressed plasma cholinesterase levels (to about 10% of normal). Recovery of plasma cholinesterase activity took 2 weeks (332).

Tacrine (tetrahydroaminoacridine) and hexafluorenium

Tacrine (tetrahydroaminoacridine) and hexafluorenium, used sometimes to potentiate and prolong the action of suxamethonium (333,334), inhibit plasma cholinesterase. Hexafluorenium also inhibits acetylcholinesterase and has a weak neuromuscular blocking action of the non-depolarizing type; a phase II block develops fairly rapidly when repeated injections of even small doses (0.2–0.3 mg/kg) of suxamethonium are given in combination with hexafluorenium (335). Fasciculation is reportedly reduced and hyperkalemia prevented (336), as is the increase in intraocular pressure (337), when hexafluorenium is given before suxamethonium. Because of a lack of consistency of successful results from various investigators, this method is not recommended for patients who are especially at risk from hyperkalemia or increased intraocular pressure. Simultaneous injection of hexafluorenium and suxamethonium can cause severe bronchospasm.

Trimetaphan

Trimetaphan can double the duration of suxamethonium block (338–340). The mechanism is not clear, but may be a competitive effect at the neuromuscular junction. Blockade of end-plate ionic channels has also been suggested (341).

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Suxibuzone

See also Non-steroidal anti-inflammatory drugs

General Information

Suxibuzone, a derivative of phenylbutazone, is an NSAID that has been used topically. Skin reactions, gastrotoxicity, nephrotoxicity, headache, and vertigo have been noted. The carcinogenic potential of suxibuzone in animals has attracted attention (1) and put an end to sales in some countries.

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Tacrine

General Information

Tacrine (tetrahydroaminoacridine) was one of the first drugs to be widely marketed for the loss of memory and intellectual decline in Alzheimer's disease. However, its efficacy is controversial. A Cochrane review of the use of tacrine in Alzheimer's disease produced results that were compatible with improvement, no change, or even harm (1). For measures of overall clinical improvement, the intention-to-treat analyses did not detect any difference between tacrine and placebo (OR = 0.87; 95%CI = 0.61, 1.23). There was no effect on behavioral disturbance (SMD = 0.04; 95%CI = –0.52, 0.43) or cognitive function (SMD = 0.14; 95%CI = –0.02, 0.30). The odds ratio for withdrawal due to an adverse event was significantly different from 1, the control group experiencing fewer events (OR = 0.7; 95%CI = 4.1, 7.9). Raised serum liver enzymes caused the most withdrawals. Gastrointestinal adverse effects (diarrhea, anorexia, dyspepsia, and abdominal pain) were the other major adverse events and the odds ratio for withdrawal was also in favor of the control group (OR = 3.8; 95%CI = 2.8, 5.1). No deaths were reported in any of the studies, which lasted up to 6 months.

In a prospective randomized, double blind, parallel-group, multicenter comparison of idebenone 360 mg/day ($n = 104$) and tacrine up to 160 mg/day ($n = 99$) for 60 weeks in 203 patients with mild-to-moderate dementia of the Alzheimer's type, idebenone produced more benefit than tacrine (2). The benefit : harm balance was favorable for idebenone compared with tacrine. More patients taking tacrine (65%) reported adverse events than those taking idebenone (50%). The dropout rate in those taking tacrine was also higher. There were statistically significant differences between tacrine and idebenone for gastrointestinal adverse events (nausea, vomiting) and hepatobiliary toxicity (raised serum transaminase activity).

Organs and Systems

Nervous system

Myoclonus has been attributed to tacrine (3).

- A 68-year-old woman, who had had dementia of probable Alzheimer's type for 4 years, was given tacrine 40 mg/day and 24 hours later progressively developed generalized uncontrolled abnormal movements affecting all her limbs and her mouth, suggestive of myoclonus and controlled by clonazepam. The myoclonus disappeared 24 hours after tacrine was withdrawn. Causation was established a few months later by rechallenge: myoclonus occurred during the next 48 hours.

Liver

Hepatic failure associated with tacrine occurred outside the usual time of onset (within 9 months) and resulted in the death of a 75-year-old woman with Alzheimer's disease who had taken tacrine for 14 months (4). Thus, the potential for delayed, life-threatening hepatotoxicity with tacrine, although unusual, should not be overlooked.

The presence of the combined alleles M1 and T1, which mark deficiencies in glutathione-*S*-transferase genes, increases susceptibility to tacrine hepatotoxicity (5). It would be interesting to use this molecular epidemiological approach to identify the role of combinations of glutathione-*S*-transferase genotypes in other adverse drug reactions.

Tacrine-induced hepatotoxicity was reduced by ursodeoxycholic acid (13 mg/kg/day for 105 days) in a pilot study in 14 patients with Alzheimer's disease (6). Serum activity of alanine transaminase in 100 patients taking ursodeoxycholic acid was normal in 93% of cases, compared with 69% of patients who had taken tacrine alone.

Authors evaluating the adverse effects of tacrine in Alzheimer's disease recommend regular monitoring for hepatotoxicity (SEDA-15, 136).

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Tacrolimus

General Information

Tacrolimus, a macrolide derivative, has similar immunosuppressive properties to ciclosporin and has effects on T lymphocytes by inhibiting interleukin-2 production. On a weight basis, tacrolimus is about 100 times more potent than ciclosporin. In view of the outcome of several multicenter trials, it has been used as an alternative to ciclosporin as a baseline regimen for the prophylaxis of renal and liver transplant rejection and in the treatment of acute rejection (SED-13, 1130) (SEDA-21, 390) (1). The clinical pharmacology, clinical use, and adverse effects profile of tacrolimus in organ transplantation have been extensively reviewed (2).

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General adverse effects

The incidence of adverse effects (for example neurotoxicity, nephrotoxicity, and hyperglycemia), particularly those requiring drug withdrawal, was initially found to be higher in tacrolimus-treated liver transplant patients, but subsequently fell after the initial tacrolimus dose was reduced. This was in accordance with the results of very early trials, which showed that the initially proposed dose of tacrolimus was too high (3). In subsequent studies, tacrolimus and ciclosporin had a similar spectrum of adverse effects for nephrotoxicity, infectious complications, and lymphoproliferative disorders, and long-term adverse effects occurred at comparable rates, that is less than 2% (SED-13, 1130) (SEDA-21, 390).

Even though the glucocorticoid-sparing effect of tacrolimus is greater than that of ciclosporin, the initial hope that tacrolimus might prove less toxic than ciclosporin has not been realized. In trials in renal transplant patients, increased serum creatinine concentrations, tremor, paresthesia, gastrointestinal disorders, hyperglycemia, diabetes mellitus, pruritus, and angina pectoris occurred more often with tacrolimus, whereas there was a higher incidence of dysrhythmias, hyperkalemia, gingival hyperplasia, acne, alopecia, and hirsutism with ciclosporin (SEDA-21, 390). In the European Tacrolimus Multicenter Liver Trial, there was some evidence of possible advantages for tacrolimus over ciclosporin in terms of hypertension, cytomegalovirus infection, hirsutism, and gum hyperplasia (SEDA-21, 390). The safety profile of tacrolimus is very similar in children to that in adults, but in sharp contrast to ciclosporin, gingival hyperplasia, hirsutism, and coarsening of facial features have not been observed (4,5).

As the adverse effects of tacrolimus and ciclosporin are not strictly comparable, switching a patient from one to the other can sometimes be beneficial. Severe or persistent tacrolimus-related adverse effects, for example neurotoxicity, gastrointestinal disorders, or diabetes mellitus, can abate after replacement by ciclosporin (SEDA-20, 347) (6). Conversely, the change from ciclosporin to tacrolimus has been safely and successfully undertaken in patients with adverse effects from ciclosporin, such as nephrotoxicity, hemolytic–uremic syndrome, hypertension, neurological disorders, gingival hyperplasia, hypertrichosis, and dyslipidemia (SED-13, 1130) (SEDA-20, 347) (7,8). Replacing one drug by another is not always advantageous; in two patients switched to tacrolimus for ciclosporin-induced cortical blindness, visual abnormalities promptly resolved, but both patients rapidly developed thrombotic thrombocytopenic purpura and severe graft-versus-host disease, and finally died 33 days after bone marrow transplantation (9).

Long-term follow-up (mean of 93 months) of tacrolimus-based immunosuppression has been reported in 121 adult patients with liver transplants (10). Infections were the most common causes of deaths (17 patients out of 42), and half of them occurred during the first year after transplantation. Cardiovascular events (seven patients) or de novo malignancies (three patients) were also important causes of death. End-stage renal disease related to tacrolimus nephrotoxicity was noted in two patients who required renal transplantation. At 7 years, other important adverse effects included hyperkalemia (30%) or hypertension (31%) requiring treatment, and insulin-dependent diabetes mellitus (13%). Seven patients developed de novo malignancies and six had post-transplant lymphoproliferative disorders. The risks of tacrolimus in renal transplantation have been discussed (11).

Organs and Systems

Cardiovascular

The incidence of hypertension and the prevalence of antihypertensive drug use are lower with tacrolimus than with ciclosporin (5,12).

Severe recurrent, but usually reversible hypertrophic cardiomyopathy has been infrequently reported, both in adults and children (SEDA-19, 352) (SEDA-20, 346). Based on experimental data and one additional case report, the interaction of tacrolimus with calcium channel blockers in the cardiac muscle has been suggested as a possible mechanism (SEDA-21, 390). However, the role of tacrolimus in the development of cardiomyopathy is still hypothetical. Echocardiographic abnormalities were relatively common before and after liver transplantation in 12 adult patients, and there was no clear evidence that oral tacrolimus specifically alters cardiac function (13). Other investigators did not show differences in heart weight, ventricular thickness, or valve circumferences between 67 liver transplant recipients treated with tacrolimus and 72 non-transplanted patients who died from end-stage liver disease (14). In addition, more than 80% of patients in both groups had left ventricular hypertrophy.

Other isolated reports and preliminary studies have suggested a possible risk of life-threatening dysrhythmias, including sinus bradycardia or sinus arrest, asymptomatic but significant mean QT/QT_c interval prolongation in 33 patients (over 500 msec in seven patients), and recurrent episodes of ventricular tachycardia or torsade de pointes in two patients (SEDA-21, 391) (SEDA-22, 390) (15,16).

Several reports have previously focused on the possible occurrence of cardiomyopathy in tacrolimus-treated transplant patients, particularly children. In two further liver transplant children aged 2.5 and 14 years who died from multiorgan system failure due to sepsis and end-stage liver failure, pathological examination showed prominent concentric left ventricular hypertrophy (17). Although tacrolimus was regarded as a possible cause of asymptomatic hypertrophic cardiomyopathy in these patients, a direct causal relation was difficult to establish. The cause is probably multifactorial, and potential confounding factors (for example hypertension, glucocorticoids) are numerous in this population. In a retrospective review of 89 pediatric heart transplant patients who had survived for at least 6 months, repeated echocardiography showed signs of cardiac hypertrophy, particularly early after transplantation and in very young infants (18). However, there was no evidence of progressive hypertrophy on follow-up examinations, and no significant differences in the degree of cardiac hypertrophy between patients aged over 1 year at the time of transplantation who received ciclosporin ($n = 26$) or tacrolimus ($n = 41$).

In a retrospective study, the prevalence of hypertension 2 years after adult liver transplantation was significantly

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lower in patients treated with tacrolimus (64% of 28 patients) than in patients treated with ciclosporin (82% of 131 patients) (19). In addition, hypertension occurred later with tacrolimus. A similar benefit of tacrolimus over ciclosporin was found in a randomized, comparative trial in 85 heart transplant patients, and 41% of 39 tacrolimus-treated patients developed new-onset hypertension requiring treatment, compared with 71% of 46 ciclosporin-treated patients (20).

In 37 patients with liver transplants there was no difference between the pre- and post-transplant QT interval in the 25 taking oral ciclosporin and the 12 taking oral tacrolimus (21).

Cardiac symptoms manifesting as myocardial ischemia are uncommon, but can occur through tacrolimus toxicity (22).

- A 20-year-old woman with chest pain, dyspnea, and protracted electrocardiographic ST depression had very high blood tacrolimus concentrations (45 ng/ml). Subsequent coronary angiography ruled out any significant organic lesions, but showed vasospastic coronary arteries. She had no other cardiac symptoms when tacrolimus was restarted with careful surveillance of serum concentrations.

Nervous system

Tacrolimus mostly produces mild to moderate neurotoxic effects that are usually not treatment-limiting and rarely clinically relevant, at least in children (23). The occurrence of neurological symptoms, sometimes severe, is a well-known complication in the early post-transplant period, particularly in liver transplant recipients. It is therefore in most cases difficult to attribute these disorders to a particular immunosuppressive regimen.

When neurological symptoms occur in patients taking tacrolimus they are very similar to those seen in patients taking ciclosporin, with more frequent insomnia, tremor, and headaches, but a similar rate of severe neurological adverse effects, such as acute psychosis, peripheral neuropathy, seizures, encephalopathy, coma, and paralysis. Persistent speech disorders (dysarthria, apraxia, expressive aphasia, akinetic mutism), and visual blurring can also occur (SEDA-21, 391) (SEDA-22, 420) (24).

The higher incidence of moderate or severe late neurotoxicity from tacrolimus compared with ciclosporin was strongly associated with severe postoperative infections, multiple organ failure, and an increased bilirubin, creatinine, and transaminases (25).

It has been suggested that anxiety rather than akathisia can account for several symptoms caused by tacrolimus, such as restlessness (SEDA-21, 391).

Posterior leukoencephalopathy, with clinical, radiological, and neuropathological features resembling those previously described with ciclosporin has been reported in several patients (SEDA-22, 420) (26). Cortical blindness, generalized tonic-clonic seizures ($n = 2$), and diffuse MRI abnormalities were found in three of 50 patients taking tacrolimus after bone marrow transplantation (SEDA-20, 347); these findings have also been observed in patients taking ciclosporin. Acute neurotoxicity was fatal in one patient despite changing from tacrolimus to ciclosporin, and autopsy showed multiple cerebral hemispheric infarcts due to cerebral vasculitis (SEDA-22, 420).

Six patients taking tacrolimus (including five children) developed signs of encephalopathy with generalized or focal seizures, reduced visual acuity or cortical blindness, altered mental status, and white matter lesions on MRI scan, particularly in the parieto-occipital regions (27–29). Three patients had tacrolimus blood concentrations above the target range before the neurological adverse event. Although there was complete resolution after tacrolimus withdrawal or reduction in dosage in four patients, two children still had persistent brain imaging abnormalities and recurrent episodes of seizures.

- A chronic inflammatory demyelinating polyneuropathy was considered to have been caused by tacrolimus in a 62-year-old patient (30).
- The presence of significant tacrolimus concentrations (5.2 and 1.3 ng/ml at 8 and 72 hours after the last dose) in the cerebrospinal fluid of a 64-year-old woman with a renal transplant, who developed an extremely severe form of encephalopathy after 21 months of treatment, suggested that tacrolimus can cross the blood–brain barrier (31).

Complete resolution of tacrolimus-induced neurotoxicity does not occur after tacrolimus withdrawal or dosage reduction (32).

- A 48-year-old man developed acute loss of speech and swallowing apraxia shortly after liver transplantation. Tacrolimus serum concentrations were very high. Although there was progressive improvement after tacrolimus withdrawal, residual speech deficits were still present 3 weeks later. A PET scan showed a marked reduction in metabolic rate in the temporal lobes and the adjacent parieto-occipital region bilaterally.

Other cases of severe neurotoxicity have been seen during tacrolimus treatment for graft-versus-host disease after allogeneic bone marrow transplantation.

- A 16-year-old girl had hypertension and generalized convulsions, which recurred after tacrolimus readministration; she subsequently died from cerebral hemorrhage and respiratory failure (33).

Based on this report and a review of previously published cases, concomitant hypertension and the use of high-dose methylprednisolone were discussed as precipitating factors of tacrolimus neurotoxicity. In two other patients aged 4 and 15 years who had prolonged leukoencephalopathy, the underlying chronic graft-versus-host disease was thought to be a risk factor (34).

In children one advantage of tacrolimus is that it can reduce the dose of glucocorticoids required for immunosuppression. This in turn improves growth. When in one center the immunosuppression protocol was changed to tacrolimus plus mycophenolate mofetil and prednisone, two patients developed transient encephalopathy associated with tacrolimus (35). In both cases, the encephalopathy was managed by treating the associated hypertension and fluid overload; tacrolimus was not withdrawn.

Both tacrolimus and ciclosporin are hydrophobic and can alter the properties of the cell membrane. They bind to an intracellular peptidylprolyl isomerase that regulates

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T cell activation and can interfere with cytoskeletal components that prevent interleukin-2 synthesis and release. Cytotoxic edema caused by acute cerebral ischemia is associated with reduced diffusion, reflecting the failure of membrane sodium pumps. Altered electrolyte or fluid balance can precede the onset of encephalopathy. This can be shown by fluid-attenuated inversion recovery and diffusion-weighted MRI images (36).

A polymorphism of the ABCB1 gene may be associated with a risk of tacrolimus-induced neurotoxicity after liver transplantation. In six patients with neurotoxicity and 11 without neurotoxicity, high tacrolimus concentration, liver dysfunction, and a mutation in position 2677 in exon 21 were positive predictive factors for tacrolimus-induced neurotoxicity (37).

Sensory systems

Eyes

- Optic neuropathy has been reported in a 58-year-old liver transplant patient who had taken tacrolimus for 2 months (38). Further deterioration of vision occurred despite withdrawal.

Ears

Sudden hearing loss has been attributed to tacrolimus (39).

- A 38-year-old woman was switched from ciclosporin to tacrolimus 44 days after kidney and pancreas transplantation and 17 days later had sudden hearing loss with tinnitus. Her tacrolimus blood concentration 3 days later was 28 ng/ml and peaked at 35 ng/ml 8 days later. Audiograms showed bilateral hearing loss—80% for speech perception and mild to moderate sensorineural hearing loss. Her hearing improved on tacrolimus dosage reduction and after the tacrolimus blood concentration reached 15 ng/ml.

Although she was taking many other drugs, including muromonab, which was withdrawn 1 month before the hearing loss occurred, the role of tacrolimus was supported by its chemical similarity to erythromycin, which is ototoxic when given intravenously.

Endocrine

The risk of post-transplant diabetes mellitus is greater with tacrolimus than with ciclosporin, but this was mostly true in black patients and during the initial months after transplantation (40). In one study, insulin sensitivity, alpha and beta cell function, and beta cell reserve were studied in 14 hepatitis C-positive patients with liver transplants, who took tacrolimus or ciclosporin maintenance for 1 year (41). The patients were matched for low prednisolone dosage (1.1 mg/day versus 1.3 mg/day), body mass index, lean body mass, and sex, and compared with eight controls. Insulin sensitivity and insulin secretory reserve were significantly different from controls, but there was no significant difference between ciclosporin and tacrolimus.

The incidence, mechanism, and risk factors of tacrolimus-associated diabetes mellitus are still debated. In 58 patients investigated 1–3 years after liver transplantation there was a significantly higher incidence of diabetes mellitus with tacrolimus ($n = 32$) compared with ciclosporin ($n = 26$) (42). Newly-diagnosed diabetes occurred in nine of 28 tacrolimus-treated patients, of whom six required insulin, and in none of 25 ciclosporin-treated patients. Five patients taking tacrolimus also had islet cell-specific autoantibodies that correlated significantly with HLA risk haplotypes.

- A 32-year-old woman with previous autoimmune disorders and a susceptible HLA haplotype developed diabetes with newly positive glutamic acid decarboxylase antibody after taking tacrolimus for 5 months (43).

Together, these reports suggest that tacrolimus does not suppress the production of autoantibodies in patients genetically prone to develop autoimmune diabetes, with induction of an autoimmune phenomenon. This also suggests that tacrolimus treatment should be undertaken cautiously in predisposed patients.

Metabolism

Of 834 primary adult liver transplant recipients, of whom 499 were alive and taking tacrolimus, 70% were glucocorticoid-free after 1 year; this did not change over the next 5 years (44). However, glucocorticoid-associated adverse effects, such as hypertension, diabetes, and hyperlipidemia, were not statistically significantly less common in patients not taking glucocorticoids. This may have been because of the diabetogenic effect of tacrolimus.

Diabetes mellitus

Altered glucose metabolism and subsequent hyperglycemia or even insulin-dependent diabetes mellitus is an important issue in transplant patients, particularly in adults or patients taking high doses. In animals, high-dose tacrolimus causes glucose intolerance and reduced insulin release (45). This resolves after withdrawal. Diabetes mellitus after transplantation is a relatively common complication in pediatric thoracic organ recipients taking tacrolimus (46). Specific risk factors have not been identified. A switch from tacrolimus to ciclosporin for other reasons in two patients did not resolve the problem.

The incidence of hyperglycemia or diabetes mellitus requiring insulin at some point during treatment was 10–20% in adults (2% in children), an incidence about 2–3 times higher than with ciclosporin (SEDA-20, 347). However, more recent studies and case reports have shown that children could be also very sensitive to the diabetogenic effects of tacrolimus, with an incidence possibly higher than previously thought (47,48). While the diabetes mellitus tends to improve or abate after the dose of tacrolimus or glucocorticoid has been reduced, glucose intolerance was more frequent in the tacrolimus group after a median of 23 months (49). However, post-transplant diabetes mellitus requiring permanent insulin treatment was as frequent in patients with liver grafts taking ciclosporin or tacrolimus after 1 year (50). Finally, there was a possible correlation between impaired glucose tolerance or a diabetic pattern detected by a pretransplant 75 g oral glucose tolerance test and the later development of post-transplant diabetes mellitus (51).

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In a pooled analysis of four randomized trials of tacrolimus versus ciclosporin after renal transplantation, the prevalence of post-transplant diabetes mellitus at 1 year (two studies, 532 patients) was five times higher with tacrolimus than with ciclosporin (OR = 5.0; 95% CI = 2.0, 12.4) (52). In the opinion of the US FDA, diabetes mellitus after transplantation was a significant hazard in tacrolimus-treated patients, even though about half of the patients were no longer taking insulin at 2 years after transplantation (53).

The exact mechanisms of tacrolimus-induced diabetes are unknown. In one renal transplant patient with genetic susceptibility, tacrolimus was associated with insulin-dependent diabetes mellitus and the simultaneous occurrence of anti-glutamic acid decarboxylase antibody (54). Within 2 months after conversion from tacrolimus to ciclosporin, the antibody was no longer detected and the patient's insulin requirements fell dramatically. Tacrolimus-induced direct beta cell toxicity, with subsequent development of beta cell autoimmunity, was therefore suggested as a possible mechanism in patients with genetic susceptibility for type I diabetes.

Hepatitis C virus infection has been associated with diabetes and is a significant risk in patients with renal transplants. In 427 patients with renal transplants and no previous diabetes mellitus, diabetes after transplantation occurred more often in hepatitis C virus-positive than hepatitis C virus-negative patients (39 versus 9.8%) (55). Diabetes mellitus after transplantation occurred more often in hepatitis C virus-positive patients taking tacrolimus than in those taking ciclosporin (58 versus 7.7%). In hepatitis C virus-negative patients, the rates of diabetes mellitus were similar. The authors concluded that hepatitis C is strongly associated with diabetes mellitus after renal transplantation because of the greater diabetogenicity of tacrolimus.

In 17 patients, in whom fasting blood samples were taken immediately before transplantation and at 1 and 3 months after transplantation for measurement of HbA, insulin, C-peptide, free fatty aids, lipids, urea, and creatinine, the incidence of diabetes mellitus was high (47%) (56). Diabetes was more common in black patients, but owing to the small number of patients the difference was not statistically significant. Insulin resistance seems to be the main pathogenic mechanism involved.

Lipid metabolism

In contrast to its effects on glucose metabolism, tacrolimus offers potential advantages over ciclosporin for lipid disorders (57). Compared with ciclosporin-based immunosuppressive regimens, total cholesterol and LDL cholesterol serum concentrations were lower in patients taking tacrolimus for 1 year (58). Both findings were considered to result from a significant glucocorticoid-sparing effect of tacrolimus.

Hematologic

Acute hemolysis occurred in eight of 1400 patients (59). Although multiple other causal factors could have been relevant, further hematological investigations suggested that tacrolimus can cause or promote hemolysis, particularly in patients with acquired anti-erythrocyte antibodies.

Pure red cell aplasia is an occasional complication of treatment (SED-13, 1131) (SEDA-20, 347) (60). In one case, tacrolimus was thought to have caused reversible pancytopenia with severely reduced granulopoiesis and megakaryocytopoiesis on bone marrow examination (SEDA-21, 391).

- The prothrombin time was prolonged to 36 seconds, with isolated factor V deficiency (5%), 2 weeks after a 46-year-old patient with a liver transplant was given tacrolimus and oxacillin (61). Factor V antigen was lower than 5%. In vitro investigations of the patient's plasma showed dose-dependent factor V inhibitory activity in the presence of tacrolimus. Factor V activity and the coagulation profile returned to normal after withdrawal.

The development of this transiently acquired inhibitor of coagulation factor V may have been due to either tacrolimus or oxacillin.

Microangiopathy and the resulting thrombotic thrombocytopenic purpura-like syndrome has been reported in three transplant patients taking tacrolimus, including one with a severe form (62). Microangiopathy was associated with high trough tacrolimus concentrations (over 24 ng/ml) and raised concentrations of endothelin and various cytokines, namely interleukin-8, interleukin-10, interleukin-12, tumor necrosis factor alfa, and interferon gamma.

Mouth and teeth

A brief case report has suggested that tacrolimus can cause gingival hyperplasia (63).

Gastrointestinal

Severe gastrointestinal toxicity with anorexia and weight loss is sometimes observed in patients taking tacrolilmus (SEDA-19, 352).

Tacrolimus-associated *Clostridium difficile* diarrhea has been reported (64).

- A 29-year-old man was given mycophenolate and tacrolimus for an episode of renal transplant rejection that occurred 6.5 years after transplantation. Four weeks after tacrolimus was begun, he had diarrhea, nausea, and malaise. There was *C. difficile* toxin in the stools, and his symptoms abated with metronidazole. About 1 month later, he developed diarrhea, fever, and severe dehydration. *Clostridium difficile* toxin was again detected in the stools, and his symptoms completely resolved with oral vancomycin and withdrawal of tacrolimus.

Similar cases have been reported to the manufacturers. A possible relation between the macrolide molecular structure of tacrolimus and the development of *C. difficile* colitis remains to be established.

Liver

In children 0.1% tacrolimus ointment has been used daily without major adverse effects.

- In a 3-year-old African-American boy with moderate atopic dermatitis, tacrolimus caused raised transaminase and lactate dehydrogenase activities. Tacrolimus was withdrawn on day 29, but no further information was given about their liver function tests (65).

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The finding of mild to moderate liver function test abnormalities that normalized on dosage reduction or withdrawal of tacrolimus has suggested possible dose-related hepatotoxicity (66). In liver transplant patients, liver biopsy showed a centrilobular hepatocellular drop-out with sinusoidal dilatation and congestion, and no features of cellular rejection or acute hepatitis.

Pancreas

Acute pancreatitis has rarely been reported in clinical trials, but no detailed cases were available before the following report (67).

- A 28-year-old woman was switched from ciclosporin to tacrolimus for prophylaxis of graft-versus-host disease after allogeneic stem cell transplantation for chronic myelogenous leukemia. She also took methylprednisolone and inhaled pentamidine. After 2 weeks she developed acute abdominal pain, tachypnea, hypoxia, and oliguria. Amylase and lipase peaked at about four and five times the upper limits of the reference ranges, and urinary analysis was consistent with acute tubular necrosis. An abdominal CT scan showed an enlarged edematous pancreas with a peripancreatic inflammatory exudate. There was no biliary obstruction or dyslipidemia. Shortly after tacrolimus withdrawal, she became anuric and had an episode of acute respiratory distress, but then improved over the next few days.

Although treatment with methylprednisolone, pentamidine, and total parenteral nutrition could have contributed in this patient, they were either continued or readministered without ill effect.

Urinary tract

Tacrolimus nephrotoxicity has been reviewed (68) and is considered to be very similar to that described with ciclosporin. The clinical and histological characteristics of acute tacrolimus nephrotoxicity have been described from a retrospective analysis of 67 patients with renal transplants, of whom 27 developed acute nephrotoxicity, in seven of whom underlying moderate-to-severe renal arteriosclerosis might have predisposed to tacrolimus nephrotoxicity (69).

Tacrolimus-induced chronic nephrotoxicity has clinical and histopathological features very similar to those induced by ciclosporin, that is tubular lesions, hyaline arteriolopathy, and hemolytic–uremic syndrome-like changes in glomeruli and vessels (70). Isolated glomerular microthrombosis has also been described (71). Although tacrolimus was successfully used in several patients suffering from ciclosporin-induced hemolytic–uremic syndrome, thrombocytopenic purpura and hemolytic–uremic syndrome, including one fatal case, have also been reported in patients taking tacrolimus (SED-13, 1131) (SEDA-20, 347). In addition, ciclosporin and tacrolimus were significant risk factors for recurrence of hemolytic–uremic syndrome in patients who had undergone renal transplantation for end-stage renal disease (72). Late nephrotoxicity evaluated by the mean serum creatinine concentration and/or glomerular filtration rate at 1 year was similar in patients taking ciclosporin or tacrolimus (73,74). However, compared with ciclosporin, tacrolimus appears to be associated with more frequent and severe proximal or distal tubular acidosis 6 months after renal transplantation, although this conclusion is based on work with only a few patients in each group (SEDA-19, 352) (75). Overall, the reported incidence of tacrolimus-associated nephrotoxicity varies from 18 to 42% in liver transplant patients; among 128 patients who had early and late episodes of renal allograft dysfunction (1–156 weeks after transplantation) requiring biopsy, tacrolimus nephrotoxicity was estimated to account for only 17% of cases (76). There were higher than expected serum tacrolimus concentrations in most patients, and the highest concentrations were detected 1.6 days before the peak serum creatinine. However, renal histological lesions were independent of tacrolimus dosage or blood concentrations (77).

The nephrotoxic adverse effects of tacrolimus and ciclosporin are clinically indistinguishable. The pathological features of renal biopsies at 2 years of treatment in patients enrolled in a large multicenter comparison of tacrolimus and ciclosporin in renal transplantation have been reported (78). Of 412 patients initially randomized, renal biopsies were available from 79 taking tacrolimus and 65 taking ciclosporin. There were features of tacrolimus or ciclosporin nephrotoxicity (hyaline arteriolar change, tubular vacuolization) in 19 and 11 patients respectively. There were no differences in the rates of biopsy-proven acute rejection (8.9 versus 9.2%) or chronic allograft nephropathy (62 and 72%). In addition, the histological features of chronic allograft nephropathy were very similar. An older age of the donor, acute rejection, cytomegalovirus infection, and ciclosporin- and tacrolimus-associated nephrotoxicity during the first year of transplantation were the most significant factors associated with the occurrence of chronic nephropathy.

As with ciclosporin, tacrolimus used as a primary immunosuppressant has sometimes been associated with de novo thrombotic microangiopathy/hemolytic–uremic syndrome. Its role has been clearly confirmed in a 52-year-old heart transplant patient in whom hemolytic–uremic syndrome recurred 6 days after tacrolimus readministration (79). From a report of two additional cases and a review of 19 other reported cases, the incidence of tacrolimus-associated thrombotic microangiopathy has been suggested to be 1.0–4.7%; 15 cases were reported in renal transplant patients (80). The mean time to diagnosis was 9 months (4 days to 31 months), and the tacrolimus trough concentrations were usually within the target range. Most patients had the clinical features of hemolytic–uremic syndrome. Final outcomes were known in 18 patients: 10 had tacrolimus dosage reduction only (six recovered, three had an acute cellular rejection, one lost his renal graft); one stopped taking tacrolimus and recovered; seven had tacrolimus dosage reduction or withdrawal and underwent plasmapheresis, fresh-frozen plasma exchange, high-dose glucocorticoids, or anticoagulation (three died of sepsis and multiorgan failure, one lost her renal graft, and three recovered). Furthermore, and in contrast to previous reports (SEDA-19, 353), a change from ciclosporin to tacrolimus in patients with ciclosporin-associated hemolytic–uremic syndrome is not always successful.

- Two renal transplant patients developed resistant late acute rejection while taking ciclosporin (81). After a

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switch to tacrolimus, they had clinical and histological features of hemolytic–uremic syndrome, with biopsy-proven thrombotic microangiopathy within 2 and 12 days after conversion. Both finally required explantation of their renal allografts.

Skin

The long-term safety of topical tacrolimus ointment 0.1% for 6–12 months has been assessed in 316 patients with atopic dermatitis (82). The most common adverse effects clearly attributed to tacrolimus were a local burning sensation (47%), pruritus (24%), and erythema (12%); the incidences fell with time. The observed incidence of infections did not exceed the expected incidence in patients with atopic dermatitis, and there were no effects on circulating cell-mediated immunity.

In 631 adult patients with moderate to severe atopic dermatitis enrolled in a randomized, double-blind, multicenter comparison of tacrolimus (0.03% or 0.1%) with a vehicle applied twice-daily for 12 weeks, the most common adverse events were skin burning, erythema, and pruritus (83). Others were flu-like symptoms and headache. Withdrawal was required in 50 patients because of adverse events, twice as many as in the vehicle group. There was pruritus in 30 patients, skin burning in 19, skin erythema in 12, and skin infections in two. Skin burning and pruritus have consistently been observed with tacrolimus ointment, typically during the first days of treatment, reducing in incidence within the first week; they tend to be mild or moderate.

In 255 children with atopic dermatitis, tacrolimus 0.1% ointment caused transient skin burning and itching as the most common adverse events (65). Two patients required hospital admittance to control skin infections. A flu-like syndrome was the major non-topical adverse event.

- A diffuse, follicular, erythematous eruption has been reported in a 45-year-old patient with a previous history of allergies to multiple medications, including clarithromycin (84). It resolved after tacrolimus withdrawal.

The authors speculated on possible cross-sensitivity between tacrolimus and clarithromycin, which are both macrolides, but confirmatory skin-testing was not performed. In addition, the patient had taken many other drugs that might have been responsible.

Hair

In several studies, alopecia has been found more often with tacrolimus than ciclosporin, and severe alopecia has sometimes followed replacement of ciclosporin by tacrolimus. However, in the light of one detailed case report, and bearing in mind the minimal effect of tacrolimus on hair growth, it is not unlikely that alopecia has sometimes been mistakenly attributed to tacrolimus rather than to concomitant glucocorticoid-induced hair loss in the absence of the counteracting effects of ciclosporin (SEDA-21, 391).

Musculoskeletal

Severe acute rhabomyolysis with subsequent fatal acute renal insufficiency has been reported in an 18-month-old girl (SEDA-19, 353).

Like ciclosporin, tacrolimus has been thought to reduce bone mineral density, but this conclusion was based on a series of seven patients, all of whom had also taken azathioprine and glucocorticoids (85).

- Severe bone pain, previously reported in ciclosporin-treated patients (SED-14, 1291), also occurred as a possible consequence of tacrolimus treatment in a 50-year-old woman (86). Bilateral knee pain occurred within 2 months after renal transplantation and bone scintigraphy showed increased uptake in both knees. Calcitonin was ineffective, and she improved only after the dose of tacrolimus was reduced.

Sexual function

Priapism has been described in a patient with a liver transplant (87).

- One month after transplantation, a 19-year-old man who was taking tacrolimus, azathioprine, and prednisone, developed nausea and vomiting. He reported a 2-week history of painful spontaneous penile erections lasting 2–3 minutes and had had no previous episodes of priapism. An episode of spontaneous erection was confirmed during a medical examination that found no physical abnormalities. The tacrolimus blood concentration was 28 ng/ml. The digestive symptoms and priapism resolved after the tacrolimus concentration had fallen. Sickle cell disease was ruled out.

The authors discussed several mechanisms, including tacrolimus-induced vasodilatation, platelet aggregation, an increase in serotonin, or a fall in endothelin concentrations, based on in vitro data only.

Immunologic

Tacrolimus reduces IgE antibody synthesis, with a subsequent dramatic increase in IgE serum concentrations. This phenomenon has been reported in one asymptomatic patient but has also been advanced as an explanation for a case in which an infant girl treated with tacrolimus had milk hypersensitivity (SEDA-21, 391).

Fish allergy with increased IgE total concentrations and specific IgE antibodies against various fish products have been reported in two children with liver transplants (88). Even though both patients had a personal or familial history of allery, this again suggested a possible relation between tacrolimus and food allergy.

An increasing blood eosinophil count was associated with *Pneumocystis jiroveci* pneumonia in patients taking tacrolimus (89). The mean absolute eosinophil count was significantly higher and absolute eosinophilia (over 350×10^6/l) was more frequent in six patients who developed *P. jiroveci* pneumonia while taking tacrolimus compared with six patients with *P. jiroveci* pneumonia who were taking ciclosporin and eight patients without *P. jiroveci* pneumonia who were taking tacrolimus. A retrospective analysis also showed that the increase in eosinophil count preceded the diagnosis of *P. jiroveci* pneumonia.

Infection risk

Tacrolimus-based immunosuppression may be associated with a lower incidence of major infectious complications,

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namely CMV and pneumonia compared with other drugs (90). However, this hypothesis is based on a single paper, and other studies have been unable to find significant differences in the incidence of major infections between tacrolimus and ciclosporin (5,91). In addition, and as a direct consequence of excessive immunosuppression, a further retrospective study found an increased incidence of symptomatic Epstein–Barr virus infections and related lymphoproliferative disorders in children under 5 years of age who had taken tacrolimus rather than ciclosporin (92).

An unexplained change in the pattern of microbial causes of pneumonia has been noted in liver transplant patients taking tacrolimus, with an unexpectedly high incidence of *Legionella* and fungal pneumonia, the latter being involved in all deaths directly due to pneumonia (93).

In a randomized, double-blind, placebo-controlled study at 23 centers in the USA, children with moderate to severe atopic dermatitis applied the vehicle, tacrolimus ointment 0.03%, or tacrolimus ointment 0.1% for 12 weeks (94). Burning and pruritus were the main adverse effects. *Varicella* infection and vesiculobullous rashes on non-application areas occurred, but with a low incidence (below 5%). Since they occurred in those who used tacrolimus 0.03%, it is likely that they were random events rather than drug-related. Regardless of dose, there were some age-related differences in the incidence of individual adverse events. For example, otitis media was more common in younger children (2–6 years). Tacrolimus ointment had no age-selective effect that was not also observed with the vehicle. Each of the adverse events resolved without sequelae.

Long-Term Effects

Tumorigenicity

It has generally been considered that the incidence and pathological features of tacrolimus-induced cancers after transplantation are similar to those observed with other immunosuppressive agents, in particular ciclosporin (95). However, in a retrospective study in 392 children, who survived for more than 6 months after liver transplantation and were followed for a mean of 4.3 years, there was a five-fold higher rate of lymphoproliferative disease after transplantation in children who took tacrolimus ($n = 141$) than in those who took ciclosporin ($n = 251$) (96). As a result, the incidence density rate of lymphoproliferative disease was 4.8 per 100 person-years in tacrolimus-treated patients, with no difference among age groups. In addition, the mean time to lymphoproliferative disease (12.6 months) was five-fold shorter with tacrolimus than with ciclosporin. Most of the patients with lymphoproliferative disease had a primary Epstein–Barr virus infection after transplantation. The authors suggested that the 10-fold higher in vivo immunosuppressive effect of tacrolimus might have accounted for these findings.

Tacrolimus-induced post-transplant lymphoproliferative diseases are similar to those of the conditions induced by other immunosuppressants, particularly ciclosporin (SED-13, 1131). However, additional data from prolonged follow-up are still awaited. In children who are frequently Epstein–Barr virus-negative, the incidence of post-transplant lymphoproliferative disease varies from 6–11% to 22% after liver transplantation (97). In 89 children, the incidence of post-transplant lymphoproliferative disease at 1 year was 20% (possibly related to Epstein–Barr virus in 89% of patients) (98). Excessive immunosuppression, for example as a result of prior muromonab or antithymocyte globulin administration and high tacrolimus blood concentrations during the period preceding Epstein–Barr virus infection are regarded as significant risk factors, emphasizing the need to secure low trough tacrolimus concentrations after the first post-transplant month. An increase in total gammaglobulin and the development of oligoclonal or polyclonal immunoglobulins were thought to be preliminary signs of this syndrome.

Second-Generation Effects

Pregnancy

Among 25 infants born after 27 pregnancies in tacrolimus-treated liver transplant patients there was an unexpectedly low incidence of hypertension, pre-eclampsia, and allograft function abnormalities, whereas preterm delivery, low birth weight, and transient mild renal impairment with hyperkalemia in neonates occurred at a similar rate (99).

It has been suggested that tacrolimus may be less likely than ciclosporin to cause maternal renal dysfunction or pre-eclampsia, but this hypothesis is based only on retrospective work in a small number of patients (100).

- Congestive heart failure with dilated cardiomyopathy occurred in twin boys born to a woman with a renal transplant who had taken tacrolimus throughout her pregnancy (101). One twin died from irreversible cardiac failure, and autopsy findings showed thrombogenic cardiomyopathy and degeneration of cardiac muscle. The other twin was more actively treated and had only mild tricuspid insufficiency on follow-up.

This report is in keeping with the possible and debated role of tacrolimus in the development of cardiomyopathy in children.

Teratogenicity

In the National Transplantation Pregnancy Registry, there was no evidence of an increased incidence of congenital malformations among 25 infants born after 27 pregnancies in tacrolimus-treated liver transplant patients (99).

Fetotoxicity

Among 25 infants born after 27 pregnancies in tacrolimus-treated liver transplant patients, there were two neonatal deaths whose conception had been close to the time of transplantation, and very high tacrolimus cord levels were found in one child who presented with neonatal anuria (99).

Drug Administration

Drug overdose

Acute tacrolimus overdosage usually produces only moderate toxicity or none at all. From the data available in 16 children or adults, overdosage up to 30 times the intended

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dose produced no symptoms in seven patients and reversible moderate increases in serum creatinine concentrations, or transaminase activities, nausea, and mild tremors in eight patients who underwent gastric decontamination and conservative measures only (102,103). An additional patient on maintenance treatment developed renal insufficiency, histoplasmosis, and sepsis within two days of overdosage. Continuous hemofiltration dramatically increased the rate of elimination of tacrolimus in two other patients who experienced acute renal and liver failure with high plasma tacrolimus blood concentrations (104).

Even large accidental overdosage of tacrolimus does not result in marked acute toxicity (105).

- The inadvertent administration of 25 times the intended dose in a 22-month-old infant produced minimal consequences, with only a five-fold reversible increase in serum amylase activity.

Drug–Drug Interactions

Antimicrobial agents

The hepatic metabolism of tacrolimus is primarily mediated by CYP3A, and experimental evidence suggests a theoretical potential for numerous interactions with drugs that induce or inhibit CYP3A. However, very few formal drug interaction studies have been carried out, and most of our current knowledge is based on case reports and small series of patients, or is derived from experience accumulated with ciclosporin. Among antimicrobial agents, erythromycin, chloramphenicol, clarithromycin, clotrimazole, danazol, oral (but not intravenous) fluconazole, itraconazole, and ketoconazole increase tacrolimus serum concentrations and can cause subsequent nephrotoxicity, whereas rifampicin reduces tacrolimus concentrations (SED-13, 1131) (SEDA-20, 348) (SEDA-22, 419) (106–109).

- A potential interaction with pristinamycin has been described in a 41-year-old renal transplant patient who had an approximate five-fold increase in tacrolimus trough concentrations within 4 days of pristinamycin treatment (110).
- A 10-fold increase in tacrolimus dosage was required in a 61-year-old patient with a renal transplant who took concomitant rifampicin (111).

The interaction of tacrolimus with rifampicin has been convincingly confirmed in six healthy volunteers who took a single oral or intravenous dose of tacrolimus (112). Rifampicin 600 mg/day for 18 days produced a significant 47% increase in tacrolimus clearance after intravenous administration and a 51% reduction in its oral systemic availability, consistent with induction by rifampicin of both hepatic and intestinal metabolism of tacrolimus.

Calcium channel blockers

A 3-day course of diltiazem 90 mg/day produced a four-fold increase in tacrolimus trough concentrations in a 68-year-old patient with a liver transplant (113).

In a non-randomized, pharmacokinetic study, four patients taking tacrolimus after kidney and liver transplantation were given diltiazem in seven incremental dosages of 0–180 mg at 2-week intervals (114). The mean tacrolimus-sparing effect was similar to the ciclosporin-sparing effect previously reported. This effect occurred at a lower dose of diltiazem in renal transplant patients than in liver transplant patients. Tacrolimus is metabolized by CYP3A4 and is also a substrate for P glycoprotein, and this interaction could have occurred by inhibition of these mechanisms.

A retrospective study has shown a significant improvement in kidney function and a 38% reduction in tacrolimus dosage requirements in patients taking both nifedipine and tacrolimus compared to patients not taking nifedipine (115).

Ibuprofen

Acute renal insufficiency in association with the use of ibuprofen and tacrolimus has been reported in two liver transplant recipients (116), and the relevance of this interaction is probably similar to that reported with ciclosporin.

Metronidazole

Metronidazole can produce a two-fold increase in blood concentrations of ciclosporin and tacrolimus, with a subsequent increase in serum creatinine in both cases (117).

Mibefradil

Mibefradil, a potent inhibitor of CYP3A, increased tacrolimus blood concentrations dramatically (118).

Nefazodone

Nefazodone may inhibit the metabolism of tacrolimus (119).

- A 16-year-old boy had a five-fold increase in tacrolimus blood concentrations and a two-fold increase in creatinine concentrations within 4 weeks of nefazodone treatment. Complete normalization occurred after replacement with paroxetine and a transient reduction in tacrolimus dosage.

Protease inhibitors

Various protease inhibitors are metabolic inhibitors and are predicted to have deleterious effects on tacrolimus metabolism.

- In a 52-year-old liver transplant patient with HIV infection, successive treatment with various antiretroviral combinations containing nelfinavir, ritonavir, or saquinavir increased tacrolimus blood concentrations and caused severe prolonged neurological symptoms suggestive of tacrolimus toxicity (120). The patient was finally stabilized with a regimen containing nelfinavir, stavudine, and lamivudine, and a more than 95% reduction in the dosage of tacrolimus.
- An acute drug interaction with nelfinavir has been described in a 49-year-old liver transplant man with HIV and hepatitis C infections (121). The patient had three consecutive episodes of increased blood tacrolimus concentrations during nelfinavir administration. Both drugs were finally continued, but the dose of tacrolimus was only one-seventieth of the usual dose.

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Theophylline

An increase in tacrolimus trough blood concentrations has been attributed to concomitant theophylline therapy in a 33-year-old man with a renal transplant (122). A subsequent pharmacokinetic study showed that theophylline increased the AUC of oral tacrolimus six-fold.

Voriconazole

In a patient who took tacrolimus after liver transplant, co-administration of voriconazole resulted in raised trough tacrolimus concentrations (nearly 10-fold); there were no changes in another patient, who took a placebo (123). Voriconazole inhibits the metabolism of tacrolimus in liver microsomes by 50% in vitro.

Monitoring Therapy

In 14 patients with renal transplants, there was a closed relation between individual tacrolimus whole blood trough concentrations and the occurrence of adverse effects (124). The incidence of tacrolimus adverse effects was 76% with tacrolimus concentrations above 30 ng/ml and only 5.3% with concentrations below 10 ng/ml. This relation was found in all separate groups of adverse effects analysed, that is nephrotoxicity, neurotoxicity, infections, and others. In contrast, there was no relation between tacrolimus concentrations and rejection episodes. Accordingly, the authors stressed that tacrolimus whole blood trough concentrations should be strictly kept under 20 ng/ml.

There is no relation between tacrolimus blood concentrations and the occurrence of major neurotoxicity (125).

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Tafenoquine

General Information

Tafenoquine is an 8-aminoquinoline derivative that is more active than primaquine (SEDA-13, 811). It is active against all human forms of malaria. In animals, tafenoquine is several times more potent than primaquine and is effective against both blood and liver stages of the malaria parasite. It has a half-life of 14 days, which makes it a good candidate for prophylaxis, with the

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possibility of monthly dosing. It was effective and safe in early trials (1).

In a randomized, double-blind, placebo-controlled trial, in a single oral dose of 4–600 mg (base) in 48 men it was well tolerated, apart from minor gastrointestinal disturbances; the half-life was 14 days (2). However, although tafenoquine may well be safer than primaquine, patients were also excluded from this trial if they had glucose-6-phosphate dehydrogenase (G6PD) deficiency, so it remains to be seen whether tafenoquine can overcome the most important practical problem with primaquine. Further widespread use will be needed before rare adverse effects, if any, emerge (SEDA-14, 958) (SEDA-21, 296) (SEDA-22, 305) (SEDA-23, 306).

There has been a randomized placebo-controlled study of tafenoquine as chemoprophylaxis for malaria in 426 Gabonese schoolchildren aged 12–20 years (1). Children with G6PD deficiency were excluded. Radical cure of malaria was achieved with halofantrine followed by placebo or tafenoquine in the following daily doses: 250 mg, 125 mg, 62.5 mg, or 31.25 mg given for 3 days. Follow-up was for 77 days. Tafenoquine was highly effective in dosages over 62.5 mg/day. There were 180 adverse events thought to be related to the study drug. All were mild and self-limiting and none was considered to be serious. They included headache, fever, and abdominal pain. However, none was significantly more common with tafenoquine than with placebo. On day 28, but at no other time, there was a small (0.4 g/dl) but significant fall in hemoglobin concentration with tafenoquine 250 mg/day.

Susceptibility Factors

Age

In 104 healthy men (mean age 29 years, weight 60 kg) who took tafenoquine for malaria prophylaxis (loading dose 400 mg/day for 3 days followed by 400 mg/month in 5 consecutive months) age and weight affected the apparent volume of distribution, and subjects who contracted malaria had higher clearance rates (3). The population estimate of the first-order absorption half-life was 1.0 hour, clearance was 3.20 l/hour, volume of distribution was 1820 liters, and half-life was 16.4 days.

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Talc

General Information

Talc is a three-layered magnesium sheet with lubricant properties; it is rarely found as a pure entity in nature. The particle size varies considerably (1) depending on the manufacturing process, and may be an important factor in the development of adverse effects. Talc is principally used as inert filler material in medicinal tablets or as a drying ingredient in baby powders. The adverse effects of talc include empyema, dysrhythmias, and respiratory failure (2).

Use of talc in pleurodesis

Intrapleural therapy in humans was first reported by Bethune in 1935, when he described the dusting of pleural surfaces with talc before lobectomy to promote pleurodesis (3). Since this initial description, many different agents have been used intrapleurally to produce pleurodesis, both in patients with pleural effusion and in patients with pneumothorax. Some of these agents, talc in particular, have been associated with potentially serious adverse events. Over the last 25 years the role of intrapleural therapy has expanded and now includes the instillation of thrombolytic agents intrapleurally to hasten the resolution of complicated pleural space infections (empyema); both streptokinase and urokinase have been used for this purpose. Malignant pleural effusions represent 25–50% of all pleural effusions seen in a general hospital (4). Lung, breast, ovarian, genitourinary, and gastrointestinal tract malignancies are often associated with pleural effusions, and malignant effusion is often the first manifestation of malignancy (5,6).

The aim of pleurodesis is to produce fusion between the visceral and parietal pleural surfaces and so prevent the accumulation of air or fluid in the pleural space. In a chemical pleurodesis, this fusion is generally achieved by the instillation of agents that induce an inflammatory response on the pleural surfaces. These agents can be introduced into the pleural space through a chest tube at the bedside or during thoracoscopy/thoracotomy.

Mechanism of action

The mechanism of action of talc in pleurodesis has not been fully elucidated, although it is thought to stimulate a typical local inflammatory response, with reduced fibrinolytic activity, mesothelial cell injury, and fibroblast proliferation. Pneumonitis or respiratory failure can be secondary to downstream inflammatory mediators from more proximal talc injury (7). This acute-phase inflammatory response is dose-related (8,9) and is inhibited by glucocorticoids (10). Talc may also have an adhesion stimulating quality, since empyema alone stimulates a typical inflammatory response but does not lead to pleurodesis (11). In fact, talc stimulates intercellular adhesion molecule-1 in mesothelial cells (12). The mechanism of chronic fibrosis may involve continuous fibroblast activation by foreign body giant cell released mediators or macrophages.

Administration

Talc can be insufflated into the pleural space in a powder form, usually at thoracoscopy or thoracotomy (talc poudrage), or can be mixed with normal saline and instilled through a standard chest tube as talc slurry.

Comparative studies

The use of talc, one of the most common agents for chemical pleurodesis, has been documented in more than 3000 patients, largely in the form of case series (13). The intrapleural use of talc has been the subject of a number of recent comprehensive reviews (11,14,15).

Of 51 patients with malignant pleural effusions, 14 underwent slurry talc pleurodesis via a chest tube, 14 had talc poudrage during Video-Assisted Thoracoscopic exploration of the pleural cavity for suspected malignant effusion, and 24 underwent chemical pleurodesis with bleomycin via a chest tube (16). The most common adverse effects were chest pain and fever. The duration of adverse effects after talc pleurodesis was longer (2–3 days) than after bleomycin. There was chest pain in 15 of the 28 patients who received talc, with a duration of 18–52 (median 31) hours. There was fever in 22 of those who received talc, with a duration of 5–34 (median 12.5) hours. Complications were more common in those who received talc, such as thoracic empyema ($n = 1$), wound infection ($n = 2$), and respiratory distress ($n = 5$).

Adverse effects

Adverse events related to agents used in pleurodesis have been rare. However, almost any agent introduced into the pleural space can reach the circulation through inflamed pleural surfaces, with potential adverse effects (17). A case of fulminant pneumonitis following talc pleurodesis prompted a review of the existing experience (18). Of 78 patients with recurrent pleural effusions or pneumothorax treated by pleurodesis, five had bilateral pleural effusions, resulting in a total of 89 procedures. In 19 procedures talc was administered by poudrage and in 70 procedures it was given as a slurry with 50–500 ml of isotonic saline and 20–30 ml of 1% lidocaine. The dose was 5 g in 85 procedures, and 2.5 and 10 g each in two procedures. Of the patients who presented with malignant effusions, 18 had a primary carcinoma in the lung, 12 in the ovary, and 10 in the breast; there were six cases of lymphoma; 13 patients had less common primaries. Nine patients had benign or undiagnosed effusions and nine had spontaneous pneumothorax.

Of the procedures evaluated, 19 involved only minor complications, including fever over 38.1°C within 12 hours of pleurodesis in 13, asymptomatic hypoxemia in 19, dyspnea relieved by oxygen in six, and an increased need for narcotics in five. Subcutaneous emphysema, local infection, and asymptomatic hypotension each occurred after one procedure. There were major complications in 11 patients, including one patient with pulmonary embolism, three with unilateral pulmonary edema, eight who developed bilateral pulmonary edema, and one who died within 24 hours after bilateral talc administration. Patients developed respiratory complications after 24 of 28 talc pleurodesis procedures. The most significant respiratory complication was adult respiratory distress syndrome, defined by bilateral diffuse infiltrates on chest X-ray and hypoxemia requiring mechanical ventilation, which occurred after eight procedures in seven patients. This figure includes one patient who died after simultaneous bilateral talc poudrage.

Minor adverse effects related to talc pleurodesis are common: chest pain occurs in about 7% of patients and fever in 16–69%. Fever characteristically starts within 4–12 hours of pleurodesis and rarely lasts more than 72 hours. Chest pain is usually only mild (11,13,14).

Respiratory complications

The most serious adverse effect of talc is a possible association between talc pleurodesis and the development of acute respiratory failure (usually in the form of ARDS); over 30 cases have been described (13) after intrapleural talc either as a slurry (8) or insufflated (18,19). The literature on acute respiratory failure after intrapleural talc has been reviewed, with recommendations on whether talc should continue to be used to produce pleurodesis (20). Some believe that intrapleural talc should not be used to produce a pleurodesis, since there are effective alternatives for producing pleurodesis (mechanical abrasion if thoracoscopy is performed, tetracycline derivatives or bleomycin if chest tubes are used).

Most cases of ARDS have occurred in patients with malignant pleural effusions, not all were clearly talc-related, and there is not enough information in some case reports to be certain of the role of talc. For example, in 1980, respiratory failure/pneumonia in seven of 197 patients who underwent talc poudrage for malignant pleural effusion was described in an abstract, but no further information regarding the clinical course of these patients is available (9). In 1983, Rinaldo et al. were the first to carefully document the development of ARDS after intrapleural talc instillation (8). They described three patients who developed progressive dyspnea and acute respiratory failure, characterized by bilateral diffuse pulmonary infiltrates, within 72 hours of the instillation of talc 10 g through a chest tube. All three had underlying malignancies and all required intubation and ventilation for respiratory failure. One patient died after 1 month of intensive care support. No other cause for ARDS was found in these patients and the authors were confident that talc had been responsible by unknown mechanisms. They recommended that other sclerosants be used for chemical pleurodesis. At around the same time, a patient who developed acute pneumonitis after chemical pleurodesis with talc 2 g was described (21). The clinical course of this patient was different to that described above: breathlessness occurred within 3 hours of pleurodesis, but the patient did not require intensive care support until 10 days later, when bilateral pulmonary infiltrates developed. At bronchoalveolar lavage 12 days after pleurodesis, talc particles were seen in the lavage fluid. No other cause for the pulmonary infiltrates was found and the patient recovered with oxygen and corticosteroid therapy alone. The authors suggested that systemic absorption of talc, with subsequent embolization to the

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lung, had produced this picture and they also suggested that pleural biopsies performed just before pleurodesis might have aided the systemic absorption of talc.

Three large case series were published after these reports. In two series (15,22) there were no episodes of respiratory distress after talc pleurodesis in 299 and 360 patients respectively. However, respiratory failure occurred in five of 58 patients treated with talc pleurodesis (23). Excess narcotic analgesia and infective pneumonia were considered causative in two patients, and two other patients recovered with oxygen and corticosteroids. No more information on these two patients was provided. The remaining patients developed bilateral pulmonary infiltrates and severe hypoxia consistent with ARDS, but recovered after intubation and ventilation for 5 days. This patient had undergone simultaneous bilateral talc pleurodesis and the authors thought that the higher dose of talc that this patient had received might have contributed to the development of ARDS. Again, the mechanism by which talc produced ARDS was unknown.

The possibility that talc can cause respiratory failure was explored further in 1997 (24). ARDS occurred in four of 338 patients treated with talc poudrage (2 g) via thoracoscopy. All four had malignant effusions and all developed bilateral pulmonary infiltrates, hypoxia, and hypotension within 24–48 hours of talc insufflation. All four required mechanical ventilation and three died. Bronchoalveolar lavage was performed in all four and talc crystals were recovered from lavage fluid in each case. Furthermore, at autopsy in one patient, talc crystals were found in almost every organ, showing that systemic distribution of talc did occur after pleurodesis. However, as the authors acknowledged, it was not possible to definitely attribute the symptoms in these patients to the talc pleurodesis. Studies in animals have shown systemic distribution of talc after pleurodesis (25). However, systemic dissemination may occur in all patients treated with pleurodesis and does not confirm that this is the cause of respiratory failure documented in a small number of patients.

The highest incidence of respiratory complications after talc pleurodesis was reported in 1999 in a retrospective review of 89 procedures in 78 patients (18). ARDS occurred in 9% (that is after eight procedures in seven patients). All seven patients had increased oxygen requirements, respiratory distress, and bilateral infiltrates on chest X-ray, and required a mean of 38 hours of mechanical ventilation. Six patients had malignant effusions. The other had AIDS, had undergone bilateral pleurodesis for pneumothoraces secondary to *Pneumocystis jiroveci* (*Pneumocystis carinii*) pneumonia, and died within 24 hours of the procedure. No more clinical information was given about the other six patients, particularly regarding the time-course of symptoms and investigations to exclude other diseases.

Since the literature on this topic largely comprises case reports and retrospective reviews, it is possible that complications may have been under-reported. In addition, there is marked variability in the reported incidence of respiratory complications from series to series, and there is the additional confounding factor that malignant pleural effusion, a condition with a poor short-term survival and significant associated morbidity, is often the indication for talc pleurodesis. Respiratory complications are common in these patients, and talc pleurodesis may be coincidental rather than causative. Other possible causes for respiratory distress in these patients include re-expansion pulmonary edema, sepsis related to the chest-tube, and bacterial contamination of talc. The presence of talc crystals in bronchoalveolar lavage fluid indicates systemic distribution but not necessarily causation of ARDS, and is likely to occur in all patients treated with talc. There is significant variability in the talc preparations available for pleurodesis, and it has been suggested that smaller particle size poses a higher risk for ARDS, although this is unproven. It has also been suggested that pleural biopsy before pleurodesis may increase the risk of ARDS (also unproven).

Organs and Systems

Respiratory

Intravenous injection of "solubilized" psychoactive pills containing talc can produce microemboli in small pulmonary vessels, leading to talc granulomatosis, a common finding in drug abusers. Medications intended for oral use can be injected or sniffed, together with talc particles. Pulmonary hypertension due to talc microemboli is a well-known cause of respiratory failure in heroin addicts.

- A heroin addicted patient, who had been followed up for 6 months for increasing dyspnea due to chronic cor pulmonale, was admitted to an intensive care unit. She died shortly after. Postmortem lung biopsies showed talc particles within alveolar walls and alveolar macrophages, as well as alterations in blood vessels (26).

Talc granulomatosis has been ascribed to sniffing cocaine (27).

Overzealous application of baby powder can cause severe pulmonary complications if the infant inhales the powder (28).

Formation of umbilical granulomas has been described as an adverse effect of talc in a newborn infant (29).

A group of patients underwent lung function testing 22–35 years after they were treated for idiopathic spontaneous pneumothorax either with talc poudrage or by simple drainage. The former caused mild restrictive impairment of lung function with a mean total lung capacity 89% of predicted, compared with a mean total lung capacity of 96% in subjects who had been treated by simple drainage. None of the subjects had developed a mesothelioma (30).

Although described in association with conglomerate masses and bullous disease in end-stage talc granulomatosis, spontaneous pneumothorax can also occur earlier in the course of talc-induced lung disease (31).

Gastrointestinal

An experimental animal study undertaken to determine whether cornstarch powder suspended in physiological saline causes intraperitoneal adhesions after laparotomy showed a significantly higher incidence of adhesions than in the control group two weeks after surgery. It was recommended that powder-free surgical gloves should

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be used to prevent adhesion formation after abdominal surgery (32).

Long-Term Effects

Tumorigenicity

Ovarian cancer has been increasing in frequency over the past 40 years, and a role for environmental factors in its etiology has been inferred from its higher incidence in industrialized countries. Cosmetic talc, deposited in the vagina after direct application to the perineum or to undergarments, sanitary napkins, or diaphragms, or through use of a talc-dusted condom during intercourse, may play an important role. In a case-control study of the use of talc in genital hygiene the risk of ovarian cancer was significantly increased in women who applied talc directly as a body powder, on a daily basis, for more than 10 years (33). The greatest risk of ovarian cancer was in the subgroup of women estimated to have made more than 10 000 talc applications during years when they were ovulating. However, this exposure was found in only 14% of women with ovarian cancer. The authors concluded that a life-time pattern of perineal talc use may increase the risk of epithelial ovarian cancer, but that it is unlikely to be the cause of most cases of epithelial ovarian cancers.

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Talipexole

General Information

Talipexole is a dopamine receptor agonist.

Long-term evaluations have indicated that no new adverse effects appear after the first 8 weeks of treatment and that overall adverse effects may abate with time.

Organs and Systems

Cardiovascular

Sinus bradycardia and hypotension have been attributed to talipexole (1).

- About 4 hours after a 65-year-old man with Parkinson's disease took talipexole hydrochloride 0.8 mg, he acutely developed sleepiness, delusion, akinesia, and faintness associated with hypotension and sinus bradycardia. A similar episode occurred when he took talipexole hydrochloride 1.2 mg/day in combination with co-careldopa (levodopa 200 mg/day plus carbidopa 20 mg/day). These symptoms persisted for 12 hours and abated gradually without any specific treatment.

The authors suggested that talipexole had caused bradycardia and hypotension by stimulating both D_2 dopamine receptors and alpha$_2$-adrenoceptors.

Nervous system

Frequent nervous system adverse effects of talipexole are drowsiness, dizziness, and fatigue (2); headache and confusion have also been reported. Talipexole can improve the negative symptoms of schizophrenia but exacerbate the positive symptoms (3).

Extrapyramidal reactions to talipexole are uncommon.

- A 60-year-old man with a 12-year history of Parkinson's disease was given talipexole for the wearing-off phenomenon 3 years after starting levodopa (4). His parkinsonism deteriorated and his serum creatine phosphokinase activity rose to 1875 IU/l. The talipexole was withdrawn after gradual dosage reduction and he gradually improved.

The authors suggested that talipexole had caused an incomplete form of the neuroleptic malignant syndrome.

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Talniflumate

See also Non-steroidal anti-inflammatory drugs

General Information

Talniflumate is an inhibitor of calcium-activated chloride channels, which has been developed to treat mucous hypersecretion (1). It is a phthalidyl ester of pyridinecarboxylic acid, related to niflumic acid.

Organs and Systems

Gastrointestinal

Gastrointestinal effects are the most frequent adverse effects of talniflumate (2).

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Tamoxifen

General Information

Tamoxifen is an estrogen receptor partial agonist with antiestrogenic properties in the breast and estrogenic effects in tissues such as bone and the cardiovascular system. In most cases there is endometrial thickening on ultrasonography, and additional tests, such as hydrosonography or hysteroscopy, are required to confirm the presence of an empty atrophic uterus, as seen in most asymptomatic women taking tamoxifen.

Tamoxifen is commonly used in the treatment of breast carcinoma (1); the overall rates published for adverse effects vary very greatly, between 1 and 60% (2,3). It has also been used as a form of HRT to reduce bone loss and the incidence of fractures in high-risk cases (4). A combination of tamoxifen with ovarian suppression is as effective as the use of cytostatic drugs, and has been claimed to be better tolerated (5–7).

The use of tamoxifen to prevent breast cancer has been reviewed (8). The merits of using tamoxifen to prevent mammary carcinoma in women who have never had the disease but are believed to be at high risk have been disputed (9), but it is clear that it would involve very long treatment and that one's view of the adverse effects might need to be revised for this class of users. The available data after 5, 10, and 15 years of follow up confirmed an increase in the incidence of endometrial cancer and of thromboembolic complications and suggested ocular toxicity, but these effects were not common and should be more than balanced by the reduced risk of coronary heart disease and osteoporosis (8).

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Tamoxifen also has beneficial side effects: it protects the myocardium, reduces the incidence of ischemic heart disease, reduces the loss of bone mineral density, and has beneficial effects on lipids (10).

Observational studies

The effect of high-dose tamoxifen as an adjunct to postoperative brain irradiation has been studied for 40 weeks in 12 patients with glioblastoma multiforme, but without controls (11). Two weeks after surgery, the patients were given high-dose oral tamoxifen (120 mg/m^2 bd for 3 months) and 2 weeks later external beam radiotherapy (59.4 Gy, three daily fractions every 6.5 weeks). In one patient tamoxifen was associated with severe vomiting, necessitating dosage reduction and subsequent withdrawal; another patient had bilateral deep venous thrombosis after 51 weeks, but a causal relation was not firmly established. The authors concluded that adjuvant high-dose tamoxifen is relatively well tolerated, although in this series it did not appear to improve the prognosis.

Placebo-controlled studies

In the Breast Cancer Prevention Trial (P-1), initiated by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in 1992, more than 13 000 eligible women were randomized to tamoxifen 20 mg/day or placebo for 5 years (12). During 69 months of follow-up tamoxifen reduced the risk of both invasive and non-invasive cancer and reduced fractures of the hip, radius, and spine; however, the rate of endometrial cancer increased (RR = 2.53; 95% CI = 1.35, 4.97), as did the frequency of vascular events.

General adverse effects

The adverse effects of tamoxifen are largely those that one would expect to be associated with a reduction in estrogenic activity, that is hot flushes (which can be severe), dry skin, mental or nervous system effects (such as mild depression, headache, fatigue, nervousness, and tremor), oligomenorrhea and amenorrhea, loss of libido, vaginal discharge, and rare events, such as pruritus, migraine, and edema (SED-12, 1034) (13). Nausea and vomiting are not uncommon. There are also reports of hirsutism, weight gain, rashes, thrombocytopenia, and leukopenia (SED-12, 1034); the hirsutism could reflect a relative dominance of endogenous androgen activity as the degree of estrogenic activity declines. The most specific and dangerous complication of tamoxifen is hypercalcemia, a direct consequence of the successful treatment of mammary carcinoma with bony metastases; the incidence varies greatly. Liver dysfunction and peliosis hepatis have been incidentally reported.

When tamoxifen is used in men (14), common adverse effects have included weight gain (25%), mood alterations (21%), hot flushes (21%), reduced libido (29%), and deep vein thrombosis (4%). The hot flushes respond well to oral clonidine 0.1 mg/day (15).

One expert in the USA (16) has publicly defended the safety of tamoxifen on the grounds that some of its supposed adverse effects may in fact have other causes. It is a difficult argument to follow, since she postulates that several of the unwanted effects referred to are in fact menopausal. However, these are largely likely to be inevitable consequences of the very changes that treatment with tamoxifen is intended to induce, that is suppression of estrogenic effects. Virtually the opposite belief can be derived from a Canadian study, which showed that 25 women taking tamoxifen were diffident about attributing adverse events to the drug, and therefore tended to under-report adverse effects (17). Menopause-like problems with these drugs are clearly likely to persist unless or until more selective SERMs become available, for example substances that act exclusively on the breast tumor.

Organs and Systems

Cardiovascular

Both deep vein thrombosis and pulmonary embolism have been described with tamoxifen.

- Cerebral sinus thrombosis, progressing to hemorrhagic cerebral infarction, occurred in a 52-year-old woman (18).

Although the authors pointed to the absence of risk factors other than the drug, it must be remembered that cerebral venous thrombosis is a recognized complication of various malignancies. In this case the breast tumor had been treated with various cytostatic drugs and stem cell transplantation, and tamoxifen had been given as an adjuvant, and it was believed that the tumor had been eliminated. Nevertheless, in this complex case one should perhaps be hesitant in attributing the complication solely to the drug.

In the light of three further cases of thrombosis, it has been suggested that there may be a particular predisposition to this complication in patients with high circulating concentrations of homocysteine, and that these should be checked for in advance of treatment (19).

In one case tamoxifen was associated with myocardial infarction (20).

Respiratory

An important synergistic reaction between radiation-related pulmonary fibrosis and tamoxifen has been described in 196 women followed for a minimum of 5 years, with a relative risk of 2.0 (21). However, others have shown that tamoxifen did not increase the pulmonary toxicity of agents such as carmustine and dacarbazine (22).

Nervous system

A short supplementary report on the US NSABP, originally published in 1999, later corrected the original data on adverse effects: among women who had used tamoxifen for an average of 29 months to complement irradiation after lumpectomy for intraductal carcinoma; there were five cases of stroke, compared with only one among the women who had not used tamoxifen (23). In a parallel study of breast cancer prevention there was also a slight but non-significant increase in the incidence of stroke in those taking tamoxifen. It may be wise to regard a history of stroke, transient ischemic attacks, uncontrolled

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hypertension, diabetes mellitus, or atrial fibrillation as relative contraindications to tamoxifen.

Sensory systems

There have been repeated reports of ophthalmic complications from tamoxifen, including irreversible retinopathy with seriously reduced visual acuity, refractile opacities, cystoid macular edema, retinal yellow-white dots, and keratopathy (SEDA-6, 356) (SEDA-7, 391) (SEDA-16, 466).

- Bilateral optic neuritis developed in a woman with breast cancer who was treated for 6 months with tamoxifen (24).

In a prospective study even in low doses (for example 10 mg/day or lower) tamoxifen caused ocular toxicity if given for a sufficiently long period; most of the changes were reversible but they justify very close monitoring (25). A related compound, MER-29 (triparanol), causes cataract and has various other adverse reactions in common with tamoxifen.

Metabolism

Steatosis and adipose tissue distribution has been evaluated using CT scanning in a cross-sectional study of 32 women taking tamoxifen for breast cancer and a similar control group (26). Tamoxifen users generally had more visceral adipose tissue and more liver fat than controls, and had a higher risk of diabetes. It is still unclear whether tamoxifen causes long-term metabolic abnormalities in obese patients, or whether patients with the metabolic syndrome X of obesity are at increased risk of the complications of tamoxifen. In view of this finding, and earlier results pointing in the same direction, it would be wise in future studies of tamoxifen to monitor metabolic changes in obese women with or without breast cancer.

Hematologic

Thrombosis and pulmonary embolism have been described with tamoxifen (27,28); the number of cases is small, but the association would not be unexpected in view of what is known about the effects of other sex hormones. The primary condition might be responsible, at least in part, for the occurrence of such complications. Tamoxifen does reduce antithrombin III but not to a degree at which a major risk would be expected, and other measurable effects on the coagulation process seem to be slight.

When tamoxifen 20 mg/day was compared with equieffective doses of anastrozole in 668 patients with advanced breast tumors that were hormone receptor-positive or of unknown receptor status, tamoxifen produced too high a rate of thromboembolism and vaginal bleeding to be considered the treatment of choice (29,30).

Liver

Liver dysfunction and peliosis hepatis are occasional complications of tamoxifen. There have also been reports of cirrhosis with fatty liver in women taking tamoxifen after surgery for breast cancer (31). The condition is reversible, and liver tests are advisable so that the tamoxifen can be promptly withdrawn if necessary.

- An elderly woman with a history of breast cancer developed multifocal steatohepatitis, but after tamoxifen was withdrawn the CT features improved dramatically, and the hepatic transaminases normalized (32).

Skin

Tamoxifen has several adverse effects on the skin, including edema, flushing, rashes, hyperhidrosis, urticaria, alopecia, and hypertrichosis. Radiation recall dermatitis, a severe painful inflammatory skin reaction in sites that have previously been exposed to ionized radiation, can occur in patients taking tamoxifen (33). In one case the tamoxifen was withdrawn and the skin healed spontaneously in 7 weeks (34). Toremifene, a tamoxifen analogue, was well tolerated: during 18 months of continuous treatment no signs of radiation recall developed.

Hair

Effects of hormonal or antihormonal products on the hair are reported sporadically.

- A woman taking tamoxifen for metastatic cancer (presumably from the breast) developed alopecia; she began to lose her hair within 3 months and was entirely bald after 13 months of treatment (35).

The authors did not make it clear whether cytostatic drugs, which can cause alopecia, were also used, but it is striking that there have been several earlier reports of baldness with tamoxifen.

Musculoskeletal

In principle an anti-estrogen might precipitate osteoporosis, but tamoxifen has not been shown to do so; indeed, there is reason to believe that it protects the skeleton against steroid-induced bone loss (36), and in some studies of the state of the bones during treatment with tamoxifen there was actually a higher bone density than in controls.

Sexual function

Tamoxifen can cause loss of libido (37). In 57 patients sexual desire, arousal, and the ability to achieve orgasm were unaffected by tamoxifen (38). There was a 54% incidence of dyspareunia, but this seemed to be a consequence of co-administration of chemotherapy, which can cause vaginal dryness and loss of libido, rather than an effect of tamoxifen.

Reproductive system

Breasts

Tamoxifen can cause a sudden rapid increase in the growth rate of uterine leiomyomas (39).

- A leiomyoma of the breast occurred in a 50-year-old woman taking tamoxifen. It appeared as a discrete mass and had a microscopic pattern akin to leiomyomas at other sites (40).

Ovaries

In premenopausal women, tamoxifen has complex effects on ovarian function, compatible with accelerated development of multiple follicles, with ovarian enlargement and cyst formation (41,42); this might be expected in

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view of its similarity to clomiphene. Ovarian cysts have also been seen in postmenopausal patients with breast cancer during long-term adjuvant therapy with tamoxifen. Some premenopausal women with breast cancer had very marked increase in estrogen concentrations as a result of increased ovarian estrogen synthesis caused by tamoxifen. All premenopausal women with breast cancer taking tamoxifen should be under close gynecological and ultrasonographic surveillance to detect such effects as soon as they occur.

Dutch workers concluded that patients who were still having a menstrual cycle had a high chance (81%) of developing ovarian cysts during tamoxifen treatment, but that postmenopausal women taking tamoxifen only developed ovarian cysts if their ovaries were able to respond to FSH stimulation, as shown by serum estradiol production (43). Differences in patient populations might explain why some workers (44) still find no association in their patients between tamoxifen and ovarian pathology.

Macroscopically visible cystic endosalpingiosis in the paraovarian region has been described in a woman who had been taking tamoxifen for breast cancer (45).

- A 2.5 cm multicystic lesion was seen on the external surface of the right ovary, and histological examination showed a mass of dilated glands lined by ciliated tubal-type epithelium and set in a fibrovascular stroma. Cystic endosalpingiosis resulting in a tumor-like mass is rarely described and is probably not well recognized by histopathologists.

Although unlikely to be mistaken for malignancy, this kind of lesion can result in diagnostic confusion. The role of tamoxifen in the development of the lesion in this case is not clear, but the estrogenic effects of tamoxifen may have contributed.

In one case, a complex cyst, thought to be due to ovarian hyperstimulation, resolved after monthly administration of a depot gonadorelin (GnRH) receptor agonist without abandoning tamoxifen (46). One might expect some patients to react to tamoxifen with ovarian hyperstimulation, since another non-steroidal antiestrogen (that is clomiphene) is used for ovarian stimulation and also on occasion produces cysts.

In one case reported from Japan, there was torsion of an ovarian cyst (47).

In a study of the mechanism and frequency of this complication, hormone concentrations in 20 premenopausal women taking tamoxifen (20 mg/day) were compared with those in untreated controls (48). Ovarian cysts were found in 80% of the treated patients but only in 8% of controls, and 17-beta-estradiol concentrations were significantly raised.

Uterus

Intermenstrual bleeding is a practical problem during tamoxifen therapy, particularly since it obliges the physician to undertake repeated endometrial investigations to exclude malignancy. Monitoring the uterine cavity in women taking tamoxifen is mandatory, especially when there is postmenopausal bleeding.

Some preliminary but well-designed work has suggested that by inserting a levonorgestrel-releasing intrauterine system it may be possible to limit considerably the problems posed by unscheduled uterine bleeding (49).

Benign thickening of the endometrium is common during tamoxifen treatment, but appears to be fully reversible within a few months of withdrawal (50,51).

Uterine polyps are not uncommon during postmenopausal treatment with tamoxifen (52), and up to 3% can show malignant changes. There has been an attempt to identify risk factors for the development of these polyps, by analysing the histories of 54 women in whom they occurred, as well as the histories of a larger control group without polyps (53). The women who developed polyps had a later menopause, had breast cancer for a longer period, and weighed more.

The pathology of tamoxifen-associated cases of myometrial adenomyosis has been compared with that in five cases of postmenopausal adenomyosis not associated with tamoxifen. The tumors were not identical: morphological features more often present in the tamoxifen-associated cases were cystic dilatation of glands (which sometimes resulted in grossly visible intramural cystic lesions), fibrosis of the stroma, and various forms of epithelial metaplasia. The proliferative activity in the adenomyosis, as determined by MIB1 staining, was higher in the tamoxifen group (54), and this could be another mechanism of postmenopausal bleeding among tamoxifen users.

Tamoxifen can be associated with the formation of endometrial polyps and polypoid endometriosis; these polyps ("basilomas") can become malignant (55,56), perhaps because they lack progesterone receptors and are exposed to unopposed estrogen (57).

Whether one should routinely screen patients for endometrial changes is disputed; there seems to be no correlation between endometrial thickness and endometrial pathology, and complications could be easily overlooked (58).

The gynecological consequences of antiestrogens (tamoxifen and toremifene) have been evaluated in 167 postmenopausal breast cancer patients in a 3-year prospective study. There was a proliferative endometrium more often in the tamoxifen group than in the toremifene group, but this did not translate into an increase in the rate of endometrial cancer. The authors did not recommend routine surveillance of the endometrium.

Immunologic

An acute inflammatory polyarthritis resembling rheumatoid arthritis has been reported in three women temporally related to the use of tamoxifen (59).

Long-Term Effects

Tumorigenicity

Several authors (60,61) have described a variety of cases, seven in all, of malignancies secondary to therapeutic dosages of tamoxifen given for 6 months to 10 years.

Uterine fibroids and endometrial polyps (sometimes with bleeding) have been reported in menopausal women who had taken tamoxifen for periods of months or years (SEDA-16, 466) (62,63). In view of this, the question of whether tamoxifen increases the risk of

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endometrial cancer has been widely discussed. The authors of a 1993 review of the outcome of six major trials tended strongly to the conclusion that tamoxifen can cause both endometrial hyperplasia and endometrial cancer proportional to the total dose (64); the figures pointed to an overall incidence of endometrial cancer of 0.5% in tamoxifen users and 0.1% in controls. Another major review up to 1992 concluded that in the world literature there were 70 cases of uterine malignancies with tamoxifen, including 61 cases of adenocarcinoma of the endometrium and four cases of uterine sarcoma (65).

Six cases of endometrial carcinoma were subsequently reported from France (66), and 36 cases in all had been reported up to that time (67). Although the effect can be caused by tamoxifen alone in women aged over 55, in younger women it is more likely to be an additive one, attributable to use of both tamoxifen and pelvic irradiation in the same subject.

Two distinct patterns of uterine cancer have been shown using magnetic resonance imaging of the tamoxifen-exposed uterus in 35 women (68). Patients with pattern 1 had homogeneous high signal intensity of the endometrium on T2-weighted images and enhancement of the endometrial–myometrial interface and a signal void in the lumen on gadolinium-enhanced images (18 patients). Patients with pattern 2 had heterogeneous endometrial signal intensity on T2-weighted images with enhancement of the endometrial–myometrial interface and lattice-like enhancement traversing the endometrial canal on gadolinium-enhanced images (17 patients).

Although the endometrial cancers associated with tamoxifen are usually pure adenocarcinomas, other types of rare tumors have also been reported. A pure uterine rhabdomyosarcoma has been reported (69), and a mesodermal mixed tumor of the endometrium occurred 5 years after 5 years of tamoxifen therapy (70). The tumor responded only to combined treatment with doxorubicin, cyclophosphamide, 5-fluorouracil, and carboplatin. It is possible that this type of tumor arises later than adenocarcinomas and should be looked for during long-term use of tamoxifen.

- Two well-documented cases of uterine carcinosarcoma have been reported in elderly women after 6 and 7 years of tamoxifen treatment (71). At laparotomy, a heterologous malignant mixed Mullerian tumor with peritoneal spread was found in each case and rapidly proved fatal; large uterine polyps with special histological features may represent an intermediate step in the formation of such tumors (72).

Ten similar cases have been described before.

When assessing the risk of endometrial malignancy in women with breast cancer taking tamoxifen, it is worth taking into account evidence that patients with breast cancer may at the outset have some endometrial pathology. In women with breast cancer scheduled for tamoxifen there were endometrial polyps in 9.3%, endometrial cysts in 16%, and synechiae in 12% at the outset. Tamoxifen significantly increased the incidence of these benign endometrial lesions, usually after less than 1 year of treatment. There were no cases of endometrial carcinoma in 34 patients who had taken tamoxifen for 12–24 months, and only one in 78 patients who had taken it for 5–72 months (73).

The risk that tamoxifen may cause endometrial cancer has been the subject of lively correspondence in the Lancet (74), fired by the paper published in 2000 by Bergman and her colleagues, who had concluded that the endometrial cancers seen with tamoxifen are unusually aggressive (75). Concern was expressed that such a conclusion could lead to even wider hesitation to use tamoxifen in breast cancer, despite the fact that it is already used very selectively, for example in women with positive estrogen receptors. A contradiction between Bergman's results and those of the NSABP P-1 were also highlighted, and doubts expressed whether Bergman's findings justify restricting the use of tamoxifen as a preventive agent. However, a Canadian group adduced its own work to support Bergman's findings, while French workers suggested that her unfavorable results, which were not seen in their own patients, could have been due to selection bias. It was also argued that a progestogen-releasing intrauterine contraceptive device might be used to counter the undesirable effects of tamoxifen on the endometrium. Clearly the issue raised by Bergman is still subject to debate, but it is obvious that physicians who use tamoxifen in advanced breast cancer or as a preventive agent should continue to do so selectively and that ways of protecting the endometrium during tamoxifen therapy need to be found.

The effects of norethisterone on endometrial abnormalities have been studied in 463 postmenopausal women taking tamoxifen or placebo (76). As in other studies, the results showed that any increased risk of endometrial cancer caused by tamoxifen is low and that transvaginal ultrasound screening is probably not justified for asymptomatic women taking tamoxifen. The authors found that 26% of women taking tamoxifen have endometrial thickening of 8 mm or more. It is possible to identify cysts in 7% of these women, polyps in 3%, and both cysts and polyps in 8%. These changes are characteristic of tamoxifen and unlike those seen with estrogen replacement therapy.

The usefulness of transvaginal ultrasound in detecting serious uterine changes in tamoxifen users has been disputed. According to one group it is a dependable diagnostic method (77), whereas others found it disappointing, with a high proportion of false positive results, even when the assessment criteria were chosen so as to exclude mild endometrial thickening (78). Setting these two papers beside one another it seems that one can detect marked endometrial changes but that ultrasound is not a dependable means of determining whether there is malignancy.

Second-Generation Effects

Teratogenicity

Since animal studies suggested the possibility of fetal and neonatal malformations it has for a long time been customary to exclude pregnancy before giving tamoxifen. However, there is currently reason to believe that the risk presented by tamoxifen to the human fetus is very slight or non-existent.

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Susceptibility Factors

Genetic factors

Certain women have a genetic predisposition to develop an endometrial malignancy during tamoxifen treatment. There were significant amounts of tamoxifen-DNA adducts in the endometrium in eight of 16 women who took the drug but none at all in others, suggesting that a genotoxic mechanism may be responsible for tamoxifen-induced endometrial cancer (79). However, there is biochemical and histological evidence that tamoxifen-associated endometrial carcinoma is likely to be similar to type I and will therefore have a relatively favorable prognosis (80).

Drug–Drug Interactions

Cytotoxic drugs

An unusual case of rapidly fatal renal failure reported in 1993 could reflect an interaction between tamoxifen and one or more cytostatic agents, with mitomycin C a prime suspect; in a series of breast cancer patients some 10% of those treated both with tamoxifen and a cytostatic agent developed abnormal renal function, progressing towards various stages of hemolytic-uremic syndrome (81).

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Tamsulosin

See also Alpha-adrenoceptor antagonists

General Information

Tamsulosin is an alpha$_1$-adrenoceptor antagonist that was specially designed for the treatment of benign prostatic hyperplasia, since it is highly selective for the urinary tract alpha$_{1A}$-adrenoceptors (1). Indeed, it produces little or no cardiovascular effects, no first-dose effect, and much less dizziness. In clinical trials, adverse effects included dizziness, weakness, headache, and nasal congestion. Abnormal ejaculation was the most frequent adverse effect, in 8% of the patients at 0.4 mg/day, and in 18% at 0.8 mg/day (2,3).

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Taxaceae

See also Herbal medicines

General Information

The family of Taxaceae contains two genera:

1. *Taxus* (yew)
2. *Torreya* (torreya).

Taxus species

Taxus (yew) trees contain alkaloids called taxanes that have anticancer activity and are the basis of the semi-synthetic anticancer drugs paclitaxel and docetaxel (see separate monographs), which are based on taxol, from *Taxus brevifolia*.

Taxus baccata has been used as a means of suicide (1–3), successfully, because of cardiac dysrhythmias (4).

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Taxoids from *Taxus cuspidata* (the Japanese yew) inhibit P glycoprotein and are candidates for reversing multidrug resistance in cancer cells (5).

Taxus celebica, which contains the flavonoid sciadopitysin, is traditionally used in China as an herbal treatment of diabetes mellitus.

Adverse effects

Hematologic

Thrombocytopenia has been attributed to the Chinese herbal mixture Jui, prepared from *T. cuspidata* (Japanese yew) (6).

- A 51-year-old Japanese woman developed gingival bleeding and petechiae. The only medication she had taken was Jui. She had thrombocytopenia and the causal relation was demonstrated by rechallenge. She recovered on withdrawal of the product.

Immunologic

Of 18 patients with seasonal allergic rhinitis, suffering mainly in April and May, five were sensitized to the pollen of *T. cuspidata* (7).

Drug overdose

In two cases the ingestion of a massive dose of *T. celebica* was followed by acute renal insufficiency; both patients initially presented with gastrointestinal upset and fever (8).

- A 40-year-old patient attempted suicide by drinking an extract made from 120 g of yew needles (*T. baccata*); recurrent episodes of ventricular tachycardia were successfully treated with high doses of lidocaine (9).
- Lethal intoxication with yew leaves (*T. baccata*) presented with dizziness 1 hour after ingestion, nausea, diffuse abdominal pain, unconsciousness, weak breathing, tachycardia, brief ventricular flutter followed by bradycardia, and finally death by respiratory arrest and cardiac standstill; the electrocardiogram showed atypical bundle branch block and absent P waves (10).
- A 14-year-old boy cut leaves from a yew tree (*T. baccata*), crushed them, and ingested them; he died soon afterwards (11). At autopsy pieces of partially crushed, partially preserved yew leaves were found in the stomach. The histological findings were non-specific.

Four prisoners drank a decoction of yew needles (*T. baccata*) (12). Two died in prison with cardiac arrest. One went into deep coma, and had several episodes of ventricular fibrillation, controlled by defibrillation; after return of consciousness his general condition deteriorated suddenly, he lost consciousness again, his circulation stopped, and he died on the fourth day. The other patient drank a much smaller amount of the decoction; he was conscious, had bradycardia requiring transient pacemaking, and had a mild ventricular dysrhythmia; he recovered after 10 days. In both cases there was excessive diuresis and severe hypokalemia and atropine was effective for a short time in the control of bradycardia.

Of 11 197 exposures to the berries of *Taxus* species children under 12 years of age were involved in 96% (under 6 years 93%; 6–12 years 3.7%) (13). When the final outcome of the exposure was documented ($n = 7269$), there were no adverse effects in 93% and minor effects in 7.0%. There were moderate (more pronounced, but not life-threatening) effects in 30 individuals and major (life-threatening) effects in four. There were no deaths. Decontamination therapy had no impact on outcome compared with no therapy. When symptoms occurred after exposure to *Taxus*, the most frequent were gastrointestinal (66%), followed by skin reactions (8.3%), nervous system effects (6.0%), and cardiovascular effects (6.0%).

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Tea tree oil

General Information

Tea tree oil is extracted from *Melaleuca alternifolia*, a plant that is native to Australia. It is considered to have antibacterial properties, including an effect on methicillin-resistant *Staphylococcus aureus* (MRSA), while the commensal flora of the skin seem to be less susceptible (1). In addition, it is said to have antifungal, antiviral, anti-inflammatory, and analgesic properties, and has been increasingly incorporated into cosmetics for aromatherapy.

Organs and Systems

Nervous system

The systemic toxicity of tea tree oil is comparable to that of eucalyptus oil, and ingestion of 10–25 ml has resulted in ataxia, drowsiness, disorientation, or coma for 2 days; recovery was full without complications (2).

- A 4-year-old boy took a small quantity of tea tree oil and within 30 minutes became ataxic and shortly thereafter progressed to unresponsiveness; he was endotracheally intubated and his neurological status improved gradually over 10 hours (3).

Immunologic

Since the beginning of the 1990s, several case reports of allergic contact dermatitis to tea tree oil have been published (4,5). Most of these adverse effects emerged after the application of aged tea tree oil, and patients who are allergic to tea tree oil do not react to patch tests with freshly distilled tea tree oil (6). In a review of tea tree oil focussing on the allergic compounds in detail, the authors concluded that *d*-limonen, alpha-terpenes, and the aromadendrens are important allergens, whereas 1,8-cineole was not believed to be important, as has been previously stated (7). Tea tree oil undergoes photo-oxidation within a few days to several months, leading to degradation products, such as peroxides, epoxides, and endoperoxides, which are moderate to strong sensitizers. Experimental sensitization in guinea pigs was followed by patch tests with 15 constituents of oxidized tea tree oil in 11 patients with tea tree oil contact dermatitis (6). All the patients reacted to alpha-terpinene, terpinolene, and ascaridol, the latter being a deterioration product of alpha-terpinene.

Many people who are allergic to tea tree oil also react to turpentine, colophony, fragrances, balsam of Peru, and plant extracts of Compositae (8).

- A 46-year-old Chinese man developed an allergic contact dermatitis to tea tree oil, colophony, balsam of Peru, and abitol. He had used the tea tree oil under an occlusive dressing on a superficial abrasion on his left shin for 2 weeks, after which the treated area became red and itchy. During the next week, skin lesions appeared on his trunk and extremities, and were diagnosed as an erythema multiforme-like id reaction.
- A 38-year-old man developed an immediate hypersensitivity reaction, characterized by pruritus, throat constriction, and light-headedness, after topical application of tea tree oil (9). An intradermal test with tea tree oil gave a wheal and flare reaction. Specific IgG and IgE were not detected.

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Teicoplanin

General Information

Teicoplanin has been used in the treatment of Gram-positive infections. Its pharmacological properties allow once-daily dosing. Its safety profile has been thoroughly investigated, and it is generally well tolerated. It diffuses well into bone tissue (1).

Teicoplanin is more effectively administered once daily than vancomycin and it can be given intramuscularly or intravenously; it is not absorbed after oral administration. It is 90% bound to plasma proteins and its elimination is primarily by renal excretion, allowing dosage adjustments to be made on the basis of the measured creatinine clearance. A dosing regimen of 12 mg/kg on day 1 followed by 6 mg/kg/day most often results in efficacious serum concentrations but premature neonates and children require higher dosages. However, doses of 10 mg/kg/day are required to achieve adequate bone concentrations, and there is little penetration into cerebrospinal fluid or aqueous or vitreous humors. In fat, concentrations can be subtherapeutic after a dose of 400 mg. Unlike vancomycin, routine drug monitoring is not required, although it may sometimes be useful for predicting the therapeutic effect of the drug.

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Observational studies

In a study of the effects of teicoplanin (6–12 mg/day intravenously), 166 of 342 patients reported one or more adverse events, and in 119 they were thought to be associated with teicoplanin (2). Most had some form of hypersensitivity response (fever, rash, chills, or pruritus), and treatment was withdrawn in 59 patients. There was a clinically significant abnormality of liver function tests in 123 patients, but in only 33 was it judged to be possibly associated with teicoplanin. There was a rise in serum creatinine in 28 patients, in five of whom an association with teicoplanin was suggested.

Cell wall agents, such as glycopeptides, have concentration-independent bactericidal activity, and the time over which the antibiotic serum concentration persists over the minimal inhibitory concentration of the pathogen is a main pharmacodynamic determination of the outcome. In a two-way, randomized, open, two-period, crossover study in 10 healthy adults, teicoplanin given in two 200 mg doses intramuscularly produced steady-state trough concentrations even higher than those after once-daily intravenous administration of 400 mg (3). Conversion from intravenous to intramuscular administration may therefore allow better compliance with preserved efficacy. Intramuscular teicoplanin was well tolerated. Adverse effects reported were mild local pain for 2–3 hours, headache, and backache.

In 76 patients receiving long-term teicoplanin for chronic osteomyelitis due to oxacillin-resistant *Staphylococcus aureus*, teicoplanin had to be withdrawn in only one subject because of low-grade fever, muscular pain, and sleeplessness; these adverse effects abated after withdrawal (4).

Comparative studies

In a prospective study 56 patients with suspected or proven severe Gram-positive infections were randomized to receive vancomycin (1 g 12-hourly intravenously) or teicoplanin (200–400 mg/day intravenously or intramuscularly) (5). Clinical and bacteriological cure rates were similar, but vancomycin was associated with significantly greater toxicity (16 vancomycin, 7 teicoplanin), predominantly histamine-associated reactions (15, including two cases of red man syndrome) (SEDA-17, 312), and nephrotoxicity (five with vancomycin compared with one with teicoplanin). Four of the five vancomycin patients who developed nephrotoxicity were receiving netilmicin at the time, some with amphotericin as well.

The overall rate of adverse reactions in comparative trials was 19%, which is comparable with the rate observed with beta-lactams, but lower than the corresponding rate (39%) associated with vancomycin (6).

Only three of 422 patients treated with a single dose of teicoplanin for antimicrobial prophylaxis during hip or knee arthroplasty (400 mg by intravenous bolus at the time of anesthesia) reported adverse events compared with nine of 424 patients treated with five doses of cefazoline: one had nausea and two had erythema (7). Six patients given teicoplanin had surgical wound infections, and 57 had proven or suspected infections involving other body systems.

In another study, a single dose of teicoplanin (6 mg/kg intravenously) was compared with three doses of cefradine plus metronidazole as prophylaxis for vascular surgery. Efficacy was similar with the two regimens. Adverse events were reported by 40 of 136 patients treated with teicoplanin (versus 39 of 139 treated with cefradine plus metronidazole), and 19 (versus 15) were considered to be related to the study drug; however, none was considered definitely related (8).

In a prospective, randomized trial in 34 drug abusers a short course of a combination of a glycopeptide (vancomycin or teicoplanin) with gentamicin was significantly less effective in right-sided endocarditis caused by *S. aureus* than a combination of cloxacillin and gentamicin (9).

Pharmacoeconomics

In a randomized, prospective, cost-effectiveness study both teicoplanin and vancomycin were assessed as second-line therapy in 66 neutropenic patients after the failure of empirical treatment with a combination of piperacillin + tazobactam and amikacin (10). The primary success of second-line therapy was equivalent, and the direct total costs were similar. Acquisition costs per dose were in favor of vancomycin, but costs derived from administering vancomycin and serum concentration monitoring led to similar costs for both regimens. With the exception of the red man syndrome, which occurred in 10% of vancomycin-treated patients but none of the teicoplanin-treated patients, toxicity (renal, liver, and ear toxicity, diarrhea, phlebitis) was also similar.

In a retrospective cost analysis, the records of 527 patients with acute leukemia were studied (11). They had been treated in a multicenter, randomized trial for febrile neutropenia with ceftazidime and amikacin plus either teicoplanin (6 mg/kg in a single dose; $n = 275$) or vancomycin (30 mg/kg/day in 2 doses; $n = 252$). Clinical responses were equivalent. Again the higher acquisition costs for teicoplanin were counterbalanced by the lower incidence of adverse events and easier administration, resulting in overall similar costs for both regimens. A total of 8% of patients treated with vancomycin reported adverse events compared with 3.2% of patients treated with teicoplanin. Rashes occurred in 6.0 versus 1.4% respectively. Nephrotoxicity, ototoxicity, fever, and hypotension occurred in very few patients.

General adverse effects

The most common adverse events associated with teicoplanin are hypersensitivity, fever, rash, diarrhea, nephrotoxicity, and thrombocytopenia (12,13). Local reactions at the injection site include pain, redness, or discomfort after intramuscular injection, or phlebitis after intravenous injection. Erythroderma has occurred during infusion of teicoplanin with fever and hypotension. Allergic reactions have been reported with teicoplanin, with cross-reactivity between teicoplanin and vancomycin documented by in vitro studies showing IgE release by basophils in response to stimulation by both vancomycin and teicoplanin. However, known hypersensitivity to vancomycin is not a contraindication to teicoplanin. Tumor-inducing effects have not been reported.

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Red man syndrome

The red man syndrome associated with rapid infusion of vancomycin, resulting in histamine release, is very rarely seen with teicoplanin. Teicoplanin can usually be safely administered to patients with a history of red man syndrome due to vancomycin, as has been confirmed in six children treated with teicoplanin for febrile neutropenia and Gram-positive bacteremia (14).

However, case reports have suggested that there can be cross-reactivity between vancomycin and teicoplanin in the induction of this syndrome, although the underlying mechanism remains elusive (15).

- A swinging pyrexia (peaking at 39–40°C during the day but settling overnight) developed after the fifth day of teicoplanin treatment in a 35-year-old man with infective endocarditis due to *Streptococcus mitis*. Two days after stopping the drug he became apyrexial. Therapy with vancomycin had previously had to be interrupted because of an extensive purpuric rash and erythema, which progressed to exfoliative dermatitis and was subsequently identified as red man syndrome secondary to vancomycin.

Organs and Systems

Cardiovascular

Hypotension has been observed as part of the manifestations of a hypersensitivity reaction to teicoplanin (16).

Respiratory

Bronchospasm required withdrawal of teicoplanin in two of 310 patients (17).

Sensory systems

Ototoxicity has been reported during treatment with teicoplanin (18). A fall in high-frequency auditory threshold was observed in one patient treated with teicoplanin for a serious Gram-positive infection (19). However, the causal relation between teicoplanin and alterations in auditory function has not been established in controlled clinical studies (20). Guinea pigs treated for 28 days with a maximum dose of 75 mg/kg/day remained without any evidence of functional, morphological, or histological changes indicative of ototoxicity (21). There were 11 cases of ototoxicity among 3377 patients treated with teicoplanin (20). It can be concluded that teicoplanin-associated ototoxicity is rare.

Hematologic

The overall rate of hematological adverse effects of teicoplanin was 2.2% in 1431 patients participating in a large non-comparative multicenter study (22).

Hemophagocytosis after vancomycin and teicoplanin occurred in a 45-year-old woman (23).

Leukocytes

The incidence of teicoplanin-induced leukopenia is low (0.33%) and the leukopenia is usually reversible.

- A 10-year-old Malay boy with G6PD deficiency received teicoplanin (300 mg/day) for an epidural abscess and 14 days later developed an erythematous, maculopapular, non-pruritic rash over his trunk and upper limbs and a mild fever with chills (24). He had a leukocyte count of 2×10^9/l. Teicoplanin was withdrawn and by 3 days the rash had almost completely subsided. After rechallenge with a single intravenous dose of teicoplanin 300 mg, he developed a fever (39.3°C), chills, and worsening of the rash on his arms. Teicoplanin was again withdrawn. His fever resolved after 4 days and his leukocyte count normalized by 7 days.
- Neutropenia developed in a patient after 20 days of treatment with teicoplanin (25).

In patients undergoing bone marrow transplantation receiving teicoplanin for the treatment of severe sepsis, the duration of neutropenia was not prolonged by teicoplanin (26).

Teicoplanin rarely causes eosinophilia (27).

Platelets

Thrombocytopenia was associated on two consecutive occasions with teicoplanin in a patient with acute myeloid leukemia (28). The exact mechanism for this adverse event is unknown. Teicoplanin does not alter platelet function or blood coagulation (29).

- Severe thrombocytopenia occurred in a 46-year-old white man treated with teicoplanin 6 mg/kg/day for methicillin-resistant *S. aureus* bacteremia (30). The platelet count fell to 25×10^9/l on day 8 (baseline 110). After drug withdrawal the platelet count improved within 4 days. The trough teicoplanin concentrations were 17 μg/ml on day 4 and 15.4 μg/ml on day 9.

Teicoplanin caused thrombocytopenia in one of 17 children (31).

In trials in the USA, thrombocytopenia occurred more commonly with teicoplanin than with vancomycin, but this was almost exclusively in patients who received much larger doses than are now recommended.

Gastrointestinal

Adverse events involving the gastrointestinal system are rare with teicoplanin. Diarrhea has been listed among non-specific events observed in 5.1% of patients (22).

Liver

In one study transient rises in liver enzymes occurred in 2.3% of patients taking teicoplanin (17). Other authors have reported abnormal liver enzymes (19,32–34).

Urinary tract

Teicoplanin can be nephrotoxic, but less often than vancomycin (6). However, concomitant aminoglycoside therapy in some patients makes the contribution of the glycopeptide antibiotic difficult to assess. Renal toxicity was observed more often in patients receiving the combination of netilmicin plus vancomycin than in patients treated with netilmicin plus teicoplanin (35). Similar differences in nephrotoxicity between vancomycin and

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teicoplanin were observed in febrile neutropenic patients receiving tobramycin plus piperacillin (36). There was significant deterioration of renal function when vancomycin and ciclosporin, but not teicoplanin and ciclosporin, were used together; the mechanism responsible for this interaction is unknown (36).

In two of 76 patients receiving long-term teicoplanin a reduction in dosage was required because of reduced renal function, which recovered within 30 days (4).

There was a fall in residual renal function during episodes of peritonitis in a prospective multicenter study in 152 children with peritoneal dialysis-associated peritonitis (37). The study evaluated the efficacy, safety, and clinical acceptance of combination treatment, including a glycopeptide (teicoplanin or vancomycin) and ceftazidime, each given either intermittently or continuously. Irreversible anuria developed in 19% of the patients with residual diuresis. In patients who retained residual renal function, there was a strong trend toward a decreased residual glomerular filtration rate (−11%). There was no difference with respect to the type of glycopeptide or the mode of use. Aminoglycosides were used concomitantly in only 12 patients and did not seem to affect the evolution of residual renal function. Underdosing/non-adherence or overdosing occurred in 8.2% of continuously treated versus 4.9% of intermittently treated patients. Intermittent and continuous intraperitoneal treatment with glycopeptides and ceftazidime were equally efficacious and safe when measured by objective clinical criteria.

In children with febrile neutropenia and Gram-positive bacteremia associated with antineoplastic drug therapy, teicoplanin was significantly less nephrotoxic than vancomycin (14).

The effect of co-administration of fosfomycin on glycopeptide antibiotic-induced nephrotoxicity for 3 days has been investigated in rats (38). Fosfomycin reduced glycopeptide antibiotic-induced nephrotoxicity, as shown by reduced urinary excretion of *N*-acetyl-beta-D-glucosaminidase and fewer histological signs of nephrotoxicity in those treated with a combination of glycopeptide and fosfomycin compared with a glycopeptide alone. In addition, the higher the dose of fosfomycin, the more it reduced urinary *N*-acetyl-beta-D-glucosaminidase activity, suggesting that the role of fosfomycin in alleviating nephrotoxicity is dose-dependent. There was significantly less accumulation of teicoplanin and vancomycin in the renal cortex of rats treated with glycopeptide antibiotics plus fosfomycin compared with the glycopeptide antibiotics alone.

Skin

A pustular skin eruption occurred in a 60-year-old woman who was given teicoplanin 400 mg as a loading dose followed by 200 mg/day (39). Following the sixth injection of teicoplanin she developed a pruritic eruption on her chest, which evolved into a widespread maculopapular eruption with tiny pustules and occasional vesicles on an erythematous base over the face, trunk, and limbs within 2 days. Teicoplanin was withdrawn and she was given prednisolone 60 mg/day. This resulted in improvement of the eruption and relieved the discomfort over the next 7 days. In other cases teicoplanin caused an acute generalized rash and exanthematous pustulosis (24,40).

Vancomycin reportedly caused a severe delayed skin reaction with allergic cross-reactivity between vancomycin and teicoplanin requiring steroid therapy (41).

- A 68-year-old woman who was being treated with vancomycin for *Staphylococcus epidermidis* bacteremia developed pruritus and a generalized maculopapular skin rash after 2 weeks. After a short course of prednisolone, she was given teicoplanin and developed general malaise, fever, conjunctival injection, an extensive rash, and later blisters on the legs, again requiring treatment with steroids.

Musculoskeletal

Teicoplanin has been successfully used to treat bone and joint infections without any adverse reactions affecting bones or joints (42).

Immunologic

Allergic reactions have been reported with teicoplanin. Erythroderma during infusion of teicoplanin with fever and hypotension was described in a single patient. Re-exposure elicited the same reaction (16). Allergic cross-reactivity between teicoplanin and vancomycin has been reported (43,44). This cross-reactivity was documented by in vitro studies showing IgE release by basophils in response to stimulation by both vancomycin and teicoplanin in a further patient who had an allergic reaction to vancomycin (45). In other studies the second drug did not elicit allergic reactions in patients known to be allergic to one of the two compounds (46–48). Based on these small studies and individual case reports one can conclude that allergic reactions to teicoplanin can occur in patients with known allergic reactions to vancomycin, but the frequency of occurrence of this type of cross-reaction appears to be low. Therefore, known hypersensitivity to vancomycin is not a contraindication to the use of teicoplanin.

Local reactions at the injection site, including pain, redness, or discomfort after intramuscular injection, and phlebitis after intravenous injection, occur in about 3% of patients (6).

Long-Term Effects

Drug tolerance

In a study of antibiotic resistance in enterococci from raw meat, there was a high prevalence of glycopeptide-resistant strains (49). Resistance to vancomycin was significantly associated with resistance to teicoplanin, erythromycin, tetracycline, and chloramphenicol.

Susceptibility Factors

Renal disease

The administration of 5 and 10 mg/kg of teicoplanin to seven anuric patients immediately after the end of hemodialysis gave mean values of C_{max} of 63 and 122 μg/ml,

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mean AUCs of 526 and 1104 hours.μg/ml, mean half-lives of 109 and 107 hours, mean clearance rates of 13 and 12 ml/minute, mean apparent volumes of distribution of 1.68 and 1.68 l/kg, and mean volumes of distribution at steady state of 0.31 and 0.28 l/kg (50). Trough serum concentrations were above 10 μg/ml for 24 hours after the 5 mg/kg dose and for 48 hours after the 10 mg/kg dose. Teicoplanin was not detected in the dialysate. Its concentrations in the arterial and the venous lines of the fistulae were similar.

Drug Administration

Drug overdose

- A 10-day-old girl with a history of postasphyxia acute renal failure, which recovered within 7 days, was given teicoplanin for sepsis due to *Staphylococcus hominis* (51). The dosage used was erroneously high (20 mg/kg 12-hourly instead of an initial dose of 16 mg/kg followed by 6–8 mg/kg/day), and therapy was suspended after 5 days. She improved, and blood cultures were negative. Serum creatinine concentrations and cystatin C (as an early marker of glomerular damage) remained in the reference ranges. Urinary parameters for tubulotoxicity (*N*-acetyl-beta-D-glucosaminidase, $beta_1$-microglobulin) were higher than in the following days, but remained in the reference ranges. Urinary concentrations of epithelial growth factor were also higher during therapy than afterwards, probably indicating repair activity. Serum concentrations of teicoplanin were not determined.

Drug–Drug Interactions

Aminoglycosides

The risk of nephrotoxicity increases with the concomitant use of other nephrotoxic drugs, especially aminoglycosides (36).

Ciprofloxacin

Teicoplanin should be administered separately from ciprofloxacin, since precipitation has been provoked by concomitant parenteral administration (52).

Colestyramine

Since colestyramine binds teicoplanin in vitro and reduces its activity against *Clostridium difficile* almost completely, there is potential for a clinically important interaction (53).

Enalapril

A possible drug interaction with enalapril has been reported; a patient with diabetes receiving teicoplanin for osteomyelitis developed renal insufficiency requiring dialysis after the addition of enalapril (54).

Monitoring Therapy

There is evidence that predose concentrations of teicoplanin are related to clinical outcome; the evidence is less conclusive for vancomycin. Predose concentrations can be linked to some toxic effects (nephrotoxicity for vancomycin and thrombocytopenia to teicoplanin) (55,56). In severe infections monitoring serum teicoplanin concentrations is indicated to assure adequate trough concentrations (over 10 μg/ml) (57). For the treatment of *S. aureus* endocarditis trough concentrations should exceed 20 μg/ml (57). Inadequately low serum concentrations of teicoplanin may have been responsible for the high failure rate in intravenous drug users treated with teicoplanin for right-sided endocarditis (58). The fact that teicoplanin pharmacokinetics are unpredictably variable in intravenous drug users adds further weight to the importance of monitoring serum drug concentrations in this population during the treatment of severe infections such as endocarditis (59). Since the half-life of teicoplanin also varies greatly in patients with various degrees of renal insufficiency, monitoring serum concentrations can be helpful in guiding therapy in some patients with markedly reduced creatinine clearance (60).

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Telenzepine

General Information

Telenzepine is a muscarinic M_1 receptor antagonist, like pirenzepine. On a weight-for-weight basis it is 25–50 times more potent than pirenzepine, but dose for dose it is, if anything, more likely to have undesired anticholinergic effects (1).

In 163 patients with endoscopically proven benign gastric ulcers randomly allocated to telenzepine 3 mg/day or ranitidine 300 mg/day for up to 8 weeks in a prospective, double-blind study, anticholinergic events occurred significantly more often in patients taking telenzepine, dry mouth being the most frequent adverse effect (2).

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Telmisartan

See also Angiotensin II receptor antagonists

General Information

Telmisartan is a highly selective antagonist at type 1 angiotensin II (AT_1) receptors.

Organs and Systems

Respiratory

The incidence of cough with telmisartan has been assessed in a multicenter, randomized, parallel-group, double-blind, placebo-controlled study, for 8 weeks using a visual analogue scale in 88 patients with hypertension who had previously had ACE inhibitor-related cough (1). Cough was reported in 60% of the patients taking lisinopril 20 mg/day, 16% of those taking telmisartan 80 mg/day, and 9.7% with placebo.

Drug–Drug Interactions

Digoxin

Multiple-dose telmisartan 120 mg od administered with digoxin 0.25 mg od resulted in higher serum digoxin concentrations (2). Digoxin AUC and C_{max} rose by 22% and 50% respectively; the rise in C_{min} (13%) was not significant. These results suggest that telmisartan reduces the clearance of digoxin. The magnitude of this effect is comparable to that observed with calcium channel blockers, carvedilol, captopril, amiodarone, quinidine, and propafenone. Monitoring serum digoxin concentrations should be considered when patients first receive telmisartan and in the event of any changes in the dosage of telmisartan.

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Paracetamol or ibuprofen

The single-dose pharmacokinetics of telmisartan 120 mg were not affected by a concurrent single dose of paracetamol 1 g or ibuprofen 400 mg tds for 7 days (3).

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Temazepam

See also Benzodiazepines

General Information

Temazepam is a benzodiazepine that was first discovered as a metabolite of diazepam. It is relatively short-acting, having a half-life of about 10 hours.

Temazepam has favorable kinetics for use as a hypnotic (1) and is widely prescribed for this purpose. Rather surprisingly, both 10 and 20 mg caused discernible and comparable psychomotor impairment the following morning (SEDA-20, 32), at a time when the subjective effects had virtually disappeared. This result emphasizes the often subtle but pervasive insight-impairing effects of benzodiazepines. Temazepam in soft capsules is more rapidly absorbed than from tablets. However, drug users have abused temazepam capsules by heating them to liquefaction and injecting the resultant fluid intravenously, often together with other substances; the resulting medical problems are varied and often serious.

Organs and Systems

Psychological, psychiatric

Temazepam produces a variety of adverse nervous system effects, including restlessness, agitation, irritability, aggression, rage, and psychosis. Perhaps because it is likely to be used recreationally, temazepam has also been used to facilitate crime, particularly in the UK (2).

The effects of oral temazepam 5, 10, and 30 mg on memory have been studied in healthy volunteers subjected to a battery of cognitive tests and analogue mood ratings (3). The lowest dose had no effect and 10 mg significantly increased only self-ratings of well-being. Temazepam 30 mg significantly improved recall of items learned before drug administration, but impaired recall and recognition of word lists acquired after drug administration. There was no impairment of retrieval, suggesting that automatic information processing was unaffected. Temazepam 30 mg significantly reduced self-ratings of anxiety and increased self-ratings of sedation. It also significantly impaired performance in symbol copying, digit-symbol substitution, and number cancellation tasks. It is striking that at a dose that was sedative and impaired many aspects of performance, temazepam nevertheless improved retrieval of items learned before drug administration. In a randomized, crossover study, psychomotor performance and memory were tested and mood assessed for 3 hours after single doses of placebo, temazepam 20 mg, or temazepam 30 mg in six healthy women aged 21–23 years (4). Psychomotor speed and explicit memory showed dose-dependent slowing and impairment, but there was no change in short-term memory.

Drug Administration

Drug dosage regimens

Benzodiazepine prescribing for sleep induction in an elderly medical inpatient population has been examined, to determine if hospital prescribing increases the use of benzodiazepines after discharge (5). The secondary objectives included monitoring for adverse effects and assessment of the quality of sleep in hospital compared with the quality of sleep at home. Inpatient and outpatient prescribing of benzodiazepines used for insomnia was recorded over 3 months. Benzodiazepines were prescribed for 20% of patients, and 94% of the prescriptions were for temazepam. Of the 57 patients who were given benzodiazepines during a hospital admission, 57% had not taken a benzodiazepine at home before admission. Benzodiazepines were effective in the short-term for inducing sleep in hospital, with little evidence of adverse effects.

Drug administration route

Inadvertent intra-arterial injection of temazepam can cause tissue damage.

- A 29-year-old unemployed man developed pain and swelling of the right hand following inadvertent intra-arterial injection of temazepam capsules (6). Over 10 days, necrotic areas involving the index, middle, and little fingers developed and the fingers had to be amputated. He reported episodes of intravenous drug use during the previous 3 days—a single heroin dose followed by temazepam four times (10 mg gel capsules dissolved in hot water). He had injected the drugs into a superficial blood vessel on the back of the right hand.

Drug overdose

In a retrospective analysis of 352 consecutive cases of fatal overdose, temazepam accounted for 65% of all deaths from benzodiazepine overdose (7). Acute rhabdomyolysis, usually associated with intravascular injection, has been seen after an oral overdose of temazepam (SEDA-17, 45).

- An 83-year-old woman developed coma, respiratory depression, hypotonia with generalized hyporeflexia, bilateral extensor plantar responses, and bullous eruptions containing serous fluid over the medial aspects of the knees after taking seven temazepam tablets (8).

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Drug–Drug Interactions

Oral contraceptives

The clearance of temazepam was increased when oral contraceptives were co-administered (9). It is unlikely that this is an interaction of clinical importance.

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Temocapril

See also Angiotensin converting enzyme inhibitors

General Information

Temocapril is an ACE inhibitor, a prodrug that is converted to the active metabolite temocaprilat after absorption.

Drug–Drug Interactions

Warfarin

Temocapril had no effect on the pharmacokinetics or pharmacodynamics of multiple-dose warfarin in 24 healthy subjects (1). There have been similar negative interaction studies with other ACE inhibitors and oral anticoagulants.

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Tenidap sodium

See also Non-steroidal anti-inflammatory drugs

General Information

Tenidap sodium, an antirheumatic drug, combines the clinical and pharmacological properties of NSAIDs with those of a disease-modifying agent. Data from clinical studies have been reviewed (SEDA-19, 100).

Pfizer abandoned tenidap sodium for use in rheumatoid arthritis after a non-approval letter from the FDA was issued because of unresolved questions about its safety. The decision related only to the 120 mg dose. The FDA's Arthritis Drugs Advisory Committee also voted against approving tenidap sodium for osteoarthritis.

Organs and Systems

Nervous system

The adverse effects of tenidap sodium include headache (3.8%) (1).

Hematologic

Acute eosinophilic pneumonia has been described in a man with osteoarthritis taking tenidap sodium (2).

Gastrointestinal

As expected with a cyclo-oxygenase inhibitor, the adverse effects most frequently reported by patients taking tenidap sodium were gastrointestinal; serious gastrointestinal events occurred in 2.1% (1).

Liver

Increases in serum transaminases can occur, and severe abnormalities in liver function tests have been reported (1,3–5).

Urinary tract

Proteinuria, by an unknown mechanism, is a frequent adverse effect of tenidap sodium (13%), but is reversible and non-progressive in the long term, and with no evidence of deteriorating renal function (1,6).

Skin

The adverse effects of tenidap sodium include alopecia (3.2%) (1).

Drug–Drug Interactions

ACE inhibitors

Tenidap sodium reduces the antihypertensive effects of ACE inhibitors (7).

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Diuretics

Tenidap sodium reduces the antihypertensive effects of diuretics (7).

Lithium

Tenidap sodium interacts with lithium, reducing its renal clearance and increasing steady-state lithium concentrations; the dosage of lithium should be reduced to avoid toxicity (7,8).

Phenytoin

Tenidap sodium displaces phenytoin from plasma albumin binding sites by about 25% (9).

Warfarin

Tenidap sodium interacts with warfarin by displacing it from plasma albumin, although there may be another mechanism; the dosage of warfarin may need to be reduced to avoid toxicity (7,10).

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Tenofovir

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Tenofovir is a nucleotide (nucleoside monophosphate) analogue reverse transcriptase inhibitor, given as a prodrug, tenofovir disoproxil fumarate. In contrast to the other members of this class, it only needs to be phosphorylated twice intracellularly before it is pharmacologically active. Adverse effects have been reported as flatulence, raised transaminases, raised creatine kinase activity, and rarely a raised serum creatinine (1). Tenofovir does not currently appear to be nephrotoxic.

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Tenoxicam

See also Non-steroidal anti-inflammatory drugs

General Information

Tenoxicam is a piroxicam analogue with a half-life of 75 hours. Whether the differences in pharmacokinetics in elderly patients have any clinical significance is unknown (SEDA-12, 93).

The pattern of adverse effects is similar to that of piroxicam, but tenoxicam causes slightly fewer serious gastrointestinal effects (1). Fecal blood loss is lower than with aspirin (SEDA-8, 111). A large, multicenter, hospital-based study confirmed that tenoxicam and piroxicam had similar tolerance ratings: 13% of patients had severe adverse effects, most often gastrointestinal (melena, hematemesis, rectal bleeding, exacerbation of ulcerative colitis) and serious rashes (SEDA-15, 103). Gastrointestinal adverse effects are more frequent with higher doses (2).

In an open, non-comparative study in 1267 patients, performed to test tenoxicam safety in general practice, the most common adverse reactions were gastrointestinal (11%), central and peripheral nervous system disorders (2.8%), and skin reactions (2.5%) (3). Patients who take long-term tenoxicam are at low risk of nephrotoxicity. The prevalence of urinary system adverse effects was 0.07% in trials that included 67 000 patients (4).

Other adverse effects include phototoxic dermatitis, thrombocytopenia, edema of the legs, pruritus, and hypersalivation (SEDA-12, 93).

Organs and Systems

Respiratory

Tenoxicam can provoke severe bronchoconstriction and nasal obstruction in aspirin-sensitive asthmatic patients (SEDA-12, 93).

Liver

Mild chronic drug-induced hepatitis has been attributed to tenoxicam (SEDA-21, 108).

Skin

Three cases of toxic epidermal necrolysis (Lyell's syndrome) have been described in patients taking tenoxicam (SEDA-17, 114).

A fixed drug eruption with cross-sensitivity to droxicam and tenoxicam has been reported (SEDA-18, 107), but tenoxicam may not cross-react in patients with photosensitivity to piroxicam (SEDA-18, 107).

Drug Administration

Drug administration route

Tenoxicam can be given intravenously, but phlebitis and pain at the injection site occur, albeit rarely (SEDA-19, 99).

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Terazosin

See also Alpha-adrenoceptor antagonists

General Information

The alpha$_1$-adrenoceptor antagonist terazosin has similar adverse effects to those of prazosin. The long-term efficacy and safety of terazosin have been reviewed, in both monotherapy and combination therapy in whites and blacks (1,2).

In order to investigate the mechanisms of adverse events associated with alpha$_1$-adrenoceptor antagonists, the Veterans Affairs Cooperative Study database was analysed with respect to the relation between adverse events and hypotension in 1229 men with benign prostate hyperplasia. Treatment with terazosin produced the following rates of adverse events: dizziness 19%, weakness 6%, postural hypotension 6%, and syncope 1%. Of these adverse events only postural hypotension was associated with orthostatic blood pressure changes. Weakness, dizziness, and postural hypotension occurred to the same extent in patients with falls in systolic blood pressure of 5 mmHg or more or less than 5 mmHg. Thus, dizziness and weakness do not seem to be associated with changes in blood pressure, suggesting that these adverse events associated with alpha-blockers are not related to vascular effects. Designing a subtype selective alpha$_1$-antagonist that has less effect on blood pressure may not result in marked improvement in tolerability over currently available alpha$_1$-antagonists (3).

Organs and Systems

Skin

Terazosin has reportedly caused a rash (4).

- A 59-year-old man developed a generalized rash 3 days after starting to take terazosin 2 mg/day for benign prostatic hyperplasia. He had mild fever, weakness, intense pruritus, and a widespread eruption of scaling erythematous plaques with a violaceous hue on the trunk and extremities. The clinical examination was otherwise unremarkable and laboratory and serological test were negative. A skin biopsy was suggestive of a drug reaction. Terazosin was stopped, and treatment with oral prednisolone and emollients resulted in complete recovery in 2 weeks.

Sexual function

Priapism is rare with alpha-blockers (5).

- A 20-year-old man with a cervical spinal cord injury and a neuropathic bladder was given terazosin 1 mg at night increasing 5 days later to 2 mg. He developed a full erection of his penis, which lasted 5 hours and subsided spontaneously. Terazosin was stopped and the patient experienced no further priapism.

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Terbinafine

General Information

The allylamine derivative terbinafine can be used orally or topically. It is active against a broad range of fungi, including filamentous fungi and, to a lesser extent, yeast-like fungi. However, probably because of irreversible protein binding, its clinical usefulness is limited to the treatment of dermatophyte infections and perhaps lymphocutaneous sporotrichosis.

Terbinafine acts by inhibiting the synthesis of fungal ergosterol at the level of squalene oxidase, leading to depletion of ergosterol and accumulation of toxic squalenes in the fungal cell membrane.

Pharmacokinetics

Numerous reviews and studies of the pharmacokinetics of terbinafine have appeared (1–13). Independent of food, its oral availability is 70–80%. With a single dose of 250 mg, plasma concentrations reach around 0.97 μg/ml after two hours. Apparent steady-state plasma concentrations are reached after 10–14 days after only two-fold accumulation, although the half-life is up to 3 weeks and microbiologically active concentrations can be measured in plasma for weeks to months after the last dose, which is consistent with slow redistribution from the peripheral tissues and fat. Protein binding is over 99% and the apparent volume of distribution over 2000 liters, high concentrations reaching adipose tissues, the dermis, epidermis, and nails. Less than 0.2% reaches the breast milk. After several weeks, no further accumulation of the compound occurs (14,15). In renal or hepatic failure, elimination is slowed. Terbinafine undergoes extensive and complex hepatic biotransformation involving at least seven CYP450 enzymes (16); none of its metabolites is mycologically active. Urinary excretion accounts for more than 70% and fecal elimination for 10% of total excretion; the extent of enterohepatic recycling is unknown. Children have a shorter half-life, a lower mean AUC, and a higher volume of distribution, reflecting their higher proportion of lipophilic tissues (17,18).

Comparative studies

The safety and efficacy of terbinafine 250 mg/day and itraconazole 200 mg/day given for 12 weeks for toenail onychomycosis have been compared in a randomized, double-blind study in 372 patients (19). Adverse events were reported in 39% of the terbinafine-treated patients and in 35% of the itraconazole-treated patients. The mean values of biochemical parameters of liver and kidney function did not change significantly. Terbinafine produced higher rates of clinical cure (76 versus 58%) and mycological cure (73 versus 46%) than itraconazole.

In a randomized, double-blind comparison of terbinafine 250 mg/day ($n = 146$) with itraconazole 200 mg/day ($n = 146$), administered for 12 weeks for toenail onychomycosis, mycological cure rates at the 36-week follow-up end-point (67 versus 61%) and the proportion of patients with adverse effects (23 versus 22%) were similar in both study arms. However, more patients taking terbinafine stopped treatment permanently because of treatment-related adverse events (8 versus 1%) (20).

In a double-blind, randomized, multicenter comparison of terbinafine (250 mg/day for 12 or 16 weeks) or itraconazole capsules (200 mg bd for 1 week every 4 weeks for 12 or 16 weeks), 236 patients reported at least one adverse event. All were within the known safety profile of both drugs, and there were no significant differences among the four treatment regimens. Continuous terbinafine was significantly more effective than intermittent itraconazole (mycological cure rates at week 72: 76, 81, 38, and 49%; significant for all comparisons between terbinafine and itraconazole) (21,22).

General adverse effects

Terbinafine is usually well tolerated. Gastrointestinal complaints (dyspepsia, nausea, diarrhea) were the most common reasons for withdrawal. Abdominal pain and loss of taste were reported, as well as mild nervous system symptoms (headache and dizziness) (23).

Organs and Systems

Sensory systems

Taste disturbance is a rare adverse effect of terbinafine. It is usually reversible, with a median time to recovery of 42 days. However, a 46-year-old woman had complete loss of taste after taking oral terbinafine, with persistent taste disturbances for 3 years after stopping the drug (24).

Hematologic

The projected rate of all blood dyscrasias associated with terbinafine has been estimated to be 32 per million patient-years (25). Pancytopenia has been reported (26).

Leukocytes

Neutropenia has been reported in patients taking terbinafine (25–28).

- A 55-year-old woman who was taking terbinafine and paroxetine presented with fever, diarrhea, and vomiting. A bone marrow biopsy showed overall reduced cellularity, and the aspirate showed a profound shift toward the production of immature myeloid cells, consistent with maturation arrest. Treatment consisted of withdrawal of all outpatient medications, hydration, intravenous fluids, broad-spectrum antibiotics, and G-CSF 5 μg/kg for 5 days. Mature granulocytes appeared in the peripheral blood on the fifth day in hospital, and she was discharged on the seventh hospital day with an absolute neutrophil count of 6.2×10^9/l. Paroxetine was resumed weeks after discharge from hospital without hematological toxicity over 6 months.
- A 60-year-old man presented with fever, oral mucositis, pedal cellulitis, and bacteremia after a 6-week course of terbinafine 250 mg. He was taking concurrent yohimbine for impotence. Bone marrow examination showed a hypocellular marrow with myeloid maturation arrest. Treatment consisted of withdrawal of outpatient medications, broad-spectrum antibiotics, hydration,

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and G-CSF, and was ultimately successful. Yohimbine was resumed later without any adverse effects.

- A 42-year-old man presented with fever and granulocytopenia (absolute neutrophil count: 340×10^6/l; temperature: 39.5°C) after a 30-day course of oral terbinafine 250 mg/day for presumed onychomycosis (27). The granulocyte count recovered promptly after withdrawal of the drug and administration of G-CSF for 2 days.
- Agranulocytosis occurred in a 15-year-old who took terbinafine 250 mg/day for toenail onychomycosis and tinea pedis (29). This effect was noted 4 weeks after starting terbinafine and resolved within 1 week after its withdrawal.

Platelets

Thrombocytopenia has been attributed to terbinafine (30), and the incidence has been estimated at 1 in 200 000 patients (25).

- A 25-year-old Yemeni woman with familial-ethnic leukopenia developed thrombocytopenia with epistaxis after taking terbinafine 250 mg for 4 weeks (30). The platelet count recovered from a nadir of 63×10^9/l to 314×10^9/l after drug withdrawal.
- A 53-year-old woman developed severe thrombocytopenia after a 6-week course of terbinafine (250 mg/day) for onychomycosis (31). A bone marrow aspirate showed a normocellular marrow. She received a platelet transfusion and recovered after a short course of prednisolone.

Mouth

- A 38-year-old man presented with acute right otitis media and unrelated painless bilateral enlargement of the parotid glands 15 days after taking oral terbinafine for tinea cruris (32). He stopped taking terbinafine and 12 days later the swelling had significantly abated and completely disappeared 4 weeks later.

Liver

Minor abnormalities in liver function tests have been reported in up to 4% of patients taking oral terbinafine (33), but have not generally been considered clinically important (SEDA-16, 297) (SEDA-18, 7) (SEDA-18, 25).

Terbinafine can cause hepatitis, with an estimated rate of about 1 in 50 000 (34). Idiosyncratic reactions can lead to liver cell necrosis as well as cholestasis. Prolonged cholestatic hepatitis and liver failure have been reported (35–39).

- In four patients with cholestatic hepatitis associated with terbinafine, all presented with jaundice and direct hyperbilirubinemia, various other clinical signs of hepatitis, and mild to moderate rises in alkaline phosphatase and hepatic transaminase activities (34,39). Biopsies in two patients showed cellular infiltrates in the portal tracts and hepatocellular and canalicular cholestasis ($n = 1$) and hepatocyte degeneration ($n = 1$). In the two cases with long-term follow-up, hepatitis was reversible after withdrawal of terbinafine and liver tests normalized within 6 months.
- A 41-year-old man developed severe hepatic dysfunction following a 3.5-week course of terbinafine (250 mg/day) (40). He had marked pruritus, jaundice, malaise, anorexia, and loin pain. His serum bilirubin rose to a peak of 718 μmol/l with alkaline phosphatase 569 U/l, alanine transaminase 90 U/l, aspartate transaminase 63 U/l, and a prolonged prothrombin time of 21 seconds, unresponsive to vitamin K. Liver biopsy showed canalicular cholestasis consistent with a drug reaction. His symptoms resolved 11 months after drug withdrawal, and his liver function tests normalized after 15 months.
- A previously healthy 46-year-old man developed acute fulminant hepatitis following treatment with rabeprazole, citalopram hydrobromide, terbinafine, and a multivitamin formulation (41). Liver biopsy showed submassive centrilobular necrosis and intrahepatic cholestasis with florid bile duct proliferation.

In the last case, because of the similarity of the clinical, laboratory, and histological effects of omeprazole and lansoprazole, as previously reported, the authors concluded that the reaction in the second patient might have been caused by the proton pump inhibitor rather than terbinafine.

- A 56-year-old woman developed chronic biliary ductopenia and portal fibrosis 2 years after a course of terbinafine (42). Terbinafine treatment at that time had resulted in jaundice and evidence of cholestasis. After withdrawal of terbinafine, she continued to have pruritus and persistently raised serum alkaline phosphatase activity. Investigations for various types of chronic liver disease were negative and so chronic bile duct loss and periportal fibrosis were attributed to terbinafine.

Because of the rare and unpredictable nature of hepatobiliary reactions to terbinafine, the mechanism of hepatotoxicity has been hypothesized to be either immunological or metabolically mediated. A potentially toxic reactive metabolite of terbinafine, 7,7-dimethylhept-2-ene-4-ynal (TBF-A), the *N*-dealkylation product of terbinafine, has been identified in vitro (43). The authors speculated that this allylic aldehyde metabolite, formed by liver enzymes and conjugated with glutathione, would be transported across the canalicular membrane of hepatocytes and concentrated in the bile. The reactive monoglutathione conjugate could bind to hepatobiliary proteins and cause direct toxicity. Alternatively, it could modify canalicular proteins and lead to an immune-mediated reaction, causing cholestatic dysfunction.

Skin

Cutaneous adverse effects reportedly occur in 1–3% of patients taking terbinafine. The overwhelming majority of these reactions consist of mild to moderate macular exanthemas.

The risk of serious skin disorders has been estimated in 61 858 users of oral antifungal drugs, aged 20–79 years, identified in the UK General Practice Research Database (44). They had received at least one prescription for oral fluconazole, griseofulvin, itraconazole, ketoconazole, or terbinafine. The background rate of serious cutaneous

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adverse reactions (corresponding to non-use of oral antifungal drugs) was 3.9 per 10 000 person-years (95% CI = 2.9, 5.2). Incidence rates for current use were 15 per 10 000 person-years (1.9, 56) for itraconazole, 11.1 (3.0, 29) for terbinafine, 10 (1.3, 38) for fluconazole, and 4.6 (0.1, 26) for griseofulvin. Cutaneous disorders associated with the use of oral antifungal drugs in this study were all mild.

Generalized rashes, fixed drug eruptions, toxic epidermolysis, and erythema exudativum multiforme have all been reported in association with terbinafine (45,46).

Pustular eruptions can occur occasionally (45–49).

- Acute generalized exanthematous pustulosis associated with terbinafine has been described in two patients (47,49). Both presented within 7–10 days after starting to take terbinafine with generalized pustular dermatosis and leukocytosis; fever was a presenting symptom in one patient. Treatment with systemic corticosteroids was successful in both cases.
- A 62-year-old diabetic man on stable oral medication with glibenclamide, metformin, Zestoretic (lisinopril + hydrochlorothiazide), gemfibrozil, and aspirin developed febrile generalized pustular eruptions after 44 days of therapy with oral terbinafine 250 mg/day (50). Withdrawal of terbinafine and symptomatic treatment with hydrotherapy and topical and systemic steroids resulted in complete resolution of fever and pustulosis within 4 days. The erythematous component responded more slowly, and mildly pruritic erythematous plaques persisted for more than 40 days.
- In another case of acute generalized exanthematous pustulosis attributed to terbinafine (250 mg/day), epicutaneous and intracutaneous skin tests were negative, and there was no evidence of viral infection (51).

Terbinafine can cause or exacerbate psoriatic lesions.

- Severe pustular psoriasis provoked de novo by oral terbinafine has been reported in a 65-year-old man 2 weeks after the start of therapy for onychomycosis (52). Treatment of psoriasis was complicated and ultimately required continuous systemic and topical antipsoriatic therapy.
- A 74-year-old woman developed inverse psoriasis after 14 days of therapy with terbinafine 250 mg/day for onychomycosis (53). The lesions resolved almost completely on withdrawal of terbinafine and topical therapy.

Probable psoriatic onychodystrophy, misdiagnosed as onychomycosis and treated with terbinafine, induced inverse psoriasis in the second case, underscoring the importance of mycological confirmation of onychomycosis before therapy.

Ten cases of severe skin reactions probably associated with terbinafine requiring drug withdrawal have been reported: erythema multiforme ($n = 5$), erythroderma ($n = 1$), severe urticaria ($n = 1$), pityriasis rosea ($n = 1$), and worsening of pre-existing psoriasis ($n = 2$) (54). All the patients made an uneventful recovery with appropriate therapy. The authors pointed out that patients should be counselled about discontinuing terbinafine at the onset of a skin eruption and about seeking medical advice about further management.

- Cutaneous lupus erythematosus attributed to terbinafine has been reported in two previously healthy women (55,56). In the first patient, the lesions improved but did not resolve completely; in the second the symptoms resolved completely with appropriate therapy and the patient remained disease-free after withdrawal of all medication.
- Another woman with a previous history suggestive of lupus erythematosus developed a widespread flare in her skin 1 week after starting oral terbinafine (57). The eruption ultimately responded to systemic treatment with corticosteroids.

Baboon syndrome has been attributed to terbinafine (58).

- A 26-year-old man developed a fixed drug eruption on his hands and inguinal and gluteal areas after oral treatment of onychomycosis with terbinafine 250 mg/day. The rash showed the characteristic distribution of the baboon syndrome. Although epicutaneous and intracutaneous tests were negative, the rash recurred 20 hours after oral rechallenge with terbinafine.

The underlying pathogenic mechanism for the baboon syndrome has been suggested to be a systemically induced allergic contact dermatitis.

Hair

Hair loss has been attributed to terbinafine (59).

- A 69-year-old woman took terbinafine 250 mg/day for 112 days for subungual hyperkeratosis and developed hair loss after 3 months. She was also taking hydrochlorothiazide, amiloride hydrochloride, and amlodipine besilate, all in the same dosage for more than 5 years. Clinical and laboratory investigations showed no other obvious causes, and hair loss completely reversed on withdrawal of terbinafine.

Musculoskeletal

Since its introduction, the Netherlands Pharmacovigilance Foundation Lareb has received eight reports of arthralgia in patients taking terbinafine (60). In four cases, skin reactions were also present and in two cases urticaria. Two patients who reported arthralgia also had a fever. Logistic regression modelling showed that both urticaria and arthralgia were statistically significantly associated with reports on terbinafine compared with all other reports in the database. These findings may point toward a clustering of these symptoms in patients using terbinafine, suggesting a shared immunological reaction.

Immunologic

Exacerbation of lupus erythematosus has been reported during terbinafine therapy (55–57,61). Of 21 consecutive patients with subacute cutaneous lupus erythematosus who attended an outpatient dermatology department in Germany during 1 year, 4 had terbinafine-associated disease (62). In addition to high titers of antinuclear antibodies with a homogeneous pattern, anti-Ro(SS-A) antibodies were present; in three of the four women, anti-La(SS-B) antibodies were also found. All the

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patients had antihistone antibodies, as in drug-induced lupus, and showed the characteristic genetic association with the HLA-B8,DR3 haplotype; moreover, in two cases HLA-DR2 was also present. After withdrawal of terbinafine, antinuclear antibody titers fell and antihistone antibodies became undetectable within 4.5 months in three patients.

- A 66-year-old man with giant cell arteritis and hypertension developed a hypersensitivity reaction 4.5 weeks after starting to take terbinafine, with a skin eruption, fever, lymphadenopathy, and hepatic dysfunction (63). Concomitant medications included prednisone, doxazosin, and aspirin. His symptoms and signs resolved within 6 weeks after withdrawal of terbinafine and continuation of all the other medications. The hypersensitivity syndrome reaction in this case was idiosyncratic, with no apparent predisposing factors.

Susceptibility Factors

Age

The pharmacokinetics of terbinafine and five known metabolites have been investigated in 12 children, (mean age 8 years; range 5–11 years), who took terbinafine 125 mg/day for 6–8 weeks for tinea capitis (15). The metabolism of terbinafine was similar to that observed in adults, and there were comparable steady-state plasma concentrations after administration of the same oral dose. Steady state was reached by day 21 with no further accumulation up to day 56. Terbinafine was effective in all patients and safe and well tolerated over 56 days.

In a randomized, double-blind comparison of terbinafine ($n = 27$) with itraconazole ($n = 28$) for 2 weeks for tinea capitis in Pakistani children (mean age 8 years), fever, body ache, and vertigo were seen with terbinafine in one patient each, and urticaria with itraconazole in two patients (64). There were no significant changes in hematological and biochemical profiles.

In an open assessment of the efficacy, safety, and tolerability of oral terbinafine 125–250 mg/day for 1, 2, and 4 weeks for tinea capitis in 132 Brazilian children aged 1–14 years, adverse events were reported in 10 patients (65). The drug was prematurely withdrawn in one patient. In the post-treatment evaluation, two patients had abnormal bilirubin concentrations and eight patients had abnormal alkaline phosphatase activities; none was considered clinically relevant.

In an open, non-comparative study of the use of terbinafine for 14 days to treat tinea capitis in 50 children and adolescents (mean age 7.6 years; range 24 months to 18 years), the clinical and mycological cure rates were 86%. The drug appeared to be well tolerated. Two children had reversible neutropenia, thought to be due to a preceding viral illness; other adverse effects were not observed (18).

In 14 children, aged 1–15 years, with *Microsporum canis* tinea capitis given oral terbinafine for 4 weeks, the recommended daily dose produced no response by week 4; the dose was doubled (to 250 mg/day) for a further 4–8 weeks in six patients and continued at the original dose in six patients (66). Two patients withdrew. Four patients were cured after 8–12 weeks of treatment, and all had taken the doubled dose of terbinafine, except for one who had taken the usual adult dose of 250 mg/day from the start. Oral terbinafine was well tolerated by all but one patient, who had gastrointestinal disturbance and slightly raised transaminase activities during the first 4 weeks of treatment.

In an open, prospective, uncontrolled study in 81 immunocompetent young children (aged 2–13 years) with tinea capitis due to *Microsporum canis*, oral terbinafine was given in dosages based on weight (62.5 mg for those weighing 10–20 kg and 125 mg for 20–40 kg), and applied topically to affected areas (1% cream bd) (67). Treatment lasted for 4 weeks, followed by an 8-week observation (treatment-free) period. All the subjects were assessed for efficacy and tolerability at 12 weeks. At 12 weeks: 32 had completely recovered, with no evidence of relapse during the observation period, and 21 had mycological cure but residual signs of infection. The effective cure rate was 65%. Terbinafine was well tolerated by these children: 75 had no adverse effects; the other six had abdominal pain ($n = 2$), vomiting ($n = 1$), generalized itching ($n = 1$), local itching ($n = 1$), and localized erythema ($n = 1$). Hematological and biochemical parameters remained normal during the study.

Drug–Drug Interactions

Rifamycins

Rifampicin 600 mg/day reduced terbinafine concentrations by about 50% by enzyme induction (68).

Theophylline

Theophylline is largely metabolized by CYP1A2 and terbinafine increases its half-life (69). In a randomized, crossover study in 12 healthy volunteers, terbinafine increased theophylline exposure by 16%, with a 14% reduction in clearance and a 24% increase in half-life (69). These pharmacokinetic changes may predispose individuals to accumulation of theophylline and unwanted toxicity. Caution should be taken in prescribing terbinafine for patients taking long-term theophylline.

Tricyclic antidepressants

Desipramine

Inhibition of CYP2D6 by terbinafine has been evaluated by assessing 48-hour concentration-time profiles of the tricyclic antidepressant desipramine in 12 healthy volunteers identified as extensive CYP2D6 metabolizers by genotyping and phenotyping (70). The pharmacokinetics were evaluated at baseline (50 mg oral desipramine given alone), steady state (after 250 mg oral terbinafine for 21 days), and 2 and 4 weeks after terbinafine withdrawal. The pharmacodynamics were evaluated before and 2 hours after each dose of desipramine, using Mini-Mental Status Examination and electroencephalography. Terbinafine inhibited CYP2D6 metabolism, as indicated by significant increases in desipramine C_{max} and AUC and reductions in the C_{max} and AUC of the CYP2D6-mediated metabolite, 2-hydroxydesipramine, both of which were still altered 4 weeks after terbinafine withdrawal. Caution should be exercised when

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co-prescribing terbinafine and drugs that are metabolized by CYP2D6, particularly those with a narrow therapeutic index.

Imipramine

- A 51-year-old patient developed imipramine toxicity and increased plasma concentrations associated with the introduction of terbinafine, possibly due to inhibition of CYP2D6 (71).

Nortriptyline

Metabolism by CYP2D6 is of major importance for the hydroxylation of nortriptyline, making it susceptible to competitive inhibition by terbinafine. Nortriptyline intoxication provoked by terbinafine has been reported (72).

- A 74-year-old man taking a stable dose of nortriptyline for depression developed signs of nortriptyline intoxication 14 days after he started to take terbinafine (72). Nortriptyline serum concentrations were several times higher than the usual target range and fell to baseline after withdrawal of terbinafine. Re-challenge led to the same clinical and laboratory findings.
- Nortriptyline intoxication secondary to terbinafine has been observed in a woman with a major depressive disorder (73). After rechallenge her serum nortriptyline concentration rose and the serum concentrations of its two hydroxylated metabolites fell. She had a normal genotype for CYP2D6, suggesting that this interaction can occur even in people without reduced CYP2D6 activity.

Warfarin

While terbinafine had no effect on warfarin in healthy volunteers, it can prolong the prothrombin time in some individuals (74–77), prompting intensification of laboratory control during terbinafine therapy.

- A 71-year-old woman taking a stable dose of warfarin and cimetidine was treated with terbinafine, and 32 days later developed profuse intestinal bleeding associated with a prothrombin time of 120 seconds, suggestive of an interaction between warfarin and terbinafine, either directly or through the mediation of cimetidine (which can reduce terbinafine clearance by 33%) (74).

However, a contrasting case has also been reported.

- A 68-year-old woman taking warfarin, glibenclamide, metformin, furosemide, and spironolactone was given terbinafine 250 mg/day and 4 weeks later required progressive increases in the warfarin dosage to maintain a therapeutic INR; after withdrawal of terbinafine, her warfarin requirements returned to baseline over 4 weeks, supporting enzyme induction with gradual onset and offset (75).

Since a pharmacokinetic study of a single dose of warfarin in 26 healthy volunteers treated with terbinafine showed no significant interaction, and since a large postmarketing study of terbinafine did not find any cases of interaction of warfarin with terbinafine, the manufacturers (78) and others (77) have cautioned about any generalization regarding an interaction between terbinafine and warfarin.

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Terbutaline

See also Beta$_2$-adrenoceptor agonists

General Information

Terbutaline is a selective beta$_2$-adrenoceptor agonist, with a similar profile to salbutamol, and its adverse effects profile is similar to that of salbutamol at equivalent doses (SEDA-21, 186) (SEDA-22, 193).

Nebulized terbutaline 5 mg has been compared with injected adrenaline (0.01 ml/kg of 1:1000 adrenaline to a maximum of 0.3 ml) in children with acute asthma. Those who received adrenaline had a significantly higher rate of adverse effects, 47 versus 11% (SEDA-21, 186).

Organs and Systems

Respiratory

The possibility of paradoxical bronchospasm due to terbutaline must be taken into consideration (SEDA-8, 145).

Nervous system

With terbutaline, somnolence has been reported in some studies, and may be characteristic of this drug, apparently occurring in some 25% of patients (SEDA-8, 145).

Acute paraparesis occurred after an injection of terbutaline sulfate for premature labor in a 26-year-old woman (1).

Metabolism

The effect of terbutaline on glucose metabolism has been studied in six healthy, pregnant women, with normal glucose tolerance, between the 30th and 34th weeks of pregnancy (2). The women took either oral terbutaline 5 mg every 6 hours for 24 hours or no medication. The study was repeated after 1 week and each subject acted as her own control. With terbutaline fasting blood glucose increased in each subject, the mean rising from 4.6 to 5.2 mmol/l (82 to 94 mg/dl). Basal serum insulin increased significantly, from 18 to 27 μU/ml. Glucagon fell from a mean of 166 to 144 pg/ml. There was a 12% rise in basal hepatic glucose production. The glucose infusion rate to maintain euglycemia fell by 33% while subjects were taking oral terbutaline. Indirect calorimetry showed that terbutaline caused a significant increase in energy expenditure. Oxygen consumption increased by 9% (270 to 294 ml/minute) and basal caloric expenditure increased by 14% (from 1.32 to 1.5 kcal/minute). Thus, oral terbutaline given for 24 hours is associated with a significant reduction in peripheral insulin sensitivity and an increase in energy expenditure. Increases in basal hepatic glucose metabolism and a reduced ability of insulin to suppress hepatic glucose output are consistent with an effect of terbutaline on maternal hepatic glucose metabolism.

Second-Generation Effects

Pregnancy

In pregnant women with a history of migraine or vascular headache the use of terbutaline (and its congeners) should be avoided because of the risk of cerebral ischemia (SEDA-8, 145). One pregnant woman with asthma suffered a hypotensive episode after treatment with subcutaneous terbutaline (SEDA-12, 123).

A severe and life-threatening hypotensive reaction in patients with quadriplegia after terbutaline medication warrants a warning against indiscriminate use of beta-adrenoceptor agonists in the absence of autonomic spinal function (SEDA-8, 145).

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Drug–Drug Interactions

Phenylephrine

Sweating, tachycardia, and headache have been reported when terbutaline was added to phenylephrine (SEDA-18, 16).

Toloxatone

Sweating, tachycardia, and headache have been reported when terbutaline was added to toloxatone (SEDA-18, 16).

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Terfenadine

See also Antihistamines

General Information

Launched as a peripherally acting antihistamine with little sedative activity, terfenadine largely fulfilled this promise, but proved to have cardiotoxic properties, which led to restrictions on its use (SEDA-17, 196) (SEDA-18, 182) (SEDA-18, 186) (SEDA-19, 176) (SEDA-20, 163) (SEDA-21, 177) (SEDA-22, 179).

Inhibitors of CYP3A4 can lead to accumulation of unchanged terfenadine, causing prolongation of the QT interval and ventricular dysrhythmias. However, little is known about the effects of terfenadine on the pharmacokinetics of other drugs, even though it is known that terfenadine itself inhibits CYP3A4 activity in human liver microsomes. In view of its mode of metabolism, interactions with many other drugs are likely.

Organs and Systems

Cardiovascular

Terfenadine can cause prolongation of the QT interval in overdose or during interactions with drugs that inhibit its metabolism, such as erythromycin (1), ketoconazole (2), and grapefruit juice (3). Torsade de pointes can result (4).

Nervous system

Terfenadine has been investigated in several thousands of patients and found to have a sedation rate comparable to placebo (5). It has not been shown to impair driving performance (6).

Liver

There have been reports of cholestatic hepatitis induced by terfenadine (SEDA-21, 177), but quantitative information has been lacking on the risk of acute liver disease among users of this drug. In a population-based cohort study using general practice data in the UK carried out by the Boston Collaborative Drug Surveillance Program, a causal connection to terfenadine could not be ruled out in only three cases of acute liver disease among 210 683 recipients (7). However, the three individuals were also taking other drugs known to cause liver toxicity.

Skin

Terfenadine has been reported to cause skin reactions, notably urticaria and rashes in a number of cases (SEDA-11, 148) (SEDA-13, 132). A photoallergic reaction to terfenadine has also been reported (SEDA-12, 143), and so have severe exacerbations of psoriasis (SEDA-14, 137).

Stevens–Johnson syndrome has been reported both with terfenadine (SEDA-21, 177).

Drug–Drug Interactions

Atorvastatin

Terfenadine is normally metabolized by CYP3A4 to fexofenadine, which has negligible cardiac effects. Atorvastatin is also a CYP3A4 substrate, and its effects on the pharmacokinetics of terfenadine have been studied in healthy volunteers who took atorvastatin 80 mg/day from 7 days before to 2 days after terfenadine 120 mg (8). Concentrations of terfenadine and fexofenadine were measured for 72 hours. There were no alterations in the pharmacokinetics of the parent compound or of its metabolite and there were no alterations in QT_c intervals after terfenadine alone or with atorvastatin.

Buspirone

Ten healthy volunteers took oral terfenadine 120 mg/day for 3 days and then took buspirone 10 mg; terfenadine had no significant effects on the pharmacokinetics of buspirone (9).

Erythromycin

Torsade de pointes has been reported in patients taking erythromycin and terfenadine (1).

Grapefruit juice

Grapefruit juice substantially increased the AUC and C_{max} of terfenadine (3).

Ketoconazole

Terfenadine can cause prolongation of the QT interval in overdose or during interactions with drugs that inhibit its metabolism, such as ketoconazole.

- Torsade de pointes occurred in a patient who was taking the recommended prescribed dose of terfenadine in addition to cefaclor, ketoconazole, and medroxyprogesterone (2). Measured serum concentrations of terfenadine and its main metabolite showed excessive levels of

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parent terfenadine and proportionately reduced concentrations of its metabolite, suggesting inhibition of terfenadine metabolism.

Nefazodone

Nefazodone is a phenylpiperazine antidepressant that is predominantly metabolized by CYP3A. In a randomized, double-blind, double-dummy, parallel-group, multiple-dose study in healthy men and women who were given terfenadine 60 mg every 12 hours or nefazodone 300 mg every 12 hours, the plasma concentrations of terfenadine were significantly increased by co-administration of nefazodone (10). The mean QT_c interval was unchanged by terfenadine alone, but was markedly prolonged with co-administration of nefazodone, and the extent of prolongation correlated with the plasma terfenadine concentration.

Norfluoxetine

A possible interaction with norfluoxetine, a metabolite of fluoxetine, has been reported (SEDA-20, 164).

Sertindole

Sertindole 30 mg/day had no effects on the pharmacokinetics of a single dose of terfenadine 120 mg or of its metabolite (11). The authors concluded that sertindole at this dose does not inhibit the metabolism of terfenadine.

Sparfloxacin

The effect of the concomitant administration of terfenadine and sparfloxacin on the QT_C interval has been studied in healthy men aged 18–49 years (12). Sparfloxacin was given in a dose of 400 mg on the first day and 200 mg/day thereafter for 3 days with terfenadine 60 mg bd. Terfenadine had no effect on the pharmacokinetics of sparfloxacin and there were no apparent effects on the QT_C interval.

Venlafaxine

Drugs used in the treatment of depression and psychosis can alter the metabolism of terfenadine. When the antidepressant venlafaxine was given to steady state (37.5 mg bd for 3 days and then 75 mg bd for 5 days), the pharmacokinetics of a single dose of terfenadine 120 mg were not altered and there were no changes in the electrocardiogram (13). The authors concluded that cardiotoxicity is unlikely to arise with co-administration of terfenadine and venlafaxine.

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Terguride

General Information

Terguride is an ergot derivative, a partial dopamine agonist with properties similar to those of bromocriptine. It has been used in the treatment of Parkinson's disease and hyperprolactinaemia.

In 21 patients with parkinsonism, terguride 0.25–0.5 mg caused improvement for periods of up to 6 hours, although eight of 21 subjects showed no improvement or deterioration with doses of 0.5–1.0 mg (1). In three patients the addition of terguride 0.75 mg/day for 5–10 days did not affect levodopa-induced psychosis. In three patients with levodopa-induced dyskinesias, the addition of terguride 0.75 mg/day for 14 days resulted in a slight increase in the severity of the involuntary movements. The adverse effects of terguride, nausea and hypotension, were similar to those of levodopa. Terguride caused prolonged inhibition of prolactin release, but unlike levodopa did not increase plasma growth hormone concentrations. Additionally, terguride caused considerable sedation. These results may have been due to the combined effects of terguride on both non-dopamine and dopamine neurotransmitter systems, rather than to partial or incomplete dopamine agonist effects.

In 32 women with ovarian dysfunction due to hyperprolactinemia treated with terguride for 2–33 months, increased prolactin concentrations were successfully normalized in 21 (2). Regular periods reappeared in 14, 13 became pregnant, 7 gave birth to healthy babies, and 2

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aborted in the first trimester. Galactorrhea disappeared in 18 patients and was markedly inhibited in the others. There were adverse effects in 11 of the patients. They were mostly mild and included in most cases nausea, headache, and stomachache. The complaints were transient and abated after prolonged treatment.

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Terodiline

See also Anticholinergic drugs

General Information

Terodiline, an anticholinergic drug that was originally used for urinary incontinence (1), but was withdrawn in most countries in 1991 because of multiple reports of drug-related cardiac dysrhythmias (SEDA-17, 174).

Organs and Systems

Cardiovascular

A retrospective analysis of data from 19 patients has shown that the effect of terodiline on the QT interval is dose-related. The authors commented that terodiline has structural similarities to prenylamine, an antianginal drug that was previously shown to have prodysrhythmic properties, so that such problems should really not have been unexpected (SEDA-20, 147).

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Tetanus toxoid

See also Vaccines

General Information

Tetanus toxoid is prepared from *Clostridium tetani* and can be given either in a fluid form (plain) or an adsorbed form. The slight local reactions that tend to occur (induration, erythema, tenderness) are more common with the adsorbed type. Intramuscular injection of tetanus toxoid is generally the route of choice, and the vaccine is best injected into a large muscle.

General adverse effects

Data on adverse events after tetanus immunization have been collected by Behringwerke, Germany (SED-12, 826) and in the framework of the US Monitoring System for Adverse Events Following Immunization (MSAEFI) (SEDA-13, 274). Some figures for particular types of complication are cited below.

Isolated reports of adverse effects have included: abscess formation (SEDA-11, 288); dermatomyositis, neuralgic amyotrophy, polyradiculoneuritis with paresis of the urinary bladder and bowel (SEDA-9, 283); asymmetrical polyneuropathy, demyelinating polyneuropathy, and Guillain–Barré syndrome (SEDA-14, 281); and subcutaneous nodules. Polyvinylpyrrolidone thesaurismosis, revealed by inflammatory manifestations after tetanus booster injection, has also been reported (SEDA-10, 288).

Combined diphtheria + tetanus + pertussis vaccination

An overview of clinical trials with a special diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine has been published (1). The vaccine contains as pertussis components purified filamentous hemagglutinin, pertactin, and genetically engineered pertussis toxin. The vaccine induces high and long-lasting immunity and is at least as efficacious as most whole-cell pertussis vaccines and similar in efficacy to the most efficacious acellular pertussis vaccines that contain three pertussis antigens. The vaccine is better tolerated than whole cell vaccines and has a similar reactogenicity profile to other acellular vaccines.

A vaccine containing diphtheria and tetanus toxoids and acellular pertussis with reduced antigen content for diphtheria and pertussis (TdaP) has been compared with a licensed reduced adult-type diphtheria–tetanus (Td) vaccine and with an experimental candidate monovalent acellular pertussis vaccine with reduced antigen content (ap) (2). A total of 299 healthy adults (mean age 30 years) were randomized into three groups to receive one dose of the study vaccines. The antibody responses (anti-diphtheria, anti-tetanus, anti-pertussis toxin, anti-pertactin, anti-filamentous hemagglutinin) were similar in all groups. The most frequently reported local symptom was pain at the injection site (62–94%), but there were no reports of severe pain; redness and swelling with a diameter of 5 cm or more occurred in up to 13%. The incidence of local symptoms was similar after TdaP and Td immunization. The most frequently reported general symptoms were headache and fatigue (20–50%). The incidence of general symptoms was similar in the TdaP and Td groups. There were no reports of fever over 39°C. No serious adverse events were reported.

Data from the Third National Health and Nutrition Survey (1988–94) have been used to analyse the possible effects of DTP or tetanus immunization on allergies and allergy-related symptoms among 13 944 infants, children, and adolescents aged 2 months to 16 years in the USA (3). The authors concluded that DTP or

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tetanus immunization increases the risk of allergies and related respiratory symptoms in children and adolescents. However, the small number of non-immunized individuals and the study design limited their ability to make firm causal inferences about the true magnitude of effect.

Tetravalent, pentavalent, and hexavalent immunization

DTaP or DTwP vaccine can be combined with other antigens, such as *Haemophilus influenzae* type b (Hib), inactivated poliovirus (IPV), and hepatitis B vaccine. In children DTaP or DTwP vaccines are the basis for such combinations, while in adults it is mostly Td vaccine, Current safety concerns regarding combination vaccines have been defined and reviewed (4). The author concluded that there is no evidence that adding vaccines to combination products increases the burden on the immune system, which can respond to many millions of antigens. Combining antigens usually does not increase adverse effects, but it can lead to an overall reduction in adverse events. Before licensure, combination vaccines undergo extensive testing to assure that the new products are safe and effective.

The frequency, severity, and types of adverse reactions after DTP-Hib immunization in very preterm babies have been studied (5). Adverse reactions were noted in 17 of 45 babies: nine had major events (apnea, bradycardia, or desaturation) and eight had minor reactions (increased oxygen requirements, temperature instability, poor handling, and feeding intolerance). Babies who had major adverse reactions were significantly younger at the time of immunization than the babies who did not have major reactions. Of 27 babies immunized at 70 days or less, 9 developed major reactions compared with none of those who were immunized at over 70 days.

The Hexavalent Study Group has compared the immunogenicity and safety of a new liquid hexavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and *H. influenzae* type b (DTP + IPV + HB + Hib vaccine, manufactured by Aventis Pasteur MSD, Lyon, France) with two reference vaccines, the pentavalent DTP + IPV + Hib vaccine and the monovalent hepatitis B vaccine, administrated separately at the same visit (6). Infants were randomized to receive either the hexavalent vaccine ($n = 423$) or (administered at different local sites) the pentavalent and the HB vaccine ($n = 425$) at 2, 4, and 6 months of age. The hexavalent vaccine was well tolerated (for details see the monograph on Pertussis vaccines). At least one local reaction was reported in 20% of injections with hexavalent vaccine compared with 16% after the receipt of pentavalent vaccine or 3.8% after the receipt of hepatitis B vaccine. These reactions were generally mild and transient. At least one systemic reaction was reported in 46% of injections with hexavalent vaccine, whereas the respective rate for the recipients of pentavalent and HB vaccine was 42%. No vaccine-related serious adverse event occurred during the study. The hexavalent vaccine provided immune responses adequate for protection against the six diseases.

Organs and Systems

Cardiovascular

Myopericarditis has been attributed to Td-IPV vaccine (7).

- A 31-year-old man developed arthralgia and chest pain 2 days after Td-IPV immunization and had an acute myopericarditis. He recovered within a few days with high-dose aspirin.

The authors discussed two possible causal mechanisms, natural infection or an immune complex-mediated mechanism. Infection was excluded by negative bacterial and viral serology and a favorable outcome occurred within a few days without antimicrobial treatment.

Nervous system

Reports of neurological adverse effects after tetanus immunization have appeared (8). The most common reported complication is a polyneuropathy. In the majority of cases the onset occurred within 14 days of the last injection, and ranged in severity from a single nerve palsy to profound sensorimotor involvement of the nervous system, including cord and cortex. Recovery was usually complete (eight of 10 patients with onset at less than 14 days after injection) but three patients with onset at more than 14 days from injection had only partial recovery.

Mononeuritis and polyneuritis after tetanus immunization during 1970 and 1977 have been reviewed (9). The frequency of this adverse effect was 0.4 per one million distributed vaccine doses.

Sensory systems

Optic neuritis has been attributed to Td-IPV vaccine (10).

- Ten days after receiving Td-IPV vaccine a 56-year-old woman developed acute unilateral optic neuritis. Complete remission occurred within 6 weeks of prednisolone treatment. No other causes were found.

Skin

Bullous pemphigoid has been attributed to DTP-IPV vaccine (11).

- A previous healthy 3.5-month-old infant developed bullous pemphigoid 3 days after receiving a first dose of DTP-IPV vaccine. *Staphylococcus aureus* was isolated from purulent bullae. The lesions resolved rapidly after treatment with antibiotics and methylprednisolone.

The authors mentioned 12 other cases of bullous pemphigoid, reported during the last 5 years, that had possibly been triggered by vaccines (influenza, tetanus toxoid booster, and DTP-IPV vaccine).

- About 2 weeks after receiving a second dose of adsorbed tetanus toxoid a 50-year-old woman developed generalized morphea, a rare condition, in which multiple patches of skin sclerosis occur over much larger areas than in the localized variant. The patient denied taking any drugs. After prednisone therapy, a month later the lesions had dramatically improved (12).

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The cause of this condition is unknown, but an autoimmune mechanism triggered by endogenous and exogenous factors has been suggested.

Immunologic

Allergic reactions to reinforcing doses of tetanus toxoid have been described by different investigators (SEDA-8, 300) (SEDA-11, 288). The association between high titers of antitoxin produced by active immunization and reactions is well established (13,14). Booster doses of tetanus toxoid are being given with unnecessary and indeed excessive frequency. Continuing to do this will produce a more highly toxoid-sensitive population without adding significantly to the already high protection that this immunized population has against tetanus. It is therefore recommended that routine boosters in individuals known to have had primary immunization including a reinforcing dose be given only at 10-year intervals, and that emergency boosters be given no less than 1 year apart (15). Allergic reactions may be due to an allergy to the toxoid or the proteins of *C. tetani* that co-purify with toxoid during the precipitation process used in its conventional preparation (16).

Susceptibility Factors

Age

In children aged 15–16 years receiving routine reinforcement tetanus immunization, adsorbed vaccine caused more intense and more frequent local reactions than did plain tetanus toxoid, and a higher incidence of pyrexia. The incidence of swelling and erythema at the inoculation site increased with serum antitoxin titre at the time of administration, whereas pain and tenderness were related to the presence of the aluminium hydroxide adjuvant (17). Based on similar experiences it has been widely recommended that plain and not adsorbed tetanus toxoid should be used when reinforcement of immunity to tetanus alone is desired.

Other features of the patient

The only contraindication to tetanus toxoid is a history of a severe allergic or neurological reaction after a previous dose. AIDS and HIV infections are not contraindications. Data on the immune response to tetanus in children with AIDS showed defective responses (18).

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Tetracaine

See also Local anesthetics

General Information

Tetracaine is a highly lipid-soluble, potent aminoester. It is primarily used as a constituent of many different topical formulations and for spinal anesthesia. It is four times as potent as lidocaine, and unless great caution is taken in dosage, serious systemic adverse effects can develop,

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owing to rapid absorption after topical use (for example in a 0.5% gargle) (1) or use in endoscopy. It is more effective than Emla in reducing the pain of venous cannulation in children.

Tetracaine can cause local reactions when applied to the skin, but because it is rapidly metabolized by plasma cholinesterase systemic reactions are unlikely (2).

Organs and Systems

Cardiovascular

- An 18-month-old child undergoing cardiac surgery developed discoloration of the hand, consistent with severe bruising, after application of 4% tetracaine gel, which was inadvertently left under an occlusive dressing for about 24 hours (3). There were no long-term sequelae and no treatment was required.

The authors blamed a combination of the vasodilatory properties of tetracaine and the fact that the child was heparinized for surgery, causing capillary leak at the area of application.

Hematologic

Adult cases of methemoglobinemia have been reported with Cetacaine (a proprietary mixture of 14% benzocaine, 2% tetracaine, and 2% butylaminobenzoate) (4–6).

Cetacaine spray used to anesthetize the oropharynx before endoscopy led to dyspnea, central cyanosis, and an oxygen saturation of 80%; methemoglobinemia was diagnosed, and the patient recovered rapidly with methylthioninium chloride 1 mg/kg over 5 minutes.

- A 77-year-old woman received two sprays of Cetacaine for an attempted emergency nasotracheal intubation. After intubation, she became cyanosed. The arterial blood was chocolate brown and the SaO_2 by CO oximetry was 54–58%, despite a high PaO_2. The methemoglobin concentration was 39% and she was treated with methylthioninium chloride. Three weeks later, Cetacaine again caused cyanosis with a drop in SpO_2 to 76% and a methemoglobin concentration of 24%, which resolved spontaneously.
- A 74-year-old man received Cetacaine spray to his oropharynx for transesophageal echocardiography. His SpO_2 fell to 85%, he became drowsy, then unresponsive, cyanotic, and apneic, and required intubation. His PaO_2 was 37 kPa (280 mmHg), SaO_2 40%, and methemoglobin concentration 60%. Intravenous methylthioninium chloride produced an immediate improvement in the cyanosis and the methemoglobin concentration fell to 0.6%.

Skin

Reported local adverse effects of tetracaine include itch and a high incidence of erythema as a consequence of vasodilatation, which may actually be an advantage. There was no evidence of dermatitis (SEDA-20, 127) (7).

In 272 children who required topical local anesthesia for venepuncture, there was no association between the duration of application of 4% tetracaine gel and the development of adverse skin reactions (8). However, two reports discussed by the same authors highlighted rare adverse reactions.

- A 4-year-old child with no previous exposure complained of severe pain, erythema, and blistering 5 minutes after the application of 4% tetracaine gel.
- An anesthetist who was suspected of occupational exposure developed redness and blistering after applying a test dose of tetracaine.

The authors recommended minimizing occupational contact and quickly removing the cream in patients who report pain after application of tetracaine.

There may be a higher incidence of skin sensitization from tetracaine gel than Emla. At one hospital, in a 3-month period, there were seven site reactions to tetracaine (9). While the Summary of Product Characteristics says that significant skin reactions are rare, the authors estimated that seven reactions in their hospital represented a higher rate than 0.01–0.1% (usually regarded as the frequency of rare events). Indeed, the reported incidence of moderate to severe local skin reactions in clinical trials is 0.6–8.8%, compared with 0–1.7% with Emla. According to the Summary of Product Characteristics there is also a risk of sensitization with repeated exposure (four of the seven children who had reactions to tetracaine had had prior exposure to it), which is not known to happen with Emla.

Immunologic

Anaphylactic shock has been reported after spinal anesthesia (SED-12, 257) (10).

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Tetrachloroethylene

General Information

Tetrachloroethylene is a chlorinated derivative of a simple hydrocarbon, $H_2C{=}CH_2$, in which each of the four hydrogen atoms is replaced by chlorine, $Cl_2C{=}CCl_2$. It is a heavy liquid that has been used to treat hookworm infection. It is given orally in a dose of 0.1 ml/kg up to a maximum of 5 ml as a single dose on an empty stomach. Usually formulated as capsules or emulsion, it is unstable, especially if exposed to light. Concurrent *Ascaris* infection should be treated first to avoid migration of worms and the risk of peritonitis.

General adverse effects

The adverse effects of tetrachloroethylene are similar to those of carbon tetrachloride (CCl_4), but less severe. Tetrachloroethylene is hepatotoxic and neurotoxic, but gastrointestinal disturbance is the only common adverse effect when it is used carefully. There is some risk of addiction to the inhaled vapor: inhalation can result in vascular reactions, loss of consciousness, pulmonary edema, and fatal hepatic and renal damage. Alcohol and fatty foods increase absorption and hepatic toxicity. Exposure to tetrachloroethylene has been known to lead to vinyl chloride disease. Allergic reactions have not been reported.

It is highly unlikely that single-dose use of tetrachloroethylene could have a tumorigenic effect; however, animal studies conducted in connection with exposure to tetrachloroethylene in the course of industrial use showed an increased occurrence of liver tumors.

Organs and Systems

Cardiovascular

In cases of poisoning with tetrachloroethylene, hypotension can occur; sympathomimetic drugs should not be used to treat it, since ventricular fibrillation can be precipitated.

Respiratory

Hypersensitivity pneumonitis has been attributed to occupational exposure to tetrachloroethylene in a 42-year-old dry cleaner; the diagnosis was confirmed by lung biopsy (1).

Nervous system

Headache and vertigo are common with tetrachloroethylene (2,3). Patients should remain at rest for 3 hours after administration and take only water.

Inhalation of tetrachloroethylene vapor can cause stupor (4).

Psychological, psychiatric

Reversible neuropsychiatric symptoms, readily resembling alcoholic intoxication, have occurred after a single dose of 5 ml. Sleep apnea causing neuropsychiatric abnormalities has been attributed to exposure to high concentrations of tetrachloroethylene and *N*-butanol vapors; however, the patient was obese and the association with the solvents was not clear (5).

Gastrointestinal

Nausea, vomiting, colicky abdominal pain, and diarrhea are common with tetrachloroethylene (2).

Liver

Hepatotoxicity from tetrachloroethylene is similar to that caused by carbon tetrachloride and can occur after oral treatment or even inhalation of the vapor (6).

Urinary tract

Tetrachloroethylene can cause renal damage, especially after inhalation (7).

Skin

If tetrachloroethylene comes into contact with the skin, either directly or after vomiting, burn-like reactions can occur (8).

Erythema multiforme has followed oral administration of tetrachloroethylene (9).

Second-Generation Effects

Pregnancy

It is unwise to use tetrachloroethylene in pregnancy in view of its potential for hepatotoxicity, but there is no specific information on the risks to the fetus as a result of therapeutic use; however, work relating to industrial use (exposure of women in the dry-cleaning industry) suggests the need for caution (10).

Susceptibility Factors

Age

It is dangerous to use tetrachloroethylene in young children (11).

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Tetracyclines

See also Individual agents

General Information

The tetracyclines are a closely related group of antibiotics with comparable pharmacological properties but different pharmacokinetic characteristics. They have both the advantages and disadvantages of broad-spectrum antibiotics. Tetracyclines are effective not only against bacteria and spirochetes, but also against some forms of *Mycoplasma*, *Chlamydia*, and *Rickettsia*, as well as protozoa. They affect multiplying microorganisms by inhibiting ribosomal protein synthesis. Their effect is therefore primarily bacteriostatic rather than bactericidal, depending on the kind of microorganism.

Most of the adverse effects of the tetracyclines depend on the concentration of the antibiotic in the affected organ. The more lipophilic drugs are more potent with regard to their bacteriostatic efficacy and hence usually require daily doses below 1 g.

Use in non-infective conditions

Tetracyclines have many effects on non-infective inflammatory processes (SEDA-24, 278). They have been tried, and claimed to be of some value, in the treatment of rheumatoid arthritis, periodontal disease, myocardial infections, gastric disorders, and experimentally in the treatment of cancers. In all of these disorders, the proposed mechanisms for effects are on the host rather than the microbial side.

Tetracyclines have many effects on cells involved in inflammatory reactions, including inhibition of neutrophilic functions, such as migration, phagocytosis, degranulation, and the production of free oxygen radical (1). Most of these effects are supposed to be due to chelation of divalent ions and can be partly reversed by the addition of calcium ions or zinc ions. Their ability to inhibit synthesis of mitochondrial proteins may be the background for their effects on lymphocytes, such as inhibition of lymphocyte proliferation in response to mitogens, inhibition of interferon gamma production, and inhibition of immunoglobulin production. Enzyme inactivation caused by tetracyclines has been studied in several models. Tetracyclines inhibited gingival collagenolytic activity in diabetic mice and in humans with periodontal disease (2). Subsequent studies showed that tetracyclines inactivated collagenases found in several places in the body (3,4). Most probably, the inhibitory effects of tetracyclines on collagenases are exerted through inactivation of metalloproteases, rather than serine proteases. Tetracycline also has radical-scavenging properties, which may be partly related to the ulcer-healing effect observed in a rat model of gastric mucosal injury (5).

As is to be expected, modified cycline molecules devoid of antibacterial effects are as effective as non-modified molecules. New derivatives with refined anti-inflammatory and enzyme inhibitory (and reduced antimicrobial) effects are being studied in experimental laboratories (6).

Tetracyclines and metalloproteinases

A major target for non-infective indications of the tetracyclines is inhibition of metalloproteinases. The following is a brief summary of what is known about tetracyclines and metalloproteinases, followed by some comments about possible adverse effects.

The matrix metalloproteinases (MMPs) are a family of calcium- and/or zinc-dependent endopeptidases involved in degradation of extracellular matrix and tissue remodelling (7). At least 21 mammalian MMPs have been described. They participate in various biological processes, such as embryonic development, ovulation, angiogenesis, apoptosis, wound healing, and nerve growth.

Under normal conditions, the activity of MMPs is very low and is strongly regulated by natural tissue inhibitors (TIMPs). The TIMPS are a family of four structurally related proteins (TIMP-1, 2, 3, and 4), exerting dual control of the MMPs by inhibiting both their active forms and their activation. In addition, the proteolytic activity of MMPs is inhibited by non-specific protease inhibitors, such as alpha$_2$-macroglobulin and alpha$_1$-antiprotease.

In the presence of specific stimuli, exemplified by cytokines and growth factors, MMPs can be up-regulated. Chronic activation of MMPs, due to an imbalance between the activity of MMPs and TIMPs, can result in excessive degradation of the extracellular matrix and is believed to contribute to the pathogenesis of several diseases, such as rheumatoid arthritis, osteoarthritis, periodontal disease, emphysema, atherosclerosis, skin ulceration, and cancer.

The physiological and pathophysiological roles of MMPs and TIMPs have been extensively studied in knockout mice (7). For most of the MMPs and TIMPs there seem to be significant overlaps in functions, and a deficiency of one enzyme can be compensated for by the presence of others (7,8). Each MMP is encoded by a distinct gene, and about half of the human MMP genes so far discovered are on chromosome 11 (7).

The mere fact that MMPs might be involved in the pathogenesis of several chronic disorders has made this field attractive to numerous pharmaceutical companies.

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One major approach for controlling abnormal MMP activity has been the use of small molecular weight inhibitors, and several excellent reviews of the design of such inhibitors have been published (7).

Rheumatoid arthritis

In 1942, the Swedish doctor Nana Svartz introduced sulfasalazine into therapy and suggested that it might be useful in rheumatoid arthritis because of its antibacterial activity. Since then, many antimicrobial agents have been tried in the treatment of rheumatoid arthritis, based on the assumption that the disease may be due to an infectious agent. Interest has focused on tetracyclines for the treatment of rheumatoid arthritis (9), reactive arthritis (10), and osteoarthritis (11) and the state of the art has been reviewed (12). The theory that rheumatoid arthritis is due to an infectious agent has been refined to a statement that it may be a gene transfer disease in which some viruses act as vectors (13), thereby excluding a direct effect of antibacterial agents on the disease.

Two further perspectives on the use of tetracyclines in rheumatoid arthritis have been published (14,15). In addition to an effect on matrix metalloproteinases, the authors focused on a potential antiarthritic action of tetracyclines by their effects in the interaction between the generation of nitric oxide, matrix metalloproteinase release, and chondrocyte apoptosis. Both minocycline and doxycycline inhibit the production of nitric oxide from human cartilage and murine macrophages (16) in concentrations that are achieved in vivo. The authors suggested that tetracyclines may have several potential chondroprotective effects: direct inhibition of matrix metalloproteinase activity and, by inhibition of nitric oxide production, further reduction of matrix metalloproteinase activity, reversal of reduced matrix synthesis, and reduced chondrocyte apoptosis.

In double-blind, placebo-controlled studies, minocycline relieved clinical symptoms and reduced some laboratory measures of disease activity in patients with rheumatoid arthritis (17–19). However, the progression of radiographic damage was not significantly reduced and minocycline caused several adverse effects. This led to investigations of the therapeutic effects of doxycycline in patients with rheumatoid arthritis. In 13 patients with moderate rheumatoid arthritis, low-dose doxycycline 20 mg bd reduced the urinary excretion of pyridinoline (20). Pyridinolines are collagen cross-links that are released from joints during cartilage and bone resorption and correlate with the severity of joint destruction (21). In a later study, doxycycline produced a significant reduction in the number of tender joints and significant improvements in disability and behavior in 12 patients with rheumatoid arthritis (22).

However, these studies were not placebo-controlled, and it was possible that the observed effects were due to factors other than doxycycline. Two double-blind, placebo-controlled trials have since been reported (23,24).

In a crossover study, 66 patients took 50 mg doxycycline or placebo twice a day for 12, 24, or 36 weeks (23). Patients' assessments, swollen and tender joint counts, duration of morning stiffness, erythrocyte sedimentation rate, and the so-called modified disease activity score (25) were used as measures of disease activity. Doxycycline had no significant effects on clinical and laboratory measures of disease activity, pyridinoline excretion, or progression of radiographic joint damage. Furthermore, there were adverse effects during treatment with doxycycline and not with placebo. The authors concluded that doxycycline 50 mg bd provided no therapeutic benefit in patients with rheumatoid arthritis.

In another study, a 16-week, randomized, double-blind, placebo-controlled trial, eligible subjects with active seropositive or erosive rheumatoid arthritis were randomly allocated to three treatment groups: doxycycline 200 mg intravenously, azithromycin 250 mg orally, or placebo (24). The primary end-points were changes between baseline and week 4 in the tender joint count, erythrocyte sedimentation rate, and urinary excretion of pyridinoline. The trial was stopped prematurely after 31 patients had been enrolled. Three subjects were withdrawn because of worsening arthritis. There were no significant differences across the groups in any of the three primary clinical endpoints. The authors concluded that doxycycline did not reduce disease activity or collagen cross-link production.

Ten chemically modified tetracyclines (CMTs), minocycline, and doxycycline have been tested for their capacity to inhibit cartilage degradation in vitro (26). CMT-8 was the most active. The authors concluded that by carefully selecting a tetracycline-based MMP inhibitor and controlling dosages it should be possible to inhibit pathologically excessive MMP-8 and/or MMP-13 activity, especially that which causes bone erosion, without affecting the constitutive activity of MMP-1 needed for tissue remodelling and normal host function. They thought that of the CMTs, CMT-8 and to a lesser extent CMT-3 and CMT-7 were the most effective. However, the effects of these CMTs in a full-scale trial in rheumatoid arthritis have not been reported.

Reactive arthritis

It is well established that a number of microorganisms found in the gastrointestinal tract are associated with reactive arthritis and that most of these organisms might be susceptible to tetracyclines. Several investigations have shown clinical effects of tetracyclines in the treatment of reactive arthritis (12). In these cases, a more direct antibacterial effect of the triggering organism (if still present in the patient) might be the mechanism involved.

Osteoarthritis

Tetracyclines have been investigated in experimental osteoarthritis, because metalloproteases are involved in the breakdown of cartilage matrix seen in this condition. Doxycycline reduced the severity of knee osteoarthritis induced in dogs by ligamentous section (27) and also reduced the degradation of type XI collagen exposed to extract of human arthritic cartilage (28).

Periodontal disease

Periodontal disease is caused by microorganisms, but host responses are in large part responsible for destruction of the periodontal support structures. In these patients, pathological activity of host-derived matrix metalloproteinases occurs in response to the bacterial infection in the

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periodontal tissues, causing destruction of collagen, the primary structural component of periodontal matrix. This in turn leads to gingival recession, pocket formation, and increased tooth mobility. The final outcome is loss of the tooth.

Tetracyclines inhibit collagenolytic activity in gingival tissue (SEDA-23, 256) (29–31). Based on these findings, a large clinical development program was initiated to demonstrate the potential of a sub-antimicrobial dose of doxycycline to augment and maintain the beneficial effects afforded by conventional non-surgical periodontal therapy in adult periodontitis. A summary of these studies has been published (32). Several different dosage regimens and placebo were compared in patients who had had a variety of adjunctive non-surgical procedures. Of the various parameters studied, the following are worthy of mention: collagenase activity in gingival crevicular fluid and gingival specimens, so-called clinical attachment levels, probing pockets depths, bleeding on probing, and subtraction radiographic measurements of alveolar bone height.

Sub-antimicrobial doses of doxycycline reduced collagenase activity in both gingival crevicular fluid and gingival biopsies, augmented and maintained gains in clinical attachment levels and reductions in pockets depths, reduced bleeding on probing, and prevented loss of alveolar bone height. These clinical effects occurred in the absence of any significant effects on the subgingival microflora and without evidence of an increase in the incidence or severity of adverse reactions relative to the controls. The authors proposed that the main mechanism underlying these effects is inhibition of pathologically high matrix metalloproteinase activity in neutrophils (MMP-8) and bone cells (MMP-13).

Acne

Over the years, various tetracyclines have been used in the treatment of acne. Their mechanism of action is not clear, but appears to be not purely antimicrobial, since they reduce chemotaxis of polymorphonuclear leukocytes, modify complement pathways, and inhibit the polymorphonuclear leukocyte chemotactic factor and lipase production in *Propionibacterium acnes* (33). They may also have a direct effect on sebum secretion (34), for example by modification of free fatty acids (35).

Adult respiratory distress syndrome

Adult respiratory distress syndrome (ARDS) has many causes, is associated with severe lung damage, and is characterized by pulmonary edema and hypoxemia. It has a high mortality. The current method of treatment is supportive and there is no specific therapy. This was the background to a thorough review of the anti-inflammatory properties of tetracyclines in the prevention of acute lung injury (36). The authors ended with an optimistic forecast, that targeting the proteases that cause ARDS with chemically modified tetracyclines may be useful in prevention and treatment. They ended by suggesting that strategies to prevent ARDS should focus on targets downstream from the initial inflammatory signals that provoke the cascade of events.

Glaucoma

Tetracyclines, especially demeclocycline, are among the most effective ocular hypotensive agents, according to studies in rabbits and cats. The biochemical mechanism of this effect is unknown. The prolonged effect and apparent lack of adverse ocular adverse effects suggest their possible usefulness for treating glaucoma in man (SEDA-15, 260).

General adverse effects

Mild gastrointestinal disturbances are common. A common and nearly unique feature of all tetracyclines is the formation of drug–melanin complexes, resulting in pigment deposition at various sites. Except for enamel defects and presumable disturbances of osteogenesis these deposits do not give rise to abnormalities of organ function. In view of tooth discoloration and enamel hypoplasia, with a tendency to caries formation, tetracyclines should be avoided in children under 8 years of age and in women after the third month of pregnancy. The risk of photosensitivity reactions largely depends on the dose of the drug and the degree of exposure to sunlight. It may be increased in long-term treatment. Skin, nail, and other organ pigmentation often occur, even with low-dose long-term treatment. The syndrome of fatty liver degeneration is rarely encountered today, because risk factors such as pregnancy are respected, and formulations with lower doses are available. Adverse effects can occur with most tetracyclines if the dosage is not altered in patients with renal insufficiency.

Allergic reactions to tetracyclines are less than half as common as allergic reactions to penicillin. For this reason, tetracyclines are alternatives in patients with allergic reactions to other antibiotics. Exceptional observations of anaphylactic shock have been reported (37,38). In a few cases tetracyclines were assumed to be the cause of hypersensitivity myocarditis (39). Pneumonitis with eosinophilia has been described in association with tetracyclines (40). A serum sickness-like syndrome was probably associated with minocycline in a 19-year-old man treated for acne (41). Allergic and toxic reactions may in some cases have been caused by degraded formulations or additives (42). Tumor-inducing effects have not been reported.

Jarisch–Herxheimer reaction

The Jarisch–Herxheimer reaction is common in patients treated with tetracyclines for louse-borne relapsing fever (43). Two forms of reaction are described at the start of tetracycline therapy: (a) fever, rigor, increased respiratory and heart rates, and occasional delirium and coma (44); (b) fever and disseminated intravascular coagulation (45). At about the time the temperature reaches its peak, spirochetes disappear from the peripheral blood (44). Meptazinol, a partial opioid antagonist, reduces the Jarisch–Herxheimer reaction in relapsing fever (46).

Bleeding with thrombocytopenia and signs of intravascular coagulation in patients treated for louse-borne relapsing fever may be due to a Jarisch–Herxheimer reaction mediated by the release of endotoxins from disintegrating spirochetes (43).

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Comparisons of individual tetracyclines

The spectra of bacterial effectiveness of the various tetracyclines are fairly similar. However, metabolism and excretion vary. In general, preference is currently given to drugs that can be given in relatively low doses (not above 1.0 g/day).

Tetracycline (chlortetracycline) and oxytetracycline

These tetracyclines are incompletely absorbed from the gastrointestinal tract. Plasma concentrations fall with half-lives of 6–12 hours. They are predominantly excreted by the kidney, extrarenal elimination amounting at most to 10–20%. They have a lower affinity for fat and membranes, which means that higher dosages to achieve therapeutic effectiveness. However, higher dosages can contribute to an increased risk of systemic toxic effects and, as absorption from oral administration is incomplete, also to an increased risk of gastrointestinal adverse reactions.

Demeclocycline (demethylchlortetracycline)

Demeclocycline produces a significantly higher rate of phototoxic skin reactions than other tetracyclines, presumably owing to its long half-life (about 16 hours), resulting in therapeutic plasma concentrations lasting 24–48 hours, and an even longer-lasting accumulation of the drug in membranes and fatty tissues. Demeclocycline is eliminated about 20–40% by glomerular filtration. In patients with liver cirrhosis, cardiac failure, or impaired renal function, it should be used cautiously, because of its pronounced effect on electrolyte and fluid balance (47).

Doxycycline and minocycline

Doxycycline and minocycline are more lipophilic tetracyclines. They are well absorbed after oral administration. Their half-lives are 16–18 hours. Their higher affinity for fatty tissues improves their effectiveness and changes their adverse effects profile. Local gastrointestinal irritation and disturbance of the intestinal bacterial flora occur less often than with the more hydrophilic drugs, which have to be given in higher oral doses for sufficient absorption.

Nevertheless, their toxic effects are similar to those of other tetracyclines and arise from accumulation in fatty tissues. Accumulation in a third compartment and the resulting long half-life may contribute to an increased incidence of various toxic adverse effects during long-term treatment, even if lower daily doses are used. This seems also to be the case for pigmentation disorders and possibly for neurological disturbances (48).

Minocycline and doxycycline are predominantly eliminated by the liver and biliary tract (70–90%). Therefore, no change in dose is needed in patients with impaired renal function. However, it should be considered that hepatic elimination of doxycycline or minocycline might be accelerated by co-administration of agents that induce hepatic enzymes.

Methacycline

Methacycline is rarely used. It has similar efficacy to ampicillin in acute exacerbations of chronic bronchitis.

Chemically modified tetracyclines

As early as the 1960s it was recognized that tetracyclines might inhibit bone growth, supposedly by interference with calcium metabolism. It was not until collagenase was discovered in 1983 (50) that intensive interest in the non-antimicrobial properties of tetracycline-based antibiotics developed. Most of the initial studies were done with doxycycline and minocycline, that is semi-synthetic tetracyclines with widespread medical and dental uses. However, in 1987, a non-antibacterial chemically modified tetracycline (CMT) that inhibited mammalian collagenase activity was described (51). At present, the CMTs (also known as COLs, from their having been introduced by CollaGenes Pharmaceuticals Inc, Newton, PA, USA) comprise a group of at least 10 analogues compounds (CMT-1 to CMT-10) that differ in their specificity and potency in inhibiting MMP. Comparative pharmacokinetic data, obtained from animals, have recently been published, as has a bibliography covering more than 75 papers and abstracts related to the basic biological properties of these compounds (52). Chemically modified tetracyclines are more active in interfering with mammalian processes than the classical tetracyclines, which is the main justification for their use in non-infective problems (52,53). From a qualitative point of view, it might be reasonable to assume similar host-related adverse effects as the classical tetracyclines, while from a quantitative point of view, dosages, duration of therapy, etc., will influence the number of adverse effects. However, the risks might be quite high.

Hematologic

Sideroblastic anemia is characterized by the accumulation of iron in the mitochondria of erythroblasts. In a Phase I study in 35 patients with refractory tumors, eight taking CMT-3 developed anemia without leukopenia or thrombocytopenia (54). Three of these patients underwent bone-marrow examination and each had ringed sideroblasts. The authors referred to several cases of aplastic anemia, megaloblastic anemia, and hemolytic anemia in which members of the tetracycline family have been implicated. However, they stated that there has been no previous reports of sideroblastic anemia associated with any tetracycline derivative and that the molecular mechanisms by which CMT-3 might cause sideroblastic anemia are unclear.

Immunologic

Based on the strategy that inhibition of angiogenesis is of importance in anticancer therapy, CMT-3 (COL-3) was used in a phase 1 study in 35 patients at the National Institutes of Health in the USA in patients with refractory metastatic cancer (55). The patients received a test dose of CMT-3, followed by pharmacokinetic testing during daily dosing for 7 days. After a few doses, three patients developed symptoms of drug-induced lupus, and the diagnoses were verified after a few days or weeks. CMT-3 was withdrawn and there was improvement.

Bacterial resistance

Prolonged treatment with the classical antibacterial tetracyclines results in bacterial resistance and/or

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opportunistic fungal infections. It has therefore been forecast, but not so far proven, that chemically modified tetracyclines without antibacterial activity may not cause microbial resistance. However, accepting that the major mechanism by which bacteria get rid of tetracyclines intracellularly is by increasing their efflux via P glycoprotein, the chemically modified tetracyclines might also trigger that mechanism, thereby causing reduced sensitivity of the exposed bacterial population to all types of tetracyclines. Before this possibility has been ruled out, the new chemically modified tetracyclines should be introduced with great care.

Organs and Systems

Cardiovascular

Cardiovascular reactions to tetracyclines have often been associated with other symptoms of hypersensitivity, such as urticaria, angioedema, bronchial obstruction, and arterial hypotension (37,56). Such reactions occurred in patients who had tolerated tetracyclines previously and were therefore considered as anaphylactic.

Respiratory

There have been a few cases of acute bronchial obstruction after the administration of a tetracycline (57).

Pneumonitis with eosinophilia has also been described (40,58).

When pleural tetracycline instillation is used to produce local inflammation for pleurodesis in spontaneous pneumothorax, there are no severe short-term or long-term adverse effects (59).

Nervous system

Tetracyclines rarely cause benign intracranial hypertension. This syndrome has primarily involved children (60,61), although it has also been observed in adults (48,62–69). Re-exposure can result in recurrence (59). As a rule, the symptoms develop within days or occasionally several months after the start of therapy, in one case only after 18 months of tetracycline therapy for acne (48). The syndrome includes headache, nausea and vomiting, dizziness, tinnitus, papilledema, and visual disturbances caused by scotoma or optic nerve damage. Intracranial pressure can be raised up to three-fold. Distinct intracerebral lesions are not visible on CT scan or angiography and the ventricular spaces are not enlarged (62). With the exception of raised intracranial pressure, all findings, including the cell count and protein concentration of the cerebrospinal fluid, are normal. After withdrawal, symptoms resolve over a period of hours to days or occasionally weeks. Increased use of long-term therapy with tetracyclines for acne may contribute to a higher prevalence of this syndrome (70).

Early studies showed that curare blockade was increased by tetracyclines (71–73). This effect can be antagonized by calcium ions (74). There was a short-term increase in muscular weakness in patients with myasthenia gravis after intravenous tetracycline. The mechanism may be a calcium-antagonizing effect of magnesium ions present in the tetracycline solvent, as the symptoms could be provoked by similar amounts of magnesium alone. The formation of calcium complexes with non-protein-bound tetracycline, thus lowering the serum concentration of free calcium, may also be involved (75).

Sensory systems

Acute transitory myopia was described as an effect of tetracycline therapy, probably due to changes in refractive power (76).

Endocrine

Hormone production in patients with "black thyroid," who had taken a tetracycline for prolonged periods, was normal (77,78).

Metabolism

Tetracyclines can increase blood urea nitrogen or serum urea concentrations without a corresponding increase in serum creatinine (that is without accompanying renal damage). The mechanism is an excess nitrogen load of metabolic origin accompanied by negative nitrogen balance. This effect is termed "anti-anabolic" (79,80), but is in fact the result of inhibition of protein synthesis, which affects not only microorganisms but to some degree mammalian cells also. Sodium and water depletion, due to the diuretic effect of some tetracyclines, can further enhance uremia (80).

Tetracyclines have been associated with hypoglycemia (81). Insulin doses may have to be reduced (82).

Hematologic

Hematological changes with tetracyclines are extremely rare. However, in individual cases, hemolytic anemia (83), neutropenia or slight leukopenia, thrombocytopenia (84), and even aplastic anemia have all been described. In the light of the fact that such blood changes are often reported without a clear description of their cause, the relation to the drug often remains doubtful, especially if reactions are listed in tabular form and information on specific details or concomitant drug therapy is lacking.

Bleeding with thrombocytopenia and signs of intravascular coagulation in patients treated for louse-borne relapsing fever may be due to a Jarisch–Herxheimer reaction mediated by the release of endotoxins from disintegrating spirochetes (43).

Mouth and teeth

The long-term esthetic results of treating severely stained teeth due to tetracyclines by endodontics and internal bleaching have been assessed in 20 patients and found to be excellent (85). A therapeutic strategy may be bleaching after the preparation for porcelain laminate veneers or night-guard vital bleaching (86,87).

Stomatitis, other signs of irritation of the oropharynx, and a rash in and around the orifices have been described in patients taking tetracyclines. This may partly be considered as mucous membrane manifestations of allergic or toxic origin. Secondary infections by pathogenic organisms, such as *C. albicans*, viruses, or bacteria, should always be considered (88).

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Gastrointestinal

Nausea, vomiting, and epigastric burning are the most common adverse effects of tetracyclines. This is also true for the lower-dose formulations. The symptoms are usually mild and seldom necessitate withdrawal. Nausea occurs in 8–15% of patients.

Esophageal damage

Esophageal ulcers have been described in association with oral doxycycline or tetracycline. Acute onset of substernal burning pain and dysphagia was noted within hours of taking the drug (89–93). Remaining parts of the ingested capsule were identified by esophagoscopy.

Thirty centers for pharmacovigilance in France have reported 81 cases of esophageal damage after treatment with tetracyclines collected between 1985 and 1992 (94). There were 64 ulcers, eight cases of dysphagia, and nine of esophagitis. Most (96%) of the cases were caused by doxycycline and 73% of the patients were female, mean age 29 years. Prescriptions were for dermatological (54%), urogenital (23%), and ENT diseases. In one patient, a 71-year-old man, an esophagobronchial fistulation required esophagectomy. In 92% the drugs were not taken correctly, that is at bedtime or without a sufficient quantity of fluid. Treatment with sucralfate 1 g tds did not change the outcome of tetracycline-induced esophageal ulcers (95).

In three studies of more than 600 children with chest pain, none had tetracycline-induced esophagitis as a cause of their pain (96–98).

Patients should not lie down immediately after taking a tetracycline capsule and the formulation should be swallowed with generous quantities of water (89,99).

Liver

A clinical syndrome, often with fatal outcome, has been recognized as a complication of high doses of tetracycline. It is characterized by nausea, vomiting, and spiking fever. Jaundice, acidosis, and uremia are also often present, while hematemesis and melena are only occasionally observed. Some patients die because of refractory hypotension. The histopathological findings are those of diffuse fatty liver degeneration (100–102). Although the syndrome was primarily described in pregnant women, it is not restricted to them. Impaired renal function, and thus reduced renal elimination of tetracyclines, as well as serious infections, increases the risk of this complication (100,103). Since the introduction of lower doses of tetracycline (under 1 g/day), the syndrome of fatty liver degeneration with severe hepatic insufficiency has become rare (101). However, a few reports have described liver reactions in previously healthy individuals with no pre-existing conditions and given usual oral doses of tetracyclines (104,105). Liver enzymes and renal function should be monitored, especially in patients at risk.

A personally experienced case of likely tetracycline-induced liver injury after low-dose tetracycline has been reported (106). The patient took oral doxycycline 200 mg/day for 8 days and had markedly altered liver function. The liver enzyme activities normalized only 109 days after withdrawal. The authors also reviewed all reports of liver damage to Swedish Adverse Drug Reactions Advisory Committee (SADRAC) in the period 1965–95. There were 23 liver reactions with a suspected causal relation to oral low-dose tetracycline derivatives. A causal relation was considered likely in three cases and possible in eight, giving an incidence of roughly one in 18 million defined daily doses. There were no deaths from these liver reactions, and liver enzyme activities normalized in all cases without any serious clinical consequences. The authors remarked that the frequency of liver reactions resulting from tetracyclines may be somewhat higher, as previous studies in Sweden suggest that only 20–50% of severe adverse reactions are reported to SADRAC (106).

Pancreas

Pancreatitis is a common feature of the clinical syndrome of fatty liver due to tetracyclines, although it has also been observed without overt liver disease in a patient after two separate exposures (107).

Urinary tract

Tetracyclines not uncommonly cause a raised serum urea concentration due to impaired protein synthesis rather than renal damage, However, renal insufficiency can occur, and patients with pre-existing renal insufficiency are particularly likely to develop raised blood urea nitrogen, serum phosphate, and serum sulfate concentrations during treatment with most tetracyclines. These changes may be associated with acidosis and even symptoms of uremia. Renal dysfunction can be missed if diuresis alone is monitored, since non-oliguric renal insufficiency has been reported (108). Interstitial nephritis is extremely rare (109–111).

Uremia, which may at least in part be due to a reduction in renal function, has been observed in patients with liver cirrhosis (112–114), cardiac failure, or interstitial nephritis (115), which is extremely rare (109–111).

Most observations suggest that a determining factor for the risk of renal insufficiency is a relative overdose of the drug in patients with pre-existing renal damage (113,114), particularly in those who are already dehydrated (for example due to diuretic therapy). The half-life of tetracyclines is prolonged several-fold in patients with renal dysfunction (116). With normal renal function, 20–70% of an intravenous dose of tetracycline is eliminated by glomerular filtration. Maintenance therapy must be adjusted to the degree of renal impairment.

Acquired Lignac–De Toni–Fanconi syndrome, with polyuria, polydipsia, glycosuria, aminoaciduria, hyperphosphaturia, and hypercalciuria, was described in a number of patients treated with outdated tetracycline formulations. The degeneration products responsible for the toxic action are probably epitetracycline, anhydro-4-epitetracycline, and anhydrotetracycline (117), as similar renal damage was produced in rats with anhydro-4-epitetracycline (118).

A few observations of a nephrogenic diabetes insipidus-like syndrome with demeclocycline (demethylchlortetracycline hydrochloride) and resistance to exogenous vasopressin suggested impairment of renal concentrating function by tubular damage (47). Demeclocycline has therefore been proposed for the treatment of inappropriate secretion of antidiuretic hormone (119–123).

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Acute interstitial nephritis leading to acute renal insufficiency has been reported after a single repeated dose of tetracycline (124).

Skin

Pronounced responsiveness of the skin and nails to light is a complication of systemic therapy with tetracyclines. In general, the pathogenesis of skin reactions promoted by sunlight exposure is mediated by phototoxicity, as suggested by the high occurrence rate (up to 9 out of 10 patients), depending on sun exposure and drug dosage. Experimental studies identified a wavelength close to 320 nm within the ultraviolet spectrum as the most potent area for the induction of phototoxic reactions (125). It has been described with various tetracyclines and presumably occurs with all of them. The skin changes resemble those of minor to severe sunburn, with erythema, edema, papules, blisters, and urticaria (126,127). In some circumstances they resemble cutaneous porphyria and have therefore been described as "porphyria-like cutaneous changes" (128).

Pigmentation due to tetracyclines occurs, but the exact frequency is not known. It has been observed with newer and lower-dose formulations as well as with older drugs, and presumably occurs with all tetracyclines. In contrast to phototoxic reactions, pigmentation can appear without light exposure and without inflammation. Pigment deposits were observed in light-exposed and non-exposed skin, the conjunctivae, the oral mucosa, the tongue, and internal organs, such as the thyroid and heart valve endothelium (77,78,129,130). The pigment is presumed to be a drug–melanin–calcium complex and depends on the chelating properties of the tetracycline molecule. Although pigmentation usually tends to persist after withdrawal, it does not provoke any symptoms or organ dysfunction, except for cosmetic problems. A number of cases occurred in patients treated for acne, and may possibly have been due to more common use of long-term treatments (131), although there is no evidence that the risk is increased in these patients.

Allergic skin and mucous membrane reactions occur with a very low incidence of 0.3%, which is about 10-fold lower than the incidence of such reactions in patients treated with other antibiotics (132). A generalized rash can occur during tetracycline treatment. Various forms have been described, including generalized urticaria, maculopapular rash, erythema exudativum, multiforme-like eruptions, and rare cases of Stevens–Johnson syndrome (133–136). Even acute generalized exanthematous pustulosis has been described (137). Fixed drug eruptions due to systemic administration are rare (138–140), as is a serum sickness-like syndrome (41,141). Allergic contact dermatitis induced by local application of a tetracycline is an exception (133,142–144).

Antimicrobial drugs, especially co-trimoxazole, ampicillin, and tetracyclines, can cause fixed drug eruptions (145).

Nails

Pronounced photosensitivity of the skin and nails is a complication of systemic therapy with tetracyclines. Onycholysis is associated with nail discoloration. Dystrophy is usually preceded by photosensitivity reactions of the skin (133). Depending on the degree and area of light exposure, onycholysis may also affect the toe nails (126). In contrast to idiopathic onycholysis, it not only affects women (146).

Musculoskeletal

Deposition of tetracyclines in bone tissue has been demonstrated in animals (147) and man (148). However, whereas osseous tissue in adult patients treated with tetracycline has shown deposits only in areas of repair or remodelling, children's bones contain extensive areas of deposition. Tetracycline deposition in bone has been reported to have an effect on longitudinal bone growth (149). In experimental tissue cultures, osteogenesis was impaired by tetracyclines in concentrations similar to serum concentrations that are associated with a therapeutic effect (that is 1 μg/ml) (150). The deposition of tetracyclines in human bone begins in utero as early as in the first trimester of pregnancy (148). With regular tissue turnover, the deposits disappear.

Infection risk

Monilial infections of the vulva and vagina in temporal association with tetracycline use can occur, even without other predisposing factors such as diabetes, pregnancy, immunodeficiency, and therapy with oral contraceptives and glucocorticoids. They also occur in patients treated with other antibiotics (151). *C. albicans* is not always the cause of vaginitis. The same is true for balanitis in men (152). If symptoms persist or change in patients with urethritis or adnexitis, this may be due to treatment failure, because of resistance of the causative pathogen (153).

Long-Term Effects

Drug resistance

Resistance to tetracyclines shows marked inter-regional variations and changes rapidly with time. The selection of resistant bacterial strains may be favored by widespread, often prophylactic, use in veterinary medicine and by long-term therapy for acne, periodontal disease, or symptomatic *Borrelia* infections. Many of the documented cases of resistance are of limited practical significance, since the tetracyclines are merely one of a number of therapeutic alternatives. The problem may be different when these drugs are the chemotherapeutic agents of first choice, that is in chronic *Borrelia* infections, especially arthritis due to Lyme disease and pulmonary or bubonic plague due to *Yersinia pestis* (154).

For infections with *Chlamydia* or *Mycoplasma*, effective alternative antibiotics are available. Increased rates of resistant strains of genital *Mycoplasma* may explain treatment failures (153,155).

A rather high resistance rate of 25–50% is reported for *Hemophilus* species (156), and this has to be taken into consideration if tetracyclines are given to patients with chronic pulmonary diseases or for the treatment of acute respiratory infections.

For infections with *Neisseria gonorrhoea*, tetracyclines are not indicated, owing to the higher prevalence of

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resistance, especially among penicillinase-producing strains (157). For these patients, better alternatives are usually available.

Second-Generation Effects

Teratogenicity

Teratogenic effects of tetracyclines have been demonstrated (158–160), as evidenced by increased rates of intrauterine death, congenital anomalies in general (161), and congenital cataracts (162) in fetuses exposed to tetracyclines. However, it is often impossible to distinguish between the drug and an underlying unidentified viral infection as a cause of the observed abnormalities.

Of 38 151 pregnant women who had babies without any defects (controls), 214 (0.6%) had taken oral oxytetracycline; in contrast, of 22 865 pregnant women who had offspring with congenital abnormalities, 216 (0.9%) had taken oxytetracycline (OR = 1.7; 95% CI = 1.4, 2.0) (163). More women whose babies had congenital abnormalities had taken oxytetracycline in the second month of pregnancy:

- neural-tube defects (OR = 9.7; CI = 2.0, 47);
- cleft palate (OR = 17; CI = 3.5, 84);
- multiple congenital abnormalities (particularly the combination of neural-tube defects and cardiovascular malformations) (OR = 13; CI = 3.8, 44).

The authors mentioned that their previous study had not shown a teratogenic potential of doxycycline (164), but concluded, far more prudently, that all tetracyclines are contraindicated during pregnancy.

Fetotoxicity

Discoloration of the first teeth is particularly likely if a tetracycline is given to the mother after the third month of pregnancy (165). Tetracyclines pass across the placenta and reach therapeutic concentrations in the fetal circulation (166,167).

Tooth discoloration is due to deposition of tetracyclines in the form of calcium complexes in the mineralizing zones of the teeth, and seems to be pathogenically related to the pigmentation of other organs. It occurs when tetracyclines are used during tooth formation. Tetracyclines pass through the placenta and are also found in high concentrations in the breast milk (168). As mineralization of the deciduous teeth takes place from the fourth month of intrauterine life until 1 year after birth and continues for the permanent teeth up to the age of 7–8 years (166), pregnant women after the third month of pregnancy, nursing women, and children under the age of 8 years should not be treated with tetracyclines. Discoloration of the teeth after intrauterine exposure to tetracyclines was observed in up to 50% of children at risk and was especially high when tetracyclines were used during the last trimester (166). Besides its merely cosmetic aspect, tooth discoloration in children is associated with enamel defects and hypoplasia in severe cases (169). Adult-onset tooth discoloration coincident with minocycline administration occurred in four of 72 patients (170).

Susceptibility Factors

Age

Pregnant women after the third month of pregnancy, nursing women, and children under the age of 8 years should not be treated with tetracyclines, because of the risk of discoloration of the teeth. Besides its merely cosmetic aspect, tooth discoloration in children is associated with enamel defects and hypoplasia in severe cases (169).

Renal disease

Tetracyclines are removed by hemodialysis, but significantly less than creatinine or urea (100,116). Severe adverse effects of tetracyclines occur almost exclusively with doses over 1.0 g/day (101) or in the treatment of pyelonephritis with concomitant renal insufficiency.

Drug Administration

Drug administration route

The intravenous formulation of tetracycline was instilled intrapleurally to produce chemical pleurodesis, with good effect, from the 1970s to the 1990s. The adverse effect most commonly seen with tetracycline was chest pain, which was often severe (171,172). In a comprehensive review of intrapleural therapy published in 1994 (173) the incidence of chest pain was estimated at 14%, and fever occurred in 10% of patients. However, the intravenous form of tetracycline has been withdrawn by the manufacturer and so this agent is no longer available for pleurodesis.

Drug–Drug Interactions

Antacids

Co-administration of tetracyclines with antacids or other drugs containing divalent or trivalent cations, such as calcium, magnesium, or iron, is contraindicated. Tetracyclines form complexes with such cations, which are very poorly or not at all absorbed (75,174,175).

To avoid this interaction, delay of 2–3 hours between the ingestion of tetracycline and the cation is recommended (175). Similarly, reduced systemic availability results from simultaneous intake of abundant quantities of milk or milk products.

Antidiarrheal drugs

Antidiarrheal drugs, such as kaolin-pectin and bismuth products (176,177), impair the absorption of tetracyclines by chelation (see the interaction with antacids in this monograph).

Coumarin anticoagulants

Although antibiotics can inhibit the production of vitamin K in the gut by intestinal bacteria, they do not thereby interfere with the actions of coumarin anticoagulation, since vitamin K that is produced by intestinal bacteria is of less importance than vitamin K that is obtained from dietary sources (178). Nevertheless, there have been

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sporadic reports that tetracyclines can enhance the effects of coumarin anticoagulants (179–182). The mechanism is not known, but evidence that tetracyclines can reduce the activity of prothrombin (183) suggests an additive pharmacodynamic interaction.

Diuretics

The combination of tetracyclines with diuretics is particularly detrimental to renal function (184). Tetracyclines accumulate in patients with pre-existing renal insufficiency (for example elderly people, even if the serum creatinine is in the reference range) and can cause nausea and vomiting, which causes dehydration and worsens renal function. This is exacerbated by the effects of diuretics.

Iron

See antacids above (174,175).

Methoxyflurane

In patients taking oral or parenteral tetracyclines who undergo methoxyflurane anesthesia, renal insufficiency and oxalate crystal formation in renal tissue was attributed to an interaction between these drugs (185–187). Tetracyclines are therefore not recommended preoperatively.

Risperidone and/or sertraline

An interaction of tetracycline with risperidone and/or sertraline has been described (188).

- A 15-year-old youth with Asperger's syndrome, Tourette's syndrome, and obsessive-compulsive disorder was stabilized on risperidone 1.5 mg bd and sertraline 100 mg od and had marked improvement in his social skills and tics, until he was given tetracycline 250 mg bd for acne. Within 2 weeks his tics were acutely exacerbated with pronounced neck jerking and guttural sounds. The sertraline was increased to 150 mg/day, but the tics did not resolve. The tetracycline was withdrawn after 1 month, and the tics improved within a few weeks.

The authors reviewed the major metabolic pathways of the three drugs used in this case. Tetracycline may have accelerated the hepatic metabolism of risperidone, but tetracycline has not been shown to induce CYP2D6, the major hepatic enzyme involved in the metabolism of risperidone. The authors claimed that it was more likely that tetracycline binds to risperidone or its active metabolite, making them inactive. They supported this suggestion by citing evidence that clozapine, which has similar pharmacology to risperidone, interacts with tetracycline in vitro (189). They also commented on the possibility that the effect could have come from increased concentrations of sertraline, which can increase tics (190). Tetracycline may inhibit the hepatic enzymes that metabolize sertraline; however, adequate evidence is lacking. Another possibility is a protein binding interaction, because all three drugs are highly protein bound. However, the observation that the tics were not worsened by an increase in sertraline dosage makes this possibility less likely. The mere fact that the withdrawal of tetracycline resulted in an improvement in the tics supports an interaction between tetracycline and risperidone.

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Tetryzoline

General Information

Tetryzoline, an alpha-adrenoceptor agonist with vasoconstrictor and decongestant properties, is widely available without prescription for symptomatic relief of "pink eye" and is found in various products in a concentration of 0.05%.

Susceptibility Factors

Age

Tetryzoline eye-drops are considered to be safe when used appropriately. However, relatively small amounts can produce profound central nervous depression and can lead to serious toxicity, especially in children under 2 years of age. A Poison Center reported 64 cases of tetryzoline poisoning over a period of 3 years; ingestions accounted for 59 cases, but three were attributable to administration into the eye, ear, or nose (1).

Reference

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Tezosentan

See also Endothelin receptor antagonists

General Information

Tezosentan is a dual endothelin-A and endothelin-B receptor antagonist. Its common adverse effects include headaches, nausea, and hypotension compared with placebo (1).

Organs and Systems

Nervous system

Tezosentan has been studied in single intravenous doses of 5, 20, 50, 100, 200, 400, and 600 mg for 1 hour in sequential groups of six men in a randomized, placebo-controlled, double-blind design (2). Headache was the most frequently reported adverse event and it was more common than with placebo at doses of 100 mg and over. There were no clinically important changes in vital signs, electrocardiography, or clinical laboratory tests. The volume of distribution at steady state, about 16 liters, and the clearance, 30 l/hour, were independent of dose. Endothelin-1 concentrations increased dose- and concentration-dependently and returned slowly to baseline after the end of the infusion.

During chronic double-blind, placebo-controlled infusion in healthy men, tezosentan 100 mg/hour for 6 hours in six subjects (total dose 600 mg) and 5 mg/hour for 72 hours in eight subjects (total dose 360 mg), headache was the most common adverse event (75–100% with tezosentan and 50% with placebo) (3).

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Thalidomide

General Information

Thalidomide was synthesized in 1953 by Wilhelm Kunz and Herbert Keller, working for Chemie Grünenthal. Kunz was preparing a series of peptides for antibiotic synthesis and in doing so isolated a non-peptide by-product, which Keller recognized as an analogue of the hypnotic glutethimide. They prepared a series of further analogues, one of which was thalidomide. It was introduced as a hypnotic in the late 1950s, as a supposedly safe sedative for children and pregnant women. Besides West Germany, Great Britain was the only country in which formulations containing thalidomide were sold on a large scale during the period 1959–60 inclusive. Following the discovery of its major teratogenic effects, thalidomide was withdrawn from the market in the early 1960s.

Modern uses

Since its withdrawal, thalidomide has been found to be effective in the treatment of erythema nodosum leprosum, and in 1997 it was marketed in the USA for this indication. The mechanism of action of thalidomide is still unclear (1,2), but it has many anti-inflammatory and immunomodulatory actions in vitro and in vivo (3,4).

In dermatological practice, thalidomide has also been used to treat patients with various diseases that are unresponsive to conventional therapy. Among these are aphthous stomatitis, Behçet's disease, discoid and systemic lupus erythematosus, uremic pruritus, actinic prurigo, prurigo nodularis, sarcoidosis, adult Langerhans cell histiocytosis, erosive lichen planus, and pyoderma gangrenosum (5). There has also been research on a possible antineoplastic action of thalidomide (6), which may be produced via antiangiogenic effects or direct effects on tumor cells, such as induction of apoptosis or G1 arrest of the cell cycle, inhibition of growth factor

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production, regulation of interactions between tumor and stromal cells, modulation of tumor immunity, modulation of adhesion molecules, and inhibition of cyclooxygenase type 2 (7,8). The malignancies in which thalidomide has been used include multiple myeloma, glioblastoma multiforme, renal cell carcinoma, and malignant melanoma.

The use of thalidomide in dermatology is based on its immunomodulatory properties. In vitro it inhibits leukocyte chemotaxis and reduces phagocytosis by monocytes and polymorphonuclear leukocytes, without signs of cytotoxicity (9,10). The production of TNF-alpha in human monocytes is selectively inhibited by enhanced degradation of TNF-alpha messenger RNA (11). In phytohemagglutinin-activated cultures of peripheral blood mononuclear cells the production of interleukin-4 and interleukin-5 (cytokines for type 2 T helper cells) is enhanced, while interferon-gamma production is inhibited by thalidomide (12). Its antiangiogenic activity is probably the cause of its teratogenic effects (13). There is evidence that angiogenesis is increased in multiple myeloma and that thalidomide is active in refractory myeloma (14). In organ bath experiments thalidomide antagonizes the actions of histamine, 5-hydroxytryptamine, acetylcholine, and prostaglandins; neither the mechanisms nor the clinical relevance of these effects is known (15).

Stereopharmacology of thalidomide

Thalidomide is given in a racemic mixture of its two enantiomers, *R*-thalidomide and *S*-thalidomide; the former is responsible for its hypnotic effects and the latter for its immunomodulatory and teratogenic effects (16).

Formulations

The full chemical name of thalidomide is α-(*N*-phthalimido)glutarimide or *N*-(2,6-dioxopiperid-3-yl)phthalimide. It has been marketed under a wide variety of brand names, including Contergan, Distaval, Glutanon, Hippuzon, Isomin, Kedavon, Kevadon, Neurosedine, Neurosedyn, Proban M, Sedalis, Softenon, Telagan, and Telargon. It has also been used in combination with various other drugs, for example in the proprietary combinations Tensival, Valgraine (with ergotamine tartrate), and Asmaval (with ephedrine).

The development of an intravenous formulation of racthalidomide is problematic, because of its poor solubility and rapid degradation in aqueous media (17). However, a chemically stable solution of the separate enantiomers of thalidomide for intravenous infusion has been described.

Pharmacokinetics

Thalidomide is slowly absorbed after oral administration; after an oral dose of 100 mg the t_{max} is 2–4 hours and the C_{max} is around 1 μg/ml (16). At larger doses its poor solubility in intestinal fluids reduces its rate of absorption even further. Co-administration with a high-fat meal causes small (<10%) changes in the AUC and C_{max} but prolongs the t_{max} markedly, to about 6 hours (18).

Thalidomide is slowly and variably absorbed after rectal administration (19). The mean availability of several formulations relative to oral administration was less than 40%.

The two enantiomers of thalidomide, *R* and *S*, undergo fast chiral interconversion at physiological pH (16). The apparent clearance rates in adults are 10 l/hour for *R*-thalidomide and 21 l/hour for *S*-thalidomide; however, each has a half-life of about 5 hours, implying different volumes of distribution (70 liters for the *R*-enantiomer and 150 liters for the *S*-enantiomer). Because of rapid interconversion, administration of *R*-thalidomide alone as a hypnotic would not avoid the teratogenic affects of *S*-thalidomide. Thalidomide does not induce its own metabolism. Its plasma protein binding is low.

The clearance of thalidomide is not altered in hepatic disease or in renal insufficiency, but hemodialysis increases it two-fold (20). Very small amounts of hydroxylated metabolites are detected in the blood and urine.

General adverse effects

Aside from teratogenicity, the main adverse effects of thalidomide include somnolence, dizziness, fatigue, tremor, rash, constipation, and edema. Although these adverse effects are generally mild and reversible, more severe adverse effects, such as peripheral neuropathy, deep vein thrombosis, and neutropenia, have occasionally been reported.

Organs and Systems

Cardiovascular

Bradycardia, hypotension, orthostatic hypotension, and dizziness have been reported with thalidomide; these effects may have been due to its central sedative effects or to vasovagal activation (21).

Of 96 patients taking thalidomide 52 had a heart rate below 60/minute at some time during follow-up and 10 developed symptomatic bradycardia; the symptoms abated with reduction of the dose in most cases (22).

Diabetic microvascular disease has been attributed to thalidomide (23).

- A 57-year-old man with type I diabetes mellitus started taking thalidomide after failed stem cell transplantation for multiple myeloma and after 10 months developed a sensory neuropathy with loss of pain sensation and ischemic changes in the legs.

The authors suggested that the antiangiogenic properties of thalidomide were implicated in the pathogenesis of diabetic foot disease in this patient.

Thromboembolic disease

DoTS classification (BMJ 2003;327:1222–5)

Adverse effect: Deep venous thrombosis with thalidomide
Dose-relation: collateral effect
Time-course: intermediate
Susceptibility factors: genetic; diseases (multiple myeloma, lupus erythematosus); drugs (chemotherapy, especially doxorubicin; darbepoetin)

Deep venous thrombosis is a common complication of thalidomide, especially when it is used in combination

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with chemotherapy and in patients with multiple myeloma (24–26).

Arterial thrombosis has also been reported. Of 23 patients with myeloma who took thalidomide 150 mg/day for 142 patient-months there were seven cases of thrombosis, five venous and two arterial; in a historical control group of 18 similar patients who did not take thalidomide there was only one case over 289 months (26,27).

Incidence

Of 50 patients with multiple myeloma, 14 developed a deep venous thrombosis after taking thalidomide 400 mg/day, compared with two of 50 patients who did not take it (24) All the episodes occurred during the first 3 cycles of therapy. One patient taking thalidomide had a pulmonary embolus. Most of the patients continued to take thalidomide with the addition of low molecular weight heparin followed by warfarin and there was no progression of deep venous thrombosis.

Of 23 men with advanced androgen-dependent prostatic cancer who received docetaxel alone, none developed a venous thrombosis, compared with nine of 47 men who received docetaxel + thalidomide (28).

Susceptibility factors

The risk of thrombosis from thalidomide may be increased in certain conditions, such as malignancies, cicatricial pemphigoid (29), and systemic lupus erythematosus. Four episodes of thrombosis (two arterial, two venous) occurred in three patients with systemic lupus erythematosus and one with severe atopic dermatitis within 10 weeks of starting treatment with thalidomide 50–100 mg/day (30). All four had at least one risk factor for thrombosis, but none had thrombosis before or after treatment with thalidomide.

The incidence of deep venous thrombosis is increased by the co-administration of doxorubicin, as suggested by a study in 232 patients with multiple myeloma who received a combination of thalidomide and chemotherapy in two protocols that differed only by the inclusion of doxorubicin in one: DT-PACE (dexamethasone + thalidomide + cisplatin + doxorubicin + cyclophosphamide + etoposide) and DCEP-T (dexamethasone + cyclophosphamide + etoposide + cisplatin + thalidomide) (25). There was an increased risk of deep venous thrombosis in those who received DT-PACE but not in those who received DCEP-T. Multivariate analysis confirmed that those who received thalidomide + doxorubicin had an increased risk of deep venous thrombosis. In two separate trials in patients taking thalidomide for multiple myeloma, deep venous thrombosis occurred in four of 15 patients who received concomitant treatment with doxorubicin + dexamethasone compared with three of 45 who received dexamethasone only (26).

Of 535 patients who received thalidomide with or without cytostatic chemotherapy, 82 developed a deep venous thrombosis (31). Multivariate analysis showed that the combination of thalidomide with chemotherapy that contained doxorubicin was associated with the highest odds ratio (OR = 4.3). Newly diagnosed disease (OR = 2.5) and chromosome 11 abnormalities (OR = 1.8) were also independent predictors. After a median period of 2.9 years, survival was worse in those with chromosome 13 abnormalities, aged over 60 years, with a raised lactate dehydrogenase activity, and a raised serum creatinine concentration.

Three episodes of thrombosis occurred in patients who had taken thalidomide (25–100 mg/day) for up to 2 years (32). However, all had other risk factors (heterozygous protein C resistance in one and surgical intervention or trauma in the others), so a causal role of thalidomide was debatable.

In a trial of thalidomide in Behçet's disease there was superficial thrombophlebitis in 10 of 32 patients taking thalidomide 100 mg/day, two of 31 patients taking thalidomide 300 mg/day, and three of 32 patients taking placebo (33). The fact that this apparent increase in the incidence of thrombophlebitis in those taking 100 mg/day was not reproduced at the higher dosage suggests that the effect occurred by chance.

Management

Of 256 patients with myeloma randomized to thalidomide or not, 221 received no prophylactic anticoagulation and 35 received low-dose warfarin 1 mg/day (31). The incidence of deep venous thrombosis was higher in those who took thalidomide (hazard ratio 4.5). Warfarin did not reduce the risk, and prophylactic subcutaneous enoxaparin 40 mg/day was therefore introduced in 68 patients of a subsequent group of 130 patients who received thalidomide. This intervention eliminated the difference in the incidence of deep venous thrombosis between those who took thalidomide and those who did not.

Pulmonary hypertension

Pulmonary hypertension has been reported in one patient taking thalidomide (34).

- A 51-year-old man with multiple myeloma and a history of cardiovascular disease took thalidomide 100 mg/day and developed reversible pulmonary hypertension (pulmonary artery pressure 70 mmHg) with normal mitral valve and left ventricular function. After withdrawal of thalidomide for 2 months the pulmonary artery pressure fell to 47 mmHg. Rechallenge with a lower dose of thalidomide was again associated with a rise in pulmonary artery pressure.

Respiratory

In some early cases an increased incidence of asthmatic attacks was reported by asthmatic patients (35).

- A 65-year-old man with IgG multiple myeloma was given thalidomide and after 37 days developed acute cough, sweating, general malaise, and dyspnea at rest (36). There was an interstitial and alveolar pattern on the right side of a chest X-ray and arterial blood gases showed partial respiratory insufficiency (pH 7.40, $PaCO_2$ 40 mmHg, PaO_2 47 mmHg). Microbiology was negative (sputum and blood cultures and urinary antigen detection for *Streptococcus pneumoniae* and *Legionella pneumophila*). He recovered when thalidomide was withdrawn and oxygen and intravenous

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glucocorticoids were given. A chest X-ray and arterial blood gases were normal 4 days later.

Nervous system

Somnolence is very common in patients taking thalidomide, and headache, dizziness, paresthesia, and peripheral neuropathy are common. Stupor, coma, and seizures have also been reported (21). The sedative effect possibly occurs through activation of the sleep center in the brainstem. However, even when it is taken in large doses, thalidomide is not associated with lack of coordination or respiratory depression (3).

In patients with leprosy, HIV infection, and multiple myeloma, the incidences of somnolence, fatigue, and weakness were 36–43%, 48%, and 6–22% respectively (21). Administration of thalidomide at bedtime minimizes appreciation of the drowsiness that it produces, and daytime drowsiness usually abates over several weeks.

Stupor has been reported in six patients with advanced refractory malignancies, complicated by severe weakness, anemia, nausea, vomiting, and dehydration, or tumor lysis syndrome with renal insufficiency; three developed fever, neutropenia, sepsis, and/or pneumonia, but the contribution of thalidomide was uncertain (21).

Seizures, including generalized tonic-clonic seizures, have been reported in patients taking thalidomide, 18 during the first 18 months of its availability in the USA; there was a past history of seizures or pre-existing nervous system disease in 11 (21).

Polyneuropathy

DoTS classification (BMJ 2003;327:1222–5)
Adverse effect: Polyneuropathy with thalidomide
Dose-relation: Collateral reaction
Time-course: Long-term
Susceptibility factors: sex (women more susceptible); age (elderly people more susceptible)

A chronic polyneuropathy was described soon after thalidomide was introduced. It is predominantly sensory, affecting distal nerves. Anatomically the lesion is a degeneration of the axis cylinder (37).

Mechanism

In six patients with multiple myeloma who developed a thalidomide-induced sensory polyneuropathy, spinal cord MRI showed high-signal intensity in the posterior columns in only one patient, with abnormal central conduction time at somatosensory-evoked potentials (38). These results suggest that thalidomide can induce either an axonal length-dependent neuropathy or, less often, a ganglionopathy.

Clinical features

The common symptoms are tingling of the hands, gradually increasing sensory disturbances, and finally motor disturbances, usually of the hands, although only after thalidomide has been taken over a lengthy period. A positive Babinsky reflex and disturbed vibration sense have also been reported (39). Unless the drug is discontinued promptly at the start of symptoms the polyneuropathy can be irreversible (40,41).

In 35 patients with polyneuropathy, mostly of the sensory type, which occurred after about 9 months of ingestion of thalidomide 100–200 mg/day, the principal symptoms were paresthesia and distal sensory disturbances in the feet. Withdrawal of the drug led to partial improvement, but complete resolution was not observed (42–45).

In 114 patients with thalidomide polyneuropathy other features included toxic psychosis, amnesic and aphasic symptoms, cerebellar syndromes, and autonomic dysfunction. An attempt was made to relate thalidomide toxicity to daily or total dose and duration of therapy but no association was found. The severity of the polyneuropathy was related to the age of the patient (46).

In 22 patients with thalidomide polyneuropathy, who were followed for 4–6 years after withdrawal, the symptoms and signs remained unchanged in 50% and improved in 25%; the rest recovered. Improvement was usually slow, and in some patients did not begin for 3 years (47).

- A 68-year-old woman took 20 tablets of thalidomide per month for 6 months and developed a severe peripheral neuropathy, which persisted for 3 years. Electromyography showed irreversible damage to several nerve trunks (48).

The distinguishing features of thalidomide polyneuropathy and of leprous polyneuropathy have been described. In thalidomide polyneuropathy the longest nerve fibers are affected first and the condition progressively involves fibers of decreasing length. Thus, the upper border of sensory loss in the limbs is roughly the same distance from the dorsal root ganglion cells; this can be estimated using a tape measure. Loss of tendon reflexes is also characteristic. In leprous polyneuropathy, the cells first affected are those in the coolest tissues, as *Mycobacterium leprae* is temperature-sensitive. This leads to the early involvement of the lobes of the ears, the nose, and the digits. Typically, deep reflexes are preserved (49).

Restlessness, agitation, queer sensations, difficulty in memorizing (40), and vertigo and convulsions (50) have also been reported. In nearly all cases there was a concomitant polyneuropathy. Muscle weakness or cramps, mild ataxia, carpal tunnel syndrome, and signs of pyramidal tract involvement have also been described (51).

Deterioration of the sensory nerve action potentials more than 40% from baseline may predict the development of neuropathy (51).

After withdrawal of thalidomide, symptoms are usually slow to recover, if they eventually do (3). The first symptoms of peripheral neuropathy can develop even after the withdrawal of thalidomide (33).

Incidence and susceptibility factors

The incidence of peripheral neuropathy, with symmetrical painful paresthesia of the hands and feet often accompanied by sensory loss in the legs, seems to vary with the condition that is being treated, and ranges from under 1% in patients with leprosy to over 70% in patients with prurigo nodularis (41,52). The symptoms do not correlate with either the duration of treatment or the dose. Women and elderly people seem to have an increased risk of neuropathy (53).

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Incidences of 21–100% have been reported after treatment for up to 5 years (38,54–57).

Some have found no correlation between the occurrence of neuropathy and the cumulative dose (56); while others have found correlations with total dose (41,57) or daily dose. In 135 patients treated with thalidomide for various skin diseases, there were no cases in those who took daily doses of 25 mg/day or less, but the relative risk of neuropathy was 8.2 at a daily dose of 50–75 mg/day, and 20 at a daily dose of over 75 mg/day (54). It has been suggested that the risk increases at total doses over 20 g (58). Below this dose the risk of neuropathy is about 10% (57).

The incidence and susceptibility factors for thalidomide neuropathy have been studied in a prospective cohort study in 135 patients (54). Structured questionnaires were administered, standardized neurological and electrophysiological examinations were performed, and neuropathic signs and symptoms were classified by investigators who did not know the dose of thalidomide or the treatment duration. Definite thalidomide neuropathy occurred in 25% of patients, and another 30% developed atypical neuropathy, discordant clinical and electrophysiological features, or typical clinical signs without electrophysiological investigation. The only significant susceptibility factor was the daily dose: neuropathy did not develop at dosages below 25 mg/day.

Diagnosis and monitoring

Changes in nerve conductivity are frequent and predictable in thalidomide-induced neuropathy. Nerve conduction studies are required before and during therapy, irrespective of dose (55).

In 135 patients treated with thalidomide for various skin diseases who were prospectively monitored for 2 years there was clinical and electrophysiological evidence of a thalidomide-induced neuropathy in 25%; however, the neuropathy was subclinical in nearly a quarter of patients and when all potential cases were included, the rate was 56% (54). The incidence was maximal during the first year of treatment (20%).

Peripheral nerve function should be monitored by reviewing symptoms, regular neurological examination, and periodic screening of sensory nerve electrophysiology (58). If there is evidence of neuropathy, withdrawal of thalidomide should be considered; the decision should be made on an individual basis and should take into account the seriousness and severity of the underlying condition and the severity of the neuropathy.

Psychological, psychiatric

Mood changes are common with thalidomide (3). Three cases of paranoid reactions have been reported in patients with multiple myeloma taking thalidomide; however, causality was not proved (21).

- Reversible dementia occurred in a patient with multiple myeloma taking thalidomide 200 mg/day plus dexamethasone (59). Memory deficit and mania occurred about 2 months after the start of therapy and did not resolve on withdrawal of dexamethasone and administration of risperidone. The memory loss worsened and proceeded to disorientation, apraxia, and tremor 4 months after the start of therapy. The dementia resolved completely within 48 hours after withdrawal of thalidomide.

Endocrine

Hypothyroidism has occasionally been reported in patients taking thalidomide (60,61).

- A 44-year-old man with an initial TSH concentration within the reference range took thalidomide 400 mg/day for multiple myeloma and within 4 weeks developed cold intolerance, fatigue, depression, dizziness, and bradycardia, and had a markedly raised TSH (62). He was given levothyroxine and the dose of thalidomide was reduced to 200 mg/day, after which he became euthyroid.

This case prompted further investigation of thyroid function in patients with multiple myeloma. TSH concentrations were measured in 174 patients who had been randomly assigned to chemotherapy plus thalidomide 400 mg/day ($n = 92$) or chemotherapy alone ($n = 82$). After 3–4 months 18 of the patients taking thalidomide had a serum TSH concentration over 5 IU/ml, including six with a concentration over 10 IU/ml (range 12–114 IU/ml), while seven receiving chemotherapy alone had a serum TSH concentration over 5 IU/ml and none had a concentration over 10 IU/ml. In 169 patients with relapsing multiple myeloma who took thalidomide 200–800 mg/day, of those with a serum TSH concentration in the reference range to begin with, 61 had increases after 2–6 months.

Metabolism

In a placebo-controlled study in six patients with type 2 diabetes mellitus thalidomide 150 mg/day for 3 weeks reduced insulin-stimulated glucose uptake by 31% and glycogen synthesis by 48% (63). However, it had no effect on rates of glycolysis, carbohydrate oxidation, non-oxidative glycolysis, lipolysis, free fatty acid oxidation, or re-esterification. The authors concluded that thalidomide increases insulin resistance in obese patients with type 2 diabetes.

This effect can have clinical consequences. For example, in patients with prostate cancer, reducing the dose of thalidomide improved hyperglycemia, suggesting that thalidomide may have exacerbated it in the first place (64).

- A 70-year-old man with no family history of diabetes or known diabetes took thalidomide 400 mg/day for refractory multiple myeloma. He developed hyperglycemia, which had to be treated with insulin and later with glipizide GITS 5 mg/day and which responded despite continuation of thalidomide (65).

Weight gain and edema have been reported in patients taking thalidomide (3). In 13 patients with minimally symptomatic HIV disease thalidomide for 14 days caused an increase in weight of 3.6% (66).

Electrolyte balance

Severe hyperkalemia occurred in six of eight patients with multiple myeloma and moderate to severe renal insufficiency who took thalidomide 100–200 mg/day for up to

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12 days; three died and one recovered after withdrawal of thalidomide (67). Hyperkalemia occurred despite the fact that most of the patients also took dexamethasone.

Fluid balance

Thalidomide can cause painful edema of the legs, which is transitory and disappears as treatment continues (68). Peripheral edema was reported in 4.2% of patients with erythema nodosum leprosum, in patients with HIV infection (3.1% of those taking 100 mg/day and 8.3% of those taking 200 mg/day), and in up to 22% of patients with refractory multiple myeloma (21).

Hematologic

Thalidomide can cause leukopenia. In controlled trials in patients with HIV infection the incidences of neutropenia were 9%, 17%, and 25% in those who took placebo, thalidomide 100 mg/day, and thalidomide 200 mg/day respectively (21).

Neutropenia occurred in 14 of 80 patients treated with thalidomide for refractory chronic graft-versus-host disease (69). The median thalidomide dose at which neutropenia developed was 200 mg qds. Erythrocyte and platelet counts were not affected. After withdrawal of thalidomide the neutropenia resolved within a month (except in three patients, who died with refractory graft-versus-host disease). Six patients were rechallenged with thalidomide and again became neutropenic.

Of 44 patients who took thalidomide for refractory multiple myeloma, 10 developed grade 3 or 4 neutropenia, usually in the first or second week of treatment (70). There was concomitant progression of thrombocytopenia in five cases and bone marrow hypoplasia without a significant increase in myeloma cell numbers in five. Neutropenia was more common in patients with low neutrophil and platelet counts, anemia, or a high percentage of plasma cells in the bone marrow before thalidomide treatment.

Of 50 Taiwanese patients with relapsed and/or refractory multiple myeloma who took thalidomide on a dose-escalation schedule, 100–800 mg/day, 18 of 22 responders had reduced leukocyte counts before there was significant reduction in M proteins, compared with only four of the 28 non-responders (71). The median time from the start of thalidomide treatment to the minimum leukocyte count was 28 (range 7–150) days, with a mean cell count of 2.19 (range 0.96–3.35) $\times 10^9$/l. The leukopenia was generally transient, with rapid recovery despite continuation of thalidomide.

Myeloproliferative reactions have been reported in three patients with myelofibrosis taking thalidomide 200 mg/day (72). Thalidomide-associated leukemic transformation has also been reported in five patients with multiple myeloma (73).

Mouth and teeth

Xerostomia is common in patients taking thalidomide (2,3).

- An oral lichenoid eruption occurred in a 33-year-old woman after she had taken thalidomide 200 mg/day for a few days for graft-versus-host disease after bone marrow transplantation for chronic myeloid leukemia (74).

Gastrointestinal

Constipation is common in patients taking thalidomide (2,3).

Liver

Severe hepatotoxicity has been attributed to thalidomide in multiple myeloma (75) and hepatic failure can occur (21,76,77).

Four post-marketing reports of hepatic failure have been reported; one patient with multiple myeloma developed severe jaundice, hepatic failure, and coma, and died 1 month after the start of thalidomide therapy; three other patients had pre-existing liver disease, and hepatic failure and death were probably not drug-related (21).

- A 50-year-old man with history of chronic hepatitis B had transient rises in serum transaminases after two successive episodes of autologous stem cell transplantation, with spontaneous resolution; at that time PCR for hepatitis B virus was negative (76). Later he was given thalidomide and after 5 months suddenly experienced dizziness and jaundice. The concentration of hepatitis B virus DNA was 1641 pg/ml and serological tests for other viruses were negative. Despite conventional supportive care, he died of septicemic shock caused by *Klebsiella* pneumonia. Other hepatotoxic agents were excluded.
- A 58-year-old woman, with a history of chronic stable hepatitis C infection, was given thalidomide 200 mg/day for end-stage plasma cell leukemia (77). Within 1 week she developed jaundice, light-coloured stools, and marked rises in serum transaminases, which had been stable before the introduction of thalidomide. The jaundice resolved promptly on withdrawal of all drugs; other drugs besides thalidomide that might have been implicated were reintroduced without ill effects.

Skin

Rash due to thalidomide is commonly described as erythematous, macular, and pruritic; it occurs over the back, trunk, and limbs and most commonly occurs 10–14 days after the start of treatment (21). In trials of thalidomide in patients with erythema nodosum leprosum the incidence of rash was 25%, in patients with HIV infection it was 42%, and in patients with myeloma it was up to 26%.

Other skin reactions to thalidomide include pustuloderma, exfoliative reactions, and hypersensitivity reactions, including toxic epidermal necrolysis (3). The frequency of erythema nodosum was increased compared with placebo during the first 8 weeks of thalidomide therapy for Behçet's syndrome, but not thereafter (33).

Redness of the palms was observed in four of 13 patients treated with thalidomide (43). Erythroderma and peripheral eosinophilia occurred in two patients with chronic renal insufficiency who were taking thalidomide for prurigo nodularis (78).

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Three of forty patients taking thalidomide for leprosy developed dermatitis herpetiformis, which was thought to have been caused by the treatment (79).

In 87 patients with multiple myeloma in an open trial given thalidomide alone ($n = 50$) or thalidomide + dexamethasone ($n = 37$), there were minor to moderate skin eruptions in 23 patients taking thalidomide alone and in 16 of those taking thalidomide + dexamethasone (80). These included morbilliform, seborrheic, maculopapular, and non-specific dermatitis. Three patients taking thalidomide + dexamethasone had severe skin reactions (exfoliative erythroderma, erythema multiforme, and toxic epidermal necrolysis) that required hospitalization and withdrawal of thalidomide.

Worsening of psoriasis has been reported in a 46-year-old woman taking thalidomide for Behçet's disease (81).

Nails

Brittle nails occurred in three patients who took thalidomide (43), and in another case brittleness was accompanied by marked ridging of the nails (82). This last patient also had amenorrhea. She was taking 50–100 mg nightly at the time.

Sexual function

Erectile dysfunction and loss of libido have occasionally been attributed to thalidomide (83).

Reproductive system

Amenorrhea

In women taking thalidomide there have been occasional reports of amenorrhea (84–89).

Four of 13 women with cutaneous lupus erythematosus (either discoid or associated with systemic disease) treated with thalidomide 100–300 mg/day had amenorrhea during the first 4–5 months of treatment (85). They had high serum concentrations of pituitary gonadotrophins, normal prolactin concentrations, and low estradiol concentrations; antiovary antibodies were not detected. In one woman an ovarian biopsy showed severe ovarian atrophy and absence of ova or follicles. In all four women menstruation resumed 2–3 months after withdrawal of thalidomide. In two women thalidomide was reintroduced: one developed oligomenorrhea again after 5 months, with high concentrations of pituitary gonadotrophins; withdrawal of thalidomide resulted in remission. Other cases of ovarian failure in women taking thalidomide for aphthous ulcers have been described (87).

Among 21 women who took thalidomide, secondary amenorrhea occurred in four who took it for refractory cutaneous lupus erythematosus and in one who took it for aphthous ulcers (84). Menstruation resumed 2–3 months after withdrawal of thalidomide, and in one case amenorrhea recurred after reintroduction, in association with raised serum concentrations of pituitary gonadotrophins.

Four of thirteen women who took thalidomide for cutaneous lupus erythematosus developed amenorrhea (85). In one case a biopsy showed severe ovarian atrophy and absence of ova or follicles. In another case rechallenge with thalidomide 50 mg/day resulted in amenorrhea, which resolved on withdrawal.

Two young women with discoid lupus erythematosus developed amenorrhea after taking thalidomide 100–150 mg/day (86). In one patient the menstrual cycle returned to normal within 5 months after withdrawal of thalidomide; in another the dosage was reduced to 50 mg on alternate days but menstruation had not returned 6 months later.

Of seven women who took thalidomide for aphthous ulcers three developed amenorrhea (87).

- A 28-year-old woman took thalidomide 100 mg/day for Behçet's disease and after 3 months developed amenorrhea (89). She took an oral contraceptive for 8 months, but then had a deep vein thrombosis in association with a factor V Leiden mutation; the oral contraceptive was withdrawn and she was given warfarin. She remained amenorrheic. She had a raised serum concentration of follicle-stimulating hormone but all other laboratory tests were normal. Ultrasonography showed a normal uterus and an endometrial lining of 4 mm. The amenorrhea was attributed to thalidomide, which she decided to continue taking; she remained amenorrheic.

Thalidomide may destroy follicular cells by an action at follicle stimulating hormone receptors, either by directly inhibiting the binding of follicle stimulating hormone or by a post-receptor mechanism (87).

Gynecomastia

In men taking thalidomide there have been occasional reports of gynecomastia.

- A 69-year-old man developed right-sided gynecomastia after taking thalidomide 200 mg/day for 2 years (90). Mammography showed diffuse dense glandular right breast tissue in the retroareolar area with no discrete masses or microcalcification. He had taken no other drugs and had serum concentrations of prolactin, estradiol, and testosterone in the reference ranges. Thalidomide was withdrawn but the gynecomastia did not change during the following 3 months.
- A 55-year-old man developed unlilateral gynecomastia after taking thalidomide 200 mg/day for 2 weeks (91). Mammography and ultrasonography showed an enlarged but otherwise normal mammary gland. He continued to take thalidomide for 4 months and the gynecomastia persisted.

Immunologic

Leukocytoclastic vasculitis has been reported in one of 260 patients (92).

Of 54 patients randomized to either placebo ($n = 26$) or thalidomide 200 mg/day ($n = 28$) starting 80 days after allogeneic bone marrow transplantation chronic graft-versus-host disease was significantly more common in those who took thalidomide; there was also a significant overall survival advantage in those who took placebo (93). These results suggest that while thalidomide is effective in treating chronic graft-versus-host disease, its use to prevent chronic graft-versus-host disease results in a paradoxical outcome.

Tumor lysis syndrome has been attributed to thalidomide in a 59-year-old woman with myeloma (94).

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Infection risk

Disseminated infection with *Herpes simplex* virus and *Varicella zoster* virus occurred in a patient taking thalidomide for relapsed multiple myeloma (95).

Body temperature

Febrile reactions are common in patients taking thalidomide. In one study of 56 patients with HIV infection who took thalidomide for 14–21 days, 24 discontinued therapy owing to adverse reactions. Cutaneous and/or febrile reactions, which occurred in 20 patients, were the most frequent adverse effects (96).

Death

A randomized, placebo-controlled study of thalidomide in toxic epidermal necrolysis, undertaken because of the potent in vitro TNF-alpha-inhibitory properties of thalidomide, was stopped because of excess mortality in the thalidomide group (10 of 12 patients died compared with three of 10 in the placebo group) (97). There was an insignificant increase in plasma TNF-alpha in the thalidomide-treated patients on day 2.

Second-Generation Effects

Teratogenicity

Thalidomide should not be used during pregnancy because of its teratogenic effects (61,98–109). In 46 examined cases of malformations, 41 of the mothers had taken thalidomide, while in the other five cases the possibility could not be ruled out, while among 300 normal controls none of the mothers had taken thalidomide (110).

History

In the late 1950s and early 1960s thalidomide was used as a sedative in pregnant women in several countries in Europe and also distributed for trials in the USA, but was then identified as a cause of severe congenital limb malformations in many of the babies whose mothers had taken it while pregnant. The thalidomide disaster produced deep distrust in the way the public control of the effects of drugs was carried out. Suddenly, the edifices for the public control of drugs were in many countries perceived as gravely deficient and barely adapted to their purposes. People realized that drugs that were not safe could be produced by respected pharmaceutical companies, prescribed by trusted doctors, and sold by authorized pharmacies. It also became widely known that many marketed drugs were not providing their purported benefits and that claims of efficacy were barely checked by the drug regulatory authorities.

The outrage over thalidomide stimulated considerable reinforcement of the public control of drugs. In the USA, an amendment of the Food, Drug, and Cosmetic Act was approved by Congress in 1962 (111). Not only the safety but also the efficacy of drugs would henceforth be part of the criteria that the FDA used as benchmarks in decisions over whether drugs should be allowed on to the market. Since then pharmaceutical companies have had to show premarketing proof of both the safety and the efficacy of any new drug they want to introduce. Moreover, manufacturers of drugs in the USA have since 1962 had a duty to report to the FDA any information on adverse effects of their products.

At that time, existing drugs on the US market also came under scrutiny, and a review of their efficacy conducted by the US National Academy of Sciences (112) led to the voluntary withdrawal by pharmaceutical manufacturers of about two-thirds of the approximately 7100 products that the FDA had previously approved (113).

Similar legislative changes were called for in other countries, with a strong emphasis on applying the principle of premarket testing of drugs, rather than relying on random, more or less voluntary, postmarket surveillance and monitoring.

In Britain the thalidomide tragedy led to calls for a revision of the existing drug safety regulations. However, the government's position was ambiguous. It expressed a belief in the value of premarket testing of all new drugs, but did not want to move against the interests of the pharmaceutical industry. The "goose which has laid so many golden therapeutic eggs" (114) was important for the economy. Instead of creating new legislation with far-reaching requirements on the testing of new drugs, a Committee on Safety of Drugs (CSD) was appointed in 1964, expecting voluntary cooperation from the pharmaceutical industry, and its chairman asserted that it was not going to impose unnecessary restraints on the industry. Moreover, a flexible approach was to be taken regarding the efficacy of medicines. The CSD would invite reports on the toxicological testing of drugs, consider whether clinical trials should be undertaken, and assess the results in terms of safety and efficacy. It pledged that information submitted to it by the manufacturers of new drugs would be kept confidential. In its first year the CSD received 600 submissions for new drugs from pharmaceutical manufacturers. Its reviews were rapid and it rejected only a small proportion of the submissions (115).

In 1967 the Association of the British Pharmaceutical Industry (ABPI) was facing radical political proposals to abolish brand names of drugs and introduce mandatory labeling with therapeutic classifications on all medicines. To avoid legislation with mandatory rules, the ABPI revised its Code of Practice to cover the inclusion in promotional material of information on adverse effects, precautions, and contraindications (116). When the Medicines Commission was established in 1969, under the 1968 Medicines Act, to regulate the quality, safety, efficacy, and promotion of drugs, the rules of confidentiality regarding data on the effects of drugs remained in place. The Medicines Commission saw its task as integrating consideration of the pharmaceutical industry's interests with the interest of public safety (115).

In Sweden, public outrage eased the acceptance of proposals for new legislation on drug control that were pending in the Riksdag (the Swedish Parliament). A new law in 1962 (115), and subsequent regulations issued in 1963 (117), stressed the importance of controlling drug safety and efficacy. Mandatory premarket testing, with results examined by the Swedish national drug control agency, was to be the main instrument in controlling the drug market.

The thalidomide disaster led to other initiatives in many countries to create mechanisms by which doctors

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could easily alert colleagues to illnesses that they suspected were due to drug exposure. Such national schemes eventually led to the establishment in 1968 of the WHO Collaborating Center for International Drug Monitoring, which receives national data on adverse drug reactions and uses them to issue warnings about hazards to the medical community.

Features

Birth defects associated with the use of thalidomide during the first trimester include phocomelia, duodenal stenosis, esophageal fistula, neural tube defects, microphthalmia, deformities of the pinnae of the ears, and mid-line hemangiomas (118). A simple nevus extending from the forehead over the nose down to the upper lip is a characteristic feature. Before the introduction of thalidomide, phocomelia was a rare malformation (119).

A summary of the types of malformations that can occur is given in Table 1, based on 14 necropsies at the Pathological Institute, University of Hamburg (120).

Table 1 A summary of the malformations caused by thalidomide

Abnormality	Number
Cardiovascular	
Anomalies of the heart and arteries	10
Fallot's tetralogy	5
Ventricular septal defect	4
Respiratory	
Bilobed right lung	5
Ear, nose, and throat	
Anomalies of the external ear	7
Sensory systems	
Microphthalmia	2
Gastrointestinal	
Duodenal atresia	4
Agenesis of appendix and cecum	5
Malrotation	7
Imperforate anus	1
Liver	
Abnormal lobulation of the right lobe of the liver	5
Biliary tract	
Absent gallbladder	8
Atresia of the common bile duct	3
Urinary tract	
Anomalies of the urinary tract	10
Skin	
Facial nevus	1
Musculoskeletal	
Hypogenesis or agenesis of long bones	5
Phocomelia	4
Defects of metacarpal and phalanges only	3
Amelia	2
Reproductive function	
Bicornuate uterus	5 (of 8 female children)
Atresia or absence of the vagina	3

The commonest abnormalities are agenesis or malformations of the upper and lower limbs; the eyes, ears, and internal organs can also be involved (108). Of 285 cases, 251 had upper-limb defects and 146 upper-limb defects alone. In 92 cases both the upper and lower limbs were affected and in five cases only the lower limbs were involved. Syndactyly and polydactyly were common. In some cases the hands and feet were attached directly to the trunk. Occasionally all four limbs are virtually absent. In 21 cases the ears were imperfectly developed without impaired hearing. In another series, in 50% of cases only the arms were involved; in 25% both arms and legs; in 16% the external ear was absent (121). In 303 cases, 37 other defects were observed, the biggest single group being cardiac abnormalities; congenital anomalies of the gut were also noted (119,122).

Of 96 children with congenital limb deformities who were born in 1962–63, 68 had a history of thalidomide administration during the first trimester (123). The results are summarized in Table 2. In addition, electroencephalographic examination of 71 of the children showed abnormalities in 32 of 48 cases with a history of thalidomide administration, and 12 of 23 in those who had not been exposed to the drug.

In another series of 22 cases there were anomalies of the heart ($n = 5$), anomalies of the external ear ($n = 4$), duodenal atresia ($n = 6$), anomalies of the urinary tract ($n = 5$), and microphthalmia, imperforate anus, and internal hydrocephalus ($n = 1$ each) (102,104).

Three cases of congenital limb deformity after the administration of thalidomide-containing formulations during the first trimester were the first of this kind to be reported from the UAR and Kuwait (124).

Children exposed to thalidomide appear to be shorter than normal children, but growth rates are relatively normal (125).

Duodenal stenosis and left-sided hydronephrosis and hydroureter due to an abnormal opening of the left ureter into the bladder have been reported associated with phocomelia in a 5-month-old male infant. The mother had taken thalidomide in early pregnancy (126).

The differential diagnosis between the Stilling–Türk–Duanesches syndrome and thalidomide embryopathy has been detailed, following a review of the case history of a boy with multiple congenital abnormalities (127).

Table 2 Abnormalities in children with congenital limb deformities

	Thalidomide taken in first trimester	No history of thalidomide exposure
Number of cases	68	28
Limb abnormality alone	13	17
Congenital heart disease	14	1
Abnormality of urogenital system	43	3
Abnormality of alimentary system	18	5
Hydrocephalus and meningocele	4	2

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Cardiovascular

- A 29-year-old primipara was delivered of a female infant who died 30 hours later after increasingly severe attacks of cyanosis. Postmortem a cor triloculare was found. The mother had taken thalidomide 25 mg on the day of conception and afterwards on average 3 tablets a week for 5 weeks, the last tablet on the 35th day of pregnancy (128).

Ear, nose, and throat

Ear defects occurred in a child whose mother took a thalidomide-containing formulation in the early months of pregnancy. The abnormalities included absence of both auricles, hypoplasia of the middle ear, deafness, ophthalmoplegia of the right eye, and retarded mental development (129).

Nervous system

In some cases the central nervous system may have been affected (109,130,131), and cranial nerve palsies have been reported (132). In a survey of ear deformities attributed to thalidomide (133) there were also 19 cases of seventh cranial nerve lesions and 18 cases of sixth nerve lesions (134).

Sensory systems

Ocular malformations, including aplasia of the macula, choroidal colobomata, microphthalmos, and extraocular muscle paresis have been attributed to thalidomide taken in early pregnancy (135). Ocular defects have been reported in four of 21 thalidomide children examined in Canada; there was strabismus in two cases, congenital blepharoptosis in one, and ocular muscle palsies associated with other central nervous system damage in one (136).

Hematologic

Panmyelophthisis, with additional features resembling the Fanconi syndrome, has been reported after the administration of thalidomide in the first months of pregnancy (137).

Mouth, teeth

Dental examination of 40 children in Stockholm with thalidomide embryopathy showed hypodontia and disturbances of mineralization. In addition, children with very shortened forelimbs are more susceptible to tooth injury when they fall (138,139).

Cleft deformities of the face are more common in thalidomide children than in other children. Two cases of cleft lip and palate have been attributed to thalidomide taken in early pregnancy (140). There was a cleft lip and/or palate in three of 161 cases in Hamburg and in six of 9l8 cases seen in other centers. These deformities are usually associated with ear deformities, an association that was observed before the introduction of thalidomide (141).

Gastrointestinal

Agenesis of the appendix due to thalidomide can cause acute abdominal pain and tenderness (142,143). In two cases of anal stenosis the malformation was isolated and of the type due to incomplete rupture of the anal membrane; there were no malformations of the extremities (144).

Excessive sweating has been seen in thalidomide-deformed children (143,145). In some patients, small doses of ascorbic acid (50 mg daily) are helpful in this condition (143).

Musculoskeletal

Two cases of Perthe's disease have been reported in children with congenital abnormalities after thalidomide ingestion by the mother during the first trimester (146). Thalidomide can cause growth disturbance at the upper end of the femur.

Frequency

The numbers of babies with phocomelia seen in university clinics in Germany and a few clinics in England are listed in Table 3 (119).

However, it is difficult to calculate how often dysmelic malformations occur in relation to the number of pregnant women who have taken thalidomide (101,103). In Hamburg 0.17% of all neonates had such malformations. Other reports state that about 20% of expectant mothers who had taken thalidomide in the early months gave birth to an abnormal infant (104,147).

The total number of afflicted children in the Rhineland and Westphalia alone before thalidomide was withdrawn was estimated at 1500–2000 (104,119,147). In England and

Table 3 Numbers of babies with phocomelia in Germany and Britain

Place	1949–59	1959	1960	1961	Total (1959–61)
Bonn	—	2	19	50	71
Bremen	—	—	4	20	24
Frankfurt	—	1	4	11	16
Göttingen	—	3	1	10	14
Hamburg (Lens)	—	1	16	57	74
Hamburg (clinics)	—	1	30	154	185
Heidelberg	—	2	5	9	16
Kiel	—	2	4	26	32
Munich	3	2	14	44	60
Munster	4	3	27	96	126
Birmingham	—	—	4	13	17
Liverpool	—	—	8	25	33
Stirling	—	—	—	—	—

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Wales the number of cases was calculated to be at least 800 (148).

The frequency in Bonn in 1962 was 3.56 per 1000 of all newborn children (200 times the frequency in 1960–61). In Liverpool, the frequency during 1960 and 1961 was lower (0.778 per 1000), but nevertheless considerably higher than in other countries. Cases have been reported from Australia, Scotland, and Sweden (149). The USA was relatively free from this adverse effect, since thalidomide (as Kevadon) failed to pass the Food and Drug Administration because of another adverse effect, namely polyneuropathy (119).

It was estimated that 10 000 deformed children were born in West Germany before thalidomide was withdrawn; of these, 4000 are believed to have survived. In Japan there were believed to be 1000 thalidomide children; in England 400; in the Scandinavian countries 280; in Canada 200; in Belgium 60; and 25 in the Netherlands. From 1958 to 1961, 223 kg of thalidomide were marketed in Austria; during this period 19 children were born showing abnormalities compatible with the dysmelia syndrome.

Dose relation

The actual dose of thalidomide taken is not as important as the fact of its ingestion (103,104,147). Neither the duration of administration of thalidomide nor the total dose was related to the teratogenic risk (77,119). Some cases have been observed after the ingestion of only 1, 2, or 3 tablets (150).

A baby with micromelia of all four limbs was born to a woman who had taken only a single dose of thalidomide 200 mg in the first weeks of pregnancy (151). In two other cases the total dose was less than 125 mg (152).

In one case the question arose as to whether ingestion of thalidomide by the father previous to or at the time of conception could have played a role (153).

- A baby was born with bilateral absence of radii and thumbs. The mother denied having taken thalidomide or any other drug. The father had been receiving thalidomide for some six months before the conception of the child.

However, the taking of a single sleeping tablet by the mother could easily have been forgotten in this case. Nevertheless, in one study in rabbits the effect on the offspring of the administration of thalidomide to the male parent was studied (154). It was concluded that in rabbits of a cross-bred colony of high fertility there was a deleterious effect on the progeny ascribable to paternal treatment with thalidomide.

Time course

During a 1-year period, 10 babies with major limb defects were born in Stirlingshire maternity units. At least eight of the mothers had had thalidomide prescribed in the early weeks of pregnancy (59,98–101).

The critical phase for teratogenic effects of thalidomide is from the 27th to the 40th day after conception or from the 37th to the 54th day after the first day of the last menstrual period (155). In 12 of 86 cases the date of conception was fairly well known and the narrowest interval of time that spanned the taking of thalidomide was from the 27th to the 44th day after conception (150). In 205 cases, the mothers that were able to give precise accounts of the timing of administration of thalidomide had taken it from the 31st to 39th day from the first day of their last menstrual period, and in two cases they had taken only two tablets at 36–39 days (156).

In contrast, one woman gave birth to a baby with typical abnormalities after having taken thalidomide for 2 months before conception but only during the first 3 weeks of pregnancy (157).

Experimental data

Experimental work on thalidomide is complicated by the fact that different species respond in different ways to the drug (158). For example, oral thalidomide 25–200 mg/kg/day in rabbits produced a large number of fetal abnormalities, whereas very few occurred in rats. In contrast, after intravenous injection of thalidomide dissolved in propylene glycol or dimethylsulfoxide, abnormalities were produced in both species with doses as low as 2.5–10 mg/kg/day in rabbits, and 10 mg/kg/day in rats (159).

In vitro experiments

In leukocyte cultures, thalidomide is a potential antimitotic agent (160). There was a reduction in the percentage of lymphocytes transformed into the "blast" and "intermediate" types. The cells showed morphological abnormalities: pyknotic changes, chromatin clumping, and perinuclear pink halo of cytoplasm.

Mesanephric tissue from human embryos is normally capable of producing cartilage in vitro. However, when chondrogenic tissues from human embryos aged 5–8.5 weeks were exposed to thalidomide, it interfered with this process and the authors suggested that it may have a specific effect on similar tissues in vivo, accounting for the types of malformation of the fetus that have been observed (161).

Chickens

When chick eggs were injected with thalidomide, gross malformations were found only in the thalidomide-treated group after breeding; they affected 20% of the chickens and included encephalocele, anencephaly, microphthalmia, beak malformations, deformities of the jaw and legs (128).

In chick embryos, malformations were induced by introducing thalidomide into the amniotic cavity. However, other types of traumatic procedures similarly resulted in abnormalities (162).

Changes in the mitochondria of the endothelial cells of the axial limb bud artery occurred in chick embryos after treatment with thalidomide (163). However, there were no macroscopic abnormalities in chicks after thalidomide administration.

Thalidomide caused profound alterations in the morphogenesis of the encephalon in the developing chick embryo in vitro. Platyneuria occurred in 82% compared with 23% in the control group. Thalidomide has an inhibitory effect on growth, as measured by failure of closure of the neural plate, which can be reversed by the addition of ATP to the cultures (164).

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The action of thalidomide on the production of limb abnormalities in the chick are similar to those produced by nitrogen mustard (165). Only mesodermal tissues are affected; differentiation is arrested and the mesodermal cells regroup beneath the ectodermal cap. The latter no longer induces development of the proximal portion of the limb, but only of its terminal part, which explains the occurrence of phocomelia.

Dogs

Of nine dogs treated with thalidomide 100 mg/kg/day in the first 3 weeks of pregnancy, three had no litters at all. Of a total of 30 pups, 19 appeared normal, two were stillborn and four died within 48 hours (of these six, two had malformations), and five survived for some days but had an abnormal tail bone (166).

Mice

In mice treated with thalidomide there was a marked reduction in litter size (167). The young had congenital anomalies, such as cleft lip, microphthalmia and malformation of the tail, in a frequency of 5–10%.

There was a high incidence (17.5%) of abnormal embryos in mice treated during the sixth to eighth days of pregnancy, whilst thalidomide-treated animals had a higher incidence of fetal resorption (168). Others, however, failed to find any malformations or other adverse effects when using doses ranging from 2 mg/kg up to 400 mg/kg (169).

In random-bred Charles River strain albino mice, thalidomide 1000 mg/kg/day given from the first day of mating failed to produce gross malformations of the offspring (170).

Monkeys

In seven pregnancies in monkeys, one normal fetus was obtained, four had deformities, and two had teratomas (171).

Rabbits

In rabbits treated with thalidomide there was a marked reduction in litter size (167). The frequency of malformations (encephalocele, anencephaly) was 30%. Experiments with thalidomide on pregnant rabbits showed that the young invariably showed deformities similar to those seen in humans (172).

In rabbits, malformations were found with doses of 5 mg/kg/day, 150 mg/kg/day, and 500 mg/day, given between the seventh and eleventh days of pregnancy. There were abnormalities of the extremities, skull, nose, and palate, as well as malformations of the kidneys. There seemed to be an increase in frequency with higher doses (173).

When 10 pregnant New Zealand white rabbits were fed thalidomide from the eighth to the eleventh days of pregnancy in doses of 150 mg/kg, 59 fetuses were produced, of which 56 were malformed. The 11 control rabbits gave birth to 94 normal fetuses (174).

In six male rabbits of proven fertility treated with 0.75–2.5 g of thalidomide for 10–21 days before mating, three of forty experimental matings did not result in pregnancies; six litters had five or fewer offspring; there was gross abnormality of one male offspring in each of two different litters fathered by the same male; eight litters showed total loss of young and in another eight litters there was marked loss of young by day 14 of the postnatal period (154).

Rabbits have been found to be very sensitive to the action of thalidomide, but the types of abnormality produced vary with the strain of rabbit. In hybrid rabbits, in which the pregnant doe received thalidomide in a dose of 150 mg/kg on days 7–13, 13% of the young were deformed (175). Apart from the femur, only preaxial structures of both forelimbs and hind limbs were affected. Abnormalities were of both the supernumerary and reduction types. In contrast, only abnormalities of the forelimbs occurred in the New Zealand white strain of rabbits under the same dosage schedule (176). The pattern of these limb defects bore no resemblance to spontaneously occurring deformities, and it is suggested it is a characteristic pattern for the drug.

In Chinchilla and New Zealand white rabbits, thalidomide 150 mg/kg on days 6–15 of pregnancy caused increased incidences of conceptions undergoing resorption and of fetal malformations, and reductions in litter size and body weight of the 28-day fetuses; 22% of fetuses were deformed, with abnormalities affecting the locomotor, nervous, cutaneous, ocular, respiratory, and renal systems (177).

In liver-damaged rabbits, thalidomide 150 mg/kg on days 7–12 of pregnancy produced an 80% rate of fetal abnormalities. The teratogenic activity correlated with high blood and tissue concentrations of thalidomide (178). There was no correlation between the dose of thalidomide and blood thalidomide concentration in healthy rabbits (179).

Experimental work in six strains of rabbit showed that defective evolution of the spiral septum underlay many of the cardiac abnormalities. Incomplete evidence in the literature suggests the same effect may be present in human cardiac deformities (180).

A synthetic analogue of thalidomide, methyl-4-phthalimido-DL-glutamate, was teratogenic in rabbits (181).

Rats

In rats treated with thalidomide, congenital malformations were not seen, but the number of young per litter was reduced by 33% (167).

In rats thalidomide produced abnormalities of the ossification centers of the sternum and cervical vertebrae (182). These changes in ossification centers were more easily found after small doses than with large doses, since in the latter many of the young do not survive until birth.

In Wistar rats that received thalidomide 0.5–1% in the diet for periods from 9 days before mating up to the 20th day of pregnancy, 1% thalidomide produced the greatest number of fetal resorptions and extensive defects of ossification of thoracic centers, sternebrae, and pelvic girdles. Of 170 observed malformations, 150 (82%) occurred in rats treated with thalidomide before mating. The authors suggested that thalidomide may have a gonadal effect (183).

A histochemical study of the development of the sternum in thalidomide-treated rats showed increased storage

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of glycogen and reduced or absent alkaline phosphatase activity. These changes resulted in a delay in calcification of cartilage (184).

There were no macroscopic abnormalities in rats after thalidomide administration, although the number of resorption sites in the latter after 18 days gestation was increased (171).

Mechanisms

The mechanism by which thalidomide causes fetal abnormalities is not known. There is a high incidence of fetal resorption, but the cause of this is not known; it could be secondary to an abnormality of the fetus.

The more marked effect of thalidomide on some systems, for example the nervous system, the fetus, and erythrocytes, may be due to differing membrane permeabilities of different tissues to the drug (185). From a study of five head autopsies, and electroencephalographic and neurological findings in 17 individuals with the thalidomide embryopathy, it has been suggested that the action of thalidomide is not confined to mesoblastic tissue (186). This is especially true in children with an aural embryopathy. Cytogenic examination of mitotic cells in five children with ear deformities showed that the proportion of non-modal chromosomes was not greater than 10% and there were no structural changes in single chromosomes (187).

The abnormality of the ossification centers found in the rat could be connected with abnormal development of long bones. Radiographs of the limbs of 92 children with deformities due to thalidomide showed joint changes similar to those in neuropathic (Charcot's) joints in adults. The authors suggested that thalidomide causes joint changes by causing an embryonic sensory neuropathy. This hypothesis can be extended to explain other visceral and congenital malformations (188).

Thalidomide prolongs the survival time of skin homografts in the mouse, and the mechanism involved is thought to be immunosuppressive, because of the inhibition of the appearance of immunoblasts in the regional lymph nodes (189). The fetus is immunogenetically a homograft, and an early spontaneous abortion is homograft rejection. Thalidomide may therefore act by preventing spontaneous abortions, allowing damaged fetuses to reach term. If this were so, the abortion rate of those women who took thalidomide should be reduced (190). However, thalidomide has a direct toxic action on the pre-implantation blastocyst, especially the embryonic disc, and the immunological theory also cannot be reconciled with the fact that thalidomide produced teratogenic effects when given to the male rabbit before mating (191).

It has been suggested that thalidomide acts by a toxic action on the initial nerve impulses in the organogenetic phase of development due to accumulation of the drug in the nervous system of the embryo (192).

It has been suggested that in some way, thalidomide interferes with the action of certain of the B vitamins, that as a result of this antagonism fetal damage can occur, and that in the adult there may be a link between this effect and the polyneuropathy that thalidomide can cause (193). Thalidomide and its two isoglutamine derivatives caused an increase in sensitivity of intracellular hemoglobin to oxidation by nitrite ions in rats; simultaneous administration of pyridoxine and riboflavin prevented or corrected this change (185).

Prevention

Women of child-bearing age should take steps not to become pregnant while taking thalidomide, for example by using reliable contraception. If a woman taking thalidomide misses a menstrual period, thalidomide should be withdrawn for at least 9 weeks (120). Counseling about therapeutic abortion will be necessary.

Susceptibility Factors

The incidences of polyneuropathy and hypersensitivity reactions seem to be higher in HIV-infected patients (2,93).

Drug–Drug Interactions

Darbepoetin

In a study of the combination of thalidomide 100 mg/day with darbepoetin alfa 2.25 mg/kg/day in patients with myelodysplastic syndromes, there was an unexpectedly high incidence of thromboembolic events (194). Of the first seven patients enrolled, two developed deep vein thromboses and one died of a massive pulmonary embolus. The authors concluded that thalidomide may increase the thromboembolic risk associated with erythropoietic proteins in patients with myelodysplastic syndromes.

Dexamethasone

An interaction of thalidomide with dexamethasone has been postulated (195).

- A 64-year-old man with myeloma took dexamethasone and thalidomide 200 mg/day for 14 days and had no adverse effects. The dosage was increased to 400 mg/day and 10 days later a rash occurred; thalidomide was withdrawn. Within 3 days he developed toxic epidermal necrolysis.

Two other patients of eight who received thalidomide plus dexamethasone for multiple myeloma had unexpected severe skin rashes, including one who became seriously ill with erythroderma. Both recovered fully after thalidomide was withdrawn.

Docetaxel

The increased risk of venous thromboembolism in patients taking thalidomide and docetaxel is discussed in the cardiovascular section.

Sedative drugs

Thalidomide enhances the sedative actions of alcohol, barbiturates, chlorpromazine, and reserpine (118), perhaps by additive effects on their several pharmacodynamic actions (196), although other mechanisms have been described (197).

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Sex steroids

Thalidomide does not interact with ethinylestradiol or norethindrone (198).

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Theaceae

See also Herbal medicines

General Information

The genera in the family of Theaceae (Table 1) include camellia.

Table 1 The genera of Theaceae

Camellia (camellia)
Cleyera (cleyera)
Eurya (eurya)
Franklinia (Franklin tree)
Gordonia (gordonia)
Laplacea (laplacea)
Stewartia (stewartia)
Ternstroemia (ternstroemia)

Camellia sinensis

Camellia sinensis (green tea) contains caffeine and antioxidant polyphenols. It has been touted as being useful in a wide variety of conditions, including cancer prevention, mostly on relatively slim epidemiological evidence (1), cardiovascular disorders, and AIDS.

Adverse effects

The adverse effects of green tea are those of caffeine, with tremulousness and insomnia and withdrawal symptoms (headache, drowsiness, and fatigue).

Reference

1. Bushman JL. Green tea and cancer in humans: a review of the literature. Nutr Cancer 1998;31(3):151–9.

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Theophylline

General Information

Owing to their ability to relax bronchial muscles, theophylline and related compounds are used chiefly in the maintenance treatment of asthma and chronic obstructive pulmonary disease. However, the availability of other therapeutic agents (for example beta-adrenoceptor agonists or steroid inhalers) with increased efficacy, fewer adverse effects, and greater ease of management has led to reduced use of these agents. Theophylline has also been used in the treatment of apnea associated with prematurity (1), congestive heart failure (2), and life-threatening Cheyne–Stokes respiration (3). In the emergency treatment of acute exacerbations of asthma (status asthmaticus), the controversy concerning the possible benefit of including theophylline or aminophylline has not been resolved (4,5) (and see the section under Drug–Drug Interactions in this monograph). A review has suggested that a combination of high doses of inhaled $beta_2$-adrenoceptor agonists, systemic corticosteroids, and oxygen is the treatment of choice; theophylline adds little to the bronchodilator effect of inhaled beta-agonists in most patients (6).

The bronchodilator effect of theophylline is related to serum concentrations, and begins at 5–8 μg/ml, with virtually no additional effects beyond 20 μg/ml. The relation of relatively minor adverse effects to serum concentration is idiosyncratic below 15 μg/ml; above that concentration, the relation becomes more consistent and more serious adverse effects also are increasingly likely, that is toxic effects; the latter are frequent at about 20 μg/ml. Therefore, the therapeutic range is usually considered to be 10–20 μg/ml; 10–15 μg/ml is optimal. However, there is still controversy. For example, the authors of one study found that the clinical response to theophylline correlated significantly with the log plasma theophylline concentration, while other authors have claimed that clinical aspects are more relevant for dose correction during therapy than the determination of serum concentrations (SEDA-12, 3). Various factors influence the metabolism of these compounds, including pronounced interindividual differences in metabolism, concurrent illnesses, and factors such as smoking, age, and weight. The use of these drugs requires extremely close attention, and many authors have stressed the importance of monitoring serum concentrations, the patient's clinical condition, and adverse effects.

An example of some of the complexity encountered is the initiation of chronic bronchodilator therapy with oral theophylline. Approximate initial daily doses are as follows: 6 mg/kg for adult nonsmokers; 10 mg/kg for adult smokers; 12 mg/kg for children under 12 years. Increases in dosage, if any, are made in small increments after about 3 days, depending on the clinical response and serum theophylline concentration. Proper dosing is complicated by two factors: variable systemic availability among the different products used and elimination kinetics in which saturable kinetics are probable but poorly defined.

Theophylline has been derivatized to produce aminophylline, choline theophyllinate, and other compounds. Several modified-release formulations are available. Maximum serum concentrations occur at 1–3 hours with most of the standard formulations and at up to 6 hours with modified-release formulations. In aminophylline, the most widely used theophylline derivative, theophylline is combined with ethylenediamine to enhance its solubility. Since ethylenediamine is therapeutically inert, all the effects of aminophylline, except for allergic reactions, are considered to stem from the theophylline component.

Among the methylated xanthines, theophylline is the least active cerebral stimulant, its most pronounced features being stimulation of the medullary respiratory center, circulatory system, and smooth muscles of the bronchi. Therapeutic use and untoward responses will derive from these basic pharmacological features, which, apart from the desired actions, can produce untoward effects. Serious adverse reactions are rare with appropriate blood concentrations; however, it is difficult to control theophylline concentrations, especially when it is taken orally, absorption being erratic. When it is given intravenously, slow administration is advised. With both oral and parenteral administration, monitoring of serum theophylline concentrations with individual adjustment of dosage is necessary.

The adverse effects of other theophylline derivatives have been reviewed (SEDA-17, 1). Whether or not newer drugs have similar efficacy and/or better tolerability than the classic theophylline derivatives has not been carefully evaluated.

General adverse effects

Nausea, vomiting, headache, dizziness, tachycardia, dysrhythmias, vascular collapse, tremor, agitation, and convulsions have been described. Although 1% of children and 4% of adults cannot tolerate even low serum concentrations, the incidence of adverse effects during therapeutic use is generally related to the logarithm of the serum concentration. However, the relation between the severity of the symptoms of theophylline poisoning and serum–drug concentration is less clear and may well depend on the chronicity of the overdose (SEDA-9, 78) (see Drug overdose in this monograph).

True allergy to theophylline is rare. Hypersensitivity to aminophylline, when it occurs, is most likely due to the ethylenediamine component. Two immunogenic types of reactions have been described, one of urticaria and general pruritus and the other involving thrombocytopenia and a hemorrhagic diathesis (SED-8, 1). Also reported have been contact dermatitis, exfoliative erythroderma accompanied by bronchospasm and pruritus, generalized dermal reactions (SED-10, 4), severe generalized symptoms with a high fever (7), and aggressive behavior in a child (8).

The observation of excess mortality from cancer of the pancreas among US male veterans admitted to hospital for bronchial asthma and discharged on various bronchodilators has raised the question of a possible connection to the theophylline (see the monograph on Caffeine). Although not fully resolved, chronic use of theophylline does not appear to be associated with an increased risk of esophageal or gastric carcinoma (9).

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Organs and Systems

Cardiovascular

The relation between toxicity and excessive serum theophylline concentrations has been confirmed, tachycardia being a frequent indication of toxic symptoms (SED-9, 3). It appears that the cardiac and metabolic effects of theophylline are at least partly related to catecholamine release (SEDA-13, 1). The importance of appropriate dosage has been stressed in several papers, all indicating the particular risk of ventricular fibrillation in subjects with respiratory distress (10). The authors have pointed to the potentially lethal effect of serum theophylline concentrations in excess of 20 μg/ml. In another study, half the patients with serum concentrations greater than 35 μg/ml had life-threatening dysrhythmias (SEDA-7, 7). In one study of the effect of oral aminophylline on cardiac dysrhythmias in 15 patients with chronic obstructive pulmonary disease, aminophylline had both dysrhythmogenic and chronotropic effects but did not change the grade of dysrhythmia (SEDA-7, 7). In another study of 16 patients there was a relation between the use of theophylline and multifocal atrial tachycardia (11). Whereas raised blood theophylline concentrations are likely in themselves to produce cardiovascular complications, patients with pre-existing cardiac disease are at greater risk.

Respiratory

Aminophylline sometimes aggravates bronchial asthma; sensitization to the ethylenediamine component is considered to be responsible (SEDA-6, 5).

Nervous system

In addition to the more common adverse effects of tremor, dizziness, anxiety, agitation, insomnia, visual disturbances, and seizures, depression, confusion (SEDA-6, 1), acute dyskinesias (SEDA-17, 1), and toxic psychosis (SED-10, 5) have also been reported.

Seizures with focal onset have been described during treatment of status asthmaticus in adult patients with no previous history of epilepsy (12). Although, serum theophylline concentrations are an unreliable predictor of seizures, seizures occur most commonly at serum concentrations over 40–50 μg/ml (13). Older patients are more likely to have seizures than younger ones at similar theophylline concentrations (14). Patients with pre-existing central nervous system abnormalities (15) or severe pulmonary disease may also be at increased risk (SEDA-17, 1). Theophylline-induced seizures have been reported in two neonates (SEDA-6, 2); the serum theophylline concentration during seizures was 51 μg/ml.

- A girl aged 3.5 months receiving theophylline had a seizure; in the next few months, she had a mixed seizure disorder and subsequently symptoms of moderately severe right brain damage (16).

Because toxic symptoms before seizures can be absent or undetected, such events underline the need for blood concentration monitoring during therapy.

Theophylline disturbs sleep more profoundly in caffeine-sensitive subjects (SEDA-15, 1). Exacerbation of spasticity has occurred when theophylline was used after a stroke (17).

Psychological, psychiatric

The concern that cognitive function may be impaired in children taking theophylline is still not resolved (SEDA-14, 1) (SEDA-15, 1); a review has suggested that detrimental effects of theophylline on various measures of cognitive function may be measure-specific (18).

Endocrine

The dangers of theophylline toxicity in hypothyroidism have been described (19).

Metabolism

The metabolic effects of intravenous infusions of aminophylline have been studied in a series of healthy young subjects with regard to serum glucose, insulin, glucagon, cortisol, and free fatty acid concentrations. Infusion of aminophylline, which produced theophylline concentrations in the usual target range (10–20 μg/ml) caused only small increases in plasma glucose concentrations but rapid, pronounced, and prolonged rises in free fatty acids. Increases in free fatty acid concentrations paralleled the rise in theophylline concentrations (SEDA-6, 6).

Gastrointestinal

The commonest gastrointestinal adverse effects of aminophylline in adults are nausea and gastrointestinal irritation, which are primarily a function of serum theophylline concentrations, although some additional local irritation may be produced by oral administration. Nausea was reported in six of 20 asthmatic patients with serum theophylline concentrations of 20 μg/ml (SED-9, 4). In a survey of 2766 theophylline-treated patients with cardiac or pulmonary diseases, 11% had adverse effects, most of which were gastrointestinal disturbances (7.8%) (SED-9, 4).

In two elderly patients hematemesis was thought to have been due to both a local irritant action of aminophylline and a susceptibility to systemic toxic effects at lower serum theophylline concentrations (SEDA-5, 5).

Esophageal ulceration can result from tablets that were taken with insufficient fluid and/or while lying down (20,21).

Non-allergic proctitis associated with an aminophylline suppository has been reported in a child (SEDA-17, 1).

Liver

Since about 90% of theophylline is eliminated by hepatic metabolism, liver function is related to toxic effects on other systems (see Susceptibility Factors in this monograph). Hepatitis has been reported in two patients (SEDA-15, 1).

Pancreas

An excess in mortality from pancreatic cancer has been noted among US male veterans admitted to hospital for bronchial asthma and discharged on various bronchodilators, suggesting a possible connection with theophylline

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(SEDA-7, 8). A relation between coffee consumption and pancreatic cancer was reported in a case-control study (SEDA-7, 8), with an unexpected increase in pancreatic cancer associated with an increase in coffee drinking (relative risk in men, 2.6). The same workers studied changes in mortality from pancreatic cancer in different countries in relation to changes in coffee consumption and found a significant relation between increases in coffee consumption and increases in mortality from pancreatic cancer. However, the data on which the findings were based were crude.

Urinary tract

Methylxanthines, especially theophylline, in healthy subjects inhibit solute reabsorption in both the proximal nephron and the diluting segment without changing either glomerular filtration rate or renal blood flow appreciably. Accordingly, an apparent increase in creatinine clearance in a heavy tea drinker has been attributed to a discrepancy between GFR and creatinine clearance (22).

Skin

Three cases of skin eruptions have been reported in patients taking aminophylline who had probably been sensitized by the use of a multiantibiotic cream formulation also containing ethylenediamine (SEDA-12, 4). A case of Stevens–Johnson syndrome after modified-release theophylline has been reported (23).

Immunologic

Salivary IgA was significantly reduced in asthmatic children treated with theophylline compared with healthy controls or unmedicated patients with asthma (24). This finding is in harmony with earlier statements that theophylline reduces the bactericidal capacity of leukocytes and affects suppressor T cells (SEDA-11, 6). Theophylline also interferes with basophil and eosinophil responses; these immunomodulatory effects might participate in its therapeutic efficacy (25,26).

Long-Term Effects

Mutagenicity

Genetic effects of theophylline are not well known. Theophylline suppresses phosphodiesterase and cyclic AMP activity, and increases calcium transport in animals (SEDA-4, 25), suggesting a potential for teratogenicity. An increased rate of sister chromatid exchange rate, an indication of mutagenicity, has also been reported (SEDA-17, 1).

Second-Generation Effects

Pregnancy

Theophylline crosses the placenta, resulting in potentially dangerous serum theophylline concentrations in the neonate (SEDA-5, 3). This is of practical importance, since 1.3% of pregnant women have asthma. Fetal tachycardia has been observed when maternal blood concentration exceeds 20 μg/ml (27). In one neonate the serum theophylline concentration of 14 μg/ml was 3 μg/ml higher than the cord or maternal serum concentrations. The authors concluded that neonates of mothers receiving theophylline products should be monitored for pharmacological effects of theophylline. In another study, women with asthma who used theophylline had a longer average duration of labor than did untreated women, since theophylline inhibited uterine contractions (SEDA-5, 3).

Fetotoxicity

Symptoms of irritability, vomiting, and jitteriness have been described in an infant, possibly related to ingestion of aminophylline during pregnancy by an asthmatic mother (28).

In pregnant women with bronchial asthma, bronchospasm can be exacerbated during labor, necessitating infusion of aminophylline. The placental transport of aminophylline and its effects on the fetus and the neonate are poorly understood. A recent report has highlighted the potential problems (29).

- A 26-year-old primigravida with bronchial asthma developed an acute exacerbation at 40 weeks gestation. She did not respond to salbutamol and was given hydrocortisone and aminophylline 250 mg intravenously, without improvement. She received two more doses of intravenous aminophylline, the last being 2 hours before delivery. At cesarean section she delivered a full-term female neonate weighing 3150 g with Apgar scores of 3 and 5 at 1 and 5 minutes respectively. Within 3 minutes of birth the neonate developed multifocal clonic convulsions, which failed to respond to intravenous glucose, calcium, phenobarbital, and phenytoin. She had a tachycardia, a normal blood pressure, and poor respiratory drive, and was comatose. The serum theophylline concentration was 8.6 μg/ml (47 μmol/l) at 1 hour of life. Despite ventilatory support and anticonvulsant therapy, she continued to have intermittent seizures and died 48 hours after birth. Postmortem showed normal brain structure and no evidence of hemorrhage or asphyxial brain injury.

The toxic concentrations for theophylline in neonates have not been well defined, and can vary from infant to infant. Other pharmacokinetic factors, such as low plasma protein binding and limited capacity for excretion could make neonates prone to aminophylline toxicity. Fetuses and neonates can develop theophylline toxicity even with plasma concentrations in the target range, since they can metabolize theophylline to caffeine, adding to the methylxanthine load.

Lactation

The kinetics of theophylline transfer into breast-milk have been studied in three lactating women given theophylline intravenously (SEDA-6, 2). The data suggested that theophylline accumulation to toxic concentrations should not occur in most breast-fed infants, but that serum theophylline concentrations in the mother should be kept as low as possible and transfer will be minimal if infants are nursed just before the mother takes the theophylline.

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Susceptibility Factors

Age

Prematurity

Serious difficulties arise in giving theophylline to premature neonates. These are explained by peculiarities in biotransformation in prematurity. Transformation of theophylline to caffeine in premature neonates is explained by the lack of enzymes for desmethylation and *C*-hydroxylation and by predominant *N*-methylase activity. High serum caffeine concentrations have been found in two studies of premature newborns with respiratory disturbances who had received theophylline (SEDA-4, 3); caffeine and theophylline synergism was incriminated in the development of toxic reactions in these children. In another study, there was clinically significant hyperglycemia in 13% of preterm infants who received theophylline (30). Blood glucose concentrations should be monitored in preterm infants who receive theophylline. There is some evidence (SED-10, 5) that administration of 4.5 mg/kg of theophylline followed by a maintenance dose (1.2–1.52 mg/kg every 8–12 hours) is most likely to correct respiratory disturbances in premature neonates, while avoiding adverse effects. Because of simpler dosing regimens, some pediatricians prefer caffeine as the drug of choice in premature neonates (27,31).

Developmental differences in the balance between metabolic and renal elimination pathways determine the unique toxicokinetics of theophylline in neonates. Three premature neonates received inadvertent intravenous doses of theophylline for apnea of prematurity (32). All had sinus tachycardia and agitation. Maximum serum theophylline concentrations were 55–123 μg/ml; theophylline-derived caffeine concentrations plateaued at 8.4–13 μg/ml and did not fall during the sampling period. The half-life of theophylline was 28–37 hours and the clearance 0.02–0.05 l/kg/hour. This study shows that, in contrast to older children, theophylline elimination remains a first-order process during acute intoxication in premature infants, and that large overdoses of theophylline in neonates, while inducing symptoms and signs of overdose, do not uniformly result in life-threatening sequelae and do not necessarily require invasive treatment. Although the literature is rather scanty, the pharmacokinetics of theophylline in premature neonates do not seem to be different from those in full-term neonates. Furthermore, toxic concentrations in neonates have not been defined. It has been speculated that various factors in neonates, such as low plasma protein binding, metabolic interconversion to caffeine, and limited excretory capacity, make them susceptible to toxicity even at plasma concentrations within the usual adult therapeutic range (SEDA-23, 1)(SEDA-25, 1).

Term infants

Caution has been urged in using theophylline for wheezing in full-term infants under 3 months of age (SEDA-4, 3).

Cerebral blood flow velocity in infants treated with an intravenous bolus dose of aminophylline was reduced, perhaps because of a reduction in PCO_2, due to aminophylline (33).

Children

Convulsions have been attributed to theophylline given for bronchial asthma in the usual recommended dosage, with serum concentrations in the target range of 10–20 μg/ml (SEDA-5, 4). Young children may be more prone to excitement and dehydration due to diuresis and vomiting. Two afebrile children reported visual hallucinations during theophylline toxicity (SEDA-13, 2). Despite the recommendation for higher initial doses in young children, dosage management is more difficult, owing to the greater likelihood of toxicity, which is probably a reflection of more erratic pharmacodynamics.

Based on a retrospective investigation of theophylline-induced convulsions in epileptic children, it was concluded that infants under 1 year of age with epilepsy have a higher risk of theophylline-induced convulsions; theophylline should be avoided in this group (34).

Elderly patients

It is not entirely clear whether the risk of toxicity in the elderly is a function of an age-related reduction in the rate of metabolism, a tendency for systemic toxic effects to develop at relatively lower serum concentrations, or the greater likelihood of conditions that affect the pharmacokinetics of theophylline, for example cardiac failure, liver disease, or chronic obstructive pulmonary disease. In a review of 72 consecutive patients referred to a regional poisons center with chronic theophylline intoxication, stratification of data by chronological age showed a stepwise increase in the frequency of life-threatening events with advancing years; the authors suggested that elderly patients have a much greater risk of such events than younger patients (35).

In an investigation of 510 episodes of raised theophylline concentrations in 214 hospitalized patients, the authors concluded that life-threatening events can occur in critically ill patients or patients with past seizures or dysrhythmias with mildly raised theophylline concentrations (21–40 μg/ml) (36).

One study showed that in order to maintain plasma concentrations in the target range in elderly people, the maintenance dosage should be reduced by about 25% (SEDA-5, 1). Other reports have implicated chronic obstructive pulmonary disease and cardiac failure in elderly patients whose reduced theophylline clearances led to toxic reactions or potentially toxic plasma concentrations (SEDA-7, 6) (SEDA-8, 1). It was suggested that aminophylline dosages be reduced by 50% when there are clinical signs of cardiac failure, in order to avoid excessive drug accumulation.

Hepatic disease

In cirrhosis of the liver, drug clearance falls, the half-life of theophylline increases about threefold, and the incidence of adverse effects increases (SED-10, 6).

Drug Administration

Drug overdose

The effect of theophylline is cumulative, and there is a danger of overdosage if it is given repeatedly. However,

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intoxication has been described in young children after a single suppository (SED-9, 4).

The symptoms of overdosage are nausea, vomiting, headache, dizziness, tachycardia, dysrhythmias, vascular collapse, tremor, agitation, and convulsions. The highly variable interindividual differences in metabolism and disease-related alterations in metabolism of the various formulations can result in iatrogenically induced overdosage. The tendency of patients to increase the dose as their condition deteriorates is a second major source of overdosing.

The amount of drug administered, whether putative or known, is less likely to correlate with untoward reactions than the serum concentration is. Likewise, the serum concentration correlates poorly with relatively minor adverse effects. More reliable is the escalating correlation of serious toxic effects with serum concentrations rising above 15 μg/ml.

The relation between the severity of clinical manifestations of theophylline poisoning and serum drug concentrations is unclear. However, a start has been made in clarifying this, with the finding that patients with theophylline overdose caused by chronic repeated overmedication often develop seizures and dysrhythmias with serum concentrations of 40–70 μg/ml, while those with acute single ingestion are highly unlikely to suffer serious complications unless serum concentrations exceed 100 μg/ml. According to this study, patients who took a single overdose were easily recognized by the presence of hypotension, hypokalemia, and a low serum bicarbonate, features not present in patients with chronic overdose (SEDA-11, 5) (37). These findings could lead to better indicators for more aggressive treatment before the advent of major complications.

In healthy volunteers, theophylline reduced circulating pyridoxal phosphate (vitamin B6) concentrations, presumably by noncompetitive inhibition of pyridoxal kinase. Theophylline concentrations of approximately 10 μg/ml produced only partial inhibition, plasma pyridoxal kinase and pyridoxal concentrations being unaffected. The authors speculated that with theophylline overdose and greater inhibition, vitamin B6 deficiency might contribute to seizures (SEDA-14, 2).

Rhabdomyolysis is a rare complication of theophylline overdose (38).

- A 73-year-old man took an unknown number of theophylline modified-release tablets and furosemide 40 mg tablets. He developed a tachydysrhythmia, vomiting, and restlessness. His maximum theophylline concentration was 67 μg/ml and he had hypokalemia (2.8 mmol/l) and hyponatremia (123 mmol/l). The maximum creatine kinase activity was (32 mol/l [sic]) and the serum myoglobin concentration was 3789 μg/l. He was treated with oral activated charcoal, continuous venovenous hemodialysis, intravenous potassium and sodium chloride, forced diuresis, and continuous intravenous metoprolol, and survived without sequelae.

Management

The use of hemodialysis or hemoperfusion in the management of theophylline toxicity was initially controversial (SEDA-8, 11) (SEDA-9, 10) (SEDA-11, 5). In one study (39) hemoperfusion provided a higher theophylline clearance rate than hemodialysis, but the latter appears to have comparable efficacy in reducing the morbidity of severe theophylline intoxication and is associated with a lower rate of procedural complications. The recommendation that these treatments be considered for patients who fail to respond to supportive care is complicated by findings that, once major complications have occurred, the benefits from these risky procedures are greatly reduced.

However, charcoal hemoperfusion is now regarded as the recommended method for rapid reduction of serum theophylline concentrations, if necessary, although access to this technique is limited in most hospitals. Venovenous hemofiltration, which is readily available in many hospitals, appears to be a realistic and practical alternative to charcoal hemoperfusion, in combination with oral activated charcoal, particularly in the hemodynamically unstable patient with severe theophylline toxicity without anticoagulation (40,41). A higher extraction ratio in neonates than in adults has also been described (41).

Drug–Drug Interactions

General

Both positive and negative drug interactions have been reported with theophylline. The usefulness of combination products has also been discussed (SEDA-6, 2) (SEDA-11, 7). The use of combinations complicates the evaluation of adverse effects, particularly those of theophylline and ephedrine. The likelihood of adverse effects of each component and synergistic effects between components must be evaluated in relation to the patient's clinical condition. A positive feature is the likelihood of greater compliance with an effective combination product.

Pharmacokinetic interactions

In one study, antacids increase the rate of theophylline absorption without a change in total systemic availability (42), although in an earlier study there was no interaction (43).

The concomitant use of drugs that reduce theophylline clearance can produce toxic serum concentrations with therapeutic doses of theophylline. Most of these drugs are believed to have this effect by inhibiting the hepatic microsomal P450-metabolizing enzymes that are responsible for the biotransformation of theophylline. Such drugs include the xanthine oxidase inhibitor allopurinol, some histamine H_2 receptor antagonists (cimetidine in particular), some antidepressants (fluvoxamine), and oral contraceptives. Also included are some antimicrobial drugs, for example tetracycline, the macrolides (erythromycin and troleandomycin), fluoroquinolones (ciprofloxacin, norfloxacin), possibly the cephalosporins, isoniazid, antihelminthic drugs (thiabendazole and possibly pyrantel), and antiviral drugs (influenza vaccine and vidarabine).

Other drugs that reduce theophylline clearance, but by unknown mechanisms, are cardiac medications: the beta-blocker propranolol, the calcium channel blockers

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nifedipine and verapamil, and mexiletine. Considering that increased theophylline concentrations can lead to an increased propensity for central and cardiac stimulation, it is prudent to avoid using a combination of theophylline and cardiac medications, especially antidysrhythmic drugs.

Lipophilic beta-adrenoceptor antagonists are metabolized to varying degrees by oxidation by liver microsomal cytochrome P450 (for example propranolol by CYP1A2 and CYP2D6 and metoprolol by CYP2D6). These agents can therefore reduce the clearance and increase the steady-state plasma concentrations of other drugs that undergo similar metabolism, potentiating their effects. Drugs that interact in this way include theophylline (44).

Conversely, drugs that induce P450 enzymes increase theophylline clearance and lower blood concentrations. These include the barbiturates, phenytoin, carbamazepine, and rifampicin. Increased clearance also occurs with a high-protein diet, marijuana, and tobacco. With phenytoin the interaction is two-sided: the plasma concentrations of both drugs fall. This can result in poor seizure and respiratory control and in drug toxicity.

Recommendations have been presented for correction of theophylline doses during concomitant medication with some of the above drugs (SEDA-8, 130) (45). Concomitant therapy with allopurinol, cimetidine, erythromycin, furosemide, isoprenaline, or propranolol requires a reduction in dose of about 20–30%; for oleandomycin the reduction should be about 50%.

Pharmacodynamic interactions

A debate was triggered by the suggestion some years ago of increased mortality because of greater use of theophylline, and additive toxicity between oral theophylline and inhaled beta-adrenoceptor agonists (SEDA-7, 1). Some authors concluded that a combination of theophylline and beta-adrenoceptor agonists in low doses will give equal and possibly superior results over full doses of either agent and may produce fewer adverse effects (SEDA-7, 2) (SEDA-8, 13). No one has yet documented any serious synergistic toxicity from a combination of theophylline and a beta-adrenoceptor agonist in appropriate doses (SEDA-15, 1), and it seems clear that the patient with severe asthma who is undertreated is much more at risk of dying than one who receives concomitant theophylline and adrenergic drug treatment in appropriate doses and sequence (SEDA-9, 10). At any rate, the most appropriate maintenance therapy continues to be debated. In recent years, it has been customary to use a combination of a beta-adrenoceptor agonist and a nontheophylline formulation, such as a steroid inhaler. However, it should be noted that the finding that theophylline has significant effects on basophils and eosinophils renewed an interest in theophylline.

Adverse reactions to theophylline are more common in patients who are concurrently taking a tetracycline (SED-9, 4).

Adenosine

Theophylline increases the dose of adenosine needed for conversion of supraventricular tachycardia, through competitive inhibition at purine receptors (46).

Caffeine

Caffeine can accumulate to toxic concentrations during treatment with theophylline (47). Likewise, concomitant administration of caffeine and theophylline can significantly increase plasma theophylline concentrations and reduce the clearance rates of theophylline and its metabolites (48).

Calcium channel blockers

Theophylline toxicity has been reported in several patients, apparently stabilized on theophylline, after the introduction of verapamil (49) or nifedipine (50).

Cephalosporins

The interaction between certain cephalosporins (including moxalactam) and the alcohol in theophylline elixir can cause a disulfiram-like reaction (51).

Citalopram

Both theophylline and citalopram are metabolized by CYP1A2. In an open, multiple-dose study in 13 healthy nonsmoking volunteers, steady-state citalopram therapy had no significant effect on theophylline metabolism. The authors suggested that dosage adjustment of theophylline may not be necessary in patients taking concurrent citalopram (52). The most frequent treatment-related adverse effects were fatigue and nausea.

Corticosteroids

In a single-dose study of the interaction of theophylline with prednisolone, the plasma concentrations of both drugs were slightly lower when they were given in combination than when given alone (53).

The kinetic behavior of theophylline given concomitantly with methylprednisolone and auranofin to six women suggested a possible interaction of theophylline with auranofin, although a role of the corticosteroid could not be ruled out. The observed concentrations of theophylline were lower than expected, suggesting the need to measure serum theophylline concentrations in patients who also take steroids and gold salts (54).

Digoxin

Despite the ability of theophylline to reduce blood concentrations of digitalis in digitalis intoxication (55), therapeutic doses of theophylline can cause dysrhythmias in the presence of concentrations of digoxin in the high part of the usual target range (56).

Fluvoxamine

Fluvoxamine is a potent inhibitor of cytochrome CYP1A2, which may lead to interactions with several tricyclic antidepressants and theophylline (57).

Furosemide

Intravenous furosemide reportedly increased steady-state theophylline concentrations by about 20% (SED-11, 428). However, this result has not been confirmed (58).

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GABA receptor antagonists

Carbapenems (imipenem more than meropenem) are believed to increase central nervous system excitation by inhibition of GABA binding to receptors. Combinations with other GABA-inhibiting drugs, such as theophylline or quinolones, have been reported to provoke seizures (59,60).

Gold salts

The kinetic behavior of theophylline given concomitantly with methylprednisolone and auranofin to six women suggested a possible interaction of theophylline with auranofin, although a role of the corticosteroid could not be ruled out. The observed concentrations of theophylline were lower than expected, suggesting the need to measure serum theophylline concentrations in patients who also take steroids and gold salts (54).

Lithium

Theophylline increased the renal clearance of lithium, with resultant lowering of the serum lithium concentration (61).

Macrolides

The most frequently observed effects of macrolides on theophylline pharmacokinetics are increases in half-life and serum theophylline concentrations and reduced clearance (62). The interaction with theophylline is mainly seen with higher doses of macrolides and can result in theophylline toxicity (63).

Ciprofloxacin

Serious theophylline toxicity has been attributed to ciprofloxacin (64).

- A 79-year-old woman presented with a generalized seizure. She had long-standing asthma, and her admission medication included steroid and salbutamol inhalers, oral prednisolone, and oral modified-release aminophylline 450 mg bd. Plasma theophylline concentrations over the previous 3 years had been 8–12 μg/ml (44–66 μmol/l) without apparent toxicity. Seven days before presentation she had developed a fever and cough productive of green sputum, and had been given ciprofloxacin 500 mg bd. Despite adequate gas exchange, she developed repeated episodes of self-terminating supraventricular tachycardia, associated with hypokalemia (serum potassium 3.2 mmol/l), acidosis (pH 7.05), hypotension, and difficulty in breathing. The theophylline concentration was 33 μg/ml (183 μmol/l). Renal function was normal, and no other causes of fits or dysrhythmias were apparent. She was unable to tolerate oral activated charcoal and hemodialysis was started. After 2 hours of dialysis, the plasma theophylline had fallen to 15 μg/ml (177 μmol/l), she was in sinus rhythm, and her serum potassium was 3.8 mmol/l. She made an uneventful recovery.

Erythromycin

Erythromycin can increase the serum concentrations of theophylline by 20–25%. However, patients with an average serum concentration of theophylline under 15 μg/ml will probably have only a small increase in their serum theophylline concentration during erythromycin therapy, whereas patients with steady-state concentrations above 15 μg/ml deserve careful monitoring and close observation for symptoms of theophylline toxicity during treatment with erythromycin (65,66).

Fatal aminophylline toxicity has been described, precipitated by the concomitant administration of erythromycin (64).

- A 55-year-old man with a long history of bronchiectasis and severe obstructive pulmonary disease presented with a chest infection, having been taking oral modified-release aminophylline 450 mg bd for 4 years, with trough concentrations always in the range 6–12 μg/ml (33–66 μmol/l) and no apparent toxicity. Two days before admission, his general practitioner had prescribed trimethoprim 200 mg bd for a suspected urinary tract infection. On the day of admission, he was given cefotaxime 1 g intravenously bd and erythromycin 500 mg orally qds. Other medications included captopril 25 mg tds, furosemide 80 mg bd, ranitidine 150 mg bd, protriptyline 10 mg tds, and inhaled budesonide. He was anxious and had a fine tremor, but his gas exchange was satisfactory. He had chronic renal impairment of uncertain cause and hyperkalemia (5.5 mmol/l). The possibility of aminophylline toxicity was raised, but despite this, he received three doses of erythromycin. The plasma theophylline was 66 μg/ml (363 μmol/l). He had an episode of ventricular tachycardia and fibrillation, was successfully resuscitated, but had a second episode of ventricular tachycardia 30 minutes later, from which he could not be resuscitated. The plasma theophylline concentration at the time of his second cardiac arrest was 58 μg/ml (319 μmol/l).

These cases of interactions of aminophylline with macrolide antibiotics illustrate that serious, even fatal, adverse effects can occur when possible interactions are not considered. In both cases, experienced physicians prescribed appropriate antimicrobial drugs, but omitted to consider the possibility of interactions with aminophylline, and failed to reduce the dose of aminophylline or to measure theophylline concentrations. In the first case the development of tachycardia, hypokalemia, acidosis, vomiting, and convulsions can be explained on the basis of theophylline toxicity caused by ciprofloxacin, while in the second the anxiety, tremor, and cardiac arrests could all have resulted from an interaction of aminophylline and erythromycin. These cases add to an extensive literature that emphasizes the potential for interaction between aminophylline and drugs metabolized by CYP1A2.

Prulifloxacin

Prulifloxacin reduced the elimination of theophylline in healthy volunteers (67) presumably by inhibiting cytochrome CYP1A2.

Mexiletine

Mexiletine reduces the clearance of theophylline, and this combination has been reported to cause ventricular

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tachycardia (68). A similar interaction with caffeine has been reported (69).

Olanzapine

In healthy subjects, olanzapine did not affect theophylline pharmacokinetics (70). These results confirm the earlier reported *in vitro* findings that olanzapine is not a potent inhibitor of CYP1A2 (71).

Pancuronium

Antagonism to pancuronium has been found with theophylline concentrations in excess of the recommended target range (SEDA-5, 4).

Aminophylline appears to facilitate neuromuscular transmission, perhaps by increasing neurotransmitter release through raising cyclic AMP concentrations at the neuromuscular junction by phosphodiesterase inhibition (72). This would account for the antagonism of pancuronium-induced blockade that has been reported to occur in the presence of very high serum concentrations of theophylline (73). A similar effect should theoretically occur with other nondepolarizing relaxants.

Phenobarbital

Co-medication with phenobarbital may require an increase in the theophylline dose by about 30%; concurrent use with phenytoin may require an increase of as much as 75% (45).

Proton pump inhibitors

Co-administration of either lansoprazole or pantoprazole in healthy subjects did not affect the steady-state pharmacokinetics of theophylline in therapeutic doses (74).

Quinine

Quinine increased serum theophylline concentrations in an elderly patient (75).

Quinolones

Levofloxacin has been reported to interact with theophylline.

- A 59-year-old Japanese man taking theophylline for emphysema had stimulation, insomnia, and tachycardia owing to theophylline toxicity after he also took levofloxacin and clarithromycin (76). His theophylline clearance returned to normal and his symptoms resolved after withdrawal of levofloxacin, while clarithromycin was continued.

In a randomized, multiple-dose, period-balanced, three-way, crossover study in healthy nonsmoking male volunteers, moxifloxacin did not alter the pharmacokinetics of theophylline (77).

In seven healthy volunteers taking modified-release theophylline, intravenous pazufloxacin mesilate increased serum theophylline concentrations; analysis of the urinary excretion of theophylline and its metabolites suggested that CYP1A2 had been inhibited (78). Theophylline concentrations need to be monitored if pazufloxacin is co-administered.

Tacrolimus

An interaction of theophylline with tacrolimus has been described (79).

- A 33-year-old man with end-stage renal disease due to diabetic nephropathy received a cadaveric kidney graft. Immunosuppressive therapy after transplantation included tacrolimus (7 mg/day), azathioprine (75 mg/day), and prednisone (7.5 mg/day). He developed erythrocytosis 3 months later and was given drugs that reduce erythropoietin production, first enalapril, without success, and then theophylline (600 mg/day). After 1 month, his serum creatinine and tacrolimus concentrations were raised. The dosage of theophylline was therefore reduced to 300 mg/day four times a week. One month later, his serum creatinine and tacrolimus trough blood concentrations increased further. On withdrawal of theophylline, both renal function and tacrolimus trough blood concentration rapidly normalized. Theophylline was then reintroduced in a lower dose and increased the AUC of tacrolimus.

CYP3A4 is primarily responsible for tacrolimus biotransformation in the liver, but it has only a minor role in theophylline metabolism. It is therefore surprising that this tacrolimus–theophylline interaction occurred. The authors suggested that as long as renal function remains stable, low-dose theophylline can be used in transplant patients with erythrocytosis, provided that tacrolimus concentrations are closely monitored.

Tegaserod

The effect of tegaserod on the single-dose pharmacokinetics and safety profile of theophylline has been determined in a randomized, open, crossover study in 18 subjects (80). Tegaserod did not alter the pharmacokinetics of theophylline and the incidence of adverse events was similar after co-administration. However, since in vitro studies have shown that tegaserod inhibits CYP1A2 (81), more evidence is needed to claim that no dosage adjustment is required when theophylline is co-administered.

Terbinafine

In a randomized crossover study in 12 healthy volunteers, terbinafine increased the AUC of theophylline by 16%, with a 14% reduction in clearance and a 24% prolongation of half-life (82). The clinical impact of these results is difficult to define because of the small sample size in this study and because it is not known what effect terbinafine has on steady-state theophylline concentrations. An earlier study (83) showed that terbinafine reduced the clearance of caffeine, which is metabolized via similar pathways. Until more information is available, clinicians who prescribe terbinafine for patients taking chronic theophylline therapy should be cautious, and serum theophylline concentrations should be monitored.

Tocainide

Tocainide reduces the clearance of theophylline and increases its half-life, but to an extent that is probably clinically insignificant (84).

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Trimethoprim

Two episodes of severe hyponatremia have been described in the same patient, one attributed to theophylline and the other to trimethoprim (85). The evidence to support an interaction is circumstantial, and the patient was taking multiple medications, making interpretations difficult.

Food-Drug Interactions

Food can affect both the absorption and the clearance of theophylline. One study showed that the absorption of a modified-release formulation of theophylline was very slow after an overnight fast, in contrast to absorption after a test meal (86). The effect may be dose-related. More specifically, dietary protein significantly affects theophylline clearance: a low-protein diet reduces theophylline clearance and a high-protein diet increases it. The implications for clinical practice have not been elaborated, but dietary extremes are contraindicated in patients taking theophylline (51).

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Thiacetazone

See also Antituberculosis drugs

General Information

Thiacetazone (thioacetazone, thiosemicarbazone) was greeted enthusiastically in 1946 as one of the first synthetic agents against tuberculosis. However, its use rapidly diminished with the increasing observation of untoward effects. It is currently rarely used and then only for economical reasons. Dosages should never exceed 200 mg/day.

Adverse effects of thiacetazone include bone marrow depression and hemolytic anemia. It can also cause serious skin rashes. Continuous laboratory and clinical observations are required (1).

Organs and Systems

Hematologic

Adverse effects of thiacetazone include bone marrow depression, with anemia, leukopenia, agranulocytosis, and thrombocytopenia (2–4). Hemolytic anemia has also been described (5).

Gastrointestinal

Anorexia, nausea, and vomiting are not uncommon with thiacetazone (1).

Urinary tract

Hepatotoxicity with jaundice is frequent with thiacetazone (1).

Skin

Adverse effects of thiacetazone on the skin are of various types, mainly erythematous and maculopapular rashes, angioedema, purpura (6), toxic epidermal necrolysis, Stevens–Johnson syndrome, and pigmentation (7).

Of 50 cases of cutaneous adverse effects of thiacetazone, there were 48 cases of erythema multiforme (25 cases of Stevens–Johnson syndrome and 23 of toxic epidermal necrolysis), one case of erythrodermia, and one case of lichenoid toxidermia; there were 20 deaths, 16 with toxic epidermal necrolysis and four with Stevens–Johnson syndrome (8).

In a retrospective study, 38 cases of toxic epidermal necrolysis were observed in Dakar, and were attributed to thiacetazone in 24 cases; 23 died, mainly because of hypovolemic shock during the first week and septic shock during the second (9). Those who died were generally aged over 50 years, had more than 50% skin involvement, and had evolving tuberculosis at the time of presentation or HIV infection. After-effects were vaginal synechia and two cases of blindness.

Immunologic

Cutaneous allergic reactions to thiacetazone are very common in HIV-positive patients, in the order of 20%. Ethambutol should therefore be used instead of thiacetazone in these patients (10).

Susceptibility Factors

Arguments have been advanced for the abandonment of thiacetazone as an antituberculosis drug (11,12), despite its cheapness, on the grounds that it often causes severe skin reactions, some rapidly fatal, in patients infected with HIV-1 (13). The WHO and IUATLD has recommended careful information and surveillance of possible adverse reactions, particularly cutaneous, in patients treated for tuberculosis in such countries and immediate replacement with ethambutol if there are any prodromal signs of toxicity.

Anergy to tuberculin and lymphopenia have been associated with an increased risk of adverse reactions to thiacetazone. In a randomized study of rifampicin- and thiacetazone-containing regimens in HIV-positive adults with pulmonary tuberculosis, eight of 13 patients who developed adverse reactions were tuberculin-anergic, compared with 12 of 77 patients who did not develop adverse reactions (13). An absolute lymphocyte count below 2.0×10^9/l was also associated with adverse reactions.

Drug–Drug Interactions

Isoniazid

Thiacetazone combined with isoniazid (and possibly thioacetazone alone) has been reported to damage chromosomes in cultured human lymphocytes (14).

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Thiamine

See also Vitamins

General Information

The requirement for thiamine depends on the utilization of energy-yielding substrates, and increases with energy expenditure; it is therefore expressed relative to energy intake (here given in mega-Joules, MJ, formerly often given per 1000 kilocalories (kcal) which is a better known but outdated terminology). The Average Requirement is 72 micrograms/MJ/day, the Population Reference Intake is 100 micrograms/MJ/day, and the Lowest Threshold Intake is 50 micrograms/MJ/day. Expressed for average energy expenditure, this would mean an Average Requirement of 0.8 mg/day for men and 0.6 for women, a Population Reference Intake of 1.1 and 0.9 mg/day, and a Lowest Threshold Intake of 0.6 and 0.4 mg/day (1).

Excess thiamine is normally readily cleared by the kidneys. Important adverse reactions are usually associated with parenteral feeding with doses much larger than the Population Reference Intake and over long periods of time. Most common are hypersensitivity reactions, which have been observed mainly after parenteral administration. The symptoms and signs are weakness, precordial pain, palpitation, dyspnea, epigastric pain, vomiting, itching, erythema, scaling of the facial skin, severe rash, tachycardia, hypotension, purpura, semicoma, and even fatal anaphylactic shock.

Despite its favorable safety profile, it cannot be assumed that thiamine is completely innocuous. Thiamine hydrochloride is routinely given to patients with Wernicke's encephalopathy or malnourished states (such as malabsorption, beri-beri, cancer, AIDS, and chronic alcohol abuse). Systemic reactions are rare but deaths can occur.

Organs and Systems

Respiratory

Respiratory failure has been reported after parenteral administration of high doses of thiamine, albeit on only a single occasion (2).

Skin

Thiamine hydrochloride, and possibly its intermediates such as thiothiamide, can cause allergic contact dermatitis (3,4). A prospective study of the toxicity of parenteral thiamine hydrochloride in a large group of patients showed adverse reactions in only 1.1% of the cases, mainly in the form of local irritation. Only one out of the 11 adverse reaction cases was serious (5).

Immunologic

Anaphylactic shock is a major adverse effect of thiamine, and can be life-threatening. It is IgE-mediated (6) and usually occurs after multiple parenteral dosages (6–10) but occasionally also after intramuscular injection. In some cases oral challenge did not produce any reaction (8,11,12).

- A 51-year-old woman with diabetes mellitus, chronic alcoholism, and anxiety disorder became acutely confused and was given 50% dextrose 25 g and thiamine hydrochloride 100 mg intravenously; 20 minutes later she became deeply cyanosed with shallow labored breathing at 28/minute, hypertensive, and tachycardic, with respiratory and metabolic acidosis and a blood alcohol concentration of 124 mg/dl (27 mmol/l) (13). The next morning she was communicative and oriented and her vital signs and blood gases were normal. She was given thiamine hydrochloride intravenously and within moments developed shortness of breath, warmth, and tightness of the throat. She had a tachycardia, hypotension, hypoxia, and central cyanosis. She recovered within 24 hours.

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In 989 consecutive patients (1070 doses) there were 12 adverse reactions (1.1% of doses), comprising local irritation in 11 cases and a major skin reaction in the 12th. The authors concluded that thiamine hydrochloride can safely be given intravenously and that intradermal test doses before administration are not warranted unless patients have had previous allergic reactions (5).

Drug–Drug Interactions

Cancer chemotherapy

In a review it was suggested that thiamine when given to patients with cancer may interfere with chemotherapy in that thiamine may promote nucleic acid ribose synthesis and tumor cell proliferation via the transketolase pathway. The authors suggest that an oversupply of thiamine may actually do harm and may be responsible for the failure of therapeutic attempts to terminate cancer cell proliferation (14). Thiamine is directly involved in ribose synthesis in pancreatic adenocarcinoma cells through transketolase-catalysed non-oxidative pentose phosphate reactions. In addition, the chemically modified co-factor oxythiamine inhibited tumor cell proliferation in vitro and in vivo by 40% and 91% in two distinct tumor models (14). According to a review of thiamine supplementation in patients with cancer this raises serious suspicions that routine thiamine administration may not be warranted and could possibly be harmful (15). Thiamine deficiency in cancer patients is most often observed during or shortly after chemotherapy. Clinical and experimental data have shown increased thiamine utilization by human tumors and its interference with experimental chemotherapy. Current thiamine administration protocols oversupply thiamine by 200–20 000% of the RDA, because it is considered harmless and needed by cancer patients. However, since the thiamine-dependent transketolase pathway is the main reaction that supplies ribose phosphate for nucleic acids in tumors, excessive thiamine supplementation may be responsible for failed therapeutic attempts to terminate cancer cell proliferation. The authors therefore recommended that cancer management should include regular evaluation of thiamine status of the patient, especially during chemotherapy, and that dosages of thiamine should not exceed 1.2 mg/day unless necessary. Future studies should clarify whether oxythiamine as an inhibitor of transketolase is really safe and whether it is especially effective against cancer.

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Thiamphenicol

General Information

Thiamphenicol is a semisynthetic derivative of chloramphenicol, an amine derivative of hydrocarbylsulfonylpropandiol. It differs in that the NO_2 group in the para position is replaced by a methylsulfonyl group. The substitution in the para position of the molecule does not influence its effects on either protein or DNA synthesis in any recognizable way. The antibacterial spectrum is almost identical to that of chloramphenicol.

The two drugs are used in similar dosages, although there are large differences in their elimination. Glucuronidation is unimportant for thiamphenicol: over 90% of a therapeutic dose is excreted by the kidneys in unchanged form. The corresponding figure for chloramphenicol is only about 10%. Thus, in contrast to chloramphenicol, the half-life of thiamphenicol is prolonged in patients with reduced renal function in whom accumulation can occur.

Although the mechanism by which chloramphenicol causes aplastic anemia is not fully understood, all the available evidence suggests that the biochemical consequences of thiamphenicol administration and the risk of serious complications differ from those of chloramphenicol (1).

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It does not seem unreasonable, therefore, to use thiamphenicol for wider indications than chloramphenicol, provided that the dosage is adjusted according to renal function. However, thiamphenicol has adverse effects on bone marrow, calling for a degree of caution. It is therefore generally recommended that thiamphenicol should not be given for more than 10–14 days.

The most important adverse effects are an immediate dose-related and reversible disturbance of erythropoiesis (2,3) and peripheral neuropathy. In contrast to chloramphenicol, aplastic anemia and the gray syndrome do not seem to occur with thiamphenicol.

Observational studies

Thiamphenicol has been used to treat 1171 patients with chancroid (4). Each patient was given granulated thiamphenicol 5.0 g orally in a single dose. Only 0.89% did not respond. A few patients had adverse effects, including epigastric pain, headache, nausea, and skin rashes; all were mild and of short duration.

Organs and Systems

Nervous system

Several cases of peripheral neuropathy after the administration of thiamphenicol for 3–5 months have been reported and were thought to be due to a vitamin deficiency. In most cases the sensory function of the nerves of the legs was primarily affected. When discovered early, the damage was reversible, but in other cases it tended to persist (5).

Hematologic

There is evidence that thiamphenicol is more potent than chloramphenicol in causing the early dose-related and therefore predictable type of bone marrow toxicity. Many studies have shown that thiamphenicol in a dose of 1.5 g, and to a much lesser extent 0.75 g/day, causes an immediate disturbance of erythropoiesis in almost every case (6). Alterations in the bone marrow become most evident in patients with renal disease and in elderly subjects (probably because of reduced renal function). Leukocytes and thrombocytes are only slightly affected (7).

Most reviewers have been impressed by the fact that the reported cases of peripheral cytopenia were never accompanied by bone marrow aplasia (8). There have been some doubtful case reports of marrow aplasia, in which factors such as advanced age (predisposing to antibiotic accumulation), neoplasia, concurrent treatment (myelotoxic drugs, anticoagulants), and major surgical interventions have to be mentioned. Even if these cases are to be ascribed to thiamphenicol, they fall within the normal spontaneous incidence of aplastic anemia (9–12).

The most severe hematological changes were reported after treatment of typhoid fever and sepsis with relatively high doses of thiamphenicol. These changes have always been reversible on withdrawal. The serum iron concentration returned to normal within a few days and was rapidly followed by reticulocytosis. Experimental results strongly suggest that the toxic effect of thiamphenicol is temporary and that recovery of the bone marrow after drug-induced suppression is complete, with no subsequent risk of myelodysplasia or leukemic transformation (13).

The occurrence of acute leukemia has been studied in relation to preceding use of drugs (before the 12 months preceding the diagnosis) in a case-control study of 202 patients aged over 15 years with a diagnosis of acute leukemia and age- and sex-matched controls (14). Among users of chloramphenicol or thiamphenicol the odds ratio for any use was 1.1 (0.6–2.2) whereas the odds ratio for high doses was 1.8 (0.6–5.3). Other systemic antibiotics showed no substantial relation with the occurrence of leukemia.

Gastrointestinal

Diarrhea, nausea, or constipation occur in under 10% of cases and are usually mild (15).

Skin

Alopecia has been reported in patients with renal insufficiency taking thiamphenicol, and can lead to complete baldness (6). After withdrawal, normal hair growth will recover. Other skin reactions are rare.

Immunologic

Thiamphenicol has immunosuppressive properties, which are ascribed to an effect on immunocompetent cells, rather than on immunoglobulin synthesis (16). In animals, thiamphenicol prolonged the survival of skin homografts (17).

Second-Generation Effects

Fetotoxicity

Although thiamphenicol penetrates the fetal circulation and is distributed evenly in fetal tissues, no fetal abnormalities have been related to thiamphenicol administration during pregnancy (18). Since mitochondrial protein synthesis in the fetal liver is inhibited by the drug concentrations normally attained, repeated administration of thiamphenicol to pregnant women is not recommended.

Susceptibility Factors

Renal disease

Impaired renal function is an important risk factor for toxic effects of thiamphenicol (19).

Other features of the patient

Pre-existing bone marrow dysfunction and prolonged treatment is an important risk factor for toxic effects of thiamphenicol (20).

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Thiamylal sodium

See also General anesthetics

General Information

Thiamylal sodium is a short-acting intravenous barbiturate anesthetic.

Organs and Systems

Electrolyte balance

Severe hypokalemia occurred in a 14-year-old boy undergoing emergency aortic arch replacement under deep hypothermic cardiopulmonary bypass (1). He was treated with thiamylal by infusion, total dose 30 mg/kg, for persistent convulsive waves on his electroencephalogram. This caused his serum potassium concentration to fall to 1.6 mmol/l. The hypokalemia was resistant to potassium chloride infusion 80 mmol/hour, but responded to replacing the thiamylal infusion with midazolam. It was noted that there have also been reports of severe hypokalemia in brain-injured patients undergoing thiopental coma therapy.

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Thiazide diuretics

See also Diuretics

General Information

Although one thiazide diuretic may be 100 times more potent than another weight for weight, all these drugs have essentially the same properties. Their mechanism of action (inhibition of sodium and chloride reabsorption in the distal convoluted tubule of the kidney) is identical and they can therefore be dealt with as a group. Thiazide-like diuretics, structurally different from the thiazides, have similar actions. Thiazide and thiazide-like diuretics are listed in Table 1.

Like all diuretics, the thiazides can cause electrolyte abnormalities, such as hypokalemia and hyponatremia, and dehydration. These complications are uncommon in patients with uncomplicated hypertension, but are more common in patients with heart failure or decompensated hepatic cirrhosis with secondary hyperaldosteronism. Until a patient is accustomed to the effect of a diuretic, dizziness may be experienced. Serum lipid concentrations are slightly raised acutely and hyperglycemia can occur during long-term therapy. Rare effects are thrombocytopenia, rashes, drug fever, cholestatic jaundice, pancreatitis, and precipitation of hepatic

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Table 1 Thiazide and thiazide-like diuretics (rINNs except where stated)

Thiazide diuretics	Thiazide-like diuretics
Althiazide	Chlortalidone
Bemetizide	Clopamide
Bendroflumethiazide	Clorexolone
Benzthiazide	Fenquizone (pINN)
Benzylhydrochlorothiazide	Indapamide
Butizide	Mefruside
Chlorothiazide	Metolazone
Cyclopenthiazide	Quinethazone
Cyclothiazide	Tripamide
Epithiazide	Xipamide
Hydrochlorothiazide	
Hydroflumethiazide	
Mebutizide	
Methylclothiazide	
Meticrane	
Paraflutizide	
Penflutizide	
Polythiazide	
Teclothiazide	
Trichlormethiazide	

encephalopathy in patients with hepatic cirrhosis. Generalized allergic vasculitis has been described occasionally. There is no evidence that the thiazides induce tumors. Second generation effects have not been reported.

Organs and Systems

Cardiovascular

Although dizziness is a fairly frequent complaint at the beginning of diuretic treatment (1), postural hypotension is rarely reported. Ischemic complaints (mesenteric infarction and transient cerebral ischemic attacks) have been observed in elderly patients, but it is not clear whether these resulted from diminished organ perfusion or from an effect of the drug itself. The former is more likely, since similar problems have arisen with any form of antihypertensive treatment in old people who have to some degree become dependent on their hypertension to ensure a blood supply through sclerotic vessels.

Criticism directed against the diuretics in recent years has among other things sought to show that they increase the risk of coronary events, including acute myocardial infarction. However, there is no real basis for such criticism. Properly used in hypertension the diuretics produce a beneficial effect out of all proportion to any incidental adverse cardiac effects.

- A 72-year-old woman had repeated episodes of sudden-onset pulmonary edema, each occurring immediately after she took a dose of hydrochlorothiazide 12.5 mg (2).

The close temporal relation between the ingestion of hydrochlorothiazide and the onset of symptoms, together with rapid and full clinical recovery after withdrawal of therapy, suggested drug-induced pulmonary edema and possible anaphylactoid hypotension.

Respiratory

In the older literature there were various reports of acute allergic interstitial pneumonitis caused by the thiazides, sometimes confirmed by rechallenge. Typically, it presents within an hour of taking the drug and causes chest pain, breathlessness, or both; the chest X-ray is characteristic (3,4). Recovery is rapid, but assisted ventilation may be needed. Most cases in the recent literature relate to hydrochlorothiazide, but that may simply reflect its wide use. A case involving chlorothiazide (5) suggests that this syndrome can arise with any thiazide, although it sometimes occurs after the first dose of hydrochlorothiazide when other thiazides have been well tolerated. The incidence is unknown, but recent work has confirmed that it is rare. No susceptibility factors have been identified. It can occur on initial exposure or subsequent rechallenge. The mechanism is obscure, but an immunological basis has been suggested.

The reason for concern about this adverse effect is that it may easily be mistaken for myocardial infarction or acute left ventricular failure, conditions that are not uncommon in patients requiring diuretics.

Diffuse interstitial pulmonary fibrosis has been reported after treatment with cyclopenthiazide and triamterene (6).

Sensory systems

Visual disturbances caused by dehydration of lens tissue or by retinal edema have been reported, particularly in the first few weeks of treatment. On the whole these effects are innocuous and transient (SED-9, 354). Presenile cataract has been attributed to long-term use of hydrochlorothiazide (7).

Electrolyte balance

Sodium balance

Hyponatremia is the most common electrolyte abnormality in the general hospital population and is associated with a wide range of diseases and a variety of drugs. Acute hyponatremic encephalopathy can develop rapidly with diuretics, particularly thiazides. Women, all patients with hypokalemia, and those with a low sodium and/or solute intake are particularly susceptible to diuretic-induced hyponatremia.

In a hospital-based survey of hypertensive patients with hyponatremia (serum sodium concentration below 135 mmol/l) the odds ratio for hyponatremia was three times higher in women. In those over 65 years there was a 10-fold higher risk. In many instances hyponatremia was insidious in its presentation and did not occur until several months after therapy had begun (8). However, hyponatremia can also develop rapidly.

- A 69-year-old woman with uncontrolled hypertension took two doses of hydrochlorothiazide 25 mg and her serum sodium fell to 115 mmol/l within 24 hours, with accompanying neurological symptoms (9). She recovered fully with the administration of 3% saline.

Potassium balance

The thiazides increase potassium excretion, but rarely to such an extent that total body potassium stores are appreciably affected. In most patients there is no reason to think

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that long-term diuretic treatment will deplete body potassium at all. This is discussed in the monograph on Diuretics.

Mineral balance

Thiazides and related diuretics reduce the renal clearance of calcium by inhibiting the tubular secretion of calcium ions. This is discussed in the monograph on Diuretics.

Metal metabolism

Magnesium

Hypomagnesemia is common with both loop and thiazide diuretics. In 242 patients the frequency was 19% (10). It was corrected with potassium magnesium citrate, whereas potassium citrate or potassium chloride alone had little corrective effect.

Diuretic-induced hypomagnesemia is of particular relevance to patients with congestive heart failure (11). There is a reduced rate of sudden cardiac death in patients who take long-term diuretic therapy when potassium- and magnesium-sparing diuretics and/or magnesium supplements are also used. All potassium-sparing diuretics are also magnesium-sparing, and diuretic-induced hypokalemia is difficult to correct unless underlying magnesium deficiency is also addressed (12).

Zinc

Thiazide diuretics promote zinc loss in the urine and can reduce the zinc content of hair in the long term (13). It has sometimes been suggested that changes in zinc balance could be responsible for the effects of thiazides on sexual potency. There is evidence that diuretics deplete body zinc, which in turn interferes with testosterone production and causes erectile impotence (14).

Hematologic

Thrombocytopenia has been reported, but its incidence is low (SED-8, 484). Even rarer complications are autoimmune hemolytic anemia, granulocytopenia, and agranulocytosis (SED-9, 354).

Acute intravascular hemolysis has been described in a single case, and in this instance there were antibodies to hydrochlorothiazide; methyldopa, which had been given concurrently, might have facilitated antibody formation (15).

Gastrointestinal

Nausea and vomiting have often been reported, but if the incidence is compared to that in a control group taking placebo (1), it seems to be negligible, even in hospital (16), and such complaints rarely necessitate a change of therapy. The high incidence reported in the past (SED-9, 354) was probably related to the sheer size of the chlorothiazide tablets, and it has almost disappeared since the general change to more potent thiazides and related drugs.

Liver

Jaundice has very rarely been attributed to thiazide diuretics (SED-9, 354).

- Rash, lymphadenopathy, splenomegaly, periorbital edema, and hepatitis occurred in an 18-year-old woman who was taking phenobarbital and hydrochlorothiazide (17). Tests for fluorescent antinuclear antibody and hepatitis-associated antigen and antibody were negative. Liver biopsy was not characteristic of viral hepatitis. She recovered within 2 weeks after withdrawal of the drugs and administration of methylprednisolone and diphenhydramine.

Biliary tract

Studies of the relation between diuretic use and cholecystitis have yielded conflicting results. A significant association of thiazide use with acute cholecystitis was reported in a case-control study (18). However, others examined the association between the use of thiazides and cholecystectomy and failed to show a relation between the use of thiazides and gallstone disease, except possibly in women who are not overweight (19).

Pancreas

Pancreatitis has been reported occasionally with thiazides (SED-9, 354) (SEDA-5, 228) (SEDA-17, 263).

Urinary tract

Toxic damage to the kidney has occasionally been reported (20), but is rare, and it is not clear whether nephrotoxicity was due to severe hypokalemia or the drug itself.

Thiazide diuretics cause hyperuricemia and can occasionally precipitate gout (21). They can also cause renal stones (22). Uric acid precipitation is not normally a problem, although it was with the uricosuric drug tienilic acid.

Renal vasculitis due to thiazides is rare (SEDA-18, 234).

Skin

Rashes due to thiazides are common but are only very occasionally severe and disabling (SEDA-11, 198). A state of chronic photosensitivity can persist for many years after drug withdrawal and is difficult to treat (23); it can mimic contact dermatitis, and there can be cross-reactivity with sulfonamides and phenothiazines. Patients who develop photosensitivity to thiazides should never take these drugs again.

Several cases of a reaction resembling systemic lupus erythematosus have been described (24–26). One patient taking hydrochlorothiazide developed unequivocal antinuclear antibody (ANA) positivity, with the homogeneous pattern most commonly found in drug-induced lupus (27). It is uncertain whether thiazides cause a lupus-like syndrome or activate latent disease in predisposed individuals.

Two of nine patients with drug-induced toxic epidermal necrolysis were taking hydrochlorothiazide, one with triamterene and allopurinol, the other with reserpine and hydralazine; both died (28).

In a patient who developed an allergic vasculitis affecting the skin during long-term treatment with hydrochlorothiazide the findings suggested that immediate (Type I) hypersensitivity may be involved in the induction of vasculitis (29).

- A 60-year-old man with a history of renal insufficiency and hypertension, taking hydrochlorothiazide,

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furosemide, and amiloride, developed pellagroid dermatitis involving light-exposed areas (30). The pigmentation disappeared slowly after withdrawal of hydrochlorothiazide and amiloride.

Hydrochlorothiazide, which is a well-known photoallergen, can also cause allergic photodermatitis (31).

- A 77-year-old man developed a florid photosensitive lichenoid eruption, histologically confirmed, while taking thiazide diuretics for heart failure (32). The eruption cleared on withdrawal of the drug. Although thiazide-induced photosensitivity is well documented, there have been no histologically proven cases of a lichenoid eruption in light exposed areas.

Immunologic

It has long been thought that loop and thiazide diuretics pose a theoretical risk of cross-sensitivity in patients with sulfonamide allergy because of their common structures. However, the available literature does not provide sufficient numbers of well-documented cases to support this impression (33). It seems that careful administration of diuretics is permissible in patients with documented sulfonamide allergy, but as always such a drug challenge should not be attempted without careful follow-up. A furosemide rechallenge protocol, based on a method that has been used to rechallenge with a sulfa-containing antimicrobial agent, safely allowed the long-term reinstitution of loop diuretic therapy with furosemide (34).

Second-Generation Effects

Pregnancy

In the past, thiazide diuretics have been considered as being contraindicated in pregnancy, because of risks to the mother and fetus. However, more recent evidence suggests that their use need not be contraindicated (35).

Susceptibility Factors

Age

The risks and benefits of distal tubular diuretics have been assessed in preterm infants under 3 weeks of age with or developing chronic lung disease (36). Acute and chronic administration of distal diuretics improved pulmonary mechanics; adverse effects were not reported. However, additional studies are needed to assess whether thiazide administration improves mortality, duration of oxygen dependency, ventilator dependency, length of hospital stay, and long-term outcome in patients exposed to corticosteroids and bronchodilators, and whether adding spironolactone to thiazides or adding metolazone to furosemide has any beneficial effect.

Other features of the patient

Thiazides should be used with caution in patients with a history of gout.

The use of thiazide diuretics in hepatic cirrhosis is associated with a high incidence of severe hypokalemia, asterixis, and precipitation of encephalopathy (9). Thiazides should not be used in patients with advanced hepatic insufficiency.

Drug–Drug Interactions

ACE inhibitors

Even low dosages of angiotensin-converting enzyme (ACE) inhibitors, such as enalapril, can cause profound first-dose hypotension in hypertensive patients treated with a thiazide (37). This is rare if volume depletion and sodium depletion are avoided.

Angiotensin-converting enzyme inhibitors can cause renal insufficiency in patients with bilateral renal artery stenosis or stenosis of the artery supplying a single functioning kidney. Concomitant diuretic treatment may play a role in this adverse reaction (38).

Allopurinol

Adverse reactions to allopurinol, particularly toxic epidermal necrolysis and a hypersensitivity syndrome, are reputed to be more common in patients taking thiazides, but evidence to support this is hard to find (SEDA-11, 198) (SEDA-13, 188).

Angiotensin-II receptor antagonists

The value of low doses of thiazide diuretics in the management of hypertension is well attested, and low doses of diuretics have synergistic actions with other antihypertensive drug classes, including the angiotensin-II receptor antagonists (39–41). It is still unclear what represents the optimal dose of a thiazide diuretic in combination with either an ACE inhibitor or an angiotensin-II receptor antagonist. The addition of an angiotensin-II receptor antagonist to diuretic therapy seems to blunt the associated electrolyte disturbances. In particular, hydrochlorothiazide-induced hyperuricemia is specifically attenuated by losartan (42).

Beta-blockers

The combination of a thiazide and a beta-blocker can cause hyperglycemia (SEDA-10, 191) (SEDA-19, 192).

Calcium carbonate

Milk-alkali syndrome occurred in a patient who was taking chlorothiazide 500 mg/day for hypertension and calcium carbonate 7.5–10 g/day for heartburn (43).

Ciclosporin

Patients taking diuretics and ciclosporin may be at higher risk of hyperuricemia and gouty complications, perhaps because of tissue breakdown caused by ciclosporin (44).

Lithium

The thiazide diuretics inhibit the tubular excretion of lithium ions and can cause frank lithium intoxication (45). This is a potentially serious and well-documented interaction.

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NSAIDs

Several non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to interfere with the natriuretic effects of thiazides (SED-11, 423). A similar interaction is seen with tenidap, an antiarthritic cytokine modulating drug (46). The salt-retaining properties of the NSAIDs probably play the central role in this interaction.

Non-steroidal anti-inflammatory drugs (NSAIDs) are often reported to interfere with the blood pressure-lowering action of thiazide diuretics (SED-14, 667). In 17 women with arthritis and hypertension taking fosinopril and hydrochlorothiazide, ibuprofen, sulindac, and nabumetone, each for 1 month, had no effect on mean arterial pressure (47). These results suggest that the ACE inhibitor fosinopril may neutralize the tendency of NSAIDs to increase blood pressure in thiazide-treated hypertensive patients. However, the design of this study precluded such a conclusion, since no evidence was provided that any of the NSAIDs increased blood pressure in the absence of fosinopril. Furthermore, the numbers were small and the precision of the comparison is likely to have been low. Careful monitoring of blood pressure is necessary when NSAIDs are introduced in thiazide-treated hypertensive patients, even when ACE inhibitors are co-prescribed.

Oral hypoglycemic drugs and insulin

Thiazide drugs can oppose the blood glucose-lowering effects of oral hypoglycemic drugs and insulin (48) (although this effect is rarely serious).

Potassium-wasting drugs

Thiazide drugs have additive potassium-lowering effects with other drugs that reduce serum potassium, such as corticosteroids and carbenoxolone. Profound hypokalemia due to the latter combination has been reported to cause massive rhabdomyolysis and acute tubular necrosis (49).

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Thiazinamium metilsulfate

See also Antihistamines

General Information

Thiazinamium is a first-generation antihistamine (SED-13, 418).

Organs and Systems

Sensory systems

In long-term, double-blind study in 12 men with chronic bronchitis, three who took thiazinamium metilsulfate 900 mg/day had visual disturbances (1).

Gastrointestinal

Thiazinamium can cause attacks of sternal and epigastric pain, perhaps due to esophageal spasm. Esophageal ulceration has been reported (2).

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Thiazolidinediones

General Information

The thiazolidinediones include pioglitazone and rosiglitazone; darglitazone is in development; ciglitazone, englitazone, and troglitazone have been withdrawn owing to adverse effects on the liver (all names are rINNs).

The thiazolidinediones reduce insulin resistance and are sometimes designated as insulin sensitizers. They promote glucose utilization in peripheral tissues by stimulating non-oxidative glucose metabolism and suppressing gluconeogenesis. They activate the so-called Peroxisome Proliferator Activated Receptor Gamma (PPARγ), a nuclear hormone receptor that enhances a number of genes encoding enzymes involved in glucose and fat metabolism. PPARγ is essential for normal insulin sensitivity (1–3). They may also intervene directly in the fuel metabolism of skeletal muscle and liver, as suggested by in vitro experiments (4). They can reduce HbA_{1c}, the glucose AUC after a glucose tolerance test, and the glucose AUC after a meal in glucocorticoid-induced diabetes, as has been shown in seven patients taking troglitazone (5). They may ameliorate albuminuria in incipient diabetic nephropathy (6).

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In some systems, troglitazone behaves as a partial agonist, but in fat cells it behaves as a full agonist. The transcriptional activities of troglitazone and rosiglitazone differ (7). The thiazolidinediones promote fat accumulation in subcutaneous tissue (8) rather than in the abdominal region, which plays such a bad role in the insulin resistance syndrome. Troglitazone lowers fasting glucose and postprandial glucose. Its effects persist for 2–3 weeks after withdrawal (9). It is also effective in insulin-resistant glucocorticoid-induced diabetes (10). It has a greater insulin-sparing effect than biguanides when given to patients on continuous subcutaneous insulin infusion (11).

The thiazolidinediones have been frequently reviewed (12–22). They can be prescribed as single drugs or in combination with other hypoglycemic drugs (23). In 12 healthy people, meals did not affect the absorption of rosiglitazone (24).

Comparative studies

In a parallel-group study in patients starting on hypoglycemic therapy with thiazolidinediones, 35 took troglitazone 600 mg/day, 36 took rosiglitazone 8 mg/day, and 30 took pioglitazone 45 mg/day (25). At 2 and 4 months, there was an equal effect on glucose lowering and greater weight gain with pioglitazone; pioglitazone had the largest beneficial effect on lipids and rosiglitazone the least.

In 203 patients, randomly assigned for 1 year to rosiglitazone 4 mg bd or glibenclamide to achieve optimal control, there was significant and sustained reduction in hyperglycemia and a significant reduction in diastolic blood pressure with rosiglitazone (26). There were no differences in adverse effects or in left ventricular mass index.

Placebo-controlled studies

Rosiglitazone monotherapy has been studied double-blind in 493 patients for 26 weeks (27). There was a dose-related fall in hemoglobin. Rosiglitazone caused more mild to moderate edema. One patient had a temporary rise in transaminases, which normalized spontaneously.

In a parallel-group, double-blind, placebo-controlled, dose-ranging study of rosiglitazone 4, 8, and 12 mg/day in 369 patients for 8 weeks after a run-in period, hematocrit and hemoglobin, C peptide, fasting blood glucose, and fructosamine all fell (28). Hepatotoxicity, significant cardiac events, or hypoglycemia were not different from placebo.

In 574 patients taking a sulfonylurea, twice-daily placebo ($n = 192$ patients) was compared with rosiglitazone 1 mg/day ($n = 199$ patients) or rosiglitazone 2 mg/day ($n = 183$ patients) for 26 weeks (29). Rosiglitazone improved HbA_{1c}. With the higher dose of rosiglitazone there were more cases of hypoglycemia and a small increase in mean body weight; some patients complained of headache and upper respiratory tract infections.

In a placebo-controlled study, 959 patients took placebo, rosiglitazone 4 mg od, 2 mg bd, 8 mg od, or 4 mg bd for 26 weeks (30). In the placebo group 38% withdrew and in the rosiglitazone groups 20%. Two patients (one in the placebo and one in the 4 mg bd group) had changes in alanine transaminase of more than three times the upper limit of the reference range. Other adverse events related to edema were seen in 1.6% of the placebo group and in 4.1% of those taking 2 mg bd and 6.6% in those taking 4 mg bd. There were small dose-dependent falls in hemoglobin and hematocrit.

In a multicenter, double-blind, placebo-controlled study, 408 patients took pioglitazone 7.5, 15, 30, or 45 mg/day (31). There was no hepatotoxicity and the overall adverse events profiles did not differ, except for edema in 12 of 329 patients who took pioglitazone. There was a significant fall in triglycerides and a small fall in LDL cholesterol. However, in another study in 150 patients, postprandial triglycerides were not reduced by pioglitazone (32).

In 561 patients with HbA_{1c} concentrations of at least 8.0% on stable treatment with a sulfonylurea, pioglitazone was added for 16 weeks in a double-blind study (33). The incidence of edema increased from 2% in the placebo group to 7%. With pioglitazone there were more episodes of hypoglycemia, a dose-related increase in body weight, and a dose-related fall in hemoglobin. The frequency of adverse cardiovascular effects was the same.

Combinations of oral hypoglycemic drugs

The different mechanisms of action of the various classes of hypoglycemic drugs make combined therapy feasible: the sulfonylureas and meglitinides stimulate insulin production by different mechanisms, the biguanides reduce glucose production by the liver and excretion from the liver, acarbose reduces the absorption of glucose from the gut, and the thiazolidinediones reduce insulin resistance in fat. It is not necessary to wait until the maximal dose of one drug has been reached before starting another. However, sulfonylureas and meglitinides should no longer be used when endogenous insulin production is minimal. Combinations of insulin with sulfonylureas or meglitinides should only be used while the patient is changing to insulin, except when long-acting insulin is given at night in order to give the islets a rest and to stimulate daytime insulin secretion.

Large studies of the effects of lifestyle changes, the effects of drugs in preventing or postponing the complications of diabetes, or the usefulness of various combinations are regularly published. The different mechanisms of action of the various classes give different metabolic effects and different adverse effects profiles (34). Comparative costs of the various therapies in the USA have been presented (35).

This subject has been reviewed in relation to combined oral therapy. In a systematic review of 63 studies with a duration of at least 3 months and involving at least 10 patients at the end of the study, and in which HbA_{1c} was reported, five different classes of oral drugs were almost equally effective in lowering blood glucose concentrations (36). HbA_{1c} was reduced by about 1–2% in all cases. Combination therapy gave additive effects. However, long-term vascular risk reduction was demonstrated only with sulfonylureas and metformin.

The adverse effects of combined drug therapy are attributable to the adverse effects of the single drugs. Increased adverse effects or new adverse effects in patients taking combinations have not been reported.

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Thiazolidinediones + biguanides

In a multicenter, randomized, double-blind study, 116 patients were treated for 26 weeks with metformin plus placebo, 119 with metformin plus rosiglitazone 4 mg/day, and 113 with metformin plus rosiglitazone 8 mg/day (37). In both rosiglitazone groups there were small but statistically significant falls in hemoglobin and hematocrit. Edema was rare but more common in the rosiglitazone groups (2.5% with 4 mg/day and 3.5% with 8 mg/day). Body weight fell by 1.2 kg from baseline with placebo but increased by 0.7 kg with rosiglitazone 4 mg/day and by 1.9 kg with 8 mg/day. No one taking rosiglitazone had an increase in alanine transaminase greater than three times the upper limit of the reference range.

In a placebo-controlled study in 116 patients who responded insufficiently to metformin 2.5 g/day, rosiglitazone 2 or 4 mg bd was added for 26 weeks (38). HbA_{1c} and fasting plasma glucose improved and hemoglobin fell. Edema was reported in 5.2% of the patients who took rosiglitazone and two patients withdrew because of headache.

Thiazolidinediones + meglitinides

In 585 patients in a double-blind, randomized, placebo-controlled, multicenter study lasting 16 weeks, nateglinide 40 mg tds alone, troglitazone 200 mg/day alone, and the combination were compared (39). The combination was most effective in lowering HbA_{1c}. The most frequent adverse effects were mild hypoglycemia, most often in the combination group. Three patients (two in the combination group and one in the troglitazone alone group) withdrew because of hypoglycemia. Most of the withdrawals were related to increased liver enzymes and weight gain, known adverse effects of troglitazone. Twelve patients withdrew because of predefined changes from baseline (transaminases more than 200% and alkaline phosphatase and bilirubin more than 100% over baseline); seven were taking troglitazone alone, four combined therapy, and one placebo.

In an open trial, 256 patients with type 2 diabetes with inadequate hypoglycemic control (HbA_{1c} over 7.0% during previous therapy) took repaglinide (0.5–4 mg at meals), troglitazone (200–600 mg/day), or a combination of the two for 22 weeks (40). Combination therapy was most effective. Repaglinide only was more effective than troglitazone only. Mean body weight increased in both groups. Serious adverse events were chest pain, cerebrovascular disorders, malignancies, dysrhythmias, electrocardiographic changes suggesting myocardial infarction, and increased aspartate transaminase activity (in one patient taking troglitazone). The serious adverse effects were similar in the different groups. Hypoglycemia occurred in 4% of the patients taking combined therapy, in 16% of those taking troglitazone only, and in 27% of those taking repaglinide only; none needed assistance. There were changes in liver function tests in three patients in the combined group and in one patient each in the two other groups; the drugs were withdrawn in the affected patients and liver function normalized. There were no differences in adverse effects in the different groups. Hypoglycemia occurred in 11 patients taking repaglinide, in seven taking combination therapy, and in one taking troglitazone. Anemia occurred in four patients taking combined therapy and in two taking troglitazone only.

Thiazolidinediones + sulfonylureas

Troglitazone 100 or 200 mg/day or placebo was given for 16 weeks to 259 patients already taking sulfonylurea therapy (41). HbA_{1c} was 0.4 and 0.7% lower and blood glucose concentrations fell. The most common event was hypoglycemia, but this did not occur more often when troglitazone was added. Liver enzymes increased to the same extent in the three groups and never rose above normal. No patients withdrew because of drug-related effects.

Insulin + thiazolidinediones

Insulin plus metformin (27 patients, 2000 mg/day) or troglitazone (30 patients, 600 mg/day) in patients with type 2 diabetes using at least 30 U/day was compared with insulin alone (30 patients) for 4 months (42). Body weight increased in the insulin and the insulin plus troglitazone groups. In the insulin plus metformin group there were significantly more gastrointestinal adverse effects but less hypoglycemia than the other groups.

The addition of rosiglitazone to insulin for 26 weeks in a double-blind study in 315 patients with inadequately controlled type 2 diabetes improved glycemic control and was well tolerated (43). There was a significant fall in hemoglobin, and some patients in both the rosiglitazone and placebo groups developed edema.

General adverse effects

The adverse effects of the thiazolidinediones are comparable and include weight gain, upper respiratory tract infections, headache, and hypoglycemia (mostly in combination with other hypoglycemic drugs). Fluid retention sometimes occurs (19,21) and can lead to or exacerbate heart failure and pulmonary and general edema, which was reported in 1.5–12% of patients taking pioglitazone. Small clinically unimportant falls in hematocrit and hemoglobin occur because of hemodilution. Changes in liver enzymes and bilirubin have not been reported with rosiglitazone, and although there have been some reports of hepatic-related adverse effects, they have not been definitive (SEDA-25, 515). However, troglitazone causes liver complications, sometimes fatal, and this has led to its withdrawal from the market. There are no drug interactions with other hypoglycemic agents.

Organs and Systems

Cardiovascular

Reductions in VLDL cholesterol, LDL cholesterol, and chylomicrons may contribute to a reduction in cardiac complications. Pioglitazone reduced both lipoprotein(a) and the remnant particles (cholesterol-rich particles after the release of triglycerides from the chylomicrons), whereas troglitazone caused increases in lipoprotein(a) (44).

Respiratory

A single case of pleuropulmonary disease possibly induced by troglitazone has been reported (45).

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Nervous system

Ataxia has been attributed to troglitazone in two patients aged about 80 years (a man and a woman) (46). The ataxia developed during treatment and disappeared in one case 2–3 days after withdrawal and in the other within 2 weeks. In one, the ataxia was accompanied by a dementia-like syndrome, which completely disappeared within 8 weeks. One of the patients was rechallenged and developed ataxia again.

Metabolism

The thiazolidinediones can cause hypoglycemia both when used alone or in combination with other hypoglycemic drugs (47).

The thiazolidinediones increase body weight. With troglitazone the increase in body weight is accompanied by changed fat distribution, but central fat, in part responsible for the cardiovascular changes seen in diabetes, remains the same; weight gain is accompanied by increased subcutaneous fat (48).

In one study, troglitazone increased body weight, adipocyte size, leptin concentrations, GLUT4 protein expression, basal and insulin-stimulated glucose transport, and insulin-stimulated whole-body glucose disposal rate (49).

In a 24-week study, in which 40 patients taking troglitazone and glibenclamide were compared with patients taking glibenclamide, serum fasting insulin, serum triglycerides, and insulin resistance were reduced when troglitazone was added. Fat deposition in the liver and the visceral fat area were reduced, but deposition in skeletal muscle was not (50).

When patients taking troglitazone were switched to equivalent amounts of rosiglitazone ($n = 60$) or pioglitazone ($n = 60$) there were no changes in HbA_{1c} or other parameters, except that with pioglitazone there was a significant improvement in lipid profile, with an average fall in total cholesterol of 0.5 mmol/l (51).

However, in 23 patients who took pioglitazone for 16 weeks, in whom fasting and mean glucose concentrations and mean free fatty acid concentrations fell, weight gain of 3.6 kg was associated with an increase in peripheral fat without edema (52).

In 38 patients taking metformin 2550 mg/day and glimiperide 6 mg/day, rosiglitazone 4 or 8 mg/day was added for 20 weeks (53). HbA_{1c} and fasting blood glucose fell significantly. There was hypoglycemia in 19% of those who took 4 mg/day and 28% of those who took 8 mg/day, and body weight increased by 4.2 and 4.6 kg respectively. There were no signs or symptoms of liver disease and no changes in liver function tests.

Fluid balance

Two cases of pulmonary and general edema have been reported with rosiglitazone (54).

- A 78-year-old man became short of breath. He had been taking rosiglitazone 8 mg/day for 6 months. He had renal insufficiency, atrial fibrillation, hypertension, and congestive heart failure, with pitting edema and bilateral pleural effusions. He was refractory to intravenous furosemide and metolazone. Withdrawal of rosiglitazone and administration of bumetanide gave a net fluid output of 9.5 litres and the edema resolved.
- A 67-year-old man, who had taken troglitazone 600 mg/day for 4 months and who had renal insufficiency, stroke, and cardiomyopathy, developed pitting edema, hepatomegaly, ascites, and a pleural effusion. The edema was resistant to treatment until troglitazone was changed to glipizide 10 mg/day, when he had a diuresis of 18 litres in 6 days. Later he took rosiglitazone 4 mg bd for 3 weeks and had weight gain of 5 kg and pitting edema. Diuretic therapy failed until rosiglitazone was withdrawn, after which he reached his baseline weight in 4 days.

Pioglitazone also causes fluid retention, possibly because of increased production of vascular endothelial growth factor (55). The safety profile of monotherapy and combined therapy with pioglitazone has been evaluated in 3500 patients over 2500 patient-years, and some data from post-marketing surveillance were included; peripheral edema and hemodilution were common (56).

Hematologic

In 303 patients who took placebo or rosiglitazone for 8 weeks after a run-in period, rosiglitazone 4 mg bd had the same effect as 6 mg bd, but hemoglobin and hematocrit were lower with 6 mg bd (57). In another study troglitazone produced small reductions in hemoglobin, hematocrit, and erythrocyte counts and increases in lactate dehydrogenase and blood urea nitrogen (58).

Liver

The thiazolidinediones are hepatotoxic (59).

Troglitazone

Troglitazone causes liver damage more often than the other members of the family. Hepatotoxicity delayed and finally prevented the registration of troglitazone in Europe. In the US, a patient with diabetes who used troglitazone in a study, developed hepatic failure necessitating liver transplantation and died. Troglitazone was withdrawn from a major National Institutes of Health evaluation of various regimens for preventing type 2 diabetes. In Japan the government recommended in December 1997 that liver function tests should be assessed every month in patients taking troglitazone. In 1998 there were 21 fatal cases of liver failure and three liver transplantations in patients taking troglitazone (60). Monitoring of liver function was intensified and in 1998 troglitazone was withdrawn for monotherapy. In 1999 the FDA received 61 reports of fatal hepatic toxicity and seven cases requiring liver transplantation (61) and in spring 2000 troglitazone was withdrawn in America and in Japan.

- A 58-year-old man developed severe hepatitis after taking troglitazone 400 mg/day and glibenclamide 5 mg/day (62). Glibenclamide was stopped after 6 weeks as his HbA_{1c} was 7.0%. About 2 weeks later he developed malaise and 1 week later jaundice. His bilirubin and transaminases were greatly raised and there was ascites. He had taken about 34 g of troglitazone. Drug-induced lymphocyte stimulation test was strongly positive for

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troglitazone and not for other drugs. Troglitazone was withdrawn and 3 days later the plasma concentration was below the limit of detection. Notwithstanding intensive therapy he died after 5 weeks. At autopsy, the liver showed yellow atrophy and massive hepatocellular coagulation necrosis with moderate neutrophil, monocyte, and eosinophil infiltration.

The positive lymphocyte stimulation test, the eosinophils, and the low blood concentrations 3 days after withdrawal suggest that hypersensitivity to troglitazone was the underlying cause. The authors reported that another patient with hepatitis after troglitazone had had a subacute course after withdrawal of the drug.

Late hepatic damage has also been reported.

- A 62-year-old woman with normal liver function tests took troglitazone 400 mg/day in combination with gliclazide 80 mg/day and pravastatin (63). After 9 months her transaminases were slightly above normal, but the HbA_{1c} was 7.0% and treatment was continued. Her liver enzymes were measured monthly and after 19 months rose abruptly. Troglitazone was withdrawn immediately and she received insulin. Her liver enzymes improved rapidly. A biopsy showed hepatic necrosis round the central vein and a mild inflammatory infiltrate and fibrosis in the portal area compatible with protracted acute hepatitis. A lymphocyte stimulation test and a skin test were negative for troglitazone.
- A 76-year-old man took troglitazone 400 mg in addition to glimepiride 4 mg/day, metformin 1 g/day, aspirin, and pravastatin (64). After 18 months his liver function deteriorated and improved after withdrawal of troglitazone.

There are no differences in outcome between these two patterns of hepatotoxicity, "rapid risers," in whom liver failure takes only a few days to develop, and "slower risers." The estimated death rate is one in 100 000, but the estimate of the FDA advisory committee was one in 15 154 at 8 months of treatment. It is unclear whether hepatotoxicity is a class effect of thiazolidinediones or whether the lipophilic alpha-tocopherol moiety of troglitazone is responsible for this effect. The basic quinone structure of alpha-tocopherol is common to other drugs that can form hepatotoxic free radicals by CYP2E1-mediated oxidation.

The relation of liver disease to oral hypoglycemic drugs has been investigated in 44 406 patients, of whom 605 had liver disease (65). When 185 patients with mild and transient disorders, 249 with a predisposing condition, and 113 with another cause were excluded, 57 cases with possibly drug-induced liver changes were left. Of these, 11 could be attributed to other drugs and eight were attributed to fatty liver disease caused by diabetes. In 51 patients, oral drugs were continued without worsening of the liver enzymes. In two cases (a 58-year-old woman, whose liver function improved after discontinuing metformin, and an 86-year-old woman, who developed jaundice and died shortly after metformin and glibenclamide were prescribed) a causal relation could not be excluded.

There has been a report of hepatic injury with troglitazone but not with rosiglitazone (66).

- A 38-year-old woman was given insulin when glibenclamide and acarbose failed. Troglitazone 400 mg/day was added and increased to 800 mg/day 1 month later. After 2 months her liver function tests were normal, but she developed jaundice after 4 months. Total and direct bilirubin were 127 and 101 μmol/l and alanine transaminase was 34 μkat/l. After withdrawal of troglitazone her symptoms disappeared and her liver function tests normalized within several months. Metformin 1000 mg bd reduced her insulin requirement. Rosiglitazone 4 mg bd was added and her liver function tests remained normal for 10 months.

Pioglitazone

Hepatocellular damage has occasionally been attributed to pioglitazone.

- A 67-year-old man took pioglitazone 30 mg/day after having taken glibenclamide 2.5 mg/day for 10 years and voglibose 0.6 mg/day for 5 years (67). His liver function was normal before and during 6 months of pioglitazone therapy, but at 7 months he had abnormal liver function tests (total bilirubin 10 μmol/l, aspartate transaminase 1.95 μkat/l, alanine transaminase 5.65 μkat/l, alkaline phosphatase 17 μkat/l, gamma-glutamyl transferase 8 μkat/l). He was asymptomatic, with negative viral serology and normal liver ultrasonography. After withdrawal of pioglitazone his liver function normalized within a month.
- A 49-year-old man developed scleral icterus with raised bilirubin and transaminases after using pioglitazone 15-30 mg for 6 months and 45 mg for 1 week (68). No other cause for hepatitis was found. After withdrawal his liver function improved substantially within 14 days.
- A 49-year-old woman developed jaundice after taking pioglitazone 30 mg/day for 6 weeks, and after 3 weeks the alanine transaminase was 131 U/l and aspartate transaminase 79 U/l (69). Tests for viral hepatitis were negative. A liver biopsy showed marked portal edema, patchy chronic inflammation, a cellular infiltrate, and marked bile duct proliferation. There was no fibrosis. The laboratory results worsened after pioglitazone was withdrawn, and 1 month after withdrawal the bilirubin reached a peak of 585 μmol/l. Over the next 8 weeks the symptoms and laboratory tests improved, and after 6 months her condition was the same as when she had started to take pioglitazone.

Rosiglitazone

The frequency of liver damage with rosiglitazone is much lower than with troglitazone and the reported cases seem to have been less serious. No deaths have been reported.

- A 61-year-old man developed hepatotoxicity 8 days after starting to take rosiglitazone 4 mg/day, and it was withdrawn (70). The alanine transaminase was 28 μkat/l, aspartate transaminase 23 μkat/l, alkaline phosphatase 8.7 μkat/l, total bilirubin 14 μmol/l, and direct bilirubin 13 μmol/l. All the tests were normal 5 months later. He had taken troglitazone for 1 week 8 months before this incident but had stopped because of nausea and an upset stomach.
- A 69-year-old man taking rosiglitazone 4 mg/day and metformin 500 mg/day developed hepatic failure within

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a week and both drugs were withdrawn (71). His alanine transaminase was 32 μkat/l, aspartate transaminase 47 μkat/l, total bilirubin 65 μmol/l, and direct bilirubin 41 μmol/l. He became comatose and the aspartate transaminase rose to 185 μkat/l. The enzyme activities were normal 7 weeks after withdrawal.

- A 58-year-old woman started to feel ill 2 weeks after starting to take rosiglitazone 4 mg/day (72). One week later her peak aspartate transaminase was 5.2 μkat/l, alanine transaminase 4.2 μkat/l, and bilirubin 41 μmol/l. Four weeks later all the values had returned to normal.
- In a 47-year-old woman, who took rosiglitazone 4 mg/day for a short, unspecified time, the alkaline phosphatase increased (11 μkat/l) and returned to normal 2 weeks after withdrawal (73).
- An obese 37-year-old man with type 2 diabetes, who used rosiglitazone for 15 months, at first 4 mg/day then 8 mg/day for 6 months, developed granulomatous hepatitis (74). His liver enzymes were normal at 6 and 8 months. After 14 months he developed fatigue, abdominal discomfort, and weight loss and 3 weeks later chills, nausea, vomiting, and diarrhea. No hepatic viruses were found. A liver biopsy showed a periportal mixed cellular infiltrate and granulomas within the portal triad and the parenchyma. There was no evidence of sarcoidosis. After withdrawal of rosiglitazone he improved and the liver enzymes became normal within 2 months.
- A 49-year-old man with pre-existing hepatic pathology took rosiglitazone 4 mg/day for 2 months and 8 mg/day for 5 months (75). He developed a "bull" face and then edema of the eyelids and neck. He had anorexia and nausea. His serum sodium was 110 mmol/l, potassium 3.3 mmol/l, chloride 81 mmol/l, cholesterol 21 mmol/l, triglycerides 33 mmol/l, and his liver enzymes were raised. Rosiglitazone was withdrawn and he was given saline and potassium, acarbose for his diabetes, spironolactone 200 mg/day for edema, and atorvastatin 10 mg/day for hyperlipidemia. He improved over 3 weeks.

Liver function was monitored in patients aged 30–80 years with type 2 diabetes taking rosiglitazone (76). When a patient had transaminase or alkaline phosphatase activities higher than 2.5 times the upper limit of the reference range, they were not included in the studies. In 5006 patients taking rosiglitazone as monotherapy or combined therapy there were no hepatotoxic effects. At entry to the studies, 5.6% of the patients had values between 1.0 and 2.5 times the upper limit. Of the placebo-treated patients, 39% had a fall to normal values and 39% had an increase, but not over three times the upper limit. In 66% of the patients treated with a hypoglycemic drug the values fell (often with a fall in HbA_{1c}); in 13% they increased to below three times the upper limit and in 2.0% to over three times (four patients).

Musculoskeletal

Rhabdomyolysis has been attributed to troglitazone in combination with alcohol (77).

- A 59-year-old man took troglitazone 400 mg/day for 6 months and alcohol about 40 g/day. He developed weakness and muscle pain. He had mild liver damage. His HbA_{1c} concentration was 9.0%. All his muscles were tender, his creatine kinase activity was 10 570 IU/ml, and his myoglobin, aldolase, and aspartate transaminase were raised. Troglitazone was withdrawn. He improved biochemically and clinically.

There was an increase in creatine phosphokinase activity to over 10 times the upper limit of the reference range in seven of 1510 patients taking pioglitazone in the USA; four normalized during treatment, two normalized after withdrawal, and one had fallen but not normalized at follow-up (21).

Immunologic

- Angioedema has been reported in an obese woman after she had taken pioglitazone 30 mg/day for 7 days (78). She developed a sore throat followed by dyspnea and swelling of the lips and tongue. There was no rash. After intravenous glucocorticoids her symptoms rapidly abated.

Susceptibility Factors

Renal disease

Dosage adjustment of rosiglitazone is not necessary when renal function is reduced (79).

Drug–Drug Interactions

Metformin

In 16 healthy men taking metformin 500 mg bd and/or rosiglitazone 2 mg bd for 4 days there were no significant effects on the steady-state pharmacokinetics of either drug (80).

Simvastatin

Troglitazone has been reported to reduce the effect of simvastatin, probably by induction of CYP3A4 (81).

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Thionamides

General Information

Several natural or synthetic substances interfere with the synthesis and/or secretion of the thyroid hormones. Two types of thionamides are used in the treatment of hyperthyroidism:

1. derivatives of thiouracil, especially propylthiouracil (rINN); methylthiouracil and iodothiouracil have

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been used in the past, but are not currently used clinically;
2. derivatives of thioimidazole, especially thiamazole (rINN; methimazole) and its carbethoxy derivative carbimazole (rINN), which is converted in the body to thiamazole (1,2).

All of these drugs interfere with the thyroid peroxidase system and inhibit the synthesis of the thyroid hormones, reducing their overproduction in hyperthyroidism. However, if they are used in too high dosages, they can cause hypothyroidism and hypersecretion of thyrotrophin (TSH) which in turn will stimulate thyroid growth and the development of goiter. To avoid these problems, regular dosage adjustment or combination with synthetic thyroid hormones is necessary as soon as the euthyroid state is obtained.

Antithyroid drugs may also suppress lymphocytic infiltration into the thyroid and thereby directly modulate the basic disorder of autoimmune hyperthyroidism (SEDA-6, 364) (SEDA-9, 344). Propylthiouracil, but not the thioimidazoles, also inhibits the conversion of thyroxine to its more active derivative triiodothyronine. This effect is significant during high-dose treatment, and propylthiouracil may therefore be preferred if a more rapid onset of action is desired, for example thyrotoxic crisis, although clear experimental proof of the advantageous effect is still lacking (3).

The antithyroid drugs are well absorbed from the intestinal tract, but the half-life of propylthiouracil is much shorter (2 hours) than that of the thioimidazoles (6 hours). However, the in vivo half-life may be longer due to accumulation and retention of the drug in the thyroid gland (4).

General adverse effects

Both the thiouracils and the thioimidazoles can produce hypothyroidism and goiter. Most of their other adverse effects are allergic rather than toxic. The overall frequency of untoward reactions is 2–14%, but severe reactions occur in less than 1% of patients. Some data suggest that the thioimidazoles have a lower incidence of adverse effects than the thiouracils (5). An association between the dosage of thionamide and the development of untoward reactions has been found in several studies (6). It has therefore been proposed that the initial dose of carbimazole should not exceed 30 mg/day and that of propylthiouracil 300 mg/day (SEDA-17, 474). Allergic reactions include drug fever, lymphadenopathy, arthralgia, agranulocytosis, thrombocytopenia, leukopenia, and skin reactions (1,7). In view of the in vivo conversion of carbimazole to thiamazole, cross-allergy between the two compounds can be expected and has been observed. Cross-allergy between thiouracil and thioimidazoles is rare, but a few cases have been reported. Tumor-inducing effects have not been reported.

Organs and Systems

Nervous system

Neuritis has been described in patients taking thiamazole (8,9).

Sensory systems

Eyes

In contrast to ^{131}I, antithyroid drugs do not seem to increase the risk of new or worse exophthalmos in patients with Graves' disease (10,11).

Retrobulbar neuritis has been reported in a patient taking thiamazole (12).

Ears

Ototoxicity has rarely been attributed to antithyroid drugs (13). In one case progressive bilateral sensorineural hearing loss attributed to propylthiouracil was associated with myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) (14).

Taste

Taste disturbance has been described in patients taking antithyroid drugs and has been attributed to zinc deficiency (SEDA-7, 398) (SEDA-11, 357).

Endocrine

Overtreatment with antithyroid drugs can cause hypothyroidism (15,16).

Metabolism

A specific form of hypoglycemia occurs in Hirata disease, a rare autoimmune syndrome in which large amounts of insulin can be released from autoantibodies. In a Japanese series of 197 cases, 43% of the patients had been taking medications before diagnosis: thiamazole for Graves' disease, alpha-mercaptopropionyl glycine for cataracts, liver disease, or rheumatoid arthritis, or glutathione for liver disease, all of which are sulfhydryl compounds. After these drugs were withdrawn, the hypoglycemic attacks subsided (17).

Hematologic

Neutropenia, agranulocytosis, aplastic anemia, and thrombocytopenia are the most important adverse effects of antithyroid drugs.

Neutropenia and agranulocytosis

There are two different types of neutropenia due to antithyroid drugs: a mild dose-related reduction in leukocyte count and a true allergic agranulocytosis (SEDA-10, 368) (18).

Allergic agranulocytosis

DoTS classification (BMJ 2003;327:1222–5)
Dose-relation: hypersusceptibility effect
Time-course: intermediate
Susceptibility factors: genetic (HLA DRB1*08032 allele); age (over 40); sex (women)

Severe agranulocytosis (or more rarely pancytopenia) is usually only observed during the first few months of therapy. Since agranulocytosis can develop very rapidly, periodic leukocyte counts are usually considered to be of little help, but it has been suggested that weekly leukocyte counts during the first month of treatment can detect presymptomatic cases and allow more rapid intervention

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(19). Patients should therefore be warned to seek immediate medical help if a fever or sore throat develops during antithyroid drug treatment. If the drug is withdrawn immediately recovery is the rule, but fatal cases have also been reported (20,21). In one case agranulocytosis unusually occurred after a second exposure to the drug, in this case propylthiouracil (22).

Frequency

The risk of agranulocytosis has been estimated during several surveys. A large European–Israeli study (23) showed a risk of about 3 per 10 000 users. However, the mortality in this survey was small (one in 45 cases) (SEDA-13, 376). In two hospital surveys of agranulocytosis (24,25) there was an increased risk in women aged over 40 years and when the dose of thiamazole (thiamazole) was more than 40 mg/day. In vitro lymphocyte testing can confirm the sensitization of the immune system to the antithyroid drugs and can occasionally indicate cross-sensitivity between thiamazole and propylthiouracil (SEDA-8, 372) (SEDA-9, 344). In a Japanese study, using an adverse drug reactions database, 24 of 91 cases of presumed drug-induced leukopenia were associated with thiamazole (26). The estimated overall risk was 3 per 10 000, largely in the first 3 months (RR = 182, 95% CI = 74, 449).

Mechanism

Laboratory studies have provided insights into the immune mechanisms underlying the hematological complications of antithyroid drugs (27). Sera from five patients taking thiamazole who presented with immune thrombocytopenia showed antibodies to the platelet cell adhesion molecule-1. Similar antibodies were present in the serum of a patient with carbimazole-associated neutropenia and mild thrombocytopenia, together with antibodies to the neutrophil-specific Fc gamma receptor IIIb (28). Antibodies against the rhesus component of erythrocyte proteins have also been described in patients with carbimazole-associated anemia, leading to the conclusion that carbimazole can induce cell lineage-specific drug-dependent antibodies that cause cytopenias.

In 24 patients with Graves' disease with thiamazole-induced agranulocytosis, 68 patients with Graves' disease without agranulocytosis, and 525 healthy controls, there was a strong positive association of the HLA DRB1*08032 allele with susceptibility to methimazole-induced agranulocytosis, suggesting that cellular autoimmunity may be involved in its development (29).

Time-course

In 18 cases of antithyroid drug-induced agranulocytosis in China, previous evidence that most cases occur early in treatment (2–12 weeks in 17 of 18 cases) and in those taking high doses was confirmed (30). This series also confirmed that agranulocytosis develops abruptly, arguing against routine monitoring of white cell count, and that fever and sore throat are the earliest symptoms.

Management

The treatment of this complication is controversial. There have been at least 15 reports of the use of granulocyte colony stimulating factor (G-CSF) in severe cases (granulocyte count under 100×10^6/l) of thionamide-induced agranulocytosis with the objective of shortening the period of neutropenia and hence the risk of infection (31). In another case the use of G-CSF in thionamide-induced agranulocytosis was associated with a number of iatrogenic complications (31). A review of treatment with G-CSF has shown that the average time to recovery from agranulocytosis is 8.2 days, not obviously different from the reported range of 7–14 days without the drug, leading the authors to argue against its routine use in afebrile patients, even in the face of a severe reduction in granulocyte count.

In 24 patients with Graves' disease who developed agranulocytosis during antithyroid drug therapy, randomized to receive G-CSF ($n = 14$) or an antibiotic only, recovery time (defined as the number of days required for neutrophil counts to exceed 0.5×10^9/l) did not differ between the treatments in patients with moderate or severe agranulocytosis, arguing against its routine use (32). These conclusions have been supported by retrospective data from a further 12 patients, four of whom received G-CSF (33). Again, there was no significant difference in terms of the speed of hematological recovery, the number of days of antibiotic treatment, or the duration of hospitalization.

In a retrospective cohort study of 90 cases of drug-induced agranulocytosis in Strasbourg, antithyroid drugs were implicated in 23% of cases, second only to antibiotics in terms of frequency of prescription in the affected cohort (34). The clinical presentation was often severe and included isolated fever (41% of cases), septicemia or septic shock (31%), and pneumonia (10%). The outcome was favorable in 98% of cases. All the patients were treated with broad-spectrum antibiotics and 42 received hemopoietic growth factors; in those given growth factors the mean durations for hematological recovery, antibiotic therapy, and hospitalization were significantly reduced. While patient selection may have contributed to these findings, they do suggest a useful role for such growth factors in supporting patients with this potentially life-threatening complication of thionamide therapy.

Aplastic anemia

Aplastic anemia due to antithyroid drugs is very rare and has been said to occur as an adverse effect of thionamide therapy with about one-tenth of the frequency of agranulocytosis.

- Aplastic anemia developed in a 58-year-old woman taking thiamazole for the third time; she responded well to drug withdrawal and treatment with human granulocyte colony stimulating factor (35).
- A 16-year-old girl who had taken thiamazole for 1 month (30 mg/day) developed a sore throat and dysphagia and had pancytopenia (36). Instead of the expected picture of hypoplasia, bone marrow aspiration showed replacement with plasma cells, a finding suggestive of myeloma and representing a picture not previously described in this context. Thiamazole was withdrawn and she was given antibiotics, dexamethasone, and granulocyte colony stimulating factor. Her

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hematology and bone marrow findings normalized within days and she was well at follow-up at 24 months.

There have been anecdotal reports of the use of G-CSF in cases of thionamide-induced agranulocytosis (37). In a retrospective review (38) the outcomes in 10 severe cases treated with G-CSF and in 10 treated without were reviewed. The time to hematological recovery, the duration of antibiotic use, and the duration of hospitalization were all shorter in those treated with G-CSF, although there were no deaths in either group. These findings are in accord with the results of other non-randomized studies of the use of G-CSF in drug-induced agranulocytosis, but conflict with the results of one randomized study that showed no benefit (32). The latest findings must therefore be interpreted with caution, although it is notable that this study was confined to those with severe suppression of leukocyte counts and clinical evidence of infection.

Liver

Both carbimazole and propylthiouracil can cause liver damage, sometimes as part of a hypersensitivity reaction associated with pruritus, rash, fever, and arthralgia. Severe liver injury is believed to be rare, with only 20 reported cases up to 1993 (39). In contrast, subclinical hepatic dysfunction, characterized by a rise in hepatic enzymes, may be common and does not necessitate drug withdrawal in the absence of symptoms (39).

Of 14 cases of suspected drug-induced liver disease presenting to a gastroenterology department over a 3-year period, one was thought to be related to thiamazole, with a hepatitic pattern of liver function tests in a 39-year-old woman 6 days after the start of therapy; recovery was swift and complete (40). Delayed cholestatic hepatitis without antineutrophil cytoplasmic antibodies has been reported (41), and there have been fatal cases of hepatic necrosis (SEDA-21, 438) (7).

In a retrospective review of 497 patients taking propylthiouracil for hyperthyroidism, clinically overt hepatitis developed in six patients at 12–49 days after starting the drug (42). Jaundice and itching were present in five, fever in two, rash in two, and arthralgia in one. Serum bilirubin, alanine transaminase, and alkaline phosphatase were increased in five, four, and six patients respectively. The type of hepatic injury was cholestatic in three, hepatocellular in one, and mixed in two. There were no differences in age, sex, drug dose, or serum thyroid hormone concentrations at time of diagnosis in those with hepatic injury compared with those without. Liver function normalized in all patients at 16–145 days after withdrawal of propylthiouracil. In addition to these cases of overt liver injury, 14% of the cohort had mild asymptomatic liver enzyme rises at a mean of 75 days after the start of treatment.

The reported incidence of liver injury in this report is higher (at 1.2%) than in previous reports, perhaps reflecting patient selection or ethnic differences in study populations. An association with propylthiouracil in the six cases described was supported by the temporal association with the start of therapy and recovery after withdrawal. This complication is likely to be a hypersusceptibility reaction, given the lack of dose association within the therapeutic range, the unpredictable occurrence, and an association with symptoms of hypersensitivity. The findings of this retrospective study do not indicate the need for regular monitoring of liver function tests in those taking propylthiouracil, but they do highlight the need to consider drug toxicity if overt hepatic injury develops, especially early in the course of propylthiouracil therapy.

Pancreas

Acute pancreatitis and parotitis without antineutrophil cytoplasmic antibodies has been attributed to thiamazole (43).

- A 33-year-old woman developed acute pancreatitis together with mild cholestatic hepatitis and erythema nodosum 1 month after starting carbimazole for Graves' disease; rechallenge with a single dose of carbimazole (10 mg) 7 days after initial recovery led to a further episode of acute pancreatitis, from which she recovered (44).

The temporal association with carbimazole therapy, the response to rechallenge, and the absence of other causes of acute pancreatitis suggested that the drug was causative in this case.

Urinary tract

Chronic tubulointerstitial nephritis with renal insufficiency without antineutrophil cytoplasmic antibodies has been attributed to propylthiouracil (45).

Skin

The most common reaction to antithyroid drugs is a benign skin rash or pruritus without rash. Although such a reaction is usually not serious and can even disappear during continuous treatment, it nevertheless indicates an allergic reaction and requires withdrawal of therapy. Thiouracil can then be replaced by thioimidazoles, but allergy to both products can occasionally occur.

Sexual function

Sexual precocity associated with hypothyroidism has been reported after long-term treatment of children with propylthiouracil, and may reflect relative overdosage (46).

Immunologic

Antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis is a well-described complication, particularly with propylthiouracil and to a lesser extent with carbimazole, and has been most often described in patients with Graves' disease. The possible drug-induced causes of ANCA-positive vasculitis with high titers of antimyeloperoxidase antibodies in 30 new patients have been reviewed (47). The findings illustrated that this type of vasculitis is a predominantly drug-induced disorder. Only 12 of the 30 cases were not related to a drug. The most frequently implicated drug was hydralazine ($n = 10$); the remainder involved propylthiouracil ($n = 3$), penicillamine ($n = 2$), allopurinol ($n = 2$), and sulfasalazine ($n = 1$).

Cutaneous vasculitis is often a feature of such cases, although severe systemic manifestations often also occur.

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Two patients with propylthiouracil hypersensitivity presented with skin manifestations but also had renal, rheumatological, and hematological features (48). A review of the literature showed that the symptoms and signs in patients with ANCA-associated thionamide-induced vasculitis are diverse. Acral purpuric skin lesions are typically seen; recognition of these classical clinical features may allow early diagnosis and limit associated morbidity and the requirement for other therapies, particularly immunosuppression. Several other reports have described cases of MPO-ANCA-positive cases of vasculitis presenting in a variety of ways in both adults and children treated with propylthiouracil (49–52).

There have been reports of propylthiouracil-induced ANCA-associated small vessel vasculitis (53,54), crescentic glomerulonephritis (55), and Wegener's granulomatosis (56). More common, however, may be a condition termed "antithyroid arthritis syndrome," which is a transient migratory polyarthritis occurring within 2 months of starting thionamides and resolving within 4 weeks of stopping therapy (57).

ANCA-positive vasculitis in a patient with multinodular goiter has been described, together with a review of the clinical features in a further 26 cases (58). Renal involvement, typically with crescentic or necrotizing glomerulonephritis on biopsy, and arthralgia were the most common manifestations. A few cases of diffuse proliferative lupus nephritis associated with ANCAs have been reported (SEDA-20, 394). Other cases of ANCA-associated disease in patients have been reported, including subjects presenting with neutrophilic dermatosis (59), pyoderma gangrenosum, secondary sterile pyoarthrosis (60), and purpura fulminans (61). Small vessel vasculitis leading to pulmonary alveolar hemorrhage and crescentic glomerulonephritis has also been described (61).

In 61 patients with Graves' hyperthyroidism, 32 of whom were taking propylthiouracil and 29 methimazole, there was a higher prevalence of antimyeloperoxidase ANCAs in those taking propylthiouracil than in those taking thiamazole (25 versus 3.4%) (62). There were no significant differences in age, duration of therapy, or drug dosage in those who developed antimyeloperoxidase ANCAs compared with those who did not. Two ANCA-positive patients in this study developed rheumatoid arthritis or membranous glomerulonephritis, but none developed classical ANCA-associated vasculitis.

There have been reports of antimyeloperoxidase ANCAs associated with diffuse pulmonary alveolar hemorrhage (63), IgA nephropathy (64), and drug-induced neutropenia (65) in patients who had Graves' hyperthyroidism taking propylthiouracil. Investigation using serum from the last of these patients implicated a complement-mediated mechanism. In another case ANCAs developed in two of three monozygotic triplets, both of whom had Graves' disease treated with propylthiouracil, supporting a genetic role in the development of this drug complication (66).

Long-term outcomes in a series of seven children who developed myeloperoxidase-specific ANCA-positive necrotizing crescentic glomerulonephritis associated with propylthiouracil were studied in Japan (67). Three had nephritis alone and four had extrarenal vasculitis. All had taken glucocorticoids, some with additional drugs, and all had achieved remission. None had progressed to end-stage renal insufficiency or death during a mean period of follow-up of 58 months. This apparently benign course, albeit with a relatively short period of follow-up, is similar to that seen in adult patients with this drug complication and implies a better prognosis than in subjects with non-drug-induced ANCA-positive vasculitic disease.

The size of this problem has been addressed using serum samples from 117 patients with Graves' disease treated either with propylthiouracil or thiamazole, and from untreated patients (68). Myeloperoxidase ANCA and proteinase-3 antineutrophil cytoplasmic antibodies (PR3-ANCA) were tested by enzyme-linked immunosorbent assay. Myeloperoxidase ANCA was negative in all untreated patients and patients taking thiamazole, but positive in 21 of 56 patients taking propylthiouracil. In contrast, PR3-ANCA was not detected in any patient in the study. The proportion of patients who were positive for myeloperoxidase ANCA increased with the duration of propylthiouracil therapy. Of the 21 patients who were positive for myeloperoxidase ANCA, 12 had no symptoms, but nine complained of myalgia, arthralgia, or coryza-like symptoms after the appearance of the antibody; none had abnormal urinary findings. These findings suggest a specific association between propylthiouracil therapy and the development of myeloperoxidase ANCA in patients with Graves' disease.

ANCA-positive microscopic polyangiitis has been associated with propylthiouracil, with a fatal outcome despite treatment with glucocorticoids and cyclophosphamide (69). Another patient presented atypically with acute pericarditis 10 months after starting to take propylthiouracil 100 mg tds (70). Another patient developed ANCA-negative leukocytoclastic vasculitis of the skin (71).

Several cases of "collagen-like" or "lupus-like" disease have been reported (joint pain, skin rash, and positive antinuclear antibodies) during treatment with either propylthiouracil or thiamazole (SEDA-8, 372) (SEDA-10, 368). Some cases of general vasculitis can be fatal, although high-dose glucocorticoid therapy can be helpful (72).

Other reports have described serious immunological complications of propylthiouracil in the absence of ANCA, including interstitial nephritis and fatal Stevens–Johnson syndrome in a 90-year-old woman treated for 5 weeks (73) and disseminated intravascular coagulation and vasculitis 2 weeks after the introduction of propylthiouracil in a 42-year-old woman (74). The latter was treated successfully by drug withdrawal and intravenous methylprednisolone.

Second-Generation Effects

Pregnancy

Both the thiouracils and thioimidazoles readily cross the placenta and can cause fetal hypothyroidism, resulting in a slight delay in neurological or bone maturation. Various degrees of goiter have also been observed, even to the extent of severe tracheal compression and death. Antithyroid drug dosage should therefore be reduced to the minimum required to maintain a euthyroid state without supplementation of levothyroxine (75).

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Teratogenicity

Aplasia cutis congenita has been attributed to carbimazole, or its active metabolite thiamazole, given during early pregnancy (SEDA-14, 367) (76), and a review revealed 16 cases of solitary skin defects associated with intrauterine exposure to thiamazole (76). The defects can be restricted to a region of the body or can be widespread. Several causes have been documented, including chromosomal abnormalities (for example trisomy 13) and single gene mutations, such as Goltz syndrome. A few cases are believed to result from in utero exposure to teratogens, including thionamides. To date, 16 cases of solitary skin defects associated with intrauterine exposure to thiamazole have been reported. Additional cases of aplasia cutis congenita in thionamide-exposed infants associated with other congenital abnormalities, such as bilateral atresia of the nasal choana, esophageal atresia, imperforate anus, and cardiovascular defects have also been reported (76).

Additional cases of aplasia cutis congenita in thionamide-exposed infants associated with other congenital abnormalities, such as choanal atresia, esophageal atresia, imperforate anus, and cardiovascular defects, were also reviewed. This pattern of abnormalities has previously led to the term "methimazole [thiamazole] embryopathy" (77).

- A 3-year-old child, whose mother had been treated for Graves' hyperthyroidism with thiamazole throughout pregnancy, had two scalp lesions and other abnormalities of tissues of ectodermal origin, including dystrophic nails and syndactyly.

The authors suggested that a history of in utero exposure to thiamazole should be sought in all children with aplasia cutis congenita, as well as other ectodermal tissue abnormalities, to allow better definition of the "methimazole embryopathy." However, cautious interpretation of the literature is required, given the small number of thiamazole-associated cases of aplasia cutis congenita compared with the widespread prescription of this drug in pregnant women with hyperthyroidism. On the other hand, the absence of an apparent association with the use of the alternative thionamide, propylthiouracil, argues in favor of using the latter in pregnant patients.

In a prospective study in 241 women referred to a teratology service because of exposure to thiamazole during pregnancy, congenital abnormalities were compared with those found in offspring of 1089 controls referred because of exposure to non-teratogenic drugs or radiography (77). There were no statistically significant differences between the two groups in terms of major abnormalities, gestational age at delivery, neonatal weight, or head circumference, but among the thiamazole-exposed infants two had a major malformation consistent with "methimazole embryopathy." One had choanal atresia (exposed at 4–7 gestational weeks) and the other had esophageal atresia (exposed at 0–16 gestational weeks) (78). These are very rare malformations, and the number of cases in the cohort was insufficient to reach statistical significance, so the possibility of a chance association with thiamazole exposure cannot be excluded. These cases do, however, lend support to the view that thiamazole may be teratogenic, although thyrotoxicosis itself may be the associated factor. Until further data are available, treatment of thyrotoxicosis with propylthiouracil may be preferable in women who are planning a pregnancy.

- Scalp atresia has been described in an infant whose mother had taken carbimazole in a high dose (60 mg/day) during the first 12 weeks of pregnancy and propylthiouracil thereafter (79). The infant had other dysmorphic features (a flat face, low-set ears, upper lip retraction, and a low-set fifth finger) in addition to transient hypothyroidism.
- Choanal atresia has been described in an infant whose mother presented in early pregnancy with Graves' hyperthyroidism and who took carbimazole in doses up to 60 mg/day in the first trimester (80). She was also clinically and biochemically severely hyperthyroid at this time.

Propylthiouracil crosses the placenta as readily as the thioimidazoles, but the rare and probably real association between thioimidazoles and fetal anomalies makes the thioimidazoles less attractive first-line alternatives (81–83). When propylthiouracil is used cautiously in minimal amounts and with frequent dose adjustments, it is probably the safest form of treatment of hyperthyroidism during pregnancy (SEDA-8, 373) (SEDA-11, 357).

Fetotoxicity

Neonatal hypothyroidism has been reported after maternal use of antithyroid drugs (84,85). Transient neonatal hyperthyroidism in a female child born to a mother who had been treated with potassium iodide and carbimazole during pregnancy was followed by sexual precocity (86).

Lactation

The antithyroid drugs appear in human milk, and breastfeeding has therefore been considered contraindicated during such treatment. However, the amount of drug transferred in human milk is too small to affect thyroid function in the breastfed infant (87,88).

Susceptibility Factors

The antithyroid drugs should not be used in patients with a large intrathoracic goiter, which can further increase in size (89).

In severe hepatic disease, the dosages of antithyroid drugs should be very cautiously determined.

Drug Administration

Drug dosage regimens

There are two general patterns of use of antithyroid drugs: monotherapy with progressive reduction in dosage during recovery from hyperthyroidism and a higher dosage of antithyroid drugs complemented by thyroid replacement therapy to avoid hypothyroidism. There is no convincing evidence for a better short-term or long-term control of Graves' disease with either form of therapy, but combination therapy followed by monotherapy with levothyroxine increased the remission rate

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substantially. The administration of levothyroxine during antithyroid drug treatment reduces both the production of antibodies to TSH receptors and the frequency of recurrence of hyperthyroidism (90). During combination therapy with propylthiouracil and levothyroxine in normal therapeutic doses the inhibition of the conversion of T4 to T3 is of no importance. A single daily dose of antithyroid drugs cannot completely block iodine organification but can nevertheless control most cases of hyperthyroidism. Such therapy can therefore be used in some patients to improve compliance. The duration of therapy is also controversial, but a more prolonged duration of therapy is usually associated with a higher remission rate (SEDA-12, 354).

Drug overdose

Acute overdose of 13 g of propylthiouracil had no serious adverse effects, except for a temporary reduction in serum triiodothyronine (SEDA-5, 382).

Drug–Drug Interactions

Iodine

Since thionamides block the organification of iodine and incorporation of iodine into iodotyrosines, they inhibit the uptake of ^{131}I used therapeutically in hyperthyroidism. For this reason, thionamides are generally withdrawn for a period of up to a week before ^{131}I therapy is planned, and re-introduction is similarly delayed until several days after ^{131}I therapy. The effect of treatment with either thiamazole or propylthiouracil before ^{131}I has been studied retrospectively (91), the thionamide being withdrawn 5–55 days before ^{131}I administration. The findings confirmed the view that propylthiouracil, but not thiamazole, significantly reduced the cure rate after ^{131}I compared with that found in subjects not pretreated with propylthiouracil, and that discontinuation for 4 months was required for the cure rates to be similar. These findings highlight the fact that thionamides cause a relative "radio-resistance," and prolonged drug withdrawal or an increased dose of ^{131}I may be required to produce an acceptable cure rate.

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Thiopental sodium

See also General anesthetics

General Information

Thiopental sodium, a barbiturate and one of the oldest anesthetics, still remains the first-choice induction drug for cesarean section (1).

Organs and Systems

Cardiovascular

Cardiovascular depression is a well-documented complication of thiopental. However, the plasma concentrations necessary to produce loss of corneal reflex and trapezius muscle tone were only minimally depressant to the heart

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(2). Problems can in any case be reduced or avoided by proper fluid administration before induction of anesthesia, as well as by cautious choice of dosage and administration in patients with uncompensated cardiac failure.

Surgery for cerebral artery aneurysms sometimes requires cardiopulmonary bypass and deep hypothermic circulatory arrest if they are to be operated on safely. During such bypass procedures patients with such aneurysms often receive large doses of thiopental, in the hope of providing additional cerebral protection. In 42 non-cardiac patients thiopental loading to the point of suppressing electroencephalographic bursts caused only negligible cardiac impairment and did not impede withdrawal of cardiopulmonary bypass; however, there were no data on patients with cardiac disease (3).

Sensory systems

Patients sometimes notice a taste of onions or garlic before they lose consciousness; the incidence of this sensation was 42% in 113 adult patients (4).

Endocrine

Thiopental given for cerebral protection after cardiac arrest to patients in intensive care caused altered thyroid function (5). Five patients received 5 mg/kg as a bolus followed by 3 mg/kg/hour for 48–72 hours. Free T3 concentrations fell dramatically in three of them and remained near normal in the other two. In those in whom T3 concentrations fell they returned to near normal on withdrawal of thiopental. Reverse T3 concentrations increased in these patients. Although the study was not controlled, the authors speculated that thiopental causes conversion of T3 to reverse T3, and that this can intensify the sick euthyroid syndrome that can occur after cardiac arrest.

Electrolyte balance

Life-threatening hyperkalemia after therapeutic barbiturate coma with thiopental has been described in three patients; it was fatal in one (6). All the episodes occurred after the withdrawal of thiopental. Hypokalemia that is resistant to potassium replacement is common during thiopental coma and clinicians may choose to manage asymptomatic barbiturate-induced hypokalemia expectantly in an attempt to avoid rebound hyperkalemia.

Hematologic

- Immune hemolytic anemia with acute renal insufficiency has been reported in a 55-year-old patient after induction of anesthesia with thiopental 450 mg; a specific thiopental antibody was detected; the patient recovered fully (7).

Gastrointestinal

Vomiting is common during many types of anesthesia (8). By reducing upper esophageal sphincter pressure during induction, thiopental can contribute to this complication (9).

Skin

Fixed drug eruptions after thiopental administration have been reported (10).

Immunologic

Anaphylaxis has been repeatedly reported after thiopental (SED-10, 190) (SED-11, 211), but is rare, with an estimated incidence of one in 30 000.

- An extreme example reported in 1993 involved a 55-year-old obese man with no history of allergy to penicillin, who had on earlier occasions received sodium thiopental without reaction; on this occasion he stopped breathing and had severe bronchial constriction and vascular collapse requiring prolonged resuscitation and mechanical ventilation (11).

Second-Generation Effects

Fetotoxicity

A mother with eclampsia was unsuccessfully treated with diazepam, total dose 120 mg, and phenytoin 750 mg; she received thiopental and had an emergency cesarean section at 33 weeks gestation (12). The infant was unresponsive and floppy, requiring intubation and ventilation. At 10 hours after delivery a flumazenil infusion was begun; the baby responded with facial and limb movements within 30 seconds, resumed spontaneous ventilation, and was extubated 4 hours later. She was maintained on a slowly reducing flumazenil infusion over the next 4 days while the benzodiazepines were metabolized.

Susceptibility Factors

In one case, undetected congenital methemoglobinemia caused severe cyanosis during anesthesia with thiopental 500 mg and nitrous oxide 50% (13).

The use of thiopental or any other barbiturate is contraindicated in acute intermittent porphyria; a progressive neuropathy can occur and can be fatal.

Drug Administration

Drug administration route

Inadvertent injection into extravascular tissues causes pain, swelling, and possibly tissue necrosis. Pain on intravenous injection has been noted in 10% of patients (14). Intra-arterial injection causes vascular spasm and can cause gangrene of a distal extremity.

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Thioridazine

See also Neuroleptic drugs

General Information

Thioridazine is a phenothiazine neuroleptic drug.

Organs and Systems

Cardiovascular

Cardiac dysrhythmias

Thioridazine has been associated with QT interval prolongation (1,2) and several cases of torsade de pointes have been reported (3,4).

Two types of T wave changes have also been described after treatment with thioridazine: type I (with rounded, flat, or notched T waves) and type II (with biphasic T waves) (5).

On July 7, 2000, doctors and pharmacists in the USA were notified about the addition of extensive new safety warnings, including a boxed warning to the professional product label for the neuroleptic drug thioridazine (Melleril, Novartis Pharmaceuticals). The text of the new boxed warning read: "Melleril (thioridazine) has been shown to prolong the QT_c interval in a dose-related manner, and drugs with this potential, including Melleril, have been associated with torsade de pointes-type arrhythmias and sudden death. Due to its potential for significant, possibly life-threatening, prodysrhythmic effects, Melleril should be reserved for use in the treatment of patients with schizophrenia who fail to show an acceptable response to adequate courses of treatment with other neuroleptic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs."

The new labelling changes were based primarily on the FDA's review of three published studies. The first of these showed increased blood concentrations of thioridazine in patients with a genetic defect, resulting in the slow inactivation of debrisoquine (6). In this study, 19 healthy subjects (six poor and 13 extensive metabolizers of debrisoquine) took a single oral dose of thioridazine 25 mg. The poor metabolizers reached higher blood concentrations of thioridazine 2.4 times more quickly than the extensive metabolizers. There was a 4.5-fold increase in the systemic availability of the drug in the poor metabolizers, in whom thioridazine remained in the blood twice as long. The second study showed dose-related prolongation of the QT_c interval from 388 (range 370–406) to 411 (range 397–425) ms 4 hours after an oral dose of thioridazine 50 mg (7). The average maximal increase was 23 ms. This change was statistically greater than that for either placebo or thioridazine 10 mg. In the third study the effect of the selective serotonin re-uptake inhibitor (SSRI) fluvoxamine, 25 mg bd for 1 week, on thioridazine blood concentrations was evaluated in 10 hospitalized men with schizophrenia (8). The concentrations of thioridazine and its two active breakdown products, mesoridazine and sulforidazine, increased three-fold after the administration of fluvoxamine.

The possibility that some of the cardiac effects of thioridazine may be related to these metabolites as well as the parent compound has been explored (5,9) but needs further investigation.

Several regulatory measures (www.mca.gov.uk) (www.medsafe.govt.nz) (www.imb.ie) (www.hc-sc.gc.ca) (www.bpfk.org) (www.fda.gov) (www.who.int/medicines) have been adopted in different countries with regard to thioridazine.

The role of cardiac effects of neuroleptic drugs in sudden death is controversial (SEDA-18, 47) (SEDA-20, 26) (SEDA-20, 36). There may be multiple non-cardiac causes, including asphyxia, convulsions, or hyperpyrexia. However, some cases of sudden death in apparently young healthy individuals may be directly attributable to cardiac dysrhythmias after treatment with thioridazine or chlorpromazine (10), and from time to time, cases of sudden death are reported (SEDA-20, 36) (SEDA-22, 46), including four cases in which thioridazine in standard doses was implicated as the cause of death or as a contributing factor (11).

- A 68-year-old man with a 5-year history of Alzheimer's disease was treated with thioridazine 25 mg tds because of violent outbursts (12). His other drugs, temazepam 10–30 mg at night, carbamazepine 100 mg bd for neuropathic pain, and droperidol 5–10 mg as required, were unaltered. Five days later, he was found dead, having been in his usual condition 2 hours before. Post-mortem examination showed stenosis of the

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coronary arteries, but no coronary thrombosis, myocardial infarction, or other significant pathology. The certified cause of death was cardiac dysrhythmia due to ischemic heart disease. Thioridazine was considered as a possible contributing factor.

Hypotension

Hypotension is the most commonly observed cardiovascular adverse effect of neuroleptic drugs, particularly after administration of those that are also potent alpha-adrenoceptor antagonists, such as thioridazine. A central mechanism involving the vasomotor regulatory center may also contribute to the lowering of blood pressure.

Severe orthostatic hypotension has been observed in older volunteers ($n = 14$; aged 65–77 years) who participated in a randomized, double-blind, three-period, crossover study, in which they took single oral doses of thioridazine (25 mg), remoxipride (50 mg), or placebo (13). Compared with placebo, there were falls in supine and erect systolic and diastolic blood pressures after thioridazine, but not remoxipride. Standing systolic blood pressures fell by a maximum of 26 mmHg. There were similar falls in blood pressure in young volunteers.

Hypotension has been reported in two other elderly patients who were taking thioridazine (14). The patients, men aged 68 and 70 years, had traumatic brain injury and were taking oral thioridazine 25 mg/day for agitation. A few days later they developed mild hypotension (100/50 and 100/60 mmHg respectively).

Ear, nose, throat

Epistaxis has been reported in three patients with hypertension taking thioridazine (15).

Nervous system

In one study, there was no significant difference in serum concentrations of thioridazine, its metabolites, or radioreceptor activity between patients with and without tardive dyskinesia (16).

Sensory systems

Acute toxic effects of thioridazine on the eyes include nyctalopia, blurred vision, and dyschromatopsia, which typically become evident after 2–8 weeks of dosages over 800 mg/day.

Lens and corneal deposits

Deposits in the lens or cornea probably result from melanin-drug complex deposition and are best detected by slit-lamp examination. These deposits are probably dose- and time-related, since they generally occur only after years of treatment. Fortunately, they are in large part reversible, but if undetected they may progress to interfere with vision. They are most often reported with chlorpromazine or thioridazine and can occur in association with pigmentary changes in the skin.

Pigmentary retinopathy

Pigmentary retinopathy, which can seriously impair vision, is specifically associated with thioridazine, and has occurred more often with high and prolonged dosage (for example 1200–1800 mg/day for weeks to months) (17), although in one case the daily dose was only 700 mg (18). Large-scale surveys have confirmed the relative safety of dosages up to 800 mg/day (19); at any dosage, however, any complaint of brownish discoloration of vision or impaired dark adaptation requires immediate evaluation.

- A 28-year-old woman with a long history of psychiatric problems was taking fluoxetine, diazepam, methylphenidate, and thioridazine 800 mg qds (17). Fluorescein angiography showed confluent areas of punctate hyperfluorescence, consistent with diffuse retinal pigment epithelial alteration secondary to acute thioridazine toxic effects.
- A 51-year-old woman with a long history of psychiatric problems and no family history of hereditary retinal degeneration had reduced vision in both eyes for several years while she was taking thioridazine 300 mg/day and chlorpromazine 600 mg/day (20). She had large patches of atrophy outside the arcades and within the macula, with sparing of foveal pigmentation; there were diffuse increases in hyperpigmentation in the peripheries of both eyes, and hypopigmented or unpigmented retinal epithelium.

The authors thought that the pigmentary changes were probably due to thioridazine, as adverse effects on the retina are rare with chlorpromazine.

Fluid balance

Water intoxication has been reported during treatment with thioridazine and may be due to its pronounced anticholinergic properties and/or direct stimulation of the hypothalamic thirst center (21).

Hematologic

The Committee on Safety of Medicines and the erstwhile Medicines Control Agency in the UK received 999 reports of hemopoietic disorders related to neuroleptic drugs between 1963 and 1996; there were 65 deaths (22). There were 182 reports of agranulocytosis; chlorpromazine and thioridazine were associated with the highest number of deaths—27 of 56 and nine of 24 respectively.

Sexual function

Thioridazine and other highly anticholinergic drugs can cause male sexual dysfunction, including impotence and retrograde ejaculation (23,24). A case of thioridazine-induced inhibition of female orgasm has also been reported (25).

Death

A retrospective case-control study conducted by the same group who first identified a relation effect of pimozide and thioridazine on the QT interval (SEDA-24, 55) has been published (26). The study was carried out in five large psychiatric hospitals in England and included all inpatients with sudden unexplained death over a period of 12 years (1984–1995) and two controls for each case from the same hospital matched for age, sex, and duration of inpatient stay, one of whom was also matched for

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primary psychiatric diagnosis. The patients were aged 18–74 years, and there were 69 cases and 132 controls (63 matched for diagnosis). Since the presence of an organic disorder was significantly associated with sudden unexpected death, this was adjusted for. Sudden death was associated with hypertension, ischemic heart disease, and thioridazine therapy (OR = 5.3; 95% CI = 1.7, 15). Among the limitations of this study was the incompleteness of the records, which often lacked information about important risk factors, including underlying cardiac disease, smoking, or the use of alcohol or illicit drugs; furthermore, the low rate of post-mortem examination raises the possibility that some of the deaths were from causes other than cardiac dysrhythmias, although other causes were found in only three of 30 cases when a post-mortem examination was done.

Long-Term Effects

Drug withdrawal

The consequences of restricting the indications for thioridazine in patients with learning disabilities have been a matter of reflection (27). Of 155 psychiatric patients, 18 were regularly taking thioridazine at the time of the directive; all stopped taking it and seven had moderate or severe difficulties during the following 3 months and one developed probable neuroleptic malignant syndrome 4 weeks after switching to an alternative drug. According to the authors, regulatory authorities should take account of the adverse consequences of drug changes when making judgements about the benefit-to-harm balance, especially in vulnerable patients, such as those with learning disabilities and psychiatric illnesses.

Other consequences of banning thioridazine have been reported in a rural general practice in Ireland, in which 29 of 40 GPs responded to a questionnaire and 17 reported management problems and adverse reactions (28). There was increased service demand, as 44% of the GPs described up to a 50% increase in referrals to the mental health service; although most of the GPs (67%) reported satisfaction with alternative agents, 37% described adverse effects associated with the alternative agents. It seems reasonable that directives should incorporate the flexibility required to accommodate the needs of patients who are already successfully stabilized on these drugs.

Susceptibility Factors

Genetic factors

The higher serum concentrations in poor CYP2D6 metabolizers are associated with an increased risk of thioridazine toxicity (11).

Age

Age increases the risk of thioridazine toxicity (11).

Sex

Female sex increases the risk of thioridazine toxicity (11).

Other features of the patient

Several factors increase the risk of thioridazine toxicity: pre-existing cardiac disease, hypokalemia, a glucose load, alcohol, exercise, and concomitant therapy with tricyclic antidepressants, erythromycin, co-trimoxazole, cisapride, risperidone, hydroxyzine, and drugs that inhibit CYP2D6 (some SSRIs, fluphenazine, and perphenazine) (11).

Drug–Drug Interactions

Beta-adrenoceptor antagonists

Lipophilic beta-adrenoceptor antagonists are metabolized to varying degrees by oxidation by liver microsomal cytochrome P450 (for example propranolol by CYP1A2 and CYP2D6 and metoprolol by CYP2D6). They can therefore reduce the clearance and increase the steady-state plasma concentrations of other drugs that undergo similar metabolism, potentiating their effects. Drugs that interact in this way include thioridazine (29).

The combination of propranolol or pindolol with thioridazine should be avoided if possible (30).

Diuretics

Diuretic-induced hypokalemia can potentiate thioridazine-induced cardiotoxicity (10).

Fluvoxamine

Fluvoxamine increased thioridazine concentrations threefold (8) in 10 patients with schizophrenia taking steady-state thioridazine who were given fluvoxamine (25 mg bd) for 1 week. Fluvoxamine interferes with the metabolism of thioridazine, probably via CYP2C19 and/or CYP1A2.

Lithium

Several cases of neurotoxicity in patients taking lithium and thioridazine have been reported. The cause of this interaction has not been resolved, but lithium seems compatible with all neuroleptic drugs, although patients should be carefully monitored (31–33).

Methylphenidate

Multiple involuntary movements, consisting of jaw grinding, oral dyskinesias, bilateral hand rolling, vermiform tongue movements, and bilateral choreiform movements of the digits, have been described in an 11-year-old boy taking thioridazine 150 mg/day and methylphenidate 10 mg bd (34). The methylphenidate was discontinued and within 4 weeks his movement disorder had completely disappeared.

Quinidine

Concurrent administration of quinidine with neuroleptic drugs, particularly thioridazine, can cause myocardial depression (10).

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Thiurams

General Information

Thiurams are a group of chemicals that have been in commercial use since the 1920s. Their main uses are as accelerators and vulcanizing agents during rubber processing and as fungicides on seeds and plants.

Organs and Systems

Immunologic

Allergic contact dermatitis following exposure to thiuram compounds in rubber products, such as disposable rubber gloves, is well recognized (1).

- A 49-year-old man developed acute pruritic dermatitis of the hand, which settled quickly with oral glucocorticoids and antibiotics (2). Six months later he developed a similar eruption, which became more widespread, involving the trunk and limbs. He had no personal or family history of atopy, and had no known allergies or previous

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history of skin disease. He had a widespread dry eczematous eruption, most marked in exposed areas. The rash had developed soon after he had handled plants that had been sprayed with a fungicide. The safety data sheet for this product indicated that it contained 80% thiuram. Full blood count and serum electrolytes were normal, and autoantibodies and a porphyrin screen were negative. Biopsy of the lesion showed significantly sun-damaged skin with a superficial perivascular chronic inflammatory infiltrate, confluent surface parakeratosis, and epidermal acanthosis with moderate spongiosis, consistent with a spongiotic dermatitis. He denied any previous contact with rubber gloves in both occupational and social settings, and had not had dermatitis before. He was treated with sun protection, topical and oral glucocorticoids, and a moisturizer. He had no further contact with the fungicide and the eruption resolved completely. He was advised to avoid all thiuram products, including rubber products and fungicides, in the future. Despite this, he subsequently developed one recurrence of hand dermatitis when he again used rubber gloves for protection at work.

Three Chinese national servicemen developed an itchy postauricular rash (3). None had a history of atopy and all three reported prior use of rubberized spectacle retainers as a curved pliable extension to the posterior ends of the earpieces of their spectacles, to stabilize them while undergoing rigorous military physical training. They were all patch-tested with the National Skin Center standard series and were positive to thiuram mix and the rubberized spectacle retainers. They were treated with topical corticosteroids and were advised to stop wearing their rubberized spectacle retainers.

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Thorotrast

General Information

Thorotrast (thorium dioxide), which has a radioactive half-life of about 400 years, was widely used in 1928–55 as an X-ray contrast medium.

By 1933 Thorotrast had been shown to induce malignancies in rats. It was prohibited in various countries from 1936 onwards, but continued to be used in some parts of the world for another three decades. Its late effects continue to be reported. Thorotrast deposits are predominantly localized in the liver and reticuloendothelial system; the major late effects have been portal fibrosis, malignant liver tumors, and myeloproliferative disorders, but granulomatous, fibrotic, and malignant changes in many other organs have been described. Thorotrast is the most potent human leukemogen yet identified. The risk of a fatal blood dyscrasia after Thorotrast is very much greater than after external radiotherapy, and the latent period (20 years) is very much longer than after external irradiation (5–7 years).

In a 1993 follow-up study in Denmark of mortality among 999 patients who had received Thorotrast between 1935 and 1947 the excess mortality was explained in part by diseases known to be induced by Thorotrast, such as cirrhosis and cancer of the liver and leukemias and other hematological disorders; it was suggested that non-specific effects induced by the alpha particles emitted by Thorotrast may have contributed to this excess mortality (1).

Organs and Systems

Hematologic

The retention of Thorotrast in the bone marrow leads to the development of leukemia. Chromosome aberrations in bone marrow cells occurred at a high frequency in Japanese patients who had been given Thorotrast (2).

Liver

Various liver neoplasms due to chronic alpha-ray irradiation have been attributed to Thorotrast, most notably hepatocellular carcinoma, angiosarcoma, and cholangiocarcinoma. Multiple Thorotrast-induced primary tumors are rare but have been reported in a report from Japan (3).

- An 86-year-old man received intravenous Thorotrast to investigate a bullet wound to his shoulder in 1939. He presented in 1993 with jaundice, leading to liver failure and death. Autopsy showed four separate carcinomas: a cholangiocarcinoma in the left lobe of the liver, a well-differentiated tubular carcinoma of the antrum of the stomach, an invasive squamous carcinoma of the lung, and a well-differentiated adenocarcinoma of the ampulla of Vater. There were multiple mutations in the p53 tumor suppression gene caused by chronic alpha-ray irradiation.
- A 74-year-old developed nausea, night sweats, generalized fatigue, and weight loss (4). Thorotrast cerebral angiography had been performed 55 years before. Computed tomography of the abdomen showed areas of calcification within the liver, spleen, and peripancreatic lymph nodes, and there was a mass in the liver. Liver biopsy confirmed cholangiocarcinoma.

There has also been a report of nodular regenerative hyperplasia of the liver associated with previous Thorotrast administration (5).

Susceptibility Factors

Genetic factors

Several studies have shown that mutations of the TP53 gene (formerly known as p53) are important in the genesis of Thorotrast-induced tumors (6–8).

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Thrombolytic agents

General Information

The major thrombolytic agents are:

- streptokinase
- urokinase
- anistreplase (anisoylated plasminogen streptokinase activator complex or APSAC)
- pro-urokinase (single-chain urokinase-type plasminogen activator or scu-PA)
- alteplase (recombinant tissue plasminogen activator or rt-PA)
- reteplase (r-PA: a deletion mutant of rt-PA)
- tenecteplase (a triple combination mutant variant of alteplase).

Although their pharmacodynamic properties do not differ significantly, some characteristics, as a result of their origin or mode of action, explain specific differences in their adverse effects and pharmacokinetics.

General adverse effects

Hemorrhage is the major risk of thrombolytic drugs; there are some differences in risks between the various agents, and certain susceptibility factors can be identified. Transient hypotensive reactions have been described with all thrombolytic agents, but they are in principle reversible. Hypersensitivity reactions are most often seen in patients who have been treated with compounds derived from cultures of streptococci (streptokinase and anistreplase). Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Transient hypotension can occur after thrombolysis, and the incidence after infusion of streptokinase in myocardial infarction is high. Hypotension has been related to plasminemia, which leads to bradykinin generation from kallikrein, activation of complement, and potentially endothelial prostacyclin release (1). During treatment of myocardial infarction, some other mechanisms may explain hypotension: vagal reflexes precipitated by posterior wall reperfusion (2) and left ventricular dysfunction associated with the infarct process. Hypotension occurs shortly after the start of infusion and can be accompanied by bradycardia, flushing, and anxiety. It is reversible if fluids are given and the infusion temporarily stopped (1); vasopressors may be needed. The magnitude of this hypotensive reaction is directly related to the rate of infusion of streptokinase. The incidence of such reactions does not seem to be affected by premedication with glucocorticoids. Like streptokinase, anistreplase can also cause transient hypotension (3). Alteplase seems to be associated with a lower risk of hypotension than streptokinase or anistreplase. In the ISIS-3 trial, the incidences of profound hypotension necessitating drug therapy were: 6.8% with streptokinase, 7.2% with anistreplase, and 4.3% with alteplase (4).

Embolic detachment of components of venous or mural thrombi can sometimes be involved in the development of thromboembolism or cholesterol embolization. There is a 10% incidence of pulmonary embolism during thrombolysis, lethal in 0–5% (5), pointing to the risk of detachment of white components of venous thrombi, especially if large veins, such as those in the pelvis, are involved (6). However, the risk has not been proven to exceed that reported in patients treated with heparin and/or oral anticoagulants.

Cholesterol embolization is thought to occur after removal of mural thrombi covering atherosclerotic plaques leading to direct exposure of the soft lipid-laden core of these plaques to the arterial circulation. The contents of the soft lipid core, including crystallized cholesterol, shower the downstream circulation. Cholesterol crystals are impervious to dissolution or lysis and they lodge in small arterioles, causing obstruction. Cholesterol embolization shortly after thrombolytic treatment is characterized by livedo reticularis or multiple necrotic lesions of the skin of both legs (7) but can also be associated with

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lower limb ischemia, gangrene, visceral ischemia, or pseudovasculitis (8). Cholesterol embolization is difficult to diagnose, and may therefore be more common than suspected. It can cause acute renal insufficiency (9), and renal biopsy shows acute tubular necrosis, in some instances with arteriolar clefts representing cholesterol crystals (10).

Reperfusion dysrhythmias can occur when thrombolytic drugs are used to treat myocardial infarction. The most common is transient ventricular tachycardia. However, controlled trials have failed to show an increase in serious ventricular dysrhythmias, the incidence of ventricular fibrillation being actually reduced by thrombolytic therapy in myocardial infarction (11).

- A coronary artery aneurysm occurred in a 49-year-old man 1 month after successful percutaneous transluminal coronary recanalization with streptokinase (12).

Phlebitis at the site of infusion of streptokinase has been reported.

Respiratory

Streptokinase can cause acute bronchospasm, sometimes fatal (13), or dyspnea.

Nervous system

Guillain–Barré syndrome has been reported in patients who were treated with streptokinase and anistreplase (14–18). As streptokinase and anistreplase are derived from streptococci, an immunological reaction is thought to have been responsible.

Sensory systems

Iritis and uveitis have been reported with streptokinase (19,20).

Hematologic

Hemorrhage is the major risk of the use of thrombolytic agents and can result from the lysis of thrombi at other sites where hemostasis is required. Hemostatic incompetence related to thrombolysis is also related to reductions in circulating fibrinogen and factors V and VIII and to the generation of fibrin and fibrinogen degradation products with anticoagulant properties. The most serious complication is intracranial hemorrhage, which has a high mortality (60% in the GUSTO-1 trial) and a high rate of severe disability (up to one-third of patients) (21).

In trials of intravenous streptokinase without angiography, hemorrhagic complications, apart from local venepuncture sites, were reported in about 4% of patients, with an absolute excess over controls of about 3% (11). Major bleeding, defined by transfusion requirements, occurred in only 0.5% of patients, and cerebral hemorrhage was seen in only 0.1%. In the AIMS trial, all hemorrhagic complications during hospitalization were 14% with anistreplase and 4.1% with placebo (22). Transfusion was required in 0.8% in each group. The absolute excess of cerebral hemorrhage rates was 0.3% with anistreplase compared with placebo. In the ASSET trial, the absolute excess risks of minor and major hemorrhagic complications with alteplase were respectively 6 and 0.9%. The excess risk of hemorrhagic strokes was 0.2% (23).

Several large clinical trials have compared alteplase and anistreplase with streptokinase. No clear-cut differences in severe or life-threatening bleeding were observed in these studies.

However, in interpreting these results, the role of adjunctive antithrombotic therapy must also be taken into account, since it can increase the risk of hemorrhage (24). In most of the trials, heparin-treated patients had significantly more major bleeding, and in the ISIS-3 trial, the incidence of cerebral hemorrhage was significantly increased by heparin (4). In the TIMI II B trial (25) in patients with unstable angina, the addition of a low dose of alteplase (0.8 mg/kg) to aspirin and heparin was associated with a 2.4% incidence of major hemorrhagic events (versus 0.6% with placebo) and a 0.55% incidence of intracranial hemorrhage (no such event occurring with placebo).

A study in general practice has suggested that intracranial hemorrhage during thrombolytic therapy for myocardial infarction may be more frequent than in clinical trials (10). The authors analysed the data accumulated in a US large registry called NRMI 2 (1484 hospitals, 71 073 patients having received alteplase in the initial treatment of acute myocardial infarction). The overall incidence of intracranial hemorrhage was 0.95%. This is a higher incidence than has been reported in clinical trials, and may have been due to the stringent enrolment criteria.

The susceptibility factors for intracranial hemorrhage have also been examined (10). The main factors were:

- advanced age; compared with patients under 65, the odds ratio was 2.71 (CI = 2.18, 3.37) for individuals aged 65–74 years and as high as 4.34 (3.45, 5.45) for patients aged 75 years or more
- female sex
- black ethnicity
- a history of stroke
- hypertension (an increased risk in patients with a systolic blood pressure of 140 mmHg or more and/or a diastolic of 100 mmHg or more)
- the dose of alteplase.

Because of the significant correlation with age and a previous history of stroke, it is now widely considered that in patients over 75 years with a history of stroke other therapies, such as primary coronary angioplasty, must be considered. As reported in the GUSTO-1 trial, patients with very high systolic blood pressures have an increased risk of death or disabling stroke (26), and the pulse pressure has been reported to be the clearest predictor of the blood pressure as regards the risk of intracranial hemorrhage (27).

The risk of major bleeding during thrombolytic therapy is undoubtedly a real problem, but it has to be considered against the background of the underlying mortality risk and the absolute benefit likely to be achieved in patients with acute myocardial infarction (28). This equation is fundamental in older patients, who have the highest mortality risk after myocardial infarction and thus the most to gain from thrombolysis (29).

Some reports of serious adverse consequences in patients with aortic dissection or pericarditis that mimic

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clinical or electrocardiographic myocardial infarction have emphasized the necessity for accurate diagnosis before thrombolysis is instituted in patients with chest pain or with atypical electrocardiographic changes (30).

The incidence of hemorrhagic complications is particularly high when high doses of streptokinase are used in the treatment of deep venous thrombosis (31). High-dose streptokinase thrombolysis for 2–3 days with an initial dose of 500 000 units followed by a maintenance dose of 3 600 000 U/day led to a 10% rate of major spontaneous bleeding complications, with a fatal outcome in four older subjects out of the total of 98 patients. The fatality rate of bleeding caused by streptokinase amounts to 7% in patients with peripheral arterial occlusion, but is much lower in younger patients with venous thromboembolism.

Secondary intraventricular hemorrhage has been described in two patients who received intraventricular tissue-type plasminogen activator to hasten the lysis of intraventricular hemorrhage (32).

Hemolysis after intravenous streptokinase is rare (33).

Transient lymphopenia, possibly related to immunological destruction of T-helper cells by streptokinase, has been described (34).

Platelet aggregation due to an antibody-mediated reaction has been suggested as a cause of streptokinase-enhanced coronary thrombosis in patients with a specific type of antistreptokinase antibodies (35).

Thrombocytopenia has been described after thrombolytic therapy but it is most probably multifactorial, since patients generally also received intravenous heparin (36).

Disseminated intravascular coagulation has been reported with urokinase (37).

Liver

There were no differences in the activities of serum transaminases, lactate dehydrogenase, or creatine kinase in patients with myocardial infarction who received an 18-hour infusion of urokinase compared with patients who received glucose alone (38), but subacute alterations of liver function tests have been described with streptokinase and anistreplase (39). Unexplained increases in transaminase activities have been reported in almost 25% of patients treated with streptokinase (40). In view of the greater prominence of liver dysfunction with streptokinase than with alteplase it could be wiser to choose alteplase rather than streptokinase in patients with previous impaired hepatic function (41).

A few cases of liver dysfunction with or without jaundice have been reported with streptokinase and urokinase (42–45). Jaundice with hepatic cytolysis can occur after allergic reactions to streptokinase (46).

Urinary tract

Hematuria and proteinuria can occur without alteration of immunohistochemical features, suggesting a non-immune cause, such as a direct effect on the glomeruli or a reflection of the hypocoagulable state.

- Acute interstitial nephritis associated with cholesterol embolization during streptokinase therapy has been reported (47). In this case, cholesterol clefts were found in the preglomerular and interlobular arterioles. Cholesterol embolization can cause acute renal insufficiency (9), and renal biopsy shows acute tubular necrosis with, in some instances, arteriolar clefts representing cholesterol crystals (10).

Immunologic

Since streptokinase is a natural product of cultures of streptococci and therefore has similar antigenic properties, most of the population have anti-streptokinase antibodies. These antibodies may explain both the allergic reactions that can occur and resistance to the drug, which occurs in some cases. Within 3 or 4 days of streptokinase administration, the titer of neutralizing antibodies has become sufficient to inactivate the usual doses. Persistence of these antibodies is observed in up to 80% of patients 1 year after treatment and in about 50% of patients after 2–4 years (48,49). If streptokinase has to be re-administered within 8 months of previous exposure, the neutralizing effects of plasma should be taken into account and the dose of streptokinase should be adjusted to overcome these effects (50). However, the extent to which streptokinase antibodies decline after earlier exposure to streptokinase is controversial, and persistently raised titers are found in a large proportion of patients (51). For this reason, an alternative thrombolytic agent should be recommended in patients who have already received streptokinase. In addition, it appears that allergic reactions occur more often when streptokinase is reused (52).

Anistreplase, a compound consisting of streptokinase and anisoylated plasminogen, can also cause allergic reactions, but has a longer half-life, allowing intravenous administration in a relatively short interval of time.

Urokinase is extracted from human urine or prepared from cultures of fetal kidney cells and does not seem to cause allergic reactions.

Pro-urokinase, alteplase, reteplase, and tenecteplase, which are recombinant products, also appear to be free from allergic reactions. Pro-urokinase and alteplase have short half-lives (3–8 minutes) and require continuous infusion administration, which may in some cases be an advantage as it allows rapid surgical intervention when necessary (53). Reteplase and tenecteplase have substantially longer half-lives, allowing bolus administration.

The incidence of acute generalized allergic reactions in patients treated with streptokinase or anistreplase was originally reported to be high, but with the introduction of more highly purified forms of streptokinase the figure has fallen to 1–5%. The most common manifestations of non-anaphylactic reactions to streptokinase or anistreplase are skin rashes and pyrexia. However, anaphylactic shock with streptokinase is also well known, although rare; it occurred in 0.1% of the patients in the GISSI trial (54). Life-threatening angioedema has been described with streptokinase (55,56) and with alteplase (57–59). Skin rashes are seen especially with streptokinase, but rarely, if ever, with alteplase.

Several cases of low back pain associated with streptokinase or anistreplase injections for acute myocardial infarction have been described, with rapid resolution once the streptokinase was stopped (60,61). It is

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presumed that the mechanism is allergic, since no such report has been published with alteplase (62).

Streptokinase is regularly reported to have induced an immune complex syndrome, characterized by plasmacytosis, often severe, and accompanied by fever and the development of hemolytic anemia, occurring as early as the first week after the start of treatment; in some cases, temporary alterations in renal function also occur (63).

Vasculitis has been rarely described after streptokinase or anistreplase (64–67), but not after urokinase or alteplase. It is characterized by lymphocyte infiltration and deposition of immune complexes, fibrin, and complement in the skin microvasculature.

Other patients have the typical picture of serum sickness, sometimes associated with acute renal insufficiency (68–70) or of Henoch–Schönlein purpura (71) with a purpuric rash, joint and abdominal pains, and sometimes hematuria (72).

Adult respiratory distress syndromes and multisystem organ failure have been reported with streptokinase and anistreplase (73–76); the timing of the onset of symptoms and the antibody profile in one case suggested an immunological response (74).

The clinical efficacy of thrombolytic drugs such as streptokinase does not appear to be compromised by the occurrence of allergic reactions, according to data from GUSTO-1 (77).

There have been three reports of anaphylactoid reactions, mostly orolingual angioedema, after therapy of acute ischemic stroke with alteplase.

- In one patient there was marked edema of the lip about 45 minutes after a bolus dose of alteplase; it subsided within 2 hours without any intervention (78).

Of 105 consecutive patients treated with alteplase for acute ischemic stroke, 2 developed anaphylactoid reactions (79). The first had a rash and extensive bilateral swelling of the tongue, epiglottis, and uvula, requiring intubation. The second developed unilateral swelling of the tongue and lips without a rash or hypotension.

In 230 patients treated with alteplase for acute ischemic stroke, there were two cases of orolingual angioedema (80). Both presented with localized symptoms only, symmetrical in one and asymmetrical in the other.

IgE-associated anaphylactic reactions can also occur.

- A 70-year-old woman was treated with intravenous alteplase for thrombolysis in acute ischemic stroke and 30 minutes later had acute sinus tachycardia and hypotension, followed by cyanosis and loss of consciousness (81). Serum samples analysed by ELISA were positive for IgE antibodies to alteplase.

Such reactions are very rare; there have been four reported cases in over 1 million administrations.

Body temperature

Pyrexia can occur after the initial dose of streptokinase (82). Concurrent administration of glucocorticoids does not prevent it completely. A marked rise in body temperature with chills can be accompanied by hypotension, abdominal pain (particularly low back pain), and very occasionally mild psychotic reactions.

Second-Generation Effects

Pregnancy

Pregnancy is not considered to be incompatible with treatment with thrombolytic agents. No adverse effects on the fetus have been reported. Nevertheless, the possibility cannot be excluded that placental separation and uterine bleeding will occur. Only minimal amounts of streptokinase cross the placenta, and these are not sufficient to cause fibrinolysis in the fetus (83). Although the passage of streptokinase is blocked by the placenta, streptokinase antibodies do cross to the fetus (84). This passive sensitization would have clinical importance only if the neonate required streptokinase therapy. Septicemia during treatment with streptokinase has been also described (85). These different hazards may preclude the use of thrombolytic drugs during pregnancy but in acute life-threatening problems, efficacy has to be weighed up against the risk of adverse effects.

Drug Administration

Drug administration route

Pleural space infection is an important cause of sepsis, and traditional treatment comprises drainage of the pleural space, either through chest tubes or surgically, combined with antibiotics. Attempts at closed drainage with a chest tube often fail, owing to the development of loculations within the fluid and the high viscosity of the infected fluid. This problem has led to the use of intrapleural fibrinolytic drugs to improve drainage, hasten resolution of infection, and reduce the need for surgical intervention. At first, the use of intrapleural streptokinase and streptodornase was complicated by frequent allergic reactions, but with the availability of purified forms of streptokinase and urokinase these agents have been widely used for intrapleural fibrinolysis and this has been reviewed.

Streptokinase

Several reports, predominantly in the form of case series, have described the use of intrapleural streptokinase for complicated pleural effusions (86–92). The dose of streptokinase used varies, but is usually around 250 000 IU instilled once or twice daily, with tube clamping for 2–4 hours, repeated over several days. Local adverse effects are rare, but transient chest pain at the time of instillation occurs occasionally (93).

There are occasional reports of fever attributed to the intrapleural instillation of streptokinase (86,88), but the most important adverse event due to intrapleural streptokinase is systemic fibrinolysis. In many of the case series cited above, simple tests of clotting activity were performed before and after treatment and there were no significant changes. However, in 1984, a case report described major hemorrhage in one patient after the intrapleural use of streptokinase 500 000 IU, with tube clamping for 6 hours (94). Within 12 hours this patient developed a generalized coagulopathy, with features of disseminated intravascular coagulation. Following this report, in a carefully designed study, the systemic fibrinolytic effects of one dose (250 000 IU) and multiple doses of intrapleural streptokinase (250 000 IU bd for 3 days) were examined in

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healthy subjects (95). There were no physiological or statistical changes in any coagulation indices after intrapleural streptokinase. This suggests that the hemorrhage seen in the 1984 case report was probably not related to streptokinase, but was perhaps a complication of underlying sepsis.

Although intrapleural streptokinase does not cause systemic fibrinolytic effects, there can be local fibrinolytic effects. In a case series describing the use of intrapleural streptokinase or urokinase in 26 patients, one developed major "oozing" from rib fractures sustained 1 month before therapy (89). This local bleeding required two thoracotomies. It is not clear from the report if streptokinase or urokinase was used in this patient, but streptokinase was used in most of patients in this series. Furthermore, the dose used was also not clear, with streptokinase doses of 100 000–750 000 IU.

In 1998, major local hemorrhage after the use of intrapleural streptokinase was described in two patients (96). One patient had undergone mitral valve replacement 6 weeks before and collapsed after 2 days of standard intrapleural streptokinase, with hemorrhage into the chest. The second had undergone a mitral valve replacement 9 months before intrapleural streptokinase and collapsed with bleeding into the chest after 3 days. Both patients recovered, but the authors felt that recent cardiac surgery presented a contraindication to the use of intrapleural fibrinolytic drugs. It is not clear from this report if these two patients were taking oral anticoagulants, such as aspirin or warfarin, which may have confounded these findings. Another report of local hemorrhage has recently been published (97). The patient died after the instillation of intrapleural streptokinase for presumed empyema; autopsy showed an unsuspected abdominal aortic dissection with extension of blood clot into the thoracic cavity. These reports suggest that intrapleural streptokinase should be used with caution when there has been prior surgery or trauma involving the thorax.

Another potential adverse event associated with the use of intrapleural streptokinase is the development of antistreptokinase antibodies. These antibodies have been documented after intravenous streptokinase and can cause serious adverse events with re-exposure to streptokinase or can limit the efficacy of streptokinase in myocardial revascularization.

Urokinase

Urokinase has also been widely used intrapleurally for fibrinolysis, in doses of 40 000–250 000 IU and is as effective as streptokinase (98–101). Furthermore, urokinase is not antigenic and does not produce febrile reactions. As with streptokinase, transient chest pain at the time of instillation has occasionally been reported. These considerations have led some authors to prefer urokinase to streptokinase for intrapleural therapy, but urokinase is about twice as expensive and there is also more published experience with streptokinase.

Drug–Drug Interactions

Diltiazem

Clinical and experimental data suggested a possible increase of hemorrhage risk during thrombolytic therapy with alteplase in combination with diltiazem (102).

Heparin

The combination of thrombolytic agents with an anticoagulant and/or aspirin has been said to be life-threatening. An excess of major bleeding episodes with combined subcutaneous heparin and streptokinase or alteplase treatments (1.0% with heparin versus 0.5% without heparin) has been reported in the International Study Group Trial (103) in patients with suspected acute myocardial infarction.

Interference with Diagnostic Tests

Coagulation tests

Thrombolytic agents interfere with the measurement of plasma fibrinogen and other coagulation tests by promoting continuing fibrinolysis after the specimen is taken; thus, fibrinogen cannot be measured in a sample that is taken less than an hour after the administration of a thrombolytic agent.

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Thrombopoietin

General Information

Thrombopoietin is an endogenous colony-stimulating factor that increases the number of megakaryocyte colonies in bone marrow and also induces maturation of megakaryocytes (1). Recombinant thrombopoietin is indicated for correction of thrombocytopenia, induced by chemotherapy or radiotherapy (1). It has been tested in subcutaneous doses up to 5 micrograms/kg/day, resulting in increased numbers of platelets at 7 days, with a peak count at 17 days (1).

Organs and Systems

Hematologic

Thrombotic complications (deep venous thrombosis, pulmonary embolism, and superficial vein thrombosis) have been described in a few patients receiving thrombopoietin (2). In none was thrombosis related to the platelet count, since none had more than 1000×10^9/l platelets. It could not be determined if the thrombosis was due to thrombopoietin or if an underlying malignancy predisposed these patients to thrombosis (2).

In in vitro studies thrombopoietin stimulates leukemic cell growth, but in clinical studies restimulation of leukemia has not been observed (2).

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Thyroid hormones

General Information

Nomenclature

In this monograph the following terms are used:

- thyroxine (T4): the endogenous hormone;
- triiodothyronine (T3): the endogenous hormone;
- levothyroxine (rINN) and dextrothyroxine (rINN): the stereoisomers of thyroxine, as used therapeutically;
- liothyronine (rINN): triiodothyronine, as used therapeutically.

Physiology

The normal adult thyroid gland secretes about 90 micrograms of thyroxine (T4) and less than 10 micrograms of liothyronine (triiodothyronine, T3) per day. Somewhat less than half of the T4 is converted to T3 by several tissues (especially the liver). Most of the daily production of T3 thus comes from peripheral 5′-deiodination of T4 and not by direct glandular secretion. The thyroid hormones are tightly bound (T4 even more than T3) to plasma transport proteins; this explains their prolonged half-lives (about 8 days for T4 and about 1 day for T3). Nuclear receptors for thyroid hormones bind T3 much more efficiently than T4, explaining the more rapid onset of action and greater biological potency of T3. The intestinal absorption and hepatic clearance of orally ingested thyroid hormones also differ. T3 has higher systematic availability than T4, only about 60% of which appears in the peripheral circulation after oral administration (1). However, some formulations provide higher intestinal absorption of T4 (80%) (2). These basic data form the background of optimal thyroid substitution.

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Thyroid hormones are used either to replace the failing function of the thyroid gland (spontaneous or drug-induced) or to suppress the endocrine function of abnormal thyroid tissues (especially non-toxic struma or goiter or after thyroidectomy for thyroid neoplasms). Although there are abnormalities of the peripheral metabolism of thyroid hormones in some forms of undernutrition or overnutrition, thyroid drug therapy cannot be considered a safe way of treating obesity.

Treatment with thyroid hormones therefore poses only a few essential questions: which dosage should be used, which formulation should be chosen, and how can therapy best be monitored so as to avoid short-term and long-term risks.

Uses

Levothyroxine is used as replacement therapy in hypothyroidism and to suppress the production of thyrotrophin (thyroid-stimulating hormone) in patients with thyroid carcinoma.

Dextrothyroxine has been used as a lipid-lowering agent. It significantly lowers the serum cholesterol (3) as does levothyroxine; however, dextrothyroxine has a much smaller hormonal effect on body tissues than levothyroxine. The literature is confusing, since older formulations of dextrothyroxine contained considerable amounts of levothyroxine.

Liothyronine can be used for thyroid substitution, but it has the disadvantage of having a short-lived action and its intestinal absorption can give rise to unusually high post-absorption peaks, causing tachycardia. Moreover, the dosage necessary to obtain euthyroidism is more difficult to evaluate, owing to fluctuations in serum T3 concentrations; furthermore, in patients taking liothyronine, measurements of thyrotrophin are also probably less reliable, since its secretion by the pituitary gland depends more on the extracellular T4 concentration than on the T3 concentration. Therapeutic use of liothyronine is therefore generally only recommended when a more rapid onset of action is necessary, for example when thyroid therapy needs to be interrupted for the administration of ^{131}I in the treatment of thyroid cancer. In myxedematous coma it is controversial whether the therapeutic choice should be liothyronine, or levothyroxine, or a combination (4). Moreover, long-term therapy with liothyronine is more likely to cause secondary osteoporosis than T4.

The drug of choice for thyroid replacement therapy is therefore levothyroxine since it is the natural secretory product of the thyroid, has a long half-life, and is metabolized to T3 in the peripheral tissues.

Doses

The optimal dosage of levothyroxine should be based on repeated measurements of T3 and TSH serum concentrations. The daily recommended dose depends on the aim of the therapy. Thyroid replacement therapy for control of spontaneous or iatrogenic hypothyroidism should aim at a dosage of levothyroxine that maintains TSH concentrations within the low reference range. This will usually be associated with a free T4 concentration in the high reference range and a T3 concentration within the reference range. The mean requirement for such patients is 112 micrograms/day (2) or 1.57 micrograms/kg per day (5). This dose is lower than that recommended previously because of better knowledge of the real production rate of T4, the availability of better pharmaceutical formulations allowing better availability, and especially because of better methods for drug monitoring (SEDA-12, 353) (SEDA-15, 444) (6–8). Patients stabilized on one pharmaceutical formulation should not be switched to another without proper monitoring of thyroid hormones.

When thyroid therapy is used not only to replace deficiency but also to prevent the growth of remnants of a differentiated thyroid carcinoma, a suppressive dosage is used, aiming at T4 concentrations in the high reference range and an undetectable TSH concentration or at least one that is below the lower end of the reference range, as measured by two-sided assays. Such therapy is warranted because of its long-term safety, efficacy, and tolerance, but some additional therapy for osteoporosis prevention should be considered.

As with all forms of long-term therapy, adherence to the prescribed dosage of levothyroxine is not always optimal, and an unwarranted fear of thyroid-induced osteoporosis can add to this lack of adherence. Inadequacy of thyroxine replacement therapy is not always easily recognized. Several patients were reported with clearly inadequate or excessive consumption of levothyroxine despite a correct prescription. All patients had depression, which could be an additional susceptibility factor by promoting lack of adherence, and the resulting hypothyroidism or hyperthyroidism could further aggravate the depression (9).

When replacement therapy is with levothyroxine only, the T4/T3 ratio is increased compared with healthy subjects, suggesting that thyroid secretion of T3 is physiologically important. Animal studies have shown that euthyroidism is not restored in all tissues by levothyroxine alone (10). Mood and neuropsychological function improved in hypothyroid patients when 50 micrograms of thyroxine was replaced by 12.5 micrograms of liothyronine (11).

Several studies have failed to confirm the benefits of combined levothyroxine and liothyronine therapy. Liothyronine given once a day results in non-physiological peak serum concentrations of T3. Modified-release triiodothyronine plus thyroxine can normalize serum biochemistry, but it is not known whether this formulation is superior to levothyroxine alone (12).

In contrast to other protein-bound drugs for which a loading dose is given to achieve rapid steady-state concentrations, a slow and stepwise increase in thyroid hormone replacement therapy is advisable. This is preferred mainly to avoid sudden cardiac adverse effects, especially in older patients with long-standing myxedema. Moreover, since thyroid hormone substitution can change the metabolic clearance of this drug, steady-state concentrations are obtained only after several months (SEDA-6, 363).

General adverse effects

Ingestion of excessive amounts of thyroid hormones can cause symptoms and signs similar to those that result from endogenous overproduction. However, the symptoms and signs are generally relatively trivial in those who take standard doses of levothyroxine replacement therapy,

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although abnormalities have been evident in detailed studies of those who take levothyroxine in doses sufficient to suppress serum TSH (13). The adverse effects can therefore largely be avoided by adjusting the dosage according to the appropriately selected laboratory tests.

The adverse effects essentially comprise the symptoms of hyperthyroidism and include weight loss despite a normal or increased appetite, increased nervousness, tachycardia or dysrhythmias of various types, and increased general metabolism and its symptoms (hyperactivity, sweating, fever, etc.). Allergic reactions to pure thyroid formulations are rare and were first reported as late as 1986. Tumor-inducing effects have been investigated but not confirmed.

Organs and Systems

Cardiovascular

Overdosage of thyroid hormones causes tachycardia or palpitation but can also cause several types of dysrhythmia, for example atrial fibrillation. Evidence from the Framingham population that suppression of serum TSH is a susceptibility factor for atrial fibrillation has heightened concern that subclinical hyperthyroidism secondary to levothyroxine can also cause atrial fibrillation (14). Five women who reported frequent bouts of palpitation were investigated while taking levothyroxine and again after levothyroxine withdrawal (15). There was a clear increase in mean 24-hour heart rate during levothyroxine treatment, as well as an increase in atrial extra beats and the number of episodes of re-entrant atrioventricular nodal tachycardia. Four of these patients had evidence of abnormal conduction pathways, even when they were not taking levothyroxine, as evidenced by a short PR interval, but exacerbation of atrial dysrhythmias in these predisposed subjects is consistent with the view that thyroid hormones increase atrial excitability and may increase the risk of cardiac morbidity, especially if given in doses sufficient to suppress serum TSH.

Pre-existing cardiac disease, always to be suspected in elderly people or after long-standing hypothyroidism, can be severely aggravated by sudden thyroid substitution, resulting in severe angina pectoris, myocardial infarction, or sudden cardiac death (SEDA-13, 375). In such patients, the initial dosage should be low and the stepwise increase should be spaced out over a prolonged period and with careful clinical and cardiographic monitoring (16). In some circumstances, for example three-vessel disease, substitution should be postponed until after coronary bypass surgery (SEDA-6, 363). Cardiac decompensation can also result from the increased circulatory demand induced by thyroid hormone substitution or overtreatment. Long-term treatment with levothyroxine in doses that suppress thyrotrophin can have significant effects on cardiac function and structure, especially in patients with hyperthyroid symptoms (13,17), but large prospective studies are needed to assess cardiovascular risk in these patients.

In two cases of hypothyroidism myocardial infarction occurred at the start of thyroxine therapy in the absence of evidence of significant coronary artery disease (18).

- A 58-year-old man with a previous smoking history and a history of hypertension was severely biochemically hypothyroid (serum TSH 221 mU/l) and was given thyroxine, initially in a low dose (25 micrograms/day), increasing to 100 micrograms/day after 2 weeks. A month later he sustained a subendocardial myocardial infarction associated with only minor abnormalities on coronary angiography.
- A 61-year-old woman with severe hypothyroidism (serum TSH 115 mU/l) had an acute myocardial infarction (but no demonstrable abnormality on coronary angiography) 1 month after a thyroxine dosage increase from 50 to 100 micrograms/day.

Cautious introduction of thyroxine, especially in elderly people and those with severe or long-standing hypothyroidism, is prudent.

Myocardial infarction can also occur during long-term use of levothyroxine.

- A 71-year-old woman who had undergone total thyroidectomy with subsequent irradiation because of follicular carcinoma 3 years before (19). Since then, she had taken oral levothyroxine 0.15 mg and 0.2 mg on alternate days. When latent hypothyroidism became evident despite replacement therapy, the dose of levothyroxine was increased to 0.3 mg/day. Three weeks later, she had formed an acute posterior myocardial infarction, although she had no previous history of coronary artery disease. Subsequent coronary arteriograms revealed no evidence of disease of the major vessels. Myocardial scintigraphy 3 weeks after infarction still showed a persistent perfusion defect.

In the US Coronary Drug Project (20) a formulation of dextrothyroxine with a so-called low levothyroxine content was used. The study had to be terminated because of an excessive number of cardiac deaths and non-fatal infarcts.

Nervous system

Insomnia, psychic stimulation, general nervousness, and tremor are among the hyperthyroid symptoms that result from relative overdosage. Pseudotumor cerebri has incidentally been observed shortly after levothyroxine was given for juvenile hypothyroidism. The headache and bilateral papilledema without focal neurological defects subsequently disappeared even when levothyroxine was continued (21).

Psychological, psychiatric

Several cases of mania have been reported even after dosages of levothyroxine that are usually considered safe (22).

Musculoskeletal

A slipped capital femoral epiphysis has been described during the treatment of hypothyroidism (SEDA-3, 340). Since slipping occurs more often during the pubertal growth spurt, it is advisable to check for the occurrence of this complication during the pubertal period in children taking thyroid treatment.

Prolonged overtreatment with levothyroxine can result in osteopenia (23). Thyroid hormones have a direct effect on bone cells, thereby increasing both bone resorption

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and formation with subsequent mild adaptation of the systemic calciotrophic hormones (24). Increased bone turnover can result in a small deficit during each cycle and therefore finally result in mild osteoporosis. There are no good data regarding the incidence of fracture, but the bone mineral content of several areas known to be at risk of fracture (lumbar spine, forearm, femur) has been measured, mainly in cross-sectional studies, but also in a few prospective studies. During replacement therapy for hypothyroidism a small bone deficit was associated with a prior history of Graves' disease and/or later therapy with dosages of liothyronine or levothyroxine that suppress TSH concentrations (SEDA-16, 471). Since overt hyperthyroidism is associated with bone loss, it is possible that the reduction in bone density reported in some studies of levothyroxine treatment reflects an adverse effect of previous thyrotoxicosis rather than levothyroxine therapy itself (SEDA-17, 473).

In 50 women taking levothyroxine either for primary thyroid failure or for hypothyroidism secondary to radioiodine treatment for hyperthyroidism, there was no difference between the two groups in terms of bone density at the hip or spine and no difference from the reference population (25). In addition, there was no correlation between bone density and circulating thyroid hormone concentrations or duration of levothyroxine replacement. These findings are reassuring, although large studies of fracture risk are required, in view of previous evidence of an adverse effect of levothyroxine on bone mineral density, especially in post-menopausal women (26).

In a meta-analysis of cross-sectional studies suppressive levothyroxine was associated with mild but significant bone loss in postmenopausal women (SEDA-20, 394). The best measure of the effects of prolonged levothyroxine therapy can probably be obtained from bone mineral content in patients treated with suppressive doses of levothyroxine for thyroid carcinoma (Table 1).

Postmenopausal women with intact parathyroid glands on prolonged suppressive levothyroxine therapy may be more susceptible to osteoporosis and should have their bone mineral density measured and/or take preventive osteoporosis therapy. Cautious use of levothyroxine, avoiding overdosage and unnecessary use, is probably safe for bone.

Immunologic

Fever, liver dysfunction, and eosinophilia occurred during liothyronine or levothyroxine treatment of a hypothyroid patient and disappeared after withdrawal of therapy (31). In vitro lymphocyte testing confirmed sensitization for thyroid hormones.

Progressive re-institution of liothyronine subsequently proved possible in this patient without recurrence of hypersensitivity. Liothyronine was considered preferable because of the shorter biological half-life.

Long-Term Effects

Drug abuse

Abuse of thyroid hormones, causing factitious hyperthyroidism, can have adverse effects (32,33), including sudden death, attributed to ventricular fibrillation (34).

Partial empty sella syndrome (pituitary atrophy) has been described in an elite body builder who had abused various hormones, including testosterone, growth hormone, and triiodothyronine 25 micrograms qds for many years (35). He presented with infertility, and investigations showed suppression of serum TSH, a raised serum T3, and a partially empty pituitary sella.

It is likely that in this case long-standing suppression of pituitary function secondary to negative feedback from exogenous hormone ingestion (including liothyronine) resulted in pituitary atrophy.

Tumorigenicity

A possible link between breast cancer in women and thyroid hormone therapy was suggested on the basis of a retrospective study of patients with breast cancer (SEDA-3, 340). A subsequent statistical re-analysis of the original data failed, as did later studies, to confirm such a relation (SEDA-3, 340) (SEDA-4, 294) (36).

Second-Generation Effects

Pregnancy

The transplacental passage of maternal iodothyronines is quantitatively modest, although it might be sufficient to

Table 1 Summary of studies on the effects of thyroid hormones on bone mineralization

Reference	Number and sex (age in years)	Disease	Follow-up period (years)	Femur	Spine	Radius
(27)	7 F 1 M	Primary hypothyroidism; levothyroxine 125 micrograms/day	1	–	–9% per year	
(28)	6 F 4 M	Hypothyroidism (50 years); levothyroxine 135 micrograms/day	1	–7%	–5%	–
(29)	24 M (50)	Primary hypothyroidism (8 years) after ^{131}I	3	NS	NS	NS
(30)	18 F (60)	Hypothyroidism treated for 14 years	2			
		(a) low TSH (levothyroxine 170 micrograms/day)		–1.4% per year	–2.9% per year	–1.2% per year
		(b) normal TSH		–0.3% per year	–1.1% per year	–0.13% per year

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ensure adequate fetal development. Maternal thyroid hormone secretion is markedly increased during pregnancy (by 25–50%); thyroid therapy should therefore be carefully adjusted during pregnancy (37).

Susceptibility Factors

Pre-existing cardiac disease and long-standing hypothyroidism carry serious risks.

Adrenal insufficiency can be associated with hypothyroidism (either by autoimmune destruction or due to hypophyseal disease) and carries the risk of acute Addisonian crisis if thyroid substitution precedes glucocorticoid therapy. The diagnostic problem presented by the fact that a few patients with central hypothyroidism have a moderately increased serum TSH should be kept in mind (38).

Some goitrous patients have autonomous thyroid hormone secretion, which is still within the reference range, but they become hyperthyroid even with relatively small amounts of exogenous thyroid hormones, since the latter accumulate with the endogenous autonomous thyroid secretion.

Rarely severe gastrointestinal disease can reduce the absorption of levothyroxine.

Since levothyroxine is occasionally used in supraphysiological doses to treat euthyroid people with refractory depression, adverse effects in healthy controls ($n = 13$) and patients with refractory depression also taking antidepressants ($n = 13$) have been studied in an 8-week, non-blind study (39). There was a higher rate of discontinuation of levothyroxine in the control subjects than in the patients, because of perceived adverse effects (38% versus 0%), together with a more marked rise in serum free T4 and free T3 in the controls. This suggests that the influence of supraphysiological doses of thyroxine is greater in healthy subjects than in those with psychiatric illness, perhaps reflecting the influence of the illness, or its therapy, on thyroid hormone metabolism in the latter.

Drug Administration

Drug overdose

Inadvertent excessive use of thyroid hormones (for example, by eating ground beef contaminated with thyroid hormones (40), the incorrect use of these drugs for the treatment of obesity (41), excessive thyroid substitution therapy, and factitious use of thyroid hormones for psychiatric reasons (42)) result in mild hyperthyroidism, but serious short-term adverse effects are rare.

Overdosage of levothyroxine causes increased metabolism resulting in increased heat production, with increased sweating and weight loss despite normal or even increased appetite. Accidental or suicidal injection of large amounts of thyroid hormones is exceptional (43). Clinical symptoms do not necessarily correlate well with plasma T4 concentrations and range from anxiety, confusion, or coma to tachycardia, atrial fibrillation, and angina. At least three lethal cases have been reported (SEDA-8, 371).

- A 34-year-old man took 900 tablets of veterinary levothyroxine, a total of 720 mg, and was given 60 g of activated charcoal (44). He became lethargic on days 2 and 3; on day 4 he had vomiting, sweating, and insomnia; on day 5 he became agitated and aggressive and stopped speaking intelligibly; and on day 6 he became combative and confused. He was sweating, mydriatic, hyper-reflexive, and tremulous, with clear lungs and active bowel sounds. He was given activated charcoal, haloperidol, diazepam, and phenobarbital, and had an endotracheal tube inserted. He was rehydrated and given propranolol and diazepam, but remained continuously tachycardic. On day 12 he became afebrile and his tachycardia resolved. Free T4 concentrations ranged from over 130 ng/l on day 6 to 12 ng/l on day 12. By discharge on day 15 he had lost 20 kg in weight, but was clinically euthyroid 2 weeks later.
- Self-induced thyrotoxicosis was associated with a marked rise in circulating free T4 and free T3 concentrations in a pregnant woman with an eating disorder who was abusing both levothyroxine and furosemide (45).

Treatment of thyroid overdosage is not standardized and can include gastric lavage, sedatives, beta-blockers, hydrocortisone, and specific antidysrhythmic drugs. Plasmapheresis (46) and exchange transfusion (47) have been used successfully to treat life-threatening cases. Iodine-containing organic radiographic agents (ipodate) can be effective, since they are potent inhibitors of the peripheral conversion of T4 to T3, but rebound effects can occur (43).

Drug–Drug Interactions

Antacids

Two patients with hypothyroidism taking a fixed dosage of levothyroxine took aluminium hydroxide and magnesium oxide (48). In both cases there was a marked increase in the serum concentration of TSH and low serum T4. After withdrawal of the antacids, TSH again fell. In vitro studies showed a dose-related adsorption of levothyroxine by a combination of aluminium hydroxide, magnesium hydroxide, and magnesium carbonate, but no effect of magnesium oxide alone.

Calcium carbonate

Calcium carbonate can reduce levothyroxine absorption (49).

- A 49-year-old woman, taking levothyroxine 150 micrograms/day and calcium carbonate (three tablets daily) for prevention of osteoporosis, developed symptoms of hypothyroidism and had a raised serum TSH concentration (22 mU/l). She was advised to continue taking the same dose of levothyroxine but to separate her medications. Repeat biochemical testing 8 months later showed a normal serum TSH (3.3 mU/l).
- A 61-year-old woman with hypothyroidism had celiac disease and a history of bowel resection for pancreatic cancer, was euthyroid taking thyroxine 175–188 micrograms/day (50). However, when she simultaneously took calcium carbonate (1250 mg/day) she had a raised serum thyrotropin (TSH) concentration of 41 mU/l. Delaying calcium carbonate ingestion by 4 hours returned her serum TSH concentration to high normal (5.7 mU/l) within a month.

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Because of the possibility that calcium carbonate might impair levothyroxine absorption, another group carried out a prospective study in 20 patients taking stable long-term levothyroxine for hypothyroidism, who were given elemental calcium as calcium carbonate 1200 mg/day, taken with their levothyroxine for 3 months (51). Mean serum concentrations of free thyroxine and total thyroxine were significantly reduced during the calcium treatment period and rose after withdrawal. Mean concentrations of T3 did not change, but serum TSH rose during the calcium period, and 20% of the subjects had a serum TSH concentration above the reference range. The authors also reported the results of an in vitro study of thyroxine binding to calcium, which showed that there is adsorption of thyroxine to calcium at acidic pH. These findings show that calcium salts can have a modest put potentially clinically significant effect on levothyroxine treatment, probably by binding it and reducing its absorption; patients should be advised to separate their medications.

Colestyramine

Colestyramine can reduce thyroxine absorption (52).

Estrogens

Oral estrogens increase circulating concentrations of thyroxine-binding globulin, thereby increasing the bound fraction and reducing the free (bioactive) fraction of circulating thyroxine; this effect does not occur with transdermal estrogens (53). Thus, oral estrogens increase levothyroxine dosage requirements in women with primary hypothyroidism, at least during the first few months after the start of therapy.

Ferrous sulfate

Iron binds thyroxine in vitro (54) and ferrous sulfate can reduce thyroxine absorption (55). This can result in hypothyroidism (54,56). A similar interaction with ferrous fumarate has been described in a patient who took both medications simultaneously (57). Separation of thyroxine from iron may be prudent, since this interaction may reflect the formation of a non-absorbable complex in the gut (54).

Indinavir

Levothyroxine is metabolized in part through the action of glucuronyl transferase, which can be inhibited by some antiretroviral drugs, such as indinavir.

- Clinical and biochemical hyperthyroidism occurred in a 36-year-old woman, after previously stable levothyroxine replacement therapy, when antiretroviral drugs for HIV infection were introduced (58). She was reported to be taking a very large dose of levothyroxine (750 micrograms/day) after partial thyroidectomy for Graves' hyperthyroidism some 6 years before. One month after starting antiretroviral treatment she developed symptoms and signs suggestive of thyroid hormone excess and had markedly raised serum free T4 and free T3 concentrations, with suppression of TSH. The dose of levothyroxine was reduced progressively to 120 micrograms/day, and after about 2 months her thyroid function tests returned to normal.

While this pattern of biochemistry does not exclude transient relapse of Graves' hyperthyroidism (despite the finding of negative TSH receptor antibodies), or a transient thyroiditis, the authors speculated that indinavir (prescribed in this patient together with stavudine and lamivudine) had inhibited the glucuronidation of thyroxine and hence caused a rise in serum thyroid hormone concentrations.

Rifampicin

There was a modest rise in serum TSH concentration when rifampicin was given to a patient previously stabilized on thyroxine replacement (59). Rifampicin is believed to increase the metabolic clearance of both thyroxine and the inactive compound reverse triiodothyronine and in healthy volunteers it reduces circulating concentrations of total and free thyroxine, although in subjects without thyroid disease it has no effect on serum TSH (60).

Monitoring Therapy

Some diseases (liver disease, kidney disease, and malnutrition) interfere with the transport or metabolism of thyroid hormones and thereby alter thyroid function tests.

Several drugs (for example amiodarone, androgens, glucocorticoids, phenytoin, and salicylates) interfere with the transport or metabolism of thyroid hormones and thereby alter thyroid function tests. These have been reviewed (61). In patients taking levothyroxine serum TSH rises after treatment with sertraline (62) and antimalarial prophylaxis with chloroquine and proguanil (SEDA-22, 469).

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Thyrotrophin and thyrotropin

General Information

Thyrotrophin is native thyroid-stimulating hormone. Recombinant human thyrotrophin is called thyrotropin.

Thyrotropin stimulates iodine uptake, and this facilitates the diagnosis and treatment of recurrent disease or metastases in the follow-up of differentiated thyroid cancer. It is used as an alternative to thyroid hormone withdrawal, to avoid symptomatic hypothyroidism (1). Headache and nausea occur in 6–40% of patients after intramuscular administration, but are usually mild and transient (2,3).

The adverse effects of thyrotropin have been reviewed (4).

Organs and Systems

Immunologic

Many years ago bovine thyrotrophin was used for diagnostic purposes and to increase ^{131}I uptake. However, for diagnostic purposes it has been replaced by sensitive TSH assays, and because of antibody development and hypersensitivity reactions it is not used therapeutically. There is no evidence that thyrotropin causes allergic reactions, even after multiple injections (4).

Rapid tumor expansion has been occasionally reported after thyrotropin, including four of 55 patients with central nervous system metastases enrolled in a compassionate use protocol (5). Two patients with locally recurrent papillary carcinoma had tumor growth 12–48 hours after their second injection of recombinant thyrotropin (rTSH); rapid improvement in neck pain, stridor, and dysphonia after glucocorticoids suggested an inflammatory etiology (5). There were no features to suggest an allergic reaction; only one such case has been reported and there are no reports of antibody formation even after repeated dosing (1).

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Tiabendazole

See also Benzimidazoles

General Information

Tiabendazole is a non-carbamate benzimidazole which inhibits cellular enzyme systems specific to some species of helminths. It is active against *Giardia lamblia*, but less effective than albendazole and mebendazole. It was at

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one time the drug of choice against *Strongyloides stercoralis*, both the enteric and tissue forms, but has been superseded by more modern drugs. It is also effective against *Enterobius*, hookworms, and *Trichuris trichiura*. Normally given orally, it is rapidly absorbed, with peak serum concentrations 1–2 hours after ingestion. It is rapidly metabolized and excreted; 40% of the drug and its metabolites are excreted during the first 4 hours and 80% during the first 24 hours. Its main metabolite, 5-hydroxythiabendazole, is inactive.

General adverse effects

Common toxic effects of tiabendazole include nausea, vomiting, and dizziness. Malaise and drowsiness are also common. Liver disorders can occur and are the most serious complications. Most systems can on occasion be affected. Allergic reactions are essentially due to parasite destruction rather than a direct effect of the drug itself. Chills, fever, lymphadenopathy, angioedema, and pruritic rashes all can occur; and treatment should in that case be stopped, since otherwise more serious reactions (for example Stevens–Johnson syndrome) can follow. Tumor-inducing effects have not been reported.

Organs and Systems

Cardiovascular

Bradycardia, hypotension, and syncope can occur with tiabendazole, even to the point of collapse (1).

Nervous system

Somnolence has been described with high doses of tiabendazole rectally or orally, and drowsiness, headache, malaise, and fatigue are common (1). Patients should be warned not to drive or carry out other potentially hazardous pursuits during treatment.

More severe symptoms of neurotoxicity are not unusual and include disorientation, confusional states, feelings of detachment, overt psychosis (2), and possibly epileptiform convulsions (3), although the latter have been observed only in a case of Down syndrome.

Sensory systems

Effects of tiabendazole on vision are not uncommon: abnormal sensations in the eyes, xanthopsia (a yellow tinge to objects), blurred vision, drying of mucous membranes, and sicca syndrome all have been described (4).

Allergic reactions to tiabendazole can cause keratoconjunctivitis sicca as part of Sjögren's syndrome (5).

Tinnitus has been attributed to tiabendazole (6).

Metabolism

Instances of both hypoglycemia and hyperglycemia have been recorded in patients taking tiabendazole.

Hematologic

Marked peripheral eosinophilia has also been described after rectal thiabendazole (7).

Gastrointestinal

Nausea, anorexia, vomiting, abdominal pain, and diarrhea are common and occur in a high proportion of patients taking tiabendazole (8).

Liver

Parenchymal liver damage can occur in patients taking tiabendazole and abnormal liver function tests have been documented (9). There have been well-studied cases of bile duct injury, which can lead to micronodular cirrhosis (10), and a case in which these various forms of liver disorder co-existed and liver transplantation proved necessary (11).

Persistent cholestasis can occur in patients taking tiabendazole (12).

- A 27-year-old patient from Surinam with beta-thalassemia took tiabendazole 1250 mg bd for 2 days for strongyloidiasis (13). One week later she became icteric, with raised total and conjugated bilirubin, alkaline phosphatase, gamma-glutamyltransferase, and transaminases. Tests for antinuclear antibodies, parietal cells antibodies, smooth muscle antibodies, mitochondrial antibodies, hepatitis A, B, C, cytomegalovirus, Epstein–Barr virus, mumps, and measles were negative. Ultrasonography showed normal intrahepatic and extrahepatic bile ducts. Liver biopsy showed intrahepatic cholestasis and a slightly increased infiltrate in the portal areas. One week later she developed a generalized urticarial rash. She had mildly abnormal liver tests for the next 7 years, at which time a liver biopsy showed a slight lymphatic infiltrate in the portal fields, without signs of cirrhosis, chronic hepatitis, or primary biliary cirrhosis.
- A 42-year-old woman, also from Surinam, with beta-thalassemia and non-insulin dependant diabetes mellitus took tiabendazole 1250 mg bd for 2 days for strongyloidiasis (13). Five weeks later she developed general malaise, anorexia, weight loss, icterus, and a tender liver. She had raised total and direct bilirubin, gamma-glutamyltransferase, and alkaline phosphatase, but only marginally raised transaminases. Tests for Hepatitis A, B, and C, cytomegalovirus, and schistosomiasis were negative. Tests for antinuclear antibodies and antibodies against liver cell membranes, smooth muscle, and mitochondria were negative, but there were parietal cell antibodies. Ultrasonography and ERCP showed normal intrahepatic and extrahepatic bile ducts. Liver biopsy showed severe centrally localized cholestasis. A year later all clinical and laboratory abnormalities had disappeared.

In view of these and previous cases of severe cholestasis after tiabendazole and the availability of less toxic equally effective drugs (albendazole or preferably ivermectin), tiabendazole must be considered obsolete in the treatment of strongyloidiasis.

Urinary tract

Crystalluria has been noted in patients taking tiabendazole, sometimes with hematuria (1).

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Tiabendazole can give the urine an asparagus-like smell because of the presence of a mercaptan metabolite of tiabendazole (14).

Skin

Pruritus and skin rashes can occur (15). Much more rarely, toxic epidermal necrolysis has occurred after a total dose of 1800 mg, and Stevens–Johnson syndrome and erythema multiforme have also been reported (16).

Very occasionally a topical form of tiabendazole is used, for example to treat rosacea, and in one such case contact dermatitis aggravated by sunlight occurred as a complication, with positive tests for tiabendazole sensitivity (17).

Musculoskeletal

Tiabendazole can cause severe muscle pain on exercise (18).

Second-Generation Effects

Teratogenicity

There is no firm information on adverse reactions during pregnancy, but animal evidence points to teratogenicity and there have been official warnings against use by pregnant women (19).

Susceptibility Factors

Renal disease

Tiabendazole is metabolized almost completely by the liver, and its active metabolites are substantially excreted by the kidney; the risk of toxicity may therefore be greater in patients with impaired renal function (20).

Hepatic disease

Because tiabendazole is metabolized almost completely by the liver (20), it should be used with caution in hepatic impairment.

Drug–Drug Interactions

Theophylline

Tiabendazole can markedly increase serum concentrations of theophylline, with a prolonged half-life and a reduced clearance rate; concomitant administration of theophylline and thiabendazole resulted in severe nausea and vomiting (21).

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Tiagabine

See also Antiepileptic drugs

General Information

Tiagabine is a nipecotic acid derivative which inhibits GABA re-uptake. It is highly bound to plasma proteins (96%) and is mainly eliminated by CYP3A-mediated oxidation, with a half-life of about 7 hours (1). It is used in add-on treatment of refractory partial seizures. Its adverse effects are mostly on the central nervous system.

In a review of safety data from nearly 3100 patients included in 53 clinical trials, tiagabine had no significant effect on hepatic metabolic processes, serum concentrations of concomitant anticonvulsants, and blood chemistry and hematology tests (2). Allergic reactions, such as skin rashes, were less common with tiagabine than with most other anticonvulsants. Adverse effects were generally mild and affected mainly the central nervous system, the most common being dizziness, weakness, nervousness, tremor, difficulty with concentration and attention, speech disorders, depression, and abdominal pain. About 1% of patients given tiagabine experienced weakness severe enough to cause falls or inability to walk, and some form of weakness occurred in about 9% of patients, especially at high dosages or after stopping a single concomitant enzyme-inducing antiepileptic drug.

The safety of long-term tiagabine has been studied retrospectively in 42 patients with refractory partial epilepsy who took tiagabine for longer than 6 months (3). The most common adverse events were tiredness (56%), headache (46%), dizziness (44%), visual symptoms (blurring, difficulty in focusing, and diplopia; 39%), altered thinking (32%), and tremor (31%). The adverse events profile was comparable among those who had taken tiagabine for 6–12 months, 12–24 months, and more than 24 months.

The use of tiagabine 4–16 mg/day in preventing migraine has been studied in 41 patients who had failed treatment with divalproex sodium because of adverse effects or lack of efficacy (4). There was at least a 50% reduction in the frequency of migraine headaches in 33 patients. There were adverse events in 12 patients, most commonly tiredness; a few patients had weight gain or confusion.

The effects of tiagabine have been studied in a 4-month, single-blind study in 52 children over the age of 2 years with different syndromes of refractory epilepsy (5). Adverse events, mostly mild to moderate, were reported by 39% of the children during the single-blind placebo period and by 83% of the children during tiagabine treatment. The events predominantly affected the nervous system; weakness (19%), nervousness (19%), dizziness (17%), and somnolence (17%) were the most common. One child had hallucinations that responded to dosage reduction. Only three children withdrew because of adverse events.

The efficacy and safety of tiagabine have been assessed in a study with an open screening phase (in which patients were titrated to the optimal tiagabine dose), followed by a double-blind, placebo-controlled, crossover phase (6). Of the 88 patients who entered the double-blind phase, seizure frequency was significantly reduced in 44, and there was an over 50% reduction of partial seizures in 33%. There were adverse events in 77% of the patients during the screening phase and 22% during the double-blind phase. The most frequent adverse events were dizziness (32%), somnolence (30%), and weakness (19%). Two patients taking tiagabine withdrew during the double-blind phase because of adverse events.

Organs and Systems

Nervous system

In add-on trials, adverse events significantly more common with tiagabine than with placebo were dizziness (30 versus 13%), weakness (24 versus 12%), nervousness (12 versus 3%), tremor (9 versus 3%), depressed mood (5 versus 1%), and emotional lability (4 versus 1%) (SEDA-19, 73) (SEDA-20, 65) (SEDA-22, 91) (7). Somnolence, amnesia, confusion, difficulty in concentrating, paresthesia, headache, and ataxia can also occur.

In a randomized, double-blind, add-on trial of tiagabine (16, 32, or 56 mg/day) in 297 patients with refractory partial seizures, adverse events significantly more common with tiagabine were dizziness in the 32 mg group (33 versus 15% with placebo), tremor in the 32 and 56 mg groups (15 and 21 versus 3%), mental lethargy or difficulty in concentrating in the 56 mg group (14 versus 3%), and depressed mood in the 16 and 56 mg groups (7% in both groups versus 0%) (8). In a similar study with a dosage of 10 mg tds, the most common adverse events were dizziness, weakness, headache, and somnolence (9), but only dizziness was significantly more common than with placebo (29 versus 10%).

A few more cases of non-convulsive status epilepticus associated with tiagabine have been reported (10–12).

Exacerbation of seizures

Tiagabine can reportedly exacerbate seizures and non-convulsive status epilepticus (SEDA-21, 74). Two of nine patients with partial epilepsy in a trial of tiagabine 30 mg/day developed non-convulsive status and features consistent with atypical absence seizures, although neither had had such seizure types before; drug withdrawal was followed by sustained remission (13). GABAergic drugs aggravate absence seizures, but the de novo occurrence of absences in patients with partial epilepsy is unusual. Tiagabine is only recommended for partial seizures (with or without secondary generalization).

- After an increase in tiagabine dose to 32 mg/day, a 28-year-old woman with partial epilepsy developed a prolonged and disoriented state associated with generalized spike-and-wave discharges on the electroencephalogram. Tiagabine was withdrawn and the status did not recur.
- Two similar episodes occurred in a 28-year-old man taking 24 and 32 mg/day (14).
- Both patients were taking a non-enzyme-inducing agent (valproate and lamotrigine respectively), which probably resulted in higher serum tiagabine concentrations than those seen in enzyme-induced patients.

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Although the manufacturer's database suggested that non-convulsive status is rare during tiagabine therapy (2), the possibility of status needs to be considered in patients who develop episodes of confusion or atypical behavior while taking tiagabine, especially high dosages. A critical analysis of the available literature suggests that misdiagnosis can occur and that some reported cases of putative non-convulsive status epilepticus might in fact have been due to drug-induced encephalopathy (2,15). Overall, the risk of tiagabine-induced generalized non-convulsive status is likely to be greater in patients with a history of absence or generalized epileptic discharges, which are known to be aggravated by GABAergic agents, but patients without such a history can be also affected.

Generalized non-convulsive status needs to be differentiated not only from non-epileptic encephalopathy, but also from partial non-convulsive status, which can also be occasionally precipitated by tiagabine (2,15).

There have been cases of generalized non-convulsive status epilepticus in patients with chronic partial epilepsy treated with tiagabine, on one occasion specifically associated with frontal lobe discharges (15).

- A 12-year-old boy with familial bilateral perisylvian polymicrogyria, mental retardation, and refractory partial seizures was given tiagabine in addition to sodium valproate, and the dosage was increased to 10 mg tds (1 mg/kg/day). This produced complete seizure control. After 1 week he developed hypoactivity, reduced reactivity, and affective detachment. Electroencephalography showed subcontinuous sharp-wave discharges, with irregular runs of atypical spike-wave complexes over the anterior regions of both hemispheres, consistent with a diagnosis of frontal non-convulsive status epilepticus. The dosage of tiagabine was reduced to 15 mg/day and there was complete regression of the behavioral and affective changes and normalization of the electroencephalogram.
- A 21-year-old woman with partial epilepsy had seizure aggravation and complex partial status epilepticus after stepwise increase of tiagabine to 60 mg/day in addition to carbamazepine and vigabatrin (16). The electroencephalogram showed bilateral rhythmic slow activity, which disappeared, together with clinical signs, when intravenous clonazepam (2 mg) was given.

Tiagabine 0.45–40.57 mg/kg/day was associated with long-standing non-convulsive status epilepticus in three girls, two aged 12 years and one aged 17 years, with refractory localization-related epilepsy (17). Resolution followed withdrawal of tiagabine or a reduction in dosage.

Dystonias

Three patients had transient dystonic reactions while taking tiagabine 20–30 mg/day in addition to carbamazepine (18). The dystonic reactions occurred during the first few weeks of treatment. The patients each had a different type of dystonia: focal limb dystonia, oromandibular dystonia, and writer's cramp. In each case the dystonia resolved spontaneously without withdrawal of tiagabine and without any other treatment. Although paroxysmal dystonic movements have been well described with carbamazepine, these patients had been taking carbamazepine for years without this adverse effect.

In placebo-controlled trials, the overall incidence of non-convulsive status epilepticus was no higher with tiagabine than with placebo. However, there have been isolated reports of tiagabine-related non-convulsive status epilepticus (19).

The frequency of status during tiagabine trials has been compared with the occurrence of status epilepticus in four large epidemiological cohorts from Rochester (Minnesota), Turku (Finland), New York, and New Haven (Connecticut) (20). A review of 13 cases with non-convulsive status showed that most of them had had generalized discharges on prior electroencephalography. Only three had encephalographic evidence of status during tiagabine treatment. In the placebo-controlled trials, there was no difference in the frequency of status or complex partial status between patients taking tiagabine or placebo (0.8–1.0 versus 1.5%). In long-term safety studies, which included 2248 patients, there was a 5% frequency of status and a 3% frequency of complex partial status in the tiagabine-treated patients, which was similar to the rates of occurrence in the four external cohorts. Thus, tiagabine does not appear to increase the risk of status or non-convulsive status.

Sensory systems

Following reports of concentric visual field defects associated with vigabatrin (SEDA-21, 78), there has been concern that other drugs that enhance GABAergic inhibition might cause a similar disorder. Although visual field defects were detected in six of 12 patients treated with tiagabine in Australia, no details were given, and this report seems to have remained isolated (21). In a controlled study, none of 15 patients who took tiagabine monotherapy for 1.5–3.5 years (mean daily dose 22 mg) had evidence of a concentric visual field defect (22).

The effect of tiagabine on visual function has been studied in 15 patients with chronic partial epilepsy treated for 23–55 months with tiagabine monotherapy after failure with standard antiepileptic drug monotherapy (23). Three patients had localized field losses (two quadrantanopic and one hemianopic) from earlier brain lesions. Tiagabine had no effect on visual fields but acquired color vision defects were found in seven of 14 patients; contrast sensitivity was unaffected.

Psychological, psychiatric

Although psychosis has been described occasionally (24), in three double-blind trials the incidence of psychotic symptoms was comparable to placebo (SEDA-21, 74). However, patients with a past history of psychiatric disturbances are often excluded from trials, and caution is recommended when using tiagabine in these patients.

Metabolism

Changes in body weight have been evaluated in 349 patients taking carbamazepine, phenytoin, or tiagabine. Carbamazepine add-on therapy caused a significant mean weight gain of 1.5% (25). However, tiagabine add-

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on therapy to either phenytoin or carbamazepine caused no significant weight change.

Hematologic

- A 42-year-old woman developed thrombocytopenia (platelet count 4×10^9/l), ecchymoses, and petechiae after taking tiagabine 50 mg/day for about 1 month (26). Bone-marrow biopsy showed a moderate increase in megakaryocytes without signs of disturbed maturation. Withdrawal of tiagabine led to gradual recovery.

However, the authors failed to mention that ecchymoses have been reported before in patients taking tiagabine, as discussed in the manufacturer's prescribing information (7).

Gastrointestinal

Nausea, vomiting, diarrhea, abdominal pain, and ecchymoses can occur, but they are not common (SEDA-22, 91) (7).

Susceptibility Factors

Hepatic disease

Hepatic dysfunction is associated with impaired tiagabine elimination and can result in greater susceptibility to adverse effects (SEDA-21, 75). Tiagabine should only be used cautiously and in reduced dosages in these patients.

Other features of the patient

Caution is also required in patients with a history of depression or behavioral disorders (24).

Drug Administration

Drug dosage regimens

Two different dosage regimens (twice or three times a day) of add-on tiagabine have been compared in a multicenter, open, randomized, parallel-group study in 347 patients (27). The tiagabine dosage was titrated over 12 weeks to a target of 40 mg/day. The patients were followed for a further 12 weeks. Significantly more patients in the thrice-daily group completed the titration period (81 versus 73%). The proportion of responders during the last 8 weeks of the flexible phase was similar in the two groups (42% for twice-daily and 47% for thrice-daily administration). Thus, although both regimens appeared to offer similar efficacy, significantly more patients completed the study in the thrice-daily group, probably because tolerability is less when high doses are given undivided.

In a large comparison of 16 mg bd with 8 mg qds, the twice-daily schedule tended to be associated with more adverse events (SEDA-22, 91).

Drug overdose

In four adults who took 300–800 mg, the most common symptoms were agitation, hostility, and myoclonus. Supportive care, including in some cases gastric lavage and activated charcoal, was effective. One patient developed status epilepticus, which was managed with phenobarbital (SEDA-21, 74).

Tiagabine overdose (1 g) was associated with convulsive status epilepticus in a 39-year-old man, previously well controlled (28). The tiagabine plasma concentration was 2620 ng/ml, over 10 times higher than the concentrations found in trials.

Drug–Drug Interactions

Contraceptive steroids

Tiagabine, unlike carbamazepine and oxcarbazepine, felbamate, phenobarbital, phenytoin, and topiramate, does not affect the metabolism of oral contraceptive steroids (29).

Enzyme-inducing anticonvulsants

The most important interactions of tiagabine involve induction of its metabolism by enzyme-inducing anticonvulsants (30). This results in larger tiagabine dosage requirements compared with patients taking monotherapy or valproic acid co-medication.

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Tiapride

See also Neuroleptic drugs

General Information

Tiapride is a substituted benzamide related to sulpiride, a selective dopamine D_2 and D_3 receptor antagonist with little propensity for causing catalepsy and sedation. It has antidyskinetic activity, reflecting its antidopaminergic action, and also anxiolytic activity mediated by mechanisms that are poorly understood. Unlike the benzodiazepines, tiapride does not affect vigilance and has a low potential for interaction with ethanol, and possibly for abuse. From a clinical point of view, it can be considered as an atypical neuroleptic drug. It has reported efficacy in neuroleptic-drug induced tardive dyskinesia, levodopa-induced dyskinesias, psychomotor agitation in elderly patients, and chorea (1).

Tiapride appears to be useful in alcohol withdrawal as an alternative to the benzodiazepines (2). It facilitates the management of ethanol withdrawal, but its use in patients at risk of severe reactions in acute withdrawal should be accompanied by adjunctive therapy for hallucinosis and seizures. Since it may prove difficult to identify such patients and since there is also a small risk of the neuroleptic malignant syndrome (particularly with parenteral administration), the usefulness of tiapride in this setting is likely to be limited. The potential risk of tardive dyskinesia at the dosage used in alcoholic patients following detoxification (300 mg/day) requires evaluation and necessitates medical supervision. It is unlikely to produce problems of dependence or abuse.

Tiapride has been assessed for the treatment of agitation and aggressiveness in elderly patients with cognitive impairment in a multicenter, double-blind study, in which patients were randomly allocated to tiapride 100 mg/day ($n = 102$), haloperidol 2 mg/day ($n = 101$), or placebo ($n = 103$) (3). The percentage of responders after 21 days, according to the Multidimensional Observation Scale for Elderly Subjects (MOSES) irritability/aggressiveness subscale, was significantly greater in both of the active treatment groups (haloperidol 63%, tiapride 69%) than in the placebo group (49%). There were 10 dropouts in the tiapride group, 21 in the haloperidol group, and 16 in the placebo group. The number of patients with at least one extrapyramidal symptom was significantly smaller with tiapride (16%) than with haloperidol (34%) and identical to that with placebo (17%); there was no significant difference across the groups in the numbers of patients with endocrinological adverse events. Four deaths were reported: one with placebo (stroke), one with tiapride (pneumonia), and two with haloperidol (stroke and heart failure).

Organs and Systems

Cardiovascular

Torsade de pointes has been attributed to tiapride.

- A 76-year-old man developed torsade de pointes while taking tiapride 300 mg/day; the QT_c interval 1 day after

starting treatment was 600 ms; the dysrhythmia resolved when tiapride was withdrawn (4).

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Tiaprofenic acid

See also Non-steroidal anti-inflammatory drugs

General Information

Data are available on the incidence of adverse effects of this drug (1–3). A review of published studies showed that about 13–15% of patients have adverse effects. The withdrawal rate because of unwanted reactions was 3.2–12% in short-term studies and 4% in one long-term trial. Adverse effects involved the gastrointestinal tract in 8–12% of patients, the central nervous system in 1–10% and the skin (rash, sweating, and itching) in 1–4%. Cutaneous photosensitivity and edema have also been reported.

The adverse effects profile does not differ from that of other propionic acid derivatives and includes the whole spectrum of gastrointestinal adverse reactions usually found with NSAIDs (SED-10, 166) (SEDA-10, 84) (4). The claim of good tolerance and gastric protection, based on animal data, which the company extrapolated to humans, has not been confirmed by appropriate clinical studies (SEDA-12, 89).

Organs and Systems

Urinary tract

Although many NSAIDs have rarely been reported to be responsible for increased urinary frequency and dysuria, and never for severe cystitis, tiaprofenic acid causes severe cystitis (SEDA-18, 106) (SEDA-20, 94) (SEDA-21, 107) (5,6).

If this complication occurs, the drug should be withdrawn immediately (7). A report has given some data on the frequency with which tiaprofenic acid cystitis-related disorders were reported to the UK's Committee on Safety of Medicines. Between 1981 and 1996, 770 adverse drug reactions involving 221 patients were reported. A peak in the reporting of cystitis was noted in 1994, when tiaprofenic acid product information was changed and advice was sent to UK doctors warning about cystitis-related disorders. This peak was followed by a fall in the number of reports, but it is not clear if this was due to reduced drug usage or also to a fall in the reporting rate of such adverse reactions (8).

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Tick-borne meningoencephalitis vaccine

See also Vaccines

General Information

Tick-borne meningoencephalitis vaccine is an adsorbed formalin-inactivated virus vaccine prepared on chicken embryo tissue. Mild local reactions (soreness, redness, swelling) have been reported in 10–25% of vaccinees; systemic reactions occur at similar rates. Fever over 39°C is rare.

Positive merthiolate tests were found in eight of 30 patients with suspected adverse reactions to tetanus or tick-borne encephalitis vaccine (local inflammatory reactions at the injection site, fever, lymphadenopathy, urticarial or lichenoid exanthemas) (1).

An improved tick-borne encephalitis vaccine for children, produced by Baxter, has been licensed and is being used without safety concerns in many countries.

Organs and Systems

Nervous system

In 1989, 172 reports on adverse effects after tick-borne meningoencephalitis immunization were collected in the Federal Republic of Germany, among them 72 reports of suspect neurological complications. Among the 72 reports, there were only three cases of peripheral neuropathy that suggested a causal link with immunization (2). Three cases of mild meningitis, encephalitis, and

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convulsions were, because of incomplete diagnosis, difficult to evaluate.

The database of the Swiss Drug Monitoring Center included 20 spontaneous reports (1987 to July 1992) of adverse events after the administration of tick-borne meningoencephalitis vaccine, among them 11 reports of cases with neurological symptoms (for example meningism, polyradiculitis, ataxia, vestibulopathy, facialis paresis). Most recovered completely within a few days. The incompleteness of the data did not allow conclusions regarding the causality of immunization (3).

Individual reports of neuropathy (SEDA-13, 290), multifocal cerebral vasculitis and infarction (4), cervical myelitis (5), myelopolyradiculitis (5), and suspected encephalitis (SEDA-17, 363) have appeared.

During the period 1987–2000, the Swiss Center for Adverse Events Drug Monitoring (Schweizerische Arzneimittel-Nebenwirkungszentrale) received 33 reports, including 39 neurological adverse events, following the receipt of tick-borne encephalitis vaccine: headache (36% of reports), neuropathy (18%), and meningeal signs (13%); 12 of 33 patients were hospitalized and all recovered (6).

Immunologic

A case of facial edema and pain and swelling of the left knee following the receipt of tick-borne meningoencephalitis vaccine was suspected to be caused by thiomersal allergy (7).

Body temperature

Following the use of tick-borne encephalitis vaccine ("Ticovac," produced by Baxter) in German children, there was a sudden increase in the number of cases of high fever, and 20–30% of vaccinees, primarily those 3 years of age and younger, reacted with a high fever (39°C or more) after the first dose (8). The increased number of cases of high fever was observed after changes in the production of tick-borne encephalitis vaccine were made: the vaccine no longer contains thiomersal and human albumin. Currently, according to the German licensing authority, the Paul Ehrlich institute, the vaccine is no longer recommended for children under 3 years; children aged 3–15 years should only receive half a dose of Ticovac, and the vaccine should only be used when strongly indicated. The reason for the changed reactogenicity is still unclear.

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Ticlopidine

General Information

Ticlopidine is a thienopyridine derivative with potent antiplatelet activity associated with inhibition of ADP-induced platelet aggregation. It was first used in Europe in 1978 in the secondary prevention of stroke and coronary events, the treatment of peripheral vascular disease, and after vascular stent placement. However, the use of ticlopidine has been progressively restricted in some countries because of its serious adverse effects. It has largely been superseded by clopidogrel.

General adverse effects

There is a risk of hemorrhage from drugs that inhibit platelet aggregation. The adverse effects most commonly reported with ticlopidine are skin rashes and gastrointestinal effects, including nausea, dyspepsia, vomiting, anorexia, epigastric pain, and diarrhea. Hypersensitivity reactions underly some of the hematological complications of ticlopidine, such as thrombotic thrombocytopenic purpura.

Organs and Systems

Respiratory

Bronchiolitis obliterans organizing pneumonia has been attributed to ticlopidine (1).

- A 76-year-old non-smoking woman with giant-cell arteritis who had a normal chest X-ray was taking prednisone 45 mg/day and ticlopidine 250 mg bd for persistence of cloudy vision. After 1 month of ticlopidine therapy, she developed increasing dyspnea and a pruritic rash. Chest radiography showed diffuse interstitial

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infiltrates, predominantly affecting the peripheries of both lungs. Transbronchial biopsy showed widening of the alveolar fields, with a mixed inflammatory infiltrate. Ticlopidine was withdrawn and prednisone was continued in the same dosage. Her symptoms completely resolved within 3 months and her chest X-ray normalized within 5 months.

Sensory systems

Two patients developed retinal vasculitis 3 and 4 weeks after starting to take ticlopidine (2). The symptoms and signs of retinitis resolved within 4–6 weeks after withdrawal of ticlopidine, with no reactivation within the next 2 or 3 years.

Hematologic

Ticlopidine can prolong bleeding time by up to 30 minutes. In well-controlled studies the incidence of minor bleeding was 10% (menorrhagia, bruises, and epistaxis) (3). Since the effect on platelet function is irreversible, the bleeding time does not return to normal sooner than 5–10 days after withdrawal, although it can be corrected immediately by platelet transfusion. In a retrospective comparison of the hemorrhagic risk in patients who had received platelet antiaggregants preoperatively for coronary surgery revascularization, there was a significant increase in postoperative hemorrhage and a higher incidence of reoperations in the patients who received ticlopidine compared with other antiaggregants (4).

Various other hematological complications have been observed during ticlopidine treatment (5). They include neutropenia, agranulocytosis, thrombocytopenia, aplastic anemia, pancytopenia, and thrombotic thrombocytopenic purpura (6). These reactions are potentially severe and some are fatal. Major bleeding is rare. Among 188 cases of hematological complications associated with ticlopidine and reported to the US Food and Drug Administration, 36 (19%) resulted in death (7).

Neutropenia

Neutropenia was the most common hematological complication in some of the major trials with ticlopidine. Severe neutropenia occurs in about 1% of patients. Neutropenia typically occurs in the first few months after the start of therapy, but is seen infrequently in the first 2–3 weeks. The mechanism has been reported to be inhibition of myeloid colony growth. On the basis of major randomized, controlled studies with ticlopidine, there is a 2.4% overall incidence of neutropenia and a 0.85% incidence of severe neutropenia and agranulocytosis (6). The neutropenia generally occurs at 2–5 weeks after the start of treatment (8). In some cases, neutropenia is delayed (9) or can develop after drug withdrawal. It has therefore been recommended that one should perform a complete blood count at baseline and every 2 weeks for the first 3 months of treatment, and that ticlopidine should be withdrawn if the neutrophil count falls below 1.2×10^9/l. In some cases, granulocyte colony-stimulating factors have been used, but their efficacy needs to be evaluated further (10). Although some fatal cases have been reported, neutropenia induced by ticlopidine is usually reversible.

Thrombocytopenia

Isolated thrombocytopenia has been reported at anything from 4 weeks to 5 years after the start of drug therapy (11,12). In these cases, platelet antibodies were also detected.

Thrombotic thrombocytopenic purpura has been repeatedly reported (6). The incidence has been estimated at 1 in 1600 (based on the observation of 5 cases out of a total of 7842 patients studied after coronary stent placements) (13). This rare adverse reaction is generally observed after a short exposure period of about 3–8 weeks. The clinical features are generally indistinguishable from those of idiopathic thrombotic thrombocytopenic purpura (14). The pathogenesis is unknown. Platelet antibodies were found in one patient, suggesting an immunologic mechanism (6). The outcome appears to be favorable in comparison to that of idiopathic thrombotic thrombocytopenic purpura, but several authors have reported cases in which death resulted (15,16). Early diagnosis and the rapid institution of plasmapheresis provide the best hope of complete recovery.

Sixty cases of thrombotic thrombocytopenic purpura have been reviewed (17). Ticlopidine had been prescribed for under 1 month in 80% of the patients, and platelet counts were normal within 2 weeks of the onset of thrombotic thrombocytopenic purpura in most patients. Mortality rates were higher among patients who were not treated with plasmapheresis than among those who underwent plasmapheresis (50% compared with 24%). The authors concluded that the onset of ticlopidine-associated thrombotic thrombocytopenic purpura is difficult to predict, despite close monitoring of platelet counts.

In 43 322 patients treated with coronary stents and ticlopidine for 1 year there were 9 cases of thrombotic thrombocytopenic purpura (0.02%) (18). The risk of thrombotic thrombocytopenic purpura during the use of ticlopidine after coronary stenting was 50-fold higher than in the general population. Ten other cases of thrombotic thrombocytopenic purpura related to ticlopidine were identified from the participating centers. Four of the 19 patients died, and all four deaths occurred in patients who were not treated with plasmapheresis. The authors stressed that early recognition and treatment is crucial for minimizing mortality.

Deficiency of, or auto-antibodies to, a von Willebrand-cleaving metalloproteinase are pathogenic in idiopathic thrombotic thrombocytopenic purpura (19). Seven consecutive patients, who developed thrombotic thrombocytopenic purpura 2–7 weeks after starting to take ticlopidine, had markedly reduced concentrations of von Willebrand factor metalloproteinase. In six cases initial samples were available and were positive for immunoglobulin G inhibitors to von Willebrand factor metalloproteinase.

Aplastic anemia

Rare cases of aplastic anemia have been reported (20). Some authors have suggested that the incidence of this complication may have been underestimated (21). The reaction is characterized by pancytopenia and the bone marrow shows profound hypocellularity, absence of precursor cells, and fatty replacement. Some studies have suggested a direct toxic effect of ticlopidine on bone

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marrow cells, particularly the myeloid line. In some cases, agranulocytosis or thrombocytopenia have been reported to precede the development of aplastic anemia. One should be alert to the fact that this reaction may still occur after the recommended 3 months of hematological monitoring have elapsed (6).

Gastrointestinal

Diarrhea is among the most common adverse effects of ticlopidine. It can occur in up to 20% of those who take it, in contrast to an incidence of 10% among placebo- and aspirin-treated patients (22) and usually occurs early in the course of treatment. It can be prevented by taking ticlopidine with food or by reducing the dosage. In rare cases, severe chronic diarrhea with marked body weight loss and anorexia can occur, sometimes long after the start of therapy (23).

In a few reports, lymphocytic colitis has been attributed to ticlopidine; in some cases the pathological features in the colon biopsy resolved after withdrawal of the drug (24–26).

Liver

Several cases of ticlopidine-induced hepatotoxicity have been reported (27). Between 10 days and 12 weeks after the start of treatment, patients develop jaundice, usually without fever, eosinophilia, or pain. Laboratory tests show a cholestatic or mixed cholestatic-hepatocellular pattern of injury. There is usually clinical and biochemical recovery within 1–11 months. Frank ticlopidine-associated liver injury is uncommon, but in one study, 44% of patients had abnormal liver function tests and about one-half of them had to stop taking the drug (22).

Skin

In a 1-year prospective study of 136 patients taking ticlopidine to prevent thrombosis after coronary stenting, 16 had adverse skin reactions (28). The most common were urticaria, pruritus, and maculopapular eruptions. Three patients had previously unreported reactions: a fixed drug eruption, an erythromelalgia-like eruption, and an erythema multiforme-like eruption.

Immunologic

A lupus-like illness (fever, rash, arthritis, renal involvement, and positive antinuclear and antihistone antibodies) developed in three patients 2–8 weeks after they started to take ticlopidine (29). After withdrawal, there was slow but complete resolution in all patients.

Susceptibility Factors

If it is considered necessary to withdraw ticlopidine before elective surgery, it should be done 1 week in advance (30). In emergencies, desmopressin or fresh platelet concentrates reduce the risk of bleeding.

Drug–Drug Interactions

Carbamazepine

In one patient taking ticlopidine and carbamazepine, serum carbamazepine concentrations rose in association with nervous system toxicity (31).

Omeprazole

In six Japanese CYP2C19 extensive metabolizers, ticlopidine 300 mg/day for 6 days significantly increased the C_{max} of a single oral dose of omeprazole 40 mg and reduced its oral clearance of omeprazole (32). The authors concluded that ticlopidine inhibits CYP2C19 but not, or to a lesser extent, CYP3A4, and that the magnitude of inhibition by ticlopidine is related to the in vivo activity of CYP2C19 before inhibition.

Phenytoin

Several reports have described ticlopidine-induced phenytoin toxicity with increased serum phenytoin concentrations (33–36). Data obtained in vitro using hepatic microsomal preparations have shown that ticlopidine inhibits the activity of CYP2C19 (37).

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Tienilic acid

See also Diuretics

General Information

Tienilic acid, a uricosuric diuretic (1), had to be withdrawn soon after its release in 1980, after it had caused several hundreds of cases of severe liver damage, many of them fatal (SEDA-5, 229). In France almost 500 reports of liver injury were received. Tienilic acid had no advantage over other diuretics; it certainly had the worst benefit:harm balance (SEDA-17, 269). For a time it was considered that the hepatic complication might be geographically limited (for example because of differences in manufacturing in different countries), but there is now no doubt that the drug itself was responsible. The hepatic complication was thoroughly studied in retrospect (SEDA-11, 424). Other adverse effects, including acute renal insufficiency, urate stones, and interactions with other drugs, such as oral anticoagulants and phenytoin, helped tienilic acid to its early demise.

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Timegadine

See also Non-steroidal anti-inflammatory drugs

General Information

Timegadine, a guanidine derivative, inhibits cyclo-oxygenase, lipoxygenase, and phospholipase activity. Reported adverse effects are skin rashes, oral lesions, epigastric pain, nausea, dysuria, dizziness, vertigo, and sleep disturbances. Liver enzyme changes and pneumonitis have also been described (1–4).

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Timolol

See also Beta-adrenoceptor antagonists

General Information

Timolol is a hydrophilic, non-selective beta-blocker with little partial agonist and membrane-stabilizing activity.

Organs and Systems

Cardiovascular

Of 153 consecutive patients treated with timolol eye-drops, three complained of unexplained falls and two of them had dizziness and blackouts (1). Two had a cardioinhibitory carotid sinus syndrome (a period of asystole greater than 3 seconds after carotid sinus massage) and the third a vasodepressor carotid sinus syndrome (a reduction in systolic blood pressure higher than 50 mmHg after carotid sinus massage). In all three cases, timolol eye-drops were withdrawn. Follow-up carotid sinus massage in the two patients with a cardioinhibitory carotid sinus syndrome was negative, and all reported complete remission of symptoms.

Significant cardiovascular adverse effects have been reported after topical administration of timolol maleate. Bradycardia with frank syncope can occur, especially in elderly patients (2). After topical administration its action begins in 20 minutes, peaks in 4 hours, and lasts 24 hours. Episodes of dizziness and occasional falls can occur 1–2 hours after instillation of timolol, as has been described in an otherwise healthy elderly patient (3).

- An 80-year-old woman with gastrointestinal bleeding had a sinus bradycardia (52/minute) despite acute blood loss. The only drug she had used that was an AV nodal depressant was timolol maleate 0.5%, one drop to both eyes every day. Continuous electrocardiography showed transient complete AV block without ventricular escape for nearly 6 seconds about 1 hour after instillation of timolol eye drops. She also reported having previously had episodes of dizziness and occasional falls 1–2 hours after instillation of her eye drops. Timolol was withheld and a temporary pacemaker was inserted. Rechallenge with timolol was associated with recurrence of third-degree AV block. She subsequently had a permanent dual chamber pacemaker implanted.

Psychological, psychiatric

Depressive symptoms were reported in 17 of 165 patients after the administration of timolol over two decades (4). Depression accounted for 17% of 369 central nervous system reactions to timolol reported to a National Registry of Drug-induced Ocular Side Effects during 7 years: of these, 20 cases were of acute suicidal depression.

Long-Term Effects

Tumorigenicity

The development of liver tumors in mice and an increased incidence of mammary fibroadenomata in female rats at one time caused concern in the USA, although animal studies elsewhere and clinical studies have shown no evidence of tumor-forming potential.

Drug–Drug Interactions

Brimonidine

The effects of topical brimonidine and timolol have been compared in two trials in 926 subjects with glaucoma or ocular hypertension already using systemic beta-blockers (5). Concurrent systemic beta-blocker therapy had no deleterious effects on ocular hypotensive efficacy and no impact on safety with topical brimonidine, but the combination of timolol and brimonidine significantly reduced systolic and diastolic blood pressures and heart rate compared with brimonidine alone. This observation suggests that ocular hypotensive agents other than beta-blockers, such as brimonidine, may be appropriate as a first-choice therapy for glaucoma in patients concurrently taking systemic beta-blockers.

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Tinidazole

General Information

The adverse effects of tinidazole resemble those of metronidazole. It can be given intravenously and is well tolerated, although thrombophlebitis has been reported. In one healthy volunteer, fainting with low blood pressure and nausea and tiredness for several hours was reported (SEDA-11, 597) (1).

Organs and Systems

Gastrointestinal

Drug-induced esophagitis is rare, accounting for about 1% of all cases of esophagitis. An incidence of 3.9 in 100 000 has been reported. After the first description, there have been more than 250 observations, with more than 50 different drugs. Among those, the principal antibiotics included tetracyclines (doxycycline, metacycline, minocycline, oxytetracycline, and tetracycline), penicillins (amoxicillin, cloxacillin, penicillin V, and pivmecillinam), clindamycin, co-trimoxazole, erythromycin, lincomycin, spiramycin, and tinidazole. Doxycycline alone was involved in one-third of all cases. Risk factors included prolonged esophageal passage, due to motility disorders, stenosis, cardiomegaly, the formulation, supine position during drug ingestion, and failure to use liquid to wash down the tablet. Direct toxic effects of the drug (pH, accumulation in epithelial cells, non-uniform dispersion) also seem to contribute to the development of drug-induced esophagitis (2).

Skin

Skin reactions can occasionally occur in patients taking tinidazole.

- A fixed eruption with pruritus was observed in a 27-year-old man treated for *Entamoeba histolytica* with tinidazole 500 mg, four tablets in a single dose for 3 days.
- An erythematous patch with a sensation of burning appeared over the left buttock in a 32-year-old man while he was taking tinidazole for giardiasis; the allergic lesion was provoked by a challenge dose.

Both of these patients reacted with the same skin reaction on rechallenge with metronidazole (SEDA-16, 310).

In a patient with a fixed drug eruption to metronidazole, a provocation test showed cross-reactivity with tinidazole but not with secnidazole (3).

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Tioguanine

See also Cytostatic and immunosuppressant drugs

General Information

Tioguanine is an analogue of the physiological purines, guanine and hypoxanthine, and is a purine antimetabolite. It is incorporated into DNA and RNA, resulting in a variety of cytotoxic effects. It has been used to treat hematological malignancies, psoriasis, and more recently, inflammatory bowel disease, such as Crohn's disease. Its main adverse effects are liver damage and hemotoxicity.

Among 111 patients taking tioguanine for inflammatory bowel disease, 29 had laboratory abnormalities, most commonly rises in liver enzymes and reduced platelet counts (1). Of the patients who underwent liver biopsy, there was nodular regenerative hyperplasia in 76% of those with laboratory abnormalities and 33% of those without.

Organs and Systems

Hematologic

Tioguanine can cause blood dyscrasias, in particular thrombocytopenia (2).

In 23 children taking tioguanine and a matched group taking mercaptopurine, there was no difference in the pattern of anemia or neutropenia between the two groups, but dose-limiting thrombocytopenia was more common in those taking tioguanine, four of whom had a fall in platelet count to below 20×10^9/l compared with only one taking mercaptopurine (3).

Liver

Nodular regenerative hyperplasia of the liver has been reported in three patients with inflammatory bowel disease who had taken tioguanine for more than a year and who had raised serum liver enzymes; all three had histological foci of nodular regenerative hyperplasia, which was best seen with reticulin silver impregnation (4).

The United Kingdom Medical Research Council Chronic Myeloid Leukemia Group reported 18 cases of tioguanine-induced non-cirrhotic portal hypertension, commonly associated with deterioration in liver function (5).

A patient developed acute sinusoidal obstruction syndrome after taking tioguanine for 14 months for Crohn's disease (6).

- A patient with acute myeloblastic leukemia, who took tioguanine for 2 months, developed severe peliosis hepatis associated with mild lesions of the centrilobular veins; withdrawal was followed by progressive improvement of liver dysfunction (7).

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Several cases of hepatic veno-occlusive disease have been reported (8–11).

- A 23-year-old man with acute lymphocytic leukemia took tioguanine for 10 months and developed intense sinusoidal engorgement which resolved on withdrawal with some residual subintimal fibrosis around the terminal hepatic veins (12).

Of 12 patients aged 3–10 years, who had taken tioguanine 25–77 mg/m^2/day for acute lymphoblastic leukemia, one had persistent pancytopenia and intermittent splenomegaly. MRI/MRA scans showed a dilated splenic vein and collaterals, consistent with portal hypertension; esophagoscopy showed esophageal varices (13). A liver biopsy showed periportal fibrosis and marked dilatation of veins and venules. Of the other 12 patients, nine had abnormal MRI/MRA scans with evidence of varices in four. Liver biopsies in two cases showed periportal fibrosis, dilatation of venules and sinusoids, and minimal focal fatty changes.

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Tiopronin

General Information

Tiopronin has been extensively used as an antirheumatic drug in France and Japan. Adverse effects occur in about 45% of patients and led to withdrawal in about one-fifth.

Observational studies

In 140 patients with classic or definite rheumatoid polyarthritis treated with tiopronin 1 g/day over a mean duration of 1 year and retrospectively studied, adverse effects occurred in 55% and required withdrawal in 40% (1). These effects occurred during the first 6 months of treatment in 75% of cases. They mainly affected the skin and mucosae: in 46 cases (33%) treatment was withdrawn because of stomatitis, pruritus, various types of erythema, and pemphigus (1 case). There was renal insufficiency in 14 patients (10%) requiring withdrawal in eight cases (5.7%) because of nephrotic syndrome ($n = 3$) or proteinuria ($n = 5$). There were hematological disorders in 13 (9.2%), justifying withdrawal in 10 cases (7.1%) because of thrombocytopenia or leukopenia. The other adverse effects included digestive disorders ($n = 15$), requiring withdrawal in three, and ageusia ($n = 6$), requiring withdrawal in one case.

Comparative studies

In 69 patients with rheumatoid arthritis, tiopronin 1500 mg/day was as effective as penicillamine (2). The adverse effects of the two drugs were similar. Tiopronin was associated with obstructive bronchiolitis in one case. There was little cross-intolerance: the same unwanted effect was only observed in four cases; one of pemphigus, one of toxic dermatitis, and two instances of proteinuria.

In 66 patients with cystinuria, adverse reactions to tiopronin (mean dose 1193 mg/day) were common, and occurred in 76% of the patients with a history of D-penicillamine treatment and 65% of those without a history of D-penicillamine treatment, compared with 84% who had adverse effects with D-penicillamine (3). Serious adverse reactions requiring drug withdrawal were less common with tiopronin. Among the patients who took both drugs 31% had to stop taking tiopronin, whereas 69% could not tolerate D-penicillamine.

General adverse effects

Tiopronin has a roughly similar pattern of adverse effects to that of penicillamine (1–6), including rashes, toxic dermatitis, ageusia, and proteinuria; these effects resolve on

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withdrawal (6). If a patient has an adverse reaction to D-penicillamine, the risk of that adverse reaction to tiopronin is only slightly increased.

Organs and Systems

Sensory systems

Tiopronin can cause impaired taste and ageusia (6).

Endocrine

Autoimmune hypoglycemia with anti-insulin antibodies, a complication of penicillamine and pyritinol, has also been reported with tiopronin (7).

- Autoimmune hypoglycemia occurred in a 49-year-old woman with regular menstrual periods accompanied by marked enlargement of the breasts, and was probably induced by tiopronin (8). Her breasts were red and painful; histological examination showed extensive lymphocytic inflammation and edema in the connective tissue. She recovered after stopping tiopronin and taking danazol.

Hematologic

Hematological reactions, such as thrombocytopenia and leukopenia, occur in about 6–9% of patients using tiopronin (1,5).

- Aplastic anemia with fever and pancytopenia developed in a 29-year-old woman, probably as a reaction to tiopronin (500 mg/day), which she had taken for 71 days for seronegative rheumatoid arthritis (9). A bone marrow examination confirmed acute marrow aplasia. She recovered within 5 weeks after withdrawal.

Another detailed case report described profound granulocytopenia, probably caused by tiopronin (10).

Gastrointestinal

Gastrointestinal adverse effects of tiopronin include nausea, vomiting, oral ulcers, and stomatitis (1–3,5,6).

Liver

Of 140 patients taking tiopronin, three had cholestasis (1). A detailed report described liver injury, with steatosis, intrahepatic cholestasis, and centrilobular inflammation, in association with tiopronin (11). In another patient cholestatic hepatitis plus toxic epidermal necrolysis developed in suspected association with tiopronin (12).

Urinary tract

Some degree of renal damage occurs in about 10% of patients taking tiopronin (1–3,5,6). As with penicillamine, proteinuria can progress to nephrotic syndrome (13,14). Biopsy may show minimal change membranous glomerulonephritis and granular depositions of IgG and C3 (13,15).

In a comparison of tiopronin and penicillamine in the treatment of cystinuria in 15 children, nephrotic syndrome developed in one of the patients taking tiopronin; no further details were given (16).

Skin

Cutaneous or mucous reactions occur in about 15–30% of patients using tiopronin. Alopecia, erythema, eczema, cutaneous vasculitis, lichenoid eruptions, skin wrinkling, or a perforating elastoma can develop (1–3,5,6).

There have been several cases of tiopronin-induced pemphigus, characterized by intra-epidermal bullae with acantholysis and epidermal intercellular deposition of IgG and C3 (17,18). The eruption can present as multiple red crusted macules. One patient first had pemphigus in association with penicillamine and later had a relapse while taking tiopronin (19). In skin explant cultures, tiopronin can cause acantholysis with intra-epidermal splits and bulla formation (20).

In a patient with a tiopronin-associated lichenoid skin eruption, the rash was associated with alopecia (21). In another report of a lichenoid eruption, positive rechallenge confirmed the role of tiopronin (22).

In four patients with pluriform skin eruptions in association with tiopronin, the pathological findings were characteristic of a graft-versus-host reaction (23).

In one patient, cholestatic hepatitis plus toxic epidermal necrolysis developed in suspected association with tiopronin (12).

Musculoskeletal

There have been a few cases of myasthenia gravis in association with tiopronin (24,25).

Immunologic

Tiopronin can cause fever, with or without a rash (3). In a patient with a prior hypersensitivity reaction to penicillamine, there was no cross-hypersensitivity to tiopronin (26).

Tiopronin has occasionally been described as a cause of polymyositis (27,28).

- A 62-year-old woman with rheumatoid arthritis, hypothyroidism, and hypertension, treated for 6 years with tiopronin (dosage not specified), developed severe polymyositis. She had dysphagia and muscle weakness and pain in all limbs; there were no skin abnormalities. Her creatine kinase activity was 12 000 U/l (reference range 25–160) and her LDH 23 000 U/l (240–480). Her C-reactive protein was 58 µg/ml and the erythrocyte sedimentation rate 42 mm/hour (both raised). Electromyography of her proximal and distal muscles showed pseudomyotonic fibrillations. A biopsy of the deltoid muscle showed necrosis of muscle fibers and interstitial mononuclear infiltrates. There was no evidence of a paraneoplastic syndrome. Tests for toxoplasmosis, trichinosis, picornavirus, HIV, and hepatitis A, B, and C were negative, and there were no autoantibodies (anti-Jo, anti-KU, anti-PM/SCL, anti-DNA, anti-SSA, anti-SSB, anti-ECT, antithyroid, rheumatoid factor, or cryoglobulins), although ANF was positive on one occasion (1/100). Tiopronin was withdrawn, she was given glucocorticoids and methotrexate, and made a good recovery.

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Tiotixene

See also Neuroleptic drugs

General Information

Tiotixene is a thioxanthene neuroleptic drug.

Organs and Systems

Nervous system

Neuroleptic malignant syndrome has been reported as a severe complication of tiotixene (SEDA-21, 49).

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- A 42-year-old man with a history of paranoid schizophrenia developed confusion and emesis. His medications included buspirone and tiotixene. He also had a generalized seizure that resolved spontaneously. His serum sodium concentration was 114 mmol/l, which was thought to be secondary to psychogenic polydipsia and which was corrected. The next day his temperature rose to 40°C and the day after that he became lethargic and non-verbal and developed generalized muscle rigidity. A diagnosis of probable neuroleptic malignant syndrome was made, and he was given dantrolene sodium 1 mg/kg intravenously; neuroleptic drugs were withdrawn. The serum creatine kinase activity was over 234 500 U/l. Urinalysis showed more than 3 g/l of protein, a trace of ketones, and hemoglobin and leukocytes. By the following day, his muscle rigidity and fever had resolved and his mental status was markedly improved.

Skin

Cutaneous lesions consisting of telangiectatic macules have been reported with tiotixene (1).

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Tiotropium bromide

See also Anticholinergic drugs

General Information

Tiotropium bromide is a long-acting anticholinergic bronchodilator that binds with similar affinity to the three muscarinic receptor subtypes (SEDA-20, 190) (1). However, it dissociates more slowly from M_1 and M_3 receptors in bronchial smooth muscle than from M_2 receptors (1). This results in a long half-life of the bound complex, allowing once-daily administration.

Tiotropium is inhaled from the HandiHaler, a dry-powder, breath-activated inhaler system that delivers particles to the lung over a wide range of airflow limitations in patients with chronic obstructive pulmonary disease (COPD); it can be effectively delivered at inspiratory flow rates as low as 20 l/minute (2). Pharmacodynamic steady-state studies have shown that most of the bronchodilator activity is achieved with one to two doses within 48 hours, although a carryover effect on forced vital capacity was observed beyond 48 hours (3).

The efficacy and safety of tiotropium have been studied in vitro and in early clinical trials, and dose-ranging studies have shown that tiotropium dry powder 18 micrograms/day is safe and efficacious (1,4,5). Since the quaternary structure of tiotropium limits its absorption through the mucous membrane of the respiratory and gastrointestinal tract, systemic adverse effects are in general minimal.

Therapeutic studies

Placebo-controlled studies

In repeated dose studies of 4.5, 9, 18, and 36 micrograms od for 28 days, in 169 patients with COPD, each dose was significantly more effective than placebo, as shown by increased effects with increasing dose on FEV_1 and peak expiratory flow. At doses of 9 micrograms and above there were detectable concentrations of the drug at peak (5 minutes after inhalation), but a trough plasma concentration was only measurable with the 36 micrograms dose. At the highest dose, three of 34 patients reported a dry mouth compared with none of 35 patients taking placebo. This preliminary study suggests that the anticholinergic activity of tiotropium will cause some systemic adverse effects at high doses.

In a randomized, double-blind study, 470 patients with stable COPD (mean FEV_1 38.6% predicted) received tiotropium 18 micrograms or placebo as a once-daily medication via a lactose-based dry-powder inhaler device (6). Spirometry was measured on days 1 and 8 and at regular intervals for 3 months. Tiotropium produced significant improvements in trough FEV_1 and FVC (measured immediately before the next dose), averaging 12% greater than baseline on day 8. The bronchodilatation resulting from tiotropium did not diminish over the 3 months of the study. Upper respiratory tract infections were reported in 15% of the patients in each of the treatment groups and exacerbations of COPD were reported in 22% of patients taking placebo and 16% of patients taking tiotropium. Dry mouth was significantly more common with tiotropium (9.3 versus 1.6%). There was a 6.8% incidence of serious adverse events or events leading to withdrawal (2.5% with tiotropium and 5.8% with placebo). A patient with a long history of cardiovascular disease, who was randomized to receive tiotropium, was found dead and was suspected to have died of a cardiac dysrhythmia. There were no differences in electrocardiograms between the treatment groups or changes in laboratory values.

In a multicenter, double-blind, placebo-controlled trial in patients with stable COPD, tiotropium 18 micrograms/day for 1 year ($n = 550$) significantly improved lung function (mean trough FEV_1, FVC, PEFR) and reduced dyspnea compared with placebo ($n = 371$) (7). Moreover, tiotropium recipients had better health status scores, fewer exacerbations of COPD, and fewer hospitalizations. There was no evidence of tachyphylaxis over one year.

Comparative studies

In a randomized, double-blind trial tiotropium 18 micrograms/day for 1 year ($n = 356$) was compared with ipratropium 160 micrograms/day ($n = 179$) in patients with COPD (8). Tiotropium maintained superior efficacy (FEV_1 and FVC) throughout the study, improved dyspnea, and reduced the number of exacerbations by 24%.

In a placebo-controlled, double-blind study, tiotropium 18 micrograms/day for 6 months ($n = 209$) was compared with salmeterol 50 micrograms bd ($n = 213$) and placebo ($n = 201$) in 623 patients with moderate to severe COPD

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(8). Tiotropium improved dyspnea and trough FEV_1 and FVC significantly more than salmeterol. The patients who used tiotropium had better quality-of-life scores than those who used salmeterol, but the difference was not statistically significant.

Organs and Systems

Mouth and teeth

In placebo-controlled studies adverse events were comparable to those with placebo, except for dry mouth, which was reported in 10–16% of patients (1,7,8).

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Titanium

General Information

Titanium is a strong, light, metallic element (symbol Ti; atomic no. 22) that is mostly found as oxides in minerals such as anatase, brookite, ilmenite, rutile, and sphene, and also as the antimonate in lewisite.

Titanium is used in medicine mainly for its mechanical benefits in surgical and dental materials in a host of orthopedic and orthodontic appliances, with or without other metals (for example nickel, cobalt, chromium), and generally without serious adverse effects. Titanium and its alloys are in use as implants in bone surgery (1,2) and in dental materials (3,4). Research on the biocompatibility of metal and tissue continues (5).

Titanium is also a constituent of some anticancer compounds (6). Titanium dioxide is used in sunscreens. Nontherapeutic exposure to the metal also occurs.

Titanium in metal implants and prostheses

Titanium is very biocompatible (7). Complications from the use of metal implants and prostheses can arise because of biochemical and histological reactions to some of the materials used (SEDA-22, 250). These include titanium, stainless steel (10–14% nickel, 17–20% chromium), and cobalt chrome alloys (27–30% chromium, 57–68% cobalt, and up to 2.5% nickel). All of these metals can produce sensitization or elicit toxic reactions when they are solubilized and come into contact with tissues; it can be difficult or even impossible to differentiate between hypersensitivity and toxic reactions.

Metals from prostheses can continue to be released into the system for many years. The development of hypersensitivity takes time, and allergic reactions are usually delayed for weeks, months, or 1–2 years. The symptoms can assume a variety of forms. Local reactions can cause loosening of the device or local pain. Dermatological reactions include eczema, bullous pemphigoid, urticaria, and "muscle tumors."

Attempts continue to predict metal sensitivity in the individual patient so that the choice of material can be made accordingly. In vitro tests for metal allergies have been developed on the basis of lymphokine (MIF) release from sensitized T lymphocytes exposed to metal-protein complexes (8). About 6% of patients without a previous metal implant had positive reactions to nickel, chromium, or cobalt. However, it is still not clear whether such a positive reaction is a reliable predictor of clinical problems. In practice few patients have either local or systemic reactions; when symptoms occur and other causes are ruled out, the implant should be removed. Some workers recommend removal of an implant whenever there is both a positive MIF test and a positive skin test, even in the current absence of a serious reaction. Allergic dermatitis will clear up as soon as the metal has begun to be cleared from the tissue. The type of metal and the amount released into the tissue will affect the time taken for the disappearance of toxic dermatological phenomena.

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Of 120 consecutive patients (66 women, 54 men; mean age 66 years) with 126 prostheses inserted between March and December 1989, who were followed prospectively both clinically and radiologically for a mean of 9.1 years (9), 40 (41 hips) died, 9 (9 hips) were interviewed by telephone, and 71 (76 hips) were available for follow-up. Four hips had been revised, two of them because of aseptic loosening of the femoral component, one because of a late infection—all after 9 years—and one because of a periprosthetic fracture after 6 years. The 9-year survival was 97% and for aseptic loosening of the stem 98%. None of the cups had to be revised for aseptic loosening. The result was excellent or good in 88%, moderate in 8%, and poor in 4%. Radiological analysis showed no osteolysis or radiolucent lines in 59 prostheses (78%). Nine stems (12%) showed a radiolucent line. Focal osteolysis was detected in eight cases (10%) in one or more Gruen zones. The distribution of the osteolytic areas showed that zones II, V, VI, and VII were predominantly affected in increasing frequency. There was no osteolysis on the acetabular side. These results do not confirm the high rate of osteolysis and revisions with the Muller titanium alloy Straight Stem used in some other institutions.

Organs and Systems

Skin

Titanium tetrachloride ($TiCl_4$) is an intermediate compound in the production of white pigment, which can cause severe chemical burns (10). In two reported cases titanium tetrachloride caused 18–20% total body surface area burns, as a combined consequence of hydrochloric acid and the heat that was generated in areas in which this otherwise stable compound was mixed with sweat. Titanium tetrachloride combined with water is extremely dangerous, and its immediate treatment (towel drying before irrigation) makes it unique among chemicals. The experience of the authors suggested that in most cases grafting will be required. These chemical burns were self-limiting and had no notable systemic sequelae. Wound biopsy specimens were taken on days 3 and 6 and the burns were subjected to immunostaining, which showed that titanium tetrachloride did not retard wound healing. The exposure time to titanium tetrachloride vapor will determine the pulmonary and ophthalmological effects in each case. Clinical awareness of the propensity of titanium tetrachloride to react with water—even in the form of sweat—is vital, because prompt management can limit the extent of injury.

Exacerbation of atopic dermatitis has been attributed to titanium clips (11).

- A 28-year-old woman with breast cancer underwent breast conservation, and three titanium clips were placed at the margin of the excision cavity, followed 2 months later by rapid exacerbation of her atopic dermatitis. The skin lesions developed progressively and involved the whole body. Patch tests and lymphocyte stimulation tests could not be performed, owing to the severity of the skin lesions. Various drugs were suspected, but the results of a bidigital O-ring test suggested an allergic reaction to titanium clips. She underwent a second operation to remove the titanium clips under local anesthesia. By 12 months after surgery, the atopic dermatitis had not completely resolved.

A contact allergic reaction has been reported in three individuals of a group of 23 volunteers who participated in a study with topically applied ammonium titanium lactate 10% (12).

Immunologic

Allergic reactions to titanium can occur (13). Inflammatory reactions and contact sensitivity have been reported after insertion of titanium implants. Osseointegration of the implant tends to occur, but around the area there can be an intense inflammatory reaction and persistent irritation of soft tissues (SEDA-22, 250) (14,15).

Occasionally, reactions to titanium can occur at a distance from a hip implant, probably because small particles of titanium become detached and enter the system.

- Distant granulomatous reactions occurred in an elderly man, who developed symptomless lymph node histiocytosis, which was discovered incidentally.
- Another man had a visceral granulomatosis reaction (liver, spleen, and lymph node) associated with hepatic and splenic enlargement; in affected tissue specimens particles from the hip arthroplasty were detected, and titanium was found in the spleen (16).

Despite its widespread use, titanium is only rarely linked with contact allergic reactions. A hypersensitivity reaction has been attributed to titanium in a pacemaker (17).

- An 86-year-old Japanese man received a pacemaker for atrioventricular block, and 2 months later developed a scaly erythema over the implantation site and later widespread nummular eczema. Histologically, the lesions showed slight spongiosis, intracellular edema, moderate acanthosis in the epidermis, and perivascular infiltration with thickened capillary walls in the dermis. The pacemaker contained titanium and a variety of other metals, but patch tests were all negative. However, titanium sensitivity was demonstrated by intracutaneous and lymphocyte stimulation tests.

Titanium is so widely used that the risk of contact sensitivity to it must be very small. If a patient shows contact sensitivity to titanium, a replacement pacemaker should be completely encased in patch-tested non-allergenic material.

Long-Term Effects

Tumorigenicity

A rhabdomyosarcoma has been reported near the site of a pacemaker (18).

- An 85-year-old man developed a voluminous, rapidly evolving tumor beneath the right clavicle where a titanium pacemaker had been implanted 5 years before. Immunohistochemistry showed that it was a rhabdomyosarcoma.

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The role of the pacemaker and especially of titanium in the development of this tumor was not clear.

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Tizanidine

General Information

Tizanidine is a centrally acting benzothiadiazol derivative with myotonolytic activity. Although its mechanism of action has not been fully clarified, facilitation of glycine-mediated transmission in the spinal cord may play an important role (1). A total daily dose of 15 mg (5 mg 3 times) is reported to be effective and well tolerated by most patients (2).

The documentation of adverse effects is still fragmentary. Tizanidine seems to be a relatively well tolerated and useful antispastic agent. The most frequently reported adverse effects include drowsiness, dry mouth, and muscle weakness (3). Occasionally, hypotension can occur; it is usually mild (4,5) but can be more severe in patients taking antihypertensive drugs (6–8), in whom tizanidine should be used with great caution. A small fall in heart rate has also been reported (9).

In an open study of tizanidine for neuropathic pain, several adverse effects were noted, such as dizziness, drowsiness, fatigue/weakness, dry mouth, gastrointestinal upset, and sleep difficulty (10).

Organs and Systems

Liver

In an open study of tizanidine for neuropathic pain, one patient developed abnormal liver function tests accompanied by nausea and vomiting, fatigue, confusion, weakness, and muscle aches (10). Within three weeks after withdrawal of tizanidine, the liver function tests returned to baseline and the symptoms resolved. Two other patients had transient asymptomatic rises in liver function tests, which returned to normal despite continuation of tizanidine. Transiently raised liver function tests during tizanidine treatment have occasionally been reported before (11–13).

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Tobramycin

See also Aminoglycoside antibiotics

General Information

Tobramycin closely resembles gentamicin in its microbiological and toxicological properties. The two drugs have similar half-lives, peak serum concentrations, lack of protein binding, volumes of distribution, and predominantly renal excretion by glomerular filtration. The main advantage of tobramycin may be its greater intrinsic activity against *Pseudomonas aeruginosa*. Not all bacterial strains resistant to gentamicin are invariably also resistant to tobramycin. Because of its inherent potential for ototoxicity and nephrotoxicity, renal function and eighth nerve function should be closely monitored (1,2).

Comparative studies

In a randomized comparison of nebulized tobramycin and nebulized colistin in patients with cystic fibrosis, 26 of 53 patients treated with tobramycin had at least one respiratory adverse event, most commonly pharyngitis (3). In 520 patients, inhaled tobramycin (300 mg bd for three 28-day cycles, each cycle being separated by a 28-day period of no treatment) was compared with placebo. Respiratory function was significantly improved as early as the second week and remained so for the rest of the study, even during periods without aerosol treatment. There was also a parallel reduction in the relative risk of hospitalization, the number of days of hospitalization, and the number of days of intravenous antibiotic treatment (4).

Organs and Systems

Respiratory

Nebulized antipseudomonal antibiotic treatment improves lung function and reduces the frequency of exacerbations of infection in patients with cystic fibrosis and Wegener's granulomatosis (5–7), but the significance of development of antibiotic-resistant organisms remains to be determined (8). In 10 healthy adults, the inhalation of tobramycin 80 mg resulted in the deposition of 11.8 mg in the lungs (9). In a double-blind, randomized, placebo-controlled study, inhaled tobramycin significantly reduced sputum density of *P. aeruginosa*. More patients in the treatment group reported increased cough, dyspnea, wheezing, and non-cardiac chest pain, but the symptoms did not limit therapy (10).

Inhalation of the intravenous formulation of tobramycin can cause bronchoconstriction, as has been confirmed in 26 children with mild to moderate cystic fibrosis (11). Nevertheless, while bronchoconstriction did occur, many patients did not have bronchoconstriction in response to the standard intravenous formulation. The risk of bronchoconstriction may further be reduced by pretreatment with salbutamol.

In a comparison of different dosage regimens, inhaled tobramycin caused bronchial obstruction (12). However, after 10 minutes of inhalation, lung function returned to baseline; the effect was independent of dose.

In two placebo-controlled, randomized studies, inhaled tobramycin significantly reduced sputum density of *P. aeruginosa*; however, more patients in the treatment group reported increased dyspnea and wheezing, although the symptoms did not limit therapy (13,14).

Neuromuscular function

The aminoglycosides have a curare-like action, which can be antagonized by calcium ions and prostigmine. In cases requiring general anesthesia, the effect of muscle relaxants such as D-tubocurarine can be potentiated by aminoglycosides.

Aminoglycoside-induced neuromuscular blockade can be clinically relevant in patients with respiratory acidosis, in myasthenia gravis, and in other neuromuscular diseases. Severe illness, the simultaneous use of anesthetics, for example in the immediate postoperative phase, and the application of the antibiotic to serosal surfaces are predisposing factors to be considered (15). Severe clinical manifestations are rare in patients treated with aminoglycosides that are administered in low doses, such as tobramycin.

Sensory systems

Eyes

Subconjunctival injection of tobramycin has caused macular infarction (SEDA-20, 238). This potentially devastating consequence suggests that care must be exercised when contemplating instillation of aminoglycosides directly into the eye.

Allergic contact dermatitis causing conjunctivitis and blepharitis has been reported with topical ophthalmic tobramycin (16).

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Ears

Tobramycin affects the cochlear and vestibular systems to a similar extent as gentamicin. A survey of 24 trials showed the following mean frequencies of ototoxicity: gentamicin 7.7%, tobramycin 9.7%, amikacin 13.8%, netilmicin 2.3% (17). There was also a lower incidence of netilmicin-induced inner-ear damage compared with tobramycin in two studies (18,19).

Of 60 adult patients with cystic fibrosis randomized to tobramycin, either 10 mg/kg/day or 3.3 mg/kg tds, two patients (one in each group) had bilateral impairment in pure tone audiography after treatment (20).

Histological examination of the temporal bones from two individuals with ototoxicity due to tobramycin showed reductions in the numbers of both ganglion cells and hair cells (21). Spiral ganglion cell loss was not necessarily subadjacent to areas of hair cell loss in cases of aminoglycoside ototoxicity. Instead, there may be a reduction in the number of ganglion cells in segments of the cochlea with normal-appearing hair cells.

Psychological, psychiatric

As with gentamicin, toxic psychoses can occur with tobramycin (22).

Metal metabolism

Repeated courses of intravenous tobramycin can cause hypomagnesemic tetany (23).

Liver

Certain aminoglycosides affect liver function tests. Increases in alkaline phosphatase after tobramycin have been described (24).

Urinary tract

The following order of relative nephrotoxicity was found in animal experiments: neomycin > gentamicin > tobramycin > amikacin > netilmicin (25,26). However, in humans, conclusive data regarding the relative toxicity of the various aminoglycosides are still lacking. An analysis of 24 controlled trials showed the following average rates for nephrotoxicity: gentamicin, 11%; tobramycin, 11.5%; amikacin, 8.5%; and netilmicin, 2.8% (17). In contrast to this survey, direct comparison in similar patient groups showed no significant differences between the various agents in most trials (27–33). One prospective trial showed a significant advantage of tobramycin over gentamicin (34). However, these findings could not subsequently be confirmed (35). Nephrotoxicity remains a serious risk with all the currently available aminoglycoside antibiotics, and no drug in this series can be regarded as safe.

- Nephrotoxicity due to inhaled tobramycin has recently been described in a 20-year-old patient with cystic fibrosis who developed acute non-oliguric renal insufficiency after taking inhaled tobramycin 300 mg bd for 1 week; the clinical and renal biopsy findings were consistent with aminoglycoside-induced changes (36).

Skin

Ultraviolet recall has been reported after piperacillin, tobramycin, and ciprofloxacin, with a reaction pattern different from that of chemotherapy-induced reactions.

- A 31-year-old woman with a *Pseudomonas* pneumonia was given intravenous ciprofloxacin 400 mg 12-hourly, tobramycin 400 mg/day, and piperacillin 4 g 6-hourly (37). Three days after the initial administration of the intravenous antibiotics, she developed a morbilliform eruption on the sun-exposed areas of her chest, back, and arms, corresponding to sites of intense sunburn that had occurred a month before.

Immunologic

- Hypersensitivity to inhaled tobramycin has been reported in a 9-year-old boy who developed a rash after a course of gentamicin (38). The rash resolved after withdrawal, but returned all over his body when inhaled tobramycin was restarted. He was desensitized using escalating doses of inhaled tobramycin, tolerated the procedure well, and was still using once-a-day tobramycin 9 months after desensitization.

Long-Term Effects

Drug tolerance

Intermittent administration of inhaled tobramycin has been recommended in patients with cystic fibrosis, as it improves pulmonary function, reduces the density of *P. aeruginosa* in sputum, and reduces the risk of hospitalization. The proportion of patients with isolates of *P. aeruginosa* with higher minimal inhibitory concentrations of tobramycin may increase (39). Treatment with inhaled tobramycin does not increase isolation of *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, or *Alcaligenes xylosoxidans*; however, isolation of *Candida albicans* and *Aspergillus* species may increase (40).

With nebulized tobramycin the introduction or selection of resistant bacteria is relatively rare but is a matter of concern (41).

Second-Generation Effects

Teratogenicity

During pregnancy the aminoglycosides cross the placenta and they might theoretically be expected to cause otological and perhaps nephrological damage to the fetus. However, no proven cases of intrauterine damage by tobramycin have been recorded.

Susceptibility Factors

Renal disease

Reduced tobramycin clearance can be associated with a normal creatinine clearance in serum concentration-adjusted dosage of once-daily tobramycin therapy in critically ill patients (42).

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Other features of the patient

The pharmacokinetics of tobramycin in patients with cystic fibrosis is significantly altered after lung transplantation, and early and close drug monitoring is recommended (43).

Hydrophilic contact lenses may increase the penetration of tobramycin into the aqueous humor (44).

Drug Administration

Drug dosage regimens

The addition of tobramycin reduced the amount of cefuroxime-induced endotoxin released per killed *Escherichia coli* to a level that was even lower than that of tobramycin alone, despite an increased killing rate (45). Increasing concentrations of tobramycin led to a reduction in endotoxin release, pointing to a possible benefit of once-daily dosing regimens.

In an analysis of sera from 60 adults with cystic fibrosis, it was suggested that the potential benefit of achieving a greater peak/MIC with once-daily aminoglycoside administration may be offset by the significantly greater time that the concentration was below the MIC, compared with that achieved with multiple daily dosing regimens (46).

Based on a study of 10 patients with automated peritoneal dialysis, it was recommended that for empirical treatment of dialysis-related peritonitis, the dosage of intermittent intraperitoneal tobramycin must be 1.5 mg/kg for one exchange during the first day and then 0.5 mg/kg thereafter, to reduce the risk of adverse effects (47).

Drug administration route

With combined inhalational and intravenous tobramycin, toxic serum drug concentrations can occur (48).

Wound irrigation

Although the efficacy of peroperative wound irrigation with aminoglycosides has yet to be firmly established in prospective comparative trials, they are often used during intra-abdominal and thoracic surgery. Depending on the amount of drug used and the nature of the operation, it is likely that significant amounts of tobramycin are absorbed (SEDA-20, 237).

Inhalation

Tobramycin has been used extensively in cystic fibrosis because of its effect on *Pseudomonas* organisms. Used as an adjunct to intravenous antibiotics in acute infections, it can lower sputum colony counts. Aerosolized antibiotics over prolonged periods can improve lung function and reduce hospital admissions, but they carry the potential risk of drug toxicity and resistance. In a review of clinical studies it was concluded that there was no evidence of nephrotoxicity or ototoxicity (49), although long-term toxicity studies at higher dosages are awaited.

The efficacy of nebulized tobramycin 300 mg bd for 4 weeks has been studied in a randomized, double-blind, placebo-controlled trial in 74 patients with bronchiectasis and *Pseudomonas* infection, without cystic fibrosis (31). After 4 weeks there was a significant fall in the density of *Pseudomonas* infection in the sputum of the treated group. This correlated with an improvement in general medical condition, as assessed subjectively 2 weeks later. There was no difference in lung function. Tobramycin resistance (MIC over 16 μg/ml) developed in 4 patients in the treated group and 1 patient in the placebo group. Adverse events were reported by 31 of the 37 patients in each arm. There were significantly increased incidences of dyspnea (32%), chest pain (19%), and wheezing (16%) in the treated group compared with placebo (8%, 0%, 0% respectively). Cough increased in 15 patients (41%) in the treated group and 9 (24%) in the placebo group. The investigators felt that the majority of these respiratory adverse events had been related to the drug. They commented that these adverse events did not generally result in withdrawal of the patients from the trial. No more details were given but the apparent adverse effects profile of nebulized tobramycin in this group is of concern.

Topical administration into the ear

The primary target for the topical effects of aminoglycosides in the ear is controversial. It has been generally believed that outer hair cells are primarily affected, followed by loss of inner hair cells; that degeneration starts basally and proceeds towards the apex; and that neural fibers and ganglion cells would degenerate secondarily to loss of hair cells. However, the possibility that spiral ganglion cells may be a primary target has been raised. In a postmortem study of 10 temporal bones from 6 patients (aged 11–40 years) with cystic fibrosis, whose pulmonary infections had been treated with systemic aminoglycosides (mainly tobramycin), in most cases combined with nebulized tobramycin, cytocochleograms were analysed for each bone (50). Four bones showed typical manifestations of aminoglycoside-induced ototoxicity, with loss of hair cells in the lower turns and degeneration of ganglion cells. Six bones showed no loss or scattered loss of hair cells, but there was degeneration of the spiral ganglion cells. This study supports the hypothesis that degeneration of spiral ganglion cells may occur as a primary manifestation in some cases of aminoglycoside-induced ototoxicity.

Drug overdose

Multiple-dose activated charcoal does not increase the elimination of tobramycin and is therefore not recommended for treatment of poisoning (SEDA24.26.74) (51).

Monitoring Therapy

During multiple daily dosing peak serum concentrations of tobramycin over 5–7 μg/ml are associated with improved survival in patients with septicemia and pneumonia caused by Gram-negative bacteria (52,53). On the other hand, excessive peak concentrations (over 10–12 μg/ml) and trough concentrations (over 2 μg/ml) of tobramycin increase the risk of ototoxicity and nephrotoxicity (54).

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Tocainide

See also Antidysrhythmic drugs

General Information

The clinical pharmacology, uses, efficacy, and adverse effects of tocainide have been extensively reviewed (1–9).

The adverse effects of tocainide occur with increasing frequency above plasma concentrations of 10 μg/ml. They are mostly related to the nervous system. In two large series withdrawal of tocainide was required in 11–16% of patients because of adverse effects (10,11). The high incidence of blood dyscrasias severely limits the use of tocainide.

Organs and Systems

Cardiovascular

Adverse cardiovascular effects have been reported in 6–55% of cases. After a single dose of tocainide the most common effect is hypotension with bradycardia (12). Angina pectoris has also been reported (13).

During repeated administration cardiovascular adverse effects are relatively uncommon. Increasing heart failure (14,15), worsening dysrhythmias (15,16), pericarditis (15,17,18), and sinus arrest with sinoatrial block (19) have all been reported. Tocainide can worsen ventricular tachycardia (20).

Respiratory

There have been several reports of interstitial pneumonitis attributable to tocainide (21,22), and it may also cause severe pulmonary fibrosis (23,24).

Nervous system

A wide variety of central nervous system symptoms has been reported in almost every study, varying in incidence from 10 to 100%. Common reactions include dizziness, tremor and tremulousness, dysesthesia and paresthesia, light-headedness, and blurred vision. Various mental changes have been described, including paranoid psychosis (25–27). Nausea is common and probably central in origin, since it occurs after intravenous as well as oral administration. These adverse effects can be reduced in frequency during oral administration by taking the tablets with food.

Sensory systems

There have been not infrequent reports of odd taste sensations (peppermint and menthol) and of coolness of the throat, hands, and feet.

Hematologic

Tocainide can cause blood dyscrasias (neutropenia, thrombocytopenia, pancytopenia, and aplastic anemia) in one in 300 patients (28–31). There have been isolated reports of eosinophilia with an allergic rash and anemia with pericarditis (17,32).

Gastrointestinal

Nausea is very common, particularly during the initial stages of treatment, after which it tends to disappear (14). There have been occasional reports of constipation (17) and of anorexia and vomiting (14).

Liver

Tocainide can increase the activities of serum transaminases (33) and can cause fatty change (33) and granulomatous hepatitis (34).

Urinary tract

Non-membranous glomerulonephritis has been reported (35).

Skin

There have been a few reports of skin rashes attributed to tocainide (17,36).

Hair, nails, sweat glands

Night sweats have been reported in three patients taking tocainide (17).

Immunologic

Arthralgia has been reported in two cases with positive antinuclear antibody titers, suggesting the possibility of a lupus-like syndrome (37). In another case tocainide treatment was associated with both a lupus-like syndrome and neutropenia (38). Cross-reactivity of tocainide with lidocaine has been reported (39).

Drug Administration

Drug overdose

Convulsions, complete heart block, and asystole developed in a case of fatal self-poisoning with 400 mg of tocainide (40).

Drug–Drug Interactions

Theophylline

Tocainide reduces the clearance of theophylline and increases its half-life, but to an extent that is probably clinically insignificant (41).

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Tolazoline

General Information

Tolazoline is an alpha$_2$-adrenoceptor antagonist that increases skin blood flow in healthy subjects and has been used to relieve acute vasospasm. However, convincing evidence of its therapeutic value in patients with chronic conditions, such as claudication or cerebrovascular impairment, is not available. It has a pulmonary vasodilator action and seems to be a useful adjunct in the management of neonates with persistent fetal circulation.

Tolazoline has a histamine-like action. Its most common adverse effects are palpitation, tachycardia, flushing, sweating, headache, and paresthesia of the skin with piloerection. Unwanted gastrointestinal effects include nausea, vomiting, and diarrhea. Postural hypotension and failure to ejaculate have also been reported.

Organs and Systems

Gastrointestinal

An infant with persistent fetal circulation treated with tolazoline developed gastric ulceration and perforation (1). The first symptoms occurred 14 hours after the start of therapy, and there was free air in the abdomen 34 hours later. Duodenal perforation also occurred in a 31-hour-old infant with meconium aspiration treated with tolazoline for 6 hours; the defect required surgical correction (2).

Drug–Drug Interactions

Clonidine

Tolazoline can antagonize the effects of intravenous clonidine and prevent the brief hypertensive reaction that it often causes (SEDA-2, 192) (SEDA-3, 180).

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Tolcapone

General Information

Tolcapone is an inhibitor of catchol-O-methyltransferase, which catalyses a relatively minor pathway of dopamine metabolism. It therefore enhances the action of dopamine.

The introduction of tolcapone had a major impact on the management of Parkinson's disease, and within months tens of thousands of patients throughout the world were treated with it. Tolcapone was considered to be useful in prolonging the half-life of levodopa, thereby allowing dosage reduction and possibly smoother therapeutic responses.

In early studies the most frequent adverse effects of tolcapone were dyskinesias, nausea, sleep disorders, dystonia, orthostatic hypotension, diarrhea, dizziness, and hallucinations (1). However, very soon tolcapone was withdrawn in most countries, because of reports of severe hepatotoxicity. The background to these events has been briefly reviewed (2).

Organs and Systems

Gastrointestinal

Raised liver enzymes due to tolcapone were often associated with diarrhea and occurred within 6 weeks to 6 months of the start of tolcapone therapy. Diarrhea

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developed in 16–18% of patients taking tolcapone and was severe in 3–4% of the cases.

Liver

A number of cases of severe hepatotoxicity (3) led the health authorities to withdraw tolcapone from most European countries following an EMEA ruling in November 1998. Increases of more than three times the upper limit of the reference range for alanine aminotransferase and aspartate aminotransferase occurred in respectively 1% and 3% of patients taking tolcapone 100 mg tds and 200 mg tds. Increases of more than eight times the upper limit of normal alanine aminotransferase and aspartate aminotransferase occurred in respectively 0.3% and 1.7% of patients taking tolcapone 100 mg tds and 200 mg tds. Subsequently there were three deaths from acute liver failure in patients taking tolcapone during a total exposure of 40 000 patient-years, leading to the complete withdrawal of the drug. An earlier review, predating the withdrawal of tolcapone, had suggested that it could be safely used provided liver function was closely monitored in the first 6 months of therapy (4), and some neurologists believe that this course of action may still be reasonable because of what they regard as the superior efficacy of this drug.

Skin

- Progressive vitiligo occurred in a 50-year-old Caucasian who took tolcapone 300 mg/day in combination with co-careldopa (5). The first depigmented lesions appeared a week after starting the drug.

The authors speculated that the increased concentrations of dopamine may have interfered with melanin synthesis.

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Tolfenamic acid

See also Non-steroidal anti-inflammatory drugs

General Information

The main adverse effects of tolfenamic acid (particularly nephrotoxicity) are similar to those of the other anthranilic acid derivatives. However, dysuria has been reported more often and confirmed by rechallenge (SEDA-4, 68). Skin disorders are frequent (40% of all reported effects), and fixed drug eruption has occurred (SEDA-18, 107). Diarrhea (10%) and upper gastrointestinal symptoms (including dyspepsia, nausea, vomiting, gastric pain, and ulcer) (6%) are common (SEDA-19, 98). Hepatitis has been described with positive rechallenge. Six patients with pulmonary infiltrates, possibly caused by tolfenamic acid, were reported to the Finnish National Centre for Adverse Drug Reaction Monitoring over a 12-year period. In some patients with hemolytic anemia, a positive Coombs' test and antinuclear antibodies suggested an immunological mechanism (SEDA-13, 83).

Organs and Systems

Electrolyte balance

Hyperkalemia has been attributed to tolfenamic acid (1).

- A hemodialysis patient with nephritic syndrome and diabetic end-stage renal disease developed severe hyperkalemia with muscle paresis after taking tolfenamic acid 300 mg/day for chronic headache. Five days after starting treatment he reported pain and tenderness affecting the muscles of his back and lower extremities. He had hyponatremia and severe hyperkalemia. During the following days he developed increasing weakness and became unable to move his head and limbs. Tolfenamic acid was withdrawn and aggressive treatment and repeated hemodialysis started, leading to complete recovery in a few days.

In this case, end-stage renal disease with nephrotic syndrome and insulin-dependent diabetes mellitus were predisposing factors to the development of hyperkalemia, but a possible role of accumulated tolfenamic acid metabolites could not be excluded. Patients with severe renal insufficiency should not receive NSAIDs.

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Tolmetin

See also Non-steroidal anti-inflammatory drugs

General Information

In 32 207 patients taking part in a short (1–4 weeks) postmarketing study of tolmetin, adverse effects occurred in 12%, and led to withdrawal in 3.6% (1). Tolerability was similar to that of naproxen, indometacin (SEDA-7, 114), and ibuprofen (SED-9, 152) (2). In another retrospective study in patients treated for 1 year or more with tolmetin, 64% reported generally mild transitory adverse effects. In controlled studies, about 10% of patients withdrew owing to adverse effects (3). In another study of 25 000 prescription records (4), tolmetin caused adverse

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reactions severe enough to merit hospitalization in only two cases (drug fever and membranous glomerulopathy).

Organs and Systems

Cardiovascular

Increased blood pressure can occur after long-term treatment with tolmetin (5).

Nervous system

The usual adverse reactions of NSAIDs on the nervous system have been attributed to tolmetin (SEDA-6, 98). One woman developed aseptic meningitis, similar to that seen with ibuprofen (6).

Sensory systems

Hearing loss has been documented (SED-9, 152) (7).

Hematologic

Acute reversible thrombocytopenic purpura and tolmetin-related antibodies have been reported in a patient with a history of multiple allergies; rechallenge was positive (8). Peripheral blood eosinophilia has also been found (SEDA-6, 98).

Gastrointestinal

Gastrointestinal adverse effects occurred in 31% of patients taking tolmetin and peptic ulceration in 2% (3). In older patients, the percentage of peptic ulceration and gastrointestinal bleeding was somewhat higher (9).

Urinary tract

Reversible renal insufficiency and acute interstitial nephritis have been reported. Nephrotic syndrome was attributed to tolmetin, but a firm causal relation was not established (10). Nephrotic syndrome has also been described in a 16-year-old girl after she had taken tolmetin for 6 months (SEDA-16, 122).

Immunologic

From early on, the high incidence of hypersensitivity reactions with tolmetin was striking, for example in spontaneous adverse reaction reports. However, the high incidence was not confirmed in a retrospective comparative review (SEDA-6, 98) (SEDA-7, 134) (11). Several factors can explain the discrepancy. For example, patients covered by the review may have persisted with treatment, since they did not experience such reactions.

Multiorgan failure

Fatal multisystem toxicity including both renal and hepatic failure, with microvesicular fatty change in the liver, has been reported with tolmetin in a young woman (12).

Drug–Drug Interactions

Warfarin

Tolmetin combined with warfarin can markedly prolong the prothrombin time and cause bleeding (SEDA-13, 82).

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Toloxatone

See also Monoamine oxidase inhibitors

General Information

Like moclobemide, toloxatone, a selective and reversible inhibitor of monoamine oxidase type A, is thought to be relatively safe in combination with sympathomimetics (SEDA-18, 16). However, sweating, tachycardia, and headache have been reported when terbutaline was added to toloxatone and phenylephrine (SEDA-18, 16). In healthy volunteers, doses up to 600 mg/day did not produce hypertensive reactions on challenge with oral tyramine (SEDA-17, 17). Two fatal cases of fulminant hepatitis have been reported (SEDA-16, 7).

Interactions with toloxatone are similar to those with moclobemide (1).

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Tolterodine

See also Anticholinergic drugs

General Information

Tolterodine is an anticholinergic drug that is used to treat bladder detrusor instability. It has antimuscarinic actions that are relatively bladder-selective. Its efficacy and tolerability have been reviewed (1,2). The general conclusion is that tolterodine is better tolerated than the previous standard medication oxybutinin, particularly with regard to the frequency and severity of dry mouth, but also comparing other autonomic adverse effects, although this is not universally agreed (SEDA-22, 157). The rate of adverse effects-related withdrawals was 2–3 times higher with oxybutinin than tolterodine.

The adverse effects of tolterodine and other antimuscarinic anticholinergic drugs have been reviewed in patients with incontinence and bladder overactivity (3–6).

The findings are not unexpected: dry mouth is by far the most commonly reported adverse effect, with a frequency of about 40% in patients taking 2 mg of the immediate-release formulation bd. The next most common effects are consistently headache, constipation, and abdominal discomfort. Hallucinations and tachycardia have also been reported. It is agreed that higher doses should not be used because of the risk of urinary retention. About 5% of patients stopped taking tolterodine because of adverse effects and in about 10% the dosage was reduced. In one comparison of tolterodine 2 mg twice-daily with 4 mg once-daily in a modified-release formulation the latter produced about a 23% lower incidence of dry mouth, with increased efficacy (7).

Comparative studies

Tolterodine and oxybutynin have been compared (8). The authors concluded that the efficacy of tolterodine 2 mg bd is equivalent to that of oxybutynin 5 mg bd, but that tolterodine causes fewer autonomic adverse effects, less need for dosage reduction, and fewer dropouts because of adverse effects.

Organs and Systems

Mouth

In over 300 patients modified-release oxybutynin once-daily produced less dry mouth (28 versus 33%) than immediate-release tolterodine 2 mg bd (9).

Immunologic

Anticholinergic drugs can rarely cause immunological reactions.

- An 81-year-old Swiss woman took immediate-release tolterodine 2 mg bd and 18 days later had fever, malaise, and nausea with vomiting (10). Liver function tests showed a mixed hepatitic and cholestatic pattern and she also had leukocytosis and eosinophilia.

The authors suggested that this was a hypersensitivity reaction; if so it is the first of its kind to be reported with tolterodine.

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Tonazocine

General Information

Tonazocine is a partial opioid receptor agonist that has not been reported to have adverse effects on the cardiovascular system or to cause clinically significant respiratory depression. When single doses of tonazocine 2, 4, and 8 mg were compared in 150 adults postoperatively,

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drowsiness was the most frequent adverse effect and visual hallucinations occurred in two patients (1).

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Topiramate

See also Antiepileptic drugs

General Information

Topiramate is used in the adjunctive therapy of partial seizures and some types of generalized seizure. Most of its adverse effects relate to the central nervous system.

Observational studies

In an open study of the effects of topiramate 100–1600 mg/day in 292 adults (mean age 33 years) with partial and/or generalized seizures previously resistant to antiepileptic drug therapy over 50% of the patients achieved at least a 50% reduction in seizures (1). The most commonly reported adverse events were related to the central nervous system, including headache, difficulty in concentrating, somnolence, anorexia, fatigue, dizziness, nervousness, nausea, confusion, and paresthesia; 32% discontinued because of adverse events.

Topiramate had a beneficial effect on benign essential tremor in an open study in nine patients (2). Six patients complained of fatigue and two discontinued therapy; four complained of paresthesia.

The effectiveness and tolerability of topiramate has been studied in an open study in 56 patients with bipolar disorder (3). The most common adverse effects were neurological and gastrointestinal, including reduced appetite ($n = 11$), cognitive impairment ($n = 10$), fatigue ($n = 5$), and sedation ($n = 5$). Six patients dropped out during acute treatment and four during maintenance therapy because of adverse effects (cognitive impairment, poor appetite and weight loss, sedation, paresthesia, psychosis, anxiety, tremor, nausea, altered taste, and rash).

In a 3-year retrospective review of the use of topiramate in 51 children aged 3–16 years with partial and generalized epilepsy, 15 children had a greater than 50% reduction in their seizure frequency and four became seizure free (4). Adverse effects were reported in 29 patients; most were related to behavioral and cognitive difficulties; less common effects included anorexia, weight loss, and headache. Topiramate was withdrawn in 25 patients; in 20 cases because of adverse effects.

In 18 patients with severe myoclonic epilepsy in infancy topiramate caused reduced seizure frequency in most (5). There were adverse effects in nine patients, eight with a weekly titration schedule and one with a fortnightly schedule. They were usually minor and transient nervous system effects, except for weight loss, which lasted longer and occurred in four patients.

Among the adverse effects of topiramate are reduced appetite and weight loss, and this has been put to use in the treatment of binge eating in an open study in 13 patients (6). Nine patients had a moderate or better response, two had moderate or marked responses that subsequently diminished, and two had a mild response or none. Neurological adverse effects were the most common. Three patients discontinued topiramate because of adverse effects, and two resumed at a later date without significant recurrence.

The efficacy and tolerability of topiramate have been studied in 170 patients with refractory epilepsy (7). The most common adverse effects resulting in withdrawal were fatigue, weight loss, irritability, paresthesia, depression, and headache. Three patients developed renal calculi but continued therapy.

The effect of topiramate for 6–18 months in 34 children with drug-resistant epilepsy has been studied (8). Adverse effects were reported in nine patients, appetite suppression in five, behavioral disturbances in three, somnolence in two, and poor concentration in one.

In a long-term open extension to a double-blind, placebo-controlled trial of topiramate in 83 children with partial-onset seizures, with or without secondary generalization, seizure frequency over the last 3 months of therapy was reduced by at least 50% in 47 children (9). Anorexia was common during long-term therapy. Five children withdrew because of adverse events.

Topiramate has been used for the treatment of psychiatric disorders, especially bipolar disease. The adverse events profile is similar to that in patients with epilepsy. In a retrospective assessment of 76 patients taking topiramate for bipolar spectrum disorders there was mild improvement in 47% and moderate-to-marked improvement in 13% (10). Responders took a significantly higher mean dose (180 mg/day) than non-responders (83 mg/day). There was weight loss (mean 6.4 kg) in 50% of the patients; the dose was significantly higher in patients who lost weight. Other adverse events were reported by 82% of patients: cognitive effects, sedation, paresthesia, nausea, insomnia, headache, and dizziness. Adverse effects led to withdrawal in 36% of the total patient population. Similar anecdotal experiences in the treatment of bipolar disorders have been reported by others (11,12).

Placebo-controlled studies

In a double-blind, placebo-controlled, add-on trial of topiramate (300 mg/day) in 177 Korean patients with epilepsy, adverse events that were significantly more common in the active treatment group were anorexia (21 versus 6% on placebo), abdominal pain or discomfort (21 versus 2%), speech disturbances (10 versus 1%), psychomotor slowing (9 versus 1%), and weight loss (9 versus 0%) (13). The relatively high incidence of gastrointestinal disturbances was not seen in Western trials, suggesting that Koreans may be more sensitive to this type of adverse effect. Of seven patients who withdrew because of adverse events, four did so because of abdominal symptoms, nausea, and/or vomiting.

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The results of six double-blind, placebo-controlled trials with topiramate in adults with treatment-resistant partial-onset seizures with or without secondary generalization have been analysed (14). Seizures were reduced by at least 50% in 43% of topiramate-treated patients and in 12% of placebo-treated patients. The most common treatment-related adverse events were dizziness, somnolence, fatigue, psychomotor slowing, nervousness, paresthesia, ataxia, memory difficulty, and speech problems. These effects were generally mild to moderate, usually occurred early in treatment, often during titration, and resolved with continued treatment. Other adverse effects were weight loss and, in a few patients, renal calculi.

The efficacy and safety of topiramate has been studied in 46 adult Chinese patients with refractory partial epilepsy in a randomized, double-blind, placebo-controlled study (15). Adverse events were mostly mild and transient, with no significant differences between treatment groups. Two patients taking topiramate had weight loss.

Organs and Systems

Cardiovascular

It is unclear whether topiramate played any role in rare cardiovascular events. These included symptoms of Raynaud's phenomenon in three patients, and third-degree atrioventricular block requiring emergency cardiac pacemaker implantation in one patient with pre-existing right bundle branch block (SEDA-21, 76).

Respiratory

Topiramate inhibits carbonic anhydrase isozymes II and IV, which are present in the central nervous system. Respiratory alkalosis in a 15-year-old girl, who presented with hyperpnea, was not therefore surprising (16). The problem resolved within 24 hours of withdrawal.

Nervous system

In controlled trials, adverse effects with a minimum incidence of 20% in any dosage group included dizziness, fatigue, diplopia, nystagmus, somnolence, confusion, mental slowing, ataxia, anorexia, impaired concentration, and headache (17). The most common complaint was dizziness (40 versus 13% on placebo) in those assigned to the highest dosage (1000 mg/day). Taking events that were probably or definitely drug-related, those with a frequency of 5% or greater were ataxia, impaired concentration, confusion, dizziness, fatigue, paresthesia, somnolence, and mental slowing. All the events were usually mild or moderate and tended to be more frequent at dosages above 600 mg/day, although some, such as dizziness and somnolence, showed no clear dose-dependency. These studies may have overestimated the adverse potential of the drug, because excessively fast dosage escalations were used and maintenance dosages in many groups were larger than those that were later found to be optimal. However, signs of cognitive dysfunction, including word-finding difficulties and impaired memory, have occurred in an appreciable proportion of patients in many studies (SEDA-20, 66).

In monotherapy studies, the incidence of adverse effects was lower than in add-on studies, except for paresthesia which tended to occur more often.

Ataxia was twice as common in patients taking two concomitant anticonvulsants compared with those taking only one other drug (17).

In the comparison of four anticonvulsants mentioned above, the commonest adverse effect of topiramate in 28 patients was irritability, which occurred in seven of ten patients who discontinued therapy because of adverse effects (18).

The response to topiramate has been evaluated in 97 patients with Lennox–Gastaut syndrome in a long-term, open-label extension to a double-blind, placebo-controlled trial (19). The most common adverse events, apart from childhood illnesses, were somnolence and anorexia.

There have been a few reports of hemiparesis in patients taking topiramate.

- Hemiparesis developed in a 41-year-old man and a 59-year-old woman during the first few weeks on topiramate at dosages up to 250 and 200 mg/day respectively (20). The condition resolved gradually after drug withdrawal.

Both patients had pre-existing cerebral damage (contralateral cerebral palsy and temporal lobe infarction respectively), which might have facilitated this hitherto unreported possible adverse effect.

Reversible hemiparesis occurred in a boy taking topiramate (21).

- A 5.5-year-old boy with partial motor seizures secondary to heterotopic gray matter in the atrium of the left lateral ventricle and postictal Todd's paresis was given topiramate in addition to baseline valproate and carbamazepine, and became seizure-free for 6 months. However, he then started to have a new type of seizure, characterized as complex partial. The dosage of topiramate was increased and carbamazepine was withdrawn. He then had a change in behavior, clumsiness, and persistent right hemiparesis. Electroencephalography showed continuous independent left and right centrotemporal epileptiform discharges. There were no changes on an MRI scan. Topiramate was withdrawn and ethosuximide was added. He became seizure-free and his hemiparesis resolved after 1 month. The electroencephalogram improved remarkably.

It is very difficult to find a causal relation between topiramate and this patient's hemiparesis. An alternative interpretation is that he had complex partial status (as suggested by his electroencephalogram) when carbamazepine was withdrawn, associated with reversible hemiparesis.

Sensory systems

On 26 September 2001 OrthoMacneil/Jansen-Cilag issued a "Dear Doctor" letter about an ocular syndrome in patients taking topiramate. The syndrome is characterized by acute myopia and secondary angle-closure glaucoma. Several case reports have been published (22–24).

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As of 17 August 2001 there were 23 reported cases (22 adults and 1 child) out of 825 000 patients. Symptoms typically occur within the first month of therapy, and the patients report acutely reduced visual acuity and/or ocular pain. There is myopia, redness, swelling of the anterior chamber, and raised ocular pressure, with or without pupil dilatation. Supraciliary effusion can displace the lens and iris anteriorly, secondarily causing angle-closure glaucoma. The symptoms are reversible if topiramate is withdrawn. Acute myopia has been described as a rare idiosyncratic reaction to other sulfonamides. It has been postulated that the pathogenic mechanism is related to partial inhibition of carbonic anhydrase and to ciliary body swelling.

Psychological, psychiatric

Psychiatric

Depression and psychosis have been observed in respectively 15 and 3% of patients taking topiramate (SEDA-22, 91) (17). Three patients taking topiramate for bipolar disorder developed substantial depression (25). The symptoms began or increased within 1 week of topiramate treatment (25 mg/day) or with an increase in dosage to 50 mg/day. All had significant relief from depression 1–2 weeks after withdrawal of topiramate. The close association with the onset of the most severe depression these patients had ever experienced suggests an adverse effect of topiramate. However, all these patients had bipolar disorder, so the onset of depression could have been coincidental. Moreover, their depression might also have been due to a synergistic interaction between topiramate and their other medications.

Two adult patients with refractory partial seizures without a previous history of psychosis had an acute psychotic episode with hallucinations and psychomotor agitation after taking topiramate 200–300 mg/day (26).

A single case report of new-onset panic attacks has been described.

- A 24-year-old woman with a history of bipolar disorder and binge eating had a history of "isolated" panic attacks 8 years before and the attacks subsided 14 days after topiramate withdrawal (27).

Because she had a history of psychiatric diseases and panic attacks, the relation of these symptoms to topiramate was doubtful.

Cognitive effects

All anticonvulsants have been associated with adverse cognitive events, and many, sometimes contradictory, studies of classical anticonvulsants have been published (28). Cognitive adverse effects are large for phenobarbital, and possibly larger for phenytoin than for carbamazepine or valproic acid (28). Most often cognitive adverse events result in mild general psychomotor slowing. Although the severity of cognitive adverse effects is considered mild to moderate for most anticonvulsants, their impact may be substantial in some patients, especially in those with pre-existing impaired cognitive function. There is relatively little reliable information on cognitive adverse events of new anticonvulsants. Most of the published studies are on polytherapy and there is little information about healthy volunteers (29).

Topiramate can cause cognitive adverse effects in some patients. Those affected often have impaired verbal learning and fluency. Slow titration reduces the likelihood of cognitive adverse events. Two patients had neuropsychological deficits during topiramate treatment and cognitive improvement after withdrawal (30). One patient was assessed during and after topiramate withdrawal and the other before, during, and after.

The cognitive adverse effects of gabapentin, lamotrigine, and topiramate in healthy volunteers have been compared in a randomized, single-blind, parallel-group study (29). Neurobehavioral testing was conducted at baseline, during the acute oral dosing period 3 hours after medication administration, and at 2 and 4 weeks during chronic dosing. Acutely, those who took topiramate (2.8 mg/kg) performed significantly worse than those who took gabapentin (17 mg/kg) or lamotrigine (3.5 mg/kg) on tasks of letter and category word fluency and visual attention; cognitive effects were not different between those who took gabapentin or lamotrigine. The doses were then increased to topiramate 5.7 mg/kg/day, lamotrigine 7.1 mg/kg/day, and gabapentin 35 mg/kg/day. At 2 and 4 weeks, those taking topiramate had significant verbal memory deficit and slow psychomotor speed compared with baseline; those taking gabapentin and lamotrigine did not. However, the clinical impact of the trial was limited, owing to the small sample size (17 patients) and the very rapid topiramate titration, much faster than is currently recommended (31).

There has been a retrospective analysis of neuropsychological scores before and after the use of topiramate 125–600 mg/day for at least 3 months in 18 patients (32). Topiramate was associated with significant deterioration in verbal IQ, learning, and fluency. Withdrawal or dosage reduction was associated with significant improvement. There was no correlation between individual topiramate dose and the change in test score. This study was retrospective and the patients were selected because they had cognitive problems; the resultant bias makes it difficult to generalize these results to wider populations.

A group of 14 US epilepsy centers has published the results of a post-marketing surveillance study of 701 patients taking topiramate (33). Although 41% of the patients reported cognitive adverse events at any time during treatment, only 5.8% of them discontinued for that reason. Cognitive effects were the most frequent reason for withdrawal because of adverse events (41/170 or 24% of those who discontinued). The central nervous system-related adverse effects profile in these patients included psychomotor slowing, fatigue, slurred speech, irritability, behavioral changes, confusion, inappropriate laughter, and hallucinations. Only 2.4% of the patients were taking monotherapy, and the mean dose of topiramate at 6 months was 385 mg/day, with a mean weekly dose during titration of 36 mg/day. Risk factors for discontinuation were evaluated. A slow titration rate (slower than 25 mg/week), but not the total dose at discontinuation, was significantly associated with a lower discontinuation rate. There was no specific population, dose titration, or concomitant antiepileptic drug that

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increased the risk of treatment discontinuation because of cognitive complaints. Psychomotor slowing was the most common complaint, but most patients elected to continue treatment because of improved seizure control.

In a retrospective survey, behavioral changes occurred in nine of 69 children (median age 12 years) taking topiramate (34). Dosages in the affected children were 2.4–8.5 mg/kg, and three children were taking monotherapy. Manifestations included school difficulties (4), mood swings (2), and aggression, irritability, and hallucinations (one case each). There was no apparent relation to dosage or titration rate.

The cognitive effects of topiramate and valproate as adjunctive therapy to carbamazepine have been compared in 53 patients (35). Topiramate was given in an initial dose of 25 mg and increased weekly by 25 mg/day increments to a minimum of 200 mg/day. Cognition was significantly worsened by topiramate and improved by valproate. Gradual introduction of topiramate reduced the extent of cognitive impairment.

The effects of topiramate and valproate, when added to carbamazepine, on cognitive status in adults have been compared in a randomized, observer-blinded, parallel-group study (35). Topiramate was introduced slowly at a starting dose of 25 mg/day and increased weekly by 25 mg/day increments over 8 weeks to a minimum dosage of 200 mg/day. The target dosages were 200–400 mg/day for topiramate and 1800 mg/day for valproate. There were significant differences between topiramate and valproate in short-term verbal memory—worsening with topiramate and improvement with valproate—but the differences were small. There were no effects on mood disorders, psychiatric symptoms, or motor and mental speed and language tests. These results suggest that if the dose of topiramate is slowly titrated cognitive adverse events can be minimized. However, although most patients tolerated topiramate if properly titrated and dosed, a subset of patients had clinically significant deficits, possibly as an idiosyncratic reaction. In another multicenter, parallel-group, randomized study similar results were obtained when topiramate or valproate was added to carbamazepine (36,37).

The effects of topiramate on tests of intellect and other cognitive processes have been studied in 18 patients (32). Repeat assessments in those taking topiramate were associated with a significant deterioration in many domains, which were not seen in controls. The greatest changes were for verbal IQ, verbal fluency, and verbal learning. There were improvements in verbal fluency, verbal learning, and digit span in patients who had topiramate withdrawn or reduced.

The factors associated with behavioral and cognitive abnormalities in children taking topiramate have been studied retrospectively (38). There were behavioral or cognitive abnormalities in 11 of 75 children at 2–4 months after the start of therapy. The mean dosage (4.6 mg/kg/day) at which these abnormalities were observed was similar to the mean final dose (5.8 mg/kg/day) in children without abnormalities. Five of the eleven children with behavioral or cognitive abnormalities had a previous history of behavioral or cognitive abnormalities, but only nine of the 64 children without abnormalities had a previous history of behavioral or cognitive abnormalities.

Angelman's syndrome, a genetic disorder that involves a defect in the DNA coding for subunits of the GABA-A receptor, is often associated with intractable epilepsy. Topiramate was effective in five children with Angelman's syndrome and epilepsy (39). One patient had transient insomnia and one had akathisia and insomnia that persisted until topiramate was withdrawn.

Slowed mental function is a relatively common adverse effect of topiramate, especially at high dosages, and has been confirmed in a randomized single-blind, parallel-group study in healthy volunteers. After single doses, topiramate (2.8 mg/kg) reduced performance in attention and word fluency tests, whereas lamotrigine (3.5 mg/kg) and gabapentin (17 mg/kg) had no effects (29). After 4 weeks of multiple dosing, topiramate (5.7 mg/kg) was still associated with impairment in verbal memory and psychomotor speed, while there was no impairment with lamotrigine (7.1 mg/kg) or gabapentin (35 mg/kg). While these data suggests that topiramate can cause greater cognitive dysfunction in the short-term than lamotrigine and gabapentin, these findings should be interpreted cautiously. First, the design was less than ideal: the use of a double-blind, crossover design and inclusion of placebo would have been preferable. Secondly, the speed of topiramate titration was much faster than currently recommended, and it is known that neurotoxicity can be reduced by slow dose escalation. Finally, the dosage of topiramate was very high, in view of the fact that no enzyme-inducing co-medication was present.

Word-finding difficulties are a known adverse effect of topiramate. Language disturbances (anomia or impaired verbal expression) without other complaints suggestive of impaired cognition were reported by four of 51 patients; five others had language problems associated with cognitive dysfunction (40). One severely retarded patient with a limited vocabulary became mute, although otherwise alert. Anomia or dysnomia were also seen in two of eight patients treated with zonisamide, which shares with topiramate a sulfa structure and carbonic anhydrase inhibitory properties. Psychotic symptoms are a significant adverse effect in occasional patients. In a retrospective survey, five of 80 patients developed psychosis 2–46 days after starting to take topiramate; manifestations included paranoid delusions in four and auditory hallucinations in three (41). The dosage at the time of onset of symptoms was 50–500 mg/day, and recovery occurred rapidly after drug withdrawal (three patients), dosage reduction (one patient), or neuroleptic drug treatment (one patient). Three of the patients had no significant psychiatric history.

Metabolism

Topiramate causes a fall in body weight, ranging from a mean of 1.1 kg at 200 mg/day to 5.9 kg at 800–1000 mg/day (17). Loss of weight may be linked to anorexia. Women tend to lose more weight than men, and weight loss is greatest in patients with the highest weight at baseline.

Weight loss with topiramate can occasionally be extensive (42).

- A 37-year-old obese white woman with affective instability and obesity taking topiramate (up to

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275 mg/day) lost 10 kg over 10 weeks, although she remained obese (BMI 52 kg/m^2). She also improved mentally.

In this case the weight loss was a beneficial collateral effect of topiramate.

In a retrospective chart review, weight loss was assessed in 214 patients with psychiatric disorders taking topiramate (43). Patients taking either lithium or valproate gained a mean (SD) of 6.3 (9.0) kg and 6.4 (9.0) kg respectively, whereas patients taking topiramate lost 1.2 (6.3) kg. Similar statistically significant results were found in the bone mass index.

Acid–base balance

Topiramate lowers serum bicarbonate by inhibiting carbonic anhydrase. In 20 of 29 children there was a greater than 10% fall in serum bicarbonate after starting topiramate (mean absolute reduction 4.7 mmol/l), but none had significant symptoms of metabolic acidosis, except possibly for anorexia in one (44). In another report, mild to moderate metabolic acidosis (bicarbonate concentrations, 16–21 mmol/l) developed in three topiramate-treated patients aged 25–51 years; the condition was not considered clinically significant, but it led to diagnostic tests to exclude other causes (45).

While the fall in serum bicarbonate is asymptomatic in most cases, special caution is required in patients already at risk of metabolic acidosis, such as those with respiratory acidosis, renal disease, frequent severe infections and sepsis, gastrointestinal disorders with recurrent dehydration, inborn errors of metabolism, or treatment with a ketogenic diet (44).

Mental changes and metabolic acidosis can occur with topiramate, through inhibition of carbonic anhydrase.

- A 20-year-old man taking topiramate, valproate, and phenytoin had acute mental changes with hyperchloremic metabolic acidosis (46). He had been receiving a modest dose of topiramate for 9 months. His mental status returned to normal within 48 hours of withdrawal.

Two children developed symptomatic metabolic acidosis while taking topiramate (47).

- An 11-year-old boy with refractory partial epilepsy who had been taking topiramate 300 mg/day for 13 months developed hyperventilation. He had a hyperchloremic metabolic acidosis with partial respiratory compensation. The hyperventilation and acidosis resolved after the administration of sodium bicarbonate and reduction of the dose of topiramate.
- A 16-month-old girl developed increasing irritability associated with topiramate; it resolved promptly on withdrawal. Venous blood showed a metabolic acidosis.

The authors postulated that the mechanism of topiramate-induced acidosis is inhibition of carbonic anhydrase in the proximal renal tubule, resulting in impaired proximal bicarbonate reabsorption. Blood gases should be obtained in patients taking topiramate who develop hyperventilation and changes in mental status.

Metabolic acidosis developed in eight of nine infants and toddlers aged 5 months to 2.3 years, weights 8.2–26 (median 11) kg, taking topiramate (48). Five patients were taking other antiepileptic drugs. The metabolic acidosis developed early in treatment (after 8–26 days). Four of the nine children had hyperventilation. This study suggests that metabolic acidosis may not be rare in young children taking topiramate, although it is often asymptomatic. However, the very rapid titration and high doses used make it difficult to generalize the data.

Gastrointestinal

Nausea, abdominal pain, and severe constipation occur rarely, although nausea and abdominal symptoms have been seen commonly in Korean patients (13).

Liver

Hepatitis, reversible on topiramate withdrawal, occurred in one child, but no details were given (49).

- Fulminant liver failure developed in a 39-year-old woman after she had taken topiramate for about 4 months, in addition to carbamazepine. The condition occurred after she increased the dosage of topiramate to 300 mg/day, and was preceded for a few days by tiredness and somnolence (50). She made an uncomplicated recovery after liver transplantation. Histological examination showed centrilobular necrosis, compatible with drug-induced fulminant liver failure.

A causative role of the drug could not be determined with certainty in this case.

Urinary tract

By inhibiting carbonic anhydrase, topiramate reduces the urinary excretion of citrate and increases urinary pH, leading to higher calcium phosphate saturation and a risk of nephrolithiasis. During 1074 patient-years of topiramate exposure in 1183 patients, 18 (1.5%) had 21 episodes of renal calculi, suggesting an incidence of nephrolithiasis comparable to that reported for acetazolamide (SEDA-20, 66).

Body temperature

Reduced sweating, heat and exercise intolerance, and fever have been associated with topiramate. Three patients (aged 17 months, 9 years, and 16 years) developed hyperthermia because of reduced sweating capacity during the summer and/or during exercise 2–3 months after reaching the target dose of topiramate (51). A reduction in the dosage of topiramate did not correct the symptoms, which disappeared on topiramate withdrawal. This adverse effect may be related to carbonic anhydrase inhibition by topiramate, as it has been described with zonisamide (another carbonic anhydrase inhibitor).

- A 9-year-old boy with partial epilepsy taking topiramate 4 mg/kg/day developed hyperthermia, reduced sweating, and tiredness after exercise 4 months after the start of treatment (51). Sudomotor function showed 180 sweat glands/cm^2 (normal 286, fifth percentile 221). After topiramate withdrawal he became asymptomatic and 5 weeks later he had 392 sweat glands/cm^2.

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Long-Term Effects

Drug withdrawal

Two patients with hemiparesis reversible after topiramate withdrawal have been reported (20).

Second-Generation Effects

Lactation

The concentrations of topiramate have been measured in plasma and breast milk in five women with epilepsy during pregnancy and lactation (52). The umbilical cord plasma/maternal plasma ratios were close to unity, suggesting extensive transplacental transfer of topiramate. The mean milk/maternal plasma concentration ratio was 0.86 (range 0.67–1.1) at 2–3 weeks after delivery. The milk/maternal plasma concentration ratios at sampling 1 and 3 months after delivery were similar. Two of the breast-fed infants had detectable (>0.9 μmol/l) concentrations of topiramate 2–3 weeks after delivery, although they were below the limit of quantification (2.8 μmol/l), and one had an undetectable concentration. Thus, breast-fed infants had very low topiramate concentrations. No adverse effects were observed in the infants.

Drug Administration

Drug dosage regimens

Slow dosage titration of topiramate has been advocated by clinicians for improving tolerability. In a multicenter, double-blind trial in adults with refractory partial epilepsy 188 patients were randomized to add-on topiramate by either "slow" titration (initial dose 50 mg/day increased weekly by 50 mg/day) or "fast" titration (initial dose 100 mg/day increased weekly by 100–200 mg/day) (31). The maximum dosage of 400 mg/day in both groups was achieved by 3 or 8 weeks. Efficacy was comparable, but slow titration was significantly associated with a lower frequency of adverse events or withdrawals because of adverse events.

Drug–Drug Interactions

Digoxin

Topiramate slightly impairs digoxin clearance (53), but the interaction is probably not clinically significant.

Enzyme-inducing anticonvulsants

Enzyme-inducing anticonvulsants reduce serum topiramate concentrations to an important extent (SEDA-20, 67).

Oral contraceptives

Topiramate reduces plasma estrogen concentrations in women taking oral contraceptives, by an unknown mechanism (53), potentially reducing the efficacy of the oral contraceptive. In one study topiramate dose-dependently reduced the plasma concentrations of ethinylestradiol by 18–30% (SEDA-20, 67) (54).

Phenytoin

An increase in serum phenytoin concentration has occasionally been observed in patients taking topiramate, possibly in relation to inhibition of CYP2C19 (SEDA-20, 67), but it is usually of little significance.

In 12 patients taking phenytoin monotherapy, topiramate 400–800 mg/day was added progressively; after stabilization phenytoin was tapered and withdrawn (55). Although there were no changes in phenytoin serum concentrations in nine patients, in three of them the peak phenytoin plasma concentrations increased (from 60 to 84 μmol/l, from 112 to 144 μmol/l, and from 108 to 164 μmol/l). Human liver microsomal studies showed that topiramate partially inhibits CYP2C19 at very high concentrations (about 5–15 times higher than the recommended dose). Topiramate clearance was about two-fold higher during co-administration of phenytoin.

Valproic acid

Topiramate can reduce serum valproic acid concentrations to a minor extent (SEDA-20, 67). Conversely, the metabolism of topiramate can be inhibited by valproate (53).

Three children taking valproate developed hyperammonemia after topiramate was added (56). Ammonia was normalized after topiramate was reduced or withdrawn. Thus, topiramate could potentially enhance the risk of hyperammonemia in patients taking valproate. The authors did not discuss the mechanism of this purported interaction.

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Topoisomerase inhibitors

See also Cytostatic and immunosuppressant drugs

General Information

Inhibitors of topoisomerase I and topoisomerase II are the most commonly used anticancer drugs. The camptothecins—topotecan and irinotecan (CPT-11)—interact with the enzyme topoisomerase I; the podophyllotoxins—etoposide and teniposide—target topoisomerase II. They cause various forms of single- and double-strand breaks in DNA (1–7). Other drugs inhibit both enzymes simultaneously (8) (see below).

The anthracyclines and related compounds, such as mitoxantrone and amsacrine (9), also exert their cytotoxic effects via inhibition of topoisomerase II. However, they differ from the camptothecins and podophyllotoxins in respect to DNA intercalation and have a different pattern of cardiac toxicity.

Inhibitors of topoisomerase I

Camptothecins were originally isolated from the wood, bark, and fruit of the oriental tree *Camptotheca acuminata* ("tree of joy"). Why the tree produces these highly toxic alkaloids is not known, but the most likely reason is that the toxins are part of a survival strategy in combating herbivores. Among a lot of isolated plant constituents, the naturally occurring alkaloid camptothecin (CAM, NSC94600) was identified as a highly potent inhibitor of topoisomerase I, which is overexpressed in many cancers. The water-soluble salt CAM-sodium, which was introduced in early preclinical trials in the 1960s, was highly toxic in animals. Hemorrhagic cystitis, leukopenia, and thrombocytopenia were its dose-limiting toxic effects. In addition, sterile hemorrhagic cystitis, myelosuppression, and gastrointestinal toxic effects were common in patients during phase I studies. Clinical testing of CAM-sodium was therefore discontinued in the 1970s. However, the semisynthetic derivatives irinotecan and topotecan are highly active in several malignancies and do not cause hemorrhagic cystitis, because of their greater physicochemical stability and solubility at lower pH values. However, the drugs differ from each other in approved therapeutic uses, recommended doses, toxicity profiles, and pharmacokinetics (1–5).

Several camptothecin analogues are currently being investigated. The water-soluble derivatives lurtotecan (GI147211) and exatecan (DX-8951-f) and the poorly water-soluble analogues 9-aminocamptothecin and 9-nitrocamptothecin, which can be given orally, are in various stages of development (3,10–13).

Exatecan is a novel synthetic camptothecin derivative with a unique hexacyclic structure. It does not require metabolic activation, whereas irinotecan does. In vitro experiments in various cell lines have suggested that exatecan may be 6 and 28 times more active than SN-38 (7-ethyl-10-hydroxycamptothecin, the active metabolite of irinotecan) and topotecan respectively. Furthermore, it has a 2–10 times higher therapeutic index than irinotecan and topotecan. In addition, exatecan may even be active in P-glycoprotein-mediated multidrug-resistant tumor cells. Its dose-limiting adverse effects are neutropenia and liver dysfunction. The recommended dosages of exatecan for phase II trials are 0.5 mg/m^2/day or 0.3 mg/m^2/day as a 30-minute infusion on 5 consecutive days for minimally pretreated and heavily pretreated patients respectively (14,15).

Current clinical investigations with topoisomerase I inhibitors include the feasibility of oral administration of topotecan and irinotecan, the use of a liposomal lurtotecan formulation (NX211), and the use of a pegylated derivative of the naturally occurring camptothecin, which is soluble in aqueous solutions even at low pH values (3,10).

Inhibitors of topoisomerase II

Etoposide and teniposide are semisynthetic derivatives of podophyllin, which was originally isolated from the root of the Indian podophyllum plant. After extensive isolation procedures, the most effective "antileukemic" factor was identified as 4′-demethylepipodophyllin benzylidiene glucoside (DEPBG). Etoposide, its water-soluble derivative etoposide phosphate, and teniposide are semisynthetic analogues of DEPBG with increased antineoplastic activity. Etoposide is active in testicular tumors, non-Hodgkin's lymphoma, Hodgkin's disease, other lymphomas, ovarian carcinoma, gastric carcinoma, breast cancer, small-cell and non-small-cell lung cancers, and cancers of unknown origin. The major indications for teniposide include lymphoma, bladder cancer, acute lymphoblastic leukemia, and glioblastoma (6,7).

Dual inhibitors of topoisomerases I and II

Intoplicin is one of the first congeners of the so-called dual inhibitors of topoisomerases I and II (16). These new antitumor drugs interact with both topoisomerase I and II simultaneously. This mechanism of action appears to be advantageous, because selective inhibition of

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topoisomerase I has been reported to increase topoisomerase II enzyme activity and vice versa, which may be important for the development of drug resistance (17–20). Intoplicin may overcome this limitation. In phase I trials, intoplicin has been reported to cause dose-limiting liver toxicity; other adverse effects were sporadic and mild (16).

Another dual inhibitor of topoisomerase I and topoisomerase II is XR 5000 (N-2-[(dimethylamino)ethyl]acriacridine-4-carboxamine). Its cytotoxicity was not affected by the presence of P-glycoprotein, and it seems to be a promising candidate, even in highly resistant tumor cells. However, neither complete nor partial remission was observed during a phase II trial in 20 patients with advanced or metastatic colorectal cancer (21).

A novel pentafluorinated epipodophylloid characterized by marked antitumor activity in vivo is F11872. It is a dual inhibitor of the catalytic activity of both topoisomerases I and II, with markedly superior activity in vivo compared with other dual inhibitors, such as intoplicin, TAS-103, and others (22).

Mechanisms of action

Topoisomerase I is the target enzyme for the inhibitory effects of camptothecins. It modulates the topological structure of DNA by inducing transient DNA breaks. Single-strand breaks help to remove excessive positive and negative DNA supercoils, which arise during DNA replication and transcription. The interaction between the camptothecins and the enzyme results in the formation of a topoisomerase-I-DNA complex (23).

Etoposide and teniposide interact with topoisomerase II within the tumor cell. This nuclear enzyme catalyses the passage of DNA across adjacent strands during cell division and is most active during the late S and G2 phases of the cell cycle. If the tumor cell is exposed to etoposide during this stage, stabilization of the enzyme-DNA complex results in double- and single-strand breaks in DNA as well as cell-cycle arrest. Several studies have shown that the activity of etoposide is schedule dependent, which means that its antiproliferative effect on tumor cells is greater when it is given over several consecutive days rather than on a single day. At higher dosages, podophyllotoxins may also act as spindle poisons (24).

In contrast to topoisomerase II, cellular concentrations of topoisomerase I are relatively independent of the cell-cycle phase in normal tissues. Thus, topoisomerase I activity is only slightly increased in cells and tissues under conditions of proliferation. However, higher constitutive activities of this enzyme can be detected in several tumor tissues (for example adenocarcinoma of the colon and rectum) compared with healthy tissues (25).

Pharmacokinetics

Camptothecins

Both irinotecan and topotecan contain lactone structures, which can be hydrolysed non-enzymatically into the open-ring form. Under acidic conditions, the equilibrium between the biologically active lactone form and the less active carboxylated form is generally shifted to the lactone form, whereas at physiological or higher values of pH, the lactone form is unstable, because hydrolysis to the open form is favored. In addition, owing to preferential binding of the salt form to serum albumin, the affinity of the carboxylated form for human serum albumin is estimated to be 100 times higher than that of the lactone form. In consequence, when irinotecan is given intravenously, more than 95% of the dose is bound to serum albumin as inactive drug, and is therefore at least transiently unavailable to exert its antineoplastic activity (26–29). Novel camptothecin derivatives, such as exatecan or lurtotecan, are more resistant to rapid hydrolysis because of structural modifications, for example the removal of the 20-OH group (3,10,14,15).

Irinotecan

Irinotecan has been approved for first-line and second-line treatment of advanced colorectal cancer. Conventional dosages range from 350 mg/m^2 intravenously every 3 weeks to 100–125 mg/m^2 intravenously weekly when it is given as a single agent, and 80–180 mg/m^2 intravenously when it is given in combination with 5-fluorouracil and folinic acid weekly (the AIO regimen) or every 14 days (the De Gramont regimen) (4,30).

In contrast to the structurally related topotecan, irinotecan is a prodrug, which has to be converted to its active form, SN-38 (4,30). Cleavage of the side-chain, a bulky piperidino moiety, at the C10 position is rapidly catalysed by carboxylesterases after intravenous administration. SN-38 (7-ethyl-10-hydroxy-camptothecin) is 1000 times more potent than the parent compound. There is an equilibrium between the active lactone and the inactive carboxylated forms in a pH- and protein-dependent manner for both irinotecan and SN-38 (31,32).

The SN-38 is inactivated by conjugation, catalysed by isoforms of uridine diphosphate glucuronosyltransferase, principally UGT 1A7 (33–35). Pharmacogenetic defects in glucuronidation (for example Gilbert's syndrome and Crigler–Najjar syndrome type I) result in impaired glucuronidation. The incidence of Gilbert's syndrome is 0.5–15% in different ethnic groups, and there is significant variability of UGT 1A activity in human livers, with a 17-fold difference between minimum and maximum rates of SN-38 glucuronidation. Patients with Gilbert's syndrome are at increased risk of irinotecan-induced gastrointestinal toxicity and leukopenia if conventional dosages are used (36–40). Paracetamol is a poor predictor of SN-38 glucuronidation capacity based on metabolism by another isozyme (UGT 1A6). However, genotype screening is increasingly becoming feasible. Thus, empirical irinotecan dosage modification or the selection of another anticancer drug is appropriate in patients with poor glucuronidation capacity (36–40).

Both irinotecan and SN-38 are primarily excreted into the bile by the canalicular multispecific organic anion transporter (cMOAT), a member of the ATP cassette of transporters. Therefore, inhibitors of cMOAT, such as ciclosporin, can reduce the clearance of irinotecan and SN-38 (41,42).

The SN-38 glucuronide can be deconjugated in the gut to active SN-38 by bacterial glucuronidases. This enterohepatic circulation of SN-38 results in a further plasma peak, and SN-38 released within the gut lumen has been

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suggested to be an important cause of delayed intestinal toxicity; in animal experiments constitutive bacterial beta-glucuronidase activity correlated with irinotecan-induced cecal damage. In contrast, the prophylactic use of oral antibiotics (for example aminoglycosides or quinolones) or specific glucuronidase inhibitors resulted in attenuation of intestinal toxicity (43).

Aminopentane-carboxylic acid (APC) is a second major metabolite of irinotecan; it is formed by oxidation of the terminal piperidine ring, catalysed by CYP3A4. APC itself is not hydrolysed to SN-38 and is only a weak inhibitor of topoisomerase I (44–48). However, potent CYP3A4 inducers (for example St. John's wort, carbamazepine, and phenytoin) or inhibitors (for example itraconazole) alter irinotecan pharmacokinetics (49–54). Other identified metabolites include NPC (7-ethyl-10-(4-amino-1-piperidono)-carbonyloxycamptothecin), 5-hydroxyirinotecan, and RPR112526 (a decarboxylated product of the acid form of the irinotecan lactone).

Further drug interactions occur if constitutive SN-38 glucuronidation capacity is modified. For example, phenobarbital may induce UGT 1A activity, whereas valproic acid may inhibit it. Thus, co-administration can alter the clearance of irinotecan.

A half-life of 5–14 hours has been reported after intravenous infusion of irinotecan over 30 and 90 minutes. The half-life of the active metabolite SN-38 (total) is 6–14 hours. However, continuous 5-day intravenous infusion schedules result in prolonged half-lives (about 27 hours and 30 hours for irinotecan and SN-38 respectively). In general, the C_{max} of SN-38 is more than 100 times lower than the corresponding value for irinotecan. Plasma concentrations of SN-38 glucuronide were higher than the corresponding concentrations of SN-38: the AUC of SN-38 glucuronide was at least 10 times higher than that of SN-38 (44–47).

Because of the importance of hepatic metabolism in SN-38 elimination by glucuronidation, the biliary clearance of irinotecan and its metabolites is delayed in patients with impaired hepatic function (55–57), and there is a negative correlation between serum bilirubin concentrations and the total body clearance of irinotecan. In a patient with moderately impaired liver function, it was necessary to reduce the dose to 100 mg/m^2 instead of 350 mg/m^2 intravenously thrice-weekly, in order to achieve half-lives and C_{max} values of irinotecan and SN-38 comparable to those observed in patients with normal liver function (55). However, the corresponding AUCs were still significantly increased, resulting in more severe leukopenia and delayed diarrhea. The authors concluded that to improve tolerance, exposure to the drug in a patient of this kind should not exceed 30 mg/m^2 intravenously.

Detailed studies of irinotecan dose modification in patients with liver dysfunction are warranted. According to the results of pharmacokinetic studies, thrice-weekly intravenous doses of irinotecan have been recommended: 350 mg/m^2 in patients with bilirubin concentrations up to 1.5 times the upper limit of the reference range and 200 mg/m^2 in patients with bilirubin concentrations 1.5–3.0 times the upper limit of the reference range (56).

The systemic availability of oral irinotecan is low and variable (10–20%). Transintestinal transport of irinotecan and SN-38 by P-glycoprotein and cytochrome P_{450}-mediated first-pass removal in the intestine accounts for the low absolute availability of irinotecan.

Topotecan

Topotecan has been approved for the treatment of advanced pretreated ovarian and small-cell lung cancer in several countries. After intravenous administration of conventional dosages (for example 1.5 mg/m^2/day for 5 consecutive days) its half-life is 2–4 hours. Prolonged infusion for 3, 5, or 21 days increases drug exposure without affecting the disposition of topotecan (29).

The ratio of the AUCs of the lactone and total topotecan appears to be relatively constant and averages about 0.3, which means that only 30% of the total drug concentration in the plasma represents the closed-ring lactone form. The distribution volume at steady state is 25–75 l/m^2, indicating extensive binding to tissues. Erythrocytes act as a depot for topotecan (lactone), with steady-state concentrations almost 1.7 times those obtained in plasma.

Topotecan is primarily excreted unchanged in the urine. About 49% of the intravenous dose is recovered in the urine as parent drug and 18% in the feces (58). Despite high urinary concentrations, topotecan does not cause urinary toxicity, because of its high water solubility (58,59). Dosage modification is warranted in patients with impaired renal function (60). Reduced doses of 0.75 mg/m^2/day and 0.5 mg/m^2/day have been recommended in untreated and extensively pretreated patients with reduced creatinine clearance (20–40 ml/minute). It has also been suggested that dosage adjustment may even be required if the creatinine clearance is 40–60 ml/minute (61). The recommended starting dose should be 1.2 mg/m^2/day intravenously on five consecutive days, in order to reduce the risk of severe myelosuppression. Because there is no information about topotecan in patients with severe renal insufficiency (creatinine clearance below 20 ml/minute), topotecan should not be given to them (60). There is some evidence that topotecan is hemodialysable (62).

Hepatic metabolism of topotecan, mediated by cytochrome P_{450} isozymes, is of minor quantitative importance (26–29,58). Metabolic pathways include N-dealkylation (producing *N*-demethyltopotecan) and glucuronidation. There is some evidence that potent inhibitors or inducers of CYP3A4 alter the clearance of topotecan (58).

After conventional intravenous dosages of topotecan (for example 1.5 mg/m^2 as a 30-minute infusion on days 1–5) the mean half-life, plasma clearance, and volume of distribution are respectively 2.7 hours, 1.1 ml/minute, and 170 litres. The plasma protein binding of topotecan is low (7–35%). In contrast to many other anticancer drugs, topotecan can penetrate the central nervous system. If the blood–brain barrier is intact, more than 30% of the plasma concentration can be recovered in the cerebrospinal fluid (26–29,58). Nevertheless, based on case reports and experimental data, intrathecal drug administration has been suggested to be advantageous, in order to achieve higher drug concentrations in the cerebrospinal fluid and to avoid systemic toxicity (63,64).

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The systemic availability of oral topotecan is about 30%. Dose-limiting toxicity was reached at a dose of 0.6 mg/m^2 bd and consisted of diarrhea, which started from day 12 to day 20. Other toxic effects, including leukopenia and thrombocytopenia, were mild. The recommended dose for phase II trials was 0.5 mg/m^2 bd for 21 days (65–67).

Podophyllotoxins

Etoposide

At low doses of oral etoposide (for example 50–100 mg), the systemic availability averages 66%, and at higher dosages (100 mg/m^2 and over) 47%. If etoposide phosphate is used, the values are higher (range 66–84%) (68–73).

After intravenous administration of etoposide 150 mg/m^2, the peak plasma concentration averages 20 micrograms/ml and the half-life 7.1 hours. Drug clearance and distribution volume are about 16 ml/minute/m^2 and 17 l/m^2 (6,7,74). With respect to plasma concentrations of etoposide, intravenous etoposide phosphate is equivalent to intravenous etoposide with conventional or intensified dose schedules (75–79). After intravenous administration, the prodrug etoposide phosphate undergoes rapid hydrolysis catalysed by alkaline phosphatase; this conversion is linear even at high intravenous doses of 1200 mg/m^2 infused over 2 hours on days 1 and 2.

About 96% of the dose of etoposide is bound to plasma proteins, the fraction 4% being unbound (80–83). There is a higher risk of myelotoxicity when the unbound fraction is increased by factors such as hyperbilirubinemia or hypoalbuminemia, which is common in patients with hepatic dysfunction or cachexia-inducing tumors (84,85). The variability in unbound drug concentrations has been suggested to be important in the setting of intravenous high-dose etoposide and reinfusion of autologous peripheral blood stem cells. If drug concentrations persist over a longer period of time, the success of engraftment may be severely impaired. Thus, plasma concentration monitoring has been suggested, in order to identify patients at increased risk (86,87).

The renal clearance of etoposide is about 30–40% of the total plasma clearance. Even in patients with nearly normal creatinine concentrations (100–130 μmol/l), there is a slight but significant increase in the AUC, but without more pronounced hematological toxicity. Hepatic etoposide metabolism is mediated by CYP3A4, and results in the production of catechol metabolites. Although these catechols contribute relatively little to the metabolism of etoposide, they may contribute to its late adverse effects, for example secondary malignancies. Further metabolic pathways include glucuronidation and hydroxyacid formation (88). Dosage reductions of 33 and 50% have been recommended for patients with creatinine clearances of 15–25 ml/minute and under 15 ml/minute respectively. In patients with obstructive jaundice and a reduced glomerular filtration rate, a 50% dosage reduction has been recommended empirically (6,7,88,89).

In patients with very severe forms of renal insufficiency, only moderate amounts of etoposide can be eliminated by hemodialysis (90). In patients with brain metastases, high intravenous dosages of etoposide may be needed in order to achieve adequate drug concentrations in the cerebrospinal fluid. In such patients, intrathecal drug administration may be an alternative, in order to reduce systemic toxicity associated with dose-intensive chemotherapy. However, this mode of etoposide administration has not been established (91,92).

There is large interindividual variability in etoposide plasma concentrations with conventional dosages, and some authors have suggested that plasma concentration monitoring would reduce the pharmacokinetic variability and optimize outcomes (93,94).

Teniposide

Teniposide undergoes more extensive metabolic degradation than etoposide, resulting in the catechol derivative 4′-demethyldeoxy-podophyllotoxin. The aglycone and the *trans*/*cis*-hydroxy acids appear to be formed by pH-dependent hydrolysis reactions (7,95,96).

Plasma concentration monitoring has been proposed to be beneficial in patients receiving teniposide. For example, in one study, maintaining steady-state concentrations above 12 micrograms/ml appeared to be important for clinical responses in patients with recurrent leukemia, lymphoma, or neuroblastoma (95). In 10 patients, whose steady-state concentrations were maintained above 12 micrograms/ml, there was shrinkage of the tumor, whereas only five of 13 patients with lower steady-state concentrations had a response. Teniposide has been used as a continuous infusion over 72 hours in intravenous doses of 300–750 mg/m^2.

The mean systemic availability of teniposide after oral administration is about 42% (range 20–71%). Teniposide capsules 50 mg have been suggested to be useful, but no oral formulation has been approved so far (96).

General adverse effects

The dose-limiting adverse effects of irinotecan depend largely on the dosage schedule. Myelosuppression, particularly leukopenia and neutropenia and rarely thrombocytopenia and anemia, have been observed. Gastrointestinal toxicity (that is, diarrhea) is also common and can be acute or subacute. The most dose-limiting adverse effect of topotecan is myelosuppression, which correlates with individual drug exposure. In contrast, gastrointestinal toxicity is generally mild (97–99).

Common adverse effects of etoposide and teniposide (100) include dose-limiting myelosuppression (causing neutropenia more often than thrombocytopenia), dose-dependent nausea or vomiting, and alopecia. Mucositis can be dose limiting, particularly in patients receiving high doses of etoposide. Hypersensitivity reactions are more common with etoposide and teniposide than with etoposide phosphate, because the formulations of the former contain sensitizing solubilizers. Both drugs have been associated with acute myelogenous leukemia.

Organs and Systems

Cardiovascular

There are reports of myocardial infarction in patients who have received combination chemotherapy containing etoposide. The mechanisms have not been clearly elucidated.

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- A 28-year-old man with a non-seminomatous retroperitoneal germ-cell cancer received etoposide (180 mg/day intravenously on days 1–5), bleomycin, and cisplatin (101). He had no cardiac risk factors and no history of cardiac symptoms. On day 3, during infusion of bleomycin, he developed chest pain and dyspnea. The infusion was discontinued and he was given glyceryl trinitrate and diazepam; his symptoms resolved. On day 4 he was given etoposide as scheduled, but four hours later developed severe angina. The electrocardiogram and raised cardiac enzymes were consistent with an acute posterolateral myocardial infarction. He was given heparin, aspirin, and nitrates, and the chemotherapy was discontinued. Within 20 hours his chest pain completely disappeared and his electrocardiogram became normal.

If hypotension occurs during drug administration, it usually subsides when the infusion ends and intravenous fluids or other supportive agents are given. Elderly patients may be particularly susceptible to etoposide-induced hypotension. During a phase I trial of etoposide by continuous infusion, 17 patients were given 75 mg/m^2/day for 5 days and later courses of 100 mg/m^2/day and 150 mg/m^2/day (102). Two patients with pre-existing cardiovascular disease developed myocardial infarctions, one at the 100 mg/m^2/day dose and the other at the 150 mg/m^2/day dose. Another patient developed congestive heart failure at the end of the 5-day infusion and died on day 8; however, this patient also received a saline load of 1500 ml/day for 5 days during etoposide administration and had had previous episodes of congestive cardiac failure. The authors concluded that in patients with underlying cardiovascular disease etoposide must be administered cautiously and that extensive saline loading should be avoided in patients with a history of previous congestive heart failure.

Nervous system

Fatigue is a frequent adverse effect of topotecan and occurs in up to 70% of patients when they receive 1.5 mg/m^2/day (30-minute infusions) for 5 days repeated at day 22; however, only 10% have severe symptoms (4). Topotecan causes headache in some patients.

Rare cases of peripheral neuropathy have been reported after intravenous topotecan, but a causal relation is uncertain.

Neurotoxicity occurs in under 1% of patients who receive teniposide or etoposide, and is more common after high dosages. Adverse nervous system effects, including headache, transient mental confusion, and vertigo, may be related to the blood alcohol concentration, since teniposide and etoposide formulations contain alcohol (103).

Acute neurological dysfunction with exacerbation of pre-existing neurological disorders has been reported after treatment with high-dose etoposide (over 800 mg/m^2/day) given with autologous bone marrow transplantation (104). This happened 9–10 days after the start of treatment, and it abated without sequelae after prompt steroid therapy. Changes in intracranial pressure may explain this acute disturbance.

Peripheral neuropathy, mainly mild and infrequent, has been observed after conventional dosages of etoposide and teniposide. However, during combination therapy with etoposide and vinca alkaloids, more serious forms of peripheral neuropathy have been reported. Of 142 patients with autologous bone marrow transplantation given high-dose etoposide (for example 60 mg/kg combined with melphalan), six developed grade 2–3 polyneuropathy starting 2–8 weeks after transplantation.

About 76% of patients given irinotecan complained of weakness. Grade 3 and 4 weakness has been described in 12–15% with weekly or thrice-weekly administration and during the administration of combination regimens containing fluorouracil.

Hematologic

Myelosuppression, neutropenia, and to a lesser extent thrombocytopenia, are dose-limiting toxic effects of topotecan. Reversible non-cumulative neutropenia usually occurs at between days 8 and 15 after an intravenous dosage of 1.5 mg/m^2 on five consecutive days. The nadir of the neutrophil count occurs on day 11, with recovery on day 21. Neutropenia, with cell counts less than 1.5×10^9/l (grade 2) and 0.5×10^9/l (grade 4), is observed in 70–97% of patients. In addition, 4–33% of patients treated with conventional dosages of topotecan develop neutropenic fever (97–99).

Thrombocytopenia, with platelet counts under 50×10^9/l (grade 3) and 25×10^9/l (grade 4), occurs in 25–77% of patients, with a nadir on day 15 and recovery on day 21. Platelet transfusions are needed in 4–27% of patients. Anemia, defined as a fall in hemoglobin below 8 g/dl (grade 3) or 6.5 g/dl (grade 4), has been reported in 21–41% of patients; erythrocyte transfusions were required in about 25% of treatment courses. More extensive myelosuppression can occur in patients who have been pretreated with cytotoxic drugs. The extent of myelosuppression correlates significantly with both the total topotecan AUC and the topotecan lactone AUC. When prophylactic G-CSF is given, thrombocytopenia is the dose-limiting myelotoxic effect (97–99).

Leukopenia is a dose-limiting adverse effect of irinotecan. Weekly intravenous doses (for example 100–125 mg/m^2) appear to produce a slightly greater incidence of grade 3–4 neutropenia compared with 3-weekly schedules (350 mg/m^2) (16–28 versus 14–22%). The median leukocyte nadir occurs on day 21 (15–27) and recovers 8 days later. Severe anemia (hemoglobin concentrations below 8 g/dl) and severe thrombocytopenia (platelet count below 50×10^9/l) occur in 15 and 2% of patients respectively. There is eosinophilia in up to one-third of patients (2,3).

Myelosuppression is a dose-limiting adverse effect of etoposide and teniposide. Leukopenia is the most common adverse effect associated with oral and intravenous etoposide. Nadirs in neutrophil counts generally occur within 7–14 days. Severe forms following conventional etoposide doses can be expected in about 17% of patients. Thrombocytopenia occurs in 23% of etoposide-treated patients and about 9% are severe (counts below 50×10^9/l). Leukopenia and thrombocytopenia occur

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respectively in 65 and 80% of patients after administration of teniposide (6,7).

Gastrointestinal

Anorexia, nausea and vomiting, and diarrhea are generally mild after the administration of conventional doses of etoposide and teniposide. Stomatitis is uncommon and mucositis starts to be more severe in patients who receive intravenous doses of etoposide up to 1000 mg/m^2. Gastrointestinal toxicity after topotecan is generally mild to moderate. Under 10% of patients complain of grade 3/4 nausea and vomiting, diarrhea or constipation, abdominal pain, or stomatitis. Mucositis is uncommon and mild after intravenous topotecan.

Besides leukopenia, diarrhea is the major dose-limiting adverse effect of irinotecan (105,106). There are two different forms. The acute form occurs very early and is due to inhibition of acetylcholinesterase. The delayed-onset form occurs simultaneously with the leukocyte nadir and depends on the concentration of the active compound SN-38 in the plasma and bowel.

The acute form of diarrhea is short-lived and can be effectively prevented or rapidly suppressed by concomitant atropine. The cholinergic symptoms are accompanied by abdominal cramps (36%), sweating (57%), salivation (11%), visual disturbances (15%), lacrimation (12%), and piloerection (3%). The recommended dose of atropine is 0.25 mg intravenously for prevention or 0.25–1.0 mg for acute treatment of patients with early cholinergic symptoms. As cholinergic symptoms have not been observed with other camptothecin derivatives, it can be speculated that these adverse effects are restricted to irinotecan, whose piperidino group bears some structural similarity to the potent nicotine receptor stimulant dimethylphenylpiperazinium (106).

Delayed-onset diarrhea of all grades of severity occurs in nearly 90% of patients during the first three treatment cycles with irinotecan. It can resemble a cholera-like syndrome, which occurs several days after completion of the infusion. There is grade 3/4 diarrhea (grade 3 being at least 7–9 stools per day, incontinence, or severe cramps; grade 4 being 10 stools or more per day, grossly bloody stools, or a need for total parenteral nutrition) in 31–37% of patients treated weekly and in 35–39% of patients treated with 3-weekly regimens. The median day of occurrence was day 6 (range days 2–12). Of the four major pathophysiological mechanisms of diarrhea (osmotic, secretory, altered motility, and exudative), irinotecan-induced watery diarrhea appears to be secretory, defined by abnormal ion transport in intestinal epithelial cells (105).

There is increasing evidence that the extent and severity of gastrointestinal toxicity correlates with concentrations of the active compound SN-38 in the plasma and bowel. The role of plasma pharmacokinetics in predicting the severity of irinotecan-induced diarrhea has been highlighted by the introduction of a biliary index, which is the product of the relative area ratio of SN-38 to SN-38 glucuronide and the total AUC. According to preliminary evidence, preventive measures should be considered when the biliary index exceeds 3.484 hours.micrograms/ml (107,108).

Because SN-38 glucuronide undergoes deconjugation by bacteria-derived beta-glucuronidase in the bowel after biliary excretion, a strategy for reducing irinotecan-induced subacute diarrhea has been proposed: inhibition of intestinal microflora by a broad-spectrum antibiotic. In one study, this ameliorated subacute diarrhea in subsequent cycles; in six of seven patients, the prophylactic oral use of neomycin resulted in less severe forms of diarrhea compared with controls (43). About 30% of irinotecan is excreted via the bile unchanged and may be directly converted to SN-38 in the bowel by intestinal carboxyesterases; however, specific non-absorbable inhibitors of intestinal carboxyesterases for oral use are not yet available.

Because the equilibrium between the active lactone form and the ring-opened carboxylate form is pH dependent, oral alkalinization with a mixture consisting of sodium bicarbonate (2.0 g/day), magnesium oxide (2.0–4.0 g/day), water (pH over 7.2, 1.5–2 l/day), and ursodeoxycholic acid (300 mg/day), combined with "controlled" defecation was used in a phase II trial to reduce subacute gastrointestinal toxicity. Anticancer activity was maintained and the incidences of diarrhea and myelosuppression were significantly reduced compared with a non-randomized control group (109–111).

The efficacy of symptomatic antidiarrheal treatment with several drugs, including loperamide, octreotide, racecadodril, and budesonide, has been assessed (105,112,113). Loperamide is recommended when the first signs of subacute, late-onset diarrhea occur; the dose is 4 mg at the start, followed by 2 mg every 2 hours, continued until the diarrhea has stopped for at least 12 hours. Premedication with loperamide is not indicated. Some authors also recommend dosage modification in subsequent cycles. If loperamide alone is insufficient, racecadodril (acetorphane, Tiorfan) 100 mg tds can be added. Racecadodril belongs to a group of drugs that block cAMP-mediated hypersecretion in the gut by inhibiting the intestinal enzyme enkephalinase. The somatostatin analogue octreotide is effective in loperamide-refractory patients with severe diarrhea despite loperamide and/or acetorphane. Subcutaneous doses of 100 micrograms tds up to 500 micrograms every 8 hours for 48–96 hours have produced improvement in diarrhea by one WHO toxicity grade or even more (105).

Oral budesonide has also been proposed to be beneficial in patients with subacute diarrhea. It has 90% first-pass removal in the liver, and so its systemic activity is low. Budesonide controls symptoms of diarrhea in most patients with inflammatory bowel disease. Preliminary data have suggested that the use of budesonide in patients with irinotecan-induced diarrhea could reduce the severity of symptoms. In addition, in a phase III trial budesonide 3 mg tds prevented irinotecan-induced diarrhea to a moderate extent. Budesonide is an option in patients who do not respond to high-dose oral loperamide (113).

The use of oral immunomodulators (for example interleukin-15 and Kampo medicines) has been suggested in order to reduce irinotecan-related diarrhea; however, randomized clinical trials are required, to assess efficacy (42).

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Liver

Etoposide has been associated with increased liver enzymes, but a causal relation has not been established (114).

Urinary tract

Camptothecin can cause hemorrhagic cystitis (115), which has not been reported with semisynthetic camptothecin derivatives, supposedly because they are highly soluble in aqueous solutions even at low pH values. However, in a study of the use of camptothecin conjugated to a water-soluble polymer, two of three patients who received 80 mg/m^2/week developed hemorrhagic cystitis (grade 1/3 dysuria and grade 2/3 hematuria) during the second and third cycles; at 120 mg/m^2/week there was grade 1 bladder toxicity in two of three patients (116).

Skin

Skin rashes involving the trunk, scalp, and limbs have been reported in 17–25% of patients receiving topotecan as a short-term infusion, whereas continuous drug infusion appears to be very rarely associated with rashes. These skin reactions typically appear on days 4–8 and resolve on day 15.

- A 45-year-old woman received topotecan and colony-stimulating factor for ovarian cancer and developed erythematous and slightly pruritic plaques on the upper and lower limbs and ear lobes about one week later (117). The lesions subsided spontaneously in about 10 days and recurred after the next dose. A skin biopsy showed neutrophilic eccrine hidradenitis; all skin cultures were negative.

Skin rashes due to podophyllotoxin derivatives may be hypersensitivity reactions and can be related to the drug itself or more commonly to the vehicles used. Dose-related, non-IgE-mediated hypersensitivity has been reported in 16 children receiving teniposide (118). Other published reports of hypersensitivity or anaphylactoid reactions to teniposide include degranulation of basophils (119,120), and eight anaphylactic reactions in children, all associated with the use of intravenous teniposide 150 mg/m^2 (121).

There has been a single report of etoposide-induced hand–foot syndrome (122).

Hair

Reversible alopecia is very common at standard doses of podophyllotoxin derivatives, starting at doses of 500 mg/m^2 of etoposide. It is also common even with low, continuous oral doses of etoposide (for example 50 mg/m^2/day). Partial or complete alopecia occurs in 12–70% of patients taking topotecan or irinotecan (123).

Immunologic

The epipodophyllotoxins etoposide and teniposide can cause hypersensitivity reactions, which appear to be of type I (124). In a review of 93 cases, the characteristic features of the hypersensitivity reactions that occurred after intravenous etoposide included bronchospasm, facial flushing, rashes, dyspnea, fever, chills, tachycardia, chest tightness, cyanosis, and changes in blood pressure (hypotension and hypertension) (125).

Hypersensitivity to etoposide or tenoposide has been reported in 50 of a series of 108 patients. The risk is related to the cumulative dose, reaching a maximum at 1500–2000 mg/m^2 in the case of tenoposide and 2000–3000 mg/m^2 for etoposide (126). Acute hypersensitivity reactions, characterized by hypotension, bronchospasm, and facial flushing, have been associated with etoposide (127,128). Rechallenge with appropriate prophylactic cover supported the association.

Very severe forms of hypersensitivity reactions, such as Stevens–Johnson syndrome, are very rare (129). Anaphylactic-like reactions have occurred in 0.7–2% of patients after etoposide administration. Some data suggest that the overall frequency of hypersensitivity reactions to teniposide may be as high as 50% if all forms of hypersensitivity are considered. With very few exceptions, patients recover quickly when the drug infusion is stopped immediately (124).

Hypersensitivity reactions to etoposide or teniposide usually occur within minutes after intravenous administration, and are probably related to release of vasoactive substances by basophils and/or mast cells. Several reports have suggested that premedication with an antihistamine and/or a corticosteroid may prevent further hypersensitivity reactions, even in patients with a history of previous reactions. However, this strategy should not be followed when patients have had severe hypersensitivity reactions, such as long-lasting bronchospasm or severe hypotension (130,131). Etoposide was successfully restarted in 78% of patients who had had a hypersensitivity reaction, especially when the drug was infused at a slower rate after premedication with an antihistamine and/or a glucocorticoid (132).

Hypersensitivity reactions to etoposide and teniposide occur in 33–51% of patients (123,124) and are primarily related to adjuvants in the parenteral formulations rather than the drugs themselves. In the case of teniposide, the solubilizing adjuvant polyethoxylated castor oil (Cremophor EL) has been implicated. However, in nine children who had facial edema and flushing after receiving teniposide, the drug alone degranulated basophils in vitro, causing histamine release, while Cremophor did not (119). In addition, etoposide formulations for parenteral use contain several adjuvants, including polysorbate 80, benzyl alcohol, and polyethylene glycol, because it is sparingly soluble in aqueous solutions, and these may contribute to hypersensitivity reactions. Polysorbate 80 may also be implicated in rare cases of hypotension and metabolic acidosis, particularly with high dosages (133).

In contrast, the structurally related etoposide phosphate is highly soluble in aqueous solutions and no solubilizing adjuvants are necessary. Preliminary data suggest that the incidence of hypersensitivity reactions is lower with etoposide phosphate than with etoposide, strengthening the hypothesis that adjuvants have a major role in the development of allergic reactions (123,124). In one case, a patient who had a type I hypersensitivity reaction to etoposide was successfully retreated with etoposide phosphate (134).

On the other hand, cross-reactivity to etoposide has been observed in patients with hypersensitivity reactions

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to teniposide, suggesting that allergic reactions are not exclusively restricted to the use of the solvents. In addition, hypersensitivity reactions have also been reported after oral etoposide (123,124).

- Hypotension, bronchospasm, and facial flushing occurred in a 38-year-old man with advanced testicular cancer associated with an intravenous infusion of etoposide (127). The reaction began within 3 minutes after the start of the infusion and resolved with intravenous fluids and diphenhydramine. Later, he was given four doses of etoposide after pretreatment with diphenhydramine and dexamethasone, without incident.

Successful rechallenge has been reported after a reaction to etoposide in a 19-year-old man, who was successfully re-treated with etoposide phosphate with only antiemetic doses of glucocorticoids as cover (134). This case tends to support the old assumption that etoposide hypersensitivity is due to the excipients in the formulation.

Long-Term Effects

Mutagenicity

Etoposide and teniposide are mutagenic in various bacterial and mammalian genotoxicity tests (135).

Tumorigenicity

Based on animal experiments, etoposide and teniposide should be classified as potential carcinogens (136).

Exposure to etoposide and teniposide has been reported to be an important risk factor for the development of secondary acute myelogenous leukemia (137–143). Etoposide has been suggested to have considerable leukemogenic activity. Of 119 patients with advanced non-small-cell lung cancers, 24 survived for more than 1 year after treatment with etoposide and cisplatin with or without vindesine (144). Of these 24 patients, four developed secondary acute myelogenous leukemia at 13, 19, 28, and 35 months from the start of treatment, having received a two-fold greater cumulative dose of etoposide (6.8 versus 3.0 g/m^2). Podophyllotoxin-related secondary acute myelogenous leukemia has a rather short latent period (2–3 years), and differs from malignancies caused by other drugs (for example alkylating agents) by its unique molecular marker, a balanced translocation involving the mixed-lineage leukemia (MLL) gene on chromosome 11 ("11q23 abnormalities") (145). Southern blot analysis of enzyme-digested DNA from etoposide-treated cell lines and from peripheral blood cells after treatment with etoposide showed frequent rearrangements of MLL, but not of other genes (146). There are differences between the chromosomal abnormalities and the subsequent acute myeloid leukemia associated with the alkylating agents and those following topoisomerase inhibition by podophyllotoxins (147). The alkylating agents cause abnormalities of chromosomes 5 and 7, singly or together, and the podophyllotoxins damage the 11q23 chromosome locus (145).

- A 15-year-old white girl with stage II Hodgkin's disease, who was treated with a combination of vincristine, doxorubicin, bleomycin, and etoposide (total dose 2000 mg/m^2) over 4 months followed by radiotherapy, developed secondary acute myelogenous leukemia 16 months after the initial diagnosis (142).
- An 11-year-old boy with virus-associated hemophagocytic syndrome was treated with intravenous and oral etoposide (0.3 g and 2.8 g/m^2 respectively) and developed acute myelogenous leukemia 26 months after the diagnosis (142).

These reports and others confirm that even conventional doses of etoposide can be associated with a risk of secondary acute myelogenous leukemia. The risk appears to be related to both the schedule and the cumulative dose, and it can be aggravated by addition of alkylating agents and/or radiotherapy (148,149).

Two of 21 adults with Hodgkin's disease developed secondary acute myelogenous leukemia after receiving a regimen that included a cumulative dose of etoposide of 945–3640 mg/m^2 given over 3–6 months (141). Both patients also received MOPP after primary treatment failure, and the disease itself is associated with a high risk of secondary malignancies; however, the short latency period before the development of acute myelogenous leukemia (17–32 months) was thought to be typical of podophyllotoxin-associated disease. Altogether the etoposide-related incidence of secondary acute myelogenous leukemia in three retrospective case series was 0.4–8.1%. Secondary leukemia developed 9–68 months after the diagnosis of the first cancer.

Teniposide is about 10 times more potent than etoposide in causing DNA damage in vitro and in vivo. In 21 of 733 children with acute lymphoblastic leukemia in remission, who received maintenance therapy with teniposide once or twice weekly in combination with other anticancer drugs, the risk of secondary acute myelogenous leukemia was about 12 times higher than in patients who had been treated with less intensive schedules (for example a short course of teniposide for induction chemotherapy) (149).

In conclusion, podophyllotoxin-containing regimens carry a small but significant risk of secondary acute myelogenous leukemia. The risk may be increased by higher total cumulative doses (for example etoposide over 2 g/m^2), weekly or twice-weekly schedules, the concomitant administration of drugs that inhibit DNA repair, concomitant radiotherapy, or the use of high doses of cisplatin. It has therefore been recommended that etoposide be used cautiously in low-risk diseases.

Second-Generation Effects

Fertility

The effects on fertility of inhibitors of topoisomerases I and II have not yet been fully elucidated. However, ovarian failure, amenorrhea, anovulatory cycles, and hypomenorrhea have been described in women receiving etoposide (150).

Teratogenicity

Anticancer drugs can be classified as potentially teratogenic and embryocidal, and can cause embryonic

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resorption, spinal defects, decreased fetal weight, and fetal abnormalities. However, there are no controlled studies of the use of these drugs in pregnant women, and women of childbearing potential should be advised to avoid pregnancy while they are receiving chemotherapy and should be informed about the potential hazards to the fetus (151).

Drug Administration

Drug administration route

The safe intraventricular administration of etoposide has been reported (152).

Drug–Drug Interactions

Ciclosporin

The coadministration of etoposide and high-dose ciclosporin resulted in increased etoposide serum concentrations (153). Lower doses of etoposide were therefore recommended when combined with high-dose ciclosporin.

Cisplatin

Co-administration of cisplatin before topotecan has a sequence-dependent effect on the disposition of topotecan. Cisplatin-related acute changes in glomerular filtration rate can temporarily alter topotecan clearance, causing more severe myelosuppression. Nevertheless, this sequence has been recommended in clinical trials, based on its high antineoplastic efficacy. Patients therefore have to be monitored closely when the two agents are given together (154).

Docetaxel

Topotecan reduced docetaxel clearance by 50% and increased the severity of neutropenia when given over three consecutive days before the combination (155). The underlying reason for this interaction has not been elucidated; however, when combination therapy is used, docetaxel should be scheduled on day 1 and topotecan on days 1–4.

Enzyme inducers

Etoposide and teniposide are substrates of CYP3A4, and their clearance rate is increased by inducers such as carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's wort (49,51–54,156).

Enzyme inhibitors

Potent inhibitors of CYP3A4, such as ketoconazole or itraconazole, reduce the formation of inactive aminopentane-carboxylic acid from irinotecan, resulting in higher concentrations of the active metabolite SN-38. In seven patients who received irinotecan 350 mg/m^2 alone intravenously for 90 minutes and followed 3 weeks later by irinotecan 100 mg/m^2 in combination with ketoconazole 200 mg orally for 2 days, ketoconazole reduced the formation of aminopentane-carboxylic acid by 87% and increased the formation of SN-38 by 109%; irinotecan clearance and the formation of SN-38 glucuronide were not affected (50).

Fluorouracil

If irinotecan is combined with 5-fluorouracil and calcium folinate, an infusion regimen of fluorouracil rather than bolus administration is associated with a lower incidence of severe toxicity (leukopenia and life-threatening sepsis) (157).

Neomycin

Diarrhea ameliorated in six of seven patients treated with irinotecan in combination with oral neomycin at 1000 mg tds (43). Neomycin had no effect on the pharmacokinetics of irinotecan and its major metabolites.

Oxaliplatin

Irinotecan (80 mg/m^2 intravenously) given as a 1-hour infusion immediately after oxaliplatin (85 mg/m^2 intravenously) was associated with hypersalivation and abdominal pain (158,159). These symptoms disappeared after an injection of atropine but recurred when irinotecan was given as a single agent or when the two drugs were separated by 24 hours. However, restarting the original schedule once more resulted in extended cholinergic symptoms. It has been postulated that oxaliplatin potentiates the direct inhibitory effect of irinotecan on acetylcholinesterase.

St. John's wort

St. John's wort (300 mg tds, starting 14 days before administration) reduced the AUC of the active metabolite of irinotecan, SN-38, by 42% and the severity of expected myelosuppression (51). Leukocyte and neutrophil counts were reduced by 8.6% and 4.3% after St. John's wort co-administration in contrast to monotherapy (reductions of 56% and 63%). In addition, the AUC of aminopentane-carboxylic acid was reduced by 28%. Whether the concomitant use of dexamethasone had some effect on this interaction has not been elucidated.

Valspodar

Valspodar significantly increased the AUC and half-life of etoposide, and dosage reductions of up to 66% are required to minimize toxicity when these drugs are used together.

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Torasemide

See also Diuretics

General Information

Torasemide is a long-acting loop diuretic promoted for use in hypertension. Like piretanide, it is claimed to be potassium neutral, but the assertion is premature. There is no evidence that torasemide has metabolic advantages over thiazides (SEDA-16, 226) (SEDA-17, 264) (SEDA-18, 237).

Organs and Systems

Skin

Torasemide has been associated with various rashes, including non-specific erythematous lesions, pruritus, and photoallergic lichenoid lesions (SEDA-22, 239).

Immunologic

Two possible cases of vasculitis with renal insufficiency have been reported in patients taking torasemide (1,2). This adverse effect is not surprising, since torasemide is structurally similar to sulfa drugs, which can cause vasculitis.

- A 70-year-old man developed heart failure secondary to ischemic heart disease and severe aortic stenosis (1). Furosemide 20 mg/day was replaced by torasemide 5 mg/day. After the second dose he developed oliguria and an erythematous morbilliform rash with palpable violet petechial lesions on the legs. Chest X-ray showed bilateral alveolar infiltrates. Serum creatinine and potassium were raised (212 μmol/l and 6.7 mmol/l respectively). Skin biopsy showed leukocytoclastic vasculitis. After withdrawal of torasemide, his renal function improved (serum creatinine 97 μmol/l) and the skin lesions resolved (leaving residual pigmented areas) within 8 days.
- An 84-year-old man with ischemic heart disease and hypertension took torasemide 10 mg/day for persistent edema (1). About 24 hours after the first dose of torasemide, he developed painless, non-palpable, petechial lesions on the limbs and trunk, with oliguria. His serum creatinine was 256 μmol/l and his serum potassium 6.2 mmol/l. Skin biopsy showed non-leukocytoclastic vasculitis with a mixed inflammatory infiltrate including eosinophils. He was symptom free 15 days after withdrawal of torasemide.

Neither patient had a previous history of drug hypersensitivity. Both patients had previously tolerated furosemide, another sulfonamide derivative. The temporal correlation with torasemide administration suggested a causal relation, but the mechanism was unclear.

Drug–Drug Interactions

NSAIDs

NSAIDs block the natriuretic effect of torasemide (SEDA-21, 229).

Probenecid

Probenecid blocks the natriuretic effect of torasemide (SEDA-21, 229).

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Tosufloxacin

See also Fluoroquinolones

General Information

Tosufloxacin is a fluoroquinolone antibacterial with properties similar to those of ciprofloxacin.

Observational studies

In 58 Japanese patients with typhoid fever, 42 with paratyphoid fever, and one with both typhoid fever and paratyphoid fever, almost 80% of whom were treated with tosufloxacin, there were adverse effects (nausea, urticaria, aphthous stomatitis) in 3.6% and raised serum amylase in 8.3% (1). All the adverse reactions resolved with or without a change in drug therapy.

General adverse effects

The most common adverse reactions to tosufloxacin are gastrointestinal disorders, including diarrhea, abdominal discomfort, nausea and vomiting, and skin disorders, including rash and pruritus (2). Central and peripheral nervous system disorders were observed in 0.36% of patients and the most common symptoms were headache and dizziness.

Organs and Systems

Respiratory

- A syndrome of pulmonary infiltration with eosinophilia occurred in an 83-year-old man who was given piperacillin plus tosufloxacin (3).

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In vitro blastogenesis of his peripheral blood lymphocytes was strongly enhanced by piperacillin and tosufloxacin, and they generated a large amount of interleukin-5.

Skin

There is a low incidence of phototoxicity with tosufloxacin (2).

Musculoskeletal

Rhabdomyolysis has been reported in 13 patients taking tosufloxacin (2).

Drug–Drug Interactions

Antacids

The C_{max} and AUC of tosufloxacin tosilate 300 mg were significantly reduced by aluminium hydroxide gel fine granules 1 g or magnesium oxide 1 g (2).

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Tosylchloramide sodium

See also Disinfectants and antiseptics

General Information

Tosylchloramide has been used as a wound disinfectant, a general surgical antiseptic, and for the disinfection of water (1).

Organs and Systems

Respiratory

Asthma has been attributed to tosylchloramide (2).

Immunologic

Contact sensitization to tosylchloramide has been reported (3).

- Urticaria, rhinitis, dyspnea, and edema of the face were reported in a female nurse after contact (SEDA-11, 492) (4). Specific IgE antibodies to tosylchloramide were demonstrated.

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Tramadol

General Information

Tramadol is a synthetic opioid analgesic with activity at OP_3 (μ) opioid receptors, but it also inhibits the re-uptake of both 5-HT and noradrenaline and stimulates the presynaptic release of 5-HT. It produces a similar analgesic effect to pethidine and is about one-tenth as potent as morphine.

The reported adverse effects of tramadol are nausea, vomiting, sweating, dry mouth, dizziness, sedation, headache, and hypertension (SEDA-17, 84) (SEDA-20, 81). The atypical analgesic effects of tramadol and its associated adverse effects profile have been reviewed (1).

The metabolism of tramadol by CYP2D6 is important for its analgesic effect; tramadol may therefore be a poor analgesic in poor metabolizers by CYP2D6, while extensive metabolizers may have better analgesia and more adverse effects (SEDA-21, 90).

In a review of the use of tramadol in musculoskeletal pain the authors concluded that tramadol can be used at Step 2 of the analgesic ladder, since its efficacy, alone or in conjunction with NSAIDs, in the management of chronic musculoskeletal pain without increasing the frequency of adverse effects has been confirmed (2,3).

Comparative studies

Bupivacaine

In a randomized, controlled study in 60 boys (aged 1–7 years) undergoing unilateral herniorrhaphy, caudal 0.25% bupivacaine 1 mg/kg plus tramadol 1.5 mg/kg resulted in superior analgesia (quality and duration) with no significant increase in opioid-related adverse effects compared with children who received 0.25% bupivacaine 1 mg/kg alone or caudal tramadol 1.5 mg/kg in 0.9% saline alone (4).

Thirty children (1–5 years old) in an open, controlled study were randomly given caudal block with 0.25% bupivacaine 0.8 mg/kg or tramadol 0.8 or 2 mg/kg (5). The duration of analgesia was longer (9.1 hours) in those given tramadol but the incidences of opioid-related

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adverse effects (gastrointestinal effects and sweating) were significantly higher.

Clomipramine + levomepromazine

Since the monoamine effects of tramadol resemble the effect of antidepressants, it has been compared with clomipramine + levomepromazine in patients with postherpetic neuralgia. The incidence of adverse effects was 77% with tramadol and 83% with clomipramine (SEDA-20, 81).

Codeine

In a 4-week, double-blind, multicenter, randomized study, tramadol plus paracetamol (37.5/325 mg) was as effective as codeine plus paracetamol (co-codamol 30/300 mg) in chronic non-malignant low back pain and osteoarthritis pain, with acceptable tolerability (6).

When tramadol was compared with codeine in 65 patients undergoing elective intracranial surgery, there was a significantly higher incidence of postoperative nausea, vomiting, and sedation with tramadol 75 mg (7). The patients given codeine had significantly lower pain scores over the first 48 hours postoperatively.

Non-steroidal anti-inflammatory drugs

Tramadol and non-steroidal anti-inflammatory drugs have been compared in two studies of patients with joint pain associated with osteoarthritis (8,9). In an open, randomized study 60 patients with osteoarthritis taking NSAIDs were given either modified-release tramadol 100 mg 8-hourly or modified-release dihydrocodeine 60 mg 8-hourly for 4 days; the controls were 30 patients who took an NSAID alone (8). Both opioids provided adequate analgesic adjuncts to NSAIDs, but tramadol caused significantly more minor initial adverse effects.

Diclofenac

In a double-blind, randomized, crossover study in 60 patients with osteoarthritis of the hip or knee, tramadol 50–100 mg up to three times daily was compared with diclofenac (25–50 mg up to three times daily) over 4 weeks (10). Both regimens gave modest pain relief, with no significant differences between the two groups, although within individual patients there were marked differences in analgesic effectiveness. Tramadol was associated with a significantly higher rate of adverse effects (20 versus 3.3%), notably headaches, nausea, constipation, tiredness, and vomiting, but there was no significant difference in adverse events that required withdrawal.

Ketorolac

Intravenous tramadol 1.5 mg/kg has been compared with a single dose of intravenous ketorolac 10 ng in 60 patients scheduled to undergo day-case laparoscopic sterilization in a prospective, randomized, double-blind comparison (11). Tramadol was associated with significantly less postoperative pain. There was no difference in the incidence or severity of nausea and vomiting between the two groups. Dry mouth was significantly more common with tramadol (60 versus 27%).

Opioid analgesics

Fentanyl

In a comparison of tramadol (1 or 2 mg/kg) and fentanyl (2 μg/kg) for postoperative analgesia after pediatric anesthesia, the two drugs had equal analgesic potency and produced similar hemodynamic stability and a similar incidence of adverse effects (12).

Hydrocodone

A randomized, double-blind comparison of the effectiveness of a single dose of tramadol 100 mg with a single dose of hydrocodone 5 mg plus paracetamol 500 mg in acute musculoskeletal pain in 68 subjects after minor trauma has been published (13). Tramadol gave significantly worse analgesia. Adverse effects (nausea and vomiting, drowsiness and dizziness, and anxiety) were uncommon and there was no significant difference between the two drugs.

Morphine

In a comparison of the analgesic effects of intermittent boluses of tramadol or morphine after abdominal surgery in 523 patients, tramadol caused more adverse effects (43 versus 34%), although the difference was not statistically significant. The commonest adverse effects were nausea (32 and 22%), vomiting (4.9 and 3.8%), urinary retention (3.0 and 2.7%), and sweating (3.8 and 0.4%) (SEDA-20, 81).

Tramadol and morphine have been compared in 40 women undergoing hysterectomy (14). At the start of wound closure, patients received either tramadol 3 mg/kg or morphine 0.2 mg/kg intravenously, which did not cause changes in arterial pressure or heart rate. There were no differences in times to spontaneous respiration, awakening, or orientation between the two groups, and ventilation frequency and pain scores were similar throughout 90 minutes. Similar numbers in each group required supplementary analgesia. Performance of the p-deletion test, a measure of psychomotor function, was more rapid in the tramadol group, but the performance of all subjects was impaired at 90 minutes compared with their preoperative scores.

In a randomized, double-blind study in 20 patients with severe postoperative pain given either intravenous tramadol 1 mg/kg or morphine 0.1 mg/kg, both drugs were effective analgesics but higher dosages than those usually administered were necessary (15). Tramadol did not cause any severe adverse effects, but with morphine there was one case each of severe sedation and respiratory depression.

A comparison of tramadol and morphine for subcutaneous patient-controlled analgesia after orthopedic surgery showed that tramadol 40 mg subcutaneously and morphine 2 mg subcutaneously were equally effective in providing analgesia (16). Drug use in the first 24 hours averaged 800 mg for tramadol and 40 mg for morphine. However, mean arterial blood pressure fell significantly in both groups after 24 hours, with a 17% mean maximal fall from baseline concentrations for tramadol and 20% for morphine; heart rate increased by 17 and 15% respectively. Oxygen saturation also fell significantly in both groups, but was not associated with changes in respiratory

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rate. Nausea and vomiting were more common with tramadol (65%). In this study, patients required significantly more tramadol than had been predicted, and the authors commented that at this dosage, the adverse effects profile was similar to that of morphine.

In a double-blind study 150 patients with post-traumatic musculoskeletal pain were allocated to either tramadol 100 mg, with possible increases to a total of 200 mg, or morphine 5 mg or 10 mg with a total increase to 20 mg (17). Analgesic efficacy and adverse effect profiles were similar in the two groups.

Non-opioid analgesics

In a double-blind, randomized study in 120 patients scheduled to undergo outpatient hand surgery with intravenous regional anesthesia, tramadol 100 mg was compared with either metamizol 1 g or paracetamol 1 g, all 6-hourly (18). Seven patients given tramadol withdrew because of severe nausea and dizziness. Tramadol was the most effective analgesic, but none of the drugs alone provided effective analgesia in all patients and 40% needed rescue analgesia.

Tramadol has been compared with a paracetamol derivative in a double-blind, randomized, controlled study in 80 patients undergoing elective thyroidectomy (19). They were randomly assigned to propacetamol (an injectable prodrug of paracetamol) 2 g or intravenous tramadol 1.5 mg/kg. A single dose of tramadol provided better analgesia than propacetamol during the first 6 hours after surgery, but failed to ensure optimal analgesia subsequently. The incidences of nausea, vomiting, and sedation were comparable in the two groups.

Placebo-controlled studies

In two randomized, double-blind studies tramadol provided effective and safe long-term relief of pain in diabetic neuropathy (20) and fibromyalgia (21). The adverse effects (constipation, nausea, and headache) were well tolerated.

The postoperative analgesic efficacy of tramadol 2 mg/kg has been studied in 80 children (aged 1–3 years) undergoing day-case adenoidectomy without premedication in a double-blind, randomized, placebo-controlled study (22). General anesthesia was induced with intravenous alfentanil 10 μg/kg plus lidocaine followed by propofol and mivacurium. The children received intravenous tramadol 2 mg/kg or placebo immediately after induction of anesthesia. Those given tramadol required fewer pethidine rescue medication doses than those given placebo. In fact, 45% of the children who were given tramadol did not require postoperative analgesia at all, compared with 15% of the children who were given placebo. The incidences of adverse effects were similar in the two groups.

The use or addition of tramadol in children undergoing lower abdominal surgery has been examined in three studies (4,5,23). In a double-blind, randomized, controlled study, 125 children undergoing inguinal herniorrhaphy were allocated to receive tramadol 2 mg/kg or morphine sulfate 0.03 mg/kg before surgery; the control group received morphine sulfate 0.03 mg/kg at the end of surgery (23). Caudal tramadol 2 mg/kg provided reliable postoperative analgesia and there were no inter-group differences in postoperative adverse effects or quality and duration of pain relief.

In 129 patients with severe joint pain associated with osteoarthritis, tramadol was significantly more effective than placebo, but 26 patients taking tramadol and 43 taking placebo withdrew because of ineffectiveness or adverse effects; the main adverse effects of tramadol were nausea and constipation (9).

Tramadol has been used in the treatment of shivering after anesthesia. In one study, 150 patients scheduled for general anesthesia and surgery were randomly allocated to intravenous tramadol 1 or 2 mg/kg or 0.9% saline given at the time of wound closure (24). The authors concluded that both doses of tramadol were effective and safe. Of the patients in the higher-dose group, 2% had shivering, compared with 4% in the lower-dose group and 48% in the control group. In a similar study in 96 patients, the optimal dose of tramadol in preventing shivering after anesthesia was 0.5–1 mg/kg intravenously (25).

Combination studies

Tramadol has been combined with various drugs in order to enhance efficacy or reduce adverse effects.

Aspirin

The analgesic efficacy of tramadol can be further enhanced by adding injectable lysine acetyl salicylate (aspirin) after orthopedic surgery with no significant increase in adverse effects (26).

Dexamethasone

In a randomized, placebo-controlled study, the addition of an intravenous bolus of dexamethasone 150 micrograms/kg with a PCA system programmed to deliver tramadol 20 mg in a 1 ml solution on demand in 50 patients after major abdominal surgery significantly reduced the incidence of nausea, vomiting, and subsequent administration of rescue antiemetic therapy (27).

Droperidol

The use of tramadol for postoperative analgesia by intravenous patient-controlled analgesia (PCA) has gained popularity, mostly because it is less likely to cause sedation and respiratory depression (28). However, it is associated with nausea, vomiting, dry mouth, and sweating. The addition of droperidol to tramadol PCA reduced the incidence of gastrointestinal symptoms without significantly increasing sedation (29). In a double-blind, randomized study, 40 patients undergoing coronary artery bypass grafting and/or valve replacement surgery were given droperidol 0.1 mg/ml plus either tramadol 10 mg/ml or morphine 1 mg/ml. The results in the two groups were comparable in efficacy, adverse effects profiles, and dose requirements, and the authors argued that there may be no advantage in using tramadol rather than morphine in conjunction with droperidol (30).

Ketamine

In 44 patients the addition of ketamine 1 mg/ml to PCA tramadol significantly reduced the consumption of tramadol at 6, 12, and 24 hours postoperatively, with no

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differences in the incidence of nausea and sedation (31). Diplopia was reported by two patients.

Magnesium sulfate

In 44 patients the addition of magnesium sulfate 30 mg/ml to PCA tramadol both significantly reduced the consumption of tramadol at 6, 12, and 24 hours postoperatively, with no differences in the incidence of nausea and sedation (31).

Morphine

In a double-blind, randomized, controlled study, the addition of a tramadol infusion to morphine for PCA in 69 patients undergoing elective abdominal surgery resulted in improved analgesic efficacy and reduced morphine requirements, with a relative lack of adverse effects (32).

Observational studies

The role of tramadol in the treatment of rheumatological pain has been reviewed (33). Tramadol causes fewer opioid adverse effects for a given level of analgesia compared with traditional opioids. Common adverse effects, such as nausea and dizziness, usually occur only at the beginning of therapy, abate with time, and are further minimized by up-titrating the dosage over several days (34).

When tramadol 1 mg/kg was given intravenously to 110 adults for postoperative shivering, few adverse effects were reported; two had transient hypotension and two complained of nausea without vomiting. Similarly, mild adverse effects were reported in 20% of patients in a trial of tramadol in cancer pain (SEDA-16, 86), and when it was used to relieve severe pain in sports injuries (SEDA-16, 86).

Organs and Systems

Respiratory

Tramadol is said not to cause respiratory depression (SEDA-17, 84) (SEDA-18, 82), but it has been reported that equipotent doses of tramadol did produce respiratory depression, albeit less severe and for a shorter time than morphine (SEDA-17, 84) (35). This was confirmed in an extensive review of the literature (SEDA-21, 90).

The effect of oral tramadol on the ventilatory response to acute isocapnic hypoxia has been studied in 20 healthy volunteers. Tramadol had a small but significant depressive effect on the hypercapnic ventilatory response but no effect on the hypoxic ventilatory response (36). This is in contrast to morphine, which causes 50–60% suppression of the hypoxic ventilatory response.

Nervous system

Tramadol-associated seizures have been studied retrospectively in 9218 adult tramadol users and 37 232 non-users (37). Seizures occurred in under 1% of all tramadol users, but the risk of seizure was increased two- to six-fold among users adjusted for selected co-morbidities and polydrug prescription. The risk of seizure was higher in those aged 25–54 years, those who had more than four tramadol prescriptions, and those who had a history of alcohol abuse, stroke, or head injury.

In a nested case-control study of 11 383 patients, there were 21 cases of idiopathic seizures, only three of whom had been exposed to tramadol alone, the other having taken other analgesics (opioids or others) (38). The findings did not suggest an increased risk of seizures among patients taking tramadol alone.

Seizures followed by opioid withdrawal symptoms have been reported in a patient taking tramadol (39).

- A 29-year-old woman took tramadol 50 mg 6-hourly for pain associated with the carpal tunnel syndrome. She slowly increased the dose of tramadol and obtained it from several physicians and different hospitals, so that after 3 years she was taking 30 tramadol 50 mg tablets daily. She had two generalized seizures and stopped taking tramadol; 1 day later she developed severe opioid withdrawal symptoms, including diarrhea, headache, insomnia, and blurred vision. She was detoxified with tapering doses of tramadol and discharged after 6 days.

Psychological, psychiatric

Hallucinations have been attributed to tramadol, both visual (40) and auditory (41).

- A 66-year-old tetraparetic man developed hallucinations while taking tramadol, paroxetine, and dosulepin for chronic pain (40).
- A 74-year-old man with lung cancer took tramadol 200 mg/day for chest pain (41). Soon afterwards (time not specified) he had vivid auditory hallucinations in the form of "two voices singing accompanied by an accordion and a banjo." They resolved 48 hours after withdrawal.

Gastrointestinal

In one study the incidence of nausea was high (30–35%) when tramadol was used for postoperative pain (SEDA-20, 81).

Intravenous tramadol (1.25 mg/kg), codeine (1 mg/kg), morphine (0.125 mg/kg), and saline have been compared for their effect on gastric emptying (using the paracetamol absorption test) in 10 healthy subjects in a randomized, double-blind study (42). Tramadol had a measurable but statistically insignificant inhibitory effect on gastric emptying, whereas morphine and codeine significantly delayed gastric emptying. The implication of this is that the risk of regurgitation is less with tramadol than with the other opioids investigated and that tramadol is less likely to alter the pharmacokinetics of other drugs administered simultaneously.

In mild to moderate postoperative pain, rectal tramadol has been compared with standard treatment with co-codamol (paracetamol plus codeine) suppositories in 40 patients who were given either tramadol 100 mg suppositories 6-hourly or 1000/20 mg of co-codamol 6-hourly (43). Nausea and vomiting were significantly more frequent with tramadol (84%) than with co-codamol (31%).

The effect of tramadol on postoperative nausea and vomiting after ENT surgery has been studied in a prospective, randomized, double-blind comparison with

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nalbuphine, pethidine, or saline in 281 patients (44). The three opioids caused a similar incidence of postoperative nausea and vomiting (40, 52, and 37% respectively) and more than placebo (32%).

In a randomized, double-blind placebo-controlled study of 76 women undergoing abdominal hysterectomy, tramadol 100 mg was a more effective analgesic than ketorolac 30 mg given every 6 hours intravenously (45). However, of those given tramadol 38% had vomiting compared with only 8% of those who were given ketorolac.

Urinary tract

The Netherlands Pharmacovigilance Foundation (LAREB), has reported five cases of transient difficulty in urinating, which spontaneously resolved on withdrawal of tramadol and was suspected to be induced by tramadol; none needed catheterization (46). In all five cases tramadol had been prescribed for back pain in relatively healthy individuals in a dose range of 50–150 mg.

Skin

- A 47-year-old man taking tramadol 100 mg for low back pain developed a maculopapular rash with secondary erythroderma, which resolved after withdrawal of tramadol (47).

Long-Term Effects

Drug abuse

Tramadol abuse was monitored in the USA during the 3 years (1995–1998) after the drug was marketed there, through the systematic collection and evaluation of reports of suspected abuse in high-risk populations from a network of drug abuse specialists and reports sent through the FDA's Med Watch system (48). The overall conclusion was that experimentation with tramadol during the first 18 months of its introduction peaked at two cases per 100 000 patients exposed. This figure subsequently fell to less than one case per 100 000 patients in the second 18 months of the study period. Of cases of abuse 97% occurred among individuals with a history of substance abuse.

Drug Administration

Drug formulations

The incidence of adverse effects is reduced with the use of an oral, modified-release formulation of tramadol in the treatment of chronic pain (49), starting at the lowest dose, increasing gradually according to the patient's response during chronic oral administration (50,51), and using a loading dose immediately after the start of surgery.

The results of postmarketing surveillance of modified-released tramadol in Germany have been published (52). Modified-release tramadol (mean daily dose 236 mg usually divided into two doses) was used in 3153 patients, of whom most had severe or very severe pain. During the 6-week trial, 316 adverse effects were reported by a total of 206 patients (6.5%). Adverse effects were, in decreasing order of frequency, nausea (3.4%), dizziness (1.5%), vomiting (1.1%), constipation (0.5%), tiredness (0.5%), sweating (0.4%), dry mouth (0.3%), and pruritus (0.3%). Confusion, hypotension, sleep disturbances, abdominal pain, stomach upset, gastrointestinal hemorrhage, and cerebral hemorrhage were all among the less frequently reported adverse events, and 28% of events were classified as severe. Age did not affect the frequency of events, but women reported a higher frequency of adverse events than men (7.3 versus 5.7%).

The use of modified-release tramadol in chronic malignant pain has been examined in an open, prospective study in 146 patients with moderate to severe cancer pain; 90 patients completed the 6-week trial (53). Dropouts were due to opioid adverse effects (20%), inadequate pain relief (9%), or both (2.5%). There was at least one adverse effect in 86%. Overall, 433 adverse effect events were reported but some reduced in frequency over the 6 weeks. Modified-release tramadol (400 mg/day) provided fast and efficient pain relief in almost 60% of patients both during initial dosing and long-term treatment.

Drug overdose

- A 26-year-old male nurse died of tramadol intoxication (54). The peripheral blood concentration of tramadol was 9.6 micrograms/ml (target concentration 0.1–0.3 micrograms/ml). There was no objective evidence at postmortem of any pre-existing disease or use/overuse of ethanol or other drugs that could have contributed to or caused death.

Drug–Drug Interactions

Ondansetron

Tramadol dosage requirements for patient-controlled analgesia increased when ondansetron was given as a prophylactic antiemetic in 40 patients undergoing lumbar laminectomy in an open, controlled study (55). During the first 4 hours postoperatively tramadol consumption increased by about 30% in those given ondansetron and remained 22–25% higher thereafter. A single dose of ondansetron 4 mg given during induction did not reduce the 24-hour incidence of nausea or vomiting.

In a randomized, controlled study of postoperative PCA using tramadol with or without ondansetron in 59 patients undergoing ear, nose, and throat surgery, ondansetron reduced the overall analgesic effect of tramadol, increased doses of tramadol being needed in the first 12 hours after surgery. This increase in tramadol requirements in those given ondansetron resulted in a significantly higher vomiting scores at 4 and 8 hours postoperatively and an overall increase in the number of episodes of vomiting, despite the use of ondansetron (56).

Oral anticoagulants

Tramadol may increase the anticoagulant effect of phenprocoumon or warfarin (SEDA-22, 103).

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Quinidine

Inhibition of the hepatic metabolism of tramadol to morphine by quinidine may reduce its opioid effects (SEDA-21, 90).

Selective serotonin re-uptake inhibitors (SSRIs)

Fluoxetine

Serotonin syndrome and mania occurred in a 72-year-old woman taking fluoxetine 20 mg/day and tramadol 150 mg/day 18 days after she started to take the combination (57). Inhibition of CYP2D6 may have played a part (58).

Sertraline

The serotonin syndrome has been reported after concurrent use of tramadol and sertraline (SEDA-22, 103).

- Serotonin syndrome occurred in an 88-year-old woman who took sertraline 50–100 mg/day and tramadol 200–400 mg/day for 10 days; the symptoms subsided 15 days after withdrawal of tramadol (59).

Venlafaxine

The death of a 36-year-old patient with a history of alcohol dependence who was taking tramadol, venlafaxine, trazodone, and quetiapine has highlighted the increased risk of seizures with concomitant use of tramadol and selective serotonin re-uptake inhibitors (60).

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Trandolapril

See also Angiotensin converting enzyme inhibitors

General Information

Trandolapril is a non-sulfhydryl ACE inhibitor that has been used in patients with hypertension, congestive heart failure, and myocardial infarction. It is a prodrug that is hydrolyzed to the active diacid trandolaprilat.

Comprehensive reviews and the results of a large trial have shown that trandolapril has a pattern of adverse effects reflecting those usually documented with other ACE inhibitors (1).

Organs and Systems

Respiratory

In 3402 patients with hypertension taking trandolapril, cough, assessed by visual analogue scale, was less common in smokers than in non-smokers (2).

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Tranexamic acid

General Information

During normal fibrinolysis, inactive circulating plasminogen binds to fibrin through an active site that binds lysine. The bound plasminogen is then converted to plasmin by activators (such as tissue plasminogen activator, t-PA) and converted to plasmin, which breaks down the fibrin. Tranexamic acid (Cyklokapron) and aminocaproic acid (ε-aminocaproic acid, EACA, 6-aminohexanoic acid, Amicar) are structural analogues of lysine, which bind irreversibly to the lysine-binding sites on plasminogen, inhibiting binding to fibrin and thus the whole process of fibrinolysis (1,2). These agents inhibit the natural degradation of fibrin and so stabilize clots.

Aminocaproic acid was the first such agent to be used widely, but it has largely been superseded in clinical practice by tranexamic acid, which is about 10 times more potent. Para-aminomethylbenzoic acid (PAMBA) is similar to aminocaproic acid, but is about three times more active in inhibiting plasminogen activators (3). However, it is no longer used despite the fact that it is well tolerated.

Uses

Antifibrinolytic agents are of benefit in the treatment of primary menorrhagia (4–7), recurrent epistaxis (8), oral bleeding in patients with congenital and acquired coagulation disorders (9,10), hemorrhage associated with thrombolytic therapy, and to reduce blood loss associated with surgery (especially cardiac surgery, joint replacement, and orthotopic liver transplantation) (11–14). Antifibrinolytic therapy can be of value in other conditions as well (15–21). It is effective in the bleeding diathesis that can accompany acute promyelocytic leukemia (22,23), but it does not improve outcome after subarachnoid hemorrhage (24).

Tranexamic acid used during cardiopulmonary bypass reduces mediastinal blood losses by about one-third, while transfusion requirements remain unchanged (25). In over 950 patients, not a single thromboembolic complication could be ascribed to it.

General adverse effects

Adverse effects of tranexamic acid are rare and mainly limited to nausea, diarrhea, or abdominal pain (4,5,26–29). These symptoms are usually associated with high doses, and subside if the dose is reduced. The dose of tranexamic acid in patients with renal insufficiency must be reduced to avoid accumulation and associated adverse effects. Hypotension is occasionally observed, typically after rapid intravenous infusion (30). The better safety profile with regard to minor adverse effects of tranexamic acid compared with aminocaproic acid is due to the lower daily dose required for tranexamic acid (3–6 g) compared with aminocaproic acid (18–30 g). Tranexamic acid has very occasionally been associated with skin rashes, including fixed drug eruption (31) and bullous eruptions (32).

Organs and Systems

Sensory systems

Central venous retinopathy was reported in two young women after oral treatment with tranexamic acid for menorrhagia (33).

- A 56-year-old man, who had been undergoing hemodialysis for 1 year after 10 years of peritoneal dialysis, was given intravenous tranexamic acid after an emergency operation for bleeding peptic ulcers; he had gradual loss of sight over about 1 week, and 2 weeks after the operation became blind (34). Retinography was flat and his visual field was narrowed. Fluorescein angiography showed microgranular hyperfluorescence, suggesting malfunction of the pigmented layer of the retina. There were no abnormalities in the brain or optic nerve on MRI scanning. Withdrawal of tranexamic acid restored his sight within a few days. He had received tranexamic acid once before because of a bleeding ulcer, and his sight had been impaired at that time too.

However, in 14 patients who had taken tranexamic acid for an average period of 6 years there was no evidence of ocular damage (35).

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Hematologic

Inhibition of plasminogen by tranexamic acid and aminocaproic acid could theoretically facilitate the development of thrombosis, but whether it actually does so has been the subject of contradictory reports. Episodes of venous and arterial thrombosis have been reported in association with treatment using either tranexamic acid or aminocaproic acid. These include thrombosis at unusual sites such as mesenteric thrombosis (36), the aorta (37), retinal artery occlusion (38), and intracranial arterial thrombosis (39–41), as well as deep-vein thrombosis in the legs (42).

- Massive pulmonary thromboembolism was reported in a 62-year-old woman 7 days after treatment with high doses for subarachnoid hemorrhage (43).

However, in a large retrospective study from Sweden, the incidence of thrombosis in women receiving tranexamic acid for menorrhagia was no different to that of the rest of the population (44). During a 9-year period, corresponding to over 238 000 women-years, 11 thromboembolic complications were reported. This corresponds to an annual incidence of 0.005%, which is not higher than the expected incidence in fertile women. Furthermore, a retrospective study of 256 pregnant women treated with tranexamic acid for abruptio placentae or other hemorrhagic problems showed no evidence of a thrombogenic effect of the drug (45), and a study of patients undergoing cardiac surgery who received tranexamic also showed no increased risk of thrombotic complications (46). Thus, the association between use of inhibitors of fibrinolysis and thrombosis appears to be fortuitous and the risk of this potential hazard is very low. However, the data sheet issued by the manufacturers still states that tranexamic acid is contraindicated in patients with a previous history of thromboembolic disease.

Caution should also be exercised in the administration of antifibrinolytic agents in disseminated intravascular coagulation (47,48).

Urinary tract

Acute renal cortical necrosis has been attributed to tranexamic acid in a patient with hemophilia A (49,50).

- A 21-year-old man developed oliguria and uremia after 3 days of treatment with tranexamic acid 3 g/day for epistaxis. He did not recover. Renal angiography showed reduced cortical contrast enhancement, compatible with renal cortical necrosis. No other susceptibility factors for renal cortical necrosis were present.

Renal impairment associated with acute renal cortical necrosis caused by tranexamic acid is rare. The authors found only three previously reported cases in English, of which at least one other was without any known susceptibility factor for acute renal cortical necrosis (49).

Second-Generation Effects

Teratogenicity

There is no evidence of a teratogenic effect with tranexamic acid (51).

Lactation

Tranexamic acid passes into breast milk but reaches a concentration of only about one hundredth of that in maternal blood (51), which should not result in significant inhibition of fibrinolysis in a neonate.

Drug–Drug Interactions

All-*trans* retinoic acid

Tranexamic acid has been used without thrombotic complications for the attempted prophylaxis of hemorrhage in patients with acute promyelocytic leukemia treated with combination chemotherapy, in whom hemorrhage is a significant problem. Since several studies have shown that all-*trans* retinoic acid can produce complete remission, it has become part of standard treatment. Fatal thromboembolism in acute promyelocytic leukemia during all-*trans* retinoic acid therapy combined with antifibrinolytic therapy has been reported (52). Of 31 patients with acute promyelocytic leukemia, treated with different combinations of all-*trans* retinoic acid and chemotherapy, 21 were given tranexamic acid (53). Of the 28 patients who received all-*trans* retinoic acid, 7 died during the study, but of these 7, only 4 were early deaths (within 42 days). All four early deaths were in those who received all-*trans* retinoic acid plus tranexamic acid, and three of the four had sudden and rapid deterioration in their condition; postmortem findings implicated thrombosis in the microvasculature as the predominant cause of death. The authors suggested that in patients taking all-*trans* retinoic acid, tranexamic acid should be used cautiously; supportive therapy with platelets and fresh frozen plasma alone can be used.

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Tranilast

General Information

Tranilast is an orally active antiallergic agent. It may have a similar mechanism of action to that of cromoglicate.

Its adverse reactions include liver function abnormalities, anorexia, nausea, vomiting, abdominal pain, reduced hemoglobin, headache, drowsiness, insomnia, dizziness, and general malaise (1).

Organs and Systems

Urinary tract

Some patients taking tranilast develop severe bladder symptoms, unrelieved by antibiotic treatment (2). Fourteen patients have been reported in detail. In patients whose bladder wall was biopsied there was eosinophilic inflammation. Drug-induced lymphocyte stimulation showed that tranilast and its major metabolite are causative agents. The symptoms disappear within a few days of stopping the drug (SEDA-12, 145) (SEDA-14, 139) (SEDA-17, 205) (3).

- A 59-year-old man who had been taking tranilast 600 mg/day for 15 weeks developed bladder irritability (4). Cystoscopy showed extensive mucosal edema, strongly suggestive of drug-induced cystitis. He stopped taking tranilast and the symptoms disappeared within 3 weeks.

Immunologic

Immune thrombocytopenia caused by tranilast has been reported in a 17-year-old man. The drug was withdrawn and oral prednisolone was started. He recovered within 1 week. Antiplatelet antibodies were not detected, but there was a platelet-associated IgG, which increased when a sample of his serum was incubated with tranilast in vitro (5).

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Tranylcypromine

See also Monoamine oxidase inhibitors

General Information

Tranylcypromine is a non-hydrazine monoamine oxidase (MAO) inhibitor with actions and uses similar to those of phenelzine, but with less prolonged inhibition. Its half-life is 90–190 minutes. It is structurally related to amfetamine, to which it is metabolized in overdose (1).

Long-Term Effects

Drug abuse

Four cases of addiction to tranylcypromine have been described, in addition to the three reported since 1965 (2). The dosage was 150–300 mg/day. The mild euphoriant properties of tranylcypromine reflect its structural resemblance to amfetamine, and probably account for tolerance and addiction in predisposed individuals. Tranylcypromine abuse in 18 patients has been reviewed (3), and two further reports have appeared (SEDA-17, 17) (4). In one case (5), the patient took 440 mg/day without any adverse effects. The patient reported that she was longing for the "energizing" effect of the drug and for the feeling of "freedom and power." Withdrawal resulted in repeated generalized seizures and status epilepticus.

Susceptibility Factors

Hepatic disease

A carefully controlled study showed that patients with impaired liver function are especially sensitive to tranylcypromine, sometimes developing obtunded consciousness and slow electroencephalograms similar to those found in hepatic encephalopathy (6).

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Drug Administration

Drug overdose

The fatal effects of antidepressants in England, Scotland, and Wales during 1975–1984 and 1985–1989 have been compared in retrospective epidemiological studies (7,8). There were 24 deaths due to tranylcypromine, the fatality index for which was significantly higher than the mean for all antidepressants, while that for the other MAO inhibitors was lower.

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Trastuzumab

See also Monoclonal antibodies

General Information

Trastuzumab is a recombinant humanized monoclonal antibody that binds to the proto-oncogene, HER-2/neu gene product, which is expressed in 25–30% of primary breast cancers. It has been used to treat selected patients with metastatic breast cancer whose tumors overexpress the HER2 protein, which is amplified in 25–30% of breast cancers and is associated with an aggressive form of disease (1). Adverse effects mostly consisted of infusion-related constitutional symptoms, digestive disorders (diarrhea, vomiting), pain, cough, headache, dyspnea, mild infections, and insomnia. Compared with chemotherapy alone, the addition of trastuzumab more often produced moderately severe adverse hematological effects (leukopenia and anemia) and diarrhea. Severe congestive cardiac failure is a major adverse effect of trastuzumab. According to the product labelling, severe cardiac failure was observed in 5–19% of patients (trastuzumab alone versus trastuzumab plus anthracycline and cyclophosphamide). Other serious adverse events, including death, have occurred in 0.25% of patients treated with trastuzumab. They fall into three categories: infusion reactions; hypersensitivity reactions, including fatal anaphylaxis; and pulmonary events, including adult respiratory distress syndrome.

Organs and Systems

Cardiovascular

Cardiotoxicity is a major concern with trastuzumab, particularly as it is often used in patients who are receiving or who have previously received anthracycline antibiotics (2). It occurs in 5% of patients given trastuzumab alone, in 13% of patients given trastuzumab with paclitaxel, and in 27% of patients given trastuzumab in combination with anthracyclines and cyclophosphamide (3).

The efficacy and safety of trastuzumab have been evaluated in 235 women with metastatic breast cancer receiving standard chemotherapy (4). The most important adverse event was cardiac failure, which occurred in 27% of those who were given anthracycline, cyclophosphamide, and trastuzumab, 8% of those who were given anthracycline and cyclophosphamide alone, 13% of those who were given paclitaxel and trastuzumab, and 1% of those who were given paclitaxel alone. The incidence of cardiac failure of New York Heart Association class III or class IV was highest among patients who had received an anthracycline, cyclophosphamide, and trastuzumab. The mechanism is unknown. In a retrospective analysis of all patients with cardiac failure by an independent review and evaluation committee, the only significant risk factor was older age. Although the cardiotoxicity was severe, and in some cases life-threatening, the symptoms improved with standard medical management.

Seven phase II and III clinical trials of trastuzumab in patients with metastatic breast cancer have been reviewed (5). The physiopathology of trastuzumab-associated cardiac disease is poorly understood, and baseline MUGA scanning is recommended to identify cardiac disease. The rates of cardiac disease were highest when trastuzumab was given in combination with anthracyclines or when there had been previous exposure to anthracyclines. Given the 25% improvement in overall survival in these patients with metastatic disease, the use of trastuzumab is justified.

- A 60-year-old woman with coronary heart disease and hypertension developed breast cancer and a core biopsy showed ER+/PR+/HER2–3+ (3). She enrolled in an institutional study with neoadjuvant trastuzumab with docetaxel. A pretreatment blood pool radionuclide angiography (MUGA) scan revealed a left ventricular ejection fraction of 56%. She had a good clinical response to treatment at 3 months. Before surgery a repeat MUGA showed a dilated left ventricle and a reduced ejection fraction (35%). She underwent surgery and 2 months later her ejection fraction was 44%.
- An overweight 59-year-old woman with hypertension and asthma developed breast cancer (ER+/PR+/HER2–2+) (3). Her MUGA scan showed a left ventricular ejection fraction of 57%. She was given trastuzumab with docetaxel and had a good response after 4 months. Before surgery she became dyspneic, and a

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MUGA scan showed an ejection fraction of 24%; even 7 months after surgery her MUGA scan showed no improvement.

The efficacy and tolerability of trastuzumab in clinical trials has been reviewed (6). Of the first 48 patients treated in Sweden with or without chemotherapy, two had serious cardiac events and both had previously been treated with an anthracycline. As not all patients who received trastuzumab had echocardiography, the number of cardiac events was probably underestimated. It has been postulated that HER2 pathways may be involved in myocyte repair, and that concomitant administration of trastuzumab may interfere with the repair of anthracycline-damaged myocytes (7). Evidence from 20 patients has shown that cardiotoxicity is related to trastuzumab uptake in the myocardium, suggesting that the extent of HER2 receptor expression, or a related cross-reactive antigen in the myocardium, may be the underlying mechanism.

Respiratory

The toxicity of five escalating doses of trastuzumab (1–8 mg/kg) when combined with a fixed dose of interleukin-2 has been determined in 45 patients with non-hematological malignancies that overexpressed HER2 (8). There was no evidence of increasing toxicity related to the dose of trastuzumab. Five patients had pulmonary toxicity of grade 3 or higher; these were primarily attributed to interleukin-2, as the patients improved on reduction of the dose of interleukin-2.

Drug–Drug Interactions

Paclitaxel

In primates, trastuzumab clearance was reduced when it was administered with paclitaxel (9).

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Travoprost

See also Prostaglandins

General Information

Travoprost is a derivative of fluprostenol and $PGF_{2\alpha}$ and has intraocular pressure-lowering activity.

Organs and Systems

Sensory systems

Travoprost causes changes in iris pigmentation (3.1–5.0%) and changes in eyelash characteristics, including length, thickness, density, and color (44–57%), similar to those described with latanoprost, after 12 months (1).

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Trazodone

See also Antidepressants, second-generation

General Information

Trazodone (SEDA-7, 19–21) is a triazolopyridine derivative that selectively but weakly inhibits 5-hydroxytryptamine (5-HT) re-uptake and is an alpha-adrenoceptor antagonist at both presynaptic and postsynaptic receptors

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(1). During long-term administration it down-regulates serotonin receptors (2).

Experience with therapeutic and toxic dose ranges of trazodone has thrown much doubt on earlier claims for its greater safety, and some unanticipated problems have surfaced.

Trazodone is rapidly absorbed, with peak plasma concentrations at 0.5–2 hours. It is extensively metabolized and eliminated mainly via the kidneys, with a half-life of 13 hours for total drug and metabolites.

A review of controlled clinical studies in depressed patients in Europe and the USA showed that trazodone is superior to placebo (3) and can be as effective as imipramine or amitriptyline (3,4). The doses needed to secure an equivalent effect (150–800 mg/day) were generally double those of the tricyclic antidepressants.

In 28 depressed patients treated with up to 600 mg/day for 4 weeks, plasma concentrations varied eightfold (5). There was a significant correlation between dosage and plasma concentration, but no association with outcome and no significant difference between the mean plasma concentrations in responders (1.51 μg/ml) and non-responders (1.64 μg/ml).

The short half-life of trazodone naturally raises the question of the optimal dosage frequency. The General Practitioner Research Group in Britain (6) has conducted a series of comparisons of trazodone given once, twice, and thrice a day to anxious and depressed patients taking up to 200 mg/day. Efficacy was the same with all three regimens, although there were more complaints of dizziness and fewer of drowsiness with the thrice-daily regimen.

Organs and Systems

Cardiovascular

Based on animal research and restricted experience in overdosage (SEDA-7, 19–21), early attempts to differentiate trazodone from tricyclic antidepressants suggested that it might be relatively free of cardiotoxic effects. However, a preliminary report of a study of the effects of trazodone on the cardiovascular system in 20 subjects mentioned two patients who had ventricular dysrhythmias (7). Others have reported ventricular tachycardia (8–10), atrial fibrillation (11), and complete heart block (12).

Additive hypotensive effects of trazodone and phenothiazines have been reported (13).

Trazodone can cause peripheral edema, as outlined in a report of 10 cases (14).

Nervous system

Trazodone is markedly sedative, very similar in profile to amitriptyline. It produces marked sedation and lethargy within an hour, lasting up to 6 hours, and is about half as potent as imipramine (4).

Although it is claimed to be relatively free of effects usually attributed to anticholinergic activity, trazodone does cause complaints of dry mouth and blurred vision, which may be mediated through its actions on alpha-adrenoceptors. Urinary retention has been reported in a 69-year-old woman taking a combination of trazodone and an anticholinergic drug (isopropamide iodide) (15). Cholinergic overactivity has also been described in two patients after withdrawal (16).

The manufacturers of trazodone received 30 unpublished reports of seizures in patients, most of whom had evidence of seizure predisposition or concurrent contributory conditions. Two reports are detailed here (17,18).

- A 50-year-old woman with an electroencephalographic abnormality but no history of epilepsy, who had taken amitriptyline and perphenazine uneventfully for years, suffered two seizures 18 days after switching to trazodone 50 mg/day.
- A 47-year-old man developed 30-second episodes of facial contortions, aphasia, garbled speech, neologism, nocturnal episodes of deep breathing, swallowing, and incomprehensible speech after taking trazodone 150 mg/day for 3 weeks. On withdrawal of trazodone, his symptoms abated, but an electroencephalogram showed a left anterior lobe spike. He was treated with carbamazepine and within 6 months was not depressed and had no further convulsive symptoms.

Sensory systems

Three cases of palinopsia (the persistence or reappearance of an image of a recently viewed object) have been reported (SEDA-17, 22); the authors speculated that this may have been due to pharmacological effects resembling those of LSD and mescaline.

Psychological, psychiatric

Conversion to mania has been reported in patients with unipolar depression (19,20) and bipolar illness (20).

Delirium, which also occurs with tricyclic antidepressants, has been reported with trazodone (21).

Liver

Hepatotoxicity, a known hazard of tricyclic compounds, has been reported with trazodone (22,23).

Skin

Trazodone has caused generalized erythematous maculopapular eruptions (24), erythema multiforme (although the patient was also taking lithium) (25), and generalized pustular psoriasis in a patient who had had stable plaque psoriasis for 19 years (26).

Sexual function

Inhibition of ejaculation was reported in a middle-aged man 1 week after he started taking trazodone 100 mg at night (27). The symptoms abated 3 days after withdrawal and did not return when treatment was changed to doxepin 50 mg/day. Because trazodone has relatively more alpha-adrenoceptor blocking action and less anticholinergic activity than doxepin, the author speculated that this was the mechanism.

Trazodone can cause severe and persistent priapism. In a communication from the manufacturers in 1987, it was noted that there had been 136 reports of "increased penile tumescence" in patients taking trazodone. These included

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all reports of abnormal erectile activity. The company reported that the incidence of all abnormal erectile activity was about one in 6000 men, that in 36 of the 136 patients surgical interventions had been performed, and that at least nine of these patients were impotent. They suggested that early intervention is the treatment of choice, and that trazodone should be withdrawn immediately at the first signs of prolonged erections. They recommended that if conservative measures fail, intracavernosal irrigation with a weak solution of adrenaline should be considered (28). This rare adverse effect has been reported previously with a number of psychoactive and antihypertensive drugs (phenothiazines, guanethidine, prazosin, hydralazine) and has been ascribed to their alpha-adrenoceptor antagonist activity. The same mechanism probably explains the effect of trazodone.

Increased libido (29) and anorgasmia (30) have been reported with trazodone.

Drug Administration

Drug overdose

In a 1980 review there were 68 cases of trazodone overdosage in amounts ranging up to 5 g (12 times the maximum therapeutic dose) (31). The predominant symptoms were drowsiness, dizziness, and rarely coma. There were no deaths in patients who took trazodone alone, and only two in those who took it in combination with other potentially lethal drugs. A brief review of data obtained from 46 cases of trazodone overdose reported to the National Poisons Information Service in London showed that 25 of the patients took overdoses of trazodone alone, while 21 took trazodone in combination with other drugs (32). This retrospective questionnaire study had inherent methodological flaws, but it did lend credence to the belief that trazodone is safe in overdose.

Trazodone is less cardiotoxic than tricyclic antidepressants, although it has rarely been reported to cause ventricular tachycardia. QT interval prolongation has been reported in overdose (33).

- A patient who took an overdose of trazodone (3 g) had sinus bradycardia (57 beats/minute) and a prolonged QT_c interval (60 msec). The abnormal QT_c interval gradually normalized over the next 3 days with supportive hospital treatment.

Drug–Drug Interactions

Amiodarone

A patient taking both trazodone and amiodarone developed prolongation of the QT interval and a polymorphous ventricular tachycardia, perhaps by mutual potentiation (34).

Carbamazepine

In a 53-year-old man, trazodone produced a clinically significant increase in carbamazepine concentrations (35). This suggests that trazodone inhibits CYP3A4. It should be used with caution in combination with carbamazepine.

MAOIs and SSRIs

Although trazodone is related to nefazodone it probably potentiates 5-HT neurotransmission less. Trazodone is often added to monoamine oxidase inhibitors and serotonin re-uptake inhibitors at low doses (50–150 mg/day) as a hypnotic. In one case the combination of trazodone with nefazodone provoked the serotonin syndrome (36).

- When a 60-year-old woman taking nefazodone 500 mg/day also took trazodone 50 mg/day she developed confusion, restlessness, sweating, and nausea after 3 days. Her symptoms settled quickly on withdrawal of both antidepressants.

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Trecovirsen

General Information

Trecovirsen is a 25-met antisense phosphorothioate oligonucleotide, which is targeted at the gag site of the HIV gene. In an early clinical experiment it was given to HIV-positive volunteers by intravenous infusion in single escalating doses of 0.1–2.5 mg/kg in groups of 6–12 subjects (1). The only significant adverse event was an isolated transitory increase in activated partial thromboplastin time at doses of 2.0 mg/kg or more; it was related to plasma trecovirsen concentrations and was attributed to the polyanionic character of the molecule. Headache occurred in 12% of subjects, and there were some cases of abdominal pain, back pain, diarrhea, and weakness.

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Triamterene

See also Diuretics

General Information

Triamterene is a potassium-sparing diuretic that acts in the distal convoluted tubule independently of the action of aldosterone, inhibiting sodium channels (1).

Patients with congenital nephrogenic diabetes insipidus are often treated with a combination of a thiazide and a potassium-sparing diuretic, without consensus on the preferred potassium-sparing diuretic. A Japanese adult was systematically studied to determine the renal effects of hydrochlorothiazide plus amiloride and hydrochlorothiazide plus triamterene (2). The combination with amiloride was superior to that with triamterene in preventing excessive urinary potassium loss, hypokalemia, and metabolic alkalosis. These results suggest that amiloride is the preferred add-on therapy to hydrochlorothiazide in nephrogenic diabetes insipidus.

Organs and Systems

Hematologic

Triamterene blocks dihydrofolate reductase and can cause folate deficiency with megaloblastic anemia and pancytopenia, particularly in patients with hepatic cirrhosis, who have reduced clearance of the drug (SED-11, 431). When this has been reported, all patients were taking doses of 150–600 mg/day for ascites and all had hepatic cirrhosis, often due to alcohol abuse (SEDA-17, 269). It is advisable to use spironolactone rather than triamterene in patients with cirrhosis.

Gastrointestinal

Of the milder adverse effects of triamterene, nausea, vomiting, and diarrhea are fairly common (3).

Urinary tract

Like other diuretics, triamterene occasionally causes interstitial nephritis (4), but it has also been responsible for other renal problems, notably reversible non-oliguric renal insufficiency when it is given along with indometacin (or presumably any other inhibitor of prostaglandin synthesis) (5).

Triamterene can cause transient asymptomatic crystalluria in acidic urine (6). In most cases, the crystals are associated with brown casts, also due to triamterene.

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Triamterene crystals should be regarded as a potential cause of severe tubular injury.

Triamterene can cause nephrolithiasis. Microcrystals of the parahydroxy metabolite form a particularly suitable nucleus for crystalline calcium oxalate deposition (7). However, a cause-and-effect relation has been questioned on epidemiological grounds and in the light of a controlled study that found no link (8), and triamterene could be an innocent bystander in stone formation (SEDA-11, 200). Nevertheless, triamterene is sometimes detected in urinary calculi. In a French analysis of 22 510 urinary calculi performed by infrared spectroscopy, drug-induced urolithiasis was divided into two categories: first, stones with drugs physically embedded ($n = 238$; 1.0%), notably indinavir monohydrate ($n = 126$; 53%), followed by triamterene ($n = 43$; 18%), sulfonamides ($n = 29$; 12%), and amorphous silica ($n = 24$; 10%); secondly, metabolic nephrolithiasis induced by drugs ($n = 140$; 0.6%), involving mainly calcium/vitamin D supplementation ($n = 56$; 40%) and carbonic anhydrase inhibitors ($n = 33$; 24%) (9). Drug-induced stones are responsible for about 1.6% of all calculi in France. Physical analysis and a thorough drug history are important elements in the diagnosis.

Skin

Rashes, including photodermatitis (10), sometimes occur with triamterene.

Pseudoporphyria has been attributed to co-triamterzide (hydrochlorothiazide plus triamterene, Dyazide) in a patient with vitiligo (11). It is uncertain which constituent was responsible.

Body temperature

Drug fever has been attributed to triamterene (12).

Second-Generation Effects

Pregnancy

Because of the potential risk of folate deficiency it is sensible to avoid triamterene in pregnancy (13).

Teratogenicity

Neural tube defects, characterized by a failure of the neural tube to close properly after conception, affect about one in 1000 live births in the USA. Periconceptional folic acid supplementation reduces the risk. To determine whether periconceptional exposure to folic acid antagonists might therefore increase the risk of neural tube defects, data from a case-control study of birth defects (1979–98) in the USA and Canada have been examined (14). Data on 1242 infants with neural tube defects (spina bifida, anencephaly, and encephalocele) were compared with data from a control group of 6660 infants with malformations not related to vitamin supplementation. Triamterene is a folic acid antagonist and in this series was associated with the development of neural tube defects, but there were too few cases to estimate an odds ratio.

Susceptibility Factors

Age

Triamterene is often given in combination with the thiazide diuretic bemetizide. The pharmacokinetics and the pharmacodynamics of a fixed combination of bemetizide 25 mg and triamterene 50 mg have been evaluated in 15 elderly patients (aged 70–84 years) and 10 young volunteers (aged 18–30 years) after single doses (on day 1) and multiple doses (at steady state on day 8) (15). Mean plasma concentrations of bemetizide, triamterene, and the active metabolite of triamterene, hydroxytriamterene, were significantly higher in the elderly subjects after single and multiple doses and urine flow and sodium excretion rates fell in tandem with the accumulation of these drugs. The glomerular filtration rate, known to be reduced in elderly people, was further reduced at higher concentrations of bemetizide and triamterene, which may explain why there were limited diuretic and saliuretic effects after multiple doses. This study clearly points to a modulating effect of the degree of renal function on the diuretic actions of these compounds in the elderly.

Drug–Drug Interactions

Methotrexate

An interaction between triamterene and methotrexate (also an inhibitor of dihydrofolate reductase), leading to pancytopenia, has been reported (16). Dehydration due to diuretic treatment may have contributed to renal impairment and reduced clearance of methotrexate, further increasing the risk of bone marrow suppression.

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Triazolam

See also Benzodiazepines

General Information

The history of the introduction of triazolam has been reviewed (SEDA-4, v). Triazolam continues to be controversial (1) and much of the controversy has been reviewed (2–5).

Much of the literature on the adverse effects of triazolam is based on doses of 0.25 mg and above; the reduction in recommended dose to 0.125 mg may improve therapeutic safety, at the cost of compromising hypnotic efficacy in most patients. A low therapeutic index is also suggested by the possibility of amnesia, even after a single dose (6), and triazolam appears to be associated with a greater incidence of behavioral disturbances than other hypnotic benzodiazepine agonists, such as temazepam and zopiclone.

A case of recurrent iatrogenic Kleine–Levin syndrome with irritability, hyperphagia, and amnesia (7) has provided a further example of the bizarre behavior not infrequently seen with triazolam in a high dose (0.5 mg); see also the monograph on flunitrazepam. At this dose, triazolam produces too many adverse effects on sleep, memory, and judgement to be useful to the military or to commercial airline pilots; elderly patients are particularly sensitive, even to lower doses, owing in part to reduced drug clearance (SED-12, 99). Amnesia and confusion, which can occur even after single doses of triazolam, are accentuated by continued use, and frank psychopathology occurred in psychiatric patients during 2 weeks' use and during withdrawal (8).

The demonstrated ability of triazolam to impair acetylcholine release (SEDA-19, 36) suggests a mechanism for its amnestic effects, and should further caution prescribers about its use in elderly people, particularly those with pre-existing cognitive impairment. The extent to which this anticholinergic effect is shared by other benzodiazepines is yet to be established. The ability of triazolobenzodiazepines, such as triazolam and alprazolam, to inhibit the noradrenergic neurons of the locus ceruleus is unlikely to explain the prominent adverse effects of these drugs (SEDA-21, 37). For one thing, all GABA enhancers share this property; for another, a far more specific and selective inhibitor in the locus ceruleus (clonidine) has an adverse effects profile that is dramatically different from that of the benzodiazepines, whose adverse effects probably relate to their actions at a far wider range of GABA-ergic synapses.

Organs and Systems

Psychological, psychiatric

The effect of triazolam on muscarinic acetylcholine receptor binding has been investigated in living brain slices by the use of a positron-based imaging technique (9). Stimulation of GABA/benzodiazepine binding sites lowered the affinity of the muscarinic acetylcholine cholinergic receptor for its ligand, which may underlie benzodiazepine-induced amnesia, a serious clinical adverse effect of benzodiazepines.

Ten healthy men participated in a randomized, double-blind, crossover study involving placebo and triazolam 0.125 mg (10). Resting electroencephalography and event-related potentials under an oddball paradigm were recorded before drug administration, and at 1, 2, 4, 6, and 8 hours after. P300 waveforms were analysed by peak amplitudes. Triazolam can cause cognitive dysfunction without general sedation or apparent sleepiness, and this effect appeared up to 6 hours after administration of a low dose of triazolam.

The subjective and behavioral effects of triazolam were investigated in 20 healthy women, who took oral triazolam 0.25 mg or placebo at the follicular, periovulatory, and luteal phases of their menstrual cycle in a within-subject design (11). After triazolam most of them reported the expected increases in fatigue and decreases in arousal and psychomotor performance. Neither plasma concentrations of triazolam nor mood and performance differed across the three phases. This study shows that the effects of triazolam are highly stable across the menstrual cycle.

Liver

Liver damage has been attributed to triazolam (12).

- A 64-year-old woman developed anorexia, fatigue, and jaundice. She had occasionally taken triazolam 0.25 mg for insomnia, and her liver function tests had been normal 5 months before. There was no history of liver disease or alcohol misuse or other serious medical history. She was jaundiced, with spider angiomata, and gradually deteriorated over the next 16 days, finally losing consciousness. Liver histology was consistent with submassive necrosis, extensive coagulation necrosis, and marked inflammation secondary to triazolam. She had a liver transplant 31 days after the initial presentation and 2 years later was in good health.

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Drug Administration

Drug overdose

Death has been attributed to an overdose of triazolam (13).

- A 77-year-old woman was found dead in her bathtub. She had a history of depression, liver disease, spinal stenosis, and diabetes mellitus. An empty bottle of triazolam was found in the bin. At autopsy there was no injury or evidence of drowning. There was triazolam 0.12 mg/l in the heart blood.

Drug–Drug Interactions

Fluconazole

Fluconazole increases blood concentrations of triazolam (14).

Grapefruit juice

In a randomized, four-phase, crossover study, the effect of grapefruit juice on the metabolism of triazolam interaction was investigated. Even one glass of grapefruit juice increased plasma triazolam concentrations, and chronic consumption produced a significantly greater increase. The half-life of triazolam is prolonged by repeated consumption of grapefruit juice, probably due to inhibition of hepatic CYP3A4 activity (15).

Isoniazid

Isoniazid is a potent hepatic enzyme inhibitor and interferes with the metabolism of many drugs (SEDA-8, 287) (SEDA-11, 271). In healthy volunteers the half-life of triazolam was prolonged from 2.5 to 3.3 hours when it was given with isoniazid, whereas isoniazid did not affect the kinetics of oxazepam (SEDA-9, 267).

Ketoconazole

Ketoconazole can increase the concentrations of triazolam through inhibition of CYP3A4 (16).

If erythromycin, also a CYP3A4 inhibitor, is given in combination with ketoconazole, there is an even more dramatic effect on triazolam concentrations.

In a double-blind, crossover kinetic and dynamic study of the interaction of ketoconazole with alprazolam and triazolam, two CYP3A4 substrate drugs with different kinetic profiles, impaired clearance by ketoconazole had more profound clinical consequences for triazolam than for alprazolam (17).

Macrolide antibiotics

Interactions of macrolides with triazolam are clinically relevant. Increases in serum concentration, AUC, and half-life, and a reduction in clearance have been documented (18–20). These changes can result in clinical effects, such as prolonged psychomotor impairment, amnesia, or loss of consciousness.

In a randomized, double-blind, pharmacokinetic–pharmacodynamic study, 12 volunteers took placebo or triazolam 0.125 mg orally, together with placebo, azithromycin, erythromycin, or clarithromycin. The apparent oral clearance of triazolam was significantly reduced by erythromycin and clarithromycin. The peak plasma concentration was correspondingly increased, and the half-life was prolonged. The effects of triazolam on dynamic measures were nearly identical when triazolam was given with placebo or azithromycin, but benzodiazepine agonist effects were enhanced by erythromycin and clarithromycin (21).

Erythromycin

Erythromycin can increase concentrations of triazolam by inhibition of CYP3A4, and dosage reductions of 50% have been proposed if concomitant therapy is unavoidable (22).

Miocamycin

CYP3A4 is mainly responsible for catalyzing the hydroxylation of miocamycin metabolites, which can alter the metabolism of concomitantly administered drugs by the formation of a metabolic intermediate complex with CYP450 or by competitive inhibition of CYP450 (23). This can cause excessive sedation with benzodiazepines such as triazolam.

Nefazodone

Nefazodone is a weak inhibitor of CYP2D6, but a potent inhibitor of CYP3A4, and increases plasma concentrations of drugs that are substrates of CYP3A4, such as triazolam (24,25).

Ritonavir

The inhibitory effect of ritonavir on the biotransformation of triazolam and zolpidem has been investigated (26). Short-term low-dose ritonavir produced a large and significant impairment of triazolam clearance and enhancement of its clinical effects. In contrast, ritonavir produced small and clinically unimportant reductions in zolpidem clearance. The findings are consistent with the complete dependence of triazolam clearance on CYP3A activity, compared with the partial dependence of zolpidem clearance on CYP3A.

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Tribenoside

General Information

Tribenoside, ethyl-3,5,6-tri-*O*-benzyl-D-glucofuranoside, is used as an anti-hemorrhoidal in oral and suppository formulations.

Organs and Systems

Skin

- A 57-year-old woman developed erythema exsudativum multiforme after using tribenoside 200 mg tds orally for 10 days (1). Patch tests with tribenoside (1% and 10% in petrolatum) showed erythema on days 2 and 3. Five controls were negative.

Reference

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Tribuzone

See also Non-steroidal anti-inflammatory drugs

General Information

The usual adverse effects of NSAIDs have been observed with tribuzone, namely gastric effects, fluid retention, and headache (SED-9, 145) (1).

Reference

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Trichloroethylene

See also General anesthetics

General Information

Trichloroethylene is a volatile halogenated anesthetic with weak anesthetic properties compared with other halogenated anesthetics and poor muscle relaxant activity. It has been used in dry cleaning, for metal degreasing, and as a solvent for oils and resins.

Long-Term Effects

Tumorigenicity

The incidence of cancer among 803 Danish workers exposed to trichloroethylene has been evaluated (1). There was no overall increase. However, the standardized incidence ratio was significantly higher in men with non-Hodgkin's lymphoma or esophageal cancer and in women with cervical cancer.

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Triclabendazole

See also Benzimidazoles

General Information

Triclabendazole is a benzimidazole derivative primarily used in veterinary medicine but has also been used experimentally in man. Chills, fever, leukopenia, and upper abdominal colic have been described (SEDA-14, 263).

Several reports have suggested that triclabendazole may be of use in the treatment of *Fasciola hepatica* infection. In 20 patients with fascioliasis treated with two single doses of triclabendazole 10 mg/kg, the plasma concentrations of triclabendazole, its active metabolite triclabendazole-SO, and its sulfone metabolite were doubled by food (1). There were no serious adverse effects, except for some right-sided upper abdominal pain in several patients, which was relieved by oral spasmolytics. Triclabendazole should be administered with food.

Reference

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Triclocarban

See also Disinfectants and antiseptics

General Information

Triclocarban is mainly used as an antibacterial agent in soaps and antiperspirants (1).

Organs and Systems

Hematologic

Methemoglobinemia was attributed to triclocarban in seven neonates (2). There was no history of familial methemoglobinemia, but in one case the mother had been taking phenacetin before labor and this was most probably the cause. In five of the six other cases the methemoglobinemia was thought to be due to the use of disinfecting solutions or ointments containing triclocarban that had been used as a vaginal disinfectant in four cases and as a powder for the umbilicus in one case. The authors advised against the use of triclocarban in maternity units and by those dealing with neonates.

Skin

Several patients developed relatively minor dermatological problems after treatment with triclocarban (3). Three developed very extensive erosive cutaneomucosal lesions after using triclocarban for periods ranging from 20 days to 3 months.

Immunologic

There have been several cases of allergic contact dermatitis after the use of antiperspirants containing triclocarban and propylene glycol (4).

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Tricyclic antidepressants

See also Individual agents

General Information

There are no accurate data on the worldwide use of the many tricyclic compounds listed in Table 1, and the availability of particular drugs varies from country to country. The dosage range for all these compounds is 50–300 mg/day, with the exception of nortriptyline, which has an upper limit of 200 mg, and protriptyline, which is more potent (range 10–60 mg/day). Well-controlled comparisons are few, but it is clear that these drugs resemble each other more than they differ. Their adverse effects will be discussed for the class as a whole, with distinguishing features of specific compounds mentioned when appropriate.

Tricyclic antidepressants interfere with the activity of at least five putative neurotransmitters by several different potential mechanisms at both central and peripheral sites. This gives rise to uncertainty in understanding the mechanisms that underlie a bewildering variety of untoward effects, which are in turn further modified by temporal factors, probably related to changes in receptor sensitivity. Differences between drugs are often inferred on the basis of selective effects on isolated organs in specific species, but their relevance to actions in man is largely unsubstantiated, owing to a lack of early clinical

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Table 1 Tricyclic antidepressants that have been widely studied or are currently available for treating depression (all rINNs)

Compound	Structure	Comments
Imipramine	Dibenzapine; tertiary amine	Prototype compound
Desipramine	Secondary amine	First metabolite of imipramine
Amitriptyline	Dibenzocycloheptene; tertiary amine	Meta-analyses suggest the most effective
Nortriptyline	Secondary amine	First metabolite of amitriptyline
Protriptyline	Secondary amine	Most potent; least sedative
Doxepin	Dibenzoxepine ring	Sedative
Clomipramine	Halogenated ring	Available for intravenous use
Dimetacrine	Acridine ring	
Lofepramine	Propylamine side-chain	Relatively safe in overdose
Noxiptiline	Oxyimino side-chain	
Butriptyline	Isobutyl side-chain	More potent dopamine effects
Imipramine oxide	Oxygenated ring	Metabolite of imipramine
Amitriptyline oxide	Oxygenated ring	Metabolite of amitriptyline
Dibenzepin	Dibenzodiazepine ring	
Melitracen	Anthracene ring	
Amoxapine	Dibenzoxazepine ring; piperazine side-chain	Less potent than other tricyclics; dopamine D_2 receptor antagonist
Iprindole	6,5,8 ring structure	Weak action on amino pump mechanism
Dosulepin	Dibenzothiepine ring	
Trimipramine	Propyl side-chain	Little effect on monoamine re-uptake
Amineptine	Seven-carbon side-chain	Less sedative than other tricyclics

pharmacology studies. There is a high base rate for spontaneously occurring complaints or placebo-induced adverse effects in psychiatric populations, which complicates interpretation, even in controlled studies. There is also a wide range of interindividual sensitivity and susceptibility between patients, and very little consistent correlation between plasma concentrations and particular adverse effects.

All tricyclic compounds (with the possible exception of protriptyline) have sedative effects, and this may be desirable or undesirable, depending on a particular patient's state of apathy or agitation. They have a spectrum of anticholinergic activity, presenting as troublesome adverse effects, such as dry mouth, sweating, confusion, constipation, blurred vision, and urinary hesitancy, depending on individual patient susceptibility. Weight gain is a common and troublesome adverse effect; it is mediated in part by histamine H_1 receptor antagonism.

The adverse effects of most serious concern relate to the cardiovascular system and seizure threshold. Actions on the adrenergic and cholinergic systems probably contribute to both hypotensive and direct cardiac effects, including alterations in heart rate, quinidine-like delays in conduction, and reduced myocardial contractility. The seizure threshold is lowered, increasing the frequency of epileptic seizures. All of these adverse effects can occur at therapeutic dosages in susceptible populations, such as elderly people, children, and people with cardiac problems or epilepsy, but are also a major cause of morbidity and mortality in accidental or intentional overdosage. Doses in excess of 500 mg can be seriously toxic, and death is fairly common when doses of 2 g or more are taken.

Tricyclic antidepressants rarely cause cholestatic jaundice and agranulocytosis due to hypersensitivity reactions. The rare liver necrosis may reflect severe hypersensitivity. Two fatal cases of hypersensitivity myocarditis and hepatitis have been described (1). A variety of dermatological manifestations have been reported (rash, urticaria, vasculitis), but their relation to drug ingestion is often uncertain. A single case of pulmonary hypersensitivity with pleural effusions and eosinophilia has been reported with desipramine (2).

Tumor-inducing effects have not been reported.

Plasma concentrations and adverse effects

Plasma concentrations of antidepressants are influenced by pharmacogenetic factors, age, and drug interactions. Several studies have attempted to define the relation between plasma concentrations of tricyclic antidepressants and their therapeutic or adverse effects. However, the results are conflicting (SEDA-3, 12) (SEDA-5, 15) (3). Sometimes there is a clear relation between cardiac toxicity and high plasma concentrations (4–6), but in some individuals cardiotoxic effects occur at presumed therapeutic concentrations. Sporadic reports of severe adverse effects, mostly of the anticholinergic type, have often been associated with high plasma concentrations of amitriptyline or nortriptyline (7,8), although these vary with each drug and from patient to patient. The risk of central nervous system toxicity in patients treated with tricyclic antidepressants may be correlated with plasma concentrations, age, and sex (SEDA-16, 8) (SEDA-17, 17). It can be concluded that routine plasma concentration monitoring is generally of little practical value in managing patients with adverse effects, but in view of the great interindividual variability in the pharmacokinetics of the tricyclic antidepressants, monitoring may be useful in those patients who report adverse effects at low doses.

Once-daily dosage

Most comparisons of once-daily with divided regimens for a variety of tricyclic compounds have shown equal efficacy and reduced adverse effects with once-daily regimens (SEDA-3, 10). However, the significance of such regimens for compliance may have been exaggerated.

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Multiple drugs have a much clearer impact on compliance than do multiple dosages of a single drug. Compliance is not usually impaired until more than three tablets a day are prescribed (9). A patient who forgets to take a single dose of a once-daily regimen loses more therapeutic effect than a patient who is equally forgetful about a divided regimen. Divided regimens may also be useful for patients who benefit from short-term sedation during the daytime.

Some adverse effects are more marked with single large doses, particularly in vulnerable patients. One study showed an increased frequency of frightening dreams when tricyclic antidepressants were given in a single bedtime dose (10). Elderly patients who take large single doses at bedtime may be at risk of dizziness, ataxia, and confusion caused by postural hypotension when they attempt to get out of bed in the dark (8).

Compatibility with electroconvulsive therapy

An important practical question concerns the compatibility of tricyclic antidepressants and electroconvulsive therapy (ECT). This has been studied in 15 patients taking 150–250 mg/day of imipramine or amitriptyline who received 4–16 ECT treatments (11). Continuous monitoring of cardiac function by oscilloscopy showed dysrhythmias in 40% of the ECT sessions. There were single extra atrial beats in 46 of 151 sessions and 1–3 premature ventricular beats in 12 sessions. Transient ventricular tachycardia occurred in one 32-year-old woman taking amitriptyline 250 mg/day who received 12 ECT treatments. The authors concluded that the cardiac effects are similar to those observed in previous studies of electrocardiographic changes during ECT in patients not taking antidepressants, and expressed the opinion that combined therapy does not involve any increased risk of serious cardiac dysrhythmias. A controlled comparison of ECT given to 19 patients taking tricyclic antidepressants and 27 control patients showed no differences in heart rate, blood pressure, or ectopic heart beats (12).

Tricyclic antidepressants in the treatment of enuresis

Although pediatric psychopharmacology is much neglected, nocturnal enuresis is an area of extensive research. An earlier review catalogued almost 100 publications on the topic (13). The tricyclic antidepressants have been shown to be effective in well-controlled trials, and over 40 publications had appeared before 1970. At that time adverse effects in children appeared to be minimal and comparable to those in adults. Since then considerable concern has developed over cardiotoxic effects and the risks of accidental overdose in children. The earlier reports have been summarized (SEDA-1, 10); managing overdose in children has been reviewed (SEDA-2, 10); death in a 16-month-old infant has been reported (SEDA-3, 9).

Sudden death, possibly related to cardiac effects in children and adolescents, has been discussed (SEDA-15, 13) (SEDA-16, 9) (SEDA-18, 18); it was concluded that children taking tricyclic antidepressants require careful monitoring of the electrocardiogram, even when relatively low doses are used (SEDA-18, 18).

Symptoms of intoxication in children taking tricyclic antidepressants may fail to be recognized in time, as shown by a number of cases published in the former German Democratic Republic (14), which led to serious consideration of the abandonment of such treatment there.

The British Committee on Review of Medicines recommended that these drugs should not be used in children under 6 years of age and should be given for periods not exceeding 3 months, and then only after a full examination (including electrocardiography) and consideration of other treatment options.

Long-term adverse effects

Treatment guidelines for depression and anxiety increasingly emphasize the value of longer-term maintenance treatment with antidepressants in order to prevent recurrence of illness. It is therefore important to assess the adverse effects burden of longer-term medication. The change in adverse effects profile over 1 year of treatment has been studied in a double-blind, placebo-controlled study of maintenance treatment with imipramine (average daily dose 160 mg) in 53 patients with panic disorder (15). Adverse effects of imipramine, such as sweating, dry mouth, and increased heart rate, persisted over the year of treatment, while rates of sexual dysfunction fell. Weight gain became increasingly problematic, and by the end of the trial imipramine-treated patients had a mean increase in weight of 4.5 kg, significantly more than the placebo-treated subjects, who gained only 1.3 kg. Data of this kind are helpful when advising patients on which adverse effects may remit and which are likely to persist during longer-term treatment. These data suggest that relative to SSRIs, such as fluoxetine and sertraline, maintenance treatment with imipramine is less likely to cause sexual dysfunction but has a greater risk of weight gain.

Organs and Systems

Cardiovascular

The cardiac toxicity of tricyclic antidepressants in overdose has been a source of continued concern. Undesirable cardiovascular effects, besides representing a major therapeutic limitation for this category of drugs, delineate an area in which tricyclic compounds with novel structures, as well as second-generation antidepressants, may have significant advantages. The cardiovascular effects of tricyclic antidepressants and the new generation of antidepressants have been reviewed (SEDA-18, 16) (16).

Since the inception of SEDA in 1977, each volume has included a review of the evolving literature, focusing on specific aspects, including direct myocardial actions (SEDA-12, 13), hypotension (SEDA-12, 13), and the incidence, severity, and management of overdosage in adults and children (SEDA-10, 19) (SEDA-11, 16) (4,17–21).

Direct myocardial actions

Tricyclic antidepressants are highly concentrated in the myocardium; this may account for the vulnerability of the

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heart as a target organ as well as for inconsistently and inconclusively reported relations between plasma drug concentrations and specific manifestations of cardiac toxicity. These drugs interfere with the normal rate, rhythm, and contractility of the heart through actions on both nerve and muscle that are mediated by at least four different mechanisms (singly, in combination, or due to imbalance), including an anticholinergic action, interference with re-uptake of catecholamines, direct myocardial depression, and alterations in membrane permeability due to lipophilic and surfactant properties.

Acute experiments in dogs have shown a negative inotropic effect sufficient to cause congestive cardiac failure, but a carefully conducted long-term study in man did not show impaired left ventricular function in depressed patients with concurrent congestive failure (SEDA-9, 18). In another study (22) nortriptyline (mean dose 76 mg/day, mean plasma concentration 107 ng/ml) was given to 21 depressed patients with either congestive heart failure or enlarged hearts. In this study, nortriptyline was effective and well tolerated, producing only one episode of intolerable hypotension.

The most readily observable change in cardiac function is sinus tachycardia, which occurs to a greater or lesser extent in more patients and which correlates weakly or inconsistently with plasma concentrations (4,17,18). The mechanism may be related to both central and peripheral effects on cholinergic and adrenergic systems, but is not simply a reflex response to hypotension (4). The presence of tachycardia can serve as an indirect measure of compliance (4), but it is seldom a cause for concern, except in individuals who anxiously monitor their own physiological functions.

The complex changes that occur in cardiac rhythm have been intensively studied using 24-hour high-speed and high-fidelity cardiographic tracings, His bundle electrocardiography (23,24), and cardiac catheterization (25,26). Changes in conduction and repolarization cause prolongation of the PR, QRS, and QT intervals and flattening or inversion of T-waves on routine electrocardiograms; conduction delay occurs distal to the atrioventricular node and is apparent as a prolonged HV interval (the time from activation of the bundle of His to contraction of the ventricular muscle). This effect resembles that due to type I cardiac antidysrhythmic drugs, such as quinidine and procainamide. These conduction changes can cause atrioventricular or bundle branch block and can predispose to re-entrant excitation currents with ventricular extra beats, tachycardia, or fibrillation.

The implications and complications of these changes in cardiac function and rhythm are less clear; knowledge of their existence provoked concern about the incidence of sudden death in patients with cardiovascular disease, but the evidence from epidemiological sources is equivocal (19). General guidelines for the use of these drugs in the elderly have been discussed above, and a review of studies on the cardiovascular effects of therapeutic doses of tricyclic antidepressants has supported their use in elderly patients and those with pre-existing cardiovascular disease, provided precautions are taken. Atrial fibrillation has been reported in predisposed elderly subjects (SEDA-18, 19). In children taking desipramine there have been reports of sudden death (27,28) and tachycardia, and cardiographic evidence of an intraventricular conduction defect (SEDA-18, 18) (29).

The antidysrhythmic effect of imipramine was first reported in 1977 during treatment of two depressed patients whose ventricular extra beats improved during treatment (30). Tricyclic compounds can trigger serious dysrhythmias at high doses and perhaps also when the myocardium is sensitized.

Care should be taken in patients with a recent myocardial infarction who show evidence of impaired conduction (first-degree heart block, bundle-branch block, or prolongation of the QT_c interval), since tricyclic antidepressants can theoretically add to the already increased risk of ventricular fibrillation in such patients (31). Reviews in earlier editions of Meyler's *Side Effects of Drugs* discussed these effects and gave practical guidelines on the use of tricyclic antidepressants in patients with heart disease (32).

There is sometimes a clear-cut correlation between cardiac toxicity and high plasma concentrations (SEDA-18, 18) (4–6), but this may not always be so in individuals who are highly sensitive to the drug or in whom prolonged treatment may have led to drug accumulation in the myocardium, despite plasma concentrations in the usual target range. Routine plasma concentration monitoring does not seem indicated, since plasma concentrations account for only a small part of the variance in cardiac effects (17). If an individual shows significant changes clinically or cardiographically, a spot measurement may show a high plasma concentration, requiring dosage reduction.

To date there have been no prospective studies that clearly show increased mortality in cardiac patients who use tricyclic antidepressants. It has been suggested that overall mortality due to cardiac disease may be higher in depressed patients who remain untreated than in those who receive either an antidepressant or electroconvulsive therapy (33). Even in patients who have chronic heart disease, the risks of effective treatment with a tricyclic appear to be minimal (34).

Hypotension

As many as 20% of patients taking adequate doses of a tricyclic antidepressant experience marked postural hypotension. This effect is not consistently correlated with plasma concentrations and tolerance does not develop during treatment (35–37). The mechanism for this effect is uncertain; it has been attributed to a peripheral antiadrenergic action, to a myocardial depressant effect, and to an action mediated by alpha-adrenoceptors in the central nervous system (38). Studies of left ventricular function in man are conflicting. One study of systolic time intervals showed a decrement in left ventricular function with therapeutic doses (39), while two in which cardiac function was observed directly during cardiac catheterization after overdosage showed no evidence of impaired myocardial efficiency, whereas the hypotension persisted after left ventricular filling pressures and cardiac output had returned to normal (40,41).

Postural hypotension can lead to falls. Its occurrence may be predictable, since patients who have raised systolic pressures and who have a pronounced postural drop before treatment are most likely to experience

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drug-induced hypotension (37). Such patients should be cautioned to rise slowly from sitting positions and, since elderly people are especially at risk of falling at night, single large bedtime doses of sedative tricyclic drugs should be avoided. These preventive measures are the most helpful, since the hypotensive effect is not directly related to plasma drug concentrations and may not improve with dosage reduction. The wisdom of using sympathomimetic drugs to counter this undesirable effect is questionable (42).

Use in patients with cardiac disease

The diagnosis of depression and the use of antidepressant medication are both associated with an increased risk of myocardial infarction. The relative contribution of these two factors is uncertain. In a case-control study of 2247 subjects, taking antidepressants was associated with a 2.2-fold (CI = 1.3, 3.7) increase in the risk of myocardial infarction (43). This increased risk seemed to be accounted for entirely by the use of tricyclic antidepressants, because selective serotonin re-uptake inhibitors were not associated with an increased risk, although the confidence intervals were wide (relative risk 0.8; CI = 0.2, 3.5). These findings support the usual clinical advice that tricyclic antidepressants are best avoided in those with known cardiovascular disease or significant risk factors.

Cardiovascular complications of overdosage

The relation between the dosage of a tricyclic antidepressant and the development of life-threatening cardiovascular complications is unclear and individually variable (44,45), although plasma concentrations above 1000 ng/ml give cause for serious concern. Plasma concentrations vary widely, and absorption can be delayed or deceptive, owing to gastric stasis and enterohepatic recycling (46). Dysrhythmias can occur for the first time up to 36 hours after drug ingestion or admission to hospital (46). The frequency of serious cardiac conditions in one series of 68 cases (47) was 46% in patients who took over 2000 mg of imipramine or its equivalent, almost twice that of those who took less (25%). An intensive study of cardiovascular complications among 35 overdose patients showed that 51% had significant hypotension and 80% had abnormal electrocardiograms (40). The latter consisted of sinus tachycardia (71%) and various abnormalities that reflect impaired conduction, including prolongation of the QT_c interval (86%), QRS complex (29%), and PR interval (11%). The ST segments and T-waves were abnormal in 28% of patients. Despite these manifestations of disturbed conduction and repolarization, there were relatively few dysrhythmias; 13 patients (37%) had ventricular extra beats, which lasted up to 72 hours after admission and subsided within 36 hours in 10 cases. No patients developed sustained repeated ventricular tachydysrhythmias, and the authors speculated that bizarre wide QRS complexes seen in aberrantly conducted supraventricular tachycardia (present in some cases) may sometimes be misinterpreted as ventricular tachycardia.

The basic principles of intensive supportive care should be applied early, and artificial ventilation is often necessary, since respiratory depression is more frequent than is commonly supposed (48,49). Patients should be monitored for 24 hours if the initial (or subsequent) electrocardiogram shows a dysrhythmia. Among 75 patients with overdose, none who had a normal electrocardiogram and level of consciousness for 24 hours went on to develop any significant dysrhythmia (50). However, a case was subsequently reported of a patient who died an acute cardiac death 57 hours after admission and 33 hours after normalization of the electrocardiogram (51). The authors suggested that prolonged monitoring may be justified in individuals who have taken antidepressants for prolonged periods, compared with those who overdose early in treatment.

More specific treatment to combat cardiotoxic effects is usually necessary in only a minority of instances; in the series reported above (40), five patients (14%) had marked hypotension. Initial low left ventricular filling pressures were corrected within 3 hours by infusion of isotonic saline. Systemic hypotension persisted and was corrected by infusion of sympathomimetic amines. Routine insertion of a pulmonary artery catheter, with continuous monitoring of blood gases, pulmonary arterial pressure, left atrial wedge pressure, and cardiac output have been recommended (40). Volume expansion is suggested for low left atrial pressure, with dopamine infusion to improve myocardial contractility if cardiac output remains low.

The management of ventricular extra beats is based on recognition of the quinidine-like basis of the conduction defect. In the series reported above (40) all 13 patients with ventricular arrhythmias responded to intravenous infusion of lidocaine (mean dose 2.0 mg/minute). This alone might account for the absence of deaths in this series.

Another indirect method of benefiting the patient with cardiotoxic effects has been the alkalinization of plasma to a pH of 7.50–7.55 using sodium bicarbonate infusion (52). This enhances plasma protein binding, making the drug less available to the tissues. It is claimed that this technique reverses both hypotension and cardiac dysrhythmias without the risk of the undesirable effects of antidysrhythmic drugs (46). Recommendations for the management of poisoning with tricyclic antidepressants given in a recent review have been summarized (SEDA-16, 8).

Differences among tricyclic compounds

There is evidence that doxepin is significantly less cardiotoxic than other tricyclic compounds (53). However, a complete review of all the animal and clinical data has suggested that doxepin overdose can still cause lethal dysrhythmias in man, probably by producing more marked respiratory depression.

Three different studies have shown that there is less risk of hypotension in patients treated with nortriptyline (54–56) than with other tricyclic compounds. However, a similar claim has been made for doxepin (57).

Increased pulse rate and blood pressure have been associated with desipramine in the treatment of bulimia nervosa (SEDA-17, 18).

Respiratory

There has been one case report of reduced ventilatory response to hypercapnia after nortriptyline in a

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woman with chronic obstructive pulmonary disease (SEDA-18, 19).

Nervous system

Miscellaneous symptoms that have been attributed to the tricyclic antidepressants include fatigue, weakness, dizziness, headache, and tremor; patients are likely to fall because of these disturbances.

Seizures are serious adverse events associated with the use of antidepressants, and the relative frequencies for different antidepressants have for a long time been a matter of controversy. The literature has been critically evaluated, taking into account predisposing factors, drug doses, plasma drug concentrations, and the duration of treatment (58). A significant proportion of seizures occurred in predisposed individuals, and the risk of seizure for most antidepressants increased with dose or blood concentration. After overdose the risk was higher for amoxapine and the tetracyclic drug maprotiline than for other antidepressants, but for several drugs there are not enough data to estimate the risk. Imipramine was the most frequently studied tricyclic, with a seizure risk of 0.3–0.6% at effective doses. For several of the second-generation antidepressants, a lower seizure risk has been reported in large clinical trials. Caution with all antidepressants should certainly be exercised in people who are predisposed to seizure activity because of brain damage or alcohol or drug abuse.

Concurrent use of lithium may be a risk factor for neurological adverse effects.

- A 34-year-old woman took amitriptyline 300 mg each night for several years. Six days after starting lithium 300 mg tds she had several generalized tonic-clonic seizures. A second episode occurred on re-exposure to lithium (59).

Patients with phobias or panic disorders are extremely sensitive to the adverse effects of tricyclic drugs early in treatment. They often have a syndrome of fine tremor, insomnia, and anxiety, which can be characterized as "jitteriness" and which is sometimes attributed to adrenergic hypersensitivity (SEDA-13, 9). Serum iron concentrations were significantly lower in jittery patients than in those who were not affected (SEDA-17, 19) (60). The authors suggested that this may be related to the role of iron as a co-factor for tyrosine hydroxylase.

Because tricyclic antidepressants suppress REM sleep, they have been used in the management of narcolepsy and cataplexy when amphetamines fail or abuse potential is high. Clomipramine is the most effective, possibly because it has more pronounced actions on serotonergic mechanisms (61).

Three reports have referred to a type of difficulty in articulation described as "speech blockage" or "dysarthria" (62–64). The disturbance was described as a delay in thinking and speech, in which the patient has difficulty in conceptualizing or transferring the next logical thought into words. The effect resembles stammering.

There have been sporadic reports of bilateral foot-drop with peroneal nerve involvement (65). A major neuropathy, with high stepping gait and inability to dorsiflex the foot, occurred in an 84-year-old woman; this presumed adverse effect remitted 8 weeks after withdrawal (66).

Unusual neurological reactions have been observed in some patients, generally when combinations of drugs (often including maprotiline) have been used (67). The symptoms were ataxia, akathisia, hypokinetic disorders of speech and motion, a dream-like state, and transiently impaired memory.

Confusion was observed in 13% of 150 patients taking tricyclic drugs, and in as many as 35% of patients over 40 years of age. All responded rapidly to drug withdrawal (SEDA-9, 26).

Aggressiveness during treatment in patients taking imipramine and amitriptyline in relatively low doses has been described (68). Violent behavior has also been attributed to amitriptyline (SEDA-17, 18).

Anticholinergic actions

Several organs are the target for the anticholinergic (antimuscarinic) activity of the tricyclic antidepressants. They constitute the most common and troublesome adverse effects of the tricyclic antidepressants, but the peripheral anticholinergic actions can also be put to therapeutic use in conditions such as irritable bowel syndrome, premature ejaculation, and nocturnal enuresis.

Experiments on receptor binding in rat brain and guinea-pig ileum have shown a spectrum of activity at muscarinic acetylcholine receptors for different tricyclic antidepressants (69). A comparison of five compounds showed that amitriptyline and doxepin were the most and desipramine the least potent, imipramine and nortriptyline being intermediate. Single-dose experiments in volunteers (given up to 100 mg of each drug) have confirmed the same rank order for both the peripheral anticholinergic actions (on salivary flow) and the central effects (sedation and other measures on a mood scale) (70). The significance of these differences between relatively low single doses of these drugs in healthy volunteers should not be uncritically extrapolated to clinical practice. However, they do provide a rationale for selecting among the different drugs for patients in whom either a high degree of sedation is desirable or anticholinergic effects are likely to be troublesome. No tricyclic is entirely free of anticholinergic action, and individual differences in susceptibility or metabolism can still cause serious problems in some patients. It is also difficult to predict which particular organ will become the major target for anticholinergic activity; some patients complain bitterly of a dry mouth, others report blurred vision, and some develop bowel or bladder symptoms. Careful history taking and physical examination will often reveal a possible cause for concern, based on the patient's previous response to similar drugs, existing disease (such as narrow-angle glaucoma, enlarged prostate, constipation), or advancing age.

Older people are supposedly susceptible to delirium caused by centrally acting anticholinergic drugs. This can take the form of anxiety, agitation, or frank hypomania. Such difficulties are more likely if the patient is also taking antipsychotic drugs (many of which also have anticholinergic effects) or anticholinergic antiparkinsonian drugs. Although such effects have long been recognized as a risk associated with the anticholinergic

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properties of these drugs, it has been suggested that their incidence may be lower than is often assumed (71). In an epidemiological study from a West German multicenter drug surveillance system in almost 14 000 patients for 5 years, exposure-related incidence rates were 1.2% for tricyclic antidepressants compared with 0.8% for both tranylcypromine and neuroleptic drugs (72). The risk increased steadily with age in both sexes and all diagnostic subgroups, and was six-fold higher (3.4%) in those over 60 years. Also at greater risk were women and patients with affective psychosis.

Adverse anticholinergic effects can occur immediately after the first dose of a tricyclic antidepressant. They are a major cause of poor compliance in patients who expect immediate relief, but who are not properly prepared for the delay that can occur in the beneficial effects of these drugs on mood and energy.

Sensory systems

Loss of accommodation and blurred vision are common inconveniences that can usually be tolerated in the knowledge that they lessen with the duration of treatment. Exacerbation of narrow-angle glaucoma in the elderly can occur, but is not an absolute contraindication to treatment with a tricyclic antidepressant, since the anticholinergic effects can be balanced by judicious use of pilocarpine (73,74).

Damage can occur to the corneal epithelium, due to reduced lacrimation and relative accumulation of mucoid secretions in patients who wear contact lenses (75).

Mouth and teeth

Rampant dental caries due to xerostomia occurred in a patient who took doxepin up to 300 mg/day for over 2 years (76). The author warned of the need to counsel patients to carry out rigorous and regular dental hygiene, as well as simple measures to promote increased salivation, such as sugarless lemon drops or chewing gum. In another study there was an increase in the number of decayed teeth in 35 children treated with amitriptyline or nortriptyline for enuresis, compared with a smaller group of untreated children with enuresis and a larger matched population control group (77).

Gastrointestinal

Simple dietary advice about bulk foods can mitigate minor bowel disturbances. More serious complications that can arise include paralytic ileus, which can be life-threatening, especially in the elderly (78). A less well-known adverse effect is the potential for aggravating or even possibly inducing a hiatus hernia, presumably due to an anticholinergic effect on the cardiac sphincter (79).

Urinary tract

The tricyclic antidepressants increase bladder sphincter tone and the volume of fluid necessary to trigger detrusor contraction (80). Such effects may account for their efficacy in nocturnal enuresis, in which the benefit occurs early and at a low dosage, consistent with anticholinergic activity. However, this pharmacological action can cause hesitancy and urinary retention, especially in predisposed men who have prostatic hyperplasia.

Renal damage from tricyclic antidepressants has been suggested on only one occasion.

- A 65-year-old man taking imipramine 300 mg/day developed toxic psychosis, anorexia, and nausea after 24 days. He was mildly azotemic, but these changes quickly reverted after withdrawal. No biopsy or renal function tests were reported.

The findings are entirely compatible with prerenal azotemia associated with diminished fluid intake during a drug-induced psychosis (81).

Neuroleptic malignant syndrome

The neuroleptic malignant syndrome, which is classically associated with antipsychotic drugs and is usually attributed to excessive dopamine D2 receptor blockade, can rarely occur with other medications, including tricyclic antidepressants.

- A 62-year-old man was found unresponsive in his apartment. He had a past history of bipolar disorder, for which he was taking nortriptyline and sodium valproate (dosages not stated). On admission to hospital his rectal temperature was 107.1 °F and he had increased muscle tone. He was intubated and cooled with ice packs. His creatine kinase activity was raised (1046 IU/l) but valproate and nortriptyline concentrations were within the target ranges. Extensive investigations, including biochemical screens and brain scans, showed no clear cause for his condition. Shortly afterwards he developed disseminated intravenous coagulation and died.

The authors concluded that the features of the illness were consistent with nortriptyline-induced neuroleptic malignant syndrome (82). However, a contributory role for sodium valproate was also possible.

The neuroleptic malignant syndrome has also been reported in association with the antidepressants trimipramine (SEDA-21, 11) (83), desipramine (SEDA-17, 18), and amoxapine (SEDA-16, 9) (SEDA-17, 18) (84). Amoxapine in particular has significant dopamine D2 receptor antagonistic properties. In most cases the patients were taking several other drugs, but there have been reports of the syndrome in association with amoxapine or desipramine alone.

Serotonin syndrome

The serotonin syndrome is usually associated with the use of combinations of drugs that potentiate brain serotonin function. This syndrome has been associated with several tricyclic antidepressants when used in combination with monoamine oxidase (MAO) inhibitors (85). Rarely it can be associated with the use of a single agent, such as clomipramine, a tricyclic antidepressant with potent serotonin re-uptake inhibitor properties (86).

- A 60-year-old woman, with a history of hypertension, type 2 diabetes mellitus, and depression, took clomipramine 200 mg/day for 8 months and then 250 mg/day for 3 months. Her other medications were glibenclamide 7.5 mg/day, lisinopril 5 mg/day, and clonazepam 0.5 mg/day. Without any change in medications or other precipitants, she began to feel confused and weak. She became pyrexial (41.6°C), confused, and

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tremulous, with myoclonic jerking. The combined plasma concentrations of clomipramine and desmethylclomipramine were 2230 nmol/l, somewhat over the usual target range (below 1900 nmol/l). Within hours her condition deteriorated, with seizures, ventricular tachycardia, and disseminated intravascular coagulation. Rhabdomyolysis led to acute renal insufficiency, which required dialysis. She remained severely ill over the next 4 weeks and eventually died of opportunistic Gram-negative infections.

This case illustrates that the serotonin syndrome can occasionally occur apparently spontaneously in patients taking a single serotonergic drug. The authors were unable to find any reason why the syndrome developed so catastrophically when it did, except for the modestly increased concentrations of clomipramine and its metabolite.

Extrapyramidal symptoms

Tricyclic antidepressants are often listed among the many drugs that can produce buccofaciolingual or choreoathetoid movements (87). A putative mechanism is a central anticholinergic action, which upsets the balance between the dopaminergic and cholinergic systems. The spontaneous occurrence of this syndrome makes it difficult to establish a cause-and-effect relation, although both patients described in the above report had symptoms again when rechallenged.

There is a more clear-cut cause-and-effect relation in the parkinsonian symptoms that occasionally occur with high-dosage tricyclic therapy in susceptible individuals (particularly elderly women). Because of its piperazine side-chain and structural resemblance to the phenothiazines, amoxapine has antidopaminergic properties that appear to produce typical dystonic reactions (88), but other tricyclic antidepressants may also be implicated in producing the full range of so-called extrapyramidal syndromes, including akathisia, dystonic reactions, parkinsonism, and tardive dyskinesia. Case reports have been described before (SEDA-16, 9) (SEDA-17, 18) (SEDA-18, 18). In the reports of tardive dyskinesia the problem is often that these patients have taken many different drugs.

Sensory systems

Eyes

Loss of accommodation and blurred vision are common inconveniences that can usually be tolerated, in the knowledge that they lessen with the duration of treatment. Exacerbation of narrow-angle glaucoma in the elderly can occur, but is not an absolute contraindication to treatment with a tricyclic antidepressant, since the anticholinergic effects can be balanced by judicious use of pilocarpine (73,74).

Treatment with bright light is used for mood disorders, and it has been suggested that antidepressants, which may act as photosensitizers, could enhance the effect of bright light on the eye, giving rise to adverse effects (SEDA-18, 17).

Ears

Tinnitus can occur after prolonged treatment with tricyclic antidepressants. In an early trial of imipramine (89) there were two cases of transient deafness, but in the subsequent 20 years no auditory effects have been recorded. In 1980, a report appeared (90) concerning four patients, all taking imipramine in dosages below 150 mg/day. Each complained of buzzing or ringing in the ears. In each case the symptoms improved or disappeared on dosage reduction, with maintenance of therapeutic benefit, and in one case the patient was switched to an equivalent dosage of desipramine without recurrence. A further report concerned a patient taking protriptyline 45 mg/day who developed ringing in both ears after 12 days (91). Symptom severity fell with dosage reduction and disappeared entirely after desipramine 100 mg/day was substituted. The authors postulated that non-vibratory tinnitus had originated from either neurological factors or changes in blood flow. In a chart review of 475 patients treated with tricyclic antidepressants there were five patients with tinnitus. Each developed the symptom in the second or third week of treatment at dosages of imipramine of 150–250 mg/day, with plasma concentrations of 200–400 ng/ml (92). In every case tinnitus subsided spontaneously within a further 2–4 weeks after onset, even though dosage and plasma concentrations remained constant.

Another unusual disturbance of hearing has been reported in a child taking tricyclic antidepressants (93). Auditory acuity was normal, but discriminative ability for both clear and distorted speech was depressed. The disorder cleared within some days of withdrawal.

Psychological, psychiatric

Cognitive impairment has been associated with nortriptyline in elderly subjects (SEDA-17, 19).

Musical hallucinations have been reported in association with clomipramine (SEDA-17, 18).

Mania

It is widely believed that there is a significant risk that tricyclic antidepressants can precipitate mania or rapid cycling in up to 10% of patients, and that various factors increase this possibility, including being female or younger, having an earlier onset of illness, and having a positive first-degree family history (SED-11, 40). Biochemical risk factors have been alleged to include patients with a low urinary excretion of the noradrenaline metabolite methoxyhydroxyphenol glycol (MHPG); the risk is possibly greater in patients taking tricyclic antidepressants rather than MAO inhibitors, and particularly in the case of clomipramine. The data on which these conclusions were based have now been rigorously analysed (94) in a review of the controversy surrounding the alternative suggestion that the so-called switch effect is a random manifestation of bipolar illness. There is a paucity of both prospective and long-term placebo-controlled studies, and existing research has suffered from unrepresentative samples and poor definition of manic outcomes. The reviewers concluded that "... some bipolar patients and few, if any, unipolar patients become manic when they are treated with antidepressants. A small number of patients develop rapid cycling."

This more cautious conclusion is supported by the results of a prospective study of 230 carefully selected patients with recurrent depression (at least two episodes,

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with an average of six) who took imipramine (200 mg/day) for an average of over 46 weeks (95). Mania and hypomania were defined and measured by the Raskin rating scale. Only six patients (2.6%) developed hypomania, and four of these did so after withdrawal. Younger patients, women, and those with a previous history of hypomania (bipolar II) were no more likely to switch than unipolar patients.

These results suggest that the risk of mania or hypomania in the long-term treatment of recurrent unipolar depressed patients is relatively small. The 12 placebo-controlled studies of acute treatment in less carefully defined samples support higher incidence rates (around 6–7% for hypomania and 1–2% for mania), but these figures may be inflated owing to the inclusion of bipolar patients with a high risk of a spontaneous switch (94).

Metabolism

Weight gain has long been recognized as a concomitant of antidepressant and antipsychotic drug therapy. This may in part reflect improvement in mental state, but there also appears to be a physiological component, with an increased craving for sweets (96). No abnormalities have been found in fasting glucose and insulin concentrations or in intravenous insulin tolerance tests (96,97). Another possible suggestion for weight gain is that taste perception in depression improves after therapy with tricyclic antidepressants (98). A study of 50 depressed patients attempted to address some of these issues (99). Increased energy efficiency during antidepressant treatment has also been suggested as a reason for weight gain (SEDA-17, 8). A warning to patients with diabetes that hypoglycemia can be masked seems appropriate (100).

Endocrine

The "Division of Drug Experience" of the US Department of Health and Welfare issued a note on five cases of the syndrome of inappropriate antidiuretic hormone secretion and drugs to which it has been attributed (101). All involved drugs with a tricyclic structure; one patient was taking imipramine, three carbamazepine, and the others the closely related muscle relaxant cyclobenzaprine. The dosage of imipramine was 50 mg/day for 3 weeks and the patient was a 72-year-old woman. Other cases have been reported, involving amitriptyline (101), imipramine, and protriptyline (SEDA-17, 17).

Tricyclic antidepressants, presumably through blocking the re-uptake of noradrenaline, can cause a crisis in a patient with a pheochromocytoma (SEDA-21, 11) (102).

Prolactin concentrations are very rarely altered during treatment with tricyclic antidepressants, but this is more likely to occur and to produce galactorrhea or amenorrhea with clomipramine and amoxapine and when there are other contributory factors that may stimulate prolactin secretion, such as stress or electroconvulsive therapy (103).

Hematologic

Occasional cases of blood dyscrasias with tricyclic antidepressants continue to be reported (SEDA-12, 46) (SEDA-18, 18) (SEDA-21, 10). Antidepressant-induced blood dyscrasias have recently been reviewed (104).

Agranulocytosis has been associated with tricyclic antidepressants (105). Of 20 cases, eight were fatal and 12 recovered after 3–20 days.

Two cases of non-thrombocytopenic purpura occurred in patients taking tricyclic antidepressants. Both improved on withdrawal (106). True thrombocytopenia, with platelets counts as low as 120×10^{12}/l, occurred in a 79-year-old woman taking doxepin. During later treatment with amitriptyline, thrombocytopenia recurred, but not when she took imipramine (107). Cross-sensitivity must be highly specific to chemical structure, doxepin and amitriptyline being more like each other than imipramine.

Liver

Cholestasis was among the first adverse effects reported with phenothiazines, tricyclic antidepressants, and MAO inhibitors. Its incidence appears to have fallen, for reasons that are not understood, but under-reporting may be a factor. Increases in liver enzymes, especially transaminases and alkaline phosphatase, are quite common during treatment with both phenothiazines and tricyclic antidepressants. Such effects are usually benign, but one careful study of a patient taking amitriptyline showed biopsy findings of mononuclear and eosinophilic infiltration; cholestasis and jaundice were absent (108). In a controlled comparison of lofepramine and fluoxetine, there were significant increases in alkaline phosphatase, alanine aminotransferase, and gammaglutamyl transferase in patients taking lofepramine but not fluoxetine (109).

More serious and sometimes fatal liver necrosis has been reported with a number of different tricyclic structures and probably represents an extreme form of hypersensitivity (110,111). Liver necrosis in a 33-year-old woman who took imipramine 300 mg/day for over 1 month led the authors to suggest that once-daily dosage may pose a special hazard, because peak concentrations can exceed the toxic concentration, even though steady-state plasma concentrations are in the usual target range (112). A particular hazard appears to be posed by amineptine (qv).

There is no indication for routine liver function tests in patients taking tricyclic antidepressants; raised transaminases and alkaline phosphatase within the limits of the reference ranges are not a cause for serious concern, unless they are accompanied by clinical signs or symptoms indicative of liver dysfunction.

Skin

Skin rashes are so common that it is difficult to determine a cause-and-effect relation. A choice must be made between waiting to see if the rash clears despite continued treatment or switching to a different compound and, if necessary, rechallenging at a later date. Serious reported skin reactions include cutaneous vasculitis, urticaria, and photosensitivity. A grey discoloration of the skin in light-exposed areas has been associated with long-term therapy with imipramine and desipramine (SEDA-17, 19) (SEDA-18, 18). Pigmentary changes in the iris were also reported in one of the cases. Amineptine has been reported (113) to cause a particularly active acne, occurring beyond the usual distribution on the body and beyond the usual age, especially in women. The remedy

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recommended is withdrawal of amineptine. A single case of a rosacea-like eruption on the face of a 76-year-old woman was also caused by this drug, and the association was confirmed by re-challenge (114).

Hyperpigmentation is a recognized adverse effect of the antipsychotic drug chlorpromazine. Four cases of hyperpigmentation have been described in patients taking the structurally related tricyclic antidepressant imipramine (115). All were women and had taken imipramine for at least 2 years. The hyperpigmentation occurred in a photodistribution on the face, arms, and the backs of the hands. In two patients who discontinued imipramine the hyperpigmentation resolved within 1 year. The authors speculated that the pigmentation might have been due to deposition of melanin in an unusual form, possibly in a complex with a metabolite of imipramine.

Sexual function

A review of sexual dysfunction due to antidepressant drugs in men, citing both published findings and reports provided by the manufacturers, drew a distinction between erectile dysfunction, ejaculatory problems, and changes in libido (116). A complicating factor is the lack of information concerning the base rate of these problems in depression itself. Erectile impotence has been reported with all of the commonly used tricyclic compounds in low normal dosages. Delayed and occasionally painful ejaculation occurs, and four cases of painful ejaculation in association with imipramine and clomipramine have been reported (SEDA-17, 18). Priapism can occur (116). Both increased and decreased libido have been reported, but it is virtually impossible to distinguish drug relatedness from the natural history of the condition. A small number of uncontrolled studies have shown therapeutic benefits in patients with premature ejaculation or disturbed sexual function accompanied by depression (117).

Delayed orgasm or loss of ability to obtain orgasm has been reported in women taking desipramine (118).

The sexual dysfunction is probably due to 5-HT re-uptake blockade, because similar effects are seen in patients taking SSRIs.

Long-Term Effects

Drug withdrawal

There is compelling evidence for a withdrawal syndrome due to abrupt discontinuation of tricyclic antidepressants (SEDA-5, 16), and the literature has been reviewed (119). Reports have involved both imipramine and doxepin (120). Symptoms occur as early as the morning after a missed dose (121), but more often after 48 hours and up to 2 weeks after withdrawal. They include anxiety, restlessness, sweating, diarrhea, hot or cold flushes, and piloerection. Amitriptyline withdrawal was followed by similar physical symptoms 36 hours after the last dose, followed by severe depressive illness (SEDA-17, 18).

Delirium after withdrawal of doxepin has been reported (122), as well as instances of mania (123). Pronounced neurological symptoms have been described after sudden withdrawal of amitriptyline (SEDA-18, 18).

The existence of a withdrawal syndrome was subjected to a controlled test (120) in seven patients who had been taking long-term amitriptyline up to 250 mg/day, imipramine 200 mg/day, or desipramine 250 mg/day. After 4 weeks placebo was substituted double-blind for 10–21 days. Both plasma and urine MHPG concentrations increased by an average of 74% above baseline, starting within 36 hours and reaching a peak 3 weeks after withdrawal. Despite these pronounced neurochemical changes there were no alterations in pulse rate or heart beat, and only two patients had definitely worse anxiety.

There is clearly a need for larger controlled studies to determine the incidence and severity of withdrawal effects after withdrawal of tricyclic antidepressants. Based on uncontrolled observations, it has been suggested that the incidence varies from under a quarter to over half of all patients.

A report of three cases (124) has suggested that central cholinergic overactivity is implicated, and that atropine sulfate 3 mg/day or synthetic anticholinergic agents (such as benzatropine mesylate 4 mg/day) ameliorate withdrawal symptoms within a few hours. The authors suggested that this technique may be especially useful in patients in whom tricyclic antidepressants must be abruptly withdrawn because of allergic or idiosyncratic reactions.

Second-Generation Effects

Teratogenicity

In chick embryos there was a high prevalence of abnormalities, including microphthalmia, micromelia, and reduced body size, after the administration of imipramine, but the dosages of imipramine were close to lethal (125).

The issue of dysmorphogenesis due to these drugs was first seriously discussed after a report on three possible cases from Australia in 1972 (126). Although the data underlying this report were later discredited, it led to a careful study of the case records of women who had taken tricyclic antidepressants in pregnancy, and more than 300 cases were rapidly identified in which such treatment had been followed by the birth of a normal infant. Other negative reports exonerating the drugs have appeared since (127–130), although sporadic case reports continue to appear (131).

In spite of these reports, which negate a possible association between tricyclic antidepressants and teratogenicity, it may be advisable to avoid these drugs during pregnancy, especially in the early stages, unless there is a compelling need. In many of the reports the drugs were given in low doses or for indications not justifying their use.

Fetotoxicity

Instances of distress in the newborn have been reported after treatment of their mothers with tricyclic antidepressants in the period before delivery (132). In one case, a neonate had signs of congestive heart failure without cardiac abnormality; another had tachycardia and myoclonus; a third had respiratory distress and neuromuscular spasms. These effects were thought to have resulted from both the adrenergic and anticholinergic effects of the

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tricyclic antidepressants, which readily pass the placenta and should be avoided during the perinatal period.

Infants born to mothers taking tricyclic antidepressants can become jittery in the first few days of life (133).

- A healthy boy (weight 3370 g) was born to a mother who had taken clomipramine 100 mg/day throughout pregnancy. On the second day after delivery, the child was jittery and on the fifth day he developed myoclonic jerking of his arms and legs. There was no epileptic activity on a 10-channel electroencephalogram, and clonazepam and phenobarbital did not suppress the movements. However, the movements were suppressed by a single dose of intravenous clomipramine 0.5 mg. The myoclonus recurred only occasionally over the next 4 days. Examination at one month later was normal, apart from mild jitteriness in response to touch.

Maternal clomipramine use is associated with seizures in neonates but this case appears to have been caused by a withdrawal state that was relieved by clomipramine administration.

Another report has suggested that effects in the neonate may be due to withdrawal from maternal antidepressants after birth (134). Two cases of neonatal convulsions have been reported in infants whose mothers had been treated with clomipramine. In both cases the seizures occurred on the first day of life coincident with a fall in plasma clomipramine concentrations. In one case the convulsions were controlled by administration of clomipramine followed by tapered withdrawal.

Hypotonia has been described in four children, one of whom also developed jitteriness (SEDA-17, 18).

Lactation

There are few reports on the excretion of antidepressant drugs in breast milk, even though postpartum depression is relatively common. In a 32-year-old woman who took imipramine 200 mg/day from 1 month postpartum imipramine and desipramine were detectable in breast milk (135). There have also been reports that amitriptyline (136), desipramine (137), and nortriptyline (138,139) were detectable in the milk of nursing mothers and in the plasma of the mothers and infants. Neither parent compound nor metabolite were detected in infants' serum, except for two infants who had low concentrations of 10-hydroxynortriptyline. There were no adverse effects in any of the infants. The use of antidepressants during lactation has been reviewed, including 15 studies in which serum concentrations of antidepressants were obtained from nursing infants (140).

There has been a report of an 8-week-old breast-fed infant whose mother was taking doxepin (141). Four days after an increase in the daily dosage from 10 to 75 mg the infant developed respiratory depression; desmethyldoxepin was detected in the baby's plasma.

Susceptibility Factors

Age

Elderly people

Elderly people have high rates of depression but tend to be excluded from randomized trials of antidepressant treatment. In general, older people metabolize tricyclic antidepressants more slowly and have higher steady-state plasma concentrations. There is an increased risk of adverse effects of tricyclic antidepressants in elderly patients (SEDA-18, 17). Elderly people often take other drugs that can cause depression or interact with its treatment (142). These potential sources of variation are superimposed on the wide range of plasma concentrations reported among individuals, and on the differences between drugs in dose–response profiles. The dictates of safe practice are that treatment in elderly people be begun with low dosages (50 mg/day of imipramine or equivalent) in divided amounts, with dosage increases in small increments (50 mg/day of imipramine each week) and a reduced total dose range (75–150 mg/day, except in exceptional circumstances) (143). Close attention should be paid to the potential anticholinergic, neurological, or cardiovascular complications to which elderly people are especially vulnerable (31).

The adverse effects profile of fixed-dose clomipramine (150 mg/day) has been assessed in 112 hospitalized depressed patients (aged 22–70 years), of whom 38 were over 55 years of age (144). The only adverse effect that distinguished patients over 55 years was orthostatic hypotension: older subjects had a significantly greater fall in systolic blood pressure on standing. Orthostatic hypotension can lead to falls and injuries, particularly in patients being treated at home, and this suggests that blood pressure should be monitored in older patients who are taking psychiatric doses of tricyclic antidepressants. It is also worth noting that the upper age limit of patients in this study was only 70 years, so it is unclear how more elderly patients would fare with this rather substantial dose of clomipramine.

Drug Administration

Drug overdose

Both accidental and intentional overdose are relatively frequent and pose difficult management problems. Particular concern has been expressed for children, either because they gain access to parents' tablets or have been treated for enuresis. During one year a Melbourne hospital admitted 35 children poisoned with tricyclic antidepressants (145). In 1979 it was reported that tricyclic antidepressants had replaced salicylates as the most common cause of accidental death in English children under the age of five. Concern was expressed about this (146), and Swiss federal statistics raised similar worries (147).

The majority of all deaths from antidepressant poisoning in Scotland, England, and Wales, during 1975–1984 and 1985–1989 were due to two tricyclic drugs, amitriptyline and dosulepin, and they, as well as the entire group of older tricyclic antidepressants, had a fatality index (deaths per million prescriptions) significantly higher than the mean (148).

A nation-wide analysis of suicide mortality in Finland showed that between 1990 and 1995 the overall suicide mortality fell significantly from 30 per 100 000–27 (149). However, the use of antidepressants in completed suicide showed an upward trend, while the use of more violent methods (gassing, hanging) fell. During this time

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prescription of moclobemide and two SSRIs (citalopram and fluoxetine) increased, while that of tricyclics (mainly doxepin and amitriptyline) remained steady. The mean annual fatal toxicity index was highest for tricyclics, such as doxepin, trimipramine, and amitripyline, and lowest for SSRIs.

Educational policies and commercial marketing of antidepressant drugs have led to an increase in the detection and treatment of depression. Conceivably this may be associated with the fall in suicide rates noted in Finland. However, overdosage of tricyclic antidepressants continues to contribute to deaths from suicide. Whether completely replacing tricyclics with less toxic compounds would lower overall suicide rate remains controversial.

The results of a British survey of all deaths due to acute poisoning due to antidepressants are shown in Table 2 (150).

A major problem in evaluating the incidence and severity of complications due to overdosage in adults has been the reporting of individual cases or selected samples, often with the inclusion of patients who have taken several drugs or who have concurrent physical disease. More reliable epidemiological surveys from different countries (45,151,152) have suggested that the mean ingested overdose of a tricyclic antidepressant in adults is around 1000 mg, and that only about 3% of patients take enough to cause fatal complications. There is considerable individual variability in response to overdosage, and there are conflicting reports concerning the degree of correlation between plasma concentrations and complications. One large study showed that plasma concentrations in excess of 1000 ng/ml were associated with coma, convulsions, cardiac dysrhythmias, and a need for supportive measures (21). In other studies there was no clear-cut correlation between plasma concentration and the incidence of toxic complications (153). Cardiac complications have been reviewed above and are serious, but should not deflect attention from other serious effects. A review of all deaths due to these drugs in Britain during 1976 showed that dysrhythmias were less common than supposed (11 of 113 patients who died in hospitals), but that respiratory depression was more frequent (54 of 113

Table 2 Deaths per million prescriptions for antidepressants in the UK

Drug	No. of prescriptions	Total deaths	Deaths per million prescriptions (95% CI)
Tricyclic antidepressants and related drugs	74 598 000	2598	35 (34, 36)
Desipramine	45 000	9	201 (92, 382)
Amoxapine	107 000	10	94 (45, 172)
Dosulepin	26 210 000	1398	53 (51, 56)
Amitriptyline	23 844 000	906	38 (36, 41)
Imipramine	3 354 000	110	33 (27, 40)
Doxepin	1 587 000	40	25 (18, 34)
Trimipramine	2 370 000	39	17 (12, 23)
Clomipramine	4 315 000	54	13 (9.4, 16)
Nortriptyline	1 269 000	7	5.5 (2.2, 11)
Maprotiline	201 000	1	5.0 (0.1, 28)
Trazodone	2 753 000	11	4.0 (2.0, 7.1)
Mianserin	922 000	3	3.3 (0.7, 9.5)
Mirtazapine	324 000	1	3.1 (0.1, 17)
Lofepramine	7 189 000	9	1.3 (0.6, 2.4)
Butriptyline	1000	0	0 (0, 3372)
Iprindole	3000	0	0 (0, 1218)
Viloxazine	10 000	0	0 (0, 357)
Protriptyline	94 000	0	0 (0, 39)
Serotonin re-uptake inhibitors	47 329 000	77	1.6 (1.3, 2.0)
Venlafaxine	2 570 000	34	13 (9.2, 19)
Fluvoxamine	660 000	2	3.0 (0.3, 11)
Citalopram	2 603 000	5	1.9 (0.6, 4.5)
Sertraline	5 964 000	7	1.2 (0.5, 2.4)
Fluoxetine	19 926 000	18	0.9 (0.5, 1.4)
Paroxetine	15 031 000	11	0.7 (0.4, 1.3)
Nefazodone	576 000	0	0 (0, 6.4)
Monoamine oxidase inhibitors	1 203 000	24	20 (13, 30)
Tranylcypromine	367 000	16	44 (25, 71)
Phenelzine	404 000	6	15 (5.5, 32)
Moclobemide	365 000	2	5.5 (0.6, 20)
Iproniazid	200	0	0 (0, 18 444)
Isocarboxazid	68 000	0	0 (0, 55)
Other antidepressants	2 523 000	1	0.4 (0, 2.2)
Flupentixol	28 000	0	0 (0, 2.4)
Tryptophan	28 000	0	0 (0, 133)
Reboxetine	175 000	0	0 (0, 21)
Lithium	5 106 000	37	7.2 (5.1, 10)

Numbers may not add up to the total because of rounding.

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patients) (48). Some such deaths might have been avoided by more frequent artificial ventilation and better attention to the principles of supportive care.

Management of overdose

The literature on poisoning with tricyclic antidepressants has been reviewed and recommendations for the management of overdose proposed (SEDA-16, 8) (154). In overdose, physostigmine can reverse life-threatening dysrhythmias, but its effect is short-lasting and it has adverse effects of its own; it should be avoided (154).

Drug–Drug Interactions

General

The large number of drugs with which tricyclic antidepressants interact are summarized in Table 3; those of major concern are discussed in more detail below.

Table 3 Interactions of tricyclic antidepressants with other substances

Interacting substance(s)	Type of interaction(s)	Comments
Alcohol	Additive sedative effects	May be more pronounced with more sedative tricyclic compounds
Anticholinergic drugs	Additive effects on pupils, nervous system, bowel, and bladder	Particularly likely to occur when a tricyclic drug, a phenothiazine, and a antiparkinsonian drug are prescribed concurrently
Anticoagulants	Increased serum concentrations of oral anticoagulant	Tricyclic drugs can interfere with the metabolism of oral anticoagulants
Antiepileptic drugs	Antagonism	Convulsive threshold lowered
	Decreased plasma concentrations of some tricyclic drugs	Hepatic microsomal enzyme induction
Antihypertensive agents	Reversal of hypotensive effects of clonidine, reserpine, α-methyldopa, and guanethidine	Hypertension should be controlled with diuretics, β-blockers, or vasodilators before treatment of depression
Barbiturates	Reduced plasma concentrations of tricyclic drugs	Hepatic microsomal enzyme induction
Calcium channel blockers	Increased plasma concentrations of imipramine and possibly other drugs	
Cigarette smoking	Decreased plasma concentrations of tricyclic drugs	Probably increased metabolism
Cimetidine	Increased systemic availability of tricyclic drugs	Probably due to impaired hepatic extraction
Disulfiram	Increased plasma concentrations of tricyclic drugs	Probably inhibition of metabolism
Diuretics	Increased risk of postural hypotension	Pharmacodynamic interaction
Halofantrine	Increased risk of ventricular dysrhythmias	Prolonged QT interval
Levodopa	Impaired gastrointestinal absorption	May apply to other drugs metabolized in the gut
Monoamine oxidase inhibitors	Increased incidence of weight gain	See text; see also monograph on Monoamine oxidase inhibitors
	Increased anticholinergic effects	
	Hyperthermia, hyper-reflexia, convulsions, death (very rare)	
Membrane-stabilizing drugs (quinidine type)	Synergism	
Methylphenidate	Increased plasma concentrations of tricyclic drugs	Probably inhibition of metabolism
Morphine	Potentiation of analgesic effect of morphine	May be partly due to increased systemic availability of morphine
Nitrates	Reduced effect of sublingual nitrates	Owing to dry mouth
Phenothiazines	Increased plasma concentrations of tricyclic drugs	Due to inhibition of metabolism
	Possible potentiation and/or increased speed of onset of antidepressant effect	
	Enhanced cardiotoxic effects with thioridazine	Presynaptic α_2-adrenoceptor blockade (animal studies)
		Ventricular dysrhythmias can occur
Rifampicin	Decreased plasma concentrations of some tricyclic drugs	Hepatic microsomal enzyme induction
Ritonavir	Possibly increased plasma concentrations of tricyclic drugs	Inhibition of metabolism
SSRIs	Increased plasma concentrations of tricyclic drugs	Inhibition of metabolism
Corticosteroids	Altered systemic availability of tricyclic drugs	Inhibition of metabolism
	Akathisia	Receptor interaction
	Exacerbation of psychosis	
Sympathomimetic agents	Potentiation of hypertensive effects with phenylephrine, noradrenaline, methylphenidate	
	Potentiation of effects of pheochromocytoma	
Thyroid hormones	Can manifest as spurious hyperthyroidism, cardiac dysrhythmias, or, in some cases, enhanced therapeutic actions of tricyclics	Increased receptor sensitivity to catecholamines

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Alcohol

Alcohol in combination with tricyclic antidepressants impairs performance, and it is customary to caution patients about the risk of impairment in their ability to drive or handle machinery. Not only can additive impairment occur (mediated at the receptor level), but alcohol can also alter the metabolism of the antidepressant (SEDA-8, 24).

Amines

Tricyclic antidepressants act on both presynaptic and postsynaptic neurons, as well as on alpha- and beta-adrenoceptors. Because their principal action is to block the re-uptake of noradrenaline at the presynaptic neuron, they potentiate the hypertensive effects of both directly acting and indirectly acting amines (155,156). The hypertensive effects of phenylephrine are increased by a factor of 2–3, and of noradrenaline by a factor of 4–8. Even the administration of local anesthetics containing noradrenaline as a vasoconstrictor has proven fatal. The types of compound that can produce this interaction and the symptoms that result have been previously reviewed in detail (SEDA-1, 11).

Anesthetics

In 190 patients taking tricyclic antidepressants that could not be discontinued before surgery, who underwent general and 61 local or regional anesthesia, there were no changes in the cardiovascular effect of halothane, induction time with pentobarbital, propanidid, or ketamine, or the duration of depolarization or recovery time (157). The general conclusion was that it is safer to continue treatment with tricyclic antidepressants than to risk potential disruption from withdrawal before surgery.

Anticoagulants

Tricyclic antidepressants can interfere with the metabolism of oral anticoagulants, increase their serum concentrations, and prolong their half-lives by as much as 300% (SEDA-21, 10) (158). Prothrombin activity should be carefully monitored in patients taking oral anticoagulants.

Antidysrhythmic drugs

Because of their similar lipophilic and surfactant properties, tricyclic antidepressants interact with antidysrhythmic drugs of the quinidine type, interfering with the voltage-dependent stimulus and producing dose-related synergy (159). Cardiac glycosides and beta-blockers are free of this interaction, although animal studies have suggested increased lethality of digoxin in rats pretreated with tricyclic antidepressants (160), while propranolol may potentiate direct depression of myocardial contractility due to tricyclic antidepressants. For all of these reasons, the preferred treatment for tricyclic-induced dysrhythmias is lidocaine, but even this is reported to be only variably effective and possibly to potentiate the hypotensive effects of tricyclic drugs (46).

Antipsychotic drugs

Tricyclic antidepressants lower the seizure threshold and should therefore be used with caution with other agents that can also lower seizure threshold, such as antipsychotic drugs (161).

- A 34-year-old man with schizophrenia responded well to olanzapine 20 mg/day. However, he then had obsessional hand washing and was given clomipramine, which was increased to a dosage of 250 mg/day. He then reported myoclonic jerks with some dizziness, and 10 days later had a generalized tonic-clonic seizure. The combined clomipramine + desmethylclomipramine concentration was 2212 nmol/l, higher than the upper end of the usual target range (1300 nmol/l). An electroencephalogram showed paroxysmal slowing and spike-and-wave activity. Both olanzapine and clomipramine were withdrawn. Later the clomipramine was restarted as monotherapy and a dose of 300 mg/day was reached, which led to an even higher clomipramine + desmethylclomipramine concentration (3234 nmol/l), but there was no clinical or electroencephalographic evidence of seizure activity. However, when olanzapine was added in a dosage of 15 mg/day, myoclonic jerking and abnormal electroencephalographic activity recurred within 7 days.

The seizures occurred in the presence of high concentrations of clomipramine in this case, suggesting a pharmacodynamic drug interaction, since neither agent given alone provoked seizure activity, whereas the combination did. It is, however, possible that clomipramine might have caused a rise in olanzapine blood concentrations, which were not measured.

Benzodiazepines

Four patients developed adverse effects attributable to combinations of benzodiazepines with tricyclic antidepressants, including exacerbations of delusional thought disorders (162).

Corticosteroids

Patients taking prednisone have experienced psychosis, perhaps due to an interaction at dopamine receptor sites (163,164).

Fluconazole

Fluconazole can increase plasma concentrations of amitriptyline, presumably by inhibiting cytochrome P450 isozymes (CYP3A4 and CYP2C19), preventing its demethylation. Two patients taking amitriptyline and fluconazole developed syncope and in one concomitant electrocardiographic monitoring showed a prolonged QT interval and torsade de pointes (165,166). In neither case were serum amitriptyline concentrations measured, but the symptoms were consistent with tricyclic antidepressant toxicity. These case reports suggest that this combination should be used with caution and probably with monitoring of amitriptyline concentrations.

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Levodopa

The anticholinergic effects of imipramine and other tricyclic antidepressants can delay gastrointestinal motility enough to interfere with the absorption of various other drugs. Such was the case in an experimental study of the absorption of levodopa in four healthy subjects (167). It is likely that this effect may interfere with absorption of other drugs, especially those, such as chlorpromazine, that are extensively metabolized in the gut.

Methylphenidate

The interaction with methylphenidate may be of particular significance, because of claims that tricyclic antidepressants and methylphenidate have a synergistic effect on mood, owing to interference by methylphenidate with the metabolism of imipramine, resulting in increased blood imipramine concentrations (168). The occurrence of this hypertensive interaction calls for caution in the use of such combinations, for which there is no established evidence.

Monoamine oxidase inhibitors

The interactions of tricyclic antidepressants with MAO inhibitors are so dangerous that they constitute a formidable barrier to their combined clinical use. The temptation to treat refractory patients with this combination is great, but considerable care should be taken (169,170), and it should be remembered that there is no firm proof of the superiority of such combinations. Several reviewers (171–173) have concluded that the dangers of these interactions have been overstated and the potential therapeutic advantages underestimated. On the other hand, reports of serious and fatal complications continue to appear (174,175). Specialists have advised that the combination of an MAO inhibitor with trimipramine or amitriptyline is usually safe, but that imipramine and clomipramine must be avoided.

Phenothiazines

Two Scandinavian patients taking combinations of neuroleptic drugs and tricyclic antidepressants developed epileptic seizures (176). The risk of seizures is greater in patients with brain damage or epilepsy and with high dosages, sudden increases in dosage, or shortly after the introduction of a second compound.

The possible mechanism for these interactions with phenothiazines is raised plasma concentrations of the tricyclic compounds due to competition for the hepatic cytochrome P450 that metabolizes both types of compound (SEDA-9, 30) (177). Antidepressant plasma concentrations may increase by up to 70% (178).

Postganglionic blockers

Tricyclic antidepressants reverse the hypotensive effects of postganglionic blocking agents, guanethidine, reserpine, clonidine, and alpha-methyldopa, and the addition of a tricyclic can result in loss of blood pressure control (159,179). Sudden withdrawal of a tricyclic compound from a patient stabilized with these compounds can also result in serious hypotension. An additional reason for avoiding drugs such as reserpine, methyldopa, and propranolol in depressed cardiovascular patients is that these drugs can also cause or aggravate depression.

Psychotropic drugs

The evidence for interactions with other commonly prescribed psychotropic drugs has been reviewed extensively (SEDA-8, 25).

Salicylates

Tricyclic antidepressants are highly bound to plasma proteins. Theoretically, other drugs that are highly protein bound could displace tricyclic antidepressants from protein binding sites; this would be expected to lead to increased plasma concentrations of unbound antidepressant and a greater likelihood of adverse effects. In practice, however, important interactions of this kind are unusual, probably because these drugs have high apparent volumes of distribution, and the amount of drug that can be displaced from plasma proteins is very small compared with tissue concentrations. Salicylates are highly protein bound, and the effect of adding acetylsalicylic acid 1 g/day for 2 days on the plasma availability of imipramine (150 mg/day) has been studied in 20 depressed patients (180). Acetylsalicylic acid reduced the protein binding of imipramine and while the total plasma concentration of imipramine was not altered, the unbound concentration rose almost four-fold. The number of characteristic adverse effects of imipramine also increased significantly. However, this study was not blind and the results must be in doubt, since it is unlikely that brain concentrations of the drug changed significantly.

Sex hormones

Oral contraceptives have a complex effect on the metabolism of tricyclic drugs, resulting in reduced systemic availability (181). Conjugated estrogens also cause akathisia in some patients taking tricyclic drugs, perhaps due to an interaction at dopamine receptor sites (182).

Sodium valproate

Sodium valproate can increase serum tricyclic drug concentrations (SEDA-21, 22).

- In a 46-year-old woman, in whom valproate 1 g/day was added to clomipramine 150 mg/day, there was a substantial increase in serum clomipramine concentrations (from 185 ng/ml to 447 ng/ml); she had feelings of numbness and sleep disturbance, which disappeared when the dose of clomipramine was reduced (183).

The increase in tricyclic concentrations following valproate is probably partly due to inhibition of CYP2C isozymes, preventing demethylation of tertiary tricyclic antidepressants to the corresponding secondary amines (desmethylimipramine in the case of clomipramine). However, valproate can also increase the plasma concentrations of secondary amine tricyclics, such as nortriptyline (183). The current data suggest that the combined use of tricyclic antidepressants and valproate should be undertaken with caution.

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SSRIs

Fluoxetine can increase blood concentrations of desipramine and nortriptyline (184–187).

St John's wort

St John's wort can cause drug interactions by inducing hepatic microsomal drug-metabolizing enzymes or the drug transporter P-glycoprotein, which causes a net efflux of substrates, such as amitriptyline, from intestinal epithelial cells into the gut lumen (SEDA-24, 12). In 12 patients (9 women, 3 men) the addition of St John's wort 900 mg/day to amitriptyline 150 mg/day led to a 20% reduction in plasma amitriptyline concentrations, while nortriptyline concentrations were almost halved (188).

Thioridazine

The interaction of thioridazine with a tricyclic antidepressant is particularly dangerous, since both cause cardiac toxicity. One report concerned two young patients who developed ventricular dysrhythmias, from which they recovered (189).

Thyroid hormone

Spurious hyperthyroidism occurred in a child taking thyroid hormone and imipramine for enuresis (190). The ability of thyroid hormone to increase receptor sensitivity to catecholamines has long been known, and has been used to enhance the clinical response in some refractory patients, especially women.

Yohimbine

Yohimbine can cause hypertension in patients taking tricyclic antidepressants. A drug history should include the use of herbal remedies before conventional treatments are prescribed.

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Trientine

General Information

Trientine is a copper chelator that is used as an alternative to penicillamine in Wilson's disease, although experience with it is limited (1–4).

Organs and Systems

Nervous system

Trientine can, like penicillamine, initially worsen the neurological manifestations of Wilson's disease, presumably by mobilizing and redistributing copper (5,6). It should be started in small doses followed by gradual increases.

Metal metabolism

Excessive excretion of metals (zinc, iron) can occur in patients taking trientine, and can cause deficiency symptoms (7).

Hematologic

There have been several cases of sideroblastic anemia, characterized by an excess of ringed sideroblasts in the bone marrow, as a suspected adverse effect of trientine (8,9).

Gastrointestinal

In two patients the use of trientine was associated with serious colitis (with concomitant duodenitis in one), raising the suspicion of a possible causal relation (6).

Immunologic

- A 44-year-old woman developed antinuclear and anti-double-stranded-DNA antibodies (without clinical signs) while taking penicillamine; the antibodies disappeared after withdrawal, but recurred when she was subsequently given trientine (10).

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Trifluoromethane

General Information

Research in animals, including primates, has shown that the inhaled fluorine gas, trifluoromethane (FC-23) can be used as an indicator of cerebral blood flow measured by magnetic resonance imaging (MRI) (1,2). The development of a fluorinated indicator to measure cerebral blood flow with MRI would allow the interleaving of images of cerebral anatomy and metabolism with images of regional cerebral blood flow, all obtainable in one setting by magnetic resonance methods. However, trifluoromethane is not inert and humans do not tolerate concentrations suitable for current MRI technology. Five healthy volunteers inhaled trifluoromethane at concentrations of 10–60% in a double fluid study (3). Concentrations over 30% produced impairment of neuropsychological function.

Organs and Systems

Psychological, psychiatric

In a phase 1, dose-ranging study, trifluoromethane 10–60% impaired neuropsychological function in five healthy men. Symptoms that occurred more often at higher doses included tiredness, difficulty in concentrating, tingling, dry mouth, and loss of appetite (3).

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Trifluridine

General Information

Trifluridine, which is active against *Herpes simplex* and *Varicella zoster*, has only been used in topical antiherpetic solutions. It is twice as potent as idoxuridine in 1% solution and 10 times more soluble. Trifluridine has been reported to heal dendritic keratitis faster than idoxuridine, to be as effective as vidarabine when used five times a day, to have no cross-toxicity with idoxuridine or vidarabine, to heal stromal corneal defects more effectively than idoxuridine, and to produce topical allergy, punctal narrowing, and punctal keratitis only rarely. Furthermore, it gives excellent results in herpetic ulcers previously treated with topical glucocorticoids and in idoxuridine-unresponsive ulcers.

Organs and Systems

Immunologic

Trifluridine can cause allergic reactions (1).

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Trihexyphenidyl

See also Anticholinergic drugs

General Information

Trihexyphenidyl (benzhexol) is an anticholinergic drug. It is given in oral doses rising from 2 to 20 mg/day, and even higher doses are used in dystonic patients. A wide range of anticholinergic adverse reactions can occur, but trihexyphenidyl is apparently particularly likely to cause excitement.

Organs and Systems

Cardiovascular

Paradoxical bradycardia has been reported; the reaction was specific to trihexyphenidyl and was not observed when the patient took other anticholinergic drugs (SEDA-12, 125).

Nervous system

Orofacial dyskinesia has been described with trihexyphenidyl in a patient who did not experience this reaction with levodopa (SEDA-18, 160).

Sensory systems

Trihexyphenidyl can precipitate glaucoma in predisposed patients, and blindness has resulted (1).

Psychological, psychiatric

Although it has been thought that high doses of trihexyphenidyl might impair learning in children, a careful study of this question suggested that there is in practice little interference (2).

As little as 8 mg/day combined with levodopa has caused an acute toxic confusional state in some patients.

- A 75-year-old man with a 10-year history of parkinsonism developed fever and acute delirium after taking levodopa plus trihexyphenidyl (3). He had visual hallucinations, was disoriented in time and place, and could respond only to simple questions. He was unable to stand or walk and had paratonic rigidity in all limbs and marked bradykinesia. There were occasional myoclonic jerks in the arms and legs. Deep reflexes were reduced bilaterally, and the plantar reflexes were absent.

Impairment of memory was attributed to trihexyphenidyl in healthy volunteers (SEDA-13, 115).

Long-Term Effects

Drug withdrawal

Acute withdrawal of trihexyphenidyl after a patient has become adapted to it can trigger an encephalopathy, requiring readministration (SEDA-22, 157).

Drug Administration

Drug overdose

Trihexyphenidyl has been misused by drug addicts to produce elation or relieve depression. One patient who took 300 mg with suicidal intent survived the resulting toxic psychosis (4).

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Trimethoprim and co-trimoxazole

General Information

Trimethoprim is a 2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl) pyrimidine that inhibits dihydrofolate reductase, the enzyme in folate synthesis after the step that is blocked by sulfonamides (1). Trimethoprim therefore inhibits the conversion of dihydrofolate to tetrahydrofolate. It has been combined with sulfonamides, including sulfamethoxazole, sulfametrol, sulfadiazine, sulfamoxole, and sulfadimidine (2,3).

A widely available fixed combination is co-trimoxazole (Bactrim, Eusaprim, Septrin), which contains trimethoprim and sulfamethoxazole in a ratio of 1:5. Both trimethoprim and sulfamethoxazole have favorable and comparable pharmacokinetics and the combination is bactericidal (4). Synergy between trimethoprim and sulfonamides has conventionally been ascribed to sequential inhibition of dihydropteroate synthetase by sulfonamides (in competition with *para*-aminobenzoic acid) and of dihydrofolate reductase by trimethoprim (in competition with dihydrofolate). However, sulfonamides in high concentrations also inhibit dihydrofolate reductase. Thus, an initial partial sequential blockade by trimethoprim (inhibition of dihydrofolate reductase) and sulfonamides (inhibition of dihydropteroate synthetase) leads to defective protein synthesis and cytoplasmic damage, which in turn results in marked increases in the uptake of both agents and "double strength" inhibition of dihydrofolate reductase (5).

Trimethoprim is fairly active against a variety of Gram-positive cocci and Gram-negative rods. Established indications for co-trimoxazole are infections of the sinuses, ears, lungs, and urinary tract, and infections due to *Salmonella*, *Nocardia*, *Brucella*, *Stenotrophomonas maltophilia*, *Pneumocystis jiroveci*, and *Toxoplasma* (1,6). Co-trimoxazole is also used in the treatment of Wegener's granulomatosis, for prevention of spontaneous bacterial peritonitis, and in patients with advanced HIV infection for the prophylaxis of opportunistic infections (1,6).

There have been few comparisons of the efficacy of trimethoprim and co-trimoxazole. In uncomplicated urinary tract, bronchopulmonary, and ear infections, no advantage of co-trimoxazole over trimethoprim has been documented (7,8). However, in complicated urinary tract infections most studies have shown better results with co-trimoxazole than with trimethoprim alone (9). Despite the widespread use of co-trimoxazole for about 35 years, bacterial resistance has not emerged as a major problem (10,11).

The adverse effects of co-trimoxazole are mostly ascribed to the sulfamethoxazole component. However,

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adverse effects can also be caused by trimethoprim or by the combination. It is important to realize that the culprit agent can only be definitely determined by re-exposure of the single drugs in the individual patient. Thus, in clinical practice it may be impossible to determine the causative compound.

Tetroxoprim is another 2,4-diaminopyrimidine derivative with comparable actions to those of trimethoprim. It is exclusively used in combinations with sulfonamides.

General adverse effects

Severe adverse drug reactions with trimethoprim and co-trimoxazole are rare (12–14). This also applies to children (15). The adverse effects of co-trimoxazole correspond to those expected from a sulfonamide (16). In HIV-infected patients, adverse effects of co-trimoxazole are more frequent and more severe (17–19). Hematological disturbances due to co-trimoxazole include mild anemia, leukopenia, and thrombocytopenia, which may be due to folic acid antagonism. Serious metabolic disturbances that are associated with trimethoprim include hyperkalemia and metabolic acidosis. Trimethoprim can cause hypersensitivity reactions. However, with co-trimoxazole, the sulfonamide is generally believed to be more allergenic (12). Generalized skin reactions predominate. Other effects, such as anaphylactic shock, are extremely rare (20–22). Carcinogenicity due to trimethoprim or co-trimoxazole has not been reported.

Organs and Systems

Respiratory

Cases of allergic pneumonitis and pulmonary infiltrates with eosinophilia have been described with co-trimoxazole (23). Such reactions have not been reported with trimethoprim alone. Pulmonary infiltrates due to co-trimoxazole hypersensitivity in patients with AIDS are particularly worrisome, since they mimic progression of underlying opportunistic pulmonary infections.

- Pneumonitis developed after the administration of co-trimoxazole in a patient with intractable ulcerative colitis complicated by *P. jiroveci* pneumonia. This patient had also previously had sulfasalazine-induced pneumonitis (24).
- A 33-year-old man taking co-trimoxazole developed bilateral pulmonary infiltrates and a fever of 39°C after 2 weeks (25). Co-trimoxazole was withdrawn. The fever resolved 6 days later. A lung biopsy showed non-specific interstitial pneumonia. A lymphocyte stimulation test for co-trimoxazole was positive.

Nervous system

Co-trimoxazole can cause tremor (26), which has been described in patients with AIDS taking co-trimoxazole (27,28).

- A 66-year-old man with pulmonary fibrosis and cor pulmonale was given intravenous co-trimoxazole for 3 weeks followed by oral treatment for an infection with Nocardia farcinica. On day 3 of oral treatment, he developed a tremor in both arms and legs, exacerbated by trying to stay calm. The symptoms resolved 3 days after drug withdrawal.

Aseptic meningitis and meningoencephalitis occur with trimethoprim and co-trimoxazole (29–39). The pathogenetic mechanism is still uncertain.

- A 15-year-old boy developed aseptic meningitis while taking trimethoprim 200 mg in the morning and 100 mg in the evening (40).

Immune complex deposition, immediate hypersensitivity, direct drug toxicity, and induction of anti-tissue antibodies have all been suggested. Interleukin-6 may be an important mediator of trimethoprim-induced aseptic meningitis in some patients. A case with three episodes after re-exposure to co-trimoxazole has been reported (41). Polymorphonuclear or mononuclear cells may preponderate (42). Interleukin-6 may be an important mediator of trimethoprim-induced aseptic meningitis in some patients (43,44).

Ataxia has been described in two patients with AIDS after intravenous use of co-trimoxazole (45).

Extrapyramidal symptoms developed with co-trimoxazole in a girl with dihydropteridine reductase deficiency and rapidly disappeared after withdrawal. This variant of phenylketonuria should be considered in all infants found to have raised phenylalanine concentrations during the neonatal period (46).

Sensory systems

Uveitis in combination with meningitis (47) and uveitis in combination with arthritis and Stevens–Johnson syndrome (48) have been reported with trimethoprim. Uveitis with retinal hemorrhages has also been described (49).

In unmedicated young and elderly volunteers and unmedicated HIV-infected patients, trimethoprim applied to the tongue was primarily described as bitter and medicinal (50).

Psychological, psychiatric

- Delirium occurred after treatment with co-trimoxazole in a patient with AIDS; the episode completely resolved within 72 hours of drug withdrawal (51).

Endocrine

In a child, co-trimoxazole was the probable cause of growth failure (52).

Co-trimoxazole has been suggested to have some antithyroid activity. However, whether this effect is due to trimethoprim alone is still unclear (53,54). Co-trimoxazole 27–31 mg/kg bd orally substantially altered serum total T4 and TSH concentrations and neutrophil counts in dogs within as short a time as a few weeks (55).

Metabolism

Co-trimoxazole can cause reversible hypoglycemia, which may be prolonged, particularly in patients with risk factors for hypoglycemia. Common risk factors include compromised renal function, prolonged fasting, malnutrition, and the use of excessive doses. It has been postulated

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that the sulfonamide mimics the action of sulfonylureas, stimulating pancreatic islet cells to secrete insulin. In elderly people, co-trimoxazole-induced hypoglycemia can cause altered mental state (56,57).

Metabolic acidosis has been observed in patients with AIDS after intravenous co-trimoxazole (58). The acidosis developed 3–5 days after the start of treatment and had a favorable course. It is likely that the sulfonamide was responsible, because of renal loss of bicarbonate.

Nutrition

A median increase in serum homocysteine of 50% (range 27–333%) was found in seven healthy male volunteers after a 2-week course of trimethoprim 300 mg bd (59). Concomitantly, serum folate concentrations fell significantly. By day 50, baseline values of homocysteine and folate were regained. Since tetrahydrofolate serves as a methyl group carrier in the remethylation of homocysteine to methionine, the inhibitory effect of trimethoprim on dihydrofolate reductase may be most important, but other mechanisms could not be excluded.

Electrolyte balance

Hyperkalemia is a relatively common complication of trimethoprim therapy and occurs at both high and standard dosages. It is thought to be caused by a potassium-sparing effect, to which elderly people appear to be particularly vulnerable (60–63). However, pre-existing renal impairment and concomitant potassium sparing diuretics may also contribute (60). In almost all cases the electrolyte changes resolve on withdrawal. Trimethoprim reduces renal potassium excretion by competitively inhibiting epithelial sodium channels in the distal nephron like triamterene. Higher dosages and pre-existing renal dysfunction are associated with an increased risk of hyperkalemia, as are probably other disturbances in potassium homeostasis, such as hypoaldosteronism and treatment with drugs that impair renal potassium excretion. Conversely, alkalinization of the urine and induction of high urinary flow rates block the antikaliuretic effect of trimethoprim in the distal nephron (64).

Co-trimoxazole can reduce potassium excretion and cause life-threatening hyperkalemia (65,66), even in therapeutic doses. In one study with standard dosages of co-trimoxazole, up to 62% of patients developed a peak serum potassium concentration of over 5.0 mmol/l and 21% a peak concentration of over 5.5.mmol/l (12,60,66). About 20–53% of patients with AIDS taking high-dosage co-trimoxazole for *P. jiroveci* pneumonia also develop hyperkalemia, and around 10% reach dangerously high concentrations (over 6.0 mmol/l). Withdrawal of trimethoprim is often required. Alkalinization of the urine and the induction of high urinary flow rates with intravenous fluids and loop diuretics block the antikaliuretic effect of trimethoprim on distal nephron cells (67,68).

Life-threatening hyperkalemia secondary to the use of standard doses of co-trimoxazole has been reported in two renal transplant recipients who developed end-stage renal disease secondary to familial Mediterranean fever, who may be at increased risk of hyperkalemia because of concurrent renal insufficiency, concomitant use of ciclosporin, and associated tubulointerstitial disease (69). In one patient, underlying adrenal insufficiency might have contributed to the hyperkalemia.

- Hyperkalemia due to high doses of co-trimoxazole (14 mg/kg/day trimethoprim and 70 mg/kg/day sulfamethoxazole) occurred in an HIV-positive patient with *P. jiroveci* pneumonia (70).
- Life-threatening hyperkalemia secondary to the use of standard oral doses of co-trimoxazole (trimethoprim 320 mg/day and sulfamethoxazole 1600 mg/day) occurred in a 77-year-old man with moderate chronic renal insufficiency from diabetic nephropathy (71). In addition to hyperkalemia, he developed severe metabolic acidosis; both resolved on appropriate medical intervention and withdrawal of co-trimoxazole.
- A 41-year-old black man with AIDS and sickle cell anemia was treated on two separate occasions with co-trimoxazole and prednisone 40 mg/day for *P. jiroveci* pneumonia (72). On both occasions he developed a hyperkalemic metabolic acidosis together with renal tubular acidosis after several days of therapy.

Concurrent acidosis in patients with trimethoprim-induced hyperkalemia is uncommon, which could be explained if the action of trimethoprim, like that of amiloride, is limited to the cortical collecting tubule but does not affect the medullary collecting tubule, which has a large capacity to secrete hydrogen ions and may therefore prevent the development of acidosis. Predisposing factors for the rare adverse effect of renal tubular acidosis in this case may have been aldosterone deficiency or resistance, medullary dysfunction of sickle cell anemia, and renal insufficiency. All these factors could contribute to impaired renal handling of secretion of hydrogen ions (72).

According to studies on animals, tetroxoprim, which is structurally similar to trimethoprim, has stronger antikaliuretic effects than trimethoprim. Tetroxoprim-induced hyperkalemia has not been described yet. However, tetroxoprim is only rarely used and dosages are low (73).

Trimethoprim uncommonly causes hyponatremia.

- A 78-year-old woman developed severe symptomatic hyponatremia after treatment with anhydrous theophylline and 6 months later developed hyponatremia after treatment with co-trimoxazole for a presumptive urinary tract infection (74).

Hematologic

Most hematological adverse effects associated with trimethoprim have been reported with co-trimoxazole. These include macrocytic and megaloblastic anemia, aplastic anemia, neutropenia, hypersegmentation of leukocytes, thrombocytopenia, and pancytopenia (12,61–63,75–79). Sulfonamides alone have not been associated with folate deficiency, but in combination with trimethoprim they can deplete folate stores in patients with pre-existing deficiency of folate or vitamin B_{12} (80). Treatment with co-trimoxazole can impair the function of mobilized autologous peripheral blood stem cells (81).

Mild hemopoietic suppression due to co-trimoxazole in an immunocompromised host is common, even with low-dose regimens. This effect is notable in combination with

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other marrow-suppressive agents (for example azathioprine, ganciclovir, cyclophosphamide, and allopurinol), malnutrition, or infection (CMV and hepatitis C virus) (82).

Pancytopenia in the setting of severe drug hypersensitivity syndrome due to co-trimoxazole has been reported (83).

- A 53-year-old woman with congenital dyskeratosis took six co-trimoxazole double-strength tablets a day (trimethoprim 960 mg/day and sulfamethoxazole 4800 mg/day) for *P. jiroveci*, plus folic acid, and after 9 days developed a fever (39°C) accompanied by a morbilliform rash and painful cervical lymphadenopathy. She had a white blood cell count of 1.7×10^9/l, with 0.5×10^9/l neutrophils; hemoglobin 7.3 g/dl; platelets 17×10^9/l; and hemolysis. A myelogram showed extensive hemophagocytosis. Polyvalent intravenous immunoglobulin (1 g/kg/day) was given for 2 days. She became apyrexial within 48 hours, accompanied by marked clinical improvement, and recovered within 1 month.

Erythrocytes

Megaloblastic anemia and aplastic anemia occur in very few patients (78,84,85). They develop particularly in patients who have pre-existing low folic acid concentrations and who are not taking folic acid supplements (79,85–87). Patients with megaloblastic anemia should not be treated with co-trimoxazole. Other predisposing factors include other drugs with antimetabolite properties or anticonvulsants (88). In patients with pre-existing folic acid deficiency or with HIV infection, the administration of folinic acid has been advised, in order to reduce the hematological adverse effects. However, preliminary data suggest that adjunctive folinic acid may be associated with an increased risk of therapeutic failure and death (89).

Leukocytes

Agranulocytosis is very rare. If leukocytes are routinely monitored during treatment (more often than clinically indicated), mild leukopenia is encountered in 0.4–10% of patients taking either co-trimoxazole (13,84,90–92) or trimethoprim alone (93).

Platelets

Mild thrombocytopenia is quite common with co-trimoxazole, affecting 0.1% to several% of patients treated (8,9,85,90,92–94). In a retrospective review in Denmark, co-trimoxazole was one of the commonest reported causes of drug-induced thrombocytopenia (11% of reports), with the exception of cytotoxic drugs (95). In a similar review in Sweden from 1985 to 1994 of all drug-induced blood dyscrasias, thrombocytopenia occurred most frequently, the major causes being furosemide (17%) and co-trimoxazole (9%) (96). Older patients were most at risk. However, clinically significant thrombocytopenia is only rarely seen. Although folic acid deficiency may contribute to thrombocytopenia, immunological reactions to either the sulfonamide (75,97) or trimethoprim (98) have been proposed (99,100).

Severe, life-threatening thrombocytopenia associated with co-trimoxazole has been reported (101).

- A 54-year-old white woman took a 10-day course of co-trimoxazole (trimethoprim 160 mg, sulfamethoxazole 800 mg) for chronic sinusitis. One day after finishing the course she developed scattered petechiae on both hands and blood blisters in her mouth. She had a low platelet count of 20×10^9/l. Other laboratory tests were normal, except for a raised blood glucose concentration. She was treated successfully with a transfusion of two units of platelets and oral prednisone. Four days after withdrawal of co-trimoxazole her platelet count increased to 110×10^9/l.

Reports of drug-induced thrombocytopenia have been systematically reviewed (102). Among the 98 different drugs described in 561 articles the following antibiotics were found with level I (definite) evidence: co-trimoxazole, rifampicin, vancomycin, sulfisoxazole, cefalothin, piperacillin, methicillin, novobiocin. Drugs with level II (probable) evidence were oxytetracycline and ampicillin.

In another retrospective analysis of drug-induced thrombocytopenia reported to the Danish Committee on Adverse Drug Reactions, 192 cases caused by the most frequently reported drugs were included and analysed (103). There were pronounced drug-specific differences in the clinical appearance. Early thrombocytopenia was characteristic of cases caused by sulfonamides and co-trimoxazole. These drugs also often caused hemorrhage. Accompanying leukopenia was observed in some cases associated with co-trimoxazole. There were no patient-specific factors responsible for the heterogeneity of the clinical appearance, and factors related to the physician seemed to be of little significance.

Gastrointestinal

Nausea and possibly vomiting occur in a few to 20% of adult patients taking normal dosages of co-trimoxazole (13,94). With trimethoprim alone in a dose of up to 400 mg/day, gastrointestinal tolerance was better and skin reactions were less frequent than with the combination (3). A review of the data from five different centers has shown that gastrointestinal complaints are less frequent with trimethoprim than with the combination (9).

Drug-induced esophagitis is rare, accounting for about 1% of all cases of esophagitis. An incidence of 3.9 in 100 000 has been reported. After the first description, there have been more than 250 observations, with more than 50 different drugs. Among those, the principal antibiotics included tetracyclines (doxycycline, metacycline, minocycline, oxytetracycline, and tetracycline), penicillins (amoxicillin, cloxacillin, penicillin V, and pivmecillinam), clindamycin, co-trimoxazole, erythromycin, lincomycin, spiramycin, and tinidazole. Doxycycline alone was involved in one-third of all cases. Risk factors included prolonged esophageal passage, due to motility disorders, stenosis, cardiomegaly, the formulation, supine position during drug ingestion, and failure to use liquid to wash down the tablet. Direct toxic effects of the drug (pH, accumulation in epithelial cells, non-uniform dispersion) also seem to contribute to the development of drug-induced esophagitis (104).

Antibiotic-associated colitis is only very rarely seen with co-trimoxazole (105,106).

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Liver

Intrahepatic cholestasis associated with phospholipidosis has been reported with trimethoprim (107). In one case trimethoprim caused cholestatic hepatitis after re-exposure (108).

The same types of liver disease occur with co-trimoxazole as with sulfonamides alone (109–111). Mild rises in serum transaminases and cholestatic hepatotoxicity are well reported, usually starting after a latent period of several weeks, and associated with a rash. There have been very few case reports of fulminant hepatic failure associated with co-trimoxazole.

- A 32-year-old woman developed a pruritic maculopapular rash and fever (112). She had taken a 12-day course of co-trimoxazole that had finished 5 days before and was taking no other drugs. She had normal hematological indices but a raised alkaline phosphatase and aspartate transaminase. Serological testing for Epstein-Barr virus, hepatitis A, B, and C, cytomegalovirus, echo virus, rubella, and measles showed no evidence of recent infection. Her rash improved but her general condition worsened and steroids were started. An abdominal CT scan showed a large liver with a moderate amount of ascites. The aspartate transaminase rose to 1330 IU/l and the prothrombin time increased. She developed progressive liver failure and died while awaiting liver transplant. At autopsy the liver showed signs of massive hepatic necrosis with no other abnormalities.
- Hepato-renal insufficiency combined with pancytopenia followed the administration of co-trimoxazole for 10 days for suspected pyelonephritis in a 48-year-old man (113). Hemodialysis was temporarily required, and renal and liver function and blood counts returned to normal afterwards.

Pancreas

Acute pancreatitis, with relapse on re-exposure, has been observed in a patient taking co-trimoxazole (114).

Urinary tract

Trimethoprim interferes with the tubular secretion of creatinine, causing an increased serum creatinine concentration and a reduced creatinine clearance, without affecting true glomerular filtration rate (115–118). Thus, a small increase in serum creatinine concentration at the beginning of treatment is not necessarily indicative of impaired renal function (119,120). Nevertheless, co-trimoxazole may have a direct nephrotoxic effect, mainly in patients with pre-existing renal impairment taking large dosages (115,116,121). This can be prevented by reducing the dose (117,118). If creatinine clearance is reduced to 15–25 ml/minute, the standard dose of co-trimoxazole should be reduced by half after an initial 3 days of treatment with the usual dose.

Treatment with co-trimoxazole (or other antibiotics) can increase the risk of the hemolytic-uremic syndrome in children with gastrointestinal infections caused by *Escherichia coli* O157:H7 compared with children with no antibiotic treatment (122).

Extremely rare instances of crystalluria followed by renal insufficiency due to obstruction have been described in patients taking trimethoprim (123).

Skin

The skin reactions observed with co-trimoxazole can be due to trimethoprim or to the sulfonamide. Data collected from five different centers have shown that skin rashes are less frequent with trimethoprim than with co-trimoxazole (9).

- Generalized erythematous skin eruptions have now been reported in a 20-year-old Japanese woman and a 70-year-old Japanese man taking co-trimoxazole (124). Patch tests showed that trimethoprim alone was responsible for the erythematous popular-type skin eruption in the young woman. The old man's skin responded to both trimethoprim and sulfamethoxazole.

The skin rashes due to trimethoprim and co-trimoxazole are mostly maculopapular and are related to the duration of treatment (125). They occur with a frequency of 1.3–5.9% (94,126–128).

In a randomized, open trial of long-term intermittent co-trimoxazole on recurrences of toxoplasmic retinochoroiditis, four of 54 patients who took a single tablet of co-trimoxazole (trimethoprim 160 mg, sulfamethoxazole 800 mg) withdrew when they developed mild cutaneous erythema that resolved when drug treatment was stopped (129).

Fixed drug eruptions

Fixed drug eruptions have been analysed in 450 patients (130). The ratio of men to women was 10:11. The mean age of the men was 30 years, and that of the women 31 years. In 13% the fixed drug eruption had occurred for the first time, 2.7% had had more than 40 episodes. There was atopy in 11%, and 23% had a positive family history of drug reactions. Co-trimoxazole was the most common cause of fixed drug eruptions. Other antibiotics included tetracycline, metronidazole, amoxicillin, ampicillin, erythromycin, and clindamycin.

Co-trimoxazole was the offender in 75% of 64 cases of fixed drug eruption. The eruption was mainly located on male genitalia, but unusual findings included familial occurrence, symmetrical and asymmetrical non-pigmented lesions, linear lesions, a solitary plaque on the cheek, and wandering lesions (131).

There may be an association between fixed drug eruption and HLA class I antigens. In 42 of 67 patients with fixed drug eruptions caused by co-trimoxazole there were significantly higher frequencies of the A30 antigen and A30 B13 Cw6 haplotype than in 2378 control subjects (132). HLA-B55 (split of B22) was present exclusively in co-trimoxazole fixed drug eruption, and in a higher frequency than in control subjects.

Topical provocation of fixed drug eruption and positive reactions with co-trimoxazole are extremely rare and have never been seen on unaffected skin.

- In a 42-year-old Caucasian woman with histopathologically confirmed fixed drug eruption induced by co-trimoxazole, positive topical provocation by trimethoprim was obtained on both involved and uninvolved skin (133).

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Cross-sensitivity to co-trimoxazole and nimesulide has been reported (134).

- A 10-year-old-boy developed an extensive fixed drug eruption when he took co-trimoxazole (trimethoprim 200 mg, sulfamethoxazole 40 mg bd) 8 weeks after having had a fixed drug eruption due to nimesulide. An oral provocation test with co-trimoxazole 1 month later showed reactivation within 12 hours in the form of severe itching and erythema at the sites of the lesions with one-quarter of the dose.

Erythema multiforme

Erythema multiforme and its related syndromes (Stevens–Johnson syndrome and toxic epidermal necrolysis) are well recognized with co-trimoxazole and can be caused by trimethoprim as a single drug (135). A European review identified sulfonamides (and particularly co-trimoxazole) as a major causative factor in Stevens–Johnson syndrome and toxic epidermal necrolysis, the crude relative risk being far in excess of any other implicated drug (136). In a histopathological study of 111 cases from Germany, co-trimoxazole accounted for 22 cases (20%) (137). There were no histological features that could have discriminated between the different causes of this severe reaction.

- A 34-year-old Asian woman developed toxic epidermal necrolysis associated with co-trimoxazole (160/800 mg bd) (138). She recovered completely without serious sequelae.
- Toxic epidermal necrolysis, associated with co-trimoxazole for sinusitis in a 16-year-old woman, was successfully treated with intravenous immunoglobulins (0.4 g/kg for 5 days) (139).
- Toxic epidermal necrolysis, associated with treatment with co-trimoxazole (480/2400 mg/day) for sepsis in a 66-year-old Caucasian man, was successfully treated with intravenous immunoglobulin (0.75 g/kg for 5 days) (140).
- An 86-year-old man developed severe and extensive toxic epidermal necrolysis within 24 hours of taking co-trimoxazole for a urinary infection (141). He had had an allergic reaction to co-trimoxazole a few years before. He recovered completely without serious sequelae.
- A 50-year-old man took oral co-trimoxazole (trimethoprim 160 mg, sulfamethoxazole 800 mg) and developed toxic epidermal necrolysis 13 days later (142).

In 20 Indian patients (of whom 70% were women) with Steven–Johnson syndrome and ocular involvement, co-trimoxazole was the commonest identifiable risk factor (143). Conjunctival involvement and its sequelae were the major ocular manifestations.

Susceptibility factors

Skin reactions occur with high frequency during co-trimoxazole therapy in patients with AIDS (18,19). Other symptoms in such patients have been described in association with skin eruptions, including fever, neutropenia, thrombocytopenia, and rises in transaminase activities (18,79). The high dosages used to treat *P. jiroveci* in these patients may partly be responsible for the high frequency of adverse effects, since low-dose co-trimoxazole for the prevention of *P. jiroveci* pneumonia reduced the adverse effects from 28 to 9% (144).

Nails

- Co-trimoxazole was suggested to have caused loss of fingernails and toenails in a 3-year-old boy (145). He was initially treated with gentamicin 2 mg/kg intravenously every 8 hours for *E. coli* urinary tract infection, and co-trimoxazole was given once daily in a prophylactic dose. After 2 weeks his fingernails and toenails began to slough. Co-trimoxazole was withdrawn, and within 2 weeks his nails had returned to normal.

Immunologic

The sulfonamide component of co-trimoxazole is generally believed to be more allergenic than trimethoprim. However, trimethoprim alone can cause hypersensitivity reactions more commonly than has previously been thought. Most of these reactions present as generalized skin reactions. The hydroxylamine and other metabolites of sulfamethoxazole can bind covalently to proteins because of their chemical reactivity, resulting in the induction of specific adverse immune responses. Therefore, changes in the activity of detoxification pathways are associated with a greater risk of allergic reactions to sulfonamides. Allergies to sulfonamides, particularly sulfamethoxazole, are more frequent in patients with AIDS, but the reason for this increased risk is not fully understood. No tools are available to predict which patients have a greater risk for developing allergies to sulfonamides. In a small study in HIV-positive patients with hypersensitivity syndrome reaction, the lymphocyte toxicity assay has a strong potential for use as a diagnostic tool to assess co-trimoxazole hypersensitivity (146). Diagnosis is essential to avoid possible progression to severe reactions and readministration of the offending drug.

In patients who absolutely require further treatment, successful desensitization can be achieved (147). Two patients with chronic granulomatous disease who had previously been intolerant of co-trimoxazole completed a 5-day desensitization protocol with a good clinical outcome (148).

Anaphylactic shock is rare, but has been reported with co-trimoxazole (20). However, it is possible that this reaction was due to the sulfonamide compound (21). The case histories of 13 patients (12 women, one man, aged 22–68 years) with anaphylactic reactions to trimethoprim alone that were reported to a national drug safety unit have been analysed (20). Nine were classified as probable anaphylaxis. The casual relation between exposure to trimethoprim and anaphylaxis was classified as definite in three reports, possible in four, and probable in six. In one patient, IgE antibodies against trimethoprim were demonstrated.

- Culture-negative arthritis, bilateral uveitis, mucocutaneous Stevens–Johnson syndrome, and eosinophilia developed in a 31-year-old woman after 3 days of therapy with oral trimethoprim 160 mg bd for a lower urinary

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tract infection (48). At the start of antibiotic therapy, glucocorticoids and local anesthetics were injected into the lateral aspect of the right knee. Recovery was rapid after trimethoprim was withdrawn. Two months later she developed headache, nausea, malaise, and bilateral uveitis after taking trimethoprim again.

With sera from patients with known hypersensitivity to trimethoprim, IgE-specific recognition of three different but related metabolites has been demonstrated, including the entire molecule itself, the 3,4-dimethoxybenzyl group, and the 2,4-diamino-5-(3′,4′-dimethoxybenzyl) pyrimidine group (149). The incidence of adverse reactions in patients with AIDS is higher than in others (12). Most of these effects are not true allergic reactions, but are related to high doses of co-trimoxazole, and include rashes, nausea, and vomiting. They can be reduced in both frequency and severity by corticosteroids, which are often given in moderate to severe *P. jiroveci* pneumonia. The risk of hypersusceptibility reactions (Stevens–Johnson syndrome, neutropenia, hepatotoxicity, aseptic meningitis, thrombocytopenia) is also higher than in other patients. Since many rashes with co-trimoxazole are not necessarily due to allergic mechanisms, a previous rash should not prevent later re-administration. It may be prudent, however, to use a rapid test dose when co-trimoxazole is the treatment of choice (150).

The incidence of adverse reactions to co-trimoxazole in HIV-infected patients is high. Several reports have shown that an incremental increase in drug dosage may allow a significant proportion of patients to tolerate prophylactic dosages of co-trimoxazole. Eight of 14 selected HIV-infected patients (13 men, 1 woman; patients who experienced severe reactions such as anaphylaxis or Stevens–Johnson syndrome were excluded) were successfully desensitized and after a regimen of gradual incremented exposure over 11 days as an outpatient procedure could continue to take co-trimoxazole (151). *N*-acetylcysteine (3 g of a 20% liquid solution bd) did not prevent hypersensitivity reactions to co-trimoxazole in HIV-infected patients (152). Although cross-reactivity can occur, dapsone can be used for patients with mild hypersensitivity reactions to co-trimoxazole for prophylaxis of *P. jiroveci* pneumonia (153).

A syndrome that resembles bacterial sepsis is well recognized in patients with AIDS (154). This reaction can occur within hours of a large dose of co-trimoxazole, but most often occurs on rechallenge.

- A sepsis-like hypersensitivity reaction occurred in 38-year-old HIV-positive Hispanic man after a 14-day course of co-trimoxazole (155).

The mechanism of this unusual reaction is unclear.

Desensitization

Desensitization can be efficient in a large proportion of patients (88%) using a 5-day protocol, in which co-trimoxazole is administered orally in a granular formulation in increasing doses, beginning with trimethoprim 0.4 mg and sulfamethoxazole 2 mg and doubling the dose every 12 hours until the therapeutic dose is achieved (156). Another dosage regimen (12 doses of increasing amounts of co-trimoxazole at half-hour intervals) resulted in an overall success rate of 91% at 1 month in 44 patients (157). Such tolerance induction protocols can be adopted, even during pregnancy without risk to the mother or to the fetus (158).

Another uncontrolled trial of a 6-day desensitization procedure in 33 cases has been reported (159). The protocol started with a dose of 0.2 mg rising to 800 mg over 6 days and 32 of the subjects successfully completed the course. In addition, 12 of 14 cases were successfully re-challenged with co-trimoxazole. However, this study lacked a clear description of follow-up or the reasons for the selection of subjects for desensitization or re-challenge, and cannot be used as a basis for recommending this desensitization technique.

Oral desensitization to co-trimoxazole was successfully achieved in patients with AIDS suffering from fever, rash, and wheezing due to the drug (160–163). In a randomized study of desensitization with rechallenge in HIV-positive patients with previous adverse effects of co-trimoxazole 73 patients were given a 14-day course of trimethoprim 200 mg/day (164). Fourteen had adverse reactions to trimethoprim. The remaining 59 subjects were randomized to a 2-day desensitization technique (34 subjects) or rechallenge (25 subjects). There were seven hypersensitivity reactions in both groups. Clearly there is no advantage of this 2-day desensitization technique over rechallenge with co-trimoxazole in HIV-positive individuals.

In a randomized, double-blind study in HIV patients, gradual introduction of co-trimoxazole was associated with significantly fewer adverse drug reactions compared with standard initiation of therapy (165).

Overall it appears that desensitization to co-trimoxazole is safe in the absence of previous serious adverse events, although it is not yet certain whether desensitization is better than re-challenge or indeed what the ideal desensitization method should be.

Infection risk

There have been rare reports of an association between sulfonamide antibiotics and increased severity of rickettsial infections. Sulfonamides do not increase the pathogenicity of *Ehrlichia* species, but a case of human monocytic ehrlichiosis complicated by ARDS has previously been reported in a patient who had taken oral co-trimoxazole. It has been speculated that oral co-trimoxazole, given for acne, may have contributed to the unusual severity of *Ehrlichia chaffeensis* infection that progressed to respiratory failure in a previously healthy 16-year-old boy (166).

Long-Term Effects

Drug tolerance

Bacteria have developed several mechanisms that make them resistant to trimethoprim. Resistance can occur rapidly, and has been reported in Europe, the USA, Asia, and South America, which may account for the fact that trimethoprim is usually used in combination (1,167,168). However, the clinical significance of resistance to trimethoprim has been debated (1,7,16,169).

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From a total of 31319 *Shigella* strains isolated in Israel between 1990 and 1996, the rates of resistance of *Shigella sonnei*, *Shigella flexneri*, and *Shigella boydii* to co-trimoxazole were 94%, 51%, and 62% respectively; the proportion of strains that exhibited multiple drug resistance was higher for *S. sonnei* than for the other serotypes studied (170).

Among 12 045 isolates of *Streptococcus pneumoniae* collected between 1995 and 1998, resistance to co-trimoxazole increased slightly, from 25% to 29% (171).

Mutagenicity

Genotoxic effects of trimethoprim on cultured human lymphocytes have been described (172). Chromosome studies performed in cultures of peripheral blood lymphocytes did not show significant differences before and after treatment. Cytogenetic studies on bone marrow cells from 12 patients with urinary tract infections treated with co-trimoxazole did not show structural chromosomal aberrations; however, there was an increased number of micronuclei in these patients compared with controls (173).

Second-Generation Effects

Fertility

Whether reported cases of impaired male fertility were due to co-trimoxazole is not clear, since most of the men were being treated for underlying urogenital infections, which may have contributed to reduced fertility (174,175).

Teratogenicity

An early review of newer case reports and placebo-controlled trials involving several hundred patients did not show an increase in fetal abnormalities (176). However, the relative risks of cardiovascular defects and oral clefts in infants whose mothers were exposed to dihydrofolate reductase inhibitors, such as trimethoprim, during the second or third month after the last menstrual period, compared with infants whose mothers had no such exposure, are 3.4 (95% CI = 1.8, 6.4) and 2.6 (1.1, 6.1) respectively (177). Multivitamin supplements containing folic acid reduced the adverse effects of dihydrofolate reductase inhibitors. There have been two reports of severe spinal malformations in the fetuses of HIV-positive women treated with combination antiretroviral therapy and co-trimoxazole (178).

Susceptibility Factors

Renal disease

In renal insufficiency, co-trimoxazole should be used with caution, particularly when there is hyperkalemia (66,115).

Other features of the patient

Co-trimoxazole should not be given to patients with malnutrition, pregnancy, severe liver damage, megaloblastic anemia, agranulocytosis, or bone marrow failure (12,14,87).

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HIV infection

The use of co-trimoxazole in HIV-positive patients has been associated with a high rate of hypersensitivity reactions (40–80%), attributed to the bioactivation of the sulfonamide component, sulfamethoxazole, to its toxic hydroxylamine and nitroso metabolites. In a study of HIV-positive patients with ($n = 56$) and without ($n = 89$) hypersensitivity to co-trimoxazole, functionally significant polymorphisms in the genes coding for enzymes involved in co-trimoxazole metabolism were unlikely to have been major predisposing factors in determining individual susceptibility to co-trimoxazole hypersensitivity (179).

In a randomized, double-blind study in 372 HIV-positive patients with CD4+ counts below 250×10^6/l, gradual initiation of co-trimoxazole treatment was associated with significantly fewer adverse drug reactions compared with standard initiation (180).

The relation between the onset of adverse reactions to co-trimoxazole in HIV-infected patients and the subsequent development of toxoplasmosis, other AIDS-defining events, and survival has been studied in 592 French patients (181). A low CD4 cell count when co-trimoxazole was introduced was the only factor associated with the onset of adverse reactions. The occurrence of toxoplasmosis and first AIDS-defining events was significantly and independently linked to a low CD4 cell count when co-trimoxazole was introduced and to previous co-trimoxazole withdrawal for adverse events, but not to previous co-trimoxazole withdrawal for reasons other than adverse events, compared with patients who did not stop taking co-trimoxazole. The survival rate was significantly shorter among patients who stopped taking co-trimoxazole for adverse events and for other reasons, compared with patients who continued to take it.

Drug–Drug Interactions

Anticonvulsants

Most interactions of trimethoprim and co-trimoxazole with other drugs are due to folic acid antagonism. This may be more pronounced with co-trimoxazole than with either drug alone. Such interactions have previously been suspected with anticonvulsants, such as barbiturates, phenytoin, and primidone, which themselves produce folic acid deficiency and megaloblastic anemia (88). In order to circumvent the risk of folate deficiency, folic acid or folinic acid can be given. There is some concern that folate replacement may antagonize the desired antimicrobial effect, particularly in some protozoal parasites, but this concern has been debated (89).

Azathioprine

In renal transplant patients, combining azathioprine with co-trimoxazole was followed by neutropenia and thrombocytopenia (92).

Coumarin anticoagulants

Co-trimoxazole can significantly augment the hypoprothrombinemic effect of warfarin (182,183), acenocoumarol (184,185), and phenprocoumon (185).

Cytotoxic drugs

Most interactions of trimethoprim and co-trimoxazole with other drugs are due to folic acid antagonism. This may be more pronounced with co-trimoxazole than with either drug alone. Such interactions have been suspected with cytotoxic drugs (186,187). In order to circumvent the risk of folate deficiency, folic acid or folinic acid can be given. There is some concern that folate replacement may antagonize the desired antimicrobial effect, particularly in some protozoal parasites, but this concern has been debated (89).

In children with acute lymphoblastic leukemia co-trimoxazole inhibited 6-mercaptopurine metabolism (186).

In another study, co-trimoxazole produced a 66% increase in systemic exposure to methotrexate (187).

Prolonged treatment with co-trimoxazole can reduce cyclophosphamide requirements in patients with Wegener's granulomatosis (188).

Glucocorticoids

Prolonged treatment with co-trimoxazole can reduce glucocorticoid requirements in patients with Wegener's granulomatosis (188).

HIV protease inhibitors

In an animal model, indinavir nephrotoxicity was potentiated by co-trimoxazole, but nelfinavir alone or in combination with co-trimoxazole was not nephrotoxic (189).

Immunosuppressants

Most interactions of trimethoprim and co-trimoxazole with other drugs are due to folic acid antagonism. This may be more pronounced with co-trimoxazole than with either drug alone. Such interactions have previously been suspected with immunosuppressant drugs (186,187). In order to circumvent the risk of folate deficiency, folic acid or folinic acid can be given. There is some concern that folate replacement may antagonize the desired antimicrobial effect, particularly in some protozoal parasites, but this concern has been debated (89).

Pronounced nephrotoxicity resulted from the interaction of co-trimoxazole with ciclosporin in patients with a renal transplant (190,191).

Lithium

Trimethoprim has the same effect on the kidney as amiloride, whose combined use with lithium can cause a raised serum lithium concentration.

- The addition of trimethoprim caused severe lithium toxicity in a 40-year-old woman with a schizoaffective disorder; following rehydration, she made a good recovery (192).

Methotrexate

Methotrexate, a folic acid antagonist, is used in the treatment of several disorders. Its major action is inhibition of dihydrofolate reductase, a critical enzyme in intracellular folate metabolism. Co-trimoxazole competes with methotrexate in inhibiting dihydrofolate reductase and further impairs DNA synthesis.

- A fatal case of toxic epidermal necrolysis that involved 90% of the total body surface has been described in a 15-year-old boy with T cell acute lymphoblastic leukemia treated concomitantly with co-trimoxazole and methotrexate (193).

The authors suggested that methotrexate toxicity was precipitated by co-trimoxazole.

- Fatal bone marrow suppression has been reported in an 82-year-old woman who took methotrexate 7.5 mg/week for one year for rheumatoid arthritis without hematological problems. She was given trimethoprim 100 mg/day at first and later 200 mg/day. One week later, she developed severe pancytopenia. The bone marrow failed to recover despite treatment with folinic acid and G-CSF, and she died of bronchopneumonia.

In a literature review, the authors found two other cases of bone marrow suppression after treatment with methotrexate and trimethoprim with full recovery of both. This interaction is also listed in the British National Formulary 1997 (194,195).

Oral contraceptives

Some antibiotics interfere with the effects of oral contraceptives, putatively by inhibiting bacterial deconjugation in the bowel and thus reducing their reabsorption after biliary excretion. However, in women taking oral contraceptives, short courses of co-trimoxazole are unlikely to cause any adverse effects on contraceptive control (196).

Phenytoin

Massive hepatic necrosis after exposure to phenytoin and co-trimoxazole is rare.

- Acute liver failure has been reported in a 60-year-old woman after concomitant ingestion of phenytoin and co-trimoxazole over 9 days (197). Autopsy showed acute fulminant hepatic failure.

Drug interactions can potentiate the hepatotoxicity of single agents; withdrawal of co-trimoxazole may be needed in the presence of early liver injury.

Procainamide

Trimethoprim inhibits the active tubular secretion of procainamide (198).

Rifamycins

In 10 HIV-positive patients who had been taking one double-strength tablet of co-trimoxazole daily for more than 1 month, the concentrations of trimethoprim and sulfamethoxazole in serum were significantly reduced after the administration of rifampicin (199).

Trimeprazine

The antihistaminic phenothiazine trimeprazine has significant antibacterial activity in vitro and in vivo, and a combination with trimethoprim is highly synergistic, as shown in vivo in Swiss white mice using *Salmonella typhimurium* as the challenge bacterium (200).

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Zidovudine

In one pharmacokinetic study in eight HIV-infected subjects, the renal clearance of zidovudine was significantly reduced by trimethoprim (201). The authors concluded that zidovudine dosages may need to be reduced if trimethoprim is given to patients with impairment of liver function or glucuronidation. Zidovudine, on the other hand, did not alter the pharmacokinetics of trimethoprim.

Interference with Diagnostic Tests

Serum folate concentration

Serum folate concentrations should not be measured by the radioisotope method in patients taking trimethoprim (202).

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Trimetrexate

General Information

Trimetrexate is a lipid-soluble analogue of methotrexate that has been used in the management of *Pneumocystis jiroveci* in patients with AIDS when other therapy has proved ineffective. It has also been used as an antineoplastic drug in the management of various solid tumors. It is given with leucovorin (folinic acid) to minimize hematological toxicity. Trimetrexate can cause neutropenia and/or thrombocytopenia (SEDA-12, 704) (1,2). Fever and raised liver transaminases, while uncommon, have been noticed. The efficacy of trimetrexate is not as high as that of co-trimoxazole and the recurrence rate is markedly higher (3).

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Trimipramine

See also Tricyclic antidepressants

General Information

Trimipramine is a sedating tricyclic antidepressant that has been used as a hypnotic (1); it shares this activity with other drugs of its class, notably amitriptyline, dosulepin, doxepin, and trazodone, and with the tetracyclics mianserin and mirtazapine. Trimipramine may be preferred for this purpose, since it has less effect on sleep architecture, including REM sleep (2), and has only a modest propensity to produce rebound insomnia in a subset of patients (3). Sedative antidepressants may be particularly appropriate for individuals at risk of benzodiazepine abuse and patients with chronic pain (4). The usual pattern of tricyclic adverse effects, especially antimuscarinic and hypotensive effects and weight gain, can be expected. Some authors, enthusiastic about GABA enhancers, contend that antidepressants are not useful hypnotic alternatives (5).

Antidepressant drugs of various classes (tricyclics, monoamine oxidase inhibitors, SSRIs) have broad efficacy in generalized anxiety and in panic disorder, for which they are the treatments of choice (6,7). While not likely to cause benzodiazepine-like dependence or abuse, they do have a significant therapeutic latency, and the older drugs are very toxic in overdose.

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Triperaquine

General Information

Triperaquine is a 4-aminoquinoline derivative, the adverse reaction pattern of which is unknown. The WHO Scientific Group's report concerning this drug dates from 1984 and there seems to be little or no later information about it in humans.

Triptans

General Information

The triptans are agonists at 5-hydroxytryptamine (5-$HT_{1b/1d}$) receptors, used in the treatment of migraine. They include almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan (all rINNs). The way in which the triptans produce their therapeutic effect is not clear. Sumatriptan penetrates the blood–brain barrier poorly and presumably acts peripherally on extracranial blood vessels.

Sumatriptan

Sumatriptan was the first drug of its type to be introduced and has been reviewed (SEDA-18, 171). Most of the information about drugs in this group relates to sumatriptan.

Sumatriptan is effective in the treatment of all features of the headache phase of an acute attack of migraine (SEDA-18, 171) (1). It is available as tablets and suppositories, as prefilled syringes for self-administered subcutaneous injection, and as intranasal spray. Its systemic availability is high (96%) after subcutaneous injection, but rather low (14%) after oral administration because of first-pass metabolism. Its half-life is short (2 hours) and 80% is removed by metabolism. The principal metabolite is an inactive indoleacetic acid analogue. Propranolol, flunarizine, and pizotifen, drugs that are all commonly used in migraine prophylaxis, do not affect the pharmacokinetics of sumatriptan (2,3).

A high proportion of patients respond to a single standard dose of therapy, with minor or mild adverse effects. Because of the short half-life, recurrence of headache within 24 hours is common (50%) but can be effectively treated by a second dose. Any adverse effect is also likely to be brief. The most common adverse effects are a feeling of pressure/stiffness in the neck and throat or of pressure/tightness or pain in the chest. Tingling sensations in the head and arms, dizziness, and tiredness are also commonly reported. Dyspnea can occur in patients with obstructive lung disease. Local reactions at the injection site are usually mild. The reported frequencies of these adverse effects vary widely between clinical trials and postmarketing surveys; this may be attributable to selection of patients in trials and differences in the questionnaires used to evaluate unwanted effects (4,5). Allergic reactions are rare.

Rizatriptan

The available data on rizatriptan have been reviewed. Only safety aspects are mentioned here. With oral administration, adverse effects were mild and transient in placebo-controlled trials. Digestive intolerance, dizziness, somnolence, weakness and fatigue, and pain or pressure sensations were the most commonly mentioned (6).

Zolmitriptan

The available data on zolmitriptan have been reviewed. Only safety aspects are mentioned here. Orally administered zolmitriptan appears to have been generally well tolerated in placebo-controlled studies (7). The most commonly reported adverse events are weakness, heaviness or tightness (other than in the chest), dry mouth, nausea, dizziness, somnolence, paresthesia, a sensation of warmth, and chest pain. They were mild to moderate and resolved without the need for intervention or drug withdrawal. Electrocardiographic changes were as frequent with placebo as with zolmitriptan and were not associated with chest tightness or pressure; changes suggesting an ischemic event were not recorded. Nevertheless, zolmitriptan is not recommended in patients with ischemic heart disease.

A spinal cord infarct temporarily related to zolmitriptan use has been reported after the use of zolmitriptan in a 50-year-old woman with a history of migraine (8).

Comparisons between triptans

Four randomized, double-blind clinical trials in which rizatriptan was compared with sumatriptan have been reviewed (9). The two drugs have similar safety profiles, but the frequency of adverse effects depends largely on the dose, which varied from trial to trial. Adverse events reported in over 5% of patients were somnolence,

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dizziness, weakness/fatigue, nausea and vomiting, abdominal pain, and chest pain.

Seven triptans have been compared and rated as generally very well tolerated (10). Naratriptan, almotriptan, and frovatriptan were considered to have the best safety profiles, although the differences are minor. Coronary vasoconstriction is a potential risk of the entire class, but the risk is minimal in the absence of coronary artery disease or uncontrolled hypertension; significant vascular disease is therefore a hazard of using any of the triptans. Patient preference, however, appears to be more closely related to efficacy than to tolerance.

Organs and Systems

Cardiovascular

Particularly when injected, sumatriptan can cause a transient increase in both systolic and diastolic blood pressures; oral doses, which are usually higher, have this effect to a lesser extent. It is unwise to use sumatriptan in patients with uncontrolled severe hypertension.

Some of the minor discomfort often experienced (tingling, flushing, sensations of heat or cold) may also reflect cardiovascular effects.

Coronary vasoconstriction is a potential risk of all triptans, but the risk is minimal in the absence of coronary artery disease or uncontrolled hypertension. Chest tightness and pain are reported in up to 15% of patients taking sumatriptan and are presumed to be due to vasoconstriction of the coronary arteries. Myocardial infarction has been reported and as a consequence sumatriptan should not be used in patients with cardiovascular disease (11). Intravenous sumatriptan causes some coronary vasoconstriction during diagnostic angiography. Myocardial infarction occurred in a patient who had received sumatriptan 6 mg subcutaneously, but the causal association was not clear.

Cardiac dysrhythmias can occur occasionally.

- A 41-year-old otherwise perfectly healthy woman developed the typical symptoms of a migraine attack after an aerobics class followed by a sauna and took sumatriptan 100 mg (12). She collapsed half an hour later and a resuscitation team diagnosed ventricular fibrillation, which was converted to ventricular tachycardia and later to sinus rhythm. Neither the electrocardiogram nor enzyme changes suggested myocardial infarction. She remained comatose and died 6 weeks later. At autopsy there was no evidence of atherosclerotic coronary disease or any other underlying cardiac disorder.
- A 34-year-old man with migraine had palpitation after taking sumatriptan by nasal spray for a severe headache (13). A similar episode had occurred after he had previously taken sumatriptan. He had atrial fibrillation with a rapid ventricular rate. Sinus rhythm returned spontaneously within a few hours. No structural cardiac abnormality was detected.

Myocardial ischemia secondary to coronary spasm was the putative trigger of atrial fibrillation in the latter case.

Vasoconstriction leading to organ ischemia has been repeatedly reported with triptans. The risk is very low in the absence of pre-existing arterial disease. Nevertheless, cases of myocardial infarction, mesenteric ischemia, and ischemic colitis have been described, as has splenic infarction (14).

- A 48-year-old woman with a low risk of atherosclerotic disease who was not taking oral contraception was admitted with sudden heavy pain in the left hypochondrium. Routine tests were normal, but there was a triangular hypodensity in the spleen on computerized tomography consistent with a splenic infarct. There was a history of postoperative venous thrombosis 15 years before, but tests for thrombophilia were all normal. No source of embolism was identified in the heart or proximal arteries. She had repeatedly taken zolmitriptan over the previous few months for migraine, and the symptoms started 3 hours after the most recent dose.

The temporal relation and the absence of an alternative cause to explain the infarct led the authors to conclude that zolmitriptan had been causative.

Nervous system

One of the main drawbacks of acute migraine therapies, including 5-HT_{1a} receptor agonists, is that headache recurs within 24 hours in about one-third of patients who initially experienced relief after first dosing. Similar recurrence rates and mean time to recurrence are observed for the new triptans as for sumatriptan (15). An increase in migraine frequency is usually the first sign of a developing drug-induced headache. It occurs with sumatriptan and is also reported with the new triptans (16). Headache has also been reported with chronic sumatriptan use and abuse (SEDA-20, 193).

The role of sumatriptan and ergotamine in drug-induced headache has been surveyed in over 2000 patients at a regional headache clinic (17). About 600 had taken ergot derivatives previously and a similar number had used sumatriptan, while nearly 250 had experience of both. Drug overuse was defined as the use of at least one dose of either drug on 18 or more days every month for at least 3 months. By these criteria the rates of ergotamine and sumatriptan overuse were estimated at 14 and 3.5% respectively. Drug-induced headache was much more common among ergotamine overusers than sumatriptan overusers (68 versus 32%).

Fatal cerebellar infarction has been described in a 39-year-old man who took sumatriptan 100 mg for an acute attack of migraine. The cerebellar infarct was diagnosed at autopsy, and intracranial vasospasm was thought to be the likely mechanism (18). It should be noted that stroke has also been documented in patients with migraine, independently of drug treatment.

Akathisia occurred in five fairly young patients after subcutaneous or oral sumatriptan (19). The symptoms were short-lived. Increased serotonergic activity, leading to inhibition of nigrostriatal dopaminergic neurons and extrapyramidal symptoms, was the postulated mechanism. A similar mechanism has been thought to provoke the same symptoms with serotonin re-uptake inhibitors.

Sensory systems

Nasal spray sumatriptan can cause taste disturbance, described as a bad, bitter, unpleasant, or unusual taste (20).

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Gastrointestinal

Ischemic colitis has been associated with the use of sumatriptan. Retrospective review and analysis of postmarketing reports showed seven confirmed cases (colonoscopy and/or biopsy) and another has been reported (21). Seven of the patients were women. Sumatriptan was mainly given subcutaneously, the dosages were not excessive, and the median time between the last administration to the onset of symptoms was less than 24 hours in only four patients. All the patients recovered on withdrawal of sumatriptan. Although many of these patients were using other drugs, particularly beta-blocking and NSAIDs, confusing the analysis, the authors suggested that vasoconstrictor effects in the mesenteric circulation associated with the use of sumatriptan played a causative role in inducing the ischemia.

- Two women were investigated for cramping abdominal pain and bloody diarrhea (22). In only one did the episodes completely disappear after withdrawal of sumatriptan. The other underwent an exploratory laparotomy and right hemicolectomy for transmural bowel necrosis.

Nausea, vomiting, and taste disturbances are more common with sumatriptan than placebo (SEDA-19, 207).

Second-Generation Effects

Teratogenicity

There are data from the Swedish Medical Birth Registry relating to 912 infants, whose mothers, at their first antenatal visit, had reported using migraine therapies, in most cases (658) sumatriptan (23). There was no increase in the rate of congenital malformations; slightly more infants than expected were preterm and had a birth weight lower than 2500 g, but none of the differences was statistically significant. These data suggest that sumatriptan is not teratogenic.

Susceptibility Factors

Age

Because of limited experience, sumatriptan is best avoided in children and elderly people.

Other features of the patient

Significant vascular disease is a contraindication to the use of any of the triptans (SEDA-20, 192).

It has been suggested that triptans should not be used in patients with basilar or familial hemiplegic migraine, although some successes have been reported without adverse effects (24).

Drug Administration

Drug formulations

Sumatriptan is available as film-coated tablets, as prefilled syringes for self-administered subcutaneous injection, as intranasal spray, and in a formulation for rectal use. Sumatriptan suppositories appear to be well tolerated: reported adverse events were similar to those during oral or subcutaneous treatment of patients with migraine. Local events involving the anus or rectum were rarely observed (25,26).

Drug–Drug Interactions

Beta-blockers

In four double-blind, placebo-controlled, randomized, crossover studies in 51 healthy subjects a single dose of rizatriptan 10 mg was administered after administration of propranolol 60 and 120 mg bd, nadolol 80 mg bd, metoprolol 100 mg bd, or placebo for 7 days (27). Propranolol 60 or 120 mg bd increased the AUC of rizatriptan by about 67% and the C_{max} by about 75%. Nadolol and metoprolol had no effects.

Similarly, in healthy volunteers co-administration of propranolol resulted in a 56% increase in the AUC of zolmitriptan and a 11% decrease in the AUC of its active metabolite (28).

Clarithromycin

In an open, randomized, 2-way crossover study in 24 healthy volunteers clarithromycin 500 mg orally every 12 hours for 4 days had no effects on the pharmacokinetics of a single oral dose of sumatriptan 50 mg (29).

Ergot alkaloids

The use of sumatriptan is discouraged and even considered contraindicated together with or within 24 hours after ergotamine or ergotamine-type medications, such as methysergide. The contraindication is based on the possibility of severe prolonged vasospasm with the combined use of agents with agonist properties at the same receptors.

- A 20-year-old woman developed generalized tonic–clonic seizures after she took sumatriptan 6 mg followed by three tablets of ergonovine for postpartum headache (30). Cerebral angiography 1 day later showed multiple narrowed segments in the vertebrobasillar and middle cerebral arteries.
- A myocardial infarction occurred in a 43-year-old woman with no known coronary artery disease who was taking methysergide and injected herself with sumatriptan 6 mg because of persisting headache (31).

5-HT re-uptake inhibitors

On theoretical grounds, sumatriptan should not be used with 5-HT re-uptake inhibitors, since this combination could theoretically cause serotonin toxicity. Although case series have suggested that sumatriptan can be safely combined with SSRIs, there are occasional reports of toxicity (SEDA-22, 14).

Treatment of 12 healthy volunteers with paroxetine (20 mg/day for 14 days) did not alter the pharmacokinetics or pharmacodynamic effects of an acute dose of rizatriptan (10 mg orally) (32). These data are reassuring, but it is possible that sporadic cases of 5-HT neurotoxicity could still occur when a triptan is combined with an SSRI.

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Lithium

On theoretical grounds, sumatriptan should not be used with lithium. However, a review of the subject found little substantiation for a severe interaction between sumatriptan and lithium (33).

Monoamine oxidase inhibitors

Some of the triptans are metabolized by monoamine oxidase and they should not be used with monoamine oxidase inhibitors. This includes almotriptan (34), rizatriptan (35), sumatriptan (36), and zolmitriptan (28). The effect of moclobemide on the pharmacokinetics of almotriptan was less than with other triptans (34).

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Tritiozine

General Information

Tritiozine is a non-anticholinergic, antisecretory agent. It has been associated with drowsiness and occasional slight increases in transaminases (1).

Organs and Systems

Nervous system

Predominantly sensory neuropathies with Wallerian degeneration of the myelinated fibers occurred in three patients taking tritiozine (2).

Liver

Acute hepatitis has been attributed to tritiozine (3,4).

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Troleandomycin

See also Macrolide antibiotics

General Information

Troleandomycin is a macrolide antibiotic with actions and uses similar to those of erythromycin.

Organs and Systems

Endocrine

Serum TSH concentrations are moderately but significantly reduced by troleandomycin compared with josamycin or placebo given over 10 days. At the same time serum estradiol concentration was significantly increased (1).

Liver

Most reports associating cholestatic jaundice with the concomitant use of oral contraceptives and macrolides have implicated troleandomycin (2–5). The exact mechanism of this interaction has not been established. Troleandomycin possibly inhibits the metabolism of estrogens and progestogens (6). In most patients jaundice persisted for more than a month after the antibiotic was withdrawn.

Drug–Drug Interactions

Alprazolam

Troleandomycin may inhibit the metabolism of alprazolam by inhibiting CYP3A4 (7).

Carbamazepine

Troleandomycin can cause carbamazepine toxicity by inhibiting CYP3A4 (8).

Ecabapide

Troleandomycin may inhibit the metabolism of ecabapide, a gastric prokinetic drug, by inhibiting CYP3A4 (9).

Ergot alkaloids

Clinically severe interactions between troleandomycin and ergotamine (10–13), resulting in ischemia of the extremities, probably result from inhibition of the metabolism of the ergopeptides (14,15), with raised serum concentrations of dihydroergotamine (16,17).

Quinine

Troleandomycin is an in vitro competitive inhibitor of quinine 3-hydroxylation, which is mediated by CYP3A4, and may therefore interact when co-administered with quinine (18).

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Tropicamide

General Information

Tropicamide is an anticholinergic drug that tends to have a greater mydriatic than cycloplegic effect. It is a short-acting atropine-like derivative and has been regarded as an effective and safe mydriatic, used for pupillary dilatation by professionals, who are not always medical doctors.

Organs and Systems

Cardiovascular

A transient ischemic attack occurred in a 64-year-old patient with cardiovascular risk factors who used topical tropicamide (1).

Nervous system

Near fatal anticholinergic intoxication has been reported after routine fundoscopy with tropicamide (2).

- A 62-year-old man underwent fundoscopy after pupillary dilatation with tropicamide eye-drops. Half an hour after fundoscopic examination he had two generalized seizures with respiratory arrest and required intubation and mechanical ventilation. He was treated with physostigmine and made a full recovery.

Immunologic

A solution containing tropicamide 1% and benzalkonium chloride 0.01% (Mydriaticum) was introduced in 1979 to obtain mydriasis and cycloplegia for diagnostic purposes. Contact dermatitis from ophthalmic formulations is common, preservatives being the most frequent causes (3). Allergic contact dermatitis has been reported, implicating tropicamide as a sensitizer (4).

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Troxerutin

General Information

Troxerutin, a flavonoid derivative, is claimed to reduce capillary fragility. It is generally well tolerated (SEDA-19, 207), but ineffective (1).

Organs and Systems

Skin

Troxerutin is a yellow substance (SEDA-13, 170), and a few cases of yellow discoloration of the skin, but not of the sclerae, have been observed. The discoloration, which can be mistaken for jaundice, vanishes when the drug is withdrawn.

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Tryptophan

General Information

The possibility that mental illness may be alleviated by biogenic amine precursors is an appealing one (SEDA-4, 18). Tryptophan is a naturally-occurring essential amino acid, which has been advocated as an innocuous health food for the treatment of depression, insomnia, stress, behavioral disorders, and premenstrual syndrome. The availability of amino acids in health food stores and a contemporary interest in natural remedies led to reported widespread use of tryptophan to treat depression. It was estimated in 1976 that up to that time several hundred patients with affective disorders had been studied, with results reported in at least 21 papers (1). However, the results of clinical trials with L-tryptophan in the treatment of depressive disorders are inconsistent (2).

It has been suggested that there may be some benefit of using tryptophan in selected patients, particularly those with psychomotor retardation (3). Unfortunately, most of these reports have appeared as letters to the editors of journals (4–6) or as preliminary communications (7). In addition to the possible absence of any consistent effect, there are many plausible reasons to explain the variability in response. Tryptophan has been given in both the racemic and monomeric (levorotatory) forms, both alone and together with a number of substances intended to increase the synthesis or availability of serotonin, including monoamine oxidase (MAO) inhibitors (8), potassium or carbohydrate supplements (9), and co-enzymes such as pyridoxine or ascorbic acid (10). It has also been suggested that tryptophan plasma concentrations have a therapeutic window (4), and that repeated administration induces hepatic tryptophan pyrrolase, resulting in lowered plasma concentrations and loss of therapeutic effect after 2 weeks of treatment (8). Attempts have been made to ameliorate this problem by coadministration of nicotinamide (4).

In addition to the difficulty of interpreting possible benefits due to tryptophan, there is a paucity of information on its adverse effects. This may be partly accounted for by the assumed safety of a natural substance, but it is also contributed to by the preliminary nature of many communications. In at least two studies (5,7) in which tryptophan was compared with a tricyclic antidepressant, inquiry about adverse effects was deliberately avoided, in order to protect the double-blind integrity of the study. Two studies have reported the lack of any consistent or definite changes in hematological values, serum electrolytes, plasma proteins, or liver function tests after 4 weeks of treatment with L-tryptophan up to 8 g/day (7,10). Nausea early in treatment (11), light-headedness, which does not appear to be related to postural hypotension (12), and deterioration in mental status (13,14) have been reported. Hypomania on combining tryptophan with a MAO inhibitor has been reported (14) and toxic effects, including muscle tremor, hypomanic mood, hyper-reflexia, and bilateral Babinski signs, were seen in a patient taking phenelzine and tryptophan.

Eosinophilia–myalgia syndrome

No severe or irreversible adverse effects of tryptophan were reported until 1989, when an eosinophilia–myalgia syndrome was described, and L-tryptophan-containing products were withdrawn from the market (SEDA-15, 518). This syndrome was characterized by an eosinophil count of at least 1×10^9/l and intense generalized myalgia. Other relatively frequent signs and symptoms were fatigue, arthralgia, skin rash, cough and dyspnea, edema of the limbs, fever, scleroderma-like skin abnormalities, increased hair loss, xerostomia, neuropathy, and pneumonia or pneumonitis with or without pulmonary vasculitis. About one-third of the cases required hospitalization, and a substantial number of patients died. The syndrome is suspected to have been due to an unidentified impurity in products from one manufacturer (SEDA-18, 22).

The syndrome appears to be only part of a spectrum of adverse effects associated with tryptophan (15). There has been much discussion, but finally it appears that the links are causal, as consistent findings were found in multiple independently conducted studies and the incidence of eosinophilia–myalgia syndrome in the USA fell abruptly once tryptophan-containing products were recalled (16).

Although L-tryptophan was withdrawn in many countries, in 1994 it became available again in the UK for combination treatment of patients with long-standing refractory depression, on the strict condition that it should only be prescribed by hospital specialists for patients with long-standing resistant depression (SEDA-18, 22). It is also still in use in Canada but not in the USA.

Organs and Systems

Respiratory

A case of interstitial pneumonitis and pulmonary vasculitis was ascribed to L-tryptophan, and unintended rechallenge supported a causal relation (17).

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Tubocurarine

See also Neuromuscular blocking drugs

General Information

D-Tubocurarine is the standard non-depolarizing neuromuscular blocking agent against which all others of the group are compared. The molecule has one quaternary and one tertiary nitrogen, the latter being protonated at body pH, making it a bisquaternary entity. Its main action at the neuromuscular junction is to block the access of acetylcholine to the receptor recognition sites competitively; it may also block some ion channels, but only to a small extent and at very high concentrations.

Blockade of neuromuscular transmission by D-tubocurarine is easily reversed (if twitch height has recovered to at least 10%) by anticholinesterases. Sensitivity to D-tubocurarine and other non-depolarizing relaxants is highly variable, even in apparently healthy patients, so that the small doses given for precurarization can lead to appreciable paralysis (1–3). More commonly, residual blockade can be detected postoperatively (4,5), long after the expected recovery of neuromuscular transmission.

About 40–50% of a normal dose of D-tubocurarine is bound to plasma proteins, mostly gammaglobulins (about 25%). This binding is highly variable, giving a variable amount of non-bound drug available for neuromuscular blockade. Metabolism does not occur. Tubocurarine is eliminated principally via glomerular filtration (about 40–60% in 24 hours), but has an alternative pathway for excretion in the bile (normally only about 12% in 24 hours). The initial dose for healthy patients is 0.2–0.5 mg/kg, dependent on the anesthetic agents used and whether suxamethonium is given beforehand or not. Maintenance doses are about one-third of the initial dose and are required at approximately 30–40-minute intervals. Accumulation can occur and is more likely if large doses are given too frequently or if excretion is impaired. Smaller doses should be given if the patient has received D-tubocurarine within the previous 24 hours.

General adverse effects

A fall in blood pressure occurs almost always with D-tubocurarine. It is often mild, but may be marked, particularly if a large dose is given rapidly or if the patient is hypovolemic, or has a diminished cardiac reserve or capacity for vasoconstriction (as is not infrequently the case in old age, in diabetes, and in other diseases with sympathetic neuropathy), and is potentiated by other anesthetic agents such as halothane. Myasthenic patients or patients with other neuromuscular pathology are markedly sensitive to non-depolarizing relaxants.

Histamine-mediated reactions are common, leading to local wheal-and-flare effects near the injection site, frequent hypotension (mostly about a 20% fall), and occasionally bronchospasm.

Malignant hyperthermia has also been reported after D-tubocurarine.

Tumor-inducing effects have not been reported.

Drug resistance

Patients with burns require more D-tubocurarine (and higher plasma concentrations) for the same degree of blockade compared with non-burned patients (6). The mechanism is not known, but it appears not to be altered pharmacokinetics (7). The resistance to non-depolarizing neuromuscular blocking agents (SEDA-8, 136) appears to be influenced by the size of the body surface area burned and by the time which has elapsed since the injury (see Atracurium). In extensive burns dose requirements are increased approximately by a factor of 2–3.

Patients with upper motor neuron lesions such as hemiplegia (8–11) and possibly multiple sclerosis (SEDA-13, 105) (12) can be resistant to various non-depolarizing blockers. Lower motor neuron injury has so far only been reported to produce this phenomenon in rats (13) and dogs. Affected muscles in these conditions are paralysed to a lesser degree than unaffected muscles, and this has to be taken into account when siting the electrodes for monitoring a block and in assessing recovery therefrom. The mechanism is probably a quantitative and/or qualitative change in acetylcholine receptors. Resistance is seen too in patients taking certain drugs such as phenytoin, carbamazepine, and, disputedly, azathioprine.

In liver disease, increased amounts of D-tubocurarine may be required. In the past it has been suggested that this could be due to reduced synthesis of acetylcholinesterase, or to increased concentrations of gammaglobulins binding the relaxant (14), although this is disputed (15). Similar kinetic mechanisms to those suggested for pancuronium may be involved, but there are no studies on D-tubocurarine. In primary liver cancer in children, resistance to D-tubocurarine (and alcuronium) has been reported (SEDA-13, 104) (16).

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Hyperkalemia tends to reduce the neuromuscular blocking effects of tubocurarine.

Organs and Systems

Cardiovascular

D-Tubocurarine commonly causes a fall in blood pressure, associated with a slight tachycardia and a reduction in total peripheral resistance; cardiac output is not affected. The frequency of hypotension is reported as being 20–90%. This wide range probably reflects the methods of measurement, the anesthetic agents used, and the general condition of the patients in the various studies, as well as the criteria for diagnosing hypotension. The magnitude of the fall in blood pressure is generally about 20%, and it occurs within 5 minutes of injection. Histamine release is considered to be the principal cause (17), but blockade of autonomic ganglia may also contribute. It has been suggested that prostacycline, released by histamine acting on H_1 receptors, is the final mediator; intravenous administration of aspirin or an H_1 receptor antagonist beforehand affords some protection (SEDA-15, 126) (18). Ganglion blockade may also contribute, particularly if high doses are used (19). Reduction in venous return secondary to muscle relaxation and alterations in intrathoracic and intra-abdominal pressures may also play a role. The fall in blood pressure can be greatly exaggerated in hypovolemic patients, in the elderly, and in others with reduced sympathetic tone. Tubocurarine should be used very cautiously in such patients or another relaxant should be chosen. Concurrent administration of agents known to cause circulatory depression aggravates the problem. The higher the halothane concentration, for example, the greater the fall in blood pressure after D-tubocurarine (20). Since the degree of hypotension seems to be linked to dose (17) and the rate of injection (21), it seems reasonable to use the smallest dose that produces adequate relaxation (under 0.5 mg/kg) and to inject it slowly (over at least 180 seconds) (SEDA-7, 141).

Respiratory

Tubocurarine can cause apnea. The muscles involved in protecting and maintaining the airway are more sensitive to D-tubocurarine than the muscles of ventilation (22,23) so that aspiration and airway obstruction are possible in the partially curarized patient at a time when spontaneous ventilation is adequate. Airway obstruction in the presence of vigorous respiratory efforts can eventually (and is rarely reported to) lead to negative pressure pulmonary edema (24,25). Hypoventilation can occur after doses as low as 1.5 mg in exceptionally sensitive patients. Postoperative hypoventilation, or apnea, is a danger in patients given certain antibiotics and antidysrhythmic drugs before or after apparently successful spontaneous reversal or antagonism of a non-depolarizing block.

Potentiation of undetected residual curarization can also occur postoperatively from respiratory acidosis.

Histamine release, common with D-tubocurarine, can cause bronchospasm. Tubocurarine is relatively contraindicated in asthmatic patients and in those with an allergic tendency.

Nervous system

Minute amounts of D-tubocurarine have been detected in cerebrospinal fluid (26). Although convulsions have been produced in animals by injection into the cerebrospinal fluid, and it has been suggested that exceptionally large doses can cause depression of medullary centers, there is insufficient information to draw any conclusions.

Pancuronium is reported to lower the MAC for halothane, but whether this is a central or peripheral action is not known.

Gastrointestinal

The motility of the gut may be reduced by tubocurarine, as a result of ganglion blockade.

Body temperature

Tubocurarine has been implicated as a trigger of malignant hyperthermia, particularly in combination with halothane (27), although doubts have been expressed (28). Increased muscular tone is not a feature with D-tubocurarine.

Second-Generation Effects

Pregnancy

Placental transfer of D-tubocurarine occurs (as with all relaxants) and low concentrations of the drug have been detected in umbilical blood. Under normal circumstances no untoward effects have been reported in neonates.

Paralysis occurred in a 28-week fetus, whose mother received D-tubocurarine for status epilepticus, and joint deformities possibly resulting from 4 weeks' maternal curarization during the first trimester have been reported (29).

Experiments in chick embryos have shown that D-tubocurarine can cause retardation of bone growth (30) and that malformations can be produced by in utero curarization (31). Long-term curarization during pregnancy is undesirable.

Susceptibility Factors

Genetic factors

Individual responses to these compounds differ (32–34). Racial differences and environmental factors can influence the response to relaxants and hence the extent of problems due to excessive activity. Patients in the USA reportedly require less D-tubocurarine than in the UK, and the West Indians need more. Difference in cholinesterase activities, perhaps brought about by more organophosphorus insecticides being used in one country than in another, or differences in protein-binding as a result of dietary factors, are possible explanations (35). Vecuronium has been reported to be approximately 30% more potent in Montreal than in Paris (36).

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Age

In the elderly extreme falls in blood pressure can occur with D-tubocurarine (37).

Renal disease

In renal insufficiency the action of D-tubocurarine is increased (38) and prolonged (39).

The half-life in the complete absence of renal function is increased by 70% or more. The reduced ability of plasma proteins to bind the drug (40), if this indeed occurs, will result in a greater proportion of unbound D-tubocurarine and therefore increased potency.

Increased biliary excretion of D-tubocurarine occurs in renal insufficiency and compensates to a varying degree for reduced renal excretion (41). The slower rate of biliary (as opposed to renal) excretion will result in sharply increasing prolongation of neuromuscular blockade if large single doses are used or if multiple doses are given (42). A single small dose will result in little or no prolongation of effect, since redistribution will be mainly responsible for termination of the drug's effect. It has been suggested for several other non-depolarizing relaxants that the initial dose produces less effect in renal insufficiency (SEDA-13, 103).

The problem of accumulation may be marked in intensive care situations, where D-tubocurarine is used to maintain long-term paralysis (42). These patients may also have impaired renal and hepatic function, with protein and electrolyte imbalance. The timing of repeat injections of D-tubocurarine (and, indeed, all relaxant drugs) in such cases should be guided by monitoring of neuromuscular function (by response to single twitch, train-of-four, or tetanic stimulation, which is more sensitive but painful), or clinically by observing the return of muscle tone.

Other features of the patient

In hypovolemic patients, in patients with impaired sympathetic autonomic activity, and in patients operated on in the anti-Trendelenburg position, extreme falls in blood pressure can occur with D-tubocurarine. Hypotension is aggravated by the use of halothane in particular, and by other drugs that produce circulatory depression. In such cases, and in patients with hypertension, coronary artery disease, and arteriosclerosis, D-tubocurarine is better avoided.

Asthmatic and atopic individuals are at special risk from D-tubocurarine's histamine-releasing potential, and severe bronchospasm can result (43).

Greatly increased sensitivity occurs in myasthenia (44) and may even be seen in "premyasthenic" patients with no overt symptoms (45). Increased sensitivity has also been reported in amyotrophic lateral sclerosis (46), von Recklinghausen's disease (47), and ocular muscular dystrophy (48). Patients with Duchenne muscular dystrophy have prolonged block in the regional curare test (49), but other investigators have disputed whether an altered response to non-depolarizing relaxants occurs in this condition.

Patients with thyrotoxic myopathy, as with all forms of myopathy, are exceedingly sensitive to all non-depolarizing agents.

Drug–Drug Interactions

Antidysrhythmic drugs

Class I antidysrhythmic drugs, such as procainamide, lidocaine, propranolol, diphenylhydantoin (50), quinidine (51), and lidocaine (52) have all been claimed to enhance neuromuscular blockade by D-tubocurarine and other non-depolarizing agents. Bretylium (53) and disopyramide (54) are also reported to have their neuromuscular blocking activities potentiated by low concentrations of D-tubocurarine in animal experiments; neostigmine failed to reverse disopyramide-induced blockade (SEDA-13, 102) (55). The greatest hazard from these agents is that they can cause "recurarization" when given postoperatively. With bretylium this can occur several hours after its administration, as a result of its slow kinetics (53). Effects in man have still to be documented for bretylium, but "recurarization" 15 minutes after adequate reversal of vecuronium blockade with neostigmine has been described in a patient given disopyramide intravenously (SEDA-14, 116) (56).

Aprotinin

Reparalysis has been reported when aprotinin was used after operations during which suxamethonium had been given alone or in combination with normal doses of D-tubocurarine (57).

Azathioprine

Azathioprine reduces sensitivity to D-tubocurarine in experimental animals, possibly as a result of phosphodiesterase inhibition, increasing transmitter release (SEDA-4, 87) (58), (SEDA-13, 104).

Calcium channel blockers

Calcium channel blockers, such as verapamil and nifedipine, can potentiate neuromuscular blocking agents (59,60) and it has been suggested that in long-term use they can accumulate in muscle and make block-reversal difficult (61).

Corticosteroids

There have been several contradictory reports of possible interactions of tubocurarine with corticosteroids. In general, it seems that the long-term use of steroids can reduce sensitivity to non-depolarizing neuromuscular blocking agents, while acute administration can cause potentiation (62). Long-term steroid treatment may be associated with the development of a myasthenic syndrome in some patients, who will therefore be very sensitive to neuromuscular blocking agents.

Diuretics

Furosemide (40–80 mg) has been reported to enhance and prolong D-tubocurarine-induced block in anephric patients (63). In animals low doses potentiated D-tubocurarine (and suxamethonium) probably via presynaptic effects, while high doses (1–40 mg/kg in cats) reversed the neuromuscular actions of these relaxants (64). The effects of high doses were similar to those of theophylline,

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and phosphodiesterase inhibition leading to increased acetylcholine release was postulated as a possible mechanism for the antagonism.

Potassium and magnesium loss as a result of the use of diuretics can affect non-depolarizing relaxants.

Doxapram

Doxapram, used as a respiratory stimulant, increased partial D-tubocurarine and pancuronium neuromuscular blockade when used in high concentrations in rats (SEDA-14, 113) (65). There have been no reports in man so far.

Ganglion-blocking agents

Trimetaphan and hexamethonium can potentiate D-tubocurarine-induced block, but clinical reports clearly showing this are lacking. Tubocurarine will increase their hypotensive effect. Neostigmine could theoretically facilitate the postulated end-plate ion channel block of trimetaphan (SEDA-13, 102) (66), which would complicate reversal of neuromuscular block.

Local anesthetics

Local anesthetics have diverse effects on the neuromuscular junction. In very large doses they produce paralysis on their own. When the recommended doses are used for local anesthesia, systemic absorption is small and interaction with relaxants is not to be expected. However, large doses injected intravascularly (accidentally, or therapeutically for dysrhythmias) can potentiate relaxants of both types (67,68).

Magnesium sulfate

Magnesium inhibits the release of acetylcholine and reduces the sensitivity of the postjunctional membrane. Thus, magnesium sulfate can cause neuromuscular transmission failure and enhance the effect of D-tubocurarine and other non-depolarizing neuromuscular blocking drugs (69). Not only have potentiation and prolongation of D-tubocurarine block been reported, but also respiratory depression when magnesium sulfate was given an hour after reversal of the relaxant. Presumably the muscle weakness resulted from potentiation of residual curarization. Whether the effects are additive or synergistic is disputed. Muscle relaxants must be used with caution and in reduced dosage in patients receiving magnesium sulfate. Reversal of the block may be difficult.

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Tumor necrosis factor alfa

General Information

Tumor necrosis factor alfa is naturally produced by activated macrophages and monocytes and has pleiotropic effects on normal and malignant cells. Unfortunately, the systemic administration of tumor necrosis factor alfa as a single agent gave disappointing results with severe adverse effects and no significant clinical antitumor effect (SED-13, 1110) (1,2). However, tumor necrosis factor alfa combined with interferon gamma, interleukin-2, or cytotoxic drugs produced positive clinical results, and these combinations reduced the maximum tolerated dose of tumor necrosis factor alfa two to four-fold.

Severe hypotension, thought to be nitrous oxide-mediated, is the main dose-limiting toxicity at all doses. Other frequent and sometimes dose-limiting adverse effects included fever, chills and rigors, myalgias, diarrhea, nausea or vomiting, and local reactions at the injection site. During combination therapy with tumor necrosis factor alfa, hyperbilirubinemia, neurotoxicity, severe febrile reactions, and hypotension were the most frequent complications (SED-13, 1110) (1–4). Transient liver dysfunction, oliguria, and raised creatinine concentrations are common.

Organs and Systems

Cardiovascular

Hypotension, perhaps nitrous oxide-mediated, is a dose-limiting adverse effect of tumor necrosis factor alfa (5).

Severe hypophosphatemia with myocardial dysfunction was noted in patients receiving tumor necrosis factor alfa by continuous hepatic arterial infusion (SEDA-17, 433).

Congestive cardiomyopathy has been attributed to tumor necrosis factor alfa in isolated patients (SED-13, 1110) (6).

Respiratory

A reversible reduction in pulmonary diffusing capacity (7) and pulmonary hemorrhage have been attributed to tumor necrosis factor alfa in isolated patients (SED-13, 1110) (8).

Nervous system

Tumor necrosis factor alfa is considered to be a major neurotoxic agent, and most patients who received large doses developed central nervous system symptoms, most commonly headache, lethargy, fatigue, confusion, disorientation, and reduced performance. Seizures, transient amnesia, aphasia, hallucinations, and diplopia sometimes occur (9).

Psychological, psychiatric

Evaluation of cognitive function in patients receiving tumor necrosis factor alfa alone or combined with interleukin-2 showed reversible attentional deficits, memory disorders, deficits in motor coordination and frontal lobe executive functions (9). There was reversible hypoperfusion in the frontal lobes.

Endocrine

Exacerbation of hypothyroidism was noted in one patient with chronic thyroiditis who received tumor necrosis factor alfa (10).

Metabolism

Metabolic effects of tumor necrosis factor alfa include a reduction in cholesterol and high-density lipoproteins, increases in triglycerides and very low-density lipoproteins, and hyperglycemia.

Hematologic

The hematological effects of tumor necrosis factor alfa mostly consist of dose-related thrombocytopenia and granulocytopenia, and decreased monocyte or lymphocyte counts (SED-13, 1111) (11,12). Septic episodes are sometimes associated with leukopenia. Coagulopathy with laboratory evidence of disseminated intravascular coagulopathy was found in 30% of patients and was sometimes associated with thromboembolic events (13). Other coagulation disorders include transient alterations in prothrombin time, and a rise in the plasma concentrations of von Willebrand factor was found in healthy volunteers (14).

Gastrointestinal

Hemorrhagic gastritis has been attributed to tumor necrosis factor alfa (15).

Immunologic

Anaphylactic-like reactions, dyspnea, or acute bronchospasm have been attributed to tumor necrosis factor alfa in patients also treated with interleukin-2 (16).

Drug Administration

Drug administration route

Local (intralesional, intra-arterial, or intraperitoneal) administration of tumor necrosis factor alfa may well prove to be a more promising and less toxic route of administration. Although mild adverse effects, namely fever, hypotension, and fatigue, were similar to those reported after intravenous administration, coagulation disorders, pulmonary, central nervous system, liver, and renal forms of toxicity were usually not observed (17).

The most interesting and encouraging experience has been obtained using hyperthermic isolated limb perfusion (HILP) of tumor necrosis factor alfa combined with cytostatic drugs (for example melphalan) in melanoma and sarcoma (18). Although systemic toxicity was moderate in this setting, there was still a risk of severe hemodynamic changes, with clinical features of septic shock and a direct nephrotoxic effect of tumor necrosis factor alfa (19,20). A mild neuropathy, marked by transient paresthesia, is also frequent (21). Other rare adverse effects included lung infiltrates, fever, neutropenia, thrombocytopenia, coagulation disorders, transient rise in transaminases and bilirubin, and an increased risk of more severe rhabdomyolysis (SED-13, 1111) (22).

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Tylosin

General Information

Tylosin is a polyketide lactone substituted with three deoxyhexose sugars. It is used as an antimicrobial growth promoter in animals. Acquired resistance has been observed in potentially human pathogenic strains isolated from animals (1). Of further concern is the fact that tylosin confers cross-resistance on erythromycin (2).

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Typhoid vaccine (including typhoid-paratyphoid vaccine)

See also Vaccines

General Information

The different typhoid vaccines commercially available for civilian use are:

- an oral live attenuated vaccine based on the Ty21a strain of *Salmonella typhi*;
- a parenteral heat-phenol-inactivated vaccine, containing either killed *Salmonella typhi* or killed *Salmonella typhi* and *Salmonella paratyphi* A, B organisms; this

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preparation is no longer recommended by the WHO, although it is still produced in some countries;
- Vi capsular polysaccharide vaccine and vaccines based on auxotrophic mutants of Vi-positive and Vi-negative *Salmonella typhi* (SED-11, 687) (SEDA-12, 278) (SEDA-13, 284) (SEDA-14, 281).

Oral live vaccine

During volunteer studies and field trials using Ty21a vaccine, adverse reactions were rare and consisted of abdominal discomfort, nausea, vomiting, and rash or urticaria. Adverse reactions occurred with equal frequencies among groups receiving vaccine or placebo. There has been a report of a typhoid-fever-like syndrome after the use of Ty21a live oral vaccine (SEDA-15, 350).

Inactivated vaccine

Vaccines administered parenterally are not well tolerated. Severe local pain and/or swelling occurred in 6–40% of vaccinees; systemic reactions have been reported in 9–30% (headache), and in 14–29% (fever); 13–24% of vaccinees missed work or school due to adverse effects. More severe reactions (hypotension, shock) have been reported sporadically (1).

General adverse effects

There have been individual reports of fatal angioimmunoblastic lymphadenopathy, hemolytic uremic syndrome (after typhoid/paratyphoid/diphtheria vaccination), fatal hyperpyrexia (SED-11, 687), transverse myelitis (SEDA-10, 288), erythema nodosum (SEDA-11, 289) (SEDA-14, 281), and Reiter's syndrome (SEDA-15, 350).

The efficacy and safety of typhoid fever vaccine have been estimated in a meta-analysis of about 1.8 million vaccinees in efficacy trials and about 11 000 vaccinees in safety studies (2). The 3-year cumulative efficacy was 73% (65–80%) for two doses of whole cell vaccines, 51% (35–63%) for three doses of Ty21 live attenuated vaccine, and 55% (30–71%) for one dose of Vi vaccine. After immunization, fever occurred in 16% (12–21%) of whole cell vaccine recipients, 2% (0.7–5.3%) of Ty21a vaccine recipients, and 1.1% (0.1–12.3%) of Vi vaccine recipients (Table 1) (3).

A meta-analysis of studies of the efficacy and toxicity of typhoid fever vaccines (SEDA-23, 343) has been criticized as an interesting mathematical exercise but of little practical relevance (4). The meta-analysis had lumped together different parenteral whole-cell vaccines (alcohol-inactivated, formalin-inactivated, acetone-inactivated, and dried whole-cell vaccines), but the only

Table 1 Local and systemic reactions after the administration of typhoid fever vaccines

Study	Age (years)	Type of study	Number vaccinated	Fever (%)	Swelling (%)	Vomiting (%)	Diarrhea (%)	Missed school or work (%)
Ty21a vaccine								
Gilman et al.	Adults	Clinic	155	1	NA	3	10	ND
Murphy et al.	0.5–2	Clinic	18	11	NA	17	11	ND
Rahman et al.	3–78	Clinic	157	2	NA	0	1	ND
Cryz et al.	2–6	Clinic	317	<1	NA	1	<1	ND
Cryz et al.	16–56	Clinic	30	2	NA	0	20	ND
Pooled estimate (95% CI)				2.0 (0.7–5.3)		2.1 (0.6–7.8)	5.1 (1.7–15)	
Vi vaccine								
Levin et al.	ND	Clinic	21	24	ND	NA	NA	ND
Tacket et al.	20–24	Clinic	19	0	ND	NA	NA	0
Klugman et al.	5–15	Field	253	<1	4	NA	NA	ND
Cumberland et al.	18–22	Clinic	388	<1	1	NA	NA	ND
Mirza et al.	5–15	Field	435	0	8	NA	NA	ND
Pooled estimate (95% CI)				1.1 (0.1–1.2)	3.7 (1.3–9.6)			
Whole-cell vaccine (heat inactivated)								
YTC	5-50	Field	214	9	5	NA	NA	11
Ashcroft et al.	5–15	Field	193	13	61	NA	NA	14
YTC	NA	Field	66	29	ND	NA	NA	17
Hejfez et al.	7–18	Field	2621	30	19	NA	NA	ND
Hejfez et al.	ND	Field	3463	26	21	NA	NA	ND
Hejfez et al.	7–20	Field	2157	13	13	NA	NA	ND
Dimache et al.	16–18	Field	94	27	ND	NA	NA	ND
Dimache et al.	21	Clinic	113	1	ND	NA	NA	ND
Dimache	20	Field	100	34	ND	NA	NA	2
Cumberland et al.	18–22	Clinic	390	2	20	NA	NA	ND
Pooled estimate (95% CI)					16 (21–21)	20 (13–30)		10 (6–16)

For references, see (3)
YTC = Yugoslav Typhoid Commission
NA = Not applicable
ND = Not described in study

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parenteral killed whole-cell vaccine that is available is the heat-inactivated phenol-preserved vaccine. The analysis should therefore have been limited to heat-phenolized vaccine. It was also mentioned that the quoted data on the occurrence of adverse reactions failed to include the largest clinical trial of Ty21a vaccine. Last but not least, the authors of the meta-analysis failed to relate the severity of reactions connected with the use of parenteral whole-cell vaccine. These adverse reactions, including high fever, malaise, and nausea, make the killed whole-cell vaccine among the most reactogenic vaccine ever licensed. In contrast, oral Ty21a and parenteral Vi vaccines are well tolerated.

Combined meningococcal and typhoid fever vaccine

A combined meningococcal and typhoid vaccine (Mérieux) was evaluated in 158 volunteers in a single-blind study (5). Comparing the effects with those in vaccinees receiving monocomponent vaccines or the combination vaccine, there was no significant difference in the reported frequency or duration of local and systemic reactions. However, vaccinees who received the monocomponent typhoid fever vaccine alone were less likely to complain of swelling or pain at the injection site.

Organs and Systems

Musculoskeletal

Two cases of arthritis temporally connected with the administration of oral typhoid vaccine have been reported (6).

- Arthritis of the knees, ankles, and hands occurred 8 weeks after immunization in a 27-year-old woman.
- Bilateral sacroiliitis was observed in a 66-year-old woman 1 day after she had completed the four-capsule series.

A rheumatologist evaluated both patients and felt that the diagnosis was reactive arthritis, in his opinion most probably vaccine-related. The two cases are the first reports of reactive arthritis following oral typhoid immunization. However, the time-courses (1 day, 8 weeks) make a causal relation doubtful.

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Ultrasound contrast agents

General Information

The ideal contrast agent for enhancing ultrasound images and Doppler signals would be non-toxic, injectable intravenously, capable of crossing the pulmonary capillary bed, stable for the duration of the ultrasound examination, and useful for both Doppler and grey scale enhancement.

The first generation of echo contrast agents comprised compounds made of air bubbles stabilized with human serum albumin or D-galactose, which pass through the lung capillaries and reach the left heart chambers. The second generation comprises agents made of stabilized microbubbles of gases of high molecular weight and low solubility in water, mainly fluorocarbons, which provide better resistance to pressure. The high molecular weight fluorocarbon gases have lower diffusivity and blood solubility and thus give better persistence of microbubbles in the circulation. These agents can actually be considered as blood pool agents. Other factors, such as the size and stability of the particles, play a major role in optimal examination. Microbubbles larger than 7 μm will not cross the pulmonary vasculature after intravenous administration and hence the mean size of the microbubbles should be 2–5 μm.

Non-thermal bioeffects can develop with ultrasound equipment with high acoustic input in the presence of ultrasound contrast agents with a high mechanical index. Mechanical index is defined as the maximal rarefactional acoustic pressure divided by the acoustic frequency. Ventricular extra beats have been reported in people subjected to strong ultrasound fields but not with diagnostic ultrasonography, which is generally considered safe and without adverse effects. However, new ultrasound machines can provide high acoustic pressures, and the maximum mechanical index currently allowed is 1.9 (1).

Albumin microspheres

Albunex is a suspension of air-filled human albumin microspheres. In an assessment of the safety of Albunex (Molecular Biosystem Inc USA, Nycomed, Oslo Norway) in imaging the left ventricle in 52 patients, there were no major or minor adverse events and no changes in vital signs (2).

Optison is a second-generation contrast agent based on sonicated human albumin (albumin microspheres containing the gas perfluoropropane). In 191 patients with chronic pulmonary disease and/or cardiomyopathy (aged 21–83 years) given intravenous Optison 0.2, 0.5, 3.0, and 5.0 ml, adverse effects were observed in 6.5% (3). The most frequent adverse events were transient alterations in taste (2.5% of patients), headache (2.0%), and a warm sensation/flushing (2.0%). The adverse events were similar to those reported with first-generation ultrasound contrast agents.

In 50 patients (mean age 59 years) in an intensive care unit who underwent echocardiography examination with intravenous Optison (dose 0.5–1.5 ml), there were no contrast-related adverse effects (4). Good quality echocardiography was obtained in all cases.

Albunex has been compared with Optison in 203 patients undergoing echocardiography (5). There were no clinically significant changes in physical examination, vital signs, or electrocardiography in either group. Adverse effects were few in each group and were most commonly related to flushing, warmth, or taste disturbance. Similar results have been reported from a comparison of Echogen (2% dodecafluoropentane emulsion) with Albunex (SEDA-22, 505) (5).

AIP10119 is a contrast agent that consists of heat-stabilized, air-filled, albumin microcapsules with a median diameter of 4 μm. It contains 1.5×10^8 microcapsules/ml after reconstitution with water for injection. It can be prepared in a formulation with a relatively high acoustic pressure (mechanical index 1.5). In a phase I study in healthy men (mean age 28 years) who received continuous infusions of 1 ml/minute of AIP10119 (mechanical index 1.5) for 10 minutes ($n = 6$) or 20 minutes ($n = 4$) there was a significant dose-dependent increase in the number of ventricular extra beats during end-systolic imaging but not during end-diastolic imaging (1). Nine volunteers received AIP10119 as a single infusion of 1 ml/minute for 25 minutes (mechanical index 1.1) followed by three rapid bolus injections of 1 ml at least 5 minutes apart, the infusion and the series of bolus injections being separated by at least 2 hours; there was no increase in the number of ventricular extra beats. The authors concluded that precautionary measures would include using formulations with a low mechanical index or end-diastolic imaging.

Galactose

The galactose-based ultrasound contrast agents include Echovist and Levovist. Levovist consists of microbubbles less than 8 μm in size. After injection it crosses the lung and enters the systemic circulation. The lack of any adverse effects has been reported in several studies and clinical trials (SEDA-20, 418).

There has been a meta-analysis of the use of Echovist in 986 patients in the assessment of fallopian tube patency. It was well tolerated, although there were adverse events in 47%. By far the most common adverse effect was abdominal pain during the examination (38%). This correlated with tubal patency and was most severe in patients with blockage of both fallopian tubes, presumably because of increased intraluminal pressure. The only other common adverse events were vasovagal reactions (2.8%) and nausea (1.5%), which may not have been directly related to contrast administration (SEDA-22, 505).

Levovist has been assessed in 5073 patients. In addition, spontaneous reporting of adverse events in 100 000 patients given injections of Levovist has been analysed (6). The incidence of adverse events (12%) was similar in the Levovist group and in the controls, who were given isotonic saline. The adverse events included sensations of pain, cold, and warmth during injection, abnormal taste sensations, headache, nausea, and vomiting. There were no serious adverse events. The overall adverse event rate in spontaneous reports was 0.02%. One patient developed bronchospasm, another had a generalized skin rash, and two other patients had urticaria. The other reported adverse events were not serious and may not have been caused by the contrast agent.

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Intravesical Levovist has been used for voiding urosonography in 118 patients (aged 3 weeks to 16 years) (7). The diagnostic accuracy of the examination was high and no adverse effects were reported.

A phase-3 assessment of the accuracy of Levovist (SHU508A, Schering, Berlin) in investigating the portal system has been reported (8). It was injected into peripheral veins in 588 patients in concentrations of 200–400 mg/ml. During the 24 hours after the last injection, pain at the site of injection, vasodilatation, and paresthesia were the only adverse effects definitely related to the injection. There were 18 adverse events in 12 patients and the only severe reaction (fever) was not considered to have been related to Levovist.

There has been further confirmation of the safety of Levovist in a phase 3b clinical trial in 38 patients with hepatocellular carcinoma (9). There were only two minor reactions of nausea and vomiting.

Perfluorocarbons

NC100100

NC100100 (Nycomed, Oslo, Norway) is composed of stabilized perfluorocarbon microbubbles. In a randomized comparison of ^{99m}technetium sestamibi single-photon emission-computed tomography (SPECT) and NC100100 in the assessment of myocardial perfusion in 203 patients with myocardial infarction, NC100100 was well tolerated, with no serious adverse events or deaths (10). Similarly there were no clinically important changes in vital signs, laboratory parameters, or electrocardiography. NC100100 correctly identified the vast majority of normally perfused segments assessed by SPECT.

Octafluoropropane

Octafluoropropane gas encapsulated as microspheres in lipid shells (Definity) is given intravenously as an echocardiographic contrast agent. In a review of its diagnostic efficacy and safety, the authors concluded that it improves the diagnostic accuracy of echocardiographic examinations and has a good safety profile (11). Minor adverse effects were reported, such as headache, back pain, flushing, and nausea. There were no serious adverse effects. However, Definity should not be used in patients with intracardiac shunts or in pregnant or lactating women. It should also be used with caution in patients with severe liver or renal disease.

Perflenapent

Perflenapent emulsion (EchoGen) is an ultrasound contrast agent for echocardiography. It is a liquid-in-liquid emulsion of dodecafluoropentane in water, which becomes a dispersion of microbubbles after hypobaric activation. The microbubbles cross the lung capillary bed and persist in solution much longer than microbubbles of air or other gases of similar size, providing prolonged contrast enhancement. A review of 21 clinical studies involving 743 patients who received perflenapent emulsion and 151 patients who received placebo showed no clinically important abnormalities in laboratory tests, pulse oximetry, vital signs, or electrocardiography. There were adverse events in 6.7% of patients after perflenapent emulsion and 2.6% of patients after placebo. The most frequent adverse effects considered relevant to perflenapent emulsion were vasodilatation (2.8%) and taste disturbances (1.2%). Adverse events were generally mild to moderate, started within 10–20 minutes of contrast administration, and resolved spontaneously within 10–20 minutes. These reassuring findings are in keeping with safety reports about other ultrasound contrast agents (SEDA-22, 505).

A double-blind, placebo-controlled evaluation of perflenapent emulsion as a contrast agent for the liver, kidneys, and vasculature has been reported in 151 patients of whom 12 had adverse effects compared with nine who received placebo (12). Injection site pain, vasodilatation, rash, and rhinitis occurred more often with perflenapent than placebo.

The safety of perflenapent has been evaluated in multicenter phase II studies in 146 patients with congestive heart failure (NYHA class III or IV, mean age 68 years), of whom 99 received perflenapent and 47 received isotonic saline, and in 134 patients with severe chronic obstructive pulmonary disease (FEV_1 no more than 60% of predicted, mean age 65 years), of whom 91 received perflenapent and 43 received isotonic saline (13). Blood pressure, heart rate, respiratory rate, oxygen saturation, the electrocardiogram, FEV_1, complete serum biochemistry, hematology, and mental state were assessed. Adverse events were mild and required no treatment. There was no significant difference in the incidence of adverse reactions between those given perflenapent (15%) and those given placebo (11%). The most frequent adverse events with perflenapent were vasodilatation ($n = 8$), taste disturbance ($n = 6$), nausea ($n = 5$), and headache ($n = 3$).

Perflubron

Perflubron (perfluoro-octylbromide) is composed predominantly of carbon and fluorine, and the absence of protons results in a signal void wherever it is found. When it is given enterically the bowel is labeled as a signal void on the abdominal image.

The enteric use of perflubron has been studied and the authors concluded that it is relatively safe and effective. The main adverse effects were vomiting, which developed in 8% of patients, and a feeling of fullness reported in 5% of cases. Other adverse events involved complaints about the taste of the agent. There were no life-threatening or fatal events (SEDA-21, 484).

An intravenous infusion of an emulsion of perflubron as a hepatic and splenic enhancement agent during CT examination caused lower back pain and transient fever (SEDA-15, 505). This problem appeared to be due to the lipid emulsion and seems to have been overcome with more recent formulations.

Perflutren

Perflutren is an ultrasound agent that consists of perfluoropropane gas encapsulated in lipid microbubbles. It has been used in patients with suspected cardiac disease and suboptimal baseline echocardiography in doses of 5 μl/kg ($n = 85$) or 10 μl/kg ($n = 84$); 42 patients received isotonic saline (14). The magnitude of clinically useful opacification was not dose-dependent, but its duration

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was 81 seconds with 5 μl/kg and 99 seconds with 10 μl/kg. There were no clinically significant changes in physical examination, vital signs, electrocardiography, biochemistry, or hematology. Headache was the most frequent averse event, in nine patients who received perflutren and in three controls.

Simethicone-coated cellulose

Artefacts that arise from gas in the stomach and adjacent bowel often limit the diagnostic accuracy of abdominal ultrasound. Research to overcome this problem has focused on cellulose-based suspensions. An agent has been developed based on simethicone-coated cellulose—SonoRx (Bracco Diagnostics, Princeton, NJ), which displaces and disperses gas bubbles. In a phase 2 clinical study, 93 patients underwent upper abdominal sonography before and after a randomized dose of the contrast agent (200, 400, 600, 800, or 1000 ml) (15). Anatomical visualization was improved as follows: the stomach in 82% of patients, the duodenum in 63%, the pancreatic head and body in 61%, and the pancreatic tail in 67%. There were 14 adverse events in 11 patients and only five were considered to be related to the contrast agent. The main adverse effects were mild diarrhea and nausea.

Sulfur hexafluoride

Sono Vue (BR1) is an ultrasound contrast medium that consists of microbubbles containing sulfur hexafluoride gas stabilized by phospholipids. The diameter of each microbubble is 2.5 μm and there are about 0.5×10^9 microbubbles/ml. It is isotonic with human plasma, has the same viscosity as blood, and has minimal antigenic potential, since it contains no protein material.

The pharmacokinetics of Sono Vue have been studied in 12 healthy volunteers (aged 20–36 years, seven men), who received two intravenous doses of 0.03 and 0.3 ml/kg in random order (16). Sono Vue was rapidly cleared from the blood, with a half-life of 5–7 minutes. About 40–50% of the dose was eliminated in the expired air during the first minute after injection and 80–90% was eliminated by 11 minutes. Within 90 minutes, sulfur hexafluoride could no longer be detected in the expired air in most cases. There were no adverse effects.

The diagnostic efficacy and the safety of Sono Vue has been assessed in 218 patients with suspected coronary artery disease who underwent echocardiography (17). Each received intravenous Sono Vue 0.5, 1.0, 2.0, and 4.0 ml in random order at intervals of at least 5 minutes between injections. There were no clinically significant changes in physical examination, vital signs, or electrocardiography. There were no serious adverse effects, even in patients who had heart failure and a history of myocardial infarction. The non-serious adverse reactions were mild and transient and required no treatment. The most common adverse effects were headache (4%) and nausea (1.4%).

Assessment of vascularity can be useful in differentiating benign and malignant breast lesions using color Doppler examination. However, some neoplasms have low blood flow and Doppler may be suboptimal. In these cases, ultrasound contrast may be beneficial. In a phase II/III, multicenter, randomized study 220 patients with breast lesions in different anatomical areas received intravenous Sono Vue 0.3, 0.6, 1.2, and 2.4 ml (18). Sono Vue improved the quality of Doppler blood flow information in both parenchymal and focal lesions. There were mild adverse events in two patients only; one complained of nausea and the other of discomfort. It is not clear whether these events were related to the contrast agent or not.

The safety of Sono Vue as an intravenous bolus injection of 0.3, 0.6, 1.2, or 2.4 ml in transcranial Doppler examination of the cerebral arteries has been investigated in 40 patients (mean age 64 years) (19). The interval between each dose was at least 10 minutes or until total disappearance of the contrast effect from the previous dose. Eight patients reported 12 adverse events. There were no serious adverse events and no patient withdrew because of an adverse event. The most common adverse events were pain at the injection site, headache, and a feeling of warmth; all were mild.

The safety of Sono Vue has been evaluated in 36 healthy volunteers who were given a single dose of isotonic saline or Sono Vue, 0.003, 0.01, 0.03, 0.06, 0.09, or 0.12 ml/kg and in 30 volunteers who were given cumulative doses of 0.15–0.6 ml/kg (20). The volunteers were aged 20–35 years. Another 12 subjects, patients with chronic obstructive airways disease, were given a single dose of Sono Vue 4 ml and placebo (isotonic saline 4 ml) in two sessions, separated by 48–72 hours. All adverse events were minor or mild and rapidly resolved. The adverse effects in the healthy volunteers were heat at the injection site, facial flushing, headache, and a tingling sensation in the hand (one patient each). There were no differences in the frequencies of adverse events in the different dosages groups or between Sono Vue and placebo. In the patient with chronic obstructive airways disease, vomiting and lethargy occurred in one patient each. There were no significant changes in respiratory function tests (FEV_1, FVC, forced mid-expiratory flow, and oxygen saturation).

The excellent safety and efficacy of Sono Vue at doses of 0.7, 1, 2, and 4 ml has been demonstrated in 138 patients (mean age 57 years) (21). There were mild adverse events, such as headache, nausea, paresthesia, and taste disturbance, but no severe adverse reactions.

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Unoprostone

See also Prostaglandins

General Information

Unoprostone is a synthetic prostaglandin analogue of $PGF_{2\alpha}$ used in the treatment of glaucoma. Its mechanism of action is believed to be by enhancing uveoscleral outflow, like latanoprost.

Organs and Systems

Sensory systems

The use of unoprostone in the treatment of open-angle glaucoma and ocular hypertension has been reviewed (1). Most of the literature is in Japanese. The adverse effects of unoprostone are similar to those of latanoprost: conjunctival hyperemia, iris pigmentation, hypertrichosis and hyperpigmentation of eyelashes, and rarely systemic effects (1).

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Urticaceae

See also Herbal medicines

General Information

The genera in the family of Urticaceae (Table 1) include various types of nettle.

Urtica dioica

Urtica dioica (stinging nettle) has been used to treat rheumatism and benign prostatic hyperplasia.

Adverse effects

Gastrointestinal

A secondary source states that tea prepared from stinging nettle leaves can occasionally cause gastric irritation, skin

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reactions, edema, and oliguria, but primary references are not provided.

Table 1 The genera of Urticaceae

Boehmeria (false nettle)
Cypholophus (lopleaf)
Elatostema
Hesperocnide (stinging nettle)
Laportea (laportea)
Neraudia (ma'oloa)
Parietaria (pellitory)
Pilea (clearweed)
Pipturus (pipturus)
Pouzolzia (pouzolzia)
Rousselia (rousselia)
Soleirolia (soleirolia)
Touchardia (touchardia)
Urera (urera)
Urtica (nettle)

Skin

The blister-raising properties of topical stinging nettle extracts are well known; there is no definitive treatment (1).

A positive patch test reaction to *U. dioica* has been obtained in a patient who had developed edematous gingivostomatitis following the regular use of stinging nettle tea as a tonic; the patient also had positive reactions to chamomile (*Anthemis nobilis*) and its allergens (sesquiterpene lactones) (2).

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Vaccines

See also Individual agents

General Information

In the early days of vaccine development the majority of untoward effects after immunization were associated with faulty production, and the control of biological products as they exist today has been developed largely as a result of major accidents. For example, the Cutter incident in the USA in 1955, in which a batch of "inactivated" poliomyelitis vaccine containing live poliovirus was inadvertently released, had devastating consequences. The World Health Organization (WHO) subsequently took over the responsibility for international biological standardization. Currently, more than 50 WHO requirements for the manufacture and control of biological substances have been adopted and updated. As a result of the incorporation of WHO requirements, and their strict observance by manufacturers and control authorities, accidents due to faulty production of vaccines have become rare (SEDA-13, 271).

However, during the last two decades rapid increases in immunization coverage have been reported worldwide; globally, 5–10 billion injections are now given each year, mainly for treatment of illness but also for prophylactic purposes such as immunization. Unavoidably, the growth of WHO's Expanded Program on Immunization has sometimes resulted in extension of immunization work into areas of the developing world where logistic support and training programs have not been adequate. In such circumstances, avoidable faults have been made, involving variously improper or inadequate sterilization, incorrect doses and routes of vaccine administration, or substitution of drugs for diluents or vaccines (SEDA-15, 340). The use of unsterilized or improperly sterilized needles and syringes is particularly common in these regions and contributes largely to the spread of hepatitis B and C as well as to the spread of human immunodeficiency virus (HIV) and other blood-borne pathogens. The WHO recognizes this as a major public health problem and has initiated a program of activities to ensure safe injections (1).

In some highly developed countries that have had great success in reducing dangerous infectious diseases through immunization, there are controversial discussions regarding the benefits to harm balance of immunization. Because the incidence of vaccine-preventable diseases is reduced by increasing coverage with an efficacious vaccine, adverse events, both those caused by vaccines themselves (that is true adverse reactions) and those associated with immunization only by coincidence or as a result of faulty routines, become increasingly frequent. Not surprisingly, vaccine safety concerns have become increasingly prominent in successful immunization programs. Chronic illnesses recently claimed to be linked with immunizations include asthma, autism, diabetes, and multiple sclerosis. Given the current increasingly "anti-vaccine" environment that has developed in some countries, it is hard to imagine that the full potential of new vaccines will be harnessed. To avoid damage to current and future immunization programs considered as among the most successful and cost-effective public health interventions, we need to examine critically the factors that have influenced this change in public attitudes.

We have been relatively slow in appreciating the importance that the public now places on vaccine safety. In fact, much of our resource allocations still unfortunately reflect safety last rather than safety first. This reflects in part an unfortunate legacy, in which we have characterized this arena for years in narrow, negative terms of adverse events, instead of the more broad and positive terms of safety. Furthermore, it shows that we have not been as interested in preventing vaccine-induced illnesses as we are in vaccine-preventable diseases (2). Increasing interest in this problem can therefore be observed in many developed and developing countries, and international institutions and organizations, for example the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and vaccine manufacturers. The careful review of the current knowledge on adverse effects after immunization is a useful contribution to vaccine safety and helps to maintain confidence in immunization programs.

On the other hand, we must not forget that the ultimate goal of an immunization program is control of disease or even its regional elimination or worldwide eradication. A successful immunization program can lead to the eradication of disease and opens up the possibility of ultimately abandoning immunization (and with it the occurrence of adverse effects) completely. Smallpox eradication made it possible to stop smallpox immunization and poliomyelitis eradication, which is expected to be achieved within a few years, will mean the end of polio vaccine.

Surveillance of adverse events following immunization

Currently, in many highly developed countries in which the incidences of dangerous infectious diseases have been markedly reduced through immunization, there are controversial discussions about the balance of benefits and harms in immunization. Vaccine adverse events, both those caused by vaccines (that is true adverse reactions) and those associated with immunization only by coincidence, become more visible than the natural disease. Not surprisingly, vaccine safety concerns have become increasingly prominent in such successful immunization programs. Vaccines have been spuriously linked by various researchers to asthma, autism, diabetes, inflammatory bowel disease, multiple sclerosis, permanent brain damage, and sudden infant death syndrome (SIDS). Modern communication is providing even more penetrating ways of communicating messages on the subject through the World Wide Web. The result is a formidable challenge to immunization service providers. Neil Halsey, head of the Institute for Vaccine Safety at Johns Hopkins University, has summarized the features common to recent publications on vaccine adverse effects:

- a causal link is usually claimed with a disease or condition of unknown or unclear cause;
- the association is claimed by one investigator or a group of investigators;

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- the association is not confirmed by peers or by subsequent research;
- the claims are made with no apparent concern for potential harm from public loss of confidence and refusal to immunize;
- findings of subsequent studies that fail to confirm the original claim never get the publicity given to the original finding, and so the public never gets a balanced view(2,3).

A critical examination (4) of a report (5) of several children whose chronic bowel and behavioral abnormalities were linked to measles, mumps, and rubella (MMR) immunization can be used as an example to underline Halsey's comments. Without effective and credible systems for the detection of vaccine-associated adverse events through pharmacovigilance, for distinguishing causal reactions from coincidental reactions by pharmacoepidemiological or other studies, and for risk communication, vaccine safety concerns may confuse the media and the public.

A concerted effort is needed to improve communications at all levels regarding the real risks associated with vaccines and immunization and helping to reassure the public of the overwhelming safety record of vaccines. The medical community is still preeminent as advice givers to the public on matters of immunization and should play the key role in improved communication (3,6).

The US Vaccine Adverse Events Reporting System (VAERS) has been described (SEDA-14, 919) and the pros and cons of the system have been discussed (7). About 1000 reports per month are submitted by manufacturers (39%), state health coordinators (34%), health care professionals (25%), and parents (2%). Manufacturers' reports are primarily based on information received from health care providers or the parents of vaccinees. As a passive reporting system, VAERS is subject to numerous well-known deficiencies, such as underreporting, incomplete and missing data, and recall bias. Resources are not adequate to allow follow-up for complete or accurate data in all cases. However, VAERS is useful to detect early warning signals and to generate hypotheses. For example, the information from a parent that her daughter had lost her hair after the second and third doses of hepatitis B vaccine initiated a study that found 59 similar cases, including three cases of positive rechallenge. As a result of this study, alopecia was added to the list of adverse reactions in the hepatitis B vaccine package insert. Individual case reports can also trigger a complete review of the VAERS database. For example, three reports of idiopathic thrombocytopenic purpura after measles-containing vaccine were received in a short period of time. The study of idiopathic thrombocytopenic purpura reported in the database found 54 other reports during the period 1990–95, including one case of positive rechallenge, which increased the likelihood that the association was causal.

Reports on adverse events after the administration of the two hepatitis B vaccines licensed in the US (Engerix-B and Recombivax HB) have been compared in two different surveillance systems: VAERS and Vaccine Safety Datalink (VSD) (8). VSD is a computerized record linkage system designed to allow more rigorous evaluation of causality of adverse events after immunization. Since 1989, VSD has actively maintained medical files on over 500 000 children, aged from birth to 6 years enrolled at four West-coast health maintenance organizations. Immunization records, medical diagnoses, and diseases from clinic, hospitalization, and emergency room visits are coded. Whereas VAERS found that the reporting rate for events after brand 1 vaccine was at least three times higher than the reporting rate after brand 2 vaccine, VSD found no difference between rates of hospitalization or emergency room visits in recipients of the two brands. The authors concluded that the results of the VAERS database are subject to the inherent limitations of a passive surveillance system. This study underlined the importance of using other analytical studies, such as VSD, to evaluate preliminary results obtained by VAERS.

Adverse events reported to the VAERS during the period 1991–2001 have been summarized and evaluated (9). The main results were as follows:

- During 1991–2001, annual reports of deaths constituted 1.4–2.3% of all reports, and reports of life-threatening illness constituted 1.4–2.8% of all reports.
- A clinical research team followed up all deaths reported to VAERS; most of these deaths were ultimately classified as SIDS; analysis of the age distribution and seasonality of infant deaths reported to VAERS showed that they matched the age distribution and seasonality of SIDS: both peaked at 2–4 months and during the winter; the reduction in the number of deaths reported to VAERS since 1992–93 parallels the overall reduction in the incidence of SIDS in the US population since the implementation of the "Back to sleep" campaign; the Food and Drug Administration (FDA) and the Institute of Medicine (IOM) reviewed 206 deaths reported to VAERS during 1990–91: only one death was believed to have resulted from a vaccine.
- Intussusception after rotavirus vaccine was described as an example to underline the value of passive surveillance systems as an indicator for carefully designed follow-up studies.
- An increase in the number of reports of Guillain–Barré syndrome after the receipt of influenza vaccine was noted in VAERS data by week 29 of the 1993–94 influenza season; the numbers of reports of Guillain–Barré syndrome increased from 23 during 1991-92 to 40 during 1992–93 and to 80 during 1993–94; a study of the VAERS signal showed that slightly more than one additional case of Guillain–Barré syndrome occurred per 1 million people immunized against influenza, a risk that is less than the risk from severe influenza, which can be prevented by the vaccine.
- A detailed review of VAERS reports received during the first 3 years after the licensure of the *Varicella* vaccine documented that the majority of reported adverse events were minor and serious adverse events were rare.

Terms and definitions used in surveillance programs of adverse events and adverse effects after immunization

Definitions are fundamental to the establishment of any functioning surveillance system. There must be different definitions for monitoring and evaluation. An

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international voluntary collaboration has been established to develop globally accepted standardized case definitions of adverse events following immunization (AEFI). The so-called Brighton Collaboration (initiated in 1999 during a vaccine meeting in Brighton, UK) took into consideration that there is a general lack of widely accepted and implemented case definitions, because only a limited set of case definitions elaborated by WHO has been available internationally. Working groups on fever, local reactions, intussusception, persistent crying, convulsion, and hypotonic-hyporesponsive episodes were already established. The website of the Brighton Collaboration contains information about the process and progress of the collaboration, the work statement for the working groups, a template format for draft definitions, and much more (10).

On behalf of the Brighton Collaboration, an electronic discussion on the wisdom of using the term "adverse event following immunization" (AEFI) has been undertaken during the year 2001. Concern has sometimes been expressed that the word "following" could imply causality. At least 10 alternative terms have been proposed and discussed. Finally, the term "adverse event possibly related to immunization" (AEPRI) received the majority of votes. However, there were many participants in the discussion who believed that the term AEFI should be kept because it is used in many countries as well as in guidelines issued by the WHO and UNICEF and because a change will create new confusion. It therefore seems that the term AEFI will not be replaced (11).

The Brighton Collaboration took into consideration the fact that there is a general lack of widely accepted and implemented case definitions in order to allow comparability between studies. Based on a network of more than 300 participants from 34 countries and collaborating with many national and international organizations, institutions, and manufacturers (for example WHO, FDA, CDC, GlaxoSmithKline), case definitions and guidelines have been developed for intussusception, fever, prolonged crying, seizure, hypotonic-hyporesponsive episodes, and local reactions, such as nodules, swelling, cellulitis, and abscesses. A Brighton Internet site has been created (10).

Monitoring

Data collection is the first step in surveillance. Terms and definitions developed for monitoring purposes should be useful both for practitioners and health workers. Monitoring definitions therefore have to cover a broad range. For monitoring purposes, the term "adverse event" has been introduced, defined as an untoward event temporally associated with immunization, which might or might not be caused by the vaccine or the immunization process. The term "adverse effect" does not seem useful for monitoring purposes, since it relates to an untoward effect after immunization that is linked to the vaccine (antigen or vaccine component) or to the immunization procedure. The term and its definition imply a distinct degree of causality. However, the term "suspected adverse effect" is acceptable.

Evaluation

Statistical analysis and expert evaluation of the collected data should be carried out centrally. Expert evaluation of reports should be based on precise evaluation definitions, taking into account current scientific knowledge. One classification of events is that concerning causality, for example certain, probable, possible, unlikely, unclassified (when no attempt to classify has been made), and unclassifiable events (for example due to lack of data) (12). Alternatively one can classify reports into those for which there is no evidence of a causal relation, those for which evidence is insufficient to indicate a causal relation, those for which the evidence does not indicate a causal relation, those for which the evidence is consistent with a causal relation, and finally those for which the evidence indicates a causal relation (13,14). An evaluated adverse event classified as either "certain" or "probable" or "consistent with a causal relation" or "indicating a causal relation" fulfils the criteria for the recognition of an adverse effect after immunization.

Following WHO's proposal to distinguish four types of adverse events after immunization, the evaluation should furthermore try to distinguish:

- vaccine-induced adverse events (for example BCG lymphadenitis, BCG osteitis, vaccine-associated poliomyelitis, allergic reactions);
- vaccine-precipitated events (for example a simple febrile seizure following DPT immunization in a predisposed child);
- programmatic errors (for example an abscess due to improper sterilization);
- coincidental events (15).

Most commonly, passive surveillance systems are used for the surveillance of adverse events after immunization. Spontaneous reports from health care providers on temporally related adverse events suspected of being caused by the vaccine or the immunization procedure are collected and evaluated. However, the significant degree of under-reporting, together with the non-specific nature of most adverse events reports, highlights the limitations of passive surveillance systems of adverse events after immunization. A critical evaluation of the limitations of the US Vaccine Adverse Event Reporting System (VAERS) (SED-13, 919) and its predecessor, the Monitoring System for Adverse Events Following Immunization (MSAEFI) (SEDA-13, 273) (SEDA-16, 320) has been made by Rosenthal and Chen (16,17). The authors concluded that reports to VAERS and MSAEFI are essentially non-controlled clinical case reports or case series, useful for generating hypotheses but not for testing them. Other controlled studies are therefore often necessary to evaluate hypotheses raised by passive surveillance system reports: whether a given adverse event can be caused by a specific vaccine and if so how commonly it occurs. However, if reporting is reasonably consistent, it may be possible to detect changes in trends of known common adverse events. In addition, passive surveillance remains a potentially cost-effective way of monitoring rare events that cannot be detected in small prelicensing trials.

Cohort studies of rare adverse events would be useful, but are generally not feasible, particularly for economic reasons. One promising alternative approach is the use of large linked databases. The databases appropriate for such studies are derived from defined populations, such

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as members of health maintenance organizations, universal health care systems, and Medicaid programs. Information on both exposure (immunization records) and outcome (for example diagnoses recording potential adverse events) is usually computerized for members of such populations. These databases can be linked for epidemiological studies assessing potential associations between immunization and outcomes. Large linked databases have already been used by various groups to examine the association between DTP vaccine and SIDS, DTP vaccine and neurological events, and MMR vaccine and seizures. The Centers for Disease Control and Prevention (CDC) in Atlanta use large linked databases (now called Vaccine Safety Datalink) in addition to VAERS Vaccine Safety Datalink, covering a defined cohort of approximately 500 000 children up to the age of 5 years (17–19).

An epidemiological and statistical method based on linkage of routinely available computerized hospital admission records with vaccination records has been described by Farrington (20). This active surveillance method has been used to assess the attributable risk of convulsions after DTP and MMR immunization and to investigate the relation between MMR vaccine and idiopathic thrombocytopenic purpura in children under 2 years of age in five districts in England.

Causality assessment of adverse events following immunization (AEFI)

Adverse events following immunization can be causally related to the inherent properties of the vaccine, linked to errors in administration, quality, storage, and transport of the vaccine (programmatic errors), but also occurring coincidentally after immunization. It is therefore necessary to investigate and evaluate AEFI, particularly those that are serious or unknown.

The most reliable way of determining the causality of an AEFI is by randomized comparisons of events in an immunized group with events in a non-immunized group. However, such trials can never be large enough to detect very rare events; postmarket surveillance is required to identify rare events. A Global Advisory Committee on Vaccine Safety, constituted by the WHO in 1999, has developed criteria for AEFI causality assessment. Criteria to be considered are consistency (the findings should be replicable), strengths of association (in an epidemiological sense), specificity, temporal relation, and biological plausibility (according to what is known about the natural history and biology of the disease). Not all these criteria need to be present to establish causality (21).

In Canada, an advisory committee on causality assessment (ACCA) has been established to evaluate serious individual adverse event reports collected through active surveillance of pediatric hospitals or a passive voluntary reporting system. The ACCA is composed of specialists in epidemiology, immunology, infectious diseases, microbiology, neurology, pathology, and pediatrics. A causality assessment form has been developed (including criteria similar to the WHO criteria described above). For final classification of the evaluated adverse events the causality assessment criteria of the WHO (see Table 1) are used. The great majority of reports collected through the surveillance system describe minor or well-known reactions (over 95%); only the most serious and unusual adverse events after immunization requiring detailed review are submitted to ACCA. At each twice-yearly meeting of the ACCA 60–110 reports of severe and unusual reports are evaluated (22).

Table 1 WHO causality assessment criteria for adverse reactions to vaccines

Probability	Criteria
Very likely/ certain	Clinical event with a plausible time relationship to vaccine administration, and which cannot be explained by concurrent disease or other drugs or chemicals
Probable	Clinical event with a reasonable time relationship to vaccine administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals
Possible	Clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals
Unlikely	Clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could plausibly be explained by underlying disease or other drugs or chemicals
Unrelated	Clinical event with an incompatible time relationship to vaccine administration, and which could be explained by underlying disease or other drugs or chemicals
Unclassifiable	Clinical event with insufficient information to permit assessment and identification of the cause

Surveillance systems in different countries and between-country collaboration

Some countries have long experience in monitoring adverse events after immunization, starting with smallpox vaccination.

Worldwide, under 10% of countries have implemented postlicensure surveillance systems. The withdrawal of rotavirus vaccine (Rotashield, Wyeth Laboratories) based on postmarketing surveillance data that showed an excess risk of intussusception after the use of the vaccine convincingly showed that such systems are essential components of vaccine program implementation. However, the event also showed the power of active surveillance systems. Active systems in Minnesota and the Northern California Kaiser Permanente Health Maintenance Organization have provided preliminary data that suggest an increased risk of intussusception after the administration of Rotashield. Further analysis of the data collected both from the passive US national AEFI reporting system (VAERS) and from various active postmarketing surveillance systems led to a decision to withdraw the vaccine from the market (23).

USA

Since March 21, 1988, health care providers and vaccine manufacturers have been required by law to report certain events following specific immunizations (SED-12, 792) to the US Department of Health and Human Services. Table 2 shows the updated table for reportable

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Table 2 Reportable events after vaccination

Vaccine/toxoid	Event	Interval from vaccination
Tetanus in any combination; DTaP, DTP, DTP-HiB, DT, Td, TT	A. Anaphylaxis or anaphylactic shock	7 days
	B. Brachial neuritis	28 days
	C. Any sequel (including death) of the above events	Not applicable
	D. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Pertussis in any combination; DTaP, DTP, DTP-HiB, P	A. Anaphylaxis or anaphylactic shock	7 days
	B. Encephalopathy (or encephalitis)	7 days
	C. Any sequel (including death) of the above events	Not applicable
	D. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Measles, mumps, and rubella, in any combination; MMR, MR, M, R	A. Anaphylaxis or anaphylactic shock	7 days
	B. Encephalopathy (or encephalitis)	15 days
	C. Any sequel (including death) of the above events	Not applicable
	D. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Rubella in any combination; MMR, MR, R	A. Chronic arthritis	42 days
	B. Any sequel (including death) of the above event	No limit
	C. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Measles in any combination; MMR, MR, M	A. Thrombocytopenic purpura	7–30 days
	B. Vaccine-strain measles viral infection in an immunodeficient recipient	6 months
	C. Any sequel (including death) of the above events	No limit
	D. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Oral polio (OPV)	A. Paralytic polio	30 days/6 months
	B. Vaccine-strain polio viral infection	30 days/6 months
	C. Any sequel (including death) of the above events	Not applicable
	D. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Inactivated polio (IPV)	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any sequel (including death) of the above events	Not applicable
	C. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Hepatitis B	A. Anaphylaxis or anaphylactic shock	7 days
	B. Any sequel (including death) of the above events	Not applicable
	C. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Hemophilus influenzae type b (conjugate)	A. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Varicella	A. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Rotavirus	A. Intussusception	30 days
	B. Any sequel (including death) of the above events	Not applicable
	C. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert
Pneumococcal conjugate	A. Events described in the manufacturers' package insert as contraindications to additional doses of the vaccine	See package insert

events after vaccination, effective from August 26, 2002. The VAERS accepts all reports of suspected adverse events after the administration of any vaccine, including but not limited to those certain events required by law to be reported.

Canada

The reporting of vaccine-associated adverse events temporally associated with immunization by health-care providers is voluntary in Canada, except in the province of Ontario, which has specific mandatory requirements. However, there is no evidence of a higher reporting rate with the latter approach. This is partly explained by the fact that immunization in Ontario is usually provided by physicians, who have lower reporting rates than public-health nurses. In addition to its spontaneous voluntary reporting system, Canada also has an active surveillance system, IMPACT, for serious adverse events, vaccination

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failures, and selected infectious diseases. It involves a network of 11 pediatric centers across Canada. The results of the Canadian surveillance system have been reviewed (SEDA-16, 367) (SEDA-17, 363) (SEDA-21, 324) (SEDA-22, 333).

The Netherlands
A special committee of the Health Council of the Netherlands has been created (12), with the task of analysing, classifying, and interpreting the adverse effects which are reported to the National Institute of Health and Environmental Protection in Bilthoven (SEDA-12, 271) (SEDA-13, 278) (SEDA-14, 269) (SEDA-15, 341) (SEDA-16, 365) (SEDA-17, 363) (SEDA-18, 325).

New Zealand
Reported adverse events after immunization in New Zealand from 1990 to 1995 have been presented (24). Reactions at the injection site following adult tetanus + diphtheria vaccine were the most commonly reported (68 reports per 100 000 immunizations). The authors concluded that the picture confirmed the overall safety of vaccines and the value of an adverse events monitoring system.

Spain
In Spain, reports on adverse events after immunization are collected through the Spanish Pharmacovigilance System by means of a yellow card. In children, the most commonly involved pharmaceutical groups were antibiotics, respiratory drugs, and vaccines. A review of reports received over 10 years (1982–91) has been provided (25). In the framework of the Global Training Network, a WHO initiative to improve the quality of vaccines and their use, a model for a simple national system for dealing with vaccine safety and emergencies as they arise has been elaborated. The authors have described the model and have outlined a training program designed to help develop such a system (26).

Other countries
There are other national surveillance programs on adverse events after immunization, for example in Denmark, Germany, Sweden, the UK, Hungary; developing countries such as India (SEDA-17, 363) and Brazil (SEDA-16, 367) have also already started to collect data on severe adverse events.

International surveillance programs
The Program on International Drug Monitoring of the WHO has participation from over 50 member states. In all member countries, national Drug Reaction Monitoring Centers collect reports from health professionals and pass them on for entry into the international database housed at the WHO Collaborating Center for International Drug Monitoring in Uppsala, Sweden. Currently, there are some 2.5 million reports on file, and each year about 200 000 new reports are added. The database generates signals of potentially severe drug toxicity and provides confirmation of signals generated in specific countries. The Center also acts as the guardian of the standardized terminology of adverse drug reactions in computerized systems. Although vaccines are considered to be safe, the work of the Center underlines the importance of collecting information on the safety of vaccines to provide sound reference data in the event of a problem. Since vaccines are administered to healthy people, mostly children, the impact of a perceived problem can be enormous. Because of these considerations, many countries have already established specific programs for the monitoring of adverse events after immunization (27).

Clinical immunization safety assessment centers
The National Immunization Program of the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA, is trying to set up a network of Clinical Immunization Safety Assessment Centers (CISA). Based on standardized clinical evaluation protocols the centers will assist health care providers in evaluating patients who may have had an adverse reaction after immunization. Furthermore, the centers will evaluate newly hypothesized syndromes or events identified through the routine VAERS (28).

Guaranteeing vaccine quality
During the last 20–30 years, great progress has been achieved in both vaccine production technologies and testing technologies. In addition to sophisticated tests, vaccine regulation entails a number of procedures that ensure safety, including the characterization of starting material, cell banking, seed lot systems, principles of good manufacturing practices, independent release of vaccines on a lot-by-lot basis by national regulatory authorities, and enhanced premarketing and postmarketing surveillance for possible rare adverse events after immunization (29).

Perspectives on prelicensure trials
The withdrawal of tetravalent rhesus-based rotavirus vaccine from the market illustrates an important problem regarding prelicensure testing and its ability to identify rare vaccine-related adverse events. A sample size of 10 000 volunteers may provide excellent estimates of reactogenicity (local and systemic reactions) and efficacy but be inadequate as a denominator for ruling out rare adverse events. Table 3 shows how trial size determines the ability to detect frequent and rare events. Plans for future large prelicensure trials, for example for newly developed rotavirus vaccines, therefore include 10 000–60 000 volunteers. These large trials can be seen as a

Table 3 Sample size necessary to have 80% power to detect an increase in the risk of a rare event

Background rate (1:1 randomization)	Detectable relative risk	Total study population required
1:100	5	1443
1:100	2	5916
1:1000	5	14 428
1:1000	2	59 160
1:10 000	5	144 280
1:10 000	2	591 600

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bridge between prelicensure and improved postlicensure surveillance (30,31).

Improving monitoring of vaccine safety through postlicensure studies

Gaps in current vaccine safety monitoring methods have been analysed and the needs for improvements outlined (32,33). The well-known limitations associated with prelicensure trials have led to the expectation that postlicensure studies would address safety issues better. To meet this expectation, steps that should be taken include bar-code labeling of vaccines to improve the accuracy and completeness of information about administered vaccines, establishing immunization registers to provide numerator data, developing generally agreed case definitions for adverse events following immunization (AEFI), to allow comparability between studies, to facilitate long-term follow-up, and to do linked database studies. Only by investing in vaccine safety infrastructure will the high expectations of postlicensure studies be met.

Passive surveillance and reported fatalities

The fatalities reported to the federally administered (US) VAERS have been examined (34). A total of 1266 deaths were reported to VAERS between July 1990 and June 1997. Table 4 shows the numbers of deaths by age (total sample 1199 individuals) and Table 5 shows the causes of death (total sample 1244 individuals).

Nearly half of the deaths were attributed to SIDS. Since 1992/93, the trend of decreasing numbers of reported deaths follows that observed for SIDS overall in the US general population following implementation of the "Back to Sleep" program. Therefore, the VAERS data support the findings of controlled studies that show that the association between infant immunization and SIDS is coincidental and not causal.

Adverse events after immunization—the need for improved research, surveillance, and communication

The success of vaccines is not only impressive and convincing but also makes immunization its own worst enemy. When a naturally occurring disease becomes less common, concerns about vaccine safety increase, particularly since no vaccine can be regarded as being completely safe, although some are very much safer than others. Progress in the development, manufacture, and control of modern vaccines has contributed to the safety of current vaccines. However, it is absolutely necessary to know what the true complications of immunization are, what the gaps in our current knowledge are, and when there is no evidence linking immunization and a suspected adverse effect.

Table 4 Deaths related in time to immunization reported to VAERS 1990–97, by age

Age (years)	Number (%)
Overall	1199 (100)
<1	808 (67)
1–4	117 (9.8)
5–9	18 (1.5)
10–17	17 (1.4)
18–45	43 (3.6)
46–64	55 (4.6)
≥65	141 (12)

Table 5 Causes of death related in time to immunization reported to VAERS 1990–97

Cause of death	Number (%)
Overall	1244 (100)
SIDS	592 (48)
Congenital	38 (3.1)
Infectious	164 (13)
Neoplastic	15 (1.2)
Other	261 (21)
Unknown	174 (14)

Current knowledge about vaccine risks is incomplete, as was noted in extensive reviews in the early 1990s by the IOM in the USA (13,14). Two-thirds of the 76 vaccine-associated adverse events evaluated by the IOM had either no evidence or inadequate evidence to assess the causal role of the vaccine. Specifically, the reviews identified the following limitations:

- inadequate understanding of the biological mechanisms that underlie adverse events;
- insufficient or inconsistent information from case reports and case series;
- inadequate size or length of follow-up of many population-based epidemiological studies;
- limitations of existing surveillance systems to provide persuasive evidence of causation;
- few experimental studies published relative to the total number of epidemiological studies published.

A concerted effort is therefore needed to improve both research on and surveillance of the risks associated with immunization, as well as better communication aiming to reassure health-care providers, parents, and the public (including the media) about the steps taken to ensure vaccine safety and the overwhelming safety record of vaccines. The medical community still has preeminence as the purveyor of advice to the public on matters of immunization and should play a key role in improving communication. Nothing will strengthen our ability to communicate risk more than ensuring that there is adequate capacity and funding for vaccine safety infrastructure and research (2).

The response to a newly published adverse event associated with immunization must be rapid. First, if the reported association is correct, urgent re-evaluation of the immunization program is necessary. However, if the reported association is false, a credible countermessage must be sent, to minimize the negative impact on the immunization program (35).

The pros and cons of the (US) VAERS (SEDA-14, 919) have been critically reviewed (SEDA-23, 336) (36).

Among the many new developments in the communication of adverse events, the increasing role of the Internet should be mentioned. Many national bodies (for example the FDA, Rockville, Maryland, USA, www.fda.gov, or the CDC, Atlanta, Georgia, USA, www.vaers.org) and intergovernmental health authorities

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responsible for licensure of vaccines (for example the European Agency for the Evaluation of Medicinal Products (EMEA), www.eudra.org/emea.html), and/or vaccine safety (for example the World Health Organization, www.who.int/vaccines-diseases/safety/), as well as vaccine manufacturers (through postmarketing surveillance of their products, for example SmithKline Biologicals, www.worldwidevaccines.com), universities, and private organizations have also launched Websites providing information on vaccine safety and immunization risks.

National compensation programs for vaccine-related injuries

The need for some form of compensation when an individual is seriously injured by vaccination, particularly when the immunization has been compulsory or recommended by the health authority, has been accepted in many countries. Table 6 shows details of compensation programs in Canada (the province of Quebec), Denmark, France, Germany, Italy, Japan, New Zealand, Norway, Sweden, Switzerland, Taiwan, the UK, and the USA (37).

In the USA, the National Childhood Vaccine Injury Act of 1986 established the National Vaccine Injury Compensation Program as a federal no-fault compensation system for individuals who may have been injured by specific vaccines. This compensation program relies on a Vaccine Injury Table that lists the vaccines that are covered by the program, as well as injuries, disabilities, illnesses, and conditions (including death) for which compensation may be awarded. To better reflect current scientific knowledge about vaccine injuries, the Vaccine Injury Table was revised in 1995 and has been subsequently further modified. The latest modification, which became effective on December 1, 2004, is shown in Table 7. This revision took into account a review of the literature on specific adverse consequences of pertussis and rubella vaccines performed and published by the IOM (SED-12, 817) (SED-12, 825). In addition to the seven vaccines (diphtheria, pertussis, tetanus, measles, mumps, rubella, and poliomyelitis) included in the first Vaccine Injury Table, the 1997 revision includes hepatitis B, *Hemophilus influenzae* type b, and *Varicella* vaccines, as well as any future licensed vaccine recommended by the Advisory Committee on Immunization Practices (ACIP) for routine administration to children (38).

There are other compensation programs, for example in Japan, where the program covers damage caused by compulsory immunizations; provisions include medical allowance, care giver's allowance, disability pension, and a funeral grant; a national expert committee reviews applications.

Although not focusing primarily on vaccine-induced injury, attention should be paid to a contribution to the field of liability for drug-induced disease (39).

On December 1, 2004, the Secretary published a notice in the Federal Register announcing the addition of hepatitis A vaccines to the Vaccine Injury Table under Category XIV with an effective date of December 1, 2004.

The balance of benefits and harms in immunization

The risks of adverse effects after immunization against diphtheria, pertussis, tetanus, poliomyelitis, measles, and tuberculosis have been discussed in the framework of the WHO Expanded Program on Immunization and compared with the complication rate following natural disease (40). Table 8 presents a comparison of the estimated risks of adverse reactions after DTP immunization with the complication rates of natural whooping cough, while Table 9 shows a similar comparison for measles immunization and natural measles. The authors concluded that no vaccine is without adverse effects, but that the risks of serious complications from vaccines used in WHO's Expanded Program on Immunization are much lower than the risks from the natural disease.

Bioterrorism and prevention through immunization

Anthrax

Human anthrax is endemic in agricultural regions of the world where animal anthrax is common; sporadic cases occur in industrialized countries. Cutaneous, intestinal, and pulmonary anthrax can be distinguished clinically. Untreated cutaneous anthrax has a case fatality rate of 5–10%; death occurs only rarely in properly treated patients. Intestinal and pulmonary anthrax have much higher case fatality rates, even in properly treated patients. Transmission from person to person is very rare. Recently, anthrax has been considered a leading potential agent in bioterrorism. As was first demonstrated in 1979 at Sverdlovsk, USSR (an environmental accident in a biological weapon manufacturing facility), inhalational anthrax accounts for most of the cases and for all deaths following the use of anthrax as an aerosolized biological weapon (41).

In 2001, the first bioterrorist anthrax attack occurred in the USA. From 3 October 2001 to 21 November 2001, the CDC had received reports of 23 human cases of anthrax, 18 confirmed and five suspected. There were five deaths from pulmonary anthrax (42).

Three human vaccines against anthrax are currently available commercially (produced in the UK, the USA, and Russia). Two are inactivated cell-free products, whereas the Russian product contains a live attenuated vaccine. Current vaccine supplies are limited; however, even if enough vaccine were available, mass immunization would not be recommended. Immunization could be considered for essential service personnel and, following a terroristic attack, would be combined with an antibiotic to protect against residual retained spores. In 1970, an anthrax vaccine, derived from a sterile filtrate of an avirulent non-encapsulated strain of *Bacillus anthracis* and adsorbed on to aluminium hydroxide, was licensed by the FDA to protect people who might be exposed to anthrax. The ACIP has recommended immunization with this vaccine for people working with *B. anthracis* in the laboratory, those working with imported animal hides or furs in conditions that are inadequate to prevent exposure to anthrax spores, and military personnel deployed to areas with high risk for exposure. The vaccine was used to protect military personnel during the 1991 Gulf War.

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Table 6 Vaccine injury compensation programs

	Denmark	France	Germany	Italy	Japan	New Zealand
Enacted	1972 (1978)	1964	1961	1992	1970 (1977)	1974
Administrative entity	National Social Security Office	Ministry of Solidarity, Health and Welfare	State (Länder) pension system (federal law guides outcome)	Ministry of Health	Ministry of Health and Welfare	Accident Rehabilitation and Compensation Insurance Corporation (semi-governmental)
Vaccines covered	Government-provided (free) (D, T, P, M, MR, polio, Hib, BCG)	Compulsory (HBV, D, T, polio, BCG, typhoid)	Recommended (most routine and specific use vaccines)	Compulsory (D, T, polio, HBV, typhoid)	Recommended (polio, D, P, M, R, JE, and others for control of epidemics)	All that are administered
Filing deadlines	1 year after onset of symptoms	4 years after injury stabilization	None (states may have limitations)	Injury: 3 years; Death: no limit	No limit	1 year (exceptions if claim is incomplete)
Compensatable injuries	Injuries with reasonable probability caused by vaccine	All damage directly attributable to vaccination	Injuries exceeding normal extent of reactions—aggravation of pre-existing	Death or injury resulting in permanent physical or mental impairment	Disability or death resulting from vaccination	Vaccine-related injury that is rare and severe
Process and decision-making	Notice must be filed within 1 year of symptoms	Choice of ministerial commission or administrative tribunal	Claims evaluated by pension office; 1971 law gives more flexibility on causation	Medical Hospital Board for eligibility; compensation based on category level of injury (8 levels)	Committee on Public Health decides eligibility and damages	Patient files claim form, reviewed by ACC Medical Misadventure Advisory Committee
Proof needed	Reasonable probability	Clear and convincing evidence	Probable cause	Not specified	Not specified	Balance of probabilities
Elements of compensation	Medical costs, lost wages, death benefits, non-economic damages	Medical costs, disability pensions, lost wages, death benefits, non-economic damages	Medical costs, disability pensions, lost wages, funeral costs, non-economic damages	Free medical care, medications, disability pension, death benefit	Medical costs, lost wages, disability pensions, death benefits	Medical costs, disability pensions, lost wages, death benefits
Funding source	National treasury	National treasury	General revenues of the state	National treasury	Treasury (50%), Municipal (25%), Prefecture (25%)	Employers, wage earners, auto licensing fees, government, investment income
Appeal rights	Yes	Yes	Yes	Yes	Yes	Yes
Litigation rights	Yes (with limits)	No	Yes (with limits)	Yes	Yes	No
Total number of claims filed to June 1999	55	51	4569	366	2982	211
Number compensated	5 (9%)	37 (73%)	1139 (25%)	260 (71%)	2720 (91%)	68 (32%)

Continued

Table 6 Continued

	Norway	Quebec	Sweden	Switzerland	Taiwan	UK	USA
Enacted	1995	1985	1978	1970	1988	1979	1988
Administrative entity	Ministry of Health and Social Affairs	Ministry of Health and Social Services	Pharmaceutical insurance (non-governmental)	State (Canton) (federal law guides outcome)	Department of Health	Department of Social Security	Department of Health and Human Services
Vaccines covered	Routine childhood (D, T, P, Hib, M, MR, polio, BCG)	Voluntary (none is compulsory) (D, T, P, MMR, BCG, HAV, HBV, typhoid)	All approved products marketed in Sweden	Recommended by cantons (D, T, P, HBV, Hib, M, MR, polio)	Compulsory (BCG, HBV, OPV, D, T, P, MMR, JE, D, T)	Routine childhood (D, T, P, M, MR, polio, BCG, Hib)	Routine childhood (D, T, P, MMR, polio, Hib, *Varicella*, HBV, rotavirus)
Filing deadlines	3 years after vaccination or death, or onset of chronic illness	3 years after being made first aware of injury	None (states may have limitations)	1 year after vaccination	Within 6 years of the later of either immunization date or age	Injury: 3 years; Death: 2 years (new vaccination or conditions—8 years)	
Compensatable injuries	Not specified	Any serious permanent damage, whether physical or mental, including death	Those noted as adverse effects in FASS or in medical literature	Injury has to exceed a normal post-vaccination reaction	Table of compensatable injuries	Severe disability to extent of 80% or more as a result of immunization	Injuries listed on the Vaccine Injury Table or by proving causation or significant aggravation
Process and decision-making	Minister of Health decides eligibility	Claim reviewed by three-member Medical Evaluation Committee; final decision by Minister of Health	Claims manager with Zurich insurance company makes decision with medical consultations as needed	Health dept. reviews claim and seeks supporting information	Vaccine Injury Comfort Fund Working Group, Department of Health	Claim evaluated by medical officer; makes recommendation to Secretary of State for Social Security	DHHS reviews claim and makes recommendation US Court of Federal Claims makes decision
Proof needed	Balance of probabilities	Balance of probabilities	Strong probability of cause and effect	Not specified	Balance of probabilities	Balance of probabilities	Balance of probabilities

	Norway	Quebec	Sweden	Switzerland	Taiwan	UK	USA
Elements of compensation	No precedent (only award to date was a lump sum payment)	Unreimbursed medical costs, lost wages, rehabilitation, death benefits	Unreimbursed medical costs, lost wages, death benefits	Medical costs, lost wages, death benefits, non-economic damages	Medical costs, health care expenses, burial expenses	Lump sum of payment of statutory sum (40 000 pounds)	Unreimbursed past and future medical expenses, non-economic damage, attorneys' fees
Funding source	National treasury with contribution from manufacturer	National treasury	Manufacturers pay premiums into fund	General revenues of the states	Manufacturers and local society and community	Consolidated fund provided by Parliament	National treasury (pre-enactment); excise tax on covered immunization (postenactment)
Appeal rights	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Litigation rights	Yes	Yes	No	Yes (with limits)	Yes	Yes (with limits)	Yes (with limits)
Total number of claims filed to June 1999	1	142	140	1	123	4012	5355
Number compensated	1 (100%)	17 (12%)	79 (56%)	1 (100%)	62 (50%)	890 (22%)	1390 (26%)

Table 7 National Childhood Vaccine Injury Act: Vaccine Injury Table

Vaccine	Illness, disability, injury, or condition covered	Time interval
I. Vaccines containing tetanus toxoid (for example DTaP, DTP-Hib, DT, Td, or TT)	A. Anaphylaxis	0–4 hours
	B. Brachial neuritis	2–28 days
	C. Any acute complication or sequel (including death) of the above events	Not applicable
II. Pertussis antigen-containing vaccines (for example DTaP, DTP, P, DTP-Hib)	A. Anaphylaxis or anaphylactic shock	0–4 hours
	B. Encephalopathy (or encephalitis)	0–72 hours
	C. Any acute complication or sequel (including death) of the above events	Not applicable
III. Vaccines containing measles, mumps, and rubella viruses in any combination (for example MMR, MR, M, R)	A. Anaphylaxis or anaphylactic shock	0–4 hours
	B. Encephalopathy (or encephalitis)	5–15 days
	C. Any acute complication or sequel (including death) of the above events	Not applicable
IV. Vaccines containing rubella virus (for example MMR, MR, R)	A. Chronic arthritis	7–42 days
	B. Any acute complication or sequel (including death) of the above event	Not applicable
V. Vaccines containing measles virus (for example MMR, MR, M)	A. Thrombocytopenic purpura	7–30 days
	B. Vaccine-strain measles viral infection in an immunodeficient recipient	0–6 months
	C. Any acute complication or sequel (including death) of the above events	Not applicable
VI. Vaccines containing live oral polio virus (OPV)	A. Paralytic polio	
	in a non-immunodeficient recipient	
	in an immunodeficient recipient	0–30 days
	in a vaccine associated community case	0–6 months
	B. Vaccine-strain polio viral infection	Not applicable
	in a non-immunodeficient recipient	
	in an immunodeficient recipient	0–30 days
	in a vaccine associated community case	0–6 months
	C. Any acute complication or sequela (including death) of the above events	Not applicable Not applicable
VII. Vaccines containing polio inactivated virus (for example IPV)	A. Anaphylaxis or anaphylactic shock	0–4 hours
	B. Any acute complication or sequela (including death) of the above event	Not applicable
VIII. Hepatitis B antigen-containing vaccines	A. Anaphylaxis or anaphylactic shock	0–4 hours
	B. Any acute complication or sequel (including death) of the above event	Not applicable
IX. *Hemophilus influenzae* type b polysaccharide conjugate vaccines	No condition specified for compensation	Not applicable
X. Varicella vaccine	No condition specified for compensation	Not applicable
XI. Rotavirus vaccine	No condition specified for compensation	Not applicable
XII. Vaccines containing live, oral, rhesus-based rotavirus	A. Intussusception	0–30 days
	B. Any acute complication or sequel (including death) of the above event	Not applicable
XIII. Pneumococcal conjugate vaccines	No condition specified for compensation	Not applicable
XIV. Any new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children, after publication of a notice of coverage by the Secretary of the HHS	No condition specified for compensation	Not applicable

Although it has a safety record based on clinical trials carried out in the 1950s and 1960s and on the experience of over 30 years of use by thousands of military personnel, woolworkers, and veterinarians (43,44), the debate over its safety has come to the forefront in recent years, including the hypothesis of an alleged link between anthrax vaccine and disease reported by military personnel after the 1991 Gulf War. As a result of this concern, Congress ordered an in-depth investigation into the safety of the anthrax vaccine. The IOM was asked to initiate a comprehensive study and to report on the safety and efficacy of the vaccine in an effort to answer the questions raised by Congress, the Department of Defense, and the public. Because of immediate concerns over anthrax vaccine safety issues, the IOM provided on 30 March 2000 a letter report to the Department of

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Table 8 A comparison of the estimated risks of adverse reactions after DTP immunization with the complication rates of natural whooping cough

Adverse reaction	Whooping cough complication rates per 100 000 cases	DTP vaccine adverse reaction rates per 100 000 immunizations
Permanent brain damage	600–2000 (0.6–2.0%)	0.2–0.6
Death	100–400 (0.1–4.0%)	0.2
Encephalopathy/ encephalitis*	90–4000 (0.09–4.0%)	0.1–3.0
Convulsions	600–8000 (0.6–8.0%)	0.3–90
Shock		0.5–30

*Including seizures, focal neurological signs, coma, and Reye's syndrome

Defense, summarizing the Institute's literature review on the safety of anthrax vaccine, prepared by its Committee on Health Effects Associated with Exposures during the Gulf War (45). The committee evaluated primary peer-reviewed literature and did not draw conclusions from secondary literature. It considered that there have been only a few published peer-reviewed studies of the safety of the anthrax vaccine in humans, and only one published series of studies discussed the long-term follow-up of individuals who received multiple vaccines including the anthrax vaccine. The committee concluded that (a) published studies have reported no significant adverse effects of the vaccine, but the literature is limited to a few short-term studies and (b) in peer-reviewed publications there is inadequate/insufficient evidence to determine whether there is or is not an association between anthrax immunization and long-term adverse health outcomes. The committee considered the findings and conclusions as an early step in the complex process of understanding the vaccine's safety, which began with its licensure in 1970 and includes the 1985 FDA advisory panel's finding that categorized the anthrax vaccine as safe and effective. The committee included in its evaluation the results of the VAERS, and considered the VAERS data as being useful as a sentinel for adverse events but of limited value for assessing the rate of causality of adverse events. The VAERS data are as follows:

(a) From 1 January 1990 to 31 August 2000, 1544 adverse events after anthrax immunization (nearly 2 million doses administered) were reported to VAERS.
(b) The most frequently reported adverse events were local reactions (864 reports).
(c) Other reports included headache (239 reports), arthralgia (232 reports), weakness (215 reports), pruritus (212 reports), and a few other systemic reactions.
(d) There were 76 (5%) serious adverse events (death or life-threatening disease, hospitalization, permanent disability); based on autopsy results, one of two reported deaths was due to aplastic anemia and the other was due to coronary arteritis (46).

- A 34-year-old man reported mild tenderness at the injection site after the first dose of anthrax vaccine; after the second dose he felt sweaty and weak and was pale; 20 hours after the third dose he had a life-threatening anaphylactic reaction (dyspnea, sweating, pallor, and urticarial wheals on the face, arms, and torso). After intensive care measures all his symptoms and signs resolved (47).

In 1997 manufacturers in South Korea started to develop a new anthrax vaccine. However, it will take a few years more to put the vaccine to practical use (42).

Botulism

Worldwide, sporadic cases and limited outbreaks of botulism can occur when food and food products are prepared or preserved by improper methods that do not destroy the spores of *Clostridium botulinum* and permit the formation of botulinum toxin. In industrially developed countries, the case fatality rate of food-borne botulism is 5–10%. Person-to-person transmission of botulism is not known. Botulinum toxin is the most poisonous substance known and poses a major bioweapon threat. In addition to the clinical forms of natural botulism (food-borne, wound, and intestinal), there is a fourth, man-made form of inhalational botulism that results from aerosolized botulinum toxin.

A pentavalent botulinum toxoid (botulinum toxin in different antigenic types) has been used for more than 30 years in some countries to prevent the disease in laboratory workers and to protect troops against attack. Pre-exposure immunization for the general population is neither feasible nor desirable; the vaccine is ineffective for postexposure prophylaxis. Treatment of botulism consists of passive immunization and supportive care. Most licensed antitoxins contain antibodies against the most common toxin types A, B, and E. About 9% of recipients of equine antitoxin developed urticaria, serum sickness, or other hypersensitivity reactions. In 2% of recipients anaphylaxis occurred within 10 minutes of antitoxin

Table 9 A comparison of the estimated risks of adverse reactions after measles immunization with the complication rates of natural measles

Adverse reaction	Measles complication rates per 100 000 cases	Adverse reaction rates per 100 000 vaccines	Background illness rate per 100 000
Encephalopathy/encephalitis	50–400 (0.05–0.4%)	0.1	0.1–0.3
Subacute sclerosing panencephalitis	500–2000 (0.5–2.0%)	0.05–0.1	—
Pneumonia	3800–7300 (3.8–7.3%)	—	—
Convulsions	500–1000 (0.5–1.0%)	0.02–190	30
Death	10–10 000 (0.01–10%)	0.02–0.3	—

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administration. Before administering antitoxin the patient should be screened for hypersensitivity (48).

Plague

The large plague pandemics (the Justinian plague in the 6th century and pandemics in the 14th–15th centuries and 19th century) killed millions of people worldwide and were feared as the Black Death, a term that was actually not introduced until Victorian times. There is evidence that all three plagues were caused by the same variant of the plague bacterium, *Yersinia pestis*, var Orientalis (49). Progress in hygiene, public health, and antibiotic therapy make future pandemics improbable.

Wild rodent plague still exists in many parts of the world, including areas of Africa, Latin America, Asia, South-Eastern Europe, and the Western half of the USA. Domestic pets, for example house cats and dogs, can bring infected wild rodent fleas into homes, and the bite of infected fleas can result in human disease. Bubonic, pulmonary, and septicemic plague are life-threatening diseases with very high case fatality rates in untreated patients and in patients in whom treatment is delayed. Pneumonic plague is highly communicable, particularly in overcrowded facilities.

The potential use of *Y. pestis*, the causative agent of plague, as a biological weapon is of great concern. A killed whole bacillus plague vaccine (limited data on reactogenicity; see SED-14, 1086) is no longer available in the USA. This killed vaccine was efficacious in preventing or ameliorating bubonic plague but was ineffective against primary pneumonic plague. A live plague vaccine is manufactured in Russia, but no data on its efficacy and safety are available. Recommendations for antibiotic therapy of plague are available (50).

Smallpox

The last natural case of smallpox occurred in 1977 in Somalia. Because of the success of worldwide coordinated efforts, particularly the use of smallpox vaccine, natural smallpox has been eradicated. In 1989, the WHO declared the global eradication of this dangerous and often deadly disease (the case fatality rate in non-immunized patients was 20–40%). During natural smallpox outbreaks the secondary attack rate in non-immunized contacts was about 50%.

The smallpox virus belongs to the limited number of organisms that could be used as a biological weapon, causing one of the most serious diseases. There is no causal treatment of smallpox available. Immunization is the most effective measure for pre-exposure prevention and postexposure infection control. However, there were severe complications associated with the use of the old vaccines: encephalitis (mainly in primary vaccines; sometimes fatal or causing permanent neurological sequelae), progressive vaccinia (in both primary and secondary vaccinees), eczema vaccinatum (in vaccinees with either active or healed eczema), and generalized vaccinia resulting from viremia.

With the global eradication of smallpox, smallpox immunization was stopped in all countries of the world, and complications of smallpox vaccination became largely of historical interest. However, recently, the threat of bioterrorism has made it necessary again to consider immunization strategies and the potential hazards of immunization. The old vaccine used for prevention of smallpox contained vaccinia virus strains grown on scarified calves. Some countries and manufacturers have retained limited stocks of vaccine, and the WHO has 500 000 doses. However, there is no reserve large enough to meet more than very limited potential emergency needs (51). Strategies for smallpox immunization in emergencies have been elaborated, focusing on priority immunization of individuals at greatest risk and immunization to contain outbreaks (52). However, the old smallpox vaccine hardly meets modern safety requirements. Therefore, the development and licensure of a modern tissue cell culture vaccine and the establishment of new vaccine production facilities is necessary. Various manufacturers have initiated such developments. A British biotechnology company announced its intention to begin clinical trials on immunogenicity and reactogenicity of a newly developed tissue culture smallpox vaccine in early 2002 (53).

Tularemia

Tularemia is a zoonotic bacterial disease that occurs in North America, China, Japan, parts of Europe, and parts of the former USSR. Various wild animals are the reservoir of the causative agent, *Francisella tularensis*, which is transmitted through the bite of arthropods, including ticks and mosquitoes, by eating insufficiently cooked meat, by drinking contaminated water, or by inhalation of dust from a contaminated environment. Clinically, an ulceroglandular type can be distinguished from an oropharyngeal type; inhalation of infectious material can be followed by pneumonia or septicemia, with a 30–60% case fatality rate in untreated patients. Person-to-person transmission of tularemia is not known.

Francisella tularensis is considered to be a dangerous potential biological weapon. Live tularemia vaccines have been developed and used in the USSR (to protect millions of persons in endemic areas) and the USA (as an investigational vaccine to protect laboratory workers). After the administration of the US vaccine, symptoms of ulceroglandular disease were considered milder; however, the vaccine did not protect all recipients against aerosol challenge with *F. tularensis*. The live vaccine is currently under review by the US Food and Drug Administration (FDA), and its future availability is undetermined. Taking into account the short incubation period of tularemia and incomplete protection through immunization with the current live vaccine, post-exposure immunization is not recommended. Treatment with antibiotics is recommended (54).

General adverse effects after immunization

The reports of the Institute of Medicine, National Academy of Sciences, Washington (on adverse events after pertussis and rubella immunization (SED-12, 817) (SED-12, 825) and on adverse events after immunization against tetanus, diphtheria, measles, mumps, poliomyelitis, *H. influenzae* type b, and hepatitis B (SEDA-18, 325) have provided useful reviews (13,14). The 1996 "Update on vaccine side effects, adverse reactions, contraindications,

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and precautions" elaborated and published by the US Advisory Committee on Immunization Practices includes summarized conclusions of evidence for possible associations between specific adverse effects and childhood vaccines (Table 10 and Table 11). The conclusions are based on the reports of the IOM mentioned above (55). The respective chapters of "Vaccines" (56) also provide useful information on adverse effects and immunization risks.

General risks of multiple immunizations

Some parents, particularly in industrialized countries, believe that infants get more vaccines than are good for them, and they fear that too many immunizations could overwhelm the infant's immune system. However, the actual number of antigens that children receive in the USA (the schedule includes 11 vaccines) or in some Western European countries (on average 9 vaccines) has declined when compared with immunization programs used during the 1960s or 1980s. Whereas smallpox vaccine contained about 200 proteins, the current routinely recommended vaccines for children in countries in which whole-cell pertussis vaccine was replaced by acellular pertussis vaccine (for example Austria, Germany, Japan, the Scandinavian countries, the USA) contain a total of 50–125 proteins and polysaccharides. The replacement of whole-cell pertussis vaccine by acellular pertussis vaccine reduced the content of immunogenic proteins and polysaccharides from about 3000 to a range of 2-5. (Table 12) (57).

If vaccines overwhelmed the immune system, smaller immune responses would be expected. However, the authors of many carefully designed studies have concluded that there is no evidence that adding vaccines to combination products increases the burden on the immune system. Young infants have a large capacity to respond to multiple vaccines, as well as to many other environmental challenges. Increased reactogenicity after the receipt of combination vaccines has not been a major issue. Combining antigens usually does not increase the risk of adverse effects, and can actually lead to an overall reduction in the numbers of adverse events (58) despite public concern (59).

The Safety Review Committee of the IOM has reviewed the evidence regarding multiple immunizations and immune dysfunction (60). The review did not support the hypothesis that an infant's immune system is inherently incapable of handling the number of antigens to which children in the USA are exposed during routine immunizations. The committee rejected a causal relation between multiple immunizations and increased risks of infections or type 1 diabetes mellitus. The evidence was inadequate to accept or reject a causal relation between multiple immunizations and allergic disease, particularly asthma.

Organs and Systems

Respiratory

There is a hypothesis that the seeds of immune system problems, perhaps including asthma, may be sown in the early weeks of life and activated later by immunization. However, studies have given inconsistent results. A randomized controlled trial showed no effect of pertussis vaccine on the risk of asthma (61), which was suggested by a cohort study (62). A British cohort study also showed no association between immunization and wheeze, but there was a lower risk of eczema (63). Data from the Christchurch Health and Development Study showed a link between immunization and asthma (64). However, the findings were based on only 23 children who had not received DTP or polio vaccine. There was no effect from measles vaccine. This is somewhat in contrast to data from Africa suggesting that measles may protect against asthma (SEDA-21, 323).

Nervous system

Guillain–Barré syndrome

Many drugs and vaccines are associated with Guillain–Barré syndrome. However, a cause-and-effect relation has generally not been established. The issue has been reviewed (SEDA-21, 323).

Haemophilus influenzae

Guillain–Barré syndrome has occasionally been reported after immunization with a conjugate vaccine against *H. influenzae* type b. In one case there were immunoglobulin antibodies against the *H. influenzae* type b polysaccharide (PRP) component of the vaccine, with a high titer of anti-PRP IgM antibody (65).

Hepatitis

Guillain–Barré syndrome has been reported after the administration of plasma-derived hepatitis B vaccines. In the 3 years between 1 June 1982 and 31 May 1985, an estimated 850 000 people received a new plasma-derived hepatitis B vaccine (Heptavax-B, Merck Sharp and Dohme) and there were 41 reports of the following neurological adverse events: Bell's palsy ($n = 10$), Guillain–Barré syndrome ($n = 9$), convulsions ($n = 5$), lumbar radiculopathy ($n = 5$), optic neuritis ($n = 5$), transverse myelitis ($n = 4$), and brachial plexus neuropathy ($n = 3$) (66). Half occurred after the first of three doses. There were no deaths.

Guillain–Barré syndrome has also occasionally been reported after the administration of recombinant hepatitis B vaccines (67,68).

Influenza

Following the swine-flu immunization campaign in 1976/77 in the USA there was a significant increase in the incidence of Guillain–Barré syndrome in immunized versus non-immunized people, from 2.6 per million to 13.3 per million (69). Peak time of onset was 2–3 weeks after receiving the vaccine, and cases among vaccinees were less likely to have a history of antecedent infection than were cases in unvaccinated persons. Since 1977 the risk of influenza vaccine–induced syndrome appears to be the same as the risk in the non-immunized population.

Measles–mumps–rubella

Guillain–Barré syndrome has been reported to be associated with measles, mumps, and rubella immunization (70).

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Table10 Evidence for possible associations between specific adverse effects and childhood vaccines

Evidence	DT/Td/tetanus toxoid	Measles vaccine	Mumps vaccine	OPV/IPV	Hepatitis B vaccine	*Hemophilus influenzae* type b (Hib) vaccine
None available to establish a causal relation	None	None	Neuropathy Residual seizure disorder	Transverse myelitis (IPV) Thrombocytopenia (IPV)	None	None
Inadequate to accept or reject a causal relation	Residual seizure disorder other than infantile spasms Demyelinating diseases of the central nervous system Mononeuropathy Arthritis Erythema multiforme	Encephalopathy Subacute sclerosing panencephalitis Residual seizure disorder Sensorineural deafness (MMR) Optic neuritis Transverse myelitis Guillain–Barré syndrome Thrombocytopenia Insulin-dependent diabetes mellitus	Encephalopathy Aseptic meningitis Sensorineural deafness (MMR) Insulin-dependent diabetes mellitus Sterility Thrombocytopenia Anaphylaxis	Transverse myelitis (OPV) Guillain–Barré syndrome (IPV) Death from SIDS	Guillain–Barré syndrome Demyelinating diseases of the central nervous system Arthritis Death from SIDS	Guillain–Barré syndrome Transverse myelitis Thrombocytopenia Anaphylaxis Death from SIDS
Favored rejection of a causal relation	Encephalopathy Infantile spasms (DT only) Death from SIDS (DT only)	None	None	None	None	Early-onset Hib disease (conjugate vaccines)
Favored acceptance of a causal relation	Guillain–Barré syndrome Brachial neuritis	Anaphylaxis	None	Guillain–Barré syndrome (OPV)	None	Early-onset Hib disease in children aged 18 months whose first Hib vaccination was with unconjugated PRP vaccine
Established a causal relation	Anaphylaxis	Thrombocytopenia (MMR) Anaphylaxis (MMR) Death from measles infection	None	Poliomyelitis in recipient or contact (OPV) Death from polio infection	Anaphylaxis	None

See the original paper for extensive notes to this table.
OPV—oral poliovirus vaccine
IPV—inactivated poliovirus vaccine
DT—diphtheria and tetanus toxoids for pediatric use
Td—diphtheria and tetanus toxoids for adult use
SIDS—sudden infant death syndrome

Table 11 Evidence for possible associations between specific adverse effects and childhood vaccines (DTP and MMR)

Evidence	Adverse effect	DTP vaccine-RA 27/3 MMR
Strong evidence against a causal relation	Autism	None
Inadequate to accept or reject a causal relation	Aseptic meningitis	Radiculoneuritis and other neuropathies
	Chronic neurological damage	Thrombocytopenic purpura
	Erythema multiforme or other rash	
	Guillain–Barré syndrome	
	Hemolytic anemia	
	Type 1 diabetes	
	Learning disabilities and attention-deficit disorder	
	Peripheral mononeuropathy	
	Thrombocytopenia	
Favored rejection of a causal relation	Infantile spasms	None
	Hypsarrhythmia	
	Reye's syndrome	
	Sudden infant death syndrome	
Favored acceptance of a causal relation	Acute encephalopathy	Chronic arthritis
	Shock and unusual shock-like state	
Causal relation established	Anaphylaxis	Acute arthritis
	Protracted inconsolable crying	

DTP—diphtheria toxoid, tetanus toxoid, and pertussis vaccine
MMR—measles, mumps, and rubella vaccine

Table 12 Number of immunogenic pathogens/polysaccharides in vaccines over the past 100 years

	1900		1960s		1980s		2000	
	Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins/ polysaccharides
	Smallpox	~200	Smallpox	~200	Diphtheria	1	Diphtheria	1
	—	—	Diphtheria	1	Tetanus	1	Tetanus	1
	—	—	Tetanus	1	WC-pertussis	~3000	AC-pertussis	2–5
	—	—	WC-pertussis	~3000	Poliomyelitis	15	Poliomyelitis	15
	—	—	Poliomyelitis	15	Measles	10	Measles	10
	—	—	—	—	Mumps	9	Mumps	9
	—	—	—	—	Rubella	5	Rubella	5
	—	—	—	—	—	—	H. influenzae	2
	—	—	—	—	—	—	Hepatitis B	1
	—	—	—	—	—	—	Varicella*	69
	—	—	—	—	—	—	Pneumococcus*	8
Total			200		3200		3040	46–49 (Germany) 123–126 (USA)

Polio

Following a mass immunization campaign against poliomyelitis in Finland (1984/85), an analysis based on hospital records covering a population of 1.17 million and 6 years showed a significantly increased incidence of Guillain–Barré syndrome coinciding with the campaign (71).

In a retrospective analysis of the incidence of Guillain–Barré syndrome in Finland in 1981–86 by examination of medical records identified from the nationwide Hospital Discharge Register, based on a population of 5 million people, 247 patients fulfilled the accepted criteria of Guillain–Barré syndrome corresponding to a mean annual incidence of 0.82 per 100 000 (72). Monthly rates showed an increased incidence of Guillain–Barré syndrome in March 1985, a few weeks after the start of the nationwide oral poliovirus vaccine campaign and partly overlapping it. However, the increase had begun just before the onset of the campaign and may have been due to wild-type 3 poliovirus in the population immediately before the campaign and could have been due to that rather than the administration of the oral poliovirus vaccine.

Rabies

Guillain–Barré syndrome was a well-known complication in the era of brain tissue rabies vaccines, and there have

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been a few cases associated with the use of human diploid cell rabies vaccines (73,74).

Tetanus and diphtheria
Tetanus and diphtheria toxoid vaccines are reportedly associated with polyradiculitis, polyneuritis, and mononeuritis (75–77).

Immunization and multiple sclerosis (encephalitis disseminata)
The possible relation between immunization and an attack of encephalitis disseminata has been investigated in an analysis of 16 confirmed cases and 24 suspected cases in connection with the distribution of approximately 100 million doses of vaccines manufactured by Behringwerke (1980–89) (78). The data did not support an increased risk of initial manifestation of encephalitis disseminata or of renewed attacks in patients with preexisting disease.

Studies of the role of influenza or influenza immunization in multiple sclerosis have been reviewed by Jeffery (79). He considers that in patients with multiple sclerosis and advanced disability influenza can constitute a life-threatening illness. Even in patients who have minimal disability, severe influenza can be followed by secondary bacterial infection. The risk of relapse after influenza may be as high as 33%, whereas the risk of relapse after influenza immunization appears to be negligible. The only exception to the general rule that influenza immunization is beneficial for patients with multiple sclerosis is in patients with rapidly evolving neurological deficits due to active disease, in whom immunization should be withheld pending treatment with high-dose glucocorticoids to suppress inflammation or stabilization through immunomodulatory treatment. In the absence of active disease, Jeffery strongly recommends influenza immunization for patients with multiple sclerosis. Regarding hepatitis B immunization and multiple sclerosis, Jeffery recommends hepatitis B immunization only for patients with multiple sclerosis at high risk of hepatitis B infection. If a high-risk patient has active multiple sclerosis, immunization should be withheld until the disease activity has been adequately treated. With regard to other immunizations, Jeffery has made similar recommendations: immunization should be postponed if a patient with multiple sclerosis shows disease activity.

Musculoskeletal

A child with fibrodysplasia ossificans progressiva developed permanent heterotopic ossification at the injection site after intramuscular DTP immunization (80). The authors considered that intramuscular injections in children with fibrodysplasia ossificans progressiva were potentially risky, but that subcutaneous injections could be carried out.

Immunologic

The questions of whether early childhood immunization affects the development of atopy and whether it causes allergic reactions have been reviewed (81). The authors concluded that immunization programs do not explain the increasing incidence of allergic diseases, but that individual children may uncommonly develop an allergic reaction to a vaccine.

Non-sterile injection equipment can transmit HIV and other infectious agents, including hepatitis viruses. There is also a possibility of needle transmission from an HIV-infected person to a vaccinator. Data from the USA show that the risk of transmission of HIV through needle stick is very low, perhaps 20 times lower than in the case of hepatitis B, and in the order of one per 100 accidents. Furthermore, the types of injections given during immunization sessions do not as a rule cause bleeding. The risk of transmission is thus extremely low. No instances of immunization-related spread of HIV to other infants have been reported, and if proper sterilization of needles and syringes is performed and vaccines are administered correctly the risk of HIV transmission is zero (82). However, the use of unsterilized or improperly sterilized needles and syringes is common, particularly in many developing countries, and contributes largely to the spread of hepatitis B and C, as well to the spread of human immunodeficiency virus and other blood-borne pathogens. These risks are recognized by the WHO as major public health problems and led the Organization to initiate a broad program of activities to ensure safe injection techniques (1). The guidelines published by WHO and UNICEF in 1986/87 (83,84), which can be set out briefly as follows, are still valid. Essentially they state that:

(a) a single sterile needle and a single sterile syringe should be used with each injection;
(b) reusable needles and syringes are recommended for use in developing countries; they should be steam-sterilized between uses; boiling is an acceptable alternative procedure when steam sterilization is not available;
(c) disposable needles and syringes should only be used if an assurance can be obtained that they will be destroyed after a single use;
(d) disease transmission by use of jet injectors is theoretically possible and has been demonstrated in human beings in a single situation (SEDA-11, 296); until further studies clarify the risks of disease transmission with different types of injectors, their use should be restricted to special circumstances in which large numbers of persons need to be immunized within a short period of time.

Jet-gun-associated infections
The first outbreak of a disease in which a jet injector was implicated as the vehicle of transmission has been reported. Thirty-one attendees at a weight-reduction clinic in Southern California experienced hepatitis B after daily parenteral injections of human chorionic gonadotrophin given by jet injectors; transmission appeared to have resulted from the multiple repeated jet injections (85). WHO and UNICEF have stated in their "Guidelines for selecting injection equipment for the Expanded Program on Immunization" that the use of jet injectors should be restricted to circumstances in which reusable or disposable equipment is not feasible because of the large number of persons to be immunized within a short period of time (83).

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A new type of needleless jet-injector (Mini-Imojet) administers liquid vaccines from a single-use, prefilled cartridge ("imule"), thereby avoiding the risk of cross-contamination. Administration of various vaccines by jet-injector has been compared with standard syringe technique. All the jet-administered vaccines were of equivalent or superior immunogenicity. The most common reactions were mild (minor bleeding, superficial papules, erythema, induration). The technical and safety advantages of the Mini-Imojet reinforce the potential use of this technique for mass immunization (86).

Mixed bacterial vaccines

Starting in the 1920s, very many different mixed bacterial vaccine products (including inactivated bacteria such as *Staphylococcus aureus*, *Streptococcus* species, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *H. influenzae*) were marketed worldwide. Currently, there are still several products available in European countries, and one product in the USA. Most vaccines have been used for treatment of recurrent and chronic infections of the respiratory tract. The efficacy of these products is doubtful. Delayed hypersensitivity to bacterial products is common. Delayed reactions, sometimes associated with vague malaise or myalgia, can occur after the administration of maintenance doses for months. If delayed skin reactions are accompanied by any systemic symptoms, administration of the mixed vaccine should be drastically reduced or stopped (87).

Immunization and autoimmune disease

Autoimmunity is characterized by the development of one or several immune responses, directed against antigenic components of the host. The detection of antibodies against host antigens (autoantibodies) or autoreactive T cells does not indicate current or future disease, and autoimmunity does not always result in autoimmune disease. An autoimmune disease results from autoimmunity when autoantibodies or autoreactive T cells reach the corresponding antigen in a target organ and become pathogenic, or when autoantibodies form pathogenic immune complexes with antigens released from host cells. An autoimmune disease can be clinically silent for months or years before the destruction of the tissues involved leads to clinical symptoms, for example the appearance of type 1 diabetes following the autoimmune destruction of pancreatic islets.

As many as 5% of individuals in Europe and North America have some form of autoimmune disease. There is clear evidence that genetic predisposition is necessary for the development of some autoimmune diseases. In genetically predisposed individuals an infection can induce or trigger an autoimmune disease. Of the many potential environmental factors, infections are the most likely cause. The causal linkage between some infections and autoimmune diseases has raised the question as to whether autoimmune diseases might also be triggered by vaccines (88).

Autoimmune diseases include autoimmune thrombocytopenia, Graves' disease, hemolytic anemia, Hashimoto's thyroiditis, insulin-dependent diabetes mellitus (diabetes type 1), multiple sclerosis, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and Reiter's syndrome (88–90).

The number of publications that include claims and counterclaims about the risk of autoimmune diseases after immunization is increasing. However, only in rare instances has evidence established a causal relation or favored acceptance of a causal relation:

(a) Rabies vaccine produced in rabbit nervous tissue caused acute disseminated encephalomyelitis in some immunized individuals (91).
(b) During the US swine flu immunization campaign (1976–77) immunized individuals had a much higher risk of Guillain–Barré syndrome than non-immunized individuals (relative risk 7.60); currently, the risk of Guillain–Barré syndrome after immunization (one additional case per million people immunized) is estimated to be substantially lower than the risk of severe influenza and its complications (92).
(c) Idiopathic thrombocytopenia can occur after MMR immunization (about one case in 30 000 immunized children); however, the risks of thrombocytopenia after natural measles or rubella are respectively five and 10 times higher (88,93).

For other potential association between vaccines and autoimmune diseases, the evidence favors rejection of a causal relation:

(a) hepatitis B vaccine and multiple sclerosis (SEDA-24, 374) (SEDA-25, 386);
(b) vaccines and diabetes mellitus (94,95);
(c) Lyme disease vaccine and a treatment-resistant form of autoimmune arthritis; however, owing to public misperception and the promotion of false concerns about its safety, the demand for Lyme disease vaccine did not reach a sustainable level and the manufacturer withdrew it (SEDA-24, 366) (SEDA-26, 357).

How to assess a potential link between a vaccine and an autoimmune condition

Careful epidemiological studies should be the basis of conclusions about an association between a specific vaccine and a particular autoimmune disease. Wraith and colleagues took into account WHO recommendations for the assessment of adverse events after immunization and established the following four basic principles that apply to autoimmune diseases:

1. consistency of findings in various studies;
2. strength (in an epidemiological sense);
3. specificity;
4. temporal relation (95).

Death

Sudden infant death syndrome and multiple immunizations

Current recommendations call for infants and very young children to receive multiple doses of vaccines during their first year of life, and since SIDS is the most frequent cause of death in highly developed countries during that early period of life, it is important to take into account concerns

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that multiple immunization might play a role in SIDS. SIDS is the diagnosis most commonly used to explain unexpected sudden death of uncertain cause occurring mainly in infancy at 2–7 months of life, sometimes later. By definition, the cause or causes of SIDS are unknown, but risk factors (for example maternal characteristics, prenatal factors, and postnatal conditions, including the infant's sleeping position) have been identified. The results of the most comprehensive analysis "Vaccinations and sudden unexpected death in infancy" have been provided by the Immunization Safety Review Committee of the IOM (96). The committee reviewed an extensive collection of material, primarily from published peer-reviewed scientific and medical literature. The causality conclusions of the committee were as follows:

(a) The evidence favors rejection of a causal relation between exposure to multiple vaccines and SIDS.
(b) The evidence favors acceptance of a causal relation between diphtheria toxoid and whole cell pertussis vaccine and death due to anaphylaxis in infants; however, anaphylaxis of infants following vaccination is very rare, and a fatal outcome is extremely rare.
(c) The committee has not recommended a policy review of the recommended (US) childhood immunization schedule on the basis of concerns about SIDS.

The committee also noted that there are studies that show that vaccinated infants are at a reduced risk of SIDS (96,97).

Susceptibility Factors

It is well known that immune deficiency can play a distinct role in the development of adverse effects after immunization, particularly in connection with the administration of live virus vaccines. The first such experience was with smallpox vaccine; people with immune defects had a markedly increased risk of complications, for example generalized vaccinia. Disseminated BCG infection is usually associated with severe abnormalities of cellular immunity. The risk of vaccine-associated poliomyelitis is increased in immunodeficient children. There have been several reports of adverse events or death after measles immunization in immunodeficient children. Based on these experiences, there is a general consensus that live vaccines should not be given to people with immune deficiency diseases or to those whose immune response is suppressed because of leukemia, lymphoma, generalized malignancy, or therapy with glucocorticoids, alkylating agents, antimetabolites, or radiation (SEDA-12, 268).

Various studies in both symptomatic and asymptomatic HIV-infected individuals have failed to show any special sensitivity to adverse effects after other immunizations, for example in children receiving live oral or inactivated polio vaccine, DPT or DT vaccine, or measles vaccine (98–101).

Recommendations by the US ACIP, WHO's Global Programme on Immunization, and the European Advisory Group on Expanded Program on Immunization have all been published in detail (SEDA-12, 270) (SEDA-13, 273). Based on the recommendations elaborated by WHO and ACIP, similar recommendations have been prepared in other countries. WHO recommends that non-immunized individuals with symptomatic HIV infection should not receive BCG, but should receive the other vaccines; whereas ACIP recommends that children with symptomatic HIV infection should not receive live virus or live bacterial vaccines. Taking into account the hazard of measles in children with AIDS and HIV-infection, ACIP additionally recommends measles vaccine for all (both symptomatic and asymptomatic) HIV-infected children.

Drug Administration

Drug additives

Thiomersal

Thiomersal (see the monograph on Mercury and mercurial salts) has been used as an additive to biologics and vaccinessince the 1930s because it is very effective in killing bacteria used in several vaccines and in preventing bacterial contamination, particularly in opened multidose containers. Some but not all vaccines contain thiomersal. Billions of children and adults have been immunized worldwide and there is no scientific data that thiomersal-containing products have caused problems of toxicity in humans. The main causes of concern with thiomersal are allergic reactions and the potential risk of neurotoxicity. The WHO has recommended a Permissible Total Weekly Intake (PTWI) of 200 μg for non-pregnant adults. Owing to the vulnerability of the developing brain, the PTWI for pregnant women and infants should be lower, but there is currently no international recommendation for maximum intake in infants. Considering the thiomersal content of some vaccines, intake of mercury in infants can exceed that which could be considered safe. The US Public Health Service, the American Academy of Pediatrics, and US vaccine manufacturers are in agreement that thiomersal should be eliminated from vaccine manufacture as soon as possible. Similar conclusions were reached in 1999 in a meeting attended by the European vaccine manufacturers, European regulatory agencies, and the FDA. Already, many new vaccines are thiomersal-free and the manufacturers are committed to the target of reducing as much as possible the thiomersal content in all vaccines. However, given that the known risks of not immunizing children far outweigh the unknown and much smaller risk of thiomersal, clinicians and parents are encouraged to continue immunizing all infants with the currently available vaccines despite their thiomersal content (102).

Questions and answers on thiomersal have been provided by the WHO, which has underlined the fact that the risk of adverse effects of thiomersal is theoretical, uncertain, and at most extremely small (103). However, the WHO aims to replace thiomersal with other preservatives in the long term. Combination vaccines can reduce the amount of mercury to an absolute minimum.

In 2001 the Immunization Safety Review Committee of the Institute of Medicine issued a report on thiomersal-containing vaccines and neurodevelopmental disorders (104). "The committee concluded that although the hypothesis that exposure to thiomersal-containing

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vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children, the hypothesis is biologically plausible. . . . [However,] the evidence is inadequate to accept or reject a causal relationship between thiomersal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit/hyperactivity disorder, and speech or language delay." Hypersensitivity to thiomersal is a contraindication to immunization (105).

Vaccine adjuvants

A vaccine adjuvant is defined as an agent that increases specific immune responses to an antigen (106). The only vaccine adjuvants currently licensed by the FDA are aluminum salts. All other adjuvants are considered experimental and must undergo special preclinical testing. Real and theoretical risks of vaccine adjuvants comprise various local acute or chronic inflammation with formation of abscesses and nodules; induction of hypersensitivity to the host's own tissues, producing autoimmune arthritis, amyloidosis, anterior uveitis; cross-reactions with human antigens, such as glomerular basement membranes or neurolemma, causing glomerulonephritis or meningoencephalomyelitis; sensitization to tuberculin or to other skin test antigens; carcinogenesis; pyogenesis; teratogenesis; abortion; and adverse pharmacological effects, such as hypoglycemia.

Drug contamination

Since the problem of bovine spongiform encephalitis (BSE) emerged in Europe around 1987, the WHO and ministries of health have been alert to the danger that BSE-contaminated materials might be used in biological products, including vaccines. Guidelines were created that ensured that when bovine materials were needed in a biological product, the materials were obtained from countries that were free from BSE. Bovine products are used in the production of certain vaccines, in creating seed lots, or in amplifying the seed lot into working lots. The material is generally calf serum, which, even if it came from an infected animal, is extremely unlikely to transmit the prions that cause the disease. An exceptional situation arose on 20 October 2000, when the UK withdrew one manufacturer's OPV because of the possibility that the vaccine had been manufactured using serum from calves that were from a BSE-infected country. Even though the risk was extremely remote, the health authorities decided to have the vaccine withdrawn. This particular product was not the main OPV used in the UK. To clarify the situation in the UK and to reassure countries throughout the world that there were no implications for OPV used in the eradication of poliomyelitis, the WHO issued the following position statement (107): "On 20 October 2000, Evans/Medeva Oral Polio Vaccine (OPV), which to the knowledge of the World Health Organization has only been used in the United Kingdom and Republic of Ireland, was recalled in the UK. This vaccine has never been used in the immunization campaigns that are ongoing as part of the Global Polio Eradication Initiative. The recall was prompted by evidence that the Evans/Medeva vaccine was manufactured in contravention of European Union guidelines, and was not based on any adverse events related to the vaccine. The specific concern is that fetal bovine calf serum (FCS) from the UK was used in the manufacture of the Evans/Medeva vaccine, at a time when there was a risk of bovine spongiform encephalopathy (BSE) in that country. WHO endorses the recall step as a precaution, even though FCS is removed in the manufacturing process of the vaccine and there is no evidence that FCS could transmit BSE. Due to this breach of EU guidelines and acting on a precautionary basis, the Health Departments in the UK have withdrawn remaining shelf stocks of the Evans/Medeva brand of polio vaccine, which had already ceased production. The World Health Organization imposes strict production and quality controls to ensure the safety and efficacy of OPV. WHO recommends that manufacturers use the safest source of materials from countries which have not reported indigenous BSE cases and have a compulsory BSE notification system, compulsory clinical and laboratory verification of suspected cases and a surveillance program. The Global Polio Eradication Initiative only distributes vaccine supplied by vaccine manufacturers who follow National Control Authorities' criteria provided by WHO."

Two advisory committees of the US FDA, the Transmissible Spongiform Encephalopathies Advisory Committee and the Vaccines and Related Biologicals Product Advisory Committee, said at a joint meeting on 3 August 2000 that vaccines made from bovine-derived materials from countries with a known or uncertain risk of BSE carry only an infinitesimal risk of new variant Creutzfeldt–Jakob disease, and that no change in US immunization practice is indicated (Evans G, personal communication, 3 August 2000).

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Vacuum devices

General Information

Vacuum tumescence constriction therapy is the use of an external device that creates a vacuum to cause penile erection, which is then maintained by a constriction band. It produces rigidity sufficient for intercourse in 91% of men, with satisfaction in 80%.

Adverse effects of this procedure have been reported (1): ecchymosis (37%), discomfort (28%), hematoma (10%), numbness (6.9%), penile skin irritation, and edema. Subcutaneous penile hematoma occurred in two patients using anticoagulants and penile gangrene occurred in one patient; all had worn the constriction band overnight (2). The current recommendation is to apply the constriction band for not more than 30 minutes.

- A 55-year-old African–American, tetraplegic after a motor vehicle accident in 1969, had been using an erection aid device for 4–5 years (3). He used the device, but forgot the constricting ring, which remained on overnight. The next morning his penis was markedly swollen and 2 days later he developed septicemia. He had a gangrenous penis and necrotizing fasciitis with a foul smelling discharge.

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Vaginal tampons

General Information

A tampon is a pad made of cotton, cotton wool, sponge, or other materials, used in surgery for the control of hemorrhage or absorption of secretions. Vaginal tampons are widely used to absorb menstrual flow, and have been used to absorb disagreeable secretions in women with inflammatory diseases of the vagina or cervix and to administer drugs locally after operations (1). They have also been used to collect vaginal material for diagnostic purposes (2). Tampons containing miconazole have been used to treat vaginal candidiasis (3).

Toxic shock syndrome

Toxic shock syndrome is generally associated with the use by women of internal vaginal tampons, but does not occur solely in those circumstances. Two large clinical epidemiological studies (4,5) have contributed to an understanding of the conditions that lead to toxic shock syndrome. Of all patients with toxic shock syndrome, 95% were women; in 98% of cases it began during the menstrual period, and in 98% *Staphylococcus aureus* phage group 1 was isolated from the vaginal swab. In no case was the organism isolated from the blood. It is clear that shock was caused not by bacteremia but by an epidermal toxin. Only some 8% of healthy controls harbored *S. aureus* vaginally. The mortality rate of toxic shock syndrome is estimated to be 10–15% (6,7). Since contamination with staphylococci, vaginal and extravaginal, usually occurs without any clinical consequences, special attention has focused on the association with vaginal tampons. A particular brand (Rely) has been withdrawn from the market, but other brands have also been linked with the syndrome.

A number of surviving patients had several recurrences during subsequent menstrual periods (up to five), these events each being progressively less severe in their clinical course (8,9). Insertion of a contraceptive diaphragm can trigger the toxic shock syndrome, even at times other than during menstruation.

Pathogenesis

The pathogenesis of toxic shock syndrome is not well understood. The tampons are not contaminated, and they cannot be regarded as the direct cause of toxic shock syndrome; they are rather a trigger for the events that lead to the syndrome. A plausible explanation is that the toxin produced by *S. aureus* accumulates in the tampon and is absorbed either directly from the vagina or after reflux of menstrual blood through the fallopian tubes into the peritoneal cavity. In support of this, some cases have occurred in women who have left the tampon in situ for a long time (up to 3 days). It is unclear why the incidence of toxic shock syndrome has increased since 1978. Highly absorbent tampons may partly explain this, but that is not the only explanation. The toxic shock syndrome is likely to be the result of the coincidence of staphylococcus in the vagina and conditions favoring their growth or colonization, such as a tampon saturated with menstrual blood.

Incidence and susceptibility factors

The risk of toxic shock syndrome in association with vaginal tampons is small: 10–15 per 100 000 menstruating women per year. Poor hygiene (leaving tampons in situ for several days) is not the only cause; toxic shock syndrome has been described in women changing their tampons regularly. Women who have previously had febrile episodes during menstruation should use tampons with utmost restraint or abandon them in favour of external tampons.

Toxic shock syndrome has also been described in association with use of a vaginal contraceptive sponge; vaginal cultures grew *S. aureus* (10).

Women using contraception, either oral contraceptive pills or topical spermicides, appear to be at lower risk of developing toxic shock syndrome. A study of patients with toxic shock syndrome found only six spermicide users and eight oral contraception users, against 60 not using a contraceptive method (11). It has been suggested that an antibacterial effect of spermicidal ingredients prevents the intravaginal growth of *S. aureus*. The postulated protective action of oral contraceptives has been explained by reduced menstrual flow and duration, and an alteration in cervical mucus.

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Valaciclovir

General Information

Valaciclovir is the L-valyl ester of aciclovir. After oral administration, it is rapidly and extensively converted to aciclovir by first-pass metabolism, resulting in plasma aciclovir concentrations previously only attainable with intravenous administration. Like aciclovir, valaciclovir is generally well tolerated. Compared with oral aciclovir, the systemic availability of aciclovir from oral valaciclovir is markedly improved.

Valaciclovir is highly active against *Herpes simplex* and *Herpes zoster*. It is also effective in suppressing recurrent episodes of genital herpes (1). Prophylactic administration of high doses of valaciclovir to prevent CMV disease was effective in patients with AIDS and in liver transplant recipients (2,3).

Observational studies

In a double-blind comparison of two regimens of valaciclovir 500 mg bd for recurrent genital herpes, a 5-day course ($n = 398$) and a 3-day course ($n = 402$), there were no significant differences in therapeutic outcome or adverse events between the two regimens (4). The most common adverse events were headache (10%), nausea (4%), diarrhea (3%), and fatigue (1.5%).

Comparative studies

The effects of aciclovir and valaciclovir for anogenital herpes have been studied in HIV-infected individuals in two controlled trials (5). In the first study, 1062 patients with CD4+ counts over 100×10^6/l received valaciclovir or aciclovir for 1 year and were assessed monthly. In the second study, 467 patients were treated episodically for at least 5 days with valaciclovir or aciclovir and were assessed daily. Valaciclovir was as effective as aciclovir for suppression and episodic treatment of herpesvirus infections. Hazard ratios for the time to recurrence with valaciclovir 500 mg bd and 1000 mg od compared with aciclovir were 0.73 (95% CI = 0.50, 1.06) and 1.31 (0.94, 1.82). Valaciclovir 1000 mg bd and aciclovir had similar effects on the duration of infective episodes (HR = 0.92; CI = 0.75, 1.14). The most common adverse events, which occurred at similar rates with all regimens, were diarrhea, headache, infections, rashes, nausea, rhinitis, pharyngitis, abdominal pain, fever, depression, and cough.

Placebo-controlled studies

In large, placebo-controlled comparisons of the efficacy of valaciclovir and aciclovir in treating or suppressing recurrent genital *Herpes simplex* infections in immunocompetent people, dosages up to 2 g/day were well tolerated, with safety profiles comparable to aciclovir (1,6). In a comparison of high-dose valaciclovir (8 g/day) with two doses of aciclovir (0.8 and 3.2 g/day) for prophylaxis of cytomegalovirus disease in patients with advanced human immunodeficiency virus infection, intention-to-treat analysis showed a trend toward earlier mortality in those who received valaciclovir. In those who actually received valaciclovir, survival was significantly shorter. In view of the unexplained trend toward earlier mortality, as well as higher frequencies of renal toxicity (see the section on Urinary tract) and premature treatment discontinuation, the authors concluded that the dose of valaciclovir was too high and that better tolerated doses, which maintain a protective effect on cytomegalovirus disease, need to be identified (2).

Organs and Systems

Nervous system

Valaciclovir is a prodrug of aciclovir and can therefore cause similar effects, as two cases of nervous system effects have demonstrated (7).

- A 65-year-old man was given valaciclovir 1 g bd for 36 hours and had reduced concentration and was incoherent. All investigations were normal or negative. He improved rapidly on withdrawal of valaciclovir.
- A 44-year-old man was given valaciclovir 1 g tds for 5 days and developed a fever, disorientation, confusion, ataxia, dysarthria, and photophobia. All investigations were normal or negative. He was given antimicrobial drugs, including aciclovir, but his symptoms did not improve until the aciclovir was withdrawn.

Elderly patients and people with chronic renal insufficiency are most susceptible to the neurotoxic effects of aciclovir: confusion, hallucinations, dizziness, irritability, ataxia, tremor, myoclonus, and seizures. The symptoms usually occur within 3 days of the start of therapy and resolve within 5 days after withdrawal. Plasma aciclovir concentrations do not correlate with symptoms. Lumbar puncture and CT scans of the head are essentially unremarkable. The most common electroencephalographic abnormality is diffuse generalized slowing of brain wave activity.

Psychological, psychiatric

At high doses (8 g/day) hallucinations and confusion were a significant concern (2,3), but similar symptoms have also occurred at lower doses and in patients with renal insufficiency.

- Ocular and auditory hallucinations have been reported in a 60-year-old female patient on CAPD (8).
- A 58-year-old man with chronic renal insufficiency, who was hemodialysed twice a week, was treated with valaciclovir (1 g tds) for *Herpes zoster* (9). Two days

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later he became disoriented, dizzy, dysarthric, and experienced hallucinations. The serum aciclovir concentration was 21 μg/ml. Treatment was discontinued and he was treated with hemodialysis for 6 hours, resulting in marked clinical improvement. The next day his symptoms of dysarthria recurred, but immediately and completely resolved after a second hemodialysis.

Hematologic

In one study, high-dose valaciclovir was associated with an increased risk of a thrombotic microangiopathy-like syndrome, reported as thrombocytopenic purpura or hemolytic-uremic syndrome (2). This syndrome occurred in 14 of 523 patients who received valaciclovir and in only four of 704 patients who received aciclovir after a median of 54 (range 8–84) weeks of treatment. The precise relation to valaciclovir remains unclear, since eight of 14 patients who were treated with valaciclovir had stopped treatment at least 1 week before the onset of the syndrome. In addition, all patients with thrombotic microangiopathy-like syndromes had taken multiple concomitant medications, and most had other intercurrent illnesses, which could have explained the hematological and renal abnormalities. The authors concluded that additional data are required to understand the role of valaciclovir and other medications for thrombotic microangiopathy-like syndromes, which are recognized with increasing frequency in patients with advanced HIV disease.

Gastrointestinal

Nausea, vomiting, and abdominal pain were commonly reported in human volunteers, but only diarrhea was significantly associated with exposure (10).

Urinary tract

Aciclovir is excreted renally. High plasma concentrations of aciclovir can lead to precipitation in renal tubules, causing impaired renal function, which is generally reversible. Since oral valaciclovir can result in plasma aciclovir concentrations comparable to those attained with intravenous dosing, reversible impairment of renal function can also occur after prolonged use of high-dose valaciclovir. Indeed, in a study of high-dose valaciclovir for prevention of cytomegalovirus disease in HIV-infected people, there was an association between treatment with valaciclovir and moderate nephrotoxicity (serum creatinine more than 1.5 times the upper limit of normal; estimated creatinine clearance under 50 ml/minute) (2).

Second-Generation Effects

Fetotoxicity

In a phase I trial, valaciclovir administered in the third trimester of pregnancy was well tolerated (11).

Susceptibility Factors

Renal disease

Adverse effects of valaciclovir, the L-valyl ester of aciclovir, can be associated with increased drug concentrations when the dose is not adjusted for reduced renal function. For example, aseptic meningitis has been associated with valaciclovir in a patient with renal insufficiency (12).

- An 88-year-old man with renal insufficiency took valaciclovir 1000 mg tds. After the first dose, he became disoriented and incontinent. Valaciclovir was withdrawn, but the symptoms continued and progressed to drowsiness and nuchal rigidity. After an extensive work-up, aseptic meningitis was diagnosed.

Given the patient's age and renal dysfunction, it is likely that excessive valaciclovir accumulation was responsible for this presentation.

Drug–Drug Interactions

Cimetidine

In an open, single-dose study of the effects of probenecid and cimetidine on the pharmacokinetics of valaciclovir and its metabolite aciclovir in 12 healthy men, valaciclovir 1 g, valaciclovir plus probenecid 1 g, valaciclovir plus cimetidine 800 mg, and valaciclovir with a combination of probenecid and cimetidine were studied (13). At three subsequent administrations, drug regimens were alternated among groups so that each group received each regimen. Probenecid and cimetidine respectively increased the mean C_{max} of valaciclovir by 23 and 53% and its AUC by 22 and 73%. Probenecid and cimetidine also respectively increased the mean aciclovir C_{max} by 22 and 8% and its AUC by 48 and 27%. The combination had a greater effect than either drug alone. Neither cimetidine nor probenecid affected the absorption of valaciclovir.

Probenecid

In an open, single-dose study of the effects of probenecid and cimetidine on the pharmacokinetics of valaciclovir and its metabolite aciclovir in 12 healthy men, valaciclovir 1 g, valaciclovir plus probenecid 1 g, valaciclovir plus cimetidine 800 mg, and valaciclovir with a combination of probenecid and cimetidine were studied (13). At three subsequent administrations, drug regimens were alternated among groups so that each group received each regimen. Probenecid and cimetidine respectively increased the mean C_{max} of valaciclovir by 23 and 53% and its AUC by 22 and 73%. Probenecid and cimetidine also respectively increased the mean aciclovir C_{max} by 22 and 8% and its AUC by 48 and 27%. The combination had a greater effect than either drug alone. Neither cimetidine nor probenecid affected the absorption of valaciclovir.

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Valerianaceae

See also Herbal medicines

General Information

The family of Valerianaceae contains four genera:

1. *Centranthus* (centranthus)
2. *Plectritis* (seablush)
3. *Valeriana* (valerian)
4. *Valerianella* (cornsalad).

Valeriana species

Valeriana (all-heal, amantilla, heliotrope, valerian), 400–900 mg 30–60 minutes before bedtime, is a traditional herbal sleep remedy (1), but although it has subjective effects on sleep objective sleep measures have been inconsistently affected (2). The roots of members of the *Valeriana* (valerian) species contain valepotriates, which have alkylating properties. Valtrate/isovaltrate and dihydrovaltrate are mutagenic in bacterial test systems in the presence of a metabolic activator, and their degradation products baldrinal (from valtrate) and homobaldrinal (from isovaltrate) are mutagenic even without metabolic activation. These latter compounds also have direct genotoxic effects. As far as is known, decomposition of dihydrovaltrate does not yield baldrinals.

The amounts of valepotriates and baldrinals in valerian extracts depend on the botanical species: root extracts of *Valeriana officinalis* contain up to 0.9% of valepotriates, compared with 2–4% and 5–7% of valepotriates in root extracts of *Valeriana wallichii* and *Valeriana mexicana* respectively.

Another relevant variable is the dosage form: when a herbal tea is prepared by hot extraction from valerian root, up to 60% of the valepotriates remain in the root material and only 0.1% can be recovered from the tea. A freshly prepared tincture contains 11% of the valepotriates originally found in the root material. Storage at room temperature rapidly reduces this to 3.7% after 1 week and 0% after 3 weeks. In view of this rapid degradation, it is not surprising that commercially available tincture samples yield baldrinals.

Valerian-containing tablets and capsules provide up to 1 mg of baldrinals per piece.

Valepotriates are poorly absorbed from the gastrointestinal tract, but 2% is degraded in vivo to baldrinals after oral administration of valtrate/isovaltrate to mice. In other words, a tablet with 50 mg of valepotriates may add 1 mg of baldrinals to the amount of baldrinals, which are already present before ingestion. In contrast to the valepotriates, the degradation product homobaldrinal is absorbed fairly well after oral administration to mice. As much as 71% of the administered dose can be recovered from the urine in the form of baldrinal glucuronide. Since no unchanged homobaldrinal can be demonstrated in body fluids or liver samples after oral administration, the compound appears to undergo substantial first-pass metabolism. As this glucuronidation leads to loss of its mutagenic properties, the primary target organs that are at risk from valepotriates and baldrinals are the

gastrointestinal tract and the liver (3). However, the toxicological significance of all these data is still unclear, since the carcinogenic potential of valerian formulations has not been evaluated.

Adverse effects

Liver

- A 13-year-old child with fulminant seronegative liver failure required liver transplantation (4). A liver biopsy showed non-specific necrosis of more than 90% of hepatocytes. Possible exogenous toxic factors were ruled out and it was thought that the most likely cause of the liver damage was self-medication with Euphytose, a herbal mixture of *V. officinalis*, *Ballota nigra*, *Crataegus oxyacantha*, *Passiflora incarnata*, and *Cola nitida*.

The authors suggested that of these medicinal plants valerian was the most likely to have caused the liver damage. However, it could just as easily have been due to one of the other constituents or some other cause entirely.

Drug withdrawal

Delirium has been attributed to valerian withdrawal (5).

- A 58-year-old man who had regularly taken excessive doses of valerian root extract for many years was given naloxone postoperatively and developed extreme tremulousness and worsening ventilation. His condition deteriorated and he became delirious. He was treated with midazolam, lorazepam, and finally reducing doses of clonazepam and made an uneventful recovery.

The authors suggested that the anxiolytic action of valerian is similar to that of benzodiazepines and that the patient had been suffering from a valerian withdrawal syndrome.

Drug overdose

In one case of overdose with about 20 times the recommended therapeutic dose, there were only mild symptoms, all of which resolved within 24 hours (6).

In 23 patients who took an overdose of "Sleep-Qik" (valerian dry extract 75 mg, mean dose 2.5 g, hyoscine hydrobromide 0.25 mg, and cyproheptadine hydrochloride 2 mg) the main problems were central nervous system depression and anticholinergic poisoning (7). There was no evidence of liver damage, subclinical, acute, or delayed. It is unlikely that valerian contributed to the adverse effects in these cases.

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Valproic acid

See also Antiepileptic drugs

General Information

Valproic acid is available as sodium, magnesium, and calcium salts, as the free acid, and as a coordination compound, valproate semisodium (divalproex sodium), which comprises the sodium salt of valproic acid and free valproic acid in a 1:1 molar ratio. All share the same active principle (valproic acid) and have virtually identical tolerability, although the formulation influences the incidence of gastrointestinal adverse effects. Valpromide (rINN) is a prodrug of valproate, to which it is converted with a half-life of less than 1 hour. Valnoctamide (rINN) is an isomer of valpromide.

The therapeutic uses of valproate in psychiatric conditions have been reviewed (1,2). The major adverse effects in one study of 150 patients were tremor (9.3%), gastrointestinal effects (8.9%), drowsiness (8.6%), hair loss (7.9%), weight gain (6.9%), weakness (6.9%), dizziness (4.1%), thrombocytopenia (2.9%), and headache (2.7%).

General adverse effects

Weight gain, gastrointestinal symptoms, hair loss, and tremor are relatively common adverse effects. Sedation, fatigue, dizziness, headache, ataxia, insomnia, and behavioral problems are less frequent than with other anticonvulsants. Hyperammonemia is relatively common, but it is often asymptomatic. Fatal liver failure has an incidence of up to 1:600 in young infants, but is extremely rare in adults. Uncommon effects include parkinsonism, encephalopathy, pseudoatrophy of the brain, pancreatitis, and disorders of hemostasis (especially thrombocytopenia).

Hypersusceptibility reactions

Hypersusceptibility reactions can affect any organ and system, but are very rare. Lupus-like syndrome has been reported.

Second-generation effects

Valproate can cause fetal malformations, particularly neural tube defects (2–3% risk).

Organs and Systems

Cardiovascular

Very rarely, valproate-induced carnitine deficiency adversely affects cardiac function (see Metabolism in this monograph).

Hypotension has been attributed to valproate (3).

- In an 11-year-old girl who was treated with intravenous valproate (30 mg/kg over 1 hour) for status epilepticus, the blood pressure fell from 130/80 mmHg to 70/55 mmHg after about 40 minutes of infusion. Her seizures stopped, but her blood pressure fluctuated for several hours between 90/60 mmHg and 60/30 mmHg, requiring intravenous fluids and pressor therapy. Endotracheal intubation was also performed and she eventually recovered.

In this case a relatively high dosage of valproate, concurrent *Varicella* infection, and previous use of benzodiazepines may have contributed.

In 775 patients who received intravenous phenytoin, valproate, or placebo, intravenous site reactions occurred in 18% of patients who received valproate (4). Most of the events (70%) occurred in the first intravenous site and all occurred in peripheral administration sites. When patients who received the drug by central line were excluded, the estimated incidence was 21%. There were fewer adverse events when phenytoin was given alone than when it was given together with valproate.

Respiratory

Respiratory failure and truncal weakness occurred in one patient given dosages up to 3200 mg/day, the association being proven by withdrawal and rechallenge (SEDA-18, 68).

Fatal pulmonary hemorrhage occurred during high-dose valproate monotherapy in a 30-year-old woman (5). It was accompanied by a low platelet count (15×10^9/l).

Nervous system

Tremor is seen in 15% of patients taking valproate (6), although its incidence can increase to over 60% at serum drug concentrations in a high range (80–150 μg/ml) (7); it is clinically reminiscent of essential tremor and responds to dosage reduction. Asterixis has been associated with intoxication by most anticonvulsants, but with valproate it can occur at therapeutic drug concentrations (SEDA-12, 133) (8).

Sedation, fatigue, dizziness, headache, ataxia, and insomnia are less frequent with valproate than with other anticonvulsants. However, encephalopathy, sometimes associated with hyperammonemia and/or liver failure, has been described on several occasions, with symptoms ranging from acute confusion to stupor and even deep coma (SEDA-18, 69) (9). The stupor tends to be associated with bilaterally synchronous high-voltage, slow-wave EEG activity. Psychiatric symptoms and increased seizure frequency can also occur. Although in some cases valproate-induced stupor can be associated with increased epileptiform activity, it appeared to be triggered by a cortical non-epileptic mechanism in six patients who developed negative myoclonus and stupor after taking valproate for a few days (SEDA-19, 74).

Rarely valproate causes a parkinsonian-like reaction (SEDA-18, 69) (SEDA-19, 74). Involuntary movements and twitching of the face and limbs have been also reported. Intermittent choreiform movements were observed in two girls and one man, all with pre-existing severe brain damage, after they had taken valproate for 27 years (SEDA-20, 68).

When a 25-year-old woman with a hypothalamic hamartoma was given valproate (up to 2500 mg/day) in addition to phenytoin and phenobarbital, she became increasingly somnolent and spike and wave activity in her electroencephalogram deteriorated to the point when she appeared to be in absence status (10). Her blood ammonia concentration was about three times the upper limit of the reference range. During wakefulness, electroencephalographic paroxysms increased with increasing plasma valproic acid concentrations and resolved (together with mental status changes and hyperammonemia) when valproate was withdrawn. The data are suggestive of a paradoxical effect of valproic acid on spike and wave activity, possibly related to the underlying pathology or hyperammonemia.

A most unusual adverse effect, uncontrollable laughter, was reported in two men aged 17 and 20 years (11). The laughter persisted for 4–6 hours after an intravenous injection of 800 mg valproate over 1 hour.

Valproate rarely causes severe mental deterioration and CT/MRI findings suggestive of cortical atrophy, reversible after withdrawal (SEDA-20, 67). Two possible additional cases have been reported in women with juvenile myoclonic epilepsy aged 22 and 46 years (12). In one case mental function and brain atrophy regressed over a few months after stopping valproate, while in the other cognitive function improved but CT/MRI abnormalities persisted. The authors suggested that valproate-induced pseudoatrophy of the brain may not be always fully reversible, especially when the interval between onset of the condition and diagnosis is prolonged (2 years in this case). However, the possibility exists that the persistent cortical atrophy had other causes in their patient.

Retrospective studies have suggested that anticonvulsants may be associated with peripheral nerve dysfunction. This has been studied prospectively in 81 patients (aged 13–67 years) without polyneuropathy who took sodium valproate ($n = 44$) or carbamazepine ($n = 37$) as monotherapy in standard daily doses (13). After 2 years one patient had clinical signs of polyneuropathy and six patients had symptoms of polyneuropathy, but electrophysiology did not show significant changes or trends. Only one patient had abnormal electrophysiological findings, which were only subclinical, and eight patients had abnormal values at two subsequent visits. There were no consistent patterns, and the data were unaffected when the drugs were examined separately or when patients were grouped according to whether or not they had symptoms of polyneuropathy. The authors concluded that previously untreated young to middle-aged patients who take valproic acid or carbamazepine for 2 years are not at risk of polyneuropathy.

Valproate can cause altered visual evoked potentials and brainstem evoked potentials (14). In 100 epileptic

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patients aged 8–18 years taking valproate in a modified-release formulation, interpeak latencies of I-III and III-V of brainstem evoked potentials were significantly delayed and N75/P100 and P100/N145 amplitudes in the visual evoked potentials were reduced.

Valproate toxicity has been reported to have caused a neurodegenerative condition that mimicked multisystem atrophy in a 67-year-old woman (15).

Valproate can occasionally cause aggravation of absence seizures in children (16). Eight patients with typical and myoclonic absence epilepsy and electroencephalography that showed generalized 3-Hz spike-and-wave had an increase in the frequency of absence seizures within days of valproate introduction. Dosage increments resulted in further aggravation. Serum concentrations of valproate were in the target range in all cases. All the children improved on valproate withdrawal; in five valproate was reintroduced, resulting in further seizure aggravation.

In one report of 36 adults chronically treated with valproate at a veterans' clinic, intellectual deterioration, sleep disorders, sexual dysfunction, personality changes, hearing difficulties, gait instability, tremor, parkinsonism, bradykinesia, abulia, and upper motor neuron signs were found in a large proportion, but selection bias was likely (17). The severity of symptoms and signs varied from minimal to a degree that could lead to diagnosis of Parkinson's disease or dementia. Improvement followed valproate withdrawal, and in two patients retested by CT scan cerebral atrophy regressed after drug withdrawal.

Psychological, psychiatric

Psychotic reactions had been reported to the WHO monitoring system on 16 occasions by 1993, and other occasional cases have been published (SED-13, 149) (18).

Behavioral problems are less frequent with valproate than with other anticonvulsants and include sedation, hyperactivity, irritability, and aggression (19).

There has been a randomized, double-blind, single crossover study of the effects of sodium valproate on cognitive performance and behavior in eight children with learning and behavioral problems associated with electroencephalographic epileptiform discharges but without clinical seizures (20). The children became more distractable, had increased delay in response time, and had lower memory scores while taking valproate. Their parents reported higher internalizing scores on the Child Behavior Checklists.

Although valproate has little effect on cognitive function compared with other anticonvulsants, it can occasionally cause reversible dementia, sometimes associated with MRI evidence of pseudoatrophy of the brain (SEDA-20, 67) (SEDA-21, 76). The presentation can be striking, with progressive motor and intellectual deterioration and apathy appearing shortly after the introduction of valproate, or sometimes after as long as 2 years. Many affected patients have relatively high serum drug concentrations (100–120 mg/l), other signs of toxicity, such as tremor and ataxia, and normal electroencephalographic background activity. The presentation differs from valproate-induced stupor, in which consciousness is impaired, and there may be clinical or electroencephalographic signs of increased seizure activity. In all cases, clinical and imaging signs improved rapidly after drug withdrawal. The incidence of this syndrome is probably very low, although there is concern about possible underdiagnosis.

Endocrine

The use of valproate in young women has been associated with an increased incidence of menstrual abnormalities (21), polycystic ovaries, and hyperandrogenism (SEDA-18, 69) (SEDA-20, 68). Of 22 valproate-treated women who underwent endocrine evaluation, 13 were obese and 11 had marked weight gain (mean 21 kg) after starting valproate (22). There were polycystic ovaries, hyperandrogenism, or both in 64%, but the clinical relevance of these findings remains uncertain.

The syndrome of polycystic ovaries and hyperandrogenism associated with weight gain and hyperinsulinemia was reversible in 16 women with valproate-related polycystic ovaries and/or hyperandrogenism who were switched to lamotrigine (23). While taking valproate, they had centripetal obesity with associated hyperinsulinism and unfavorable serum lipid profiles. After switching to lamotrigine, in the 12 patients available for follow-up at 1 year, body-mass index and fasting serum insulin and testosterone concentrations fell, whereas HDL cholesterol/total cholesterol ratios increased from 0.17 to 0.26. The total number of polycystic ovaries fell from 20 to 11 after 1 year of lamotrigine.

Pubertal growth arrest has been described in a 12-year-old girl who had taken valproate for 18 months (SED-13, 152) (24).

Among 45 valproate-treated girls aged 8–18 years, hyperandrogenism (serum testosterone concentrations more than two standard deviations above the mean for healthy controls) was seen in 38% of prepubertal girls, 36% of pubertal girls, and 57% of postpubertal girls (25). Obesity was more common in postpubertal valproate-treated girls than in controls. The authors concluded that valproate may cause hyperandrogenism in girls with epilepsy during the sensitive period of pubertal maturation.

There were increased serum androgen concentrations in 60% of those who took valproate (22).

The endocrine consequences of valproate or carbamazepine monotherapy have been evaluated in a cross-sectional study in two groups of women with epilepsy, who were treated for at least 2 years with valproate ($n = 52$) or carbamazepine monotherapy ($n = 53$) (26). Menstrual disturbances were reported by 29 of the women, 12 of those taking valproate and 17 of those taking carbamazepine. Polycystic ovaries were found in 28 patients, of whom 13 were taking valproate and 15 carbamazepine. Postprandial concentrations of insulin, C-peptide, and proinsulin were significantly higher with valproate than carbamazepine, but there were no differences in the fasting state. In conclusion, this study did not show an increase in the frequency of polycystic ovaries in valproate-treated women, although valproate does appear to increase glucose-stimulated pancreatic insulin secretion.

Metabolism

Valproate can cause hyperglycinemia and hyperglycinuria, sometimes with raised spinal fluid glycine

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concentrations (SED-12, 133). These changes are usually asymptomatic.

Chronic valproate treatment did not change serum concentrations of lipids, vitamin B12, or folic acid in 26 children with epilepsy (27).

Weight gain

Weight increase, sometimes associated with increased appetite, occurs in 8–60% of patients taking valproate (6) and may be unrelated to dose.

A randomized, double-blind study was conducted for 32 weeks to analyse weight change in patients taking lamotrigine ($n = 65$; mean age 35 years; target dosage 200 mg/day) and valproate ($n = 68$; mean age 30 years; target dosage 20 mg/kg/day) (28). Weight remained stable in the patients taking lamotrigine. However, there was significant weight gain in the patients taking valproate by the 10th week of treatment, and weight continued to increase throughout the study. After 32 weeks, mean weight gain was significantly higher in those taking valproate (5.8 kg) compared with lamotrigine (0.6 kg). Similar proportions of patients taking lamotrigine (29%) or valproate (26%) were seizure-free. The frequencies of adverse events were similar in the two groups.

The mechanisms involved have been assessed in 40 women with epilepsy evaluated before and after 1 year of therapy (29). At the end of follow-up, 15 patients were obese and had higher serum leptin and insulin concentrations than patients who did not gain weight. The rise in serum leptin is consistent with that observed in other types of obesity.

In a prospective cohort study of the role of insulin and leptin (a signal factor that regulates body weight and energy expenditure) in valproate-related obesity, 81 patients with epilepsy taking valproate and 51 healthy controls were analysed (30). Mean serum insulin concentrations were significantly higher in the valproate-treated patients than in the controls, despite similar body mass indexes. Furthermore, serum insulin concentrations were significantly higher both in lean men and lean women compared with lean controls of same sex and similar body mass indexes. This implies that the hyperinsulinemia seen in obese people taking valproate is not merely a consequence of insulin resistance induced by weight gain. Serum leptin concentrations did not differ between the valproate-treated patients and the controls. Thus, both obese and lean patients taking valproate have hyperinsulinemia, suggesting insulin resistance. This may be one of the factors that leads to weight gain during valproate treatment. Similar findings, that is increased insulin concentrations without changes in leptin concentrations, have also been published in three other reports from one center (26,31,32).

Hyperammonemia

Hyperammonemic encephalopathy has been attributed to valproate (33).

- A 61-year-old man with epilepsy had altered consciousness after his dose of valproate was increased because of poor seizure control. Electroencephalography showed triphasic waves and high-amplitude delta-wave activity with frontal predominance. Although serum aspartate transaminase and alanine transaminase were normal, the serum ammonium concentration was high at 960 ng/ml (reference range 30–470). Serum amino acid analysis showed multiple minor abnormalities. Valproate was withdrawn. He improved within 4 days and the electroencephalogram, serum ammonium concentration, and amino acid profile were normal by day 8.

In two other cases the addition of topiramate was thought to have precipitated valproate-induced hyperammonemic encephalopathy (34). Recovery occurred after withdrawal of valproate or topiramate. The authors suggested that topiramate may have contributed to the hyperammonemia by inhibiting carbonic anhydrase and cerebral glutamine synthetase.

Asymptomatic hyperammonemia, with ammonia concentrations as high as 140 mmol/l, has been found in up to over 50% of patients (35) and may be due to increased renal production or inhibition of nitrogen elimination, although carnitine deficiency, nutritional influences, metabolic abnormalities secondary to increased glycine or propionic acid concentrations, and multiple drug therapy may play a role (SED-13, 149) (35). In individual patients, the condition can be associated with severe symptoms (SEDA-20, 69). Deaths have occurred after the use of valproate in patients with ornithine transcarbamylase deficiency (SED-12, 133) (36), (SED-13, 149) (37). Additional evidence points to a need for caution in patients with any enzyme disorder: an 18-year-old woman with progressive dementia and spastic paraparesis became comatose with hyperammonemia when taking valproate; moderate hyperammonemia persisted for months after drug withdrawal, coma recurred without exposure to valproate, and congenital argininemia was diagnosed (38). Carnitine supplementation has been proposed in symptomatic hyperammonemia caused by valproate (see below).

Valproate-induced hyperammonemic encephalopathy has been reviewed (39). Proton magnetic resonance spectroscopy was performed in a patient with valproate-induced hyperammonemic encephalopathy; there was a significant fall in the choline and myoinositol resonances and an increase in glutamine in the hyperintense basal ganglia lesions (40). A similar pattern has been observed in other hyperammonemic encephalopathies, such as hepatic encephalopathy. In another study in seven patients with valproate-related hyperammonemia serum or cerebrospinal fluid glutamine concentrations were initially raised in most patients, sometimes in the absence of hyperammonemia (41).

Carnitine deficiency

Valproate is often associated with low carnitine concentrations and occasionally with true carnitine deficiency, especially in young children with neurological disabilities taking several anticonvulsants. The condition is usually asymptomatic, but it can occasionally cause significant toxicity (42).

- Life-threatening cardiac dysfunction in a 7-year-old boy required urgent carnitine supplementation (SEDA-17, 74).
- In one patient with acute valproate-associated encephalopathy associated with biochemical evidence of severe carnitine deficiency and a defect in valproate

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metabolism, L-carnitine substitution corrected the biochemical abnormalities, but the patient died (SED-13, 150) (43).
- In another case, there was late-onset lipid storage myopathy, with secondary carnitine deficiency (SED-13, 150) (44).

While measurement of carnitine concentrations is advisable in patients with symptoms and signs suggestive of carnitine deficiency (SED-12, 133) (45), indiscriminate carnitine supplementation is unwarranted. A panel of pediatric neurologists recently recommended intravenous carnitine for valproate hepatotoxicity and for valproate overdose (SEDA-20, 69), whereas oral supplementation was suggested for patients with symptomatic valproate-associated hyperammonemia, multiple risk factors for valproate hepatotoxicity, and infants and young children receiving valproate (46). It was mentioned that carnitine might be deleterious in some disorders of long-chain fatty acid oxidation. Others have considered carnitine to be valuable in valproate-induced hyperammonemia, but have suggested reserving it for patients with subnormal blood carnitine concentrations or known risk factors for carnitine deficiency (47). In a double-blind trial in 47 children taking carbamazepine or valproate, carnitine (100 mg/kg/day for 4 weeks) was not more effective than placebo in improving subjective well-being (SEDA-19, 74).

Nutrition

Concentrations of plasma homocysteine, plasma pyridoxal 5′-phosphate (active vitamin B6), serum folate, erythrocyte folate, and serum vitamin B12 have been measured both fasting and after methionine in 60 epileptic patients (aged 14–18 years) and 63 sex- and age-matched controls before therapy and after 1 year of therapy with valproate or carbamazepine (48). After 1 year the patients who took valproate and carbamazepine had significantly increased plasma homocysteine concentrations compared with both baseline and control values and there was a significant fall in serum folate and plasma pyridoxal 5′-phosphate. Serum vitamin B12 and erythrocyte folate were unchanged.

The genetic determinants of this effect on homocysteine have been determined in 136 epileptic children taking carbamazepine or valproate as monotherapy (49). Nutritional determinants (folate and vitamins B6 and B12) and genetic determinants (MTHFR 677CT) of plasma homocysteine were studied in a random sample of 59 of those children. Total homocysteine concentrations were significantly increased and folate and vitamin B6 concentrations were significantly reduced. Carbamazepine lowered folate concentrations in association with hyperhomocysteinemia, which seemed to be related to the homozygous MTHFR 677CT mutation. Valproate, although also associated with hyperhomocysteinemia, only reduced vitamin B6 concentrations, independent of the MTHFR genotype.

In 15 patients who had a serious adverse reaction to valproate (including behavioral changes and emesis in six, raised aspartate transaminase in three, raised aspartate transaminase and pancreatitis in one, thombocytopenia in two, and unexpected death in two), erythrocyte glutathione peroxidase activity and plasma selenium and zinc concentrations were significantly reduced, whereas erythrocyte glutathione reductase activity was significantly raised relative to matched healthy controls or patients with good tolerance of valproate (50). These findings may indicate a role for selenium-dependent antioxidant activity in individual susceptibility to the adverse effects of valproate.

Mineral balance

- Hyponatremia (serum sodium of 128 mmol/l) was discovered accidentally in a 50-year-old man during follow-up for Henoch-Schönlein nephritis (51). He was taking sodium valproate 2000 mg/day. Repeated water loads at different dosages of valproate confirmed that the ability to excrete water was dose-dependently reduced.

Fluid balance

Edema has been attributed to valproate.

- A 42-year-old man with bipolar disorder developed peripheral edema 14 days after starting treatment with valproate in a dosage of 1400 mg/day (52). Within 3 weeks he gained 11 kg in body weight, his legs were very swollen, and periorbital edema was present after a night's sleep. Blood chemistry and hematology tests were normal. The diagnosis was avid salt retention by the renal tubules, secondary to treatment with valproate, and recovery occurred when diuretics were given and valproate was substituted with lithium.
- An 18-year-old woman also developed leg edema while taking valproate 800 mg/day for epilepsy (53). Although she had taken valproate for 10 years without edema, the lack of alternative explanations and the disappearance of the condition after withdrawal suggested a drug-related effect. She also had dysmenorrhea, hirsutism, and obesity, which were thought to have been caused by valproate.

There have been eight other published cases of valproate-induced edema, plus two additional cases in whom edema developed when risperidone was added to valproate.

- Severe peripheral edema occurred in a 42-year-old man taking valproate 1.5 g/day and resolved on withdrawal (52).

The authors proposed that increased GABA activity had inhibited natriuresis by altering the action of nitric oxide in the kidneys or by inhibiting the central production of C-type natriuretic peptide.

Hematologic

Hematological abnormalities, mostly of little or no clinical significance, occur in about 30% of patients taking valproate (SEDA-18, 69).

Thrombocytopenia can be caused by autoimmune mechanisms (SED-13, 150) (54), tends to be related to high serum drug concentrations, and often responds to dosage reduction (SEDA-19, 74). Of 131 patients randomized to high plasma concentrations of valproic acid (80–150 μg/ml), 36 (27%) had at least one platelet count below 75×10^9/l, compared with only one patient in a group randomized to drug concentrations of 25–50 μg/ml (55).

As well as reducing platelet count or function valproate can impair procoagulatory thrombocytic functions as reflected by reduced platelet activation and an increased thrombin time (56). Valproate-induced platelet

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dysfunction may be related, at least in part and in some patients, to inhibition of the arachidonic acid cascade (57).

- There was a small reduction in platelet count (from 150 to 110 × 10^9/l) in association with gastrointestinal symptoms in a 45-year-old man when he took valproate 750 mg tds, but not when he took the same dose of divalproex, an enteric-coated formulation (58).
- A small reduction in platelet count (from 170 to 110 × 10^9/l) in a 37-year-old woman was associated with disproportionate perioperative bleeding (59). An antiplatelet antibody was also detected and the authors therefore proposed that valproate must also have caused reduced platelet aggregation.
- Small reductions in red cell, white cell, and platelet counts occurred in a 65-year-old man taking valproate; the changes were dose-related but did not merit the description of pancytopenia that the authors used in the title of their paper (60).

Bleeding complications occasionally occur. In an unusual case, thrombocytopenic purpura, anemia, and reticulocytosis occurred in a 3-month-old breast-fed infant whose mother was taking valproic acid 1200 mg/day. The serum valproic acid concentration in the infant was 6.6 μg/ml, and recovery occurred when breast-feeding was stopped (61).

Depressed fibrinogen concentrations have been reported (SED-12, 134) (62,63), but they are unlikely to be important, except perhaps in patients due to undergo surgery. However, two neonates from mothers who had taken valproate during pregnancy developed bleeding associated with fibrinogen depletion soon after birth, and one of them died from afibrinogenemia (SEDA-19, 75).

In one study there were marked reductions in von Willebrand factor and ristocetin co-factor in most valproate-treated children (SEDA-17, 74), leading to deranged hemostasis, although not always to a clinically important extent. In the event of bleeding or need for surgical procedures, a high-purity factor VIII concentrate (Haemate P) provided sufficient hemostasis in valproate-induced von Willebrand's disease, despite the fact that Haemate P is ineffective in the platelet type of the disease (64). Despite frequent changes in hemostasis and blood coagulation in patients taking valproate, bleeding complications during or after neurosurgery are uncommon (SEDA-21, 76).

Very rare effects include bone-marrow suppression associated with platelet autoantibodies and coagulopathy, transient leukopenia, lethal bone-marrow failure due to self-poisoning, reversible intravascular hemolysis, and pure red cell aplasia (SED-12, 134) (65–68).

A 5-year-old girl with acquired protein C deficiency had a stroke while taking valproate (69). The authors then measured protein C concentrations in 20 children taking valproate monotherapy and 20 children taking other anticonvulsants. There were significantly lower protein C concentrations in those taking valproate. Protein S and antithrombin III were not affected. Despite this, there is no known association between valproate therapy and a risk of thromboembolic disease, and the clinical relevance of this effect on protein C is not clear.

Gastrointestinal

Gastrointestinal symptoms, such as nausea, anorexia, vomiting, gastritis, and diarrhea, occur in 36% of patients (6), although over 20% may be affected at high dosages (7). Stomatitis, parotid gland enlargement, and gingival hyperplasia are exceedingly rare (SED-13, 151) (70–72).

In a retrospective survey, gastrointestinal adverse effects were less common in 150 patients taking valproate semisodium than in an equal number taking valproic acid (15 versus 29%), despite the fact that serum valproic acid concentrations were comparable in the two groups (73). Patients taking valproate semisodium were less likely to discontinue medication because of gastrointestinal adverse effects (4 versus 13%). The difference was ascribed to the enteric-coated formulation of valproate semisodium.

The suggestion that divalproex (valproate semisodium) causes fewer gastrointestinal adverse reactions than valproate (SEDA-23, 94) (58) has been challenged (74). In other cited studies divalproex was associated with a higher risk of gastrointestinal effects.

Liver

Liver abnormalities due to valproate range from transient dose-related asymptomatic rises in liver enzymes (in as many as 40% of patients) to rare and often fatal hepatic failure. Rises in liver enzymes up to three times normal may abate, even without a reduction in dosage, but the drug should be withdrawn if the rise in enzyme concentrations is greater.

At least 132 patients have died of liver failure (and/or pancreatitis) (75). The risk is highest (1:600) in children under 2 years of age with complex neurological disorders taking valproate as part of a multidrug regimen (46,76). In older patients the incidence is no more than 1:37 000 for monotherapy and 1:12 000 for multidrug therapy. Deaths beyond 20 years of age are exceedingly rare. Risk factors include mental retardation, congenital abnormalities, neurological disorders, familial hepatic disease, the addition of valproate within 3 months of liver dysfunction, and concomitant salicylate use. Fatal hepatotoxicity usually occurs within the first 3 months, although the proportion of patients who developed their first symptoms after 6 months has increased lately, possibly because of greater awareness of the problem and a reduced death rate, owing to rapid drug withdrawal (75). The presenting symptoms include nausea, vomiting, loss of appetite, reduced alertness, apathy, coma, fever, jaundice, hemorrhage, edema, and increased seizure frequency, including status epilepticus. The importance of fever and increased seizure frequency as diagnostic features may have been underestimated in the past.

A Reye-like syndrome, as yet only in children, has also been described. The mechanisms involved remain elusive, and possible roles of carnitine deficiency (46) and hepatotoxic metabolites (SED-13, 151) (77) have been discussed.

Knowledge of symptoms is more important than laboratory tests in early detection and prevention, although monitoring liver function during the first 6 months of therapy is recommended. There is some

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evidence that hepatotoxicity is related to carnitine deficiency, and retrospective data suggest that the outcome can be improved by early intravenous administration of carnitine (46).

- Valproate-induced fatal liver failure developed in a 29-year-old woman with Friedreich's disease (78). The first symptoms (apathy during febrile upper airways infection) occurred after 2 months of therapy at a dosage of 20 mg/kg. The drug was withdrawn 10 days later, when she had hepatic encephalopathy and a severe bleeding diathesis; supportive treatment was provided but she died after 4 weeks.

This was the third published case of fatal valproate liver toxicity in an adult with Friedreich's disease, suggesting that this condition is a predisposing factor. Although the risk of valproate hepatotoxicity in adults is much lower than in children, adults still represented over 15% of the cases known to the authors. Overall, a total of 26 other adults (age range 17–62 years) with fatal valproate-induced liver failure have been reported: of these, 3 were taking monotherapy and 12 had no underlying disease or a clearly non-metabolic and non-hepatic disease. The duration of treatment before the first symptoms varied between 6 days and 6 years.

Fatal hepatitis has been reported in a child taking valproate (79).

- An 8-year-old boy with complex partial seizures had taken valproate for more than 3 years. His sister developed uncomplicated hepatitis A, and 1 month later he became jaundiced, developed fulminant hepatic failure, quickly became encephalopathic, and died, despite withdrawal of valproate, aggressive supportive therapy, and treatment with carnitine. He had positive hepatitis A IgM; other causes for acute hepatitis were ruled out. Liver pathology showed distended hepatocytes with cholestasis and microvesicular changes.

The authors thought that valproate-induced hepatotoxicity may have exacerbated this child's infective hepatitis.

Hepatotoxicity due to valproate has been attributed to reactive hepatotoxic metabolites of valproate, which are normally detoxified by glutathione conjugation followed by mercapturic acid metabolism to their respective *N*-acetylcysteine conjugates (80).

The Alpers–Huttenlocher syndrome, progressive neuronal degeneration of childhood, which is associated with seizures and abnormal liver function tests, can lead a clinician to use valproate, which can then precipitate acute liver damage, as has been reported in five cases (81). In all cases liver transplantation for valproate-induced liver damage was then associated with worsening neurological function. In another case Alpers–Huttenlocher syndrome was misdiagnosed as valproate toxicity (82).

The association between valproate and raised transaminase activities has been studied in a retrospective review of the medical records of patients positive for hepatitis C virus (83). Of 214 patients 28 were taking valproate and 186 were not. The controls and those who had been hepatitis-positive for longer were significantly more likely to have worse hepatotoxicity. Valproate, either alone or in the presence of other potential hepatotoxins, was not associated with raised transaminases.

Pancreas

There have been over 50 published reports of acute pancreatitis associated with valproate (SEDA-18, 70) (84), including several confirmed by rechallenge. Deaths have occurred from hemorrhagic pancreatic necrosis; complications can include pleural and pericardial effusions, coagulopathy, pseudocyst, ascites, wound infection, and pneumonia (SED-13, 151) (85). Hepatotoxicity can coexist. There is suggestive evidence that end-stage renal insufficiency (SEDA-22, 92) and mental retardation (84) can be predisposing factors.

In a study of intravenous valproate in status epilepticus, three of 19 patients (ages and dosages not specified) developed a rise in serum lipase activity above 4000 IU/ml within 1–3 weeks (86); one of these developed overt exudative pancreatitis. Based on these data, it may be prudent to monitor serum lipase when using intravenous valproate.

However, in a review of valproate-induced pancreatitis (87) the author discouraged routine checking of amylase activity in the absence of other clinical signs and symptoms.

Urinary tract

Enuresis in children can occasionally be a problem (88). There have been single cases of Fanconi syndrome (SED-13, 151) (89), and hematuria with acute renal insufficiency (SEDA-20, 69).

A child with developmental delay and epilepsy developed glycosuria about 16 months after starting to take valproic acid (90). Laboratory evaluation showed global defects in proximal tubule function, consistent with the De Toni–Debré–Fanconi syndrome. The authors reviewed the literature on this rare complication, which is reversible on valproate withdrawal.

Skin

Skin rashes are uncommon (2–4%), and photosensitivity and cutaneous vasculitis, if they occur at all, are exceedingly rare (SED-13, 152) (91,92).

Cutaneous pseudolymphoma has been attributed to valproate (93).

- A 41-year-old man presented with an erythematous papule, histologically mimicking a non-epidermotropic T cell lymphoma. Polymerase chain reaction in the skin biopsy showed monoclonal rearrangement of the T cell receptor gamma gene. Withdrawal of valproate was followed by regression of the lesion, but 5 months after substitution by carbamazepine, two further papules appeared, with similar histological features. Carbamazepine was withdrawn and the lesions disappeared without relapse over 4 years.

Hair

Hair loss and changes in hair texture or color are seen in 1–11% of patients (SED-12, 135) (6,94,95). Alopecia has been reported in 4% of patients with concentrations below 50 μg/ml and in 28% of patients with serum drug concentrations above 80 μg/ml (7).

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Musculoskeletal

Accumulation of microvesicular lipid droplets between myofibrils adjacent to mitochondria was found in muscle biopsies from seven children taking valproate (SEDA-22, 92). Ultrastructural abnormalities in the mitochondria suggested that these could have resulted from impaired mitochondrial fatty acid oxidation.

Sexual function

- A 32-year-old man developed infertility and a low sperm count (under 50×10^6/l), with no motile sperm, less than 10% viability, and 100% with abnormal structure while taking valproate monotherapy for 5 years (96). Within 4 months of switching to felbamate, he and his wife conceived twin girls, and the sperm abnormalities were largely reversed.

These findings suggest that occasionally valproate can cause male infertility.

Reproductive system

Polycystic ovary syndrome (polycystic ovaries, hyperandrogenism, obesity, hirsutism, anovulatory cycles, and menstrual disorders) is more common in women with epilepsy. Valproate has been associated with alterations in reproductive hormonal function beginning in the first month of treatment. Serum androgen concentrations increase in patients taking valproate but the profile of hormonal changes is different in women and men (97). Animal studies have corroborated the adverse ovarian and endocrine effects of valproate (98). Four review articles have dealt with this reported adverse event, highlighting controversial views (99–102).

The estimated prevalence of polycystic ovary syndrome in patients with epilepsy is 13–25%, compared with 4–6% in the general population (99). Polycystic ovary syndrome has been described in women with epilepsy taking valproate, especially those who start treatment before 20 years of age (22,103), and the frequency is high: in a cross-sectional study of 22 women taking valproate monotherapy, 59% were obese and 64% had polycystic ovaries, hyperandrogenism, or both (22).

In a prospective study of polycystic ovary syndrome in 52 controls and 72 women with epilepsy (37 taking valproate monotherapy and 35 carbamazepine monotherapy), the frequency of polycystic ovaries, hyperandrogenism, or both was significantly higher in those taking valproate than in the controls (70 versus 19%) (104). They occurred in 20% of the patients taking carbamazepine. The obese women taking valproate who had polycystic ovaries or hyperandrogenism or both had hyperinsulinemia and associated unfavorable changes in serum lipid concentrations consistent with insulin resistance. In both obese and lean women, polycystic ovaries and related hyperandrogenism were similarly found. Most of the abnormalities were reversed when valproate was withdrawn (23).

Three women taking valproate developed hyperandrogenism and polycystic ovaries, associated in two cases with weight gain and menstrual disorders (105). Valproate was replaced by lamotrigine, and the serum testosterone concentrations fell in all three women, the polycystic changes disappeared from the ovaries in two, and the two women who had gained weight and developed amenorrhea lost weight and started menstruating. In the light of this report others have clarified the distinction between polycystic ovary syndrome and polycystic ovary morphology, and have pointed out that it was not clear which of these valproate had actually caused (106,107). The report also contrasts with a report that polycystic ovary syndrome was identified in two of 19 patients taking no medications, four of 38 patients taking valproate or carbamazepine monotherapy, and one of 36 patients taking more than one antiepileptic drug, suggesting that polycystic ovary syndrome in women with focal epilepsy is not related to valproate or carbamazepine (108).

Although the association between polycystic ovary syndrome and valproate treatment appears to be established, current published studies are limited, owing to small sample sizes and diverse definitions of polycystic ovary syndrome. Thus, the true clinical relevance and frequency of the association needs further investigation in large, multicenter, prospective studies.

Women taking valproate should be asked about menstrual disorders. The presence of a menstrual disorder, hirsutism, or weight gain should trigger thorough evaluation and, if necessary, valproate withdrawal.

Immunologic

Hypersensitivity reactions to valproate are rare. Lupus-like syndrome has been reported occasionally with valproate (SEDA-19, 75) (SEDA-20, 69) and valpromide (109).

In vitro tests have shown that valproate can increase the viral burden in HIV-infected individuals by potentiating replication of the virus (110). In a retrospective review of 11 HIV-positive patients with behavioral disturbances taking valproate HIV-1 viral load did not increase in six of the nine patients who had measurements between the first week and 3.5 months after the start of valproate treatment; no follow-up was available for the other three (111). These data suggest that, contrary to in vitro data, HIV-1 viral load is not adversely affected by valproate in the presence of effective antiretroviral therapy.

Body temperature

Hypothermia related to valproate has been reported in a child (112). There have been five previously described cases in adults or elderly patients (113).

- A 2-year-old boy was admitted after a prolonged febrile seizure that stopped only after he was given several doses of benzodiazepines plus phenobarbital. A CT scan showed a right arachnoid cyst. He was given valproate 13 mg/kg/day and 2 days later developed hypothermia (33.8–34.5°C). He was lethargic and irritable. Valproate was withdrawn. His lethargy improved within 48 hours and the temperature slowly returned to normal over the course of 1 week.

Second-Generation Effects

Teratogenicity

The association of valproate with spina bifida, cardiac malformations, hypospadias, porencephaly, and other

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specified anomalies of the brain, anomalies of the face, coarctation of the aorta, and limb reduction defects has been found.

There has been a case-control study of the relation between prenatal exposure to valproate and the presence of limb deficiencies in newborn infants, using data from the Spanish Collaborative Study of Congenital Malformations (ECEMC) (114). Of 22 294 consecutive malformed infants (excluding genetic syndromes) and 21 937 control infants with specified data on anticonvulsants during gestation, 57 malformed infants and 10 control infants had been exposed to valproate during the first trimester of pregnancy. Of the malformed infants who had been exposed to valproate 21 had congenital limb defects of different types (including overlapping digits, talipes, clubfoot, clinodactyly, arachnodactyly, hip dislocation, and preaxial and postaxial polydactyly); three had limb deficiencies. After controlling for potential confounding factors there was an odds ratio of limb deficiencies of 6.2 (CI = 1.3, 30). The estimated risk for women taking valproate of having a baby with limb deficiencies was around 0.42%.

Fetotoxicity

Two neonates born of mothers who had taken valproate during pregnancy developed bleeding associated with fibrinogen depletion soon after birth, and one of them died from afibrinogenemia (SEDA-19, 75).

Of 17 infants born of mothers taking valproate, 12 had possible withdrawal effects (irritability, jitteriness, abnormal tone, seizures, feeding problems), which correlated with the dosage of valproate during the last trimester, and four of the affected children also had hypoglycemia (SEDA-18, 70).

Three cases of lung hypoplasia after prenatal exposure to valproate have been reported in two female siblings and an unrelated girl (115). The two siblings had no other malformations, whereas the third neonate had a number of major birth defects. All three died a few hours after birth. The possibility that lung hypoplasia was caused by valproate remains speculative.

Fetal valproate syndrome comprises a number of typical dysmorphic features and major organ system anomalies (116). In a case file review of 2220 children with craniosynostosis, detailed maternal health information was obtained in 1676 cases (117). Of these, 17 mothers had taken valproate monotherapy during pregnancy. All 17 children had trigonocephaly (caused by premature fusion of the metopic suture). Their IQs were 45–100 (mean 75). IQs were significantly higher in patients who underwent surgery before 6 months of age. This is the first study to have reported trigonocephaly associated with fetal valproate syndrome.

Five patients with fetal valproate syndrome and autism have been described (118).

Lactation

In an unusual case, thrombocytopenic purpura, anemia, and reticulocytosis occurred in a 3-month-old breast-fed infant whose mother was taking valproic acid 1200 mg/day. The serum valproic acid concentration in the infant was 6.6 μg/ml; recovery occurred when breast-feeding was stopped (61).

Susceptibility Factors

Genetic factors

Deaths have occurred after the use of valproate in patients with ornithine transcarbamylase deficiency (SED-12, 133) (36) (SED-13, 149) (37). Additional evidence points to a need for caution in patients with any enzyme disorder.

- An 18-year-old woman with progressive dementia and spastic paraparesis became comatose with hyperammonemia when taking valproate; moderate hyperammonemia persisted for months after drug withdrawal, coma recurred without exposure to valproate, and congenital argininemia was diagnosed (38).

Carnitine supplementation has been proposed for the treatment of symptomatic hyperammonemia caused by valproate.

Since glutathione peroxidase deficiency could predispose to severe reactions such as pancreatic or hepatic failure in children, screening for such deficiency might prove useful (SEDA-17, 72).

Age

At least 132 patients have died of liver failure (and/or pancreatitis) (75). The risk is highest (1 : 600) in children under 2 years of age with complex neurological disorders taking valproate as part of a multidrug regimen (46,76). In older patients the incidence is no more than 1:37 000 for monotherapy and 1:12 000 for multidrug therapy. Deaths beyond 20 years of age are exceedingly rare.

Valproate should not be prescribed for children with metabolic defects possibly associated with Reye-like symptoms, including acyl CoA-dehydrogenase deficiency (SEDA-22, 92) (75). In patients under 2 years old and in children with psychomotor retardation metabolic screening should be performed before therapy, and the drug should be avoided whenever a metabolic defect is known or suspected.

Hepatic disease

Valproate should be avoided in patients with a personal or family history of liver disorders or pancreatic dysfunction (75,119).

Other features of the patient

At least 132 patients have died of liver failure (and/or pancreatitis) (75). Risk factors include mental retardation, congenital abnormalities, neurological disorders, a family history of hepatic disease, the addition of valproate within 3 months of liver dysfunction, and concomitant salicylate use.

- A 24-year-old man with demyelinating disease had fulminant progression of the disease after he experienced valproate-induced hyperammonemic encephalopathy (120).

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Although the role of hyperammonemia is uncertain, this case raises concern for possible risks in using valproic acid in patients with fulminant demyelinating disease.

The importance of hypoalbuminemia as a risk factor in valproate toxicity has been emphasized (121).

- A 53-year-old woman had a heart transplantation and developed worsening cardiac function, possible rejection, and increased lethargy. Her dose of valproate had been adjusted based on the total serum valproate concentration, but hypoalbuminemia prompted the measurement of the unbound serum valproate concentration, which was high. When the dose of valproate was adjusted based on the unbound rather than the total serum concentration she eventually improved.

Non-linear protein binding of valproate can result in disproportionate increases in unbound drug; adverse effects can then result when dosage adjustments are based solely on measurement of total valproate serum concentrations in patients with hypoalbuminemia.

Drug Administration

Drug formulations

Extended-release (ER) divalproex (valproate semisodium) is not bioequivalent to delayed-release (DR) divalproex. In a randomized, crossover study in 36 healthy volunteers the bioequivalence of divalproex ER once a day and divalproex DR at 14% and 20% lower daily doses given twice a day were compared (122). The two formulations gave equivalent exposure (AUC) with lower peak and higher trough concentrations, that is less fluctuation during the dosage interval, with divalproex DR.

Drug administration route

The successful use of intravenous valproate in psychiatric practice has been described (123). The safety of rapid infusion of valproate has been studied in 20 patients with acute repetitive seizures, who received 20 mg/kg loading doses at rates of 33–555 mg/minute (124). Consciousness and respiratory function were not affected. There was no significant local irritation. Two patients with significant contributing factors developed hypotension and required vasopressors.

Drug overdose

- After a valproate overdose a 27-year-old man developed seizures, hypernatremia, respiratory failure, metabolic acidosis, liver failure, and bone marrow depression (125). His plasma valproic acid concentration was 1414 μg/ml. Treatment with hemodialysis was effective in enhancing valproic acid clearance, while hemoperfusion was relatively less effective, because of saturation of the column. Overall, the half-life of the drug was reduced from over 20 hours before treatment to less than 3 hours during hemodialysis/hemoperfusion; drug removal was probably favored by saturation of drug binding to plasma proteins, which resulted in a low unbound fraction (32% at the start of treatment). He was comatose for 5 days but recovered fully thereafter.

A beneficial effect of high-flux hemodialysis without hemoperfusion has been described in valproate overdose (126).

- A 25-year-old white woman took an unknown amount of valproic acid, became comatose, and developed hypotension and lactic acidosis. Her valproic acid concentrations rose to over 8400 μmol/l. High-flux hemodialysis was performed for 4 hours; the calculated half-life during the procedure was 2.7 hours, compared with a posthemodialysis value of 23 hours, suggesting that high-flux hemodialysis had increased the clearance rate of valproic acid. Her hemodynamic status and mental function improved in conjunction with the acute reduction in valproic acid concentrations.

Three patients who took overdoses of valpromide presented with no symptoms or only moderate ones and serum valproate concentrations below or within the usual target range; in two cases more than 3 hours after ingestion (127). However, there was marked deterioration more than 10 hours after ingestion, when serum valproate concentrations were in the toxic range.

Drug–Drug Interactions

General

An encephalopathy leading to stupor is occasionally observed after valproate is added to other anticonvulsants.

Valproate has no enzyme-inducing properties and does not interact with oral contraceptives.

Carbamazepine

In patients taking carbamazepine, valproate slightly increases the serum concentration of the active metabolite carbamazepine-10,11-epoxide, by inhibiting epoxide hydrolase and perhaps also by inhibiting the glucuronidation of carbamazepine-10,11-trans-diol (128).

Valpromide is a more potent inhibitor than valproate of carbamazepine epoxide hydrolase in vitro (129) and in six healthy volunteers it caused a marked rise in carbamazepine-10,11-epoxide, prolonging the half-life of carbamazepine-10,11-epoxide from 6.4 to 21 hours and reducing its clearance three-fold, suggesting that valpromide inhibits epoxide hydrolase in the liver in vivo as well as in vitro, despite the fact that it is rapidly converted in vivo to valproate (130).

In 12 adults with epilepsy taking carbamazepine, valpromide produced a larger increase in plasma concentrations of carbamazepine-10,11-epoxide than valproate (131).

In healthy subjects valnoctamide 200 mg tds for 8 days prolonged the half-life of carbamazepine-10,11-epoxide from 7 to 20 hours and reduced its oral clearance fourfold, suggesting that valnoctamide, like its isomer valpromide, is a potent inhibitor of carbamazepine epoxide hydrolase (130).

Clozapine

Chronic valproate (600–1500 mg/day) has been associated with a slight increase in plasma clozapine concentrations and a slight fall in norclozapine concentrations (132). These changes are unlikely to be clinically significant.

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Lamotrigine

Valproate inhibits the metabolism of lamotrigine (133).

Levodopa

Valproate caused a fall in growth hormone concentrations at varying times after the administration of levodopa (134).

Panipenem–betamipron

- The intravenous administration of panipenem + betamipron in a 22-year-old man and in two young girls resulted in a marked and rapid fall in the serum concentrations of valproic acid to 0–40% of the pretreatment concentration (135). In two patients, the effect was associated with epileptic seizures. Serum valproic acid began to rise again within 2 hours of stopping the antibiotic.

Although the mechanism of this interaction is unknown, animal studies suggest that suppression of the enterohepatic circulation of valproic acid may have been involved (136).

Phenobarbital

Valproate inhibits the metabolism of phenobarbital (137).

Phenytoin

Serum phenytoin concentrations can be increased or reduced by valproate (138): since valproic acid displaces phenytoin from plasma proteins, therapeutic and toxic effects of phenytoin occur at total phenytoin concentrations lower than usual.

Risperidone

Steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone have been measured in 23 patients taking risperidone alone and in 10 co-medicated with sodium valproate (139). Valproate had no effect on the kinetics of risperidone.

Salicylates

Simultaneous use of salicylates and valproate should be avoided (140).

Sertraline

- In a 34-year-old man with bipolar depression treated with valproate, the addition of sertraline (100 mg/day) was associated with signs of valproate intoxication and an increase in serum valproic acid concentration from 378 to 1127 μmol/l (141). The serum valproic acid concentration returned to baseline after sertraline withdrawal.

Inhibition of valproic acid metabolism was a probable cause for this interaction.

Tricyclic antidepressants

In 10 patients taking amitriptyline 125 mg/day, for 20 days valpromide increased amitriptyline and nortriptyline plasma concentrations from 71 to 106 ng/ml for amitriptyline, and from 61 to 101 ng/ml for nortriptyline (142).

Zidovudine

At a concentration of 100 μg/ml, valproic acid inhibits the glucuronidation of zidovudine in human liver microsomes by 50% (143). This observation explains the previously reported effect of valproate to increase plasma zidovudine concentrations in HIV-infected patients.

Diagnosis of Adverse Drug Reactions

The tentative target range for plasma concentrations is 350–700 μmol/l (50–100 μg/ml).

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Valsartan

See also Angiotensin II receptor antagonists

General Information

Valsartan is a highly selective antagonist at angiotensin II type 1 (AT_1) receptors (1). It has a half-life of about 8 hours, and is metabolized to a negligible extent. Most of its clearance is via the feces.

In 1378 patients with mild to moderate hypertension valsartan 80 mg/day has been compared with losartan 50 mg/day and placebo for 8 weeks (2). This study confirmed the excellent tolerance profile, not different from placebo, of both angiotensin II receptor antagonists.

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Vancomycin

General Information

Vancomycin is a narrow-spectrum glycopeptide antibiotic with potent antistaphylococcal activity. It was developed in the early 1950s. Early formulations contained substantial impurities, which were presumably responsible for some adverse reactions (1). When rapid infusion rates are avoided, vancomycin is rarely associated with serious toxicity. Reviews have suggested that the potential for vancomycin to cause significant ototoxicity or nephrotoxicity has been exaggerated (2,3). Improved manufacturing has resulted in a purer product and fewer toxic effects, but vancomycin is still associated with potentially serious adverse reactions (4).

Vancomycin inhibits bacterial cell wall synthesis and is bactericidal during cell division at therapeutic concentrations. Bacterial resistance to vancomycin has not been an issue during the first decades of its use. More recently, vancomycin-resistant enterococci have been recovered with increasing frequency from hospitalized patients. In some institutions, multidrug-resistant and vancomycin-resistant enterococci have become important nosocomial pathogens, difficult to treat. Vancomycin-resistant enterococcal bacteremia is associated with a poor prognosis. Judicious use of vancomycin and broad-spectrum antibiotics is recommended, and strict infection control measures must be implemented to prevent nosocomial transmission of these organisms (5).

Vancomycin is particularly useful in infections caused by meticillin-resistant or penicillinase-producing staphylococci and diphtheroids, as well as in the prophylaxis of bacterial endocarditis and in the treatment of antibiotic-associated colitis. Sufficient fecal concentrations can be achieved with oral therapy. It is poorly absorbed from the gastrointestinal tract and painful when injected intramuscularly. It diffuses moderately well into bone tissue (6).

Lactoferrin, a protein contained in tears, increases the activity of vancomycin against biofilms of strains of *Staphylococcus epidermidis* and may be therapeutically helpful in the treatment of infections such as endophthalmitis associated with intraocular lenses (7).

Observational studies

In a prospective, observational study of 742 consecutive patients (390 men; mean age 51 years, range 17–86), the incidence, outcomes, and predictive factors of vancomycin-associated toxic effects in general oncology practice were assessed (8). In all, 47% had hematological malignancies, and of the patients with solid tumors, primary urogenital (12%) and breast (10%) tumors were most common. In 72% vancomycin was given in a dosage of 2 g/day, 16% received a prophylactic dose of 1 g/day, and 12% had another regimen not specified. Phlebitis occurred in 3%, predominantly those with recently inserted central venous catheters. All responded promptly to local therapy, and withdrawal of the catheter or vancomycin was never required. Skin rashes occurred in 11%. However, all but four patients concomitantly received a beta-lactam antibiotic. None of the rashes

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required withdrawal, although the beta-lactam antibiotic was often withdrawn. There was clinical evidence of ototoxicity in 6% of the patients who received other ototoxic drugs and only 3% of patients who were not receiving other ototoxic drugs. There was nephrotoxicity in 17%. Logistic regression was used to derive a model of risk of nephrotoxicity. Factors associated with an increased risk of nephrotoxicity included administration of other mild to moderate nephrotoxic agents or APACHE II scores over 40. Raised serum vancomycin concentrations did not reliably predict subsequent nephrotoxicity. The derived model was prospectively tested in a validation set of 359 patients. Sensitivity of the Nephrotoxicity Risk Index for any nephrotoxicity was 71% and for serious nephrotoxicity 100%. Specificity for any nephrotoxicity was 90% and for serious nephrotoxicity 81%. A main limitation of the study was the lack of patients who received only vancomycin. The concomitant administration of other agents may therefore have confounded the results.

The adverse effects of once-daily or twice-daily vancomycin were not significantly different in 121 hospitalized patients (9). Nephrotoxicity developed in 11 and 7.7% of the patients respectively; hearing loss in 3.2 and 16%; phlebitis in 14 and 23%; and red man syndrome in 14 and 9.6%.

Comparative studies

In a prospective, randomized trial in 34 drug abusers a short course of a combination of a glycopeptide (vancomycin or teicoplanin) with gentamicin was significantly less effective in right-sided endocarditis caused by *Staphylococcus aureus* than a combination of cloxacillin and gentamicin (10).

Use in non-infective conditions

Many parents of children with regressive-onset autism have noted antecedent antibiotic exposure followed by chronic diarrhea. In a subgroup of children, disruption of indigenous gut flora might promote colonization by one or more neurotoxin-producing bacteria, contributing at least in part to their autistic symptoms. In 11 children with regressive-onset autism who had broad-spectrum antimicrobial exposure followed by chronic persistent diarrhea, oral vancomycin resulted in short-term improvement; however, these gains had largely waned at follow-up (11).

Red man syndrome

A unique and peculiar adverse reaction related to the rapid infusion of large doses is the so-called red neck or red man syndrome. It is the most common adverse reaction to vancomycin, characterized by fever, chills, paresthesia, and erythema at the base of the neck and the upper back, and can be followed by a hypotensive episode (12). It is not a true allergic reaction. It seems to be due to vancomycin-induced release of histamine and possibly other vasoactive substances without the involvement of preformed antibodies (13,14). In rat peritoneal mast cells vancomycin provoked histamine release dose-dependently; fosfomycin inhibited this effect (15).

Antihistamines (H_1 receptor antagonists) prevent anaphylactoid reactions to vancomycin (16). The recommended method of administration is by intravenous infusion of a solution of 0.25–0.5% over 60 minutes, and patients have to be monitored closely. A possible red man syndrome has also been associated with systemic absorption of oral vancomycin in a patient with normal renal function (17).

In a prospective, randomized, double-blind, placebo-controlled study in 30 patients who required vancomycin chemoprophylaxis before elective arthroplasty, oral pretreatment with either a histamine H_1 receptor antagonist (diphenhydramine 1 mg/kg) or a histamine H_2 receptor antagonist (cimetidine 4 mg/kg) significantly reduced the histamine-related adverse effects of rapid vancomycin infusion (18).

It has been stressed that near-fatal red man syndrome can also occur after slow administration of vancomycin (19).

- An 83-year-old white man became distressed and had nausea and facial flushing after 10 minutes of a slow infusion of vancomycin (1 g scheduled over 2 hours). Despite interruption, he developed suffocating respiratory distress requiring intubation and mechanical ventilation. Uncharacteristic of anaphylactoid reactions, he became severely hypertensive. Subsequently, his condition rapidly normalized. During the acute event, there was an increase in serum troponin concentration.
- A 45-year-old man developed hypotension, bradycardia, a change in consciousness, and an erythematous macular rash 10 minutes after the slow infusion of 0.1% vancomycin (20). After appropriate management, he recovered well and was discharged on the following day.

In 50 patients, in whom vancomycin 15 mg/kg was continuously infused at a constant rate over 30 minutes, the occurrence of pruritus suggested that systemic vascular resistance was falling, exposing the patient to a risk of hypotension (21). Therapy with a beta-blocker appeared to confer protection against this hemodynamic effect.

Pretreatment with H_1 and H_2 receptor antagonists (diphenhydramine 1 mg/kg and cimetidine 4 mg/kg) intravenously serially over 3 minutes starting 10 minutes before the infusion of vancomycin permitted rapid vancomycin administration (1 g over 10 minutes) in 17 of 19 patients compared with eight of 19 patients treated with placebo in a prospective, randomized, double-blind, placebo-controlled study of patients undergoing elective arthroplasty (22). Hypotension occurred in 2 versus 12 of the patients, and 12 versus 19 of the patients had a rash. Serum histamine concentrations were raised after vancomycin administration in both groups.

Possible synergism between vancomycin and narcotics in the induction of red man syndrome due to histamine release has been suggested in a 19-year-old women treated with fentanyl and vancomycin during orthopedic surgery (23). Evidence from an animal study has suggested that the risk can also be enhanced by the co-administration of muscle relaxants, resulting in enhanced release of histamine (24).

Pharmacoeconomics

The pharmacoeconomic impact of adverse effects of antimicrobial drugs is enormous. Antibacterial drug reactions

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account for about 25% of adverse drug reactions. The adverse effects profile of an antimicrobial agent can contribute significantly to its overall direct costs (monitoring costs, prolonged hospitalization due to complications or treatment failures) and indirect costs (quality of life, loss of productivity, time spent by families and patients receiving medical care). In one study an adverse event in a hospitalized patient was associated on average with an excess of 1.9 days in the length of stay, extra costs of $US2262 (1990–93 values), and an almost two-fold increase in the risk of death. In the outpatient setting, adverse drug reactions result in 2–6% of hospitalizations, and most of them were thought to be avoidable if appropriate interventions had been taken. In a review, economic aspects of antibacterial therapy with vancomycin have been summarized and critically evaluated (25).

In a randomized, prospective, cost-effectiveness study both teicoplanin and vancomycin were assessed as second-line therapy in 66 neutropenic patients after the failure of empirical treatment with a combination of piperacillin + tazobactam and amikacin (26). The primary success of second-line therapy was equivalent, and the direct total costs were similar. Acquisition costs per dose were in favor of vancomycin, but costs derived from administering vancomycin and serum concentration monitoring led to similar costs for both regimens. With the exception of the red man syndrome, which occurred in 10% of vancomycin-treated patients but none of the teicoplanin-treated patients, toxicity (renal, liver, and ear toxicity, diarrhea, phlebitis) was also similar.

In a retrospective cost analysis, the records of 527 patients with acute leukemia were studied (27). They had been treated in a multicenter, randomized trial for febrile neutropenia with ceftazidime and amikacin plus either teicoplanin (6 mg/kg in a single dose; $n = 275$) or vancomycin (30 mg/kg/day in 2 doses; $n = 252$). Clinical responses were equivalent. Again the higher acquisition costs for teicoplanin were counterbalanced by the lower incidence of adverse events and easier administration, resulting in overall similar costs for both regimens. A total of 8% of patients treated with vancomycin reported adverse events compared with 3.2% of patients treated with teicoplanin. Rashes occurred in 6.0 versus 1.4% respectively. Nephrotoxicity, ototoxicity, fever, and hypotension occurred in very few patients.

Organs and Systems

Cardiovascular

Vancomycin can cause phlebitis if infused peripherally (28,29).

Nervous system

It is still controversial whether vancomycin can cause ototoxicity when given alone. However, vancomycin can augment the ototoxicity of aminoglycosides (30). Tinnitus and dizziness have been noted, resolving on withdrawal (31). Hearing loss can be transient or permanent. If vancomycin is combined with aminoglycosides, toxicity may be additive (32).

Sensory systems

Eyes

In 118 consecutive patients undergoing cataract surgery, the use of supplementary prophylactic vancomycin in the irrigating solution during extracapsular lens extraction was significantly associated with an increased incidence of angiographic and clinical cystoid macular edema (33).

Ears

The risk of ototoxicity has been assessed in a prospective study in 16 patients on continuous ambulatory peritoneal dialysis treated with two infusions of vancomycin (30 mg/kg) in 2 liters of peritoneal dialysate administered at 6-day intervals for episodes of peritonitis (34). Patients who were too ill to respond appropriately, those with pre-existing sensorineural hearing loss, those with a narrow auditory canal, those with a discharging ear or perforated tympanic membrane, and those receiving concurrent ototoxic drugs were excluded. The authors found no evidence of ototoxicity (pure-tone audiometry, electronystagmography, and clinical assessment), even with repeated courses of vancomycin. Average serum concentrations were in the target range. No adverse effects were recorded, except for a transient generalized pruritus in one patient after the start of infusion.

In a prospective multicenter study in 152 children with peritoneal dialysis-associated peritonitis one patient with vancomycin intoxication had a 20–30 dB increase in hearing threshold (35).

Hearing loss due to vancomycin toxicity has been treated by hemoperfusion and hemodialysis (36).

- A 14-month-old girl with chronic renal insufficiency due to renal dysplasia was empirically treated with ceftazidime and vancomycin for fever. Her calculated creatinine clearance was 10 ml/minute/1.73 m^2. She erroneously received vancomycin 1.5 g in 3 doses 6 hours apart. Her serum creatinine concentration increased and her vancomycin concentrations remained markedly high (338 mg/l 5 hours after the third dose). The half-life of vancomycin was 145 hours. Hearing loss developed. Continued charcoal hemoperfusion and hemodialysis were used to treat the disorder. Thrombocytopenia was noted as significant consequence of hemoperfusion. The patient did not fully recover her previous renal function and became dialysis dependent. The audiogram normalized by 6 months.

Metabolism

Lactic acidosis occurred in a 56-year-old woman who was given intravenous vancomycin 1 g bd for 10 days (37).

Hematologic

Hemophagocytosis after vancomycin and teicoplanin occurred in a 45-year-old woman (38).

Treatment with vancomycin can rarely cause reversible pancytopenia (39).

- Neutropenia occurred in a 48-year-old man 16 days after the start of vancomycin therapy (40). Vancomycin was withdrawn and he was given a granulocyte-colony

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stimulating factor. He was then rechallenged with a single dose of vancomycin 1 g. His white blood cell count fell to 600 $\times$ 10^9/l but returned to normal with continued granulocyte-colony stimulating factor therapy.

- A 43-year-old white woman was given vancomycin for a suspected methicillin-resistant *S. aureus* infection (41). On day 10 she developed a fever, chills, and a disseminated lacy macular rash. Vancomycin was withdrawn but reinstituted 48 hours later. Another 24 hours later, she again developed a fever, chills, and a confluent erythematous rash. Sepsis developed, and ceftazidime was added. There was thrombocytopenia (118 $\times$ 10^9/l), and a fall in the white blood count (from 7.6 to 3.5 $\times$ 10^9/l) and hemoglobin (from 13.8 to 12.2 g/dl). One day later the leukocyte count was 2.6 $\times$ 10^9/l and the hemoglobin fell to 10 g/dl. Both drugs were withdrawn. The rash disappeared, the temperature returned to normal, and the blood cell counts completely recovered 4 days later.
- An 87-year-old white woman was treated with vancomycin for an abscess due to methicillin-resistant *S. epidermidis* (42). On day 30, her white blood cell count fell to 0.5 $\times$ 10^9/l after a total dose of 55 g of vancomycin. Vancomycin was withdrawn, and the white blood cell count returned to normal within 5 days. After 6 weeks vancomycin was reintroduced, and the white blood cell count fell to 0.325 $\times$ 10^9/l after a total dose of 14 g of vancomycin on day 9, but resolved rapidly after vancomycin was withdrawn.

Leukocytes

Vancomycin-induced neutropenia occurs in about 2% of treated patients, and complete recovery takes place in 2–5 days after withdrawal (43,44). It occurs after prolonged treatment with high doses in patients with normal renal function (for example more than 20 days of more than 15–20 mg/kg) or in the prolonged presence of high serum concentrations in patients with severe renal insufficiency (45). After withdrawal of vancomycin, neutropenia disappeared promptly. The bone marrow seemed to be unaffected. Other cases of agranulocytosis related to vancomycin therapy have been reported (46–48).

Neutropenia normally recovers after drug withdrawal, and the neutrophil count can recover when vancomycin is replaced by teicoplanin (49).

- A 35-year-old man was given vancomycin (1.5 g bd) for a wound infection with a coagulase-negative staphylococcus, a peptostreptococcus, and a coryneform Gram-positive bacillus. On day 37 hi white blood cell count was 2.8 $\times$ 10^9/l (baseline 5.2) with a low neutrophil count (0.5 $\times$ 10^9/l). Vancomycin was withdrawn and 2 days later he was given teicoplanin 400 mg/day, by which time the cell count had increased to 3.5 $\times$ 10^9/l, neutrophils 0.9 $\times$ 10^9/l. On day 45, the total white cell count was 4.9 $\times$ 10^9/l, neutrophils 2.3 $\times$ 10^9/l. Teicoplanin was continued for 1 month, and the white cell count remained normal.

A direct toxic effect of vancomycin and/or an immune-mediated mechanism (antineutrophil antibodies, sensitized lymphocytes) have been discussed.

- A typical case of vancomycin-induced neutropenia has been reported in a 39-year-old woman with sickle cell SS disease treated with vancomycin for methicillin-resistant coagulase-negative staphylococcal bacteremia (50). However, in addition to neutropenia, the clinical course was defined by a febrile period characteristic of drug fever, with delayed onset and resolution 48 hours after vancomycin was withdrawn. In this case, fluconazole and cefazoline were also administered, but their contribution to neutropenia was judged unlikely (negative rechallenge with fluconazole, withdrawal of cefazoline after less than 5 days of therapy).

Platelets

Thrombocytopenia is a rare adverse effect of vancomycin and may be associated with the presence of vancomycin-dependent antiplatelet IgG antibodies. Reports of drug-induced thrombocytopenia have been systematically reviewed (51). Among the 98 different drugs described in 561 articles the following antibiotics were found with level I (definite) evidence: co-trimoxazole, rifampicin, vancomycin, sulfisoxazole, cefalothin, piperacillin, methicillin, novobiocin. Drugs with level II (probable) evidence were oxytetracycline and ampicillin.

- Vancomycin-associated thrombocytopenia has been reported in a 72-year-old woman who was treated with gentamicin and vancomycin for infectious endocarditis due to *Clostridium pseudodiphtheriticum* (52). On the 4th day of treatment, the platelet count fell and reached a nadir of 14 $\times$ 10^{12}/l on day 7. Two days after withdrawal of vancomycin (day 8) the platelet count began to rise and reached 150 $\times$ 10^{12}/l within 5 days. Vancomycin-dependent antiplatelet IgG antibodies were not detected 10 days after vancomycin.
- Thrombocytopenia also developed in a 72-year-old man who was treated with vancomycin for staphylococcal sepsis after treatment with gemcitabine for metastatic pancreatic cancer (53). On day 12 thrombocytopenia developed, reached a nadir on day 18 (13 $\times$ 10^{12}/l), and did not respond to platelet transfusions. Bone-marrow megakaryocytes were adequate. Platelet-associated IgG and IgM were increased. Vancomycin was withdrawn on day 28, with prompt recovery of the platelet count to 136 $\times$ 10^{12}/l in 10 days.

Vancomycin was associated with subsequent thrombocytopenia in a retrospective study that included 193 patients in a surgical trauma intensive care unit (54).

Patients undergoing allogeneic hemopoietic stem cell transplantation always require platelet transfusions, but the increase in platelet count is often less than expected. The factors responsible for poor responses to platelet transfusions in this clinical setting are largely unknown. In a prospective study in 87 consecutive transplanted children univariate analysis showed that concomitant therapy with vancomycin is significantly associated with a lower post-transfusion corrected increment in platelet count (55).

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Gastrointestinal

Antibiotic-associated diarrhea can develop with any antibacterial agent. Vancomycin has been implicated as a rare cause of diarrhea associated with *Clostridium difficile* (56), despite the fact that vancomycin is often used to treat it.

- Diarrhea developed in a 60-year-old man on chronic hemodialysis after 20 doses of parenteral vancomycin (250 mg at each dialysis) (57). Although culture for *C. difficile* was not performed, latex agglutination was positive for *C. difficile* toxin.

A few other cases of antibiotic-associated diarrhea with vancomycin have been described in association with *C. difficile*. This paradoxical association, although very uncommon, should be considered in patients who develop diarrhea during vancomycin therapy.

Urinary tract

Of 69 neonates (including 8 with peak vancomycin concentrations over 40 μg/ml) with culture-proven *S. aureus* or coagulase-negative staphylococcal septicemia who received vancomycin for more than 3 days, 6 had a doubling of serum creatinine concentration during vancomycin treatment, and all were in the group with peak serum vancomycin concentrations under 40 μg/ml (58).

Nephrotoxicity of vancomycin is often mild and reversible after withdrawal. It occurs in 6–17% of courses (59). Higher frequencies of nephrotoxicity were reported when vancomycin was used in combination with an aminoglycoside, which is consistent with toxicological data obtained in rats (60). Nevertheless, evidence of synergistic toxicity between vancomycin and aminoglycosides is controversial (2,31,59). Endotoxins seem to potentiate the nephrotoxic effect of vancomycin, at least in rats (61).

Acute interstitial nephritis has been reported in a patient receiving vancomycin (62).

- A 64-year-old white man was treated with intravenous cloxacillin 2 g 4-hourly for a *S. aureus* sternal wound infection and osteomyelitis. On day 14, cloxacillin was discontinued because of a fall in renal function. Urinalysis was positive for occasional red blood cells and hyaline casts, but there were no eosinophils. He was given intravenous vancomycin 1.5 g 36-hourly. Renal function gradually improved and the dosing regimen was adjusted to 1.5 g/day. Predose vancomycin serum concentrations were 11.0 and 6.3 mg/l on days 23 and 30 respectively. On day 32, oral ciprofloxacin 500 mg bd was added for suspected sepsis (catheter tip cultures grew *Klebsiella pneumoniae*, although blood cultures were negative). Other medications were enteric-coated aspirin, warfarin, acebutolol, and digoxin. The next day, a progressing maculopapular rash developed and the patient continued to have a fever. Acute interstitial nephritis was confirmed by kidney biopsy. Hemodialysis was required, and he was treated with prednisone and made a gradual recovery. Four months later, he was treated with vancomycin for a relapse of the sternal infection. His eosinophil count rose and peaked at 18%, and there were eosinophils in the urine.

The authors found four other published cases of vancomycin-induced acute interstitial nephritis.

There was a fall in residual renal function during episodes of peritonitis in a prospective multicenter study in 152 children with peritoneal dialysis-associated peritonitis (35). The study evaluated the efficacy, safety, and clinical acceptance of combination treatment, including a glycopeptide (teicoplanin or vancomycin) and ceftazidime, each given either intermittently or continuously. Irreversible anuria developed in 19% of the patients with residual diuresis. In patients who retained residual renal function, there was a strong trend toward a decreased residual glomerular filtration rate (−11%). There was no difference with respect to the type of glycopeptide or the mode of use. Aminoglycosides were used concomitantly in only 12 patients and did not seem to affect the evolution of residual renal function. Underdosing/non-adherence or overdosing occurred in 8.2% of continuously treated versus 4.9% of intermittently treated patients. Intermittent and continuous intraperitoneal treatment with glycopeptides and ceftazidime were equally efficacious and safe when measured by objective clinical criteria.

In children with febrile neutropenia and Gram-positive bacteremia associated with antineoplastic drug therapy, teicoplanin was significantly less nephrotoxic than vancomycin (63).

The effect of co-administration of fosfomycin on glycopeptide antibiotic-induced nephrotoxicity for 3 days has been investigated in rats (64). Fosfomycin reduced glycopeptide antibiotic-induced nephrotoxicity, as shown by reduced urinary excretion of *N*-acetyl-beta-D-glucosaminidase and fewer histological signs of nephrotoxicity in those treated with a combination of glycopeptide and fosfomycin compared with a glycopeptide alone. In addition, the higher the dose of fosfomycin, the more it reduced urinary *N*-acetyl-beta-D-glucosaminidase activity, suggesting that the role of fosfomycin in alleviating nephrotoxicity is dose-dependent. There was significantly less accumulation of teicoplanin and vancomycin in the renal cortex of rats treated with glycopeptide antibiotics plus fosfomycin compared with the glycopeptide antibiotics alone.

Skin

Epidermolysis bullosa acquisita occurred in a 73-year-old man after a course of vancomycin for 15 days (65).

A fixed drug eruption after the fifth dose of vancomycin 1 g occurred in a 45-year-old white woman (66).

Vancomycin reportedly caused a severe delayed skin reaction with allergic cross-reactivity between vancomycin and teicoplanin requiring steroid therapy (67).

- A 68-year-old woman who was being treated with vancomycin for *S. epidermidis* bacteremia developed pruritus and a generalized maculopapular skin rash after 2 weeks. After a short course of prednisolone, she was given teicoplanin and developed general malaise, fever, conjunctival injection, an extensive rash, and later blisters on the legs, again requiring treatment with steroids.

Erythema multiforme

Erythema multiforme has been attributed to vancomycin (67).

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- A 70-year-old woman given vancomycin postoperatively developed fever on day 5 and vancomycin was withdrawn. She then developed a generalized urticarial rash with oral and vaginal erosive lesions on day 6, requiring treatment with steroids and antihistamines. The diagnosis was confirmed by skin biopsy.

Vancomycin can cause the severe forms of erythema multiforme, both Stevens–Johnson syndrome (involvement of 10–30% of the skin surface) (68) and toxic epidermal necrolysis (more than 30% of the skin surface involved); both conditions include mucosal involvement.

- A 53-year-old white woman with liver cirrhosis took vancomycin (1 g bd) for sepsis due to methicillin-resistant *S. aureus* and a catheter-associated infection due to *Enterococcus faecalis*, developed oral and vaginal mucositis and conjunctivitis followed by a maculopapular rash (69). The diagnosis was confirmed by skin biopsy. Vancomycin was replaced by teicoplanin and corticosteroids; the symptoms disappeared within 7 days.
- A 36-year-old white woman with relapsing acute myeloid leukemia took ceftazidime (2 g tds) and aciclovir for febrile neutropenia and *Herpes labialis*. She developed an itchy rash and treatment was changed to imipenem (500 mg qds for 5 days), vancomycin (1 g bd for 3 days), and gentamicin (2 mg/kg for 3 days); chemotherapy included idarubicin, cytarabine, etoposide, ondansetron, and dexamethasone for 3 days. Within a few days the rash developed into blisters and erosions, affecting more than 80% of the skin. The diagnosis was confirmed histologically, and she subsequently died from shock (70).

Linear IgA bullous disease

Linear IgA bullous disease is an autoimmune subepidermal disorder, characterized by a linear deposition of IgA along the blister base, with a predominantly neutrophilic dermal infiltrate. Most often idiopathic, a subset of linear IgA bullous disease is induced by drugs, and intravenous vancomycin is the best-documented drug that triggers it (71). The diagnosis can be confirmed by direct immunofluorescence (72,73). In some cases the blisters resolve only after withdrawal of therapy and in others glucocorticoid therapy is required.

In a review of 17 cases the features were: mean age 65 years; 11 men/6 women; eruption latency 1–15 days; normal trough concentrations (when reported); cutaneous manifestations included bullous, urticarial, erythematous, and targetoid erythema multiforme-like lesions favoring the trunk, extremities, palms, and soles, and sparing the head and neck; six patients had mucosal involvement (74). The gold standard for diagnosis is direct immunofluorescence of the perilesional skin. Circulating antibasement membrane zone antibodies were identified only in a minority of patients. Therapies included drug withdrawal, prednisone, and dapsone. No spontaneous recurrences were reported.

Linear immunoglobulin A bullous disease has been reported in a 69-year-old white woman treated with vancomycin and ciprofloxacin, in a 53-year-old white man with septic shock, and in other cases in which both vancomycin and *Varicella zoster* infection were present as triggers (75–78).

- An 87-year-old white woman treated with vancomycin and phenytoin and a 65-year-old white man with renal insufficiency developed linear immunoglobulin A bullous disease (79,80).
- A 72-year-old woman developed a bullous eruption on her palms, soles, and conjunctivae a day after receiving vancomycin (intravenously and via a cecostomy tube) for staphylococcal sepsis (81). Immunofluorescence of the skin biopsy showed linear IgA deposition along the basement membrane. The lesions cleared over the next 2 weeks after withdrawal of vancomycin.
- A blistering eruption developed in the skin and buccal mucosa of a 79-year-old man after 8 days of vancomycin therapy for an infected leg ulcer (82). Biopsy showed linear IgA deposition along the basement membrane. The lesions cleared spontaneously within two days of withdrawal.
- After 7 days of antibiotic therapy with intravenous vancomycin, gentamicin, and ticarcillin + clavulanate for *Pseudomonas aeruginosa* and *S. aureus* sepsis, confluent erythematous-based vesicobullae developed in a 65-year-old woman with subarachnoid hemorrhage secondary to a ruptured aneurysm (72). Other medications included ranitidine, glyceryl trinitrate, nimodipine, ferrous sulfate, and phenytoin.
- On the tenth day of antibiotic therapy with vancomycin, imipenem, and gentamicin for an infected enterocutaneous fistula, widespread bullae developed in a 60-year-old woman (72).
- In a 71-year-old woman with pneumonia, vesicles and bullae developed on the eighth day of antibiotic therapy that consisted of one dose of intravenous vancomycin followed by a course of nafcillin (73).
- A 52-year-old woman was given vancomycin 1 g intravenously bd and within 12 hours developed a generalized pruritic maculopapular rash (83). Over the next few days, the lesions progressively worsened and transformed into hemorrhagic and non-hemorrhagic vesicles and bullae. Mucosal surfaces, palms, and soles were spared. The skin lesions completely healed without scarring within 2 weeks of vancomycin withdrawal. There was no recurrence 5 months later.

Sexual function

- Prostatitis due to vancomycin-resistant enterococci has been reported in a 42-year-old liver transplant recipient (84). The organism, *Enterococcus faecium*, was resistant to vancomycin, ampicillin, ciprofloxacin, and doxycycline. Treatment with a combination of rifampicin and nitrofurantoin for 6 weeks resulted in a long-lasting cure.
- Priapism has been reported in a 37-year-old man with a 30-year history of severe diabetes mellitus after two doses of vancomycin 1 g intravenously for treatment of methicillin-resistant *S. aureus* bursitis (85).

The authors noted that an interaction between vancomycin and other medications (cefazolin, aztreonam, ciclosporin, prednisone, mycophenolate mofetil, and co-trimoxazole) could not be ruled out.

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Immunologic

Allergic reactions with vancomycin, such as rashes, chills, fever, and eosinophilia, can occur in up to 5% of patients. Severe anaphylactic reactions are rare. Alpha-tryptase is only detected in the blood during systemic anaphylactic reactions, having been released by degranulation from activated mast cells. Plasma tryptase activities were unchanged, independent of increased histamine concentrations, antihistamine pretreatment, and clinical symptoms of anaphylactoid reaction in 40 patients receiving vancomycin (1 g over 10 minutes) before elective arthroplasty (86). The authors conclude that plasma tryptase activities can be used to distinguish chemical from immunological reactions.

Vancomycin anaphylaxis is a major management problem in patients with methicillin-resistant *S. aureus* sepsis. However, desensitization in patients with previous anaphylaxis is possible (87).

- An anaphylactic reaction occurred in a 77-year-old woman 5 minutes after the start of a vancomycin infusion, when she had received only 40 mg (88). She became unconscious and had a severe cardiovascular collapse, from which she was resuscitated with intravenous ephedrine and adrenaline.
- A 47-year-old white woman with end-stage renal disease had had anaphylactoid shock after vancomycin 1 g intravenously infused over 1.5 hours and gentamicin 90 mg 3 years before, despite premedication with diphenhydramine (89). She was treated with doubling doses of vancomycin every 30 minutes for methicillin-resistant *S. epidermidis*. She had no reaction.

The authors of the second report could not exclude that the previous anaphylactoid reaction had not been due to gentamicin, as no specific testing was done. Although successful vancomycin desensitization has been described, this would be the first time in a patient with a history of anaphylactoid reaction.

In some patients the clinical presentation of red man syndrome is identical to that of acute IgE-mediated anaphylaxis. Vancomycin desensitization should therefore be considered for severe red man syndrome reactions that do not respond to premedication and a slower rate of infusion, and in anaphylactic reactions to vancomycin when substitution of another antibiotic is not feasible. Rapid desensitization is preferred, as it is effective in the majority of patients and enables administration of vancomycin within 24 hours. In patients who fail rapid desensitization, a slow desensitization protocol may be tried (90).

Vasculitic rashes have been described rarely. Two case reports have suggested that there may be cross-reactivity between vancomycin and teicoplanin with respect to biopsy-proven leukocytoclastic vasculitis (91). In both cases, vancomycin-induced vasculitis improved after drug withdrawal. Teicoplanin was started and the rash reappeared several days later. In one case the rash faded after teicoplanin had been withdrawn. In the other, teicoplanin was continued, but the rash improved after prednisolone was given.

Long-Term Effects

Drug resistance

The increasing rate of antimicrobial drug resistance has been a matter of great concern and is the most serious unwanted effect of these drugs. However, in spite of the fact that the problem is now very well recognized (SEDA-25, 279), it continues to grow.

History

Most antimicrobial drugs are natural products, that is they are produced by micro-organisms such as bacteria or fungi, often found in the soil. In fact, they can be looked upon as nature's regulatory principle for microbial society. Resistance to antimicrobial drugs is therefore a natural phenomenon. Before the introduction of penicillin in the 1940s, resistance to antimicrobial drugs was not a clinical problem. At that time, the large majority of commensal and infectious bacteria associated with infections in man were susceptible.

Over the last six decades, however, increased use of antimicrobial drugs, not only in human medicine, but in other areas, such as veterinary medicine, agriculture, and fish farming, has had an enormous impact on the microbial society. Nearly everywhere, the numbers of susceptible strains have reduced and resistant strains or variants have increased in numbers. It has been repeatedly reported that the susceptibility profile of bacteria in any human compartment, such as the skin, intestine, and respiratory tract, is very different from what it was in the pre-antibiotic era, and even 15 years ago. The same trend is reported from hospitals and homes. Multidrug resistance, that is resistance to several antimicrobial drugs, is commonly found in bacteria that cause infections as well as in commensal organisms.

A few decades ago, it was a common opinion that various compartments in nature have their own flora. As an example, it was claimed that you could use antimicrobial drugs relatively freely in fish farming without increasing the burden of resistance in humans. Now we have learned the lesson. Micro-organisms circulate everywhere, and there is a continuous exchange of strains between all compartments in nature (humans, animals, birds, fish, etc.). Even if a bacterial species is host-specific, the genetic material that codes for resistance is not. In fact, antibiotics have shown that bacteria have great genetic adaptability, in terms of their ability to exchange genetic traits among genera and species which are evolutionarily millions of years apart. Antibiotic resistance genes on plasmids and transposons flow to and from nearly all types of bacteria. Sometimes they leave the plasmid and jump into bacterial chromosomes; sometimes they jump back again.

However, this knowledge is not being heeded everywhere. Small doses of antimicrobial drugs as "growth promoters" are still commonly used, even in countries in which the health authorities should be aware of the problems. It is easy to blame developing countries for using antimicrobial drugs as growth promoters, or for selling antimicrobial drugs over the counter without prescription, but it took the European Community many years before it started to look into the problem of using antimicrobial

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drugs as growth promoters. The history of cross-resistance between avoparcin and vancomycin may have provided important background for this alteration in attitude.

Avoparcin and vancomycin are glycopeptide antibiotics, large molecules that are produced by a variety of environmental micro-organisms, which may therefore contain genes that code for antimicrobial drug resistance. Both of these drugs are mostly active against Gram-positive bacteria, such as enterococci and staphylococci. In Europe, avoparcin was allowed to be used as an animal food additive in many countries, while the use of vancomycin was limited to humans. Nobody bothered about the possibility of cross-resistance between avoparcin and vancomycin until 10 years ago. After the emergence of vancomycin-resistant enterococci and after more than 2 years of hard lobbying by several groups, avoparcin was withdrawn from the market in the European Community. However, in the meantime, vancomycin-resistant enterococci had become widespread in many European countries.

Instead of focusing on the development of resistance to a specific antimicrobial drug in a specific species, we should focus on the microbial community as a single entity or a "metagenome". Any use of any microbial agent might cause resistance to develop in one or more microbial species. When such genes have first become established, they may float around and be picked up by other species. This approach to the development and spread of resistance can, and should, be applied to the microbial flora in all mammals, as well as in the environment. The consequence of this approach is that we should, every time we prescribe an antimicrobial drug, try to find a drug that hits nothing but the pathogen in the infected organ(s). Of course, this can be difficult and sometimes even close to impossible. But that should not stop us from trying. For example, in nearly all cases, a third-generation cephalosporin for acute pharyngitis caused by Group A streptococci, or of a fluoroquinolone for acute cystitis, are not the best alternatives.

Ecology

In our struggle for prudent use of antimicrobial drugs, the so-called eco-shadow concept represents a challenging way of following alterations in mammalian and environmental ecosystems produced by exposure of these systems to antibiotics (92). In brief, an eco-shadow (ecological shadow) can be defined as any alteration in any ecosystem following exposure of the system to an antimicrobial drug (or any compound that influences the system). The alterations can be of variable length and may involve a variable number of species and functions, including the development and spread of resistance. When possible, the sum of all the alterations caused by an antibiotic can be included in an "eco-shadow index." A large eco-shadow or high eco-shadow index indicates a high tendency to the development of microbial resistance.

At present, it seems that Europe has taken the lead in the fight against antimicrobial drug resistance. At the Fourth European Conference on Antibiotic Resistance, organized by the European Commission and held in Rome in November 2003, it was strongly emphasized that only a multidisciplinary approach, involving all stakeholders—physicians, researchers, industry, politicians, and patients—can overcome the problem of increasing resistance. It is to be hoped that this problem will be established as a major objective for the forthcoming European Centre for Disease Prevention and Control.

Reports of organisms that are resistant to vancomycin

The first case of methicillin-resistant *S. aureus* with intermediate resistance to vancomycin was documented in May 1996. Additional cases have been described in the USA:

- a 59-year-old man with diabetes mellitus and chronic renal insufficiency suffering from peritonitis;
- a 66-year-old man with diabetes who developed a septicemia after 18 weeks of vancomycin treatment for recurrent methicillin-resistant *S. aureus* bacteremia;
- a 79-year-old man with diabetes and chronic renal insufficiency, who developed intermediate vancomycin-resistance after a 6-week therapy with vancomycin for MRSA bloodstream infection.

In the last case the strain was identical to eight MRSA isolates obtained from hospitals in the New York City metropolitan area, and all eight isolates, but not control isolates, could be transformed in vitro to develop intermediate resistance to vancomycin. Both the presence of glycopeptides and environmental factors, as demonstrated by increased resistance of *S. aureus* to antibiotics in the presence of prosthetic material in animals, can exert selective pressure to develop new resistance mechanisms (93–95).

There are reports of vancomycin-dependent enterococci that grow only in the presence of vancomycin and are best treated by withdrawal of the compound (96).

Vancomycin/glycopeptide intermediately resistant and methicillin-resistant *S. aureus* have been described in Japan, Europe, the Far East, and the USA. Some vancomycin-susceptible strains of *S. aureus* contain subpopulations with intermediate resistance to vancomycin (heterogeneous strains), and these may escape laboratory detection (93,94,97–99).

Numerous risk factors have been identified for infection with vancomycin-resistant enterococci. In one study the severity of mucositis in cancer patients was significantly associated with vancomycin-resistant enterococci (100). Previous vancomycin therapy was also believed to be a risk factor. However, a meta-analysis concluded that the reported strong association between vancomycin treatment and hospital-acquired vancomycin-resistant enterococci results from selection bias, confounding by duration of hospitalization, and publication bias (101).

Glycopeptide resistance in a cluster of three clinical isolates of vancomycin-resistant *Enterococcus faecium* was due to vanD, which was located on the chromosome and was not transferable to other enterococci. These isolates were indistinguishable but differed from the strain in which vanD-mediated resistance has been reported previously (102). A type of acquired glycopeptide resistance, named vanE, has been characterized in *E. faecalis* BM 4405. It results in low-level resistance of vancomycin but susceptibility to teicoplanin (103). Defects in penicillin-binding protein 4 result in a distorted peptidoglycan composition of the cell of vancomycin-resistant and teicoplanin-resistant laboratory mutants of *S. aureus* and are suggested to be part of the mechanism of glycopeptide resistance in these microbes (104).

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Vancomycin-dependent enterococci growing only in the presence of vancomycin are best treated by withdrawing vancomycin (96). However, vancomycin-independent revertants can rapidly emerge in vitro, endangering the cure of patients treated by interruption of vancomycin only (105).

In a study of antibiotic resistance in enterococci from raw meat, there was a high prevalence of glycopeptide-resistant strains (106). Resistance to vancomycin was significantly associated with resistance to teicoplanin, erythromycin, tetracycline, and chloramphenicol.

The prevalence of vancomycin-resistant enterococci (VRE) has been investigated in 49 laboratories from 27 European countries, which collected 4208 clinical isolates; 18 vanA and 5 vanB isolates of VRE were identified (107). The prevalence of vanA VRE was highest in the UK (2.7%), while the prevalence of vanB VRE was highest in Slovenia (2%). Most vanA and vanB vancomycin-resistant enterococci were identified as *E. fecium*. A total of 71 isolates containing the vanC gene were identified. The prevalence of vanC VRE was highest in Latvia and Turkey, where rates were 14 and 12% respectively. Two-thirds of these isolates were identified as *Enterococcus gallinarum* and one-third as *Enterococcus casseliflavus*.

In 155 methicillin-resistant strains of *S. aureus* isolated from patients in Thailand, one-point population analysis identified three methicillin-resistant strains, which contained subpopulations of cells with reduced susceptibility to vancomycin (108).

Susceptibility Factors

Renal disease

Vancomycin is eliminated almost exclusively by renal excretion. In oliguria 1 g can produce therapeutic plasma concentrations for 10–14 days. Hemodialysis fails to remove vancomycin from the body to any significant extent. If renal function is compromised, even oral therapy with vancomycin can lead to high and potentially toxic serum and CSF drug concentrations (109).

Drug Administration

Drug contamination

Vancomycin underwent spontaneous chemical modification when kept at room temperature at neutral pH in aqueous solutions containing traces of formaldehyde or acetaldehyde (110). In vitro studies on two different strains of bacteria showed that the resulting compounds had reduced antibacterial activity.

Drug administration route

In a multicenter, prospective, randomized comparison of continuous infusion of vancomycin (targeted serum plateau concentrations of 20–25 μg/ml) and intermittent infusions of vancomycin (targeted serum trough concentrations of 10–15 μg/ml) in 119 critically ill patients, microbiological and clinical outcomes and safety were similar (111). Continuous infusion of vancomycin produced the target concentration faster, and fewer samples were required for monitoring. Serum creatinine concentrations and creatinine clearance increased non-significantly from baseline to the end of treatment in the two groups. There was nephrotoxicity in 21 patients (10 of whom received the continuous infusion). Vancomycin given concomitantly with other antibiotics was associated with a significant increase in the serum creatinine concentration, but not when it was given alone. Dialysis was required for three of those who were given intermittent infusions and six of those who were given continuous infusions. Red man syndrome was reported in one patient who was given an intermittent infusion, and phlebitis and fever in two patients who were given continuous infusions.

Drug overdose

- Accidental 10-fold vancomycin overdose in a 6-month-old girl resulted in flushing and a transient rise in serum creatinine concentration, but she recovered completely without specific therapeutic intervention (112).
- Two preterm twins, born in the 35th week of gestation, accidentally received an overdose of vancomycin as an intravenous bolus injection (113). Both were treated from the day of birth with piperacillin (100 mg/kg/day) and cefotaxime (100 mg/kg/day) for congenital pneumonia. On the 6th day of antibiotic therapy, vancomycin (38 and 35 mg/kg respectively) was given over 1 minute. A few minutes later the twins developed flushed faces and trunks and peripheral cyanosis. Other findings were a prolonged capillary refill time, apnea and hypoxemia, bradycardia (40–60/minute), a fall in systolic blood pressure of 10 mmHg, and metabolic acidosis (pH 7.29 and 7.24 and base excess −10.5 and −10.9 respectively). Metabolic acidosis and the red man syndrome disappeared after 30 minutes. Serum vancomycin concentrations were 32 and 34.5 μg/ml respectively 9 hours after administration. Fundoscopy and repeated otoacoustic emissions were normal. There was minimal reduction in creatinine clearance. Tubular proteinuria, paralleled by increased activity of *N*-acetyl-beta-D-glucosaminidase in the urine, resolved completely within 1 week.
- Hemodialysis with high-efficiency dialysis membranes resulted in a removal of plasma vancomycin of about 60% (calculated half-life 2 hours) in two children with initial plasma vancomycin concentrations of 238 μg/ml and 182 μg/ml (114).
- In a 6-day-old neonate with a solitary hypodysplastic kidney, suspected sepsis, and acute renal insufficiency, venovenous hemodiafiltration with a high-flux membrane was successfully used to treat a 10-fold overdose of vancomycin (115).

Multiple-dose activated charcoal does not increase the elimination of vancomycin and is therefore not recommended for detoxification of acute poisoning (116).

Drug–Drug Interactions

Aminoglycoside antibiotics

Vancomycin is more nephrotoxic than teicoplanin when it is combined with aminoglycosides (117).

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Beta lactam antibiotics

Vancomycin and ceftazidime are incompatible in vitro because of precipitation due to the alkaline pH of vancomycin relative to ceftazidime. This phenomenon was encountered in two cases of post-traumatic endophthalmitis (118). Immediately on local administration of the antibiotics, which were injected using different needles and syringes for each drug, dense yellow-white precipitates were observed along the needle tract in the vitreous cavity. During follow-up the vitreous opacities gradually disappeared over a period of 2 months, with complete resolution.

Co-administration of imipenem + cilastatin may reduce the nephrotoxicity of vancomycin, as suggested by a study in rats (119).

Dexamethasone

Intravitreal application of dexamethasone may reduce the elimination of intravitreal vancomycin and may enhance this therapy, as suggested by an in vivo study in rabbits (120).

Dobutamine

In critically ill patients, co-administration with dobutamine can enhance vancomycin clearance by increasing cardiac output and renal blood flow and by interacting with the renal anion transport system, increasing glomerular filtration rate and renal tubular secretion (121).

Dopamine

In critically ill patients, co-administration with dopamine can enhance vancomycin clearance by increasing cardiac output and renal blood flow and by interacting with the renal anion transport system, increasing glomerular filtration rate and renal tubular secretion (121).

Fosfomycin

Co-administration of fosfomycin may reduce the nephrotoxicity of vancomycin, as suggested by a study in rats (119).

Furosemide

Preterm infants often receive theophylline for apnea of prematurity and furosemide to improve dynamic lung compliance and to reduce total pulmonary resistance. In 10 preterm infants receiving furosemide plus theophylline, vancomycin was introduced according to the generally recommended dosing schedules but failed to achieve anticipated therapeutic concentrations (122). In nine infants the addition of furosemide to vancomycin plus theophylline resulted in a fall in serum vancomycin concentrations to subtherapeutic within 24 hours, and only in one did vancomycin concentrations remain within the target range. The addition of furosemide reduced the serum creatinine concentration by 24% (range 12–43). These data suggest that furosemide enhances the excretion of vancomycin, and an acute and transient increase in glomerular filtration rate and creatinine clearance may be the explanation.

Gelatin

Vancomycin is incompatible with gelatin-containing fluids, resulting in precipitation (123).

Levofloxacin

Changes in pharmacokinetics were studied in male Wistar rats when intravenous vancomycin 100 mg/kg and levofloxacin 20 mg/kg were administered together (124). There was an increase in the AUC and half-life of vancomycin. There was also an increase in the AUC and a delay in the t_{max} of levofloxacin, but no effect on C_{max}; these data suggested delayed absorption of levofloxacin. Concomitant administration had no effect on the correlation between serum and hepatic tissue concentrations of levofloxacin, but it markedly reduced the correlation between the serum and renal tissue concentrations of vancomycin. Vancomycin increased serum creatinine concentrations 8 hours after administration. However, there was no difference in animals who received monotherapy compared with animals who received combined therapy. The authors suggested the cautious use of a combination of levofloxacin and vancomycin and advised monitoring blood concentrations of vancomycin in such cases.

Neuromuscular blocking drugs

Some authors stress the fact that vancomycin can interact with anesthetic drugs, particularly muscle relaxants. In the reported cases anaphylactoid reactions were seen, with intense erythema and marked permeability changes (125).

Monitoring Therapy

There is evidence that predose concentrations of teicoplanin are related to clinical outcome; the evidence is less conclusive for vancomycin. Predose concentrations can be linked to some toxic effects (nephrotoxicity for vancomycin and thrombocytopenia to teicoplanin) (SEDA23.26.77) (126,127). Monitoring of serum concentrations has therefore been advocated to reduce potential nephrotoxicity and ototoxicity due to interpatient variability in vancomycin pharmacokinetics. However, routine monitoring is probably unnecessary in most patients (3,128). Clinical settings in which monitoring is wise include combination therapies with an aminoglycoside and treatment of patients with poor or unstable renal function (2). Vancomycin-induced nephrotoxicity is clearly related to drug plasma concentrations: trough vancomycin concentrations over 15 μg/ml were associated with significantly more nephrotoxicity (129).

In a prospective study to determine if standardized vancomycin doses could produce adequate serum concentrations in 25 full-term neonates with sepsis 13 had adequate peak vancomycin serum concentrations (20–40 mg/ml) and one had a peak concentration with a risk of ototoxicity (over 40 μg/ml) (130). Only 12 had adequate trough concentrations (5–10 mg/ml) and 7 had a risk of nephrotoxicity (over 10 μg/ml). There was no significant difference between peak or trough concentrations and good or bad clinical outcomes.

Intravenous vancomycin 30–40 mg/kg/day, divided every 6 hours, was given to167 infants and children without cancer and 42 cancer patients aged 3 months to 17.5

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years with normal serum creatinine concentrations and without evidence of renal dysfunction (131). In 93% of the children without cancer, peak serum vancomycin concentrations were in an adequate target range (8–55 μg/ml). However, 10% of the children with cancers had peak serum vancomycin concentrations below 10 μg/ml, and 21% had trough concentrations less than 5 μg/ml; an increased dosage was required to achieve adequate peak concentrations. There were no treatment failures. The authors suggested the following guidelines:

- the serum creatinine concentration should be measured within 24 hours of beginning therapy, to verify normal renal function, and weekly thereafter to detect an eventual reduction in creatinine clearance;
- an increase of serum creatinine of more than 44 μmol/l (0.5 mg/dl) over baseline should be followed by monitoring serum vancomycin concentrations;
- peak and trough vancomycin serum concentrations measurements are not necessary in children without cancer receiving 40 mg/kg/day or less who have normal renal function and do not receive other potentially nephrotoxic drugs; this approach should be individualized, based on factors such as degree of illness, poor clinical response, or persistent positive cultures;
- monitoring should be considered for patients with cancer, neonates, those receiving concurrent nephrotoxic drugs, patients with renal insufficiency, and for dosages over 40 mg/kg/day.

Fluorescence polarization immunoassay determination of serum vancomycin concentrations can result in falsely high vancomycin concentrations in excess of 30–80% in patients with renal dysfunction. This is due to the formation of a non-toxic, non-microbiologically active pseudometabolite, the vancomycin crystalline degradation product (132). A report on a 48-year-old man underlies the significance of resulting underdosing and eventually suboptimal clinical response (133).

Managing Adverse Effects

Vancomycin clearance is minimally altered by hemodialysis using standard cuprophane membranes. However, it is significantly increased using a high-flux polysulfone membrane.

- A 17-year-old anuric woman with end-stage renal insufficiency received a massive overdose of vancomycin (40 mg/kg/day for 8 days) and was treated three times with high-flux hemodiafiltration with a polysulfone membrane (134). The vancomycin concentration fell from 101 to 17 mg/l at the end of the procedure. There were no adverse effects of either vancomycin or hemodiafiltration.
- In a 46-year-old African-American woman with sickle-cell disease there was clinically significant removal of vancomycin during a plasma exchange transfusion (135).

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Varicella vaccine

See also Vaccines

General Information

A live attenuated *Varicella* vaccine was developed in 1973 by Takahashi using the Oka strain, which was isolated from a boy with chickenpox and named after the boy. Several producers use this live vaccine strain, for example Biken Institute, Merck, Sharp & Dohme, and SmithKline Beecham. Whereas the first Oka strain vaccines needed to be stored at −20°C, subsequent reformulation of the vaccine provided a shelf-life of up to 2 years at +2°C, with

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immunogenicity and safety comparable to other Oka strain *Varicella* vaccines (1). The safety and efficacy of *Varicella* vaccine have been critically reviewed (2).

Non-infective uses

In an experimental model of multiple sclerosis, repeated high doses of antigen (myelin basic protein) deleted both the clinical and pathological manifestations of the disease. The effects of *Varicella* vaccine on 50 patients with chronic progressive multiple sclerosis have therefore been studied (3). The patients were immunized with *Varicella* vaccine and followed for 1 year. All were seropositive for *Varicella* before immunization and all had rises in *Varicella* antibodies after being given the vaccine. There was improvement in 14 patients, 4 became worse, and 29 were unchanged. Four patients developed mild chickenpox after immunization. No other untoward adverse effects occurred.

General adverse effects

There have been many clinical trials to assess the immunogenicity and safety of *Varicella* vaccine, in both healthy and immunocompromised individuals (SEDA-12, 285) (SEDA-13, 290) (SEDA-14, 285) (SEDA-15, 289) (SEDA-17, 379). The vaccine was safe and immunogenic. The reports of different investigators were similar. Mild local reactions at the injection site were the most commonly reported adverse effects, occurring in about 10% after the first and second dose. Vaccine-associated rashes about 1 month after the first dose were reported in about 6% of vaccinees, sore throat in 8%, and fever over 37.8°C in 2%. Rash and fever after the second dose of vaccine were reported by less than 1% of vaccinees. Maculopapular or papulovesicular rashes occurred much more often in vaccinees with suspended chemotherapy (42%) (4,5).

Oka strain *Varicella* vaccine (Merck) has been evaluated in immunocompromised children with leukemia in remission (6,7). Most children had chemotherapy stopped 1 week before and 1 week after immunization; glucocorticoids were also stopped for 3 weeks (from 1 week before to 2 weeks after immunization). *Varicella* vaccine was safe, immunogenic, and effective in leukemic children at risk of serious disease or death from chickenpox. The major adverse effect was a mild rash in 50% of the children within 1 month of immunization, about 40% of whom were treated with aciclovir. A mild form of *Varicella* developed in 14% of immunized children exposed to *Varicella* (household contacts). The vaccine protected completely against severe *Varicella*. Leukemic vaccinees were less likely to develop zoster than were comparable children with leukemia who had wild type *Varicella*.

Between 1987 and 1993, *Varicella* vaccine developed by the Biken Institute was given to 1.39 million individuals in Japan and 1.93 million individuals in South Korea. Adverse effects occurred in 6.9% of vaccinees. Despite more than 100 well-documented contacts with *Varicella* patients, only 2% of those immunized developed breakthrough *Varicella*, with very mild clinical features (8).

In 1995, live virus *Varicella* vaccine (Oka strain) was licensed in the USA. Of the 6574 reported adverse events 4% (67.5 per 100 000 doses) after immunization were serious, while the majority were minor reactions, such as rash, redness, or injection site pain (9). About 10% of immunized children developed mild chickenpox. A total 193 vaccinees reported neurological symptoms, including Bell's palsy, convulsions, and demyelinating syndromes; febrile seizures accounted for half of the cases of convulsions. There were 14 deaths, but a role for the vaccine was not proven.

Organs and Systems

Hematologic

Acute thrombocytopenic purpura developed 3 weeks after *Varicella* immunization (10).

Skin

Extensive *Varicella* vaccine-associated rashes occurred in four leukemic children; there was a relation between rash and glucocorticoid treatment (11).

Immunologic

In one case a hypersensitivity vasculitis developed 2 weeks after *Varicella* immunization (12).

Infection risk

Spread of infection to the siblings of immunized leukemic children has been observed. Between 18 and 36 days after the receipt of *Varicella* vaccine 2–10% of exposed children developed mild *Varicella* and/or seroconversion to *Varicella* virus.

Transmission of the *Varicella* vaccine virus from a toddler (with a history of allergic diathesis) to his pregnant mother has been reported and discussed (SEDA-22, 354).

Complicated wild *Varicella* in immunized individuals has been reported (13); among the two cases the first reported case of *Varicella* meningitis occurring in a child with documented immunization and seroconversion (14).

Cases of zoster both in healthy and in immunosuppressed persons have been reported (15–17).

A 19-month-old girl was immunized against *Varicella* at 15 months of age and later developed zoster infection (18). Viral cultures from various lesions isolated *Varicella zoster* virus. The Oka vaccine strain was revealed by polymerase chain reaction.

There have been three case reports of suspected reactivation of *Varicella zoster* through hepatitis A vaccine, influenza vaccine, and simultaneous administration of rabies and Japanese encephalitis vaccine (19).

- A 53-year-old woman without signs of immunodeficiency developed zoster in the left T10 dermatome 14 days after influenza immunization. The rash resolved without sequelae. Five months later she received another injection of influenza vaccine and 12 days later developed zoster in the left T1 dermatome. Recovery was prolonged.
- An 80-year-old woman with carcinoma developed long-lasting left thoracic zoster 6 days after influenza

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immunization. Influenza vaccination before and after the event had no adverse effect.
- A 27-year-old man developed zoster in the second and third branches of the trigeminal nerve 1 day after immunization against rabies and Japanese encephalitis.

Zoster in childhood is unusual and probably even less common after *Varicella* immunization.

- A 6-year-old boy developed a zoster infection (with a vesicular rash in a left second thoracic dermatome pattern on his back extending to the back of his left arm) 15 days after the receipt of *Varicella* vaccine (Oka strain) (20). Molecular biological analysis of the virus isolated from the vesicles showed a pattern consistent with wild-type *Varicella zoster* virus.

The authors felt that this case mandated a careful review of all cases of zoster after *Varicella* immunization. Zoster induced by *Varicella* immunization could have implications for the use of immunization to prevent zoster in the elderly, a population with almost uniform *Varicella zoster* latent virus and at higher risk of zoster.

Susceptibility Factors

Age

In 29 children aged 1–12 years with chronic liver disease who received one dose of *Varicella* vaccine, seroconversion rates at 8 weeks after immunization were 100% (21). The geometric mean titers tended to relate to the severity of liver disease. Local and systemic reactions did not differ from reactions reported in healthy children.

- A 5-year-old boy developed zoster-like vesicular lesions 4 years after *Varicella* immunization. Virological examination showed *Herpes simplex* virus type 1, and so the vesicular lesions could not be attributed to the *Varicella zoster* virus vaccine strain, demonstrating the difficulty in confirming causality between time-related events (22).

Other features of the patient

To determine the safety and immunogenicity of *Varicella* immunization in HIV-infected children, 41 children (aged 1–8 years) who were asymptomatic or mildly affected (according to CDC stages) received two doses of live attenuated *Varicella* vaccine 12 weeks apart (23). Two months after the second dose, 60% of the recipients had anti-*Varicella* antibody in their serum. A minority of recipients developed mild local or systemic reactions. The immunization had no effect on the clinical stage of HIV infection or the HIV RNA plasma load.

Live virus vaccines, such as *Varicella*, are contraindicated in pregnancy.

Drug–Drug Interactions

Other vaccines

Reaction rates were not increased if the administration of *Varicella* vaccine was combined with other vaccines, for example MMR vaccine (SEDA-15, 358).

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Vasopressin and analogues

See also Individual agents

General Information

Vasopressin, a hypothalamic octapeptide that is secreted by the neurohypophysis, has both antidiuretic and vasoconstrictor properties. Its short half-life (about 10 minutes) necessitates continuous intravenous infusion or frequent nasal application.

Because its vasoconstrictor effects limit the use of the native hormone, analogues with greater or lesser affinity for vasopressin V_2 receptors and more selective antidiuretic effects have been developed:

- argipressin (8-arginine vasopressin)
- desmopressin (*N*-deamino-8-D-arginine vasopressin, DDAVP); desmopressin is covered in a separate monograph
- felypressin (2-phenylalanine, 8-lysine vasopressin)
- lypressin (8-lysine vasopressin; pig vasopressin)
- ornipressin (8-onithine vasopressin)
- terlipressin (triglycyl-lysine vasopressin).

Vasopressin receptor antagonists, such as relcovaptan (an antagonist at V_{1a} receptors), lixivaptan and tolvaptan (V_2), and conivaptan (mixed V_{1a}/V_2), are also under development (1).

Desmopressin has little vasoconstrictor effect but has potent antidiuretic action, through renal vasopressin V_2 receptors, and at high doses hemostatic properties, by increasing concentrations of factor VIII and von Willebrand factor in the blood.

Ornipressin is a selective agonist at vasopressin V_1 receptors and has weaker antidiuretic activity than the native hormone.

Terlipressin, a long-acting vasopressin analogue, is metabolized to the active drug lysine vasopressin. The use of terlipressin to treat acute variceal bleeding has been reviewed (2,3).

Although vasopressin and its analogues have been used in the acute management of bleeding esophageal varices, they do not reduce mortality (2,3) and the rate of adverse effects is higher than with octreotide (3).

Uterine and abdominal cramps, nausea, and an urge to defecate have been reported in vasopressin-treated patients.

Organs and Systems

Cardiovascular

Dose-related adverse effects of vasopressin include skin pallor, hypertension, cardiac dysrhythmias, and myocardial ischemia or infarction; treatment has to be stopped in 20–30% of patients because of these effects (3).

Intestinal and peripheral vasoconstriction can follow prolonged infusion, resulting in gangrene of intestinal segments or of skin, fingers, or limbs. This has been fatal in several cases, and vasopressin should be withdrawn if skin necrosis occurs (SEDA-13, 1310) (4).

Of 10 patients with hepatorenal syndrome one had to be withdrawn 2 hours after receiving 12 units of ornipressin (6 IU/hour) because of a ventricular tachydysrhythmia, and an infusion of dopamine 2–3 micrograms/kg/minute was started (5).

Terlipressin has similar, but less pronounced, systemic hemodynamic effects to vasopressin, including increases in mean arterial pressure and reduced heart rate (6). Of 105 patients who had continuous terlipressin infusions for variceal bleeding in a multicenter study, lower limb ischemia developed in two and cardiac ischemia in one (7).

Of 86 cirrhotic patients treated with terlipressin 10 developed a tachycardia, four developed atrial fibrillation, and one developed ventricular tachycardia. Four patients in the same study developed hypertension (8). In another study, tachycardia occurred in 23% of patients randomized to pitressin for acute variceal bleeding and 8% developed transient hypertension (9).

Myocardial ischemia has been associated with terlipressin (10).

- A 61-year-old man with coronary artery stenosis became hypotensive during elective surgery, refractory to ephedrine (cumulative dose of 36 mg over 45 minutes). Immediately after terlipressin 1 mg, he developed hypertension and bradycardia, with evidence of myocardial ischemia.

One of 21 patients with hepatorenal syndrome developed finger ischemia on the fourth day of intermittent intravenous terlipressin and recovered after terlipressin was stopped (11).

Respiratory

An elderly patient (over 70 years old) with cirrhosis and hepatorenal syndrome developed severe bronchospasm and died after intravenous terlipressin administration; the mechanism was not determined (12).

Electrolyte balance

Profound hyponatremia due to reduced free water clearance is a predictable dose-related effect of vasopressin (13). This is a particular risk in patients who are unconscious or who have disturbed thirst sensation (SEDA-22, 487).

Of 105 patients who had continuous infusions of terlipressin for variceal bleeding in a multicenter study, four developed hyponatremia, severe in one case (7).

High-dose terlipressin (1 mg intravenously every 4 hours for 5 days) was associated with severe hyponatremia and

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loss of consciousness in one of 45 cirrhotic patients in a randomized trial (8). Of course, cirrhosis itself is associated with hyponatremia.

Hematologic

Mild lymphangitis was reported in one of 105 patients in a multicenter study of the effects of terlipressin (7).

Gastrointestinal

Tongue ischemia and ischemic colitis have been described after 4–9 days of treatment with ornipressin 6 IU/hour combined with plasma volume expansion (14).

Skin

Skin necrosis is often reported after vasopressin therapy. In a retrospective study, two of five patients treated with a continuous infusion of terlipressin developed skin necrosis at the infusion site and a third developed scrotal necrosis (12).

- A 46-year-old woman with septic shock had a peripheral venous infusion of vasopressin 0.04 U/minute in addition to dobutamine, via the subclavian vein; extravasation of vasopressin to local soft tissue resulted in ischemic skin necrosis (15).

Purpuric skin necrosis, due to local vasoconstriction, has been reported in 19 patients within a few days of starting vasopressin infusion (16).

Bullous necrosis developed within 48 hours of starting an infusion of terlipressin in a 44-year-old man (17). There have been only four previous reports of skin necrosis.

Musculoskeletal

Rhabdomyolysis has been attributed to terlipressin (18).

- A 36-year-old man with nephrotic syndrome was given an infusion of terlipressin (an intravenous bolus of 2 mg followed by 2 mg over 24 hours) to treat diffuse gastric bleeding, and 12 hours later developed acute pain and livedo reticularis in both legs. High plasma concentrations of myoglobin and creatine kinase confirmed the diagnosis of toxic rhabdomyolysis, thought to be due to the vasoconstrictor action of terlipressin. He made a gradual recovery over the next few weeks after terlipressin was withdrawn.

Pre-existing blood vessel disease due to amyloidosis may have contributed to the outcome in this patient.

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Vecuronium bromide

See also Neuromuscular blocking drugs

General Information

Vecuronium is a monoquaternary analogue of pancuronium, with a similar speed of onset, a duration of action of 15–30 minutes, rapid spontaneous recovery, and virtually no cumulative effects (1). Being monoquaternary, it is more lipophilic than pancuronium. About 30% is bound to plasma proteins. It is deacetylated in the liver, the principal metabolite being 3-desacetylvecuronium, which is believed to have about 50% of the neuromuscular blocking potency of the parent drug in man; small amounts of 17-desacetylvecuronium and 3,17-didesacetylvecuronium are also formed. In balanced anesthesia vecuronium is slightly more potent than pancuronium, but during halothane anesthesia it has been reported to be 1.4 times as potent as the latter. Suitable doses during balanced anesthesia are similar to those for pancuronium; potentiation by volatile agents (2) allows these doses to be reduced, after equilibration has occurred between the volatile agent and the tissues, by 25 or 45% when halothane or enflurane are used (3,4). In another study, after 1 hour of constant 90% neuromuscular blockade under nitrous oxide (60%), isoflurane (1.2% end-tidal), or enflurane (1.2% end-tidal) anesthesia the vecuronium infusion requirements were reduced by as much as 70% (compared with the nitrous oxide/fentanyl group) (SEDA-13, 105) (5).

In animals, histamine release, cholinesterase inhibition, and autonomic effects are minimal and occur only at concentrations of vecuronium considerably greater than those required for neuromuscular block (6–9). Interactions with antimicrobial drugs, analgesics, and anesthetic agents were similar to those known for other non-depolarizing relaxants, apart from a possible potentiating effect by metronidazole (6). These animal findings have been confirmed in man by the relative paucity of reported adverse effects. In man, the intradermal injection of vecuronium produces a considerably smaller local histamine reaction than d-tubocurarine, metocurine, pancuronium, or atracurium do (10,11) and plasma histamine is not raised in the clinical dose range (12,13). Nevertheless, minor skin reactions have been reported (14,15), as well as hypotension (16) and severe anaphylactoid reactions with circulatory collapse (17,18) and bronchospasm (19,20). Cross-sensitivity with pancuronium may occur (SEDA-10, 111).

Organs and Systems

Cardiovascular

The expected cardiovascular stability of vecuronium has been confirmed in man (2,21–23). Even doses as large as 0.28 mg/kg in patients undergoing coronary artery bypass grafting produced negligible effects (24). Bradycardia is the only cardiovascular adverse effect reported, and this is seen in association with opioids such as fentanyl (25) and sufentanil (SEDA-11, 125) (26) or other drugs that are themselves capable of producing bradycardia. The lack of vagolytic and sympathomimetic activity of vecuronium means that it does not counteract the bradycardia or the hypotensive effects of other drugs or surgical manipulations. It is an ideal relaxant for patients with pheochromocytoma (27).

Musculoskeletal

Masseter muscle rigidity is a rare but potentially dangerous adverse effect of suxamethonium and can prevent successful airway management. Furthermore, it can be the first sign of malignant hyperthermia and rhabdomyolysis. Non-depolarizing neuromuscular blocking agents are thought to be safe with regard to masseter muscle rigidity. However, masseter muscle rigidity not associated with the use of suxamethonium can also complicate airway management (28).

- A 42-year-old woman had anesthesia induced with propofol 200 mg, vecuronium 8 mg, and mask ventilation with oxygen, nitrous oxide, and 2% isoflurane. Laryngoscopy proved impossible because of spasm of the masseter muscles, and the airway was secured by blind nasal intubation. There was no evidence of rigidity of other muscle groups. Body temperature and end-tidal carbon dioxide concentration remained in the reference ranges. Masseter muscle rigidity persisted throughout the operation and resolved during recovery from anesthesia after neostigmine 2.5 mg had been given.

The authors suggested that in this case the phenomenon had been caused by vecuronium. Masseter muscle rigidity persisted during anesthesia and resolved during recovery from anesthesia after neostigmine had been given and isoflurane inhalation had been stopped. If vecuronium caused muscle rigidity in this case it was probably not mediated by effects on acetylcholine receptors, but rather by an interaction of vecuronium with ion channels (sodium, potassium, and/or calcium), but it is hard to imagine how this effect could have been antagonized by a cholinesterase inhibitor. It therefore seems likely that the masseter muscle rigidity was rather caused by isoflurane, which would explain why the symptoms improved after withdrawal of isoflurane. There have been previous reports of masseter muscle rigidity associated with non-depolarizing neuromuscular blocking agents (SEDA-21, 144) (29,30). The mechanism is unclear. One wonders how muscle specimens from these patients might react to exposure to an inhalational anesthetic during in vitro contracture testing. Regarding the link between masseter muscle rigidity and malignant hyperthermia, muscle biopsy would not be inappropriate in patients who have masseter muscle rigidity severe enough to prevent mouth opening and conventional orotracheal intubation.

Second-Generation Effects

Fetotoxicity

There is placental transfer of vecuronium, but no effects have been detected in the newborn (the feto-maternal concentration ratio is about 10% less than for pancuronium (31). Postpartum, vecuronium has been reported to have an appreciably longer duration of action (SEDA-13, 105) (32,33) when given in a dose of 0.1 mg/kg.

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Susceptibility Factors

Age

Spontaneous recovery of neuromuscular function after a bolus dose of vecuronium (0.1 mg/kg) was significantly prolonged in elderly patients compared with younger adults (SEDA-17, 153). The elimination half-life was significantly prolonged (125 versus 78 minutes) and the plasma clearance reduced (2.5 versus 5.6 ml/kg/minute) in the elderly versus the younger patients.

Renal disease

About 25–30% of an injected dose of vecuronium is excreted in the urine in normal patients, mostly as unchanged drug. Renal dysfunction has been reported as having no significant effect on the duration of action of vecuronium (SEDA-11, 125) (34–36). Nevertheless, slight resistance to the neuromuscular blocking effect of an initial dose (ED_{50} increased by 20%) and a small reduction (of 23%) in infusion requirements to maintain a 90% block after 1 hour of relaxation have been described in end-stage renal insufficiency (SEDA-13, 103) (37). These findings are in line with those for other non-depolarizing agents, with the exception of atracurium; the changes, however, are minor compared with the older relaxants, as is to be expected from the kinetics of vecuronium. There is a slight tendency for the action of vecuronium to be prolonged in renal insufficiency, and monitoring of neuromuscular transmission is advisable if several doses are to be given.

Hepatic disease

In liver disease (cirrhosis and cholestasis), the plasma clearance of vecuronium is reduced, its half-life is increased, and its duration of action is prolonged (SEDA-10, 112) (38,39). Rapid uptake in the liver appears to be an important factor in its plasma clearance and in determining its relatively short duration of action; it is estimated that about 40% of the injected drug is excreted via the bile (40). Prolongation of the action of large single doses and accumulation after repeated doses are therefore to be expected in liver disease.

Drug–Drug Interactions

Azathioprine

In humans with renal insufficiency, azathioprine 3 mg/kg produced a negligible and transient reduction in neuromuscular blockade maintained by infusion of vecuronium (37).

Carbamazepine

Resistance to vecuronium has been described in patients taking carbamazepine (41).

Ciclosporin

Ciclosporin can cause considerable prolongation of the neuromuscular paralysis induced by vecuronium (42), causing difficulties with reversal (SEDA-14, 116) (43). Potentiation of vecuronium in cats has also been described (SEDA-12, 188) (44).

Disopyramide

Disopyramide has also been associated with impairment of neostigmine antagonism of vecuronium-induced neuromuscular blockade (45).

- A 63-year-old man was given vecuronium 70 μg/kg followed by increments of 20 μg/kg, and three intravenous doses of disopyramide 10 mg for supraventricular extra beats, followed by an infusion of 25 mg/hour. Paralysis was reversed using atropine 0.75 mg and neostigmine 2.5 mg. The twitch height returned to normal and the train-of-four was above 85%, but the responses to tetanic stimulation at 100 and 50 Hz remained severely depressed (10 and 45% respectively). The plasma concentration of disopyramide was 5.1 μg/ml.

Phenytoin

Acute administration of phenytoin (10 mg/kg intravenously) has been reported to enhance slightly, but statistically significantly, steady blockade maintained by an infusion of vecuronium (SEDA-15, 124) (46). This is in contrast to reports of resistance to non-depolarizing neuromuscular blocking agents, including vecuronium, associated with long-term phenytoin (SEDA-13, 104) (47).

Testosterone

Testosterone enanthate, given over 10 years to produce virilization, has been claimed to have been responsible for a case of marked resistance to vecuronium (SEDA-14, 116) (48).

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Venlafaxine

See also Antidepressants, second-generation

General Information

Venlafaxine inhibits the re-uptake of both serotonin and noradrenaline. Trials have shown efficacy comparable to that of tricyclic antidepressants, and it may be particularly effective in refractory depression (1)(2).

Reported adverse effects were nausea, somnolence, dry mouth, insomnia, dizziness, constipation, weakness, nervousness, and sweating. Other adverse effects include nervousness, weight loss, and a dose-dependent increase in blood pressure.

Because of its serotonin-potentiating effect, venlafaxine can cause a serotonin syndrome when combined with monoamine oxidase (MAO) inhibitors (SEDA-20, 9) (SEDA-21, 13).

Adverse sexual effects are reported in a frequency similar to that of SSRIs (SEDA-20, 9).

Withdrawal reactions have been reported in several cases after abrupt discontinuation (SEDA-21, 13) (3)(4).

Preliminary data suggest that venlafaxine is safer in acute overdose than tricyclic antidepressants but more dangerous than SSRIs. Seizures have been reported in several cases of overdose (5–7).

Organs and Systems

Cardiovascular

A meta-analysis of the effect of venlafaxine on blood pressure in patients studied in randomized placebo-controlled trials of venlafaxine, imipramine, and placebo showed that at the end of the acute phase (6 weeks) the incidence of a sustained rise in supine diastolic blood pressure (over 90 mmHg) was significantly higher in both active treatment groups: venlafaxine 4.8% (135/2817), imipramine 4.7% (15/319), and placebo 2.1% (13/605) (8). The effect of venlafaxine in causing a rise in diastolic blood pressure appeared to be dose related, with an incidence of 1.7% in patients taking under 100 mg/day and 9.1% in those taking over 300 mg/day.

These data confirm that venlafaxine, particularly in higher dosages, can significantly increase blood pressure. At high doses, venlafaxine inhibits the re-uptake of noradrenaline as well as that of serotonin, which probably accounts for the pressor effect.

In physically healthy subjects venlafaxine has a generally benign cardiovascular profile, although hypotension and dose-related hypertension have been reported (SEDA-23, 20).

Venlafaxine is often used in high doses in patients with treatment-resistant depression. If there is continuing failure to respond, electroconvulsive therapy might be used, often in combination with venlafaxine. A 73-year-old woman taking venlafaxine (112.5 mg/day) had sustained hypertension for several hours after her first treatment (9). However, electroconvulsive therapy can cause transient hypertension, and the patient had essential hypertension controlled by bendroflumethiazide. It is therefore possible that the reaction might have occurred had she not been taking venlafaxine. Nevertheless, the fact that venlafaxine can cause hypertension when used as sole treatment suggests that blood pressure should be monitored carefully in patients receiving electroconvulsive therapy and venlafaxine together, particularly if there is a history or current evidence of hypertension.

Venlafaxine has not been studied systematically in patients with cardiovascular disease, although there are reports that older patients can have clinically significant disturbances of cardiac rhythm (10).

- A 69-year-old woman with stable angina and mild single-vessel coronary artery disease developed acute myocardial ischemia within a week of starting venlafaxine (75 mg/day).

Taken together with the information that the authors cited in their review, the current data suggest that venlafaxine should be used with caution in patients with established cardiovascular disease.

Nervous system

Antidepressant drugs, such as tricyclic antidepressants and SSRIs, suppress rapid eye movement (REM) sleep, the period of sleep during which dreaming occurs. Despite this, antidepressant treatment is sometimes associated with recurrent nightmares. Venlafaxine also suppresses REM sleep and was associated with nightmares in a 35-year-old woman with body image disturbance; the nightmares remitted when the venlafaxine was withdrawn (11). The authors speculated that indirect activation of 5-HT_2 receptors might have played a causal role, because 5-HT_2 receptor antagonists, such as nefazodone, can be helpful in the treatment of nightmares, for example in patients with post-traumatic stress disorder.

Sensory systems

Tricyclic antidepressants predispose to acute angle closure glaucoma, probably through an anticholinergic action. However, acute angle closure has also been reported with SSRIs, suggesting that all serotonin-potentiating drugs can cause glaucoma (SEDA-21, 13) (SEDA-23, 17).

- Acute angle closure glaucoma has been reported in a 45-year-old woman taking venlafaxine (75 mg/day) and chlorpromazine (150 mg/day) (12). She had previously taken low-dose dosulepin (75 mg/day), chlorpromazine, and SSRIs without ophthalmic problems.

Chlorpromazine has mild anticholinergic properties and may have contributed to the angle closure in this case. She also had hypermetropia which is an another risk factor for glaucoma. However, this case supports the view that potent blockade of serotonin re-uptake can cause glaucoma in predisposed subjects.

Psychological, psychiatric

The use of antidepressants in patients with documented bipolar illness is often associated with a risk of manic illness (13).

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- A 63-year-old man with a long history of bipolar illness and alcohol dependence took nefazodone 400 mg/day for 8 months, with no relief of a depressive episode. He was also taking valproate 1500 mg/day as a mood stabilizer, aspirin 81 mg/day, ranitidine 300 mg/day, and docusate calcium 240 mg/day. Nefazodone was tapered over 4 days and venlafaxine begun in a dosage of 37.5 mg/day and gradually increased to 150 mg/day over 3 weeks. Venlafaxine led to improvement in depressive symptoms, but 6 days after the dose reached 150 mg/day he became agitated, verbally and physically threatening, grandiose, and sexually disinhibited. He also had paranoid thinking and appeared to be hallucinating. The venlafaxine was withdrawn but the manic symptoms persisted and eventually required increases in the dosages of valproate and antipsychotic drugs.

This report illustrates the difficulty of treating depression in bipolar disorder with antidepressants. The presence of a mood stabilizer did not prevent the manic episode that emerged during venlafaxine treatment, and it is in any case difficult to know whether the mania was in fact due to the venlafaxine or instead represented a spontaneous mood swing.

Electrolyte balance

It is well established that SSRIs can cause hyponatremia. Similar cases have now been reported with venlafaxine.

- A 90-year-old woman had a depressive disorder in addition to other medical problems, including congestive cardiac failure, seizures, dementia, and osteoporosis (14). She was also taking phenobarbital 120 mg/day, enalapril 40 mg/day, furosemide 80 mg/day, calcium carbonate 1300 mg/day, and nortriptyline 50 mg at night. She was given additional paroxetine 20 mg/day, but there was no clinical response and she was changed to venlafaxine, increasing to 75 mg/day. Two months later her sodium concentration had fallen to 130 mmol/l and the furosemide was withdrawn. However, 4 months later the sodium concentration had fallen to 124 mmol/l. The venlafaxine was then withdrawn and the sodium normalized within a week and remained within the reference range for the following year.

This was a complex case, because of the multiple medical problems and treatments. However, it has been reported that since the launch of venlafaxine in Australia in 1996, the Adverse Drug Reactions Advisory Committee there has received 15 reports of hyponatremia, suggesting that the association is real (15).

Liver

Raised liver enzymes have been rarely found in patients taking venlafaxine, and it appears that hepatitis may also be rare adverse effect (16).

- A 44-year-old woman developed weakness with abnormal liver function tests (aspartate transaminase 661 IU/l) about 6 months after starting to take venlafaxine 150 mg/day. Biopsy showed confluent necrosis in zone 3, with unaffected portal tracts. No other cause for the hepatitis could be found. The clinical and biochemical features resolved within 12 weeks of withdrawal of venlafaxine.

Hair

SSRIs can cause occasional, idiosyncratic hair loss in some patients (SEDA-19, 10), and this has also been attributed to venlafaxine (17).

- A 50-year-old woman took venlafaxine 75 mg/day for depression, and the dosage was increased to 150 mg/day after 2 weeks. After 4 weeks she noted increased hair loss when brushing or washing her hair. After 3 months she stopped taking venlafaxine and 1 month later her hair loss stopped completely. However, 10 months later she had another depressive episode and was again successfully treated with venlafaxine. Once again she noted excessive hair loss. She was subsequently treated with sertraline 50 mg/day, which helped her depression without causing hair loss.

The fact that sertraline did not cause hair loss in this patient suggests that the mechanism was not related to blockade of serotonin re-uptake.

Sexual function

Antidepressant drugs can rarely cause priapism. The agent most often implicated has been trazodone, perhaps because of its α_1-adrenoceptor antagonist properties. In general venlafaxine has an inhibitory effect on sexual function, but perhaps, like SSRIs, it can rarely cause priapism (18).

- A 16-year-old youth taking venlafaxine (150 mg/day) had several episodes of prolonged erections, which persisted for several hours after intercourse. The episodes remitted after the venlafaxine was withdrawn.

Pain on ejaculation is also a rare adverse effect of tricyclic antidepressants and SSRIs and has been reported with venlafaxine (19).

- Painful ejaculation occurred in a 59-year-old man taking venlafaxine 150 mg/day. It remitted when the venlafaxine was withdrawn and did not recur when citalopram 40 mg/day was used instead.

Long-Term Effects

Drug withdrawal

Both SSRIs and venlafaxine can cause troublesome withdrawal symptoms (SEDA-22, 12) (SEDA-22, 17). Because venlafaxine blocks the re-uptake of both serotonin and noradrenaline the mechanism of venlafaxine-induced abstinence symptoms is not clear.

- A 72-year-old woman taking venlafaxine 150 mg/day for depression was abruptly switched to the noradrenaline re-uptake inhibitor maprotiline 75 mg/day; 1 day later she developed agitation, sweating, nausea, vomiting, tinnitus, and insomnia (20). These symptoms continued for another week, but disappeared on the second day of sertraline treatment 50 mg/day.

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The symptoms experienced by this patient were typical of venlafaxine and SSRI withdrawal (although they could also be experienced after sudden withdrawal of tricyclic antidepressants). The fact that they were relieved by a serotonin but not a noradrenaline re-uptake inhibitor suggests that venlafaxine-induced withdrawal symptoms are mediated by serotonergic mechanisms.

Drug Administration

Drug overdose

Venlafaxine is generally regarded as being reasonably safe in overdose relative to conventional tricyclic antidepressants.

However, it has been associated with occasional reports of cardiac conduction disturbances at both therapeutic doses and in overdose (SEDA-24, 19).

Deaths have been described after venlafaxine overdose, but in combination with other agents and alcohol. However, there have been two fatal cases of overdosage in which venlafaxine was the only agent detected postmortem (21). It therefore appears that venlafaxine can occasionally prove fatal in overdosage, probably through cardiac conduction abnormalities and seizures (21,22). It is possible that poor metabolizers may be especially liable to develop toxic effects.

- A 44-year-old woman took an overdose of venlafaxine 3 g. An electrocardiogram showed sinus rhythm and incomplete right bundle branch block (23). She was monitored in an intensive care unit and 10 hours later a further electrocardiogram showed atrial fibrillation with a wide QRS complex. Both of these abnormalities resolved with sodium bicarbonate (100 ml of a 1 M solution). No further conduction disturbances were noted over the following days.

The authors suggested that the effect of venlafaxine on cardiac conduction is mediated by its ability to block the fast inward sodium current in cardiac myocytes. This might promote membrane stabilizing effects in a similar way to tricyclic antidepressants. They recommended that the management of venlafaxine overdose should include cardiac monitoring.

Drug–Drug Interactions

Caffeine

Venlafaxine 150 mg/day did not alter the disposition of caffeine, a probe of CYP1A2 activity (24). This suggests that at therapeutic doses venlafaxine, in contrast to fluvoxamine (SEDA-22, 13), does not inhibit CYP1A2.

Dexamfetamine

Psychostimulants, such as dexamfetamine, are being increasingly prescribed for patients who meet the criteria for adult attention deficit disorder. Many such patients also have co-morbid major depression.

- A 32-year-old man taking dexamfetamine 15 mg/day developed the serotonin syndrome, with shivering, sweating, myoclonus, and pyrexia, following the addition of venlafaxine 150 mg/day (25). Venlafaxine and dexamfetamine were withdrawn, and he was given the serotonin receptor antagonist, cyproheptadine (32 mg over 3 hours). His symptoms remitted a few hours later and he subsequently restarted dexamfetamine without incident. A later trial of citalopram, while he was still taking dexamfetamine, also led to symptoms of serotonin toxicity.

The combination of stimulants and SSRIs is not uncommon in clinical practice, but reports of serotonin toxicity are unusual, perhaps because drugs such as dexamfetamine and methylphenidate predominantly release dopamine and noradrenaline rather than serotonin. However, psychostimulants do cause some degree of serotonin release, which might have been sufficient to cause serotonin toxicity in this case.

Fluoxetine

Four depressed patients (age range 21–73 years) had anticholinergic adverse effects when venlafaxine 37.5 mg/day was added to fluoxetine 20 mg/day (26). Venlafaxine does not have direct anticholinergic effects, but could cause them indirectly as a result of its ability to increase noradrenergic neurotransmission. This effect would be expected only at much higher doses of venlafaxine than those used here, which led the author to suggest that in the presence of CYP2D6 inhibition by fluoxetine, venlafaxine concentrations could have been substantially higher than expected.

Imipramine

In six healthy men, venlafaxine (150 mg/day for 10 days) produced an increase of 28% in the systemic availability of a single dose of imipramine (100 mg); the availability of the active metabolite of imipramine, desipramine, was also increased (27). These data suggest that venlafaxine inhibits CYP2D6; the effects appear to be modest relative to those of fluoxetine and are similar to those produced by sertraline.

Monoamine oxidase inhibitors

There have been previous reports of serotonin toxicity when venlafaxine was combined with therapeutic doses of conventional MAO inhibitors (SEDA 20, 21). The serotonin syndrome has been reported in four patients who were switched from the MAO inhibitor phenelzine to venlafaxine (28). In two of the subjects, the 14-day washout period recommended when switching from phenelzine to other antidepressant drugs had elapsed.

- A 25-year-old woman had been taking phenelzine 45 mg/day for refractory migraine and tension headache, but suffered intolerable adverse effects (weight gain, edema, and insomnia). Phenelzine was withdrawn and 15 days elapsed before she took a single dose of venlafaxine 37.5 mg. Within 1 hour she developed agitation, twitching, shakiness, sweating, and generalized erythema with hyperthermia (38°C). Her symptoms resolved within 3 hours with no sequelae.

These cases suggest that even after the recommended 2-week washout from MAO inhibitors, venlafaxine can

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provoke serotonin toxicity in some patients. In principle it should be possible to switch from one conventional MAO inhibitor to another without a washout period. However, there have been reports that patients who switched from phenelzine to tranylcypromine had hypertensive reactions, with disastrous consequences (29). Whenever possible, a 2-week washout period when switching MAO inhibitors or when introducing serotonin re-uptake inhibitors seems advisable.

Quinidine

Venlafaxine is metabolized by CYP2D6. In healthy volunteers the oral clearance of venlafaxine (37.5 mg/day for 2 days) was fourfold less in poor metabolizers ($n = 6$) than extensive metabolizers ($n = 8$) (30). Administration of the CYP2D6 inhibitor quinidine, 200 mg/day for 2 days, to the extensive metabolizers reduced the oral clearance of venlafaxine to the level seen in poor metabolizers. Quinidine had no effect on venlafaxine clearance in subjects who were poor metabolizers before treatment. The authors suggested that poor metabolizers may be at particular risk of venlafaxine toxicity, as could subjects who take inhibitors of CYP2D6.

Risperidone

Unlike SSRIs, venlafaxine only weakly inhibits CYP2D6. Venlafaxine (up to 150 mg/day for 10 days) modestly but significantly increased the plasma AUC of a single dose of risperidone (1 mg) in 38 healthy volunteers in an open longitudinal design, but did not affect its active metabolite, 9-hydroxyrisperidone (31). The authors suggested that their study had shown a small potentiating effect of venlafaxine on risperidone availability, probably through weak inhibition by venlafaxine of CYP2D6. Venlafaxine is therefore less likely to increase risperidone concentrations than are fluoxetine and paroxetine.

Trifluoperazine

Drugs that potentiate the function of serotonin, such as venlafaxine, can produce pharmacodynamic interactions with dopamine receptor antagonists, perhaps because serotonin pathways can inhibit dopamine neurotransmission.

- A 44-year-old man with major depression had been taking the antipsychotic drug trifluoperazine (3 mg/day) for anxiety for several years (32). He was given venlafaxine 75 mg/day, and 12 hours after the first dose developed anxiety and malaise. He was sweating and had tremor and rigidity. His blood pressure fluctuated and his creatine phosphokinase activity was raised at 11 320 IU/l. A diagnosis of neuroleptic malignant syndrome was made and he was given dantrolene and bromocriptine. His symptoms settled within 24 hours and trifluoperazine was reintroduced uneventfully.

This case suggests that venlafaxine can rarely increase the risk of neuroleptic malignant syndrome in patients taking a dopamine receptor antagonist. However, this combination of drugs is often used, and it is not clear why only very few patients appear to be susceptible to this reaction, and then only on some occasions.

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Verapamil

See also Calcium channel blockers

General Information

Verapamil is a phenylalkylamine calcium channel blocker, with actions mainly on the heart.

Organs and Systems

Cardiovascular

Heart failure

Verapamil can cause cardiac failure, because it has a potent negative inotropic effect and causes increased capillary filtration pressure by vasodilatation (1). There are also reports of drug-induced acute right heart failure in patients with pulmonary hypertension due to valvular heart and chronic pulmonary obstructive airways diseases (2).

- A 16-year-old boy who took long-term verapamil after a Mustard operation for transposition of the great arteries developed severe congestive heart failure, which did not respond to diuretics. Systemic vascular resistance was increased by 75% and pulmonary vascular resistance by 150%; the cardiac index was reduced from 3.0 to 1.8 l/minute/m^2. Ejection fraction and atrial pressure were unchanged and neurohormonal causes were excluded. The heart failure resolved after withdrawal of verapamil.

Cardiogenic shock after the ingestion of verapamil has been reported, in one case with a small dose (3).

- A 78-year-old woman with a history of biventricular heart failure developed cardiogenic shock after she took a single tablet of verapamil 80 mg. She was resuscitated with artificial ventilation, dobutamine, noradrenaline, and calcium gluconate. Toxicological analysis showed an unexpectedly high plasma verapamil concentration, which was attributed to liver failure.

In patients with advanced heart failure a single oral therapeutic dose of verapamil may have a severe toxic effect.

Cardiac dysrhythmias

Relatively harmless and asymptomatic disturbances of heart rhythm are common during treatment with verapamil. For example, Wenckebach phenomenon (Mobitz type I second-degree atrioventricular block), sinus bradycardia and junctional escape, and accelerated junctional rhythm have been seen during the treatment of angina pectoris (4). In the DAVIT II study (5), 23 of 878 patients who took verapamil and seven of 897 who took placebo in a survival study after myocardial infarction developed second- or third-degree AV block. It has been suggested that the extent of PR prolongation may be proportional to the pharmacological effect of verapamil in patients with sinus rhythm (6). Patients with diseased conduction systems can develop atrioventricular block, sinoatrial block, sinus arrest, or sinus bradycardia with verapamil (7).

Severe cardiac conduction disturbances have been reported in patients with chronic renal insufficiency taking verapamil, mainly related to modified-release formulations.

- A serious bradydysrhythmia with complete atrioventricular block occurred after some months of conventional verapamil at normal doses and dose-adjusted digoxin in a 72-year-old woman with chronic renal insufficiency of unknown cause; the atrioventricular block resolved after 2 hours of hemodialysis (8).

Problems can also occur in patients with aberrant conduction pathways; for example, verapamil caused an increased ventricular response in patients with Wolff–Parkinson–White syndrome associated with atrial fibrillation (9–11). The danger lies in provocation of ventricular fibrillation from advanced anterograde conduction in accessory pathways (12).

Nervous system

Myoclonic dystonia has been described in a 70-year-old man who took verapamil for supraventricular tachycardia for 10 months; the abnormal movements disappeared within 3 weeks of substituting diltiazem, but rechallenge was not attempted (13).

Myoclonic seizures have been attributed to verapamil (14).

- An 18-month-old girl with supraventricular tachycardia was given intravenous verapamil 0.2 mg/kg, which was discontinued after half the dose had been given, because she developed irregular, repetitive, jerky movements in both upper and lower limbs which lasted for 2 minutes. As the supraventricular tachycardia had not responded, second and third doses of 0.2 mg/kg

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were given intravenously under diazepam cover, but similar myoclonic seizures occurred again. There were no predisposing factors.

Fasciculation occurred when a patient with background peripheral neuropathy was given verapamil (SEDA-16, 197).

Feelings of "painful coldness and numbness" in the legs, in the absence of a neurological deficit, have been reported with verapamil (15); the symptoms disappeared with drug withdrawal and recurred with rechallenge.

Endocrine

There was a significant rise in serum alkaline phosphatase of skeletal origin in a group of patients taking verapamil for hypertension. It was associated with a slight increase in parathyroid hormone, indicating involvement of bone metabolism, although there was no change in the urinary excretion of calcium, phosphate, or potassium. It has yet to be shown whether verapamil causes osteopenia in man, as it does in animals (SEDA-16, 197).

Verapamil-induced hyperprolactinemia has been reported in a 74-year-old man, who presented with impotence and who was subsequently found to have a benign 6 mm pituitary microadenoma (16). The withdrawal of verapamil was associated with the normalization of serum prolactin concentrations.

The mechanism for this adverse effect is unclear and has not been reported with other calcium channel blockers.

Hair

Increased hair growth has been associated with modified-release verapamil (SEDA-17, 238).

Musculoskeletal

Arthralgia has been associated with verapamil (17).

- A 28-year-old man with migraine and vascular pain of the face was given verapamil 480 mg/day when sumatriptan did not control the pain. Verapamil was withdrawn after 1 month and reintroduced in a dosage of 960 mg/day after a new episode of pain. He then developed arthralgia in the right hand and arm, which disappeared after withdrawal and recurred after rechallenge.

Susceptibility Factors

In therapeutic doses, verapamil has a negative dromotropic effect, reflected in plasma concentration-dependent prolongation of the PR interval and AV nodal block. PR interval prolongation is detectable even after small single doses. The effects of rheumatoid arthritis on the pharmacokinetics and pharmacodynamics of verapamil have been studied in eight patients and eight age- and sex-matched healthy volunteers (18). Verapamil and norverapamil concentrations were substantially increased in the patients with rheumatoid arthritis, accompanied by significantly less dromotropic activity. Regardless of the mechanism involved in the altered pharmacokinetics of verapamil, the rise in drug concentrations was accompanied by a significant reduction in dromotropic activity. Therefore, administration of verapamil to patients with rheumatoid arthritis may require close attention to prevent therapeutic failure.

Drug Administration

Drug overdose

Verapamil poisoning can cause cardiac toxicity with cardiogenic shock, conduction abnormalities (including life-threatening dysrhythmias), hypotension, and death.

- A 15-year-old woman survived a total of 65 minutes cardiac arrest after taking 7200 mg of verapamil and 240 mg of paroxetine, which potentiates verapamil toxicity (19). Despite the length of cardiopulmonary resuscitation, with evidence of subsequent myocardial damage and renal impairment, she was discharged 17 days after admission, having made a full recovery, without evidence of neurological impairment.

The authors considered that the lack of neurological damage may have been related to the possible neuroprotective effect of a large dose of verapamil.

- A 28-year-old man developed rhabdomyolysis and acute renal insufficiency 10 hours after taking four capsules containing verapamil 180 mg plus trandolapril 2 mg. He survived with gastric lavage and activated charcoal 70 g. By 4 hours after admission he was awake and complained of diffuse muscle cramps and myalgia. Creatinine and creatine kinase reached 565 μmol/l (6.7 mg/dl) and 10 700 U/l respectively. After 6 days the laboratory tests were all within the reference ranges.

The authors suggested that rhabdomyolysis should be considered in patients with myalgia and muscle cramps taking verapamil plus trandolapril, and that routine serum creatinine kinase should be checked (20).

Non-cardiogenic pulmonary edema has been reported after the ingestion of a large quantity of verapamil (21).

- Two 19-year-old-girls developed pulmonary edema after taking massive overdoses of verapamil (6000 mg and 7200 mg). In each case a chest X-ray showed diffuse bilateral patchy infiltration. Left ventricular size and function was normal on transthoracic echocardiography. They were both treated successfully with mechanical ventilatory support.

Several mechanisms may be involved in non-cardiogenic pulmonary edema subsequent to verapamil intoxication, including leaky capillary syndrome attributable to inhibition of prostacyclin, a cellular membrane protector. Prolonged hypotension and a shock-like state may also contribute. The authors recommended pressor/inotropic therapy and mechanical ventilation as therapy.

Different therapeutic approaches have been described in suicide attempts with verapamil.

- Enoximone has been used to treat cardiogenic shock in a case of self-poisoning with verapamil 2.4 g in a 40-year-old woman; treatment with calcium and noradrenaline had been unsuccessful (22).

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- A 41-year-old man who had taken 4800–6400 mg of verapamil presented 5 hours later and had a cardiac arrest; cardiopulmonary resuscitation was started and he underwent percutaneous cardiopulmonary by-pass, to maintain adequate tissue perfusion and sufficient cerebral oxygen supply until the drug concentration was reduced and restoration of spontaneous circulation was achieved (23).
- Severe poisoning with modified-release verapamil was associated with respiratory failure in a 27-year-old man, who presented 2 hours after taking 24 g, one of the largest reported overdoses (24). He survived after receiving 4 days of partial liquid ventilation as a part of his medical management.
- A 61-year-old woman developed profound hypotension, bradycardia, oliguria, and multifocal myoclonus after verapamil overdose. Her serum verapamil concentration was 800 ng/ml (1760 nmol/l) (usual target range 50–200 ng/ml, 110–440 nmol/l). She was treated with supportive care, vasopressin, dopamine, and calcium gluconate. After about 60 hours the myoclonus and hemodynamic compromise resolved completely (25).
- Two patients took 2400 mg and 9600 mg of verapamil, resulting in life-threatening hypotension and bradycardia, needing cardiac pacing and resuscitation (26). Gastric lavage was not carried out in the first patient, owing to clouded consciousness. Both patients underwent plasmapheresis within 4 hours of ingestion, with dramatic improvement. However, the first patient died 38 hours after admission with multiorgan failure, probably because of the long period of cardiogenic shock. The second patient survived without infirmity, despite the higher verapamil dose.

The authors of the last report emphasized the role of vigorous gastrointestinal lavage with repeated administration of activated charcoal to reduce gastrointestinal absorption of the drug.

Drug–Drug Interactions

ACE inhibitor

The addition of low doses of verapamil to ACE inhibitor therapy reversed ACE inhibitor-induced increases in creatinine concentrations in eight elderly hypertensive patients (27). During an average of 25 weeks, ACE inhibitors significantly reduced blood pressure, but serum creatinine concentrations rose. During an average of 10 weeks, the addition of verapamil did not reduce the blood pressure further, but the serum creatinine concentrations were normalized. Verapamil appears to have a beneficial effect, through dilatation of constricted afferent and efferent arterioles and reduction of the mesangial cell contraction induced by endothelin-1, factors that have been implicated in the increase in intraglomerular pressure and proteinuria due to ACE inhibitors.

Calcium adipinate and calciferol

Treatment of osteoporosis with calcium adipinate and calciferol counteracts the antidysrhythmic effect of verapamil (28).

Ciclosporin

Calcium channel blockers are given to transplant patients for their protective effect against ciclosporin-induced nephrotoxicity. Verapamil has been particularly preferred, as it causes a significant increase in plasma ciclosporin concentrations and also seems to have a direct immunosuppressive action. However, in a study in 152 kidney transplant recipients, verapamil increased the incidence of postoperative infections (29). The patients, all of whom were taking ciclosporin, were assigned either to verapamil 240 mg/day or to no verapamil; during a postoperative period of 2–14 months, the incidence of infections was 22% (17/77) of those given verapamil compared with 5% (4/75) of the others. However, since the study was not randomized, it is not possible to draw reliable conclusions.

Dofetilide

By increasing its rate of absorption, verapamil produced transient rises in peak plasma concentrations of dofetilide in 12 young healthy male volunteers (30). During combination treatment at steady state there was a significant, albeit modest, increase in the mean C_{max} and AUC of dofetilide. These changes were associated with corresponding short-lived increases in its pharmacodynamic effect, as measured by changes in the QT_c interval. These two drugs should not be administered concurrently.

Grape fruit juice

The interaction with grapefruit juice observed with several calcium channel blockers, including felodipine, nifedipine, and nisoldipine, has not been confirmed with verapamil. A single dose of grapefruit juice had no effect on the pharmacokinetics of verapamil in 10 hypertensive patients taking chronic verapamil (31).

Macrolide antibiotics

Verapamil is both a substrate and an inhibitor of CYP3A4, which is inhibited by clarithromycin and erythromycin. Giving these macrolide antibiotics during verapamil therapy is likely to reduce the first-pass metabolism of verapamil, increase its systemic availability, and impair its elimination. In patients taking this combination, verapamil should be started in a low dosage and its hemodynamic effects should be monitored closely.

Clarithromycin

- A 53-year-old woman had periods of dizziness and episodes of fainting when she stood up 24 hours after having been given clarithromycin for an acute exacerbation of chronic obstructive pulmonary disease and verapamil for atrial fibrillation (32). One day later she developed severe hypotension and bradycardia (32). Since her symptoms matched those of severe verapamil overdosage, the drug was withdrawn and her condition improved within two days.
- A 77-year-old hypertensive woman receiving both verapamil and propranolol for hypertrophic cardiomyopathy and paroxysmal atrial fibrillation developed symptomatic bradycardia within 2–4 days of initiation of both

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erythromycin or clarithromycin on two separate occasions, for pneumonia and sinusitis respectively (33).

Erythromycin

- A 79-year-old white woman developed extreme fatigue and dizziness (34). Her heart rate was 40/minute and her blood pressure 80/40 mmHg. An electrocardiogram showed complete atrioventricular block, an escape rhythm at 50/minute, and QT_c interval prolongation to 583 milliseconds. This event was attributed to concomitant treatment with verapamil 480 mg/day and erythromycin 2000 mg/day, which had been prescribed 1 week before admission.

This is the first report of complete AV block and prolongation of the QT interval after co-administration of erythromycin and verapamil, both of which are principally metabolized by CYP3A4. Both drugs are potent inhibitors of CYP3A4 and P-glycoprotein, which may be the basis of this interaction.

The effects of a combination of erythromycin and verapamil on the pharmacokinetics of a single dose of simvastatin have been studied in a randomized, double-blind, cross-over study in 12 healthy volunteers simultaneously taking the three drugs. Both erythromycin and verapamil interacted with simvastatin, producing significant increases in the serum concentrations of simvastatin and its active metabolite simvastatin acid. The mean C_{max} of active simvastatin acid was increased about five-fold and the AUC_{0-24} four-fold by erythromycin; verapamil increased the C_{max} of simvastatin acid 3.4-fold and the AUC_{0-24} 2.8-fold. There was a substantial interindividual variation in the extent of these interactions. Concomitant use of erythromycin, verapamil, and simvastatin should be avoided (35).

Rifampicin

Rifampicin reduces the systemic availability of verapamil, presumably by enzyme induction in the liver (36).

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Verbenaceae

See also Herbal medicines

General Information

The genera in the family of Verbenaceae (Table 1) include mangrove and vervain.

Vitex agnus-castus

Vitex agnus-castus (chaste tree, hemp tree, monk's pepper) is a plant with estrogen-like activities, used for a variety of gynecological problems, particularly on the European continent, particularly premenstrual symptoms (1).

Adverse effects

Vitex agnus-castus can cause ovarian hyperstimulation and increase the risk of miscarriage.

- A woman took *V. agnus-castus* during an unstimulated cycle while undergoing in vitro fertilization (2). She had considerable derangements of gonadotrophin and ovarian hormone concentrations.

Table 1 The genera of Verbenaceae

Aegiphila (spiritweed)
Aloysia (bee brush)
Avicennia (mangrove)
Bouchea (bouchea)
Callicarpa (beauty berry)
Caryopteris (caryopteris)
Citharexylum (fiddlewood)
Clerodendrum (glory bower)
Congea (congea)
Cornutia (cornutia)
Duranta (duranta)
Faradaya
Glandularia (mock vervain)
Gmelina (gmelina)
Holmskioldia (holmskioldia)
Lantana (lantana)
Lippia (lippia)
Nashia (nashia)
Petitia (petitia)
Petrea (petrea)
Phryma (phryma)
Phyla (fog fruit)
Premna (premna)
Priva (priva)
Stachytarpheta (porterweed)
Stylodon (stylodon)
Tamonea (tamonea)
Tectona (tectona)
Tetraclea (tetraclea)
Verbena (vervain)
Vitex (chaste tree)

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Vesnarinone

See also Phosphodiesterase type III, selective inhibitors of

General Information

Vesnarinone is an inhibitor of phosphodiesterase type III, and has a positive inotropic effect. Although vesnarinone was originally developed for the treatment of cardiac failure, its action on tumor cells has prompted its use in the treatment of cancer. In 26 patients who received combinations of vesnarinone and gemcitabine there was no pharmacokinetic interaction between the two drugs (1). Although there were cases of neutropenia and thrombocytopenia, those effects could have occurred with gemcitabine alone and could not necessarily be attributed to vesnarinone. Other adverse effects of the combination included nausea and vomiting, anorexia and fatigue,

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diarrhea, headache, and fever. There were no cases of QT interval prolongation or ventricular dysrhythmias. There were rises in hepatic transaminase activities in up to 25% of cases. Again it was not possible to distinguish between adverse effects of gemcitabine and vesnarinone.

Organs and Systems

Hematologic

Vesnarinone causes reversible neutropenia in up to 2.5% of patients (2,3). In 3833 patients with heart failure of Class III or IV and a left ventricular ejection fraction of 30% or less despite optimal treatment, followed for 286 days, there was dose-dependent agranulocytosis, in 0.2% of those taking vesnarinone 30 mg/day and 1.2% of those taking 60 mg/day (3).

Gastrointestinal

In 3833 patients with heart failure of Class III or IV and a left ventricular ejection fraction of 30% or less despite optimal treatment, followed for 286 days, there was a slight increase in the risk of diarrhea, which occurred in 17% of those taking 60 mg/day compared with 12% of those taking placebo and 14.5% of those taking 30 mg/day (3).

Death

Vesnarinone has been reported to reduce mortality at low doses and to increase it at high doses (SEDA-18, 199) (2,4). In 3833 patients with heart failure of Class III or IV and a left ventricular ejection fraction of 30% or less despite optimal treatment, followed for 286 days, vesnarinone 60 mg/day was associated with significantly more deaths and a shorter duration of survival (3). The increased death rate was due to an increase in sudden deaths, presumably because of cardiac dysrhythmias. There were similar trends in patients who took 30 mg/day, but the changes were not significant. In contrast to the increased mortality with vesnarinone there was a short-term increase in quality of life, which occurred during the first 16 weeks but was not maintained at 6 months. Probably the increased mortality due to vesnarinone outweighs the improvement in quality of life.

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Vidarabine

General Information

Intravenous vidarabine is effective in the treatment of kerato-uveitis in animals and man, and has been used intravenously to treat herpetic eye infections in man (1). It has also been used as an ointment for treating superficial keratitis that does not respond to idoxuridine, but it penetrates the eye poorly (2). It is no longer used because of unacceptable toxicity and inferior activity compared with newer drugs for *Herpes simplex* and *Varicella zoster*. Its rapid inactivation and poor solubility are practical disadvantages.

Long-Term Effects

Mutagenicity

Vidarabine is oncogenic and mutagenic in animals (3).

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Vigabatrin

See also Antiepileptic drugs

General Information

Vigabatrin is used mainly in the treatment of refractory partial seizures and infantile spasms. Weight gain and mostly transient sedation are its most common adverse effects, but visual field defects are the main cause for concern and severely restrict its use.

In a placebo-controlled add-on comparison of three dosages of vigabatrin (1, 3, and 6 g/day) in 174 patients with partial epilepsy, fatigue, drowsiness, and dizziness were the most common treatment-related adverse events, especially at the highest dosage (1). The incidence of severe events was 2.2% in the placebo group and 8.7, 11, and 16% with 1, 3, and 6 g/day respectively. The

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proportion of patients who withdrew owing to adverse events was 2.2% in the placebo group and 6.5, 11, and 18% with 1, 3, and 6 g/day respectively. Four vigabatrin patients (three of whom were taking 6 g/day) had a reduction in erythrocyte counts to 3.4–3.5 $\times$ 10^9/l. Symptoms suggestive of retinal toxicity were not reported, but the duration of treatment was short (18 weeks) and there was no formal ophthalmological testing. Overall, efficacy and safety data from this trial suggested that 3 g/day gave optimal results. Although higher dosages may provide additional benefit in selected patients, the occurrence of retinal toxicity (see below) warrants caution about the use of high doses.

Vigabatrin has been studied in an open 1-year extension of a randomized, double-blind, placebo-controlled Canadian trial in 97 adults with resistant partial epilepsy (2). There was a mean weight gain of 3.7 kg by the end of the study. Treatment was discontinued in 12% because of adverse effects. Neurological/psychiatric adverse effects were the most common reason for withdrawal, including three behavioral reactions attributed to the drug.

In a single-blind, randomized trial of vigabatrin for 2 weeks in children with newly diagnosed infantile spasms the children were randomly assigned to low-dose vigabatrin (18–36 mg/kg/day) or high-dose vigabatrin (100–148 mg/kg/day) (3). The time to response was evaluated during the first 3 months, and safety was evaluated during the entire study. Eight of 75 children who took low-dose vigabatrin and 24 of 67 who took high-dose vigabatrin responded. The time to response was significantly shorter in those who took high-dose vigabatrin and in those with tuberous sclerosis. The most common treatment-related adverse events were sedation (42/167), insomnia (15/167), and irritability (15/167). There were no dose-related adverse events, and adverse event rates were similar in the low-dose and high-dose groups. Only nine patients withdrew because of adverse events.

Vigabatrin efficacy and tolerability have been evaluated for a mean of 16 months in children in a retrospective study of 73 patients (mean age 87 months) (4). In 16% of the children vigabatrin was given as monotherapy and patients with either partial or generalized seizures were included. Vigabatrin was highly effective in 30 children (over 90% seizure reduction) and partially effective in 4 (50–90% seizure frequency reduction). There were adverse effects in 24%, the commonest being irritability, aggression, opposition/defiance, self-injurious behaviors, and deterioration in behavioral control. There was seizure deterioration in 7% of the children; worsening of myoclonic seizures was most common. Visual field testing by perimetry was possible in only 12 of the children; 2 had visual field constriction.

Organs and Systems

Nervous system

Central nervous system adverse events are mostly mild and transient and consist especially of drowsiness and fatigue. Other effects include irritability, nervousness, dizziness, headache, confusion, and depression. In a double-blind add-on trial at dosages of 2 or 3 g/day, drowsiness, diplopia, ataxia, and visual abnormalities were the only adverse effects that increased with dosage (5).

In a randomized open comparison of carbamazepine and vigabatrin in newly diagnosed epilepsy (6), patients randomized to vigabatrin reported less frequent drowsiness (44 versus 62%) and dizziness (7 versus 20%), and more frequent myoclonic jerks (14 versus 2%) and visual scintillae (16 versus 0%).

Like other GABAergic drugs, vigabatrin can aggravate absence seizures and may precipitate absence status in patients with generalized epilepsies. Occasionally, absence seizures are also precipitated in patients with partial epilepsy, as in a 28-year old man who developed de novo absence status 4 days after the dosage of vigabatrin was increased to 2 g/day (7).

Vigabatrin produces intramyelinic edema (neuronal vacuolization) in rats, mice, and dogs, but probably not in non-human primates (8). These findings have been reassessed on the background of clinical safety data, to determine the potential for a similar effect in man (8). In animals intramyelinic edema correlates with changes in multimodality-evoked potentials and MRI, but many studies in patients treated with vigabatrin in dosages of 1–6 g/day for up to 12 years have failed to provide evidence for similar changes in humans. Histological examinations of autopsy brain tissue from 24 patients exposed to vigabatrin for 0.6 months to 9.6 years also failed to show any evidence of astrocytosis or axonal changes similar to those associated with vigabatrin-induced microvacuolization. These findings do not provide any support to the hypothesis that intramyelinic edema occurs in patients treated with vigabatrin.

Acute encephalopathy has previously been attributed to vigabatrin in adults. There has also been a case in a child (9).

- A 6-month-old girl with infantile Alexander disease with hydrocephalus developed apathy, somnolence, and stupor, with slowing of background encephalographic activity, 3 days after starting vigabatrin, which was withdrawn. During the next 2 days her symptoms abated and after 10 days her electroencephalogram normalized.

Vigabatrin can exacerbate myoclonic and absence seizures and occasionally other seizure types, especially in children with generalized epilepsies. After the administration of vigabatrin, seizures worsened in all of four children with Angelman syndrome (10), and generalized seizures occurred for the first time in a boy with succinic semialdehyde dehydrogenase deficiency (SEDA-21, 77). De novo myoclonic jerks and precipitation of status epilepticus have also been reported (SEDA-20, 70).

There have been several reports of acute encephalopathy (SEDA-18, 71) and occasional cases of akathisia, hyperkinesia, and dyskinesias. Toxicology studies in mice, rats, and dogs showed dose-related intramyelinic edema, with microvacuoles in the white matter of the brain, but there is no evidence that these have clinical relevance (SEDA-21, 77).

Sensory systems

Vigabatrin causes a variety of changes in visual function, including reductions in visual field, visual acuity, color

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vision, and electroretinographic and electro-oculographic amplitudes (11–16).

Visual field defects

DoTS classification (BMJ 2003;327:1222–5)
Dose-relation: collateral
Time-course: long-term
Susceptibility factors: male sex

Severe symptomatic visual field constriction, affecting mostly the peripheral fields and without loss of visual acuity, was first reported in 1997 in three patients who had taken vigabatrin for 2–3 years (17), and reports continue to appear (18–24). Electrophysiological investigations suggested damage to the outer retina, and there was no recovery for up to 12 months after withdrawal. Over 50 other cases of visual field defects (including asymptomatic cases) were published thereafter, and 28 were known to the manufacturer before the initial publication (SEDA-21, 78) (SEDA-22, 92).

Features

Visual field loss due to vigabatrin has been studied in 18 patients taking long-term treatment (0.5–9.5 years) and five controls (25). Of the 18 patients taking vigabatrin, there were mild visual field defects in six right eyes and eight left eyes, and severe defects in nine right eyes and eight left eyes. Most of the defects were peripheral constriction with nasal predominance.

Even patients with relatively severe constriction can partly compensate through adjustments in eye movements. Because the disorder develops insidiously, these patients may remain unaware of their condition, even though their visual impairment puts them at risk in special circumstances, such as driving a car.

The safety of continuing vigabatrin therapy in adults who have taken prolonged treatment (over 2 years) has been assessed by serially monitoring changes in visual function over 1 year of continued therapy (26). Fifteen patients who continued to take vigabatrin had visual function testing (visual acuity, color vision, and kinetic and static perimetry) every 3 months for 1 year. Nine had normal visual fields and six had visual field constriction. During follow-up, they showed no worsening of visual acuity, color vision, or visual field constriction, beyond that measured in the initial test. This study showed that mild changes in visual function after long-term vigabatrin generally remain stable with continued treatment. However, patient consistency was variable and repeated testing was necessary in some cases to assess the reliability of the apparent worsening or improvement experienced by some patients.

Frequency

Visual field defects have been commonly reported in patients taking vigabatrin (10–30%) (27,28), although if asymptomatic cases are included, the incidence may be as high as 40% (29) or even 60% (30). In an observational cohort study the prevalence was relatively low, at 0.8% of 7228 patients (31); however, this result was challenged as a probable underestimate, because of the use of a questionnaire to elicit the diagnosis (12–14). These different rates have probably been related to the diverse methods of patient inclusion and visual field testing.

In a prospective study in patients evaluated for epilepsy surgery, absolute concentric contraction of the visual field of 10–30 degrees was found in 20 (17%) of 118 patients who had ever taken vigabatrin, compared with none of 39 patients who had never taken vigabatrin (27). Men were more frequently affected than women (21 versus 6%), and the degree of visual field loss was more severe in patients who had taken vigabatrin for more than 2 years. None of the affected patients complained spontaneously of visual field loss.

Expert review of 25 cases of visual field defects reported to the manufacturer suggested that in 13 of the patients the visual field loss could not be assigned to an alternative known cause and had to be ascribed to vigabatrin (11). In an open extension study in Japan, 29 of 99 patients treated with vigabatrin for 2.7–6.7 years had visual field defects attributed to vigabatrin (11).

Among 57 patients aged 19–73 years treated with vigabatrin as add-on or as monotherapy for 2–14 years, there were mildly abnormal or severely abnormal fields in 14 and 8 patients respectively (32). Two patients with severe field abnormalities were symptomatic.

Of 20 consecutive patients treated with vigabatrin 12 had visual field constriction, severe in four and symptomatic in two (33). Visual field defects were more common in patients who were also taking valproate. Although most reports concerned adults, children may also be affected (34).

In a randomized monotherapy trial in newly diagnosed epilepsy, seven of 32 patients who were still taking vigabatrin after 3–9 years had concentrically constricted visual fields, and the defect was rated as severe in two (35). Of the seven patients with field defects, five had reduced oscillatory potentials and two also had abnormal a and b waves in rod and cone electroretinography. In contrast, none of the 20 patients who were still taking carbamazepine had abnormal visual fields. There is also preliminary evidence that a pre-existing visual field defect increases susceptibility to vigabatrin-induced visual field constriction.

In a double-blind, randomized study in patients with partial epilepsy three of 32 patients taking vigabatrin had abnormal visual perimetry after the end of the study (36).

In a retrospective study in 158 patients with partial epilepsy visual field defects were detected in 21 (13%); 13 patients had concentric visual field constriction without subjective spontaneous manifestations. Of these 13 patients, 9 were taking vigabatrin (37).

The efficacy and adverse effects of steroids and vigabatrin in children with infantile spasms have been reviewed (38). The authors found a high rate of visual field defects and concluded that although vigabatrin is efficacious it does not seem to be more effective than steroids or corticotrophin, and that the benefits of vigabatrin do not justify the associated risks of possible irreversible visual changes.

The prevalence of visual field constriction associated with vigabatrin has been evaluated in 91 children aged 5.6–18 years (39). There were visual field defects in 17,

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but there was wide intrasubject variation between successive test sessions, and children often performed better in later test sessions, making evaluation difficult.

Pathophysiology

Electroretinographic findings in affected patients are consistent with reduced inner retinal cone response (40,41), but interpretation of the results has been disputed (42,43).

Visual fields have been studied in eight patients with vigabatrin-attributed visual field loss; six were no longer taking vigabatrin (44). Seven patients had marked visual field constriction with some sparing of the temporal visual field; the eighth had concentric constriction. Two patients had subnormal Arden electro-oculography indices; one patient had an abnormally delayed photopic b wave; five patients had delayed 30-Hz flicker b waves; and seven patients had delayed oscillatory potentials. Multifocal electroretinography confirmed that the effects occurred at the retinal level.

Visual fields, visual evoked potentials, and electroretinography have been assessed in 24 children treated with vigabatrin; 13 had at least one abnormal study (45). There was visual field constriction in 11 of 17 patients who had perimetry; five of 15 patients who underwent visual evoked potential testing and four of 11 who underwent electroretinography had abnormal examinations. Abnormal visual evoked potentials and electroretinography were mostly found in children who also had visual field constriction. Of five patients who were taking vigabatrin alone, three had abnormalities; however, all the other patients were taking other antiepileptic drugs and additive effects could not be ruled out.

The retinal electrophysiological markers associated with vigabatrin-attributed visual field loss have been distinguished from those associated with current vigabatrin therapy in 8 previous and 18 current vigabatrin users (46). They underwent electro-oculography, electroretinography, and automated static threshold perimetry and 22 healthy subjects underwent electroretinography. Of 26 patients exposed to vigabatrin, 18 had visual field loss; none taking other antiepileptic drugs had this type of visual field abnormality. The presence and severity of the visual field loss were significantly associated with the latency (implicit time) and amplitude of the electroretinographic cone function. The amplitude of the cone flicker response was the strongest predictor of visual field loss. The electro-oculogram, the photopic and scotopic electroretinogram, and the latency of the electroretinographic second oscillatory potential were not significantly related to the presence of visual field loss. Vigabatrin was significantly associated with the photopic amplitude, the scotopic a-wave latency, and the latency of the second oscillatory potential.

The pathological features of visual field constriction have been described in a patient taking vigabatrin (47).

- A 41-year-old man who had taken vigabatrin for 2 years in doses of 3–6 g/day developed bilateral concentric visual field defects, with greater loss in the nasal fields. Vigabatrin was withdrawn. Later he had a cardiopulmonary arrest and died. At postmortem there was peripheral retinal atrophy with loss of ganglion cells, severe in the peripheral retina and less severe in the maculae. There was loss of nerve fibers in the optic nerves, chiasm, and tracts. There was no evidence of intramyelin edema.

These findings suggest that vigabatrin may be directly associated with direct retinal injury (to the ganglion cells). The degree of cell loss suggested that the visual field loss was irreversible.

Mechanism

The mechanism responsible for the development of the visual field defects is unknown. However, they may be related to accumulation of GABA in the retina. In rats treated either with vigabatrin or tiagabine, vigabatrin reduced the activity of GABA transaminase and increased GABA concentrations in the brain, but these effects were more pronounced in the retina, in which vigabatrin concentrations are as much as five-fold higher than in the brain (48). On the other hand, tiagabine concentrations are considerably lower in the retina than in the brain. Tiagabine has not been associated with visual field defects.

Vigabatrin-induced inhibition of ornithine transaminase has been suggested as an alternative mechanism (49).

Diagnosis

Visual field defects are difficult to detect by simple clinical examination, even in patients with severe constriction at perimetric assessment. Visual field testing should be done before treatment and at regular intervals thereafter. Patients should be questioned about visual disturbances and referred to an ophthalmologist if relevant symptoms are recognized.

Potential correlations between visual field defects and the results of ophthalmological tests have been assessed. The use of the electroretinogram as a marker for vigabatrin-induced visual field alterations has been questioned (42), and the suggestion has been made that the electroretinographic changes described in some patients on vigabatrin may be due to a physiological effect of GABA not necessarily related to retinal toxicity (43). Of 20 consecutive patients 14 had a reduced light/dark ratio (Arden ratio) in the standard electro-oculogram and 10 had absent oscillatory potentials in the electroretinogram (33). Overall, 17 patients had abnormal electro-oculography, electroretinography, or both, although only 12 had constricted visual fields at perimetric testing.

The value of electroretinography and electro-oculography in the early diagnosis of vigabatrin-associated visual field defects has been assessed in 30 patients with temporal lobe epilepsy (50,51). The patients were stratified into three groups: (A) concentric contraction of the visual field associated with vigabatrin ($n = 15$), (B) normal visual field with vigabatrin use ($n = 11$), and (C) normal visual field without vigabatrin ($n = 4$). There were abnormal electrophysiological results in 50% of the patients in group A. The electro-oculographic Arden ratio was lowered in 57%. The amount of visual field loss and the total dose of vigabatrin used correlated only weakly with the results of electroretinography and electro-oculography. These results suggest that ocular electrophysiology is not a good method for detecting patients at risk of vigabatrin-related visual field defects. Regular visual field examination remains the

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cornerstone in screening. This has been confirmed by a retrospective, comparative case series in which the degree of electroretinal dysfunction was analysed using electroretinography in 40 patients taking vigabatrin, 24 as monotherapy (52). There was no statistically significant relation between the frequency of electrodiagnostic abnormalities and the duration of use or the total cumulative dosage of vigabatrin.

Dose-relation

Visual function has been studied in 21 epileptic patients taking vigabatrin and compared with visual function in 11 similar epileptic patients who had never taken it, in order to investigate whether the severity of visual field defect is related to the dose of vigabatrin and to consider other factors that may correlate with severity (53). Nine of 20 patients taking vigabatrin complained of blurring of vision compared with two of 11 controls. Four patients taking vigabatrin described flickering lights compared with one control. None had a posterior vitreous detachment. Three of 30 eyes of patients taking vigabatrin had distant visual acuity of 6/12 or worse compared with three of 22 controls, and five of 30 had near visual acuity worse than N6 compared with one of 22 controls. A mean of 1.73 Ishihara plates were misread by patients taking vigabatrin compared with 0.18 in the controls. There was a significant correlation between the severity of visual field defect and the total dose of vigabatrin.

In a cohort study of 99 patients taking vigabatrin, the prevalence of visual field defects increased significantly with increasing total vigabatrin dose. The prevalence ranged from four of 51 patients who had been exposed to 1 g/day or less to six of 8 patients taking a total dose of 3–5 g/day (28).

Time-course

The longer the duration of vigabatrin treatment and the higher the dose the greater the probability of field defects (28,30,51).

In a reference cohort of 42 patients exposed to other antiepileptic drugs without vigabatrin, 7 had visual field defects, but in all of them this could be ascribed to a known cause (11). The prevalence of visual field loss ascribed to the drug did not differ between patients treated for less than 4 years and those treated for more than 4 years (32 versus 28%), suggesting that the disorder is unlikely to increase with continuous treatment beyond 4 years. Visual field loss occurred in 17 of 45 men (38%) versus 12 of 54 women (22%), indicating that men have a two-fold increase in risk. Age, body weight, daily or cumulative vigabatrin dose, and concomitant antiepileptic drugs did not predict the occurrence of visual field loss. The appearance in the central field out to 30° eccentricity was typically that of a localized bilateral binasal loss, particularly with static threshold perimetry, extending in an annulus over the horizontal midline, together with a relative sparing of the temporal field. In severe cases, there was a concentric appearance. All cases except one were asymptomatic. The authors concluded that the visual field defect induced by vigabatrin is unique in pattern and profound in terms of frequency of occurrence and location and severity of the loss.

Susceptibility factors

Concentric visual field loss found in the presurgical evaluation of patients with drug-resistant temporal lobe epilepsy taking vigabatrin has been studied and related to potential susceptibility factors in 157 consecutive patients with drug-resistant temporal lobe epilepsy (27). There was absolute concentric contraction of the visual field of 10–30 degrees presurgically in 20 of 118 patients who had ever used vigabatrin and in none of 39 who had not. Men were significantly more often affected than women (15 of 72 versus 5 of 85). The degree of visual field loss correlated with the duration of vigabatrin medication. There was no correlation of visual field contraction with a history of meningitis as potential cause of the epilepsy, duration of the epilepsy, status epilepticus in the medical history, or histological abnormality of the brain tissue removed. Ophthalmological examination of the patients with concentric contraction showed no abnormalities. None of the patients with concentric contraction complained spontaneously of their visual field loss.

The long-term retinal effects of vigabatrin in children are unknown, and visual field testing is usually impossible. Recent evidence has suggested that a short course of vigabatrin (6 months) in children with infantile spasms may be sufficient (54) and minimizes the potential for visual adverse effects.

Reversibility

Vigabatrin-induced visual field loss is generally considered to be irreversible (28,51), although partial reversibility has been described in some cases.

Long-term changes in the concentric contraction of the visual field have been studied in 27 patients with temporal lobe epilepsy taking vigabatrin (55). Concentric contraction of the visual field did not change in 16 patients who stopped taking vigabatrin before the first examination but there was slight but significant worsening of visual field loss in 11 patients who continued taking vigabatrin. The authors concluded that vigabatrin-associated visual field loss is not reversible and that progression can occur when vigabatrin is continued.

The reversibility of visual function loss from vigabatrin has been studied in 13 patients who had discontinued the drug up to a year before because of lack of efficacy or reductions in visual field (56). Although electroretinographic cone implicit time improved, most of the patients did not have improvement in either clinical measures of visual function (that is visual acuity, color vision, visual fields) or in electroretinographic amplitudes. However, several patients who had minimal visual field loss while taking vigabatrin had substantial recovery of the electroretinographic amplitudes. There was no association between recovery of function and either duration of treatment or cumulative dosage. Multifocal electroretinography showed a diffuse loss of function that was not isolated to the periphery.

In contrast, in another study there was partial reversibility of visual field constriction and retinal function after withdrawal in two patients (57).

Of 30 children with epilepsy (14 boys and 16 girls, aged 4–20 years) taking vigabatrin for infantile spasms and simple and complex partial epilepsy, who had never complained of ophthalmologic disturbances, 4 had visual field

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constriction in the nasal hemifield (58). In one child, visual abnormalities were stable even 10 months after vigabatrin withdrawal, while in another there was improvement 5 months after withdrawal.

- Although in a 10-year-old girl a severe visual field defect was said to have reversed after withdrawal (59), repeat confirmatory testing was not performed before the withdrawal of vigabatrin and the pattern of constriction was suggestive of an artefact related to inadequate compliance with the testing procedure (J Wild, personal communication, 1999).

However, other preliminary reports have suggested that reversibility of the visual field defects may in fact occur following early withdrawal (57,60).

Of 12 vigabatrin-treated patients with visual field defects re-examined 2–10 years after vigabatrin withdrawal, all still had visual field defects (28). In five cases there was apparent worsening. Exceptional cases of reversible visual field defects have been reported in children (61). However, perimetry assessment in children is burdened with multiple methodological problems that usually preclude reliable results.

In a study in 60 adults with partial epilepsy, progression or reversibility of vigabatrin-associated visual field defects were examined (51). The patients had taken vigabatrin for 7 months to 14 years as monotherapy or add-on therapy and were examined with repeated kinetic Goldmann perimetry. A follow-up examination was performed after 4–38 months in 55 patients. There was vigabatrin-associated visual field constriction in 40%, and in 13% the defect was severe. During follow-up after withdrawal of vigabatrin, there was no significant recovery of visual fields in any patient. Conversely, there was no progression in those who continued therapy.

Effects of other antiepileptic drugs and interaction with vigabatrin

Other antiepileptic drugs can also alter visual evoked potentials and brainstem evoked potentials. Visual field defects associated with various antiepileptic drugs (carbamazepine, diazepam, gabapentin, phenytoin, tiagabine, and vigabatrin) have been reviewed (37).

In 100 epileptic patients aged 8–18 years taking carbamazepine or valproate in modified-release formulations either alone or with added vigabatrin interpeak latencies of I-III and III-V of brainstem evoked potentials were significantly delayed and N75/P100 and P100/N145 amplitudes in the visual evoked potentials were reduced (62). However, the addition of vigabatrin did not worsen the effects caused by the other two drugs alone.

Retinal dysfunction

Retinal dysfunction has been retrospectively assessed in 29 children taking vigabatrin 25–114 mg/kg/day for 6.5 years (63). Ophthalmic examination was performed before treatment and every 6 months thereafter. Four children developed eye changes (retinal pigmentation, hypopigmented retinal spots, vascular sheathing, and optic atrophy). Visual evoked potentials were abnormal in 16. Electroretinography and electro-oculography were not performed.

Color vision defects

There was abnormal color perception in 32% of 32 patients taking vigabatrin monotherapy; in four cases there was an abnormality in the blue-yellow axis (64). In the same patients there was a positive correlation between visual contrast sensitivity and the size of the visual field; macular photo-stress and glare tests were equal in both groups and did not differ from normal values; there was no effect on glare sensitivity (65).

Changes in color vision have been investigated in healthy volunteers who took a single oral dose of either vigabatrin or carbamazepine in a single-blind, placebo-controlled, randomized trial (66). All underwent color visual-evoked potential testing and color perimetry at baseline and after taking placebo, vigabatrin (2000 mg), or carbamazepine (400 mg). Carbamazepine caused mild overall impairment of the chromatic and achromatic systems. Vigabatrin caused selective blue impairment, consistent with GABAergic inhibition in the retina. The relation of this change in color perception to visual field defects, if any, is unknown.

Psychological, psychiatric

Although abnormal behavior, psychosis, and depression occur with increased frequency (around 2–4% or even higher) in patients with refractory epilepsy, the risk is increased during treatment with vigabatrin or on its abrupt withdrawal (SEDA-18, 71) (SEDA-19, 76) (SEDA-20, 70) (SEDA-21, 77) (67). The risk depends on the patient's characteristics, the dosage, and the rate of dose escalation. In the manufacturer's safety database, the incidence of psychosis was reported as being 1.1% or 0.64% based on postmarketing Prescription Event Monitoring (68). However, in adults with refractory partial epilepsy, severe behavioral or mood disturbances can be anticipated in 26% of treated cases (SEDA-18, 72), although higher figures have also been presented (SEDA-20, 70). In one study depression occurred with a frequency of about 9% with vigabatrin and 1% with placebo (5).

Psychiatric complications occur in both children and adults. While there is some evidence that a positive psychiatric history may increase the risk (and may represent a relative contraindication), behavioral and mood disturbances can occur in patients who had no similar episodes in the past. A retrospective survey of 50 patients with vigabatrin-associated psychosis ($n = 28$) or depression ($n = 22$) suggested that psychosis tends to occur in patients with more severe epilepsy and may be related to a right-sided EEG focus or suppression of seizures (64% of patients were free of seizures). On the other hand, patients with depression tended to have a past history of depressive illness and to have had little or no change in seizure frequency (69). To minimize risks, vigabatrin should be introduced in low dosages and increased slowly, and it should not be withdrawn abruptly. Psychiatric symptoms usually remit with drug withdrawal, although if treatment needs to be continued, neuroleptic medication may be useful.

That vigabatrin can cause psychosis and depression has been confirmed in an analysis of data from double-blind, controlled, add-on trials (70). Compared with placebo, vigabatrin-exposed patients had a significantly higher

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incidence of events coded as depression (12 versus 3.5%) and psychosis (2.5 versus 0.3%). Although these events occurred during the first 3 months, most of the studies lasted 12–18 weeks and therefore definite conclusions could not be reached about timing.

Metabolism

Weight gain occurs in as many as 40% of patients during the first 6 months of therapy.

Mouth and teeth

Gingival overgrowth occurred in a 29-year-old man who had taken vigabatrin for 5 years for partial epileptic seizures (71).

Liver

Liver toxicity, if it occurs, is exceedingly rare. Fatal acute hepatic failure was described in a 3-year-old boy (SEDA-21, 78).

Pancreas

Pancreatitis occurred in a patient whose polytherapy included vigabatrin (SEDA-20, 58), but cause and effect was uncertain.

Skin

Skin reactions to vigabatrin are very rare. One case of erythema multiforme was complicated by concomitant multiple pathology, and cause and effect was dubious (SEDA-20, 71).

Susceptibility Factors

Renal disease

Acute encephalopathy with stupor and generalized slow wave electroencephalographic activity developed in three men with mild renal insufficiency aged 24–74 years within 1–3 days of starting vigabatrin (1–2 g/day) or increasing the dosage (from 2 to 3 g/day) (72). The symptoms subsided rapidly after drug withdrawal or dose reduction. Special caution is recommended when vigabatrin is used in patients with impaired renal function.

Drug Administration

Drug overdose

Doses of vigabatrin up to 10 g have been taken without serious effects. Toxic manifestations include vertigo, tremor, sedation, coma, myoclonic jerks, and psychosis. Gastric lavage within 1–2 hours is recommended after doses in excess of 12 g in adults and 2 g in children (SEDA-22, 85). The development of discontinuous partial complex status epilepticus in a patient with partial epilepsy who had taken a 20 g overdose 6 days earlier was considered to be a possible effect of withdrawal (SEDA-22, 85).

- After an overdose of vigabatrin 45 g, a 17-year-old girl developed a behavioral disorder (73). A CT scan of the brain was normal but an electroencephalogram showed abnormal delta waves.

Drug–Drug Interactions

Carbamazepine

One report suggesting that carbamazepine reduces serum vigabatrin concentrations (SEDA-21, 80) requires confirmation.

Although vigabatrin is not metabolized by liver enzymes it increased serum carbamazepine concentrations by at least 10% in 66 epileptic patients aged 10–66 years with focal seizure onset with or without secondary generalization (74).

Ethinylestradiol

Vigabatrin does not produce enzyme induction and did not generally alter the kinetics of ethinylestradiol and levonorgestrel, although two women had an approximate 50% reduction in ethinylestradiol concentrations during vigabatrin treatment (SEDA-21, 80).

Phenytoin

Vigabatrin can reduce serum phenytoin concentrations by about one-third, but this interaction is inconsistent.

Interference with Diagnostic Tests

General

Vigabatrin can produce an abnormal urinary amino acid pattern, which can be diagnostically confusing (SEDA-16, 74). It increases plasma and urinary alpha-aminoadipic acid concentrations, possibly complicating the diagnosis of alpha-aminoadipicaciduria (SEDA-20, 71).

Vigabatrin inhibits alanine transferase, and the resulting underestimation of enzyme activity could mask evidence of hepatic disease (SEDA-20, 70).

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Viloxazine

See also Antidepressants, second-generation

General Information

Viloxazine, a bicyclic compound, is related structurally (but not pharmacologically) to the beta-adrenoceptor antagonists. In animal tests, its profile shows properties of both the imipramine-like compounds (reversal of reserpine-induced hypothermia) and amphetamine (stimulation of the electroencephalogram). A review of animal and clinical data confirmed the impression that viloxazine has efficacy comparable to that of imipramine but with a different adverse effects profile (1). There is a reduced frequency of anticholinergic and sedative effects and a tendency to lose rather than to gain weight. However, viloxazine has some limiting adverse effects of its own. These include nausea, vomiting, and gastrointestinal distress, which may be reduced by the use of an enteric-coated formulation (2,3). Viloxazine has also been implicated in migraine, even in patients with no previous history (4).

Organs and Systems

Cardiovascular

Although hypotension and tachycardia can occur, an extensive review of its animal and clinical pharmacology

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suggested that viloxazine is relatively free of direct cardiotoxic effects (1). In a controlled comparison of doxepin and viloxazine (150–450 mg/day), one patient taking viloxazine developed chest pain after 26 days; an electrocardiogram confirmed changes compatible with ischemia but there were no progressive electrocardiographic or enzyme changes, and the patient recovered fully after being dropped from the study (5).

Nervous system

Viloxazine has previously been reported to lack epileptogenic properties (SEDA-10, 52). In a review of eight patients (six reported to the UK Committee on Safety of Medicines and two in Japan) it was concluded that there was a possible causal connection with seizures in only two cases, and that such an association was inconsistent with the results of animal studies and with a worldwide review of clinical trials (6). The reviewers concluded that if there is a risk of inducing epilepsy with viloxazine, it is probably only one-tenth that of tricyclic compounds.

Drug Administration

Drug overdose

It has been claimed that viloxazine is relatively free of cardiotoxic effects and therefore safe in patients who take an overdose. Indeed, 12 cases of overdose have been reported, with complete recovery and no electrocardiographic changes (SEDA-1, 9). In an authoritative review it was concluded that although coma, hypotension, and loss of tendon reflexes have been reported, serious complications do not develop in most cases (7).

Drug–Drug Interactions

Carbamazepine

In seven patients with epilepsy taking carbamazepine the addition of viloxazine 300 mg/day resulted in a pronounced increase in plasma carbamazepine concentrations (8.1–12.1 ng/ml), with symptoms of intoxication (dizziness, fatigue, ataxia, and drowsiness), resolving on withdrawal of viloxazine (8). The mechanism was unclear, but serum concentrations of phenytoin in two patients were unchanged.

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Vinca alkaloids

See also Cytostatic and immunosuppressant drugs

General Information

From among nearly 30 different alkaloids that have been isolated from the periwinkle *Catharanthus roseus* (Apocynaceae), vincristine and vinblastine have been assessed to have the highest antitumor activity. Both have a large dimeric asymmetric structure composed of a dihydroindole nucleus (vindoline ring) and an indole nucleus, linked by a carbon–carbon bond. In contrast, the derivatives vindesine (deacetyl vinblastine amide sulfate (DVAS)) and vinorelbine are semisynthetic (1–3). Finally, vinflunine, the latest semisynthetic vinca alkaloid, is a fluorinated derivative that is still under clinical investigation and has a different inhibitory action than other vinca alkaloids. Preliminary results suggest that this congener may be less toxic on the peripheral and autonomic nervous systems (4).

Vincristine (rINN)

Vincristine is part of many chemotherapeutic regimens, based on its lack of myelosuppressive toxicity. It is used, for example, in the treatment of acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), lymphomas, neuroblastoma, brain tumors, and Wilms' tumor. The generally recommended dose in adults is 1.4 mg/m^2/week intravenously (5). Some clinicians have recommended an absolute upper limit of 2 mg, but this limitation is still a matter of debate (6). The usual pediatric dosage is 1.5–2 mg/m^2, but for children weighing 10 kg or less or who have a body surface area less than 1 m^2, the manufacturers recommend that treatment should be begun at 0.05 mg/kg once a week (5).

Vinblastine (rINN)

Vinblastine is used in combination with other cytotoxic agents for the treatment of disseminated Hodgkin's disease stages III and IV, non-Hodgkin's lymphoma, histiocytic lymphoma, and advanced carcinoma of the testis. It has also been used for the treatment of bladder cancer, melanoma, and renal cell cancer. The usual adult dosage is 3–6 mg/m^2 intravenously for the treatment of testicular germ cell tumors and Hodgkin's disease (1,2).

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Vindesine (rINN)

Vindesine (DVAS) was the first semi-synthetic vinca alkaloid derivative introduced into clinical oncology. It differs solely from vinblastine in the nature of the substituted functional group attached to the vindoline ring. Vindesine has been most extensively studied in the treatment of non-small cell lung cancers. A randomized study has shown that vindesine (3 mg/m^2 intravenously) was substantially better than vincristine (1.4 mg/m^2 intravenously) both given weekly for 4 weeks, then every 2 weeks for 1 month, then monthly. However, another study showed that vindesine may be inferior to the structurally related vinorelbine in the treatment of advanced non-small cell lung cancers with overall response rates of 9 and 29%, respectively. Vindesine has also been used in patients with advanced malignant melanomas. Potential indications that have been studied with vindesine include head and neck cancer, ALL, lymphomas, and breast cancer. However, its precise role and clinically relevant advantages to other available vinca alkaloids needs further investigation (7–10).

Vinorelbine (rINN)

Vinorelbine has become a pivotal agent for treating adjuvant non-small cell lung cancer (stages IB-III) and the palliative treatment of non-small cell lung cancer (stages IIIB and IV), often in combination with drugs like cisplatin. In addition, vinorelbine plays an important part in the treatment of advanced and metastatic breast cancer. Its role in the treatment of advanced cervical cancer is still under investigation. The usual intravenous dosage is 20–30 mg/m^2 (vinorelbine base) given once a week. In contrast to the other congeners, vinorelbine can also be taken orally based on its absolute systemic availability of about 44% after administration as a capsule. Oral dosages of 60 and 80 mg/m^2 have been said to be pharmacokinetically and clinically equivalent to intravenous dosages of 25 and 30 mg/m^2 respectively (2,11).

Mechanism of action

All four vinca alkaloids block mitosis with metaphase arrest. Their antitumor activity is based on their high binding affinity to intracellular tubulin, which is the protein subunit of the spindle microtubules. The binding constants of vincristine, vinblastine, and vindesine for tubulin are 8, 6, and 3.3 nmol/l respectively (9,10). The formation of complexes between the vinca alkaloids and tubulin prevents the polymerization of the tubulin subunits to microtubules, which results in depolymerization of microtubules and inhibition of microtubule assembly. Based on the fact that microtubule assemblies also play a pivotal role in the movement of neurotransmitter substances along neuronal axons, vinca alkaloids can cause neurotoxicity, particularly at higher concentrations (9,10).

Pharmacokinetics

After intravenous administration, plasma concentrations of vinca alkaloids fall triphasically, with an initial rapid phase. All four congeners are extensively distributed into peripheral compartments, but passage across the blood–brain barrier is limited (11,12). In addition to tissue binding, vinca alkaloids bind to blood constituents like human platelets and lymphocytes. Binding to plasma proteins has been estimated to be from about 80% to more than 90%, with an unbound fraction of about 0.10–0.20. Binding to whole blood is usually higher than in serum, which reflects substantial binding to platelets (11,12).

All four congeners are extensively metabolized in the liver and excreted in the bile (13). Their metabolic biotransformation is primarily mediated by CYP3A. Deacetylvinorelbine, the primary metabolite of vinorelbine, has remarkable antitumor activity; however, the amounts detected in blood after conventional doses of vinorelbine are very low, which suggests that this metabolite does not contribute significantly to the overall antitumor activity of vinorelbine (14,15). Based on the pivotal role of CYP3A isozymes during the catabolism of vinca alkaloids, care is warranted when using concomitant drugs that inhibit these isozymes (16,17).

The half-lives of vinblastine, vindesine, and vinorelbine are all about 24 hours; vincristine has a much longer half-life of about 3.5 days (5). Because biliary and fecal drug excretion is of major quantitative importance during the elimination of vinca alkaloids, patients with impaired hepatic clearance and increased bilirubin concentrations may need dosage modification in order to avoid critical drug accumulation. CYP3A4 activity measurement (for example by the monoethylglycinexylidide test) might be the most appropriate method to estimate individual capacity to metabolize drugs like vinorelbine; however, such methods have not yet been routinely established in most cancer centers. Empirically, it is prudent to reduce doses by about 50% in patients with liver volume replacement by tumor that exceeds 75% (18).

Vinorelbine is the only vinca congener that can also be used orally. Its oral availability averages 43% and is not affected by food (19). The interpatient variability in blood concentrations is in the same range as after intravenous administration (15).

General adverse effects

The most important adverse effects of vinca alkaloids include nervous system disorders, hematological effects, and gastrointestinal discomfort. Respiratory and cardiovascular adverse effects have to be particularly considered during combination chemotherapy. All the vinca alkaloids are tissue irritants, and extravasation without any adequate supportive management can result in severe local ulceration (1,2,5,8,20).

Vinca alkaloids are primarily metabolized by CYP3A4, inducers, inhibitors of which can significantly change their pharmacokinetics (16,17,21).

Organs and Systems

Cardiovascular

Vinca alkaloid-associated myocardial infarction, angina pectoris, and transient electrocardiographic changes related to coronary ischemia are limited to case reports (22–24). In addition, patients with these adverse effects

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received combination cancer chemotherapy, containing drugs such as bleomycin and cisplatin, which both have been suggested to cause cardiovascular adverse effects.

- A 64-year-old Japanese man developed chest pain with concomitant lateral ST segment depression after treatment with intravenous cisplatin 70 mg/m^2, vincristine 1.2 mg/m^2, and bleomycin 12 U/m^2. There was no history of predisposing factors and the symptoms disappeared quickly with glyceryl trinitrate. During the following cycle, containing cisplatin and verapamil as an antianginal agent, chest pain did not reoccur (23).
- A 46-year-old man developed a Q-wave inferior and a right ventricular myocardial infarct with postinfarction angina after the third cycle of vincristine + doxorubicin for multiple myeloma. The patient had no risk factors for ischemic heart disease, except for a positive smoking history, nor for hyperviscosity (24).

There is some evidence that both vincristine and doxorubicin are more often associated with ischemic heart disease than other cancer chemotherapeutic agents. Whether drug-induced platelet activation, altered clotting, or endovascular damage are responsible for vascular toxicity is still unclear. The risk of ischemic heart disease must therefore be kept in mind when patients receive a combination of doxorubicin and vincristine, especially when potential risk factors have been identified. Whether the structural similarity between vinca alkaloids and ergot alkaloids, which are vasospastic, is relevant is highly speculative.

After administration of vinorelbine, chest pain occurs in up to 5% of patients. However, subsequent analysis showed that most patients had underlying cardiovascular disease or a tumor in the chest, making interpretation difficult (2,20). Three patients developed acute cardiopulmonary toxicity after vinorelbine therapy (25). The symptoms mimicked acute cardiac ischemia, but with no electrocardiographic changes or raised cardiac enzymes. In two patients, tachypnea, râles, wheezing, and severe dyspnea responded to inhaled salbutamol. One patient developed pulmonary edema and bilateral pleural effusions, which contained no malignant cells when drained.

Venous discomfort and venous chemical phlebitis have been reported with vinorelbine 30 mg/m^2, with an incidence of up to 31% (26,27). The risk is increased in obesity (27). Pain along the vein occurred in five of 43 patients receiving vinorelbine 30 mg/m^2/week; none developed extravasation, but their symptoms were very similar (28). A similar rate of toxicity, 4.5%, has been reported in a review of the use of vinorelbine in 321 patients with breast cancer (29).

Respiratory

Acute shortness of breath and bronchospasm have been reported after the administration of vinca alkaloids, for example vinblastine and vindesine (30–34). The respiratory effects, including abrupt onset of progressive dyspnea, non-productive cough, pleuritic chest pain, profound wheezing, and diffuse basal crackles, were more common when mitomycin was used concomitantly. The onset of symptoms can be rapid (for example a few minutes to 1–5 hours after administration) or subacute (for example up to 2 weeks). If patients have pre-existing pulmonary dysfunction, intensified treatment, including glucocorticoids, may be indicated. Most case reports with vinca alkaloid-associated pulmonary toxicity included vinblastine, usually in combination with other known pneumotoxic agents, or thoracic irradiation. Patients receiving combination chemotherapy including vinca alkaloids should be monitored carefully for pulmonary symptoms. The underlying mechanism of vinca alkaloid pulmonary toxicity is unclear, but may involve a hypersensitivity reaction.

Nervous system

The most commonly reported dose-limiting toxic effect of vinca alkaloids is a mixed sensorimotor polyneuropathy (35). Vincristine has been associated with highest incidence, followed by vindesine and vinblastine; vinorelbine causes less neurotoxicity than the other congeners (2,5,8,36). The neurotoxic effects of vinca alkaloids are reversible (5).

The vinca alkaloids may have synergistic effects on the nervous system. Amongst 17 patients with metastatic breast cancer given the four-drug combination, vincristine + vinblastine + doxorubicin + cyclosphosphamide, there was a high incidence of acute neurotoxicity at half the usual therapeutic dose of vincristine and vinblastine (37).

Nerve palsies

Cranial nerve palsies can occur with the vinca alkaloids (38–42).

There have been several reports of isolated vincristine-induced recurrent laryngeal nerve paralysis (38,43–47).

Peripheral neuropathy

The features of vinca alkaloid-induced polyneuropathy include early loss of tendon reflexes at the ankles and distal paresthesia, followed by loss of touch, pain, and vibration sensations. Other symptoms include headache, malaise, weakness, dizziness, severe face and jaw pain, and vocal cord paralysis. The first symptoms usually occur a few days after drug administration (36). Gastrointestinal discomfort, particularly constipation, abdominal pain, and adynamic ileus, can occur through an autonomic neuropathy (5,48).

Higher drug concentrations during monotherapy (possibly related to impaired drug excretion in patients with hepatic dysfunction) or prolonged periods of treatment are important predisposing factors for more severe forms of neurotoxicity. The same is true of concomitant use of potent CYP3A inhibitors, such as erythromycin, itraconazole, or quinupristin/dalfopristin, which can increase plasma vinca alkaloid drug concentrations (5).

Of 22 patients given vindesine 2 mg/m^2 on 2 consecutive days weekly, four developed a peripheral neuropathy with paresthesia, and five developed muscle weakness with loss of deep tendon reflexes (49). Neuropathies were pronounced at sites of pre-existing nerve damage. If a tumor had previously damaged peripheral nerves, or if a chordotomy had been performed, the paresthesia that developed at that site was often painful. Neurotoxicity

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was reversible, and the longest interval to full recovery was 3 months.

In 40 patients, orofacial pain developed as a manifestation of neuropathy about 3 days after vincristine administration, lasting for a mean duration of 2 days. Half of the patients were affected in the first week, and pain was commonest in young patients and in smokers (50).

With vinorelbine, incidence rates of 1.3% for peripheral neuropathies (mainly loss of deep tendon reflexes) and 4.1% for autonomic neuropathies (manifested by constipation) have been reported from a European overview of 321 patients (29).

The pathogenesis of vincristine-induced neuropathy has not been fully elucidated, but very probably altered axoplasmic transport processes are of major importance, since neurons treated with vincristine lose portions of their axonal microtubules (35). There is marked interindividual variability in sensitivity to this toxic effect, partially based on different predisposing factors, for example diabetes mellitus, pretreatment with other potentially neurotoxic agents (such as cisplatin and taxanes), or familial disorders (such as Charcot–Marie–Tooth syndrome) (37,51,52).

Several drugs have been proposed to be neuroprotective, including folinic acid, vitamin B_1, vitamin B_6, glutamic acid, Org 2766, insulin-like growth factor (IGF-1), and nerve growth factor. However, most drugs have been studied in experimental systems and there are only a few case reports suggesting clinical benefit. In contrast, folinic acid, vitamins B_1, B_{16}, and B_{12}, which were promising in experimental systems, failed to provide protection from vincristine-induced neuropathy in clinical studies. In the case of L-glutamic acid, which can be given orally, there was some neuroprotective activity; however, more information is needed to exclude any impairment of vincristine-induced antineoplastic activity, when both agents are used together on the same day (5).

The ACTH analogue Org 2766 was studied in a randomized, double-blind, placebo-controlled trial as a neuroprotective agent in patients receiving vincristine (53). In spite of positive results, the study design was later criticized because of a significantly higher number of younger patients in the Org 2766 group. In addition, there are contradictory results on the potential effect of Org 2766 on the overall antineoplastic activity of vincristine.

In a prospective, double-blind, placebo-controlled study, concurrent oral administration of 500 mg glutamic acid tds with vincristine reduced the incidence of subjective and objective signs of vincristine neurotoxicity (54). There were no differences in constipation, weakness, or loss of knee reflexes. There were no severe gastrointestinal adverse effects.

During recent years, more attention has been paid to nerve growth factor as a neuroprotective agent, since it may induce microtubule assembly, especially during neurite outgrowth. For instance, patients with a sensory neuropathy related to the use of cancer chemotherapy including paclitaxel, vincristine, or cisplatin had a significant reduction in plasma nerve growth factor concentrations (5). Acetyl-L -carnitine has been considered for neuroprotection because it increases nerve growth factor expression. However, as in the case of L-glutamine or Org 2766, more information is needed to evaluate any potential effect on vincristine antitumor efficacy.

Pre-existing neurological disease can predispose to severe vincristine neuropathy (55). For example, Charcot–Marie–Tooth disease is regarded as a contraindication to the use of vincristine (56). There have been four cases of vincristine-induced neuropathy in Charcot–Marie–Tooth disease; one was fatal, and in the other three there was severe quadriplegia, which resolved. A predisposition to vincristine neuropathy has been described in a patient with pre-existing Friedreich's ataxia (56). When vincristine 0.625 mg/m^2/week was given to 264 patients for a maximum of 10 weeks, the incidence of grade 3/4 neuropathy rate was 7%, suggesting that dose intensity rather than total dose may be important for determining the severity of this toxic effect. The rate of grade 1–4 neuropathy was 56% (57).

Finally, the aminothiol amifostine has been proposed to be effective in preventing vincristine-induced neurotoxicity; however, clinical data are still lacking to assess its role as a neuroprotective agent in terms of vinca alkaloids (5).

Myeloencephalopathy

Central nervous system toxicity is unusual with vinca alkaloids, because they do not readily cross the blood–brain barrier. However, fatal myeloencephalopathy can occur a few hours after accidental intrathecal drug administration (58,59), with severe bilateral leg pain, and over the next 36 hours progressive leg weakness, urinary retention, meningism, fever, and somnolence. Other effects include absence of deep tendon and gag reflexes and disappearance of rectal tone. In spite of high-dose folinic acid rescue, patients became comatose, for example by the fourth day after injection, with loss of brain stem function a few days later.

Seizures

Seizures associated with intravenous use of vinca alkaloids are very rare (60–62). Some cases may have been due to SIADH-associated hyponatremia. Other forms include tumor-related effects, nervous system infections, or cerebral hemorrhage, which often make direct causal relations between drug exposure and nervous system adverse effects very difficult.

- An 8-year-old girl with leukemia had tonic-clonic convulsions and life-threatening encephalopathy after intravenous vincristine. After the second dose (1.5 mg/m^2 in combination with prednisone) she developed seizures and bilateral translucencies in the CT scan. When vincristine was withdrawn in subsequent cycles, the symptoms disappeared (61).

Four of 350 patients without a history of seizures developed generalized seizures 5–6 days after the first, second, and eleventh doses of intravenous vincristine. However, seizures did not recur in later cycles. It is difficult to implicate vincristine as a cause of these adverse effects (62). Tonic-clonic seizures were only reported in four patients 7 days after vindesine administration. All patients had pre-existing cerebral deposits

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of melanoma, possibly mimicking nervous system adverse effects (8).

Sensory systems

Eyes

Reversible visual damage has been attributed to vincristine.

- An 18-year-old man with lymphocytic leukemia became completely blind for 6 months after a fifth 10-day cycle of therapy with vincristine 2 mg intravenously followed by cyclophosphamide 600 mg orally for 5 days with prednisolone 100 mg orally for 5 days (63).
- A 15-year-old girl developed bilateral optic atrophy after treatment with weekly vincristine, posterior craniectomy, and whole neuraxis radiation therapy (64). Withdrawal resulted in recovery of visual function.

In 50 patients, ptosis and diplopia related to vincristine occurred in 16 (64). The exact pathomechanism of this adverse effect has not been elucidated.

Studies on monkeys have demonstrated visual loss and optic atrophy with intravitreous injection of vincristine. Clinical reports of postvincristine optic atrophy are rare. Most are irreversible, progressing to permanent blindness. There is commonly coexistent peripheral or cranial neuropathy (65). It is possible that certain patients are predisposed to vincristine-induced optic atrophy. Optic neuropathy after a single small dose of vincristine has been reported in a single case; the dose of vincristine was small (1275 mg), and the latent period before onset of visual loss was brief (6–8 weeks) (66). Previously reported cases have had multiple injections of vincristine and the latent period was longer than 3 months.

Ears

Vinca alkaloids can have ototoxic effects, such as tinnitus and transient hearing loss. In addition, vestibular disorders can cause dizziness, nystagmus, and vertigo (67,68).

- A 29-year-old man with recurrent Hodgkin's disease was treated with the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) (69). He complained of tinnitus after each treatment cycle, with an onset of about 6 hours and a duration of 7–10 days. These symptoms interfered with reading, watching television, and general concentration. Based on audiography before and several hours after several cycles, there was evidence of mild sensorineural hearing loss in the high-decibel range 48 and 72 hours after drug administration. Six months after the completion of cancer chemotherapy, there was still some mild high-frequency sensorineural hearing loss in the left ear.

The authors concluded that vinblastine may have been responsible, because the other agents have not yet been associated with ototoxicity and because vincristine can cause ototoxicity too. The mechanism of this adverse effect is unclear but it may involve vinca alkaloid-associated damage to the eighth cranial nerve. This means that care should be taken when vinca alkaloids are used together with platinum compounds, especially cisplatin.

Endocrine

A rare but well-known adverse effect of vinca alkaloids, including vinorelbine, is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (70–72). The diagnosis is usually based on clinical and laboratory findings. There are falls in plasma sodium (below 120 mmol/l), chloride (below 90 mmol/l), and osmolality (below 230 mosm/kg). Further features include lethargy, anorexia, nausea, listlessness, and rarely coma, particularly when serum sodium falls below 110 mmol/l. Treatment is based on withdrawal of the causative agent and the administration of 0.9% saline and potassium (for example 40 mmol/l) at an infusion rate of 200 ml/hour. Further treatment strategies include demeclocycline (for example 300 mg bd), which can be continued for the duration of further vinca alkaloid-containing cycles. In one case demeclocycline prevented SIADH during further courses of vinorelbine (72).

Asian patients have been proposed to be at higher risk of SIADH during treatment with vincristine. Between 1983 and 1999, 76 cases of hyponatremia and/or SIADH related to the use of vincristine were reported to the global adverse event database of Eli Lilly and Company. The average age of the patients was 36 years (range 2 weeks to 86 years) and 62% were male. Most of the patients had received vincristine for leukemia or lymphomas. Of the 76 reports, 39 included background information on race: 35 patients were Asian, three were Caucasian, and one was black. The authors concluded that there may be a correlation between race and vinca alkaloid-associated SIADH/hyponatremia; however, the reasons are still unclear (73).

Hematologic

The most frequent adverse effect of vinblastine, vindesine, and vinorelbine is hematological toxicity (1,2,5,7,8). Leukopenia, particularly neutropenia, occurs more often than thrombocytopenia or anemia. The nadir in the leukocyte count after vinblastine occurs 4–10 days after administration, with recovery within another 7–14 days. Blood counts should generally be measured weekly and before the administration of each dose, in order to avoid severe forms of myelosuppression, neutropenic fever, or infections (20).

Oral vinorelbine is also associated with neutropenia. In one small study in patients with breast cancer treated with 50–160 mg/week, the incidence of grade 3–4 neutropenia was 32% (14). The incidence of severe neutropenia is higher with vinorelbine than the other vinca alkaloids. However, mean recovery (about 9 days) appears to be somewhat shorter with vinorelbine than with compounds vinblastine and vindesine (average 14–21 days) (1,2).

Gastrointestinal

Constipation is common when vinca alkaloids cause an autonomic neuropathy. Laxatives such as lactulose or polyethylene glycol-containing solutions can prevent

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adynamic subileus during treatment courses containing vinca alkaloids (48,74).

In contrast to constipation, nausea and vomiting are neither frequent nor dose-limiting adverse effects of vinca alkaloids. The regular use of antiemetics, such as 5-HT_3 receptor antagonists in combination with dexamethasone, is not recommended. However, oral vinorelbine has been associated with more severe forms of nausea and vomiting, with a frequency that is higher than after intravenous administration; in these patients and in particular those with predisposing factors for nausea and vomiting, metoclopramide and 5-HT_3 receptor antagonists are justified (75).

Skin

Vinca alkaloids are potential vesicants (76–78) and accidental drug extravasation can cause severe soft tissue ulceration. The initial symptoms include marked pain, erythema, and local swelling for several hours up to a day; later effects include blisters and severe painful skin ulcers, several days and 3 weeks after extravasation respectively. The lesions usually heal very slowly and sometimes require surgical intervention. Because vinca alkaloid extravasation can have severe effects, the use of antidotes is highly recommended when extravasation is suspected. In addition, venous irritation can be worsened if the vinca alkaloid is infused over at least 20–30 minutes rather than 6–10 minutes.

Among several antidotes for the treatment of vinca alkaloid extravasation, hyaluronidase is the most effective (79). Seven patients with extravasation of vincristine, vinblastine, or vinorelbine received hyaluronidase 250 units diluted in 6 ml of 0.9% saline, through the indwelling needle or, when the needle had been already removed, as six subcutaneous injections around the extravasation site. None developed skin necrosis. Local mild skin warming in order to produce local vasodilatation may have an additional beneficial effect, but should be avoided when simultaneous extravasation of a vinca alkaloid and an anthracycline is suspected, because local warming can worsen the anthracycline-associated local reaction, whereas local cooling, which is generally beneficial in anthracycline-related extravasation alone, can worsen skin necrosis due to vinca alkaloids (76).

Hair

Vinca alkaloids are associated with a low incidence of alopecia. In about 10% of patients, there can be gradual thinning of hair, but very few patients develop total hair loss (1,5,7).

Reproductive system

Based on comparative studies of the relative gonadal toxicity of several antineoplastic agents in experimental models and humans, the vinca alkaloids vinblastine and vincristine have negligible potency for killing stem cells. Permanent recovery of sperm counts and preserved ovarian function, depending on the patient's age at the time of treatment and the total cumulative dose, can be expected after treatment with vinca alkaloids (80–82).

Body temperature

Nine of 31 Japanese children receiving maintenance vincristine chemotherapy for either leukemia or lymphoma developed a fever over 38°C (83). An allergic mechanism was proposed. Concurrent glucocorticoids as part of the regimen appeared to be protective. Younger children were at greater risk. Peak temperatures occurred within 24 hours of vincristine administration. The pyrexia lasted from 6 hours to 4 days and the condition was self-limiting.

Long-Term Effects

Drug tolerance

Resistance to vinca alkaloids can be mediated by glycoprotein B, a transmembrane pump that is part of the multidrug resistance (MDR) phenotype (5).

Mutagenicity

Vinca alkaloids are less mutagenic than other cytotoxic agents like the *N*-Lost derivatives or bleomycin. Positive or negative results in mutagenicity tests depend on the test system used. For instance, vinorelbine significantly increased the frequencies of micronuclei in binucleate lymphocytes (84). In Chinese hamster ovary cells vinorelbine arrested cells at the first metaphase and caused an increase in abnormal anaphases, containing chiefly lagging chromosomes and multipolar spindles (85). These results suggest that vinorelbine does not directly damage DNA, but acts on spindle microtubules, altering chromosome movement and causing aneuploidy. However, it has no mutagenic effects in the Ames test.

Tumorigenicity

In the International Agency for Research and Treatment of Cancer (IARC), the vinca alkaloids were classified in group 3, which means that they cannot yet be classified in group 1 (proven human carcinogens), 2A (probably carcinogenic), or 2B (possibly carcinogenic) (86,87).

Second-Generation Effects

Teratogenicity

There is evidence that vinca alkaloids are teratogenic. Vinblastine caused malformations after first trimester administration (88–90). However, since vinca alkaloids are often combined with other cytotoxic drugs, it is difficult to relate any teratogenic effect to the vinca alkaloid alone (88). In mice and rabbits, vinblastine was embryotoxic and fetotoxic (89). However, it is unclear whether vinca alkaloids can cross the placenta because of their high molecular weights (about 1000 g/mol).

- Two pregnant women with breast cancer received two or three courses of intravenous vinorelbine 20–30 mg/m^2 and fluorouracil 500–750 mg/m^2 at 24, 28,

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and 29 weeks of gestation; there were no adverse effects in the two newborns (90). A third patient also had epirubicin and cyclophosphamide and her infant, who had been exposed to the four-drug regimen, developed transient anemia at 21 days of age which resolved spontaneously. All three infants were developing normally at 2–3 years of age.

According to the FDA classification, the potential therapeutic benefits of vinca alkaloids have to be outweighed with the potential teratogenic risks (FDA classification D). All women of childbearing potential should be advised to avoid becoming pregnant while receiving cytotoxic cancer chemotherapy (80).

Drug Administration

Drug administration route

In seven patients (median age 7 years), limb and jaw muscle pain, starting at days 3–5 of an intravenous infusion of vincristine and requiring opiate analgesia, was the most pronounced adverse effect (68).

Guidance on the safe administration of intrathecal chemotherapy has been issued in the UK (91), following a case in which vincristine was fatally injected into the cerebrospinal fluid (92).

Drug–Drug Interactions

Asparaginase

Asparaginase and vincristine should not be used together on the same day, since simultaneous administration can cause increased vincristine toxicity. It has been suggested that this is due to a deleterious effect of asparaginase on hepatic function, reducing the metabolism of vincristine (5).

Carbamazepine

In a small pharmacokinetic study the clearance of vincristine was 65% greater than in patients who were not taking carbamazepine and the half-life and AUC of vincristine were reduced by 35 and 43% respectively (93).

Erythromycin

Toward the end of a phase I study of vinblastine plus oral ciclosporin to reverse multidrug resistance, three patients also received erythromycin to raise their ciclosporin concentrations; all developed severe toxicity consistent with a much higher dose of vinblastine than was actually given (94).

Itraconazole

The concomitant use of itraconazole with vincristine increased the incidence of neurotoxicity in children and adults with ALL (95,96).

- A 19-year-old woman developed severe abdominal pain and constipation 28 days after starting to take itraconazole as antifungal prophylaxis when receiving vincristine for ALL. She had hypertension, marked abdominal distension and tenderness, and absent bowel sounds. Withdrawal of itraconazole resulted in resolution of symptoms and vincristine was continued (96).
- A 72-year-old patient developed painful oral mucositis and constipation 3 days after being given vinorelbine and itraconazole (97). Further complications included neutropenia and hypoxia and he died.

Concomitant use of itraconazole 2.5 mg/kg/day and vincristine in five children receiving vincristine resulted in hypertension, paralytic ileus, and SIADH (95).

Phenytoin

In a small pharmacokinetic study, the clearance of vincristine was 65% greater than in patients who were not taking phenytoin and the half-life and AUC of vincristine were reduced by 35 and 43% respectively (93).

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Vincamine

General Information

Vincamine is an alkaloid extracted from the plant *Vinca minor*. Ethyl apovincaminate is a related synthetic ethyl ester of vincaminic acid. These drugs have spasmolytic effects similar to those of reserpine, but also have metabolic effects, including, in high doses, inhibition of phosphodiesterase. Although increased cerebral blood flow has been reported after the intravenous administration of vincamine, there have been no reliable studies of blood flow after oral medication. Improvement in scores on some psychometric tests have been obtained in some patients with cerebrovascular disease, but no clear-cut practical benefit has been demonstrated.

Organs and Systems

Cardiovascular

Commercial formulations obtained from the alkaloids in *Vinca minor* may not be free from adverse effects. Ventricular dysrhythmias have been observed, but only after intramuscular or intravenous administration, and they seem to reflect a direct effect on myocardial cells. Hypokalemia and a prolonged QT interval seem to be predisposing factors. Vincamine should therefore be avoided in patients with a prolonged QT interval (SEDA-2, 183) (SEDA-5, 206) (SEDA-5, 207) (SEDA-7, 228).

Psychological, psychiatric

Vincamine has minor psychoactive effects (1).

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Vinegar

General Information

Vinegar was used topically in a Turkish neonate with suspected sepsis (1). The child was treated with antibiotics and his grandmother decided in addition to rub his upper thorax, back, and arms with vinegar. As a result the child developed chemical burns on the treated areas. Fortunately he made a full recovery after the grandmother stopped the treatment.

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Viscaceae

See also Herbal medicines

General Information

The family of Viscaceae contains four genera of mistletoe:

1. *Arceuthobium* (dwarf mistletoe)
2. *Korthalsella* (korthal mistletoe)
3. *Phoradendron* (American mistletoe)
4. *Viscum* (mistletoe).

Phoradendron flavescens

In 14 cases of accidental exposure to *Phoradendron flavescens* (*Phoradendron serotinum*, American mistletoe) there were no symptoms, but there was one death from intentional ingestion of an unknown amount of an elixir brewed from the berries (1). In 92 patients aged 4 months to 42 years (median 2 years), 14 were symptomatic, 11 related to mistletoe exposure. All the symptomatic cases had onset of symptoms within 6 hours. The symptoms included gastrointestinal upsets ($n = 6$), mild drowsiness ($n = 2$), eye irritation ($n = 1$), ataxia ($n = 1$), and seizures ($n = 1$). Treatment included gastrointestinal decontamination in 54 patients, ocular irrigation in one, and an intravenous benzodiazepine in one; decontamination did not affect the outcome. The amount ingested ranged from one berry or leaf to more than 20 berries or five leaves. Eight of ten patients who had taken at least five berries were symptom-free. Of 11 patients who took only leaves (range 1–5 leaves), three had gastrointestinal upsets. There were no cardiovascular effects in any case.

Viscum album

The stems and leaves of *Viscum album* (all heal, bird lime, devil's fuge, golden bough, mistletoe) contain alkaloids, viscotoxins, and lectins. While the toxicity of

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the alkaloids remains to be assessed, the viscotoxins and lectins have been found to be very poisonous in animals when given parenterally. Mistletoe is a widely used alternative treatment for cancer, without convincing evidence of efficacy (2).

Adverse effects

Liver

Mistletoe is sometimes assumed to have hepatotoxic potential, based on a case report of hepatitis due to an herbal combination product claimed to have had mistletoe as one of its ingredients (3). However, the allegation that mistletoe was the probable cause of the illness has been rightly criticized, inter alia because the botanical material was not authenticated. The incriminated product also contained skullcap, which is hepatotoxic.

Immunologic

Parenteral administration of *V. album* can cause serious allergic reactions (4), and anaphylactic reactions have been described (5).

Tumorigenicity

- A 73-year-old man with a 5-year history of centrocytic non-Hodgkin's lymphoma presented with subcutaneous nodules in the abdominal wall at the sites where he had previously received subcutaneous injections of mistletoe (6). The nodules turned out to be infiltrations by the centrocytic lymphoma. The patient died 6 weeks later of bilateral pneumonia. The authors hypothesized that mistletoe has a growth-promoting action on lymphoma cells, mediated by high local concentrations of interleukin-6 liberated from the skin by mistletoe lectins.

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Vitamin A: Carotenoids

See also Vitamins *and* Vitamin A: Retinoids

General Information

The carotenoids are a class of hydrocarbons (carotenes) and their oxygenated derivatives (xanthophylls) that consist of eight isoprenoid units joined in such a manner that the arrangement of the units is reversed at the center of the molecule, so that the two central methyl groups are in a 1,6-positional relationship and the remaining nonterminal methyl groups are in a 1,5-positional relationship. Their nomenclature has been standardized by IUPAC [http://www.chem.qmul.ac.uk/iupac/carot/], and their formal names are all based on the term "carotene."

Vitamin A is a family of fat-soluble vitamins, of which retinol is the most active form. Beta-carotene is a provitamin carotenoid that is converted to retinol more efficiently than other provitamin carotenoids. Other provitamin carotenoids include alpha-carotene and (trivial names) b-cryptoxanthin, lycopene, lutein, and zeaxanthin; they are widely available in foods.

Canthaxanthin is an orange carotenoid that occurs naturally in fruits, vegetables, mushrooms, shellfish, algae, and other forms of marine life. It has been approved by the US Food and Drug Administration as a food coloring agent and has been promoted as a skin-tanning agent in oral formulations that supply larger amounts than would be normally consumed as a food additive. Unlike other carotenoids, canthaxanthin is not a precursor of vitamin A, and therefore does not carry the risk of hypervitaminosis A. Retinopathy, due to deposition of canthaxanthin, causes gold-yellow deposits around the macula. Canthaxanthin-associated aplastic anemia has been reported (1).

Vitamin A activity can be expressed either as international units IU (1 IU equaling 0.3 micrograms of all-*trans*-retinol or 0.6 micrograms of all-*trans*-beta-carotene) or, more correctly, in retinol equivalents (RE) where 1 RE equals 1 microgram of all-*trans*-retinol, 6 micrograms of all-*trans*-beta-carotene or 12 micrograms of other provitamin A carotenoids. Table 1 gives the activities of different forms of vitamin A in RE and IU.

The Average Requirement for vitamin A is 500 and 400 micrograms RE/day for adult men and women respectively, the Population Reference Intake 700 and 600 micrograms RE/day, and the Lowest Threshold Intake 300 and 250 micrograms RE/day. While a slightly higher Population Reference Intake is advised in pregnancy and lactation (700 and 950 micrograms RE/day respectively), concern about the possible teratogenic effect of vitamin A has led many European health authorities to advise pregnant women against taking vitamin A

Table 1 Relative activities of different forms of vitamin A

Vitamin A	Activity in RE	Activity in IU
Retinol (1 mg)	1000	3330
Retinyl acetate (1 mg)	870	2900
Retinyl palmitate (1 mg)	550	1830

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supplements (2). However, much higher doses (over 60 000 micrograms RE/day or 200 000 IU/day) are routinely distributed at half-yearly intervals to children in populations deemed to be suffering from vitamin A deficiency, mainly in developing countries. Toxicity is occasionally observed during these massive-dose prophylactic programs (3), and their safety has sometimes been called into question (4,5). One study has suggested that high-dose vitamin A supplements cause modest adverse effects in children recovering from pneumonia (6).

Chronic toxic reactions are generally more frequent than acute toxic reactions, which are uncommon at dosages below 30 000 micrograms RE/day (7). Supplements that contain 8000 micrograms RE (25 000 IU) or more of vitamin A per capsule are available as over-the-counter formulations in many countries (8). The "Nutrient and Energy Intakes for the European Community" (9) advises against single doses over 120 000 micrograms RE, and regular doses over 9000 micrograms RE/day in men and 7500 micrograms RE/day in women.

The recommended daily allowance of vitamin A for children up to 12 years of age is 1500–4500 IU. Toxic reactions occur when retinol-binding proteins in the plasma are saturated with vitamin A. Excess vitamin A is bound to plasma lipoproteins, and in this form it causes toxic effects when it comes into contact with cells (10). Acute vitamin A intoxication can occur after ingestion of 500 000 IU in adults and proportionately less in children. Chronic intoxication is more common, and in children it can occur even with doses as small as 1500 IU/kg/day. The problem is under-recognized in children, and cases often present as diagnostic dilemmas.

The reference range for serum concentrations of vitamin A is 300–1500 IU/l (0.5–2.8 μmol/l) (11).

General adverse effects

Acute intoxication has been observed after ingestion of vitamin A-rich liver from the polar bear, halibut, or shark, or after the use of fish oil supplements used to lower plasma lipids. In adults, toxic doses have been in the range of one or more million units of vitamin A, but in children as low as 10 000 micrograms RE, or even in a few children under 650 micrograms RE/day (12). Symptoms occur at 6–24 hours after ingestion and include acute drowsiness, irritability, vertigo, headache, delirium and convulsions, intolerance of food, and diarrhea (SEDA-8, 344).

Long-term administration of 3000 micrograms RE/day (10 000 IU/day) can cause chronic hypervitaminosis A, and at greatest risk in this regard are those with impaired liver function (12,13). The risk further increases with low body weight, protein malnutrition, renal disease, hyperlipoproteinemia, high alcohol consumption, and ascorbic acid deficiency (7). Because of the multisystem manifestations of hypervitaminosis A, the symptoms are often misjudged and the diagnosis delayed. The main symptoms of chronic intoxication include malaise, intracranial hypertension, chronic headache, vertigo, nystagmus, photophobia, hyperkeratosis, gastrointestinal complaints, changes in the skin and mucous membranes, tenderness and pain in the bone and joints, and fever.

Chronic intoxication with vitamin A has been reported to cause variously hypercalcemia, hyperglycaemia, increased alkaline phosphatase, hypoproteinemia, hypoprothrombinemia, increased sulfobromphthalein retention, raised serum transaminases, low serum ascorbic acid, reduced protein content of the cerebrospinal fluid, raised urinary hydroxyproline, and hypercalciuria (SED-8, 800) (14). It is not always clear, however, whether these deviations are a cause or an effect of hypervitaminosis A.

In some patients, adverse effects, especially disturbed liver function, become evident only when irreversible damage, for example liver cirrhosis or fibrosis with portal hypertension, is already present. It seems that the total cumulative intake of vitamin A, rather than the level of dosage, may be the critical factor for damage to the liver (15); this might hold true also for other adverse effects. A review found dosage ranges in reported cases of adverse events over the last 50 years to range from 650 to 20 000 micrograms RE/kg/day, and duration of administration to range from 41 to 3600 days, with an exponential relation between dose and duration with regard to symptoms of hypervitaminosis A (7). To avoid toxic reactions, the authors recommended, as a rule of thumb, that the daily dose (NB: in IU/kg) multiplied by the duration (in days) should not exceed one million.

Allergic reactions do not occur, but increased serum IgM concentrations were reported in patients with severe liver disease after prolonged administration of vitamin A (15).

Tumor-inducing effects of vitamin A have so far been suggested only with regard to prostatic cancer, especially in those 70 years of age and over (SEDA-13, 346).

Organs and Systems

Nervous system

Acute poisoning with vitamin A produces symptoms such as drowsiness, sluggishness, irritability, an irresistible desire to sleep, severe headache, and papilledema. In some cases papilledema is the only symptom (SEDA-11, 333) (16,17). In young children, raised intracranial pressure with bulging of the fontanelle, papilledema, and diplopia have been observed (SED-8, 799, 801) (SEDA-15, 411) (18).

In 50% of chronic vitamin A intoxications intracranial hypertension occurs, sometimes together with skin and hair changes, musculoskeletal pain, and fatigue (19). Benign intracranial hypertension (pseudotumor cerebri), vertigo, and papilledema have appeared after the intake of 3500–7000 micrograms RE/day of vitamin A for 2 years; in young children even a few months of treatment may precipitate these conditions (20) and symptoms can occur at low doses (even in a few children as low as 650 micrograms RE/kg/day) (12). Nystagmus, diplopia, photophobia, palsy of the ocular muscles, retinal hemorrhage, and protrusio bulbi (SED-8, 801) (21) have all been reported with vitamin A, and are an effect of raised intracranial pressure.

- A 15-year-old girl developed headache, vertigo, nausea, and epistaxis, diplopia, and reduced visual

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acuity (22). She had taken Arovit corresponding to vitamin A 200 000 IU/day for 6 months for acne. Ophthalmoscopy showed bilateral papilledema and minor bilateral abducens paresis. She had hypercalcemia (3.24 mmol/l) and a reduced parathyroid hormone concentration, a mild anemia (10.5 g/dl), and thrombocytopenia (112×10^9/l). Lumbar puncture showed a pressure of 62 cm H_2O with otherwise normal liquor. Her serum vitamin A concentration was 1.5 micrograms/ml (reference range 0.3–0.7 micrograms/ml).

Pseudotumor cerebri due to hypervitaminosis A is a serious complication, which can cause permanent visual impairment. Patients who take retinoids require proper surveillance. Raised serum concentrations of retinoids can persist for weeks after withdrawal.

Hypervitaminosis A can be a frequently overlooked cause of chronic headache (23). The precise cause of this, and of increased intracranial pressure in hypervitaminosis A, is controversial and unclear (24).

Psychological, psychiatric

Daily doses of 1 000 000 μg RE of vitamin A can cause acute symptomatic psychosis, with striking disturbances in the electroencephalogram and pathological changes in the cerebrospinal fluid (25). After withdrawal of vitamin A and administration of low doses of neuroleptic drugs the psychotic symptoms disappeared within a week.

Neuropsychiatric changes were reported to be the earliest dose-limiting symptomatic toxicity in patients with cancer taking high doses of retinol (26).

Metabolism

People with severe hypertriglyceridemia associated with Type V hyperlipoproteinemia may be at increased risk of hypervitaminosis A, even with moderate degrees of vitamin A supplementation (27). Long-term vitamin A administration is associated with an increase in serum cholesterol and serum triglyceride concentrations (28) and consequently might be linked with atherosclerosis (SEDA-8, 345) (29,30).

Mineral balance

Vitamin A toxicity in an adult woman resulted in hypercalcemia with renal insufficiency (31).

- An 86-year-old woman developed anorexia, thirst, and nocturia. During the previous 7 months her weight had fallen by 11 kg. She was taking domperidone and 1–6 vitamin tablets daily, each of which contained retinol palmitate 600 IU and colecalciferol 200 IU. She had hypercalcemia (serum calcium 3.34 mmol/l) and renal insufficiency (serum creatinine 333 μmol/l). Other causes of hypercalcemia were excluded.

In chronic vitamin A ingestion, risk factors for vitamin A toxicity are age, body weight, and renal insufficiency. The hypercalcemia caused by chronic vitamin A ingestion is explained by upregulation of osteoclasts by retinol metabolites.

Fluid balance

Edema and ascites are sometimes seen in chronic intoxication (SEDA-8, 799) (32,33).

Hematologic

High doses of vitamin A reduce the stability of the lipoprotein boundary layer of the erythrocytes, which can lead to hemolysis and anemia (34). Neutropenia, leukocytosis, thrombocytopenia, aplastic anemia, and increased sedimentation rate have also been reported after high doses of vitamin A (35–38).

Vitamin A toxicity appears to occur only when the amount of vitamin A exceeds the binding capability of the retinol binding protein. Hypervitaminosis A can cause severe anemia and thrombocytopenia, resulting from retinol-dependent bone marrow cell growth inhibition (39).

- A 3-month-old boy who was given Arovit (an aqueous solution of vitamin A palmitate, Roche, Italy), corresponding to vitamin A 62 000 IU/day for 80 days, developed signs of retinol intoxication (severe normochromic normocytic anemia, hemoglobin 5.9 g/dl, leukocyte count 6.2×10^9/l with lymphocytes 74%, neutrophils 17%, eosinophils 3%, and monocytes 6%, platelet count 20×10^9/l). The blood film showed anisopoikilocytosis. He had increased concentrations of unbound retinol, with high concentrations of retinyl esters and a raised retinol:retinol binding protein ratio. Vitamin A was withdrawn and 15 days later his hemoglobin rose to 7.5 g/dl and the platelet count to 105×10^9/l. The reticulocyte count increased from 8 to 300×10^9/l. The bone marrow showed normal populations of erythroid and myeloid cells and megakaryocytes. The retinyl esters fell by about 80% after 3 months.

These are the first findings to suggest that infant hypervitaminosis A can cause severe anemia and thrombocytopenia, probably due to the direct effect of vitamin A on the growth of all bone marrow cells. Investigation of the effect of retinol on the growth of the pluripotent hemopoietic cell line K-562 and on bone marrow mesenchymal stem cells showed strong inhibition of cell proliferation at concentrations similar to those found in vivo. Subsequent biochemical analysis of the cell cycle suggested that the effect was mediated by upregulation of the cyclin-dependent kinase-inhibitors $p21^{Cip1}$ and $p27^{Kip1}$.

Mouth and teeth

Dryness and scaling of the lips, gingivitis, and bleeding from the gums are common symptoms of acute vitamin A intoxication (32,35).

Gastrointestinal

Nausea, vomiting, and anorexia are common symptoms of acute vitamin A intoxication (34).

Liver

Enlargement of the liver, spleen, and lymph nodes in adults taking vitamin A were first reported many years ago (34–36).

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The hepatotoxic effects of vitamin A have been reported after consumption of doses of about 100 000 IU/day for periods ranging from weeks to months, as well as after daily supplementation with 25 000 IU for a couple of years, accompanied by an increase in plasma vitamin A concentration to 10 times normal in users of health foods. The smallest daily supplement of vitamin A reported to be associated with liver cirrhosis is 25 000 IU taken for 6 years (15).

Liver biopsies have been performed in some patients with chronic vitamin A intoxication. Perisinusoidal fibrosis and massive accumulation of lipid-storing cells were found. Impairment of blood flow by perisinusoidal fibrosis probably resulted in secondary alterations in hepatocytes, including cellular atrophy and formation of cytoplasmic bullae. Histological examination also showed central vein sclerosis and focal congestion associated with perisinusoidal storage. The vitamin A concentration in the liver was increased (40–42).

For the diagnosis of hypervitaminosis A, plasma concentrations and retinol-binding protein may be misleading. Cases have been reported of hepatic fibrosis, secondary to chronic ingestion of massive doses of vitamin A, where plasma concentrations of vitamin A and retinol-binding protein at the time of diagnosis were within the reference range (43).

Long-term observation of 41 patients with varying forms of liver disease, all caused by prolonged vitamin A consumption, has given further insight into the range of histological lesions and the prognosis of liver disease related to hypervitaminosis A (15). Clinical examination showed hepatomegaly in 18 of the patients, splenomegaly in 13, signs of chronic hepatic disease in 12, ascites in 9, and icterus in 8. Repeat liver biopsies in three patients 3–6 years after diagnosis showed progression from steatosis or fibrosis to fully developed micronodular cirrhosis in all cases, showing that the liver damage can be irreversible. Nine patients died during follow-up, six of terminal liver failure. However, plasma retinol concentrations were above the reference range in only about 40%.

Liver damage due to vitamin A is not always irreversible; one patient, after prolonged intake of excessive amounts of vitamin A for treatment of psoriasis (90 000 micrograms RE/day), had not only reversible chronic intoxication, but reversible portal hypertension and deranged liver function tests without any histological signs of cirrhosis (44). In a similar case, portal hypertension disappeared after 6 months on a low vitamin A diet. The fact that there was no reduction in Ito cells either in size or number suggests that lipid venous obstruction is unlikely to be the only mechanism responsible for portal hypertension in vitamin A-induced liver disease (45).

Even moderate doses of vitamin A, when taken over a prolonged period of time, can cause significant hepatocellular injury, as seen in three family members with symptoms and biochemical evidence of hepatitis, who had taken 7000–15 000 micrograms/day RE (20 000–45 000 IU/day) for 7–10 years (46). A similar case involved a 45-year-old woman who had taken an over-the-counter supplement over 6 years, and developed severe and fatal liver damage (47).

Clinical presentations, changes in liver function tests, and liver morphology have previously been examined in 41 consecutive patients with vitamin A hepatotoxicity (15). The cause of liver disease was suspected at initial interview in only 13 instances, and there was histological evidence of fat-storage hyperplasia with fluorescent vacuoles in the other cases. Cirrhosis was found in 17 cases, mild chronic hepatitis in 10, non-cirrhotic portal hypertension in 5, and "increased storage" alone in 9. During a mean follow-up period of 4.6 years, six patients died of causes related to the liver disease. Precise appraisal of drug consumption was obtained in 29 cases. Among them the total cumulative intake was the highest in patients with cirrhosis (423 MIU) and significantly lower in those with non-cirrhotic liver disease (89 MIU). The smallest continuous daily consumption leading to cirrhosis was 25 000 IU for 6 years, whereas higher doses (greater than or equal to 100 000 IU/day) taken for 2.5 years resulted in similar histological changes.

Liver fibrosis induced by beta-carotene therapy for pigmentary retinopathy has been reported (48).

- A 66-year-old woman with a pigmentary retinopathy that had been treated for 30 years with antocyanosides combined with beta-carotene (total dose 165 g) developed anicteric cholestasis. Liver biopsy showed pronounced portal fibrosis with normal bile ducts and no evidence of portal inflammation. The usual causes of chronic hepatic diseases were excluded. The serum concentration of vitamin A was 0.43 (reference range: 0.5–0.8) mg/ml. After withdrawal of beta-carotene and administration of ursodeoxycholic acid for 6 months the cholestasis resolved.

Another feature of vitamin A hepatotoxicity, namely respiratory symptoms caused by hepatic hydrothorax, associated with excessive vitamin A consumption has been reported (49).

- A 52-year-old woman, who had taken multivitamin supplements daily for 17 years and vitamin A whenever she had a cold, became progressively breathless, with 18 kg weight loss, increasing abdominal girth, increasing fatigue, leg weakness and pain, worsening chronic diarrhea, and intermittent nose bleeds. Her total vitamin A intake over 17 years had been at least 63 MIU (average 10 273 IU/day) and in the previous year she had taken at least 98 MIU (270 000 IU/day). When she noted pruritus, epistaxis, hair loss, and nail degeneration, she reduced her vitamin A intake to 66 000–150 000 IU/day. She was thin with alopecia, dry skin, and dystrophic nails, and was in mild respiratory distress with reduced breath sounds throughout the right lung and mild expiratory wheezes at the apices. There was no hepatomegaly or splenomegaly, but her liver was tender. Her serum vitamin A concentration was within the reference range. She had marked ascites, a pleural effusion, and partial collapse of the right lung. Liver biopsy showed changes consistent with vitamin A hepatotoxicity, namely prominent aggregates of hypertrophied perisinusoidal hepatic stellate cells, focal pericellular fibrosis, and mild perivenular fibrosis.

Urinary tract

In chronic intoxication, polyuria, increased frequency of micturition, urinary incontinence, enuresis, and acute

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renal insufficiency due to tubular necrosis can occur (SED-11, 800).

Patients with renal dysfunction are known to have raised circulating vitamin A concentrations. In chronic dialysis patients, the concentration can rise steadily. The significantly increased osmotic fragility of erythrocytes observed in hemodialysed patients also seems to be related to high vitamin A concentrations. However, the similarity between uremic symptoms and those of vitamin A excess may explain why hypervitaminosis A in uremic patients is rarely reported as being associated with clinical toxicity (SEDA-12, 327).

Skin

In acute intoxication, peeling of the entire skin can occur as a delayed symptom (50). Among the early and most commonly reported symptoms of chronic vitamin A intoxication are erythema, pruritus, hyperkeratosis, and dryness, hemorrhages, and fissures of the lips. A yellow to yellow-orange discoloration of the skin, reduced tolerance to sunlight, changes in pigmentation, hair loss, and brittle nails have been observed (34,36,51–53).

Musculoskeletal

Excessive doses of vitamin A lead to accelerated resorption of trabecular and cortical bone because of increased osteoclastic activity. A raised alkaline phosphatase, increased urinary hydroxyproline concentrations, and hypercalciuria correlate with these findings (54). One study suggested that high dietary intake of retinol might be associated with osteoporosis (55).

Pain in the bones and joints is a common symptom in patients taking vitamin A. Bone tenderness often occurs without other bone symptoms, but possible complications include elevation of the periosteum, hyperostosis, and in children premature closure of the epiphyses of the long bones, causing growth arrest (54,56).

- There were skeletal deformities involving the lower limbs and the spine in a 15-month-old girl who had received a total dose of 3.5 million micrograms RE (10.5 million IU) of vitamin A during the previous few months (57).
- Skeletal signs were seen in a nursing infant who was given 35 drops of a vitamin formulation five times a day during the first month of life, corresponding to vitamin A 8000 micrograms RE/day, plus vitamin D 5000 IU/day, vitamin E 15 mg/day, and vitamin C 250 mg/day. Other symptoms included hydrocephalus, cutaneous effects, and hepatic signs (58).
- A fatal case of hypervitaminosis A involved a premature neonate who died after having ingested 30 000 micrograms RE/day (90 000 IU/day), that is 60 times the recommended intake of vitamin A, for 11 days. On autopsy the skeleton showed marked alterations of endochondral bone formation. There was also evidence of accelerated resorption of bone, hypercalcemia, and metastatic calcification of the skin, soft tissues, and organs (59).

These three cases illustrate a common misunderstanding with regard to vitamins found among medical and nonmedical people alike: vitamins are believed to be innocuous substances, and since a little of them is good for you, much must be even better. Table 2 puts this misconception into perspective (60).

Table 2 Toxic doses of vitamin A

Exposure	Population	Country or region	Retinol equivalents (micrograms)
Toxic concentrations	Adults	Nordic	7500
	Adults	Australia	20 000
	Pregnant woman	Australia	10 000
	Pregnant woman	USA	5000–10 000
Chronic intoxication[a]	Children		758/kg
	Adults		15 000–30 000
Acute intoxication[b]	Children		22 500–30 000
	Adults		300 000–600 000

[a] Defined as repeated and prolonged intake of high doses
[b] Defined as intake of single (or multiple) very high doses

Reproductive system

The effects of all-*trans*-retinoic acid on the male reproductive system include gynecomastia, discomfort, potency disorders, reduced fertility, and ejaculatory failure (61). The incidence is reported to be very high, but exact figures do not seem to be available.

Immunologic

Large doses of vitamin A in children in poor socioeconomic conditions have often for logistic reasons been combined with other health-care interventions, such as immunization. A randomized, case-control study of 336 infants receiving either 33 000 micrograms RE/day (100 000 IU) of vitamin A or placebo simultaneously with measles vaccine showed a lower seroconversion to measles in the vitamin A group (62).

Long-Term Effects

Tumorigenicity

Negative outcomes in several supplementation trials of beta-carotene, especially the results of the Finnish Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study (63) (SEDA-20, 363), have again revived discussion about the carcinogenic potential of beta-carotene. The ATBC trial showed that there was a statistically significant increase in the incidence of lung cancer in heavy smokers who took beta-carotene.

Problems concerning the interactions of cigarette smoking, cancer, and carotenoids have been reviewed (64).

Over several decades, evidence has accumulated that a diet rich in fruit and vegetables is associated with a lower risk of cardiovascular disease and various forms of cancer, principally cancer of the lung and stomach, but also esophageal, oral, breast, and prostate cancer (65,66). It is possible that this effect is in part due to their beta-carotene content.

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Beta-carotene and other micronutrients have been claimed to counteract oxidative processes that participate in various stages of carcinogenesis, and increased consumption of fruit and vegetables rich in carotenoids lowered urinary indices of oxidized lipids and DNA in healthy subjects (67). Although beta-carotene and other carotenoids are excellent in vitro quenchers of singulett oxygen and beta-carotene, and may also protect lipids from radical-initiated peroxidation under certain conditions, evidence for antioxidant properties of beta-carotene in vivo is much less compelling (68). Assessment of the antioxidant benefit of beta-carotene is especially complicated by the fact that carcinogenesis is a very complex multistage process, in which oxidative pathways play variable and incompletely understood roles. While a few early supplementation trials suggested a beneficial role of beta-carotene (66), many other studies did not show such an effect. The proposed beneficial properties of carotenoids appear to be consistent with findings that cigarette smokers generally have subnormal serum concentrations of various carotenoids and other micronutrients, such as vitamin C, supposed to be caused by the increased oxidative stress associated with smoking and its attendant activation of the inflammatory and immune systems. On the other hand, the low concentrations in smokers could also result from lower intake of these micronutrients. Lower concentrations of carotenoids and other micronutrients are also observed in passive smokers (69,70).

The constituents of cigarette smoke can degrade beta-carotene (71,72), but the conclusion that smoking causes increased carotenoid metabolism demands the demonstration of raised carotenoid oxidation products. Moreover, the consistent observation of subnormal carotenoid concentrations but unchanged alpha-tocopherol concentrations (70) suggests that factors other than oxidative stress contribute to the relative carotenoid deficiency.

The assumption that remedying the carotenoid deficit would minimize the risks of cancer and heart disease associated with passive smoking has not been supported by several large randomized supplemention trials. In two major trials there was an increased incidence of cancer with beta-carotene supplementation in both smokers and asbestos workers. Of course, both high-risk groups might already have been in the early stages of cancer development at the start of the studies (63,64).

These surprising findings have raised an interesting apparent paradox: how can supplementation with beta-carotene, a presumed antioxidant and possible chemoprotective agent, enhance cancer formation, even though this is thought to involve oxidative processes? In some experimental systems carotenoids have prooxidant properties at high concentrations, but these are not reached in vivo (69,70). Another mechanism is an increase or alteration in carotenoid metabolism in high-risk groups, resulting in the formation of metabolites or oxidation products that could be procarcinogenic (for instance by interfering with retinoid signaling pathways, by promoting DNA damage, or by inducing cytochrome P450 enzymes that might promote carcinogen activation) (66,73). Such induction of cytochrome P450 enzymes might also enhance the catabolism of retinoic acid, which plays an important role in lung epithelial proliferation and differentiation. Down-regulation of the retinoic acid receptor, RARb, by beta-carotene supplementation has been shown in recent studies in ferrets (73). RARb may act as a tumor suppressor gene. Moreover, lung expression of the proto-oncogenes c-jun and c-fos was increased in animals exposed to cigarette smoke and also receiving beta-carotene supplements (73).

In general, the negative outcomes of several supplementation trials and the lack of proof that carotenoids form the primary beneficial component of fruit and vegetables should serve as a warning against unregulated supplementation with these individual micronutrients, especially in view of the potential carcinogenic effect of carotenoids.

The carcinogenic effect of beta-carotene has recently been found to be reduced by vitamin E (74), suggesting that, rather than individual micronutrient supplementation, combinations of various such substances might be more advantageous.

Second-Generation Effects

Pregnancy

The benefits and safety of maternal and infant vitamin A supplementation administered with each of the three diphtheria-tetanus-pertussis (DPT) and poliomyelitis immunizations and with a fourth dose of measles immunization have been assessed in a randomized, double-blind, placebo-controlled study in 9424 mother–infant pairs from Ghana, India, and Peru (75). Vitamin A 200 000 IU was given to 4716 mothers and 25 000 IU to their infants with each of the first three doses of DPT/poliomyelitis immunization at 6, 10, and 14 weeks. Placebo was given to 4708 mothers and their infants. At 9 months, with measles immunization infants in the vitamin A group were given a further dose of 25 000 IU and those in the placebo group received 100 000 IU. At 6 months there was a small reduction in vitamin A deficiency in the vitamin A group compared with controls; this effect was no longer apparent at 9 months. There were no significant differences in mortality throughout the study. Adverse effects were a bulging fontanelle (in under 1% of the infants) and vomiting. Among the infants without a bulging fontanelle before the start of the study, more of the vitamin A recipients than placebo recipients had a bulging fontanelle within 48 hours of the dose at 6, 10, and 14 weeks. After the fourth dose at 9 months, a bulging fontanelle was more common among the controls than among the infants given vitamin A. However, after each dose under 1% of the infants in either group had a bulging fontanelle. Of the 62 infants in the vitamin A group who had a bulging fontanelle reported at 24 hours after a dose, the bulging had resolved within 48 hours in 445 (73%). Among the controls, in whom almost all the instances of bulging were reported with the 100 000 IU dose, 25 of 42 had resolution of bulging within 48 hours. Under 3% of mothers in each group reported a bulging fontanelle after each dose. Vomiting occurred only within 48 hours after administration of the fourth dose in 167

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(4.9%) infants in the vitamin A group versus 236 (6.5%) in the control group. There were no significant differences in convulsions or raised temperature at any dose.

Teratogenicity

Although the retinoids are markedly teratogenic, vitamin A is less so. In animals vitamin A excess can be teratogenic, as can vitamin A deficiency. In humans several cases of teratogenicity associated with vitamin A have been observed (76–78), and high incidences of spontaneous abortions and birth defects have been observed in women who have taken therapeutic doses of isotretinoin (13-*cis*-retinoic acid) during the first trimester of pregnancy. Recommendations about dosages of vitamin A in pregnant women have been issued by several institutions (2), including the Teratology Society (8) and the American College of Obstetricians and Gynecologists (79). The Health Protection Branch of Health and Welfare Canada accepted the recommendation that the use of retinoic acid for acne be regarded as contraindicated in women during pregnancy and in those of childbearing age (80).

A study in Hungary of 1203 births to women who had taken a supplement containing 2000 micrograms RE (6000 IU)/day, compared with 1510 who had taken placebo, did not show any evidence of teratogenic effect (81). The lower limit of supplementation recommended varied between 1600 and 3300 micrograms RE (5000 and 10 000 IU) of vitamin A per day (SEDA-14, 330).

However, vitamin A may be harmful at even lower doses than had previously been appreciated, the prevalence of cranial neural crest tissue defects being 3.5 times higher when dietary and supplemental consumption of preformed vitamin A, taken together, exceeded 5000 micrograms RE (15 000 IU) than when it was 1600 (5000 IU) or less (82). For supplements considered alone, the prevalence of such defects was 4.8 times higher in the group consuming over 3300 micrograms RE (10 000 IU) than in the group consuming under 1600 micrograms RE (5000 IU). The risk seemed to start rising when consumption passed a threshold of about 3300 micrograms (10 000 IU).

The minimum human teratogenic daily dose of vitamin A is estimated to be 25 000–50 000 IU, and one report has suggested that it may be as little as 10 000 IU (82). The National Research Council's Committee on Dietary Allowance advocates a recommended daily allowance (RDA) of 800 retinol equivalents/day for non-pregnant women of childbearing age and pregnant women. The RDA is equivalent to 2700 IU of vitamin A obtained from a supplement as retinol or 4800 micrograms of beta-carotene. The committee of the American College of Obstetricians and Gynecologists recommends supplementation with 5000 IU/day as the maximum intake before and during pregnancy. This is well below the probable minimum human teratogenic dose. Prenatal multivitamin formulations in common use contain 5000 IU or less vitamin A, but vitamin tablets containing 25 000 IU or more of vitamin A are available as over-the-counter formulations. Pregnant women or those planning to become pregnant should be cautioned about the potential teratogenicity of high doses of vitamin A supplements. Warnings on labels were recommended as early as 1987 (8).

A summary of some cases of birth defects associated with high maternal intake of vitamin A is given in Table 3 (12).

To get further information about the teratogenicity of high doses of vitamin A, the European Network of the Teratology Information Services (ENTIS) prospectively evaluated data from 423 pregnancies exposed during the first 9 weeks of gestation to 10 000 IU/day or more (83). The presence of major structural malformations, excluding chromosomal and genetic diseases, was evaluated in 311 infants exposed to a median daily dose of vitamin A of 50 000 (range 10 000–300 000) IU/day. Three infants had a major malformation: pulmonary stenosis, stenotic anus with fistula, and bilateral inguinal hernia. There were no congenital malformations among 120 infants exposed to more than 50 000 IU/day. When the birth prevalence rate of major malformations in the study group was compared with two internal control groups of infants exposed to "high" doses of vitamin A later in pregnancy, and non-teratogenic doses, the respective rate ratios were 0.28 (CI = 0.06, 1.23) and 0.50

Table 3 Some cases of birth defects associated with high material intake of vitamin A

Maternal intake	Duration	Symptoms	Other conditions
Reports of individual cases			
~500 000 IU	Single dose, 2nd month	Preauricular appendices, epibulbar dermatoid (eye malfunctions similar to Goldenhar's syndrome)	Dose caused acute toxicity in the pregnant woman
150 000 IU	Periconceptual 2 to +3 months	Facial dysmorphism, pterygium colli, distended abdomen, absence of external genitalia and of anal and urethral openings, polycystic kidneys, dysmorphism of lumbar spine	Fetus aborted at 20 week because of spinal abnormality and polycystic kidney
25 000 IU	0–13 weeks	Unilateral ureteral duplication with one ureter ending in the vagina, hydronephrosis, hydroureters	
50 000 IU	14th week to term		
Reports of multiple cases			
18 000–100 000 IU	Before and throughout pregnancy	Abnormalities of the head, face, ears, eyes, mouth, lips, jaws, heart, and urinary system; other defects	Cases reported by physicians to the FDA; cases reported to the State Birth Defects Registry

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(CI = 0.14, 1.76). There was no evidence for an increased risk of major malformations, associated with high vitamin A doses during organogenesis.

The incidence of the acute adverse effects of an oral dose of vitamin A 400 000 IU given to a newly delivered mother and a oral dose of 50 000 IU given at the same time to her baby has been assessed in a randomized, double-blind, placebo-controlled study, with follow-up 1 or 2 days after dosing in 839 mothers and babies, of whom 788 were assessed (84). The incidence of reported adverse effects was low. Only two mothers in each group spontaneously reported bulging fontanelles in their babies. One of these babies (in the placebo group) was reported to have been vomiting. The rates of bulging fontanelles were 1.5% and 1.0% in the treatment and control groups respectively (OR 1.48; CI = 0.35, 7.19) Only one baby (in the vitamin A group) of the 11 who had bulging fontanelles was symptomatic (with vomiting, possibly due to raised intracranial pressure). Maternal symptoms did not differ between the groups. Other reported symptoms in the vitamin A group ($n = 398$) compared with the controls ($n = 390$) were vomiting (6 versus 4.8%) and irritability (7.5 versus 5.4%). From these results it can be concluded that these large doses of vitamin A are well tolerated by newly delivered mothers and babies.

Susceptibility Factors

Age

Young children seem to be particularly at risk of vitamin A toxicity. Symptoms of chronic intoxication are seen with intakes of 800–16 000 micrograms/kg RE (2500–50 000 IU/kg) (21). Children with restricted protein intake may have reduced tolerance to vitamin A.

The National Prophylaxis Program for Prevention of Blindness due to Vitamin A Deficiency has been implemented in India since the 1970s and covers all children aged 9 months to 3 years (85). Children aged 9–12 months received a single dose of 100 000 IU and those aged 1–3 years received 200 000 IU every 6 months. According to the Assam State Government, 700 children of 3.2 million who were given vitamin A became ill and more than 15 children died. Whether all these cases were a direct consequence of high-dose vitamin A is being investigated. One of the possible reasons is overdose of vitamin A, because of use of a new 5 ml measuring cup, which was used instead of the traditional 2 ml spoon.

Hepatic disease

At special risk of vitamin A toxicity are those whose liver function is compromised by drugs, viral hepatitis, or protein-energy malnutrition (12). Elderly people may also be at increased risk for similar reasons but also from different causes. In addition to protein deficiency, alcohol intake and co-existing liver and renal disease may be present (86).

In alcoholics vitamin A supplementation, which might be a useful therapeutic measure, is complicated by the hepatotoxicity of large doses of the vitamin and the fact that chronic alcohol consumption results in an enhanced susceptibility to this effect (87).

Drug Administration

Drug formulations

The effects of variations in pharmaceutical formulation on plasma concentrations of vitamin A have only been partly documented. Vitamin A in aqueous dispersion results in higher plasma concentrations than in oily formulations (88).

Drug administration route

Vitamin A added to infusions can be absorbed by the plastic containers often used (89).

Drug overdose

Two children with vitamin A toxicity have been reported (90).

- A 2-year-old girl developed anorexia, lethargy, and bilateral leg pain and refused to walk. She had been unwell for the previous 3 weeks. She was lethargic and irritable and had tenderness over both tibial surfaces and an erythematous rash over her back and both elbows. She had a raised calcium concentration (3.05 mmol/l), a serum phosphate concentration in the reference range, and a raised serum vitamin A concentration (3.9 μmol/l; reference range 1.3–2.9 μmol/l). A skull X-ray showed widening of the coronal suture, and a leg X-ray showed abnormal metaphyseal densities at the knees and ankles. Radionuclide bone scans showed increased uptake in both anterior tibiae, anteriorly in multiple ribs close to the costochondral junctions, in the distal right ulnar shaft, and in the distal left femoral shaft. Her parents had given her a vitamin supplement containing 9000 IU/ml vitamin A 3 ml/day for several months. On withdrawal of the vitamin supplement her symptoms resolved over 2 weeks.
- A 4-year old boy presented with a 4-day history of bilateral leg pain and refusal to walk. He had tenderness over both tibial surfaces, generalized skin exfoliation, and reduced visual acuity in both eyes. Symmetrical bone scan changes (increased uptake throughout each ulna and tibia and foci in the 10th and 11th ribs and 11th thoracic vertebra), together with benign intracranial pressure, suggested vitamin A toxicity. His dermatologist had prescribed oral etretinate, but his parents had withdrawn it after consulting a naturopath. He was then given numerous medications, including vitamin A, D, and E supplements, calcium, and magnesium. After withdrawal of all vitamin supplements his condition steadily improved, except for visual acuity, which was unchanged.

These two cases clearly underline the importance of a detailed drug history, including the use of complementary medicines.

Drug–Drug Interactions

Ethanol

Ethanol and retinol are converted to their corresponding aldehydes by isozymes of alcohol dehydrogenase and

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other dehydrogenases. The pathways of retinol metabolism have been described in hepatic microsomes, partly involving cytochrome P450 isozymes, which can also metabolize various drugs. Multiple interactions of retinol, ethanol, and other drugs can therefore occur (91).

It is not therefore surprising that prolonged use of alcohol, drugs, or both not only results in reduced dietary intake of retinoids and carotenoids, but also accelerates the breakdown of retinol, through cross-induction of degradative enzymes. There is also competition between ethanol and retinoic acid precursors. Depletion of retinol and retinoic acid precursors is associated with hepatic and extrahepatic pathology, including carcinogenesis and fetal defects. Unfortunately, correction of vitamin A deficiency by supplementation is complicated by the intrinsic hepatotoxicity of retinol, which is potentiated by concomitant alcohol consumption. Furthermore, the precursor of vitamin A, beta-carotene, interacts with ethanol, interfering with the conversion of beta-carotin to retinol, while the combination of beta-carotene with ethanol results in hepatotoxicity.

In smokers who also consume alcohol, beta-carotene supplementation promotes pulmonary cancer and possibly cardiovascular complications.

It was already known in 1987 that foods that provide large amounts of retinol increase the risk of cancer of the esophagus (92,93), and in an epidemiological study the increased risk of cancer associated with the use of cigarettes and alcohol was enhanced by the ingestion of foods containing retinol (94).

The effect of alcohol abuse, one of the most common aggravating factors in vitamin A toxicity, has been elucidated. Vitamin A toxicity was potentiated in patients who took 10 000 IU/day for sexual dysfunction, and this effect was attributed to excess alcohol consumption (95). In animals, potentiation of vitamin A toxicity by ethanol resulted in striking hepatic inflammation and necrosis accompanied by a rise in serum glutamate dehydrogenase and aspartate transaminase (96).

Alcohol may also act indirectly by causing liver disease, which in turn can affect the capacity of the liver to export vitamin A, thereby enhancing its local toxicity. In alcoholics the carrying capacity of retinol binding protein was increased, even in those with low serum retinol concentrations (97). In such cases, caution in the amount of vitamin A used for therapy is recommended. Similarly, diets that are severely deficient in protein can affect the capacity of the liver to export vitamin A and enhance its hepatotoxicity.

In contrast to retinoids, carotenoids were considered non-toxic, even when taken chronically in large amounts, until recently, when it was found that ethanol interacts with carotenoids, interfering with their conversion to retinol. In baboons, the consumption of ethanol together with beta-carotene resulted in more striking hepatic injury than consumption of either compound alone (98). This interaction occurred at a total dose of 7.2–10.8 mg of beta-carotene per Joule of diet. This dose is common in people who take supplements and is the same order of magnitude used in the Beta-Carotene and Retinol Efficacy Trial (CARET) (30 mg/day) (99) and in another study (20 mg/day for 12 weeks) (100). The amount of alcohol given to the baboons was equivalent to that taken by an average alcoholic. The well-known toxicity of ethanol was potentiated by large amounts of beta-carotene, and the concomitant administration of both beta-carotene and alcohol resulted in striking liver lesions, characterized by increased activity of plasma liver enzymes, an inflammatory response, and striking autophagic vacuoles and alterations in the endoplasmic reticulum and mitochondria (101).

Besides its hepatotoxic effects, beta-carotene supplementation can also cause cardiovascular complications in smokers and potentiate carcinogenicity. The Alpha-Tocopherol, Beta-Carotene and Cancer Prevention Study (ATBC) (72) and CARET (99) showed that supplementation of beta-carotene in smokers increased the incidence of death from coronary artery disease. Recent results suggest that beta-carotene participates as a pro-oxidant in the oxidative degradation of LDL, and that raised LDL concentrations may cancel the protective effect of alpha-tocopherol (102).

The two trials also showed that beta-carotene supplementation increased the incidence of pulmonary cancer in smokers. Because heavy smokers are commonly heavy drinkers it was supposed that alcohol might have contributed to the increased incidence of lung cancer. Subsequent analysis showed that there was indeed a relation between the incidence of pulmonary cancer and the amount of alcohol consumed.

As detrimental effects result from deficiency as well as an excess of retinoids and carotenoids, and since both have similar adverse effects in terms of fibrosis, carcinogenesis, and possibly embryotoxicity, therapeutic measures must pay attention to the narrow therapeutic window, especially in drinkers, in whom alcohol narrows the therapeutic window even further by promoting the depletion of retinoids and by potentiating their toxicity (91).

Liquid paraffin

Liquid paraffin used as a laxative can reduce the absorption of vitamin A and other fat-soluble vitamins (D, E, and K) (103).

Oral contraceptives

Earlier studies suggested that oral contraceptives could lead to an increase in plasma concentrations of vitamin A (104), the inference being that increased vitamin A concentrations might have a negative effect on conception, and that this might provide an explanation for the reduced fertility sometimes seen during the period immediately following withdrawal of contraceptive steroids. More recent work has not supported this theory.

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Vitamin A: Retinoids

See also Vitamins *and* Vitamin A: Carotenoids

General Information

Vitamin A (retinol) is a key regulator of epithelial cell proliferation and differentiation. Aberrations in these processes are a feature of many skin diseases, and dermatologists have therefore long taken an interest in vitamin A as a therapeutic agent. However, marginal efficacy and unacceptable adverse effects (Table 1) have minimized the usefulness of vitamin A itself. Therefore, derivatives of vitamin A (retinoids) have been developed.

Tretinoin

Tretinoin (*all-trans*-retinoic acid), a natural metabolite of vitamin A, was the first vitamin A analogue to be used orally, with some success, but its general therapeutic ratio did not differ markedly from that of vitamin A itself.

Tretinoin cream is used extensively for the treatment of acne and photodamaged skin, and local irritant dermatitis is common. With normal use, absorption is minimal and systemic adverse effects are therefore not expected.

Topical tretinoin has also been used as an ophthalmic ointment 0.01% in the treatment of squamous metaplasia associated with dry eyes. In 161 patients with either keratoconjunctivitis sicca or conjunctival cicatricial diseases (Stevens–Johnson syndrome, inactive pemphigoid, radiation-induced dry eye, drug-induced pseudopemphigoid, and toxic epidermal necrolysis) there were no beneficial effects in the former, but significant reversal of conjunctival keratinization in the temporal bulbar site in the latter (1). Adverse effects were limited to blepharoconjunctivitis and resolved on withdrawal.

Tretinoin has been evaluated in 26 patients with histologically confirmed adenocarcinoma of the prostate and manifestations of progressive metastatic disease (2). They received a single oral dose of tretinoin 45 mg/m^2/day for 7 days followed by no treatment for 7 days before starting to take tretinoin again. Toxicity was mostly mild. There was cheilosis in eleven patients and vomiting in one. In eight patients there were transient rises in serum

Table 1 Clinical effects of chronic hypervitaminosis A, in order of decreasing frequency (3,4)

Scaling of skin, erythema, pruritus, altered hair growth
Dry mucous membranes, cheilitis, angular stomatitis, gingivitis, glossitis
Pain and tenderness of the bones, restricted movement
Occipital headache
Hyperirritability, sleep disturbances
Papillary edema, diplopia
Anorexia, weight loss
Hepatomegaly, sometimes with splenomegaly
Peripheral edema
Fatigue, lassitude, occasionally somnolence
Hemorrhages, epistaxis, increased menstrual bleeding

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triglyceride concentrations up to three times normal, returning to normal within 3–6 weeks, despite continuation of tretinoin. One patient had a severe headache with vomiting on day 1 and required a 30% dosage reduction. No patient withdrew because of toxicity.

Fatal adverse effects have been reported in patients given tretinoin for acute promyelocytic leukemia (5). Of 82 patients with acute promyelocytic leukemia, 35 developed leukocytosis and 22 had fatal adverse effects (15 with the retinoic acid syndrome and 7 with intracranial bleeding). Leukocytosis was a risk factor for fatal adverse effects. The authors suggested that the combination of tretinoin with low-dose harringtonine can reduce the incidence of leukocytosis-related intracranial bleeding and glucocorticoids can reduce mortality from the retinoic acid syndrome.

In another study of 413 patients with acute promyelocytic leukemia treated with tretinoin plus daunorubicin, the retinoic acid syndrome occurred in 64 cases, of which 5 were fatal (6).

Tretinoin 70, 110, 150, 190, or 230 mg/m^2/day has been given to 26 patients with advanced potentially hormone-responsive breast cancer taking tamoxifen 20 mg/day (7). At all doses headaches, nausea, skin changes, and bone pain occurred. The headaches were most severe during the first week of treatment, peaking at the end of the first week. They were sometimes associated with nausea and occasionally with vomiting, although there was no other evidence of raised cerebrospinal fluid pressure. Headaches and nausea tended to subside during the weeks when tretinoin was not given and recurred during the weeks of tretinoin reintroduction, although their severity tended to wane with subsequent cycles of treatment. Similarly, skin reactions, such as erythema and desquamation, were dose-related and were most severe during the initial cycles of treatment. Bone pain occurred intermittently. There was life-threatening hypercalcemia in one patient, but it was felt to be due to disease progression. The dose of 230 mg/m^2/day produced unacceptable headache and skin toxicity, but doses of up to 190 mg/m^2/day were tolerable.

A dry scaling skin rash and cheilitis were the most common adverse effects in 14 patients with prostate cancer treated with tretinoin and 20 patients treated with a combination of *cis*-retinoic acid and interferon α-2a (8). There was anorexia and significant weight loss in under 10% of the patients, but one patient discontinued treatment because of persistent fatigue and anorexia. Hematological toxic effects included leukopenia, neutropenia, anemia, and thrombocytopenia. Two patients with mild urinary hesitancy had acute urinary outlet obstruction within 1 week of starting *cis*-retinoic acid plus interferon. There were mild rises in hepatic transaminases and serum triglycerides in over half of the patients. Most triglyceride concentrations were below 2.3 (reference range 0.6–1.9) mmol/l, but one patient had an extreme rise of triglycerides to 3280 mg/dl. Sensory and mood changes were mild and occurred mostly in those given *cis*-retinoic acid plus interferon. Headaches were the most common neurological abnormality with tretinoin. Pulmonary adverse effects were dyspnea and a non-fatal pulmonary embolism in one patient treated with tretinoin. Other adverse effects included constipation, fever, nausea, vomiting, diarrhea, fatigue, and stomatitis.

In 21 patients with squamous cell carcinomas of the head and neck randomized to tretinoin 45, 50, or 150 mg/m^2 either once daily or as divided doses every 8 hours for 1 year, severe adverse effects included headache in five patients, hypertriglyceridemia in six, mucositis in two, and hyperbilirubinemia, raised alkaline phosphatase, colitis, raised lipase, xerostomia, eczema, and arthritis in one patient each (9). The dose had to be reduced in seven of eight patients with severe toxicity at 90 mg/m^2/day. Three of nine patients taking 45 mg/m^2/day required dose reductions. The plasma AUC of tretinoin did not correlate with the severity or frequency of adverse effects. From these results it can be concluded that 15 mg/m^2/day every 8 hours is a tolerable dose for 1 year in patients with squamous cell carcinomas of the head and neck.

The adverse effects of tretinoin 50 mg/m^2/day for 3 months have been studied in 20 patients with emphysema in a randomized, double-blind, placebo-controlled trial (10). The treatment was well tolerated and associated with only mild adverse effects, including skin changes, such as dry skin and cracking lips in 15 (1 placebo), transient headache in 13 (1), hyperlipidemia in 11 (5), pruritus in 6 (2), muscle/bone pain in 6 (0), generalized fatigue in 6 (2), raised transaminases in 5 (1), a sensation of clogged ears in 3 (2), nausea in 2 (0), hair loss in 2 (0), and blurred vision in 1 (1).

Etretinate and isotretinoin

Since the beginning of the 1980s two synthetic retinoids, etretinate (the ethyl ester of trimethoxymethylphenyl retinoic acid; Tigason; Tegison) and isotretinoin (13-*cis*-retinoic acid; Acutane; Roaccutane), have been successfully administered for a variety of skin disorders, all of which involve disordered epidermal or epithelial cell growth and differentiation as prominent pathogenic features, for example psoriasis, ichthyosis, Darier's disease, lichen planus, and pityriasis rubra pilaris. Isotretinoin has been of great value in the treatment of cystic acne and acne conglobata, with no serious long-term adverse effects (11,12). It has also been used for milder forms of acne (13,14).

Acitretin

In 1990, etretinate (Tigason) was replaced by acitretin (Neo-Tigason), an aromatic retinoid, a carboxylic acid metabolite of etretinate (15). It is effective in pustular psoriasis and psoriatic palmoplantar keratoderma and in combination with PUVA or topical therapy (calcipotriol or glucocorticoids) in the treatment of other forms of psoriasis. It has also been used to treat disorders of keratinization (ichthyosis, palmoplantar keratoderma, Darier's disease) and severe cutaneous forms of lichen planus. It prevents new skin carcinomas in patients with xeroderma pigmentosum and those who are immunosuppressed. The main advantage of acitretin is its short half-life of 50 hours, compared with over 80 days for etretinate (16).

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Adapalene

Topical retinoids and similar drugs, including tretinoin, adapalene, and tazaroten, are the most commonly used topical drugs for acne (17). Adapalene is a synthetic polyaromatic retinoid and is formulated in a water-based gel (1.0%, Galderma Labs Inc, San Antonio, TX). In a double-blind, multicenter, parallel-group, randomized study the efficacy and adverse effects of 0.1% adapalene gel and 0.1% tretinoin gel in a microsphere formulation were compared over 12 weeks (18). The two drugs had similar effects on the resolution of acne lesions, but tretinoin was significantly more effective in reducing the number of comedones. There were no statistically significant differences between tretinoin and adapalene in the incidences of erythema, burning/stinging, or itching. Most patients had at least one sign of cutaneous irritation over the course of the study (tretinoin 95%, adapalene 91%). The most common adverse effect was erythema (tretinoin 83%, adapalene 66%), followed by peeling (80% and 66%), dryness (67% and 65%), burning/stinging (45% and 36%), and itching (37% and 35%). There were significant differences in the incidence of cutaneous effects in favor of adapalene for dryness at week 8 (tretinoin 34%, adapalene 18%) and week 10 (29% and 12%), and for peeling at week 3 (56% and 39%), week 6 (46% and 26%), week 8 (45% and 17%), and week 10 (35% and 17%). There were no serious adverse events in either group.

In another comparison of the efficacy and adverse effects of adapalene gel 1% or 0.025% tretinoin gel in 150 Chinese patients, similar effects were observed (19). In both groups skin irritation was mild, but it was more pronounced with tretinoin. Burning was the most common unwanted effect in those who used tretinoin compared with adapalene (34 versus 11%). There was dryness of the skin in 34% of those who used tretinoin and in 22% of those who used adapalene. The respective frequencies of scaling were 26 and 15%, and of erythema 26 and 2.7%. Pruritus was the only adverse effect experienced exclusively by those who used adapalene, and it occurred in under 4%. Overall, 46% of those who used tretinoin had some form of irritation, compared with 32% of those who used adapalene.

General adverse effects

Although the various retinoids have similar toxicity profiles, they differ in the extent to which they affect various body systems. Cutaneous and mucous membrane symptoms (up to 70%) are by far the most prominent adverse effects; patients who use isotretinoin have a 50% incidence of conjunctivitis and irritation of the eyes. Musculoskeletal symptoms occur in up to 15% of users. Hypersensitivity reactions are rare and consist of occasional drug rashes. The occurrence of sarcomas in patients treated with isotretinoin may well be a chance finding (SEDA-21, 164); retinoids may prevent or even cure certain malignancies (20). All the retinoids are strongly teratogenic (21–23).

The incidence and time-course of adverse events during a 4-month course of oral isotretinoin (1 mg/kg) for severe acne have been studied prospectively in 189 patients (24). Most of the adverse events were most often reported during the first 3 months of treatment. However, only a few patients were seen every month as scheduled and only 50 of 189 filled in the questionnaire at 4 months.

Table 2 Features of tretinoin toxicity in 22 patients

Organ system	N (%)	Symptoms	N (%)
Tretinoin-related toxicity	12 (55)	Retinoic acid syndrome	3 (14)
Cardiovascular	5 (23)	Pericardial effusion	1 (5)
		Weight gain	5 (23)
		Arterial hypotension	2 (9)
Respiratory	3 (14)	Adult respiratory distress syndrome	2 (9)
		Pleural effusion	1 (5)
		Pulmonary infiltrates	1 (5)
Nervous system	6 (27)	Headache	6 (27)
		Raised intracranial pressure	1 (5)
Liver and metabolism	12 (55)	Raised transaminases	6 (27)
		Raised bilirubin	1 (5)
		Raised triglycerides	2 (9)
Hematologic	4 (18)	Leukocytosis	4 (18)
Skin and musculoskeletal	4 (18)	Dry skin	1 (5)
		Itching	1 (5)
		Joint/bone/muscle pain	3 (14)
		Osteonecrosis	1 (5)

In a retrospective study, 22 children taking tretinoin (median age 9.3 years, range 1.8–16.3) for a median of 38 (6–138) days were compared with 22 taking conventional therapy (median age 12.3 years, range: 3.2–16.7) (25). Overall, 12 of 22 patients had symptoms associated with tretinoin (Table 2). Three developed the retinoic acid syndrome.

Retinoic acid syndrome

The retinoic acid syndrome is a generalized severe capillary leakage syndrome with leukocyte activation, which results in weight gain, pulmonary infiltrates or pleural effusions with acute respiratory distress, and fever without infection. It occurs in up to 25% of patients. Postmortem reports of patients who have died from this syndrome have shown infiltration of maturing myeloid cells and edema in the lungs (26). The myeloid cells are considered to release various types of cytokines responsible for symptoms such as fever, weight gain, and heart failure. Improvement can be obtained by glucocorticoid treatment, which suppresses the effects of cytokines. Chest CT provides an accurate assessment of the size, number, and distribution of pulmonary opacities associated with the syndrome, as has been demonstrated anecdotally (27).

Of 69 patients with acute promyelocytic leukemia treated with tretinoin for 5 years, 15 developed retinoic acid syndrome (28). The following features were found on chest radiographs: an increased cardiothoracic ratio, an increased pedicle width, pulmonary congestion in 13, pleural effusion in 11, ground-glass opacities, septal lines, and peribronchial cuffing in 9,

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consolidation and nodules in 7, and an air bronchogram in 5. Three patients had pulmonary hemorrhages and bilateral, diffuse, poorly delineated nodules and ground-glass opacities on radiography. Lung infiltrates cleared completely within 8 days after administration of prednisolone.

- A 69-year-old man developed dyspnea, hypoxia, and heart failure 4 days after starting to take tretinoin 70 mg/day. His highest white blood cell count was 72 × 109/l. A plain chest X-ray showed two pulmonary opacities, increased attenuation in the left lower lobe, and bilateral pleural effusions, but a chest CT also showed multiple irregular-shaped opacities localized in the centrilobular and subpleural regions. He improved over 10 days with prednisolone (total dose 5750 mg) and daunorubicin (total dose 360 mg).

The retinoic acid syndrome, its incidence and clinical course, has been investigated in 167 patients taking tretinoin as induction and maintenance therapy for acute promyelocytic leukemia (29). The syndrome did not occur during maintenance therapy. During induction it occurred in 44 patients (26%) at a median of 11 (range 2–47) days. The major manifestations included respiratory distress (84%), fever (81%), pulmonary edema (54%), pulmonary infiltrates (52%), pleural or pericardial effusions (36%), hypotension (18%), bone pain (14%), headache (14%), congestive heart failure (11%), and acute renal insufficiency (11%). The median white blood cell count was 1.45×10^9/l at diagnosis and 31×10^9/l (range 6.8–72×10^9/l) at the time the syndrome developed. Tretinoin was continued in eight of the 44 patients, with subsequent resolution in 7. It was withdrawn in 36 patients and then reintroduced in 19, after which the syndrome recurred in 3, with one death attributable to reintroduction of the drug. Ten of these 36 patients received chemotherapy without further tretinoin, and 8 achieved complete remission. Of seven patients in whom tretinoin was not reintroduced and who were not given chemotherapy, five achieved complete remission and two died. Two deaths were definitely attributable to the syndrome.

In 63 patients with acute promyelocytic leukemia taking tretinoin (60 mg/day) the rates of leukocytosis, intracranial hypertension, and retinoic acid syndrome were 57%, 9.5%, and 3.2% respectively; the death rate was 11% (30). The authors suggested that progressive leukocytosis during tretinoin therapy should be an indication for chemotherapy (for example, with homoharringtonine); if the white cell count excceds 10×10^9/l before treatment, the patient should be given homoharringtonine only; if it is below 5.0×10^9/l homoharringtonine plus tretinoin should be used.

A syndrome similar to that of the retinoic acid syndrome occurred after 10 days of tretinoin therapy in a patient with a relapse of acute myeloblastic leukemia (31).

- A 75-year-old woman whose acute myeloblastic leukemia relapsed was treated with one dose of intravenous idarubicin (10 mg/m^2), cytarabine 20 mg subcutaneously for 10 days, and oral tretinoin 45 mg/m^2/day. Ten days later she developed a persistent fever. A chest X-ray and a CT scan showed bilateral pleural effusions and interstitial infiltrates, but no pulmonary embolus. Tretinoin was withdrawn and she was given intravenous dexamethasone 10 mg every 12 hours. Her fever disappeared within 24 hours and her respiratory distress gradually improved during the next 24–48 hours. A chest X-ray 7 days later showed total resolution.

The incidence, clinical features, and outcome of retinoic acid syndrome have been analysed in 413 cases of newly diagnosed acute promyelocytic leukemia (26). Patients under 65 years old with a white blood cell count below 5 x 10^9/l were initially randomized to tretinoin followed by chemotherapy or to tretinoin with chemotherapy started on day 3. In patients with white cell counts over 5×10^9/l chemotherapy was rapidly added if the white cell count was greater than 6, 10, and 15×10^9/l by days 5, 10, and 15 of tretinoin treatment. The retinoic acid syndrome occurred during induction treatment in 64 of 413 patients (15%). Clinical signs developed after a median of 7 (range 0–35) days. In two cases they were present before the start of treatment; in 11 they occurred on recovery from the phase of aplasia due to the addition of chemotherapy. Respiratory distress (98% of patients), fever (81%), pulmonary infiltrates (81%), weight gain (50%), pleural effusion (47%), renal failure (39%), pericardial effusion (19%), cardiac failure (17%), and hypertension (12%) were the main clinical signs. Mechanical ventilation was required in 13 patients and dialysis in 2. A total of 55 patients (86%) who experienced the retinoic acid syndrome achieved complete remission, compared with 94% of patients who had no retinoic acid syndrome, and nine died of the syndrome. None of the patients with complete remission who received tretinoin for maintenance had recurrence of the syndrome. The syndrome was associated with a lower event-free survival and survival at 2 years.

Retinoic acid syndrome has been reported in a patient who developed diffuse alveolar hemorrhage while being treated with tretinoin for acute promyelocytic leukemia (32).

- An 18-year-old woman developed promyelocytic leukemia and was given tretinoin and dexamethasone. At 15 days she developed significant hemoptysis and respiratory failure, requiring mechanical ventilation. Her temperature was 39.1°C and she had disseminated intravascular coagulation. A lung biopsy showed diffuse interstitial neutrophilic infiltration, interstitial fibrinoid necrosis, and diffuse alveolar hemorrhage; pulmonary capillaritis was diagnosed. She was given intravenous methylprednisolone 1 g/day for 3 days followed by a tapering dose of oral prednisolone. She subsequently completed a full 45-day course of tretinoin.

Organs and Systems

Cardiovascular

An increased risk of thrombotic events, especially coronary thrombosis, has been reported in elderly patients taking retinoids (33). Two patients with acute promyelocytic leukemia developed thrombus in the right ventricle during induction treatment with tretinoin plus idarubicin (34).

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- A 51-year-old man with acute promyelocytic leukemia suddenly developed hypoxemia, pulmonary infiltrates, and arterial hypotension, without fever or thoracic pain on day 11 of tretinoin treatment. He was pancytopenic, his coagulation parameters were normal, and cardiological examination was normal. High-dose dexamethasone (10 mg bd) was started, with prompt resolution of the clinical and radiological signs. Eight days later echocardiography showed a 3 cm non-homogeneous mass in the right ventricle. He was given subcutaneous low molecular weight heparin and the thrombus started to get smaller after 17 days. Oral anticoagulant therapy was started, and there was a further reduction of the size of the thrombus over the following year.
- A 32-year-old woman with acute promyelocytic leukemia developed severe retinoic acid syndrome after 3 days, with respiratory failure, fever, and bilateral lung infiltrates. Withdrawal of tretinoin and treatment with dexamethasone and antibiotics rapidly ameliorated the syndrome, and on day 10 tretinoin was restarted. However, routine echocardiography showed a 3 cm pedunculated mass in the right ventricle. There was consistent and stable reduction of the mass after 1 year of oral anticoagulant therapy.

Respiratory

The manufacturers have on record in the USA several pulmonary adverse effects during isotretinoin therapy, including worsening of asthma (SEDA-21, 162), recurrent pneumothorax, pleural effusion, interstitial fibrosis, pulmonary granuloma, and deterioration in lung function tests. Exercise-induced asthma (35) may be caused by a significant reduction in the forced expiratory flow rate (36) and a drying effect of isotretinoin on the mucous membranes of the respiratory tract (37).

Respiratory distress has been attributed to tretinoin.

- A 56-year-old woman with acute promyelocytic leukemia developed a fever of unknown origin, weight gain of 5 kg, and respiratory distress 9 days after the start of treatment with tretinoin 45 mg/m^2 (38). Her white cell count rose to 21 $\times$ 10^9/l despite treatment with cytosine arabinoside and idarubicin. A chest X-ray showed bilateral alveolar opacities. She recovered fully after 5 days of treatment with dexamethasone 10 mg bd.
- A 24-year-old woman with acute promyelocytic leukemia took tretinoin, and 2 days later developed dyspnea and general aching (39). Her total leukocyte count was 5.04 $\times$ 10^9/l, her PaO_2 was 42.5 mmHg, and a chest X-ray showed bilateral parenchymal infiltration consistent with respiratory distress syndrome. She recovered within 3 days of treatment with low-dose cytarabine and glucocorticoids, without withdrawal of the retinoic acid.

Although the retinoic acid syndrome involves the lungs, pulmonary hemorrhage has only rarely been reported. Two patients with acute promyelocytic leukemia developed severe lung hemorrhage during the first 3 weeks of treatment with tretinoin, shortly after the administration of chemotherapy (40).

- A 36-year-old man with acute promyelocytic leukemia was given tretinoin 45 mg/m^2/day, daunorubicin, and cytarabine. A week later his platelet count fell to 10 $\times$ 10^9/l, and the next day he developed dyspnea, hemoptysis, and fever. A chest X-ray showed diffuse bilateral patchy pulmonary infiltrates. Tretinoin was withdrawn, but despite high doses of glucocorticoids and blood products, hemoptysis and respiratory failure continued for 6 weeks, when he improved.
- A 59-year-old man with acute promyelocytic leukemia was given tretinoin 45 mg/m^2/day and chemotherapy. On day 6, his fibrinogen concentration fell to 940 mg/l and he developed a fever (39°C), dyspnea, and hypotension. A chest X-ray showed a right pleural effusion. Tretinoin was withdrawn and he was given dexamethasone. However, he deteriorated and developed hemoptysis. Despite glucocorticoids and blood products his pulmonary bleeding continued unabated. On day 29 he developed Gram-negative sepsis and died.

Eosinophilic pleural effusion has been attributed to isotretinoin (3).

Pneumonia has also been reported as a possible adverse effect (SEDA-20, 155) (36).

Nervous system

Nervous system disturbances include fatigue, lassitude, vertigo, sweating, hypesthesia, paresthesia, dizziness, fever, amnesia, delirium, flu-like symptoms, somnolence, pseudotumor cerebri, hyperirritability, sleep disturbance, lethargy, depression (41), and psychological changes. There was a direct correlation between intracranial hypertension and the use of isotretinoin in a retrospective study of spontaneous reports (42).

- An 8-year-old girl with acute promyelocytic leukemia was given cytarabine, etoposide, idarubicin, and tretinoin 25 mg/m^2/day (43). Five days later she developed fever, pleural effusions, and ascites, but the symptoms resolved spontaneously. On day 65 (cumulative dose of tretinoin 1.6 g/m^2) she had nausea and vomiting, severe headache, and diplopia. There was paralysis of the left trochlear nerve bilateral papilledema. A cranial MRI scan was normal. The intracranial pressure was not measured. Tretinoin was withdrawn and she was given glucocorticoids, mannitol, acetazolamide, and pethidine. Her symptoms resolved within 2 days.

A case of multiple mononeuropathies has been attributed to tretinoin (44). The neurological symptoms resembled atypical pseudotumor cerebri with focal neurological signs.

- A 23-year-old woman with acute promyelocytic leukemia was given tretinoin (45 mg/m^2/day) together with daunorubicin and cytarabine. She had a slight headache after the administration of tretinoin. On the 17th day an acute subdural hematoma required operation. Her headache persisted and she complained of diplopia, and burning pain and contact dysesthesia of the back of the left hand and the right foot, with accompanying weakness on

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day 21. Electrophysiology showed reduced conduction velocity and amplitude in the right peroneal nerve. She also had a right abducens nerve palsy and visual disturbance. There was no papilledema. MRI scan of the brain was normal. On day 51 tretinoin was discontinued. Her symptoms of peripheral neuropathy and the electrophysiological findings gradually improved as did her headache and dry skin, despite continued chemotherapy. The right abducens nerve palsy partly resolved.

The relation between isotretinoin and seizures is still unclear (SEDA-18, 169).

The possible negative effects of short-term oral acitretin 1 mg/kg/day on peripheral nerve function have been assessed in a small prospective study in 13 patients (45). Patients with conditions related to peripheral neuropathy were excluded. There was a fall in the mean amplitude of the sensory action potential of the superficial peroneal nerve after 1 and 3 months of therapy. There was a significant change in one or more neurophysiological parameters in three of 13 patients after 1 month and in nine of 13 patients after 3 months. None of the patients had detectable neurological abnormalities at any time during therapy. Acitretin was withdrawn, and after 6 months three patients gradually improved. Further studies are needed to determine whether neurophysiological evaluation should be routine during treatment with oral retinoids. Peripheral neuropathy has rarely been observed (SEDA-17, 183).

Sensory systems

Eyes

Ocular findings are among the more frequent adverse effects in patients taking isotretinoin (46,47), the most common being blepharoconjunctivitis, which also occurs in those who use tretinoin ophthalmic ointment (1).

Ocular adverse effects secondary to isotretinoin are generally benign in nature and reversible on reduction or withdrawal of therapy. However, papilledema necessitates withdrawal. Corneal opacities should be monitored closely. Although they do not usually interfere with vision, prudence dictates withdrawal of isotretinoin or reduction of the dosage when corneal opacities develop (48). Several cases of cataract have been (unconvincingly) ascribed to isotretinoin (SEDA-19, 157). Etretinate and isotretinoin have caused photophobia and reduced night vision (SEDA-17, 183), and possibly ectropion (SEDA-16, 152).

Corneal opacities after treatment with oral isotretinoin generally disappear after withdrawal. However, in one case they were persistent (49).

- A 39-year-old woman developed corneal opacities while taking oral isotretinoin 1 mg/kg for 6 months. The opacities persisted for at least 6 years after discontinuation of the drug. She had worn soft hydrophilic contact lenses for 10 years before, but without signs of corneal opacity 1 month before treatment was started.

Xerophthalmia, carrying a high risk of blindness, requires the immediate administration of massive doses of vitamin A. An infant who received intramuscular vitamin A for xerophthalmia secondary to cystic fibrosis developed an acute sixth nerve palsy (50).

- A 5-month-old boy with cystic fibrosis and xerophthalmia was given intramuscular vitamin A 50 000 IU (water-miscible retinyl palmitate). After the first dose prominent bulging of the fontanelle developed, but the infant remained alert and was feeding well. Two days later another dose of 50 000 IU was given in two divided doses over 2 days. These doses were well tolerated, with gradual improvement of the bulging fontanelle over 1 week. Five days later, a complete abduction deficit of the left eye developed, in keeping with an acute sixth nerve palsy. There were no other signs of raised intracranial pressure. The sixth nerve palsy resolved fully over the next 2 months. There were no other neurological sequelae. After discharge the infant continued to take oral vitamin A supplements.

In one study, 236 cases of adverse ocular reactions possibly associated with isotretinoin were evaluated (Table 3) (48).

Ears

Unilateral earache has been reported in two patients (SEDA-9, 134). Excessive cerumen production and otitis externa have also been reported.

Taste and smell

Taste and smell can be altered by isotretinoin (SEDA-16, 153) and loss of taste has been attributed to it (SEDA-21, 163).

Table 3 Adverse ocular effects associated with isotretinoin exposure in 236 patients (51)

Adverse effects	No. of patients
Eyelids	
Blepharoconjunctivitis or meibomianitis (52)	88
Photodermatitis	6
Cornea	
Corneal opacities	12
Dry eyes	47
Contact lens intolerance	19
Optic nerve	
Papilledema or pseudotumor cerebri	18
Optic neuritis	3
Congenital abnormalities	
Microphthalmos	5
Orbital hypertelorism	2
Optic nerve hypoplasia	4
Cortical blindness	1
Others	
Blurred vision	39
Myopia	5
Impaired night vision and dark adaptation (SEDA-10, 25)	3
Ocular inflammation (uveitis, scleritis, retinitis, ophthalmitis, iritis)	7

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Psychological, psychiatric

In 1998 depression, psychosis, and suicidal ideation, suicide attempts, and suicide were added to the product label of isotretinoin. Since then the FDA has received increasing number of reports of these problems (53). From the time that isotretinoin was marketed in 1982 up to May 2000 the FDA received 37 reports of patients taking isotretinoin who committed suicide, 110 reports of patients who were hospitalized for depression, suicidal ideation, or suicide attempts, and 284 reports of patients with depression who did not need hospitalization (54). In 62% of the suicide cases a psychiatric history or possible contributing factors were identified, and 69% of patients hospitalized for depression had either a previous psychiatric history of possible contributing factors. Drug withdrawal led to improvement in about one-third of the patients, while in 29% depression persisted after withdrawal. In 24 cases dechallenge and rechallenge were positive. However, since this was a series of spontaneous reports, and since there are no good data on the incidence of depression and suicide among adolescents with acne, a causal relation cannot be concluded.

A change in dreaming pattern has been reported in two patients, occurring within 2–3 weeks after the start of treatment with isotretinoin 40 mg/day for cystic acne (55). One patient also reported increased irritability and bouts of depression. In both patients all the symptoms abated after 4–5 weeks without a change in isotretinoin dosage.

Endocrine

Small reductions in indices of thyroid function have been observed in patients taking etretinate (56). Thyrotoxicosis may have been triggered by isotretinoin in one patient (SEDA-12, 136).

Metabolism

Alterations in lipid metabolism are common and include increases in serum triglyceride and cholesterol concentrations, sometimes persisting after withdrawal of the therapy, and reductions in high-density lipoprotein cholesterol. The incidence of raised serum lipids during therapy with oral isotretinoin 1 mg/kg/day for acne has been reviewed retrospectively in 876 patients, of whom 54 had raised serum cholesterol concentrations (over 5.2 mmol/l) and 45 had triglyceride concentrations above 2.26 mmol/l (57).

Symptoms of hyperlipidemia and the metabolic syndrome have been investigated in a cross-sectional study in young adults who had used isotretinoin for acne for at least 4 weeks (mean dosage 0.56 mg/kg). Those in whom triglyceride concentrations increased by at least 1.0 mmol/l during therapy were termed hyper-responders ($n = 102$), and those in whom triglyceride concentrations changed by 0.1 mmol/l or less were termed non-responders ($n = 100$) (58). Despite similar pretreatment body weights and plasma lipid concentrations, 4 years after completion of isotretinoin therapy the hyper-responders were more likely to have hypertriglyceridemia (OR = 4.8; 95% CI = 1.6, 14), hypercholesterolemia (OR = 9.1; CI = 1.9, 43), truncal obesity (OR = 11.0; CI = 2.0, 59), and hyperinsulinemia (OR = 3.0, CI = 1.6, 5.7) than non-responders. In addition, more hyper-responders had at least one parent with hypertriglyceridemia. Genotypes containing apoE ε2 and apoE ε4 alleles were over-represented among hyper-responders. Although a comparison of hyper-responders with non-responders may lead to overestimation of the risk, these data suggest that those who develop hyperlipidemia while taking isotretinoin are those who are already at risk of hyperlipidemia and the metabolic syndrome.

The consequences of hypertriglyceridemia are not well understood, but there may be an increased risk of cardiovascular disease and pancreatitis (SEDA-13, 123). Patients with an increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake, and a positive family history. With a short course (16 weeks) of isotretinoin it is sufficient to ensure there is no hyperlipidemia before the start of therapy, and to determine the triglyceride response to therapy on one occasion after 4 weeks (59).

Mineral balance

Hypercalcemia has been reported as an adverse effect of systemic retinoid therapy (60).

- A 12-year-old girl with neuroblastoma and normal renal function developed severe hypercalcemia while receiving isotretinoin 160 mg/m^2/day (61). Her hypercalcemia resolved with hydration, diuretic therapy, and temporary withdrawal of isotretinoin. Despite a dosage reduction to 80 mg/m^2/day, severe hypercalcemia recurred during the next treatment cycle. Further treatment with isotretinoin was made tolerable by shortening the duration of the remaining cycles.
- An 11-year-old boy with acute promyelocytic leukemia was given *all-trans*-retinoic acid 47 mg/m^2/day (62). On day 10 he developed headache and nausea. The dose was reduced to 39 mg/m^2/day and he was given glycerol, but his symptoms of pseudotumor cerebri continued. Cranial CT showed neither space-occupying lesions nor brain edema. On day 25, hypercalcemia (3.2 mmol/l) was observed. In spite of conventional therapy the serum calcium concentration continued to rise to 4.0 mmol/l. Tretinoin was withdrawn on day 33. Within 1 week his symptoms resolved. On the second day of a second phase of *all-trans*-retinoic acid therapy, he again developed nausea and headache and the serum calcium concentration gradually increased to 3.3 mmol/l by day 7. Raised concentrations of type 1 cross-linked *N*-telopeptide and deoxypyridinoline suggested increased bone resorption. A bisphosphonate (pamidronate 30 mg) was administered intravenously; the calcium normalized within 2 days and the nausea and headache resolved.

Fluid balance

Generalized edema has been attributed to etretinate (63).

Hematologic

Altered blood clotting due to hypoprothrombinemia, raised erythrocyte sedimentation rate (64), altered red cell count (64), reduced white cell count (64),

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thrombocytopenia (SEDA-12, 136), and eosinophilia (SEDA-13, 122) have all been observed incidentally (SEDA-17, 184).

Of 31 patients with acute promyelocytic leukemia (15 men and 16 women, median age 43 years) 4 received tretinoin 45 mg/m^2/day and intravenous tranexamic acid 1–2 g for 6 days, 9 received tretinoin, daunorubicin, and cytarabine followed by thioguanine, 15 received chemotherapy, tretinoin, and tranexamic acid, 2 received chemotherapy and tranexamic acid, and 1 received chemotherapy only (65). Three of the four patients who received tretinoin plus tranexamic acid had sudden and rapid deterioration in their condition, leading to early death. At postmortem there were widespread microvascular thromboses in unusual sites (for example the brain and kidneys). The rapid progression to multiorgan failure and the widespread nature of the microthrombi suggests the need for caution in the simultaneous use of tretinoin and tranexamic acid.

Thrombosis during induction treatment with tretinoin, aprotinin, and chemotherapy has been described (66).

Transient polycythemia has been reported during treatment with isotretinoin for severe nodular acne (67).

- A 53-year-old man's hematocrit increased from 0.46 to 0.51 after he had taken isotretinoin for 11 months (180 mg/day for 3 months, 80 mg/day for 6 months, then 20 mg/day). No secondary causes of polycythemia were found and the hematocrit fell to 0.48 3 months after withdrawal of isotretinoin.

The reference range for hematocrit in men is 0.41–0.49, and so the clinical relevance of this observation is unclear.

Attacks of paroxysmal nocturnal hemoglobinuria may possibly be provoked by isotretinoin (SEDA-19, 156).

Extramedullary relapse of acute promyelocytic leukemia, which is rare after chemotherapy alone, was more common after tretinoin, but it is not clear whether it truly increases the risk of extramedullary recurrence and what the risk factors are. In a retrospective analysis of the incidence of extramedullary relapse in patients after prior treatment with tretinoin and in patients previously treated with chemotherapy alone (68) three of the 13 patients who received tretinoin had extramedullary involvement compared with none of the 11 patients previously treated with chemotherapy alone (RR = 2.1; CI = 1.34, 3.29). The retinoic acid syndrome during prior induction treatment was significantly associated with extramedullary relapse (three of five patients with the retinoic acid syndrome versus none of eight without the syndrome (RR = 5.0; CI = 1.4, 17)). Thus, tretinoin may predispose patients with acute promyelocytic leukemia to extramedullary involvement at relapse and the retinoic acid syndrome is a risk factor.

Gastrointestinal

The gastrointestinal adverse effects of retinoids include anorexia, nausea, vomiting, weight loss, stomach pain, thirst, splenomegaly, and acute esophagitis (SEDA-21, 162). Proctosigmoiditis has been reported (SEDA-13, 123).

- Ulcerative colitis occurred in a 17-year-old boy shortly after he had completed a 5-month course of isotretinoin (dose not stated) for acne (69). There was no family history of inflammatory bowel disease.

Although three other cases of inflammatory bowel disease during isotretinoin therapy have been reported (70–72), there have also been reports of the safe use of isotretinoin in patents with a history of inflammatory bowel disease (that is without exacerbation of the inflammatory bowel disease) (70,73,74). Since retinoids are being increasingly used to treat moderately severe acne, larger studies are needed to elucidate the relation between retinoid use and inflammatory bowel disease.

Vasculitis and necrosis of the ileum developed in a patient with acute promyelocytic leukemia treated with *all-trans*-retinoic acid (75).

- A 29-year-old woman with acute promyelocytic leukemia was given tretinoin 45 mg/m^2. On day 20 she developed pain in both hands, wrists, feet, and ankles, with erythema and edema. On day 24 her fever increased to over 38°C and the white blood cell count was 10.9×10^9/l. She was given dexamethasone (8 mg intravenously on three consecutive days) and all her symptoms quickly resolved, but on day 37 she developed a low-grade fever and polyarthralgia, which persisted. On day 42 she had a profuse bloody stool and her abdominal pain worsened and spread all over the abdomen. At emergency operation there was segmental necrosis in several parts of the ileum, with inflammation invading the serosa. Histology of the ileum showed a leukocytoclastic vasculitis. After operation tretinoin was withdrawn and she had no fever, edema, arthralgia, or abdominal pain thereafter.

Liver

Hepatomegaly is an adverse effect of retinol and tretinoin. Transient slight rises in liver enzymes, notably aspartate transaminase, alanine transaminase, and alkaline phosphatase, are common, but some cases of hepatotoxicity due to etretinate and acitretin (SEDA-20, 154) have also been reported (76), as has cholestatic jaundice due to etretinate (77). Etretinate may have played a role in a case of liver failure leading to death (76).

The incidence of raised liver enzymes during therapy with oral isotretinoin 1 mg/kg/day for acne has been retrospectively reviewed in 876 patients (57). Liver enzymes (aspartate transaminase, alanine transaminase, and γ-glutamyl transferase) were transiently raised in a minority of patients (number not stated).

Acute liver damage has been attributed to tretinoin (78).

- A 40-year-old man with acute promyelocytic leukemia was given tretinoin 45 mg/m^2/day and intravenous daunorubicin. After 3 weeks his alkaline phosphatase rose to 370 (reference range 82–198) U/l, the gamma-glutamyltranspeptidase to 198 (reference range 7–43) U/l, and the direct bilirubin to 39 (reference range below 10) μmol/l. He had painful hepatomegaly without splenomegaly. Abdominal Doppler ultrasound ruled out biliary tract injury. Percutaneous liver biopsy showed intracellular cholestasis with preservation of hepatic architecture. He was given dexamethasone and

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tretinoin was withdrawn. After 3 days the symptoms and hepatomegaly abated.

Pancreas

Acute pancreatitis is a rare but serious adverse effect of tretinoin. Three cases associated with isotretinoin-induced hyperglyceridemia have previously been described and two cases associated with tretinoin (79,80).

- A 48-year-old man received tretinoin (45 mg/m^2/day) followed 9 days later by combination chemotherapy for 5 days (81). On day 15 he developed acute epigastric and upper left quadrant pain. He had raised serum lipase (1312 IU/l; reference range 27–208), amylase (509 IU/l; 30–110), and triglycerides (7.77 mmol/l; 0.45–1.82). Abdominal CT showed mild trabeculation of the peripancreatic adipose tissue, but no lithiasis or dilatation of the biliary ducts. Acute pancreatitis caused by hypertriglyceridemia was diagnosed and he was given supportive treatment plus fenofibrate (200 mg/day), without withdrawal of tretinoin. His lipase, amylase, and triglycerides normalized over 10 days.

Urinary tract

Impaired renal function has rarely been caused by isotretinoin (82) and etretinate (83). Abnormalities in urinary proteins, inflammation of the urethral meatus, and nephrolithiasis have rarely occurred. Urethritis may occur more often than has been realized (SEDA-21, 162) (84).

Nephrotic syndrome developed after 4 months treatment with isotretinoin 40 mg/day (85). No other causes were found and the symptoms disappeared within some months with appropriate treatment.

During tretinoin therapy, some patients with retinoic acid syndrome or with a hypercoagulable state develop acute renal insufficiency, usually accompanied by dysfunction of other organs. A patient with acute promyelocytic leukemia developed renal insufficiency alone during tretinoin treatment (86).

- A 72-year-old Japanese man with acute promyelocytic leukemia was given tretinoin 48 mg/m^2 plus idarubicin. On day 17 oliguria occurred and tretinoin was withdrawn on day 20 when the serum creatinine concentration rose to 619 μmol/l (7.0 mg/dl). There were no signs or symptoms of retinoic acid syndrome. A needle biopsy of the left kidney on day 38, when the serum creatinine concentration was 212 μmol/l (2.4 mg/dl), showed granulomatous tubulointerstitial nephritis. The glomeruli were mostly intact and there were no fibrin thrombi or leukemic cell infiltration. After one course of consolidation therapy he was discharged with a normal serum creatinine concentration.

Two cases of bone-marrow transplant nephropathy that developed coincident with retinoid therapy have been reported (87).

- A 3-year-old boy with a neuroblastoma was given cisplatin, adriamycin, and cyclophosphamide for five induction cycles and radiation to sites of residual bony metastases 1 month before autologous bone-marrow transplant, which resulted in an absolute neutrophil count of 500 × 10^6/l on day 9 and a self-sustaining platelet count over 50 × 10^{12}/l on day 72. He was randomized to receive retinoids 80 mg/m^2 bd by mouth, beginning on day 100 after bone-marrow transplant. Before beginning *cis*-retinoic acid, his highest serum creatinine concentration was 44 μmol/l on day 8. When *cis*-retinoic acid was begun, his hemoglobin was 9.8 g/dl and his platelet count 97 × 10^{12}/l. At the end of the second 2-week cycle of retinoic acid he developed a severe headache and diastolic hypertension (BP 120/108 mmHg), a blood urea nitrogen concentration of 4 mmol/l, serum creatinine of 133 μmol/l, hemoglobin of 5.8 g/dl, and platelet count of 57 × 10^{12}/l. Urinalysis showed erythrocytes and protein. Renal biopsy showed mesangiolysis, wide capillary loops, focal intimal thickening, and vacuolization of glomerular and tubular cells. His hematuria and proteinuria persisted for 4 weeks, and his blood urea nitrogen and serum creatinine gradually improved, as did the hypertension.
- A 5-year-old boy with a neuroblastoma was treated in the same way. On day 105 after bone-marrow transplantation he developed hypertension (BP 140/92 mmHg), hematuria, proteinuria, and a raised serum creatinine. His hemoglobin and platelet count fell. His urine contained protein 800 mg/l, a few hyaline casts, and 25–30 erythrocytes per high-power field. When nephritis developed, *cis*-retinoid acid was withdrawn. He gradually improved, and his urine cleared of casts, erythrocytes, and protein within 4 weeks.

Skin

Adverse effects of oral retinoids on the skin are common (up to 70%). The symptoms and signs are listed in Table 4. Three cases of scrotal ulceration during *all-trans*-retinoic acid therapy for a microgranular variant of acute promyelocytic leukemia (88,89), together with eight other reported cases (90–92), suggest that this adverse effect is specific for tretinoin. The incidence has been estimated at 12% (88). The pathogenesis is unknown, but it has been suggested to be a manifestation of the retinoic acid syndrome (88). Improvement after the withdrawal of tretinoin and the administration of glucocorticoids supports this assumption. However, activation of neutrophils by superoxide production may also be involved.

Acute febrile neutrophilic dermatosis (Sweet's syndrome) can occur in patients with acute promyelocytic leukemia given a retinoid. Sweet's syndrome is characterized by five cardinal features: fever, neutrophilia, multiple raised painful asymmetric erythematous cutaneous plaques, dermal infiltrates consisting of mature neutrophils, and a rapid response to glucocorticoid therapy. In up to 10–20% of cases it precedes or coincides with a diagnosis of malignancy, most commonly acute myelogenous leukemia. In cases associated with tretinoin the symptoms come on at 7–34 days and the skin lesions are seen on the face, limbs, and back.

- A 58-year-old woman was given tretinoin 45 mg/m^2/day for acute promyelocytic leukemia and after 9 days she developed symptoms of upper respiratory tract infection and fever (38.2°C) (96). The next day

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Table 4 The adverse effects of oral retinoids on the skin and hair

Acne fulminans (SEDA-11, 137)
Angular stomatitis
Balanitis (rare)
Blepharoconjunctivitis
Bullous pemphigoid (SEDA-17, 184)
Cheilitis
Cystic and comedonal acne (SEDA-15, 142)
Dissemination of *Herpes simplex*
Dry mucous membranes
Epistaxis
Eruptive xanthomas (one report)
Erythema multiforme (SEDA-14, 124)
Erythema nodosum (SEDA-21, 163)
Erythroderma
Excess granulation tissue (SEDA-9, 134)
Facial cellulitis (*Staphylococcus aureus*)
Facial dermatitis
Facial erythema
Follicular eczema
Generalized edema
Gingivitis, bleeding gums
Glossitis
Hair curly, possibly due to the combination of isotretinoin + azathioprine (SEDA-21, 163)
Hair discoloration (SEDA-19, 157)
Hair growth disturbed
Hair loss
Hair thinning
Hair "unruly" (SEDA-11, 136)
Hirsutism
Hyperhidrosis
Hyperpigmentation
Hypopigmentation
Irritant dermatitis
Melasma (SEDA-21, 163)
Mucosal erosions
Mycosis fungoides-like dermatitis (SEDA-10, 125)
Nail deformities (softening, fragility, Beau's lines, onycholysis, onychomadesis, onchoschizia, paronychia, curly fingernails) (37)
Nail growth reduced
Nasal carriage of *Staphylococcus aureus* (SEDA-12, 131)
Nummular eczema (SEDA-12, 136)
Osteoma cutis exacerbation
Papulopustular palmoplantar eruptions
Pemphigus vulgaris (SEDA-20, 155)
Petechiae
Photoallergy (SEDA-17, 184)
Phototoxicity (SEDA-17, 184)
Pityriasis rosea-like dermatitis
Polyarteritis nodosa (93)
Porokeratosis exacerbation (SEDA-16, 152)
Prurigo nodularis (SEDA-12, 131)
Pruritus
Pseudoporphyria (SEDA-17, 184)
Psoriasis as a Koebner phenomenon (SEDA-13, 123)
Pyogenic granuloma
Rosacea-like eruption
Ruptured striae atrophicae
Sarcoid-like granulomas (SEDA-19, 157)
Scaling of the skin
Scalp folliculitis
Skin fragility and erosions (SEDA-22, 168)
Skin odor abnormal
Skin sticky
Thyroglossal cyst (SEDA-20, 155)
Toxic epidermal necrolysis
Vasculitis (94,95)
Vulvitis
Wound healing delayed
Xeroderma

multiple erythematous and painful cutaneous plaques appeared on her limbs. Her white cell count was 5.71×10^9/l. A skin biopsy showed a normal epidermis with subepidermal edema and dense diffuse perivascular aggregates composed of granulocytes and scattered eosinophils, compatible with Sweet's syndrome. Prednisolone 20 mg/day had no effect, but after 2 days treatment with cytarabine and daunorubicin the rash started to fade and gradually disappeared. Remission was achieved after one course and *all-trans*-retinoic acid was subsequently renewed without complications.

- A 39-year-old man with acute promyelocytic leukemia was given tretinoin 45 mg/m^2 (97). His leukocyte count rose to 34.3×10^9/l on day 11. On day 18 he developed rigors, mild dyspnea, and a fever (39°C). He had exquisite pain in the right posterior tibial muscle and had several 2-mm erythematous papular and pustular lesions on his limbs and trunk. He was given a cephalosporin and developed painful bilateral nodules in the quadriceps, posterior tibial, and right biceps muscles. An MRI scan showed focal areas of increased T2 signals in the quadriceps muscles bilaterally, in most of the left sartorius and soleus muscles, and in all the compartments of the right leg. There was thickening of the adjacent fascia with subcutaneous edema. Tretinoin was withdrawn and he was given dexamethasone 16 mg/day. The cutaneous lesions improved dramatically and tretinoin 45 mg/m^2 was restarted. The symptoms did not recur.
- A 35-year-old woman with acute promyelocytic leukemia was given tretinoin 45 mg/m^2/day. On day 9 she became febrile (39.5°C) and had a sore throat with pharyngeal erythema and tender lymphadenopathy. The fever persisted despite cephalosporins, vancomycin, and antibiotics for anaerobic cover. On day 20 she developed severe bilateral anterior leg pain and both anterior tibial muscles were tender. Creatine kinase activity was 348 (reference range 38–176) U/l. Tretinoin was withdrawn and she was given intravenous dexamethasone 10 mg/day. Her fever resolved, her pain abated, and her leg muscles felt softer and less tender. Tretinoin was reintroduced and her symptoms returned.
- A 46-year-old man with promyelocytic leukemia was given tretinoin 45 mg/m^2 plus daunorubicin 60 mg/m^2/day for 3 days and cytarabine 200 mg/m^2/day by continuous infusion for 7 days (98). He became febrile on day 3 and was given cefotaxime and vancomycin. On day 6 he developed non-pruritic, erythematous, violaceous vesicles on the limbs and upper trunk. His temperature rose to 40°C and he gained 4.5 kg, which was attributed to a mild retinoic acid

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syndrome. Skin biopsy showed infiltration by neutrophilic granulocytes and marked edema in the dermis, without vasculitis or evidence of leukemic cells, fungi, or herpesvirus. Hepatic enzymes were moderately increased. The clinical presentation and histopathological findings were consistent with Sweet's syndrome. Tretinoin was withdrawn and he was given dexamethasone 40 mg/day for 10 days and then tapering doses of prednisone. He improved, and tretinoin was reintroduced without recurrence.

With topical application of tretinoin, special care should be taken when other drugs are given simultaneously. Dramatic photosensitivity has been associated with the combination of fluorouracil, prochlorperazine, and topical tretinoin (99).

- A 52-year-old woman with a colonic cancer was treated with chemotherapy after surgical resection. She had been applying topical tretinoin (Renova; Ortho Pharmac, Raritan N) cream 0.05% nightly to her face for about 5 years. During that time she had applied a sunscreen while outdoors and had tolerated tretinoin without incident. Her daily oral multivitamin supplement contained 5000 IU of retinol equivalents. About 3 days after her last dose of chemotherapy (leucovorin, fluorouracil, prochlorperazine) she exposed her face to the sun for about 1 hour after applying her usual sunscreen. Shortly afterwards the skin on her face became erythematous and worsened over several days. Her eyes became edematous, itchy, and painful. Within a week the skin on her face had completely desquamated. She stopped using tretinoin. The reaction began to improve and she was pain-free within 1 week. Her appearance returned to normal after about 10 days. During a second cycle of chemotherapy she received the same drugs as during the first, except tretinoin, and reported no significant change in sun exposure or sunscreen application. She tolerated subsequent cycles without adverse skin effects. After completing her monthly chemotherapy cycles, she resumed topical tretinoin without adverse effects.

Leukemia cutis is very rare in acute myelocytic leukemia. Cutaneous relapse in acute promyelocytic leukemia has been reported during a period of complete hematological remission after treatment with tretinoin (100).

- A 51-year-old man with acute promyelocytic leukemia was given induction chemotherapy and tretinoin 45 mg/m^2. After 1 month he developed discrete erythematous papules, although marrow biopsy suggested hematological remission. The papules were disseminated on all his limbs, trunk, and scalp, and were scattered, discrete, and 2–3 mm in diameter. Biopsy showed a moderate perivascular infiltration of medium to large atypical cells, mainly in the upper dermis, suggesting infiltrating promyelocytes. The clinical, histological, and histochemical findings were compatible with leukemia cutis. One week later, a bone-marrow biopsy still showed hematological remission.

Musculoskeletal

Musculoskeletal symptoms occur in 15% of patients who take isotretinoin. These are usually mild and consist of pain, tenderness, and muscle stiffness. Creatine kinase activity can rise, especially in individuals engaging in strenuous physical activity (SEDA-10, 124). Clinical and subclinical muscle damage has been reported from etretinate, acitretin, and isotretinoin (SEDA-21, 162, 163).

Skeletal abnormalities associated with retinoid therapy include Achilles tendonitis (SEDA-17, 185), acute arthritis (SEDA-18, 168) (101), bridging of vertebral bodies, diffuse idiopathic skeletal hyperostosis (DISH), disc narrowing, nasal bone osteophytosis, osteoma cutis, hyperostosis, extraspinal calcifications, costochondritis, enthesiopathy, ossification of tendons and ligamentous insertions, ossification of the posterior longitudinal ligament, periosteal thickening, premature epiphyseal closure, reduced bone density/osteoporosis (102), skeletal aches and pains, slender long bones, and Tietze's syndrome.

Stiff man syndrome has been described 10 days after the start of oral isotretinoin treatment (1 mg/kg/day) and resolved completely within 2 weeks of withdrawal (103). There were no motor or sensory nerve conduction abnormalities. There were no conditions known to be associated with stiff man syndrome, either at the time or during 5 years of follow up.

Adult onset Still's disease occurred after 3 months of oral isotretinoin (104). No other causes were found and the symptoms disappeared with appropriate treatment within some months.

Reproductive system

Breast discharge has been reported (105). Menstrual disturbances occur, and may be under-reported (SEDA-13, 121, 123). Vaginal bleeding in a 64-year-old woman was convincingly ascribed to the daily use of tretinoin cream 0.05% to her face, suggesting a systemic effect (SEDA-16, 159).

Adverse effects of isotretinoin affecting the male reproductive system reported to the manufacturer include gynecomastia, local inflammation/discomfort, potency disorders, reduced fertility, and ejaculatory failure (SEDA-18, 168) (106).

Immunologic

Hypersensitivity reactions to retinoids are rare and consist of occasional drug rashes.

- Immunomodulatory effects of isotretinoin in the treatment of facial acne (40 mg/day for 4 weeks) were blamed for a recurrence of pulmonary alveolar proteinosis in a 16-year-old girl, in whom it had been in spontaneous remission for 2 years (107).

Although the time-course of this effect was suggestive, it should be borne in mind that about 25% of patients with this disease have exacerbations without a clear cause.

Body temperature

An increase in the frequency of attacks of familial Mediterranean fever has been reported after the start of systemic therapy with isotretinoin for nodulocystic acne (108).

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- A 32-year-old man with familial Mediterranean fever had one or two attacks per year while taking colchicine twice daily for 10 years. During the first month after starting to take isotretinoin 50 mg/day he had three typical attacks, increasing to one attack a week after dosage increments to 60 mg/day and later 80 mg/day. Isotretinoin was withdrawn and he had no further attacks of familial Mediterranean fever during the following 10 months. Rechallenge was not performed.

Long-Term Effects

Mutagenicity

The reported occurrence of sarcomas in some patients treated with isotretinoin may be a chance finding (SEDA-21, 164); retinoids may prevent or even cure certain malignancies (20).

Second-Generation Effects

Teratogenicity

Retinoids are strongly teratogenic (21). Pregnancy should be ruled out and an effective form of contraception must be used for at least 1 month before starting therapy, during therapy, and for at least 1 month (isotretinoin) or 2 years (acitretin) after therapy is stopped. Retinoid-induced teratogenicity has been reviewed (22,23).

There are few data about the safety of topical retinoids during pregnancy. The risk of teratogenicity of topical tretinoin, if any, appears to be minimal (SEDA-18, 164) (109). However, there is a case report (110).

- A baby was born missing its right ear and external auditory canal. At 20 months an MRI scan of the brain showed focal atrophy and encephalomalacia of the right parieto-occipital lobe. His mother had used topical tretinoin (Retin A 0.025%) on her face and a large surface of the back before conception and during the first 2–3 months of pregnancy. His father had used oral isotretinoin before conception.

This type of ear abnormality is a typical feature of retinoic acid embryopathy. Given the pattern of malformations in this child, the authors thought that maternal use of topical tretinoin had been responsible. Three other cases of fetal malformations after topical tretinoin use have been reported (111–113).

Multiple congenital anomalies occurred after exposure to isotretinoin in the first trimester (114).

- A neonate whose mother had taken isotretinoin 40 mg/day during the first 2 months of pregnancy had absent auricles, tachypnea, and feeding difficulties. There were signs of heart failure, and echocardiography showed a large subpulmonary ventricular septal defect (Taussig–Bing malformation) and a secundum atrial septal defect. Both great arteries originated from the anterior right ventricle, and there was tricuspid insufficiency. A cranial CT scan showed atresia of the external ear canal, tympanic membrane, middle ear, and antrum. Other ear structures were normal. The child died at home.

Previously published information on outcomes after maternal exposure to topical tretinoin has been limited to three case reports (111–113). A fourth case has been reported (110).

- A boy, born at 41 weeks weighing 4090 g, had no right auricle or external auditory canal. Before conception and during the first months of pregnancy his mother had used topical tretinoin (Retin A 0.025%) on her face and a large area of her back. She had also used vitamins during pregnancy. His father had used oral isotretinoin before conception. At 16 months the baby was babbling. Optokinetic response was diminished and there was no oculovestibular response. At 20 months he was non-verbal and had poor receptive language, compatible with cognitive impairment. A cranial CT scan showed calcification of the right posterior hemisphere and MRI showed reduction in the volume of the right cerebral hemisphere, an infarct in the deep basal ganglia, focal atrophy, and encephalomalacia of the right parieto-occipital lobe. MRA showed marked attenuation of the posterior cerebral artery with poor declination of the more distal cortical, temporal, and occipital branches. A PET scan showed severe hypometabolism of the right posterior parietal, occipital, and temporal lobes, right basal ganglia, and thalamus, and mild hypometabolism of the left cerebellum.

Susceptibility Factors

Renal disease

The concentration of vitamin A is raised in chronic renal insufficiency, because reduced filtration of low molecular proteins results in increased concentrations of retinol binding protein. A retrospective evaluation of 18 liver biopsies in 71 patients on hemodialysis taking therapeutic doses of vitamin A showed hyperplasia of stellate cells in 7, but no evidence of fibrosis (115).

In a patient with renal insufficiency, stellate cell hyperplasia was accompanied by fibrosis (116).

- A 51-year-old man, with a 9-year history of renal insufficiency and an alcohol intake of 4 U/week, underwent transplant nephrectomy. At surgery, ascites and liver cirrhosis were noted. A needle biopsy of the liver 1 month later showed nodular regenerative hyperplasia but no cirrhosis. There were subendothelial vacuolated cells, suggestive of modified stellate cells, and there was adjacent focal perisinusoidal fibrosis. His medications included one multivitamin/mineral supplement per day containing vitamin A 4000 IU. His vitamin A concentration was 1045 (reference range 490–720) ng/ml. Viral and antibody studies were negative.

Drug Administration

Drug formulations

A novel intravenous liposomal formulation of tretinoin (Atragen®, Aronex Pharmaceuticals Inc, The Woodlands, TX), which provides a reliable dose for

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patients who are unable to swallow or absorb medications, has been evaluated in 69 patients with acute promyelocytic leukemia (117). Liposomal tretinoin (90 mg/m^2) was given every other day until complete remission or a maximum of 56 days. Treatment after complete remission was liposomal tretinoin with or without chemotherapy. Adverse effects (grade 1–2 according to the NCI common toxicity criteria) were the retinoic acid syndrome in 18 patients (grade 3/4 in 10), leukocytosis ($n = 36$), headache ($n = 46$), dry skin ($n = 23$), hypertriglyceridemia ($n = 23$), fever ($n = 18$), nausea ($n = 13$), stomatitis ($n = 11$), vomiting ($n = 10$), cheilitis ($n = 9$), exfoliative dermatitis ($n = 9$), rash ($n = 8$), myalgia ($n = 8$), liver enzyme abnormalities ($n = 7$), bone pain ($n = 6$), arthralgia ($n = 5$), raised LDH activity ($n = 4$), pseudotumor cerebri ($n = 4$; with severe headache, papilledema, increased CSF pressure, and absence of structural cranial lesions by CT or MRI scanning), hypercholesterolemia ($n = 4$), chills ($n = 4$), pruritus ($n = 3$), and diarrhea ($n = 2$).

Drug overdose

The possible symptoms and signs of overdosage are essentially the same as in hypervitaminosis A (see Table 1). The toxicity of overdosage appears to be low, and symptoms are restricted to headache and mucocutaneous adverse effects (118).

Drug–Drug Interactions

Alcohol

Concomitant intake of alcohol induces the transformation of acitretin to etretinate, which has a much longer half-life (84–168 days) (119).

Carbamazepine

No increase in seizure susceptibility was noted in a number of epileptic patients taking concomitant phenytoin, sodium valproate, or carbamazepine. However, it is recommended that carbamazepine concentrations be measured during therapy (12).

Tetracycline

Concurrent use of tetracycline has been considered contraindicated because of the risk of benign intracranial hypertension. However, although either compound alone can provoke this rare adverse effect, there is no evidence of any additive effect (12).

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Vitamin B_{12} (cobalamins)

See also Vitamins

General Information

Vitamin B_{12} is a mixture of cobalamins. Dietary vitamin B_{12} is converted to the active forms, methylcobalamin (mecobalamin) and adenosylcobalamin. The Average Requirement of total cobalamins in adults is 1.0 microgram/day and the Population Reference Intake is 1.4 micrograms/day. The Lowest Threshold Intake is 0.6 micrograms/day. Hydroxocobalamin (rINN; vitamin B_{12a}) and cyanocobalamin (rINN) have been used therapeutically.

All the cobalamins have the same pattern of adverse reactions. The adverse effects of high doses of cobalamins include urticaria, eczematous and exanthematous skin lesions, and anaphylactic reactions (SEDA-4, 265), but it is not clear whether the reactions are caused by the drug itself, a preservative, or possibly by contaminants. High oral or parenteral doses of vitamin B_6 and especially hydroxocobalamin are also on rare occasions suspected to induce acne which is, however, always benign (SEDA-5, 347) (1). Several cases of vitamin B_{12}-induced folliculitis and acneiform eruptions have been described, in one case in connection with a patient receiving total parenteral nutrition (2).

Organs and Systems

Cardiovascular

Syncope was induced by intramuscular injection of hydroxocobalamin in a paraplegic patient (3).

- An 81-year-old man had been a prisoner of war 58 years before and had been fed mainly rice. At that time he had developed complete loss of power and sensation in the right leg, weakness in the left leg, and weakness and impaired sensation in the right arm; he had become almost blind and deaf in both ears. When he was given vitamin B tablets his sight became almost normal within 1 month, but recovery

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of motor power was slower. In 1945 he returned home and was given injections of vitamin B_{12} on and off without adverse effects. In 1997 he had a serum vitamin B_{12} concentration of 91 ng/l (reference range 223–1132), a normal folate concentration, a hemoglobin of 15.7 g/dl, and an MCV of 95 fl. He was given intramuscular vitamin B_{12} 1 mg every 4–6 weeks. In 1998 he fainted about 10 minutes after an injection of vitamin B_{12}. His blood pressure was 60/30 mmHg. Soon after the next injection the patient fainted again and developed red patches and blisters over his arms, chest, and legs. Oral vitamin B_{12} without intrinsic factor resulted in 3.47% excretion in 24 hours. Vitamin B_{12} with intrinsic factor led to a urinary excretion of 1.49%. No reactions to oral vitamin B_{12} were reported.

Hematologic

A mild form of polycythemia with peripheral vascular thrombosis has been described in patients with pernicious anemia treated with high doses of vitamin B_{12} (4).

Immunologic

Allergy to vitamin B_{12} injection is infrequent, but can be serious. Positive results of basophil histamine release assay and skin testing suggest an IgE-mediated mechanism (5). Severe hypersensitivity to cyanocobalamin or hydroxocobalamin has been reported in patients who took the other cobalamin without further allergic reactions (6).

- A 45-year-old woman with pernicious anemia was given intramuscular hydroxocobalamin and developed mild generalized pruritus (7). Subsequent monthly injections of hydroxocobalamin 1 mg were followed by incrementally worsening pruritus and then frank urticaria. The last of nine injections was followed by urticaria, bronchospasm, and oropharyngeal angioedema, which responded to adrenaline. She underwent skin prick and intradermal testing with hydroxocobalamin and cyanocobalamin. Wheal-and-flare reactions occurred after injection of hydroxocobalamin, suggesting an IgE-mediated response. There was no reaction to cyanocobalamin. She subsequently had a reaction to subcutaneous cyanocobalamin 0.1 ml (100 micrograms) and then intramuscular cyanocobalamin 0.5 ml (500 micrograms). Her macrocytic anemia resolved with monthly cyanocobalamin. After 1 year she had an episode of delayed urticaria after a routine injection of cyanocobalamin. Skin prick and intradermal tests were again negative with cyanocobalamin, but there were wheal-and-flare reactions to hydroxocobalamin. She then tolerated monthly intramuscular cyanocobalamin for over 12 months.
- A 42-year-old woman who had received monthly intramuscular cyanocobalamin for 4 years developed Quincke's edema. She was given hydroxocobalamin instead, each injection being preceded by 4 mg of dexamethasone. After 13 years of this treatment she had not had any allergic reactions.
- A 35-year-old woman who had received monthly intramuscular hydroxocobalamin for 6 years developed anaphylactic shock immediately after a dose. Later she was given cyanocobalamin with terfenadine 120 mg/day for 2 days before each injection. After 3 years she had not had any allergic reactions.

Skin prick and intradermal tests, with increasing concentrations of hydroxocobalamin and cyanocobalamin, and histamine release tests on blood basophils with hydroxocobalamin and cyanocobalamin were negative in the second and third patients.

One way of dealing with vitamin B_{12} allergy is to use the alternative compound after skin testing to exclude cross-reactivity. If cross-reactivity occurs, desensitization may be considered. Alternatively, oral B_{12} can be used.

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Vitamin D analogues

See also Vitamins

General Information

The group of D vitamins includes the following naturally occurring compounds:

- lumisterol (vitamin D_1)
- ergocalciferol (calciferol or vitamin D_2)
- colecalciferol (vitamin D_3)
- dihydrotachysterol (vitamin D_4)

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- 25-hydroxycolecalciferol (calcifediol)
- 1α,25-dihydroxycolecalciferol (calcitriol)
- 24,25-dihydroxycolecalciferol.

Ergocalciferol is derived from ergosterol in the diet. Colecalciferol is derived from endogenous cholesterol. Both are also synthesized in the skin. Colecalciferol and ergocalciferol are converted in the liver by hydroxylation to calcifediol, which is weakly active. Calcifediol is activated in the kidneys by further hydroxylation to alfacalcidol, which is highly active, and calcitriol, which is weakly active. Calcitriol is deactivated by further hydroxylation in the kidney to 1α,24,25-trihydroxycolecalciferol.

Synthetic derivatives of vitamin D include:

- 1α-hydroxycolecalciferol (alfacalcidol)
- 19-nor-1,25-dihydroxycalciferol (paracalcitol) (1)
- 1α-hydroxycalciferol (doxercalciferol).

Of these alfacalcidol has been the most widely used. It is hydroxylated in the liver to calcitriol, thus bypassing the kidney. Unlike calcitriol, which acts in the small intestine to stimulate absorption, doxercalciferol remains inactive until it reaches the liver, where it undergoes transformation to active vitamin D (2). As a result, doxercalciferol minimizes the risk of hypercalcemia by 67–80%. The manufacturers claim that doxercalciferol is as potent as calcitriol in lowering parathyroid hormone concentrations.

Dietary intake and synthesis of vitamin D in the skin under the influence of ultraviolet light complement one another. In practice, the Population Reference Intake for adults is 5–10 micrograms/day and for infants and children 10–25 micrograms/day. Colecalciferol 1 microgram = vitamin D 40 IU.

The reference ranges for serum concentrations are [http://europa.eu.int/comm/food/fs/sc/scf/]:

- calcifediol 130–150 nmol/l
- calcitriol 50–145 pmol/l
- 24,25-dihydroxycolecalciferol 2–10 nmol/l.

Alfacalcidol and calcitriol have some advantages over calciferol, but their high potency involves a risk of hypercalcemia even after small dosage increments, because of increased intestinal calcium absorption. Because of this, constant vigilance is required to prevent hypercalcemia, especially in patients with chronic renal insufficiency and associated renal osteodystrophy.

Comparative studies

The efficacy of intravenous paricalcitol and calcitriol and the risks of hypercalcemia and hyperphosphatemia have been studied in an international, randomized, double-blind comparison in 38 patients in dialysis units (3). The end points were a reduction of at least 50% in baseline parathyroid hormone concentration and the occurrence of hypercalcemia and hyperphosphatemia. Paricalcitol was started at a dose of 0.04 micrograms/kg and increased in 0.04 micrograms/kg increments every 4 weeks to a maximum allowable dose of 0.24 micrograms/kg or until there was at least a 50% fall in serum parathyroid hormone concentration. Calcitriol was started at a dose of 0.01 micrograms/kg and increased in 0.01 micrograms/kg increments every 4 weeks to a maximum allowable dose of 0.06 micrograms/kg or until there was at least a 50% fall in serum parathyroid hormone concentration. Mean baseline serum parathyroid hormone, calcium, and phosphorus concentrations were similar. Reductions in parathyroid hormone occurred more rapidly with paricalcitol than with calcitriol, but there were no differences in serum calcium concentrations throughout the study between the groups. However, the respective percentages of subjects who had severe hyperphosphatemia (serum phosphorus over 0.84 mmol/l) after 8, 16, and 20 weeks were about 18, 16, and 14% in 19 patients treated with calcitriol and 6.8, 8.6, and 9.8% in 19 patients treated with paricalcitol. The results of this study suggest that paricalcitol reduces parathyroid hormone concentrations more rapidly than calcitriol does, with fewer episodes of hyperphosphatemia.

Placebo-controlled studies

In two placebo-controlled trials, 90% of dialysis patients with moderate to severe secondary hyperparathyroidism who received doxercalciferol for 16–24 weeks had about a 70% reduction in parathyroid hormone concentrations. The most frequently reported adverse effects include edema, headache, and malaise.

General adverse effects

Vitamin D intoxication is characterized by hypercalcemia and hypercalciuria as a result both of excessive gastrointestinal calcium absorption and of enhanced mobilization of calcium from bone (SEDA-8, 804) (4–6). Unintentional intoxication can result from the addition of vitamin D to food, especially to milk and milk products, for prevention of vitamin D deficiency. The established dosage for prophylaxis of vitamin D deficient rickets, 400 IU (10 micrograms), is commonly regarded as safe. The large vitamin D doses used in hypoparathyroidism, renal osteodystrophy, vitamin D-resistant rickets, and osteomalacia can predispose to intoxication. Close clinical and biochemical monitoring of patients taking vitamin D or vitamin D analogues is necessary, since intoxication can occur independent of dose and the period over which the drug has been taken.

The initial symptoms of hypervitaminosis D include weakness, fatigue, lassitude, headache, nausea, vomiting, and diarrhea. Renal function can be impaired at an early stage, with polyuria, polydipsia, nocturia, reduced urinary concentrating ability, and proteinuria.

The characteristic features of chronic intoxication are deposition of calcium salts in various tissues. A follow-up study of 24 children with vitamin D intoxication (13 900–200 000 IU/day) for up to 13 years showed that 23% of the patients had permanent damage. The severity of renal, neurological, and digestive symptoms was related to the daily dose, but the final consequences depended on the duration of overdosage (7). Vitamin D intoxication has also been seen after so-called "Stoss" prophylaxis in children, that is the use of single very

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high doses of vitamin D, and it has therefore been suggested that this procedure should be avoided (8).

It has been postulated that it is calcifediol that is the main factor involved in vitamin D intoxication (9). The serum concentration of this metabolite can remain high for several months after ingestion of excessive amounts, at least in infants (SEDA-12, 329) (10).

In elderly people, the amount of body fat is usually increased and total body fluid is reduced. These changes affect drug distribution and should be considered when administering lipophilic substances such as vitamin D, which can have a higher relative distribution volume, a longer half-life, increased accumulation, and prolongation of the pharmacological effect. Reduced dosages of vitamin D should therefore be considered in older patients (11).

Allergic reactions to vitamin D are rare and tumor-inducing effects are not reported.

Organs and Systems

Cardiovascular

Some individuals develop hypertension in response to vitamin D, which in some of them may be directly related to hypercalcemia and which may be reversible when renal function is normalized (12). Metastatic calcification is observed in various tissues (13), but arterial calcification is the most usual. In some patients undergoing dialysis, calcification of the blood vessels has been so extensive that cannulation could not be performed (14).

Respiratory

Calcification of the lung from vitamin D is rare, but has been reported in an infant after ingestion of toxic doses (15).

Nervous system

There have been very occasional reports of mental disturbances, including depression (16), cerebellar ataxia, peripheral facial paresis, apathy, lack of interest, and (in cases of acute poisoning) even stupor (SEDA-8, 804) (17–19). Mental changes can occur before the appearance of any somatic symptoms. There may be a correlation between the seriousness of hypervitaminosis D and the extent of electroencephalographic changes (20–22).

Sensory systems

Band keratopathy has been reported in patients taking vitamin D (23), as have calcium deposits in the cornea and the conjunctiva (24).

Tympanic membrane calcification can lead to severe, irreversible conductive deafness (25).

Mineral balance

Hypercalcemia

A single high dose of vitamin D can usually be given without ill effects, even though some workers have described subsequent characteristic changes in the concentrations of phosphorus and calcium in the blood (SEDA-8, 804) (5,26,27). However, long-term administration, especially with intoxication, is characterized by hypercalcemia and hypercalciuria as a result both of excessive gastrointestinal calcium absorption and of enhanced mobilization of calcium from bone (SEDA-9, 637) (4–6). Hypercalcemia is not necessarily accompanied by clinical symptoms and disappears within 48 hours when the drug is withdrawn. In patients with hypoparathyroidism or chronic renal insufficiency, the rate of reversal of hypercalcemia after stopping treatment with the vitamin D analogues is slower than in healthy subjects. In these diseases, frequent control of blood biochemistry is recommended during treatment with vitamin D analogues (28).

In a comparative study the efficacy and adverse effects of calcitriol and ergocalciferol were investigated in 18 children with chronic renal insufficiency and histological evidence of renal osteodystrophy. Whereas therapeutic effects were similar with ergocalciferol and calcitriol, hypercalcemia was more common in the calcitriol-treated patients (11 episodes following calcitriol therapy and three episodes following ergocalciferol therapy) (29).

Calcitriol + calcium carbonate has been compared with calcium carbonate alone over 12 months in a prospective, randomized trial in 15 patients with secondary hyperparathyroidism (30). Calcitriol 2 micrograms was given after each dialysis; the dose of calcium carbonate was adjusted as needed to maintain calcium and phosphate concentrations at 2.4–2.6 and 1.0–1.5 mmol/l respectively. During the first 6 months, one patient taking calcitriol had an asymptomatic episode of hypercalcemia (2.8 mmol/l), which resolved on reduction of the dose of calcitriol to 1 microgram. In the control group two patients had asymptomatic episodes of hypercalcemia (each 2.9 mmol/l) during the first 6 months. There were two episodes of asymptomatic hypercalcemia (3.2 and 2.9 mmol/l) in two patients taking calcitriol during the last 6 months of the study, requiring a reduction in dose to 0.5 micrograms in one patient. There was one episode of hypercalcemia (2.8 mmol/l) in the control group during the last 6 months of the study.

Two cases of hypercalcemia following the administration of vitamin D analogues in end-stage renal insufficiency have been reported (31).

- A 10-year-old boy with terminal renal insufficiency and secondary hyperparathyroidism was treated with calcitriol (0.5 mg/day; 0.02 mg/kg). His serum calcium rose to 3.05 mmol/l with a parathyroid hormone concentration of 51 pg/ml (reference range 15–65 pg/ml; the target range is 2–4 times higher). Calcitriol was withdrawn, hemodialysis was performed, and oral calcium acetate 2 g/day was administered as a phosphate binder. His calcium returned to normal after 4 months.
- A 12-year-old girl with terminal renal insufficiency was given alfacalcidol (0.5 mg/day; 0.02 micrograms/kg) and calcium carbonate (1 g/day) and developed calcification of the papillary muscles, of the ventricular septum, and of the atrioventricular valves, with sinus bradycardia and heart block that required a cardiac pacemaker. Her serum calcium was 2.7 mmol/l, phosphate 3.14 mmol/l, and parathyroid hormone 23 pg/ml. Calcidiol and calcium carbonate

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were withdrawn and hemodialysis was continued. She was given Sevelamer hydrochloride 4 g/day as a phosphate-binder and then several months later calcium acetate 5.2 g/day. After a further 4 months her laboratory values were near the upper limit of the reference ranges.

Because of its potent effects on parathyroid hormone, intestinal calcium absorption, and bone calcium mobilization, calcitriol can cause hypercalcemia, often precluding its use in therapeutic doses (32). Hyperphosphatemia is also a persistent problem in patients on chronic hemodialysis and can be aggravated by therapeutic doses of calcitriol. The use of large doses of calcium carbonate or acetate to control phosphate absorption can increase the risk of hypercalcemia from calcitriol (33).

Severe vitamin D intoxication with spontaneously reversible anemia and bisphosphonate-responsive hypercalcemia has been reported (34).

- A 31-year-old woman developed diffuse musculoskeletal pain. She had been taking calcium and dihydrotachysterol up to 4 mg/day for 6 months for hypoparathyroidism after subtotal thyroid resection. She had severe hypercalcemia (4.1 mmol/l), no detectable intact parathyroid hormone, renal insufficiency (serum creatinine 486 μmol/l), and a normochromic anemia (6.6 g/dl). Rehydration and forced diuresis initially improved renal function and reduced the serum calcium concentration, but the calcium concentration after 4 weeks was still 3.0 mmol/l and it did not normalize until she was given a single intravenous dose of pamidronate 15 mg.

Severe hypercalcemia in a child receiving vitamin D was associated with hyperlipidemia (35).

- An 11-month-old girl developed polyuria, polydipsia, and vomiting. She had been given vitamin D 400 IU/day for just 1 month. A misdiagnosis of rickets was made, and 1 month before admission she was given bolus vitamin D 600 000 IU in two doses 15 days apart. Her serum calcium concentration was 5.5 mmol/l; total cholesterol, high density lipoprotein cholesterol, very low density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglyceride concentrations were respectively: 6.37 mmol/l, 0.77 mmol/l, 1.37 mmol/l, 4.1 mmol/l, and 3.0 mmol/l. After 16 days of therapy with intravenous fluids, furosemide, glucocorticoids, calcitonin, magnesium sulfate, and phosphorus, her serum calcium concentration fell below 3 mmol/l. Her hyperlipidemia resolved gradually.

Ectopic calcification

The prevalence and etiology of ectopic calcification due to alfacalcidol and associated susceptibility factors have been examined in 60 patients with systemic lupus erythematosus (13). The prevalence of ectopic calcification was 40%. Localization of calcification was in peripheral arteries (6.7%), in periarticular areas (33%), and in other soft tissues (17%). The incidence of lupus nephritis and nephrotic syndrome were significantly higher in those with ectopic calcification. Total protein concentrations (70 g/l) in patients with ectopic calcification were significantly lower than in patients without calcification (75 g/l). Significantly more of the patient with ectopic calcification had received alfacalcidol (63 versus 19%). The authors concluded that alfacalcidol therapy and lupus nephritis increase the risk of ectopic calcification in patients with systemic lupus erythematosus.

Hypomagnesemia

Primary infantile hypomagnesemia is an uncommon cause of neonatal hypocalcemic seizures, but it is an important condition to recognize, because magnesium supplementation corrects the magnesium deficit, reverses the hypocalcemia due to hypoparathyroidism, and prevents further seizures (36). There is evidence of genetic heterogeneity, but the number of gene loci is not known and phenotypic classification is still evolving. Several reports have described primary infantile hypomagnesemia in children of unaffected Arab parents (37,38). One of the first reported patients, now an affected adult, used calcitriol as an alternative to the parenteral magnesium injections that had been part of his life for more than 20 years and developed hypomagnesemia (39).

- A 22-year-old man, first reported at 4 months of age and currently free of neurological deficits, had had intermittent and chronic diarrhea due to large oral doses of magnesium for hypomagnesemic tetany. On the hypothesis that modest hypercalcemia might prevent the tetany, he was given calcitriol 5 micrograms/day for 5 days. Despite the resultant increase in serum calcium concentration, he developed tetany and a fall in serum magnesium concentration from 0.63 to 0.39 mmol/l (reference range over 0.65 mmol/l). The calcitriol was withdrawn, and 33% of his usual oral magnesium supplement was given by continuous nasogastric infusion; the serum magnesium concentration rose to 0.60 mmol/l.

Mouth and teeth

High doses of vitamin D can affect dental development. In one case, caused by incorrectly fortified milk, there was dental hypoplasia and focal pulp calcification (40).

Pancreas

In patients with pancreatitis associated with hypercalcemia of unclear origin, vitamin D poisoning can be responsible, especially when episodes are recurrent (41). Metastatic calcification of the pancreatic ducts has also been reported (42,43).

Urinary tract

Daily doses of more than 40 micrograms of vitamin D can cause calcium deposition in the kidneys. Renal damage is largely due to this. Tubular function is impaired first, glomerular function later (44,45). Medullary nephrocalcinosis can develop as a result of therapy with high doses of vitamin D combined with calcium; this is mainly seen in infants and schoolchildren. Ultrasound screening of children treated with high doses of vitamin D and calcium is therefore recommended (46). Early high-dosage prophylaxis or treatment can cause nephrocalcinosis and hypercalciuria in children (47,48).

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There is controversy about whether the long-term use of C1-hydroxylated vitamin D analogues in non-dialysed patients with chronic renal insufficiency is associated with an impairment of glomerular filtration rate (SEDA-9, 639) (49). Treatment with these drugs should be restricted to patients with severe renal osteodystrophy. A proper dose should be administered in order to avoid a deleterious effect on renal function. Serum calcium and creatinine concentrations should be monitored carefully. The treatment should be withdrawn if hypercalcemia develops.

A comparison between treatment of postmenopausal osteoporosis with calcitriol together with etidronate or calcitonin showed no improvement in spinal bone mineral density, but rather a high rate of adverse events indicating nephrotoxicity (50).

There have been increasing numbers of reports of nephrocalcinosis diagnosed by renal ultrasound in patients with X-linked hypophosphatemia treated with vitamin D and phosphate, and a study of a small group of treated and untreated patients pointed to an association between this therapy and nephrocalcinosis (51).

In a French analysis of 22 510 urinary calculi performed by infrared spectroscopy, drug-induced urolithiasis was divided into two categories: first, stones with drugs physically embedded ($n = 238$; 1.0%), notably indinavir monohydrate ($n = 126$; 53%), followed by triamterene ($n = 43$; 18%), sulfonamides ($n = 29$; 12%), and amorphous silica ($n = 24$; 10%); secondly, metabolic nephrolithiasis induced by drugs ($n = 140$; 0.6%), involving mainly calcium/vitamin D supplementation ($n = 56$; 40%) and carbonic anhydrase inhibitors ($n = 33$; 24%) (52). Drug-induced stones are responsible for about 1.6% of all calculi in France. Physical analysis and a thorough drug history are important elements in the diagnosis.

Skin

The efficacy, safety, and tolerability of twice-daily calcitriol ointment 3 micrograms/g ($n = 60$) has been investigated and compared with 0.25–2% dithranol cream (once daily for 30 minutes; $n = 54$) in an 8-week prospective, randomized, open, parallel-group trial in 114 patients with plaque psoriasis (53). Skin irritation was reported by three patients who used calcitriol and by 39% of those who used dithranol. Three patients who used calcitriol and four who used dithranol reported adverse effects on the skin (pruritus, erythema, rash, dry skin, eczema). One patient with 75% skin involvement used 3.38 mg of calcitriol over 56 days (about 140 g of ointment per week without any effect on serum calcium).

Vitamin D_3 has been reported to cause hyper-reactivity of skin with pseudoxanthoma elasticum (39).

- A 68-year-old woman with pseudoxanthoma elasticum was given oral vitamin D_3 0.25 micrograms/day. After 2 weeks she developed new yellow papules on pre-existing plaques on the neck and abdomen, without itching or pain. Biopsy showed a thicker epidermis and more abundant calcium deposition than in a biopsy before treatment. Electron microscopy showed electron-dense deposits between the degenerated elastic fibers, which had been surrounded by normal collagen fibers before treatment. After treatment with vitamin D_3 there were lucent areas that suggested unusual mineralization in association with electron-dense deposits. Serum concentrations of calcium were within the reference range throughout.

Musculoskeletal

In children with chronic renal insufficiency, secondary hyperparathyroidism has been treated with intermittent calcitriol therapy. There is some reason to believe that growth is negatively influenced by this therapy, possibly due to the direct inhibitory effects of calcitriol on chondrocyte activity (54).

Of 19 chronic hemodialysis patients taking a combination of alfacalcidol and calcitriol for 12 months, six had increased bone resorption, six had reduced bone resorption, and seven had no change. Histologically documented aggravation of hyperparathyroidism was associated with a statistically significant increase in plasma concentrations of phosphate and parathyroid hormone. The administration of vitamin D analogues may therefore be either beneficial or noxious depending on whether or not induced hyperphosphatemia is adequately prevented (55).

A child with X-linked hypophosphatemic rickets developed vitamin D intoxication during treatment with alfacalcidol and phosphorus. Besides the usual findings in this condition he had precocious synostosis of the skull, with signs of raised intracranial pressure. In view of earlier reports of coincidence of craniostenosis and X-linked hypophosphatemic rickets the authors pointed to the possibility that intoxication with alfacalcidol was the precipitating factor. In addition, hypersensitivity to alfacalcidol was found 2 months after the end of treatment, with normal concentrations of calcitriol (56).

In severe hypervitaminosis D signs of hypomineralization and demineralization of the long bones and calcification of the soft tissues can be seen radiologically. Some cases of hypervitaminosis D with hypercalcemia and acute renal insufficiency have been reported in patients with osteoporosis or osteomalacia who have taken pharmacological doses of vitamin D for extended periods of time. This suggests that such therapy should be avoided. Vitamin D for prophylaxis or treatment of osteoporosis has no benefits greater than those from calcium alone or calcium with estrogens and fluoride (SEDA-14, 332) (57).

Second-Generation Effects

Teratogenicity

High doses of vitamin D during pregnancy, possibly together with genetic factors, can precipitate a severe form of idiopathic hypercalcemia and a clinical abnormality in the offspring, comprising valvular stenosis of the aorta, peculiar facies, mental retardation, and abnormal tooth formation. However, such abnormalities can also occur in the absence of hypervitaminosis D, and the doses needed to treat hypoparathyroidism in pregnancy, for example 100 000 IU/day, have been well tolerated (58,59).

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- A 28-year-old woman with hereditary insensitivity to calcitriol took oral calcitriol in doses of 17–36 micrograms/day (usual dose for hypocalcemia 0.25–1.0 micrograms/day) during pregnancy (60). Her serum calcitriol concentration was extraordinarily high throughout gestation. At delivery, the calcium concentration was 2.40 mmol/l in maternal serum and 2.52 mmol/l in cord serum. The concentration of total calcitriol in cord serum was high (470 pg/ml; normal mean for placental venous serum 19 pg/ml); mostly derived from transplacental passage of maternal calcitriol and not from fetoplacental biosynthesis. The child had mild hypercalcemia in the first 2 days of life, showing that the calcitriol measured in the cord serum was active in vivo. The child had no somatic features of the syndrome of elfin facies and supravalvular aortic stenosis.

This case demonstrates that high serum vitamin D concentrations need not be teratogenic, although the maternal metabolite can enter the fetal circulation.

Susceptibility Factors

Age

Neonates with subcutaneous fat necrosis can have transient hypersensitivity to vitamin D (61). There is a relation between the syndrome known as infantile idiopathic hypercalcemia and vitamin D intake and/or vitamin D metabolism (26).

Renal disease

There is increased sensitivity to vitamin D in patients who are undergoing renal dialysis and who have an abnormal calcium/phosphorus ratio. Patients on continuous ambulatory peritoneal dialysis (CAPD) who develop secondary hyperparathyroidism may already have low bone turnover or adynamic bone lesions, and if treated indiscriminately with calcitriol their low bone turnover can get worse (62).

Other features of the patient

There is increased sensitivity to vitamin D in sarcoidosis (63).

Drug Administration

Drug formulations

Calcium combined with colecalciferol in one tablet (Orocal) has been compared with calcium administered in a sachet (Ostram) plus colecalciferol as a separate tablet (Devaron) in 119 elderly women (64). Three patients taking the combined formulation withdrew because of adverse effects (all gastrointestinal disturbances), but none of those taking the separate tablets. Of those taking the combined tablet ($n = 59$) 43 and 39 patients had adverse effects at 6 and 12 months respectively, compared with 46 and 41 of the 60 patients taking separate tablets. For the most part, patients complained of arthralgia and gastrointestinal complaints. None of the patients had symptomatic calcium nephrolithiasis.

Drug overdose

Fortification of margarine and dairy products with vitamin D is mandatory in some countries, and permitted in others. Infant formula and liquid milk are commonly fortified with vitamin D, and two studies have shown that fortification can be vastly in excess of what is stated on the label (65,66). In one case this was detected when hypervitaminosis D was found in the population. In one case hypercalcemia occurred after prolonged feeding with a premature formula that was higher than normal in vitamin D (67).

Vitamin D intoxication occurred in a 7-week-old infant after an overdose of calcitriol (68).

- A 7-week-old boy lost weight, became dehydrated and apathetic, and developed muscular hypotonia and mild leukocyturia. His serum calcium was 4.1 mmol/l, his urine calcium 3.1 mmol/l, and his serum phosphate 51 micrograms/ml. He had been given vitamin D 200 000 U/day for 30 days in error, instead of the usual 500 U/day. Parathyroid hormone was unmeasurably low. The serum concentration of calcitriol on day 1 was 61 pg/ml (reference range 20–135), and the serum concentrations of calcifediol were 980, 2660, and 8280 ng/l (reference range 100–620) on days 8, 20, and 34 respectively. He was treated with a calcium-free diet, prednisolone, phenobarbital, fluids, and furosemide for 8 weeks. His nephrocalcinosis persisted and after 8 months a large area of suppurative, aseptic, subcutaneous necrosis in the left upper leg perforated. At 2 years of age he was well.

As routine prophylaxis with vitamin D is not entirely safe, because of errors of prescription or dispensing, and because of its narrow therapeutic range one should remember that the daily requirements of 100–400 U are usually met by the fortification of formula milk with 40 U/100 g alone. When an infant is breastfed the mother should ensure that her diet is adequate in vitamin D.

A case of accidental ingestion of a veterinary vitamin D concentrate (colecalciferol in peanut oil; 2 million IU/g) as a cooking oil sheds some light on the mechanism of pathogenesis in hypercalcemia in vitamin D toxicity. Serum concentrations of calcifediol in nine of the cases were 8–15 times greater than the upper limit of the reference range, while total calcitriol concentrations were increased in only three patients. The percentage of unbound calcitriol was increased in all patients, as was the total calcitriol concentration. Increased unbound calcitriol concentrations might play a role in the pathogenesis of hypercalcemia in vitamin D toxicity (69).

Hypercalcemia has been associated with the ingestion of an over-the-counter vitamin D supplement (70).

- A 42-year-old man who for 2 years had taken a supplement containing vitamin D_2 had a serum calcium concentration of 3.75 mmol/l and a serum calcifediol concentration of 487 ng/ml (reference range 9–47). He had normal concentrations of calcitriol, parathyroid hormone, angiotensin-converting enzyme, and thyroid hormone, and had normal bone marrow, radiography, and CT of the chest, neck, and abdomen. Vitamin D_2

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was withdrawn and he was rehydrated. He was advised to wear sunscreen at all times when outdoors. Three months after discharge the results of all blood tests were in the reference ranges, including serum concentrations of calcium and calcifediol.

Examination of three lots of the over-the-counter formulations the patient had used showed mean vitamin D contents of 1.3, 13, and 22 mg/g of powder. The patient had taken 3 g/day, or 156 000–2 604 000 IU/day of vitamin D_2, which is about 80–1300 times the recommended safe upper limit of 2000 IU/day.

Drug–Drug Interactions

Anabolic steroids

The combined effects of vitamin D, calcium, and anabolic steroids in the treatment of senile osteoporosis have been investigated (71). Neither methandienone nor vitamin D_3 alone but only the two together seemed to increase coronary morbidity and mortality, and possibly in women only. Simultaneous use of these two drugs should be avoided.

Calcium carbonate

Symptomatic reversible hypercalcemia was seen in two elderly patients taking apparently safe amounts of vitamin D and thiazide diuretics. Their unusual susceptibility to this effect resulted from an interaction with calcium carbonate which had been taken simultaneously. In the presence of other predisposing factors, hypercalcemia can develop in patients taking calcium carbonate 5–10 g/day (72,73).

Enzyme inducers

Anticonvulsants (barbiturates and phenytoin) and other drugs that induce liver enzymes (such as rifampicin) can accelerate the hepatic catabolism of vitamin D and can lead to reduced serum concentrations of calcifediol and osteomalacia. Prophylactic vitamin D treatment of patients taking long-term enzyme inducers can be helpful and should be given at least in cases of anticonvulsant-drug-induced osteomalacia (74,75).

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Vitamin E

See also Vitamins

General Information

Vitamin E is a family of compounds that include several different isomers of tocopherols and tocotrienols, of which the most important is thought to be alpha-tocopherol, the form of vitamin E that has mostly been used in clinical trials (1). The actions of the different isoforms have not been fully elucidated.

It was suggested many years ago that vitamin E could be useful in patients with peripheral arterial disease, but the evidence is meager and incomplete. Nowadays, vitamin E is expected to have a role in the prevention of atherosclerosis, through inhibition of oxidation of low-density lipoprotein. The hypothesis that oxidative modification of low-density lipoprotein contributes to the progression of atherosclerosis is supported by an impressive amount of in vitro and animal data. Some epidemiological studies have associated high dietary intake or high serum concentrations of alpha-tocopherol with a reduced risk of cardiovascular events. Large intervention studies with clinical endpoints have tested the hypothesis that daily supplementation with a high dose of alpha-tocopherol reduces ischemic vascular events. In over 2000 patients there was a substantial reduction in non-fatal myocardial infarction, but not in cardiovascular deaths (2). Daily administration of 400 and 800 IU of vitamin E was well tolerated, and only 11 patients stopped treatment because of diarrhea, dyspepsia, or a rash. Withdrawals due to adverse effects were equally distributed between the placebo group and the two treatment groups.

Since vitamin E requirements depend on dietary polyunsaturated fatty acids, which vary considerably between individuals, it has not been seen as expedient to establish a single Population Reference Intake value.

General adverse effects

Several reviews of the adverse effects of vitamin E have been published (3,4), especially relating to premature infants (5), in whom high doses have been associated with infectious complications and fatal hepatic failure. In adults, thrombophlebitis, thromboembolism, pulmonary embolism, hypertension, fatigue, gynecomastia, and breast tumors have been described as particularly serious effects of vitamin E, but there is little evidence about their frequency. Diarrhea and abdominal pain can occur. For some of these effects there seems to be a dose relation. A dose of 800 mg/day for 30 days had no reported adverse effects in healthy elderly subjects (6). Table 1 shows reported adverse effects related to dosage in a review of about 50 publications on vitamin E (7).

Organs and Systems

Cardiovascular

Vitamin E 300 mg/day can increase serum cholesterol by an average of 1.9 mmol/l (74 mg/100 ml) (8). It is therefore advisable to use vitamin E with caution in patients with a family history of heart disease. Some studies have shown that vitamin E can prevent atherosclerosis and serious adverse events were not reported in these studies (2,9,10).

Hematologic

Significant depression of bactericidal activity of leukocytes and mitogen-induced lymphocyte transformation occurred after the administration of dl-tocopherol 300 mg/day for 3 weeks (11).

Reduced platelet adhesion to collagen has been described (12), and experimentally confirmed (13) and has been seen with doses of vitamin E from 400 mg/day (14).

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Table 1 Adverse effects of high doses of vitamin E

Dosage (mg/day)	Symptoms or changes
	Clinical effects
>300	Gastrointestinal irritation, nausea, vomiting, headache, muscular weakness, dizziness, stomatitis, visual complaints
400	Thrombophlebitis, urticaria, vaginal bleeding
800	Faintness, fatigue, creatinuria
1200	Ecchymoses
1600	Deterioration of angina pectoris
Unknown	Deterioration of diabetes mellitus
Unknown	Transient hypertension
Unknown	Allergic contact dermatitis
Unknown	Gynecomastia, breast cancer
	Laboratory findings
300	Increased concentrations of lipids, cholesterol, carotenoids, and coagulation factors
>300	Reduced incorporation of thymidine into phytohemagglutinin-stimulated lymphocytes, reduced bactericidal activity of leukocytes, and reduced blood glucose concentrations
600	Decreased concentrations of triiodothyronine and thyroxine in serum
600	Increased concentrations of free cholesterol in LDL and VLVD fractions
800	Increased serum creatine kinase, creatinuria
1000	Increased excretion of steroids in the urine
1200	Increased warfarin action
Unknown	Increased dehydroepiandrosterone concentrations in blood
Unknown	Increased gonadotrophin concentrations

Skin

Although there is no proof of any beneficial effects of topical use of vitamin E, it continues to be popular. Allergic contact dermatitis has been reported rarely (15).

Susceptibility Factors

Age

Premature neonates are reported to have a relative deficiency of vitamin E at birth, which has been associated with hemolytic anemia (16). Since there was an increased incidence of necrotizing enterocolitis when oral tocopherol was given to such infants (7,8,17,18), parenteral tocopherol was for a while recommended for use in very ill neonates (19,20).

There were increasing numbers of commonly fatal cases of the so-called "E-Ferol syndrome" during the 1980s (SEDA-12, 329) (21), a condition characterized by progressive unexplained thrombocytopenia, renal dysfunction, cholestasis, and ascites (22). E-Ferol was an intravenous vitamin E formulation, but the syndrome was subsequently shown to be due to polysorbate 80, which was used as an emulsifier in the formulation (23–25).

Preterm infants receiving under 25 mg/kg/day of tocopherol acetate intravenously had highly variable serum tocopherol concentrations. High serum concentrations correlated with the occurrence of necrotizing enterocolitis (26).

An increased incidence of infection, even sepsis after intramuscular injection, as an adverse effect of megadose vitamin E therapy in very low birth weight infants was first reported in Japan in 1986 (SEDA-12, 330). In a review of the literature in 1992 it was concluded that pharmacological serum concentrations of vitamin E might predispose premature infants to infectious complications, possibly caused by an inhibitory effect of vitamin E on the formation of superoxide anion in leukocytes (27).

There was a statistically significant increase in the risk of retinal hemorrhage with parenteral vitamin E in premature infants (28). This has led some researchers to conclude that tocopherol should not be recommended for the prevention of retinopathy in prematurity (29), particularly in infants with birth weights of less than 1 kg.

Other features of the patient

An increased tendency towards gingival bleeding was noted in a recent 7-year prospective study of smokers who had been given alpha-tocopherol supplementation in comparison with non-receivers. Acetylsalicylic acid further increased the risk of bleeding.

Drug–Drug Interactions

Acetylsalicylic acid

Alpha-tocopherol supplementation may increase the risk of clinically significant bleeding, particularly when it is combined with acetylsalicylic acid (30). Although acetylsalicylic acid and its derivatives are widely used, reliable pharmacoepidemiological data about drug usage frequency in the population are sparse. Among reports of serious adverse effects resulting from acetylsalicylic acid and other salicylates (31–37), of special interest are potential adverse effects in those who concurrently take vitamin E formulations (38,39).

The first pharmacoepidemiological survey was published in 1995, covering data from 1984 to 1988 (40), and the population-based data collected in Germany from 1984 to 1999 have been analysed, including data from five epidemiological surveys, concerning total drug usage, physiological, clinical chemistry and hematological data, and information about the serum concentrations of active drugs and/or their metabolites (40). The data were analysed with regard to the usage of salicylates and drugs

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with potential interactions relevant to the highly sensitive balance between hemostasis and bleeding. Special attention was paid to serum concentrations of the various tocopherols, because of their potential activity in anticoagulation processes (39,41,42).

The data are representative of the resident population aged 25–69 years in the first four surveys and the age group 18–79 years in the last (1997–99), covering more than 20 000 study participants.

Patient drug usage data for the 7 days before the clinical examination were recorded using a standardized questionnaire in all the surveys (40). Measurements of salicylic acid and tocopherols were by HPLC with fluorescence detection or GC/MS (43).

In male users of salicylates and vitamin E the frequency of co-medication with lipid lowering drugs was 14%, with cardiovascular drugs 11%, and with analgesics 9%. Of female users of salicylates and vitamin E, 23% also took mineral products, 11% thyroid drugs, 10% estrogens, and 9% beta-blockers.

In all surveys salicylate use was higher in women (14%) than men (12%). Owing to massive advertising, vitamin E consumption has risen since the first survey, and was 5.6% in women and 3.6% in men in the German population aged 18–79 years (survey 1997–99). Co-medication with salicylates was observed in 17% of the vitamin E users (55% women, 45% men) and 90% of the reported concomitant use was in those over 50 years.

Mean salicylate concentrations in those who used acetylsalicylic acid as an analgesic were 8.3 μmol/l in 1985, and 16.5 μmol/l in 1988, 1991, and 1998, while salicylate concentrations in subjects who used acetylsalicylic acid as an antiplatelet drug fell from 9.8 μg/ml in 1985 to 7.8 μg/ml in 1988, 3.0 μg/ml in 1991, and 0.8 μg/ml in 1998. This fall in serum salicylate concentrations reflects changes in the usual dose of acetylsalicylic acid.

In contrast the mean concentrations of α-tocopherol in vitamin E users increased from 28 μmol/l in 1985 to 29 μmol/l in 1988, 35 μmol/l in 1991, and 56 μmol/l in 1998. Controls not taking any medications had much lower serum concentrations of α-tocopherol (7.5, 9.8, 11.8, and 18.3 μg/ml). Concentrations of β-tocopherol, γ- tocopherol, and δ-tocopherol in users of vitamin E were lower by up to 50% in users of vitamin E formulations. From these data the authors concluded that there is a considerable risk in the availability of over-the-counter drugs, especially those that can affect the balance between blood clotting and hemorrhage, such as salicylates and α-tocopherol. Since women over 40 in particular tend to use so-called dietary supplements, in the belief that such products might prevent illness, and because there is unrestricted advertising in the mass media, physicians should obtain a clear medication history from their patients.

The fact that blood concentrations of β-tocopherol, γ-tocopherol, and δ-tocopherol are lowered by α-tocopherol (42) should be taken into account in investigations on the clotting and bleeding balance and in cancer research.

Oral anticoagulants

Vitamin E therapy in vitamin K-deficient subjects and subjects taking anticoagulants reduces active plasma prothrombin concentrations (44).

There have been two cases of coagulation disorders with the herbal drug cucurbicin, each tablet of which contains vitamin E 10 mg (45). Cucurbicin is an approved herbal drug in Sweden, traditionally used for micturition difficulties. The active components are extracts from the fruit of *Serenoa repens* and the seed of *Cucurbita pepo*.

- A 73-year-old man with a common cold, who had been taking cucurbicin three tablets daily for more than 1 year, developed a coagulation disorder, with an international normalized ratio (INR) of 2.1, despite a normal albumin concentration and no anticoagulant treatment. His INR improved to 1.4 on treatment with vitamin K, but did not normalize until cucurbicin was withdrawn 1 week later.
- A 61-year-old man, who had taken warfarin and simvastatin for a long time and had an INR of 2.4, started to take cucurbicin five tablets daily for micturition difficulties. After 6 days his INR had increased to 3.4. After withdrawal of cucurbicin the INR returned to the previous value within 1 week.

No anticoagulant effect has been reported with either of the major components of cucurbicin. However, vitamin E antagonizes the effect of vitamin K and can cause an increased risk of bleeding, especially in patients taking oral anticoagulants. The amount of vitamin E in cucurbicin that these two patients consumed was 30–50 mg/day, corresponding to the recommended dose of 40–50 mg daily for vitamin E deficiency. The two cases suggest that caution should be exercised when cucurbicin is used concurrently with warfarin.

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Vitamin K analogues

See also Vitamins

General Information

Vitamin K is the name of a group of compounds, all of which contain the 2-methyl-1,4-naphthoquinone moiety. Common nomenclature is:

- vitamin K_1 (phytomenadione; rINN)
- vitamin K_2 (phytonadione; rINN)
- vitamin K_3 (menadione; rINN).

Vitamin K is routinely administered in many countries to newborn babies in varying doses and by various routes, most commonly either orally or by intramuscular injection, to prevent hemorrhagic disease of the newborn (see Table 1).

Phytomenadione given intravenously is generally tolerated well. However, intravenous administration of small amounts (2–5 mg) can be followed by severe short-lasting cyanosis, dyspnea, tachycardia, and low blood pressure in patients with cardiac failure. Flushing and sweating can occur. Anaphylactoid reactions may be due to the excipient Cremophor EL. The most important adverse effects are jaundice and kernicterus, which can occur in small and premature babies, even after small doses, probably because of immature liver function.

Organs and Systems

Cardiovascular

Results of intravenous administration of 100 sequential doses of vitamin K in 45 patients (34 men, 11 women) have been retrospectively reviewed (1). Vitamin K_1 was administered as Aquamephyton. The dose averaged 9.7 (range 1–20) mg. The mean age was 44 (range 18–66) years. Many of the patients were seriously ill and had significant underlying surgical and medical problems, as evidenced by the fact that 16 died. However, none of the deaths was attributable to vitamin K. In the 11 instances in which the duration of administration was noted, the mean time was 49 (range 12.5–60) minutes. Only one patient had an episode of transient hypotension.

- A 37-year-old man with a history of ethanol abuse presented with hepatic failure and non-cardiogenic pulmonary edema after an overdose of paracetamol, codeine, ibuprofen, and diazepam. He received two doses of Aquamephyton (phytonadione) over 2 days and 10 minutes after the second dose his blood pressure fell to 79/40 mmHg.

In this study the incidence of adverse effects was 1%, contrasting with the impression that one obtains from reading the medical literature on vitamin K, which suggests an overall incidence of less than 1%.

Nervous system

Kernicterus can occur in small and premature babies, even after small doses of vitamin K, probably because of immature liver function. In its 1997 clinical practice guidelines, the Canadian Paediatric Society recommended that, in order to prevent haemorrhagic disease of the newborn, phytomenadione be given as a single intramuscular injection to all newborns within 6 hours of birth, in a dose of 1 mg for infants with a birth weight of more than 1500 g and half this dose for smaller infants. The dose is crucial, since overdosage carries a serious risk of kernicterus, especially in premature infants. There is only a remote possibility that this treatment might increase the risk of childhood cancer.

Cerebral vein thrombosis developed after the administration of 10 mg of phytomenadione in two patients with chronic intestinal inflammation assumed to be part of an autoimmune disease (2).

Hematologic

High doses of vitamin K can occasionally cause hemolytic anemia (3).

Severe hemolysis has been attributed to vitamin K in patients with glucose-6-phosphate dehydrogenase deficiency, particularly if infection is present (4,5).

In severe hepatocellular disease the prothrombin concentration can be further depressed by high doses of vitamin K (6,7).

Skin

Skin reactions have been observed after intramuscular injection of phytomenadione.

Presentation

The English-language literature on adverse skin reactions associated with intramuscular or subcutaneous phytomenadione has been reviewed (8). Vitamin K is generally well tolerated subcutaneously or intramuscularly. However, erythematous eczematous plaques have been well documented. Of 39 skin reactions due to

Table 1 Classification of hemorrhagic disease of the newborn

Syndrome	Time of presentation	Common bleeding sites	Comments
Early disease	0–24 hours	Cephalohematoma, intracranial, intrathoracic, intra-abdominal	Maternal drugs a frequent cause (for example warfarin, anticonvulsants)
Classic disease	1–7 days	Gastrointestinal, skin, nasal, circumcision	Mainly idiopathic, maternal drugs
Late disease	2–12 weeks	Intracranial, skin, gastrointestinal	Mainly idiopathic, can be the presenting feature of an underlying disease (for example cystic fibrosis, α_1-antitrypsin deficiency, biliary atresia; there is often some degree of cholestasis

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phytomenadione, 32 were eczematous and 91% of the patients were women, average age 39 (range 9–64) years; in four cases there were small vesicles within the plaques (9–12).

As a rule, only a rash occurs, generally after high doses of the oil-soluble analogue. However, intramuscular injection of phytomenadione can also cause lumbar scleroderma around the injection site. The scleroderma is reported to develop in four stages; erythematous, erythematous pigmented, established scleroderma, and resolvent scleroderma. Localized pseudoscleroderma (Texier's syndrome) has also been reported (13). This particular adverse reaction has occurred mainly in patients with hepatic insufficiency (SEDA-12, 330), but skin reactions have also been seen in patients with a normal hepatic condition (14,15). Brown pigmentation in the trochanteric region has been reported in a patient with cirrhosis.

Localized eczema at the site of subcutaneous injection has been reported (8).

- A 50-year-old woman taking warfarin had an INR of 8 and was given phytomenadione 10 mg subcutaneously (Sabex, containing propylene glycol 2% and polyethylene glycol 10%) and 12 hours later another 5 mg. One week later she developed two red, pruritic, warm, indurated areas, measuring 2 × 4 and 8 × 10 cm, at the two separate injection sites. A skin biopsy showed minimal spongiosis of the epidermis and an edematous dermis with a dense perivascular lymphocytic infiltrate and numerous eosinophils.

A severe localized and subsequently generalized dermatitis occurred after intramuscular injection of phytomenadione (16).

- A 40-year-old woman with no pre-existing hepatic disease was given intramuscular phytomenadione (Konakion) 1 ml/day (10 mg/ml) on 4 days before open cholecystectomy for gallstones. She then noticed a pruritic erythematous patch on her anterior left thigh, and over the next 4 weeks four patches appeared on her thighs and became larger (maximum diameter 15 cm), vesicular, weeping, hot, indurated, and intensely itchy. Topical calamine lotion, 1% hydrocortisone cream, and Paxyl cream (lidocaine and benzalkonium chloride) and oral cefalexin had no effect. The eruption then spread to the operation wound site, the face, neck, and arms. Oral prednisolone resulted in gradual improvement over the next 4 weeks, but residual erythema persisted for nearly 6 months.

Other presentations include erythematous pruritic plaques associated with epidermal keratosis, focal spongiosis, and perivascular infiltrates of lymphocytes and eosinophils or scleroderma-like hypodermic indurations (17). In such cases, intradermal tests may be positive for phytonadione.

Timing

The lesions usually appear 4–16 days after intramuscular injection, and persist for up to 2 months (18,19), sometimes leaving a scar lasting for years (20). The median number of days between the administration of phytomenadione and the appearance of the eruption was 13 days, but eruptions have appeared as early as 30 minutes and as late as 4 weeks after injection. In 13 of 32 cases it took more than 2 months for the reaction to resolve.

Frequency

Skin reactions to vitamin K are rare, only about 40 cases having been reported.

Relation to dose

In some early reports it was postulated that a minimum dose was necessary to cause eruptions, but there have been later reports of adverse skin reactions after small doses (range 10–440 mg).

Histopathology

Histopathological examination typically shows epidermal changes, including spongiosis with or without intraepidermal vesicles. In the dermis there is a perivascular mononuclear cell infiltrate, which may also be interstitial, often containing eosinophils.

Mechanism

Various formulations of phytomenadione contain different inactive ingredients, including polysorbate 80, propylene glycol, sodium acetate, glacial acetic acid, polyethoxylated castor oil (Cremophor EL), dextrose, and benzyl alcohol. Based on negative results with these ingredients, it appears that phytomenadione itself is the antigen that leads to adverse skin reactions. Of 10 patients with liver disease and prior exposure to phytomenadione (Konakion), 4 had positive results to patch-testing with vitamin K (21). Intracutaneous tests have supported the generally accepted hypothesis that the phenomenon is due to type IV hypersensitivity.

Treatment

No particular therapy is effective. It is not known whether the minute quantities of phytomenadione that are present in some foods, such as parsley, kale, brussels sprouts, spinach, cucumber, soy bean oil, and green and black tea leaves, preclude effective dietary therapy. Since the mechanism of this reaction is thought to be delayed hypersensitivity, another potential therapeutic approach is topical application of tacrolimus (FK-506), a potent inhibitor of interleukin 2 and T cell activation. Tacrolimus up to now has only been shown to suppress allergic contact dermatitis to dinitrophenol.

Immunologic

Allergic reactions have been attributed to phytomenadione, menadione, and vitamin K_4. In mice, menadione caused marked hypodynamia and hypothermia. This effect was potentiated by riboflavin. Allergic reactions to the systemic administration of vitamin K are immunologically mediated, and generally arise in patients with coagulation or liver problems.

Intradermal tests with phytomenadione and menadione caused an allergic skin reaction 7–22 days after injection in 13 of 145 healthy subjects. The results suggested that the index of cutaneous sensitivity lies somewhere between 5.5 and 8.9%. On the other hand, the absence of adverse effects with oral phytomenadione is striking. Continuation of treatment orally can in some cases prevent dermatitis (10). No cross-sensitivity has been seen between phytomenadione and menadione (22). Anaphylactoid reactions, some fatal, to phytomenadione

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have been reported (SEDA-15, 416) mainly from intravenous use (23).

The recommendation that prolongation of the international normalized ratio (INR) to over 6.0 should be corrected with parenteral phytomenadione (24,25) is not accompanied by the caveat that the intravenous route entails the risk of life-threatening, non-IgE-mediated anaphylactic reactions and even death, due to the use of polyethoxylated castor oil (Cremophor EL) as a solvent (26). A severe reaction to intravenous phytomenadione has been reported (27).

- A 74-year-old woman, taking warfarin, presented with an INR of 6.2. She was given a slow intravenous injection of phytomenadione (Konakion, Roche Products Ltd) 0.25 ml (500 μg) over about 60 seconds, and soon after felt profoundly unwell and complained of severe backache. She was given chlorphenamine 10 mg by rapid intravenous injection and adrenaline 1 mg in 10 ml of water over 30 minutes, with a good result.

An unusual case of allergy to vitamin K, with a relapsing and remitting eczematous reaction, has been described after an intramuscular injection of vitamin K_1 (28).

- A 27-year-old woman with cystic fibrosis and pancreatic insufficiency was given intramuscular vitamin K_1 into her thigh. The next day transient erythema occurred over the injection site and 6 weeks later there was localized pain, erythema, and edema. She was given intravenous cefuroxime for presumed cellulitis, but over the next few days the features became more consistent with localized eczema; she was given oral prednisolone 30 mg/day, super-potent topical corticosteroids, corticosteroid injections, and corticosteroids under occlusion with Duoderm, all of which failed to result in improvement. She then also developed an eczematous reaction to the Duoderm dressing. Patch tests were positive to vitamin K_1 and cross-reacted with vitamin K_4. She was also positive to colophonium and ester gum rosin, the dressing adhesive. Recurrent angio-edema persisted for several months and 2 years later she still had symptoms at the injection sites.

In all reported cases, only the whole formulation of vitamin K_1 (in its vehicle) or vitamin K_1 alone elicited positive patch tests. When individual additives were tested the results were negative. No previous exposure to vitamin K_1 was required for the development of type IV hypersensitivity, and primary sensitization occurred within 1–2 weeks or after a longer time period, as in the patient described here.

Long-Term Effects

Tumorigenicity

The relation between neonatal vitamin K administration and childhood cancer has been investigated in three case-control studies.

In a retrospective study 685 children who developed cancer before their 15th birthday were compared with 3442 controls matched for date and hospital of birth (29). There was no association between the administration of vitamin K and the development of all childhood cancers (unadjusted odds ratio 0.89; 95% CI = 0.69, 1.15) or of all cases of acute lymphoblastic leukemia (1.20; 0.75, 1.92), but there was a raised odds ratio for acute lymphoblastic leukemia 1–6 years after birth (1.79; 1.02, 3.15).

However, no such association was seen in a separate cohort-based study not dependent on case-note retrieval, in which the rates of acute lymphoblastic leukemia in children born in hospital units in which all babies received vitamin K were compared with those born in units in which less than a third received prophylaxis. It was concluded that on the basis of currently published evidence neonatal intramuscular vitamin K administration does not increase the risk of early childhood leukemia.

In another study children aged 0–14 years with leukemia ($n = 150$), lymphomas ($n = 46$), central nervous system tumors ($n = 79$), a range of other solid tumours ($n = 142$), and a subset of acute lymphoblastic leukemia ($n = 129$) were compared with 777 children matched for age and sex (30). Odds ratios showed no significant positive association for leukemias (1.30; 0.83, 2.03), acute lymphoblastic leukemia (1.21; 0.74, 1.97), lymphomas (1.06; 0.46, 2.42), central nervous system tumors (0.74; 0.40, 1.34), and other solid tumors (0.59; 0.37, 0.96). There was no association with acute lymphoblastic leukemia in children aged 1–6 years. The authors concluded that they had not confirmed the observation of an increased risk of childhood leukemia and cancer associated with intramuscular vitamin K.

In another study 597 cases and matched controls were compared. The association between cancer generally and intramuscular vitamin K was of borderline significance (odds ratio 1.44); the association was strongest for acute lymphoblastic leukemia (1.73) (31). However, there was also an effect of abnormal delivery. The authors suggested from the lack of consistency between the various studies so far published, including their own, and the low relative risks found in most of them, that the risk, if any, attributable to the use of vitamin K cannot be large, but that the possibility that there is some risk cannot be excluded. They recommended that prophylaxis using the commonly used intramuscular dose of 1 mg should be restricted to babies at particularly high risk of vitamin K deficiency; alternatively, a lower dose might be given to a larger proportion of those at risk.

Ecological studies of the relation between hospital policies on neonatal vitamin K administration and subsequent occurrences of childhood cancer have been analysed using data from selected large maternity units in Scotland, England, and Wales (32). The study covered 94 hospitals, with a total of 2.3 million births during periods when intramuscular vitamin K was routinely used and 1.4 million births when a selective policy was in operation. An increased risk was occasionally associated with vitamin K (highest odds ratio 1.25 for acute lymphoblastic leukemia in one hospital), but the overall results were not significant, and there was no evidence to support the previously suggested doubling of the risk of childhood cancer.

On the basis of all these results it is unlikely that there is a greatly increased risk of childhood cancer attributable to intramuscular vitamin K given to newborns, if indeed there is any risk at all.

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Susceptibility Factors

High doses of vitamin K can cause relapses in patients with thrombosis and myocardial infarction treated with dicoumarol (33).

Drug Administration

Drug formulations

In a worldwide post-marketing surveillance program a conventional formulation of phytomenadione (Konakion), which contains Cremophor EL (polyethoxylated castor oil), was compared with a new mixed micellar formulation (Konakion MM) (34). During 1974–95 an estimated 635 million adults and 728 million children were given Konakion or Konakion MM. Of the 404 adverse events reported in 286 subjects (see Table 2) 387 (96%) were associated with Konakion, which had 95% of sales. Konakion MM accounted for 4% ($n = 17$) of the reported adverse effects and 5% of sales. Of the 17 adverse events 13 reported with Konakion MM were minor injection site reactions. Overall, 120 of the adverse events were serious, of which 117 (98%) were associated with Konakion. There were 85 probable anaphylactoid reactions (of which six were fatal) with conventional Konakion, compared with one non-fatal anaphylactoid reaction with Konakion MM. During the last 12 months of postmarketing surveillance, there were 14 serious adverse events reported in an estimated 21 million individuals treated with Konakion, but none in the 13 million who received Konakion MM. These results suggest that formulations of phytomenadione that are solubilized with Cremophor EL have a higher profile of adverse events, including anaphylactoid reactions, than the newer mixed micellar formulation Konakion MM.

Drug administration route

A case-control study in 1990 suggested a causal relation between intramuscular administration of vitamin K to neonates and the subsequent development of leukemia (35). Later studies have not been able to confirm this finding (30,36–38), although the results are not sufficiently conclusive to rule out the possibility that there is some risk (29,31).

Rapid intravenous administration of vitamin K can cause facial flushing, sweating, fever, a rise in blood pressure, a feeling of constriction in the chest, and cyanosis. Cases of cardiovascular collapse after intravenous injection of phytomenadione and phytonadione have been reported (39). Intravenous injection of phytomenadione is recommended to be performed slowly at a rate not exceeding 5 mg/minute.

The safety and efficacy of intravenously administered phytonadione have been retrospectively studied in patients taking long-term oral anticoagulants (40). Of 105 patients, 85 initially received intravenous phytonadione 0.5–1 mg,

Table 2 The distribution of 404 adverse events associated with phytomenadione in 286 patients, by system; the figures in parentheses refer to serious adverse events

System	Konakion (Cremophor EL)	Konakion (mixed micelles)	Total	% of total ($n = 404$)
General disorders	83 (37)	2 (1)	85 (38)	21.0
Cardiovascular				
Heart rate and rhythm disorders	31 (10)	1 (0)	32 (10)	7.9
Vascular	18 (11)		18 (11)	4.5
Extracardiac	8 (3)		8 (3)	2.0
Myocardial, endocardial, pericardial and valve disorders	1 (1)		1 (1)	0.2
Respiratory	31 (15)	1 (1)	32 (16)	7.9
Nervous system				
Central nervous and peripheral nervous systems	10 (4)		10 (4)	2.5
Autonomic nervous system	3 (0)		3 (0)	0.7
Sensory systems				
Hearing and vestibular disorders	2 (0)		2 (0)	0.5
Endocrine, metabolic, nutritional	1 (0)		1 (0)	0.2
Hematologic				
Erythrocyte disorders	3 (1)		3 (1)	0.7
Leukocyte and reticuloendothelial system disorders	2 (2)		2 (2)	0.5
Platelet, bleeding, and clotting disorders	5 (2)		5 (2)	1.2
Liver, biliary	14 (3)		14 (3)	3.4
Gastrointestinal	14 (2)		14 (2)	3.4
Urinary system	3 (3)		3 (3)	0.7
Skin	90 (9)	5 (0)	95 (9)	23.5
Musculoskeletal	2 (1)		2 (1)	0.5
Neonates and infants	13 (7)		13 (7)	3.2
Application site disorders	53 (6)	8 (1)	61 (7)	15.1
Total	387 (117)	17 (3)	404 (120)	100%

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and 29 received a second dose. Only two of the 105 patients had suspected adverse reactions to phytonadione. Both were men with prior lung disease (one with an adenocarcinoma and one with chronic obstructive lung disease) and were to receive a 0.5 mg dose of phytonadione. During the phytonadione infusion both patients developed dyspnea and chest tightness, which resolved within 15 minutes of stopping the infusion; neither patient had hypotension.

Drug–Drug Interactions

Warfarin

An interaction of warfarin with a nutritional supplement containing vitamin K has been reported (41).

- A 72-year-old man taking warfarin (42.5 mg/week) to prevent thromboembolism related to atrial fibrillation/flutter wanted to take an over-the-counter nutritional supplement containing vitamin K (Nature's Life Greens, a blend of more than 20 herbs). He was instructed to withhold two doses of warfarin. Two weeks later he had an INR of 1.68; however, he had missed three doses of warfarin within the previous 10 days because of cataract surgery. Two weeks later his INR was 3.34. The warfarin dosage was reduced from 42.5 to 40.5 mg/week and the INR was in the target range 2 weeks later.

This report underlines the need for monitoring the use of nutritional and herbal products in patients taking warfarin.

Ubidecarenone (coenzyme Q10; ubiquinone-10) is chemically closely related to phytonadione. It is also widely available as a non-orthodox over-the-counter product, and several patients have been described in whom a reduced effect of warfarin was observed after the addition of non-orthodox ubidecarenone (42,43).

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Vitamins

See also Individual agents

General Information

Vitamins are essential organic substances, usually obtained from food. They are required by humans in amounts ranging from micrograms to milligrams per day. The fat-soluble vitamins are:

- vitamin A (carotenoids)
- vitamin D (calciferols)
- vitamin E (tocopherols and tocotrienols)
- vitamin K

The water-soluble vitamins include:

- vitamin B_1 (thiamine, aneurin)
- vitamin B_2 (riboflavin)
- vitamin B_3 (niacin)
- vitamin B_5 (pantothenic acid)
- vitamin B_6 (pyridoxine)
- vitamin B_7 (folic acid)
- vitamin B_{10} (biotin)
- vitamin B_{12} (cobalamins)
- vitamin C (ascorbic acid)

The vitamins are chemically heterogeneous, but all are essential for normal growth, development, and maintenance of the human organism (1). They cannot be synthesized by the organism itself, with the exception of vitamin D, and have to be supplied externally. The main indications for vitamin supplementation are threatening or manifest deficiency states.

The word "vitamin" itself is a misnomer, created in 1911 by one of the early nutrition researchers, the Polish biochemist Casimir Funk (1884–1967). He knew that the substances he was trying to identify were not necessarily "amines," but felt that because of the great public health importance of these newly identified substances, a name was needed "that would sound well and serve as a 'catch word'" (2). His choice proved successful; the label "vitamin" has proved to have extraordinary appeal.

Vitamins are not infrequently used by medical workers as placebos against poorly defined general malaise, often without consideration of the patient's actual vitamin status (3). Self-medication with vitamin supplements is very common in most countries, and commonly the users are not objectively vitamin deficient (4). In general, physicians in an industrialized society can expect that about half of their adult patients will currently be taking vitamin supplements (5); among athletes 75% have been found to use supplements (6).

As micronutrient deficiencies more or less ceased to be a large public health problem in Western countries, the attention of scientists and manufacturers turned towards the many other functions that vitamins have in human metabolism. For the last several decades, pharmacological doses of most vitamins have been claimed to be of therapeutic value in a wide variety of conditions, which have only a superficial resemblance to the classic vitamin deficiency syndromes. The literature on which many of these claims are based unfortunately often consists of poorly conducted clinical trials or anecdotal reports. Properly designed studies are relatively few in number. No authoritative body has proposed quantitative recommendations or reference values for public health policy.

Reference values for vitamins

In the early 1990s European nutritionists, in the light of an increasing body of evidence, changed the nomenclature with regard to what used to be called the Recommended Dietary Allowance (RDA), Recommended Daily Intake (RDI), or Nutrient Reference Value (NRV) (7). When in 1993 the Scientific Committee for Food of the European Communities published a report entitled "Nutrient and Energy Intakes for the European Community" (8), a new approach was introduced, allowing for more flexibility in regard to quantitative values. Based on what is known about the Average Requirement (AR) for a nutrient in a population, and assuming a normal distribution of requirements, a value two standard deviations above the Average Requirement is called the Population Reference Intake, a dose at which deficiency of the micronutrient is probable in under 2.5% of any population. Similarly, a value two standard deviations below the Average Requirement, called the Lowest Threshold of Intake, denote a dose at which the probability of deficiency in a population is almost 97.5%. These values are given in Table 1. In the USA, the National Academy of Sciences has a different procedure and nomenclature (9). Each vitamin is treated separately and the reports of expert panels are published separately as they become available. US Dietary Reference Intakes commonly establishes four levels of reference values, including a Tolerable Upper Intake, which is the dose of greatest interest in the context of adverse effects. Values of Tolerable Upper Intake have also been recommended by

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Table 1 Daily vitamin requirements for adults (men; women in parentheses if different)

Vitamin	Lowest Threshold of Intake	Average Requirement	Population Reference Intake	Tolerable Upper Intake
Vitamin A (carotenoids; micrograms RE)	300 (250)	500 (400)	700 (600)	3000
Vitamin B_1 (thiamine; micrograms/MJ)	50	72	100	–
Vitamin B_2 (riboflavin; micrograms)	0.6	1.3 (1.1)	1.6 (1.3)	–
Vitamin B_3 (niacin; mg/MJ)	1.0	1.3	1.6	8
Vitamin B_6 (pyridoxine; micrograms/g protein)	–	1.3	1.5	25
Vitamin B_7 (folic acid; micrograms)	160	230	300	1000
Vitamin B_{12} (cobalamins; micrograms)	0.6	1.0	1.4	–
Vitamin C (ascorbic acid; mg)	32	46	60	1000
Vitamin D (ergocalciferol; micrograms)	–	–	5–10	50

the European Commission's Scientific Committee on Food [http://europa.eu.int/comm/food/fs/sc/scf/out80_en.html].

Drug Administration

Drug overdose

The symptoms that are commonly reported in vitamin overdose are listed in Table 2.

Table 2 Notable symptoms reported with chronic and acute vitamin overdosage (SEDA-13, 345) (6,10)

Vitamin	Adverse effects
Vitamin A	Hypercarotenosis
	Increased intracranial pressure
	Headache
	Sleep disturbances
	Nausea, vomiting, diarrhea
	Chronic liver disease
	Dry skin, fissures, depigmentation, and pruritus
	Alopecia
	Bone tenderness
	Teratogenesis (renal and nervous system)
Vitamin B_3 (niacin)	Hypotension
	Dysrhythmias
	Headache
	Hyperglycemia
	Hyperuricemia, gout
	Peptic ulcer
	Hepatotoxicity
	Skin flushing
	Pruritus
	Alopecia
Vitamin B_6 (pyridoxine)	Peripheral sensory neuropathy
	Ataxia
Vitamin C	Impairment of work at high altitudes
	Gastrointestinal symptoms
	Oxalate stones in predisposed persons
	Possible teratogenesis and carcinogenesis in very high doses
Vitamin D	Hypertension
	Hypercalcemia
	Metastatic calcification
	Bone demineralization
	Renal calcinosis and kidney failure
Vitamin E	Increased action of warfarin
Vitamin K	Hemolytic anemia
	Neonatal jaundice

There is widespread and easy availability of high-dose single and multiple vitamin formulations, often presented as food supplements. This creates a potential for chronic or sporadic intake of high doses of vitamins and the occurrence of unanticipated adverse effects (11,12). The cases often involve children, who may be specially vulnerable to the effects of overdosage. The Canadian Paediatric Society's Nutrition Committee in 1990 issued a warning to physicians, based on an estimate that as many as 10% of healthy Canadian children were being exposed to vitamin polypharmacy and a substantial risk of accidental overdose (13).

According to some authors, the increased accessibility and use of high-dose vitamin formulations has been encouraged by the multi-million-dollar health food industry, increased emphasis placed by physicians on more "natural" approaches to disease treatment, a population of consumers interested in so-called "holistic medicine," and the marketing of these formulations in many countries without regulatory control. In therapeutic use, the physician has to keep in mind the benefit to harm balance of using high-dose vitamin supplements for disorders in which proof of efficacy is lacking (14).

Since vitamin overdose can produce unexpected, often vague, signs and symptoms, physicians should ask patients who present with inexplicable symptoms, including those listed in Table 2 (15), about their use of unusual or unapproved therapies, including vitamins in megadoses (10). It has been suggested that a medical history is not complete without vitamin/mineral supplement information (6).

Food fortification and "designer foods" specially formulated to prevent chronic diseases are enthusiastically advocated by the vitamin industry and its proponents (16). Unrestrained vitamin fortification added to unrestrained supplementation with these substances has now in some countries led to the potential for rather high cumulative amounts of intake in some populations. There is growing concern about the safety of chronically high doses of some of these, where the therapeutic margin between deficiency and toxicity may not be all that wide (15,17–19).

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Voriconazole

See also Antifungal azoles

General Information

Voriconazole is a triazole that is structurally related to fluconazole. It has two interesting properties, activity against *Aspergillus* species and sufficient solubility in water to be administered parenterally. It is active against a wide spectrum of clinically important fungi, including *Candida* species, *Trichosporon beigelii*, *Cryptococcus neoformans*, *Aspergillus* species, *Fusarium* species, and other hyaline, dematiaceous, and dimorphic molds (1,2). It has demonstrated efficacy in various animal models of invasive fungal infections (1,2).

Pharmacokinetics

Voriconazole has a half-life of about 6 hours and undergoes complex hepatic metabolism. There is wide intersubject variability in the disposition of voriconazole, which is at least partly related to a CYP2C19 polymorphism. Voriconazole has the potential for drug–drug interactions mediated by CYP3A4, CYP2C9, and CYP2C19.

The kinetics of voriconazole are non-linear, as shown in 42 healthy men (3). Two groups of subjects participated. Group 1 ($n = 28$) took part in two study periods, each consisting of 14 days separated by a minimum 7-day washout period. During one of the periods, 14 subjects received intravenous voriconazole 6 mg/kg bd on day 1 followed by 3 mg/kg bd on days 2–7 and were then switched to 200 mg bd orally on days 8–14. During the other period, they received 6 mg/kg bd intravenously on day 1 followed by 5 mg/kg bd on days 2–7 and were then switched to 400 mg orally bd on days 8–14. The other 14 subjects in group 1 received a matching placebo throughout the study. In group 2 ($n = 14$), 7 subjects received 6 mg/kg intravenously bd on day 1 followed by 4 mg/kg bd on days 2–7 and were then switched to 300 mg bd orally on days 8–14. The other seven received a matching placebo. Voriconazole had non-linear pharmacokinetics, attributed to saturable metabolism. For intravenous dosing, a 1.7-fold increase in dose resulted in 2.4- and 3.1-fold increases in C_{max} and AUC respectively; a two-fold increase in oral dosing resulted in 2.8- and 3.9-fold increases in C_{max} and AUC respectively. The mean C_{max} after oral dosing was 63–90% of the intravenous C_{max}. After the switch from intravenous to oral dosing, most subjects achieved steady state by day 4. Voriconazole was well tolerated; the most commonly reported adverse events were mild to moderate headache, rash, and abnormal vision. Visual function tests conducted on all subjects detected no further abnormalities during voriconazole treatment and one abnormality (abnormal color vision test) during placebo treatment. All visual disturbances were mild to moderate in intensity, and all resolved spontaneously within 2 days of onset. No subject in any treatment group had a serious adverse event.

Observational studies

The efficacy of voriconazole has been demonstrated in non-comparative phase I/II studies in patients with oropharyngeal and esophageal candidiasis and acute and chronic invasive aspergillosis (4). In phase III clinical trials, it was superior to conventional amphotericin for first-line therapy of invasive aspergillosis and yielded comparable success rates but less proven and probable breakthrough infections compared with liposomal amphotericin as empirical antifungal therapy in patients with persistent neutropenia (5).

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Voriconazole had excellent clinical efficacy in a non-comparative phase I/II studies in patients with oropharyngeal and esophageal candidiasis and acute and chronic invasive aspergillosis (6).

In an open, non-comparative, multicenter study in immunocompromised patients with proven or probable invasive aspergillosis, 116 patients were treated with intravenous voriconazole 6 mg/kg bd twice and then 3 mg/kg bd for 6–27 days, followed by 200 mg bd orally for up to 24 weeks; voriconazole was given as primary therapy in 60 (7). There were good responses in 56; 16 had a complete response and 40 a partial response; there was a stable response in 24 patients. There were adverse events in 91% of the patients who received at least one dose of voriconazole, but only 15% were attributed to the drug. The most common adverse events attributed to voriconazole were skin rash (8.7%), reversible visual disturbances (11%), and raised liver function tests (15%). There was evidence of a concentration-dependent incidence of adverse events: six of seven patients with voriconazole plasma concentrations over 10 μg/ml developed adverse events requiring drug withdrawal.

Comparative studies

Amphotericin

Voriconazole has been compared with liposomal amphotericin for empirical antifungal therapy in a randomized, international, multicenter trial in 837 patients (415 assigned to voriconazole, 4 mg/kg bd (6 mg/kg bd on day 1) and 422 to liposomal amphotericin, 3 mg/kg/day) (8). The overall success rates were similar (26% with voriconazole and 31% with liposomal amphotericin); however, there were significantly fewer documented breakthrough fungal infections in patients who received voriconazole (8 versus 21). Those who received voriconazole had fewer severe infusion-related reactions, less mild nephrotoxicity, as defined by increases in serum creatinine to over 1.5 times baseline, and less hypokalemia; however, there was no difference whatsoever in the proportion of patients with more profound renal compromise (increased serum creatinine to over 2.0 times baseline; 7.0 versus 7.6%). The incidence of hepatotoxicity, as measured by raised hepatic transaminases and alkaline phosphatase, was similar in the two groups; increased serum bilirubin to over 1.5 times baseline was more common in patients who took amphotericin. Patients who received voriconazole had more episodes of transient visual changes than those who received liposomal amphotericin (22 versus 1%) and more episodes of visual hallucinations (4.3 versus 0.5%). Parenteral voriconazole was changed to the oral formulation in 22%, with a reduction in the mean duration of hospitalization by 1 day in all patients but by 2 days in patients at high risk (with relapsed leukemia or after allogeneic bone marrow transplant). Toxicity or lack of efficacy caused 9.9% of those who received voriconazole and 6.6% of those who received amphotericin to withdraw.

In a comparative, randomized, unblinded trial for primary therapy of invasive aspergillosis, 144 patients received either intravenous voriconazole (6 mg/kg bd on day 1, then 4 mg/kg bd for at least 7 days) followed by 200 mg bd orally, and 133 received intravenous amphotericin deoxycholate (1–1.5 mg/kg/day); other licensed antifungal treatments were allowed if the initial therapy failed or if the patient had an intolerance to the first drug used (9). Most patients had allogeneic hemopoietic cell transplants, acute leukemia, or other hematological diseases. At week 12, 53% of the patients in the voriconazole group and 32% of those in the amphotericin group (difference = 21%; 95% CI = 10, 33%) had a successful outcome. The survival rate at 12 weeks was 71% in the voriconazole group and 58% in the amphotericin group (hazard ratio = 0.59; 95% CI = 0.40, 0.88). Transient visual disturbances were more common with voriconazole (45 versus 4.3%). The most frequent descriptions of such disturbances were blurred vision, altered visual perception, altered color perception, and photophobia. Of the patients who received voriconazole, 9% had hallucinations or confusion considered possibly related to the drug compared with 3.7% of those who received amphotericin. Infusion-related reactions (fever, chills, or both) were more common in those who received amphotericin (3.1 versus 25%), as were severe, potentially related adverse events (13 versus 24%); the most frequent events were renal impairment (14%) in those who received amphotericin and liver function abnormalities (4.8%) in those who received voriconazole.

Other antifungal azoles

In a multicenter, randomized, double-blind, double-dummy, parallel-group, dose-escalation comparison with fluconazole, the safety, tolerability, and pharmacokinetics of oral voriconazole were investigated in 24 subjects at high risk of fungal infections (with hematological malignancies, solid tumors, or autologous bone marrow transplants) (10). The subjects were randomized to receive voriconazole 200 mg bd ($n = 9$), voriconazole 300 mg bd ($n = 9$), or fluconazole 400 mg od ($n = 6$) for 14 days. There was an approximate five-fold accumulation of voriconazole during the dosing period and evidence of non-linear pharmacokinetics. Voriconazole was generally safe and well tolerated. Mild, reversible visual disturbances were the most commonly reported adverse events but they were not associated with treatment withdrawal. No patient developed a breakthrough fungal infection.

The efficacy, safety, and tolerability of voriconazole and fluconazole have been compared in 391 immunocompromised adults with esophageal candidiasis in a randomized, double-blind, multicenter trial (11). Most of the patients (94%) had AIDS. Following randomization, they took either voriconazole (200 mg bd) or fluconazole (400 mg on day 1 followed by 200 mg od) for a median of 14 or 15 days respectively. Treatment was continued for 7 days after the resolution of all signs and symptoms but was not allowed to exceed 42 days. The two drugs achieved comparable success rates (98% voriconazole, 95% fluconazole), as assessed by esophagoscopy in the primary efficacy analysis in 256 patients. More patients discontinued voriconazole because of laboratory test abnormalities (3.5 versus 1%) or treatment-related adverse events (2.5 versus 0.5%). The most frequent

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adverse event with voriconazole was transient visual disturbances (23 versus 8%); other clinical adverse events were similar in frequency. Increases of over three times the upper limit of the reference range in aspartate transaminase (20 versus 8%), alanine transaminase (11 versus 7%), and alkaline phosphatase (10 versus 8%) were more frequent with voriconazole.

Organs and Systems

Sensory systems

Visual adverse events, in particular enhanced brightness of light and color, are common with voriconazole (11). These visual adverse effects are transient and reversible. So far, comprehensive ophthalmological investigations have not shown any morphological correlates or long-term visual sequelae in any patient.

Liver

Liver function test abnormalities in patients taking voriconazole are not unexpected for an azole and can be explained by its extensive hepatic metabolic clearance (12).

Susceptibility Factors

Age

Although the disposition of voriconazole in children aged 12 years and over is similar to that in adults, children aged 2–11 years need larger dosages to achieve the same exposure that was effective in interventional trials in adults (13).

The safety and efficacy of voriconazole have been studied in 58 children (aged 9 months to 15 years; median 7 years) who were treated in the manufacturer's compassionate release program (14). They received voriconazole for an invasive fungal infection if they were refractory to or intolerant of conventional antifungal drugs. Voriconazole was given intravenously as a loading dose of 6 mg/kg every 12 hours on day 1 followed by 4 mg/kg every 12 hours thereafter. When feasible, the route of administration was changed from intravenous to oral (100 or 200 mg bd for patients weighing under or over 40 kg, respectively). At the end of therapy (mean 93 days, range 1–800), 26 patients had a complete or partial response, 4 had a stable response, 25 failed therapy, and 4 were withdrawn because of intolerance of voriconazole. Two had treatment-related serious adverse events (ulcerated lips with rash and raised hepatic transaminases or bilirubin). A total of 23 patients had voriconazole-related adverse events, three of which required withdrawal of voriconazole. The most commonly reported adverse events included raised hepatic transaminases or bilirubin ($n = 8$), skin rashes ($n = 8$), abnormal vision ($n = 3$), and a photosensitivity reaction ($n = 3$). The authors concluded that these data support the use of voriconazole for invasive fungal infections in children who are intolerant of or refractory to conventional antifungal drugs.

Drug–Drug Interactions

Ciclosporin

The interaction of voriconazole with ciclosporin has been investigated in a randomized, double-blind, placebo-controlled, crossover study in kidney transplant recipients with stable renal function (15). During the first study period (7.5 days), subjects taking ciclosporin 150 mg/day received either concomitant voriconazole (200 mg every 12 hours) or a matching placebo. After a washout period of at least 4 days, they were switched to the other treatment. In the seven subjects who completed both regimens, concomitant administration with voriconazole resulted in a 1.7-fold increase (90% CI = 1.47, 1.96) in mean ciclosporin AUC during a dosage interval. Ciclosporin C_{max} and t_{max} were not significantly affected, but C_{min} was increased by voriconazole by a mean of 2.48 (range 1.88–3.03) times. Seven subjects withdrew during voriconazole administration, six for reasons that were considered to be drug-related; most were attributable to increased ciclosporin concentrations. Although not serious, all causality-related adverse events were more frequent during voriconazole administration than during placebo administration. Thus, when voriconazole is initiated or withdrawn in patients who are already taking ciclosporin, blood ciclosporin concentrations should be carefully monitored and the dose of ciclosporin adjusted as necessary.

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Wound dressings, substances used in

General Information

Substances that are used in wound dressings include hydrogels, hydrocolloids, alginates, and polyurethane foams. Medicaments that they contain include wool wax alcohols (amerchol, cetearyl alcohol, propylene glycol), plant resins/ethereal oils (balsam of Peru, colophony, fragrance mix, propolis), and topical antibiotics.

Organs and Systems

Immunologic

Patients with chronic venous insufficiency and venous leg ulcers are at risk of sensitization to topical medications. The frequency of sensitization in these patients is up to 67% (1). In a study using an expanded European standard series and 20 different wound dressings for patch-testing in 36 patients with chronic venous insufficiency, sensitization to modern wound dressings was found in 8.3% (three cases) and was caused by propylene glycol as an ingredient of hydrogels (2). However, it must be emphasized that positive patch test reactions to propylene glycol can indicate irritation rather than contact allergy. There were no cases of sensitization to hydrocolloids, alginates, or polyurethane foams. The rank order of allergens was headed by ointment bases (sensitization to wool wax alcohols in 33% of patients; amerchol 19%; cetearyl alcohol 14%; propylene glycol 8.3%), followed by plant resins/ethereal oils (balsam of Peru 22%; colophony 14%; fragrance mix 8.3%; propolis 5.6%), and topical antibiotics (neomycin sulfate 17%; chloramphenicol 14%) (3).

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WR-242511

General Information

WR-242511 is an 8-aminoquinoline that is being tested for activity against *Pneumocystis jiroveci* (1). In animals, it was more likely than primaquine to cause methemoglobinemia (SEDA-12, 703) (2).

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WR-243251

General Information

WR-243251 is a floxacrine analogue, a dihydroacridinedione. It is active in vitro against chloroquine-resistant, mefloquine-resistant, and pyrimethamine-resistant strains of malaria (1). By analogy to quinacrine and floxacrine, there is concern about possible dermatological, cardiac, and neuropsychiatric toxicity and vascular adverse effects.

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Xamoterol

See also Beta-adrenoceptor antagonists

General Information

Xamoterol is a beta-adrenoceptor antagonist/partial agonist that was developed for use in mild cases of cardiac failure and to treat atrial fibrillation (1). In more severe cases, however, it can actually worsen heart failure and increase mortality (2), because when sympathetic nervous system activity is high its beta-adrenoceptor antagonist properties predominate. It has therefore been withdrawn from the market (SEDA-18, 159).

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Xenon

See also General anesthetics

General Information

Xenon is a heavy gas (symbol Xe; atomic no 54) that is normally present in the atmosphere. It has been used as an anesthetic and as a diagnostic tool in functional neuroimaging (1).

Xenon has many characteristics of the ideal anesthetic (2). It has no effects on the cardiovascular system and has low solubility, enabling faster induction of and emergence from anesthesia. Although its high cost limits its use, the development of closed rebreathing systems has led to further interest. A European multicenter trial is under way.

Xenon-enhanced CT scanning in functional neuroimaging is based on the use of stable xenon gas, which is radiodense and lipid-soluble, as an inhaled contrast agent. The patient inhales a mixture of xenon, usually 26–33%, and oxygen for several minutes via a face mask. The inhaled xenon dissolves in the blood and passes into the brain parenchyma. CT scans can be acquired before, during, and after inhalation. Fast spiral CT has improved the capability of this technique.

General adverse reactions

Overall, about 10% of patients have unpleasant but usually transient adverse reactions. Xenon is a narcotic gas, more potent than nitrous oxide, and inhalation of 71% xenon is sufficient for anesthesia in 50% of patients. Lower concentrations of xenon are currently used, but some euphoric or dysphoric effects are still observed and can cause temporary exacerbation of neuropsychiatric symptoms. Mild nausea can also occur, and patients should have an empty stomach before the scan to reduce the risk of vomiting and possible aspiration. Very rarely, apnea can occur and can be reversed by instructing the patient to breathe. Like other narcotic gases, xenon causes mild cerebral vasodilatation.

Organs and Systems

Psychological, psychiatric

The subjective, psychomotor, and physiological properties of subanesthetic concentrations of xenon have been studied in 10 volunteers (3). Xenon sedation was well tolerated and was not associated with any adverse physiological effects. In particular, there was no nausea or vomiting. It was preferred to sedation with nitrous oxide and was subjectively dissimilar (xenon was more pleasant).

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Xipamide

See also Diuretics

General Information

Xipamide is a non-thiazide diuretic that acts mainly on the distal tubule (1). Its maximal diuretic effect is as great as that of furosemide, but its duration of action is longer and similar to that of the thiazides. Thus, like metolazone, it occupies an intermediate position between the two main groups of diuretics and can be used in renal insufficiency. However, xipamide does appear to present some risks, and it is not clear that these are outweighed by any advantages.

Organs and Systems

Metabolism

At equivalent therapeutic doses, the metabolic effects of xipamide are greater than those of the thiazides or furosemide (SED-11, 200).

Skin

A photoallergic skin reaction has been described in a patient taking xipamide (SEDA-16, 222).

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Yellow fever vaccine

See also Vaccines

General Information

Yellow fever vaccine contains the 17D virus strain grown in chick embryo tissue. The older (Dakar) yellow fever vaccine was prepared from more virulent material and often caused encephalitis, the risk in children being particularly high (SED-8, 712).

General adverse effects

The adverse effects of yellow fever vaccine have been documented by an expert group of the WHO (1).

Apart from minor postimmunization reactions the most common adverse effects are on the nervous system and allergic reactions.

On about the sixth day after immunization, under 5% of vaccinees develop fever, headache, and backache, lasting for 1–2 days.

Organs and Systems

Nervous system

About 20 cases of encephalitis have been recorded over a period of 40 years (SEDA-14, 1097). They all occurred in children: 12 in infants under 4 months old, two at 4 months, one at 6 months, one at 7 months, and one at 3 years of age. The last mentioned case was the only fatal one (17D virus was isolated from the brain), all the others recovered fully.

Encephalitis occurred after yellow fever immunization in a child older than 3 years of age and one over 9 months; a 13-year-old boy developed the disease 1 week after receipt of vaccine (2). The patient recovered after 1 month. There have been reports of encephalitis in a 29-year-old man and meningoencephalitis in two adults, suspected to be caused by the 17D yellow fever vaccine (3,4).

A case report of provocation of multiple sclerosis was published in 1967 (5), but this has not been confirmed.

Immunologic

Rash, erythema multiforme, urticaria, angioedema, and asthma occur infrequently, predominantly in people with a history of allergy, especially to eggs (1).

Severe immediate hypersensitivity reactions (type 1), sometimes accompanied by anaphylactic shock and circulatory collapse, have been described very rarely (1). Allergic reactions of the Arthus phenomenon type, characterized by local swelling and necrosis following less than 24 hours after immunization, have occurred in rare instances. Some of these cases have been fatal.

Two episodes have been reported from the Ivory Coast (1974) and Ghana (1982) (1). In the Ivory Coast, there were 39 cases of severe reactions with eight deaths following a mass campaign, in which 730 000 persons were immunized. The clinical features were uniform: a few hours after immunization the vaccinees developed signs of local inflammation. In severe cases, edema and inflammation were followed by cardiovascular collapse. Bacterial contamination could have been the cause: during the campaign, five-dose vaccine ampoules were pooled to prepare 50 and 100 doses for use in jet injectors. In Ghana, six vaccinees developed fulminant reactions 2–6 hours after immunization, including two deaths. The clinical features resembled those in the Ivory Coast episode. In 2001, during a mass vaccination campaign against yellow fever in Abidjan, the Ivory Coast, more than 2.6 million doses were administered and 87 adverse events were notified, of which 41 were considered to be vaccine-related. There was one case of anaphylaxis and 26 cases of urticaria, five of which were generalized (6).

People who are known to be suffering from allergy must be tested intradermally before immunization.

Multiorgan failure

There have been reports of seven cases of serious adverse events (including six deaths) after yellow fever immunization (7–11). The cases occurred from 1996 to 2001 in Australia ($n = 1$), Brazil ($n = 2$), and the USA ($n = 4$). The two people in Brazil were immunized with vaccine containing the live attenuated 17DD yellow fever strain and the others received vaccine containing the live attenuated 17D-204 strain; both strains are derived from the original 17D vaccine strain. All seven became ill within 2–5 days after immunization and required intensive care. Illness was characterized by fever, lymphocytopenia, thrombocytopenia, raised hepatocellular enzymes, hypotension, and respiratory failure. Most also had headache, vomiting, myalgia, hyperbilirubinemia, and renal insufficiency requiring hemodialysis. In some aspects the disease was similar to natural yellow fever. The causal association between multiorgan failure and the receipt of yellow fever vaccine is supported in most cases by isolation of the vaccine virus and histopathological changes; in cases with lack of specimens the temporal association and the similarity of the clinical presentations makes a causal association likely.

Susceptibility Factors

Age

Infants under 9 months old are not generally immunized, except if they live in rural areas with a history of yellow fever epidemics (immunization at 6 months) or in an active epidemic focus (immunization at 4 months) (1).

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Yohimbine

General Information

Yohimbine is a major carboline alkaloid in the bark of *Pausinystalia* species, such as *Pausinystalia yohimbe* (*Corynanthe yohimbe*), *Pausinystalia macrocerus*, *Pausinystalia paniculata*, and *Pausinystalia trilles*i. It is also found in *Pseudocinchona africana* and *Rauwolfia canescens*.

Yohimbine is an alpha$_2$-adrenoceptor antagonist and has been used in the treatment of erectile dysfunction. At high doses its most common effects are increased blood pressure, slight anxiety, and increased frequency of micturition (1). In a systematic review of randomized controlled trials (2), the following adverse events were noted: hypertension, allergic skin reactions, anxiety, dizziness, chills, headache, sweating, agitation, tachycardia, gastrointestinal symptoms, diarrhea, loss of energy, and increased urinary frequency.

Organs and Systems

Cardiovascular

In 25 unmedicated subjects with hypertension yohimbine 22 mg increased mean blood pressure by an average of 5 mm Hg, plasma noradrenaline by 66%, and plasma dihydroxyphenylglycol by 25% at 1 hour after administration (3). The magnitude of the pressor response was unrelated to baseline pressure but correlated positively with baseline noradrenaline concentration and with the yohimbine-induced increment in plasma noradrenaline.

In 25 healthy volunteers and 29 sex- and age-matched untreated hypertensive patients yohimbine 10 mg caused a significant increase in diastolic pressure only in the hypertensive patients (4).

In patients taking tricyclic antidepressants, hypertension can occur at a dose of 4 mg tds. The toxicity of yohimbine can be enhanced by other drugs, such as phenothiazines.

Angina pectoris has been attributed to yohimbine (5).

- A patient with CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) paradoxically experienced worsening of Raynaud's phenomenon when using yohimbine for erectile dysfunction (6).

Respiratory

Bronchospasm has been attributed to yohimbine (7).

Nervous system

In a double-blind, placebo-controlled study in eight patients receiving methadone, yohimbine 4 mg/kg intravenously caused objective and subjective opioid withdrawal symptoms and increased craving for opioids (8). This was attributed to increased sensitivity of postsynaptic responses to noradrenaline.

Sensory systems

In a placebo-controlled, crossover study in seven healthy subjects oral yohimbine 0.4 mg/kg caused a significant but transient reduction in P50 auditory gating (9).

Psychological, psychiatric

Yohimbine commonly causes anxiety; in eight patients with panic disorder this effect was reduced by fluvoxamine (10).

Manic symptoms have been attributed to yohimbine (11).

In a placebo-controlled study in 18 combat veterans with post-traumatic stress disorder and 11 healthy controls, intravenous yohimbine 0.4 mg/kg significantly increased the amplitude, magnitude, and probability of the acoustic startle reflex (used as a model to investigate the neurochemical basis of anxiety and fear states) in the veterans with post-traumatic stress disorder but not in the controls (12).

Hematologic

Agranulocytosis has been attributed to yohimbine (13).

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Immunologic

A lupus-like syndrome in conjunction with generalized erythroderma and progressive renal insufficiency has been attributed to yohimbine (14,15).

Drug Administration

Drug overdose

- In a 62-year-old man who took yohimbine 200 mg the only adverse effects were tachycardia, hypertension, and anxiety of brief duration (16).

This case suggests that yohimbine overdose is relatively benign.

- A 16-year-old girl who took yohimbine in the form of an alleged aphrodisiac known as "yo-yo" had an acute dissociative reaction accompanied by weakness, paresthesia, and incoordination, followed by anxiety, headache, nausea, palpitation, and chest pain; she also had hypertension, tachycardia, tachypnea, sweating, pallor, tremor, and an erythematous rash (17). Serum adrenaline and noradrenaline concentrations were raised. Her symptoms lasted about 36 hours and resolved spontaneously.

Drug–Drug Interactions

Phenytoin

Yohimbine can cause loss of the antiepileptic action of phenytoin (2).

Tricyclic antidepressants

Yohimbine has a sialogenic effect in depressed patients with a dry mouth due to tricyclic antidepressants or neuroleptic drugs (18).

However, there is an increased risk of hypertension when tricyclic antidepressants are combined with yohimbine (19).

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Zafirlukast

See also Leukotriene receptor antagonists

General Information

Zafirlukast is a leukotriene receptor antagonist, used in the treatment of asthma.

Organs and Systems

Liver

In the early clinical trials a range of doses of zafirlukast were used. With higher doses (80 mg bd) serum liver enzymes were occasionally raised. In subsequent clinical trials with 20 mg bd, a raised alanine transaminase activity was twice as common as in patients taking placebo (1).

Sporadic cases of severe hepatotoxicity (2–4), requiring orthotopic liver transplantation for subacute liver failure in two cases (5), prompted a revision of the "Adverse Events" section in the Physicians' Desk Reference (6).

Hepatitis has been attributed to zafirlukast in two cases.

- A 54-year-old asthmatic man developed subacute hepatitis and hepatic encephalopathy while taking zafirlukast 20 mg bd for 8 months and co-amoxiclav 2 g/day for a few days (3). He also took antihistamines, inhaled glucocorticoids, and beta-blockers (not specified). A percutaneous liver biopsy showed severe hepatocellular necrosis and eosinophilic infiltrates without prominent cholestasis. Raised transaminases and total serum bilirubin normalized within 3 months after withdrawal of zafirlukast and co-amoxiclav and the use of intermittent, high-dose, parenteral glucocorticoids, followed by oral tapering.
- A 55-year-old asthmatic woman had subacute liver injury with severe hepatic necrosis and eosinophilic infiltrates while taking zafirlukast 20 mg bd and salbutamol sulfate nasal spray for 5 months (4). There was no evidence of viral, metabolic, alcohol-related, or autoimmune hepatitis. Zafirlukast was withdrawn and liver function normalized within 2 months.

The authors concluded that subacute hepatitis in the second patient had been related to zafirlukast, but suggested that co-amoxiclav might also have been a precipitating factor. The long latency between the start of zafirlukast treatment and the onset of hepatotoxicity and the slow response to drug withdrawal and glucocorticoid treatment are reminiscent of previous cases of zafirlukast-related hepatotoxicity.

Drug–Drug Interactions

Aspirin

The plasma concentrations of zafirlukast rise when it is administered concurrently with aspirin (7).

Macrolide antibiotics

Zafirlukast 20 mg bd for 12 days did not interfere with the metabolism of azithromycin or clarithromycin (8). However, the plasma concentrations of zafirlukast are reduced when it is administered concurrently with erythromycin (7).

Terfenadine

The plasma concentrations of zafirlukast are reduced when it is administered concurrently with terfenadine (7).

Theophylline

The plasma concentrations of zafirlukast are reduced when it is administered concurrently with theophylline (7). Conversely, zafirlukast can increase serum theophylline concentrations.

- A 15-year-old girl with asthma, who had taken theophylline 300 mg bd for several years, with serum concentrations of about 61 μmol/l started to take zafirlukast (9). Her serum theophylline concentration increased to 133 μmol/l. Rechallenge confirmed the effect.

The authors proposed that zafirlukast had inhibited CYP1A2, by which theophylline is metabolized.

Warfarin

Zafirlukast reduces the clearance of warfarin, resulting in a clinically significant prolongation of prothrombin time (10). The mechanism for this interaction is thought to be inhibition of cytochrome P450 enzymes, such as CYP2C9.

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Zalcitabine

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Zalcitabine is a nucleoside analogue reverse transcriptase inhibitor. Because of the high incidence of nervous system adverse effects and the availability of less toxic alternatives, zalcitabine is no longer used.

Comparative studies

Several large-scale studies of the efficacy of combined antiretroviral treatment with zalcitabine and zidovudine in HIV-infected patients (compared with zidovudine monotherapy or a combination of zidovudine and didanosine) have not shown unexpected adverse effects (1–4). The most common adverse effects in patients taking zalcitabine were peripheral neuropathy and aphthous mouth ulcers.

Organs and Systems

Nervous system

A peripheral neuropathy is often observed in patients treated with didanosine, stavudine, and zalcitabine (5,6). It usually occurs after prolonged treatment (more than 4 months), most often with zalcitabine, and often requires drug withdrawal, but it is sometimes not fully reversible. Mitochondrial alterations have been demonstrated in Schwann cells of peripheral nerves and dorsal root ganglia in rabbits treated with zalcitabine (7).

Hematologic

Thrombocytopenia has been observed in patients using zalcitabine and didanosine (8,9).

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Zaleplon

General Information

Zaleplon is a non-benzodiazepine that induces sleep comparable to other hypnotics but with significantly fewer residual effects (1), related at least in part to its short half-life. It is a pyrazolopyrimidine hypnotic that binds selectively to the $GABA_{A1A}$ receptor, previously known as the benzodiazepine type 1 (BDZ_1) receptor. Whereas such agonist selectivity was hoped to confer advantages in terms of the risk of adverse effects, in practice zaleplon is similar to the older non-selective benzodiazepines in terms of both efficacy and safety (2–4). The so-called "Z drugs," including zaleplon, are significantly more expensive than benzodiazepines and are therefore likely to be less cost-effective (5).

Pharmacokinetics

After oral administration zaleplon is well absorbed (71%) and peak concentrations are reached in about 60 minutes. However, it undergoes presystemic elimination and has a systemic availability of about 30%. Its adverse effects include anterograde amnesia, depression, paradoxical reactions (for example restlessness, agitation), dependence, and withdrawal symptoms (related to the dose and duration of treatment). Although the data are limited, it is thought to be relatively safe in overdose, unless it is combined with other CNS depressants.

The pharmacokinetics and absolute oral systemic availability of zaleplon have been assessed in a partially randomized, single-dose, crossover study in 23 healthy subjects, who received intravenous infusions of zaleplon 1 and 2.5 mg during the first and second periods and were

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then randomly assigned to receive an oral dose of 5 mg or an intravenous infusion of 5 mg in a crossover design (6). The oral and intravenous doses of zaleplon were well tolerated. Somnolence, abnormal vision, diplopia, and dizziness were the most commonly reported adverse events.

Pharmacological effects

Initial pharmacodynamic data suggested that sleep latency is improved by zaleplon and there is no significant next-day psychomotor impairment or memory impairment (7), and evaluations at zaleplon peak plasma concentrations show much less impairment than with other hypnotics, suggesting an improved benefit-to-harm balance for zaleplon compared with older agents. However, outcome data are mainly from industry-sponsored trials and are often difficult to compare. Differences between zaleplon and benzodiazepine hypnotics may have been exaggerated (3,4).

Zaleplon can be used to treat symptoms of insomnia with little next-day psychomotor or memory impairment. However, further research is needed.

Comparative studies

A review of published studies of zaleplon has shown that it has a quick onset of action and undergoes rapid elimination, which results in an arguably better safety profile than previously available agents (8). In addition, rebound insomnia and other withdrawal effects have not been demonstrated with zaleplon, and it is well tolerated in both young and older patients. These characteristics may be advantageous for patients who should not receive benzodiazepines.

Placebo-controlled studies

Three doses of zaleplon have been compared with placebo in outpatients with insomnia in a 4-week study (9). During week 1, sleep latency was significantly shorter with zaleplon 5, 10, and 20 mg than with placebo. The significant reduction in sleep latency persisted to week 3 with zaleplon 10 mg and to week 4 with zaleplon 20 mg. Compared with placebo, zaleplon 10 mg and 20 mg also had significant positive effects on sleep duration, number of awakenings, and sleep quality. Pharmacological tolerance did not develop with zaleplon and there were no indications of rebound insomnia or withdrawal symptoms after discontinuation. There was no significant difference in the frequency of adverse events with zaleplon compared with placebo. The authors concluded that zaleplon provides effective treatment of insomnia with a favorable safety profile.

Zaleplon versus triazolam

Zaleplon and triazolam have been compared in two concurrent multicenter, randomized, double-blind, placebo-controlled crossover studies in chronic insomniacs (10). Study 1 compared zaleplon (10 and 40 mg) with triazolam (0.25 mg) and placebo; study 2 compared zaleplon (20 and 60 mg) with triazolam (0.25 mg) and placebo. All doses of zaleplon produced significant reductions in sleep latency, and triazolam 0.25 mg reduced sleep latency comparable with zaleplon 10 mg. Only triazolam and zaleplon 60 mg produced significant increases in total sleep time compared with placebo. Zaleplon 40 and 60 mg and triazolam also reduced the percentage of REM sleep compared with placebo. There was no evidence of residual daytime impairment with zaleplon, but triazolam produced significant impairment in performance on a digit copying test. There were more adverse events with zaleplon 60 mg compared with triazolam 0.25 mg and placebo. The most frequently reported adverse events with all treatments included headache, dizziness, and somnolence.

Zaleplon versus zolpidem

Zaleplon and zolpidem have been compared in two concurrent multicenter, randomized, double-blind, placebo-controlled crossover studies in chronic insomniacs (10). In study 1, zaleplon 10 mg, zolpidem 10 mg, or placebo were given double-blind to 36 healthy subjects under standardized conditions in a six-period, incomplete-block, crossover study (11). The subjects were gently awakened and given the medication at predetermined times, 5, 4, 3, or 2 hours before morning awakening, which occurred 8 hours after bedtime. When they awoke in the morning, subjective and objective assessments of residual effects of hypnotics were administered. There were no serious adverse experiences during the study; all adverse events were mild to moderate. The most commonly reported adverse events associated with zaleplon were weakness and somnolence. Weakness, depersonalization, dizziness, and somnolence were the most frequent nervous system adverse events associated with zolpidem.

Zaleplon has been compared with zolpidem 10 mg and placebo in 615 adult outpatients with insomnia (12). After a 7-night placebo (baseline) period, the patients were randomly assigned to receive one of five treatments in double-blind fashion for 28 nights (zaleplon 5, 10, or 20 mg; zolpidem 10 mg; or placebo), followed by placebo for 3 nights. Sleep latency, sleep maintenance, and sleep quality were determined from sleep questionnaires each morning. Rebound insomnia and withdrawal effects on withdrawal were also assessed. There was no evidence of rebound insomnia or withdrawal symptoms on withdrawal of zaleplon after 4 weeks. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group.

The pharmacokinetics and pharmacodynamics of zaleplon (10 or 20 mg) and zolpidem (10 or 20 mg) have been investigated in a randomized, double-blind, crossover, placebo-controlled study in 10 healthy volunteers with no history of sleep disorder (13). The half-life of zaleplon was significantly shorter than that of zolpidem. Zaleplon produced less sedation than zolpidem at the two doses studied, and the sedation scores in the zaleplon groups returned to baseline sooner than in the zolpidem groups. Zaleplon had no effect on recent or remote recall, whereas zolpidem had a significant effect on both measures.

Organs and Systems

Psychological, psychiatric

- A 25-year-old unmarried Asian woman with high intellectual functioning and psychiatric history developed

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illusions and hallucinations and a feeling of superior psychosocial adjustment, with no current or prior medical or depersonalization within several minutes of taking zaleplon 10 mg (14). The illusions and visual hallucinations resolved after 15 minutes, but she continued to have light-headedness and fatigue, which gradually resolved by the next day.

Drug–Drug Interactions

Alcohol

The addition of alcohol to the Z drugs, zaleplon, zolpidem, and zopiclone, produces additive sedative effects without altering their pharmacokinetics (15).

The effects of alcohol combined with either zaleplon or triazolam have been studied in 18 healthy volunteers (16). Triazolam, with and without ethanol, impaired digit symbol substitution, symbol copying, simple and complex reaction times, and divided attention performance compared with placebo. Zaleplon without ethanol impaired only digit symbol substitution and divided attention tracking, but when it was combined with ethanol all measures were impaired. However, zaleplon without ethanol was consistently better than triazolam alone. Zaleplon produced less performance impairment and a shorter period of ethanol potentiation than triazolam.

Cimetidine

Cimetidine increases plasma concentrations of the Z drugs and increases their sedative effects (15); this occurs to a lesser extent than the similar effect on benzodiazepines that are exclusively metabolized by CYP3A4.

Digoxin

The interaction of zaleplon with digoxin has been investigated in 20 subjects (17). There were one or more adverse effects in 18% of those who took digoxin alone and 35% of those who took digoxin plus zaleplon, but these were all mild and resolved quickly. Zaleplon had no significant effects on selected pharmacokinetic and pharmacodynamic properties of digoxin.

Erythromycin

Erythromycin increases plasma concentrations of the Z drugs and increases their sedative effects (15); this occurs to a lesser extent than the similar effect on benzodiazepines that are exclusively metabolized by CYP3A4.

Ibuprofen

The interaction of zaleplon with ibuprofen has been investigated in 17 subjects (18). Healthy adult volunteers were given zaleplon 10 mg alone, ibuprofen 600 mg alone, or zaleplon 10 mg plus ibuprofen 600 mg in an open, randomized, crossover study. The adverse effects were mild and resolved without intervention. The authors concluded that there was no evidence of a significant interaction between zaleplon and ibuprofen.

Ketoconazole

Ketoconazole increases plasma concentrations of the Z drugs and increases their sedative effects (15); this occurs to a lesser extent than the similar effect on benzodiazepines that are exclusively metabolized by CYP3A4.

Rifampicin

Rifampicin significantly induces the metabolism of zaleplon and reduces its sedative action (15), although the effect is less than the effect of rifampicin on triazolam or midazolam, probably because they are more exclusively metabolized by CYP3A4.

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Zidometacin

See also Non-steroidal anti-inflammatory drugs

General Information

Zidometacin differs from indometacin in having an azido group in the *para*-position, where indometacin has a benzyl group. It appears to be less ulcerogenic in animals. However, epigastric pain, burning, and nausea have been experienced by patients taking zidometacin (1).

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Zidovudine

See also Nucleoside analogue reverse transcriptase inhibitors (NRTIs)

General Information

Zidovudine is a nucleoside analogue reverse transcriptase inhibitor. Its adverse effects include hematological complications, severe headache, insomnia, confusion, nausea, vomiting, abdominal discomfort, myalgia (myopathy), and nail pigmentation (1).

Observational studies

Oral zidovudine in a dosage of 200 mg every 4 hours for 42 days was used as prophylaxis in health-care workers after percutaneous exposure to blood or body fluids from HIV-infected patients. Adverse reactions occurred in 73%, the most frequent being nausea (47%), headache (35%), and fatigue (30%). Of selected hematological laboratory markers only platelet counts increased significantly over 4 weeks. Although adverse reactions were not very severe and none of the laboratory changes was considered clinically significant, treatment was poorly accepted and stopped prematurely by 30% (2). Current guidelines for postexposure prophylaxis recommend a much lower dosage (300 mg bd) with much better tolerance (3).

Comparative studies

The safety and efficacy of lamivudine (300–600 mg/day) in combination with zidovudine (600 mg/day) in the treatment of antiretroviral-naive and zidovudine-experienced HIV-infected persons has been compared with zidovudine monotherapy in two placebo-controlled studies of 129 and 223 patients (4,5). There were no significant differences in the incidence or severity of adverse effects between patients taking zidovudine alone or in combination with lamivudine. In both studies gastrointestinal symptoms, notably nausea, were the most commonly observed adverse reactions, occurring in 5–11% of zidovudine-experienced patients and 23–29% of antiretroviral drug-naive individuals. Although one antiretroviral drug-naive patient taking combined therapy had an asymptomatic rise in pancreatic amylase activity, acute pancreatitis was not observed in either study. Grade 1 peripheral neuropathy was reported in one zidovudine-experienced patient taking low-dosage lamivudine (150 mg bd) and zidovudine.

Several large-scale studies of the efficacy of combined antiretroviral treatment with zalcitabine and zidovudine in HIV-infected patients (compared with zidovudine monotherapy or a combination of zidovudine and didanosine) have not shown unexpected adverse effects (6–9). The most common adverse effects in patients taking zalcitabine were peripheral neuropathy and aphthous mouth ulcers.

Organs and Systems

Nervous system

Various nervous system adverse effects of zidovudine have been reported, which may or may not be directly related to the drug. These include seizures, confusion, and acute encephalopathy occurring after zidovudine dosage reduction (10).

Metabolism

Lipodystrophy is a common adverse effect of antiretroviral drugs, particularly the NRTIs and has been reported with zidovudine (11).

- A 42-year-old woman developed abdominal and dorsocervical fat enlargement after having taken zidovudine for over 10 years. Zidovudine was withdrawn and the lesions improved considerably over the next 26 months.

Hematologic

The main dose-limiting adverse reactions of zidovudine therapy in HIV-infected adults and children are hematological complications (12). When zidovudine was introduced it was given in about twice the dosage used today. Consequently, hematological adverse effects occur at a much lower frequency than previously reported (13,14).

Almost uniformly, zidovudine treatment results in a progressive increase in the erythrocyte mean cell volume, which cannot be prevented by supplementation with vitamin B_{12} and folinic acid (15). Zidovudine can cause anemia (16) and reversible pure red cell aplasia (17). While recombinant erythropoietin is useful in correcting

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zidovudine-induced anemia, some cases of anemia are associated with high serum erythropoietin concentrations and normocytic cells, indicating bone marrow unresponsiveness to erythropoietin (18). Measuring baseline serum erythropoietin concentrations may help to predict the response to this very costly hormone supplementation.

Zidovudine can cause neutropenia (16).

Thrombocytopenia has been observed in patients using zidovudine and didanosine (19,20).

Skin

Fatal toxic epidermolysis has been attributed to zidovudine (21) as has cutaneous hypersensitivity (22).

Zidovudine can occasionally cause unusual pigmentation, probably depending on the individual's pigmentary pattern (23).

Nails

The presenting sign of neutropenia in a neonate treated with prophylactic zidovudine for reduction of perinatal transmission was, unusually, severe paronychia of the large toes as a result of *Candida albicans* and *Escherichia coli* infection (24). The paronychia resolved after treatment with oral fluconazole and topical antiseptics. Paronychia of the large toes has also been observed when filgrastim (recombinant granulocyte colony stimulating factor) was used alongside chemotherapy in poor-risk patients with myelodysplastic syndrome (25), and there is some evidence that paronychia (even in the absence of blood disorders) can occur as an independent adverse reaction to various antiretroviral drugs, including indinavir and lamivudine (26).

Closely similar is the strong evidence from case-control studies that ingrowing toenails are associated with the use of indinavir (27) and possibly other similar compounds, but not lamivudine.

Musculoskeletal

Myopathy has been well described with long-term zidovudine and is reversible after withdrawal (28). Phosphorus magnetic resonance spectroscopy has been used to study the changes in phosphorylated metabolites (ATP, phosphocreatine, and inorganic phosphate) during exercise in 19 healthy volunteers, 6 untreated HIV-positive individuals, and 9 zidovudine-treated patients with biopsy-proven myopathy (29). Zidovudine altered the normal muscle energy metabolism in the patients with myopathy, suggesting that it reduces maximal work output, and thus the maximal rate of mitochondrial ATP synthesis, in human muscle. So far, the syndrome has not been associated with any other NRTI (30) and it has been suggested that other factors might contribute to the development of zidovudine-associated myopathy (31). Mitochondrial abnormalities have also been observed in biopsies from untreated patients infected with HIV-1, suggesting that the virus itself can also cause myopathy.

To assess the contribution of zidovudine to the mitochondrial damage, the effects of zidovudine on non-infected co-cultures of spinal ganglia, spinal cord, and skeletal muscle in fetal rats have been studied (32). There were significant changes not only in the mitochondria but also in the nuclei of all cells tested. These changes depended less on the concentration of zidovudine than on the duration of exposure.

Multiorgan failure

A well-documented case has shown that zidovudine can cause type B lactic acidosis and acute respiratory and hepatic failure (33).

- A 34-year-old obese woman developed nausea, vomiting, and intermittent diarrhea. Her current medications included zidovudine. She had tachypnea and tender hepatomegaly, and a CT scan of the abdomen showed hepatomegaly with fatty infiltration. The serum bicarbonate concentration was low and the lactate concentration three times normal. The tachypnea and dyspnea worsened as the lactate concentration rapidly increased to 15 times normal, and she died in acute respiratory and hepatic failure with multiorgan dysfunction.

Second-Generation Effects

Pregnancy

Zidovudine during pregnancy and delivery, followed by treatment of the infant for 6 weeks, prevents maternofetal transmission of HIV, and is associated with minimal short-term toxicity to both mother and child and no increased incidence of neonatal structural abnormalities (SEDA-19, 279) (34).

Zidovudine is relatively well tolerated in pregnancy, with anemia, neutropenia, or thrombocytopenia occurring in 10% and abnormalities of serum electrolytes and liver function in 5% (34).

Teratogenicity

There has been a randomized cohort study in the USA of children from 122 pregnancies in which zidovudine was given and of children from 112 pregnancies in which only a placebo was used (35). The median age of the children at the last follow-up visit was 4.2 years. There were no significant differences between children exposed to zidovudine and those who received placebo in terms of sequential data on lymphocyte subsets, weight, height, head circumference, and cognitive/developmental function. There were no deaths or malignancies. Two children (both exposed to zidovudine) were still being followed for unexplained abnormal fundoscopy. One child exposed to zidovudine had a mild cardiomyopathy on echocardiography at the age of 48 months but was clinically asymptomatic.

Lactation

Since zidovudine seems to be relatively well tolerated both in pregnancy and in neonates, there is also much reason to consider its use during lactation in order to reduce vertical transmission of HIV. Indeed, many would regard it as highly preferable to abandoning breastfeeding by HIV-infected women. In a critical double-blind West African study the effects of a 6-month course of treatment in prenatal and lactating

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mothers were examined (36). Eligible participants were women aged 18 years or older who had confirmed HIV-1 infection, were 36–38 weeks pregnant, and gave written informed consent. Exclusion criteria were severe anemia, neutropenia, abnormal liver function, and sickle cell disease. They were randomly assigned to zidovudine ($n = 214$; 300 mg bd until labor, 600 mg at the start of labor, and 300 mg bd for 7 days) or to matching placebo ($n = 217$). The Kaplan-Meier probability of HIV infection in the infant at 6 months was 18% in the zidovudine group and 28% in the placebo group, a relative efficacy of 0.38. In current and follow-up observations over 6 months, no major adverse biological or clinical events were reported in excess among women or children in the zidovudine group. The authors concluded that a short course of oral zidovudine given during the peripartum period is well tolerated and provides significant reduction in early vertical transmission of HIV-1 infection despite breastfeeding.

A second related study showed similar results (37), and the two papers together provide impressive evidence that it is proper and defensible to use zidovudine in breastfeeding mothers.

Susceptibility Factors

Age

The only recognized toxic effect in infants is anemia within the first 6 weeks of life, which is not associated with premature delivery, duration of maternal treatment, degree of maternal immunosuppression, or maternal anemia. An 18-month follow-up of 342 children born to mothers who had taken zidovudine or placebo during pregnancy has recently been reported (38). There were no differences in growth parameters or immune function in uninfected children. In addition, no childhood neoplasias were reported in either group.

Drug–Drug Interactions

Atovaquone

Atovaquone can potentiate the activity of zidovudine by inhibiting its glucuronidation (39).

Clarithromycin

Clarithromycin has an unpredictable effect on the absorption of zidovudine; blood concentrations may rise or fall (40,41).

Cytotoxic drugs

In 13 HIV-infected patients with cancer, the mean pharmacokinetics of zidovudine (AUC, half-life, oral clearance, and oral apparent volume of distribution) were no different with or without chemotherapy (42). However, there was a 57% reduction in C_{max} and a 66% increase in t_{max} after chemotherapy. There were no differences in the urinary excretion of zidovudine or zidovudine glucuronide. The authors concluded that these minor changes did not warrant any change in the dosage of zidovudine during concurrent chemotherapy.

Oxazepam

There was a striking incidence of headache in a small series of patients when zidovudine was given with oxazepam (43).

Paracetamol (acetaminophen)

Paracetamol (acetaminophen) increased the clearance (and possibly reduced the effects) of zidovudine (44,45).

Probenecid

In two healthy volunteers, co-administration of probenecid 500 mg every 6 hours altered the pharmacokinetics of a single oral dose of zidovudine 200 mg (46). There was an increase in the average AUC, with a corresponding reduction in oral clearance, attributed to an inhibitory effect of probenecid on the glucuronidation and renal excretion of zidovudine.

Eight subjects took zidovudine for 3 days with and without probenecid 500 mg every 8 hours for 3 days, and then additional quinine sulfate 260 mg every 8 hours (47). Probenecid increased the AUC of zidovudine by 80%. Quinine prevented the probenecid effect but had no effect on zidovudine kinetics when it was taken without probenecid by four other subjects. All of the effects were secondary to changes in zidovudine metabolism, since neither probenecid nor quinine changed the renal elimination of zidovudine.

Rifamycins

Rifampicin, a well-known enzyme inducer, increased the metabolism of zidovudine, and the effect persisted for 2 weeks after rifampicin had been withdrawn (48).

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Zileuton

General Information

Zileuton is an inhibitor of 5-lipoxygenase, the first step in the conversion of arachidonic acid to cysteinyl leukotrienes. It is starting to be used in the long-term control of asthma (1). It has also been used to treat acne (2), atopic dermatitis (3), and the Sjögren–Larsson syndrome (4).

Organs and Systems

Hematologic

In 10 patients with asthma, zileuton treatment for 2 weeks significantly increased thromboxane B2 concentrations and spontaneous platelet aggregation (5). These results suggest that zileuton may be associated with an increased risk of thrombosis.

Liver

In 2947 patients at 233 centers in the USA randomly assigned in a 5:1 ratio to zileuton plus usual asthma care or usual asthma care alone, the patients who took zileuton had significantly fewer corticosteroid rescues, required less emergency care, had fewer hospitalizations, and had greater increases in FEV_1 (6). They also had significantly greater improvements in asthma symptoms. There were increases in alanine transaminase activity to three times or more the upper limit of the reference range in 4.6% of patients taking zileuton and 1.1% of those receiving usual care; most of the increases occurred during the first 2–3 months. There were no cases of jaundice or chronic liver disease.

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Zinc

General Information

Zinc is a bluish-white metallic element (symbol Zn; atomic no. 30) that is found in minerals such as franklinite, ghanite, goslarite, hemimorphite, smithsonite,

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sphalerite, willemite, and wurtzite. Sphalerite, which contains zinc sulfide, is the most abundant source.

Zinc deficiency and toxicity have been reviewed (1,2). Zinc supplementation reduces the incidence of infection and increases the survival rate after infections in elderly people (3). However, oral zinc sulfate has been overused in many fields of therapy, particularly in dermatology, despite the fact that some of the indications once claimed for it have been discredited and only a few disorders have been clearly shown to result from zinc deficiency. Dosages have often been high, for example the equivalent of 45 mg of metallic zinc three times a day. Zinc oxide is used topically as an astringent and protectant. Zinc chloride is used as an astringent and a desensitizer for dentine. Zinc sulfate is sometimes used as an ophthalmic astringent. Zinc oxide is used as an anti-infective agent. Zinc is also found in some freely available alternative remedies and in non-medicinal products such as shampoos.

Zinc acetate (Galzin, Gate Pharmaceutical Co), developed for the treatment of Wilson's disease (4), has been used in maintenance therapy of adult and pediatric disease, but it also has efficacy in the treatment of pregnant women and presymptomatic patients from the start. It also has value as adjunctive therapy for the initial treatment of symptomatic patients. Its mechanism of action involves induction of intestinal cell metallothionein, which blocks copper absorption from the intestinal tract. Negative copper balance is caused by blockade not only of absorption of food copper but by blockade of reabsorption of the considerable amount of endogenously secreted copper in saliva, gastric juice, and intestinal secretions. It is therefore effective in controlling copper concentrations and toxicity in Wilson's disease.

The main advantage of zinc over other anticopper agents is its extremely low toxicity. The only adverse effect is some degree of initial gastric irritation in about 10% of patients, which usually abates and becomes insignificant over time. As with all long-term therapies, compliance is a problem in some patients and dictates regular monitoring by measurement of 24-hour urine copper and zinc. As with all anticopper therapies, overtreatment can cause copper deficiency over a long period of time. This is to be avoided, particularly in children, because copper is required for growth.

Zinc can be beneficial in zinc deficiency. Severe depletion of zinc in two patients with advanced cancer and malnutrition was accompanied by cutaneous bleeding, a prolonged bleeding time, and abnormal platelet aggregation (5). Both had very low serum and urinary zinc concentrations. Oral zinc without any additional therapy was rapidly followed by control of bleeding and normalization of bleeding time and platelet aggregation. Discontinuation of zinc caused the return of the bleeding and abnormal laboratory findings.

Organs and Systems

Nervous system

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) was used 30 years ago as an oral antiparasitic agent and to increase the intestinal absorption of zinc in patients with acrodermatitis enteropathica, a genetic disorder of zinc absorption. However, the use of clioquinol was epidemiologically linked to subacute myelo-optic neuropathy (SMON), characterized by peripheral neuropathy and blindness, which affected 10 000 patients in Japan. Withdrawal of oral clioquinol led to the elimination of SMON, but the mechanism of how clioquinol induces neurotoxicity is unclear. There is now evidence that zinc may have been implicated.

The effect of clioquinol-metal chelates has been tested on neural crest-derived melanoma cells (6). The effect of clioquinol chelates on cells was further studied by electron microscopy and by a mitochondrial potential-sensitive fluorescent dye. Of the ions tested, only clioquinol-zinc chelate was cytotoxic. This cytotoxicity was extremely rapid, suggesting that its primary effect was on the mitochondria, and electron microscopic analysis showed that the chelate caused mitochondrial damage. This was further confirmed by the observation that the chelate reduced the mitochondrial membrane potential. The phenomenon of clioquinol-mediated toxicity appeared to be specific to zinc and was not seen with other metals tested. Since clioquinol causes increased systemic absorption of zinc, it is likely that clioquinol-zinc chelate was present in appreciable concentrations in patients with SMON and may have been the causative toxin.

Hematologic

The use of megadoses of vitamin and mineral supplements has become common, and adverse effects can occur.

- A 17-year-old man developed fatigue after taking large daily doses of zinc supplements for 6–7 months in an attempt to treat his acne (7). He initially took 50 mg/day, but because his acne did not improve he increased the dosage to 100 mg tds. He had anemia and neutropenia. His plasma zinc concentration was 1.95 (reference range 0.50–0.95) μg/ml 1 month after withdrawal and 1.69 μg/ml 1 month later. His plasma copper concentration was 0.12 (reference value 0.90–2.35) μg/ml. When his anemia and neutropenia had resolved 4 months later, the zinc and copper concentrations had returned to normal.

Zinc sulfate can cause copper deficiency by inducing the production of metallothionein in intestinal cells and thus lowering copper absorption; copper deficiency can lead in turn to sideroblastic anemia (8), neutropenia, and osteopenia (9).

- A 17-year-old man with anaemia, leukopenia, and neutropenia had been self-medicating with over-the-counter zinc formulations for acne for almost 2 years at doses of up to 300 mg/day (10). Serum copper and serum ceruloplasmin concentrations were less than 100 (reference range 70–155) ng/ml and 20 (23–49) μg/ml respectively. His serum zinc concentration was 2 (0.6–1.3) μg/ml. Within 1 month of withdrawal, and without copper supplementation, the ceruloplasmin concentration had risen to 90 μg/ml. By 2 months his complete blood count was normal.

It is not clear whether zinc itself also causes anemia directly, or whether the effect is exerted solely through

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this interaction with copper, but with the increasingly popular sale of zinc supplements this adverse effect merits attention as a possible cause of unexplained blood disorders (11).

Gastrointestinal

Zinc compounds that are soluble in water or in gastric fluid are poisonous. If zinc sulfate is given on an empty stomach, gastric acid can convert it to zinc chloride, which is a powerful caustic agent; it is therefore not surprising that gastric irritation, nausea, vomiting, hemorrhagic erosive gastritis, and diarrhea are common adverse reactions.

Bacitracin zinc has been used for giardiasis (12), in which it appears effective. In the doses used, adverse effects have been limited to nausea, abdominal discomfort, and diarrhea in a small number of patients. Similar effects have been noted when zinc gluconate lozenges were administered for the common cold (13).

- A 10-year-old girl accidentally ingested an acid soldering flux solution (pH 3.0; zinc chloride 30–60%) (14). Systemic effects after ingestion were unremarkable, except for lethargy. Thus, chelation therapy was not considered. Severe gastric corrosion was caused by local caustic action. An antral stricture of the stomach developed about 3 weeks later, and she had a modified Heineke–Mikulicz antropyloroplasty. Postoperatively, she made an uneventful recovery. However, although she was tolerating a normal diet, a barium meal showed that her stomach was totally aperistaltic.

In this case careful long-term follow-up was considered necessary, because of the potential risk of malignancy in the damaged stomach.

Liver

The use of zinc acetate in Wilson's disease has been reviewed and recommended rather than copper chelation, because of limited adverse effects. However, liver damage has been attributed to zinc in a patient with Wilson's disease (15).

- A 25-year-old woman with Wilson's disease took oral zinc acetate 50 mg tds and 21 days later developed right hypochondrial pain, nausea, vomiting, fever, arthralgia, and tender hepatomegaly. Her hemoglobin was at 10.5 g/dl, aspartate transaminase 393 U/l, and alanine transaminase 911 U/l. Oral zinc was withdrawn and oral D-penicillamine (250 mg qds) was prescribed. One week later she was asymptomatic, and her liver enzymes returned to normal within 4 months.

Skin

Lichen planus has been attributed to zinc in dental materials.

- A 74-year-old woman, who had extensive odontitis treated with root canal disinfection and dental metal restorations, developed painful erosion and erythema of the upper lip mucosa, white streaks on the buccal mucosa, and white lesions on the gums (16). Histology showed lichen planus. Her 14 dental metal restorations contained 5.3% zinc, and patch-testing was positive with zinc chloride and negative with all the other metal components. The lichen planus resolved 3 months after removal of the metal restorations.

Zinc products are extensively used in shampoos and other non-medical items and severe reactions occasionally occur. In one instance a shampoo based on zinc pyrithione caused a serious relapse in a woman with stable psoriasis (SEDA-22, 251).

Reproductive system

The efficacy and safety of intravaginal zinc sulfate + usnic acid as adjuvant therapy for human papillomavirus genital infection has been studied before or after radiosurgical treatment in 100 patients (17). Papillomavirus lesions disappeared in 93% of the patients in the control group and in 100% of the others. Re-epithelialization after 1 month was complete in only 28% of the control group but in 65% of the treated patients; after 2 months it was complete in 76% of the controls and in 94% of the others. Treatment before radiosurgical treatment resulted in a reduction of the overall area of lesions in 88% of cases. Three months after radiosurgical treatment there was significantly less recurrence in those treated with usnic acid and zinc sulfate. Adverse effects were limited to local pain and irritation and were well tolerated.

Immunologic

Zinc can reportedly impair immune responses (18).

Drug Administration

Drug dosage regimens

When zinc is used therapeutically, the dosage of zinc often considerably exceeds the recommended daily allowance for healthy adults (15 mg of elemental zinc). In view of its adverse effects, it is advisable to limit the dosage to two or three times this amount. To reduce the unwanted gastrointestinal effects it may be helpful to use zinc acetate rather than zinc sulfate (19).

Drug overdose

- A very old woman accidentally ingested a formulation containing zinc and copper sulphate (20). At 90 minutes after ingestion, the peak plasma concentrations were 20 mg/ml for zinc and 2 μg/ml for copper. The major complications were gastric and bronchial inflammation, due to the corrosive properties of these compounds. There were also systemic manifestations, with cardiovascular failure and renal insufficiency, but the patient made a complete recovery.
- A schizophrenic patient died after ingesting 461 coins, the first reported case of a death associated with zinc intoxication (21). The patient presented with clinical manifestations consistent with the local corrosive as well as systemic effects of zinc intoxication and died 40 days after admission with multisystem organ failure. Many British post-1981 pennies, which contain mostly

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zinc, were severely corroded through prolonged contact with gastric juice. Tissue samples of the kidneys, pancreas, and liver obtained at autopsy contained high concentrations of zinc and showed acute tubular necrosis, mild fibrosis, and acute massive necrosis respectively.

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Zingiberaceae

See also Herbal medicines

General Information

The genera in the family of Zingiberaceae (Table 1) include cardamom and ginger.

Zingiber officinale

Zingiber officinale (ginger) contains a variety of compounds, including diarylheptanoids and the phenol gingerol. It has been used to treat motion sickness and other forms of nausea and vomiting, and may have some efficacy (1).

Adverse effects

Skin

Of about 1000 patients with occupational skin diseases, five had occupational allergic contact dermatitis from spices (2). They were chefs, or workers in kitchens, coffee rooms, and restaurants. In all cases the dermatitis affected the hands. The causative spices were garlic, cinnamon, ginger, allspice, and clove. The same patients had positive patch test reactions to carrot, lettuce, and tomato.

Among 55 patients with suspected contact dermatitis, skin patch tests that were positive at concentrations of both 10% and 25% were most common with ginger ($n = 7$), nutmeg ($n = 5$), and oregano ($n = 4$); other spices produced no responses or one positive response (3). Positive

Table 1 The genera of Zingiberaceae

Aframomum (aframomum)
Alpinia (alpinia)
Amomum (cardamom)
Boesenbergia (boesenbergia)
Curcuma (curcuma)
Elettaria (elettaria)
Etlingera (waxflower)
Hedychium (garland-lily)
Hitchenia (hitchenia)
Kaempferia (kaempferia)
Renealmia (renealmia)
Zingiber (ginger)

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reactions at only one concentration were more likely at 25%: nutmeg ($n = 5$), ginger and cayenne ($n = 4$), curry, cumin, and cinnamon ($n = 3$), turmeric, coriander, and sage ($n = 2$), oregano ($n = 1$), and basil and clove ($n = 0$).

Drug interactions

Ginger may potentiate the effects of oral anticoagulants (4).

- A 76-year-old white woman taking long-term phenprocoumon, with an INR in the target range, began using ginger products (5). Several weeks later, her INR rose to 10 and she had epistaxis. The INR returned to the target range after ginger was stopped and vitamin K1 was given.

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Zipeprol

General Information

Zipeprol is a centrally acting cough suppressant. Because it has hallucinogenic effects, it has been abused, particularly in Korea.

Long-Term Effects

Drug abuse

Abuse of zipeprol can be a problem (SEDA-17, 211), and has been associated with severe neurological symptoms.

Drug Administration

Drug overdose

A retrospective study of cases of eprazinone, eprozinol, and zipeprol intoxication collected at the Poison Control Center in Paris from 1975 to 1982 noted 199 cases of accidental or intentional acute poisoning. In seven cases, seizures were observed, all after ingestion of eight times the therapeutic dose. They resolved rapidly and without recurrence with symptomatic treatment (1).

In Korea, from 1991 to 1998, a total of 69 zipeprol-related deaths were reported (2). In 96% of cases involving zipeprol alone, the victims were in their teens and twenties. The male/female ratio was 3.5:1. The blood concentration of zipeprol was 0.8–38 μg/ml when zipeprol was taken alone and 0.1–35 μg/ml zipeprol when it was taken with dextromethorphan.

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Ziprasidone

See also Neuroleptic drugs

General Information

Ziprasidone is a dibenzotheolylpiperazine compound with a receptor binding profile similar to that of other atypical antipsychotic drugs, and a high affinity for serotonin (5-HT_{2A}) receptors and a lower affinity for dopamine (D_2) receptors; it also has high affinities for 5-HT_{1A}, 5-HT_{1D} and 5-HT_{2C} receptors and inhibits serotonin and noradrenaline reuptake. Two extensive reviews of the clinical pharmacology of ziprasidone have appeared (1,2).

On February 5, 2000, the FDA approved ziprasidone for the treatment of schizophrenia (www.fda.gov). However, the FDA has been concerned with the possibility that ziprasidone and a number of other drugs might increase the risk of the specific potentially fatal cardiac dysrhythmia, torsade de pointes. The FDA did not approve ziprasidone in 1998, because of evidence that it can cause prolongation of the QT interval, and they asked that specific safety data be gathered. The safety data were submitted in 1999. Although QT prolongation is still a theoretical concern, over 4000 patients have been treated in clinical trials without evidence of torsade de pointes. In addition, overall mortality in the trials was similar to that seen with placebo and other neuroleptic drugs. The FDA labelling does not include a so-called "black-box warning" and does not require an electrocardiogram before or during treatment. However, the labelling does warn physicians and patients about QT interval prolongation and the possible risk of sudden death. The labelling suggests that doctors use their best judgment, based on the health status of the individual, as to whether to use ziprasidone as first-line treatment or only after other available drugs have failed. There is no requirement that patients have regular heart check-ups while taking this drug.

Comparison with placebo

Ziprasidone has been used in 28 children and adolescents (aged 7–17 years) with Tourette's syndrome in

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an 8-week pilot study (3). They were randomly assigned to ziprasidone (5–40 mg/day; $n = 16$) or placebo ($n = 12$). Ziprasidone significantly reduced tic frequency. There was one case each of somnolence and akathisia, both with the highest dose of ziprasidone; these were considered to be severe but did not necessitate withdrawal.

Comparison with benzodiazepines

Ziprasidone 20 mg ($n = 30$) has been compared with diazepam 10 mg ($n = 30$) and placebo ($n = 30$) in a randomized, parallel-group, double-blind study in nonpsychotic subjects who were anxious before undergoing minor dental surgery (4). The peak anxiolytic effect of ziprasidone compared with placebo was similar to that of diazepam but had a later onset. However, at 3 hours after the dose, the anxiolytic effect of ziprasidone was significantly greater than that of placebo and somewhat greater than that of diazepam. The sedative effect of ziprasidone was never greater than that of placebo, whereas diazepam was significantly more sedative than placebo 1–1.5 hours after the dose. Ziprasidone was generally well tolerated; only one patient reported treatment-related adverse events (nausea and vomiting) and, unlike diazepam, ziprasidone did not reduce the blood pressure. Dystonia, extrapyramidal syndrome, akathisia, and postural hypotension were not seen with ziprasidone. Ziprasidone may therefore have anxiolytic effects in addition to its neuroleptic properties.

Organs and Systems

Cardiovascular

Three extensive reviews of ziprasidone have devoted particular attention to the possibility of QT interval prolongation (5–7). Ziprasidone up to 160 mg/day prolongs the QT_c interval on average 5.9–9.7 ms (data from 4571 patients); a QT_c interval of over 500 ms was seen in two of 2988 ziprasidone recipients and in one of 440 placebo recipients. In an open study in 31 patients with schizophrenia, ziprasidone given for 21–29 days prolonged the QT_c interval by 20 ms (95% CI = 14, 26).

- A 38-year-old woman with a psychosis who took 4020 mg of ziprasidone had borderline intraventricular conduction delay (QRS duration 111 ms); the QT_c interval was 445 ms (8). She oscillated between being drowsy and calm, and alert and agitated; her blood pressure fell from 129/81 to 99/34 mmHg 4 hours later. She also had diarrhea and urinary retention.

Nervous system

In a randomized, Phase III, double-blind study, ziprasidone 80 mg/day and 160 mg was more effective than placebo in patients with acute exacerbations of schizophrenia or schizoaffective disorders ($n = 302$) (9). After 6 weeks, somnolence (19%) and akathisia (13%) were more frequent with ziprasidone 160 mg than with placebo (5 and 7% each). Benzatropine was required at some time during the study by 20% of the patients taking ziprasidone 80 mg/day, 25% of those taking ziprasidone 160 mg/day, and 13% of those taking placebo. The long-term safety of ziprasidone is unknown.

Tardive dyskinesia has been associated with ziprasidone in a 49-year-old man with bipolar disorder (10).

Psychological, psychiatric

Three cases of hypomania in patients with depression have been reported (11).

Metabolism

Ziprasidone is said to be associated with less weight gain than the other atypical neuroleptic drugs and than most typical ones (1,2).

Musculoskeletal

Rhabdomyolysis with pancreatitis and hyperglycemia has been reported in a middle-aged woman with schizoaffective disorder (12).

Drug–Drug Interactions

Pfizer, the marketing authorization holder of ziprasidone, has promoted several pharmacokinetic studies. Oral contraceptives (ethinylestradiol 30 μg/day plus levonorgestrel 150 μg/day) (13), lithium 900 mg/day (14), ketoconazole 400 mg/day (15), and carbamazepine (100–400 mg/day) (16) had no effects on the pharmacokinetics of ziprasidone (40 mg/day).

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Zirconium

General Information

Zirconium is a metallic element (symbol Zr; atomic no. 40) that occurs in minerals such as baddeleyite and eudialyte.

Topical zirconium can cause hypersensitivity granulomas in sensitized persons, which has led to the removal of zirconium salts from antiperspirants (SEDA-22, 242). Complexes of zirconium and aluminum are non-sensitizing and are still commonly used as active ingredients in topical antiperspirants. However, a granulomatous reaction to this material has been reported (1).

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Zofenopril

See also Angiotensin converting enzyme inhibitors

General Information

Zofenopril is a prodrug that, once absorbed, undergoes rapid and complete hydrolysis to the sulfhydryl-containing active ACE inhibitor zofenoprilat. The use of zofenopril in hypertension and in acute myocardial infarction has been extensively reviewed (1).

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Zolpidem

General Information

Zolpidem and alpidem are imidazopyridines, chemically distinct from the benzodiazepines and appear to bind selectively to a subset of benzodiazepine receptors (1). This property may account for their apparently milder withdrawal effects and, in the case of alpidem, a relative dominance of anxiolytic over sedative and cognitive effects (2). Zolpidem has hypnotic efficacy comparable to short- and medium-acting benzodiazepines, and has similar or possibly fewer adverse effects at therapeutic doses (3–5), except for gastrointestinal disturbances, which appear to be more common, and visual hallucinations, especially in women (SEDA-17, 46) (SEDA-18, 45) (SEDA-21, 40). On the other hand, zolpidem unexpectedly causes as much memory impairment as triazolam, if not more, at least in young healthy adults (SEDA-19, 33). Also surprising is the same author's later contention that zolpidem causes less memory impairment than do the benzodiazepine hypnotics (SEDA-21, 40), presumably including triazolam. Zolpidem may also be relatively toxic in overdose, owing to respiratory depression (6), but later observations have suggested that it may not be any more toxic than the benzodiazepines (SEDA-21, 40). At normal doses zolpidem is said to be at least as safe as standard benzodiazepines in patients with respiratory compromise (SEDA-21, 40). The effects of zolpidem are reversed by flumazenil (7).

Subjective responses to treatment with zolpidem were assessed in 16 944 outpatients with insomnia. Nausea, dizziness, malaise, nightmares, agitation, and headache were the most common adverse events reported. There was one serious adverse reaction in a 48-year-old woman, who developed paranoid symptoms during the documentation phase. There were no life-threatening adverse events (8).

The safety and tolerability of zolpidem have been investigated in two multicenter studies, in which 8.9% and 7.5% of the patients reported an adverse event (9). The most frequent events were related to the central nervous system (somnolence, headache, confusion, vertigo), but gastrointestinal and cutaneous symptoms were also frequently reported.

In a double-blind, placebo-controlled, crossover study, 10 patients with "probable progressive supranuclear palsy" took single oral doses of zolpidem (5 and 10 mg), co-careldopa (levodopa 250 mg plus carbidopa 25 mg), or placebo in four separate trials in random order (10). Zolpidem, unlike levodopa or placebo, reduced voluntary saccadic eye movements, and the 5 mg dose produced a statistically significant improvement in motor function. The adverse effects of zolpidem included drowsiness and

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increased postural instability and were more marked after a dose of 10 mg.

Zolpidem has been investigated in a multicenter, double-blind, placebo-controlled, parallel-group, randomized study in 138 adults, who were experienced air travelers (11). They were randomized to zolpidem 10 mg or placebo for three (or optionally four) consecutive nights, starting with the first night-time sleep after travel. Sleep was assessed with daily questionnaires. Compared with placebo, zolpidem was associated with significantly improved sleep, longer total sleep time, reduced numbers of awakenings, and improved sleep quality. It was not associated with improvement in sleep latency. No unexpected or serious adverse events were reported and the most common adverse event was headache in both groups.

Zolpidem 10 mg/day and zopiclone 7.5 mg/day, given at night, have been compared in a 14-day, double-blind study in 479 chronic primary insomniacs (12). With zolpidem 68% of the patients were rated at least "moderately improved," versus 62% with zopiclone. However, with zolpidem sleep-onset latency improved in significantly more patients (86 versus 78%). In addition, significantly fewer patients who took zolpidem had drug-related adverse events (31 versus 45%); bitter taste accounted for 5.8% of such complaints with zolpidem compared with 40% with zopiclone. In conclusion, zolpidem was at least as effective as zopiclone but showed significantly less rebound on withdrawal; overall it was better tolerated.

Improvement in social and occupational function has been attributed to zolpidem (13).

- A recovering 60-year-old alcoholic woman developed reduced cognitive function, including considerable memory loss, praxis disorders, and an inability to join in conversation. A CT scan showed non-specific cerebral atrophy. She was given zolpidem 10 mg for insomnia, which she took at first at 2200 hours, but then earlier, at 1900 hours. After starting to take it at the earlier time she talked more easily and could wash the dishes and do the housework, things that she had lost the ability to do. This beneficial effect was detectable 45–60 minutes after the dose of zolpidem, lasted for 3 hours after each administration, and then abated. The subjective improvement in cognitive function was confirmed several times by her general practitioner.

Three patients had improvements in dystonia and parkinsonism after taking zolpidem 10 mg (14). The improvement in dystonia began at 15–45 minutes and optimal benefits were observed after 1–2 hours. The mean duration of action was 4.5 hours initially, falling to 2–3 hours with chronic use. This is similar to that reported in patients with progressive supranuclear palsy, and corresponds to the drug's half-life (2.5 hours). Sleepiness was noted at doses over 10 mg bd.

Organs and Systems

Nervous system

Zolpidem 10 mg, temazepam 15 mg, and placebo have been compared in 630 healthy adults in a multicenter study (15). They were given 15 minutes before lights out, with polysomnographic monitoring for 7.5 hours. Subjective questionnaires and performance tests, including digit symbol substitution and symbol copying, were administered before and after sleep. Neither drug significantly reduced objective sleep latency, but zolpidem reduced awakenings compared with temazepam. Both improved sleep efficiency and most subjective sleep measures, and zolpidem was superior to temazepam in five of six subjective outcome measures. Symbol copying, morning sleepiness, and morning concentration were not altered. Zolpidem 10 mg provided greater subjective hypnotic efficacy than temazepam 15 mg in this model of transient insomnia, with reduced polysomnographic awakenings.

Zolpidem was identified in the blood of 29 subjects arrested for impaired driving (16). In those in whom zolpidem was present with other drugs and/or alcohol, the symptoms reported were generally those of nervous system depression and included slow movements and reactions, slow and slurred speech, poor coordination, lack of balance, flaccid muscle tone, and horizontal and vertical gaze nystagmus. In five subjects in whom zolpidem was the only drug detected, signs of impairment included slow and slurred speech, slow reflexes, disorientation, and lack of balance and coordination. Therapeutic doses of zolpidem can affect driving adversely, and concentrations above the target range further impair both driving ability and consciousness.

Psychological, psychiatric

Like the benzodiazepines, zolpidem can produce a variety of paradoxical effects, including disturbances of mood, perception, and behavior. In 192 surgical patients zolpidem 8 mg but not 16 mg caused such effects, particularly anxiety, 1 hour after administration (17).

The acute effects of zolpidem and triazolam have been compared in 10 non-drug-abusing subjects using a Digit-Enter-and-Recall task with varying delay intervals (9, 10, and 20 seconds) (18). Zolpidem and triazolam impaired performance as a function of dose after all intervals. However, zolpidem produced significantly less impairment than triazolam after the longest delay (20 seconds). Zolpidem and triazolam produced comparable dose-related impairment of the digit symbol substitution, circular lights, and picture recall/recognition tasks. The results suggested that zolpidem may have less potential than triazolam to impair recall, which may be due to differences between these compounds in terms of their benzodiazepine-receptor binding profiles.

Delirium has been attributed to zolpidem (19,20).

- A 26-year-old woman was treated at a psychiatric inpatient unit for psychotic depression. She had neither formal thought disorder nor perceptual disturbances and was cognitively intact. Ten days later she was stabilized on fluoxetine, risperidone, and benzatropine. She then developed flu-like symptoms, and 3 days later took zolpidem 10 mg to help her to sleep. After 30 minutes she was found agitated, confused, and rambling, and wanted to go to the beach. Her speech was disorganized and she had visual hallucinations. Her gait was ataxic. There were no signs of meningeal irritation. Her temperature was 37.3°C, her

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pulse 114/minute, and her blood pressure 116/78 mmHg. When she was evaluated the next morning, her delirium had cleared and she made a full recovery.

- An 86-year-old white woman with headaches and diplopia took zolpidem 5 mg and about 2 hours later became restless, disoriented, and physically agitated. She was given haloperidol and needed restraining for her own safety. Her symptoms resolved by day 5 and she had no recollection of the incident. Rechallenge was not attempted.

Liver

Liver damage has been attributed to zolpidem (21).

- A 53-year-old woman first took zolpidem for insomnia in July 1996. In September 1996 she again took zolpidem 20 mg/day and 2 days later had developed sudden epigastric pain associated with pale stools and dark urine but no fever; she stopped taking zolpidem and the abdominal pain resolved spontaneously within 12 hours. In April 1997, she had another episode of abdominal pain after taking zolpidem. Eleven days later her serum alanine transaminase and gamma-glutamyltranspeptidase activities were 50 IU/l and 89 IU/l respectively. In June 1997 ultrasound showed a normal biliary tract. Viral hepatitis and concurrent infections with Epstein-Barr virus and cytomegalovirus were excluded.

Long-Term Effects

Drug abuse

There has been a literature review of the abuse potential of zolpidem (22). There were 15 published cases of abuse or dependence. In six patients the abuse was secondary to other forms of abuse or dependence. The authors concluded that the abuse potential of zolpidem is much less than with other hypnotics and that it is also safer than conventional hypnotics. Patients with a history of other substance abuse may be considered as being at risk of later abuse of zolpidem.

However, there is a risk of abuse and dependence from chronic use of zolpidem in high doses (23).

- A 67-year-old Caucasian woman, who had previously been treated for depression, anxiety, and insomnia, as well as alcohol, barbiturate, and benzodiazepine dependence, was given zolpidem 10 mg at bedtime for insomnia. She increased the dose without the knowledge of her physicians, using up to 100 mg/day for 1.5 years, alternating it with various benzodiazepines obtained from multiple physicians when zolpidem was unobtainable. She developed severe generalized tremor, psychomotor agitation, facial flushing, and anxiety, despite taking chlordiazepoxide 300 mg in divided doses during the first 24 hours of detoxification. A tapering dose of zolpidem was initiated and the chlordiazepoxide was tapered. Her symptoms completely subsided within 30 minutes of a single dose of zolpidem 15 mg.

Drug dependence

Four cases of former drug or alcohol abusers with personality disorders have been described; all developed dependence while taking high doses of zolpidem (24).

Drug withdrawal

Zaleplon has been compared with zolpidem 10 mg and placebo in 615 adult outpatients with insomnia (25). After a 7-night placebo (baseline) period, the patients were randomly assigned to receive one of five treatments in double-blind fashion for 28 nights (zaleplon 5, 10, or 20 mg; zolpidem 10 mg; or placebo), followed by placebo for 3 nights. Sleep latency, sleep maintenance, and sleep quality were determined from sleep questionnaires each morning. Rebound insomnia and withdrawal effects on withdrawal were also assessed. After withdrawal of zolpidem, the incidence of withdrawal symptoms was significantly greater than after withdrawal of placebo, and there was suggestion of significant rebound insomnia in some patients who had taken zolpidem compared with placebo. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group.

Withdrawal-induced seizures have been described in a woman taking various benzodiazepines and zolpidem (26).

- A 43-year-old woman had had insomnia since she was a child. At the age of 15 benzodiazepine therapy improved her sleeping, but when she gradually stopped taking benzodiazepines the insomnia returned after a few days. At the age of 26 she was abusing several benzodiazepines, including diazepam and flunitrazepam. At the age of 30 she was taking high doses of bromazepam every evening before going to sleep. After 1 month, she abruptly stopped taking bromazepam and during withdrawal had an epileptic seizure. During the next few years, she had periods of relative well-being, but also two further periods of benzodiazepine abuse, both resulting in seizures after withdrawal. Finally, a physician prescribed zolpidem. Two months later she increased the dose to 450–600 mg/day. After another month of abuse, she was forced by an unexpected event to discontinue the zolpidem and 4 hours later had an epileptic seizure, similar to the previous ones. She started taking zolpidem again, the drug abuse continued, and her fits settled. Six months later she underwent a planned program of zolpidem withdrawal.

Susceptibility Factors

Hepatic disease

The adverse effects of zolpidem can be enhanced in hepatic cirrhosis (27).

- A 41-year-old white man developed postoperative complications 11 months after liver transplantation. His mental status began to deteriorate secondary to hepatic encephalopathy. One day before admission he was given zolpidem 5 mg for sleep and 1 hour later he awoke in a stupor and was not oriented to place or

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time. He became increasingly incoherent and verbally abusive.

Although this patient's worsening mental state could have been explained by the natural history of the encephalopathy, it is possible that zolpidem exacerbated his decline.

Drug Administration

Drug dosage regimens

A review of six studies in over 4000 patients has suggested that non-nightly administration of zolpidem is effective and does not appear to be associated with withdrawal symptoms or dose escalation (28). On the other hand, a case report has suggested that stopping and restarting zolpidem can trigger visual hallucinations; the same phenomenon was observed three times in a healthy 23-year-old Chinese woman (29).

Drug overdose

Two deaths due to acute intentional zolpidem overdose have been reported (30).

- A 36-year-old woman with a history of psychiatric illness, including paranoid disorder, depression with panic episodes, and stress disorder, was found dead in bed. Caffeine, risperidone, and zolpidem were found in her urine.
- A 58-year-old woman with a history of hypertension and mental illness (manic depression and schizophrenia) was found dead in bed, with white foam around her mouth. Zolpidem and carbamazepine were found in her urine.

The cause of death in both cases was thought to have been acute zolpidem overdose, but it is not clear how risperidone and carbamazepine could have been excluded as possible contributors.

- A 44-year-old white man, who had had major depression and anxiety disorder for 25 years, became drowsy after swallowing 20 tablets (10 mg) of zolpidem (31). He was not taking any other medications at the time. A few hours later he became unresponsive and comatose and developed respiratory depression with hypoxia and mild hypercapnia. He subsequently made a full recovery after appropriate medical support.

Drug–Drug Interactions

Antifungal imidazoles

Potential interactions of zolpidem with three commonly prescribed azole derivatives (ketoconazole, itraconazole, and fluconazole) have been evaluated in a controlled clinical study. Co-administration of zolpidem with ketoconazole impaired zolpidem clearance and enhanced its benzodiazepine-like agonist pharmacodynamic effects. Itraconazole and fluconazole had a small effect on zolpidem kinetics and dynamics. The findings were consistent with in vitro studies of differentially impaired zolpidem metabolism by azole derivatives (32).

Similarly, itraconazole 200 mg did not alter the pharmacokinetics and pharmacodynamics of zolpidem 10 mg in 10 healthy volunteers (33). Therefore, unlike triazolam, zolpidem may be used in normal or nearly normal doses together with itraconazole.

Drugs that compete for hepatic oxidative pathways

Omeprazole, like cimetidine, can impair benzodiazepine metabolism and lead to adverse effects (SEDA-18, 43). Other drugs, including antibiotics (erythromycin, chloramphenicol, isoniazid), antifungal drugs (ketoconazole, itraconazole, and analogues), some SSRIs (fluoxetine, paroxetine), other antidepressants (nefazodone), protease inhibitors (saquinavir), opioids (fentanyl), calcium channel blockers (diltiazem, verapamil), and disulfiram also compete for hepatic oxidative pathways that metabolize most benzodiazepines, as well as zolpidem, zopiclone, and buspirone (SEDA-22, 39) (SEDA-22, 41).

Fluoxetine

The possible pharmacokinetic and pharmacodynamic interactions of repeated nightly zolpidem dosing with fluoxetine were evaluated in 29 healthy women. There were no clinically significant pharmacokinetic or pharmacodynamic interactions (34).

Rifampicin

Rifampicin, and presumably other CYP3A inducers, reduces concentrations of zolpidem (SEDA-22, 42).

Ritonavir

The inhibitory effect of ritonavir on the biotransformation of triazolam and zolpidem has been investigated (35). Short-term, low-dose ritonavir produced a large and significant impairment of triazolam clearance and enhancement of its clinical effects. In contrast, ritonavir produced small and clinically unimportant reductions in zolpidem clearance. The findings are consistent with the complete dependence of triazolam clearance on CYP3A activity, compared with the partial dependence of zolpidem clearance on CYP3A.

Sertraline

Interactions between zolpidem and sertraline have been studied in 28 healthy women, who took a single dose of zolpidem alone and five consecutive doses of zolpidem 10 mg while taking chronic doses of sertraline 50 mg (36). Co-administration of sertraline 50 mg and zolpidem 10 mg was safe but could result in a shortened onset of action and increased effect of zolpidem.

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Zomepirac

See also Non-steroidal anti-inflammatory drugs

General Information

Although zomepirac is a pyrrole-acetic acid compound closely related to tolmetin, it was originally claimed to be a new type of analgesic drug. Its history is not unlike that of benoxaprofen. In 1982, because of the severity and frequency of hypersensitivity reactions, it was withdrawn voluntarily by the manufacturers worldwide on a temporary basis (1). It has not been relaunched.

The overall incidence of its adverse effects, according to numerous reviews (SEDA-7, 114), is similar to or somewhat higher than with other NSAIDs. After single oral doses 36% of 496 patients had some adverse effects. The percentage was even higher (43%; 458 of

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1079 patients) during short-term therapy (2 weeks). Owing to adverse reactions, 3.5% of patients dropped out. When it was given over 2–3 weeks, 65–70% patients had adverse effects, but the discontinuation rate was similar to or lower than that of other NSAIDs (2,3). Only the most important adverse effects are presented here.

Organs and Systems

Gastrointestinal

Adverse effects of zomepirac on the gastrointestinal tract were the most frequent reason for interruption of treatment. They increase with duration of administration. Nausea, vomiting, dyspepsia, discomfort, abdominal pain, and diarrhea or constipation have been recorded, as have stomatitis and tongue pain (4). Zomepirac 300 mg/day increases fecal blood loss, but less than aspirin.

Urinary tract

In five patients with prior normal renal function, zomepirac caused acute renal insufficiency, with varying degrees of uremia, proteinuria, and oliguria (5). All recovered either after withdrawal or with prednisone therapy. In another case renal biopsy showed a tubulointerstitial nephritis (6).

Immunologic

The manufacturers received 1100 reports of allergic reactions in the first 2 years after launch. Fatal anaphylactic and anaphylactoid reactions have been reported: 10% of all reports on anaphylactic reactions in the USA named zomepirac, making it second only to the much older drug tolmetin. Hypersensitivity reactions are characterized by hypotension, bronchospasm, and serious respiratory distress, with or without oropharyngeal edema. Type-III allergic reactions have also been described.

Long-Term Effects

Drug dependence

Suspicions based on cluster reports that zomepirac may be addictive have not been confirmed (7).

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Zonisamide

See also Antiepileptic drugs

General Information

Original attempts to market zonisamide in the USA were halted by reports of nephrolithiasis, but successful marketing in Japan resulted in renewed interest elsewhere (1). Zonisamide has a broad spectrum of efficacy in the treatment of seizures, including infantile spasms and myoclonic seizures. It may also have neuroprotective and antimanic effects. Its mechanism of action is not known, but it blocks sodium channels and T-type calcium channels and scavenges free radicals.

In a large Japanese survey, adverse effects occurred in 51% of patients treated with zonisamide and led to drug withdrawal in 18%. The most common were drowsiness, ataxia, anorexia, mental slowing, and gastrointestinal symptoms (2). Other adverse effects include dizziness, nystagmus, dysarthria, diplopia, asterixis, tremor, confusion, anorexia, and weight loss. Some of these may be related to the rate of dosage escalation.

In a double-blind, placebo-controlled, add-on, randomized trial of zonisamide 400 mg/day in 203 patients over 14 years of age with refractory partial-onset seizures, the response rate was 42% (3). The most common treatment-emergent adverse events were somnolence, anorexia, rhinitis, dizziness, nausea or vomiting, ataxia, fatigue, and headache. With zonisamide, 22% of the patients lost over 2.3 kg compared with 10% on placebo.

In a Cochrane Collaboration meta-analysis of trials of zonisamide, levetiracetam, oxcarbazepine, and remacemide, there were no significant differences in efficacy among the four drugs (4). The relative risks for treatment withdrawal were also not significantly different.

Organs and Systems

Psychological, psychiatric

Behavioral problems and acute mania have been described (SEDA-16, 75) (SEDA-19, 76).

Of 74 epileptic patients who had taken zonisamide 14 had psychotic episodes, diagnosed retrospectively (5). The authors estimated that the incidence of psychotic episodes during zonisamide treatment was several times higher than the previously reported prevalence of epileptic psychosis, and that the risk was higher in young patients. In 13 patients, psychotic episodes occurred within a few years of starting zonisamide. In children, obsessive-compulsive symptoms were related to psychotic episodes.

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A unique form of paramnesia has been attributed to zonisamide (6).

- After an episode of zonisamide-induced psychosis, a 28-year-old man with epilepsy consistently mistook people who were unknown to him, such as hospital staff, for people whom he had met long ago. However, he did not misidentify their names or other attributes, such as their occupations.

The authors could not fit this extraordinary form of misidentification into any known subcategory of misidentification syndromes, but rather thought that it fitted Kraepelin's description of "assoziierende Erinnerungsfälschungen".

Acid–base balance

Metabolic acidosis has been reported in patients taking zonisamide (7). Zonisamide inhibits carbonic anhydrase (8), which might have contributed, as has been suggested by another case of metabolic acidosis in a 7-year-old boy, in which the mechanism was renal tubular acidosis.

Ammonium chloride, bicarbonate, and furosemide loading tests in an epileptic man with metabolic acidosis and episodic hypokalemia taking zonisamide showed evidence of distal renal tubular acidosis (9). On re-examination 7 weeks after zonisamide had been replaced with phenytoin, the renal tubular acidosis had resolved.

Urinary tract

Zonisamide inhibits carbonic anhydrase, but the risk of nephrolithiasis seems to be lower than initially suspected (SEDA-21, 80). Further cases have been reported (10).

- A 13-year-old boy who had taken zonisamide and acetazolamide for 2 months developed abdominal pain due to left-sided hydronephrosis, which resolved after the passage of a stone. He had an alkaline urine, and acetazolamide was withdrawn. However, 2 months later he formed another stone. Zonisamide was withdrawn and he formed no more stones.
- A 7-year-old boy took zonisamide for 3 months and then formed a thick sludge of calcium phosphate in the bladder when dehydrated because of pneumonia.
- A 15-year-old girl, who had a history of recurrent urinary obstruction, formed a thick sludge of calcium oxalate in the bladder.

In all three patients the urine was alkaline and there was hypercalciuria.

Sweat glands

Zonisamide can cause lack of sweating (11).

- A 10-year-old boy who had taken zonisamide for about 9 months noticed that he had a dry skin and that he seldom sweated. His zonisamide blood concentration was very high. He discontinued zonisamide and became able to sweat.

The authors suggested that this effect was due to ion channel blockade.

In 16 patients taking zonisamide, acetylcholine stimulation testing after about 1 month was normal in four cases and reduced in 12 (12). There was reduced sweating in four of the 12 who had a reduced test response, but not in the four with a normal response.

Children have a higher risk of zonisamide-associated oligohidrosis and hyperthermia (13). Elan Pharma issued a "Dear Doctor" letter reporting this adverse event in June 2002. During the zonisamide development program in Japan one case of oligohidrosis was reported among 403 children (an incidence of 1/285 patient-years of exposure). There were no cases reported in the US or European development programs, although under 100 children were included in those programs. In the first 11 years of marketing in Japan, 38 cases have been reported (about 1 per 10 000 patient-years). In the first year in the USA, two cases were reported (an estimated reporting rate of 12/10 000 patient-years). This rate might be an underestimate, owing to under-reporting.

There have been reports of heat stroke associated with reduced sweating in young patients.

- A 2-year-old mentally retarded boy with frontal lobe epilepsy developed hyperpyrexia with oligohidrosis and central neurological symptoms, including chorea-like involuntary movements, resting tremor, and cogwheel rigidity, while receiving zonisamide (14). A sweat test using pilocarpine iontophoresis showed a marked reduction in the sweat response, which suggested a postganglionic sweating dysfunction. A skin biopsy showed no morphological abnormality in the sweat glands. He regained the ability to sweat within 2 weeks of withdrawal.

Children receiving zonisamide should be monitored closely for evidence of reduced sweating and increased body temperature, especially in warm or hot weather and when taking other drugs that predispose to this (carbonic anhydrase inhibitors, anticholinergic drugs, topiramate).

Immunologic

Zonisamide-induced lupus erythematosus has been reported in a 5-year-old child taking zonisamide and ethosuximide (15). He had raised titers of antinuclear antibodies and anti-DNA antibodies and presented with fever, pericarditis, pleurisy, and arthralgia. Clinical recovery and a reduction in the anti-DNA-antibody titer promptly followed withdrawal. A lymphocyte transformation test against zonisamide was positive.

Second-Generation Effects

Lactation

Zonisamide concentrations in plasma and breast milk were measured, in order to investigate the transfer of zonisamide through the placenta and breast milk in two neonates (16). The transfer rates were 92% via the placenta and 41–57% via breast milk.

Drug–Drug Interactions

Carbamazepine

Evidence that zonisamide reduces serum carbamazepine concentrations is conflicting (SEDA-19, 61). Zonisamide

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can reduce carbamazepine-10,11-epoxide to carbamazepine ratios, possibly by reducing the rate of epoxidation.

CYP3A4 inhibitors

In vitro data suggest that the CYP3A4 inhibitors ketoconazole, ciclosporin, and miconazole reduce zonisamide clearance by 31%, 23%, and 17% respectively (SEDA-22, 93).

Enzyme-inducing anticonvulsants

Serum zonisamide concentrations are reduced by enzyme-inducing anticonvulsants (17).

Lamotrigine

Preliminary evidence suggests that serum zonisamide concentrations can be increased by lamotrigine (17).

Diagnosis of Adverse Drug Reactions

The recommended target plasma zonisamide concentration is 10–20 μg/ml.

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Zopiclone

General Information

Although it is chemically distinct to the benzodiazepines, zopiclone, a cyclopyrrolone, has similar pharmacology, binding close to the same site of the GABA receptor–chloride channel complex.

Zopiclone has been widely used as a hypnotic, comparable to estazolam (1), and appears to be relatively safe in overdose. It has no adverse effects that would not be expected from its pharmacological and pharmacokinetic properties, with three exceptions: bitter taste (in 3.6% of 20 513 patients) and, like zolpidem, increased risks of gastrointestinal disturbances and visual hallucinations (2,3). Subchronic zopiclone produces minimal changes in the sleep electroencephalogram (4), a potential advantage over benzodiazepines, and in direct comparisons was at least as effective as triazolam or flunitrazepam, with no rebound insomnia after 1 month (SEDA-19, 37). On the other hand, longer administration of zopiclone can cause physical dependence (5), emphasizing the importance of restricting treatment duration. Likewise, its potential for abuse and release of aggression (6) is similar to that of the benzodiazepines (SEDA-17, 47).

Organs and Systems

Nervous system

In a two-part, placebo-controlled, crossover comparison of the effects of zopiclone and zaleplon on car driving, memory, and psychomotor performance, zaleplon 10 mg had no residual effect on driving when taken at bedtime, 10 hours before driving (7). In contrast, zopiclone 7.5 mg caused marked residual impairment. Patients should be advised to avoid driving the morning after taking zopiclone.

Further concern that zolpidem can impair performance comes from a Chinese study (8). Zopiclone 7.5 mg, but not triazolam 2.5 mg, impaired simulated flight performance 2 hours and 3 hours after a dose at midday and sleeping for 1 hour; performance recovered after 4 hours.

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Endocrine

The syndrome of inappropriate secretion of antidiuretic hormone has been attributed to zopiclone (9).

- A woman with a 2-week history of insomnia took zopiclone 7.5 mg nightly and over the next 9 days became confused, lethargic, and depressed, culminating in an overdose of six zopiclone tablets. Her previous medical history included hypertension and two episodes of diuretic-induced SIADH. Her serum sodium was 129 mmol/l and 4 days later fell to 113 mmol/l. Her serum osmolality was low (240 mmol/kg) and her urine sodium was 20 mmol/l. The serum sodium returned to normal 12 days after withdrawal of zopiclone.

The rapid resolution of symptoms and correction of the hyponatremia after withdrawal was consistent with an effect of zopiclone.

Long-Term Effects

Drug withdrawal

The acute polysomnographic effects of withdrawal of standard doses of zopiclone ($n = 11$), zolpidem ($n = 11$), triazolam ($n = 10$), and placebo ($n = 7$) have been studied in healthy men (10). They took zopiclone 7.5 mg, zolpidem 10 mg, triazolam 0.25 mg, or placebo for 4 weeks in double-blind, randomized order. Sleep EEG was performed. Total sleep time and sleep efficiency were lower in the first night after withdrawal of triazolam. After withdrawal from zopiclone or zolpidem there were slight but not significant rebound effects. Self-rating scales showed minimal rebound insomnia after withdrawal of all three hypnotics. In the placebo group there were no changes in sleep. These results suggest that the risks of tolerance and dependency are low after short-term zopiclone or zolpidem in the recommended doses.

Drug Administration

Drug overdose

- A 72-year-old with respiratory debilitation due to bronchogenic carcinoma died after taking zopiclone about 200–350 mg (11).

Drug–Drug Interactions

Nefazodone

An 86-year-old white woman taking nefazodone for depression started to take zopiclone for insomnia, but subsequently had morning drowsiness (12). The plasma concentration of zopiclone was measured 8 hours after administration on two occasions, during and after nefazodone therapy. After withdrawal of nefazodone, the plasma concentration of the *S*-enantiomer of zopiclone fell from 107 to 17 ng/ml, while the plasma concentration of the *R*-enantiomer fell from 21 to 1.5 ng/ml.

The substantial fall in plasma zopiclone concentration after withdrawal of nefazodone probably reflected a drug interaction due to inhibition of CYP3A4 by nefazodone (13). Despite the normally short half-life of zopiclone, the residual sedation initially observed in this case suggests that the interaction had clinical significance.

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Zotepine

See also Neuroleptic drugs

General Information

Zotepine is a dibenzothiepine neuroleptic drug, an antagonist at D_1 dopamine receptors and at 5-HT_1 and 5-HT_2 receptors (1). It rarely causes extrapyramidal disturbances, and when they do occur they are usually mild.

The efficacy and safety of zotepine have been explored in a 1-year open study in 253 patients with schizophrenia

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(mean age 38 years, range 18–65) who took zotepine 75–450 mg/day (2). The mean total BPRS score was reduced from 52 at baseline to 41. Since concomitant treatment was allowed, 173 patients reported 205 ongoing and 448 new neuroleptic medicaments during the study. A total of 826 adverse events were reported by 220 patients; 50 had serious adverse events and 5 died during the study, 2 taking zotepine; one death was a suicide and the other was due to a ventricular dysrhythmia. In all, 138 patients (55%) withdrew from the study; 60 withdrawals were due to adverse events. The most frequently reported adverse events were weight gain (28%; mean weight gain 4.3 kg), somnolence (15%), and weakness (13%). There were adverse events that could be related to extrapyramidal effects in 5%. In 14 patients with normal baseline electrocardiography there were abnormalities at the end of the study, most commonly sinus tachycardia; there were no reports of torsade de pointes. No clinically important hematological abnormalities have been reported to date.

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Zuclopenthixol

See also Neuroleptic drugs

General Information

Zuclopenthixol is a thioxanthene neuroleptic drug.

Organs and Systems

Hematologic

Neutropenia has been associated with zuclopenthixol (1).

- A 66-year-old man with schizophrenia took zuclopenthixol 10 mg tds for 18 days and developed a mild leukopenia (2.9×10^9/l) and thrombocytopenia (109×10^9/l). He was asymptomatic, with no evidence of infection or a bleeding tendency. Zuclopenthixol was withdrawn, without any change in the rest of his drug therapy (glibenclamide 5 mg tds, biperiden 2 mg bd, oxazepam 10 mg tds, dipyridamole 75 mg tds, and ranitidine 150 mg/day). The leukocyte and platelet counts rose over the next 5 days.

Sexual function

Priapism, although infrequent, can occur during treatment with neuroleptic drugs and necessitates prompt urological consultation and sometimes even surgical intervention (SEDA-14, 149). A case has been associated with zuclopenthixol (2).

- A 31-year-old man developed priapism after taking zuclopenthixol 30 mg/day for 8 days, the dose having been increased to 75 mg the day before, while he was still taking oral carbamazepine 600 mg/day and clorazepate dipotassium 30 mg/day. He had a history of perinatal anoxic encephalopathy with severe motor sequelae and dyslalia, alcohol dependence, and a personality disorder. On the day before the priapism occurred, he had been physically restrained and given an extra dose of intramuscular clorazepate dipotassium 50 mg. When priapism occurred, all drugs except clorazepate were withdrawn and about 6 hours later the corpora cavernosa were washed and infused with noradrenaline in glucose (8 doses of 40 μg), after which the priapism resolved.

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Zygophyllaceae

See also Herbal medicines

General Information

The family of Zygophyllaceae (Table 1) contains nine genera.

Larrea tridentata

The major phenolic component of *Larrea tridentata* (chaparral, creosote bush) is a catechol lignan called nordihydroguaiaretic acid. It causes lymphatic and renal lesions when given chronically in high doses to rodents.

Table 1 The genera of Zygophyllaceae

Balanites (balanites)
Bulnesia (lignum vitae)
Fagonia (fagon bush)
Guajacum (lignum vitae)
Kallstroemia (caltrop)
Larrea (creosote bush)
Peganum (peganum)
Tribulus (punturevine)
Zygophyllum (bean caper)

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Adverse effects

There have been several reports of hepatotoxicity attributed to herbal medicines containing *L. tridentata* leaves (1,2). Of 18 reports of illnesses associated with the ingestion of chaparral, there was evidence of hepatotoxicity in 13 cases (3). The presentation was characterized by jaundice with a marked increase in serum liver enzymes at 3–52 weeks after ingestion, and it resolved 1–17 weeks after withdrawal. The predominant pattern of liver damage was cholestatic; in four cases there was progression to cirrhosis and in two there was acute fulminant liver failure that required liver transplantation.

Chaparral-induced hepatotoxicity in 16 published cases has been summarized in the light of a further report (4).

- A 27-year-old Hispanic man presented with nausea and vomiting, diarrhea, and upper abdominal pain 12 months after starting to take chaparral capsules. A liver biopsy showed hepatocellular injury with necrosis and periportal inflammation. His liver function stabilized after withdrawal of chaparral.

However, in four patients who were given topical chaparral tincture there was no evidence of liver damage (5).

Contact dermatitis has been attributed to *L. tridentata* (6).

A cystic renal cell carcinoma and acquired renal cystic disease associated with consumption of chaparral tea has been reported (7).

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Appendix: List of miscellaneous compounds

General Information

Compound	Adverse effect(s)	References
Amaranth	Allergic reactions (asthma etc.)	(1)
Apnea monitors	Electrocution/burns	(SED-13, 1463)
Balsam of Peru	Dermatitis	(SEDA-21, 501)
Benzalkonium chloride	Exacerbation of rhinitis (nose-drops)	(2)
	Eye irritation or keratitis (eye-drops)	(3)
Benzyl alcohol	Gasping syndrome and infant deaths	(SEDA-19, 446)
Blue dye	Contact dermatitis	(4)
Butyl hydroxyanisole	Allergic contact dermatitis	(5)
Cementless hip arthroplasty	Failure	(SEDA-20, 435)
Cetyl-stearyl alcohol	Dermatitis	(SEDA-21, 501)
Chlorhexidine-impregnated devices	Hypersensitivity reactions	(SEDA-22, 525)
Cosmetics	Dermal reactions	(SEDA-19, 441)
Cinnamic aldehyde	Cutaneous vasodilatation	(6)
	Lichenoid skin eruptions, eczematous erythroderma	(7,8)
Dental amalgam fillings	Allergies	(SEDA-20, 440)
Dental materials	Allergic skin rash	(SED-13, 1456)
Detergents	Allergic contact dermatitis	(9)
Dimethylacetamide	Hallucinations, delusions, pulmonary edema	(10)
Dinitrochlorobenzene	Pruritic reaction	(SEDA-19, 446)
Electric heating pads	Burns, electric shocks	(SEDA-20, 435)
Enoxolone	Allergic contact dermatitis	(11)
Ethanolamine	Chest pain, dysphagia, strictures	(SEDA-20, 438)
Ethyl aminobenzoate	Allergic contact dermatitis	(SEDA-21, 497)
FD and C Blue No 1	Intense green hyperpigmentation	(12)
Food additives	Urticaria	(13)
Fructose	Hypoglycemia	(SEDA-21, 501)
Fructose-1,6-diphosphate	Nausea, local burning	(SEDA-19, 446)
Fumaric acid	Gastrointestinal disorders	(SEDA-21, 501)
Fumaric acid (alkyl ester)	Leukopenia, eosinophilia	(SEDA-20, 440)
Gamma-hydroxybutyric acid	Vomiting, dizziness, tremors, seizures	(SEDA-21, 501)
Gamolenic acid	Inadequate efficacy	(14)
	Hyperparathyroidism	(15)
Glycolic acid	Dermal wounding	(SEDA-19, 446)
Hair implants	Foreign body reactions, infections	(SEDA-20, 435)
Hemodiafiltration	Hypophosphatemia	(16)
Indigo carmine	Anaphylactoid reaction; cardiac arrest	(17)
	Allergic alveolitis	(18)
	Anaphylactoid reaction	(SEDA-19, 446)
K4-herbal product	Liver problems	(SEDA-21, 498)
Lactose	Skin eruptions	(19)
	Diarrhea, vomiting, hypoglycemia	
	Availability problem	(SEDA-19/21, 501)
Lanolin alcohol	Allergic contact eczema	(SEDA-21, 501)
Lecithin	Atopic dermatitis	(20)
Lipokinetix	Liver injury	(21)
Metabisulfite sodium	Allergic contact dermatitis	(22)
	Bronchospasm, anaphylaxis, contact dermatitis	(23)
	Nasal syndromes	(SEDA-19, 446)
Metered-dose inhalers	Bronchoconstriction	(SEDA-19, 446)
Methyl glucose dioleate	Erythematous dermatitis	(24)
Monofluorophosphate	Leg pain	(25)

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Compound	Adverse effect(s)	References
Para-phenylenediamine	Contact allergies	(SEDA-20/21, 501)
Parabens	Allergic contact eczema	(SEDA-21, 501)
Parathion	Death	(26)
	Acute intoxication	(27)
Pharmaceutical excipients	Asthma, anaphylaxis, local irritation	(28)
Phenazone salicylate	Drug eruption	(SEDA-19, 446)
Phenol	Burns	(29)
Phosphate infusion	Calcified right atrial thrombus	(30)
Phosphate, sodium	Electrolyte disturbances	(SEDA-21/22, 526)
Polidocanol	Embolia cutis medicamentosa	(31)
	Allergic contact dermatitis	(32)
	Allergic reactions, thrombosis	(SEDA-20, 440)
Polyoxyethylene lauryl ether	Follicular contact dermatitis	(33)
	Contact dermatitis	(33)
Polyvinylpyrrolidone	Contact allergy (facial eczema)	(34)
	Allergic contact dermatitis	(35)
Potassium dichromate	Contact allergy	(SEDA-20, 440)
Potassium salts	Complex ventricular dysrhythmias	(36)
	Drug-induced esophagitis	(37)
Rasburicase	Skin rash, respiratory reaction, hemolysis	(38)
Royal jelly	Allergic reactions, death	(SEDA-22/21, 526)
"Slim 10"	Contamination with nicotinamide, fenfluramine, and thyroid gland components	(39)
Sodium picosulfate	Electrolyte disturbance, convulsions, syncope, metabolic alkalosis	(40)
Sodium prasterone sulfate	Anaphylactic reactions	(41)
Sorbic acid	Systemic contact dermatitis	(42)
Sorbitol	Adominal pain, diarrhea	(SEDA-21, 500)
Stearyl alcohol	Contact dermatitis	(43)
Sterile water	Hemolysis	(SEDA-22, 524)
Sulfan blue	Anaphylactic reactions	(44)
Synthetic food coloring	Hyperactivity, irritability children	(SED-13, 1462)
Tetraethylthiuram disulfide	Contact dermatitis	(45)
Thiuram mix	Contact allergy	(SEDA-20, 440)
Tiaprofenic acid	Cystitis	(SEDA-19, 446)
Tincture of orange	Nausea, vomiting, abdominal pain	(SEDA-19, 446)
Titanium alloy prosthesis	Cytogenetic damage	(46)
Trichloracetic acid	Dermal wounding	(SEDA-19, 446)
Visicol	Risk of seizures	(47)
Volume ventilators	Injuries and deaths	(SED-13, 1464)
Walnut oil	Foreign body reactions, tumors, pulmonary complications	(48)
White flower	Contact dermatitis	(49)
Yasmin	Venous thromboembolism	(50)

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